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# Risk Determinants of Multidrug Resistant *Enterobacteriaceae* among Patients Diagnosed with Urinary Tract Infection

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**ABSTRACT**

Urinary tract infection (UTI) is a prevalent health issue in community and healthcare settings. The emergence of ESBL-producing and carbapenem-resistant Enterobacteriaceae limits treatment options, leading to multidrug resistance. This study investigated risk factors for multidrug resistance in Enterobacteriaceae isolated from UTI cases at a Gujarat tertiary care center, aiming to enhance understanding and develop effective treatment strategies. This retrospective observational study was conducted in a tertiary-care hospital, where urine samples from various departments, including the outpatient department (OPD), were analyzed. The isolates belonging to the Enterobacteriaceae group were identified using a range of biochemical methods. Subsequently, the ESBL and Carbapenemase producing organisms underwent antibiotic susceptibility testing following the guidelines provided by the Clinical and Laboratory Standards Institute (CLSI). In a Central Indian tertiary care hospital, 294 *Enterobacteriaceae* organisms were isolated from processed urine samples. Higher prevalence was observed among individuals aged 46-65 years and 16-30 years. Females had a higher incidence of UTIs caused by ESBL and Carbapenemase producers. Multidrug-resistant *Enterobacteriaceae* were more prevalent among indoor patients, particularly in the Surgery department. Common predisposing factors included catheterization, diabetes mellitus and obstructive uropathy. Among indoor patients, particularly those in the Surgery department, the prevalence of multidrug-resistant *Enterobacteriaceae* was notably higher. The most common risk factor associated with the presence of ESBL and carbapenemase producing organisms was catheterization.

## INTRODUCTION

Urinary tract infection (UTI) is a prevalent health issue that affects individuals in both community and healthcare settings. It is particularly common among women. According to the National Ambulatory Medical Care Survey, UTI accounts for approximately seven million patient visits in the outpatient department (OPD) and up to one million visits in hospital emergency departments. This high burden of UTI leads to approximately 100,000 hospitalizations annually[1]. It is estimated that approximately 50-60% of women experience at least one episode of urinary tract infection (UTI) during their lifetime[2]. If the underlying predisposing factors contributing to UTI are not promptly identified and treated, recurrent UTI episodes are also commonly observed[3].

Various anatomical and physiological factors contribute to an increased incidence of urinary tract infection (UTI). For instance, females have a shorter urethral length compared to males, which increases the likelihood of acquiring UTI. Inadequate bladder emptying, especially in older individuals, can lead to the accumulation of residual urine in the bladder. Vesicoureteral reflux, a condition frequently observed in pregnant women, is another crucial factor that predisposes the host to UTIs[4].

Urinary tract infections (UTIs) are primarily caused by bacterial pathogens, with Gram-negative bacteria being the most common culprits. *Escherichia coli*, *Proteus* species, *Pseudomonas aeruginosa*, *Acinetobacter* species, *Klebsiella* species, *Enterobacter* species and *Citrobacter* species are frequently isolated Gram-negative bacteria associated with UTIs. Gram-positive bacteria also play a role, with *Staphylococcus saprophyticus*, *Enterococcus* species and Coagulase-negative *Staphylococcus* being common pathogens responsible for UTIs[5,6].

Unfortunately, the emergence of extended spectrum beta-lactamase (ESBL) and carbapenem-resistant *Enterobacteriaceae* (CRE) poses a challenge in the treatment of urinary tract infections (UTIs). These bacteria possess genes that encode resistance to a variety of antimicrobial agents, including aminoglycosides and fluoroquinolones. Furthermore, these resistance genes are often located near the genes encoding ESBL on bacterial plasmids, resulting in the development of multidrug resistance patterns[7]. Consequently, the available treatment options for UTIs caused by ESBL and CRE strains become limited due to their ability to resist multiple antibiotics.

This study aimed to investigate and identify various risk factors contributing to the development of multidrug resistance in *Enterobacteriaceae* associated with UTIs at a tertiary care center in Central India. By examining these risk factors, the study aimed to enhance our understanding of the mechanisms behind multidrug resistance in *Enterobacteriaceae*-related UTIs and provide valuable insights for the development of effective treatment strategies.

## MATERIALS AND METHODS

The study was conducted retrospectively as an observational study at a Government Medical College located in Central India. Ethical considerations were given paramount importance and the study obtained clearance from both the Research Committee and Institutional Ethical Committee. The study strictly adhered to standard ethical guidelines to ensure the protection of participants' rights and privacy[8,9].

The study included a total of 100 cases and 100 controls. The cases consisted of women who were diagnosed with GDM based on the established criteria outlined by the American Diabetes Association (ADA). The diagnosis of GDM was established through either a glucose challenge test with a blood sugar value exceeding 200 mg $dL^{-1}$ or a glucose tolerance test with two or more abnormal blood sugar values. The control group comprised pregnant women at 24-28 weeks of gestation who did not have GDM, following the ADA criteria. Notably, all participants in the study received iron supplementation as part of the national program.

The sample size for the study was determined considering an Odds ratio of 2, which was derived from previous research findings. This resulted in a sample size of 190. Hemoglobin and packed cell volume (PCV) levels were measured using automated hematology analyzers, ensuring accuracy and reliability.

The collected data underwent statistical analysis using SPSS Version 21. The data were entered into MS Excel for systematic analysis. The association between variables was evaluated using the Chi-square test and a significance level of $p \leq 0.05$ was established as the threshold for determining statistical significance.

## RESULTS

A total of 294 *Enterobacteriaceae* isolates were obtained and tested in this study. The age of the patients included a wide range, from infants to individuals aged 85 years. Analysis of the data presented in Table 1 revealed that UTIs caused by *Enterobacteriaceae* were most commonly observed in the age group of 46-65 years, followed by the age group of 16-30 years.

Table 1: Age wise distribution of all isolates, ESBL and Carbapenemase producers

| | ESBL producer | | Carbapenemase producer | | Total | |
|---|---|---|---|---|---|---|
| Age (years) | No. | Percentage | No. | Percentage | No. | Percentage |
| 0-15 | 10 | 3.40 | 8 | 2.72 | 18 | 6.12 |
| 16-30 | 45 | 15.31 | 20 | 6.80 | 65 | 22.11 |
| 31-45 | 36 | 12.24 | 11 | 3.74 | 47 | 15.99 |
| 46-65 | 86 | 29.25 | 45 | 15.31 | 131 | 44.56 |
| >65 | 22 | 7.48 | 11 | 3.74 | 33 | 11.22 |
| Total | 199 | 67.69 | 95 | 32.31 | 294 | 100.00 |

Table 2: Gender wise distribution of all isolates, ESBL and Carbapenemase producers

| | ESBL producer | | Carbapenemase producer | | Total | |
|---|---|---|---|---|---|---|
| | No. | Percentage | No. | Percentage | No. | Percentage |
| Male | 84 | 40.19 | 37 | 43.53 | 121 | 41.16 |
| Female | 125 | 59.81 | 48 | 56.47 | 173 | 58.84 |
| Total | 209 | 100.00 | 85 | 100.00 | 294 | 100.00 |

Table 3: All isolates, ESBL and Carbapenemase producers in Indoor and Outdoor patients

| | ESBL producer | | Carbapenemase producer | | Total | |
|---|---|---|---|---|---|---|
| | No. | Percentage | No. | Percentage | No. | Percentage |
| Indoor | 154 | 76.62 | 69 | 74.19 | 223 | 75.85 |
| Outdoor | 47 | 23.38 | 24 | 25.81 | 71 | 24.15 |
| Total | 201 | 100.00 | 93 | 100.00 | 294 | 100.00 |

Table 4: All isolates, ESBL and Carbapenemase producers in different departments

| | ESBL producer | | Carbapenemase producer | | Total | |
|---|---|---|---|---|---|---|
| Departments | No. | Percentage | No. | Percentage | No. | Percentage |
| OBG | 33 | 13.31 | 6 | 13.04 | 39 | 13.27 |
| Medicine | 39 | 15.73 | 9 | 19.57 | 48 | 16.33 |
| Surgery | 111 | 44.76 | 16 | 34.78 | 127 | 43.20 |
| Padeatrics | 22 | 8.87 | 5 | 10.87 | 27 | 9.18 |
| Orthopaedics | 24 | 9.68 | 7 | 15.22 | 31 | 10.54 |
| Other | 19 | 7.66 | 3 | 6.52 | 22 | 7.48 |
| Total | 248 | 100.00 | 46 | 100.00 | 294 | 100.00 |

Table 5: Risk factors for multi drug resistance *Enterobacteriaceae*

| | ESBL producer | | Carbapenemase producer | | Total | |
|---|---|---|---|---|---|---|
| Departments | No. | Percentage | No. | Percentage | No. | Percentage |
| Catheterisation | 110 | 44.35 | 16 | 34.78 | 126 | 42.86 |
| Pregnancy | 38 | 15.32 | 8 | 17.39 | 46 | 15.65 |
| Diabetes mellitus | 34 | 13.71 | 9 | 19.57 | 43 | 14.63 |
| Prolonged ICU stay | 22 | 8.87 | 5 | 10.87 | 27 | 9.18 |
| Obstructive Uropathy | 24 | 9.68 | 7 | 15.22 | 31 | 10.54 |
| Chronic kidney disease | 18 | 7.26 | 3 | 6.52 | 21 | 7.14 |
| Total | 246 | 100.00 | 48 | 100.00 | 294 | 100.00 |

According to the data presented in Table 2, UTIs caused by ESBL and carbapenemase producers were more frequently isolated in females (n = 173, 58.84%) compared to males (n = 121, 41.16%). This observation indicates a higher incidence of UTIs associated with ESBL and carbapenemase production in the female population.

According to the data provided in Table 3, it was observed that indoor patients had a higher prevalence of ESBL isolations (154 cases, 69.05%) compared to carbapenemase isolations (69 cases, 30.95%). On the other hand, OPD (Outpatient Department) patients had lower rates of ESBL isolations (47 cases, 66.20%) and carbapenemase isolations (24 cases, 33.80%). These findings suggest that the occurrence of ESBL and carbapenemase producers was more prominent among indoor patients in the study.

Based on the information presented in the Table 4, it can be observed that among the *Enterobacteriaceae*, the prevalence of ESBL and carbapenemase producers was more commonly observed in the Surgerydepartment, followed by the medicine department. This indicates that the Surgery department had a higher occurrence of *Enterobacteriaceae* strains exhibitingmulti drug resistance.

According to the findings of our study, the most common predisposing factor for UTIs was catheterization. This was followed by diabetes mellitus and obstructive uropathy. Additionally, pregnancy and ICU stay were also recognized as predisposing factors, as indicated in Table 5. These findings highlight the importance of considering these factors in the assessment and management of UTIs.

## DISCUSSIONS

Urinary tract infection (UTI) stands as the most widespread infectious ailment within the general populace. Among the causative agents, *Enterobacteriaceae* have emerged as the predominant contributors to UTI incidence. A noteworthy observation reveals that majority of the isolates examined exhibited extended-spectrum beta-lactamase (ESBL) production, while lesser number of the isolates were identified as carbapenemase producers. Similar findings were reported by previous studies[10-12].

In the current investigation, the prevalence of extended-spectrum beta-lactamases (ESBLs) and carbapenemases was found to be higher among individuals belonging to the age group of 45-65 years. This aligns with the findings of Modi *et al*.[12], who identified ESBLs to be more commonly observed in individuals aged 60-65 years, followed by those aged 45-60 years. Conversely, Eshetie *et al*.[13] observed that the age group with the highest prevalence of ESBLs was 31-45 years, followed by the age group of 46-60 years. These varying results highlight the need for further investigation to elucidate the precise association between age and the prevalence of ESBLs and carbapenemases in UTI cases.

Within our study, UTI was found to be more prevalent in females compared to males. Furthermore, the distribution of ESBL producers and carbapenem producers exhibited a higher proportion in females compared to males. This female preponderance in terms of ESBL and carbapenem production aligns with the higher incidence of UTI observed in females. Similar findings were also reported by Sasirekha *et al*.[14]. These consistent observations underline the increased susceptibility of females to UTI and the associated production of antibiotic-resistant pathogens.

The data obtained from this study indicate a higher prevalence of ESBL production among inpatients compared to outpatients. This finding aligns with the study conducted by Sasirekha *et al*., where they observed that 61.9% of isolates with ESBL production were derived from inpatients[14]. In terms of carbapenemase production, it was observed to be more prevalent among inpatients as opposed to outpatients. Interestingly, Nair *et al*.[15] reported that carbapenem-resistant *Enterobacteriaceae* (CRE) isolates were detected in patient samples from both the wards (42%) and the intensive care unit (ICU) (26%)[15]. These results collectively emphasize the greater likelihood of ESBL and carbapenemase production among inpatients, suggesting the significance of nosocomial settings in the spread of antibiotic resistance.

Among the various departments, the department of Surgery exhibited the highest incidence of ESBL producers, followed by the department of Medicine. Furthermore, a higher prevalence of carbapenemase producers was observed in the Surgery department, including the ICU, followed by the Medicine department. The increased occurrence of ESBL and carbapenemase producers in the Surgery department can be attributed to catheterization, which is recognized as a major risk factor associated with UTI, as indicated in the study conducted by Jayakaran *et al*.[16]. Additional risk factors identified in the study included female sex, pregnancy, diabetes, previous hospitalization, prolonged ICU stay, renal calculus, chronic kidney disease and previous use of antibiotics. These risk factors collectively contribute to the higher incidence of ESBL and carbapenemase production within the Surgery department, highlighting the importance of considering these factors in the management and prevention of UTIs.

## CONCLUSION

UTIs are primarily caused by ESBL and carbapenemase producing *Enterobacteriaceae*. They are more prevalent in females aged 45-65 and in inpatients, particularly from the Surgery department. Catheterization is a common risk factor. Effective infection control practices and antimicrobial stewardship programs can prevent their spread.

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