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

ESGE

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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 choledocholithiasis to reduce the conversion rate and the risk of recurrent biliary events.
Strong recommendation, moderate quality evidence.

PUBLICATION INFORMATION
This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It provides practical advice on how to manage common bile duct stones. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was adopted to define the strength of recommendations and the quality of evidence.

1 Introduction

Gallstones are a very common problem in developed countries [1 – 3]. Most patients with gallstones remain asymptomatic throughout their lifetime [4, 5], but 10 % – 25 % of them may develop biliary pain or complications [6 – 9], with an annual risk of about 2 % – 3 % for symptomatic disease [10] and 1 % – 2 % for major complications [11]. The development of symptomatic disease and complications is mostly related to the migration of stones into the common bile duct (CBD). Common bile duct stones (CBDSs) may be treated by endoscopic retrograde cholangiopancreatography (ERCP) or surgically during cholecystectomy. The aim of this evidence- and consensus-based Guideline, commissioned by the European Society of Gastrointestinal Endoscopy (ESGE), is to provide practical advice on how to manage patients with CBDSs. It considers diagnostic strategies in patients with suspected CBDSs, as well as the different therapeutic options available for CBDSs.

2 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 1 s**; 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

ABBREVIATIONS

ABP	acute biliary pancreatitis
ASGE	American Society for Gastrointestinal Endoscopy
CBD	common bile duct
CBDS	common bile duct stones
CI	confidence interval
CT	computed tomography
DPOC	direct peroral cholangioscopy
EHL	electrohydraulic lithotripsy
EPLBD	endoscopic papillary large-balloon dilation
ERCP	endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
ESWL	extracorporeal shock wave lithotripsy
EUS	endoscopic ultrasonography
IOC	intraoperative cholangiography
IRR	incidence rate ratio
LFT	liver function test
MBC	mother – baby cholangioscopy
MRCP	magnetic resonance cholangiopancreatography
NR-ERCP	non-radiation ERCP
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
OTS	out of the scope
PTBD	percutaneous transhepatic biliary drainage
RCT	randomized controlled trial
RR	relative risk
SD	standard deviation
SEMS	self-expanding metal stent
SOC	single-operator cholangioscopy
TTS	through the scope
UDCA	ursodeoxycholic acid

2018, a draft prepared by the coordinating team was sent to all group members.

After agreement of all group members, the manuscript was reviewed by two members of the ESGE Governing Board, and by two external reviewers and was then sent for further comments to the ESGE National Societies and Individual Members. The manuscript was then submitted to *Endoscopy* for publication. All authors agreed on the final revised manuscript. This Guideline was issued in 2019 and will be considered for review in 2023, or sooner if new and relevant evidence becomes available. Any updates to the Guideline in the interim will be noted on the ESGE website: http://www.esge.com/esgeguidelines.html.

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

RECOMMENDATION

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.

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 1 s**). 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**).

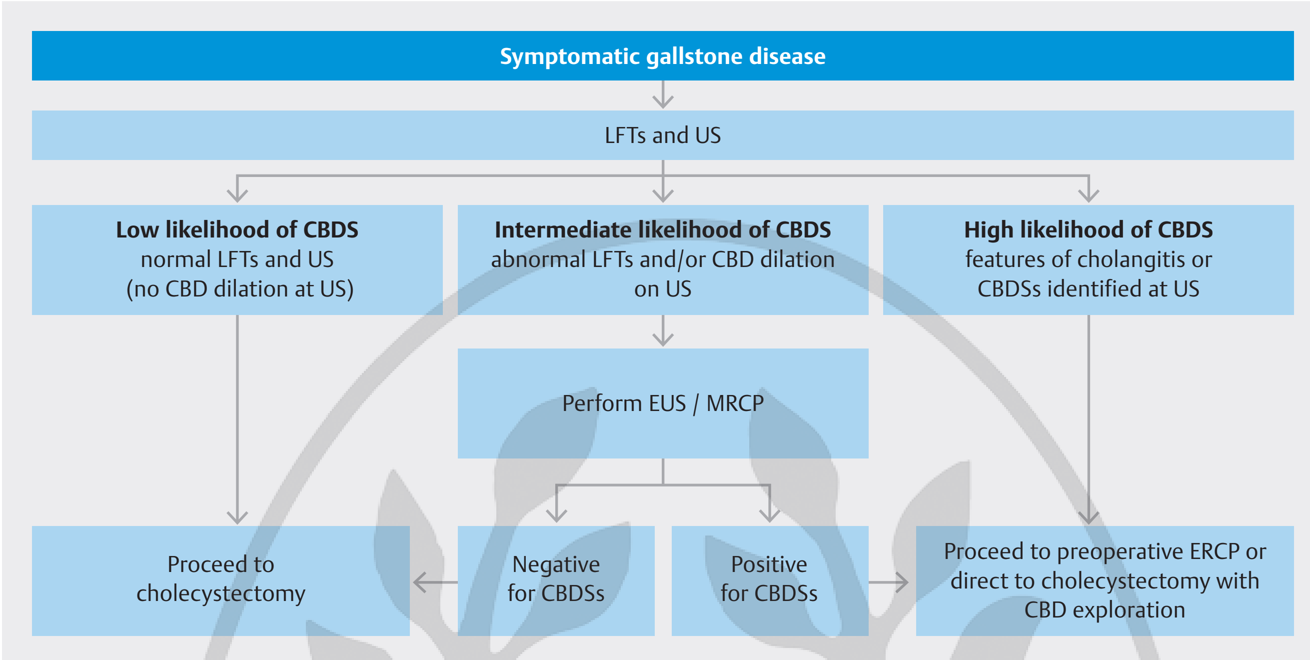
The risk of having CBDSs in spite of normal LFTs and ultrasonography has been adequately evaluated in two studies [35, 36]. In a large study including 765 patients with ERCP-proven CBDSs, 541 had previously documented LFTs and 29 (5.4 %) had normal LFTs. Age more than 55 years and the presence of pain 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 2 s**).

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. Meeralam 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-



▶ **Fig. 1** Diagnostic algorithm for suspected common bile duct stones (CBDSs). LFTs, liver function tests; US, ultrasound; CBD, common bile duct; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography.

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 s**) [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 s**).

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 CBDSs 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 CBDSs sized ≤ 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 CBDSs

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 CBDSs [65]. When CBDSs 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 4 s**). The success rate for stone removal after previous ERCP with biliary stenting has been reported to range from 44 % to 96 % (**Table 5 s**) [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 (≥ 65 years) with large (≥ 20 mm) or multiple (≥ 3) CBDSs 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 6 s**) [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
ESGE 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
ESGE 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 7 s**).

5.6 Role of dissolution therapy

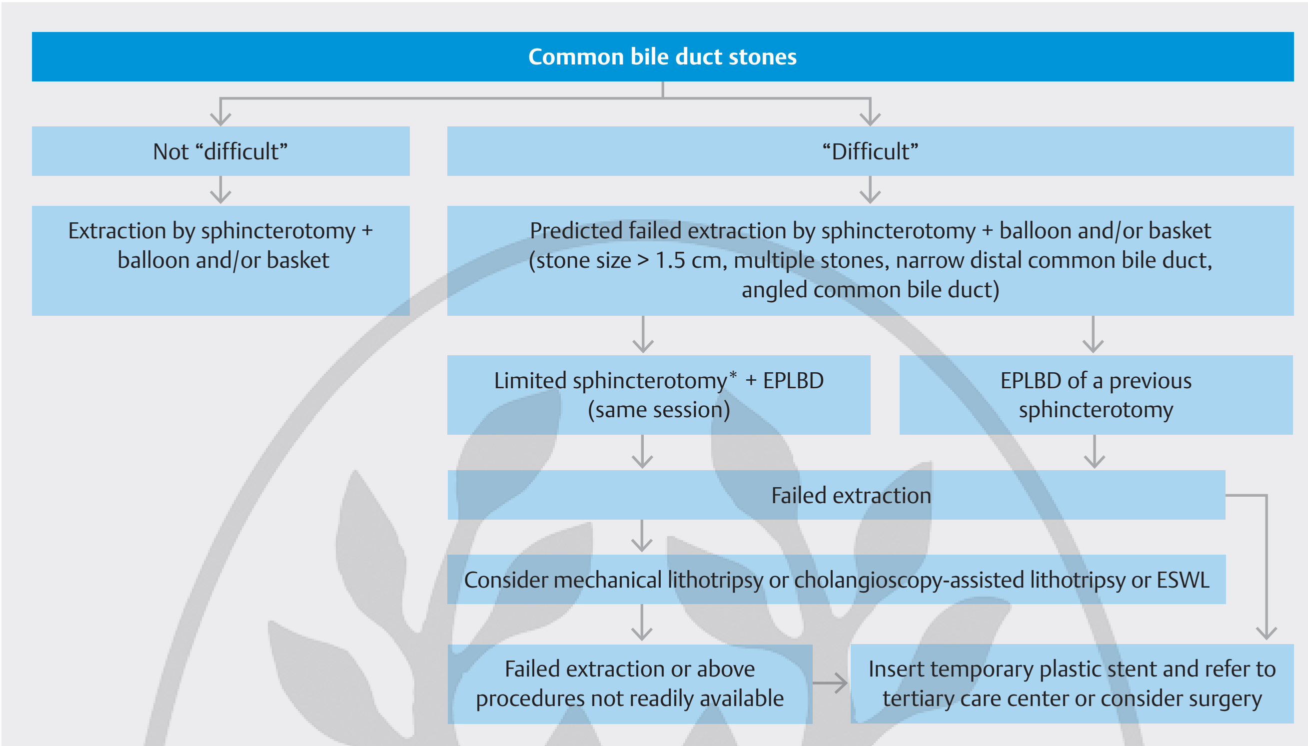
RECOMMENDATION
EGSE suggests against the use of ursodeoxycholic acid or other choleretic agents, either for the treatment of CBDSs or to prevent the recurrence of CBDSs after endoscopic clearance.
Weak recommendation, moderate quality of evidence.

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 endoprosthetic 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].



▶ **Fig. 2** Therapeutic algorithm for management of common bile duct stones when ERCP is selected as the primary treatment. ERCP, endoscopic retrograde cholangiopancreatography; EPLBD, endoscopic papillary large-balloon dilation (12 – 20 mm); ESWL, extracorporeal shock wave lithotripsy.
* EPLBD without sphincterotomy suggested in those with coagulopathy.

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 8 s**).

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 Stefanidis 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 CBDSs 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. A 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

RECOMMENDATION

ESGE recommends mechanical lithotripsy for difficult stones when sphincterotomy plus endoscopic papillary large-balloon dilation has failed or is inappropriate.
Strong recommendation, moderate quality evidence.

Mechanical lithotripsy is the simplest available method of fragmenting CBDSs. 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 s**). 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

RECOMMENDATION

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.

RECOMMENDATION

ESGE suggests that the type of cholangioscopy and lithotripsy should depend on local availability and experience.
Weak recommendation, low quality evidence.

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 ultraslim 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 (included 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 10 s**; ▶ **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 CBDSs [143].

ESWL is a complex and technically demanding procedure. A nasobiliary drain is inserted to allow fluoroscopic identification and targeting of CBDSs 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 hematoma 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 CDBS 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 performance after ERCP is a critical issue [155, 157, 162 – 167] (**Table 11 s**). 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 CBDSs; 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 CBDS 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 12 s** and **13 s**). 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 12 s**); if this happens, the endoscopist must rely on conventional cannulation techniques and their associated risks.

7.3 Surgical treatment of CBDSs

RECOMMENDATION

ESGE suggests that, in patients undergoing laparoscopic cholecystectomy, transcystic or transductal 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 CBDSs 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 approach [218].

It is of note that the results of surgical treatment of CBDSs, which are generally excellent in published reports, usually originate 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 occur 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 therapy. 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 fundamental 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 cholangitis 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 /mm^3, 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 (http://www.jshbps.jp/modules/en/index.php?content_id=47 Accessed 30 January 2019).

8.2 Timing of ERCP in acute cholangitis

RECOMMENDATION

ESGE recommends the following timing for biliary drainage, preferably endoscopic, in patients with acute cholangitis, classified according to the 2018 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.

Twelve studies (18 206 patients), all retrospective, have analyzed the relationship between the timing of biliary drainage and different outcomes (**Table 14 s**). An international study from 28 intensive care units published in 2016 included 260 patients with septic shock (defined as hypotension requiring vasopressors 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 disease 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 (percutaneous, surgical) in patients with acute cholangitis due to common bile duct stones when ERCP is not feasible/successful within the recommended timeframes.
Strong recommendation, low quality evidence.

Failure of biliary drainage is a strong determinant of mortality, 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

The legal disclaimer for ESGE Guidelines [12] applies to the current Guideline.

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Competing interests

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Topics and key questions	Task forces (leads in bold)
1.Generality on CBDSs	
- Which is the prevalence and the natural history of gallstones? - Which is the prevalence of CBDSs in symptomatic/asymptomatic gallstones patients? - Which is the rate of spontaneous clearance (passage into duodenum) of symptomatic/asymptomatic CBDSs? - Which are the complications of untreated CBDSs? - Do we always treat CBDSs?	**L. Aabakken** G. Karamanolis A. Tringali E. J. Williams
2. Diagnosis of common bile duct stones	
- **2.1. First diagnostic approach to CBD stones** - Which is the accuracy of clinical features, laboratory tests, abdominal US, and CT in diagnosing CBDSs? - Can diagnosis of CBDSs can reliably be done by these tests? - How could clinical, laboratory and US features be combined to diagnose CBDSs? - How can we stratify the risk of having CBDSs according to the results of these tests? - Which is the chance of having CBDSs in patients with normal US, CT, and laboratory findings?	**M. Arvanitakis** A. Anderloni A. Laghi D. Domagk
- **2.2. Use of EUS and MR in diagnosing CBDSs** - Which is the accuracy of EUS and MR in the diagnosis of CBDSs? - When should we use EUS or MR in the diagnosis of CBDSs? - How to decide between EUS or MR in the diagnosis of CBDSs?	
3.Performing ERCP and stone removal	
- How to define the indication for ERCP? Do we need to discuss the cases in a multidisciplinary setting? - When do we need antibiotic prophylaxis for ERCP in CBDSs? - How to create an adequate exit for the stones during ERCP: sphincterotomy; balloon dilation of the papilla with or without sphincterotomy? - Removal of CBDSs: do we have data to decide between basket and balloon catheters? - Do we have data about effectiveness and safety of different (shape and material) catheters?	**G. Paspatis** I. Hritz G. Karamanolis A. Tringali K. Paraskeva
4. Difficult stones	
- **4.1. Generality on difficult stones approach** - How to define difficult stones: Anatomy of the bile duct, number and size of stones; post-surgical anatomy? - Defining the complexity of managing difficult stones: need for multiple procedures and for different devices - How to open the papilla in difficult CBDSs?	**T. Ponchon** G. Karamanolis A. Tringali

- Is a large sphincterotomy always a prerequisite to remove difficult stones? - How large should sphincterotomy be?	
- **4.2. Endoscopic papillary large balloon dilation** - Can we consider EPLBD a first line approach for patients with difficult stones? - How safe and effective is EPLBD? - Which are the criteria to decide the balloon size for EPLBD: the size of the bile duct, the size of the stones, the size of the papilla?	
5. Stenting for difficult stones	
- When should we perform stenting for CBDSs? - Is stenting a reliable procedure as a bridge to further treatments? - Is definitive stenting safe for old/comorbid patients? - Which is the timing of stent exchange? - Do we have data to decide on the number and type of stent (plastic, SEMS) to use? - Does stenting reduce the stones size? - Is there any role for ursodeoxycholic acid for patients with difficult CBDS? - Does ursodeoxycholic acid prevent stone recurrence after CBDS clearance?	**A. Mariani** P. Ah-Soune I. Hritz M. Barthet
6. **Surgical therapy of CBDS**	
- **6.1. Patients with CBD stones and gallbladder in situ** - Which is the timing of cholecystectomy following ERCP clearance of CBDSs? - Which is the strategy to be adopted if CBDSs are diagnosed during surgery: rendezvous-ERCP vs laparoscopic/laparotomic bile duct exploration and stone removal vs sequential post-surgery ERCP?	**F. Swahn** J.F. Gigot R.W.F. ter Steege A. Vezakis
- **6.2. Intraoperative ERCP** - In patients with diagnosed CBDSs candidate to cholecystectomy, is rendezvous-ERCP a valuable option? - Is rendezvous-ERCP to be considered only if ERCP/stone removal fails? - Do we have clinical and economic data to decide between sequential ERCP-surgery vs rendezvous vs sequential surgery-ERCP?	
- **6.3. Patients with CBDS unfit for surgery** - May sphincterotomy be a definitive treatment for patients with gallbladder stones unfit for surgery? - Which is the risk of CBD recurrence and which is the clinical outcome?	
- **6.4. Patients without gallbladder and CBD stones**	

- What do we have to do in case of ERCP failure in patients without gallbladder: percutaneous approach/ EUS guided approach/surgery?	
7. Lithotripsy	
- **7.1. Mechanical lithotripsy** - Definition of mechanical lithotripsy and its safety and effectiveness. - When should we use mechanical lithotripsy? - Use of salvage mechanical lithotripsy.	**R.W.F. ter Steege** A. Anderloni J. Pohl A. Vezakis,
- **7.2. Cholangioscopy-guided intraluminal lithotripsy** - Which are the different methods of intraluminal lithotripsy (laser, electrohydraulic)? - Which are the different methods of cholangioscopy? - Do we have data to choose between the different techniques of lithotripsy? - Do we have data to choose between the different techniques of cholangioscopy? - How effective and safe are they? - Which should be the diffusion of these techniques?	
8**. Special situations**	
- **8.1. Acute cholangitis** - How to define severity of acute cholangitis: is the Tokyo classification reliable? - Which is the timing of ERCP in acute cholangitis? - Is there any role for percutaneous drainage/surgery if ERCP fails.	**J.M. Dumonceau** D. Domangk A. Tringali
- **8.2. Management of CBDSs in pregnancy** - Which is the best timing for ERCP during pregnancy? - How to minimize the RX exposure?	
- **8.3. Management of CBDSs in biliary pancreatitis.** - Which are the indications of ERCP in acute pancreatitis? - Which is the timing of ERCP in acute pancreatitis? - Which is the timing of cholecystectomy in patients with biliary pancreatitis after ERCP?	

Appendix 1s: The endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline: key questions and task force subgroups.

First author, year	Study design	Intervention	Participants	Outcomes	Results	Level of evidence
Murison, 1993 [1]	RCT	IOC vs no IOC	285 patients at low risk of CBDS undergoing CS	Morbidity and mortality related to missed CBDS	16/132 patients (12%) had unsuspected CBDS at IOC. Clinical outcome similar in the two groups after at least 3 years follow up	High
Soper, 1992 [2]	RCT	IOC vs no IOC	115 patients at low risk of CBDS undergoing CS	Morbidity and mortality related to missed CBDS	2/56 patients (3.6%) had unsuspected cystic stone at IOC. No case of retained CBDS in the two groups at 2-12 months follow up	High
Nies, 1997 [3]	RCT	IOC vs no IOC	275 patients at low risk of CBDS undergoing CS	Morbidity and mortality related to missed CBDS	3/111 patients (2.7%) had unsuspected CBDS at IOC. 5 patients with retained CBDS in the no IOC group (3 symptomatic passage, 1 ERCP and 1 pancreatitis) at 12-month follow up	High
Khan, 2011 [4]	RCT	IOC vs no IOC	190 patients at low risk of CBDS undergoing CS	Morbidity and mortality related to missed CBDS	3/91 patients (3.3%) had unsuspected CBDS at IOC. 4 cases of retained CBDS in the no IOC group at 1-year follow up (conservative treatment)	High
Hauer-Jensen, 1993 [5]	RCT	IOC vs no IOC	280 patients at low risk of CBDS undergoing CS	Morbidity and mortality related to missed CBDS	Additional follow up of a previous study (19) up to 8 years. No case of residual CBDS was present in both group	High

Table 1s: Randomized controlled trials (RCTs) evaluating the outcome of retained common bile duct stones after cholecystectomy.

IOC: intraoperative cholangiography; CS: cholecystectomy; CBDSs: common bile duct stones

First author, year	Study design	Intervention	Participants	Outcomes	Results	Level of evidence
Barkun, 1994 [6]	Retrospective with prospective validation	Predictive model	106 patients undergoing ERCP before CS and 33 after CS	Diagnostic accuracy for CBDS	Independent predictive factors: age>55, bili>30 µmol/L and positive US findings	Low
Onken, 1996 [7]	Retrospective	Predictive model	1264 patients undergoing CS	Diagnostic accuracy for CBDS	Independent predictive factors: bili, CBD diameter, AST, ALP, age (limited effect)	Moderate
Prat, 1999 [8]	Prospective	Predictive model	880 patients undergoing EUS for CBDS	Diagnostic accuracy for CBDS	For patients < 70 y: GGT >7 x normal; pathologic gallbladder; dilated bile duct For patients <70y: GGT >7 x normal; fever > 38°; dilated CBD	Moderate
Abboud, 1996 [9]	Systematic review	Performance indicators		Diagnostic accuracy for CBDS	Positive likelihood ratio ≥ 10: cholangitis, jaundice, US evidence of CBDS	Moderate

Tse, 2004 [10]	Systematic review	All diagnostic procedures/ Predictive models		Diagnostic accuracy for CBDS	Predictive models are useful in stratifying the risk of patients bearing CBDS	High

Table 2s: Studies assessing the probability of common bile duct stones by combining different predictive factors

CBD: common bile duct; CBDSs: common bile duct stones; US: ultrasonography; EUS: endoscopic ultrasonography; CS: cholecystectomy

First author, Year	**Study design**	**Intervention (Antibiotics)**	**Participants**	**Outcomes**	**Results**	**Level of evidence**
Sauter, 1990 [11]	RCT	2 g cefotaxime iv.	96 ERCP patients: 48 AP group vs. 48 controls	Occurrence of bacteremia and cholangitis	Bacteremia was 2% in AP group and 16% in control group (p<0.02); cholangitis was 2% in AP group and 4% in control group	Moderate
Lorenz, 1996 [12]	RCT	1.5 g cefuroxime iv.	99 ERCP or PTBD patients: 49 AP group vs. 50 controls	Occurrence of bacteremia and cholangitis	Bacteremia was 6.1% (3/49) in cefuroxime group and 16% (8/50) in control group (NS)	Moderate
van den Hazel, 1996 [13]	RCT	4 g piperacillin iv. vs. placebo	551 pts with CBD stone or distal stricture: 270 AP group vs. 281 controls	Occurrence of bacteremia and cholangitis	Rate of cholangitis was 4.4% (12/270) in piperacillin group and 6.0% (17/281) in control group	Moderate
Harris, 1999 [14]	Meta-analysis, 5 RCTs	2 g cefotaxime iv; 2 g cefotaxime iv; 1 g cefonicid iv; 4 g piperacillin iv; 1.5 g cefuroxime iv.	1013 ERCP patients: AP group vs. controls	Occurrence of bacteremia and cholangitis	Summary relative risk of the association between antibiotic prophylaxis and bacteremia was 0.39 (95% CI, 0.12-1.29); for sepsis/cholangitis the summary relative risk was 0.91 (95 % CI, 0.39-2.15)	Moderate

Bai, 2009 [15]	Meta-analysis, 7 RCTs	2 g cefotaxime iv; 2 g cefotaxime iv; 1 g cefonicid iv; 4 g piperacillin iv; 1.5 g cefuroxime iv; 2 g ceftazidime iv; 600 mg clindamicin + 80 mg gentamicin im	1389 ERCP patients: AP group vs. controls	Occurrence of bacteremia and cholangitis	Cholangitis occurred in 3.4% (23/684) of AP treated pts vs. 5.8% (41/705) of controls, without statistical significance (RR 0.58; 95% CI, 0.22-1.55)	Moderate
Niederau, 1994 [16]	RCT	2 g cefotaxime iv.	100 ERCP patients: 50 AP group vs. 50 controls	Occurrence of bacteremia and cholangitis	Bacteremia or clinical sepsis developed in 8/50 pts (16%) in control group (all had biliary obstruction), vs. in 0 pts in AP group ($p<0.01$)	Moderate
Byl, 1995 [17]	RCT	4 g piperacillin iv. vs. placebo	68 patients with biliary tree obstruction: 34 AP group vs. 34 controls	Occurrence of bacteremia and cholangitis	No signs of fever, cholangitis or sepsis was documented in 32/34 pts (94%) in piperacillin group and 24/34 pts (71%) in placebo group ($p=0.01$); complete biliary drainage influenced clinical outcome favorably	Moderate
Räty, 2001 [18]	RCT	2 g ceftazidime iv.	321 ERCP patients: 161 AP group vs. 160 controls	Occurrence of bacteremia and cholangitis	Cholangitis developed in 0/155 (0%) pts in AP group and in 7/160 (4.4%) pts in control group ($p=0.009$)	Moderate

Brand, 2010 [19]	Meta-analysis, 9 RCTs	200 mg minocycline per os; 4 g piperacillin iv; 600 mg clindamicin + 80 mg gentamicin im; 1.5 g cefuroxime iv; 2 g cefotaxime iv; 2 g ceftazidime iv; 2 g cefotaxime iv; 2.4 g amoxicillin-clavulanic acid; 4 g piperacillin iv;	1573 ERCP patients: AP group vs. controls	Occurrence of bacteremia and cholangitis	fixed-effect meta-analyses significantly favored the use of AP in preventing cholangitis (relative risk (RR) 0.54, 95% CI 0.33 to 0.91), septicemia (RR 0.35, 95% CI 0.11 to 1.11) and bacteremia (RR 0.50, 95% CI 0.33 to 0.78); 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 AP to prevent cholangitis (RR 0.98, 95% CI 0.35 to 2.69, only three trials)	High

Table 3s: Studies assessing the effect of antibiotic prophylaxis on the rate of bacteremia, cholangitis and other infections after ERCP

RCT: randomized controlled trial; ERCP: endoscopic retrograde cholangiopancreatography; AP: antibiotic prophylaxis; PTBD: percutaneous transhepatic biliary drainage

First author, year	Study Design	Stent diameter	Scheduled stent exchange (months)	Oral dissolution agent	No. patients	Complete stone removal (%)	Stone size before stenting (mean ± SD, mm)	Stone size after stenting (mean ± SD, mm)	P
Chan, 1998 [20]	Retrospective monocenter	10 Fr	Variable	No	28	25 (89.3)	24.9 (range 11-46)	20.1 (range 5-46)	<0.0001
Katsinelos, 2003 [21]	Retrospective monocenter	7 or 10 Fr (one or two)	6	No	25	11 (44)	23 (range 16-33)	11.3 (range 11-21)	not reported
Katsinelos, 2008 [22]	RCT	10 Fr	6	750 mg UDCA or placebo	41	31 (75.6)	1.61 ± 0.35	1.24 ± 0.22	<0.05*
Han, 2009 [23]	Prospective multicenter	10 Fr	6	600 mg UDCA + 300 mg terpene prep	28	26 (92.8)	21.6 x 29.5 (t x l)°	12.2 x 20.1 (t x l)°	<0.01
Horiuchi, 2010 [24]	Retrospective monocenter	7 Fr	2	no	40	37 (92.5)	4.6^ (3.0^^)	2.0^ (1.5^^)	<0.01

Lee, 2011 [25]	RCT	multiple 7 Fr	6	600 mg UDCA + 300 mg terpene prep	41	33 (80.5)	19.1 ± 4.5 (t)° x 20.5± 3.9 (l)°	12.0 ± 3.3 (t)° x 13.3 ± 5.1 (l)°	<0.01 *
Hong, 2011 [26]	Retrospective monocenter	8.5 Fr	3	no	52	49 (94.2)	16.6 ± 6.4 (t x l)°	10.0 ± 6.3 8 (t x l)°	<0.01
Fan, 2011 [27]	Retrospective monocenter	7 or 8.5 Fr	3	no	45	43 (95.5)	23.1 (range 16-33)	15.4 (range 11-21)	<0.05
Ye, 2016 [28]	Retrospective monocenter	7 or 8.5 Fr	3	no	64 ◊	62 (96.8)	19.1±5.8 §	10.8±4.4 §	<0.001

Table 4s: Effects of plastic biliary stents on the size of difficult common bile duct stones.

UDCA: ursodeoxycholic acid; RCT: randomized controlled trial.

*significant difference also after stent plus oral ursodeoxycholic acid; § longitudinal size; ° t=transverse size, l=longitudinal size; ^ stone index= sum of diameter x number of stones; ^^ interquartile; ◊ elderly patients only.

First author, year	Study design	Intervention	Participants	Outcomes	Results	Level of evidence
Maxton, 1995 [29]	Retrospective	Stenting for failed CBDS removal	85 patients	Relief of biliary obstruction	Successful stone removal in 50/79 (63%) after biliary stenting with 7 Fr double pigtail. Time between procedures 4.3 (1-12) months. 13 cholangitis were registered	Low
Chan, 1998 [20]	Retrospective	Stenting for failed CBDS removal	28 patients	Relief of biliary obstruction	Successful stone removal in 25/28 (89%) after biliary stenting. Time between procedures 2.1 (0.6-33.4) months. CBDS diameter decreased from 24.9 mm (11-46) to 20.1 mm (5-46 mm)	Low
Jain, 2000 [30]	Prospective	Stenting for failed CBDS removal	20 patients	Relief of biliary obstruction	Successful stone removal in 11/20 (55%) after biliary stenting with 7 Fr double-pigtail stents. Time between procedures 6 months. 1 stent migration was registered	Moderate
Katsinelos, 2003 [21]	Retrospective	Stenting for failed CBDS removal	25 patients	Relief of biliary obstruction	Successful stone removal in 11/25 (44%) after biliary stenting with 7 Fr double-pigtail stents or 10 Fr straight plastic stent. Time between procedures 6-17 months. Late complications in 30,4%: 9 cholangitis and 6 jaundice were registered	Low

Katsinelos, 2008 [22]	Prospective	Stenting for failed CBDS removal	41 patients	Relief of biliary obstruction	Successful stone removal in 33/41 (75%) after biliary stenting with 10 Fr straight plastic stent. Time between procedures 6 months. No complications registered	Moderate
Han, 2009 [23]	Prospective	Stenting for failed CBDS removal	28 patients	Relief of biliary obstruction	Successful stone removal in 26/28 (93%) after biliary stenting with 10 Fr straight plastic stent. Time between procedures 6 months. No complications registered	Low
Horiuchi, 2010 [24]	Retrospective	Stenting for failed CBDS removal	40 patients	Relief of biliary obstruction	Successful stone removal in 37/40 (93%) after biliary stenting with 7 Fr double-pigtail stents. Time between procedures 2.2 (1.7–2.7) months. No complications registered	Low
Fan, 2011 [27]	Retrospective	Stenting for failed CBDS removal	45 patients	Relief of biliary obstruction	Successful stone removal in 43/45 (96%) after biliary stenting with 7–8.5 Fr plastic biliary stents. Time between procedures 3-6 months. No complications registered. CBDS disappeared or changed to sludge in 10 (10/45) patients, and stone decreased in 33 patients from 23.1 mm to 15.4 mm ($P<0.05$).	Low
Hong, 2011 [26]	Retrospective	Stenting for failed CBDS removal	52 patients	Relief of biliary obstruction	Successful stone removal in 49/52 (94%) after biliary stenting with 8.5-F straight plastic stent. Time between procedures 4,1 (3,5-5,7) months. 2 cholangitis and 1 stent migration were registered	Low

Lee, 2011 [25]	Prospective	Stenting for failed CBDS removal	41 patients	Relief of biliary obstruction	Successful stone removal in 33/41 (80%) after biliary stenting with 7 Fr double-pigtail stents. Time between procedures 6 months. 1 cholangitis and 2 stent migration were registered	Moderate

Table 5s: Effects of biliary plastic stents on non-retrievable common bile duct stones

CBDS: common bile duct stone

First author, year	Study design	Intervention	Participants	Outcomes	Results	Level of evidence
Minami, 2003 [31]	Retrospective	Stenting for failed CBDS removal	38 patients	Relief of biliary obstruction	Successful stone removal in 36/38 (95%) after biliary stenting with partly covered and uncovered SEMS. 1 pancreatitis, 1 cholangitis and 2 stent migration were registered	Low
Cerefice, 2011 [32]	Retrospective	Stenting for failed CBDS removal	36 patients	Relief of biliary obstruction	Successful stone removal in 29/36 (81%) after biliary stenting with partly covered and fully covered SEMS. 4 of the remaining patients were treated after multiple stent exchange. Time between procedures 6.4 weeks. Migration of 4/42(9.5%) stent was registered	Low
Hartery, 2017 [33]	Retrospective	Stenting for failed CBDS removal	44 patients	Relief of biliary obstruction	Successful stone removal in 36/44 (82%) after biliary stenting with fully covered SEMS. Time between procedures 56 days (2-538). 4 pancreatitis and 1 stent migration were registered	Low

Table 6s: Effects of biliary metal stents on non-retrievable common bile duct stones

CBDS: common bile duct stone; SEMS: self-expandable metal stent

First author, year	Study design	Intervention	Participants	Outcomes	Results	Level of evidence
Bergman, 1995 [34]	Retrospective	Definitive stenting for failed CBDS removal	58 patients Mean age 80 years	Complications and biliary-associated mortality	In a mean follow up of 36 (1-117) months 34 complications occurred in 23 patients (40%), mainly cholangitis. Biliary-associated mortality occurred in 9 (15.5%) patients	Low
Chopra, 1996 [35]	RCT	Short EST+stenting with 7 Fr double-pigtail stents vs EST+stone clearance	86 patients, 43 for each group Mean age 79 years	Relief of biliary obstruction, complications and biliary-associated mortality	Biliary drainage achieved in the first session in 42/43 patients. In EST group, 24 patients had duct clearance at the first attempt and 35 (81%) after a median of 2 sessions (range 2-4); eight of this group had an endoprosthesis inserted to maintain long-term drainage. In a mean follow up of 16 months 36% of patients developed complications. Biliary-associated mortality occurred in 2.3% of patients	High

De Palma, 1999 [36]	Retrospective	Definitive stenting for failed CBDS removal vs surgical therapy	62 patients, 31 patients for each group, mean age 77.5 years	Relief of biliary obstruction, complications and biliary-associated mortality	Biliary drainage achieved in the first session in 100% in both groups. In a mean follow up of 39 months 35.5% of patients developed complications. Biliary-associated mortality in 3 patients (9.6%)	Low
De Palma, 2001 [37]	Retrospective	Definitive stenting for failed CBDS removal	49 patients, mean age 75.5 years	Relief of biliary obstruction, complications and biliary-associated mortality	Biliary drainage achieved in the first session in all patients. In a mean follow up of 39 months 40.8% of patients developed complications. Biliary-associated mortality occurred in 3 patients (6.1%)	Low
Hui, 2003 [38]	Prospective	Definitive stenting for failed CBDS removal	19 patients, mean age 74 years	Relief of biliary obstruction, complications and biliary-associated mortality	Biliary drainage achieved in the first session in 94.7% of patients. In a mean follow up of 21.9 months 63% of patients developed complications. Biliary-associated mortality occurred in 23.5% of cases	Low
Pisello, 2008 [39]	Prospective	Definitive stenting for failed CBDS removal	30 patients, mean age 82 years	Relief of biliary obstruction, complications and biliary-associated mortality	Biliary drainage achieved in the first session in all patients. In a mean follow up of 38 months 34% of patients developed complications. Biliary-associated mortality occurred in 6.6% of cases	Low

Table 7s: Effects of definitive biliary plastic stents on non-retrievable common bile duct stones.

CBDS: common bile duct stone; EST: endoscopic sphincterotomy

First author, year	Study design	Intervention	Participants	Outcomes	Results	Level of evidence
Heo, 2007 [40]	RCT	EPLBD + EST vs EST	200	One-session success Overall success Need for ML Complications	83 vs 87% ns 97 vs 98% ns 8 vs 9% ns 5 vs 7% ns	High
Kim, 2009 [41]	RCT	EPLBD + EST vs EST	55	One-session success Overall success Need for ML Complications	85 vs 86% ns 100 vs 100% ns 33 vs 32% ns 0 vs 0% ns	High
Stefanidis, 2011 [42]	RCT	EPLBD + EST vs EST+ML	90	Overall success Complications	97.7 vs 91.1% ns 4.4 vs 20% p=0.049	High
Teoh, 2013 [43]	RCT	EPLBD + EST vs EST	156	One-session success Overall success Need for ML Complications	88.5 vs 89% ns 100 vs 97.3% ns 28.8 vs 46.2% p=0.028 6.8 vs 10.3% ns	High
Li, 2014 [44]	RCT	EPLBD + EST vs EST	462	One-session success Overall success Need for ML Complications	87.7 vs 71.4% p<0.05 97.4 s 94.7% ns 12.3 vs 35.2% p<0.05 7 vs 11.9% ns	High

Jun Bo, 2013 [45]	RCT	EPLBD + EST vs EST	132	One-session success Overall success Need for ML Complications	80.9 vs 60.8% p=0.046 95.2 vs 91.3 ns 7.9 vs 24.6% p=0.041 7.9 vs 11.6% ns	High
Karsenti, 2017 [46]	RCT	EPLBD + EST vs EST	150	One-session success Need for ML Complications	96.1 vs 74% p<0.001 3.9 vs 35.6 % p<0.001 8.1 vs 9.3% ns	High
Yang, 2013 [47]	Meta-analysis	EPLBD + EST vs EST	835 6 RCTs	One-session success Overall success Need for ML Complications	OR=1.02, 95%CI: 0.65-1.61 OR=1.41, 95%CI: 0.63-3.17 OR=0.26, 95%CI: 0.08-0.82 OR = 0.53, 95%CI: 0.33-0.85	High
Feng, 2012 [48]	Meta-analysis	EPLBD + EST vs EST	790 7 RCTs	One-session success Overall success Need for ML Complications	OR 1.31, 95% CI 0.81-2.11 OR 1.28, 95% CI 0.58-2.82 OR 0.51, 95% CI 0.30-0.86 OR 0.41, 95% CI 0.24-0.68	High
Jin, 2014 [49]	Meta-analysis	EPLBD + EST vs EST	621 5 RCTs	One-session success Overall success Need for ML Complications	82.2% vs 77.7% ns 93.7% vs 92.5% ns 15.5% vs 25.2%, p=0.003 7.9% vs 10.7% ns	High

Madhoun, 2014 [50]	Meta-analysis	EPLBD + EST vs EST	902 3 RCTs, 4 retrospective studies	One-session success Overall success Need for ML Complications	RR 1.11, 95% CI 0.98-1.25 RR 1.01, 95% CI 0.97-1.05 RR 0.49 95% CI 0.32-0.74 RR 0.58 95% CI 0.41-0.81	High
Liu, 2013 [51]	Meta-analysis	EPLBD + EST vs EST	1295 3 RCTs, 6 retrospective studies	One-session success Overall success Need for ML Complications	Similar rates of clearance, ML need and complications in 3 RCTs; higher clearance, less ML need and less complications in 6 retrospective studies	High

Table 8s: Efficacy and safety of endoscopic papillary large balloon dilation + sphincterotomy vs sphincterotomy alone in the management of difficult common bile duct stones.

RCT: randomized controlled trial; EPLBD: endoscopic papillary large balloon dilation; EST: endoscopic sphincterotomy; ML: mechanical lithotripsy; ns: not significant; OR: odds ratio; CI: confidence interval; RR: relative risk

First author, year	**Study design**	**Intervention**	**Participants**	**Outcomes**	**Results**	**Level of evidence**
Chang, 2005 [52]	retrospective	TTS	304	Stone clearance	Success 272 (90%) Complications 49 (16%) Mortality 0	Low
Garg, 2004 [53]	retrospective	TTS	87	Stone clearance	Success 69 (79%) Complications 45(6%) Mortality 0	Low
Cipolletta, 1997 [54]	prospective	TTS OTS	162	Stone clearance	Success 136 (84%) Complications 5(3%) Mortality 0	Moderate
Lee, 2007 [55]	retrospective	TTS	134	Stone clearance	Success 102 (76%) Complications 46 (34%) Mortality 0	Low
Chung, 1991 [56]	retrospective	TTS	68	Stone clearance	Success 55 (81%) Complications 2 (3%) Mortality 1 (1.4%)	Low
Hintze, 1996 [57]	retrospective	TTS	84	Stone clearance	Success 77 (91%) Complications - Mortality -	Low

Table 9s: Efficacy and safety of mechanical lithotripsy in common bile duct stones

TTS: through the scope; OTS: out of the scope

First author, year	**Study design**	**Intervention**	**Participants**	**Outcomes**	**Results (number of studies)**	**Level of evidence**
Korrapati, 2016 [58]	Meta-analysis 33 studies	Different methods of cholangioscopy and lithotripsy (EHL, LL, basket)	894	Stone clearance, recurrence and complications for lithotripsy	Success 88%, 95% CI 85-91% Recurrence 13%, 95% CI 7-20% Complications NR	Moderate
Farrell, 2005 [59]	Single center, prospective	EHL	26	Stone clearance, clearance in 1 session and procedural complication*	Success 100% (69% in 1 session) Complications NR	Low
Chen, 2011 [60]	Multicenter prospective	EHL and LL	66 (50 EHL, 15 LL)	Stone clearance, clearance in 1 session and procedural complication*	Success 100% (71% in 1 session) Complications 6.1%	Low
Maydeo, 2011 [61]	Single center, prospective	LL	60	Stone clearance, clearance in 1 session and procedural complication*	Success 100% (83% in 1 session) Complications 13%	Low

Patel, 2014 [62]	Multicenter, prospective	LL	69	Stone clearance, clearance in 1 session and procedural complication*	Success 97% (74% in 1 session) Complications 4.1%	Low
Buxbaum, 2018 [63]	RCT	LL vs conventional treatment	60 (42 LL, 18 conventional)	Stone clearance in 1 session and procedural complication*	Higher success in 1 session for LL (93% vs 67%); longer procedure time for LL	High

Table 10s: Success rate and safety of intraluminal lithotripsy

EHL: electrohydraulic lithotripsy; LL: laser lithotripsy; CI: confidence interval; NR: not reported; * e.g. pancreatitis, bleeding, cholangitis, bile duct perforation.

First author, year	**Study design**	**Intervention (CS timing)**	**Participants**	**Outcomes**	**Results**	**Level of evidence**
Reinders, 2010 [64]	RCT	<72hrs vs 6-8wks	96	Conversion Biliary events	Conversion 4.3 vs 8.7% Biliary events 2.1 vs 36.2%	High
De Vries, 2005 [64]	Retrospective	<2wks vs 2-6wks	83	Conversion	Conversion 4 vs 31%	Low
Schiphorst, 2008 [66]	Retrospective	7wks (median)	167	Conversion Biliary events	Conversion 20% Biliary events 20% (76% of events after 1 w)	Low
Hamy, 2003 [67]	Prospective	3d (median)	298	Conversion	Conversion 7%	Low
Boerma, 2002 [68]	RCT	<6wks vs od	120	Conversion Biliary events	Conversion 23 vs 55% Biliary events 2 vs 47%	High
Lau, 2006 [69]	RCT	26d (median) vs od	178	Conversion Biliary events	Conversion 20 vs 50% Biliary events 7 vs 24%	High
Heo, 2015 [70]	RCT	2.2wks (median) vs od	90	Conversion Biliary events	Conversion 12.6 vs 28.6% Biliary events 10.3 vs 26.6%	High

Zargar, 2014 [71]	RCT	Scheduled vs od (timing not mentioned)	162	Biliary events	Biliary events 5 vs 26%	High
Donkervoort, 2010 [72]	Retrospective	53d (median)	140	Conversion Biliary events	Overall complications 20% Overall conversion 14% Not affected by CS timing	Low

Table 11s: Studies assessing timing of cholecystectomy after ERCP and EST.

CS: Cholecystectomy; od: on demand; RCT: randomized controlled trial

First author, year	**Study design**	**Intervention**	**Participants**	**Outcomes**	**Results**					**Level of evidence**
					Cannulation success *n* (%)	Stone clearance *n* (%)	Post-ERCP pancreatitis *n* (%)	Mortality *n* (%)	Hospital stay (mean days)	
Miscusi, 1997 [73]	case series	Rendezvous ERCP	8	Success and complications	8 /8 (100)	8/8 (100)	0 (0)	0 (0)	NA	Low
Cavina, 1998 [74]	case series	Rendezvous ERCP	16	Success and complications	16/16 (100)	16/16 (100)	NA	1 (6.2)	2.5	Low
Filauro, 2000 [75]	case control	Rendezvous vs sequential	21	Success and complications	21/21 (100)	18/21 (86)	0 (0)	0 (0)	4.9	Low
Tatulli, 2000 [76]	case series	Rendezvous ERCP	45	Success and complications	43/45 (96)	43/45 (96)	0 (0)	0 (0)	3	Low
Iodice, 2001 [77]	case series	Rendezvous ERCP	52	Success and complications	52/52 (100)	49/52 (94)	0 (0)	0 (0)	3.1	Low
Tricarico, 2002 [78]	case series	Rendezvous ERCP	43	Success and complications	37/43 (86)	37/43 (86)	0 (0)	0 (0)	3±1	Low
Enochsson, 2004 [79]	case series	Rendezvous ERCP	34	Success and complications	31/34 (91)	29/31 (94)	0 (0)	0 (0)	2.6	Low
Saccomani, 2005 [80]	case series	Rendezvous ERCP	28	Success and complications	27/28 (96)	27/28 (96)	0 (0)	0 (0)	4.8 ± 3	Low

Morino, 2006 [81]	RCT	Rendezvous vs sequential	46	Success and complications	46/46 (100)	44/46 (96)	1 (2.2)	0 (0)	4.3	High
Rabago, 2006 [82]	RCT	Rendezvous vs sequential	59	Success and complications	52/59 (89)	48/59 (81)	1 (1.7)	0 (0)	5 ± 3	High
Lella, 2006 [83]	RCT	Rendezvous vs sequential	60	Success and complications	59/60 (98)	58/60 (97)	0 (0)	0 (0)	3 ± 1	High
La Greca, 2007 [84]	case series	Rendezvous ERCP	19	Success and complications	19/19 (100)	19/19 (100)	0 (0)	0 (0)	2.7	Low
Ghazal, 2009 [85]	case series	Rendezvous ERCP	36	Success and complications	33/36 (92)	33/36 (92)	0 (0)	0 (0)	2.6	Low
Tzovaras, 2010 [86]	case series	Rendezvous ERCP	22	Success and complications	20/22 (91)	21/22 (95)	0 (0)	0 (0)	2	Low
Borzellino, 2010 [87]	case series	Rendezvous ERCP	110	Success and complications	105/110 (96)	105/110 (96)	0 (0)	0 (0)	10.3	Low
Tzovaras, 2012 [88]	RCT	Rendezvous vs sequential	50	Success and complications	44/50 (88)	47/50 (94)	0 (0)	1 (2)	4	High
Swahn, 2013 [89]	case control	Rendezvous vs conventional ERCP	40	Success and complications	40/40 (100)	38/40 (95)	0 (0)	0 (0)	NA	Low
Tommasi, 2013 [90]	case series	Rendezvous ERCP	96	Success and complications	78/96 (81)	90/96 (94)	0 (0)	0 (0)	5 ± 3	Low

Noel, 2013 [91]	case series	Rendezvous ERCP	307	Success and complications	264/307 (86)	271/307 (88)	1 (0.4)	0 (0)	2.5	Medium
Sahoo, 2014 [92]	RCT	Rendezvous vs sequential	42	Success and complications	39/42 (93)	38/42 (90)	0 (0)	0 (0)	6.8	High
Di Mauro, 2014 [93]	case series	Rendezvous ERCP	103	Success and complications	103/103 (100)	102/103 (99)	0 (0)	0 (0)	4	Medium
Cumulative			1237		1140/1237 (92)	1141/1237 (92)	3/1237 (0.2)	2/1237 (0.2)	4	

Table 12s: Stone clearance, post-ERCP pancreatitis, mortality and hospital stay in studies investigating rendezvous ERCP

RCT: randomized controlled trial; ERCP: endoscopic retrograde cholangiopancreatography; NA: not available

First author, year	**Study design**	**Intervention**	**Partic-ipants**	**Outcomes**	**Results**							**Level of evidence**
					Cannulation success *n* (%)	Stone clearance n (%)	Post-ERCP pancrea-titis *n* (%)	Other ERCP morbidity (%)	Mortality *n* (%)	Hospital stay (mean range)	Costs (€)	
Morino, 2006 [81]	RCT	Sequential	45	Success and complications	38/45 (84)	36/45 (80)	1 (2.2)	3/45 (7)	0 (0)	8 (2-34)	3834	High
		Rendezvous	46		45/46 (98)	44/46 (96)	0 (0)	3/46 (7)	0 (0)	4 (2-20)	2829	
Rabago, 2006 [82]	RCT	Sequential	64	Success and complications	62/64 (97)	62/64 (90)	8 (12.7)	12/64(19)	0 (0)	8 (3-12)	2708	High
		single step	59		52/59 (89))	48/59 (81)	1 (1.7)	3/59 (5)	0 (0)	5 (2-8)	2414	
Lella, 2006 [83]	RCT	Sequential	60	Success and complications	60/60 (100)	58/60 (98)	6 (10)	2/60 (3)	0 (0)	3 (2-4)	NA	High
		single step	60		59/60 (98)	58/60 (97)	0 (0)	2/60 (3)	0 (0)	6 (5-11)	NA	
Tzovaras, 2012 [88]	RCT	Sequential	49	Success and complications	45/49 (90)	45/49 (90)	0 (0)	6/49 (12)	1/49 (2)	4 (2-19)	NA	High
		single step	50		44/50 (88)	47/50 (94)	0 (0)	7/50 (14)	0 (0)	5.5 (3-22)	NA	
Sahoo, 2014 [92]	RCT	Sequential	41	Success and complications	33/41 (80)	29/41 (71)	0 (0)	NA	0 (0)	7 (NA)	NA	High
		single step	42		39/42 (93)	38/42 (90)	0 (0)	NA	0 (0)	11 (NA)	NA	
ElGeidie	RCT	Sequential	100	Success and	99/100 (99)	90/93 (97)	0 (0)	3/100 (3)	0 (0)	3 (2-11)	NA	High

2011 [94]		single step	91	complications	91/91 (100)	89/91 (98)	0 (0)	4/89 (4.5)	0 (0)	1.3 (1-4)	NA	

Table 13s: RCTs between sequential management (preoperative ERCP + laparoscopic cholecystectomy) versus single step management (laparoscopic cholecystectomy + intraoperative ERCP with rendezvous cannulation).

ERCP: endoscopic retrograde cholangiopancreatography; RCT: randomized controlled trial; NA: not available

First author, year	**Participants**	**Intervention**	**Outcome**	**Result**	**Remark**	**Level of evidence**
Karvellas, 2016 [95]	260 (septic shock)	ERCP (91), PTBD (90), Surgery (34), other (53)	In-hospital mortality	Biliary drainage >12 h associated with higher mortality (OR, 3.40; 95%CI, 1.12– 10.31)	Severe patients (in-hospital mortality, 37%) Multivariate analysis	Low
Patel, 2016 [96]	69	ERCP	In-hospital mortality, LOS	No significant association with mortality; shorter delay of ERCP associated with shorter LOS	LOS for ERCP within 24h, 24-48h and >48h; 7, 6 and 14 days, respectively (“statistically significant” with no P value stated)	Low
Schwed, 2016 [97]	196	ERCP	Composite outcome (death or organ failure)	No significant association between timing of ERCP and outcome, including when stratified by severity of cholangitis		Low

Park, 2016 [98]	331 (>75-y-o)	ERCP (284), PTBD in surgically altered anatomy or failed ERCP. (23), other (24)	30-day mortality, LOS	No significant association with mortality; urgent (<24h) vs. early (24-48h) biliary drainage: 7.0±3.7 vs. 8.8±5.8 days (P=0.02)*	Low (1.5%) mortality LOS association tested using univariate analysis	Low
Lee, 2015 [99]	203	ERCP	Organ failure at >48h after hospitalization	ERCP ≥48h associated with organ failure (OR, 3.1; 95% CI, 1.4–7.0)	Every 1-day delay in ERCP was associated with a 17% (95% CI = 5–29%) relative risk increase in organ failure. Multivariate analysis	Low
Navaneethan, 2015 [100]	16,184	ERCP	Mortality, LOS, hospitalization charges	ERCP within vs. after 72h: mortality 1.7% vs.3.1% (P=0.14); LOS, 4 vs. 9 days (P<0.001); cost, 31,695 vs. $61,904USD (P<0.001)	Abstract only. In subgroup of patients with cholangitis and choledocholithiasis, ERCP>72h was associated with higher mortality (OR, 1.49; 95% CI 1.23-1.74). Multivariate analysis	Low

Navaneethan, 2014 [101]	172	ERCP	Persistent organ failure and/or 30-day mortality; LOS	ERCP later than 72h associated with persistent organ failure and/or 30-d mortality (OR = 3.36; 95%CI: 1.12-10.20) as well as 70% increase in LOS (P< 0.001)	Multivariate analysis	Low
Navaneethan, 2013 [102]	168	ERCP	30-day readmission	ERCP later than 48h associated with 30-d hospital readmission (P=0.04)	Multivariate analysis	Low
Jang, 2013 [103]	212 (mild to moderate cholangitis with CBD stones)	ERCP	Technical and clinical success rate, LOS, intervention-related complications	ERCP <24h vs. >24h: no difference except for LOS (6.8 vs. 9.2 days, P <0.001)	Intervention to discharge time 6.1 vs.7.2 days (P=0.035)	Low
Khashab, 2012 [104]	90	ERCP	Composite outcome (death, persistent organ failure, and/or intensive care unit stay), LOS, hospitalization charges	ERCP >72h associated with composite clinical outcome (OR, 7.8; 95% CI, 1.1–58; P=0.04), longer LOS (OR, 19.8; 95% CI, 2.18 –178; P=0.008), higher hospitalization cost (OR, 11.3; 95% CI, 1.30–98; P=0.03)	Multivariate analysis	Low

Mok, 2012 [105]	250 (moderate to severe ascending cholangitis, Tokyo Guidelines)	ERCP (n=227), PTBD (n=22), laparotomy (n=1, failed non-surgical approach)	In-hospital mortality, multiple organ failure, surgery, readmission, LOS	Shorter delay of ERCP associated with lower mortality (<11h vs. >42h; RR, 0.34; 95%CI, 0.12-0.99; P=0.049) and fewer readmissions (Q1 v. 3: RR 0.27, 95%CI 0.12 to 0.62, p=0.002, Q1 v. Q4: 0.38, 95%CI 0.16 to 0.91, p=0.030). No difference in other endpoints	Comparison of quartiles of delays of ERCP (Q1, <11h; Q2, 12-21h; Q3, 22-42h; Q4, >42 h). Univariate analysis, no correction for multiple comparisons	Very low
Chak, 2000 [106]	71	ERCP	Intensive care unit admission, LOS	No difference in intensive care unit admission, shorter delay of ERCP associated with shorter LOS (median, 4 [2-7] vs. 7 [4.5-10] days, P<0.005)	Difference was mostly related to pre-procedure LOS (median 1 day for early ERCP group vs. 3 days for delayed ERCP group)	Very low

Table 14s: Retrospective studies investigating the timing of biliary drainage on the outcome of acute cholangitis

ERCP: endoscopic retrograde cholangiopancreatography; LOS, length of hospital stay; PTBD: percutaneous trans-hepatic biliary drainage; OR: odds ratio; CI: confidence interval; RR: relative risk.

*Association was also statistically significant, in separate analyses, for mild, moderate and severe cholangitis (Tokyo classification).

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