Original Article

Predictors of post-percutaneous nephrolithotomy sepsis: The Northern Malaysian experience

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Abstract

Objectives: Percutaneous nephrolithotomy (PCNL) carries a small risk of postoperative sepsis due to the liberation of bacteria into the patients' bloodstream during stone fragmentation. The study aims to identify the incidence of post-PCNL sepsis in our center, as well as to delineate perioperative characteristics associated with increased rates of sepsis.

Materials and Methods: We performed a retrospective review on all PCNLs performed in our center between July 2012 and June 2017, with emphasis on preoperative urine results, intra-operative findings, and postoperative septic complications.

Results: Among 425 cases of PCNL performed, 16 (3.76%) developed sepsis postoperatively. Patients with positive preoperative urine cultures were almost four times as likely to develop post-PCNL sepsis compared to those with negative cultures (8.41% vs. 2.2%, $P = 0.004$). Among patients with positive urine leukocytes and positive urine cultures, the presence of Staghorn calculi and multiple PCNL punctures both predicted significantly higher risks of postoperative sepsis. In contrast, diabetes mellitus and preoperative stenting were not found to be associated with a greater risk of post-PCNL sepsis.

Conclusions: Patients who had positive preoperative urine leukocytes and/or cultures, and either harbor Staghorn calculi or are deemed to require more than one puncture on PCNL, were at an increased risk of developing post-PCNL sepsis. Such at-risk patients should be identified preoperatively, given aggressive perioperative antibiotic treatment, and monitored closely for septic complications during the convalescence period.

Keywords: Nephrolithiasis, percutaneous nephrolithotomy, prophylactic antibiotics, sepsis, urine culture

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is an established and effective method in treating renal and upper ureteric stones. In trained hands, it is a relatively safe procedure, and high stone-free rates are consistently achievable.

Its main known complications fall into three major categories; infectious sequelae (fever, sepsis, and septic shock), bleeding (from pseudo-aneurysms or arteriovenous fistulae), and injury to adjacent organs including pleura, colon, and duodenum.

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Post-PCNL sepsis is a relatively uncommon but potentially life-threatening complication that has been reported to occur in 0.3%–9.3% of PCNLs;[1-3] sepsis is also the leading cause of post-PCNL mortality,[4] with mortality rates as high as 80% were reported.[5] The bacteria most commonly implicated in fulminant infective episodes is *E. coli*, with others being Proteus, *Klebsiella,* and *Pseudomonas* spp.[6] During stone manipulation and fragmentation, bacteria contained within the stones and pelvic urine are liberated and introduced into the patient's circulatory system through pyelotubular, pyelolymphatic, and pyelovenous reflux; these processes are enhanced by elevated intrarenal pressures intraoperatively.[7] The intravasated bacteria, as well as associated endotoxins, subsequently trigger multiple inflammatory cascades that culminate in full-blown systemic inflammatory response syndrome (SIRS). In some cases, the infection may be introduced via a nephrostomy tract placed at the end of a procedure.[8]

In light of the significant mortality risk associated with post-CNL sepsis, numerous precautions and maneuvers have been formulated to reduce the risk of this complication, one of which has been extensively studied and utilized is the use of prophylactic antibiotics. Most guidelines recommend the use of prophylactic antibiotics in the perioperative period;[9,10] the choice of antibiotic is based on local bacteriological sensitivity data. The duration of antibiotic treatment with respect to PCNL has been subject to intense research in recent years; current evidence supports the use of antibiotics for not >24 h postoperatively.[11,12]

Sultanah Bahiyah Hospital is a tertiary hospital located in northern Malaysia, serving a population of 2.3 million, spreading an area of 10,248 square kilometers in the northern Malaysian states of Kedah and Perlis.[13] Northern Malaysia is a relatively rural area; therefore, logistic issues preclude the routine collection of urine samples for culture from prospective PCNL patients 1 week before their procedure. As such, our standard operating procedure is to admit patients 2 days before the procedure, collect urine samples for FEME and culture, and then commence patients on prophylactic antibiotics. Patients who are asymptomatic of UTI and have clear urine at renal pelvis urine aspirate will proceed with PCNL. Notwithstanding present guidelines, postoperatively, our patients are administered a 5-day course of antibiotics (initially intravenous, then converted to oral form once they are able to tolerate orally); as such, all patients receive 7 days of antibiotics irrespective of their preoperative urine culture results.

Objectives

This is a retrospective study examining septic outcomes among patients who had PCNL done for 5 years between July 01, 2012 and June 30, 2017 at the Urology Department of Sultanah Bahiyah Hospital, Kedah, Malaysia. Through our study, we sought to identify the rate of post-PCNL sepsis among the patients who underwent the procedure in our center, to delineate the demographic and perioperative risk factors that may have contributed to increased risk of sepsis.

MATERIALS AND METHODS

Patients with upper urinary tract stones that needed PCNL were either referred from other departments within the hospital, neighboring state hospitals, district hospitals, public primary care clinics, or private general practice clinics. Noncomplicated cases were all seen in the outpatient urology clinic. During preoperative assessment, information on patients' demographic characteristics, comorbidities and relevant medical history were recorded. Initial investigations included complete blood count, renal profile, serum uric acid, corrected serum calcium, urine analysis, computed tomography urography, and KUB X-ray. Upper tract urinary stones that were complicated by infection, recurrent intractable pain, or renal impairment attributable to ureteric obstruction were treated initially with the relief of obstruction by ureteric stenting, as well as intravenous antibiotics if an infected pelvicalyceal system was deemed to be present. PCNL was subsequently performed only when such patients had fully recovered from their septic episodes; usually, at least 2 weeks from the time treatment was commenced for the sepsis.

All patients were admitted 2 days prior to the date of PCNL. Upon admission urinalysis and urine culture were obtained, and patients were started preemptively with intravenous antibiotics. Our antibiotics of choice were either ampicillin-sulbactam or cefuroxime, in accordance with our hospital's bacterial antibiotic sensitivity studies. Of note, as urine cultures require a minimum of 48 h' incubation time before a definite result can be obtained, most patients will only have their preoperative urine culture results known after the PCNL has been done.

All PCNL procedures were carried out by a qualified consultant urologist or a urology trainee under close supervision of the consultant, with the procedure being performed under general anesthesia. During surgery, the patient was first placed in lithotomy position, and a 5 French ureteral-renal catheter was introduced into the renal pelvis. If renal pelvis urine aspirate was clear on gross

examination, PCNL was performed. On the other hand, surgery was abandoned if turbid urine or pus was aspirated, and appropriate cultures were sent. This ureteric catheter was then used for contrast injection to guide subsequent fluoroscopic puncture. The patient was then positioned in prone with adequate padding. Fluoroscopy-guided puncture of a renal calyx was done using either the triangulation or the bullseye technique. After securing the calyceal puncture, the tract was serially dilated using Amplatz dilators (Cook Medical) to fit a 28 French Amplatz sheath. Following that nephroscopy was performed with a rigid 25 French Olympus nephroscope. Stone fragmentation was then carried out using a combination of ultrasonic, pneumatic, or holmium laser lithotripsy. On completion of stone fragmentation and evacuation, a ureteric stent was inserted antegrade if deemed necessary, followed by an 18 French Foley catheter with its balloon inflated to 3cc into the sheath tract as a nephrostomy tube.

Postoperatively, complete blood count, renal profile, chest X-ray, and KUB X-ray were ordered. The nephrostomy tube was removed within 48 h if a re-look PCNL was not necessary. Ureteric stents, if inserted intra-operatively, were removed via flexible cystoscopy at 1 month post-PCNL if there were no other indications to keep the stent *in situ.*

A patient was considered to have SIRS if there were two or more of the following: (1) core temperature >38°C or <36°C; (2) heart rate >90 beats/min; (3) respiratory rate >20 breaths/min or PaCO2 of <32 mmHg; (4) white blood cell count of >12,000/µL or <4000/µL.

All data pertaining to patients who had undergone PCNL within the study period were retrieved from the central operating database and reviewed. Fifty-three cases were excluded due to having at least one exclusion criteria, which included bilateral PCNL within the same operation (5 cases), encrusted stents (15 cases), patients with ileal conduits (1 case), pre-existing nephrostomy (29 cases), and incomplete data (5 cases). Two patients had two exclusion criteria each.

Parametric data were statistically examined with the Student's *t*-test, whereas for nonparametric data, the Chi-square test was used. A value of $P < 0.05$ was considered to represent statistical significance.

RESULTS

A total of 483 PCNLs were performed in 478 subjects within a 5-year period. Four hundred and twenty-five PCNLs were considered in the study, including five patients

who underwent bilateral PCNLs performed at separate sittings.

A hundred and ninety-five PCNLs (46%) were performed for Staghorn calculi, while 230 cases (54%) were nonstaghorn calculi. Diabetes mellitus was present in 142 (34%) patients, whereas 283 patients (66%) were nondiabetic. One hundred and fifty-one subjects (36%) had preoperative ureteric stents, while 274 patients (64%) were not stented preoperatively. Three hundred and forty-six out of 425 subjects (81%) were positive for urinary leukocytes on preoperative urine analysis. Meanwhile, 18% (77 out of 425) of patients had positive preoperative urinary nitrates. A hundred and seven cases (25%) documented positive urinary cultures (which was only known postoperatively), while the other 318 (75%) had negative urine culture results [Table 1].

Postoperatively, 24 patients (5.65%) developed SIRS, while 16 cases (3.76%) were complicated with sepsis; however, no sepsis-related mortality was recorded [Table 2]. All cases of sepsis or SIRS had manifested within 48 h of the procedure.

For patients with positive preoperative urine leucocytes, 15 of 346 cases (4.36%) were complicated by postoperative sepsis. In contrast, only one of 79 subjects (1.27%) with negative preoperative urine leucocytes had sepsis; this, however, failed to reach statistical significance ($P = 0.196$). Among patients with positive preoperative urine nitrates, 2.60% (2 of 77) had postoperative sepsis. Surprisingly, for subjects with negative pre-operative urine nitrates, 14 of 348 (4.02%) developed post-PCNL sepsis; this too, was not statistically significant ($P = 0.552$). Nine of 107 patients (8.41%) with positive preoperative urine

Table 1: Preoperative variables

	n=425; 100%, n (%)
Type of stones	
Staghorn	195 (46)
Nonstaghorn	230 (54)
Diabetes mellitus	
Diabetic	142 (34)
Nondiabetic	283 (66)
Preoperative stenting	
Stented	151 (36)
No stent	274 (64)
Preoperative urine leucocytes	
Positive	346 (81)
Negative	79 (19)
Preoperative urine nitrates	
Positive	77 (18)
Negative	348 (89)
Preoperative urine cultures (not known preoperatively)	
Positive	107 (25)
Negative	318 (75)

cultures had postoperative sepsis. On the contrary, 2.20% or 7 of 318 cases with negative preoperative urine cultures were complicated by postoperative sepsis. This finding was statistically significant, with $P = 0.004$ [Table 3].

In an effort to establish a correlation between preoperative urine results, preoperative patient and stone characteristics, and the prevalence septic outcomes, we performed subgroup analyses on patients with positive urine leukocyte, nitrate, and culture results. Among subjects with positive preoperative urine leukocytes, there was no statistical difference between diabetic and nondiabetic patients who developed post PCNL sepsis with $P = 0.552$. Six of 114 (5.26%) diabetics had sepsis, whereas 9 of 232 (3.88%) nondiabetics were septic. Patients with staghorn calculi had a statistically significant higher incidence of postoperative sepsis (12 of 165 [7.27%] cases, $P = 0.010$). In comparison, 3 of 181 (1.66%) nonstaghorn cases were complicated with sepsis. Six of 145 (4.14%) patients with preoperative stenting had sepsis, whereas 9 of 201 (4.48%) patients with no preoperative stenting were complicated by sepsis. This was not statistically significant with $P = 0.878$. Cases, in which multiple calyceal punctures, were made (7 of 57, 12.28%) were significantly more likely to develop post-PCNL sepsis compared to cases involving single punctures (8 out of 289, 2.77%), with a $P = 0.001$ [Table 4].

In the subgroup analysis of patients with positive preoperative urine nitrates, it was found that glycaemic status did not significantly influence the risk of postoperative sepsis ($P = 0.560$). One of 24 (4.17%) diabetic patients had sepsis, and similarly, only one of 53 (1.89%) nondiabetic patients developed sepsis postoperatively. There was no

statistical significance in septic complication rates across types of stones. Among patients with Staghorn calculi, 2 of 44 (4.55%) had sepsis, whereas no patients with nonstaghorn calculi developed septic complications ($P = 0.215$). Similarly, there was no statistical significance in septic rates between patients with and without preoperative ureteric stenting. The incidence of sepsis was 1 out of 41 (2.44%) and 1 out of 36 (2.78%), respectively, with $P = 0.926$. Although there were more patients (one out of 11, 9.09%) with multiple calyceal punctures who developed sepsis as compared to those with single punctures (one out of 66, 1.52%), there was no statistical significance with $P = 0.144$ [Table 5].

Among cases with positive preoperative urine cultures, diabetic patients had a higher risk of getting post PCNL sepsis (6 out of 46, 13.04%) compared to nondiabetic subjects (3 out of 61, 4.92%). However, it failed to show any statistical significance with $P = 0.134$. On the other hand, PCNL done on Staghorn stones resulted in a statistically significant ($P = 0.010$) higher risk of postoperative sepsis, in which 8 of 51 cases (15.69%) were afflicted. In contrast, for nonstaghorn calculi, only one of 56 cases had sepsis. Among patients who were stented preoperatively, 5 of 54 (9.26%) patients had sepsis, whereas 4 of 53 (7.55%) patients who did not have ureteric stents developed sepsis; there was no statistical difference ($P = 0.75$). Multiple PCNL punctures lead to a significantly higher risk of sepsis when compared to cases performed with a single puncture. In these two groups, 6 of 15 (40%) and 3 of 92 (3.26%) cases developed sepsis, respectively, and the P value for this was 0.005 [Table 6].

DISCUSSION

It is within general consensus that before PCNL, a preoperative voided urine culture should be obtained, as a positive preoperative urine culture has been associated with increased infectious risk (with an odds ratio of 2.2–16.7).[6,14] This has been well demonstrated in our study, in which patients with positive preoperative urine cultures had a nearly four-fold increase in the risk of post-PCNL sepsis (8.41% vs. 2.2%, $P = 0.004$). However, it is also well known that negative bladder urine cultures do not exclude the presence of bacteria within stones or the renal pelvis.[15] In fact, among patients with negative bladder urine cultures, as many as a third harbor infected pelvic urine, and half of these patients have positive stone cultures.[16]

In view of the high probability of pelvic bacteriuria among PCNL patients, it would be logical to administer prophylactic antibiotics to all patients undergoing the procedure. Indeed, it has been demonstrated that antibiotic

Table 2: Postoperative septic outcomes

Outcome	n=425; 100%, n (%)
No SIRS or sepsis	385 (90.59)
SIRS (without sepsis)	24 (5.65)
Sepsis	16 (3.76)
SIRS + sepsis	40 (9.41)

SIRS: Systemic inflammatory response syndrome

Table 3: Comparison of preoperative urine results and rates of sepsis

	Sepsis (n=16), n (%)	No sepsis (n=409), n (%)	P
Preoperative urine leucocytes			
Positive, 346 (100)	15 (4.36)	331 (95.66)	0.196
Negative, 79 (100)	1 (1.27)	78 (98.73)	
Preoperative urine nitrates			
Positive, 77 (100)	2 (2.60)	75 (97.40)	0.552
Negative, 348 (100)	14 (4.02)	334 (95.98)	
Preoperative urine culture s			
Positive, 107 (100)	9 (8.41)	98 (91.59)	0.004
Negative, 318 (100)	7 (2.20)	311 (97.80)	

Table 4: Subgroup analysis of patients with positive preoperative urine leucocytes

Positive urine leucocytes (n=346), n (%)	Sepsis (n=15), n (%)	No sepsis (n=331), n (%)	P
Diabetic status			
Diabetic, 114 (100)	6 (5.26)	108 (94.74)	0.552
Nondiabetic, 232 (100)	9 (7.27)	223 (96.12)	
Type of stone			
Staghorn, 165 (100)	12 (7.27)	153 (92.73)	0.010
Nonstaghorn, 181 (100)	3 (1.66)	178 (98.34)	
Preoperative stenting			
Prestented, 145 (100)	6 (4.14)	139 (95.86)	0.878
Not prestented, 201 (100)	9 (4.48)	192 (95.52)	
Number of punctures			
Single puncture, 289 (100)	8 (2.77)	281 (97.23)	0.001
Multiple puncture, 57 (100)	7 (12.28)	50 (87.72)	

Table 5: Subgroup analysis of patients with positive preoperative urine nitrates

Positive urine nitrates (n=77), n (%)	Sepsis (n=2), n (%)	No sepsis (n=75), n (%)	P
Diabetic status			
Diabetic, 24 (100)	1 (4.17)	23 (95.83)	0.560
Nondiabetic, 53 (100)	1 (1.89)	52 (98.11)	
Type of stone			
Staghorn, 44 (100)	2 (4.55)	42 (95.45)	0.215
Nonstaghorn, 33 (100)	0 (0)	33 (100)	
Preoperative stenting			
Prestented, 41 (100)	1 (2.44)	40 (97.56)	0.926
Not prestented, 36 (100)	1 (2.78)	35 (97.22)	
Number of punctures			
Single puncture, 66 (100)	1 (1.51)	65 (98.48)	0.144
Multiple puncture, 11 (100)	1 (9.09)	10 (90.91)	

Table 6: Subgroup analysis of patients with positive preoperative urine cultures

Positive urine cultures (n=107), n (%)	Sepsis (n=9), n (%)	No sepsis (n=98), n (%)	P
Diabetic status			
Diabetic, 46 (100)	6 (13.04)	40 (86.96)	0.134
Nondiabetic, 61 (100)	3 (4.92)	58 (95.08)	
Type of stone			
Staghorn, 51 (100)	8 (15.69)	43 (84.31)	0.010
Nonstaghorn, 56 (100)	1 (1.79)	55 (98.21)	
Preoperative stenting			
Prestented, 54 (100)	5 (9.26)	49 (90.74)	0.750
Not prestented, 53 (100)	4 (7.55)	49 (92.45)	
Number of punctures			
Single puncture, 92 (100)	3 (3.26)	89 (96.74)	<0.005
Multiple puncture, 15 (100)	6 (40.00)	9 (60.00)	

prophylaxis did result in fewer infective postoperative sequelae, even in patients with negative preoperative urine cultures.[17,18] While current recommendations favor the use of single-dose prophylaxis, real-world evidence on the duration of antibiotic prophylaxis has been conflicting. Some studies suggest that even "high risk" cases (previous history of urinary tract infection, hydronephrosis, or stone size 2 cm or larger), prolonged preoperative antibiotics regimes may not alter the risk of SIRS;[19] while others have found that antibiotics given for as long as a week preoperatively may significantly reduce infective complications.[17,20] When the type of antibiotic used is taken into consideration, it has been shown that the most commonly used antibiotics are equally effective.[21] Of particular relevance to our practice is the study by Seyrek *et al.*; in their study, a head-to-head comparison was made between ampicillin-sulbactam and cefuroxime (the two most commonly used antibiotics in our center), and both were found to be equally effective.[12]

As mentioned earlier, patients undergoing PCNL in our center are admitted 2 days before surgery and have their voided urine cultures collected. Unfortunately, results of these urine samples are usually not available until after the procedure, which means we were unable to utilize culture results to decide if a patient should proceed with PCNL or not, and also if a patient requires a full course of antibiotic therapy to eradicate preexisting infection before PCNL. Hence, we commence all patients on 2 days of antibiotics before surgery, with the aim to provide adequate urinary bacterial clearance in all patients planned for PCNL.

In an effort to preemptively identify patients who are at greater risk of developing post-PCNL sepsis, numerous authors have put forward various demographic, clinicopathological, and preoperative characteristics that may render patients more susceptible to severe infective sequelae. The risk factors that have been most consistently identified are larger stone size,[22,23] Staghorn calculi,[22] multiple tracts for access,[16,22] and significant intra-operative bleeding requiring transfusion.[3,23] Diabetes mellitus was found to be a risk factor for postoperative fever but not sepsis.[6] In this study, we identified Staghorn calculi and multiple punctures as risk factors for sepsis, consistent with the results above. There were no published studies that implicated preoperative ureteric stenting as a risk factor for sepsis. Two studies suggested that preoperative nephrostomy significantly increased the risk of postoperative fever;[6,24] however, such patients in our center were excluded from the study. It is worthy to note that positive urine leucocytes have also been named as a risk

factor for post-PCNL septic shock;[25] as will be described in the next paragraphs, this may have implications on the preoperative management of our patients.

Based on the data of this study, it is clear that even multiple doses of preoperative antibiotics may be inadequate in sufficiently clearing urinary tract infection among certain patient populations. Among patients whose preoperative urine samples that were positive for leukocytes or bacterial cultures, the risk of developing post-PCNL sepsis was significantly higher if they either had Staghorn calculi or if they required more than one puncture for stone clearance. Both these clinicopathological features result in greater bacterial loads that intravasate into the circulatory system during PCNL, thus leading to a higher risk of sepsis. In addition, both Staghorn calculi and multi-puncture procedures may result in greater blood loss, which has also been identified as a risk factor for post-PCNL sepsis.

The practical implications of our study may be summarized as follow. In patients with Staghorn calculi and/or are anticipated to require multiple PCNL punctures for stone clearance, positive preoperative voided urine cultures may indicate that 2-day preoperative antibiotics are inadequate for the prevention of sepsis, and hence, such patients require a longer course of antibiotic treatment for complete eradication of bacteriuria prior to their PCNL. In the absence of urine culture results, urine leukocytes may serve as a surrogate marker for the risk of sepsis (in this particular subgroup of patients only). Simple examination of urine for leucocytes may be performed in the health-care facility most convenient for the patient as early as a week before PCNL, and if found to be positive, definitive antibiotic treatment may be commenced a few days prior to admission.

Another interesting finding obtained from our study is that a significant majority (91.59%) of patients who had positive preoperative urine cultures eventually did not develop post-PCNL sepsis. A few postulations can be made to explain this phenomenon. First, the preexisting urinary tract infection may have been adequately eradicated by empirical preoperative antibiotics (with the exception of some cases, as highlighted in the next paragraph). Second, bacteriuria in voided samples merely represents colonization of the patients' lower urinary tracts while the upper tracts remain relatively sterile. Finally, but also very importantly, bacterial growth in voided samples may be a result of *ex-vivo* contamination, especially if the cultured bacterial species is not consistent with common urinary tract flora.

CONCLUSION

In general, patients who underwent PCNL in northern Malaysia had a high incidence of staghorn calculi, diabetes mellitus, and preoperative ureteric stent placement. At the same time, positive findings in preoperative voided urine samples were highly prevalent. The overall rate of post-PCNL sepsis was 3.76%. Among asymptomatic patients with positive preoperative urinary leucocytes and positive urinary cultures, a greater risk of postoperative sepsis was predicted by the presence of staghorn calculi, as well as the utilization of multiple calyceal punctures intra-operatively.

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Conflicts of interest
There are no conflicts of interest.

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