15.25 Diseases of the gallbladder and biliary tree

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ESSENTIALS Diseases of the gallbladder and bile ducts are common, with gall- stones and their complications being most frequent. Less common are biliary strictures, usually malignant, which are caused by adeno- carcinomas of the pancreas, bile ducts, ampulla of Vater, and gallbladder. Rarely encountered are sclerosing cholangitis and a var- iety of congenital disorders. Disorders of the biliary system include gallstones, which cause biliary colic (severe right hypochondrial pain, often with nausea and vomiting) and cholecystitis by obstruction of the cystic duct, and bile duct obstruction (cholestasis), with jaun- dice, dark urine, and pale stools, itching, and sometimes constant right hypochondrial pain. Fevers and rigors may indicate bac- terial infection of the biliary tract (cholangitis), which frequently accompanies partial obstruction. Weight loss may be due to fat malabsorption but can also be caused by malignancy. Prolonged biliary obstruction leads to skin changes of increased pigmenta- tion (due to melanin) and cholesterol deposition (xanthelasma and xanthoma). Biliary cirrhosis can cause portal venous hyper- tension and liver cell failure. Disorders of the biliary system generally give rise to the bio- chemical picture of cholestasis: the serum (conjugated) bilirubin concentration may be normal or raised; serum alkaline phos- phatase, γ-glutamyl transferase, and bile acids are elevated; serum transaminases show only modest elevation. Bilirubinuria is present, with the disappearance of urobilinogen from the urine indicating complete biliary obstruction. Imaging is critical in the diagnosis of biliary disease, initially by ultrasonography, with CT and MRI in more complicated cases. However, these investigations sometimes provide insufficient anatomical detail for diagnosis or planning of treatment, and fur- ther imaging with the cholangiographic techniques of magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) are required. ERCP and PTC can be used to place biliary stents. Introduction Diseases of the gallbladder and the biliary tree are common. Symptomatic gallstones are the most frequently encountered problem and are found in the bile

duct as well as in the gallbladder. Bile duct strictures are also common and have multiple causes, both benign and malignant, posing a diagnostic and therapeutic challenge. Cholangiocarcinoma encompasses malignancy at sites throughout the biliary tree. Choledochal cysts and other congenital abnormalities are rare but important disorders. Investigation of biliary disease comprises distinct phases. First, the pathology causing the symptoms should be located. This will be either primarily in the gallbladder (usually due to gallstones) or bile ducts (often obstructive, causing cholestasis and jaundice), or both. It is important to differentiate biliary tract problems causing jaundice from parenchymal liver disease and haemolytic and other 'prehepatic' hyperbilirubinaemias; to locate the site of the problem or level of obstruction; and then to define the type of pathology. Treatment of biliary tract disease comprises treatment of the primary pathology. This may mean removal of gallstones and the gallbladder, or relief of cholestasis/obstruction by surgical, endo- scopic, or interventional radiology techniques. Cholestatic disease with normal bile ducts will often indicate the need for a liver biopsy to identify a hepatic parenchymal cause. Anatomy The biliary system comprises all structures between the biliary canaliculus and the ampulla of Vater, including the gallbladder (Fig. 15.25.1). Bile collects in the biliary canaliculi, which co- alesce into ever larger bile ducts to create the 'biliary tree'. The common hepatic duct forms at the junction of left and right hep- atic ducts that drain the two halves of the liver. The common bile duct forms below the junction of the common hepatic duct and the cystic duct and runs in the posterior aspect of the head of the pancreas, usually joining the pancreatic duct before passing out through the sphincter of Oddi at the ampulla of Vater. Anatomical variants are common and of surgical importance, particularly in 15.25 Diseases of the gallbladder and biliary tree Colin Johnson and Mark Wright

 regard to the arrangements of the ducts draining the right liver and the insertion of the cystic duct. Failure to recognize these variants can lead to duct injury and subsequent bile leak during cholecystectomy. Biliary physiology Bile is made by hepatocytes and excreted into the biliary canaliculi as they coalesce to form the biliary tree. Bile has digestive and excretory functions and its components are extensively re- cycled during enterohepatic recirculation. The principal compo- nents of bile are shown in Box 15.25.1. Bilirubin is formed from haemoglobin breakdown. Bile salts are products of cholesterol metabolism, and 95% of bile salts secreted are reabsorbed at the terminal ileum and undergo enterohepatic circulation. Those primary bile salts entering the large intestine are converted to secondary bile salts by the large intestinal microbiota. Some sec- ondary bile acids are reabsorbed in the colon, but most are ex- creted in the stool. The normal bile acid pool is about 3 to 5 g and recirculates throughout the day. Synthesis is controlled by negative feedback from bile acids reabsorbed into the portal vein. Normally bile acids are coalesced with phospholipids into micelles which contain chol- esterol in their interior and thus solubilize it. Drugs and drug metabolites are also excreted in bile. Fluid and electrolyte composition is controlled by cholangiocyte absorption during passage down the bile ducts. Bile sterility is maintained by free flow of bile, with some innate immunity. Between meals, some bile is stored in the gallbladder where it is concentrated. The gallbladder contracts and empties in response to cholecystokinin released by the presence of food (mainly fat and protein digestion products) in the duodenum. Clinical features of biliary disease Irrespective of pathology, certain features are consistent throughout the range of bile duct disorders and include the features of cholestasis (jaundice, pale stools, dark urine, pruritus), nausea and vomiting, weight loss and malabsorption, sepsis and pain (which may range from dyspepsia-type discomfort to acute biliary colic). Complications include secondary biliary cirrhosis, portal hyper- tension, progressive

liver failure, and development of malignancy (Table 15.25.1). Physical signs specific to the biliary tree include jaundice, ex- coriations of the skin, tenderness in the right upper quadrant, and palpable organomegally. The presence of a palpable gallbladder implies obstruction below the origin of the cystic duct and also indicates the absence of chronic inflammation of the gallbladder, which most commonly arises due to gallstones (Courvoisier de- scribed that in a patient with jaundice and a palpable nontender gallbladder, the diagnosis is not likely to be gallstones). Investigation of biliary disease Laboratory investigation The typical features of cholestasis include elevated conjugated hyperbilirubinaemia (with bilirubinuria), alkaline phosphatase, and γ-glutamyl transferase. Transaminases are more typically ele- vated in hepatitic conditions but may be raised in biliary sepsis. Malabsorption of vitamin K may lead to a prolonged prothrombin time. Levels of other fat-soluble vitamins will also be low. Associated sepsis will result in a raised peripheral white cell count and elevated C-reactive protein. Gallstones in the gallbladder frequently do not affect liver biochemistry. Stone CBD Cystic duct Gallbladder Pancreatic duct Common hepatic duct Intrahepatic ducts Fig. 15.25.1 MRCP revealing stones in the distal common bile duct (CBD) (white arrow). Biliary anatomy is also shown (blue arrows). Box 15.25.1 Bile composition • Water (97%) • Electrolytes • Primary bile acids: cholic and chenodeoxycholic acid • Secondary bile acids • Phospholipid (e.g. lecithin) • Cholesterol • Bilirubin • Drugs and drug metabolites • IgA
Table 15.25.1 Complications of biliary disease Complication Manifestation Cholestasis Cholangitis Malabsorption: • weight loss • vitamin deficiencies Osteoporosis Chronic obstruction Secondary biliary cirrhosis: • portal hypertension • liver failure Chronic inflammation Cholangiocarcinoma

section 15 Gastroenterological disorders 3198 Tumour markers Carbohydrate antigen 19-9 (CA19-9) is widely used as a diagnostic test in biliary malignancy but is severely limited by low sensitivity and specificity. The latter is especially affected by its elevation in ob- structive jaundice from other causes. CA125 is not useful. New bio- markers are needed. Imaging Cross-sectional imaging techniques (ultrasonography (including endoscopic ultrasonography (EUS)), CT, MRI) are used to identify obstructed bile ducts and to determine the level of obstruction and likely cause, as well as associated features such as metastases, local invasion of tumours, and complications such as portal vein throm- bosis and the development of portal hypertension. Cholangiography (magnetic resonance cholangiopancreato graphy (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC)) and cholangioscopy either via the Spyglass System or ultraslim biliary endoscopes give further information including direct visualization and biopsy of biliary epithelium (Fig. 15.25.2). EUS is used in the visualization of the extrahepatic bile ducts, hilar masses including perihilar lymph nodes, and gallbladder. EUS can also be used for tissue acquisition via fine needle aspiration as well as staging of tumours. Intraductal ultrasonography, though not widely available, is good for assessing periductal tumour extension and portal vein invasion. Endoscopic retrograde cholangiopancreatography ERCP is useful as both a diagnostic and therapeutic tool. Because of the potential complications, ideally the technique should only be used where there are therapeutic or tissue acquisition procedures to be performed. The main therapeutic indications are to decom- press obstructed biliary systems and to remove gallstones from the common bile duct. The technique is also a useful platform for direct cholangioscopy and electrohydraulic and laser lithotripsy. Brushings obtained via ERCP have variable sensitivity and spe- cificity depending on the disease present. Sensitivity is generally low for cancers, although specificity is high if detected. Modalities to improve sensitivity in cholangiocarcinoma include looking for chromosomal aneuploidy with fluorescent in situ hybridization (FISH) or digital image analysis (DIA), although at the time of writing these techniques

are not widely available even in advanced healthcare settings (see Chapter 15.24.6). Gallstones Epidemiology Gallstones are common, with incidence varying across different populations. They are found in 8% of the United Kingdom popu- lation aged over 40. The incidence increases with age, and women are more often affected than men, particularly before menopause. Obesity is an independent factor leading to an increased incidence of gallstones in younger individuals: between 19 and 45% of mor- bidly obese patients have gallstones. Although gallstones are common, most affected individuals have no symptoms. In population studies, as few as 10% of people with gallstones have current or previously reported symptoms. In people in whom gallstones are discovered incidentally, only 2 to 4% will develop symptoms over the course of a year and the removal of the gallbladder in asymptomatic people is not recommended, especially in the elderly. Pathophysiology Bile is a complex mix of cholesterol and phospholipids, which in equilibrium maintain a saturated solution of cholesterol. If choles- terol content rises (or bile salt or lecithin concentrations fall), then cholesterol will crystallize (Fig. 15.25.3). Cholesterol gallstones con- tain over 70% cholesterol and are the most common type of stone seen in Western populations. Mixed stones contain cholesterol and calcium bilirubinate, and tend to be hard, multiple, and multifa- ceted, often radiopaque. (a) (b) Fig. 15.25.2 Spyglass cholangioscopy showing the change in mucosa between an indeterminate stricture (a) and normal bile duct (b). Biopsies can be obtained under direct vision. 50 100 0 50 100 0 50 Vesicles and liquid crystals (multilamellar vesicles) Micellar phase Percentage of bile acids Solid crystals (cholesterol monohydrate) Percentage of cholesterol Percentage of phosphatidycholines 100 0 Fig. 15.25.3 Triangular solubility plot of cholesterol. Crystals will form outside of the micellar phase.

 Primary pigment stones are composed of calcium bilirubinate and are hard, black, and associated with haemolytic anaemias (including anaemia due to mechanical heart valves) and cirrhosis. The mechanism of their formation is less well understood, but probably represents a high relative concentration, allowing crystal- lization. Pigment stones in the bile duct are associated with para- sitic infestation (in Asia) and with duct obstruction. These duct stones are soft and friable. Bacterial β-glucuronidase deconjugates bilirubin, which then combines with calcium and forms calcium bilirubinate stones. Biliary sludge can also accumulate in the bile ducts and is commonly found on stents which have been in place for prolonged periods of time and also on other foreign bodies, pro- viding evidence for nucleation as a step in the pathophysiology. Consumption of a ‘Western diet’ results in cholesterol super- saturation of bile, which favours precipitation and crystal growth (Fig. 15.25.4). Oestrogen exposure (pregnancy, hormone replace- ment therapy) or other conditions with increased steroid hormone turnover increases cholesterol content in bile and therefore favours gallstone formation. Bile also contains crystal growth inhibitors which slow the increase in size of cholesterol crystals. This allows the evacuation of crystals from the gallbladder during normal emptying before progression to gallstones. In some individuals (or families), these growth inhibitors may be deficient, leading to a predisposition to gallstones. Most stones start in the gallbladder; some migrate into the common bile duct. Impaired gallbladder motility (reduced emptying) is an important component of gallstone formation. It explains the increase in gallstones after vagotomy, in diabetics (autonomic neuropathy), after prolonged treatment in an intensive therapy unit, and in people treated with somatostatin. Reduced bile salt reabsorption in terminal ileal Crohn’s disease or after re- section of the terminal ileum is the reason for the high incidence of gallstones seen in those conditions. Clinical features The clinical features of gallstones include acute presentation with biliary colic or acute cholecystitis, and less severe upper gastrointes- tinal symptoms,

sometimes nonspecific. Gallstones may also first present with complications such as obstructive jaundice or acute pancreatitis. In addition, there are many patients with chronic upper abdominal symptoms which may be attributed to the presence of gallstones. Symptoms occur when gallstones start to move from the gallbladder, either obstructing the cystic duct causing biliary colic or cholecystitis (acute or chronic), or entering the common bile duct where they cause obstructive jaundice, cholangitis, colic, or pan- creatitis (Table 15.25.2). Laparoscopic cholecystectomy should be offered to symptomatic patients. About 10 to 20% of patients with symptomatic gallbladder stones have stones in the bile ducts as well. Gallstones in the common bile duct carry a risk of severe complications and therefore should be removed wherever possible. The method of choice is ERCP, although if the patient requires cholecystectomy, some centres will offer laparoscopic bile duct clearance at the same procedure. Intraoperative cholangiography is recommended for patients with a high pretest probability of stones, such as those with dilated bile ducts on imaging. Acute presentations Biliary colic Biliary colic arises when a gallstone impacts in the neck of the gallbladder and obstructs the cystic duct. Sustained gallbladder contraction raises pressure within the gallbladder and generates the pain perceived as biliary colic. This is usually centred in the right upper quadrant or epigastrium. The pain may radiate around the lower ribs to the right lower chest at the back, or it may seem to Pathogenesis of stone formation is different for cholesterol stones, soft brown stones, and pigment stones Cholesterol stones Excess cholesterol in bile Western diet Obesity Pregnancy Oral contraceptive Reduced bile salt excretion Terminal ileal Crohn’s Ileal resection Reduced gallbladder motility Vagotomy Octreotide Prolonged fasting Reduced antinucleating factors in bile Cholesterol crystals or other debris Bacterial colonization Bilirubin deconjugation Pigment precipitation Excess bile pigment production Haemolytic anaemias Spherocytosis Growth into stones Crystal formation Pigment stones Mixed or soft stones
Fig. 15.25.4 Pathogenesis of the three types of gallstones—cholesterol, mixed/soft stones, and pigment stones.

section 15 Gastroenterological disorders 3200 pass directly through from the front to back. Occasionally, the pos- terior radiation is to the lower pole of the scapula and rarely, the pain may be felt on the left. These radiations are explained by the origin of the gallbladder from lower thoracic segments and the transmis- sion of visceral sensation through the splanchnic nerves to the lower thoracic spinal cord. The pain may be severe enough to require par- enteral opioids, and it resolves when the gallbladder contraction re- solves and the stone disimpacts. Biliary colic has a slower periodicity than colic from other organs. Biliary colic usually rises and falls over a period of 30 min to 2 h and may last up to 6 h, in contrast to small-bowel colic, ureteric colic, or colonic colic which peaks every 20 or 30 s to a few minutes. Biliary colic often arises after a large meal. There is little evidence to sup- port the commonly held belief that the consumption of fatty food is particularly likely to stimulate an attack. Patients often describe retching or vomiting with the pain, and a substantial minority report being woken by the pain. Acute cholecystitis Acute cholecystitis arises when a stone remains impacted in the neck of the gallbladder (Fig. 15.25.5). Increased pressure in the gallbladder leads to mucosal injury by sequential ischaemia, chem- ical irritation by bile salts, and eventually bacterial infection. The symptoms may initially resemble biliary colic, but the pain persists for more than 12 h. The ensuing inflammation leads to tender- ness over the gallbladder (which is often minimal in biliary colic). Inflammation affecting the diaphragm may cause referred pain over the acromion, and an inflammatory mass may be palpable in the right upper quadrant. The patient will have systemic signs of infec- tion (fever, leucocytosis) and will be anorexic. Complications in- clude the following: • Perforation—in severe cases the inflammatory

process may lead to necrosis of the gallbladder wall, allowing perforation and biliary peritonitis. As a result of transmural inflammation, the omentum may be adherent around the gallbladder and the resulting perfor- ation can be localized into a pericholecystic abscess. If the perfor- ation occurs on the hepatic aspect of the gallbladder, the abscess may penetrate into the liver. • Empyema—in the absence of a perforation, cholecystitis may resolve by drainage of bile through the cystic duct, but often the impacted stone prevents this. The gallbladder remains in- flamed, perhaps encased in a protective fold of omentum. The gallbladder content becomes purulent, due to bacterial proliferation and by the exudation of neutrophils. This is effect- ively an abscess contained within the lumen of the gallbladder and is termed an empyema. • Mucocele—occasionally, an impacted stone will isolate the gallbladder content from the rest of the biliary tree in the ab- sence of bacterial infection. The mucosa, although inflamed, continues to absorb water from bile, and secrete mucus: this scenario leaves the gallbladder containing clear or bile-stained mucus. The patient with a mucocele will often recall a severe episode of biliary pain, consistent with cholecystitis. Symptoms may partly resolve, but there is usually ongoing right upper quadrant pain and tenderness, with symptoms of sufficient se- verity to cause repeated admissions to hospital until cholecyst- ectomy is performed. • Mirizzi's syndrome—occasionally, a patient will become jaun- diced as a result of stones in the gallbladder in the absence of common duct stones. This situation arises when a stone im- pacted in the neck of the gallbladder causes sufficient inflamma- tion around the gallbladder and adjacent bile duct to compress the duct (Fig. 15.25.6). Chronic presentation Biliary dyspepsia and chronic cholecystitis Patients with vague, mild, and nonspecific upper abdominal symp- toms who are found to have gallstones are a diagnostic challenge. As noted previously, approximately 90% of gallstones are asymptom- atic, but huge numbers of patients suffer dyspeptic symptoms. One survey in the United Kingdom found that 40% of people suffered upper abdominal dyspepsia, and that 25% of these had consulted their general practitioner for these symptoms in the preceding 6 months. There was no difference in symptoms between patients Table 15.25.2 Complications of gallstones Gallbladder stones Biliary colic Acute cholecystitis leading to: • abscess formation • gallbladder necrosis • perforation Chronic cholecystitis Common bile duct stones Acute cholangitis Acute pancreatitis Obstructive jaundice Other Fistulation to other hollow organs Gallstone ileus Perforation Stone impacted in cystic duct Bile duct Bile injures ischaemic mucosa, leading to inflammation of wall Mucosa suffers ischaemic injury Stones in gallbladder Tension in wall impairs blood flow Fig. 15.25.5 Pathogenesis of acute cholecystitis.

 with gallstones and those that were gallstone free, so it is difficult to attribute these 'vague' symptoms to the presence of stones. There is little evidence that so-called biliary dyspepsia is associated with the presence of stones. Many surveys of patients in the United Kingdom who have had cholecystectomy find that 20 to 30% of patients con- tinue to suffer dyspeptic symptoms postoperatively. Symptoms other than typical biliary colic are often not related to gallstones, and there is no evidence to link gallstones with epigas- tric discomfort, belching, nausea, or idiosyncratic food intolerance. Heartburn and reflux symptoms may be more common in patients with gallstones but are not directly related to the presence of gall- stones and may be exacerbated by cholecystectomy. If cholecystec- tomy is done in patients with these symptoms (whether or not they have typical biliary colic or acute cholecystitis), then these symp- toms will still be present after operation. The differential diagnosis of a patient with gallstones and upper abdominal symptoms includes peptic ulcer, nonulcer dyspepsia, antroduodenal dysmotility, and irritable bowel syndrome. Complications Acute

cholangitis Symptoms and signs include pain, fever, and jaundice. The right upper quadrant is tender. The patient may be jaundiced with a tachycardia and hypotension. Investigation reflects these findings. Ultrasonography may show dilated bile ducts. Acute cholangitis not rapidly responding to antibiotics or with signs of shock requires urgent biliary decompression with sphincterotomy, and stenting with or without stone extraction. If ERCP is not possible or available, then PTC or cholecystostomy are options. Acute open surgery should be avoided in critically ill patients. Gallstone pancreatitis Gallstone pancreatitis occurs when a gallstone lodges in the common channel or compresses the septum between the distal biliary and pancreatic ducts. This causes increased pressure in the pancreatic duct and reflux of digestive enzymes into the gland. Acute gallstone pancreatitis associated with biliary obstruction or cholangitis war- rants urgent ERCP, sphincterotomy, and stone extraction. Optimal timing is unclear. Studies have shown benefit with reduced mortality and complications if ERCP is performed within 72 h where there is concurrent cholangitis or biliary obstruction but have not been designed to answer whether earlier (within 24 h) ERCP would be better. Most clinicians experienced in this situation will aim for ERCP as soon as logistically possible and once the patient is stable enough to undergo the procedure safely. After complications have settled, cholecystectomy should be con- sidered, although the sphincterotomy will have prevented further episodes of pancreatitis and removal of the gallbladder is only re- quired if the gallstones are symptomatic. Cholecystoduodenal fistula This is a rare and potentially serious complication of gallstone dis- ease, which can be recognized as pneumobilia on a plain abdom- inal X-ray or ultrasonography. This is thought to result from erosion (usually) into the duodenum by a gallstone in the gallbladder. Rarely such fistulas may involve the colon or the stomach. The stone will either be passed naturally or may cause small bowel obstruction. With improved laparoscopic techniques, laparoscopic stapling of the cholecystoduodenal fistula and cholecystectomy is sometimes possible. Gallstone ileus This more commonly affects elderly women and may be the first presentation of gallstone disease. It accounts for 1 to 4% of all cases of mechanical intestinal obstruction, but up to 25% of cases in pa- tients over 65 years of age. The bowel obstruction can be managed relatively easily with an open or laparoscopic ileotomy. Because there is usually dense fibrosis around the gallbladder and the fistula, cholecystectomy may be difficult and it is best to defer surgery on the gallbladder until the patient has recovered from the emergency presentation and treatment. Diagnosis Ultrasonography is commonly the first investigation for biliary symptoms because of its wide availability and ease of use, and it is highly sensitive and specific for diagnosis of gallbladder stones (>95% in good hands). The presence of dilated ducts gives evidence of obstruction, and ultrasonography is around 30 to 70% sensitive and 90% specific for common bile duct stones depending on symp- toms and blood tests (pretest probability). A normal examination does not, therefore, rule them out, and where suspicion is high, other tests should be used. MRCP or EUS are the usual next steps depending on avail- ability, with sensitivities of around 95% when pretest probability is moderate to high. Each has its advantages and disadvantages. MRCP has no endoscopic or sedation risks, is useful where there is altered anatomy, and allows later independent review of images (Fig. 15.25.7). EUS can often be used where MRCP is not possible due to the presence of a pacemaker/implanted cardiac defibril- lator, mechanical heart valves, intracranial metal clips, morbid obesity, or severe claustrophobia. CT also has a role as it is often used when the cause of pain or sepsis is uncertain and is useful for differential diagnosis. Obstructing disease of the bile ducts is most commonly due to gallstones (Fig. 15.25.8), but a wide range of stricturing disorders both benign and malignant must also be considered. Large stone in cystic duct causes inflammation and fibrosis around the bile duct, compressing it Bile duct Cystic duct Stone Fig. 15.25.6 Mechanism of biliary obstruction in Mirizzi’s

syndrome: there are no stones in the bile duct.

section 15 Gastroenterological disorders 3202 Management Laparoscopic cholecystectomy With the introduction of laparoscopic cholecystectomy, a shift oc- curred in the balance between benefit of operation and the asso- ciated risks and discomfort. Very few patients are now treated by alternative techniques. Laparoscopic surgery allows most patients to be treated as a day case, with return to normal activities within 2 weeks. Complication rates are low, the most serious being injury to the bowel or a bile duct, which occur in less than 1% of cases. About half of those with persistent bile leak after surgery arise from injury to a duct within the gallbladder bed, which usually closes with simple drainage or drainage combined with duct decompression by sphincterotomy and stent. Cholecystectomy relieves symptoms of biliary colic and acute cholecystitis, but other nonspecific symptoms often persist after operation. Common bile duct stones Optimal elective management of common bile duct stones is by ERCP. If the gallbladder is in situ this may be either before or soon after laparoscopic cholecystectomy. ERCP during cholecyst- ectomy may be cost-effective and convenient for patients but is rarely practical. Laparoscopic bile duct exploration with a flexible choledocoscope is another option and is preferred to open duct ex- ploration because of a lower rate of trauma to the duct, increased chance of primary duct closure, and less use of T tubes with a lower risk of biliary strictures in the future. Preoperative imaging or intraoperative cholangiography is recommended for patients with a high pretest probability of stones (principally those with dilated ducts on ultrasound). Endoscopic removal of gallstones ERCP is an evolving technique for the removal of stones and em- ploys increasingly complex therapeutic options. The basic principles of treating stone disease are as follows: (1) gain and then increase access to the common bile duct by cutting (sphincterotomy) (Fig. 15.25.9) with or without stretching (sphincteroplasty) the
Fig. 15.25.7 MRCP revealing stones in the distal common bile
duct (arrow). CBD stones Fig. 15.25.8 ERCP cholangiogram demonstrating stones (seen as filling defects) in the common bile duct (CBD). Fig. 15.25.9 Balloon sphincteroplasty to facilitate removal of large common bile duct stones. Variable sizes of balloon are available, but in general it is wise not to exceed the diameter of the common bile duct above in order to reduce the risk of perforation.

15.25 Diseases of the gallbladder and biliary tree 3203 sphincter of Oddi; (2) obtain a cholangiogram to identify the number and size of the stones; (3) where necessary, reduce the size of stones in order to facilitate their removal, either by crushing (Fig. 15.25.10) or applying direct energy to them; (4) remove the stones by dragging or grasping them from the duct (Fig. 15.25.11); (5) where removal is not possible, ensure biliary drainage is secured with appropriate stenting. Other methods of treating gallstones Extracorporeal shock wave lithotripsy, oral bile acid therapy, and contact dissolution of gallstones are seldom used in the era of lap- aroscopic surgery and ERCP. These treatments lost their appeal when laparoscopic surgery became available because they are slow, requiring many months, and cumbersome, with repeated imaging needed to monitor progress. They also leave the gallbladder in situ and the patient is thus at risk of recurrence of gallstones. By contrast, laparoscopic cholecystectomy and ERCP are day-case treatments that remove the gallbladder, permanently relieve symptoms in most patients, and have a very low complication rate in skilled hands. Direct cholangioscopy-facilitated electrohydraulic lithotripsy (EHL) or laser lithotripsy Under direct vision at cholangioscopy, energy can be delivered directly to large troublesome stones to cause fragmentation. EHL uses a high-voltage spark to create rapid thermal expansion of fluid and a subsequent hydraulic pressure wave. Laser litho- tripsy (Fig.

15.25.12) uses pulsed energy to create the same effect. Following fragmentation, stones can be removed by traditional methods including balloons and baskets. Open surgery Despite all of these techniques, endoscopic therapy occasionally fails and a surgical solution may be sought. Where the gallbladder is still present, this may involve laparoscopic bile duct explor- ation at the time of cholecystectomy. Where the gallbladder has Fig. 15.25.10 Clearance of common bile duct stones with a balloon trawl (black arrow). Note previous cholecystectomy clips (white arrows).
Fig. 15.25.11 Crushing lithotripter for stone removal. (a) (b) (c) (d) Fig. 15.25.12 Laser lithotripsy of difficult common bile duct stones. Gallstones are targeted and fragmented with high-energy lasers under direct vision using cholangioscopy, thereby allowing extraction with baskets and balloons. Panels (a) and (b), before lithotripsy; panels (c) and (d), after lithotripsy.

section 15 Gastroenterological disorders 3204 previously been removed, open duct exploration may be required. In rare cases where stones cannot be removed (usually after mul- tiple attempts), hepaticojejunostomy may be required because of the long-term risk of secondary biliary cirrhosis and recurrent cholangitis. Laparoscopic-assisted ERCP in altered surgical anatomy Increasing use of bariatric surgery means that it may not be possible to access the bile duct from the duodenum via the mouth. Nevertheless, gallstone disease is very common after bariatric sur- gery and stones in both the gallbladder and common bile duct represent a difficult problem. This may be overcome by a com- bined approach of the surgical team using laparoscopic techniques to access the stomach remnant and hence duodenum via the transperitoneal route. The ERCP can then be carried out as normal. Alternatives to cholecystectomy In some very frail, elderly persons, those with significant comorbidi ties, and those with advanced cirrhosis, cholecystectomy presents too great a risk. In these situations, ERCP is often undertaken as definitive treatment of bile duct stones, or to prevent recurrence of pancreatitis, with biliary sphincterotomy and ductal clearance. Where stone extraction is not possible, biliary stenting is often used, usually with placement of double-pigtail stents to ensure that drainage is maintained, although cholangitis is still a common com- plication. With this approach, regular stent changes every 3 months are associated with much lower rates of cholangitis and mortality than with an ‘on-demand’ stent change practice. Complications of management of gallstones Complications of ERCP ERCP is an invasive surgical procedure and must not be under- taken lightly. The most common complication is pancreatitis, which overall occurs in 2 to 3% of cases, even in expert hands. Risk factors for pancreatitis include multiple cannulation attempts, multiple cannulations, and injection of contrast into the pancre- atic duct. Perforation may occur in any part of the upper gastro- intestinal tract in relation to passage of the endoscope but is most commonly related to sphincterotomy and/or precut papillotomy. Guide-wire perforation also occurs. When recognized and treated by keeping the patient nil by mouth and administering antibiotics, most cases of guide-wire perforation settle without the need for surgery. Sepsis and bleeding also occur. Rectal indomethacin (100 mg) has been shown to halve the rate of post-ERCP pancreatitis. In difficult cases where access to the pan- creatic duct inadvertently occurs, the placement of a pancreatic duct stent can further reduce incidence of pancreatitis. Postcholecystectomy syndromes This is a poorly defined group of symptoms which includes some specific conditions (e.g. bile salt-related diarrhoea and gastro- oesophageal reflux) that result from cholecystectomy. However, many patients given this label in fact have some other condition which has not been affected by the removal of the gallbladder. It is self-evident that, if cholecystectomy has been performed in patients with symptoms unrelated to the gallbladder (whether or not they have typical biliary colic or acute cholecystitis), then these symp- toms will still be present after operation. Most patients with symptoms after cholecystectomy have nonulcer dyspepsia. If the

symptoms are troublesome, investigations should aim to exclude other pathology. Liver function and liver ultrason- ography will exclude parenchymal disease; upper gastrointestinal endoscopy may be helpful to look for peptic ulceration and gastro- oesophageal reflux, and colonoscopy or CT colonography may be considered if there are lower gastrointestinal symptoms. Serology for Helicobacter pylori and for endomysial antibody to exclude coeliac disease may be helpful. Any treatable condition should be managed appropriately. Gastro-oesophageal reflux Reflux symptoms occur or are increased after cholecystectomy in at least 10% of patients as a result of disruption of the feedback mech- anism that controls release of cholecystokinin (CCK). After chole- cystectomy, postprandial and fasting CCK levels in the blood are raised. In addition to causing gallbladder contraction and relaxation of the sphincter of Oddi, CCK also causes relaxation of the gastric cardia and a fall in lower oesophageal sphincter pressure, which facilitates reflux. In most patients these symptoms settle within 12 months, but some will require temporary or long-term proton pump inhibitors. Bile salt diarrhoea After cholecystectomy, between 1 and 5% of patients report in- creased bowel frequency. Stools may be softer than previously but are rarely loose. This occurs in the absence of identifiable bowel path- ology and is caused by disruption of circulation of bile salts so that more enter the colon where they are irritant to the mucosa. Normal enterohepatic circulation of bile salts requires almost complete re- absorption in the terminal ileum. The absence of the gallbladder re- duces the capacitance of the biliary system so that bile production during fasting cannot be accommodated. Some bile enters the duo- denum as a result. In addition, the raised fasting levels of CCK after cholecystectomy may reduce sphincter pressure, and also favour re- lease of bile in the absence of food. The higher concentration of bile salts reaching the colon in the absence of luminal residue which usu- ally adsorbs some of the bile salts leads to mucosal irritation in the caecum. This impairs water absorption leading to passage of softer, more frequent stools. The diagnosis can be confirmed with a SeHCAT test. Radiolabelled bile salt is ingested and 1 week later the amount of retained isotope indicates normal or impaired bile salt absorption. Mild symptoms may require no treatment other than explanation of the cause. More severe symptoms often respond to reduction of dietary fibre and/or antidiarrhoeal medication (codeine or loperamide). Cholestyramine which binds intraluminal bile salts is effective, but many patients find it unpalatable and prefer other measures or adjust to their new bowel habit. There is often improvement in symptoms during the months after operation, but if symptoms are still present after 1 year they are likely to be permanent. Sphincter of Oddi dysfunction Sphincter of Oddi dysfunction is an increasingly recognized clinical syndrome comprising right upper quadrant pain with or without ab- normal liver biochemistry and with or without dilated bile ducts.

 The gold standard for diagnosis is biliary manometry. An alternative strategy involves injection of botulinum toxin into the sphincter and clinical assessment of symptoms. When the diagnosis is confirmed, formal sphincterotomy can be performed, often resulting in long- lasting relief of pain. Risk of pancreatitis is very high in this group and the patient should be counselled to this effect. This syndrome can be subclassified into types 1, 2, and 3 by the Milwaukee system (Table 15.25.3) with the best results reported in type 1 patients who have abnormal liver function associated with di- lated ducts during an attack of pain. See Chapter 15.26.1 for further discussion of sphincter of Oddi dysfunction in the context of acute pancreatitis, including the Rome III diagnostic criteria. Indeterminate biliary strictures Biliary strictures are a diagnostic challenge because of their wide differential diagnosis, common lack of unequivocal features on imaging, and the need to obtain tissue, which can be difficult to get. The wide range of possible pathologies (Table 15.25.4) have very dif- ferent outcomes and

management. Pragmatic approaches which assume a cancer diagnosis run the risk of high-morbidity surgery or inappropriate metal stenting in benign cases. Watchful waiting risks missing cancers when they are potentially curable. This is a common problem in hepatobiliary medicine and the diagnostic algorithms are con- tinuously evolving: a suggested approach to diagnosis is shown in Fig. 15.25.13. With the increasing recognition of IgG4 disease in these difficult cases, a trial of steroids for 4 to 6 weeks may be jus- tified on the grounds that major surgery can be avoided in some. The disadvantage to this approach is that time may be lost where a tumour becomes impossible to resect, and infective complications might be more common. Obstructive jaundice due to biliary tract disease Regardless of the type of obstruction, effective biliary decompres- sion (either endoscopically or percutaneously) is of benefit to pa- tients. This improves symptoms of cholestasis, improves nutrition, and, in some cases, improves survival. In gallstone-related disease, removal of the offending stone is usually sufficient to relieve obstruc- tion. In stricturing disease, stenting is usually required. In malignant disease, drainage allows palliative chemotherapy or neoadjuvant chemotherapy to be given. For palliation, stenting has less morbidity than surgical bypass. At least a third of the liver needs to be drained for decompres- sion to be effective. The best mode of decompression therefore de- pends on the location of the obstruction. Distal disease involving the common bile duct or common hepatic duct can be treated with a single stent, which is best placed endoscopically. Between 75 and 80% of hilar strictures can be successfully decompressed with a single stent, but strictures at the hilum may require multiple stents, which can sometimes be achieved at ERCP although more often PTC is required. For malignant disease, there is increasing use of self-expanding metal stents which give longer palliation and long- term patency (Fig. 15.25.14, Fig. 15.25.15). In malignant disease where strictures are present, there are sev- eral novel endoscopic approaches to therapy aimed at maintaining longer patency of the stent. These include photodynamic therapy, Table 15.25.3 Milwaukee Classification for sphincter of Oddi dysfunction 1 Biliary pain, abnormal liver function tests (LFTs), dilated bile ducts 2 Biliary pain, abnormal LFTs or dilated ducts 3 Biliary pain
Table 15.25.4 Aetiology of biliary strictures with key clinical features Pathology Clinical features Cholangiocarcinoma Imaging, cytology/FISH/histology PSC with dominant stricture Imaging, negative cytology/histology Autoimmune (IgG4) cholangitis Imaging, serology, IgG4 cytology/histology Involvement of other organs Mirrizi’s syndrome History compatible with cholecystitis Postoperative History of gallbladder/bile duct surgery, often with associated complications. History of liver transplant, type of anastomosis Stone-related stricture History, stones on imaging Trauma History Post radiation History Ischaemic/post-transarterial chemoembolization History Vasculitis History, serology Infection, e.g. HIV, tuberculosis, worms History, serology Extraluminal compression: • Pancreatic cancer • Chronic pancreatitis • Lymph node metastases • Lymphoma • Pancreatic cysts • Retroperitoneal disease History, imaging Indeterminate stricture History, examination, CT/MRI/bloods Associated mass? Yes EUS/percutaneous biopsy No ERCP +/-Spyglass +cytology/fish/dia/biopsy Diagnosis? No Yes Definitive treatment Re-evaluate ? Trial of steroids Fig. 15.25.13 Algorithm for investigation of indeterminate biliary strictures.

 radiofrequency ablation, and brachytherapy. All of these tech- niques need to be combined with self-expanding metal stents for optimal results. Specific causes of biliary strictures Primary sclerosing cholangitis Primary sclerosing cholangitis (PSC) is discussed in Chapter 15.23.4. Dominant strictures of the extrahepatic bile ducts are defined as a stenosis of 1.5 mm or less in the common bile duct or 1 mm or less in the hepatic

duct. The presence of a dominant stricture in patients with PSC is a common clinical problem and one which carries a worse overall prognosis (especially in the setting of inflammatory bowel disease). They may be present at presentation, when evalu- ation is as for an indeterminate stricture. If a dominant stricture develops in a patient with known PSC, it is crucial to exclude a cholangiocarcinoma. Symptomatic strictures warrant endoscopic therapy with ERCP which should also include the acquisition of brush cytology with or without FISH/DIA where available. Biliary sphincterotomy and bal- loon dilatation of stricture under antibiotic cover appears to improve survival and reduce the risk of cholangiocarcinoma developing sub- sequently. The role of placing biliary stents is unclear; there is no evidence of benefit for plastic stents, although fully covered self- expanding metal stents may help by slowly dilating the stricture. IgG4-related sclerosing cholangitis IgG4-related disease is a multisystem disorder, first described in 2003 as autoimmune pancreatitis. It is now recognized to affect many organs with several clinical phenotypes. IgG4 disease of the bile duct is increasingly recognized as an important cause of inde- terminate strictures. Its diagnosis is important as it has a specific treatment, and diagnosis avoids major surgery or problems related to ‘pragmatic’ metal stent placement. Tissue acquisition with direct cholangioscopy and immunostaining of biopsies for IgG4 facilitates diagnosis. The HISORt criteria (histology, imaging, serology, other organ involvement, and response to therapy) (Table 15.25.5) en- compass a number of clinical features to assist with diagnosis. There is a male preponderance and it mainly occurs in the fifth and sixth decades of life. The natural history is not yet established and the differential diagnosis includes cholangiocarcinoma, pancre- atic carcinoma, and primary and secondary sclerosing cholangitis depending on the location of the strictures. Pathogenesis is poorly understood but differs from many other autoimmune diseases in that there appears to be T helper (Th)-2 and regulatory T-cell drivers as opposed to the more normal Th1/Th17 phenotype. Treatment is typically with steroids, although there are no high- quality trials at the time of writing: 30 to 40mg of prednisolone is typ- ically given for 4 weeks, then tapering 5 mg every 2 weeks. Response to steroids helps make the diagnosis, with CT/ERCP changes seen within 4 to 6 weeks. A nonresponse may indicate the wrong diag- nosis but may also result from burnt-out disease or a more fibrotic phenotype. Relapse is common and, if it occurs, can be retreated with steroids followed by azathioprine. (a) (b) Fig. 15.25.14 (a) Hilar stricture with almost complete occlusion of the hepatic duct going into the right hepatic duct and with no filling of left ducts. (b) Placement of an uncovered self-expanding metal stent with decompression of right-sided biliary ducts. (a) (b) Fig. 15.25.15 Biliary stricture just below the hilum before (a) and after (b) placement of an uncovered self-expanding metal stent. The stent is traversing the ampulla and extends up into the intrahepatic ducts. Bile in the side branches will drain through the mesh of the stent. Table 15.25.5 HISORt diagnostic criteria for IgG4-related sclerosing cholangitis Histology of
the bile duct Lymphoplasmacytic sclerosing cholangitis Lymphoplasmacytic infiltrate with >104 IgG4 positive cells/high powered field Storiform fibrosis Obliterative phlebitis Imaging of the bile duct Axial imaging reveals 1 or more strictures (intrahepatic, proximal extrahepatic, or pancreatic bile duct with thickening and inflammation) Fleeting or migratory strictures Serology IgG4 in serum (can be normal in up to 20%, can be elevated in other conditions, e.g. 9% of PSC) Other organ involvement Pancreas, kidney, salivary glands (sclerosing sialadenitis), lungs, pericardium, meninges, pituitary and encompasses retroperitoneal fibrosis, Reidel’s thyroiditis and Mikulicz’s disease Response to steroid therapy Normalization of liver enzymes or resolution of stricture

15.25 Diseases of the gallbladder and biliary tree 3207 Secondary sclerosing cholangitis Secondary sclerosing cholangitis develops in response to an identifi- able process involving biliary obstruction, including chronic obstruc- tion of any cause, stones, parasites, surgical trauma of biliary tree, ischaemic cholangitis (e.g. after transarterial chemoembolization), and recurrent pancreatitis. Cholangiocarcinoma Cholangiocarcinoma is discussed in Chapter 15.24.6. Gallbladder cancer Except when discovered incidentally after laparoscopic cholecystec- tomy, when the cancer is often confined to the gallbladder wall and metastatic spread is minimal, gallbladder cancer often presents at an advanced stage with direct invasion into bile duct, liver, duodenum, or colon, and spread to local nodes, or liver metastases. It is often asymptomatic until obstructive symptoms arise. On imaging, gallbladder cancer appears as irregular thickening of the gallbladder wall or an intraluminal mass with enhancement after intravenous contrast. In patients with symptoms of biliary dis- ease, ultrasonography is often the first test used. This may show the mass and will detect dilated ducts. However, cross-sectional imaging using CT or MRI is best, obtaining good views of masses, dilated ducts and enlarged lymph nodes. MRI allows excellent views of hepatobiliary anatomy and when combined with an MRCP shows ductal involvement, demonstrates hilar vascular involvement, and is also good for viewing liver metastases. MRI is not as good as CT for identifying distant metastases, and in clinical practice both are commonly used. Treatment is by surgical resection if possible, with extensive lymphadenectomy to clear the hepatoduodenal ligament and resec- tion of the adjacent liver segments (4 and 5). Some surgeons advocate clearance of bile duct and lymph nodes from the hepatoduodenal ligament, to leave only skeletonized hepatic arteries and portal vein. When gallbladder cancer is discovered incidentally after laparo- scopic cholecystectomy, the patient should be referred urgently to a hepatobiliary surgeon for consideration of early repeat operation to resect segments 4 and 5 of the liver with lymph node clearance. This policy greatly improves the chance of cure, and the BILCAP trial has also shown survival benefit for adjuvant capecitabine after surgical resection of gallbladder cancer Congenital disorders of the bile ducts Choledochal cysts These are rare congenital abnormalities of the bile ducts, most commonly diagnosed in children and most prevalent in east Asian populations. They may be found incidentally or as a result of their complications which include malignant transformation, cholangitis, pancreatitis, and cholelithiasis. Adult patients typically present with biliary or pancreatic symptoms such as abdominal pain or jaundice. The cysts represent increased risk for stone disease during biliary stasis, and for biliary malignancy. Anomalous pancreaticobiliary duct union outside of the duo- denal wall is present in 30 to 70%, with a long common channel TYPE 1 TYPE 3 TYPE 4 TYPE 5 TYPE 2 Fig. 15.25.16 Classification of choledochal cysts.

section 15 Gastroenterological disorders 3208 (>15 mm from the ampulla). This allows reflux of pancreatic juice into the biliary tree. It is thought that the enzymes may then con- tribute to cyst formation with inflammation of the cyst walls and hyperplasia. Intrahepatic cysts are associated with portal fibrosis and bile duct proliferation as well. Cysts are classified into five types depending on location and shape (Fig. 15.25.16, Table 15.25.6). Cholangiography is the most sensitive way to define ductal anatomy. Associations include double common bile duct, sclerosing cholangitis, hepatic cysts, and annular pancreas. Types 1 and 4 are most associated with cholangiocarcinoma (Fig. 15.25.17). Management of type 1 and 4 cysts is by excision, which depending on cyst involvement may include hepatic or Whipple’s resections. Types 2 and 3 are usually left alone. Type 5 (Caroli’s disease) may require transplantation due to recurrent sepsis and progressive liver failure. FURTHER READING Johnson CD (2003). Arris & Gale lecture. Regulation and responses of gallbladder muscle activity in health and disease. Ann R Coll Surg Engl, 85, 297–305. National Institute for Health and Care Excellence (NICE) (2014). Gallstone disease: diagnosis and

management of cholelithiasis, chole- cystitis and choledocholithiasis. NICE, London. Soares KC, et al. (2014). Choledochal cysts: presentation, clinical dif- ferentiation, and management. J Am Coll Surg, 219, 1167–80. Table 15.25.6 Types of choledochal cyst Type Comment 1 90% of cases. Cystic lesion of the bile duct. May present as a dilated common bile duct . Lacks biliary mucosa 2 Diverticulum of common bile duct 3 Intraduodenal (lined by duodenal mucosa) 4 Intra- and extrahepatic duct involvement 5 Caroli’s disease. Intrahepatic saccular dilatations, communicating with bile ducts. Can be associated with extensive fibrosis Fig. 15.25.17 Type 1 choledochal cyst with anomalous pancreaticobiliary duct union (white arrow) complicated by cholangiocarcinoma (blue arrow).

Revision #1
Created 2026-01-22 16:38:52 UTC by Omar Ayman
Updated 2026-01-22 16:38:52 UTC by Omar Ayman