Original Article

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A comparative analysis of multidrug-resistant *Escherichia coli* in urinary tract infections among males and females (2022–2023)

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ABSTRACT

Background: Uropathogenic *Escherichia coli* (UPEC) is a primary cause of urinary tract infections (UTIs) globally. The increasing antibiotic resistance of UPEC strains poses a significant challenge for treatment in countries like Iraq. **Aim**: The study aims to evaluate antimicrobial resistance patterns of *Escherichia coli* (*E. coli*) among UTI patients, considering age and sex, and to compare these findings with data from other geographical locations**. Methods**: Our study investigated antibiotic resistance patterns among *E. coli* strains responsible for UTIs in patients at Karbala Teaching Hospital for Children, Iraq. We specifically examined age and sex differences. Data on 144 *E. coli* isolates were collected and analyzed for their susceptibility to six antibiotics from January 1, 2022, to December 31, 2023. **Results**: There were no statistically significant sex-based differences in antibiotic resistance. Ceftriaxone (76%) and nalidixic acid (67%) demonstrated the highest resistance rates among the tested antibiotics in both sexes. In contrast, amikacin (91%) and gentamicin (60%) exhibited higher sensitivity rates compared to other antibiotics. A general trend of increasing antibiotic resistance with age was evident, particularly pronounced for nalidixic acid and ceftriaxone. **Conclusion**: Amikacin consistently demonstrated relatively low resistance rates across all age groups. Infants under one year of age displayed heightened susceptibility to certain antibiotics, as reflected in lower resistance rates. Conversely, nalidixic acid and ceftriaxone exhibited notably elevated resistance rates across all age groups.

Keywords: urinary tract infection, UPEC, multidrug resistance, antibiotic sensitivity, antibiotic resistance

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INTRODUCTION

Urinary tract infections (UTIs) are among the most prevalent bacterial infections, impacting approximately 40% of women at some point in their lives.[1] The prevalence of UTIs is influenced by age and sex, with women exhibiting a higher incidence across all age groups. In particular, sexually active women in their twenties and postmenopausal women over 60 are at increased risk of UTIs.[2] Despite both sexes being susceptible to the infection, women are more vulnerable than men due to their anatomy and reproductive physiology.[3] UTIs can be caused by both gram-negative and gram-positive species and are categorized as either uncomplicated or complicated. This poses a severe public health concern, particularly with the emergence of

multidrug-resistant (MDR) strains.[4] *Escherichia coli* (*E. coli*) is the primary causative agent of UTIs, accounting for 80 to 90% of community-acquired infections and 30 to 50% of hospital-acquired (nosocomial) infections.[5] Certain *E. coli* strains, known as uropathogenic *E. coli* (UPEC), have adapted to thrive in the urinary tract's challenging environment. Infections caused by UPEC can progress to bloodstream infections, which can lead to potentially fatal outcomes.[6] These UPEC strains possess various virulence factors that facilitate infection, such as adhesins, toxins, and mechanisms, to evade host defenses and systems for iron acquisition.[7] Excessive and inappropriate use of antimicrobials is a primary driver of the emergence of MDR uropathogenic bacteria.[8] Antibiotic resistance patterns vary significantly between countries, underscoring the importance of early diagnosis and appropriate antibiotic therapy for managing UTIs and preventing severe outcomes such as mortality.[9]

The objective of this study was to define the antimicrobial resistance patterns of *E. coli* in UTIs, analyzing the impact of age and sex. The resulting data will be compared with those from diverse geographical locations to identify potential trends and variations.

MATERIALS AND METHODS

A cross-sectional study was performed at the Microbiology Laboratory of Karbala Teaching Hospital for Children in Iraq. Data on antimicrobial susceptibility testing (AST) results for *E. coli*-positive urine samples and clinically suspected UTI cases were collected. The analysis focused on six commonly used antibiotics between January 1, 2022, to December 31, 2023. This study was restricted to data collection and analysis, with no direct patient contact involved. Ethics approval was obtained from the Karbala Health Directorate, number 3110, on October 23, 2023.

Data on antibiotic susceptibilities was gathered for 144 *E. coli* isolates against six different antibiotic discs (Oxoid, UK) through the standard disk diffusion technique recommended by the Clinical and Laboratory Standards Institute (CLSI) using the Kirby–Bauer disk diffusion test. The antibiotic concentrations were as follows: ceftriaxone (30 µg), nalidixic acid (30 µg), ciprofloxacin (5 µg), levofloxacin (5 µg), gentamicin (10 µg), and amikacin (30 µg). MDR was defined as resistance to at least three antimicrobial classes, as per the referenced guideline.[10] Cases with inconclusive *E. coli* diagnoses in urine samples or missing data for any specified antibiotics were excluded from the study. Data was conducted using the Statistical Package for Social Science (SPSS) version 24 (SPSS Inc., Chicago, IL, USA), utilizing frequency distribution, cross-tabulation, Fisher exact test, pie chart, and bar chart for the statistical estimation of the variables.

RESULTS

The sex distribution among the study data is represented in Figure 1. A total of 144 urine samples results were collected from patients suspected of UTIs across varying age groups and sex to examine antibiotic resistance patterns. Of these, 72% (n = 105) were from female patients and 28% (n = 39) were from male patients, resulting in a male-to-female ratio of approximately 1: 2.7.

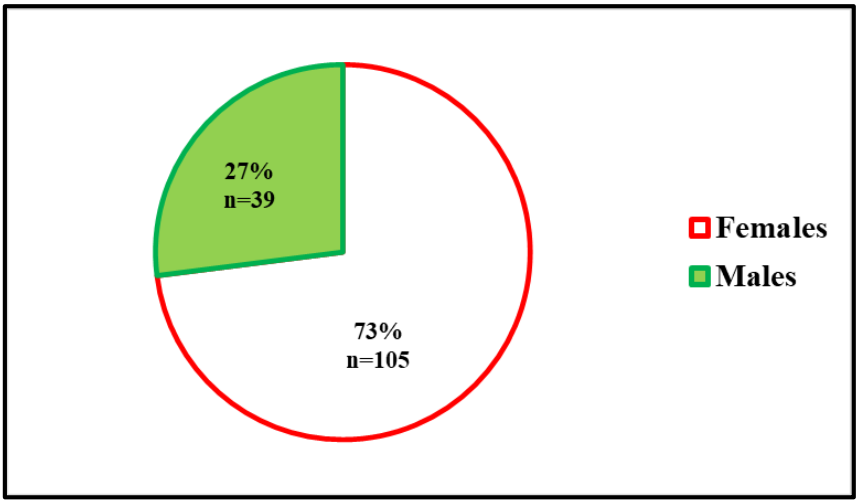

Figure 1: Pie chart shows the sex distribution of male and female patients.

Figure 2 illustrates the sex distribution of UTI patients according to age category in a bar chart, indicating the frequency of individuals within each group. The data is categorized into four age groups: < 1, 1–5, 6–10, and 10+ years. The highest frequency of both males and females is observed in the 6–10 age group. While the female population is higher across all age groups, the disparity is more pronounced in the younger age groups.

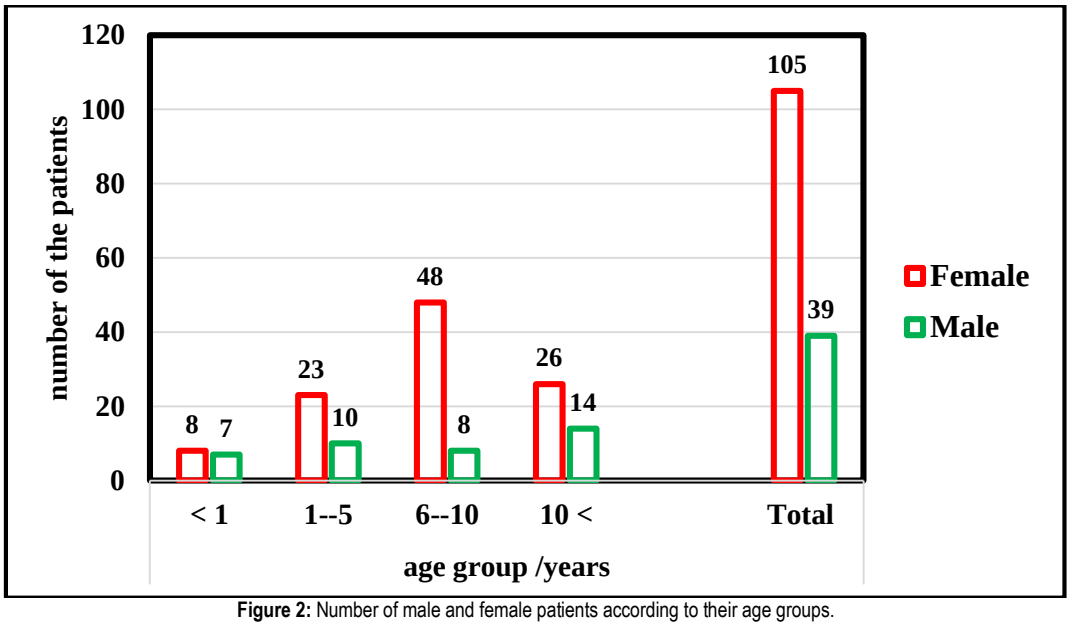

Figure 2: Number of male and female patients according to their age groups.

Figure 3 presents a comparison of antibiotic resistance patterns for six different antibiotics: amikacin, ciprofloxacin, gentamycin, levofloxacin, nalidixic acid, and ceftriaxone. Ceftriaxone exhibited the highest resistance rate at 76%, followed by nalidixic acid at 66%, levofloxacin at 43%, gentamycin at 40%, and amikacin at 9%, which showed the lowest resistance rate. UPEC sensitivity was highest rate to amikacin (91%) and gentamycin (60%) compared to the other antibiotics.

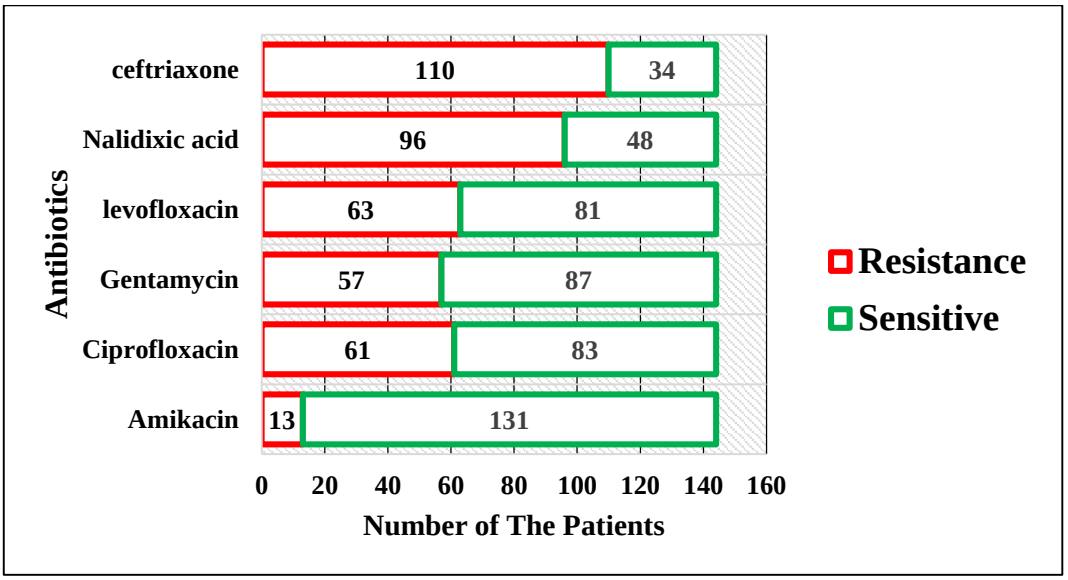

Figure 3. The number of resistance and sensitivity patterns of antibiotics against UPEC.

Table 1 displays data representing antibiotic resistance patterns among different age groups and the antibiotics included in the study. The data is categorized by age group: < 1, 1–5, 6–10, and 10+. For each antibiotic, the number of resistant (R) and sensitive (S) cases is provided, along with their respective percentages and total count for each age group.

Among the 144 isolates analyzed, 5% (n = 7) were found to be resistant to all six antibiotics, while 10% (n = 14) were found sensitive to all six antibiotics. Moreover, 47% (n = 67) were found resistant to three or more classes of antibiotics, classifying them as MDR. *E. coli* exhibited the most resistance to ceftriaxone (76%), followed by nalidixic acid (67%) and levofloxacin (44%). Conversely, *E. coli* demonstrated greater sensitivity to amikacin (91%), gentamicin (60%), and ciprofloxacin (58%). The 6–10 age group showed the highest resistance pattern, followed by other age categories among the patients.

Table 1: Antibiotic susceptibility pattern of UPEC according to patient age group

Antibiotics	Age group / years				Total
	< 1	1–5	6–10	> 10	
	N (%)	N (%)	N (%)	N (%)	N (%)
Amikacin	**1 (8)**	**3 (23)**	**6 (46)**	**3 (23)**	**13 (9)**
	14 (11)	30 (23)	50 (38)	37 (28)	131 (91)
Ciprofloxacin	**10 (16)**	**12 (20)**	**28 (46)**	**11 (18)**	**61 (42)**
	5 (6)	21 (26)	28 (32)	29 (36)	83 (58)
Gentamycin	**6 (11)**	**14 (25)**	**25 (44)**	**12 (21)**	**57 (40)**
	9 (10)	19 (22)	31 (36)	28 (32)	87 (60)
Levofloxacin	**10 (16)**	**14 (22)**	**28 (44)**	**11 (17)**	**63 (44)**
	5 (6)	19 (24)	28 (33)	29 (37)	81 (56)
Nalidixic acid	**15 (16)**	**22 (23)**	**40 (42)**	**19 (20)**	**96 (67)**
	0 (0)	11 (23)	16 (33)	21 (44)	48 (33)
Ceftriaxone	**14 (13)**	**28 (25)**	**39 (35)**	**29 (26)**	**110 (76)**
	1 (3)	5 (15)	17 (50)	11 (32)	34 (24)

Note: Bolded cells represent the resistance of antibiotics

In terms of gender differences, nalidixic acid (74%) and ceftriaxone (79%) demonstrated the highest resistance rates in both sexes. On the other hand, amikacin (92%) and gentamycin (64%) exhibited higher sensitivity rates compared to other antibiotics.

Table 2: Antibiotic susceptibility pattern of *E. coli* in male and female patients.

Antibiotics	Sex			p-value*
	Male	Female	Total	
	n (%)	n (%)	n (%)	
Amikacin	**3 (8)**	**10 (10)**	**13 (9)**	1
	36 (92)	95 (90)	131 (91)	
Ciprofloxacin	**15 (38)**	**46 (44)**	**61 (42)**	0.705
	24 (62)	59 (56)	83 (58)	
Gentamycin	**14 (36)**	**43 (41)**	**57 (40)**	0.702
	25 (64)	62 (59)	87 (60)	
Levofloxacin	**16 (41)**	**47 (45)**	**63 (44)**	0.701
	23 (59)	58 (55)	81 (56)	
Nalidixic acid	**29 (74)**	**67 (64)**	**96 (67)**	0.302
	10 (26)	38 (36)	48 (33)	
Ceftriaxone	**31 (79)**	**79 (75)**	**110 (76)**	0.664
	8 (21)	26 (25)	34 (24)	

Notes: (n) - indicates the number of isolates *Using Fisher Exact test because expected frequency < 0.05. Bolded cells represent the resistance of antibiotics

DISCUSSION

UTIs are the second most common infectious disease, affecting over 150 million people worldwide annually.[11] MDR UPEC is strongly associated with recurrent, complicated, and persistent UTIs.[12] The rise of antimicrobial resistance in UPEC has compromised the effectiveness of current treatment regimens, leading to increased treatment failures and persistent infections.[13] Most patients in this study were female (73%), with males accounting for 27%. This finding is consistent with the established knowledge that women are more susceptible to developing UTIs compared to men.[14] In this context, our findings are highly correlated with Laswad, Grigoryan et al., and Momtaz et al.[15-17] Anatomical variances between males and females, particularly the shorter female urethra and its proximity to the anus, create a more conducive environment for bacterial growth, thereby increasing the incidence of UTIs in women. Additionally, the antibacterial properties of prostate secretions in males provide some degree of protection against UTIs.[18-20]

Different epidemiological and etiological characteristics of UTIs may vary depending on age and gender.[21] A study discovered that individuals above 6 years were more prevalent in the study site, a result that aligns with Huang[22] and contrasts with Nguyen Sn.[23]

Amikacin, a widely used aminoglycoside antibiotic derived from kanamycin, has a short half-life of approximately two to three hours.[24] There is a general trend towards increased amikacin resistance with increasing age, with the 6–10 age group exhibiting the highest percentage of resistance (46%) and the < 1 age group demonstrating the lowest percentage of resistance (8%), in line with Kulkarni et al.'s study.[25] It is also worth noting that the majority of patients across all age groups are sensitive to amikacin.

Amikacin exhibits a higher overall sensitivity rate in both males and females, with no statistically significant difference in amikacin resistance between males and females. This finding is consistent with Abduzaimovic et al., Ali et al., and Yasmeen et al.'s studies.[26-28]

Ciprofloxacin, an antibiotic agent belonging to the fluoroquinolone class, is used to treat bacterial infections like pneumonia and UTIs.[29] There is a clear trend of increasing ciprofloxacin resistance with age, with the highest resistance rate observed in the 6–10 age group (46%), followed by the 10+ age group (18%). The < 1 and 1–5 age groups exhibit lower resistance rates to ciprofloxacin, suggesting higher susceptibility to this antibiotic in younger patients; this result is supported by Kulkarni et al.'s study.[25] There is no statistically significant difference in ciprofloxacin resistance between males and female, a result that corresponds with Jadoon et al.'s study.[30]

One aminoglycoside antibiotic commonly used to treat a variety of gram-negative infections is gentamicin.[31] Research indicates a clear orientation of increasing gentamicin resistance with advancing age. The highest resistance rate is observed in the 6–10 age group (44%), followed by the 10+ age group (21%). The < 1 age group demonstrates the lowest resistance rate (11%), suggesting a higher susceptibility to gentamicin. There is no statistically significant difference in gentamicin resistance between males and females. Although not statistically significant, the percentage of resistant cases is slightly higher in females (41%) compared to males (36%) when compared with Abduzaimovic et al and Hasegan et al.[26,32] but shows a similar trend to Ait-Mimoune N. et al.[33]

Bacterial DNA gyrase and topoisomerase IV are inhibited by levofloxacin, the L-isoform of the fluoroquinolone antibacterial agent ofloxacin.(34) Resistance of levofloxacin is highest in the 6–10 age group (44%) and sensitivity is highest in the 10+ age group (37%). The < 1 age group has the lowest resistance and sensitivity percentages in the dataset. The resistance to levofloxacin is slightly higher in females (45%) compared to males (41%). Additionally, sensitivity is slightly higher in males (59%) compared to females (55%). The p-value of 0.701 suggests that there is no statistically significant difference in resistance and sensitivity patterns between males and females when compared to Singh Randhir et al.,[35] but aligns with findings from Huang et al.[22]

Nalidixic acid, the first synthetic quinolone that inhibits bacterial DNA synthesis by interfering with DNA gyrase—an enzyme essential for DNA replication—results in rapid bacterial cell death.[35] Resistance to nalidixic acid is the highest in the 6–10 age group (42%), but sensitivity is the highest in the 10+ age group (44%), with no sensitivity observed in the < 1 age group. The percentage of resistant cases is lower in females (64%) compared to males (74%), although this difference is not statistically significant (p-value = 0.302), in comparison to Sharma et al.[36] but aligns closely with Kulkarni et al.'s study.[25]

Ceftriaxone is a third-generation parenteral cephalosporin with a long elimination half-life that allows once-daily administration.[37] It exhibits a notable trend of increasing resistance with advancing age. The highest resistance rate is observed in the 6–10 age group (35%), followed by the 10+ age group (26%). The < 1 age group exhibits the lowest resistance rate (13%), suggesting higher susceptibility to ceftriaxone. There is no statistically significant difference in ceftriaxone resistance between males and females, with both exhibiting relatively high resistance rates to the antibiotic compared to the studies conducted by Hossain et al., Fatima et a., and Lin et al.[38-40]

Numerous factors contribute to the high rate of antibiotic resistance in children aged six to 10. These factors include frequent infections leading to increased antibiotic use, overprescription, incomplete antibiotic courses, and the spread of resistant bacteria in communal settings like schools and playgrounds. Children's developing immune systems may also increase their susceptibility to infections, leading to increased antibiotic use.

Several factors contribute to the development and spread of antibiotic resistance. These include overuse and misuse of antibiotics through inappropriate prescribing, incomplete treatment courses, and excessive hospital use. Additionally, the natural ability of bacteria to mutate and develop resistance plays a crucial role. Other contributing factors are the unregulated access to antibiotics in some regions, ineffective

infection control practices, and the use of antibiotics in livestock production.[41]

CONCLUSIONS

The data reveals a high prevalence of antibiotic resistance among the study population, particularly among children aged six to 10 years, with notable resistance observed for nalidixic acid and ceftriaxone. Interestingly, no significant difference in resistance rates between males and females was observed for any of the antibiotics studied. Furthermore, there is a clear trend of increasing resistance with age across most antibiotics, with older age groups exhibiting higher resistance rates.

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