ORIGINAL ARTICLE

Carbapenem-Resistant Enterobacteriaceae Bacteraemia in Intensive Care Unit: A Descriptive Study on Risk Factors and Clinical Outcome

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ABSTRACT

INTRODUCTION: Over the past 10 years, the prevalence of carbapenem-resistant Enterobacteriaceae (CRE) has been increasing dramatically with numerous hospital outbreaks reported. Bacteraemia caused by CRE have limited treatment options and have been associated with high mortality rates. As a result, preventing both CRE transmission and CRE bloodstream infections have become important objectives in managing intensive care unit (ICU) patients. The study aims to determine the incidence and risk factors of CRE bacteraemia in intensive care settings, and its' clinical outcome. **MATERIALS AND METHODS:** A retrospective, descriptive study was conducted, where data of the patients admitted to general ICU of Hospital Pulau Pinang from January 2017 till December 2018 were collected and assessed for incidence, presence of predisposing factors and clinical outcome for CRE bloodstream infection. **RESULTS:** Out of 2,585 total ICU admissions, there were 37 cases of CRE bacteraemia with an incidence rate of 1.43%. An analysis of risk factors revealed that the use of indwelling catheter has the highest association with CRE bacteraemia in which 95% of the patients were exposed. The commonest organisms of CRE bacteraemia were Klebsiella pneumoniae (97.3%) and Escherichia coli (2.7%). The 30-day mortality rate after CRE bacteraemia was 78.4%. **CONCLUSION:** CRE bacteraemia among ICU patients showed a high mortality rate. Most of the patients were exposed to multiple risk factors. A high index of suspicion and rapid identification of patients at risk for CRE infection are important for effective therapy and initiation of infection control measures to prevent further spread.

Keywords
Carbapenem Resistant Enterobacteriaceae, Intensive Care Unit, Clinical Outcome, Risk Factors

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INTRODUCTION

Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, *Morganella morganii*, *Proteus mirabilis*, *Enterobacter* species, and *Serratia* species are examples of Enterobacteriacea which are causative agents for multiple infections including sepsis, meningitis, pneumonia, peritonitis and pyelonephritis.[1,2] Carbapenem class of antibiotics have been the choice of treatment for infections caused by Enterobacteriacea as they could overcome extended spectrum beta-lactamases through several mechanisms.[1–3]

Enterobacteriacea resistant to Carbapenem is noted to have high mortality and has raised alarms in the medical fraternity as it frequently noted to be the causative agent of infections as well has high potential for transmission of carbapenem resistance through genetic elements.[2–6] The World Health Organization cited CRE as bacteria with a critical priority and urged development of new antibiotics.[7]

Several factors have been identified as the culprit for increasing the risk of CRE colonisation and infection such as underlying diseases, prolonged hospital stay, presence of indwelling devices and exposure to antimicrobials.[2,8] CRE infections are associated with clinical and economic adverse effects, which includes decreased functional status, increased risk of death and increased healthcare associated costs. [8]

However, information regarding CRE bloodstream infection in the Intensive Care Unit (ICU) is not widely available. A study of CRE bacteraemia in our population is thus essential and would help to refine the criteria used for target active surveillance screening for CRE amongst patients admitted in our local hospital setting. [5,7]

CRE is a global threat and most of the information available is from western literature. Malaysian literatures on CRE bloodstream infection is scarce even though CRE infection in our country is increasing in trend and alarming.[9] In view of the scarcity of information of CRE bacteraemia in critically ill patient, this study will provide valuable information that may guide decision making in the ICU, to prevent the emergence and spread of CRE bacteraemia.[2,7] Hence a study on CRE bloodstream infection in a tertiary Malaysian Hospital with clinical outcome would be imperative.

Our primary objective was to determine the incidence of CRE bacteraemia among critically ill patients while our secondary objective was to analyse the presence of predisposing factors and its clinical outcome.

MATERIALS AND METHODS

Study Design and population

This was a retrospective descriptive study conducted in a tertiary hospital general ICU of Hospital Pulau Pinang, where data was collected from the ICU, infectious disease department and medical records from January 2017 till December 2018. Critically ill patients admitted to the ICU during the study period with CRE bloodstream infection were selected. Adult patients more than 18 years of age and were in the ICU at the time of study were included. Those who have been transferred out from ICU upon diagnosis of CRE bacteraemia were excluded from the study.

Data Collection

The data collected were the total number of GICU admission during the study period, total number of CRE infections in the study hospital (Hospital Pulau Pinang), total number of CRE infections in ICU, number of patients who developed CRE bacteraemia in ICU, demographic data, presence of predisposing risk factors such as underlying diseases, prolonged hospitalization more than 2 weeks, antibiotic exposure 30 days prior to CRE bacteraemia, type of device present 30 days prior to CRE bacteraemia including mechanical ventilation, presence of tracheostomy, urinary catheter and central venous catheter (CVC). These data were tabulated and analysed. Incidence of CRE bacteraemia and mortality rate were calculated.

Ethical approval

Ethical approval was obtained from the local ethics committee Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH), Malaysia prior to study. This study was registered under National Medical Research Registration (NMRR-19-1953-48797 IIR).

RESULTS

Total number of admission to the ICU of Hospital Pulau Pinang during the study period was 2,585 patients in which 104 patients developed CRE infection and 37 patients were diagnosed with CRE bacteraemia. There were a total of 373 reported cases of CRE infection in Hospital Pulau Pinang in 2017 and 2018. *Refer Table I.*

The positive CRE patients showed a high male preponderance and majority of them aged between 50-70 years. *Refer Table II.* CRE *K. pneumoniae* was the major causative organism isolated (n=36, 97.3%) while *E. coli* was isolated in 1 patient only (2.7%).

Table I CRE infection

	Total n (%)
CRE infection in ICU	104 (4%)
CRE bacteraemia in ICU	37 (1.43%)
CRE infection in the hospital	373 (0.32%)

The analysis of risk factors shown that the CRE bacteraemia were detected in 73% (n=27) of patients with underlying comorbidities such as diabetes mellitus (DM), hypertension, malignancy and end stage renal disease (ESRD); 89.2% (n=33) in patients who had prolonged hospitalisation of more than 2 weeks; 89.2% (n=33 in mechanically ventilated patients; 46% (n=17) in post

Table II Gender and age-based comparison

Gender	n (%)
Male	23 (62.15%)
Female	14 (37.85%)
Age group (years)	**n (%)**
< 30	3 (8.1%)
30-50	8 (21.6%)
51-70	22 (59.5%)
>70	4 (10.8%)

tracheostomy patients; 83.8% (n=31) in patients with central venous catheter (CVC); and 94.5% (n=35) in patients with continuous bladder drainage (CBD). *Refer Figure 1.*

Table III Antibiotics with highest exposure prior to CRE bacteraemia

Antibiotic/Antifungal	Total (n)
Cefepime	19
Meropenem	18
Piperacillin Tazobactam	16
Colistin	13
Ampicillin Sulbactam	9
Imipenem	8
Vancomycin	6
Amphotericin B	6

All patients were exposed to antibiotics in the last 30 days prior to isolation of CRE in which majority of them received a combination of multiple groups of antibiotics. An antibiotic exposure is shown in Table III. The commonest antibiotics exposed prior to CRE bacteraemia were cefepime, meropenem and piperacillin-tazobactam. As majority of patients were on multiple antibiotics, the total antibiotic days prior to developing CRE bacteraemia was added up. The analysis for duration of exposure to the antibiotics prior to the detection of CRE bacteraemia shown that 35.8% had exposure of more than 7 days prior; 41.6% for 3-7 days prior; and 22.6 % were exposed less than 3 days prior. The 30-day mortality for patients with CRE bacteraemia was 78.4%.

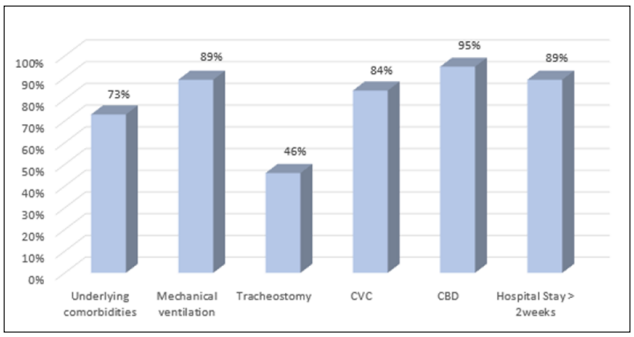

Figure 1 Predisposing Risk Factors

DISCUSSION

The incidence of CRE infections and bacteraemia in our study was 0.33 and 0.12 per 100,000 persons per years respectively. Studies on incidence of CRE in United States population reported the incidence were 0.3–2.93 infections per 100,000 person-years.[10] However, the data on CRE bacteraemia incidence was limited.

A total of 37 CRE bacteraemia isolates were collected during the study period, among which the predominant organism was *K. pneumoniae* (97.3%) and *E. coli* was (2.7%). There were two previous studies which shown *K. pneumoniae as a predominant* organism with incidence ranging from 42.2 -78%.[7,11] Ling ML et al reported *E. coli* is the next commonly seen CRE after *K. pneumoniae.*[7] The predominance of *K. pneumoniae* being the cause of CRE bacteraemia could be due to the mechanism for carbapenem resistance via production of *Klebsiella pneumoniae* carbapenemase (KPC), an Ambler molecular class A enzyme that utilizes serine at the active site to facilitate hydrolysis of a broad variety of β-lactams.[3,12–14]

Majority of our study patients who were shown to have CRE bacteraemia during our study period were exposed to almost all the possible predisposing factors which includes presence of underlying comorbidities, mechanical ventilation, presence of tracheostomy, urinary catheter, CVC and prior exposure to antibiotics. Similar studies on risk factors of CRE bacteraemia shown that mechanical ventilation and urinary catheter played a significant role in causing CRE bacteraemia.[3,5,12,15–18] An indwelling devices especially CVC is an independent risk factor for developing CRE bacteraemia in a previous study.[7] Meanwhile, Rosenthal VD *et al* found that mechanical ventilation, CVC and indwelling urinary catheter were the main causes of device-associated nosocomial infections leading to CRE infections. [19]

Prior usage of antibiotics is a crucial risk factor for developing CRE bacteraemia. All of our studied patients who developed CRE bacteraemia were exposed with antibiotics; with piperacillin /tazobactam, cefepime and meropenem being the three commonest antibiotics used.

Several studies reported an increased risk of CRE bacteraemia in patients with a prior exposure to the antibiotics from penicillin group.[7,16,20] There were studies reported an increased risk of CRE infections in patients with prior usage of fluoroquinolone and carbapenem group of antibiotics.[2,21] Our study results were similar with other results in which previous exposure to any broad-spectrum antibiotic had led to CRE bacteraemia.[3,4,6,12,15,22]

Our study shown that the mortality rate of patients with CRE bacteraemia was 78.4%. In a meta-analysis conducted in 2018, the CRE mortality rate ranged from 18.6–94.1%.[23] The commonest pathogen isolated in previous study was *K. pneumonia*, was similar to our study results.[23] The general reasons for higher mortality in CRE bacteraemia includes lack of general overview of the prevalence of CRE infections and bacteraemia. Thus the patients at risk should be prioritised in screening and control of the spread. Apart from the common risk factors mentioned earlier, patients with mobility restriction and prolonged hospitalisation are also associated with CRE infection.[24] Similarly to our study population, CRE related death appears to be higher among medical patients rather than surgical patients.[24,25] In subgroup analyses, patients with carbapenem-resistant *K. pneumoniae* bloodstream infection have a higher mortality rate.[23]

Time to initiate effective antibiotic treatment may have played a part in higher mortality. Several studies demonstrated that patients with CRE are at an increased risk for delayed administration of a microbiologic active antibiotic.[22,23] It has been widely accepted that prompt initiation of treatment during the initial critical hours of the infection process has an important impact on survival and each hour of delay increases mortality by 7%.[23,26] We could not ascertain from the data collected whether delay in initiation of antibiotics contributed to mortality in these patients.

Treatment regimens for CRE infections vary widely nowadays.[27,28] Mono- and combination therapy could be used to combat CRE infections. Carbapenem-containing combination therapy may be more beneficial than carbapenem-sparing combination therapy in the treatment of CRE bacteraemia.[1] Survival of patients with CRE bacteraemia significantly improved with combination therapy as compared to monotherapy. [29,30] Several combinations appeared to be effective with the most common successful combination regimens used were either colistin-polymyxin B or tigecycline, in combination with a carbapenem.[29] More recently, several newer antibiotics such as ceftazidime-avibactam and meropenem -vaborbactam for CRE and ceftolozane-tazobactam for carbapenem-resistant *P. aeruginosa* infections were developed and becoming important treatment options.[31]

Lastly, strict and timely measures need to be taken to prevent and spread of CRE. Screening for patients at risk for CRE carriage should begin upon admission to a healthcare setting.[32] A simplified questionnaire can be used as a tool to assist frontline workers for evaluation and decision making when admitting patients to healthcare settings. Based on the results of the active screening, the patient should be admitted and managed according to their risk. The European Centre for Disease Prevention and Control recommends pre-emptive isolation of patients on admission, active screening on admission and contact precautions for CRE "at risk" patients with known or unknown microbiological results.[32] Use of accurate and fast methods of CRE detection can provide rapid notification of results which is vital for both effective therapy and infection control measures. Limit the use of invasive devices when possible and daily review of the need. Every hospital should implement an antimicrobial stewardship programme to provide appropriate antimicrobial therapy and prevent the development of resistance.[32,33] Involvement of staff at every level is essential to curb spread of CRE infection. Regular training and monitoring of compliance to infection control measures should be done routinely. [32,33]

CONCLUSION

The incidence of CRE bacteraemia during this study period and the mortality rate following CRE infection and bacteraemia are comparable with previous studies. The predisposing factors to CRE bacteraemia in our study were underlying comorbidities, mechanical ventilation, presence of tracheostomy, urinary catheter, CVC and

prior exposure to antibiotics. Routine screening and rapid identification of patients at risk for CRE infection or bacteraemia should be done and appropriate barrier precautions should be applied when necessary. Continuous education and training of staff is essential to spread awareness. A prospective multicentre clinical trial is warranted to establish causal relationships and further evaluate the response to treatment among patients with CRE bacteraemia.

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CONFLICT OF INTEREST

I hereby declare that we do not have any conflict of interest.

REFERENCES

1. Li C, Li Y, Zhao Z, Liu Q, Li B. Treatment options and clinical outcomes for carbapenem-resistant Enterobacteriaceae bloodstream infection in a Chinese university hospital. J Infect Public Health. 2019;12:26–31.
2. Kritsotakis EI, Tsioutis C, Roumbelaki M, Christidou A, Gikas A. Antibiotic use and the risk of carbapenem-resistant extended-spectrum-β-lactamase-producing Klebsiella pneumoniae infection in hospitalized patients: results of a double case–control study. J Antimicrob Chemother. 2011;66:1383–91.
3. Patel N, Harrington S, Dihmess A, Woo B, Masoud R, Martis P, et al. Clinical epidemiology of carbapenem-intermediate or-resistant Enterobacteriaceae. J Antimicrob Chemother. 2011;66:1600–8.
4. Lee HJ, Choi JK, Cho SY, Kim SH, Park SH, Choi SM, et al. Carbapenem-resistant Enterobacteriaceae: prevalence and risk factors in a single community-based hospital in Korea. Infect Chemother. 2016;48:166–73.
5. Gould C V, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA, Committee HICPA. Guideline for prevention of catheter-associated urinary tract infections 2009. Infect Control Hosp Epidemiol. 2010;31:319–26.
6. Li X, Ye H. Clinical and mortality risk factors in bloodstream infections with carbapenem-resistant Enterobacteriaceae. Can J Infect Dis Med Microbiol. 2017;2017.
7. Ling ML, Tee YM, Tan SG, Amin IM, How KB, Tan KY, et al. Risk factors for acquisition of carbapenem resistant Enterobacteriaceae in an acute tertiary care hospital in Singapore. Antimicrob Resist Infect Control. 2015;4:1–7.
8. Zawawi RD, Ramli R, Sidik TMITAB, Naina-Mohamed I, Loon LC. Clinical Characteristics and Risk Factors of Carbapenem-Resistant Enterobacteriaceae: A Case-Control Study in a Tertiary Hospital in Malaysia. Malaysian J Med Heal Sci. 2021;14:189–95.
9. Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. Emerg Infect Dis. 2014;20:1170.
10. Livorsi DJ, Chorazy ML, Schweizer ML, Balkenende EC, Blevins AE, Nair R, et al. A systematic review of the epidemiology of carbapenem-resistant Enterobacteriaceae in the United States. Antimicrob Resist Infect Control. 2018;7:1–9.
11. Perovic O, Ismail H, Quan V, Bamford C, Nana T, Chibabhai V, et al. Carbapenem-resistant Enterobacteriaceae in patients with bacteraemia at tertiary hospitals in South Africa, 2015 to 2018. Eur J Clin Microbiol Infect Dis. 2020;39:1287–94.
12. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis. 2011;53:60–7.
13. Bratu S, Landman D, Haag R, Recco R, Eramo A, Alam M, et al. Rapid spread of carbapenem-resistant Klebsiella pneumoniae in New York City: a new threat to our antibiotic armamentarium. Arch Intern Med. 2005;165:1430–5.
14. Bradford PA, Urban C, Mariano N, Projan SJ, Rahal JJ, Bush K. Imipenem resistance in Klebsiella pneumoniae is associated with the combination of ACT-1, a plasmid-mediated AmpC beta-lactamase, and the foss of an outer membrane protein.

Antimicrob Agents Chemother. 1997;41:563–9.
15. Varma M, Reddy LR, Vidyasagar S, Holla A, Bhat NK. Risk factors for carbapenem resistant enterobacteriaceae in a teritiary hospital—A case control study. Indian J Med Spec. 2018;9:178–83.
16. Hyle EP, Ferraro MJ, Silver M, Lee H, Hooper DC. Ertapenem-resistant Enterobacteriaceae risk factors for acquisition and outcomes. Infect Control Hosp Epidemiol. 2010;31:1242–9.
17. Zhang Y, Guo LY, Song WQ, Wang Y, Dong F, Liu G. Risk factors for carbapenem-resistant K. pneumoniae bloodstream infection and predictors of mortality in Chinese paediatric patients. BMC Infect Dis. 2018;18:1–10.
18. Correa AAF, Fortaleza CMCB. Incidence and predictors of health care–associated infections among patients colonized with carbapenem-resistant Enterobacteriaceae. Am J Infect Control. 2019;47:213–6.
19. Rosenthal VD, Maki DG, Salomao R, Moreno CA, Mehta Y, Higuera F, et al. Device-associated nosocomial infections in 55 intensive care units of 8 developing countries. Ann Intern Med. 2006;145:582–91.
20. Falagas ME, Rafailidis PI, Kofteridis D, Virtzili S, Chelvatzoglou FC, Papaioannou V, et al. Risk factors of carbapenem-resistant Klebsiella pneumoniae infections: a matched case–control study. J Antimicrob Chemother. 2007;60:1124–30.
21. Hussein K, Sprecher H, Mashiach T, Oren I, Kassis I, Finkelstein R. Carbapenem resistance among Klebsiella pneumoniae isolates risk factors, molecular characteristics, and susceptibility patterns. Infect Control Hosp Epidemiol. 2009;30:666–71.
22. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant Klebsiella pneumoniae infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol. 2008;29:1099–106.
23. 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. In: Open forum infectious diseases. Oxford University Press US; 2018. p. ofy150.
24. Chang HJ, Hsu PC, Yang CC, Kuo AJ, Chia JH, Wu TL, et al. Risk factors and outcomes of carbapenem-nonsusceptible Escherichia coli bacteremia: a matched case–control study. J Microbiol Immunol Infect. 2011;44:125–30.
25. Bleumin D, Cohen MJ, Moranne O, Esnault VLM, Benenson S, Paltiel O, et al. Carbapenem-resistant Klebsiella pneumoniae is associated with poor outcome in hemodialysis patients. J Infect. 2012;65:318–25.
26. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589–96.
27. Daikos GL, Tsaousi S, Tzouvelekis LS, Anyfantis I, Psichogiou M, Argyropoulou A, et al. Carbapenemase-producing Klebsiella pneumoniae bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother. 2014;58:2322–8.
28. Trecarichi EM, Tumbarello M. Therapeutic options for carbapenem-resistant Enterobacteriaceae infections. Virulence. 2017;8:470–84.
29. Qureshi ZA, Paterson DL, Potoski BA, Kilayko MC, Sandovsky G, Sordillo E, et al. Treatment outcome of bacteremia due to KPC-producing Klebsiella pneumoniae: superiority of combination antimicrobial regimens. Antimicrob Agents Chemother. 2012;56:2108–13.
30. Hirsch EB, Tam VH. Detection and treatment options for Klebsiella pneumoniae carbapenemases (KPCs): an emerging cause of multidrug-resistant infection. J Antimicrob Chemother. 2010;65:1119–25.
31. Doi Y. Treatment options for carbapenem-resistant gram-negative bacterial infections. Clin Infect Dis. 2019;69:S565–75.
32. Magiorakos AP, Burns K, Rodríguez Baño J, Borg M, Daikos G, Dumpis U, et al. Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant Enterobacteriaceae into healthcare settings: guidance from the European Centre for Disease Prevention and Control.

Antimicrob Resist Infect Control. 2017;6:1–17.
33. Kruse E., Wisplinghoff H. Guide to Infection Control in the Hospital: Carbapenem Resistant Enterobacteriaceae. In: International Society for Infectious Diseases. 2018.