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## CHANGING TRENDS IN ANTIMICROBIAL RESISTANCE OF GRAM-NEGATIVE UROPATHOGENS OVER A PERIOD OF TWO YEARS IN A TERTIARY CARE CENTRE

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### ABSTRACT

Antimicrobial Resistance (AMR) poses a major threat to human health around the world. This study aimed to assess the of Antimicrobial Resistance (AMR) trends of common gram negative uropathogens over 2 years among patients with UTI in a tertiary care centre. A retrospective analysis was performed using patients medical records and institutional database over a 2 years period (2019-2021). Changing trends in antimicrobial resistance of gram-negative uropathogens and risk factors of UTI were identified. From a total of 184 patients, the most common organisms were *Escherichia coli* (13.04%), *Enterobacter cloacae* (2.17%) and others (8.6%). Female gender (59.24%), age group of 60-79 years (55.43%), history of catheterisation (21.7%) & UTI (18.47%), comorbidities like diabetes mellitus (37.2%) & hypertension (30.43%) were found to be the major risk factors. Ceftriaxone & Cotrimoxazole showed increase in resistance for *E. coli* over 2 years. Antimicrobials such as piperacillin & tazobactam and Amikacin shows increasing trend of resistance to *Pseudomonas aeruginosa* over 2019-2021. Our study shows the trends of antimicrobial resistance of *Escherichia coli* and *Pseudomonas aeruginosa*. Knowledge of this trends will help clinicians to choose the right empirical antibiotic treatment. Antimicrobial Stewardship Programs (ASPs) should be implemented which will help curb inappropriate antibiotic use in our region.

**Keywords:** Urinary tract infections, gram-negative uropathogens, susceptibility testing, antimicrobial resistance, Antimicrobial stewardship, South Kerala

## INTRODUCTION

Urinary tract infection (UTI) is one of the most common bacterial infection, particularly in developing countries, overwhelmed with healthcare and economic constraints. It accounts for approximately 150 million cases annually [1]. It is a major public health problem in terms of morbidity and financial cost. Of the various uropathogens, gram-negative enteric bacteria such as *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are the most common causative agents [2].

The increasing rates of antimicrobial resistance (AMR) worldwide has become a major concern threatening in the twenty-first century which makes the treatment of UTI more complex. It is associated with increased resistance to antimicrobial agents such as multidrug resistance (MDR) with substantial medical and a financial burden [3].

Antimicrobial stewardship (AMS) is one of the crucial elements of tackling AMR globally to improve the quality of antibiotic prescribing including the monitoring of local antimicrobial susceptibility patterns [4]. In the era of rising antimicrobial resistance, studies showing the prevalence and AMR trend of uropathogens are very essential to coming up with this problem. This up-to-date evidence will help clinicians and health policymakers in implementing locally efficient therapy and preventive guidelines [5].

The AMR patterns have shown large interregional differentiation. It vary from country to country, state to state, large hospital to small hospital and hospital to community. In our country, the problem of antibiotic resistance is increasing because of overuse and misuse of antibiotics [6]. Epidemiological surveillance and reporting is necessary in order to guide antibiotic stewardship, which has shown to significantly reduce duration of antibiotic therapy and related costs without worsening treatment efficacy or prognosis. In recent years, various studies have shown rising drug resistance patterns to gram negative uropathogens across the globe. Previous studies in our study settings found *P. aeruginosa* and *E.coli* are the most prevalent uropathogens and it is particularly difficult to treat. Although there are snapshot studies in Kerala on the change in resistance rate of uropathogenic *E. coli*, less attention has been devoted to other common uropathogen like *Pseudomonas aeruginosa* especially in our study setting [7, 8]. Hence, this study aimed to assess the prevalence of common gram negative uropathogens and its AMR trends over 2 years between 2019 and 2021 among patients with UTI in a tertiary care teaching hospital of South Kerala.

## METHODS

### Study design

A hospital-based retrospective observational study was conducted in the department of

urology at a tertiary care teaching hospital in South Kerala after the approval from Institutional Ethics Committee (IEC). Prescription information of UTI patients were identified through our institutional database.

### Study population

The study population consisted of 184 patients with UTI between January 2019 and December 2021. Patients were considered eligible if they met the following criteria: patients who had done culture sensitivity test and above 18 years of age. Patients who were on treatment with antibiotics for other diseases, pregnant women and patients with incomplete data were excluded.

### Data collection

Data were collected through direct examination of the patients's medical records and through the institutional database. Since it was a retrospective chart review, patient consent form was waived. The primary outcome measures the trends in susceptibility and resistance data for common gram negative uropathogens like *E.coli* and *Pseudomonas aeruginosa* and the secondary outcome was to identify the risk factors related to the development of UTI.

### Data analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). To obtain the association of categorical variables, Pearson Chi- square test was applied and a  $P < 0.05$  were considered statistically

significant.

## RESULTS

The study group included 184 patients with a mean age of 66 years and median age of 69 years. Of the total patients, more cases of UTI were observed in females (59.24%) than in males (40.76%). As expected, *Escherichia coli* (44.56%) and *Pseudomonas aeruginosa* (31.52%) was the most common isolate throughout the two years followed by *Klebsiella pneumonia* (13.04%), *Enterobacter cloacae* (2.17%) and others (8.6%).

In the present study, we classified the risk parameters for UTI into patient specific and diseasespecific risk factors. In patient specific risk factors, the prevalence of UTIs was highest in females and for age group of 60-79 years (55.43%). History of catheterisation (21.7%) & UTI(18.47%), comorbidities like diabetes mellitus (37.2%) & hypertension (30.43%) were found to be the major disease specific risk factors. Stratified by age, the most commonly isolated uropathogens in male (37.8%) and female (62.19%) patients were *E. coli* ( $p=0.015$ ) (Table 1).

As seen in Table 2, *E. coli* displays resistance to Cotrimoxazole & Meropenem (69.23%), Levofloxacin (66.93%), Tetracycline and Ampicillin (61.53%) in 2019-20 and higher resistance to Ceftriaxone, Tetracycline, Norfloxacin and Ampicillin (76.67%), Ciprofloxacin and Levofloxacin (73.4%), Meropenem and Cotrimoxazole (73.3% and

70%) in 2020-21 respectively. Analysis of the results year wise indicated that *E. coli* displays a statistically significant increase in resistance to ceftriaxone and cotrimoxazole ( $p=0.049$ ) from 2019 to 2021.

**Table 3** shows that the *Pseudomonas aeruginosa* shows resistance to Cotrimoxazole (72.23%), Ciprofloxacin (72.22%), Meropenem (61.11%), Nitrofurantoin and Levofloxacin (55.55%), Imipenem and Tetracycline (50%) and Piperacillin and Tazobactam (22.22%) in

2019-20 and higher resistance for Nitrofurantoin and Levofloxacin (85.71%), Ciprofloxacin (78.66%), Norfloxacin, Tetracycline, Imipenem and Cotrimoxazole; Meropenem and Ampicillin (71.43% and 69.57%), Amikacin, Piperacillin and Tazobactam and Ceftriaxone (64.28%) in 2020-21 respectively. In the present study, resistance rate of *Pseudomonas aeruginosa* for Piperacillin/Tazobactam ( $p=0.016$ ) and Amikacin ( $p=0.038$ ) was significantly increased from 2019 to 2021.

**Table 1: Distribution of uropathogens among male and female patients**

Organisms	Male	Female	p-value
<i>E.coli</i>	31 (37.8%)	51 (62.19%)	0.015
<i>Klebsiella pneumonia</i>	10 (41.66%)	14 (58.33%)	0.06
<i>Pseudomonas aeruginosa</i>	25 (43.10%)	33 (56.89%)	0.069
<i>Enterobacter cloacae</i>	4 (100%)	0 (0%)	0.225
Others*	6 (37.5%)	10 (62.5%)	0.442

Others\*: *Proteus mirabilis*, *Serratia spp.*, *Citrobacter koseri*, *Acinetobacter baumannii*

**Table 2: Antibiotic resistance trends of *E.coli* for years 2019-2021**

Drugs	2019-2020	2020-2021	p – value
Piperacillin/tazobactam	23.07%	46.6%	0.146
Ceftriaxone	46.15%	76.6%	0.049
Cotrimoxazole	69.23%	70%	0.049
Nitrofurantoin	30.76%	76.6%	0.309
Tetracycline	61.53%	70%	0.959
Meropenem	69.23%	73.3%	0.782
Amikacin	30.76%	43.3%	0.952
Ciprofloxacin	53.84%	73.4%	0.21
Norfloxacin	56.93%	76.67%	0.804
Levofloxacin	66.93%	73.4%	0.804
Imipenem	46.15%	63.38%	0.294
Ampicillin	61.53%	76.67%	0.309

**Table 3: Antibiotic resistance trends of *Pseudomonas aeruginosa* for years 2019-2021**

Drugs	2019-2020	2020-2021	p – value
Piperacillin/tazobactam	22.22%	64.28%	0.016
Ceftriaxone	33.33%	64.28%	0.081
Cotrimoxazole	55.55%	85.71%	0.067
Nitrofurantoin	50%	78.6%	0.097
Tetracycline	61.11%	71.43%	0.68
Meropenem	27.77%	64.28%	0.542
Amikacin	72.22%	78.66%	0.038
Ciprofloxacin	44.44%	78.69%	0.68
Norfloxacin	55.55%	85.71%	0.051
Levofloxacin	55.55%	85.71%	0.067
Imipenem	50%	78.6%	0.097
Ampicillin	41.17%	69.57%	0.178

## DISCUSSION

Antimicrobial resistance (AMR) poses a major threat to human health around the world. Antibiotic susceptibility or resistance pattern of uropathogens have been changing over the years and its resistance rates vary from one region to another. One of the important factors contributing to the high resistance rates may be due to the increasing use of antibiotics without knowing the causative organism and its susceptibility pattern towards the antibiotics. There are very few studies done in South Kerala for keeping a check on the changing trend in antimicrobial resistance of common gram negative uropathogens. Due to the paucity of studies, we aimed to identify changing trends in Antimicrobial Resistance of common gram-negative uropathogens to various antibiotics.

Gram-negative organisms such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia* are the leading etiologic agents of UTI. In the present study, *E. coli* (44.56%) & *Pseudomonas aeruginosa* (31.52%) accounted for approximately of all clinically significant urinary isolates followed by *Klebsiella pneumonia* (13.04%) & *Enterobacter cloacae* (2.17%). The spectrum of uropathogens isolated in this study is very similar to the studies done in different regions of India [9].

Appropriate preventive measures are the best tactic to alleviate the burden of recurrent

UTIs. The demographic data indicates that women are more prone to UTI [10]. According to the statistical analyses in our study, a significant relationship was observed between *E. coli* and gender. The high prevalence of (62.19%) *E. coli* in the women could be due to the close proximity of the anus to the vagina. This is in consistence with findings of other studies around the globe in which *E. coli* is more prevalent in women [11]. This high possibility of UTIs in women is due to the inherent virulence of *E. coli* for urinary tract colonization such as its abilities to adhere to the urinary tract. Fecal-perineal-urethral contamination is the most probable route for infections [12, 13]. The prevalence of UTI in diabetic patients is found to be high in our sample population. High blood sugar level gives favourable growth environment to the pathogens maybe the plausible reason behind this. Particular attention should be given to these patients as they are more prone to UTI. One of the vital findings of this study is the significant increase in resistance of *E. coli* to Ceftriaxone & Cotrimoxazole over the 2 years. This is in line with results of study performed in Punjab in regard to the increasing resistance of *E. coli* to 3<sup>rd</sup> generation cephalosporins [14]. Similar results were also obtained from a study from Iran in which *E. coli* shows maximum resistance to amoxicillin (96%), ceftriaxone (78%), co-trimoxazole (70%), etc. [15].

Moreover, our results are also supported by a report from Iran which showed high level of resistance to co-trimoxazole [16]. The drug resistance among *E. coli* strains observed in our study is alarming, and this could be attributed due to rampant use of antibiotics, particularly beta-lactam antibiotics.

Antimicrobials such as piperacillin & tazobactam and aminoglycoside such as Amikacin shows increasing trend of resistance to *Pseudomonas aeruginosa* over the 2 years. Similar results were obtained in a study conducted in Saudi Arabia which reports high rate of resistance to piperacillin & tazobactam, whereas study performed in Dhahran showed low resistance to piperacillin [17, 18]. With regard to Amikacin, a study from Dhaka reported high resistance to *Pseudomonas aeruginosa* [19]. However, we noted dissimilarity in a study performed in Iran which shows low resistance of amikacin to *Pseudomonas aeruginosa* [20]. These deviation in the resistance rates are probably due to differences in antibiotic use in different settings. High resistance of these antibiotics in our study can be due to inappropriate use and these should be prescribed after proper identification and according to the antibiotic sensitivity reports. Thus, these antibiotics will remain available for a long time for the treatment of potentially serious infections caused by *E. coli* & *Pseudomonas aeruginosa*, which has the capability to

become quickly resistant to antibiotic therapy.

The overall trends of the present study indicated that there are increasing resistance of *E.coli* & *Pseudomonas aeruginosa* to commonly used antibiotics. Present study urge a need for a large scale monitoring of drug resistance problems in different parts of the country. Healthcare professionals and other stakeholders should be curious about the supply and control of antimicrobial agents. The constant and uninhibited use of antibiotics can lead to resistant mutants and emergence of drug resistance. The global community would understand the burden of resistance and possible solution would be designing a comprehensive antibiotic policies by aggregating reports from diverse geographic settings.

While promising, our study does have its limitations. The major limitation were the retrospective nature and provided only a single-centre experience. Resolution of symptoms and unintended effects cannot be assessed. In addition, we are unable to further examine the antibiotics prescribed for each patient and its clinical outcomes.

## CONCLUSION

Multidrug resistance in this study alarms a need for problem resolution by using antimicrobials susceptibility testing rather than empirical treatment. In addition, judicious use of hospital antibiotic policy, proper record keeping, prospective surveillance

system is needed in order to facilitate regular surveillance of antibiotic resistance as these levels and patterns continue to change. Nationwide surveillance is urgently needed to provide policy makers, antimicrobial stewardship committees, microbiologists, and epidemiologists with essential information to guide proper action plans. Furthermore, our data emphasize the importance of establishing an Antimicrobial Stewardship Program (ASP) in our hospital. Incorporation of clinical pharmacist also must be brought into practice in our study setting which will improve overall patient care and survival.

#### Conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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