ORIGINAL ARTICLE

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Predictors of Post-percutaneous Nephrolithotomy Sepsis – A Prospective Comparative Study of Bacteriology of Mid-stream Urine Culture, Renal Pelvis Urine Culture, and Stone Culture with a View to Prevent and Treat Sepsis

ABSTRACT

Aim: The aim of the study was to find the correlation between pre-operative midstream urine culture, intraoperative renal pelvis urine culture, and renal stone culture with the post-operative infections and clinical episodes suggestive of urosepsis, in patients treated with percutaneous renal surgeries for renal stone disease. **Background**: The objectives of the study are as follows: (1) To study correlation between pre-operative midstream urine culture, intraoperative renal pelvis urine culture, and intraoperative renal stone culture. (2) To understand which of these culture specimens, that is, pre-operative midstream urine culture, intraoperative renal pelvis urine culture, or intraoperative renal stone culture, will predict urosepsis in patients undergoing percutaneous renal surgery for renal stone disease. **Conclusion:** Post-operative sepsis is one of the most feared events associated with percutaneous nephrolithotomy (PCNL). We found that pre-operative midstream urine culture may not accurately reflect the bacteriological status of the renal stone and pelvic urine. Both positive renal pelvis urine culture and positive pre-operative midstream urine culture had statistically significant association with stone culture positivity. Positive renal pelvis urine culture had stronger association with stone culture positivity compared to pre-operative midstream urine culture. Pre-operative midstream urine culture is not a good predictor of systemic inflammatory response syndrome/sepsis following PCNL. Sepsis-related complications can arise despite sterile urine or adequately treated pre-operative urine culture. Intraoperative renal pelvis urine culture and renal stone cultures are better predictors of post-operative sepsis/relevant clinical events. These culture results can help to identify causative organism of urosepsis and help to direct antimicrobial treatment, if sepsis develops. **Clinical Significance**: Sepsis-related complications can arise despite sterile urine or adequately treated pre-operative urine culture. Intraoperative renal pelvis urine culture and renal stone cultures are better predictors of post-operative sepsis/relevant clinical events.

Key words: Renal pelvis urine culture, Stone culture, Urine culture, Urosepsis

INTRODUCTION

Sepsis is a major complication of percutaneous nephrolithotomy (PCNL). Early bacterial identification by culture is the key to starting appropriate antibiotic early. Pre-operative midstream urine culture is essential, but it is not sufficient alone to predict post-operative sepsis. Several studies have proven that even with the adequate treatment of urinary tract infection preoperatively or even with sterile preoperative urine and with prophylactic perioperative antibiotics, patient can develop sepsis during post-operative period.[1] Pre-operative midstream urine, intraoperative renal pelvis urine, and renal stone for culture and sensitivity were analyzed in 100 PCNL cases in this study. The purpose of this study is to correlate these cultures with post-operative sepsis.

Aim

The aim of the study was to find the correlation between pre-operative midstream urine culture, intraoperative renal pelvis urine culture, and renal stone culture with the post-operative infections and clinical episodes suggestive of urosepsis, in patients treated with percutaneous renal surgeries for renal stone disease.

Primary objectives

The objectives of the study are as follows:

1. To study correlation between pre-operative midstream urine culture, intraoperative pelvic urine culture, and

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Table 1: Demographic characteristics of cases studied

Parameters	No. of cases (*n*=100)	% of cases
Age (years)		
21–39	14	14.0
40–59	51	51.0
>60	35	35.0
Mean±SD	52.8±13.2 years	--
Gender		
Male	60	60.0
Female	40	40.0
Comorbidity		
Nil	39	39.0
Hypertension	44	44.0
Diabetes	33	33.0
CKD	9	9.0
Other*	14	14.0
Guy's stone score		
Score 1	44	44.0
Score 2	29	29.0
Score 3	7	7.0
Score 4	20	20.0

*Other comorbidities – ischemic heart disease, cardiomyopathy, atrial fibrillation, hypothyroidism etc

Table 2: Correlation of positive stone culture in patients with positive/negative preoperative midstream urine and renal pelvis urine culture

???	Stone Culture				*P*-value
	Positive (*n*=33)		Negative (*n*=67)		
	N	%	*n*	%	
Pre-op midstream urine culture					
Positive (*n*=35)	19	54.3	16	45.7	0.001***
Negative (*n*=65)	14	21.5	51	78.5	
Renal Pelvis urine culture					
Positive (*n*=23)	21	91.3	2	8.7	0.001***
Negative (*n*=77)	12	15.6	65	84.4	

P-value by Chi-square test (Fisher's exact probability test). $P<0.05$ is considered statistically significant. ***$P<0.001$

intraoperative renal stone culture

2. To understand which of these culture specimens, that is, pre-operative midstream urine culture, intraoperative renal pelvis urine culture, or intraoperative renal stone culture will predict urosepsis in patients undergoing percutaneous renal surgery for renal stone disease.

MATERIALS AND METHODS

This was a prospective and observational study of all PCNL, miniperc, and ultraminperc procedures conducted in Deenanath Mangeshkar hospital, Pune from 2018 to 2020. All PCNL, miniperc, and ultraminperc procedures were included in the study. Some cases were excluded due to contraindications for PCNL or cases in which bacterial colonization is introduced due to an earlier intervention or indwelling foreign body. These cases included patients with prior nephrostomy, bleeding diathesis, concomitant bladder, and renal stone and patients with indwelling catheter.

Table 3: Diagnostic efficacy measures for predicting the positive stone culture with positive pre-operative midstream urine culture and positive renal pelvis urine culture

	Diagnostic efficacy measures			
Culture	Sensitivity	Specificity	PPV	NPV
Pre-operative midstream urine	57.6	76.1	54.3	78.5
Renal pelvis urine culture	63.6	97.0	91.3	84.4

Table 4: Incidence of positive pelvic urine culture in cases with dilated pelvicalyceal system

	Dilated pelvicalyceal system				*P*-value
	Yes (*n*=73)		No (*n*=27)		
	n	%	*n*	%	
Pelvic urine culture					
Positive	18	24.7	5	18.5	0.517^{NS}
Negative	55	75.3	22	81.5	
Total	73	100.0	27	100.0	

P-value by Chi-square test. $P<0.05$ is considered to be statistically significant. NS: Statistically non-significant

Methodology

A pre-operative evaluation was carried out in all patients with demographic data such as age, gender, height, weight, and detailed clinical history, physical examination including, associated medical comorbidities, and current medications. Routine pre-operative investigations include complete blood count, renal function test (serum electrolytes, serum creatinine, and blood urea levels), urine routine and microscopy, random blood sugar level, and coagulation profile (prothrombin time, I.N.R., and activated partial thromboplastin time). Pre-operative midstream urine was collected for culture and sensitivity 1 week before the planned procedures. Imaging studies included ultrasonography with X-ray KUB/IVU or CT KUB/IVU as necessary. Guy's stone score (GSS) was calculated in all patients.

Patient with positive pre-operative urine cultures received appropriate antibiotics for duration of minimum 1 week. Depending on clinical situation, decision was taken to decompress obstructed system before stone treatment. If urine demonstrated persistent bacterial growth (two or more positive culture) despite appropriate antibiotic treatment in asymptomatic patient with positive pre-operative mid-stream urine culture, those patients underwent surgery under appropriate antibiotic coverage. On induction, patient

Table 5: Types of microorganisms isolated and their percentage in different culture samples in study population

Microorganism	Types of microorganisms in different culture								
	Pre-operative midstream urine culture			Pelvic urine culture			Stone culture		
	Total and (%)	Sepsis		Total and (%)	Sepsis		Total and (%)	Sepsis	
		No	Yes		No	yes		No	Yes
Non ESBL *Escherichia coli*	15 (41.7)	14	1	4 (16.7)	1	3	5 (11.6)	2	3
ESBL *Escherichia coli*	3 (8.3)	0	3	5 (20.8)	3	2	9 (20.9)	4	5
Pseudomonas aeruginosa	5 (13.9)	5	0	5 (20.8)	4	1	15 (34.9)	13	2
Klebsiella pneumoniae	4 (11.1)	4	0	1 (4.2)	1	0	1 (2.3)	0	0
Proteus mirabilis	2 (5.6)	2	0	0	-	-	1 (2.3)	1	0
Streptococci	2 (5.6)	2	0	0	-	-	2 (4.7)	2	0
Enterococcus spp.	2 (5.6)	2	0	3 (12.5)	2	1	3 (7)	2	1
Candida	3 (8.3)	3	0	4 (16.7)	4	0	4 (9.3)	4	0
Burkholderia cepacia	0	-	-	2 (8.3)	2	0	0	-	-
Enterobacter cloacae	0	-	-	0	-	-	2 (4.7)	2	0
Pantoea agglomerans	0	-	-	0	-	-	1 (2.3)	1	0
Total No. of microorganisms	36	32	4	24	17	7	43	32	11

Table 6: Incidence of sepsis in various culture groups

	Sepsis				*P*-value
	Yes (*n*=12)		No (*n*=88)		
	n	%	*n*	%	
Preoperative midstream urine culture					
Positive (35)	4	11.4	31	88.6	0.999^{NS}
Negative (65)	8	12.3	57	87.7	
Pelvic urine culture					
Positive (23)	7	30.4	16	69.6	0.002**
Negative (77)	5	6.5	72	93.5	
Stone culture					
Positive (33)	9	27.3	24	72.7	0.001***
Negative (67)	3	4.5	64	95.5	

P-value by Chi-square test (Fisher's exact probability test). $P<0.05$ is considered to be statistically significant. $^{**}P<0.01$, $^{***}P<0.001$, NS: Statistically non-significant

Table 7: Diagnostic efficacy measures for predicting sepsis with various cultures

Culture	Predicting sepsis using various cultures				
	Sensitivity	Specificity	PPV	NPV	Accuracy
Pre-operative midstream urine culture	33.3	64.7	11.4	87.7	61.0
Pelvic urine culture	58.3	81.8	30.4	93.5	79.0
Stone culture	75.0	72.7	27.3	95.5	73.0

was administered fluoroquinolones or second generation cephalosporin or antibiotics as per culture reports.

Cystoscopy was done and ureteric catheter was placed up to the renal pelvis, its position confirmed on c arm and patient turned prone.

Table 8: Distribution of demographic variables and patient characteristics in cases with sepsis

Characteristics	Sepsis status (SIRS/sepsis/septic shock/mortality)				*P*-value
	No (*n*=88) (%)		Yes (*n*=12) (%)		
Female (%)	34	35.22%	6	50.0%	0.451^{NS}
Age Mean±SD (years)	52.7	±13.6	53.4	±10.7	0.832^{NS}
Staghorn stone (%)	21	23.9%	6	50.0%	0.056^{NS}
Diabetes mellitus (%)	29	32.9%	4	33.3%	0.999^{NS}
GSS Mean±SD	1.95	±1.08	2.58	±1.51	0.075^{NS}

P-value for age and operative time by independent sample t-test. The rest of the *P* values by Chi-square test. $P<0.05$ is considered to be statistically significant. $^{*}P<0.05$, NS: Statistically non-significant

Intraoperative renal pelvis urine sample was collected by aspiration on puncture of calyceal system under image intensification and sent for culture sensitivity.

The tract was then dilated using fascial dilators of appropriate size. Nephroscopy and pneumatic, laser, or ultrasonic lithotripsy was performed with normal saline irrigation, stone fragments were collected with forceps or through sheath. At the completion of procedure, either a double J stent was placed in antigrade fashion or a ureteric catheter was placed at the time of cystoscopy and kept *in situ* and percutaneous nephrostomy tube was deployed at the end of the procedure.

Stones were cleaned with normal saline to remove surface contamination and sent for microbiological evaluation in sterile container (mechanically crushed and crushed stone fragments cultured in 5 ml thioglycolate broth which were incubated at 37°C for 18–24 h, and then subcultures were made on blood agar and Maconkeys agar plate for isolation of etiological agents).

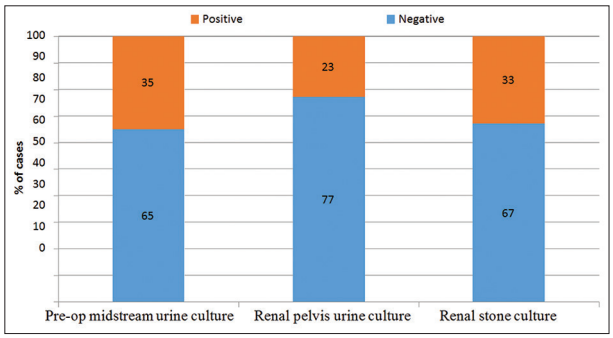


Figure 1: Culture results

Evaluation of complication

Postoperatively, antibiotics were continued minimum till removal of nephrostomy tube. During post-operative period, patient's temperature, pulse rate, respiratory rate, blood pressure, oxygen saturation, urine output, and other vital parameters were monitored. Postoperatively, laboratory investigations including complete blood count and renal function test were performed in all patients. To rule out presence of any residual fragments, X-ray or ultrasound (USG) KUB was done as necessary, apart from routine intraoperative fluoroscopy. Any fragment that was visible on X-ray or fluoroscopy or a fragment >3 mm on USG was considered as significant. Nephrostomy tube was removed on 1st or 2nd post-operative day and Foley's catheter was removed on the next day. Patients were followed up till discharge. Patients were monitored for sepsis/systemic inflammatory response syndrome (SIRS) (defined as two or more of the following, [1] temperature >38 c or <36 c [2] heart rate >90/min [3] respiratory rate >20 or $PaCO_2$ <32 mm hg, and [4] WBC count >12,000/cu mm or <4000/cu mm or >10% immature forms) and septic shock (sepsis induced hypotension with presence of perfusion abnormalities including lactic acidosis/oliguria/altered mentation). SIRS, sepsis, or septic shock were included under infectious complications and patients with post-operative fever alone who did not meet criteria for SIRS were excluded from the study. Serum procalcitonin level was measured in patients with suspected SIRS/sepsis, blood culture was also sent in these patients. Patients showing altered parameters s/o sepsis/SIRS/septic shock were treated aggressively, antibiotics were stepped up, either empirically or as per pre-operative culture report, till new urine, stone, or blood culture reports became available, vasopressors and other supportive medications were continued as necessary, and unstable patients were transferred to intensive care unit. Relevant data were collected and results were tabulated.

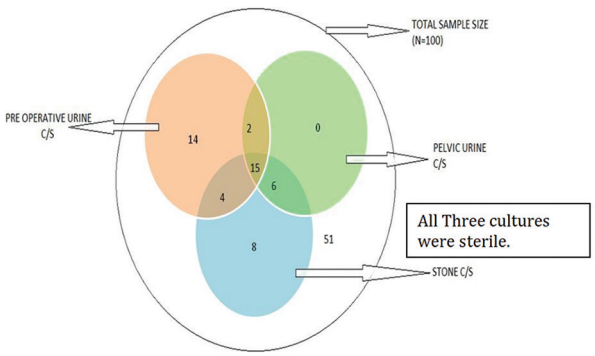
Statistical methods

Statistical analysis was carried out with the help of SPSS (version 20) for Windows package (SPSS Science, Chicago, IL, USA). The description of the data was done in the form of arithmetic mean ± SD for quantitative data while in the form of frequencies (%) for qualitative (categorical) data. $P < 0.05$ was considered significant. For quantitative data, Unpaired Students *t*-test was used to test statistical significance of difference between means of variables among two independent groups. For comparison of categorical variables (i.e., to examine the associations between qualitative/quantitative variables), Chi-square test was used if the number of elements in each cell was 5 or higher and Fishers exact test, otherwise. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the renal stone culture, pre-operative midstream urine culture, and intraoperative pelvic urine culture for urosepsis were estimated.

OBSERVATIONS AND RESULTS

A total of 100 patients who underwent PCNL, miniperc, or ultraminiperc and fulfilled the selection criteria during August 2018–May 2020 were included in this study [Tables 1-8 and Figure 1].

Culture results in-patient who developed sepsis



We found that, of the 100 cases, 15 cases had all three positive culture samples, two cases had positive pre-operative midstream urine and pelvic urine culture, four cases had positive pre-operative midstream urine and renal stone culture, six cases had positive pelvic urine and stone culture. In 51 cases, all cultures were sterile. Upper tract urine culture (renal pelvic urine and renal stone) positivity was in 35 patients.

Twelve patients developed sepsis in our study, of these 12 patients, all three cultures were sterile in three patients, stone culture was positive in all the remaining nine patients whereas renal pelvis urine culture was positive in seven patients and pre-operative urine culture was positive in only four patients.

Although both positive pre-operative midstream urine culture and positive pelvic urine culture had statistically significant association with positive stone culture, this association was higher with positive pelvic urine culture as compared with midstream urine samples (91.3% vs. 54.3%).

Pelvic urine culture in cases with dilated pelvicalyceal system

Out of 73 cases who had evidence of dilated pelvicalyceal system, "The incidence of positive pelvic urine culture did

not differ significantly between patients with or without pelvicalyceal dilatation ($P = 0.517$)."

Concordance between different culture with respect to type of microorganism isolated

In this study, 15 cases had all three, that is, preoperative midstream urine, pelvic urine, and stone culture positivity. Of these 15 cases, nine cases had identical microorganism isolated on all three culture samples; three cases had identical microorganism isolated on pelvic urine and renal stone culture. Two cases had positive pre-operative midstream urine and pelvic urine culture, one of them had concordant growth.

We found concordant growth in four of the six cases with positive stone and pelvic urine culture. All four cases with positive pre-operative midstream urine and renal stone culture had concordant growth.

Incidence of sepsis in various culture groups

Out of 100 patients included in this study, 12 developed sepsis and one of them died. Data showed that renal stone culture positivity and pelvic urine culture positivity was significantly associated with the sepsis ($P < 0.05$), whereas pre-operative midstream urine culture positivity was not significantly associated with incidence of sepsis ($P > 0.05$).

Stone culture had the highest sensitivity to predict sepsis

Pre-operative midstream culture had a sensitivity of only 33% to predict sepsis.

Variables such as female gender, mean age, staghorn stone configuration, diabetes, and mean GSS did not differ significantly between cases who developed sepsis and cases who did not developed sepsis ($P > 0.05$ for all).

DISCUSSION

There is a risk of post-PCNL sepsis even with sterile/adequately treated pre-operative urine. This complication would increase morbidity, increase cost of care, and rarely could turn out to be fatal.

Factors which could be responsible for these complications are infected renal stone and infected renal pelvic urine. These sites could harbor microorganisms despite sterile pre-operative midstream urine. In addition to bacteria residing in the upper tract (urine/stone), endotoxins released from the stone breakage can also be implicated for sepsis. PCNL and under pressure irrigation will increase bacteremia during stone manipulation through pyelovenous, pyelolymphatic and pyelotubular backflows, and forniceal rupture. Longer duration of surgery, increased stone burden, multiple punctures will increase the severity of bacteremia and increase chance of septicemia.

One of the most important therapeutic option derived from "surviving sepsis" theme is the timely administration of the appropriate antibiotic, ideally within 1 h of the onset of sepsis. This is the single most important factor proven to reduced morbidity and mortality from sepsis.[2]

The aim of this study is to analyze correlation between pre-operative midstream urine culture, intraoperative pelvic urine culture, and renal stone culture. We documented sepsis associated with the PCNL and attempted to analyze whether these different culture specimens correlate with the development of sepsis.

Twelve patients had sepsis postoperatively, with one death (he had atrial fibrillation as preexisting condition). Of the remaining 11 patients, five required intensive care. Initially, antibiotics were upgraded empirically or as per pre-operative urine culture results, in three patients, antibiotics were changed based on pelvic/renal stone culture sensitivity results. All these patients eventually recovered and discharged after nephrostomy tube and Foleys removal.

Most common culture positive specimen in our study group was pre-operative midstream urine culture, which was positive in 35% cases followed by renal stone culture in 33% cases, renal pelvic urine culture was positive in 23% cases. None of patient in our study had positive blood culture. In the study by Mariappan *et al*., none of the patient with SIRS had positive blood culture, whereas Devraj *et al*. found one patient with positive blood culture among 23 patients with SIRS.[3,4] Possible explanation for these findings could be role of the endotoxins in causation of SIRS. Renal stone can harbor endotoxins, which would get released in blood stream during stone fragmentation, resulting in SIRS.[5] In our study, total 35 patients had infected upper tract (i.e., either positive pelvic urine culture or positive renal stone culture or both), 14 of these cases (40%) had sterile preoperative midstream urine. Margel *et al*. reported 25% incidence of sterile urine culture with positive stone culture.[6] Similar result was seen in study by Korets *et al*., of the 97 cases with infected upper tract in their study, 62 (63%) had sterile preoperative urine culture.[7] This finding emphasizes the need of regular microbiological analysis of upper tract samples and stone even with sterile pre-operative urine. The possible explanation of sterile midstream urine culture with positive upper tract culture may be that there can be complete block of the upper tract due to stone, resulting in this discrepancy in the culture result. The intermittent bacterial drainage from the upper tract is another possible explanation for this finding. A study of sending multiple midstream urine sample culture preoperatively to see if that increase the yield of culture can be designed to test this hypothesis.

Positive pre-operative midstream urine culture and positive intraoperative pelvic urine culture had statistically significant association with positive renal stone culture. Sensitivity and specificity of pelvic urine culture for detecting positive stone culture were higher compared to pre-operative urine culture (63.6% vs. 57.6% and 97% vs. 76.1%, respectively). Pelvic urine culture has a better correlation to stone culture as sometimes the upper tract may be blocked allowing midstream

urine sample to be falsely negative with actually positive upper tract culture. Mariappan *et al*. also found similar results.

Hydronephrosis is a manifestation of poor drainage of the renal collecting system and there is possibly an increased risk of infection in these patients. A higher proportion of cases (24.7%) in the group with dilated pelvicalyceal system had positive pelvic urine culture compared to the group without dilated pelvicalyceal system (18.5%) although this difference was not statistically significant ($P = 0.517$). The previous study by Mariappan *et al*. found higher incidence of positive pelvic urine culture in a group of patients with dilated pelvicalyceal system.[3] This point needs further study.

We could not find statistically significant difference in occurrence of sepsis in patient with different GSS. The study done by Lojanapiwat *et al*. found higher incidence of sepsis in patients with GSS 3 and 4.[8] GSS uses multiple variables to grade complexity of renal stone disease. Higher GSS 3 and 4 are designated for staghorn stone configuration. With increase in time of scopy, the number of tracts and increased stone burden is associated with complex stones.

We observed highest concordance observed between renal pelvic urine and renal stone culture (14/21), similar results were seen in study by Korets *et al*.[7] The study by Walton-Diaz *et al*. found 83.3% concordance between renal pelvic urine and renal stone culture.[9] Both of these culture correlated to sepsis. Sensitivity of renal stone culture for predicting sepsis was 75% in our study and 80.95% in study by Devraj *et al*.[4] The study by Korets *et al*. showed that patients with post-operative SIRS had a significantly higher prevalence of positive pelvic urine culture and renal stone culture.[7] Again, this emphasizes not to just rely on midstream culture to guide antibiotic therapy. A change in practice of sending upper tract urine and stone culture as a routine to better guide antibiotic therapy is suggested.

CONCLUSION

Post-operative sepsis is one of the most feared events associated with PCNL. We found that pre-operative midstream urine culture may not accurately reflect the bacteriological status of the renal stone and pelvic urine.

Both positive pelvic urine culture and positive pre-operative midstream urine culture had statistically significant association with stone culture positivity. Positive pelvic urine culture had stronger association with stone culture positivity compared to pre-operative midstream urine culture.

Pre-operative midstream urine culture is not a good predictor of SIRS/sepsis following PCNL. Sepsis-related complications can arise despite sterile urine or adequately treated pre-operative urine culture. Intraoperative pelvic urine culture and renal stone cultures are better predictors of post-operative sepsis and relevant clinical events.

These culture results can help identify causative organism of urosepsis and help to direct antimicrobial treatment, if sepsis develops.

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