

Treatment of bladder stones in adults and children: A Systematic review and meta-analysis on behalf of the European Association of Urology Urolithiasis Guideline Panel

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Abstract:**Context:**

Bladder stones (BS) constitute 5% of urinary stones. Currently, there is no systematic review on their treatment.

Objective:

To assess the efficacy (primary outcome: stone-free rate; SFR) and morbidity of BS treatments.

Evidence Acquisition:

This systematic review was conducted in accordance with the EAU Guidelines Office. Database searches (1970-2019) were screened, abstracted and assessed for risk of bias for comparative RCTs and non-randomized studies (NRS) with ≥ 10 patients per group. Quality of evidence (QoE) was assessed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Evidence Synthesis:

2742 abstracts and 59 full-texts were assessed: 25 studies (2340 patients) were included. In adults, one RCT found a lower SFR following shock wave lithotripsy (SWL) than transurethral cystolithotripsy (TUCL) (RR 0.88, $p=0.03$; low QoE). Four RCTs compared TUCL vs. percutaneous cystolithotripsy (PCCL): meta-analyses demonstrated no difference in SFR, but hospital stay (mean difference; MD; 0.82days, $p<0.00001$) and procedure duration (MD 9.83minutes, $p<0.00001$) favored TUCL (moderate QoE).

Four NRS comparing open cystolithotomy (CL) vs. TUCL or PCCL found no difference in SFR; hospital stay and procedure duration favored endoscopic surgery (very low QoE). Four RCTs compared TUCL using a nephroscope vs. cystoscope: meta-analyses demonstrated no difference in SFR; procedure duration favored using a nephroscope (MD 22.74 minutes, $p<0.00001$; moderate QoE).

In children, one NRS showed lower SFR following SWL than TUCL or CL. Two NRS comparing CL vs. TUCL/PCCL found similar SFRs; catheterization time and hospital stay favored endoscopic treatments. One RCT comparing laser vs. pneumatic TUCL found no difference in SFR. One large NRS comparing CL techniques found a shorter hospital stay after tubeless CL in selected cases, QoE was very low.

Conclusion

Current available evidence indicates TUCL is the intervention of choice for BS in adults and children, where feasible. Further high quality research on the topic is required.

Patient Summary

We examined the literature to determine the most effective and least harmful procedures for bladder stones in adults and children. The results suggest that endoscopic surgery is equally effective as open surgery. It is unclear if stone size affects outcomes. Shock wave lithotripsy appears to be less effective. Endoscopic treatments appear to have a shorter catheterization time and convalescence compared with open surgery in adults and children. Trans-urethral surgery, where feasible, appears to have a shorter hospital stay than percutaneous surgery. Further research is required to clarify the efficacy of minimally invasive treatments for larger stones and in young children.

1. Introduction

Despite constituting only approximately 5% of all urinary tract stones [1], bladder stones (BS) are responsible for 14% of hospital admissions [2] and 8% of urolithiasis-related deaths in developed nations [3]. BS are more prevalent in men and in developing countries [4-6]. BS have a bimodal age distribution: incidence peaks at 3 [5, 7] and 60 years [4]. BS may cause lower urinary tract symptoms (LUTS), infections, pain, haematuria and have been associated with bladder cancer [8].

BS can be classified as primary, secondary or migratory [9]. Primary or endemic BS occur in the absence of other urinary tract pathology, typically seen in children in areas with a diet lacking animal protein, poor hydration and recurrent diarrhea [10]. Secondary BS occur in the presence of other urinary tract abnormalities including bladder outlet obstruction (BOO), neurogenic bladder dysfunction, chronic bacteriuria, foreign bodies including catheters, bladder diverticulae and bladder augmentation or urinary diversion. Migratory BS formed in the upper urinary tract [9].

Although open cystolithotomy (CL), is the traditionally accepted treatment modality [8] minimally invasive treatments have been widely adopted to reduce hospital stay and convalescence. However, it is unclear whether these treatments may compromise stone-free rates (SFR) and to what morbidity they may expose patients to [8, 9]. We present the first systematic review that addresses benefits and harms of procedures to remove BS in either adults or children.

2. Evidence Acquisition

2.1. Search strategy

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [11] and the Cochrane Handbook for Systematic Reviews of Interventions [12]. Medline, Embase, and Cochrane controlled trials databases and clinicaltrial.gov were searched between January 1970 and February 2019 for relevant English-language publications.

The published *a priori* protocol includes the search strategy [13]. Following de-duplication, two review authors (J.D., Y.R.) independently screened the abstracts for eligibility. The full-texts were retrieved and scrutinized independently by two review authors. For any incompletely reported data, study authors were contacted. Disagreements were resolved by discussion or by consulting a third author (A.N., C.T.).

2.2. Types of study design included

All RCTs and comparative non-randomized studies (NRSs) comparing any treatments of BS with ≥ 10 patients per arm were included. Conference abstracts were excluded.

2.3. Types of participants included

Male and female adults and children of any ethnicity with single or multiple BS were included. Recurrent or first time stone formers and all stone sizes and compositions were

eligible. Patients with pre-existing bladder augmentation or diversion were excluded. Mixed populations which accounted for <10% of the cohort were accepted.

2.4. Types of interventions included

Open cystolithotomy (CL), trans-urethral cystolithotripsy (TUCL), percutaneous cystolithotripsy (PCCL), shock wave lithotripsy (SWL) and laparoscopic removal were evaluated. Any technique or lithotripsy modality was accepted for all interventions [9].

2.5. Types of outcomes measures included

The primary benefit outcome was: SFR, measured at any time point up to 1 month post-operatively using any modality. Any definition of stone-free used by trialists was accepted. The primary harm outcome was unplanned procedures (including intra-operative and post-operative).

Secondary outcomes were: complications of treatment (intraoperative, postoperative and late). Post-operative complications were classified using the Clavien-Dindo (CD) classification [14] by the review team where sufficiently reported, or details were obtained by contacting the authors. Post-operative complications were defined as up to 4 weeks and late complications after 4 weeks, or as defined by trialists.

Other included outcomes were: re-treatment rate (including second session SWL), recurrence rate (≥ 1 month), duration of procedure, catheterization and hospital stay, pain, quality of life, patient satisfaction and ionising radiation exposure. All reported definitions or measures were accepted.

2.6. Assessment of risks of bias

Risk of bias for RCTs was assessed in accordance with Cochrane guidance [12]. Extra domains were used to assess confounders in NRS: a pragmatic approach informed by methodological literature [15]. We assessed whether each prognostic confounder was considered, whether the confounder was balanced between the intervention and control group, and whether, if necessary, the confounder was controlled for in analysis. A list of the most important potential confounders for harm and benefit outcomes was developed *a priori* with clinical content experts (the EAU Urolithiasis Guideline panel): stone size, aetiology, gender, preoperative catheterization, and previous open surgery.

2.7. Quality of evidence (QoE) assessment

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool [16] was used to assess the quality of evidence for critical and important outcomes for decision making, including assessment of study design, risk of bias, directness, consistency, and precision [16]. The outcomes that were assessed were: SFR, unplanned procedures, major post-operative complications, late complications and length of hospital stay (all rated as critical for decision making), duration of procedure and re-treatment (rated as important).

2.8. Data analysis

We report data at available time points and reported p-values where available, or if unavailable we calculated these using RevMan®. We conducted an intention-to-treat analysis, if data were available; otherwise, an available case analysis was performed. We did not impute missing data. In the case of incompletely reported data we contacted the authors.

For dichotomous outcomes, we report risk ratios (RR) and 95% confidence intervals (CI) in forest plots: odds risks are less robust when data includes 100% [17]. Where deemed clinically appropriate meta-analysis was performed using a random effects model due to heterogeneity in study design, intervention schedule, outcome definition and time-point or modality of measurement.

For continuous outcomes, we report mean difference (MD) with standard deviation and/or range and corresponding 95% CIs and p-values, where available.

3. Evidence Synthesis

Description of the included studies

2742 abstracts were screened and 59 full-text articles were assessed: 27 articles on 25 studies were included with 2340 patients: 1526 adults and 814 children. Reasons for exclusion are listed in Figure 1.

Study characteristics

The characteristics of included studies are listed in Supplementary Table 1. Twenty studies on adults were included: 9 RCTs and 11 NRS; two studies compared four interventions, and four studies compared three interventions. Five studies in children were included: one RCT and four NRS; two studies compared three interventions.

Risk of bias in included studies

The risk of bias assessment of included studies are summarised in Figure 2. GRADE QoE assessments are reported in Supplementary Tables 2-3. Stone sizes were well matched in all RCTs.

Outcome data

Outcome data are summarised in Table 1. SFR was only defined by three RCTs in adults [18] [19] [18] and one NRS in children [20]. SFR was assessed using direct visualisation, X-Ray, US or a combination of X-Ray and US (Supplementary Table 1). Post-operative complications were graded using the CD classification by one RCT and two NRS in adults [21-23]. There were no reported CD 4-5 complications. No study reported QoL, satisfaction, cost or ionising radiation exposure outcomes. Minor post-operative complications were not defined or reported separately in any study hence meta-analysis was not deemed appropriate (Supplementary Tables 3-4).

Studies in Adults

SWL vs. TUCL

One RCT (n=100) found a lower SFR following SWL vs. TUCL (RR0.88, p=0.03) (Supplementary Figures 1a-c)[23]. Retreatment appeared to favor TUCL (p=0.06). Multiple SWL sessions were performed: after 3 SWL sessions SFR were not significantly different than with one TUCL (94% vs. 98%, p=0.3). There were no unplanned procedures or major complications. Length of hospital stay favored SWL (MD 1d). These outcomes were assessed as low QoE.

Two NRS in 226 adults [24, 25] found a slightly higher SFR for TUCL compared to SWL (97.7% vs. 89.7%; p=0.07 and 97.0% vs. 93.9%; p=0.50). Urethral strictures were a very low incidence event (1.5% overall) and were not significantly different in either study. Duration of procedure was shorter for SWL in one study (MD 50min). Very low QoE supported these outcomes. One NRS reported a higher rate of unplanned procedures following SWL (5.2% vs. 1.2%, p=0.19) in 144 patients despite SWL including continuous irrigation in all patients and fragment evacuation in 15.9% [25].

TUCL vs. CL

One RCT and two NRS (n=160) compared TUCL vs. CL [24, 26]. Meta-analysis was not deemed appropriate (Supplementary Figures 2a-d). SFR was similar in all studies. The duration of the procedure (p=0.016), catheterization time (p=0.023) and the duration of hospital stay favored TUCL (MD 6.10d, p=0.02, 5.0d) [26]. No unplanned procedures or major post-operative/late complications were reported. Re-treatment was not significantly different except in one NRS conducted in 1973-1980 which reported lower recurrence rates following CL (p<0.005)[27]. The QoE was very low for all outcomes.

PCCL vs. CL

One NRS compared PCCL vs. CL in patients with urethral strictures (n=37) found no difference in outcomes except duration of catheterization (p= 0.016) procedure (p=0.023) and estimated blood loss (p=0.035) which favored PCCL [28].

PCCL vs. TUCL

Four RCTs compared PCCL vs. TUCL in 409 adults. All used pneumatic lithotripsy. Stone-free was not defined and was assessed using X-Ray or US on Day 1 [29, 30] or day of discharge [31] or the modality and timing of assessment was unclear [32]. Meta-analysis demonstrated no difference in SFR when using either a nephroscope (RR 1.00; CI 0.98-1.03, p=0.77) or cystoscope (RR 1.00; CI 0.97-1.03 p=1.00; QoE was moderate), see Figure 3.

Meta-analysis demonstrated that compared to PCCL, TUCL was quicker using a nephroscope (MD 9.83min; range: 1.32-18.34, p<0.00001) but slower when using a cystoscope (MD 13.21min; CI: -32.61-6.19, p=0.002) (moderate QoE).

Convalescence and pain score favored TUCL with either nephroscope (RR 1.90; CI 0.99 – 2.81 p<0.0001 and RR 1.10; CI 0.44 – 1.76, p =0.001) or cystoscope (RR 2.50; CI 1.53 – 3.47, p<0.00001 and RR 2.20; CI 1.60-2.80 p<0.00001; Supplementary Figure 3)[32]. Similarly, the meta-analysis demonstrated shorter hospital stay for TUCL using both nephroscope (MD 0.82d; CI 0.59-1.05, p<0.00001) and cystoscope (MD 0.97d; CI 0.72-1.22, p<0.00001; moderate QoE).

There were no differences in unplanned procedures or major post-operative complications (low QoE) [32]. For late complications, one RCT reported a low event rate (3.6% overall) at 24 months follow-up, suggesting a small non-significant benefit for PCCL compared with both TUCL nephroscope (RR 0.09; CI 0.01-1.61, p=0.10) or TUCL cystoscope (RR 0.19; CI 0.01-3.90, p=0.28 very low QoE).

There was no significant difference for re-treatment rate: QoE was low for TUCL nephroscope (with two RCTs; meta-analysis found RR 1.02 (0.96-1.09, p=0.53) and very low for TUCL cystoscope (with two NRS; p= 0.09, p=0.30)[33, 34].

TUCL: Nephroscope, Cystoscope or Resectoscope?

Four RCTs compared TUCL using a Nephroscope vs. Cystoscope (n=271) using pneumatic ± ultrasonic lithotripsy. Stone-free assessment was with X-Ray or US on Day 1 [29, 30] or day of discharge [31] or was not stated [32]. Meta-analysis revealed no difference in SFR (RR 1.00; CI 0.98–1.02, p=1.00; Figure 4) as all patients were rendered stone-free (moderate QoE).

Using a nephroscope was significantly quicker (MD 22.74 minutes; CI 31.64–13.84, p<0.00001; moderate QoE). Hospital stay was similar (MD 0.15 days; CI 0.13–0.43, p=0.30; low QoE). Bansal et al. reported a benefit for using a cystoscope in post-operative VAS for pain (MD 1.10; CI 0.57-1.63, p<0.0001) and a benefit for using a nephroscope in convalescence (MD 1.90 days; CI 2.82-0.98, p<0.0001; Supplementary Figure 4)[32]. There were no unplanned procedures or major complications. A low late-complications event rate was reported (3.4% overall) and no difference (RR 0.97; CI 0.91-1.04, p=0.38; low QoE). No patient received re-treatment (low QoE).

Two NRS compared TUCL using resectoscope vs. cystoscope (n=171). Outcomes were similar except procedure duration: using a resectoscope was significantly quicker (MD 10.6 minutes; CI 17.2-4.0, p<0.01 and MD 16.6 minutes; CI 23.51-9.69, p<0.0001 [22, 35]. One NRS used laser in both cases [22] whilst the other used laser with a resectoscope and pneumatic with a cystoscope [35].

TUCL Lithotripsy modalities:

Five NRS compared TUCL lithotripsy modalities (n=385; Supplementary Figure 5) [21, 22, 27, 36, 37]. No difference in SFR was found between any lithotripsy modality (mechanical, laser, pneumatic, ultrasonic, EHL or washout alone).

Laser lithotripsy was faster than pneumatic lithotripsy (MD 16.6 minutes; CI 23.51-9.69, p<0.0001) in one NRS (n=62) however laser used a resectoscope and pneumatic used a cystoscope [22]. High (100W; 3.5J, 5Hz) power laser was not significantly faster than low (30W; 2.5J, 5Hz) power (MD 11.8 minutes; CI -8.1-31.7, p=0.25) in an NRS (n=56)[21].

Unplanned procedures and major postoperative complications were low rate events and were not significantly different between lithotripsy modalities, although one NRS suggested they might be higher with EHL or mechanical lithotripsy than pneumatic or ultrasonic lithotripsy [37]. All outcomes had very low QoE.

Studies in Children

The QoE was assessed as very low for all outcomes for all comparisons. Forest plots are available in Supplementary Figures 6-10.

SWL vs. CL and SWL vs. TUCL

One large NRS (n=447) compared SWL (for <1cm stones), TUCL (1.1-3cm stones) and CL (>3cm stones or previous failed SWL or TUCL) [38]. SFR was lower in SWL than CL or TUCL ($p<0.00001$, $p<0.00001$). Length of hospital stay appeared to favor SWL and TUCL over CL, but detailed descriptors were not reported[20]. No other outcomes were reported for SWL.

TUCL vs. CL

Two NRS compared TUCL and CL: cohorts had unmatched stone sizes; meta-analysis was not deemed appropriate [20, 39]. TUCL had a significantly lower SFR (93.5% vs. 100%, $p=0.02$) in one study [20] and equal in the other (100% vs. 100%). Length of hospital stay and duration of procedure appeared to favor TUCL [20]. Unplanned procedures and late complications were not significantly different in one NRS which reported no major post-operative complications, recurrences or re-treatments[39]. “Complications” were reported without further details (despite contacting the authors) in the other NRS which favored TUCL (11.5% vs. 29%, $p=0.003$) [20].

PCCL vs. CL

Two NRS compared PCCL and CL (n=139): cohorts had unmatched stone sizes; meta-analysis was not deemed appropriate[39, 40]. There was no significant difference in SFR (100% in all), unplanned procedures (6.2% vs. 1.4%) or major post-operative complications (4.6% vs. 0%).

A benefit for PCCL was suggested for length of hospital stay (MD 6d), procedure (MD 20min) and catheterization (8d) in one study however other descriptors (standard deviation and p-values) were not reported[40]. There were no late complications, recurrence or re-treatment.

PCCL vs. TUCL

One NRS compared PCCL vs. TUCL (n=54): age and stone size determined intervention choice[39]. All patients were rendered stone-free. PCCL appeared to have a clinically significantly higher rate of unplanned procedures (14.8% vs. 3.7%, $p=0.19$) and major post-operative complications (11.1% vs. 0%, $p=0.19$). There was one urethral stricture, which occurred in the TUCL group ($p=0.50$). There was no difference in intra-operative complications [39].

TUCL with laser vs. pneumatic lithotripsy

One small quasi-RCT compared TUCL with laser vs. pneumatic lithotripsy: all 25 children were stone-free ($p=1.00$; defined as <3mm fragments on X-Ray and ultrasound at 3

weeks)[19]. There was no significant difference in unplanned procedures or major complications (RR0.36; CI 0.02-8.05, p=0.52) for both. There were no late complications or re-treatments. Length of hospital stay (MD 0.60d; CI 1.19-0.01, p=0.05) and procedure (MD 1.10; CI -10.33-8.13, p=0.82) were similar overall. However, for <1.5cm stones there was a suggestion of a slightly quicker procedure using laser (MD 6.0 minutes (1.68-0.32, p=0.04)[19].

Tubeless CL vs. Traditional CL

One large NRS (n=176) compared tubeless CL (no catheter or drain) and traditional CL[38]. SFR was not available, despite contacting authors. Unplanned procedures and major complications both suggested a clinically significant benefit for traditional CL (6.6% vs. 0%, p= 0.22). However, all patients requiring an unplanned post-operative procedure had had previous surgery or urine infection. Hospital stay was shorter with tubeless CL (2.0 vs. 6.0 days, p<0.01). Urethral strictures were a very low rate event (0.56% overall) so were not robustly compared although appeared lower with tubeless CL (0% vs. 2.5%, p=0.16).

4. Discussion:

This study provides the first ever systematic review and meta-analyses on the treatment of BS and has informed the first national or international guideline on BS[41]. Complete removal of a stone constitutes the most important outcome when evaluating the efficacy of any stone treatment. Our results indicate that SWL was less effective than endoscopic or open surgery in both adults and children in terms of SFR, although the QoE was low or very low. An RCT on small (<2cm) BS in adults found ≤ 3 SWL sessions were required to equal the SFR achieved in one TUCL treatment [42]. It remains unclear whether SWL technique optimisation might improve SFR.

Our results also suggest that the adoption of endoscopic treatments (TUCL and PCCL) have reduced the morbidity of BS procedures, in terms of hospital stay, convalescence and catheterization time compared to CL, whilst providing comparable SFR for both adults and children. However, overall QoE for SFR ranged from moderate to very low. Included studies reported inconsistent timing and modality of stone-free status assessment. Only three RCTs [18] [19] [18] and one NRS [20] defined stone-free status. It is unclear whether higher quality studies would be likely to find different outcomes.

Interventions were not robustly compared for differing stone size or, in children, age. It is unclear whether SFR are impaired for larger stones in endoscopic treatments or if TUCL is less effective and/or more morbid in infants. However, one RCT on endoscopic surgery in adults included >4cm stones, with an average of 6cm BS yet achieved an overall 97% SFR[31]. Higher quality RCTs stratified by stone size and patient characteristics are required.

SFR were not significantly different for endoscopic techniques. However, the results on secondary outcomes from this systematic review and meta-analyses were informative. TUCL is superior to PCCL in terms of procedure duration and hospital stay (from meta-analyses) and also pain and convalescence (from a single RCT) [32] in adults. Higher quality trials are likely only to strengthen these findings.

Our meta-analysis of 4 RCTs and the results of two NRS [22, 35] demonstrated that TUCL is quicker when a nephroscope or a resectoscope respectively were used compared to a cystoscope in adults. This suggests that using a scope with continuous flow shortens TUCL procedure time, with equal SFR.

The type and rate of complications related to different therapeutic approaches are important in treatment decision-making. Complications were only classified or defined by three included studies [21-23] although we were able to apply CD classification using published data or by contacting authors. However, major post-operative complications, unplanned procedures and late complications (urethral strictures) are low incidence events and therefore the included studies are likely to have been underpowered to detect a difference between procedures, so could not be robustly assessed in this systematic review.

Overall, there were no differences in unplanned procedures and major post-operative complications (low QoE) between PCCL and TUCL in adults. PCCL appeared to have a higher rate of major post-operative complications (14.8%) and unplanned procedures (11.1%) than TUCL in a small NRS in children [39], although this event rate wasn't replicated in a larger NRS comparing PCCL and CL in children (0% and 0%) [43].

Major post-operative complications, including bladder perforation and bleeding, may be higher when using mechanical lithotripsy (e.g. Mauermeyer, Lithotrite) or EHL compared with pneumatic or laser lithotripsy in adults [21, 37]. SFR were not significantly different between lithotripsy modalities. We therefore concluded that the optimum lithotripsy modality is that with which the individual surgeon has the most experience.

Major post-operative complications and unplanned procedures were clinically significantly increased in tubeless (no catheter or drain) vs. traditional CL in a large NRS in children [38]. However, only patients with previous infection or surgery developed major complications. Furthermore, tubeless CL reduced hospital stay and catheterization time and is therefore preferable in carefully selected children with endemic BS [38].

The most important long-term complication of BS treatments is urethral stricture formation, which was the only reported late complication. Follow-up was typically ≥ 1 year in RCTs, many of which included routine uroflowmetry screening: suggesting that urethral strictures would be detected. However, the incidence of urethral strictures among adults included in RCTs was very low (overall 2.8% with TUCL) and was not significantly different for TUCL vs. PCCL [26, 30, 44]. This incidence is similar to that reported following TURP (2.2-9.8%) [45, 46].

Whether PCCL or TUCL (using a cystoscope or nephroscope) was performed did not affect urethral stricture formation rates, however included studies were underpowered for this outcome. Therefore, the risk of urethral stricture formation should be considered for individual patients.

This systematic review did not consider conservative or medical management of BS, BS in patients with augmented or reconstructed bladders or the concomitant treatment of benign prostatic hyperplasia (BPH). The literature supports concomitant BS and BPH treatment: without increasing major complications compared to BPH treatment alone [41, 47, 48]. We found no studies comparing conservative or medical BS management to procedural intervention. Asymptomatic migratory BS in adults may be left untreated, especially if < 1 cm [41]. However, primary and secondary bladder stones are usually symptomatic, unlikely to pass spontaneously and thus active treatment is typically required [13].

Our systematic review indicates that further research comparing the benefits and harms of treatments for BS in adults and children is required, particularly comparing minimally invasive treatments with CL, which should stratify patients by stone size and characteristics (including age) as well as define and robustly measure outcomes.

5. Conclusions

This systematic review demonstrates that endoscopic, trans-urethral and percutaneous BS treatments are associated with comparable SFR but with a shorter operation and catheterization duration as well as shorter length of hospital stay, compared to open cystolithotomy in both adults and children. SWL appears to offer inferior SFR when compared to other procedures but offers the shortest duration of hospital stay. TUCL using an instrument with continuous flow (e.g. a nephroscope or resectoscope) is quicker than when using a cystoscope in adults. Mechanical, pneumatic and laser lithotripsy appear equivalent

for endoscopic bladder stone treatments in adults and children, although there is a lack of robust evidence comparing modalities. Tubeless CL (without a drain or catheter) can be safely performed in children with endemic bladder stones and no prior bladder surgery or infections. There is an urgent need for high quality research comparing treatment modalities for differing stone sizes and in very young children.

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