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Antibiogram of *Klebsiella pneumoniae* among population with community acquired urinary tract infection in Enugu State, Nigeria

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Abstract

Antibiotic resistance possesses a serious challenge in the treatment of Urinary Tract Infections (UTIs). This study was therefore designed to determine the antibiogram of *K. pneumoniae* isolated from individuals presenting with UTIs in communities within Enugu state. A cross-sectional study was conducted from February, 2021 to June, 2021 and a total of 735 patients with community-acquired UTIs in Enugu state, Nigeria, were involved in the study. The patients were assessed clinically and microbiologically for *Klebsiella pnuemoniae* and antibiogram of the isolates were investigated. Out of 77 isolates of *Klebsiella pneumaniae* obtained, 29 (37.7%) showed multiple resistant to the antibiotics used, whereas 48 (62.3%) were either susceptible or intermediate. Of all the antibiotics tested, meropenem showed the highest recorded sensitivity to the test organism 63(19.93%), whereas the least sensitivity was observed in co-amoxiclav 11 (3.48%). Antibiogram of urinary *K. pneumoniae* isolated from rural dwellers showed a significantly high resistance to commonly used antibiotics; thus, the need for regular awareness campaign and antimicrobial resistance surveillance to increase knowledge, improve infection control measures, and check abuse of antibiotics.

Keywords: Community-acquired UTI; Antibiotics; susceptibility; Resistance; *Klebsiella pneumoniae*

1 Introduction

During the pre-antibiotic era, infectious diseases had high morbidity and mortality, causing widespread outbreak, epidemics, or pandemics [1]. The introduction of antibiotics came with jubilations, as these infections were contained. Unfortunately, these excitements have been tampered by a phenomenon called "Antibiotic resistance", which occurs when microbes evolve mechanisms that protect them from the effects of antimicrobials [2]. In developing countries, key contributors of antimicrobial resistance (AMR) identified included: lack of surveillance of resistance development, poor quality of available antibiotics, clinical misuse, and ease of availability of antibiotics. In developed countries, poor hospital-level regulation and excessive antibiotic use in food-producing animals play a major role in leading to antibiotic resistance [3]

The six leading pathogens for deaths associated with resistance (*Escherichia coli*, followed by *Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa*), were responsible for 929, 000 (660, 000–1,270, 000) deaths attributable to AMR and 3·57 million (2·62–4·78) deaths

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associated with AMR in 2019 [4]. This group of pathogens are the major cause of urinary tract infection (UTI), which ranks the second commonest infection after respiratory infections [5]. In poor-resourced and tropical countries, UTIs are still the major source of morbidity and death [6], with an estimated annual global incidence of at least 250 million in developing countries [7]. Symptoms associated with urinary tract infection include – pain or burning (discomfort) sensation at urination; a feeling of urgency at urination; cramps or pain in the lower abdomen; the need to urinate more often than usual; urine that looks turbid and has foul smell; pain, pressure or tenderness in the area of the bladder and when bacteria spread to the kidneys, there can be back pain, chills, fever, nausea and vomiting. Treatment is by the use of efficacious antibiotics.

Furthermore, of particular concern are UTIs caused by *Klebsiella species*, as these bacteria are continuously evolving versatility of immune evasion strategies and complexity of drug resistance mechanisms that ensure survival during infection [8, 9], thereby, making it very difficult to treat with common antibiotics. The consequences of not addressing the silent pandemic of drug-resistant infections now could result in a future where we are unable to treat common infections with antibiotics, a post antibiotic era and the end of modern medicine. At this stage, very common infection can be fatal in both adults and neonates. Therefore, there is need to learn from COVID-19 pandemic, so we can tackle the issue of antibiotic resistance with utmost concern. In doing this, special attention should be paid to rural communities where abuse of broad-spectrum antibiotics is high [10]. This study is aimed at assessing the antibiogram of *K. pneumoniae* isolated from individuals with UTIs in rural communities within Enugu state. The result of this study will give informed decisions to policy issues and interventions necessary to check klebsiella UTIs and antimicrobial resistance.

2 Material and methods

2.1 Study Area

This study was conducted in The Enugu State University of Science and Technology Teaching Hospital, and The University of Nigerian Teaching Hospital, Ituku/Ozalla, all in Enugu state.

2.2 Sample size

This population-based, cross-sectional survey was conducted between February 2021 and, June, 2021 in Enugu state, Nigeria. A random sample of males and females aged 10-70 years residing in the selected communities within the three senatorial districts of Enugu state were selected. Simple random sampling technique was used to select three communities from the three senatorial zones in Enugu state, who participated in the study.

2.3 Study instruments

A well-structured questionnaire was used to collect data from the subjects on antibiotic usage, symptoms of UTI (pain or burning sensation at urinating; a feeling of urgency at urination; cramps or pain in the lower abdomen; the need to urinate more often than usual; urine that looks turbid and has foul smell; pain, pressure or tenderness in the area of the bladder and, back pain, chills, fever), physiological state, and some sociodemographic factors, like age and sex, etc., in order to ascertain their suitability for either inclusion or exclusion. Screw tight sterile universal containers (with boric acid) was used to collect urine samples for bacterial isolation.

2.4 Ethical approval

The ethical clearance for this study was sought from The Enugu State University of Science and Technology Teaching Hospital (ESUT TH), and The University of Nigerian Teaching Hospital.

2.5 Inclusion and Exclusion criteria

Subjects who represented at least three of the symptoms of UTIs, as outlined in the questionnaire were recruited for the study. Also included were those who were neither on antibiotic therapy, nor have taken antibiotics within the last two weeks before this study, and women who were not in their menstrual period. Subjects excluded from the study were those who did not meet up with the criteria for inclusion and those who did not give their consent for participation.

2.6 Data/Sample collection

Questionnaires were administered as self or by interviewer for the literate or illiterate respondents respectively. Subjects who met the inclusion criteria were educated on how to collect clean catch mid-stream urine aseptically, and thus were given urine bottles for sampling. Using a sterile, wide mouthed, and leak proof boric acid universal containers, a total of 740 urine samples were collected from selected communities. The samples were pre-stored in a cooler, maintained at +2 to +6°C, using an ice pack, before transportation to testing site.

2.7 Urine culture and molecular analysis

A 10 µl (0.01 ml) well-mixed urine sample was inoculated on MacConkey agar (Oxoid, UK), and Chromagar Orientation Media (M6: Plasmatec Laboratories, United Kingdom), and incubated at 37°C for 24 hours. The colony count with at least 10^5 CFU/ml for single midstream urine was taken as positive urine culture. All isolates were preliminarily screened by their colonial morphology, pigment production, colour and Gram reactions. Isolates showing the identity of Klebsiella were subjected to biochemical tests. Isolates that gave Methyl-red negative, Citrate positive, and Motility negative were considered as Klebsiella. These isolates were subjected to molecular studies, where *Klebsiella pneumonia* was typed down, using PCR, carried out using Amplitaq® 360 Polymerase and ran in an Eppendorf Mastercycler [11], Gel electrophoresis [12] and Sanger Sequencing by Genewiz® [13]. Isolates typed down as *Klebsiella pneumoniae* were used for antimicrobial susceptibility testing. Isolates were temporally stored at +2 to +8°C in the nutrient broth for not more than 24 hours prior to antimicrobial susceptibility testing.

2.8 Antimicrobial susceptibility testing

An antibiotic susceptibility assay was performed using the Kirby Bauer disk diffusion method, of NCCLS [14], and resistance and sensitivity were interpreted according to the National Committee for Clinical Laboratory Standards criteria [15]. The antimicrobial discs used include gentamycin, ofloxacin (30 µg), co-amoxiclav (30 µg), ciprofloxacin (5 µg), levofloxacin (10 µg), cefotaxime (30 µg) ceftazidime (30 µg), cefepime (30 µg), ceftriaxone (10 µg), and meropenem (10 µg). Multiple drug resistant microorganisms were identified as resistant to three or more antibacterial classes.

2.9 Data analysis

Data generated from questionnaire and antibiogram were analyzed by descriptive statistics and regression models, using IBM SPSS version 25. Frequency and contingency table were used to show the distributions of data. Quantitative data were summarized using mean and standard deviation. Chi-square was used as a statistical test of significance.

3 Results

Table 1 Culture result

Occurrence	frequency	prevalence
Total number of participants recruited	780	100%
Total number of participants accepted for inclusion	745	95.5%
Total number of participants rejected	35	4.48%
Total number of samples received	745	100%
Total number of samples accepted for culture	735	98.66%
Total number of samples rejected	10	1.34%
Total number of bacterial isolates obtained	649	88.3%
Total number of *klebsiella species* obtained	85	13.97%
Total number of *Klebsiella pneumoniae* obtained	77	11.86%
Total number of other *Klebsiella specie* (*Klebsiella quasipneumoniae*) obtained	8	9.4%
Total number of samples showing negative uropathogen (no bacterial growth and no significant bacterial growth)	86	11.2%

Of the total number of 77 isolates tested for antibiogram against 10 different antibiotics, resistance to the drugs was observed in 217 (28.18%), whereas sensitivity was observed in 316 (41.04%). Of all the drugs tested, meropenem showed the highest recorded sensitivity to the test organism 63(19.93%), whereas the least sensitivity was observed in co-amoxiclav, 11 (3.48%).

In table 2, a total of 735 samples were cultured, with a total number 85(13.97%) *klebsiella species* isolated and 77(11.86%) isolates of *Klebsiella pneumonia* obtained.

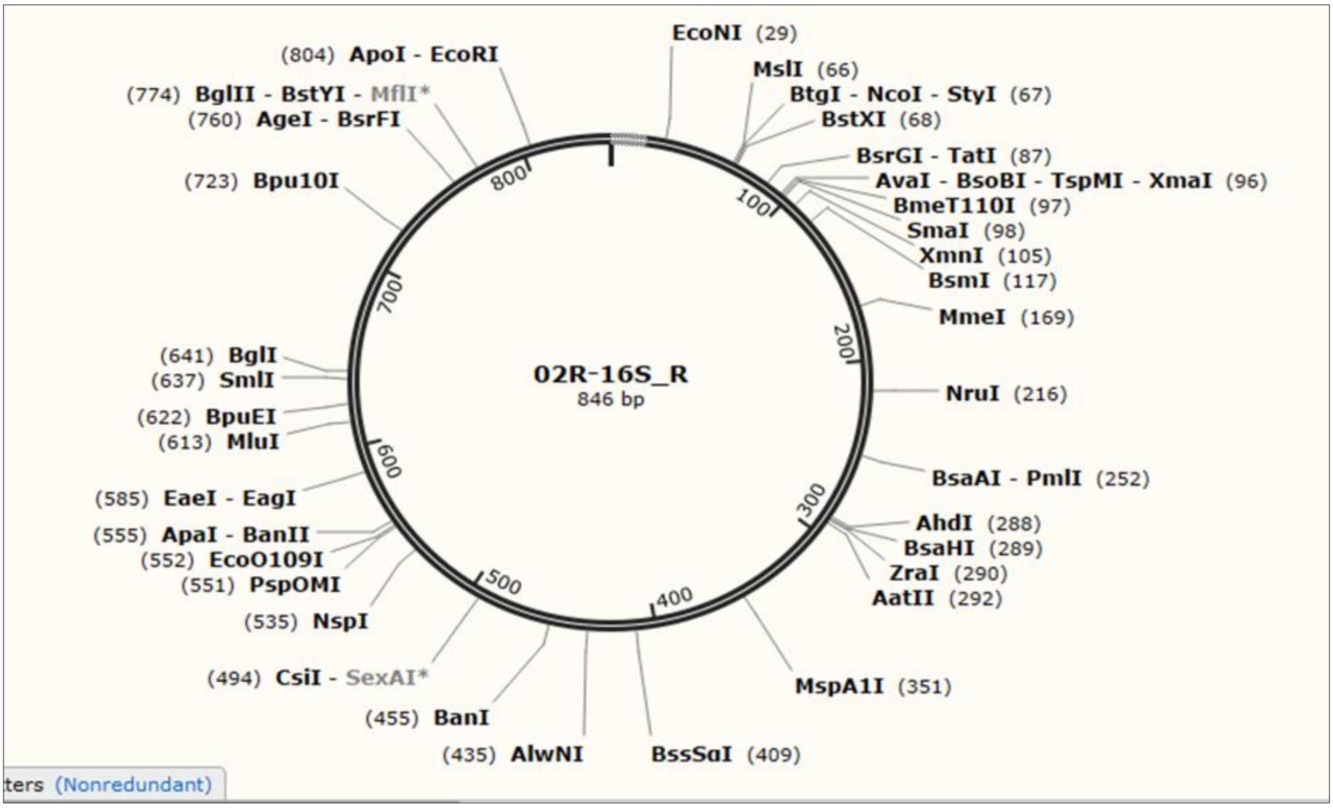

Figure 1 Genomics of *Klebsiella pneumoniae* obtained from sample 002 in this study

002:

TGCAAGTCGAGCGGTAGCACAGAGAGCTTGCTCTCGGGTGACGAGCGGCGGACGGGTGAGTAATGTCTGGGAAACTGCCTGATG
GAGGGGGATAACTACTGGAAACGGTAGCTAATACCGCATAACGTCGCAAGACCAAAGTGGGGGACCTTCGGGCCTCATGCCATC
AGATGTGCCCAGATGGGATTAGCTAGTAGGTGGGGTAACGGCTCACCTAGGCGACGATCCCTAGCTGGTCTGAGAGGATGACCA
GCCACACTGGAACTGAGACACGGTCCAGACTCCTACGGGAGGCAGCAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCA
GCCATGCCGCGTGTGTGAAGAAGGCCTTCGGGTTGTAAAGCACTTTCAGCGGGGAGGAAGGCGTTAAGGTTAATAACCTTGGCG
ATTGACGTTACCCGCAGAAGAAGCACCGGCTAACTCCGTGCCAGCAGCCGCGGTAATACGGAGGGTGCAAGCGTTAATCGGAAT
TACTGGGCGTAAAGCGCACGCAGGCGGTCTGTCAAGTCGGATGTGAAATCCCCGGGCTCAACCTGGGAACTGCATTCGAAACTG
GCAGGCTAGAGTCTTGTAGAGGGGGGTAGAATTCCAGGTGTAGCGGTGAAATGCGTAGAGATCTGGAGGAATACCGGTGGCGA
AGGCGGCCCCCTGGACAAAGACTGACGCTCAGGTGCGAAAGCGTGGGGAGCAAACAGGATTAGATACCCTGGTAGTCCACGCCG
TAAACGATGTCGATTTGGAGGTTGTGCCCTTGAGGCGTGGCTTCCGGAGCTAACGCGTTAAATCGACCGCCTGGGGAGTACGGC
CGCAAGGTTAAAACTCAAATGAATTGACGGGGGCCCGCACAAGCGGTGGAGCATGTGGTTTAATTCGATGCAACGCGAAGAAC
CTTACCTGGTCTTGACATCCACAGAACTTTCCAGAGATGGATTGGTGCCTTCGGGAACTGTGAGACAGGTGCTGCATGGCTGTC
GTCAGCTCGTGTTGTGAAATGTTGGGTTAAGTCCCGCAACGAGCGCAACCCTTATCCTTTGTTGCCAGCGGTTAGGCCGGGAAC
TCAAAGGAGACTGCCAGTGATAAACTGGAGGAAGGTGGGGATGACGTCAAGTCATCATGGCCCTTACGACCAGGGCTACACACG
TGCTACAATGGCATATACAAAGAGAAGCGACCTCGCGAGAGCAAGCGGACCTCATAAAGTATGTCGTAGTCCGGATTGGAGTCT
GCAACTCGACTCCATGAAGTCGGAATCGCTAGTAATCGTAGATCAGAATGCTACGGTGAATACGTTCCCGGGCCTTGTACACAC
CGCCCGTCACACCATGGGAGTGGGTTGCAAAAGAAGTAGGTAGCTTAACCTTCGGGAGGGC

Table 2 Antibiotics patterns of *K. pneumoniae* from urinary tract infections

Antibiotic	Sensitive	Prev.	Intermediate	Prev.	Resistance	Prev.
Gentamycin	29	9.18%	30	12.61%	18	8.29%
Co-amoxiclav	11	3.48%	28	11.76%	38	17.51%
Ciprofloxacin	29	9.18%	24	10.08%	24	11.06%
Levofloxacin	40	12.66%	17	7.14%	20	9.22%
Cefotaxime	25	7.91%	27	11.35%	25	11.52%
Ceftazidime	28	8.86%	26	10.92%	23	10.60%
Cefepime	23	7.28%	28	11.77%	26	11.98%
Ceftriaxone	46	14.56%	19	7.98%	12	5.53%
Meropenem	63	19.93%	9	3.78%	6	2.77%
Ofloxacin	22	6.96%	29	12.61%	25	11.52%
10	316(41.04%)	100	237(30.78%)	100%	217(28.18%)	100%

In table 3, a total of 29 isolates of the test organism showed multidrug resistant to the antibiotics used. Age range of 21-30 showed the highest percentage of multidrug resistance 11(37.93%), followed by age range 31-40: 7(24.14%), 41-50: 5(17.24%), 10-20: 3(10.35%), 51-60: 2 (6.89%), and finally 61-70: 1(3.45%).

Table 3 Multidrug resistant isolates and age distribution of participants

Age range	frequency of multiple drug resistant	Prevalence
10-20	3	10.35%
21-30	11	37.93%
31-40	7	24.14%
41-50	5	17.24%
51-60	2	6.89%
61-70	1	3.45%
	29	100%

4 Discussion

Klebsiella has been known as an opportunistic pathogen, with the vast majority of infections, associated with hospitalization, and attacking primarily, immunocompromised individuals who suffer from severe underlying diseases such as diabetes mellitus or chronic pulmonary obstruction [16]. However, recent studies have shown that Klebsiella cause primary infections in the community settings, and as well, have access to a mobile pool of virulence and antimicrobial resistance genes [17, 18], making then possible the emergence of a multidrug, hypervirulent *K. pneumoniae* clone capable of causing untreatable infections in healthy individuals. Unfortunately, there are already reports describing the isolation of such strains [19, 20, 21].

This present work is a community-based study, which was aimed at isolating *Klebsiella pneumaniae* from apparently healthy individuals who are based in the community, and who are presenting with symptoms of UTIs. To our knowledge, this is the first report in Enugu state, Nigeria, on *Klebsiella pneumoniae* UTIs among rural dwellers, where presence of symptoms of UTI was used as a major inclusion criterion for study participation. The results give strong correlations between UTIs and presence of symptoms. This approach will help improve urine culture ordering and as well, inform appropriate use of antibiotics in extreme need of empirical treatment.

This study was caried out on specimens of 745 subjects presenting with at least three of the signs and symptoms of UTI. The overall prevalence of the uropathogens was 649 (88.3%), which is higher than prevalence obtained in related studies, with a culture positivity rate of 61.4% as reported [22], and another work by [23], which reported a prevalence rate of 58.3%. The reason for this variation in prevalence is probably on the selection of subjects for sampling. While most studies based their inclusion criteria on individuals presenting with a symptom of UTI, others do a general survey on both asymptomatic and symptomatic subjects. The outcome of this study goes a long way in stressing the diagnostic value of symptoms in the interpretation of culture result for uropathogens, its consideration and the management of UTIs, as stressed by [24]. Adopting this principle will help save patients from undue financial burden and acquisition of antibiotic resistance occasioned by unnecessary antibiotic administration.

Furthermore, of the 649(88.3%) that were UTI positive, 20 (25.97%) were males, whereas 57(74.03%) were females. This agrees with research findings on the more prevalence of UTIs in females than in males [25]. The higher prevalence of UTI in females is chiefly attributed to anatomic factors in women, such as shorter urethral length, shorter distance from the anus to urethral meatus, and permissiveness of the vaginal and perineal environments to microbial colonization [26]. In this study, the highest prevalence of UTIs was observed among age range of 31-40 (25.97%), followed by age range 21-30 (23.38%), and 41-50 (23.38%). We therefore report that young and middle-aged adults are mostly affected by UTIs. This is consistent with the risk age for UTIs that has been reported in other settings elsewhere [23, 26, 27].

Out of the 649 (88.3%) positive isolates obtained, 85 (11.86%) was Klebsiella species, of which *Klebsiella pneumoniae* was the most prevalent, 77(90.6%), followed by *Klebsiella quasipneumoniae* 8(9.4%), which were the two species identified. The prevalence of *Klebsiella* species in this study (11.86%) is in conformity with a report from Morocco, where urinary *K. pneumoniae* was isolated in 10% of the urine samples in the Meknes [28], but differ markedly with the findings reported in Ethiopia:19–21% [29] and in Cameroon: 18.5% [30], and 18.4% reported in Nigeria [31]. This could be attributed to differences in exposure, and places where research was conducted, as more prevalent isolation is expected in hospital settings, more especially from the in-patients, since *Klebsiella pneumoniae* is a common nosocomial pathogen, as reported by [32].

The antibiogram of *Klebsiella pneumoniae* in this study shows that the most promising drug of choice for the treatment of UTIs caused by *Klebsiella pneumoniae* was meropenem, followed by ceftriaxone, the least sensitivity was observed in co-amoxiclav, followed by cefepime. This report is in conformity with a resent research findings in Northwest Ethiopia [33], where high efficacy of meropenem and ceftriaxone were reported against *Klebsiella pneumoniae*. Another study in India also demonstrated high susceptibility of *K. pneumoniae* to meropenem, where 65.7% of *K. pneumoniae* isolates were meropenem susceptible [34]. In a similar study conducted in Romania [35], *Klebsiella pneumoniae* was reported to be highly resistant to co-amoxiclav and cefepime, which is in line with the findings of this study. We report that co-amoxiclav should not be used for the treatment of UTIs, except when antibiogram has proven so, more especially in empirical therapy.

In this study, 29 isolates of the test organism (37.7%) were resistant to ≥3 antimicrobial drugs, and thus, they exhibited multidrug resistance (MDR). This is in line with a work done in Equatorial Guinea, which gave a prevalence rate of 33.3% [36]. However, rate of MDR in *K. pneumoniae* in the current study are lower than a report from Dessie, Ethiopia, where 63% of *Klebsiella species* showed MDR [37]. Age range of 21-30 contributed the highest percentage of MDR 11(37.93%), followed by age range of 31-40: 7 (24.14%). The least contribution was among age range of 61-70: 1(3.45%), followed by 51-60: 2 (6.89%). We therefore report that multidrug resistance as observed in this study has an inverse relationship with increasing age.

5 Conclusion

Resistance rates of *K. pneumoniae* isolates to commonly used antibiotics as obtained in this study were consistently high. More than one-third of the isolates showed MDR to the antibiotics used, with the highest resistant and susceptibility observed in co-amoxiclav and meropenem respectively. The greatest part of the MDR isolates came from the young and sexually active age group, thus there are speculations of worse scenario in the future, though this study reports an inverse relationship between age and multidrug resistant rate.

Recommendation

Generally, antibiotic resistance rate as observed in this study was high, so empirical use of common antibiotics for the treatment of UTIs should be discouraged. Urine culture must be performed for any suspected UTI, and antimicrobial susceptibility reports must be awaited before treatment is commenced, and health education should be taken to the rural communities for necessary awareness campaign on antimicrobial resistance.

Compliance with ethical standards

Acknowledgments

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Data Availability

All the data supporting the conclusion of the study are included in the paper.

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

Statement of informed consent

Research details were made known to the participants and their informed consent in the form of signature or thumbprint were obtained.

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