Characterization and Plasmid Profile of Resistant *Klebsiella pneumoniae* Isolates in Patients with Urinary Tract Infection in Nasarawa State, Nigeria

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**Abstract**

*Klebsiella pneumoniae* has been identified as an urgent threat to human health based on its increasing antimicrobial resistance to the beta-lactamases and Carbapenemases. The pathogen has become a threat to both patients and healthcare providers as its incidence is on the increase, becoming a major global healthcare issue. The study was aimed at characterizing and determining the plasmid profile of resistant *Klebsiella pneumoniae* isolates from urinary tract of patients at Dalhatu Araf Specialist Hospital Lafia, Nasarawa State, Nigeria. Early morning mid-stream urine samples were collected from patients with urinary tract infections between April and May, 2019 and *Klebsiella pneumoniae* characterized on the basis of its antibiotic resistance pattern, and the plasmid DNA profile determined. Thirty-eight strains of resistant *Klebsiella pneumoniae* were obtained of which 33 showed resistance to more than three antibiotics. About 51.1% of the isolates were resistant to Tetracycline, while the isolates were least resistant to Azithromycin and Cefotaxime (30.3%) respectively. *Klebsiella pneumoniae* isolates showed 32 different resistance patterns, 24 of the strains had the capacity to produce Extended Spectrum Beta-lactamases enzymes: CTX-M 24(72.7%), SHV 19(57.6%) and TEM 16(48.5%) respectively. All the resistant *Klebsiella pneumoniae* isolated had the same plasmid size of 48.5 kilobases and only 1 plasmid each though they all obtained a multiple antibiotic resistance (MAR) index > 0.2. The study concluded that *Klebsiella pneumoniae* harbours genes which confer antibiotic resistance on the isolates. The study exposes further the challenge of antibiotic resistance and need for concerted effort at stopping the challenge of drug resistance.

**Keywords:** Resistance; *Klebsiella*; Plasmid; Beta-lactamases; Antibiotics

**Introduction**

*Klebsiella pneumoniae* and other bacteria of health importance are pathogens causing concern globally due to resistance acquired to more than two lines of antibiotic classes (Nordmann *et al.*, 2009). *Klebsiella pneumoniae* strains have the capacity to take up traits (genetic) leading to more virulence and resulting in multidrug resistance. These resistant bacterial strains produce enzymes like cephalosporinase or Carbapenemases that can deactivate antibiotic drug administered on patients (Long *et al.*, 2018), and so integrons, plasmid genes, and transposons harboured by the pathogen induces resistance to antibiotics drugs (Paterson and Bonomo, 2005).

*Klebsiella pneumoniae* causes nosocomial infection and it is a prevalent bacterium that abound in health facilities with special ability to take-up resistance genes from the environment. It is implicated in developing states of the world and poor communities as one of the major cause of diseases. About 78 serogroups have been identified each with a different capsular K antigen in the bacteria (Janda,
2015; Pan et al., 2019). Spagnolo et al. (2014) reported that *K. pneumoniae* is responsible for some healthcare-associated and community-associated infections. Colonization of the gastrointestinal (GI) tract is usually a pre-requisite for induction of infection, and medical personnel are culpable reservoir of infection contagion (Calbo et al., 2011). *Klebsiella pneumoniae* exerts resistance using a) the capability to produce resistance enzymes that inactivates cephalosporins and monobactams, b) ability to express production of carbapenemases which confers resistance to all β-lactams antibiotics, including the carbapenems (CDC, 2015).

The burden of infection caused by the pathogen is associated with high morbidity and mortality which might not be unconnected with the high number of resistance genes the bacteria harbours (CDC, 2013; Hoban et al., 2014). The bacterium attaches to host cells employing fimbrae and adhesins which promote tissue infection (Ong et al., 2010). Prolong hospital stay, prior use of antibiotics and ventilation type are risk factors associated with colonization and infection by *Klebsiella pneumoniae*. The study was aimed at characterizing and determining the plasmid profile of resistant *Klebsiella pneumoniae* isolates from urinary tract of patients at Dalhatu Araf Specialist Hospital Lafia, Nasarawa State, Nigeria.

**Materials and Methods**

**Sampling and Collection of Samples**

A total of 194 urine samples were collected from Dalhatu Araf Specialist Hospital (DASH), Lafia, Nasarawa State determined by a prevalence rate of 14.8% (Yusuf et al., 2014), after obtaining ethical approval from DASH, Ethical committee. Early morning Mid-stream urine samples were collected from patients with urinary tract infections with symptoms such as vomiting, fever lasting more than 7 days, and those who had lower abdominal pain.

**Inclusion and Exclusion Criteria**

Samples were obtained from patients of both sexes and all ages to include: inpatients and out patients. Patients already on antibiotics and intensive care unit were excluded from the sampled group.

**Isolation and Identification**

Urine samples was inoculated on Cysteine Lactose Electrolyte Deficient (CLED) agar plates and streaked to obtain discrete colonies which were then sub-cultured unto Mac-Conkey agar to obtain pure colonies and incubated overnight at 37°C. Identification was based on colonial appearance, Gram reactions and biochemical tests.

**Determination of Antibiotic Susceptibility Profile of Isolated Klebsiella pneumoniae**

Antibiotic susceptibility pattern of *Klebsiella pneumonia* isolate from urinary tract patients was determined using the methods of Clinical and Laboratory Standards Institute Guidelines CLSI (2012). Broth cultures containing the different isolates were separately prepared using sterile peptone water comparable to 0.5 McFarland’s standard and inoculated using Kirby-Bauer disc diffusion method on Mueller Hinton agar, and tested against antibiotics. The antibiotics tested were Ceftriaxone/Cefotaxime (30/30 μg), Cefotaxime (30 μg), Ofloxacin (30 μg), tetracycline (30 μg), Gentamycin (10 μg), levofloxacin (5 μg), Imipenem (10 μg), Amoxicillin + Clavulanic acid (20/10 μg) Azithromycin (30 μg), and Ciprofloxacin (5 μg). Incubation was done at 37°C for between 18-24 h after which the inhibition zones around the discs were measured and interpreted according to Performance Standards for Antimicrobial Disk Susceptibility Tests, CLSI.

**Determination of Plasmid Patterns in Resistant Klebsiella Pneumoniae Isolates**

**i) Extraction of DNA from resistant Klebsiella pneumoniae isolates**

One thousand microliters of phosphate buffer saline (PBS) was added to each tube containing the isolates. It was then added into a tube and centrifuge at 2000 rpm for 5 minutes. Discard the supernatant. Two- hundred and fifty μl of PBS was again added to the pelleted isolates and re-suspend 250 μl p2 buffer was then added and turn upside then down the tube for like four times (p2 is a lysis buffer). Three hundred and fifty μl N3 buffer (N3 is a neutralization buffer). The tubes were turn upside then down for four times. It was then centrifuge at 1300 rpm for 10 minutes. Eight- hundred microliters of the supernatant of the supernat was now added into a column and centrifuge at 13000 rpm for 1 minute. Five-hundred microliters of PB buffer was also added to the binding column and centrifuge at 13000 rpm for 1 min. Three-hundred microliters of wash buffer 1 was added and centrifuge for 1 min, 300 μl of wash buffer 2 was added and centrifuge for 1 min. The empty tube was centrifuge at 13000 rpm to remove residual. The tube was transferred to a new tube for elution in which 500 μL of elution was added. It was centrifuge at 8,000 rpm for 1 min to elute the DNA.

**ii) Multiplex Polymerase Chain Reaction**

A mixture of 20 mL in 0.5 mL tube containing 2 mL of Sulphhydryl variable primer, 2 mL of Temoneria primer, 2 mL of Cefotaximase primer, 12 mL of H2O and 2 mL of the extracted DNA was mix together. An addition of 50 mL of nuclease was added to avoid evaporation during the cycling period. The PCR begins with: Pre-denaturation at one cycle for 5 min at a temperature of 94°C then denaturation for 30 s at a temperature of 94°C, followed by annealing at a temperature of 52°C for 30 s and, extension at 72°C for 1 min at 35 cycles. Finally, extension for 5 min at a temperature of 72°C. At the end of cycling, the tubes were stored at – 20°C.
Bacterial count in urine samples from UTI patients

| Isolates                   | Number of isolates | Percentage (%) |
|----------------------------|--------------------|----------------|
| Klebsiella pneumoniae      | 66                 | 33             |
| Escherichia coli           | 6                  | 3              |
| Staphylococcus sp          | 9                  | 5              |
| Proteus sp                 | 5                  | 2.5            |
| Pseudomonas sp             | 3                  | 1.5            |
| Streptococcus sp           | 7                  | 3.5            |
| Chlamydia trachomatis      | 3                  | 1.5            |

Susceptibility Profile of Klebsiella pneumoniae Isolates

As shown in the Table 2 below, Klebsiella pneumoniae strains were most susceptible to Azithromycin and Cefotaxime (69.7%) respectively, followed by Gentamicin (68.2%), Imipenem, Ceftriaxone, Levofloxacin, and Ofloxacin (63.6%) each, while Augmentin and Ciprofloxacin (57.6%) respectively. The least sensitivity was observed in Tetracycline (34.8%). Hence, Klebsiella pneumoniae strains were most resistant to Tetracycline (65.2%) and least resistant to Azithromycin and Cefotaxime (30.3%).

Antibiotic Resistance Pattern of Klebsiella Pneumoniae Isolated from Urine

Klebsiella pneumoniae strains showed 32 different resistance patterns with Ceftriaxone (CRO), Ciprofloxacin (CIP), Imipenem (IMP) and Tetracycline (TET) been the most encountered (Table 3). Out of the 33 isolates, 2 isolates showed resistance to 9 antibiotics, 1 isolate showed resistance to 7 antibiotics, 3 isolates to 6 antibiotics while 14 isolates showed resistance to 5 antibiotics respectively. The multidrug resistant Klebsiella pneumonia strains identified in the present study all had one plasmid with 48.5 kilobases each, and a MAR index greater than 0.2 each as reported in Table 3. Klebsiella pneumoniae isolates with MAR index of 0.5 were 14 which was the highest recorded, while the least occurrence was a MAR index of 0.7.

Table 2: Antibiotic Susceptibility pattern of Klebsiella pneumoniae isolates from UTI patients

| Antibiotics   | Resistance (%) | Susceptibility (%) | Correlation coefficient |
|---------------|----------------|--------------------|-------------------------|
| Number of isolates = 66 | 0.962 |
| Augmentin     | 28(42.4)       | 38(57.6)           |                         |
| Ceftriaxone   | 24(36.4)       | 42(63.6)           |                         |
| Cefotaxime    | 20(30.3)       | 46(64.9)           |                         |
| Levofloxacin  | 24(36.4)       | 42(63.6)           |                         |
| Ciprofloxacin | 28(42.4)       | 38(57.6)           |                         |
| Imipenem      | 24(36.4)       | 42(63.6)           |                         |
| Ofloxacin     | 24(36.4)       | 42(63.6)           |                         |
| Gentamicin    | 21(31.8)       | 45(68.2)           |                         |
| Azithromycin  | 20(30.3)       | 46(69.7)           |                         |
| Tetracycline  | 43(65.2)       | 23(34.8)           |                         |
Table 3: Antibiotic resistance pattern and plasmid profile of *Klebsiella pneumoniae* isolates in patients with urinary tract infection

| Bacterial isolates | Number of plasmid | Plasmid size (kb) | Resistance pattern | Antibiotic resistance | MAR index |
|--------------------|-------------------|-------------------|--------------------|-----------------------|-----------|
| Kleb 1             | -                 | -                 | Cro, Cip, Gn       | 3                     | 0.3       |
| Kleb 2             | 1                 | 48.5              | Lev, Cip, Ofx, Azn | 4                     | 0.4       |
| Kleb 3             | 1                 | 48.5              | Aug, Lev, Cip, Imp| 4                     | 0.4       |
| Kleb 4             | 1                 | 48.5              | Cro, Cip, Ofx, Gn  | 5                     | 0.5       |
| Kleb 5             | 1                 | 48.5              | Aug, Lev, Cip, Gn  | 4                     | 0.4       |
| Kleb 6             | 1                 | 48.5              | Aug, Cro, Zem, Lev, Cip, Ofx, Azn, Tet| 9| 0.9 |
| Kleb 7             | 1                 | 48.5              | Aug, Cip, Ofx, Gnz | 5                     | 0.5       |
| Kleb 8             | 1                 | 48.5              | Cro, Lev, Cip, Imp, Tet| 5| 0.5       |
| Kleb 9             | 1                 | 48.5              | Aug, Lev, Imp, Gnz, Tet| 5| 0.5       |
| Kleb 10            | 1                 | 48.5              | Cro, Lev, Cip, Gnz, Tet| 5| 0.5       |
| Kleb 11            | 1                 | 48.5              | Cro, Zem, Lev, Gnz | 4                     | 0.4       |
| Kleb 12            | 1                 | 48.5              | Zem, Imp, Azn     | 3                     | 0.3       |
| Kleb 13            | 1                 | 48.5              | Cip, Imp, Azn     | 3                     | 0.3       |
| Kleb 14            | 1                 | 48.5              | Cro, Cip, Imp, Tet| 4                     | 0.4       |
| Kleb 15            | 1                 | 48.5              | Zem, Lev, Cip, Ofx, Gnz, Tet| 6| 0.6       |
| Kleb 16            | 1                 | 48.5              | Aug, Zem, Lev, Tet| 4                     | 0.4       |
| Kleb 17            | 1                 | 48.5              | Aug, Zem, Lev, Ofx, Azn | 5| 0.5       |
| Kleb 18            | 1                 | 48.5              | Zem, Lev, Ofx, Azn, Tet| 5| 0.5       |
| Kleb 19            | 1                 | 48.5              | Cip, Imp, Gnz, Azn, Tet| 5| 0.5       |
| Kleb 20            | 1                 | 48.5              | Aug, Lev, Cip, Gnz, Azn | 5| 0.5       |
| Kleb 21            | 1                 | 48.5              | Aug, Zem, Tet   | 3                     | 0.3       |
| Kleb 22            | 1                 | 48.5              | Aug, Zem, Ofx, Gnz, Azn, Tet| 6| 0.6       |
| Kleb 23            | 1                 | 48.5              | Aug, Cro, Zem, Ofx, Gnz, Azn, Tet| 7| 0.7       |
| Kleb 24            | 1                 | 48.5              | Zem, lev, Cip, Gnz, Azn, Tet| 6| 0.6       |
| Kleb 25            | 1                 | 48.5              | Cro, Cip, Imp, Azn, Tet| 5| 0.5       |
| Kleb 26            | 1                 | 48.5              | Cro, Lev, Cip, Imp, Tet| 5| 0.5       |
| Kleb 27            | 1                 | 48.5              | Cro, Cip, Ofx, Gnz, Tet| 5| 0.5       |
| Kleb 28            | -                 | -                 | Aug, Cro, Lev, Ofx, Gnz, Tet| 6| 0.6       |
| Kleb 29            | 1                 | 48.5              | Aug, Cro, Zem, Lev, Cip, Imp, Ofx, Gnz, Tet| 9| 0.9       |
| Kleb 30            | 1                 | 48.5              | Zem, Ofx, Gnz, Azn | 4                     | 0.4       |
| Kleb 31            | 1                 | 48.5              | Cip, Imp, Gnz     | 3                     | 0.3       |
| Kleb 32            | 1                 | 48.5              | Aug, Cro, Lev, Imp, Azn | 5| 0.5       |
| Kleb 33            | -                 | -                 | Cro, Zem, Ofx, Gnz, Tet| 5| 0.5       |

CRO: ceftriaxone, AUG: Augmentin, OFX: Ofloxacin, LEV: Levofloxacin, TET: Tetracycline, AZN: Azithromycin, CIP: Ciprofloxacin, GN: Gentamicin, IMP: Imipenem, ZEM: Cefotaxime

Table 4: Antimicrobial Resistance Gene Profiles of *Klebsiella pneumoniae* strains

| ESBL-Enzyme | Strains | Number of isolates (%) |
|-------------|---------|------------------------|
| Temonemia   | 2,3,4,5,6,7,8,9,10,12,13,14,15,17,20,29 | 16 (48.5) |
| Sulphhydryl Variable | 2,3,4,5,6,7,8,9,12,13,14,15,17,19,22,24,26,29,30 | 19 (57.6) |
| Active on cefotaxime | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,22,24,26,29,30 | 24 (72.7) |

Molecular Detection of Antimicrobial Resistance Genes

24 strains out of the 33 strains isolated contained extended spectrum beta-lactamase (ESβL) enzymes with CTX-M as the highest (72.7%), followed by SHV (57.6%) and TEM (48.5%) respectively. However, 9 strains such as strain 1, 21, 23, 25, 27, 28, 31, 32 and 33 did not produce such enzymes as shown in Fig. 1 and 2.
Discussion

Treatment of nosocomial infections is becoming a challenge as a result of resistance to antibiotics and the associated burden (Cao et al., 2014). Klebsiella pneumoniae, Staphylococcus aureus, Escherichia coli, Proteus spp, Pseudomonas spp., and other isolated bacteria have been implicated as contributing agents of nosocomial infections, and were also reported in the study by Kibret and Abera (2014), Derese et al. (2016), and Anejo-Okopi et al. (2015). The Klebsiella pneumoniae obtained in the study though had the highest incidence of occurrence when compared with other isolates at 33% was still low generally which aligns with other studies where the occurrence was reported to be low (Farajnia et al., 2009; Kamrul et al., 2012).

Isolates obtained in this study are known to be ubiquitous in nature, and are easily acquired and transmitted due to poor hygienic conditions in the hospital setting and community. High occurrence of Klebsiella pneumoniae in this study agrees with findings by Idomir et al. (2014) who reported that the pathogen can be readily isolated at high percentage in urinary diseased patients. High occurrence of Klebsiella pneumoniae in this study agrees with findings by Idomir et al. (2014) who reported that the pathogen can be readily isolated at high concentration in urinary diseased patients.

The prevalence obtained for E. coli in our study was 3.50% which was similar to the value recorded in the study by Derese et al. (2016) but, contrasted by the report of Kibret and Abera (2014) and Oladehinde et al. (2011). The presence of Pseudomonas aeruginosa agrees with the study of Oladehinde et al. (2011). The presence of these bacterial isolates could be result in multiple infections and were
likely introduced through sexual activities or poor hygienic conditions or disease conditions. The *Klebsiella pneumoniae* isolates showed varied susceptibility to the tested antibiotics and many of the isolates were susceptible to Azithromycin followed by Gentamicin. The result obtained in the study was similar to results recorded in the research carried out by Iyoha and Tula (2015).

Resistance recorded by the *K. pneumoniae* could be attributed to drug abuse through self-medication, over the counter access to drugs, and consumption of residual antibiotics present in food as meat (chicken, beef, pork, fish – growth promoters), and plants (roots, leaves, tubers, stems, grains). The resistance exhibited by the *Klebsiella pneumoniae* isolates against tetracycline corroborates findings by Olusola *et al.* (2013) who explained that the pathogens were ineffective against the antibiotic using mechanisms such as biofilm formation, evasion, and their capacity to acquire resistance gene and plasmid to overcome the stress factor.

Antibiotic resistance patterns exhibited by the *Klebsiella pneumoniae* isolates showed that 32 patterns were found with Ceftriaxone, Ciprofloxacin, Imipenem and Tetracycline being the most encountered. This finding agrees with the study of Arezoo *et al.* (2018) who reported several resistance patterns. The different antibiotic resistance patterns observed is an indication of a widespread unregulated use of these antimicrobials coupled with factors such as sexual activity, age, sex, poor immunity, personal hygiene, history of recurrent UTI’s, and social behaviour.

Pathogenicity of MDR *Klebsiella pneumoniae* has been attributed to the possession and production of resistance genes, virulence genes, integrons, production of toxins (Li *et al.*, 2013; Firoozeh *et al.*, 2019). Extended Spectrum Beta-Lactamases genes from isolated resistant *Klebsiella pneumoniae* include TEM, SHV, and CTX-M. These genes promote virulence and resistance in the bacteria hence Akingbade *et al.* (2012) reiterated the importance of determining the plasmid profile of isolates along with the resistance pattern for effective and efficient diagnosis because plasmid harbouring these genes confers broad antibiotic resistance on the bacteria. Generally, it was observed in the study that all *Klebsiella pneumoniae* strains were multidrug resistant as they were resistant to three or more antibiotics. *Klebsiella pneumoniae* MDR isolates from this study produced extended β-lactamase. Further analysis using sequencing showed the isolates contained CTX-M, SHV and TEM Extended Spectrum Beta-Lactamases genes. CTX-M (Active on Cefotaxime) was the highest being harbour by 24 isolates. The three ESBL genes detected in the isolates have been reported to confer resistance on the bacterial isolates and peculiar to the Enterobacteriaceae family (Arcilla *et al.*, 2017).

High prevalence of resistance genes obtained in the present study agrees with the report of Anes *et al.* (2017). The SHV and TEM both contributed to conferring resistance on the isolates which is transferable. The issues of *Klebsiella pneumoniae* resistance genes between human and animals have been raised by Wu *et al.* (2019). The authors investigated the mechanism of multiple resistance and dissemination of resistance genes by the pathogen, and recommended proactive surveillance of florfenicol-resistant strains in animals. The MAR index obtained in the study were many with only two isolates been ineffective against 9 antibiotics, 14 isolates scoring MAR index of 0.5, and one isolate scoring 0.7. The isolates were multidrug resistant. Our finding agrees with that of Christopher *et al.* (2013) who obtained a MAR index of 0.89 in their study. All MDR *K. pneumoniae* isolates analysed possess only one plasmid with the same size of 48.5 base pairs.

**Conclusion**

The study established the possession of Temoneria, Sulphydryl Variable, and Active on Cefotaxime genes in the isolated *Klebsiella pneumoniae* strains with only one plasmid (48.5bp). The finding affirms the fact that resistance is not only conferred by the presence of plasmid bearing genetic agents but that other factors are involved in resistance noted in pathogens. CTX-M genes was found more in the isolates and reports showed that the genes are also found in animals which calls for concern so as to avoid cross dissemination. The study also revealed that a host of antibiotics employed in the treatment of *Klebsiella pneumoniae* infections are becoming ineffective. Use of multiple antibiotics in treatment is not encouraged to reduce resistance but we are left with little option of surveillance to better manage the challenge of resistant pathogens. Based on the results obtained *Klebsiella pneumoniae* is the frequent pathogen associated with urinary tract infections (UTI) in DASH, Lafia.

**Author’s Contribution**

O.O. Orole Author 1 conceptualize and designed the research, did critical revision of the manuscript, and participated in the interpretation of data. N.S. Hadi Author 2 designed the research, acquired data, drafted the manuscript, and carried out analysis of data. Final form of manuscript was approved by both authors.

**Conflict of Interest**

The authors declare that there is no conflict of interest with present publication.

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