Choledocholithiasis

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Epidemiology

The presence of gallstones in the common bile duct, termed choledocholithiasis, is a significant cause of surgical disease that affects millions of people worldwide. The incidence cannot be precisely determined, because it is not always symptomatic. However, symptomatic cholelithasis affects between 10% and 15% of the adult population in developed countries [1], and up to 25% of these patients are also found to have choledocholithiasis at the time of cholecystectomy [2]. The prevalence of choledocholithiasis has been rising with life expectancy. Its global burden is therefore increasing, with annual medical expenses exceeding $2.2 billion USD [2]. Morbidity and mortality from choledocholithiasis result from the many associated complications. These are classified as acute or chronic, either of which can be life-threatening.

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Pathophysiology

The pathogenesis of choledocholithiasis is dependent on the type of stone. Primary bile duct stones form in the bile ducts, while secondary bile duct stones form in the gallbladder and are subsequently released into the biliary system.

Primary bile duct stones are usually brown or black pigment stones. These form from bacterial infection: hydrolysis of glucuronic acid from bilirubin occurs by bacterial beta-glucuronidase. This results in a decreased solubility of deconjugated bilirubin and the formation of stones. Brown pigment stones are, consequently, composed of calcium salts of unconjugated bilirubin, deconjugated bile acids, and varying amounts of cholesterol and saturated long-chain fatty acids.

Secondary bile duct stones are of mixed composition but are composed largely of cholesterol in the majority of cases. The minority of secondary bile duct stones are pigmented, also referred to as black pigment stones, and are composed primarily of bilirubin due to hemolytic disease.

Risk factors for choledocholithiasis include male sex (ratio of 1.2:0.9) and increasing age, with the average age of diagnosis being 67 years [2]. In addition, conditions leading to bile stasis, inflammation, and infection predispose to stone formation. Examples include biliary anatomic abnormalities, primary and secondary sclerosing cholangitis, parasites, or cholecystectomy at a young age, leading to common bile duct dilation.

C. V. R. Brown et al. (eds.), *Emergency General Surgery*, https://doi.org/10.1007/978-3-319-96286-3_11

Dietary risk factors, such as malnutrition, and genetic risk factors have also been implicated.

Ethnic differences have also been observed. Secondary bile duct stones are more common in Native Americans and Hispanic populations than in Caucasians and are less common in African Americans. In addition, secondary bile duct stones predominate in Western countries and Japan, while primary bile stones occur more frequently in Southeast Asia.

Diagnosis

The first step in securing a diagnosis of choledocholithiasis is performing an appropriate history and physical examination. A proper history should take into consideration the known risk factors for biliary tract disease. Though cholelithiasis is more common in females, choledocholithiasis is more prevalent in males. Specific risk factors for choledocholithiasis include patients with known choledochal cysts and those with recurrent biliary tract inflammation (e.g., primary sclerosing cholangitis) or infection (which occurs most frequently among East Asian populations).

Choledocholithiasis should be suspected in patients with right upper quadrant pain, nausea, emesis, and signs or symptoms of cholestasis, such as acholic stools, dark urine, pruritus, jaundice, and scleral icterus. However, jaundice and scleral icterus are not generally observed until the serum bilirubin has risen to approximately 2.5 mg/dL. Therefore, these presenting symptoms are less common than may be expected. Patients with choledocholithiasis typically report an antecedent history of biliary colic, characterized by postprandial right upper quadrant pain that is precipitated by large or fatty meals. Less commonly, choledocholithiasis may be asymptomatic and found incidentally on imaging.

On physical examination, a general inspection of the patient can be informative. An obese body habitus is more suspicious for biliary tract disease. The eyes and skin should be inspected for icterus and jaundice, respectively. Vital signs are essential for differentiating choledocholithiasis from ascending cholangitis; fever and tachycardia favor the latter. Examination of the abdomen in choledocholithiasis typically reveals localized right upper quadrant or epigastric tenderness. Murphy's sign, the classic examination finding in acute cholecystitis, is generally absent in choledocholithiasis. If a patient's history and physical examination raise concern for choledocholithiasis, the clinician should proceed to laboratory investigations.

Laboratory Values

The laboratory findings most suggestive of choledocholithiasis include elevated cholestatic markers: hyperbilirubinemia, elevated alkaline phosphatase (ALP), and elevated gamma-glutamyl transpeptidase (GGT). A mild leukocytosis and transaminitis may also occur; however, a markedly elevated white blood cell count with a clinical picture suggestive of choledocholithiasis raises concern for the diagnosis of ascending cholangitis. Similarly, more than a moderate rise in transaminases (>800) is suspicious for alternate diagnoses, including viral hepatitis.

Bilirubin is typically elevated to a mean of 1.5–1.9 mg/dL [3, 4]. Bilirubin may be more useful than ALP in predicting choledocholithiasis, because bilirubin typically rises within hours of biliary obstruction. ALP, on the other hand, takes longer to rise because its synthesis from the biliary epithelium must be induced by the presence of cholestasis. ALP has also been shown to be less sensitive (57% vs. 69%) and less specific (86% vs. 88%) than bilirubin in the diagnosis of choledocholithiasis [5]. However, an elevated ALP is a more common finding than an elevated bilirubin among patients with choledocholithiasis (80% vs 60%) [6].

Non-cholestatic sources of ALP also exist, including bone and placenta. For this reason, measuring serum GGT can be useful to confirm a cholestatic source when a patient's ALP is elevated. A recently published study demonstrated that a GGT $\geq$ 300 units/L on admission was one of the most predictive factors of choledocholithiasis unlikely to resolve spontaneously [7].

In practice, transaminases, bilirubin, and ALP are routinely obtained at admission for all patients with suspected biliary tract disease. GGT, conversely, is ordered more selectively, in cases where there is clinical suspicion for extra-biliary sources of elevated ALP. All laboratory values are then used in conjunction with the clinical presentation to determine the need for imaging and to guide further decision-making.

Imaging

A variety of imaging modalities are available to assess the bile ducts for choledocholithiasis. Common options are transabdominal ultrasonography and various forms of cholangiography, including endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), and intraoperative cholangiogram (IOC). Less frequently utilized modalities include CT cholangiography (CTC), endoscopic ultrasonography (EUS), intraductal ultrasonography (IDUS), and percutaneous transhepatic cholangiography (PTC).

Transabdominal ultrasound (US) is an excellent modality for assessment of the biliary tree and should be the first investigation performed in all patients with suspected biliary tract pathology. It is relatively inexpensive, widely available, and noninvasive. Its main disadvantage is operator dependency. US is especially useful in suspected choledocholithiasis, as visualization of a stone in the common bile duct (CBD) on ultrasound is the strongest predictor of choledocholithiasis confirmed on ERCP or surgically [5, 8, 9], with a specificity of 1.00 [5] (Fig. 11.1). Patients with a stone in the CBD demonstrated on US have such a high probability of having a final diagnosis of choledocholithiasis that no confirmatory test is required, and the patient can proceed directly to stone extraction [8]. A dilated (>6 mm) CBD on US is also a strong predictor of choledocholithiasis [8]. However, it is not considered diagnostic. For this reason, an additional confirmatory test in these patients may be indicated prior to proceeding with invasive attempts at stone extraction.

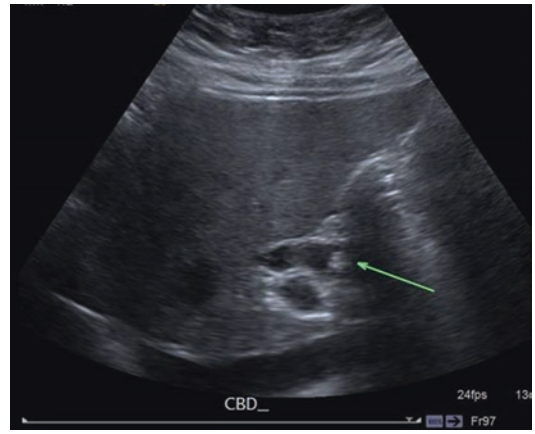

Fig. 11.1 Ultrasound of the right upper quadrant with evidence of choledocholithiasis (arrow)

In contrast to the high specificity of US at detecting stones in the CBD, the sensitivity of US for choledocholithiasis is less than 60% in most studies [10]. Therefore, patients with clinical or laboratory evidence of biliary stasis but nondiagnostic ultrasonography benefit from confirmatory testing.

Confirmatory testing is accomplished with cholangiography, which is available in several modalities. ERCP has long been regarded as the gold standard for diagnosis of choledocholithiasis; however, it is also the most invasive form of cholangiography. It is performed with a side-viewing duodenoscope, with cannulation of the ampulla and injection of contrast into the biliary and pancreatic ducts. It is a very useful technique because it allows for stone extraction and therefore can be therapeutic in addition to diagnostic. However, its high-risk profile, significant-associated costs, and requirement for skilled personnel have relegated the primary role of ERCP to stone extraction if alternative diagnostic tests are available.

MRCP is a favored diagnostic modality by many centers because it is noninvasive and it does not require a physician to be present. MRCP is an MRI performed of enhanced T2-weighted sequences, emphasizing stationary fluid in the biliary and pancreatic ducts. It therefore does not require administration of contrast material. MRCP has a sensitivity of 83–92% and specific-

ity of 91–97% [11–13], making it a very useful confirmatory test. Its main weakness is its inability to reliably detect small (<6 mm) stones [8]. It is also not available at all centers, and has several relative and absolute contraindications. Patients with surgical clips or air in the biliary system from bilioenteric anastomoses may have inconclusive results, and patients with implanted metal, pacemakers, or claustrophobia may not be able to safely undergo the examination.

IOC at the time of laparoscopic cholecystectomy is another viable option to interrogate the CBD for stones. IOC has a sensitivity of 97% and specificity of 95–100% [11, 14], making it an excellent test to rule in or out suspected choledocholithiasis. Major society guidelines recommend either IOC or MRCP as the diagnostic test of choice for patients with intermediate risk of choledocholithiasis [8]. In most centers, resource and personnel availability are the deciding factors between these two modalities. However, the available evidence suggests that IOC is more sensitive, specific, and cost-effective than MRCP [11]. Barriers to its use include added operative time (approximately 10–20 min) and the requirement by some states for a fluoroscopy license to perform IOC. In addition, the management of stones discovered at IOC can often be challenging.

Less common modalities for diagnosis of choledocholithiasis include CTC, EUS, IDUS, and PTC. CTC involves the administration of either oral or IV contrast agents and is a helical CT scan with 3D reconstructions. It has been used successfully in Europe for many years. Despite good results, it has not gained widespread use in North America, largely because of concerns about the safety of the contrast agents. The contrast agents have been associated with nausea and vomiting, hepatorenal toxicity, hypotension, cardiopulmonary symptoms, severe skin reactions, anaphylaxis, and, rarely, death. An additional limitation of CTC is that insufficient opacification of the bile ducts may occur in cases of hyperbilirubinemia or liver insufficiency. Finally, it exposes patients to a high level of radiation. CTC does have the benefits of operator independence, low level of invasiveness, and low technical failure rate. It may be especially useful in locations that lack an MRI scanner.

EUS has a sensitivity of 93–97% and specificity of 94–95% for diagnosing choledocholithiasis [10, 15]. It is performed transgastrically or transduodenally. Its advantage over other modalities is its ability to reliably detect very small stones. However, it is invasive, requires skilled personnel, and is not widely available, all of which are factors limiting its routine use. It is most frequently utilized to evaluate idiopathic pancreatitis for occult stones or to evaluate common bile duct dilatation prior to possible ERCP.

Similar to EUS, IDUS is an invasive form of ultrasonography that can be performed at the time of ERCP. It is performed with a thin probe, inserted through the working channel of a duodenoscope. IDUS is a relatively new technology and is not available at many centers. It is the most sensitive form of ultrasonography for detection of small stones and sludge. IDUS has been successfully utilized after ERCP to confirm duct clearance and prevent subsequent recurrence of choledocholithiasis.

Similar to ERCP, PTC is a more invasive form of cholangiography which allows for possible stone extraction. The liver is punctured percutaneously under fluoroscopic guidance, and contrast is injected into the intrahepatic biliary ductal system. PTC is more successful in patients with dilated biliary ducts. Like ERCP, PTC is used primarily for stone extraction and not for diagnosis of choledocholithiasis, unless other less invasive methods have failed or are unavailable. Additionally, ERCP has been demonstrated to be superior to PTC in terms of complication and success rates, so PTC is generally reserved for situations when ERCP is unsuccessful or not possible, such as in altered biliary anatomy.

Although national society guidelines recommend that the choice of confirmatory test be made according to both cost and local expertise [8], in-depth analyses of cost-effectiveness of these strategies are limited. Therefore, the decision-making in most centers is guided by resource availability. Ultimately, patients with choledocholithiasis demonstrated on any of the above

modalities require stone extraction by one of several methods.

Management

After the diagnosis of choledocholithiasis has been secured, there are a number of management decisions that follow. These include the administration of antibiotics, the method of stone retrieval, and the timing of cholecystectomy.

Antibiotics for Choledocholithiasis

The use of routine antibiotics in choledocholithiasis as prophylaxis against cholangitis is not well studied and remains controversial. Antibiotics are clearly indicated for patients with cholangitis. Most clinicians would also consider initiating antibiotics for patients with choledocholithiasis who present with fever or leukocytosis, despite not meeting all diagnostic criteria for cholangitis. At our center, we administer antibiotics to patients with choledocholithiasis for prophylaxis against cholangitis if the patient is febrile (≥38.5 C) or has a marked leukocytosis (generally ≥15,000). We also consider antibiotic proxphylaxis for patients with certain high-risk comorbidities, including diabetes mellitus and immunosuppression.

In selecting an appropriate antibiotic, the clinician must factor in both the typical causative agents as well as the local antibiogram. Blood cultures should be sent on all patients with concern for cholangitis. Biliary samples taken during ERCP or CBDE should also be collected. A positive biliary culture can be expected in most patients with cholangitis (93% in one study), but blood cultures are infrequently positive (26%) [16]. The most common agent isolated from biliary cultures is *E. coli*, followed by *Enterococcus* species, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [16]. Appropriate regimens include a third-generation cephalosporin, penicillin derivative, or fluoroquinolone, with no need for routine anaerobic coverage unless the patient has had a previous bilioenteric anastomosis [17]. At our institution, we commonly use ceftriaxone as the empiric agent of choice and subsequently tailor therapy according to culture results.

Method of Stone Retrieval

The options for stone retrieval include ERCP, either preoperatively or postoperatively, PTC, and CBD exploration (CBDE), performed either open or laparoscopically. Practically, the method selected must take into account patient factors, local expertise and equipment, cost, and the available evidence on successful stone clearance rates for each method.

ERCP

ERCP is considered by most to be the standard approach to stone retrieval for cases of choledocholithiasis. In ERCP, an experienced endoscopist passes a side-viewing endoscope through the mouth and upper GI tract until the second stage of the duodenum is encountered. The ampulla of Vater is cannulated through the sphincter of Oddi in order to gain access to the biliary tree. A cholangiogram is then obtained, and the presence of choledocholithiasis is established or confirmed, depending on the extent of the pre-procedure investigations. Next, deep cannulation of the biliary tree and attempts at stone removal are performed, using baskets and/or extraction balloons to sweep stones antegrade into the duodenum. After stone removal, a sphincterotomy is typically performed, using electrocautery to cut through the sphincter of Oddi to widen it and facilitate passage of stones.

Due to concern for long-term complications after sphincterotomy, papillary balloon dilation of the sphincter was developed as an alternative to sphincterotomy. It is a common practice in Asia but is infrequently used in North America [18]. Available high-quality evidence comparing sphincterotomy to balloon dilation is limited, although one RCT and a subsequent study

with 6.5 years of follow-up data showed significantly more post-ERCP pancreatitis but fewer long-term complications among patients who underwent balloon dilation as compared to sphincterotomy [19, 20]. In the absence of further evidence in support of balloon dilation, most consider sphincterotomy to be the standard approach. If stone extraction cannot be accomplished before sphincterotomy or balloon dilation, management of the sphincter can precede stone extraction and may facilitate stone removal.

Laser lithotripsy for choledocholithiasis involves the application of a laser to a stone in the biliary tree, which aids in its removal by fragmenting it. It can be accomplished during a standard ERCP through the endoscope, and it is an especially helpful adjunct for extracting large stones after removal attempts with conventional methods have failed. It is successful in approximately 90% of cases [21]. However, high costs limit the widespread use of this technology.

The success rates of ERCP depend upon the size of the stone, with success rates of roughly 85% in stones <2 cm and 60% in stones >2 cm [22]. ERCP also requires an experienced endoscopist and the availability of fluoroscopy. Additionally, the use of ERCP is limited to patients with appropriate anatomy. Patients who have undergone previous gastric bypass with either Billroth II or Roux-en-Y reconstruction typically cannot undergo conventional ERCP. After Billroth II, ERCP can be attempted through the mouth but requires the endoscopist to pass the scope through the gastrojejunostomy and retrograde up into the duodenum, which is technically challenging and can be a prohibitively long route for the endoscope. In patients with a previous Roux-en-Y gastric bypass, ERCP cannot be performed through the mouth because of the distance that must be traversed through the reconstructed GI tract to access the duodenum. These patients can undergo laparoscopic-assisted ERCP, in which a surgeon accesses the gastric remnant laparoscopically and passes the endoscope into it, from which point a relatively conventional ERCP can ensue. Post-gastric bypass patients frequently require operative management of their choledocholithiasis due to their anatomic reconfigurations.

Although ERCP is a preferred method of stone extraction, it carries well-described risks which must be considered. There is 5% risk of post-ERCP pancreatitis and a 2% risk of bleeding after a sphincterotomy [23]. There is also a risk of duodenal perforation, either from the endoscopy or sphincterotomy. Post-ERCP perforation may require operative intervention and can be fatal in rare cases. Patients must therefore be appropriately consented for the procedure.

ERCP is typically performed preoperatively and followed by cholecystectomy at the same hospital admission. Preoperative timing was historically preferred due to concerns about cystic duct stump leak induced by postoperative ERCP [24]. More recent evidence suggests that postoperative ERCP is safe and does not increase the rate of cystic duct stump leaks [25]; therefore, laparoscopic cholecystectomy followed by postoperative ERCP is an option for choledocholithiasis. However, there is also evidence that this approach increases hospital length of stay, costs, and healthcare utilization [25], making it potentially not the preferred management strategy. Instead, postoperative ERCP may be better reserved for instances of retained CBD stones.

Percutaneous Transhepatic Cholangiography (PTC)

As discussed previously, PTC is both diagnostic and therapeutic in the management of choledocholithiasis. After percutaneous transhepatic cannulation of the biliary tree, many of the methods used for stone extraction parallel the techniques used in ERCP. These include balloons, baskets, and laser lithotripsy via the PTC catheter. Although PTC can play an important role in the diagnosis, treatment, and palliation of biliary tract malignancies, its use in choledocholithiasis is generally reserved for stone extraction among patients with anatomy that is unfavorable for extraction with ERCP.

CBDE

When other methods of stone retrieval have failed or are impossible, CBDE is indicated for stone extraction. CBDE can be performed open or laparoscopically. While an open CBDE should be within the skill set of any general surgeon, laparoscopic CBDE may require more advanced training in laparoscopy and/or hepatobiliary surgery.

Laparoscopic CBDE is an attractive management strategy because it can be performed concurrently with laparoscopic cholecystectomy, thereby allowing a one-stage procedure. Prior to performing a CBDE, the surgeon performs laparoscopic dissection of Calot's triangle, identifies the cystic duct, and performs an intraoperative cholangiogram through the cystic duct. If choledocholithiasis is confirmed, the surgeon may flush the duct with normal saline. Often, intravenous glucagon is administered to relax the sphincter of Oddi. If the stone does not clear from the duct with flushing, the surgeon can proceed with a laparoscopic bile duct exploration, convert to an open procedure for common bile duct exploration, or finish the laparoscopic cholecystectomy and proceed with postoperative ERCP, as described above. An important disadvantage of the last option is that unsuccessful postoperative ERCP would then mandate a second operation for common bile duct exploration.

Laparoscopic CBDE can be accomplished by one of two routes: transcystic or transductal. In the transcystic approach, access to the cystic duct is achieved during the intraoperative cholangiogram. Stone extraction is then accomplished by the use of balloons, Fogarty catheters, baskets, or forceps, with or without the aid of a choledochoscope. The transcystic approach is preferred over the transductal approach when feasible, as it allows for shorter operative time and hospital length of stay [26]. However, it is most successful for relatively small stones (<10 mm) that are located distal to the cystic duct/common hepatic duct confluence. If the transductal approach is required, the CBD is identified laparoscopically as described above, and stone extraction proceeds through a choledochotomy. Both transcystic and transductal laparoscopic CBDE carry a success rate of greater than 90% [27–29].

An open CBDE is typically performed through a right subcostal incision, but can also be approached through an upper midline laparotomy. A Kocher maneuver is performed, and the hepatoduodenal ligament is identified. The peritoneum overlying the portal triad is opened carefully, and the CBD is then distinguished from the proper hepatic artery and the portal vein based on anatomic position (Fig. 11.2a). The CBD is located anteriorly and on the patient's right within the hepatoduodenal ligament, while the proper hepatic artery is located more medially, and the portal vein is posterior. If the anatomy is unclear, a seeker needle can be used prior to suture placement or choledochotomy, with the aspiration of bile confirming the identity of the CBD.

Once the CBD has been identified, a longitudinal choledochotomy, approximately 1.5–2 cm in length, is planned distally on the CBD near the duodenum. Stay sutures are placed at the apices of the planned choledochotomy (Fig. 11.2b). An 11-blade scalpel is then used to begin the choledochotomy, which is completed with Potts scissors (Fig. 11.2c–d). Once the lumen of the CBD is accessed, a variety of methods can be employed for stone extraction. The surgeon should begin by flushing normal saline into the bile duct lumen to see if this will allow for stone passage. If it does not, balloon dilators, Fogarty catheters, baskets, forceps, or a choledochoscope can be used to facilitate stone removal (Fig. 11.2e). In cases of impacted stones that cannot be retrieved, a choledochoduodenostomy or Roux-en-Y choledochojejunostomy can be created proximal to the site of impaction to allow for biliary drainage.

After stone extraction, a completion cholangiogram is obtained to confirm biliary tract clearance, and the choledochotomy is closed. Although choledochotomies were classically closed over a T-tube, the contemporary management does not include routine T-tube placement. A recent meta-analysis showed that T-tube placement after laparoscopic CBDE had no effect on the rates of postoperative biliary complications or the need for re-intervention, and therefore the authors argue against the routine use of T-tubes [30].

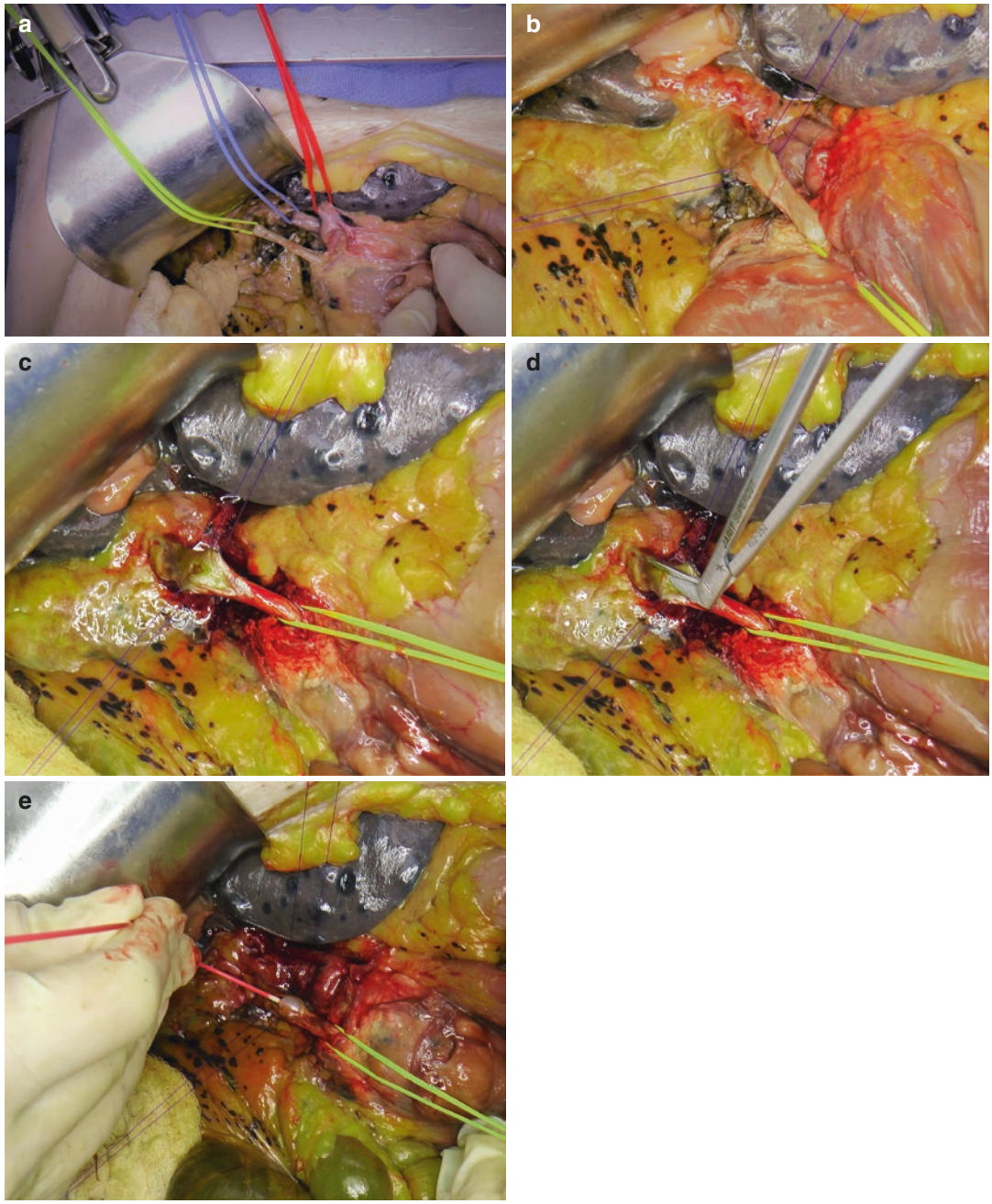

Fig. 11.2 (a–e) Common Bile Duct Exploration. (**a**) After Kocherization, the structures in the portal triad are identified based on anatomical location. Yellow, common bile duct. Red, proper hepatic artery. Blue, portal vein. (**b**) Stay sutures are placed at the 3 o'clock and 9 o'clock positions around the planned choledochotomy. (**c**–**d**) An 11-blade is used to begin the longitudinal choledochotomy between stay sutures. Potts scissors are used to complete it. (**e**) A Fogarty catheter can be used to attempt stone retrieval through the choledochotomy

Another recent meta-analysis showed that primary duct closure after laparoscopic CBDE resulted in fewer complications, shorter duration of surgery, lower hospital costs, and a shorter postoperative length of stay [31]. The evidence for the role of T-tube placement after open CBDE parallels the literature after laparoscopic CBDE. A Cochrane review of six randomized studies (n = 359) showed that T-tube placement after open CBDE resulted in longer operative time and hospital length of stay without any improvement in other clinical outcomes [32]. These authors advocate for future study on the long-term effects of T-tube drainage prior to dismissing the routine use of T-tubes entirely; however in the interim, T-tube drainage should be restricted to RCTs.

After closure of the choledochotomy, the final step in CBDE is to perform a cholecystectomy.

Timing of Cholecystectomy

There are multiple studies, including one large (n = 266), multicenter, randomized controlled trial [33], confirming the utility of cholecystectomy at the index admission for complicated biliary tract disease after duct clearance. Although these studies principally evaluated same-admission cholecystectomy after gallstone pancreatitis, the literature is often extrapolated to the patient population with choledocholithiasis due to similarities in pathophysiology. These well-designed studies have demonstrated that index admission cholecystectomy is more cost-effective than delayed elective cholecystectomy [34] and prevents readmission for gallstone-related complications [33, 34]. It is our practice to perform same-admission cholecystectomy for patients with choledocholithiasis after clearing the ducts.

Summary

There are many management options and sequences which can be used to clear the bile ducts of stones and remove the gallbladder. All methods are relatively effective, with ≥85% rates of successful stone extraction for most stones. Local expertise often dictates the preferred management strategy. Although cost must be considered, available cost data comparing strategies for stone retrieval are limited. One recent study showed that one-stage management with laparoscopic cholecystectomy and transcystic laparoscopic CBDE was the most cost-effective strategy when compared to ERCP and laparoscopic cholecystectomy or laparoscopic cholecystectomy and transductal laparoscopic CBDE [35]. This took into consideration successful CBD clearance, number of procedures required, hospital length of stay, and overall costs. However, the expertise required to effectively and safely perform laparoscopic CBDE significantly limits the widespread implementation of this as the preferred method of stone clearance.

In patients with conventional anatomy (i.e., without previous gastric bypass), the approach preferred in most centers [36], including our own, is for patients with diagnosed choledocholithiasis to undergo preoperative ERCP. If the completion cholangiogram demonstrates duct clearance, it is followed by laparoscopic cholecystectomy at the same hospital admission. We reserve CBDE for patients in whom ERCP is not technically possible. Although postoperative ERCP appears to be a safe alternative, we typically reserve this approach for patients in whom a retained CBD stone is discovered postoperatively.

Complications

Important complications of choledocholithiasis can be either acute, such as ascending cholangitis and gallstone pancreatitis (GSP), or chronic, including biliary stricture formation, intrahepatic stones, recurrent pyogenic cholangitis, hepatic abscesses, secondary biliary cirrhosis, and bile duct carcinomas.

Acute

Ascending Cholangitis

Ascending cholangitis, which can range from mild to life-threatening, is defined as infection of the biliary tree resulting from cholestasis. The clinical presentation of ascending cholangitis is classically described as Charcot's triad: fever, jaundice, and right upper quadrant pain. This constellation of symptoms is observed in up to 75% of patients with ascending cholangitis [37]. Although choledocholithiasis also frequently presents with pain and jaundice, fever is not typically present unless ascending cholangitis is developing. Reynold's pentad describes the presence of all three components of Charcot's triad, and also mental status changes and hypotension, suggesting life-threatening cholangitis.

Although both Charcot's triad and Reynolds' pentad are highly specific for ascending cholangitis, neither is sufficiently sensitive for screening for the diagnosis. The 2013 Tokyo Guidelines therefore set forth criteria for diagnosing ascending cholangitis [38]. The diagnosis of ascending cholangitis should be suspected if fever, shaking chills, or laboratory evidence of inflammation is present, in addition to evidence of cholestasis or imaging suggestive of the diagnosis. Cholestasis is demonstrated by the clinical presence of jaundice or with elevated bilirubin or ALP. Suggestive imaging is qualified in the guidelines as biliary dilatation or the demonstration of a precipitating factor, such as a gallstone or stricture. If fever, shaking chills, or laboratory evidence of inflammation is present in addition to both cholestasis and suggestive imaging, the diagnosis of cholangitis is said to be definite [38].

Management of cholangitis consists of fluid resuscitation, antibiotic therapy, close clinical monitoring, and urgent decompression of the biliary tree.

Gallstone Pancreatitis (GSP)

Gallstones are the most common cause of pancreatitis worldwide, accounting for nearly half of all cases [39]. The pathophysiology of GSP is incompletely understood but involves the transient passage of stones from the CBD. The proposed mechanisms by which choledocholithiasis induces pancreatitis include bile reflux from partial occlusion of the ampulla and edema of the pancreatic duct induced by the transient presence of the stone.

Gallstone pancreatitis is managed initially with fluid resuscitation, close clinical monitoring, and a brief period of bowel rest. Patients with mild pancreatitis only require bowel rest until the inflammation begins to subside, typically not lasting more than 24–48 h. The resolution is heralded by a decrease in epigastric pain and the downtrending of the white blood cell count or serum lipase. More severe cases of pancreatitis may result in ileus and intolerance of oral nutrition. Enteral nutrition should be initiated in these patients through an nasogastric or nasojejunal feeding tube, with parenteral nutrition reserved only for those patients who cannot tolerate enteral feeding.

Clinicians should maintain a high suspicion for concomitant choledocholithiasis in patients with gallstone pancreatitis, so laboratory biomarkers should be followed serially. Also, once the pancreatitis has resolved, patients should be managed with cholecystectomy at the index hospital admission [40]. This is recommended to prevent recurrence, and the associated morbidity and mortality. For patients who cannot tolerate cholecystectomy, ERCP with sphincterotomy is a suitable alternative [40].

Chronic

Biliary Strictures

Biliary strictures result from the inflammatory response of bile ducts to choledocholithiasis, characterized by collagen deposition, fibrosis, and narrowing of the lumen of the ducts. When strictures become symptomatic, patients present with features of biliary stasis, similar to the typical acute presentation of choledocholithiasis. Although MRCP is an excellent imaging modality for biliary strictures, ERCP has the additional diagnostic advantage of allowing for endoscopic

brushings to exclude malignancy, and also the therapeutic advantage of endoscopic interventions, such as dilation of the stricture or placement of a biliary stent. However, symptomatic biliary strictures, even if found to be benign, often require surgery with resection and reconstruction.

Intrahepatic Stones

Intrahepatic stones are found in the hepatic bile ducts. Similar to common bile duct stones, these stones can be primary or secondary. In general, intrahepatic stones will be primary in populations at risk for primary choledocholithiasis and secondary in populations at risk for secondary choledocholithiasis. Intrahepatic stones are also noted to occur at a higher incidence in malnutrition and low socioeconomic class. Intrahepatic stones can be challenging to manage because there is a high rate of recurrence. ERCP and PTC can be used for stone extraction; however, surgical resection of the involved lobe may be required due to high rates of recurrence with stone extraction alone [41].

Recurrent Pyogenic Cholangitis

Recurrent pyogenic cholangitis can develop in patients with intrahepatic stones, wherein the presence of intrahepatic stones causes repeated cycles of inflammation and infection in the intrahepatic bile ducts. It is marked by biliary stricturing and obstruction, leading to recurrent episodes of bacterial cholangitis. It is especially prevalent among people of Southeastern Asian origin. In the acute phases of the disease, when cholangitis is present, the management principles are the same as in ascending cholangitis, with emphasis on fluid resuscitation, early antibiotic therapy, and prompt biliary drainage. Over the long term, these patients require either repeated stone extraction using PTC or ERCP or surgical resection of the involved lobe with reconstruction by hepaticojejunostomy.

Hepatic Abscesses

Infections in the biliary tree related to choledocholithiasis can spread to the liver hematogenously, via the portal vein or hepatic artery, or directly through the biliary system. Both routes of spread can result in pyogenic hepatic abscesses. Patients present with right upper quadrant pain and infectious signs and symptoms. US and CT are the most useful diagnostic modalities and can also be used for image-guided drainage, which in conjunction with antibiotic therapy is the recommended treatment for this complication.

Secondary Biliary Cirrhosis and Portal Hypertension

Secondary biliary cirrhosis develops when repeated episodes of infection and inflammation from biliary stasis and strictures of the bile ducts cause injury to the liver over time, which can progress to cirrhosis. This is an unusual complication of choledocholithiasis but does rarely occur. Secondary biliary cirrhosis carries the same risks and complications as other types of cirrhosis, including the development of portal hypertension. Prompt treatment of choledocholithiasis is recommended to prevent this severe complication. Once cirrhosis occurs, early involvement of a hepatologist is prudent, because liver transplantation may ultimately be necessary.

Bile Duct Carcinomas

Hepatolithiasis, recurrent pyogenic cholangitis, and (to a lesser degree) choledocholithiasis are established risk factors for bile duct carcinomas, likely due to chronic inflammation and repeated mechanical manipulation. Although these patients do not necessarily warrant routine screening for cholangiocarcinoma, a retrospective cohort study of patients with hepatolithiasis showed that age >40, weight loss, elevated ALP (mean 426 u/L), and CEA > 4.2 ng/mL were associated with an increased risk of cholangiocarcinoma [42].

Conclusions

Choledocholithiasis is a common condition whose diagnosis is secured using a combination of clinical history, physical examination, laboratory values, and imaging investigations. US is the initial imaging modality of choice. Patients with US findings that include a stone visualized within the CBD do not require

confirmatory imaging and should go directly for stone extraction. Patients with US findings suggestive of choledocholithiasis or laboratory values concerning for cholestasis should undergo MRCP or IOC before attempts at stone extraction. Options for stone extraction include ERCP, PTC, and laparoscopic or open common bile duct exploration, the choice of which depends upon local expertise and cost considerations. Stone extraction should precede same-admission cholecystectomy when feasible. When available, a one-step procedure consisting of laparoscopic transcystic common bile duct exploration and laparoscopic cholecystectomy appears to be the most cost-efficient approach to choledocholithiasis; however, this option may not be widely available.

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