Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline

Authors
Gianpiero Manes1, Gregorios Paspati2, Lars Aabakken3, Andrea Anderloni4, Marianna Arvanitakis5, Philippe Ah-Soune6, Marc Barthet7, Dirk Domagk8, Jean-Marc Dumonceau9, Jean-François Gigot10, Istvan Hritz11, George Karamanos12, Andrea Laghi13, Alberto Mariani14, Konstantina Paraskeva15, Jürgen Pohl16, Thierry Ponchon17, Fredrik Swahn18, Rinze W. F. ter Steege19, Andrea Tringali20, Antonios Vezakis21, Earl J. Williams22, Jeanin E. van Hooff23

Institutions
1 Department of Gastroenterology, ASST Rhodense, Rho and Garbagnate M.se Hospitals, Milan, Italy
2 Gastroenterology Department, Benizelion General Hospital, Heraklion, Crete, Greece
3 GI Endoscopy, Rikshospitalet University Hospital, Hospital and Faculty of Medicine, University of Oslo, Oslo, Norway
4 Digestive Endoscopy Unit, Division of Gastroenterology, Humanitas Research Hospital, Rozzano, Milan, Italy
5 Department of Gastroenterology, Hepatology and Digestive Oncology, Erasme University Hospital Université Libre de Bruxelles, Brussels, Belgium
6 Service d’Hépato-Gastroentérologie, Hôpital Saint-Musse, Toulon, France
7 Service d’Hépato-gastroentérologie, Hôpital Nord, Marseille, France
8 Department of Medicine B, University of Münster, Münster, Germany
9 Gedyt Endoscopy Center, Buenos Aires, Argentina
10 Department of Abdominal Surgery and Transplantation, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
11 Semmelweis University, 1st Department of Surgery, Endoscopy Unit, Budapest, Hungary
12 Academic Department of Gastroenterology, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
13 Pathological Sciences, Sapienza University, Rome, Italy
14 Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational & Clinical Research Center, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy
15 Gastroenterology Unit, Konstantopoulio General Hospital, Athens, Greece
16 Department of Gastroenterology and Interventional Endoscopy, Klinikum Friedrichshain, Berlin, Germany
17 Department of Digestive Diseases, Hôpital Edouard Herriot, Lyon, France
18 Center for Digestive Diseases, Karolinska University Hospital and Division of Surgery, CLINTEC, Karolinska Institute, Stockholm, Sweden
19 Department of Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
20 Digestive Endoscopy Unit, Catholic University, Rome, Italy
21 Gastroenterology Unit, 2 Department of Surgery, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
22 Department of Gastroenterology, Royal Bournemouth Hospital, Bournemouth, UK
23 Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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Corresponding author
Gianpiero Manes, MD, Department of Gastroenterology, ASST Rhodense, Rho and Garbagnate M.se Hospitals, Viale Forlanini 95, 20024 Garbagnate M.se, Milano, Italy
gimanes@tin.it

Appendix 1s, Tables 1s–14s
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**MAIN RECOMMENDATIONS**

ESGE recommends offering stone extraction to all patients with common bile duct stones, symptomatic or not, who are fit enough to tolerate the intervention.  
Strong recommendation, low quality evidence.

ESGE recommends liver function tests and abdominal ultrasonography as the initial diagnostic steps for suspected common bile duct stones. Combining these tests defines the probability of having common bile duct stones.  
Strong recommendation, moderate quality evidence.

ESGE recommends endoscopic ultrasonography or magnetic resonance cholangiopancreatography to diagnose common bile duct stones in patients with persistent clinical suspicion but insufficient evidence of stones on abdominal ultrasonography.  
Strong recommendation, moderate quality evidence.

ESGE recommends the following timing for biliary drainage, preferably endoscopic, in patients with acute cholangitis, classified according to the 2018 revision of the Tokyo Guidelines:  
- severe, as soon as possible and within 12 hours for patients with septic shock
- moderate, within 48–72 hours
- mild, elective.  
Strong recommendation, low quality evidence.

ESGE recommends endoscopic placement of a temporary biliary plastic stent in patients with irretrievable biliary stones that warrant biliary drainage.  
Strong recommendation, moderate quality of evidence.

ESGE recommends limited sphincterotomy combined with endoscopic papillary large-balloon dilation as the first-line approach to remove difficult common bile duct stones.  
Strong recommendation, high quality evidence.

ESGE recommends the use of cholangioscopy-assisted intraluminal lithotripsy (electrohydraulic or laser) as an effective and safe treatment of difficult bile duct stones.  
Strong recommendation, moderate quality evidence.

ESGE recommends performing a laparoscopic cholecystectomy within 2 weeks from ERCP for patients treated for cholecystolithiasis to reduce the conversion rate and the risk of recurrent biliary events.  
Strong recommendation, moderate quality evidence.

1 Methods

The ESGE commissioned this Guideline (chair J.v.H.) and appointed a guideline leader (G.M.), who invited the listed authors to participate in the project development. The key questions were prepared by the coordinating team (G.M. and G.P.) and then approved by the other members. The coordinating team formed task-force subgroups, each with its own leader, and divided the key topics among these task forces (Appendix 1s; see online-only Supplementary Material).

Each task force performed a systematic literature search to prepare evidence-based and well-balanced statements on their assigned key questions. The coordinating team independently performed systematic literature searches, with PubMed/Medline, EMBASE, the Cochrane Library, and the internet being finally searched for papers published until April 2018. The search focused on fully published randomized controlled trials (RCTs), meta-analyses, and prospective series. Retrospective analyses, case series, and abstracts were also included if they addressed topics not covered in the prospective studies. The literature search was restricted to papers published in English after 1990. After further exploration of their content, articles that contained relevant data were then included and summarized in the literature tables for the key topics (Tables 1s–14s). All selected articles were graded by the level of evidence and strength of recommendation according to the GRADE system [12]. Each task force developed a draft and proposed statements on their assigned key questions, which were discussed and voted on during plenary meetings held in February 2017 in Düsseldorf, Germany, and in October 2017 in Barcelona, Spain. In April
3 General principles

3.1 Epidemiology

Gallstones are common with a prevalence as high as 10%–15% in developed countries [1–3] and an overall cumulative incidence of gallstone formation of 0.60% per year [13].

According to a large Swedish registry [14], the prevalence of CBDSs detected during intraoperative cholangiography (IOC) is 11.6% in patients with symptomatic gallbladder stones; other prospective studies have described a prevalence of CBDSs detected during IOC ranging from 4.6% to 12% in Europe [15, 16], and up to 20.9% in South America [17]. A prevalence of 8%–18% for CBDSs in patients with symptomatic gallbladder stones has been proposed [18].

No studies have focused on the prevalence of CBDSs in patients with asymptomatic gallbladder stones, as most studies are based on IOC during cholecystectomy for symptomatic disease.

3.2 The natural history of CBDSs and recommended handling

The natural history of CBDSs is not well described, but data from the GallRiks study [14] suggest that, if CBDSs are detected, they should be removed to reduce the risk of complications over time: of the 3969 patients with CBDSs on IOC, 594 had their CBDSs left in place. During follow-up, ranging from 0 to 4 years, 25.3% of patients with CBDSs in situ developed complications (pancreatitis, cholangitis, or obstruction of the bile duct) vs. 12.7% of patients who had undergone CBDS removal (odds ratio [OR] 0.44, 95%CI 0.35–0.55). The likelihood of an unfavorable outcome increased with the size of the CBDS, but the incidence of complications even for CBDSs less than 4 mm was 5.9% vs. 8.9% for larger CBDSs (OR 0.52, 95%CI 0.34–0.79).

These data support a strategy of extracting CBDSs regardless of size, although some previous studies have suggested that small unsuspected stones can pass spontaneously without the need for intervention [16, 19–22] (Table 1s). The spontaneous passage of small CBDSs without serious complications has been documented by Collins [15] in 24 of 46 patients with a filling defect observed on IOC in whom a cystic duct catheter was left in place after laparoscopic cholecystectomy. The asymptomatic migration of small (less than 8 mm) stones has also been noted in the interval between diagnosis at endoscopic ultrasonography (EUS) and ERCP [23].

In spite of the absence of controlled studies, some factors favor a policy of stone extraction in asymptomatic CBDSs: the occurrence of unfavorable outcomes is not different in patients...
classified as asymptomatic or symptomatic [14]; the lifetime risk of untreated CBDSs is unknown and may be higher than that reported; severe complications such as cholangitis, pancreatitis, or obstructive jaundice can occur without preceding warning symptoms [24]. A conservative approach can only be considered in patients where the risks of surgical or endoscopic CBDS extraction are higher than the risks of leaving stones in situ. When offering stone extraction to asymptomatic patients with CBDSs, patients should be made aware of the limited evidence regarding this recommendation and of the risk of ERCP, which may be elevated in asymptomatic patients [25].

4 Defining the risk of having CBDSs

4.1 Initial evaluation

**RECOMMENDATION**

ESGE recommends liver function tests and abdominal ultrasonography as the initial diagnostic steps for suspected common bile duct stones. Combining these tests defines the probability of having common bile duct stones. Strong recommendation, moderate quality evidence.

Patients at risk of having CBDSs, such as patients with gallstones who present with symptoms, undergo non-invasive tests such as liver function tests (LFTs) and abdominal ultrasound as triage to determine the need for further evaluations to confirm the presence of CBDSs.

A recent systematic review including five studies assessed the diagnostic accuracy of LFTs (1 study) and ultrasonography (5 studies) for CBDSs [26]. All studies were of poor methodological quality. The sensitivities of bilirubin (cutoff > 22.23 μmol/L or > 1.3 mg/dL) and alkaline phosphatase (cutoff > 125 U/L) for CBDSs were 84% (95% confidence interval [CI] 64%–95%) and 91% (95% CI 74%–99%), respectively; the specificities were 91% (95% CI 86%–94%) and 79% (95% CI 74%–84%), respectively. Regarding ultrasonography, sensitivity was 73% (95% CI 44%–95%) and specificity was 91% (95% CI 84%–95%). Ultrasonography findings were considered positive if there was visualization of CBDSs and/or CBD dilatation.

Multidetector multiphase computed tomography (CT), when used to investigate patients with CBDSs, had a sensitivity of 78% and a specificity of 96% in a retrospective study [27]. The size and composition of the stones significantly affects CT accuracy, which is significantly lower when stones are less than 5 mm (56.5% vs. 81.2%) or have a similar density to bile [28]. Coronal reconstruction does not increase the diagnostic efficiency of CT scanning [29].

The pretest probability of CBDSs in suspected patients is essential to select which patients will benefit most from a more accurate assessment. Several predictive models have been developed combining clinical, biochemical, and ultrasonography findings in order to identify high risk patients [30–34] (Table 2s).

The risk of having CBDSs in spite of normal LFTs and ultrasonography has been adequately evaluated in two studies [35, 36]. In a large study including 765 patients with ERCP-proven CBDSs, 541 had previously documented LFTs and 29 (5.4%) had normal LFTs. Age more than 55 years and the presence of pain were independently associated with normal LFTs in patients with CBDSs [35]. A more recent retrospective study including 413 patients with gallstones who underwent ultrasonography and magnetic resonance cholangiopancreatography (MRCP) for suspected CBDSs showed that 109/413 (26.3%) had CBDSs revealed on the MRCP, but in 7/109 (6.4%) ultrasonography and LFTs (one or more of total bilirubin, ALP, AST, ALT, or GGT) were normal [36] (Table 2s).

4.2 Role of EUS and MRCP

**RECOMMENDATION**

ESGE recommends endoscopic ultrasonography or magnetic resonance cholangiopancreatography to diagnose common bile duct stones in patients with persistent clinical suspicion but insufficient evidence of stones on abdominal ultrasonography. Strong recommendation, moderate quality evidence.

The diagnostic accuracy of EUS and MRCP for the detection of CBDSs has been widely investigated. Meerimal and co-workers in a recent meta-analysis of five head-to-head studies [37] demonstrated that diagnostic accuracy was high for both methods (sensitivity 97% vs. 90% and specificity 87% vs. 92% for EUS and MRCP, respectively), but the overall diagnostic OR of EUS was significantly higher (P = 0.008). They showed that this was mainly because of the significantly higher sensitivity of EUS, as compared with that of MRCP, especially in the detection of small stones, while the specificity was not significantly different. High accuracy for both methods was demonstrated by another meta-analysis including 18 studies (2 comparative, 5 evaluating MRCP alone and 11 EUS alone) [38]. Sensitivity and specificity were respectively 95% (95% CI 91%–97%) and 97% (95% CI 94%–99%) for EUS, and 93% (95% CI 87%–96%) and 96% (95% CI 90%–98%) for MRCP.

Various considerations may help to select the most adequate procedure if both are available and the patient does not present any factors that would impede MRCP, such as claustrophobia, obesity, cardiac pacemaker, or metal clips. Sonnemberg and colleagues [39], performing a threshold analysis on costs, concluded that, for a pretest probability of CBDSs < 40%, MRCP would represent the procedure of choice. For a pretest probability in the range 40%–91%, EUS should be the preferred imaging modality, because it allows an ERCP to be performed in the same session if the EUS results are positive for CBDSs. However, the applicability of their results is limited because they are strictly influenced by the costs of each procedure and local rules of reimbursement. Furthermore, logistic issues regarding the scheduling of an EUS and an ERCP during the same examination slot should be taken into consideration. The minimally invasive nature of MRCP, its suitability if there is al-
tered gastroduodenal anatomy, and its ability to visualize the whole biliary tree should also be considered when deciding between the two methods.

4.3 An algorithm for investigating suspected CBDSs

Fig. 1 depicts an algorithm for investigating suspected CBDSs. ERCP can be performed in patients without cholangitis only when CBDSs are visible on imaging modalities that have a high specificity. Normal LFTs and ultrasonography indicate a low risk of CBDSs and no further evaluations are recommended, unless the patient continues to have symptoms that suggest CBDSs. All other pictures depict an intermediate risk of CBDSs, which should prompt further investigation by EUS or MRCP. In the absence of a morphological diagnosis of CBDSs, ERCP should be performed immediately only in patients with a clinical picture of cholangitis (see section 8.1).

5 Performing ERCP

5.1 Antibiotic prophylaxis

RECOMMENDATION

ESGE suggests against the use of routine antibiotic prophylaxis before ERCP for bile duct stones.

Weak recommendation, moderate quality evidence.

The ERCP procedure is often associated with the occurrence of bacteremia [40], which is mostly transient. The occurrence of cholangitis is an infrequent event, which occurs mainly in a subgroup of patients at higher risk, such as those with biliary obstruction and incomplete biliary drainage [41].

The role of antibiotic prophylaxis in reducing the rate of cholangitis has been evaluated by several RCTs, which differed significantly in terms of type of antibiotic, duration of administration, and indications for ERCP [42–47] and three meta-analyses (Table 3) [48–50].

The most recent meta-analysis of nine RCTs [50] (1573 patients) indicated that antibiotic prophylaxis could reduce bacteremia and may prevent cholangitis and septicemia in patients undergoing elective ERCP. However, in random-effects meta-analyses, only the effect on bacteremia remained significant; if ERCP resolved the biliary obstruction at the first procedure, there was no significant benefit in using antibiotic prophylaxis to prevent cholangitis (relative risk [RR] 0.98, 95% CI 0.35–2.69, only three trials) [50].

Cotton et al. [51] reported in a retrospective series of 11 484 ERCPs performed over 11 years that, in spite of a progressive reduction in the use of antibiotic prophylaxis over the years (from 95% to 25% of ERCP patients), the incidence of infections decreased from 0.48% to 0.25%. In the multivariate model, endoscopic treatment of CBDSs was not associated with an increased risk of developing cholangitis after ERCP. All these data suggest that not all patients benefit from antibiotic prophylaxis and that patients with CBDSs should not routinely receive antibiotic prophylaxis before ERCP (Table 3).

Patients with ongoing acute cholangitis should already be receiving antibiotics at the time of intervention and additional antibiotics are not recommended.
Antibiotic prophylaxis should be considered for patients with refractory CBDs undergoing extracorporeal shock wave lithotripsy (ESWL) for CBD clearance [52, 53]. No data are available for patients undergoing cholangioscopy-assisted lithotripsy; nevertheless, antibiotic prophylaxis is likely to be advisable as two recent prospective studies have demonstrated that cholangioscopy per se may carry a risk of bacteremia that ranges from 8.8% to 13.9% and that up to 9.7% of patients may develop infective complications despite the use of post-procedure antibiotics [54]. Biopsy sampling, older age, previous stent placement, and laser lithotripsy or electrohydraulic lithotripsy (EHL) were likely to increase the risk of developing either infection or persistent bacteremia.

Antibiotic prophylaxis in some special conditions, such as in liver transplant patients, was considered to be out of the scope of this guideline.

5.2 Gaining access to the biliary tree

**RECOMMENDATION**

ESGE recommends that an adequate exit for the stones that are to be removed should be provided according to the papilla and common bile duct anatomy and the stone size.

Strong recommendation, low quality evidence.

The various technical aspects, either of deep biliary cannulation or endoscopic sphincterotomy, have been reviewed in other guidelines [55, 56]. A critical step to obtain successful stone extraction is to provide an adequate exit for the stones that are to be removed by endoscopic sphincterotomy alone, endoscopic papillary balloon dilation alone, or a combination of both [55, 57]. Papillary balloon dilation alone however remains unpopular and is not advocated for routine use as it is associated with a lower technical success for stone clearance, the need for mechanical lithotripsy more frequently than with endoscopic sphincterotomy, and a presumed increased risk of pancreatitis [55, 58, 59]. At present, the use of primary papillary balloon dilation without endoscopic sphincterotomy is considered mainly in patients with coagulopathy or with altered anatomy who have stones smaller than 8 mm [55]. The appropriate length of endoscopic sphincterotomy should be adjusted according to the papillary anatomy and stone size. Data on the effect of endoscopic sphincterotomy length on the rate of stone recurrence are presently contradictory [60, 61].

5.3 Stone extraction

**RECOMMENDATION**

ESGE recommends that balloon and basket catheters are equally effective and safe for common bile duct stone removal.

Strong recommendation, moderate quality evidence.

Two multicenter RCTs have compared the efficacy of balloon vs. basket catheters for the extraction of CBDs sized $\leq 10$ mm or $< 11$ mm after endoscopic sphincterotomy [62, 63]. In one RCT (158 patients), the balloon catheter achieved a higher clearance rate than the basket catheter (92.3% vs. 80.0%) [62]. The other RCT (184 patients) reported similar efficacies for basket and balloon catheters for stone extraction, but a stone diameter of $<6$ mm was independently associated with failed stone removal within 10 minutes using a basket catheter, because of the inability to grasp the stone with the basket [63]. No differences in safety were reported in the two studies.

Stone extraction baskets and balloons are commercially available in various configurations. As yet, no comparative studies between various models of basket catheters exist [64]. In general, choosing which device to use depends mainly on the anatomy of the bile duct, the stone characteristics, financial considerations, and personal preferences.

5.4 Biliary stenting for incomplete removal of CBDs

**RECOMMENDATION**

ESGE recommends endoscopic placement of a temporary biliary plastic stent in patients with irretrievable biliary stones that warrant biliary drainage.

Strong recommendation, moderate quality of evidence.

Endoscopic sphincterotomy with stone extraction has success rates of 80%–90% in the treatment of CBDs [65]. When CBDs cannot be completely removed, a plastic stent is often placed to relieve the obstruction, before a second attempt at stone extraction is made or a subsequent surgical intervention is undertaken. An indwelling endoprosthesis may reduce the volume and number of stones, as reported by nine studies (three prospective [66–68] and six retrospective [69–74]) involving a total of 364 patients (Table 4s). The success rate for stone removal after previous ERCP with biliary stenting has been reported to range from 44% to 96% (Table 5s) [66–73, 75, 76].

The mechanism by which stones change in number and size is unclear. It is likely that continuous friction between the plastic stent and the stones produces stress forces that facilitate the disintegration of stones and reduce their size [71].

There are no studies comparing the different types of biliary plastic stents or plastic vs. metal stents. Similarly, there are no specific prospective comparative data with regard to whether one or more than one biliary stent is preferable in patients with incomplete stone removal. In the only retrospective published study, 64 elderly patients ($\geq 65$ years) with large ($\geq 20$ mm) or multiple ($\geq 3$) CBDs underwent placement of single or double plastic stents at the time of initial ERCP. Approximately 3 months later, stone removal was attempted at a second ERCP using standard techniques. Double plastic biliary stenting (7 or 8.5 Fr) was superior to single stenting (8.5 Fr) in maintaining higher 3-month stent patency rates ($P = 0.008$), but was similar in terms of reducing the size and
number of stones [77]. No differences in complications were found.

In recent years, some studies with small patient series have evaluated the management of incomplete stone removal using fully covered self-expanding metal stents (SEMSs) (Table 6s) [78–80]. In the largest retrospective case series [80], 44 patients received covered SEMSs (diameter 10 mm, length 60 mm). After a median in-stent duration of 8 weeks, 36/42 stents (82 %) were removed with successful duct clearance. The median post-procedure follow-up was 15 months. Four patients (9 %) developed post-ERCP pancreatitis (mild in 3, moderate in 1), two patients (4 %) developed post-procedure cholangitis, and one (2 %) hematemesis. During follow-up, 10 patients (22.7 %) had incidental stent migration (distally in 6, proximally in 4), but in none of them was it clinically significant, with all being discovered at the time of subsequent ERCP.

At present, covered SEMSs can be considered as an alternative to plastic stents to drain the bile ducts after unsuccessful stone removal, but there are uncertainties over how long the stents should be left in place and the cost–benefit ratio of the treatment.

5.5 Timing of stent removal/exchange

**RECOMMENDATION**

EGSE recommends that a plastic stent placed because of incomplete common bile duct stone clearance should be removed or exchanged within 3–6 months to avoid infectious complications.

Strong recommendation, moderate quality of evidence.

**RECOMMENDATION**

EGSE recommends against the use of definitive biliary stenting in patients with incomplete common bile duct stone clearance because of the high complication and mortality rates on medium-term follow-up.

Strong recommendation, moderate quality of evidence.

Intervals of 3–6 months for routine ERCP and stent change are commonly recommended to reduce the rate of complications, mainly cholangitis [70, 76]. One randomized prospective study including 78 patients with primary failure for biliary stone removal who had undergone insertion of a 10-Fr plastic stent compared two different managements: either systematic stent exchange every 3 months or stent exchange on demand if symptoms occurred. Cholangitis was significantly more frequent in the group with on-demand stent exchange (35.9 % vs. 7.7 %; P<0.03) [81].

Definitive stenting has been suggested for difficult CBDSs in the elderly with co-morbidities and a limited life expectancy, given that ERCP in patients aged >90 years may carry risks of bleeding, cardiopulmonary events, and mortality that are increased two to three fold (incidence rate ratio [IRR] 2.4; 95 % CI 1.1–5.2; IRR 3.7, 95 % CI 1.0–13.9; and IRR 3.8, 95 % CI 1.0–14.4, respectively), and that patients aged >80 years had a two-fold risk of procedure-related death (IRR 2.4; 95 % CI 1.3–4.5) [82]. However, definitive stenting for CBDSs should be approached with caution. Six series, including 230 patients [83–88], have reported a complication rate for definitive biliary stenting, mainly cholangitis, of 34 %–63 %, with a 2.3 %–23.5 % mortality rate during 16–39 months of follow-up (Table 7s).

5.6 Role of dissolution therapy

**RECOMMENDATION**

EGSE suggests against the use of ursodeoxycholic acid or other choleretic agents, either for the treatment of CBDSs or to prevent the recurrence of CBDSs after endoscopic clearance.

Weak recommendation, moderate quality of evidence.

Ursodeoxycholic acid (UDCA) with or without terpene preparation (Rowachol) has been suggested as a complementary treatment to induce stone reduction when used together with biliary endoprostheses, but in two RCTs the addition of UDCA therapy to endoprosthesis treatment showed no effect on stone size reduction or successful duct clearance [66, 68].

UDCA has been administered with the aim of reducing the rate of stone recurrence after successful removal of CBDSs in patients with risk factors such as CBD dilatation, delayed biliary emptying (biliary stricture, papillary stenosis), or the presence of gallstones, a periampullary diverticulum, or systemic diseases that cause stone formation [89–91]. Two RCTs have investigated this issue and both revealed no significant difference regarding stone recurrence [92, 93].

6 Difficult stones

“Difficult” biliary stones are defined according to their diameter (>1.5 cm), number, unusual shape (barrel-shaped), or location (intrahepatic, cystic duct), or because of anatomical factors (narrowing of the bile duct, distal to the stone, sigmoid-shaped CBD, stone impaction, shorter length of the distal CBD, or acute distal CBD angulation <135°) [94, 95]. Clearance of a difficult stone cannot usually be obtained using standard techniques, so multiple procedures and additional interventional techniques (large-balloon dilation, mechanical lithotripsy, cholangioscopy-assisted electrohydraulic/laser lithotripsy, or ESWL) may be required [96].
6.1 Gaining access to the biliary tree and basic treatment for the management of difficult stones

**RECOMMENDATION**

ESGE recommends limited sphincterotomy combined with endoscopic papillary large-balloon dilation as the first-line approach to remove difficult common bile duct stones.

Strong recommendation, high quality evidence.

Since the original description in 2003 by Ersoz et al., the use of endoscopic papillary large-balloon dilation (EPLBD) after endoscopic sphincterotomy has become widespread for the management of difficult CDBSs [97]. Overall, seven RCTs [98 – 104] and five meta-analyses [105 – 109] have compared the efficacy and safety of EPLBD with endoscopic sphincterotomy vs. endoscopic sphincterotomy alone (Table 8s).

In summary, endoscopic sphincterotomy + EPLBD reduces the need for mechanical lithotripsy by about 30% – 50% in comparison with endoscopic sphincterotomy alone [100, 102, 103], while the overall rate of successful stone removal remains identical [105 – 108]. The rate of major adverse events, mainly pancreatitis, bleeding, and perforation, between the two groups was similar in 6 of 7 RCTs [99 – 104], whereas it was significantly lower for EPLBD plus endoscopic sphincterotomy compared with endoscopic sphincterotomy alone in the study by Stefani-dis et al. [98]. In a systematic review (30 studies considered), the rate of overall adverse events (pancreatitis, bleeding, perforation) was lower for endoscopic sphincterotomy with EPLBD than for endoscopic sphincterotomy alone (8.3% vs. 12.7%, OR 1.60; P<0.001) [110].

Based on these data, if large bile duct stones are seen on ERCP or cross-sectional imaging, endoscopic sphincterotomy combined with EPLBD can be used as a first-line approach to facilitate difficult biliary stone removal [111]. Another possible indication for performing EPLBD is the treatment of recurrent CBDs in individuals with a previous endoscopic sphincterotomy because extension of an endoscopic sphincterotomy may be associated with a high risk of bleeding and perforation [112 – 115] (Fig. 2).

EPLBD can be performed after either a large [97, 98, 114, 116 – 121] or limited endoscopic sphincterotomy [99, 120, 122 – 127]. A multicenter retrospective analysis from Asia including 946 patients [120] found large endoscopic sphincterotomy before EPLBD to be independently associated with an increase in overall adverse events (OR 3.4, 95% CI 1.8 – 6.6; P<0.001). The risk of bleeding was higher in the large vs. limited endoscopic sphincterotomy group (OR 6.2, 95% CI 2.4 – 16.3; P<0.001). Perforation was found in only nine patients but it was fatal in three of them. Although only distal CBD stricture and not size of endoscopic sphincterotomy was an independent predictor of perforation, two of the three fatal cases were associated with a large endoscopic sphincterotomy.
recent literature review suggested performing a small or mid-sized endoscopic sphincterotomy (1/3 to 1/2 of the distance to the papillary roof) rather than a large one before EPLBD [128]. Nevertheless, in real life most endoscopists decide to perform EPLBD when their attempts to remove the stones have failed after having already performed a complete endoscopic sphincterotomy.

EPLBD is performed with a dilation balloon diameter that ranges from 12 to 20 mm. Criteria for deciding the balloon size for EPLBD have not been specifically evaluated in prospective studies. In most published studies, the diameter of the distal part of the CBD has been used as the criterion to select the size of the balloon [98–100, 120, 121]. The risk of perforation increases when the diameter of the balloon is larger than the diameter of the distal part of the CBD and in the presence of a stricture [111].

The vast majority of studies have reported a dilation duration of 10–180 seconds from the disappearance of the waist, with only three studies reporting a duration in excess of 60 seconds [110]. One RCT has demonstrated that the rate of complications is similar whether EPLBD duration is either 30 or 60 seconds [121]. Moreover, a meta-analysis has demonstrated that a short duration (<1 minute) vs. a long duration (≥1 minute) for EPLBD does not significantly affect the rate of CBD clearance [105]. According to these data, the duration of balloon dilation should be between 30 and 60 seconds from the disappearance of the waist [111].

6.2 Mechanical lithotripsy

Mechanical lithotripsy is the simplest available method of fragmenting CBD stones. It consists of entrapping the stone within a reinforced basket and then crushing it by closing the basket against a metal spiral sheath. Two techniques of mechanical lithotripsy are used: out of the scope (OTS) and through the scope (TTS). The OTS technique represents a “salvage” procedure to be performed when a standard basket engages a large stone and becomes impacted in the papilla, while the TTS technique is preferred in elective cases.

Mechanical lithotripsy has been reported to be an effective and safe technique, but multiple sessions may be required. The reported success rates range between 76% and 91% and overall complications from 3% to 34% with minimal mortality [129–134] (Table 9). Three studies have evaluated the predictors of mechanical lithotripsy failure using multivariate analysis. In a retrospective study [130], stone size was the only variable that affected the success rate. A subsequent prospective study [129] reported that stone size should be considered together with the diameter of the bile duct, suggesting that only the presence of stone impaction significantly predicted the failure of mechanical lithotripsy. In another more recent retrospective study [132], stone impaction, stone size >30 mm, and stone to CBD diameter ratio >1 were significant predictors of mechanical lithotripsy failure.

The most common and feared complications of mechanical lithotripsy are entrapment of the basket, a broken basket, a traction wire fracture, or a broken handle. In a multicenter study by Thomas et al. [135], including 643 patients and using the TTS technique, the incidence of mechanical lithotripsy-related technical complications was 3.5%. These complications are usually treated by other types of lithotripsy (OTS, ESWL, or cholangioscopy-assisted lithotripsy), sphincterotomy extension, or stenting.

6.3 Cholangioscopy-assisted lithotripsy

Intraductal shock wave lithotripsy represents an alternative method to fragment bile stones and allow their removal. There are two methods of generating shock waves in a fluid, using either a bipolar probe capable of generating a spark in the case of EHL or a pulsed dye laser system in the case of laser lithotripsy. Both EHL and laser lithotripsy are preferably performed under direct visualization with cholangioscopic guidance.

There are three major techniques for cholangioscopy: (i) a dual-operator dedicated mother–baby cholangioscopic (MBC) system; (ii) a single-operator catheter-based cholangioscopic system (SOC); and (iii) direct use of an ultrasmall endoscope or slim gastroscope (direct peroral cholangioscopy [DPOC]). The procedures vary with respect to the number of operators, maneuverability, image quality, and method of access, resulting in variable success rates. A detailed ESGE technology review on cholangioscopy techniques was published recently [136]. All three techniques allow laser lithotripsy and EHL.

Korrapati et al. have reviewed the efficacy of peroral cholangioscopy for difficult bile duct stones [137]. They estimated an overall rate of stone clearance of 88% (95% CI 85–91%), with SOC showing a high technical success rate. No attempt was made to compare EHL and laser lithotripsy.

Both EHL and laser lithotripsy are effective methods for the removal of difficult bile duct stones, with a 69%–81% clearance rate in one session and a 97%–100% clearance rate after multiple sessions [138–141]. However, no direct comparisons between the different methods have been published. In one
recent RCT, patients with bile duct stones > 1 cm were treated with either laser lithotripsy or conventional therapy (including EPLBD and mechanical lithotripsy) and achieved one-session endoscopic clearance rates of 93% and 67%, respectively [142].

When looking at the rough data of Korrapati et al. [137], the complication rate ranged between 0% and 25% (mean 7%, 95% CI 6%–9%). Cholangitis is the most frequently reported complication [139–141]. Pancreatitis is a rare complication, probably owing to the high percentage of pre-existent sphincterotomies [139].

Overall, the available data suggest that intraluminal lithotripsy is an effective and safe method to treat difficult biliary stones (Table 10s; Fig. 2), but there are no data supporting the superiority of one method over another.

6.4 Extracorporeal shock wave lithotripsy

**RECOMMENDATION**

ESGE suggests considering extracorporeal shock wave lithotripsy when conventional techniques have failed to achieve bile duct clearance and the intraluminal lithotripsy techniques are not available. Weak recommendation, low quality evidence.

ESWL uses electrohydraulic or electromagnetic energy to generate shock waves that then travel through the soft tissues of the body to fragment CBDs [143].

ESWL is a complex and technically demanding procedure. A nasobiliary drain is inserted to allow fluoroscopic identification and targeting of CBDs and to perform continuous irrigation of the bile duct with saline during ESWL. In addition, multiple ESWL sessions and subsequent ERCP procedures to extract stone fragments are required.

Ductal clearance rates of 70%–90% have been reported with ESWL [52, 144–150].

Several controlled trials have compared ESWL with EHL or laser lithotripsy for stone disruption. These studies suggest that the efficacy of final duct clearance with laser lithotripsy is superior to that of ESWL (83%–97% vs. 53%–73%) [146, 151], while it is similar for EHL and ESWL (74% vs. 78.5%) [145].

ESWL-related adverse events range from 9% to 35.7%, including mostly cholangitis and pancreatitis [143, 145, 146, 152, 153]. Minor side effects such as pain, local hematomata formation, and microhematuria are common.

7 Endoscopic CBDS management and surgery

ERCP with stone clearance represents the primary and definitive treatment in patients with CBDSs and previous cholecystectomy. In patients with CBDSs and in situ gallbladder, both the management of CBDSs and gallbladder removal should be considered.

When ERCP is the selected technique to treat CBDSs, different options are available with regards to the sequencing of endoscopy and surgery. Basically, ERCP can be performed prior to (preoperative ERCP), during ongoing (intraoperative ERCP), or after (post-operative ERCP) cholecystectomy. Preoperative ERCP is most commonly practiced, as it is highly effective and both the endoscopist and the surgeon treat the patient in an environment that is tailored to their own needs and routines.

7.1 The sequential strategy

**RECOMMENDATION**

ESGE recommends performing a laparoscopic cholecystectomy within 2 weeks from ERCP in patients treated for choledocholithiasis to reduce the conversion rate and the risk of recurrent biliary events. Strong recommendation, moderate quality evidence.

Laparoscopic cholecystectomy represents the standard treatment for patients with CBDSs and gallbladder stones following endoscopic CBDs clearance. A Cochrane review in 2007 [154], which considered five RCTs involving 662 patients treated for choledocholithiasis with cholecystolithiasis, revealed an advantage of cholecystectomy. Over a follow-up time varying from 17 months to more than 5 years, mortality was higher in the wait-and-see group compared with the cholecystectomy group (14.1% vs. 7.9%; RR 1.78, 95% CI 1.15–2.75) and the difference persisted when only patients at high surgical risk were considered.

Similarly, endoscopic sphincterotomy followed by “wait and see” also resulted in a higher risk of biliary events, such as cholangitis, pancreatitis, jaundice, and biliary colic, as well as a higher risk for repeated biliary intervention (i.e. ERCP or percutaneous procedure): 35% of the patients managed with endoscopic sphincterotomy followed by “wait and see” eventually underwent rescue cholecystectomy. The outcome of rescue cholecystectomy in patients with an ASA >3 was not significantly different compared to elective cholecystectomy; however, patients unfit for surgery (i.e. ASA 4 and 5) were excluded in three of the five selected RCTs [155–157]. In the study by Suc et al. [158], 20% of the included patients were classified as ASA 3–4, and mortality was not significantly different between the two groups in the intention-to-treat analysis (3.1 vs. 0.9%). Also, in the RCT by Targarona et al. [159], mortality was not significantly different between the groups but, in the multivariate analysis, age, and not surgical risk, was an independent predictor of mortality.

Laparoscopic cholecystectomy after ERCP with endoscopic sphincterotomy is more difficult and when compared to standard laparoscopic cholecystectomy is mostly associated with a higher conversion rate and a higher rate of recurrent biliary events [157, 160, 161]. In this way, the timing of cholecystectomy is a critical issue [155, 157, 162–167] (Table 11s). The timing of cholecystectomy may be defined as early, delayed, or on demand, but definitions of “early” or “delayed” differ among the studies. In general, with the exception of the study by Donkervoort et al. [168], where the timing of cholecystectomy did not affect the outcomes, conversion
rate results are lower in the “early group” in all studies (4%–23% vs. 8%–55%); recurrent biliary events are lower when the laparoscopic cholecystectomy is performed “early” vs. “delayed or on demand” (2%–10% vs. 24%–47%) [155, 157, 162–167]. Overall, data are in favor of “early” laparoscopic cholecystectomy, but the exact timing remains controversial; despite this, waiting no longer than 2 weeks to perform laparoscopic cholecystectomy after ERCP seems to be advisable.

In patients with acute biliary pancreatitis (ABP) and in situ gallbladder, cholecystectomy is recommended to avoid a recurrence of pancreatitis. Some of these patients may have previously undergone ERCP and endoscopic sphincterotomy. The timing of cholecystectomy in mild ABP has been examined in two RCTs that randomized patients either to cholecystectomy within 48 hours of admission vs. after resolution of abdominal pain and normalizing trend of laboratory enzymes (n=50) [169], or to cholecystectomy during the same admission vs. 4 weeks later (n=266) [170]. Both studies concluded in favor of early cholecystectomy because it prevents recurrent gallstone-related complications (one study), shortens hospitalization (one study), and is equally safe (both studies). Similar conclusions were reached in a meta-analysis (eight cohort studies and one RCT, 998 patients) [171]. For severe ABP, data are limited and, based on observational studies [172, 173], it is recommended that cholecystectomy is performed once peripancreatic collections and local complications have resolved, generally beyond 6 weeks, to minimize the risk of infection in the peripancreatic collection.

In patients who do not undergo cholecystectomy following ABP, endoscopic biliary sphincterotomy reduces biliary events, in particular pancreatitis, during follow-up [171, 174, 175]. The most recent retrospective study (1119 patients) found that recurrent pancreatitis developed in 8.2% vs. 17.1% of patients with their gallbladder left in situ after ABP who had ERCP vs. no ERCP, respectively [174]. However, the gallbladder should be left in situ only in patients who are unfit for surgery as a meta-analysis (five RCTs, 662 patients) has shown that endoscopic CBD clearance alone is inferior to prophylactic cholecystectomy associated with CBD clearance in terms of mortality and recurrent biliary events [154].

7.2 Intraoperative ERCP

**RECOMMENDATION**

ESGE suggests considering intraoperative rendezvous ERCP in patients with common bile duct stones undergoing cholecystectomy.

Weak recommendation, moderate quality evidence.

Intraoperative ERCP can be performed during laparoscopic cholecystectomy when an IOC demonstrates the presence of CBDs; alternatively, it can be planned either as a one-stage approach in the treatment of combined cholecysto-choledocholithiasis or after the failure of a preoperative endoscopic attempt at CBD clearance.

Conventional ERCP can be performed intraoperatively, but it exposes the patient to similar risks to a conventional ERCP performed preoperatively, albeit it is performed during the same anesthesia [176, 177]. Conversely, intraoperative ERCP with rendezvous cannulation offers the advantages of being a single-stage procedure and decreasing the risk of post-ERCP pancreatitis. Although each individual clinical trial is underpowered to validate this, there are six RCTs [176, 178–182] and approximately 15 observational studies pointing in the same direction [177, 183–197] (Tables 12s and 13s). These results have been confirmed by six recent meta-analyses [198–202]. The most recent of these, comparing intraoperative rendezvous ERCP with sequential management, mainly laparoscopic cholecystectomy and preoperative ERCP, reported equal efficacy in terms of stone clearance rate (93% vs. 95%), but a significantly lower rate of morbidity (6% vs. 11%; OR 0.54, 95% CI 0.31–0.96; P < 0.03), including post-ERCP pancreatitis (0.6% vs. 4.4%; OR 0.19, 95% CI 0.06–0.67; P = 0.01) and length of hospital stay in the intraoperative ERCP group [202]. In addition, the Swedish GallRiks registry, comprising 12 718 ERCP procedures, demonstrated a substantial 50% risk reduction in post-ERCP pancreatitis (3.6% vs. 2.2%; OR 0.5, 95% CI 0.2–0.9; P < 0.002) when rendezvous cannulation was practiced [203].

Intraoperative rendezvous ERCP does however carry logistical problems related to the prolonged surgical time and the need to perform ERCP in an environment that is not adapted for endoscopy [180, 182, 189, 191, 204]. Failure to pass the guidewire along a narrow cystic duct or papilla is reported in about 8% of cases (Table 12s); if this happens, the endoscopist must rely on conventional cannulation techniques and their associated risks.

7.3 Surgical treatment of CBDs

**RECOMMENDATION**

ESGE suggests that, in patients undergoing laparoscopic cholecystectomy, transcystic or transduodenal exploration of the common bile duct is a safe and effective technique for common bile duct stone clearance. The recommendation takes into account that management is dependent on local expertise and resources.

Weak recommendation, moderate quality evidence.

The surgical treatment of CBDs can be performed during both laparoscopic and open cholecystectomy. It offers the valuable opportunity to definitively treat patients with combined cholecystolithiasis and choledocholithiasis in a one-stage procedure.

Several studies have compared laparoscopic bile duct exploration during laparoscopic cholecystectomy with pre- or postoperative ERCP and have demonstrated no significant differences in clinical outcomes [205–207]. However, one-stage procedures, such as laparoscopic CBD exploration or combined endo-laparoscopic approaches, usually result in a shorter hospital stay [208–217]. Moreover, a recent meta-analysis has demonstrated that the one-stage laparoscopic procedure has
a higher success rate than the sequential endo-laparoscopic ap-
proach [218].

It is of note that the results of surgical treatment of CBDSs,
which are generally excellent in published reports, usually origi-
nate from laparoscopic centers of excellence, and there are
hardly any data on outcomes by less experienced surgeons.
Moreover, there is a trend over the last decades that the use of
endoscopic management is increasing and surgical trainees are
not gaining adequate experience in CBD exploration [219].

8 Special situations

Acute cholangitis and ABP may complicate CBDSs, resulting in a
more difficult therapeutic approach. Moreover, CBDSs may oc-
cur in special clinical settings, such as in pregnant women. The
endoscopic management of ABP was the object of the ESGE
Guideline on endoscopic treatment of necrotizing pancreatitis
[220].

8.1 Acute cholangitis

The majority of patients with gallstone cholangitis have mild-
to-moderate disease that usually responds to antibiotic ther-
apy. However, 15%–30% of patients have severe disease that
needs to be handled with urgent biliary decompression [221].

Identification and stratification of cholangitis severity is fun-
damental to selecting the appropriate treatment.

**RECOMMENDATION**

ESGE recommends using the 2018 revision of the Tokyo
Guidelines to classify the severity of acute cholangitis. Strong recommendation, low quality evidence.

The 2013 revision of the Tokyo Guidelines [221], recently
confirmed by the 2018 revision [222], classifies acute cholangi-
tis as:

- severe, dysfunction of at least one of the following systems:
  cardiovascular, neurological, respiratory, renal, hepatic, or
  hematological system (specific criteria are stated for each
  item)
- moderate, any of the following: white blood cell count
  >12,000 or <4000/mm³, fever ≥39 °C, age ≥75 years, total
  bilirubin ≥5 mg/dL, or hypoalbuminemia
- mild, no criteria of moderate/severe cholangitis.

Companion mobile applications of the 2018 Tokyo Guidelines
allow easy assessment of the severity of acute cholangitis

8.2 Timing of ERCP in acute cholangitis

**RECOMMENDATION**

ESGE recommends the following timing for biliary drain-
age, preferably endoscopic, in patients with acute cho-
langitis, classified according to the 2018 Tokyo Guid-
elines:

- severe, as soon as possible and within 12 hours for pa-
  tients with septic shock
- moderate, within 48–72 hours
- mild, elective.

Strong recommendation, low quality evidence.

Twelve studies (18,206 patients), all retrospective, have an-
alyzed the relationship between the timing of biliary drainage
and different outcomes (Table 14). An international study
from 28 intensive care units published in 2016 included 260 pa-
tients with septic shock (defined as hypotension requiring vaso-
pressors plus several other criteria); it found that waiting longer
than 12 hours from the onset of shock to successful biliary
drainage was associated with higher in-hospital mortality (OR
3.4, 95% CI 1.12–10.31) [223]. Overall, in-hospital mortality
was 37% and median time to biliary drainage was 12 hours,
with 10% of patients having drainage after 48 hours [223].

The other 11 studies were not restricted to patients with dis-
ease that was so severe [224–234]; they revealed, among the
studies that analyzed the specific matter, that: mortality was
associated with delayed ERCP in two of four studies [223, 233];
organ failure (alone or as part of a composite index) was
associated with delayed ERCP in three of five studies
[226, 227, 230]; length of hospital stay was associated with the
timing of ERCP in seven of eight studies [225, 227, 229, 230,
232–234]; hospitalization costs were higher when ERCP was
delayed in both studies that analyzed that association [230,
233].

**RECOMMENDATION**

ESGE recommends other biliary drainage modalities (per-
cutaneous, surgical) in patients with acute cholangitis
due to common bile duct stones when ERCP is not feasi-
ble/successful within the recommended timeframes. Strong
recommendation, low quality evidence.

Failure of biliary drainage is a strong determinant of mortal-
ity, particularly in patients with severe cholangitis. For example,
in the abovementioned study of patients with septic shock
[223], 40 of 42 patients with failed biliary drainage (95.3%) died
as compared with 55 of 213 patients with successful biliary
drainage (25.8%). In that study, biliary drainage was achieved
by ERCP, percutaneous transhepatic biliary drainage (PTBD),
and surgery in 91, 90, and 34 patients, respectively. Similarly,
in a study not restricted to patients with severe disease [225],
three of six patients with failed biliary drainage (50%) died as
compared with two of 321 patients with successful biliary
drainage (0.6%).
8.3 Management of CBDSs in pregnant woman

RECOMMENDATION
ESGE recommends that therapeutic ERCP is a safe and effective procedure in pregnant women, provided that it is performed by experienced endoscopists and the radiation exposure to the fetus is kept as low as possible. Strong recommendation, moderate quality of evidence.

According to six retrospective studies (144 patients), ERCP in pregnant women seems to be a relatively safe examination throughout the whole gestation [235–240]. ERCP should only be performed for therapeutic purposes as EUS and MRCP are highly accurate for the diagnosis of biliary obstruction. Furthermore, it should be performed by experienced endoscopists as radiation dose, as well as the overall complication rate, decreases with the experience of the endoscopist [241–244].

With respect to the potential harm related to X-rays, ERCP is best carried out during the second trimester of pregnancy; during the first trimester, the phase of organogenesis, the fetus is especially sensitive to radiation and, during the third trimester, there is a close topographic proximity of the growing fetus to the path of the X-rays.

Guidelines have usually recommended using as little radiation as reasonably achievable [243,245]. A threshold radiation dose is assumed for deterministic effects only (10 mGy), not for stochastic effects (cancer induction) [246]. Therefore, as many steps as possible should be taken to keep radiation exposure as low as possible. These are described in the ESGE Guideline on radiation protection in digestive endoscopy [243]. Non-radiation ERCP (NR-ERCP) has also been proposed; it uses various techniques such as aspiration of bile through the cannulation catheter to confirm biliary cannulation, ultrasound guidance, peroral cholangioscopy, or a two-stage approach consisting of biliary stenting followed by stone extraction after parturition. A systematic review summarized 22 case reports and retrospective studies that used NR-ERCP (180 patients in total) [247]. They concluded that pregnancy outcomes were not significantly affected by NR-ERCP, although whether the avoidance of radiation is beneficial for the baby remains unknown, but noted that NR-ERCP is technically demanding.

Disclaimer

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