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A CASE-CONTROL STUDY OF RISK FACTORS FOR UNCOMPLICATED URINARY TRACT INFECTIONS CAUSED BY ESBL-PRODUCING ESCHERICHIA COLI AMONG FEMALE PATIENTS

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ABSTRACT

Background: Infections caused by extended-spectrum β -lactamase-producing *Escherichia coli* (ESBL-EC) complicate urinary tract infection (UTI) management. Identifying patient-specific risk factors is key to guiding empiric therapy. This study aimed to identify risk factors for ESBL-EC UTIs among Nigerian women, with a focus on demographic and behavioural characteristics. **Methods:** A case-control study was conducted at Federal Medical Centre, Owerri. There were 43 women with UTIs caused by ESBL-EC. Controls were 86 women with UTIs caused by non-ESBL-EC. Data on demographic, clinical, and behavioural factors were collected via questionnaire and medical records. Multivariable logistic regression was used to identify independent risk factors. **Results:** In the final model, frequent sexual activity (≥ 3 times per week) was the strongest behavioural predictor ($aOR = 4.85$, 95% CI: 1.98-11.89, $p<0.001$). Being under 35 years of age ($aOR = 3.41$, 95% CI: 1.51-7.72,

$p=0.003$) and being nulliparous (no history of childbirth) ($aOR = 2.92$, 95% CI: 1.18-7.21, $p=0.020$) were also significant independent risk factors. Previous antibiotic use ($aOR = 5.10$, 95% CI: 2.30-11.30, $p<0.001$) remained a strong clinical predictor. Conclusion: This study identifies a risk profile for ESBL-EC UTI centred on young, nulliparous women with high sexual frequency. These findings suggest that community-based selection pressure, driven by antibiotic use and behavioural factors, is a key driver of ESBL-EC in this setting. Empiric therapy guidelines and antimicrobial stewardship programs should consider this high-risk demographic.

KEYWORDS: ESBL, Escherichia coli, Uncomplicated Urinary Tract Infection, Risk Factors, Sexual Behaviour, Nigeria, Antimicrobial Resistance.

1. INTRODUCTION

Extended-spectrum beta-lactamase (ESBL)-producing *E. coli* are antibiotic-resistant strains of *E. coli*. *E. coli* are prevalent bacteria that usually live harmlessly in the gut. ESBL-producing strains are bacteria that produce an enzyme called an extended-spectrum beta-lactamase, which makes them more resistant to antibiotics and harder to treat infections. Extended-spectrum beta-lactamase (ESBLs) – producing *Enterobacteriaceae* can hydrolyse penicillins, extended-spectrum cephalosporins, and monobactams [23, 25]. ESBLs are commonly classified into three types: CTX-M, SHV, and TEM [3]. Gram-negative bacilli produce these enzymes, and ESBL-producing *E. coli* has been isolated not only in the hospital setting but also in the community.

Uncomplicated urinary tract infection (UTI) is a bacterial infection of the bladder and associated structures. This condition occurs in patients without structural abnormalities of the urinary tract or comorbidities such as diabetes, an immunocompromised state, recent urologic surgery, or pregnancy. An uncomplicated UTI is also referred to as cystitis or lower tract UTI. Urinary Tract Infections (UTIs) caused by extended-spectrum β -lactamase-producing *Escherichia coli* (ESBL-EC) represent a critical threat to global health, leading to increased treatment failure, healthcare costs, and mortality [7]. The main challenge with ESBL-producing bacteria is that their encoded genes are constantly changing, and they have recently been shown to harbour genes conferring resistance to several non- β -lactam antibiotics, resulting in limited medical options and high mortality rates [13].

These resistant strains have been associated with increased morbidity, mortality, and healthcare costs, as they limit the effectiveness of standard antibiotic therapies. , driven by inappropriate antimicrobial therapy during initial phases of treatment [24, 26, 15, 17] and facilitated by global interconnectedness through international travel, trade, and food distribution [19]. In Nigeria, the burden of antimicrobial resistance is severe, as our previous work at the Federal Medical Centre (FMC) Owerri demonstrated a high prevalence of ESBL-EC, predominantly harbouring the blaCTX-M gene [9].

While established risk factors for ESBL-EC include recent antibiotic use, history of recurrent urinary tract infections, presence of a urinary catheter at admission, healthcare exposure, and comorbidities [10, 16], there is a pressing need to elucidate the role of demographic and behavioural factors, particularly in community-onset infections. Young, sexually active women bear the highest incidence of UTIs overall [20, 12], but it is unclear if this group is disproportionately affected by antimicrobial-resistant UTIs. Frequent sexual activity is a well-recognised trigger for recurrent cystitis, which often leads to repeated antibiotic exposure, potentially selecting for resistant strains in the vaginal and gut flora [1]. Conversely, the relationship between childbirth (parity) and ESBL-EC risk is complex. In contrast, childbirth can cause functional changes that predispose to UTIs, it is also associated with different healthcare exposures and antibiotic use patterns.

The hypothesis that young, nulliparous women with high sexual frequency represent a distinct, high-risk group for ESBL-EC UTIs has not been thoroughly investigated in our setting. Therefore, this case-control study aimed to identify risk factors for ESBL-EC UTIs among female patients at FMC Owerri, with a specific focus on age, sexual history, and parity, to inform targeted prevention and empiric therapy strategies.

2. MATERIALS AND METHODS

2.1 Study Setting and Data Sources

We conducted a cross-sectional case-control study among adult females who registered at the outpatient department of Federal Medical Centre, Owerri and received ambulatory care from February 2023 to September 2023 with complaints of uncomplicated urinary tract infection. The physician in charge assessed, documented, and referred these patients to the hospital's microbiology laboratory for urine microbiological culture and sensitivity testing. The symptoms reported by the patients included dysuria, urgency to urinate, frequency, suprapubic pain and cloudy, strong-smelling or dark urine. Federal Medical Centre, Owerri, is

a large-scale tertiary teaching hospital located in the urban capital city of Imo State, Owerri, with a reported 700-bed capacity.

We identified patients with urine cultures growing $\geq 100,000$ colony-forming units (CFU)/mL of ESBL-producing *Enterobacteriaceae*, *E. coli*. *E. coli* was considered an ESBL producer if it met the Clinical and Laboratory Standards Institute (CLSI) criteria for positive phenotypic combined-disc testing for ESBL production.

2.2 Ethical Approval

Ethical approval was sought and obtained from the FMC Owerri ethics committee. Further permission was obtained from the physician in charge of the outpatient department and the medical laboratory scientist in charge of the microbiology laboratory.

2.3 Exclusion criteria

Several factors constituted the exclusion criteria for this study, including those who refused to be enrolled or interviewed; those with asymptomatic bacteriuria; those with unavailable or incomplete medical records; those with CFUs less than 100,000; women in correctional custody; pregnant women; women in admission; and women under 18 years.

2.4 Study Participants and Sample Size

Cases were 43 consecutive, non-repetitive female patients (aged ≥ 18 years) with a laboratory-confirmed UTI caused by ESBL-EC. Controls were 86 female patients with a UTI caused by non-ESBL-EC, recruited during the same study period. A case-to-control ratio of 1:2 was used. Control subjects were simultaneously recruited at the outpatient department. Controls consisted of symptomatic adult female outpatients with urine cultures positive for $\geq 100,000$ CFU/mL of non-ESBL-producing *E. coli*. Cases were matched 1:2 with controls based on age to ensure compatibility of the underlying population.

2.5 Data Collection

Data were collected manually using a structured questionnaire and hospital records. The review of hospital records was conducted by an infectious disease-trained nurse. Variables included:

Demographics: age (categorised as <35 vs. ≥ 35 years),

Clinical Factors: History of diabetes, repeated or recurrent UTI (defined as > 3 episodes of UTI within one year), previous hospitalization (for longer than 24h within three months preceding hospital visit), previous antibiotic use (defined as any prior exposure to antibiotic for longer than 24h within three months preceding hospital visit [10, 22, 14].

Behavioural And Obstetric Factors: Sexual Frequency: self-reported frequency of sexual intercourse (categorised as <3 times per week vs. ≥ 3 times per week). Parity: categorised as nulliparous (no childbirths) vs. parous (≥ 1 childbirth).

2.6 Laboratory Methods

2.6.1 Specimen Collection & Transport

Sterile, leak-proof containers were provided for patients at the laboratory. They were advised correctly on how to collect the study samples. Clean-catch midstream urine samples were provided by the study population and processed within 2 hours of collection. The samples that could not be handled immediately were refrigerated at 4°C for up to 24 hours.

2.6.2 Sample Processing

All well-mixed mid-stream urine samples were cultured on routine culture media by the semi-quantitative method as described in the World Health Organisation (WHO) manual [28]. Using a 0.001 mL sterile calibrated wire loop, 1 μ L of urine was inoculated onto MacConkey and blood agar plates (HiMedia Laboratories Pvt. Ltd., India) by streaking, and the plates were incubated aerobically for 18-24 hours at 37°C to yield Colony-Forming Units per mL (CFU/mL). The cultures were extended to 48h if no growth was observed at 24h. The colonies were examined after 18-24h. On Blood Agar, *E. coli* colonies were typically greyish and moist. They may be beta-haemolytic, whereas on MacConkey, *E. coli* was identified by the formation of pink/red colonies due to acid precipitation of the neutral red dye.

Significant bacteriuria was defined as $CFU \geq 10^5$. Plates having at least 100 colonies were accepted. Calculation was done as follows:

$$(\text{Number of colonies}) \times (1/\text{loop volume}) = \text{CFU/mL}$$

$$100 \text{ colonies with a } 0.001 \text{ mL loop} = 100 \times 1000 = 10^5 \text{ CFU/mL}$$

2.6.3 Pure Culture and Biochemical Tests

To obtain a pure culture, a sterile wire loop was used to pick a single, well-isolated colony that appeared to be *E. coli* (pink on MacConkey agar) from the primary culture plate. The colony was subcultured onto a freshly prepared Blood agar (Merck, Germany) plate using the quadrant streak method to ensure proper separation. The plate was incubated aerobically at 35-37 °C for 16-18 hours, and it showed growth of a single colony type, similar in shape, size, colour, and texture, thereby confirming the purity of the culture. Confirmation tests were performed to verify that it was *E. coli*. Gram stain showed gram-negative rods, and two biochemical tests, indole and oxidase, were positive and negative, respectively [29].

2.6.4 ESBL Detection

ESBL was detected by a screening test using the disk diffusion method. All the *E. coli* isolates were tested against an indicator cephalosporin (ceftriaxone, 30 µg) on Mueller-Hinton agar (Merck, Germany) according to the Clinical and Laboratory Standards Institute. For quality control, the *E. coli* ATCC 25922 standard strain was used in parallel. The isolate was suspected to be an ESBL producer if the zone of inhibition was $\leq 19\text{mm}$.

2.6.5 ESBL Confirmation

The presence of *E. coli*, which is an ESBL producer, is confirmed using a combination disk test. A standardised *E. coli* suspension (0.5 McFarland standard) was prepared and lawn cultured on Mueller-Hinton agar. Four disks were placed: cefotaxime (CTX, 30 µg) and ceftazidime (CAZ, 30 µg) alone, and the combination disks cefotaxime + clavulanic acid (CTX/CLA, 30/10 µg) and ceftazidime + clavulanic acid (CAZ/CLA, 30/10 µg). The plates were cultured aerobically at 35°C. An increase in the zone diameter of $\geq 5\text{mm}$ for the combination disks versus the antibiotic disk alone confirmed the presence of an ESBL.

2.6.6 Statistical Analysis

Data were analysed using SPSS version 25. Categorical variables were compared using the Chi-square test. Variables with p-values < 0.10 in the univariate analysis were entered into a binary logistic regression model to identify independent risk factors, and the results were presented as adjusted Odds Ratios (aOR) with 95% Confidence Intervals (CI). A p-value < 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Participant Characteristics

A total of 129 participants (43 cases, 86 controls) were included. The median age was significantly lower in Cases (29 years, IQR: 24-34) than in Controls (38 years, IQR: 30-47), $p<0.001$.

3.2 Univariate Analysis of Risk Factors

The results of the univariate analysis are presented in Table 1. Cases were significantly more likely to be under 35, nulliparous, report frequent sexual activity, and have a history of previous antibiotic use and hospitalisation.

Table 1. Univariate Analysis of Risk Factors for ESBL-EC UTI.

Risk Factor	Cases (n=43) n(%)	Controls (n=86) n(%)	p-value
Age < 35 years	32 (74.4%)	38 (44.2%)	0.001
Previous Antibiotic Use	30 (69.8%)	28 (32.6%)	<0.001
Previous Hospitalization	22 (51.2%)	25 (29.1%)	0.012
History of Diabetes	4 (9.3%)	8 (9.3%)	1.000
Previous UTI	18(41.9%)	26 (30.2%)	0.183
Frequent Sexual Activity(≥3/week)	26 (60.5%)	23 (26.7%)	<0.001
Nulliparous (No Childbirth)	18 (41.9%)	19 (22.1%)	0.017

3.3 Multivariate Logistic Regression Analysis

All significant variables from the univariate analysis were included in the multivariate model (Table 2). After adjustment, **frequent sexual activity** (aOR = 4.85, 95% CI: 1.98-11.89, p<0.001), **age < 35 years** (aOR = 3.41, 95% CI: 1.51-7.72, p=0.003), and **nulliparity** (aOR = 2.92, 95% CI: 1.18-7.21, p=0.020) remained strong and independent risk factors for ESBL-EC UTI. **Previous antibiotic use** (aOR = 5.10) also remained a powerful predictor.

Table 2. Multivariate Analysis of Risk Factors for ESBL-EC UTI.

Risk Factor	Adjusted Odds Ratio (aOR)	95% Confidence Interval	p-value
Previous Antibiotic Use	5.10	2.30 - 11.30	<0.001
Frequent Sexual Activity (≥3/week)	4.85	1.98 - 11.89	<0.001
Age < 35 years	3.41	1.51 - 7.72	0.003
Nulliparous	2.92	1.18 - 7.21	0.020
Previous Hospitalization	1.95	0.86 - 4.41	0.110

This study identifies a distinct risk profile for uncomplicated UTIs caused by ESBL-EC: young, nulliparous women with high sexual frequency. This finding shifts the narrative of ESBL-EC risk away from being solely a healthcare-associated problem and highlights its firm establishment in the community, driven by specific behavioural patterns.

The strong independent association with frequent sexual activity (aOR=4.85) is a cornerstone of this profile. Urinary tract infections (UTIs) in females are acute, often recurring infections thought to be caused by bowel flora that have ascended into the bladder [10]. Frequent sexual intercourse may cause trauma as well as move vaginal or bowel bacteria (or both) into the urethral opening, facilitating ascent to the bladder. Sexual activity may also transmit

uropathogens. It has been shown that UTI diagnosis rapidly increases following the first sexual activity. The risk of UTI increases 3-5 fold after initiating sexual activity of any type. Epidemiologic evidence and several case reports suggest that *Escherichia coli* causing urinary tract infection (UTI) may be transmitted between sex partners [4]. Sexual intercourse facilitates the mechanical introduction of uropathogenic *E. coli* into the urethra [12]. Women with high sexual frequency have more exposure events, increasing the probability of inoculation with an ESBL-EC strain, particularly if they or their partners have a colonised gut flora. This behaviour, when combined with antibiotic use for prior UTIs, creates a powerful cycle that selects and maintains resistant bacteria.

The significant risk associated with nulliparity ($aOR=2.92$) is a notable finding. It suggests that the risk factors in these young women are behavioural and community-based, rather than linked to the anatomical and physiological changes of childbirth. This risk factor agrees with the review documentation of [21]. In a prospective study by Haylen et al (2009), 1140 women aged 18–98 years were examined for recurrent UTI in different physiologic and pathologic conditions. A correlation was observed between nulliparity and recurrent UTI, particularly in women younger than 50 years. The authors suggested that stretch and relaxation of the birth canal caused by pregnancy and delivery may be beneficial in preventing recurrent UTI by reducing the frictional effect of intercourse. A reduced frequency of intercourse and number of sexual partners may also account for these findings [21].

Nulliparous women in this present study may be more sexually active on average, or may experience different patterns of antibiotic prescribing for UTIs, potentially receiving shorter courses or different agents that could select for resistance. This contrasts with parous women, whose UTIs might be more related to functional changes and whose healthcare interactions are often dominated by antenatal and postnatal care, which may involve different antibiotic stewardship environments.

The result in this current research that youthful age (<35) contributes significantly to uncomplicated UTI in females is in line with the findings of [18]. However, it contradicts the research findings of [2, 6, 8, 25]. In their study, patients with recurrent urinary tract infections (UTIs) were significantly older (over 65 years) than those with single episodes. It is important to note, however, that people over 65 could have comorbidities and significant anatomical and physiological changes of ageing, which can impact their frequency and complications of UTIs. Younger women are likely to have more sex than older women.

Sexual behaviours, especially sexual activity and multiple partners, are risk factors for uncomplicated urinary tract infections. Among young females, sexual activity is recognised as a crucial risk factor specifically related to the frequency of sexual activity and multiple partners [18, 25]

The potent combination of young age (<35) and high sexual frequency defines a core demographic for community-acquired UTIs. This group is frequently prescribed antibiotics, often empirically. Our data indicate that when these women present with a UTI, there is a high probability that it is caused by an ESBL-EC, making standard empiric therapy with oral cephalosporins or fluoroquinolones likely to fail. The persistence of previous antibiotic use as the strongest overall predictor (aOR=5.10) confirms that it is the critical fuel for this fire, with behavioural factors providing the spark.

3.4 LIMITATIONS

This study is subject to the limitations of a single-centre design and the potential for recall bias in self-reported behavioural data. However, the use of a control group with UTI and the strength of the adjusted associations support the validity of the conclusions.

4. CONCLUSION

This study establishes that young, nulliparous women with high sexual frequency constitute a high-risk group for ESBL-EC UTIs in our setting, with recent antibiotic use acting as a significant accelerant. This profile underscores the community-driven nature of antimicrobial resistance. Empiric therapy guidelines must be refined to account for these demographic and behavioural risk factors, and public health efforts must focus on preventing resistance in this key population.

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