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Resistant Uropathogens in Gulmi Hospital: High Time to Take Action

Reena Shrestha[1], Uttam Pachya[2,3], Tulsi R Thapa[4], Ambika Thapa Pachya[4,5]

Author(s) affiliation

[1]*Department of Obstetrics and Gynecology, Patan Academy of Health Sciences, Lalitpur, Nepal*

[2]*Department of Emergency Medicine and General Practice, Patan Academy of Health Sciences, Lalitpur, Nepal*

[3]*Gulmi Hospital, Ministry of Health and Population, Nepal*

[4]*School of Public Health, Patan Academy of Health Sciences, Lalitpur, Nepal*

[5]*Department of Community Health Sciences, Patan Academy of Health Sciences, Lalitpur, Nepal*

Corresponding author

Ambika Thapa Pachya, MPH
ambikathapapachya@gmail.com

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ABSTRACT

Introduction

Recent study in Nepal showed 29.5% culture positive cases of Urinary Tract Infections (UTIs). Extensive consumption of broad-spectrum antibiotics leading to increased AMR rates amongst uropathogens. This study has been carried out to determine the proportion and types of uropathogens causing infections and their antibiotics susceptibility pattern based on WHO classification of antibiotics- access, watch and reserve ('AWaRe') categories.

Methods

Record review of the urine isolates with antibiotic susceptibility testing reported from Laboratory of Gulmi Hospital from April 2019 to April 2021. Ethics approval was obtained from Nepal Health Research Council (NHRC). Calculation of frequencies and proportions and cross-tabulation was done.

Results

Bacterial yield was found in more than one-third of the total 315 samples. Majorities (84.48%) of them were gram negative bacteria. More than three-fourth of the urine isolates were of female. Urinary isolates showed variable resistance to the 'access' and 'watch' group of antibiotics. There was high resistance to the conveniently prescribed antibiotics like cefixime, ciprofloxacin, ofloxacin, for UTIs. Among tested urine isolates, 75.7% were sensitive to Nitrofurantoin.

Conclusion

The yield of urine culture was 36.83% in our study with higher proportions in female. The resistance was high for conveniently prescribed antibiotics. Sensitive antibiotics like Nitrofurantoin were incorporated in the empirical therapy for UTI in this hospital after the study. It is an awakening call to implement measures to strengthen antimicrobial surveillance with inclusion of the peripheral hospitals to the reporting by capacitating them for quality reporting of the antibiograms.

Keywords
Antimicrobial resistance, AWaRe category, peripheral level hospital, urinary tract infections, urine culture

INTRODUCTION

Urinary tract infections (UTIs) are the commonest infections encountered by clinicians and proportionately more common among females than males in all age group.[1] It is one of the most common infection during pregnancy.[2] Recent study in tertiary hospital in Nepal showed 29.5% culture positive UTIs cases.[3] Escherichia coli, Staphylococcus species and Klebseilla species are commonest bacterial cause of UTI.[4] The excessive burden of these organisms causing UTIs has led to extensive consumption of broad-spectrum antibiotics leading to increased AMR rates amongst uropathogens. Multiple epidemiological studies in Nepal showed that there are differences in the resistance pattern of the bacteria seen in the tertiary level hospitals.[5-9]

One of the factors of these differences are the types of the patients these hospitals receive which usually are referred cases from the periphery. The resistance to newer and potent antibiotics leads to limited therapeutic options and making choice from the WHO reserve category of the antibiotics for treatment.[8] However there is dearth of information on AMR among UTI cases in the periphery, thus this study has been carried out to determine the proportion and types of uropathogens causing infections and their antibiotics susceptibility pattern based on WHO classification of antibiotics- access, watch and reserve (AWaRe) categories and this will facilitate in informing the empirical therapy for UTI in one of the peripheral level hospital, Gulmi Hospital, Nepal.

METHODS

This was a cross-sectional record review of the urine isolates with antibiotic susceptibility testing reported from Laboratory of Gulmi Hospital from April 2019 to April 2021. Gulmi Hospital is a one of the peripheral hospital in Lumbini Province in western Nepal. At the laboratory, urine samples received for culture and susceptibility testing were provided with unique identifier and were inoculated on cystine–lactose–electrolyte-deficient (CLED) agar. Cultures were incubated aerobically at 35±2°C for 24 hours; standard microbiological procedures identified those with the growth of the organism.[12] The susceptibility testing against different antimicrobial was done following the Clinical and Laboratory Standards Institute (CLSI) guidelines.[10] In this laboratory, testing for the reserve antibiotics is not done and cases with all tested antibiotics resistance are referred to the higher centers.

All patients visiting Gulmi hospital between the aforementioned periods whose urine samples were sent for culture and sensitivity test (CST) at the hospital laboratory were included in the study. Laboratory records for the study were extracted in Microsoft Excel using secondary data extraction sheet which was developed based on culture and sensitivity reporting pattern of the laboratory. Administrative permission and approval were obtained for the usage of routine laboratory data from hospital authorities. Ethics approval for conduction of study was obtained from Nepal Health Research Council (NHRC). The archived electronic database from laboratory was retrieved

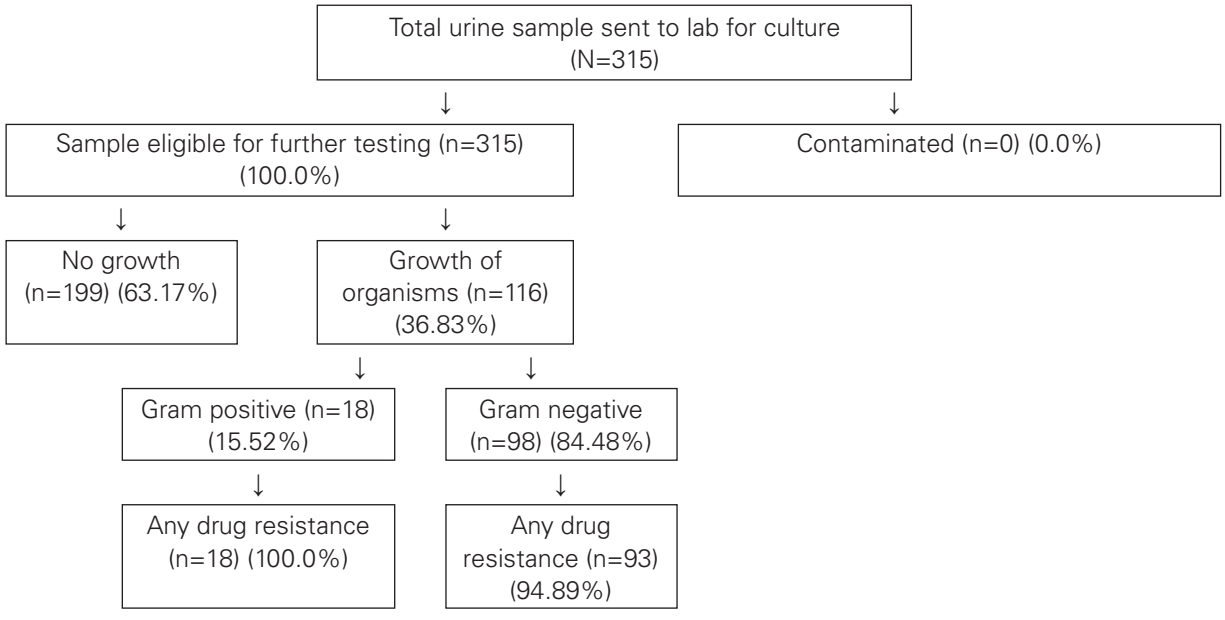

Figure 1. Cascade of culture and susceptibility testing of the urine samples

for study period and exported in Microsoft excel format. Data were cleaned to remove duplicates and missing values and analysis was done in International Business Machine SPSS version 26. The frequencies and proportions were calculated for all the variables, and cross-tabulation was done for selected variables.

RESULTS

Over two-year periods, all 315 samples sent for CST were eligible for further testing. Bacterial growth was found in more than one-third (36.83%) of samples and majority (84.48%) of them were gram negative bacteria. Among isolates, 94.89% were resistant to at least one of the antibiotics that were tested.

Majority of cases were from age group 15 to 43 years (61.20%) and more than three-fourth of urine isolates were of female (78.44%). The isolated gram-negative uropathogens were Escherichia coli (80.61%), Citrobacter species (12.24%), Klebsiella species (6.12%) and Enterobacter species (1.03%) and gram-positive uropathogens isolated was Staphylococcus species (100.0%) [Table 1].

Table 2 provides details on antibiotic drug susceptibility of bacteria isolated from urine samples. The resistance was highest for Cloxacillin (79.0%), followed by Cephalexin (66.7%), Ampicillin (65.60%) and Amoxycillin (55.1%) among 'access' group whereas resistance was higher for Vancomycin (75.0%), Cefixime (62.2%) and Piperacillin/Tazobactam (60.0%) among 'watch' group.

Table 3 provides details on antibiotic drug susceptibility of Escherichia coli and Staphylococcus species isolated from urine samples. Among 56 out of 79 isolates of Escherichia coli tested for Cloxacillin of 'access' group, 87.5% were found resistant, followed by resistance to Ampicillin (63.93%) and Amoxycillin (52.94%). Staphylococcus species were more resistant to Ampicillin (42.85%), Cloxacillin (40.0%), and Sulphamethaxazole/Trimethoprim (40.0%) among 'access' group of antibiotics.

There were five antibiotics in 'watch' group to which at least 50% of bacterial growth/isolates underwent drug susceptibility testing for Escherichia coli and they were Levofloxacin, Ceftriaxone, Cefixime, Ciprofloxacin and Ofloxacin. Out of these antibiotics, resistance levels were found to be highest in Cefixime (52.30%) and lowest in Levofloxacin (23.94%). For Staphylococcus species, five antibiotics to which at least 50% of isolates underwent drug susceptibility testing were Levofloxacin, Ceftriaxone, Cefixime, Cefotaxime and Ofloxacin. Among these, resistance levels were found to be highest in Cefixime (87.5%) and lowest in Ceftriaxone (18.75%). [Table 3]

Table 1. Characteristics of study population and uropathogens cultured in the urine sample (n=116)

Characteristics	Number (%)
Age group (years)	
<=14	6 (5.17)
15-43	71 (61.20)
44-63	22 (18.96)
>= 64	17 (14.65)
Sex	
Female	91 (78.44)
Male	25 (21.56)
Year	
April 2019-April 2020	58 (50.0)
April 2020- April 2021	58 (50.0)
Gram Negative (n=98)	
Escherichia coli	79 (80.61)
Citrobacter spp.	12 (12.24)
Klebsiella spp.	6 (6.12)
Enterobacter spp.	1 (1.03)
Gram Positive (n=18)	
Staphylococcus spp.	18 (100.0)

Table 2. Resistance pattern for 'access'and 'watch' group of antibiotics

AWaRe group / Antibiotics	Isolates Tested	Resistant isolates n (%)
Access Group		
Amoxycillin	78	43 (55.10)
Ampicillin	90	59 (65.60)
Sulphamethoxazole/ Trimethoprim	29	13 (44.80)
Cloxacillin	81	64 (79.00)
Cephalexin	3	2 (66.70)
Nitrofurantoin	115	16 (13.90)
Gentamicin	24	6 (25.00)
Watch Group		
Ciprofloxacin	77	23 (29.90)
Ofloxacin	78	23 (29.50)
Levofloxacin	103	24 (23.30)
Norfloxacin	31	11 (35.5)
Cefixime	98	61 (62.20)
Ceftriaxone	95	27 (28.40)
Cefotaxime	57	16 (28.10)
Piperacillin/tazobactam*	15	9 (60.00)
Azithromycin	6	3 (50.00)
Nalidixic acid	3	1 (33.33)
Vancomycin	8	6 (75.00)
Ceftazidime*	8	3 (37.50)
Tobramycin*	4	2 (50.00)

** Tested only for multidrug resistant organism*

Table 3. Resistance pattern for 'access' and 'watch' group of antibiotics for isolated organisms

AWaRe group / Antibiotics	Escherichia coli (n=79)		Staphylococcus spp. (n=18)	
	Total tested n (%)	Resistant among tested n (%)	Total tested n (%)	Resistant among tested n (%)
Access Group				
Ampicillin	61 (77.21)	39 (63.93)	14 (77.77)	6 (42.85)
Amoxycillin	51 (64.56)	27 (52.94)	15 (83.33)	5 (33.33)
Cloxacillin	56 (70.89)	49 (87.5)	15 (83.33)	6 (40.00)
Sulphamethoxazole/ Trimethoprim	14 (17.72)	6 (42.85)	10 (55.55)	4 (40.00)
Nitrofurantoin	78 (98.73)	11 (14.10)	18 (100.00)	3 (16.67)
Gentamicin	14 (17.72)	4 (28.57)	7 (38.88)	1 (14.28)
Cephalexin	2 (2.50)	1 (50.00)	-	-
Watch Group				
Levofloxacin	71 (89.87)	17 (23.94)	16 (88.88)	4 (25.00)
Norfloxacin	22 (27.85)	8 (36.36)	4 (22.22)	2 (50.00)
Ceftriaxone	64 (81.10)	17 (26.56)	16 (88.88)	3 (18.75)
Cefixime	65 (82.28)	34 (52.30)	16 (88.88)	14 (87.5)
Cefotaxime	38 (48.10)	10 (26.31)	11 (61.11)	3 (27.27)
Piperacillin/ Tazobactam*	11 (13.92)	6 (54.54)	1(5.56)	1 (100.0)
Ciprofloxacin	57 (72.15)	16 (28.07)	8 (44.44)	2 (25.00)
Ofloxacin	55 (69.62)	15 (27.27)	12 (66.67)	5 (41.67)
Azithromycin	3 (3.80)	1(33.33)	-	-
Tobramycin*	2 (2.53)	1 (50.00)	1 (5.56)	1 (100.0)
Ceftazidime*	5 (6.39)	2 (40.00)	1 (5.56)	0 (0.00)
Vancomycin	4 (5.06)	3 (60.00)	2 (11.11)	1 (50.00)
Nalidixic acid	3 (3.79)	1 (33.33)	-	-

** Tested only for multidrug resistant organism*

Table 4. Resistance to all drugs Access and Watch drugs tested in urine culture and susceptibility testing

Resistant to Access Drugs Tested	Resistant to Watch Drugs Tested		Total
	Not resistant to at least one tested Watch drugs	Resistant to all tested Watch drugs	
Not resistant to at least one tested Access drugs	97 (87.4%)	14 (12.6%)	111 (100.0%)
Resistant to all tested Access drugs	4 (80.0%)	1 (20.0%)	5 (100.0)
Total	101	15	116

Table 5. Sensitivity to Nitrofurantoin (Access drug) among isolates that were resistant to all Watch drugs

Nitrofurantoin	Resistant to All Watch Tested		Total
	Not resistant to at least one tested Watch drugs	Resistant to all tested Watch drugs	
Sensitive	75 (75.0%)	12 (80.0%)	87 (75.7%)
Resistant	15 (15.0%)	1 (6.7%)	16 (13.9%)
Intermediate	10 (10.0%)	2 (13.3%)	12 (10.4%)
Total	100 (100.0%)	15 (100.0%)	115 (100.0%)

Table 4 shows that out of 111 isolates not resistant to at least one tested 'access' drugs about 13 percent (12.6%) were resistant to all tested 'watch' drugs while 5 isolates resistant to all tested 'access' drugs were also resistant to all tested 'watch' drugs. These cases were referred to higher center for treatment.

Among 115 urine isolates that were tested for antibiotic susceptibility testing with Nitrofurantoin, it was seen that 87 isolates (75.7%) were sensitive to Nitrofurantoin including the 12 isolates which were resistant to all tested watch drugs. [Table 5]

DISCUSSION

Our study was done in periphery level hospital to understand the magnitude of uropathogens and their resistance pattern based on 'AWaRe' classification of antibiotics. Our study showed a yield of 36.83%. This is higher than the findings from study done in the tertiary level hospitals.[7-9] These differences can be result of smaller denominator in our study as compared to these studies. At peripheral level, Gulmi hospital is a referral center for people from the grassroots where there is lack of access to antibiograms testing, however there is easy access to pharmacies from where people get over the counter antibiotics.[11] Findings from study in Nepal show that there is financial incentive of saving money by patients when they bypass the formal health care workers along with distance and time, difficulties faced in navigating different departments of hospitals and little confidence in quality of services provided by the health care workers as factors driving use of over the counter antibiotics.[12]

Most of the isolates were from female cases. This is similar to the findings of other studies on UTIs.[13,14] Poor menstrual hygiene is also one of the contributor of UTI in women.[15] In addition to this resistant UTIs have impact on quality of sleep and mental health of patients as well.[16] Thus, in setting like ours where female are already with limited access to health care and water hygiene and sanitation facilities, UTI and its proper management is an important gender issue.

Furthermore, our study findings have some major programmatic implications. Firstly, study shows that in cases where conventional watch group antibiotics were resistant to the isolates, Nitrofurantoin was sensitive to these isolates. This has implication in the empirical therapy for the UTIs in this setting. The results were discussed with the hospital team and the empirical therapy for UTI was updated with inclusion of Nitrofuration.

Secondly, capacity building of hospital team to routinely carryout analysis of trend of antibiotic resistance for local surveillance so that they can have rationale prescribing of antibiotics and treating physicians get informed about tailored antibiotics for treatment of uropathogens.

Thirdly, in the peripheral setting, reserve drugs are not used as part of antibiograms testing, resistance to tested drugs from the 'Access' and 'Watch' groups results to referral of the patients for treatment. Thus, the stock keeping of optimally required 'Access' and 'Watch' group antibiograms need to be routinely ensured in peripheral level hospitals to get real time data and reduce load of referral for treatment of UTIs.

Fourthly, hospitals similar to Gulmi hospitals are first contact point in community from where testing of antibiograms is available, capacitating these facilities for quality of testing is crucial to get the update in pattern of AMR in peripheries; as that will ultimately be circulating to community and then to higher referral centers; we recommend the reporting to the surveillance system for AMR to be started from these level of peripheral hospitals.

Major strength of the study was that we included all the cases reported by the laboratory during the study period. Limitation of the study was that we were not able to relate the results with the treatment of the patients being a laboratory based retrospective study; a prospective longitudinal study can draw stronger evidences for bringing light in rational prescribing in this hospital.

CONCLUSION

The yield of urine culture was 36.83% in our study with higher proportions in female. Urinary isolates showed variable resistance to the 'access' and 'watch' group of antibiotics of 'AWaRe' categories among the antibiotics tested in the laboratory of Gulmi Hospital. The resistance was high for conveniently prescribed antibiotics and sensitive antibiotic Nitrofurantoin was advised and incorporated in the empirical therapy for UTI in this hospital. It is an awakening call to implement measures to strengthen antimicrobial surveillance with inclusion of the peripheral hospitals to the reporting by capacitating them for quality reporting of the antibiograms.

CONFLICT OF INTEREST

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