Infection and Drug Resistance

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ORIGINAL RESEARCH

Characteristics of Bacteria in Urine and Stones from Patients Treated with Percutaneous Nephrolithotomy and Association with Postoperative Infection

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Background: The purpose of this study was to identify bacterial differences between urine cultures (UC) and stone cultures (SC) in patients with complex kidney stones and to determine any correlation with post-percutaneous nephrolithotomy Systemic Inflammatory Response Syndrome (SIRS).

Methods: Perioperative data of 1055 patients with complex kidney stones treated with first-stage Percutaneous Nephrolithotomy (PCNL) from September 2016 until September 2021 were included. Preoperative mid-stream urine samples and surgically obtained stone material were subjected to bacterial culture and antibiotic sensitivity tests. Preoperatively, antibiotic usage was determined by the UC or local bacterial resistance patterns. After PCNL treatment, antibiotic selection was guided by stone bacterial culture result and clinical symptoms. The effect of different preoperative antibiotic regimens based on urine cultures and postoperative antibiotic treatment based on stone cultures were assessed.

Results: Positive stone cultures (SC+) were significantly more common than positive urine cultures (UC+) (31.9% vs 20.9%, $p < 0.05$). *Escherichia coli* (*E. coli*) was the most common uropathogen in both urine (54.3%) and stones (43.9%). The difference was statistically significant ($p < 0.05$). Moreover, UC+SC-, UC-SC+, UC+SC+, and preoperative serum creatinine were independent risk factors of postoperative SIRS. The incidence of SIRS in the UC+SC+ patients with different bacteria in stones and urine (51.6%) was higher than that in other culture groups. The antibiotic resistance of *E. coli* inside the stone was increased when prolonged preoperative antibiotics were administered to UC+ patients.

Conclusion: The bacterial spectrum and positive outcome of culture in urine and stones were significantly different. The incidence of postoperative SIRS was highest in patients with UC+SC+ but with different bacteria strains. Prolonged pre-surgical antibiotic treatment apparently induced higher drug resistance for bacteria inside the stone.

Keywords: kidney stones, bacterial spectrum, antibiotic resistance, stone culture, urine culture

Introduction

Urolithiasis is one of the most common urological diseases.[1,2] Percutaneous nephrolithotomy (PCNL) is still the most common treatment option for surgical removal of kidney stones with a size exceeding 2 cm.[3] Nevertheless, some postoperative complications may occur following PCNL, such as postoperative urosepsis and septic shock, which

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seriously can threaten the patients' life.[4,5] Previous studies showed that both positive urine culture (UC+) and stone culture (SC+) were independent risk factors for urosepsis in patients treated with PCNL.[6,7] *E. coli, Klebsiella pneumoniae, Proteus mirabilis*, and *Pseudomonas aeruginosa* currently remain the most common urine bacteria in urolithiasis patients.[8–10] Lorenzis E et al reported that *Enterococcus* and *E. coli* were common bacteria in stones,[8] while another study showed that *Staphylococcus* was the most common bacteria in stones.[6] Those results indicate that in patients with kidney stones, the culture of mid-stream urine is insufficiently reliable to reflect the bacteriology inside the stone. When both UC and SC are positive, their bacterial spectra may be different. Currently, only a few studies have compared in detail the bacterial spectra between urine and stones, but the association between the bacterial findings and SIRS after PCNL deserves to be further explored.

On the other hand, multiple doses of antibiotics might decrease the risk of postoperative infection for PCNL patients with UC+.[11,12] For patients with UC-, a single-dose of antibiotics was reported to be sufficient because multi-dose antibiotic regimens did not reduce the incidence of postoperative SIRS,[13] irrespective of positive or negative stone cultures. The occurrence of SC+ was considered invariable, regardless of the results of UC and the duration or grade of pre-PCNL antibiotics.[12] These results suggested that the bacteria encountered in stones may not be the therapeutic targets of preoperative antibiotics based on urine cultures. Moreover, irrespective of SC+ or SC-, the incidence of SIRS would increase with long antibiotic treatment before PCNL.[13] It has not been reported, however, whether long-term pre-surgical use of antibiotics will affect antibiotic resistance of bacteria inside the stone and the occurrence of postoperative infection. It should be noted that with increased duration of antibiotic treatment, the bacterial resistance seems to be unfavorably altered.[14,15]

In the present study, we compared the differences in the bacterial spectra between urine and stones in patients with complex kidney stones. The patients were sub-grouped according to the results of the two cultures, and the development of SIRS after PCNL was evaluated. In addition, the relationship between the duration of preoperative antibiotic treatment and postoperative bacterial resistance inside the stones was investigated.

Patients and Methods

General Information

The perioperative data of 1055 patients with complex kidney stones who underwent first-stage PCNL at the First Affiliated Hospital of Guangzhou Medical University and the Second Affiliated Hospital of Guangzhou Medical University from September 2016 until September 2021 were included. Complex kidney stones were defined as staghorn stones or renal pelvic stones accompanied by stone branches in at least two calices, regardless of the stone burden.[16] The diagnosis of complex kidney stones was based on findings from NCCT-examinations. Analyzed by FITC, the main components include one of the magnesium ammonium phosphate, carbonate apatite or ammonium urate which are defined as infection stones.[17] Preoperatively, antibiotic usage was determined by urine culture result or empirically selected based on local bacterial resistance patterns. After PCNL treatment, antibiotic selection was guided by stone bacterial culture result and clinical symptoms. The diagnostic criteria for SIRS were at least two of the following: (1) Body temperature > 38 °C or < 36 °C. (2) Heart rate > 90/min. (3) Respiration > 20/min or $PaCO_2$ < 32 mm Hg. (4) blood leukocytes > 12 × 10^9/L or < 4 × 10^9/L.[18]

Ethics Committee approval was obtained from the First Affiliated Hospital of Guangzhou Medical University. All patients were analyzed with mid-stream urine and stone cultures. To detect changes in bacterial resistance in stones, patients were divided into four groups according to the duration of antibiotic treatment before surgery: 0 days (one single shot before operation), 1–3 days, 4–6 days, and more than 7 days.

Collection of Urine and Stones Samples and Bacterial Culture

After cleansing the perineal area, collect approximately 10 milliliters of urine in a sterile container. Transport the specimen to the lab within an hour. If delayed, store it at 4 degrees Celsius and test within 24 hours. For analysis, inoculate 10 μL of urine onto a 5% Columbia blood agar plate (Jiangmen Kailin Trading Co, Ltd) using a sterile loop and incubate at 37°C for 18–24 hours. A culture is positive if a single type of bacterium grows, exceeding 10^5 CFU/mL.

All stones were disintegrated with pneumatic or ultrasonic lithotripsy during PCNL. The core of the stone was removed with stone forceps and immediately immersed in sterile saline. Following elimination of impurities from the stone surface by washing 3 times with sterile PBS, an aliquot of 10 mL of saline was added, and the stone was ground. This suspension is then incubated in nutrient broth at 37°C for 18–24 hours to promote bacterial growth. A sample of the bacterial culture is inoculated onto a 5% Columbia Blood Agar Plate and incubated at 37°C for colony formation.

Identification of Bacterial Strain

The strains found in positive mid-stream UC and ground SC were recorded by the VITEK®2 automatic bacteria identification instrument (BioMérieux). Among 337 patients with SC+, antibiotic resistance, data from 269 patients were collected. Of these patients 139 were UC+ and 130 UC-. Broad-spectrum antibiotics are utilized to assess antibiotic sensitivity, which was performed with the Kirby-Bauer (Kmurb) method, and the results were interpreted according to the standards established by guidelines from the Clinical and Laboratory Standards Institute (CLSI).

Stone Composition Analysis

Regarding the analysis of stone composition, the dry stone sample is crushed and mixed with KBr powder in a 1:80 ratio, then finely ground into a microfine powder. Afterward, it is pressed into a thin disc using a hardened press. The composition of the stone is analyzed using infrared spectroscopy.

Statistical Methods

The SPSS 25.0 software was used for statistical analysis. Continuous variables were represented by mean ± standard deviation (SD), and categorical variables were reported as number (percentage). The continuous variables in this study obeyed normal distribution. The chi-square test or Fisher´s exact probability test was performed to detect differences between categorical variables. Logistic regression analysis was used to determine independent risk factors associated with SIRS after PCNL. Significance was considered at the 0.05 two-sided level.

Result

Bacterial Findings in Urine and Stones

Based on the analysis of stone composition in totally 1055 patients, 582 (55.2%) patients were categorized as calcium oxalate stone formers and 199 (18.9%) as uric acid stone formers. 12 (1.1%) patients had formed cystine stones and 262 (24.8%) infection stones. It is of note that, bacteria were detected in 148 calcium oxalate stones (25.4%), 47 uric acid stones (23.6%), 5 cystine stones (41.7%) and 137 infection stones (52.3%). These levels were significantly higher than those in urine from the corresponding patients ($p<0.05$). Bacteria were detected in urine from 93 patients (16%) with calcium oxalate stones, 34 patients with uric acid stones (17.1%), 3 patients with cystine stones (25%) and in 91 patients infection stones (34.7%).

Overall, positive SC was recorded in 31.9% of the patients, whereas only 20.9% patients had positive UC ($p<0.05$). The number and relative occurrence of common microorganisms in urine and stones are given in Table 1. *E. coli* was the most common microorganism observed in both urine and stones, but the relative occurrence in urine (54.3%) was significantly higher than that in stones (43.9%) $p=0.016$. Other common bacteria in urine comprised *Proteus mirabilis* (7.7%), *Enterococcus faecalis* (6.8%), and *Pseudomonas aeruginosa* (5.9%). *Proteus mirabilis* (12.2%), *Pseudomonas aeruginosa* (5.3%) and *Staphylococcus epidermidis* (4.2%) were frequently isolated from the stones. The 4.2% incidence of *Staphylococcus epidermidis* in stones was higher than that in urine (0.9%; $p=0.024$). In contrast, *Enterococcus faecalis* was more common in urine (6.8% vs 3.0%; $p=0.033$).

The Association Between Bacterial Spectrum and Postoperative SIRS

According to the culture Results in urine and stones, patients were sub-grouped into three categories. There were 666 patients in the double negative group (UC- and SC-), 220 patients in the single positive group (single UC+ or single SC+), and 169 patients in the double positive group (both UC+ and SC+). As shown in Table 2, the frequency of SIRS in 41.4% of the patients in the

Table 1 Analysis of Bacterial Spectrum of Urine and Stones (All Patients, N = 1055)

Bacterial Classification	Urine N =221 (%)	Stone N =337 (%)	P
Escherichia coli	120 (54.3)	148 (43.9)	**0.016***
Proteus mirabilis	17 (7.7)	41 (12.2)	0.090
Pseudomonas aeruginosa	13 (5.9)	18 (5.3)	0.785
Klebsiella pneumoniae	13 (5.9)	10 (3.0)	0.090
Enterococcus faecalis	15 (6.8)	10 (3.0)	**0.033***
Enterococcus faecium	5 (2.3)	7 (2.1)	1.000
Staphylococcus epidermidis	2 (0.9)	14 (4.2)	**0.024***
Streptococcus agalactiae	9 (4.1)	5 (1.5)	0.056
Other common bacteria/fungi	27 (12.2)	84 (24.9)	**<0.001***

Note: *Statistically significant based on chi- square test (p<0.05).

Table 2 Subgroup Analysis for Postoperative SIRS Associated with Bacterial Cultures in Patients with Complex Kidney Stones

Bacterial Culture Groups	Total N=1055	Positive rate of SIRS, n (%) N=149
Three categories		
Double negative	666	36 (5.4%)*
Single positive	220	43 (19.5%)*
Double positive	169	70 (41.4%)*
Five categories		
UC-SC-	666	36 (5.4%)
UC+SC-	52	11 (21.2%)$^{\#}$
UC-SC+	168	32 (19.0%)$^{\#}$
UC+SC+(Consistent)	138	54 (39.1%)$^{\#\&}$
UC+SC+(Inconsistent)	31	16 (51.6%)$^{\#\$\&}$

Notes: *Significantly different for all pairwise comparisons among those three groups (Bonferroni correction, all p<0.001). $^{\#}$Significantly different compared with the group of UC-SC- (p<0.001). $^{\$}$Significantly different compared with the group of UC+SC- (p<0.001). $^{\&}$Significantly different compared with the group of UC-SC+ (p<0.001).

double positive group of was significantly higher than that in the other two groups (19.5% and 5.4%). Subsequently, the double positive group was divided into two other groups (UC+SC+) with the same bacterial strains in the two samples and UC+SC+ with different bacterial strains. Finally, and based on the results of UC and SC, the whole group of patients was divided into five subgroups (Table 2). As shown in the Table, the frequencies of SIRS in the five sub-groups varied from 5.4% to 51.6%.

Univariate analysis of risk factors for postoperative SIRS in patients with complex kidney stones is shown in Table 3. There were significant differences between patients with or without SIRS for UC-SC- (24.2% vs 69.5%), UC+SC- or UC-SC+ (28.9% vs 19.5%), UC+SC+ with the same bacterial strains (36.2% vs 9.3%), UC+SC+ with different strains (10.7% vs 1.7%), infection stones (39.6% vs 22.4%), females (55.0% vs 40.0%), preoperative serum creatinine (137.6 μmol/L vs 114.7 μmol/L), and multiple accesses (15.4% vs 10.7%).

Multivariate logistic regression analysis (Table 4) showed that UC+SC- or UC-SC+, UC+SC+ with the same bacteria, UC+SC+ with different bacteria and preoperatively increased serum creatinine were independent risk factors for SIRS. The incidence of SIRS was significantly higher in UC+SC+ with different bacteria (51.6%) than in the UC+SC- patients (21.2%) or UC-SC+ patients (32/168, 19.0%; p<0.05). (Table 2)

Table 3 Risk Factors for Postoperative SIRS in Patients with Complex Stones

Groups, n(%)	All N=1055	SIRS N=149	Non-SIRS N=906	p value
UC-SC-, n,(%)	666(63.1%)	36 (24.2%)	630(69.5%)	<0.001*
UC+SC- or UC-SC+, n,(%)	220(20.8%)	43(28.9%)	177(19.5%)	0.009*
UC+SC+(Consistent), n,(%)	138(13.1%)	54 (36.2%)	84(9.3%)	<0.001*
UC+SC+(Inconsistent), n,(%)	31(3.0%)	16(10.7%)	15(1.7%)	<0.001*
Stone burden, mm^2, mean±SD	1500.2±1438.2	1685.3±1690.6	1469.8±1391.1	0.090
Infection stone, n(%)	262(24.8%)	59(39.6%)	203(22.4%)	<0.001*
Operating time, min, mean±SD	97.3±35.4	96.7±34.5	97.4±35.6	0.822
Female, n(%)	444(49.0%)	82(55.0%)	362(40.0%)	0.001*
Age, mean±SD	52.3±12.2	52.1±12.5	52.3±12.2	0.834
Hydronephrosis, n(%)	820(77.7%)	123(82.6%)	697(76.9%)	0.127
Preoperative serum creatinine, umol/L, mean±SD	118.0±86.2	137.6±117.6	114.7±79.4	0.023*
Diabetes mellitus, n(%)	93(8.8%)	10(6.7%)	83(9.2%)	0.329
Hypertension, n(%)	265(25.1%)	33(22.1%)	232(25.6%)	0.367
Previous urinary surgery, n(%)	451(42.7%)	67(45.0%)	384(42.4%)	0.555
Access no. ≥2, n(%)	108(10.2%)	23(15.4%)	85(10.7%)	0.024*

Note: *Significantly different between SIRS and Non-SIRS (p<0.05).

Table 4 Multivariate Logistic Regression Analysis of Variables Associated with SIRS After PCNL in Stone Patients

Risk Factors	OR	(95% CI)	p value
UC+SC- or UC-SC+, n,(%)	3.860	2.341–6.366	<0.001*
UC+SC+(Consistent), n,(%)	10.016	6.017–16.672	<0.001*
UC+SC+(Inconsistent), n,(%)	16.726	7.455–37.527	<0.001*
Infection stone	1.232	0.813–1.869	0.325
Access no. ≥2	1.295	0.744–2.254	0.361
Preoperative serum creatinine	1.003	0.730–1.670	0.006*
Female	1.104	0.599–1.371	0.640

Note: *Values indicate statistically significant (p<0.05).

Comparison of Resistance of *E. Coli* in Stones Exposed to Antibiotic Treatment During Different Preoperative Periods

The antibiotic resistance of *E. coli* in UC and SC was analyzed for different preoperative treatment periods (Figures 1 and 2). There was no significant difference in the four subgroups of UC (p>0.05), which indicated that the antibiotic resistance for *E. coli* preoperatively was similar regardless of the length of the preoperative antibiotic treatment.

For patients with positive urine cultures, the antibiotic resistance of *E. coli*, extracted from stones, was highest for amoxicillin/clavulanic acid (9.1%), cefuroxime (76.9%), cefuroxime sodium (100.0%), cefuroxime axetil (100.0%), ceftriaxone (59.1%), cefotaxime (63.6%), and cefazolin (68.2%), when the treatment period was 4–6 days. There was a statistically significant difference between patients in the 0-day treatment group and the other three treatment groups (1–3 days, 4–6 days and more than 7 days; p<0.05). When the pre-PCNL treatment period was increased, the antibiotic resistance of *E. coli* for ampicillin increased from 62.5 to 100%, for nitrofurantoin from 0 to 20.0%, for trimethoprim/sulfamethoxazole from 36.4 to 75.1%, for cefepime from 10.0 to 33.3%, for ceftazidime from 9.1 to 25.0% and for levofloxacin from 30.0 to 58.3%. Except for amoxicillin/clavulanic acid (9.1% vs 0%) and nitrofurantoin (5.0% vs 20%), there were no differences in antimicrobial resistance between patients treated during 4–6 days and those treated for more than 7 days (p<0.05).

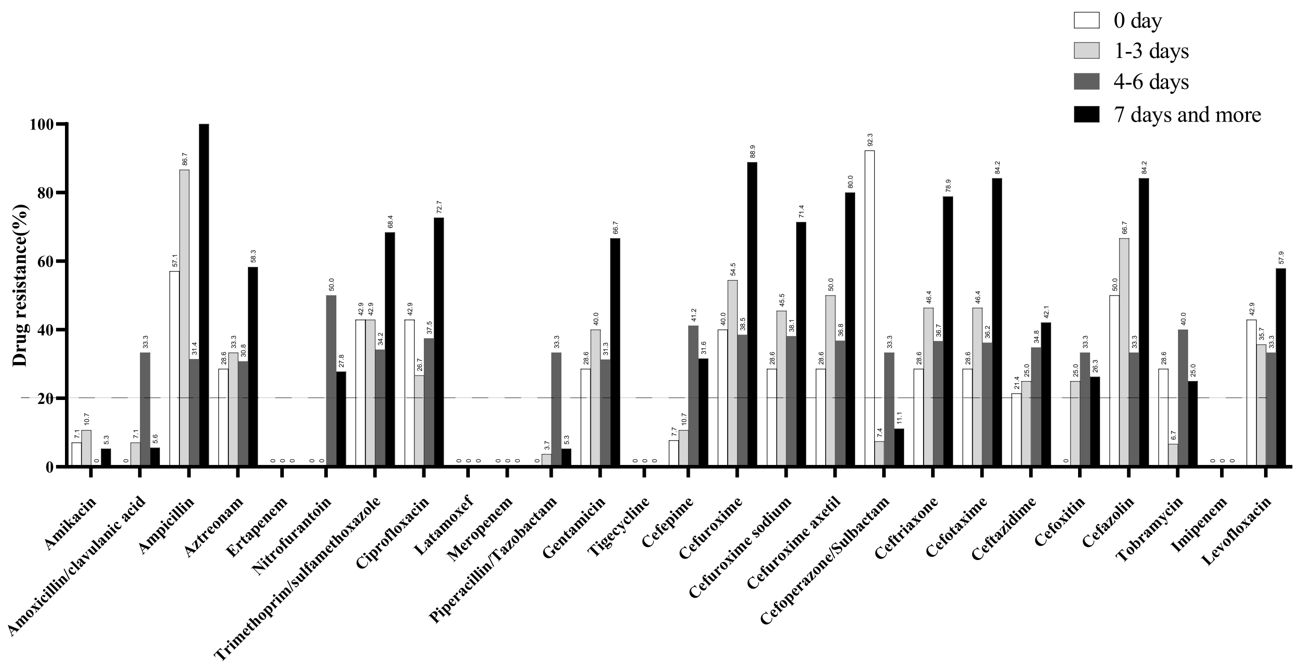

Figure 1 Comparison of antimicrobial resistance of *E. coli* in urine between different preoperative antibiotic treatment periods.

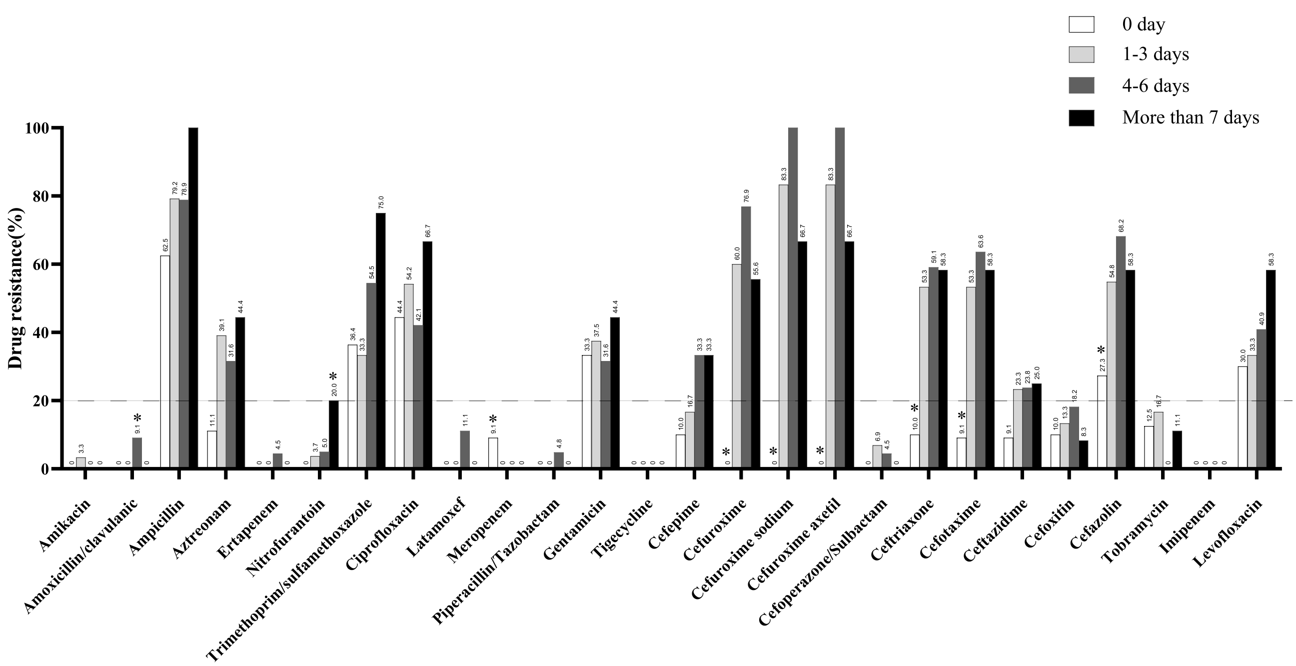

Figure 2 Comparison of antimicrobial resistance of *E. coli* in stones between different preoperative antibiotic treatment periods.
Note: *Significantly different compared with the other three groups (P < 0.05).

Discussion

Our findings indicated that urine and stones from patients with complex kidney stones had distinct characteristics in terms of bacterial spectra and growth. The demonstration of positive cultures in stones was higher than those in urine, regardless of the stone composition. This observation is consistent with results from previous studies.[19,20] Therefore, stone bacteria may play a significant role in the formation or growth of the kidney stone. Understanding the distribution pattern and antibiotic resistance characteristics of bacteria within the stone is crucial for the prevention and treatment of kidney stones. Despite negative UC, as many as 15.9% (168/1055) of the patients had positive SC, which indicated that the spectrum of bacteria in stones was more complex and not reflected by findings in UC. *Staphylococcus* was the most common bacteria in urine and stones according to results presented by Paonessa et al.[6] This observation was followed by *Proteus mirabilis* in urine and *Enterococci* in stones. In contrast, our results showed that *E. coli* and *Proteus mirabilis* were the most common bacteria in both urine and stones. These differences may be explained by differences in the distribution of urinary pathogens in various geographical areas. Moreover, isolation of *E. coli, Enterococcus faecalis*, and *Staphylococcus epidermidis* were significantly different between urine and stones. Similar to previous reports[21] and albeit SC and UC, both were positive, and there were still 18.3% (31/169) of the patients who presented different bacteria in the two samples.

The incidence of 14.1% (149/1055) of SIRS after PCNL in the present study was close to previously published results.[12,22,23] Several risk factors for SIRS have been identified such as female gender, long operative time, multiple accesses, infection stones, as well as positive urine and stone cultures.[22–25] In these articles, the authors only discussed positive urine cultures or positive stone cultures separately, whereas we found that UC+SC+ with the same bacteria, UC+SC+ with different bacteria, UC+SC- or UC-SC+, and increased preoperative serum creatinine were independent risk factors for SIRS. Our results also showed that the incidence of SIRS in UC+SC+ patients with different bacteria was highest compared with other culture results. In addition, as a widely used indicator of renal function, the increase in serum creatinine indicates abnormal renal function and it has been reported as an independent risk factor for the growth of stones associated with obstructive urosepsis or septic shock.[26] Infection-related complications seem more likely to occur in patients with poor basal renal function. In general, the results of UC and SC were both important for PCNL patients, and it is obvious that we need to pay more attention to patients with differences in cultures and abnormal preoperative levels of serum creatinine.

There seems to be some evidence that preoperatively extended use of antibiotics significantly might reduce the incidence of post-PCNL infections in UC+ patients[11,12] and that this outcome not was associated with antibiotic-related complications.[14] In the current study, however, it is noteworthy that resistance of stone bacteria to most antibiotics was significantly increased for UC+ patients with long preoperative antibiotic treatment ($p<0.05$). Antibiotics thus seem to act exclusively on urine bacteria, but they may cause increased antibiotic resistance to bacteria in stones. To further elaborate on this finding, it is possible that the extended use of antibiotics before surgery might have created a selective pressure on the bacteria residing in the stones, leading to the development of antibiotic resistance. Additionally, the differences in the composition of the bacterial flora between urine and stones might also account for the varying response to antibiotics. This finding has significant clinical implications, as it emphasizes the need for a more targeted and rational use of antibiotics in the management of UC+ patients undergoing PCNL. Efforts should be made to minimize the unnecessary and inappropriate use of antibiotics to prevent the development and spread of antibiotic-resistant bacteria.

Moreover, our speculations are supported by the findings that extended preoperative antibiotics did not reduce the frequency of positive stone cultures, although this regime can reduce the risk of postoperative SIRS.[11,13,27] As mentioned above, we still observed that as many as 15.9% of the patients had SC+ but UC-. Attributable to the too generous attitude of antibiotic use in some areas, patients may choose to self-medicate before seeking medical advice, and this situation may result in false UC-. We therefore suggest that stone cultures routinely should be carried out to guide post-PCNL antibiotic management. Simultaneously, urologists should fully realize the adverse effects of the increased antibiotic resistance and therefore educate patients to correctly understand the dual nature of antibiotics and to avoid the overuse of antibiotics.

Finally, while traditional bacterial culture methods remain the gold standard for diagnosing urinary tract infections, they are complex and time-consuming. Emerging rapid detection technologies, such as the HB&L uroquattro system and expanded quantitative urinary culture, can reduce testing time and directly quantify bacterial counts, swiftly guiding empirical antimicrobial therapy.[28,29] However, these rapid systems have limitations: positive samples require confirmation through traditional cultures, and negative results must be interpreted with clinical judgment to avoid overreliance on preliminary results, which could lead to antibiotic overuse. Moreover, while molecular detection technologies like metagenomic sequencing show promise in identifying all nucleic acids and analyzing resistance, the lack of unified standards and validation restricts their clinical adoption.[30,31] Therefore, rapid screening methods should complement traditional culture techniques to enhance diagnostic accuracy and treatment effectiveness.

Overall, our study not only described different characteristics of the bacterial spectra between urine and stones but also emphasized the relevance of these differences for post-surgical SIRS. Moreover, the changes in bacterial resistance of bacteria in stones with different preoperative antibiotic treatment were evaluated. These findings may be of great importance for future perioperative antibiotic strategies for patients with kidney stones. Urologists must be reminded that preoperative antibiotics should be used cautiously because the duration of preoperative antibiotics might have negative effects on antibiotic resistance of bacteria in stones.

This report's limitation lies in its status as a retrospective study conducted within specific geographical region. It is necessary to update and establish more information on antibiotic resistance for common pathogens to support our results. Additionally, retrospective studies inevitably carry biases.

Conclusion

The microbial spectra of UC and SC in patients with kidney stones were significantly different. The occurrence of positive SC was higher than that of positive UC. The incidence of postoperative SIRS in the group of patients with UC +SC+ but with different bacteria in the two samples was the highest. A prolonged pre-surgical antibiotic treatment might potentially increase the antibiotic resistance to bacteria inside stones. We therefore suggest that preoperative antibiotics should be used cautiously.

Abbreviations

UC, urine cultures; SC, stone cultures; SIRS, Systemic Inflammatory Response Syndrome; *E. coli, Escherichia coli*; CLSI, the Clinical and Laboratory Standards Institute; SD, standard deviation.

Statements and Declarations

This paper has been uploaded to Research Square as a preprint: https://www.researchsquare.com/article/rs-1056064/v1.

Data Sharing Statement

The data used and analyzed during the current study is not publicly available. For any inquiries, please contact the corresponding author.

Ethics Approval and Consent to Participate

This study was approved by the Committee of Ethics at the First Affiliated Hospital of Guangzhou Medical University and the Second Affiliated Hospital of Guangzhou Medical University (No. 2015 # 76). The research involved the retrospective analysis of existing medical records where all patient data were anonymized and de-identified prior to analysis. This exemption aligns with the ethical guidelines and complies with the Declaration of Helsinki regarding the use of human data.

Author Contributions

ML: wrote the first draft of the manuscript. ZJ: analyzed the data. PX, LYa, and ZLc: modified figures and tables. All authors contributed to collecting the data. YYz, SJl, YHz, TZ and SKz revised the manuscript. WQw, GHz and HT assisted in reviewing and revising the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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