www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i3.64

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Predictors for the Acquisition of Carbapenem Resistance *Enterobacteriaceae* (CRE) from a Teaching Hospital of Northeastern Nigeria

Authors
Yahaya Mohammed[1], Sambo B. Zailani[2], Anthony O. Onipede[3], Galadima B. Gadzama[2] Baffa Sule Ibrahim[4]
[1]Department of Medical Microbiology and Parasitology, Faculty of Basic Medical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto State, Nigeria
[2]Department of Medical Microbiology and Parasitology, College of Medical Sciences, University of Maiduguri, Borno State, Nigeria
[3]Department of Medical Microbiology and Parasitology, Faculty of Basic Medical Sciences, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.
[4]Aminu Kano Teaching Hospital, Kano, Nigeria
Corresponding Author
Email: *yahyakt@yahoo.com, Mobile:+234(0)8036867478*

ABSTRACT
Background: *Carbapenem resistance Enterobacteriaceae (CRE) has emerged as global pathogen capable of widespread transmission and complicating treatment options for patients. CRE have been reported globally. However, there is dearth of study on knowledge for predictors of CRE in patients from our setting. We set out to determine predictors of infection among patients infected with CRE.*
Methodology: *We isolated species of Enterobacteriaceae from patients that were admitted in various units of University of Maiduguri Teaching Hospital (UMTH) Maiduguri. We obtain data on socio-demographic characteristics, co-morbidities and some associated factors. We determined their CRE status and then classified them as CRE positiveor CRE negative based on the possession the resistance genes. We conducted univariate, bivariate and multivariate analyses to compute proportions and odd ratios with 95% CI using SPSS version 20.*
Results: *The factors significantly associated with the acquisition of carbapenem resistance Enterobacteriaceae (CRE) based on chi-square test were; level of education (X^2 = 15.570, P-value = 0.004) of the patients, ward of admission (X^2 = 21.765, P-value = 0.000), number of days on admission (X^2 = 11.218, P-value = 0.004), use of medical device (X^2= 26.893, P-value = 0.000) and prior antibiotic usage (X^2 = 35.729, P-value = 0.000). Predictors of CRE using multivariate analysis were; secondary school level of education (OR = 8.330, 95% CI = 3.000-50.401), admission in intensive care unit (OR = 11.135, 95% CI = 8.000-19.110), admission days greater than 20 days (OR = 2.580, 95% CI = 1.011-15.101), use of urethral catheter (OR = 3.518, 95% CI = 2.00-9.821) and prior administration of third generation cephalosporin's (OR = 15.303, 95% CI = 7.034-19.107).*
Conclusion: *Our study shows that patients admitted in ICU, those with indwelling urinary catheter and those placed on third generation cephalosporin's are at higher risk of CRE acquisition. Consequently, we recommend that patient and caregiver education, antibiotic stewardship programs, enforcement of infection control practices and continuous surveillance should be given priority.*
Keywords: *Carbapenem, Resistance, Risk factors, Antibiotic.*

INTRODUCTION

Carbapenems belong to the beta lactam group of antibacterial agents. The spread of carbapenem resistant bacteria has caused grave concern due to the limited choice of antibiotics for treating infections caused by them.[1] Resistance of bacteria to carbapenems is due to the production of carbapenem hydrolysing enzymes called carbapenemases. These bacteria have the potential to spread rapidly within the hospital environment and also across continents.[2] Mechanism of carbapenem resistance is mainly due to the production of carbapenemases coded by bla_{KPC}, bla_{VIM} and bla_{IMP} amongst others. These belong to Class B of the Ambler system of classification of Beta lactamases.[3] Bacteria producing these carbapenemases have been associated with high rates of morbidity and mortality; particularly among persons with prolonged hospitalization and those who are critically ill and exposed to invasive devices.[4, 5]

There is paucity of literature for the studies on risk factors of carbapenem resistance from our study setting. We set out to determine predictors of infection among patients infected with carbapenem resistance *Enterobacteriaceae* (CRE).

MATERIALS AND METHODS

Two hundred and twenty-five (225) patients that were admitted in various units and wards of University of Maiduguri Teaching Hospital (UMTH) Maiduguri were recruited between June to December, 2014.We performed a descriptive cross-sectional study. We obtain data on their socio-demographic characteristics, co-morbidities and some associated factors. We isolated species of *Enterobacteriaceae* from them and determined their CRE status. Thereafter, we classified them as CRE positive or CRE negative based on the possession their resistance genes. We conducted univariate, bivariate and multivariate analyses to compute proportions, chi-square and odd ratios with 95% CI using Epi-Info version 7.

RESULTS

Two hundred and twenty-five (225) clinical isolates of *Enterobacteriaceae* were detected during the study period from an equal number of patients. Twenty-eight of the isolates were determined as CRE positive while 197 were determined as CRE negative.

Table 1 shows the association between acquisition of CRE and socio-demographic factors. Among the various socio-demographic factors analyzed only the level of education (X^2 = 15.570, *p*-value = 0.004) of the patients was significantly associated with the acquisition of CRE based on chi-square test. Table 2 shows the association between some risk factors and infection with CRE. The parameters significantly associated with CRE infection using Chi square test were; ward of admission (X^2 = 21.765, *p*-value = 0.000), number of days on admission (X^2 = 11.218, *p*-value = 0.004), use of medical device (X^2= 26.893, *p*-value = 0.000) and prior antibiotic usage (X^2 = 35.729, *p*-value = 0.000).

Table 3 shows the logistic regression analysis of some risk factors for CRE infection. Secondary school level of education (X^2=13.104, *p*-value = 0.004, OR = 8.330, 95% CI = 0.003-1.504) was the positive predictor of CRE infection in education level based on logistic regression model. Admission in intensive care unit (X^2 = -3.091, *p*-value = 0.003, OR = 11.135, 95% CI = 0.008-2.080) was the positive predictor for CRE infection.

Among the parameters in the number of days of admission, patients with admission days greater than 20 days (X^2 = 0.067, *p*-value = 0.001, OR = 2.580, 95% CI = 0.001-0.015) was found to be the positive predictor for CRE infection. The use of urethral catheter (X^2 = -20.362, *p*-value = 0.000, OR = 3.518, 95% CI = 0.000-0.000) was the positive predictor for CRE infection amongst the various medical devices used on the patients. Administration of third generation cephalosporins (X^2 = -3.320, *p*-value = 0.008, OR = 15.303, 95% CI = 0.007-0.191) was found to have the highest risk for CRE infection amongst the patients.

Table 1: Association between socio-demographic factors and infection with CRE

Variable	Presence of CRE		Total	X^2	*p* value
	Yes (%)	No (%)			
Age groups					
Children	0(0%)	58(100%)	58(100%)	8.624	0.103
Young Adults	5(7.4%)	63(92.6%)	68(100%)		
Adults	13(13.1%)	86(86.9%)	99 (100%)		
Sex					
Male	12(9.8%)	110(90.2%)	122(100%)	1.221	0.269
Female	6(5.8%)	97(94.2%)	103(100%)		
Tribe					
Kanuri	4(6.9%)	54(93.1%)	58(100%)	12.481	0.209
Babur	1(2.6%)	38(97.4)	39(100%)		
Shuwa Arab	7(17.5)	33(82.5%)	40(100%)		
Marghi	5(16.1%)	26(83.9%)	31(100%)		
Hausa	1(2.6%)	38(97.4%)	39(100%)		
Others	0(0%)	18(100%)	18(100%)		
Place of Residence					
Urban	9(9%)	92(92.7%)	101(100%)	0.207	0.649
Rural	9(7.3%)	115(92.7%)	124(100%)		
Education Level					
No Formal Education	10(20.4%)	39(79.6%)	49(100%)	15.570	0.004*
Pre-School	2(11.1%)	16(88.9%)	18(100%)		
Primary Level	4(6.3%)	59(93.7%)	63(100%)		
Secondary Level	0(0%)	37(100%)	37(100%)		
Tertiary Level	2(3.4%)	56(96.6%)	58(100%)		
Occupation					
Civil Servant	5(9.1%)	50 (90.9%)	55(100%)	0.766	0.682
Self Employed	8(9.3%)	78(90.7%)	86(100%)		
Not Gainfully Employed	5(6%)	79(94%)	84(100%)		

*=statistically significant (i.e. $p<0.05$)

Table 2: Association between some risk factors and infection with CRE

Variable	Presence of CRE		Total	X^2	*p* value
	Yes	No			
Ward of Admission					
ICU	11(25%)	33(75%)	44(100%)	21.765	0.000*
SCBU	2(5.4%)	35(94.6%)	37(100%)		
Medical	2(2.7%)	73(97.3%)	75(100%)		
Surgical	3(4.3)	66(95.7%)	69(100%)		
Number of Days on Admission					
< 10 days	5(5.2%)	91(94.8%)	96(100%)	11.218	0.004*
11-19 days	3(4%)	73(96%)	76(100%)		
> 20 days	10(18.9%)	43(81.1%)	53(100%)		
Past Medical History					
History of Diabetes	4(19%)	17(81%)	21(100%)	11.660	0.070
History of HIV/AIDS	2(12.5%)	14(87.5%)	16(100%)		
Recent Fracture/Surgery	1(6.3%)	15(93.7)	16(100%)		
Recent Hospital Admission	5(16.1%)	26(83.9%)	31(100%)		
Recent Haemodialysis	2(11.1%)	16(88.9%)	18(100%)		
Prior culture of resistant pathogen	2(7.7%)	24(92.3%)	26(100%)		
Nil Significant past medical history	2(2.1%)	95(97.9%)	97(100%)		
Use of Medical Device					
Urethral Catheter	5(25%)	15(75%)	2 0(100%)	26.893	0.000*
Nasogastric tube	5(26.3%)	14(73.7%)	19(100%)		
Endotracheal tube	5(13.2$)	33(86.8%)	38(100%)		
Ventilator use	3(6.5%)	3(93.5%)	46(100%)		
Nil Device used	0(0%)	102(100%)	102(100%)		
Prior Antibiotic Usage					
Third generation Cephalosporins	8(40%)	12(60%)	20(100%)	35.729	0.000*
Penicillins group	0(0%)	26(100%)	26(100%)		
Quinolones/Fluoroquinolones	3(9.7%)	28(90.3%)	31(100%)		
Amoxicillin/Clavulanate	1(3.2%)	30(96.8%)	31(100%)		
Aminoglycosides	4(12.5%)	28(87.5%)	32(100%)		
Nil prior (4/52 to admission) Antibiotic use	2(2.3%)	83(97.6%)	85(100%)		

*= Statistically significant (i.e. $p<0.05$)

Table 3: Logistic regression analysis of some risk factors for CRE infection

Variable	B	*p*-value	Odds ratio	95% CI
Education Level				
No Formal Education	0.324	0.525	10.962	0.037-1.537
Pre-School	3.851	0.504	2.663	0.530-12.555
Primary Level	2.200	0.569	3.142	0.288-7.155
Secondary	13.104	0.004*	8.330	0.003-1.504
Tertiary Level	1.804	1.380	0.113	0.804-1.380
Ward of Admission				
ICU	-3.091	0.003*	11.135	0.008-2.080
SCBU	-1.221	0.988	1.005	0.037-2.892
Medical	-0.469	0.879	0.205	0.092-4.432
Surgical				
Number of Days on Admission				
< 10 days	1.773	0.110	1.000	0.004-0.539
11-19 days	2.561	0.110	8.109	0.048-3.298
> 20 days	0.067	0.001*	2.580	0.001-0.015
Use of Medical Device				
Urethral Catheter	-20.362	0.000*	3.518	0.000-0.000
Nasogastric tube	-18.925	9.459	0.002	0.003-0.910
Endotracheal tube	-18.542	1.653	0.199	0.002-0.153
Ventilator use	-18.122	0.179	0.679	0.036-1.416
Prior Antibiotic Usage				
Third generation Cephalosporins	-3.320	0.008*	15.303	0.007-0.191
Penicillins group	-17.477	0.998	0.000	0.000-0.000
Quinolones/Fluoroquinolones	-1.492	0.112	2.527	0.036-1.416
Amoxicillin/Clavulanate	-0.324	0.794	0.0794	0.063-8.265
Aminoglycosides	-1.780	0.064	3.971	0.029-0.971

*= Statistically significant (i.e. $p<0.05$)

DISCUSSION

The study set out to determine predictors of infection among patients infected with CRE. We were able to establish some factors association using bivariate and multivariate analysis. The following factors were positively associated with the risk of developing infection with CRE based on the chi-square test; patient with secondary school level of education, admission in intensive care unit, admission days greater than 20 days, use of urethral catheter and prior administration of third generation cephalosporin's. The finding of this study that admission in intensive care unit is a positive predictor for CRE infection agrees with a study done by Patel and colleagues where admission in intensive care unit stay was strongly associated with carbapenem resistant *Klebsiella pneumoniae*.[6]The implication for this finding is that we must give infection control practices topmost priority most especially in our intensive care units. Personnel screening and patient screening transferred in and out of the ICU might help to ameliorate this threat.

Patient with admission days greater than 20 days and prior administration of third generation cephalosporin's were also significantly associated with the risk of CRE infection in this study. This was similar to a study done in South Africa to determine the risk factors of CRE acquisition where prolonged hospital stay, prior hospital admission and the use of third generation cephalosporins three weeks prior to admission were independently associated with the acquisition of CRE.[7]

The explanation for the use of third generation as predictor for carbapenem resistance has been earlier explained by literature. Studies have also shown that prior carbapenem therapy is not a pre-requisite for carbapenem resistance among *Escherichia coli* or *Klebsiella pneumoniae.*[8] The plasmids that confer such resistance frequently carry additional resistance determinants that confer cross-resistance to most other antibiotic classes. Consequently, prior use of any antibiotic may select for a carbapenemase producing Gram negative bacilli (GNB).[9]

The finding that the use of urethral catheter is associated with acquisition of CRE in this study reinforces the fact that urinary catheters can play an important role in facilitating infection with

CRE infection. On a practical level, this finding further strengthens the importance of programs to reduce unnecessary use of urinary catheters and to ensure their removal at the earliest opportunity. The finding is also in agreement with a study done by Schwaber and colleagues where the use of urinary catheters and mechanical ventilators were independently associated with infection by carbapenem resistant *Klebsiella pneumoniae* among hospitalized adults.[10]The finding from this study that patients with secondary level of education are more at risk of developing CRE infection is puzzling and not supported by previous research findings. However, it can be hypothesized that maybe because secondary school leavers are teenagers with higher risk of urinary tract/sexually tract infections and they interact more and have higher mobility than other groups hence they are more predisposed to infection by this resistance pathogens. Further analytic studies on this particular group would provide us with a better picture.

CONCLUSION

The findings from our study demonstrates the predictors of CRE acquisition to be; admission at intensive care unit, use of indwelling urinary catheter and placement on third generation cephalosporin's. We hereby, recommends that we should strengthened infection control practices and antibiotic stewardship programs. Patient and caregivers' education should also be given top priority.

REFERENCES

1. Patrice N, Laurent P, Laurent D. Rapid Detection of Carbapenemase producing *Enterobacteriaceae*. *Emerg Infect Dis* 2012; 18(9): 1503–1507.
2. Mammeri H, Guillon HE, Nordmann P. Phenotypic and biochemical comparison of the carbapenems hydrolyzing activities of five plasmid-borne AmpC beta lactamases. *Antimicrob Agents Chemother* 2010; 54:4556–4560.
3. Winn W, Allen S, Janda W, Koneman E, Procop G, Schreckenberger P, et al. Introduction. Koneman'scolor atlas and text book of diagnostic microbiology. Baltimore and Philadelphia: Lippincott Williams & Wilkins; 2006. Pg 21-25.
4. 16. Tafur JD, Torres JA, Villegas MV. Mechanisms of antibiotic resistance in Gram-negative bacteria. *CIDEIM* 2008; 12: 217-226.
5. Centre for Disease Control. Guidance for Control of Infections with Carbapenem resistant or Carbapenemase producing *Enterobacteriaceae* in Acute Care Facilities. *MMWR Weekly* 2009; 58(10): 256-260.
6. Patel G, Huprikar S, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infect Control Hosp Epidemiol* 2008; 29: 1099-1106.
7. Adrian B, Jennifer C, Cornelis C, Craig C, Johan VG, Deetlefs JD, Louise N, Charles F, et al. The spread of CRE in South Africa: risk factors for acquisition and prevention. *S Afr Med J* 2012; 102(7): 599-601.
8. Poirel L, Benouda A, Hays C, Nordmann P. Emergence of NDM-1 producing *Klebsiella pneumoniae* in Morocco. *J AntimicrobChemother* 2011; 66: 2781-2783.
9. Aliyu S. Carbapenemase producing Gram negative bacteria: An emerging threat to health care in Africa. *Ann Nigerian Med* 2013; 7: 1-2.
10. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem resistant *Klebsiella pneumoniae* among hospitalized adults and the effect of acquisition on mortality. *Antimicrob Agents Chemother* 2008; 52: 1028-1033.