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Original Article

Carbapenem-Resistant Enterobacteriaceae among In-Patients of Tertiary Hospitals in Southwest, Nigeria

Ibikunle I. ANIBIJUWON, Ifeoluwa D. GBALA*, Olusoji O. ADEBISI

*University of Ilorin, Faculty of Life Sciences, Department of Microbiology, Ilorin, Nigeria; ifeoluwagbala@yahoo.com (*corresponding author)*

Abstract

The present study assessed the incidence and risk factor associated with the occurrence of carbapenem-resistant Enterobacteriaceae (CRE) among hospitalized patients at three tertiary hospitals in Southwest, Nigeria. A cross-sectional study was performed over a six-month surveillance period in the locations with a total of 300 blood and urine samples. A structured close-ended questionnaire was also administered to all subjects for review of demographics and potential risk factors. Fifty-nine isolates belonging to genera *Escherichia* (52.5%), *Enterobacter* (23.8%), *Klebsiella* (10.2%) and *Proteus* (13.6%) were isolated. All the isolates were multi-drug resistant with a notable resistance (100%) to cephalosporins and significant sensitivity to nitrofurantoin. A total of 23 isolates including *Escherichia coli* (n = 8), *Enterobacter aerogenes* (n=9), *Klebsiella pneumoniae* (n = 1) and *Proteus mirabilis* (n = 5) exhibited resistance to one or both of imipenem and meropenem. The overall incidence of CRE in the three locations at the time of study was 7.7%. Age (p = 0.01) and exposure to invasive devices were significant risk factors for CRE colonization. Although at low incidence, the occurrence of CRE among this group calls for active monitoring because of its implication fatality of infections as well as the propensity to spread.

Keywords: carbapenem; carbapenem-resistant; enterobacteriaceae; in-patients; multi-drug resistance

Introduction

The increase in the rate of antimicrobial resistance exhibited by bacteria, especially the Enterobacteriaceae family, is a threat to public health (Albiger *et al*., 2015). This threat decreases the ability to successfully treat numerous infectious diseases, while simultaneously increasing health risks for vulnerable patients. Carbapenem-resistant Enterobacteriaceae (CRE) are able to inactivate carbapenems which are revered to possess higher antibacterial spectrum against Gram negative bacteria than penicillin, cephalosporins and other β-lactams (ECDC, 2013; Jeong *et al*., 2015).

CRE produce seriously difficult to treat infections (urinary tract infections, septicemia, pneumonia, or intra-abdominal infections) in debilitated and immune-compromised patients, in association with prolonged hospitalization and increased fatality, with mortality rates up to 50% (Guh *et al*., 2015). Few studies have been carried out on CPE strains in Nigeria, with reports of incidence ranging between 10-33.5% (Yusuf *et al*., 2012a, 2012b; Ejikeugwu *et al*., 2013; Motayo *et al*., 2013; Mohammed *et al*., 2015; Oduyebo *et al*., 2015). Although carbapenems are unusually prescribed in Nigerian hospitals, there still remains a necessity for a focused approach on the dissemination of CRE. Also, CRE has the disposition to spread quite promptly, especially in an hospital environment where the risk of transmission is much higher; therefore a low incidence is not to be ignored, but rather a charge to curb further spread.

The objective of the present study was to determine the occurrence, frequency of distribution and risk factors associated with the colonization of CRE in three tertiary hospitals situated in Southwest Nigeria.

Materials and Methods

Description of study area

The study was conducted in three states in the Southwestern part of Nigeria. The region's population is predominantly heterogenous with people of varied religious and ethnic beliefs. The study was carried out in three tertiary hospitals from Ekiti, Osun and Oyo states (Fig. 1).

Study population and description

The study was carried out among all consenting age groups (children, adults and aged) who were hospitalized and also met the inclusion criteria in the selected hospitals that were surveyed. The survey/ sample collection was carried out in all three locations from October 2016 to March 2017.

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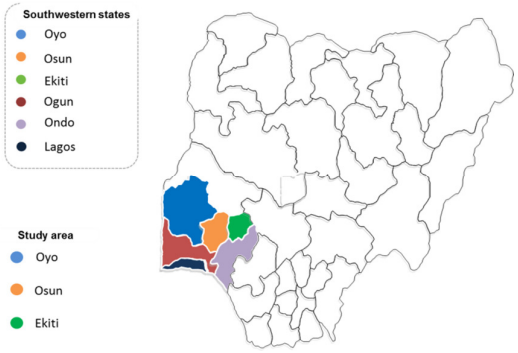

Fig. 1. Map showing study areas

Inclusion criteria for CRE screening

- Patients who had been hospitalized within 3 weeks and above
- Patients who undergone surgery
- Patients with urinary tract infections
- Patients with invasive devices such as catheter
- All age groups who met the aforementioned criteria

Ethical consideration

Ethical approval for the research was obtained foremost from the Ethics Review Board of the Faculty of Life Sciences, University of Ilorin. Then, approval was obtained from the Ethics Review Committee of the selected hospitals after which informed consent was obtained from the subjects and/or their caretakers.

Data collection

Questionnaires were administered to all subjects who participated in the study. The response to the questionnaires was used to collate information about the socio-demographic characteristics such as age, gender and socioeconomic status (level of education and occupation) of the participants. The questionnaire also provided information on the patients' medical history, use of antibiotics and patients' exposures to the risk factors associated with the colonization of CRE.

Sample collection

Blood or urine samples were obtained from subjects who met the inclusion criteria, placed in an ice chest and transported to the laboratory for analysis.

Procedure for isolation of Enterobacteriaceae

Blood sample: Following the collection of the blood samples directly into brain heart infusion broth (Rapid Labs, UK), the samples were incubated for 5 days at 37 °C. After 5 days, the blood culture was subcultured by streaking a loopful of the culture suspension on solidified MacConkey and Blood agars (Oxoid, UK) and incubated at 37 °C for 24-48 hours.

Urine sample: the samples obtained were analyzed within 6 hours of collection. A loopful of urine was aseptically picked from the urine sample and streaked on a solidified CLED (Lab M, UK) agar; then incubated at 37 °C for 24 hours.

Identification of isolates

The isolates were identified by using the Hi25™ Enterobacteriaceae identification kit (HiMedia Laboratories Ltd., India) and PCR.

Antibiotic susceptibility test

Assay for the antibiogram pattern of the isolates was carried out using the disc diffusion method as described by Bauer *et al.* (1985). The antibiotics used (Rapid labs, UK and Oxoid, UK) and their corresponding concentrations are as follows: Ceftazidime (30 µg), Cefuroxime (30 µg), Gentamicin (10 µg), Ciprofloxacin (5 µg), Ampicillin (10 µg), Ofloxacin (5 µg), Augmentin (30 µg), Nitrofurantoin (300 µg), Imipenem (10 µg) and Meropenem (10 µg).

Determination of susceptibility to antibiotics

Solidified Mueller Hinton agar (Rapid Lab, UK) plates were seeded with 100 µl of the standardized organisms and were spread evenly over the total surface area of the agar using a glass spreader. Multiple antibiotics discs containing eight of the aforementioned antibiotics were carefully and firmly placed on the surface of the agar using sterile forceps. For imipenem and meropenem, single discs of each of the antibiotics were placed. Afterwards, the plates were incubated at 37 °C for 18-20 hours. After incubation, the zones of inhibition generated by the antibiotics were measured. The values for each organism against the antibiotics were interpreted using the breakpoints interpretative criteria of Clinical and Laboratory Standard Institutes (CLSI, 2016).

Statistical analysis

The descriptive statistics of the data obtained in the study was analyzed and/ or plotted using SPSS 22.0, SigmaPlot. The odd ratio was calculated using MEDCALC and Vassarstats online statistical software to measure the association of variables as risk factor in CRE colonization. The *p*-value for significance was at $p \leq 0.05$.

Results

Demographic characteristics and risk factor assessment

All age groups specified for the study participated in all three hospitals except at Oyo state where none of the subjects was older than 60 years. Equal ratio of the genders was used in all the three locations (Table 1). Over 80% of the subjects have been on hospitalization within 3 weeks in the three hospitals, while 14-18% were hospitalized for over 3 weeks. Also, more of the participants in the three hospitals (66%, 88% and 89% respectively) had no recent surgical procedures. On the evaluation of antibiotics use, it was gathered that most of the participants in the three hospitals were on antibiotics within 1-3 weeks (64%, 78% and 75%). A similar trend of 21% or 22% was recorded in all locations for use of antibiotics from 3 weeks to 3 months. Exposure to catheter or other invasive devices during hospitalization in the three hospitals ranged between 17-42%. Subjects with previous diagnosis of UTI ranged from 28-34% in the hospitals, while records of previous hospitalization were < 40% (Table 2).

Isolation of Enterobacteriaceae

In summary, a total of 34 (57.6%) of all fifty-nine (59) isolates obtained in the present study were recovered from urine samples, while 25 (42.4%) were from blood samples. Thirty-one (52.5%) of the isolates were *Escherichia coli*, 14 (23.8%) were *Enterobacter aerogenes*, 6 (10.2%) were *Klebsiella* sp. and 8 (13.6%) belonged to *Proteus* sp. (Table 3).

Antibiotic susceptibility test

Isolates that showed multiple resistances to one to five antibiotics were categorized as multi-drug resistant (MDR); resistance to six to nine antibiotics was categorized as extensive drug resistance (XDR), while complete resistance to all antibiotics was categorized as pan-drug resistance (PDR). In TE, out of the 21 isolates tested, 28.6% exhibited MDR, while 71.4% were XDR. All the isolates showed complete resistance to augmentin, ampicillin, ceftazidime and cefuroxime. Resistance to other antibiotics was as follow: ciprofloxacin (61.9%), gentamicin (57.1%), ofloxacin (57.1%), nitrofurantoin (19%), imipenem (19%) and meropenem (19%) (Fig. 2a). Notably, there was a fairly low level of resistance against the carbapenems (imipenem and meropenem), with four of the twenty-one isolates being resistant (Fig. 3).

In TOY, all the isolates were completely resistant to augmentin, ceftazidime and cefuroxime. The resistant pattern to other antibiotics include- ampicillin (95%), ciprofloxacin (50%), gentamicin (40%), ofloxacin (40%), nitrofurantoin (30%), meropenem (30%) and imipenem (20%) (Fig . 2b). Four (4) and six (6) isolates out of the total 20, showed resistance to imipenem and meropenem, respectively (Fig. 3). In TOS, 15 isolates (83.3%) exhibited XDR with resistance to at least six antibiotics while 11.1% showed MDR (Fig. 2c). Also, PDR was observed in one of the *Enterobacter aerogenes* isolates. All the isolates were completely resistant to ampicillin, ceftazidime and cefuroxime.

Resistance to other antibiotics include- augmentin (94.4%), gentamicin (83.3%), ciprofloxacin (83.3%), ofloxacin (72.2%), meropenem (50%), imipenem (33.3%) and nitrofurantoin (16.7%). Six (6) and nine (9) out of 18 isolates were resistant to imipenem and meropenem, respectively (Fig. 3). A total of 23 isolates exhibited resistance to one or both of imipenem and meropenem in all the three locations.

Table 1. Demographic characteristics of the subjects used in the study

Characteristics	Frequency and percentage of respondents *		
	TE	TOY	TOS
Age			
6 – 10	5	8	7
11 – 20	13	13	7
21 – 30	14	35	27
31 – 40	32	22	17
41 – 50	12	16	18
51 – 60	11	6	12
61 – 70	10	0	1
70+	3	0	11
Gender			
Female	50	50	50
Male	50	50	50
Type of education			
Formal	54	70	64
Informal	46	30	36
Marital status			
Single	29	36	27
Married	66	62	70
Widowed	3	1	2
Divorced	2	1	1
Occupation			
Top civil servant/ executive	18	24	23
Middle class/ small scale business	10	9	13
Junior staff/ petty trader	13	28	31
Artisan	42	13	11
Others	17	26	22

* indicates that the values presented in the table represent both the frequency and corresponding percentage (n = 100); TE- tertiary hosp. at Ekiti; TOY- tertiary hosp. at Oyo; TOS- tertiary hosp. at Osun

Table 2. Risk factors evaluated among subjects

Characteristics	Percentage of respondents *		
	TE	TOY	TOS
Duration of hospitalization			
Within 3 weeks	82	86	83
More than 3 weeks	18	14	17
Recent surgical procedure			
Yes	34	12	11
No	66	88	89
Duration of antibiotics use			
1 - 3 weeks	64	78	75
3 weeks – 3 months	22	21	22
3 months +	14	1	3
Exposure to invasive devices			
Yes	42	17	30
No	58	83	70
Quality of hospital hygiene			
Poor	4	1	1
Fair	21	14	9
Good	45	41	41
Very good	20	24	26
Excellent	10	20	23
Response to treatment			
Poor	2	0	0
Fair	13	3	5
Good	54	61	57
Excellent	31	36	38
Previous diagnosis of UTI			
Yes	28	34	31
No	72	66	69
Previous hospitalization			
Yes	39	31	36
No	61	69	64

Table 3. Summary of isolates obtained from the three study sites

Sample	No. of isolates/ Proportion (%)	Isolate distribution			
		Escherichia coli	*Enterobacter aerogenes*	*Klebsiella* sp.	*Proteus* sp.
Urine	34 (57.6)	21 (35.6)	7 (11.9)	0	6 (10.2)
Blood	25 (42.4)	10 (16.9)	7 (11.9)	6 (10.2)	2 (3.4)
Total	59 (100)	31 (52.5)	14 (23.8)	6 (10.2)	8 (13.6)

Table 4. Univariate analysis of the risk factors in association with CRE colonization

S/N	Variable		CRE		*p-value*	Odd ratio	95% CI
			Positive	Negative			
1.	Age	21 – 50	13	180	**0.01**	0.32	0.13 – 0.77
		51 – 70	10	44			
2.	Gender	Male	14	136	0.28	1.61	0.68 – 3.85
		Female	9	141			
3.	Duration of hospitalization	≤ 3 weeks	16	235	0.06	0.41	0.16 – 1.05
		> 3 weeks	7	42			
4.	Nature of illness	Infectious	10	148	0.36	0.67	0.28 – 1.58
		Non- infectious	13	129			
5.	Recent surgical procedure	Yes	3	54	0.45	0.62	0.18 – 2.16
		No	20	223			
6.	Duration of antibiotic use	≤ 3 weeks	13	204	0.08	0.47	0.20 – 1.11
		> 3 weeks	10	73			
7.	Exposure to invasive devices	Yes	11	78	**0.05**	2.34	0.99 – 5.52
		No	12	199			
8.	Previous hospitalization	Yes	12	94	0.08	2.12	0.90 – 4.99
		No	11	183			

CI: Confidence Interval Significance ($p \leq 0.05$)

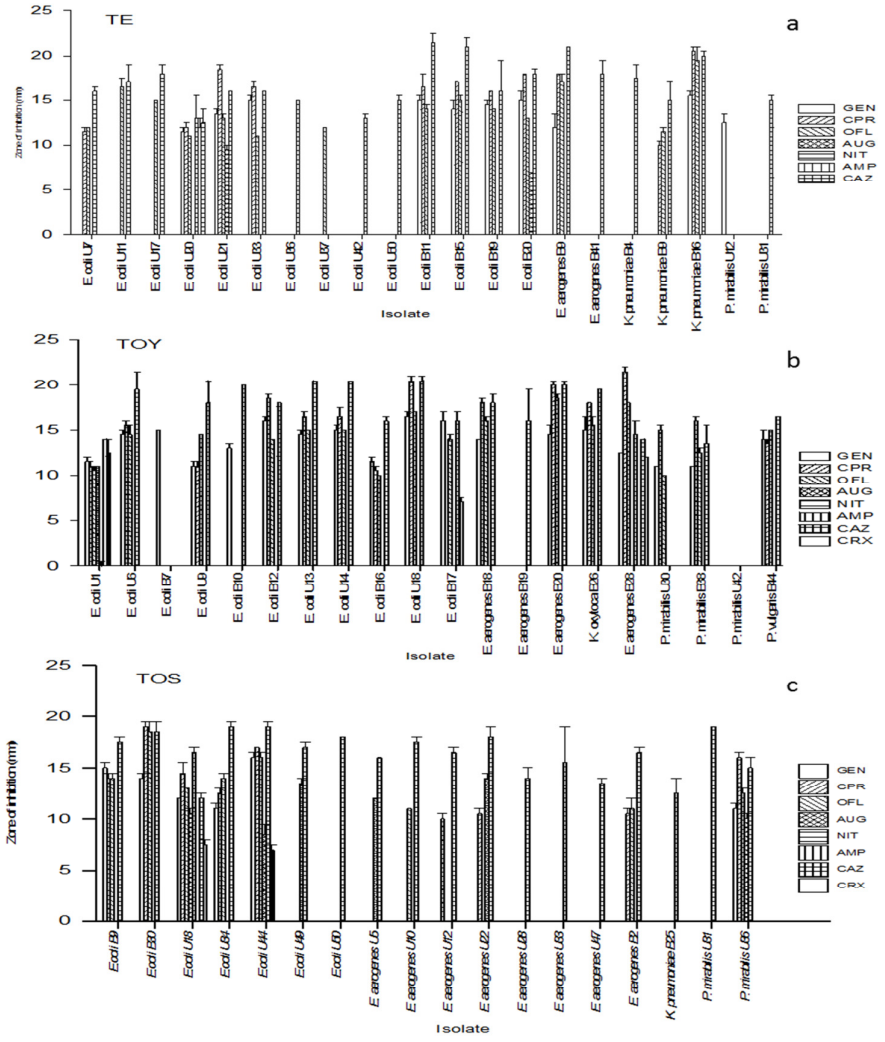

Fig. 2. Antibiotic susceptibility pattern of the isolates from the three locations

Incidence proportion and risk factor association

The incidence proportion of CRE in TE was 6%, while the incidence rate was 3 cases per 100 people; in TOY, 7% with an incident rate of 3.5 cases per 100 people; in TOS, 10%, while incident rate was 5 cases per 100 people. Age (p = 0.01) and exposure to invasive devices (p = 0.05) were significantly associated with CRE colonization. The duration of hospitalization (p = 0.06), prolonged use of antibiotics (p = 0.08) and previous hospitalization (p = 0.08) were also associated with CRE colonization.

The odds of CRE colonization was 68% higher in patients of ages 51 years and above. Patients who had been on hospitalization for over 3 weeks had 59% higher odds of CRE colonization compared to patients who were on hospitalization within 3 weeks (Table 4). Gender was not a confounding factor in CRE colonization (p = 0.28) although odds of CRE colonization was 16.1% lower in males. Presence of underlying medical condition (p = 36) and recent surgical procedures (p = 45) were also not associated with CRE colonization (Table 4).

Discussion

Demographic characteristics of the subjects

Over 50% of the participants in each location belonged to the age group 21-50 years old; less than 10% were aged 6-10 years old and ≤ 11% were 70 years and above. For the present study, a higher number of the participants were adults (21-50 years) and thus may be considered to be a mixed population of individuals at the peak of their immunity, as well as those with a probable decline in immune system efficacy. The gender of the respondents was evenly distributed in all the locations. This was done in order to critically assess the possible influence of gender on colonization or infection by CRE.

Isolation of Enterobacteriaceae

Enterobacteriaceae are known to be the most representative bacteria family in the cause of nosocomial infections and outbreaks (Cai *et al*., 2017).

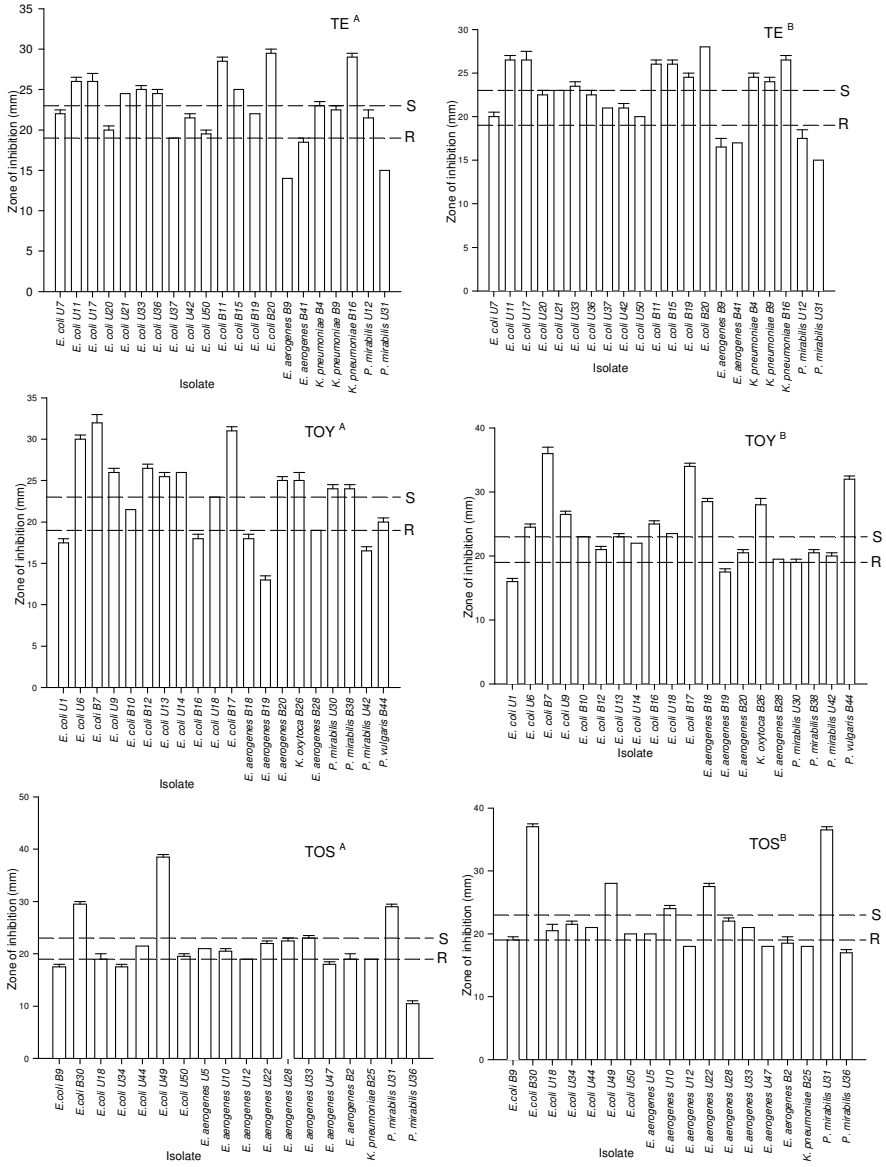

Fig. 3. Susceptibility of the isolates to meropenem and imipenem; [A] represents meropenem; [B] represents imipenem

Nosocomial agents have the propensity to spread at an alarming rate among patients with incidence rate at about 4.5 cases per 100 people (Cunha *et al*., 2016; Demiraslan *et al*., 2017). Notably in the hereby study, *Escherichia coli* and *Enterobacter aerogenes* were the most dominant. The high frequency of *E. coli* has also been reported by Yusuf *et al.* (2012), Motayo *et al.* (2013) and Mohammed *et al.* (2015) in hospitals at Kano and Abeokuta, Nigeria. It can therefore be said that in this study, bacteria belonging to the Enterobacteriaceae family that are principal etiology of nosocomial infections have been isolated, which may be an indicator of an existing or impending nosocomial infection. Overall, 57.6% of the isolates were recovered from urines samples, while 42.4% were from blood samples. The higher frequency in urine samples observed was similar to the reports of 57.1% by Mohammed *et al.* (2015) and 52% by Lixandru *et al.* (2015).

Antibiotic resistance of isolates

The antibiotics used in the study belonged to different classes of antibiotics including aminoglycosides, fluoroquinolones, penicillins, nitrofurans, beta-lactam, cephalosporins and carbapenems. All the 59 Enterobacteriaceae isolates recovered from blood and urine samples in the three hospitals were multi-drug resistant. The isolates considered as most susceptible were resistant to at least 4 out of 10 antibiotics. Complete resistance to second and third- generation cephalosporins (cefuroxime and ceftazidime) was also observed in all the isolates. This observation is higher than the report of about 52.1% resistance to cephalosporins by Mohammed *et al.* (2015) in a hospital in Kano state, Nigeria. Resistance to cephalosporins has been reported to be an indicator of beta lactamase production and also, carbapenemase production in Enterobacteriaceae (Huang *et al*., 2014).

According to the CLSI (2012) guidelines on the phenotypic determination of ESBL production in Enterobacteriaceae, non-susceptibility of isolates to cephalosporins (ceftazidime, ceftriaxone, cefotaxime or cefuroxime) or beta-lactam (aztreonam or amoxicillin-clavulanate) could be taken as potential ESBL producers. The results of the present study are therefore suggestive that these isolates carry any of the aforementioned resistance genes.

Incidence of CRE and risk factor association

The overall incidence of CRE in EKSUTH, LAUTECH Ogbomoso and LAUTECH Osogbo at the time of study from October 2016 to March 2017 was 7.7% (12.8 cases per 1,000 people). Age and exposure to invasive devices were significantly associated with CRE colonization. More so, CRE distribution was higher in patients aged 51 years and above. According to the concept of immunosenescence which explains the change in immune responses as a result of aging, individuals belonging to older age groups are more susceptible to infectious diseases, cancer development and auto immune (Castelo-Branco and Soveral, 2013; Simon *et al*., 2015). Montencino-Rodriguez *et al.* (2013) also reported that individuals that are 70 years and above have an increased vulnerability to infectious diseases. Duration of hospitalization and prolonged use of antibiotics were also factors implicated in CRE colonization. Although presence of a medical condition and surgical procedures are existing risk factors of CRE acquisition, they were not confounding factors in the hereby study. Gender of the patients was also not associated with CRE colonization.

Conclusions

The study revealed the incidence of carbapenem-resistant Enterobacteriaceae (CRE) among in-patients receiving healthcare in three selected tertiary hospitals in Southwest, Nigeria. Also, the strong association of age with CRE colonization may pose high complications in older patients. Succinctly, the low incidence of CRE isolates in the study locations at the time of the survey does not nullify possible incidence in subsequent surveys. It is therefore crucial to establish a surveillance program that will ensure routine check to allow early detection of CPE in order to prevent outbreaks.

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