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Combination Regimens for Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infections

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Previous studies reported decreased mortality in patients with carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections (BSIs) treated with combination therapy but included carbapenem-susceptible and -intermediate isolates, as per revised CLSI breakpoints. Here, we assessed outcomes in patients with BSIs caused by phenotypically carbapenem-resistant *K. pneumoniae* (CRKP) according to the number of *in vitro* active agents received and whether an extended-spectrum beta-lactam (BL) antibiotic, including meropenem, or an extended-spectrum cephalosporin was administered. We retrospectively reviewed CRKP BSIs at two New York City hospitals from 2006 to 2013, where all isolates had meropenem or imipenem MICs of ≥4 μg/ml. Univariate and multivariable models were created to identify factors associated with mortality. Of 141 CRKP BSI episodes, 23% were treated with a single active agent (SAA), 26% were treated with an SAA plus BL, 28% were treated with multiple active agents (MAA), and 23% were treated with MAA plus BL. Ninety percent of isolates had meropenem MICs of ≥16 μg/ml. Thirty-day mortality was 33% overall and did not significantly differ across the four treatment groups in a multivariable model ($P = 0.4$); mortality was significantly associated with a Pitt bacteremia score of ≥4 (odds ratio [OR], 7.7; 95% confidence interval [CI], 3.2 to 18.1; $P = 0.1$), and immunosuppression was protective (OR, 0.4; 95% CI, 0.2 to 1.0; $P = 0.04$). Individual treatment characteristics were also not significantly associated with outcome, including use of SAAs versus MAA (26% versus 38%, $P = 0.1$) or BL versus no BL (26% versus 39%, $P = 0.1$). In summary, in patients with CRKP BSIs caused by isolates with high carbapenem MICs, the role of combination therapy remains unclear, highlighting the need for prospective studies to identify optimal treatment regimens.

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has emerged as a global threat over the past decade and is now endemic in many countries, largely due to the dissemination of carbapenem-hydrolyzing beta-lactamases such as the *K. pneumoniae* carbapenemase (KPC) (1, 2). In New York City, where KPC-producing *K. pneumoniae* isolates were identified as early as 1997, carbapenem resistance is now detected in up to 30% of hospital *K. pneumoniae* isolates (3, 4). These pathogens often harbor genes conferring resistance to multiple antibiotic classes in addition to beta-lactams, severely limiting treatment options (5). Invasive infections due to CRKP are associated with poor outcomes (6, 7), with hospital mortality rates of 40 to 70% in patients with bloodstream infections (BSIs) compared to 20 to 30% among matched patients with carbapenem-susceptible infections (8, 9).

Previous retrospective studies of BSIs caused by carbapenemase-producing *K. pneumoniae* found that patients treated with a combination of antibiotics were significantly more likely to survive than patients who received monotherapy (10–14). In these studies, combination regimens typically included colistin and tigecycline or an aminoglycoside, often in combination with a carbapenem antibiotic. Notably, for a large percentage of isolates in these studies MICs to carbapenems were relatively low, and the isolates may have retained phenotypic susceptibility in spite of molecular confirmation of carbapenemase gene carriage.

In this study, we assess the use of combination therapy for the treatment of CRKP BSI at two hospitals in New York City, where nosocomial CRKP isolates with MICs of >8 μg/ml are frequently encountered and where polymyxin B, rather than colistin, is the primary polymyxin agent in use. We chose to restrict our analysis to BSIs caused by *K. pneumoniae* isolates with phenotypic carbapenem resistance rather than isolates found to harbor carbapenemase genes as molecular testing is often unavailable in the clinical setting. The impact of adding a beta-lactam (BL) antibiotic, including a carbapenem or extended-spectrum cephalosporin (ESC), was also examined.

MATERIALS AND METHODS

Setting and patient population. We included all adult patients (age of ≥18 years) hospitalized at two large academic medical centers in New York City who had a blood culture positive for CRKP from 2006 to 2013. Patients who did not receive at least 48 h of antibiotic therapy with at least one active agent (an agent to which the isolate was susceptible *in vitro*) or who had polymicrobial bacteremia within 5 days of CRKP BSI onset (with the exception of a single positive blood culture for coagulase-negative *Staphylococcus* spp.) were excluded. Successive BSIs occurring in an individual patient were also excluded when they occurred ≤30 days after

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treatment completion for the previous infection. The study protocol was approved by the Institutional Review Boards at both participating centers.

Data collection. Data were extracted from patient electronic medical records at each institution and pooled for data analysis, including chronic disease comorbidities, hemodynamic parameters, laboratory values, and need for intensive care unit (ICU) admission, mechanical ventilation, or renal replacement therapy (RRT). Neutropenia was defined as having an absolute neutrophil count of ≤500 cells/mm^3 on the date of positive blood culture. Comorbidities were summarized using the Charlson comorbidity index score (CCIS) (15), and the Pitt bacteremia score (PBS) (16) was used to assess disease severity at the time of positive blood culture. Presumed source of infection was determined using CDC/National Healthcare Safety Network (NHSN) surveillance definitions (17) and then grouped into the following categories: catheter-associated, respiratory tract, intra-abdominal, mucosal translocation, soft tissue or wound, or urinary tract infection. Receipt of a source control measure was defined as removal or change of a central line or Foley catheter or as removal or drainage of an intra-abdominal source of infection, if present, within 7 days of positive blood culture.

Microbiology. Isolate identification and antibiotic susceptibility profiles were based on the index blood culture isolate only and were primarily obtained using Vitek2 automated testing (bioMérieux, Durham, NC), with confirmatory Etests (bioMérieux) of a small number of isolates, per a routine clinical microbiology laboratory protocol at each institution. Antibiotic susceptibilities were reviewed for all isolates and were reported according to current Clinical and Laboratory Standards Institute (CLSI) interpretive breakpoints (18). Carbapenem resistance was defined as resistance to meropenem or imipenem using an MIC breakpoint of ≥4 μg/ml, following revision of MIC breakpoints in 2010 (19). MICs of polymyxin B and tigecycline were derived from Etest results or from broth microdilution panels (Thermo Scientific TREK Diagnostic Systems, Cleveland, OH). Isolates with polymyxin B MICs of >2 μg/ml were considered to be resistant to this agent, and tigecycline susceptibilities were determined using U.S. FDA breakpoints (20). For a subset of isolates, the presence of the bla_{KPC} gene was determined by PCR using previously established primers and PCR parameters (21, 22).

Treatment regimens. During the study period, there was no standard hospital protocol guiding clinicians' selection of therapeutic regimens for patients with CRKP BSI. However, the use of polymyxin B, tigecycline, carbapenems, and ESCs required telephone or formal consultation and approval by an infectious diseases pharmacist or physician. The definitive regimen was defined as the agent(s) used for the greatest number of days during the first 7 days after collection of the index blood culture and included antibiotics with *in vitro* activity against the CRKP isolate as well as BLs. Patients were categorized according to whether they received a single *in vitro* active agent (SAA) or multiple active agents (MAA), and BL use was defined as addition of a carbapenem or ESC to the definitive regimen. Meropenem was the only carbapenem used to treat CRKP BSI during the study period at our centers, and its dosing was classified into conventional (500 mg every 6 h or equivalent dosing for patients with renal insufficiency), high-dose (2 g every 8 h or equivalent), or high-dose, extended-infusion (2 g administered over 3 h every 8 h or equivalent) dosing categories. ESCs included cefepime and ceftazidime.

Statistical analysis. The primary outcome was all-cause mortality within 30 days of the index blood culture. The secondary outcome was a composite of survival and clearance of blood cultures within 7 days after the index blood culture. In a univariate analysis, categorical variables were compared using χ^2 or Fisher's exact tests, and continuous variables were compared using Mann-Whitney-Wilcoxon or Kruskal-Wallis tests as appropriate. Treatment regimen was operationalized using two distinct binary variables (SAA versus MAA and addition of a BL versus no BL use) or a four-level categorical variable (SAA without a BL, SAA plus a BL, MAA without a BL, and MAA plus a BL). Variables with *P* value of <0.1 in the univariate analysis were considered for inclusion in a multivariable logistic regression model examining the association between treatment regimen and outcome. For the final parsimonious model, covariates were selected using backward, stepwise multivariable logistic regression modeling with *a priori* inclusion of treatment variables. In all analyses, *P* values of <0.05 were considered statistically significant. Data were analyzed using SAS, version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Patient population. Between 2006 and 2013, 313 episodes of CRKP bacteremia were identified, of which 141 episodes (occurring in 134 patients) were included in the following analyses. Of the 172 episodes that were excluded, 72 were polymicrobial, 54 did not receive at least 48 h of active antibiotic therapy, 26 occurred within 30 days of treatment completion for a previous CRKP BSI, 17 were not treated within 5 days of the initial positive blood culture, and 3 occurred in children.

Among included patients, the median patient age was 62 (interquartile range [IQR], 50 to 74 years), and 61% were male. Patients had multiple chronic disease comorbidities, including diabetes (33%), advanced kidney (23%) or liver disease (20%), hematologic malignancies (12%), and metastatic solid tumors (8%). Many were transplant recipients (23%) or were receiving immunosuppressant medications for other reasons (23%), while 4% were neutropenic at the time of BSI. At the onset of bacteremia, 62% of patients were in or required transfer to the ICU, and 31% developed septic shock within 48 h.

BSI characteristics. Bacteremias were largely hospital associated; 71% occurred more than 48 h after admission, and the median time to positive culture was 12 days from the date of admission (IQR, 2 to 42 days). The most frequent presumed source of BSI was intra-abdominal (23%), followed by urinary tract (22%) and respiratory tract (13%). Multiple sources were suspected in 16% of patients, and the source of infection could not be determined for 5% of patients. Of the 111 isolates for which meropenem MICs were available, 90% had a meropenem MIC of ≥16 μg/ml. Of the 82 isolates with reported MICs, 64% were resistant to cefepime (MIC of ≥16 μg/ml), and all tested isolates were resistant to ceftazidime. *In vitro* resistance to potential active agents is shown in Table 1. Resistance to polymyxin B and tigecycline occurred in 14% and 5% of isolates, respectively. Although most isolates (64%) were susceptible to gentamicin, rates of resistance to other aminoglycosides, levofloxacin, and trimethoprim-sulfamethoxazole were high. In a subset of 33 isolates that were tested for the presence of the bla_{KPC} gene using PCR amplification, 32 (97%) were positive.

Treatment regimens. Tigecycline (n = 85, 60%) and polymyxin B (n = 79, 56%) were the most commonly used active agents, followed by aminoglycosides (n = 44, 31%). Other active agents received by 12 patients (9%) included levofloxacin, trimethoprim-sulfamethoxazole, or minocycline. Meropenem was used to treat 49 patients (35%), and 20 patients (14%) received an ESC, all but one of whom received cefepime. Among patients treated with meropenem, 66% received conventional dosing (500 mg every 6 h), 21% were treated with high-dose (2 g every 8 h) meropenem, and 13% were treated with high-dose, extended-infusion (2 g administered over 3 h every 8 h) meropenem. The majority of patients receiving tigecycline received conventional dosing (100-mg loading dose, followed by 50 mg every 12 h; 96%). There were 56 patients (39%) for whom antibiotics were discontinued or changed within the first 7 days of therapy.

As shown in Table 2, definitive antibiotic regimens varied

TABLE 1 Antibiotic resistance profiles of CRKP isolates

Group or regimen	% of isolates resistant to:[a]							
	AMK (137)	GEN (140)	LVX (140)	MIN (5)	PMB (100)	TGC (130)	TOB (120)	SXT (114)
All treatment groups	68	36	92	0	14	5	93	84
SAA without a BL ($n = 32$)	71	35	89	0	9	3	91	75
SAA plus a BL ($n = 36$)	66	44	90	N/A	18	3	93	92
MAA without a BL ($n = 40$)	67	33	88	0	11	5	91	82
MAA plus a BL ($n = 33$)	73	33	100	0	18	6	94	89

[a] AMK, amikacin; GEN, gentamicin; LVX, levofloxacin; MIN, minocycline; PMB, polymyxin B; TGC, tigecycline; TOB, tobramycin; SXT, trimethoprim-sulfamethoxazole; SAA, single active agent; BL, beta-lactam antibiotic; MAA, multiple active agents. The number of isolates for which MICs were reported is indicated in parentheses next to the abbreviation.

widely. Overall, 68 patients (48%) received an SAA, of which 36 (26% of total) also received a BL and 32 (23% of total) did not. Polymyxin B or tigecycline was used to treat 75% of patients receiving an SAA. Of the 73 patients (52%) who received MAA, 33 (23% of total) received a BL, and 40 (28% of total) did not. MAA regimens included polymyxin B and tigecycline in 43 patients (59%), and 18 of these patients also received meropenem. As shown in Table 1, patients with polymyxin-resistant isolates appeared to be more likely to receive a BL, but isolate resistance profiles did not otherwise vary substantially across treatment categories.

TABLE 2 Mortality rates based on definitive regimen

Antibiotic regimen[e]	Patients (n)	30-day mortality rate (%)
All	141	33
With a BL	69	26[a]
Without a BL	72	39
SAA	68	26[b]
With a BL	36	19[c]
Without a BL	32	34
Polymyxin B	25	28
With a BL	18	28
Without a BL	7	29
Tigecycline	26	27
With a BL	9	11
Without a BL	17	35
Aminoglycoside	14	14
With a BL	9	11
Without a BL	5	20
Other[f]	3	67
MAA	73	38
With a BL	33	33[d]
Without a BL	40	43
Polymyxin B/tigecycline	43	44
With a BL	22	36
Without a BL	21	52
Polymyxin B/aminoglycoside	13	38
With a BL	5	60
Without a BL	8	25
Tigecycline/aminoglycoside	19	37
With a BL	8	50
Without a BL	11	27
Polymyxin B/tigecycline/aminoglycoside	5	60
With a BL	2	100
Without a BL	3	33
Other combinations	8	38

[a] $P = 0.1$ for use of a BL versus no BL.
[b] $P = 0.1$ for SAA versus MAA.
[c] $P = 0.2$ for SAA plus a BL versus SAA without a BL.
[d] $P = 0.4$ for MAA plus a BL versus MAA without a BL.
[e] SAA, single active agent; BL, beta-lactam antibiotic; MAA, multiple active agents.
[f] Other active agents included levofloxacin, trimethoprim-sulfamethoxazole, or minocycline.

Patient and infection characteristics grouped according to treatment category are shown in Table 3. Significant differences in sex, underlying neutropenia, and serum creatinine were identified across the four treatment groups. Females and neutropenic patients were more likely to receive SAA or MAA therapy plus a BL, and patients receiving MAA without a BL had higher serum creatinine levels on the date of positive blood culture. However, no significant differences in other baseline comorbidities, disease severity markers, or sources of infection were noted. There were no significant differences between patients who received SAAs and those who received MAA in the presumed sources of infection (overall, $P = 0.3$) or in the numbers of patients with CCISs of ≥4 (49% versus 60%, $P = 0.2$) or with disease severity markers such as PBSs of ≥4 (44% versus 42%, $P = 0.8$), ICU admission (57% versus 66%, $P = 0.3$), or development of septic shock (28% versus 33%, $P = 0.5$). Similarly, there were no significant differences between patients who received a BL and those who did not in the presumed source of infection (overall, $P = 0.3$), in the proportion of patients with CCISs of ≥4 (54% versus 56%, $P = 0.8$) or PBSs of ≥4 (41% versus 46%, $P = 0.5$), or in the numbers who required ICU admission (61% versus 63%, $P = 0.3$) or developed septic shock (28% versus 33%, $P = 0.5$).

Outcome. Overall, the 30-day mortality rate was 33%, and 72% of cases met the secondary outcome of survival and clearance of blood cultures at 7 days. There were no significant differences in 30-day mortality rates among patients who were treated with an SAA versus treatment with MAA (26% versus 38%, $P = 0.1$) and who received a BL versus no-BL treatment (26% versus 39%, $P = 0.1$). Similarly, the proportion of patients meeting the secondary outcome did not significantly differ between those treated with an SAA versus treatment with MAA (75% versus 70%, $P = 0.5$) or between those who received a BL versus those who did not (74% versus 71%, $P = 0.7$). When regimens were examined according to both the number of active agents received and whether or not patients received a BL, there were no significant differences across the four treatment groups in 30-day mortality (overall, $P = 0.2$) or in the composite secondary outcome (overall, $P = 0.6$). A lower proportion of patients who received meropenem died (24% versus 37%). However, this difference was not statistically significant ($P = 0.1$), even after adjustment for a meropenem MIC of ≤8

TABLE 3 Clinical characteristics based on treatment category

Parameter[a]	Value for the parameter by treatment[b]				*P* value[d]
	SAA without a BL ($n = 32$)	SAA plus a BL ($n = 36$)	MAA without a BL ($n = 40$)	MAA plus a BL ($n = 33$)	
Baseline patient characteristics					
Age (yr)[c]	67 (55–78)	60 (47–74)	69 (54–74)	58 (48–66)	0.051
Male sex	23 (72)	16 (44)	29 (73)	18 (55)	0.04*
CCIS of ≥4	16 (50)	17 (47)	24 (60)	20 (61)	0.6
Immunosuppressed	15 (47)	20 (56)	13 (33)	17 (52)	0.2
Neutropenic	1 (3)	6 (17)	0	5 (15)	0.02*
Severity of illness at time of BSI					
In or transferred to the ICU within 48 h	20 (63)	19 (53)	25 (63)	23 (70)	0.5
Serum creatinine (mg/dl)[c]	1.3 (0.9–2.4)	1.3 (0.8–2.4)	2.0 (1.1–2.8)	1.2 (0.7–1.8)	0.01*
Serum WBC (10^9/liter)[c]	12.2 (7.9–22.5)	9.5 (4.9–17.3)	10.9 (8.1–16.8)	13.2 (7.9–18.4)	0.8
Serum albumin (g/dl)[c]	2.4 (1.8–2.9)	2.7 (2.2–3.1)	2.2 (2.0–2.7)	2.7 (2.4–2.9)	0.07
RRT	9 (28)	9 (25)	18 (45)	12 (36)	0.3
PBS of ≥4	17 (53)	13 (36)	16 (40)	15 (45)	0.5
Septic shock	11 (34)	8 (22)	13 (33)	11 (33)	0.7
Presumed source of BSI					
Catheter-associated	4 (13)	2 (6)	2 (5)	2 (6)	0.5
Respiratory tract	4 (13)	1 (3)	9 (23)	5 (15)	
Intra-abdominal	6 (19)	10 (28)	8 (20)	8 (24)	
Mucosal translocation	3 (9)	4 (11)	1 (3)	4 (12)	
Soft tissue or wound	3 (9)	1 (3)	1 (6)	2 (3)	
Urinary tract	6 (19)	13 (36)	7 (18)	5 (15)	
Multiple	5 (16)	3 (8)	10 (25)	5 (15)	
Unknown	1 (3)	2 (6)	2 (5)	2 (6)	
Isolate susceptibility (MIC)					
Cefepime (≤8 μg/ml)	9 (50)	9 (60)	9 (35)	3 (14)	0.02*
Meropenem (≤8 μg/ml)	2 (7)	5 (21)	3 (9)	1 (4)	0.2
Polymyxin B (≤2 μg/ml)	22 (85)	26 (87)	33 (85)	24 (80)	0.9
Tigecycline (≤2 μg/ml)	28 (93)	28 (88)	29 (78)	27 (87)	0.4

[a] CCIS, Charlson comorbidity index score; BSI, bloodstream infection; ICU, intensive care unit; WBC, white blood cell count; RRT, renal replacement therapy; PBS, Pitt bacteremia score.
[b] Values represent the number (%) of patients unless otherwise indicated. SAA, single active agent; BL, beta-lactam antibiotic; MAA, multiple active agents.
[c] Values are medians (interquartile range).
[d] Significant differences are indicated. (*, $P < 0.05$).

μg/ml versus >8 μg/ml or for meropenem dosing category (conventional, high-dose, or high-dose, extended-infusion dosing) ($P = 0.4$). Moreover, in the subset of patients with CRKP isolates with meropenem MICs of ≤8 μg/ml ($n = 11$), 30-day mortality did not significantly differ between patients treated with an SAA and those treated with MAA (33% versus 67%, $P = 0.5$), but only three patients met this outcome. Similarly, in patients treated with ESCs, outcomes did not significantly differ based on isolate susceptibilities and treatment regimens (data not shown). No other individual regimen components were significantly associated with outcome. In the subset of patients with PBSs of ≥4 ($n = 61$), there was no significant difference in mortality between patients treated with an SAA and those treated with MAA (50% versus 61%, $P = 0.4$).

In a univariate analysis (Table 4), 30-day mortality was significantly associated with a CCIS of ≥4 and several markers of disease severity, including a higher PBS, need for RRT, and presence of septic shock. Receipt of immunosuppressants was associated with lower mortality. A multivariable model including the four treatment categories, adjusted for underlying comorbidities and disease severity, is shown in Table 5. Here, there were no statistically significant differences in outcomes between any of the treatment categories (overall, $P = 0.4$). A PBS of ≥4 was found to be independently associated with outcome (odds ratio [OR], 7.7; 95% confidence interval [CI], 3.2 to 18.1; $P < 0.0001$), and immunosuppression appeared to be protective (OR, 0.4; 95% CI, 0.2 to 1.0; $P = 0.04$). In a separate model considering the number of active agents and BL use as separate binary predictors, differences were again not statistically significant (data not shown).

DISCUSSION

In contrast to previous retrospective studies assessing carbapenemase-producing, but not necessarily carbapenem-resistant, *K. pneumoniae* BSIs, we did not find a significant association between use of multiple agents with *in vitro* activity and mortality. Similarly, addition of a BL to either an SAA or MAA did not significantly improve outcome. These findings were confirmed in multivariable models that adjusted for comorbid conditions and disease severity.

Five previous retrospective studies using a similar methodology found a positive association between the number of agents used to treat carbapenemase-producing *K. pneumoniae* BSIs and

TABLE 4 Univariate analysis of factors associated with 30-day mortality

Variable[a]	Value for the survival period[b]		*P* value[d]
	Death within 30 days ($n = 46$)	Survival to 30 days ($n = 95$)	
Baseline patient characteristics			
Age (yr)[c]	67 (55–73)	59 (49–74)	0.1
Male sex	25 (54)	61 (64)	0.3
CCIS of ≥4	31 (67)	46 (48)	0.03*
Immunosuppressed	14 (30)	51 (54)	0.009*
Neutropenic	2 (4)	10 (11)	0.3
Severity of illness at time of BSI			
In or transferred to the ICU within 48 h	36 (78)	51 (54)	0.005*
Serum creatinine (mg/dl)[c]	1.25 (0.9–2.5)	1.5 (0.9–2.2)	0.5
Serum WBC (10^9/liter)[c]	13.1 (8.1–17.9)	10.6 (6.9–17.7)	0.07
Serum albumin (g/dl)[c]	2.4 (2.0–2.8)	2.5 (2.1–3.0)	0.08
RRT	23 (50)	25 (26)	0.005*
PBS of ≥4	34 (74)	27 (28)	<0.0001*
Septic shock	24 (52)	19 (20)	0.0001*
BSI treatment-related factors			
Days from BSI to active therapy	1 (0–3)	2 (1–3)	0.4
Source control within 7 days	29 (67)	49 (67)	1.0
Presumed source of BSI			
Catheter-associated	3 (7)	7 (7)	0.7
Respiratory tract	8 (17)	11 (12)	
Intra-abdominal	11 (24)	21 (22)	
Mucosal translocation	4 (9)	8 (8)	
Soft tissue or wound	2 (4)	5 (5)	
Urinary tract	6 (13)	25 (26)	
Multiple	10 (22)	13 (14)	
Unknown	2 (4)	5 (5)	
Initial isolate susceptibility (MIC)			
Cefepime (≤8 μg/ml)	12 (39)	18 (36)	0.8
Meropenem (≤8 μg/ml)	3 (8)	8 (11)	1.0
Polymyxin B (≤2 μg/ml)	35 (83)	70 (84)	0.9
Tigecycline (≤2 μg/ml)	38 (86)	74 (86)	0.9

[a] CCIS, Charlson comorbidity index score; BSI, bloodstream infection; ICU, intensive care unit; WBC, white blood cell count; RRT, renal replacement therapy; PBS, Pitt bacteremia score.
[b] Values represent the number (%) of patients unless otherwise indicated.
[c] Values are medians (interquartile range).
[d] Significant differences are indicated (*, $P < 0.05$).

TABLE 5 Multivariable analysis of factors associated with 30-day mortality

Variable[a]	Odds ratio of 30-day mortality	95% CI[b]	*P* value[c]
CCIS of ≥4	1.9	0.8–4.5	0.1
Immunosuppression	0.4	0.2–1.0	0.04*
PBS of ≥4	7.7	3.2–18.1	<0.0001*
SAA without a BL (reference)[d]			
SAA plus a BL[d]	0.6	0.2–2.1	0.4
MAA without a BL[d]	1.8	0.6–5.6	0.3
MAA plus a BL[d]	1.1	0.3–3.6	0.9

[a] CCIS, Charlson comorbidity index score; PBS, Pitt bacteremia score; SAA, single active agent; BL, beta-lactam antibiotic; MAA, multiple active agents.
[b] CI, confidence interval.
[c] Significant differences are indicated (*, $P < 0.05$).
[d] Overall *P* value of 0.4.

survival. In two small studies, use of multiple agents was significantly associated with improved survival, including in a multivariable analysis (10, 11). A study by Tumbarello et al. assessed factors associated with 30-day mortality in 125 patients with KPC-producing *K. pneumoniae* (KPC-*Kp*) BSI (12). In this study, 54% of patients who received monotherapy died, in contrast to 34% of patients who received combination therapy, and postantibiogram treatment with a combination of tigecycline, colistin, and meropenem was independently associated with 30-day survival. Daikos et al. reported similar findings in a study of 205 patients with a BSI caused by KPC- or VIM-producing *K. pneumoniae* (13). Here, use of combination therapy was independently associated with 28-day survival, mortality was lowest in patients who received a carbapenem-containing combination regimen, and the use of combination therapy appeared to have the greatest benefit in patients with severe sepsis, septic shock, and rapidly fatal underlying disease (13). A more recent, larger study by Tumbarello et al. of KPC-*Kp* infections, including 447 BSIs, also found use of two or more *in*

vitro active agents to be associated with higher survival (14). Notably, Tzouvelekis et al. also identified a survival benefit associated with the use of combination therapy in a large analysis of 899 patients previously included in 20 studies with carbapenemase-producing *K. pneumoniae* infection at any site, in whom 75% had KPC-*Kp* infections (23).

In a univariate analysis, 30-day mortality was lower among patients treated with an SAA (26%) than in patients treated with MAA (38%) although the difference was not statistically significant ($P = 0.1$). This association remained nonsignificant after values were adjusted for patient comorbidities and severity of illness. The basis of our disparate findings is unclear. Notably, polymyxin B was the primary polymyxin agent used in this study, whereas previous studies were conducted in centers using colistin. Polymyxin B may offer pharmacologic advantages compared to colistin, including faster achievement of target blood levels and more predictable pharmacokinetics independent of renal function (24–26), diminishing the benefit of additional agents. However, tigecycline monotherapy was used with equivalent frequency and produced relatively low mortality rates. In prior analyses, patients treated with tigecycline had an increased risk of death versus those treated with comparator antibiotics (27).

In this study, 30-day mortality was lower among patients who received a BL (26%) than among those who did not (39%). However, this difference was not statistically significant ($P = 0.1$) and narrowed further after adjustment for comorbidities and disease severity. Importantly, we limited our analysis to phenotypically carbapenem-resistant *K. pneumoniae* isolates. The MIC of meropenem was >8 μg/ml in 90% of bloodstream isolates in this study, compared to 62 to 67% in two studies by Tumbarello et al. (12, 14). These authors reported successful treatment in 87% of patients treated with meropenem-containing regimens when the meropenem MIC was ≤4 μg/ml, compared to 67% when the meropenem MIC was ≥8 μg/ml (12), and Daikos et al. describe similar findings (13). Our results suggest that the benefit of adding a carbapenem to one or more active agents for the treatment of CRKP bacteremia is diminished when meropenem MICs are >8 μg/ml. Adjusting for meropenem dosing or MIC did not significantly alter the association between meropenem treatment and outcomes. Whereas in previous studies high doses of meropenem were used (2 g administered every 8 h) (12, 13), the number of patients receiving high-dose, extended-infusion meropenem in this study was small. We also did not find a mortality benefit associated with cefepime use although 30% of isolates were susceptible or susceptible, dose-dependent to cefepime. Additional studies are needed to evaluate the use of meropenem and cefepime in this patient population.

Our study had several limitations. Given the retrospective study design, our sample size was restricted to historical cases and may have been too small to allow us to detect subtle differences in treatment-related outcomes, particularly across the four treatment groups. We were unable to define all clinical factors influencing antibiotic selection and may have failed to fully account for disease severity in patients who received MAA in our multivariable model. In order to operationalize treatment regimens, we were required to assign a definitive treatment regimen to each BSI episode although antibiotic changes during the course of treatment may have affected outcomes. Similarly, only patients who received at least 48 h of active therapy and did not have polymicrobial bacteremia were included, which may have led to the exclusion of patients highly likely to have a poor outcome. For example, patients with hematologic malignancies who develop CRKP BSIs were previously shown to die often within 4 days of BSI onset (28). Exclusion of these patients may also account for the paradoxically lower mortality rates seen in immunosuppressed patients. Although we did not perform molecular testing on all isolates to identify carbapenem resistance mechanisms, two recent studies of CRKP BSI in New York City, both of which included the centers in this study, reported that 94% and 100% of CRKP isolates were KPC producers (29, 30). Our molecular testing of a limited number of isolates in this study confirmed these findings. Last, we did not evaluate susceptibility to ceftazidime/avibactam among our clinical isolates as this analysis predated FDA approval of this agent. Although this compound has been shown to have *in vitro* activity against KPC-*Kp* (31), its utility in clinical settings has not been assessed.

In summary, in this retrospective study of treatment regimens for CRKP BSI in an area where CRKP is endemic, we did not find that the use of multiple *in vitro* active agents or the addition of a BL antibiotic is associated with improved survival compared to monotherapy. Differences in the degree of carbapenem resistance and the use of polymyxin B instead of colistin may explain differences in our findings compared to those of previous studies that showed a survival benefit with the use of multiple agents. These discrepant results from observational studies highlight the need for adequately powered prospective, randomized trials to resolve the role of combination therapy in the treatment of CRKP BSI.

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