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Treatment Outcome of Bacteremia Due to KPC-Producing *Klebsiella pneumoniae*: Superiority of Combination Antimicrobial Regimens

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***Klebsiella pneumoniae* producing *Klebsiella pneumoniae* carbapenemase (KPC) has been associated with serious infections and high mortality. The optimal antimicrobial therapy for infection due to KPC-producing *K. pneumoniae* is not well established. We conducted a retrospective cohort study to evaluate the clinical outcome of patients with bacteremia caused by KPC-producing *K. pneumoniae*. A total of 41 unique patients with blood cultures growing KPC-producing *K. pneumoniae* were identified at two medical centers in the United States. Most of the infections were hospital acquired (32; 78%), while the rest of the cases were health care associated (9; 22%). The overall 28-day crude mortality rate was 39.0% (16/41). In the multivariate analysis, definitive therapy with a combination regimen was independently associated with survival (odds ratio, 0.07 [95% confidence interval, 0.009 to 0.71], $P = 0.02$). The 28-day mortality was 13.3% in the combination therapy group compared with 57.8% in the monotherapy group ($P = 0.01$). The most commonly used combinations were colistin-polymyxin B or tigecycline combined with a carbapenem. The mortality in this group was 12.5% (1/8). Despite *in vitro* susceptibility, patients who received monotherapy with colistin-polymyxin B or tigecycline had a higher mortality of 66.7% (8/12). The use of combination therapy for definitive therapy appears to be associated with improved survival in bacteremia due to KPC-producing *K. pneumoniae*.**

Since the initial report in 2001, *Klebsiella pneumoniae* that produces KPC (*K*lebsiella *p*neumoniae *c*arbapenemase)-type β-lactamase has proliferated in hospital environments in the United States and worldwide (3, 12). KPC-producing *K. pneumoniae* is typically resistant to carbapenems as well as cephalosporins and other classes of antimicrobials, leaving few choices for treatment of infections. Mortality from infections due to KPC-producing *K. pneumoniae* has been reported to be at least 50% (2, 11, 15, 18). Whereas some KPC-producing *K. pneumoniae* are reported as susceptible to carbapenems, especially imipenem, the clinical significance of this phenomenon is not well defined. A recent report from New York City, NY, pointed out high clinical failure rates of carbapenem monotherapy when it was given to treat patients with KPC-producing *K. pneumoniae* reported to be susceptible to imipenem or meropenem (17). However, a limitation of that study and some previous studies addressing clinical outcome in patients from whom KPC-producing *K. pneumoniae* have been isolated has been distinguishing between colonization and actual infection. To address this problem, we conducted a retrospective cohort study to assess the clinical and microbiologic outcome after various treatment regimens that included only patients with documented bacteremia due to KPC-producing *K. pneumoniae*.

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MATERIALS AND METHODS

Study design and patients. Cases of bacteremia due to *K. pneumoniae* were identified at two medical centers, one in New York City, NY, and the other in Pittsburgh, PA, between 2005 and 2009. Clinical data were collected from electronic medical records and deidentified for further review; only the first episode of bacteremia was included for each patient. At least one isolate was collected from each case for microbiologic analysis. All ertapenem nonsusceptible *K. pneumoniae* isolates, as determined by either the disk diffusion method or MicroScan (Siemens Healthcare Diagnostics, Deerfield, IL) based on the breakpoints at the time of the case identification, were subjected to PCR analysis for identification of the KPC gene (8). Only the cases whose isolates were confirmed to carry the KPC gene were included in this analysis. The study was approved by the institutional review boards at both participating sites.

Definitions. The source of infection leading to bacteremia was determined as pneumonia, urinary tract infection, surgical site infection, intra-abdominal infection, line-related infection, or primary bacteremia using the definitions by the Centers for Disease Control and Prevention (9). Severity of illness at the time of onset of infection was assessed by the acute physiology and chronic health evaluation II (APACHE II) score (14). Immunocompromised state was defined as the presence of diabetes mellitus, neutropenia, HIV infection, or receipt of steroids (at least 20 mg of prednisone or equivalent a day for at least a month) or other immunosuppressive agents in the 30 days prior to bacteremia. Appropriate therapy was defined as treatment with at least one agent for at least 48 h to which the isolate was susceptible *in vitro* based on the interpretative criteria from the Clinical and Laboratory Standards Institute (CLSI) published in 2011 (6). Empirical therapy was defined as treatment given before final culture results became available. Definitive therapy was defined as antimicrobial therapy given after the susceptibility testing results became available, regardless of the *in vitro* susceptibility to the agent. Combination therapy was defined as administration of two antimicrobials with Gram-negative

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activity for at least 48 h after the susceptibility results became available, regardless of the *in vitro* susceptibility to each agent.

Predictors of mortality. The primary outcome measure was death within 28 days from the onset of bacteremia. Risk factors for mortality in patients having bacteremia due to KPC-producing *K. pneumoniae* were investigated by comparing clinical variables of patients who died within 28 days of infection against those who survived. The variables reviewed included demographic data, admission from a nursing home, any surgery or prior use of antimicrobials with Gram-negative activity in the prior 30 days, presence of indwelling devices at the time of infection, prior hospitalization, intensive care unit (ICU) admission, surgery, or dialysis in the preceding year, length of hospital stay before the onset of bacteremia, inappropriate empirical therapy, combination therapy for definitive treatment, appropriate therapy at any time, ICU stay at the time of infection, the source of bacteremia, APACHE II score, immunocompromised state, history of organ transplant, and history of various underlying diseases.

Microbiologic methods. The MICs of various antimicrobials, including carbapenems, were determined by the broth microdilution method using Sensititre GNX2F plates (TREK Diagnostic Systems, Cleveland, OH). The results were interpreted according to the breakpoints published by CLSI in 2011, which include the revised breakpoints for cephalosporins and carbapenems for *Enterobacteriaceae* (6). In addition, carbapenem MICs were determined using Etest (bioMérieux, Durham, NC) for isolates of the cases treated with this group of agents.

The KPC type was determined as KPC-2 or KPC-3 for each isolate by nucleotide sequencing using an ABI3730xl instrument (Applied Biosystems, Foster City, CA). Genetic relatedness of the isolates was determined by pulsed-field gel electrophoresis (PFGE) using SpeI (New England BioLabs, Ipswich, MA).

Statistical analysis. Statistical analysis was performed by using the SPSS statistical software (version 19; SPSS Inc., Chicago, IL). The Student *t* test was used to compare the continuous variables. Categorical variables were evaluated by using the χ^2 test or Fisher's exact test, as appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. To identify independent predictors of mortality, variables with a *P* value of $\leq$0.15 on a univariate analysis were included in a stepwise conditional multivariate logistic regression model. All *P* values were two-tailed, and a *P* value of $\leq$0.05 was considered statistically significant.

RESULTS

A total of 41 unique cases of bacteremia with KPC-producing *K. pneumoniae* were identified during the study period. The demographics and clinical characteristics of the cases are shown in Table 1. The ages of the patients ranged from 25 to 90 years, with a median of 62 years. There were 17 male and 24 female patients. Most of the infections (32; 78.0%) were hospital acquired, while the rest of cases (9; 22.0%) were health care associated. There were no community-acquired cases. All but one patient (40; 97.5%) had been admitted to the hospital within a year prior to the episode of bacteremia, with the majority of them (28; 70%) having been admitted to an ICU. The most common sources of infection were an intravascular catheter (13; 31.7%), pneumonia (10; 24.4%), and urinary tract infection (7; 17.1%). The source of bacteremia could not be identified in 6 patients, and these cases were defined as primary bacteremia. The majority of the patients received inappropriate empirical antimicrobial therapy before the susceptibility results became available (26 [63.4%] by the CLSI 2009 breakpoints prior to the revision and 32 [78.0%] by the revised CLSI 2011 breakpoints).

The overall 28-day mortality was 39.0% (16/41). The results of univariate and multivariate analyses for predictors of mortality are shown in Table 1. In the univariate analysis, pneumonia as the source of infection (OR, 5.7 [95% CI, 0.98 to 3.68], $P = 0.03$), presence of cardiovascular disease (OR, ∞ [95% CI, 1.59 to ∞], $P = 0.01$), and chronic liver disease (OR, ∞ [95% CI, 0.72 to ∞], $P = 0.05$) were significantly associated with mortality, while combination therapy was strongly associated with survival (OR, 0.13 [95% CI, 0.01 to 0.82], $P = 0.01$). In the multivariate analysis, no risk factor was found to be independently associated with the mortality. However, combination therapy as definitive therapy still remained as an independent predictor of survival (OR, 0.07 [95% CI, 0.009 to 0.71], $P = 0.02$) as shown in Table 1.

We thus further analyzed the cases which received definitive antimicrobial therapy. Seven cases were excluded from this analysis either because they did not receive any definitive antimicrobial therapy or received it for less than 48 h or because they died before receiving any definitive therapy. The 28-day mortality for the remaining 34 cases was 38.2% (13/34). Of these 34 cases, 15 patients (44.1%) received combination therapy and 19 patients (55.9%) received monotherapy as definitive therapy. There were no statistically significant differences between the demographics and the clinical characteristics, including severity of illness at the time of infection, among patients treated with combination therapy or monotherapy, except that the transplant patients were more common in the combination therapy group (Table 2).

Two of the 15 patients (13.3%) receiving combination therapy died within 28 days of the onset of bacteremia, compared with 11 of 19 patients (57.8%) receiving monotherapy ($P = 0.01$). The regimens of combination therapy and monotherapy are shown in Table 3. The most common combination regimens were a carbapenem with either colistin-polymyxin B (5 cases) or tigecycline (3 cases). Only 1 of these 8 patients died within 28 days. All of these 8 isolates were susceptible to colistin-polymyxin B (MIC range, $\leq$0.25 to 0.5 μg/ml) or tigecycline (MIC range, $\leq$0.25 to 1 μg/ml). For carbapenems, all 8 isolates were resistant according to the CLSI 2011 breakpoints (6). Under the CLSI 2009 breakpoints which were in place at the time of the cases (4), 5 were nonsusceptible, while 3 were susceptible to respective carbapenems with MICs of 4 μg/ml. The isolate from the only patient who died in this carbapenem combination group was nonsusceptible to doripenem with an MIC of $>$2 μg/ml. In the monotherapy group, 7, 5, and 4 patients received colistin-polymyxin B, tigecycline, or carbapenem, respectively. The isolates from all 7 patients who received colistin-polymyxin B as monotherapy had MICs in the susceptible range of $\leq$0.25 to 0.5 μg/ml, but the mortality was 57.1% (4/7) nonetheless. Isolates from the 5 patients who received tigecycline as monotherapy also had MICs in the susceptible range ($\leq$0.25 to 0.5 μg/ml) but 4 (80.0%) died. Among the 4 patients who received carbapenem monotherapy, 3 received imipenem (MICs, 2 to 4 μg/ml) and 1 of them (33.3%) died. The last patient in the carbapenem monotherapy group received meropenem (MIC, $>$8 μg/ml). This patient also died within 28 days. Each of the remaining 3 patients received ampicillin-sulbactam (resistant), gentamicin (susceptible), or piperacillin-tazobactam (resistant).

Table 4 shows the susceptibility of the 41 isolates, interpreted according to the breakpoints before and after the revision. Some KPC-producing *K. pneumoniae* are reported as susceptible to carbapenems, in particular imipenem, when automated susceptibility testing methods are used under the previous CLSI breakpoints (5). In our series, 23 isolates (56.1%) were susceptible to imipenem according to the breakpoints prior to the revision. How-

TABLE 1 Predictors of mortality in 41 patients with bacteremia due to KPC-producing *K. pneumoniae*

Variable	Survived ($n = 25$)[a]	Died ($n = 16$)[a]	Univariate analysis		Multivariate analysis[b]	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Demographics						
Caucasian	14 (56)	6 (37.5)	0.4 (0.10–2.02)	0.34		
Age ≥65	9 (36)	8 (50)	1.5 (0.35–6.44)	0.74		
Male	10 (40)	7 (43)	1.1 (0.27–5.02)	1.00		
APACHE II ≥20	12 (48)	9 (56)	0.7 (0.13–4.24)	0.72		
In ICU at enrollment	13 (52)	9 (56)	1.5 (0.35–6.45)	0.75		
Therapy						
Inappropriate empirical therapy	21 (65.6)	11 (34.3)	0.2 (0.07–2.33)	0.27		
Combination definitive therapy	13 (60)	2 (12.5)	0.13 (0.01–0.82)	0.01	0.07 (0.009–0.71)	0.02
Appropriate therapy at any time	18 (78.2)	10 (62.5)	0.46 (0.08–2.35)	0.30		
Source of bacteremia						
Pneumonia	3 (12)	7 (43.7)	5.7 (0.98–3.68)	0.03		
Line related	9 (36)	4 (25)	0.5 (0.12–2.88)	0.51		
Urinary tract	5 (20)	2 (12.5)	0.5 (0.12–2.88)	0.51		
Primary bacteremia	5 (20)	1 (6.2)	0.2 (0.01–2.87)	0.38		
Underlying diseases						
Diabetes mellitus	5 (20)	5 (31.2)	1.8 (0.35–9.67)	0.48		
Chronic renal failure	5 (20)	4 (25)	1.3 (0.24–7.47)	0.72		
COPD[c]	2 (8)	0 (0)	0.0 (0.00–6.72)	0.51		
Cardiovascular	0	5 (31.2)	∞ (1.59–∞)	0.01		
Cerebrovascular	2 (8)	0	0.0 (0.00–6.72)	0.51		
Chronic liver disease	0	3 (18.7)	∞ (0.72–∞)	0.05		
Malignancy	5 (20)	3 (18.7)	0.9 (0.14–5.67)	1.00		
Solid organ malignancy	5 (20)	2 (12.5)	0.5 (0.06–4.16)	0.68		
Transplant	7 (28)	2 (12.5)	0.3 (0.04–2.46)	0.44		
HIV	2 (8)	1 (6.2)	0.7 (0.02–2.47)	1.00		
Immunocompromised state	16 (64)	10 (66.6)	0.9 (0.21–4.18)	1.00		
Renal dialysis	5 (20)	6 (37.5)	2.4 (0.48–12.39)	0.28		
Events in prior 30 days						
Prior use of antimicrobials	18 (72)	13(81.2)	1.6 (0.30–10.27)	0.71		
Surgery	9 (36)	6 (37.5)	1.0 (0.24–4.73)	1.00		
Events in prior year						
Hospitalization	24 (96)	16 (100)	∞ (0.03–∞)	1.00		
Surgery	17 (68)	8 (50)	0.5 (0.10–2.05)	0.33		
Admitted to ICU	18 (72)	10 (62.5)	0.6 (0.14–3.00)	0.73		
Indwelling devices						
Urinary catheter	9 (36)	9 (56)	2.2 (0.53–0.12)	0.33		
Tracheostomy tube	12 (48)	5 (31.2)	0.4 (0.11–2.19)	0.34		
Vascular catheter	18 (72)	13 (81.2)	1.7 (0.30–10.27)	0.71		
Gastrostomy tube	9 (36)	7 (43.7)	1.4 (0.32–6.04)	0.75		

[a] Data are presented as *n* (%).
[b] Combination definitive therapy, pneumonia as the source of bacteremia, chronic liver disease, and coronary artery disease were included in the multivariate analysis.
[c] COPD, chronic obstructive pulmonary disease.

ever, only 2 (4.9%) were susceptible under the revised breakpoints. When we tested the MICs of imipenem using the Etest method against 11 isolates for which the cases were treated with this agent, 9 isolates had MICs of >32 μg/ml. This included 3 isolates that were reported as susceptible and another 3 isolates that were reported as intermediate at the time of infection.

Twenty-one isolates produced KPC-2, while 20 produced KPC-3. According to PFGE, the isolates were grouped into 14 pulse types using a similarity cutoff value of 85%. The two largest pulse types had 9 and 7 isolates, all of which were from the study site in New York City, NY. However, using a cutoff value of 75%, 36 of the 41 isolates clustered together, including isolates from both study sites (data not shown).

DISCUSSION

KPC-producing *K. pneumoniae* has become a major hospital pathogen worldwide, and infections due to this organism have been associated with high mortality (2, 11, 15, 18). The increasing prevalence and the high mortality associated with the organism underscore the importance of effective antimicrobial therapy for these serious infections. However, optimal treatment for infections caused by KPC-producing *K. pneumoniae* has not yet been defined (13).

Our study involved 41 unique patients with bacteremia due to KPC-producing *K. pneumoniae*. The overall 28-day mortality rate of 39.0%, which is slightly lower than the rates reported for KPC-producing *K. pneumoniae* bacteremia in previous studies (2, 18),

TABLE 2 Analysis of clinical variables in 34 patients that received definitive therapy

Variable	Combination therapy ($n = 15$)[a]	Monotherapy ($n = 19$)[a]	*P* value	OR (95% CI)
Demographics				
Age ≥65	6 (40)	11 (57.8)	0.49	0.4 (0.09–2.35)
Male	8 (53.3)	7 (36.8)	0.50	1.7 (0.36–8.31)
Severity of illness				
In ICU at enrollment	10 (66.6)	10 (52.6)	0.49	1.8 (0.36–9.28)
APACHE II	17.4 ± 6.65	21.3 ± 8.69	0.15	
LOS[b]	35 ± 28	34.9 ± 72	0.99	
Underlying diseases				
Immunocompromised state	11 (73.3)	9 (47.3)	0.17	3.0 (0.58–17.14)
Chronic renal failure	3 (20)	3 (15.8)	1.00	1.3 (0.17–10.54)
Malignancy	3 (20)	5 (15.8)	1.00	0.7 (0.02–4.51)
Transplant	8 (53.3)	0	≤0.001	∞ (3.01–∞)

[a] Data are presented as *n* (%) or mean ± standard deviation (SD).
[b] LOS, length of stay before bacteremia.

may reflect the increased awareness of this highly resistant organism over time and consequent early institution of active antimicrobial therapy. Alternatively, the difference may be due to unrecognized confounding variables. Nonetheless, the mortality still remains considerably higher than for bacteremia due to *K. pneumoniae* not producing KPC (16).

We did not identify any independent clinical risk factor for mortality. This may be due to the small number of cases in this series or our failure to identify and analyze a pertinent confounding risk factor. Another possibility is that 28 days is not a discriminating endpoint, as by 28 days, mortality may be influenced by underlying comorbidities. However, the use of an earlier endpoint such as 14 days is also problematic in this patient population as they are typically still receiving antimicrobial therapy at the time. One intriguing observation in the univariate analysis was that pneumonia as the source of bacteremia was associated with mortality. This probably is a reflection of higher severity of illness in this group, as manifested by a mean APACHE II score of 25 and also the relative difficulty in controlling the source of infection compared with other sources.

TABLE 3 Definitive antimicrobial therapy and mortality in 17 patients who received combination therapy and 19 patients who received monotherapy

Definitive treatment	*n* (%)	Mortality *n* (%)
Combination therapy	15 (44)	2 (13.3)
Colistin-polymyxin B combined with:		
Carbapenem	5 (33)	1 (20)
Tigecycline	1 (7)	0
Fluoroquinolone	1 (7)	0
Tigecycline combined with:		
Carbapenem	3 (20)	0
Aminoglycoside	2 (12)	0
Carbapenem-fluoroquinolone	1 (7)	1 (100)
Aztreonam-fluoroquinolone	1 (7)	0
Cefepime-gentamicin	1 (7)	0
Monotherapy	19 (46)	11 (57.8)
Colistin-polymyxin B	7 (36.8)	4 (57.1)
Tigecycline	5 (26.3)	4 (80)
Carbapenem	4 (21)	2 (50)
Gentamicin	1 5.2)	0
Ampicillin-sulbactam	1 (5.2)	0
Piperacillin-tazobactam	1 (5.2)	1 (100)
Total	34 (83)	13 (38.2)

Our study demonstrated that survival in patients with KPC-producing *K. pneumoniae* bacteremia was significantly improved when combination therapy rather than monotherapy was given. Several combinations appeared to be effective, but the most common successful combination regimens used in our patients were either colistin-polymyxin B or tigecycline in combination with a carbapenem. These combination regimens were more successful than monotherapy with either colistin-polymyxin B or tigecycline, even when *in vitro* testing confirmed susceptibility to the respective antimicrobials. These findings are consistent with a cohort study on bacteremic cases recently published from Greece (18) and also a review of case series (13), where higher clinical failure rates were observed with monotherapy. While the mechanisms underlying the effectiveness of these combinations are not known, synergistic activity between carbapenems and colistin has been observed *in vitro* among our KPC-producing *K. pneumoniae* isolates, which is consistent with the clinical observation presented here, at least for this particular combination (Ryan Shields, University of Pittsburgh Medical Center, personal communication).

In light of the concern for underdosing of colistin, we also compared the colistin regimens (dosed as colistin base activity of colistin methanesulfonate) in those receiving monotherapy versus recently published recommendations (10). All three of these patients were dosed at the recommended frequency and received greater total daily doses compared to these recent recommendations, even when targeting an average steady-state concentration of 2 μg/ml. Furthermore, in addition to inferior clinical outcome, monotherapy with colistin-polymyxin B has been associated with emergence of colistin-polymyxin B resistance (1, 19). As such, colistin-polymyxin B monotherapy needs to be employed with caution in patients having infection with KPC-producing *K. pneumoniae*.

Clinical failures with carbapenem monotherapy were also frequently observed in our study, which is not surprising and is consistent with previous studies (7, 18). Of note, although carbapenem treatment was inadequate as monotherapy, the addition of imipenem to colistin-polymyxin B or tigecycline was clearly

TABLE 4 Antimicrobial susceptibility of 41 KPC-producing *K. pneumoniae* bacteremic isolates

Antimicrobial agent	CLSI 2009 breakpoints			CLSI 2011 breakpoints			MIC (μg/ml)	
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant	50%	90%
Ertapenem	3[a]	8	30	0	0	41	>4	>4
Imipenem	23	7	11	2	8	31	4	>8
Meropenem	21	5	15	1	11	29	4	>8
Doripenem				8	11	22	>2	>2
Ceftazidime	0	1	40	0	0	41	>16	>16
Cefepime	22	7	12				8	>16
Ticarcillin-clavulanate	0	0	41				>128/2	>128/2
Piperacillin-tazobactam	0	1	40				>64/4	>64/4
Amikacin	24	15	2				16	32
Gentamicin	6	16	19				8	>16
Tobramycin	0	0	41				>8	>8
Ciprofloxacin	2	1	38				>2	>2
Levofloxacin	3	0	38				>8	>8
Doxycycline	33	5	3				4	8
Minocycline	28	9	4				4	16
Tigecycline	40	0	1				0.5	1
Colistin	37	0	4				≤0.25	>4
Polymyxin B	37	0	4				0.5	>4

[a] These isolates initially tested as intermediate in the clinical laboratories based on the CLSI 2009 breakpoints and were positive for the KPC gene by PCR and sequencing but tested as susceptible using the manual broth microdilution method in the research laboratory.

beneficial, even in patients whose isolates would now be classified as resistant to carbapenems, including imipenem. Overall, our data confirm that combination therapy appears to have a significant survival benefit in patients with bacteremia due to this organism.

Our study is limited by its observational nature and relatively small number of cases, as we limited the analysis to cases with bacteremia only. In addition, there were more transplant patients in the combination therapy group than the monotherapy group. However, given the degree of immunosuppression and underlying comorbidities in this patient population, this was more likely to underestimate, rather than overestimate, the effectiveness of combination therapy.

In conclusion, mortality associated with bacteremia due to KPC-producing *K. pneumoniae* continues to be high. The use of a combination therapy, in particular with either colistin-polymyxin B or tigecycline and a carbapenem, seems to have a survival benefit in this critically ill population.

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