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Impact of a Rapid Molecular Test for *Klebsiella pneumoniae* Carbapenemase and Ceftazidime-Avibactam Use on Outcomes After Bacteremia Caused by Carbapenem-Resistant Enterobacterales

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Background. Patients with bacteremia due to carbapenem-resistant Enterobacterales (CRE) experience delays until appropriate therapy and high mortality rates. Rapid molecular diagnostics for carbapenemases and new β-lactam/β-lactamase inhibitors may improve outcomes.

Methods. We conducted an observational study of patients with CRE bacteremia from 2016 to 2018 at 8 New York and New Jersey medical centers and assessed center-specific clinical microbiology practices. We compared time to receipt of active antimicrobial therapy and mortality between patients whose positive blood cultures underwent rapid molecular testing for the *Klebsiella pneumoniae* carbapenemase (KPC) gene (bla_{KPC}) and patients whose cultures did not undergo this test. CRE isolates underwent antimicrobial susceptibility testing by broth microdilution and carbapenemase profiling by whole-genome sequencing. We also assessed outcomes when ceftazidime-avibactam and polymyxins were used as targeted therapies.

Results. Of 137 patients with CRE bacteremia, 89 (65%) had a KPC-producing organism. Patients whose blood cultures underwent bla_{KPC} PCR testing (n = 51) had shorter time until receipt of active therapy (median: 24 vs 50 hours; $P = .009$) compared with other patients (n = 86) and decreased 14-day (16% vs 37%; $P = .007$) and 30-day (24% vs 47%; $P = .007$) mortality. bla_{KPC} PCR testing was associated with decreased 30-day mortality (adjusted odds ratio: .37; 95% CI: .16–.84) in an adjusted model. The 30-day mortality rate was 10% with ceftazidime-avibactam monotherapy and 31% with polymyxin monotherapy ($P = .08$).

Conclusions. In a KPC-endemic area, bla_{KPC} PCR testing of positive blood cultures was associated with decreased time until appropriate therapy and decreased mortality for CRE bacteremia, and ceftazidime-avibactam is a reasonable first-line therapy for these infections.

Keywords. carbapenem-resistant Enterobacterales; *Klebsiella pneumoniae* carbapenemase; rapid diagnostics; ceftazidime-avibactam.

Carbapenem-resistant Enterobacterales (CRE) are a global public health threat because they cause infections that are associated with high mortality rates and few antimicrobial therapeutic options [1, 2]. CRE became endemic in New York and New Jersey (NY/NJ) 2 decades ago due to the emergence of *Klebsiella pneumoniae* carbapenemase (KPC), an enzyme that confers resistance to carbapenems and most β-lactam agents [3]. KPC-producing CRE then spread globally and KPC is now the most common carbapenemase among Enterobacterales in the United States, Europe, and Latin America [4–7].

We previously conducted a multicenter study of CRE bacteremias in 2013 in NY/NJ and found that there was a median of 47 hours from bacteremia onset until initiation of active

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antimicrobial therapy and a 49% 30-day mortality rate [8]. Most patients in that study received polymyxin- and tigecycline-based therapies. Since then, important advances in CRE diagnostics and therapeutics have emerged that might improve outcomes of CRE-infected patients. First, molecular panels are available that detect the KPC gene (bla_{KPC}) within 1–2 hours of blood culture positivity [9, 10]. These tests rapidly detect carbapenem resistance in KPC-producing organisms, compared with a 2–3-day delay with conventional culture and antimicrobial susceptibility testing. However, the impact of these assays on shortening the time to administration of effective therapies and improving outcomes of infected patients is unknown. Second, new β-lactam/β-lactamase inhibitors are approved for the treatment of CRE infections [11–13]. Although prior studies demonstrated improved outcomes with these newer agents [11, 14], these studies primarily compared these agents with colistin-based regimens, not to regimens with polymyxin B, which has more favorable pharmacological properties than colistin [15].

Here, we present a follow-up study of CRE bacteremias in NY/NJ to evaluate the potential benefits of rapid molecular diagnostics and novel β-lactam/β-lactamase inhibitors for CRE infections. Our primary objectives were to determine if the use of a molecular assay that detects bla_{KPC} directly from positive blood culture broths and/or treatment with ceftazidime-avibactam was associated with improved outcomes in patients with CRE bacteremia.

METHODS

Study Cohort

We conducted an observational study of patients with CRE bacteremia from January 2016 to June 2018 at 8 academic medical centers in NY/NJ. Institutional review board approval was obtained at each site. Patients were initially enrolled based on detection of carbapenem resistance at local clinical microbiology laboratories and only the first episode of CRE bacteremia per patient was included. The final cohort consisted of patients whose CRE bloodstream isolates underwent antimicrobial susceptibility testing and whole-genome sequencing (WGS) by a central laboratory, and whose isolates were carbapenem-resistant based on central laboratory testing [16].

Clinical Data Collection

Clinical data were abstracted from electronic medical records at each study site and recorded in a central database [17], including patient demographics, comorbidities [18], clinical status, and Acute Physiologic Assessment Chronic Health Evaluation II (APACHE II) and Pitt Bacteremia scores at the time of bacteremia onset [19, 20]. We also reviewed diagnostic methods and the time from blood culture collection until CRE detection in the local clinical microbiology laboratories. Finally, we recorded antimicrobial therapies, time until receipt of active therapy (an agent to which the bloodstream CRE pathogen[s] tested susceptible in the central laboratory), bacteremia source and source control (determined by an infectious diseases physician at each site), 14- and 30-day mortality, and acute kidney injury (AKI) [21]. Bacteremia onset was defined as the time of collection of the first blood culture from which CRE was recovered. Initial targeted therapy was defined as antimicrobial agents that were administered within 1 day after the availability of antimicrobial susceptibility testing results and that were continued for 2 or more days.

Microbiologic Analyses

Bloodstream isolates were shipped to a central laboratory. There, isolates were identified to the species level by matrix-associated laser desorption/ionization time-of-flight mass spectrometry (Bruker Daltonics, Billerica, MA) and antimicrobial susceptibility testing was performed for 18 antimicrobial agents by reference broth microdilution (ThermoFisher Scientific, Waltham, MA) [22]. Interpretive criteria of the Clinical and Laboratory Standards Institute were applied [23], except isolates for which colistin minimum inhibitory concentrations (MICs) were 2 μg/mL or less were considered susceptible to colistin and polymyxin B and those for which tigecycline MICs were 2 μg/mL or less (the US Food and Drug Administration [FDA] susceptible breakpoint) were considered tigecycline susceptible.

Isolates also underwent WGS using previously described methods [5]. In brief, genomes were sequenced using an Illumina Hiseq platform, followed by raw reads quality control check, filter, and assembly. Bacterial species were examined by Mash 2.3 using the NCBI RefSeq genome database [24]. Antimicrobial resistance genes were determined using Kleborate v2.0.4, AMRFinderPlus v3.10.5, and ARIBA v2.14.6 [25–27]. Multilocus sequence typing (MLST) was performed using *mlst* v2.19.0 (https://github.com/tseemann/mlst) utilizing pubmlst (https://pubmlst.org/databases/) databases. The raw reads of the sequenced genomes were deposited in GenBank bioproject accession no. PRJNA549322.

Statistical Analyses

We first compared baseline characteristics and treatments of patients who died within 30 days of bacteremia onset with those of patients who survived. Chi-square and Fisher's exact tests were used for categorical variables, and the Wilcoxon rank-sum test was used for continuous variables. $P < .05$ indicated statistical significance. We then compared time to detection of CRE bacteremia, time to receipt of active antimicrobial therapy, and 14- and 30-day mortality between patients whose positive blood culture broths underwent

bla_{KPC} polymerase chain reaction (PCR) and those whose blood cultures did not undergo this test. We also made these comparisons among patients with KPC-producing CRE bacteremia (wherein bla_{KPC} testing might yield benefit) and non–KPC-producing CRE bacteremia (when we did not expect benefit).

We then estimated adjusted associations between bla_{KPC} PCR testing and 30-day mortality using Targeted Maximum Likelihood Estimation (TMLE), a method that leverages flexible regression for both the outcome and propensity score, in order to achieve robustness to misspecification of either model [28] (Supplementary Methods and Supplementary Figure 1). This technique helps ensure associations between mortality and bla_{KPC} PCR testing are not driven by differences in baseline characteristics between patients whose blood cultures did and did not undergo bla_{KPC} PCR testing. The TMLE analysis was conducted in R, version 4.0.3, and using the open-source package ltmp [29]. We also describe 14- and 30-day mortality based on initial targeted therapies.

RESULTS

Study Cohort

Of 178 patients initially enrolled, 17 were excluded because their CRE bloodstream isolate was not available for central laboratory analysis and 24 because their isolate was not carbapenem-resistant at the central laboratory, leaving 137 patients in the study cohort. The median age was 64 years, 61% were male, and cancer (42%) and diabetes (34%) were the most common comorbidities (Table 1). The most common sources of infection were intra-abdominal (33%), vascular catheters (13%), and the respiratory (13%) and urinary (12%) tracts.

Active therapy was administered to 107 (78%) patients (Table 1). Of the 30 patients who never received active therapy, 14 died or pursued comfort care prior to the availability of antimicrobial susceptibility testing results. Among patients who received active therapy, there was a median of 29 hours (interquartile range [IQR]: 9–78 hours) from blood culture collection until receipt of active therapy. Polymyxins were the most common agents used for initial targeted therapy (40% of patients), followed by carbapenems (35%) and ceftazidime-avibactam (29%). Sixty-one percent of patients who received targeted therapy received a single active agent and 21% received 2 or more active agents. Infectious diseases consultation was obtained in 91% of patients.

Forty (29%) patients died within 14 days of bacteremia onset and 52 (38%) died within 30 days. Among baseline characteristics, the presence of cancer (particularly a hematologic malignancy), onset of infection in the intensive care unit, receipt of renal replacement therapy or mechanical ventilation, and increasing APACHE II and Pitt Bacteremia scores were associated with increased 30-day mortality. Fever, receipt of a solid-organ transplant, and urinary source were associated with decreased mortality (Table 1).

Table 1. Baseline Characteristics and Treatments of CRE Bacteremias and Associations With 30-Day Mortality

	Total (n = 137)	Survivors (n = 85)	Died Within 30 Days (n = 52)	*P*
Patient characteristics				
Demographics				
Age, median (IQR), years	64 (51–76)	63 (49–76)	67 (56–74)	.84
Male gender	83 (61)	54 (64)	29 (56)	.37
Comorbidities				
Myocardial infarction	11 (8)	7 (8)	4 (8)	1.00
Congestive heart failure	18 (13)	10 (12)	8 (15)	.54
Peripheral vascular disease	16 (12)	10 (12)	6 (12)	.97
Cerebrovascular disease	17 (12)	14 (16)	3 (6)	.065
Dementia	16 (12)	11 (13)	5 (10)	.56
COPD	22 (16)	16 (19)	6 (12)	.26
Peptic ulcer disease	10 (7)	5 (6)	5 (10)	.50
Liver disease	9 (7)	4 (5)	5 (10)	.30
Diabetes	46 (34)	32 (38)	14 (27)	.20
Moderate or severe kidney disease	29 (21)	19 (22)	10 (19)	.66
Cancer	58 (42)	29 (34)	29 (56)	**.013**
Solid tumor	35 (26)	20 (24)	15 (29)	.49
Hematologic malignancy	25 (18)	9 (11)	16 (31)	**.003**
HIV infection	5 (4)	3 (4)	2 (4)	1.00
Charlson Comorbidity Index score [18]	5 (3–7)	5 (3–7)	5 (4–8)	.53
Transplant recipient	27 (20)	18 (21)	9 (17)	.58

Table 1. Continued

	Total (n = 137)	Survivors (n = 85)	Died Within 30 Days (n = 52)	*P*
Solid-organ transplant	14 (10)	13 (15)	1 (2)	**.012**
Hematopoietic cell transplant	13 (9)	5 (6)	8 (15)	.078
Place patient admitted from				
Home	80 (58)	50 (59)	30 (58)	.90
Rehabilitation or long-term care facility	36 (26)	21 (25)	15 (29)	.59
Transfer from a different hospital	21 (15)	14 (16)	7 (14)	.64
Variables at time of bacteremia onset				
Outpatient	41 (30)	30 (35)	11 (21)	.079
Medical ward, non-ICU	52 (38)	32 (38)	20 (39)	.92
Surgical ward, non-ICU	13 (9)	11 (13)	2 (4)	.13
ICU	31 (23)	12 (14)	19 (37)	**.002**
Days from hospital admission until BSI onset	14 (1–31)	13 (0–35)	14 (2–30)	.85
Receiving RRT	26 (19)	11 (13)	15 (29)	**.021**
Baseline creatinine clearance (mL/minute) among patients not on RRT [30]	59 (31–87)	59 (29–87)	62 (43–100)	.53
Neutropenia	21 (15)	12 (14)	9 (17)	.62
Bacteremia source				
Intra-abdominal	45 (33)	23 (27)	22 (42)	.065
Vascular catheter	18 (13)	14 (16)	4 (8)	.14
Urinary tract	17 (12)	16 (19)	1 (2)	**.004**
Respiratory tract	18 (13)	8 (9)	10 (19)	.099
Gastrointestinal translocation during neutropenia	13 (9)	8 (9)	5 (10)	1.00
Skin/soft tissue	7 (5)	4 (5)	3 (6)	1.00
Other	5 (4)	5 (6)	0	.16
Unknown	14 (10)	7 (8)	7 (13)	.33
Fever (temperature ≥38.0°C)	86 (63)	60 (71)	26 (50)	**.016**
Receiving mechanical ventilation	48 (35)	24 (28)	24 (46)	**.033**
APACHE II score [19]	20 (15–25)	18 (14–22)	25 (18–31)	**<.0001**
Pitt Bacteremia score [20]	3 (1–5)	2 (1–4)	4 (2–7)	**.0003**
Treatment				
Active therapy at any time	107 (78)	75 (88)	32 (62)	**<.001**
Hours until active therapy (n = 107)	29 (9–78)	32 (13–86)	25 (7–66)	.16
Active therapy within 24 hours	43 (31)	27 (32)	16 (31)	.90
Initial targeted therapy[a] (n = 112)		n = 84	n = 28	
Polymyxin[b]	45 (40)	31 (37)	14 (50)	.22
Carbapenem[c]	39 (35)	28 (33)	11 (39)	.57
Ceftazidime-avibactam	32 (29)	26 (31)	6 (21)	.33
Fluoroquinolone[d]	16 (14)	13 (15)	3 (10)	.76
Tigecycline	13 (12)	10 (12)	3 (11)	1.00
Piperacillin-tazobactam	7 (6)	7 (8)	0	.19
Aminoglycoside[e]	8 (7)	5 (6)	3 (11)	1.00
TMP-SMX	7 (6)	5 (6)	2 (7)	1.00
Minocycline	5 (4)	4 (5)	1 (4)	1.00
No. of active agents				
None	21 (19)	15 (18)	6 (21)	.68
Single active agent	68 (61)	56 (67)	12 (43)	**.025**
≥2 active agents	23 (21)	13 (15)	10 (36)	**.022**
Infectious diseases consult	124 (91)	79 (93)	45 (87)	.22
Source control	46 (34)	36 (42)	10 (19)	**.005**

Variables are expressed as n (% of total) or median (IQR). Bolded *P* values indicate statistical significance. Abbreviations: APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; CRE, carbapenem-resistant Enterobacterales; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; RRT, renal replacement therapy; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Antimicrobial agents that are active against gram-negative bacteria and were administered within 1 day of the availability of susceptibility results for ≥2 calendar days. Only antimicrobial therapies that were administered to ≥5 patients are displayed in the table. One hundred twelve patients received initial targeted therapy; 24 patients died prior to or within 1 day after the availability of susceptibility results and 1 patient was discharged alive prior to the availability of susceptibility results.

[b]Polymyxin targeted therapy was with polymyxin B (n = 39) and colistin (n = 6).

[c]Carbapenem targeted therapy was with meropenem (n = 36), ertapenem (n = 2), and imipenem (n = 1). The carbapenem was administered in combination with a second agent in 26 patients and was active in vitro against the CRE bloodstream pathogen in 4 patients.

[d]Fluoroquinolone targeted therapy was with levofloxacin (n = 11) and ciprofloxacin (n = 5).

[e]Aminoglycoside targeted therapy was with gentamicin (n = 4), amikacin (n = 3), and tobramycin (n = 1).

Table 2. CRE Bloodstream Pathogens and 30-Day Mortality Rates by Pathogen Type

Bloodstream Pathogen	No. (% of Total Cohort)	No. (%) of Patients Who Died Within 30 Days, per Pathogen
Klebsiella pneumoniae	88 (64)	38 (43)
ST258	51 (58)[a]	22 (43)
Escherichia coli	20 (15)	8 (40)
ST131	7 (35)[a]	3 (43)
Enterobacter cloacae complex	15 (11)	4 (27)
ST171	5 (33)[a]	3 (60)
Klebsiella oxytoca	5 (4)	1 (20)
Serratia marcescens	3 (2)	0
Multiple CRE	4 (3)	1 (25)
Other	2 (2)	2 (100)
Meropenem-resistant	103 (75)	41 (40)
Difficult-to-treat [31]	89 (65)	37 (42)
Carbapenemase-producer[b]	106 (77)	40 (38)
KPC-producer[c]	89 (65)	34 (38)
OXA-48–like-producer[d]	8 (6)	4 (50)
NDM-producer[e]	7 (5)	2 (29)
Non–carbapenemase-producer	31 (23)	12 (39)
Polymicrobial bacteremia[f]	44 (32)	18 (41)

Abbreviations: CRE, carbapenem-resistant Enterobacterales; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-B-lactamase; ST, multilocus sequence type.

[a]The denominator for this percentage is the number of patients infected with the corresponding species.

[b]One patient was infected with a non-metallocarbapenemase class A (NMC-A)–producing *E. cloacae*, 1 patient with a *Serratia marcescens* enzyme (SME)–producing *S. marcescens*, and 1 patient with a Verona integron-encoded metallo-ß-lactamase (VIM)–producing *E. coli*. Two patients were infected with 2 different carbapenemase-producing bacteria (KPC-2–producing *K. pneumoniae* and KPC-3–producing *E. cloacae* [n = 1] and KPC-2–producing *K. pneumoniae* and KPC-3–producing *S. marcescens* [n = 1]), and 1 patient was infected with a *K. pneumoniae* that harbored NDM-5 and OXA-232.

[c]Patients were infected with KPC-3–producing organisms (n = 52), KPC-2-producers (n = 37), and KPC-4 producers (n = 2). Two patients were infected with both KPC-2– and KPC-3–producing organisms.

[d]Patients were infected with OXA-181–producing organisms (n = 4), OXA-48-producers (n = 2), and OXA-232-producers (n = 2).

[e]Patients were infected with NDM-5–producing organisms (n = 4) and NDM-1-producers (n = 3). One patient was infected with an NDM-5–producing and OXA-232–producing *K. pneumoniae*.

[f]Polymicrobial infection was defined as a non-CRE bloodstream infection (BSI) that occurred within 2 days of CRE BSI.

Characterization of CRE Bloodstream Isolates

CRE bacteremia was most commonly caused by *K. pneumoniae* (64%), *Escherichia coli* (15%), and *Enterobacter cloacae* (11%; Table 2). The most common *K. pneumoniae* sequence type was ST258 (58% of *K. pneumoniae*). One hundred and six patients (77%) were infected with carbapenemase-producing CRE (CP-CRE), including 89 (65%) with bla_{KPC}, 8 (6%) with bla_{OXA-48}, and 7 (5%) with bla_{NDM}. The 30-day mortality rate was 38% in patients infected with CP-CRE and 39% in patients with non-CP CRE.

The most frequently active antimicrobial agents in vitro were ceftazidime-avibactam (89% susceptible), tigecycline (89%), colistin (87%), amikacin (80%), and gentamicin (64%; Table 3). Ninety-five percent of KPC-producing isolates were susceptible to ceftazidime-avibactam and 90% of non–CP-CRE and OXA-48–producing isolates were ceftazidime-avibactam susceptible.

Impact of bla_{KPC} PCR Testing on Positive Blood Culture Broths

Three of the eight study hospitals used the BioFire FilmArray Blood Culture Identification Panel (BCID; BioFire Diagnostics, Salt Lake City, UT) on positive blood culture broths during the study period (Supplementary Table 1). This assay detects bla_{KPC} and 24 pathogens but does not detect other carbapenemase genes [9]. The bacterial species and bla_{KPC} results from this panel were reported to clinicians at the 3 hospitals. The BCID assay detected bla_{KPC} in 32 of 33 patients where the gene was detected by WGS of bloodstream isolates. No other molecular assays that detect carbapenemase genes from blood cultures were used at study hospitals.

Characteristics of the 51 patients whose blood cultures underwent bla_{KPC} PCR testing (PCR patients) were similar to those of the 86 patients whose blood cultures did not undergo this test (non-PCR patients), except PCR patients were less likely to have bacteremia onset as an outpatient, had a longer duration of hospitalization prior to bacteremia onset, and were more likely to receive initial targeted therapy with ceftazidime-avibactam (35% vs 16%; $P = .011$; Supplementary Table 2). The PCR patients had a median of 22 hours (IQR: 15–72 hours) from blood culture collection until detection of CRE bacteremia, compared with 67 hours (IQR: 54–88 hours) in non-PCR patients ($P < .0001$; Figure 1*A*). Decreased time to CRE bacteremia detection with bla_{KPC} PCR testing occurred exclusively in KPC-producing CRE bacteremia, where the median time until CRE bacteremia detection was 16 hours (IQR: 14–22 hours; Figure 1*B* and 1*C*).

PCR patients were more likely to receive active antimicrobial therapy within 24 hours (22/51 [43%] vs 21/86 [24%]; $P = .02$) and within 48 hours (32/51 [63%] vs 32/86 [37%]; $P = .004$) after bacteremia onset than non-PCR patients. Among patients who received active therapy, the median time from blood culture collection until active therapy was 24 hours (IQR: 4–50 hours) in PCR patients and 50 hours (IQR: 18–89 hours) in non-PCR patients ($P = .009$; Figure 2*A*). This decreased time to receipt of active therapy in PCR patients compared with non-PCR patients was only observed in patients with KPC-producing CRE bacteremia (Figure 2*B* and 2*C*).

Fourteen- and 30-day mortality rates were lower among PCR patients compared with non-PCR patients (Figure 3*A*): 14-day: 8 of 51 (16%) versus 32 of 86 (37%) ($P = .007$); 30-day: 12 of 51 (24%) versus 40 of 86 (47%) ($P = .007$). This decrease in mortality in PCR patients was only observed in patients with KPC-producing CRE bacteremia (Supplementary Figure 2*A* and 2*B*). bla_{KPC} PCR testing was associated with decreased unadjusted odds of 30-day mortality using logistic regression (odds ratio: .35; 95% confidence interval [CI]: .16–.75; $P =$

Table 3. Antimicrobial Susceptibilities Among CRE Bloodstream Isolates Stratified by Carbapenemase Type

	Percent Susceptible				
Antimicrobial Agents	All CRE (n = 143)[a]	KPC-Producers (n = 93)	MBL-Producers[b] (n = 8)	OXA-48-Producers[c] (n = 10)	Non-CP CRE (n = 31)
Amikacin	80%	83%	38%	70%	81%
Aztreonam	5%	0%	13%	10%	16%
Cefepime	8%	7%	0%	10%	10%
Ceftazidime	9%	4%	0%	10%	19%
Ceftazidime-avibactam	89%	95%	13%	90%	90%
Ceftriaxone	4%	0%	0%	10%	13%
Ciprofloxacin	13%	11%	0%	0%	19%
Colistin[d]	87%	85%	100%	100%	90%
Ertapenem	3%	3%	0%	0%	3%
Gentamicin	64%	67%	13%	40%	71%
Imipenem	9%	1%	0%	10%	35%
Levofloxacin	16%	14%	0%	10%	23%
Meropenem	16%	15%	0%	30%	19%
Minocycline	49%	48%	63%	40%	48%
Piperacillin-tazobactam	1%	0%	0%	0%	3%
Tigecycline[e]	89%	90%	88%	90%	81%
Tobramycin	21%	18%	0%	40%	26%
TMP-SMX	20%	16%	13%	20%	29%

Abbreviations: CP, carbapenemase; CRE, carbapenem-resistant Enterobacterales; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]There were 143 CRE bloodstream isolates collected from the 137 patients.

[b]Metallo-β-lactamase–producing CRE included 4 organisms with $bla_{\text{NDM-5}}$, 3 with $bla_{\text{NDM-1}}$, and 1 with $bla_{\text{VIM-1}}$.

[c]OXA-48–producing CRE included 5 organisms with $bla_{\text{OXA-181}}$, 3 with $bla_{\text{OXA-48}}$, and 2 with $bla_{\text{OXA-232}}$.

[d]An organism was considered susceptible if the colistin minimum inhibitory concentration (MIC) was ≤2 µg/mL.

[e]An organism was considered susceptible if the tigecycline MIC was ≤2 µg/mL.

.01) and decreased adjusted odds of 30-day mortality using TMLE (adjusted odds ratio: .37; 95% CI: .16–.84; $P = .02$).

Initial Targeted Therapy With Ceftazidime-Avibactam and Mortality

There were 112 patients who survived to receive 2 or more days of targeted therapy. Six (19%) of 32 patients who received ceftazidime-avibactam as part of their initial targeted therapy died within 30 days, compared with 22 (28%) of 80 patients who did not receive ceftazidime-avibactam ($P = .33$; Table 1). None of the 21 patients who received ceftazidime-avibactam monotherapy as initial targeted therapy died within 14 days and 2 (10%) died within 30 days (Table 4; Figure 3*B*). In contrast, 5 (19%) of 26 patients who received polymyxin monotherapy as initial targeted therapy died within 14 days and 8 (31%) died within 30 days. Patients whose initial targeted therapy consisted of 2 or more active agents (combination therapy) had higher mortality rates than patients who received 1 active agent (monotherapy). Risk of AKI was similar among treatment regimens.

DISCUSSION

Our study of CRE bacteremia in 2013 in NY/NJ identified long delays until active therapy and a 49% 30-day mortality rate [8]. We conducted this follow-up study to evaluate the impact of 2 new interventions: the availability of bla_{KPC} PCR testing on positive blood culture broths and of ceftazidime-avibactam for treatment. We found the 30-day mortality rate among patients with CRE bacteremia had decreased to 38%. However, this decreased mortality was observed primarily in patients whose blood cultures underwent bla_{KPC} PCR testing, in whom the 30-day mortality rate was 24%, but not in patients whose blood cultures did not undergo this test, for whom the 30-day mortality rate was 47%. We believe that the mortality reduction with bla_{KPC} PCR testing was related to the earlier initiation of active therapy observed in these patients compared with non-PCR patients. Earlier initiation of active antimicrobial therapy is consistently associated with decreased mortality in patients with sepsis [32, 33].

To our knowledge, this is the first study to identify an association between bla_{KPC} PCR testing on positive blood culture broths and decreased mortality. Given that this was not a randomized trial, and patients at hospitals that used bla_{KPC} PCR testing may differ from those at other study hospitals, this association warrants careful assessment for confounding. We compared characteristics of PCR and non-PCR patients and did not find baseline characteristics of PCR patients that would predispose to lower mortality, including similar APACHE II, Pitt Bacteremia, and Charlson Comorbidity Index scores (Supplementary Table 2). PCR patients were more likely to

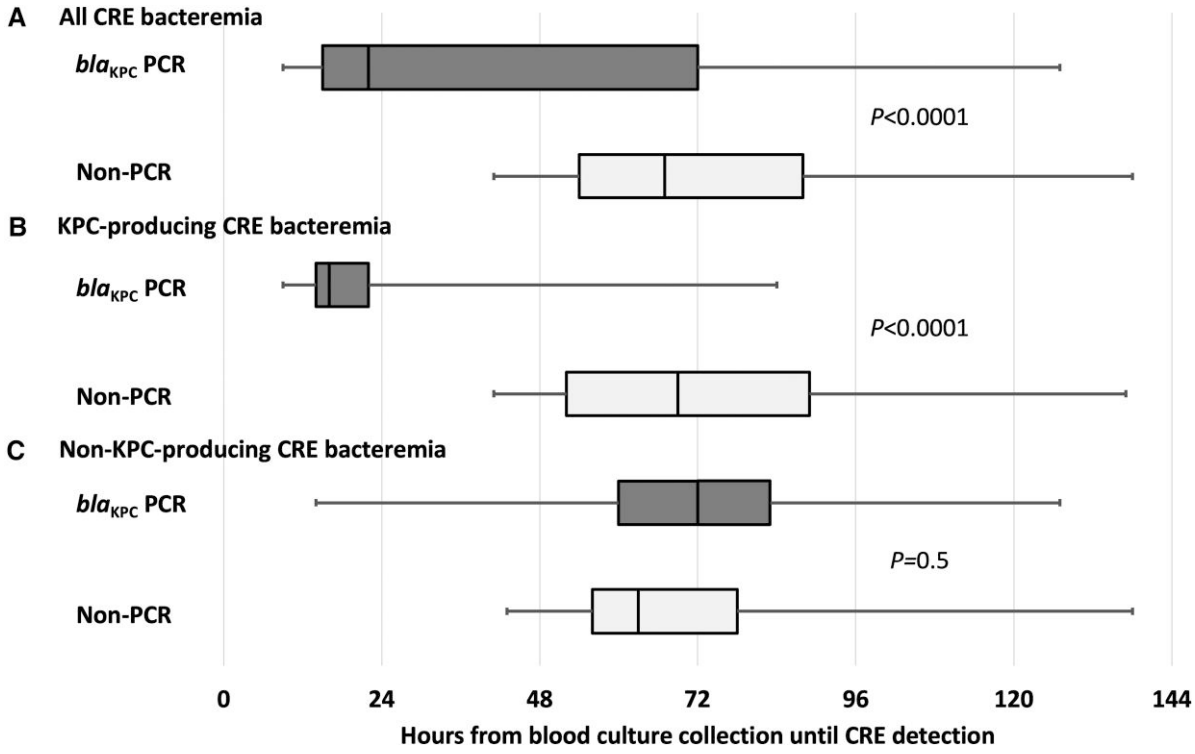

Figure 1. Hours from blood culture collection until CRE detection in patients whose positive blood culture broths underwent bla_{KPC} PCR testing (bla_{KPC} PCR) and those whose blood culture broths did not undergo bla_{KPC} PCR testing (non-PCR). Results are displayed for (*A*) all CRE bacteremia, (*B*) KPC-producing CRE bacteremia, and (*C*) non–KPC-producing CRE bacteremia. Boxes represent 25th and 75th percentiles, and the vertical line in the box represents the median. The range is represented by the whiskers. *P* values compare bla_{KPC} PCR patients with non-PCR patients. Abbreviations: CRE, carbapenem-resistant Enterobacterales; KPC, *Klebsiella pneumoniae* carbapenemase; PCR, polymerase chain reaction.

receive ceftazidime-avibactam, but this choice in therapy may have been related to detection of bla_{KPC}, providing clinicians with confidence to use this agent given its reliable in vitro activity against KPC-producing Enterobacterales [34]. The association between bla_{KPC} PCR testing and decreased 30-day mortality also persisted in a propensity score–adjusted analysis. Furthermore, if other characteristics of the 3 study hospitals that used bla_{KPC} PCR testing were responsible for the improved outcomes, then one would expect to identify improved outcomes with both KPC-producing and non–KPC-producing CRE bacteremia at these centers. However, the decreases in time to active therapy and mortality were only observed in patients with KPC-producing CRE bacteremia. Based on these considerations, we believe that our finding of improved outcomes with bla_{KPC} PCR testing was not due to confounding. Ultimately, we believe that a multicenter clinical trial with randomization to PCR testing at the individual or hospital level would be ideal to confirm our findings.

Although not statistically significant, the numerically lower 30-day mortality with ceftazidime-avibactam compared with polymyxin monotherapy (10% vs 31%) is consistent with prior studies that documented decreased mortality with this new β-lactam/β-lactamase inhibitor compared with polymyxins [11, 14]. In our study, polymyxin B was the predominant polymyxin used, whereas prior studies compared ceftazidime-avibactam with colistin. Polymyxin B has favorable pharmacological properties compared with colistin because it does not require conversion into its active form [15], yet this study suggests that it is also unlikely to be as effective as ceftazidime-avibactam for non–metallo-β-lactamase-producing CRE bacteremia. Even though ceftazidime-avibactam was available throughout the study period, polymyxins were still used more than ceftazidime-avibactam for initial targeted therapy. This finding is consistent with national data that showed that colistin was used more than ceftazidime-avibactam during the 2 years after FDA approval of ceftazidime-avibactam [35]. In addition to leading to more rapid administration of appropriate therapy, another potential advantage of using a molecular assay that detects bla_{KPC} is that knowledge of the carbapenem resistance mechanism could lead to increased use of ceftazidime-avibactam and other newer agents for KPC-producing organisms and decreased use of polymyxins.

This study identified changes in the organisms causing CRE bacteremia in the NY/NJ area. In 2013, 90% of CRE bacteremias were caused by *K. pneumoniae* and 92% were KPC-producers [8]. In this study, only 64% of CRE bacteremias

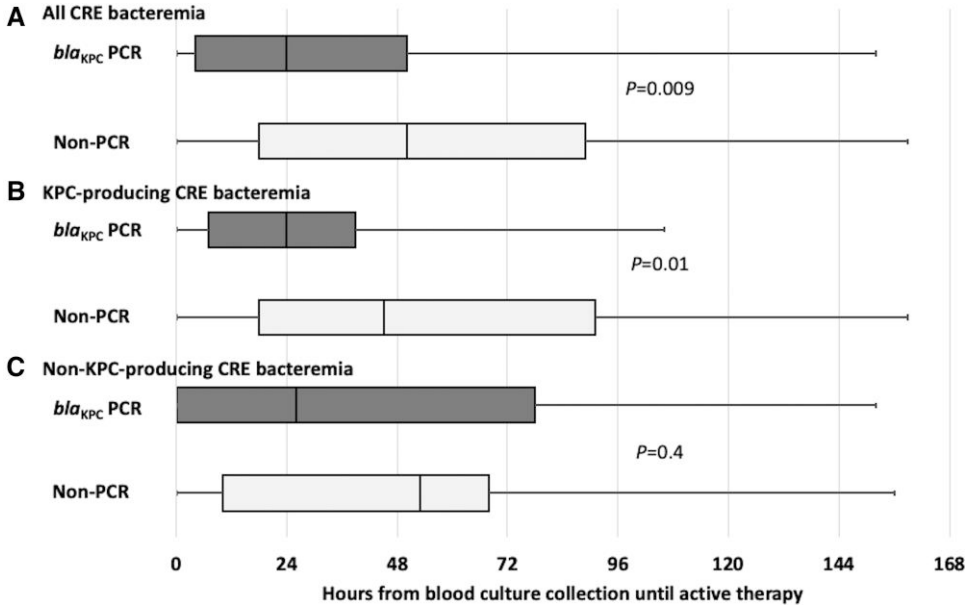

Figure 2. Hours from blood culture collection until receipt of active therapy in patients whose positive blood culture broths underwent bla_{KPC} PCR testing (bla_{KPC} PCR) and those whose blood culture broths did not undergo bla_{KPC} PCR testing (non-PCR). Results are displayed for (*A*) all CRE bacteremia, (*B*) KPC-producing CRE bacteremia, and (*C*) non–KPC-producing CRE bacteremia. Boxes represent 25th and 75th percentiles, and the vertical line in the box represents the median. The range is represented by the whiskers. *P* values compare bla_{KPC} PCR patients with non-PCR patients. Only data from the 107 patients who received active therapy are included. Abbreviations: CRE, carbapenem-resistant Enterobacterales; KPC, *Klebsiella pneumoniae* carbapenemase; PCR, polymerase chain reaction.

were caused by *K. pneumoniae*, only 65% were KPC-producers, and OXA-48- and NDM-producing organisms were more common than in the earlier study. We found similar 30-day mortality rates between CP-CRE and non–CP-CRE bacteremias. This contrasts with findings from a single-center study that identified an increase in mortality with CP-CRE [36] but is consistent with more recent studies that have not demonstrated increased mortality with CP-CRE [5, 37]. In this study, the presence of bla_{KPC} may have permitted rapid diagnosis and earlier appropriate therapy of CRE bacteremia in PCR patients, and this may have decreased the overall mortality with CP-CRE.

This study has strengths and limitations. Among its strengths include its multicenter design and use of reference antimicrobial susceptibility testing and genotyping on all isolates to provide comprehensive assessments of carbapenemases and of the activity of antibacterial therapies. A limitation is that all centers are

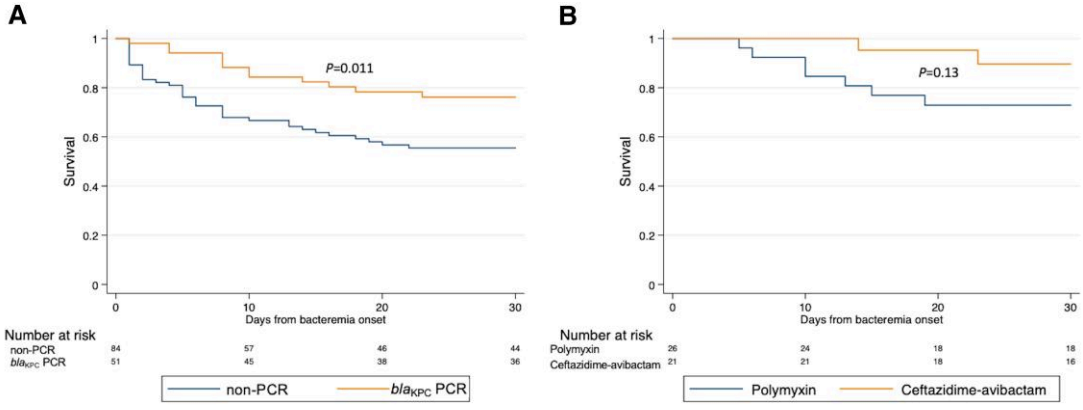

Figure 3. Comparisons of 30-day survival after bacteremia onset between (*A*) patients whose positive blood culture broths underwent bla_{KPC} PCR testing (bla_{KPC} PCR) and those whose blood culture broths did not undergo bla_{KPC} PCR testing (non-PCR) and (*B*) patients who received ceftazidime-avibactam monotherapy as initial targeted therapy and patients who received polymyxin monotherapy. *P* values compare survival curves by log-rank testing. Abbreviation: PCR, polymerase chain reaction.

Table 4. Initial Targeted Therapies and Clinical Outcomes

Antimicrobial Therapy	No.	14-Day Mortality	30-Day Mortality	AKI[a]
Monotherapy (1 active agent)	68	9%	18%	22%
Polymyxin[b]	26	19%	31%	26%
Ceftazidime-avibactam[c]	21	0%	10%	22%
Fluoroquinolone	12	8%	17%	22%
Other[d]	9	0%	0%	13%
Combination therapy (≥2 active agents)	23	17%	43%	29%

Abbreviation: AKI, acute kidney injury.

[a]AKI was defined by RIFLE criteria and the denominator included only patients who did not require renal replacement therapy at the time of bacteremia onset [21].

[b]Polymyxin monotherapy consisted of polymyxin B (n = 24) and colistin (n = 2). Additional inactive agents were administered to 17 (65%) of these patients, including 12 patients who also received a carbapenem and 3 patients who received a non-carbapenem β-lactam agent.

[c]Additional inactive agents were administered to 4 (19%) of these patients.

[d]Patients were treated with the following monotherapy regimens: minocycline (n = 2), tigecycline (n = 2), ertapenem (n = 1), gentamicin (n = 1), trimethoprim-sulfamethoxazole (n = 1), cefepime (n = 1), and piperacillin-tazobactam (n = 1).

from NY/NJ, and the epidemiology and clinical impact of bla_{KPC} PCR testing on positive blood cultures may be different in other geographic areas where KPC-producing CRE are less prevalent [38]. Molecular panels are now available that detect not only bla_{KPC} but also genes that encode other carbapenemases [39–41]. We encourage future investigations of clinical outcomes associated with use of these panels in other geographic areas where other carbapenemases are more common. Given the diversity in antimicrobial therapies in this study, we had limited power to detect differences in outcomes by treatment regimen. Furthermore, the study was not designed to compare outcomes with combination therapy versus monotherapy, and we suspect that the unexpected finding of worse outcomes with combination therapy may have been due to confounding by indication. This study also predated the use of other new β-lactam/β-lactamase inhibitors, such as meropenem-vaborbactam and imipenem-relebactam, and thus we were unable to assess treatment outcomes with these agents.

In conclusion, we found that PCR testing for bla_{KPC} in positive blood culture broths was associated with more prompt administration of effective therapy and decreased mortality among patients with CRE bacteremia in a geographic area where KPC production was the most common carbapenem resistance mechanism. This study suggests that rapid molecular assays have a role in improving outcomes in regions where CP-CRE are prevalent pathogens. We also found that ceftazidime-avibactam use led to favorable outcomes in patients with CRE bacteremia, and thus it should be considered as a first-line agent for non–metallo-β-lactamase-producing CRE bacteremia.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. M. J. S has received grant/contract support from Affinity Biosensors, Allergan (payments were made to his institution through an investigator-initiated grant [CAZ-IT-21]), BioFire Diagnostics, and Merck; served as consultant to Shionogi; and served on a Data Safety Monitoring Board for Spero Therapeutics. Y.-W. T. is an employee of Cepheid. T. J. W. has received grant support from Allergan, Amplyx, Astellas, Leadiant Biosciences, Medicines Company, Merck, Scynexis, Shionogi, T2 Biosystems, Tetraphase, and Viosera and has served as consultant to Amplyx, Astellas, Allergan, ContraFect, Gilead, Karyopharm, Leadiant Biosciences, Medicines Company, Merck, Methylgene, Partner Therapeutics, Pfizer, Scynexis, Shionogi, and T2 Biosystems. L. F. W. has received grant support from Accelerate Diagnostics, BioFire Diagnostics, and Roche Molecular Systems and has served as consultant to Roche Molecular Systems, Shionogi, and Talis Biomedical. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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