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Combination therapy with polymyxin B for carbapenemase-producing *Klebsiella pneumoniae* bloodstream infection

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ABSTRACT

Klebsiella pneumoniae carbapenemase-producing *K. pneumoniae* (KPC-KP) bloodstream infections (BSIs) are related to high mortality rates, and combination therapy has been associated with lower mortality in patients treated mostly with colistin. There is a paucity of studies addressing polymyxin B (PMB) treatment for KPC-KP infections. This was a retrospective cohort study of patients with monomicrobial KPC-KP BSIs. The primary outcome was 30-day mortality. Antimicrobial therapy was defined as empirical (started within the first 48 h) or definitive (initiated after >48 h) and was evaluated as follows: monotherapy (only one in vitro active agent or combination therapy of one in vitro active agent plus one or more in vitro non-active agents); and combination therapy with two or more in vitro active agents. A total of 82 KPC-KP BSIs were included; 40 patients (48.8%) died in the first 30 days. Mortality of patients treated with the combination of two in vitro active antimicrobial agents, mostly PMB plus amikacin, was significantly lower (37.5%) compared with monotherapy (64.7%) ($P=0.01$). Combination therapy [adjusted hazard ratio (aHR) = 0.40, 95% confidence interval (CI) 0.22–0.83; $P=0.01$] was independently associated with lower 30-day survival when controlled for non-surgical admission (aHR = 2.33, 95% CI 1.14–4.80; $P=0.02$) and use of vasoactive drugs (aHR = 7.37, 95% CI 3.01–18.02; $P < 0.01$). In conclusion, combination therapy with two in vitro active agents, mostly PMB plus amikacin, showed a survival benefit compared with other regimens.

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1. Introduction

Klebsiella pneumoniae is among the most common bacteria causing hospital-acquired infections, including bloodstream infections (BSIs) [1,2]. Carbapenems used to be the antimicrobials of last-resort against Enterobacteriaceae, including *K. pneumoniae*; however, the activity of this class has been threatened by the emergence of carbapenemase-producing isolates, notably *K. pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-KP) [1,2]. Infections caused by KPC-KP usually affect patients with multiple co-morbidities and are associated with higher mortality rates [3].

BSIs by KPC-KP are life-threatening infections that are associated with even higher mortality rates [4]. Currently, there are limited treatment options for KPC-KP BSIs, which usually relies on one of the old polymyxins, either colistin or polymyxin B (PMB) [5]. Combination therapy regimens with colistin plus a second antimicrobial with in vitro activity appear to be related to lower mortality rates in several studies [6–9], although this potential benefit may be limited to a subset of more severely ill patients [8].

PMB has been shown to present pharmacokinetic advantages over colistin (which is administered as a prodrug), including faster achievement of therapeutic plasma levels and potential for lower renal toxicity, and it has been considered the preferred polymyxin for systemic infections [10–12]. However, experience with PMB for KPC-KP is still limited to a few studies in which the association of combination therapy with improved survival is controversial [13–15]. The aim of this study was to evaluate risk factors for 30-day mortality in monomicrobial KPC-KP BSI in a hospital where PMB is available, with particular emphasis on combination therapy.

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2. Materials and methods

2.1. Study design, settings and participants

This was a single-centre, retrospective cohort study performed in a public tertiary-care teaching hospital with 59 intensive care beds in Porto Alegre, Brazil, from August 2015 to December 2016. Patients aged ≥18 years with KPC-KP BSI were included. Data were collected from the electronic patient register; the database was generated by the informatics department through retrospective query. Patients were excluded if they did not receive at least one in vitro susceptible drug or had polymicrobial infection (defined as blood culture with isolation of KPC-KP plus any other microorganism). Patients who had more than one KPC-KP BSI were included as a new patient if infection occurred >30 days after the last treatment.

2.2. Microbiological tests

Bacterial identification and antimicrobial susceptibility testing were performed using a VITEK®2 automated system (bioMérieux, Marcy-l'Étoile, France). Susceptibility was interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria [16]. Isolates with a minimum inhibitory concentration (MIC) of ≤2 mg/L were considered susceptible to PMB (colistin breakpoint for Enterobacteriaceae) [17] and those with an MIC of ≤1 mg/L were considered susceptible to tigecycline [17].

KPC-2 was identified by multiplex PCR as described previously [18].

2.3. Variables and definitions

The primary outcome was 30-day mortality after BSI. KPC-KP BSI was defined as one or more positive blood cultures with recovery of KPC-KP. Variables potentially related to 30-day mortality were patient demographics, weight, body mass index (BMI), baseline creatinine clearance (estimated by the Cockcroft–Gault equation), co-morbidities and Charlson comorbidity index [19], length of hospital stay before BSI, Pitt bacteraemia score [20], admission to the intensive care unit, use of vasoactive agents and mechanical ventilation at the time of BSI diagnosis, and renal replacement therapy at or after BSI diagnosis. The primary site of infection was defined according to the US Centers for Disease Control and Prevention and National Healthcare Safety Network (CDC/NHSN) [21]. Antimicrobial therapy maintained for ≥48 h was considered for analysis. Therapy was defined as empirical (started within first 48 h) or definitive (initiated or maintained after 48 h) and was evaluated as follows: monotherapy (only one in vitro active agent or combination therapy of one in vitro active agent plus one or more in vitro non-active agents); and combination therapy (two or more in vitro active agents). Meropenem was considered an active drug when the isolate presented a MIC ≤ 8 mg/L.

2.4. Statistical analysis

Statistical analysis was performed using PASW Statistics for Windows v.18.0 (SPSS Inc., Chicago, IL). Univariate analyses were performed using χ^2 test or Fisher's exact test for categorical variables and Student's *t*-test or Mann–Whitney *U*-test for continuous variables. Kaplan–Meier survival estimates were calculated and the difference was evaluated using the log-rank test. One-way analysis of variance (ANOVA) was used to determine differences between antimicrobial doses, MIC and treatment groups. All tests were two-tailed and a *P*-value of <0.05 was considered statistically significant.

A Cox regression model was performed to identify independent factors related to monotherapy or combination therapy and 30-day mortality. Variables with $P \leq 0.20$ in the univariate analysis were included in the model in a forward stepwise manner. Those with $P \leq 0.05$ were maintained in the final model. Variables were checked for confounding and collinearity, and no interactions were tested.

3. Results

A total of 152 KPC-KP BSIs was identified during the study period. Of these, 47 polymicrobial BSIs and 23 without in vitro active treatment were excluded, resulting in a total of 82 episodes included for analysis (two of them occurring after 66 days and 82 days from the first episode in two patients, respectively, were considered as new cases). A total of 40 patients (48.8%) died in the first 30 days after BSI. The median (interquartile range) time to death was 22 days (7–30 days). The characteristics of the entire cohort and the combination and monotherapy groups as well as the univariate analysis for 30-day mortality are presented in Table 1.

There was no significant association between different empirical therapeutic regimens and 30-day mortality. Definitive combination therapy with two in vitro active antimicrobials was significantly associated with lower overall mortality rate (Table 2).

The 30-day mortality was 64.7% (22/34) in the monotherapy or combination of one in vitro active agent plus an agent without in vitro activity group compared with 37.5% (18/48) in the combination therapy group ($P = 0.01$). Survival curves of patients are shown in Fig. 1.

The mean doses of the antimicrobials used in treatments were 2.8 mg/kg/day PMB, 15.1 mg/kg/day amikacin, 6 g/day meropenem and 100 mg/day tigecycline. There were no significant differences between doses and treatment groups, i.e. combination of two in vitro active, combination of one in vitro active with one in vitro non-active or monotherapy (one-way ANOVA) for PMB ($P=0.24$), amikacin ($P=0.72$), meropenem ($P=0.82$) and tigecycline ($P=0.12$). There were also no significant differences between MICs and treatment groups (one-way ANOVA) for amikacin ($P=0.32$), PMB ($P=0.53$), meropenem ($P=0.72$) and tigecycline ($P=0.63$).

In the multivariate analysis, definitive combination therapy was independently associated with lower 30-mortality. Non-surgical admission and requirement for vasoactive drugs were independent factors associated with higher mortality risk (Table 3). Combination therapy remained independently associated with lower 30-day mortality when including the variable 'administration of at least one antimicrobial with in vitro activity as empirical therapy' into the model (Table 3).

Since in 34 isolates (22 in the combination group and 12 in the monotherapy group) susceptibility testing to PMB could not be performed, and the isolates were considered susceptible to this antibiotic, a worst-case scenario analysis was performed considering all PMB non-tested isolates as resistant to this drug. In this scenario, the 30-day mortality rates of combination and monotherapy groups were 37.9% (11/29) and 51.2% (22/43), respectively ($P=0.34$). Combination therapy tended to a protective effect in this scenario as shown in Table 3.

4. Discussion

In this study, combination therapy with two in vitro active agents as the definitive treatment was independently associated with lower 30-day mortality in KPC-KP BSI.

Table 1
Characteristics of the patient cohort, and univariate analysis of risk factors associated with 30-day mortality[a].

Variable	Total ($n=82$)	Monotherapy ($n=34$)	Combination therapy ($n=48$)	*P*-value	30-day mortality		
					Yes ($n=40$)	No ($n=42$)	*P*-value
Age (years)	57.6 ± 17	58.2 ± 19	57.2 ± 16	0.80	60.71 ± 17	54.62 ± 17	0.11
Male sex	53 (64.6)	21 (61.8)	32 (66.7)	0.65	27 (67.5)	26 (61.9)	0.6
BMI (kg/m^2)	24.8 ± 6	25.2 ± 5	24.6 ± 7	0.71	25.6 ± 7	24.1 ± 6	0.34
Charlson comorbidity index	5 (2–8)	5 (2–8)	5 (2–8)	0.72	5 (2–8)	5 (2–8)	0.74
Cardiovascular disease	39 (47.6)	17 (50.0)	22 (445.8)	0.71	20 (50.0)	19 (45.2)	0.7
Cancer	33 (40.2)	12 (35.3)	21 (43.8)	0.44	18 (45.0)	15 (35.7)	0.4
Chronic lung disease	13 (15.9)	6 (17.6)	7 (14.6)	0.71	8 (20.0)	5 (11.9)	0.32
Chronic kidney disease	24 (29.3)	10 (29.4)	14 (29.2)	0.98	15 (37.5)	9 (21.4)	0.11
Cirrhosis	13 (15.9)	3 (8.8)	10 (20.8)	0.14	4 (10.0)	9 (21.4)	0.16
Diabetes	21 (25.6)	10 (29.4)	11 (22.9)	0.51	13 (32.5)	8 (19.0)	0.16
HIV	6 (7.3)	3 (8.8)	3 (6.2)	0.66	4 (10.0)	2 (4.8)	0.36
CNS disease	19 (23.2)	10 (29.4)	9 (18.8)	0.26	10 (25.0)	9 (21.4)	0.70
Baseline CL_{Cr} (mL/min)	54.7 (32.7–91.2)	52.3 (31.8–77.4)	67.5 (35.0–94.5)	0.67	47.4 (31.8–82.1)	68.2 (39.2–97.7)	0.29
Non-surgical patients	50 (61.0)	26 (76.5)	24 (50.0)	0.01	28 (70.0)	22 (52.4)	0.10
Length of stay before BSI (days)	23.0 (12–45)	24 (10–40)	31 (14–53)	0.06	25 (15–41)	31 (12–60)	0.21
Combination therapy	45 (54.9)	–	–	–	18 (45.0)	30 (71.4)	0.03
Pitt bacteraemia score	4 (1–10)	4 (1–10)	4 (1–8)	0.86	7 (2–10)	2 (0–5)	<0.01
Primary infection site							
Catheter-associated BSI	11 (13.4)	4 (11.8)	7 (14.6)	0.71	7 (17.5)	4 (9.5)	0.29
Pulmonary	25 (30.5)	12 (35.3)	13 (27.1)	0.43	13 (32.5)	12 (28.6)	0.70
Urinary	9 (11.0)	5 (14.7)	4 (8.3)	0.36	2 (5.0)	7 (16.7)	0.09
Abdominal	14 (17.1)	2 (5.9)	12 (25.0)	0.02	7 (17.5)	7 (16.7)	0.92
Endocarditis	1 (1.2)	0	1 (2.1)	0.40	0	1 (2.4)	0.37
Skin and soft tissue	9 (11.0)	5 (14.7)	4 (8.3)	0.36	4 (10.0)	5 (11.9)	0.78
Not defined	13 (15.9)	6 (17.6)	7 (14.6)	0.71	7 (17.5)	6 (14.3)	0.69
ICU admission[b]	50 (61.0)	21 (61.8)	29 (60.4)	0.90	33 (82.5)	17 (40.5)	<0.01
Vasoactive drugs[b]	44 (53.7)	20 (64.5)	24 (52.2)	0.28	32 (80.0)	12 (28.6)	<0.01
Mechanical ventilation[b]	46 (56.1)	19 (61.3)	27 (58.7)	0.82	32 (80.0)	14 (33.3)	<0.01
RRT	35 (42.7)	17 (50.0)	18 (38.3)	0.29	25 (62.5)	10 (23.8)	<0.01

BMI, body mass index; HIV, human immunodeficiency virus; CNS, central nervous system; CL_{Cr}, creatinine clearance; BSI, bloodstream infection; ICU, intensive care unit; RRT, renal replacement therapy.
[a] Variables are *n* (%), mean ± standard deviation or median (interquartile range).
[b] At the time of infection diagnosis.

Table 2
Thirty-day mortality [*n* (%)] according to antimicrobial therapy regimen received for bloodstream infection.

Antimicrobial regimen	Empirical therapy 30-day mortality		*P*-value	Definitive therapy 30-day mortality		*P*-value
	Yes ($n=40$)[a]	No ($n=42$)[b]		Yes ($n=40$)	No ($n=42$)	
One in vitro active agent as monotherapy or combination of one in vitro active agent plus one or more in vitro non-active agents	27 (67.5)	15 (35.7)	0.09	22 (55.0)	12 (28.6)	0.03
Polymyxin B	0	5		4	4	
Meropenem	1	0		1	0	
Amikacin	1	1		1	1	
Polymyxin B + meropenem	25	8		15	7	
Amikacin + meropenem	0	1		0	0	
Polymyxin B + amikacin + meropenem	0	0		1	0	
Combination therapy with two or more in vitro active agents	3 (7.5)	6 (14.3)		18 (45.0)	30 (71.4)	
Polymyxin B + amikacin	1	1		4	7	
Polymyxin B + amikacin + meropenem	0	3		7	15	
Polymyxin B + meropenem	0	2		0	2	
Polymyxin B + meropenem + tigecycline	1	0		4	3	
Polymyxin B + amikacin + tigecycline	0	0		0	1	
Polymyxin B + amikacin + meropenem + tigecycline	1	0		3	2	

[a] Tenpatients in this group did not receive any appropriate therapy in the first 48 hours.
[b] Twenty-one patients in this group did not receive any appropriate therapy in the first 48 hours.

Table 3
Multivariate analysis of factors associated with 30-day mortality in patients with KPC-producing *Klebsiella pneumoniae* bloodstream infections.

Variable	Model 1			Model 2[a]			Model 3[b]		
	aHR	95% CI	*P*-value	aHR	95% CI	*P*-value	aHR	95% CI	*P*-value
Definitive combination therapy[c]	0.40	0.22–0.83	0.01	0.31	0.11–0.87	0.02	0.53	0.25–1.12	0.10
Vasoactive drugs	7.37	3.01–18.02	<0.01	6.61	1.95–22.42	<0.01	7.80	2.90–20.76	<0.01
Non-surgical admission	2.33	1.14–4.80	0.02	1.71	0.60–4.93	0.31	2.85	1.25–6.46	0.01
Adequate empirical therapy	–	–	–	0.61	0.13–2.81	0.53	–	–	–

aHR, adjusted hazard ratio; CI, confidence interval.
[a] Model including adequate empirical therapy in the analysis.
[b] Model considering the worst-case scenario in which all polymyxin B non-tested isolates were considered resistant.
[c] Combination therapy with two in vitro active antimicrobial agents.

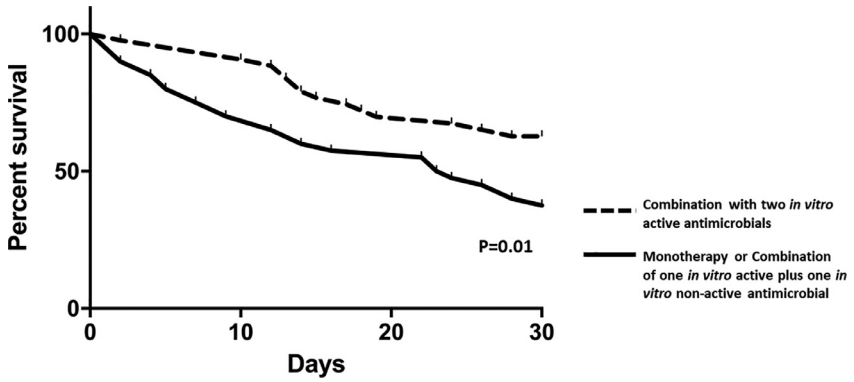

Fig. 1. Survival curves of combination therapy with two in vitro active antimicrobials versus other appropriate therapies (monotherapy or combination with one in vitro non-active antimicrobial) in patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* bloodstream infections (log-rank, $P = 0.01$).

Although a beneficial effect of combination schemes for KPC-KP has been previously shown, this study provides distinguishing findings. First, combination therapy has been found to be associated with lower mortality in KPC-KP infections, mostly BSIs, in patients whose therapy, either as part of a combination scheme or in monotherapy, has been mostly based on colistin [6,8,9,22,23]. Since colistin is administered as the prodrug colistimethate, and 'therapeutic' levels of colistin may take several hours to be achieved [24,25], one could argue that monotherapies including colistin might be inferior largely because of its intrinsic pharmacokinetic limitation. Here, PMB, which is administered as the active drug, has been used in most of the combination and monotherapy schemes and the benefit of combination with another in vitro active agent could be shown as well. It should be mentioned that previous observational studies addressing combination therapy with PMB have not found different outcomes with combination schemes, although limitations discussed in each of these studies might have hampered such findings [13–15].

To our knowledge, the few available randomised clinical trials addressing combination therapy have analysed combinations with colistin (two with rifampicin [26,27] and one with meropenem [28]), with no statistically significant clinical benefit. However, two of them studied *Acinetobacter baumannii* infections [26,27] and one had >75% of infections by *A. baumannii* [28]. Extrapolation of the findings of these trials to other pathogens and other antibiotic combinations with polymyxins warrants caution. Interestingly, in the most recent trial, in the subgroup of patients with Enterobacteriaceae infection, clinical failure (the primary outcome) was 22% lower in the combination group compared with the monotherapy group (46% and 68%, respectively) ($P = 0.185$); moreover, 28-day mortality in the combination group was 21% compared with 35% ($P = 0.235$) [28]. Thus, even though without statistical significance, likely due to the low number of patients, the subgroup analysis of this randomised clinical trial suggests an overall survival benefit with combination therapy for Enterobacteriaceae infections.

The current study provides some data supporting the use of amikacin in combination with PMB when the isolate is in vitro susceptible to both agents. In previous studies, the major components of combination schemes have been colistin and meropenem (for isolates with MIC ≤ 8 mg/L) or tigecycline [29]. None the less, although PMB plus amikacin was the most frequent combination among schemes containing two or more in vitro active agents, overall mortality was similar among all combinations schemes (40–50%), which included PMB plus tigecycline and triple combination with PMB, tigecycline and amikacin, with the exception of schemes containing meropenem against isolates with meropenem MIC ≤ 8 mg/L (all of three were survivors). Thus, we were not able to demonstrate superiority of any combination scheme over another.

Another distinct feature of this study was that dosage regimens of each agent in different schemes were compared and thus we could rule out this issue as a potential cause of the observed differences. It is important since previous studies have not fully addressed the dosage of all antimicrobials in different schemes, and this has still been a point of controversy on the potential benefit of combing two in vitro active antimicrobials, i.e. potential differences in dosages that had not been addressed might explain the distinct outcomes between combination and monotherapy regimens. Actually, the mean doses administered to patients in the current study may be considered generally adequate, i.e. 2.8 mg/kg/day PMB, 6 g/day meropenem (2 g every 8 h over 3-h infusion), with the exception of tigecycline, since the mean dose corresponds to the usual dosage regimen (50 mg every 12 h) that may be suboptimal for isolates with MICs of 1.0 mg/L or even 0.5 mg/L [30]. Finally, the mean dose of amikacin (15.1 mg/kg administered once daily) may also be considered low, especially for susceptible isolates with MICs of 8 mg/L or 16 mg/L [31]. However, most (60%) of the isolates from patients receiving amikacin had an MIC ≤ 2 mg/L, for which these doses might be effective especially in combination with another active antimicrobial.

Regarding the other variables independently associated with 30-day mortality, one could be expected and has been found in previous studies, i.e. requirement for vasoactive drugs which was associated with increased risk of death [6,9,13,23,32,33]. The exception is the finding of non-surgical admission as a factor associated with a high mortality rate. Indeed, we could not find any difference in Charlson comorbidity index and Pitt bacteraemia score (data not shown) between surgical and non-surgical patients. Although a residual confounding of higher disease severity not captured by these scores might be determining such a finding, we cannot rule out a spurious association or confounding by other non-assessed factors.

Noteworthy, a recent multicentre observational study performed so far could only demonstrate a benefit for combination therapy in the subgroup of patients with high risk for mortality [8]. Although we could not stratify our patients by mortality risk, our cohort included patients with a median Charlson comorbidity index and Pitt bacteraemia score of 4 and 5, respectively, which are higher than the median values for these variables in the entire cohort of the INCREMENT study (2 and 2, respectively) [8]. Thus, it might suggest that the illness severity of the patients in the current study resembles that of the high-risk group of INCREMENT where combination therapy has been shown to be superior to monotherapy.

This study has some limitations that must be acknowledged, such as the relatively small number of patients, which precluded the evaluation of specific drug combinations. In addition, it is a single-centre study so any extrapolation warrants caution. Finally, 34 isolates were not tested for PMB MIC and were considered susceptible to this agent based on the 90% susceptibility rate that was found in tested isolates. This might have biased the overall results if, in fact, isolates from the group of monotherapy plus one in vitro non-active agent were resistant and not susceptible to PMB. On the other hand, if isolates from the group of combination with two in vitro active agents were resistant, it would favour the null hypothesis. However, based on the resistance rate of tested isolates, it would be not expected to have occurred in >10% of isolates, which in absolute numbers represent one isolate. To further test the impact that this PMB non-tested isolates could have on the results, a worst-case scenario analysis was performed considering all non-tested isolates as non-susceptible to PMB. Although not statistically significant, the combination therapy group presented better outcomes than the monotherapy group also in the worst-case scenario. Thus, we believe that the main results have not been affected by this limitation.

In conclusion, this retrospective cohort showed a 30-day mortality rate of 48.8% in KPC-KP BSIs. PMB-containing schemes in combination with another in vitro active antimicrobial, mostly amikacin, were independently associated with lower 30-day mortality. Further studies are necessary to evaluate specific drug combinations.

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Competing interests

APZ is a research fellow of the National Council for Scientific and Technological Development (CNPq), Ministry of Science and Technology, Brazil, and has received honoraria for speaking engagements and consultancy from AstraZeneca, Cipla, MSD, Pfizer and United Pharmaceuticals; DRF has given paid lectures and consultancy for Pfizer, United Medical and Gilead Sciences. All other authors declare no competing interest.

Ethical approval

This study was approved by the local ethics committee of Hospital Nossa Senhora da Conceição (Porto Alegre, RS, Brazil) [CAEE 52205315.0.3001].

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