Diagnostic and Therapeutic Endoscopy of Biliary Diseases

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The therapeutic approach to biliary diseases has undergone a paradigm shift over the past decade toward minimally invasive endoscopic interventions. This paper reviews the advances and different diagnostic and therapeutic endoscopic approaches to common biliary diseases including choledocholithiasis, benign and malignant biliary strictures and bile leaks.

INTRODUCTION

With the introduction of innovative endoscopic implements and options allowing for unprecedented access to the biliary tree, the therapeutic approach to biliary diseases has undergone a significant paradigm shift over the past decade toward minimally invasive endoscopic interventions. The days where biliary diseases were exclusively managed surgically are long gone, and much has changed since the first reported biliary sphincterotomies in 1974. The recent developments in peroral cholangioscopy and new modalities of anchoring high resolution nasogastric scopes in the bile duct offer the opportunity of direct visualization of the bile duct lumen, which allows for not only better identification of the underlying disease process but also for targeting of biopsies and directed lithotripsy. Other modalities that add to the growing world of biliary luminal imaging include endoscopic ultrasound (EUS) and intraductal ultrasound, which enable the endoscopist to assess extrabiliary disorders. EUS-assisted fine needle aspiration (FNA) tissue sampling and immediate preliminary histopathologic analysis also assist in immediate decision making and therapeutics. Other recent advances include cutting-edge molecular imaging technology that allows the endoscopist to differentiate between benign and malignant features, thus guiding decision making in real time.

COMMON BILE DUCT STONES

Over 98% of biliary disorders are linked to gallstones. Stones are found in the common bile duct (CBD) in up to 18% of patients with symptomatic cholelithiasis (1). The vast majority of gallstones are cholesterol-rich, form in the gallbladder and gain access to the CBD via the cystic duct. De novo CBD stone formation is also well described and is more common in patients of Asian descent. These primary duct stones typically have a higher bilirubin and a lower cholesterol content and biliary stasis; further, bacterial infections have been implicated in their pathogenesis (2,3). CBD stones can lead to several complications including biliary colic, obstructive jaundice and cholangitis.

Diagnostic Imaging Tests

While a minority of patients with a straight-forward clinical presentation consistent with choledocholithiasis may immediately be treated with ERCP, the vast majority will benefit from diagnostic imaging studies to confirm the diagnosis. Performing a diagnostic ERCP with no prior imaging is not optimal due to the potential risks associated with the procedure. Current imaging modalities available for this purpose include transabdominal ultrasound, regular- and high-resolution...
tion computed tomography (CT) scans, magnetic resonance cholangiopancreatography (MRCP) and EUS.

A transabdominal ultrasound remains the initial test of choice in suspected cases of choledocholithiasis because of its wide-spread availability and relatively lower costs. Dilated ducts seen on ultrasound are highly suggestive of biliary obstruction; however, normal caliber ducts do not exclude a CBD stone. Furthermore, differentiating between causes of obstruction may also be difficult using this imaging modality. Even still, while the transabdominal ultrasound’s sensitivity in detecting choledocholithiasis is low (ranging between 25% and 58%), its specificity can be greater than 95% (4–6).

MRCP has catapulted to the frontlines of diagnostic imaging and is typically the next test physicians perform following an indeterminate transabdominal ultrasound. Its sensitivity and specificity is 95% and 97%, respectively, in detecting the presence and level of biliary obstruction. However, its sensitivity in detecting stones is a function of stone size. While it ranges from 67%–100% for stones larger than 1 cm, it can be as low as 33%–71% in stones less than 6 mm (7–9).

Conventional CT scans have relatively good accuracy (70%–94%) when it comes to identifying both the presence and the cause of biliary obstruction (10,11). A newer technique, the helical CT cholangiography (hCTC), is yet another diagnostic option and allows for three-dimensional reconstitution of images through the use of volumetric data after the administration of both oral and intravenous (IV) contrast. It has proven to be beneficial in detecting CBD stones with a sensitivity of ~87% and a high specificity of 97%, accounting for an overall accuracy of 95% (12,13). However, hCTC remains underused due to its limited availability as compared with MRCP.

Over the past few years, the use of EUS as a diagnostic imaging modality for CBD stones has gained significant momentum. While more invasive than the above methods, its associated risks and complications are lower than those with ERCP. The sensitivity and specificity at detecting CBD stones are 95% and 98%, respectively, with a total accuracy of 96% (14,15). Furthermore, studies have shown that in cases with moderate or low clinical suspicion for choledocholithiasis, the use of EUS may prevent up to 30% of unnecessary ERCPs (16). Figure 1A illustrates an EUS showing a stone in the CBD.

**Endoscopic Therapy**

Prior to the introduction of ERCP with sphincterotomy in the 1970s, choledocholithiasis was mainly managed with surgical extraction and open bile duct exploration (17). Now, endoscopic techniques are first-line therapy for CBD stones.

ERCP should be reserved for patients in whom a therapeutic intervention is likely to occur. Nevertheless, in certain rare situations where the diagnosis remains uncertain despite multiple imaging modalities, ERCP may be required. Once the diagnosis is suspected or established, stone extraction and ductal clearance become the therapeutic goals. Using a side-viewing scope which allows direct visualization and easy access to the papilla, cannulation of the bile duct can be performed using a variety of available instruments including cannulas and sphincterotomes. In the hands of an experienced endoscopist, cannulation success rates average ~95% (18). Once ductal access is established, contrast can be used to opacify and visualize the lumen. Typically stones are identified on the cholangiogram as filling defects around which the contrast flows. Opacification of the ducts also allows for measurement of the severity of the dilation proximal to the stone if any. Frey et al quote the accuracy of ERCP at detecting CBD stones to be at 96% (19).

Once the stone is identified, the focus shifts to extracting it from the duct. Figure 1B shows gallstone extraction during ERCP. In the majority of cases, a biliary sphincterotomy is needed prior to stone removal.
In certain cases where such a cut may be problematic, such as in patients on anticoagulation, the endoscopist may elect to balloon dilate the sphincter area. It should be noted though that there are reports of higher risks of post-ERCP pancreatitis in cases where balloon dilation has been used (20). In cases where cannulation is difficult to achieve, a needle knife papillotome can be used in a technique known as “precutting” to establish direct access into the bile duct. Once access is achieved, a variety of instruments are available to attempt ductal clearance. Most stones up to 15 mm in size can be removed by sweeping the ducts with an extraction balloon, or alternatively by using a Dormia basket provided that a large enough sphincterotomy has been performed (21). In certain instances, though, the stone size may be too large to extract, and as such, alternative methods such as lithotripsy should be considered.

Different lithotripsy modalities are available including mechanical, electrohydraulic, laser and extra-corporeal shock wave (22,23). Mechanical lithotriptors are widely available. They consist of a basket with two sheaths: plastic and metal. Once the stone is caught in the basket wires, the metal sheath is advanced over the plastic sheath, and the stone is crushed into smaller pieces against the metal. Mechanical lithotripsy has high success rates but can be limited in the setting of stone impaction (24). Most tertiary care centers have the capability of performing intraductal lithotripsy through the use of a SpyGlass® choledochoscope (Boston Scientific Corp, Natick, MA, USA), which allows for direct visualization of the ductal lumen (25). Laser lithotripsy amplifies light energy to break up the stone, while the electrohydraulic method relies on shock waves produced by a power generator and transmitted through a bipolar electrode (22,26).

Under certain circumstances, only partial ductal clearance is achieved, and a repeat ERCP is needed. In such situations, it is typical to insert a temporary biliary stent to secure ductal patency while the patient awaits the second procedure (27). In most cases, the ERCP can be performed on an outpatient basis and does not require an overnight hospital stay unless early post-procedure complications are suspected.

The readmission rates following biliary sphincterotomy and same day discharge are approximately 6%, with the majority of cases being readmitted for post-ERCP pancreatitis. Readmission is more likely to occur in patients who have one or more of the following risk factors: suspected sphincter of Oddi dysfunction, cirrhosis, difficult bile duct cannulation, precut sphincterotomy, or combined percutaneous-endoscopic procedure. The majority of complications requiring readmission occur within six hours following the procedure (28).

**PREVENTING RECURRENCE**

Recurrent CBD stones occur most frequently in patients with concurrent choledocholithiasis and cholelithiasis (29). A study of 371 patients who underwent an ERCP with sphincterotomy but who did not undergo subsequent cholecystectomy over a span of 7.7 years found a 10% recurrence rate of choledocholithiasis (30). A smaller study of 120 patients who had undergone a biliary sphincterotomy for CBD stones and who were randomized to laparoscopic cholecystectomy or a “wait and see” policy found that recurrent biliary events were observed more frequently over the next 2 years in the watchful waiting group as compared to the treated group (47% versus 2%, respectively) (31). It is therefore recommended that an elective cholecystectomy be performed as soon as possible following ductal clearance if the patient is deemed to be a surgical candidate.

**BILIARY STRICTURES**

Biliary strictures can be benign or malignant. The general approach to treatment is based on the need to re-establish bile flow through the narrowed area in order to avoid complications including biliary stasis, jaundice and infections. A wide spectrum of clinical presentations has been described with biliary strictures ranging from asymptomatic patients with mild liver function test abnormalities to full blown obstructive jaundice, hyperbilirubinemia and recurrent episodes of cholangitis. Many classifications have been generated for biliary strictures. However, the Bismuth classification is the most widely used. It subdivides strictures into five groups depending on the stricture location within the biliary tree (Table 1) (32).

Differentiating between benign and malignant etiologies is of high clinical importance. A full discussion about the clinical indices of possible malignancy is beyond the scope of this review; however, certain ele-
ments in the patient history such as recent biliary surgical interventions, liver transplantation, pancreatitis, inflammatory bowel disease, unexplained weight loss, and presence of palpable lymph nodes may point to the likely etiology. Lower alkaline phosphatase (ALP) and aspartate aminotransferase (AST) levels have been noted in benign strictures while elevated tumor markers levels such as Ca19-9 and carcinoembryonic antigen (CEA) increase the suspicion of a malignant process (33,34).

Non-invasive Imaging in Biliary Strictures
A wide array of noninvasive imaging modalities are available for evaluation of biliary strictures including ultrasonography, CT, cholangiogram, MRCP, and positron emission tomography (PET). More invasive imaging including EUS with FNA may be used to further investigate the nature of the stricture.

The transabdominal ultrasound is usually the first imaging investigation performed to evaluate possible biliary obstruction with a 78%–98% accuracy at detecting an extrahepatic biliary obstruction; however, it fails at accurately determining the level and etiology of such an obstruction (14). HIDA scans are of little value beyond pointing out that an actual obstruction is present (35). MRCP is currently the best noninvasive imaging study available and has an overall sensitivity of 95% and a specificity of 97% in demonstrating both the presence and the level of a stricture. Furthermore, the cholangiogram obtained can serve as a roadmap which will help plan and guide endoscopic interventions. Ampullary lesions and pancreatic cancers with no pancreatic duct dilations may not be detected by an MRCP (14). In certain instances, a PET study may be used to help differentiate malignant etiologies such as cholangiocarcinoma and metastatic lesions from benign processes (36).

Endoscopic Diagnostic Approaches
More invasive diagnostic modalities allow for better imaging and tissue sampling. They include EUS, ERCP and intraductal ultrasonography (IDUS).

EUS with FNA can help determine the nature of the stricture. The sensitivity of EUS-FNA in diagnosing malignant strictures by a trained advanced endoscopist can be as high as 86% (37). Furthermore, EUS has been shown to be superior to CT scan imaging in detecting distal biliary malignant processes (38). Additionally, EUS can be used for staging purposes if a malignancy is suspected or established.

ERCP is both diagnostic and therapeutic in its application to strictures. It allows for the application of a basic approach to this disease process including dilation and stenting to allow bile flow through the narrowed portion of the duct (Figure 2). In addition, ERCP techniques allow direct visualization of the strictured segment through the use of cholangioscopy, therefore improving diagnostic outcomes through the use of targeted brushing and biopsies. In general, biliary brush cytology has a relatively low sensitivity ranging from 35%–70% in detecting a malignancy (39, 40). The addition of fluorescence in situ hybridization (FISH) analysis to routine brush (continued on page 36)
cytology improves the brushing’s diagnostic accuracy (41). Targeted intraductal forceps biopsies through the use of a cholangioscope can improve the sensitivity to as high as 96% (42). The use of SpyGlass® cholangioscopy results in a sensitivity of 71% and specificity of 100% in diagnosing malignancy in an indeterminate stricture (43). IDUS is a relatively newer technique which can better evaluate and distinguish between benign and malignant lesions when coupled with ERCP, increasing the diagnostic accuracy to up to 90% (14).

Image-enhanced cholangioscopy techniques include chromocholangioscopy, autofluorescence imaging (AFI) and narrow band imaging (NBI). These may further enhance the ability to detect malignancies in indeterminate lesions but have a limited availability and require a high level of training (44). Confocal endomicroscopy has been recently introduced as an additional imaging modality. The miniprobe is used in conjunction with a cholangioscope, and it allows for the detection of specific vasculature patterns. The presence of irregular vessels predict a neoplastic process with an accuracy of 86%, a sensitivity of 83%, with a specificity of 88%. Further investigative studies are ongoing to better determine its future application (44–46).

Managing Malignant Strictures

Common etiologies of malignant biliary strictures include pancreatic carcinoma, ampullary carcinoma, cholangiocarcinoma, gallbladder cancer, hepatocellular carcinoma and metastatic lesions. Once a malignancy has been established, the focus switches to determine the extent of the disease and its resectability. Patients should be referred for surgical and oncologic evaluation. Immediate relief of the obstruction should be established if possible. The use of temporary plastic stents is favored in patients who may be surgical candidates or in cases where the diagnosis is unclear. Self expanding metal stents (SEMS) are usually reserved for patients with unresectable disease and a life expectancy exceeding five to six months (47).

Special Patient Populations: Chronic Pancreatitis, Primary Sclerosing Cholangitis and Liver Transplant Recipients

Chronic pancreatitis related distal bile duct strictures deserve special attention as they account for up to 10% of all CBD strictures and carry a significant amount of morbidity. Inflammation and fibrosis can make it difficult to establish adequate access during an ERCP, and endoscopic management can therefore be limited. Studies suggest that the use of multiple stents may be superior to single stents in this patient population. In cases refractory to repeated stenting and endoscopic therapy, surgery may be required and is usually complicated because this patient population typically suffers from comorbid conditions and additional complications such as vascular thrombosis and liver involvement (43).

In patients with primary sclerosing cholangitis (PSC), chronic inflammation leads to multiple fibrotic strictures of the entire biliary tree and eventually results in significant liver disease and cirrhosis (Figure 3). Medical therapy has not proven to be of benefit, and the use of ursodeoxycholic acid is no longer recommended. Liver transplantation is the only long-term option for
severe cases. Dominant extrahepatic strictures are common in PSC patients occurring in up to 50% of cases. They may lead to cholangitis, which in turn can worsen the extent of damage to the liver. Their presence is typically suspected clinically based on worsening jaundice and pruritis and increasing liver function test abnormalities. It is important to rule out a malignant process in these patients in view of the substantially increased risk of cholangiocarcinoma (8%-14% of patients) (48).

Endoscopic therapy consists of dilation of the dominant stricture and extraction of any stones or sludge that may be lodged above the strictured area. Short-term stenting may be effective in a small number of patients. However stent occlusion remains a problem. Repeat dilations may be required in many cases. Stenting after balloon dilation may not have any additional benefit (49).

Anastomotic strictures are common post orthotopic liver transplantation (OLT) with an incidence around 5%-10%. These typically are short segment strictures and occur within one year of the transplant with early strictures resulting from technical complications of the surgery and later ones from vascular insufficiency and fibrosis (50). Risk factors include tension at the anastomosis, caliber mismatch between donor and recipient ducts, and excessive use of electrocauterization for control of intra-operative bleeding (51). Endoscopic management with repeated dilation and stenting remains the treatment of choice. Newer data suggest that the use of fully covered metal stents may be beneficial in these patients by spacing out the ERCPs needed and therefore decreasing costs and associated risks (52).

**BILE LEAKS**

Bile leaks occur mainly as a complication of biliary surgery, including laparoscopic cholecystectomy (up to 1.1% of cases) and cadaveric OLT. The leak can occur at the cystic duct stump or can involve the smaller ducts of Luschka. The presentation is typically acute within the first few days following surgery but may be delayed with a few cases presenting up to one month later. Imaging studies, such as an ultrasound or CT scan of the abdomen, are usually diagnostic, but the absence of a biloma on imaging does not exclude the diagnosis. Endoscopic cholangiography can establish the diagnosis in the vast majority of patients and can provide therapeutic means in the same setting (53).

Figure 4 shows a cholangiogram illustrating a bile leak in a patient with a recent cholecystectomy.

The therapeutic goal is to establish an area of lower resistance for the bile to flow through. This is usually achieved by the insertion of a short temporary biliary stent, therefore relieving the high transpapillary pressure gradient. A biliary sphincterotomy may be enough in certain milder cases. Response is typically measured by the clinical improvement and decreased outputs from percutaneous surgical drains. Stents are typically left in place for about four to six weeks. Bile leaks refractory to endoscopic treatment typically require surgical interventions to correct the defect (54).

**CONCLUSIONS**

In summary, much progress has been made over recent years in diagnosing and treating biliary tract disorders. Endoscopic therapy has become the predominant modality used in both the diagnosis and treatment of these disorders. The future of therapeutic endoscopy promises to be quite interesting as it continues to evolve and offer more innovative new techniques.

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**References**


