

# Antibiotic Susceptibility Pattern of Bacteria Causing Urinary Tract Infection

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## ABSTRACT

**Background:** Urinary tract infection is one of the commonest infectious diseases worldwide. This study was carried out to determine the antimicrobial susceptibility pattern of bacteria causing urinary tract infection visiting Kathmandu University Hospital.

**Methods:** A total of 3,500 urine samples were processed and antibiotic resistance pattern was determined following Clinical Laboratory Standard Institute guidelines. Patients' information was obtained after informed consent.

**Results:** Total number of samples with positive growth was 434 (12.40%). 331 (76.27%) of the isolates were *Escherichia coli* followed by *Klebsiella pneumoniae*, *Enterococcus* spp., *Pseudomonas aeruginosa*, *Staphylococcus saprophyticus*, *Proteus mirabilis*, *Enterobacter* species, *Klebsiella oxytoca*, *Citrobacter freundii*, *Proteus vulgaris*, *Staphylococcus aureus* and *Acinetobacter* species. Over all 224 (51.61%) were multidrug resistant strains. All strains were sensitive to colistin, vancomycin and linezolid. Over all ampicillin and cefazolin had least sensitivity. Multidrug resistant strains were detected more among elderly patients with complicated urinary tract infection and diabetes which was 25 (83.33%) compared to elderly patients with uncomplicated urinary tract infection and having no diabetes or any other comorbid illnesses which was only 11(22.22%) (p-value<0.05). 21 (70.00%) of the pregnant females had multidrug resistant isolates and only 18 (36.73%) of pediatric age group patients had multidrug resistant isolates (p-value<0.05)

**Conclusion:** Drug-resistant bacteria were observed in urine samples. Effective treatment and prevention of urinary tract infection need detailed microbiological diagnosis and drug susceptibility testing.

**Keywords:** ESBL; MDR; UTI

## INTRODUCTION

About 150 million people develop a urinary tract infection each year globally and the most common cause of infection is *Escherichia coli*.<sup>1</sup> Recent studies conducted in Nepal has also revealed that *E. coli* is the commonest bacteria causing UTI followed by *Klebsiella*, *Proteus*, *Citrobacter* etc.<sup>2,3</sup>

Drug resistant strains isolated in urine sample have become major issue in Nepal.<sup>2,3</sup> Carbapenems are considered as the drugs of choice for treatment of the infections caused by multidrug resistant (MDR) bacteria.<sup>4</sup>

Resistance strains like Extended Spectrum Beta-lactamase (ESBL) and Metallo-beta lactamase (MBL) producers are already disseminating on a worldwide

scale.<sup>5</sup> In Nepal, due to the lack of antibiotic policies MDR organisms are increasing.

## METHODS

This was an descriptive cross-sectional study carried out at Kathmandu University Hospital, Dhulikhel, Nepal between September 2021 to February 2022.

Ethical clearance was taken from the Institutional Review Committee of Kathmandu University Hospital before the study was conducted. (IRC-KUSMS Approval No. 102/2021)

Informed consent was taken from the patients whose urine culture was positive for bacteria and clinical

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information was obtained by history and clinical examination.

Urine was cultured on Cysteine lactose electrolyte deficient media and identification was done by colony morphology, microscopy and biochemical tests and drug susceptibility testing was performed as recommended by Clinical Laboratory Standards Institute (CLSI) 2018. <sup>6</sup>

For colistin susceptibility broth microdilution method was done in which a susceptibility breakpoint is  $\leq 2$  mg/liter. <sup>6</sup> *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as the control organisms.

ESBL strains are those strains that are capable of hydrolyzing penicillins, broad-spectrum cephalosporins and monobactams, but they do not affect the cephamycins or carbapenems and their activity is inhibited by clavulanic acid. <sup>7</sup>

The initial screen test for the production of ESBL was performed by using ceftriaxone 30 $\mu$ g, ceftazidime 30 $\mu$ g and cefotaxime 30 $\mu$ g disks. If the zone of inhibition was  $\leq 25$  mm for ceftriaxone,  $\leq 22$ mm for ceftazidime and/or  $\leq 27$ mm for cefotaxime, the isolate was considered ESBL- producer. <sup>8</sup>

An uncomplicated UTI is one occurring in a normal host who has no structural or functional abnormalities, is not pregnant, or who has not been with a catheter. All other UTIs are considered complicated. <sup>9</sup> Patients of age 65 years or older was considered as elderly. <sup>10</sup>

Multidrug resistant (MDR) was defined as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories. <sup>11</sup>

Data was analyzed by SPSS version 18.0 and p-value  $< 0.05$  was considered significant.

## RESULTS

A total of 3500 samples were included in the study and the samples with positive growth was 434 (12.40%). 405(93.32%) were Gram negative and 29(6.68%) were Gram positive. 298(68.66%) were female and 136(31.34%) were male patients. Bacterial growth detected among elderly patients were 80(19.35%) whereas 49(11.29%) in pediatric patients. 30(37.50%) elderly patients had complicated UTI with diabetes. Among 298 females 30(10.07%) were pregnant ladies. 331(76.27%) of the isolates were *Escherichia coli* followed by *Klebsiella pneumoniae* 45(10.37%), *Enterococcus* species 19(4.38%), *Pseudomonas aeruginosa* 11(2.53%), *Staphylococcus*

*saprophyticus* 9(2.07%), *Proteus mirabilis* 6(1.38%), *Enterobacter* species 5(1.15%), *Klebsiella oxytoca* 3(0.70%), *Citrobacter freundii* 2(0.46%) and only 1(0.23%) of isolates were from *Proteus vulgaris*, *Staphylococcus aureus* and *Acinetobacter* species.

For *E. coli*, ampicillin had least sensitivity with only 77(23.26%) sensitivity followed by cefazolin, cefixime, cefoperazone, ceftriaxone, amoxicillin-clavulanic acid, quinolones, cotrimoxazole, gentamicin, piperacillin-tazobactam and nitrofurantoin. More than 90% isolates were sensitive to amikacin and carbapenem. All isolates were sensitive to colistin. 44(13.30%) were ESBL producer.

For *K. pneumoniae*, cefixime and cefazolin had least sensitivity with only 18(40%) followed by quinolones, cotrimoxazole, cefoperazone, ceftriaxone, nitrofurantoin, amoxicillin-clavulanic acid, piperacillin-tazobactam, gentamicin, amikacin, carbapenem and all isolates were sensitive to colistin. 2(4.44%) were ESBL producer.

For *P. aeruginosa*, ceftazidime and cefoperazone was the least effective drug with only 4(36.36%) being sensitive followed by aminoglycosides, fluoroquinolones, piperacillin-tazobactam and carbapenem. All strains were sensitive to colistin.

For *P. mirabilis*, ampicillin and cefazolin were least effective drug followed by quinolones, cotrimoxazole, cefixime, ceftriaxone, amoxicillin-clavulanic acid, cefoperazone and gentamicin. All isolates were sensitive to piperacillin-tazobactam, amikacin and carbapenem.

For *Enterobacter* spp., 3(60%) isolates were sensitive to nitrofurantoin and cotrimoxazole and 4 (80%) isolates were sensitive to cefixime. All isolates were sensitive to quinolones, cefoperazone, ceftriaxone, piperacillin-tazobactam, gentamicin, amikacin, carbapenem and colistin.

For *K. oxytoca*, none of the isolates were sensitive to gentamicin and only one was sensitive to cefazolin and cefixime. Two isolates were sensitive to quinolones and cefoperazone and all isolates were sensitive to nitrofurantoin, cotrimoxazole, ceftriaxone, amoxicillin-clavulanic acid, piperacillin-tazobactam, amikacin, carbapenem and colistin.

For *C. freundii*, one isolates was sensitive to quinolones, nitrofurantoin, cotrimoxazole, cefoperazone, ceftriaxone and gentamicin and both isolates were sensitive to piperacillin-tazobactam, amikacin, carbapenem and colistin.

*P. vulgaris* was sensitive to all antibiotics and *Acinetobacter* spp. was sensitive to only gentamicin and colistin.

**Table 1. Antibiotic sensitivity pattern of Gram negative bacteria causing UTI .**

Drugs	E. coli (n=331) n (%)	K. pneumoniae (n=45) n (%)	P. aeruginosa (n=11) n (%)	P. mirabilis (n=6) n (%)	Enterobacter spp. (n=5) n (%)	K. oxytoca (n=3) n (%)	C. freundii (n=2) n (%)	P. vulgaris (n=1) n (%)	Acinetobacter spp. (n=1) n (%)
Ciprofloxacin (5µg)	151(45.62%)	21(46.66%)	6(54.54%)	3(50%)	5(100%)	2(66.67%)	1(50%)	1(100%)	0(0%)
Norfloxacin (10 µg)	151 (45.62%)	21(46.66%)	6(54.54%)	3(50%)	5(100%)	2(66.67%)	1(50%)	1(100%)	0(0%)
Nitrofurantoin(300µg)	292 (88.21%)	29(64.44%)			3(60%)	3(100%)	1(50%)	1(100%)	0(0%)
Cotrimoxazole(25µg)	193 (58.31%)	25(55.55%)		4(66.67%)	3(60%)	3(100%)	1(50%)	1(100%)	0(0%)
Cefazolin(30µg)	104 (31.42%)	18 (40%)		2(33.33%)		1(33.33%)			0(0%)
Cefixime (5µg)	143 (43.20%)	18 (40%)		4(66.67%)	4 (80%)	1(33.33%)		1(100%)	0(0%)
Cefoperazone (75µg)	151 (45.62%)	23(51.11%)	4(36.36%)	5(83.33%)	5(100%)	2(66.67%)	1(50%)	1(100%)	0(0%)
Ceftriaxone(30µg)	151 (45.62%)	23(51.11%)		4(66.67%)	5(100%)	3(66.67%)	1(50%)	1(100%)	0(0%)
Ceftazidime(30µg)			4(36.36%)						
Ampicillin(10µg)	77(23.26%)			2(33.33%)		0(0%)			
Amoxicillin-clavulanic acid (20/10µg)	151 (45.62%)	28(62.22%)		4(66.67%)		3(100%)		1 (100%)	0(0%)
Piperacillin- tazobactam(100/10µg)	287 (86.70%)	34(75.55%)	8(72.72%)	6(100%)	5(100%)	3(100%)	2(100%)	1(100%)	0(0%)
Gentamicin (10µg) and (120µg for Enterococcus)	277 (83.68%)	36(80%)	5(45.45%)	5(83.33%)	5(100%)	0(0%)	1(50%)	1(100%)	1(100%)
Amikacin(30µg)	313 (94.56%)	38(84.44%)	5(45.45%)	6(100%)	5(100%)	3(100%)	2(100%)	1(100%)	0(0%)
Imipenem(10µg)	325 (98.19%)	40(88.89%)	9(81.82%)	6(100%)	5(100%)	3(100%)	2(100%)	1(100%)	0(0%)
Meropenem(10µg)	325 (98.19%)	40(88.89%)	9(81.82%)	6(100%)	5(100%)	3(100%)	2(100%)	1(100%)	0(0%)
Colistin(10µg)	331 (100%)	45(100%)	11(100%)		5(100%)	3(100%)	2(100%)		1(100%)

Fluoroquinolone sensitivity was detected more among *Enterobacter* spp. and *P. vulgaris* isolates in comparison to *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *P. mirabilis*, *K. oxytoca*, *C. freundii* and *Acinetobacter* spp. When *E. coli* and *Enterobacter* spp. were compared for fluoroquinolone sensitivity using Chi-square test, the p-value was 0.0490.

More than 50% *Enterococcus* isolates were sensitive to ampicillin and gentamicin. 12(63.16%) isolates were sensitive to ciprofloxacin, 16(84.21%) isolates were sensitive to nitrofurantoin and all isolates were sensitive

to vancomycin and linezolid as depicted in table 2.

For *S. saprophyticus*, erythromycin was the least sensitive drug with only 5(55.55%) being sensitive and 7(77.78%) isolates were sensitive to cloxacillin and clindamycin. 8(88.98%) isolates were sensitive to cotrimoxazole and all strains were sensitive to ciprofloxacin, norfloxacin, nitrofurantoin, vancomycin and linezolid. 2(22.22%) of the isolates were detected to be MRCoNS (methicillin resistant coagulase negative Staphylococcus). The single isolate of *S. aureus* was sensitive to all drugs.

**Table 2. Antibiotic sensitivity pattern of Gram positive bacteria causing UTI.**

Drugs	<i>Enterococcus</i> spp. (n=19) n(%)	<i>S. saprophyticus</i> (n=9) n(%)	<i>S. aureus</i> (n=1) n(%)
Ciprofloxacin(5µg)	12(63.16%)	9(100%)	1(100%)
Norfloxacin(10 µg)		9(100%)	1(100%)
Nitrofurantoin(300µg)	16(84.21%)	9(100%)	1(100%)
Cotrimoxazole(25µg)	-	8(88.98%)	1(100%)
Ampicillin(10µg)	10(52.63%)		
Gentamicin (10µg) and (120µg) Enterococcus)	1(52.63%)		
Cloxacillin(5µg)		7(77.78%)	1(100%)
Clindamycin(2µg)		7(77.78%)	1(100%)
Erythromycin(15µg)		5(55.55%)	1(100%)
Vancomycin(30µg)	19(100%)	9(100%)	1(100%)
Linezolid(30µg)	19(100%)	9(100%)	1(100%)

Over all 224(51.61%) were multidrug resistant strains. MDR strains were detected more among elderly patients with complicated UTI and diabetes which was 25(83.33%) compared to elderly patients with uncomplicated UTI and having no diabetes or any other comorbid illnesses which was only 11(22.22%). p-value was statistically significant.

21(70.00%) of the pregnant females had MDR isolates and only 18(36.73%) of pediatric age group patients had MDR isolates when comparison was done the p-value was statistically significant. Among remaining patients, the MDR isolates were 149(54.18%).

**Table 3. Risk factors in the patients.**

Patients with risk factors	Multidrug resistant	Non-multidrug resistant	Total	p-value
Elderly with complicated UTI and diabetes	25(83.33%)	5(16.67%)	30	<0.05
Elderly without complicated UTI and diabetes	11(22.00%)	39(78.00%)	50	
Pregnant	21(70.00%)	9(30.00%)	30	<0.05
Pediatric patient	18(36.73%)	31(63.27%)	49	
Other patients	149(54.18%)	126(45.82%)	275	

## DISCUSSION

This study detected bacterial isolates from urine samples and observed the antibiotic susceptibility pattern along with few predisposing factors. Out of 3,500 samples included in the study, 12.40% had positive growth. This is close to the study finding by Pradhan et al, in which 13.80% were culture positive.<sup>2</sup> In our study 93.32% were Gram negative bacteria and 6.68% were Gram positive. In our study total number of female patients with positive growth was 68.66% and the total

number of male patients with positive growth was 31.34% which is quite close to the finding by Khatiwada et al.<sup>12</sup> In our study 76.27% of the bacteria causing UTI was *E. coli* followed by 10.37% *K. pneumoniae*. This is in accordance with other studies.<sup>2,3,12</sup> In our study 51.61% were multidrug resistant strain which is more than in the study conducted by Baral et al, in which it was 41.1%.<sup>13</sup> MDR strains were detected more among elderly patients with complicated UTI and diabetes which was 83.33% compared to elderly patients with uncomplicated UTI

and having no diabetes or any other comorbid illnesses which was only 22.22%. (p-value <0.05) Underlying urological diseases, diabetes can be complicating factors in UTI among elderly as observed by Alpay et al.<sup>14</sup> In our study 70% of pregnant ladies had UTI caused by MDR strains whereas only 36.73% of pediatric age group patients had MDR strains. (p-value <0.05) A study conducted in western part of Nepal showed that more than 50% of the strains causing UTI in pregnant ladies were drug resistant.<sup>15</sup>

For *E. coli*, ampicillin was the least effective drug with only 23.26% being sensitive but all isolates were sensitive to colistin. Study conducted by Vranic et al, observed minimum and even lesser sensitivity of *E. coli* towards ampicillin (17.21%).<sup>16</sup> It seems that we are also heading towards burden of ampicillin resistance. Fluoroquinolone sensitivity among *E. coli* in our study was less compared to the study conducted by Yilmaz et al.<sup>17</sup> Hence, less sensitivity of *E. coli* towards fluoroquinolone in our settings should be controlled. In our study amikacin and carbapenem sensitivity was lesser than in the study conducted by Yilmaz et al, in which amikacin sensitivity was 99.7% and carbapenem sensitivity was 100%.<sup>17</sup> It seems we also might face carbapenem and colistin resistance in future. For *K. pneumoniae*, cefazolin and cefixime were least sensitive and all strains were sensitive to colistin. In our study just more than 40% strains of *K. pneumoniae* were sensitive to fluoroquinolones. Fluoroquinolone resistant *K. pneumoniae* has been reported by Geetha et al, due to presence of several genes encoding fluoroquinolone resistance.<sup>18</sup> In our study ESBL producing strains among *K. pneumoniae* was much less in comparison to *E. coli* strains.

For *P. aeruginosa*, ceftazidime and cefoperazone were the least effective drug but all strains were sensitive to colistin. Ceftazidime sensitivity in *P. aeruginosa* strain in our study was less than the finding in the study conducted by Baral et al, in which 41.6% of the strains of *P. aeruginosa* was sensitive to ceftazidime.<sup>19</sup> Only 45.45% of *P. aeruginosa* were sensitive to aminoglycosides and more than 50% were sensitive to fluoroquinolones. More than 70% were sensitive to piperacillin-tazobactam and carbapenem. In the study conducted by Baral et al, more than 70% *P. aeruginosa* strains were sensitive to aminoglycosides and fluoroquinolones and 80% were sensitive to piperacillin-tazobactam, which is much more compared to our study.<sup>19</sup> Overexpression of efflux system MexXY/OprM is a cause of resistance to aminoglycosides, fluoroquinolones, and  $\beta$ -lactam antibiotics in *P. aeruginosa*.<sup>20</sup>

For *P. mirabilis*, ampicillin and cefazolin were least

sensitive drug but all isolates were sensitive to piperacillin-tazobactam, amikacin and carbapenem. Only 50% were sensitive to fluoroquinolones. In the study conducted by Singh et al, all strains of *P. mirabilis* were resistant to ampicillin and only 50% were sensitive to cefazolin and ciprofloxacin.<sup>21</sup> Hence, we are facing similar problem of antimicrobial resistance. Ceftriaxone and gentamicin sensitivity in our study also correlates with their findings.<sup>22</sup> For *Enterobacter* spp., 60% isolates were sensitive to nitrofurantoin and cotrimoxazole and 80% isolates were sensitive to cefixime. A study conducted by Hrbacek et al, showed that 40.9% *Enterobacter* were sensitive to nitrofurantoin which is lesser than ours but in their study 77.7% *Enterobacter* spp. were sensitive to cotrimoxazole which is more than ours.<sup>22</sup> None of the isolates of *K. oxytoca* were sensitive to gentamicin and only 33.33% isolate was sensitive to cefazolin and cefixime but 66.67% isolates were sensitive to fluoroquinolones and cefoperazone and all isolates were sensitive to nitrofurantoin, cotrimoxazole, ceftriaxone, amoxicillin-clavulanic acid, piperacillin-tazobactam, amikacin, carbapenem and colistin. In the study by Singh et al, less than 50% strains of *K. oxytoca* were sensitive to fluoroquinolones, carbapenem, amikacin, ceftriaxone but similar to our study all strains were sensitive to colistin.<sup>23</sup> *C. freundii* strains in our study strains were fully sensitive to piperacillin-tazobactam, amikacin, carbapenem and colistin. Single isolate of *P. vulgaris* was sensitive to all drugs but the single isolate of *Acinetobacter* spp. was sensitive to only gentamicin and colistin. MDR *Acinetobacter* spp. from urine has been found in the study conducted by Yadav et al.<sup>24</sup> In our study fluoroquinolone sensitivity was detected more among *Enterobacter* spp. and *P. vulgaris* isolates in comparison to *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *P. mirabilis*, *K. oxytoca*, *C. freundii* and *Acinetobacter* spp. (p-value=0.04900) Quinolone resistant genes can coexist with ESBL producing genes as detected by Salah et al.<sup>25</sup> Such type of studies should be conducted in future in our healthcare center too.

In our study the third commonest bacteria was *Enterococcus* spp. and 50% were sensitive to ampicillin and gentamicin. 63.16% were sensitive to ciprofloxacin, 84.21% were sensitive to nitrofurantoin and all isolates were sensitive to vancomycin and linezolid. *Enterococcus* spp. was the third commonest cause of UTI in the study conducted by Yadav et al.<sup>26</sup> *S. saprophyticus*, was least sensitive to erythromycin and all strains were sensitive to ciprofloxacin, norfloxacin, nitrofurantoin, vancomycin and linezolid. Similar to our study, in the study conducted by Shrestha et al. all CoNS were sensitive to vancomycin and linezolid.<sup>27</sup> In our study 22.22% of *S. saprophyticus* isolates were methicillin resistant. Methicillin-resistant *S. saprophyticus* isolates

carrying Staphylococcal Cassette Chromosome *mec* have emerged in UTI as reported by Higashide et al.<sup>28</sup> The single isolate of *S. aureus* was sensitive to all drugs.

## CONCLUSIONS

This study showed that *Escherichia coli* was the commonest bacteria causing urinary tract infection. Drug resistance especially due to ESBL producers and carbapenemase producers along with predisposing factors have become a major concern in the past and today.

Proper management of urinary tract infection by early investigation and analysis of infection and controlling of risk factors might help to reduce the burden of urinary tract infection.

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## CONFLICT OF INTEREST

None declared

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