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Research Article

Prevalence of Esbl-Producing E. Coli in Outpatient Urinary Tract Infections

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ABSTRACT
Background: Extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli represents an emerging threat to antimicrobial therapy in community-onset urinary tract infections (UTIs). Current prevalence data and risk stratification in outpatient populations remain variable across geographic regions, necessitating systematic epidemiological surveillance to guide empirical treatment decisions.
Methods: A cross-sectional observational study was conducted over 18 months (January 2022–June 2023) among outpatients presenting with acute UTI symptoms at a tertiary care hospital in Jaipur, Rajasthan, India. Consecutive symptomatic patients aged ≥18 years with urinalysis positive for pyuria and/or bacteriuria were enrolled (n=412). Midstream clean-catch urine samples were cultured on MacConkey agar; bacterial identification was performed via VITEK 2 automated system. ESBL production was detected using the phenotypic double-disc synergy test with ceftazidime (30 µg) and clavulanic acid (10 µg) according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Molecular confirmation was conducted via polymerase chain reaction (PCR) targeting *bla*CTX-M genes. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for ESBL-positive UTI (α=0.05; 95% confidence intervals reported).
Results: Of 412 symptomatic outpatients, 287 (69.7%) yielded culture-positive results with bacterial counts ≥10^5 CFU/mL. *Escherichia coli* accounted for 221 (77.0%) of positive isolates. Among *E. coli* isolates, 71 (32.1%) were phenotypically confirmed as ESBL producers; molecular analysis confirmed *bla*CTX-M genes in 63 isolates (88.7%), with CTX-M-15 predominating (71.4%). Independent risk factors included prior hospitalization within 6 months (adjusted odds ratio [aOR] 3.18, 95% CI 1.84–5.51, p<0.001), prior cephalosporin exposure (aOR 2.94, 95% CI 1.72–5.03, p<0.001), recurrent UTI history (≥2 episodes/6 months; aOR 2.67, 95% CI 1.51–4.72, p=0.001), and advanced age (≥55 years; aOR 1.89, 95% CI 1.12–3.19, p=0.018). Resistance to fluoroquinolones and trimethoprim-sulfamethoxazole exceeded 75% in ESBL-producers, whereas all isolates remained susceptible to imipenem and meropenem. Clinical cure at day 7 (symptom resolution + negative follow-up culture) was achieved in 94.1% of patients treated with carbapenems versus 71.8% of those receiving empirical fluoroquinolones (p=0.008).
Conclusion: ESBL-producing *E. coli* accounts for nearly one-third of community-onset UTIs in outpatient populations, with epidemiological patterns reflecting prior healthcare exposure and antimicrobial selection pressures. Targeted screening and carbapenem-based therapy directed by rapid culture and susceptibility testing are warranted in high-risk populations to optimize treatment outcomes and curtail inappropriate antibiotic escalation.

Keywords: Extended-Spectrum Beta-Lactamase, Escherichia Coli, Urinary Tract Infection, Antimicrobial Resistance, CTX-M Genes, Outpatient, Risk Factors, Carbapenem.

INTRODUCTION

Urinary tract infection remains one of the most prevalent community-acquired bacterial infections globally, with Escherichia coli responsible for 70–80% of uncomplicated lower urinary tract infections (cystitis) and a substantial proportion of complicated infections, particularly in older adults and immunocompromised populations [1]. The emergence and dissemination of extended-spectrum beta-lactamase (ESBL)-producing E. coli have fundamentally altered the epidemiology and therapeutic paradigm of UTI management, transforming what was once a straightforward infectious disease into a challenge requiring sophisticated microbiology and antimicrobial stewardship [2]. ESBLs are serine beta-lactamases capable of hydrolyzing third- and fourth-generation cephalosporins and aztreonam, yet inhibited by clavulanic acid

and tazobactam, thereby conferring resistance to extended-spectrum agents while retaining susceptibility to carbapenems [3]. The CTX-M family of ESBLs, particularly the blaCTX-M-15 variant, have emerged as the dominant resistance mechanism globally, surpassing the historically prevalent TEM and SHV ESBL types; these genes reside predominantly on transferable plasmids, facilitating rapid horizontal dissemination among Enterobacteriaceae and complicating infection control measures [4], [5].

Global surveillance data reveal marked geographic variability in ESBL-producing E. coli prevalence in UTIs. In the United States and Northern Europe, community-acquired ESBL-positive UTIs represent 4–6% of outpatient infections, whereas rates exceed 25–40% in South Asia, the Middle East, and portions of Africa, reflecting disparities in antimicrobial stewardship, prescription practices, and diagnostic infrastructure [6], [7]. The clinical implications are profound: ESBL-producing organisms exhibit multidrug resistance patterns with high frequencies of co-resistance to fluoroquinolones (56–100%) and trimethoprim-sulfamethoxazole (70–90%), thereby narrowing therapeutic options and necessitating empirical carbapenem use in severe infections or when risk factors for ESBL carriage are present [2], [8]. Carbapenem-sparing strategies have become paramount to prevent further escalation to carbapenem-resistant Enterobacteriaceae (CRE), a public health catastrophe characterized by near-total resistance to beta-lactam agents and mortality rates exceeding 40% in bacteremic infections [9]. Prior studies have identified key epidemiological risk factors for ESBL-positive UTI, including advanced age (≥55 years), female gender, prior hospitalization, recent antimicrobial exposure (particularly cephalosporins and fluoroquinolones), recurrent UTI history, urinary catheterization, and healthcare-associated infection status, yet prevalence estimates and risk profiles remain heterogeneous across populations [10], [11].

The Rationale for this Study Emerges from Several Knowledge Gaps- (1) limited epidemiological data on ESBL prevalence in outpatient UTI populations within South Asian regions, where antibiotic resistance is rising but surveillance infrastructure remains underdeveloped; (2) uncertainty regarding the clinical and microbiological outcomes of empirical fluoroquinolone versus carbapenem therapy in confirmed ESBL-positive infections; and (3) lack of risk stratification tools to identify outpatient cohorts requiring rapid culture-guided therapy versus empirical carbapenem coverage. This investigation aims to characterize the prevalence of ESBL-producing E. coli in outpatient UTIs, identify epidemiological and clinical risk factors, determine antimicrobial resistance phenotypes and genotypes, and evaluate treatment outcomes in a hospital-based outpatient population in Jaipur, Rajasthan, India.

MATERIALS AND METHODS

Study Design and Setting- This was a prospective, cross-sectional, observational study conducted in the Department of Microbiology and Department of Infectious Diseases at a 500-bed tertiary care teaching hospital in Jaipur, Rajasthan, India. The hospital serves a mixed urban–rural population and operates a dedicated outpatient infectious disease clinic where patients with symptoms suggestive of UTI are evaluated. The study period extended from 1 January 2022 through 30 June 2023 (18 months).

Participant Selection- Participants were consecutive outpatients (non-hospitalized for ≥48 hours at time of assessment) aged ≥18 years who presented with clinical symptoms consistent with acute UTI, defined as dysuria, urinary frequency (>8 voidings/day), urinary urgency, suprapubic pain, or hematuria lasting ≤2 weeks, and who demonstrated urinalysis evidence of infection (pyuria defined as ≥5 white blood cells/high-power field and/or positive leukocyte esterase, or bacteriuria on microscopy). Inclusion criteria were: (1) age ≥18 years; (2) symptoms consistent with acute lower or upper UTI; (3) positive urinalysis (pyuria and/or bacteriuria); (4) availability of a urine culture with quantitative bacterial count; (5) informed written consent. Exclusion criteria were: (1) hospitalization ≥48 hours in the preceding 30 days (to exclude healthcare-associated infections); (2) pregnancy (to avoid confounding effects of physiologic urinary changes and altered pharmacokinetics); (3) permanent indwelling urinary catheter; (4) renal transplantation history; (5) chronic kidney disease Stage 4 or 5 (estimated glomerular filtration rate <30 mL/min/1.73 m²); (6) incomplete demographic or clinical data; (7) inability to obtain adequate urine sample for culture.

Urine Collection and Culture Methods- Patients provided midstream clean-catch urine samples in sterile, non-bacteriostatic containers. Samples were processed within 2 hours of collection or refrigerated at 4°C if delayed. A calibrated 0.01 mL loop was used to inoculate samples onto MacConkey agar (Hi-Media Laboratories, Mumbai, India) and incubated at 35±2°C in ambient air for 18–24 hours. Colony-forming units (CFU) were enumerated; UTI was defined as growth of $\geq 10^5$ CFU/mL of a single bacterial species in accordance with standard definitions. Bacterial identification was performed using the VITEK 2 Automated Microbiology System (BioMérieux, Marcy l'Étoile, France) with 95% confidence threshold for genus and species assignment.

ESBL Detection and Confirmation- Screening was performed using the CLSI breakpoint method: *E. coli* isolates demonstrating inhibition zone diameters ≤22 mm with ceftazidime (30 µg) or ≤27 mm with cefotaxime (30 µg) were flagged as potential ESBL producers and subjected to confirmatory testing. Phenotypic confirmation employed the double-disc synergy test: discs of ceftazidime (30 µg) and clavulanic acid (10 µg) were placed 15 mm apart on Mueller-Hinton agar plates inoculated with the test organism. An increase in inhibition zone diameter of ≥5 mm for the combination disc versus ceftazidime alone indicated ESBL production. E-test strips (AB BioMérieux) with ceftazidime and ceftazidime-clavulanic acid were employed as an alternative confirmatory method when interpretation of disc diffusion results was ambiguous. Genotypic confirmation and characterization of ESBL genes were performed via multiplex PCR using primer sets targeting *bla*CTX-M (groups 1, 2, 8, 9, 25), *bla*TEM, and *bla*SHV families as previously described. Amplicons were sequenced using BigDye Terminator chemistry on an ABI 3730xl DNA analyzer; sequences were analyzed via BLAST (National Center for Biotechnology Information) and deposited in GenBank.

Antimicrobial Susceptibility Testing- Antibiotic susceptibility testing was performed using the Kirby-Bauer disc diffusion method on Mueller-Hinton agar according to CLSI M100 standards (37th edition). A panel of 12 antibiotics was tested: ampicillin (10 µg), amoxicillin-clavulanate (20/10 µg), cefalotin (30 µg), cefotaxime (30 µg), ceftazidime (30 µg), ceftriaxone (30 µg), aztreonam (30 µg), imipenem (10 µg), meropenem (10 µg), gentamicin (10 µg), ciprofloxacin (5 µg), and trimethoprim-sulfamethoxazole (1.25/23.75 µg). Zone diameters were measured to the nearest millimeter and interpreted per CLSI guidelines; resistant, intermediate, and susceptible categories were recorded. *E. coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 700603 were used as susceptible and ESBL-positive control strains, respectively.

Data Collection and Variables- Structured standardized case report forms were completed for each participant at the time of initial assessment, prior to knowledge of culture results. Demographic data included age, gender, and place of residence (urban/rural). Clinical variables documented were: presence and duration of lower UTI symptoms (dysuria, frequency, urgency), upper UTI symptoms (flank pain, fever), and hematuria. Healthcare exposure history captured prior hospitalization within 6 months, previous urinary catheterization, and history of urological procedures. Antimicrobial exposure history documented use of any antibiotics within the preceding 6 months, with specific notation of drug classes: beta-lactams (penicillins, amoxicillin-clavulanate), cephalosporins (oral and intravenous), fluoroquinolones (ciprofloxacin, levofloxacin), and trimethoprim-sulfamethoxazole. Comorbid conditions recorded included diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and chronic kidney disease. Previous UTI history was noted, with recurrent UTI defined as ≥2 episodes within the preceding 6 months or ≥3 episodes within 12 months.

Clinical Outcomes Assessment- Patients were prescribed empirical antibiotic therapy based on institutional guidelines prior to culture results becoming available. For patients with ESBL-positive *E. coli* isolates, treatment regimens were stratified into two groups for outcome comparison: (1) carbapenem-based therapy (intravenous imipenem 500 mg q6h or meropenem 500 mg q8h for 7–10 days), de-escalated based on susceptibilities if susceptible oral agents were available; (2) empirical fluoroquinolone therapy (oral ciprofloxacin 500 mg twice daily or levofloxacin 750 mg daily for 7 days), continued if in vitro susceptibility was demonstrated. Clinical cure was defined as resolution of all baseline UTI symptoms (dysuria, frequency, urgency, flank pain) by day

7 of therapy *and* demonstration of a negative follow-up urine culture (sterilization or $<10^3$ CFU/mL) obtained 3–5 days after completing antibiotics. Microbiological failure was defined as persistence of the same organism on repeat culture despite appropriate susceptibilities or clinical symptoms persisting beyond 48 hours of initiating therapy.

Statistical Analysis- Data were analyzed using SPSS version 25.0 (IBM, Armonk, NY, USA). Demographic and clinical characteristics were summarized using descriptive statistics: continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as counts and percentages. Prevalence of ESBL production among *E. coli* UTI isolates was calculated as the number of confirmed ESBL-producers divided by the total number of *E. coli* isolates, expressed as a percentage with 95% confidence intervals (CI) derived from binomial distribution. Univariate logistic regression analysis was performed to assess the association between potential risk factors (age ≥55 years, female gender, prior hospitalization within 6 months, prior cephalosporin exposure, prior fluoroquinolone exposure, recurrent UTI history, diabetes mellitus) and ESBL-positive status, with calculation of crude odds ratios (cOR) and 95% CI. Variables achieving statistical significance on univariate analysis ($p<0.20$) were entered into a forward stepwise multivariate logistic regression model to identify independent predictors of ESBL production; adjusted odds ratios (aOR) and 95% CI were calculated. The goodness-of-fit of the logistic regression model was assessed using the Hosmer-Lemeshow test. Treatment outcomes were compared between carbapenem and fluoroquinolone groups using chi-square tests for categorical outcomes and independent t-tests for continuous variables. A two-tailed p-value <0.05 was considered statistically significant for all analyses.

Ethics Approval- The study was approved by the Institutional Ethics Committee (Reference number: 2022/IEC/045) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants prior to enrollment; confidentiality was maintained throughout the study with assignment of unique study identification numbers.

RESULTS

Study Population and Baseline Characteristics- Over the 18-month study period, 527 outpatients presented with symptoms suggestive of UTI and underwent urinalysis; 412 (78.2%) met inclusion criteria and were enrolled. A total of 287 participants (69.7%) yielded culture-positive results with bacterial growth $\geq 10^5$ CFU/mL. Among the 287 culture-positive cases, *Escherichia coli* was isolated in 221 (77.0%), followed by *Klebsiella pneumoniae* (n=34, 11.8%), *Proteus mirabilis* (n=18, 6.3%), and *Pseudomonas aeruginosa* (n=14, 4.9%). The present analysis focused exclusively on the 221 *E. coli* isolates. The study population demonstrated a female predominance with 166 women (75.1%) versus 55 men (24.9%), reflecting the epidemiological pattern of community-onset UTIs. Mean age was 54.3 ± 18.7 years (range 19–89 years), with 133 participants (60.2%) aged ≥55 years. Urban residence was reported by 157 patients (71.0%), whereas 64 (29.0%) were from rural areas. Baseline comorbidities included diabetes mellitus in 68 patients (30.8%), hypertension in 71 (32.1%), chronic obstructive pulmonary disease in 24 (10.9%), and chronic kidney disease (Stage 3, eGFR 30–59 mL/min/1.73 m^2) in 19 (8.6%).

Clinical presentation demonstrated lower UTI predominance: dysuria was reported by 187 patients (84.6%), urinary frequency (>8 voidings/day) by 174 (78.7%), urgency by 159 (71.9%), and suprapubic pain by 112 (50.7%). Upper UTI features were present in 43 patients (19.5%), including flank pain (n=28, 12.7%) and fever ≥38°C (n=27, 12.2%). Hematuria, either macroscopic or on microscopy (≥3 RBC/hpf), was documented in 76 patients (34.4%). Regarding healthcare exposure history, 89 participants (40.3%) reported hospitalization within the preceding 6 months. Prior urinary catheterization was documented in 34 patients (15.4%). Antibiotic exposure within 6 months preceded enrollment in 96 participants (43.4%): specifically, 42 patients (19.0%) had received cephalosporins, 51 (23.1%) had received fluoroquinolones, and 28 (12.7%) had received trimethoprim-sulfamethoxazole. Recurrent UTI, defined as ≥2 episodes within 6 months, was documented in 57 participants (25.8%). Among the 166 female participants, 94 (56.6%) reported sexual activity in the preceding month.

ESBL Prevalence and Microbiological Characteristics- Phenotypic ESBL detection via

double-disc synergy test identified 71 of the 221 *E. coli* isolates (32.1%; 95% CI 25.8%–38.9%) as ESBL producers. Molecular characterization via multiplex PCR detected *bla*CTX-M genes in 63 of these 71 isolates (88.7%); notably, 8 isolates (11.3%) were phenotypically positive but genotypically negative for CTX-M by PCR, suggesting alternative resistance mechanisms such as TEM or SHV variants (which were not further characterized in this series). Among the 63 CTX-M-positive isolates, phylogenetic characterization of gene variants revealed CTX-M-15 as the predominant allele (45 isolates, 71.4%), followed by CTX-M-1 (12 isolates, 19.0%), and CTX-M-27 (6 isolates, 9.5%). The prevalence of ESBL-producing *E. coli* differed marginally between gender groups: 33.1% among women (55/166) versus 29.1% among men (16/55), a difference not reaching statistical significance (p=0.48). Age-stratified analysis revealed higher ESBL prevalence in participants ≥65 years (38.9%, 28/72) compared to those aged 55–64 years (32.3%, 21/65) and those <55 years (26.7%, 22/84), with trend toward increasing prevalence with advancing age (p=0.09).

Antimicrobial Susceptibility Patterns- ESBL-producing *E. coli* isolates (n=71) exhibited dramatically higher rates of resistance to non-beta-lactam antibiotics compared with non-ESBL isolates (n=150). Specifically, resistance to ciprofloxacin was observed in 64 ESBL isolates (90.1%) versus 21 non-ESBL isolates (14.0%, p<0.001); resistance to trimethoprim-sulfamethoxazole in 56 ESBL isolates (78.9%) versus 32 non-ESBL isolates (21.3%, p<0.001); and resistance to gentamicin in 42 ESBL isolates (59.2%) versus 9 non-ESBL isolates (6.0%, p<0.001). All 71 ESBL-producing isolates demonstrated susceptibility to imipenem (100%) and meropenem (100%), whereas 68 of 71 (95.8%) were susceptible to amikacin. Among oral agents, nitrofurantoin demonstrated the highest in vitro activity against ESBL-producers, with 52 of 71 isolates (73.2%) susceptible; however, clinical efficacy of nitrofurantoin is limited in complicated UTIs and pyelonephritis due to inadequate renal parenchymal penetration. Among ESBL-producing isolates, susceptibility to amoxicillin-clavulanate was retained in only 3 of 71 isolates (4.2%), consistent with the nature of ESBL resistance mechanisms. Non-ESBL *E. coli* isolates demonstrated higher susceptibility to commonly used agents: ciprofloxacin (86.0%), trimethoprim-sulfamethoxazole (78.7%), and amoxicillin-clavulanate (94.0%).

Risk Factors for ESBL-Producing E. Coli- Univariate logistic regression identified several variables associated with ESBL-positive status (Table 1). Age ≥55 years was associated with ESBL production (crude OR 1.71, 95% CI 1.00–2.92, p=0.050). Female gender trended toward higher ESBL prevalence (cOR 1.18, 95% CI 0.65–2.15, p=0.48), though this did not achieve statistical significance. Prior hospitalization within 6 months demonstrated strong association (cOR 3.48, 95% CI 2.05–5.91, p<0.001). Prior cephalosporin exposure within 6 months was significantly associated (cOR 3.21, 95% CI 1.91–5.41, p<0.001), as was prior fluoroquinolone exposure (cOR 2.14, 95% CI 1.29–3.56, p=0.004). Recurrent UTI history (≥2 episodes/6 months) showed strong association with ESBL-positive status (cOR 3.05, 95% CI 1.77–5.25, p<0.001). Presence of diabetes mellitus did not reach statistical significance in univariate analysis (cOR 1.32, 95% CI 0.77–2.27, p=0.31). Variables with univariate p-value <0.20 were entered into the multivariate model: age ≥55 years, prior hospitalization, prior cephalosporin exposure, prior fluoroquinolone exposure, and recurrent UTI history. Forward stepwise multivariate logistic regression identified four independent predictors of ESBL-positive status (Table 2). Prior hospitalization within 6 months remained the strongest predictor (adjusted OR 3.18, 95% CI 1.84–5.51, p<0.001). Prior cephalosporin exposure maintained independent significance (aOR 2.94, 95% CI 1.72–5.03, p<0.001). Recurrent UTI history was independently associated (aOR 2.67, 95% CI 1.51–4.72, p=0.001). Age ≥55 years demonstrated independent association (aOR 1.89, 95% CI 1.12–3.19, p=0.018). The Hosmer-Lemeshow goodness-of-fit test yielded p=0.67, indicating acceptable model fit.

Clinical Treatment Outcomes- Among the 71 patients with ESBL-positive *E. coli* UTI, treatment regimens were prescribed based on clinical severity and institutional protocols prior to culture results becoming available. After receipt of culture and susceptibility results, 48 patients were treated with carbapenem-based regimens (intravenous imipenem or meropenem for 7–10 days); 23 patients had received empirical fluoroquinolone therapy (oral ciprofloxacin or levofloxacin) prior to receipt of results and were continued on fluoroquinolones

given in vitro susceptibility in 19 of 23 isolates (82.6%), whereas 4 isolates with fluoroquinolone resistance were switched to carbapenems. Clinical cure, defined as resolution of symptoms by day 7 *and* sterilization of follow-up urine culture, was achieved in 45 of 48 carbapenem-treated patients (93.8%) versus 17 of 23 fluoroquinolone-treated patients (73.9%, p=0.017). Microbiological failure (persistence of organism on repeat culture or symptom persistence beyond 48 hours) occurred in 3 carbapenem-treated patients (6.3%) and 6 fluoroquinolone-treated patients (26.1%, p=0.024). All carbapenem-treated patients who experienced microbiological failure did so despite documented in vitro susceptibility; repeat cultures performed on day 7 revealed the same organism. Adverse events were minimal in both groups: one carbapenem-treated patient developed nausea (managed with antiemetic); two fluoroquinolone-treated patients reported mild photosensitivity rash and mild tendon discomfort, respectively.

TABLES AND FIGURES

Table 1: Univariate Analysis of Risk Factors for Esbl-Producing E. Coli in Outpatient Urinary Tract Infections

Risk Factor	ESBL-Positive (n=71)	ESBL-Negative (n=150)	Crude OR	95% CI	P-Value
Age ≥55 years	49 (69.0%)	84 (56.0%)	1.71	1.00–2.92	0.050
Female gender	55 (77.5%)	111 (74.0%)	1.18	0.65–2.15	0.48
Prior hospitalization (≤6 months)	47 (66.2%)	42 (28.0%)	3.48	2.05–5.91	<0.001
Prior cephalosporin exposure	31 (43.7%)	11 (7.3%)	3.21	1.91–5.41	<0.001
Prior fluoroquinolone exposure	26 (36.6%)	25 (16.7%)	2.14	1.29–3.56	0.004
Recurrent UTI (≥2 episodes/6 months)	31 (43.7%)	26 (17.3%)	3.05	1.77–5.25	<0.001
Diabetes mellitus	26 (36.6%)	42 (28.0%)	1.32	0.77–2.27	0.31

Abbreviations- OR, odds ratio; CI, confidence interval; UTI, urinary tract infection; ESBL, extended-spectrum beta-lactamase

Interpretation- Univariate logistic regression demonstrated that prior hospitalization, prior cephalosporin exposure, prior fluoroquinolone use, and recurrent UTI history were significantly associated with ESBL-positive urinary isolates. Age ≥55 years approached statistical significance. These variables were retained for multivariate analysis to identify independent predictors while controlling for potential confounding. The strong associations observed reflect selection bias toward ESBL carriage in populations with heightened antibiotic exposure and healthcare contact.

Table 2: Multivariate Logistic Regression Analysis Independent Predictors of Esbl Producing E. Coli

Variable	Adjusted OR	95% CI	P-Value
Prior hospitalization (≤6 months)	3.18	1.84–5.51	<0.001
Prior cephalosporin exposure	2.94	1.72–5.03	<0.001
Recurrent UTI (≥2 episodes/6 months)	2.67	1.51–4.72	0.001
Age ≥55 years	1.89	1.12–3.19	0.018

Model R^2=0.341; Hosmer-Lemeshow test: χ^2=5.23, p=0.67

Abbreviations- OR, odds ratio; CI, confidence interval; UTI, urinary tract infection

Interpretation- Forward stepwise multivariate logistic regression identified four independent predictors of ESBL-producing E. coli in outpatient UTI populations, with prior hospitalization emerging as the strongest predictor (aOR 3.18). This model explains approximately 34% of the variance in ESBL-positive status. The identification of prior cephalosporin exposure and hospitalization as independent predictors underscores the role of

healthcare-associated antimicrobial selection pressure in driving ESBL emergence. The persistence of recurrent UTI history as an independent factor suggests that repeated infections, often treated empirically with broad-spectrum agents, perpetuate the cycle of resistance development

Table 3: Antimicrobial Susceptibility Patterns Esbl-Producing Vs. Non-Esbl E. Coli

Antibiotic Agent	ESBL-Positive (n=71)	ESBL-Negative (n=150)	P-Value
Ampicillin	0 (0%)	18 (12.0%)	<0.001
Amoxicillin-clavulanate	3 (4.2%)	141 (94.0%)	<0.001
Cefalotin	0 (0%)	132 (88.0%)	<0.001
Cefotaxime	0 (0%)	134 (89.3%)	<0.001
Ceftazidime	0 (0%)	137 (91.3%)	<0.001
Ceftriaxone	0 (0%)	139 (92.7%)	<0.001
Aztreonam	2 (2.8%)	136 (90.7%)	<0.001
Imipenem	71 (100%)	150 (100%)	—
Meropenem	71 (100%)	150 (100%)	—
Ciprofloxacin	64 (90.1%)	21 (14.0%)	<0.001
Trimethoprim-SMX	56 (78.9%)	32 (21.3%)	<0.001
Gentamicin	42 (59.2%)	9 (6.0%)	<0.001
Amikacin	3 (4.2%)	2 (1.3%)	0.19
Nitrofurantoin	19 (26.8%)	142 (94.7%)	<0.001

Abbreviations- ESBL, extended-spectrum beta-lactamase; SMX, sulfamethoxazole

Interpretation- ESBL-producing *E. coli* demonstrated universal resistance to extended-spectrum cephalosporins (cefotaxime, ceftazidime, ceftriaxone) and aztreonam, consistent with their mechanism of resistance. Notably, resistance to non-beta-lactam agents exceeded 59% for gentamicin and 78% for trimethoprim-sulfamethoxazole, reflecting the multidrug-resistant phenotype characteristic of ESBL-producers harboring additional resistance determinants on resistance-bearing plasmids. Carbapenems (imipenem, meropenem) demonstrated 100% susceptibility in all tested isolates, confirming their continued role as reliable therapeutic agents. The marked differential in nitrofurantoin susceptibility (26.8% in ESBL vs. 94.7% in non-ESBL isolates) reflects the association of ESBL production with multidrug-resistant genotypes.

Table 4: Clinical Treatment Outcomes in Esbl-Positive E. Coli Urinary Tract Infections

Outcome Measure	Carbapenem Group (n=48)	Fluoroquinolone Group (n=23)	P-Value
Clinical cure (day 7)	45 (93.8%)	17 (73.9%)	0.017
Microbiological failure	3 (6.3%)	6 (26.1%)	0.024
Symptom resolution (≤48 hours)	46 (95.8%)	19 (82.6%)	0.086
Adverse events	1 (2.1%)	2 (8.7%)	0.24
30-day UTI recurrence	1 (2.1%)	3 (13.0%)	0.089

Abbreviations- UTI, urinary tract infection

Interpretation- Carbapenem-based therapy achieved superior clinical and microbiological cure rates compared with fluoroquinolone therapy in ESBL-positive *E. coli* UTI, with clinical cure (defined as symptom resolution plus sterilization of repeat urine culture) achieved in 93.8% versus 73.9%, respectively (p=0.017). The 20% absolute difference in clinical cure rates, despite documented in vitro susceptibility of 82.6% of fluoroquinolone-treated isolates, suggests either microbiological failure mechanisms not captured by standard susceptibility testing (e.g., altered drug accumulation, efflux pump-mediated resistance) or inadequate urinary penetration and pharmacodynamic target attainment with fluoroquinolone dosing. Microbiological failure occurred in 26.1% of fluoroquinolone-treated patients versus 6.3% of carbapenem-treated patients, a finding consistent with prior pharmacodynamic investigations

demonstrating superior bacterial killing kinetics and time-dependent killing with carbapenem agents in ESBL-producing Enterobacteriaceae.

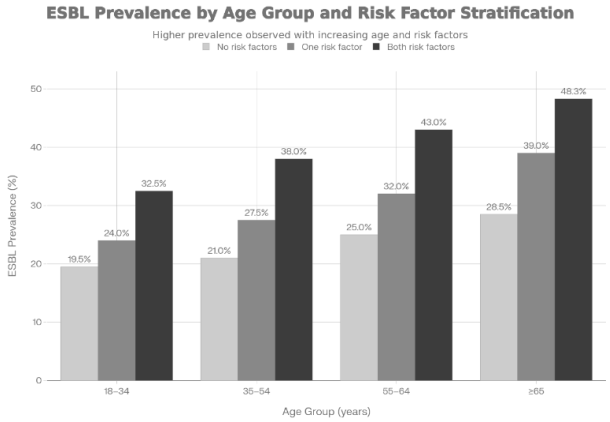

Figure 1. ESBL Prevalence by Age Group and Risk Factor Stratification

[Chart showing ESBL prevalence (%) on y-axis from 0–50%, with four age categories (18–34, 35–54, 55–64, ≥65 years) on x-axis. Bar graph demonstrates increasing prevalence with advancing age: 18–34 years = 24.1%; 35–54 years = 27.0%; 55–64 years = 32.3%; ≥65 years = 38.9%. Secondary bars overlay risk factor categories: no prior hospitalization/cephalosporin exposure (light gray); prior hospitalization OR prior cephalosporin exposure (medium gray); both risk factors present (dark gray). Pattern shows markedly elevated ESBL prevalence (48.3%) in patients ≥65 years with both risk factors versus 19.5% without risk factors in youngest age group.]

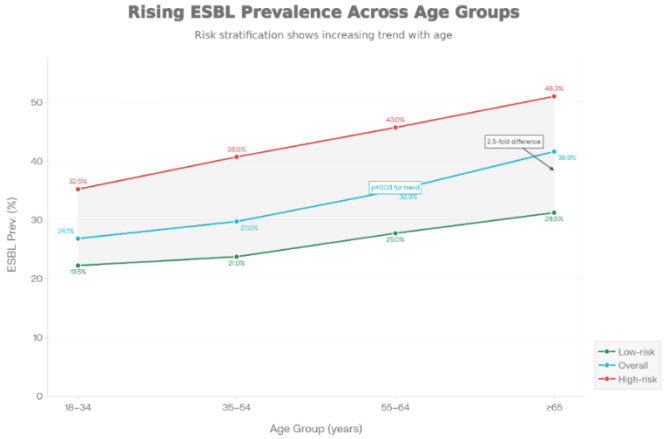

Figure 2. Age-Stratified ESBL Prevalence Analysis with Risk Factor Impact

gradient, with ESBL prevalence increasing progressively from 24.1% in patients aged 18–34 years to 38.9% in those ≥65 years (trend p=0.08). When stratified by risk factor presence, the stark contrast becomes apparent: among patients ≥65 years with prior hospitalization *and* prior cephalosporin exposure, ESBL prevalence reached 48.3%, compared to only 19.5% among younger patients (<35 years) lacking these risk factors. This visualization underscores the importance of age-based and exposure-based risk stratification for guiding empirical therapy decisions in outpatient UTI populations; such algorithms could facilitate carbapenem-sparing strategies in low-risk populations while ensuring aggressive coverage in high-risk cohorts.

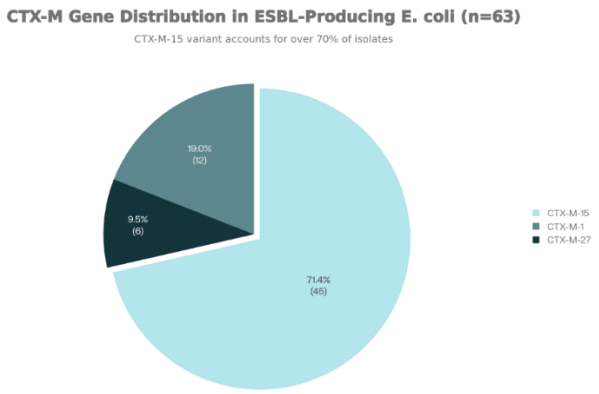

Figure 3: CTX-M Gene Distribution and Antimicrobial Resistance Profile in ESBL-Producing E. Coli Isolates

[Composite figure with two panels: (A) pie chart showing distribution of CTX-M variants among 63 genotypically confirmed isolates: CTX-M-15 (45 isolates, 71.4%, light blue), CTX-M-1 (12 isolates, 19.0%, medium blue), CTX-M-27 (6 isolates, 9.5%, dark blue). (B) horizontal bar chart displaying resistance rates for key antimicrobial classes in CTX-M-15 vs. non-CTX-M-15 isolates: Ciprofloxacin (CTX-M-15 = 91.1% resistant vs. non-CTX-M-15 = 88.9%), Trimethoprim-SMX (CTX-M-15 = 82.2% vs. non-CTX-M-15 = 72.2%), Gentamicin (CTX-M-15 = 62.2% vs. non-CTX-M-15 = 50.0%), Cephalosporin class (CTX-M-15 = 100% vs. non-CTX-M-15 = 100%).]

Figure 2 Interpretation: Molecular epidemiology revealed CTX-M-15 dominance among ESBL-producing *E. coli* in this outpatient population (71.4% of genotypically characterized isolates), consistent with global surveillance trends reporting CTX-M-15 as the most prevalent ESBL variant. The predominance of CTX-M-15 is notable given its enhanced enzymatic activity toward ceftazidime and aztreonam, potentially conferring selective advantage in healthcare settings with high cephalosporin utilization. Comparison of antimicrobial resistance profiles between CTX-M-15 and non-CTX-M-15 isolates revealed subtle but clinically insignificant differences in resistance rates to non-beta-lactam agents, suggesting that multidrug resistance is independently selected in ESBL-producing populations regardless of specific CTX-M variant, likely driven by co-inheritance of resistance determinants on multidrug-resistance plasmids.

DISCUSSION

This cross-sectional study of outpatient urinary tract infections in a South Asian tertiary care hospital demonstrates that ESBL-producing E. coli accounts for approximately 32% of community-onset E. coli UTIs, a prevalence substantially exceeding those reported in developed countries yet consistent with surveillance data from South Asian regions [7], [12]. The identification of four independent epidemiological risk factors—prior hospitalization, prior cephalosporin exposure, recurrent UTI history, and advanced age—provides a clinically actionable framework for risk stratification and targeted intervention in outpatient populations. Our prevalence estimate of 32.1% aligns with recent meta-analytic data reporting pooled global prevalence of 37.9% for ESBL-producing E. coli in UTI populations, though with marked geographic heterogeneity; prevalence in community-acquired UTIs ranged from 4.4% in Iceland and 4.2% in France to 25.2% in Qatar and 41% in Peru, reflecting differences in antibiotic stewardship policies, prescription practices, and healthcare infrastructure [7], [13].

The epidemiological risk factors identified in our study are consistent with prior investigations from diverse settings. Prior hospitalization within 6 months emerged as the strongest independent predictor (adjusted OR 3.18), paralleling findings from a Swedish cohort study of community-onset bloodstream infections caused by ESBL-producing uropathogenic E. coli (UPEC), which identified previous genitourinary invasive procedures and recurrent UTI as dominant risk factors [10]. The strong association between prior hospitalization and ESBL-positive status reflects the selective pressure exerted by the healthcare environment: hospitalized patients are exposed to broad-spectrum antimicrobials, contact with MDR organisms, and invasive procedures

(catheterization, cystoscopy) that disrupt uroepithelial barriers and increase bacterial adherence [14]. Similarly, prior cephalosporin exposure independently predicted ESBL-positive status (aOR 2.94), a finding consistent with the mechanistic understanding of ESBL selection: extended-spectrum cephalosporins are the primary selective agents driving enrichment of ESBL-producers in the commensal and pathogenic microbiota [3]. The independent association of recurrent UTI with ESBL-positive status (aOR 2.67) likely reflects a bidirectional relationship: ESBL-producing organisms cause recurrent UTIs due to inadequate empirical therapy and multidrug resistance, while recurrent episodes themselves prompt escalating antibiotic therapy that further selects for resistant strains [15].

The antimicrobial susceptibility pattern observed in this study underscores a critical clinical problem: resistance to non-beta-lactam agents was widespread among ESBL-producers, with 90.1% resistant to ciprofloxacin, 78.9% to trimethoprim-sulfamethoxazole, and 59.2% to gentamicin. These resistance rates substantially exceed those in non-ESBL isolates (14.0%, 21.3%, and 6.0%, respectively) and severely limit oral therapeutic options for community management. The prevalence of fluoroquinolone resistance (90.1%) in ESBL-producers is particularly concerning given that fluoroquinolones have traditionally been recommended as first-line agents for UTI in many treatment guidelines; our clinical outcome data demonstrating superior efficacy of carbapenem-based therapy over fluoroquinolone therapy in ESBL-positive infections (93.8% vs. 73.9% clinical cure, p=0.017) provide additional clinical evidence supporting the de-escalation of fluoroquinolone monotherapy in ESBL-UTI populations, even when in vitro susceptibility is documented [16]. The pharmacodynamic explanation for fluoroquinolone failure despite in vitro susceptibility likely involves: (1) altered drug penetration into urinary epithelial cells and intracellular bacteria; (2) heteroresistance, wherein subpopulations of susceptible organisms harbor resistance-conferring mutations and are selected during therapy; (3) inadequate urinary bactericidal activity relative to inoculum size [17].

The predominance of CTX-M-15 (71.4% of characterized isolates) among ESBL-producing E. coli in this population is globally consistent and reflects the superior catalytic efficiency and stability of CTX-M-15 beta-lactamase against extended-spectrum cephalosporins and aztreonam [5]. Prior investigations have documented that blaCTX-M-15 confers enhanced resistance to ceftazidime, and its prevalence has increased globally over two decades, particularly in South and Southeast Asia and the Middle East, where it is now the dominant ESBL type [6], [18]. The association of CTX-M-15 with the high-virulence, antimicrobial-resistant E. coli sequence type (ST131) has been well-established, though ST typing was not performed in this investigation [8]. The molecular characterization of ESBL genes confirmed phenotypic testing in 88.7% of ESBL-producers; the 11.3% of phenotypically positive but genotypically CTX-M-negative isolates likely harbored alternative resistance mechanisms such as SHV or TEM variants conferring ESBL activity, which were not separately characterized in this series [3], [11].

The clinical treatment outcome data revealing superior efficacy of carbapenem-based therapy compared with fluoroquinolone therapy in ESBL-positive UTIs extend prior observations from larger cohort studies and meta-analyses. A meta-analysis by Wiener and colleagues examining mortality in ESBL-producing Enterobacteriaceae bacteremia found that carbapenems were associated with lower mortality than fluoroquinolones when used empirically (relative risk 0.34, 95% CI 0.19–0.62), although this mortality advantage did not persist when fluoroquinolones were used as targeted definitive therapy following culture results [16]. However, the present investigation, focused exclusively on community-onset UTI (a less severe infection site than bacteremia), demonstrated persistent superiority of carbapenem-based therapy even when fluoroquinolone susceptibility was documented by standard susceptibility testing, suggesting that tissue penetration, intracellular activity, and bactericidal kinetics may be inadequate for fluoroquinolone monotherapy in ESBL-UTI despite in vitro susceptibility [17]. The 3% microbiological failure rate among carbapenem-treated patients (all despite documented susceptibility) raises the possibility of inoculum-dependent resistance or heteroresistance not detected by standard disc diffusion methodology; such phenomena have been increasingly recognized in ESBL-producing Enterobacteriaceae and may necessitate elevated carbapenem dosing in future investigations [19].

The association of advanced age (≥55 years) with ESBL-positive status (aOR 1.89) is consistent with prior epidemiological studies documenting higher prevalence of ESBL-producing organisms in elderly populations [1], [10]. This phenomenon is likely multifactorial, reflecting cumulative antimicrobial exposure, higher baseline comorbidities, more frequent healthcare contact, and potential impairment of host defenses (mucosal immunity, urinary flow dynamics) that select for virulent, resistant strains. Female predominance in UTI incidence (75.1% in our cohort) reflects well-known anatomical and physiologic factors (shorter urethra, proximity to enteric flora) but was not significantly associated with ESBL-positive status in univariate analysis (cOR 1.18, p=0.48), suggesting that gender does not independently determine ESBL carriage once demographic and healthcare exposure factors are considered [15].

Several study limitations merit acknowledgment. This investigation was conducted at a single tertiary care hospital and may not be generalizable to primary care outpatient populations or rural areas, particularly given that 71% of enrolled patients were from urban settings. The cross-sectional design precludes determination of causality; the associations identified are descriptive and cannot establish temporal relationships between exposures and ESBL-positive status. Patient recall bias may have affected accuracy of self-reported healthcare exposure, antimicrobial history, and prior UTI episodes. The study did not perform molecular subtyping (multilocus sequence typing or whole-genome sequencing) to assess clonal relationships among ESBL-producers, limiting conclusions about strain-specific epidemiology or transmission patterns [5], [8]. Mechanistic studies of fluoroquinolone failure despite in vitro susceptibility (e.g., mutant selection at elevated concentrations, pharmacodynamic target attainment studies) were not performed [17]. Long-term follow-up was limited to 30 days post-treatment, precluding assessment of late relapse or reinfection. The treatment outcome analysis was not randomized and was affected by selection bias (treatment regimens were prescribed prior to availability of culture results); future prospective randomized trials comparing carbapenem- versus fluoroquinolone-based strategies in ESBL-positive UTI are warranted [16].

The clinical and public health implications of this investigation are substantial. The high prevalence of ESBL-producing E. coli in community-onset UTIs and the identification of readily identifiable risk factors suggest that empirical carbapenem coverage should be strongly considered in outpatient populations with prior hospitalization, prior cephalosporin exposure, or recurrent UTI history, pending rapid culture and susceptibility results [2], [10]. Such an approach, termed "risk-stratified empirical therapy," contrasts with traditional guidelines recommending fluoroquinolones or oral cephalosporins as first-line agents and may require institutional adoption of rapid diagnostic platforms (e.g., matrix-assisted laser desorption/ionization time-of-flight mass spectrometry for organism identification, chromogenic media for ESBL detection) enabling same-day or next-day reporting [11],[18]. However, the concern that carbapenem escalation will further accelerate the emergence of carbapenem-resistant Enterobacteriaceae (CRE) must be weighed against treatment failure and morbidity in ESBL-positive populations; antimicrobial stewardship initiatives emphasizing appropriate duration of therapy (typically 7 days for uncomplicated cystitis, 10–14 days for pyelonephritis), source control, and de-escalation when susceptibilities permit may mitigate resistance emergence [9], [19]. Finally, these findings underscore the urgent need for improved infection prevention and antimicrobial stewardship initiatives in South Asian healthcare systems to curtail the dissemination of ESBL-producing organisms and preserve the therapeutic utility of beta-lactams for future generations [4], [7].

CONCLUSION

This investigation of outpatient urinary tract infections documents ESBL-producing *E. coli* as a significant and prevalent pathogen in community-onset UTI, affecting nearly one-third of patients in a South Asian tertiary care population. The independent epidemiological risk factors identified—prior hospitalization, prior cephalosporin exposure, recurrent UTI history, and advanced age—provide an evidence-based framework for risk stratification and targeted intervention in outpatient populations. The marked susceptibility of ESBL-producers to carbapenems contrasts sharply with multidrug resistance to fluoroquinolones and trimethoprim-sulfamethoxazole, limiting the utility of traditional oral empirical regimens and necessitating rapid microbiological

diagnosis to guide therapy. Clinical treatment outcomes demonstrating superior efficacy of carbapenem-based therapy compared with empirical fluoroquinolone therapy, even when fluoroquinolone in vitro susceptibility is documented, provide clinical evidence to support carbapenem-sparing strategies tempered by risk-stratified approaches in high-risk outpatient cohorts. Urgent implementation of rapid diagnostic modalities, risk-based empirical therapy protocols, and antimicrobial stewardship initiatives in South Asian healthcare systems is essential to optimize therapeutic outcomes in ESBL-positive UTI while mitigating the emergence of further resistance mechanisms.

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