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CLINICAL THERAPEUTICS

Mortality Associated with Bacteremia Due to Colistin-Resistant *Klebsiella pneumoniae* with High-Level Meropenem Resistance: Importance of Combination Therapy without Colistin and Carbapenems

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ABSTRACT Combination therapy including colistin and a carbapenem has been found to be associated with lower mortality in the treatment of bloodstream infections (BSI) due to KPC-producing *Klebsiella pneumoniae* when the isolates show a meropenem or imipenem MIC of <16 mg/liter. However, the optimal treatment of BSI caused by colistin- and high-level carbapenem-resistant KPC-producing *K. pneumoniae* is unknown. A prospective cohort study including episodes of bacteremia caused by colistin-resistant and high-level meropenem-resistant (MIC ≥ 64 mg/liter) KPC-producing *K. pneumoniae* diagnosed from July 2012 to February 2016 was performed. The impact of combination therapy on crude 30-day mortality was analyzed by Cox regression using a propensity score as a covariate to control for indication bias and in an inverse probability of treatment weighting (IPTW) cohort. The study sample comprised 104 patients, of which 32 (30.8%) received targeted monotherapy and 72 (69.2%) received targeted combination therapy; none of them received either colistin or a carbapenem. The 30-day crude mortality rate was 30.8% (43.8% in patients treated with monotherapy and 25% in patients receiving combination therapy). In the Cox regression analysis, 30-day mortality was independently associated with septic shock at BSI onset (hazard ratio [HR], 6.03; 95% confidence interval [CI], 1.65 to 21.9; $P = 0.006$) and admission to the critical care unit (HR, 2.87; 95% CI, 0.99 to 8.27; $P = 0.05$). Targeted combination therapy was associated with lower mortality only in patients with septic shock (HR, 0.14; 95% CI, 0.03 to 0.67; $P = 0.01$). These results were confirmed in the Cox regression analysis of the IPTW cohort. Combination therapy is associated with reduced mortality in patients with bacteremia due to colistin-resistant KPC-producing *K. pneumoniae* with high-level carbapenem resistance in patients with septic shock.

KEYWORDS *Klebsiella pneumoniae*, bacteremia, carbapenems, colistin, mortality

Carbapenem-resistant *Klebsiella pneumoniae* infections are a public health problem in many areas due to the difficulties involved in treating these infections and their high associated mortality (1–8). Colistin, gentamicin, tigecycline, and fosfomycin are the

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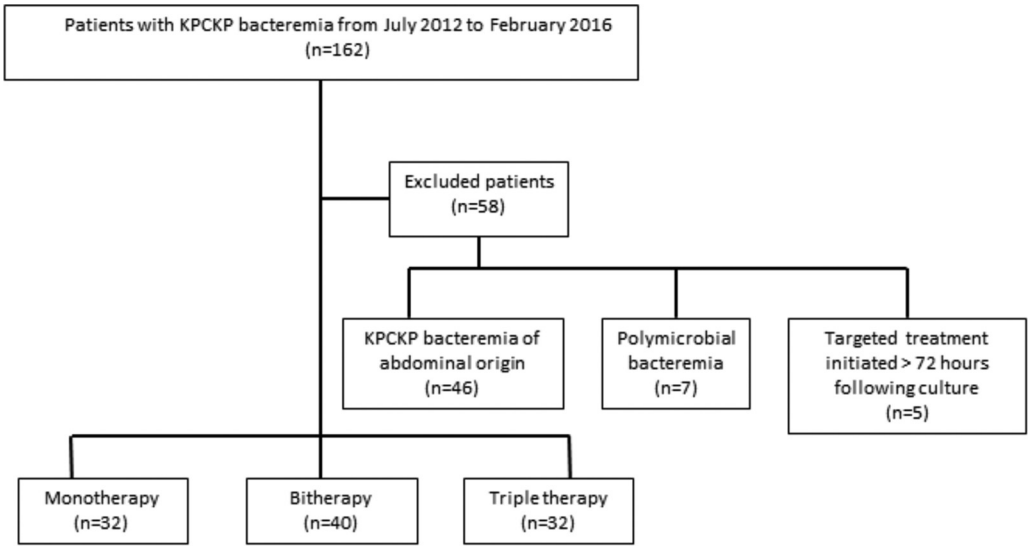

FIG 1 Study flow diagram.

most frequently used active antibiotics that are currently available to treat KPC-producing *K. pneumoniae* (9). For bacteremic infections, combination treatment regimens that include meropenem (at least when the MIC is ≤8 mg/liter) are recommended (6, 10); however, recent data suggest that combination therapy is needed only in patients at high risk of death (11). In recent years, outbreaks of colistin-resistant KPC-producing *K. pneumoniae* infections with high-level meropenem resistance (MIC ≥ 64 mg/liter) have been reported. For these isolates, the usefulness of colistin (a keystone in the treatment of carbapenem-resistant organisms) and the potential benefits of associating meropenem are reduced or lost (12). In such settings, carbapenem-sparing treatment regimens using the few available active drugs can be designed. To date, the best treatment regimen for bloodstream infections due to colistin-resistant KPC-producing *K. pneumoniae* with high-level carbapenem resistance is unknown. Additionally, avoiding the use of carbapenems may also reduce the selecting pressure in centers with ongoing transmission of KPC-producing *K. pneumoniae*.

This study, which is based on an analysis of daily clinical practice during a KPC-producing *K. pneumoniae* outbreak, examines the variables associated with mortality due to colistin-resistant KPC-producing *K. pneumoniae* bacteremia with high-level carbapenem resistance. Particular attention is given to the impact of targeted combination therapy not including carbapenems.

RESULTS

Of the 162 KPC-producing *K. pneumoniae* BSIs occurring during the study period, 104 met all the inclusion criteria (Fig. 1). Of these, 93.3% were considered nosocomial and the rest were health care associated (6.7%). The main characteristics of the patients with colistin-resistant KPC-producing *K. pneumoniae* bacteremia with high-level meropenem resistance receiving monotherapy or combination therapy are shown in Table 1.

Phenotypic characteristics of the isolated strains. The 104 isolates were resistant to colistin, penicillins, cephalosporins, ertapenem, meropenem, ciprofloxacin, and cotrimoxazole. Some of the isolates were susceptible to tigecycline (n = 84, 80.8%), fosfomycin (n = 30, 28.8%) and gentamicin (n = 49, 47.1%); 45 strains (43.3%) showed intermediate sensitivity to gentamicin (MIC = 4 mg/liter). At the time of this study, ceftazidime-avibactam was not available in Spain.

Antimicrobial therapy. All patients received empirical therapy with anti-Gram-negative antibiotics (alone or in combination with other antibiotics) at currently recommended doses. Empirical therapy was classified as inappropriate in 49 patients (47.1%) according to the antimicrobial sensitivity test. When the isolate was classified

TABLE 1 Characteristics of patients with bacteremia due to colistin-resistant *Klebsiella pneumoniae* with high-level meropenem resistance receiving monotherapy or combination therapy[d]

Variable	Monotherapy patients ($n = 32$)	Combination therapy patients ($n = 72$)	*P* value
Male, *n* (%)[a]	14 (43.8)	43 (59.7)	0.13
Median age (yr) (IQR)[c]	72 (78–61.25)	62 (74.25–47)	0.17
Comorbidities			
Chronic renal disease, *n* (%)[a]	7 (21.9)	20 (27.8)	0.53
Diabetes mellitus, *n* (%)[a]	16 (50)	20 (27.8)	0.03
Chronic obstructive pulmonary disease, *n* (%)[a]	4 (12.5)	11 (15.3)	0.7
Active solid tumor, *n* (%)[a]	8 (25)	22 (30.6)	0.4
Transplant, *n* (%)[b]	2 (6.2)	9 (12.5)	0.50
Median Charlson index (IQR)[c]	6 (7–2.5)	3 (6–2)	0.5
Admission from a care facility, *n* (%)[b]	3 (9.4)	7 (9.7)	0.9
Prior known colonization, *n* (%)[a]	8 (25)	23 (31.9)	0.5
Admission in previous 3 mo, *n* (%)[a]	18 (56.3)	29 (40.3)	0.13
Surgery in previous week, *n* (%)[a]	10 (31.3)	26 (36.1)	0.63
Invasive procedures in previous wk[a]			
Central venous catheter, *n* (%)	19 (59.4)	53 (73.6)	0.15
Urinary catheter, *n* (%)	26 (81.3)	63 (87.5)	0.4
Mechanical ventilation, *n* (%)	10 (31.3)	40 (56.3)	0.02
Admission ward[a]			0.01
Medical, *n* (%)	9 (28.1)	20 (27.8)	
Surgical, *n* (%)	11 (34.4)	8 (11.1)	
Critical care, *n* (%)	12 (37.5)	44 (61.1)	
Renal failure at time of diagnosis, *n* (%)[a]	11 (34.4)	33 (45.8)	0.28
Source of infection[a]			0.12
Pneumonia, *n* (%)	8 (25)	31 (43.1)	
Primary bacteremia, *n* (%)	16 (50)	22 (30.6)	
Urinary tract infection, *n* (%)	8 (25)	19 (26.4)	
Median length of hospitalization (days) during follow-up (IQR)[c]	16.5 (14.25–22.75)	17 (12–24)	0.92
Septic shock, *n* (%)[a]	8 (25)	40 (55.6)	0.004
Median Pitt score (IQR)[c]	3 (5–2)	4 (5–2)	0.30
Appropriate empirical therapy, *n* (%)[a]	11 (34.4)	44 (61.1)	0.01
Mortality at 30 days of follow-up, *n* (%)[a]	14 (43.8)	18 (25)	0.05

[a]*P* values were determined using Pearson's χ^2 test.
[b]*P* values were determined using Fisher's exact test.
[c]*P* values were determined using the Mann-Whitney test.
[d]Abbreviations: IQR, interquartile range; HR, hazard ratio; *n* (%), number and percentage of patients.

as KPC-producing *K. pneumoniae* (typically after 24 to 72 h of culture), the patients were treated with at least one active drug against the KPC-producing *K. pneumoniae* clone circulating in the hospital. A definitive treatment regimen was designed according to the results of the antimicrobial sensitivity test.

Variables associated with mortality. Table 2 shows the variables associated with 30-day mortality in the univariate analysis. Thirty-two patients died (30.8%) at day 30 of follow-up. Mortality was 43.8% (14/32 patients) in patients receiving monotherapy and 25% (18/72 patients) in patients receiving combination therapy ($P = 0.05$). The different treatment regimens and their crude associated mortality rates are shown in Table 3. The Kaplan-Meier curves for targeted treatment with monotherapy or with combination therapy are presented in Fig. 2. In the Cox regression multivariate analysis using propensity score as a covariate (Table 2), 30-day mortality was independently associated with septic shock at BSI onset (hazard ratio [HR], 6.03; 95% confidence interval [CI], 1.65 to 21.9; $P = 0.006$) and admission to the critical care unit (HR, 2.87; 95% CI, 0.99 to 8.27; $P = 0.05$). Combination therapy was not associated with decreased mortality by itself, but its interaction with septic shock was statistically significant (HR, 0.14; 95% CI,

TABLE 2 Univariate and multivariate analysis of variables associated with 30-day mortality rate in patients with bacteremia due to colistin-resistant *Klebsiella pneumoniae* with high-level meropenem resistance[a]

Variable	No. (%) of patients		Univariate analysis		Multivariate analysis with propensity score as covariable		Multivariate analysis using the inverse probability weighted-cohort	
	Survivors (n = 72)	Nonsurvivors (n = 32)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (yr), median (IQR)	65.0 (51–73.2)	63.5 (47–72.25)	0.99 (0.98–1.02)	0.87				
Male sex	39 (54.2)	18 (56.2)	1.16 (0.58–2.3)	0.68				
Diabetes mellitus	23 (31.9)	13 (40.6)	1.32 (0.65–2.67)	0.45				
Charlson score, Median (IQR)	4 (2–6)	4 (2–6)	1.00 (0.9–1.11)	0.9				
Pitt score, Median (IQR)	3 (2–5)	4 (2–6)	1.1 (0.95–1.28)	0.22				
Septic shock	31 (43.1)	17 (53.1)	1.59 (0.79–3.2)	0.19	6.03 (1.65–21.9)	0.006	6.53 (3.00–14.24)	<0.001
Source of bacteremia								
Primary bacteremia	29 (40.3)	9 (28.1)	Reference	Reference	Reference		Reference	
Urinary tract infection	19 (26.4)	8 (25)	1.16 (0.45–3)	0.76	1.9 (0.71–5.33)	0.2	2.97 (1.42–6.24)	0.004
Pneumonia	24 (33.3)	15 (46.9)	1.45 (0.64–3.3)	0.37	2.5 (0.9–6.97)	0.08	4.75 (2.34–9.67)	<0.001
Ward of admission when the bacteremia was diagnosed								
Medical	24 (33.3)	5 (15.6)	Reference	Reference	Reference		Reference	
Surgical	13 (18.1)	6 (18.8)	1.86 (0.57–6.11)	0.3	2.04 (0.5–8.9)	0.34	2.10 (0.74–5.97)	0.17
Critical care	35 (48.6)	21 (65.6)	2.61 (0.98–6.92)	0.05	2.87 (0.99–8.27)	0.05	4.22 (1.97–9.03)	<0.001
Mechanical ventilation	34 (47.9)	16 (50)	1.1 (0.54–2.18)	0.81				
Appropriate empirical therapy	41 (57.7)	14 (43.8)	0.6 (0.28–1.12)	0.1	0.53 (0.26–1.1)	0.09	0.48 (0.26–0.88)	0.02
Targeted treatment								
Monotherapy	18 (25)	14 (43.8)	Reference	Reference	Reference	Reference	Reference	
Combination therapy	54 (75)	18 (56.2)	0.52 (0.26–1.05)	0.07	0.81 (0.27–2.42)	0.71	0.62 (0.27–1.41)	0.25
Interaction of septic shock and combination therapy					0.14 (0.03–0.65)	0.01	0.10 (0.03–0.32)	<0.001
Propensity score			1.1 (0.26–4.56)	0.63	0.54 (0.04–6.59)	0.93		

[a]Abbreviations: IQR, interquartile range; HR, hazard ratio; CI, confidence interval.

TABLE 3 Outcome of patients with bacteremia due to colistin-resistant *Klebsiella pneumoniae* with high-level meropenem resistance according to treatment regimen

Treatment regimen	No. dead/treated	Mortality (%)
Monotherapy		
Tigecycline	8/15	53.3
Gentamicin	4/9	44.4
Fosfomycin	2/8	25
Total for monotherapy	14/32	43.8
Combination therapy		
Tigecycline + gentamicin	3/13	23.1
Tigecycline + fosfomycin	6/16	37.5
Gentamicin + fosfomycin	3/11	27.3
Tigecycline + fosfomycin + gentamicin	6/32	18.8
Total for combination therapy	18/72	25

0.03 to 0.65; $P = 0.01$), meaning that combination therapy has a protective effect for mortality among patients with septic shock. In the Cox regression analysis of the IPTW cohort, similar results were obtained; in this model, other variables such as urinary tract source (HR, 2.97; 95% CI, 1.42 to 6.24; $P = 0.004$), pneumonia (HR, 4.75; 95% CI, 2.34 to 9.67; $P < 0.001$), and appropriate empirical therapy (HR, 0.48; 95% CI, 0.26 to 0.88; $P = 0.02$) were also associated with mortality. Combined treatment alone was not significant, but its interaction with septic shock was also statistically significant (HR, 0.10; 95% CI, 0.03 to 0.32; $P < 0.001$) (Table 2).

The Kaplan-Meier curves for targeted treatment with monotherapy or with combination therapy in patients with and without septic shock are presented in Fig. 3.

DISCUSSION

The reported mortality among patients with KPC-producing *K. pneumoniae* bacteremia is very high, ranging from 20 to 70% depending on the prescribed treatment

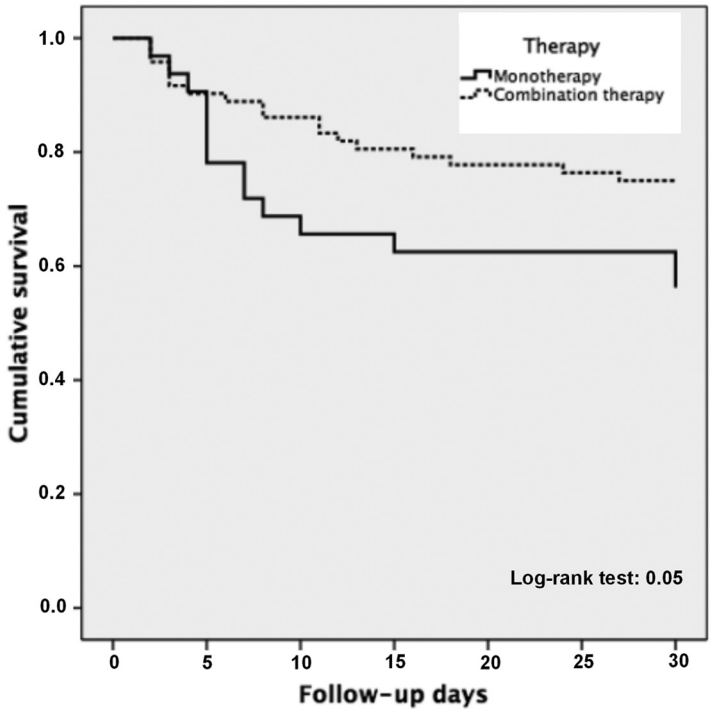

FIG 2 Kaplan-Meier curves for targeted treatment with monotherapy or with combination therapy.

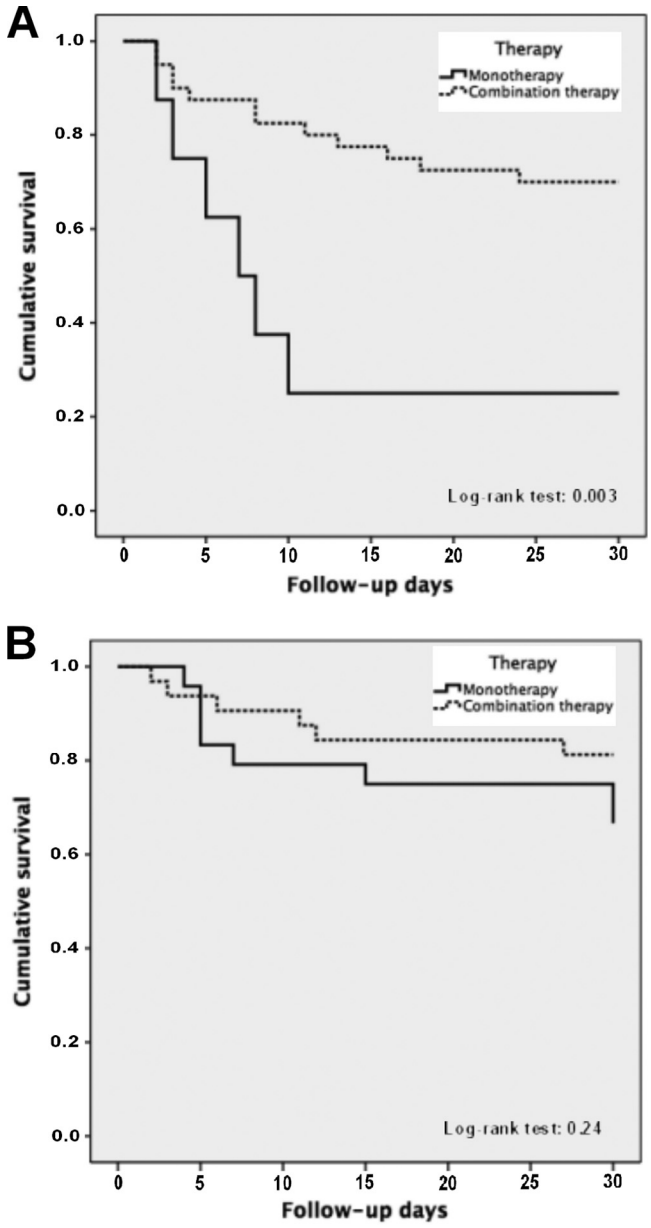

FIG 3 Kaplan-Meier curves for targeted treatment with monotherapy or combination therapy in patients with septic shock (A) and without septic shock (B).

regimen and the underlying severity of disease in the patients (6–8, 10). This series, which includes only colistin-resistant KPC-producing *K. pneumoniae* with high-level meropenem resistance, confirms these findings (overall crude mortality, 30.8%). No randomized clinical trials published to date have defined the most effective therapeutic regimen for these patients. Current recommendations are based on the results of retrospective cohort studies (4, 6, 10), which suggest that (i) combination therapy is superior to monotherapy and (ii) combination therapy should include a carbapenem. However, recent data suggest that combination therapy is probably not needed in low-risk patients (11) and information to guide therapy for colistin-resistant and high-level meropenem-resistant isolates is lacking. The availability of new drugs such as ceftazidime-avibactam is promising but will probably not solve all the problems (13).

We found that the interaction between combination therapy and septic shock was

statistically significant; that means that combination therapy was protective for mortality only among patients with septic shock, but the protective effect could not be proven in patients without septic shock. However, the confidence interval was wide, and therefore, we cannot discard a protective effect that is not apparent due to a presumably high beta error. Of note, appropriate empirical therapy was less frequent among patients receiving monotherapy; however, the effect of this variable was controlled in the multivariate analyses.

As stated, carbapenems were not used in our patients. The use of meropenem has been recommended for strains with moderate resistance to meropenem (MICs of up to 8 mg/liter), for which an optimized dose of meropenem would theoretically allow a high probability of attaining the pharmacodynamics target (4, 6, 10, 14, 15). Tumbarello et al. (6) and Daikos et al. (10) observed that the efficacy of combination regimens including meropenem is lower when the MIC of this antibiotic increases. In these studies, mortality rates were 18.7% and 19.3% when the MIC was $<$16 mg/liter and 35.2% and 35.9% when the MIC was $\geq$16 mg/liter, respectively. These data suggest that meropenem would be ineffective when the strain exhibits high-level resistance. In fact, meropenem (2 g every 8 h in extended infusion) did not reach any pharmacokinetic-pharmacodynamic target in 19 patients with infections due to KPC-producing *K. pneumoniae* with meropenem MICs of $>$16 mg/liter in a recent study (16). Additionally, a recent study found a higher rate of failure for the carbapenem-colistin combination in patients with KPC-producing *K. pneumoniae* bacteremia caused by isolates highly resistant to colistin and doripenem (17). Finally, the combination of ertapenem and doripenem was also shown to be efficacious only against isolates with a doripenem MIC of $<$32 mg/liter (18).

Data about the efficacy of carbapenem-spare regimens are scarce. To the best of our knowledge, two case series with a low number of cases have been reported. Sbrana et al. showed a high clinical response rate (92%) in 22 polytrauma patients (19), and Papadimitriou-Olivgeris et al. (20) observed a 43.4% mortality in 53 patients. The mortality rate observed in combination regimens not including carbapenems found in this study (25%) is more similar to that reported in the literature for strains with low resistance when regimens including carbapenems were used (4, 6, 10). However, the figures might not be comparable despite the similarities in the features of the patients across the studies. Therefore, despite the lack of data, it seems reasonable to avoid the use of carbapenems in infections caused by highly resistant isolates in order to avoid further selection pressure.

Because of the limited therapeutic options, the combined regimens in this series included different combinations of tigecycline, gentamicin, and fosfomycin. The low number of patients in each group precludes elaborate comparisons among them. It is also necessary to determine whether the use of gentamicin in susceptible or intermediate strains improves the prognosis of patients with severe sepsis, as previously reported by our group (21). However, due to the small sample size of this study, we could not analyze this. The most frequent combination in this study was tigecycline and gentamicin (45 patients, 32 of which also received fosfomycin). Mortality in this group was 20%; interestingly, the combination of tigecycline and gentamicin was more efficacious than each of them combined with colistin and meropenem in a murine model (22).

Our article has some limitations. We were unable to compare the efficacy of combination therapy with and without carbapenems and with or without colistin, as these drugs were not used. The study was not randomized, and despite attempts to control for confounders by using a propensity score and multivariate analysis, residual confounding might have occurred. The study was performed in the context of an outbreak. Finally, the sample size, which was constrained by the available cases, is a further limitation of the analysis.

In conclusion, combination regimens were associated with improved outcomes in patients with bacteremia due to KPC-producing *K. pneumoniae* presenting with septic shock and showing colistin resistance and high-level carbapenem resistance. Further

studies are required to determine whether combination therapy is needed in patients without septic shock.

MATERIALS AND METHODS

Study design and patients. This prospective cohort study includes patients with BSI caused by KPC-producing *K. pneumoniae* strains belonging to the ST512 clone in the setting of a nosocomial outbreak in a single teaching hospital with 1,233 beds. Approximately 40,000 patients are admitted to the center yearly. The patients were recruited from July 2012 to February 2016. All blood cultures collected at the center were revised daily, and medical infectious disease consultants (I.M., C.N., and J.T.-C.) evaluated the prescribed treatment and followed each case. During the study period, screening cultures were routinely performed in the intensive care unit (ICU) and the hematology unit (weekly rectal swab sampling). The analyses were performed following STROBE recommendations (23) (data not shown).

Patients were required to meet the following inclusion criteria: (i) age, ≥18 years; (ii) episode of clinically significant bacteremia due to colistin-resistant KPC-producing *K. pneumoniae* with high-level meropenem resistance (see below); (iii) targeted treatment initiated in the first 72 h after blood cultures were taken, which included at least 1 active antibiotic *in vitro*. Patients with polymicrobial bacteremia or with an intra-abdominal source (which are usually polymicrobial), patients who survived <48 h after initiating active antibiotic treatment, those under palliative care or with nonresuscitation orders, and previously included patients who suffered subsequent episodes were excluded from this study. Bacteremia due to KPC-producing *K. pneumoniae* was defined as the presence of at least one set of positive blood cultures for colistin-resistant KPC-producing *K. pneumoniae* with high-level meropenem resistance in patients with evidence of systemic inflammatory response. The day of onset of infection (day 0) was defined as the day of collection of the blood culture in which the microorganism was isolated.

The study was approved by the Spanish Agency for Medicines and Health Products (AEMPS, code FIC-KPC-2015-01) and by the Ethics Committees of the participating hospitals (code 2848), which exempted the need to seek written informed consent due to the observational nature of the study. All the data collected were anonymized.

Variables. The main outcome variable was crude mortality at 30 days following the diagnosis of bacteremia.

The variables collected for each patient were the following: sex; age; underlying chronic diseases; disease severity measured by the Charlson comorbidity index (24); admission from a care facility; prior known KPC-producing *K. pneumoniae* colonization; admission in the previous 3 months; surgery in the previous week; invasive procedures performed in the week prior to the diagnosis of infection (need for mechanical ventilation, use of central venous catheter, urinary catheter); ward of admission when the bacteremia was diagnosed (medical, surgical, or intensive care); presence of renal failure at the time of diagnosis of infection; source of bacteremia (pneumonia or urinary or primary bacteremia); overall length of hospital stay; presentation with septic shock (25); Pitt bacteremia score (26); appropriate empirical therapy, targeted monotherapy, or targeted combination therapy; and antimicrobial susceptibility.

Treatment regimens. *In vitro*-active antibiotics were included in the therapeutic regimen and selected according to the clinical judgment of the treating physician. Patients whose therapeutic regimen included a single *in vitro*-active drug were considered to be undergoing monotherapy. Patients whose regimen included 2 or 3 *in vitro*-active drugs were considered to be undergoing combination therapy. In patients with nosocomial pneumonia or septic shock, tigecycline was administered at a loading dose of 200 mg followed by 100 mg every 12 h. In all other cases, a loading dose of 100 mg followed by 50 mg every 12 h was administered. Gentamicin was given intravenously in a single daily dose of 5 mg/kg of body weight/day, and the dose was adjusted according to concentrations in blood. Fosfomycin was administered at an intravenous dose of 4 g every 6 h and corrected according to renal function. The duration of treatment ranged from 10 to 14 days upon judgment of the attending physician.

Definitions. The definitions were established prior to the data collection and statistical analysis. Crude mortality was defined as death by any cause. The strain was considered to have high-level meropenem resistance when the MIC was ≥64 mg/liter. The source of bacteremia was defined according to the criteria of the Centers for Disease Control and Prevention (CDC/NHS) for nosocomial infections (27) irrespective of the acquisition type. Infection was considered nosocomial when the index blood culture was collected >48 h after admission and there was no clinical evidence of infection at the time of admission. The rest were classified as health care- or community-associated infections in accordance with previous definitions (28). Primary bacteremia was defined as any catheter-related bacteremia and bacteremia of unknown source. Septic shock was defined according to the most recent criteria when the study began in 2012 (29). The Cockroft-Gault formula was used to calculate creatinine clearance (CL_{CR}). The presence of a CL_{CR} of <60 ml/min was considered renal failure.

Empirical therapy was defined as treatment administered within the first 24 h following the collection of blood cultures and prior to determining the susceptibility of the isolate. Empirical therapy was considered appropriate when the isolate was susceptible *in vitro* to at least one of the prescribed antibiotics. Treatment that was initiated or maintained after receiving the susceptibility results was considered targeted therapy. A targeted antibiotic treatment regimen was considered active when including at least one antibiotic to which the isolate was susceptible *in vitro* (for gentamicin, intermediate isolates were also considered; see below). To classify patients as receiving a specific regimen, the regimen should have been initiated in the first 72 h following the index blood culture and maintained for at least

50% of the duration of treatment (or at least 48 h if the patient died before) in order to guarantee a minimum exposure time to the regimen.

Microbiological variables and antibiotic susceptibility studies. Blood cultures were performed using the Bactec 9240 automatic blood culture detection system (Becton Dickinson, USA). Blood culture bottles flagged as positive and with Gram-negative stains were processed as follows: (i) direct inoculation of microorganisms from positive-blood-culture bottles into the matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) system for identification combined with inoculation in chromogenic media (bioMérieux) and/or PCR (GeneXpert Carba-R; Cepheid, USA) for carbapenemase detection; (ii) standard culture involving overnight agar medium subcultures from the positive-blood-culture bottles for identification using standard microbiological techniques and antibiotic susceptibility testing by microdilution using the Gram-negative REV.2 Wider panel (Siemens Healthcare Diagnostics, Camberley, UK) or Etest strips when needed (Liofilmchem, Italy). Colistin susceptibility was performed by microdilution and was checked, in selected strains, using a broth dilution method. Those selected strains yielded a negative screening for *mcr-1* and *mcr-2* genes using PCR with specific primers. MICs were interpreted following the breakpoint recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (30) and the U.S. Food and Drug Administration (FDA) recommendations for tigecycline. Meropenem was not considered active against any isolate because the MIC was ≥64 mg/liter in all cases. Colistin was not considered active treatment because the MIC was always ≥2 mg/liter. Tigecycline, gentamicin, and fosfomycin were considered active when the MIC was ≤2 mg/liter, ≤4 mg/liter, and ≤32 mg/liter, respectively.

The *K. pneumoniae* index isolates in this outbreak were characterized as belonging to the ST512 clone by the reference laboratory of the Virgen Macarena University Hospital of Seville, Seville, Spain. The characteristics of the strain have been previously reported (31).

Statistical analysis. The results were expressed as medians and interquartile ranges (IQR) for the continuous variables or as percentages for the categorical variables. Comparisons for continuous variables were performed using the Mann-Whitney U test; for categorical variables, the Pearson's χ^2 test with Yates' continuity correction or Fisher's exact test was used as appropriate. Survival curves were obtained using the Kaplan-Meier method and compared using the log rank test. A propensity score for receiving active combination treatment was calculated using a multivariate logistic regression analysis that included the following variables: age, sex, prior known colonization, admission from a care facility, hospital admission in the previous 3 months, surgery in the previous week, invasive procedures in the previous week (mechanical ventilation, central venous catheter, urinary catheter), admissions unit following diagnosis (medical, surgical, ICU), focus of infection (pneumonia, primary bacteremia, urinary tract infection), septic shock, appropriate empirical therapy, Charlson comorbidity index, Pitt score on the day of bacteremia, and renal failure at time of diagnosis of infection. The model obtained had an area under the receiver operating characteristic (ROC) curve of 0.90. The propensity score was used in 2 ways: (i) as a covariate in multivariate Cox regression analysis and (ii) to form an inverse probability of treatment weighting (IPTW) cohort.

The variables associated with mortality were studied using the Cox regression. The scale of the continuous variables was assessed using the Box-Tidwell test. Possible interactions between variables were studied. Variables with a P value of <0.05 were studied as potential confounders and considered to be confounders if the percentage change in the coefficients was greater than 20%. To assess the goodness of fit of the model, the likelihood ratio test was performed. The condition of proportional hazards was verified by the Kleinbaum-Klein method. Analyses were performed using R software (version 3.0.1) and SPSS 15.0 (SPSS Inc.).

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Conflict of interest: J.R.-B. served as scientific advisor for a research project for AstraZeneca, Pfizer, and InfectoPharm and has been a speaker in unrestricted accredited educational activities funded by Merck. All other authors declare no conflict of interest.

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