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Phenotypic Carbapenem-Resistant *Enterobacterales* Isolates in Selected Tertiary Hospitals in South-Eastern Nigeria

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Abstract: Carbapenems are broad spectrum β-lactam antibiotics that were introduced in response to the emergence of ESBL-producing Gram-negative bacteria. This study aimed at determining the occurrence of carbapenem resistant *Enterobacterales* isolates among patients attending five tertiary hospitals with southeastern region of Nigeria. A total of 400 *Enterobacterales* were isolated from different participants. Carbapenem-resistance was detected using Kirby-Bauer disc diffusion method with ertapenem, meropenem, imipenem and doripenem. Results showedthat atotal of 117 isolates (29.2%) were resistant to the four carbapenems. When compared among the states, the prevalence was33.6, 29.1, 28.8, 26.9 and 24.7% for Enugu, Ebonyi, Imo, Anambra and Abia states respectively. The highest resistance was observed among *P. mirabilis* (52.6%) followed by *K. oxytoca* (35.7%), *S. enterica* (35.7%) and *K. pneumoniae* (33.8%). *Conclusion*: The overall prevalence was high and this is a cause for concern and urgent need for emergency intervention to forestall widespread emergence of pandrug resistant infections.

Key words: Carbapenem · *Enterobacterales* · Southeast-Nigeria

INTRODUCTION

The carbapenems are a group of broad-spectrum beta-lactamase enzymes that possess hydrolytic activities against all cephalosporins, penicillins and carbapenems [1]. However, in the early 1990s the first carbapenem resistant bacterium was isolated in Japan [2]. The CDC recognized the public health threat and declared that carbapenem resistant organisms require aggressive action. The CDC also reported that up to half of all bloodstream infections caused by carbapenem-resistant *Enterobacterales* results in death [3, 4].

The development of carbapenem resistance has become a public health malady. They produce difficult to treat infections of all types with associated increase in morbidity, prolonged hospital stay, increased cost of treatment and a mortality rate that is greatly increased to about 50% [5, 6]. The carbapenemases are grouped according to the Ambler classification [7, 8]. Other mechanisms for carbapenem resistance include; production of AmpC enzymes and production of extended spectrum beta-lactamases [9, 10].

Gram-negative organisms are responsible for most clinical infections therefore the emergence of carbapenem resistance among them is of public health significance [11]. Also, there is limited treatment option as approved drugs used against them (colistin and tigecycline) are fraught with high toxicities [12] and they can be easily disseminated [13].

There is limited data on the epidemiology of carbapenem resistance among *Enterobacterales* especially in most sub-Saharan African countries [14]. This study aimed at providing data on the current status of carbapenem-resistant *Enterobacterales* isolates in selected tertiary hospitals in South-eastern Nigeria.

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MATERIALS AND METHODS

Study Design and Sampling Technique: This was a cross – sectional study designed and carried out across five tertiary hospitals in South-eastern Nigeria. Among eleven tertiary hospitals that are located within the region, five of them were selected using simple random sampling technique.

Study Population: The participants were patients who presented with clinical manifestations that suggested the presence of infection(s) with any of the *Enterobacterales* based on the provisional diagnosis and who had laboratory requests for microscopy, culture and sensitivity. Specimens were collected from the participants as requested in their laboratory forms and the isolates were identified to species level. A total of 400 *Enterobacterales* isolates were obtained from each of the participants.

Ethical Consideration: Ethical approval was obtained from the ministries of health of Abia, Ebonyi, Enugu, Imo and Anambra States. Informed consent was obtained from the participants or from their parents/guardians (for those below 18years).

Sample Size: The sample size was calculated using standard statistical methods (Ref.??) and a sample size of 400 was obtained. To determine the number of samples that would be collected from each centre, the probability proportion by size was calculated and the sample size obtained from each centre is presented in Table 1.

Inclusion/Exclusion Criteria: Patients who gave informed consents and in whom *Enterobacterales*were isolated from their specimens were included in this study. Patients who gave consent but in whom *Enterobacterales* were not isolated from their specimens were excluded from the study. Also, based on the prescription on the patients' folder and on verbal interview, patients that were on combined antibiotic therapy were excluded from the study.

Specimen Collection and Identification: *Enterobacterales* were isolated fromvarious specimens such as urine, sputum, cerebrospinal fluids, stool, blood, semen, wound, high vaginal, ear, throat, urethral and eye swabs. The identification of the isolates was performed using standard microbiological methods described by Cheesbrough [15] and Forbes *et al.* [16], which include Gram reaction and conventional biochemical tests such as indole, methyl red, Voges-Proskauer, citrate utilization, oxidase, urease, triple sugar iron and sugar fermentation reactions.

Carbapenem Susceptibility and Phenotypic Screening for Resistance: Phenotypic detection of carbapenem resistance was done using Kirby-Bauer disc diffusion method using discs with potency of 10µg each for Ertapenem, Imipenem, Meropenem and Doripenem. The bacterial isolates were suspended in sterile normal saline to match 0.5 McFarland standard (Ref.). A sterile swabstick was used to inoculate the surface of the Mueller-Hinton agar which had been prepared by following the Manufacturer's instruction and sterilized in an autoclave at 121°C for a holding time of 15 minutes.

The antimicrobial discs were placed after the surface of the media had been allowed to dry. The plates were subsequently incubated at 37°C for 18 hours. The inhibition zone diameters were measured and the results were interpreted based on guidelines of the European Committee on Antimicrobial Susceptibility Testing version 10 [17]. Isolates were recorded as carbapenem–resistant if they showed simultaneous resistance to ertapenem, doripenem, meropenem and imipenem.

Table 1: Sample size calculation from the probability proportion by size

S/N	Centre	Collected samples	Sample size
1	Federal Medical Centre Umuahia, Abia State	900	77
2	Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Ebonyi State	1200	103
3	Enugu State University Teaching Hospital, Parklane, Enugu State	1350	116
4	Imo State University Teaching Hospital, Imo State	600	52
5	ChukwuemekaOdumegwuOjukwu University Teaching Hospital, Anambra State	600	52
	Total	4650	400

Data Analysis: Data were analysed with the aid of Statistical package for social sciences (SPSS) version 20.0. Bar charts and pie charts were used for the presentation of some analyses, descriptive analysis, frequency tables and percentages were used for the univariate analysis while Chisquare test was used for the bivariate analysis. P-value < 0.05 was considered significant in all analyses.

RESULTS

Enterobacterales isolates were obtained from a total of 400 participants who gave informed consent to be part of this study. Among the participants 208 (52%) were females while 192 (48%) were males. The ratio of the sex was approximately 1:1. The participants' ages ranged from 3 years to over 70 years.

The distribution of the specimens obtained for this study as well as the *Enterobacterales* isolates obtained from each of them is presented in Table 2. Urine was the highest specimen collected (137 of 400), followed by wound swab (57), stool (50) and blood (34). The isolates obtained are presented in Table 2.

Overall, a total of 117 (29.2%) of the *Enterobacterales* isolates were resistant in all the isolates obtained from the five tertiary hospitals. Among these, the highest resistance was observed among *P. mirabilis* (52.6%) followed by *K. oxytoca* (35.7%), *S. enterica* (35.7%) and *K. pneumoniae* (33.8%). However, *Proteus vulgaris* and *Y. enterocolytica* were fully susceptible to the carbapenems (Table 3). However, there was no significant relationship between the distribution of the isolates and their susceptibility to the carbapenems (p = 0.346).

Table 2: The distribution of the specimens and the *Enterobacteriaceae* isolates obtained

	Specimen											
Bacterial	Urine	ECS	Wound Swab	Blood	HVS	Stool	Urethral swab	Throat swab	Sputum	Ear swab	Semen	Eye swab
Escherichia coli	46(33.6%)	8(27.6%)	13(22.8%)	16(47.1%)	11(34.4%)	9 (18.0%)	2(25.0%)	1(10.0%)	4(28.6%)	3(27.3%)	10(58.8%)	0 (0.0%)
Klebsiella pneumoniae	34(24.8%)	6(20.7%)	18(31.6%)	5 (14.7%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	3(30.0%)	9(64.3%)	0 (0.0%)	1 (5.9%)	0 (0.0%)
Citrobacter freundii	13 (9.5%)	6(20.7%)	10(17.5%)	0 (0.0%)	2 (6.2%)	0 (0.0%)	1(12.5%)	3(30.0%)	1 (7.1%)	2(18.2%)	3(17.6%)	0 (0.0%)
Klebsiella oxytoca	8 (5.8%)	1 (3.4%)	3 (5.3%)	0 (0.0%)	5 (15.6%)	0 (0.0%)	1(12.5%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)
Morganella morganii	7 (5.1%)	0 (0.0%)	3 (5.3%)	0 (0.0%)	2 (6.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2(18.2%)	0 (0.0%)	0 (0.0%)
Serratia marcescens	5 (3.6%)	2 (6.9%)	3 (5.3%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	1(12.5%)	0 (0.0%)	0 (0.0%)	1(9.1%)	0 (0.0%)	0 (0.0%)
Proteus mirabilis	14(10.2%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	2 (6.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Enterobacter cloacae	7 (5.1%)	0 (0.0%)	7(12.3%	1 (2.9%)	3 (9.4%)	0 (0.0%)	0 (0.0%)	1(10.0%)	0 (0.0%)	2(18.2%)	0 (0.0%)	1(100.0%)
Shigella dysenteriae	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	17(34.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Salmonella enterica	0 (0.0%)	0 (0.0%)	0 (0.0%)	10(29.4%)	0 (0.0%)	17(34.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Proteus vulgaris	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1(12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Yersinia enterocolitica	3 (2.2%)	5(17.2%)	0 (0.0%)	1 (2.9%)	5 (15.6%)	7 (14.0%)	2(25.0%)	2(20.0%)	0 (0.0%)	0 (0.0%)	3(17.6%)	0 (0.0%)
Total	137(100%)	29(100%)	57(100%)	34(100%)	32(100%)	50(100%)	8(100%)	10(100%)	14(100%)	11(100%)	17(100%)	1(100%)

Key: ECS implies Endocervical swab, HVS implies High Vaginal Swab

Table 3: Carbapenems resistant bacteria identified

	Carbapenems Resistant				
Isolate	Non- carbapenems Resistant	Carbapenems Resistant	Total	χ^2	P-value
Escherichia coli	85(69.1%)	38(30.9%)	123(30.8%)	12.242	0.346
Klebsiella pneumoniae	51(66.2%)	26(33.8%)	77 (19.3%)		
Citrobacter freundii	35(85.4%)	6 (14.6%)	41 (10.3%)		
Klebsiella oxytoca	18(64.3%)	10(35.7%)	28 (7.0%)		
Morganella morganii	18(66.7%)	9 (31.6%)	27 (6.8%)		
Serratia marcescens	16(72.7%)	6 (27.3%)	22 (5.5%)		
Proteus mirabilis	9 (47.4%)	10(52.6%)	19 (4.8%)		
Enterobacter cloacae	12(66.7%)	6 (33.3%)	18 (4.5%)		
Shigella dysenteriae	12(70.6%)	5 (29.4%)	17 (4.3%)		
Salmonella enterica	9 (64.3%)	5 (35.7%)	14 (3.5%)		
Proteus vulgaris	13(100%)	0 (0.0%)	13 (3.3%)		
Yersinia enterocolitica	1 (100%)	0 (0.0%)	1 (0.3%)		
Total	283(70.8%)	117(29.2%)	400(100%)		

Table 4: Relationship between the age distribution and Carbapenems resistant N = 400

	Carbapenems Resistant				
Ag Group	S	R	Total	χ^2	P-value
<20	50(70.4%)	21(29.6%)	71(17.8%)	4.104	0.663
20-29	85(68.5%)	39(31.5%)	124(31.0%)		
30-39	31(67.4%)	15(32.6%)	46(11.5%)		
40-49	29(82.9%)	6 (17.1%)	35 (8.8%)		
50-59	18(64.3%)	10(37.5%)	28 (7.0%)		
60-69	47(71.2%)	19(28.8%)	66(16.5%)		
70 & above	23(76.7%)	7 (23.3%)	30 (7.5%)		
Total	283(70.8%)	117(29.2%)	400(100%)		

Table 5: Relationship between the specimen distribution and Carbapenems resistant N = 400

	Carbapenems Resistant				
Specimen	S	R	Total	χ^2	P-value
Urine	92(67.2%)	45(2.8%)	137(34.3%)	17.753	0.123
Stool	35(70.0%)	15(30.0%)	50 (12.5%)		
W/S	37(74.0%)	13(26.0%)	50 (12.5%)		
Blood	20(58.8%)	14(41.2%)	34 (8.5%)		
HVS	26(81.2%)	6 (18.8%)	32 (8.0%)		
ECS	23(79.3%)	6 (20.7%)	29 (7.3%)		
Semen	12(70.6%)	5 (29.4%)	17 (4.3%)		
Sputum	7 (50.0%)	7 (50.0%)	14 (3.5%)		
Ear swab	10(90.9%)	1 (9.1%)	11 (2.8%)		
Throat swab	7 (70.0%)	3 (30.0%)	10 (2.5%)		
Urethral swab	8 (100%)	0 (0.0%)	8 (2.0%)		
Wound swab	6 (85.7%)	1 (14.3%)	7 (1.8%)		
Eye swab	0 (0.0%)	1 (100%)	1 (0.3%)		
Total	283(70.8%)	117(29.2%)	400(100%)		

Table 6: Relationship between the state distributions and Carbapenems resistant N = 400

	Carbapenems Resistant				
State	S	R	Total	χ^2	P-value
Abia	58(75.3%)	19(24.7%)	77 (19.3%)	1.990	0.738
Ebonyi	73(70.9%)	30(29.1%)	103 (25.8%)		
Enugu	77(66.4%)	39(33.6%)	116(29.0%)		
Imo	37(71.2%)	15(28.8%)	52 (13.0%)		
Anambra	38(73.1%)	14(26.9%)	52 (13.0%)		
Total	283(70.8%)	117(29.2%)	400(100%)		

We compared the relationship between the age of the participants and the presence of carbapenem-resistant *Enterobacterales* isolates but there was no significant relationship (p = 0.663). The highest resistance was observed among the age group of 50 – 59 years (37.5%) this was followed by the 30 – 39 age group (32.6%) and the 21 – 29 age group (31.5%). As presented in Table 4, the age group with the least frequency of resistance was participants within the 40 -49 age group (17.1%).

The presence of carbapenem resistant isolates were compared among the specimens they were obtained from and there was no significant relationship (p = 0.123) as presented in Table 5. However, there were more carbapenem-resistant isolates in specimens obtained from eye swab (100%), sputum (50.0%), blood (41.2%), stool (30.0%), throat swab (30.0%) and semen (29.4%).

Resistance to carbapenems was compared among the various states, there was an almost even distribution of carbapenem resistant isolates, hence there was no significant difference in the relationship between the state distributions and resistance to carbapenems. Isolates with the highest resistance were obtained from Enugu (33.6%), while Abia state had isolates with the least resistance to carbapenems (24.7%). Overall, each tertiary hospital had high prevalence of carbapenem-resistant isolates as presented in Table 6.

DISCUSSION

This study reports the occurrence of carbapenem-resistant *Enterobacterales* among tertiary hospitals in South-eastern Nigeria. We used strict criteria by recording an isolate as carbapenem-resistant if the isolate was simultaneously resistant to doripenem, meropenem, imipenem and ertapenem. A study which compared phenotypic screening methods for carbapenem resistance determined that 10µg of ertapenem and imipenem discs had 100% sensitivity while meropenem disc had 95.7% sensitivity when compared with the E-test and Modified Hodge Test methods [18]. This is comparable to the Kirby-Bauer method for phenotypic detection of carbapenem resistance which was used by this study.

The significance of this finding is far reaching considering the dependence placed on this class of antibiotics by clinicians who use them as drugs of last resort for multidrug resistant *Enterobacterales* isolates.

Among all the centres studied, there has only been one study on carbapenem resistance at Chukwuma Odumegwu Ojukwu University Teaching Hospital by Oli, *et al.* [9] who reported a prevalence of 14.38% of carbapenem-resistant *Klebsiella pneumoniae* and an overall prevalence of 28.21% of carbapenem-resistant *Enterobacterales* which is comparable to the reports of this study. However as at the time of this study, there are no other reports of carbapenem-resistant *Enterobacterales* within other areas studied for comparative assessment of our results.

Our report is comparable with the prevalence of 28.2% carbapenem resistant *Enterobacterales* reported by Olowo-Okere *et al.* [1] in Northern Nigeria. Enwuru *et al.* [19] reported a higher prevalence of 36.8% in Southwest Nigeria while Yusuf *et al.* [10] reported a 34.5% carbapenemases production in Kano, Nigeria. Other studies that reported lower prevalence than this study are Oduyebo *et al.* [20] who reported 15.5% prevalence in Lagos and Mohammed *et al.* [21] who reported 10.2% prevalence in Maiduguri. Also, a low prevalence of 7.7% CRE was reported in Southwest Nigeria [6]. However a much higher prevalence of 66% carbapenem-resistant *Klebsiella pneumoniae* was reported in Isparta, Turkey [7].

When the distribution of carbapenem-resistant isolates was compared among the various organisms isolated, the highest resistance was observed in *P. mirabilis* (52.6%) followed by *K. oxytoca* (35.7%), *S. enterica* (35.7%) and *K. pneumoniae* (33.8%). Even though these organisms were highest, the difference amongst all the isolates was not significant ($p = 0.346$), implying that there was no wide difference among them. However, *S. marcescens* and *K. oxytoca* were fully susceptible to the carbapenems. Our findings contrast the reports of Olowo-Okere *et al.* [1] who found *E. coli* as the most prevalent resistant isolates. However it reveals the dynamic nature of antimicrobial – resistant genes which can easily spread among various organisms of different genera and families through horizontal gene transfer.

We also found higher occurrence of *Y. enterocolitica* in extra-intestinal infections (Table 2) in contrast to previous reports. This is a call for further studies to determine if there is a changing epidemiology and pathogenesis in its infection within the study area.

CONCLUSIONS

The presence of carbapenem-resistant *Enterobacterales* signals an urgent call for the strengthening of antimicrobial resistance surveillance programs. Across Nigeria, there is almost a dearth of data on antimicrobial resistance among isolates from hospitals and almost an absent emergency reporting channel when multidrug resistant isolates are detected in clinical laboratories. There is an abundance of last resort antibiotics which are sold over the counter without control. Worst still is the practice of empirical therapy by clinicians as well as self -medication and abuse of antibiotics. Together, the factors that trigger the development and spread of antimicrobial resistance genes are numerous and multifaceted. However, there can be effective control with necessary actions. The need for strict control of antibiotics cannot be over-emphasized. Also is the urgent need for the institution and implementation of infection-control policies and programs in secondary and tertiary healthcare facilities. The high prevalence of carbapenem-resistant isolates in the various centres studied and the reports from other geographic regions of Nigeria begs the question; are we entering the post-antibiotic era?.

Limitation: Due to paucity of funds, this study did not detect the genomic mechanism (s) of resistance to the carbapenems.

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Manuscript has been read and approved by all the authors, the requirements for authorship have been met by both authors.

Competing Interests: The authors declare no competing interest.

Authors Contributions:

UIU - concept, design, data acquisition, data analysis, statistical analysis,

TKU - manuscript preparation, manuscript editing and manuscript review.

Conflicts of Interest: We declare no conflicts of interest whether financial or otherwise.

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