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Antimicrobial Resistance in Pregnancy: Prevalence and Characterization of ESBL-Producing Uropathogens in a Nigerian Tertiary Hospital

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Abstract

Extended-spectrum beta-lactamases (ESBLs) are increasingly contributing to antibiotic resistance, particularly in urinary tract infections (UTIs) among pregnant women. This study aimed to determine the prevalence of ESBL-producing bacterial strains and assess their antibiotic resistance profiles in urine samples collected from pregnant women at General Hospital Ilorin. Antimicrobial resistance (AMR) remains a critical global health issue, compounded by the rise of multidrug-resistant (MDR) organisms such as ESBL producers. These pathogens pose significant challenges in infection control, especially in pregnant women who are more susceptible to UTIs. A six-month cross-sectional study was conducted in the Department of Medical Laboratory Science at General Hospital Ilorin. A total of 250 urine samples were aseptically collected from pregnant women aged 15–40 years who were clinically suspected of having UTIs. The samples were screened for ESBL-producing bacteria using selective media, and antibiotic susceptibility testing was performed using standardized protocols. Out of the 250 samples analyzed, 95 (38%) demonstrated significant bacterial growth. The predominant uropathogens were *Escherichia coli* (14%) and *Klebsiella* species (24%), with *Klebsiella pneumoniae* and *Klebsiella oxytoca* each constituting 12% of the isolates. The highest infection rates were observed among women aged 21–30 years. ESBL-producing isolates exhibited resistance to commonly used antibiotics including gentamicin, levofloxacin, ceftazidime, and ciprofloxacin, while maintaining susceptibility to imipenem and piperacillin. The findings of this study highlight a worrisome prevalence of ESBL-producing bacteria and underscore the growing challenge of antibiotic resistance in pregnant women. A strong correlation was observed between ESBL production and multidrug resistance, emphasizing the urgent need for continuous surveillance, proper antibiotic stewardship, and the development of effective treatment strategies tailored for this vulnerable population.

Introduction

The history of β-lactam antibiotics began in 1928, when Alexander Fleming observed that the *Penicillium* mold secreted a substance with antibacterial properties (Sebastian *et al*., 2019). Although Fleming recognized the importance of his discovery, it was not immediately pursued or validated, particularly due to the limited focus on its potential during World War II (Kardos and Demain, 2013). There was initially considerable debate regarding the chemical structure of penicillin discovered by Fleming. This uncertainty was resolved in 1945 through the work of Dorothy Hodgkin, who determined that penicillin contains a four-membered ring structure known as the β-lactam ring, or 2-azetidinone (Sebastian *et al*., 2019). The β-lactam structure was viewed with suspicion since it was thought that its ring strain would remove the usual amide resonance, making it extremely reactive with nucleophiles. This notion appeared to be supported by early synthesis difficulties in turning β-amino acids into β-lactams. But by applying carbodiimide activation, Sheehan eventually broke through this synthetic barrier and famously called the β-lactam the "enchanted ring." However, simple β-lactams do not demonstrate exceptional reactivity in acyl transfer reactions with nucleophiles, according to later experimental studies (Fisher *et al*., 2016). Despite this, the β-lactams used as antibiotics are more complex than the basic β-lactam ring. Their antibacterial activity depends on carefully tuned reactivity towards nucleophiles and the presence of a nearby negative charge for biological recognition (Pratt *et al*., 2010). In penicillins, cephalosporins, and carbapenems, this activation is achieved by fusing a second ring to the β-lactam, and a carboxylate group provides the required negative charge. In contrast, monobactams and monosulfactams integrate both the activating features and negative charge through specific functional groups attached to the nitrogen atom of the β-lactam ring.

Methodology

A cross-sectional descriptive study was conducted at the Department of Medical Laboratory Science, General Hospital Ilorin, Kwara State, Nigeria. The research spanned a period of six months and focused on evaluating the prevalence of Extended Spectrum Beta-Lactamase (ESBL)-producing bacteria in pregnant women with symptoms suggestive of urinary tract infections (UTIs). This study included 250 pregnant women aged between 15–40 years, who were suspected to have UTIs based on clinical signs and symptoms. A purposive sampling technique was employed to select participants. Each subject provided a single midstream urine sample for microbiological evaluation. Clean-catch midstream urine samples were collected aseptically using sterile, wide-mouth, leak-proof universal containers. Participants were educated on proper sample collection procedures to avoid contamination. Collected samples were promptly labeled and transported to the laboratory within one hour under cold chain conditions for immediate processing. Urine samples were subjected to microbiological analysis immediately upon arrival at the laboratory. Each specimen was thoroughly mixed and inoculated using a standard calibrated platinum wire loop delivering 0.001 mL of urine. Inoculation was performed on two types of culture media which were Cysteine Lactose Electrolyte Deficient (CLED) agar and MacConkey agar. After inoculation, the agar plates were incubated in an aerobic environment at 37°C for 18 to 24 hours. Following incubation, plates were examined for colony morphology, color, hemolysis, and lactose fermentation status. Colony counts were estimated by multiplying the number of colonies by the loop factor (1000), and results were expressed in colony-forming units per milliliter

(CFU/mL). A bacterial count of $\geq 10^5$ CFU/mL was interpreted as significant bacteriuria, consistent with clinical infection criteria, especially in asymptomatic or mildly symptomatic individuals. Mixed growths or counts below the threshold were considered contamination unless clinically justified and supported by microscopy and symptomatology. Isolated bacterial colonies were first subjected to Gram staining, a differential staining technique used to classify bacteria into Gram-positive or Gram-negative groups based on the composition of their cell walls. This initial step provides essential information regarding the bacterial morphology and structural characteristics. Following Gram staining, a series of biochemical tests were performed to further identify the species of the isolated bacteria. Presumptive ESBL production was screened using MacConkey agar supplemented with cefotaxime and ceftazidime (2 µg/mL each). Isolates that showed reduced susceptibility were subjected to the combined disc synergy test (CDST) using discs of ceftazidime (30 µg) and cefotaxime (30 µg) alone and in combination with clavulanic acid (10 µg). A ≥5 mm increase in zone diameter in the presence of clavulanic acid was interpreted as ESBL positive. Antimicrobial susceptibility testing was performed using the Kirby-Bauer disc diffusion method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines. Plates were incubated at 37°C for 18–24 hours, and the zones of inhibition were measured and interpreted according to CLSI breakpoints. Multidrug resistance was defined as non-susceptibility to at least one agent in three or more antimicrobial categories. Plates were incubated at 37°C for 18 to 24 hours, after which the zones of inhibition around antibiotics were measured and interpreted using CLSI breakpoints to determine susceptibility. Multidrug resistance was defined as resistance to at least one antibiotic in three or more different antimicrobial categories. To identify the bacteria, several biochemical tests were performed. The urease test involved using urea broth or slants, where a color change to pink indicated positive urease activity. The indole test assessed the bacteria's ability to metabolize tryptophan, with a red ring forming after adding Kovac's reagent to indicate a positive result. The citrate utilization test was done using Simmons' citrate agar, where a color change from green to blue showed the bacteria could utilize citrate. The triple sugar iron test evaluated the fermentation of glucose, lactose, and sucrose, as well as hydrogen sulfide production, by observing changes in color and gas formation. The motility test used motility agar, where the presence of diffused growth away from the stab line confirmed motility. Together, these biochemical tests helped confirm the identity of ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* isolates.

Summary table of current options to treat infections due to ESBL-producing Enterobacteriaceae in different groups of patients

Group[1]	Characteristics of infection in each group	Options for treatment (dosing with normal renal function)
1	Severe infections; or Infections with a high-risk source; or/and Severely-immunocompromised patients	Imipenem (500 mg/6 h) Meropenem (1 g/8 h)
2	Non-severe infections from intermediate-risk source	Ertapenem (1 g/day) Piperacillin-tazobactam (4.5 g/6–8 hr in extended infusion) Imipenem (500 mg/8 hr) Meropenem (1 g/8 hr)
3	Non-severe urinary tract infection	Ertapenem (1 g/day) Piperacillin-tazobactam (4.5 g/6–8 hr in extended infusion) Amoxicillin-clavulanic acid (intravenous: 2.2 g/8 hr; oral for UTI: 1.250 g/8 hr) Aminoglycosides (amikacin: 15–20 mg/kg/day; gentamicin or tobramycin: 5–7 mg/kg/day) Plazomycin (15 mg/kg/day) Cephamycins (flomoxef: 1 g/8 hr; cefmetazole: 1 g/8 hr) Imipenem (500 mg/8 hr) Meropenem (1 g/8 hr) Fosfomycin iv (4 g/6 hr) Trometh amol-oral for non-bacteraemic UTIs (3 g/48 hr) Ciprofloxacin-oral for non-bacteraemic UTIs (400 mg/8–12 hr)

Fig 1: Current Options for treatment of infections due to ESBL-producing Enterobacteriaceae (Gutierrez-Gutierrez and Rodriquez-Bano, 2019).

RESULT

Table 1: A total of 250 urine samples were collected from pregnant women for this study. Out of these, 95 samples (38.0%) showed significant bacteriuria upon culture. Among the positive cultures, Escherichia coli was isolated from 35 cases, while Klebsiella species (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*) were identified in 60 cases. The distribution of isolates indicated that Klebsiella species accounted for nearly half of all bacterial isolates, with *Klebsiella pneumoniae* and *Klebsiella oxytoca* each contributing 30 isolates (12.0%), making up a combined 24.0% of the total specimens analyzed.

Table 1: Prevalence of uropathogens isolated from the specimens

Organisms	Number of specimen	Percentage (%) Occurrence
Escherichia coli	*35*.00	14.00
Klebsiella pneumonia	*30*.00	12.00
Klebsiella oxytoca	30.00	12.00
Total	95.00	38.00

Table 2: In the 15–20 age group, bacterial presence is minimal, with only *Klebsiella pneumoniae* and *Escherichia coli* detected each in 5 cases, totaling 10. In contrast, the 21–25 age group shows a lower overall case count of 5 but a more varied bacterial profile like the *Klebsiella oxytoca* and *Escherichia coli* appear in 10 cases each, while *Klebsiella pneumoniae* is found in 5 cases. The 26–30 age group also reports 25 cases, with *Escherichia coli* being more prevalent at 15 cases and *Klebsiella pneumoniae* at 10. no *Klebsiella oxytoca* cases are observed in this group. For individuals aged 31–35, the distribution is relatively even, with `10 cases of *Klebsiella oxytoca*, and 5 cases each of *Klebsiella pneumoniae* and *Escherichia coli*, amounting to 20 cases. Lastly, the 36–40 age group records a slight decline in bacterial cases, showing 10 instances of *Klebsiella oxytoca* and 5 of *Klebsiella pneumoniae*, while *Escherichia coli* is absent, making a total of 15 cases.

Table 2: Prevalence of bacteria species in relation to age

Age group	Klebsiella *oxytoca*	*Klebsiella pneumoniae*	*Escherichia coli*	Total
15-20	0	5	5	10
21-25	5	5	10	25
26-30	0	10	15	25
31-35	10	5	5	20
36-40	10	5	0	15
Total	**25**	30	35	95

Table 3: Analysis of specimen growth across age groups revealed that individuals aged 21–25 and 26–30 exhibited the highest levels of bacterial growth, each with 25 cases, accounting for 10.00% respectively. In contrast, the lowest growth was observed in the 15–20 age group, with only 10 cases

(4.00%), as shown in Table 3. Furthermore, the distribution of *Klebsiella* species and *Escherichia coli* across age groups indicated that patients aged 21–25 and 26–30 years had the highest prevalence, each contributing 25 cases (10.00%) to the total.

Table 3: Prevalence of bacteria species in relation to age giving in percentage

Age group(years)	Number examined (%)	Number of significant growth (%)
15-20	45(18)	10(4)
21-25	50(20)	25(10)
26-30	55(22)	25(10)
31-35	60(24)	20(8)
36-40	40(16)	15(6)
Total	250(100)	95(38)

Table 4: Out of the 95 bacterial isolates analyzed, *Escherichia coli* demonstrated alarming resistance trends. Every isolate (100%) was resistant to Augmentin, Ciprofloxacin, Ceftazidime, and Imipenem. This widespread resistance to vital antibiotics including penicillins and cephalosporins strongly suggests the presence of extended-spectrum beta-lactamase (ESBL) enzymes, which deactivate these drugs by breaking down their beta-lactam structures. Supporting this, 85.7% of *E. coli* isolates also showed resistance to piperacillin-tazobactam. However, 14.3% remained sensitive to piperacillin-tazobactam, and notably, all isolates (100%) were susceptible to both nitrofurantoin and amikacin. *Klebsiella pneumoniae* displayed a similarly high resistance pattern, with 100% resistance to ceftazidime, Augmentin, Imipenem, and Ciprofloxacin.

Table 4: Antibiotic susceptibility pattern of bacternuria Isolates

Bacterial IsolatesPattern	AST	AUG	LEV	CAZ	IMI	PTZ	NI	CRO	AK	GM

Eschericia coli S		5(14.3)	35(100)		35(100)		-	
(*n=35*)	**I**	25(71.4)					-	
	R	35(100)	10(28.5)	35(100)	35(100)	30(85.7)	35(100)	-
Klebsiella	**S**				30(100)	-	30(100)	20(66.6)
pnemoniae (n=30)	**I**		5(16.6)					2(28.6)
	R	**30**(100)	25(83.3)	30(100)	30(100)	-	30(100)	
Klebsiella	**S**				30(100)	-	20(66.6)	
Oxytoca(n=6)	**I**		**15**(50)			-	10(28.6)	
	R	**30**(100)	15(50)	30(100)	30(100)	-	30(100)	30(100)
Total (*n=95*)	**S**				65(68.4)	7(100)	85(89.4)	20(33.3)
	I		45(47.3)				10(10.5)	10(16.6)
	R	95(100)	50(52.6)	95(100)	95(100) 3	0(31.5)	95(100)	30(50)

AUG: augumentin, LEV: levofloxacin, CAZ: ceftazdime, IMI:imipenem PTZ: piperacillin-tazobactam,NI: nitofurantoin, AK:amikacin, GM: gentamcin,CRO:ciprofloxacin

The observed resistance pattern, including 83.3% resistance to Levofloxacin, is consistent with the behavior of ESBL-producing organisms, which are capable of hydrolyzing beta-lactam antibiotics and rendering them ineffective. All *Klebsiella pneumoniae* isolates were fully sensitive to Amikacin and Piperacillin-Tazobactam, and 66.6% remained susceptible to Gentamicin, suggesting these antibiotics still offer some therapeutic potential despite widespread resistance. *Klebsiella oxytoca* isolates also showed complete resistance (100%) to Augmentin, Ciprofloxacin, Imipenem, Ceftazidime, and Gentamicin, and demonstrated 50% resistance to Levofloxacin. These resistance trends further point to ESBL activity, as the bacteria's ability to neutralize beta-lactam antibiotics supports the presence of such enzymes. However, all *K. oxytoca* isolates were fully susceptible to Piperacillin-Tazobactam, and 66.6% were responsive to Amikacin. Across all 95 isolates, there was universal resistance to Augmentin, Ciprofloxacin, Imipenem, and Ceftazidime. Levofloxacin resistance was recorded at 52.6%, while Piperacillin-Tazobactam showed 31.5% resistance. Among *Klebsiella* species, Gentamicin resistance reached 50%. On the other hand, complete sensitivity to Nitrofurantoin was noted (excluding *Klebsiella* spp.), Amikacin had an 89.4% sensitivity rate, and Piperacillin-Tazobactam showed 68.4% effectiveness. Gentamicin had the lowest susceptibility overall, at just 33.3%.

DISCUSSION

This study focused on the frequency and distribution of significant bacteriuria in urine samples collected from pregnant women at General Hospital Ilorin. The findings revealed a noteworthy occurrence of bacteriuria, with many specimens showing significant bacterial growth. However, these results contrast with recent research conducted in Ethiopia (Wong *et al.*, 2018), which reported a lower prevalence. This discrepancy may be attributed to differences in personal hygiene standards, educational levels, sample sizes, and social behaviors. All 95 bacterial uropathogens identified in this study were Gram-negative, with no Gram-positive bacteria detected.

This contrasts with some studies but is consistent with findings from tertiary care hospitals in India, where Gram-positive bacteria accounted for only 8.7% of isolates compared to 91.3% for Gram-negative ones (Murty *et al*., 2011). Similar trends were also reported in other studies, such as 67.5% in Gondar (Derese *et al*., 2016), 73.1% in Dire Dewa, Ethiopia (Alemu *et al*., 2012), and 75% in Kenyatta National Hospital, Kenya (Wiuy *et al*., 2015). The predominance of Gram-negative bacteria may be due to their unique structural features that facilitate adherence to uroepithelial cells, proliferation, and tissue invasion, which contribute to more invasive infections during pregnancy (Hamdan *et al*., 2011). The present study also found that Gram-negative isolates showed a high rate of resistance to commonly prescribed antibiotics. Resistance levels among these isolates ranged from 0% to 100%, which is consistent with findings from Tikur Anbessa Hospital (Hailu *et al*., 2017). *Klebsiella pneumoniae* and *Klebsiella oxytoca* emerged as the most frequent ESBL (Extended-Spectrum Beta-Lactamase) producers, aligning with findings from a study conducted in Uyo, Nigeria (Orok *et al*., 2015). Even higher ESBL prevalence rates were reported in Northwestern Nigeria (Giwa *et al*., 2018) and Tikur Anbessa Specialized Hospital (Desta *et al*., 2016). *Escherichia coli* was the second most common ESBL-producing organism. Notably, *K. oxytoca* accounted for 16.7% of ESBL producers in this study, which contrasts with the 6% reported in Uyo (Orok *et al*., 2015). These variations may be due to differences in sample size, institutional settings, geographic regions, and country-specific factors. Referral hospitals often report higher ESBL rates due to frequent antibiotic use and patient transfers from peripheral centers. In contrast, Western countries report lower ESBL prevalence, likely due to strict infection control policies, effective antibiotic stewardship, shorter hospital stays, and better healthcare infrastructure. The relatively lower ESBL proportion in our study could also be attributed to the controlled use of third-generation cephalosporins at the study site. Urinary tract infections (UTIs) are classified based on anatomical location into upper UTIs (such as pyelonephritis) and lower UTIs (such as cystitis, urethritis, and prostatitis) (Yee *et al*., 1668). UTIs can also be categorized as complicated or uncomplicated, and symptomatic or asymptomatic (Okonko *et al*., 2009). Women are approximately eight times more likely than men to develop UTIs due to anatomical and physiological factors (Malk *et al*., 2012). According to Behzadi *et al*. (2012), one in five adult women will experience a UTI in their lifetime. Pregnant women are particularly vulnerable to UTIs due to hormonal, anatomical, and physiological changes, as well as hygiene-related challenges (Ali *et al*., 2019). UTIs are a significant health concern, affecting about 20% of pregnant women and representing a common cause of hospital admissions in obstetric wards (Dietz *et al*., 2005). If untreated, UTIs during pregnancy can lead to serious complications, including low birth weight, intrauterine growth restriction, preterm labor, premature birth, intrauterine fetal death, and increased prenatal mortality and morbidity. Maternal complications may include anemia, preeclampsia, renal failure, septicemia, and acute respiratory distress syndrome (Meini *et al*., 2008). In developing countries, the prevalence of UTIs is rising due to factors such as malnutrition, low socioeconomic status, and inappropriate antibiotic use (Baby *et al*., 2014). Several studies in Ethiopia have reported a prevalence of UTIs in pregnancy ranging from 9% to 14% (System *et al*., 1992). Treatment is often not initiated based on antimicrobial susceptibility testing (Astrat *et al*., 2008). Globally, the emergence of antibiotic resistance among urinary pathogens is increasing (Wong *et al*., 2013) and is recognized by the World Health Organization (2015) as a serious public health threat. This issue is especially critical in

developing nations, where contributing factors include poverty, poor hygiene practices, and the widespread availability of counterfeit or substandard medications (Abubakar *et al*., 2009). Understanding the distribution of uropathogens and their antibiotic resistance profiles in specific settings is essential for guiding effective empirical treatment (Farajinia *et al*., 2008; Farrell *et al*., 2003). As antimicrobial resistance varies by region and evolves over time, regular surveillance and monitoring are crucial (Beyene *et al*., 2011)

Conclusion

This study underscores a notably high prevalence of bacteriuria among pregnant women, highlighting a pressing public health concern. The observed antibiotic resistance patterns among uropathogens emphasize the critical need for routine screening, timely diagnosis, and the implementation of targeted antimicrobial therapy. These findings reinforce the importance of robust antibiotic stewardship programs and continuous surveillance to curb the spread of resistant strains, particularly in vulnerable populations such as expectant mothers. To strengthen the reliability and generalizability of these results, future studies should incorporate larger sample sizes and more diverse demographic groups. Establishing region-specific treatment guidelines based on updated resistance profiles is essential to improving maternal and neonatal health outcomes.

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