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Research article

Urinary tract infection in urolithiasis: Antimicrobial resistance and clinico-microbiological association between risk factors and positive stone culture from a tertiary care hospital in south India

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Abstract

Urinary tract infections and urolithiasis are common conditions encountered in the healthcare setup. Urinary calculi with infection can lead to recurrence. Isolation of multidrug-resistant (MDR) bacteria is rising and seriously threatens public health. In the present study, a total of 221 urinary calculi and midstream urine samples were collected and processed. Antibiotic susceptibility testing (AST) was performed for all the isolates along with the detection of drug-resistant bacteria like extended-spectrum beta-lactamase (ESBL) producers and methicillin-resistant *Staphylococcus aureus* (MRSA). ESBL genes, i.e., *bla*SHV, *bla*CTX-M, and *bla*TEM, were identified by Polymerase Chain Reaction (PCR). The significance of the association between age group, gender, risk factors, and positive stone culture was analyzed by the chi-square test. *Escherichia coli* was the predominant bacteria isolated from 21 (30.88%) of both the midstream urine and urolithiasis samples, followed by *Klebsiella pneumoniae* 13 (19.11%). High susceptibility was observed for amikacin, nitrofurantoin, and ofloxacin. ESBL-producing bacteria were identified in 25 (36.76%) isolates from urinary calculi and from 46 (39.31%) midstream urine samples. The *bla*SHV and *bla*TEM genes were detected among them. MRSA was detected in 9.09% (2 out of 7) of *S. aureus* isolates recovered from midstream urine samples and 9.09% (1 out of 11) of isolates recovered from urinary calculi. A significant association was observed among cases of diabetes mellitus, hypertension, obesity, and a family history of renal stones (p-*value* < 0.05). Isolation of MDR bacteria from the calculi is alarming and can lead to treatment failure if not treated appropriately. Performing the culture of the urinary calculi and detecting drug resistance will be of immense value for adequately treating the infection.

Keywords: Infection stones, MDR, Urinary calculi, Urolithiasis

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1Introduction

Urinary tract infections (UTIs) remain among the most common infections in the hospital setting (Stephenson and Brown, 2016). Urinary calculi have a 3-5% prevalence among adults and are frequently encountered (Copelovitch, 2012). However, the incidence of urolithiasis is based on several factors such as geography, climate, diet style, ethnicity, gender, and age (Sorokin et al., 2017; Li et al., 2023). Recently, it was found that the age-standardized incidence rate and disability-adjusted life years of urolithiasis decreased globally by 0.459% and 1.898% per year, respectively, with an observed increase in countries with low and low-middle income countries (Li et al., 2023).

Urolithiasis can occur following urinary tract infections (infection stone) or as a result of metabolic alterations (metabolic stone/stone with infection). In the case of an infection stone, the urinary tract infection plays a major role in the pathogenesis of stone formation. In stones with infection, the bacteria become

trapped in the matrices of the calculi (Miano et al., 2007; Meissner et al., 2010). Any type of urinary calculi associated with an infectious agent can cause recurrence. It was estimated that 80% of antimicrobial compounds are prescribed in primary health care, frequently for UTIs (Moragas Moreno et al., 2023). Due to the extensive use of antibiotics, multidrug-resistant (MDR) bacteria are being isolated from urinary tract infections and urinary calculi. These MDR bacteria are difficult to eradicate, increasing mortality and morbidity and posing a serious threat (Shafi et al., 2013; Moragas Moreno et al., 2023).

Therefore, identifying bacteria in the calculi and therapy with an appropriate antibiotic will also prevent recurrences. The present study aims to isolate the bacterial agents from urinary calculi and midstream urine samples to investigate the antibiotic susceptibility pattern and to identify the drug-resistant phenotypes like methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamase (ESBL) producer. The present study also aimed to identify the association between various risk factors and positive stone culture.

2Materials and methods

iEthical approval

The present cross-sectional study was carried out over one year from December 2012 to December 2013 at the Department of Microbiology, Govt Kilpauk medical college, and hospital, The TN Dr. MGR Medical University, Guindy, Chennai, Tamil Nadu, India. The study was approved by the institutional ethical committee (Institutional ethical committee, Govt Kilpauk Medical College, Chennai-10. Ref. No.10319/ME-1/Ethics/2011. Date of approval:27.12.2012).

iiSamples

A total of 221 urinary calculi and a clean catch of corresponding midstream urine samples were collected and transported to the laboratory in a sterile container. Both male and female patients aged above 20 years with ultrasonography proved urinary calculi and recurrent calculi were included in the study.

iiiProcessing of the urinary calculi and midstream urine specimen

Urinary calculi were thoroughly washed in sterile saline and crushed with aseptic precautions. The crushed particles were inoculated into 5 mL thioglycollate broth (Himedia labs, Chennai, India) and incubated at 37°C for 18-24 hours. After incubation, subcultures were done onto blood agar and McConkey agar (Shafi et al., 2013).

The clean catch midstream urine samples were processed by a semi-quantitative method using the standard loop technique onto cystine–lactose–electrolyte-deficient agar (CLED agar, Himedia Labs, Chennai, India) and incubated at 37°C for 18-24 hours. Growth of more than 10^5 colony-forming units (CFU/mL) was considered a significant bacteriuria. All the isolates were identified using standard microbiological techniques, e.g., Gram staining, catalase test, oxidase test, motility, and biochemical reactions such as indole test, triple sugar iron test, urease, and citrate test (Shafi et al., 2013).

ivAntibiotic susceptibility testing by Kirby Bauer disc diffusion method

Antibiotic susceptibility testing (AST) was performed by the Kirby Bauer disc diffusion method using Meuller Hinton agar(Himedia Labs, Chennai, India). The following antibiotics discs (Himedia Labs, Chennai, India) were used: ampicillin (10 μg), amikacin (30 μg), nitrofurantoin (200 μg), norfloxacin (10 μg), ciprofloxacin (5 μg), cephalexin (30 μg) cefotaxime (30 μg), ceftazidime (30 μg), imipenem (10 μg), piperacillin-tazobactam (100/10 μg), and linezolid (30 μg). The plates were incubated overnight at 35°C, and the results were interpreted according to CLSI 2013 guidelines (Shafi et al., 2013; CLSI, 2021).

vDetection of extended-spectrum beta-lactamases (ESBL) producers

The ESBL-producing bacteria were identified by the phenotypic confirmation test and (Minimum inhibitory concentration reduction test (MIC reduction test). All the isolates resistant to ceftazidime and cefotaxime were considered probable ESBL$^+$ and further confirmed by a phenotypic confirmatory test (CLSI, 2021). The isolates that showed resistance to ceftazidime and cefotaxime were confirmed to be ESBL$^+$ by testing along with the combination of ceftazidime 30 μg and ceftazidime 30 μg plus 10 μg clavulanic acid. The isolates with a 5 mm increase in zone of inhibition for the combination ceftazidime/clavulanic acid (30 μg/10 μg) were confirmed as ESBL$^+$ (Manoharan et al., 2011; CLSI, 2021).

viMinimum Inhibitory Concentration (MIC) reduction test (Agar dilution method)

Bacterial isolates were tested for different concentrations of 3rd generation cephalosporin (cefotaxime and ceftazidime) from 0.5 μg to 2048 μg/mL. The MIC was the lowest concentration at which no visible growth occurred. The MIC reduction test was performed by combining the 3rd generation cephalosporin (cefotaxime and ceftazidime) with 4 μg/mL of clavulanic acid from 0.5 μg to 2048 μg/mL concentration. More than or equal to three doubling dilution reduction in the MIC of 3rd generation cephalosporin in the presence of clavulanic acid indicates the production of ESBL (CLSI, 2021).

viiDetection of methicillin-resistant *Staphylococcus aureus* (MRSA)

The MRSA isolates were detected by the cefoxitin disc diffusion method. A zone of inhibition of less than or equal to 21 mm is considered positive for MRSA (CLSI, 2021).

Table 1: Total number of bacterial isolates recovered from urinary calculi and midstream urine samples of 221 patients

Bacterial isolate	Urinary calculi	Corresponding midstream urine samples
E. coli	21 (30.8%)	16 (32.65%)
P. mirabilis	13 (19.11%)	11 (22.44%)
K. pneumoniae	17 (25%)	14 (28.57%)
K. oxytoca	1 (1.47%)	1 (2.04%)
P. aeruginosa	5 (7.35%)	Nil
S. aureus	11 (16.17%)	7 (14.28%)
Total	68	49

viii**Detection of ESBL-producing genes SHV, CTX-M, and TEM using PCR**

The bacterial isolates from urinary calculi that showed positive phenotype for ESBL$^+$ were subjected to DNA extraction using a spin column-based DNA extraction kit (Helini biomolecules Chennai, India). DNA amplification was performed using the following specific forward and reverse primers (Manoharan et al., 2011; Nandagopal et al., 2015): *bla*TEM gene (F: 5´-TTCTGCTATGTGGTGCGGTA-3´ and R: 5-GCAGAAGTGGTCCTGCAACT-3´), *bla*CTX-M gene (F: 5´- CGCAGATAATACGCAGGTGCTTT-3´ and R: 5´-GGCCGCCATAACTTTACTGG-3´, *bla*SHV gene (F: 5´-CTTTCCCATGATGAGCACCT-3´ and R: 5´-CAATGCGCTCTGCTTTGTTA-3´) (Helini biomolecules Chennai, India). PCR program was set as the following: Initial denaturation: 94°C for 3 min, denaturation at 94°C for 30 seconds, and annealing at 56°C for 30 seconds. Extension at 72°C for 30 seconds and final extension at 72°C for 5 minutes for 35 cycles. After the amplification for 35 cycles, the products were loaded onto 2% agarose gel along with the Gel loading dye and Helini 100 bp DNA ladder. The size of the products was visualized under UV transilluminator, and the results were interpreted (*bla*TEM gene product at the size of 450 bp, *bla*SHV product at 581 bp, and *bla*CTX-M product at 350 bp) as previously reported (Manoharan et al., 2011; Nandagopal et al., 2015).

ix**Statistical analysis**

The significance of the association between age group, gender, diabetes mellitus, hypertension, obesity, family history of renal stones, and positive stone culture was analyzed by Fischer chi-square test (Graph pad Quick Calcs software), and a *p-value* less than 0.05 was considered as statistically significant.

3**Results**

A total of 221 patients with ultrasonography-proven urolithiasis were included in the current study. Out of the 221 cases, 145 (65.61%) were male, and 76 (34.38%) were females. Of the 221 urinary calculi cultured, culture positivity was observed among 68 (30.7%) samples. *Escherichia* (*E.*) *coli* was the predominant bacteria isolated from 21 (30.88%) calculi, followed by *Klebsiella* (*K.*) *pneumoniae* 13 (19.11%). Among the Gram-positive isolates, *Staphylococcus* (*S.*) *aureus* was isolated from 11 (16.17%) cases (Table 1). Among the 221 urine samples cultured, 117 (52.94%) showed culture positivity. *E. coli* was the most common bacteria isolated from 31 (26.49%) samples, followed by *S. aureus* 7 (14.28%) and *K. pneumoniae* 20 (17.09%) (Table 1). Among the 68 urinary calculi specimens that were culture positive, 49 (72.05%) also showed culture positivity in their midstream urine samples. Among the *S. aureus* isolated from the urinary calculi, high susceptibility was observed for amikacin 8 (72.72%), nitrofurantoin 7 (63.63%), and cotrimoxazole 7 (63.63%). MRSA was detected in one sample (9.09%) of the 11 *S. aureus* isolates using the cefoxitin disc diffusion method. All the *S. aureus* were susceptible to vancomycin and linezolid. Among the Gram-positive bacteria isolated from the midstream urine specimen, ofloxacin susceptibility was found in 11 (52.38%) samples. MRSA was detected in 9.09% (2 out of the seven) *S. aureus* isolates.

Among the Gram-negative bacteria isolated from the urinary calculi, *E. coli* and *P. mirabilis* showed high susceptibility to ciprofloxacin in 18 (85.71%) and 10 (76.92%), respectively. Among the Gram-negative bacteria isolated from the midstream urine specimen, *E. coli* showed high susceptibility to cotrimoxazole and amikacin in 27 and 87.09% of samples, respectively. *P. mirabilis* showed high susceptibility to ceftazidime and cefotaxime in 13 and 81.25% of samples, respectively. Overall, good susceptibility was observed among the Gram-negative isolates for amikacin 44 (77.19%) and ofloxacin 43 (75.41%). All the isolates showed 100% susceptibility to imipenem. Among the Gram-negative isolates from the urinary calculi, ESB-producing bacteria were identified among 25 (36.76%) isolates by the Double disc method and MIC reduction method for ceftazidime (Table 2). Among the ESBL producers, *E. coli* was the predominant bacteria identified in 11 (44%), followed by *K. pneumoniae* in 9 (36%). In the present study, *bla*TEM and *bla*SHV genes were detected among the 14 (56%), and 11 (44%) isolates, respectively (Table 2). The *bla*CTX M gene was not detected among the 25 isolates.

The significance of the association between age group and culture positivity among male and female patients was analyzed, and the patients in the age group of 31-40 years showed a statistically significant association between positive stone culture and age group ($p\text{-value} < 0.0326$) (Table 3). The significance

Table 2: ESBL-producing bacteria among the bacterial isolates from urinary calculi

Organisms	Phenotypic confirmatory test	MIC reduction test	PCR No. of positive (%)	
	No. of positive (%)	No. of positive (%)	*bla*SHV	*bla*TEM
E. coli	11 (44)	11 (44)	3 (12)	4 (16)
K. pneumoniae	9 (36)	9 (36)	5 (20)	6 (24)
P. mirabilis	4 (16)	4 (16)	3 (12)	4 (16)
P. aeruginosa	1 (4)	1 (4)	0	0
Total	25	25	11 (44)	14 (56)

Table 3: Association of culture positivity from the urinary calculi with age group

Age/year	Bacterial isolation	Male No. (%)	Female No. (%)	*p-value**
20-30	Positive	11 (68.75)	10 (52.63)	0.4906
	Negative	5 (31.25)	9 (47.36)	
31-40	Positive	13 (41.93)	31 (68.88)	0.0326
	Negative	18 (58.06)	14 (31.11)	
41-50	Positive	5 (45.45)	37 (64.91)	0.3117
	Negative	6 (54.54)	20 (35.08)	
51-60	Positive	4 (66.66)	7 (46.66)	0.6351
	Negative	2 (33.33)	8 (53.33)	
61-70	Positive	2 (50)	9 (60)	1
	Negative	2 (50)	6 (40)	

* *p-value* < 0.05 is statistically significant.

Table 4: Association of culture positivity from the urinary calculi with gender

Sex	Culture positive No. (%)	Culture negative No. (%)	*p-value**
Male	35 (51.47)	94 (61.43)	0.1848
Female	33 (48.52)	59 (38.56)	

* *p-value* < 0.05 is statistically significant.

of the association between positive stone culture and gender was found to be statistically insignificant in the present study (*p-value* < 0.1848) (Table 4).

Various risk factors were analyzed, and their association with the positivity of the urinary calculi was evaluated. Out of the 221 patients included, a significant association was observed among patients suffering from diabetes mellitus 36 (16.28%), hypertension 45 (20.36%), obesity 26 (11.76%), and family history of renal stones 14 (6.33%) (*p-value* < 0.001) (Table 5).

4Discussion

In the present study, the prevalence of stones with infection was 68 (30.7%). A previous study reported positive stone culture as 10 (22.2%) (Shafi et al., 2013), and another study reported 47% culture positivity in calculi and urine samples (Sohshang et al., 2000). Mariappan et al. (2005) showed a stone culture positivity of 35.2%. We also compared the culture positivity rate of infection stone with the urine samples collected from the same patients, and 49 (72.05%) samples also showed culture positivity in their respective midstream urine samples. Urinary calculi can block the urine outflow pathway, leading to stasis of urine, which can lead to attachment and multiplication of bacteria onto the epithelium, leading to infection.

In most studies, the retrieved urinary calculi might not be sent for culture, leading to a lack of information regarding the bacterial etiology and the MDR patterns. This might have serious effects on patient management because urinary calculi can block the urine outflow pathway causing stasis of urine which in turn facilitates the bacteria to attach and multiply onto the epithelium causing infection. Studies have indicated that positivity in calculi culture and midstream urine samples can indicate urosepsis (Eswara et al., 2013; Roushani et al., 2014). Owing to these factors, in the present study, all the stone and midstream urine samples were cultured along with antimicrobial susceptibility patterns with the correlation of various risk factors.

Various studies have also reported a high level of concordance between the bacteria isolated from the stone and urine culture. The incidence of infectious stones ranges from 2.7 % in the Asian region to 42.9% in the Sub-Saharan African region (Daudon et al., 2004). The present study observed a significant association between stones with infection and diabetes mellitus, hypertension, obesity, age, and family history of renal stones. The significant association between renal stones and socio-demographic details and comorbidities like hypertension, diabetes, obesity, and family history of renal stones have been reported previously (Trinchieri, 2008; Arias Vega et al., 2017). A study by (Lieske et al., 2006) has found that diabetes mellitus might be implicated in the formation of uric acid stones. Hypertension and obesity were associated with calcium oxalate stones (Ramey et al., 2004; Hamano et al., 2005). Obese patients are at risk of forming uric acid stones (Ross and McGill, 2006). Hence the

Table 5: Risk factors versus culture positivity from urinary calculi

Bacterial isolation	Variable No. (%)		*p-value**
	Presence of diabetes	Absence of diabetes	
Isolation of bacteria	26 (72.22)	42 (22.7)	<0.0001
No isolation of bacteria	10 (27.77)	143 (77.29)	
	Presence of hypertension	Absence of hypertension	
Isolation of bacteria	29 (64.44)	39 (22.15)	<0.0001
No isolation of bacteria	16 (35.55)	137 (77.84)	
	Presence of obesity	Absence of obesity	
Isolation of bacteria	18 (69.23)	50 (25.64)	0.0001
No isolation of bacteria	8 (30.76)	145 (74.35)	
	Family history of urinary calculi	No family history of urinary calculi	
Isolation of bacteria	11 (78.57)	57 (27.53)	0.0002
No isolation of bacteria	3 (21.42)	150 (72.46)	

* *p-value* < 0.05 is statistically significant.

different risk factors must be considered along with biochemical stone analysis while encountering patients with infectious stones for optimal management. In the present study, *E. coli* was the most common bacteria recovered from urinary calculi, as previously reported (Tavichakorntrakool et al., 2012; Jena et al., 2013). Among the Gram-negative isolates from infected calculi, high susceptibility was observed for amikacin, as previously discussed (Tavichakorntrakool et al., 2012). Among the Gram-positive bacteria, high susceptibility was observed for amikacin and nitrofurantoin. Drug-resistant bacteria like MRSA and ESBL were also detected among the urinary stones with infection by phenotypic and genotypic methods. Tavichakorntrakool et al. (2012) reported 22 % ESBL among E.coli in midstream urine and 14% among calculi, whereas, in our present study, ESBL-producing bacteria represented 11 (44%) among calculi and was higher. This could be attributed to the difference in the prior usage of antibiotics and variations in risk factors among the patients.

5Conclusion

The presence of drug-resistant organisms like ESBL-producing bacteria and MRSA among the isolates obtained from the urine culture and the calculi is alarming, as such drug-resistant organisms can lead to treatment failure if not treated appropriately. The present study highlights the importance of performing a culture of the urinary stone and midstream urine and detecting drug resistance by phenotypic or genotypic methods before initiating therapy. The information regarding the resistance pattern can help physicians select an appropriate drug for treatment that can be individualized, considering the risk factors and chances of drug resistance for better treatment outcomes and hospital infection control.

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Ethical approval. The study was approved by the institutional ethical committee (Institutional ethical committee, Govt Kilpauk medical college, Chennai-10. Ref. No.10319/ME-1/Ethics/2011. Date of approval:27.12.2012).

Authors contributions. SK, LV, and TR conceptualized the study design. SK and ALJ conducted the study. SK, LV, TR, RK, and ALJ contributed to the interpretation and analysis. ALJ drafted the manuscript, and all the authors contributed to the final approval of the manuscript.

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