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Diseases of the

Gallbladder and Bile Ducts PHYSIOLOGY OF BILE PRODUCTION

AND FLOW ■ ■BILE SECRETION AND COMPOSITION Bile formed in hepatocytes is secreted into a complex network of canaliculi lined by hepatocytes that flow into the canals of Hering lined partially by hepatocytes and partially by cholangiocytes, leading to small bile ductules and larger bile ducts lined by cholangiocytes that run with lymphatics and branches of the portal vein and hepatic artery in portal tracts situated between hepatic lobules. These interlobular bile ducts coalesce to form larger septal bile ducts that join to form the right and left hepatic ducts, which in turn, unite to form the common hepatic duct. The common hepatic duct is joined by the cystic duct of the gallbladder to form the common bile duct (CBD), which enters the duodenum (often after joining the main pancreatic duct) through the ampulla of Vater. Hepatic bile is an isotonic fluid with an electrolyte composition resembling blood plasma. The electrolyte composition of gallbladder bile differs from that of hepatic bile because most of the inorganic anions, chloride, and bicarbonate have been removed by reabsorption across the gallbladder epithelium. As a result of water reabsorption, total solute concentration of bile increases from 3–4 g/dL in hepatic bile to 10–15 g/dL in gallbladder bile. Major solute components of bile by moles percent include bile acids (80%), phospholipids (lecithins, cephalins, and sphingomyelin) (16%), and unesterified cholesterol (4.0%). In the lithogenic state, the choles terol value can be as high as 8–10%. Other constituents include conju gated bilirubin; proteins (all immunoglobulins, albumin, metabolites of hormones, and other proteins metabolized in the liver); electrolytes; mucus; heavy metals; and, often, drugs and their metabolites. The total daily basal secretion of hepatic bile is ~500–600 mL. Many substances taken up or synthesized by the hepatocyte are secreted into the bile canaliculi. The canalicular membrane forms microvilli and is associated with microfilaments of actin, microtubules, and other con tractile elements. Prior to their secretion into the bile, many substances are taken up into the hepatocyte, while others, such as phospholipids, a portion of primary bile acids, and some

cholesterol, are synthesized de novo in the hepatocyte. Three mechanisms are important in regu lating bile flow: (1) active transport of bile acids from hepatocytes into the bile canaliculi, (2) active transport of other organic anions, and (3) cholangiocellular secretion. The last is a secretin-mediated and cyclic AMP–dependent mechanism that results in the secretion of a bicarbonate-rich fluid into the bile ducts. Active vectorial trans-hepatocellular movement of bile acids from the portal blood into the bile canaliculi is driven by a set of trans port systems at the basolateral (sinusoidal) and the canalicular apical plasma membrane domains of the hepatocyte. Two sinusoidal bile salt uptake systems have been cloned in humans, the Na+/taurocholate cotransporter (NTCP, SLC10A1) and the organic anion–transporting proteins (OATP1B1/1B3), which also transport a large variety of non– bile salt organic anions. Several ATP-dependent canalicular transport systems, “export pumps” (ATP-binding cassette transport proteins, also known as ABC transporters), have been identified, the most important of which are the bile salt export pump (BSEP, ABCB11); the anionic conjugate export pump (MRP2, ABCC2), which mediates the canalicular excretion of various amphiphilic conjugates formed by phase II conjugation (e.g., bilirubin mono- and diglucuronides and *Deceased.

drugs); the multidrug export pump (MDR1, ABCB1) for hydropho bic cationic compounds; and the phospholipid export pump (MDR3, ABCB4). Two hemitransporters, ABCG5/G8, functioning as a couple, constitute the canalicular cholesterol and phytosterol transporter. F1C1 (ATP8B1) is an aminophospholipid transferase (“flippase”) essential for maintaining the lipid asymmetry of the canalicular membrane. The canalicular membrane also contains ATP-independent transport sys tems such as the Cl/HCO3 anion exchanger isoform 2 (AE2, SLC4A2) for canalicular bicarbonate secretion. For most of these transporters, genetic defects have been identified that are associated with various forms of cholestasis or defects of biliary excretion. F1C1 (ATP8B1) is defective in progressive familial intrahepatic cholestasis type 1 (PFIC1) and benign recurrent intrahepatic cholestasis type 1 (BRIC1) and results in ablation of all other ATP-dependent transporter functions. BSEP (ABCB11) is defective in PFIC2 and BRIC2. Mutations of MRP2 (ABCC2) cause the Dubin-Johnson syndrome, an inherited form of conjugated hyperbilirubinemia (Chap. 349). A defective MDR3 (ABCB4) results in PFIC3. ABCG5/G8, the canalicular half transport ers for cholesterol and other neutral sterols, are defective in sitosterol emia. The cystic fibrosis transmembrane regulator (CFTR, ABCC7), located on bile duct epithelial cells but not on canalicular membranes, is defective in cystic fibrosis, which is associated with impaired cholan giocellular pH regulation during ductular bile formation and chronic cholestatic liver disease, occasionally resulting in biliary cirrhosis.

■ ■THE BILE ACIDS The primary bile acids, cholic acid and chenodeoxycholic acid (CDCA), are synthesized in hepatocytes from cholesterol, conjugated with gly cine or taurine, and secreted into the bile canaliculus. Secondary bile acids, including deoxycholate and lithocholate, are formed in the colon as bacterial metabolites of the primary bile acids. However, lithocholic acid is much less efficiently absorbed from the colon than deoxycho lic acid. Another secondary bile acid, found in low concentration, is ursodeoxycholic acid (UDCA), a stereoisomer of CDCA. In healthy subjects, the ratio of glycine to taurine conjugates in bile is ~3:1. CHAPTER 357 Diseases of the Gallbladder and Bile Ducts Bile acids are detergent-like molecules that in aqueous solutions and above a critical concentration of ~2 mM form molecular aggre gates called micelles. Cholesterol alone is sparingly soluble in aqueous environments, and its solubility in bile depends on both the total lipid concentration and the relative molar percentages of bile acids and leci thin. Normal ratios of these constituents favor the formation of solubi lizing mixed micelles, while abnormal ratios promote the

precipitation of cholesterol crystals in bile via an intermediate liquid crystal phase. In addition to facilitating the biliary excretion of cholesterol, bile acids facilitate the normal intestinal absorption of dietary fats, mainly cholesterol, and fat-soluble vitamins, via a micellar transport mecha nism (Chap. 336). Bile acids also serve as a major physiologic driving force for hepatic bile flow and aid in water and electrolyte transport in the small bowel and colon. Bile acids also function as hormones binding to nuclear (farnesoid X receptor [FXR]) and G protein–coupled (TGR5) receptors that regulate bile acid metabolism and their enterohepatic circulation. ■ ■ENTEROHEPATIC CIRCULATION Bile acids are efficiently conserved under normal conditions. Uncon jugated, and to a lesser degree also conjugated, bile acids are absorbed by passive diffusion along the entire gut. Quantitatively much more important for bile salt recirculation, however, is the active transport mechanism for conjugated bile acids in the distal ileum (Chap. 336). The reabsorbed bile acids enter the portal bloodstream and are taken up rapidly by hepatocytes, reconjugated, and resecreted into bile (enterohepatic circulation). The normal bile acid pool size is ~2–4 g. During digestion of a meal, the bile acid pool undergoes at least one or more enterohepatic cycles, depending on the size and composition of the meal. Normally, the bile acid pool circulates ~5–10 times daily. Intestinal reabsorption of the pool is ~95% efficient; therefore, daily fecal loss of bile acids is in the range of 0.2–0.4 g. In the steady state, this fecal loss is compensated by an equal daily synthesis of bile acids by the liver, and thus, the size

of the bile acid pool is maintained. Bile acids in the intestine stimulate the release of fibroblast growth factor 19 (FGF19), which suppresses the hepatic synthesis of bile acids from cholesterol by inhibiting the rate-limiting enzyme cytochrome P450 7A1 (CYP7A1). FGF19 also promotes gallbladder relaxation. While the loss of bile salts in stool is usually matched by increased hepatic synthesis, the maximum rate of synthesis is ~5 g/d, which may be insufficient to replete the bile acid pool size when there is pronounced impairment of intestinal bile salt reabsorption.

The expression of ABC transporters in the enterohepatic circulation and of the rate-limiting enzymes of bile acid and cholesterol synthesis are regulated in a coordinated fashion by nuclear receptors, which are ligand-activated transcription factors. The hepatic BSEP (ABCB11) is upregulated by the FXR that also represses bile acid synthesis. The expression of the cholesterol transporter, ABCG5/G8, is upregulated by the liver X receptor (LXR), which is an oxysterol sensor. ■ ■GALLBLADDER AND SPHINCTERIC FUNCTIONS In the fasting state, the sphincter of Oddi (SOD) offers a high-pressure zone of resistance to bile flow from the CBD into the duodenum. Its tonic contraction serves to (1) prevent reflux of duodenal contents into the pancreatic and bile ducts and (2) promote filling of the gallblad der. The major factor controlling the evacuation of the gallbladder is the peptide hormone cholecystokinin (CCK), which is released from the duodenal mucosa in response to the ingestion of fats and amino acids. CCK produces (1) powerful contraction of the gallbladder, (2) decreased resistance of the SOD, and (3) enhanced flow of biliary con tents into the duodenum. Hepatic bile is “concentrated” within the gallbladder by energydependent transmucosal absorption of water and electrolytes. Almost the entire bile acid pool may be sequestered in the gallbladder follow ing an overnight fast for delivery into the duodenum with the first meal of the day. The normal capacity of the gallbladder is ~30 mL. PART 10 Disorders of the Gastrointestinal System DISEASES OF THE GALLBLADDER ■ ■CONGENITAL ANOMALIES Anomalies of the biliary tract are not uncommon and include abnor malities in number, size, and shape (e.g., agenesis of the gallbladder, duplications, rudimentary or oversized “giant” gallbladders, and diver ticula). Phrygian cap is a clinically innocuous entity in which a partial or complete septum (or fold)

separates the fundus from the body. Anomalies of position or suspension are not uncommon and include left-sided gallbladder, intrahepatic gallbladder, retrodisplacement of the gallbladder, and “floating” gallbladder. The latter condition predis poses to acute torsion, volvulus, or herniation of the gallbladder. ■ ■GALLSTONES Epidemiology and Pathogenesis Gallstones are quite prevalent in most Western countries. Gallstone formation increases after age 50. In the United States, the prevalence is highest in Native Americans fol lowed by Hispanics, non-Hispanic whites, and black Americans. The prevalence is higher in women than men across all ages. Gallstones form because of abnormal bile composition. They are divided into two major types: cholesterol stones and pigment stones. Cholesterol stones account for >90% of all gallstones in Western indus trialized countries. Cholesterol gallstones usually contain >50% choles terol monohydrate plus an admixture of calcium salts, bile pigments, proteins, and fatty acids. Pigment stones are composed primarily of calcium bilirubinate; they contain <20% cholesterol and are classified into “black” and “brown” types, the latter forming secondary to chronic biliary infection. CHOLESTEROL STONES AND BILIARY SLUDGE Cholesterol is essen tially water-insoluble and requires aqueous dispersion into either micelles or vesicles, both of which require the presence of a second lipid to solubilize the cholesterol. Cholesterol and phospholipids are secreted into bile as unilamellar bilayered vesicles, which are con verted into mixed micelles consisting of bile acids, phospholipids, and

ABCG5/G8 CYP7A1 MDR3 (ABCB4) I. Normal cholesterol Normal bile acids Lecithin Cholesterol Normal bile acids Normal lecithin Normal cholesterol Bile acids Normal lecithin II. Supersaturation Inhibit nucleation Apolipoproteins Lecithin vesicles Promote nucleation Mucous glycoproteins Heat-labile proteins III. Nucleation IV. Microstone Gallstone FIGURE 357-1 Scheme showing pathogenesis of cholesterol gallstone formation. Conditions or factors that increase the ratio of cholesterol to bile acids and phospholipids (lecithin) favor gallstone formation. ABCB4, ATP-binding cassette transporter; ABCG5/8, ATP-binding cassette (ABC) transporter G5/G8; CYP7A1, cytochrome P450 7A1; MDR3, multidrug resistance protein 3, also called phospholipid export pump. cholesterol by the action of bile acids. If there is an excess of cholesterol in relation to phospholipids and bile acids, unstable, cholesterol-rich vesicles remain, which aggregate into large multilamellar vesicles from which cholesterol crystals precipitate (Fig. 357-1). There are several important mechanisms in the formation of lithogenic (stone-forming) bile. The most important is increased biliary secretion of cholesterol. This may occur in association with obesity, the metabolic syndrome, high-caloric and cholesterol-rich diets, or drugs (e.g., clofibrate) and may result from increased activity of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of hepatic cholesterol synthesis, and increased hepatic uptake of cholesterol from blood. In patients with gallstones, dietary cholesterol increases biliary cholesterol secretion. This does not occur in nongallstone patients on high-cholesterol diets. In addition to environmental factors such as high-caloric and cholesterol-rich diets, genetic factors play an important role in gallstone disease. A large study of symptomatic gallstones in Swedish twins provided strong evidence for a role of genetic factors in gallstone pathogenesis. Genetic factors accounted for 25%, shared environmental factors for 13%, and individual environmental factors for 62% of the phenotypic variation among monozygotic twins. A single nucleotide polymorphism of the gene encoding the hepatic cholesterol transporter ABCG5/G8 has been found in 21% of patients with gallstones, but only in 9% of the general population. It is thought to cause a gain of function of the cholesterol transporter and to contribute to cholesterol hypersecretion. A high prevalence of gallstones is found among first-degree relatives of gallstone carriers and in certain ethnic populations such as American Indians, Chilean Indians, and Chilean Hispanics. A common genetic

trait has been identified for some of these populations by mitochon drial DNA analysis. In some patients, impaired hepatic conversion of cholesterol to bile acids may also occur, resulting in an increase of the lithogenic cholesterol/bile acid ratio. Although most cholesterol stones have a polygenic basis, there are rare monogenic (Mendelian) causes. Mutations in the CYP7A1 gene have been described that result in a deficiency of the enzyme cholesterol 7-hydroxylase, which catalyzes the initial step in cholesterol catabolism and bile acid synthesis. The homozygous state is associated with hypercholesterolemia and gall stones. Because the phenotype is expressed in the heterozygote state, mutations in the CYP7A1 gene may contribute to the susceptibility to cholesterol gallstone disease in the population. Mutations in the MDR3 (ABCB4) gene, which encodes the phospholipid export pump in the canalicular membrane of the hepatocyte, may cause defective phospho lipid secretion into bile, resulting in cholesterol supersaturation of bile and formation of cholesterol gallstones in the gallbladder and in the bile ducts. Thus, an excess of biliary cholesterol in relation to bile acids and phospholipids is primarily due to hypersecretion of cholesterol, but hyposecretion of bile acids or phospholipids may contribute. An additional disturbance of bile acid metabolism that is likely to con tribute to supersaturation of bile with cholesterol is enhanced conver sion of cholic acid to deoxycholic acid, with replacement of the cholic acid pool by an expanded deoxycholic acid pool. It may result from enhanced dehydroxylation of cholic acid and increased absorption of newly formed deoxycholic acid. An increased deoxycholate secretion is associated with hypersecretion of cholesterol into bile. A recent study suggested a role for the gut microbiota as an environmental factor con tributing to gallstone formation through an influence on cholesterol and bile acid metabolism. While supersaturation of bile with cholesterol is an important pre requisite for gallstone formation, it is generally not sufficient by itself to produce cholesterol precipitation in vivo. Most individuals with supersaturated bile do not develop stones because the time required for cholesterol crystals to nucleate and grow is longer than the time bile remains in the gallbladder. An important mechanism is nucleation of cholesterol monohydrate crystals, which is greatly accelerated in human lithogenic bile. Accel erated nucleation of cholesterol monohydrate in bile may be due to either an excess of pronucleating factors or a deficiency of antinucleating factors. Mucin and certain nonmucin glycoproteins, principally immu noglobulins, appear to be pronucleating factors, while apolipoproteins A-I and A-II and other glycoproteins appear to be antinucleating factors. Pigment particles may possibly play a role as nucleating fac tors. In a genome-wide analysis of serum bilirubin levels, the uridine diphosphate-glucuronyltransferase 1A1 (UGT1A1) Gilbert’s syndrome gene variant was associated with the presence of gallstone disease. Because most gallstones associated with the UGT1A1 variant were cholesterol stones, this finding points to the role of pigment particles in the patho genesis of gallbladder stones. Cholesterol monohydrate crystal nucle ation and crystal growth probably occur within the mucin gel layer. Vesicle fusion leads to liquid crystals, which, in turn, nucleate into solid cholesterol monohydrate crystals. Continued growth of the crystals occurs by direct nucleation of cholesterol molecules from supersatu rated unilamellar or multilamellar biliary vesicles. A third important mechanism in cholesterol gallstone formation is gallbladder hypomotility. If the gallbladder emptied all supersaturated or crystal-containing bile completely, stones would not be able to grow. A high percentage of patients with gallstones exhibits abnormalities of gallbladder emptying. Ultrasonographic studies show that gallstone patients display an increased gallbladder volume during fasting and after a test meal (residual volume) and that fractional emptying after gallbladder stimulation is decreased. The incidence of gallstones is increased in conditions associated with infrequent or impaired gall bladder emptying such as fasting, parenteral nutrition, or pregnancy and in patients using drugs

that inhibit gallbladder motility. Biliary sludge is a thick, mucous material that, upon microscopic examination, reveals lecithin-cholesterol liquid crystals, cholesterol monohydrate crystals, calcium bilirubinate, and mucin gels. Biliary sludge typically forms a crescent-like layer in the most dependent

portion of the gallbladder and is recognized by characteristic echoes on ultrasonography (see below). The presence of biliary sludge implies two abnormalities: (1) the normal balance between gallbladder mucin secretion and elimination has become deranged, and (2) nucleation of biliary solutes has occurred. That biliary sludge may be a precursor form of gallstone disease is evident from several observations. In one study, 96 patients with gallbladder sludge were followed prospectively by serial ultrasound studies. In 18%, biliary sludge disappeared and did not recur for at least 2 years. In 60%, biliary sludge disappeared and reappeared; in 14%, gallstones (8% asymptomatic, 6% symptomatic) developed; and in 6%, severe biliary pain with or without acute pan creatitis occurred. In 12 patients, cholecystectomies were performed, 6 for gallstone-associated biliary pain and 3 in symptomatic patients with sludge but without gallstones who had prior attacks of pancreatitis; the latter did not recur after cholecystectomy. It should be emphasized that biliary sludge can develop with disorders that cause gallbladder hypo motility; that is, surgery, burns, total parenteral nutrition, pregnancy, and oral contraceptives—all of which are associated with gallstone formation. However, the presence of biliary sludge implies supersatura tion of bile with either cholesterol or calcium bilirubinate.

Two other conditions are associated with cholesterol-stone or bili ary-sludge formation: pregnancy and rapid weight reduction through a very-low-calorie diet. There appear to be two key changes during preg nancy that contribute to a “cholelithogenic state”: (1) a marked increase in cholesterol saturation of bile during the third trimester and (2) slug gish gallbladder contraction in response to a standard meal, resulting in impaired gallbladder emptying. That these changes are related to pregnancy per se is supported by several studies that show reversal of these abnormalities quite rapidly after delivery. During pregnancy, gall bladder sludge develops in 20–30% of women and gallstones in 5–12%. Although biliary sludge is a common finding during pregnancy, it is usually asymptomatic and often resolves spontaneously after delivery. Gallstones, which are less common than sludge and frequently associ ated with biliary colic, may also disappear after delivery because of spontaneous dissolution related to bile becoming unsaturated with cholesterol postpartum. CHAPTER 357 Diseases of the Gallbladder and Bile Ducts Approximately 10–20% of persons with rapid weight reduction achieved through very-low-calorie dieting develop gallstones. In a study involving 600 patients who completed a 3-month, 520-kcal/d diet, UDCA in a dosage of 600 mg/d proved highly effective in pre venting gallstone formation; gallstones developed in only 3% of UDCA recipients, compared to 28% of placebo-treated patients. In obese patients treated by gastric banding, 500 mg/d of UDCA reduced the risk of gallstone formation from 30 to 8% within a follow-up of 6 months. To summarize, cholesterol gallstone disease occurs because of sev eral defects, which include (1) bile supersaturation with cholesterol, (2) nucleation of cholesterol monohydrate with subsequent crystal retention and stone growth, and (3) abnormal gallbladder motor function with delayed emptying and stasis. Other important factors known to predispose to cholesterol-stone formation are summarized in Table 357-1. PIGMENT STONES Black pigment stones are composed of either pure calcium bilirubinate or polymer-like complexes with calcium and mucin glycoproteins. They are more common in patients who have chronic hemolytic states (with increased conjugated bilirubin in bile); cirrhosis, especially related to alcohol; Gilbert’s syndrome;

or cystic fibrosis. Gallbladder stones in patients with ileal diseases, ileal resection, or ileal bypass generally are also black pigment stones. Enterohepatic recycling of bilirubin in ileal disease states contributes to their pathogenesis. Brown pigment stones are composed of calcium salts of unconjugated bilirubin with varying amounts of cholesterol and protein. They are caused by the presence of increased amounts of unconjugated, insoluble bilirubin in bile that precipitates to form stones. Deconjugation of an excess of soluble bilirubin mono- and diglucuronides may be mediated by endogenous β-glucuronidase but may also occur by spontaneous hydrolysis. Sometimes, the enzyme is also produced when bile is chronically infected by bacteria, and such

TABLE 357-1 Predisposing Factors for Cholesterol and Pigment Gallstone Formation Cholesterol Stones

1. Demographic/genetic factors: Prevalence highest in North American Indians, Chilean Indians, and Chilean Hispanics, greater in Northern Europe and North America than in Asia, lowest in Japan; familial disposition; hereditary aspects
2. Obesity, metabolic syndrome: Normal bile acid pool and secretion but increased biliary secretion of cholesterol
3. Rapid weight loss: Mobilization of tissue cholesterol leads to increased biliary cholesterol secretion while enterohepatic circulation of bile acids is decreased
4. Female sex hormones a. Estrogens stimulate hepatic lipoprotein receptors, increase uptake of dietary cholesterol, and increase biliary cholesterol secretion b. Natural estrogens, other estrogens, and oral contraceptives lead to decreased bile salt secretion and decreased conversion of cholesterol to cholesteryl esters
5. Pregnancy: Impaired gallbladder emptying caused by progesterone combined with the influence of estrogens, which increase biliary cholesterol secretion
6. Increasing age: Increased biliary secretion of cholesterol, decreased size of bile acid pool, decreased secretion of bile salts
7. Gallbladder hypomotility leading to stasis and formation of sludge a. Total parenteral nutrition b. Fasting c. Pregnancy d. Drugs such as octreotide
8. Clofibrate therapy: Increased biliary secretion of cholesterol
9. Decreased bile acid secretion PART 10 Disorders of the Gastrointestinal System a. Genetic defect of the CYP7A1 gene
10. Decreased phospholipid secretion: Genetic defect of the MDR3 gene
11. Miscellaneous a. High-calorie, high-fat diet b. Spinal cord injury Pigment Stones
12. Demographic/genetic factors: Asia, rural setting (presumed due to increased prevalence of parasitic biliary infections; the incidence has been dropping with time)
13. Chronic hemolysis (example: sickle cell disease)
14. Alcohol related liver cirrhosis
15. Ineffective erythropoiesis (example: pernicious anemia)
16. Cystic fibrosis
17. Chronic biliary tract infection, parasite infections
18. Increasing age
19. Ileal disease, ileal resection or bypass stones are brown. Pigment stone formation is frequent in Asia and is often associated with parasitic infections in the gallbladder and biliary tree (Table 357-1). Diagnosis Procedures of potential use in the diagnosis of choleli thiasis and other diseases of the gallbladder are detailed in Table 357-2. Ultrasonography

of the gallbladder is very accurate in the identifica tion of cholelithiasis and has replaced oral cholecystography (OCG) (Fig. 357-2A). Stones as small as 1.5 mm in diameter may be con fidently identified provided that firm criteria are used (e.g., acoustic “shadowing” of opacities that are within the gallbladder lumen and that change with the patient’s position [by gravity]). In major medical cen ters, the false-negative and false-positive rates for ultrasound in gall stone patients are ~2–4%. Biliary sludge is material of low echogenic activity that typically forms a layer in the most dependent position of the gallbladder. This layer shifts with postural changes but fails to pro duce acoustic shadowing; these two characteristics distinguish sludges from gallstones. Ultrasound can also be used to assess the emptying function of the gallbladder. The plain abdominal film may detect gallstones containing suf ficient calcium to be radiopaque (10–15% of cholesterol and ~50% of

TABLE 357-2 Diagnostic Evaluation of the Gallbladder DIAGNOSTIC ADVANTAGES DIAGNOSTIC LIMITATIONS COMMENT Ultrasound Rapid Accurate identification of gallstones (>95%) Simultaneous scanning of GB, liver, bile ducts, pancreas “Real-time” scanning allows assessment of GB volume, contractility Not limited by jaundice, pregnancy May detect very small stones Bowel gas Massive obesity Ascites Procedure of choice for detection of stones Plain Abdominal X-Ray Low cost Readily available Relatively low yield Contraindicated in pregnancy Pathognomonic findings in: calcified gallstones, limey bile, porcelain GB, emphysematous cholecystitis, gallstone ileus Cholescintigraphy (HIDA, DISIDA, etc.) Accurate identification of cystic duct obstruction Simultaneous assessment of bile ducts Contraindicated in pregnancy Serum bilirubin

> “ 103–205 µmol/L

(6–12 mg/dL) Cholecystogram of low resolution Indicated for confirmation of suspected acute cholecystitis; less sensitive and less specific in chronic cholecystitis; useful in the diagnosis of acalculous cholecystopathy, especially if given with CCK to assess GB emptying Abbreviations: CCK, cholecystokinin; DISIDA, diisopropyl iminodiacetic acid; GB, gallbladder; HIDA, hydroxyl iminodiacetic acid. pigment stones). Plain radiography may also be of use in the diagnosis of emphysematous cholecystitis, porcelain gallbladder, limey bile, and gallstone ileus. OCG was historically a useful procedure for the diagnosis of gall stones but has been replaced by ultrasound and is now regarded as obsolete. It may be used to assess the patency of the cystic duct and gallbladder emptying function. Further, OCG can also delineate the size and number of gallstones and determine whether they are calci fied, useful information if medical dissolution is being considered. Radiopharmaceuticals such as 99mTc-labeled N-substituted iminodi acetic acids (HIDA and DISIDA) are rapidly extracted from the blood and are excreted into the biliary tree in high concentration even in the presence of mild to moderate serum bilirubin elevations. Failure to image the gallbladder in the presence of biliary ductal visualization may indicate cystic duct obstruction, acute or chronic cholecystitis, or surgical absence of the organ. Such scans have application in the diagnosis of acute cholecystitis and may play a role in the detection of a postcholecystectomy bile leak. Symptoms of Gallstone Disease Gallstones usually produce symptoms by causing inflammation or obstruction following their migration into the cystic duct or CBD. The most specific and charac teristic symptom of gallstone disease is biliary colic that is a constant and often long-lasting pain (see below). Obstruction of the cystic duct or CBD by a stone produces increased

intraluminal pressure and distention of the viscus that cannot be relieved by repetitive biliary contractions. The resultant visceral pain is characteristically a severe,

chd gb cbd shadow pd A B C D FIGURE 357-2 Examples of ultrasound and radiologic studies of the biliary tract. A. An ultrasound study showing a distended gallbladder (GB) containing a single large stone (arrow), which casts an acoustic shadow. B. Endoscopic retrograde cholangiopancreatogram (ERCP) showing normal biliary tract anatomy. In addition to the endoscope and large vertical gallbladder filled with contrast dye, the common hepatic duct (CHD), common bile duct (CBD), and pancreatic duct (PD) are shown. The arrow points to the ampulla of Vater. C. Endoscopic retrograde cholangiogram (ERC) showing choledocholithiasis. The biliary tract is dilated and contains multiple radiolucent calculi. D. ERCP showing sclerosing cholangitis. The CBD shows areas that are strictured and narrowed. steady ache or fullness in the epigastrium or right upper quadrant (RUQ) of the abdomen with frequent radiation to the interscapular area, right scapula, or shoulder. Biliary colic begins quite suddenly and may persist with severe intensity for 30 min to 5 h, subsiding gradually or rapidly. It is steady rather than intermittent, as would be suggested by the word colic, which must be regarded as a misnomer, although it is in widespread use. An episode of biliary pain persisting beyond 5 h should raise the suspicion of acute cholecystitis (see below). Nausea and vomiting fre quently accompany episodes of biliary pain. An elevated level of serum bilirubin and/or alkaline phosphatase suggests a common duct stone. Fever or chills (rigors) with biliary pain usually imply a complication, that is, cholecystitis, pancreatitis, or cholangitis. Complaints of shortlasting, vague epigastric fullness, dyspepsia, eructation, or flatulence, especially following a fatty meal, should not be confused with biliary pain. Such symptoms are frequently elicited from patients with or without gallstone disease but are not specific for biliary calculi. Bili ary colic may be precipitated by eating a fatty meal, by consumption of a large meal following a period of prolonged fasting, or by eating a normal meal; it is frequently nocturnal, occurring within a few hours of retiring. Natural History Gallstone disease discovered in an asymptomatic patient or in a patient whose symptoms are not referable to choleli thiasis is a common clinical problem. Sixty to 80% of persons with asymptomatic gallstones remain asymptomatic over follow-up periods of up to 25 years. The probability of developing symptoms within 5 years after diagnosis is 2–4% per year and decreases in the years thereafter to 1–2%. The yearly incidence of complications is about 0.1–0.3%. Patients remaining asymptomatic for 15 years were found to be unlikely to develop symptoms during further follow-up, and most patients who did develop complications from their gallstones experi enced prior warning symptoms. Similar conclusions apply to diabetic patients with silent gallstones. Decision analysis has suggested that (1) the cumulative risk of death due to gallstone disease while on expect ant management is small, and (2) prophylactic cholecystectomy is not warranted. Complications requiring cholecystectomy are much more common in gallstone patients who have developed symptoms of biliary pain. Patients found to have gallstones at a young age are more likely to develop symptoms from cholelithiasis than are patients >60 years at the time of initial diagnosis. Patients with diabetes mellitus and gallstones may be somewhat more susceptible to septic complications, but the

magnitude of risk of septic biliary complications in diabetic patients is incompletely defined. CHAPTER 357 TREATMENT Gallstones SURGICAL THERAPY In asymptomatic gallstone patients, the risk of developing symp toms or complications requiring surgery is quite small (see above). Thus, a recommendation for cholecystectomy in a patient with gallstones should probably be based on assessment of three factors: (1) the presence of symptoms that are frequent enough or severe

enough to interfere with the patient’s general routine; (2) the pres ence of a prior complication of gallstone disease, that is, history of acute cholecystitis, pancreatitis, gallstone fistula, etc.; or (3) the presence of an underlying condition predisposing the patient to increased risk of gallstone complications (e.g., a previous attack of acute cholecystitis regardless of current symptomatic status). Patients with very large gallstones (>3 cm in diameter) and patients harboring gallstones in a congenitally anomalous gallbladder might also be considered for prophylactic cholecystectomy. Although young age is a worrisome factor in asymptomatic gallstone patients, few authorities would now recommend routine cholecystectomy in young patients with silent stones. Laparoscopic cholecystectomy is a minimal-access approach for the removal of the gallbladder together with its stones. Its advantages include a markedly short ened hospital stay, minimal disability, and decreased cost, and it is the procedure of choice for most patients referred for elective cholecystectomy. Diseases of the Gallbladder and Bile Ducts From several studies involving >4000 patients undergoing lapa roscopic cholecystectomy, the following key points emerge: (1) com plications develop in ~4% of patients, (2) conversion to laparotomy occurs in 5%, (3) the death rate is remarkably low (i.e., <0.1%), and (4) the rate of bile duct injuries is low (i.e., 0.2–0.6%) and compa rable with open cholecystectomy. These data indicate why laparo scopic cholecystectomy has become the “gold standard” for treating symptomatic cholelithiasis. MEDICAL THERAPY—GALLSTONE DISSOLUTION In carefully selected patients with a functioning gallbladder and with radiolucent stones <10 mm in diameter, complete dissolution can be achieved in ~50% of patients within 6 months to 2 years. For

good results within a reasonable time period, this therapy should be limited to radiolucent stones <5 mm in diameter. The dose of UDCA should be 10–15 mg/kg per d. Stones >10 mm in size rarely dissolve. Pigment stones are not responsive to UDCA therapy. Prob ably ≤10% of patients with symptomatic cholelithiasis are candidates for such treatment. However, in addition to the vexing problem of recurrent stones (30–50% over 3–5 years of follow-up), there is also the factor of taking a drug for up to 2 years and perhaps indefinitely. The advantages and success of laparoscopic cholecystectomy have largely reduced the role of gallstone dissolution to patients who wish to avoid or are not candidates for elective cholecystectomy. However, patients with cholesterol gallstone disease who develop recurrent choledocholithiasis after cholecystectomy should be on long-term treatment with UDCA.

■ ■ACUTE AND CHRONIC CHOLECYSTITIS Acute Cholecystitis Acute inflammation of the gallbladder wall usually follows obstruction of the cystic duct by a stone. Inflammatory response can be evoked by three factors: (1) mechanical inflamma tion produced by increased intraluminal pressure and distention with resulting ischemia of the gallbladder mucosa and wall, (2) chemical inflammation caused by the release of lysolecithin (due to the action of phospholipase on lecithin in bile) and other local tissue factors, and (3) bacterial inflammation, which may play a role in 50–85% of patients with acute cholecystitis. The organisms most frequently isolated by culture of gallbladder bile in these patients include Escherichia coli, Klebsiella spp., Streptococcus spp., and Clostridium spp. PART 10 Disorders of the Gastrointestinal System Acute cholecystitis often begins as an attack of biliary pain that pro gressively worsens. Approximately 60–70% of patients report having experienced prior attacks that resolved spontaneously. As the episode progresses, however, the pain of acute cholecystitis becomes more generalized in the right upper abdomen. As with biliary colic, the pain of cholecystitis may radiate to the interscapular area, right scapula, or shoulder. Peritoneal signs of inflammation such as increased pain with jarring or on deep

respiration may be apparent. The patient is anorectic and often nauseated. Vomiting is relatively common and may produce symptoms and signs of vascular and extracellular volume depletion. Jaundice is unusual early in the course of acute cholecystitis but may occur when edematous inflammatory changes involve the bile ducts and surrounding lymph nodes. A low-grade fever is characteristically present, but shaking chills or rigors are not uncommon. The RUQ of the abdomen is almost invari ably tender to palpation. An enlarged, tense gallbladder is palpable in 25–50% of patients. Deep inspiration or cough during subcostal palpa tion of the RUQ usually produces increased pain and inspiratory arrest (Murphy's sign). Localized rebound tenderness in the RUQ is com mon, as are abdominal distention and hypoactive bowel sounds from paralytic ileus, but generalized peritoneal signs and abdominal rigidity are usually lacking, in the absence of perforation. The diagnosis of acute cholecystitis is usually made on the basis of a characteristic history and physical examination. The triad of sudden onset of RUQ tenderness, fever, and leukocytosis is highly suggestive. Typically, leukocytosis in the range of 10,000–15,000 cells per microli ter with a left shift on differential count is found. The serum bilirubin is mildly elevated (<85.5 µmol/L [5 mg/dL]) in fewer than half of patients, whereas about one-fourth have modest elevations in serum aminotransferases (usually less than a fivefold elevation). Ultrasound will demonstrate calculi in 90–95% of cases and is useful for detection of signs of gallbladder inflammation including thickening of the wall, pericholecystic fluid, and dilatation of the bile duct. The radionuclide (e.g., HIDA) biliary scan may be confirmatory if bile duct imaging is seen without visualization of the gallbladder. Approximately 75% of patients treated medically have remission of acute symptoms within 2–7 days following hospitalization. In 25%, however, a complication of acute cholecystitis will occur despite conservative treatment (see below). In this setting, prompt surgical intervention is required. Of the 75% of patients with acute cholecystitis

who undergo remission of symptoms, ~25% will experience a recur rence of cholecystitis within 1 year, and 60% will have at least one recurrent bout within 6 years. In view of the natural history of the disease, acute cholecystitis is best treated by early surgery whenever possible. Mirizzi's syndrome is a rare complication in which a gallstone becomes impacted in the cystic duct or neck of the gallbladder causing compression of the CBD, resulting in CBD obstruction and jaundice. Ultrasound shows gallstone(s) lying outside the hepatic duct. Endo scopic retrograde cholangiopancreatography (ERCP) (Fig. 357-2B), percutaneous transhepatic cholangiography (PTC), or magnetic reso nance cholangiopancreatography (MRCP) will usually demonstrate the characteristic extrinsic compression of the CBD. Surgery consists of removing the cystic duct, diseased gallbladder, and impacted stone. The preoperative diagnosis of Mirizzi's syndrome is important to avoid CBD injury. ACALCULOUS CHOLECYSTITIS In 5–14% of patients with acute chole cystitis, calculi obstructing the cystic duct are not found at surgery. In

> 50% of such cases, an underlying explanation for acalculous inflam mation is not found. An increased risk for the development of acalcu lous cholecystitis is especially associated with prolonged fasting, with serious trauma or burns, in the postpartum period following prolonged labor, and with orthopedic and other nonbiliary major surgical opera tions in the postoperative period. It may possibly complicate periods of prolonged parenteral hyperalimentation. For some of these cases, biliary sludge in the cystic duct may be responsible. Other

> precipitating factors include vasculitis, obstructing adenocarcinoma of the gallblad der, diabetes mellitus, torsion of the gallbladder, “unusual” bacterial infections of the gallbladder (e.g., Leptospira, Streptococcus, Salmonella, or Vibrio cholerae), and parasitic infestation of the gallbladder. Acalcu lous cholecystitis may also be seen with a variety of other systemic dis ease processes (e.g., sarcoidosis, cardiovascular disease, tuberculosis, syphilis, actinomycosis). Although the clinical manifestations of acalculous cholecystitis are indistinguishable from those of calculous cholecystitis, the setting of acute gallbladder inflammation complicating severe underlying ill ness is characteristic of acalculous disease. Ultrasound or computed tomography (CT) examinations demonstrating a large, tense, static gallbladder without stones and with evidence of poor emptying over a prolonged period may be diagnostically useful in some cases. The complication rate for acalculous cholecystitis exceeds that for calculous cholecystitis. Successful management of acute acalculous cholecystitis appears to depend primarily on early diagnosis and surgical interven tion, with meticulous attention to postoperative care. ACALCULOUS CHOLECYSTOPATHY Disordered motility of the gall bladder can produce recurrent biliary pain in patients without gall stones. Infusion of an octapeptide of CCK can be used to measure the gallbladder ejection fraction during cholescintigraphy. The surgical findings have included abnormalities such as chronic cholecystitis, gallbladder muscle hypertrophy, and/or a markedly narrowed cystic duct. Some of these patients may well have had antecedent gallbladder disease. The following criteria can be used to identify patients with acalculous cholecystopathy: (1) recurrent episodes of typical RUQ pain characteristic of biliary tract pain, (2) abnormal CCK cholescin tigraphy demonstrating a gallbladder ejection fraction of <40%, and (3) infusion of CCK reproducing the patient’s pain. An additional clue would be the identification of a large gallbladder on ultrasound exami nation. Importantly, it should be noted that SOD dysfunction can also give rise to recurrent RUQ pain and CCK-scintigraphic abnormalities. EMPHYSEMATOUS CHOLECYSTITIS So-called emphysematous cho lecystitis is thought to begin with acute cholecystitis (calculous or acalculous) followed by ischemia or gangrene of the gallbladder wall and infection by gas-producing organisms. Bacteria most frequently cultured in this setting include anaerobes, such as Clostridium welchii or C. perfringens, and aerobes, such as E. coli. This condition occurs most frequently in elderly men and in patients with diabetes mellitus. The clinical manifestations are essentially indistinguishable from those of nongaseous cholecystitis. The diagnosis is usually made on plain

abdominal film by finding gas within the gallbladder lumen, dissecting within the gallbladder wall to form a gaseous ring, or in the perichole cystic tissues. The morbidity and mortality rates with emphysematous cholecystitis are considerable. Prompt surgical intervention coupled with appropriate antibiotics is mandatory. Chronic Cholecystitis Chronic inflammation of the gallbladder wall is almost always associated with the presence of gallstones and is thought to result from

repeated bouts of subacute or acute cholecys titis or from persistent mechanical irritation of the gallbladder wall by gallstones. The presence of bacteria in the bile occurs in >25% of patients with chronic cholecystitis. The presence of infected bile in a patient with chronic cholecystitis undergoing elective cholecystectomy probably adds little to the operative risk. Chronic cholecystitis may be asymptomatic for years, which may progress to symptomatic gallblad der disease or to acute cholecystitis or may present with complications (see below). Complications of Cholecystitis • EMPYEMA AND HYDROPS

Empyema of the gallbladder usually results from progression of acute cholecystitis with persistent cystic duct obstruction to superinfection of the stagnant bile with a pus-forming bacterial organism. The clini cal picture resembles that of cholangitis with high fever; severe RUQ pain; marked leukocytosis; and often, prostration. Empyema of the gallbladder carries a high risk of gram-negative sepsis and/or perfora tion. Emergency surgical intervention with proper antibiotic coverage is required as soon as the diagnosis is suspected. Hydrops or mucocele of the gallbladder may also result from pro longed obstruction of the cystic duct, usually by a large solitary calcu lus. In this instance, the obstructed gallbladder lumen is progressively distended, over a period of time, by mucus (mucocele) or by a clear transudate (hydrops) produced by mucosal epithelial cells. A visible, easily palpable, nontender mass sometimes extending from the RUQ into the right iliac fossa may be found on physical examination. The patient with hydrops of the gallbladder frequently remains asymptom atic, although chronic RUQ pain may also occur. Cholecystectomy is indicated, because empyema, perforation, or gangrene may complicate the condition. GANGRENE AND PERFORATION Gangrene of the gallbladder results from ischemia of the wall and patchy or complete tissue necrosis. Underlying conditions often include marked distention of the gall bladder, vasculitis, diabetes mellitus, empyema, or torsion resulting in arterial occlusion. Gangrene usually predisposes to perforation of the gallbladder, but perforation may also occur in chronic cholecys titis without premonitory warning symptoms. Localized perforations are usually contained by the omentum or by adhesions produced by recurrent inflammation of the gallbladder. Bacterial superinfection of the walled-off gallbladder contents results in abscess formation. Most patients are best treated with cholecystectomy, but some seriously ill patients may be managed with cholecystostomy and drainage of the abscess. Free perforation is less common but is associated with a mor tality rate of ~30%. Such patients may experience a sudden transient relief of RUQ pain as the distended gallbladder decompresses; this is followed by signs of generalized peritonitis. FISTULA FORMATION AND GALLSTONE ILEUS Fistula formation into an adjacent organ adherent to the gallbladder wall may result from inflammation and adhesion formation. Fistulas into the duodenum are most common, followed in frequency by those involving the hepatic flexure of the colon, stomach or jejunum, abdominal wall, and renal pelvis. Clinically “silent” biliary-enteric fistulas occurring as a compli cation of acute cholecystitis have been found in up to 5% of patients undergoing cholecystectomy. Asymptomatic cholecystoenteric fistulas may sometimes be diagnosed by finding gas in the biliary tree on plain abdominal films. Barium contrast studies or endoscopy of the upper gastrointestinal tract or colon may demonstrate the fistula. Treatment in the symptomatic patient usually consists of cholecystectomy, CBD exploration, and closure of the fistulous tract. Gallstone ileus refers to mechanical intestinal obstruction result ing from the passage of a large gallstone into the bowel lumen. The

stone customarily enters the duodenum through a cholecystoenteric fistula at that level. The site of obstruction by the impacted gallstone is usually at the ileocecal valve, provided that the more

proximal small bowel is of normal caliber. Most patients do not give a his tory of either prior biliary tract symptoms or complaints suggestive of acute cholecystitis or fistula formation. Large stones, >2.5 cm in diameter, are thought to predispose to fistula formation by gradual erosion through the gallbladder fundus. Diagnostic confirmation may occasionally be found on the plain abdominal film (e.g., smallintestinal obstruction with gas in the biliary tree [pneumobilia] and a calcified, ectopic gallstone) or following an upper gastrointestinal series (cholecystoduodenal fistula with small-bowel obstruction at the ileocecal valve). Laparotomy with stone extraction (or propulsion into the colon) remains the procedure of choice to relieve obstruc tion. Evacuation of large stones within the gallbladder should also be performed. In general, the gallbladder and its attachment to the intestines should be left alone.

LIMEY (MILK OF CALCIUM) BILE AND PORCELAIN GALLBLADDER

Calcium salts in the lumen of the gallbladder in sufficient concentra tion may produce calcium precipitation and diffuse, hazy opacifica tion of bile or a layering effect on plain abdominal roentgenography. This so-called limey bile, or milk of calcium bile, is usually clinically innocuous, but cholecystectomy is often performed, especially when it occurs in a hydropic gallbladder. In the entity called porcelain gallblad der, calcium salt deposition within the wall of a chronically inflamed gallbladder may be detected on the plain abdominal film. In the past, cholecystectomy was advised in all patients with porcelain gallbladder because there was felt to be a high incidence of carcinoma of the gall bladder associated with this condition, an association challenged by a number of studies. Two patterns of gallbladder wall calcification have now been appreciated: complete intramural calcification and selective mucosal calcification. The incidence of cancer in those with selective intramural calcification is higher than those with complete mucosal wall calcification, but the risk is very small. As such, the need for chole cystectomy for porcelain gallbladder is not absolute; close surveillance in these patients is also acceptable. CHAPTER 357 Diseases of the Gallbladder and Bile Ducts TREATMENT Acute Cholecystitis MEDICAL THERAPY Although surgical intervention remains the mainstay of therapy for acute cholecystitis and its complications, a period of in-hospital stabilization may be required before cholecystectomy. Oral intake is eliminated, nasogastric suction may be indicated, extracellular volume depletion and electrolyte abnormalities are repaired, and analgesia is provided. Intravenous antibiotic therapy is indicated in patients with severe acute cholecystitis, even though bacterial superinfection of bile may not have occurred in the early stages of the inflammatory process. Antibiotic therapy is guided by the most common organisms likely to be present including E. coli, Klebsiella, Enterococcus, Enterobacter, and Streptococcus. Effective antibiot ics include piperacillin plus tazobactam, imipenem, meropenem, ceftriaxone plus metronidazole, and levofloxacin plus metronida zole (Chap. 166). Postoperative complications of wound infection, abscess formation, and sepsis are reduced in antibiotic-treated patients. SURGICAL THERAPY The optimal timing of surgical intervention in patients with acute cholecystitis depends on stabilization of the patient. The clear trend is toward earlier surgery, and this is due in part to require ments for shorter hospital stays. Urgent (emergency) cholecystec tomy or percutaneous cholecystostomy is probably appropriate in most patients in whom a complication of acute cholecystitis such as empyema, emphysematous cholecystitis, or perforation is sus pected or confirmed. Patients with uncomplicated acute cholecys titis should undergo early elective laparoscopic cholecystectomy,

ideally within 48–72 h after diagnosis. The complication rate is not increased in patients undergoing early as opposed to delayed (>6 weeks after diagnosis) cholecystectomy. Delayed surgical intervention is probably best reserved for (1) patients in whom the overall medical condition imposes an unacceptable risk for early surgery and (2) patients in whom the diagnosis of acute cho lecystitis is in doubt. Thus, early cholecystectomy (within 72 h) is the treatment of choice for most patients with acute cholecystitis. Mortality figures for emergency cholecystectomy in most centers range from 1 to 3%, whereas the mortality risk for early elective cholecystectomy is ~0.5% in patients under age 60. Of course, the operative risks increase with age-related diseases of other organ systems and with the presence of long- or short-term complica tions of gallbladder disease. Seriously ill or debilitated patients with cholecystitis may be managed with percutaneous drainage (a cholecystostomy tube), transpapillary drainage (an endoscopically placed transpapillary drainage catheter via the cystic duct), or transmural drainage (an endoscopically placed covered, lumenapposing stent). Elective cholecystectomy may then be done at a later date.

Postcholecystectomy Complications Early complications fol lowing cholecystectomy include atelectasis and other pulmonary disorders, abscess formation (often subphrenic), external or internal hemorrhage, biliary-enteric fistula, and bile leaks. Jaundice may indi cate absorption of bile from an intraabdominal collection following a biliary leak or mechanical obstruction of the CBD by retained calculi, intraductal blood clots, or extrinsic compression. Overall, cholecystectomy is a very successful operation that pro vides total or near-total relief of preoperative symptoms in 75–90% of patients. The most common cause of persistent postcholecystectomy symptoms is an overlooked symptomatic nonbiliary disorder (e.g., reflux esophagitis, peptic ulceration, pancreatitis, or—most often— irritable bowel syndrome). In a small percentage of patients, however, a disorder of the extrahepatic bile ducts may result in persistent symp tomatology. These so-called postcholecystectomy syndromes may be due to (1) biliary strictures, (2) retained biliary calculi, (3) cystic duct stump syndrome, (4) stenosis or dyskinesia of the SOD, or (5) bile salt–induced diarrhea or gastritis. PART 10 Disorders of the Gastrointestinal System CYSTIC DUCT STUMP SYNDROME In the absence of cholangiographi cally demonstrable retained stones, symptoms resembling biliary pain or cholecystitis in the postcholecystectomy patient have frequently been attributed to disease in a long (>1 cm) cystic duct remnant (cystic duct stump syndrome). Careful analysis, however, reveals that post cholecystectomy complaints are attributable to other causes in almost all patients in whom the symptom complex was originally thought to result from the existence of a long cystic duct stump. Accordingly, con siderable care should be taken to investigate the possible role of other factors in the production of postcholecystectomy symptoms before attributing them to cystic duct stump syndrome. SOD STENOSIS, SOD DYSKINESIA, AND BILIARY DYSKINESIA Symp toms of biliary colic accompanied by signs of recurrent, intermittent biliary obstruction may be produced by acalculous cholecystopathy, SOD stenosis, or SOD dyskinesia. SOD stenosis is thought to result from acute or chronic inflammation of the papilla of Vater or from glandular hyperplasia of the papillary segment. Five criteria have been used to define SOD stenosis: (1) upper abdominal pain, usually RUQ or epigastric; (2) abnormal liver tests; (3) dilatation of the CBD upon MRCP or ERCP examination; (4) delayed (>45 min) drainage of con trast material from the duct; and (5) increased basal pressure of the SOD. Treatment consists of endoscopic or surgical sphincteroplasty to ensure wide patency of the distal portions of both the bile and pancre atic ducts. The greater the number of the preceding criteria present, the greater is the likelihood that a patient does have a degree of SOD suf ficient to justify correction. The factors usually considered as indica tions for sphincterotomy

include (1) prolonged duration of symptoms, (2) lack of response to symptomatic treatment, (3) presence of severe disability, and (4) the patient's choice of sphincterotomy over surgery

(given a clear understanding on the patient's part of the risks involved in both procedures). Biliary SOD disorders are characterized by three criteria: (1) biliary pain, (2) absence of bile duct stones or other abnormalities, and (3) elevated liver enzymes or a dilated CBD, but not both. In this setting, either hepatobiliary scintigraphy or SOD manometry can support the diagnosis. Importantly, the presence of both elevated liver enzymes and a dilated CBD should raise the question of obstruction. Proposed mech anisms to account for SOD dysfunction include spasm of the sphincter, denervation sensitivity resulting in hypertonicity, and abnormalities in the sequencing or frequency rates of the sphincteric-contraction waves. When thorough evaluation has failed to demonstrate another cause for the pain and when cholangiographic and manometric criteria suggest a diagnosis of SOD dyskinesia, medical treatment with nitrites or anticholinergics to attempt pharmacologic relaxation of SOD has been proposed but not evaluated in detailed studies. Endoscopic biliary sphincterotomy (EBS) or surgical sphincterotomy may be indicated in patients who fail to respond to a 2- to 3-month trial of medical therapy, especially if SOD pressures are elevated. Approximately 45% of such patients have long-term pain relief after EBS. EBS has become the procedure of choice for removing bile duct stones and for other biliary and pancreatic problems. BILE SALT–INDUCED DIARRHEA AND GASTRITIS Postcholecystectomy patients may develop symptoms of dyspepsia, which have been attrib uted to duodenogastric reflux of bile. However, firm data linking these symptoms to bile gastritis after surgical removal of the gallbladder are lacking. Cholecystectomy induces persistent changes in gut transit, and these changes effect a noticeable modification of bowel habits. Chole cystectomy shortens gut transit time by accelerating passage of the fecal bolus through the colon with marked acceleration in the right colon, thus causing an increase in colonic bile acid output and a shift in bile acid composition toward the more diarrheagenic secondary bile acids, that is, deoxycholic acid. Diarrhea that is severe enough, that is, three or more watery movements per day, can be classified as postcholecys tectomy diarrhea, and this occurs in 5–10% of patients undergoing elective cholecystectomy. Treatment with bile acid–sequestering agents such as cholestyramine or colestipol is often effective in ameliorating troublesome diarrhea. ■ ■THE HYPERPLASTIC CHOLECYSTOSES The term hyperplastic cholecystoses is used to denote a group of dis orders of the gallbladder characterized by excessive proliferation of normal tissue components. Adenomyomatosis is characterized by a benign proliferation of gallbladder surface epithelium with glandlike formations, extramural sinuses, transverse strictures, and/or fundal nodule ("adenoma" or "adenomyoma") formation. Cholesterolosis is characterized by abnormal deposition of lipid, especially cholesteryl esters, within macrophages in the lamina propria of the gallbladder wall. In its diffuse form ("strawberry gallbladder"), the gallbladder mucosa is brick red and speckled with bright yellow flecks of lipid. The localized form shows solitary or multiple "choles terol polyps" studding the gallbladder wall. Cholesterol stones of the gallbladder are found in nearly half the cases. Cholecystectomy is only indicated in adenomyomatosis or cholesterolosis when biliary symp toms are present. The prevalence of gallbladder polyps in the adult population is 3–6% with a marked male predominance. Types of gallbladder polyps include cholesterol polyps, adenomyomas, inflammatory polyps, and adenomas (rare). No significant changes have been found over a 5-year period in asymptomatic patients with gallbladder polyps <6 mm and few changes in polyps 7–9 mm. Currently, cholecystectomy is recom mended in symptomatic patients as well as in asymptomatic patients

> 50 years whose polyps are >10 mm or associated with gallstones or polyp growth on serial ultrasonography. A recent consensus conference of the Society of Radiologists in Ultrasound recommends that patients with polyps between 10 and 14 mm and low-risk radiologic features could be monitored instead of undergoing cholecystectomy.

DISEASES OF THE BILE DUCTS ■ ■CONGENITAL ANOMALIES Biliary Atresia and Hypoplasia Atretic and hypoplastic lesions of the extrahepatic and large intrahepatic bile ducts are the most com mon biliary anomalies of clinical relevance encountered in infancy. The clinical picture is one of severe obstructive jaundice during the first month of life, with pale stools. When biliary atresia is suspected on the basis of clinical, laboratory, and imaging findings, the diagnosis is confirmed by surgical exploration and operative cholangiography. Approximately 10% of cases of biliary atresia are treatable with Roux-en-Y choledochojejunostomy, with the Kasai procedure (hepatic portoenter ostomy) being attempted in the remainder in an effort to restore some bile flow. Most patients, even those having successful biliary-enteric anastomoses, eventually develop chronic cholangitis, extensive hepatic fibrosis, and portal hypertension. Choledochal Cysts Cystic dilatation may involve the free portion of the CBD, that is, choledochal cyst, or may present as diverticulum formation in the intraduodenal segment. In the latter situation, chronic reflux of pancreatic juice into the biliary tree can produce inflamma tion and stenosis of the extrahepatic bile ducts, leading to cholangitis or biliary obstruction. Because the process may be gradual, ~50% of patients present with onset of symptoms after age 10. The diagnosis may be made by ultrasound, abdominal CT, MRCP, or cholangiog raphy. Only one-third of patients show the classic triad of abdominal pain, jaundice, and an abdominal mass. Ultrasonographic detection of a cyst separate from the gallbladder should suggest the diagnosis of choledochal cyst, which can be confirmed by demonstrating the entrance of extrahepatic bile ducts into the cyst. Surgical treatment involves excision of the “cyst” and biliary-enteric anastomosis. Patients with choledochal cysts are at increased risk for cholangiocarcinoma. Congenital Biliary Ectasia Dilatation of intrahepatic bile ducts may involve either the major intrahepatic radicles (Caroli’s disease), the inter- and intralobular ducts (congenital hepatic fibrosis), or both. In Caroli’s disease, clinical manifestations include recurrent cholangitis, abscess formation in and around the affected ducts, and, often, brown pigment gallstone formation within portions of ectatic intrahepatic biliary radicles. Ultrasound, MRCP, and CT are of great diagnostic value in demonstrating cystic dilatation of the intrahepatic bile ducts. Treatment with ongoing antibiotic therapy is usually undertaken in an effort to limit the frequency and severity of recurrent bouts of cholangitis. Progression to secondary biliary cirrhosis with portal hypertension, extrahepatic biliary obstruction, cholangiocarcinoma, or recurrent episodes of sepsis with hepatic abscess formation is common. ■ ■CHOLEDOCHOLITHIASIS Pathophysiology and Clinical Manifestations Passage of gall stones into the CBD occurs in ~10–15% of patients with cholelithiasis. The incidence of common duct stones increases with increasing age of the patient, so up to 25% of elderly patients may have calculi in the common duct at the time of cholecystectomy. Undetected duct stones are left behind in ~1–5% of cholecystectomy patients. The overwhelming majority of bile duct stones are cholesterol stones formed in the gallbladder, which then migrate into the extrahepatic biliary tree through the cystic duct. Primary calculi arising de novo in the ducts are usually brown pigment stones developing in patients with (1) hepatobiliary parasitism or chronic, recurrent cholangitis; (2) congenital anomalies of the bile ducts (especially

Caroli’s disease); (3) dilated, sclerosed, or strictured ducts; or (4) an MDR3 (ABCB4) gene defect leading to impaired biliary phospholipids secretion (low phospholipid–associated cholesterol cholelithiasis). Common duct stones may remain asymptomatic for years, may pass spontaneously into the duodenum, or (most often) may present with biliary colic or a complication. Complications • CHOLANGITIS Cholangitis may be acute or chronic, and symptoms result from inflammation, which usually is

caused by at least partial obstruction to the flow of bile. Bacteria are present on bile culture in ~75% of patients with acute cholangitis early in the symptomatic course. The characteristic presentation of acute cholangitis involves biliary pain, jaundice, and spiking fevers with chills (Charcot’s triad). Blood cultures are frequently positive, and leukocytosis is typical. Nonsuppurative acute cholangitis is most com mon and may respond relatively rapidly to supportive measures and to treatment with antibiotics. In suppurative acute cholangitis, however, the presence of pus under pressure in a completely obstructed ductal system leads to symptoms of severe toxicity—mental confusion, bac teremia, and septic shock. Response to antibiotics alone in this setting is relatively poor, multiple hepatic abscesses are often present, and the mortality rate approaches 100% unless prompt endoscopic or surgical relief of the obstruction and drainage of infected bile are carried out. Endoscopic management of bacterial cholangitis is as effective as surgi cal intervention. ERCP with endoscopic sphincterotomy is safe and the preferred initial procedure for both establishing a definitive diagnosis and providing effective therapy.

OBSTRUCTIVE JAUNDICE Gradual obstruction of the CBD over a period of weeks or months usually leads to initial manifestations of jaundice or pruritus without associated symptoms of biliary colic or cholangitis. Painless jaundice may occur in patients with choledocho lithiasis but is much more characteristic of biliary obstruction second ary to malignancy of the head of the pancreas, bile ducts, or ampulla of Vater. In patients whose obstruction is secondary to choledocholithiasis, associated chronic calculous cholecystitis is very common, and the gallbladder in this setting may be unable to distend. The absence of a palpable gallbladder in most patients with biliary obstruction from duct stones is the basis for Courvoisier’s law, that is, that the presence of a palpably enlarged gallbladder suggests that the biliary obstruction is secondary to an underlying malignancy rather than to calculous disease. Biliary obstruction causes progressive dilatation of the intra hepatic bile ducts as intrabiliary pressures rise. Hepatic bile flow is suppressed, and reabsorption and regurgitation of conjugated bilirubin into the bloodstream lead to jaundice accompanied by dark urine (bili rubinuria) and light-colored (acholic) stools. CHAPTER 357 Diseases of the Gallbladder and Bile Ducts CBD stones should be suspected in any patient with cholecystitis whose serum bilirubin level is >85.5 μmol/L (5 mg/dL). The maximum bilirubin level is seldom >256.5 μmol/L (15.0 mg/dL) in patients with choledocholithiasis unless concomitant hepatic or renal disease or another factor leading to marked hyperbilirubinemia exists. Serum bilirubin levels ≥342.0 μmol/L (20 mg/dL) should suggest the pos sibility of neoplastic obstruction. The serum alkaline phosphatase level is almost always elevated in biliary obstruction. A rise in alkaline phosphatase often precedes clinical jaundice and may be the only abnormality in routine liver function tests. There may be a two- to tenfold elevation of serum aminotransferases, especially in association with acute obstruction. Following relief of the obstructing process, serum aminotransferase elevations usually return rapidly to normal, while the serum bilirubin level may take 1–2 weeks to return to normal. The alkaline phosphatase level usually falls slowly, lagging behind the decrease in serum bilirubin. PANCREATITIS The most common associated entity

discovered in patients with nonalcoholic acute pancreatitis is biliary tract disease. Biochemical evidence of pancreatic inflammation complicates acute cholecystitis in 15% of cases and choledocholithiasis in >30%, and the common factor appears to be the passage of gallstones through the common duct. Coexisting pancreatitis should be suspected in patients with symptoms of cholecystitis who develop (1) back pain or pain to the left of the abdominal midline, (2) prolonged vomiting with para lytic ileus, or (3) a pleural effusion, especially on the left side. Surgical treatment of gallstone disease is usually associated with resolution of the pancreatitis. SECONDARY BILIARY CIRRHOSIS Secondary biliary cirrhosis may complicate prolonged or intermittent duct obstruction with or with out recurrent cholangitis. Although this complication may be seen in patients with choledocholithiasis, it is more common in cases of

prolonged obstruction from stricture. Once established, secondary bili ary cirrhosis may be progressive even after correction of the obstruct ing process, and increasingly severe hepatic cirrhosis may lead to portal hypertension, hepatic failure and death. Prolonged biliary obstruction may also be associated with clinically relevant deficiencies of the fatsoluble vitamins A, D, E, and K.

Diagnosis and Treatment The diagnosis of choledocholithiasis is made by cholangiography (Table 357-3), either preoperatively by endoscopic retrograde cholangiogram (ERC) (Fig. 357-2C) or MRCP or intraoperatively at the time of cholecystectomy. As many as 15% of patients undergoing cholecystectomy will prove to have CBD stones. When CBD stones are suspected prior to laparoscopic cholecystec tomy, preoperative ERCP with endoscopic papillotomy and stone extraction is the preferred approach. It not only provides stone clear ance but also defines the anatomy of the biliary tree in relationship to the cystic duct. CBD stones should be suspected in gallstone patients who have any of the following risk factors: (1) a history of jaundice TABLE 357-3 Diagnostic Evaluation of the Bile Ducts DIAGNOSTIC ADVANTAGES DIAGNOSTIC LIMITATIONS CONTRAINDICATIONS COMPLICATIONS COMMENT Ultrasound Rapid Simultaneous scanning of GB, liver, bile ducts, pancreas Accurate identification of dilated bile ducts Not limited by jaundice, pregnancy Guidance for fine-needle biopsy Bowel gas Massive obesity Ascites Barium Partial bile duct obstruction Poor visualization of distal CBD PART 10 Disorders of the Gastrointestinal System Computed Tomography Simultaneous scanning of GB, liver, bile ducts, pancreas Accurate identification of dilated bile ducts, masses Not limited by jaundice, gas, obesity, ascites High-resolution image Guidance for fine-needle biopsy Extreme cachexia Movement artifact Ileus Partial bile duct obstruction Magnetic Resonance Cholangiopancreatography Noninvasive modality for visualizing pancreatic and biliary ducts Has excellent sensitivity for bile duct dilatation, biliary stricture, and intraductal abnormalities Can identify pancreatic duct dilatation or stricture, pancreatic duct stenosis, and pancreas divisum Cannot offer therapeutic intervention High cost Endoscopic Retrograde Cholangiopancreatography Simultaneous pancreatography Best visualization of distal biliary tract Bile or pancreatic cytology Endoscopic sphincterotomy and stone removal Biliary manometry Gastroduodenal obstruction Roux-en-Y biliary-enteric anastomosis Percutaneous Transhepatic Cholangiogram Best when bile ducts dilated Best visualization of proximal biliary tract May be used to obtain bile cytology/culture Allows for percutaneous transhepatic drainage Nondilated or sclerosed ducts Pregnancy Uncorrectable coagulopathy Massive ascites Hepatic abscess Endoscopic Ultrasound Most sensitive method to detect ampullary stones and exclude pathology in the head of the pancreas Abbreviations: CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; GB, gallbladder; US, hepatobiliary ultrasound.

or pancreatitis, (2) abnormal tests of liver function, and (3) ultraso nographic or MRCP evidence of a dilated CBD or stones in the duct. Alternatively, if intraoperative cholangiography reveals retained stones, postoperative ERCP can be carried out. The need for preoperative ERCP is expected to decrease further as laparoscopic techniques for bile duct exploration improve. The widespread use of laparoscopic cholecystectomy and ERCP has decreased the incidence of complicated biliary tract disease and the need for choledocholithotomy and T-tube drainage of the bile ducts. EBS followed by spontaneous passage or stone extraction is the treatment of choice in the management of patients with common duct stones, especially in elderly or poor-risk patients. ■ ■TRAUMA, STRICTURES, AND HEMOBILIA Most benign strictures of the extrahepatic bile ducts result from surgi cal trauma and occur in about 1 in 500 cholecystectomies. Strictures may present with bile leak or abscess formation in the immediate post operative period or with biliary obstruction or cholangitis as long as None None Initial procedure of choice in investigating possible biliary tract obstruction Pregnancy Reaction to iodinated contrast, if used Indicated for evaluation of hepatic or pancreatic masses or for assessing for complications related to gallstones (pancreatitis) Procedure of choice in investigating possible biliary obstruction if diagnostic limitations limit US Claustrophobia Certain metals (iron) None First choice to assess for choledocholithiasis given comparable sensitivity and specificity to ERCP Pregnancy Acute pancreatitis Severe cardiopulmonary disease Pancreatitis Cholangitis, sepsis Infected pancreatic pseudocyst Perforation (rare) Hypoxemia, aspiration Cholangiogram of choice if there is believed to be a need for intervention: Diagnosed or high clinical probability of choledocholithiasis Biliary stricture requiring sampling and stenting Need for sphincterotomy such as sphincter of Oddi dysfunction Bleeding Hemobilia Bile peritonitis Bacteremia, sepsis Indicated for the drainage of obstructed and infected ducts when ERCP is contraindicated or failed Excellent for detecting choledocholithiasis

2 years or more following the inciting trauma. The diagnosis is estab lished by percutaneous or endoscopic cholangiography. Endoscopic brushing of biliary strictures may be helpful in establishing the nature of the lesion and is more accurate than bile cytology alone. When posi tive exfoliative cytology is obtained, the diagnosis of a neoplastic stric ture is established. This procedure is especially important in patients with primary sclerosing cholangitis (PSC) who are predisposed to the development of cholangiocarcinomas. Successful operative correction of non-PSC bile duct strictures by a skillful surgeon with duct-to-bowel anastomosis is usually possible, although mortality rates from surgical complications, recurrent cholangitis, or secondary biliary cirrhosis are high. Hemobilia may follow traumatic or operative injury to the liver or bile ducts, intraductal rupture of a hepatic abscess or aneurysm of the hepatic artery, biliary or hepatic tumor hemorrhage, or mechanical complications of choledocholithiasis or hepatobiliary parasitism. Diag nostic procedures such as liver biopsy, PTC, and transhepatic biliary drainage catheter placement may also be complicated by hemobilia. Patients often present with a classic triad of biliary pain, obstructive jaundice, and melena or occult blood in the stools. The diagnosis is sometimes made by cholangiographic evidence of blood clot in the biliary tree, but selective angiographic verification may be required. Although minor episodes of hemobilia may resolve without interven tion, arteriography and transcatheter embolization or surgical ligation of the bleeding vessel may be required. ■ ■EXTRINSIC COMPRESSION OF THE BILE DUCTS Partial or complete biliary obstruction may be produced by extrinsic compression of the ducts. The most common cause of this form of obstructive jaundice is carcinoma of the head of the pancreas. Biliary obstruction may also occur as a complication of either acute or chronic pancreatitis or involvement of lymph nodes in the porta

hepatis by lymphoma or metastatic carcinoma. The latter should be distinguished from cholestasis resulting from massive replacement of the liver by tumor. ■ ■HEPATOBILIARY PARASITISM Infestation of the biliary tract by adult helminths or their ova may pro duce a chronic, recurrent pyogenic cholangitis with or without multiple hepatic abscesses, ductal stones, or biliary obstruction. This condition is relatively rare but does occur in inhabitants of southern China and elsewhere in Southeast Asia. The organisms most commonly involved are trematodes or flukes, including Clonorchis sinensis, Opisthorchis viverrini or Opisthorchis felineus, and Fasciola hepatica. The biliary tract also may be involved by intraductal migration of adult Ascaris lumbricoides from the duodenum or by intrabiliary rupture of hydatid cysts of the liver produced by Echinococcus spp. The diagnosis is made by cholangiography and the presence of characteristic ova on stool examination. When obstruction is present, the treatment of choice is laparotomy under antibiotic coverage, with common duct exploration and a biliary drainage procedure. ■ ■SCLEROSING CHOLANGITIS PSC is characterized by a progressive, inflammatory, sclerosing, and obliterative process affecting the extrahepatic and/or the intrahepatic bile ducts. PSC is strongly associated with inflammatory bowel disease, especially ulcerative colitis. Immunoglobulin G4 (IgG4)–associated cholangitis is a biliary disease of unknown etiology that presents with biochemical and chol angiographic features indistinguishable from PSC, is often associated with autoimmune pancreatitis and other fibrosing conditions and is characterized by elevated serum IgG4 and infiltration of IgG4-positive plasma cells in bile ducts and liver tissue. All patients diagnosed with sclerosing cholangitis should have a serum IgG4 level checked to rule out IgG4 disease as a cause of secondary sclerosing cholangitis, particu larly if they do not have inflammatory bowel disease. Glucocorticoids are the initial treatment of choice. Relapse is common after steroid withdrawal, especially with proximal strictures. Steroid-sparing agents such as azathioprine or rituximab may be needed after relapse or for inadequate response (Chap. 359).

Patients with PSC often present with signs and symptoms of chronic or intermittent biliary obstruction: RUQ abdominal pain, pruritus, jaun dice, or acute cholangitis. Late in the course, complete biliary obstruction, secondary biliary cirrhosis, hepatic failure, and/or portal hypertension with bleeding varices may occur. The diagnosis is established by finding multifocal, diffusely distributed strictures with intervening segments of normal or dilated ducts, producing a beaded appearance on cholangi ography (Fig. 357-2D). The cholangiographic technique of choice in suspected cases is MRCP. When a diagnosis of sclerosing cholangitis has been established, causes of secondary sclerosing should be considered before reaching a diagnosis of PSC. Patients with PSC should undergo testing for associated diseases, especially inflammatory bowel disease, if that diagnosis has not already been established.

Small duct PSC is defined by the presence of chronic cholestasis and hepatic histology consistent with PSC in a patient with IBD, but with normal findings on cholangiography. Small duct PSC is found in ~5% of patients with PSC and is associated with a significantly better long-term prognosis. However, such patients may progress to classic PSC and/or end-stage liver disease with consequent necessity of liver transplantation. In patients with AIDS, cholangiopancreatography may demon strate a broad range of biliary tract changes as well as pancreatic duct obstruction and occasionally pancreatitis (Chap. 208). Further, biliary tract lesions in AIDS include infection and cholangiopancreatographic changes of sclerosing cholangitis. Changes noted include (1) diffuse involvement of intrahepatic bile ducts alone, (2) involvement of both intra- and extrahepatic bile ducts, (3) ampullary stenosis, (4) stricture of the intrapancreatic portion of the CBD, and (5) pancreatic duct involvement. Associated infectious organisms include Cryptosporid ium,

Mycobacterium avium-intracellulare, cytomegalovirus, Microspo ridia, and Isospora. ERCP sphincterotomy can provide significant pain reduction in patients with AIDS-associated papillary stenosis. CHAPTER 357 TREATMENT Primary Sclerosing Cholangitis Diseases of the Gallbladder and Bile Ducts There is no proven medical therapy for PSC. Therapy to treat pruritus associated with PSC includes cholestyramine, rifampin, fenofibrate/ bezafibrate, sertraline, and naltrexone. Antibiotics are useful when bacterial cholangitis complicates the clinical picture. Vitamin D and calcium supplementation may be used as initial therapy to help prevent the loss of bone mass frequently seen in patients with chronic cholestasis. In cases where high-grade biliary obstruction (dominant strictures) has occurred, balloon dilatation is preferred over stenting due to the higher complication rate associated with stenting including pancreatitis and cholangitis. Only rarely is sur gical intervention indicated. PSC is a progressive disease with a median survival of 12–18 years following the diagnosis, regardless of therapy. Four variables (age, serum bilirubin level, histologic stage, and splenomegaly) predict survival in patients with PSC and serve as the basis for a risk score. PSC is a common indication for liver transplantation. ■ ■FURTHER READING Baron TH et al: Interventional approaches to gallbladder disease. N Engl J Med 373:357, 2015. Hu H et al: Gut microbiota promotes cholesterol gallstone formation by modulating bile acid composition and biliary cholesterol secre tion. Nature Comm 13:252, 2022. Kamaya A et al: Management of incidentally detected gallbladder polyps: Society of Radiologists in Ultrasound consensus conference recommendations. Radiology 305:227, 2022. Lindor K et al: American College of Gastroenterology (ACG) guide lines: Primary sclerosing cholangitis. Hepatology 51:660, 2010. Ryl JK et al: Clinical features of acute acalculous cholecystitis. J Clin Gastroenterol 36:166, 2003. Strasberg S: Clinical practice. Acute calculous cholecystitis. N Engl J Med 358:2804, 2008.

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