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## Endoscopic management of difficult common bile duct stones: Where are we now? A comprehensive review

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### Abstract

Endoscopic management for difficult common bile duct (CBD) stones still presents a challenge for several reasons, including anatomic anomalies, patients' individual conditions and stone features. In recent years, variable methods have emerged that have attributed to higher stone removal success rates, reduced cost and lower adverse events. In this review, we outline a stepwise approach in CBD stone management. As first line therapy, endoscopic sphincterotomy and large balloon dilation are recommended, due to a 30%-50% reduction of the use of mechanical lithotripsy. On the other hand, cholangioscopy-assisted lithotripsy has been increasingly reported as an effective and safe alternative technique to mechanical lithotripsy but remains to be reserved in special settings due to limited large-scale evidence. As discussed, findings suggest that management needs to be tailored to the patient's characteristics and anatomical conditions. Furthermore, we evaluate the management of CBD stones in various surgical altered anatomy (Billroth II, Roux-en-Y and Roux-en-Y gastric bypass). Moreover, we could conclude that cholangioscopy-assisted lithotripsy needs to be evaluated for primary use, rather than following a failed management option. In addition, we discuss the importance of dissecting other techniques, such as the primary use of interventional endoscopic ultrasound for the management of CBD stones when other techniques have failed. In conclusion, we recognize that endoscopic sphincterotomy and large balloon dilation, mechanical lithotripsy and intraductal lithotripsy substantiate an indication to the management of difficult CBD stones, but emerging techniques are in rapid evolution with encouraging results.

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**Core Tip:** The endoscopic management of difficult common bile (CBD) stones remains a challenge, whilst emerging techniques such as endoscopic sphincterotomy and large balloon dilation, mechanical lithotripsy and intraductal lithotripsy provide a procedural indication that align with the patient's condition, comorbidities, feature of the CBD stone and the patient's anatomical features. This review focuses on comprehensively outlining a stepwise approach for the management of difficult CBD stones and comparatively discusses indications depending on surgical altered anatomy and future indications in the management of difficult CBD stones.

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## INTRODUCTION

About 10%-15% of biliary stone extraction procedures are demanding and require additional endoscopic techniques in order to allow stone clearance[1]. Factors that influence the technical difficulty of common bile duct (CBD) endoscopic clearance can be attributed to the patient's clinical condition, the stone's characteristics and anatomical factors (Table 1). Furthermore, the concomitant presence of Mirizzi syndrome and/or primary sclerosing cholangitis are also agreed upon by experts to make stone extraction a challenging procedure[2,3].

In accordance with the European Society of Gastrointestinal Endoscopy (ESGE) guidelines on endoscopic management of common bile duct stones, endoscopic sphincterotomy combined with endoscopic papillary large balloon dilation is considered the first line approach, reserving mechanical lithotripsy in case of failure [4]. Cholangioscopy-assisted lithotripsy has been increasingly reported as an effective and safe alternative technique to treat difficult CBD stones, even though its availability is still limited to referral centers[4,5]. Moreover, endoscopic management of CBD stones in patients with surgically altered anatomy (SAA) is technically demanding with a reduced rate of technical success[6]. Balloon assisted enteroscopy (BAE) has revealed to be effective in this setting, although its rate of failure has been reported to be up to 35%[7]. The use of interventional endoscopic ultrasonography (I-EUS) has been reserved to cases of BAE failure, due to its higher rate of adverse events when compared with BAE in previous reports[8-10]. Nevertheless, recent studies showed that I-EUS is efficacious with a low risk of adverse events, so it should be considered as first line treatment in expert hands and in referral centers[11]. The future of I-EUS requires the development of dedicated devices, making the procedure easier and safer with expanded indications[6,12]. Further studies will help to assess the role of I-EUS as the first approach for the management of CBD stones in patients with SAA. Finally, percutaneous cholangioscopy is also a novel alternative technique that should allow to treat difficult CBD stones in patients with SAA[13].

## STEPWISE APPROACH FOR THE MANAGEMENT OF DIFFICULT COMMON BILE DUCT STONES

The first step is gaining access to the biliary tree, in order to remove the stone, which can be achieved by three different techniques: Endoscopic sphincterotomy (EST), endoscopic papillary large balloon dilation (EPLBD) and a combination of EST and

**Table 1 Causes of difficult stone extraction**

Category	Risk factors
Patient's clinical condition	Age > 65 yr; Bleeding tendency; Very poor medical condition
Stone characteristics	Stone size > 15 mm; Barrel or square shaped; Multiple stones > 3; Hard stone consistency; Intrahepatic/cystic duct location
Anatomical factors	Anatomical CBD factors: Narrowing of the bile duct distal to the stone, sigmoid-shape CBD, distal CBD angulation > 135°, short distal CBD < 36 mm; Periampullary diverticulum; Duodenal stricture; Surgically altered anatomy (Roux-en-Y gastric bypass or Billroth II with long afferent limb)

EPLBD [endoscopic sphincterotomy and large balloon dilation (ESLBD)]. Although the optimal choice remains debatable among endoscopists, the recently published ESGE guidelines[4] recommend ESLBD as the first-line approach to difficult CBD stones (in particular large stones), due to a 30%-50% reduction of the use of mechanical lithotripsy (ML) and a similar rate of technical success when compared to EST alone [14-20] (Figure 1).

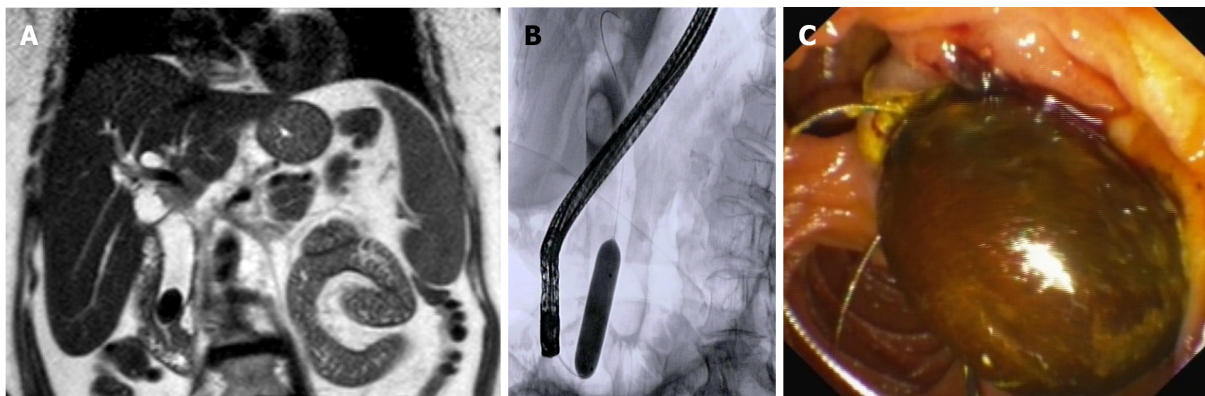
However, balloon dilation is contraindicated in cases with distal biliary strictures, due to the increased risk of perforation[21], whereas EST increases the risk of bleeding in patients on antithrombotic agents[22]. A recently published systematic review and metaanalysis including 13 randomized controlled trials conducted on 1990 patients[23] focused on the treatment of large CBD stones using the three techniques. Analyzing the surface under the cumulative ranking curve index, Lyu *et al*[23], concluded that EPLBD had the highest overall and initial success rates and the lowest probability of bleeding. ESLBD also had the lowest probabilities for the need for ML, risk of perforation, morbidity rates and risk of mortality. On the other hand, EST was associated with the lowest rates of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) and cholangitis. However, when each outcome was analyzed on pooled network analysis, no significant differences among the three groups emerged. There are many limitations in this study: The definition of the success rate and post-procedure complications varied in the included studies, the details of the different endoscopic procedures, such as the size of the dilation balloon, differed in the studies and the patient's characteristics changed among studies, such as bleeding predisposing factors and anatomical factors (*e.g.*, the presence of a peripapillary diverticulum and the size of the distal bile duct). To conclude, the technique for removing difficult CBD stones is still debated among endoscopists and needs to be tailored to patient's characteristics and anatomical conditions[24]. Higher numbers of high-quality trials are required.

When the size of CBD stones, even after balloon dilation, exceeds the diameter of the distal CBD, ML should be performed (Figure 2). The success of ML has been reported to range between 79% and 96% [25-29], with a low mortality rate and an overall adverse events (AEs) rate of 3.5% in a multicenter study[30], including trapped/broken basket, wire fracture and broken handle perforation/duct injury. Even though previous studies have focused on the importance of stone size as the factor that hampers stone clearance[29], Garg *et al*[28] demonstrated that the only predictor of unsuccessful ML was the stone impaction into the CBD. This determined the inability to push the basket proximal to the stone or the incapability to open fully the basket to grasp the stone.

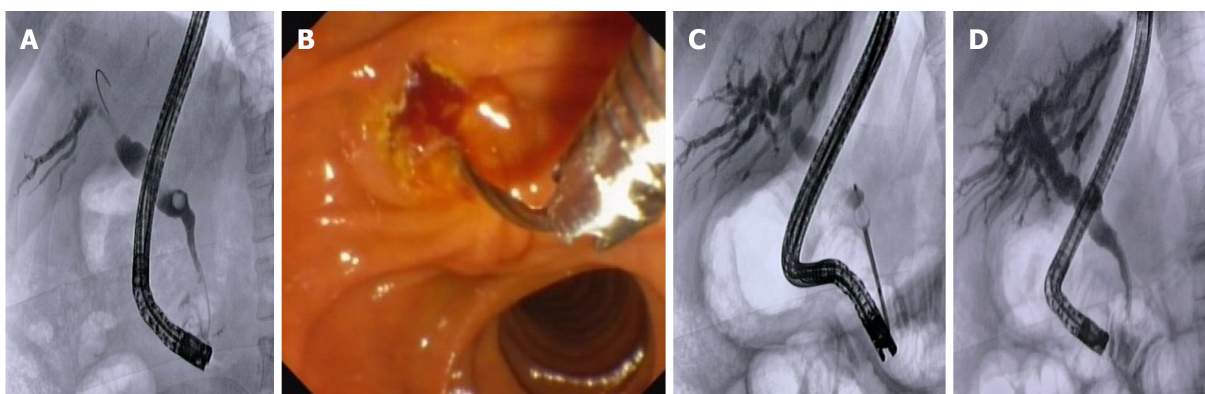
ML can require multiple sessions to achieve stone clearance, undergo AEs and still be ineffective for difficult CBD stones[31]. In such cases, cholangioscopy-assisted intraluminal lithotripsy with electrohydraulic (EHL) or laser lithotripsy (LL) is the technique of choice to fragment large stones under direct visualization. There are three cholangioscopy techniques available: The oldest "dual-operator" mother-baby approach, the "single-operator" mother-baby approach (Spyglass, Boston Scientific, Natick, MA, United States) and the "direct" technique using currently available ultrathin gastroscopes[32].

Each of the three cholangioscopy technique allows EHL or LL under direct visualization (Figure 3). Nevertheless, in regards to which specific type of cholangioscopy and lithotripsy to use, it depends on local expertise and availability, as mentioned in ESGE guidelines[4]. There are currently no studies that compare cholangioscopy techniques. Concerning the type of lithotripsy used, Veld *et al*[33] recently published a systematic review comparing LL, EHL and extracorporeal shock wave lithotripsy (ESWL) in the treatment of difficult CBD stones after a previously failed ERCP. In their study, LL had a significantly higher complete ductal clearance rate (95.1%) compared

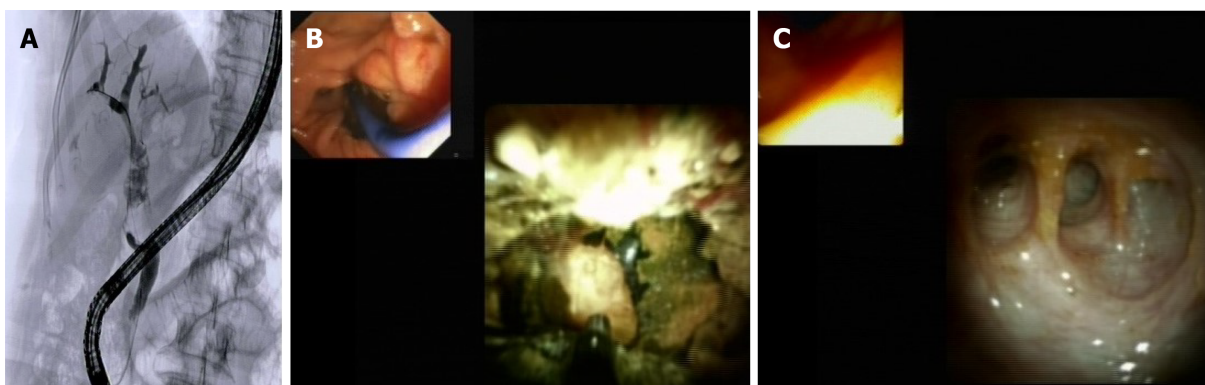




**Figure 1** Management of difficult common bile duct stone by endoscopic sphincterotomy and large balloon dilation. A: Magnetic resonance imaging showing a large stone in the distal common bile duct; B: Fluoroscopic appearance of endoscopic papillary large balloon dilation with a pneumatic balloon filled with contrast medium; C: Final endoscopic view of the stone extracted by a Dormia basket.



**Figure 2** Management of common bile duct stones with distal biliary stricture by mechanical lithotripsy. A: Cholangiogram showing distal common bile duct (CBD) stricture with stone in the medium CBD; B: Introduction of a mechanical lithotripter over the Dormia basket; C: Mechanical lithotripsy under fluoroscopic control; D: Final cholangiogram showing complete CBD clearance.



**Figure 3** Management of impacted common bile duct stones with distal biliary stricture by cholangioscopy assisted lithotripsy. A: Cholangiogram showing distal common bile duct (CBD) stricture with large impacted stone in the medium CBD and multiple stones above; B: Cholangioscopy assisted lithotripsy by electrohydraulic of the impacted stone; C: Final cholangioscopy showing complete CBD clearance with biliary confluence appearance.

with EHL (88.4%) and ESWL (84.5%), while EHL had a higher post-procedural AEs rate (13.8%, including cholangitis, hemobilia and pancreatitis) compared with ESWL (8.4%) or LL (9.6%). In opposition to these results, a more recent meta-analysis[34] reported a superiority of EHL *vs* LL (mean successful endoscopic clearance rate 91.4% and 88.6%, respectively), explaining a more selective study inclusion than that made by Veld *et al*[33]. The last published meta-analysis comparing cholangioscopy-guided lithotripsy *vs* conventional therapy for complex bile duct stones[34] showed no

significant difference between ERCP and cholangioscopy in terms of therapeutic success, AEs rate and mean fluoroscopy time, but a shorter mean procedure time for conventional ERCP methods were found. In detail, cholangioscopy-guided lithotripsy showed a successful endoscopic clearance rate of 88.29% [95% confidence interval (CI): 86.9%-90.7%], first session successful endoscopic clearance rate of 72.7% (95%CI: 69.9%-75.3%), mean procedure time of  $47.50 \pm 6$  min for session, number of sessions to clear bile duct of  $1.5 \pm 0.18$  and adverse event rate of 8.7% (95%CI: 7%-10.9%). The majority of patients in the considered studies had a history of failure to remove stones on prior ERCP attempt. Therefore, Galetti *et al*[34] concluded that cholangioscopy-guided lithotripsy should be reserved to cases where the conventional techniques failed to achieve initially stone clearance. The majority of data published by Galetti *et al*[34] are in line with an older meta-analysis by Korrapati *et al*[35]. Regarding AEs, cholangitis is the most frequently reported, while PEP and perforation rarely occur [35].

Cholangioscopy-assisted lithotripsy should be reserved to selected cases and in the setting of tertiary care centers due to its costs, complexity and AEs rate. However, an increasingly number of authors claim that cholangioscopy-assisted lithotripsy may be considered first-line therapy for patients with difficult CBD stones in order to avoid serial procedures[36-38] and decrease costs[39]. Moreover, this procedure must be performed at tertiary centers by expert endoscopists.

When conventional ML fails and intraluminal lithotripsy is not available, the ESGE guidelines suggest to perform ESWL[4]. However, this procedure often requires multiple sessions, the placement of a naso-biliary drainage and subsequent ERCP to extract stone fragments. Ductal clearance rate appeared lower compared with LL (53%-73% *vs* 83%-97%, respectively)[40,41] but similar to EHL (78.5% *vs* 74%, respectively)[42]. ESWL-related AEs, including mostly cholangitis and pancreatitis, range from 9%-35.7%[40,42].

When biliary stones remain irretrievable but patients still need biliary drainage due to the risk of cholangitis, the placement of a temporary plastic stent is highly recommended before a second attempt at stone extraction can be made[4]. Horiuchi *et al*[43] documented that stent placement for 2 mo is associated with large and/or multiple CBD stones becoming smaller and/or disappearing without any complications, with a successful stone removal of 93% on a second ERCP[43]. Likewise, the disintegration of stones depends on the continuous friction between the plastic stent and the stones, which produces stress forces on the stone[43]. In a recent retrospective study, Jang *et al*[44] compared the use of different stents (7-Fr rather than 10-Fr plastic stents) in this setting, showing that the mean stone size reduction did not differ between the stents (5.7 mm in the 7-Fr stent group and 5.5 mm in the 10-Fr stent group;  $P = 0.91$ ). However, when performing multivariate analyses, 7-Fr double pigtail stents significantly improved the complete clearance rate. On the other hand, the reduction in stone size was greater in the double-stenting group than in the single-stenting group, but the use of a double stent did not alter the complete stone clearance rate[44]. Covered self-expandable metal stent have been also used as an alternative to plastic stents to drain CBD after unsuccessful difficult stone removal. However, their high cost has not been certainly related to improved benefits[45-48].

## DIFFERENT APPROACHES FOR PATIENTS WITH ALTERED ANATOMY

Endoscopic management in patients with SAA is still challenging for the endoscopists. Before performing ERCP, it is paramount to understand the anatomy and length of the afferent limb in order to select the appropriate approach, through the revision of the surgical report. The success of interventional endoscopy will depend on the correct choice of the endoscope and devices that should be tailored to the patient's anatomy [49].

### **Billroth II reconstruction**

According to the ESGE guideline, a duodenoscope should be the first choice, reserving a forward-viewing endoscope (gastroscope, pediatric colonoscope, device assisted enteroscope) in case of failure[50]. Endoscopic sphincterotomy, where an inverted sphincterotome rather than precut following biliary stent placement in case of dedicated sphincterotome unavailability is used, is the standard of care in this setting. Furthermore, EPLBD could be used as an alternative method to sphincterotomy for CBD stones extraction, especially for stones larger than 10 mm[51,52]. Usually, the length of the afferent limb is short (less than 50 cm), but in cases of antecolic gastroje-



junostomy, it could be too long to be reachable by a duodenoscope. In this case, a forward viewing endoscope, allowing better visualization and easier intubation of the afferent limb compared with the lateral viewing endoscope, should be used. However, duodenoscope makes biliary cannulation easier using the elevator, even though it emerged to be associated with a higher perforation rate when compared with the forward viewing endoscope. This is due to limited visualization, difficult control of the scope, and the need to apply more pressure to overcome looping[53,54]. However, according to a recently published review by Krutsri[53], in patients with Billroth II gastrectomy, the duodenoscope has an afferent limb intubation success rate ranging from 62.5%-100%, cannulation success rate 88.2%-100% and complication rate 0%-12.5%. On the other hand, gastroscope with or without cap is reported to have similar results with an afferent loop intubation success rate of 76.8%-100%, cannulation success rate 81.4%-100% and complication rate 0%-10%. A subsequent retrospective study comparing sideviewing duodenoscope and forwardviewing endoscope to perform ERCP in patients with Billroth II gastrectomy reported afferent loop intubation rates of 95.1% for the side-viewing duodenoscope and 100% for the forward-viewing endoscope ( $P = 0.49$ ). The rates of reaching the papilla were 70.7% and 91.1%, respectively ( $P = 0.06$ ). Cannulation success rate after reaching the papilla was 100% in the side-viewing duodenoscope group and 90.3% in the forward-viewing endoscope group[55].

In 2015, Bove *et al*[56] reported a 30-year experience, showing that, in tertiary referral centers, patients with Billroth II (BII) that underwent ERCP had similar rates of morbidity and mortality when compared with patients with normal anatomy. In a recent systematic review and meta-analysis, Park *et al*[57] compared the efficacy and safety of forward viewing *vs* lateral viewing endoscopes and demonstrated that there was no statistically significant difference between the two endoscopes.

In referral centers, device-assisted enteroscopies (DAE) could be the first option because of higher technical success rate and lower adverse events, when compared with duodenoscopes and forward viewing endoscopes[53]. The majority of CBD stones in patients with Billroth II anatomy can still be removed by standard techniques such as EST and EPBD.

In a recent retrospective study, Duo *et al*[58] analyzed the risk factors for technical ERCP failure in Billroth II anatomy, demonstrating that in two or more CBD stones where the largest CBD stone measures to 12 mm or larger in size, stone characteristics for failed stone removal were included. Moreover, after the first ERCP attempt, Braun anastomosis and the use of no cap-assisted gastroscope were risk factors for technical failure of ERCP in this patients' cluster[58]. The initial stone removal rates of EPLBD have been reported to range from 66.7%-92.5%, while the overall stone clearance rates were from 96%-100%[51,59,60]. EPLBD, with or without EST, showed a high rate of first session stone clearance, reducing the need of endoscopic ML[51]. EPLBD has resulted to be associated with higher risk of post-ERCP pancreatitis in some studies [61-63], unlike most of the recent papers which showed the efficacy of EPLBD without increasing adverse events, including PEP[59,64]. On the other hand, EST is associated with a higher risk of bleeding[65]. However, sometimes lithotripsy is necessary to achieve stone clearance, especially when stones are too large to extract even after EPLBD, or when EPLBD is too risky in cases of distal bile duct narrowing or stricture [66].

There are three treatment options for lithotripsy: Endoscopic ML, cholangioscopic guided lithotripsy (LL or EHL) and ESWL. ML is a first treatment option, although it failed in cases where bile duct stones were larger than 2-3 cm, due to the difficulty to catch with a mechanical lithotripter. In those cases, intraductal lithotripsy could be used, although cholangioscopy is difficult to carry out in patients with SAA. In these setting of patients, ESWL should be considered as a second option. However, endoscopic naso-biliary drainage is necessary before performing ESWL, which has a lower efficacy compared to LL or EHL[40].

Finally, EUS-guided intraductal lithotripsy or percutaneous transhepatic biliary drainage should be considered if ESWL is ineffective. In the percutaneous transhepatic biliary drainage approach, CBD stones are extracted in the antegrade fashion after balloon dilation of the papilla. In cases with large CBD stones, percutaneous transhepatic cholangioscopy with intraductal lithotripsy or ESWL could be attempted to facilitate stone removal. EUS-guided approach has gained popularity in the management of bile duct stones in patients with BII anatomy. In a retrospective study [9], EUS-guided antegrade (EUS-AG) treatment had a technical success rate of 72%, due to the technical difficulty of the antegrade stone extraction. Moreover, mechanical or intraductal lithotripsy, through an enterobiliary fistula after fistula maturation, could be made[67].

### Roux-en-Y reconstruction

Roux en Y reconstruction can be divided in Roux en Y without gastric bypass (*e.g.*, Roux en Y gastrojejunostomy, Roux en Y hepaticojejunostomy, pancreatico-duodenectomy) and with gastric bypass (RYGB). Roux-en-Y reconstruction, compared to BII surgery, results in a longer and tortuous limb, increasing the difficulty to reach the papilla. In this setting, patients should be managed in referral centers where DAEs are the first option[68], with a reported cannulation rate ranging from 58%-95.6%, and an AEs rate between 7% and 10%, with a perforation rate of 0%-3.2%[69,70].

A systematic review and meta-analysis showed that BAE has a high diagnostic and procedural success rate in patients with Roux-en-Y reconstruction (69.4% and 61.7%, respectively), with an overall AEs rate of 6.5%[71]. Different studies have shown that there is no superiority among different DAE methods [single balloon enteroscopy (SBE), double balloon enteroscopy (DBE) and spiral enteroscopy][72]. Nevertheless, three systematic review and meta-analyses demonstrated better results for DBE compared to SBE (the success rate of reaching the papilla and treatment were 89.7% and 63.5% for DBE and 80.9% and 61.7% for SBE, respectively)[71,73,74].

The success rate of forward viewing endoscopes could be increased by using an underwater cap assisted technique, which combines the use of a cap applied to the tip of a pediatric colonoscope, with the injection of water as an alternative medium to carbon dioxide or air to distend the bowel lumen. It appeared that on one side the underwater technique reduces loop formation and bowel distension, while on the other side, the use of a cap improves the visualization of the papilla and helps in maintaining a stable position[75].

Even after cannulation, extraction of CBD stones can be difficult in patient with Roux-en-Y reconstruction, although different techniques have been described in this cluster of patients. EPLBD has been reported to achieve complete stone removal on a single-session in 66.7%-100%, while overall complete stone removal was obtained in 96.7%-100% of cases[49]. ML can be used, even though it is often technically challenging during enteroscopy-assisted ERCP and may fail.

Therefore, direct peroral cholangioscopy, through direct insertion of an ultra-slim endoscope or an enteroscope into the bile duct, allowing to perform lithotripsy, has been described in some case reports[76-80]. Some authors have also described the placement of an overtube through the scope, which allows the insertion of a cholangioscope (Spyglass, Boston Scientific) and direct lithotripsy[81,82].

EUS-AG stone treatment has also gained popularity. Biliary access is achieved from the stomach or jejunum under EUS-guidance, using a guidewire that is passed through the ampulla into the duodenum. Then the ampulla is dilated using a balloon, and finally, CBD stones are pushed into the duodenum using a stone extraction balloon.

The reason for technical failure is the failed puncture of the intrahepatic bile duct, guidewire passage and difficulty to stone extraction due to large stones size. However, these reasons could be overcome using large balloon dilation. Nevertheless, the maximum balloon size is limited to the size of the distal CBD, therefore intraductal lithotripsy is needed in cases with stones larger than the size of the distal CBD, increasing the risk of bile leak. However, a two-step approach has been proposed to prevent bile leaks and allowing safe usage of ML and cholangioscopy in EUS-AG stone treatment[67].

Mechanical lithotripter can be introduced over the guidewire and into the bile duct, through the fistula. A fistula dilation up to 10-F using a plastic stent, a fully covered self-expandable metal stent after endoscopic ultrasound-guided hepaticogastrostomy or endoscopic ultrasound-guided hepaticojejunostomy, should be made in order to prevent bile leak and to allow easy access of the cholangioscope into the biliary system [83].

For the management of complex CBD stones, with the use of DAEs in patients with SAA has been studied in larger cohort of patients, EUS-guided therapy in this setting has been increasingly reported in case reports[8-11,84-86]. There are advantages and disadvantages in enteroscopy-assisted stone management and EUS-guided interventions in patients with Roux-en-Y anatomy.

Enteroscopy-assisted ERCP uses the physiological biliary access and has a lower risk of bile duct leakage, although scope insertion can be challenging. On the other hand, EUS-guided approach involving the puncture of the left intrahepatic bile duct has a lower risk of bile leak but can be challenging when the intrahepatic bile duct is minimally dilated. Enteroscopy-assisted ERCP should be the first approach, reserving EUS-guided approach in case of failure as a salvage technique. We should keep in mind that enteroscopy-assisted ERCP and EUS-AG stone treatment need expertise as well as dedicated devices, therefore these procedures should be performed by skilled endoscopists in high volume referral centers.

### **Roux-en-Y gastric bypass**

The treatment of CBD stones in patients who underwent weight loss surgery, especially RYGB, is challenging due to difficult access to the CBD. In fact, in Roux en-Y reconstruction, the afferent limb length can be more than 200 cm, with sharp angulation of the jejunojejunal anastomosis, severe adhesion and looping of the scope. Moreover, the incidence of symptomatic gallbladder disease is around 15% after significant weight loss, therefore prophylactic cholecystectomy has been suggested [87]. The percentage of therapeutic success of ERCP using a pediatric colonoscope or with DAEs has been reported around 60% [88]. New techniques to perform ERCP in this setting are EUS-directed transgastric ERCP (EDGE) and laparoscopic-assisted transgastric ERCP (LA-ERCP), which reach a success rates of 80%-100% [89-91]. However, both procedures have some limits. EDGE requires expertise in interventional EUS and ERCP, has higher costs and can be associated with stent migration and subsequent perforation [92,93] and permanent gastro-gastric fistula with weight regain [94]. On the other hand, LA-ERCP needs coordination between surgeon and endoscopist with a gastrostomy tube left *in situ*, if multiple ERCP procedures are required to obtain stones clearance [95].

EDGE is a two-step procedure; procedures can be performed in the same session or in two separate sessions (Figure 4). Single session EDGE is associated with a higher risk of perforation due to lumen apposing metal stent dislodgement, while dual session has a lower perforation risk, but it requires 10-14 d interval to allow fistula maturation. A shortened interval dual session (2-4 d) has been proposed to overcome this limitation, decreasing the risk of intraprocedural 20 mm lumen apposing metal stent dislodgement and allowing a timely transgastric ERCP [96].

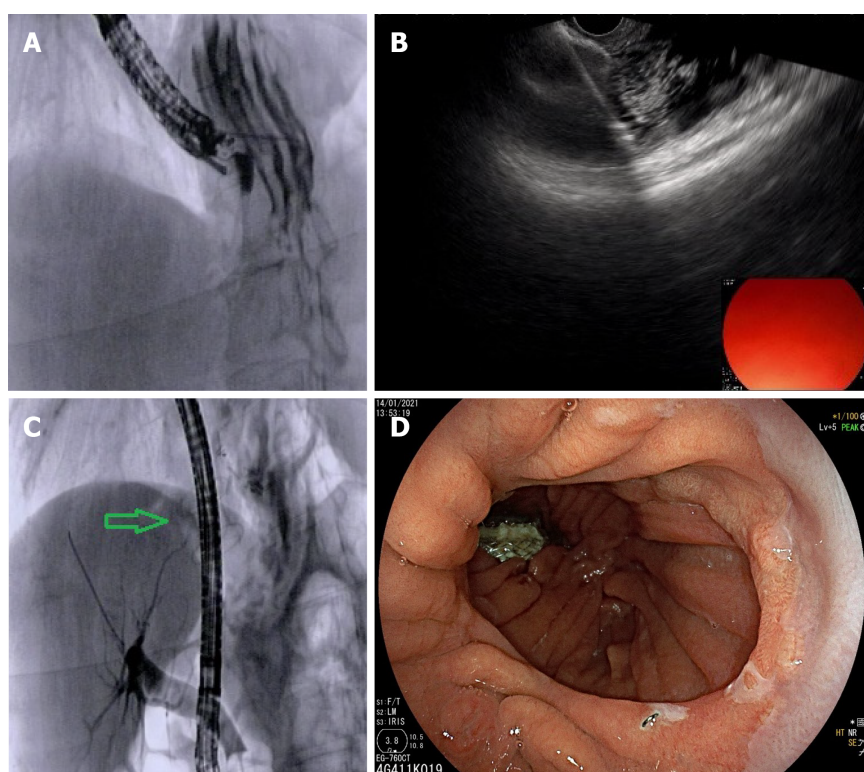
An international, multicenter trial comparing EUS-guided gastro-gastrostomy-assisted ERCP *vs* enteroscopy-assisted ERCP (e-ERCP) in patients with RYGB has shown that EUS-guided gastro-gastrostomy-assisted ERCP may be superior to e-ERCP in terms of higher technical success and shorter procedural time, with similar safety profile [97]. LA-ERCP provides the opportunity to perform cholecystectomy concomitantly with CBD stones clearance, in case the gallbladder is still in place [98].

### **Post-liver transplantation**

CBD stones after liver transplantation have an incidence between 4% and 10% of cases [99]. Biliary strictures are the major predisposing risk factor for biliary CBD stones, occurring in up to 90% of liver transplant patients with biliary stones [100]. Other possible agents for stone formation are cold ischemia, hyperlipidemia, hypercholesterolemia, infections and cyclosporine assumption [100,101]. Biliary stones in post-liver transplantation patients may cause severe complications such as pancreatitis, biliary infections and biliary cirrhosis, which can drastically worsen the graft's course. The endoscopic management of CBD stones in this setting of patients is successful in over 90% of cases, although the presence of anastomotic strictures results in a challenging and demanding procedure and increases the difficulty of stones removal [99]. In this context the strictures have to be treated simultaneously with stone extraction, using balloon dilation and mechanical lithotripsy and reserving the use of cholangioscopy-assisted lithotripsy in case of failure [102]. CBD stones may be mistaken with biliary casts, which occur in 2.5%-18% of post-liver transplant patients due to hepatic ischemic injury and are associated with poorer graft survival [103]. The differential diagnosis is mainly based on cholangiography features in addition to the endoscopist experience and can be confirmed by cholangioscopy direct visualization. This is fundamental to direct the treatment approach.

## **FUTURE RESEARCH DIRECTIONS IN THE MANAGEMENT OF DIFFICULT CBDS**

The use of cholangioscopy-assisted lithotripsy in patients with difficult CBD stones as a first step rather than after failed traditional treatment, need to be assessed in randomized controlled trials. Many endoscopic techniques have been used in patients with difficult CBD stones and altered anatomy, with variable results. Percutaneous transhepatic cholangioscopy, which has been recently reported as a novel and alternative approach for patients with SAA, allows access to the biliary tree and stones fragmentation under direct visualization [13,104,105]. However, efficacy and safety of its use need to be further investigated.



**Figure 4** Endoscopic ultrasonography-directed transgastric endoscopic retrograde cholangiopancreatography for management of common bile duct stone in patient with previous Roux-en-Y gastric bypass for bariatric surgery. A: Endoscopic ultrasonography (EUS)-guided puncture of the excluded stomach with a 19G EUS needle with injection of contrast medium and sterile saline for gastric distension under fluoroscopic control; B: EUS guided first flange deployment of 20 mm lumen apposing metal stent (LAMS) into the gastric remnant; C: Endoscopic retrograde cholangiopancreatography for stone removal was performed after advancing the duodenoscope through the LAMS (green arrow); D: Endoscopic image confirming placement of the LAMS within the gastric pouch.

EUS guided interventions for biliary drainage after failed ERCP are in rapid evolution[106-107], including management of CBD stones in patients with normal anatomy when other techniques have failed[108]. Two retrospective studies and a recent review have compared EUS-rendezvous with precut papillotomy technique, showing that treatment success was significantly higher for EUS-rendezvous than for those with precut papillotomy, without significant differences in terms of complication rate[109-111]. Therefore, in tertiary referral centers, EUS-rendezvous could be used instead of precut papillotomy. The role of EUS-guided biliary treatment in patients with SAA should be investigated as primary technique in well-designed studies comparing safety and efficacy of EUS-guided interventions with enteroscopy-assisted ERCP. Finally, regarding patients with RYGB, more studies are needed in order to assess the role of the three different methods used in this setting (EDGE, LA-ERCP, e-ERCP), allowing endoscopists to tailor the technique to the patient.

## CONCLUSION

The step-up approach involving ESLBD, ML and intraductal lithotripsy for patients with difficult CBD stones has been quite well validated. On the other hand, many different techniques involving the use of EUS in this setting are in rapid evolution with encouraging results. In patients with SAA, the endoscopic management of CBD stones is still challenging and should be managed in referral centers. The role of EDGE compared with LA-ERCP, e-ERCP as well as the efficacy and safety of percutaneous transhepatic cholangioscopy need to be evaluated in further well-designed studies. Finally, the definition of difficult CBD stones includes many different clinical scenarios with distinctive outcomes depending on the treatment choice. The correct pre-operative evaluation of the patient could help in choosing the best treatment strategy, in order to avoid unnecessary, ineffective ERCP session/attempt and can offer the best therapeutical approach to our patients.



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