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Klebsiellae Infections and Antimicrobial Susceptibility Patterns in the 21st Century: A Paradigm Shift

Jombo GTA[1], **Emanghe UE**[2], **Akpan S**[2], **Bolarin DM**[3]

[1]Department of Medical Microbiology and Parasitology, College of Health Sciences, Benue State University, PMB 102119 Makurdi, Nigeria.
[2]Department of Medical Microbiology and Parasitology, University of Calabar Teaching Hospital, Calabar, Nigeria.
[3]Department of Chemical Pathology, College of Medicine, Lagos State University Lagos, Nigeria

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***Corresponding author:**

E-mail: jombogodwin@yahoo.com
Phone: +2348039726398

ABSTRACT

With the general growing trend of antimicrobial resistance among bacteria, this study was set out to ascertain the prevailing antimicrobial resistance pattern of *Klebsiella pneumoniae,* a hitherto highly susceptible bacterium from clinical specimens. The study was retrospective in nature. Data generated from clinical specimens processed at the University of Calabar Teaching hospital Microbiology laboratory were compiled over a five year period (2004-2009). Relevant data such as type and nature of specimen, microscopy and culture results, antibiotic susceptibility results, and age and gender of the respective subjects were obtained. From the 152 *Klebsiella pneumoniae* isolates from 54.6% (83) males and 45.4% (69) females, 62.5% (95) and 37.5% (57) were community acquired (CA) and nosocomial (NC) isolates respectively. At least 52.0% (79), 32.0% (49), and 16.0% (24) of the isolates were resistant to ≥5, 3-4, and 1-2 antibiotics respectively while no isolate (0.0%) was susceptible to all the antibiotics tested. The resistance of the NC isolates of *Klebsiella pneumoniae* against chloramphenicol, erythromycin, co-trimoxazole, tetracycline, amoxicillin, cloxacillin and ampicillin was significantly higher than their CA counterpart ($P < 0.05$). Augmentin, colistin, Ofloxacin, ceftriaxone and nalidixic acid were the most active agents. Extreme restraint should be exercised in the use of antibiotics among clinicians while their general use adequately regulated to help control this growing pattern of multiple resistance.

INTRODUCTION

The second world war (1939-1945) though a man made global catastrophe contributed significantly to the revolution in antimicrobial chemotherapy with the successes achieved with crude penicillin extracts on military and civilian casualties[1-3]. Since then medical advancements and innovations in drug formulations and preparations appear to have been on a collision course with the microbial world with the continuous increase in antimicrobial resistance[4-6]. The world's Seven billion people appear to be at the mercy of the increasingly highly resistant bacteria and it is difficult to accurately predict the fate of the immediate and further generations in the hands of these microbes[7,8].

Klebsiella pneumoniae, an *Enterobacteriaceae* has been associated with several infections both local and systemic and has accounted for several morbidities and mortalities in community and hospital settings[9,10]. Furthermore the growing rate of resistance of *Klebsiella species* has thrown up an additional challenge of effectively managing diseases and infections associated with the organism. In Lagos and Benin-city in Nigeria, most isolates of *Klebsiella pneumoniae* were found to be susceptible to amikacin, ceftazidime, ceftriaxone, aztreonam and nalidixic acid but up to 50% resistant to gentamicin and septrin[11,12]. Also in India all the *Klebsiella spp.* recovered from urine of patients were resistant to trimethoprim and sulphanethoxazole combinations[13]; and in Turkey a nationwide gram negative antimicrobial resistance survey showed that 45% of the isolates were amonoglycoside resistant which was commoner among the nosocomial strains[14]. In Boston USA, the resistance of *Klebsiella spp.* to antibiotics was attributable to TEM-1, TEM-2 and SHV-1 beta-Lactamases produced by the organism which hydrolysed penicillins, cephalosporins and monobactams[15]. In Paris, France in addition, resistance of *Klebsiella pneumoniae* to ceftazidime was also attributed to a single amino acid substitution in the Omega loop[16].

In several parts of sub-saharan Africa including Nigeria as well as other parts of developing world, bacterial infections generally still constitute a major threat to human survival[17,18. Lack of adequate laboratory facilities for both diagnostic and

prognostic purposes often hampers effective treatment of bacterial infections. This more often than not leads to empirical treatment of patients of which ab ini-tio should be based strictly on the antibiotic susceptibility pattern of bacteria in the locality[19-21]. It is in this regard that antimicrobial susceptibility profile of *Klebsiella species* from clinical specimens was carried out to offer a guide to health personnel who may be confronted with such limitations in the course of patient management.

MATERIALS AND METHODS

Setting

The study was carried out at University of Calabar Teaching Hospital (UCTH), which is situated in Calabar city, the capital of Cross Rivers state, south-south Nigeria.

Procedure

The study was retrospective in nature; data generated from the antibiotic susceptibility pattern of bacteria recovered from clinical specimens by the Microbiology laboratory of UCTH were compiled for a period of five years (1st February, 2004 - 31st January, 2009). Specimens such as blood, sputum, urine, wound swab, and urethral, eye or ear swabs were collected, transported and processed using standard laboratory procedures while modified Kirby-Bauer's diffusion method was used to carry out susceptibility testing[22,23]. Microorganisms recovered were grouped into nosocomial or community acquired based on the epidemiological circumstance of the blood culture specimens.

Nosocomial infection

Micro-organisms recovered from blood culture specimens of patients who have been on admission for more than 24 h for which features of bacterial colonization were not present at the time of initial presentation to the hospital.

Community acquired infection

Micro-organisms recovered from blood culture specimens of patients who were not on admission in the hospital, and from patients within 24 h of admission or patients originally admitted for probable blood related infections. Other relevant information such as: age, sex were obtained from patients records.

Analysis of results

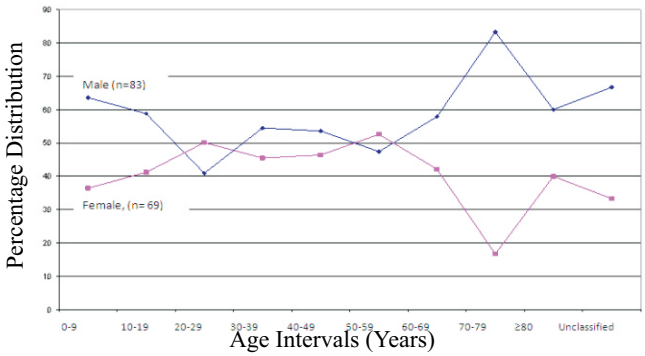
The results were analyzed using Epi Info-6, statistical software, values ≤0.05 were considered significant.

RESULTS

The total number of clinical specimens processed by the laboratory during the study period (2004-2009) was 34,253 while 2,706 (7.9%) organisms were recovered from them. *Klebsiella pneumoniae* constituted 152 (5.6%) of the microbial isolates recovered, 95 (62.5%) were community acquired (CA) while 57 (37.5%) were nosocomial in origin.

A review of the age distribution pattern of the subjects infected with *Klebsiella pneumoniae* showed that the age range was 3 months to 81 years; mean age range was 40-49 years and median age range 40-49 years while the modal age was 43 years. There was no significant difference in rate of infection among the age groups (F= 7.707) (Fig. 1). Based on gender distribution, 54.6% (83) of those infected were males while 45.4% (69) were females with no significant gender difference (P> 0.05) (Fig. 1).

Analysis of the clinical specimens from which *Klebsiella pneumoniae* was recovered showed that 0.93% (68), 0.52% (24), 0.50% (14), and 0.205 (13) of the isolates were recovered from urine, wound swabs or pus, sputum, and endocervical swabs (ECS) or high vaginal swabs (HVS) respectively (Table 1).



*SST= 273.611, Df= 17, MST= 29.889, F= 7.707
**X^2(Yates Corrected)= 0.38, df= 1, P= 0.53

Fig. 1: Age* and gender** distribution of *Klebsiella pneumoniae* recovered from clinical specimens in Calabar, Nigeria (N=152).

Table No.1: Sources of isolation of Pathologic *Klebsiella pneumoniae* species from clinical specimens in Calabar, Nigeria.

Specimen Type	Number of Specimens	*Klebsiella spp.* Isolates (%)
Urine	7,348	68 (0.93)
Wound Swab/Pus	4,533	24 (0.52)
Blood	3,255	3 (0.10)
Sputum	2,886	14 (0.50)
Pleural/Peritoneal fluid	73	1 (1.4)
Cerebrospinal fluid	688	3 (0.40)
ECS/HVS	6,722	13 (0.20)
Urethral Swab	593	6 (1.00)
Semen	773	3 (0.40)
Eye/Ear/Nose Swabs	1,457	16 (1.1)
Stool	5,879	0 (0.0)
Others	46	1 (2.20)

NB: Total number of Specimens= 34,253; Number of *Klebsiella pneumoniae* isolates= 152; ECS= Endocervical swab; HVS= High vaginal swab.

Antimicrobial susceptibility patterns of *Klebsiella pneumoniae* from clinical specimens showed that activity of the antibiotics against both the CA and NC isolates of the organisms were less than 50% against ampicillin, cloxacillin, amoxicillin, tetracycline and co-trimoxazole. Both the CA and NC isolates of the organism were 75% - 100% susceptible to augmentin, colistin, Ofloxacin, ceftriaxone, nalidixic acid, gentamicin and rifampicin. The resistance of NC isolates of the organism were significantly higher than the CA isolates against chloramphenicol, erythromycin, co-trimoxazole, tetracycline, amoxicillin, cloxacillin and ampicillin (P< 0.05) (Table 2). Among the Klebsiella isolates, 52.0% (79) were resistant to 5 or more antibiotics, 32.0% (49) were resistant to 3-4 antibiotics, 16.0%

Table No.2: Antimicrobial susceptibility pattern of *Klebsiella pneumoniae* recovered from clinical specimens in Calabar, Nigeria.

Antibiotic	Community acquired Isolates (CA)		Nosocomial Isolates (NC)		P Values
	Total	Number Sensitive (%)	Total	Number Sensitive (%)	
Penicillin G	-	-	-	-	-
Ampicillin	90	35 (38.9)	57	11 (19.3)	< 0.05
Cloxacillin	86	41 (47.7)	45	13 (28.9)	< 0.05
Amoxicillin	93	49 (52.7)	31	9 (29.0)	< 0.05
Tetracycline	94	43 (45.7)	56	10 (17.9)	< 0.05
Co-Trimoxazole	95	56 (59.0)	57	18 (31.6)	< 0.05
Augmentin®	95	88 (92.6)	50	46 (92.0)	
Colistin	71	62 (87.3)	26	26 (100)	
Streptomycin	95	88 (92.6)	57	56 (98.2)	
Gentamicin	95	95 (100)	57	49 (86.0)	
Amikacin	87	85 (97.7)	55	53 (96.4)	
Ofloxacin	94	94 (100)	57	56 (98.2)	
Ciprofloxacin	89	89 (100)	44	44 (100)	
Ceftazidime	87	85 (97.7)	30	30 (100)	
Cefuroxime	83	83 (100)	36	35 (97.2)	
Ceftriaxone	76	75 (98.7)	19	19 (100)	
Chloramphenicol	93	72 (77.4)	57	22 (38.6)	< 0.05
Erythromycin	112	76 (67.9)	32	11 (34.4)	< 0.05
Rifampicin	78	78 (100)	54	54 (100)	
Nalidixic acid	73	73 (100)	23	23 (100)	
Nitrofurantoin	61	57 (93.4)	17	17 (100)	

NB: ® = Clavulanic acid + Amoxicillin, - = Not applicable

(24) were resistant to 1-2 antibiotics while none (0.0%) was susceptible to all the antibiotics tested.

DISCUSSION

Both the nosocomial (NC) and community acquired (CA) isolates of *Klebsiella pneumoniae* were over 50% resistant against ampicillin, cloxacillin, amoxicillin, tetracycline, co-trimoxazole and NC isolates against erythromycin and chloramphenicol. The resistance to chloramphenicol, erythromycin, ampicillin, cloxacillin, amoxicillin, tetracycline and co-trimoxazole among the NC isolates was significantly higher than the CA isolates ($P < 0.05$).

The high resistance recorded by *Klebsiella pneumoniae* against several antibiotics in the present study could be attributed to the uncontrolled sale and consumption of antibiotics among the people in the community[24]. Also the unregulated pattern of prescriptions among health personnel often leading to under-treatment in terms of dosage and duration are all probable contributory factors[25,26]. The findings from the present study compares well with that of: Roh et al in South Korea[27] where a countrywide survey showed *K. pneumoniae* to be multiply resistant to a significantly large number af antibiotics in common use; Akram et al in India[28] and Baraniak et al in Poland[29] where resistance against some penicillins and cephalosporins were over 70%; and Cai et al in China where clavulanic acid inactivating *K. pneumoniae* were identified and were resistant to several cephalosporins, penicillins and carbapenemes[30].

The higher resistance shown by the NC isolates of *K. pneumoniae* compared to CA species against chloramphenicol, erythromycin, ampicillin, cloxacillin, tetracycline and co-trimoxazole may not be unconnected with the prolonged and overuse of these antimicrobial agents in the hospital setting. Empirical treatment with these antibiotics becomes a challenging decision owing to their imminent failure especially in resource poor communities where sensitivity report may not be readily available despite their affordability[24,26]. This probably explains the relatively higher activity of augmentin, Ofloxacin, ciprofloxacin, ceftazidime, cefuroxime, ceftriaxone and rifampicin whose prescriptions are generally influenced by cost and specific disease conditions in hospital settings[31,32].

The findings from the present study however partly differ from those in: China where over 82%, 77% of *Klebsiella pneumoniae* isolates were resistant to co-trimoxazole and augmentin respectively[33]; Turkey, where resistance of 17.7% against cefoperazone/sulbactam was noted[34]; and in Israel where emerging isolates of *K. pneumoniae* were found to be resistant to ciprofloxacin and piperacillin-tazobactam[35]. This clearly shows the current regional and geographical variations in antimicrobial resistance and rapidly changing pattern. This contrasts sharply with the immediate post world war II era where resistance among bacteria was not a common finding and probably could not have been anticipated to grow to this magnitude[1,36,37].

Recommendations

In view of the high resistance of *K. pneumoniae* resistance against several antibiotics in the locality, prescription and consumption of antibiotics should be strictly regulated in order to checkmate abuse. Also the quality of antibiotics produced locally or imported should be appropriately certified by appropriate authorities before wide scale use and fortification of animal feeds with antibiotics properly regulated.

Clinicians may endeavour to carry out likelihood of inadequate therapy (LIT, the frequency of inadequately treated patients per antibiotic and drug-resistant strain) ratio in order to predict which antimicrobial agents will provide adequate therapy[38].

As way of accommodating probable treatment failures due to multiple resistance, clinicians should also consider the option of antibiotic therapy rotation at intervals as was found to reduce mortalities at intensive care units in Italy[39,40]. Also adequate initial empirical antimicrobial treatment should be part of standard practice so as to help slow the rate of onset and progression of resistance among in-patients[41].

Hospital epidemiology division along with a well organized and functional nosocomial infections control programme should be established in major hospitals in the country and also lengths of hospital stay be shortened as much as practicable as possible. Data generated and other useful information could be distributed to secondary and primary healthcare centres in the vicinity for a general collaborative patient management. This would reduce the rate of spread of nosocomial infections in the hospital settings which might eventually prove difficult to treat[42,43].

CONCLUSION

The present study has shown that the antimicrobial susceptibility pattern of *K. pneumoniae* may have changed significantly over the past seven decades. While the resistance presently high appears to be transiting to a much higher level with the involvement of much newer drugs, and poses great challenge to clinical practice in perspective. Extreme caution should be exercised in the management of patients involving antibiotics so as to contain this ongoing resistance trend. Where sensitivity reports are readily unavailable, augmentin, gentamicin, Ofloxacin, ciprofloxacin, ceftriaxone and amikacin could be considered for empirical treatment of *Klebsiella pneumoniae* infections.

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