SUPPLEMENTAL TEXT

METHODS

Bloodstream CRE isolate collection. 106 previously described bloodstream CRE isolates from eight medical centers in New York and New Jersey were utilized (1). All carbapenem-resistant *K. pneumoniae* previously underwent additional analysis to identify: 1) the multilocus sequence type; 2) mutations in genes encoding for outer membrane porin proteins that allow for passage of β-lactam agents through the bacterial outer membrane; and 3) *wzi* gene alleles that correspond to *K. pneumoniae* capsular type (1).

OXA-48-like CRE isolate collection. Twenty OXA-48-like-expressing isolates were tested. Isolates were derived from three sources: bloodstream CRE isolates described above (*n* = 1) (1), the Centers for Disease Control and Prevention and United States Food and Drug Administration (CDC-FDA) Antibiotic Resistance Isolate Bank (*n* = 9) (2), and clinical strains from the New York/New Jersey area provided by B.N.W. and L.C (*n* = 10).

Antimicrobial susceptibility testing of isolate collections. Quality Control (QC) testing was performed daily using *Pseudomonas aeruginosa* ATCC®27853 (MIC QC ranges of 0.5/4 - 4/4 μg/mL and 0.25/4 - 1/4 μg/mL for ceftazidime-avibactam and imipenem-relebactam, respectively), *E. coli* ATCC®25922 (MIC QC ranges of 0.06/4 - 0.5/4 μg/mL and 0.06/4 - 0.25/4 μg/mL for ceftazidime-avibactam and imipenem-relebactam, respectively), *E. coli* ATCC®35218 (MIC QC ranges of 0.03/4 - 0.12/4 μg/mL and 0.06/4 - 0.25/4 μg/mL for ceftazidime-avibactam and imipenem-relebactam, respectively), and *Klebsiella pneumoniae* ATCC®700603 (MIC QC ranges of 0.25/4 - 2/4 μg/mL and 0.03/4 - 0.25/4 μg/mL for ceftazidime-avibactam and imipenem-relebactam, respectively). Findings for isolates were only accepted if QC testing results were within established ranges (3).

Data analysis. The Wilcoxon rank-sum test was used to compare MIC distributions between different antimicrobial agents and/or different resistance mechanisms. *Wzi* alleles were compared using the Kruskal-Wallis test. All data analysis was performed in Excel (Microsoft, Redmond, WA), GraphPad Prism (La Jolla, CA), or MATLAB (Mathworks, Natick, MA) software.

RESULTS

The MIC values for KPC-3-*Kp* isolates were significantly increased for ceftazidime-avibactam as compared to KPC-2-*Kp* isolates (MIC_{90}, 8/4 μg/mL vs. ≤2/4 μg/mL; $P = 2.6 \times 10^{-5}$). Co-harboring an ESBL gene did not increase ceftazidime-avibactam MICs. Additionally, the *in vitro* activity of ceftazidime-avibactam was not affected by MLST type. Of note, the presence of outer membrane porin mutations had a significant impact on ceftazidime-avibactam MIC values for KPC-3-*Kp* isolates, but not for KPC-2-*Kp* isolates (**Supplemental Table 6**). For KPC-3-*Kp* isolates, the MIC_{90} increased from ≤2/4 μg/mL for isolates with wild-type *ompK35* and *ompK36* to 4/4 μg/mL for isolates with an *ompK35* mutation only ($P = 0.037$). For KPC-3-*Kp* isolates with *ompK35* and *ompK36* mutations, the ceftazidime-avibactam MIC_{90} increased to 8/4 μg/mL ($P = 0.022$ compared to wild-type), which is the CLSI susceptible breakpoint for these organisms. In contrast, the MIC_{90} for ceftazidime-avibactam was ≤2/4 μg/mL for all KPC-2-*Kp* isolates harboring *ompK35* ($P = 0.78$) or *ompK35*/*ompK36* ($P = 0.95$) porin mutations. Of note, the presence of *wzi29*, *wzi50*, *wzi83*, or *wzi154* (associated far more frequently with KPC-3 producing strains than KPC-2 producers) alleles significantly altered ceftazidime-avibactam MIC values among KPC-*Kp* isolates ($P = 2.0 \times 10^{-4}$).

Ceftazidime alone was active *in vitro* against 3/4 OXA-48-like CRE that did not also harbor an ESBL (**Supplemental Table 7**). However, 15/16 OXA-48-like CRE that co-harbored an ESBL were ceftazidime-resistant. The addition of avibactam restored the *in vitro* activity of ceftazidime in all but one of the OXA-48-like CRE that also possessed an ESBL (**Supplemental Table 7**).

DISCUSSION

Our data indicate that imipenem-relebactam and ceftazidime-avibactam both demonstrate substantial *in vitro* activity against KPC-*Kp* CRE isolates. The ceftazidime-avibactam MIC values were elevated for KPC-3-*Kp* isolates as compared to KPC-2-*Kp* isolates, which is consistent with previous work (1, 4). Of note, these elevated MIC values still largely fell within the susceptible range based upon CLSI interpretive criteria. In contrast, we did not identify an association between imipenem-relebactam MIC values and KPC-2-*Kp*/KPC-3-*Kp* status.

Our data suggest that the co-occurrence *ompK35* and *ompK36* mutations resulted in increased MIC values for both ceftazidime-avibactam and imipenem-relebactam in KPC-*Kp* isolates. For ceftazidime-avibactam, the increase in MIC values with mutations in *ompK35* and *ompK36* was limited to KPC-3-*Kp* isolates; whereas, for imipenem-relebactam, the presence of these mutations correlated with elevated MIC values regardless of KPC allele. Notably, the bloodstream CRE collection lacked isolates with *ompK36* mutations in isolation, which limited the ability to evaluate the association of *ompK36* mutation alone with MIC values. Therefore, it remains unclear if co-occurrence of *ompK35* and *ompK36* mutation is required for increased MIC values or if *ompK36* mutation alone is sufficient to induce increased MIC values for ceftazidime-avibactam and imipenem-relebactam.

Our study also suggests MIC values for ceftazidime-avibactam are increased in the setting of *ompK35* mutations (with wild-type *ompK36*); however, this effect was only observed in the subset of KPC-3-*Kp* isolates and was not observed when considering all KPC-*Kp* isolates nor the subset of KPC-2-*Kp* isolates. Therefore, our data in conjunction with prior studies may suggest that porin mutations require evaluation in a broader genotypic context to fully appreciate their significance in driving antimicrobial resistance.

OXA-48-like CRE are a newly emerging public health threat (5, 6) and treatment of OXA-48-like isolates remains a therapeutic challenge given the paucity of effective antimicrobial agents (7). Our results suggest that ceftazidime, imipenem, and imipenem-relebactam are ineffective against most OXA-48-like isolates while ceftazidime-avibactam retains activity in this context, which is consistent with previous work (8, 9).

This disparity in *in vitro* activity between ceftazidime-avibactam and imipenem-relebactam may be related to the parent β-lactam agent, as OXA-48-like enzymes hydrolyze cephalosporins less efficiently than carbapenems (5). Most of the OXA-48-like CRE in this study that were resistant to ceftazidime co-harbored an ESBL. We hypothesize that the ability of avibactam to restore the activity of ceftazidime against OXA-48-like CRE is related to inhibition of both OXA-48-like and ESBL enzymes (10).

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91 **Supplemental Table 1.** Resistance mechanisms for the 106 CRE bloodstream isolates.

Organism	Carbapenemase	Other β-lactamases
Enterobacter cloacae	KPC-3	ACT; TEM-WT
Enterobacter cloacae	KPC-3	TEM-WT; ACT
Enterobacter cloacae	KPC-2	TEM-WT; ACT
Escherichia coli	KPC-2	TEM-WT
Escherichia coli	None	CTX-M gp
Escherichia coli	NDM	CTX-M-1 gr; CMY2
Klebsiella (formerly *Enterobacter*) *aerogenes*	KPC-3	TEM-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT
Klebsiella pneumoniae	KPC-3	None
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	SHV-WT; CTX-M group 1
Klebsiella pneumoniae	KPC-3	SHV-WT; CTX-M group 1
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT; CTX-M-1 gr
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT

Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	OXA-48	CTX-M-1 gp; SHV-WT
Klebsiella pneumoniae	None	CTX-M-9 gp; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	None	TEM-WT; CTX-M-1 gp
Klebsiella pneumoniae	None	TEM-WT; SHV-ESBL; CTX-M-1 gp
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	None	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT

Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	SHV-WT
Klebsiella pneumoniae	KPC-3	SHV-WT
Klebsiella pneumoniae	KPC-2	SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	SHV-WT; CTX-M group 1
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	SHV-WT; CMY2
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT

Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-2	TEM-WT; SHV-ESBL
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-WT
Klebsiella pneumoniae	KPC-3	TEM-WT; SHV-ESBL
Morganella morganii	KPC-2	DHA
Pluralibacter (formerly *Enterobacter*) *gergoviae*	None	ACT; CTX-M-1 gp

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Supplemental Table 2. Identified resistance mechanisms present in isolates without carbapenemases from the 106 CRE bloodstream isolate collection.

Isolate	Porin Mutations	Number of Narrow Spectrum β-Lactamases	Number of Extended Spectrum β-Lactamases
Klebsiella pneumoniae	-	1 (SHV-WT)	1 (CTX-M-1)
Klebsiella pneumoniae	*ompK35* and *ompK36*	2 (TEM-WT; SHV238240SK)	1 (CTX-M-1)
Klebsiella pneumoniae	*ompK35*	1 (SHV-WT)	1 (CTX-M-9)
Klebsiella pneumoniae	*ompK35*	2 (TEM-WT; SHV-WT)	-
Pluralibacter gergoviae	-	-	1 (CTX-M-1)
Escherichia coli	-	1 (ACT AmpC)	1 (CTX-M-1)
Escherichia coli	-	1 (CMY-2 AmpC)	1 (CTX-M-1)

WT = wildtype

Supplemental Table 3. Identified resistance mechanisms for the 20 OXA-48-type CRE isolates.

Organism	OXA Type	Resistance Mechanisms
Escherichia coli	OXA-48	OXA-48, AmpC (chromosomal)
Escherichia coli	OXA-48	OXA-181, TEM-1, AmpC (chromosomal)
*Klebsiella (*formerly *Enterobacter) aerogenes*	OXA-48	ARR-3, OXA-48
*Klebsiella (*formerly *Enterobacter) aerogenes*	OXA-181	OXA-181, TEM-1, CTX-M-15, AmpC (chromosomal)
Klebsiella ozaenae	OXA-181	aac(3)-IId, aac(6')Ib-cr, aadA2, armA, ARR-3, catA1, CTX-M-15, dfrA12, dfrA14, OmpK35, OXA-181, SHV-26, sul1, sul2, tet(A)
Klebsiella pneumoniae	OXA-163	OXA-163, OXA-9, TEM-1, SHV-11, OmpK35 (stop codon)
Klebsiella pneumoniae	OXA-48	OXA-48, OXA-1, TEM-1, SHV-11, CTX-M-15, OmpK35 (IS1_ins_pro)
Klebsiella pneumoniae	OXA-48	OXA-48, OXA-1, TEM-1, SHV-11, CTX-M-15, VEB-8, OmpK35 (Stop codon), OmpK35 (134-135DG)
Klebsiella pneumoniae	OXA-181	OXA-181, OXA-1, OXA-9, TEM-1, SHV-11, CTX-M-15, OmpK36 (IS102_ins_pro)
Klebsiella pneumoniae	OXA-181	OXA-181, OXA-1, OXA-9, TEM-1, SHV-11, CTX-M-15, OmpK36 (IS102_ins_pro)
Klebsiella pneumoniae	OXA-181	aac(3)-IId, aac(6')Ib-cr, aadA2, ARR-3, catA1, CTX-M-15, dfrA12, dfrA14, OmpK35, OXA-181, SHV-26, strA, strB, sul1, sul2, tet(A)
Klebsiella pneumoniae	OXA-232	aac(3)-IId, aac(6')-Ib, ARR-3, catA1, cmlA1, CTX-M-15, dfrA1, fosA, OmpK35, oqxA, oqxA, OXA-1, OXA-232, OXA-9, strA, strB, sul1, sul2, TEM-1A
Klebsiella pneumoniae	OXA-232	aac(6')Ib-cr, CTX-M-15, dfrA1, OmpK35, oqxA, oqxA, OXA-1, OXA-232, SHV-1, sul1, tet(A)
Klebsiella pneumoniae	OXA-181	aac(3)-IId, aac(6')Ib-cr, aadA2, armA, catA1, CTX-M-15, dfrA12, dfrA14, OmpK35, OXA-181, SHV-26, sul1, sul2, tet(A)
Klebsiella pneumoniae	OXA-181	aac(3)-IId, aac(6')Ib-cr, aadA2, armA, CTX-M-15, dfrA12, dfrA14, OmpK35, OXA-181, SHV-26, sul1, sul2, tet(A)
Klebsiella pneumoniae	OXA-181	aac(3)-IId, aac(6')Ib-cr, aadA2, armA, CTX-M-15, dfrA12, dfrA14, OmpK35, OXA-181, SHV-26, sul1, sul2, tet(A)
Klebsiella pneumoniae	OXA-48	fosA, oqxA, oqxA, oqxB, OXA-48, SHV-11
Klebsiella pneumoniae	OXA-232	OXA-232, TEM-1, SHV-1, CTX-M-15, OmpK36 (134-135DG)
Klebsiella pneumoniae	OXA-48	135-136DT, 184-186del
Proteus mirabilis	OXA-48	OXA-48, TEM-1, CTX-M-14

Supplemental Table 4. *In vitro* activity of antimicrobial agents against 106 bloodstream CRE isolates[#]

Antimicrobial Class	Antimicrobial Agent	% Susceptible (*n*)	MIC_{50} (μg/mL)[&]	MIC_{90} (μg/mL)[&]
Penicillins	Amoxicillin-Clavulanate	2 (2)	-	-
	Piperacillin-Tazobactam	5 (5)	-	-
Cephalosporins	Cefepime	5 (5)	-	-
	Ceftazidime	4 (4)	-	-
	Ceftazidime-Avibactam	97 (103)	≤2/4	8/4
Monobactam	Aztreonam	4 (4)	-	-
Carbapenems	Doripenem	9 (9)	-	-
	Ertapenem	7 (7)	-	-
	Imipenem	7 (7)	-	-
	Imipenem-Relebactam*	95 (101)	≤0.25/4	0.5/4
	Meropenem	9 (9)	-	-
Fluoroquinolone	Ciprofloxacin	9 (9)	-	-
Aminoglycosides	Amikacin	59 (62)	≤16	32
	Gentamicin	65 (69)	4	>16
Tetracyclines	Minocycline	50 (53)	≤4	>16
	Tigecycline[‡]	88 (93)	≤2	4
Folate Synthesis Inhibitor	Trimethoprim-Sulfamethoxazole	12 (13)	-	-
Polymyxins	Colistin[‡]	79 (84)	0.5	>8
	Polymyxin B[‡]	79 (84)	1	>8

[#]The 106 CRE isolates consisted of 98 KPC-producing, 1 OXA-48-producing, and 7 non-carbapenemase producing CRE.
[‡]Isolates for which the tigecycline, colistin, and polymyxin B MIC values were ≤2 μg/mL were considered susceptible to these agents. Although neither CLSI nor FDA interpretive criteria exist for assessing susceptibility to the polymyxins when testing members of the *Enterobacteriaceae*, isolates for which the MIC values are ≤2 μg/mL fall within the CLSI-approved wild-type range (3).
*The CLSI interpretive criteria for imipenem were applied to imipenem-relebactam (susceptible: ≤1/4 μg/mL).
[&]MIC_{50} and MIC_{90} values were only calculated for agents to which ≥50% of isolates were susceptible.

Supplemental Table 5. *In vitro* activity of antimicrobial agents against 20 OXA-48-like isolates

Antimicrobial Class	Antimicrobial Agent	% Susceptible (n)	MIC_{50} (µg/mL)[&]	MIC_{90} (µg/mL)[&]
Penicillins	Amoxicillin-Clavulanate	0 (0)	-	-
	Piperacillin-Tazobactam	5 (1)	-	-
Cephalosporins	Cefepime	10 (2)	-	-
	Ceftazidime	20 (4)	-	-
	Ceftazidime-Avibactam	90 (18)	≤2/4	8/4
Monobactam	Aztreonam	20 (4)	-	-
Carbapenems	Doripenem	15 (3)	-	-
	Ertapenem	10 (2)	-	-
	Imipenem	15 (3)	-	-
	Imipenem-Relebactam*	15 (3)	-	-
	Meropenem	25 (5)	-	-
Fluoroquinolone	Ciprofloxacin	15 (3)	-	-
Aminoglycosides	Amikacin	40 (8)	-	-
	Gentamicin	25 (5)	-	-
Tetracyclines	Minocycline	30 (6)	-	-
	Tigecycline[‡]	75 (15)	≤2	4
Folate Synthesis Inhibitor	Trimethoprim-Sulfamethoxazole	15 (3)	-	-
Polymyxins	Colistin[‡]	95 (19)	1	1
	Polymyxin B[‡]	90 (18)	1	2

[‡]Isolates with MIC values of ≤2 µg/mL for tigecycline, colistin, and polymyxin B were considered susceptible to these agents. Although neither CLSI nor FDA interpretive criteria exist for assessing susceptibility to the polymyxins when testing members of the *Enterobacteriaceae*, isolates for which the MIC values are ≤2 µg/mL fall within the CLSI-approved wild-type range (3).
*The CLSI interpretive criteria for imipenem were applied to imipenem-relebactam (susceptible: ≤1/4 µg/mL).
[&]MIC_{50} and MIC_{90} values were only calculated for agents to which ≥50% of isolates were susceptible.

Supplemental Table 6. Ceftazidime-avibactam MIC values for KPC-*Kp* bloodstream isolates stratified by ESBL status, ST258 status, *wzi* allele, and mutations in *ompK35* and *ompK36* outer membrane porin genes. MIC values >16/4 μg/mL are not displayed as isolates for which MIC values were >16/4 μg/mL were not identified.

	No. (%) of isolates for which ceftazidime-avibactam MIC values (μg/mL) were:						
	≤2/4	**4/4**	**8/4**	**16/4**	**MIC_{50} (μg/mL)**	**MIC_{90} (μg/mL)**	**MIC Range (μg/mL)**
KPC-*Kp* (n = 92)	66 (72%)	15 (16%)	9 (10%)	2 (2%)	≤2/4	8/4	≤2/4 to 16/4
ESBL (n = 34)	25 (74%)	8 (24%)	1 (3%)	0 (0%)	≤2/4	4/4	≤2/4 to 8/4
ST258 (n = 77)	52 (68%)	15 (20%)	8 (10%)	2 (3%)	≤2/4	8/4	≤2/4 to 16/4
Non-ST258 (n = 15)	14 (93%)	0 (0%)	1 (7%)	0 (0%)	≤2/4	≤2/4	≤2/4 to 8/4
wzi29 (n = 19)	19 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
wzi50 (n = 8)	8 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
wzi83 (n = 7)	4 (57%)	2 (29%)	1 (14%)	0 (0%)	≤2/4	8/4	≤2/4 to 8/4
wzi154 (n = 43)	21 (49%)	13 (30%)	7 (16%)	2 (5%)	4/4	8/4	≤2/4 to 16/4
ompK35 and *ompK36* wild-type (n = 15)	14 (93%)	0 (0%)	1 (7%)	0 (0%)	≤2/4	≤2/4	≤2/4 to 8/4
ompK35 mutation only (n = 45)	33 (73%)	9 (20%)	2 (4%)	1 (2%)	≤2/4	4/4	≤2/4 to 16/4
ompK35 and *ompK36* mutations (n = 31)	19 (61%)	6 (19%)	5 (16%)	1 (3%)	≤2/4	8/4	≤2/4 to 16/4
KPC-2-*Kp* (n = 44)	41 (93%)	1 (2%)	2 (5%)	0 (0%)	≤2/4	≤2/4	≤2/4 to 8/4
ESBL (n = 19)	18 (95%)	1 (5%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to 4/4
ST258 (n = 35)	33 (94%)	1 (3%)	1 (3%)	0 (0%)	≤2/4	≤2/4	≤2/4 to 8/4
Non-ST258 (n = 9)	8 (89%)	0 (0%)	1 (11%)	0 (0%)	≤2/4	8/4	≤2/4 to 8/4
wzi29 (n = 18)	18 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
wzi50 (n = 7)	7 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
wzi83 (n = 6)	4 (67%)	1 (17%)	1 (17%)	0 (0%)	≤2/4	8/4	≤2/4 to 8/4
wzi154 (n = 4)	4 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
ompK35 and *ompK36* wild-type (n = 9)	8 (89%)	0 (0%)	1 (11%)	0 (0%)	≤2/4	8/4	≤2/4 to 8/4
ompK35 mutation only (n = 25)	23 (92%)	1 (4%)	1 (4%)	0 (0%)	≤2/4	≤2/4	≤2/4 to 8/4
ompK35 and *ompK36* mutations (n = 10)	10 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
KPC-3-*Kp* (n = 48)	25 (52%)	14 (29%)	7 (15%)	2 (4%)	≤2/4	8/4	≤2/4 to 16/4
ESBL (n = 15)	7 (47%)	7 (47%)	1 (7%)	0 (0%)	4/4	4/4	≤2/4 to 8/4
ST258 (n = 42)	19 (45%)	14 (33%)	7 (17%)	2 (4%)	4/4	8/4	≤2/4 to 16/4
Non-ST258 (n = 6)	6 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
wzi29 (n = 1)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
wzi50 (n = 1)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
wzi83 (n = 1)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	4/4	4/4	4/4 to 4/4
wzi154 (n = 39)	17 (44%)	13 (33%)	7 (18%)	2 (5%)	4/4	8/4	≤2/4 to 16/4
ompK35 and *ompK36* wild-type (n = 6)	6 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
ompK35 mutation only (n = 20)	10 (50%)	8 (40%)	1 (5%)	1 (5%)	≤2/4	4/4	≤2/4 to 16/4
ompK35 and *ompK36* mutations (n = 21)	9 (43%)	6 (2%)	5 (24%)	1 (5%)	4/4	8/4	≤2/4 to 16/4

Supplemental Table 7. (A) Ceftazidime MICs in OXA-48-like isolates stratified by ESBL status, OXA-like enzyme, and mutations in *ompK35* and *ompK36* outer membrane porin genes. Only MIC values of ≤2 µg/mL and >64 µg/mL are displayed as this accounted for the MIC values for all isolates. **(B)** Ceftazidime-avibactam MIC values for OXA-48-like isolates stratified by ESBL status, OXA-like enzyme, and mutations in *ompK35* and *ompK36* outer membrane porin genes. An MIC value of 16/4 µg/mL is not displayed because MIC values of 16/4 µg/mL were not identified for any of the isolates.

A.

	No. (%) of isolates for which ceftazidime MICs (µg/mL) were:				
	≤2	**>64**	**MIC_{50} (µg/mL)**	**MIC_{90} (µg/mL)**	**MIC Range (µg/mL)**
OXA-48-Like (n = 20)	4 (20%)	16 (80%)	>64	>64	≤2/4 to >64
ESBL (n = 16)	1 (6%)	15 (94%)	>64	>64	≤2/4 to >64
OXA-48 (n = 8)	4 (50%)	4 (50%)	≤2	>64	≤2 to >64
OXA-163 (n = 1)	0 (0%)	1 (100%)	>64	>64	>64 to >64
OXA-181 (n = 8)	0 (0%)	8 (100%)	>64	>64	>64 to >64
OXA-232 (n = 3)	0 (0%)	3 (100%)	>64	>64	>64 to >64
OXA-48-Like-*Kp* (n = 14)	1 (7%)	13 (93%)	>64	>64	≤2 to >64
ompK35 and *ompK36* wild-type (n = 2)	1 (50%)	1 (50%)	≤2	>64	≤2 to >64
ompK35 mutation only (n = 9)	0 (0%)	9 (100%)	>64	>64	>64 to >64
ompK36 mutation only (n = 2)	0 (0%)	2 (100%)	>64	>64	>64 to >64
ompK35 and *ompK36* mutations (n = 1)	0 (0%)	1 (100%)	>64	>64	>64 to >64

B.

	No. (%) of isolates for which ceftazidime-avibactam MICs (µg/mL) were:						
	≤2/4	**4/4**	**8/4**	**>64/4**	**MIC_{50} (µg/mL)**	**MIC_{90} (µg/mL)**	**MIC Range (µg/mL)**
OXA-48-Like (n = 20)	16 (80%)	1 (5%)	1 (5%)	2 (10%)	≤2/4	8/4	≤2/4 to >64/4
ESBL (n = 16)	13 (81%)	1 (6%)	1 (6%)	1 (7%)	≤2/4	8/4	≤2/4 to >64/4
OXA-48 (n = 8)	6 (75%)	0 (0%)	0 (0%)	2 (25%)	≤2/4	>64/4	≤2/4 to >64/4
OXA-163 (n = 1)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	4/4	4/4	4/4 to 4/4
OXA-181 (n = 8)	8 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
OXA-232 (n = 3)	2 (67%)	0 (0%)	1 (33%)	0 (0%)	≤2/4	8/4	≤2/4 to 8/4
OXA-48-Like-*Kp* (n = 14)	11 (79%)	1 (7%)	1 (7%)	1 (7%)	≤2/4	8/4	≤2/4 to >64/4
ompK35 and *ompK36* wild-type (n = 2)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
ompK35 mutation only (n = 9)	6 (67%)	1 (11%)	1 (11%)	1 (11%)	≤2/4	>64/4	≤2/4 to >64/4
ompK36 mutation only (n = 2)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4
ompK35 and *ompK36* mutations (n = 1)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	≤2/4	≤2/4	≤2/4 to ≤2/4

Supplemental Table 8. Imipenem-relebactam MIC values for KPC-*Kp* bloodstream isolates stratified by ESBL status, ST258 status, *wzi* allele, and mutations in *ompK35* and *ompK36* outer membrane porin genes. The CLSI interpretive criteria for imipenem were applied to imipenem-relebactam. MIC values >1/4 µg/mL are not displayed as isolates for which MIC values were >1/4 µg/mL were not identified.

	No. (%) of isolates for which imipenem-relebactam MICs (µg/mL) were:					
	≤0.25/4	**0.5/4**	**1/4**	**MIC_{50} (µg/mL)**	**MIC_{90} (µg/mL)**	**MIC Range (µg/mL)**
KPC-*Kp* (n = 92)	77 (84%)	10 (11%)	5 (5%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
ESBL (n = 34)	29 (85%)	4 (12%)	1 (3%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
ST258 (n = 77)	62 (81%)	10 (13%)	5 (7%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
Non-ST258 (n = 15)	15 (100%)	0 (0%)	0 (0%)	≤0.25/4	≤0.25/4	≤0.25/4 to ≤0.25/4
wzi29 (n = 19)	15 (79%)	3 (16%)	1 (5%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
wzi50 (n = 8)	7 (88%)	1 (13%)	0 (0%)	≤0.25/4	0.5/4	≤0.25/4 to 0.5/4
wzi83 (n = 7)	5 (71%)	1 (14%)	1 (14%)	≤0.25/4	1/4	≤0.25/4 to 1/4
wzi154 (n = 43)	35 (81%)	5 (12%)	3 (7%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
ompK35 and *ompK36* wild-type (n = 15)	15 (100%)	0 (0%)	0 (0%)	≤0.25/4	≤0.25/4	≤0.25/4 to ≤0.25/4
ompK35 mutation only (n = 45)	39 (87%)	5 (11%)	1 (2%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
ompK35 and *ompK36* mutations (n = 31)	22 (71%)	5 (16%)	4 (13%)	≤0.25/4	1/4	≤0.25/4 to 1/4
KPC-2-*Kp* (n = 44)	38 (86%)	3 (7%)	3 (7%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
ESBL (n = 19)	16 (84%)	2 (11%)	1 (5%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
ST258 (n = 35)	29 (83%)	3 (9%)	3 (9%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
Non-ST258 (n = 9)	9 (100%)	0 (0%)	0 (0%)	≤0.25/4	≤0.25/4	≤0.25/4 to ≤0.25/4
wzi29 (n = 18)	15 (83%)	2 (11%)	1 (6%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
wzi50 (n = 7)	6 (86%)	1 (14%)	0 (0%)	≤0.25/4	0.5/4	≤0.25/4 to 0.5/4
wzi83 (n = 6)	5 (83%)	0 (0%)	1 (17%)	≤0.25/4	1/4	≤0.25/4 to 1/4
wzi154 (n = 4)	3 (75%)	0 (0%)	1 (25%)	≤0.25/4	1/4	≤0.25/4 to 1/4
ompK35 and *ompK36* wild-type (n = 9)	9 (100%)	0 (0%)	0 (0%)	≤0.25/4	≤0.25/4	≤0.25/4 to ≤0.25/4
ompK35 mutation only (n = 25)	21 (84%)	3 (12%)	1 (4%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
ompK35 and *ompK36* mutations (n = 10)	8 (80%)	0 (0%)	2 (20%)	≤0.25/4	1/4	≤0.25/4 to 1/4
KPC-3-*Kp* (n = 48)	39 (81%)	7 (15%)	2 (4%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
ESBL (n = 15)	13 (87%)	2 (13%)	0 (0%)	≤0.25/4	0.5/4	≤0.25/4 to 0.5/4
ST258 (n = 42)	33 (79%)	7 (17%)	2 (5%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
Non-ST258 (n = 6)	6 (100%)	0 (0%)	0 (0%)	≤0.25/4	4/4	≤0.25/4 to ≤0.25/4
wzi29 (n = 1)	0 (0%)	1 (100%)	0 (0%)	0.5/4	0.5/4	0.5/4 to 0.5/4
wzi50 (n = 1)	1 (100%)	0 (0%)	0 (0%)	≤0.25/4	≤0.25/4	≤0.25/4 to ≤0.25/4
wzi83 (n = 1)	0 (0%)	1 (100%)	0 (0%)	0.5/4	0.5/4	0.5/4 to 0.5/4
wzi154 (n = 39)	32 (82%)	5 (12.8%)	2 (5%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4
ompK35 and *ompK36* wild-type (n = 6)	6 (100%)	0 (0%)	0 (0%)	≤0.25/4	≤0.25/4	≤0.25/4 to ≤0.25/4
ompK35 mutation only (n = 20)	18 (90%)	2 (10%)	0 (0%)	≤0.25/4	0.5/4	≤0.25/4 to 0.5/4
ompK35 and *ompK36* mutations (n = 21)	14 (67%)	5 (24%)	2 (10%)	≤0.25/4	0.5/4	≤0.25/4 to 1/4

Supplemental Table 9. (A) Imipenem MIC values for OXA-48-like isolates stratified by ESBL status, OXA-like enzyme, and mutations in *ompK35* and *ompK36* outer membrane porin genes. MIC values of 0.5 and 2 µg/mL are not displayed because no isolates exhibited MIC values of 0.5 or 2 µg/mL. **(B)** Imipenem-relebactam MIC values in OXA-48-like isolates stratified by ESBL status, OXA-like enzyme, and mutations in *ompK35* and *ompK36* outer membrane porin genes. The CLSI interpretive criteria for imipenem were applied to imipenem-relebactam.

A.

	No. (%) of isolates for which imipenem MICs (µg/mL) were:								
	≤0.25	**1**	**4**	**8**	**16**	**≥32**	**MIC_{50} (µg/mL)**	**MIC_{90} (µg/mL)**	**MIC Range (µg/mL)**
OXA-48-Like (n = 20)	1 (5%)	2 (10%)	4 (20%)	4 (20%)	3 (15%)	6 (30%)	8	≥32	8 to ≥32
ESBL (n = 16)	1 (6%)	0 (0%)	4 (25%)	3 (19%)	3 (19%)	5 (31%)	8	≥32	0.5/4 to ≥32
OXA-48 (n = 8)	0 (0%)	2 (25%)	0 (0%)	1 (13%)	2 (25%)	3 (38%)	16	≥32	≤0.25/4 to ≥32
OXA-163 (n = 1)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	≤0.25	≤0.25	≤0.25 to ≤0.25
OXA-181 (n = 8)	0 (0%)	0 (0%)	4 (50%)	3 (38%)	0 (0%)	1 (13%)	4	≥32	4 to ≥32
OXA-232 (n = 3)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (33%)	2 (67%)	≥32	≥32	16 to ≥32
OXA-48-Like-*Kp* (n = 14)	1 (7%)	0 (0%)	3 (21%)	2 (14%)	2 (14%)	6 (43%)	16	≥32	≤0.25 to ≥32
ompK35 and *ompK36* wild-type (n = 2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)	16	≥32	16 to ≥32
ompK35 mutation only (n = 9)	1 (11%)	0 (0%)	2 (22%)	2 (22%)	0 (0%)	4 (44%)	8	≥32	≤0.25 to ≥32
ompK36 mutation only (n = 2)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	1 (50%)	4	≥32	4 to ≥32
ompK35 and *ompK36* mutations (n = 1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	16	16	16 to 16

B.

	No. (%) of isolates for which imipenem-relebactam MICs (µg/mL) were:										
	≤0.25/4	**0.5/4**	**1/4**	**2/4**	**4/4**	**8/4**	**16/4**	**≥32/4**	**MIC_{50} (µg/mL)**	**MIC_{90} (µg/mL)**	**MIC Range (µg/mL)**
OXA-48-Like (n = 20)	1 (5%)	1 (5%)	1 (5%)	1 (5%)	9 (45%)	2 (10%)	1 (5%)	4 (20%)	4/4	≥32/4	≤0.25/4 to ≥32/4
ESBL (n = 16)	0 (0%)	1 (6%)	0 (0%)	1 (6%)	8 (50%)	2 (13%)	1 (6%)	3 (19%)	4/4	≥32/4	0.5/4 to ≥32/4
OXA-48 (n = 8)	1 (13%)	0 (0%)	1 (13%)	0 (0%)	3 (38%)	0 (0%)	0 (0%)	3 (38%)	4/4	≥32/4	≤0.25/4 to ≥32/4
OXA-163 (n = 1)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.5/4	0.5/4	0.5/4 to 0.5/4
OXA-181 (n = 8)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	6 (75%)	0 (0%)	0 (0%)	1 (13%)	4/4	≥32/4	2/4 to ≥32/4
OXA-232 (n = 3)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (67%)	1 (33%)	0 (0%)	8/4	16/4	8/4 to 16/4
OXA-48-Like-*Kp* (n = 14)	0 (0%)	1 (7%)	0 (0%)	1 (7%)	5 (36%)	2 (14%)	1 (7%)	4 (29%)	8/4	≥32/4	0.5/4 to ≥32/4
ompK35 and *ompK36* wild-type (n = 2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	1 (50%)	8/4	≥32/4	≤0.25/4 to ≥32/4
ompK35 mutation only (n = 9)	0 (0%)	1 (11%)	0 (0%)	1 (11%)	3 (33%)	1 (11%)	1 (11%)	2 (22%)	4/4	≥32/4	0.5/4 to ≥32/4
ompK36 mutation only (n = 2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	1 (50%)	4/4	≥32/4	4/4 to ≥32/4
ompK35 and *ompK36* mutations (n = 1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	4/4	4/4	4/4 to 4/4

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