NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of electrohydraulic lithotripsy for difficult-to-treat bile duct stones

Stones in the bile ducts can block the flow of bile out of the liver and the gallbladder. This procedure is done under general anaesthetic. A flexible tube with a camera on the end (an endoscope) is passed through the mouth, stomach and the small intestine and into the bile ducts. A probe is passed through the tube. It sends an electric current into liquid surrounding the stone. This creates very small pressure-waves (electrohydraulic) that break up the stone (lithotripsy).

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Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2020 and updated in December 2020.

Procedure name

- Electrohydraulic lithotripsy for difficult-to-treat bile duct stones

Professional societies

- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
- British Society of Gastroenterology
- Royal College of Radiologists

Description of the procedure

Indications and current treatment

Bile duct stones that form from cholesterol or bile pigments can block the bile ducts. Difficult-to-treat bile duct stones are defined by their diameter (above 15 mm), number, unusual shape (such as barrel-shaped), location (intrahepatic or cystic duct), stone impaction, narrowing of the bile duct distal to the stone, or the anatomy of the common bile duct (sigmoid-shaped, short distal length or acute distal angulation of less than 135 degrees).

Diagnosis and management of bile duct stones is described in NICE's clinical guideline on gallstone disease. Treatments for bile duct stones include bile duct clearance and laparoscopic cholecystectomy. Conventional stone extraction involves endoscopic retrograde cholangiopancreatography and a sphincterotomy, then extracting the stones from the ducts using balloon and basket catheters. For

difficult-to-treat bile duct stones, treatment options include temporary stenting to allow biliary drainage if the stones cannot be removed or stone fragmentation (lithotripsy).

What the procedure involves

Electrohydraulic lithotripsy (EHL) aims to fragment bile duct stones that cannot be treated using conventional stone removal techniques.

This procedure is usually done using general anaesthesia and direct visualisation of the stones using an endoscope inserted into the biliary tract. An EHL probe is inserted through the endoscope and the tip of the probe is positioned near the stone. Liquid is then injected around the stone and high-voltage energy from the probe generates shock waves that break the stone into smaller pieces. The procedure is usually done with the endoscope passed orally and through the stomach into the duodenum. However, a percutaneous approach is also possible.

When the stone fragmentation is complete, the fragments are flushed out or removed by standard techniques (such as a basket or balloon catheter). The endoscope is then removed. This procedure usually takes about 60 minutes to complete.

Efficacy summary

Stone fragmentation

In a systematic review of 32 studies (n=1,969) of patients with retained biliary tract stones, complete stone fragmentation rates for electrohydraulic lithotripsy (EHL), laser lithotripsy (LL) and extracorporeal shock wave lithotripsy (ESWL) were 76% (176/233), 93% (394/426) and 89% (1,130/1,266) respectively. The difference between groups was statistically significant ($p<0.001$)[1]. In the same review, after excluding studies without direct visualisation of the biliary system using cholangioscopy (n=642), stone fragmentation rates for EHL and LL were 76% (176/255) and 92% (337/365) respectively ($p<0.001$).

In a randomised controlled trial of 98 patients with difficult biliary stones, stone fragmentation was complete after the first session of the single-operator cholangioscopy-guided electrohydraulic lithotripsy (SOC-EHL) in 73% of patients (35/48), partial in 21% (10/48) and unsuccessful in 6% (3/48)[2].

In a non-randomised comparative study of 125 patients with difficult intrahepatic and common bile duct stones, successful stone fragmentation was reported in

93% (38/41) of patients who had peroral cholangioscopy-guided electrohydraulic lithotripsy (POC-EHL) compared with 97% (69/71) of patients who had ESWL[7].

In a case series of 94 patients with difficult bile duct stones, successful stone fragmentation was reported in 96% (89/93) of patients after peroral endoscopic EHL, including 66% (61/93) complete stone fragmentation and 30% (28/93) partial stone fragmentation[8].

In a systematic review and meta-analysis of 35 studies (n=1,762) of patients with difficult biliary stones, the pooled rate of overall successful stone fragmentation was not statistically different for POC-EHL (90%, 95% CI 82.1% to 94.8%, I^2=76.8%; 12 studies) compared with POC-LL (93%, 95% CI 88.5% to 95.7%, I^2= 52.0%; 16 studies; p=0.36)[9].

Stone clearance

In the systematic review of 32 studies (n=1,969), complete ductal clearance rates were 88% (245/277) for EHL, 95% (405/426) for LL and 85% (1,070/1,266) for ESWL, and the difference between groups was statistically significant (p<0.001)[1]. In the same study, after excluding studies without direct visualisation of the biliary system using cholangioscopy, ductal clearance rates for EHL and LL were 88% (245/277) and 96% (350/365) respectively (p<0.001).

In the randomised controlled trial of 98 patients, complete ductal clearance after the first session was reported in 77% (37/48) of patients who had SOC-EHL compared with 72% (36/50) of patients who had endoscopic papillary large balloon dilation, and the difference between the 2 groups was not statistically significant (95% confidence interval [CI] -12.13% to 22.29%)[2]. In the same study, overall complete ductal clearance rates after the second session with crossover of the methods between the 2 groups were not statistically significantly different (85% [40/47] in SOC-EHL compared with 95% [42/44] in endoscopic papillary large balloon dilation, 95% CI -22.24% to 1.546%).

In a randomised controlled trial of 35 patients with difficult bile duct stones, complete stone clearance was reported in 76% (13/17) of patients who had POC-EHL compared with 72% (13/18) of patients who had extracorporeal piezoelectric lithotripsy (ESWL)[3]. The difference between the 2 groups was not statistically significant.

In a non-randomised comparative study of 407 patients with difficult bile duct stones, complete ductal clearance was reported in 97% (296/306) of patients in the digital single-operator cholangioscopy-guided electrohydraulic lithotripsy (D-SOC-EHL) group compared with 99% (100/101) of patients in the digital single-operator cholangioscopy-guided laser lithotripsy (D-SOC-LL) group (p=0.31)[4]. In the same study, complete ductal clearance in a single session was

reported in 75% (228/306) by D-SOC-EHL compared with 86% (87/101) by D-SOC-LL (p=0.20).

In a non-randomised comparative study of 299 patients with difficult intrahepatic bile duct stones, stone clearance after a maximum of 4 sessions was reported in 100% of patients who had percutaneous transhepatic cholangioscopy with electrohydraulic lithotripsy (PTCS-EHL), in 99.6% of patients who had PTCS-EHL plus radiological techniques, and in 100% of patients who had radiological techniques alone[5]. The difference between groups was not statistically significant.

In a non-randomised comparative study of 281 patients with refractory residual biliary calculi, stone clearance rates were about 98% of patients for both cholangioscopy-guided EHL and mechanical clamping plus EHL[6].

In the non-randomised comparative study of 125 patients, the complete stone clearance rate was 74% (34/46) of patients who POC-EHL compared with 79% (62/79) of patients who had ESWL[7]. The difference between the 2 groups was not statistically significant.

In the case series of 94 patients, postfragmentation stone clearance was reported in 90% (85/94) of patients[8].

In the systematic review and meta-analysis of 35 studies (n=1,762) of patients with difficult biliary stones, the pooled rate of complete fragmentation and bile duct clearance after a single session was statistically significantly lower for EHL (71%, 95% CI 63.8% to 77.1%, I^2=63.5%; 12 studies) than LL (83%, 95% CI 75.0% to 88.7%, I^2=72.4%; 13 studies; p=0.02)[9].

Recurrence

In the non-randomised comparative study of 299 patients, recurrence rates after 10 years were statistically significantly different between groups (25% in PTCS-EHL, 13% in PTCS-EHL and radiological techniques, and 9% in radiological techniques alone; p<0.05)[5].

In the non-randomised comparative study of 281 patients, recurrence rate at six-month follow up was about 5% of patients in both the cholangioscopy-guided EHL group and the mechanical clamping plus EHL group (p=0.929). The recurrence rate at 1 year was 11% compared with 9% respectively (p=0.618)[6].

Hospital stays

In the randomised controlled trial of 35 patients, mean length of hospital stay was 15.5 days after POC-EHL compared with 17 days after ESWL[3].

In the non-randomised comparative study of 125 patients, mean length of hospital stay was 11 days (range 1 to 31 days) after POC-EHL compared with 13 days (range 3 to 30 days) after ESWL[7].

Safety summary

Cholangitis and jaundice

Cholangitis was reported in 8% (17/218) of patients who had EHL in the systematic review of 32 studies (n=1,969)[1]. This was a statistically significantly higher proportion than after LL (less than 1% [3/418]) and ESWL (3% [37/1,266]; p<0.001).

Acute cholangitis was reported in 1 patient in the SOC-EHL group and no patients in the endoscopic papillary large balloon dilation group in the randomised controlled trial of 98 patients[2].

Acute cholangitis was reported in 10% (19/182) of patients who had PTCS-EHL, 13% (10/77) of patients who had PTCS-EHL plus radiological techniques, and 5% (2/40) of patients who had radiological techniques alone (p<0.05) in the non-randomised comparative study of 299 patients[5]. All cases were managed with medical therapy or intervention.

Postoperative acute cholangitis was reported in 14% (18/128) of patients who had cholangioscopy-guided EHL compared with 7% (10/153) of patients who had mechanical clamping plus EHL in the non-randomised comparative study of 281 patients (p=0.036). Intraoperative cholangitis was reported in 14% (18/128) and 7% (10/153) of patients, respectively (p=0.036)[6]. Postoperative jaundice was reported in 5% (7/128) of patients who had cholangioscopy-guided EHL compared with 3% (5/153) of patients who had mechanical clamping plus EHL (p=0.854) in the same study.

Cholangitis was reported in 1 patient who had POC-EHL compared with 2 patients who had ESWL in the non-randomised comparative study of 125 patients[7].

Cholangitis, jaundice or both were reported in 14% (13/94) of patients in the case series of 94 patients. These were treated with antibiotics, repeat ERCP or both[8].

Cholecystitis

Cholecystitis was reported in 1 patient who had EHL and 1 patient who had ESWL in the systematic review of 32 studies (n=1,969)[1].

Pancreatitis

Pancreatitis was reported in 1% (3/218) of patients who had EHL, 2% (8/418) of patients who had LL and 2% (21/1,266) of patients who had ESWL in the systematic review of 32 studies (n=1,969)[1].

Acute pancreatitis was reported in 1 patient who had SOC-EHL and 2 patients who had endoscopic papillary large balloon dilation in the randomised controlled trial of 98 patients[2].

Mild pancreatitis was reported in 1 patient 2 days after peroral endoscopic EHL in the case series of 94 patients and this resolved within 48 hours[8].

Haemobilia

Haemobilia was reported in 3% (6/218) of patients who had EHL, 3% (13/418) of patients who had LL and 3% (37/1,266) of patients who had ESWL in the systematic review of 32 studies (n=1,969)[1].

Postoperative haemobilia was reported in 7% (9/128) of patients in the cholangioscopy-guided EHL group compared with 2% (3/153) of patients in the mechanical clamping plus EHL group in the non-randomised comparative study of 281 patients (p=0.036)[6]. Intraoperative haemobilia was reported in 11% (14/128) and 5% (7/153) of patients in these groups, respectively (p=0.043).

Mild haemobilia (with no decrease in haemoglobin) was reported in 1 patient in the case series of 94 patients. This was treated successfully with a local adrenaline injection through the babyscope into the wall of the bile duct[8].

Haemorrhage

Haemorrhage was reported in 1 patient who had POC-EHL, after shock-wave administration to the wall of the common bile duct. The bleeding stopped spontaneously without treatment. A cutaneous haematoma immediately after treatment was reported in 1 patient who had ESWL in the randomised controlled trial of 35 patients[3].

Major bleeding was reported in 2% (3/182) of patients who had PTCS-EHL, 3% (2/77) of patients who had PTCS-EHL plus radiological techniques, and in no patients who had radiological techniques alone in the non-randomised comparative study of 299 patients[5]. All cases required embolisation and were reported during the first 9 years of clinical experience, particularly when using the larger cholangioscopes (4.9 mm and a 16 Fr introducer sheath).

Postoperative bleeding was reported in about 2% of patients who had cholangioscopy-guided EHL (3/128) or mechanical clamping plus EHL (3/153) in the non-randomised comparative study of 281 patients (p=0.985)[6].

Mucosal haemorrhage with minimal amounts of luminal bleeding was reported in 1 patient who had POC-EHL in the non-randomised comparative study of 125 patients. A cutaneous haematoma immediately after ESWL treatment was reported in 2 patients[7].

Biliary leakage

Biliary leakage was reported in 1 patient who had EHL and 3 patients who had LL in the systematic review of 32 studies (n=1,969)[1].

Bile leakage was reported in 4% (5/128) of patients who had cholangioscopy-guided EHL compared with 2% (3/153) of patients who had mechanical clamping plus EHL in the non-randomised comparative study of 281 patients (p=0.537)[6].

Biliary leakage was reported in 1 patient in the case series of 94 patients. This was caused by stone obstruction and successfully resolved with a biliary stent[8].

Perforation

Perforation of the common bile duct during advancement of the guidewire was reported in 1 patient in the PTCS-EHL group, 1 patient in the PTCS-EHL plus radiological techniques group and no patients in the radiological techniques alone group in the non-randomised comparative study of 299 patients[5]. All were treated by repositioning of the transhepatic tube and they were not strictly related to the PTCS-EHL procedure.

Sinus perforation was reported in 1 patient who had cholangioscopy-guided EHL compared with 2 patients who had mechanical clamping plus EHL in the non-randomised comparative study of 281 patients[6].

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never was reported). For this procedure, the professional expert did not list any anecdotal and theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to electrohydraulic lithotripsy for difficult-to-treat bile duct stones. The following

databases were searched, covering the period from their start to 14 December 2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with difficult-to-treat bile duct stones.
Intervention/test	Electrohydraulic lithotripsy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 5,073 patients from 2 systematic reviews (and meta-analysis), 2 randomised controlled trials, 4 non-randomised comparative studies and 1 case series[1 to 9].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on electrohydraulic lithotripsy for difficult-to-treat bile duct stones

Study 1 Veld JV (2018)

Details

Study type	**Systematic review**
Country	Included studies: US (n=8), Korea (n=7), China (n=3), Germany (n=3), India (n=3), Italy (n=2), Brazil (n=1), Canada (n=1), New Zealand (n=1), Saudi Arabia (n=1), Thailand (n=1) and UK (n=1).
Recruitment period	Publication date: 2000 to 2017
Study population and number	n=**1,969 (32 studies; 277 electrohydraulic lithotripsy, 426 laser lithotripsy and 1,266 extracorporeal shock wave lithotripsy)** Patients with retained biliary tract stones
Age and sex	Where reported, mean 47 to 76 years; 40% to 70% female
Patient selection criteria	Inclusion criteria: all original studies reporting on endoscopy-assisted EHL, laser lithotripsy, and ESWL for retained intrahepatic and extrahepatic biliary tract stones, with respect to efficacy and safety; full-text articles in English. Exclusion criteria: reviews, editorials, case reports, abstracts, letters, animal studies, studies in children, cohort studies containing fewer than 5 patients, studies published before 2000, studies not written in English, studies including patients with altered upper gastrointestinal tract anatomy, solely pancreatic duct stones, and the presence of a PTC drain.
Technique	Endoscopy-assisted EHL, LL and ESWL were done but the equipment for lithotripsy methods varied among the studies.
Follow-up	**Not reported**
Conflict of interest/source of funding	MAB received consulting and/or speaker fees from Acelity/KCI, LifeCell/Allergan, Bard, Gore, Johnson & Johnson, and Smith & Nephew, and research grants from Acelity, LifeCell, Bard, Mylan, Johnson & Johnson, Baxter. and IPF received consulting fees from Boston Scientific, Cook Medical, Fujifilm, Medtronic, and Olympus. JEvH received research grants from Cook Medical and Abbott, and consulting fees from Boston Scientific and Medtronic.

Analysis

Study design issues: This systematic review evaluated the efficacy and safety of endoscopy assisted EHL, laser lithotripsy and ESWL in patients with retained biliary stones refractory to the conventional endoscopic or percutaneous methods. This study was performed according to the preferred reporting items for systematic reviews and meta-analyses guidelines. The primary outcome was complete ductal clearance. Secondary outcomes were complete ductal clearance after the first endoscopic session, complete stone fragmentation rate, overall morbidity, procedure-related complications, and anaesthesia related complications. Complete ductal clearance was defined as the ability to retrieve all biliary tract stones with EHL, laser lithotripsy, and ESWL, including additional ERCP when applied. Stone fragmentation was defined as the rupture of stones by 1 of the 3 lithotripsy methods.

Two independent reviewers assessed the eligibility of titles, abstracts, and subsequently full-text articles. Discrepancies were resolved through discussion and consensus, and in cases of doubt, were resolved with the senior author. Quality assessment of the studies was performed using the Oxford Centre for Evidence-Based Medicine Levels of Evidence. The Newcastle – Ottawa Quality Assessment Scale for cohort studies was used to evaluate any risk of bias. Any doubt regarding the methodological quality assessment was discussed by 2 independent reviewers.

Descriptive statistics were computed for all study variables. Sensitivity analysis was performed by excluding retrospective studies and by excluding studies without direct visualization of the biliary tract using cholangioscopy.

Study population issues: Each of the included studies was performed in a tertiary centre. Most of the studies included patients in whom conventional ERCP techniques failed to clear the bile duct. The included studies were performed in various countries with different patient demographics, varying aetiologies for stone formation, and different types of stones. Multiple factors have been related to the failure of endoscopic extraction of biliary stones: size of the stone, location of the stone, stone composition, impaction, biliary strictures, and biliary anatomy. These baseline characteristics were not available for all of the included studies. Therefore, no comparison could be performed between the baseline characteristics of the study groups.

There was a lack of consensus among studies on the definition, classification, and grading of gastrointestinal procedure-related complications. No scoring system has been validated to define, classify, and grade negative outcomes of gastrointestinal procedures. Therefore, it is difficult to compare studies examining negative outcomes of gastrointestinal procedures. Although the methodological quality of the included studies was adequate, studies were mostly small and retrospective. No randomised studies were available, and no studies directly compared EHL with LL. Cholangioscopy (direct visualisation of the biliary tract) was done in some studies but not all.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **1,969 (277 EHL, 426 LL and 1,266 ESWL)**

Complete stone fragmentation (n=1925):

- Complete stone fragmentation: 88.3% (1700/1925)
- Incomplete stone fragmentation: 11.7% (225/1925)

Complete ductal clearance (n=1,969):

- Complete ductal clearance: 87.4% (1720/1,969)
- Incomplete ductal clearance: 12.6% (249/1,969)

Binary logistic regression of efficacy

Lithotripsy method	%	OR	P value	95% CI
Complete stone fragmentation, n=1925				
EHL	75.5 (176/233)	REF	<0.001	-
LL	92.5 (394/426)	3.99	<0.001	2.50 to 6.37
ESWL	89.3 (1,130/1,266)	2.69	<0.001	1.09 to 3.81
Complete ductal clearance, n=1,969				
EHL	88.4 (245/277)	REF	<0.001	-
LL	95.1 (405/426)	2.529	0.002	1.42 to 4.47
ESWL	84.5 (1,070/1,266)	0.71	0.10	0.48 to 1.06

Safety

Number of patients analysed: **1902 (218 EHL, 418 LL and 1,266 ESWL)**

Binary logistic regression of safety

Lithotripsy method	% (n)	OR	P value	95% CI
Overall morbidity				
EHL	14.2	REF	0.29	-
LL	10.0	0.63	0.12	0.41 to 1.11
ESWL	11.2	0.76	0.20	0.50 to 1.16
Total	11.3 (215)	-	-	-
Post-procedural complications				
EHL	13.8 (30)	REF	0.04	-
LL	9.6 (40)	0.66	0.11	0.40 to 1.10
ESWL	8.4 (106)	0.57	0.01	0.37 to 0.88
Total	9.3 (176)			
Anaesthesia-related complications				
EHL	0.5	REF	0.01	-
LL	0.5	1.04	0.97	0.09 to 11.57
ESWL	2.8	6.35	0.07	0.87 to 46.57

Procedure-related complications

	EHL, % (n)	LL, % (n)	ESWL, % (n)	Total, % (n)
Pancreatitis	1.4 (3)	1.9 (8)	1.7 (21)	1.7 (32)
Cholangitis*	7.8 (17)	0.7 (3)	2.9 (37)	3.0 (57)
Cholecystitis	0.5 (1)	0 (0)	0.1 (1)	0.1 (2)
Haemobilia	2.8 (6)	3.1 (13)	2.9 (37)	2.9 (56)
Abdominal pain	0 (0)	1.7 (7)	0 (0)	0.4 (7)
Fever	0 (0)	0.7 (3)	0 (0)	0.2 (3)

Complete ductal clearance after first session, n=1658				
EHL	65.8 (152/231)	REF	<0.001	-
LL	68.9 (215/312)	1.15	0.44	0.80 to 1.66
ESWL	31.6 (352/1115)	0.24	<0.001	0.18 to 0.32

Sensitive analysis of prospective studies

Lithotripsy method	%	OR	P value	95% CI
Complete stone fragmentation				
EHL (n=111)	82.4	REF	0.10	-
LL (n=297)	90.6	2.06	0.04	1.04 to 3.34
ESWL (n=596)	87.2	1.47	0.22	0.87 to 2.69
Complete ductal clearance				
EHL	90.1	REF	<0.001	-
LL	94.9	2.07	0.08	0.92 to 4.65
ESWL	82.0	0.50	0.04	0.26 to 0.97
Complete ductal clearance after first session				
EHL	59.2	REF	<0.001	-
LL	62.3	1.14	0.64	0.66 to 1.97
ESWL	40.3	0.46	0.002	0.29 to 0.76

Sensitive analysis after excluding studies without direct visualisation of the biliary system using cholangioscopy, n=642:

- Stone fragmentation rate: EHL 75.5% (176/255) compared with LL 92.3% (337/365), p<0.001
- Ductal clearance rate: EHL 88.4% (245/277) compared with LL 95.9% (350/365), p<0.001
- Complete ductal clearance within the first session: EHL 65.8% (152/231) compared with LL 71.6% (187/261)

All patients who had ESWL were excluded.

Bleeding	0 (0)	0 (0)	0.6 (8)	0.4 (8)
Perforation	0 (0)	0 (0)	0.2 (2)	0.1 (2)
Biliary leakage	0.5 (1)	0.7 (3)	0 (0)	0.2 (4)
Other	0.9 (2)	0.7 (3)	0 (0)	0.3 (5)

*The incidence of cholangitis was statistically significantly higher for EHL than for LL and ESWL (p<0.001).

Anaesthesia-related complications

	EHL, % (n)	LL, % (n)	ESWL, % (n)	Total, % (n)
Tachycardia	0 (0)	0.2 (1)	0 (0)	0.1 (1)
Bradycardia	0.5 (1)	0 (0)	1.3 (17)	0.9 (18)
Palpitations	0 (0)	0 (0)	0.7 (9)	0.5 (9)
Resuscitation	0 (0)	0 (0)	0.1 (1)	0.1 (1)
Nausea	0 (0)	0 (0)	0.5 (6)	0.3 (6)
Vomiting	0 (0)	0 (0)	0.2 (3)	0.2 (3)
Pneumonia	0 (0)	0.2 (1)	0 (0)	0.1 (1)

Sensitive analysis of prospective studies

Lithotripsy method	%	OR	P value	95% CI
Overall morbidity				
EHL (n=111)	14.1	REF	0.40	-
LL (n=297)	9.1	0.61	0.18	0.29 to 1.26
ESWL (n=596)	10.1	0.68	0.26	0.35 to 1.33
Postprocedural complications				
EHL	14.1	REF	0.30	-
LL	8.4	0.56	0.12	0.27 to 1.17
ESWL	10.1	0.68	0.26	0.35 to 1.33
Anaesthesia-related complications				
EHL	0	REF	>0.99	-
LL	0.7	>0.99	>0.99	<0.001
ESWL	0	>0.99	>0.99	<0.001

Sensitive analysis after excluding studies without direct visualisation of the biliary system using cholangioscopy, n=642:

- Overall morbidity: EHL 14.2% (31/218) compared with LL 9.5% (34/357), p=0.08

Abbreviations used: CI, confidence interval; EHL, electrohydraulic lithotripsy; ESWL, extracorporeal shock wave lithotripsy; LL, laser lithotripsy; OR, odds ratio.

Study 2 Franzini T (2018)

Details

Study type	**Randomised controlled trial**
Country	Brazil (single centre)
Recruitment period	2014 to 2016
Study population and number	n=**98 (48 single-operator cholangioscopy-guided EHL compared with 50 endoscopic papillary large balloon dilation)** Patients with difficult biliary stones
Age and sex	Mean 56 years; 75.5% (74/100) female
Patient selection criteria	Inclusion criteria: patients were 18 years or older and had difficult biliary stones defined as multiple (more than 10), size greater than 15mm, presence of disproportion between the stone and distal common bile duct (greater than 2 mm) or biliary stricture with a stone upstream. Exclusion criteria: pregnancy, patients who underwent gastrointestinal surgery or liver transplant previously, and acute cholangitis.
Technique	SOC-EHL: The first generation of SpyGlass™ platform was used. With this system, a delivery catheter (SpyScope™) is introduced through the duodenoscope into the biliary tree under a guidewire. After proper positioning, the lithotripter fibre was used with a generator with a 70- to 100-watt power output, depending on the response of stone fragmentation. In both groups (SOC-EHL and endoscopic papillary large balloon dilation), after fracture/dilation, the stones were retrieved using a Dormia basket and/or a retrieval balloon catheter. In case of failure, either biliary drainage with plastic stents or crossover to the other method was performed immediately. Patients who received a plastic stent were scheduled for crossover in a second attempt. Mechanical lithotripsy was not performed in any patient. Ciprofloxacin, 400mg IV, was given as prophylaxis to all patients in both groups.
Follow-up	**1 week**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: In the single-operator cholangioscopy-guided electrohydraulic lithotripsy (SOC-EHL) group , 2 patients were excluded after initial randomisation due to different diagnosis, verified during cholangioscopy, and 1 was lost to follow up. In the endoscopic papillary large balloon dilation group, 6 patients were lost to follow up. Detailed follow up was not described.

Study design issues: The prospective randomised controlled trial (RBR-5wx47j) evaluated the 2 methods (SOC-EHL compared with endoscopic papillary large balloon dilation) regarding complete stone removal, occurrence of adverse events and the association of techniques, optimising the endoscopic approach to difficult biliary stones. The primary outcome of the study was complete stone removal after 2 sessions with different techniques under analysis, if needed. Secondary end points included adverse events, procedure time and x-ray exposure time.

Cholangitis was defined as abdominal pain, fever, chills and/or jaundice. Pancreatitis was defined as persistent abdominal pain and vomiting associated with a serum amylase level more than 3 times the upper limit, which required hospitalisation or an extension of it. Perforation was considered if disruption of duodenal or biliary wall, was identified under direct endoscopic visualization, or with fluoroscopy evidence of contrast medium extravasation or by imaging tests. Bleeding was defined as occurrence of papillary or biliary bleed after the endoscopic procedure that needs transfusion or interventions.

The expected success rate was approximately 91%. A non-inferiority margin of 17% was considered, so in the worst-case scenario the success rate would be 74%, after the 2 sessions. Considering that, to obtain tests with 5% significance and

80% power, 45 cases would be necessary in each group. Foreseeing a possible loss of follow-up of 10%, the ideal sample was 50 cases in each group. Randomisation was performed using a computer-generated system but the investigators were unblinded to the methods used in each patient. During the Endoscopic retrograde cholangiopancreatography (ERCP) procedure, after cholangiography confirmed presence of a complex biliary stone, conventional techniques were performed in an attempt to remove the stone and clear the common bile duct (CBD). When these methods failed, the eligible patients were randomly assigned in 2 groups. All procedures were performed by 2 investigators, both with considerable experience in ERCP (over 350 procedures per year).

Study population issues: There was a statistically significant difference between the 2 groups in terms of age (mean 52.13 years in the SOC-EHL group compared with 59.76 years in the endoscopic papillary large balloon dilation group, p=0.032) but not for gender, symptoms, previous endoscopic procedures and stone characteristics such as number, size, shape and location.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **98 (48 SOC-EHL compared with 50 endoscopic papillary large balloon dilation)**

Stone characteristics and procedure outcomes

	SOC-EHL	**endoscopic papillary large balloon dilation**	**P value**
Stone number, % (n)			
<3	64.6 (31)	76 (38)	0.216
3	35.4 (17)	24 (12)	
Size, % (n)			
<15 mm	18.8 (9)	18 (9)	0.995
15 to 20 mm	37.5 (18)	38 (19)	
20 mm	43.8 (21)	44 (22)	
Shape, % (n)			
Rounded	41.7 (20)	24 (12)	0.062
Faceted	41.7 (20)	40 (20)	0.867
Longitudinal	16.7 (8)	38 (19)	0.018
Associated conditions, % (n)			
Biliary stricture	10.4 (1)	(3)	
Duodenal diverticulum	2.1 (5)	(3)	0.865
Stone-choledochal disproportion	(16)	(20)	
First session technical success rate[a]	77.1 (37)	72 (36)	0.930
[b]Procedure time, minutes	72.3±33.95	47.1±29.37	<0.001
X-ray exposure, minutes	10.85±6.95	9.73±6.61	0.371
Overall per protocol technical success rate after second session (crossover)[c]	85.1 (40/47)	95.4 (42/44)	0.1147

[a]95% CI -12.13% to 22.29%

[b]Procedure time was significantly lower in the endoscopic papillary large balloon dilation group, 25.2min (95% CI 12.48 to 37.91).

Safety

Adverse events, % (n)

	SOC-EHL	**endoscopic papillary large balloon dilation**
Acute pancreatitis	2.1 (1)*	4 (2)**
Acute cholangitis	2.1 (1)*	0
Bleeding	0	4 (2)**
Laceration	0	2 (1)**
Perforation	0	2 (1)**

*mild intensity and recovered after standard clinical treatment.

**treated conservatively with good recovery.

The rates of adverse events were not significantly different between the 2 groups (4.2% [2/48] compared with 12% [6/50], p>0.05). there were no late complications (after 7 days).

[c]After the second session, the overall success rate increased from 74.5% to 90.1% with no significant difference between the 2 groups, with a 95% CI -22.24% to 1.546%. **Stone fragmentation after 1 session of EHL** was complete in 35 patients (72.9%), partial in 10 patients (20.8%) and unsuccessful in 3 (6.2%). **Overall cases of failure**: n=25 (20 returned to perform another ERCP as a crossover process) • SOC-EHL: there were 11 failures, 1 (2.1%) was lost to follow-up and 10 (20.8%) were submitted to a second ERCP session. Of these, 10 patients had endoscopic papillary large balloon dilation performed, in 7 (70%) of whom the procedure failed and in 3 (30%) of whom it was a success. • Endoscopic papillary large balloon dilation: there were 14 cases of failure, 4 (8%) were lost to follow-up and 2 (4%) chose to receive surgical treatment. 8 patients (16%) had undergone a second session, with success in 6 (75%) after SOC-EHL.	
Abbreviations used: CI, confidence interval; EHL, electrohydraulic lithotripsy; ERCP, endoscopic retrograde cholangiopancreatography; SOC-EHL, single-operator cholangioscopy-guided electrohydraulic lithotripsy.	

Study 3 Adamek HE (1995)

Details

Study type	**Randomised controlled trial**
Country	Germany (single centre)
Recruitment period	1991 to 1993
Study population and number	n=**35 (17 peroral cholangioscopy-guided EHL compared with 18 extracorporeal piezoelectric lithotripsy)** Patients with difficult bile duct stones
Age and sex	EHL: mean 68 years; **sex not reported** Extracorporeal piezoelectric lithotripsy: mean 77 years; **sex not reported**
Patient selection criteria	Inclusion criteria: stone visualisation through ultrasound was possible; the papilla was within easy reach of the endoscope; stones were not accessible to routine endoscopic extraction; and at least 1 attempt at mechanical lithotripsy had failed.
Technique	EHL was done under strict cholangioscopic guidance. Peroral cholangioscopy was performed with 2 operators using the TJF-M 20 ("mother scope") duodenoscope and the CSF-B 20 ("daughter scope") cholangioscope (Olympus Optical, Hamburg). Physiological saline was applied, a 4.5 Fr EHL probe was passed down the 2.8-mm-diameter working channel of the cholangioscope and its tip positioned close to the concretion. At an output voltage of 2000 V, shock waves of increasing frequency and an intensity of 260 mJ were applied with a continuous sequence of discharges. In both groups (EHL and extracorporeal piezoelectric lithotripsy), antibiotics were not given prophylactically.
Follow-up	**30 days**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Detailed follow-up and its completeness were not reported.

Study design issues: This prospective randomised controlled trial ascertained the differences in EHL and extracorporeal piezoelectric lithotripsy (ESWL) with special regard to fragmentation rate, complete stone removal, patient comfort and average hospital stay. Patients fulfilling the inclusion criteria were randomly treated by either EHL or ESWL. Study power, randomisation method, blinding and allocation concealment were unclear.

Study population issues: Existing symptoms included painless jaundice in 46% of patients (n=16; 8 EHL compared with 8 ESWL), 17% (n=6; 3 EHL compared with 3 ESWL) patients complained of abdominal pain, and 37% (n=13; 6 EHL compared with 7 ESWL) had cholangitis. The main reasons that conventional endoscopy failed were due to the large size of the stones (n=13; 6 EHL compared with 7 ESWL), impacted stones (n=16; 9 EHL compared with 7 ESWL), or the presence of a biliary stricture (n=6; 2 EHL compared with 4 ESWL).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **35 (17 POC-EHL compared with 18 ESWL)** **Stone characteristics and lithotripsy results**	**POC-EHL** **Haemorrhage**: n=1 (following shock-wave administration to the wall of the CBD, and the bleeding stopped

	POC-EHL	ESWL
Stone size, mean (range, mm)	21.3 (8 to 35)	26.6 (12 to 44)
Stone number, n		

Solitary	5	7
2 stones	3	0
>2 stones	9	11
Visualisation, % (n)	94 (16)	89 (16)[b]
Fragmentation	100 (16)	94 (15)
Stone clearance[d]	81 (13/16)	81 (13/16)
	76 (13/17)[a]	72 (13/18)[c]

[a]In 4 patients, stone fragmentation was not reported because coupling to the stone under direct vision failed or the concrement was impacted Prepapillary, so making primary introduction of the cholangioscope impossible. Of these patients, 3 were treated successfully by ESWL, 1 was resistant to extracorporeal shock-wave lithotripsy and, therefore, was referred to surgery.

[b]Of 2 patients, 1 with a prepapillary stone also had a duodenal diverticulum that consistently lay over the CBD, so making sonographic localisation on the lithotripter impossible. In another, sonographic localisation on the lithotripter was not possible because patient noncompliance, so treatment had to be abandoned.

[c]In 5 patients ESWL failed for the following reasons: failure to locate the stone on the lithotripter (n=2), no fragmentation (n=1) and incomplete fragmentation because of too many stones located in the CBD (n=2). Of these patients, 2 were cleared of their stones by additional use of EHL via peroral cholangioscopy, 1 was successfully treated with endoscopic extraction in combination with laser lithotripsy, and 2 with residual fragments in the CBD palliatively received an endoscopic endoprosthesis, even after laser lithotripsy had failed to clear the bile duct in 1 patient.

[d]Comparing 2 groups, statistically significant difference in stone free rates was not reported (p>0.5, one-tailed Fisher's exact test).

Success rate of lithotripsy in correlation to stone localisation, %

Location	POC-EHL	ESWL
Intrahepatic and hilus	50 (2/4)	50 (2/4)
Choledochus	100 (7/7)	86 (6/7)
Prepapillary	67 (4/6)	71 (5/7)

Treatment characteristics

	POC-EHL	ESWL
Number of lithotripsy sessions, mean (range)[e]	1.4 (1 to 3)	2.3 (1 to 8)
Procedure time, mean (range, minutes)	45	63 (40 to 140)
Spontaneous clearance	0	1
Additional endoscopy	17	17
1 intervention, % (n)	18 (3)	35 (6)
2 interventions, % (n)	29 (5)	24 (4)
3 interventions, % (n)	53 (9)	41 (7)
Mortality at 30 days	0	0
Hospital stay, mean (days)	15.5	17

[e]Comparing 2 group, statistical significance was not reported (p>0.1)

Combined treatment including ESWL, EHL, and intracorporeal laser lithotripsy was finally successful in 91.5% of patients (32/35).

spontaneously without treatment).

ESWL

Cutaneous haematoma: n=1 (immediately after treatment)

Leukocytosis without clinical signs of cholangitis: n=1

Abbreviations used: CBD, common bile duct; EHL, electrohydraulic lithotripsy; ESWL, extracorporeal piezoelectric lithotripsy; POC-EHL, peroral cholangioscopy-guided electrohydraulic lithotripsy.

Study 4 Brewer Gutierrez OI (2018)

Details

Study type	**Non-randomised comparative study (retrospective)**
Country	US (19 centres), UK (2 centres) and Korea (1 centre)
Recruitment period	2015 to 2016
Study population and number	n=**407 (306 D-SOC-EHL compared with 101 D-SOC-LL)** Patients with difficult bile duct stones
Age and sex	Mean 64.2 years; 60% (246/407) female
Patient selection criteria	Inclusion criteria: adult patients (>18 years) who had D-SOC using either EHL or LL for the management of difficult bile duct stones, which were defined as large (>15 mm), multiple (>3), intrahepatic duct/cystic duct stones and/or impacted stones, and those with Mirizzi syndrome or any associated common bile duct (CBD) anatomic abnormality, such as stricture below the stone or duodenal diverticula and patients with altered anatomy. Exclusion criteria: patients were treated with other types of cholangioscopes.
Technique	Difficult bile duct stones were treated by D-SOC (Spyglass DS, Boston Scientific) with EHL or LL. EHL (AUTOLITH, Northgate Technologies Inc, Elgin, IL): shock waves were delivered in brief pulses, which range from a single discharge to continuous firing, until the stone is fragmented. The power setting ranged between 50% and 100% and delivered over 1 to 2 seconds. LL: The Versa-Pulse P20, Slim line 365 mm fibre holmium laser (holmium: yttrium-aluminum-garnet; Lumenis Inc, San Jose, CA) was used with power settings of 20 W (2.5 J X 8 Hz), in bursts of no more than 5 seconds. During the D-SOC procedure, 92% of patients received antibiotic prophylaxis.
Follow-up	**Median 83.5 days (interquartile range, 33 to 155 days)**
Conflict of interest/source of funding	IR is a consultant and speaker for Boston Scientific and Covidien; and co-owner of EndoRx. RT has received financial support from Boston Scientific to attend scientific meetings. SS is a consultant for Boston Scientific. RJS is consultant for Cook and for Boston Scientific. WW is a consultant for Boston Scientific and Abbvie. DGA is a consultant for Boston Scientific. VK is a consultant for Boston Scientific. AYW has received research support from Cook Medical. KK is a speaker for Boston Scientific; and a consultant for Olympus. VK is a consultant for Cook Medical. CJD is a consultant for Boston Scientific. BP is a consultant for Boston Scientific. GJMW is a consultant for Boston Scientific. SK is a consultant for Cook Medical and Boston Scientific. MAK is a consultant for Boston Scientific and Olympus. The remaining authors disclose no conflicts.

Analysis

Follow-up issues: Follow up time was recorded in 63.6% (259/407) of patients.

Study design issues: This retrospective, international, multicentre study assessed technical success, defined as bile duct clearance, in a large cohort of patients with difficult biliary stones. This study also assessed the safety of digital single-operator cholangioscopy (D-SOC) either with electrohydraulic lithotripsy (EHL) or with laser lithotripsy (LL) and to compare the effectiveness of EHL with LL. The safety was defined by the rate and severity of adverse events as graded per the American Society for Gastrointestinal Endoscopy lexicon (mild, moderate, severe, fatal). Other outcomes included number of EHL/LL sessions needed to clear the bile duct; the need for other therapies; incomplete stone removal or stone recurrence after the duct was declared clear; and addition to procedure time. Univariate and multivariable analyses were performed to identify factors associated with technical failure and the need for more than 1 D-SOC-EHL or -LL session to clear the bile duct.

Study population issues:

At baseline, there were (statistically significant) differences between the 2 groups as shown in the table below.

	Total (n=407)	D-SOC-EHL (n=306)	D-SOC-LL (n=101)	P value
Symptoms (>1), % (n)				
Abdominal pain	48.8 (166)	35.3 (108)	57.4 (58)	<0.001
Jaundice	40.8 (166)	49.7 (152)	13.9 (14)	<0.001
Cholangitis	16.9 (69)	19.3 (59)	9.9 (10)	0.03
Pancreatitis	1.5 (6)	1.6 (5)	1 (1)	1
Others	11.8 (48)	5.9 (18)	29.7 (30)	<0.001
Prior ERCP with failed stone extraction, % (n)	85.7 (349)	88.5 (271)	77.3 (78)	0.005
Prior interventions for stone removal (>1), % (n)				
Sphincterotomy	62.6 (253)	67.3 (206)	46.5 (47)	<0.001
Papillary balloon dilation	0.5 (2)	0.6 (5)	0	1
Sphincterotomy+papillary balloon dilation	17.2 (70)	17.3 (53)	16.8 (17)	0.91
Balloon extraction	73.2 (298)	82.3 (252)	45.5 (46)	<0.001
Retrieval basket	22.8 (93)	19.6 (60)	32.7 (33)	0.007
Mechanical lithotripsy	24.8 (101)	21.6 (66)	34.6 (35)	0.008
Laser lithotripsy	1.7 (7)	1.3 (4)	3 (3)	0.37
Electrohydraulic lithotripsy	7.6 (31)	10.1 (31)	0	<0.001
Indwelling biliary stent, % (n)	75.9 (309)	82.3 (252)	56.4 (57)	<0.001

Key efficacy and safety findings

Efficacy

Number of patients analysed: **407 (306 D-SOC-EHL compared with 101 D-SOC-LL)**

Stone and procedure characteristics

	Total (n=407)	D-SOC-EHL (n=306)	D-SOC-LL (n=101)	P value
CBD size, mm (mean±SD)	15.1±5.95	14.2±5.24	18.3±6.98	<0.001
Stone locations, % (n)				<0.001
CBD	59.7 (243)	55.9 (171)	71.3 (72)	
CHD	9.6 (39)	9.1 (28)	10.9 (11)	
Cystic duct	11.3 (46)	14.4 (44)	10.9 (11)	
IHD	15.2 (62)	17.3 (53)	8.9 (9)	
Hilar	1.5 (6)	2 (6)	0	
More than 1 location	2.7 (11)	1.3 (4)	6.9 (7)	
Stone size, mm (mean±SD)	16.01±7.14	15.93±7.17	16.24±7.10	0.71
Stone number, % (n)				0.60
1	41.3 (168)	41.5 (127)	40.6 (41)	
2 to 3	4.9 (20)	5.6 (17)	3 (3)	
>3	53.8 (219)	52.9 (162)	56.4 (57)	
Stone impaction, % (n)	38.1 (155)	39.9 (122)	32.7 (33)	0.20
Stone proximal to a stricture, % (n)	19.7 (80)	16.7 (51)	28.7 (29)	0.008

Safety

AE rates were not statistically significantly different between EHL (3.3%) and LL (5%; p<0.54).

AE: 15 patients (3.7% based on 407 patients)

- Cholangitis: n=6
- Pancreatitis: n=1
- Bleeding: n=1
- Transient bacteraemia: n=1
- Bile duct perforation: n=1
- Abdominal pain: n=5

These were rated as mild (n=10; 66.7%), moderate (n=3; 20%), and severe (n=2; 13.3%), as per American Society for Gastrointestinal Endoscopy lexicon. All patients, including the ones with AE rated as moderate and severe, were treated conservatively with intravenous fluids, pain medication, and

Difficult cannulation/anatomy, % (n)[b]	14 (57)	10.5 (32)	24.7 (25)	<0.001
Mirizzi syndrome, % (n)	8.6 (35)	10.8 (33)	2 (2)	0.004
Devices used for stone extraction after lithotripsy, % (n)				0.03
Extraction balloon	81.8 (328)	80.3 (241)	86.1 (87)	
Retrieval basket	8.2 (33)	9.3 (28)	5 (5)	
Extraction balloon and basket	6.5 (26)	5.7 (17)	8.9 (9)	
Other	3.5 (14)	4.7 (14)	0	
Stent placed, % (n)	30.2 (123)	30.1 (92)	30.7 (31)	0.90
Plastic	86.2 (106)	84.8 (78)	90.3 (28)	
Metallic	13.8 (17)	15.2 (14)	9.7 (3)	
Procedure time, min (mean±SD)	67±34.9	73.9±33.5	49.9±32.4	<0.001

[a]Presence of duodenal diverticula, altered anatomy

Procedure outcomes

	Total (n=407)	**D-SOC-EHL (n=306)**	**D-SOC-LL (n=101)**	**P value**
Technical success (complete bile duct clearance), % (n)	97.3 (396)	96.7 (296)	99.0 (100)	0.31
Sessions of EHL/LL to clean the bile duct, % (n)				0.20
1	77.4 (315)[b]	74.5 (228)	86.1 (87)	
>1	19.9 (81)	22.2 (68)	12.9 (13)	
N/A	2.7 (11)	3.3 (10)	1 (1)	
No. of EHL/LL sessions to clear bile duct, median (range)	1 (1 to 4)	1 (1 to 4)	1 (1 to 4)	0.12
ERCPs for additional therapy (remove stents, treat strictures), % (n)	33.7 (137)	34 (104)	32.7 (33)	0.21
Need for ESWL, % (n)	0.5 (2)	0.3 (1)	1 (1)	0.44
Need for surgery, % (n)	2.0 (8)	2.6 (8)	0	0.21
Need for ESWL and surgery, % (n)	0.2 (1)	0.3 (1)	0	1
No. of patients followed up, % (n)	63.6 (259)	74.2 (227)	31.7 (32)	<0.001
Total follow-up, d (median) (IQR)	83.5 (33 to 155)	84 (34 to 151)	86 (32 to 129)	0.65
Incomplete stone removal/occult stones, % (n)	6.6 (17)	7 (16)	3.1 (1)	0.07
Management of stone recurrence (n=17) (>1 technique/device used), % (n)				
D-SOC with EHL/L	29.4 (5)	31.2 (5)	0	0.34
Balloon/basket	64.7 (11)	62.5 (10)	100 (1)	0.20
Mechanical lithotripsy	23.5 (4)	25 (4)	0	0.58
ESWL	11.8 (2)	6.2 (1)	100 (1)	0.44
Surgery	5.9 (1)	6.2 (1)	0	1

[b]Of 315 patients, 31 (9.8%) had the gallbladder in situ at the time of the procedure, and a stent was placed (83.9% plastic stents).

antibiotics. The patient with bile duct perforation was treated endoscopically with a fully covered self-expandable metal stent (FSEMS). The 2 patients with severe AE had cholangitis and were managed with intravenous antibiotics.

Of patients requiring surgery, 6 had Mirizzi syndrome and underwent cholecystectomy with cystic duct stone removal and CBD repair over a tube. One patient failed to clear the bile duct with 2 EHL/LL sessions and a stent was placed; then developed gallstone ileus and underwent laparotomy, enterotomy, and removal of gallstone and CBD stones. One patient had intrahepatic stones and had hepatectomy with stone removal (segments 2, 3, 6 and 7). The patient who required ESWL and surgery had a retained cystic duct stone in the context of prior cholecystectomy and had a laparoscopy with stone removal. **Recurrence: Incomplete stone clearance/occult stones** after a median follow-up of 56 days (IQR, 38.5 to 154 days) after reported stone clearance: 6.5% (17/259) **Management of incomplete stone removal**: • Extraction balloon: 64.7% (n=11) • Repeat D-SOC with EHL/LL: 29.4% (n=5) • Mechanical lithotripsy: 23.5% (n=4) • ESWL: 11.8% (n=2) • Surgery: 5.9% (n=1) **Predictors of outcomes:** **Difficult anatomy/cannulation** was the only predictor that was significantly associated with technical failure on univariable analysis (OR, 3.70; 95% CI 1.05 to 13.1; p=0.04). This association remained statistically significant after multivariable adjustment (adjusted OR, 5.18; 95% CI 1.26 to 21.2; p=0.02). Prior failed ERCP (OR, 2.85; 95% CI 1.10 to 7.39; p=0.03), more than 1 prior ERCP attempt (OR, 3.77; 95% CI 1.41 to 10.1; p<0.008), and duration of the index D-SOC EHL/LL procedure (OR, 1.02; 95% CI 1.01 to 1.03; p<0.001) were associated with the need for more than 1 D-SOC EHL/LL session on univariable analysis. On multivariate analysis, and after adjusting for potential confounders, only duration of the index procedure (adjusted OR, 1.02; 95% CI 1.01 to 1.03; p<0.001) was a significant predictor of the need for more than 1 D-SOC EHL/LL session.	
Abbreviations used: AE, adverse event; CI, confidence interval; D-SOC-EHL, digital single-operator cholangioscopy-guided electrohydraulic lithotripsy; ; D-SOC-LL, digital single-operator cholangioscopy-guided laser lithotripsy; EHL, electrohydraulic lithotripsy; ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shockwave lithotripsy; IQR, interquartile range; LL, laser lithotripsy; N/A, not available; OR, odds ratio; SD, standard deviation.	

Study 5 Cannavale A (2015)

Details

Study type	**Non-randomised comparative study (retrospective)**
Country	Italy (single centre)
Recruitment period	1994 to 2012
Study population and number	n=**299 (182 PTCS-EHL, 40 radiological techniques, and 77 PTCS-EHL and radiological techniques)** Patients with difficult intrahepatic bile duct stones
Age and sex	Mean 62.5 years; 33.8% (101/299) female
Patient selection criteria	Not reported
Technique	Percutaneous transhepatic cholangiography (PTC)/biliary drainage/s was done, dilating the PTC track to 10 or 16 French within 3 to 7 days, followed by percutaneous transhepatic cholangioscopy (PTCS) with EHL and/or interventional radiology techniques. For EHL, it was done with 3 or 4.5 Fr probes. After each session, a 10 Fr biliary drainage was inserted in order to manage any possible adverse event and removed 24 to 48 hours later if complete clearance was confirmed. Cholangioscopy also allowed to introduce biopsy forceps or to take off surgical stitches.
Follow-up	**Mean 66 months (range 12 to 120)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: After discharge, patients were followed up with laboratory tests and with US examination initially after 6 months then yearly thereafter. If there was suspicion of recurrence, CT or MRCP (since 1999 onwards) were performed.

Study design issues: This observational retrospective study analysed the 18-year experience in the management and treatment of difficult intrahepatic bile duct stones with PTCS/EHL and/or radiological techniques. CT and/or magnetic resonance (MR) findings were classified according to the Tsunoda classification (stone distribution – unilateral or bilateral – and the presence of associated intrahepatic duct stricture): I) No marked dilatation or strictures of intrahepatic ducts; II) Diffuse dilatation of intrahepatic ducts without strictures; III) Unilateral solitary or multiple cystic dilatation of intrahepatic ducts with strictures; IV) Bilateral. Technical success for EHL was defined as immediate complete removal of stones. The assessment of complete removal of stones was made by cholangioscopy, cholangiography or US.

Study population issues: Of the 299 patients, 97% (290/299) had previous history of surgical interventional abdominal procedures (duodeno-cephalo-pancreatectomy, cholecystectomy, liver transplant and biliary stenting). In 26.7% (80/299) of patients, an endoscopic approach was unsuccessfully attempted with ERCP; 73.3% (219/299) of patients underwent directly biliary drainage/s due to evident anatomical alterations. Mild pancreatitis was the only ERCP related complication happening in 3.7% (3/80) and was treated with fasting and intravenous gabexate 900 mg/day for 3 days; in all cases, blood test normalization occurred within 5 days. In these patients, PTC was postponed until pancreatitis was completely resolved.

According to Tsunoda classification, 22.1% of patients (66/299), 30.7% (92/299), 30.4% (91/299) and 16.7% (50/299) were classified as type I, II, III and IV, respectively. In terms of PTC, 85.6% (256/299) were performed after biliary drainage access and 14.4% (43/299) using a T-tube previously surgically positioned. Differences in patients' clinical features at baseline between groups were not reported.

Key efficacy and safety findings

Efficacy and safety

Number of patients analysed: **299 (182 PTCS-EHL, 40 radiological techniques, and 77 PTCS with EHL and radiological techniques)**

Procedure characteristics and results

	Overall	PTCS-EHL	PTCS-EHL and radiological techniques	Radiological techniques	P value
Procedure time, min (mean±SD)	54±12	55±15	60±17	45±10	>0.05
Patient dose, mGy (mean±SD)	5.6±0.7	6±1.5	8±1	3±0.8	<0.05
Bilateral PTC access, % (n)	29.7 (89)	19.2 (34)	45.4 (35)	25 (10)	0.05
Tsunoda class I, % (n)	22.1 (66)	8.2 (15)	19.4 (15)	90 (36)	<0.05
Tsunoda class II, % (n)	30.7 (92)	40.1 (73)	19.4 (15)	10 (4)	<0.05
Tsunoda class III, % (n)	30.4 (91)	37.9 (69)	28.5 (22)	0	<0.05
Tsunoda class IV, % (n)	16.7 (50)	13.7 (25)	32.4 (25)	0	<0.05
Sessions, mean (range)	2 (1 to 4)	3.5 (3 to 4)	3 (2 to 4)	2.5 (2 to 4)	>0.05
Clearance rate, %	99.8	100	99.6	100	>0.05
Recurrence rate (10 years), %	15	24.7	13.4	9.1	<0.05

Complete stone clearance was reported in 1 to 2 sessions of PTCS in Tsunoda type I and II. Patients with types III and IV needed 3 to 4 sessions ($p<0.05$).

In 1 patient with multiple biliary stones (Tsunoda class IV), PTCS-EHL (CS 4.9 mm) did not clear all the intrahepatic stones; after 4 attempts and the patient still have residual stones in the left liver lobe. During the fourth procedure, a bleeding from the transhepatic tract was detected; an angiogram revealed an active bleeding from a segmental branch of the right hepatic artery, that was successfully embolised. Hence the patient underwent surgical resection of the left liver lobe.

Technical success:

- After the first session: n=66
- After the second session: n=121
- After the third session: n=88
- After the fourth session: n=25

Recurrence within 2 years after discharge: 15% (45/299), referring episodes of cholangitis with increased total bilirubin, GGT and fever (88.9% [40/45]) or biliary colic alone (10.1% [5/45]) and were successfully retreated.

- Within 12 months: 44.4% (20/45; intrahepatic stones)
- Within 18 months:31.1% (14/45)
- Within 24 months: 24.4% (11/45)

Complications, % (n)

	Overall	PTCS with EHL	PTECS with EHL and radiological techniques	Radiological techniques	P value
Major complications					
Major bleeding	1.7 (5)*	1.6 (3)	2.5 (2)	0	>0.05
Perforations	0.6 (2)**	0.5 (1)	1.2 (1)	0	>0.05
Cholangitis	10.3 (31)***	10.4 (19)	12.9 (10)	5 (2)	<0.05
Major complications	12.3 (37)****	7.1 (13)	15.5 (12)	30 (12)	>0.05

*required embolisation

**perforations of the CBD were caused by the tip of the guidewire and thus were not strictly related to the PTCS/EHL procedure. All cases were treated with repositioning of the transhepatic tube.

***treated with antibiotic therapy. Usual medical therapy was ceftriaxone, 2 g i.v., acetaminophen and fasting. Repeatedly flushing with saline and changing the biliary drainage/s were required in some cases.

**** 22 patients experienced severe pain or nausea (16 cases of acute mild pancreatitis resolved with medical therapy and 6 cases of fluid overload) and 15 presented self-limiting bleeding and did not require blood transfusions or urgent angiography.

No cases of procedure-related death were reported.

Learning curve analysis showed that most minor and major adverse events (5 major bleeding events and 1 perforation of the CBD) occurred during the first 9 years of experience and in particular when authors used the larger cholangioscopes (4.9 mm, 16 Fr introducer sheath). In the last 9 years authors encountered fewer adverse events due to the predominant use of the smaller cholangioscopes (3.9 mm and 2.7 mm in size). Also, the number of sessions to achieve complete clearance of stones significantly decreased proportionally with the size of cholangioscopes (data were not reported).

Abbreviations used: CBD, common bile duct; EHL, electrohydraulic lithotripsy; CCGT, gamma glutamyl transpeptidase; PTCS-EHL, percutaneous transhepatic cholangioscopy with electrohydraulic lithotripsy; SD, standard deviation.

Study 6 Wen XD (2020)

Details

Study type	**Non-randomised comparative study (retrospective)**
Country	China (single centre)
Recruitment period	2016 to 2018
Study population and number	n=**281 (128 cholangioscopy-guided EHL compared with 153 combined lithotripsy of mechanical clamping and electrohydraulics)** Patients with refractory residual biliary calculi
Age and sex	EHL: mean 51.9 years; 51.56% (66/128) female Combined lithotripsy: mean 51.5 years; 53.59% (82/135) female
Patient selection criteria	Inclusion criteria: patients with a first episode of hepatolithiasis that underwent hepatectomy with a T-tube drainage; patients with a diagnosis of residual biliary calculi by imaging and cholangioscopy; patients with characteristics of refractory calculi (a. impacted calculus; b. not impacted but the diameter of calculus was >15 mm and had hard consistency); and patients needing EHL in POC treatment. Exclusion criteria: less than 4 weeks of T-tube indwelling for sinus maturation; general conditions contraindicating the POC, or signs of uncontrolled cholangitis (fever, shivering, abdominal pain, progressive jaundice); residual calculi in grade III or above bile branches which cholangioscopy is basically not feasible; tumour invading the bile duct, duodenal papilla, or anastomotic stoma; and age under 18 years or over 80 years.
Technique	EHL or combined lithotripsy of mechanical clamping and electrohydraulics was done. Before treating calculi, if strictures in bile ducts were found, dilatation and stenting were first considered. Before surgery, all patients were given pethidine (50 mg) by intramuscular injection and positioned supine.
Follow-up	**EHL: median 10.34 months** **Combined lithotripsy: median 10.7 months**
Conflict of interest/source of funding	None

Analysis

Follow up issues: The follow-up time ranged from 2 to 12 months. Losses to follow up were not reported.

Study design issues: This retrospective study investigated the efficiency and safety of the combined lithotripsy of mechanical clamping and electrohydraulics in treating refractory calculi in patients with residual biliary calculi. The diagnosis and confirmation of the calculi location was assessed by 2 or more experienced radiologists. All procedures were done in the centre by experienced endoscopists. Of 281 patients, the first 128 patients involved from August 2016 to June 2017 had traditional EHL, and the later 153 patients from June 2017 to June 2018 were all subjected to combined lithotripsy of mechanical clamping and electrohydraulics.

Different presentations of complications occurring in 1 patient were recorded as 1, and the same presentation occurred in different sessions was also defined as 1. Intraoperative haemobilia was defined as the observation of mucosal bleeding under direct cholangioscopic vision, and post-POC haemobilia was defined as the presence of non-congealable drainage from the T-tube. Post-POC delayed bleeding was defined as clinical evidence of bleeding, such as melena, hematemesis or haematochezia, or a decrease in haemoglobin by more than 2 g/dL from the baseline within 14 days of operation. Haemobilia several hours after the lithotripsy indicated the delayed bleeding. Patients who suffered from epigastric pain, fever, and tremble were considered to have cholangitis. Diarrhoea is defined as the condition of having at least 3 loose, liquid, or watery bowel movements after the POC. Bile leakage was defined as high total bilirubin or amylase levels in the abdominal drains (> 3 times serum levels). Wound infection was defined as the presence of bacteria from the wound. Sinus perforation was defined as the presence of links between sinus and enterocoelia or bile ducts.

Study population issues: There was no statistically significant difference in terms of gender, age, biochemical parameters, Child-Pugh classification and total surgical modalities between 2 groups. Most patients were classified as Child-Pugh A. From the 148 patients who had choledocholithotomy and T-tube drainage (CLT), 65 in the EHL group and 83 were in the combined lithotripsy of mechanical clamping and electrohydraulics group; whereas from the 133 patients who had choledochojejunostomy and T-tube drainage (CJT), 63 in the EHL group and 70 were in the combined lithotripsy of mechanical clamping and electrohydraulics group.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **281 (128 cholangioscopy-guided EHL compared with 153 combined lithotripsy of mechanical clamping and electrohydraulics**)

Calculi characteristics

	Cholangioscopy-guided EHL	Combined lithotripsy	P value
Calculi distribution, n			0.977
Right anterior lobe (V+VIII)	41	56	
Right posterior lobe (VI+VII)	40	50	
Left internal lobe (IV)	42	47	
Left external lobe (II+III)	52	64	
Caudate lobe (I)	19	21	
Common bile duct	16	23	
Calculi numbers	3.2±1.43	3.1±1.42	0.346
Calculi property, n (%)			0.528
Brown pigment	49.22 (63)	52.94 (81)	
Black pigment	35.16 (45)	35.94 (55)	
Cholesterol	15.63 (20)	11.11 (17)	
Calculi impaction, n			0.706
Intrahepatic duct	88	105	
Common bile duct	11	16	
Basket	14	22	

Intraoperative results

	Cholangioscopy-guided EHL	Combined lithotripsy	P value
Overall POC sessions	2.9±1.21	2.0±0.65	0.000

Safety

Intraoperative complications, % (n)

	Cholangioscopy-guided EHL	Combined lithotripsy	P value
Haemobilia, % (n)	10.93 (14)	4.58 (7)	0.043
Cholangitis, % (n)	14.06 (18)	6.54 (10)	0.036

Postoperative complications, % (n)

	Cholangioscopy-guided EHL	Combined lithotripsy	P value
Overall complication	21.87 (28)	10.45 (16)	0.009
Acute cholangitis	14.06 (18)	6.54 (10)	0.036
Diarrhoea	15.63 (20)	7.84 (12)	0.041
Haemobilia	7.03 (9)	1.96 (3)	0.036
Postoperative bleeding	2.34 (3)	1.96 (3)	0.985
Bile leakage	3.91 (5)	1.96 (3)	0.537
Jaundice	5.47 (7)	3.27 (5)	0.854
Wound infection	3.91 (5)	2.61 (4)	0.723
Sinus perforation	0.78 (1)	1.31 (2)	0.985

	Cholangioscopy-guided EHL	Combined lithotripsy	P value
Hospitalisation conversation*, % (n)	6.25 (9)	3.27 (7)	0.236
Surgery conversion, % (n)	0.78 (1)	0.65 (1)	1.000
TAE conversion, % (n)	3.13 (4)	1.96 (3)	0.811

*Of the 2 groups, 8 patients with bleeding (4 in the EHL group and 4 in the combined lithotripsy group) and 8 with

Overall operating time, min	128.6±72.87	99.1±34.88	0.000
Injected physiological saline volume, mL	6472.2±2426.52	4544.4±1149.10	0.000
Clearance rate, %	98.44	98.70	1.000

After the first time of POC, the T-tube retaining time significantly differed between the 2 groups (28.1 ± 8.28 days in the EHL compared with 20.7±5.35 days in the combined lithotripsy group; p=0.000).

Recurrence postoperatively

	Cholangioscopy-guided EHL	**Combined lithotripsy**	**P value**
Half-year, %	5.46	5.23	0.929
1 year, %	10.94	9.15	0.618

bile leakage (5 in the EHL group and 3 in the combined lithotripsy group) were hospitalised.

Abbreviations used: EHL, electrohydraulic lithotripsy; POC, postoperative cholangioscopy; TAE, transcatheter arterial embolisation.

Study 7 Adamek HE (1996)

Details

Study type	**Non-randomised comparative study**
Country	Germany (single centre)
Recruitment period	1989 to 1993
Study population and number	n=**125 (46 POC-EHL compared with 79 extracorporeal piezoelectric lithotripsy)** **Patients with difficult intrahepatic and common bile duct stones**
Age and sex	EHL: median 69 years; 74% (34/46) female ESWL: median 70 years; 71% (56/79) female
Patient selection criteria	Inclusion criteria: patients with intrahepatic and extrahepatic bile duct stones were selected if their stones were not accessible to routine endoscopic extraction and if at least 1 attempt at mechanical lithotripsy had failed.
Technique	EHL was carried out under cholangioscopic guidance. Peroral cholangioscopy was performed with 2 operators utilising the TJF-M 20 ("motherscope") duodenoscope and the CSF-B 20 ("daughter scope") cholangioscope (Olympus Optical, Hamburg). A 4.5F EHL probe was passed down the 2.8 mm-diameter working channel of the cholangioscope and its tip positioned close to the concretion. For electrohydraulic shock wave generation, the Lithotron EL-23 (Walz Electronic Inc., Rohrdorf, Germany) was used. At an output voltage of 2000 V, shock waves of increasing frequency and an intensity of 260 mJ were applied with a continuous sequence of discharges. For both EHL and ESWL, a balloon catheter or a Dormia basket was used to remove residual fragments. Antibiotics were not given prophylactically.
Follow-up	**30 days**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Detailed follow-up and its completeness were not reported.

Study design issues: This prospective clinical comparative trial studied the application, efficacy, and side-effects of EHL and ESWL. This study also evaluated whether a combination of different lithotripsy techniques was superior to surgical exploration of the common bile duct. Selection for each individual treatment depended on institutional reasons and was not affected by stone or patient characteristics. If both methods were available, authors always started with ESWL.

Study population issues: Of the 125 patients, 47% (n=59) had previously received cholecystectomy. Existing symptoms included painless jaundice in 47 patients (38%); 41 patients (33%) had cholangitis. The main reasons that conventional endoscopy failed were the large size of the stones (n=41), impacted stones (n=48), the presence of a biliary stricture (n=24), or anatomic reasons (such as Billroth II operation) (n=12). There were no statistically significant differences for baseline characteristics including age, sex, symptoms, stone number, and stone localisation.

Other issues: This study's population might cover the population in Adamek et al. (1995).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **125 (46 POC-EHL compared with 79 ESWL)** **Procedure characteristics**	**Complications, n**

	POC-EHL	ESWL

	POC-EHL	ESWL

Mean number of lithotripsy sessions (range)	1.1 (1 to 3)	2.0 (1 to 8)
Mean procedure time (range), minutes	55 (45 to 90)	63 (40 to 140)
Spontaneous clearance	7	7
Additional endoscopy	27	55
Mortality at 30 days	0	0
Days in hospital (range)	11 (1 to 31)	13 (3 to 30)

Additional mechanical lithotripsy to break down larger fragments was used in 4 patients after EHL and in 7 patients after ESWL.

Results of POC-EHL compared with ESWL, %

	POC-EHL	ESWL	P value
Visualisation	89 (41/46)	90 (71/79)	
Fragmentation	93 (38/41)	97 (69/71)	
Stone clearance	74 (34/46)[a]	78.5 (62/79)[b]	>0.1

[a]In 12 patients, stone fragmentation was not reported because either coupling to the stone under direct vision failed or the concrement was impacted in front of the papilla, thus making primary introduction of the cholangioscope impossible. Ten patients were later treated successfully by ESWL; another patient was resistant to ESWL and, therefore, was referred to surgery. One patient received an endoprosthesis for palliation.

[b]In 17 patients extracorporeal lithotripsy failed for the following reasons: failure to locate the stone by ultrasound (n=8), no fragmentation (n=3), incomplete fragmentation (n=4), and a large number of stones in the common bile duct (n=2). Ten patients were cleared of their stones by additional use of EHL. Two patients were successfully treated by peroral laser lithotripsy. Three patients palliatively received an endoprosthesis and two patients were referred to surgery.

Stone-free rates after procedure were affected by stone locations:

- POC-EHL: the lowest rate of stone clearance was reported in the group of patients with intrahepatic stones and stones in the upper part of the choledochus.
- ESWL: best results were reported when the stones presented in the middle part of the choledochus. Intrahepatic stones and stones in the upper third of the choledochus were frequently missed.

ESWL, EHL, and intracorporeal laser lithotripsy as complementary modalities for treating difficult bile duct stones were finally successful in 94% (118/125) of patients.

Cholangitis	1*	2***
Mucosal haemorrhage or cutaneous hematoma	1**	2
Fever	2**	2**
Abdominal pain	0	12****
Biliary colic associated with spontaneous expulsion of fragment	0	3
Leukocytosis	0	4

*Another nasobiliary catheter was placed and the patient was treated conservatively with intravenous fluid and antibiotics. The cholangitis resolved within 4 days and the patient was discharged a week later.

**Resolved without further intervention.

***These were resolved within 48 hours with antibiotic treatment. These 2 patients initially received the adjunctive dissolution therapy. After discontinuing this treatment there were no more cases of cholangitis.

****All were successfully treated with pethidine and midazolam. One 90-year-old patient developed a short respiratory arrest after the injection of midazolam, which could be neutralized by the application of flumazenil, a midazolam antagonist. After a short (15-minute) rest, treatment could be completed.

Abbreviations used: EHL, electrohydraulic lithotripsy; ESWL, extracorporeal piezoelectric lithotripsy; POC-EHL, peroral cholangioscopy-guided electrohydraulic lithotripsy.

Study 8 Arya N (2004)

Details

Study type	**Case series (retrospective)**
Country	Canada (2 centres)
Recruitment period	1990 to 2002
Study population and number	n=94 Patients with difficult bile duct stones
Age and sex	Mean 67.1 years; 50% (47/94) female
Patient selection criteria	Inclusion criteria: patients had large stones (>2 cm) or a narrow calibre bile duct below a stone of average size (<2 cm).
Technique	Peroral endoscopic EHL: Under direct cholangioscopic control using a "mother-baby" endoscopic system, EHL was done using a 1.9 French coaxial electrode probe (Nortech, Elgin, Ilinois, US) with a Northgate SD-100 generator (Northgate Research Inc., Arlington Heights, Ilinois, US). The energy setting was set at 75 volts and increased slowly to a maximum of 90 volts, if necessary, to create an effective shock at the stone surface. This was applied in bursts of variable duration, at a frequency of 5 or 6 shocks per second. Antibiotics were not routinely given prophylactically, but patients with acute biliary sepsis were continued on antibiotics. Following EHL, 26 patients (28%) were started on 32 courses of antibiotics, 10 of whom had clear ducts at the end of their procedure.
Follow-up	**Mean 26.2 months (range 0 to 80)**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Follow-up was done by contacting the patient directly usually via telephone or by interviewing the referring and/or primary care physician. When neither the patient nor their physician could be reached, the follow-up period was considered to have been until the last recorded hospital visit. Although 111 patients had peroral EHL between October 1990 and March 2002, complete data were available on 94 patients which form the basis of this study.

Study design issues: This study was a retrospective review of consecutive patients at 2 hospitals, who had peroral endoscopic fragmentation of bile duct stones with EHL under direct cholangioscopic control using a "mother-baby" endoscopic system, aiming to assess the efficacy and safety profile of EHL. Failure of stone clearance necessitating surgical bile duct exploration was considered a failure of stone clearance; hence the patient who was cleared of bile duct stones prior to elective cholecystectomy and CBD exploration was not considered a failure of stone clearance. Peroral EHL was done by skilled endoscopists.

Study population issues: Of the 94 patients, 81 had large stones and 13 had a narrow calibre bile duct below a stone of average size (<2 cm). Prior to EHL, 37% (35/94) had cholecystectomy, and 99% (93/94) had endoscopic retrograde cholangiopancreatography (ERCP) and failed standard stone extraction techniques (mean 1.9 ERCP sessions per patient, range 0 to 5). Presented symptoms included cholangitis (28%; 26/94), painful jaundice (10%; 9/94), painless jaundice (31%; 29/94), pain only (18%; 17/94) and other (14%; 13/94).

Other issues: This study was included in Veld et al. (2018).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **94**	**Complications: 18% (17/94)**

Stone characteristics

	Number of patients	%
Stone location		
Common bile duct	53	56
Intrahepatic/common hepatic	19	20
Combination	11	12
Cystic duct	11	12
Stone number		
1	47	50
2	7	7
3	40	43
EHL indication		
Stone size >2 cm	81	86
Distal narrow duct and stone size <2 cm	13	14

Fragmentation/stone clearance

	Number of patients, n=93[a]	%
Stone fragmentation		
Complete	61	66
Partial	28	30
Failed	4[b]	4
EHL sessions		
1	71	76
2	13	14
>2	10	10
Additional therapy		
Mechanical lithotripsy	19	20
ESWL	2	2
Biliary drainage		
None	66	70
Stents	27	29
Nasobiliary/cystic tubes	3	3
Additional ERCP[c]		
NONE	54	57
1	32	34
2	5	5
>	4	4

[a]One patient excluded form analysis due to broken baby-cholangioscope.

[b]Reasons for failure of stone fragmentation: hard stones (n=2) and targeting problems (n=2 - left intrahepatic duct angle too acute for babyscope to visualize stones n=1 and CBD stone difficult to visualize with babyscope, n=1)

[c]Of the 41 patients who needed additional ERCP, 18 had a biliary stent in place.

Eleven of 59 patients, with their gallbladders still in place, had a cholecystectomy during the follow-up period.

	Numbers of patients	%
Cholangitis and/or recurrent jaundice*	13	14
Mild haemobilia (no drop in haemoglobin)**	1	1
Mild pancreatitis***	1	1
Bradycardia ****	1	1
Biliary leak*****	1	1

*Treated promptly with antibiotics and/or repeat ERCP. Of these 13 episodes, 7 had intrahepatic or common hepatic duct stones.

**Treated successfully with local adrenaline injection through the babyscope into the wall of the bile duct.

***This happened 2 days post-EHL, which resolved within 48 hours.

****Self-limited symptomatic bradycardia developed during EHL requiring abortion of the procedure.

*****Biliary leak due to stone obstruction that successfully resolved with a biliary stent.

Postfragmentation stone clearance: 90% (85/94) One patient who died of end-stage liver disease prior to complete stone clearance, having refused further intervention was not considered a failure of stone clearance. One patient died of congestive heart failure 21 months after complete stone clearance. A second patient was detected to have a hepatocellular carcinoma 4 months after complete resolution of their CBD stones above a stricture. **Reasons for failure of stone clearance**: • Difficult stone location: n=4 • Stricture below stone(s): n=2 • Poor patient health status precluding additional interventions treated with stent only: n=1 • Failure of stone clearance requiring common bile duct exploration: n=1 • A broken baby cholangioscope during the procedure: n=1	
Abbreviations used: CBD, common bile duct; EHL, electrohydraulic lithotripsy; ERCP, endoscopic retrograde cholangiopancreatography.	

Study 9 McCarty TR (2020)

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported for individual studies
Recruitment period	Publication date: 1993 to 2020
Study population and number	n=1,762 (35 studies; EHL in 12 studies, LL in 15 studies and both modalities in 8 studies) Patients with difficult biliary stones
Age and sex	Mean 61.5 years; 56.7% female
Patient selection criteria	Inclusion criteria: Only human studies investigating the use of the peroral cholangioscopy modality for the treatment of difficult biliary stones were included. All generations of the device, including the mother-daughter system and subsequent generations of the single-operator cholangioscopy device including the Spyglass DS systems were included. Exclusion criteria: Pancreatic stones or studies with both biliary and pancreatic stones were excluded if individual biliary outcomes were not reported. A study was also excluded if it was deemed to have insufficient data, as were review articles, editorials, and correspondence letters that did not report independent data. Case series and reported studies with fewer than 10 patients were excluded to minimize selection bias.
Technique	Peroral cholangioscopy-assisted EHL and LL.
Follow-up	**Not reported**
Conflict of interest/source of funding	TR was a consultant for Boston Scientific and Cook Endoscopy. The remaining authors declared that they had no conflict of interest.

Analysis

Study design issues: This systematic review and meta-analysis (ID number CRD42020169509) evaluated the efficacy and safety of peroral cholangioscopy with intraductal lithotripsy for treatment of difficult biliary stones. The outcomes included overall fragmentation success rate (such as ability to visualise the bile duct stone and perform successful fragmentation), adverse events reported, the percentage of cases with complete fragmentation and bile duct clearance after a single session of cholangioscopy-assisted intraductal lithotripsy.

A comprehensive search of the literature was done in 4 databases. Two reviewers independently screened the titles and abstracts of all the articles according to predefined inclusion and exclusion criteria. They also independently extracted data and assessed the risk of bias and study quality for each of the articles. Any differences were resolved by mutual agreement and in consultation with the third reviewer. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement outline and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines for reporting systematic reviews and meta-analyses was used to report findings.

Study population issues: Three randomised controlled trials, 15 prospective studies, and 17 retrospective studies were included. There were 12 multicentre studies, with the remainder being of single-centre design. All the included studies were considered to be of high quality.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **1,762 (35 studies**; EHL in 12 studies, LL in 15 studies and both modalities in 8 studies) Mean time for peroral cholangioscopy: 67.1 (SD 21.4) minutes Mean lithotripsy sessions: 1.3 (SD 0.6)	**Adverse events rate**: 8.9% (95% CI 6.5% to 12.2%; I^2= 60.7%; prediction interval -85.6 to 89.7)

Overall stone fragmentation success: 91.2% (95% CI 88.1% to 93.6%; I^2=63.2%; prediction interval 3.4 to 99.6)

With the Duval and Tweedie's trim-and-fill method, the overall fragmentation success of cholangioscopy with intraductal lithotripsy was slightly decreased from 91.2% (95%CI 88.1% to 93.6%) to 87.9% (95% CI 83.6% to 91.4 %).

Complete fragmentation and duct clearance: 76.9% of patients with a single lithotripsy session (95% CI 71.6% to 81.4%; I^2=74.3%; prediction interval 22.5 to 97.9)

Fragmentation success: EHL compared with LL

	EHL		LL		P value
	Pooled rate (95% CI)	**I^2**	**Pooled rate (95% CI)**	**I^2**	
Overall fragmentation success	90.1% (82.1 to 94.8) 12 studies, n=678	76.8%	92.8% (88.2 to 95.7) 16 studies, n=682	52.0%	0.36
Single-session fragmentation success and duct clearance	70.9% (63.8 to 77.1) 12 studies, n=682	63.5%	82.9% (75.0 to 88.7) 13 studies, n=588	72.4%	0.02

Mean procedure time: 75.5 (SD 6.9) minutes for EHL compared with 54.3 (SD 12.5) minutes for LL, p<0.001

Mean size of stone treated: 1.70 (SD 0.42) mm for EHL compared with 1.87 (SD 0.28) mm for LL, p<0.001

Fragmentation success: peroral cholangioscopy

	Mother-daughter system		First-generation SOC		Second-generation SOC	
	Pooled rate (95% CI)	**I^2**	**Pooled rate (95% CI)**	**I^2**	**Pooled rate (95% CI)**	**I^2**
Overall fragmentation success	89.3% (81.5 to 94.1) 10 studies, n=366	62.1%	90.1% (82.1 to 94.6) 10 studies, n=321	54.5%	95.0% (92.2 to 96.8) 7 studies, n=662	21.5%
Single-session fragmentation success and duct clearance	66.8% (54.0 to 77.5) 7 studies, n=278	72.9%	80.6% (65.5 to 90.1) 9 studies, n=304	81.2%	82.0% (74.9 to 87.5) 6 studies, n=614	64.0%

Adverse events: EHL compared with LL, p=0.75

- **EHL** (9 studies n=261): 11.9% (95% CI 6.7 to 20.2), I^2=42.9%
- **LL** (13 studies, n=510): 11.2% (95% CI 7.8 to 15.9), I^2=41.7%

Adverse events:

- Mother-daughter system (9 studies, n=331): 13.5% (95% CI 8.5 to 20.7), I^2=48.8%
- First generation SOC (8 studies, n=275): 9.8% (95% CI 6.5 to 14.4), I^2=4.9%
- Second-generation SOC (4 studies, n=514): 4.6% (95% CI 3.1 to 6.9), I^2=0.0%

Abbreviations used: CI, confidence interval; EHL, electrohydraulic lithotripsy; LL, laser lithotripsy; SD, standard deviation; SOC, single-operator cholangioscopy.

Validity and generalisability of the studies

- Studies were done in various countries, including studies from the UK.
- There were a few publications that included the same population; there was likely to be some overlap between them[1, 3, 4, 7, 8, 9].
- Where reported, the mean age ranged from 47 to 76 years and more than 50% were female in most of the studies. The follow-up period ranged from 1 week to 120 months.
- There was variation in the aetiologies for stone formation, stone characteristics, previous procedures, and procedure techniques.
- Experience of carrying out the procedure and size of the cholangioscope might affect the occurrence of adverse events and number of sessions needed.
- For efficacy, evidence on recurrence is lacking.
- Two randomised controlled trials were included but intention-to-treat analysis was not used. Although there were 4 non-randomised controlled trials, 3 were retrospective.
- There were no randomised controlled trials that directly compared electrohydraulic lithotripsy with laser lithotripsy.

Existing assessments of this procedure

The American Society for Gastrointestinal Endoscopy (ASGE) guideline on the role of endoscope in the evaluation and management of choledocholithiasis was published in 2019. ASGE recommended that 'for patients with difficult and large choledocholithiasis ASGE suggest intraductal therapy (cholangioscopy and fluoroscopically guided laser and EHL) or conventional therapy with papillary dilation. The choice of therapy may be impacted by local expertise, cost, and patient and physical preferences (conditional recommendation, very low quality of evidence)'. This recommendation was based on 182 studies (123 studies of conventional therapy, 57 cohort studies of intraductal therapy, and a single randomized trial that compared the 2 approaches).

The European Society of Gastrointestinal Endoscopy (ESGE) guideline on endoscopic management of common bile duct stones (2019) recommended that '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 suggested that the type of cholangioscopy and lithotripsy should depend on local availability and experience (weak recommendation, low quality evidence)'. This recommendation was based on 1 RCT, 4 prospective observational studies and 1 meta-analysis (33 studies)

The British Society of Gastroenterology guideline on the management of common bile duct stones (updated in 2016) recommended that 'cholangioscopy-guided electrohydraulic lithotripsy (EHL) or laser lithotripsy (LL) be considered when other endoscopic treatment options fail to achieve duct clearance (low-quality evidence, strong recommendation)'. This recommendation was based on 6 studies.

The Health Technology Wales evidence appraisal report (2020) summarised evidence on the use of single operator per-oral cholangioscopy (SOPOC) for diagnostic and therapeutic use in the hepato-biliary-pancreatic system. It stated that 'SOPOC can be used with ERCP to directly visualise and collect biopsy specimens, in addition to providing therapeutic intervention such as laser-based stone removal.' For therapeutic use of SOPOC for treating difficult biliary stones when conventional removal methods were not appropriate or failed, the report identified 1 systematic review (Jin et al. 2019). Complete stone clearance after SOPOC-guided lithotripsy was reported in 23 studies, with a pooled clearance rate of 94% (95% CI 90.2% to 97.5%). Comparative data was limited. There were 4 studies that compared SOPOC with another ERCP modality, but the comparator varied among these studies. These studies showed stone clearance was similar or better with SOPOC compared to alternative modalities.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Single-incision laparoscopic cholecystectomy. NICE interventional procedures guidance 508 (2014). Available from https://www.nice.org.uk/guidance/ipg508

NICE guidelines

- Gallstone disease: diagnosis and management NICE clinical guideline 188 (2014). Available from https://www.nice.org.uk/guidance/cg188

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One professional expert questionnaire for electrohydraulic lithotripsy for difficult-to-treat bile duct stones was submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE did not receive a completed submission.

References

1. Veld, JV, van Huijgevoort, NCM, Boermeester, MA et al. (2018) A systematic review of advanced endoscopy-assisted lithotripsy for retained biliary tract stones: laser, electrohydraulic or extracorporeal shock wave. Endoscopy 50(9): 896-909

2. Franzini, T, Moura, RN, Bonifacio, P et al. (2018) Complex biliary stones management: Cholangioscopy versus papillary large balloon dilation - A randomized controlled trial. Endoscopy International Open 6(2): e131-e138

3. Adamek, HE, Buttmann, A, Wessbecher, R et al. (1995) Clinical comparison of extracorporeal piezoelectric lithotripsy (EPL) and intracorporeal electrohydraulic lithotripsy (EHL) in difficult bile duct stones. A prospective randomized trial. Digestive diseases and sciences 40(6): 1185-1192

4. Brewer Gutierrez, OI, Bekkali, NLH, Raijman, I et al. (2018) Efficacy and Safety of Digital Single-Operator Cholangioscopy for Difficult Biliary Stones. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 16(6): 918-926e1

5. Cannavale, A, Bezzi, M, Cereatti, F et al. (2015) Combined radiological-endoscopic management of difficult bile duct stones: 18-year single center experience. Therapeutic Advances in Gastroenterology 8(6): 340-351

6. Wen, XD, Ren, LN, Wang, T et al. (2020) Combined lithotripsy of mechanical clamping and electrohydraulics in facilitating endoscopic management of refractory residual biliary calculi after surgery. Scientific reports 10(1): 2604

7. Adamek, HE, Maier, M, Jakobs, R et al. (1996) Management of retained bile duct stones: a prospective open trial comparing extracorporeal and intracorporeal lithotripsy. Gastrointestinal endoscopy 44(1): 40-47

8. Arya, N, Nelles, SE, Haber, GB et al. (2004) Electrohydraulic lithotripsy in 111 patients: a safe and effective therapy for difficult bile duct stones. The American journal of gastroenterology 99(12): 2330-4

9. McCarty TR, Gulati R and Rustagi T (2020) Efficacy and safety of peroral cholangioscopy with intraductal lithotripsy for difficult biliary stones: a systematic review and meta-analysis. Endoscopy

10. Buxbaum, JL, Abbas Fehmi, SM, Sultan, S et al. (2019) ASGE guideline on the role of endoscopy in the evaluation and management of choledocholithiasis. Gastrointestinal Endoscopy 89(6): 1075

11. Manes, G, Paspatis, G, Aabakken, L et al. (2019) Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 51(5): 472-491

12. Williams, E, Beckingham, I, El Sayed, G et al. (2017) Updated guideline on the management of common bile duct stones (CBDS). Gut 66(5): 765-782

13. Health Technology Wales (2020) Evidence appraisal report: single-operator per-oral cholangioscopy for the evaluation and treatment of hepato-biliary-pancreatic disorders. Retrieved from: https://www.healthtechnology.wales/wp-content/uploads/2019/11/EAR015-SOPOC.pdf

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	14/12/2020	Issue 12 of 12, December 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	14/12/2020	Issue 12 of 12, December 2020
MEDLINE (Ovid)	14/12/2020	1946 to December 09, 2020
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	14/12/2020	1946 to December 11, 2020
EMBASE (Ovid)	14/12/2020	December 11, 2020
International HTA database (INAHTA)	14/12/2020	-

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Number	Search term
1	Lithotripsy/
2	Lithotripsy, Laser/

3	((electro-hydraul* or electro hydraul* or Electrohydraul* or laser*) adj4 lithotrip*).tw.
4	EHL.tw.
5	cholangioscop*.tw.
6	biliary* tract* endoscop*.tw.
7	or/1-6
8	Biliary Tract/
9	biliary tract*.tw
10	8 or 9
11	Calculi/
12	(Calculi* or stone*).tw.
13	11 or 12
14	10 and 13
15	cholelithiasis/ or cholecystolithiasis/ or choledocholithiasis/ or gallstones/
16	((Biliar* or bile-duct or blie duct) adj4 (stone* or calcul* or colic*)).tw
17	Lithiasis/
18	lithias*.tw
19	stone* format*.tw
20	(cholelit* or cholecystolit* or choledocholit* or gallstone* or gall stone*).tw
21	CPDS.tw.
22	or/14-21
23	7 and 22
24	Holmium laser systems.tw.
25	Autolith Touch Biliary electrohydraulic lithotripsy system.tw.
26	24 or 25
27	23 or 26
28	Animals/ not Humans/
29	27 not 28

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Akerman S, Rahman M and Bernstein DE (2012) Direct cholangioscopy: The North Shore experience. European Journal of Gastroenterology & Hepatology 24: 1406-1409	Case series n=34 (mean 66 years; 65% [22/34] female) EHL=9	EHL was used to fragment the stones. Five cases resulted in complete stone removal and 4 cases had small residual stones.	Studies with a larger sample and/or better design are included in table 2.
Alameel T, Bain V and Sandha G (2013) Clinical application of a single-operator direct visualisaiton system improves the diagnostic and therapeutic yield of endoscopic retrograde cholangiopancreatography. Can J Gastroenterol 27: 15-19	Case series n=30 (mean 66 years; 57% [17/30] female) EHL=10	Successful EHL with stone clearance was reported in 90% of the 10 patients who failed previous conventional therapy. One patient developed mild post endoscopic retrograde cholangioscopy pancreatitis.	Studies with a larger sample and/or better design are included in table 2.
Aljebreen AM, Alharbi OR, Azzam N et al. (2014) Efficacy of Spyglass-guided electrohydraulic lithotripsy in difficult bile duct stones. Saudi J Gastroenterol 20: 366-370	Non-randomised comparative study n=58 (EHL n=13 compared with ESWL n=45)	The complete CBD clearance rates were 100% (13/13) in the EHL group and 64.4% (30/45) in the ESWL group (p=0.16). Complications happened in 1 patient who had cholangitis in the EHL group and in 7 patients (of these 5 had cholangitis and 2 pancreatitis) in the ESWL group.	Studies with a larger sample and/or better design are included in table 2.
Aloreidi K, Patel B and Atiq M (2016) Intraductal cholangioscopy-guided electrohydraulic lithotripsy as a rescue therapy for impacted common bile duct stones within a dormie basket. Endoscopy 48: E357-E358	Case report n=1 (72 years; female)	Optimum visualization and ease of operability make intraductal cholangioscopy-guided EHL an ideal rescue therapy for impacted stones within a Dormia basket.	This is a single case report.
Anjum MR, Dyer J, Curran F et al. (2018) Cholangioscopy-guided electrohydraulic lithotripsy of a large bile duct stone through a percutaneous T-	Case report n=1 (73 years; male)	Cholangioscopy plays an important role in endotherapy for biliary stones in unconventional situations.	This is a single case report.

tube tract. VIDEOGIE 3: 390-391			
Attila T, May GR and Kortan P (2008) Nonsurgical management of an impacted mechanical lithotripter with fractured traction wired: Endoscopic intracorporeal electrohydraulic shock wave lithotripsy followed by extra-endoscopic methanical lithotripsy. Can J Gastroenteral 22: 699-702	Case report n=1 (72 years; female)	Evidence showed that endoscopic intracorporeal electrohydraulic shock wave lithotripsy could be safely and effectively applied with direct visualization even after failure of ESWL to fragment a stone entrapped within an impacted mechanical lithotriptor basket.	This is a single case report.
Barakat MT, Girotra M, Choudhary A et al. (2018) A prospective evaluation of radiation-free direct solitary cholangioscopy for the management of choledocholithiasis. Gastrointest Endosc 87: 584-589	Case series n=40 (median 51.5 years; 70% [28/40] female) EHL=3	This study establishes the feasibility of fluoroscopy/radiation-free, cholangioscopic management of non-complex choledocholithiasis, with, success and adverse event rates similar to standard ERCP.	The reported outcomes for EHL are limited and studies with a larger sample and/or better design are included in table 2.
Bokemeyer A, Gerges C, Lang D et al. (2020) Digital single-operator video cholangioscopy in treating refractory biliary stones: a multicentre observational study. Surgical Endoscopy 34: 1914-1922	Non-randomised comparative study n=60 (median 66 years; 51.7% female)	The per procedure analyses revealed that the success rates for a complete stone removal were similar between LL and EHL (66% vs. 68%; p=0.87). Complications, such as postinterventional cholangitis and pancreatitis occurred in 16% of examinations; however, except from 1 case, all were mild or moderate and no procedure-associated mortality occurred.	The reported outcomes for EHL are limited and studies with a larger sample and/or better design are included in table 2.
Bratcher J (2009) Choledochoscopy-assisted intraductal shock wave lithotripsy. Gastrointestinal endoscopy clinics of North America 19: 587-596	Review	Success rates using EHL are variable and depend on whether other methods are used concurrently. Using EHL alone, a success rate of 40% to 80% can be expected.	Review article
Brauer BC, Chen YK and Shah RJ (2012) Single-step direct cholangioscopy by freehand intubation using standard endoscopes for diagnosis and therapy of biliary	Case series n=18 (mean 69 years; 56% [10/18] female)	A total of 18 patients underwent 22 DC procedures. Direct intubation was successful in all procedures. Complications were cholangitis managed with	Studies with a larger sample and/or better design are included in table 2.

diseases. Am J Gastroenterol 107: 1030-1035	EHL n=3	intravenous antibiotics (n=1).	
Brown NG, Camilo J, Nordstrom E et al. (2018) Advanced ERCP techniques for the extraction of complex biliary stones: a single referral centre's 12-year experience. Scandinavian journal of gastroenterology 53: 626-631	Non-randomised comparative study n=349 POC with EHL/LL n=46	Complete clearance achieved at the index ERCP was higher in the EPLBD group (89.7%; 35/39) vs. the POC with EHL/LL group (60.9%; 28/46) or the ML group (79.7%; 67/84), p=0.014.	Clinical outcomes for EHL and LL are not separated.
Buxbaum J (2013) Modern management of common bile duct stones. Gastrointestinal endoscopy clinics of North America 23: 251-276	Review	Cholangioscopic-guided and fluoroscopic-guided EHL have been used to clear bile duct stones in 77% to 90% of cases. Complications occurred in 6% to 18%, mostly recurrent jaundice or cholangitis.	Review article
Caddy GR and Tham TCK (2006) Symptoms, diagnosis and endoscopic management of common bile duct stones. Best practice & research clinical gastroenterology 20: 1085-1101	Review	The use of EHL has been used successfully in patients with difficult to remove CBD stones but its use is limited to specialised centres.	Review article
Chang MA, Anand G and Fehmi A (2018) Electrohydraulic lithotripsy to treat basket impaction of large common bile duct stone. VIDEOGIE 3: 135-136	Case report n=1 (68 years; female)	Digital cholangioscopy and EHL can be used to facilitate the removal of an impacted bile duct stone and basket.	This is a single case report.
Chen YK (2007) SypGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). Gastrointestinal endoscopy 65: 832-841	Case series n=35 (mean 63 years; 63% [22/35] female) EHL=5	SpyGlass-directed EHL succeeded in 5 of 5 patients. Complete stone clearance was reported with no further procedures in 2 patients and after repeat SpyGlass directed EHL in 2 and follow-up ERCP in 1.	Studies with a larger sample and/or better design are included in table 2.
Chen YK, Nicholas MT and Antillon MR (2008) Peroral cholecystoscopy with electrohydraulic lithotripsy for treatment of symptomatic cholelithiasis in end-stage liver disease (with videos).	Case report n=1 (52 years; male)	The gallbladder wall and stones were adequately visualized. EHL achieved stone clearance after 2 sessions. Mild post procedure pancreatitis occurred after the first treatment. The patient remained symptom free, stent free, and stone free	This is a single case report.

Gastrointestinal endoscopy 67: 132-135		until a liver transplantation, which was performed 25 months later.	
Cremer A and Arvanitakis M (2016) Diagnosis and management of bile stone disease and its complications. Minerva gastroenterological e dietologica 62: 103-129	Review	EHL achieves a stone fragmentation rate ranging from 82% to 98%, with the majority of patients requiring a single treatment session. However, complete clearance of the bile duct is obtained in approximately 74% of patients. stone fragmentation or clearance rates of CBD stones are similar using either EHL or ESWL (79% compared with 74%, respectively).	Review article
De Moura EGH, Franzini T, Moura RN et al. (2014) Cholangioscopy in bile duct disease: a case series. Arq Gastroenterol 51: 250-254	Case series n=20 (median 48 years; 60% female)	EHL was applied in 8 patients and was successful in 7 patients.	Studies with a larger sample and/or better design are included in table 2.
Doshi B, Yasuda I, Ryozawa S et al. (2018) Current endoscopic strategies for managing large bile duct stones. Digestive endoscopy 30: 59-66	Review	If the CBD stone is >3 cm or if the stone to CBD diameter ratio is >1.0, then cholangioscopy with EHL or LL is likely to be better at stone extraction than ML alone.	Review article
Easler JJ and Sherman S (2015) Endoscopic retrograde cholangiopancreatography for the management of common bile duct stones and gallstone pancreatitis. Gastrointestinal endoscopy clinics of North America 25: 657-675	Review	EHL has reported a high rate of technical success for extraction of large, complex common bile duct stones. EHL demonstrates a favourable safety profile and offers lower rates of complications when compared with such alternative approaches as biliary indwelling biliary prostheses.	Review article
Farrell JJ, Bounds BC, Al-Shalabi S et al. (2005) Single-operator duodenoscope-assisted cholangioscopy is an effective alternative in the management of choledocholithiasis not removed by conventional methods, including	Case series For EHL, n=26 (median 62 years; 46% [12/26] female)	All of the patients were free of stones at the end of the study period, as documented by either cholangiography or cholangioscopy. Fifteen patients required just EHL session to eradicate their stones; 5 required 2 sessions; 3 required 3	Studies with a larger sample and/or better design are included in table 2.

mechanical lithotripsy. Endoscopy 37: 542-547		sessions; and single patients required 4, 5, and 9 sessions respectively, before complete stone eradication was achieved.	
Fenner J, Croglio MP, Tzimas D et al. (2018) Successful treatment of an impacted lithotripter basket in the common bile duct with intracorporeal electrohydraulic lithotripsy. Endoscopy 50: 447-448	Case report n=1 (62 years; female)	This study presents a case in which an impacted lithotripter and CBD stone were treated with EHL resulting in destruction of the retained stone so that the lithotripter basket could then be pulled out.	This is a single case report.
Ghersi S, Fuccio L, Bassi M et al. (2015) Current status of peroral cholangioscopy in biliary tract diseases. World journal of gastrointestinal endoscopy 7: 510-517	Review	Several studies have reported high success rates in clearing the bile ducts of stones after a cholangioscopic EHL or LL, ranging from 80% to 100%; these results are frequently achieved in only 1 session. For intrahepatic stones, the thinner LL probe is generally preferred to the EHL probe, whereas the EHL is the most widely used technique, particularly with the SpyGlass system, because of the dedicated irrigation channel providing the flowing water that is required to perform the EHL.	Review article
Franzini TAP, Moura RN and de Moura EGH (2016) Advances in therapeutic cholangioscopy. Gastroenterology research and practice.	Review	Several studies report success rates of 80% to 90% and these results are frequently achieved in just 1 session. Thus, lithotripsy under direct visualization is safer because it helps prevent bile duct injury and reduces the need for mechanical lithotripsy.	Review article
Frossard JL and Morel PM (2010) Detection and management of bile duct stones. Gastrointestinal endoscopy 72: 808-816	Review	Stone clearance after EHL or ILL with or without additional ERC varies from 77% to 90% after failure of conventional endoscopic fragmentation of BDSs	Review article

Han JH, Park DH, Moon SH et al. (2009) Peroral direct cholangioscopic lithotripsy with a standard upper endoscope for difficult bile duct stones (with videos) 70: 183-185	Case report n=1 (57 years; female)	peroral direct cholangioscopy - lithotripsy with a standard upper endoscope may be feasible and effective for difficult bile duct stones	This is a single case report.
Hochberger J, Tex S, Maiss J et al. (2003) Management of difficult common bile duct stones. Gastrointestinal endoscopy clinics of North America 13: 623-634	Review	ESWL, EHL, and laser lithotripsy yield similar success rates of 80% to 95% and may be used complementarily in endoscopic centres. EHL is rarely used because of its high potential for tissue damage and bleeding.	Review article
Hosmer A, Abdelfatah MM, Law R et al. (2018) Endoscopic ultrasound-guided hepaticogastrostomy and antegrade clearance of biliary lithiasis in patients with surgically altered anatomy. Endoscopy international open 06: E127-E130	Case series n=9 (mean 60 years; 89% female) Cholangioscopy-guided EHL n=4	Complete ductal clearance was accomplished using various techniques: antegrade balloon sweeps (9), transpapillary balloon dilation (8), cholangioscopy with electrohydraulic lithotripsy (4), and mechanical lithotripsy (1).1 adverse event (cholangitis) occurred after cholangioscopy and prolonged intraductal EHL.	Studies with a larger sample and/or better design are included in table 2.
Hakuta R, Kogure H, Isayama H et al. (2015) Electrohydraulic lithotripsy of large bile duct stones under direct cholangioscopy with a double-balloon endoscope. Endoscopy 47: E519-E520	Case report n=1 (82 years; female)	Large stones were successfully fragmented with EHL, followed by complete removal with a balloon catheter. No procedure-related complications were observed.	This is a single case report.
Hubers J, Patel R, Dalvie P et al. (2019) Percutaneous transhepatic cholangioscopy with electrohydraulic lithotripsy in a patient with choledocholithiasis complicating a benign stricture. VIDEOGIE 4: 423-425	Case report n=1 (88 years; female)	The single use cholangioscope provided optimum tip deflection and maneuverability for a safe performance of EHL in this angulated bile duct.	This is a single case report.
Hui CK, Lai KC, NG M et al. (2003) Retained common bile duct stones: a comparison between biliary stenting and	Non-randomised comparative study	In the EHL group, successful stone clearance was reported in 76.5%, whereas, in the stent group, the success	Studies with a larger sample and/or better design were included in table 2.

complete clearance of stones by electrohydraulic lithotripsy. Aliment Pharmacol Ther 17: 289-296	n=36 (17 EHL compared with 19 stent)	of stenting was 94.7%. A significant difference was found in the actuarial incidence of recurrent acute cholangitis when the EHL group was compared with the stent group [1 patient (7.7%) compared with. 12 patients (63.2%), respectively; p=0.002]. A significant difference was detected in the actuarial frequency of mortality between the EHL and stent groups [7 patients (41.2%) compared with 14 patients (73.7%), respectively; p=0.01].	
Imanishi M, Ogura T, Kurisu Y et al. (2017) A feasibility study of digital single-operator cholangioscopy for diagnostic and therapeutic procedure (with videos). Medicine 96:15(e6619)	Case series n=28 (median 73 years; 25% [7/28] female) EHL n=4	EHL was performed to fragment the common bile duct stones and the fragments were completed removed using a balloon catheter.	Studies with a larger sample and/or better design are included in table 2.
Itoi T, Sofuni A, Itokawa F et al. (2010) Evaluation of residual bile duct stones by peroral cholangioscopy in comparison with balloon-cholangiography. Digestive Endoscopy 22: S85-S89	Case series n=108 (mean 73 years; 40% [43/108] female) EHL and Mechanical Lithotripter n=11	POCS may be useful, particularly when lithotripsy using ML or EHL is performed and a large pneumobilia exists in the bile duct.	Outcomes for EHL are not reported separately.
Jalali F, Roorda AK and Sundaram U (2011) Biliary stone extraction techniques: old and new. Practical gastroenterology 35: 17-46	Review	If mechanical lithotripsy fails or is predicted to fail, intracorporeal electrohydraulic lithotripsy (EHL) is a commonly utilised method to achieve stone fragmentation. Advantages of EHL include excellent success, safety and low cost.	Review article
Jeng KS, Sheen LS and Yang FS (2002) Are modified procedures significantly better than conventional procedures in percutaneous transhepatic treatment for complicated right hepatolithiasis with intrahepatic biliary	Non-randomised comparative study n=100 (60 in the modified methods group compared with 40 in the conventional treatment group)	Evidence suggested that the modified methods (simplification of tract establishment and stricture dilation and EHL) were superior to conventional treatment in that they effectively decreased procedural	Studies with a larger sample and/or better design are included in table 2.

strictures. Scandinavian journal of gastroenterology 37: 597-601		complications and cost, and significantly improved treatment results.	
Jin Z, Wei Y, Tang X et al. (2019) Single-operator peroral cholangioscope in treating difficult biliary stones: A systematic review and meta-analysis. Digestive Endoscopy. 31(3): 256-69	Systematic review and meta-analysis n=2,786 (24 studies)	Pooled proportion of patients with complete stone clearance was 94.3% (95% CI: 90.2% to 97.5%). Single-session stone clearance was achieved in 71.1% (95% CI: 62.1% to 79.5%) of the pooled patients. Pooled number of sessions needed for stone clearance was 1.26 (95% CI: 1.17% to 1.34%). Pooled adverse event rate was 6.1% (95% CI: 3.8% to 8.7%). Potential publication bias was detected but had no significant influence on the results.	Majority of the studies were included in McCarty (2020)
Kalaitzakis E, Webster GJ, Oppong KW et al. (2012) Diagnostic and therapeutic utility of signle-operator peroral cholangioscopy for indeterminate biliary lesions and bile duct stones. European journal of gastroenterology & hepatology 24: 656-664	Case series n=167 (33 EHL)	Complete stone clearance was reported in 24 (73%); whereas in 6 patients (18%), only partial clearance was achieved, with 3 patients being referred for surgery, 2 declining further interventions and 1 awaiting further ERCP at the end of the study. In 3 out of 33 patients who underwent SOC, EHL treatment was not possible, and these patients were also referred for surgery.	Studies with a larger sample and/or better design are included in table 2.
Kamiyama R, Ogura T, Okuda A et al. (2018) Electrohydraulic lithotripsy for difficult bile duct stones under endoscopic retrograde cholangiopancreatography and peroral transluminal cholangioscopy guidance. Gut and Liver 12: 457-462	Case series n=42 (mean 77.1 years; 36% [15/42] female)	Median procedure time was 31 minutes (range, 19 to 66 minutes). The rate of complete stone clearance was 98% (41/42). Adverse events such as cholangitis and acute pancreatitis were reported in 14% (6/42), which could be treated conservatively.	Studies with a larger sample and/or better design are included in table 2.
Kao K and Batra B (2014) Single-balloon assisted ERCP with electrohydraulic lithotripsy for the treatment of a bile	Case report n=1 (54 years; female)	Two large stones were fragmented by using electrohydraulic lithotripsy and the stone	This is a single case report.

duct stone in a patient with a hepaticojejunostomy. Gastrointestinal endoscopy 80: 1173		fragments were then removed.	
Katanuma A, Maguchi H, Osanai M et al. (2010) Endoscopic treatment of difficult common bile duct stones. Digestive endoscopy 22: S90-S97	Review	The advantages of EHL are the high success rate and the capacity to directly confirm status of the stones while performing the fragmentation.	Review article
Kawakami H, Kubota Y, Kawahata S et al. (2016) Peroral transhepatic cholangioscopy-guided electrohydraulic lithotripsy via an endoscopic ultrasonography-guided hepaticogastrostomy route for bile duct stones in a patient with Roux-en-Y anatomy. Endoscopy 48: E146-E147	Case report n=1 (84 years; male)	This is the first report of treatment for bile duct stones with EHL via an EUS-HGS route guided by direct antegrade cholangioscopy.	This is a single case report.
Kedia P and Tarnasky PR (2019) Endoscopic management of complex biliary stone disease. Gastrointestinal endoscopy clinics of North America 29: 257-275	Review	Evidence shows that index and overall biliary clearance was 77.4% (74.5% EHL and 86.1% LL) and 97.3% (96.7% EHL and 99% LL) of patients. The severe and overall AE rate was 0.5% and 3.7%.	Review article
Korrapati P, Ciolino J, Wani S et al. (2016) The efficacy of peroral cholangioscopy for difficult bile duct stones and indeterminate structures: a systematic review and meta-analysis. Endoscopy International Open 04: E263-E275	Systematic review and meta-analysis n=49 studies	The overall estimated stone clearance rate was 88% (95% CI 85% to91%). The accuracy of POC was 89% (95%CI 84% to 93%) for making a visual diagnosis and 79% (95% CI 74% to 84%) for making a histological diagnosis. The estimated overall adverse event rate was 7% (95% CI 6% to 9%).	The outcomes for EHL are not reported separately.
Kudaravalli P, Aslam B and Gabr M (2018) A review of lithotripsy applications in gastroenterology. Practical gastroenterology 42: 50-59	Review	Lithotripsy is used for various gastrointestinal conditions and electrohydraulic lithotripsy is 1 of the commonly used lithotripsy methods in gastroenterology.	Review article
Laing PJ and Adler DG (2013) Difficult bile duct stones: a review of current endoscopic treatments.	Review	In general, stone extraction rates with EHL range from 77% to 98%. Complications associated	Review article

Practical gastroenterology 37: 10-26		with EHL are very similar to those associated with laser lithotripsy. Delayed ductal injury from EHL is always a possibility but is relatively uncommon in practice.	
Li Z, Wu HF, Zhang JQ et al. (2019) Ultrasound-guided percutaneous transhepatic cholan gioscopicelectrohydraulic lithotripsy for difficult bile duct stones. Int J Clin Exp Med 12: 2767-2772	Case series n=42 (mean 57 years; 55% [23/42] female)	After the first round of therapy, complete stone clearance was reported in 36 patients, with few residual stones in the left or right hepatic duct found in 6 patients. The stone clearance rate was up to 85.71%. All calculi were completely removed after the second round of therapy. The time to recovery was 12±3.7 hours, food intake began 23±6.5 hours after operation, and the average length of hospital stay was 5±2 days. No severe complications occurred. After 1 to 24 months of follow-up, there were no serious postoperative complications of residual calculi or calculus recurrence and no biliary strictures.	Studies with a larger sample and/or better design are included in table 2.
Lo Menzo E, Schnall R and Von Rueden D (2005) Lithotripsy in the laparoscopic era. Journal of the Society of Laparoendoscopic Surgeons 9: 358-361	Case report n=1 (50 years; male)	The patient underwent a single 2.5-hour session of EHL via the T-tube tract. Mild pulmonary oedema occurred intraoperatively. Complete clearance of the CBD was obtained without the need for additional ERCP.	This is a single case report.
Matsumoto K (2019) Successful removal of impacted large bile duct stones using electrohydraulic lithotripsy with an ultraslim endoscope after Billroth II gastrectomy. Endoscopy 51: E265-E266	Case report n=1 (75 years; male)	This combined method was useful for the removal of large stones using EHL and achieved clear vision during the endoscopic procedure.	This is a single case report.
Maubach J, Gruber M, Nett P et al. (2018) EUS-guided hepaticojejunostomy with transjejunal per-oral	Case report n=1 (66 years; male)	Transenteric per-oral cholangioscopy in combination with EHL appears to be safe and	This was a single case report.

cholangioscopy and electrohydraulic lithotripsy in a patient with complicated choledocholithiasis after Roux-en-Y gastric bypass. VIDEOGIE 3: 351-353		effective, but long-term data are definitely warranted.	
Maydeo AP, Rerknimitr R, Lau JY et al. (2019) Cholangioscopy-guided lithotripsy for difficult bile duct stone clearance in s single sessions of ERCP: results from a large multinational registry demonstrate high success rates. Endoscopy 51: 922-929	Case series (registry) n=156 (median 62 years; 61% [95/156] female) EHL n=39	POCS-guided lithotripsy is highly effective for clearance of difficult bile duct stones in a single procedure and successfully salvages most prior treatment failures. It may also be considered first-line therapy for patients with difficult choledocholithiasis to avoid serial procedures.	This study (limited outcomes for EHL) was included in table 2 (McCarty et al. 2020) and studies with a larger sample and/or better design were included in table 2.
McHenry L and Lehman G (2006) Difficult bile duct stones. Current treatment options in gastroenterology 9: 123-132	Review	EHL is an effective therapy for difficult bile duct stones and serves as a backup to mechanical lithotripsy.	Review article
Mizrahi M, Khoury T, Wang Y et al. (2017) "Apple far from the tree": comparative effectiveness of fiberoptic single-operator cholangiopancreatoscopy (FSOCP) and digital SOCP (DSOCP).	Non-randomised comparative study n=324 (FSOCP n=198 compared with DSOCP n=126) Electrohydraulic lithotripsy n=94 (FSOCP n=31 compared with DSOCP n=63)	Stone clearance rate was successful after first EHL in 83% (52/63) patients using the DSOCP system, while only 58% (18/31) patients using the FSOCP ($p<0.01$). Mean procedure time for completion of ERCP with cholangioscopy was shorter with DSOCP compared with FSOCP (49±17 min vs. 57±21, $p=0.032$). During EHL for stone extraction radiation doses were lower with the use of DSOCP compared to the use of FSOCP (361±250 vs. 620±452 mGy, $p=0.02$).	Studies with a larger sample and/or better design were included in the overview.
Mori T, Sugiyama M and Atomi Y (2006) Management of intrahepatic stones. Best practice & research clinical gastroenterology 20: 1117-1137	Review	Evidence suggests that percutaneous transhepatic cholangioscopic lithotripsy by using electrohydraulic shock wave is an effective and safe method to fragment biliary stones and to facilitate their removal.	Review article

Moon JH, Cha SW, Ryu CB et al. (2004) Endoscopic treatment of retained bile-duct stones by using a balloon catheter for electrohydraulic lithotripsy without cholangioscopy. Gastrointestinal endoscopy 60: 562-566	Case series n=19 (mean 67 years; 58% [11/19] female)	Stones were successfully fragmented in 17 of 19 patients. In 16 patients (84.2%), the bile duct was cleared of all stones. Additional mechanical lithotripsy was performed in 9 (56.2%) of the 16 patients. Minor complications were noted in 4 patients (2 haemobilia, 1 pancreatitis, 1 cholangitis). There was no 30-day mortality.	Studies with a larger sample and/or better design are included in table 2.
Moon JH, Cho YD, Ryu CB et al. (2001) The role of percutaneous transhepatic papillary balloon dilation in percutaneous choledochoscopic lithotomy. Gastrointestinal endoscopy 54: 232-236	Case series n=16 (mean 58.6 years; 56% [9/16] female) EHL=5	In addition to percutaneous transhepatic papillary balloon dilation (PTPBD), 5 patients required EHL for fragmentation of large stones. So, with PTPBD and EHL it is possible to remove a large EHD stone through the percutaneous route, especially in cases in which it is impossible to reach the papilla endoscopically via a transoral approach.	Studies with a larger sample and/or better design are included in table 2.
Moon JH, Choi HJ and Ko BM (2011) Therapeutic role of direct peroral cholangioscopy using an ultra-slim upper endoscope. J Hepatobiliary Pancreat Sci 18: 350-356	Review	Evidence shows that the overall success rate of bile duct clearance by lithotripsy (EHL or LL) under direct POC by a single endoscopist was 88.9%, with an average of 1.6 treatment sessions per patient. No procedure-related complications were observed.	Review article
Moon JH, Ko BM, Choi HJ et al. (2009) Direct peroral cholangioscopy using an ultra-slim upper endoscope for the treatment of retained bile duct stones. J Hepatobiliary Pancreat Sci 18:350–356	Case series n=18 (mean 66.5 years; 61% [11/18] female)	The overall success rate of bile duct clearance by lithotripsy under direct POC by a single endoscopist was 88.9% (16/18). Stone fragmentation under direct POC was successfully performed in 9 patients using EHL and in 7 patients using LL. Procedure-related complications were not observed.	Studies with a larger sample and/or better design are included in table 2.

Mori A, Sakai K, Ohashi N et al. (2007) Electrohydraulic lithotripsy of the common bile duct stone under transnasal direct cholangioscopy. Endoscopy 39: E63-E63	Case report n=1	This is the first report of EHL performed under transnasal direct cholangioscopy. The stone was fragmented and the fragments were then successfully removed without any complications.	This is a single case report.
Nakai Y, Sato T, Hakuta R et al. (2020) Management of difficult bile duct stones by large balloon, cholangioscopy, enteroscopy and endosonography. Gut and Liver 14: 297-305	Review	Evidence shows that in general EHL had a lower complete ductal clearance rate than laser lithotripsy. The adverse event rate was significantly higher in EHL than in laser lithotripsy.	Review article
Nakaji S, Hirata N, Shiratori T et al. (2013) Endoscopic lithotripsy with peroral direct cholangioscopy using a conventional endoscope. World journal of gastrointestinal endoscopy 5: 132-134	Case report n=1 (80 years; female)	After insertion of endoscopes, the crushing by EHL and suction were repeated. The fragments were removed using a retrieval net. In this way, stones were cleared completely.	This is a single case report.
Neuhaus H (2003) Endoscopic and percutaneous treatment of difficult bile duct stones. Endoscopy 35:31-34	Review	A limited number of patients have been treated successfully without complications in endoscopic referral centres	Review article
Obatake M, Inamura Y, Taura Y et al. (2012) Percutaneous transhepatic electrohydraulic lithotripsy for intrahepatic bile duct stones after choledochal cyst excision. Acta medica nagasakiensia 56: 99-102	Case report n=1 (17 years; male)	Evidence showed that EHL was an elective and less invasive treatment for intrahepatic bile duct stones after choledochal cyst excision.	This is a single case report.
Ogawa K, Ohkubo H, Abe W et al. (2002) Percutaneous transhepatic small-caliber choledochoscopic lithotomy: a safe and effective technique for percutaneous transhepatic common bile duct exploration in high-risk elderly patients. J Hepatobiliary Pancreat Surg 9: 213-217	Case series n=65 (mean 73.9 years; 47% [29/65] female)	The common bile duct was successfully accessed and the stones removed in all 65 patients. The average time for the entire procedure was 45min. There were no serious procedure-related complications.	Studies with a larger sample and/or better design are included in table 2.
Phillip Fejleh M, Thaker AM, Kim S et al. (2019) Cholangioscopy-guided	Case series	One patient presented with cholangitis from an impacted common bile	Studies with a larger sample and/or better

retrieval basket and snare for the removal of biliary stones and retained prostheses. VIDEOGIE 4: 232-234	n=3 (EHL=1)	duct stone. Fragmentation with electrohydraulic lithotripsy was performed, and the fragments were removed with the SpyGlass retrieval basket.	design are included in table 2.
Piraka C, Shah RJ, Awadallah NS et al. (2007) Transpapillary cholangioscopy-directed lithotripsy in patients with difficult bile duct stones. Clinical gastroenterology and hepatology 5: 1333-1338	Case series n=32 (median 61 years; 66% [21/32] female) EHL n=30 and mechanical lithotripsy n=2 Follow-up: mean 29.2 months	A mean of 1.4 lithotripsy sessions achieved complete (n=26, 81%), partial (n=5, 16%), or failed (n=1, 3%) stone clearance. Stone recurrence occurred in 4 of 22 (18%) patients with complete clearance and follow-up data; 3 had primary sclerosing cholangitis. There were 2 minor periprocedural complications and 1 late complication.	Studies with a larger sample and/or better design are included in table 2.
Raijman I (2000) Intracorporeal lithotripsy in the management of biliary stone disease. Seminars in laparoscopic surgery 7: 295-301	Review	The reported success rate for EHL is 95% to 100%. Failures are primarily caused by the inability to make contact between the fibre and the stone, malfunctioning of the fibre, or producing bleeding from touching the wall that may obliterate visualisation. Perforation of the bile duct wall may occur if the EHL probe touches the wall. Lastly, the application of EHL over a long period of time may lead to increasing temperatures on the stone surface and surrounding tissues.	Review article
Ray AA, Davies ET, Duvdevani M et al. (2008) The management of treatment-resistant biliary calculi using percutaneous endourologic techniques. Can J Surg 52: 407-412	Case series n=19 (mean 69.3 years; 74% [14/19] female)	Overall, treatment led to successful removal of the biliary drainage tube in 94.7% of patients and 76.2% were stone-free. cholangiograms an average of 21.8 days after treatment were done. The average length of stay in hospital was 1.9 days. One patient experienced a perioperative acute coronary syndrome and	Studies with a larger sample and/or better design are included in table 2.

		another experienced prolonged biliary drainage. Both had successful endoscopic treatment of their calculi. There were no cases of treatment-related sepsis, and no other complications were observed.	
Rosenkranz L, Patel SN and Kahaleh M (2012) Endoscopic retrograde cholangiopancreatography for stone burden in the bile and pancreatic ducts. Gastrointestinal endoscopy clinics of North America 22: 435-450	Review	EHL appears to be effective in the fragmentation and removal of large bile duct stones in 79% to 98% of cases. Overall complication rates reported with this technique range from 3% to 15%. The potential for major complications (perforation, haemothorax and bile leak) represent the major obstacle to using this technique.	Review article
Sandha J, van Zanten SV and Sandha G (2018) The safety and efficacy of single-operator cholangioscopy in the treatment of difficult common bile duct stones after failed conventional ERCP. Journal of the Canadian Association of Gastroenterology 1: 181-190	Case series n=51 (mean 66 years; 69% [35/51] female)	Median procedure time was 67 minutes (95% CI, 61.5 to 73.5). The CBD was successfully cleared in 93% (47/51) of patients. Minor adverse events were reported in 14% (7/51) of patients.	Studies with a larger sample and/or better design are included in table 2.
Sato T, Kogure H, Nakai Y et al. (2018) Electrohydraulic lithotripsy under double-balloon endoscope-assisted direct cholangioscopy for treatment of choledocholithiasis in a patient with Roux-en-Y gastrectomy. VIDEO 3: 113-114	Case report n=1 (74 years; male)	Despite the potential effectiveness of EHL under direct cholangioscopy with use of a DBE, this study shows that EHL can be a treatment option for difficult stones in cases of altered anatomy with a relatively small orifice.	This is a single case report.
Seelhoff A, Schumacher B and Neuhaus H (2011) Single operator peroral cholangioscopic guided therapy of bile duct stones. J Hepatobiliary Pancreat Sci 18: 346-349	Review	First clinical data show a high stone clearance rate of single operator guided SpyGlass lithotripsy in patients with previous failure of conventional endoscopic therapy.	Review article

Sheen-Chen SM and Chou FF (1995) Intraoperative choledochoscopic electrohydraulic lithotripsy for difficultly retrieved impacted common bile duct stones. Archives of surgery 130: 430-432)	Non-randomised comparative study n=20 (EHL n=20 compared with transduodenal sphincteroplasty n=10)	Stones were fragmented and successfully removed by a basket and flushing with normal saline solution. Mild oozing was noted in 1 patient but soon stopped spontaneously. The mean postoperative stay of the clinical trial group was 4 days shorter than that of the comparison group. The complication rate of the clinical trial group (10%) was lower than that of the comparison group (40%).	Studies with a larger sample and/or better design are included in table 2.
Shim CS (2010) How should biliary stones be managed? Gut and Liver 4: 161-172	Review	EHL seems to provide the best combination of technical success, low cost, and practicality. EHL and LL usually require direct visualization, which is technically difficult.	Review article
Shima H, Yamataka A, Yanai T et al. (2004) Intracorporeal electrohydraulic lithotripsy for intrahepatic bile duct stone formation after choledochal cyst excision. Pediatr Surg Int 20: 70-72	Case report n=1 (18 years; female)	EHL is a simple, effective alternative method for removing IHBD stones after choledochal cyst excision.	This is a single case report.
Sioulas AD, El-Masry MA, Growth S et al. (2017) Prospective evaluation of the short access cholangioscopy for stone clearance and evaluation of indeterminate structures. Hepatobiliary Pancreat Dis Int 16: 96-103	Case series n=49 (mean 60.2 years; 47% [23/49] female) EHL n=21	Complete stone clearance defined as lack of stones in cholangiography and stone removal during cholangioscopy was achieved in 15 (71.4%) patients. Clinical stone clearance defined as lack of symptoms, laboratory abnormalities and hospital visits during follow-up, irrespective of stone clearance was evident in 17 (81.0%) patients. One serious adverse event occurred (bile duct perforation).	Studies with a larger sample and/or better design are included in table 2.
Sninsky BC, Sehgal PD, Hinshaw L et al. (2014) Expanding endourology for biliary stone disease: the efficacy of intracorporeal lithotripsy on refractory	Case series n=13 (mean 52 years; 23% [3/13] female)	Stone clearance was reported in 93% of patients (12/13); 62% (8/12) after 1 procedure, and 31% (4/12) after 2 procedures. One patient	Studies with a larger sample and/or better design are included in table 2.

biliary calculi. Journal of Endourology 28: 877-880	EHL=8	with biliary cast syndrome needed 4 interventions over 9 years. Major complications were low, with 1 patient with hypotension and cholangitis that resolved with 24 hours of administration of intravenous fluids and antibiotics.	
Stefanidis G, Christodoulou C, Manolakopoulos S et al. (2012) Endoscopic extraction of large common bile duct stones: A review article. World journal of gastrointestinal endoscopy 4: 167-179	Review	EHL and LL yield similar success rates and may be used complementarily in referral centres. However, EHL under direct cholangioscopy or under fluoroscopy presents high rates of successful clearance in large stones (over 90%) when performed by skilled endoscopists.	Review article
Takeshi O and Higuchi K (2016) A review of treatment options for bile duct stones. Expert review of gastroenterololyg & hepatology 10: 1271-1278	Review	The rate of complete bile duct stone removal using EHL under the mother-baby method of POCS is reported to range from 64% to 97%, and the rate of adverse events, such as bile duct bleeding or cholangitis ranges from under 2% to 9%.	Review article
Trikudanathan G, Arain MA, Attam R et al. (2014) Advances in the endoscopic management of common bile duct stones. Nature reviews: Gastroenterology & Hepatology 11: 535-544	Review	Cholangioscopically directed electrohydraulic and laser lithotripsy enables fragmentation of refractory stones.	Review article
Trikudanathan G, Singh D, Shrestha P et al. (2017) Percutaneous transhepatic cholangioscopy with intraductal electrohydraulic lithotripsy for management of choledocholithiasis in an inaccessible papilla. VIDEOGIE 2: 152-154	Case report n=1 (81 years; female)	This case report demonstrates the successful use of percutaneous transhepatic cholangioscopy with intraductal EHL, a technique that should be considered when anatomic considerations preclude the traditional per-oral approach for ERCP.	This is a single case report.
Trikudanathan G, Navaneethan U and Parsi	Review	Ductal clearance can be safely achieved with	Review article

MA (2013) Endoscopic management of difficult common bile duct stones. World J Gastroenterol 19: 165-173		peroral cholangioscopy guided laser or electrohydraulic lithotripsy in most cases where other endoscopic treatment modalities have failed.	
Tonozuka R, Itoi T, Sofuni A et al. (2019) Novel peroral direct digital cholangioscopy-assisted lithotripsy using a monorail technique through the overtube in patients with surgically altered anatomy (with video). Digestive endoscopy 31: 203-208	Case series n=5 (mean 69 years; 60% [3/5] female]	Complete removal of biliary stones in 1 session was accomplished in 4 patients and only 1 case required 2 sessions. There was no adverse event in any of the cases. PDCS-assisted EHL using the monorail technique was effective and safe for difficult biliary stones in patients with surgically altered anatomy.	Studies with a larger sample and/or better design are included in table 2.
Tsujino T and Lee JG (2016) Electrohydraulic lithotripsy for large bile duct stones under direct cholangioscopy using double-balloon enteroscopy. Digestive endoscopy 28:104	Case report n=1 (66 years; female)	EHL was done under cholangioscopic guidance to fragment the large stones. The fragmented stones and sludge were cleared using a retrieval balloon, and stone clearance was confirmed on cholangioscopy and fluoroscopy. The patient developed no complications after the procedure.	This is a single case report.
Turowski F, Hugle U, Dormann A et al. (2018) Diagnostic and therapeutic single-operator cholangiopancreatoscopy with SpyGlassDS™: results of a multicentre retrospective cohort study. Surgical endoscopy 32: 3981-3988	Case series n=250 (50 EHL)	In 50 patients (69 procedures), SOC guided EHL was used for the destruction of large bile duct stones. A complete lithotripsy during the first session with 1 EHL probe was possible in 34/51 procedures (66.7%) and final stone removal was achieved in 66/69 cases (95.6%). A mean of three procedures (range 1 to 6) was necessary to achieve final stone clearance.	Studies with a larger sample and/or better design are included in table 2.
Wamsteker EJ (2006) Updates in biliary endoscopy. Current opinion in gastroenterology 22: 300-304	Review	EHL may be reserved for cases where mechanical lithotripsy fails or more specifically where stones are above a narrow duct	Review article

		segment, in the presence of impacted stones or where stones are lodged in the cystic duct.	
Watson RR, Parsi MA, Aslanian HR et al. (2018) Biliary and pancreatic lithotripsy devices. Gastrointest Endosc 3: 329-338	Review	EHL and laser lithotripsy are effective at ductal clearance when conventional techniques are unsuccessful, although they usually require direct visualization of the stone by the use of cholangiopancreatoscopy and are often limited to referral centres.	Review article
Weigand K (2018) Cholangioscopy-guided electrohydraulic lithotripsy of large bile duct stones through a percutaneous access device. Endoscopy 50: E111-E112	Case series n=5	The stones were directly fragmented under optic visualization using an electrohydraulic lithotripsy device. All fragments were completely removed by flushing and suction. Complete stone removal was achieved in all patients. There were no major complications.	Studies with a larger sample and/or better design are included in table 2.
Wen XD, Ren LN and Liu WH (2019) Efficient clearance of intractable biliary calculi by combination of mechanical clamping and electrohydraulic lithotripsy. Digestive endoscopy 31: e94-e96	Case report n=1	Considering its efficiency and cost-effectiveness, CEHL may be applied in the treatment of intractable calculi when traditional EHL fails.	This is a single case report.
Yamauchi H, Kida M, Miyazawa S et al. (2015) Electrohydraulic lithotripsy under peroral direct cholangioscopy using short-type single-balloon enteroscope for large common bile duct stone in patients with Roux-en-Y gastrectomy. Endoscopy 47: E240-E241	Case report n=1 (78 years; male)	The results suggest that EHL with a single-balloon enteroscope during PDCS is a useful procedure in patients with Roux-en-Y gastrectomy.	This is a single case report.
Yasuda I and Itoi T (2013) Recent advanced in endoscopic management of difficult bile duct stones. Digestie endoscopy 25: 376-385	Review	Large bile duct stones are typically treated by mechanical lithotripsy. However, if this fails, laser or electrohydraulic lithotripsy (EHL) is carried out under the guidance of conventional mother-baby	Review article

		cholangioscopy. In cases of altered anatomy, it is often difficult to reach the papilla; in such cases, a percutaneous transhepatic approach, such as EHL or laser lithotripsy under percutaneous transhepatic cholangioscopy, can be a treatment option.	