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Management of Carbapenem-Resistant Enterobacteriaceae Bloodstream Infections: An Experience from a Tertiary Care Centre in Oman

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Abstract

The emergence of Carbapenem-resistant Enterobacteriaceae (CRE)is a public health concern worldwide. It is associated with increased mortality due to limited antibiotics available to treat CRE infections. The aim of this study was to understand the epidemiology of CRE infections, associated mortality, and available treatment options. All patients with CRE isolated in blood culture were identified between December 2011 and October 2019. Risk factors and mortality associated with each risk factor at 14 and 30 days were determined.55 cases of CRE bloodstream infections were isolated, with a median age of 56 years. Eighty-four percent of patients received treatment in the ICU. All cases were caused by Klebsiella pneumonia. The rate of resistance to the tested antibiotics was as follows: meropenem 92% (50/54), imipenem 75% (40/53), etrapenam 95% (19/20), Amikacin 71% (37/52), cotrimoxazole 73% (40/53), Gentamicin 47% (25/53) and colistin 7% (3/41). Major risk factors associated were the presence of a urinary catheter (84%), central venous catheter (78%), mechanical ventilation (74%) and post-surgery (67%). Mortality at 14 days and 30 days was 41%, and 52%, respectively. Univariate analysis showed that 14 days mortality was higher in patients with central venous catheter (*P=0*.01). Charlson's comorbidity index was associated with an increased risk of death at 30 days (*P*=0.04). There was no statistically increased survival in those treated with combination therapy at 30 days (*P*=0.5*).* The mortality of CRE infections seems to be high and optimal therapy is not yet well defined. Combination therapy is not associated with increased survival in this cohort of patients.

Keywords: Carbapenem-resistant Enterobacteriaceae (CRE) bacteremia, risk factors of CRE bacteremia, outcomes of CRE bacteremia, Colistin monotherapy, Colistin combination therapy.

INTRODUCTION

Enterobacteriaceae are gram-negative bacilli that can cause severe infections, including bloodstream infection (BSI), pneumonia, meningitis, line-related infection, skin and soft tissue infections, intra-abdominal, urinary tract infections, and device-related infections. Carbapenemase enzymes, are a type of beta-lactamase enzymes produced by gram-negative bacteria that hydrolyze carbapenems and other β-lactam agents, resulting in resistance to carbapenems [1]. These enzymes are produced by mobile genes found on the plasmid of GNR, easily transmissible to other bacilli resulting in the widespread of CRE [2]. There are predominantly five types of carbepenemases [2-4]. Klebsiella pneumonia is the most commonly isolated carbapenemase-producing organism [1-3, 5-7]. The emergence of CRE has led to high mortalities (>50%) due to the limited options of sensitive antibiotics in treating severe infections [1, 8-10]. The optimal treatment of infections due to CRE is yet unknown. Antibiotics such as colistin and tigecycline, alone or in combination with carbapenems, aminoglycosides or fosfomycin, are used to treat these infections [3, 11, 12]. Falagas *et al*., in a systemic review, showed that combination therapy resulted in lower mortality than monotherapy, especially among severely ill patients

[13]. Among combination therapy, mortality was up to 67% among those who received a carbapenem-colistin combination [13]. This study examines CRE epidemiology, risk factors associated with mortality, and if combination therapy is superior to monotherapy in the treatment of CRE.

MATERIALS AND METHODS

This retrospective cohort study was conducted in Khoula Hospital, a tertiary care institution in Oman. The study population included all patients with CRE bacteremia, admitted to the hospital between December 2011 to October 2019. Demographic data, risk factors, microbiology data (including date of blood collection, the focus of infection, susceptibility, and organism isolated), definitive therapy (duration, monotherapy, or combination therapy), patient outcomes (at 14 days and 30 days, either cure/discharge or death) were collected from the hospital database. Risk factors collected include hospitalization within the previous three months, antibiotic use within three months prior to the index admission, admission to ICU, presence of a central venous catheter (CVC), urinary catheter, mechanical ventilation, dialysis, the presence of comorbid conditions such as cardiovascular disease, lung disease, diabetes mellitus, solid tumors or hematological malignancy, liver disease, renal failure, and chemotherapy. Definitive therapy was defined as targeted antimicrobial therapy based on the blood culture susceptibility results. All CRE bacteremia were identified using API for identification and E-test for susceptibility testing from 2011 to 2016 and an automated system (Vitek) since 2017. Antibiotic susceptibility was interpreted as per criteria published by the Clinical and Laboratory Standards Institute (CLSI). Tigecycline and colistin susceptibility were interpreted based on breakpoints set according to the U.S. Food and Drug Administration's standards and the European Committee of Antimicrobial Susceptibility Testing (EUCAST) guidelines, respectively. The first episode of CRE bacteremia was included for patients with more than one episode of CRE bacteremia in one admission. Data was transferred to data sheet using the Epidata program. The SPSS program was used for data analysis. Mean and median were used to describe continuous variables and proportions for categorical variables. A *P* value of < 0.05 was considered significant. The chi-square test was used to test for the associations depending on the statistics needed by the study. No multivariate analysis was done as the univariate analysis does not show multiple independent variables with significant risk. Ethical approval was obtained from the hospital Research and Ethical Committee.

RESULTS

A total of 55 CRE bacteremia cases with median age 56 years (IQR 40-71 years), 76% (42/55) males, 78 % Omani were included. All cases were caused by Klebsiella pneumonia. The rate of resistance to the tested antibiotics was as follows: meropenem 92% (50/54), imipenem 75% (40/53), etrapenam 95% (19/20), Amikacin 71% (37/52), Gentamicin 47% (25/53) and cotrimoxazole 73% (40/53), Tigecycline 10/17 (59%) colistin 7% (3/41). Colistin susceptibility was available for 24 cases; with only 7% (3/21) resistant. The number of cases per year was more in 2018, accounting for 26% (14) of total CRE cases and was associated with an outbreak of CRE in the ICU unit (Table 1). The most common cases were bacteremia secondary to central line related infection at 53% (29/55) followed by ventilator-associated pneumonia at 24% (13/55). Other sources of infection were-surgical wound infection, catheter-associated urinary tract infection, hospital-acquired pneumonia, skin and soft tissue infections, and urinary tract infections (11%,5%,4%,1%, and 1%, respectively) (Fig 1).

The 14 days and 30 days mortality rates of CRE bacteremia were 41% and 52%, respectively. Risk factors associated with 14 and 30-days morality are mentioned in Table 1. Univariate analysis showed that the presence of central line catheters was significantly associated with 14 days mortality (P = 0.010) (Table 1). In contrast, the Charlson comorbidity index is associated with higher 30 days mortality (P value 0.04). Adequate source control of the focus of infection was significantly associated with better outcome (P value <0.001) at 14 and 30 days. The survival rate was higher among those who had adequate source control (78% at 14 days and 69% at 30 days) compared to those with no adequate source control (18% at 14 days and 6% at 30 days).

49 patients received definitive therapy, 29% (16/55) received colistin monotherapy 58% received Colistin based combination therapy. Six patients did not receive definitive therapy as they died while they were on empirical therapy for less than 48 hours of bacteremia. Univariate analysis of outcomes of definitive therapy showed no statistically significant difference in 14-day and 30-day mortality among those who received combination therapy vs monotherapy (Table 2).

Table 1: Univariate analysis of factors associated with 14 and 30 days mortality

		Mortality at 14 days		Mortality at 30 days	
		%(No)	P value	%(No)	P value
Gender	Male	34 (14/41)	0.080	49 (19/39)	0.423
	Female	62 (8/13)		62 (8/13)	
Hospitalisation within the previous 3 months prior to admission		43 (9/21)	0.801	48 (10/21)	0.609
ICU admission		44 (20/45)	0.215	57 (25/44)	0.203

Hospitalisation >48 hrs		42 (22/52)	0.644	52 (26/50)	1.000
Patient location at the time of infection	ICU	45 (18/40)	0.414	54 (21/39)	0.554
	Plastic surgery	50 (1/2)		100 (2/2)	
	Orthopedic ward	25 (1/4)		33 (1/3)	
	Neurosurgical ward	0 (0/3)		33 (1/3)	
	Burns unit	40 (2/5)		40 (2/5)	
Antibiotic use within 3 months prior to the index admission		50 (4/8)	0.851	50 (4/8)	1.000
Presence of central venous catheter		50 (21/42)	0.010	58 (23/40)	0.142
Mechanical ventilation		48 (19/40)	0.088	56 (22/39)	0.262
Dialysis		60 (3/5)	0.658	100 (4/4)	0.138
Urinary catheter		42 (9/45)	0.620	49 (21/43)	0.544
Cardiovascular disease		46(11/24)	0.496	61 (14/23)	0.250
Diabetes mellitus		50(10/20)	0.288	61(11/18)	0.335
Solid tumors		25 (1/4)	0.891	50 (2/4)	1.000
Renal disesse		50 (3/6)	0.961	80 (4/5)	0.395
Surgery		33 (12/36)	0.117	43 (15/35)	0.060
Trauma		29 (5/17)	0.251	50 (8/16)	0.853
Burn		43 (3/7)	1.000	43 (3/7)	0.913
CRE colonisation or previuos infection		43 (12/28)	0.743	56 (15/27)	0.586

Table 2: Univariate Analysis Of Mortality Among Patients Who Received Definitive Therapy

	14 days mortality		30 days mortality	
	% (No)	P value	% (No)	P value
Colistin Monotherapy	31% (5/16)	0.742	50% (8/16)	0.616
Colistin Combination Therapy	36% (11/31)		45% (13/29)	
Other Antibiotics (Ciprofloxacin)	0% (0/1)		0% (0/1)	

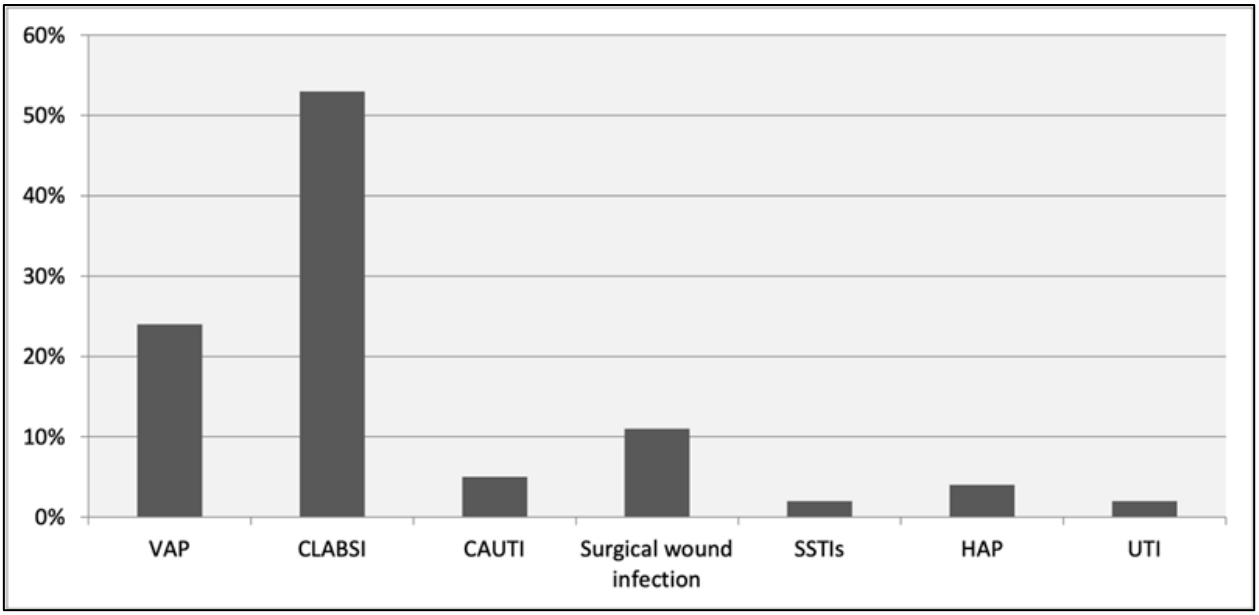

Figure 1: Focus of CRE bacteremia

DISCUSSION

Carbapenem-resistant Enterobacteriaceae (CRE) is becoming a global health burden. Limited antibiotic options are available to treat such infections; hence, most centres rely on older generations antibiotics, including colistin, tigecycline, and fosfomycin alone or in combination with other antibiotics like carbapenems and aminoglycosides. Few newly developed antibiotics used against multidrug-resistant bacteria, including CRE, have been reported globally; however, availability is limited, including our centre.

CRE is associated with high mortality rates, with more than 50% reported in some studies [3, 5, 9, 15-18]. Our study showed 41% and 52% mortality rates at 14 and 30 days. Klebsiella pneumonia has been the most frequently reported type of CRE [1, 3, 5, 14, 19]. Wang *et al*., found that Klebsiella pneumonia (K.P.) accounted

for 69.5% of all isolates, and Garbati *et al*., reported that CRE K.P accounted for 51.7% [3, 5]. Central line-associated bloodstream infection and ventilator-associated infection were the highest sources of CRE bacteremia (53% and 24% respectively). Few studies have reported other sources of CRE bacteremia; Park *et al*., showed that the most common sources of CRE were pneumonia, primary bacteremia, and biliary tract infection [14].

Multiple risk factors were demonstrated by previous studies to be associated with CRE, including ICU admission, length of hospital admission, recent solid organ transplant or stem cell transplant, previous antibiotics use, indwelling catheters, urinary catheters, mechanical ventilation, dialysis, comorbidities, and surgery [3-5, 9, 16]. The risk factors associated with CRE infection among our patients were prolonged hospital admission (96%), ICU admission (84%), urinary catheters (84%), CVC (78%), mechanical ventilation (74%), and previous CRE colonization/infection (53%). However, univariate analysis showed that only the presence of CVC was significantly associated with 14-days mortality (P=0.010) but not with 30-days mortality (P=0.142). Charlson Comorbidity index was associated with high mortality at 30 days (P =0.04). Adequate source control was shown to increase the survival at (P <0.001) at 14 and 30 days).

Treatment of CRE infection is challenging; first, most available antibiotics are resistant, and second, non-availability of newer anti-CRE antimicrobials in our centre. When CRE BSI infection is suspected or proven microbiologically, clinicians have to depend on antimicrobials like colistin or tigecycline alone or in combination with meropenem or quinolones, cotrimoxazole or aminoglycosides. In this study, most tested isolates were resistant to meropenem, ciprofloxacin, amikacin, gentamycin, and cotrimoxazole (91%, 87%, 67%, 45%, and 73%, respectively). Colistin was sensitive among 21/24 isolates. The majority of our patients received colistin therapy as definitive backbone therapy. Only one patient received ciprofloxacin monotherapy as definitive therapy with favourable 14- and 30-day outcome. Among patients who received colistin as a definitive therapy, 16 received colistin monotherapy (29%), and 32 received colistin-based combination therapy (58%). Univariate analysis of therapy effect on 14- and 30-day mortality showed that, statistically, there was no significant effect of monotherapy compared to combination therapy on mortality. A case-control study conducted by Garbati *et al*., showed that colistin-based therapy for CRE as monotherapy or in combination was associated with a high mortality rate (50%) [5]. Wang *et al*., found that appropriate therapy for CRE BSI was not associated with a protective effect on mortality, and there was no statistically significant difference between monotherapy and combination therapy [20]. Porwal *et al*., also found that the mortality was lower among combination therapy than colistin monotherapy; however, this difference was statistically insignificant (P value = 0.35). (20) Similar studies also showed that combination therapy is not significantly superior to monotherapy [21, 22].

We could perform colistin susceptibility only in 56% of our patients because of the nonavailability of recommended testing in our centre. Colistin susceptibility was interpreted using EUCAST guideline breakpoints, which may have influenced the colistin Susceptibility rate and might have affected treatment and outcomes.

CONCLUSION

In this cohort of CRE bacteremia, Klebsiella pneumonia was the only organism identified as a carbapenemase-producer. The mortality of these difficult-to-treat infections seems to be high and optimal therapy is not yet well defined. Further studies with a larger number of patients are needed to characterize CRE in isolates, genotypes, and antibiograms and assess the impact of different combination therapies.

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