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ORIGINAL ARTICLE

Predicting the risk of sepsis and causative organisms following urinary stones removal using urinary versus stone and stent cultures

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Abstract

The association between foreign objects in the urinary system and urinary tract infections (UTI) is well established. The incidence of bacteriuria in patient with urinary catheters increases as dwelling time lengthens. The presence of ureteral stents and kidney stones is also associated with increased risk for bacteriuria and urinary tract infection. The aim of this study was to assess the bacterial characteristics of urine culture (UC) and foreign body culture (FBC), the concordance between them, and to identify risk factors for postoperative infections, in order to improve the treatment in these patients, using a prospectively collected database of patients who underwent ureteroscopy or percutaneous nephrolithotomy (PCNL) for the treatment of urinary stones between 2005 and 2016 at our institute. Preoperative UC was obtained from voided mid-stream urine for all patients. FBCs were obtained from ureteral stents removed and stones collected during the surgery. The cohort included 1011 patients. Mean age was 53 (SD 15.8), and 679 (67.2%) patients were male. Two hundred eighteen (21.6%) had a UTI in the year prior to the surgery. Among 795 patients who had sterile UC, 98 (12.3%) patients had positive FBC. Positive FBC was found in 53.7% of the patients with positive UC; however, FBC pathogens were similar to those identified in UC in 31% patients. The sensitivity of UC to detect FBC pathogens was 31.3%, and the PPV was 0.31. Urine cultures do not recognize all cases of pathogens colonizing foreign bodies in the urinary system. The colonization may be associated with an increased risk for SIRS. In more than one-quarter of the patients, the causative pathogen of sepsis is identified by FBC, but not by UC.

Introduction

Foreign objects in the urinary system, such as urinary catheters, are associated with an increased risk for urinary tract infections (UTIs) and have been a leading cause of morbidity and mortality in hospitalized patients [1, 2]. This is mainly due to quick bacterial colonization, in an estimated rate of 3% to 8% per day, and 100% after 1 month [3]. The presence of other foreign objects in the urinary system, namely, ureteral stents and kidney stones, is not uncommon and is also associated with increased risk for bacteriuria and urinary tract infection. For instance, the prevalence of kidney stones in the general population is roughly 10% [4], but they were found in one-fifth of patients with UTI and no prior history of kidney stones [5]. Furthermore, multiple studies have shown that bacteriuria is very common in patients with urinary stones, reported in 21% to 34% [6–8]. Similarly, ureteral stents, an important tool in the urologic armamentarium, are associated with higher incidence of infectious complications, which further increases with a longer dwelling time [9].

Identifying the bacterial flora is not always possible in the environment of a foreign body, since it is partially masked by a biofilm [10]. Many studies assessing the concordance between urine culture (UC) and stent or stone cultures (hence forward—foreign body culture, FBC), obtained from the same patients, found 20% to 70% of the pathogens isolated from FBC were not identified by UC (either UC was negative or grew different pathogen). Furthermore, colonization of the foreign body has been associated with postoperative infectious complications, regardless of the UC results [11–14]. These findings can explain situations in which a patient does

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not respond to a culture-guided antibiotic treatment or a patient develops UTI despite sterile UC.

As it has been our practice for over a decade to obtain FBC from patients undergoing urologic procedure for the treatment of urinary stones, we aimed to study the bacterial characteristics of UC and FBC, the concordance between them, and to identify risk factors for postoperative infections, in order to improve the treatment in these patients.

Materials and methods

Participants and study design

After obtaining approval from the IRB, we queried the prospectively collected database of patients who underwent surgical treatment for urinary stones (percutaneous nephrolithotomy (PCNL) or ureteroscopy) between 2005 and 2016 at our institute. Data regarding age, gender, comorbidities, age-adjusted Charlson comorbidity index [15], previous UTIs, and postoperative course were collected. Stent and stone cultures were obtained from patients who had undergone ureteroscopy and PCNL, respectively. Patients who did not have UC or FBC results and patients with indwelling urethral or suprapubic catheters were excluded from the study.

Preoperative UC was obtained from voided mid-stream urine for all patients. Patients with a positive UC were treated with a 1-week oral or intravenous antibiotic course per the UC results followed by a second UC to verify urine sterilization, and a single preoperative dose of culture-guided intravenous antibiotic prior to the procedure. Patients with sterile UC were treated with a single preoperative dose consisting of 1 g ampicillin and 80 mg to 240 mg gentamicin. FBCs were obtained as follows: Ureteral stents were removed at the beginning of the surgery, and stones were obtained during the surgery. The specimens were washed with sterile water, placed in a container, and sent to the microbiology laboratory. The stent tip was rolled across an agar several times, while stone fragments were crushed and placed on the agar.

Definitions and outcomes

Urine cultures were analyzed for bacterial infection using the Diaslide method [16]. Upon colony growth, bacterial identification was performed using Bruker MALDI-TOF MS system [17]. Urine cultures were considered positive if bacteriuria of $\geq 10^3$ colony forming units (CFUs)/mL of a single pathogen was demonstrated.

The study outcome was SIRS within 48 h of the procedure, defined in accordance with International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 [18]. Since essentially every foreign body in the urine becomes colonized within a short time, any SIRS event was considered urosepsis. Patients with respiratory symptoms or radiographic findings suspicious for pneumonia were excluded.

Statistical analysis

Continuous variables were described as mean ± standard deviation for normal distribution and median and interquartile range (IQR) for non-normal distribution; categorical variables were presented as number and percent. Positive predictive value (PPV) was calculated to assess the yield of UC to accurately predict FBC results. The associations between preoperative characteristics and FBC and the occurrence of SIRS within 48 h after the procedure were evaluated with univariable and multivariable logistic regression analyses. All statistical analyses were two-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, 2116 patients were treated for urinary stones, of which 1011 patient had both UC and FBC results available and were included in the study. Mean age was 53 (SD 15.8), and 679 (67.2%) patients were male. Median Charlson comorbidity index was 0 (IQR 0–3) and 218 (21.6%) had a UTI in the year prior to the surgery. Patient characteristics are presented in Table 1.

Preoperative UC was positive in 216 (21.4%) patients, and FBC was positive in 214 (21.2%) patients. Both cultures were positive in 116 (11.5%) patients and negative in 697 (69%) patients. Among 795 patients who had sterile UC, 98 (12.3%) had positive FBC. Positive FBC was found in 116/216 (53.7%) of the patients with positive UC; however, FBC pathogens were similar to those identified in UC in 67/216 (31%) patients. Therefore, in 147/1011 (14.5%) patients, the FBC identified pathogens not isolated from UC. The sensitivity of UC to detect FBC pathogens was 31.3%, and the PPV was 0.31.

The most frequent pathogens isolated from stents were *Enterococcus* spp. (19 patients, 18.4%), *Escherichia coli* (17 patients, 16.5%), and Candida spp. (10 patients, 9.7%), while *E. coli* (36 patients, 36.7%), *Enterococcus* spp. (18 patients, 18.4%), and *Klebsiella* spp. (13.3%) were the most common isolates from UC obtained from the same patients. Pathogens isolated from stones were *E. coli* (24 patients, 21.6%), *Enterococcus* spp. (23 patients, 20.7%), and *Pseudomonas aeruginosa* (15 patients, 13.5%), while UC obtained from these patients grew *E. coli* (37 patients, 31,4%), *Proteus mirabilis* (19 patients, 16.1%), and, *Pseudomonas aeruginosa*

Table 1 Patient's characteristics

	Total	*Stone cultures (512)*	*Stent cultures (509)*
Mean age (SD)	53 (15.8)	14.6) 52.8(	53.9 (16.9)
Male sex (%)	679 (67.2)	316 62.9)(	363 (71.3)
Diabetes (%)	194 (19.2)	118 23.5)(	76 (14.9)
Median age-adjusted Charlson score (IQR)	0 (0–3)	1 (0–4)	0 (0–2)
Mean BMI (SD)	7.3) 26.8(	26.9 7.53)(	(7.1) 26.8
Positive UC (%)	216 21.4)(	118 23.5)(	98 (19.3)
Positive FBC (%)	214 21.2)(	111 22.1)(	103 (20.2)
Previous UTI (%)	218 21.6)(	125 24.9)(	93 (18.3)
Stone size in mm (SD)	15.5) 18.9(	30.8 13.8)(	8.8 (7.8)
Mean operative time in min (SD)	72 39.7)(	100.9 30.6)(	48.5 (23.3)
SIRS (%)	72 7.1)(	47 9.4)(	25 (4.9)

SIRS systemic inflammatory response syndrome

(17 patients, 14.4%). Table 2 presents the frequency of different pathogens among the different cultures, as a percentage of positive cultures. Among *E. coli* isolates, extended spectrum beta-lactamase (ESBL) producers were identified in 27 (37%) and 15 (36.6%) of UCs and FBCs, respectively.

Postoperative SIRS occurred in 72/1011 (7.1%) patients, of whom 34 (47.2%) had positive preoperative UC, and 53 (73.6%) had positive FBC. On univariate logistic regression analysis, positive FBC (OR = 13.5, 95% CI 7.75–23.25, $p < 0.001$), diabetes (OR = 13.04, 95% CI? $p < 0.001$),

Table 2 Pathogens isolated for stones, stents, and urine cultures

		Overall		PCNL		Ureteroscopy	
		FBC (*N* = 214)	UC (*N* = 216)	Stone (111)	Urine (118)	Stent (103)	Urine (98)
Gram −	*Escherichia coli*	41 (19.2)	73 (33.8)	24 (21.6)	37 (31.4)	17 (16.5)	36 (36.7)
	Klebsiella pneumoniae	16 (7.5)	28 (13)	7(6.3)	14 (11.9)	9 (8.7)	14 (14.3)
	Klebsiella oxytoca	1 (0.5)	0	1(0.9)	0	0	0
	Pseudomonas aeruginosa	18 (8.4)	21 (9.7)	15 (13.5)	17 (14.4)	3 (2.9)	4 (4.1)
	Proteus mirabilis	16 (7.5)	28 (13)	11 (9.9)	19 (16.1)	5 (4.9)	9 (9.2)
	Providencia stuartii	3 (1.4)	1 (0.5)	3 (2.7)	1 (0.8)	0	0
	Enterobacter cloacae	5 (2.3)	4 (1.9)	4 (3.6)	4 (3.4)	1 (1)	0
	Oligella urethralis	1 (0.5)	0	0	0	1 (1)	0
	Stenotrophomonas maltophilia	1 (0.5)	0	1 (0.9)	0	0	0
	Citrobacter spp.	3 (1.4)	5 (2.3)	2 (1.8)	2 (1.7)	1(1)	3 (3.1)
	Morganella spp.	2 (0.9)	2 (0.9)	0	2 (1.7)	2 (1.9)	0
	Acinetobacter spp.	4 (1.9)	6 (2.8)	1 (0.9)	4 (3.4)	3 (2.9)	2 (2)
	Serratia spp.	0	1 (0.5)	0	0	0	1 (1)
Gram +	*Enterococcus fecalis*	40 (18.7)	29 (13.4)	21 (18.9)	11 (9.3)	19 (18.4)	18 (18.4)
	Enterococcus faecium	2 (0.9)	0	2 (1.8)	0 ()	0	0
	Staphylococcus aureus	13 (6.1)	6 (2.8)	4 (3.6)	3 (2.5)	9 (8.8)	3 (3.1)
	Staphylococcus coagulase negative	13 (6.1)	2 (0.9)	7 (6.3)	1 (0.8)	6 (5.9)	1 (1)
	Streptococcus viridans	17 (7.9)	1 (0.5)	2 (1.8)	1 (0.8)	15 (14.6)	0
	Streptococcus agalactia	0	2 (0.9)	0	0	0	2 (2)
	Candida spp.	16 (7.5)	7 (3.2)	6 (5.4)	2 (1.7)	10 (9.7)	5 (5.1)
	Diphteroids	2 (0.9)	0	0	0	2 (1.9)	0

Data are presented as number and (percentage) of positive cultures

PCNL percutaneous nephrolithotomy

positive UC (OR = 3.72, 95% CI 2.27–6.06, $p < 0.001$), type of procedure (OR = 2, 95% CI 1.2–3.3, $p = 0.007$), Charlson index (OR = 1.15, 95% CI 1.08–1.28, $p < 0.001$), and age (OR = 1.02, 95% CI 1.01–1.03, $p = 0.003$) were associated with the occurrence of postoperative urosepsis. In multivariate logistic regression analysis adjusted for FBC, UC, type of surgery, Charlson index, and age, only positive FBC (OR = 10.3, 95% CI 5.58–19.2, $p < 0.001$), and type of procedure (OR = 1.97, 95% CI 1.11–3.5, $p = 0.02$) remained significantly associated with SIRS, as shown in Table 3.

Postoperative blood cultures (BCs), obtained during the septic event, were positive in 35/72 (48.6%) of the patients who developed SIRS and were predicted by UC and FBC in 13/35 (37.1%) and 21/35 (60%) patients, respectively. FBC, but not UC, predicted these results in 10 (28.6%) patients. Pathogens isolated from blood during sepsis were *Klebsiella* spp. in eight (22.8%) patients, followed by *E. coli* and *Enterococci* in six (17.1%) patients each, and *Pseudomonas aeruginosa* and *Acinetobacter* spp. in four (11.4%) and three (8.6%) of the patients, respectively. Table 4 depicts the blood culprits and their relation to UC and FBC.

Discussion

Two main themes arise from studies assessing the colonization of foreign bodies in the urinary system. First, there is a substantial discordance between UC and FBC obtained from the same individual. Second, there is a statistical association between foreign body colonization and the risk for postoperative infectious complications. Our results are in line with previous studies. Moreover, we found a causative relationship between both UC and FBC and sepsis culprits, with FBC being by far more predictive then UC.

The bacteriologic diversity of the urinary system has been described by many authors. Hugosson et al. obtained cultures from 215 kidney stones and found that 48% of infection stones and 32% of metabolic stones were colonized, while urinary pathogens were isolated in only 8% of the patients [19]. Similarly, Margel et al. found that 25% of the patients who were treated for kidney stones, stone culture was positive while UC was sterile, and in 8% of the patients, both cultures were positive, but different pathogens were isolated. Therefore, in one-third of the patients, the UC failed to detect important pathogens [13]. Similar discrepancies were found between UC and cultures obtained from ureteral stents. Klis et al. compared the results of urine and stent cultures obtained from 65 patients. Urine and stent colonization were found in 26% and 98.5% of the patients, respectively [20]. These discrepancies are not limited to UC and FBC results, as several studies have demonstrated that in the presence of a foreign body, UC obtained from different sites in the urinary system grow different pathogens. Most cited is the study by Mariappan et al., in which cultures from urinary stones, bladder urine, and renal pelvis urine were obtained from 56 patients. While the latter two were almost identical, there was no correlation between them and the bladder urine culture, suggesting that there is a local bacterial flora in proximity to the foreign body, which is not always consistent with the flora in the bladder. This phenomenon probably results from biofilm formation, which usually comprises several bacterial species. When an expanding colony shed bacteria into the urine, it is identified by UC, but identifying all pathogens is unlikely [10]. Even in the absence of a foreign body in the urinary system, UC results are not consistent. In a multicenter cohort study by McFadden et al., the ability of one UC to predict a subsequent culture was evaluated by examining the probability that the same organism being identified from the same patient's positive urine culture as a function of time elapsed

Table 3 Univariate and multivariate analysis of risk factors for postoperative SIRS

Variable	SIRS (70)	No SIRS (940)	Univariate analysis		Multivariate analysis	
			95% CI	*p* value	95% CI	*p* value
Positive FBC (%)	53 (73.6)	161 (17.1)	13.5 (7.75–23.2)	0.001	10.3 (5.6–19.2)	0.001
Diabetes (%)	24 (33.3)	180 (17.1)	13.4	0.001		
Female sex (%)	37 (51.4)	295 (31.4)	2.3(1.42–3.74)	0001 .	1.33 (.76–2.3)	0.31
Positive UC	34 (47.2)	182 (19.4)	3.72 (2.27–6.1)	0.001	0.96 (0.5–1.8)	0.91
Previous UTI (%)	33 (45.8)	185 (19.7)	3.45 (2.11–5.62)	0.001	1.26 (0.7–2.3)	0.45
Procedure type (% PCNL)	47 (65.3)	455 (48.5)	2 (1.2–3.3)	0.001	1.97 (1.1–3.5)	0.02
Median Charlson index (IQR)	2 (q1 = 2,q3 = 7)	0 (q1 = 0,q3 = 3)	1.15 (1.08–1.28)	0.001	1 (0.9–1.16)	0.68
Mean age (SD)	58.8 (14.4)	52.9 (15.9)	1.02 (1.01–1.03)	0.003	1 (0.99–1.03)	0.37
Mean BMI (SD)	27 (7.4)	26.6 (7.3)	1.2 (0.76–1.64)	0.11		
Mean stone size in mm (SD)	22 (15)	18.3 (15.5)	1.01 (0.99–1.02)	0.1		
Mean operating time (SD)	83.8 (42.9)	71.3 (39.3)	1.005 (1–1.01)	0.065		

Table 4 Pathogens isolated from blood cultures and their correlation with FBC and UC results

Culture results	Number	
FBC and UC identical to BC	11	1 *Enterococcus* spp. 5 *Klebsiella* spp. 3 *E. coli* 1 *Pseudomonas aeruginosa* 1 *Proteus* spp.
UC identical to BC FBC different from BC	2	1 *E. coli* 1 *Klebsiella* spp.
UC different from BC FBC identical to BC	10	4 *Pseudomonas* 1 *Proteus* spp. 1 *Candida* spp.1 *Klebsiella* spp. 1 *MRSA* 1 *Enterococcus* spp. 1 *E. coli*
UC and FBC different from BC	11	4 *Enterococcus* spp. 3 *Acinetobacter* spp. 1 *Morganella* spp. 1 *Klebsiella* spp. 1 *Enterococcus* spp. 1 *E. coli*

MRSA methicillin-resistant *Staphylococcus aureus*

between obtaining the cultures. Over 22,000 pairs of positive UCs were obtained, and the correspondence in the results was 57% and 49% at 4–8 weeks and after 32 weeks, respectively [21]. Because of the elusive identity of urinary culprits, any additional knowledge of the variety of pathogens may direct the antibiotic regimen either prophylactically or for the treatment of septic patients.

The spectrum of pathogens isolated from UC and FBC and its clinical implications are noteworthy. While *E. coli* was the most common pathogen overall, a substantial proportion of the culture grew *Enterococci*, *Pseudomonas*, *Klebsiella*, and *Proteus* spp., followed by Candida and Staphylococci. A remarkably similar distribution of pathogens was reported among 154,000 catheter-associated UTI in acute-care hospitals and long-term acute-care facilities in the USA between 2011 and 2014. *E. coli* (24%) was the most frequent pathogen, followed by *Enterococci* (14%), *Klebsiella* (10%), and *Pseudomonas* (10%). *Candida* spp. was isolated more frequently than in our study (24%). However, this pathogen rarely causes UTI [22]. In the current study, colonization of a urinary stone or a stent, but not of urine, was associated with higher risk for post-operative sepsis, as was demonstrated by previous studies. The odd ratios for the occurrence of sepsis in patients with positive FBC range from 2.55 to 34.8 [23, 24]. We found a causatively between urinary and foreign body pathogens and the sepsis culprits, which were identified in 35 of 72 patients. UC and FBC predicted the identity of these culprits in 37% and 60% of the 35 patients, respectively, and in 10 (28.6%) patients, only by FBC.

Should FBC be tested in every urinary stones procedure? The cost-efficiency has not been determined. A similar example is that of an infected vascular catheter. Current guidelines recommend that catheter culture should be performed only when a vascular catheter is removed for suspected bloodstream infection, but not routinely [25]. In realm of urology, obtaining FBC during sepsis is extremely uncommon, as it requires a surgical intervention which is generally contraindicated in during sepsis. In our case, is it reasonable to obtain 1000 cultures in order to identify pathogen in 20 patients? Proponents of such a policy would argue that the enormous expenditures and devastating consequences of mistreating a few patients exceed the minimal cost of additional cultures. A reasonable opposing argument is that most patients who develop sepsis will receive broad-spectrum antibiotic based on their medical and surgical background, which will render the yield of FBC even smaller. Truly, in a recently published study from our center, aimed to evaluate the yield of stone cultures in patients undergoing PCNL, 2.3–14.2% of the patients would have their treatment changed, had sepsis occurred [26]. The decision to obtain FBC from a healthy patient depends on multiple parameters, including cultures' costs, hospitals' resources, local bacterial flora, and the antibiotic protocol being used. Two overlapping groups of patients are likely to benefit from performing FBC: frail patients with multiple comorbidities in whom sepsis may have devastating consequences and patients with history of multiple interventions and prior UTIs, in whom resistant pathogens are more likely to be isolated.

This study is limited by its retrospective design. 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. Furthermore, as our main outcome was postoperative sepsis, it remains unknown whether the same conclusions apply to "sporadic" UTIs.

Conclusion

Foreign objects in the urinary system are frequently colonized with pathogens that are not recognized by urine cultures. Their colonization is associated with increased risk for SIRS. In more than one-quarter of the patients, the causative pathogen of sepsis is identified by FBC, but not by UC.

Compliance with ethical standards

Ethical approval Approved by the IRB.

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