



ESBL-Producing Uropathogenic Escherichia coli: A Comparative Study of Hospital-Acquired versus Community-Sourced Isolates in Central India

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Abstract

Background: Third-generation cephalosporins are hydrolysed by Enzymes known as extended-spectrum β -lactamases (ESBLs) are encoded by plasmids, which drastically restrict the alternatives for treating Gram-negative infections. ESBL-producing Escherichia coli is being reported with growing frequency from UTIs in India, but the relative burden in community versus hospital isolates is not well characterised in central India.

Objectives: To determine the frequency of ESBL synthesis in urine E. Coli isolates, to compare outpatient and inpatient strains, and to examine the association between ESBL status and multidrug resistance (MDR).

Methods: A cross-sectional research was conducted in the Microbiology department of a 1,200-bed tertiary care hospital in Indore over 18 months. Urine in midstream specimens from 350 clinically suspected UTI patients were processed by the calibrated loop method on CLED and MacConkey agar, with significant bacteriuria defined as $\geq 10^5$ CFU/mL. E. coli isolates were determined using standard biochemical testing. Kirby-Bauer disc diffusion was used to test for antibiotic susceptibility on Mueller-Hinton agar following CLSI M100 (2023) breakpoints. ESBL production was screened with ceftazidime, cefotaxime and ceftriaxone discs and verified phenotypically Utilising the Combined Disc Test with ceftazidime (30 μ g) and ceftazidime-clavulanic acid (30/10 μ g). The Magiorakos criteria were used to define MDR.

Results: Out of 97 culture-positive specimens (61.9% of all uropathogens), sixty E. coli isolates were found. Thirty-seven (61.7%) were phenotypic ESBL producers. ESBL prevalence was 63.4% in outpatient isolates (26 of 41) and 57.9% in inpatient isolates (11 of 19) ($p = 0.681$). ESBL producers showed significantly higher resistance to cefotaxime (94.6% vs 17.4%), ceftriaxone (89.2% vs 13.0%), ceftazidime (94.6% vs 8.7%), ciprofloxacin (83.8% vs 30.4%) and cotrimoxazole (83.8% vs 39.1%) compared with non-ESBL isolates (all $p < 0.001$). All 37 ESBL producers were multidrug-resistant (100%), versus 20 of 23 non-ESBL isolates (87.0%) ($p = 0.045$). Imipenem retained activity against 94.6% of ESBL producers.

Conclusions: In central India, ESBL-producing E. coli is now often seen in community-acquired UTIs and is almost always associated with antibiotic resistance. Empirical use of third-generation

cephalosporins and fluoroquinolones is no longer rational in this setting. Routine ESBL screening, restrictive prescribing policies and active stewardship are now urgent.

Keywords: *Escherichia coli*, urinary tract infections, community-acquired infections, multidrug resistance, central India, antimicrobial stewardship, combined disc test, and extended-spectrum β -lactamase.

1. Introduction

A class of plasmid-encoded enzymes known as ESBLs susceptible to inhibition by clavulanic acid, sulbactam, or tazobactam but provides resistance to aztreonam, penicillins, and third-generation cephalosporins [1,2]. Since their description in the 1980s, the global epidemiology of ESBLs has shifted twice. The early enzymes were largely TEM and SHV variants confined to hospital outbreaks. From the late 1990s onwards, the CTX-M family, especially CTX-M-15, expanded quickly in community settings thanks to conjugative plasmids and mobile genetic elements like ISEcp1 [2, 3].

Among species carrying these enzymes, *Escherichia coli* is now the principal reservoir. Travel, food-animal exposure, environmental contamination and antibiotic pressure have together produced a worldwide pandemic of CTX-M-15-positive ST131 *E. coli* [3,4]. In south Asia the situation is particularly serious: ESBL prevalence among *E. coli* isolates in Indian tertiary care has been reported at between 30% and 75%, depending on the centre and specimen type [5,6].

Two consequences follow. First, ESBL production almost always co-exists with resistance to fluoroquinolones, aminoglycosides and cotrimoxazole, because the relevant resistance determinants are co-carried on the same plasmids [4,7]. The clinical effect is multidrug resistance with very limited oral options. Second, the carbapenems are pushed forward as default empirical therapy for serious infections, which in turn selects for carbapenemase production. The trajectory from ESBL to carbapenem-resistant Enterobacterales (CRE) is now well documented in Indian hospitals [8,9].

Over the past ten years, there has been a significant erosion of the conventional difference between hospital-acquired and community-acquired ESBL infections. Several Indian studies have shown that ESBL rates among outpatient urinary isolates now equal, and in some series exceed, those in inpatient isolates [5,10,11]. Likely contributors include over-the-counter antibiotic availability, prolonged outpatient courses for recurrent UTI, and the ESBL-producing bacteria found in the faeces of healthy community members [12].

Central India is underrepresented in this literature, with only a handful of studies from tertiary centres in Madhya Pradesh and adjoining states reporting ESBL prevalence among urinary uropathogens [13,14]. The clinical question is straightforward but consequential. If ESBL production is now common in community-acquired urinary isolates, then empirical regimens for uncomplicated UTI in this region need urgent revision, and routine phenotypic ESBL screening must be embedded in routine microbiology workflows rather than reserved for unusual cases.

Three specific goals guided the current investigation: to determine the phenotypic frequency of ESBL production in our tertiary care center's urine *E. coli* isolates; to compare ESBL prevalence and resistance patterns between inpatient and outpatient isolates; and to investigate the statistical relationship between ESBL production and multidrug resistance as determined by the Magiorakos criteria [15].

2. Materials and Methods

2.1 Study design

The 1,200-bed tertiary care teaching hospital's Microbiology Department at IMCHRC, Indore, served as the site of the cross-sectional, comparative study affiliated to Malwanchal University, Madhya Pradesh, India. Recruitment and laboratory work were carried out over a consecutive 18-month period.

2.2 Ethics

Before recruiting began, the Institutional Ethics Committee examined and approved the protocol. The 2013 version of the Declaration of Helsinki [16] was followed while conducting the study. All participants provided written informed permission, or for those under the age of eighteen, a parent or legal guardian did so. Confidentiality was upheld throughout, and personal identities were removed from the analytical dataset.

2.3 Study population

Patients of all ages and genders who were either endorsed to IPD or attended OPD and had clinical signs indicative of a UTI were included in the study. Dysurias, frequency, urgency, suprapubic discomfort, costovertebral angle soreness, temperature over 38°C, haematuria, and, in the elderly, unexplained altered sensorium were among the clinical characteristics deemed diagnostic. Patients taking ongoing chemotherapy, those who refused permission, and those who had taken any antibiotics within the previous 72 hours were not included.

2.4 Specimen collection and primary processing

Using usual procedure, Urine samples from mid-stream clean-catch were collected in sterilised, wide-mouthed containers. Specimens were aspirated aseptically from the sampling port in catheterised patients following disinfection. The specimens were sent to the lab in less than half an hour, or if that was not possible, they were chilled at 4°C and processed in four hours.

A 0.001 mL calibrated platinum loop was used to inoculate each specimen onto CLED and MacConkey agar, after which it was aerobically incubated for 18 to 24 hours at 37°C [17, 18]. Significant bacteriuria was defined as ≥ 10 CFU/mL of a single organism. Polymicrobial growth above this threshold was treated as contamination unless clinical suspicion was strong and a repeat specimen confirmed the same organisms.

2.5 Identification of E. coli

Gram staining, motility, colony shape, and a typical biochemical panel that includes urease, triple sugar iron, Voges-Proskauer, indole, methyl red, and citrate utilisation and lysine decarboxylase were used to identify the isolates [17]. The characteristic IMViC pattern (++) - -, positive motility, E. coli was identified via lactose fermentation on EMB agar with a metallic sheen.

2.6 Antibiotic susceptibility testing

According to CLSI M100 (2023) criteria, susceptibility was tested on Mueller-Hinton agar using the Kirby-Bauer disc diffusion method [19]. The test organism was made into a 0.5 McFarland solution using a fresh overnight culture, which was then lawn-inoculated in 15 minutes. Using a disc dispenser, antibiotic discs (HiMedia Laboratories, Mumbai, India) were positioned on the agar with a minimum center-to-center spacing of 24 mm. For 16 to 18 hours, The plates underwent aerobic incubation at 37°C while inverted. A sliding calliper was used to assess zone diameters, which were then classified as resistant, intermediate, or vulnerable to CLSI 2023 breakpoints.

Ampicillin (10 µg), piperacillin-tazobactam (100/10 µg), cefotaxime (30 µg), ceftriaxone (30 µg), ceftazidime (30 µg), nitrofurantoin (300 µg), imipenem (10 µg), amoxicillin-clavulanate (20/10 µg), gentamicin (10 µg), cotrimoxazole (1.25/23.75 µg) and amikacin (30 µg).

2.7 ESBL detection

Every E. coli isolate was subjected to ESBL screening using the CLSI 2023 screening criteria: ESBL generation was probably suspected if the zone of inhibition was smaller than 22 mm for ceftazidime (30 µg), 27 mm or less for cefotaxime (30 µg), or 25 mm or less for ceftriaxone (30 µg) [19].

For phenotypic confirmation, the Combined Disc Test (CDT) was employed [19, 20]. On a Mueller-Hinton lawn culture, Discs with 30 µg of ceftazidime by itself and 30/10 µg of ceftazidime plus clavulanic acid were placed 30 mm apart and incubated for the whole night at 37°C. ESBL generation was confirmed when the zone width surrounding the ceftazidime-clavulanic acid disc increased by at least 5 mm as compared to ceftazidime alone. The scientific explanation is simple: clavulanate restores ceftazidime activity against producers by inhibiting the β -lactamase active site.

2.8 Multidrug resistance definition

According to the worldwide expert suggestion of Magiorakos et al., developed resistance to a minimum of one agent across three or more antimicrobial categories is the definition of multidrug resistance [15]. Intermediate results were not counted as non-susceptible for this purpose, in line with the cautious approach recommended by CLSI.

2.9 Quality control

Three CLSI reference strains were used for quality control [19]: *Escherichia coli* ATCC 25922 for general susceptibility testing, *Klebsiella pneumoniae* ATCC 700603 for the Combined Disc Test, and *Pseudomonas aeruginosa* ATCC 27853 for aminoglycoside and antipseudomonal β -lactam discs. Reference strains were tested with every new batch of Mueller-Hinton agar and every new lot of discs, and weekly thereafter. Out-of-range readings prompted investigation, retesting and corrective action before patient isolates were reported.

2.10 Statistical analysis

Version 27 of IBM SPSS Statistics for Windows (IBM Corp., Armonk, New York, USA) was used for analysis after data was input into Microsoft Excel 2019 with a 10% random recheck for transcription mistakes. For categorical variables, percentages and frequencies were employed. When any anticipated cell frequency was less than five, Fisher's exact test or the Pearson chi-square test were used to look for relationships. A two-tailed p value of less than 0.05 was considered statistically significant.

3. Results

3.1 Culture positivity and study population

Three hundred and fifty urine specimens were collected over 18 months, of which 97 (27.7%) yielded significant bacteriuria. The cohort comprised 213 outpatients (60.9%) and 137 inpatients (39.1%). Females accounted for 60.9% of the total sample. *E. coli* was the dominant uropathogen, recovered from 60 of 97 culture-positive specimens (61.9%); the remaining isolates were *Klebsiella pneumoniae* (11.3%), *Pseudomonas aeruginosa* (9.3%), *Proteus mirabilis* (4.1%) and other organisms in small numbers.

3.2 Phenotypic ESBL prevalence

Of the 60 *E. coli* isolates, 37 (61.7%) were verified to be ESBL producers by the CD Test. The distribution by patient type is shown in Table 1 and figure 1. ESBL prevalence was slightly higher in outpatient isolates (26 of 41, 63.4%) than in inpatient isolates (11 of 19, 57.9%). Despite this, There was no statistically significant difference ($\chi^2 = 0.169$; $p = 0.681$; $df = 1$).

Table 1. Phenotypic ESBL prevalence among outpatient and inpatient *E. coli* isolates.

Patient category	Total <i>E. coli</i> isolates (n)	ESBL positive n (%)	ESBL negative n (%)
Outpatients (OPD)	41	26 (63.4)	15 (36.6)
Inpatients (IPD)	19	11 (57.9)	8 (42.1)
Total	60	37 (61.7)	23 (38.3)

Chi-square test, OPD vs IPD ESBL prevalence: $\chi^2 = 0.169$; $df = 1$; $p = 0.681$ (not significant).

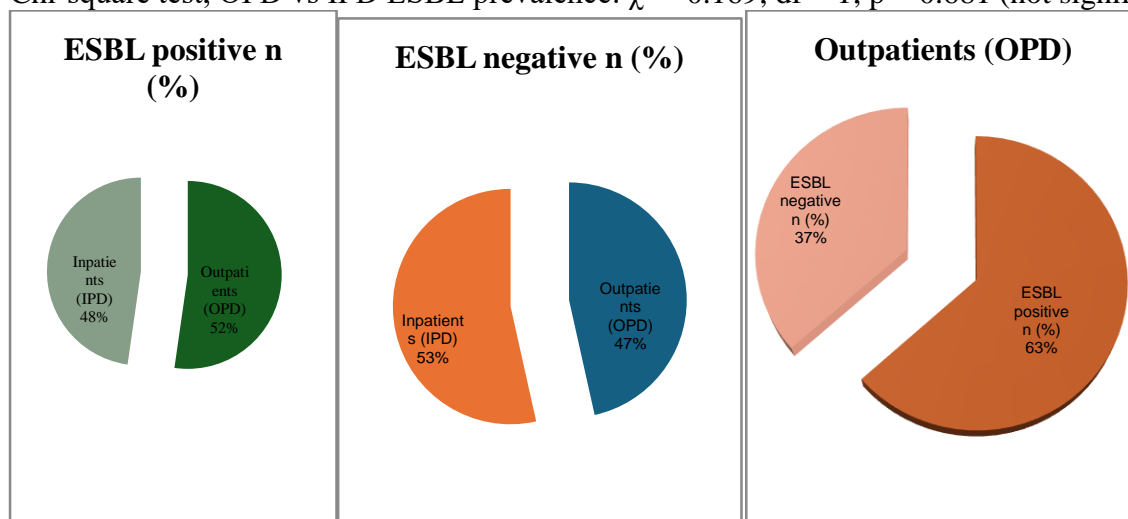


Figure 1. Phenotypic ESBL prevalence among outpatient and inpatient *E. coli* isolates

3.3 ESBL versus non-ESBL isolates' profiles of antibiotic resistance

Resistance rates differed substantially between ESBL producers and non-producers across the cephalosporin, fluoroquinolone and folate-inhibitor classes (shown in Table 2 and Figure 2). The differences for cefotaxime, ceftriaxone, ceftazidime, ciprofloxacin and cotrimoxazole were all highly significant. Carbapenem activity remained good in both groups, with imipenem resistance below 10% in ESBL producers as well.

Table 2. Comparative resistance rates between isolates of *E. coli* that produced ESBL (n = 37) and those that did not (n = 23).

Antibiotic	ESBL-positive n (%)	ESBL-negative n (%)	p value
Ampicillin	37 (100.0)	15 (65.2)	<0.001
Amoxicillin-clavulanate	23 (62.2)	5 (21.7)	0.003
Cefotaxime	35 (94.6)	4 (17.4)	<0.001
Ceftriaxone	33 (89.2)	3 (13.0)	<0.001
Ceftazidime	35 (94.6)	2 (8.7)	<0.001
Ciprofloxacin	31 (83.8)	7 (30.4)	<0.001
Norfloxacin	26 (70.3)	6 (26.1)	<0.001
Cotrimoxazole	31 (83.8)	9 (39.1)	<0.001
Gentamicin	20 (54.1)	3 (13.0)	0.002
Amikacin	11 (29.7)	2 (8.7)	0.059
Nitrofurantoin	7 (18.9)	2 (8.7)	0.460
Piperacillin-tazobactam	7 (18.9)	1 (4.3)	0.230
Imipenem	2 (5.4)	2 (8.7)	0.638

Chi-square or Fisher's exact test, depending on the situation; all p values are two-tailed.

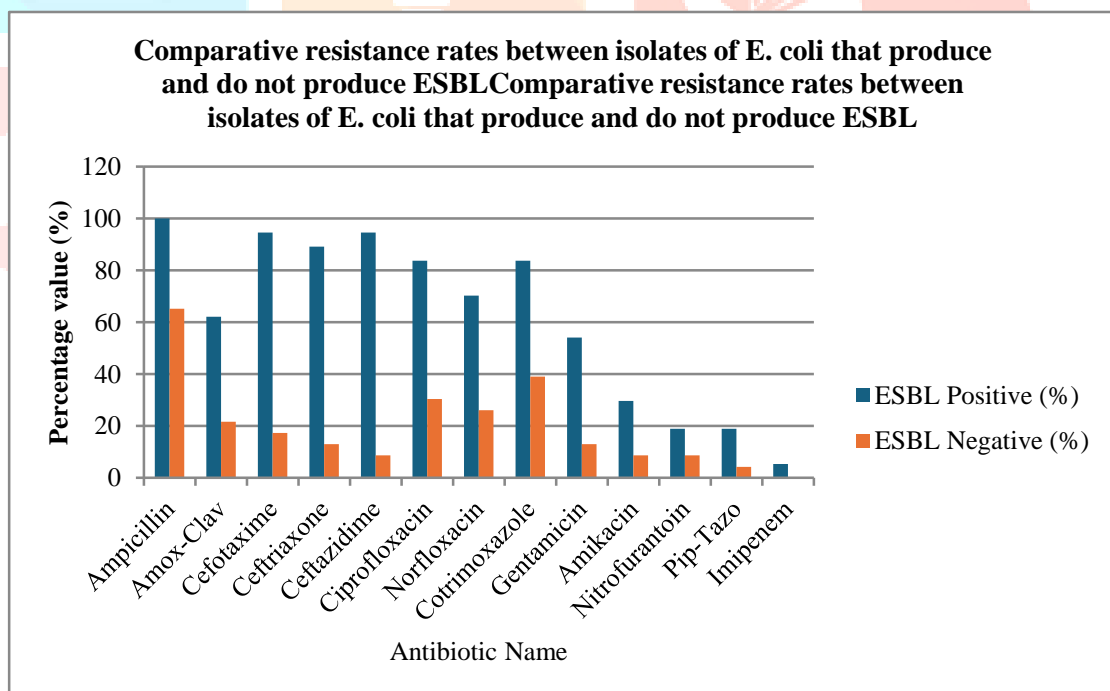


Figure 2. Comparative resistance rates among ESBL-producing and non-ESBL *E. coli* isolates

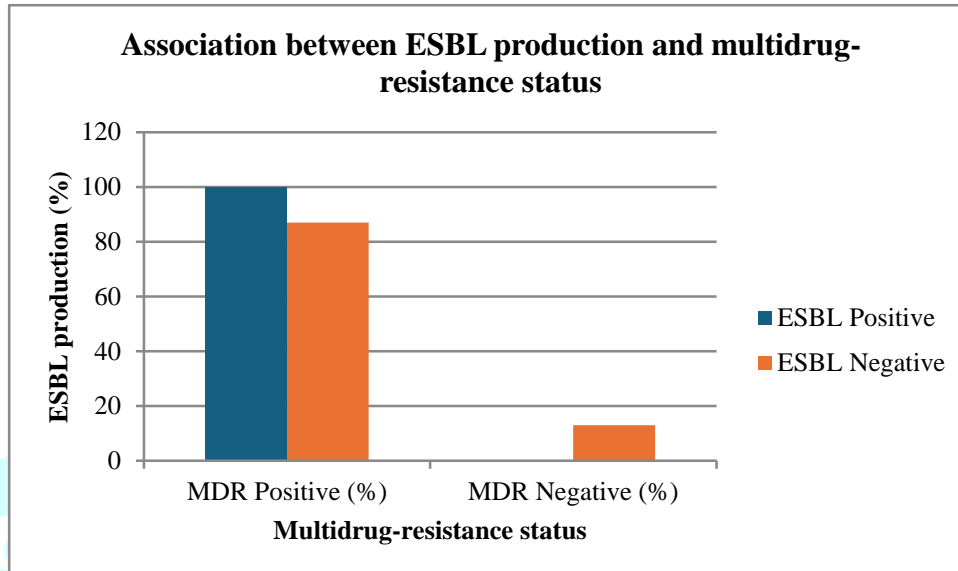
3.4 Association between ESBL production and multidrug resistance

According to the Magiorakos criteria listed in Table 3 and Figure 3, all 37 ESBL producers (100%) met the requirements for multidrug resistance. Of the 23 isolates that were not ESBL, 20 (87.0%) were also resistant to several drugs, whereas 3 (13.0%) were still sensitive to every category examined. Fisher's exact test revealed a statistically ESBL production and MDR status are significantly correlated ($p = 0.045$).

Table 3. Association between ESBL production and multidrug-resistance status (n = 60).

Category	MDR positive n (%)	MDR negative n (%)	Total
ESBL positive	37 (100.0)	0 (0.0)	37
ESBL negative	20 (87.0)	3 (13.0)	23
Total	57 (95.0)	3 (5.0)	60

Fisher's exact test: statistically significant, $p = 0.045$.

**Figure 3.** Association between ESBL production and multidrug-resistance status

3.5 Demographic and clinical correlates

ESBL prevalence by age group is summarised in Table 4 and Figure 4. The 40 to 59-year band carried the highest absolute number of ESBL producers, despite the fact that differences across age groups were not statistically significant ($p = 0.61$). ESBL prevalence was similar between female (62.5%) and male isolates (60.7%) ($p = 0.89$).

Table 4. Age-wise distribution of ESBL-producing *E. coli* (n = 60).

Age group (years)	Total <i>E. coli</i> (n)	ESBL positive n (%)
0-19	6	3 (50.0)
20-39	25	15 (60.0)
40-59	20	14 (70.0)
60 and above	9	5 (55.6)
Total	60	37 (61.7)

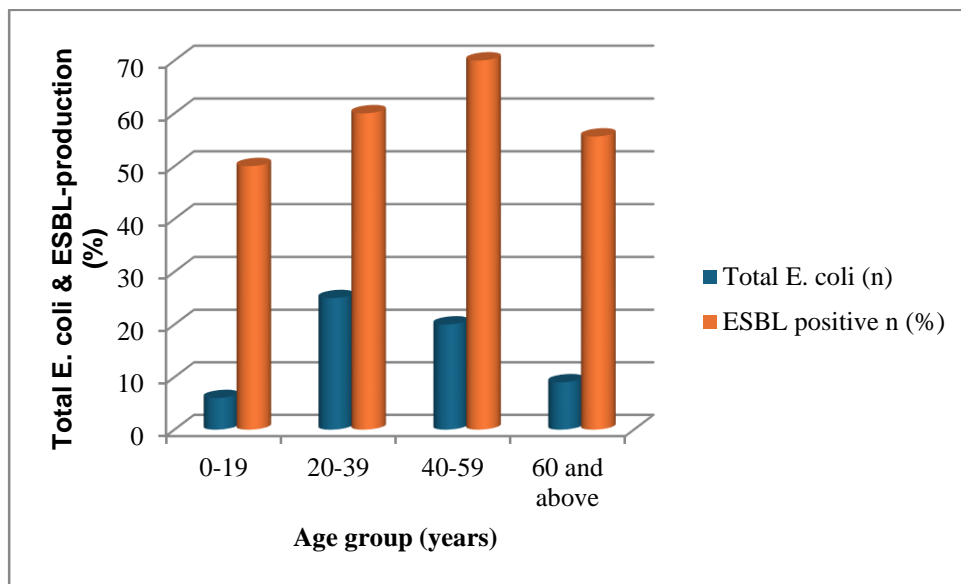


Figure 4. Distribution of ESBL-producing *E. coli* by age

4. Discussion

This study set out to quantify the phenotypic burden of ESBL production among urinary *E. coli* isolates at a tertiary care centre in central India, to compare the rates between outpatient and inpatient strains, and to examine its statistical association with multidrug resistance. Three findings stand out and merit detailed discussion.

4.1 ESBL prevalence and its meaning for empirical therapy

An ESBL prevalence of 61.7% places our cohort within the upper bracket of recent Indian reports, which have generally ranged between 30% and 75% in tertiary care settings [5,6,13,14]. Bajpai et al. from a tertiary centre in Indore reported an ESBL rate of 51% in uropathogens [13], while Taneja et al. described 73% ESBL production among complicated urinary *E. coli* isolates [14]. The number we report sits on the higher side, and the most likely explanation is referral bias: a tertiary care institution receives patients who have failed earlier empirical regimens, which selects for resistant organisms. Even allowing for this, the figure is uncomfortable.

Once 60% of urinary *E. coli* isolates produce ESBL, the empirical use of third-generation cephalosporins is essentially indefensible for any condition more serious than uncomplicated cystitis. Our resistance data underline this point: Ceftriaxone, cefotaxime, and ceftazidime resistance was found in 89% to 95% of ESBL-producing isolates, which is nearly the opposite of what many previous treatment guidelines expected. The empirical role of these drugs in UTI now needs to be reconsidered from first principles, not by incremental updating of dosing tables.

4.2 Outpatient versus inpatient ESBL prevalence: the collapse of the community-hospital boundary

The most striking observation in our data is that ESBL prevalence was marginally higher in outpatient isolates (63.4%) than in inpatient isolates (57.9%). The difference was not statistically significant, but the direction matters more than the *p* value. The conventional view that resistance is largely a hospital-acquired problem no longer holds in this setting. Several other recent Indian and global studies have made the same observation [5,10,11,21]. Venugopal et al. reported significant rises in community *E. coli* resistance in India between the pre-pandemic and pandemic periods [22], and Bevan et al. documented a global expansion of CTX-M-15-carrying ST131 lineages well beyond hospital boundaries [3].

The reasons are not difficult to identify. Antibiotics in India are still widely sold without a prescription, despite the 2014 Schedule H1 regulations [23]. Patients with recurrent UTI often receive several outpatient courses of fluoroquinolones or cephalosporins from successive providers, each course adding to the selective pressure. Studies conducted in India have shown that healthy community members carry ESBL-producing microbes in their faeces, reaching 50% or higher in

some surveys [12]. Environmental contamination of water and soil with antibiotic-resistant bacteria has also been described and probably contributes [12,24].

The practical consequence is that local antibiograms for UTI need to be stratified separately for OPD and IPD samples, and OPD empirical regimens must no longer be designed on the assumption that community isolates are more susceptible. In our cohort, they were not.

4.3 ESBL production and multidrug resistance

Every ESBL-producing isolate in our series was also multidrug-resistant (100%), and ESBL status and MDR were statistically significantly correlated ($p = 0.045$). This finding is biologically expected. ESBL genes such as blaCTX-M-15 are typically carried on large conjugative plasmids of the IncF group, alongside resistance determinants for fluoroquinolones (qnr genes, aac(6')-Ib-cr), aminoglycosides (16S rRNA methylases) and cotrimoxazole [2,4]. The single resistance phenotype is therefore rarely encountered; what one usually sees is a cluster of resistances co-selected by the same plasmid backbone.

Clinically, this means that an ESBL-positive result on a urinary isolate must trigger more than the substitution of carbapenem for cephalosporin. It should prompt re-evaluation of every empirical drug under consideration, because fluoroquinolone, aminoglycoside and cotrimoxazole resistance will commonly travel with it. Imipenem retained activity in 94.6% of our ESBL producers, which is reassuring, but the wider this drug is used, the faster carbapenemase-producing organisms will appear [8,9]. The conservation of carbapenems is the single most important stewardship objective at this point.

4.4 Drugs that still work, and how to use them

Three findings from our data carry direct practical relevance for empirical prescribing in this region. First, nitrofurantoin retained activity against 81.1% of ESBL producers and 91.3% of non-ESBL isolates. Resistance to nitrofurantoin has remained low globally despite more than seventy years of clinical use, a function of its multiple intracellular targets and the limited tissue distribution that restricts selection pressure to the urinary tract [25]. For uncomplicated lower UTI in non-pregnant women, even when the isolate is ESBL-positive, nitrofurantoin remains a defensible oral option, with the caveat that it is not effective against upper tract infections because of its low parenchymal levels.

Second, piperacillin-tazobactam retained activity against 81.1% of ESBL producers. Since the MERINO study revealed that this combination of β -lactam and β -lactamase inhibitor was inferior to meropenem in bacterial ESBL infections, there has been much discussion about it [26]. The bulk of evidence, however, supports its use for non-bacteraemic urinary tract infection, particularly for source control or step-down therapy [27]. In our setting, where carbapenem conservation is a high priority, piperacillin-tazobactam is a sensible parenteral option for complicated UTI caused by susceptible ESBL producers.

Third, amikacin retained activity in 70.3% of ESBL producers, a substantially better performance than gentamicin (45.9%). Single-daily-dose amikacin, given its concentration-dependent killing and predictable pharmacokinetics, is a reasonable adjunct or step-down agent in pyelonephritis with susceptible isolates, particularly where renal function permits.

4.5 Strengths and limitations

The prospective sequential inclusion of 350 participants over an 18-month period is one of the study's strengths, strict adherence to CLSI 2023 standards for both general susceptibility testing and ESBL confirmation, Three ATCC reference strains are used for quality assurance, and the explicit comparison of community and hospital isolates within a single laboratory and a single set of methods. The use of the Combined Disc Test for ESBL confirmation, although phenotypic, has well-characterised performance against molecular gold standards and remains the workhorse method in resource-limited settings [20,28].

There are a few restrictions to be aware of. The incidence of ESBL may vary in primary and secondary care institutions or in different parts of India, as the study was limited to a single tertiary care facility. Second, ESBL detection was phenotypic; the specific resistance genes (blaCTX-M, blaTEM, blaSHV variants) were not characterised, and clonal relationships between isolates were not examined. Whole genome sequencing or at least targeted PCR would add substantial epidemiological depth. Third, the cross-sectional design provides a snapshot of resistance at one

point in time and cannot capture temporal trends. Fourth, clinical results such as treatment response, recurrence and length of stay were not recorded, so the link between in-vitro ESBL status and in-vivo failure could not be analysed directly. Lastly, the statistical strength of the comparison between OPD and IPD is limited by the small number of the inpatient subgroup (n = 19); a larger sample might either confirm or revise the observed equivalence.

5. Conclusion

This tertiary care center in central India now often produces phenotypic ESBL from urinary *Escherichia coli* isolates, with a frequency of 61.7%. The rate is essentially indistinguishable between outpatient and inpatient isolates, verifying the extensive distribution of ESBL-producing microbes within the community. ESBL production is almost invariably accompanied by multidrug resistance, and resistance to third-generation cephalosporins, fluoroquinolones and cotrimoxazole is so high among ESBL producers that empirical use of these drugs is no longer defensible. Nitrofurantoin retains useful activity for uncomplicated lower UTI; piperacillin-tazobactam, amikacin and the carbapenems remain reliable parenteral options, though their use must be governed by stewardship if their longevity is to be preserved.

Three actions follow directly from these findings. Routine phenotypic ESBL screening should be incorporated into every urine culture report from this centre. Empirical regimens for UTI, in both OPD and IPD settings, need to be revised to acknowledge that the boundary between community-acquired and hospital-acquired resistance has effectively dissolved. A formal antimicrobial stewardship programme, with regular institutional antibiograms and prescription audit, is now an urgent institutional priority rather than an aspirational one.

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Conflicts of Interest

The authors affirm that they have no conflicting interests that are pertinent to this study.

Ethical Approval

Before the study began, the Institutional Ethics Committee of IMCHRC, Malwanchal University, Indore, evaluated and approved the protocol (Ref No: MU/Research/EC/Ph.D/2022/291B). All participants provided written informed permission, and the study was carried out in compliance with the 2013 edition of the Declaration of Helsinki.

Author Contributions

Aneesh Kumar Sharma planned the study, carried out the lab work, gathered and examined the data, and wrote the article. Kailash Jatav oversaw the research, helped with the study's design, analysed the data, critically edited the article, and gave the go-ahead for its publication. The final document was read and approved by both writers, who both agreed to take full responsibility for the work.

Data Availability

The corresponding author can provide the dataset used in this work upon reasonable request.

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