ORIGINAL ARTICLE

Bacteriology and Antibiotic Sensitivity Pattern of Isolates in Patients who Underwent Percutaneous Nephrolithotripsy (PCNL) at the Philippine General Hospital: A Retrospective Cohort Study

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ABSTRACT

Background. Despite being a clean-contaminated procedure, performed only in patients with sterile urine preoperatively, percutaneous nephrolithotripsy (PCNL) is associated with significant infectious perioperative complications. A local antibiogram is of paramount importance in optimizing antibiotic prophylaxis in PCNL because of the substantial variation in bacterial distribution and antibiotic sensitivity worldwide.

Objectives. The incidence of post-PCNL infectious complications, microorganism distribution, and antibiotic sensitivities from patients admitted for PCNL was determined. The risk factors associated with positive cultures and the development of fever and bacteremia were also analyzed.

Methods. A retrospective study of 102 patients who underwent PCNL under a surveillance protocol was done. The susceptibility of isolates from different specimens was evaluated against the most common antibiotics in the hospital. Chi-square and Student's t-test were used to determine differences in the frequencies and means for other risk factors for those who developed fever and urosepsis and those who did not.

Results. The incidence of fever and urosepsis was 25% and 4%, respectively. The most common organism on urine specimens was *Escherichia coli* which showed high sensitivity to aminoglycosides. The most common isolate on stones was *Pseudomonas aeruginosa*, which showed higher sensitivities to the fluoroquinolones. The isolates showed nearly consistent resistance to ceftriaxone. No significant association was found between the clinical variables studied and the occurrence of infectious complications.

Conclusion. There are comparable rates of infectious complications to published literature. A change in antibiotic prophylaxis was warranted, given the high resistance to ceftriaxone and the predominance of *Pseudomonas aeruginosa* on stone isolates. Further surveillance is required to identify significant risk factors for the development of post-PCNL infectious complications.

Key Words: percutaneous nephrolithotomies, bacteriology, antibiogram, urosepsis, nephrolithiasis

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INTRODUCTION

Percutaneous nephrolithotripsy (PCNL) is considered the standard treatment for high volume renal stones, stones resistant to extracorporeal shockwave lithotripsy (ESWL), and multiple and inferior calyx renal stones.[1] Through a small incision in the flank area, the kidney stones are visualized via a nephroscope and broken up most commonly using ultrasonic or pneumatic lithotripter. A minimally-invasive surgery, PCNL is more cost-effective. It is associated with shorter operative time, less postoperative pain and morbidity, and a shorter hospital stay than its open surgery counterpart.[1,2]

Although classified as a clean-contaminated procedure, PCNL is associated with significant rates of infection-related perioperative complications, such as pyrexia (74%) and postoperative bacteremia (37%), and with extended hospital stays as a result.[1] Postoperative fever is characterized by a core body temperature of 38.5°C or higher, and its occurrence with positive urine/ blood culture results indicates urosepsis. The risk of infection, often caused by surgical manipulation and instrumentation and by the release of inflammatory mediators and microorganisms into the bloodstream upon stone fragmentation, is increased by a higher stone burden, longer operative time, and the use of more irrigation. Antibiotics are therefore often administered prophylactically and postoperatively.[2,3]

A considerable variation in bacterial distribution and antibiotic susceptibility worldwide has been established.[4-6] Hence, local and institutional antibiograms, based on previous culture results, is of paramount importance in optimizing antibiotic prophylaxis in PCNL.

At the time of the study, the standard prophylactic antibiotic used for PNCL at the hospital was 2 grams of ceftriaxone given intravenously before induction of anesthesia, with patients developing postoperative pyrexia and bacteremia started on culture-guided antibiotics. This protocol has yet to be validated in the effective prevention of postoperative infection.

This study aimed to determine the incidence of post-PCNL infectious complications, the microorganism distribution, and the antibiotic sensitivity patterns of the microorganisms isolated at different time points of the patient's admission among patients admitted for elective PCNL at a tertiary, government-funded hospital in Manila, Philippines. It also determined the association of different clinical variables with positive urine culture results and postoperative fever and bacteremia development.

MATERIALS AND METHODS

Study Design, Setting, and Participants

A retrospective cohort study was conducted of adult patients who underwent PCNL from January 2018 to December 2018 at Philippine General Hospital (PGH), a tertiary, government-funded hospital in Manila, Philippines. Patients eligible for inclusion in the study were adults aged >18 years. They were admitted for elective PCNL, with a greater than 2 cm stone burden or stones resistant to extracorporeal shockwave lithotripsy.

Variables

All patients were handled according to the PGH-Urology PCNL Urinary Tract Infection Surveillance Protocol, illustrated in Figure 1. Under the protocol, a baseline urine culture was obtained at the outpatient clinic for patients who underwent PCNL (initial urine CS). Only patients with sterile preadmission urine culture were admitted for PCNL within two weeks of the culture result. Patients with positive initial urine cultures underwent appropriate outpatient antibiotic therapy. A urine culture was repeated to ensure that urine was sterile when the patient was admitted for PCNL.

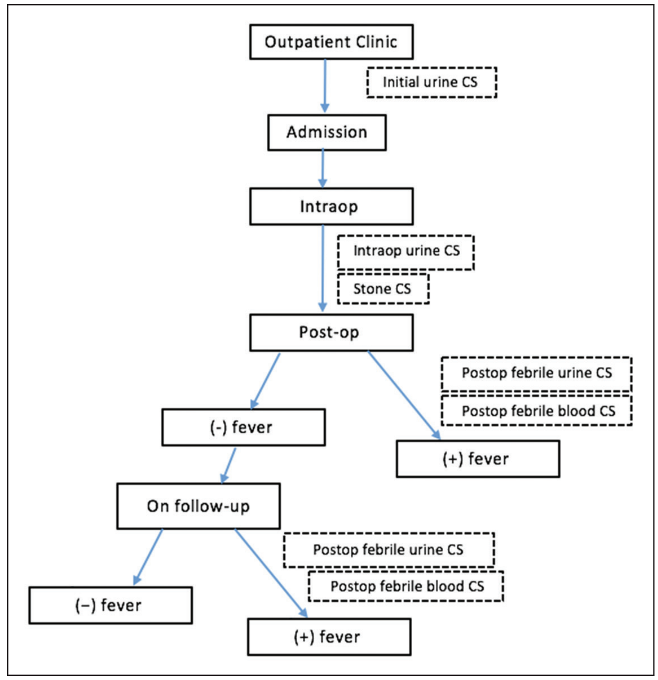

Figure 1. Flowchart depicting the PGH- Urology PCNL Urinary Tract Infection Surveillance Protocol. Texts in dashed boxes represent specimen samples to be obtained at a particular step in the algorithm.

PCNL was performed no later than 48 hours from the time of admission. All patients were administered Ceftriaxone 2g IV at anesthesia induction within 1 hour before starting the PCNL procedure, conducted as standard practice.

Under the surveillance protocol, several specimens were collected and submitted for culture and sensitivity studies. On the first successful percutaneous puncture into the renal collecting system, a sample for intraoperative urine culture study was obtained (Intraop urine CS), and stone fragments with an aggregate volume of at least 0.5 cm^3 were submitted for culture studies (Stone CS). All postoperative patients were monitored for the occurrence of fever. If fever occurred before hospital discharge, when a tube nephrostomy is still in place, urine was collected from the tube nephrostomy for culture studies (Postop Febrile Urine CS). Midstream voided urine was collected if the tube nephrostomy has been removed when fever develops. At the same time, blood from two sites was also collected at the height of fever (Postop Febrile Blood CS).

Patients were discharged on the day of tube nephrostomy removal, typically 1-3 days postoperatively. At discharge, patients were advised to proceed to the emergency room for immediate admission if fever occurs within 30 days of the surgery. Within 12 hours of readmission, other urine and blood specimens were collected as above. Patients who developed postoperative fever (temperature of 38.5°C or higher) and had positive urine culture and blood culture results were diagnosed and managed as cases of urosepsis.

Data Sources/Measurements

Data from the PGH Urology PCNL Urinary Tract Infection Surveillance Form, patient records, and microbiology logbooks were collected and collated by a research assistant in an electronic database. The susceptibility and resistance pattern of isolated bacteria from urine, stone, and blood cultures was evaluated against the most commonly available antibiotics in the PGH: Ampicillin-sulbactam, Amoxicillin-clavulanic acid, Cotrimoxazole, Cefazolin (1st generation cephalosporin), Cefuroxime (2nd generation cephalosporin), Ceftriaxone (3rd generation cephalosporin), Ciprofloxacin (quinolone), Nitrofurantoin, Gentamicin, and carbapenems (Imipenem and Meropenem). Counts, frequencies, and frequency distributions were computed. A more limited sensitivity pattern was employed for particular isolates due to the lack of breakpoints in the antibiotic discs.

Statistical Methods

Statistical analysis was performed using the Statistical Package for Social Sciences, version 25.0 (SPSS, Inc., Chicago, IL). The baseline patient characteristics and outcomes are presented as frequencies and percentages or means and standard deviations tables. The differences in means were analyzed using the student's t-test. The Chi-square test was used to determine differences of proportions for categorical variables for those with and without postoperative fever and those who had and did not have urosepsis. Logistic regression was used to consider associations between clinical and operative factors and dichotomous postoperative fever and urosepsis outcomes while controlling for other factors. The variables analyzed included: the presence of diabetes mellitus, immunocompromised state, results of initial urine, intraoperative urine, and stone cultures, presence of a staghorn calculus, stone burden, intake of antibiotics within the previous one-month, preoperative nephrostomy or urinary stent placement, operative time, and the amount of irrigating fluid used. A difference was considered statistically significant if the p-value was less than 0.05.

The study protocol was reviewed and approved by the hospital's Research Ethics Board. The study was conducted following ICH-GCP principles, the provisions of the National Ethical Guideline for Health-related research of 2017, and the Data Privacy Act of 2012 (RA10173).

RESULTS

Population characteristics, clinical and intraoperative parameters

Between January to December 2018, 103 PCNLs were initially qualified for inclusion, having had all necessary samples were taken preoperatively, intraoperative, and upon the development of fever. One case was excluded due to incomplete clinical data and lack of intraoperative urine and stone specimens' analyses. Patient characteristics and intraoperative parameters for the remaining 102 are shown in Table 1.

Preoperatively, 97 (95.1 %) of the included PCNLs had sterile urine before elective admission, 5 (4.9 %) had positive initial urine cultures.

Incidence of infectious complications

Twenty-five percent (26/102) and 3.9% (4/102) of PCNL-treated patients developed fever and urosepsis, respectively, in the postoperative period despite receiving antibiotic prophylaxis. Of the 26 febrile patients, none (0%) showed positive isolates on the febrile urine, and 4 (3.9%) grew microorganisms in the febrile blood cultures.

Frequency distribution and antibiogram of isolates

The frequency distribution of the different isolates found in the initial urine CS, intraoperative urine CS, stone CS, febrile urine CS, and febrile blood CS is outlined in Table 2. Seven isolates were recovered from the initial urine CS

Table 1. Patient characteristics and intraoperative parameters of 102 patients who underwent PCNL from January to December 2018

Patient characteristic	Value	
Age (years) – mean (SD)	49.34 (3.54)	
Stone Burden (cm³) – mean (SD)	7.28 (3.67)†	
Creatinine (µmol/L) – mean (SD)	104.70 (4.24)	
Diabetes – n/102 (%)	16 (15.7)	
Immunocompromised state – n/102 (%)	1 (0.98)*	
With staghorn calculus – n/102 (%)	40 (39.2)	
Antibiotics within 1 month – n/102 (%)	15 (14.7)	
Preoperative nephrostomy / DJS insertion – n/102 (%)	7 (6.9)	
Positive initial urine CS – n/102 (%)	5 (4.9)	
Intraoperative parameter	**mean (SD)**	**Range**
OR time (minutes)	121.63 (180.31)	15-405
Amount of Irrigating fluid used (liters)	15.31 (45.25)	0.2-120
	n/102 (%)	
Positive intraoperative urine CS	6 (5.9)	
Positive stone CS	44 (43.1)	

SD = standard deviation
† computed as: stone burden for each stone = 0.785 x length x width (sum of individual stone burdens if multiple stones)
** diagnosed with stage IV breast cancer*

Table 2. The frequency distribution of the different isolates found in the preadmission urine CS, intraoperative urine CS, stone CS, febrile urine CS, and febrile blood CS

Isolates	Number of isolates by timing and type of culture study					
	Initial urine CS (n = 102)	Intraoperative urine CS (n = 102)	Stone CS (n = 102)	Febrile urine CS (n = 26)	Febrile blood CS (n = 26)	Any CS (n = 102)
Escherichia coli ESBL (-)	2	3	5		1	11
Escherichia coli ESBL (+)	2		5			7
Pseudomonas aeruginosa		1	23			24
Proteus mirabilis	1		1			2
Providencia rettgeri	1					1
Morganella morganii	1					1
Enterococcus faecalis		2	1			3
Methicillin-resistant *Staphylococcus aureus*		1				1
Pseudomonas aeruginosa carbapenemase (+)			1			1
Klebsiella pneumonia			1			1
Pseudomonas maltophilia			4			4
Stenotrophomonas maltophilia			3			3
Acinetobacter baumanii			1			1
Staphylococcus epidermidis			1			1
Achromo dentrificans			1			1
Staphylococcus capitis			1			1
Spingomonas paucimobilis					1	1
Methicillin-resistant *Staphylococcus epidermidis*					1	1
Staphylococcus hominis SS hominis					1	1

in five patients, seven from intraoperative urine CS in six patients, forty-eight from stone CS in forty-four patients, none from febrile urine CS, and four from febrile blood CS in four patients. The most common organism isolated on the urine specimens was *Escherichia coli*, both ESBL (-) and ESBL (+) strains. This organism is also among the most common isolate found in stone CS, but a significant number of *Pseudomonas aeruginosa, Pseudomonas maltophilia,* and *Stenotrophomonas maltophilia* were also cultured.

The antibiotic sensitivities of the different isolates found in the initial urine CS, intraoperative urine CS, stone CS, and febrile blood CS are outlined in Figures 2 to 5. The isolates showed nearly consistent resistance to ceftriaxone.

The *Escherichia coli* isolated from the initial urine CS showed the highest sensitivity to cefepime, carbapenems, and piperacillin-tazobactam. This sensitivity was also similar to the isolates of *E. coli* cultured in the intraoperative urine GSCS. The ESBL (+) *E. coli* cultured on the stone samples also showed high sensitivity to carbapenems along with the aminoglycoside, gentamicin. The ESBL (-) isolates on stone samples were also most sensitive to carbapenems and piperacillin-tazobactam, less to gentamicin.

The other major pathogens that grew on stone cultures were *Pseudomonas aeruginosa, Pseudomonas maltophilia,* and *Stenotrophomonas maltophilia*. These microorganisms showed higher sensitivities to the fluoroquinolones, Ciprofloxacin and Levofloxacin.

Risk factor analysis

Tables 3 and 4 present the demographic, clinical, and intraoperative factors between those with and without postoperative fever and urosepsis development. Neither univariate analysis nor logistic regressions showed that any of the parameters analyzed were significantly associated with the development of postoperative fever or urosepsis.

DISCUSSION

Twenty-five percent (26/102) and 3.9 % (4/102) of PCNL-treated patients developed fever and urosepsis, respectively, in the postoperative period despite receiving antibiotic prophylaxis. These rates are consistent with those cited in previous literature, which showed 21-39.8% incidence of postoperative fever, 0.3-4.7% of which eventually succumb to potentially life-threatening sepsis.[7-9]

These data support previous findings that antibiotic prophylaxis fails to eliminate the risk of infection associated with the PCNL procedure. The failure to eradicate this common PCNL morbidity may be attributed mainly to (1) the administration of inappropriate antibiotics for the bacterial culture present in the upper, often obstructed, upper urinary tract or (2) to bacterial antibiotic resistance.[10, 11] Antibiogram of the isolates in our cases showed nearly consistent resistance to ceftriaxone. This finding suggests a need to change the antibiotic prophylaxis utilized in the surveillance protocol.

The isolates obtained from the different specimens obtained were found to be discordant. Only 1 showed similar microorganism (ESBL (+) E. coli) obtained in the initial urine CS and stone CS. It may be that the perioperative antibiotics may suppress the growth and inhibit colony formation in one specimen but not in another. It may also

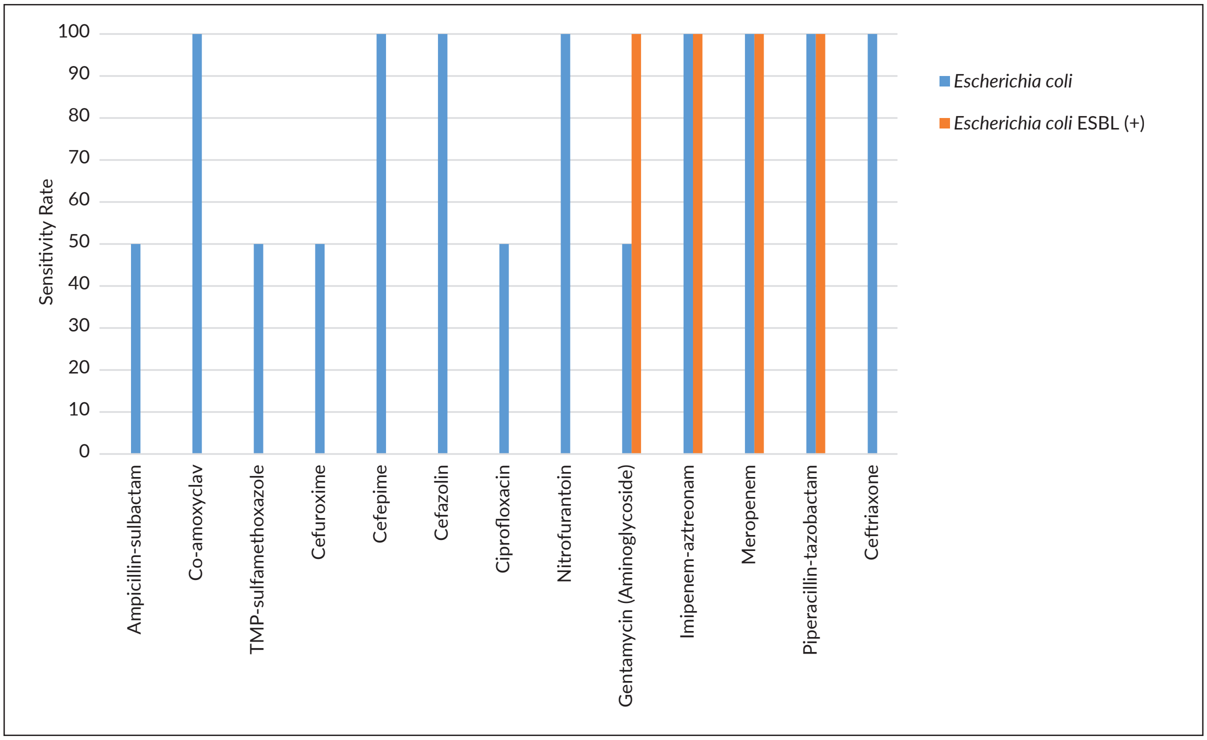

Figure 2. Antibiotic Sensitivity Rates of the most common isolates on Initial Urine CS.

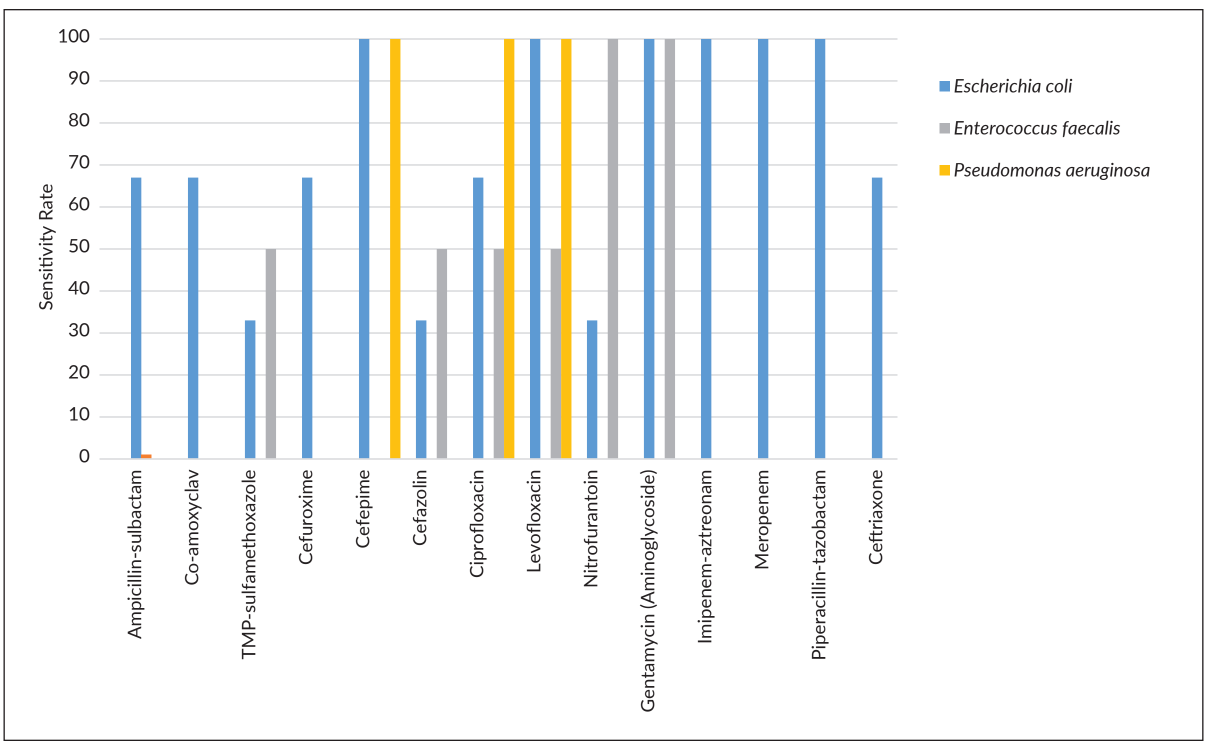

Figure 3. Antibiotic Sensitivity Rates of the most common isolates on Intraoperative Urine CS.

be because microorganisms of crushed stones are often distinct from the surface of the stones or the bacteria that reside inside the stone.[3] The discordant microorganisms isolated in the initial urine CS, intraoperative urine CS, stone CS, and febrile blood CS also prompt investigation of other sources of infection involved during the operation.

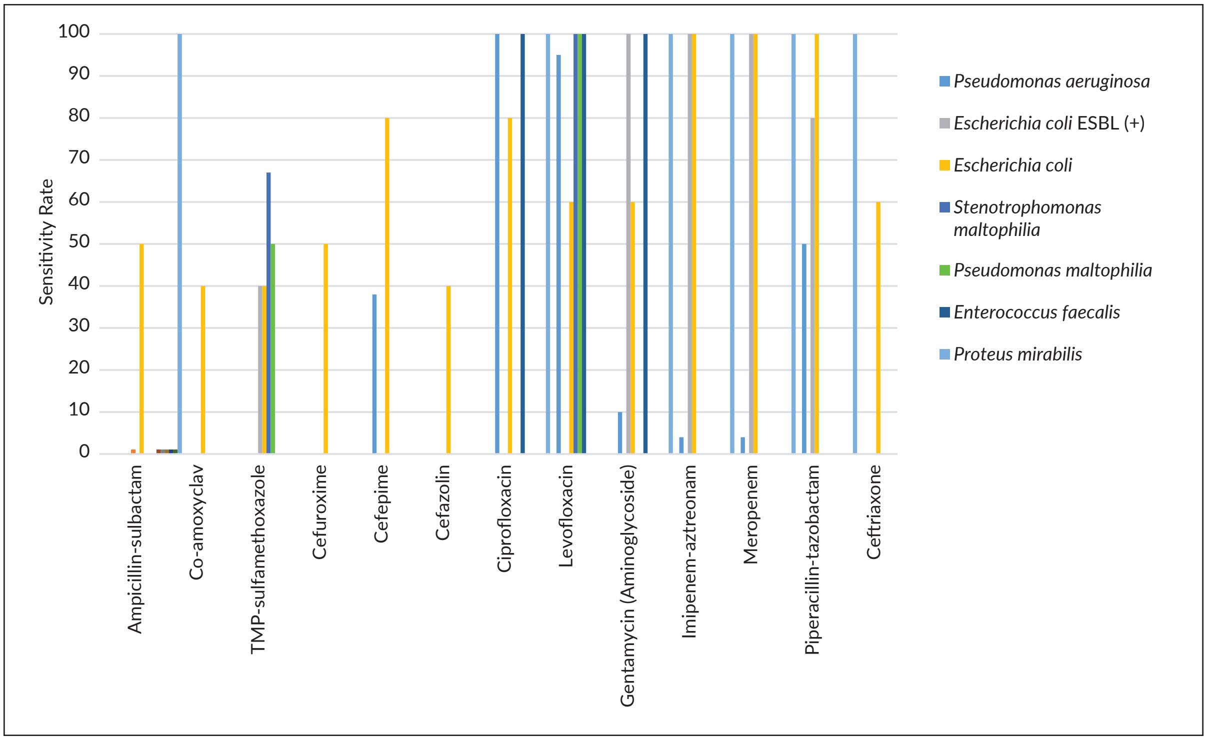

Figure 4. Antibiotic Sensitivity Rates of the most common isolates on Stone CS.

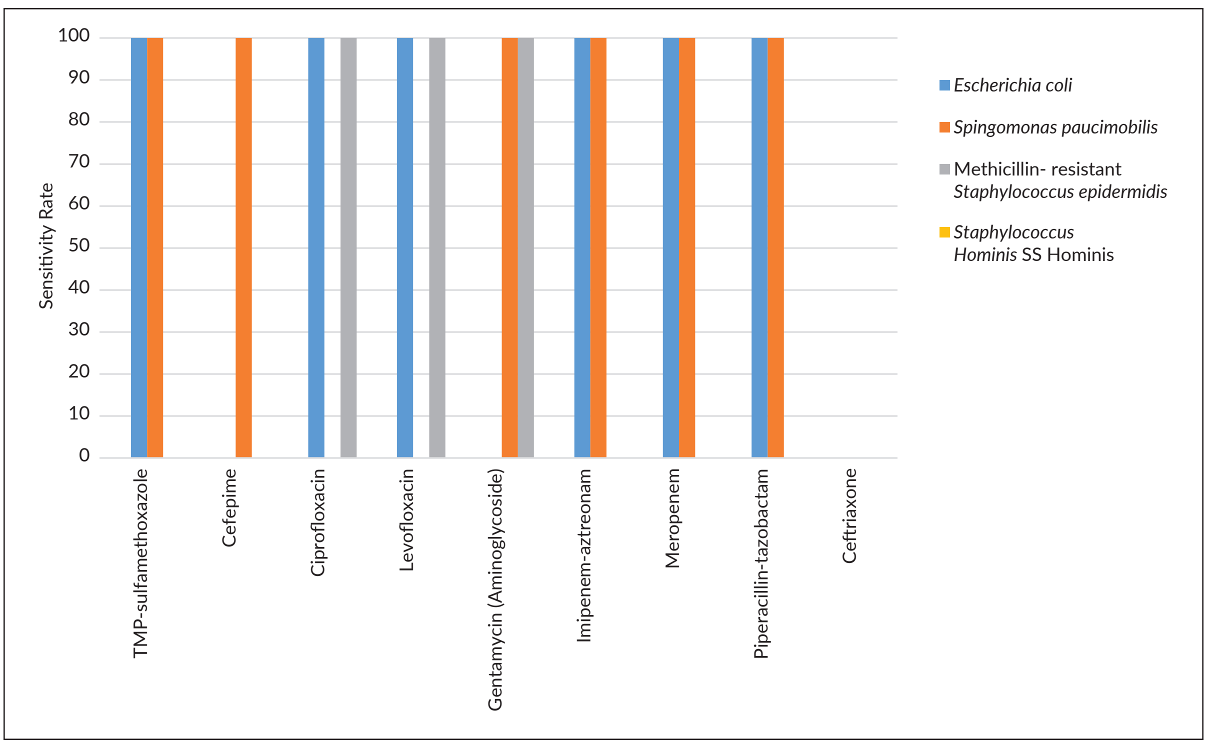

Figure 5. Antibiotic Sensitivity Rates of the isolates on Postoperative Febrile Blood CS.

Table 3. Comparison between those with and without the development of postoperative fever

Risk factors	(+) postoperative fever (n=26)	(-) postoperative fever (n=76)	p-value
Diabetes	1 (3.85)	15 (19.74)	0.054**
Immunocompromised state	1 (3.85)	0 (0)	0.860**
Positive initial urine culture	3 (11.54)	5 (6.58)	0.417**
Positive intraoperative urine culture	0 (0)	6 (7.9)	0.140**
Positive stone culture	14 (53.85)	32 (42.1)	0.299**
Staghorn calculus	12 (46.2)	28 (36.8)	0.401**
Stone Burden	7.76 ± 7.53	7.11 ± 7.29	0.702*
Intake of antibiotics within one month	3 (11.5)	12 (15.8)	0.597**
Preoperative nephrostomy/ DJS insertion	1 (3.8)	6 (7.9)	0.481**
OR time (minutes)	134.35 ± 61.35	117.27 ± 79.48	0.321*
Amount of Irrigating fluid used (liters)	18.46 ± 18.65	14.23 ± 18.88	0.325*

Values are presented as mean ± standard deviation, or number (%)
**T-test for the difference in means **Chi-square test*

Table 4. Comparison between those with and without the development of urosepsis

Risk factors	(+) Urosepsis (n=4)	(-) Urosepsis (n= 98)	p-value
Diabetes	0 (0)	16 (16.3)	0.379**
Immunocompromised state	0 (0)	1 (1)	0.839**
Positive initial urine culture	0 (0)	8 (8.2)	0.552**
Positive intraoperative urine culture	0 (0)	6 (6.1)	0.610**
Positive stone culture	2 (50)	44 (44.9)	0.841**
Staghorn calculus	2 (50)	38 (38.8)	0.652**
Stone Burden	6.57 ± 1.48	7.31 ± 7.47	0.844*
Intake of antibiotics within one month	0 (0)	15 (15.3)	0.397**
Preoperative nephrostomy / DJS insertion	0 (0)	7 (.1)	0.580**
OR time (minutes)	114 ± 43.52	121.94 ± 76.49	0.838*
Amount of Irrigating fluid used (liters)	15. 5 ± 25.67	15.3 ± 18.67	0.367*

Values are presented as mean ± standard deviation, or number (%)
**T-test for the difference in means **Chi-square test*

It also emphasizes the importance of the routine collection of intraoperative urine, stone culture, febrile urine, and blood culture because the microorganisms isolated are different in the different specimens. Stricter septic techniques may have to be implemented because of other extraneous sources of microorganisms.

The four febrile patients with positive blood culture results were readmissions. Septic workup consisting of chest X-ray and blood leukocyte count was done in addition to postoperative febrile urine and blood culture to investigate other causes of fever and bacteremia. Other sources of sepsis such as pneumonia, gastrointestinal infections, intravenous catheter infection, or contamination were excluded based on clear breath sounds on chest auscultation, unremarkable chest X-ray findings, absence of upper and lower respiratory tract as well as GI tract symptoms, and the absence of skin swelling and inflammation on previous IV site during admission and after the patients' discharge. This led to the diagnosis of urosepsis, albeit the lack of bacteriuria, as the focus of infection, was localized to the urinary tract, and no other causative factor was found for these patients except for the previous instrumentation and fragmentation of stones during PCNL. This definition of urosepsis as utilized in this study is the development of fever (temperature of 38.5°C or higher) and positive urine culture and blood culture results.

Among the four patients treated as urosepsis cases, the organisms isolated differed in one patient who had positive postoperative febrile blood culture (grew *Spingomonas paucimobilis*) and stone culture (grew *Stenotrophomonas maltophila*). The other three patients with positive febrile blood cultures had negative stone cultures. The poor correlation between the febrile specimens and the intraoperative specimens needs further investigation, given that we are limited by a small number of patients who had positive postop febrile blood culture results. Still, stringent adherence to aseptic techniques during specimen collection is again emphasized.

Several studies have found that the risk of post-PCNL infectious complications correlates better with positive stone cultures.[12] Microorganisms in stones can potentially disseminate in the bloodstream during intracorporeal lithotripsy. A shift in antibiotic prophylaxis may be warranted given the predominance of *Pseudomonas aeruginosa* isolated on stone CS. This shifting pattern of microbiology in PCNL patients should be continuously monitored to provide harder evidence to recommend a shift in antibiotic prophylaxis. We recommend an antibiotic with higher *Pseudomonas* coverage, such as aminoglycosides, fluoroquinolones, or carbapenems.

The failure of this study to show any significant association between the development of postoperative fever or urosepsis and the different clinical variables may be due to the relatively small sample size. Gutierrez and associates found the following factors associated with an increased risk of postoperative fever: positive preoperative bladder urine culture, staghorn calculus, preoperative nephrostomy, lower patient age, and diabetes.[13] A retrospective study by Dogan and associates analyzed 338 patients who underwent PCNL from January 2001 to December 2002 to analyze the importance of microbiological evaluation in managing post-PCNL infectious complications. The analysis showed concordance of positive perioperative urine and stone cultures in the development of fever. The study also concluded that a larger stone burden, longer operative time, and longer postoperative hospital stay contributed to increased incidence of postoperative fever and bacteriuria.[4]

Since the risk of having post-PCNL infectious complications is similar across all variables, including whether not preoperative and intraoperative cultures are positive, equal surveillance of postoperative fever for all patients admitted for PCNL should be continued until a large enough sample population could be studied to point out significant factors that are associated with the development of post-PCNL fever and sepsis. Appropriate follow-up of culture results is paramount in managing these infectious complications.

The relatively small sample size of the present study failed to find an association between the presence of diabetes, immunocompromised state, large stone burden, staghorn calculus, positive preadmission urine culture, positive intraoperative urine culture, positive stone culture, intake of antibiotics within one month, presence of tube nephrostomy or double-J stents before PCNL, longer operative time, increased amount of irrigating fluid used and the infectious morbidities post-PCNL.

CONCLUSION

The incidence of postoperative fever and urosepsis after PCNL was consistent with that reported in the literature. The current antibiogram obtained in the study showed higher sensitivity to carbapenems and fluoroquinolones. The nearly consistent resistance to ceftriaxone of the isolates in our cases and the predominance of *Pseudomonas aeruginosa* on stone specimens necessitate a change in the antibiotic prophylaxis utilized in the surveillance protocol.

Since the risk of having post-PCNL infectious complications is similar across all variables, including whether or not preoperative and intraoperative cultures are positive, equal surveillance of postoperative fever for all patients admitted for PCNL should be continued. Although positive cultures have not been shown to predict the development of post-PCNL infectious complications, it is still prudent to continue with the surveillance protocol as it has proved to be substantial in deciding required culture-guided changes during treatment.

Statement of Authorship

Both authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising and approved the final version submitted.

Author Disclosure

Both authors declared no conflicts of interest.

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