# *Stone culture in patients undergoing percutaneous nephrolithotomy: a practical point of view*

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***Introduction:*** *To determine the clinical yield of stone culture in patients undergoing percutaneous nephrolithotomy (PCNL), and to identify patients who may benefit from this test.*

***Materials and methods:*** *We queried our database for all patients who underwent PCNL from 2005 to 2017, from whom urine culture (UC) and stone culture (SC) were obtained. Study endpoint was systemic inflammatory response syndrome (SIRS) within 48 hours of PCNL. Risk factors for SIRS and for stone colonization with highly resistant pathogens were evaluated. Based on UC and SC results, we determined the proportion of patients in whom SC may alter the treatment, had SIRS occurred, with respect to the initial empiric treatment.*

***Results:*** *The study group comprised of 512 patients with a median age of 53, of whom 323 (63%) were male. Positive UC were found in 137 (26.7%) patients, and positive SC in 117 (22.8%) patients. UC did not identify pathogens isolated from SC in 66 (12.8%) patients. Postoperative SIRS occurred in 50 (9.8%) patients. On multivariate analysis only SC was associated with postoperative SIRS. SC pathogens resistance rates ranged from 67% for treatment with 2nd generation cephalosporins to 9% for treatment with meropenem, and may alter the choice of antibiotics in 73 to 12 patients (14.2%-2.3% of the whole cohort), respectively.*

***Conclusions:*** *In similar and earlier studies, we found substantial discordance between SC and UC results, and an association between stone colonization and SIRS. However, the practical yield of this test varies with the type of antibiotic given, and is limited when broad spectrum antibiotic is used.*

**Key Words:** percutaneous nephrolithotomy, stone culture, SIRS, infection

## Introduction

Colonization of renal calculi was historically attributed to infectious stones. Nevertheless, it has become clear that as many as 70% of metabolic renal calculi also harbor infectious organisms.[1]

Two main findings were consistently demonstrated throughout studies assessing stone colonization in patients undergoing percutaneous nephrolithotomy (PCNL). First, there is a considerable discordance between pathogens isolated in urine culture (UC) and stone culture (SC) obtained from the same patients, ranging from 20% to 70%.[2-4] Furthermore, there is a strong association between stone colonization and the occurrence of sepsis following PCNL, first demonstrated by Marriapan et al and further supported by other groups. According to these studies, the odds of developing postoperative sepsis following PCNL are three to ten times higher for patients with an infected stone in comparison to patients with a non-infected stone, regardless of UC results.[3,5-7] These two findings have led several authors, including us, to conclude that SC should be obtained routinely, during every PCNL, in order to direct the antibiotic treatment in patients with postoperative sepsis; however, few reports have evaluated the true clinical impact of performing routine SC for all patients undergoing PCNL.

After adhering to this practice for more than a decade, in this current study, we aimed to evaluate whether obtaining SC is clinically beneficial, and whether this benefit is limited to certain clinical scenarios. After presenting the clinical and bacteriological

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characteristics of our cohort, we assessed the antibiotic susceptibility profile of each pathogen, evaluated the probability of SC to change the antibiotic treatment had sepsis occurred, and identified risk factors for stone colonization with resistant organisms.

## Materials and methods

We queried our institutional, ethics committee approved, database of patients undergoing PCNL, collected retrospectively from 2005 to 2012 and prospectively from 2012 to 2017, for all consecutive patients for whom preoperative UC and intraoperative SC were available.

Preoperative UC were obtained up to 1 month prior to the PCNL from voided mid-stream urine or from a newly inserted catheter in patients with an indwelling catheter. Patients with a positive UC or a recent history of urinary tract infection (UTI) were treated with a 1 week oral or intravenous antibiotic course per the UC results followed by a second UC after the completion of treatment to verify urine sterilization, and a single preoperative dose of culture guided intravenous antibiotic prior to the procedure. Patient with sterile UC were treated with a single preoperative dose consisting of 1 g Cefamezine. For the treatment of postoperative sepsis, a combination of gentamicin and ampicillin are given to patients with sterile preoperative UC, while additional treatment is used for patients with positive UC, according to the isolated pathogen.

All PCNLs were performed in the prone position. In most cases, access to the renal collecting system was gained at the beginning of the procedure under fluoroscopic guidance. Few patients had a nephrostomy tube or ureteral stent placed before the procedure for alleviation of sepsis or pain. The tract was then dilated using a balloon dilator to 30F and an Amplatz sheath was inserted.

Stone fragmentation was performed with an ultrasonic or ballistic lithotripter. Stone fragments were retrieved for culture and stone analysis, and flexible nephroscopy was routinely performed to evaluate for residual stone fragments. At the end of the procedure, either a nephrostomy tube or ureteral stent were inserted at the surgeon's discretion.

We collected patient and procedure characteristics including patient age and sex, the presence of diabetes mellitus (DM), age-adjusted Charlson comorbidity index (CCI),[8] the number of hospitalizations during the year prior to the PCNL, presence of a UTI event during the year prior to PCNL, preexsisting stent or nephrostomy tube, operative time, stone burden and stone composition. UC and SC status were determined for all patients, and involved pathogens and their antibiotic susceptibilities were noted.

The study outcome was postoperative SIRS, within 48 hours of the procedure. Systemic inflammatory response syndrome (SIRS) was defined in accordance with the International Guidelines for Management of Severe Sepsis and Septic Shock: 2012, as UTI in the presence of temperatures > 38°C or < 36°C within 48 hours of surgery in addition to one or more of the following: heart rate > 90 beats/min, respiratory rate > 20 breaths/min or arterial carbon dioxide pressure < 32 mmHg, systolic blood pressure < 90 mm Hg, mean arterial pressure < 70 mm Hg, or a systolic blood pressure decrease > 40 mm Hg, and white blood cell count > 12,000/$mm^3$ or < 4000/$mm^3$ or > 10% bandforms.[9]

### *Evaluating the clinical impact of SC*

In order to evaluate the clinical implication of SC, we compared the antibiotic susceptibility profiles of pathogens isolated from SC and preoperative UC. Assuming any patient with stone colonization may develop postoperative sepsis we calculated the proportion of patients in whom SC results may alter an empiric antibiotic regime that was initiated. SC was not considered beneficial if the preoperative UC (including all UC results 2 months prior to surgery) revealed the same resistance pattern to the empiric antibiotic regime chosen. The following antibiotic regimes were used as possible treatment of post-PCNL urinary tract infection: second and third generation cephalosporins, ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin/penibrin, amikacin/penibrin, gentamicin/clindamycin, amikacin/clindamycin, piperacillin/tazobactam and meropenem. We further identified patients in whom SC grew highly resistant pathogens, not covered by commonly used empiric treatment. Pathogens with multiple drug resistance, who were susceptible only to vancomycin, carbapenems, or antifungal antibiotics, were included within this group, and risk factors for colonization with these pathogens were evaluated.

### *Statistical analysis*

Continuous variables were described as median and interquartile range and categorical variables as number and percent. The associations between preoperative characteristics and SC and the occurrence of SIRS within 48 hours after the procedure were evaluated with univariable and multivariable logistic regression analyses. Similarly, we used univariable and multivariable analyses to identify predictors of stone colonization with highly resistant pathogens. Bonfferoni correction was used to calculate $\alpha$ when

multiple comparisons were required. All statistical analyses were 2-sided. Data were analyzed with SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA). A p value of < .05 was considered statistically significant.

## Results

During the study period, 860 consecutive patients underwent PCNL, 512 of whom had both a preoperative UC and intraoperative SC, and were included in the study cohort. Median age at the time of PCNL was 53 years (IQR 41, 64) and 189 (37%) patients were female. UTI occurred in 132 (25.8%) patients during the year prior to the procedure. Table 1 summarizes patients' characteristics of the study cohort.

Positive UC were found in 137 (26.7%) patients, and positive SC in 117 (22.8%) patients. Most patients, 341 (66.6%), had both a sterile UC and SC. Thirty-four (9.1%) patients had positive SC in the presence of sterile urine, and in 32 (6.2%) patients UC were positive with different pathogens than SC. Overall, in 66 (12.8%) patients, UC did not identify pathogens that were isolated from SC.

The most common pathogens isolated from urine were *Escherichia coli* in 42.3% of positive UCs, followed by *Proteus mirabilis* in 17.5% and *Pseudomonas aeruginosa* in 15.3%. *Escherichia coli, Enterococcus fecalis*, and *Pseudomonas aeruginosa* were commonly isolated from SC, at an incidence of 22.2%, 19.7%, and 13.7%, respectively. Gram positive bacteria accounted for 33.6% of SC and

TABLE 1. **Patients' characteristics of the study cohort stratified by the presence or absence of postoperative SIRS including univariable and multivariable analysis of risk factors for postoperative SIRS**

| Covariate | Total (n = 512) | SIRS (n = 50) | No SIRS (n = 462) | Univariate analysis OR (95% CI) | p | Multivariate analysis OR (95% CI) | p |
|---|---|---|---|---|---|---|---|
| Positive SC (%) | 117 (22.8) | 31 (62) | 86 (18.6) | 7.1 (3.85-13.2) | 0.001 | 5.8 (2.7-12.6) | 0.001 |
| Indwelling urethral catheter (%) | 36 (7) | 6 (12) | 30 (6.5) | 6.1 (2.1-17.7) | 0.001 | 2.3 (0.72-7.5) | 0.146 |
| Prior UTI (%) | 132 (25.7) | 25 (50) | 107 (23.1) | 3.32 (1.8-6) | 0.001 | 1.45 (0.68-3.1) | 0.33 |
| Positive UC (%) | 137 (26.7) | 25 (50) | 112 (24.2) | 3.12 (1.7-5.65) | 0.001 | 0.91 (0.41-2) | 0.82 |
| Prior drainage (%) | 132 (25.8) | 20 (40) | 112 (24.2) | 1.5 (1.07-2.13) | 0.017 | | |
| Nephrostomy (%) | 81 (15.8) | 13 (26) | 68 (14.7) | 1.42 (1.01-2) | 0.04 | | |
| Double-J stent (%) | 51 (10) | 7 (14) | 44 (9.5) | 1.55 (0.65-3.6) | 0.32 | | |
| Median Charlson index (q1, q3) | 1 (0, 4) | 3 (2, 6) | 1 (0, 4) | 1.13 (1.01-1.25) | 0.03 | | |
| Stone composition | | | | 1.15 (0.84-1.57) | 0.39 | | |
| Calcium oxalate (%) | 222 (63) | 15 (50) | 207 (64) | | | | |
| Uric acid (%) | 69 (19.6) | 9 (30) | 60 (18.6) | | | | |
| Calcium phosphate (%) | 25 (7.1) | 2 (6.7) | 23 (7.1) | | | | |
| Struvite (%) | 24 (6.8) | 4 (13.3) | 20 (6.2) | | | | |
| Cystine (%) | 12 (3.4) | 0 (0) | 12 (3.7) | | | | |
| Male gender (%) | 323 (63) | 30 (60) | 293 (63) | 1.15 (0.64-2.1) | 0.63 | | |
| Median age (q1, q3) | 53 (41, 64) | 58 (40, 68) | 53 (41, 62) | 1.02 (1-1.04) | 0.03 | | |
| Median BMI (q1, q3) | 27.5 (22.4, 30.5) | 29.1 (27.5, 31.7) | 27.1 (23.8, 30.4) | 1 (0.94-1.06) | 0.96 | | |
| Median operative time (q1, q3) | 96 (75, 120) | 110 (68, 130) | 90 (80, 120) | 1 (0.99-1.01) | 0.99 | | |
| Median stone size (q1, q3) | 30 (22, 36) | 30 (20, 40) | 30 (19, 39) | 0.99 (0.97-1.02) | 0.84 | | |
| Diabetes mellitus (%) | 123 (24) | 15 (30) | 108 (23.4) | 0.7 (0.37-1.35) | 0.3 | | |

SIRS = systemic inflammatory response syndrome; OR = odds ratio; CI = confidence interval; SC = stone culture; UTI = urinary tract infection; UC = urine culture; q1 = first quarter; q3 = third quarter; BMI = body mass index

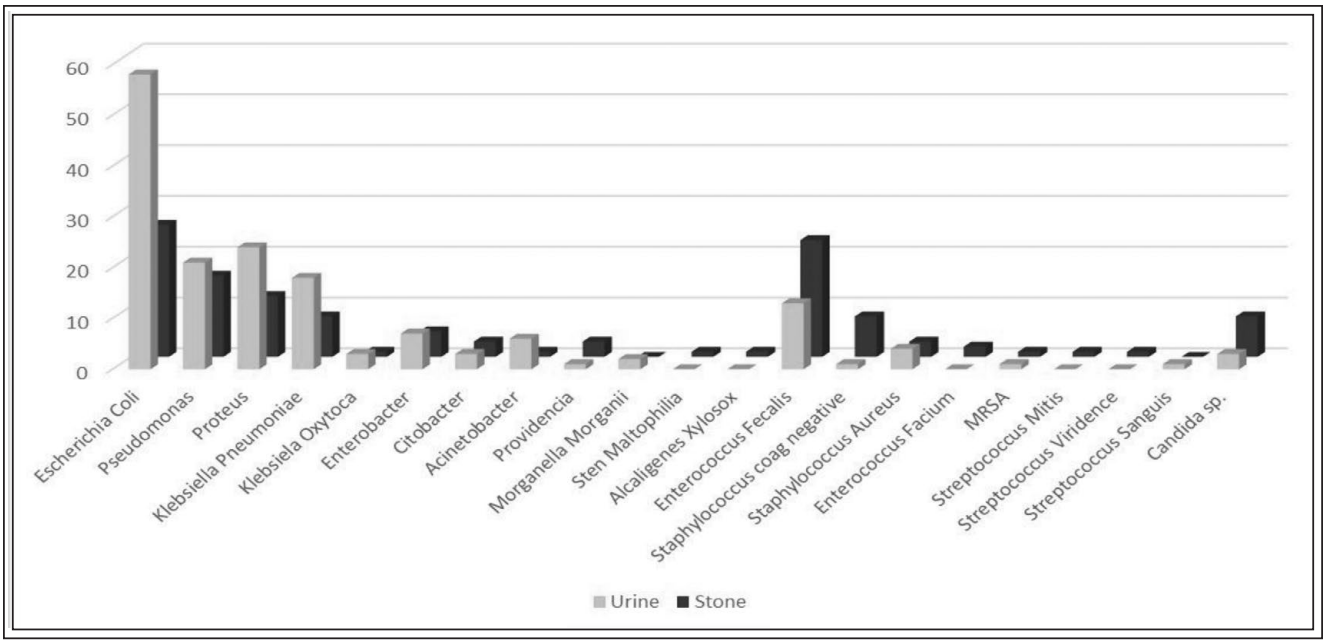


**Figure 1.** Pathogens isolated from stone and urine.

12.7% of UC, ($p < 0.001$). Frequencies of pathogen isolated from urine and stones are illustrated in Figure 1.

Postoperative SIRS occurred in 50 (9.8%) patients. On univariable logistic regression analysis, using a p value of 0.004 to account for multiple testing, positive SC (OR = 7.13, 3.85-13.2, 95% CI, $p < 0.001$), indwelling urethral catheter (OR = 6.15, 2.1-17.7, 95% CI, $p = 0.001$), prior UTI (OR = 3.32, 1.83-6.2, 95%CI, $p < 0.001$), and positive UC (OR = 3.12, 1.73-5.66, 95% CI, $p < 0.001$), were associated with postoperative SIRS. On multivariable logistic regression analysis adjusted for significant findings on univariable analyses, only

TABLE 2. **The calculated probability of SC results to change the antibiotic regime according to the empiric treatment initiated**

| | Cephalosporin generation 2nd | Ceftriaxone cephalosporin generation 3rd | Sulfamethoxazole-trimethoprim | Quinolones | Antipseudomonal cephalosporin generation 3rd | Clindamycin gentamicin+ | Clindamycin+ amikacin | +Ampicillin gentamicin | +Ampicillin Amikacin | Tazobactam+ piperacillin | Meropenem |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SC pathogens resistance to various antibiotic regimes (% from positive SCs) | 67% | 57% | 56% | 51% | 49% | 44% | 37% | 32% | 25% | 23% | 9% |
| % of patients in whom SC may change Tx for postoperative sepsis (from the cohort) | 14.2% | 12.5% | 12.3% | 11.9% | 10.1% | 9.7% | 8.4% | 7% | 5.6% | 4.7% | 2.3% |

SC = stone culture; Tx = treatment

SC (OR = 5. 8, 2.7-12.6, 95% CI, p < 0.001) remained significantly associated with SIRS, Table 1.

Table 2 depicts resistance rates of pathogens isolated from SC to various antibiotic regimens, and the number of patients in whom the resistance profile in SC may change treatment when compared to that in UC (including pathogens that were susceptible to the specific antibiotics in UC but resistant in SC, or patients who had resistant bacteria on SC and sterile UC). Overall, SC pathogens resistance rates ranged from 9% for treatment with meropenem to 67% for treatment with 2nd generation cephalosporins, and may alter the choice of antibiotics in 73 to 12 (14.2%-2.3% of the whole cohort) patients, respectively.

In 25 patients, resistant pathogens were isolated from SC. Thirteen patients had gram-negative bacteria

TABLE 3. **Univariable and multivariable analysis of risk factors for harboring resistant pathogens**

| Covariate | Total (n = 512) | Resistant (n = 25) | Not resistant (n = 487) | Univariate analysis OR (95% CI) | p | Multivariate analysis OR (95% CI) | p |
|---|---|---|---|---|---|---|---|
| Positive UC (%) | 137 (26.8) | 18 (72) | 119 (24.4) | 7.95 (3.2-19.5) | 0.001 | 3.64 (1.24-10.7) | 0.02 |
| Median number of hospitalization during the last year (q1, q3) | 0 (0, 1) | 2 (1, 3) | 0 (0, 1) | 2.33 (1. 7-3.1) | 0.001 | 1.87 (1.38-2.54) | 0.001 |
| Median Charlson Index (q1, q3) | 1 (0, 4) | 4 (2, 7) | 1 (0, 4) | 1.29 (1.13s-1.49) | 0.001 | 1.13 (0.91-1.32) | 0.11 |
| Prior UTI (%) | 132 (25.8) | 16 (64) | 116 (23.8) | 5.7 (2.45-13.2) | 0.001 | 1.45 (0.52-4.2) | 0.46 |
| Indwelling urethral catheter (%) | 16 (3.1) | 3 (12) | 13 (2.7) | 4.96 (1.3-18.7) | 0.018 | | |
| Prior drainage (%) | 132 (25.8) | 11 (45.8) | 121 (24.8) | 1.5 (1.07-2.13) | 0.017 | | |
| Nephrostomy (%) | 81 (15.8) | 11 (44) | 70 (14.4) | 2.16 (1.43-3.27) | | | |
| Double-J stent (%) | 51 (10) | 0 (0) | 51 (10.5) | 0 (0) | | | |
| Stone composition | | | | 1.63 (1.15-2.3) | 0.007 | | |
| Calcium oxalate (%) | 222 (62.7) | 5 (31.3) | 217 (64.2) | | | | |
| Uric acid (%) | 69 (19.5) | 5 (31.3) | 64 (18.9) | | | | |
| Calcium phosphate (%) | 25 (7.1) | 1 (6.3) | 24 (7.1) | | | | |
| Struvite (%) | 24 (6.8) | 4 (25) | 20 (5.9) | | | | |
| Cystine (%) | 12 (3.4) | 1 (6.3) | 11 (3.3) | | | | |
| Median age (q1, q3) | 54 (44, 64) | 64 (52, 72) | 54 (44,64) | 1.03 (1.01-1.06) | 0.01 | | |
| Male gender (%) | 323 (63.1) | 13 (52) | 310 (63.7) | 1.6 (0.72-3.72) | 0.24 | | |
| BMI (q1, q3) median | 27.3 (24.3, 30.5) | 28.1 (26.6, 30.7) | 27.2 (24.1, 30.5) | 1.04 (0.96-1.13) | 0.3 | | |
| Median stone size (q1, q3) | 30 (20 ,40) | 28 (21, 30) | 30 (20,40) | 0.97 (0.93-1.01) | 0.12 | | |
| Diabetes mellitus (%) | 123 (24) | 9 (36) | 114 (23.4) | 0.54 (0.23-1.26) | 0.16 | | |

OR = odds ratio; CI = confidence interval; UC = urine culture; q1 = first quarter; q3 = third quarter; UTI = urinary tract infection; BMI = body mass index

susceptible only to carbapenems, while *candida sp*. and gram-positive bacteria susceptible only to vancomycin were isolated in six patients each. Seven (28%) patients developed postoperative SIRS, a significantly higher rate than observed in patients without highly resistant pathogens (43 of 487 (9%) patients, p = 0.008) on univariable logistic regression analysis, using a p value of 0.004 to account for multiple testing, positive UC (OR = 7.95, 3.2-19.5, 95% CI, p < 0.001), prior UTI (OR = 5.7, 2.45-13.2, 95% CI, p < 0.001), the number of hospitalizations during the previous year (OR = 2.33, 1.7-3.1, 95% CI, p < 0.001), and CCI (OR = 1.29, 1.13-1.49, 95% CI, p < 0.001), were associated with resistant bacteria in SC. On multivariate analysis adjusted for the significant findings on univariable analysis, positive UC (OR = 3.64, 1.24-10.7, 95% CI, p = 0.02), and the number of hospitalizations during the previous year (OR = 1.87, 1.38-2.54, 95% CI, p = 0.001), remained statistically significant, as shown in Table 3.

## Discussion

In the current study, we used a large database of patients who underwent PCNL to determine the yield of intraoperative SC in this setting. Our data supports the discordance between preoperative UC and intraoperative SC, demonstrated in earlier cohorts, and demonstrates a difference between common pathogens in UC and SC. Moreover, depending on the initial antibiotic regimen used for treating post-PCNL sepsis, and accounting for a SIRS rate of 10%, between 0.2% to 1.42% of the patient would have had their treatment changed, had sepsis occurred.

Infectious complications following PCNL are not uncommon; the incidence of post-PCNL SIRS approaches 35%, and sepsis is reported after 0.9% to 4.7% of cases.[3,10,11] Sepsis can rapidly deteriorate to septic shock and death, therefore, large efforts are made to decrease its incidence. Among previously identified risk factors for postoperative sepsis, the most prominent is the colonization of renal stones, as reported by several researchers. Studies on SC have also demonstrated a substantial discordance between UC and SC results, leading many authors to recommend obtaining SC routinely after PCNL.[3-5]

Consistent with the results of earlier series, we report that the risk for postoperative SIRS in patients with positive SC was nearly six times higher than in patients with negative SC. The utilization of SC to detect patients at high risk for sepsis is limited by the culture incubation time, delaying test results until after the occurrence of sepsis. Cockerill et al attempted to overcome this limitation by performing Gram staining on stones removed during PCNL. Only 31 of 81 colonized stones stained positively, with a calculated sensitivity of 38%. Thus, the authors concluded that stone Gram staining cannot reliably detect a positive stone culture.[12] Even with more sensitive and rapid tests such as Polymerase Chain Reaction, identification of a pathogen on a urinary stone is not likely to change their management, since most patients with positive SC will not have sepsis, rendering it's use as a screening tool for sepsis unrealistic.

A possible implication for SC may be directing the antibiotic treatment in patients with a UTI. Few previous studies reported the number of patients in whom antibiotic treatment in post-PCNL infections was modified following the use of SC. In a study of 200 patients by Lojanapiwat et al SC changed the treatment in 3 (1.5%) patients.[13] Margel at el reported that 13 of 75 (17.3%) patients undergoing PCNL had their treatment changed, as opposed to one of 79 (1.3%) patients reported by Osman et al.[3,14]

While all previous studies have related to the discordance between UC and SC as a surrogate for inappropriate antibiotic treatment, in reality, SC may have a true clinical impact only if they lead to a change in antibiotic treatment compared to the treatment that would have been used had UC been the only indicator to direct therapy. Hence, the discordance between antibiotic susceptibility of urine and stone pathogens should be sought to evaluate the true clinical implication of SC. In the current study, we evaluated the probability of SC to change the antibiotic treatment when using several treatment regimens. The probability of changing antibiotic treatment ranged from 12.5% for patient treated with ceftriaxone, to 2.3% for patients treated meropenem. Considering a SIRS rate of 10%, the calculated number needed to screen with SC for one change in treatment would roughly range from 80 to 400, depending on the initial regimen. In this cohort, SC results changed the treatment in four patients, consistent with our calculation of 8.4% probability to change treatment when gentamicin and ampicillin are used.

Few patients will almost invariably benefit from obtaining SC. In the current study, we identified 25 patients in whom resistant pathogens grew on SC. This group was characterized by multiple hospitalizations and comorbidities, and prior urine colonization. Among these patients, 7 (28%) had SIRS, a significantly higher rate than in the rest of the patients (p = 0.008), making the preoperative identification of this group of patients even more desirable. Since infection rate was higher within this group, the actual number needed to screen is probably lower than the calculated number.

The spectrum of pathogens isolated from the urine and stones in the current study is also noteworthy. One third of colonized stones harbored gram positive bacteria, a trend which was observed in earlier studies.4 Furthermore, 13% of colonized stones harbored *Pseudomonas*. Importantly, over half of the pathogens were resistant to cephalosporins and quinoloes, thus making them less appropriate to use in this clinical scenario.

Limitations of the current study include the retrospective data collection used for part of the cohort. There may also have been a selection bias, since the study was conducted in a tertiary referral center, possibly including a higher rate of patients who were treated with multiple antibiotics and therefore had more resistant pathogens. As in any study in the field of infectious diseases, our results represent the local bacterial flora, which may limit the applicability to other centers. Finally, even though we aimed to evaluate the yield of SC in patients undergoing PCNL, we have not discussed economic considerations, due to their complexity and diversity between different centers.

## Conclusions

Similar to previous studies, we found an association between the presence of a positive SC and post-PCNL SIRS on multivariable analysis, and a discordance rate of 47% between UC and SC among patients who developed post-PCNL sepsis.

Nevertheless, when evaluating the true clinical impact of stone culture, despite the high discordance rate, a change in antibiotic treatment would occur in 2.3%-14.2% of patients depending on the drug regimen used to treat sepsis. Considering our findings, the benefit of post-PCNL SC may be limited when routinely treating post-PCNL sepsis using broad spectrum antibiotics. □

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