Risk factors for sepsis after percutaneous renal stone surgery

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Abstract | Since its introduction into the endourologist's armamentarium almost 40 years ago, percutaneous nephrolithotomy (PCNL) has become the standard of care for patients with large-volume nephrolithiasis. Postoperative infection is one of the most common complications of the procedure, and postoperative sepsis is one of the most detrimental. A number of factors have been found to increase the risk of postoperative sepsis. These include patient characteristics that are known preoperatively, such as urine culture obtained from the bladder or from the renal pelvis if percutaneous access to the renal pelvis is obtained in advance to the procedure. Neurogenic bladder dysfunction secondary to spinal cord injury and anatomical renal abnormalities, such as pelvicalyceal dilatation, have also been associated with increased incidence of fever and sepsis after the procedure. Several intraoperative factors, such as the average renal pressure sustained during PCNL and the operative time, also seem to increase the risk of sepsis. Finally, the contribution of postoperative factors, such as presence of a nephrostomy tube or a urethral catheter, has also been investigated. A short preoperative course of antibiotics has been found to significantly decrease the rate of postoperative fever and sepsis. Novel agents targeted at sepsis prevention and treatment, such as anti-endotoxin antibodies and cholesterol-lowering drugs statins, are currently under investigation.

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Introduction

Since its introduction in 1976, percutaneous nephrolithotomy (PCNL) has become the standard of care at many institutions for the treatment of large renal stones.[1] Ongoing advancements in imaging and endourological instrumentation have made PCNL an effective and safe procedure. However, postoperative fever, pyelonephritis and sepsis are common complications of the procedure that can require additional antibiotic treatment, longer hospital stays and, occasionally, intensive care unit support and auxiliary procedures.

In several series examining the outcomes of PCNL, sepsis was reported to be the most common perioperative cause of death.[2,3] Thus, minimizing the risk of post-PCNL sepsis, in addition to predicting which patients are at greatest risk, is of paramount importance. Many investigators have examined the factors that increase the likelihood of post-PCNL sepsis and several approaches have been implemented to avert it. Here, we will describe the incidence and pathogenesis of sepsis after percutaneous renal stone surgery, before discussing the available literature regarding risk factors, prevention and future treatment possibilities for post-PCNL sepsis.

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Incidence

Although many studies have reported the incidence of sepsis after PCNL, it should be noted that analysis of the literature is difficult owing to the use of differing definitions of sepsis. In 2001, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) published a joint consensus statement on the definitions of sepsis and systemic inflammatory response syndrome (SIRS) (Box 1).[4] Although many recent series use the terms sepsis and SIRS according to these definitions, older reports and smaller retrospective studies often do not conform to the strict definitions. As a result, the quantification of post-PCNL infectious complications across multiple series can be extremely challenging. Furthermore, a number of studies do not differentiate between sepsis and SIRS, even though the latter might not be infectious in aetiology. Here, where relevant, we include the outcome variable that was defined for each series.

Several large series have reported the incidence of sepsis causing mortality after PCNL. In 1993, O'Keefe *et al.*[3] identified six patients who died of sepsis among 700 patients who underwent PCNL. A more recent series (the Clinical Research Office of the Endourological Society [CROES] study) examined an international cohort of >5,000 patients who underwent PCNL and identified only two who died of sepsis.[2]

Less serious infectious complications of PCNL are much more frequent than sepsis and increase in frequency as their severity decreases. For example, in the

CROES study, postoperative fever (although not universally infectious) was the most common postoperative event, reported in 598 patients (10.5%).[2] UTI (that is, fever and positive urine culture requiring prolonged antibiotic course) was less common, with fewer than 30 occurrences (0.6%), and sepsis occurred in fewer than 10 patients (0.2%).[5] In other studies, the rates of post-PCNL sepsis have been reported to range from 0.3% (University of Heidelberg, Germany)[6–8] to 4.7% (Siriraj and Potharam Hospitals, Thailand).[6–8]

Pathogenesis

PCNL is thought to carry a higher risk of infection and sepsis than other 'clean-contaminated' surgical or endourological procedures for a number of reasons. Firstly, bacterial colonization of large renal stones might not permit sterilization of the urine before PCNL, despite antibiotic treatment.[9] Secondly, preoperative obstruction of parts or all of the urinary system by stone burden might impair drainage of infected material, creating a persistent abscess-like bacterial niche.[9,10] Lastly, the minimally invasive nature of PCNL has the potential to create high intrarenal pressure, contributing to pyelotubular, pyelolymphatic and pyelovenous backflow, which can, in turn, introduce bacteria into the systemic circulation.[11,12]

Because the cells of the immune system cannot penetrate their interstitial lattices, kidney stones associated with infected urine (whether struvite or calcareous in composition) are thought to create an optimal environment for bacterial growth and protection. Acting essentially as a foreign body, stones provide bacterial pathogens with the opportunity to form protective biofilms and, therefore, escape eradication with antibiotics.[13] This effect was particularly well illustrated in the classic study by Fowler and colleagues,[14] who demonstrated that pathogenic bacteria can persist in extracted stones even after being soaked in antibacterial solution for several hours.

In addition to bacterial persistence, some researchers have hypothesized that bacterial endotoxins have a major role in post-PCNL sepsis. McAleer *et al.*[15] studied the concentration of endotoxins in infected stones and found that they could reach levels high enough to cause severe sepsis. McAleer's group[16] also reported a case of fatal endotoxemia in a patient who had undergone PCNL and had neither bacteriuria nor bacteremia at any time in the postoperative period. Elevated endotoxin concentrations in the absence of positive blood cultures have been found in multiple other studies of febrile patients after PCNL, providing a satisfactory explanation for sepsis occurring without any bacteriological evidence.[3,17,18]

Other mechanisms might be involved in the development of infectious complications after PCNL. In 1998, a newly discovered class of bacteria, known as nanobacteria, was demonstrated to produce calcium apatite in its cellular envelope.[19] A subsequent study from the same research group examined the presence of nanobacteria in 72 renal stones recovered after lithotripsy; nanobacteria was identified in 70 of these stones.[20] Although a cause-and-effect relationship has not been established between nanobacteria and stone formation or post-PCNL infectious complications, the apparent prevalence of nanobacteria warrants further investigation of these organisms to elucidate their role in the pathogenesis of nephrolithiasis and postoperative infection.

Factors intrinsic to PCNL are also thought to contribute to the risk of infectious complications and sepsis. One such factor is the increased pressure caused by leakage of irrigant fluid into the renal pelvis. The renal calyces abut the collecting duct portion of the nephron and the venules and lymphatic vessels of the renal papillae. When access to the renal pelvis is obtained via calyceal puncture, the normal urothelium is disrupted and lymphatic and venous channels are directly exposed to the irrigant fluid and the renal pelvic environment.[13] If irrigation of the renal pelvis creates pressure that exceeds the resting pressure of these structures, backflow of infected urine can occur and bacteria can become introduced into the systemic circulation. Hinman and Redewill[11] showed that pyelovenous backflow occurs at pressures of 30–35 mmHg in a canine model, and further animal studies have found that this phenomenon can occur at pressures as low as 10–20 mmHg.[12] A number of investigators have measured intrapelvic pressure during PCNL and attempted to correlate this parameter with the incidence of postoperative infectious complications.[21,22]

Key points

- Sepsis after percutaneous nephrolithotomy (PCNL) is uncommon but potentially life threatening
- The most common risk factors associated with post-PCNL sepsis are bacteriuria (in bladder urine or renal pelvis urine), stone size and operative time
- Patient groups with unique anatomical characteristics, such as horseshoe kidney or spinal cord injury, might be at increased risk of sepsis
- Close monitoring is important in patients with risk factors for sepsis as they might require more intense supportive care or admission to an intensive care unit
- Further studies are necessary to understand how to prevent sepsis in high-risk patients

Box 1 | SIRS, infection and sepsis definitions

Systemic inflammatory response syndrome (SIRS)
Two or more of the following:
- Body temperature >38°C or <36°C
- Heart rate >90 bpm
- Respiratory rate >20 breaths/min or PaCO2 <32 mmHg
- White blood cell count >12,000 cells/μl or <4,000 cells/μl

Infection
Pathological process caused by invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic micro-organisms

Sepsis
Clinical syndrome defined by the presence of both SIRS and infection

Severe sepsis
Sepsis resulting in organ dysfunction

Septic shock
Sepsis resulting in acute circulatory failure characterized by persistent arterial hypotension

Table 1 | Preoperative risk factors for infectious complications after PCNL

Study	*n*	End point	Risk factors
Retrospective			
Sharifi Aghdas *et al.* (2006)[29]	217	Postoperative fever	Positive preoperative urine culture ($P=0.02$) Female gender ($P=0.005$) Preoperative nephrostomy ($P=0.041$)
Dogan *et al.* (2007)[28]	338	Postoperative fever	Positive preoperative urine culture ($P<0.05$)
Fernandez *et al.* (2011)[36]	125	Postoperative fever or sepsis	Presence of urinary diversion ($P=0.0387$)
Chen *et al.* (2008)[41]	209	Postoperative SIRS	Stone size ($P=0.001$) Hydronephrosis ($P=0.007$) Staghorn stone ($P=0.001$)
Wang *et al.* (2012)[52]	420	Postoperative septic shock	Leukouria ($P=0.027$)
Prospective			
Mariappan *et al.* (2007)[45]	132	Postoperative SIRS	Stone bulk ($P=0.04$)
Gonen *et al.* (2008)[31]	61	Postoperative fever	Stone size ($P=0.023$)
Draga *et al.* (2009)[33]	90	Postoperative SIRS	Paraplegia (OR 10.7, $P=0.005$) Previous PCNL (OR 3.1, $P=0.022$) Stone in calyceal location (OR 5.8, $P=0.031$)
Kumar *et al.* (2011)[59]	30	Postoperative sepsis (definition not provided)	Serum creatinine ($P=0.008$)
Gutierrez *et al.* (2012)[32]	4,456	Postoperative fever	Preoperative positive urine culture* (OR 2.26, $P<0.001$) Preoperative nephrostomy* (OR 1.77, $P<0.001$) Staghorn calculus* (OR 1.88; $P<0.001$) Diabetes* (OR 1.28, $P=0.046$) Age‡ (OR 0.99, $P=0.022$)

*On univariate and multivariate analysis. ‡On multivariate analysis only. Abbreviations: PCNL, percutaneous nephrolithotomy; SIRS, systemic inflammatory response syndrome

Risk factors for sepsis

Preoperative factors

A number of preoperative factors have been found to increase postoperative sepsis risk in patients undergoing PCNL (Table 1). Most urologists rely on preoperative urine culture to evaluate a patient's likelihood of developing an infectious complication after PCNL.[23–25] If a patient has a positive urine culture, it is common practice to perform sterilization or suppression with antibiotics prior to PCNL.[26,27] The majority of studies that have investigated the significance of preoperative bacteriuria for postoperative infection have found a positive correlation—that is, preoperative bacteruria was a risk factor for postoperative infection.[17,28,29] In their seminal 1991 study examining 117 patients undergoing PCNL or ureteroscopy, Rao *et al.*[17] found that a positive preoperative urine culture was strongly predictive of postoperative infectious complications. A more recent study that retrospectively assessed the incidence of SIRS after PCNL demonstrated that the rate of postoperative SIRS in patients with positive preoperative urine culture was nearly twice that of patients with a sterile urine culture.[30] Similarly, Dogan *et al.*[28] retrospectively compared 82 patients who developed fever and 286 patients who were free from fever after PCNL, and found that individuals in the former group were more than twice as likely to have a positive preoperative urine culture than those in the latter group. A prospective study by Gonen *et al.*[31] showed that only 17% of patients with a sterile urine culture developed postoperative fever compared with 50% of those who had preoperative bacteriuria. Initial analysis of the CROES data also confirmed the importance of preoperative urine culture in predicting the occurrence of infectious complications after PCNL, demonstrating in both univariate and multivariate analyses that a bladder urine culture demonstrating bacteriuria was independently predictive of postoperative fever of ≥38.5°C.[32]

The distribution of bacterial species in preoperative urine culture also seems to differ between patients who develop infectious complications after PCNL and those who do not. In their analysis of the CROES data, Gutierrez *et al.*[32] demonstrated that a fever of ≥38.5°C developed more frequently among patients who had a Gram-negative pathogen in their preoperative urine culture than among those whose urine was colonized with a Gram-positive organism.

In addition to preoperative bacteriological status, many patient characteristics that are routinely ascertained prior to PCNL have been shown to affect infectious complications after the procedure, and these include age, gender, stone composition, stone size, renal insufficiency, metabolic syndrome, paraplegia and neuromuscular disease.[7,9,29] Draga *et al.*[33] assessed >10 preoperative parameters in their retrospective review of 117 patients who underwent PCNL. Using fever that occurred >24 h after the procedure as their primary end point, they found that only history of previous PCNL, paraplegia resulting in neurogenic bladder dysfunction and stone location in the renal pelvis predicted the occurrence of fever. The finding that neurogenic bladder secondary to spinal cord injury predisposes to post-PCNL infectious complications is in agreement with previous studies.[34,35] For example, in a prospective study of 100 patients, Culkin *et al.*[34] found that those with spinal cord injury were three times more likely to develop postoperative fever >101.5°F than ambulatory patients. The only death reported in this cohort was related to postoperative sepsis and occurred in a patient with spinal cord injury.[34] Patients with spinal cord injury are thought to exhibit higher rates of post-PCNL infection and sepsis for a number of reasons, including almost universal bacterial colonization of the urinary tract, propensity to form infected struvite stones and poor mobility, which often results in poor drainage of the urinary system.[35]

In 2011, Fernandez *et al.*[36] investigated perioperative complications of PCNL in patients with a urinary diversion. PCNL was performed in 25 patients with a urinary diversion and the outcomes were retrospectively compared with a group of 100 patients with a native bladder. The researchers found that patients with a urinary diversion had a significantly higher incidence of fever or sepsis than the control group (8% versus 0%; $P=0.0387$), which they attribute to the universally present chronic bacteriuria that occurs in patients with urinary diversion and the comorbidities, such as spinal cord injury, that often exist in patients with urinary diversion.[36] To date, this is the largest series examining infectious complications after PCNL in patients with urinary diversion, and further analysis of larger cohorts, such as that of the global CROES study, might substantiate these findings.

Other patient characteristics have been suggested to predispose patients to post-PCNL infectious complications. A number of studies have examined renal abnormalities, such as horseshoe or pelvic kidney, and found that the rates of postoperative infection were the same or slightly higher than the expected rates in the general population. Gupta *et al.*[37] performed PCNL in 52 anatomically abnormal renal units and found that sepsis occurred in two renal units (in two patients), although sepsis was not defined according to SIRS criteria in this study. In a similar study of 16 patients with renal abnormalities, serious complications, which presumably included sepsis, were not encountered.[38] In an international multi-institutional series that consisted of 17 patients with horseshoe kidneys, fever of unknown origin was reported in one patient and UTI was reported in three patients. No incidence of sepsis was reported.[39] Other studies that have examined larger cohorts of patients found no correlation between kidney anatomy and postoperative infection.[33] The lack of consensus on whether abnormal renal anatomy predisposes to post-PCNL infectious complications suggests this might be an area for future clinical investigation. Although not a congenital renal anatomical abnormality, hydronephrosis has been found to be associated with increased risk of postoperative infectious complications in two studies.[40,41] Most commonly, hydronephrosis is a manifestation of poor drainage of the renal collecting system and, therefore, it is logical to assume that a renal unit with impaired drainage is more likely to experience urinary stasis and infection.

Patients with diabetes mellitus, hypertension or other manifestations of metabolic syndrome were more likely to develop major complications after PCNL (including bleeding requiring intervention, damage to adjacent structures and serious infections) in a study by Tefekli and colleagues,[42] although the types of complications were not stratified. In a more recent study of 30 patients with preoperative renal failure, six patients (20%) developed postoperative sepsis.[43] Interestingly, this study demonstrated a strong, statistically significant association between the preoperative creatinine level (that is, degree of renal failure) and the likelihood of postoperative sepsis.

Early analysis of the CROES study revealed higher Clavien scores (which measure the severity of a complication) to be associated with higher preoperative score according to the American Society of Anaesthesiologists Physical Status Classification System (ASA). Again, however, complications were not stratified and, therefore, the association can be explained by the general debilitation of patients with higher ASA scores.[5] In later, multivariate analysis of the CROES study, Gutierrez *et al.*[32] found that—in addition to a positive preoperative urine culture—patient age, diabetes, preoperative nephrostomy and staghorn calculus were all predictive of postoperative fever ≥38.5°C. The CROES study is the largest multi-institutional database of PCNL outcomes and, therefore, factors that were identified as significant in the analysis of the CROES data, certainly deserve further investigation in order to obtain a mechanistic explanation of their significance. For example, whether diabetes predisposes to postoperative infection because of overall immune suppression or for other reasons is a potential avenue of study.

Table 2 | Intraoperative risk factors for infectious complications after PCNL

Study	*n*	End point	Risk factors
Retrospective			
Dogan *et al.* (2007)[28]	338	Postoperative fever	Positive stone culture ($P<0.05$)
Chen *et al.* (2008)[41]	209	SIRS	Operative time ($P<0.001$) Multiple punctures ($P=0.001$) Blood transfusion ($P<0.001$)
Wang *et al.* (2011)[52]	420	Septic shock	Operative time ($P=0.001$)
Prospective			
Muriappan *et al.* (2007)[45]	132	Postoperative SIRS	Purulent material obtained on first puncture (RR 2.64, $P=0.02$) Positive pelvic urine culture (RR 3.2, $P=0.001$) Positive stone culture (RR=3.2, $P=0.001$)
Zhong *et al.* (2008)[22]	80	Postoperative fever	Mean renal pelvic pressure ≥20 mmHg ($P=0.013$)
Gonen *et al.* (2008)[31]	61	Postoperative fever	Operative time ($P=0.028$) Positive pelvic urine culture ($P=0.028$) Positive stone culture ($P=0.041$)

Abbreviations: PCNL, percutaneous nephrolithotomy; SIRS, systemic inflammatory response syndrome

Intraoperative factors

The bacteriological status of the renal pelvis, revealed when percutaneous access is obtained, is perhaps the most well-studied and well-established risk factor for postoperative infectious complications after PCNL (Table 2). Microorganisms that occupy an obstructed renal pelvis can be quite different from those that colonize the bladder.[40,44] Moreover, colonization of the renal pelvis might exist even in the absence of bacteriuria from a voided or catheterized urine specimen.[45] Margel *et al.*[30] compared organisms identified on a preoperative urine culture with renal pelvis isolates obtained during PCNL and found that patients who developed sepsis postoperatively were much more likely to have a positive renal pelvic urine culture than a positive preoperative voided urine culture. Furthermore, patients who had a negative preoperative urine culture and developed sepsis after PCNL had a distinctly different bacteriological profile from their counterparts who had preoperative bacteriuria. Gram-negative organisms were most commonly isolated from the latter group, whereas enterococci and other Gram-positive organisms were found to be predominantly responsible for sepsis in patients with a negative preoperative culture.[30]

Many other studies have confirmed the importance of stone culture (in other words, the pathogens obtained when stone fragments are incubated in culture media) and renal pelvic urine cultures in predicting infectious complications after PCNL.[9,46,47] Dogan *et al.*[28] demonstrated that stone culture and pelvic urine culture were strongly associated with postoperative sepsis. In fact, all five patients in their study who developed severe sepsis after PCNL had a positive stone culture. However, echoing the findings of Margel and colleagues,[30] they found no association between preoperative urine culture and stone culture; the same organism was isolated from both stone and preoperative urine in only 7% of patients. Although it is difficult to assess which organism was responsible for postoperative sepsis in this context (the investigators did not compare pathogens isolated from the blood of septic patients with their urinary tract cultures), this study strongly suggests that stone colonization rather than preoperative bacteriuria is responsible for infectious complications after PCNL. This finding, as well as the apparent disparity between preoperative urine cultures and the organisms responsible for postoperative sepsis, underscores the importance of broad antibiotic coverage for patients who develop infectious complications after PCNL.

In addition to bacteriological evaluation, other intraoperative parameters have been shown to have an association with sepsis after PCNL. One of these factors is the finding of purulent urine on the initial percutaneous puncture for renal access. Mariappan *et al.*[45] have demonstrated that the finding of cloudy urine on percutaneous puncture is an independent predictor of postoperative SIRS. In this circumstance, it is generally considered safest to abort the procedure, enable maximal drainage of the purulent material with an indwelling nephrostomy tube and return to the operating room after completing a course of antibiotics.[25] However, three studies have challenged this practice. Etemadian *et al.*[48] excluded patients who had an untreated UTI or were found to have thick or foul-smelling purulent urine on the initial percutaneous puncture from their prospective analysis and, in the remaining 31 patients, found no statistical difference in the rates of postoperative fever among patients who had immediate PNCL and those who underwent delayed PCNL owing to the aspiration of purulent urine from the renal pelvis. Hoseini *et al.*[49] assessed 45 patients with purulent urine on initial calyceal puncture without any exclusion criteria and found that infectious complication rates were not statistically different in patients who underwent immediate or delayed PCNL. Aron *et al.*[50] also found statistically identical incidence of fever in patients who underwent delayed PCNL after purulent urine was encountered during the initial access puncture, although the authors offer cautious recommendations owing to the lack of large randomized trials in this field of research.

Intrapelvic pressure during PCNL has been associated with postoperative sepsis in several studies. During lithotripsy, the renal pelvis must be continuously irrigated in order to provide appropriate visibility for the surgeon. At the same time, pyelovenous backflow, whereby infected material might enter the systemic circulation, is thought to be an important mechanism for postoperative bacteremia. When Zhong and co-workers[22] measured intrapelvic pressure during PCNL, they found that persistent renal pelvic pressure of ≥20 mmHg was associated with postoperative fever. Zhong *et al.*[22] also demonstrated a strong association between the period of time that high intrapelvic pressures were maintained and the occurrence of postoperative fever. Specifically, they found that patients who had sustained an intrapelvic pressure ≥30 mmHg for more than 30 s were more likely to develop postoperative fever than patients who did not reach this threshold. Postoperative fever was progressively more likely to occur as the total time that intrapelvic pressure reached 30 mmHg increased from 30 s to 40 s and then to 50 s. On the other hand, in an earlier study by Troxel and Low,[21] no association was found between intrapelvic pressures and the incidence of postoperative fever. However, in this series, when intrapelvic pressure reached 30 mmHg, steps were taken to decrease it and the total time that an elevated pressure was maintained was not documented. In circumstantial support of the findings of Zhong *et al.*,[22] other investigators have found that the amount of irrigant fluid absorbed during PCNL and the overall duration of the operative procedure were also associated with postoperative infectious complications.[10,41,51,52] For example, in a retrospective analysis of 209 patients, Chen *et al.*[41] found that post-PCNL SIRS was associated with a longer mean operative time (132 min compared with 96 min in patients who did not experience SIRS), a difference that was statistically significant. Similarly, Wang *et al.*[52] demonstrated that operative time >90 min was strongly associated with occurrence of septic shock in their cohort of 420 patients. Taken together, these data suggest that minimization of operative time and, perhaps more specifically, minimization of the time that the renal pelvis is exposed to elevated pressures during PCNL results in decreased incidence of infectious complications.

Postoperative factors

In addition to the appropriate choice of antibiotics, a number of factors might have a role in sepsis prevention in the postoperative setting. These include the presence of a percutaneous nephrostomy tube or ureteral stent, presence and size of residual stones and presence and time to removal of a urethral catheter. Tubeless PCNL—which involves internal drainage with a ureteral stent or no drainage at all rather than a nephrostomy tube—has been assessed for safety and compared with traditional 'nephrostomy' PCNL in a number of studies, but none has shown a significant difference in the incidence of postoperative infectious complications between the two procedures.[53–56] However, the findings of the most recent and most extensive series (the CROES study) did demonstrate that leaving a nephrostomy tube in place after the procedure was associated with fever (OR = 1.45, $P = 0.048$) on univariate analysis.[32] Whether this finding is related to the more widespread acceptance of tubeless PCNL remains to be determined.

The contribution of residual stones to postoperative infection has been evaluated in two studies. Gutierrez *et al.*[32] found that the presence of residual stones was associated with increased likelihood of postoperative fever on univariate analysis, whereas Draga *et al.*[33] found that the presence of residual stones was not associated with postoperative fever. Other parameters, such as presence of a urethral catheter postoperatively and the time to its removal, have been investigated less thoroughly but they do not seem to significantly affect the rate of postoperative fever, SIRS or sepsis.[31,33]

The effect of stone composition on the incidence of postoperative infection has not been directly assessed. However, it is likely that PCNL of struvite and apatitie stones carries a particularly high risk of infection. Both struvite and apatite form as a by-product of bacterial metabolism and these stones are almost universally infected. Indeed, in a study of 34 renal calculi, McAleer *et al.*[15] found that 94% of the infected calculi were composed of struvite or apatite and that the levels of endotoxin in these stones were approximately 40 times higher than in uninfected stones, which were represented by calcium oxalate, uric acid and cystine stones.

Prevention of postoperative sepsis

One of the most active areas of study in the management of PCNL complications is the use of antibiotic prophylaxis for sepsis prevention. American Urological Association (AUA) guidelines currently recommend preoperative antibiotic prophylaxis for all patients for a duration of <24 h.[23,57] This recommendation is based on a nonrandomized prospective study that demonstrated a decreased risk of UTI when preoperative ciprofloxacin was given.[51] The European Association of Urology (EAU) also recommends one dose of a prophylactic antibiotic preoperatively, specifying cephalosporins, aminoglycosides and penicillins as acceptable agents.[24] These recommendations were confirmed by the CROES data, which demonstrated a significant increase in the incidence of postoperative fever >38.5°C in a group of patients who did not receive antibiotic prophylaxis before undergoing PCNL compared with a matched cohort of patients who did.[58]

Mariappan *et al.*[26] evaluated prophylactic antibiotic use in patients with stones >2 cm or with a dilated pelvicalyceal system, having previously demonstrated that these patients had a rate of postoperative sepsis fourfold higher than patients without these characteristics.[40] Using patients with stones >2 cm or a dilated pelvicalyceal system from this earlier study as a control, they assessed the effect of a 1-week course of prophylactic dose ciprofloxacin (250 mg twice a day) before PCNL on postoperative sepsis in newly-recruited patients with identical anatomical and stone characteristics.[26,40,45] They found that patients who received preoperative ciprofloxacin were significantly less likely to have infected urine in the renal pelvis and to have positive urine culture than those who did not. Moreover, patients who had received prophylaxis were three times less likely to develop sepsis postoperatively than those who had not. Interestingly, no effect was observed on bladder urine culture sterilization, perhaps underscoring the importance of the upper tract organism (rather than the bladder isolates) in causing postoperative infectious complications.[40]

A number of studies have assessed extended courses of antibiotics both before and after PCNL. In 2011, Bag *et al.*[27] reported on the effectiveness of a 1-week course of nitrofurantoin before PCNL for prevention of postoperative sepsis. They randomized 110 patients with a large renal stone (>2.5 cm) or hydronephrosis (or both) who also had a negative preoperative midstream urine culture to receive either preoperative nitrofurantoin or no antibiotic prophylaxis and assessed them for a number of manifestations of sepsis after the procedure. The investigators found a significantly lower incidence of positive renal pelvic and stone cultures, decreased likelihood of fever, less frequent leukocytosis and decreased endotoxemia in the pretreated group. These outcomes were both statistically and clinically significant; risk analysis revealed that 1 week of preoperative nitrofurantoin decreased the likelihood of sepsis and endotoxemia by 69% and 78%, respectively. In a subsequent study in a different patient cohort, the same research group reported sepsis rates of 19% and 49% in the nitrofurantoin prophylaxis group and control group, respectively.[59] These rates are higher than those reported in most studies in the literature and might reflect a particularly high-risk population treated by these investigators.

Dogan *et al.*[51] compared 41 patients who received a single dose of ofloxacin intraoperatively with 38 patients who received olfloxacin until their nephrostomy tube was removed on postoperative day 3 or 4. No statistical difference was observed in the frequency of fever, bacteriuria and bacteremia between the two groups. The authors concluded that an extended course of antibiotics was not necessary after PCNL. However, this study only included patients with a sterile preoperative urine culture, and whether or not these findings will extend to patients whose preoperative urine demonstrates bacterial growth is unclear.

Because endotoxemia might be involved in post-PCNL sepsis, endotoxin seems to be an attractive target for the prevention and treatment of sepsis in this patient population. Many approaches, including immunomodulation and sequestration of endotoxin by endotoxin-directed antibodies, have been evaluated in clinical trials, but so far none has demonstrated efficacy in decreasing sepsis-related mortality.[60,61] Most recently, a number of observational series have reported that use of cholesterol-lowering statins correlates positively with sepsis-related survival. Although the exact mechanism for this phenomenon remains unknown, statin-mediated modification of the immune response to endotoxins is a possibility.[62] Whether current or future therapies directed against bacterial endotoxins have a role in the prevention and treatment of post-PCNL sepsis remains to be determined.

Conclusions

Minimizing the risk of infectious complications is critically important to reduce the morbidity associated with PCNL. Although serious infections resulting in sepsis or septic shock are rare, they can be devastating and account for the vast majority of post-PCNL mortalities. Fortunately, infection is usually a correctable or modifiable risk. Each patient undergoing PCNL should be assessed and stratified according to his or her risk of developing a serious infection before the procedure.

In our practice, it is standard to obtain a bladder urine culture—or a renal pelvic urine culture if percutaneous access is obtained prior to PCNL—and to treat accordingly. Particular attention is paid to coexisting risk factors and comorbidities. Patients with known struvite or apatite calculi, recurrent pyelonephritis or neurogenic bladder resulting in recurrent UTI and renal deterioration are often referred to the infectious diseases service for preoperative evaluation and might be admitted prior to their scheduled PCNL to receive broad spectrum intravenous antibiotics.

Intraoperatively, care must be taken to minimize intrarenal pressures by ensuring effective continuous drainage of irrigant fluid. Although every effort must be made to render the patient stone-free at the conclusion of PCNL, we also strive to decrease operative time in order to minimize the extent to which the potentially infected contents of the renal pelvis are in contact with the sterile renal parenchyma and bloodstream. The need to abort PCNL if purulent material is encountered on initial access puncture has been called into question by several studies, but it is our practice to delay the procedure until after adequate drainage of the infected material has been achieved.

Postoperatively, the patient must be monitored closely for any signs of SIRS. If preoperative or intraoperative factors raise suspicion for a serious infectious complication postoperatively, the patient should be maintained on broad-spectrum antibiotics for at least 24 h postoperatively. If signs of haemodynamic instability develop, the patient should be transferred to the intensive care unit for continuous monitoring and vasomotor support. If the infectious diseases service is not already involved, a consultation can be obtained for guidance regarding proper antibiotic choice.

Although the risk of serious infectious complications can be decreased, it is unlikely to be eliminated. Future studies aimed at better understanding of sepsis physiology and management will have an important role in decreasing the morbidity associated with this difficult postoperative complication. Although novel agents, such as the anti-endotoxin antibody, have not proven to be beneficial in decreasing the severity of sepsis to date, effective treatment options are likely to become available as research in this area continues to develop.

Review criteria

We performed an extensive PubMed search using the search terms “PCNL”, “percutaneous”, “lithotripsy”, “complication”, “infection”, “fever”, “sepsis” and “SIRS” in various combinations to identify both reviews and original articles. Limits on the year of publication and type of publication were not applied. All publications, including one abstract, were in the English language and all were available in full-text format. The reference list of each publication was reviewed to identify additional articles of interest.

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Author contributions

E. I. Kreydin and B. H. Eisner researched data for the article, contributed to discussion of content, wrote the article and reviewed the manuscript prior to submission.