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KEY POINTS
1. Understand extrahepatic and intrahepatic liver anatomy and physiology.
2. Understand hepatic molecular signaling pathways.
3. Know the features of acute liver failure and cirrhosis, along with treatment options.
4. Formulate a plan for the work-up of an incidental liver lesion.
5. Understand the current treatment options for primary and metastatic liver cancer.
6. Describe the nomenclature and steps in performing an anatomic right or left hepatic resection.

HISTORY OF LIVER SURGERY
The ancient Greek myth of Prometheus reminds us that the liver is the only organ that regenerates. According to Greek mythology, Zeus was furious with the titan Prometheus because he gave fire to the mortals. In return, Zeus chained Prometheus to Mount Caucasus and sent his giant eagle to eat his liver during the day, only to have it regenerate at night. Although this is an exaggeration, the principles are correct that after hepatic resection, the remnant liver will hypertrophy over weeks to months to regain most of its original liver mass. It is interesting to note that the ancient Greeks seem to have been aware of this fact, because the Greek word for the liver, ἕπαρ, derives from the verb ἑπάομαι, which means "mend" or "repair." Hence ἕπαρ roughly translates as "repairable." The importance of the liver dates back to even biblical times, for the Babylonians (c. 2000 B.C.) considered the liver to be the seat of the soul. There are scattered reports of liver surgery for battlefield injuries, but the first recorded elective hepatic resection was done in 1888 in Germany by Langenbuch. There followed reports of liver resections in the United States (Tiffany, 1890) and Europe (Lucke, 1891), as well as the first large series of hepatic resections by Keen in 1899. In 1908, Pringle described in Annals of Surgery the "arrest of hepatic hemorrhage due to trauma" by compression of the porta hepatis, a maneuver that now bears his name. Possibly due to the potential for massive hemorrhage during liver surgery, very little progress in surgical techniques was recorded for the next half-century. Work by Rex, Cantlie, and others laid the groundwork for experimental and clinical reports in the 1950s by Couinaud, Hjortsjo, Healey, Lortat-Jacob, and Starzl. These seminal contributions paved the way for the modern era of hepatic resection surgery.

LIVER ANATOMY
The liver is the largest organ in the body, weighing approximately 1500 g. It sits in the right upper abdominal cavity beneath the diaphragm and is protected by the rib cage. It is reddish brown and is surrounded by a fibrous sheath known as Glisson's capsule. The liver is held in place by several ligaments (Fig. 31-1). The round ligament is the remnant of the obliterated umbilical vein and enters the left liver hilum at the front edge of the falciform ligament. The falciform ligament separates the left lateral and left medial segments along the umbilical fissure and anchors the liver to the anterior abdominal wall. Deep in the plane between the caudate lobe and the left lateral segment is the fibrous ligamentum venosum, which is the obliterated ductus venosus and is covered by the plate of Arantius. The left and right triangular ligaments secure the two sides of the liver to the diaphragm. Extending from the triangular ligaments anteriorly on the liver are the coronary ligaments. The right coronary ligament also extends from the right undersurface of the liver to the peritoneum overlying the right kidney, thereby anchoring the liver to the right retroperitoneum. These ligaments (round, falciform, triangular, and coronary) can be divided in a bloodless plane to fully mobilize the liver to facilitate hepatic resection. Centrally and just to the left of the gallbladder fossa, the liver
attaches via the hepatoduodenal and the gastrohepatic ligaments (Fig. 31-2). The hepatoduodenal ligament is known as the *porta hepatitis* and contains the common bile duct, the hepatic artery, and the portal vein. From the right side and deep (dorsal) to the porta hepatitis is the foramen of Winslow, also known as the *epiploic foramen* (see Fig. 31-2). This passage connects directly to the lesser sac and allows complete vascular inflow control to the liver when the hepatoduodenal ligament is clamped using the Pringle maneuver.

**Fig. 31-1.**

![Hepatic ligaments suspending the liver to the diaphragm and anterior abdominal wall.](image1)

**Fig. 31-2.**

![In situ liver hilar anatomy with hepatoduodenal and gastrohepatic ligaments. Foramen of Winslow is depicted.](image2)

**Segmental Anatomy**

The liver is grossly separated into the right and left lobes by the plane from the gallbladder fossa to the inferior vena cava (IVC), known as *Cantlie's line*. The right lobe typically accounts for 60 to 70% of the liver mass, with the left lobe (and caudate lobe) making up the
The caudate lobe lies to the left and anterior of the IVC and contains three subsegments: the Spiegel lobe, the paracaval portion, and the caudate process. The falciform ligament does not separate the right and left lobes, but rather it divides the left lateral segment from the left medial segment. The left lateral and left medial segments also are referred to as sections as defined in the Brisbane 2000 terminology, which is outlined later in the section "Hepatic Resection Techniques." A significant advance in our understanding of liver anatomy came from the cast work studies of the French surgeon and anatomist Couinaud in the early 1950s. Couinaud divided the liver into eight segments, numbering them in a clockwise direction beginning with the caudate lobe as segment I. Segments II and III comprise the left lateral segment, and segment IV is the left medial segment (Fig. 31-3). Thus, the left lobe is made up of the left lateral segment (Couinaud's segments II and III) and the left medial segment (segment IV). Segment IV can be subdivided into segment IVB and segment IVA. Segment IVA is cephalad and just below the diaphragm, spanning from segment VIII to the falciform ligament adjacent to segment II. Segment IVB is caudad and adjacent to the gallbladder fossa. Many anatomy textbooks also refer to segment IV as the quadrate lobe. Quadrate lobe is an outdated term, and the preferred term is segment IV or left medial segment. Most surgeons still refer to segment I as the caudate lobe, rather than segment I. The right lobe is comprised of segments V, VI, VII, and VIII, with segments V and VIII making up the right anterior lobe, and segments VI and VII the right posterior lobe.
Couinaud's liver segments (I through VIII) numbered in a clockwise manner. The left lobe includes segments II to IV, the right lobe includes segments V to VIII, and the caudate lobe is segment I. IVC = inferior vena cava.

Additional functional anatomy was highlighted by Bismuth based on the distribution of the hepatic veins. The three hepatic veins run in corresponding scissura (fissures) and divide the liver into four sectors. The right hepatic vein runs along the right scissura and separates the right posterolateral sector from the right anterolateral sector. The main scissura contains the middle hepatic vein and separates the right and left livers. The left scissura contains the course of the left hepatic vein and separates the left posterior and left anterior sectors. Although many other investigators contributed to the description of liver anatomy, it was clearly the work of Couinaud that provided the most detailed understanding of segmental liver anatomy. Couinaud devoted decades to understanding the anatomy of the liver—a PubMed search of "Couinaud C" and "liver" yields 72 publications.

**Hepatic Artery**

The liver has a dual blood supply consisting of the hepatic artery and the portal vein. The hepatic artery delivers approximately 25% of the blood supply, and the portal vein approximately 75%. The hepatic artery arises from the celiac axis (trunk), which gives off the left gastric, splenic, and common hepatic arteries (Fig. 31-4). The common hepatic artery then divides into the gastroduodenal artery and the hepatic artery proper. The right gastric artery typically originates off of the hepatic artery proper, but this is variable. The hepatic artery proper divides into the right and left hepatic arteries. This "classic" or standard arterial anatomy is present in only approximately 75% of cases, with the remaining 25% having variable anatomy. It is critical to understand the arterial (and biliary) anatomic variants to avoid surgical complications when operating on the liver, gallbladder, pancreas, or adjacent organs.
Arterial anatomy of the upper abdomen and liver, including the celiac trunk and hepatic artery branches. a. = artery; LHA = left hepatic artery; RHA = right hepatic artery.

The most common hepatic arterial variants are shown (Fig. 31-5). The right hepatic artery is replaced coming off the superior mesenteric artery (SMA) 18 to 22% of the time. When there is a replacement or accessory right hepatic artery, it traverses posterior to the portal vein and then takes up a right lateral position before diving into the liver parenchyma. This can be recognized visually on a preoperative computed tomographic (CT) or magnetic resonance imaging (MRI) scan, and confirmed by palpation in the hilum where a separate right posterior pulsation is felt distinct from that of the hepatic artery proper that lies anteriorly in the hepatoduodenal ligament to the left of the common bile duct. A replacement (or accessory) left hepatic artery comes off of the left gastric artery in 12 to 15% of cases and runs obliquely in the gastrohepatic ligament anterior to the caudate lobe before entering the hilar plate at the base of the umbilical fissure. Other less common variants (approximately 2% each) are an early bifurcation of the left and right hepatic arteries, as well as a completely replaced common hepatic artery coming off the SMA (see Fig. 31-5). Although not well demonstrated in the illustration, the clue for a completely replaced common hepatic artery coming off the SMA is the presence of a strong arterial pulsation to the right of the common bile duct, rather than the left side, in the porta hepatis. Another important point is that the right hepatic artery passes deep and posterior to the common bile duct approximately 88% of the time but crosses anterior to the common bile duct in approximately 12% of cases. The cystic artery feeding the gallbladder usually arises from the right hepatic artery in Calot's triangle.

Fig. 31-5.
Replaced right hepatic artery from SMA (18-22%)

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Replaced left hepatic artery from left gastric artery (12-15%)

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Early bifurcation of common hepatic artery (1-2%)

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Common hepatic artery anatomic variants. SMA = superior mesenteric artery.

**Portal Vein**

The portal vein is formed by the confluence of the splenic vein and the superior mesenteric vein. The inferior mesenteric vein usually drains into the splenic vein upstream from the confluence (Fig. 31-6). The main portal vein traverses the porta hepatis before dividing into the left and right portal vein branches. The left portal vein typically branches from the main portal vein outside of the liver with a sharp bend to the left and consists of the transverse portion followed by a 90-degree turn at the base of the umbilical fissure to become the umbilical portion before entering the liver parenchyma (Fig. 31-7). The left portal vein then divides to give off the segment III and II branches to the left lateral segment, as well as the segment IV feedback branches that supply the left medial segment. The left portal vein also provides the dominant inflow branch to the caudate lobe (although branches can arise from the main and right portal veins also), usually close to the bend between the transverse and umbilical portions. The division of the right portal vein is usually higher in the hilum and may be close to (or inside) the liver parenchyma at the hilar plate.

**Fig. 31-6.**
Portal vein anatomy. The portal vein is formed by the confluence of the splenic and superior mesenteric veins. The inferior mesenteric vein drains into the splenic vein. The coronary (left gastric) vein drains into the portal vein in the vicinity of the confluence. v. = vein.

**Fig. 31-7.**

Anatomy of the left portal vein (LPV). Cadaver cast shows the transverse and umbilical portions of the LPV. LIG. VEN = ligamentum venosum; RD LIG. = round ligament.

(Reproduced with permission from Botero AC, Strasberg SM: Division of the left hemiliver in man—segments, sectors, or sections. *Liver Transpl Surg* 4:226, 1998.)

The portal vein drains the splanchnic blood from the stomach, pancreas, spleen, small intestine, and majority of the colon to the liver before returning to the systemic circulation. The portal vein pressure in an individual with normal physiology is low at 3 to 5 mmHg. The portal vein is valveless, however, and in the setting of portal hypertension, the pressure can be quite high (20 to 30 mmHg). This results in decompression of the systemic circulation through portocaval anastomoses, most commonly via the coronary (left gastric) vein, which produces esophageal and gastric varices with the propensity for major hemorrhage. Another branch of the main portal vein is the superior pancreaticoduodenal vein (which comes off low in an anterior lateral position and is divided during pancreaticoduodenectomy). Closer to the liver, the main portal vein typically gives off a short branch (posterior lateral) to the caudate process on the right side. It is important to identify this branch and ligate it during hilar dissection for anatomic right hemihepatectomy to avoid avulsion.

**Hepatic Veins and Inferior Vena Cava**

There are three hepatic veins (right, middle, and left) that pass obliquely through the liver to drain the blood to the suprahepatic IVC and eventually the right atrium (Fig. 31-8). The right hepatic vein drains segments V to VIII; the middle hepatic vein drains segment IV as well as segments V and VIII; and the left hepatic vein drains segments II and III. The caudate lobe is unique because its venous drainage feeds directly into the IVC. In addition, the liver usually has a few small, variable short hepatic veins that directly enter the IVC from the undersurface of the liver. The left and middle hepatic veins form a common trunk approximately 95% of the time before entering the IVC, whereas the right hepatic vein inserts separately (in an oblique orientation) into the IVC. There is a large inferior accessory right hepatic vein in 15 to 20% of cases that runs in the hepatocaval ligament. This can be a source of torrential bleeding if control is lost during right hepatectomy. The hepatic vein branches bisect the portal branches inside the liver parenchyma (i.e., the right hepatic vein runs between the right anterior and posterior portal veins; the middle hepatic vein passes between the right anterior and left portal vein; and the left
hepatic vein crosses between the segment III and II branches of the left portal vein.

**Fig. 31-8.**

Bile Duct and Hepatic Ducts

Within the hepatoduodenal ligament, the common bile duct lies anteriorly and to the right. It gives off the cystic duct to the gallbladder and becomes the common hepatic duct before dividing into the right and left hepatic ducts. In general, the hepatic ducts follow the arterial branching pattern inside the liver. The bifurcation of the right anterior hepatic duct usually enters the liver above the hilar plate, whereas the right posterior duct dives behind the right portal vein and can be found on the surface of the caudate process before entering the liver. The left hepatic duct typically has a longer extrahepatic course before giving off segmental branches behind the left portal vein at the base of the umbilical fissure. Considerable variation exists, and in 30 to 40% of cases there is a nonstandard hepatic duct confluence with accessory or aberrant ducts (Fig. 31-9). The cystic duct itself also has a variable pattern of drainage into the common bile duct. This can
lead to potential injury or postoperative bile leakage during cholecystectomy or hepatic resection, and the surgeon needs to expect these variants. The gallbladder sits adherent to hepatic segments IVB (left lobe) and V (right lobe) (see Chap. 32).

**Fig. 31-9.**

A: Normal bifurcation 57%
B: Trifurcation of 3 ducts 12%

C: R anterior (C1, 16%) or R posterior (C2, 4%) duct draining into CHD

D: R posterior (D1, 5%) or R anterior duct (D2, 1%) draining into the left hepatic duct

E: Absence of hepatic duct confluence 3%

F: Drainage of R posterior duct into cystic duct 2%

Main variations of hepatic duct confluence. As described by Couinaud in 1957, the bifurcation of the hepatic ducts has a variable pattern in approximately 40% of cases. CHD = common hepatic duct; lh = left hepatic; R = right; ra = right anterior; rp = right posterior.

Neural Innervation and Lymphatic Drainage

The parasympathetic innervation of the liver comes from the left vagus, which gives off the anterior hepatic branch, and the right vagus, which gives off the posterior hepatic branch. The sympathetic innervation involves the greater thoracic splanchnic nerves and the celiac ganglia, although the function of these nerves is poorly understood. The denervated liver after hepatic transplantation seems to function with normal capacity. A common source of referred pain to the right shoulder and scapula as well as the right side or back is the right phrenic nerve, which is stimulated by tumors that stretch Glisson’s capsule or by diaphragmatic irritation.

Lymph is produced within the liver and drains via the perisinusoidal space of Disse and periportal clefts of Mall to larger lymphatics that drain to the hilar cystic duct lymph node (Calot's triangle node), as well as the common bile duct, hepatic artery, and retropancreatic and celiac lymph nodes. This is particularly important for resection of hilar cholangiocarcinoma, which has a high incidence of lymph node metastases. The hepatic lymph also drains cephalad to the cardiophrenic lymph nodes and the latter can be pathologically identified on a staging CT or MRI scan.

LIVER PHYSIOLOGY

The liver is the largest gland in the body and has an extraordinary spectrum of functions. These many functions comprise processes such as storage, metabolism, production, and secretion. One crucial role is the processing of absorbed nutrients through the metabolism of glucose, lipids, and proteins. The liver maintains glucose concentrations in a normal range over both short and long periods by performing several important roles in carbohydrate metabolism. In the fasting state, the liver ensures a sufficient supply of glucose to the central nervous system. The liver can produce glucose by breaking down glycogen through glycogenolysis and by de novo synthesis of glucose through gluconeogenesis from noncarbohydrate precursors such as lactate, amino acids, and glycerol. In the postprandial state, excess circulating glucose is removed by glycogen synthesis or glycolysis and lipogenesis. The liver also plays a central role in lipid metabolism through the formation of bile and the production of cholesterol and fatty acids. Protein metabolism occurs in the liver through amino acid deamination resulting in the production of ammonia as well as the production of a variety of proteins. In addition to metabolism, the liver is also responsible for the synthesis of most circulating plasma proteins. Among these proteins are albumin, factors of the coagulation and fibrinolytic systems, and compounds of the complement cascade. Furthermore, the detoxification of many substances through drug metabolism occurs in the liver, as do immunologic responses through the many immune cells found in its reticuloendothelial system.

Bilirubin Metabolism

Bilirubin is the breakdown product of normal heme catabolism. The bilirubin is bound to albumin in the circulation and sent to the liver. In the liver, it is conjugated to glucuronic acid in a reaction catalyzed by the enzyme glucuronyl transferase, which makes it soluble in water. Each bilirubin molecule reacts with two uridine diphosphoglucuronic acid molecules to form bilirubin diglucuronide. This glucuronide is then excreted into the bile canaliculi. A small amount of bilirubin glucuronide escapes into the blood and is then excreted in the urine. The majority of conjugated bilirubin is excreted in the intestine as waste, because the intestinal mucosa is relatively impermeable to conjugated bilirubin. However, it is permeable to unconjugated bilirubin and urobilinogens, a series of bilirubin derivatives formed by the action of bacteria. Thus, some of the bilirubin and urobilinogens are reabsorbed in the portal circulation; they are again excreted by the liver or enter the circulation and are excreted in the urine.

Formation of Bile

Bile is a complex fluid containing organic and inorganic substances dissolved in an alkaline solution that flows from the liver through the biliary system and into the small intestine. The main components of bile are water, electrolytes, and a variety of organic molecules including bile pigments, bile salts, phospholipids (lecithin), and cholesterol. The two fundamental roles of bile are to aid in the digestion and absorption of lipids and lipid-soluble vitamins and to eliminate waste products (bilirubin and cholesterol) through secretion into bile and elimination in feces. Bile is produced by hepatocytes and secreted through the biliary system. In between meals, bile is stored in the gallbladder and concentrated through the absorption of water and electrolytes. Upon entry of food into the duodenum, bile is released from the gallbladder to aid in digestion. About 1 L of bile can be produced by the human liver daily. However, >95% of the bile salts secreted in bile are reabsorbed in the intestine and then excreted again by the liver (enterohepatic circulation).
Bile salts, in conjunction with phospholipids, are responsible for the digestion and absorption of lipids in the small intestine. Bile salts are sodium and potassium salts of bile acids conjugated to amino acids. The bile acids are derivatives of cholesterol synthesized in the hepatocyte. Cholesterol, ingested from the diet or derived from hepatic synthesis, is converted into the bile acids cholic acid and chenodeoxycholic acid. These bile acids are conjugated to either glycine or taurine before secretion into the biliary system. Bacteria in the intestine can remove glycine and taurine from bile salts. They can also convert some of the primary bile acids into secondary bile acids by removing a hydroxyl group, producing deoxycholic from cholic acid, and lithocholic from chenodeoxycholic acid.

Bile salts are amphipathic, containing both hydrophobic and hydrophilic domains. The amphipathic nature of bile salts allows for the emulsification of lipids, which results in the breakdown of fat globules into microscopic droplets. This greatly increases the surface area of lipids, which permits their digestion by lipases. Bile salts are also able to carry and solubilize lipids by forming micelles. Lipids collect in the micelles, with cholesterol in the hydrophobic center and amphipathic phospholipids with their hydrophilic heads on the outside and their hydrophobic tails in the center. The micelles play an important role in keeping lipids in solution and transporting them to the brush border of the intestinal epithelial cells, where they are absorbed.

Bile salts secreted into the intestine are efficiently reabsorbed and reused. Approximately 90 to 95% of the bile salts are absorbed from the small intestine at the terminal ileum. The remaining 5 to 10% enters the colon and is converted to the secondary salts of deoxycholic acid and lithocholic acid. The mixture of primary and secondary bile salts and bile acids is absorbed primarily by active transport in the terminal ileum. The absorbed bile salts are transported back to the liver in the portal vein and re-excreted in the bile. Those lost in the stool are replaced by synthesis in the liver. The continuous process of secretion of bile salts in the bile, their passage through the intestine, and their subsequent return to the liver is termed the enterohepatic circulation.

**Drug Metabolism**

The liver plays an important role in providing mechanisms for ridding the body of foreign molecules (xenobiotics) that are absorbed from the environment. In most cases, a drug is relatively lipophilic to ensure good absorption. The liver participates in the elimination of these lipid-soluble drugs by transforming them into more readily excreted hydrophilic products. There are two main reactions that can occur in the liver important for drug metabolism. Phase I reactions include oxidation, reduction, and hydrolysis of molecules that result in metabolites that are more hydrophilic than the original chemicals. The cytochrome P-450 system is a family of hemoproteins important for oxidative reactions involving drug and toxic substances. Phase II reactions, also known as conjugation reactions, are synthetic reactions that involve addition of subgroups to the drug molecule. These subgroups include glucuronate, acetate, glutathione, glycine, sulfate, and methyl groups. These drug reactions occur mainly in the smooth endoplasmic reticulum of the hepatocyte.

Many factors can affect drug metabolism in the liver. When the rate of metabolism of a pharmacologically active metabolite is increased (i.e., enzyme induction), the duration of the drug action will decrease. However, when the metabolism of a drug is decreased (i.e., enzyme inhibition), then the drug will be metabolically active for a longer period of time. It is important to note that some drugs may be converted to active products by metabolism in the liver. An example is acetaminophen when taken in larger doses. Normally, acetaminophen is conjugated by the liver to harmless glucuronide and sulfate metabolites that are water soluble and eliminated in the urine. During an overdose, the normal metabolic pathways are overwhelmed, and some of the drug is converted to a reactive and toxic intermediate by the cytochrome P-450 system. Glutathione can normally bind to this intermediate and lead to the excretion of a harmless product. However, as glutathione stores are diminished, the reactive intermediate cannot be detoxified and it combines with lipid bilayers of hepatocytes, which results in cellular necrosis. Thus, treatment of acetaminophen overdoses consists of replacing glutathione with sulfhydryl compounds such as acetylcysteine.

**Liver Function Tests**

Liver function tests is a term frequently used to refer to measurement of the levels of a group of serum markers for evaluation of liver dysfunction. Most commonly, levels of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AP), \( \gamma \)-glutamyltranspeptidase (GGTP), and bilirubin are included in this panel. This term is a misnomer, however, because most of these tests measure not liver function but rather cell damage. More accurate measurement of the liver's synthetic function is provided by serum albumin levels and prothrombin time. Although measuring liver enzyme levels is important in the assessment of a patient's liver disease,
these test results can be nonspecific. Thus, evaluation of patients with suspected liver disease should always involve careful interpretation of abnormalities in these liver test results in the context of a thorough history and physical examination. The approach to evaluating abnormal laboratory values can also be simplified by categorizing the type of abnormality that predominates (hepatocellular damage, abnormal synthetic function, or cholestasis).

**Hepatocellular Injury**

Hepatocellular injury of the liver is usually indicated by abnormalities in levels of the liver aminotransferases AST and ALT. These enzymes participate in gluconeogenesis by catalyzing the transfer of amino groups from aspartic acid or alanine to ketoglutaric acid to produce oxaloacetic acid and pyruvic acid, respectively (these enzymes were formerly referred to as glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase). AST is found in the liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lungs, and red blood cells and thus is less specific for disorders of the liver. ALT is predominately found in the liver and thus is more specific for liver disease. Hepatocellular injury is the trigger for release of these enzymes into the circulation. Common causes of elevated aminotransferase levels include viral hepatitis, alcohol abuse, medications, genetic disorders (Wilson's disease, hemochromatosis, alpha1-antitrypsin deficiency), and autoimmune diseases.

The extent of serum aminotransferase elevations can suggest certain etiologies of the liver injury. However, the levels of the enzymes in these tests correlate poorly with the severity of hepatocellular necrosis, because they may not be significantly elevated in conditions of hepatic fibrosis or cirrhosis. In alcoholic liver disease, an AST:ALT ratio of >2:1 is common. Mild elevations of transaminase levels can be found in nonalcoholic fatty liver disease, chronic viral infection, or medication-induced injury. Moderate increases in the levels of these enzymes are common in acute viral hepatitis. In conditions of ischemic insults, toxin ingestions (i.e., acetaminophen), and fulminant hepatitis, AST and ALT levels can be elevated to the thousands.

**Abnormal Synthetic Function**

Albumin synthesis is an important function of the liver and thus can be measured to evaluate the liver's synthetic function. The liver produces approximately 10 g of albumin per day. However, albumin levels are dependent on a number of factors such as nutritional status, renal dysfunction, protein-losing enteropathies, and hormonal disturbances. In addition, level of albumin is not a marker of acute hepatic dysfunction due to albumin's long half-life of 15 to 20 days.

Most clotting factors (except factor VIII) are synthesized exclusively in the liver, and thus their levels can also be used as a measure of hepatic synthetic function. Measurements of the prothrombin time and international normalized ratio (INR) are one of the best tests of hepatic synthetic function. The prothrombin time measures the rate of conversion of prothrombin to thrombin. To standardize the reporting of prothrombin time and avoid interlaboratory variability, the INR was developed. The INR is the ratio of the patient's prothrombin time to the mean control prothrombin time. Because vitamin K is involved in the γ-carboxylation of factors used to measure prothrombin time (factors II, VII, IX, and X), values may be prolonged in other conditions such as vitamin K deficiency and warfarin therapy.

**Cholestasis**

Cholestasis is a condition in which bile flow from the liver to the duodenum is impaired. Disturbances in bile flow may be due to intrahepatic causes (hepatocellular dysfunction) or extrahepatic causes (biliary tree obstruction). Cholestasis often results in the release of certain enzymes and thus can be detected by measuring the serum levels of bilirubin, AP, and GGTP, which will be abnormal. Bilirubin is a breakdown product of hemoglobin metabolism. Unconjugated bilirubin is insoluble and thus is transported to the liver bound to albumin. In the liver, it is conjugated to allow excretion in bile. Measured total bilirubin levels can be low, normal, or high in patients with significant liver disease because of the liver's reserve ability to conjugate significant amounts of bilirubin. Thus, to help aid in the diagnosis of hyperbilirubinemia, fractionation of the total bilirubin is usually performed to distinguish between conjugated (direct) and unconjugated (indirect) bilirubin. **Indirect bilirubin** is a term frequently used to refer to unconjugated bilirubin in the circulation because the addition of another chemical is necessary to differentiate this fraction from the whole. Normally, >90% of serum bilirubin is unconjugated. The testing process for conjugated bilirubin, in contrast, is direct without the addition of other agents. The direct bilirubin test measures the levels of conjugated bilirubin and delta bilirubin (conjugated bilirubin bound to albumin).

The patterns of elevation of the different fractions of bilirubin provide important diagnostic clues as to the cause of cholestasis. In general,
an elevated indirect bilirubin level suggests intrahepatic cholestasis and an elevated direct bilirubin level suggests extrahepatic obstruction. Mechanisms that can result in increases in unconjugated bilirubin levels include increased bilirubin production (hemolytic disorders and resorption of hematomas) or defects (inherited or acquired) in hepatic uptake or conjugation. The rate-limiting step in bilirubin metabolism is the excretion of bilirubin from hepatocytes, so conjugated hyperbilirubinemia can be seen in inherited or acquired disorders of intrahepatic excretion or extrahepatic obstruction. Conjugated bilirubin cannot be excreted and accumulates in the hepatocytes, which results in its secretion into the circulation. Because conjugated bilirubin is water soluble, it can be found in the urine of patients with jaundice.

AP is an enzyme with a wide tissue distribution but is found primarily in the liver and bones. In the liver, it is expressed by the bile duct epithelium. In conditions of biliary obstruction, levels rise as a result of increased synthesis and release into the serum. Because the half-life of serum AP is approximately 7 days, it may take several days for levels to normalize even after resolution of the biliary obstruction.

GGTP is another enzyme found in hepatocytes and released from the bile duct epithelium. Elevation of GGTP is an early marker and also a sensitive test for hepatobiliary disease. Like AP elevation, however, it is nonspecific and can be produced by a variety of disorders in the absence of liver disease. Increased levels of GGTP can be induced by certain medications, alcohol abuse, pancreatic disease, myocardial infarction, renal failure, and obstructive pulmonary disease. For this reason, elevated GGTP levels are often interpreted in conjunction with other enzyme abnormalities. For example, a raised GGTP level with increased AP level supports a liver source.

**Jaundice**

Jaundice refers to the yellowish staining of the skin, sclera, and mucous membranes with the pigment bilirubin. Hyperbilirubinemia is usually detectable as jaundice when blood levels rise above 2.5 to 3 mg/dL. Jaundice can be caused by a wide range of benign and malignant disorders. However, when present, it may indicate a serious condition, and thus knowledge of the differential diagnosis of jaundice and a systematic approach to the work-up of the patient is necessary. Work-up of a patient with jaundice is simplified by organizing the possible causes of the disorder into groups based on the location of bilirubin metabolism. As mentioned previously, bilirubin metabolism can take place in three phases: prehepatic, intrahepatic, and posthepatic. The prehepatic phase includes the production of bilirubin from the breakdown of heme products and its transport to the liver. The majority of the heme results from red blood cell metabolism and the rest from other heme-containing organic compounds such as myoglobin and cytochromes. In the liver, the insoluble unconjugated bilirubin is then conjugated to glucuronic acid to allow for solubility in bile and excretion. The posthepatic phase of bilirubin metabolism consists of excretion of soluble bilirubin through the biliary system into the duodenum. Dysfunction in any of these phases can lead to jaundice.  

**PREHEPATIC**

Jaundice as a result of elevated levels of unconjugated bilirubin occurs from faulty prehepatic metabolism and usually arises from conditions that interfere with proper conjugation of bilirubin in the hepatocyte. Insufficient conjugation is often seen in processes that result in excessive heme metabolism. Subsequently, the conjugation system is overwhelmed, which results in unconjugated hyperbilirubinemia. Causes of hemolysis include inherited and acquired hemolytic anemias. Inherited hemolytic anemias include genetic disorders of the red blood cell membrane (hereditary spherocytosis), enzyme defects (glucose-6-phosphate dehydrogenase deficiency), and defects in hemoglobin structure (sickle cell anemia and thalassemias). Hemolytic anemias can also be acquired, and these can be further divided into those with immune-mediated and those with non-immune-mediated causes. Immune-mediated hemolytic anemias result in a positive finding on a direct Coombs' test and have a variety of autoimmune and drug-induced causes. In contrast, direct Coombs' test results are negative in nonimmune hemolytic anemias. The causes in this latter category are varied and include drugs and toxins that directly damage red blood cells, mechanical trauma (heart valves), microangiopathy, and infections. Prehepatic dysfunction of bilirubin metabolism can also result from failure in the transport of unconjugated bilirubin to the liver by albumin in any condition that leads to plasma protein loss. A poor nutritional state or excess protein loss as seen in burn patients can lead to elevated levels of unconjugated bilirubin in the circulation and jaundice.

**INTRAHEPATIC**
Intrahepatic causes of jaundice involve the intracellular mechanisms for conjugation and excretion of bile from the hepatocyte. The enzymatic processes in the hepatocytes can be affected by any condition that impairs hepatic blood flow and subsequent function of the liver (ischemic or hypoxic events). Furthermore, there are multiple inherited disorders of enzyme metabolism that can result in either unconjugated or conjugated hyperbilirubinemia. Gilbert syndrome is a genetic variant characterized by diminished activity of the enzyme glucuronyltransferase, which results in decreased conjugation of bilirubin to glucuronide. It is a benign condition that affects approximately 4 to 7% of the population. Typically, the disease results in transient mild increases in unconjugated bilirubin levels and jaundice during episodes of fasting, stress, or illness. These episodes are self-limited and usually do not require further treatment. Another inherited disorder of bilirubin conjugation is Crigler-Najjar syndrome. It is a rare disease found in neonates and can result in neurotoxic sequelae from bilirubin encephalopathy.

In addition to defects in conjugation, disorders in bilirubin excretion in the hepatocyte can also lead to jaundice. Rotor's syndrome and Dubin-Johnson syndrome are two uncommon genetic disorders that disrupt transport of conjugated bilirubin from the hepatocyte and result in conjugated hyperbilirubinemia. There are also multiple acquired conditions that result in inflammation and intrahepatic cholestasis by affecting hepatocyte mechanisms for conjugation and excretion of bile. Viruses, alcohol abuse, sepsis, and autoimmune disorders can all result in inflammation in the liver with subsequent disruption of bilirubin transport in the liver. In addition, jaundice can also occur from the cytotoxic effects of many medications, including acetaminophen, oral contraceptives, and anabolic steroids.

POSTHEPATIC

Posthepatic causes of jaundice are usually the result of intrinsic or extrinsic obstruction of the biliary duct system that prevents the flow of bile into the duodenum. There is a wide spectrum of pathologies that may present with obstructive jaundice. Intrinsic obstruction can occur from biliary diseases, including cholelithiasis, choledocholithiasis, benign and malignant biliary strictures, cholangiocarcinoma, cholangitis, and papillary disorders. Extrinsic compression of the biliary tree is commonly due to pancreatic disorders. Patients with pancreatitis, pseudocysts, and malignancies can present with jaundice due to external compression of the biliary system. Finally, with the growing armamentarium of endoscopic tools and minimally invasive surgical approaches, surgical complications are becoming more frequent causes of extrahepatic cholestasis. Misadventures with surgical clips, retained stones, and inadvertent ischemic insults to the biliary system can result in obstructive jaundice recognized immediately postoperatively or many years later.

MOLECULAR SIGNALING PATHWAYS IN THE LIVER

Acute Phase Reaction

The liver is the site of synthesis of acute phase proteins that consist of a group of plasma proteins that are rapidly released in response to inflammatory conditions elsewhere in the body. The synthesis of these proteins in the liver is influenced by a number of inflammatory mediators. Cytokines such as tumor necrosis factor alpha (TNF-α), interferon-γ, interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8) are released by inflammatory cells into the circulation at sites of injury and modulate the acute phase response. In response to these cytokines, the liver increases synthesis and release of a wide variety of proteins, including ceruloplasmin, complement factors, C-reactive protein, D-dimer protein, alpha1-antitrysin, and serum amyloid A. There are proteins such as serum albumin and transferrin whose levels also decrease (negative acute phase proteins) in response to inflammation.

The acute phase response of the liver can be initiated in reaction to infection, trauma, or malignancy. The purpose of the release of these proteins from the liver is to contain infectious processes, prevent further tissue damage, and begin reparative and regeneration processes to restore body homeostasis. For example, products of the complement pathways can attach to microbes to allow for phagocytosis and act as chemoattractants to the areas of inflammation. C-reactive protein is an important acute phase protein that is also involved in the clearance of microorganisms by binding to their membranes and functioning as an opsonin to facilitate phagocytosis. Other proteins such as alpha1-antitrypsin are protease inhibitors and restrict the protease activity of enzymes of inflammatory cells. Thus, the secretion of acute phase proteins from the liver during the acute phase response is an early defense measure against harmful stimuli before the full activation of the immune response.11

Lipopolysaccharide Signaling
The liver is a complex organ with an important function in immune surveillance and clearance of bacteria and their products. This function is facilitated by the fact that the liver receives all of the drainage of the GI tract via the portal blood flow, which makes it the last barrier preventing bacteria and their toxins from reaching the systemic circulation. The importance of preventing bacteria and their products from reaching the systemic bloodstream is evident in patients who are infected with gram-negative bacteria. Gram-negative bacterial infection produces an acute inflammatory reaction that can lead to septic shock and multiple organ failure. The complications of gram-negative sepsis are initiated by endotoxin (lipopolysaccharide, or LPS). LPS is a glycolipid constituent of the outer membranes of gram-negative bacteria composed of a hydrophilic polysaccharide portion and a hydrophobic domain called lipid A. The lipid A structure is the LPS component responsible for the biologic effects of LPS. Mere nanogram amounts of LPS injected into humans can result in the manifestations of septic shock. The profound effects of LPS are caused not only by the direct effect of LPS itself but also by activation of LPS-sensitive cells, which results in the excessive release of cytokines and other inflammatory mediators.

Because sepsis from gram-negative bacterial infection continues to be a major cause of morbidity and mortality, significant efforts have been made to identify the molecules involved in LPS binding and signaling (Fig. 31-10). Lipopolysaccharide-binding protein (LBP), CD14, myeloid differentiation-2 (MD-2), and toll-like receptors all have been identified as important mediators in the pathway of LPS stimulation. LBP is an acute phase protein synthesized by hepatocytes that binds the lipid A moiety of LPS and forms a soluble LBP-LPS complex. This LBP-LPS complex then interacts with CD14, a receptor identified as important in LPS recognition, which results in the release of inflammatory cytokines and mediators. Studies have shown that although LBP is important, it is not required for LPS to interact with CD14; however, its presence markedly decreases the concentration of LPS necessary for cellular activation. This may be important especially at the low concentrations of LPS found under physiologic conditions. CD14 exists in two forms: membrane form and soluble form. The interaction of LPS with membrane CD14 or soluble CD14 is important in host clearance of LPS. This interaction is also responsible for the toxic effects of LPS seen in the liver and systemic circulation after the release of inflammatory cytokines and mediators. Although membrane CD14 is a membrane protein found on the surface of cells of myeloid lineage and mediates the activation of these cells by LPS, soluble CD14 is found in the serum and enables responses to LPS by cells that do not express CD14. In addition to playing an important role in the release of LBP as an acute phase reactant during LPS-mediated inflammatory insults, the liver is also one of the major sources of release of soluble CD14 into the circulation.

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Lipopolysaccharide (LPS) and toll-like receptor 4 (TLR4) signaling in the liver. Circulating LPS-binding protein (LBP) binds to LPS in the plasma and is recognized by CD14. LPS signaling requires the formation of a complex consisting of dimerized TLR4 receptors and the adaptor MD-2. Subsequent signals activated by TLR4 can be subdivided into those dependent on MyD88 and MAL and those independent of MyD88, which require the adaptors TRIF and TRAM. LPS signaling leads to the activation of multiple inflammatory pathways, including nuclear factor κB (NF-κB), interferon regulatory factor 3 (IRF-3), and mitogen-activated protein kinase kinase (MKK). IκB = inhibitor of κB kinase; JNK = c-Jun N-terminal kinase; MAL = MyD88-adaptor-like; MD-2 = myeloid differentiation-2; MyD88 = myeloid differentiation factor 88; TIR1 = TANK-binding kinase 1; TIR = toll/interleukin-1 receptor; TRAF6 = tumor necrosis factor receptor–associated factor 6; TRAM = TRIF-related adaptor molecule; TRIF = TIR domain–containing adaptor-inducing interferon-β.

The binding of the LBP-LPS complex to CD14 is not enough to transduce an intracellular LPS signal. Membrane CD14 is a glycosylphosphatidylinositol-anchored protein without a membrane-spanning domain. Thus, signaling further downstream of LPS requires additional elements. In studies using chemically modified, radiolabeled LPS capable of cross-linking to nearby proteins, LPS has been shown to cross-link specifically to two other molecules, TLR4 and MD-2. TLR4 is a member of the family of proteins called Toll-like receptors and has been identified as the transmembrane coreceptor to CD14. TLR4 was originally identified as the molecular sensor for bacterial LPS when studies demonstrated that mutations in the tlr4 gene were responsible for defective LPS signaling in mutant mice. Thus, initiation of the LPS signaling cascade requires the interaction of LPS directly with the heteromeric receptor complex of CD14, TLR4, and MD-2. Activation of this complex senses the presence of bacterial LPS at the cell surface and then transmits a signal into the cytoplasm through two distinct pathways. One pathway is dependent on an adaptor known as myeloid differentiation factor 88 (MyD88). The other pathway is MyD88 independent and relies on an adaptor known as toll/IL-1 receptor domain–containing adaptor-inducing interferon-β (TRIF).

The liver is the main organ involved in the clearance of LPS from the bloodstream and so plays a critical role in the identification and processing of LPS. Kupffer cells are the resident macrophages of the liver and have been shown to participate in LPS clearance. Studies have demonstrated that the majority of radiolabeled LPS injected IV is quickly cleared from the circulation and found in the liver, primarily localized to the Kupffer cells. Kupffer cells also contribute to the inflammatory cascade by producing cytokines in response to LPS. Interestingly, hepatocytes, the parenchymal cells of the liver, also have all the components required for LPS recognition and signaling and can participate in the response to LPS and process LPS for clearance.

Although the liver is essential in the host response to gram-negative bacterial infection by contributing to LPS clearance and to the LPS-induced inflammatory reaction, evidence reveals that LPS may actually have a reciprocal role in the pathogenesis of liver disorders. A relationship between LPS and liver disease is not a novel concept. Early studies showed a correlation between the presence or absence of gut-derived LPS and the development of liver injury. Attempts to eliminate gut-derived LPS have had protective effects in various animal models of liver injury, including models of alcohol-induced liver disease. Other studies have shown the synergism between LPS and hepatotoxins in worsening liver injury. Strategies of endotoxin antagonism have been examined in animal models and clinical trials.

In summary, the liver is essential in the clearance of LPS, but it can also contribute to the negative systemic effects seen in gram-negative bacterial sepsis by excessive activation of the LPS signaling pathway. In addition, there is evidence that this signaling pathway may participate in the pathogenesis of a variety of liver diseases. An understanding and characterization of the LPS pathway within the liver is an important step to understanding the molecular basis for the lethal effect of LPS during sepsis and liver disorders.

**Nitric Oxide**

Nitric oxide (NO) is a diffusible, free-radical gas that was first identified in 1980 as endothelium-derived relaxing factor. Its physiologic and pathophysiologic importance in the cardiovascular system was discovered with the identification of its vital role as a vasodilator. However, its mediation of a variety of other diverse biologic activities has since been recognized. In the liver, the influence of NO in normal physiology as well as in states of disease has been extensively studied. The activation of inflammatory cascades in the liver almost universally includes the upregulation of the inducible or inflammatory isofrom of nitric oxide synthase (iNOS) and subsequent NO production. The functions of iNOS and NO in the liver are complex, and a clear dichotomy in their roles in liver dysfunction, whether being protective or detrimental, has been demonstrated.

NO can be produced by one of three nitric oxide synthases (NOSs): neuronal NOS (nNOS), iNOS, and endothelial NOS (eNOS). These enzymes catalyze the conversion of l-arginine to NO and l-citrulline. The enzymes nNOS and eNOS are constitutively expressed in a wide range of tissues. The activity of iNOS and eNOS is primarily controlled by calcium-mediated signaling that results in transient...
activation of these enzymes to produce small amounts of NO. As its name implies, iNOS is not normally expressed in resting states in most tissues but is upregulated by gene transcription under conditions of stress. In contrast to nNOS and eNOS, iNOS produces a large and sustained amount of NO. Although iNOS was first identified in macrophages, it has been shown to be expressed in most cell types if appropriately stimulated. Interestingly, studies of the liver with hepatocytes provided the first evidence that parenchymal cells could express iNOS. It is now known that iNOS can be expressed in all cell types of the liver, but hepatocyte expression appears to be the most prominent. Studies have shown that many inflammatory mediators, including cytokines, microbial products, and oxidative stress, are all capable of stimulating iNOS expression in the liver.\(^{16}\)

**Fig. 31-11.**

The L-arginine/nitric oxide synthase (NOS)/nitric oxide (NO) pathway. NO is implicated in a wide range of regulatory mechanisms as well as inflammatory processes. L-Arginine is converted to NO by the enzyme NOS. NO has been found to have a dichotomous action in various inflammatory settings, mediating both protective and deleterious effects.

The chemical action of NO in biologic systems has been difficult to study due to its short-lived nature. NO is highly reactive with other molecules due to its one unpaired electron. These interactions can result in either nitrosation or oxidation with subsequent varied effects on cellular processes. NO also can signal through cyclic nucleotides by activating the soluble isoform of guanylyl cyclase, which increases levels of cyclic guanosine monophosphate (cGMP). The functions of cGMP include acting as a second messenger that transmits signals by activating downstream kinases or cyclic nucleotide-gated channels. In addition to affecting cGMP signaling, NO also has been found to modulate the expression of many genes.

The role of NO in inflammatory states of the liver is complex and is at times conflicting.\(^{16}\) Under physiologic conditions, NO is important in maintaining hepatic perfusion. However, under inflammatory conditions, such as ischemia/reperfusion (I/R), NO can play either a protective or harmful role depending on the enzymatic source (iNOS vs. eNOS) and the type of ischemia reperfusion (cold vs. warm). It appears that the low level of constitutively expressed eNOS-derived NO is primarily beneficial in models of I/R injury, with vasodilation and subsequent improvement in hepatic microcirculation as the proposed mechanism of protection. Interestingly, activation of iNOS in similar models suggests a potentially harmful role for iNOS. NO, through its reaction with reactive nitrogen and oxygen intermediates generated in the course of reperfusion injury, can contribute to much of the hepatocellular damage, depending on the intracellular ratio of these intermediates to NO. The production of iNOS and NO are also closely tied to multiple other inflammatory mediators in the liver, and
activation of these downstream signals may explain some of the detrimental effects of NO in I/R injury of the liver. Thus, given its diverse biologic effects as a signaling molecule, it is not surprising that NO plays both a protective and potentially harmful role in the setting of hepatic I/R injury. The final effect of NO varies in different liver diseases and depends on the overall hepatic environment. The potential use of NO pharmacologic manipulation to treat hepatic disease will require careful balance of the risks and benefits of this simple yet extremely complicated molecule.

**Heme Oxygenase System**

Heme oxygenase (HO) is the rate-limiting enzyme in the degradation of heme to yield biliverdin, carbon monoxide (CO), and free iron (Fig. 31-12). The HO system, which is activated in response to multiple cellular stresses, has been shown to be an endogenous cytoprotectant in a variety of inflammatory conditions. Currently three HO isozymes have been identified. HO-1 is the inducible form of HO, whereas HO-2 and HO-3 are constitutively expressed. The function of HO in heme degradation is essential due to the potentially toxic effects of heme. An excess of heme can cause cellular damage from oxidative stress due to its production of reactive oxygen species. Thus, the HO system is an important defense mechanism against free heme-mediated oxidative stress.

Heme oxygenase 1 (HO-1) and carbon monoxide (CO) signaling. HO-1 is an enzyme involved in the degradation of heme. Its protective effects in settings of hepatic stress are mediated by the catalytic products of heme degradation: ferritin, bilirubin, and CO.

HO-1 has been shown to be induced in a variety of organs during diverse conditions such as hypoxia, endotoxemia, I/R, hyperthermia, and radiation exposure. HO-1 is involved in maintaining redox homeostasis during cellular stress. In the liver, HO-1 is thought normally to modulate hepatic microvasculature tone through its generation of CO and, like NO, its activation of guanylyl cyclase. This important role is demonstrated in animal models of portal hypertension in which inhibition of HO-1 exacerbates hypertension. Because HO-1 is induced as a protective mechanism in response to various stimuli, targeted induction of HO-1 has been studied as a therapeutic strategy for protection against inflammatory processes. HO-1 overexpression exerts hepatoprotective effects in models of I/R injury, hemorrhagic shock and resuscitation, acetaminophen-induced hepatonecrosis, and sepsis-mediated liver injury.

Although HO-1 has been shown to provide protective effects in a variety of inflammatory states, the specific mechanisms by which HO-1 mediates its protective effects remains to be fully elucidated. Originally thought to be only potentially toxic waste, the by-products generated during heme catabolism now appear to play important roles in protecting against cellular stress. The well-known hazardous effects of high doses of CO are attributable to its ability to bind hemoglobin and myoglobin, which prevents the release of oxygen to tissues. However, only recently have the physiologic and beneficial roles of CO been identified. CO is produced in injured tissues via induction of HO-1 and contributes to the attenuation of proinflammatory processes. Similar to NO, CO plays an important role in maintaining the microcirculation through its activation of soluble guanylyl cyclase and subsequent elevation of intracellular cGMP. The signaling activities of
cGMP lead to smooth muscle relaxation and inhibition and platelet aggregation. In addition, CO also has been shown to inhibit proinflammatory cytokines (TNF-\(\alpha\), IL-1) and chemokines while simultaneously inducing anti-inflammatory cytokines (IL-10). Exogenous low-dose CO has been shown to protect the liver from I/R injury and endotoxemia.

Biliverdin and bilirubin are other metabolites of heme that also are recognized as possible mediators of HO-1’s protective function (see Fig. 31-12). The cytosolic enzyme biliverdin reductase catalyzes the reduction of biliverdin to bilirubin. Both biliverdin and bilirubin have important endogenous antioxidant properties. Free iron, the third by-product of heme oxidation, is known to be cytotoxic by catalyzing the production of hydroxyl radicals. However, HO-1 induction is associated with increased levels of ferritin, the free iron–sequestering protein. Thus, the increase in ferritin levels with the subsequent decrease in intracellular concentrations of free iron results in a net antioxidant effect. Importantly, both bilirubin and ferritin have been shown to protect against liver injury in a variety of I/R models.17

In summary, HO-1 is upregulated and protective in multiple conditions of hepatic stress. Until recently, the degradation products of the HO system were thought to be only potentially toxic waste. It now appears that CO, biliverdin and bilirubin, and ferritin are important in the maintenance of cellular redox homeostasis and may play a role in the mechanism of hepatoprotection in disease. Studies involving induction of HO-1 expression and use of its metabolic products hold therapeutic promise for novel agents to protect against disorders of hepatic inflammation.

**Toll-Like Receptors**

The liver is a central regulator of the systemic immune response after acute insults to the body. Not only does it play a crucial role in modulating the systemic inflammatory response to infection or injury, it is also subject to injury and dysfunction from these same processes. Recent advances in the study of mechanisms for the activation of the innate immune system have pointed to the TLRs as a common pathway for immune recognition of microbial invasion and tissue injury.18 By recognizing either microbial products or endogenous molecules released from damaged sites, the TLR system is capable of alerting the host to danger by activating the innate immune system. Initially, this is manifested by the production of inflammatory mediators and the rapid uptake of invading microbes and their products. When excessive, this inflammatory response can contribute to organ damage and dysfunction.

To date, 13 TLRs have been described in mice and 10 in humans.18 TLRs are a family of proteins that are mammalian homologues to the *Drosophila* Toll, a protein that functions in development and immunity. The cytoplasmic portion of TLRs is similar to that of the IL-1 receptor (IL-1R) family and is called the **toll/IL-1 receptor (TIR) domain**. Unlike the IL-1R extracellular portion that consists of an immunoglobulin-like domain, the TLRs have leucine-rich repeats in their extracellular portion. The TLRs have many structural similarities, both extracellularly and intracellularly, but they differ from each other in ligand specificities and expression patterns, and show some variability in the signaling pathways they activate.

The TLRs were initially identified as components of the innate immune system that acted as a front-line defense mechanism against infections. Their recognition of patterns on pathogens, such as microbial peptides, LPS, lipoteichoic acids, bacterial DNA, and single-stranded RNA, resulted in the activation of an inflammatory response meant for controlling the invading organisms. In situations of noninfectious inflammation such as seen in trauma, clinicians have long recognized similar activation of the same inflammatory pathways and systemic manifestations. This observation, among others, led to the hypothesis that the immune system is designed to recognize any threats, whether from pathogens or tissue damage, that may lead to disruption of homeostasis. Under conditions of sterile inflammation, the activation of immune cells is through the release of endogenous danger molecules, normal cell constituents released by damaged or dying cells, or components of the extracellular matrix, released by the action of proteases at the site of tissue damage. Recent observations show that both microbial products and endogenous danger molecules can be recognized through the TLR system.

Perhaps more than any of the other TLR family members, TLR4 sits at the interface of microbial and sterile inflammation. Whereas the role of TLR4 in the recognition of LPS is well established, only recently has it become apparent that TLR4 also participates in the recognition of endogenous danger molecules18 (see Fig. 31-10). In vivo evidence for TLR4-mediated danger signaling comes from studies of acute tissue injury in hemorrhagic shock, trauma, and I/R models.19 In each case, TLR4-mutant animals exhibited reduced injury or inflammation compared with wild-type controls. In efforts to identify the ligands responsible for TLR4-dependent signaling in noninfectious insults, multiple molecules have been suggested. These include heat shock proteins, fibrinogen, hyaluronic acid, heparin sulfate, and high mobility
group box 1 (HMGB1). Although a central role for TLR4 in recognizing tissue injury is building, studies are beginning to suggest that other TLR family members may also participate in the recognition of endogenous molecules released by tissue injury. The very recent realization that certain TLR family members also respond to endogenous molecules released from stressed or damaged tissues points to a molecular basis for a shared mechanism of innate immune activation by infection and injury.

**RADIOLOGIC EVALUATION OF THE LIVER**

**Ultrasound**

Abdominal ultrasound is a commonly applied imaging modality used to evaluate abdominal symptoms. Ultrasound technology is based on the pulse-echo principle. The ultrasound transducer converts electrical energy to high-frequency sound energy that is transmitted into tissue. Although some of the ultrasound waves are transmitted through the tissue, some are reflected back, and the ultrasound image is produced when the ultrasound receiver detects those reflected waves. This real-time gray scale (B-mode) imaging is augmented by Doppler flow imaging. Doppler ultrasound not only can detect the presence of blood vessels but also can determine the direction and velocity of blood flow. Ultrasonography is a useful initial imaging test of the liver because it is inexpensive, is widely available, involves no radiation exposure, and is well tolerated by patients. It is excellent for diagnosing biliary pathology and focal liver lesions. In addition, liver injury can be evaluated in trauma patients using the focused abdominal sonography for trauma examination. Limitations of ultrasound include incomplete imaging of the liver, most often at the dome or beneath ribs on the surface, and incomplete visualization of lesion boundaries. Moreover, obesity and overlying bowel gas also can interfere with image quality. Thus, ultrasonographically detected masses usually require further evaluation by other imaging modalities due to the lower sensitivity and specificity of ultrasound compared with CT and MRI.

The advent of contrast-enhanced ultrasound has improved the ability of this modality to differentiate among benign and malignant lesions. The injection of gas microbubble agents can increase the sensitivity and specificity of ultrasound in detecting and diagnosing liver lesions. Microbubbles are <10 μm and, when given IV, allow for more effective echo enhancement. Contrast-enhanced ultrasound imaging of the liver improves delineation of liver lesions through identification of dynamic enhancement patterns and the vascular morphology of the lesion. In addition, some agents exhibit a late liver-specific phase in which the bubbles are taken up by cells in the reticuloendothelial system and accumulate in normal liver parenchyma after the vascular enhancement has faded.

The use of intraoperative ultrasound of the liver has rapidly expanded over the years with the increasing number and complexity of hepatic resections being performed. It has the ability to provide the surgeon with real-time accurate information useful for surgical planning. Intraoperative ultrasound is considered the gold standard for detecting liver lesions, and studies have shown that it can identify 20 to 30% more lesions than other preoperative imaging modalities. Importantly, it has been shown to influence surgical management in almost 50% of planned liver resections for malignancies. Applications for intraoperative ultrasound of the liver include tumor staging, visualization of intrahepatic vascular structures (Fig. 31-13), and guidance of resection plane by assessment of the relationship of a mass to the vessels. In addition, biopsy of lesions and ablation of tumors can be guided by intraoperative ultrasound.
Intraoperative liver ultrasound images of the portal veins, hepatic veins, and inferior vena cava (IVC). *Upper panel* shows the portal vein bifurcation with echogenic Glissonian sheath. The confluence of the three hepatic veins [right hepatic vein (RHV), middle hepatic vein (MHV), and left hepatic vein (LHV)] and the IVC is shown in the *middle panel*. An accessory LHV is present in this patient. *Lower panel* is a color Doppler image showing flow.

**Computed Tomography**

Computed tomography (CT) produces a digitally processed cross-sectional image of the body from a large series of x-ray images. The introduction of helical (spiral) CT has tremendously improved the imaging capabilities of this technique compared to earlier conventional axial CT. This is especially true with regard to the liver. Helical CT scanners combine a continuous patient-table motion with continuous rotation of the CT gantry, which allows rapid acquisition of a volume of data within a single breath hold. This increased scan speed eliminates artifacts due to variations in inspiration and facilitates optimal contrast delivery.

Contrast medium is routinely used in CT evaluation of the liver because of the similar densities of most pathologic liver masses and normal hepatic parenchyma. A CT scan with a dual- or triple-phase bolus of IV contrast agent is performed to achieve the greatest enhancement of contrast between normal and pathologic tissues. Ideally, contrast media should be selectively delivered to either the tumor or the liver, but not both. Radiologists use the dual blood supply of the liver and the hemodynamics of hepatic tumors to achieve this goal. The liver is unique in that it has a dual blood supply. The portal vein supplies approximately 75% of the blood flow and the hepatic artery the remaining 25%. However, many liver tumors receive the majority of their blood supply from the hepatic artery. After injection of the contrast agent, the rapid scan time of helical CT allows for CT sections through the liver in both the arterial dominant phase (20 to 30 seconds after the beginning of contrast delivery) and venous or portal dominant phase (60 to 70 seconds after contrast injection) (Fig. 31-14). Thus, many hepatic tumors that derive the majority of their blood supply from the hepatic artery as well as other hypervascular lesions are well delineated in the arterial phase. On the other hand, the portal phase provides optimal enhancement of the normal liver parenchyma because the majority of its blood supply is derived from the portal vein. This allows for detection of hypovascular lesions because they will appear hypoattenuated in relation to the brighter normal liver parenchyma.

![Image of liver ultrasound](image-url)
Computed tomographic (CT) images of hepatic veins and Couinaud's liver segments. The images show the three hepatic veins and inferior vena cava (IVC) (upper panel), as well as Couinaud's liver segments (lower panels). LHV = left hepatic vein; MHV = middle hepatic vein; RHV = right hepatic vein.

**Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) is a technique that produces images based on magnetic fields and radio waves. The MRI scanner creates a powerful magnetic field that aligns the hydrogen atoms in the body, and radio waves are used to alter the alignment of this magnetization. Different tissues absorb and release radio wave energy at different rates, and this information is used to construct an image of the body. Most tissues can be differentiated by differences in their characteristic T1 and T2 relaxation times. T1 is a measure of how quickly a tissue can become magnetized, and T2 measures how quickly it loses its magnetization. As with CT technology, advances in MRI now provide the opportunity to perform single-breath T1-weighted imaging and respiration-triggered T2-weighted imaging. The development of breath-hold imaging techniques has eliminated many of the motion artifacts that previously limited the sensitivity and application of MRI for imaging of the liver. As with the iodinated contrast media use in CT scanning, multiple contrast agents have been developed for MRI to increase the difference in signal intensity between normal liver and pathologic lesion. Gadopentetate dimeglumine (salt of the gadolinium complex of diethylenetriamine pentaacetic acid) is an MRI contrast agent that behaves in a manner very similar to iodine in CT. Liver-specific MRI contrast agents also have been developed that rely on excretion by Kupffer cells (ferumoxides) or secretion in bile by hepatocytes (iminodiacetic acid–derivative radionuclides) to further improve the sensitivity and specificity of MRI.22

**Positron Emission Tomography**

Positron emission tomography (PET) is a nuclear medicine test that produces images of metabolic activity in tissues by detecting gamma rays emitted by a radioisotope incorporated into a metabolically active molecule. Fluorodeoxyglucose is the most common metabolic molecule used in PET imaging. Although traditional imaging such as CT, ultrasound, and MRI provide anatomic information, PET offers functional imaging of tissues with high metabolic activity, including most types of metastatic tumors. PET has emerged as another modality useful for detection of recurrent colorectal cancers. More than 20% of patients with colorectal cancer initially present with hepatic metastasis, and a large percentage of patients undergoing resection for their primary colorectal cancer eventually experience disease
reurrence in the liver. Although hepatic resection of colorectal metastases provides survival rates nearing 50%, the presence of extrahepatic disease is a poor prognosticator and usually precludes aggressive surgical intervention. Thus, accurate information regarding the extent of the disease is necessary for management of patients with colorectal metastases. PET imaging is increasingly used as a tool in the diagnostic work-up of a patient with potentially resectable hepatic disease. In nonrandomized trials, PET demonstrated better sensitivity and specificity than CT scanning for both hepatic disease and extrahepatic disease. Importantly, the information provided by PET resulted in changes to clinical management in up to 25% of cases. However, a disadvantage of images obtained from PET is the lack of exact localization of lesions due to poor resolution. For this reason, integrated PET and CT are increasingly available to potentially improve diagnostic accuracy over standard PET or CT alone. Although the benefit of a synergistic combination of PET and CT has yet to be fully established, this combined modality is rapidly becoming a valuable tool with its increasing availability and use for detection of recurrent colorectal cancer (Fig. 31-15).

**Fig. 31-15.**

Computed tomography–positron emission tomography (CT-PET) scans before and after resection of liver metastasis from colorectal cancer in a 54-year-old patient. CT scan shows large 10-cm right lobe liver metastasis (*left panel*), and PET scan findings are strongly positive (*middle panel*). Two years after right hepatectomy, the patient has no evidence of recurrence and significant hypertrophy of the left lobe (*right panel*).

**ACUTE LIVER FAILURE**

Acute liver failure (ALF) occurs when the rate and extent of hepatocyte death exceeds the liver’s regenerative capabilities. It was initially described as a specific disease entity in the 1950s. It also has been referred to as *fulminant hepatic failure*. ALF is a rare disorder affecting approximately 2000 patients annually in the United States. ALF has devastating consequences and is defined by the presence of hepatic encephalopathy occurring as the consequence of severe liver damage in a patient without a history of previous liver disease or portal hypertension. The manifestations of ALF may include cerebral edema, hemodynamic instability, increased susceptibility to bacterial and fungal infections, renal failure, coagulopathy, and metabolic disturbances. Even with current medical care, ALF can progress rapidly to hepatic coma and death. The most common cause of death is intracranial hypertension due to cerebral edema, followed by sepsis and multisystem organ failure. The causes of ALF, which are the most important variables in determining outcome, are numerous and can include viral infection as well as drug overdose, reaction, and toxicity. It has been determined that the etiologic factor leading to ALF varies according to geographic location. Before the introduction of orthotopic liver transplantation (OLT), the chance for survival was <20%. Currently, most series report survival rates of >65% for affected patients.

**Etiology**

Differences in etiology, management, and patient outcomes have been described for various regions of the globe. In the East and developing portions of the world, the most common causes of ALF are viral infections, primarily hepatitis B, A, and E. In these areas there are a relatively small number of drug-induced cases. In contrast, 65% of cases of ALF in the West are thought to be due to drugs and toxins, with acetaminophen (paracetamol) being the most common etiologic agent in the United States, Australia, United Kingdom, and most of Europe. It is interesting that in France and Spain, where acetaminophen sales are restricted, the rate of acetaminophen-induced ALF is quite low. Acetaminophen-induced ALF is also uncommon in South America. The U.S. Acute Liver Failure Study Group identified several other causes of ALF, including autoimmune hepatitis, hypoperfusion of the liver (in cardiomyopathy or cardiogenic shock),
pregnancy-related conditions, and Wilson's disease. Even with exhaustive efforts to identify a cause, approximately 20% of all cases of ALF remain indeterminate in origin.

**Clinical Presentation**

In a multicenter study involving 17 tertiary care centers and 308 patients in the United States, 73% of all patients with ALF were female, with a median age of 38 years. The most common ethnic group affected was whites (74%), followed by Hispanics (9%) and African Americans (3%). Patients were ill for a median of 6 days before the onset of encephalopathy and had a median of 2 days between the onset of jaundice and the development of encephalopathy. Hepatic coma grade at presentation was approximately equally distributed across grades I to IV. Eighty-four percent of the patients in the study were referred from outside hospitals, 40% had a serum creatinine level exceeding 2.0 mg/dL, and 14% had an arterial pH of <7.30. In addition, 44% of the patients acquired a culture-proven infection.

**Diagnosis and Clinical Management**

When the medical history is obtained, it is important to address the possibility of exposure to viral infections, medications, and other possible toxins. The possibility of previous liver disease needs to be explored. The physical examination must assess and document the patient's mental status as well as attempt to identify findings of chronic liver disease. The initial laboratory examination must evaluate the severity of the ALF as well as attempt to identify the cause (Table 31-1). A liver biopsy should be performed if certain disease entities such as autoimmune hepatitis or lymphoma are a possibility. Because of the associated coagulopathy, if a liver biopsy is needed, it is usually safest to obtain the tissue via a transjugular approach. Patients with ALF should be admitted to the hospital and monitored frequently. Due to the rapidity with which this disease process may progress, a liver transplant center should be contacted and the affected patient transferred to the center early in the evaluation period.

<table>
<thead>
<tr>
<th>Table 31-1 Acute Liver Failure Laboratory Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
</tr>
<tr>
<td>Complete metabolic panel</td>
</tr>
<tr>
<td>Amylase and lipase levels</td>
</tr>
<tr>
<td>Liver function tests</td>
</tr>
<tr>
<td>Prothrombin time/international normalized ratio</td>
</tr>
<tr>
<td>Factor V level</td>
</tr>
<tr>
<td>Factor VII level</td>
</tr>
<tr>
<td>Arterial blood gas concentrations</td>
</tr>
<tr>
<td>Arterial serum ammonia level</td>
</tr>
<tr>
<td>ABO typing</td>
</tr>
<tr>
<td>Acute hepatitis panel</td>
</tr>
<tr>
<td>Autoimmune marker levels</td>
</tr>
<tr>
<td>Ceruloplasmin level</td>
</tr>
<tr>
<td>Toxicology screening</td>
</tr>
<tr>
<td>Acetaminophen level</td>
</tr>
<tr>
<td>HIV screening</td>
</tr>
<tr>
<td>Pregnancy test (females)</td>
</tr>
</tbody>
</table>

If acetaminophen overdose is suspected to have occurred within a few hours of presentation, administration of activated charcoal may be useful to reduce the volume of acetaminophen present in the GI tract. *N*-acetylcysteine (NAC), the clinically effective antidote for acetaminophen overdose, should be administered as early as possible to any patient with suspected acetaminophen-associated ALF. NAC also should be administered to patients with ALF of unclear etiology, because glutathione stabilization may be beneficial in this patient population as well. NAC can be administered either orally (140 mg/kg initial dose, followed by 70 mg/kg every 4 hours x 17 doses) or via the intravenous route (loading dose of 150 mg/kg, followed by a maintenance dose of 50 mg/kg). For patients who are suspected of having
drug-induced hepatotoxicity, it is important to obtain details regarding all prescription and nonprescription drugs, herbs, and dietary supplements that may have been taken in the previous year. Most instances of drug-induced hepatotoxicity occur in the first 6 months after drug initiation. Any suspected offending agent must be discontinued and an attempt should be made to administer only essential medications.

The majority of patients with ALF need to be monitored in the intensive care unit (ICU) setting, and specific attention needs to be given to fluid management, ulcer prophylaxis, hemodynamic monitoring, electrolyte management, and surveillance for and treatment of infection. Surveillance cultures should be performed to identify bacterial and fungal infections as early as possible. Serum phosphorus levels need to be monitored. Hypophosphatemia, which may indicate a higher likelihood of spontaneous recovery, needs to be corrected via IV administration of phosphorus. Sedation should be avoided, and the head of the bed should be elevated at least 30 degrees. Neurologic examinations should be performed frequently. Intracranial pressure monitoring is reserved for patients in whom a neurologic examination is no longer reliable. CT scans of the head should be performed only to rule out mass lesion or hemorrhage, because they provide limited information regarding increased intracranial pressure. The administration of blood products for thrombocytopenia and prolonged prothrombin time is recommended only in the setting of hemorrhage or before invasive procedures. Acute renal failure is a frequent complication in patients with ALF, and efforts should be made to protect renal function by maintaining sufficient perfusion and avoiding nephrotoxic medications. Should renal replacement therapy become necessary, continuous venovenous hemodialysis should be used rather than intermittent hemodialysis, because continuous venovenous hemodialysis provides better hemodynamic and intracranial stability. The most severely affected patients have a poor prognosis with medical management alone and require liver transplantation. To identify these patients early in the clinical course is important both to maximize the time available to obtain a donor liver allograft for those in need and to avoid transplant in those who will recover without it.

**Prognosis**

Accurate identification of those ALF patient who will recover spontaneously is important because of the severe shortage of donor liver allografts and the potential complications of lifelong nonspecific immunosuppression. The most widely applied prognostic scoring system is the King's College Hospital ALF criteria. This scoring system has separate criteria predicting a poor medical management outcome for acetaminophen-related and non–acetaminophen-related forms of ALF (Table 31-2). Additional prognostic information may be gained from the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores as well as the actin-free Gc-globulin serum concentration. Overall, prognostic scoring systems have proven to have acceptable specificity but low sensitivity in determining patient outcome and therefore should not replace the judgment of an experienced clinician.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Selection Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Arterial pH &lt;7.30 irrespective of hepatic coma grade</td>
</tr>
<tr>
<td></td>
<td>Or</td>
</tr>
<tr>
<td>Not acetaminophen</td>
<td>Prothrombin time &gt;100 s + serum creatinine level &gt;3.4 mg/dL + grade III or IV hepatic coma</td>
</tr>
<tr>
<td></td>
<td>Prothrombin time &gt;100 s irrespective of hepatic coma grade</td>
</tr>
<tr>
<td></td>
<td>Or</td>
</tr>
<tr>
<td></td>
<td>Any three of the following, irrespective of hepatic coma grade:</td>
</tr>
<tr>
<td></td>
<td>Cryptogenic or drug-induced hepatitis</td>
</tr>
<tr>
<td></td>
<td>Jaundice to coma interval &gt;7 d</td>
</tr>
<tr>
<td></td>
<td>Prothrombin time &gt;50 s</td>
</tr>
<tr>
<td></td>
<td>Serum bilirubin level &gt;17.5 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Age &lt;10 y or &gt;40 y</td>
</tr>
</tbody>
</table>

**Liver Transplantation**

Despite advances in medical management, OLT remains the only definitive therapy for patients unable to regenerate sufficient hepatocyte
mass in a timely manner. The advent of OLT has coincided with a rise in overall ALF survival rates from approximately 20% in the pretransplantation era to >65% at the present time. One-year posttransplantation survival for patients with ALF has been reported to be as high as 80 to 90%. Although these improvements in survival rates are impressive, it must be noted that 10% of patients still die while awaiting OLT, which confirms that the potential for improved patient outcome still has not been realized because of the ongoing liver allograft shortage.

Extracorporeal Liver Support
As mentioned earlier, patient survival could be improved if additional time could be gained for the patient while awaiting liver replacement or hepatocyte regeneration. The development of a support device to replace the acutely failing liver has been a highly sought after (and elusive) goal. Several systems have been tested without definitive evidence of efficacy. Transient improvement in hepatic encephalopathy has been observed in several trials, but improvement in hepatocyte function and long-term benefit have not been realized with or without OLT. Liver support trials are difficult to perform due to access to liver replacement, the rarity of affected patients, and the heterogeneous causes and varying levels of disease severity. Therefore, additional data are necessary, and liver support systems should be used only as part of an approved clinical trial.

CIRRHOSIS AND PORTAL HYPERTENSION
Cirrhosis
Cirrhosis, the final sequela of chronic hepatic insult, is characterized by the presence of fibrous septa throughout the liver subdividing the parenchyma into hepatocellular nodules (Fig. 31-16). Cirrhosis is the consequence of sustained wound healing in response to chronic liver injury. The etiology of liver injury includes viral, autoimmune, drug-induced, cholestatic, and metabolic diseases. The clinical manifestations of cirrhosis vary from no symptoms to liver failure. Approximately 40% of cirrhotic patients are asymptomatic, but progressive deterioration leading to the need for OLT or death is typical after the development of end-stage liver disease (ESLD). The complications of ESLD include progressive hyperbilirubinemia, malnutrition, decreased synthetic function of the liver, portal hypertension (i.e., ascites and varix-related GI bleeding), hepatic encephalopathy, and life-limiting fatigue. ESLD carries a 5-year mortality of 50%, with 70% of deaths due to liver failure. In the United States, cirrhosis accounts for 30,000 deaths per year and is the most common non-neoplastic cause of death among patients with hepatobiliary and digestive diseases. An additional 10,000 to 12,000 deaths occur annually due to hepatocellular carcinoma (HCC), the most rapidly increasing neoplasm in the United States.
Histology of cirrhotic liver with regenerating macronodules. Upper panel: Grossly cirrhotic liver. Lower panel: Regenerative nodules and bridging fibrosis representative of cirrhosis seen on standard light microscopy (hematoxylin and eosin stain).

An understanding of the fibrous septa that cause cirrhosis is essential, because fibrosis is felt to be the disease process leading to cirrhosis. Hepatic fibrosis is the accumulation of extracellular matrix or scar tissue in response to acute or chronic liver injury. It is postulated that the stellate cell is activated by hepatic necrosis; the production of cytokines, including IL-1, IL-6, and TNF-α; and the growth factors transforming growth factor beta1 and epidermal growth factor. Activation of the stellate cell is associated with pathologic matrix degeneration due to increased production of membrane-type matrix metalloproteinase-1, matrix metalloproteinase-2, and tissue inhibitors of metalloproteinases. The activated stellate cells undergo phenotypic changes, including proliferation, contraction, chemotaxis, retinoid loss, and proinflammatory responses that lead to the accumulation of extracellular matrix and cirrhosis. Activated stellate cells impede portal vein blood flow and increase portal resistance by constricting individual sinusoids and by contracting the cirrhotic liver. Endothelin-1, arginine vasopressin, adrenomedullin, and eicosanoids are all mediators of stellate cell contraction and appear to play a significant role in portal hypertension, as does a diminished production of NO by the endothelial cell.32

CLASSIFICATION OF CIRRHOSIS

Morphologically, cirrhosis can be described as micronodular, macronodular, or mixed. Micronodular cirrhosis is characterized by thick regular septa, small uniform regenerative nodules, and involvement of virtually every hepatic lobule. Macronodular cirrhosis frequently has septa and regenerative nodules of varying sizes. The regenerative nodules consist of irregularly sized hepatocytes with large nuclei and cell plates of varying thickness. Mixed cirrhosis is present when regeneration is occurring in a micronodular liver and over time converts to a macronodular pattern. This morphologic categorization is limited, and cirrhosis is a dynamic process in which nodule size varies over time. The three patterns correlate poorly with etiology, and the same pattern can result from a variety of disease processes. Conversely, a single disease process can demonstrate several morphologic patterns. Irrespective of etiology and morphologic pattern, the cirrhotic liver frequently demonstrates right hepatic lobe atrophy, caudate lobe and left lateral segment hypertrophy, recanalization of the umbilical vein, a nodular surface contour, dilatation of the portal vein, gastroesophageal varices, and splenomegaly on radiographic evaluation.
ETIOLOGY AND CLINICAL MANIFESTATIONS OF CIRRHOSIS

Cirrhosis can result from a wide range of disease processes (Table 31-3). Regardless of cause, cirrhosis leads to two consequences: hepatocellular failure and portal hypertension. Patients are then evaluated to determine if the cirrhosis is "compensated" (lacking manifestations of ESLD) or "decompensated" (with evidence of ESLD and certain clinicopathologic associations). Medical history and physical examination findings of cirrhosis are outlined (Table 31-4). Fat stores and muscle mass are reduced, and resting energy expenditure is increased. Muscle cramps occur frequently in the cirrhotic patient and are felt to correlate with ascites, low mean arterial pressure, and plasma renin activity. Cramps usually respond to administration of quinine sulfate and human albumin. Abdominal hernias are common with ascites and should be electively repaired only in patients with well-compensated cirrhosis; otherwise the hernia should be repaired at the time of or after the patient's OLT. HCC can occur in all forms of cirrhosis, and every cirrhotic patient should undergo screening for the development of HCC every 6 months via cross-sectional imaging and measurement of serum alpha-fetoprotein (AFP) level. It must be kept in mind that only 60 to 75% of HCCs produce AFP; therefore, a normal serum AFP level does not rule out HCC. Cirrhosis is associated with increased cardiac output and heart rate as well as decreased systemic vascular resistance and blood pressure. Cirrhotic patients are more prone to infections due to impaired phagocytic activity of the reticuloendothelial system. Bacterial infections, often of intestinal origin, are common and must be suspected in a patient with unexplained pyrexia or clinical deterioration. Spontaneous bacterial peritonitis also is seen in cases of cirrhosis with ascites. Intrinsic drug metabolism is reduced in the cirrhotic liver, and this fact needs to be recognized when prescribing medications.

Table 31-3 Etiology of Cirrhosis

<table>
<thead>
<tr>
<th>Etiology of Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis (hepatitis B, C, and D)</td>
</tr>
<tr>
<td>Cryptogenic</td>
</tr>
<tr>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Metabolic abnormalities</td>
</tr>
<tr>
<td>Iron overload (hemochromatosis)</td>
</tr>
<tr>
<td>Copper overload (Wilson's disease)</td>
</tr>
<tr>
<td>Alpha1-antitrypsin deficiency</td>
</tr>
<tr>
<td>Glycogen storage disease (types IA, III, and IV)</td>
</tr>
<tr>
<td>Tyrosinemia</td>
</tr>
<tr>
<td>Galactosemia</td>
</tr>
<tr>
<td>Cholestatic liver disease</td>
</tr>
<tr>
<td>Hepatic vein outflow abnormalities</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
</tr>
<tr>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Toxins and drugs</td>
</tr>
</tbody>
</table>

Table 31-4 Clinical History and Physical Examination Findings Associated with Cirrhosis

<table>
<thead>
<tr>
<th>Clinical History and Physical Examination Findings Associated with Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
</tr>
<tr>
<td>Life-limiting fatigue or weight loss</td>
</tr>
<tr>
<td>Jaundice (icterus; skin, urine, and stool color)</td>
</tr>
<tr>
<td>Anorexia and cachexia</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Peripheral edema</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
<tr>
<td>GI bleeding, hemorrhoids</td>
</tr>
<tr>
<td>Loss of libido</td>
</tr>
</tbody>
</table>
Loss of menstrual cycle
Hepatic encephalopathy
Physical examination
Malnutrition
Fetor hepaticus
Jaundiced skin, icteric sclera
Spider angiomata
Finger clubbing, white nail beds, palmar erythema, Dupuytren's contracture
Gynecomastia, testicular atrophy
Hyperdynamic cardiovascular status
Parotid enlargement
Ascites, pleural effusion
Abdominal hernia
Caput medusa
Abnormal liver size
Splenomegaly
Temporal muscle wasting
Asterixis

LABORATORY FINDINGS ASSOCIATED WITH CIRRHOSIS

Laboratory findings vary in the cirrhotic patient depending on the degree of compensation; however, in general a number of trends are seen. The cirrhotic patient usually has a mild normocytic normochromic anemia. The white blood cell and platelet counts are reduced, and the bone marrow is macronormoblastic. The prothrombin time is prolonged and does not respond to vitamin K therapy, and the serum albumin level is depressed. Urobilinogen is present and urinary sodium excretion is diminished in the presence of ascites. The serum levels of bilirubin, transaminases, and alkaline phosphatase may all be elevated. However, normal liver function test results do not eliminate the possibility of cirrhosis.

LIVER BIOPSY

Cirrhosis is identified by histopathologic examination of the liver; however, the diagnosis can be made in many cases from a constellation of clinical features, laboratory values, and radiographic findings. Liver biopsy, usually performed via a percutaneous approach, may be useful in determining the cause of the disease, disease activity, and disease progress. If there are contraindications to percutaneous liver biopsy, such as ascites or a coagulation defect, the transjugular approach should be used. If needed, ultrasound or CT guidance can be helpful in obtaining an adequate sample and avoiding other viscera.

Hepatic Reserve and Assessment of Surgical Risk in the Cirrhotic Patient

Assessing the hepatic reserve of the cirrhotic patient is important, because cirrhosis and portal hypertension can have a negative impact on the outcome of nontransplant surgical procedures. A number of laboratory tests have been used to assess hepatic reserve in patients with cirrhosis. Tests of indocyanine green, sorbitol, and galactose elimination capacity as well as the carbon 13 galactose breath test and carbon 13 aminopyrine breath test have all been disappointing clinically due to their dependence on flow to the liver as well as the unavailability and complexity of the tests. The monoethylglycinexylidide (MEGX) test, which measures MEGX formation after the administration of lidocaine, depends on the hepatic cytochrome P-450 3A4 isoenzyme and although approximately 80% sensitive and specific in determining cirrhosis, loses both sensitivity and specificity as the serum bilirubin level rises secondary to interference with the fluorescent readout system.

Child-Turcotte-Pugh Score
The Child-Turcotte-Pugh (CTP) score was originally developed to evaluate the risk of portocaval shunt procedures secondary to portal hypertension and subsequently has been shown to be useful in predicting surgical risks of other intra-abdominal operations performed on cirrhotic patients (Table 31-5). Numerous studies have demonstrated overall surgical mortality rates of 10% for patients with class A cirrhosis, 30% for those with class B cirrhosis, and 75 to 80% for those with class C cirrhosis.33 The CTP score is derived from five variables as shown in Table 31-5. The problems with the CTP score are the presence of subjective variables (encephalopathy and ascites), its narrow range (5 to 15 points), and the equal weighting given to each variable.

### Table 31-5 Child-Turcotte-Pugh (CTP) Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin level</td>
<td>&lt;2 mg/dL</td>
<td>2–3 mg/dL</td>
<td>&gt;3 mg/dL</td>
</tr>
<tr>
<td>Albumin level</td>
<td>&gt;3.5 g/dL</td>
<td>2.8–3.5 g/dL</td>
<td>&lt;2.8 g/dL</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt;1.7</td>
<td>1.7–2.2</td>
<td>&gt;2.2</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Controlled</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Controlled</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>Child-Turcotte-Pugh class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class A = 5–6 points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class B = 7–9 points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class C = 10–15 points</td>
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</table>

### Model for End-Stage Liver Disease Scoring System

The Model for End-Stage Liver Disease (MELD) is a linear regression model based on objective laboratory values (INR, bilirubin level, and creatinine level). It was originally developed as a tool to predict mortality after transjugular intrahepatic portosystemic shunt (TIPS) but has been validated and has been used as the sole method of liver transplant allocation in the United States since 2002. The MELD formula is as follows:

\[
\text{MELD} = 3.78 \times \log_2\left(\frac{1}{\text{INR}}\right) + 1.15 \times \log_2\left(\frac{\text{bilirubin level}}{2.8}\right) + 1.09 \times \log_2\left(\frac{\text{creatinine level}}{1.26}\right) + 8.64
\]

where Scr is serum creatinine level (in milligrams per deciliter) and Tbil is serum bilirubin level (in milligrams per deciliter).

A number of recent studies have examined the relative values of MELD and CTP scores in predicting postoperative mortality in cirrhotic patients undergoing nontransplant surgical procedures. Northup and colleagues demonstrated that MELD score was the only statistically significant predictor of 30-day mortality.34 In this study, mortality increased by approximately 1% for each MELD point up to a score of 20 and by 2% for each MELD point above 20. It also has been demonstrated that cirrhotic patients who undergo emergent surgery or major surgical procedures have a greater risk of mortality.35 In these studies, the relative risk of mortality increased by 14% for each 1-point increase in MELD score. The American Society of Anesthesiologists scoring system also has been shown to be useful in predicting 7-day mortality rates after surgery in cirrhotic patients.

### Portal Hypertension

The portal venous system contributes approximately 75% of the blood and 72% of the oxygen supplied to the liver. The portal vein is formed by the confluence of the superior mesenteric vein and the splenic vein. In the average adult 1000 to 1500 mL/min of portal venous blood is supplied to the liver. However, this amount can be significantly increased in the cirrhotic patient. The portal venous system is without valves and drains blood from the spleen, pancreas, gallbladder, and abdominal portion of the alimentary tract into the liver. Tributaries of the portal vein communicate with veins draining directly into the systemic circulation. These communications occur at the gastroesophageal junction, anal canal, falciform ligament, splenic venous bed and left renal vein, and retroperitoneum (Fig. 31-17). The normal portal venous pressure is 5 to 10 mmHg, and at this pressure very little blood is shunted from the portal venous system into the systemic circulation. As portal venous pressure increases, however, the communications with the systemic circulation dilate, and a large amount of blood may be shunted around the liver and into the systemic circulation. NO is believed to be an important mediator of this venous dilatation.
Intra-abdominal venous flow pathways leading to engorged veins (varices) from portal hypertension. 1, Coronary vein; 2, superior hemorrhoidal veins; 3, paraumbilical veins; 4, Retzius' veins; 5, veins of Sappey; A, portal vein; B, splenic vein; C, superior mesenteric vein; D, inferior mesenteric vein; E, inferior vena cava; F, superior vena cava; G, hepatic veins; a, esophageal veins; a₁, azygos system; b, vasa brevia; c, middle and inferior hemorrhoidal veins; d, intestinal; e, epigastric veins.

**IMAGING OF THE PORTAL VENOUS SYSTEM AND MEASUREMENT OF PORTAL VENOUS PRESSURE**

The patency of the portal vein and the nature of the collateral circulation should be established. An understanding of portal vein patency and anatomy is crucial before undertaking portosystemic shunts, hepatic resection, or hepatic transplantation. The simplest initial investigation is abdominal ultrasonography. A large portal vein suggests portal hypertension but is not diagnostic. Doppler ultrasound is capable of outlining the anatomy of the portal vein, ruling out thrombosis, and indicating portal venous flow direction. Doppler ultrasound also is useful in evaluating surgical shunt and TIPS flow. Abdominal CT arteriography and magnetic resonance angiography both are capable of revealing portal vein anatomy as well as patency. Visceral angiography and portal venography are reserved for cases that cannot be evaluated satisfactorily by noninvasive methods and require further clarification of portal patency or anatomy.
The most accurate method of determining portal hypertension is hepatic venography. The most commonly used procedure involves placing a balloon catheter directly into the hepatic vein and measuring the free hepatic venous pressure (FHVP) with the balloon deflated and the wedged hepatic venous pressure (WHVP) with the balloon inflated to occlude the hepatic vein. The hepatic venous pressure gradient (HVPG) is then calculated by subtracting the free from the wedged venous pressure (HVPG = WHVP – FHVP). The HVPG represents the pressure in the hepatic sinusoids and portal vein and is a measure of portal venous pressure.

DEFINITION OF PORTAL HYPERTENSION

A WHVP or direct portal venous pressure that is >5 mmHg greater than the inferior vena cava (IVC) pressure, a splenic pressure of >15 mmHg, or a portal venous pressure measured at surgery of >20 mmHg is abnormal and indicates portal hypertension. A portal pressure of >12 mmHg is necessary for varices to form and subsequently bleed.

ETIOLOGY AND CLINICAL FEATURES OF PORTAL HYPERTENSION

The causes of portal hypertension can be divided into three major groups: presinusoidal, sinusoidal, and postsinusoidal. Although multiple disease processes can result in portal hypertension (Table 31-6), in the United States the most common cause of portal hypertension is usually an intrahepatic one, namely, cirrhosis. The most significant clinical finding associated with portal hypertension is the development of gastroesophageal varices. The major blood supply to gastroesophageal varices is the anterior branch of the left gastric or coronary vein. Portal hypertension also results in splenomegaly with enlarged, tortuous, and even aneurysmal splenic vessels. Splenomegaly frequently is associated with hypersplenism, causing leukopenia, thrombocytopenia, and anemia. The umbilical vein may recannulate and dilate, which leads to visible collaterals on the abdominal wall. If flow in the umbilical vein becomes great enough, a caput medusa will form and there may be an audible venous hum (Cruveilhier-Baumgarten murmur). Large spontaneous venous shunts may form between the portal venous system and the left renal vein. These shunts, however, are ineffective in reducing portal venous pressure and preventing upper GI bleeding from esophageal varices. Ascites occurs when portal hypertension is particularly high and when hepatic dysfunction is present. Anorectal varices are present in approximately 45% of cirrhotic patients, and incidence is increased in patients with bleeding from esophageal varices. Anorectal varices must be distinguished from hemorrhoids, which do not communicate with the portal system and are not present at increased incidence in patients with portal hypertension.

<table>
<thead>
<tr>
<th>Table 31-6 Etiology of Portal Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presinusoidal</td>
</tr>
<tr>
<td>Sinistral/extrahepatic</td>
</tr>
<tr>
<td>Splenic vein thrombosis</td>
</tr>
<tr>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Splenic arteriovenous fistula</td>
</tr>
<tr>
<td>Intrahepatic</td>
</tr>
<tr>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Congenital hepatic fibrosis</td>
</tr>
<tr>
<td>Nodular regenerative hyperplasia</td>
</tr>
<tr>
<td>Idiopathic portal fibrosis</td>
</tr>
<tr>
<td>Myeloproliferative disorder</td>
</tr>
<tr>
<td>Sarcoid</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td>Sinusoidal</td>
</tr>
<tr>
<td>Intrahepatic</td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Viral infection</td>
</tr>
<tr>
<td>Alcohol abuse</td>
</tr>
</tbody>
</table>
Primary biliary cirrhosis  
Autoimmune hepatitis  
Primary sclerosing cholangitis  
Metabolic abnormality  
Postsinusoidal  
Intrahepatic  
Vascular occlusive disease  
Posthepatic  
Budd-Chiari syndrome  
Congestive heart failure  
Inferior vena caval web  
Constrictive pericarditis

Portal hypertension is the consequence of both increased portal vascular resistance and increased portal flow. Increased portal resistance may be due to the abnormal architecture and nodularity of cirrhosis or an obstructed portal vein. Myofibroblasts, Ito cells, and sinusoidal endothelium all play a role in portal venous contraction. As portal venous collaterals develop, diverting blood into the systemic circulation, portal hypertension is maintained by increasing portal flow and splanchnic vasodilatation. This leads to a hyperdynamic portal venous circulation that seems to be related to the severity of the liver failure. Cardiac output increases, and there is a generalized vasodilation. Arterial blood pressure is normal to mildly depressed with a low systemic vascular resistance. The factors maintaining the hyperdynamic circulation are complex and only partially understood. There appears to be a complex interaction between vasodilators and vasoconstrictors that might be formed or fail to be inactivated by the hepatocyte or may be of gut origin. NO, endothelin-1, prostacyclin, and glucagon are all postulated to play a role in the hyperdynamic splanchnic circulation.

**MANAGEMENT OF ESOPHAGEAL VARICES**

The most significant manifestation of portal hypertension and the leading cause of morbidity and mortality associated with portal hypertension is variceal bleeding. Approximately 30% of patients with compensated cirrhosis and 60% of patients with decompensated cirrhosis have esophageal varices. One third of all patients with varices experience variceal bleeding. Each episode of bleeding is associated with a 20 to 30% risk of mortality. Seventy percent of patients who survive the initial bleed will experience recurrent variceal hemorrhage within 1 year if left untreated.

**Prevention of Variceal Bleeding**

Current measures aimed at preventing variceal bleeding include improvement of liver function (i.e., abstention from alcohol), avoidance of aspirin and NSAIDs, and administration of propranolol or nadolol, both of which are nonselective beta blockers. Meta-analyses have demonstrated that beta blockade reduces the index variceal bleed by approximately 45% and reduces bleeding mortality by 50%.

Approximately 20% of patients do not respond to beta blockade and another 20% cannot tolerate beta blockade due to medication side effects. It has recently been demonstrated that prophylactic endoscopic variceal ligation (EVL) is associated with a lower incidence of first variceal bleed. EVL is recommended for patients with medium to large varices, performed every 1 to 2 weeks until obliteration, followed by esophagastroduodenoscopy (EGD) 1 to 3 months later and surveillance EGD every 6 months to monitor for recurrence of varices.

**Management of Acute Variceal Bleeding**

Patients with acute variceal hemorrhage should be admitted to an ICU for resuscitation and management. Blood resuscitation should be performed carefully to a hemoglobin level of approximately 8 g/dL. Overreplacement of packed red blood cells and the overzealous administration of saline can lead to both rebleeding and increased mortality. Administration of fresh-frozen plasma and platelets can be considered in patients with severe coagulopathy. Use of recombinant factor VIIa has not been shown to be more beneficial than standard therapy and therefore is not recommended at this time. Cirrhotic patients with variceal bleeding have a high risk of developing bacterial infections, which are associated with rebleeding and a higher mortality rate. The use of short-term prophylactic antibiotics has been shown
both to decrease the rate of bacterial infections and to increase survival. Therefore, their use is recommended, and ceftriaxone 1 g/day IV is often given. Pharmacologic therapy for the variceal hemorrhage can be initiated as soon as the diagnosis of variceal bleeding is made. Vasopressin, administered IV at a dose of 0.2 to 0.8 units/min, is the most potent vasoconstrictor. However, its use is limited by its large number of side effects, and it should be administered for only a short period of time at high doses to prevent ischemic complications. Somatostatin and its analogue octreotide (initial bolus of 50 μg IV followed by continuous infusion of 50 μg/h) also cause splanchnic vasoconstriction. Octreotide has the advantage that it can be administered for 5 days or longer, and it is currently the preferred pharmacologic agent for initial management of acute variceal bleeding. In addition to pharmacologic therapy EGD should be carried out as soon as possible and EVL should be performed. This combination of pharmacologic and EVL therapy has been shown both to improve the initial control of bleeding and to increase the 5-day hemostasis rate.38

Even when aggressive pharmacologic and endoscopic therapies are initiated and these treatment options are maximized, 10 to 20% of patients with variceal bleeding will continue to bleed. Shunt therapy, with either surgical shunts or TIPS, has been shown to control refractory variceal bleeding in >90% of treated individuals. Shunt surgery usually is considered only in patients with preserved hepatic function (i.e., CTP class A); TIPS is used in patients with decompensated liver disease (i.e., CTP class B or C). However, the use of these treatment options is dependent on local expertise.

Balloon tamponade using a Sengstaken-Blakemore tube will control refractory variceal bleeding in >80% of patients. However, its application is limited due to the potential for complications, which include aspiration and esophageal perforation. Therefore, use of a Sengstaken-Blakemore tube should be limited to short-term therapy (<24 hours) in those patients awaiting definitive care.

MANAGEMENT OF GASTRIC VARICES

Gastric varices that occur along the lesser curvature of the stomach should be considered an extension of the patient’s esophageal varices and treated in a manner similar to esophageal varices. Gastric varices along the greater curvature, however, require the evaluation of the splenic vein to assure patency. In the presence of cirrhosis and a patent splenic vein, greater curvature gastric varices can be managed with gastric variceal obturation using N-butyl-cyanoacrylate if available. If gastric variceal obturation is unavailable or if endoscopic therapy fails, the patient should be considered for TIPS, which will control variceal bleeding in >90% of cases.

SURGICAL SHUNT

The need for surgical shunts has been reduced since the introduction of the TIPS procedure and hepatic transplantation. At this time the recommendation is that surgical shunts be considered only in patients who have MELD scores of <15, who are not candidates for hepatic transplantation, or who have limited access to TIPS therapy and the necessary follow-up. The aim of the surgical shunt is to reduce portal venous pressure, maintain total hepatic and portal blood flow, and avoid a high incidence of complicating hepatic encephalopathy. Patient survival is determined by hepatic reserve. The portacaval shunt, as first described by Eck in 1877, either joins the portal vein to the IVC in an end-to-side fashion and completely disrupts portal vein flow to the liver, or joins it in a side-to-side fashion and thereby maintains partial portal venous flow to the liver. Currently this shunt is rarely performed due to the high incidence of hepatic encephalopathy and decreased liver function resulting from the reduction of portal perfusion. The Eck fistula also makes subsequent hepatic transplantation much more technically difficult. The mesocaval shunt uses a Dacron graft of 8 to 10 mm in diameter and connects the superior mesenteric vein to the IVC. This procedure is technically easier and does not adversely affect subsequent hepatic transplantation. The shortcomings of this shunt include a higher incidence of shunt thrombosis and rebleeding. The surgical shunt currently used most often is the distal splenorenal or Warren shunt (Fig. 31-18). This shunt is technically the most difficult to perform. It requires division of the gastroesophageal collaterals and allows venous drainage of the stomach and lower esophagus through the short gastrosplenic veins into the spleen, and ultimately decompresses the left upper quadrant by allowing the splenic vein to drain directly into the left renal vein via an end-to-side splenic to left renal vein anastomosis. This shunt has the advantages of being associated with a lower rate of hepatic encephalopathy and decompensation, and not interfering with subsequent hepatic transplantation.

Fig. 31-18.


TRANSGUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

The TIPS procedure involves implantation of a metallic stent between an intrahepatic branch of the portal vein and a hepatic vein radicle. The needle track is dilated until a portal pressure gradient of $\leq 12$ mmHg is achieved. TIPS can be performed in 95% of patients by an experienced interventional radiologist, can control variceal bleeding in $>90\%$ of cases refractory to medical treatment, and should not affect subsequent hepatic transplantation. Possible complications include bleeding either intra-abdominally or via the biliary tree, infections, renal failure, decreased hepatic function, and hepatic encephalopathy, which occur in 25 to 30% of patients undergoing the TIPS procedure. After the TIPS procedure the hyperdynamic circulation of cirrhosis also can be worsened, and a patient with underlying cardiac problems can experience cardiac failure.

NONSHUNT SURGICAL MANAGEMENT OF REFRACTORY VARICEAL BLEEDING

In the patient with extrahepatic portal vein thrombosis and refractory variceal bleeding, the Sugiura procedure may be considered. The Sugiura procedure consists of extensive devascularization of the stomach and distal esophagus along with transection of the esophagus, splenectomy, truncal vagotomy, and pyloroplasty. As with performance of surgical shunts, patient survival is dependent on hepatic reserve at the time of the surgical procedure. Experience in Western countries is somewhat limited, and a number of modifications have been made to the original Sugiura procedure over time.

Hepatic Transplantation

Patients with cirrhosis, portal hypertension, and variceal bleeding usually die as a result of hepatic failure and not acute blood loss. Therefore, hepatic transplantation must be considered in the patient with ESLD, because it represents the patient’s only chance for definitive therapy and long-term survival. Hepatic transplantation also can be considered for the patient with variceal bleeding refractory to all other forms of management. Survival after hepatic transplantation is not affected adversely by the previous performance of EVL, TIPS, or splenorenal or mesocaval shunts. Previous creation of an Eck fistula, however, does make hepatic transplantation much more technically difficult, and therefore this procedure should be avoided in the transplantation candidate. In addition to saving the patient’s life, hepatic transplantation reverses most of the hemodynamic and humoral changes associated with cirrhosis.

Budd-Chiari Syndrome

Budd-Chiari syndrome (BCS) is an uncommon congestive hepatopathy characterized by the obstruction of hepatic venous outflow. Patients may present with acute signs and symptoms of abdominal pain, ascites, and hepatomegaly or more chronic symptoms related to long-standing portal hypertension. The obstruction may be thrombotic or nonthrombotic anywhere along the venous outflow system from the hepatic venules to the right atrium. Variations in the level of obstruction is one of the factors explaining the heterogeneity of the disease. The incidence of BCS is 1 in 100,000 of the general population worldwide.39
BCS is defined as primary when the obstructive process involves an endoluminal venous thrombosis. BCS is considered as a secondary process when the veins are compressed or invaded by a neighboring lesion originating outside the vein. A thorough evaluation demonstrates one or more thrombotic risk factors in approximately 75 to 90% of patients with primary BCS. Twenty-five percent of primary BCS patients have two or more risk factors.\(^{39}\) BCS remains poorly understood, however, and primary myeloproliferative disorders account for approximately 35 to 50% of the primary cases of BCS. In most cases the myeloproliferative disorder can be classified as essential thrombocythemia or polycythemia rubra, but forms that are more difficult to classify also occur. In >90% of affected patients the myeloproliferative disorder was not diagnosed before the development of BCS. Most patients (80%) are women of a relatively young age (mean age is 30 years). The diagnosis of myeloproliferative disorder is made by demonstrating clusters of dystrophic megakaryocytes in a bone marrow biopsy specimen or by demonstrating formation of spontaneous colonies in cultures of erythroid progenitors on erythropoietin-poor media.

All known inherited thrombophilias have been implicated in the development of BCS. Activated protein C resistance, generally related to heterozygous or homozygous factor V Leiden mutation, is seen in approximately 25% of patients with BCS. Factor V Leiden mutation is present in the majority of cases related to pregnancy or oral contraceptive use. Anticardiolipin antibodies and hyperhomocysteinemia are also risk factors for BCS. Protein S, protein C, and antithrombin III are all produced in the liver, and their levels are affected by liver dysfunction. Therefore, although levels of these proteins may be found to be low in patients with BCS, it is difficult to prove this as the causative factor. Oral contraceptive use has also been shown to be a risk factor for BCS.\(^{39}\)

Clinically significant BCS is usually the result of obstruction of two or more of the major hepatic veins. The obstruction results in increased sinusoidal pressure and decreased sinusoidal blood flow. Therefore, liver congestion, right upper quadrant pain, and ascites may occur. In addition, liver perfusion via the portal vein is decreased, and 70% of affected patients have noninflammatory centrilobular necrosis on biopsy. Acute liver failure is rare, and most patients go on to develop chronic portal hypertension and ascites. Within a few weeks of obstruction centrilobular fibrosis begins and is followed by progressive fibrosis, nodular regeneration, and cirrhosis. Caudate lobe hypertrophy occurs in approximately 50% of cases and is due to the fact that the caudate lobe has direct venous drainage into the IVC. This caudate lobe hypertrophy can result in obstruction of the IVC.

Abdominal ultrasonography is the initial investigation of choice and can demonstrate absence of hepatic vein flow, spiderweb hepatic veins, and collateral hepatic veins.\(^{40}\) Abdominal ultrasonography has a sensitivity and specificity of approximately 85%. MRI of the abdomen also is capable of demonstrating hepatic vein thrombosis and evaluating the IVC but is limited in that it cannot show direction of blood flow. The definitive radiographic study to evaluate BCS is hepatic venography to determine the presence and extent of hepatic vein thrombus as well as IVC pressures. Hepatic venography with measurement of IVC pressures should be performed before undertaking TIPS or a surgical shunt. Liver biopsy specimens demonstrate congestion, hepatocyte loss, and centrilobular fibrosis. Liver biopsy is necessary to differentiate BCS from veno-occlusive disease that is due to nonthrombotic obstruction of the hepatic venules by subendothelial swelling.

Initial treatment consists of diagnosing and medically managing the underlying disease process and preventing extension of the hepatic vein thrombosis through systemic anticoagulation. The BCS-associated portal hypertension and ascites are medically managed in a manner similar to that in most cirrhotic patients. Thrombolytic therapy alone for acute thrombosis may be attempted. However, the risk:benefit ratio is still unknown. Hepatic decompression aims to decrease sinusoidal pressure by restoring the outflow of blood from the liver via either medical therapy, recanalization of the obstructed hepatic veins, or side-to-side portacaval shunt. Radiographic and surgical intervention should be reserved for those patients whose condition is nonresponsive to medical therapy. Percutaneous angioplasty and TIPS, in combination with thrombolytic therapy, are currently preferred to surgical shunt because the procedural mortality is low and caudate lobe hypertrophy does not affect the outcome of these procedures. Side-to-side portacaval shunt attempts to turn the portal vein into a hepatic outflow tract. Usually a venous or prosthetic interposition graft is necessary. Patients with a hemodynamically significant IVC stricture due to caudate lobe hypertrophy require preshunt IVC stenting. Most patients with portacaval shunt show improvement in hepatic function and fibrosis at 1 year without significant hepatic encephalopathy.\(^{40}\) However, the enthusiasm for this procedure has been curbed due to the relatively high rate of operative mortality and shunt dysfunction. Hepatic transplantation should be considered for patients with manifestations of ESLD and can be expected to produce a 10-year survival rate of 75%. Whether hepatic transplantation should be a
primary treatment for BCS, should replace other hepatic decompressive treatment options, or should be used only as a rescue operation remains unclear and somewhat controversial. It must be noted that, irrespective of the nontransplantation treatment modality initially used, the manifestations of BCS may progress and ultimately require hepatic transplantation.

**INFECTIONS OF THE LIVER**

The liver contains the largest portion of the reticuloendothelial system in the human body and is therefore able to handle the continuous low-level exposure to enteric bacteria that it receives through the portal venous system. Due to the high level of reticuloendothelial cells in the liver, nonviral infections are unusual.

**Pyogenic Liver Abscess**

Pyogenic liver abscesses are the most common liver abscesses seen in the United States. Previously they were felt to be due to portal infection, often occurring in young patients secondary to acute appendicitis. However, with earlier diagnosis this cause of abscesses has decreased. Pyogenic liver abscesses also occur as a result of impaired biliary drainage, hematogenous infection arising from sources such as IV drug abuse and teeth cleaning, and local spread of infection (diverticulitis or Crohn's disease). Patients may also develop pyogenic abscess as a complication of subacute bacterial endocarditis and infected indwelling catheters. There appears to be an increasing incidence due to infection by opportunistic organisms among immunosuppressed patients, including transplant and chemotherapy recipients and the AIDS population. Pyogenic hepatic abscesses may be single or multiple and are more frequently found in the right lobe of the liver. The abscess cavities are variable in size and, when multiple, may coalesce to give a honeycomb appearance. Approximately 40% of abscesses are monomicrobial, an additional 40% are polymicrobial, and 20% are culture negative. The most common infecting agents are gram-negative organisms. *Escherichia coli* is found in two thirds, and *Streptococcus faecalis*, *Klebsiella*, and *Proteus vulgaris* are also common. Anaerobic organisms such as *Bacteroides fragilis* are also seen frequently. *Staphylococcus* and *Streptococcus* are more common in patients with endocarditis and infected indwelling catheters.

Patients usually are symptomatic with right upper quadrant pain and fever. Jaundice occurs in up to one third of affected patients. A thorough history and physical examination are necessary to attempt to localize the primary causative site. Leucocytosis, an elevated sedimentation rate, and an elevated alkaline phosphatase (AP) level are the most common laboratory findings. Significant abnormalities in the results of the remaining liver function tests are unusual. Blood cultures reveal the causative organism in approximately 50% of cases. Ultrasound examination of the liver reveals pyogenic abscesses as round or oval hypoechoic lesions with well-defined borders and a variable number of internal echoes. CT scan is highly sensitive in the localization of pyogenic liver abscesses. The abscesses are hypodense and may contain air-fluid levels indicating a gas-producing infectious organism as well as peripheral enhancement (Fig. 31-19). MRI of the abdomen also can detect pyogenic abscesses with a high level of sensitivity but plays a limited role because of its inability to be used for image-guided diagnosis and therapy.

*Fig. 31-19.*
Computed tomographic scan of pyogenic liver abscesses. Multiple hepatic abscesses are seen in a patient after an episode of diverticulitis. Note the loculated large central abscess as well as the left lateral segment abscess.

The current cornerstones of treatment include correction of the underlying cause, needle aspiration, and IV antibiotic therapy. On presentation, percutaneous aspiration and culture of the aspirate may be beneficial to guide subsequent antibiotic therapy. Initial antibiotic therapy needs to cover gram-negative as well as anaerobic organisms. Aspiration and placement of a drainage catheter is beneficial for only a minority of pyogenic abscesses, because most are quite viscous and drainage is ineffective. Antibiotic therapy must be continued for at least 8 weeks. Aspiration and IV antibiotic therapy can be expected to be effective in 80 to 90% of patients. If this initial mode of therapy fails, the patients should undergo surgical therapy, including laparoscopic or open drainage. Anatomic surgical resection can be performed in patients with recalcitrant abscesses. It must be kept in mind throughout the evaluation and treatment of the presumed pyogenic abscess that a necrotic hepatic malignancy must not be mistaken for a hepatic abscess. Therefore, early diagnosis and progression to surgical resection should be advocated for patients who do not respond to initial antibiotic therapy.

**Amebic Abscess**

*Entamoeba histolytica* is a parasite that is endemic worldwide, infecting approximately 10% of the world's population. Amebiasis is most common in subtropical climates, especially in areas with poor sanitation. *E. histolytica* exists in a vegetative form and as cysts capable of surviving outside the human body. The cystic form passes through the stomach and small bowel unharmed and then transforms into a trophozoite in the colon. Here it invades the colonic mucosa forming typical flask-shaped ulcers, enters the portal venous system, and is carried to the liver. Occasionally, the trophozoite will pass through the hepatic sinusoid and into the systemic circulation, which results in lung and brain abscesses.

Amebae multiply and block small intrahepatic portal radicles with consequent focal infarction of hepatocytes. They contain a proteolytic enzyme that also destroys liver parenchyma. The abscesses formed are variable in size and can be single or multiple. The amebic abscess is most commonly located in the superior-anterior aspect of the right lobe of the liver near the diaphragm and has a necrotic central portion that contains a thick, reddish brown, pus-like material. This material has been likened to anchovy paste or chocolate sauce. Amebic abscesses are the most common type of liver abscesses worldwide.

Amebiasis should be considered in patients who have traveled to an endemic area and present with right upper quadrant pain, fever, hepatomegaly, and hepatic abscess. Leukocytosis is common, whereas elevated transaminase levels and jaundice are unusual. The most common biochemical abnormality is a mildly elevated AP level. Even though this disease process is secondary to a colonic infection, the
presence of diarrhea is unusual. For most patients findings of the fluorescent antibody test for *E. histolytica* are positive, and results can remain positive for some time after a clinical cure. Amebiasis is unlikely to be present if the serologic test results are negative.

Ultrasound and CT scanning of the abdomen are both very sensitive but nonspecific for the detection of amebic abscesses. CT scanning also is useful in detecting extrahepatic involvement. Amebic abscesses usually appear as well-defined low-density round lesions that have enhancement of the wall. They also usually appear somewhat ragged in appearance with a peripheral zone of edema. The central cavity may have septations as well as fluid levels.

Metronidazole 750 mg tid for 7 to 10 days is the treatment of choice and is successful in 95% of cases. Defervescence usually occurs in 3 to 5 days. The time necessary for the abscess to resolve depends on the initial size at presentation and varies from 30 to 300 days. Both ultrasound and CT of the liver can be used as follow-up after the initiation of medical therapy. Aspiration of the abscess is rarely needed and should be reserved for patients with large abscesses, abscesses that do not respond to medical therapy, abscesses that appear to be superinfected, and abscesses of the left lobe of the liver that may rupture into the pericardium.

**Hydatid Disease**

Hydatid disease is due to the larval or cyst stage of infection by the tapeworm *Echinococcus granulosus*, which lives in the dog. Humans, sheep, and cattle are intermediate hosts. The dog is infected by eating the viscera of sheep that contain hydatid cysts. Scolecites, contained in the cysts, adhere to the small intestine of the dog and become adult taenia, which attach to the intestinal wall. Each worm sheds approximately 500 ova into the bowel. The infected ova-containing feces of the dog contaminate grass and farmland, and the ova are ingested by sheep, pigs, and humans. The ova have chitinous envelopes that are dissolved by gastric juice. The liberated ovum burrows through the intestinal mucosa and is carried by the portal vein to the liver, where it develops into an adult cyst. Most cysts are caught in the hepatic sinusoids, and 70% of hydatid cysts form in the liver. A few ova pass through the liver and are held up in the pulmonary capillary bed or enter the systemic circulation, forming cysts in the lung, spleen, brain, or bones.

Hydatid disease is most common in sheep-raising areas, where dogs have access to infected offal. These include South Australia, New Zealand, Africa, Greece, Spain, and the Middle East. The disease is uncommon in Britain. Hydatid cysts commonly involve the right lobe of the liver, usually the anterior-inferior or posterior-inferior segments. The uncomplicated cyst may be silent and found only at autopsy or incidentally. Occasionally, the affected patient presents with dull right upper quadrant pain or abdominal distention. Cysts may become secondarily infected, involve other organs, or even rupture, which leads to an allergic or anaphylactic reaction.

The diagnosis of hydatid disease is based on the findings of an enzyme-linked immunosorbent assay (ELISA) for echinococcal antigens, and results are positive in approximately 85% of infected patients. The ELISA results may be negative in an infected patient if the cyst has not leaked or does not contain scolices, or if the parasite is no longer viable. Eosinophilia of >7% is found in approximately 30% of infected patients. Ultrasonography and CT scanning of the abdomen are both quite sensitive for detecting hydatid cysts. The appearance of the cysts on images depends on the stage of cyst development. Typically, hydatid cysts are well-defined hypodense lesions with a distinct wall. Ring-like calcifications of the pericysts are present in 20 to 30% of cases. As healing occurs, the entire cyst calcifies densely, and a lesion with this appearance is usually dead or inactive. Daughter cysts generally occur in a peripheral location and are typically slightly hypodense compared with the mother cyst. MRI of the abdomen may be useful to evaluate the pericyst, cyst matrix, and daughter cyst characteristics.

Unless the cysts are small or the patient is not a suitable candidate for surgical resection, the treatment of hydatid disease is surgically based because of the high risk of secondary infection and rupture. Medical treatment with albendazole relies on drug diffusion through the cyst membrane. The concentration of drug achieved in the cyst is uncertain but is better than that of mebendazole, and albendazole can be used as initial treatment for small, asymptomatic cysts. For most cysts surgical resection involving laparoscopic or open complete cyst removal with instillation of a scolicidal agent is preferred and usually is curative. If complete cystectomy is not possible, then formal anatomic liver resection can be used. During surgical resection caution must be exercised to avoid rupture of the cyst with release of protoscolices into the peritoneal cavity. Peritoneal contamination can result in an acute anaphylactic reaction or peritoneal implantation of scolices with daughter cyst formation and inevitable recurrence.

Alveolar echinococcosis (caused by *Echinococcus multilocularis*) occurs in the Northern Hemisphere, produces a more generalized granulomatous reaction, and can present in a manner similar to that of a malignancy. Resection is the treatment of choice.
Ascariasis

Ascariasis is particularly common in the Far East, India, and South Africa. Ova of the roundworm *Ascaris lumbricoides* arrive in the liver by retrograde flow in the bile ducts. The adult worm is 10 to 20 cm long and may lodge in the common bile duct, producing partial bile duct obstruction and secondary cholangitic abscesses. The ascaris may be a nucleus for the development of intrahepatic gallstones. The clinical presentation in an affected patient may include any of the following: biliary colic, acute cholecystitis, acute pancreatitis, or hepatic abscess.43 Plain abdominal radiographs, abdominal ultrasound, and endoscopic retrograde cholangiography (ERCP) all can demonstrate the ascaris as linear filling defects in the bile ducts. Occasionally worms can be seen moving into and out of the biliary tree from the duodenum. Treatment consists of administration of piperazine citrate, mebendazole, or albendazole in combination with ERCP extraction of the worms. Failure of endoscopic extraction warrants surgical removal of the ascaris.

Schistosomiasis

Schistosomiasis affects >200 million people in 74 countries. Hepatic schistosomiasis is usually a complication of the intestinal disease, because emboli of schistosomiasis ova reach the liver via the mesenteric venous system. Eggs excreted in the feces hatch in water to release free-swimming embryos, which enter snails and develop into fork-tailed cercariae. They then re-enter human skin during contact within infected water. They burrow down to the capillary bed, and at that point there is widespread hematogenous dissemination. Those entering the intrahepatic portal system grow rapidly, and a granulomatous reaction occurs. The degree of resultant portal fibrosis is related to the adult worm load.

Schistosomiasis has three stages of clinical symptomatology: the first includes itching after the entry of cercariae through the skin; the second includes fever, urticaria, and eosinophilia; and the third involves hepatic fibrosis followed by presinusoidal portal hypertension. During this third phase the liver shrinks, the spleen enlarges, and the patient may develop complications of portal hypertension while hepatic function is maintained. Active infection is detected by stool examination. Serologic tests indicate past exposure without specifics regarding timing. A negative serologic test result rules out schistosomal infection. Serum levels of transaminases are usually normal, but the AP level may be mildly elevated. A decreased serum albumin level is usually the result of frequent GI bleeds and decreased nutrition.

Medical treatment of schistosomiasis includes education regarding hygiene and the avoidance of infected water. Treatment with praziquantel 40 to 75 mg/kg as a single dose is the treatment of choice for all forms of schistosomiasis and produces few side effects. GI bleeding usually is controlled by endoscopic variceal ligation. However, in a patient with refractory GI portal hypertensive bleeding, distal splenorenal shunt or gastric devascularization and splenectomy need to be considered.

Viral Hepatitis

The role of the surgeon in the management of viral hepatitis is somewhat limited. However, the disease entities of hepatitis A, B, and C need to be kept in mind during any evaluation for liver disease. The findings of hepatitis A in many cases will be acute, nonspecific, and similar to those associated with hepatic metastases, biliary obstruction, and cirrhosis. Hepatitis B and C can both lead to chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). Current hepatitis B vaccination programs as well as treatment protocols involving nucleoside analogues and hepatitis B immunoglobulin have dramatically improved the treatment options for affected patients. The incidence of ESLD and HCC are both diminished by these protocols. Currently, the same therapeutic options are not available for hepatitis C, and although some patients do maintain a sustained viral response after interferon-based therapy, many either do not respond or have recurrences of their disease. The unraveling of the crystal structures of all three major hepatitis C viral enzymes involved in replication has led to the development of several novel drugs, including protease inhibitors, polymerase inhibitors, and hepatitis C vaccines. Although early results are encouraging, longer-term data are required to determine the effectiveness of these new treatment options.

WORK-UP OF AN INCIDENTAL LIVER MASS

A liver mass often is identified incidentally during a radiologic imaging procedure performed for another indication. For example, a liver mass may be discovered during evaluation for gallbladder disease or kidney stones. In addition, with advances in imaging technology, previously undetected lesions are now identified. Although many of these lesions are benign and will require no further treatment, the concern for malignancy requires a thorough evaluation. Thus, an orderly approach should be taken to the work-up of an incidental liver mass.
The evaluation of an incidental liver mass begins with a history and physical examination (Fig. 31-20). The patient should be asked about abdominal pain, weight loss, previous liver disease, cirrhosis, alcohol use, viral hepatitis, blood transfusions, tattoos, oral contraceptive use (in women), and personal or family history of cancer. On physical examination, jaundice, scleral icterus, hepatomegaly, splenomegaly, palpable mass, or stigmata of portal hypertension should be noted. After completion of the history and physical examination, blood work should be performed, including complete blood count; platelet count; measurement of levels of electrolytes, blood urea nitrogen, creatinine, glucose, and albumin; liver function tests; serum ammonia level; coagulation studies; hepatitis screen; and measurement of levels of the tumor markers carcinoembryonic antigen, alpha-fetoprotein, and cancer antigen 19-9.

**Fig. 31-20.**

Algorithm for diagnostic work-up of an incidental liver lesion. The evaluation includes history and physical examination, blood work, imaging studies, and liver biopsy (if needed). AFP = alpha-fetoprotein; BUN = blood urea nitrogen; CA 19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; creat = creatinine; CBC = complete blood count; CT = computed tomography; EGD = endoscopy; Gyn = gynecological; PAP = Papanicolaou.
The differential diagnosis for an incidental liver mass includes cysts, benign solid lesions, and primary or metastatic cancers (Table 31-7). Ultrasound or CT is commonly performed to evaluate respiratory or abdominal symptoms, and these scans are usually what leads to the discovery of an incidental liver lesion. Although hepatic ultrasound is inexpensive, technical limitations are often encountered due to interference by bowel gas, obesity, or overlying ribs; a mass seen on liver ultrasound should be further evaluated with a dedicated contrast helical CT or MRI scan. Additional imaging studies should be performed as indicated. For example, if the working diagnosis is a liver hemangioma and the CT scan findings are not classical for this diagnosis, then a contrast liver MRI should be performed. If the MRI is inconclusive, then an old-fashioned nuclear medicine tagged red blood cell scan can be helpful. If the radiologic imaging results are classic for a benign hemangioma or focal nodular hyperplasia (FNH), then a liver biopsy is not indicated (and actually risks hemorrhage, because both lesions are hypervascular) and observation is warranted as long as the patient is asymptomatic.

### Table 31-7 Classification of Liver Lesions

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<th>Benign</th>
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<tr>
<td>Cyst</td>
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<td>Hemangioma</td>
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<td>Focal nodular hyperplasia</td>
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<td>Adenoma</td>
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<tr>
<td>Biliary hamartoma</td>
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<tr>
<td>Abscess</td>
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<tr>
<td>Malignant</td>
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<tr>
<td>Hepatocellular carcinoma</td>
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<td>Cholangiocarcinoma (bile duct cancer)</td>
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<td>Gallbladder cancer</td>
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<td>Metastatic colorectal cancer</td>
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<td>Metastatic neuroendocrine cancer (carcinoid)</td>
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<td>Other metastatic cancers</td>
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If all imaging studies are inconclusive, then an image-guided percutaneous liver biopsy should be considered. If the lesion is too small to biopsy or cannot be well visualized or targeted for percutaneous biopsy, then options are either close follow-up imaging (e.g., 3 to 6 months) to document stability or laparoscopic liver biopsy. Laparoscopic liver biopsy also is indicated in cases of cirrhosis with ascites and coagulopathy, in which the bleeding risk is excessive by percutaneous route. If liver biopsy findings demonstrate adenocarcinoma, then the differential diagnosis narrows to metastatic adenocarcinoma from an unknown or occult primary; a primary liver adenocarcinoma, which also is known as cholangiocarcinoma; or bile duct cancer (see "Malignant Liver Tumors"). Although pathologic staining can provide clues to the origin, a primary liver cholangiocarcinoma is usually a diagnosis of exclusion after an occult extrahepatic primary malignancy is ruled out. In these cases the work-up for an occult primary carcinoma should include colonoscopy; EGD (upper endoscopy); mammogram, gynecologic examination, and Papanicolaou smear (in women); and prostate-specific antigen testing and prostate evaluation (in men).

**HEPATIC CYSTS**

**Congenital Cysts**

The majority of hepatic cysts are asymptomatic. Hepatic cysts are usually identified incidentally and can occur at any time throughout life. The most common benign lesion found in the liver is the congenital or simple cyst. The exact prevalence of simple hepatic cysts in the U.S. population is not known, but the female: male ratio is approximately 4:1, and the prevalence is approximately 2.8 to 3.6%. Simple cysts are the result of excluded hyperplastic bile duct rests. Simple cysts usually are identified in hepatic imaging studies as thin-walled, homogeneous, fluid-filled structures with few to no septations. The cyst epithelium is cuboidal and secretes a clear nonbilious serous fluid.
With the exception of large cysts, simple cysts are usually asymptomatic. Large simple cysts may cause abdominal pain, epigastic fullness, and early satiety. Occasionally the affected patient presents with an abdominal mass. Asymptomatic simple cysts are best managed conservatively. The preferred treatment for symptomatic cysts is ultrasound- or CT-guided percutaneous cyst aspiration followed by sclerotherapy. This approach is approximately 90% effective in controlling symptoms and ablating the cyst cavity. If percutaneous treatment is unavailable or ineffective, treatment may include either laparoscopic or open surgical cysts fenestration. The laparoscopic approach is being used more frequently and is 90% effective. The excised cyst wall is sent for pathologic analysis to rule out carcinoma, and the remaining cyst wall must be carefully inspected for evidence of neoplastic change. If such change is present, complete resection is required, either by enucleation or formal hepatic resection.

### Biliary Cystadenoma

Biliary cystadenomas are slow-growing, unusual, benign lesions that most commonly present as large lesions in the right lobe of the liver. Although these lesions are usually benign, they can undergo malignant transformation. Biliary cystadenomas usually present with abdominal pain. An abdominal mass occasionally can be identified on physical examination. In contrast to simple cysts, biliary cystadenomas have walls that appear thicker with soft tissue nodules and the cyst's septations usually enhance. The protein content of the fluid can be variable and can affect the radiographic images on CT and MRI. Surgical resection is the preferred mode of treatment.

### Polycystic Liver Disease

Adult polycystic liver disease (ADPCLD) occurs as an autosomal dominant disease and usually presents in the third decade of life. Some 44 to 76% of affected families are found to have mutations of PKD1 and approximately 75% have mutations of PKD2. The prevalence and number of hepatic cysts are higher in females and increase with advancing age and with increasing severity of renal cystic disease and renal dysfunction. At age 60 years, approximately 80% of ADPCLD patients will have hepatic cysts, with women having more and larger cysts. This gender difference may be due to the effects of estrogen. Patients with a small number of cysts or with small cysts (<2 cm) usually remain asymptomatic. In contrast, patients who develop many or large cysts, with a cyst:parenchymal volume ratio of >1, usually develop clinical symptoms, including abdominal pain, shortness of breath, and early satiety. Progressive ADPCLD will result in renal failure and the need for hemodialysis. In most patients, the liver parenchymal volume is preserved despite extensive cystic disease. Hepatic decompensation, variceal hemorrhage, ascites, and encephalopathy develop rarely in patients with ADPCLD and only in patients with massive cystic disease. The most common hepatologic complications associated with ADPCLD are intracystic hemorrhage, infection, and posttraumatic rupture. The most common abnormal biochemical test finding is a modestly elevated \( \gamma \)-glutamyltransferase level and the most useful imaging test is CT scanning of the abdomen, which will demonstrate the characteristic polycystic appearance. Other conditions that may be associated with ADPCLD include cerebral aneurysm, diverticulosis, mitral valve prolapse, and inguinal hernia. There is no effective medical therapy for ADPCLD. Cyst aspiration and sclerosis may be considered if the patient has one or a few dominant cysts; however, most patients have multiple cysts and do not improve when this technique is used. Cyst fenestration via an open or laparoscopic approach can be attempted in symptomatic patients; however, approximately 50% of treated patients will have recurrence of their symptoms. The only definitive therapy for patients with symptomatic ADPCLD is orthotopic liver transplantation. If the patient has renal involvement (polycystic kidney disease) with renal failure, consideration should be given to combined liver-kidney transplantation. Because of the genetic basis of ADPCLD, living-donor transplantation should be considered only if the presence of ADPCLD in the donor can be ruled out.

### Caroli’s Disease

Caroli’s disease is a syndrome of congenital ductal plate malformations of the intrahepatic bile ducts and is characterized by segmental cystic dilatation of the intrahepatic biliary radicals. Caroli’s disease also is associated with an increased incidence of biliary lithiasis, cholangitis, and biliary abscess formation. Caroli’s disease usually occurs in the absence of cirrhosis and is associated with cystic renal disease. The most common presenting symptoms include fever, chills, and abdominal pain. Most patients present by the age of 30 years, and males and females are affected equally. Rarely, patients can present later in life with complications secondary to portal hypertension. Approximately 33% of affected patients develop biliary lithiasis and 7% develop cholangiocarcinoma. The diagnosis of Caroli’s disease is made based on imaging studies. Magnetic resonance cholangiopancreatography, ERCP, and percutaneous transhepatic cholangiography provide more detailed imaging of the biliary tree and confirm communication of the intrahepatic cysts with the biliary tree, which is necessary to solidify the diagnosis. Treatment consists of biliary drainage, with ERCP and percutaneous transhepatic cholangiography.
serving as first-line therapeutic modalities. If the disease is limited to a single lobe of the liver, hepatic resection can be beneficial. Liver resection can be considered in the patient with hepatic decompensation or unresponsive recurrent cholangitis and possibly in the patient with a small T1 or T2 cholangiocarcinoma.

BENIGN LIVER LESIONS

The liver is an organ that is commonly involved either primarily or secondarily with vascular, metabolic, infectious, and malignant processes. Many classification schemes are used to help narrow the differential diagnosis of liver lesions: solid or cystic, single or multiple, cell of origin (hepatocellular, cholangiocellular, or mesenchymal), and benign or malignant. The most common benign lesions are cysts, hemangiomas, FNH, and hepatocellular adenomas. Many of these lesions have typical features in imaging studies that help confirm the diagnosis.

Cyst

Hepatic cysts are the most frequently encountered liver lesion overall and are described in detail in the section "Hepatic Cysts." Cystic lesions of the liver can arise primarily (congenital) or secondarily from trauma (seroma or biloma), infection (pyogenic or parasitic), or neoplastic disease. Congenital cysts are usually simple cysts containing thin serous fluid and are reported to occur in 5 to 14% of the population, with higher prevalence in women. In most cases, congenital cysts are differentiated from secondary cysts (infectious or neoplastic origin) in that they have no visible wall or solid component and are filled with homogeneous, clear fluid. For benign solid liver lesions, the differential diagnosis includes hemangioma, adenoma, FNH, and bile duct hamartoma (see Table 31-7).

Hemangioma

Hemangiomas (also referred to as hemangiomata) are the most common solid benign masses that occur in the liver. They consist of large endothelial-lined vascular spaces and represent congenital vascular lesions that contain fibrous tissue and small blood vessels which eventually grow. They are more common in women and occur in 2 to 20% of the population. They can range from small (≤1 cm) to giant cavernous hemangiomas (10 to 25 cm). The most common symptom is pain, which often occurs with lesions larger than 5 to 6 cm. Spontaneous rupture (bleeding) is rare, and the main indication for resection is pain. Surgical resection can be accomplished by enucleation or formal hepatic resection, depending on the location and involvement of intrahepatic vascular structures and hepatic ducts.

The majority of hemangiomas can be diagnosed by liver imaging studies. On biphasic contrast CT scan, large hemangiomas show asymmetrical nodular peripheral enhancement that is isodense with large vessels and exhibit progressive centripetal enhancement fill-in over time (Fig. 31-21). 21 On MRI, hemangiomas are hypointense on T1-weighted images and hyperintense on T2-weighted images. 49 With gadolinium enhancement, hemangiomas show a pattern of peripheral nodular enhancement similar to that seen on contrast CT scans. Caution should be exercised in ordering a liver biopsy if the suspected diagnosis is hemangioma because of the risk of bleeding from the biopsy site, especially if the lesion is at the edge of the liver.

Fig. 31-21.
Computed tomographic scans showing classic appearance of benign liver lesions. Focal nodular hyperplasia (FNH) is hypervascular on arterial phase, isodense to liver on venous phase, and has a central scar (upper panels). Adenoma is hypovascular (lower left panel). Hemangioma shows asymmetrical peripheral enhancement (lower right panel).

**Adenoma**

Hepatic adenomas are benign solid neoplasms of the liver. They are most commonly seen in young women (aged 20 years to the forties) and are typically solitary, although multiple adenomas also can occur. Prior or current use of estrogens (oral contraceptives) is a clear risk factor for development of liver adenomas, although they can occur even in the absence of oral contraceptive use. On gross examination, they appear soft and encapsulated and are tan to light brown. Histologically, adenomas lack bile duct glands and Kupffer cells, have no true lobules, and contain hepatocytes that appear congested or vacuolated due to glycogen deposition. On CT scan, adenomas usually have sharply defined borders and can be confused with metastatic tumors. With venous phase contrast, they can look hypodense or isodense in comparison with background liver, whereas on arterial phase contrast subtle hypervascular enhancement often is seen (see Fig. 31-21). On MRI scans, adenomas are hyperintense on T1-weighted images and enhance early after gadolinium injection. On nuclear medicine imaging, they typically appear as "cold," in contrast with FNH.

Hepatic adenomas carry a significant risk of spontaneous rupture with intraperitoneal bleeding. The clinical presentation may be abdominal pain, and in 10 to 25% of cases hepatic adenomas present with spontaneous intraperitoneal hemorrhage. Hepatic adenomas also have a risk of malignant transformation to a well-differentiated HCC. Therefore, it usually is recommended that a hepatic adenoma (once diagnosed) be surgically resected.\(^4\)

**Focal Nodular Hyperplasia**

FNH is another solid, benign lesion of the liver. Similar to adenomas, they are more common in women of childbearing age, although the link to oral contraceptive use is not as clear as with adenomas. A good-quality biphasic CT scan usually is diagnostic of FNH, on which such lesions appear well circumscribed with a typical central scar (see Fig. 31-21). They show intense homogeneous enhancement on arterial phase contrast images and are often isodense or invisible compared with background liver on the venous phase. On MRI scans, FNH lesions are hypointense on T1-weighted images and isointense to hyperintense on T2-weighted images. After gadolinium administration, lesions are hyperintense but become isointense on delayed images. The fibrous septa extending from the central scar are also more readily seen with MRI. If CT or MRI scans do not show the classic appearance, radionuclide sulfur colloid imaging may be used to diagnose FNH based on select uptake by Kupffer cells. Unlike adenomas, FNH lesions usually do not rupture spontaneously and have no significant risk of malignant transformation. The main indication for surgical resection is abdominal pain. Oral contraceptive or estrogen use should be stopped when
either FNH or adenoma is diagnosed.

**Bile Duct Hamartoma**

Bile duct hamartomas are typically small liver lesions, 2 to 4 mm in size, visualized on the surface of the liver at laparotomy. They are firm, smooth, and whitish yellow in appearance. They can be difficult to differentiate from small metastatic lesions, and excisional biopsy often is required to establish the diagnosis.

**MALIGNANT LIVER TUMORS**

Malignant tumors in the liver can be classified as primary (cancers that originate in the liver) or metastatic (cancers that spread to the liver from an extrahepatic primary site) (see Table 31-7). Primary cancers in the liver that originate from hepatocytes are known as *hepatocellular carcinomas* (HCCs or hepatomas), whereas cancers arising in the bile ducts are known as *cholangiocarcinomas*.

In the United States, approximately 150,000 new cases of colorectal cancer are diagnosed each year, and the majority of patients (approximately 60%) will develop hepatic metastases over their lifetime. Hence, the most common tumor seen in the liver is metastatic colorectal cancer. This compares with approximately 18,000 new cases of HCC diagnosed annually. Interestingly, in a Western series of 1000 consecutive new liver cancer patients seen at a university medical center, 47% were HCC, 17% were colorectal cancer metastases, 11% were cholangiocarcinomas, 7% were neuroendocrine metastases, and 18% were other tumors. Although these figures do not reflect the incidence or prevalence of these liver cancers, they are indicative of referral patterns in a tertiary academic medical center with a large liver transplantation team and active hepatology clinic.

**Hepatocellular Carcinoma**

HCC is the fifth most common malignancy worldwide, with an estimated 1,000,000 new cases diagnosed annually. Major risk factors are viral hepatitis (B or C), alcoholic cirrhosis, hemochromatosis, and nonalcoholic steatohepatitis. In Asia, the risk is as high as 30 to 65 per 100,000 persons per year, whereas in the United States the risk is only 2 per 100,000 persons per year. Although cirrhosis is not present in all cases, it has been estimated to be present 70 to 90% of the time. In a person with cirrhosis, the annual conversion rate to HCC is 3 to 6%. In patients with chronic hepatitis C virus infection, cirrhosis usually is present before the HCC develops; however, in cases of hepatitis C virus infection, HCC tumors can occur before the onset of cirrhosis. HCCs are typically hypervascular with blood supplied predominantly from the hepatic artery. Thus, the lesion often appears hypervascular during the arterial phase of CT studies and relatively hypodense during the delayed phases due to early washout of the contrast medium by the arterial blood. MRI imaging also is effective in characterizing HCC. HCC is variable on T1-weighted images and usually hyperintense on T2-weighted images. As with contrast CT, HCC enhances in the arterial phase after gadolinium injection because of its hypervascularity and becomes hypointense in the delayed phases due to contrast washout. HCC has a tendency to invade the portal vein, and the presence of an enhancing portal vein thrombus is highly suggestive of HCC.

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**Fig. 31-22.**
Computed tomographic (CT) images of hepatocellular carcinoma (HCC) and peripheral cholangiocarcinoma. CT scans reveal a large (upper panel) and small (middle panel) hypervascular HCC. A hypovascular left lobe peripheral cholangiocarcinoma (Cholangio CA) is also shown (lower panel).

The treatment of HCC is complex and is best managed by a multidisciplinary liver transplant team. A complete algorithm for the evaluation and management of HCC is shown (Fig. 31-23).

**Fig. 31-23.**
For patients without cirrhosis who develop HCC, resection is the treatment of choice. For those patients with Child's class A cirrhosis with preserved liver function and no portal hypertension, resection also is considered. If resection is not possible because of poor liver function and the HCC meets the Milan criteria (one nodule <5 cm, or two or three nodules all <3 cm, no gross vascular invasion or extrahepatic spread), liver transplantation is the treatment of choice.52

The Barcelona-Clinic Liver Cancer Group has refined its HCC management strategy and has developed the American Association for the Study of Liver Diseases Practice Guidelines.53,54 Management guidelines vary slightly in Asia, Europe, the United States, and other countries based in part on availability of organ donors for liver transplantation. Living-donor liver transplantation is also an alternative for patients with HCC awaiting transplantation to avoid dropout due to tumor progression.52 Specific treatment options are described in the next section.

**Cholangiocarcinoma (Bile Duct Cancer) (see also Chap. 32)**

Cholangiocarcinoma, or bile duct cancer, is the second most common primary malignancy within the liver. Cholangiocarcinoma is an adenocarcinoma of the bile ducts that forms in the biliary epithelial cells and can be subclassified into peripheral (intrahepatic) bile duct cancer and central (extrahepatic) bile duct cancer. Extrahepatic bile duct cancer can be distally or proximally located. When proximal, it is referred to as a **hilar cholangiocarcinoma** (Klatskin's tumor). Hilar cholangiocarcinoma originates in the wall of the bile duct at the hepatic duct confluence and usually presents with obstructive jaundice rather than an actual liver mass. In contrast, a peripheral (or intrahepatic) cholangiocarcinoma represents a tumor mass within a hepatic lobe or at the periphery of the liver. A biopsy specimen from the cholangiocarcinoma will show adenocarcinoma, but the pathologist is often unable to differentiate metastatic adenocarcinoma to the liver...
from true primary bile duct adenocarcinoma. Therefore, a search for a primary site should be undertaken in cases in which an incidentally discovered liver lesion is proven to be an adenocarcinoma on biopsy.

Hilar cholangiocarcinoma is difficult to diagnose and typically presents as a stricture of the proximal hepatic duct causing painless jaundice. It preferentially grows along the length of the common bile duct, often involving the periductal lymphatics with frequent lymph node metastases. Surgical resection offers the only chance for cure of cholangiocarcinoma. The location and extent of tumor dictates the operative approach. In one series of 225 patients with hilar cholangiocarcinoma, 29% were deemed to have unresectable tumors by initial imaging. Of the remaining 160 patients who underwent exploratory surgery with curative intent, 50% were found to have inoperable tumors. Histologically negative margins, concomitant hepatic resection, and well-differentiated tumor histology were associated with improved outcome after resection. In another series of 61 patients undergoing surgical exploration for hilar cholangiocarcinoma, the 5-year actuarial survival rates for an R0 or R1 resection were 45% and 26%, respectively. In a large series reported by Nagino and colleagues, 132 patients with hilar cholangiocarcinoma underwent extended hepatectomy with resection of the caudate lobe and extrahepatic bile duct, and/or portal vein resection (n = 63) after portal vein embolization. The 3- and 5-year survival rates were 41.7% and 26.8%, respectively.

In the absence of associated primary sclerosing cholangitis (PSC), surgical resection is the treatment of choice for hilar cholangiocarcinoma. However, approximately 10% of patients with cholangiocarcinoma have PSC. Furthermore, cholangiocarcinoma in the setting of PSC is frequently multicentric and often is associated with underlying liver disease, with eventual cirrhosis and portal hypertension. As a result, experience has shown that resection of cholangiocarcinoma in patients with PSC yields dismal results. This led transplant centers to consider OLT for patients with hilar cholangiocarcinoma. The results of transplantation were disappointing, however, with high recurrence and overall 3-year survival rates of <30%.

Because the growth of hilar cholangiocarcinoma indicates that this disease spreads in a locoregional manner, a rationale for the use of neoadjuvant chemoradiation was developed by the transplant team at the University of Nebraska in the late 1980s. This was adapted in 1993 by the transplant team at the Mayo Clinic, which led to the current Mayo Clinic protocol. The pretransplant Mayo protocol consists of external beam radiation therapy plus a protracted course of IV 5-fluorouracil followed by iridium 192 brachytherapy. Patients then undergo an abdominal exploration with staging. If findings are negative, patients are given capecitabine for 2 of every 3 weeks until OLT. Even after restaging with CT/MRI and endoscopic ultrasonography, approximately 15 to 20% of patients will have positive findings on abdominal exploration for tumor. The 5-year survival rate for those undergoing transplantation for cholangiocarcinoma at the Mayo Clinic is approximately 70% and compares favorably with the rate for resection. Current eligibility criteria for this Mayo Clinic protocol include unresectable hilar cholangiocarcinoma or hilar cholangiocarcinoma with PSC. The tumor must have a radial dimension of ≤3 cm with no intrahepatic or extrahepatic metastases, and the patient must not have undergone prior radiation therapy or transperitoneal biopsy. Whether these same outstanding results can be reproduced at other transplant centers remains unknown.

Peripheral, or intrahepatic, cholangiocarcinoma is less common than hilar cholangiocarcinoma. In a series of 53 patients at Memorial Sloan-Kettering Cancer Center who underwent surgical exploration for a diagnosis of intrahepatic cholangiocarcinoma, 33 (62%) were found to have resectable tumors. Actuarial 3-year survival for patients undergoing resection was 55%. Factors predictive of poor survival included vascular invasion, histologically positive margins, and multiple tumors. In a large series in Taiwan, 373 patients with peripheral cholangiocarcinoma underwent surgical treatment from 1977 to 2001. Absence of mucobilia, nonpapillary tumor type, tumor of advanced stage, nonhepatectomy, and lack of postoperative chemotherapy were five independent prognostic factors that adversely affected overall survival. Liver transplantation has been performed for peripheral cholangiocarcinoma; however, most centers have abandoned this approach because of organ shortages and relatively high recurrence rates.

**Gallbladder Cancer (see also Chap. 32)**

Gallbladder cancer is a rare aggressive tumor with a very poor prognosis. Over 90% of patients have associated cholelithiasis. In one study examining the mode of presentation over a 10-year period from 1990 to 2000 in 44 patients diagnosed with gallbladder cancer, the diagnosis was found to be made preoperatively in 57%, intraoperatively in 11%, and incidentally after cholecystectomy in 32%. Surgical approaches can be classified into (a) reoperation for an incidental finding of gallbladder cancer after cholecystectomy, and (b) radical
Resection in patients with advanced disease. The results are dismal for radical resection in patients with advanced disease and positive hilar lymph nodes.\textsuperscript{67,68} For incidental gallbladder cancer beyond stage T1, reoperation with central liver resection, hilar lymphadenectomy, and evaluation of cystic duct stump is most commonly performed.\textsuperscript{69,70} The role of formal lobectomy or extended lobectomy as well as common bile duct resection is more controversial. In a single-center study of 23 patients undergoing attempted curative treatment by surgical resection, survival was 85% at 1 year, 63% at 2 years, and 55% at 3 years.\textsuperscript{70} In a multicenter study encompassing 115 patients with incidentally discovered gallbladder cancer who underwent resection,\textsuperscript{69} residual disease in the liver was identified in 46% of patients (0% of those with stage T1 disease, 10% of those with T2 tumors, and 36% of those with T3 disease). T stage also was associated with the risk of metastasis to locoregional lymph nodes (lymph node metastasis for T1 of 13%; for T2, 31%; and for T3, 46%). In another study, a German registry of incidental gallbladder cancer identified 439 patients. Patients with tumors staged as T2 or T3 after cholecystectomy had better survival if they underwent reoperation than if they were managed with observation.\textsuperscript{71} Hence, reoperation should be considered for all patients who have T2 or T3 tumors or for whom the accuracy of staging is in question.

\subsection*{Metastatic Colorectal Cancer}

Over 50% of patients diagnosed with colorectal cancer will develop hepatic metastases during their lifetime. Traditional teaching suggested that hepatic resection for metastatic colorectal cancer to the liver, if technically feasible, should be performed only for fewer than four metastases.\textsuperscript{72} However, recent studies have challenged this paradigm. In a series of 235 patients who underwent hepatic resection for metastatic colorectal cancer, the 10-year survival rate of patients with four or more nodules was 29%, nearly comparable to the 32% survival rate of patients with only a solitary tumor metastasis.\textsuperscript{73} In the Memorial Sloan-Kettering Cancer Center series of 98 patients with four or more colorectal hepatic metastases who underwent resection between 1998 and 2002, the 5-year actuarial survival was 33%.\textsuperscript{74} Furthermore, improved chemotherapeutic regimens and surgical techniques have produced aggressive strategies for the management of this disease. Many groups now consider volume of future liver remnant and the health of the background liver, and not actual tumor number, as the primary determinants in selection for an operative approach.\textsuperscript{75,76} Hence, resectability is no longer defined by what is actually removed, but indications for hepatic resection now center on what will remain after resection.\textsuperscript{77} Use of neoadjuvant chemotherapy, portal vein embolization, two-stage hepatectomy, simultaneous ablation, and resection of extrahepatic tumor in select patients have increased the number of patients eligible for a surgical approach.\textsuperscript{78}

\subsection*{Neuroendocrine Cancer (Carcinoid Tumor)}

Hepatic metastases from neuroendocrine tumors have a protracted natural history and commonly are associated with debilitating endocrinopathies. Several groups have advocated an aggressive surgical approach of cytoreductive surgery, both to control symptoms and to extend survival.\textsuperscript{79,80} In a series of 170 patients undergoing resection of hepatic metastases from neuroendocrine tumors between 1977 and 1998 at the Mayo Clinic, overall survival was 61% and 35% at 5 and 10 years, respectively.\textsuperscript{81} There was no difference in survival between patients with carcinoid tumors and those with islet cell tumors. Major hepatectomy was performed in 91 patients (54%), and recurrence rate was 84% at 5 years. Belghiti’s group has described a two-stage strategy used in 41 patients with a primary neuroendocrine tumor and synchronous bilobar liver metastases.\textsuperscript{82} In the first stage, the primary tumor is resected and limited resection of metastases in the left hemiliver, combined with right portal vein ligation, is performed. After 8 weeks of hypertrophy, a right or extended right hepatectomy is performed.\textsuperscript{82} In patients treated using this strategy, the 2-, 5-, and 8-year Kaplan-Meier overall survival rates were 94%, 94%, and 79%, respectively, and disease-free survival rates were 85%, 50%, and 26%, respectively.

\subsection*{Other Metastatic Tumors}

Nearly every cancer has the propensity to metastasize to the liver. Historically, enthusiasm was low for resecting metastases other than those from a colorectal cancer primary. This was due in part to the recognition that many other primary cancers (such as breast cancer) represent a systemic disease when liver metastases are present. However, more recent studies have shown acceptable 5-year survival rates in the 20 to 40% range for resection of hepatic metastases from breast, renal, and other GI tumors.\textsuperscript{83–85} In a large study of hepatic resection for noncolorectal, nonendocrine liver metastases in 1452 patients, negative prognostic factors were nonbreast origin, age >60 years, disease-free interval of <12 months, need for major hepatectomy, performance of R2 resection, and presence of extrahepatic metastases.\textsuperscript{86}
TREATMENT OPTIONS FOR LIVER CANCER

In general, the major treatment options for liver cancer can be categorized as shown in Table 31-8. The decision making for any given patient is complex and is best managed by a multidisciplinary liver and GI tumor board. The treatments listed in Table 31-8 are not mutually exclusive, and the important point is to select the most appropriate initial treatment after a complete evaluation. In general, surveillance imaging (CT or MRI) is performed every 3 to 4 months during the first year after diagnosis to observe for response, progression, or recurrence. The treatment plan is individualized and modified according to the response of the patient.

### Table 31-8 Treatment Options for Liver Cancer

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### Hepatic Resection

For primary liver cancers or hepatic metastases, hepatic resection is the gold standard and treatment of choice. Although there are anecdotal reports of long-term survival after ablation and other regional liver therapies, liver resection remains the only real option for cure. For HCC in the setting of cirrhosis, liver transplantation also offers the potential for long-term survival, albeit with the consequences of immunosuppression. Hepatic resection also has been advocated for HCC in select patients with cirrhosis before secondary liver transplantation, although this approach remains controversial. Many large series of patients undergoing major hepatectomy now report mortality rates of <5%. Previously, a 1-cm tumor margin was considered desirable; however, recent studies have reported comparable survival rates with smaller margins. The technical aspects of anatomic hepatic lobectomies are described later.

### Liver Transplantation

The rationale supporting liver transplantation (OLT) for HCC includes the fact that most HCCs (>80%) arises in the setting of cirrhosis. The cirrhotic liver often does not have enough reserve to tolerate a formal resection. Also, HCC tumors are commonly multifocal and are underestimated by current CT or MRI imaging. Further, recurrence rates are high at 5 years after resection (>50%). Hence, OLT is an appealing treatment, because it removes the cancer and the cirrhotic liver that leads to HCC. Approximately 6000 liver transplantations are performed each year in the United States, with 1-year survival rates approaching 90%. In April 2008, approximately 16,400 patients were on the waiting list for liver transplantation.

Initial series of OLT for HCC reported in the 1990s included advanced cases of HCC, and the 5-year survival rates were only 20 to 50%. This compared poorly with overall 5-year survival rates of 70 to 75% for OLT in the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) database. Mazzaferro and colleagues at Milan subsequently showed that survival rates were markedly improved when OLT was limited to patients with early-stage HCC (stage I or stage II) with one tumor ≤5 cm, or three tumors
with the largest being 8.3 cm, along with an absence of gross vascular invasion or extrahepatic spread. Multiple studies have validated these findings, although some groups have proposed an expansion of the Milan criteria. In 2002, OPTN/UNOS adopted the Model for End-Stage Liver Disease (MELD) score [a 6- to 40-point scale based on serum total bilirubin level, creatinine level, and international normalized ratio (INR)] for allocation of deceased donor liver organs in the United States. In an attempt to decrease the high mortality rate for patients with preserved liver function and progressive HCC, patients with stage II HCC were given priority points (currently 22 MELD points). This had a positive effect for HCC liver transplant candidates, leading to decreased waiting list dropout and increased transplant rates with excellent long-term outcomes. The goal is to better equate death rates on the liver transplant waiting list for patients with stage II HCC with rates for patients with chronic liver disease without HCC.

Radiofrequency Ablation

In 1891, d'Arsonval discovered that radiofrequency (RF) waves delivered as an alternating electric current (>10 kHz) could pass through living tissue without causing pain or neuromuscular excitation. The resistance of the tissue to the rapidly alternating current produced heat. This discovery contributed to the development of the surgical application of electrocautery. In 1908, Beer used RF coagulation to destroy urinary bladder tumors. Cushing and Bovie later applied RF ablation to intracranial tumors. In 1961, Lounsberry studied the histologic changes of the liver after RFA in animal models. He found that RF caused local tissue destruction with uniform necrosis. In the early 1990s, two groups proposed that RFA can be an effective method for destroying unresectable malignant liver tumors. Both groups found that RFA produced lesions with well-demarcated areas of necrosis without viable tumor cells present. Clinical reports after short-term follow-up suggested that RFA was safe and effective in the treatment of liver tumors. However, Abdalla and colleagues examined data for 358 consecutive patients with colorectal liver metastases treated with curative intent over a 10-year period (1992 to 2002). Liver-only recurrence after RFA was four times the rate after resection (44% vs. 11% of patients), and RFA alone or in combination with resection did not provide survival rates comparable to those with resection alone. Nonetheless, RFA remains a common procedure that can be performed by a percutaneous, minimally invasive laparoscopic, or open approach. It also has been used successfully to ablate small HCCs as a bridge to liver transplantation. Recently, results were reported for the first randomized clinical trial involving RFA treatment for HCC in 291 Chinese patients with three or fewer HCC tumors ranging in size from 3 to 7.5 cm. Patients were randomly assigned to treatment arms of RFA alone (n = 100), transarterial chemoembolization (TACE) alone (n = 95), or combined TACE plus RFA (n = 96). At a median follow-up of 28.5 months, median survival was 22 months in the RFA group, 24 months in the TACE group, and 37 months in the TACE plus RFA group. Patients treated with TACE plus RFA had significantly better overall survival than those treated with TACE alone (P < .001) or RFA alone (P < .001).

Ethanol Ablation, Cryosurgery, and Microwave Ablation

Percutaneous ethanol injection has been shown to be a safe and effective treatment for small HCCs. The ethanol usually is delivered by percutaneous injection under ultrasound or CT guidance. Percutaneous ethanol injection also is used to treat small HCC tumors as a bridge to liver transplantation in some centers to avoid patient dropout. Although cryosurgery was used in the late 1980s and 1990s for ablation of liver tumors, many have abandoned this approach in favor of RFA because of the latter's fewer side effects and ease of use. Microwave ablation is the newest thermal ablative technique and is used in the management of unresectable liver tumors to produce a coagulation necrosis. A multicenter phase II U.S. trial was recently reported using a 915-MHz microwave generator. Eighty-seven patients underwent 94 ablation procedures for 224 hepatic tumors. Forty-five percent of the procedures were performed using an open approach, 7% laparoscopically, and 48% percutaneously. The average tumor size was 3.6 cm (range, 0.5 to 9.0 cm). At a mean follow-up of 19 months, 47% of the patients were alive with no evidence of disease. Local recurrence at the ablation site occurred in 2.7% of tumors, and regional recurrence occurred in 43% of patients. There were no procedure-related deaths. Further studies are required to define the role of this technology in relation to the other ablation options available.

Chemoembolization and Hepatic Artery Pump Chemoperfusion

Chemoembolization is the process of injecting chemotherapeutic drugs combined with embolization particles into the hepatic artery that supplies the liver tumor using a percutaneous, transfemoral approach. It is most commonly used for treatment of unresectable HCC. Two randomized trials as well as a meta-analysis have shown a survival benefit with chemoembolization. In a study by Lo and
colleagues, 80 Asian patients were randomly assigned to receive either chemoembolization with cisplatin in lipiodol or symptomatic treatment only.\textsuperscript{112} Chemoembolization resulted in a marked tumor response, and the actuarial survival was significantly better in the chemoembolization group (1- and 3-year survival of 57% and 26%, respectively) than in the control group (1- and 3-year survival of 32% and 3%, respectively). In another randomized trial, a Barcelona group compared chemoembolization with doxorubicin vs. supportive care and showed that chemoembolization significantly improved survival.\textsuperscript{113} Finally, in a large prospective cohort study of 8510 patients with unresectable HCC in Japan who received transcatheter arterial lipiodol chemoembolization, the 5-year survival rate was 26% and median survival time was 34 months.\textsuperscript{115} The TACE-related mortality rate after the initial therapy was 0.5%. Complications of TACE include liver dysfunction or liver failure, hepatic abscess, and hepatic artery thrombosis. Recent studies also have shown promising results for chemoembolization with drug-eluting beads (doxorubicin) in treatment of HCC.\textsuperscript{116}

In the 1990s hepatic artery pump chemoperfusion with floxuridine for colorectal cancer metastases to the liver was used both for treatment of inoperable disease and in the adjuvant setting.\textsuperscript{117} However, in the modern era of improved chemotherapeutic options, this treatment modality is seldom used outside of a clinical trial.

**Yttrium 90 Microspheres**

Selective internal radioembolization is a promising new treatment modality for patients with inoperable primary or metastatic liver tumors. The treatment is a minimally invasive transcatheter therapy in which radioactive microspheres are infused into the hepatic arteries via a transfemoral percutaneous approach. The yttrium 90 microspheres are directly injected into the hepatic artery branches that supply the tumor. Once infused, the microspheres deliver doses of high-energy, low-penetration radiation selectively to the tumor. The main indications are inoperable HCC\textsuperscript{118} and colorectal cancer hepatic metastases for which systemic chemotherapy has failed.\textsuperscript{119,120} In a recent study involving 137 patients with unresectable chemorefractory liver metastases treated with radioembolization, there was a response rate of 42.8% (2.1% complete response, 40.7% partial response) according to World Health Organization criteria.\textsuperscript{120} One-year survival rate was 47.8% and 2-year survival rate was 30.9%. Median survival was 457 days for patients with colorectal tumor metastases, 776 days for those with neuroendocrine tumor metastases, and 207 days for those with noncolorectal, nonneuroendocrine tumor metastases. The two products available in the United States are SIR-Spheres and TheraSphere.

**Stereotactic Radiosurgery**

Although stereotactic radiosurgery (with CyberKnife and other systems) is in widespread use for brain and spinal tumors, body application to HCC or metastatic liver tumors has only recently occurred. In a phase I study, 31 patients with unresectable HCCs and 10 with unresectable cholangiocarcinomas completed a six-fraction course of stereotactic body radiotherapy.\textsuperscript{121} The treatment was well tolerated, and median survival was 11.7 and 15.0 months for the two groups, respectively. A similar safety profile was observed in a study in the Netherlands.\textsuperscript{122} Further clinical trials are required to define the future role of stereotactic radiosurgery in treatment of HCC and metastatic tumors.

**Systemic Chemotherapy**

A complete review of chemotherapy options for primary and metastatic liver cancers is beyond the scope of this chapter. For treatment of HCC, a phase II trial of the multikinase inhibitor sorafenib showed some efficacy,\textsuperscript{123} and therefore a phase III randomized international multicenter trial (Sorafenib HCC Assessment Randomized Protocol, or SHARP) was initiated enrolling 602 patients with Child’s class A cirrhosis and inoperable HCC. At interim analysis, the trial was discontinued because a survival benefit was found in the treatment group. Llovet and associates presented the findings at the 2007 American Society of Clinical Oncology annual meeting, which showed that sorafenib leads to a 44% improvement in overall survival compared with placebo.\textsuperscript{124} The median overall survival for patients receiving sorafenib was 10.7 months vs. 7.9 months for patients in the control arm. Based on these findings, sorafenib received accelerated Food and Drug Administration approval for the treatment of advanced unresectable HCC. Future studies will likely examine the role of sorafenib in combination with other treatment modalities.

**HEPATIC RESECTION SURGICAL TECHNIQUES**

**Nomenclature**
Due to the confusion in language with regard to anatomic descriptions of hepatic resections, a common nomenclature was introduced at the International Hepato-Pancreato-Biliary Association meeting in Brisbane, Australia, in 2000 (Table 31-9).\textsuperscript{125,126} The goal was to provide universal terminology for liver anatomy and hepatic resections, because there was much overlap among the designations for hepatic lobes, sections, sectors, and segments used by surgeons worldwide (Fig. 31-24). The most common or prevailing anatomic pattern was used as the basis for naming liver anatomy, and the surgical procedure nomenclature adopted for hepatic resections was based on the assigned anatomic terminology.\textsuperscript{127} Adoption of a common language should enable hepatic surgeons to better understand and interpret liver surgery publications from different continents and disseminate their knowledge to the next generation of hepatobiliary surgeons. Nonetheless, even today the literature is full of both old and new liver resection terminology, so the surgeon in training must be familiar with all the various classifications.

<table>
<thead>
<tr>
<th>Older hepatic resection terminology</th>
<th>Brisbane 2000 hepatic resection terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hepatic lobectomy</td>
<td>Right hepatectomy or right hemihepatectomy</td>
</tr>
<tr>
<td>Left hepatic lobectomy</td>
<td>Left hepatectomy or left hemihepatectomy</td>
</tr>
<tr>
<td>Right hepatic trisegmentectomy</td>
<td>Right trisectionectomy or extended right hepatectomy (or hemihepatectomy)</td>
</tr>
<tr>
<td>Left hepatic trisegmentectomy</td>
<td></td>
</tr>
<tr>
<td>Left lateral segmentectomy</td>
<td>Left trisectionectomy or extended left hepatectomy (or hemihepatectomy)</td>
</tr>
<tr>
<td>Right posterior lobectomy</td>
<td></td>
</tr>
<tr>
<td>Caudate lobectomy</td>
<td>Left lateral sectionectomy or bisegmentectomy 2, 3</td>
</tr>
<tr>
<td></td>
<td>Right posterior sectionectomy</td>
</tr>
<tr>
<td></td>
<td>Caudate lobectomy or segmentectomy 1</td>
</tr>
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</table>

**Alternative "sector" terminology**

| Right anterior sectorectomy           |                                             |
| Right posterior sectorectomy or right lateral sectorectomy |                                             |
| Left medial sectorectomy or left paramedian sectorectomy (bisegmentectomy 3, 4) |                                             |
| Left lateral sectorectomy (segmentectomy 2) |                                             |
left hepatic vein; MHV = middle hepatic vein; RHV = right hepatic vein.

**Techniques and Devices for Dividing the Hepatic Parenchyma**

Hepatic resection surgery has evolved over the past 50 years. A better understanding of liver anatomy and physiology, coupled with improved anesthesia techniques and widespread use of intraoperative ultrasound, has led to virtually "bloodless" liver surgery in the modern era (the year 2000 to the present). Innovations in technology have expanded the list of liver parenchymal transection devices\textsuperscript{128–130} and hemostatic agents (Table 31-10). Suffice it to say that each device or agent has a learning curve and that undoubtedly every experienced hepatic surgeon has his or her personal preferences.

<table>
<thead>
<tr>
<th>Table 31-10 Techniques and Devices for Dividing Liver Parenchyma and Achieving Hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunt fracture and clips</td>
</tr>
<tr>
<td>Monopolar cauter (Bovie)</td>
</tr>
<tr>
<td>Bipolar cauter</td>
</tr>
<tr>
<td>Argon beam coagulator</td>
</tr>
<tr>
<td>CUSA ultrasonic dissector</td>
</tr>
<tr>
<td>Hydro-Jet water-jet dissector</td>
</tr>
<tr>
<td>Harmonic Scalpel, AutoSonix ultrasonic transector-coagulator</td>
</tr>
<tr>
<td>LigaSure tissue fusion system</td>
</tr>
<tr>
<td>SurgRx EnSeal tissue sealing and transection system</td>
</tr>
<tr>
<td>Gyrus PK cutting forceps</td>
</tr>
<tr>
<td>Endovascular staplers</td>
</tr>
<tr>
<td>TissueLink sealing devices</td>
</tr>
<tr>
<td>Habib 4X Laparoscopic sealer</td>
</tr>
<tr>
<td>InLine bipolar linear coagulator</td>
</tr>
<tr>
<td>Topical agents (fibrin glues, Surgicel, Gelfoam, Avitene, Tisseel, Floseal, Crosseal)</td>
</tr>
</tbody>
</table>

One major advance was the application of vascular stapling devices for division of the hepatic and portal veins.\textsuperscript{131–133} Based on early reports of successful stapling of extrahepatic vessels, stapling devices have now been used in the parenchymal transection phase, which remains a source of potential blood loss due to back bleeding from the middle hepatic vein.\textsuperscript{134,135} One advantage of the stapling technique is the speed with which the transection can be performed, which minimizes surface bleeding and period of ischemia for the remnant liver. However, a major disadvantage of the stapling technique is the cost of multiple stapler cartridges. This is balanced by the decreased expenses reported with avoidance of ICU admission and blood transfusion, as well as shortened operating room time. Another consideration in the use of staplers for parenchymal transection is the potential for bile leaks. However, in a large series of 101 consecutive right hemihepatectomies performed using the stapling technique, there was only one reported bile leak (1%), which sealed after ERCP.\textsuperscript{135}

**Steps in Commonly Performed Hepatic Resections**

A fundamental understanding of hepatic anatomy is vital for any surgeon with the desire to perform hepatobiliary surgery. Each hepatic resection surgery can be broken down into a series of orderly steps. The key to being a proficient hepatic surgeon is not to move one’s hands swiftly but rather to accomplish the operation by completing the steps in an orchestrated fashion. The surgeon should not move to step 5 until steps 1 through 4 are complete. Mastery of the operative steps coupled with knowledge of liver anatomy and the common anatomic variants provides the foundation for safe hepatic surgery. (The same basic principle can be applied to any complex surgical procedure.) There are many different techniques and sequences for accomplishing each of the anatomic (and nonanatomic) hepatic operations. The authors present their preferred approach in a stepwise fashion for right hepatic lobectomy (right hemihepatectomy), left hepatic lobectomy (left hemihepatectomy), and left lateral segmentectomy (left lateral sectionectomy). Provision of a detailed approach for every type of liver resection is beyond the scope of this chapter, and readers are referred to several excellent descriptions.\textsuperscript{136}

**STEPS COMMON TO ALL OPEN MAJOR HEPATIC RESECTIONS**
1. Make the skin incision—right subcostal with midline extension.
2. Open the abdomen and place a fixed table retractor (Thompson).
3. Take down the round and falciform ligaments, and expose the anterior surface of the hepatic veins.
4. For a left hepatectomy, divide the left triangular ligament; for a right hepatectomy, mobilize the right lobe from the right coronary and triangular ligaments.
5. Open the gastrohepatic ligament and assess for replaced hepatic arteries.
6. Perform an open cholecystectomy; leave the gallbladder with the cystic duct intact (until end of case).
7. Perform liver ultrasound and confirm the operation to be performed.

**RIGHT HEPATIC LOBECTOMY (RIGHT HEPATECTOMY OR HEMIHEPATECTOMY)**

8. Mobilize the liver from the inferior vena cava (IVC) in "piggyback" fashion; ligate the short hepatic veins up to the right hepatic vein (RHV).
9. Perform a right hilar dissection—gently lower the hilar plate, then doubly ligate and divide the right hepatic artery (RHA), staying high on the right side of the common bile duct.
10. Divide the inflow (right portal vein, or RPV) with a vascular stapler (white 2.5-mm cartridge), after taking the small lateral portal vein branch off the RPV to the caudate/right lobe.
11. Divide the outflow (right hepatic vein, or RHV) with the vascular stapler (white cartridge).
12. Notch or divide the caudate process crossing to the right hepatic lobe.
13. Make a counterincision at the right base of the gallbladder fossa; pass a large Kelly clamp deep to the hilar plate and emerge anterior to the IVC; place an umbilical tape in the tunnel behind the hilar plate.
14. Divide the right hilar plate with right hepatic ducts using the vascular stapler (white cartridge).
15. Repeat ultrasound and confirm the transection plane, staying just to the right of the middle hepatic vein (MHV).
16. Bovie down approximately 1 cm in the liver parenchyma, then switch to a LigaSure device.
17. Continue parenchymal division with a LigaSure device until segment V/VIII MHV branches are encountered.
18. Initiate the Pringle maneuver around the porta hepatis (Potts loop cinched up with right angle clamp).
19. Complete the parenchymal slice with sequential crushing vascular stapling (pretunnel with a large Kelly clamp), usually 4 to 6 minutes for the entire slice.
20. Check the cut edge for surgical bleeding; place a figure-of-eight suture if bleeding is encountered.
21. Release the Pringle maneuver and dry up the cut edge with a saline-cooled radiofrequency sealant device.
22. Inspect the IVC and right retroperitoneal space for hemostasis.
23. Perform completion ultrasound to confirm left portal vein (LPV) inflow and hepatic vein outflow.
24. Shoot a saline cholangiogram via the cystic duct stump to confirm that the cut edge is watertight.
25. Shoot a contrast fluoroscopic cholangiogram (optional) to confirm the patency of the proximal left hepatic duct and distal common bile duct; secure the cystic duct stump in the usual manner.
26. Tack the proximal falciform ligament back to the diaphragm side with a single figure-of-eight suture.
27. Place a Jackson-Pratt drain in the right subphrenic space and close the abdomen (Fig. 31-25).

Fig. 31-25.
Completed right hepatic lobectomy (right hepatectomy) with the right portal vein, right hepatic artery, and right bile duct ligated and divided. The right hepatic vein is ligated and divided with a vascular stapler. Middle hepatic vein branches inside the liver are divided with the vascular stapler.

**Comments**

Although some liver surgeons advocate a one-step division of the entire intrahepatic Glissonian pedicle as described by Launois and Jamieson, it is the authors’ preference to divide the RHA and RPV in an extrahepatic fashion and restrict the intrahepatic maneuver for division of the right hilar plate with the right hepatic ducts. As for the transection plane, the key is to perform accurate ultrasound visualization and mapping of the MHV and to stay just to the right of it. Weaving in and out or bisecting the MHV can leading to torrential back bleeding. Also, for bulky right lobe tumors adherent to the diaphragm or retroperitoneum, an anterior approach with division of the parenchyma can be performed before right lobe mobilization. The anterior approach also can be facilitated by use of the “hanging maneuver.”

**LEFT HEPATIC LOBECTOMY (LEFT HEPATECTOMY OR HEMIHEPATECTOMY)**

8. Widely open the gastrohepatic ligament flush with the undersurface of the left lateral section and the caudate lobe.
9. Doubly ligate and divide a replaced or accessory left hepatic artery (LHA) if present.
10. Clamp the round ligament (ligament teres) and pull it anteriorly as a handle to expose the left hilum.
11. Divide any existing parenchymal bridge between segments III and IVB.
12. Dissect the left hilum at the base of the umbilical fissure and lower the hilar plate anterior to the left portal pedicle.
13. Incise the peritoneum overlying the hilum from the left side and doubly ligate the LHA (after test clamping and confirming a palpable pulse in the RHA).
14. Dissect the portal vein at the base of the umbilical fissure (it will take a nearly 90-degree bend from the transverse to the umbilical portion).
15. Divide the LPV with a vascular stapler (white cartridge), staying just distal to (beyond) the take-off of the caudate inflow branch (if the caudate lobe is being preserved).
16. Divide the ligamentum venosum (Arantius' ligament) caudally.
17. Make a counterincision in segment IVb 1 cm above the base of the umbilical fissure and pass a blunt Kelly clamp behind the left hilar plate, aiming for the left lower quadrant and exiting just anterior (and superficial) to the caudate lobe.
18. Place an umbilical tape in the tunnel behind the left hilar plate.
19. Divide the left hilar plate and left hepatic duct with a vascular stapler (white cartridge).
20. Fold the left lateral segment up and back to the right, exposing the window at the base of the left hepatic vein (LHV) as it enters the IVC. This is facilitated by dividing any loose areolar tissue overlying the ligamentum venosum (Arantius' ligament), which is divided proximally.
21. Pass a large, blunt right-angle clamp in the window between the RHV and the MHV, and hug the back of the MHV, aiming for the deep edge of the LHV. Do not force it or make a hole in the IVC or MHV.
22. Pass an umbilical tape through this window and divide the LHV and MHV common trunk with a vascular stapler.
23. Repeat ultrasound and confirm the transection plane on the anterior surface, staying close to the demarcated line. Do not bisect the MHV as it passes tangentially from the left to the right lobe.
24. Bovie down approximately 1 cm in the liver parenchyma, then switch to a LigaSure device.
25. Continue parenchymal division with the LigaSure device until segment V/VIII MHV branches are encountered.
26. Initiate a Pringle maneuver around the porta hepatis (Potts loop cinched up with right angle clamp).
27. Complete the parenchymal slice with sequential crushing vascular stapling (pretunnel with a large Kelly clamp). As the slice is deepened, gradually carry the transection down to exit just anterior to the caudate at the level of Arantius' ligament.
28. Check the cut edge for surgical bleeding; place a figure-of-eight suture if bleeding is encountered.
29. Release the Pringle maneuver and dry up the cut edge with a saline-cooled radiofrequency sealant device.
30. Perform completion ultrasound to confirm RPV inflow and RHV outflow.
31. Shoot a saline cholangiogram via the cystic duct stump to confirm that the cut edge is watertight.
32. Shoot a contrast fluoroscopic cholangiogram (optional) to confirm the patency of the proximal right hepatic duct and the distal common bile duct; secure the cystic duct stump in the usual manner.
33. Place a Jackson-Pratt drain in the left subphrenic space and close the abdomen (Fig. 31-26).
Completed left hepatic lobectomy (left heptectomy) resecting segments II, III, and IV.

Comments

Because the right posterior duct comes off the left hepatic duct in approximately 20% of cases (see Fig. 31-9) and the right anterior duct comes off the left hepatic duct in approximately 5% of cases, it is vital to divide the left hepatic duct at the base of the umbilical fissure and not more centrally in the hilum as it bifurcates. If the left hepatic duct were divided as it appears to bifurcate from the right hepatic duct, then approximately 20 to 25% of the time either the right posterior or right anterior duct would be transected. After the left hepatic duct is divided as described earlier (steps 17 through 19), the liver parenchyma is scored and divided horizontally approximately 1 cm above the left hilum; the surgeon thus assumes that an aberrant right anterior or posterior duct is coming off the left hepatic duct in the hilum and preserves it. Then as the parenchymal transection reaches the left side of the gallbladder fossa, the transection plane turns vertical to run parallel to Cantlie’s line (or the left edge of the gallbladder bed). The left lobe of the liver will be well demarcated at this point (after the vascular inflow has been divided), which guides the transection plane on the anterior surface. In general, the transection plane should be close to the demarcation line to minimize the amount of devascularized liver remaining. When dividing the LHV and MHV, the surgeon should keep in mind that they have a common trunk approximately 90% of the time. If it is not easy to open the window deep to the MHV and LHV, then division of the MHV and LHV can be accomplished after the parenchymal transection.

LEFT LATERAL SEGMENTECTOMY (LEFT LATERAL SECTIONECTOMY)

8. Widely open the gastrohepatic ligament flush with the undersurface of the left lateral section and the caudate lobe.
9. Doubly ligate and divide a replaced or accessory LHA if present.
10. Clamp the round ligament and pull it anteriorly as a handle to expose the left hilum.
11. Divide any existing parenchymal bridge between segments III and IVB.
12. Carry the dissection down from the end of the round ligament, and the segment III pedicle will be encountered.
13. Incise the peritoneal reflection on the left side of the round ligament as it inserts into the umbilical fissure. This will facilitate encircling the segment III and II pedicles, which can be divided separately with a vascular stapler. When encircling the segment II
14. Divide the liver parenchyma, staying flush on the left side of the falciform ligament using a Bovie cautery and/or LigaSure device.

15. Divide the LHV inside the liver parenchyma with a vascular stapler (white cartridge) as the parenchymal transection is complete.

16. A Pringle maneuver usually is not required for a left lateral sectionectomy because complete devascularization occurs before transection and little back bleeding is encountered.

Comments

If the segment III and II LHA branches are large, they can be individually ligated in the left hilum before the pedicles (with portal vein and hepatic duct branches) are taken. If the tumor is more peripheral in the left lateral segment, then the segment III and II pedicles can be divided with a vascular stapler inside the liver during the parenchymal transection.

Pringle and Ischemic Preconditioning

Pringle described clamping of the portal triad a century ago in the landmark paper "Notes on the Arrest of Hepatic Hemorrhage Due to Trauma." Although the Pringle maneuver was initially described for controlling bleeding due to traumatic liver injury, it is commonly used during elective hepatic resections. The goal is to minimize blood loss and hypotension, which add significant morbidity to the operation. Further, intraoperative blood transfusion has been shown to be an independent risk factor for increased postoperative infection as well as worse patient survival in some studies. Therefore, all efforts should be made to minimize blood loss during hepatic resection.

Although the liver has been shown to tolerate up to 1 hour of warm ischemia, some technical variations of the Pringle maneuver include intermittent vascular occlusion with cycles of approximately 15 minutes on and 5 minutes off. Experimental and clinical studies have demonstrated the efficacy of intermittent vascular occlusion in decreasing ischemia/reperfusion injury compared with continuous vascular occlusion, with less elevation of postoperative liver enzyme levels. Another variation is selective hemihepatic vascular occlusion, which can reduce the severity of visceral congestion and total liver ischemia. In one prospective trial of total vs. selective portal triad clamping, both techniques of inflow clamping were found to be equally effective for patients with normal livers, but greater liver damage was observed with total inflow occlusion in patients with cirrhotic livers.

In an attempt to decrease the ischemic damage associated with inflow occlusion, some hepatic surgeons have advocated the use of ischemic preconditioning. Ischemic preconditioning refers to the brief interruption of blood flow to an organ, followed by a short reperfusion period, and then a more prolonged period of ischemia. In a randomized clinical trial involving 100 patients undergoing major hepatic resection, Clavien and colleagues reported significantly less liver injury in the group who received ischemic preconditioning with a 10-minute clamp, a 10-minute reperfusion, and then a 30-minute clamp than in those who received a 30-minute clamp alone. Patients with steatosis also were especially protected by ischemic preconditioning, and the mechanism was shown to be related in part to preservation of the adenosine triphosphate content of liver tissue.

Preoperative Portal Vein Embolization

The observation that tumor thrombosis of a major portal vein branch induced ipsilateral lobar atrophy and contralateral lobe hypertrophy led to the concept of intentional preoperative portal vein embolization (PVE) to induce compensatory hypertrophy of the remnant liver. This procedure was first described in the 1980s and is accomplished via a percutaneous, transhepatic route. Numerous studies have subsequently confirmed that PVE is effective in inducing hypertrophy of nonembolized hepatic segments. PVE usually is performed in the setting of a planned right or left trisectionectomy or extended hepatic lobectomy when it is thought that the patient's remnant liver will be too small to support liver function. The future liver remnant volume (e.g., the volume of segments II, III, and I) in a patient undergoing a planned right trisectionectomy can be directly measured by helical CT and then divided by the total estimated liver volume to calculate the percentage of the future liver remnant. If the future liver remnant is thought to be too small, then PVE should be considered to increase the size of the future liver remnant. In general, surgery is planned approximately 4 weeks after PVE to allow adequate time for hypertrophy.

There is no universal agreement on what constitutes a future liver remnant adequate to avoid postoperative liver failure. It is thought that
25 to 30% of the total liver volume is adequate in patients with normal background liver. Vauthey and associates reported that major postoperative complications were increased when the estimated future liver remnant was <25%. Farges and colleagues conducted a prospective study to assess the benefits of PVE before right hepatectomy. They demonstrated that PVE had no beneficial effect on the postoperative course in patients with normal livers but significantly reduced postoperative complications in patients with chronic liver diseases. A larger remnant may be necessary even in patients with normal livers when a complex hepatectomy is planned or when the background liver is steatotic. This is especially relevant with the rise in fatty liver disease. A larger remnant may also be needed when patients have received preoperative chemotherapy. Some have suggested that 40% of the total hepatic volume should remain to minimize postoperative complications in patients who have underlying liver disease or who have received preoperative chemotherapy for colorectal cancer metastases. In a recent study encompassing 112 patients who underwent PVE, major complications, hepatic insufficiency, length of hospital stay, and 90-day mortality rate were significantly greater in patients with a standardized future liver remnant of ≤20% or a degree of hypertrophy of <5% than in patients with higher values. In another study, the authors performed PVE during neoadjuvant chemotherapy for colorectal cancer metastases. After a median wait of 30 days after PVE, patients receiving neoadjuvant chemotherapy showed median liver growth of 22% in the contralateral (nonembolized) lobe compared with 26% for those not receiving chemotherapy (not a statistically significant difference), which indicated that liver growth occurs after PVE even when cytotoxic chemotherapy is administered. PVE-related complications occur at a relatively low rate and include bleeding, hemobilia, liver abscess, incomplete embolization, and small bowel obstruction.

**Staged Hepatectomy and Repeat Hepatic Resection for Recurrent Liver Cancer**

A two-stage hepatectomy is a sequential resection strategy to remove all metastatic liver tumors when it is impossible to resect all disease in a single operative procedure. The first-stage hepatectomy usually consists of clearance of the left hemiliver by nonanatomic resection, followed by right portal vein ligation or embolization to induce left lobe hypertrophy. This is followed by a second-stage major right hepatectomy or extended right hepatectomy to resect the right liver metastases. This approach is most commonly used in cases of initially unresectable colorectal hepatic metastases and has yielded very good results.

The majority of patients undergoing hepatic resection for colorectal cancer metastases experience a recurrence. For those with limited disease recurrence confined to the liver, repeat hepatectomy is a reasonable option and can be performed with low morbidity and mortality in experienced hands. In one study, 126 patients who underwent a second liver resection for colorectal cancer metastases had 1-, 3-, and 5-year survival rates of 86%, 51%, and 34%, respectively. By multivariate analysis, the presence of more than one lesion and a tumor size of >5 cm were independent prognostic indicators of reduced survival. In another study, 40 patients underwent a second hepatectomy for liver metastases from colorectal cancer and experienced a survival benefit similar to that from the first hepatectomy; however, the results suggested that this approach should be limited to those patients who do not have extrahepatic disease and for whom >1 year has elapsed since the first operation. A meta-analysis of 21 studies examining clinical outcomes after first and second liver resections for colorectal cancer metastases showed that repeat hepatectomy was safe and provided a survival benefit equal to that from the first liver resection.

Repeat hepatectomy also has been performed in patients with HCC. Nakajima and colleagues reported on follow-up of 94 patients who underwent curative liver resection for HCC from 1991 to 1996. Of these, 57 patients had isolated recurrent disease in the liver. Twelve of these 57 patients underwent repeat hepatic resection, whereas the other 45 patients received ablation therapy. The overall survival rate in those undergoing a second hepatectomy was 90% at 2 years; however, the disease-free survival rate was only 31% at 2 years, significantly lower than the 62% rate after initial hepatectomy. Likewise, in another group of 84 patients who underwent second hepatectomy for recurrent HCC, the overall 5-year survival rate was 50%, but the recurrence-free survival rate was only 10%. In a report of 67 patients undergoing a second resection for HCC, overall 1-, 3-, and 5-year survival rates were 93%, 70%, and 56%, respectively. Multivariate analysis showed that absence of portal invasion at the second resection, single HCC at primary hepatectomy, and disease-free interval of ≥1 year after primary hepatectomy were independent prognostic factors after the second resection.

**LAPAROSCOPIC LIVER RESECTION**

Laparoscopic liver surgery has expanded from simple unroofing of hepatic cysts to resection of peripheral benign lesions to formal anatomic
lobectomies for malignancy and more recently to laparoscopic hepatectomy for live donor liver transplantation. This evolution can been attributed largely to advances in technology as well as to a better understanding of hepatic anatomy and physiology. The result is a growing spectrum of hepatic lesions that can potentially be treated with a minimally invasive surgical approach. There is general agreement that surgeons getting started with the techniques should begin with cases involving giant hepatic cysts and peripheral (segment II and III or segment V and VI) benign lesions (Fig. 31-27).168–171 Then, with experience, more difficult cases can be taken on, including cirrhotic livers, malignancies, and anatomic resections.171–174 Large central lesions and bulky right lobe lesions with hepatic vein, IVC, or proximal hilar involvement are best addressed through an open approach. Also, there is consensus that laparoscopic liver resection should be performed by surgeons who are experienced in both open hepatic resection surgery and minimally invasive surgery.171 Intraoperative laparoscopic liver ultrasonography is imperative to identify lesions and major vasculature to guide the operation. Technologies used to facilitate the parenchymal transection include the bipolar cautery, CUSA ultrasonic dissector, Harmonic Scalpel, LigaSure tissue fusion system, TissueLink wound-sealing devices, Habib 4X Laparoscopic sealer, SurgRx EnSeal sealer, and vascular stapling devices. These devices can be used for precoagulation, transection, and hemostasis, with each device having its strengths and weaknesses.

Results with laparoscopic liver resections have been excellent. Advantages of laparoscopic liver resection include decreased postoperative pain, faster return of GI function, shorter length of hospital stay, and quicker recovery time.175 Although no randomized trials of laparoscopic liver resection for cancer have been performed, studies of laparoscopic surgery for HCC and colorectal cancer metastases yield overall and disease-free survival rates after short- and medium-term follow-up that are comparable to those for open surgical series.176–178 A meta-analysis of eight nonrandomized studies (409 resections) compared laparoscopic hepatic resection (165 cases) with open resection (244 cases).179 When matched for the presence of cancer and extent of resection, the laparoscopic cases showed no difference in oncologic clearance (margins), overall 5-year survival (61% for laparoscopic vs. 62% for open), or 5-year disease-free survival (31% for laparoscopic vs. 29% for open). The largest series reported to date consists of 335 hepatic resections, of which 105 were for malignancy.171 Importantly, there was no perioperative mortality and no episodes of tumor seeding. In addition to the laparoscopic hepatic surgery for certain benign lesions and malignant tumors, Cherqui and colleagues described laparoscopic living-donor hepatectomy for liver transplantation in children,180 and Koffron and colleagues recently reported laparoscopically assisted right lobe donor hepatectomy.181

REFERENCES

Entries Highlighted in Bright Blue Are Key References.


113. Llovet JM, Real MI, Montaña X, et al: Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with


