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Original Article

Catheter Associated Urinary Tract Infection: Characterization of Bacterial Pathogens and their Antimicrobial Susceptibility Pattern at Two Major Tertiary Care Hospitals

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ABSTRACT

Background: Catheter Associated Urinary Tract Infection (CAUTI) remains a leading cause of Hospital Acquired Infections (HAIs), leading to increased morbidity, mortality and financial impact on healthcare delivery systems.

Objectives: To isolate bacterial pathogens from urine specimens of patients with CAUTI and determine their Antimicrobial susceptibility pattern.

Materials and Methods: Urine samples were cultured on blood agar, MacConkey agar, and cysteine lactose electrolyte deficient agar. Species identification was achieved using gram stain and biochemical tests. Resistance profile of each isolate was recorded using Kirby Bauer disc diffusion method as per Clinical and Laboratory Standard Institute (CLSI) M-100 version 2021.

Results: Gram Negative bacteria accounted for 79% of all the CAUTIs with *Escherichia coli* (54%) as a major pathogen. *Enterococci* (19%) were predominant among gram positive bacteria (21%). While *E. coli* isolates revealed 100% resistance to ampicillin and co-amoxiclav, resistance to cefoperazone-sulbactam was observed in 75% and 100% of *E. coli* and *Citrobacter freundii* respectively. *E. coli*, *Enterococci* and *Klebsiella pneumoniae* were found resistant to fosfomycin in 1%, 17% and 36% of the isolates respectively. *E coli* resistance to nitrofurantoin was observed as 23%. In total 50% of the *K. pneumonia* and *C. freundii isolates* were resistant to nitrofurantoin. Among *K. pneumoniae* isolates 82% were resistant to meropenem and 55% were resistant to piperacillin tazobactam. Vancomycin resistant enterococci were observed only in 6% of CAUTIs.

Conclusion: *Multidrug resistant E. coli, Klebsiella* and *Enterococci* are leading pathogens in CAUTIs. Nitrofurantoin, aminoglycosides, carbapenems and fosfomycin has good invitro activity against bacterial pathogens isolated from patients with CAUTI. Prior knowledge of bacterial etiology and its associated AMR pattern could help clinicians for selection of appropriate antimicrobial therapy.

Keywords: Catheter Associated Urinary Tract Infection, Antimicrobial Resistance, Hospital Acquired Infection, Multidrug resistance, *Escherichia coli, Enterococcus*.

Introduction

Healthcare-associated infections affect a substantial number of patients globally, leading to increased mortality, morbidity, and financial impact on healthcare delivery systems both in developed and developing countries.[1] Common infections arising secondary to healthcare are surgical site infections (SSIs), pneumonia, urinary tract infections (UTIs), and bloodstream infections (BSIs).[2] In modern healthcare, invasive procedures and surgery, indwelling medical devices, and prosthetic devices are frequently associated with HAIs.[3]

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Indwelling Urinary catheters are well recognized as a cause of UTIs commonly acquired by patients in healthcare facilities. According to the CDC, an estimated 75% of UTIs are associated with indwelling urinary catheters.[4] The clinical phenotypes of UTIs are heterogeneous and ranges from mild self-limiting illness to severe life-threatening complications including BSIs usually caused by gram negative bacteria.[5]An estimated 20% of episodes of healthcare acquired bacteremia in acute care facilities, and over 50% in long term care facilities are CAUTI related.[6] Each day an indwelling urinary catheter remains, patient has a 3%-7% increased risk of acquiring a CAUTI.[7]

Common bacterial pathogens causing UTIs are *Staphylococcus aureus,* Coagulase-Negative *Staphylococci*, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus, Serratia, Escherichia coli,* *Enterobacter* spp., and *Enterococcus* spp.[8] These bacteria demonstrate high level of resistance to antimicrobials compared to those isolated in community setting.[9] In recent years, the free availability and widespread use and misuse of antibiotics in infection treatment has led to a significant rise in antimicrobial resistance originating from hospitals. Consequently, AMR become one of the greatest challenges in health care today. Compared with infections that could be treated with antibiotics, antibiotic-resistant infections call for greater medical care expenses, lengths of stay, and health care resources, as well as increased suffering of the patients.[10]

With the development of AMR, the spectrum of effective empirical therapies is slowly narrowing. In addition, the spectrum of bacterial pathogens causing CAUTI, and their pattern of AMR might change over times as result of antibiotic policies in each clinical setting. Therefore, it is critically important to know about the current situation of AMR related to CAUTIs in healthcare settings. Monitoring of AMR phenomena of bacterial pathogens and generation of local data towards Global Antimicrobial Resistance Surveillance System might help in developing effective strategies to limit the emergence of multidrug resistant pathogens and their associated infections.

Objectives

To isolate bacterial Pathogens from urine specimens of patients with CAUTI and determine their Antimicrobial susceptibility pattern.

Methods

This descriptive cross-sectional was carried out at two major tertiary care hospitals of Peshawar including Khyber Teaching Hospital, Peshawar and Rehman Medical Institute, Peshawar. A non-probability consecutive sampling technique was used to select study participants. Urine samples included those that were received from hospitalized patients with history of indwelling urinary catheters. Urinary foleys catheter tips, contaminated/unlabeled samples, samples collected less than 48 hours of admission and catheters inserted in other healthcare facilities were excluded. Samples were processed for pathogen identification and AMR testing at respective institutes after approval from ethical review committee of Khyber Medical College and Teaching hospital, Peshawar (IREB 1068/DME/KMC).

In total 610 urine samples fulfilling the inclusion criteria were collected over a period of 10 months from January to October 2021. Urine samples were cultured onto blood agar, MacConkey agar, and cysteine lactose electrolyte deficient agar. Bile esculin agar was used for isolation of enterococcal species. A calibrated inoculating loop with the capacity to hold 0.001 mL urine was used for inoculating respective culture media. Culture plates were observed after 18h aerobic incubation at 37°C for any visible growth. Significant bacteriuria was defined as a pure culture yielding $\geq 10^5$ colony forming unit (CFU)/ml. Species level identification was achieved using colony morphology on gram stain. For biochemical identification, Analytical Profile Index (API 20E, biomerieux, France) was used for members of the *Enterobacteriaceae*. For antimicrobial susceptibility the isolates were platted on Mueller- Hinton agar by Kirby-Bauer disc diffusion method.[11] The antibiotic inhibitory zones diameters were measured after 16-18 hours of incubation, at 37°C and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines M100 (2021). Following antibiotic discs (Oxoid, ThermoFisher Scientific, USA) with their respective concentrations were used: penicillin (P^{10U}), ampicillin ($AMP^{10\mu g}$), gentamicin ($CN^{10\mu g}$), ciprofloxacin ($Cip^{5\mu g}$), tetracycline ($Te^{30\mu g),}$ erythromycin ($Ery^{15\mu g}$), vancomycin ($Van^{30\mu g}$), chloramphenicol ($Cap^{30\mu g}$), nitrofurantoin ($F^{00\mu g}$), cefoxitin ($Fox^{30\mu g}$), and ceftriaxone (CRO, $^{30\mu g}$) for Gram-positive bacteria. ampicillin (Amp, 10µg), tazobactam-piperacillin ($TZP^{110\mu g}$), cefoxitin ($Fox^{30\mu g}$), cefepime ($Fep^{30\mu g}$), ceftriaxone ($CRO^{30\mu g}$), gentamicin ($CN^{10\mu g}$), Ciprofloxacin ($Cip^{5\mu g}$), tetracycline ($Te^{30\mu g}$), meropenem ($MEM^{10\mu g}$), amikacin ($AK^{30\mu g}$), nalidixic acid ($na^{30\mu g}$), norfloxacin (10µg), cefoperazone-sulbactam ($SCF^{75/30\mu g}$), Fosfomycin ($FOS^{200\mu g}$), nitrofurantoin ($N^{300\mu g}$) and ceftazidime ($CAZ^{30\mu}$g) were used for Gram-negative bacteria. Reference strain of *Escherichia coli* (ATCC 25922) were used as controls for the Gram-negative bacteria, while for gram- positive bacteria *S. aureus* (ATCC 25923) was used as control strain.

Data was analyzed using SPSS version 21. Qualitative variables were described using percentages and quantitative variables were described as mean and standard deviation. Data was presented as tables and graphs.

Results

Out of total 610 samples processed for urine culture, 154 patients were identified as having CAUTI out of which 73 (40%) were identified as female and 81 (60%)

were male patients. Mean Age of the studied groups was 46.68±27.73 years. Age distribution of the patients is represented in Table 1.Majority of the patients 89 (64%) were those over 40 years of age when compared to 65 (36%) patients with age less than 40 years.

Table 1: Age distribution of Patients with Catheter Associated Urinary Tract Infection (CAUTI).

Age Range	N=154 (%)
<20	38 (25%)
20-40	17 (11%)
40-60	37 (24%)
>60	62 (40%)

Gram negative bacteria were the predominant pathogens accounting for 79% of all the CAUTIs. Gram positive bacteria were found only in 21% of the patients and with *Enterococci* as a predominant pathogen (19%). *Staphylococcus aureus* was detected only in 2% of urine samples. Distribution pattern of bacterial pathogens associated with CAUTI is represented in Figure 1.

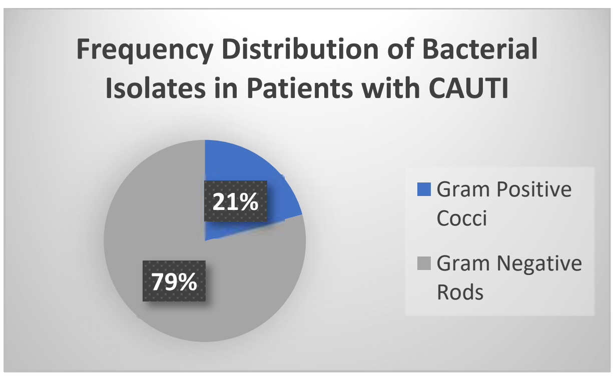

Figure 1: Frequency of gram negative and gram-positive bacterial pathogens isolated from patients with CAUTI.

Among Gram negative bacterial isolates, *E. coli* accounted for 54% of all the infections followed by *K. pneumoniae* (11%). *Pseudomonas aeruginosa* and *Klebsiella aerogenes* showed an equal distribution of 9% while *Klebsiella oxytoca* and *Citrobacter freundii* were present in 6% and 4% of the patients respectively. Frequency distribution of uropathogens isolated from urine samples of catheterized patients is shown in Figure 2.

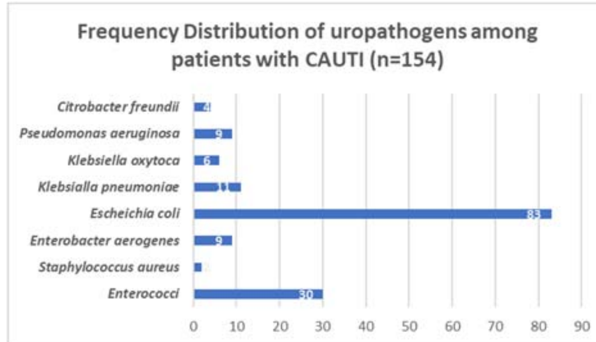

Figure 2: Represents the total number of each bacterial species isolated in patients with CAUTI (n=154)

Antimicrobial resistance profiles of all the pathogens tested against various antibiotics is represented in Table 2. Almost all the isolates including gram negative and gram-positive organisms (>70%) were found resistant to ampicillin, amoxicillin clavulanate, ciprofloxacin and trimethoprim sulphamethoxazole. About 75% of *E. coli* isolates were resistant to cefoperazone-sulbactam compared to 67% of *K. oxytoca* and 36% of *K. pneumoniae* isolates. *Citrobacter spp.* (100%) were resistant to cefoperazone-sulbactam as well as ceftazidime. While *E coli and Enterococcus* spps demonstrated resistance to Fosfomycin in 1% and 17% of the cases respectively, 36% of the *K. pneumoniae* isolates were found resistant to Fosfomycin. About 50% of *K. aerogenes* isolated were resistant to amikacin with a low level of resistance (19%) for *E. coli*, 27% *K. pneumoniae* and 11% *Pseudomonas aeruginosa*. *P. aeruginosa* showed high resistance to piperacillin tazobactam (78%), ciprofloxacin (67%) and cefepime (44%). Low resistance was seen to gentamicin in *P. aeruginosa*. (11%), *E. coli* (19%), *E. aerogenes* (22%), *K. pneumoniae* (27%) were resistant to gentamicin with 50% resistance observed for *K. oxytoca.* Among *K. pneumoniae* isolates 82% were resistant to meropenem and 55% were resistant to piperacillin tazobactam. *Pseudomonas aeruginosa* and *E. coli* isolates showed susceptibility rate of 78% and 88% against meropenem respectively. Collectively *K. oxytoca* and *C. freundii* had 50% resistance rate were noted against meropenem. *E. coli* showed only 23% resistance to nitrofurantoin. Relatively high resistance rates were observed for *K. pneumonia* (45%) and *Citrobacter freudii* (50%) with nitrofurantoin. Less resistance was seen in *E. coli* (18%) for meropenem. *S. aureus* and *Enterococci* showed 100% sensitivity to linezolid. Vancomycin Resistant Enterococci (VRE) were observed only in 6% of CAUTIs. Low resistance rates were observed for gentamicin and amikacin with a susceptibility rate of 81% and 73% for *E. coli* and *K. pneumoniae* respectively.

Table 2: AMR pattern of bacteria pathogens against commonly used antimicrobials in patients with CAUTI (IR= Intrinsic resistance)

Gram Negative Rods	% Resistance of Bacterial isolates against various antibiotics												
	AMP	**SXT**	**F**	**CIP**	**AMC**	**TZP**	**CTX**	**AK**	**MEM**	**FEP**	**CN**	**FOS**	**SCF**
Klebsiella aerogenes	IR	100	50	100	IR	33	89	22	22	50	22	0	50
Escherichia Coli	100	93	23	88	100	46	84	19	18	39	19	1	75
Klebsiella pneumoniae	IR	82	45	100	91	55	82	27	82	64	27	36	36
Klebsiella oxytoca.	IR	67	33	83	77	77	67	50	50	67	50	0	67
Pseudomonas spp.	IR	IR	IR	67	IR	78	IR	11	22	22	11	50	44
Citrobacter freundii	IR	100	50	100	IR	100	100	0	50	50	0	0	100
Gram Positive Cocci	**AMP**	**DO**	**F**	**CIP**	**VAN**	**P**	**TEC**	**RIF**	**LZD**	**CEP**	**CN**	**FOS**	**SXT**
Enterococcus spps.	73	60	60	97	6	80	10	73	0	50	0	17	IR
Staphylococcus aureus	100	0	0	100	0	100	100	100	0	100	50	0	100

Discussion

Microorganisms capable of causing CAUTIs mostly originate from patients' endogenous intestinal flora, however occasional acquisition from the hospital environment is not uncommon.[12] In the present study we found that majority of the bacterial isolates from CAUTI patients were multidrug resistant and predominant isolates (79%) were of gram-negative rods. Consistent with an earlier study by *Hyun et al*, *E. coli* (54%) was the most frequent pathogen followed by *Klebsiella spp.* (11%).[13] The preponderance of gram-negative bacteria as members of the normal colonic flora could contribute towards potential UTIs through contamination of the urethra and ascending infection up the bladder as a result of catheterization *P. aeruginosa* and *E. aerogenes* were detected only in 6% of the cases respectively. This contrasts with earlier reports from Italy, Ethiopia and Sudan demonstrating *P. aeruginosa* as the most common bacterial isolate.[14] Observed differences in the distribution of uropathogens might be the result of variability in environmental conditions, duration of catheterization and the characteristics of organisms unique to each facility.[15] Majority of the patients (64%) were those over 40 years of age when compared to 36% patients with age less than 40 years. Older adults are more prone to UTIs as compared with young individuals due to the high rates of urinary retention, urinary incontinence, long-term hospitalizations, presence of comorbidities, accompanying urinary catheterizations, and declining immune responses.[16]

Antibiotic resistance is a major clinical problem when treating infections caused by microorganisms. Resistance to antimicrobials has increased over the years and variability in resistance rates exists amongst countries[17] In the current study, the antibiotic susceptibility test result for isolated uropathogens revealed resistance to commonly used first and second-line antibiotics recommended for treating UTI, such as beta-lactams, aminoglycosides, and fluoroquinolones. Gram-negative bacterial isolates especially *E. coli* was found highly resistant to ampicillin (100%) and amoxicillin-clavulanate (100%), ciprofloxacin (88%) and cotrimoxazole (93%) which is agreement with earlier studies from Korea and Nigeria.[18] Concordant results were observed for CAUTI uropathogens in Bangladesh where *E. coli* was the most common pathogen isolated from patients with CAUTI and showing a high level of resistance to ampicillin (94.6%), co-amoxiclav (67.1%), ciprofloxacin (65.2%), and co-trimoxazole (72%).[19] Nonetheless, in the present study *E. coli* was found susceptible to nitrofurantoin (77%), amikacin (81%) and meropenem (82%). These findings might reflect either decreased local availability or could be related to the higher costs of these drugs. In contrast nitrofurantoin resistance rates were comparatively high when compared to studies from Uganda and Nigeria.[14] Of note was the finding of *K. pneumoniae* isolates which demonstrated only 18% susceptibility to meropenem in our study. Increased resistance reported for meropenem leave the clinician with no choice except for polymyxins. Increasing resistance to carbapenems that are most often the last line of therapy is being noted in hospitals in critically ill patients.[20]

Fosfomycin worked effectively *against E. coli* isolates with only 1% resistance among all the isolates. This is an agreement with a local study from Pakistan where susceptibility to fosfomycin was recorded at 100% (21). Similarly, another study conducted in Thailand, on uropathogenic *E. coli,* susceptibility to fosfomycin was noted in 98.7% of isolates (22).

One of the most common gram positive cocci isolated in hospitalized patients are *Enterococci* causing device associated infections including urinary tract infections, bacteremia, intra-abdominal infections, and endocarditis (23). Enterococcal UTIs are more likely to be acquired in hospital or long-term care settings, and thus, are more likely to be resistant to many antibiotics (16). In the present study, among gram positive bacteria, *Enterococci* (19%) was the most frequent uropathogen followed by *S. aureus* detected only in 1% of the cases. The high prevalence of enterococcus related CAUTI had been reported in several studies especially *E. faecalis* and *E. faecium*, accounting for 15% to 30% of CAUTI (14). Though *E. coli* has been reported as the leading cause of CAUTI in various studies (7, 11), *Enterococci* is also gaining importance in the causation of CAUTI and has emerged as a predominant pathogen in different nosocomial infections (23). In the present study *Enterococcus* was the second most common organism after *E. coli*, isolated from culture in CAUTI in hospital settings. Increased prevalence of these opportunistic pathogens might be related to the continuing progress of modern medical care toward more invasive medical therapies for human disease as well as use of broad-spectrum antimicrobials. Indirectly, attributing to the increasing antibiotic resistance among clinical isolates of enterococci (24). In the present study, *Enterococci* found resistant to vancomycin were detected in only 6% of the cases. As, Vancomycin-resistant enterococci are emerging as an important multidrug-resistant pathogen causing nosocomial infections, predominantly bacteremia and urinary tract infections (25, 26). These infections could contribute toward significant increase in the duration of the hospital stay, mortality and associated high public health threat due to limited treatment options. Some of the limitations of our study was small sample size and limited resources to characterize some bacterial isolates.

Conclusion

Findings of current study show *Multidrug resistant E. coli, Klebsiella* and *Enterococci* as leading pathogens in patients from CAUTI. Fosfomycin could be a hope for patients suffering from various drug resistant uropathogens. Management of CAUTIs requires prior knowledge of bacterial etiology and its associated local AMR prevalence. Further large-scale studies focusing on regular surveillance of AMR phenomena among catheterized patients in hospital settings are required. Furthermore, generation of local antibiograms may help physicians to select appropriate antibiotics for its treatment of CAUTIs, further reducing associated morbidity, and financial impact on health care delivery systems.

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A. Conception/Study/Designing/Planning
B. Active Participation in Active Methodology
C. Interpretation/ Analysis and Discussion