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Emerging Threats in Urinary Tract Infections: Revealing Antimicrobial Susceptibility and Resistance trends of Developed Extended-Spectrum Beta-Lactamases Producing E. coli

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ABSTRACT

Background: The main aim of the study was to identify the development of antimicrobial susceptibility and resistance in Extended-Spectrum Beta-Lactamase (ESBL) producing E. coli. that cause UTI and to determine suitable antibiotic choices in the said organisms.
Methodology: It was a Cross-sectional retrospective study, where 200 clinical uropathogenic E. coli isolates were picked and assessed antimicrobial resistance by the Kirby buyer method and confirmation was performed using a double disc synergy test to detect ESBN producers.
Findings: The paper illustrates that females (82%), adults (50%), have a high risk of developing such infections because of several changes in the anatomy and behaviours. Imipenem, amikacin, Fosfomycin and tazobactam/piperacillin possess 98.5, 91.0, 84.5 and 86 patterns of sensitivity to E. coli isolates collected and thus can be used as a choice of treatment against UTIs caused by E. coli 46/65 65 E. coli isolates were found to be multidrug-resistant by initial screening of antimicrobial susceptibility test and therefore confirmed to be 60.7.
Conclusion: It was ascertained that although the E. coli has since developed resistance to many of the medicines yet there are a few

antibiotics that can be considered when writing the prescription. These infections are more prevalent among women and adults, and they should be educated adequately to avoid them.

Introduction

UTIs that are acquired within the community are a significant percentage of communicable diseases when considered among various populations (1). These infections are precipitated because E. coli is a common form of infections these days that contrive severe complications on the health of the people(2). These pathogens have been increasing relapse rates as well as high antimicrobial tolerance, thus rapidly increasing the financial burden of these diseases(3).

E. coli is increasingly becoming more antimicrobial tolerant, making medical practitioners hesitant to prescribe orally administered antimicrobials(4). UTIs are treated by administering considerable volumes of oral antibiotics every day in outpatient health care institutions that are focused on the public. In turn, the awareness of the local predisposition facts and figures in relation to E. coli is extremely important in terms of selecting the appropriate empirical antimicrobials. UTIs are most common within the general population and hospital-acquired infections with bacteria and tend to relapse in individuals who lack anatomical or functional aberrations(5). The infections are significant causes of hospitalization and relate to the increasing economic expenses and morbidity and mortality. UTI medical armamentarium may include anything as simple as cystitis to something as deadly as uroseptic shock. UTI is a significant basis of morbidity in infant boys, women of all ages and elderly men(6). Reflective risk that comes with these infections are recurrent relapses, renal destruction in young children, pyelonephritis associated with sepsis, pre-term delivery and issues that are induced by repeated antibiotic use, including increased antibiotic tolerance and Clostridium difficile colitis (7, 8) .The study will establish that; the study will establish the difference between rational and irrational use of antibiotics in recurrent UTIs in the ESBL producing E. Coli strains; and it will offer a guiding framework to the appropriate choice of treatment therapy in UTIs.

Methodology

A retrospective Cross-sectional study was done whereby 200 isolates of E. coli were obtained of urine sample at Dr. Essa laboratory at Karachi in Pakistan. The basis of inclusion of these isolates was under various selection criteria which included Isolates of specimen of patients with known case of UTI's and regardless of gender and ages. The patients who did not have UTI and negative E. coli isolates were not involved in the research. Kirby-Bauer disc diffusion method according to Clinical and Laboratory Standard Guidelines (CLSI) had been used to determine antibiotic susceptibilities. Findings made using antimicrobial sensitivities were further evaluated by a double-disc synergy test to achieve a phenotypic analysis of the ESBL producing isolates where all the isolates that gave zone diameter of 25mm or less with ceftriaxone 27mm or less with cefotaxime and 22mm or less with ceftazidime were selected .There was synergy between amoxicillin/clavulanic acid and third generation (3GC) cephalosporin on Muller Hinton agar. The conducted research follows proper guidelines according to the principles of declaration. Therefore, it was approved through institutional IERB for approval and was approved by the committee with. Ref No. JUW/IERB/PHARM-ARA-015/2022. Data were analysed using Student's Package for Social Sciences SPSS version 21 software, and the results were estimated using frequency comparisons, percentages and the

chi-square test (χ^2) considering $P<0.05$ as statistically significant.

1 **Results:**

This investigation was conducted on 200 uropathogenic isolates of *E. coli*. Initial demographic analysis confirms its presence, mostly in adults, especially among female patients. It was found that >80% female patients were affected as compared to male patients accounting for up to <20%. Adults aged 19-59 years make up almost 50% of isolates, followed by senior adults making up 30% respectively **(Table 1).**

Table 1: Demographic representation of isolates sampled in selected cohort.

Categories		No. of Organisms isolated (N* 200)	Percentages (%)
Gender	Male	30	15%
	Female	170	85%
Age range*	0-12 (child)	30	15%
	13-18 (adolescence)	10	4%
	19-59 (adults)	100	50%
	60 and above (senior adults)	60	30%

Table 2 illustrates a complete demonstration of susceptibility patterns of all isolates and concluded that high resistance patterns were observed among cephalosporins with comparatively high resistance in cefuroxime (65%) followed by cefixime (62.5%), cefotaxime (53%), ceftazidine (52.5%), and ceftriaxone (53%), respectively. Similar patterns were observed among fluoroquinolones, where major resistance was shown by ofloxacin (52.5%), whereas around 50% resistance was shown by anoxacin and ciprofloxacin, respectively. Major resistant patterns were shown against trimethoprim/sulfamethoxazole (64.5%), amoxicillin/clavulanic acid (36.5%), whereas 3% resistance was demonstrated in tazobactam/piperacillin among β-lactam/β-lactamase inhibitor combination drugs. Resistance levels among miscellaneous antibiotics showed satisfactory trends with 2.5% resistance against fosfomycin, followed by 2.5% resistance against amikacin and 0.5% for imipenem.

Table 2: Susceptibilities of clinical E. coli isolates collected in detail, in numbers and percentages.

S.no	Name of Antibiotic	Susceptibility numbers and percentages		
		Resistant	**Intermediate**	**Susceptible**
	Cefuroxime	130 (65 %)	22 (11 %)	48 (24%)
	Cefixime	125 (62.5 %)	3 (1.5 %)	72 (36 %)
	Cefotaxime	106 (53 %)	7 (3.5%)	87 (43.5 %)
	Ceftazidime	105 (52.5 %)	13 (6.5 %)	82 (41.0 %)
	Ceftriaxone	106 (53 %)	6 (3%)	88 (44%)
	Ofloxacin	105 (52.5 %)	20 (10 %)	75 (37.5%)
	Ciprofloxacin	101 (50.5%)	9 (4.5 %)	90 (45 %)
	Enoxacin	101 (50.5%)	9 (4.5 %)	90 (45 %)
	Amoxicillin/ clavulanic acid	73 (36.5%)	39 (19.5 %)	88 (44%)
.	Tazobactam/piperacillin	6 (3%)	22 (11 %)	172 (86 %)
.	Imipenem	1 (0.5%)	2 (1.0%)	197 (98.5%)
.	Fosfomycin	25 (12.5%)	6 (3%)	169 (84.5%)
.	trimethoprim/sulfamethoxazole	129 (64.5%)	3 (1.5 %)	68 (34%)
.	Amikacin	5 (2.5%)	13 (6.5%)	182 (91.0%)

65 isolates were confirmed as ESBL-positive out of 200 and showed major resistance trends against all cephalosporins used for this study with 98% against cefuroxime and cefixime, followed by 97% against cefotaxime and ceftriaxone, and 95% against ceftazidime, respectively. A substantial level of resistance patterns against fluoroquinolones was also observed, with approximately 60% against all three drugs (enoxacin, ciprofloxacin and ofloxacin).

On the other hand, other antibiotics used for this study showed positive susceptibility patterns with 95% sensitivity against imipenem and 94% sensitivity against amikacin, 78% susceptibility against fosfomycin and tazobactam/piperacillin combination. But combination trimethoprim/sulfamethoxazole showed major resistance against ESBL isolates which was 82% which may contribute to its limited use against ESBL-positive urinary tract infections in future. **(Table 3)**

Table 3: The antimicrobial susceptibilities of ESBL positive E. coli isolates in details.

Antibiotics Used	Intermediate Isolates (%)	Susceptible Isolates (%)	Resistant Isolates (%)
Ceftazidime	3 (5%)	0 (0%)	62 (95%)
Cefixime	0 (0%)	1 (2%)	64 (98%)
Ceftriaxone	1 (2%)	1 (2%)	63 (97%)
Cefotaxime	2 (3%)	0 (0%)	63 (97%)
Cefuroxime	0 (0%)	1 (2%)	64 (98%)
Amoxicillin/ clavulanic acid	16 (25%)	21 (32%)	28 (43%)
Tazobactam/piperacillin	10 (15%)	51 (78%)	4 (6%)
Ciprofloxacin	2 (3%)	24 (37%)	39 (60%)
Enoxacin	3 (5%)	23 (35%)	39 (60%)
Ofloxacin	7 (11%)	19 (29%)	39 (60%)
Amikacin	2 (3%)	61 (94%)	2 (3%)
Fosfomycin	1 (2%)	51 (78%)	13 (20%)
Imipenem	2 (3%)	62 (95%)	1 (2%)
Trimethoprim/sulfamethoxazole	0 (0%)	12 (18%)	53 (82%)

Figure 1 highlights that, 46% isolates showed multi-drug-resistant strains, as these showed resistance against three antibiotics of three different classes. >75% of multidrug resistant isolates were found in female patients and >40% belongs to adult patients, respectively.
These observations reflect a considerable MDR burden within the population most susceptible to urinary tract infections.

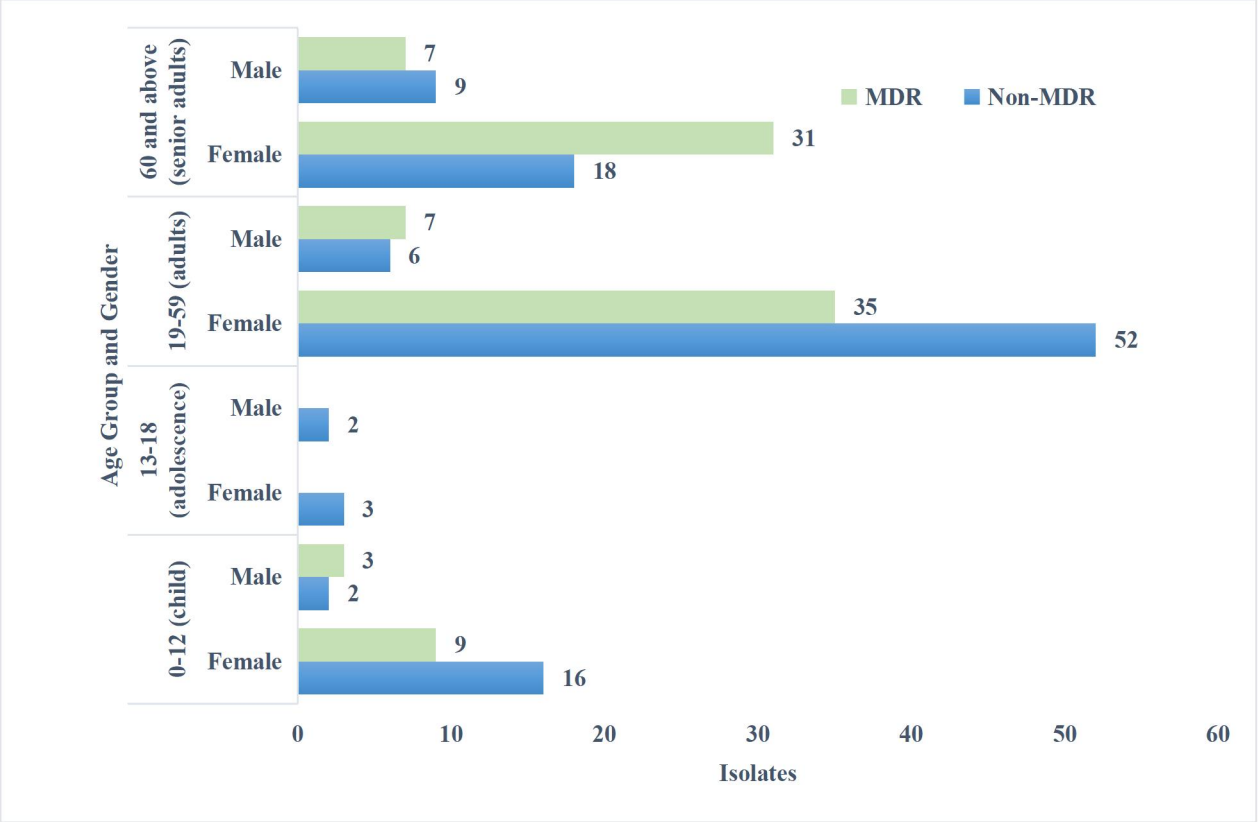

Figure 1: Multidrug profile prevalence on Gender and Age

Table 4 demonstrate a complete picture of associations among multiple factors by chi-square analysis and found to have a statistically significant relationship among the presence of multi-drug resistance strains and ESBL – producers confirming that all isolates once confirm to be the multidrug resistant are ESBL-producers. A non-significant association between ESBL-presence with age group (p-value 0.17) and gender (p-value 0.359) reveals negative association of ESBL strains among specific gender and age groups and can occur irrespective of gender and age group. Also, **Figure 2** gives a complete picture of ESBL-prevalence among gender and age groups and were found majorly in female adults and female senior adults respectively. **Figure 3** illustrates positive results of double-disc synergy test.

Table 4: Significant relationship between Age, Gender and Multidrug resistant profile and ESBL/Non-ESBL producing Uropathogens.

Characteristics	Non ESBL n=42 (%)	ESBL n=65 (%)	*p-value*
Age			
0-12 (child)	6 (5.6%)	7 (6.5%)	0.17
13-18 (adolescence)	0 (0%)	2 (1.9%)	
19-59 (adults)	20 (19%)	32 (30%)	
60 and above (senior adults)	16 (15%)	24 (22.4%)	
Gender			
Male	9 (8.4%)	12 (11.2%)	0.359
Female	33 (30.8%)	53 (50%)	

Multi Drug Resistance			
MDR	29 (27.1%)	46 (43%)	**0.000***
non-MDR	13 (12.1%)	19 (17.7%)	

P-value <0.05 statistically significant

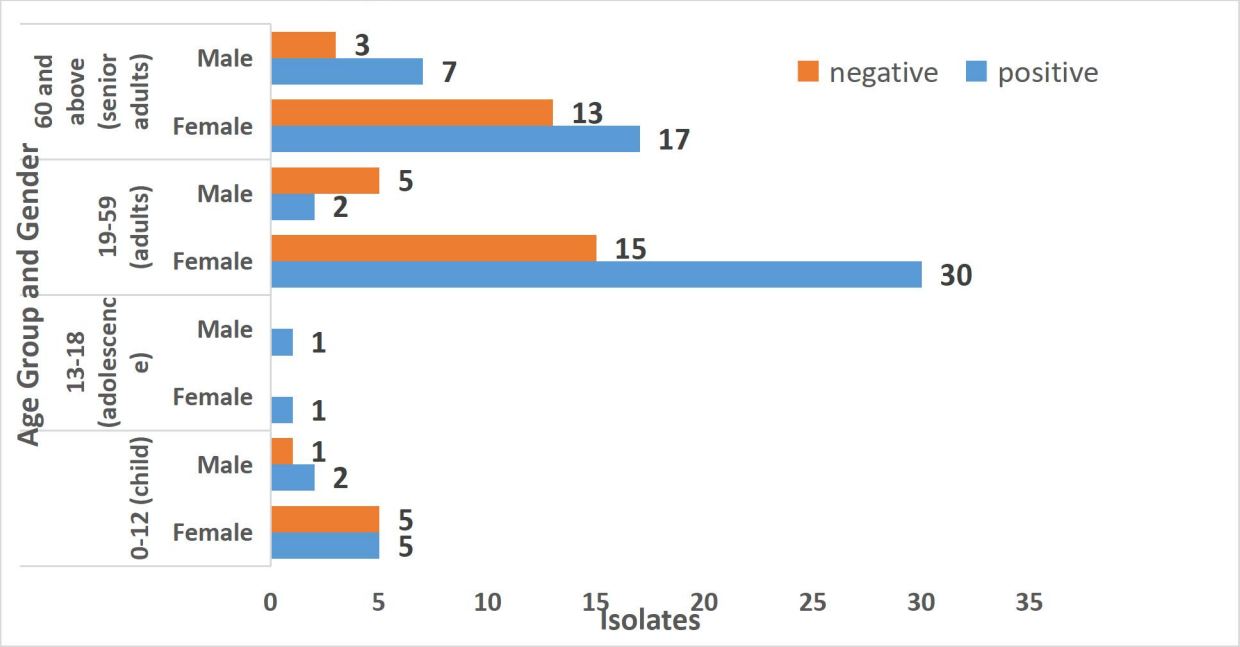

Figure 2: ESBL/non-ESBL profile Prevalence in Gender and Age

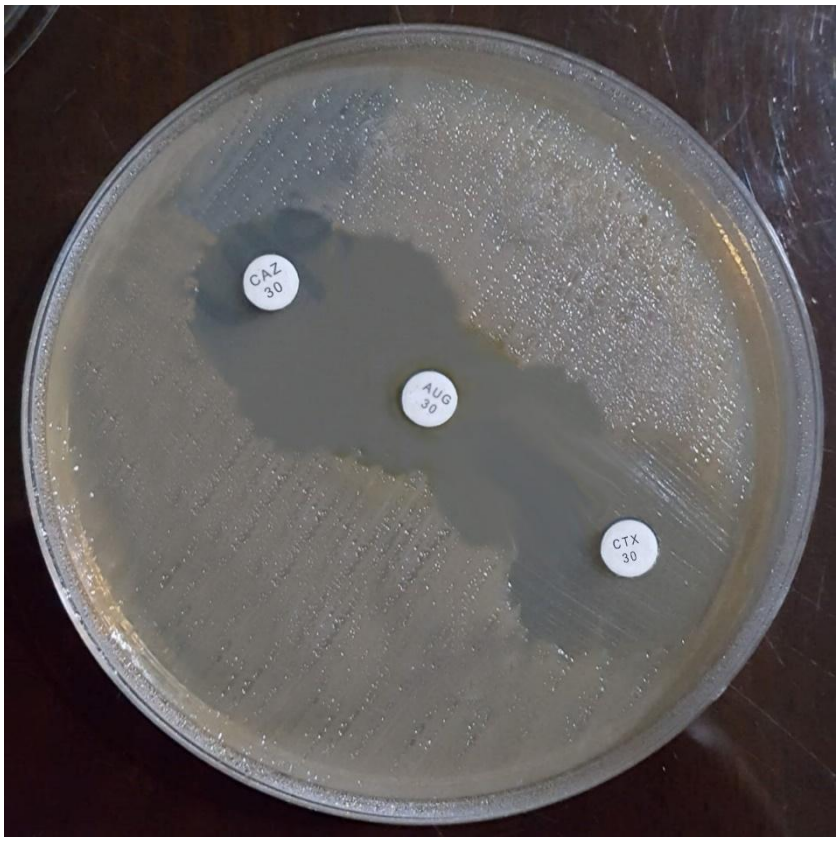

Figure 3: Double Disc Synergy Test has a positive result

Discussion

This study presents a detailed insight about development of antimicrobial resistance by *E. coli* developed against multiple antibiotics in urinary tract infections, its prevalence among different gender and age groups, and most significantly occurrence of multidrug resistance and ESBL-producers respectively. This investigation confirms the prevalence of these infections in 82% females because of multiple anatomic and behavioural factors such as hormonal fluctuations, shorter urethra, etc. Also, greater patterns were observed among adults and senior adults, which may be due to lifestyle, environmental factors, comorbidities, etc. adolescence and children forms minor portion in this study.

Focussing on antimicrobial resistance trends, major resistance patterns were observed among the first line agents against *E. coli*-induced UTI's, (third generation cephalosporins and fluoroquinolones). Resistance patterns against >50% isolates were observed among ceftriaxone, cefixime, ceftazidime, cefotaxime, and cefuroxime. Also, ofloxacin, ciprofloxacin, and enoxacin had similar resistance patterns(9). Causes of these drastic changes include but are not limited to the availability of prescription-free accessibility, excessive prescribing of antibiotics, and above all, self-medication, which will continue to raise disturbing issues in the future. The result of the prevalence and behaviour of ESBL-producing E. coli in the study on the subject also points out the complexity of the issue of managing UTIs in clinical environments. It was noted that all the third-generation cephalosporins were resisted in more than 95 percent in the analysis of the 65 ESBL-positive isolates and it is consistent with the enzymatic activity of the ESBLs that specifically avail itself to the β-lactam antibiotics. Moreover, the resistance of ESBL isolates to commonly used fluoroquinolones was observed in 60 percent of isolates, which revealed that diverse resistance factors may coexist in the same isolates. Multidrug resistance is a serious threat to the effectiveness of treatment that contributes to an increased risk of unsuccessful outcomes, prolonged morbidity, and growing medical costs(10). The high level of statistical association measured in the case of ESBL production and multidrug resistance patterns as determined in this study highlights the need of specific antimicrobial stewardship measures(11). Nearly half of all isolates were multidrug resistant with a substantial percentage of them falling under the ESBL-producing category(12). This is made possible by the plasmid transmission of resistance genes, which probably contributes to the simultaneous dissemination of ESBL activity with non- -lactam antibiotic resistance. Unless appropriate measures are put in place, such strains may continue to proliferate across the community and the healthcare facilities, making it harder to manage the UTI treatment costs. Based on the trends of resistance above, the study guided us to a series of viable preferable therapeutic option, which remain useful. Amikacin, imipenem and piperacillin - tazobactam proved to be highly effective in treating ESBL as well as non-ESBL isolates, and this reflects their relevance in the treatment of complex or tolerant based infections(13). In simple cases of infections, where fluoroquinolones and cephalosporins resistance is now established, Fosfomycin showed significant sensitivity and might present as a preferred oral agent(14). These findings are concerned with the relevance of culturally informed therapy, especially where an environment with a high incidence of ESBL is situated. The results indicate that there has been significant alteration on the trend of antimicrobial susceptibility whereby the resistance is on the rise and posing a challenge to proper management. The trends point to the critical need of strict antibiotic control, raising awareness of people, and prescribing it carefully. The development of better diagnostic techniques, early culture sensitivity analysis, and effective surveillance mechanisms play a

critical role in reducing the development and spread of tolerant strains.

Conclusion

This research verifies the presence of E. coli as a significant contribute aetiology in the development of urinary tract infections and significant prevalence is recorded in females and adults with high tolerance rate to first line empirical antibiotics (cephalosporins and fluoroquinolones), which restricts their use. The use of evidence-based counselling practices should be put in place because the prevalence of multidrug resistant and ESBL positive strains are on the rise. In addition, sensitisation on antibiotic stewardships should be encouraged at community level and health care facilities as it is a tremendous effect on control of diseases hence, future resistance will be minimized. There is a need to promote continuous monitoring at the community level to defend efficacy of the remaining antibiotics and greater clinical results in the face of augmented load of multidrug and ESBL-positive strains.

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