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Antibiotic Resistance Phenotypes of *Klebsiella pneumoniae* in Urinary Tract Infection among Patients attending a Tertiary Healthcare Facility in Ekiti State, Nigeria

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ABSTRACT

Urinary tract infections (UITs) are the most common infectious disease worldwide with significant morbidities, both in clinical and community settings. The *Klebsiella pneumoniae* is a leading cause of UTIs in clinical settings with significant complications and morbidity. The use of antibiotics for treatment of UTIs increases the risk of emergence of antibiotic resistance. This present study was carried out to determine the susceptibility of *K. pneumonia* isolates recovered from suspected cases of UTIs at a tertiary clinical facility in Ekiti State, Nigeria. *K. pneumonia* were isolated from urine samples of patients referred to the microbiology laboratory of the healthcare facility. The isolates were identified using standard biochemical tests. Subsequently, the bacterial isolates were subjected to antibiotic susceptibility tests via the agar disk diffusion method using a panel of twelve (12) antibiotics which included the following: tetracycline (10µg), cotrimoxazole (25 µg), gentamicin (10 µg), cefuroxime (30 µg), chloramphenicol (10 µg), ceftriaxone (30 µg), cefotaxime (30 µg), ceftazidime (30 µg), ciprofloxacin (5 µg) and amikacin (30 µg), vancomycin (30 µg) and meropenem (30 µg). This results showed that all the isolates demonstrated resistance to cefuroxime, ceftriaxone, ceftazidime and vancomycin. The organisms also showed considerable resistance to tetracycline 24 (92.3%), cotrimoxazole 21 (80.8%), meropenem 25 (96.2%) and amikacin 20 (76.9%). Resistance to chloramphenicol was the least with 8 (31.0%) of the isolates showing reduced susceptibility to the antibiotic. Twenty four (14) different antibiotic resistance patterns were observed among the isolates. This study showed that bacterial uropathogens recovered from the patients showed high resistance to antibiotics. The findings in this study should enable clinicians to prioritize antimicrobial stewardship in management of UTIs in clinical settings.

Keywords: UTI, antibiotic resistance, antibiotics, *Klebsiella* spp.

INTRODUCTION

The urinary tract infection (UTI) is the most common infection affecting humans in clinical and community globally (David Otobo, 2020; Jalil and Al Atbee, 2022; Tocut *et al.,* 2022). It affects the different parts of the urinary system, notably the kidneys, bladders and the urethras (AL-Mahfoodh *et al.,* 2021). It contributes significantly to mortality and morbidity across the globe with attendant increase on overall loss of quality of healthcare and economic burden (Odoki *et al.,* 2019; Okoroiwu *et al.,* 2020). It is estimated that the economic cost of UTI due to increased burden of healthcare is in the region of 2.8 billion dollars, with global cases of 404.61 million and 236,790 deaths (McCann *et al.,* 2020; Yang *et al.,* 2022). UTI can occur both as symptomatic and asymptomatic infections and apparently healthy individuals have been known to carry the infection for significant period of time (David Otobo,

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2020). The epidemiology of the UTI may vary across different countries, communities and clinical settings but there are generalisations that characterise the disease. The prevalence tends to be higher among women, elderly and immunocompromised individuals ((Haindongo *et al.,* 2022). Furthermore, there are variations in the prevalence of UTI across clinical and community settings. In addition, UTI has been attributed to a number of clinical complications that contribute to increased cost of treatment and prolonged hospital care (Okoroiwu *et al.,* 2020).

There are different aetiologies, which include bacteria, viruses and in some cases, yeasts that are attributed to UTI. However, the bacterial aetiologies are the most common with different Gram-positive and Gram-negative bacteria attributed to the infection. Overall, the Gram-negative organisms are the most common bacterial pathogens recovered from the patients. They include *Escherichia coli* and *Klebsiella pneumonia*. The *K. pneumonia* occupy a prominent feature in UTI in different clinical and community settings. Different studies have since linked UTI in different settings to *K. pneumonia* (Jalil and Al Atbee, 2022; Pruss *et al.,* 2023). A study reported the presence of *Klebsiella* spp. among apparently health students with UTI in some parts of Nigeria (Alfa *et al.,* 2022). The predominance of the *Klebsiella* spp. as a leading uropathogen is partly due to specific virulence characteristics that adapts the organism to establish within the urinary tract. The most common virulence traits reported among *Klebsiella* spp. and other related bacteria is the capsular lipopolysaccharide that facilitate attachment to the epithelial cells that line the walls of the urinary tract. These features also protects the bacterium against phagocytosis at the onset of immune response (Bobbadi *et al.,* 2021; Foysal *et al.,* 2018; Kao *et al.,* 2023).

Antibiotic therapies are the treatment of choice for UTIs (Jancel, 2002). Different antibiotic regimens are used for treatment but the most common ones include the fluoroquinolones and the third generation cephalosporins (Bartoletti *et al.,* 2016; Jancel, 2002). However, the carbapenems are gradually occupying a commonplace as last resort options for the treatment and management of UTI (Adegoke *et al.,* 2022). Within the immediate study setting, the third-generation cephalosporins appear to be treatment of choice for UTIs, especially in clinical settings (Abayneh *et al.,* 2018; Ameshe *et al.,* 2022). The extensive use of antibiotics in treatment of UTIs has contributed immensely to the upsurge in antibiotic resistance in different clinical and community settings. The *K. pneumonia* has been notorious for the production of extended spectrum beta-lactamases (ESBLs), which is the most notable antibiotic resistance mechanism among *K. pneumonia* (Ameshe *et al.,* 2022; Haindongo *et al.,* 2022). They have also been confirmed to produce carpanemases that confer resistance to carbapenems like meropenem and ertapenem, which are the most commonly used carbapanem antibiotics in Nigeria (Adegoke *et al.,* 2022). This development adds complication to the treatment and management of UTIs that originate from clinical and community settings.

Several studies have confirmed UTIs caused by *K pneumonia* in different clinical settings in Nigeria (Ige *et al.,* 2011). Such studies vary depending on the target populations, existing morbidities and peculiarity of the clinical setting (David Otobo, 2020; Dibua *et al.,* 2014; Okoroiwu *et al.,* 2020). It is therefore necessary to determine the current prevalence of antibiotic resistant *K pneumonia* among humans that attend clinics in Ekiti-State. In view of the public health threat posed by UTIs,

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it is necessary to determine the current prevalence of antibiotic resistant *K pneumonia* in Ado Ekiti. Although some studies have been carried out, such studies tend to focus more on other bacteria that are not specifically *K pneumonia*. This study was therefore carried out to determine the prevalence of antibiotic resistant *K. pneumonia* isolated from patients with UTIs attending a particular healthcare facility in Ado Ekiti, Nigeria. This will encourage routine surveillance of antibiotic resistant infection and also provide possible guide for physician regarding appropriate treatment routine for UTIs in such settings.

MATERIALS AND METHODS

Study setting

Samples were collected and processed at a designated healthcare facility in Nigeria and the cross sectional study design was used. Within the immediate study setting, patients were referred to the microbiology laboratory for urine culture. Appropriate ethical approval was obtained before access to urine samples was given.

Sample collection and processing

Mid-stream urine samples were collected from patients referred to the laboratory and the urine samples were cultured using standard microbiological methods. Ten (10 µl) microliters of urine sample was pipetted per urine sample and transferred to sterile MacConkey agar and Cysteine Lactose Electrolyte Deficient medium (CLED) and thereafter incubated for 24 hours at 37 °C. For each sample, colony counts equivalent to ≥ 10^5 CFU/mL on CLED was considered as bacteriuria. Colonies were presumptively selected from the corresponding MacConkey agar plates and were sub-cultured into fresh agar plates. Standard biochemical tests were carried out to identify the *K. pneumonia* isolates derived from the urine cultures (Cheesbrough, 2006). All the colonies of *K. pnumoniae* obtained from urine samples were purified and stored appropriately for future use.

Antibiotic susceptibility testing

The *K. pneumoniae* isolates were subcultured onto freshly prepared nutrient agar and incubated at 37^{O}C for 18 hours to start the antibiotic susceptibility. The tests were carried out on all *K. pneumonia* isolates from urine samples using the agar disk diffusion procedure as specified by the Clinical Laboratory Science Institute CLSI (2020). About 4-5 colonies of each isolate was picked and suspended into sterile normal saline in clear test tubes. The mixture was homogenized and matched with the MacFarland turbidity standard to derive a standard inoculum. The standard inoculum for each isolated was inoculated onto sterile Mueller Hinton (MH) agar plates.

Furthermore, antibiotic paper disks containing the following antibiotics: tetracycline (10µg), cotrimoxazole (25 µg), gentamicin (10 µg), cefuroxime (30 µg), chloramphenicol (10 µg), ceftriaxone (30 µg), cefotaxime (30 µg), ciprofloxacin (5 µg) and amikacin (30 µg) (Biomark) were placed onto the inoculated medium. The MH agar plates were incubated at 37^{O}C for 18-24 hours. After incubation, the plates were examined for zones of inhibition and the zones obtained measured and interpreted accordingly. All results were tabulated and charted appropriately.

RESULTS

A total of twenty six (26) isolates of *Klebiella pneumonia* were isolated from the urine samples of the patients sampled. Identification was based on standard biochemical tests of the isolates. The results showed that the organisms showed a high rate of resistance to

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the antibiotics tested. More specifically, all the isolates of *Klebsiella pneumonia* showed resistance to ceftriaxone, vancomycin, cefotaxime, ceftriaxone, and ceftazidime (Table 1).

Table 1: Frequency of resistance to individual antibiotics (n=26)

S/N	Antibiotics	No. resistant isolates (%)
1	Cefuroxime	26 (100.0%)
2	Vancomycin	26 (100.0%)
3	Chloramphenicol	8 (31.0%)
4	ceftriaxone	26 (100.0%)
5	Cefotaxime	26 (100.0%)
6	Ceftazidime	26 (100.0%)
7	Tetracycline	24 (92.3%)
8	Cotrimoxazole	21 (80.8%)
9	Gentamicin	23 (88.5%)
10	Meropenem	25 (96.2%)
11	Ciprofloxacin	14 (53.9%)
12	Amikacin	20 (76.9%)

High number of the isolates also showed resistance to tetracycline while the organism showed the least resistance to chloramphenicol 8 (23.0%) and ciprofloxacin 14 (40.0%). Overall, the bacterial strains showed twenty four different antibiotic phenotypes with the highest antibiotic resistance phenotypes shown as: CRX-VAN-CTR-CTX-CPZ-TET-COT-GEN-MEM-CIP-AMK with five (5) isolates. Various phenotypes showed low frequency with only one strain each showing the resistance phenotypes. The details of the different antibiotic resistance phenotypes demonstrated by different strains of *Klebsiella pneumonia* are shown in Table 2. The organisms showed high frequency of multiple resistance to antibiotics with 4 isolates that showed reduced susceptibility to all the antibiotics tested with multiple resistance index of 1 (Table 3).

Table 2: Antibiotic resistance patterns

No of antibiotics	Resistance patterns	Frequency
Seven antibiotics	CRX-VAN-CTR-CTX-CPZ-TET-GEN	1
Eight antibiotics	CRX-VAN-CTR-CTX-CPZ-TET-MEM-AMK	1
	CRX-VAN-CTR-CTX-CPZ-COT-GEN-MEM	1
Nine antibiotics	CRX-VAN-CTR-CTX-CPZ-TET-MEM-CIP-AMK	1
	CRX-VAN-CTR-CTX-CPZ-COT-GEN-MEM-CIP	1
	CRX-VAN-CTR-CTX-CPZ-TET-COT-MEM-AMK	1
	CRX-VAN-CTR-CTX-CPZ-TET-GEN-MEM-AMK	1
Ten antibiotics	CRX-VAN-CTR-CTX-CPZ-TET-COT-GEN-MEM-AMK	5
	CRX-VAN-CTR-CTX-CPZ-TET-COT-GEN-MEM-CIP	1
	CRX-VAN-CHL-CTR-CTX-CPZ-TET-GEN-MEM-CIP	1
Eleven antibiotics	CRX-VAN-CHL-CTR-CTX-CPZ-TET-COT-GEN-MEM-AMK	2
	CRX-VAN-CHL-CTR-CTX-CPZ-TET-COT-GEN-MEM-CIP	1
	CRX-VAN-CTR-CTX-CPZ-TET-COT-GEN-MEM-CIP-AMK	5
Twelve antibiotics	CRX-VAN-CHL-CTR-CTX-CPZ-TET-COT-GEN-MEM-CIP-AMK	4
Total		**26**

Keys: CRX-cefuroxime, VAN- vancomycin, CHL- chloramphenicol, CTR- ceftriaxone, CTX-cefotaxime, CPZ- ceftazidime, TET- tetracycline, COT- cotrimoxazole, GEN- gentamycin, MEM- meropenem, CIP- ciprofloxacin, AMK- amikacin

Table 3: Summary of multiple antibiotics resistance index

S/N	Multiple resistance index	Frequency
1	0.58	1
2	0.67	2
3	0.75	5
4	0.83	6
5	0.92	8
6	1.00	4

DISCUSSION

The *K. pneumonia* is a leading cause of UTIs in clinical and community settings with

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significant morbidity associated with the organism (Ameshe *et al.,* 2022; Bobbadi *et al.,* 2021; Kao *et al.,* 2023). The organisms is also a causative agent of UTIs in the community setting and therefore constitutes an extra burden to healthcare (Abayneh *et al.,* 2018; James A. *et al.,* 2020; Oladeinde *et al.,* 2011). The continued prognosis of untreated and poorly managed UTIs can lead to other complications which include pneumonia and bacteraemia (Ige *et al.,* 2011; Tocut *et al.,* 2022). More importantly, the use of antibiotics in the treatment of different forms of UTIs caused by *K. pneumonia* increases the risk of emergence of antibiotic resistance in the organisms. This increases antibiotic consumption and contributes to the overall increase in cost of healthcare (Bakhashween *et al.,* 2020; Bobbadi *et al.,* 2021; Jalil and Al Atbee, 2022) .

The organisms isolated from UTIs in this present study appeared to show a high level of resistance to antibiotics. Generally, the *Klebsiella pnaumoniae* is a significant part of the groups of uropathogenes, after *Escherichia coli* and this organism is notoriously reputed for its ability to resist a wide array of antibiotics in different infections. This has been attributed to the hypermucoid nature of the organisms that serve as outer protective layer to enable the organism withstand high concentrations of antibiotics (Li *et al.,* 2022). Several studies have confirmed the growing incidence of antibiotic resistance among uropathogens, particularly *Escherichia coli* and *K. pneumonia* in different clinical and community settings (Alfa *et al.,* 2022; Dibua *et al.,* 2014; Haindongo *et al.,* 2022).

The majority of *Klebsiella pneumonia* isolates in this study showed a high rate or resistance to the beta lactam antibiotics tested, especially against the third-generation cephalosporins. This finding agrees with several other studies that have reported an increase in the level of resistance to beta lactam antibiotics and more importantly, the third and extended generation antibiotics (Abayneh *et al.,* 2018; Ameshe *et al.,* 2022; Tiemtoré *et al.,* 2022). The cephalosporins have emerged as leading antibiotic options for the treatment of UTIs in core clinical settings and this phenomenon favours the emergence of resistance to the third generation cephalosporins. The most important mechanism of action of resistance to the third generation cephalosporins is the production of extended spectrum beta lactamases and this enzyme has become widespread in healthcare settings (Aboumarzouk, 2014; Ameshe *et al.,* 2022; Tamma *et al.,* 2022).

Some of the bacterial strains recovered from the urine samples also showed resistance to meropenem, which is also a critical antibiotic in hospital settings. This antibiotic belongs to a class of antibiotic family call the carbepenems and these antibiotics are considered critical due to their designation as last resort antibiotics in hospital and clinical setting. The increasing resistance of bacteria to other major classes of antibiotics is a single factor for use of meropenem and related antibiotics in treatment of UTIs. The serious implication of the emergence of resistance against the carbepenems is the severe limitation of options of antibiotics available for the treatment of critical infections in healthcare settings.

Some of the isolates also showed resistance to tetracycline. This antibiotic is a common drug for treatment of different infections in healthcare settings. Some studies have reported the incidence of bacterial uropathogens to tetracycline. A study by Abayneh *et al.,* (2018) reported that *Klebsiella pneumonia* isolates recovered from patients with community onset UTIs also showed resistance to tetracyclines. The high

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incidence of resistance to cotrimoxazole observed in this study also agrees with previous findings. A study by (Ameshe *et al.,* 2022) reported some level or resistance to cotrimixazole among *Klebsiella pneumonia* from clinical sources. Similarly, similar study by (Setiawan *et al.,* 2022) showed some strains of *Klebsiella pneumonia* that showed reduced susceptibility to cotrimoxazole and tetracycline.

Another important finding in this study is that only 14 isolates of *Klebsiella pneumonia* showed resistance to ciprofloxacin. This antibiotic is also commonly used for treatment of various infections in the study setting. The lower resistance demonstrated by the bacteria against this antibiotic could justify its use for treatment of various infections, including UTIs. However, the resistance of clinical isolates to specific antibiotics often depends on the local epidemiology of the hospital. Some studies confirm that resistance to fluoroquinolones among uropathogens is prevalent and it is a serious problem in healthcare settings (Geetha *et al.,* 2020). Fluoroquinolone resistance is also common among bacterial isolates that produce ESBLs (Araújo *et al.,* 2023). The increasing incidence of resistance among uropathogens is a serious problem of concern among clinicians worldwide (Thompson *et al.,* 2024).

All the bacteria isolated in this study showed high level of multiple antibiotic resistance to different combinations of antibiotics tested. Multiple antibiotic resistance is a serious problem in healthcare as it complicates the treatment of different infections in clinical settings. It has a serious consequence in the severe limitation it poses in the antibiotic treatment options for the treatment of different infectious diseases. Other studies have equally reported the increasing incidence of multiple resistance in UTIs. Multiple antibiotic resistance among bacteria from patients with chronic kidney infections have been reported (Haque Sumon *et al.,* 2023). Similar study by Khan *et al.* (2020) revealed the high prevalence of antibiotic resistance among *Klebsiella pnaumoniae* and *Pseudomonas aeruginosa* from patients at a medical centre. In a similar study earlier carried out in Nigeria, multidrug resistant Gram-negative bacteria were isolated from patients with UTIs (Akingbade *et al.,* 2015). The high frequency of multiple resistance limits the treatment options patients, prolongs hospital stay and contribute to the overall public health burden.

CONCLUSION

Twenty six *Klebsiella pneumonia* strains were recovered from UTIs and all of them showed resistance to third generation cephalosporins. The bacteria showed various degrees of resistance to other antibiotics but resistance to chloramphenicol was least. The bacteria also showed high level of multiple antibiotic resistance, which is also evident in the high multiple antibiotic resistance index (Table 3). This finding buttresses the importance of continuous surveillance for UTIs and the need for proper antimicrobial stewardship in the study setting to maximise the use of antibiotics for antibiotic resistant *Klebsiella pneumonia* and other uropathogens in the hospital.

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