Prevalence of multidrug resistant Enterobacteriaceae isolated from UTI - comparison between males and females above 60 years of age having Type 2 diabetes mellitus for more than 10 years.

Background: Urinary tract infections (UTIs) are a common issue in elderly patients, particularly those with Type 2 diabetes mellitus (T2DM). Enterobacteriaceae, often resistant to multiple antibiotics, are the most common pathogens in such cases. This study aims to assess the prevalence of multidrug-resistant (MDR) Enterobacteriaceae in elderly diabetic patients with UTIs and explore gender differences in resistance patterns.

Materials & Methods: This prospective study was conducted at the Padmashree Diagnostic Center in Bengaluru from December 2023 to May 2024, involving 84 participants aged over 60 with T2DM for more than 10 years. Midstream urine samples were collected and processed using the VITEK 2 system for pathogen identification and antibiotic susceptibility testing. Data analysis was performed using SPSS software, with significance set at $p < 0.05$.

Results & Discussion: Escherichia coli (55.88%) and Klebsiella spp. (32.35%) were the most common pathogens. High resistance was observed in both genders, with males showing significantly higher resistance to Amoxicillin-Clavulanic acid ($p = 0.0046$) and Piperacillin/Tazobactam ($p = 0.0265$) compared to females. Overall, both groups exhibited high resistance to Ciprofloxacin, Ampicillin, and Ceftriaxone, indicating the growing threat of MDR Enterobacteriaceae.

Conclusion: This study highlights the high prevalence of MDR Enterobacteriaceae in elderly diabetic patients with UTIs, with significant gender-based differences in antibiotic resistance. Continuous surveillance and tailored treatment strategies are necessary to manage this growing issue effectively.

Keywords:
Multidrug resistance, Enterobacteriaceae, UTI, Type 2 diabetes, Antibiotic resistance

Introduction

Urinary tract infections (UTI) are a frequent healthcare problem often seen in elderly subjects with comorbid conditions like Type 2 diabetes mellitus (T2DM) [1]. Numerous factors contribute to increased prevalence of UTIs in the diabetic population; these factors include altered immune responses, favorable conditions for bacterial colonization due to poor glycemic control, and enhanced susceptibility of the lower urinary tract to bacterial infection as a result of diabetic neuropathic changes1,2. Enterobacteriaceae with Multiple Drug Resistance (MDR) have gained importance as effective organisms in UTIs extending management and suffering difficulties [3]. This study aims to assess the prevalence of multidrug-resistant (MDR) Enterobacteriaceae among UTI patients, over 60 years of age with T2DM history of > 10 years and to look for gender variation from Bangalore, Karnataka. Detailed knowledge on their epidemiology and resistance patterns among this population is necessary for optimizing treatment strategies.

Review of Literature

UTI in patients with T2DM is highly widespread compared to non-diabetic persons due to defective immune responses and poor glycemiccontrol[4]. It has been well documented in the literature that elderly diabetic patients have the highest recurrence rates for UTIs with higher risk factors that are related to chronicity of diabetes and aging immune senescence [5]. Diabetes is an important public health problem in India where prevalence has increased rapidly which is the cause of significant morbidity and mortality. Diabetes care for Indian population should comprise of extensive and multi pronged research, with an integrated health care delivery models, which addresses the spectrum of diabetes and non diabetes related micro and macrovascular complications like UTI [6].

It is now documented that in diabetic patients, Enterobacteriaceae, notably Escherichia coli, and some species of Klebsiella are the most prevalent uropathogens. These pathogens are frequently resistant to several antibiotics, making treatment regimes complex [7, 8]. The other study from a tertiary care hospital of Bangalore where prevalence of E. coli was found 55.88% in diabetic patients of UTI and significance antimicrobial resistance pattern was seen against ciprofloxacin and ceftriaxone [19]. Frequently the use of antibiotics combined with more extensive and often indiscriminate use has led to the selection of a strain of resistant [9].

Gender differences in the prevalence and resistance patterns of UTIs among diabetic patients have also been observed. Female patients are generally more susceptible to UTIs due to anatomical and hormonal factors [10]. Nevertheless, it was reported that male patients with

62 T2DM are more susceptible to get infected with serious bacteria and to acquire more

63 resistance; this could be due to longer period of illness before diagnose and treatment [11]. In

64 diabetics, non-Escherichia coli (E. coli) uropathogensUTIs areacommonform ofUTI

65 susceptibility whichmaybepresented with wide spectrumpathogens, including E. coli,

66 Klebsiellasp., enterococci, group B streptococci, Pseudomonassp., Proteusmirabilis,

67 Mycoplasmasp., Enterobactersp., Staphylococcus aureus, and/or Candida [8,12].

68 Antimicrobials resistant to clinically relevant ESBL-producing strains, carbapenem-resistant

69 Enterobacteriaceae (CRE), and other MDR Enterobacteriaceae include phenicols,

70 sulfonamides, fluoroquinolones, tetracyclines, and aminoglycosides. These sorts of massive

71 resistances also can become so powerful they are effectively untreatable [13].

72 The strategies to control MDR UTI include strict antibiotic stewardship program,

73 development of better diagnostic tools and patient education regarding hygiene and

74 glycemiccontrol[14]. In conclusion, due to the high level of resistance detected, continuous

75 surveillance remains of utmost importance, and more needs to be done to better understand

76 the emergence of more resistant patterns and to establish successful empirical therapy for

77 UTIs in diabetic patients.

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80 **Materials and Methods**

81 **Study Design**

82 This study was designed as a prospective study conducted at the Padmashree Diagnostic

83 Center in Vijaynagar, Bangalore. The study period extended from December 2023 to May

84 2024.

85 **Population and Sampling**

86 The study focused on the population of Vijayanagar, Bangalore, targeting individuals above

87 60 years of age with Type 2 diabetes mellitus (T2DM) for more than 10 years. A random

88 sampling method was employed to select the participants.

89 • **Sample Size**: 84 participants

- **Sample Collection**: Mid-stream clean catch urine samples were collected aseptically in wide-mouth sterile containers. The samples were examined within 1-2 hours of collection, and not stored for more than 24 hours.

- **Transport and Storage**: Samples were stored and transported in containers with secure, leak-resistant lids at 4ºC.

Inclusion Criteria

- Patients with Type 2 diabetes mellitus for over 10 years

- Age above 60 years

- Midstream urine samples collected prior to antibiotic administration

- Isolates showing multidrug resistance (MDR)

Exclusion Criteria

- Patients without Type 2 diabetes mellitus

- Patients with Type 2 diabetes mellitus for less than 10 years

- Age below 60 years

- Samples collected after antibiotic administration

- Isolates not demonstrating MDR

Sample Processing

- **Colony Identification and Antibiotic Susceptibility Testing**: The samples were processed using the VITEK 2 system for colony identification and antibiotic susceptibility testing.

Statistical Analysis

The statistical analysis was performed using SPSS software to evaluate the antibiotic resistance patterns among male and female patients. The data was expressed as mean ± standard deviation (SD), and an independent t-test was conducted to compare the resistance percentages between the two groups. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

118   Ethical clearance for the study was obtained from the Institutional Review Board of
119   Padmashree Group of Institutions. The study did not involve any interventional work on
120   humans or animals.

121   This detailed methodology ensures the reliability and validity of the study findings, providing
122   a comprehensive approach to understanding the prevalence of multidrug-resistant
123   Enterobacteriaceae in elderly diabetic patients with UTIs.

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125   **Results**

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127   **Table-1 :Gender Distribution**

Sex	Percentage
F	66.67%
M	33.33%

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129   The gender distribution table shows the percentage of male and female patients in the study,
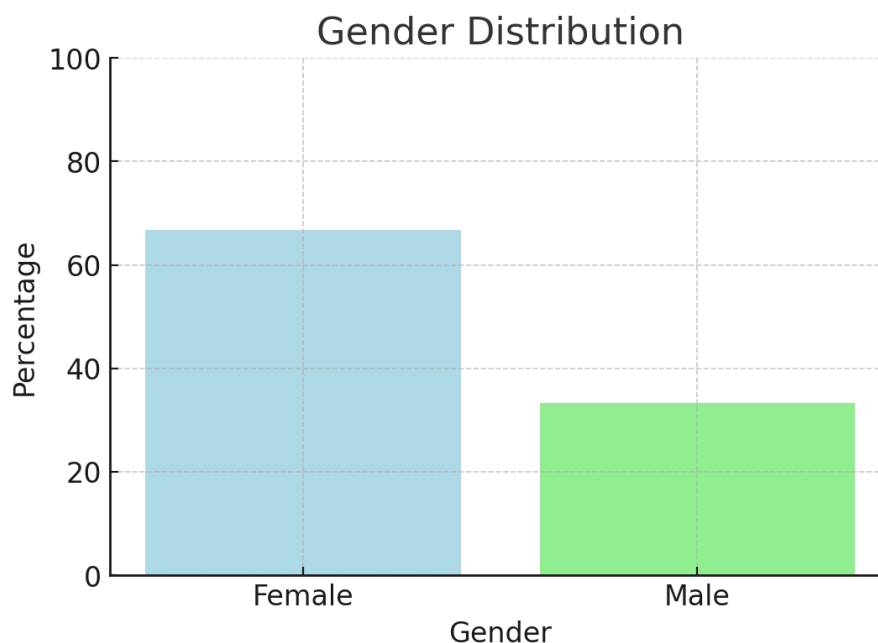130   with a higher prevalence of female patients.

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135   **Table-2:Mean Age Table**

Category	Mean Age
Male	70.82
Female	72.91
Overall	72.15

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137 The table shows the mean age of male, female, and overall patients in the study. Female
138 patients have a slightly higher mean age compared to male patients. The overall mean age of
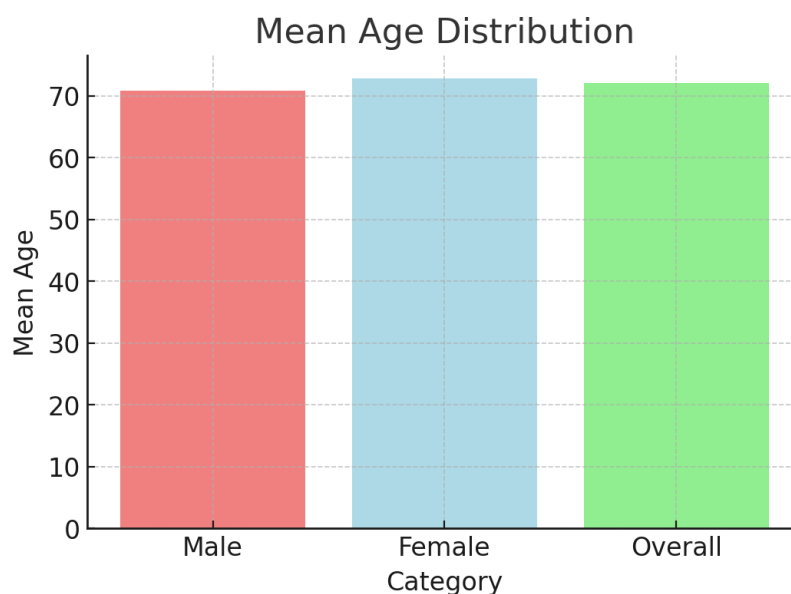139 the patients is approximately 72.15 years.

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Mean Age Distribution

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144 **Table-3: Organism Distribution**

Organism	Percentage
E.coli	55.88%
Klebsiella	32.35%
Morganellamorgani	5.88%
Proteus	5.88%

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146 The organism distribution table presents the percentage of different organisms isolated from
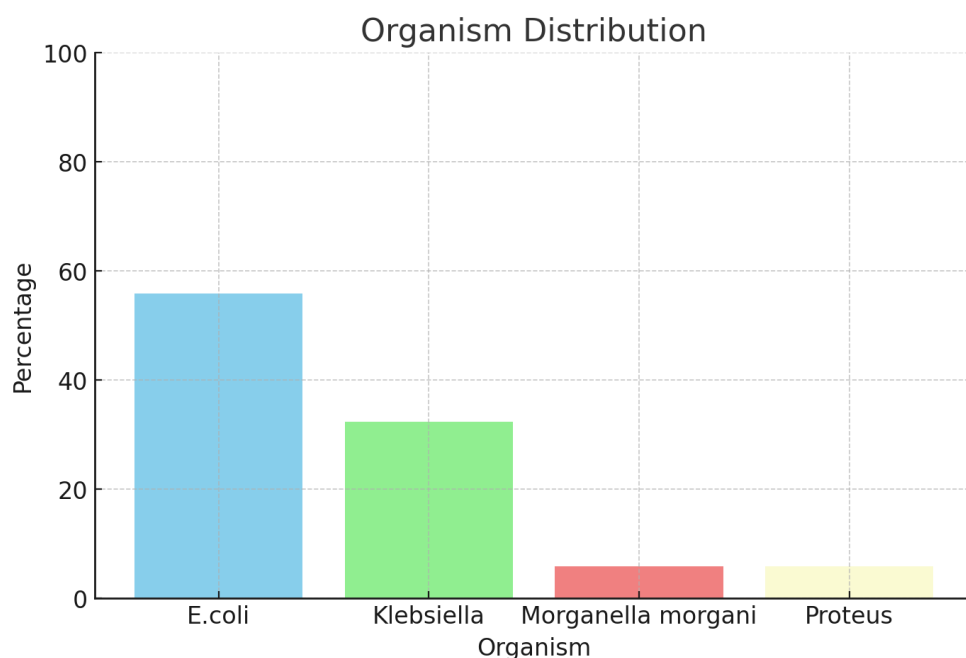147 the patients, with E. coli being the most common.

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Table-4: Resistance Percentage of Enterobacteriaceae antibiotics among Male Diabetic patients

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Antibiotic	Resistance Percentage
Amikacin	63.64%
Amoxicillin-Clavulanic acid	90.91%
Ampicillin	90.91%
Ciprofloxacin	100.00%
Cefixime	90.91%
Ceftriaxone	81.82%
Ertapenem	36.36%
Gentamicin	36.36%
Nitrofurantoin	63.64%
Piperacillin/Tazobactam	63.64%
Trimethoprim/Sulfamethoxazole	72.73%
Cephalothin	90.91%
Levofloxacin	9.09%

Cefoxitin	0.00%

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The male resistance percentage table indicates the percentage of male patients showing resistance to each antibiotic, highlighting high resistance rates to most antibiotics except Levofloxacin and Cefoxitin
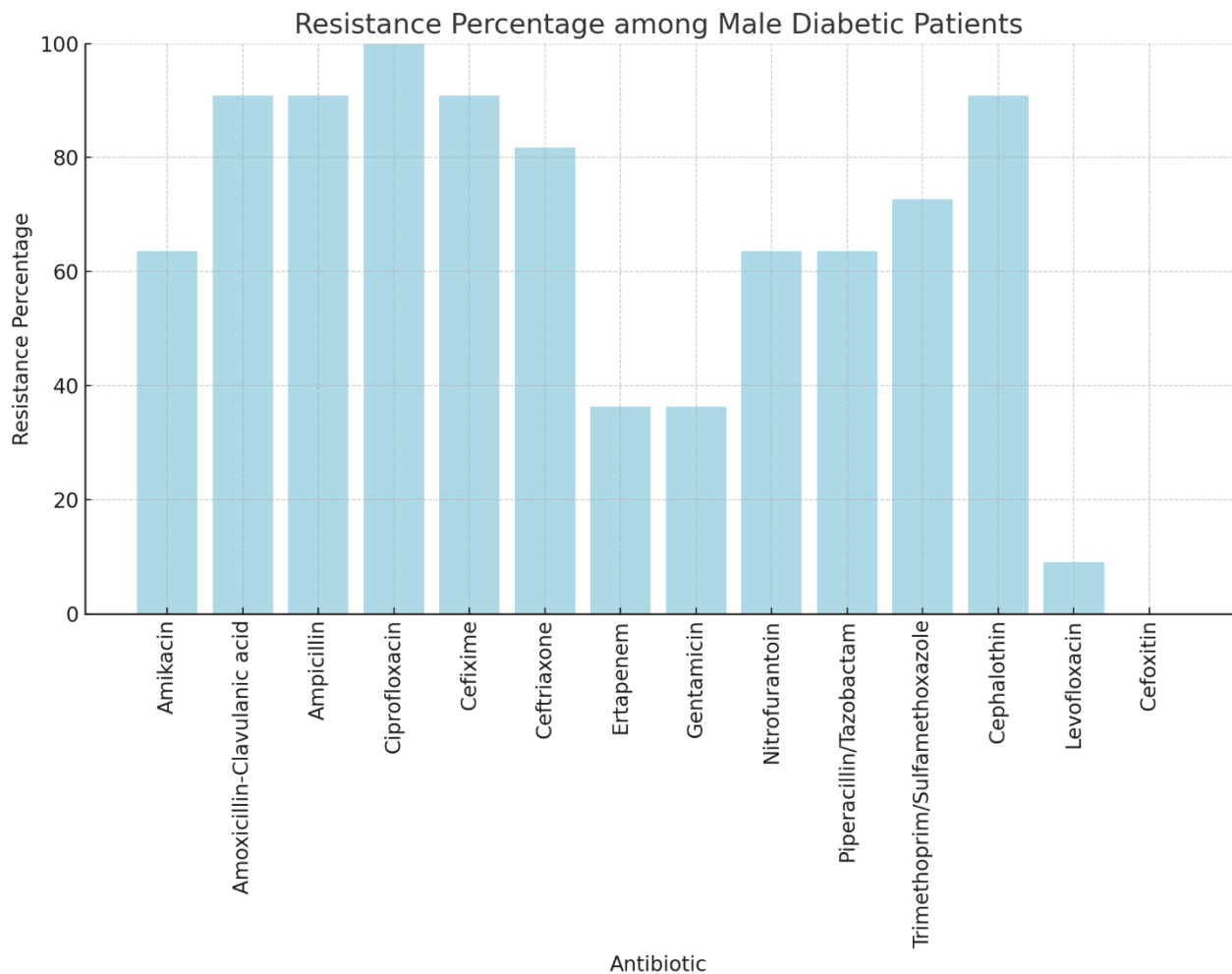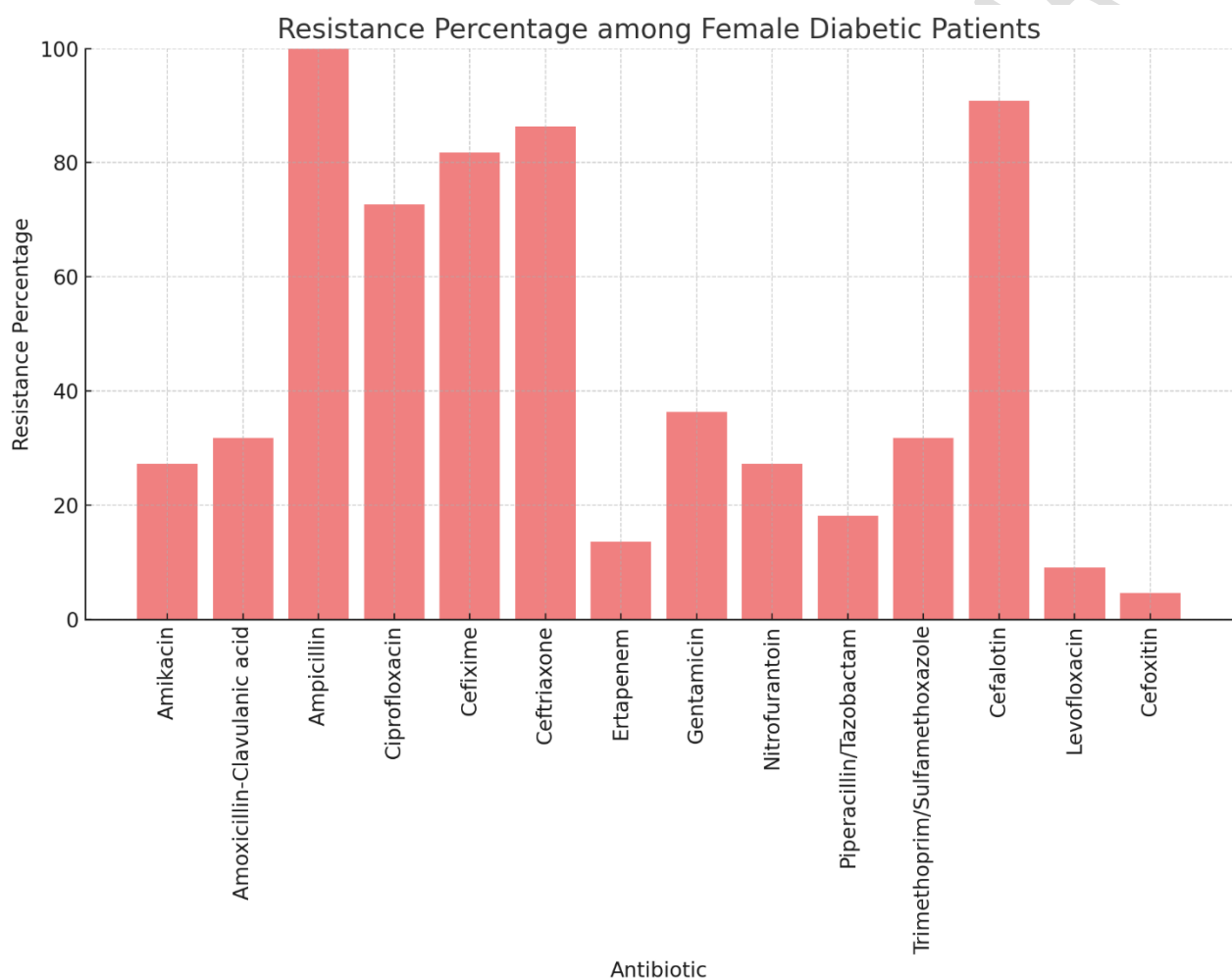

Resistance Percentage among Male Diabetic Patients

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Table-5: Resistance Percentage of Enterobacteriaceae to antibiotics among Female Diabetic patients

Antibiotic	Resistance Percentage
Amikacin	27.27%
Amoxicillin-Clavulanic acid	31.82%
Ampicillin	100.00%
Ciprofloxacin	72.73%
Cefixime	81.82%
Ceftriaxone	86.36%
Ertapenem	13.64%
Gentamicin	36.36%

Nitrofurantoin	27.27%
Piperacillin/Tazobactam	18.18%
Trimethoprim/Sulfamethoxazole	31.82%
Cefalotin	90.91%
Levofloxacin	9.09%
Cefoxinin	4.55%

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The female resistance percentage table indicates the percentage of female patients showing resistance to each antibiotic, with Ampicillin showing the highest resistance, followed by Cefixime and Ceftriaxone.

Resistance Percentage among Female Diabetic Patients

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Table-6: Comparison of Resistance percentage of Enterobacteriaceae to antibiotics among Male and Female diabetic patients"

Antibiotic	Male Resistance %	Female Resistance %	P-value	Significant Difference

Amikacin	63.64%	27.27%	0.1015	No
Amoxicillin-Clavulanic acid	**90.91%**	**31.82%**	**0.0046**	**Yes**
Ampicillin	90.91%	100.00%	0.7196	No
Ciprofloxacin	100.00%	72.73%	0.151	No
Cefixime	90.91%	81.82%	0.8637	No
Ceftriaxone	81.82%	86.36%	1	No
Ertapenem	36.36%	13.64%	0.292	No
Gentamicin	36.36%	36.36%	1	No
Nitrofurantoin	63.64%	27.27%	0.1015	No
Piperacillin/Tazobactam	**63.64%**	**18.18%**	**0.0265**	**Yes**
Trimethoprim/Sulfamethoxazole	72.73%	31.82%	0.0637	No
Cefalotin	90.91%	90.91%	1	No
Levofloxacin	9.09%	9.09%	1	No
Cefoxinin	0.00%	4.55%	1	No

Significant gender-based differences in antibiotic resistance were observed for **Amoxicillin-Clavulanic acid** and **Piperacillin/Tazobactam**, with males showing higher resistance.

For most other antibiotics, no statistically significant differences in resistance were found between male and female patients.

Comparison of Resistance Percentage between Male and Female Diabetic Patients

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Discussion

188 The study was conducted to determine the burden of urinary tract infections (UTIs) caused by
189 multi drug resistant (MDR) Enterobacteriaceae in elderly diabetic patients and compare the
190 resistance patterns in males and females. Results: MDR Enterobacteriaceae are highly
191 prevalent, with substantial gender-associated antibiotic resistance patterns.
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193 Escherichia coli 55.88% and Klebsiella species 32.35% were the most common pathogens
194 identified, which are also in agreement with other studies carried out in India. Numerous
195 studies have cited E. coli consistently as the predominant uropathogen responsible for
196 community-acquired and hospital-acquired UTIs .This is corroborated by the study conducted
197 by Niranjan and Malini (2014), which also found a high prevalence of E. coli among UTI
198 patients in a tertiary care hospital in Puducherry, India [15].The resistance patterns observed
199 in this study are concerning. Male patients exhibited high resistance rates to several
200 antibiotics, including ciprofloxacin (100%), amoxicillin-clavulanic acid (90.91%), and
201 cefixime (90.91%). Similarly, female patients showed high resistance to ampicillin (100%)
202 and ceftriaxone (86.36%). The high resistance rates to ciprofloxacin and ceftriaxone have

also been reported in other Indian studies, indicating a widespread issue of antibiotic resistance among UTI pathogens in diabetic patients [16,17] .

Significant gender-based differences were observed in resistance to amoxicillin-clavulanic acid and piperacillin/tazobactam, with males showing higher resistance. This difference may be attributed to various factors, including differences in healthcare-seeking behavior, antibiotic usage patterns, and physiological differences between genders. A study by Gupta et al. (2014) highlighted similar gender differences in antibiotic resistance, emphasizing the need for gender-specific treatment strategies [18] .

The high prevalence of MDR Enterobacteriaceae in this study underscores the urgent need for effective antibiotic stewardship programs. Reducing the inappropriate use of antibiotics and promoting adherence to treatment guidelines are crucial steps in combating antibiotic resistance. This is particularly important in managing UTIs in diabetic patients, who are more susceptible to infections due to compromised immune systems [19,20].

Furthermore, the study highlights the importance of continuous surveillance of antibiotic resistance patterns. Regular monitoring can help in updating treatment protocols and ensuring the use of effective antibiotics. A study by Mathai et al. (2008) emphasized the need for local antimicrobial guidelines to address the specific resistance patterns observed in different regions of India [21].

Limitations of the study

In conclusion, this study reveals a high prevalence of MDR Enterobacteriaceae among elderly diabetic patients with UTIs, with significant gender-based differences in antibiotic resistance. The findings underscore the need for tailored treatment strategies, effective antibiotic stewardship programs, and continuous surveillance to manage and mitigate the impact of antibiotic resistance. Further research is needed to explore the underlying factors contributing to gender differences in antibiotic resistance and to develop targeted interventions.

Conclusion

The study concludes that there is a high prevalence of multidrug-resistant (MDR) Enterobacteriaceae among elderly diabetic patients with urinary tract infections (UTIs) in Bangalore, Karnataka. The most common pathogens identified were Escherichia coli (55.88%) and Klebsiella species (32.35%). Significant gender-based differences were observed in antibiotic resistance, with male patients showing higher resistance to certain antibiotics, including amoxicillin-clavulanic acid and piperacillin/tazobactam. These findings emphasize the need for gender-specific treatment strategies and the implementation of effective antibiotic stewardship programs to combat antibiotic resistance.

Furthermore, continuous surveillance of antibiotic resistance patterns is crucial for updating treatment protocols and ensuring the efficacy of antibiotics used in managing UTIs in diabetic patients. The study highlights the importance of reducing inappropriate antibiotic use

and promoting adherence to treatment guidelines to mitigate the impact of antibiotic resistance.

Further research is needed to explore the underlying factors contributing to gender differences in antibiotic resistance and to develop targeted interventions for managing UTIs in diabetic patients.

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