Current Trend in Bacteriological Profile and Antibiograms of Urinary Tract Infection at a Tertiary Care Center in Nepal

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ABSTRACT

Background

Urinary tract infections pose a significant global public health threat due to increasing multi-drug resistance among the uropathogens. Therefore, continuous surveillance and profiling of uropathogens and their antibiogram is essential to guide efficient empirical therapy.

Objective

To explore and display the etiological profile of urinary tract infection and their antibiograms at a tertiary care center.

Method

This is a retrospective cross-sectional study conducted at Dhulikhel Hospital (January 2023 to December 2024) under Anti-microbial stewardship program, analyzing laboratory records of urine culture and antimicrobial susceptibility testings. STATA 17 and R software (version 4.5.0) were used for calculation of frequency, percentage and mean. Chi-square test was applied to determine association where p-value < 0.05 was considered significant. Ethical approval was obtained from KUSMS-IRC.

Result

Overall urine culture positivity was 16.4% (4263/25983), including 113 fungal growths, and 211 dual organism growths. Out of the total bacterial species isolated (n=4361), *Escherichia coli* predominated (63.2%). Overall, multidrug resistance rate was 45.9%. *Escherichia coli* showed high resistance to ampiclillin (71.8%), cefixime (55.4%), ceftriaxone (47.4%), ciprofloxacin (49.1%) and norfloxacin (38.3%). Overall prevalence of carbapenem resistant gram-negative bacilli accounted for 8.9%. *Enterocccus* species were the most common gram-positive cocci with 6.1% of vancomycin-resistant isolates.

Conclusion

The increasing multi-drug resistance rate among uropathogens, along with evidence of carbapenem resistance and vancomycin resistance warrant for urgent need of continuation of surveillance and strengthening of antimicrobial stewardship initiatives.

KEY WORDS

Antibioigram, Multi-drug resistance, Urinary tract infections

INTRODUCTION

Urinary tract infection (UTI) represents an infectious entity of urethra, bladder, ureters or kidneys and is most frequently caused by diverse bacterial species.[1] It is one of the most common infectious diseases, affecting more than 150 million people annually.[2,3] Due to underlying pre-disposing factors such as shorter urethra, pregnancy, contamination of urethra with gastrointestinal tract flora and variations in hormonal activities, women have an estimated three times higher incidence of UTI compared to men.[4] The major pathogens affecting various parts of human urinary tract are mostly Gram-negative bacterial species as *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter* spp., *Enterobacter* spp., *Acinetobacter* spp., *Pseudomonas* spp., and Gram-positive species as *Enterococcus spp.* and *Staphylococcus aureus*.[5,6] UTI can range from uncomplicated to complicated infections and can sometimes lead to uro-septic condition where outcomes can be very severe.[7,8]

Timely initiation of appropriate antibiotic therapy is central to effective management of UTI, however its effectiveness has been compromised due to increasing anti-microbial resistance (AMR) among the uropathogens.[9,10] The prevalence of multi-drug resistant pathogen attributed to UTI are reportedly high (21%) even in the absence of any known risk factors.[11] Few of the key factors behind increasing antimicrobial resistance rate are inappropriate and frequent use of the antibiotics.[12,13]

Surveillance data of antibiotic resistance patterns play a crucial role in guiding infection prevention and control strategies, addressing the growing burden of antibiotic resistance. Regular analysis of these data promotes optimal antibiotic use, improves clinical outcomes and provides strategic insights for the development of novel antimicrobials.[14] Therefore the objective of this study was to determine the profiling of bacterial uropathogens and analyze their antimicrobial susceptibility patterns utilizing retrospective urine culture data collected during two year period with the goal of generating local antimicrobial susceptibility data to support evidence-based empirical therapy and antimicrobial stewardship programs.

METHODS

This is a retrospective cross-sectional study conducted from January 2023 to December 2024 under Antimicrobial Stewardship Program (AMSP) at Dhulikhel Hospital-Kathmandu University Hospital. The urine culture and antibiotic susceptibility test (AST) patterns of the specimens collected from the UTI suspected patients, attending Dhulikhel Hospital-Kathmandu University Hospital during the study period, were included following the census sampling technique and analyzed in the study.

The 1.36 mm diameter calibrated loop was used to inoculate exactly 0.001 mL of mid-stream urine samples on well-dried and sterile Cysteine Lactose Electrolyte Deficient (CLED) medium, which was followed by an overnight incubation at 35 ± 2°C aerobically. The growth of ≥ 10^5 colony forming unit of bacteria was interpreted as a significant bacteriuria based on the Kass criteria.[15]

Identification of each bacterial species was done by conventional technique based on combined interpretation of various biochemical test results. Each suspected uropathogen was screened by gram staining followed by standard biochemical tests viz; catalase, coagulase, mannitol fermentation test and novobiocin sensitivity test for Gram-positive and inoculation on triple sugar iron (TSI) agar, sulfide indole motility medium (SIM), Christensen's urea agar, Simon's citrate medium and oxidase test for Gram-negative bacteria. The isolated yeasts were grouped into *Candida albicans* and other *Candida* species based on the morphology in Gram-staining and germ tube test. Antimicrobial Susceptibility Test (AST) was performed on Mueller Hinton Agar plate by Kirby & Bauer disc diffusion method, utilizing 2 to 3 similar type colonies. Selection of antibiotics and interpretation of zone of inhibition (ZOI) for each isolates were performed as per the criteria given by Clinical & Laboratory Standard Institute (CLSI) guideline 2022.[16] The antibiotic discs used for AST were ampicillin (10 µg), cephalexin (30 µg), cefuroxime (30 µg), amoxycillin-clavulanic acid (20/10 µg), cefixime (5 µg), cefotaxime (30 µg), ceftazidime (30 µg), cefepime (30 µg), cefoperazone (75 µg), ciprofloxacin (5 µg), nitrofurantoin (300 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), ofloxacin (5 µg), gentamicin (10 µg), amikacin (30 µg), piperacillin-tazobactam (100/10 µg), imipenem (10 µg), and meropenem (10 µg), penicillin (10 µg), erythromycin (15 µg), clindamycin (2 µg), cefoxitin (30 µg), high-level gentamicin (120 µg), vancomycin 30 (µg) and linezolid (30 µg).

Organisms were considered multi-drug resistant, if they were resistant to at least one antibiotic from ≥ 3 antibiotic classes.[17] For the calculation of and preparation of heatmap of overall percentage resistivity across all uropathogens, bacterial species with ≥ 30 isolates were included, following CLSI Guideline M39-A4 2014, where as bacterial species with ≥ 10 isolates were included in case of carbapenem-resistant Gram-negative bacilli GNB) due to lower isolate numbers across various bacterial species.

The study was conducted as a sub-analysis of a larger research project that received ethical approval from Kathmandu University School of Medical Sciences Institutional Review Committee (KUSMS-IRC). The current analysis was performed within the scope of the original approval, and therefore the same ethical clearance number was applied (KUSMS-IRC Approval No: 356/24). As the study was retrospective analysis of anonymized patient records, informed consent was not required. The patients aged ≥ 1 years old visiting our hospital setting or admitted in the wards during the study period, were eligible for inclusion.

Urine culture and antibiotic susceptibility results of suspected cases of UTI were first extracted as excel file and imported to STATA 17 software, then frequency, mean and percentage were calculated. Chi-square test was applied to find the association of bacterial species with occurrence of multi-drug resistance (MDR) and P value < 0.05 was considered significant. R 4.5.0 was used to prepare the error bar plot of prevalence of carbapenem resistance and heatmap of percentage (%) resistance of overall isolates and carbapenem resistant isolates to various antibiotics.

RESULTS

During the study period a total of 25,983 mid-stream urine specimens received from various out-patient, in-patient, and emergency units were processed. 17,838 specimens were from female and 8,145 specimens were from male patients. Mean age of the participants was 37.5 years (Table 1). 16.4% (4,263/25,983) of the specimen showed urine culture positivity (4150 bacterial and 113 fungal pathogens), out of which 211 had growth of dual organisms as significant uropathogens (Table 2). Out of 4361 total bacteria recovered, the most prevalent uropathogen was found to be *Escherichia coli* (63.2%) followed by *Enterococcus* spp. (11.9), *Kelbsiella pneumoniae* (11.1%) other enterobacterales (2.5%), *Pseudomonas* aeruginosa (2.63%), *Candida albicans* (0.98) and other *Candida* spp. (1.43%), *Trichosporon* spp. (0.1%), *Acinetobacter* spp. (1.5%), *Burkholderia* spp. (0.06%), and *Staphylococcus aureus* (0.6%), *Staphylococcus saprophyticus* (0.6%) (Table 3). Overall multi-drug resistant (MDR) isolates for all species combined was found to be 45.9%.

Table 1. Sociodemographic characteristics of participants (N=25983)

Variables	Frequency (n)	Percentage (%)
Age in years (Mean ± SD)	37.5 ±21.4	-
Gender		
Male	8145	31.3
Female	17838	68.6
Origin		
Out-Patient	19305	74.3
In-patient	2587	9.9
Emergency Unit	4092	15.7

Values are expressed as number (n) and percentage (%)
Abbreviation: SD = standard deviation

There was a significant association between bacterial species and MDR status (chi-squared test, p value < 0.001). When MDR percent was calculated for the species with ≥ 10 isolates, the proportion of MDRs was highest in *Acinetobacter spp.* (75%) followed by *Proteus vulgaris* (52.3%), *Escherichia* coli (51.4%) and others, and was lowest for *Staphylococcus saprophyticus* (6.4%) (Table 4). The most common gram-positive isolate was found to be *Enterococcus* spp. of which 6.1% (33/533) were VRE

Table 2. Urine culture positivity and distribution by sex and calendar year

Variables	Categories	Number Positive (n)	Total Samples (N)	Percentage (%)
Overall urine cultures status	Urine culture Positive (bacterial + fungal)	4263	25,983	16.4
	Bacterial growths (including dual bacterial growth)	4150	4,263	97.3
	Fungal growth)	113	42,63	2.6
Bacterial isolates	Total bacteria isolated	4361	-	-
	Dual bacterial growth	211	4,150	5.1
Culture positivity by sex	Male	1,349	8,145	16.5
	Female	2,914	17,838	16.3
Bacterial growth by calendar year	Year 2023	1,972	12,145	16.2
	Year 2024	2,389	13,829	17.2

Values are expressed as number and percentage unless otherwise specified.
Percentage are calculated among culture-positive samples.
Total bacterial isolates exceed the number of culture-positive urine samples due to dual bacterial growth in some specimens.
Year-wise analysis includes bacterial growths only.
n=number of positive samples or isolates; N= total samples processed

Table 3. Distribution of uropathogens isolated from urine samples

Uropathogens	Frequency (n)	Percentage (%)
Percentage		
Escherichia coli	2,828	63.20
Klebsiella pneumoniae	497	11.10
Klebsiella oxytoca	44	0.98
Proteus mirabilis	47	1.05
Proteus vulgaris	42	0.93
Proteus spp.	8	0.17
Enterobacter spp.	49	1.09
Citrobacter spp.	46	1.02
Morganella morganii	12	0.26
Serratia marcescens	4	0.08
Providencia spp.	2	0.04
Edwardsiella spp.	1	0.02
Pseudomonas aeruginosa	118	2.63
Acinetobacter spp.	68	1.51
Burkholderia spp.	3	0.06
Enterococcus spp.	533	11.91
Staphylococcus aureus	28	0.62
Staphylococcus saprophyticus	31	0.69
Candida albicans	44	0.98
Other *Candida spp.*	64	1.43
Trichosporon spp.	5	0.11
Total	4474	100

n = number of each bacterial species isolated

Table 4. Association of multi-drug resistance (MDR) with bacterial species

Bacterial Species	Total Isolates	MDR %	p-value
Acinetobacter spp.	68	75	
Proteus vulgaris	42	52.38	
Escherichia coli	2828	51.45	
Proteus mirabilis	47	48.94	
Citrobacter spp.	39	48.72	
Enterobacter spp.	49	46.94	
Pseudomonas aeruginosa	118	44.92	< 0.001
Klebsiella pneumoniae	497	44.67	
Klebsiella oxytoca	44	43.18	
MRSA	11	36.36	
Morganella morganii	12	33.33	
MSSA	17	17.65	
Enterococcus spp.	533	16.14	
Staphylococcus saprophyticus	31	6.45	

(Vancomycin resistant enterococci), 1.6% were resistant to Linezolid and 28.7% were resistant to high-level gentamicin. 39.2% (11/28) of the *Staphylococcus aureus* were methicillin-resistant strains (MRSA). *E. coli* showed highest resistance to ampicillin (71.8%) while *Klebsiella* spp. showed > 30% resistivity to most of the antibiotic classes except few. The highest percent resistivity of *Enterococcus* spp. was seen with ciprofloxacin (58%) (Fig. 1).

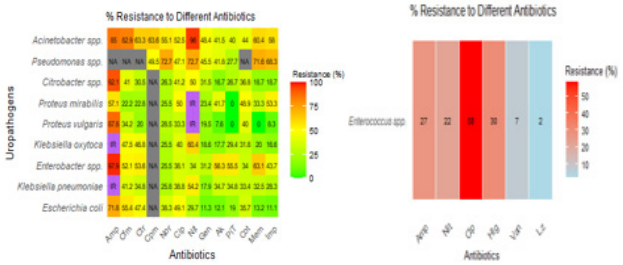

Figure 1. Heatmap showing overall antibiotic resistance rate among various bacterial species (Note: Darker color intensity represents higher resistance rate)

Abbreviations: Amp: ampicillin, Cfm: cefixime, Ctr: ceftriaxone, Cpm: cefepime, Cip: ciprofloxacin, Nor: norfloxacin, Nit: nitrofurantoin, Gen: gentamicin, Ak: amikacin, PiT: piperacillin-tazobactam, Cot: cotrimoxazole, Mem: meropenem, Imp: imipenem, HLG: high-level gentamicin, Van: vancomycin, Lz: linezolid, IR: intrinsic resistance

The overall prevalence of carbapenem resistance among gram-negative bacilli (enterobacteriaceae and non-fermenting gram-negative bacilli combined), was estimated to be 8.9% (95% CI: 8.0-9.9). Year-wise trend of prevalence was 9.4% (95% CI: 8.-10.9) in 2023 and 8.4% (95% C.I: 7.3-10.0) in 2024, with no significant difference between the two years (p = 0.85) (Fig. 2). Carbapenem-resistant uropathogens demonstrated high levels of co-resistance to multiple non-carbapenem antibiotics. Non-fermenting gram-negative bacilli, particularly *Pseudomonas aeruginosa* and *Acinetobacter* spp., showed consistently high resistance across fluoroquinolones, aminoglycosides, cotrimoxazole, and nitrofurantoin. Among Enterobacterales, carbapenem-resistant *Klebsiella pneumoniae* and *Escherichia coli* also exhibited substantial resistance to cirpfloxacin, norfloxacin and cotrimoxazole (Figure 3).

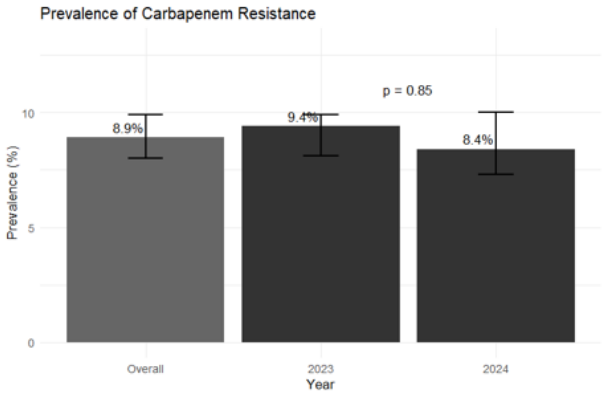

Figure 2. Prevalence of carbapenem-resistance overall and by year (2023-2024). Bars represents prevalence estimates and error bars indicate 95% confidence intervals

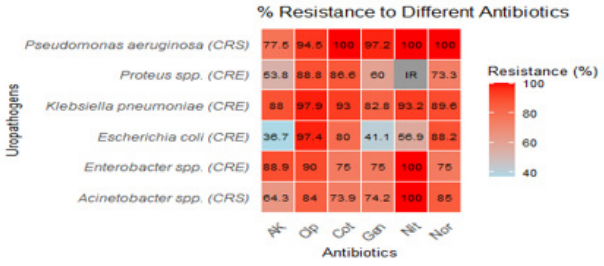

Figure 3. Heatmap depicting percentage resistance of carbapenem-resistant uropathogens to selected non-carbapenem antibiotics (Darker color intensity represents higher resistance rate)

Abbreviations: AK: amikacin, Cip: ciprofloxacin, Cot: cotrimoxazole, Gen: gentamicin, Nit: nitrofurantoin, Nor: norfloxacin, IR: intrinsic resistance, CRE: carbapenem resistant enterobacteriaceae, CRS: carbapenem resistant strains.

DISCUSSIONS

Antibiotic resistance associated to UTI is one of the major public health threats, especially in the low and middle income countries due to common existence of indiscriminate and irrational use of antibiotics.[18,19] This study was conducted to describe out the bacteriological profile and antibiograms for organisms urine cultures in patients at a tertiary-care hospital in Nepal. The specific goal of this study was to gather detailed antibiotic susceptibility pattern data for uro-pathogenic isolates and to inform the development of guidelines for the management of UTIs at our center because the microorganisms and their patterns of antimicrobial resistance can vary greatly regionally and among different clinical settings.[20,21] This study provides valuable data regarding different species of uropathogens and information regarding percentage resistance of each antibiotics to be considered during formulation of empirical regimens.

Overall urine culture positivity was found to be similar (16.4%) to that of study conducted by Shakya et al. (16%) at Tribhuwan University Teaching Tertiary Care Hospital, Kathmandu Nepal, whereas lower than the finding depicted by KC et al. (20.3%), which highlights the varying prevalence of Urinary tract infection in Nepal.[22,23] Although UTIs are more common in females, the slightly higher urine culture positivity among males (16.5% Vs 16.2%) may reflect natural variations in participant characteristics within the study population. Due to several predisposing factors such as urinary retention mainly due to prostatic hypertrophy, the risk of UTI incidences increase with age relatively in male patients.[24] The sex related occurrence rate of UTI might not always be a stable finding as several other factors such as presence of various risk factors and varying ages of patients often largely affects the incidences rates.[25]

Among various bacterial species isolated, *Escherichia coli* (63.2%) was found to be the most common urinary pathogen which is a consistent finding with the studies conducted by KC et al. (59.8%), Ghimire et al. (47.5%) and Pai et al. (52.5%).[23,26,27] Additionally various other age specific and gender-based studies show the predominance of *Escherichia coli* in UTI, highlighting the organism being the most common urinary pathogen.[28-30] *Enterococcus* spp. (11.91%) was the second most common organism isolated, similar to the study conducted by Rai et al.[31]

The overall prevalence of multi-drug resistant urinary isolates accounted for 45.9% which is also supported by the study conducted by Baral et al. at Kathmandu Model Hospital reflecting 41.1% as the overall MDR rate, but is lower than MDR rate(75%), displayed by the study done by Pradhan et al. at Tribhuwan University teaching Hospital, Nepal.[32,33] In our study, 75% of *Acinetobacter* isolates were MDR which was found comparable to the 76.8%, reported in studies including all clinical specimen. The findings suggest, the urinary isolates follow a similar trend of multi-drug resistance, however specimen related differences might exist.[34] The most common uropathogen in our study i.e *Escherichia coli*, showed MDR rate of 51.4% which is higher than 38.2% and 42.5% rates reported at BP Koirala Institute of Health Sciences (BPKIHS) and at Kathmandu Model Hospital Nepal respectively, reflecting variations with diverse clinical settings within the country.[32,35]

The antibiogram analysis of *E. coli* showed higher resistance rate to several key antibiotics designated for treating UTI. The isolates were highly resistant to ampicillin (71.8%), third generation cephalosporins as cefixime (55.4%) and ceftriaxone (47.4%), as well as to the fluoroquinolones as norfloxacin (38.3%) and ciprofloxacin (49.1%). Similar trends have been reported by various clinical studies addressing UTI. A study done by Rai et al. at Karnali Academy of Health Sciences teaching hospital in Nepal, tabulates the resistance rate of 63.6% and 71.2% and 33.3% for ampicillin, cefixime and ciprofloxacin respectively.[31] The isolates of *E. coli* from inpatients in India showed even higher resistance to ampicillin (88.4%), norfloxacin (74.2%) and ceftriaxone (71.4%) indicating widespread loss of efficacy of these agents.[36] The second most common organism among the gram negative bacilli, *Klebsiella pneumoniae* showed high resistance not only to first line antibiotics including cephalosporins (cefixime; 41.2%, Ceftriaxone; 34.8%), fluoroquinolone (ciprofloxacin; 38.8%) and nitrofurantoin (54.%), but also to the second line agents as amikacin (34.7%), piperacillin-tazobactam (34.8%) and meropenem (32.5%). Subedi et al. also showed the Similar higher resistance of *Klebsiella pneumoniae* with third generation cephalosporins and fluoroquinolones in their study whereas Neelambike et al. showed increasing trend of resistance to second line antibiotics including carbapenems (38.5%).[37,38] Among the gram negative isolates *Pseudomonas* spp. and *Acinetobacter* spp. have shown alarming high resistance rates to carbapenems of 71.8% and 60.4% respectively along with first line and second line antibiotics. Equally higher resistance across multiple classes of antibiotic has been reported not only in the urinary isolates by Yadav et al. but also from other specimens reflecting diverse distribution over several other infections too.[39-42]

For the past few decades, carbapenem resistant enterobacteriaceae (CRE) has become one of the consistent and concerning findings of numerous studies globally.[7,43] The efficacy of carbapenems, a common drug class for the treatment of infections caused by MDR gram negatives, has been significantly compromised due to its frequent use for the treatment of extended-spectrum-β-lactamase (ESBL) producing enterobaceriaceae.[7,44-46] The overall prevalence of carbapenem resistant GNBs was found to be 8.9% (377/4361) in our study, while various other studies from Nepal, India and other countries, addressing urinary isolates and other clinical isolates present even higher prevalences.[36,41,46-48] Despite the relatively low prevalence of carbapenem resistance observed in present study, the detection of carbapenem-resistant uropathogens is of considerable clinical and public health concern owing to the limited therapeutic options and and the potential for rapid dissemination of carbapenem resistance mechanisms.[50] Carbapenem resistance is cause of concern, as the drug is often considered as last resort antibiotic and utilized as an ultimate option for treating many infections caused by multidrug-resistant GNB.[51] While comparing the prevalence of carbapenem resistance in 2023 (9.4%) and 2024 (8.4%) the rate was found to be decreased in 2024 by 1%. Although the reduction was marginal without significant association with calendar years, the finding may reflect the positive impact of improved application of infection prevention and control strategies and antimicrobial stewardship program (AMSP), which was launched in the month of February

2023 onwards at our hospital setting.[52] However the year-to-year fluctuation of carbapenem resistance trends has been reported by Chang et al. which might be due to the change in intensity of antibiotic use as well as change in the local epidemiological dynamics. Therefore, regular surveillance becomes necessary to explore and capture the actual trend over the years.[53]

The most common gram-positive pathogen in our study was documented to be *Enterococcus* species. It was found that, 6.1% of Enterococci were VRE (vancomycin-resistant enterococci), 1.6% were resistant to linezolid and 28.7% were resistant to high-level gentamicin (120 µg) (HLG). The findings are consistent with the study outcomes displayed by Pradhan et al. at Gandaki Medical College Teaching Hospital and Research Center, Pokhara, Nepal.[54] Although the prevalence of VRE, seem relatively low, but its presence even at the lower level can portrait higher clinical values as it can cause life-threatening infections and they are usually resistant to several other relevant antibiotics too.[55] Similarly even low level of linezolid resistance can be problematic and frequently associated with poor patient outcome as it is the first choice of drug to treat the VRE associated infections.[56,57] Furthermore the substantial portion of Enterococci was found to be resistant to HLG which tend to compromise application of combined therapy utilizing aminoglycosides and cell-wall-active agents in severe infections.[58]

This study has certain limitations. The retrospective and single-center study design limits the generalizability of our findings to other hospitals or regions due to local variations in antimicrobial prescribing practices and resistance patterns. The patterns of the colistin resistance could not be analyzed and included due to lack of CLSI recommended Minimum Inhibitory Concentration (MIC) testing, at the settings. The study is also limited by unavailability of confirmatory extended spectrum-β-lactamase (ESBL) testing; so ESBL producing isolates could not be analyzed separately. However, we believe the resistance patterns and carbapenem resistance data provide clinically relevant information for guiding the empirical therapy in resource-limited settings.

CONCLUSION

The study highlights the etiological profiling of UTIs, along with the local patterns of antibiotic resistance at a tertiary care setting in Nepal. Escherichia coli remained the predominant agent causing UTIs, exhibiting high levels of resistance to commonly prescribed first-line antibiotics, including ampicillin, 3rd generation cephalosporins, fluoroquinolones and cotrimoxazole, compromising the empirical treatment options. Carbapenem resistance rate seem relatively lower than reported in other regional studies, yet remains as significant threat provided that, it is one of the few last-resort agents. The modest decline in year-to-year carbapenem resistance rate might display the early positive impact of application of antimicrobial stewardship programs and infection prevention strategies, but continued and regular surveillance is essential. The entities of vancomycin resistance among *Enterococcus* spp. (the most common gram-positive agent), resistance to linezolid and high-level-gentamicin portrait the undermined therapeutic options for enterococcal UTIs. In general, these findings emphasize the urgent need for regular local antibiogram-based surveillance, efficient application and strengthening the antimicrobial stewardship programs to optimize the UTI management and tackle dissemination of antimicrobial resistance.

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