



Predictors of Urinary Infections and Urosepsis After Ureteroscopy for Stone Disease: a Systematic Review from EAU Section of Urolithiasis (EULIS)

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Abstract

Purpose of Review To present the latest evidence related to the predictors of urinary tract infections (UTIs) and urosepsis after ureteroscopy (URS) for stone disease.

Recent Findings Our review suggests that almost half of all post-URS complications are related to infectious complications although reported rates of urosepsis were low. The use of antibiotic prophylaxis, treatment of pre-operative UTI, and low procedural time seem to reduce this risk. However, the risk is higher in patients with higher Charlson comorbidity index, elderly patients, female gender, long duration of pre-procedural indwelling ureteric stents and patients with a neurogenic bladder and with high BMI.

Summary Infectious complications following ureteroscopy can be a source of morbidity and potential mortality. Although majority of these are minor, efforts must be taken to minimise them especially in high-risk patients. This includes the use of prophylactic antibiotics, limiting stent dwell and procedural time, prompt identification and treatment of UTI and urosepsis, and careful planning in patients with large stone burden and multiple comorbidities.

Keywords Ureteroscopy · Sepsis · Urosepsis · UTI · Complication · Stent · Urine culture · Antibiotic · Access sheath

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Introduction

The prevalence and incidence of kidney stone disease (KSD) have been increasing globally in the last 50 years [1]. In England, national data from 2006/2007 to 2013/2014 shows that there has been an increase in the lifetime prevalence of urolithiasis-based admissions and intervention from the historically reported 10 to 14% [2]. This is due to a rise in metabolic syndrome, lifestyle changes but also partly due to global warming as higher monthly ambient temperatures are positively associated with incidence of kidney stones [3]. Treatment options include ureteroscopy (URS), shock wave lithotripsy (SWL) and percutaneous nephrolithotomy (PCNL) [4–6].

Published data from the last 15–20 years has shown a steep rise in the use of URS and PCNL, while the use of SWL and open surgery have declined [7, 8]. Moreover, URS has shown to achieve higher stone-free rates than SWL and lower complication rates compared with PCNL [4, 5].

Following URS, the overall rate of complications varies between 9 and 25% although the majority of these are minor and does not require intervention [9–11]. Infectious complications ranging from fever, systemic inflammatory response

syndrome to urinary tract infection (both upper and lower) are some of the more common post-ureteroscopy complications, alongside haematuria and post-operative pain [11], with overall complication rates of up to 25% [12, 13]. As ureteroscopy is being performed in increasing numbers with the rising prevalence of KSD [2], it is to be expected that the rate of infectious post-URS complications is consequently also increasing [13, 14]. Similarly, the indications of ureteroscopy have expanded, and it is now being performed for high-risk patients such as solitary kidneys, paediatrics, pregnancy and upper tract tumours [15–17].

In the literature, there are many small, medium and high-volume prospective studies that have reported on the infectious complications following URS for renal stone disease [18–29]. Some studies have also looked at the risk factors for urinary infections following ureteroscopy and advised on strategies to reduce these risks. However, there is a lack of data on the predictors of post-ureteroscopy infectious complications. We conducted a systematic review of literature looking at the infection-related post-ureteroscopy complications reported from high-volume centres.

Materials and Methods

Search Strategy and Study Selection

The systematic review was performed according to the Cochrane review guidelines and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist from January 2009 to November 2019 for English language articles [30, 31]. The search strategy was

conducted to find relevant studies from the Medline, EMBASE, Scopus, Cochrane Library, CINAHL, Clinicaltrials.gov, Google Scholar and individual urologic journals. The search terms included ‘ureteroscopy’, ‘URS’, ‘complications’, ‘urosepsis’, ‘urinary tract infection’, ‘UTI’, ‘retrograde intrarenal surgery’, ‘RIRS’, ‘systemic inflammatory response syndrome’, ‘SIRS’, ‘infection’, ‘bacteraemia’, ‘mortality’ and ‘death’.

A cutoff of 400 patients was set to include studies from high-volume endourological centres with relevant endourological experience. All original studies were included and where more than one article was available, the study with the longest follow-up was included. The review was carried out by two reviewers (SC and BKS) independently, and all discrepancies were resolved with mutual agreement.

Evidence Acquisition

Inclusion criteria:

1. Studies reporting on infectious complications post-ureteroscopy
2. Studies from high-volume endourological centres reporting on a minimum of 400 patients
3. Studies in English language

Exclusion criteria:

1. Reviews, commentaries or studies with less than 400 patients
2. Paediatric population
3. Ureteroscopy performed for non-stone disease

Fig. 1 PRISMA flowchart of the included studies

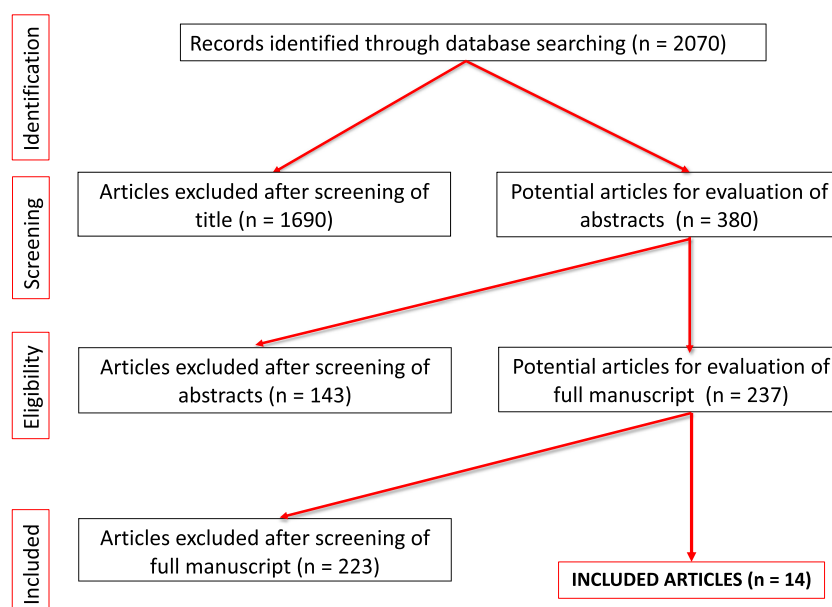


Table 1 Details of the included study

Paper	Year	Author	Country	Journal	Sample size (N = number of procedures)	Male:female ratio	Mean age (years)	Mean BMI
Antibiotic prophylaxis in retrograde ureteroscopy: what strategy should we adopt?	2013	Pricop C, Dorobăţ C, Puia D et al.	Romania	Germes	473	39.5/60.5	46.35	N/A
Post-operative infection rates in patients with a negative baseline urine culture undergoing ureteroscopic stone removal: a matched case-control analysis on antibiotic prophylaxis from the CROES URS global study.	2015	Martov A, Gravas S, Etemadian M et al.	Russia	J Endourol	2650	72/28	46	26.5
Impact of gender on success and complication rates after ureteroscopy.	2015	Özsoy M, Acar Ö, Sarıca K et al.	Austria	World J Urol.	927	70.5/29.4	47	N/A
Unplanned Hospital Return for Infection following Ureteroscopy. Can We Identify Modifiable Risk Factors?	2016	Moses RA, Ghali FM, Pais VM Jr. et al.	Lebanon	J Urol	550	55/45	57	N/A
Analysis of Factors' Association with Risk of Post-operative Urosepsis in Patients Undergoing Ureteroscopy for Treatment of Stone Disease.	2016	James P. Blackmur, Neil U. Maitra, Rajendar R. Marri et al.	UK	J Endourol	462	30/41 (for pre-operative UTI)	59 (for pre-operative UTI)	majority 26–30
Flexible Ureteroscopy for Renal and Proximal Ureteral Stone in Patients with Previous Ureteral Stenting: Impact on Stone-Free Rate and Morbidity	2016	Dessyn JF, Balssa L, Chabannes E et al.	France	J Endourol	497	60.2/39.8	51.2	25.8
Infective complications after retrograde intrarenal surgery: a new standardized classification system	2016	Berardinelli F, De Francesco P, Marchioni M et al.	Italy/Austria	Int Urol Nephrol	403	64/36	53.4	26.4
Ureteric stent dwelling time: a risk factor for post-ureteroscopy sepsis	2017	Nevo A, Mano R, Baniel J et al.	Israel	BJU	1256	69.3/30.7	56	N/A
Complications associated with ureteroscopy (URS) related to treatment of urolithiasis: the Clinical Research Office of Endourological Society URS Global study	2017	Somani BK, Giusti G, Sun Y et al.	Global	World J Urol	11,885	64.7/35.2	49	26.9
Results of day-case ureteroscopy (DC-URS) for stone disease: prospective outcomes over 4.5 years	2017	Ghosh A, Oliver R, Way C, et al.	UK	World J Urol	544	63.8/36.2	56	N/A
Is Neurogenic Bladder a Risk Factor for Febrile Urinary Tract Infection After Ureteroscopy and, if so, Why?	2018	Staufler CE, Snyder E, Ngo TC et al.	USA	Urology	467	N/A	42	N/A
Risk Factors of Infectious Complications after Flexible Uretero-rensoscopy with Laser Lithotripsy.	2018	Cagri Senocak, Cihat Ozcan, Tolga Sahin, et al.	Turkey	Urol J	492	56.3/43.7	42	26.4
Predictive risk factors for systemic inflammatory response syndrome following ureteroscopic laser lithotripsy	2018	Uchida Y, Takazawa R, Kitayama S et al.	Japan	Urolithiasis	469	64/36	61	23.7
Risk Factors for Post-operative Fever and Systemic Inflammatory Response Syndrome After Ureteroscopy for Stone Disease	2019	Southern JB, Higgins AM, Young AJ et al.	USA	J Endourol	3298	49.4/50.6	N/A	31.8

Table 2 Details of infectious and non-infectious complications from the included studies

Paper	Number of procedures (<i>N</i>)	Stone length (mm) (range)	Stone location	Ureteral access sheath utilisation (<i>n</i>) (%)	Mean operating time (mins)	Stone-free rate (%)	Non infective complications (<i>n</i>) (%)
Pricop C, Dorobăt C, Puia D et al.	473	Majority 6–8	Ureteric—100%	N/S	N/S	N/S	N/S
Martov A, Gravas S, Etemadian M et al.	2650	N/S	Ureteric—85.7%; renal—13.2%	N/S	51.3	90.80%	4.75%— intraoperative
Özsoy M, Acar Ö, Sarica K et al.	927	N/S	N/S	N/S	41.4	87%	15.20%
Moses RA, Ghali FM, Pais VM Jr. et al.	550	N/S	N/S	N/S	N/S	N/S	N/S
James P. Blackmur, Neil U. Maitra, Rajendar R. Marri et al.	462	N/S	Ureteric—212 (45.9%); renal—250 (54.1%)	240 (56%)	Majority 30–40 min	83.40%	N/S
Dessyn JF, Balssa L, Chabannes E et al.	497	9.3	Ureteric—126 (25.3%); renal—398 (79.7%); multiple—118 (23.7%)	377 (75.9%)	96.8	68%	N/S
Berardinelli F, De Francesco P, Marchioni M et al.	403	12.21 ± 5.31	N/S	322 (79.9%)	62.42	70.7%	N/S
Nevo A, Mano R, Baniel J et al.	1256	8 (7–12)	N/S	239 (19%)	45	N/S	N/S
Somani BK, Giusti G, Sun Y et al.	11,885	N/S	Ureteric—69.6%; renal—18.1%; mixed—8.9%	2263(19%)	40.7	85.8%	7.2%
Ghosh A, Oliver R, Way C, White L, Somani BK	544	14.3 (10.9–34.3)	Multiple—25.9%; renal—57.9%; ureteric—43.6%; lower pole—28.3%	206 (38%)	46.6	94.2%	9 (1.65%)
Stauffer CE, Snyder E, Ngo TC et al.	467	9.2	N/S	N/S	N/S	N/S	N/S
C Senocak, C Ozcan, T Sahin et al.	492	13 (10–16)	Ureteric—18.0%; renal—81.8%	458 (93.1%)	57	N/S	61 (12.4%)
Uchida Y, Takazawa R, Kitayama S et al.	469	10 (3–47)	Renal—77 (16.4%); ureteric—392 (83.5%)	N/S	64	84.4	N/S
Southern JB, Higgins AM, Young AJ et al.	3298	N/S	Ureteral—32.7%; renal—43.4%; both—23.9%	2183 (66.2%)	49	N/S	N/S

Paper	Stone-free rate (%)	Infectious complications (<i>n</i>) (%)					Total complications (<i>n</i>) (% of <i>N</i>)	Overall grade of complications (<i>n</i>) (% of <i>n</i>)
		Fever	SIRS	UTI	Sepsis	Total		
Pricop C, Dorobăt C, Puia D et al.	N/S	108 (22.8%)	N/S	N/S	N/S	108 (22.8%)	108 (22.8%)	Grade I—108 (22.8%)
Martov A, Gravas S, Etemadian M et al.	90.80%	27 (1.0%)	N/S	17 (0.64%)	N/S	44 (1.66%)	170 (6.41%)	Grade I—26 (1.58%); grade II—16 (0.6%); grade IIIa—6 (0.23%); grade IIIb—7 (0.26%); grade IVa—4 (0.11%); grade IVb—0; grade V—2 (0.08%)
Özsoy M, Acar Ö, Sarica K et al.	87%	N/S	N/S	18 (1.9%)	1 (0.1%)	19 (2.0%)	17.20%	Grade I—51 (5.5%); grade II—21 (2.2%); grade IIIa—26 (2.8%); grade IIIb—60 (6.5%); grade IV—1 (0.1%)
Moses RA, Ghali FM, Pais VM Jr. et al.	N/S	N/S	N/S	19 (3.4%)	N/S	19 (3.4%)	47 (8.50%)	N/S
James P. Blackmur, Neil U. Maitra, Rajendar R. Marri et al.	83.40%	N/S	N/S	N/S	34 (7.4%)	34 (7.4%)		Grade IV—33 (7.1%); grade V—1 (0.22%)
Dessyn JF, Balssa L, Chabannes E et al.	68%	N/S	N/S	N/S	1 (0.2%)	N/S	55 (11%)	

Table 2 (continued)

Berardinelli F, De Francesco P, Marchioni M et al.	70.7%	18 (4.4%)	7 (1.7%)	3 (0.7%)	3 (0.7%)	31 (7.7%)	7.7%	Grade I—16 (3.2%); grade II—37 (5.4%); grade III—0; grade IV—1 (0.2%)
Nevo A, Mano R, Baniel J et al.	N/S	N/S	N/S	N/S	36 (2.9%)	N/S	36 (2.9%)	Grade IV—36 (2.9%)
Somani BK, Giusti G, Sun Y et al.	85.8%	204 (1.72%)	N/S	113 (0.95%)	36 (0.3%)	353 (3.0%)	874 (7.35%)	Grade I—141 (1.2%); grade II—152 (1.3%); grade IIIa—31 (0.26%); grade IIIb—14 (0.12%); grade IVa—11 (0.09%); grade IVb—1 (0.008%); grade IV—5 (0.042%)
Ghosh A, Oliver R, Way C, White L, Somani BK	94.2%	N/S	N/S	4 (0.7%)	9 (1.65%)	13 (2.4%)	22 (4%)	Grade I—8 (1.5%); grade II—12 (2.2%); grade III—1 (0.18%); grade IV—0.18%
Stauffer CE, Snyder E, Ngo TC et al.	N/S	N/S	N/S	10 (2.1%)	N/S	10 (2.1%)	10 (2.1%)	Clavien I—10 (2.1%)
C Senocak, C Ozcan, T Sahin et al.	N/S	14 (2.8%)	23 (4.7%)	N/S	5 (1.0%)	42 (8.5%)	22.1%	N/S
Uchida Y, Takazawa R, Kitayama S et al.	84.4	42 (8.9%)	27 (5.7%)	N/S	1	70 (14.9%)	70 (14.9%)	Grade I—42 (8.9%); grade II—27 (5.7%); grade IV—1 (0.2%)
Southern JB, Higgins AM, Young AJ et al.	N/S	229 (6.9%)	N/S	N/S	N/S	229 (6.9%)	229 (6.9%)	Grade I—229 (6.9%)

Data Extraction and Analysis

Data was extracted for journal title, author's details, year of publication, country of origin, patient demographics, stone characteristics, overall and infection-related complications. Where the infectious complications were reported separately, it was recorded as such. The severity of complications was also categorised according to the Clavien-Dindo classification system for grading complications [32]. Studies which described risk factors for post-URS infection, prevention and management strategies for post-URS infections were also recorded. All data was recorded using Microsoft Excel 2019 (version 16.28).

Results

A total of 2070 articles were initially identified, and 14 full-text English language articles were included in the final review which fit our inclusion criteria (Fig. 1) [13, 15, 18–28]. The total number of ureteroscopies included in these papers was 24,373, and the mean age was 51.2 years (range 42–61 years), male:female ratio of 3:2 and a mean BMI of 26.9 (range 23.7–31.8) (Table 1). All patients' demographic and procedure details were explored as possible risk factors for post-ureteroscopy infections (Table 2). These were gender, stone size or total stone burden, stone location, ureteral access sheath use and mean operative time. Other risk factors included patient comorbidities, history of recurrent UTIs or positive urine culture, immunocompromised patients, longer procedural time, pre-operative stent dwell time, previous indwelling catheter or neurogenic bladder (Table 3).

For the papers which mentioned the stone size and location, the mean stone size (stone length) was 10.5 mm (range 8–14.3 mm). The stone location was reported in 9 papers of which 54% ($n = 13,148$) were ureteric stones, 22% ($n = 5373$) were renal stones, 8.6% ($n = 2115$) were in multiple locations and in 15.4%, it was not reported. A ureteral access sheath use was used in 25.8% ($n = 6288$) patients and ranged across studies from 206 to 2263 cases. The mean operating time was 52.7 min (range 40–62.4 min). The stone-free rate across studies was 83% (range 68–84.4%).

The total number of complications were noted in 7.9% ($n = 1919$), of which 3.9% ($n = 972$) were infectious complications and 4% ($n = 1147$) were non-infectious complications. Of all the infectious complications, fever was reported in 66% ($n = 642$). Urosepsis was reported in 7 papers, and there were 126 patients with urosepsis which was 0.51% of the whole cohort and 6.5% of the total reported complications.

Of the complications, grade I complication was reported in 67.6% ($n = 1298$), grade II complication in 14.3% ($n = 275$), grade IIIa complication in 5% ($n = 98$), grade IIIb complication in 4.2% ($n = 82$), grade IV complication in 4.7% ($n = 91$) and grade V complication in 0.15% ($n = 3$) patients.

Discussion

Our systematic review for high-volume centres shows a post-URS urosepsis rates of 0.51%. Antibiotic prophylaxis was practiced in most of the included studies and offers to reduce this risk [12]. It seems that there are several pre-disposing factors which

Table 3 Infectious complications from the studies including risk factors, modifiable strategies and proposed management of complications (as mentioned by authors)

Author	Risk factors	Risk modification strategies	Details of complications management
Pricop C. et al.	<ul style="list-style-type: none"> • Absence of antibiotic prophylaxis • Stone size 0.9–1.2 cm 	<ul style="list-style-type: none"> • Antibiotic prophylaxis 	N/S
Martov A. et al.	<ul style="list-style-type: none"> • Female gender • High ASA score • Older age • Long pre-operative hospital stay • Deficient nutritional status • History of recurrent UTIs • Impaired immune response • Bowel surgery • Diabetes mellitus • Smoking • Urinary obstruction • Lack of control of risk factors 	<ul style="list-style-type: none"> • Antibiotic prophylaxis for all patients undergoing URS 	N/S
Özsoy M. et al.	<ul style="list-style-type: none"> • Female gender 	N/S	N/S
Moses RA. et al.	<ul style="list-style-type: none"> • Longer OR time • Pre-operative stent 	<ul style="list-style-type: none"> • Understanding local resistance patterns • Antibiotic prophylaxis • Choose broadened prophylaxis, in pre-stented and longer operations 	N/S
James P. et al.	<ul style="list-style-type: none"> • Positive pre-operative culture 	N/S	<ul style="list-style-type: none"> • 1 case ITU—death
Dessyn JF. et al.	<ul style="list-style-type: none"> • Stone size and number 	N/S	N/S
Berardinelli F. et al.	<ul style="list-style-type: none"> • Coronary heart disease • Anticoagulant therapy • CKD • Alteration of lipid metabolism • Presence of residual fragments • Past surgery for renal stone 	N/S	<ul style="list-style-type: none"> • Fever—antipyretics • SIRS—Abx, IV fluids • Sepsis—Abx, IV fluids, Inotropes • Obstructive pyelonephritis—DJ placement • Hospital re-admission, 1.2%
Nevo A. et al.	<ul style="list-style-type: none"> • Female gender • Pre-operative stent long indwelling time 	N/S	N/S
Somani BK. et al.	N/S	N/S	N/S
Ghosh A. et al.	<ul style="list-style-type: none"> • Long hospital stay • Older age • Positive pre-operative culture • Longer OR time 	N/S	<ul style="list-style-type: none"> • Sepsis managed with IV antibiotics; • 1 case—ITU for candidaemia
Stauffer CE. et al.	<ul style="list-style-type: none"> • Neurogenic bladder • Indwelling catheter • Bacterial colonization 	N/S	N/S
Senocak C. et al.	<ul style="list-style-type: none"> • Positive pre-operative MDR culture 	N/S	N/S
Uchida Y. et al.	<ul style="list-style-type: none"> • Female gender • Lower BMI • Deficient nutritional status • Previous obstructive pyelonephritis • Positive pre-operative culture • Struvite stones • Pre-operative stent 	N/S	<ul style="list-style-type: none"> • 1 case—ITU with vasopressors
Southern JB. et al.	<ul style="list-style-type: none"> • Female gender • Longer OR time • Multiple comorbidities • Positive pre-operative culture 	<ul style="list-style-type: none"> • Pre-operative counselling 	<ul style="list-style-type: none"> • Sepsis—ward-based management

increases this risk and includes positive pre-operative UTI or prior history of UTIs, patients with higher Charlson comorbidity index or elderly patients, female gender, presence and duration of indwelling ureteric stents, procedural time and patients with a neurogenic bladder and with high BMI [18–28]. Infectious

complications vary from fever, urinary tract infection, pyelonephritis, systemic inflammatory response syndrome and urosepsis. Antibiotics should therefore be tailored to local resistance profiles which tend to reduce rates of infection and urosepsis [33]. Baboudjian et al. propose that limiting operative times and

treating pre-operative UTI should lead towards reduced post-operative infection rates [29].

There is a substantial patient and economic cost associated with sepsis, which is >\$24 billion per year in the USA alone [34]. Urosepsis leads to morbidity and mortality and hence, prevention, early detection and management are paramount [14]. It is the leading cause of mortality for patients with KSD and is more common in patients with comorbidities, high stone burden, obesity, with spinal cord injury or neurogenic bladders. The CROES study revealed a mortality rate of 0.04% which confirms that although the mortality rate of URS is negligible, but, it is not zero, and all precautions must be taken for it [13]. Prevention strategies included the use of prophylactic antibiotics, aggressive treatment of pre-operative UTIs, reducing operating duration, caution in elderly and patients with high stone burden [14].

Previous work by Traxer et al. showed that the use of ureteral access sheath (UAS) helps to reduce post-URS infectious complication [35]. However, the use of UAS was not helpful in reducing infectious complications in another study looking at treatment of large renal stones [36]. The presence of indwelling stents more than 1 month was associated with a higher risk of sepsis [20]. Hence, any pre-procedural ureteric stent must be kept as short as possible prior to offering a definitive ureteroscopy.

In patients with urosepsis due to obstructed ureteric stone, an immediate drainage via a nephrostomy or ureteric stent is needed, in addition to antibiotics and supportive care [37]. A delayed ureteroscopy and stone treatment in these cases lead to good clinical outcome [37].

Urosepsis-related mortality was found to be 2.5 times higher in patients with urinary obstruction and is largely due to urolithiasis [38]. Urgent decompression in obstructed calculus-related sepsis is warranted; otherwise, the mortality is doubled, and this drainage should be early (within 48 h) to reduce the hospital stay [39, 40]. Although there is no consensus on the time duration between emergency drainage and elective ureteroscopy, it is generally agreed that this should be as soon as the patient has recovered from the initial sepsis and is stable to undergo the ureteroscopy [37].

Conclusion

Infectious complications following ureteroscopy can be a source of morbidity and potential mortality. Although majority of these are minor, efforts must be taken to minimize them especially in high-risk patients. This includes use of prophylactic antibiotics, limiting stent dwell and procedural time, prompt identification and treatment of UTI and urosepsis, and careful planning in patients with large stone burden and multiple comorbidities.

Compliance with Ethical Standards

Conflict of Interest The authors declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article is a systematic review of literature and hence, no direct patient involvement was recorded or analysed.

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