



## PREVALENCE AND ANTIMICROBIAL RESISTANCE OF UROPATHOGENS IN PATIENTS WITH UROSEPSIS SECONDARY TO UROLITHIASIS

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### Abstract

#### Introduction:

**Methods:** A Cross-Sectional Study was performed with the inclusion of 190 patients from Sheikh Zaid Hospital Lahore. Patients were informed about the research and their consent was taken. Demographic factors included name, age, gender, BMI, duration of stone and infective symptoms, and diagnosis. Sterile containers were used to collect freshly voided urine and sent to pathology department for urine culture and antimicrobial resistance pattern. Reports were assessed for isolated pathogens and their resistance against antibiotics was noted as per operational definition. All this information was taken on Performa and patients were managed as per departmental protocol.

**Results:** Total of 90 patients, 7.8% (n=7) were in the age group of 20-45 years and 92.2% (n=83) were in 46-70 years age group. Mean age was 54.48±7.401 years. Distribution of BMI was 27.52±5.043 kg/m<sup>2</sup>, duration of stone was 4.63±1.495 months and duration of symptoms was 5.40±1.668 days. 51.1% (n=46) were male patients and 48.9% (n=44) females. The frequency E. coli, Klebsiella spp., Enterococcus spp., and Gram-positive bacteria was 57.8%, 11.1%, 14.4%, and 16.7% respectively. Fluoroquinolones were sensitive 1.1%, Sulfonamides 2.2%, Penicillin 2.2%, Cephalosporin 57.8%, Aminoglycoside 17.8%, Carbapenems 3.3%, Vancomycin 12.2%, Tazobactam/piperacillin 2.2% and sensitivity of Fosfomycin trometamol was 1.1%. Distribution of antimicrobial sensitivity pattern of isolated pathogen was done (p=0.293).

**Conclusion:** The most prominent bacteria was E.coli. Antimicrobial resistance makes the selection of empiric antibiotic treatment challenging in patients with urosepsis secondary to urolithiasis. This study would help in the updating of Local population-specific antimicrobial guidelines and timely treatment of urolithiasis will be ensured. Condition specific antibiograms would be recommended.

**Key Words:** Urolithiasis, obstructive uropathy, urosepsis, antimicrobial resistance.

## INTRODUCTION

Urolithiasis is a disease characterized by one or more stones in the urinary tract. It is one of the oldest and most widespread disease known to man [1]. Urolithiasis, also known as king's disease, is one of the most common diseases and a major public health problem around the world [2]. The estimated prevalence ranges from 1% to 13% globally [3, 4]. The epidemiological characteristics and etiological factors of urinary lithiasis are constantly evolving, reflecting to a large extent the health conditions, dietary habits and population's standard of living [5]. Urolithiasis can hinder renal functioning by obstructive uropathy, renal tissue damage, or urological treatments [6].

Obstructive uropathy is a common clinical condition that leads to acute or chronic kidney failure [7]. Renal obstruction greatly affects the renal physiology causing a number of changes leading to the chronic kidney diseases which currently affect 10% and 4% cases of end-stage kidney disease population, worldwide [8, 9]. Obstructive uropathy (73.4%) and urinary stone disease (33.5%) are 2 common factors associated with the development of a complicated Urinary Tract Infection (UTI) [10]. Urolithiasis causes a vicious cycle of these events including stone, obstruction, stasis, (UTI) [11].

The clinical spectrum of urinary tract infection (UTI) is remarkably broad, ranging from asymptomatic bacteriuria to life-threatening septic shock [12]. A key determinant of severity is the presence of obstruction. When urinary flow is impeded, stasis allows for pronounced bacterial multiplication and ascending migration, transforming a potential colonization into a significant infection [13, 14]. This connection is of substantial clinical importance, as UTI represents one of the most frequent bacterial infections acquired in the community and critically the most common identifiable source of bacteremia [15]. The burden of disease is evident even in the youngest patients: among nearly 2000,000 febrile infants under two months of age evaluated annually in U.S. emergency department, 7-10% are diagnosed with a UTI, and 2-3% have a concomitant bacteremia [16, 17].

The microbiology of these infections heavily influences their potential to cause systemic illness. Gram-negative bacilli are the predominant pathogens in urinary-source bacteremia [18]. *E. coli* is the primary etiological agent, accounting for approximately half of all cases. Other notable Gram-negative bacteria include *Proteus* species, and members of the *Klebsiella-Enterobacter* complex, which together contribute to roughly 30% of cases, while *Pseudomonas aeruginosa* is implicated in about 5%. In contrast, Gram-positive bacteria are responsible for only a minority, approximately 15%, of these serious infections [19].

Bacteremia originating from a urinary focus represents a critical turning point in disease progression, responsible for initiating severe sepsis in an estimated 38%-69% of related cases [20]. The initial urological infection may manifest across a spectrum of severity, including cystitis, pyelonephritis, intrarenal or perinephric abscess formation, and ultimately urosepsis [21]. Patients diagnosed with complicated urinary tract infection, particularly those involving anatomical or functional abnormality, face a substantially elevated risk of deteriorating into a full-blown urosepsis [22]. Epidemiological studies indicate that among all sepsis cases, a urinary tract origin accounts for a significant proportion, with reported prevalence rates ranging from 9%-31% [23]. The pivotal role of obstruction in this pathway is underscored by a decade-long retrospective analysis, which found that obstruction was a concurrent condition in 78% of men and 54% of women diagnosed with urosepsis, highlighting it as a dominant risk factor for systemic dissemination [24].

The host response to infection is precisely balanced, yet precarious, system involving both aggressive defense and regulated containment. Following pathogenic invasion, the immune system activates concurrent inflammatory and anti-inflammatory pathways [25]. Pro inflammatory mechanisms, primarily driven to eradicate invading pathogens, are often implicated in causing collateral tissue damage and precipitating acute organ dysfunction. Conversely, the compensatory anti-inflammatory response, crucial for modulating this injury and promoting recovery, can induce a state of relative immune suppression. This suppression heightens susceptibility to secondary infections and may perpetuate a dysregulated inflammatory cycle [26]. Thus, the trajectory from

localized infection to severe sepsis and organ failure is largely governed by the timing, magnitude, and eventual loss of equilibrium between these opposing immunological responses.

The anti-microbial resistance profile of the causative pathogens is a critical determinant in the progression from a urinary tract infection to systemic illness. Organisms isolated from complicated UTIs and urosepsis consistently demonstrate higher rates of antibiotic resistance compared to those found in uncompleted community acquired infections[27]. This is particularly concerning for Enterobacterales, the family of Gram-negative bacteria that are the most common pathogens. Resistance among these organisms now constitute an escalating clinical challenge extending beyond traditional nosocomial settings to increasingly complicate community-acquired UTIs[28]. This rise in antibiotic resistance has escalated into a major public health crisis, profoundly complicating treatment protocols and worsening patient outcomes. The last decade has witnessed a marked increase in both the carriage and infection rates of multi drug resistant organisms a trend that directly threatens the effective management of severe urological sepsis[29].

Pathogens isolated from patients with complicated urinary tract infection and urosepsis tend to be more resistant to antibiotics than strains isolated in uncomplicated urinary tract infection [27]. Enterobacterales, which present an escalating problem of antibiotic resistance, not only in nosocomial infections but also in community-acquired urinary tract infections [28]. Antibiotic resistance has become a significant public health problem with grave consequences for the treatment of infections. Over the past decade, there has been an increasing prevalence of carriage and infection with multidrug-resistant organisms (MDROs) [29].

Although this is a global problem, antimicrobial resistance tends to be more important in developing countries than in developed countries [30]. The continuous and periodic monitoring of the local prevalence of uropathogens and their susceptibility profile will be of public health importance to promote the appropriate use of existing antibiotics [31].

## **MATERIAL AND METHOD:**

**Study Design:** A cross-sectional study was carried out from the department of Urology, Sheikh Zaid Hospital, Lahore. A six-month approval was taken from the hospital administration from 03-03-2022 to 03-09-2022. Sample size of 90 cases was used 95% confidence interval, 7.5% margin of error and percentage of enterococcus specie as 15.7% in patients with obstructive uropathy and urosepsis secondary to stone disease.

**Sampling Technique:** Non-probable, consecutive sampling technique was used. Patients with the age of 20-70 years, including both genders were used. These patients were diagnosed with kidney stones with obstructive uropathy and urosepsis. Patients with recurrent urinary tract infection, bladder and renal cancer, and patients presenting non-obstructing stones, were not included in this study. Demographic sampling included name, age, gender, BMI, duration of stones and infective symptoms, and diagnosis reports.

**Data Collection Procedure:** The whole of the demographic analysis was performed on a Performa. The fresh urine samples were obtained in sterile bottles and was sent to the pathology department for urine culture and antimicrobial resistance pattern assessment.

**Ethical Consideration:** The patients were informed about the research and their consent was taken. After collecting the data from the patients, they were managed as per standard protocol.

**Data Analysis plan:** Data was analyzed on SPSS version 21.0. Mean and Standard Deviation was calculated for quantitative variables like age, BMI, duration of stone and duration of symptoms. Frequency and percentage were calculated for categorical variables like gender, isolated pathogens, and antimicrobial resistance pattern. Data was stratified with respect to gender and age. Chi-square was used for statistical significance P-values of <0.05 was considered statistically significant.

## RESULTS

Total of 90 patients fulfilling inclusion and exclusion criteria were selected to determine the frequency of common pathogen and antimicrobial resistance in cases of obstructive uropathy and urosepsis secondary to stone disease.

About 92.2% patients were in the age group of 45-70 years while only 7.8% were in 25-45 years age group. The gender distribution was with a high percentage of male with the rate of about 51.1% while 48.9% were female with the mean age of Mean  $\pm$  S.D = 54.48 $\pm$ 7.401 years. (Table 1)

The distribution of isolated pathogens represented that E. coli was the most prevalent pathogen (57.8%) of the urinary tract infection among the whole of the pathogens followed by the Gram-Positive bacteria. (Table 2) Among the antimicrobial resistance, Cephalosporin was the most resistant drug for the urosepsis patients. (Table 3-5)

**Table:1** Table for the age distribution.

| Age Group   | Frequency | Percent |
|-------------|-----------|---------|
| 20-45 years | 7         | 7.8%    |
| 45-70 years | 83        | 92.2%   |
| Total       | 90        | 100%    |

Mean  $\pm$  S.D = 54.48 $\pm$ 7.401 years

**Table:2** Table for the gender frequency.

| Gender | Frequency | Percentage |
|--------|-----------|------------|
| Male   | 46        | 51.1%      |
| Female | 44        | 48.9%      |
| Total  | 90        | 100%       |

**Table:3** Table for the pathogen's frequency.

| Isolated Pathogens     | Frequency | Percentage |
|------------------------|-----------|------------|
| E. coli                | 52%       | 57.8%      |
| Klebsiella spp.        | 10%       | 11.1%      |
| Enterococcus spp.      | 13%       | 14.4%      |
| Gram Positive Bacteria | 15%       | 16.7%      |
| Total                  | 90%       | 100%       |

### Distribution of isolated pathogens

**Table:4** Table for the antimicrobial resistance frequency.

| Isolated Pathogens      | Frequency | Percentage |
|-------------------------|-----------|------------|
| Fluoroquinolones        | 1         | 1.1%       |
| Sulfonamide             | 2         | 2.2%       |
| Penicillin              | 2         | 2.2%       |
| Cephalosporin           | 52        | 57.8%      |
| Aminoglycosides         | 16        | 17.8%      |
| Carbapenem              | 3         | 3.3%       |
| Vancomycin              | 11        | 12.2%      |
| Tazobactam/piperacillin | 2         | 2.2%       |
| Fosfomycin trometamol   | 1         | 1.1%       |
| Total                   | 90        | 100%       |

### Distribution of antimicrobial resistance pattern

**Table:** Table for the antimicrobial resistance against the pathogens frequency.

| Isolated Pathogens           | Antimicrobial Sensitivity Pattern |              |            |               |                |            |            |            |            | Total | P value |
|------------------------------|-----------------------------------|--------------|------------|---------------|----------------|------------|------------|------------|------------|-------|---------|
|                              | Fluoroquinolones                  | Sulfonamides | Penicillin | Cephalosporin | Aminoglycoside | Carbapenem | Vancomycin | Tazobactam | Fosfomycin |       |         |
| <i>E. coli</i>               | 0                                 | 1            | 1          | 32            | 9              | 2          | 6          | 1          | 0          | 52    | 0.293   |
|                              | 0.0%                              | 1.9%         | 1.9%       | 61.5%         | 17.3%          | 3.8%       | 11.5%      | 1.9%       | 0.0%       | 100%  |         |
| <i>Klebsiella pneumoniae</i> | 0                                 | 0            | 0          | 3             | 2              | 1          | 3          | 1          | 0          | 10    |         |
|                              | 0.0%                              | 0.0%         | 0.0%       | 30.0%         | 20.0%          | 10.0%      | 30.0%      | 10.0%      | 0.0%       | 100%  |         |
| <i>Enterococcus spp.</i>     | 1                                 | 1            | 0          | 9             | 1              | 0          | 1          | 0          | 0          | 13    |         |
|                              | 7.7%                              | 7.7%         | 0.0%       | 69.2%         | 7.7%           | 0.0%       | 7.7%       | 0.0%       | 0.0%       | 100%  |         |
| Gram Positive Bacteria       | 0                                 | 0            | 1          | 8             | 4              | 0          | 1          | 0          | 1          | 15    |         |
|                              | 0.0%                              | 0.0%         | 6.7%       | 53.3%         | 26.7%          | 0.0%       | 6.7%       | 0.0%       | 6.7%       | 100%  |         |
| Total                        | 1                                 | 2            | 2          | 52            | 16             | 3          | 11         | 2          | 1          | 90    |         |
|                              | 1.1%                              | 2.2%         | 2.2%       | 57.8%         | 17.8%          | 3.3%       | 12.2%      | 2.2%       | 1.1%       | 100%  |         |

## DISCUSSION

Urinary tract infection and its progression to urosepsis, represents a complex and escalating clinical challenge. Globally the prevalence of complicated urinary tract infection is significant, with estimates ranging from 20.8%-32% of all cases[27].The progression from a localized infection to a systemic life-threatening condition is influenced by a multitude of establish risk factors these include advanced age female sex com orbit conditions such as diabetes mellitus and liver cell houses states of immunosuppression including AIDS, anemia, the presence of indwelling catheters, and specific urological features such as renal calculi with a diameter exceeding 2.5cm

In our study, out of 90 patients, 7.8% (n=7) were in the age group of 20-45 years and 92.2% (n=83%) were in the age group of 40-46 years. Mean age was  $54.48 \pm 7.401$  years. Distribution of BMI was  $27.52 \pm 5.043$  kg/m<sup>2</sup>, duration of stone was  $4.63 \pm 1.495$  months and duration of symptoms was  $5.40 \pm 1.668$  days. 51.1% (n=46) were male patients and 48.9% (n=44) females. The frequency of *E. coli*, *Klebsiella spp.*, *Enterococcus spp.*, and Gram-positive bacteria was 57.8%, 11.1%, 14.4%, and 16.7% respectively. Fluoroquinolones were sensitive 1.1%, Sulfonamides 2.2%, Penicillin's 2.2%, Cephalosporin 57.8%, Aminoglycosides 17.8%, Carbapenem 3.3%, Vancomycene12.2%, Tazobactam/piperacillin 2.2% and sensitivity of Fosfomycin trometamol was 1.1%. Distribution of antimicrobial sensitivity pattern of isolated pathogen was done (p=0.293).

Among 325 isolates, Gram-negative bacteria (GNB) appeared more frequently 252 (51.7%) than Gram-positive bacteria 63 (19.4%) and it is in concordance to our findings. In GNB, *E. coli* 168(66.7%), *Klebsiella species* 32(12.7%), and *Enterobacter species* 13 (5.2%) were dominated isolates whereas in GPB accounted for coagulase-negative staphylococcus (CoNS) 33(52.4%), *Enterococcus species* 16(25.4%), and *Staphylococcus aureus* 10(15.9%)[29]. *Escherichia coli* was the causative agent in 615 episodes (67%), *Klebsiella spp* in 73 (7.9%) and *Proteus ssp* in 61 (6.6%)[10]. *E. coli* (57%), *K. pneumoniae* (12.4%), *P. aeruginosa* (7.4%), and *E. faecalis* (6.6%) were the most common microorganisms in bacteremia patients, without statistically significant differences between bacteremia and non-bacteremia patients [32].

Buonaiuto et al., results concord with ours having male 52% rate of pyelonephritis then female with 48% contribution[10]. In a previous study, it was found that among UTIs patients, 583(57.6%) were females and 429(42.4%) were males. The UTIs of 179 (55%) women is relatively higher than that of men 146 (45%). Which is contrary to our results [29]. In another study carried out between 2016 and 2018, reveal 61% (n = 52) female patients[33]. Bacteriuria is more prevalent among the elderly, with 50% of geriatric women having bacteriuria [27].

Historically it has been observed that the highest pathogenicity is caused by *E. coli* as our findings[33]. A study carried out by showed Wegenlehner, Weidner, and Nabeir., (2007) about 50% gram-negative bacteria was *E. coli* [27, 34]. *E. coli* bloodstream infection rate is a UK National Health Service oversight metric[35].

These pathogenic strains are resistant to a large number of antibiotics. The problem is attributed to the misuse of antimicrobials, which create selective pressures that facilitate the emergence of resistant strains [36]. Among the tested gram-positive isolates, 70%, 81%, 69.7%, and 50% were relatively sensitive to Nitrofurantoin, clindamycin, Gentamycin, and vancomycin, respectively. erythromycin 15(62.5%), ciprofloxacin 34(74%), penicillin 17(66.7%), Tetracycline 21(65.6%), Oxacillin 12(48%), and Norfloxacin 21(75%) resistance rate was observed for the tested isolates. Gram-negative bacteria were highly resistance to piperacillin 50(82%), Trimethoprim-sulfamethoxazole 130(79%), Augmentin (amoxicillin-clavulanate) 95(63.8%), ceftriaxone 87(58.4%), cefuroxime 106 (69.7%), 44(51.2%), ciprofloxacin 144(62.8%) for the tested isolates [29]. Data from recent years indicate that approximately 20–75% of uropathogens are resistant to fluoroquinolones [37, 38] whereas 23–76% of isolates are resistant to TMP-SMX [39–41]. *E. coli* has been to highly resistant to cotrimoxazole with rate of about 83% [42]. It has been observed that for the UTI-specific antimicrobials, 11.2% of all patients (72,705) prescribed trimethoprim had a treatment failure, while 16.7% (38,625) of those prescribed nitrofurantoin had a treatment failure. Resistance rates were high, with 71.2% patients had an *E. coli* that was resistant to at least one of the antimicrobials examined. Resistance was greater for amoxicillin (68.2% of those tested), followed by trimethoprim (44.9%), amoxicillin/clavulanic acid (34.8%), ciprofloxacin (21.1%) and nitrofurantoin (9.8%)[43].

## CONCLUSION

In our study the frequency of common pathogen and anti-microbial resistance in the cases of obstructive neuropathy and urosepsis secondary to stone diseases was determined it is concluded that the most prominent uropathogens in most patients and microbial resistance makes the selection of empiric antibiotic treatment challenging in patients with obstructive pyelonephritis secondary to ureteral stones. Local population specific anti-microbial guidelines that are frequently updated are essential to ensure adequate coverage and treatment of obstructive by yellow nephritis and conditions specific antibiograms would be recommended in the future.

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