

Original Article

## Factors associated with mortality in Infections caused by Carbapenem-resistant *Enterobacteriaceae*

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### Abstract

**Introduction:** There is little information about weigh of factors possibly associated with mortality, in infections caused by Carbapenem-resistant *Enterobacteriaceae* (CRE) in Latin America.

**Methodology:** A case-controls study nested in a historical cohort was performed including all patients with CRE infections diagnosed between June 2013 and December 2018 at Hospital Universitario San Ignacio in Bogotá, Colombia. Univariate and multivariate analysis were performed to compare cases of mortality within the first month after the infection diagnosis with surviving patients.

**Results:** A total of 131 patients were included. The overall 30-day mortality rate was 38.17%. In the multivariate analysis, a direct association was found between mortality and septic shock (OR 26.7 CI 6.6-107.3  $p < 0.01$ ), post-chemotherapy febrile neutropenia (OR 3.3 CI 1.06-10.8  $p = 0.04$ ) and Charlson Index  $\geq 3$  (OR 5.5 CI 1.5-20.06  $p < 0.01$ ). An inverse association was found with interventions to control the infectious focus (OR 0.3 CI 0.1-0.7  $p < 0.01$ ). The MIC of different antibiotics and the use of combined antibiotic therapy (triple therapy vs. double therapy or monotherapy) were not associated with mortality.

**Conclusions:** In patients with CRE infections, septic shock, a Charlson comorbidity index  $\geq 3$ , and post-chemotherapy febrile neutropenia are independently related to an increase in mortality. The control of the infectious focus is a protective factor. A rapid identification of these patients, and the implementation of measures to control infectious focus and to detect CRE colonization in patients who are going to be taken to myelosuppressive chemotherapy could impact positively the prognosis of these patients.

**Key words:** Carbapenemase; carbapenem resistance; combination therapy; meropenem MICs.

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### Introduction

Carbapenem-resistant *Enterobacteriaceae* (CRE) infections have become a public health problem worldwide, with increasing prevalence rates of both infection [1] and colonization [2]. In the United States [3] and Colombia [4], have been reported carbapenem resistance rates between 9% and 13% in patients with *Klebsiella pneumoniae* healthcare-related infections. The rates reported in Italy and Greece are even higher [5]. The problem is greater when considering that there are few therapeutic options for their management [6–9] and the high mortality rate reported, close to 40% [10–12].

It is very important to identify the modifiable factors associated with mortality, in order to generate strategies to optimize CRE infection management.

Different studies have identified some of these factors. Tumbarello showed that septic shock, bacteremia and high Acute Physiology And Chronic Health Evaluation (APACHE) scores are associated with an increase in mortality, while combined antibiotic therapy decreases it [11]. Other authors have reported an increase in mortality associated with the late onset of empirical antibiotic therapy [13], and the presence of critical diseases during hospital stay [14].

In Latin America we have little information, and it is important to weigh other factors possibly associated with mortality, such as the minimum inhibitory concentrations (MICs) of different antibiotics or the effect of combined therapy with two or more medications.

The objective of this study is to evaluate the association between mortality and known prognostic factors (septic shock, type of infection, empiric antibiotic therapy, chronic kidney disease). We also seek to determine whether there is an association with other factors that are frequently used to define the choice of antibiotics, such as MIC in carbapenems, the pattern of susceptibility to other therapeutic options, and combined therapy with three vs. fewer drugs, in a population with carbapenem-resistant *Enterobacteriaceae* infections.

## Methodology

An analytical observational study of cases and controls was designed, nested in a historical cohort. All patients with CRE infection admitted to the Hospital Universitario San Ignacio (HUSI) in Bogotá, Colombia, were identified between June 2013 and December 2018, using the HUSI microbiology database as a source of information. This database systematically collects the information of the microorganisms identified in patients managed at the emergency unit, the general hospitalization ward, and in the intensive care unit. The inclusion criteria were: 18 years of age or older, hospital stay > 72 hours, and microbiological isolation with carbapenemase producing *Enterobacteriaceae* defined by Hodge test or by positive boronic acid and EDTA synergy test. The presence of infection should be confirmed by at least two internal medicine specialists and/or by the Infectology unit, according with CDC (Centers for Disease Control) definitions (Supplementary Table 1). Patients with recurrent, polymicrobial infections or with colonization were excluded. The study was approved by the institutional ethics and research committee.

The data about the characteristics of the patients, comorbidity, antibiotic therapy used, clinical manifestations, and the complementary treatment used were taken from the institutional medical records, using a standardized and previously piloted format. The infection onset date was defined according to the date of index culture collection; the place of acquisition of the infection (community-acquired, healthcare-related or nosocomial) was defined according to the CDC criteria [15]. The type of infection was defined according to the sampling site and the clinical assessment. Interventions for the control of the infectious focus were defined as drainage of a collection, removal of osteosynthesis material or removal of central venous catheter.

Bacterial resistance evaluation was performed using *in vitro* microdilution techniques for meropenem,

confirmatory tests for the presence of carbapenemases, and *in vitro* microdilution studies for tigecycline, fosfomicin and colistin. We used Strains of *Escherichia coli* ATCC® 25922, and for carbapenemase phenotypic tests, we used *Klebsiella pneumoniae* ATCC® BAA-1705 (positive carbapenemases) and *Klebsiella pneumoniae* ATCC® BAA-1706 (negative carbapenemase). The MIC for meropenem, colistin, tigecycline and fosfomicin was determined by broth microdilution using MicroScan panels Ref. NC 66 (Beckman Coulter®) with an inoculum in McFarland 0.5 concentration. The MIC was read at 18-24 hours of incubation at 35°C. According with the Clinical and Laboratory Standards Institute (CLSI) 2017, the cut-off points for defining antibiotic resistance were: for meropenem (sensitive  $\leq 1$   $\mu\text{g/mL}$ ., intermediate 2  $\mu\text{g/mL}$ , resistant  $\geq 4$   $\mu\text{g/mL}$ ), fosfomicin (sensitive  $\leq 64$   $\mu\text{g/mL}$ , resistant  $> 64$   $\mu\text{g/mL}$ ), in the case of *Klebsiella*, *E. coli*, *Enterobacter cloacae* and *E. aerogenes*  $\leq 2$   $\mu\text{g/mL}$ . Considering that tigecycline does not have CLSI cut-off points, the interpretation was performed according to food and drug administration (FDA) recommendations (sensitive  $\leq 2$   $\mu\text{g/mL}$ , intermediate 4  $\mu\text{g/mL}$ , resistant  $\geq 8$   $\mu\text{g/mL}$ ). Supplementary Table 1 shows additional information regarding the quality control techniques for the sensitivity tests and the synergy tests used.

The outcome measured was mortality within the first month after the infection diagnosis, and was defined from the data recorded in the hospital's medical record, telephone calls, and the review of government sources (specifically from of the Solidarity and Guarantee Fund, FOSYGA, database).

The association between CRE infection and the factors under study was initially assessed by a univariate analysis, calculating ORs and 95% confidence intervals. Subsequently, a multivariate analysis was performed to identify independent risk factors using a logistic regression model, including the variables that showed statistically significant association  $p < 0.05$  in the univariate analysis, and using a stepwise backward methodology. The data were analyzed with the STATA 14 statistical package.

## Results

We identified 303 patients with CRE-positive cultures, 53 of which were excluded because they had polymicrobial or recurrent infections, and 119 because they had colonization. A total of 131 patients were finally included in the analysis. Table 1 shows the sociodemographic and clinical characteristics of the population. The majority of patients were men

(63.36%). Out of all, 68.7% had a Charlson comorbidity index  $\geq 3$ .

The majority of infections were nosocomial, n = 85 (64.89%). Table 1 shows the type of infection. The most frequent was bacteremia, with 43.51%, followed by urinary tract infection, with 30.53%. At the time of diagnosis, 21.37% of the patients presented septic shock. One hundred and seven participants (81.68%) had received prior antibiotic therapy.

Table 2 shows the microbiological characteristics, the bacterial resistance identified, and the treatment established. The most frequently isolated microorganism was *Klebsiella pneumoniae*, with a frequency of 64.89%. Out of all, 25.95% of the isolated microorganisms showed resistance to colistin. Of these,

**Table 1.** Sociodemographic and clinical characteristics of the patients included.

Variable	n = 131
<b>Male gender, n (%)</b>	83 (63.36%)
<b>Age in years, Median (IQR)</b>	58 (37-70)
<b>At admission, the patient came from, n (%)</b>	
Home	117 (89.31%)
Another hospital	13 (9.92%)
Nursing home	1 (0.77%)
<b>History, n (%)</b>	
Charlson comorbidity index $\geq 3$	90 (68.70%)
Sugery <sup>1</sup>	45 (34.35%)
Chronic kidney disease	34 (25.95%)
Mechanical ventilation <sup>1</sup>	29 (22.14%)
Dialysis	12 (9.16%)
Autologous BMT	6 (4.58%)
Allogeneic BMT	4 (3.05%)
Solid organ transplant	4 (3.06%)
<b>Place of acquisition of the infection, n (%)</b>	
Nosocomial	85 (64.89%)
Healthcare-associated	33 (25.19%)
Community	13 (9.92%)
<b>Type of infection<sup>2</sup>, n (%)</b>	
Bacteremia	57 (43.51%)
Intraabdominal	19 (14.50%)
Urinary tract infection	40 (30.53%)
Respiratory tract	14 (10.69%)
Soft tissues	13 (9.92%)
Bone	12 (9.16%)
Catheter-associated	10 (7.63%)
Bile duct	3 (2.29%)
Central nervous system	1 (0.76%)
<b>Clinical presentation, n (%)</b>	
Acute kidney injury	43 (32.82%)
Mechanical ventilation requirement <sup>1</sup>	29 (22.14%)
Febrile neutropenia	28 (21.37%)
Septic shock	28 (21.37%)
qSOFA $\geq 2$	19 (14.50%)

BMT: Bone marrow transplant; IQR: Interquartile range; <sup>1</sup> Thirty days before infection; <sup>2</sup> If the patient has multiple infections, they are all reported by the same germ.

**Table 2.** Microbiological characteristics and treatment established.

Microorganisms <sup>1</sup> , n (%)	
<i>Klebsiella pneumoniae</i>	85 (64.89)
<i>Enterobacter cloacae</i>	11 (8.40)
<i>Serratia marcescens</i>	10 (7.63)
<i>Enterobacter aerogenes</i>	9 (6.87)
<i>Eschericia coli</i>	7 (5.34)
<i>Klebsiella oxytoca</i>	4 (3.05)
<i>Citrobacter freundii</i>	4 (3.05)
<i>Providencia rettgeri</i>	1 (0.76)
<b>Targeted treatment, n (%)</b>	
Triple or quadruple therapy	60 (45.80)
Double therapy	57 (43.51)
Monotherapy	5 (3.82)
<b>Antibiotics used, n (%)</b>	
<b>Monotherapy</b>	
Meropenem	3 (2.29)
<b>Double therapy</b>	
Meropenem + colistin	39 (29.77)
Meropenem + tigecycline	9 (6.87)
Doripenem + colistin	4 (3.05)
Meropenem + ciprofloxacin	3 (2.29)
<b>Triple therapy</b>	
Meropenem + colistin + tigecycline	41 (31.30)
Meropenem + colistin + fosfomicin	8 (6.11)
Meropenem + tigecycline + ciprofloxacin	3 (2.29)
Meropenem + tigecycline + fosfomicin	2 (1.53)
Meropenem + fosfomicin + amikacin	1 (0.76)
Ertapenem + tigecycline + colistin	1 (0.76)
Meropenem + fosfomicin + gentamicin	1 (0.76)
<b>Quadruple therapy</b>	
Meropenem + colistin + tigecycline + fosfomicin	2 (1.53)
<b>Minimum inhibitory concentration, <math>\mu\text{g/mL}</math>, n (%)</b>	
Meropenem MIC	
$\leq 8$	30 (22.90)
$> 8$	101 (77.10)
Tigecycline MIC, n, (%)	
$< 8$	126 (96.92)
$> 8$	4 (3.08)
Fosfomicin MIC, n, (%)	
$\leq 64$	79 (60.31)
$> 64$	52 (39.69)
Colistin MIC, n, (%)	
$\leq 2$	97 (74.05)
$\geq 4$	34 (25.95)
<b>Empiric antibiotic therapy</b>	
No	95 (72.52)
Yes	36 (27.48)
<b>Start time of appropriate antibiotic therapy</b>	
More than 72 hours	83 (63.36)
Less than 72 hours	48 (36.64)
<b>Infectious focus control<sup>2</sup>, n (%)</b>	
Not required	55 (49.62)
Yes	45 (34.35)
No	21 (16.03)

<sup>1</sup> If the patient has multiple infections, they are all reported by the same germ; <sup>2</sup> Defined as drainage of the collection, removal of osteosynthesis material or removal of central venous catheter.

10 microorganisms (7.63%) corresponded to *Serratia marcescens*, which presented intrinsic resistance. Forty-five patients (34.4%) received measures to control the infectious focus.

In total, there were 50 cases of mortality (38.17%). Nine patients died before germ isolation was available. Seven patients never received appropriate targeted antibiotic therapy (adjusted for isolates and sensitivity profile), because at that time of death the physician did not have the antibiogram report or because it was decided not to escalate the treatment, due to the patient’s clinical situation. The most commonly used combined treatment was meropenem, colistin and tigecycline.

In the univariate analysis there was an increase in the risk of mortality associated with the presence of fosfomycin resistance (OR 2.2 95% CI 1.1-4.7  $p = 0.03$ ), and the use of triple antibiotic therapy vs double therapy or monotherapy (OR 2.39 95% CI 1.10-5.19  $p = 0.03$ ). Likewise, an association was found between mortality and septic shock (OR 17 CI 5.6-56  $p < 0.01$ ), prior antibiotic treatment (OR 5.4 95% CI 1.5- 19.4  $p < 0.01$ ), febrile neutropenia (OR 2.7 CI 1.1-6.3  $p = 0.02$ ), mechanical ventilation in the 30 days prior to infection (OR 4.4 CI 1.8-10.4  $p < 0.01$ ), Charlson index  $\geq 3$  (OR 3.61 CI 1.50-8.67  $p < 0.01$ ) and qSOFA  $> 2$  (OR 3.38 CI 1.23-9.31  $p = 0.02$ ). The establishment of therapeutic measures to control the infectious focus had an inverse association with mortality (OR 0.4 CI 0.2-0.6  $p < 0.01$ ) (Table 3).

In the multivariate analysis, an independent direct association was found between mortality and septic shock (OR 26.7 CI 6.6 - 107.3  $p < 0.01$ ), post-chemotherapy febrile neutropenia (OR 3.3 CI 1.06 – 10.8  $p = 0.04$ ) and Charlson Index  $\geq 3$  (OR 5.5 CI 1.5-20.06  $p < 0.01$ ). On the contrary, an inverse association was found with the implementation of interventions to control the infectious focus (OR 0.3 CI 0.1- 0.7  $p < 0.01$ ) (Table 3). The MIC and the use of combined antibiotic therapy (triple therapy vs. double therapy or monotherapy) lost statistical significance after adjustment for confounding variables.

**Discussion**

Our study evaluates the factors associated with 30-day mortality in patients with CRE infections. The factors identified in our study were: septic shock at the time of diagnosis, post-chemotherapy febrile neutropenia, Charlson comorbidity index greater than or equal to 3, and absence of therapeutic measures to control the infectious focus. We also evaluated the impact of MICs for different antibiotics or the use of triple therapy vs. double therapy or monotherapy, and we did not find that these factors were independently associated with mortality. However, it is noteworthy that only 2.29% of patients received monotherapy, and 100% of the schemes incorporated a carbapenem.

We found a high mortality rate of 38%, very similar to that reported in previous studies [11,12], which highlights the importance of CRE infections in Colombia and Latin America. With respect to the

**Table 3.** Univariate and multivariate analysis.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Charlson index ( $\geq 3$ )	3.61 (1.50 - 8.67)	0.004	5.5 (1.5 - 20.06)	0.009
Bacteremia	1.5 (0.7 - 3.11)	0.240		
UTI* vs. Infection in other sites	4.2 (1.6 - 10.5)	0.002		
Respiratory infection vs. Infection in other sites	3.3 (1.0 - 10.6)	0.041		
Acute kidney injury	1.9 ( 0.9 - 4.1)	0.081		
Mechanical ventilation	4.4 (1.8 - 10.4)	0.001	6.6 (2.1 - 19.2)	0.001
Febrile neutropenia	2.7 (1.1 - 6.3)	0.022	3.3 (1.06 - 10.8)	0.039
Septic shock	17 (5.6 - 56)	$< 0.001$	26.7 (6.6 - 107.3)	0.000
qSOFA ( $\geq 2$ )	3.38 (1.23 - 9.31)	0.018		
Previous antibiotic treatment	5.4 (1.5 - 19.4)	0.009		
Control of infectious focus	0.4 (0.2 - 0.6)	0.001	0.3 (0.1 - 0.7)	0.004
Appropriate empiric antibiotic therapy	0.5 (0.2 - 1.2)	0.135		
Start time of appropriate antibiotic therapy	0.6 (0.3 - 1.01)	0.058		
Type of targeted treatment (3 antibiotics vs 1 or 2)	2.39 (1.10 - 5.19)	0.027		
Colistin MIC	0.4 (0.2 - 1.1)	0.106		
Tigecycline MIC	0.5 (0.1 - 5)	0.58		
Meropenem MIC	1.9 (0.7 - 4.8)	0.14		
Fosfomycin MIC	2.2 (1.1 - 4.7)	0.025		

\*UTI Urinary tract infection.

factors associated with mortality, our findings are compatible with those reported in the literature for both bacteremia and for infections of specific focuses by Carbapenem-resistant *Klebsiella pneumoniae*, where the presence of septic shock was a factor strongly associated with mortality [11,12]. It is necessary to quickly identify these patients, accelerate as much as possible the identification of the causative agent and establish appropriate support measures with adequate therapeutic regimen.

The presence of febrile neutropenia was independently associated with mortality. These data highlight the importance of establishing measures to detect CRE colonization in patients who are going to be taken to myelosuppressive chemotherapy, especially taking into account that an incidence of CRE infections of 14%, and a mortality greater than 50% have been reported in patients with hematological malignancies, considering this group of patients at high risk of mortality [16].

Bacteremia was the most frequent infection in our study. However, it had no statistically significant association with mortality when compared to other infection sites [17]. This differs from the results of previous studies (12), and suggests that importance should be given to all CRE infections, regardless of the focus where they are detected. Likewise, we did not find an independent association between mortality and a history of chronic kidney disease, which may be secondary to the severity of the underlying renal pathology, if we consider that in our study the proportion of patients that required dialysis before the onset of the infectious process (9.16%) was lower than that reported in previous studies [12,13,18].

Our data also highlights the importance of intervening quickly to control the infectious focus, which includes draining collections and removing catheters in cases of device-associated bacteremias.

Unlike what has been reported in previous studies (5), our analysis did not show that a meropenem MIC equal to or greater than 8 µg/mL was associated with higher mortality or resistance for other antibiotics such as fosfomycin, colistin or tigecycline.

In our sample, only 2.29% of patients received monotherapy, while 41.98% and 43.51% received double and triple therapy, respectively. The foregoing corresponds to the policy established in our institution to give combined therapy to patients with CRE infections based on previous studies that suggest that mortality is higher in patients with monotherapy [12]. For this reason, it was not possible to evaluate the impact on mortality of monotherapy use. In the

univariate analysis, it was noted that the use of combined antibiotic therapy with three drugs could be associated with higher mortality than double therapy. However, this association lost statistical significance after the multivariate analysis adjustment for confounding variables. This suggests that patients with more comorbidities or with more severe clinical manifestations at admission (e.g., septic shock) are most frequently given triple therapy, and that these conditions are the ones that increase mortality. Similar findings were reported by Ghafur *et al.*, who found no statistically significant differences between monotherapy and combination therapy [19].

There are limitations that must be taken into account. We could not evaluate the patients' APACHE score at the beginning, since we did not have the necessary information to calculate it, because it was a retrospective study. However, the documented association with septic shock suggests that the severity of the clinical presentation at admission is an important marker of mortality. Finally, the study design has limitations to assess the impact of triple vs. double therapy on the mortality of these patients, so randomized clinical experiments evaluating these therapies will be required.

## Conclusions

In patients with carbapenem-resistant *Enterobacteriaceae* infections, septic shock, a Charlson comorbidity index greater than or equal to 3, and post-chemotherapy febrile neutropenia are independently related to an increase in mortality. The control of the infectious focus is related as a protective factor. Our data suggest that there is no significant relationship between carbapenem MIC and mortality.

## Authors' contributions

SG, OMV, SV, BA contributed to research idea and study design; SG, SV, MV, DR, BA, GC, DS contributed to data collection, OMV, MV, DR, YP, AN contributed to data analysis, all authors interpreted results, MV, DR, YP, AN wrote the initial version of the manuscript, all authors critically revised the manuscript and may be held accountable for their contents.

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**Conflict of interests:** No conflict of interests is declared.

**Annex – Supplementary items****Supplementary Table 1.** Cut-off points to define antibiotic resistance, quality control techniques of the sensitivity tests, and synergy tests used.

<b>Variable</b>	<b>Operational definition</b>
Septic shock	Sepsis associated with organic dysfunction and persistent hypotension despite volume replacement (20)
Community-acquired infection	According to CDC definition: (15) - Infection that appears 48 hours or more before hospital admission, in people without previous contact with the hospital environment.
Healthcare-associated Infection	According to CDC definition: (15) - Infection that appears within 48 hours of admission if the patient has received specialized home care (intravenous therapy, wound clinic or home nursing)
Nosocomial infection	According to CDC definition: (15) - Infection that appears after 48 hours or more from hospital admission
Healthcare-associated Infection	According to CDC definition: (15) - Infection that appears after 48 hours or more from hospital admission or within 48 hours of admission if the patient has received specialized home care (intravenous therapy, wound clinic or home nursing)
Quality control of antimicrobial sensitivity tests	Strains of <i>E. coli</i> ATCC® 25922 were used, and for carbapenemase phenotypic tests <i>Klebsiella pneumoniae</i> ATCC® BAA-1705 (positive carbapenemases) and <i>Klebsiella pneumoniae</i> ATCC® BAA-1706 (negative carbapenemase) were used. A modified Hodge test was performed as a phenotypic confirmatory test for the presence of carbapenemases based on a McFarland 0.5 suspension of <i>Escherichia coli</i> ATCC 25922, which was diluted 1:10 to subsequently perform a massive seeding in Mueller Hinton agar. Starting with the ertapenem disk (10 µg), the problem microorganism and the above mentioned positive and negative <i>Klebsiella pneumoniae</i> controls were traced. The reading was made at 16-20 hours of incubation at 35°C, interpreting that a positive result is evidenced by the growth of the ATCC 25922 <i>E. coli</i> strain at the intersection part between the inhibition halo generated by the diffusion of the antibiotic and the stretch mark of the problem isolation forming a cleft in the part next to the disk and being interpreted as the presence of carbapenemases (positive result) (21).
Synergy tests	For the same purpose, boronic acid synergy and EDTA tests were carried out using imipenem (10 µg), meropenem (10 µg), boronic acid (300 µg) and EDTA sensidisks, with a distance of 15 mm between them on the massive seeding of the problem microorganism, incubated for 16-20 hours at 35°C in Mueller Hinton agar. Synergy was sought among the disks in which a deformity in the inhibition halos was evidenced and in this way the result was positive, and those in which no synergy was evidenced were reported as negative (22).