

Risk Factors and Outcomes of Bacteremia Caused by Carbapenem Resistant Enterobacterales Compared to Carbapenem Susceptible Enterobacterales

Fasih Ali Ahmed

Aga Khan University

Omair Ahmed

Yale University

Sameer Ahmad Khan

Children's Hospital of Philadelphia

Naveera Khan

MedStar Washington Hospital Center

Sara Ahmed

Aga Khan University Hospital

Muneeba Ahsan Sayeed

Sindh Infectious Diseases Hospital and Research Centre

Safia Awan

Aga Khan University Hospital

Faraz Siddiqui

University of York

Syed Faisal Mahmood (✉ faisal.mahmood@aku.edu)

Aga Khan University Hospital

Research Article

Keywords: Bacteremia, Developing Countries, Antibacterial Agents, Antimicrobial Resistance, Carbapenem-Resistant Enterobacterales

Posted Date: August 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-811962/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

Due to shrinking therapeutic options, infections due to Carbapenem-resistant Enterobacterales (CRE) are an urgent threat in healthcare systems. We compared the risk factors and outcomes of bacteremia secondary to CRE with bacteremia secondary to carbapenem susceptible Enterobacterales (CSE).

Methods

We conducted a retrospective cross-sectional study on patients admitted to a tertiary care hospital in Karachi, Pakistan between 2013 and 2016. Patients with CRE bacteremia were matched to those with CSE bacteremia while excluding those with polymicrobial cultures.

Results

A total of 131 patients were enrolled (65 CRE and 66 CSE) with the mean age of 51.8 years and 57.1 years in CRE and CSE groups respectively. Compared with CSE, CRE bacteremia was more likely to occur in patients with Diabetes Mellitus or those with a tracheostomy ($P = 0.002$ and 0.014 , respectively). The most common source of CRE bacteremia was central line associated (24.6% of all cases) as opposed to urinary tract infections in those with CSE bacteremia (62.1% of all cases). Fewer patients with CRE bacteremia received appropriate antibiotics (72.3% vs. 81.8%). Mortality was significantly higher in the CRE group (41.5% vs. 12.1%, $P = 0.001$) even when adjusted for the severity of illness using the PITT-bacteremia score. Increased mortality was also associated with central venous catheterization in both groups. The median length of hospital stay was longer in patients with CRE (8 vs. 6 days, $P = 0.021$).

Conclusion

CRE bacteremia was associated with central lines and led to significantly higher mortality and length of stay.

Background

Infections from antibiotic-resistant organisms occur in 2.8 million individuals and result in 35,000 deaths annually in the United States alone(1). Globally, these infections result in an estimated 700,000 deaths annually- a number expected to rise to 10 million by 2050 if no action is taken to counter antimicrobial resistance (AMR)(2). The global economic loss from AMR is projected to be between USD 1 trillion to USD 3.4 trillion annually by 2030, with a greater impact on low-income countries(3).

Carbapenems have been considered one of the last treatment options for infections caused by multidrug-resistant pathogens(4). In recent years, increased carbapenem use coupled with poor infection prevention practices has led to an increase in the global rates of Carbapenem-Resistant Enterobacterales (CRE)(5). CRE are typically resistant to other beta-lactams and often resistant to other antimicrobial classes,

significantly limiting treatment options. Additionally, infections with CRE result in higher morbidity when compared to non-CRE strains(6–8). This had led the Centers for Disease Control and Prevention to classify CRE as an “urgent threat”.

Carbapenemase production is one of the more concerning mechanisms of carbapenem resistance in Enterobacterales. Carbapenemase-encoding genes on mobile genetic elements can rapidly transmit resistance to other bacteria, and infections from CP-CRE result in higher mortality compared to those with non-CP CRE(9). The multi-national PANORAMA study from low and middle-income countries found most CRE to be Carbapenemase producers (93.75%)(7) in these regions. In contrast, carbapenemase production accounts for only 30% of carbapenem resistance in the US(1). Despite this evidence of geographic variation in the more virulent CP-CRE strains, data from low and middle-income countries on surveillance and outcomes from CRE infections remains scarce to date(10).

We, therefore, aimed to compare the risk factors for bacteremia caused by CRE compared to Carbapenem Susceptible Enterobacterales (CSE) strains and subsequently assess outcomes of bacteremia caused by CRE in an area of high CRE endemicity in a low-middle income country.

Methods

We conducted a retrospective cross-sectional study at a 700 bedded tertiary care teaching hospital in the south of Pakistan. All adult patients admitted between January 2013 and July 2016 with bacteremia due to Enterobacterales were included. For every case of CRE bacteremia identified, a CSE control was randomly selected from the same month. We excluded patients with polymicrobial bacteremia.

Clinical data was collected from patients' medical records using a structured proforma. Data was analyzed using the SPSS 19.0. The baseline parameters of patients with CRE and the CSE bacteremia were compared. Comparison of differences in proportions was assessed by using the Chi-square test or Fisher exact test where appropriate. In univariate analyses, a comparison between CRE and CSE was done for each variable of interest. Multivariable analysis was conducted to identify the factors associated with poor outcomes. All p-values were two-sided and considered statistically significant if < 0.05 .

For this study, CRE was defined according to the clinical breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI) in the 21st edition of their document released in 2011 (11), as Enterobacterales showing decreased susceptibility to carbapenems (diameter for imipenem greater than 19mm, meropenem greater than 19mm). On the other hand, CSE was also identified via blood culture and susceptibility reports which showed Enterobacterales sensitive to any antibiotic of the carbapenem family.

Appropriate antibiotic regimens were defined as one containing at least one agent to which the organism was susceptible. For the CRE group, the antibiotic regimen considered appropriate in our setting was primarily a meropenem-based regimen with or without Colistin. Patients receiving appropriate antibiotic

therapy within 48 hours of having blood drawn for culture and susceptibility were defined to have received early therapy. Outcomes studied included length of stay and inpatient mortality.

Results

Sixty-five patients with CRE bacteremia and 66 patients with CSE bacteremia were identified during the study period. Basic demographics are described in Table 1. Both groups had a similar age distribution. CRE bacteremia was more common in males ($n = 45(69.2\%)$) than in females ($n = 20(30.8\%)$). The most common organism identified was *E. coli* for CRE ($n = 40(61.5\%)$) and CSE ($n = 55(83.3\%)$) respectively. A greater proportion of patients with CRE bacteremia had underlying comorbidities ($n = 58(89.5\%)$) as compared to patients with CSE bacteremia ($n = 42(64.4\%)$, $p = 0.003$). However, Diabetes Mellitus was less common in the CRE group ($n = 20(30.8\%)$) than in the CSE group ($38(57.6\%)$, $p = 0.002$). Most cases of CRE bacteremia were attributed to Central Line-Associated Bloodstream Infections (CLABSI) ($n = 16(24.6\%)$) while CSE bacteremia was more commonly secondary to Urinary Tract Infections (UTI) ($n = 39(59.1\%)$). Similarly, more patients with CRE bacteremia had an indwelling central venous catheter ($n = 41(60.5\%)$) than did patients with CSE bacteremia ($n = 27(39.7\%)$). As shown in Table 2, patients with CRE bacteremia also had more severe disease with a higher PITT bacteremia score (score > 4 in 20 patients (40%)) than patients with CSE (score > 4 in 11 patients, (20.4%), p value = 0.047) and were more likely to be admitted in the Intensive Care Unit (24 vs. 5; 37.5% vs. 7.7%; p -value < 0.01).

Table 1
Demographics

	CRE (65)	CSE (66)	P value
Male	45 (69.2%)	24(36.4%)	< 0.001
Female	20(30.8%)	42(63.6%)	
Mean age in years	51.8 ± 16.6	57.4 ± 15.7	0.367
16–35 years	10 (15.6%)	8 (12.1%)	
36–55 years	25 (39.1%)	18(27.3%)	
56–75 years	24 (37.5%)	32 (48.5%)	
76–96 years	5 (7.8%)	8 (12.1%)	
Year of Presentation	2 (40%)	3 (60%)	0.167
2013	18 (46.2%)	21 (53.8%)	
2014	27 (44.3%)	34 (55.7%)	
2015	18 (69.2%)	8 (30.8%)	
2016			
Location in the Hospital	24 (37.5%)	5 (7.7%)	< 0.01
ICU	40 (62.5%)	60 (92.3%)	
Ward			

CLABSI = Catheter Line Associated Blood Stream Infection

	CRE (65)	CSE (66)	P value
Comorbidities	20(30.8%)	38(57.6%)	0.396
Diabetes Mellites	19(29.2%)	15 (22.7%)	0.142
Malignancy	10(15.4%)	17(25.8%)	0.82
Ischemic Heart Disease	11 (16.9%)	12(18.5%)	0.492
Chronic Kidney Disease	1(1.5%)	0(0)	0.077
HIV	3(4.6%)	0 (0%)	0.245
Hepatitis B	9(13.8)	5(7.6)	0.067
Hepatitis C	28(43.1)	39(59.1)	0.302
Hypertension	3(4.6)	1(1.5)	0.478
Organ Transplant	14(21.5)	11(16.7)	0.249
Chemotherapy	13(20)	8(12.5)	
Hemodialysis			
Surgery within past year	33(52.4%)	22(34.4%)	0.041
ICU Stay	19 (24.6%)	5 (7.6%)	0.421
Duration	9 (47.4%)	3 (60%)	0.615
< 1 Weeks	10 (52.6%)	2 (40%)	
>1 Weeks			
Indwelling Lines	41(60.3%)	27(39.7%)	0.014
PICC Line	12 (22.2%)	7 (17.1%)	0.214
CVP Line	32(59.6%)	23 (56.1%)	0.11
Jo Cath Line	10 (18.5%)	11(26.8%)	0.812
Foley's Catheter	55 (84.6%)	53 (81.5%)	0.64
Tracheostomy	10(15.6%)	2(3.1%)	0.14
Time of First Positive Culture from Admission	31 (47.7%)	51 (77.3%)	< 0.01
Before or within 48h of admission	34 (52.3%)	15 (22.7%)	
After 48 hours of admission			

CLABSI = Catheter Line Associated Blood Stream Infection

	CRE (65)	CSE (66)	P value
Source	16 (24.6%)	6 (9.1%)	0.001
CLABSI	6 (9.2%)	0 (0%)	
Primary	14 (21.5%)	39 (59.1%)	
Urinary Tract Infection	6 (9.2%)	7 (10.6%)	
Intra-abdominal infection	6 (9.2%)	3(4.5%)	
Others	5(7.7%)	4(6.1%)	
Cholangitis	3(4.6%)	0(0%)	
Postoperative infection	8(12.3)	2(3%)	
Chest	1(1.5%)	5(7.6%)	
Multiple			
Negative Culture Prior to Discharge	25 (38.5%)	25 (37.9%)	0.001
Yes	20 (30.8%)	4 (6.1%)	
No	19 (29.0%)	37 (56.1%)	
No culture sent further			
Pitt Bacteremia Score	14 (28%)	26 (48.1%)	0.047
0–1	16 (32%)	17 (31.5%)	
2–3	20 (40%)	11 (20.4%)	
4 or more			
CLABSI = Catheter Line Associated Blood Stream Infection			

Table 2
Treatment and Outcomes

	CRE	CSE	P-value
Appropriate Antibiotics	47(72.3%)	57 (86.4%)	0.195
Yes	18 (27.7%)	9(13.6%)	
No			
Empiric appropriate antibiotic therapy	34(52.3%)	50 (75.8%)	0.073
Within 48 hours of Culture Request	13(20.0%)	7 (10.6%)	
After 48 hours of Culture Request	18 (27.7%)	9(13.6%)	
Missing data			
Mortality	32 (54.2%)	50 (86.2%)	< 0.001
Dead	27 (45.8%)	8 (13.8%)	
Alive	6	8	
LAMA			
Inpatient mortality among those who received appropriate antibiotics	18(38.3%)	5(8.7%)	< 0.001
Inpatient mortality among those who did not receive appropriate antibiotics	9 (50.0%)	3(33.3%)	0.653
Mortality in Relation to Pitt Bacteremia Score	2 (14.3%)	2 (7.7%)	0.148
0–1	7(43.8%)	0 (0%)	
2–3	13(65.0%)	5(45.5%)	
≥ 4			
Median Length of Hospitalization	8	6	0.021
LAMA = Leave Against Medical Advice			

The Susceptibility pattern of the CRE and CSE organisms to various antibiotics is displayed in Fig. 1. The CSE organisms were most often susceptible to aminoglycosides (n = 47, 71.2%) followed by Ceftriaxone (n = 18, 27.3%). Similarly, the greatest number of CRE organisms were susceptible to Colistin (n = 59, 90.8%) followed by aminoglycoside (n = 36, 55.4%).

There was no significant difference observed in the time to initiate appropriate empiric antibiotic therapy between the 2 groups. Appropriate empiric antibiotics were started within 48 hours of sending the cultures in 34 patients with CRE bacteremia (52.3%) versus 50 patients with CSE bacteremia (75.8%). As definitive treatment, 47 (72.3%) of the patients with CRE bacteremia and 57 (86.4%) of the patients with

CSE bacteremia received at least one appropriate antibiotic during the course of the hospital stay. Fewer patients with CRE bacteremia received appropriate antibiotics compared to the CSE subset, although this difference was not statistically significant (72.3% vs 86.4%, $P = 0.195$).

The results of univariate and multivariate analysis are summarized in Table 3 and 4. The overall inpatient mortality was significantly higher in the CRE group compared to the CSE group (27 vs 8, 41.5% vs 12.1%, p -value 0.001). Inpatient mortality in those that received appropriate therapy was significantly higher in the CRE group compared to the CSE group (18 vs. 5, 38.3% vs. 8.7%). However, mortality was higher in the CRE group when appropriate therapy was administered for 48 hours or more (14 vs.4, 38.9% vs. 7.7%). Moreover, a higher Pitt bacteremia score correlated with higher mortality (13 vs. 5; 65.0% vs. 45.5%). The median length of hospital stay for patients with CRE bacteremia was 8 days, while that for patients with CSE bacteremia was 6 days ($p < 0.05$). As shown in Table 3, CRE bacteremia (27, 45.8%; $p < 0.01$), ICU admission (20, 71.4%; $p < 0.01$), PITT bacteremia score ≥ 4 (18, 62.1%; $p, 0.01$), no negative blood culture prior to discharge, indwelling lines (31, 49.2%; $p < 0.01$), central line (29, 50%; $p, 0.01$) and presence of Foley catheter (33, 34.7%; $p = 0.023$) were significantly associated with mortality. However, on multivariate analysis, mortality was significantly associated with CRE bacteremia, placement of central line, no negative blood culture (either not sent or not negative) before discharge, and ICU admission. In the overall outcome among CRE patients, there was no significant difference in survival rates between patients receiving colistin monotherapy and those receiving combination therapies of meropenem and colistin (7 vs. 25; 58.3% vs. 61%).

Table 3
Univariate Analysis

		Mortality	Odds Ratio[95% CI]	P-value
CRE/CSE	CRE	27 (45.8%)	0.190[0.077, 0.469]	< 0.001
	CSE	8 (13.8%)		
Negative Blood culture prior to discharge	No	12 (44.4%)	0.079[0.22,0.288]	< 0.001
	Yes	5 (10.6%)		
ICU admission	Yes	20 (71.4%)	13.03[4.79,65.42]	< 0.001
	No	14 (16.1%)		
Pitt Bacteremia Score	>=4	18 (62.1%)		< 0.001
	2-3	7 (26.9%)		
	0-1	4 (10.8%)		
Indwelling lines	Yes	31 (49.2%)	0.084 [0.027, 0.262]	< 0.001
	No	4 (7.5%)		
Central Line	Yes	29 (50%)	0.113 [0.042, 0.304]	< 0.001
	No	6 (11.3%)		
Foley Catheter	Yes	33 (34.7%)	5.056[1.1, 23.0]	0.023
	no	2 (10%)		

Table 4
Multivariate Analysis

Inpatient Mortality		
Variable	Odds ratio [95% CI]	<i>p</i> value
Group	1.0	0.01
CSE	5.40[1.43–20.42]	
CRE		
Negative culture	1.0	0.002
No	0.07[0.01–0.39]	
Yes		
ICU Stay	1.0	0.01
No	9.05[1.55–52.84]	
Yes		
Central Venous Catheter	1.0	0.001
No	12.27[2.94–51.09]	
Yes		

Discussion

This study was designed to investigate the risk factors and outcomes of bacteremia caused by Carbapenem-resistant (CRE) Enterobacterales compared to Carbapenem Susceptible Enterobacterales (CSE). We found that infections with CRE were more severe than those with CSE, with a higher Pitt bacteremia score, and led to significantly higher mortality, higher rates of ICU admission, and longer median length of hospital stay. Moreover, CRE infections were most commonly nosocomial and associated with central line placement.

Nearly a third of CSE were resistant to 3rd generation cephalosporins, possibly reflecting a high endemicity of Extended-Spectrum Beta-Lactamase producers in the community. The increased prevalence of ESBL producing species in India and South Asia in general have been hypothesized to have driven the use of Carbapenems leading to selection pressure for the emergence of Carbapenem Resistance among Enterobacterales(12–14). While overall most infections were community-acquired, the frequency of nosocomial infections (37.4%) exceeded that reported in other resource-limited settings (5.7%- 19.1%) (15). Additionally, we observed a higher proportion of nosocomial infections with CRE (52.3%) than that observed in a multi-center study in resource-limited settings (40%) (7). These variations can be due to differences in compliance with infection control, antibiotic stewardship, and endemicity of

antimicrobial resistance, and highlight the relevance of individual institutional data to guide clinical practice.

Outcomes and disease severity in patients with CRE infection remained worse compared to those with CSE infection, even though there was no statistically significant difference in the initiation of timely and appropriate antibiotic therapy between the groups. Existing literature in both developed and resource-limited settings has consistently reported similar outcomes for infections(7, 16–22) with CRE. Similar to the findings of a meta-analysis(22), we observed a higher odds for mortality for CRE bacteremia compared with CSE bacteremia on multivariate analysis. Similarly, compared to the multi-center PANORAMA study that reported a 35% inpatient mortality for CRE bacteremia in resource-limited settings, we found a higher mortality rate of 45.8% at our center(7). However, mortality in our study was slightly higher than reported in the PANORAMA study. Mortality due to bacteremia is influenced by several factors, including patient characteristics, source control, and appropriate antibiotic therapy. In our study, patients with CRE had a higher PITT bacteremia score (Pitt score 4 or greater in 40% vs 20%). This may be reflective of the higher proportion of CLABSI which is associated with more severe disease. Source control also affects mortality; however, we were unable to document source control in our patients. Finally, while there was no difference in the time to initiation of appropriate therapy in both groups, most patients received colistin (71.2% vs 52%), due to limited availability of alternative agents in Pakistan. Colistin may have contributed to the morbidity given the higher rates of adverse effects and possible suboptimal efficacy(23, 24). Furthermore, due to resource constraints, we were unable to conduct genetic analysis and were therefore unable to assess the proportion of carbapenemase-producing Enterobacterales in our cohort, which are known to cause a 3-fold higher mortality compared to non-carbapenemase producing CRE(9).

Our study is limited by its retrospective design and restriction to a single, private tertiary care hospital in Karachi- limiting generalizability to public sector hospitals in the region. Additionally, although by using equal numbers of CRE and CSE infections we aimed to draw comparisons in outcomes and risk factors between the two groups, we were unable to estimate the incidence of the CRE and CSE infections during the study period.

Conclusion

Nevertheless, our study highlights that differences exist in the epidemiology and outcomes of infections with CRE and CSE within the developing world, emphasizing the relevance of exploring local data. Future studies are needed across multiple centers in Pakistan where antibiotic stewardship and quality assurance for antibiotic procurement is inadequate (25, 26). The results of such studies should be utilized to develop infection control policies tailored for this part of the world.

Abbreviations

CRE = Carbapenem Resistant Enterobacterales

CSE = Carbapenem Sensitive Enterobacterales

USD = United States Dollars

CLSI = Clinical and Laboratory Standards Institute

CP =Carbapenemase Producing

CLABSI = Central Line-Associated Bloodstream Infections

UTI = Urinary Tract Infection

Declarations

Patient Consent Statement and Ethical Considerations

The study was exempted by the Ethics and Review Committee (IRB) of Aga Khan University Hospital prior to its start (4461-Med-ERC-16). The study was exempted from patient consent as it only involved retrospective chart reviews with subsequent deidentification of data to ensure confidentiality.

Consent for Publications

Not Applicable

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that they have no competing interests

Funding

Not Applicable

Authors' Contributions

OA, SAK, and FAA developed the proposal, collected and analyzed data and prepared the manuscript. NK wrote the manuscript along with other authors. SA (Sara) and MAS assisted with data collection. SA (Safia) and FS conducted the statistical analysis of the cleaned data. SFM supervised and assisted in all steps including the development of proposal, data cleaning and analysis and preparation of the manuscript.

Acknowledgements

References

1. Centers for Disease Control and Prevention (U.S.). Antibiotic resistance threats in the United States, 2019 [Internet]. Centers for Disease Control and Prevention (U.S.); 2019 Nov [cited 2021 Apr 19]. Available from: <https://stacks.cdc.gov/view/cdc/82532>
2. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations [Internet]. Government of the United Kingdom; 2016 May [cited 2021 Apr 24]. Available from: <https://apo.org.au/node/63983>
3. Bank W. Drug-Resistant Infections [Internet]. World Bank, Washington, DC; 2017 Mar [cited 2021 Apr 24]. Available from: <https://openknowledge.worldbank.org/handle/10986/26707>
4. Cantón R, González-Alba JM, Galán JC. CTX-M Enzymes: Origin and Diffusion. *Front Microbiol* [Internet]. 2012 [cited 2021 Mar 23];3. Available from: <http://journal.frontiersin.org/article/10.3389/fmicb.2012.00110/abstract>
5. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, et al. Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Annual Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infect Control Hosp Epidemiol*. 2008 Nov;29(11):996–1011.
6. Wang Q, Zhang Y, Yao X, Xian H, Liu Y, Li H, et al. Risk factors and clinical outcomes for carbapenem-resistant Enterobacteriaceae nosocomial infections. *Eur J Clin Microbiol Infect Dis*. 2016 Oct;35(10):1679–89.
7. Stewardson AJ, Marimuthu K, Sengupta S, Allignol A, El-Bouseary M, Carvalho MJ, et al. Effect of carbapenem resistance on outcomes of bloodstream infection caused by Enterobacteriaceae in low-income and middle-income countries (PANORAMA): a multinational prospective cohort study. *Lancet Infect Dis*. 2019 Jun;19(6):601–10.
8. WHO. Health care-associated infections Fact Sheet. [Internet]. World Health Organization; [cited 2021 Apr 24]. Available from: http://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf
9. Tamma PD, Goodman KE, Harris AD, Tekle T, Roberts A, Taiwo A, et al. Comparing the Outcomes of Patients With Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae Bacteremia. *Clin Infect Dis*. 2017 Feb 1;64(3):257–64.
10. World Health Organization, editor. Antimicrobial resistance: global report on surveillance. Geneva, Switzerland: World Health Organization; 2014. 232 p.
11. M100-S21: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement.:172.
12. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis*. 2010 Sep;10(9):597–602.

13. Hawkey PM. Prevalence and clonality of extended-spectrum β -lactamases in Asia. *Clin Microbiol Infect.* 2008 Jan;14:159–65.
14. Harish BN, Menezes GA, Shekatkar S, Parija SC. Extended-spectrum β -lactamase-producing *Klebsiella pneumoniae* from blood culture. *J Med Microbiol.* 2007 Jul 1;56(7):999–1000.
15. gpssc_ccisc_fact_sheet_en.pdf [Internet]. [cited 2021 Mar 23]. Available from: https://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf
16. Yang Y, Chen J, Lin D, Xu X, Cheng J, Sun C. Prevalence and drug resistance characteristics of carbapenem-resistant Enterobacteriaceae in Hangzhou, China. *Front Med.* 2018 Apr;12(2):182–8.
17. Yoon E-J, Yang JW, Kim JO, Lee H, Lee KJ, Jeong SH. Carbapenemase-producing Enterobacteriaceae in South Korea: a report from the National Laboratory Surveillance System. *Future Microbiol.* 2018 Jun;13(7):771–83.
18. Davoudi-Monfared E, Khalili H. The threat of carbapenem-resistant gram-negative bacteria in a Middle East region. *Infect Drug Resist.* 2018 Oct;Volume 11:1831–80.
19. Perez F, Bonomo RA. Carbapenem-resistant Enterobacteriaceae: global action required. *Lancet Infect Dis.* 2019 Jun;19(6):561–2.
20. Soria-Segarra C, Soria-Segarra C, Catagua-González A, Gutiérrez-Fernández J. Carbapenemase producing Enterobacteriaceae in intensive care units in Ecuador: Results from a multicenter study. *J Infect Public Health.* 2020 Jan;13(1):80–8.
21. Dias VM de CH, Silva DMW da, Burger M, Oliveira AAS de, Capelo P de J, Specian FA da R, et al. Active surveillance of carbapenem-resistant Gram-negative healthcare-associated infections in a low-middle-income country city. *Braz J Infect Dis.* 2021 Mar;25(2):101540.
22. Martin A, Fahrbach K, Zhao Q, Lodise T. Association Between Carbapenem Resistance and Mortality Among Adult, Hospitalized Patients With Serious Infections Due to Enterobacteriaceae: Results of a Systematic Literature Review and Meta-analysis. *Open Forum Infect Dis.* 2018 Jul 1;5(7):ofy150.
23. Pogue JM, Ortwine JK, Kaye KS. Clinical considerations for optimal use of the polymyxins: A focus on agent selection and dosing. *Clin Microbiol Infect.* 2017 Apr;23(4):229–33.
24. Zusman O, Altunin S, Koppel F, Dishon Benattar Y, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. *J Antimicrob Chemother.* 2017 Jan;72(1):29–39.
25. Khalid L, Mahsood N, Ali I. The public health problem of OTC antibiotics in developing nations. *Res Soc Adm Pharm.* 2016 Sep;12(5):801–2.
26. Khan J, Hassan Z, Tajik M. Antibiotic Resistance: Recommendations for Procurement Agencies of Public Sector Hospitals in Pakistan. *J Coll Physicians Surg Pak.* 2020 Mar 1;30(03):340–1.

Figures

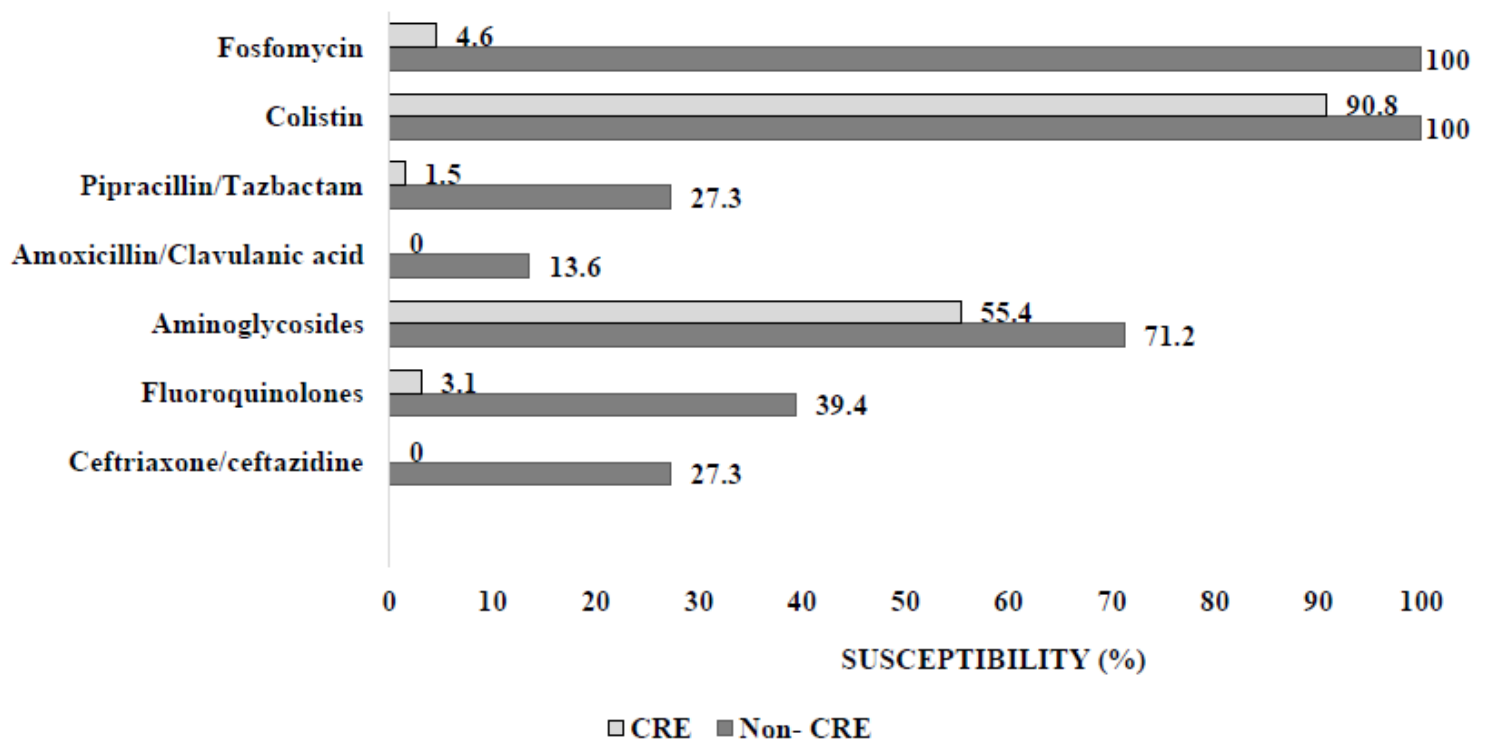


Figure 1

Antibiotic Susceptibility Pattern (%)