

Assessment of the incidence and risk factors of postoperative urosepsis in patients undergoing ureteroscopic lithotripsy

Krystian Kaczmarek, Marta Jankowska, Jakub Kalembkiewicz, Jakub Kienitz, Ositadima Chukwu, Artur Lemiński, Marcin Słojewski

Department of Urology and Urological Oncology, Pomeranian Medical University, Szczecin, Poland

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Corresponding author

Krystian Kaczmarek
Pomeranian Medical
University
Department of Urology
and Urological Oncology
72 Powstańców
Wielkopolskich Street
70-111 Szczecin, Poland
k.kaczmarek.md@gmail.com

Introduction Ureteroscopic lithotripsy (URSL) is an approved, minimally invasive, low-risk procedure for urolithiasis treatment. However, some patients may develop urinary tract infection (UTI) post-procedure, eventually leading to urosepsis. Determining the predictors of infection after URSL would help identify patients at a high risk of urosepsis, thereby enabling the early implementation of effective treatment. Therefore, we aimed to establish the incidence and predictors of urosepsis after URSL.

Material and methods We assessed 231 patients who underwent URSL using a holmium laser. The incidence of urosepsis during the 30-day post-treatment period was analysed, and potential predictors of urosepsis, including patient characteristics and individual clinical factors, were examined.

Results Statistical analysis revealed that 16.88% of patients had a confirmed positive urine culture before the procedure. Post-procedure urosepsis occurred in 4.76% of patients. Univariable analysis revealed that 3 factors were significantly associated with the risk of postoperative urosepsis: double-J stent insertion before URSL, pre-operative positive urine culture, and MDR pathogen found preoperatively. In multivariable analysis, only positive urine culture remained significantly associated with the risk of urosepsis after URSL.

Conclusions Patients with positive urine culture before URSL are at significantly higher risk of urosepsis in the postoperative period. Hence, urine culture should be routinely performed before planned endoscopic urolithiasis treatment.

Key Words: urolithiasis ↔ ureteroscopic lithotripsy ↔ URSL ↔ postoperative complications
↔ urosepsis ↔ urinary tract infection ↔ Ho:YAG laser

INTRODUCTION

Urinary stone disease remains the most common urological problem even though it has been known for centuries. Currently, epidemiology, risk factors, and the mechanisms of stone formation are well-documented. The aetiology includes geographical, climatic, ethnic, dietary, and genetic factors [1]. Additionally, urolithiasis incidence depends on various disorders such as obesity, diabetes mellitus, or hyperparathyroidism [2]. Despite the numerous studies conducted in this field and the vast knowledge of the disease, the incidence of urolithiasis is still signifi-

cantly increasing globally [3, 4, 5]. According to epidemiological studies, its prevalence in adults ranges from 1 to 20%, which may increase to as much as 25% in developing countries [2, 5, 6].

Stones in the urinary tract might be classified based on their location. According to previous studies, urolithiasis mainly affects the upper urinary tract [7]. The incidence in kidneys and ureters is 75.08% and 13.62%, respectively, whereas 9.56% of stones are diagnosed in the vesicoureteric junction [8]. Stones located in the bladder are considerably less frequent in populations with high socioeconomic levels, with a prevalence of less than 10%.

The locality of the stone in the urinary tract greatly determines the treatment approach. Ureteroscopy (URS) has already been established as a treatment option for urolithiasis. To date, many studies have reported its increasing role not only in treating standard ureteric and renal calculi but also in patients with more complex stone disease or with co-morbidities [9]. Ureteroscopic lithotripsy (URSL) is the method of first choice for the management of ureteral stones, with an overall stone-free rate between 77% and 97.5% [10]. URSL does not require breaking the anatomical barriers of the urinary system. Therefore, it is relatively safe and easy to perform. According to the current European Association of Urology (EAU) Guidelines, flexible URS should be used in cases where percutaneous nephrolithotomy or SWL are not an option (even for stones >2 cm). Additionally, they strongly recommend holmium:yttrium-aluminum-garnet laser (Ho:YAG laser) lithotripsy as the most effective treatment for all kinds of stones [11]. However, despite its many advantages, this procedure is not free from complications, including the postoperative development of urinary tract infection (UTI) [12]. In some scenarios, UTI after URSL might progress to urosepsis and further to septic shock with severe organ failure or even death [5]. Therefore, a prompt diagnosis of urosepsis is mandatory to administer effective and timely treatment. Thus, familiarity with risk factors for urosepsis might help to identify patients who are at a high risk of this serious complication. So far, many studies have investigated complications following URSL and identified risk factors of post-URSL infectious complications, including urosepsis [12–16]. However, considering the changing pattern of urolithiasis worldwide, these factors should be continuously analysed and established in each urological department. Therefore, in the presented study, we aimed to assess the incidence of urosepsis in patients undergoing URSL at the Department of Urology and Urological Oncology of Pomeranian Medical University in Szczecin. Furthermore, we investigated the potential risk factors for urosepsis that could be used as predictors of its development in the postoperative period.

MATERIAL AND METHODS

Study methods

This single-centre, retrospective study was exempt from further review by the Institutional Review Board (Bioethical Committee) of the Pomeranian Medical University, Szczecin, Poland, due to the nature of the study, and it was conducted according

to the regulations set forth in the Declaration of Helsinki. Consent for research participation was routinely obtained from all patients involved for the use of their anonymized medical data collected during hospitalization. The study population included all consecutive patients with urinary stone disease who underwent URSL in 2022 at our Urology Department.

Preoperative evaluation

Patients qualified for elective procedures underwent preoperative assessment one week before their operation and had a routine mid-stream sample of urine (MSSU) sent for culture. Patients with a positive MSSU were treated with a 5-day course of an appropriate antibiotic according to their sensitivities. Antibiotic therapy was continued throughout hospitalization up to a complete 7-day course. Repeat samples of urine were not routinely obtained to confirm clearance if there were no symptoms of ongoing infection. In cases of emergency surgery, MSSU was sent for culture on the day of admission, and prophylactic antibiotic therapy was administered. Cefuroxime was used in a prophylactic setting and was switched to targeted therapy if the urine culture was positive. Abdominal ultrasonography and non-contrast-enhanced computed tomography (CT) were performed in all patients before URSL to assess the presence of hydronephrosis and stone burden. For each patient, the following preoperative data were collected from medical records: age, sex, body mass index, concomitant diseases (diabetes mellitus and hypertension), previous history of urosepsis and endoscopic urological treatment, results of urinalysis and urine culture, stone size, location, and laterality, number of stones, stone density (measured in Hounsfield units), and hydronephrosis. Additionally, procedural time, length of stay (LoS), and the presence of residual fragments after URSL were evaluated. Moreover, if urosepsis occurred, blood cultures were collected to identify the pathogen and analyse the most common aetiological factors of post-URSL urosepsis in our department.

The surgical technique

All URSL procedures were performed with a semi-rigid 8.6/9.8F ureteroscope (Olympus) under general or spinal anaesthesia. To improve vision during the endoscopy a manual irrigation pump was used. After identification of the ureteral orifice, a flexible-tip 0.035-inch guidewire was introduced into the ureter and followed into the renal collecting system under X-ray supervision. Then, using guidewires, ureteroscopy was performed until ureteral

stones were localized. A single-use laser fibre and the Ho:YAG laser device were used for lithotripsy. The energy was applied at the setting of 1.0–1.5 J at a pulse rate of 10–15 Hz. A 6F double-J stent was routinely placed at the end of URSL and was extracted 5 days after the operation.

Follow-up

After the endoscopic procedure, the patients were prospectively observed for 30 days. The incidence of postoperative urosepsis was noted. Parameters such as temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 beats/minute, respiratory rate >20 breaths/minute or $\text{PaCO}_2 <4.3$ kPa, and white blood cell (WBC) count over $12 \times 10^9/\text{L}$ or below $4 \times 10^9/\text{L}$ were indicators of possible sepsis [17]. However, because sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, the diagnosis of urosepsis was based on the current definition. Therefore, organ dysfunction was identified as an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, with co-occurrence of confirmed or suspected infection of urinary tract origin [18, 19, 20]. The infection of urinary tract origin was confirmed by positive urine culture, whereas suspected UTI was defined as sterile pyuria (>400 WBC/ μL) with inhibitory substances present (in-keeping with antibiotic use) and a C-reactive protein (CRP) over 10 mg/L, or the above plus a positive blood culture [21].

Statistical analysis

Two independent reviewers checked the obtained data for internal consistency. Descriptive statistics included mean and standard deviation (SD) for normally distributed data. Qualitative data were presented as numbers. Univariable and multivariable logistic regression analyses were used to examine the association of collected variables with the incidence of urosepsis after URSL. The odds ratios (ORs) were estimated with their 95% confidence intervals (CIs). V-fold cross-validation was used to build logistic regression models. The calibration was assessed with the Hosmer-Lemeshow goodness of fit test. We considered p value < 0.05 as statistically significant, and all p values were two-sided. All tests were performed using StatSoft statistical software, version 13.5 (StatSoft, Inc., Tulsa, OK, USA).

RESULTS

A total of 231 patients undergoing URSL were enrolled in this study. The mean age of the patients

Table 1. Patients' baseline characteristics.

Variables	Study population (n = 231)	% of the study population
Age, years		
Mean	56.41	–
SD	13.72	–
Gender		
Female	92	39.83
Male	139	60.17
BMI, kg/m ²		
<30	174	75.32
≥ 30	57	24.68
Hypertension		
No	119	51.52
Yes	112	48.48
Diabetes mellitus		
No	192	83.17
Yes	39	16.88
Length of stay, days		
Mean	2.7	–
SD	1.32	–
Previous history of endoscopic treatment of urolithiasis		
No	150	64.94
Yes	81	35.06
Previous history of urosepsis		
No	220	95.24
Yes	11	4.76
Positive preoperative culture		
No	192	83.12
Yes	39	16.88
Multidrug-resistant pathogen		
No	223	96.54
Yes	8	3.46
Hydronephrosis		
No	178	77.06
Yes	53	22.94
DJ/PCN		
No	186	80.52
Yes	45	19.48
No. stones		
Single	182	78.79
Multiple	49	21.21
Maximum diameter of calculi, mm		
≤ 10	148	64.07
>10	83	19.48
Location of calculi		
Upper ureter (including UPJ)	59	25.54
Middle ureter	55	23.81
Lower ureter	83	35.93
Laterality of calculi		
Right	88	38.10
Left	138	59.74
Bilateral	5	2.16
Mean CT attenuation value of calculi, HU		
<500	95	41.13
500–1000	95	41.13
>1000	41	17.75
Presence of residual fragments after URSL		
No	123	53.25
Yes	108	46.75

Table 1. *Continued*

Variables	Study population (n = 231)	% of the study population
Operative time, minutes		
<30	117	50.65
30–60	86	37.23
>60	28	12.12
Postoperative urosepsis		
No	220	95.24
Yes	11	4.76

SD – standard deviation; BMI – body mass index; DJ – double-J stent; PCN – percutaneous nephrostomy; UPJ – ureteropelvic junction; CT – computer tomography; HU – Hounsfield units; URSL – ureteroscopic lithotripsy

Table 2. *Pathogens isolated from blood culture in patients with urosepsis.*

Pathogen causing urosepsis	Population with urosepsis (n = 11)	% of the urosepsis population
Escherichia coli	4	36.36
Pseudomonas aeruginosa	3	27.27
Klebsiella pneumoniae	1	9.09
Klebsiella oxytoca	1	9.09
Enterococcus faecalis	1	9.09
Proteus mirabilis	1	9.09

was 56.41 ± 13.72 years, and the female-to-male ratio was 2:3. The general characteristics of the study population are presented in Table 1. Lifestyle diseases, which can be a risk factor for urinary stone disease, such as obesity, hypertension, or diabetes mellitus were present in 24.68%, 48.48%, and 16.88% of the study population, respectively. The length of stay deviated between 2 and 14 days, with a mean duration of 2.7 ± 1.32 days.

During the 30-day follow-up of the study population, 11 patients (4.76%) developed urosepsis after URSL. Of these 11 patients, 6 were male and 5 were female, with a mean age of 66.66 years. Out of 11 patients with urosepsis, 3 (27.27%) had obesity (BMI >30 kg/m²), 8 (72.72%) had hypertension, 4 (36.36%) had diabetes mellitus, and 9 (81.81%) had a previous history of endoscopic treatment of urolithiasis. However, only one patient with post-URSL urosepsis had been previously diagnosed with urosepsis (p = 0.499). The most common pathogen identified in the urosepsis population was Escherichia coli. Other pathogens isolated from blood culture are presented in Table 2. Whereas a multidrug-resistant (MDR) pathogen was found in 3 out of 11 patients. Urosepsis in all patients was diagnosed within 2 days of the surgery. All patients with post-URSL urosepsis suffered from fever > 38°C. Additionally, other clinical symptoms

Table 3. *Multivariable statistical analysis regarding the assessment of the association between the analysed parameters and the development of urosepsis in the 30-day post-procedure period.*

Variables	OR	Upper 95% CI	Lower 95% CI	p-value
Age	1.010	0.966	1.056	0.661
Gender				
Male	Ref.			
Female	1.274	0.377	4.303	0.967
BMI, kg/m ²				
<30	Ref.			
≥30	1.153	0.295	4.500	0.838
Hypertension				
No	Ref.			
Yes	2.974	0.769	11.509	0.114
Diabetes mellitus				
No	Ref.			
Yes	3.020	0.839	10.869	0.091
Previous history of urosepsis				
No	Ref.			
Yes	2.100	0.244	18.052	0.499
Positive preoperative culture				
No	Ref.			
Yes	6.800	1.962	23.573	0.003
Multidrug-resistant pathogen				
No	Ref.			
Yes	16.125	3.269	79.541	0.001
Hydronephrosis				
No	Ref.			
Yes	0.323	0.040	2.584	0.287
DJ/PCN				
No	Ref.			
Yes	3.750	1.090	12.898	0.036
No. stones				
Single	Ref.			
Multiple	0.818	0.171	3.915	0.801
Maximum diameter of calculi, mm				
≤10	Ref.			
>10	1.020	0.290	3.592	0.975
Location of calculi				
Upper ureter (including UPJ)	Ref.			
Middle ureter	1.077	0.208	5.575	0.930
Lower ureter	1.197	0.275	5.214	0.811
Laterality of calculi				
Right	Ref.			
Left	6.797	0.855	54.060	0.070
Bilateral	0.000	0.000	0.000	0.998
Mean CT attenuation value of calculi, HU				
<500	Ref.			
5000–1000	0.791	0.206	3.042	0.733
>1000	0.923	0.172	4.964	0.926
Operative time, minutes				
<30	Ref.			
30–60	0.669	0.162	2.752	0.577
>60	1.423	0.272	7.457	0.676

OR – odds ratio; CI – confidence interval; BMI – body mass index; DJ – double-J stent; PCN – percutaneous nephrostomy; UPJ – ureteropelvic junction; CT – computer tomography; HU – Hounsfield units

manifested in urosepsis patients included chills, nausea, vomiting, lower abdominal pain, and haematuria. Blood tests were performed in all symptomatic patients. In 10 cases WBC count was over $12 \times 10^9/L$. Whereas in one case the WBC count was below $4 \times 10^9/L$. If urosepsis was suspected, volume resuscitation was administered along with intravenous antibiotic therapy with a broad spectrum of antimicrobial activity. All patients with diagnosed urosepsis had implantation of a double-J ureteral stent at the time of URSL. One patient did not respond well to conservative treatment and presented hydronephrosis in ultrasonography despite the inserted double-J stent. In this patient, the ureteral stent was extracted and a new one was implemented. No patient presented vasopressor-refractory shock and required further treatment in the intensive care unit. Moreover, no patient died during the 30-day follow-up.

Univariable analysis of the obtained data revealed that 3 factors were significantly associated with the risk of postoperative urosepsis, which increased if the double-J stent was inserted before URSL (OR 3.750; 95%CI 1.090–12.898; $p = 0.036$), the patient had a positive urine culture (OR 6.800; 95%CI, 1.962–23.573; $p = 0.003$) and MDR pathogen was found preoperatively (OR 16.125; 95%CI, 3.269–79.541; $p = 0.001$), Table 3. To further determine the risk factors for urosepsis after URSL, variables significantly associated with the risk of postoperative urosepsis in univariable analysis were selected for multivariable analysis. In the further analysis, only positive urine culture remained significantly associated with the risk of postoperative urosepsis incidence, with corresponding OR 6.800; 95%CI 1.962–23.573; $p = 0.003$.

DISCUSSION

The URSL is the first common application of upper urinary tract endoscopy. In the evolution of this technique, new instruments are being systematically introduced. Smaller and more precise instruments were continuously popularized to cause less trauma to normal tissues. Progress in endourology resulted in the introduction of fiberoptic-based rigid endoscopes with a diameter of 8 F on average. This facilitates the passing of a ureteroscope through a narrow and delicate distal ureter without forceful balloon dilations [22, 23, 24]. Currently, small rigid ureteroscopes combined with both laser and pneumatic lithotripters are used to treat ureteral stones. Mastery of this technique has allowed us to proceed with endourology while minimizing complications. However, despite the new, smaller, semirigid ureteroscopes, this minimally invasive surgery can be

traumatic. The overall rate of complications after URSL varies between 9% and 25% [25]. According to the available literature and our own experience, most intraoperative incidents such as mucosal injury, ureteral perforation, extra-ureteral stone migration, or bleeding require only double-J insertion. However, early postoperative adverse events usually are more serious and often require readmission. Urosepsis is one of the most life-threatening possible consequences of URSL. It is noted in as many as 10% of patients in early post-operative follow-up and is related to the underlying pathology and morbidity of patients rather than to the applied endourological treatment. Therefore, considering changing trends in the prevalence and composition of urinary stones, patient demographics and risk factors of urosepsis after URSL should be routinely evaluated to enable adequate and timely treatment of urosepsis. Thus, in our study, we reassessed the influence of known preoperative and intraoperative factors on the risk of urosepsis after endoscopic treatment of ureteral stones.

The urosepsis in our cohort was diagnosed in 11 of 231 patients, constituting 4.76% of the study population. According to the largest systematic review with meta-analysis, performed by Bhojani et al., the urosepsis ratio after URSL varies from 0.2% to 17.8%, with a pooled incidence of 5.0% (95%CI 2.4–8.2) [13]. However, the studies included in this meta-analysis differ in diagnostic criteria of urosepsis, and some studies restricted the follow-up to in-hospital stay. Additionally, urosepsis occurred in the same number of patients after performing URSL in our clinic as the patients reporting its occurrence in their past medical history. Nevertheless, among 11 patients with urosepsis diagnosed in the 30-day follow-up, only one subject had previously been diagnosed with this condition. Statistical analysis revealed that a previous history of urosepsis did not significantly contribute to the more frequent incidence of urosepsis in our study population (OR 2.100; 95%CI 0.244–18.052; $p = 0.499$).

Statistical analysis also revealed that positive MSSU before URSL was significantly associated with the incidence of post-surgery urosepsis. These results are consistent with studies conducted by other researchers. Ma et al. in their meta-analysis reported that patients with positive preoperative urine culture were at a higher risk of septic complications, with pooled OR 2.18; 95%CI (1.34–3.57) [14]. These results may be attributed to the fact that bacterial infection of the urinary tract combined with the insertion of the ureteroscope during the procedure and normal saline washing enables many bacteria to enter the upper urinary tract and the bloodstream through injuries in the mucous membrane. What is more,

it is thought that performing retrograde pyelography at the time of initial management of obstructing ureteral stones with concomitant UTI might cause pyelovenous backflow of bacteria, thereby additionally accelerating the risk of urosepsis [26]. Moreover, urologists should always bear in mind that in the setting of obstructing ureteral stones renal fornical rupture might be present before URSL, which in the case of UTI might be associated with severe morbidities, including perinephric abscesses and urosepsis [27].

Another explanation for the higher risk of urosepsis in patients with positive urine culture after URSL, despite definitive antibiotic therapy and controlling UTI before surgery, might be the presence of the MDR pathogen. Bai et al. did not find a significant association between positive preoperative urine cultures and post-URSL urosepsis. However, they observed that positive preoperative MDR urine culture was significantly associated with postoperative urosepsis despite proper preoperative antibiotic therapy, with corresponding OR 5.090; 95%CI (1.312–19.751). Additionally, they confirmed their results in matched-pair analysis [28]. In our study, overall, 39 (16.88%) of 231 patients had a positive preoperative urine culture. Out of these 39 patients, 8 (20.5%) had MDR pathogens. In the non-urosepsis group, 5 (2.27%) patients had a positive pre-operative MDR urine culture. In the urosepsis group, 3 (27.3%) patients had a positive preoperative MDR urine culture. However, univariable logistic regression analysis indicated that MDR pathogen-related UTI before URSL was a risk factor of postoperative urosepsis, with corresponding OR 16.125; 95%CI (3.269–79.541).

In the univariable analysis, we found that preoperative urinary tract decompression by ureteral stent or nephrostomy tube significantly increased the risk of post-URSL urosepsis, with corresponding OR 3.750; 95%CI (1.090–12.898). However, this result was not confirmed in multivariable analysis. Comparable results were also presented by other authors. Pre-URSL stenting was a crucial determinant of UTI following URSL as well as for urosepsis, with corresponding OR 1.91; 95%CI (1.26–2.91) and 3.04; 95%CI (1.67–5.54), respectively [29, 30]. This is mainly attributed to a biofilm formation on the stents [31, 32]. The biofilm is characterized by multiple bacterial layers that are additionally protected by a thick exopolysaccharide layer excreted by the bacteria. The presence of the protective layer results in significant resistance to antimicrobial therapy. Moreover, such colonization is also observed even when the stent is placed under sterile conditions and is mostly associated with dwelling time [32]. An additional mechanism that leads to the more frequent development of urosepsis with current ureteral

stents is vesicoureteral reflux (VUR). The frequency of naturally occurring VUR is not fully investigated [33], but VUR occurring with a current double-J stent is a common finding. This mechanism promotes the spread of infection from the bladder to the renal collecting system [34]. Moreover, VUR might also increase intrapelvic pressure, which additionally promotes the entry of pathogens into the renal parenchyma [35]. Furthermore, the presence of the stent reduces the peristaltic movements of the ureteral musculature, which might also promote bacterial movement to the upper urinary tract [35].

Despite these interesting findings, our study has several limitations. Firstly, this is a single-centre study with a relatively small sample size. Conducting similar studies in other academic centres would enable a more profound and thorough analysis of the problem presented in our study and more reliable conclusions to be drawn. Secondly, our study was restricted by constraints inherent to the retrospective nature of the data analysis. Therefore, we were unable to control all preoperative confounding factors that may have influenced the risk of postoperative urosepsis such as stone composition, stone impaction, stone culture, or pelvis urine culture. Additionally, our study population included only patients with ureteral stones. Hence, we did not analyse the influence of other stone locations in the urinary tract on the incidence of urosepsis after endoscopic treatment. Finally, we did not analyse the stone-free rate, which may also have had a significant impact on patients' postoperative recovery. Authors should discuss the results and how they can be interpreted from the perspective of previous studies and the working hypotheses. The findings and their implications should be discussed in the broadest possible context. Future research directions may also be highlighted.

CONCLUSIONS

Patients with positive urine culture before URSL are at significantly higher risk of urosepsis in the postoperative period. Therefore, urine culture should be routinely performed on every patient before the planned endoscopic treatment of urolithiasis. Moreover, targeted antibiotic therapy before URSL does not eliminate this risk. Therefore, urologists should have increased awareness of this serious complication despite adequate preoperative treatment.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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