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Mortality-related factors in patients with OXA-48 carbapenemase-producing *Klebsiella pneumoniae* bacteremia

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Abstract

Carbapenemase-producing Enterobacterales constitute a serious public health threat; however, information on the oxacilinasa (OXA-48)-type is limited. The objective of the study was to evaluate the risk factors associated with 14-day mortality for patients with bacteremia due to OXA-48 carbapenemase-producing *Klebsiella pneumoniae*.

We conducted a retrospective, single-center observational study of adult patients with *K. pneumoniae* bacteremia, classifying the strains as carbapenem-susceptible *K. pneumoniae* (CSKp) and carbapenem-resistant *K. pneumoniae* (CRKp). All of the CRKp strains were the OXA-48-type.

The study included 202 cases of bacteremia: 114 due to CSKp and 88 due to CRKp. The clinical cure rate was higher for the patients with CSKp (85% vs 69% for CSKp and CRKp, respectively; $P = .010$), while the 14-day mortality rate was lower (13% vs 30%, $P = .005$). An INCREMENT-CPE score ≥7 (HR 3.05, 95% CI 1.50–6.25, $P = .002$) was the only independent factor associated with 14-day mortality for the patients with *Klebsiella* spp. bacteremia. Other factors related to 14-day mortality were a rapidly fatal prognosis (McCabe) (HR 7.1, 95% CI 2.75–18.37, $P < .001$), dementia (HR 5.9, 95% CI 2.0–7.43, $P = .001$), and a high-risk source of infection (HR 2.7, 95% CI 1.06–6.82, $P = .038$).

The most important factors associated with 14-day mortality for the patients with *K. pneumoniae* bacteremia was an INCREMENT-CPE score ≥7, dementia, a McCabe score indicating a rapidly fatal prognosis and a high-risk source of infection. We found no relationship between a poorer outcome and CRKp isolation or inadequate antibiotic therapy.

Abbreviations: CRKp = carbapenem-resistant *Klebsiella pneumoniae*, CSKp = carbapenem-susceptible *Klebsiella pneumoniae*, ESBL = extended-spectrum beta-lactamases, GES = Guiana extended spectrum, IMI = imipenem-hydrolyzing β-lactamase, IMP = active on imipenem, IQR = interquartile range, KPC = *Klebsiella pneumoniae* carbapenemase, MB = metallo-β-lactamase, MIC = minimum inhibitory concentration, NDM = New Delhi metallo-beta-lactamase, OXA-48 = oxacilinasa, VIM = Verona integron-encoded metallo-β-lactamase.

Keywords: bacteremia, carbapenemase-producing, *Klebsiella pneumoniae*, mortality, OXA-48-type

1. Introduction

Bacteremia caused by gram-negative bacilli is common, both in community-acquired and healthcare-associated infections, and has high morbidity and mortality.[1] Although *Escherichia coli* is the most frequently implicated etiological agent,[2] there has been a worldwide increase in bacteremia due to other Enterobacterales, especially resistant strains of *Klebsiella pneumoniae*.[3] These resistant strains are usually linked to healthcare-associated infections and represent a significant challenge due to their limited therapeutic options.[4,5]

These bacteria's main resistance mechanisms are the production of extended-spectrum β-lactamases and carbapenemases. Various types of carbapenemases have been described including class A (e.g., *K. pneumoniae* carbapenemase [KPC], Guiana extended spectrum [GES], imipenem-hydrolyzing β-lactamase [IMI]), class B or metallo-β-lactamase (MBL) (e.g., Verona integron-encoded metallo-β-lactamase [VIM], active on imipenem [IMP], New Delhi metallo-beta-lactamase [NDM]), and class D (mainly oxacilinasa [OXA-48]).[6] The KPC-types have the most extensive global distribution, follow by MBL and OXA-48.[6] Since the first description of OXA-48 carbapenemase in Turkey in 2004, these strains have been extensively reported in

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

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nosocomial outbreaks in many parts of the world, particularly in the Mediterranean area.[6] In Spain, the first hospital outbreak due to OXA-48-type carbapenemase-producing *K. pneumoniae* was identified in Barcelona in 2009,[7] and this type of carbapenemase is still the most common in Spain.[6]

In most published studies on this topic, isolates of KPC-carbapenemase-producing strains are predominant[4,8–11]; however, the clinical information on OXA-48-type infections is scarce.[12–14] We also do not know whether the clinical characteristics, response to treatment, and disease evolution differ among the various types of carbapenemase. The aim of this study was to compare the mortality rate of patients with OXA-48-carbapenemase-producing bacteremia with that of patients with carbapenem-susceptible *K. pneumoniae* (CSKp) bacteremia. The secondary objectives were to study the risk factors associated with 14-day mortality for patients with *K. pneumoniae* bacteremia and risk factors for acquiring carbapenem-resistant *K. pneumoniae* (CRKp) bacteremia.

2. Methods

We conducted a retrospective, single-center observational study at the University Hospital of Vigo, a 1200-bed tertiary teaching hospital. The study included all adult patients (≥18 years old) with *K. pneumoniae*-positive blood cultures between January 2017 and December 2018. Blood cultures were performed for patients with fever or signs of sepsis. Only the first episode of *K. pneumoniae* bacteremia was included in the study. We also collected the patients' clinical and epidemiological characteristics: age, sex, antibiotic treatment during the previous 90 days, invasive procedures performed in the previous month (urinary catheterization, temporary or permanent central venous catheter, peripheral catheter, parenteral nutrition, surgical intervention, endoscopic procedure).

We employed the Charlson index[15] and McCabe score[16] to assess the patients' comorbidity. The severity and prognosis of the infection was established according to the Pitt index[17] and INCREMENT-CPE score,[18] which were measured on the first day of the bacteremia. Likewise, the patients were classified according to whether or not they presented sepsis or septic shock, according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria.[19]

Infection was classified as community-acquired, healthcare-associated or nosocomial, according to Friedman's criteria.[20] We classified patients with pneumonia, an abdominal source, or primary bacteremia as having a high-risk source, and considered urinary and biliary as low-risk sources. The empiric and targeted antibiotic therapy were recorded and classified as adequate or not. We considered that the patients had undergone adequate targeted antibiotic therapy when they underwent proper therapy within 72 hours of drawing the blood cultures. We considered the therapy to be CSKp-appropriate when at least 1 of the antibiotics was active in vitro. For the patients with CRKp bacteremia, we considered the adequacy of the therapy based on the source: low-risk source when there was at least 1 active antibiotic. For the other patients, the combination of 2 active drugs was necessary, one of them a carbapenem (provided the minimum inhibitory concentration [MIC] was <8 μg/mL)[8,10,21] or when they underwent monotherapy with ceftazidime–avibactam. Meropenem, with a dose of 2 g every 8 hours in extended-infusion was the first therapeutic option. Imipenem, 1 g every 6 hours in extended-infusion, was used when meropenem MIC was >8 μg/mL and imipenem MIC was ≤8 μg/mL.

Clinical cure was defined as the absence of signs of infection (fever, leukocytosis, elevation of acute phase reactants) after a week of antibiotic therapy.[22] Recurrence was defined as the appearance of clinical symptoms of infection and isolation of the same microorganism in the blood cultures, within 2 weeks after the end of the antibiotic therapy. Reinfection was defined as the presence of clinical signs of infection and isolation of the same microorganism, more than 2 weeks after the end of the antibiotic therapy. Related death was considered when the cause of death was the bacteremia.

2.1. Ethical approval

When conducting the study, we followed the indications of the Declaration of Helsinki, and the study was evaluated and approved by the regional ethics committee (2017/336). Informed consent was not required, due to the retrospective design of the study.

2.2. Microbiology

For species identification and susceptibility testing, we employed the Vitek 2 system (bioMérieux, Marcy l'Etoile, France), classifying isolates as extended-spectrum beta-lactamases (ESBL) producers based on positive Vitek 2 ESBL results. All isolates were retested using the combination disc diffusion test with cefotaxime with or without clavulanic acid and ceftazidime with or without clavulanic acid, as well as the double ESBL Etest (bioMérieux) strip to confirm the ESBL status.[23]

We performed the carbapenemase detection following the European Committee on Antimicrobial Susceptibility Testing protocol: a meropenem disc diameter < 28 mm or an MIC > 0.125 mg/L in all Enterobacteriaceae.[24] We performed the confirmation with ChromID CARBA SMART medium (BioMérieux) and determined the type of carbapenemase by PCR (Cepheid Xpert Carba-R, Sunnyvale, CA). There was no change in the method used for identifying the microorganisms or analyzing antibiotic susceptibility during the study period. We determined the bacteria's susceptibility to ceftazidime/avibactam using the disc diffusion method as described elsewhere.[25] A disc diffusion zone diameter ≥21 mm was interpreted as susceptible (equivalent to an MIC < 8/4 mg/L for ceftazidime/avibactam). All of the CRKp strains were the OXA-48-type. Our hospital has endemicity of an extremely resistant OXA-48 strain since 2015. During the period of study, we have only an isolation of KPC-3 *K. pneumoniae*, that it was not included in the analysis.

2.3. Statistical analysis

Continuous variables are presented as mean ± standard deviation or as median and interquartile range (IQR), depending on whether the variables' distribution was normal or not. We employed Student's *t* test or the Mann–Whitney *U* test for the comparison, according to the variables' distribution. Categorical variables are presented as percentage (%) and were compared using the chi-squared test (χ^2) or Fisher's Exact Test, as appropriate.

For the analysis of the factors associated with CRKp infection, we compared only the healthcare-associated and nosocomial-associated bacteremia, because no community-acquired CRKp bacteremia was identified. We performed a multivariate analysis using logistic regression to identify the factors related to acquire CRKp bacteremia.

For the analysis of the mortality-associated factors, we excluded those patients for whom the therapeutic effort was limited (e.g., patients with a poor short-term prognosis and for whom antimicrobial therapy was not administered). We employed a Cox regression to analyze the factors related to mortality within 14 days after the bacteremia. In the multivariate analysis, we included all variables that had a *P*-value < .2 in the univariate analysis. Variables with a $P < .05$ were considered statistically significant.

We employed the Statistical Package for the Social Sciences (SPSS version 24) for the statistical analysis.

Table 1

Clinical characteristics of patients with *Klebsiella pneumoniae* bacteremia.

	CSKp (n = 114)	CRKp (n = 88)	*P*
Age > 70 yr*	46 (40)	40 (46)	.477
Male sex	74 (65)	61 (70)	.549
Comorbidities			
Heart failure	25 (22)	35 (40)	.008
Dementia	5 (4)	14 (16)	.007
Diabetes mellitus	25 (22)	29 (33)	.108
Solid tumor	40 (35)	27 (31)	.549
Hematological cancer	6 (5)	13 (14)	.027
Metastatic neoplasia	19 (17)	3 (3)	.003
Charlson index ≥ 3	57 (50)	48 (55)	.571
McCabe index			
Non-fatal	66 (58)	41 (47)	.126
Ultimately fatal	30 (26)	35 (40)	
Rapidly fatal	18 (16)	12 (14)	
Previous antimicrobial therapy	67 (59)	84 (96)	<.001
Cephalosporins	24 (21)	49 (56)	<.001
Carbapenem	9 (8)	37 (42)	<.001
Quinolone	16 (14)	44 (50)	<.001
Acquisition type			
Community	32 (28)	0	<.001
Nosocomial	57 (50)	65 (74)	.001
Healthcare	24 (21)	23 (26)	.407
Admission to a ward with CRKp outbreak	35 (31%)	67 (76%)	<.001
Previous admission for ≥20 d	26 (24)	40 (50)	<.001
Type of service			<.001
Critical care	10 (9)	32 (36)	
Medical	79 (69)	47 (53)	
Surgical	25 (22)	9 (10)	
Previous procedures			
Urinary catheter	31 (27)	43 (49)	.002
Central venous catheter	28 (25)	48 (55)	<.001
Peripheral catheter	55 (48)	42 (48)	1
Parenteral nutrition	4 (4)	4 (5)	.729
Surgery	19 (17)	22 (25)	.158
Source of infection			
Urinary	43 (38)	34 (39)	1
Catheter	20 (18)	23 (26)	.166
Respiratory	7 (6)	14 (16)	.035
Abdominal	30 (26)	9 (10)	.004
Unknown	14 (12)	8 (9)	.504
High-risk source	21 (18)	22 (25)	.300
Severity of infection			
Pitt index > 2	38 (33)	43 (49)	.030
Septic shock	38 (33)	42 (48)	.043
INCREMENT-CPE score ≥ 7	33 (29)	42 (48)	.008
Adequate treatment			
Empirical	108 (95)	32 (36)	<.001
Targeted	111 (97)	70 (80)	<.001

CPE = carbapenemase-producing Enterobacteriaceae, CRKp = carbapenem-resistant *Klebsiella pneumoniae*, CSKp = carbapenem-susceptible *Klebsiella pneumoniae*.
* All values are presented n (%).

3. Results

The study included 202 cases of bacteremia: 114 CSKp and 88 CRKp. Table 1 shows the patients' clinical characteristics. There was a high rate of comorbidities in both groups, although the patients with CRKp had more frequent heart failure and dementia and less frequent metastatic neoplasia. Previous antibiotic use was more frequent in the patients with CRKp bacteremia (59% vs 95% for CSKp and CRKp, respectively; $P < .001$), especially the use of cephalosporins (21% vs 56%, $P < .001$).

Nosocomial acquisition was most frequent in the patients with CRKp bacteremia (50% vs 75% for CSKp and CRKp, respectively; $P < .001$), and there were no cases of community infection by CRKp. The urinary source was the most common for both groups (38% vs 39%, $P = .884$), followed by catheter-related bacteremia (18% vs 26%, $P = .165$). There was a significant difference between the 2 groups in the respiratory (6% vs 15%, $P = .056$) and abdominal source (26% vs 10%, $P = .006$).

Patients with CRKp bacteremia had a more severe disease. Both the Pitt index (Pitt index > 2, 33% vs 48% for CSKp and CRKp, respectively; $P = .042$) and the rate of septic shock (33% vs 47%, $P = .058$) were higher in the patients with CRKp. The INCREMENT-CPE score was also higher in the patients with CRKp bacteremia (INCREMENT-CPE score ≥ 7, 29% vs 48%, $P = .008$).

The clinical cure rate was higher for the patients with CSKp bacteremia, while the rates of recurrence and reinfection were lower (Table 2). In contrast, a higher mortality rate was observed in the patients with infection produced by resistant strains, as well as a higher rate of infection-related mortality.

3.1. Antimicrobial therapy

Appropriate empirical (95% vs 36% for CSKp and CRKp, respectively; $P < .001$) and targeted therapy (97% vs 80% for CSKp and CRKp, respectively; $P < .001$) were most frequent in CSKp group. The median of appropriate antimicrobial therapy was lower in CPKp group (12 days [IQR 9–14] vs 10 days [5–14], CSKp and CPKs, respectively; $P = .002$).

The antimicrobials used as targeted therapy in CSKp patients were amoxicillin/clavulanic acid (33 patients, 29%), cephalosporins (22 patients, 28%), carbapenems (22 patients, 19%),

Table 2

Outcome of patients with *Klebsiella pneumoniae* bacteremia.

	CSKp (n = 114)	CRKp (n = 88)	*P*
Clinical cure	97 (85)	61 (69)	.010
Recurrence	4 (4)	9 (10)	.080
Reinfection	24 (21)	28 (32)	.104
14-d mortality	15 (13)	26 (30)	.005
Infection-related mortality	13 (11)	28 (32[)	.034

* All values are presented n (%).

Table 3

Univariate and multivariate analysis of 14-d mortality-related factors in patients with *Klebsiella pneumoniae* bacteremia.

	N (%)	Univariate analysis RR (95% CI)	P	Multivariate analysis HR (95% CI)	P
Age >70 yr		1.96 (1.02–3.77)	.047		
Yes	18 (23)				
No	13 (12)				
McCabe index					
Non-fatal	10 (10)	Ref.			
Ultimately fatal	11 (18)	1.88 (0.85–4.15)	.147	7.10 (2.75–18.37)	<.001
Rapidly fatal	10 (39)	4.00 (1.86–8.62)	.001		
Dementia		2.62 (1.27–5.43)	.027	5.9 (2.0–17.43)	.001
Yes	6 (36)				
No	25 (14)				
Catheter-related bacteremia		0.39 (0.13–1.23)	.096		
Yes	3 (7)				
No	28 (19)				
High-risk source		2.05 (1.06–3.97)	.046	2.7 (1.06–6.82)	.038
Yes	10 (28)				
No	21 (14)				
Septic shock		3.14 (1.60–6.17)	.001		
Yes	20 (29)				
No	11 (9)				
INCREMENT-CPE score ≥ 7		2.75 (1.44–5.23)	.003	3.05 (1.50–6.23)	.002
Yes	18 (28)				
No	13 (10)				
CRKp bacteremia		2.20 (1.13–4.26)	.027		
Yes	19 (24)				
No	12 (11)				
Adequate empirical treatment		1.08 (0.51–2.25)	1		
Yes	23 (17)				
No	8 (15)				
Adequate targeted treatment		0.52 (0.19–1.41)	.209		
Yes	28 (16)				
No	3 (30)				

quinolones (9 patients, 8%), others (18 patients 16%). Combination therapy, with aminoglycoside or Gram-positive coverage, was used in 10 patients (10%).

Most of the strains in our study had a meropenem MIC ≥ 32 mg/L. For this reason, imipenem was the antimicrobial most commonly used in patients con CRKp strains (50 patients, 57%; 44 of them in combination). Ceftazidime–avibactam was used in 19 patients (22%, only 1 in combination) and meropenem in 7 patients (8%, all of them in combination). Other antimicrobials were used in 12 patients (14%).

3.2. Factors associated with mortality at 14 days for the patients with K. pneumoniae bacteremia

For the analysis of mortality-related factors, we excluded 11 patients with limitation of therapeutic effort. Table 3 shows the results of the univariate and multivariate analysis for 14-day mortality-related factors. An INCREMENT-CPE score ≥ 7 (HR 3.05, 95% CI 1.50–6.23, $P = .002$) was the only factor associated with mortality at 14 days. After separately analyzing the variables included in the INCREMENT-CPE score, the independent factors associated with 14-day mortality were a rapidly fatal prognosis (McCabe) (HR 7.1, 95% CI 2.75–18.37, $P < .001$), dementia (HR 5.9, 95% CI 2.0–17.43, $P = .001$), and a high-risk source (HR 2.7, 95% CI 1.06–6.82, $P = .038$). We found no association between mortality and a Pitt index > 2, CRKp isolation, or inadequate antimicrobial treatment (both empirical and targeted).

3.3. Factors associated with carbapenemase-producing K. pneumoniae bacteremia

Table 4 shows the risk factors associated with CRKp bacteremia. Admission to a unit with a CRKp outbreak (OR 7.98, 95% CI 3.64–17.48, $P < .001$), previous antibiotic treatment (OR 8.55, 95% CI 2.23–32.77, $P = .002$), and a hospital stay longer than 21 days during the previous year (OR 2.34, 95% CI 1.08–5.27, $P = .031$) was associated with CRKp.

4. Discussion

This study is the largest series to analyze the clinical features and outcome of patients with bacteremia due to OXA-48-type CRKp. Several studies have found higher mortality rates in patients with CRKp isolates[26–32] ranging from 44% to 72%. These studies presented a critical limitation, because the appropriate cut-off (MIC < 8 μg/mL) for the use of carbapenems in treating CRKp was unknown.[31] In other studies, carbapenem-based combined treatment was not employed.[8,10] Moreover, new highly active drugs against CRKp, such as ceftazidime/avibactam, were not employed.

In our study, imipenem was the most frequent carbapenem used in patients with CRKp, due to a highly resistant strain that shown lower MIC for imipenem than to meropenem. We applied the published recommendations of MIC cut-off for meropenem.[10,21] We observed a shorter duration of antimicrobial therapy in patients with CRKp. Recently, different studies have shown that short- (7–10 days) are as effective as long-course

Table 4

Risk factors related to carbapenem-resistant *Klebsiella pneumoniae* bacteremia.

	N (%)	Univariate analysis RR (95% CI)	*P*	Multivariate analysis OR (95% CI)	*P*
Age > 70		1.35 (1.01–1.79)	.058		
Yes	40 (62)				
No	48 (46)				
Admission to a ward with CRKp outbreak		2.83 (1.93–4.17)	<.001	7.98 (3.64–17.48)	<.001
Yes	67 (74)				
No	21 (26)				
Heart failure		1.42 (1.07–1.88)	.022		
Yes	35 (65)				
No	53 (46)				
Dementia		1.70 (1.29–2.14)	.010		
Yes	14 (82))				
No	74 (48)				
Diabetes mellitus		1.32 (0.99–1.77)	.085		
Yes	29 (63)				
No	59 (48)				
Neoplasia		0.73 (0.52–1.02)	.059		
Yes	27 (42)				
No	61 (58)				
Previous antimicrobial therapy		4.88 (1.93–12.35)	<.001	8.55 (2.23–32.77)	.002
Si	84 (61)				
No	4 (13)				
Previous admission for ≥20 d		1.36 (1.03–1.81)	.043	2.34 (1.08–5.27)	.031
Yes	45 (45)				
No	43 (61)				

treatments (>10 days).[33,34] Patients with CRKp strains received a higher supervision from infectious diseases specialist, that could collaborate to a more adequate duration of therapy.

We found a study in which CRKp strains were not related to higher mortality.[35] However, the mortality was analyzed at 30 days, and most of the other studies analyzed in-hospital or 14-day mortality. The study also draws attention to the high mortality of patients with bacteremia due to susceptible strains (29%), a rate much higher than that observed in our study (13%) and others (13–20%).[27–31] We observed a higher mortality rate in the patients with CRKp, but this increase in mortality was associated with more severe disease, rather than the microbiological characteristics.

Other mortality factors associated with CRKp include age, comorbidity, infection severity, infection source, source control, and adequate treatment.[26,29–32,35] Many of these factors are included in the validated mortality scale INCREMENT-CPE.[18] By separately analyzing the variables included in the INCREMENT-CPE scale, we found that a rapidly fatal McCabe score, dementia, and a high-risk source were the most important factors related to 14-day mortality.

As with other studies,[8,11,26,35] our study found no association between mortality and adequate antibiotic treatment, while several studies have found an association between inadequate treatment and higher mortality.[10,21,36,37] Most of these studies were performed before the combined carbapenem-based regimen was recommended[10] and, of course, before the use of ceftazidime–avibactam. In our study, the percentage of adequate treatment among the patients with CRKp bacteremia was high (80%). Moreover, 19 of the 88 patients with CRKp bacteremia underwent ceftazidime–avibactam therapy, and the mortality rate was 8%, which was similar for the patients with CSKp (data not shown).

We also analyzed the factors associated with the onset of CRKp. As in previous studies, the use of antibiotics in the previous 90 days was related to an increased risk of CRKp bacteremia.[11,27,35,38] A recent study showed an increased risk of acquiring a CRKp infection for each day meropenem (OR 1.18), cefepime (OR 1.22), and ciprofloxacin (OR 2.37) were administered.[39] As with other studies,[14,28,29] we found a greater likelihood of bacteremia due to CRKp in those patients admitted to a ward with a CRKp outbreak, which could be related to several factors include greater patient fragility (immunosuppression, greater comorbidity), higher use of antibiotics, and invasive procedures.[27,40,41] We also found an increased risk of CRKp bacteremia in patients with a hospital stay exceeding 20 days during the previous year. Prolonged hospital stay is also a recognized CRKP infection risk factor.[14,30]

Our study has several limitations, the most significant of which is its single-center and retrospective nature. Moreover, we could not perform PFGE analysis to establish a clonal relation among the collected strains. Finally, the molecular method employed, Cepheid Xpert Carba-R, exhibit certain limitations to detect IMP-type variants. These variants are really uncommon in Spain.[13] On the other hand, we did not find any strain in which the mechanism of resistance type was not recognized by the method used in the study.

This study has the largest OXA-48-type CRKp bacteremia series, and the number of patients who underwent inadequate targeted therapy was low (21 patients, 10%), which prevented us from demonstrating the impact of inadequate therapy on mortality.

In conclusion, this retrospective study shows that INCREMENT-CPE score > 7, rapidly fatal McCabe score, dementia, and a high-risk source of infection were the most important factor related with 14-day mortality for the patients with *K. pneumo-*

niae bacteremia. Identification of these risk factors upon admission could help to select patients who should receive early adequate antibiotic treatment. On the other hand, we could not find association between 14-day mortality and the isolation of carbapenemase-producing strains or inadequate antibiotic therapy, that were previously related with poor prognosis.

Author contributions

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