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ISOLATION AND ANTIMICROBIAL RESISTANCE PHENOTYPE OF *Klebsiella pneumonia* FROM THE URINE OF SUSPECTED UTI PATIENTS ATTENDING PUBLIC HOSPITALS IN NASARAWA SOUTH SENATORIAL DISTRICT, NASARAWA STATE, NIGERIA

[*1,2]Ashefo, D. P., [2]Ngwai, Y. B., [2]Ishaleku, D.

[1]Department of Science Laboratory Technology, Isa Mustapha Agwai 1 Polytechnic, Lafia, Nasarawa State, Nigeria.
[2]Department of Microbiology, Faculty of Natural and Applied Sciences, Nasarawa State University, Keffi.

*Corresponding authors' email: ashefo39@yahoo.com Phone: +2348032058952

ABSTRACT

The emergence of antibiotic resistant uropathogenic *Klebsiella pnuemoniae* is causing major public health crisis worldwide. This study is aimed at Determining the prevalence and antimicrobial resistance phenotypes of the urinary *Klebsiella pnuemoniae* isolated from patients attending public hospitals in Nasarawa South Senatorial District, Nasarawa State, Nigeria. During the duration of study, urine samples of 375 patients was cultured for the presence of *K. pneumonia*. A loopful of urine collected in a sterile container was streaked on MacConkey Agar, CLED, and blood agar plates and incubated for 24 hours at 37°C. The identification and resistance to selected antimicrobials were processed in accordance with the approved standards. *K. pnuemoniae* was found in 38 of the 375 urine samples tested, resulting in an overall prevalence of 10.13%. GHO and GHK shows a lower prevalence of 4.00% each, while DASH demonstrated a higher prevalence of 14.29%. Out-patient (13.19) and females (11.88%) shows higher prevalence of K. pneumonia than in-patient (6.74%) and males (6.14%). Patients aged 25-34 had the highest prevalence (13.82%), while the age group of 54-64 had the lowest prevalence (3.57%). The bacterial isolates demonstrated more resistance to ampicillin (94.74%) and amoxicillin-clavulanic acid (73.6%) compared to cefotaxime (13.16%), ceftriazone (18.42%), ceftazidime and cefoxitin (23.60%), and gentamicin (28.94%). Thirty-three (33) distinct phenotypes were found, with the most common (7.98%) being Ampicillin (AMP), Amoxicillin-Clavulanic acid (AMT), Ciprofloxacin (CIP), Co-trimoxazole (SXT) and Streptomycin (S). The highest multiple antibiotic resistance score (31.57%) is for resistance to three antibiotics, while the lowest (2.63%) is for resistance to one, seven, or eight antibiotics. To maintain the efficacy of antibiotics and for improved patient treatment, an effective antibiotic policy and guidelines should be introduced. Health care professionals, patients, and anybody else who visits hospitals are advised to practice good hygiene by washing their hands frequently, using hand sanitizer, and cleaning surfaces in hospitals with antiseptics more than once a day is recommended.

Keywords: Prevalence, Antimicrobial Resistance, Urinary Tract Infection, *Klebsiella pnuemoniae*, Nasarawa State

INTRODUCTION

Klebsiella pneumoniae (*K. pneumoniae*) is a Gram-negative, rod-shaped, facultative anaerobic bacterium that causes infections such as wound infections, sepsis, respiratory and gastrointestinal tract infections, urinary tract infections, pyogenic liver abscesses, soft tissue infections, and wound infection (Ranjbar *et al*., 2019; Yazdansetad *et al*., 2019; Akinyemi *et al*., 2021). This organism is among the most important bacteria responsible for UTIs in both genders and in all age groups in the world (Magliano *et al*., 2012; Yazdansetad *et al*., 2019).

Antimicrobial resistance is a natural phenomenon, although it is exacerbated by the inappropriate use of antibiotics (Nwafia *et al*., 2021). Due to the overuse and misuse of antibiotics, as well as the expansion of organisms that produce extended-spectrum beta-lactamases (ESBLs), the advent of multidrug-resistant uropathogens such as *K. pneumoniae* has increased in recent decades (Cerceo *et al*., 2016). β-lactam antibiotics have long been the most often used antibiotics for treating UTIs caused by members of the Enterobacteriaceae family, but the development of ESBL has rendered this class of antibiotics mostly ineffective (Eltai *et al*., 2018). The rise of antibiotic resistant uropathogenic *K. pneumoniae* is causing a severe public health problem worldwide, resulting to poor patient outcomes; increased duration of hospital stay and higher treatment costs (Ohanu *et al*., 2018; Nwafia *et al*., 2021). This problem is especially prevalent in third world nations such as Nigeria, where huge levels of counterfeit medications are in circulation, as well as abuse and inappropriate use of antibiotics (Keke *et al*., 2005; Nwafia *et al*., 2021).

Saleem (2016) asserts that the emergence of multidrug-resistant *K. pneumoniae* is widely viewed as a serious public health concern. The utilization of broad-spectrum antibiotics for hospitalized patients has led to an increase in *K. pneumoniae* carriage and the emergence of multidrug-resistant bacteria (Chakraborty 2016). According to Naqid et al. (2020), *K. pneumoniae* has evolved resistance to routinely used antibiotics as well as higher classes such as third-generation cephalosporins in several nations.

Several reports have described and characterized antimicrobial resistance in *K. pneumoniae* (Eltai *et al*., 2018; Yazdansetad *et al*., 2019; Chinyere *et al*., 2020; Akinyemi *et al*., 2021) but there is paucity of information in respect to prevalence and phenotypic characterization of antimicrobial resistant *K. pneumoniae* in the study area. Hence, this study seeks to investigate the prevalence, antibiotic resistance pattern and phenotypic characteristics of *K. pneumoniae* isolated from urine of patients attending public hospitals in Nasarawa South, Nigeria.

METHODS

Study Area and Locations

The study area was Nasarawa South Senatorial District, Nasarawa State, Nigeria. The locations were: General Hospital Awe (GHA), General Hospital Doma (GHD), General Hospital Keana (GHK), General Hospital Obi (GHO) and Dalhatu Araf Specialist Hospital (DASH) Lafia.

Key: △ Study Areas

Figure 1: Map of Nasarawa State

Ethical Clearance

Ethical clearance for this study was obtained from the National Health Research Ethic Committee (NHREC) in the Nasarawa State Ministry of Health, Lafia.

Sample Size

The sample size was determined using the formula (Fisher *et al.*, 1998):

$$N = \frac{Z^2 pq}{d^2}$$

Where:

N= calculated sample size

Z= level of confidence according to the standard normal distribution (for a level of confidence of 95%, z = 1.96)

p= prevalence rate of *K. pneumoniae*(33.0% by Orole and Hadi, 2020)

q= (1-p)

d= tolerated margin of error (5%)

$N = \frac{(1.96)^2 x\ 0.33\ x\ (1-0.33)}{(0.05)^2}$The recent prevalence of

$N = 340N$

Actual Sample size= Calculated sample size + 10% Attrition rate

But 10% Attrition rate =34

Actual Sample size= 340 + 34= 374

Inclusion Criteria

Patients with suspected UTIs attending the selected hospitals were selected for this study.

Exclusion Criteria

Patients with suspected UTIs and on antibiotics attending the selected hospitals were excluded from this study.

Sample Collection

A total of 375 (175 from DASH and 50 from the other three hospitals) early morning mid-stream urine samples of patients with suspected cases of UTI were collected using sterile container and transported in ice pack to Microbiology Laboratory, Dalhatu Araf Specialist Hospital (DASH), Lafia for analyses. *Klebsiella pneumoniae* was isolated from urine samples as follows: a loopful of urine sample was streaked on MacConkey Agar/CLED plate and incubated at 37°C for 24 h. Pinkish mucoid colonies that grew on MacConkey agar were selected as presumptive *K. pneumoniae.*

Phenotypic characterization of *Klebsiella pneumoniae*

The presumptive *K. pneumoniae* isolates were confirmed using the KB003 H125™ Kit following the manufacturer's instructions. First, two pure colonies of suspected isolates from an agar plate were transferred to 5 ml of sterile normal saline in a tube to prepare a suspension, and the suspension's turbidity was adjusted to match that of a 0.5 McFarland standard. Next, the kit was opened aseptically by peeling off

the sealing foil, and 50 µl of the adjusted suspension was inoculated into each well of the kit. The sealing foil was then replaced, and the kit was incubated at 37ºC for 24 hours. After incubation, specific reagents were added to different wells (e.g., 3 drops of reagent R036 and 1 drop of reagent R015 were added to well No. 5, 2 drops of reagent R009 was added to well No. 6; 3 drops of reagent R029 and 1 drop of reagent R030 were added to well No. 9; 1 drops of reagent 1007 was added to well No. 10 and finally 1 drops of reagent R008 was added to well No. 11), and the results were interpreted according to the standard given in the identification index.

Antimicrobial Susceptibility Testing

The bacterial isolates underwent antimicrobial susceptibility testing following the Clinical and Laboratory Standards Institute protocol (CLSI, 2017). Three pure colonies of each isolate were inoculated into 5 ml sterile 0.85% (w/v) NaCl (normal saline) and the turbidity was adjusted to match 0.5 McFarland's standard, which was prepared by adding 0.5 ml of 1.172% (w/v) $BaCl_2.2H_2O$ into 99.5 ml of 1% (w/v) H_2SO_4. Standardized bacteria suspension was applied to Mueller-Hinton agar plates using a sterile swab stick, and antibiotic discs were placed at the center of the plates. The plates were left to stand for 1 hour to allow for pre-diffusion, and then incubated at 37ºC for 24 hours. The diameter of the resulting zone of inhibition in millimeters was measured, and the susceptibility of the bacteria was determined using the susceptibility breakpoint as described by the CLSI (2017).

Determination of Multiple Antibiotic Resistance (MAR) Index

The MAR index of the isolates was determined using the formula as described Ngwai *et al.*, (2014).

RESULTS

Isolation and Identification of *Klebsiella pneumoniae*

The bacterium under study was isolated and identified based on cultural, morphological and biochemical characteristics as shown in Table 1. Colonies (pink, round, smooth, mucoid colonies on MacConkey agar; gray on blood agar; and large, yellowish, elevated, mucoid on CLED agar) that were Gram negative, rod in shape, with indole-negative, catalase-positive, oxidase-negative, Voges-Proskauer positive, slide agglutination positive, glucose-positive, and lactose-positive were taken as *Klebsiella pneumoniae*.

Prevalence of *Klebsiella pneumoniae*

The overall prevalence of *K. pneumoniae* in the 375 clinical samples from Nasarawa South Senatorial District is 38 (10.13%) as shown in Table 2. GHO and GHK recorded the least prevalence of K. pneumonia with 4.0% each, while the highest prevalence of 14.29% was recorded in DASH The prevalence varies by patient type and is 6.74 % for in-patients and 13.19 % for out-patients. Gender is associated with a prevalence of 31 (11.88%) in females and 7 (6.14%) in males. Patients aged 25-34 had the highest prevalence 13 (13.82%), while the age group of 54-64 had the lowest prevalence 1(3.57%).

Antimicrobial Resistance Profile of the *Klebsiella pneumoniae* isolates

The resistance profile of the isolates to common antimicrobial agents is as shown in Table 3. Resistance was high to ampicillin 36 (94.74%) and amoxicillin- clavulanic acid 28 (73.6%) but low (less than 30%) to cefotaxime 4(13.16%), ceftriazone 7(18.42%), ceftazidime and cefoxitin 9 (23.60%) and gentamicin 11 (28.94%).

Antimicrobial Resistance Phenotype of the *Klebsiella pneumoniae* isolates

The antimicrobial resistance phenotypes of the isolates are shown in Table 4. Thirty three (33) distinct phenotypes were seen, with ampicillin (AMP), amoxicillin-clavulanic acid (AMT), ciprofloxacin (CIP), co-trimoxazole (SXT), and streptomycin (S) being the most frequent (7.89%)

Multiple Antibiotic Resistance (MAR) Index of the *Klebsiella pneumoniae* isolates

The MAR index of the isolates is shown in Table 5. The highest 12 (31.57%) MAR index is for resistance to three antibiotics; while the least 1 (2.63%) is for resistance to one, seven or eight antibiotics.

Table 1: Cultural, Morphological and Biochemical characteristics of *Klebsiella pneumoniae*

Cultural characteristic	Morphological characteristics		Biochemical characteristics							Inference
	Gram stain	Morphology	In	Cat	Ox	VP	SL	Gl	La	
Smooth, mucoid pink round colonies on MacConkey agar, Gray on Blood agar and Large, yellowish, elevated, mucoid colonies on CLED agar	-	Rod	-	+	-	+	-	+	+	*Klebsiella pneumoniae*

MCA= MacConkey Agar; CLED Agar; - = Negative; + = positive; Ind= Indole; Cat= Catalase; VP= Voges Proskauer; Oxd= Oxidase; La= Lactose fermentation; Gl= Glucose fermentation; SL= Slide Agglutination.

Table 2: Prevalence of *Klebsiella pneumoniae* in urine from suspected patients attending public hospitals.

Parameters	Number Examined	Number (%) Positive
Overall	375	38 (10.13%)
Location-Based		
DASH	175 (46.66)	25 (14.29)
GHD	50 (13.33)	6 (12.00)
GHA	50 (13.33)	3 (6.00)
GHO	50 (13.33)	2 (4.00)
GHK	50 (13.33)	2 (4.00)
Patient type		
Inpatient	178 (47.46)	12 (6.74)
Outpatient	197 (52.53)	26 (13.19)
Gender		
Male	114 (30.4)	7 (6.14)
Female	261 (69.6)	31 (11.88)
Age Range (Years)		
<15	21 (5.60)	2 (9.52)
15-24	56 (14.93)	7 (12.50)
25-34	110 (29.33)	13 (11.82)
35-44	54 (14.40)	4 (7.41)
45-54	43 (11.46)	2 (4.65)
54-64	28 (7.46)	1 (3.57)
64-74	26 (6.93)	1 (3.85)
≥75	37 (9.86)	8 (21.62)

Key: **DASH**= Dalhatu Araf Specialist Hospital Lafia; **GHD**= General Hospital Doma; **GHA**= General Hospital Awe; **GHO**= General Hospital Obi; **GHK**= General Hospital Keana

Table 3: Antimicrobial Resistance Profile of the urinary *Klebsiella pneumoniae* isolates.

Antimicrobial Agent	Disc Content (µg)	Number (%) Resistance
Ampicillin (AMP)	10	36 (94.74)
Amoxicillin-Clavulanic acid (AMT)	30	28 (73.60)
Cefotaxime (CTX)	30	4 (13.16)
Ceftazidime (CAZ)	30	9 (23.60)
Ceftriaxone (CRO)	30	7 (18.42)
Cefoxitin (FOX)	30	9 (23.60)
Ciprofloxacin (CIP)	5	15 (39.47)
Co-trimoxazole (SXT)	25	14 (36.84)
Gentamicin (CN)	10	11 (28.94)
Streptomycin (S)	10	18 (47.36)

Table 4: Antimicrobial Resistance Phenotypes of the urinary *Klebsiella pnuemoniae* isolates

Antibiotic resistance phenotypes	Number (%) *K. pnuemoniae*isolates (n=38)
SXT	1 (2.63)
AMP AMT	2 (5.26)
AMP, CAZ	1 (2.63)
AMP, CIP	1 (2.63)
AMP, FOX	1 (2.63)
AMP, FOX, S	1 (2.63)
AMP, FOX, CN	1 (2.63)
AMP, AMT, CIP	1 (2.63)
AMP, CAZ, S	1 (2.63)
AMP, AMT, S	1 (2.63)
AMP, CIP, CN	1 (2.63)
AMP, CIP, S	1 (2.63)
AMP, AMT, CAZ	1 (2.63)
AMP, AMT, CRO	1 (2.63)
AMP, AMT, CN	2 (5.26)
CXT, SXT, S	1 (2.62)
AMP, AMT, FOX, S	2 (5.26)
AMP, AMT, CRO, CN	1(2.63)
AMP, CTX, FOX, S	1 (5.26)

AMP, AMT, CIP, S	1 (2.63)
AMP, AMT, CIP, SXT, S	3(7.98)
AMP, AMT, CRO, SXT, CN	1(2.63)
AMP, AMT, CAZ, FOX, S	1 (2.63)
AMP, AMT, CAZ, CIP, SXT	1 (2.63)
AMP, AMT, CAZ, CIP,, S	1 (2.63)
AMP, AMT, CAZ, CRO, SXT	1 (2.63)
AMP, AMT, CAZ, CRO, FOX, S	1 (2.63)
AMP, AMT, CTX, CIP, SXT,S	1 (2.63)
AMP, AMT,CIP,SXT,CN, S	1 (2.63)
AMP, AMT, CTX,CRO,CN,S	1 (2.63)
AMP,AMT, FOX, CIP, CN, S	1 (2.63)
AMP,AMT, CAZ,FOX,CIP,SXT, S	1 (2.63)
AMP, AMT, CAZ, CRO, CIP, SXT, CN, S	1 (2.63)

AMP= Ampicillin; AMT= Amoxicillin-Clavulanic acid; CTX= Cefotaxime, CAZ: Ceftazidime, CRO= Ceftriaxone; FOX= Cefoxitin; CIP= Ciprofloxacin; SXT= Co-trimoxazole; CN= Gentamicin; S= Streptomycin

Table 5: Multiple Antibiotic Resistance (MAR) Indices of the urinary *Klebsiella pnuemoniae* isolates

Number of Antibiotics isolate is resistant to (a)	Number of Antibiotics tested (b)	MAR index (a/b)	Frequency (%)
8	10	0.8	1 (2.63)
7	10	0.7	1 (2.63)
6	10	0.6	5 (13.16)
5	10	0.5	6 (15.79)
4	10	0.4	4 (10.52)
3	10	0.3	12 (31.57)
2	10	0.2	6 (15.79)
1	10	0.1	1 (2.63)

DISCUSSION

Identification of the species is crucial in the diagnosis and management of *K. pneumoniae* infections. It is also necessary in disease prevention, patient management, and infection surveillance. However, due to limited resources, time, and labor, most of our hospitals overlook this practice. Also, resistance to antimicrobials used to treat urinary infections is increasing, and the number of hospitalized patients is increasing as antimicrobial resistance grows (Zilberberg and Shorr 2013; Ostojic *et al*., 2021). *Klebsiella pneumoniae* was isolated in this study from patients with urinary infections being treated at general hospitals in Nasarawa South, Nasarawa State, Nigeria. The sensitivity of the isolates to several conventional antibiotics is subsequently given. These findings principally gave insight on the possibility of efficient isolation, differentiation, and treatment of urinary tract infections caused by distinct *K. pneumoniae* strains.

A total of 38 of the 375 processed samples tested positive for significant *K. pneumoniae* growth, indicating a prevalence rate of 10.13% (Table 2.). These findings are consistent with one carried out in Kano State Nigeria, where 8.0% prevalence rate for *K. pneumoniae* was discovered (Hamza *et al*., 2016). Other studies reported similar results with prevalence rates of 8.33% and 10.0% (Vranic *et al*., 2018; Sokhn *et al*., 2020). This result was somewhat lower than the percentage observed in different research performed in Anambra, which was 18.2% (Ogbukagu *et al*., 2016). Research in Benin, Edo State, however, found a much higher prevalent rate of 33.3% (Osazuwa *et al*., 2010).

Geographically, the higher frequency of *K. pnuemoniae* UTI reported in DASH Lafia (Table 2) compared to the other areas was due to the huge number of samples received and analysed at the specialist hospital, which acts as a referral centre for Nasarawa South's general hospitals. Lafia is likewise a suburb with a higher population density than the surrounding districts. The presence of higher education institutions in Lafia is likely to have contributed to the relative rise in sexual activity. According to Nicolle, (2008) and Ogbukagu *et al*. (2016), sex is the major cause of 75% to 90% of bladder infections, and sex frequency is reliably connected with the risk of infection.

In the study, the prevalence of *K. pneumoniae* infection was 26 (13.19%) in outpatients and 12 (6.74%) in hospitalised patients (Table 2). These findings are consistent with that of Ostojic *et al*, (2021) whose findings reveal that 153 (35.6%) patients with *K. pneumoniae* urinary infection were hospitalized while 277 (64.4%) were outpatients. This result is also in agreement with those of Sokhn *et al*., (2020) who reported that in-patients had a lower *K. pneumoniae* urinary infection rate of 39.7% as compared to outpatients with 60.3% infection rate. However, the findings of Acheampong *et al*., (2011) differ in that of the 152 *K. pneumoniae* recovered, 58.6% were from in-patients and 41.4% were from out-patients. The reduced prevalence of *K. pneumoniae* urine infection among in-patients might be attributed to antibiotic exposure, notably carbapenems and fluoroquinolones (Kritsotakis *et al*., 2011; Liu *et al*., 2012), for purposes other than *K. pneumoniae* urinary infection (Effah *et al*., 2020).

Females had a greater incidence of *K. pneumoniae* urinary infection (11.88%) than men (6.14%). (Table 2). The findings of Hamza *et al*., (2016) and Ogbukagu *et al*., (2016) support this observation. Ostojic *et al*., (2021) observed that infection was more commonly confirmed in female patients (244% or 56.74%) than male patients (186% or 43.26%). In contrast, Otajevwo (2013) found a prevalence rate of 58.3% in men and 41.7% in females. However, no explanation was provided. Female urethras are significantly shorter and closer to the anus than male urethras, and they lack the bacteriostatic characteristics of prostatic secretions, which may account for the higher incidence rate of urinary tract infection in females (Manjunath *et al*., 2011; Ogbukagu *et al*., 2016; Varghese *et al*., 2016; Vranic *et al*., 2018). As a result, the higher

incidence in females observed in this study could be attributed to unsanitary practices such as cleaning the vagina with stored water that has been left out in the open for some time and cleaning the vagina incorrectly by going from back to front after urinating, which results in autoinfection (Ogbukagu *et al*., 2016). Pregnancy and sexual activity can enhance a woman's chances of developing UTI. Female sexual activity raises the risk of urethra contamination because germs can be pushed into the urethra during sexual contact, and bacteria can be massaged up the urethra into the bladder after delivery (Varghese *et al*., 2016).

The age-specific data was analysed to assess the prevalence of *K. pneumoniae* urine infection in various age groups. According to this study, persons aged 25 to 34 were more likely to get *K. pnuemoniae* infection (Table 2). This is congruent with the findings of Hamza *et al*. (2016), who discovered that the age range with the highest occurrence was 21 to 30 years old, with 33 (16%) of the 79 (39.5%) specimens analysed in the group falling into this category. This might be explained by the fact that persons in this age group participate in sexual activity greater than those in other age groups, which could involve a single partner or several partners (Ogbukagu *et al*., 2016).

Cephalosporins (Cefotaxime (86.84%), Ceftazidime (73.60%), Ceftriaxone (73.60%), and Cefoxitin (73.60%), together with gentamicin (71.05%), obtained acceptable sensitivity (Table 2). This is in accordance with the findings of Ostojic *et al.* (2021). Co-trimoxazole, Ciprofloxacin (Ostojic *et al.*, 2021), and Streptomycin (Hamza *et al*., 2016) all had satisfactory therapeutic effects with sensitivity values of 63.16%, 57.89%, and 52.53%, respectively.

Klebsiella pneumoniae isolated from the urine samples in the study areas were most resistant to Ampicillin (94.74%) and Amoxicillin-Clavulanic acid (73.60%) these findings are in agreement with those of Varghese *et al*., (2016) and Hamza *et al*., (2016) whose findings reveals that 100% of the *K. pnuemoniae* isolated from urine are resistant to Ampicillin. As stated by Varghese *et al*., (2016), *K. pneumoniae* isolates are naturally resistant to Amoxicillin and Ampicillin, due to a constitutively expressed chromosomal class β lactamase.

CONCLUSION

Conclusively, an overall prevalence of 38(10.13%) of Klebsiella pnuemoniae was observed in this study. Females had a greater incidence of *K. pnuemoniae* urinary infection (11.88%) than men (6.14%). Antimicrobial sensitivity shows that *K. pnuemoniae* is a highly resistant bacteria with multiple drug resistance. Cefotaxime and Ceftriaxone were the most sensitive antibiotics and hence they should be kept as reserved drugs. To maintain the efficacy of antibiotics and for improved patient treatment, an effective antibiotic policy and guidelines should be introduced. Health care professionals, patients, and anybody else who visits hospitals are advised to practise good hygiene by washing their hands frequently, using hand sanitizer, and cleaning surfaces in hospitals with antiseptics more than once a day is recommended.

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