

ENDOSCOPY

Efficacy of Single-Operator Cholangioscopy-Guided Lithotripsy Compared With Large Balloon Sphincteroplasty in Management of Difficult Bile Duct Stones in a Randomized Trial



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BACKGROUND & AIMS: Although single-operator cholangioscopy (SOC)-guided lithotripsy and large balloon sphincteroplasty (LBS)-based techniques are effective rescue measures, the ideal approach to management of difficult bile duct stones is unclear. We conducted a randomized trial to compare the effectiveness of SOC-guided lithotripsy and LBS-based approaches for endoscopic management of difficult bile duct stones.

METHODS: Patients with difficult bile duct stones who failed retrieval using balloon or basket were randomly assigned to groups that received SOC-guided laser lithotripsy (SOC-LL, $n = 33$) or LBS ($n = 33$), from June 2016 through August 2018. When assigned treatment was unsuccessful, patients underwent mechanical lithotripsy before crossing over to the other group. The main outcome was treatment success, defined as ability to clear the duct in 1 session. Secondary outcomes were adverse events and treatment costs.

RESULTS: A higher proportion of patients in the SOC-LL group had treatment success (93.9%) than in the LBS group (72.7%; $P = .021$). On multiple logistic regression analysis, treatment success was significantly associated with use of SOC-LL (odds ratio [OR], 8.7; 95% CI, 1.3–59.3; $P = .026$), stone to extrahepatic bile duct ratio of 1 or less (OR, 28.8; 95% CI, 1.2–687.6; $P = .038$), and lack of a tapered bile duct (OR, 26.9; 95% CI, 1.3–558.2; $P = .034$). There was no significant difference between groups in adverse events (9.1% in the SOC-LL group vs 3.0% in the LBS group, $P = .61$) or overall treatment cost (\$16,684 in the SOC-LL group vs \$10,626 in the LBS group; $P = .097$).

CONCLUSIONS: In a randomized trial of patients with difficult bile stones that cannot be cleared by standard maneuvers, SOC-guided lithotripsy leads to duct clearance in a significantly higher proportion of patients than LBS—particularly when stone size exceeds the diameter of the extrahepatic bile duct. Adjunct lithotripsy might be required in patients with tapered distal bile duct, because LBS alone is less likely to be successful. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00852072) no: NCT00852072.

Keywords: Sphincteroplasty; ERCP; CBD; Direct Comparison.

The first-line treatment option for common bile duct (CBD) stones is endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy and stone extraction. Standard devices, such as balloons and baskets, are usually effective in retrieving small stones,¹ but larger or impacted stones may require advanced maneuvers.^{2,3} The 3 most commonly practiced advanced maneuvers for extraction of difficult CBD stones are mechanical lithotripsy (ML), large balloon sphincteroplasty (LBS), and single-operator cholangioscopy (SOC)-guided lithotripsy using laser (SOC-LL) or electrohydraulic probes (SOC-guided electrohydraulic

lithotripsy).⁴ Although ML has historically been the preferred approach, it has become less popular⁵ with the emergence of LBS and SOC-guided lithotripsy.

Abbreviations used in this paper: CBD, common bile duct; CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; IQR, interquartile range; LBS, large balloon sphincteroplasty; ML, mechanical lithotripsy; OR, odds ratio; SOC, single-operator cholangioscopy; SOC-LL, single-operator cholangioscopy-guided laser lithotripsy.



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Despite being a common indication for ERCP,⁶ there is no standardized approach to endoscopic management of difficult CBD stones, particularly when standard methods fail. Consequently, ERCP procedures become prolonged and inefficient in these cases because of the use of multiple devices, techniques, or alternate treatment modalities.⁷⁻¹¹ This not only leads to multiple reinterventions but also makes the procedure less cost-effective.¹²

Therefore, with the objective of improving technical outcomes and standardizing key procedural steps, we conducted a randomized trial comparing the effectiveness of SOC-guided lithotripsy and LBS-based approaches for endoscopic management of difficult bile duct stones. Our hypothesis was that the investigation may identify predictors of treatment outcomes that will help optimize the management strategy.

Materials and Methods

Patients

After institutional review board approval, consecutive patients with difficult bile duct stones were recruited from inpatient ward services or outpatient referrals. Procedure selection criteria included patients ≥ 18 years who were suspected to have CBD stones on ERCP/magnetic resonance cholangiopancreatography and attempts at ductal clearance using retrieval balloons and baskets were unsuccessful at outside facilities or at our institution. Patients with intrahepatic ductal stones, altered surgical anatomy, suspected pancreaticobiliary malignancy, pregnancy, abnormal coagulation parameters, and those on anticoagulation or antiplatelet therapy were excluded. Written informed consent was obtained from all patients before enrollment in the study. All authors had full access to study data and have reviewed and approved the final manuscript.

Randomization and Masking

Computer-generated randomization assignments using a block randomization method (block sizes of 4) was placed in sequentially numbered, sealed, opaque envelopes that were opened by a study coordinator intra-procedurally to determine the treatment allocation. Once inclusion criteria were met, patients were randomized equally (1:1 allocation) to either treatment cohort. Given innate differences in procedural techniques, endoscopists were not blinded to the treatment allocation.

Procedural Technique

All interventions were performed using a therapeutic duodenoscope (TJF 180V, Olympus America Inc, Center Valley, PA) under general anesthesia with patients in prone position. In patients who had undergone a prior

What you need to know

Background

Although single-operator cholangioscopy (SOC)-guided lithotripsy and large balloon sphincteroplasty (LBS)-based techniques are effective rescue measures, it is not clear which approach is best for treatment of patients with difficult bile duct stones.

Findings

In a randomized trial of patients with difficult bile stones that cannot be cleared by standard techniques, SOC-guided lithotripsy led to duct clearance in a significantly higher proportion of patients than LBS—particularly when stone size exceeded the diameter of the extrahepatic bile duct. Adjunct lithotripsy might be required in patients with tapered distal bile duct, because LBS alone is less likely to be successful.

Implications for patient care

Patients with difficult bile stones that cannot be cleared by standard techniques should undergo SOC-guided lithotripsy to clear the duct.

ERCP with biliary endoprosthesis placement, stents were removed using a snare. CBD was selectively cannulated using a wire-guided sphincterotome (CleverCut3V sphincterotome, VisiGlide guidewire, Olympus) and fully opacified using contrast. Stone diameter was estimated intraprocedurally based on relationship of the stone size on cholangiography to the duodenoscope shaft diameter. In patients with native papillas or inadequate papillotomy, biliary sphincterotomy was performed up to the duct-duodenal junction. Stone retrieval was first attempted using balloons ranging from 11.5 to 18 mm in diameter (based on duct size) (Multi-3V Plus Extraction Balloons, Olympus) and then a 22-mm Dormia basket (Olympus) when needed. Patients were randomized after up to 6 attempts using both devices were unsuccessful.

Single-operator cholangioscopy-guided laser lithotripsy-based approach. The cholangioscope (SpyGlass DS, Boston Scientific Corp, Marlborough, MA) was advanced through the accessory channel and cannulation was achieved using the free-hand technique ([Supplementary Video 1](#)). After biliary access, suction was used to clear bile and contrast media, sterile saline was infused to optimize image quality, and the device was positioned enface to the most distal stone. Laser lithotripsy (energy settings, 1 J and 10 Hz) was performed by insertion of a holmium laser probe (Lumenis, San Jose, CA) through the biopsy channel of the cholangioscope. Lithotripsy was continued until all fragmented stones were small enough to be retrieved using a basket or balloon. When unsuccessful, retrieval was attempted using a 30-mm mechanical lithotripter (Trap-ezoid, RX Wireguided Retrieval Basket, Boston Scientific).

Large balloon sphincteroplasty-based approach. The major duodenal papilla was dilated using 12- to 15-mm or 15- to 18-mm radial expansion balloon (CRE Balloon Dilation Catheter, Boston Scientific) depending on distal CBD diameter ([Supplementary Video 2](#)). The balloon was gradually filled with diluted contrast medium under endoscopic and fluoroscopic guidance, to observe the gradual disappearance of the waist in the balloon, which was taken to indicate progressive dilation of the orifice. The balloon was kept inflated for 60 seconds. After deflation of the balloon, stone extraction was attempted using a retrieval balloon or basket. A 30-mm mechanical lithotripter was used if extraction by other methods failed (Trapezoid, Boston Scientific).

Crossover. If the previously discussed attempts failed to achieve ductal clearance, patients were crossed over to the alternate treatment arm. Occlusion cholangiogram was obtained as final step to confirm ductal clearance. In all cases, if stones were still present after 90 minutes, a 10F plastic stent was placed for biliary drainage.

All fluoroscopic images were reviewed by a dedicated radiologist to document (1) largest stone size, (2) ratio of largest stone to extrahepatic bile duct diameter (measured 1 cm distal to the stone), and (3) ratio of distal bile duct (measured 1 cm above the ampullary orifice) to proximal bile duct diameter (measured at widest point in the proximal CBD) ([Supplementary Figure 1](#)).

Follow-up

All outpatients were discharged home the same day if they met discharge criteria. In patients with residual stones, repeat ERCP was undertaken at 30 days with the method of stone extraction left to discretion of the endoscopist. Research coordinators blinded to treatment arm contacted patients by telephone at 5 days, 30 days, and 6 months after the index intervention to assess for adverse events. Hospital records were reviewed in patients who were hospitalized for the management of adverse events.

Outcome Measures and Definitions

The primary outcome was treatment success. Secondary outcomes were adverse events and treatment costs. Treatment success was defined as ability to achieve ductal clearance in 1 session using the assigned treatment. Difficult bile duct stones were defined as stones in which attempts at extraction after biliary sphincterotomy using a retrieval balloon and basket were unsuccessful. Stone/duct ratio was defined as size of largest stone divided by diameter of the extrahepatic bile duct at 1 cm distal to the stone. Tapered bile duct was defined as ratio of diameter of distal bile duct, measured 1 cm above the ampullary orifice, to widest point in proximal CBD being less than 0.5. Procedural duration was defined as time from duodenoscope

insertion until withdrawal. Adverse events were graded by established criteria.¹³

Sample Size Calculation

Two-tailed sample size calculation was performed based on the rate of treatment success, which was estimated at 95% for SOC-guided lithotripsy and 65% with LBS.¹⁴⁻¹⁶ This resulted in sample size estimation of 31 patients per group, at 80% power and type I error rate (α) of 0.05. Total sample size was set at 66 patients to account for 5% dropout rate.¹⁷ Sample size calculation was performed using PASS Power Analysis and Sample Size Software (NCSS LLC, Kaysville, UT).

Statistical Analysis

Patient characteristics, disease characteristics, procedural details, and treatment outcomes were summarized and compared between groups. Continuous variables were summarized as means with standard deviations and median with interquartile ranges (IQRs) and ranges and compared using the Wilcoxon rank sum test or 2-sample Student *t* test as indicated. Categorical variables were summarized as frequencies and proportions and compared using the Fisher exact test or chi-square test as indicated.

Because of the occurrence of separation with logistic regression analysis, penalized logistic regression with Firth's correction was performed to identify predictors of treatment success.¹⁸ Clinically relevant variables, namely prior ERCP, treatment arm, stone location, number of stones, largest stone size, presence of tapered bile duct, and ratio of stone to extrahepatic bile duct diameter, were taken as predictor variables for inclusion in the analysis. Statistical significance was determined as $P < .05$. Datasets were compiled using Microsoft Excel (Microsoft Corporation, Richmond, WA), and analyses were performed using Stata version 14 (StataCorp LP, College Station, TX).

Cost Analysis

All relevant costs related to bile duct stone management were considered including procedure costs, inpatient hospitalization from date of procedure to discharge, pharmacy, supplies, anesthesia, radiology, and laboratory. All costs were based on Medicare reimbursement fee structure and expressed in 2018 US dollars.

Generalized linear models were used to examine differences in cost between study groups. Before fitting the generalized linear models, skewness of cost data was assessed and determined to be highly positively skewed. The Pregibon and modified Park tests indicated that the generalized linear models should be fitted to the study data using a log link and gamma distribution for the mean-variance relationship of the response variable.^{19,20}

Adjusted mean cost estimates by cost categories and study group were calculated using the method of recycled predictions.²¹

Results

Study Enrolment and Termination

Between June 2016 and August 2018, 418 patients were screened, 107 patients were enrolled, and 66 with difficult bile duct stones underwent equal randomization to the 2 treatment arms (Supplementary Figure 2). Forty-one patients were not randomized after study enrollment because of successful stone removal using the standard techniques in 39 patients and stones located in the intrahepatic ducts or cystic duct in 2 patients. More than 60% of patients in both cohorts had failed ERCP stone extraction at outside hospitals. All patients were followed for a minimum duration of 6 months.

Single-Operator Cholangioscopy-Guided Laser Lithotripsy

Patients randomized to SOC-LL were significantly older with a smaller proportion having undergone prior cholecystectomy (Table 1). Median size of the largest stone was 15 mm, 54.5% of patients had 3 or more stones, and median stone/duct ratio was 1.5 (IQR, 1.0–1.8) (Table 2). Treatment was successful in 31 patients (93.9%); 1 patient with stone fragments in the proximal bile duct required a 30-mm mechanical lithotripter to achieve ductal clearance because both retrieval

Table 1. Baseline Patient Characteristics

	LBS (n = 33)	SOC-LL (n = 33)	P value
Age, y			
Mean (SD)	63.9 (18.0)	72.8 (16.4)	
Median	68	77	.034
IQR	53–75	61–83	
Range	23–90	27–94	
Gender, n (%)			
Female	25 (75.8)	21 (63.6)	.284
Male	8 (24.2)	12 (36.4)	
Race, n (%)			
Asian	0	2 (6.1)	.999
Black	4 (12.1)	0	
Hispanic	6 (18.2)	8 (24.2)	
White	23 (69.7)	23 (69.7)	
Prior ERCP at outside facility for attempt at stone removal, n (%)	22 (66.7)	21 (63.6)	.796
Prior cholecystectomy, n (%)	24 (72.7)	14 (42.4)	.013

ERCP, endoscopic retrograde cholangiopancreatography; IQR, interquartile range; LBS, large balloon sphincteroplasty; SD, standard deviation; SOC-LL, single-operator cholangioscopy-guided laser lithotripsy.

Table 2. Procedure Details and Clinical Outcomes

	LBS (n = 33)	SOC-LL (n = 33)	P value
Location of stone, n (%)			
Distal bile duct ^a	22 (66.7)	22 (66.7)	.999
Proximal bile duct	3 (9.1)	2 (6.1)	
Distal and proximal bile duct	8 (24.2)	9 (27.3)	
Size of largest stone, mm			
Mean (SD)	15.3 (5.6)	17.2 (8.7)	
Median	14	15	.097
IQR	12–15	12–18	
Range	12–40	12–60	
Total number of stones			
Mean (SD)	3.1 (2.4)	3.7 (4.0)	
Median	3	3	.915
IQR	1–4	1–4	
Range	1–12	1–20	
1–2	16 (48.5)	15 (45.5)	.805
≥3	17 (51.5)	18 (54.5)	
Ratio of stone size to extrahepatic bile duct diameter ^b			
Mean (SD)	1.3 (0.6)	1.6 (1.1)	
Median	1.3	1.5	.098
IQR	1.0–1.3	1.0–1.8	
Range	0.7–3.1	.8–7.5	
Total procedure duration, min			
Mean (SD)	37.3 (25.2)	39.2 (2.1)	
Median	27	38	.379
IQR	15–58	25–50	
Range	5–88	12–85	
Treatment success, n (%)	24 (72.7)	31 (93.9)	.021
Crossover to alternate treatment arm, n (%)	9 (27.3) ^c	2 (6.1) ^d	.021
Reintervention performed, n (%)	2 (6.1)	0	.492
Total no. of interventions to achieve ductal clearance			
Mean (SD)	1.1 (0.4)	1.0 (0)	
Median	1	1	.154
IQR	1–1	1–1	
Range	1–3	1–1	
1	31 (93.9)	33 (100)	.492
2	1 (3.0)	0	
3	1 (3.0)	0	
Adverse events, n (%)	1 (3.0)	3 (9.1)	.613

IQR, interquartile range; LBS, large balloon sphincteroplasty; SD, standard deviation; SOC-LL, single-operator cholangioscopy-guided laser lithotripsy.

^aDistal bile duct is defined as the distal 50% of the main bile duct. Proximal bile duct is defined as the proximal 50% of the main bile duct.

^bExtrahepatic bile duct diameter was measured 1 cm distal to the largest stone.

^cDuctal clearance was achieved in 7 of 9 patients in LBS group who were crossed over to SOC-LL. In the remaining 2 patients who were crossed over to SOC-LL, complete stone removal was not achieved during the index session despite crossover to SOC-LL and required repeat interventions.

^dDuctal clearance was achieved in both patients in SOC-LL group who were crossed over to LBS.

balloon and basket were unsuccessful in capturing the stone (Supplementary Figure 3). In 2 patients with numerous small stone fragments in the distal CBD, ductal clearance was achieved only after crossover and underwent LBS (15 mm). No significant difference was observed in rate of ductal clearance using SOC-LL regardless of the presence/absence of a tapered bile duct (89.5% vs 100%; $P = .496$).

Table 3. Multiple Penalized Logistic Regression With Firth's Correction Examining the Factors Associated With Treatment Success

Variable	Odds ratio	95% CI	P value
Treatment arm: SOC-LL vs LBS	8.74	1.29–59.3	.026
Stone location: distal vs proximal bile duct	0.90	0.14–5.69	.908
Total no. of stones: 1 vs ≥ 2 stones	1.68	0.26–10.6	.584
Size of largest stone: <15 mm vs ≥ 15 mm	1.28	0.19–8.78	.801
Ratio of stone size to extrahepatic bile duct diameter: ≤ 1.0 vs >1.0	28.8	1.21–687.6	.038
Presence of tapered bile duct: No vs Yes	26.9	1.29–558.2	.034
Prior ERCP for stone removal: Yes vs no	1.35	0.18–9.88	.769

CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; LBS, large balloon sphincteroplasty; SOC-LL, single-operator cholangioscopy-guided laser lithotripsy.

Adverse events were encountered in 3 (9.1%) patients that included, cricopharyngeal perforation ($n = 1$), bile peritonitis caused by perforation in the distal bile duct after laser lithotripsy ($n = 1$), and mild post-ERCP pancreatitis ($n = 1$). The patient with cricopharyngeal perforation had undergone suctioning of the oropharynx using a rigid probe and hence the precise reason for adverse event was unclear. The patient with bile duct perforation underwent surgical repair of the fistula, and the patient with acute pancreatitis was managed conservatively.

Large Balloon Sphincteroplasty

Median size of the largest stone was 14 mm, 51.5% of patients had 3 or more stones, and the median stone/duct ratio was 1.3 (IQR, 1.0–1.3) (Table 2). Treatment was successful in 24 (72.7%) patients; 7 of 24 patients required adjunctive ML to achieve ductal clearance. Of the remaining 9 patients who failed assigned treatment, 7 achieved ductal clearance on crossover to SOC-LL; 2 underwent biliary stenting and required additional interventions at follow-up using SOC-LL (Supplementary Figure 3).

In the 7 patients who required adjunctive ML for ductal clearance, the median stone/duct ratio was 1.0 (IQR, 0.9–1.0); 5 of 7 patients had multiple stones and 2 had a single large stone in the mid-bile duct. All 9 patients treated with SOC-LL had impacted bile duct stones with stone/duct ratio >1 .

A tapered bile duct was observed in significantly more patients in whom ductal clearance failed using LBS as compared with patients in whom LBS was successful (56.3% vs 5.9%; $P = .002$). One patient (3%) developed moderate severity post-ERCP pancreatitis that was managed conservatively.

Outcome Measures

Treatment success was significantly higher for SOC-LL as compared with LBS-based approach (93.9% vs 72.7%; $P = .021$). On multiple logistic regression analysis, use of SOC-LL (odds ratio [OR], 8.7; 95% confidence

interval [CI], 1.3–59.3; $P = .026$), stone/duct ratio ≤ 1 (OR, 28.8; 95% CI, 1.2–687.6; $P = .038$), and not having a tapered bile duct (OR, 26.9; 95% CI, 1.3–558.2; $P = .034$) were significantly associated with treatment success (Table 3). There was no significant difference in the rate of adverse events (9.1% vs 3.0%; $P = .613$) or procedural duration.

Cost Analysis

Of 66 patients, 30 were outpatients and 36 were transferred from outside facilities to undergo ERCP. The overall average treatment cost at our center was \$16,684 for SOC-LL and \$10,626 for LBS with no significant difference between groups ($P = .097$) (Table 4). Although the costs for procedural supplies were significantly

Table 4. Cost Analysis^a

	LBS (US \$)	SOC-LL (US \$)	P value ^b
Total ^c	10,626	16,684	.097
Procedure	3522	2536	.118
Pharmacy	565	623	.860
Hospital	1996	2824	.672
Radiology	1292	1033	.649
Anesthesia	650	858	.180
Laboratory	636	1041	.513
Procedural supplies	3349	7221	.004

LBS, large balloon sphincteroplasty; SOC-LL, single-operator cholangioscopy-guided laser lithotripsy.

^aCost-to-charge ratio was applied for hospital-related expenses.

^bCost estimates and P values are reported for a generalized linear model with gamma distribution and log link function.

^cAlthough costs pertaining only to endoscopic retrograde cholangiopancreatography (inclusive of SOC) were reported as procedure costs, total costs included costs for the procedure, post-procedure hospitalization, pharmacy, anesthesia, radiology, laboratory, and supplies. Procedure costs included all costs pertaining to the endoscopic procedure, including service fees, facility fees, and equipment costs. Hospital costs included costs incurred during hospital stay. Radiology costs included costs pertaining to the use of fluoroscopy and other radiology services during hospitalization. Anesthesia costs included all anesthesia costs pertaining to the provision of anesthesia care for endoscopic procedures. Laboratory costs included costs pertaining to the use of laboratory services. Procedural supply costs included all costs associated with sterile supplies.

higher for SOC-LL, there was no significant difference in the overall procedure costs.

Discussion

The present study demonstrates that by using SOC-guided lithotripsy as first-line treatment measure in patients with difficult bile duct stones, ductal clearance can be achieved in 90% of patients, particularly when stone/duct ratio is >1 . Also, when the diameter of distal bile duct is less than half of the proximal bile duct, LBS may be ineffective and adjunctive lithotripsy (SOC-guided or ML) may be required to achieve ductal clearance.

Approximately 10%–15% of bile duct stones encountered at ERCP are considered difficult, because they cannot be removed using conventional techniques.²² Difficulties in clearing bile duct stones include large size, multiple stones, impacted stones, and presence of a tapered distal CBD. The basic premise for treatment is to fragment the stone so that it can be extracted via the distal bile duct or to enlarge the distal bile duct so that a large stone can be extracted. Although the objective is stone fragmentation, there is a fundamental difference in the technique of lithotripsy using mechanical and SOC platforms. Although ML is an effective rescue measure, as evident by its ability to facilitate ductal clearance in 7 of 16 (43.8%) patients who failed treatment using LBS, it seems ineffective in patients with impacted stones, particularly when stone/duct ratio is >1 . Impacted stones impede complete opening of the basket or even its passage into the proximal bile duct. However, a cholangioscope can be positioned distal to the stone and its fragmentation by laser can be visualized in real-time. Consequently, ductal clearance could be achieved in $>90\%$ of patients in the SOC-LL cohort. Failure was encountered only when it was not possible to advance the cholangioscope to the distal bile duct; this is usually observed in patients with occlusive stones or strictures. In such instances, LBS performed as adjunctive measure helps to accomplish ductal clearance.

LBS has been proven in randomized trials to be a simple, safe, and effective technique for extraction of large stones.^{2,23} This has been found to be particularly advantageous for patients unable to undergo a biliary sphincterotomy or when sphincterotomy alone is insufficient in widening the papillary orifice.²⁴ In the present study, although $>70\%$ of patients randomized to LBS achieved ductal clearance, failure was observed in 2 circumstances (not well reported by others).²⁴ The first was when stones were large and impacted in the proximal bile duct with stone/duct ratio >1 . The second was when the diameter of the distal bile duct was less than half the proximal bile duct, LBS as sole treatment measure was more likely to fail. The latter circumstance is particularly important because the degree of dilation during sphincteroplasty is limited by the maximum

diameter of the distal bile duct to minimize the risk of perforation.

What new lessons can be learned from this randomized trial that can impact the practice of difficult bile duct stone management? First, when the ratio of stone size to extrahepatic bile duct diameter is >1 , SOC-guided lithotripsy should be the first-line treatment measure because it ensures ductal clearance in greater than 90% of patients at index session. Therefore, patients who fit this clinical picture based on cross-sectional imaging studies or prior ERCP should be referred to institutions or endoscopists with expertise in performing SOC-guided lithotripsy. Second, when the stone-duct ratio is ≤ 1 , stone retrieval can be attempted after performing a balloon sphincteroplasty, particularly when the distal bile duct diameter is $\geq 50\%$ the proximal bile duct. Should the approach fail, lithotripsy (mechanical or SOC-guided) may be performed as an adjunctive treatment measure. Third, although the cost of procedural supplies was significantly higher for SOC-LL, based on Medicare reimbursement structure, there was no significant difference in procedural and overall treatment costs between groups. Therefore, if patients with difficult bile duct stones (stone/duct ratio >1) are treated using SOC-LL at index intervention, cost savings of approximately \$10,000/patient can be achieved.

Based on our observations, we propose a simple algorithm for the management of patients with difficult bile duct stones (Figure 1). In all patients, conventional methods (biliary sphincterotomy followed by use of retrieval balloon and/or basket) should be attempted first. When conventional methods fail, the stone/duct ratio must be ascertained. If the ratio is >1 , SOC-guided lithotripsy should be considered the first-line treatment measure. When the ratio is ≤ 1 , LBS may be attempted with the highest likelihood of success being reserved for patients without a tapered distal CBD; when the distal CBD is tapered, adjunctive mechanical or SOC-guided lithotripsy may be required. This algorithm is currently being validated in a prospective, international, multicenter trial (IRB# 1504680). Although many patients with bile duct stones are inherently different with a unique set of challenges and the algorithm may not be uniformly applicable to all situations, we believe that it will serve as a roadmap to most patients enabling a tailored treatment strategy that leads to improved clinical outcomes and cost-effective care. Despite the lack of specific recommendations, although experienced endoscopists can often intuitively select the appropriate accessories or techniques that are specific to unique challenges, novice endoscopists bereft of this experience lack a framework. Should this algorithm be validated prospectively, it will serve as a platform for evidence-based practice and the design of future clinical trials.

Our study has several limitations. One, by including only patients with extrahepatic bile duct stones and normal anatomy, findings are not applicable to patients with intrahepatic stones or altered surgical anatomy.

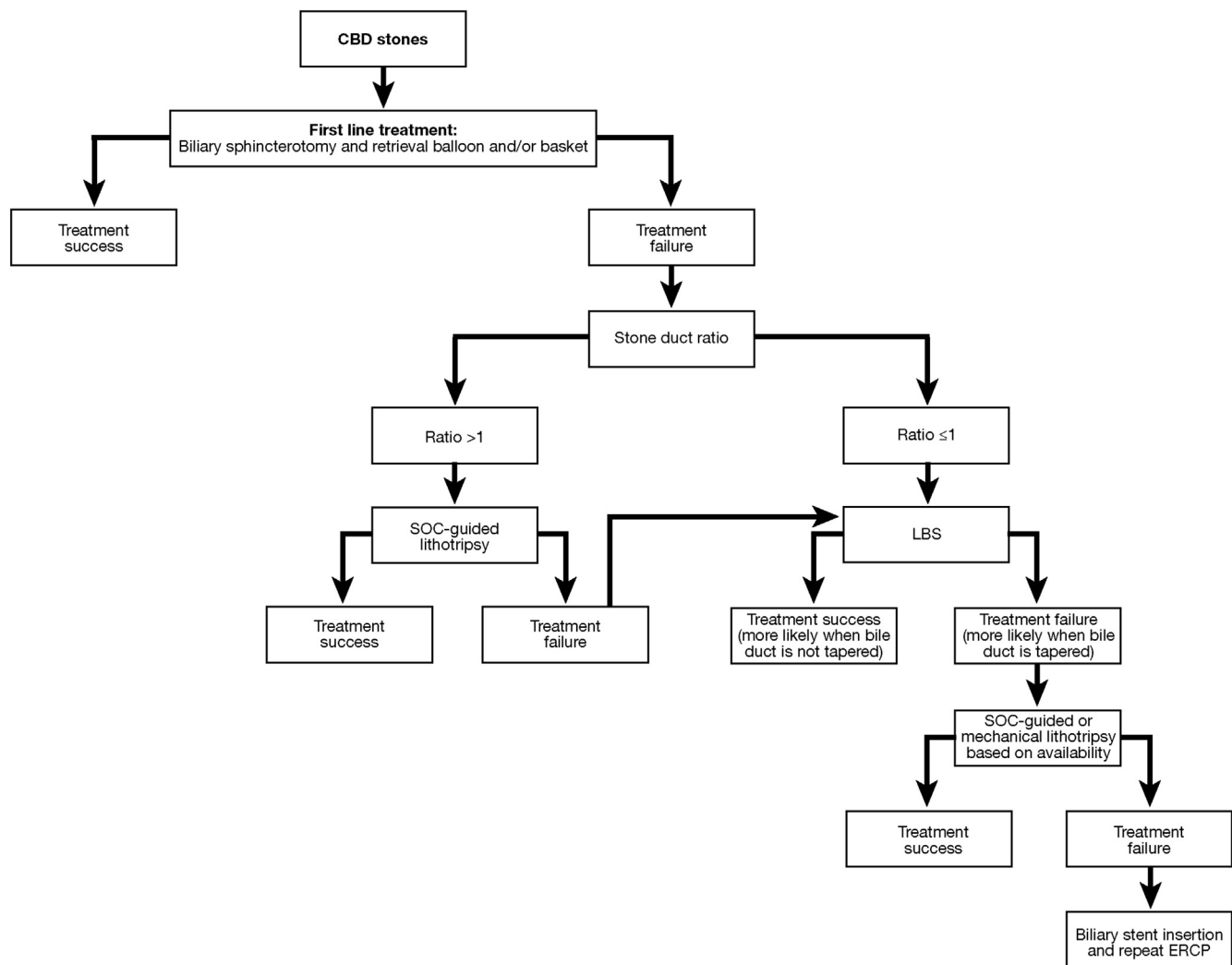


Figure 1. Algorithm for bile duct stone management.

Two, given the different definitions attributed to difficult bile duct stones in prior studies, the observed difference in treatment success rates was smaller in this study. Three, although procedural duration is a surrogate marker for efficiency, the study design precluded meaningful comparison of this variable because all patients were randomized equally to either cohort. Four, given that we did not include a third comparative arm, these data may not be applicable to centers that use only ML for stone fragmentation. Five, because only 1 type of mechanical lithotripter was used in this study, the outcomes for other types of mechanical lithotripters are unclear. Six, laser was the only modality used for lithotripsy in the study. However, in a retrospective study, the outcomes of SOC-LL and SOC-guided electrohydraulic lithotripsy were found to be comparable.³ Seven, because the primary outcome of the study was comparison of treatment success, definitive conclusions regarding adverse event rates could not be made. Also, the 95% CIs of the ORs in the regression analysis to elucidate factors associated with treatment success are large for some predictor variables and hence may require evaluation in

larger studies. Finally, the generalizability of cost data to other centers may be limited because of regional variations in wages and hospital variations in operating costs, service mix, and volume.

In summary, our study demonstrates that SOC-guided lithotripsy should be the preferred first-line treatment approach for patients with difficult bile duct stones, particularly when stone/duct ratio is >1 . Also, LBS alone may be ineffective when diameter of the distal bile duct is less than half the proximal bile duct diameter and adjunctive lithotripsy may be required in these patients. Incorporating the previously mentioned variables in clinical practice is likely to improve treatment outcomes and yield cost savings.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2020.02.003>.

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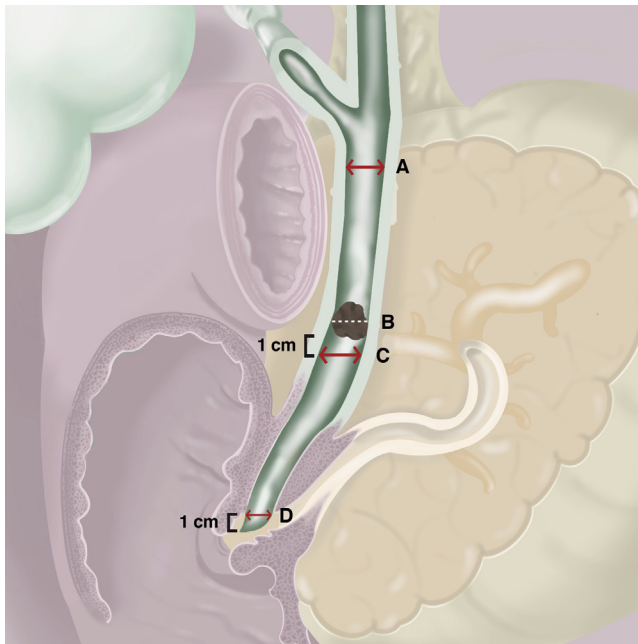
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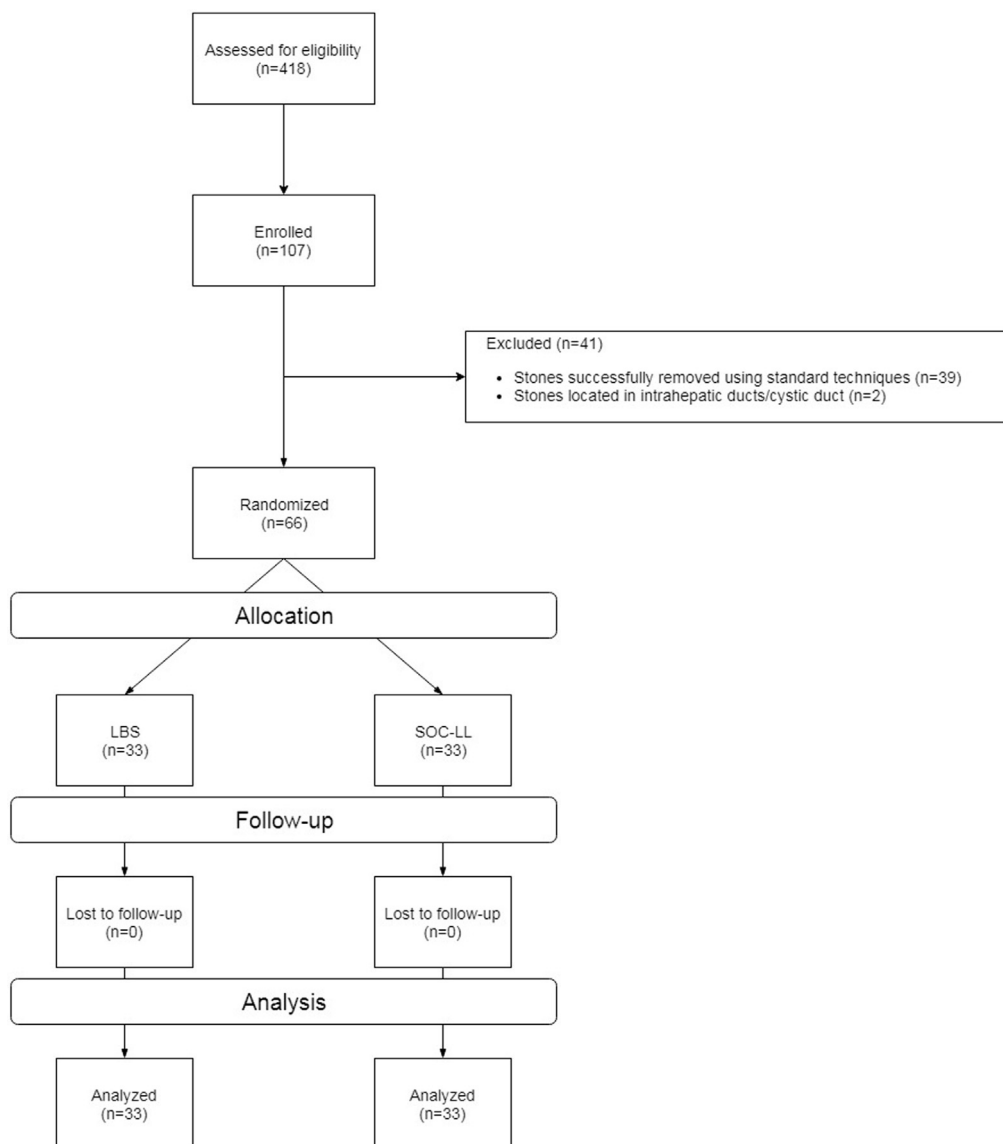
Ji Young Bang (Conceptualization: Supporting; Data curation: Equal; Formal analysis: Lead; Investigation: Lead; Methodology: Equal; Writing – original draft: Equal; Writing – review and editing: Equal)
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Conflicts of interest

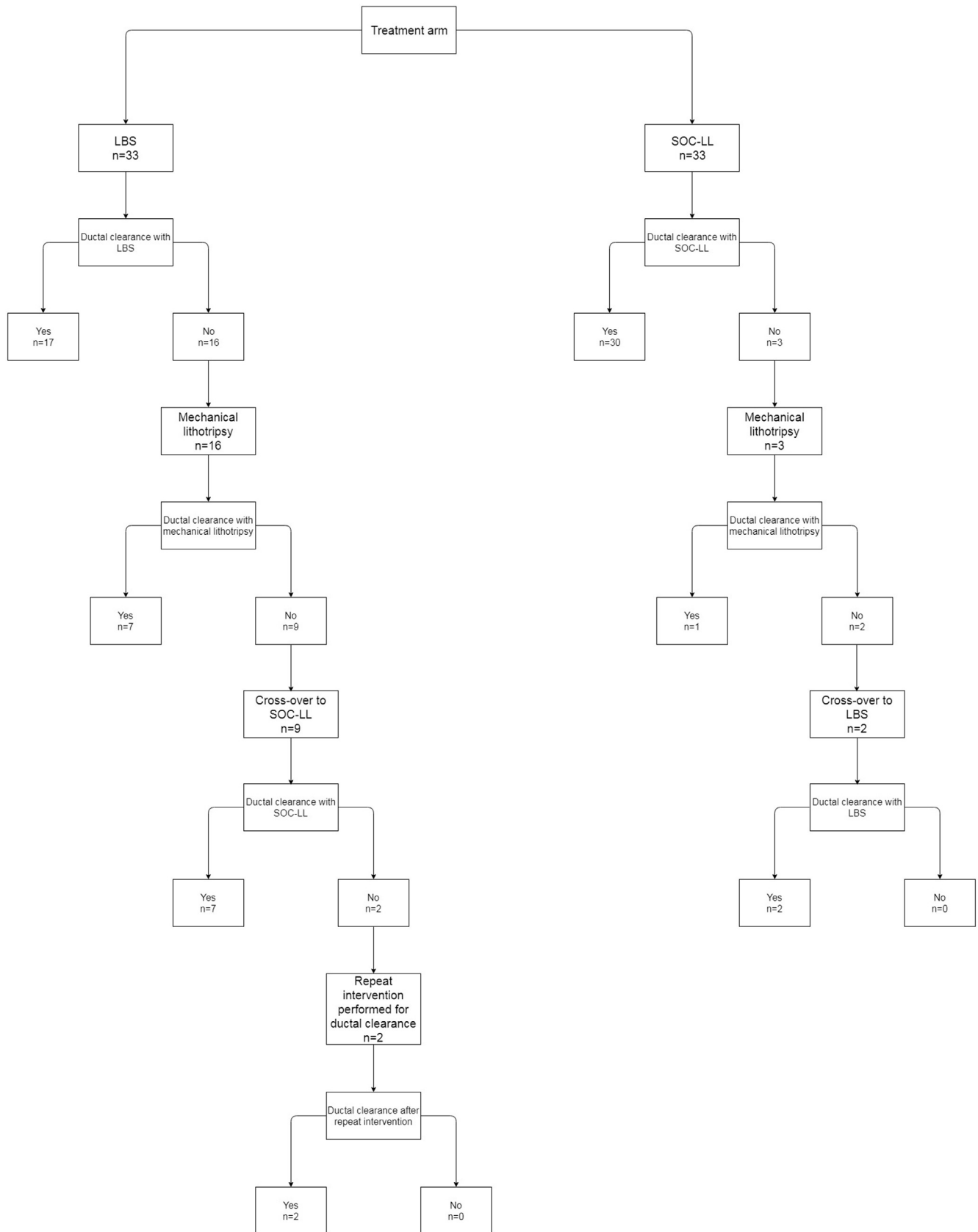
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Supplementary Figure 1. Illustration depicting areas of measurement for stone size and bile duct diameter. (A) Proximal bile duct diameter. (B) Largest stone size. (C) Extrahepatic bile duct diameter. (D) Distal bile duct diameter.



Supplementary
Figure 2. CONSORT flow diagram.



Supplementary Figure 3. Flow diagram of procedure outcomes.