**Greener Journal of Medical Sciences**
**Vol. 11(2), pp. 181-186, 2021**
**ISSN: 2276-7797**

**https://gjournals.org/GJMS**

# Molecular Detection and Antibiotic Susceptibility Profile of ESBL-producing Klebsiella pneumoniae Isolates in a Central Nigerian Tertiary Hospital

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**ARTICLE INFO**

***Article No.:*** *110521113*
***Type*:** *Research*
***Full Text*:** *HTML;EPUB*

***Accepted:*** *05/11/2021*
***Published:*** *15/11/2021*

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***Keywords:*** *Klebsiella pnuemoniae; ESBL; Multiplex-PCR; Antibiotic Resistance.*

**ABSTRACT**

**Background**: Production of extended-spectrum β-lactamases (ESBLs) is the most common mechanism of resistance to third-generation cephalosporins among Enterobacteriaceae including *Klebsiella pneumonia* and this presents therapeutic challenges managing infections caused by these strains of bacteria.
**Aim:** To determine the prevalence, antibiotic susceptibility profile and major ESBL encoding genes among *Klebsiella pneumoniae* in clinical specimens.
**Methods**: Four hundred (400) consecutive and non-duplicate isolates of *Klebsiella pneumoniae* from clinical specimens were identified by standard laboratory methods at the National Hospital Abuja, subjected to antimicrobial susceptibility testing using the Kirby-Bauer disc diffusion method and identified ESBL phenotypes were confirmed using E-test. Multiplex PCR was used to detect ESBL genes.
**Results**: Out of the 400 *Klebsiella pneumoniae* isolates, 114 (28.5%) were ESBL producers, out of which 111 (97.4%) were sensitive to meropenem, 101 (88.6%) to amikacin, 100 (87.7%) to fosfomycin, 96 (84.2%) to tigecycline, and 58 (50.9%) to nitofurantoin. All the ESBL producers were resistant to cefotaxime while 107 (93.9%) and 105 (92.1%) were resistant to amoxicillin-clavulanate, and ceftazidime respectively . There was a significantly higher distribution of multidrug resistance among ESBL producing isolates compared to non-ESBL producing isolates (chi-square =63.29, p-value = 0.0001). The distribution showed that 78 (70.3%) had the *bla*SHV gene, 99 (89.2%) had the *bla*CTX-M gene, 88 (79.3%) had the *bla*TEM gene and 3 (2.6%) had none of the major *bla* genes.
**Conclusion**: This study showed a relatively high prevalence of ESBL-producing *Klebsiella pneumoniae* isolates and a significant occurrence of multidrug-resistant *Klebsiella pnuemoniae*. Meropenem and amikacin are excellent therapeutic choices for empirical therapy of ESBL-producing *Klebsiella pneumoniae* infections and their use should be properly guarded through efficient infection control and antimicrobial stewardship..

## INTRODUCTION

Extended spectrum beta-lactamase (ESBL) producing *Klebsiella pneumoniae* was first reported in Germany in 1983 with subsequent increased global reporting over the decades[1]. It was later reported in *Escherichia coli, Pseudomonas aeruginosa* and other gram-negative bacilli[2]. ESBLs are a large, rapidly evolving group of plasmid-mediated enzymes that confer resistance to the oxyimino cephalosporins and monobactams but not to cephamycins or carbapenems, and are inhibited by β-lactamase inhibitors such as clavulanic acid[3]. They are the first example in which β-lactamase–mediated resistance to β-lactam antibiotics resulted from fundamental changes in the substrate spectra of the enzymes[4]. ESBL producing *Klebsiella pneumonia*e is among the commonest Gram-negative bacilli implicated in community- and hospital-acquired infection[5–7], causing intra-abdominal infection, urinary tract infection, respiratory infection and sepsis[8]. Infections caused by ESBL producing *Gram-negative* bacteria*, including K. pneumoniae* are associated with severe adverse outcomes, including higher overall and infection-related mortality, increased length of hospital stay, discharge to chronic care, and higher costs[9]

Production of extended-spectrum β-lactamases (ESBLs) is the most common mechanism of resistance to third-generation cephalosporins among Enterobacteriaceae, including *Klebsiella pneumoniae* and *Escherichia coli*. ESBL-producing *K. pneumoniae* usually express multidrug resistance and the spread of these multidrug-resistant bacteria has become a public health concern on a global scale, and particularly affects low- and middle-income countries[10]. These strains of bacteria also have the capacity to acquire resistance to other antimicrobial classes such as the quinolones, tetracyclines, cotrimoxazole, trimethoprim, and aminoglycosides, in addition to the penicillins, cephalosporins and aztreonam, and this further limits therapeutic options[11–13]

It has been established that epidemiological data on multidrug-resistant organisms in sub-Saharan Africa are scarce [14]. A recent systematic review revealed that the lack of data on the occurrence of multidrug-resistant Gram-negative bacteria, including *Klebsiella pneumoniae*, is greatest in West Africa[15]. This situation applies to Abuja, Nigeria where this study was carried out; previous study on ESBL-producing K. *pneumoniae* are scanty, thus leaving a huge knowledge gap which this study aims to bridge. Knowledge of the magnitude and antimicrobial susceptibility profile of ESBL producing *K.pneumoniae* will go a long way in assisting clinicians optimise antimicrobial therapy with improved patient outcomes.

## METHODS

### Study Design and Area

This was a cross-sectional study carried out in the Department of Medical Microbiology and Parasitology, National Hospital Abuja, a 500-bed tertiary hospital located in the Federal Capital Territory, Abuja. It is a referral centre for the federal capital territory and neighbouring states of Nigeria, providing health care services to about 50,000 patients monthly. The study involved 400 *K pneumoniae* isolated from consecutively selected clinical specimens from blood, urine, wound biopsy/swab, cerebrospinal fluid (CSF), sputum, aspirates, ear and eye swabs.

### Isolation and Identification of *K pneumoniae*

All samples were first inoculated on blood agar, MacConkey agar, and CLED agar (for urine samples) plates and incubated at $35^0$C for 24 hours in ambient air. Lactose-fermenting, convex, entire edge, large, mucoid colonies that were gram-negative short bacilli , non-motile, indole negative, methyl red negative, voges prausker positive, citrate-positive, and urease-positive were identified as *K. pneumoniae* following established procedures[16,17] .

### Antibiotic susceptibility testing

Antimicrobial susceptibility was done by the disc diffusion method using the modified Kirby-Bauer method.[18] The susceptibility of all isolates was tested to the following antimicrobial agents: Ampicillin (10µg), Amoxicillin/Clavulanic acid (20/10µg), Cefuroxime (30µg), Meropenem (10µg), Chloramphenicol(30µg), Gentamicin (10µg), Ciprofloxacin (5µg), Amikacin (30µg), Fosfomycin (200µg), Tigecycline (30µg), Nitrofurantoin (300µg) according to CLSI guideline.[19] These antibiotics were selected according to previously published recommendations and their widespread use in treatment of various diseases.[18] E-test (Liofilchem Diagnostics, Abruzzi, Italy) for confirming the ESBL phenotype was performed according to manufacturer's guidelines. ESBL results were considered positive if the isolates had an MIC (µg/ml) of ≥1 for ceftazidime (CAZ), ≥0.5 for cefotaxime (CTX), and the ratio for ceftazidine/ceftazidine +clavulanic acid (CAZ-CLA) and cefotaxime/cefotaxime+clavulanic acid (CTX-CTL) was more than or equal to 8 .[20]

### Molecular Characterization

Multiplex PCR was performed in a single tube with primers of $bla_{TEM}$, $bla_{SHV}$, $bla_{OXA}$ and *16S rRNA* genes. PCR assay was performed in a total volume of 50 µl which contained; 25 pmol of the primers of *16S rRNA* (Fd 5′-TGTGGGAACGGCGAGTCGGAATAC-3′ and Rev 5′-GGGCGCAGGGGATGAAACTCAAC-3′),

10 pmol primers of each of the $bla_{TEM}$, $bla_{SHV}$, and $bla_{OXA}$ as described by Trung et al.[21] 200 µM each of the dNTPs, 1U of *Taq* DNA polymerase, 1×PCR assay buffer with 1.5 mM $MgCl_2$ and 100 ng of template DNA. PCR conditions were used as described by Trung et al.[21] PCR was run in a PTC-100 Thermal Cycler (MJ Research, Inc., USA). 5 µl of the amplified PCR product was used for electrophoresis and visualization was done with a UV transilluminator. Amplified productsof $bla_{TEM}$, $bla_{SHV}$, $bla_{OXA,}$ and $bla_{CTX-M}$ genes were purified by QIAquick gel extraction kit (Qiagen, Hilden, Germany) according to the instructions of the manufacturer. Positive and negative controls were used.

### Data Collection

Data of all the *K. pneumoniae* isolates from the various specimens, their antibiotic susceptibility testing, phenotypically confirmed ESBL strains as well as their responsible ESBL genes detected via molecular method were collected.

### Data Analysis

All data collected was analysed using the software statistical package for social sciences (SPSS) version 25 by IBM SPSS Statistics. Percentage prevalence of ESBL and non- ESBL isolates, multidrug resistance among non ESBL and ESBL isolates and other results were presented using tables and charts. All analyses were done at a 95% confidence interval and a p value of < 0.05 was considered statistically significant.

### Ethical approval

Ethical approval was obtained from the Health Research Ethics Committee (HREC) of National Hospital Abuja.

## RESULTS

Findings showed that 114 (28.5%) out of the 400 *Klebsiella pneumoniae* isolated were ESBL producers. **Table 1** shows the susceptibility pattern of all the four hundred isolates. Among the 114 ESBL producing isolates, 111 (97.4%) were sensitive to meropenem, 100 (87.7%) to fosfomycin, 98 (84.2%) to tigecycline, 101 (88.6%) to amikacin, and 58 (50.9%) to nitofurantoin. only 2 (1.8%) to ceftazidine. All the 114 ESBL producers were resistant to ceftriaxone while 107 (93.9%) and 105 (92.1%) were resistant to amoxicillin-clavulanate and ceftazidime respectively. **Table 2** shows a significantly higher distribution of multidrug resistance among ESBL producing isolates compared to non-ESBL producing isolates (chi-square =63.29, p= 0.0001). Distribution of the *bla* genes among the *Klebsiella pneumoniae* isolates showed that 78 (70.3%) had the *bla*SHV gene, 99 (89.2%) had the *bla*CTX-M gene, 88 (79.3%) had the *bla*TEM gene and 3 (2.6%) had no *bla* genes as shown in table 3.

**Table 1: Antibiotic susceptibility pattern of *K. pneumoniae* isolates**

| Antibiotics | *ESBL Producing K. pneumoniae* | | | *Non-ESBL producing K. pneumoniae* | | |
|---|---|---|---|---|---|---|
| | ***S*** | ***I*** | ***R*** | ***S*** | ***I*** | ***R*** |
| **Amikacin** | 101 (88.6) | 2 (1.8) | 11 (9.7) | 272 (95.1) | - | 14 (4.9) |
| **Amoxicillin-clavulanate** | 1 (0.9) | 6 (5.3) | 107 (93.9) | 71 (24.8) | 65 (22.7) | 150 (52.5) |
| **Ampicillin** | - | - | 114 (100) | - | - | 286 (100) |
| **Chloramphenicol** | 56 (49.1) | - | 58 (50.9) | 199 (69.6) | 31 (10.9) | 56 (19.6) |
| **Ceftazidime** | 2 (1.8) | 7 (6.1) | 105 (92.1) | 286 (100) | - | - |
| **Ciprofloxacin** | 9 (7.9) | 4 (3.5) | 101 (88.6) | 103 (36) | 111 (38.8) | 72 (25.2) |
| **Gentamicin** | 5 (4.4) | - | 109 (95.6) | 206 (72) | 2 (0.7) | 78 (27.3) |
| **Cefotaxime** | - | - | 114 (100) | 286 (100) | - | - |
| **Cefuroxime** | - | 2 (1.8) | 112 (98.3) | 262 (91.6) | 10 (3.5) | 14 (4.9) |
| **Nitrofurantoin** | 58 (50.9) | 4 (3.5) | 52 (45.6) | 202 (70.6) | 10 (3.5) | 74 (25.9) |
| **Fosfomycin** | 100 (87.7) | 2 (1.8) | 12 (10.5) | 282 (98.6) | - | 4 (1.4) |
| **Meropenem** | 111 (97.4) | - | 3 (2.6) | 286 (100) | - | - |
| **Tigecycline** | 96 (84.2) | 15 (13.2) | 3 (2.6) | 240 (83.9) | 38 (13.3) | 8 (2.8) |

*S: Sensitive, I: Intermediate, R: Resistant*

**Table 2: Distribution of Multidrug Resistant isolates among *K. pneumoniae***

| Multidrug Resistance | ESBL | | Chi-square (p-value) |
|---|---|---|---|
| | Yes (n, %) | No (n, %) | |
| **Yes** | 114 (100.0) | 147 (51.40) | *63.29 (0.0001)** |
| **No** | 0 (0.0) | 139 (48.60) | |
| **Total** | **114 (100.0)** | **286 (100.0)** | |

**Distribution is statistically significant (p < 0.005).*

**Table 3: Distribution of *bla* genes among ESBL-*Klebsiella pnuemoniae* isolates**

| Genes | Frequency n =114 (%) |
|---|---|
| ***bla*CTX-M alone** | 12 (10.8) |
| ***bla*TEM alone** | 6 (5.4) |
| ***bla*SHV +*bla* CTX-M** | 11 (9.9) |
| ***bla*SHV +*bla* TEM** | 6 (5.4) |
| ***bla*CTX-M +*bla* TEM** | 15 (13.5) |
| ***bla*SHV+*bla*CTX-M+*bla*TEM** | 61 (55.0) |
| **None of the major *bla*** | 3(2.6) |
| **Total CTX-M** | 99 (89.2) |
| **Total TEM** | 88 (79.3) |
| **Total SHV** | 78 (70.3) |

## DISCUSSION

The study showed a 28.5% prevalence of ESBL-producing *Klebsiella pneumoniae* among the isolates, and compares well with the 30% [22] and 31.6% [23] reported by Raji *et al* in Lagos, but differs widely from 60.8% [24] reported by Aibinu *et al* in Lagos. The relatively lower prevalence of ESBL-producing *K. pneumoniae* observed in the current study could be attributed to the variation in antibiotic use, sensitivity and specificity of test methods compared to the other study sites of the aforementioned studies.The high rate of multidrug resistance among both ESBL and Non-ESBL producing *K.pneumoniae* found in this study has similarly been reported from studies done in Kano[25] and Ibadan[26]. This could be due to previous exposure to antibiotics resulting from self medication that is widely prevalent in this part of the world due to easy access and purchase of antibiotics across the counter for use without prescription. This has led to major challenge in the therapeutic management of serious life threatening infections due to these strains with poor outcome.[26,27] It is particularly noteworthy that about 81% of all blood isolates were ESBL-producers, technically eliminating the third generation cephalosporins as empiric treatment for blood stream infections.

Notwithstanding the observed high rate of multidrug resistance, all the ESBL-producing *K. pneumoniae* isolates had relatively high rate of susceptibility to meropenem, amikacin, fosfomycin, and tigecycline, serving as safety valves and giving some hope of rescue when the third generation cephalosporins fail. When considered against the background of high ESBL prevalence, meropenem obviously stands out as the drug of first choice for empiric treatment in serious life-threatening infections. Amikacin would appear to be an alternative empiric therapy drug based on susceptibility and cost, but its choice may be limited by its side effect especially in neonates .[28] The use of tigecycline, an antibiotic recently introduced into the hospital and used mainly in the burns unit for non-pseudomonal infections, when indicated, is limited to skin and soft tissue infections[29].

In this study, the predominant gene was $bla_{CTX-M}$ and it exists alone or in association with other genes, TEM and SHV, but predominantly with TEM genes. This very high prevalence of $bla_{CTX-M}$ type ESBL genes among *K.pneumoniae* isolates supports the worldwide pandemic spread of the CTX-M β-lactamase enzyme as reported in America[30],Europe[31], Middle east [32],Asia [33] and Africa[34]. Studies in Nigeria by Iroha *et al* [35] , Raji *et al* [23] and Aibinu *et al*[36] also lend credence to the high prevalence of $bla_{CTX-M}$ type. ESBL mediated by $bla_{CTX-}$

$_{M}$ type β-lactamase genes are undoubtedly the most widespread enzymes produced among *K. pneumoniae*.

The large proportion of the ESBL producers that harboured multi-genes in this study is worrisome and may partly explain the observed high level of drug resistance, even in the presence of β-lactamase inhibitors. It is likely these isolates hyper produce β–lactamase enzymes which overwhelm the β–lactamase inhibitors [37]. The carriage of these genes on plasmids enhances the spread and therefore requires good infection control measures to limit dissemination.

## CONCLUSION

ESBL producing *K. pneumoniae* strains are relatively high among K. pneumoniae isolates. The isolates were significantly associated with multi-drug resistance. Interestingly, both the ESBL and non-ESBL strains were highly sensitive to meropenem amikacin, fosomycin, and tigecycline. The predominant ESBL gene among *K. pneumoniae* isolates was $bla_{CTX-M}$ , and a significant proportion of the ESBL isolates harboured 2 or 3 ESBL genes together. This study highlights the need for efficient infection control and antibiotics stewardship practices to mitigate the rising cases of antimicrobial resistance. The remarkable difference in sensitivities between ESBL-producing and non-ESBL-producing isolates makes it imperative to test for ESBL-production routinely

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**Cite this Article:** Enyinnaya SO; Iregbu KC; Uwaezuoke, NS; Abdullahi, N; Lawson, SD (2021). Molecular Detection and Antibiotic Susceptibility Profile of ESBL-producing Klebsiella pneumoniae Isolates in a Central Nigerian Tertiary Hospital. *Greener Journal of Medical Sciences*, 11(2): 181-186.