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Bacterial Uropathogens causing Urinary Tract Infection at Hetauda Hospital

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ABSTRACT

Introduction: Urinary tract infection is the infection of the uroepithelium that mainly affects kidney, ureter, urinary bladder and urethra. The causative agents of urinary tract infections are bacteria and fungi. Among these, bacteria are the most causative uropathogens of urinary tract infections.

Objectives: The objective of this study is to isolate, identify, characterized and perform antibiotic sensitivity test from the bacterial isolates.

Methods: A descriptive cross-sectional study was conducted from March 2023 to May 2023. Ethical approval was obtained from Institutional Review Committee (IRC), Madan Bhandari Academy of Health Sciences, IRC-32-079. Total of 1120 urine samples were collected during this study.

Convenient sampling technique was used for this study. Clean catch or mid-stream urine was collected in a sterile container. All urine samples were submitted to Department of Microbiology for culture. A set of biochemical tests were done for bacterial identification. Antibiotic sensitivity test was performed by Kirby-Bauer disk diffusion method.

Results: Total of 1120 urine samples were collected from patients suspected to Urinary Tract Infections. Total urine culture positive was 340 (30.36%). Of these bacterial isolates, *Escherichia coli* (248, 73%) was the most common species, followed by *Klebsiella* species (26, 7.6%), *Staphylococcus saprophyticus* (23, 6.76%) and *Enterococcus fecalis* (18, 5.3%).

Conclusion: As prevalence of bacteria causing urinary tract infections is increasing day by day; so its proper isolation, identification, characterization with their antibiotic profile is necessary as it forms the base line for the clinicians to choose appropriate antimicrobial agents for empirical as well as rational treatment for UTIs.

Keywords: Uropathogens, urinary tract infection, *Escherichia coli*

INTRODUCTION

Urinary tract infection (UTI) is any infection of the urinary tract leading to an inflammatory response in the uroepithelium[1]. UTIs refer to the presence of microbial pathogens within the urinary tract and is usually classified by the infection site: - upper UTI (kidney and ureter) and lower UTI (urinary bladder and urethra). UTIs that occur in a normal

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genitourinary tract with no prior instrumentation are considered as "uncomplicated," whereas "complicated" infections are diagnosed in genitourinary tracts that have structural or functional abnormalities that includes instrumentation such as indwelling catheters[2].

UTIs affect both males and females of all ages. UTI among Nepalese patients attending general hospitals ranges from 23.1 to 37.4%[3,4]. Globally, the number of UTI cases is increased by 60.4%, i.e. from 252.25 million in 1990 to 404.61 million in 2019[5].UTIs are primarily caused by Gram-negative bacteria. Pathogens responsible for it is *Escherichia coli* (81%)[6,7] followed by *Staphylococcus saprophyticus*, *Klebsiella, Enterobacter, Proteus*, and *Enterococci*[8]. Quick and accurate diagnosis of UTI is very important to shorten the course of illness, as well as to prevent disease progression towards upper UTIs and renal impairment[9].

Resistances to antibiotics in different parts of the world due to genetic changes in strains, diversity in the use of antibiotics and division in the availability to broad-spectrum of new antibiotics are different[8]. In many infectious diseases including UTIs, physician needs to start the empirical treatment before a definitive diagnosis and antibiogram; therefore, to administer the appropriate antibiotic, the physician must have sufficient information about the probable cause of infection and antibiotic susceptibility[10]; hence, empirical therapy is started before culture (bacterial identification) and antibiotic sensitivity profile in each region[8,11]. This study is conducted with an aim to find out the bacteria causing UTI and their antimicrobial resistance which would help the clinician in using appropriate antibiotics for the clinical management.

METHODS

A descriptive cross-sectional study was conducted from March 2023 to May 2023. An Ethical approval was obtained from Institutional Review Committee (IRC), Madan Bhandari Academy of Health Sciences, Hetauda. All methods in this study was carried out in the hospital premises of MBAHS in accordance with guidelines provided by "MBAHS- code no IRC-32-079". A total of 1120 urine samples were collected during the study. All aged groups were included in this study.

Convenient sampling technique was used for this study. Clean catch or mid-stream urine was collected in a sterile, wide mouth, clean and dry, leak proof sterile container. All urine samples were submitted to Department of Microbiology for culture. Only bacterial isolates were included in this study, isolates other than bacteria falls under exclusion criteria.

Bacterial isolation and identification

Isolation of uropathogens was performed by a surface streak procedure on Cysteine Lactose Electrolyte Deficient agar (CLED) (Hi Media, Mumbai, India) using calibrated loops for semi-quantitative method and incubated aerobically at 37^0C for 24 hours. After incubation, if bacterial colony was at a concentration of $\geq 10^5$ cfu/ml, further processing was done, considering as a significant bacteriuria. If bacterial concentration was at a concentration of $\leq 10^5$ cfu/ml, urine sample was re-collected from the patient and further processing was done as per standard microbiological technique. Bacterial identification was made using battery of biochemical tests: namely, triple sugar iron agar (TSI), sulphide indole motility (SIM), citrate, urease, oxidase, lysine decarboxylase, lactose fermentation, catalase, coagulase, mannitol fermentation and novobiocin susceptibility test[12].

Antimicrobial susceptibility test of all the isolates was performed on Mueller Hinton agar (MHA) (Hi Media, Mumbai, India) by the standard disk diffusion technique of Kirby-Bauer method and interpreted as per CLSI recommendations[13].

Antibiotics discs and their concentrations were: used were several beta-lactam and tigecycline (TGC) (15µg). Beta-lactam antibiotics used were Amikacin (AK, 30 µg), Ceftriaxone (CTR, 30 µg), Cefixime (CFM, 30 µg), Levofloxacin (LE, 5 µg), Linezolid (LZ, 30 µg), Meropenem (MRP, 10 µg), Nitrofurantoin (NIT, 300 µg), Ofloxacin (OF, 15 µg), Penicillin (P, 10 µg), Piperacillin-Tazobactam (PIT, 30/6 µg), Tobramycin (TOB, 10 µg). All these antibiotics were obtained from Hi-Media, Mumbai, India. Mueller –Hinton Agar (MHA) plate of 150 mm diameter was used for antibiotic sensitivity test. For antibiotic sensitivity test, 0.5 McFarland standard was prepared by using Barium chloride and Sulfuric acid. Bacterial suspension was prepared in a peptone water and was compared to 0.5 McFarland standard. Cotton swab stick was soaked in bacterial suspension and was squeezed on the wall of peptone water bottle. Lawn culture was made on a MHA with charged cotton swab stick. Antibiotic discs were placed as per standard microbiological techniques and this process should be done within 20 minutes of bacterial inoculation. Inoculated MHA plate was aerobically incubated at 35^oC in incubator for 18-24 hours[4,14].

After 18-24 hours of incubation, each plate was examined for the zone of inhibition. Interpretation of antibiotic susceptibility test results was made as per the guidelines provided by the Clinical and Laboratory Standards Institute (CLSI)[13]. For the antibiotic sensitivity test, *Escherichia coli* ATCC 25922 was used as the control organisms for gram negative bacilli and *Staphylococcus aureus* ATCC 25923 for gram positive cocci[13]. Isolates showing resistant to at least one antibiotic in three antimicrobial classes were confirmed as multidrug-resistant (MDR) phenotype[15].

Sample size: Sample size will be collected by using prevalence sample size formula.

$n = \frac{Z^2PQ}{L^2}$=340

n=sample size

Z=Confidence level at 95% (standard value of 1.96)

P=Expected prevalence (10/30=0.33), As from the laboratory records, it was found that per day average samples for urine culture was thirty and culture positive was found to be ten.

Q=1-P (1-0.33=0.67)

L=Allowable error (5%)

Data and statistical analysis

The data generated during the study period were analyzed by using SPSS version 16.0 and were analyzed according to frequency distribution and percentage.

Consent to participate/consent to publish

Informed consent form was not included as this study deals with the bacterial isolates that cause UTI.

Fund

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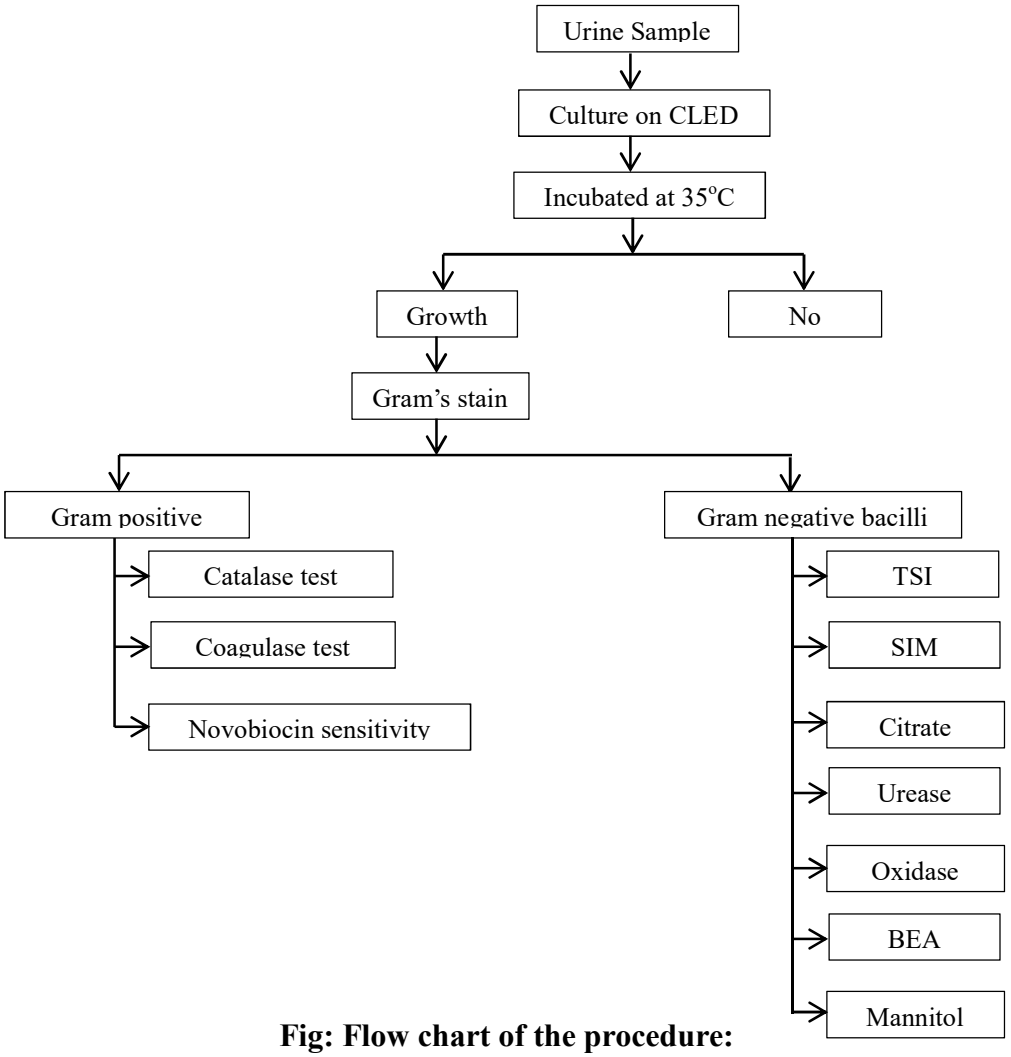

Fig: Flow chart of the procedure:

RESULTS

During the study period, a total of 1120 urine samples were collected from patients suspected to Urinary Tract Infections. Total urine culture positive was 340 (30.36%). Of these bacterial isolates, *Escherichia coli* (248, 73%) was the most common species, followed by *Klebsiella* species (26, 7.6%), *Staphylococcus saprophyticus* (23, 6.76%), *Enterococcus fecalis* (18, 5.3%), *Pseudomonas aeruginosa* (11, 3.23%), *Proteus mirabilis* (8, 2.35%), and *Proteus vulgaris* (6, 1.76%). The overall species distribution is further elucidated on figure 1.

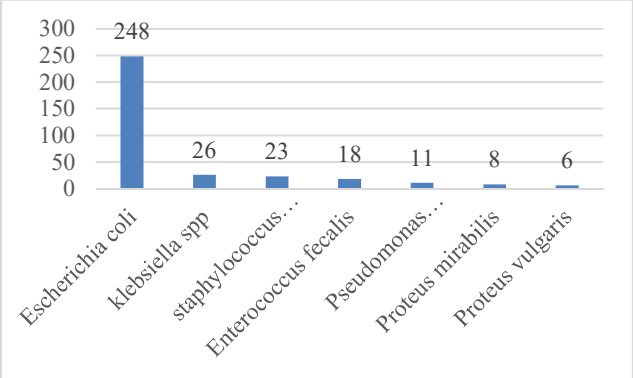

Figure 1: Frequency of bacterial isolates (n=340) isolated form UTI suspected patients

Bacterial uropathogens isolates from patients with UTIs revealed the presence of high levels of single and multiple antimicrobial resistances against commonly prescribed drugs (Table 1). *E. coli* which is the most predominant cause of UTI showing high resistance to nitrofurantoin and cefixime, each 76%, and ceftriaxone 62%, and low resistance to levofloxacin 12.5%, amikacin 12% and piperacillin-tazobactum 6%. Only one of the isolates of *E. coli* showed resistance to meropenem. *Klebsiella* species showed maximum resistance to cefixime (73%), ceftriaxone (65.4%) and ofloxacin (42), and showed least resistance to piperacillin-tazobactam (7.7%) and meropenem (11.5%), and only 3.8% resistance to nitrofurantoin.

Similarly, *Pseudomonas* showed maximum resistance to tobramycin 81.2% followed by amikacin (27.3), ofloxacin (27.3) and piperacillin-tazobactam (9%). None of the isolates of *Pseudomonas* showed resistance to meropenem.

Table 1: Isolates showing resistant to different antibiotics

Bacteria	Bacteria showing resistant (%) to antibiotics										
	AK	OF	LE	CTR	CFM	NIT	P	TOB	PIT	MRP	LZ
Escherichia coli (n=248)	30 (12)	92 (37)	31 (12.5)	154 (62)	189 (76)	189 (76)	ND	ND	6 (2.4)	1 (0.4)	ND
Klebsiella spp (n=26).	6 (23)	11 (42)	10 (38.5)	17 (65.4)	19 (73)	1 (3.8)	ND	ND	2 (7.7)	3 (11.5)	ND

Staph. saprophyticus (n=23)	1 (4.3)	2 (8.7)	2 (8.7)	18 (78)	20 (87)	0	20 (87)	ND	ND	ND	0
Enterococcus fecalis (n=18)	1 (5.6)	2 (11)	1 (5.9)	17 (94)	9 (50)	9 (50)	17 (94)	ND	ND	ND	0
Pseudomonas aeruginosa (n=11)	3 (27.3)	3 (27.3)	1 (9)	ND	ND	11 (100)	ND	9 (81.2)	1 (9)	0	ND
Proteus mirabilis (n=8)	3 (37.5)	1 (12.5)	2 (25)	6 (75)	4 (50)	8 (100)	ND	ND	0	0	ND
Proteus vulgaris (n=6)	0	1 (16.7)	1 (16.7)	3 (50)	1 (16.7)	6 (100)	ND	ND	0	0	ND

AK: Amikacin, OF: Ofloxacin, LE: Levofloxacin, CTR: Ceftriaxone, CFM: Cefixime, NIT: Nitrofurantoin, P: penicillin, TOB: Tobramycin, PIT: Piperacillin-Tazobactam, MRP: Meropenem, LZ: Linezolid, ND: Not done.

Proteus mirabilis showed maximum resistance to ceftriaxone (75%), followed by cefixime (50%), levofloxacin (25%). None of the isolates showed resistance to piperacillin-tazobactam and meropenem.

Similar resistance pattern was shown by *Proteus vulgaris* that showed maximum resistance to ceftriaxone (50%). It showed equal resistance to ofloxacin, levofloxacin and cefixime, i.e. 16.7%.

Among gram positive cocci, *Staphylococcus saprophyticus* showed maximum resistance to penicillin and cefixime each showing resistance to (87%) and ceftriaxone (78%). None of the isolates of *Staphylococcus saprophyticus* showed resistance to nitrofurantoin and linezolid.

Enterococcus faecalis showed maximum resistance to penicillin (94%) and ceftriaxone (94%). All bacterial isolates of *Enterococcus faecalis* showed sensitive to Linezolid (100%).

All *Proteus* and *Pseudomonas* species showed resistance to nitrofurantoin.

DISCUSSION

Bacterial infection of the urinary tract is one of the common causes for seeking medical attention in the community[16]. The observed high levels of antimicrobial resistance among uropathogenic bacteria in this study raise concerns about the choice of empirical therapy for UTIs. The resistance rates of *E. coli* to nitrofurantoin, cefixime and ceftriaxone are particularly alarming, as these antibiotics are commonly prescribed for UTIs. This highlights the need for regular surveillance of resistance patterns to guide appropriate empirical therapy. Effective management of patients suffering from bacterial UTIs commonly relays on the identification of the type of organisms that caused the disease and selection of an effective antibiotic agent to the organism in question[2].

In this study, the isolation rate of bacteria from urine was 30.36% which is equal to the reports within the country[1]. However, this finding is higher as compare to the studies done in Addis Ababa[17] and one from Iran which had a rate of 13.2%[18].

Escherichia coli (E. coli) is the major etiological agent in causing UTI, which accounts for 80% of cases[19], which is slightly lower as compared to our study 73%. In this study, the most frequent uropathogens were gram negative bacilli which accounts for 88% of the isolates. *E. coli* is the most common bacteria isolated from urine samples in both outpatients and inpatients from both the sexes, and this finding is in agreement with others finding too [2,20]. *Klebsiella* species (7.6%) is the second most common followed by *Staphylococcus saprophyticus* (6.7%). This concords with other studies[4,21,22].

Antibiotics play crucial role in treating such infections as long as the etiological bacteria is susceptible to the antibiotic activity. Thus, determining accurate antibiotic susceptibility is essential in the clinical care of bacterial infections. Bacteria capable of acquiring resistance demands more attention[1].

High sensitivity to ofloxacin is found in all isolates, except for *E. coli* (92% resistant), *Klebsiella* (89% resistant), and *Staphylococcus (*98% resistant). *E. coli* showing resistance to ofloxacin in the most done studies by other researchers were reported, for example, resistance rates in Nigeria, Ethiopia, Senegal, India, South Korea, Turkey, Mexico, America, North America, Canada, Italy, and Germany about 5.5%–31.9%. The resistance rate in urinary isolates of *E. coli* to ofloxacin in studies done in Pakistan and Bangladesh was medium while in Lebanon with a frequency of 54% was too high. In this study, like many other studies, it has been determined that urinary tract pathogens have high sensitivity to quinolones and particularly ofloxacin that can be used as the first drug in the treatment of patients with UTI[8]. In general, this study illustrates that ofloxacin still can be used as the first-line therapy of UTIs in Hetauda, Nepal.

Aminoglycosides are another group of antibiotics that are used in UTIs. In this study, resistance to amikacin in *E. coli* 12%, *Klebsiella* 23% and *Staphylococcus* 4.3% is reported. In most studies similar to our study, high sensitivity to amikacin was reported in UPEC. For example, *E. coli* sensitivity to amikacin in India was found to be 90.6%, Saudi 93.7%,[23] South Korea 99.4%,[8] and Taiwan 100%[24].

In the present study, 78% of *Staphylococcus saprophyticus* and 94% of *Enterococcus faecalis* was found resistant to ceftriaxone. Furthermore, resistant pattern of ceftriaxone and cefixime (third-generation cephalosporins) was investigated. The resistance rate of studied

isolates to these group antibiotics was 65%–55%. Ethiopian, Senegal and Lebanon[8] studies were almost equal with the current study. In these studies, intermediate resistance has reported in isolates of *Escherichia* to cephalosporins, but a study conducted in Taiwan, high sensitivity was observed in *E. coli* (cefazolin 81%, ceftriaxone 74% and ceftazidime 89%) and also in *Klebsiella* (cefazolin 80%, ceftriaxone 85%, and ceftazidime 83%);[24] in South Korea, high sensitivity to cephalosporins was observed in *E. coli* (cefotaxime 89.4%, ceftazidime 89.2% and cephalothin 58.4%) and in *Klebsiella* (cefotaxime 78.8%, ceftazidime 77.8%, and cephalothin 70.5%) has reported. A study conducted in Europe suggested that *E. coli* resistance to the third generation of cephalosporins was around 19.2%–1.8%[8] and also low resistance has reported to these antibiotics in America[25].

In the present study, isolates were most sensitive to meropenem (99% in *E. coli* and 97% in *Klebsiella*). *E. coli* sensitivity to meropenem in Taiwan was 100%, South Korea 100%, India 98.89%, Saudi Arabia 91.71%, Turkey 93% and Europe and North America 99.7% and 99.8%[8] respectively. Similarly, sensitivity pattern *Klebsiella* against meropenem in Taiwan[25] and South Korea was 100%[25] that these results were coincides with the results of this study. As mentioned above, the most effective antimicrobial agent was meropenem for gram negative bacilli in this study that was consistent with the results of previous studies. Similarly, for gram positive cocci, linezolid is the most effective antimicrobial agent.

The varying resistance profiles among different bacterial species emphasize the importance of individualized treatment strategies. In the present study, *E. coli,* highest sensitivity obtained to nitrofurantoin 76% after meropenem, but high sensitivity to these antibiotics was observed in *Staphylococcus* and *Klebsiella* isolates (99%-100%).The sensitivity of *E. coli* to nitrofurantoin in Ethiopia was 89.6% and India 77.4% reported[8]. These studies are consistent with the present study. For instance, nitrofurantoin demonstrated relatively low resistance rates in *Klebsiella,* suggesting its potential efficacy against these pathogens. In this study, *Proteus* species showed high resistance to third generation cephalosporin drugs (75%), which is low as compared to the study done by K Cohen-Nahum et.al where resistant against cephalosporins were 100%[26]. However, careful consideration is required due to the higher resistance rates observed in other bacteria.

The emergence of multidrug-resistant *Pseudomonas* isolates highlights the limited treatment options for *Pseudomonas*-associated UTIs. The high resistance rates to tobramycin (81.2%) and moderate resistance to other commonly prescribed antibiotics necessitate the

exploration of alternative therapeutic approaches. A study conducted in a Saheed Ziaur Rahman Medical College Hospital (SZMCH), Bogura, Bangladesh; MDR isolates of Pseudomonas were found to be 90.5% [27] which is in contrast to this study (30%).

In this study, all species of Proteus and Pseudomonas are found to be resistant against nitrofurantoin, as these species were intrinsically resistant to nitrofurantoin[28,29].

The resistance patterns observed in *Staphylococcus saprophyticus* and *Enterococcus faecalis* indicate the importance of selecting appropriate antibiotics, considering their susceptibility profiles. Nitrofurantoin and linezolid emerged as potential treatment options due to their efficacy against these gram-positive cocci. It is noteworthy that this antibiotic resistance of these bacterial agents is different in diverse parts of the world. Hence, in the treatment of urinary infections, antibiotic selection should be based on knowledge of the region, and international reports are not an appropriate choice for antimicrobial drug selection[8,30].

CONCLUSION

In conclusion, the present study showed that *Escherichia coli* (76%) is the most prevalence uropathogens among the isolates. This study also reveals sensitivity pattern of amikacin, ofloxacin and levofloxacin, showing good efficacy against almost all uropathogens. As for selection of antibiotics, empiric and proper treatment depends on bacterial isolation and identification. The isolation of bacterial uropathogens with a higher resistance rates for commonly used antimicrobials leaves the clinicians with very few options to choose drug used for empirical treatment of UTIs. Therefore, it is important to urge physician and other health worker in the field on the need of re-evaluation of empiric treatment of UTI. As drug resistance among pathogens is an evolving process, routine surveillance and monitoring studies should be conducted to provide physicians with knowledge about the most effective empirical treatment of UTIs.

Conflict of Interest: None

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