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TOPIC PAPER

Antibiotic use and the prevention and management of infectious complications in stone disease

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Abstract The importance of assessing perioperative urine/stone cultures and providing appropriate antibiotic prophylaxis prior to shock wave lithotripsy (SWL) or endoscopic intervention cannot be minimized. Urinary tract infection (UTI) is the most common complication relating to stone intervention. Adequate assessment of culture data and adherence to appropriate guidelines may prevent the development of UTI and the potential for post-intervention urosepsis. This review outlines the current evidence for prophylaxis in the prevention of UTI and urosepsis, as well as the interpretation of stone culture data to provide an evidence-based approach for the judicious use of antibiotics in urologic stone practice.

Keywords Antibiotic · Prophylaxis · Nephrolithiasis · Shock wave lithotripsy · Ureteroscopy · Percutaneousnephrolithotomy · Sepsis

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Introduction

The importance of assessing perioperative urine/stone cultures and providing appropriate antibiotic prophylaxis prior to shock wave lithotripsy (SWL) or endoscopic intervention cannot be minimized. Urinary tract infection (UTI) is the most common complication relating to stone intervention. Adequate assessment of culture data and adherence to appropriate guidelines may prevent the development of UTI and the potential for post-intervention urosepsis. This review outlines the current evidence for prophylaxis in the prevention of UTI and urosepsis, as well as the interpretation of stone culture data to provide an evidence-based approach for the judicious use of antibiotics in urologic stone practice.

Perioperative cultures and the role of antibiotics in patients scheduled for active stone removal procedures

Urinary tract infection is the most common complication arising from active stone removal procedures, such as SWL, ureteroscopy (URS), and percutaneous nephrolithotomy (PCNL). Any intravasation of bacteria or endotoxins into the blood stream may lead to urosepsis, a potentially lethal complication. Careful consideration of any relevant clinical history and bacteriological status is, therefore, mandatory in patients undergoing active stone intervention.

Preoperative evaluation

Stone intervention should not be underestimated. All patients should be evaluated with a complete medical history, proper physical examination, and laboratory tests, including midstream urine (MSU) culture and sensitivity. A

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full preoperative evaluation will identify high-risk patients with the potential for infectious complications (Table 1).

Bacteriology

Urine microscopy as well as MSU culture and sensitivity must be obtained before any active stone intervention. Local evaluation of the prevalence of pathogenic organisms and antibiotic resistance patterns is of significant importance in the management of potential infection-related complications arising from stone removal procedures [1, 2]. Escherichia coli remains the most common pathogen causing UTI, followed by other bacteria associated with "infection" stones, such as Klebsiella and Proteus; Gram-positive bacteria, including Enterococcus and Staphylococcus, must also be considered [3]. With the increasing antibiotic resistance patterns in common pathogens, it is important to establish local strategies to reduce the risk for antibiotic resistance, such as rationalization of the empiric use of antibiotics and limiting antibiotic prophylaxis only to those patients with predetermined risk factors for such procedures [4].

In patients undergoing URS or PCNL, attempts should be made to retrieve a stone fragment under sterile conditions and send it for stone culture. Stone-contained bacteria may enter the urine with possible systemic transudation and result in sepsis or systemic inflammatory response syndrome (SIRS). Along with living bacteria, stones may contain endotoxins that can potentially result in a systemic immune response clinically similar to sepsis. Stone cultures have been shown to be a better predictor of sepsis and SIRS than voided cultures, and they are associated with a four-fold risk for SIRS when positive [5–9]. Since the stone culture is not available until at least 48 h after the procedure, these results cannot influence immediate perioperative treatment. However, they may become essential in guiding antibiotic treatment in the event of sepsis following URS or PCNL.

Infectious issues related to shock wave lithotripsy

The guidelines regarding preoperative SWL prophylaxis have changed in recent years. In general, the incidence of UTI occurring after uncomplicated SWL is less than 1%, and rises to 2.7% during the management of staghorn calculi [10]. This risk for sepsis increases in the presence of bacteriuria prior to SWL, especially if there is any distal ureteric obstruction [11].

Duvdevani and colleagues reported fever of at least 38 °C in 1.4% of 11,500 SWL treatments [12]. The risk factors for the development of fever were a positive urine culture ($p < 0.05$), the presence of an indwelling nephrostomy tube or ureteral stent ($p < 0.001$), and the presence of preoperative symptomatic UTI or sepsis ($p < 0.05$). Interestingly, the incidence of UTI was higher in patients with renal or upper ureteral stones undergoing SWL when compared to patients with mid- or lower ureteral calculi. The authors postulated that renal trauma from shock wave administration may occur when treating renal and upper ureteral calculi, resulting in microvasculature disruption and allowing bacteria to enter the blood stream. They suggested that treating selected high-risk patients with prophylactic antibiotics may decrease both the overall amount of antibiotics used and the risk for fever after SWL.

The practice of administering perioperative prophylactic antibiotics is controversial in patients undergoing SWL who have a negative pre-procedural urine culture. It has been reported that bacteriuria can develop in 5–6% of patients undergoing SWL even in the presence of sterile urine prior to the procedure; the subsequent risk for clinical UTI can be seen in 2–3% of patients [13].

The 2008 American Urological Association (AUA) Best Practice Guidelines on antibiotic prophylaxis initially recommended prophylactic antibiotics for all patients undergoing SWL for urinary stone disease [14]. This recommendation was made in part based on a 1997 meta-analysis that reviewed eight randomized controlled trials (RCTs) comprising 885 patients [15]. This meta-analysis demonstrated

Table 1 Risk factors associated with the development of postoperative infections

Patient-related risk factors	
Immunosuppression secondary to malignancy or autoimmune diseases	Presence of coexistent infection at another site at time of surgery
Chemotherapy or chronic corticosteroid use	Obesity
Diabetes mellitus	Female gender
Advanced age	Significant kidney or liver disease
Poor nutritional status	Prolonged hospitalization
Urinary tract-related risk factors	
Anatomic anomalies	Voiding dysfunction
Urinary diversion	Urinary tract obstruction
Presence of indwelling tubes (stent, catheter, nephrostomy)	

that the rate of UTI after SWL was 5.7% for the group without prophylaxis and only 2.1% for the group that received prophylactic antibiotics.

The current European Association of Urology (EAU) Guidelines on Urolithiasis, updated in 2015, conversely recommended antibiotic prophylaxis before SWL only in cases of internal stent placement or in patients with increased bacterial burden. This recommendation was based on two prospective studies from the 1990s [16]. One study randomized patients with a negative urine culture before treatment to 1- or 7-day antibiotic (cefuroxime or ciprofloxacin) prophylaxis starting 30 min before SWL or to placebo [17]. Only 2–3% of the patients had clinical and bacteriological signs of UTI, with no significant difference between those who received placebo and those who received prophylactic treatment. Moreover, there was no beneficial effect of antibiotic prophylaxis in patients with a nephrostomy tube or hydronephrosis. The other prospective study compared 250 patients with sterile urine who did not receive antibiotic prophylaxis prior to SWL to 90 patients with UTI who received antibiotic treatment prior to SWL [18]. Infectious problems occurred in 5.2% of patients with pre-SWL sterile urine and in 27.8% of patients with pre-SWL UTI, suggesting that administration of prophylactic antibiotics may prove useful only in the case of pre-SWL UTI.

A more recent meta-analysis, published in 2012, included nine RCTs of patients undergoing SWL ($n = 1364$) for urinary stones with sterile urine cultures. The study reported no significant differences between the prophylactic group and the control group in terms of symptoms, fever, or positive urine culture rates, nor in the incidence of UTI [19]. This study suggests that antibiotic prophylaxis is not necessary prior to SWL in low-risk patients and the updated AUA Best Practice Guidelines reflect this, by suggesting—as with the EAU Guidelines—that only patients with risk factors should undergo SWL on prophylactic antibiotics.

Another prospective study examined the administration of antibiotics pre-SWL (on the day of procedure) and post-SWL (on day 3 post-procedure) [20]. The authors found that only 0.3% of patients developed symptomatic UTI, and 2.8% developed asymptomatic bacteriuria. This study found that patients with ureteral stents were more likely to develop asymptomatic bacteriuria but not symptomatic UTI, and the authors suggested that this group would not need antibiotic prophylaxis. The authors, however, would consider antibiotic prophylaxis in high-risk patients with infective stones, recent instrumentation, or dipstick positive urine for leukocytes or nitrites. Hsieh et al. randomized 206 patients with preoperative sterile urine to single-dose periprocedural levofloxacin or placebo and, similarly, noted very low rates of febrile UTI with or without treatment [21]. With these new data, the updated AUA guidelines no longer recommend antibiotic prophylaxis for patients with a negative urine culture undergoing SWL [14].

In light of the most recent publications, prophylactic antibiotics are recommended only in high-risk groups with infected stones, recent instrumentation, nephrostomy tubes, positive urine culture, or a history of recent UTI or sepsis. In addition, special consideration should be given to certain high-risk patient groups, such as those with as advanced age, anatomical anomalies of the urinary tract, poor nutritional status, chronic smokers, chronic steroid users, immunodeficiency, externalized catheters, or prolonged hospitalization.

In general, to minimize infective complications, SWL should only be performed if the patient's urine is sterile and when there is no distal obstruction. Currently, periprocedural prophylactic antibiotics should be considered only in high-risk patients (see Table 2 for summary of SWL recommendations).

Infectious issues related to ureteroscopy

Ureteroscopy is an increasingly routine urological procedure. Technological advances, such as smaller semi-rigid and flexible endoscopes, and improved intracorporeal lithotripters, with newer disposable wires and baskets to access the ureter and kidney, have significantly decreased the complication rate of URS. This is despite an expanding indication for URS and retrograde intrarenal surgery (RIRS). However, infectious complications are still one of the most feared problems after URS. Recently, the Clinical Research Office of the Endourological Society (CROES) Ureteroscopy Global Study reported a multicenter study that enrolled 11,885 patients with a low incidence of

Table 2 Recommendations for prevention of infection and sepsis before SWL

Recommendation	Level of evidence	Grade of recommendation
Risk of sepsis increases with presence of preop bacteriuria	II	A
Antibiotic prophylaxis is not necessary for low- or no-risk patients undergoing SWL	I	A
Prophylactic antibiotics are only recommended in high-risk stone patients (e.g. infection stones, recent instrumentation, nephrostomy tubes, positive urine culture, or history of recent UTI/sepsis)	I	A

postoperative infectious events, reflecting "real world practice". It was noted that postoperative fever was observed in 1.8% of the patients, urinary tract infection in 1.0%, and sepsis in 0.3% [22]. Similarly, a recent multicenter review of infectious complications after URS noted a 4.4% risk of postoperative fever and 0.7% risk of sepsis with all patients receiving perioperative antibiotic prophylaxis [23].

In fact, in a subset analysis of the CROES database, patients with a negative baseline urine culture undergoing URS for either ureteral stones ($n=1141$) or kidney stones ($n=184$) not receiving antibiotic prophylaxis were matched with patients who were predefined by certain risk factors [24]. It was determined that in patients with a negative baseline urine culture undergoing URS for ureteral or renal stones, the rates of postoperative UTI and fever were not reduced by pre- or perioperative antibiotic prophylaxis. However, the retrospective nature of this study allows for confounding regarding the benefits of perioperative prophylaxis. In this study, female gender and a high American Society of Anesthesiologists (ASA) score were specific risk factors for postoperative infection. In similar retrospective studies, preoperative hydronephrosis, pyelonephritis, bacteriuria, longer operative time, indwelling drainage tube, and preoperative positive urine culture—despite preoperative treatment course—were all associated with postoperative fever [25–28].

Antibiotic prophylaxis

The consensus at this time is that the use of perioperative antibiotics in endourology can reduce the risk for UTI or surgically related infection. However, the EAU and AUA recommendations for best practice on antibiotic prophylaxis in URS differ slightly [14, 16]. The EAU guidelines differentiate between low-risk procedures, such as simple diagnostic URS and distal ureteral stone treatment, and higher risk procedures, such as treatment of impacted proximal ureteral stones. As well, the EAU guidelines no longer recommend the use of fluoroquinolones as an alternative antibiotic prophylaxis for diagnostic URS. The EAU guidelines also consider other potential risk factors, such as stone size, bleeding, and surgeon experience (Table 3). Conversely, the AUA guidelines recommend perioperative prophylaxis for all patients undergoing ureteroscopy.

An assessment of urine for sterility by MSU culture and sensitivity is an essential prerequisite for endoscopic stone treatment. Nevertheless, it is important to recognize that MSU cultures do not always correlate with obstructed urine or stones, and sepsis may present in 1–3% of cases with a negative MSU culture. In a prospective study, Mariappan et al. cultured midstream urine, renal pelvic urine, and obstructing ureteric stones from patients who had undergone ureteroscopic lithotripsy [7]. Clinical bacteremia was seen in 19% of patients. Of these patients, 58.3% developed features of SIRS. Blood and stone culture and sensitivity were positive in 25% of cases, and pelvic urine culture and sensitivity were positive in 66.7%, while none of these patients had positive midstream urine ($p=0.04$).

Eswara et al. retrospectively reviewed their experience with stone cultures in patients undergoing URS. The authors found that urine cultures were only positive in 7% of patients, whereas stone cultures were positive in 29%. Their overall sepsis rate was about 3–4% for all patients, 8% for patients with positive stone culture, and only 1% for those who had a negative stone culture [29].

A 2003 study by Knopf et al. found that a single prophylactic oral dose of levofloxacin reduced the risk of postoperative bacteriuria compared to placebo (1.8 vs 12.5%, $p=0.02$), although no symptomatic UTIs were noted [30]. In a more recent study, Hsieh et al. randomized 206 patients with sterile urine to either perioperative cefazolin, ceftriaxone, levofloxacin, or no treatment; while prophylaxis decreased the risk of febrile UTI and bacteriuria, this difference was not significant [31]. However, few other randomized and prospective trials have explored the role of antibiotic prophylaxis in ureterolithotripsy in recent

Table 3 Recommendations for best practice in antibiotic prophylaxis in ureteroscopy

Procedure	Indication		Antimicrobial Scheme		Duration	Remarks
	AUA	EAU	1st Choice	Alternative		
Diagnostic Ureteroscopy	All	Risk factors	2nd generation cephalosporin TMP-SMX	Aminoglycoside +/− ampicillin Amoxicillin/clavulanate	≤ 24 h	If urine culture is negative, prophylaxis is not necessary
Therapeutic Ureteroscopy	All	Not in uncomplicated distal stones	2nd /3rd generation cephalosporin TMP-SMX Aminopenicillin/BLI Fluoroquinolone	Aminoglycoside +/− ampicillin/1st generation cephalosporin Amoxicillin/clavulanate	≤ 24 h	

AUA, American Urological Association; EAU, European Association of Urology; BLI, beta-lactamase inhibitors; TMP-SMX, trimethoprim–sulfamethoxazole

years; in fact, a recent meta-analysis was only able to combine 500 patients over four trials, showing merely a trend towards reduction of postoperative febrile UTI [32]. Still, as a consequence of the potential risk for infection from the presence of infected stones and the low risk associated with a single dose of perioperative treatment, antibiotic prophylaxis is indicated for any ureteroscopic intervention performed for the management of urinary tract calculi.

Intraoperative factors

Modifiable pre- and intraoperative factors may influence the risk for infectious complications. Good practice mandates that the presence of any active UTI associated with urinary tract obstruction requires the relief of the obstruction with either an internal double J stent or percutaneous nephrostomy (to allow kidney decompression and treatment of the infection), followed by a staged procedure [33].

During URS, the hydrostatic pressure generated by the irrigation fluid may result in bacterial and endotoxin translocation into the systemic circulation. It is, therefore, important to maintain a low-pressure irrigation system to reduce the incidence risk for systemic infection. Within the closed urinary tract, only enough irrigation to maintain adequate visibility should be used. In their institutional series (>3000 procedures), Kau et al. attributed the low incidence of infection complications to the use of forced diuresis, with the administration of 20 mg of intravenous furosemide once access to the kidney was reached. This forced diuresis presumably helped to prevent pyelo-venous and pyelo-lymphatic reflux, thus reducing the subsequent risk for bacteremia [34].

Other maneuvers that help to reduce intrarenal pressure include gravity irrigation only (<60 cm of water above patient level) as well as the use of an intermittent irrigation/aspiration system or routine use of a ureteral access sheath when performing flexible ureteroscopy [34]. Similarly, continuous or intermittent bladder drainage with a small-caliber bladder catheter may help maintain low intrarenal pressures during ureteroscopic intervention [35]. Studies have demonstrated that routine use of a ureteral access sheath during flexible URS can significantly reduce intrarenal pressures and thus lessen the likelihood of pyelovenous and pyelo-lymphatic backflow [36, 37].

Postoperative care/management of postoperative infections

Ramaswamy et al. retrospectively reviewed their experience with post-ureteroscopic prophylaxis in patients with ureteral stents. They evaluated two groups of patients: group 1 received fluoroquinolones for 1 week after surgery until stent removal, and group 2 received 3 days of cephalexin immediately prior to ureteral stent removal within 1 week of surgery. They did not observe any differences in asymptomatic bacteriuria or in the rate of symptomatic UTI (2% for both groups) [38]. Similarly, Chew et al. evaluated 81 patients undergoing ureteroscopy who were either treated with a single dose of perioperative antibiotics or given additional postoperative antibiotics as well; no difference in postoperative infection was noted (4.8 vs 10.2%, $p=0.15$) [39].

Early recognition and management of sepsis is important in optimizing the outcome following ureteroscopic stone manipulation. Patients in whom this problem is suspected after URS or RIRS should be prioritized to receive urgent care. Clinical and laboratory recognition of any septic complication is mandatory. High levels of early biochemical markers, such as procalcitonin and protein C, in the initial postoperative period may help identify a severe inflammatory response from bacteremia and necessitate the prompt institution of therapeutic measures. At this point, it is important to re-culture urine that was obtained preoperatively or during surgery and, based on these results, redirect antibiotic therapy.

If culture results are not available, empiric broad spectrum antibiotics should be initiated immediately. Suggested primary regimens include ampicillin/gentamicin, piperacillin–tazobactam, or carbapenems (doripenem, imipenem, or meropenem); the duration of treatment is determined by the patient's clinical response. It is imperative to modify the antibiotic regimen to a culture-directed agent when possible [38].

Inappropriate or delayed antibiotic treatment is associated with increased mortality in severe sepsis/septic shock. Besides empiric antibiotic therapy, prompt resuscitative measures should include repletion of intravascular volume with crystalloid intravenous fluids. The only immunomodulatory therapy currently advocated is a short course of hydrocortisone (200–300 mg per day for up to 7 days or until vasopressor support is no longer required) for patients with refractory septic shock [40].

The best management of any infectious complication is prevention. It is imperative to establish and to adhere to a preoperative evaluation protocol and follow well-defined intraoperative surgical techniques. Once an infectious complication is suspected, it is essential to act promptly and accurately in a multidisciplinary fashion to minimize the risk for progression in the natural history of sepsis and to provide a better opportunity for a complete recovery (see Table 4 for summary of ureteroscopy recommendations).

Infectious issues relating to percutaneous nephrolithotomy

Percutaneous nephrolithotomy is the recommended treatment for large or complex stone burdens [41, 42]. Fever as a complication of PCNL may occur in 21–39.8% of patients

Table 4 Recommendations for prevention of infection and sepsis in therapeutic ureteroscopy

Recommendation	Level of evidence	Grade of recommendation
Identify high-risk patients	II	B
Treat active UTI pre-procedure	II	A
Ensure a negative preoperative urine culture	II	B
Antimicrobial prophylaxis in call cases	II	A
Never perform stone manipulation in setting of active infection; relieve obstruction, treat infection, and carry out staged treatment	I	A
In patients with chronic bacteriuria, administer at least 5 days of culture-specific antibiotics before instrumentation	II	B
Maintain low intrarenal pressure during the procedure	III	B
Force diuresis with diuretics during surgery	IV	C

[43–45]. Although the temperature increase is transient in the majority of cases, potentially life-threatening sepsis can develop in 0.3–9.3% of patients [43–45]. The main reasons for the development of UTI after PCNL include the release of bacteria from the surgical manipulation, fragmentation of calculi (struvite or large non-struvite stones), and the introduction of bacteria through the nephrostomy tract, which traverses through skin, retroperitoneum, and renal tissues [46].

There is overwhelming clinical experience and expert consensus that prior to any endourological procedures, including PCNL; a preoperative urine culture should be obtained and confirmed to be sterile. In patients with positive urine culture, antibiotic treatment prior to PCNL is recommended. It should be noted that a positive preoperative urine culture has been associated with increased infectious risk [odds ratio (OR) 2.2–16.7] [6, 9, 47–49]. However, a negative bladder urine culture does not exclude the presence of bacteria in stones or in urine within the renal pelvis. In a study examining the correlation between different sites of urine sampling in patients undergoing PCNL, 35% of patients had positive stone cultures compared with 21% of renal pelvic and 11% of bladder urine cultures [8]. Recently, it was found that in patients with negative bladder cultures, about one-third had infected pelvic urine and half had positive stone cultures [50].

Few studies have investigated the need for preoperative antibiotic prophylaxis for patients undergoing PCNL who present with sterile urine. In the only randomized, placebo-controlled trial, patients who received cefotaxime had a lower rate of postoperative UTIs (3 of 27 patients) compared to the placebo group (7 of 22 patients) [51]. However, due to the limited sample size of the study, this difference did not reach statistical significance. In a case series of 107 patients with preoperative sterile urine who did not receive antibiotic prophylaxis, post-PCNL bacteriuria was found in 35% of the cases, while only 10% of patients developed post-PCNL fever [52].

The CROES global PCNL study reported data from 162 patients from multiple institutions who underwent PCNL without preoperative antibiotics and matched them to patients who did receive antibiotics [53]. All patients had negative preoperative urine cultures, and the two groups were matched based on infectious risk factors, such as diabetes, nephrostomy tubes, and staghorn stones. This matched case-control study demonstrated that antibiotic prophylaxis resulted in fewer incidents of fever (2.5 vs 7.4%) and other complications (1.9 vs 22%), and had a higher stone-free rate (86.3 vs 74%).

Antibiotic regimens peri- and postoperatively for PCNL

Different antimicrobial regimens have been evaluated for the antibiotic perioperative prophylaxis of patients undergoing PCNL and have been proven to be safe and effective in preventing postoperative infection-related outcomes [6, 53–58]. This finding is also reflected in the varied antibiotic regimens proposed by the EAU (trimethoprim/sulfamethoxazole, second- or third-generation cephalosporin, aminopenicillin/beta-lactamase inhibitors, and fluoroquinolones) and AUA (first- or second-generation cephalosporin, aminoglycoside plus metronidazole or clindamycin, ampicillin/sulbactam, and fluoroquinolones) guidelines [14, 16].

In addition, the efficacy of single dose vs short-course antibiotic prophylaxis has been investigated [46, 55, 57, 58]. In an RCT comparing ampicillin/sulbactam to cefuroxime in 198 patients treated with PCNL, patients were further randomized according to duration of antibiotic maintenance (single-dose prophylaxis vs an additional dose 12 h after prophylaxis vs beginning with prophylactic dose until nephrostomy tube removal). No relation between duration of antibiotic treatment and SIRS development was found in any group [57].

In a similar study, 90 patients who received either ciprofloxacin or ceftriaxone were divided into three subgroups based on the duration of antibiotic prophylaxis (ranging

from single dose to until removal of nephrostomy tube) [55]. There was no statistical difference in the distribution of SIRS-positive patients between the ciprofloxacin or ceftriaxone groups, nor between the long-term and short-term antibiotic administration groups.

In another study, patients with sterile preoperative urine cultures were randomized to receive a single intravenous dose of either 200 or 400 mg ofloxacin per day until withdrawal of the nephrostomy tube. No statistical difference was observed between the two groups in terms of bacteriuria, bacteremia, positive stone cultures, or postoperative fever [6].

Similarly, a single dose of ceftriaxone did not show any benefit when compared to a short course of antibiotic prophylaxis (oral third-generation cephalosporin after ceftriaxone until nephrostomy tube removal). There was no statistically significant difference between the two groups in terms of occurrence of fever of >38 °C or rate of positive urine culture sent at the time of nephrostomy tube removal [58]. Even more recently, uncomplicated PCNL patients were shown to have similar rates of febrile UTI whether receiving less than 24 h of antibiotic prophylaxis vs 5–7 days of antibiotics [59].

These studies, therefore, suggest that when the preoperative urine culture is negative, a single dose of antibiotics appears to be as effective in preventing postoperative infections as multiple doses, irrespective of the type of antibiotic used. A systematic review published in 2008 concluded that in the presence of a negative preoperative culture, there was low evidence of postoperative UTI, suggesting a more favorable outcome after PCNL using antibiotic prophylaxis. Furthermore, when prophylaxis was used, there was no advantage for any specific antimicrobial regimen [5].

Risk factors for fever/sepsis/SIRS after PCNL

Several studies have attempted to identify the pre- and intraoperative factors that affect the development of fever, SIRS, or sepsis following PCNL. Importantly, non-febrile SIRS can be very common after PCNL, with one study documenting a 43% rate of SIRS within the day following surgery; there was no association seen between non-febrile SIRS and unplanned re-admissions to the hospital for urosepsis [60]. Similarly, Bozkurt et al. showed that while leukocytosis is common after PCNL, a value greater than 14,000 cells/μL was associated with true postoperative urosepsis [61]. With this in mind, it is important to understand the true infectious risk from PCNL and not solely the inflammatory response associated with percutaneous procedures.

A positive preoperative urine culture is associated with an increased infectious risk (OR 2.2–16.7), as were positive pelvic urine culture (OR 10.2–24.1), and stone culture (OR 4.88–25.6) [6, 48, 49]. In addition, multidrug resistant bacteriuria (resistant to three or more AUA-recommended antibiotic options) was recently shown to carry a substantial independent risk for postoperative sepsis, even despite proper preoperative antibiotic coverage [62]. Stone culture has been shown to be a better predictor of sepsis and SIRS than voided cultures, and when positive, they are associated with a fourfold risk for SIRS [8, 29, 49, 50, 63, 64].

One study of 328 patients treated with PCNL or ureteroscopic lithotripsy showed that the pathogen found in the urine culture obtained on re-admission for sepsis correlated with the stone culture in 64% of patients and with the preoperative urine culture in only 11%. This suggests that the stone culture pathogen has a higher concordance with the offending bacteria causing sepsis [29]. In addition, in a study comparing 45 patients with a positive stone culture to similar patients with a negative stone culture, the stone culture result was the only significant predictor of postoperative sepsis (OR 6.89, $p=0.001$) [65]. The main limitation of stone and renal pelvis urine cultures is that they are only available after PCNL and they, therefore, cannot be used to prevent complications related to infection. Stone cultures often require multiple days for speciation and antibiotic sensitivity testing, but simple gram stain can be reported much faster and give useful clinical information, although the sensitivity of this test is poor [66]. Despite the inherent delay in stone culture, the results definitively help with the optimal selection of antibiotic treatment in the event of SIRS/sepsis after PCNL.

Several preoperative factors, including female gender, hydroureteronephrosis, preoperative nephrostomy tube, large or complex stone burden (including staghorn calculi), neurogenic bladder, and diabetes mellitus, have been associated with an increased risk for post-PCNL fever or sepsis [47, 48, 50, 67, 68]. Two studies included only patients with very large renal calculi and/or dilated pelvicalyceal systems with a higher risk for urosepsis and evaluated the role of 1-week preoperatively-administered antibiotics for the prevention of sepsis/SIRS. The first study reported that 1 week of ciprofloxacin prophylaxis before PCNL significantly reduced the risk for urosepsis among patients who were free of pre-existing UTIs, preoperative nephrostomy, or diabetes [69]. The second study investigated the impact of prophylaxis with nitrofurantoin for a week before PCNL and found a significantly lower rate of endotoxemia (17.5 vs 41.9%) and SIRS (19 vs 49%) in the nitrofurantoin group [70]. These studies indicate that a 7-day pre-PCNL course of antibiotics may play an important role in the prevention of infective complications in patients at a higher risk for the development of urosepsis. Currently, due to the low level of evidence, this pre-surgical treatment policy cannot be generalized to the broader population of patients undergoing PCNL.

It is worth noting that in addition to antibiotic management, other medications have been examined regarding their ability to reduce the risk of postoperative sepsis after PCNL. While previous studies seemed to suggest that the anti-inflammatory effects of statin medications could reduce postoperative infection in certain surgical patients, and a recent study of 2046 patients showed that statin use did not decrease the risk of post-PCNL sepsis (5.3 vs 3.5%, $p=0.105$) [71].

Intraoperative risk factors for post-PCNL fever or sepsis have also been identified, including number of access tracts, operative time, incomplete stone extraction, and volume of irrigation fluid [6, 47, 50, 70, 72, 73]. Multiple access tracts were associated with increased risk for SIRS (OR 4.8) when controlling for patient gender, stone culture, and composition [50]. Several other studies have demonstrated that prolonged operative time was an independent risk factor for fever and septic shock [20, 41, 44, 73]. The volume of irrigation fluid used in PCNL was also a significant predictor for fever [6]. These factors suggest a large stone size and complex surgical procedure and are likely not independent risk factors for postoperative infectious complications, although incomplete stone extraction could independently lead to residual infectious material and increase the risk of postoperative sepsis.

A special mention of the finding of purulent urine during the percutaneous access puncture is warranted. In these rare cases, it has been recommended to postpone the surgical procedure, to insert a drain (nephrostomy tube), and to administer appropriate antibiotics [2, 44, 74]. However, some recent retrospective comparative case series have highlighted the high incidence of negative fluid cultures in such cases and the absence of more febrile or septic events if the surgical procedure is continued after puncture [75, 76]. Etemadian et al. reported the only RCT on the subject in a group of asymptomatic patients without recent treatment of any UTI [77]. Group 1 received PCNL during the initial session while group 2 received a nephrostomy drain and delayed intervention. Infected fluid was found in 43% of the patients in group 1 and in 40% of the patients in group 2. The rates of postoperative fever were also similar between the two groups (25 and 27% in groups 1 and 2, respectively). There were no statistical differences between the two groups in terms of bacteriuria, bacteremia, positive calculus cultures, stone-free rate, or duration of hospitalization. While the sample size in this study was small (31 patients), it is still noteworthy that the incidence of septic events was very low (<4%) and affected predominantly patients with staghorn calculi. Based on this study, it seems that in the absence of untreated UTI, the aspiration of purulent fluid does not necessarily preclude the continuation of the PCNL.

It should be noted that although antibiotic prophylaxis is efficacious in reducing the risk for postoperative fever and other complications, this risk is never completely eliminated, even in low-risk patients who receive antibiotic prophylaxis. Bacterial resistance to antibiotic treatment or the administration of an inappropriate antibiotic may explain this failure. In addition, antibiotic prophylaxis is just one of the methods available for preventing infections after PCNL; general surgical recommendations must be followed to reduce surgical infections, such as hand-washing protocol and sterile preparation of the operative field [14] (see Table 5 for summary of PCNL recommendations).

Table 6 General recommendations before an active stone removal procedure

Recommendation	Level of evidence	Grade of recommendation
Obtain preoperative urine microscopy and culture	II	A
Treat preoperative UTI if present	II	A
Drain urine if UTI is associated with significant urinary obstruction	I	A

Conclusions

Patients with a positive urine culture must receive preoperative antibiotics appropriately tailored to culture-specific organisms, and a repeat urine culture should be considered before instrumentation (Table 6). If the UTI is

Table 5 Recommendations for prevention of infection and sepsis in therapeutic percutaneous nephrolithotomy

Recommendation	Level of evidence	Grade of recommendation
A urine culture should be performed prior to PCNL	III	A
Preoperative positive culture should be treated prior to PCNL	II	A
All patients who undergo PCNL should receive prophylactic antibiotics	II	A
When antibiotic prophylaxis is used, no specific regimen can be recommended; prophylaxis should be chosen according to regional antibiograms, local resources, and safety of the agent	II	A

associated with significant urinary obstruction, it should be mandatory to drain urine from the affected system for several days with an internal ureteral stent or a percutaneous nephrostomy tube. For any persistent UTI that is not associated with urinary obstruction but rather related to urinary tract or stone bacterial colonization, antibiotics tailored to the culture-specific organism must be administered orally at least 5–7 days or parenterally 24 h before surgery. In uncomplicated patients, SWL does not require periprocedural prophylaxis. Although a single dose of perioperative antibiotics should be adequate in uncomplicated ureteroscopic surgery, the data are not sufficient to comment on the utility of preoperative prophylaxis leading up to percutaneous procedures; still, the data do not support more than 24 h of antibiotics post-PCNL. While a large amount of data exists regarding the use of antibiotics peri-operatively in urinary stone surgery, further studies will help to elucidate the safest practices that will also reduce the growing antibiotic resistance seen today.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest regarding the material and information discussed within this manuscript.

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