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CLINICAL THERAPEUTICS

Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia

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ABSTRACT There are no data comparing outcomes of patients treated with ceftazidime-avibactam versus comparators for carbapenem-resistant *Enterobacteriaceae* infections. At our center, ceftazidime-avibactam treatment of carbapenem-resistant *Klebsiella pneumoniae* bacteremia was associated with higher rates of clinical success ($P = 0.006$) and survival ($P = 0.01$) than other regimens. Across treatment groups, there were no differences in underlying diseases, severity of illness, source of bacteremia, or strain characteristics (97% produced *K. pneumoniae* carbapenemase). Aminoglycoside- and colistin-containing regimens were associated with increased rates of nephrotoxicity ($P = 0.002$).

KEYWORDS carbapenem-resistant *Enterobacteriaceae*, *Klebsiella pneumoniae* carbapenemase, ceftazidime-avibactam, *Klebsiella pneumoniae*, bacteremia, clinical success

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Optimal management of carbapenem-resistant *Enterobacteriaceae* (CRE) infections is limited by a paucity of effective treatment options. Before 2015, frontline regimens included combinations of agents with high toxicity rates (aminoglycosides, colistin), suboptimal pharmacokinetics (aminoglycosides, colistin, tigecycline), and/or known microbiological resistance (carbapenems). In 2015, the U.S. Food and Drug Administration (FDA) approved ceftazidime-avibactam (C-A), a novel β-lactam/β-lactamase inhibitor with *in vitro* activity against CRE expressing *Klebsiella pneumoniae* carbapenemases (KPCs) but not Ambler class B or some class D β-lactamases. Since the majority of CRE infections in the United States are caused by KPC-producing *K. pneumoniae*, C-A may offer a significant improvement over previous treatment regimens. At present, however, there are no data directly comparing the outcomes of CRE-infected patients treated with C-A versus other regimens.

Shortly after FDA approval, C-A was endorsed at the University of Pittsburgh Medical Center (UPMC) as the frontline agent against CRE infections. Our objective in this study was to compare the outcomes of patients with carbapenem-resistant *K. pneumoniae* (CR-Kp) bacteremia who received definitive treatment with a regimen containing C-A or alternative regimens (carbapenem plus aminoglycoside [CB+AG], carbapenem plus colistin [CB+COL], or others [including monotherapy with AG or COL]).

We conducted a retrospective study of UPMC patients with CR-Kp bacteremia between January 2009 and February 2017 who received ≥3 days of treatment. CR-Kp

was defined by resistance to any carbapenem (1); only the first episode of CR-Kp bacteremia was included. Clinical success was defined at 30 days as survival, resolution of signs and symptoms of infection, sterilization of blood cultures within 7 days of treatment initiation, and absence of recurrent infections.

MICs were determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods. Based on our previously published *in vitro* studies and relevant pharmacokinetic-pharmacodynamic (PK-PD) data, carbapenems were considered inactive if MICs were >8 μg/ml (2–4). Strains were tested for KPC variants and the presence of other β-lactamases as described previously (5).

Comparisons between groups were made by Fisher's exact or chi-square tests for categorical variables and the Mann-Whitney U test for continuous variables. The Kruskal-Wallis test was used to compare two or more groups. Multivariate logistic regression was performed by backward selection procedures to identify factors associated with clinical success.

One hundred nine patients with CR-Kp bacteremia were included (Table 1). Median age of the patients was 61 years (range, 25 to 91 years); 56% (61/109) of the patients were men. At the onset of bacteremia, 50% (55/109) of the patients resided in an intensive care unit. Median APACHE II and Pitt bacteremia scores were 18 (4 to 38) and 4 (0 to 9), respectively. Primary bacteremia was diagnosed in 26% (28/109) of the patients; secondary bacteremia resulted from abdominal (46%, 50/109), respiratory tract (13%, 14/109), urinary tract (13%, 14/109), or soft tissue (3%, 3/109) sites.

Ninety-seven percent (106/109) of the isolates harbored bla_{KPC}, of which 76% (81/106) and 24% (25/106) encoded KPC-2 and KPC-3 subtypes, respectively. All isolates were meropenem resistant (median MIC, 32 μg/ml; range, 4 to 512 μg/ml). Eighty-four percent (92/109) and 76% (83/109) of isolates were susceptible to COL and gentamicin, respectively. Among baseline CR-Kp isolates from patients treated with C-A, the median C-A MIC was 1 μg/ml (range, 0.25 to 2 μg/ml); all isolates were susceptible according to the FDA breakpoint (MIC, $\leq$8 μg/ml).

Thirty- and 90-day mortality rates were 28% (31/109) and 40% (44/109), respectively. Clinical success at 30 days was achieved in 46% (50/109) of patients. Treatment failures were due to death ($n = 31$; 4 patients had persistent bacteremia before death), recurrent CR-Kp infection ($n = 18$), or persistent bacteremia ($n = 10$). Bacteremia recurred within 90 days in 17% (19/109) of the patients, at a median of 42 days (range, 13 to 90 days). Definitive treatment was initiated with monotherapy or combination therapy in 33% (36/109) and 67% (73/109), respectively. Treatment regimens included $\geq$2, 1, or 0 *in vitro* active agents in 29% (32/109), 60% (65/109), and 11% (12/109) of the patients, respectively. Seventeen percent (19/109) of patients received *in vitro* active empirical therapy. The median time to *in vitro* active treatment initiation was 58 h (interquartile range [IQR], 29.5 to 92.0) after the first positive blood culture.

Across treatment groups, there were no differences in underlying diseases, severity of illness, source of bacteremia, or strain characteristics (Table 1). Treatment regimens included C-A ($n = 13$), CB+AG ($n = 25$), CB+COL ($n = 30$), and others ($n = 41$); the corresponding clinical success rates by regimen were 85% (11/13), 48% (12/25), 40% (12/30), and 37% (15/41), respectively (Fig. 1; $P = 0.02$). C-A was administered as monotherapy ($n = 8$) or in combination with gentamicin ($n = 5$; median duration of gentamicin, 4 days; range, 3 to 7 days); corresponding success rates were 75% (6/8) and 100% (5/5), respectively (Table 2).

Clinical success was achieved more frequently among patients treated with a regimen including C-A than with other regimens ($P = 0.006$), including those comprised of $\geq$2 *in vitro* active agents (44% [12/27]; $P = 0.02$). By multivariable logistic regression, primary bacteremia (odds ratio [OR], 4.50; 95% confidence interval [CI], 1.53 to 13.21; $P = 0.006$) and receipt of C-A (OR, 8.64; 95% CI, 1.61 to 43.39; $P = 0.01$) were independent predictors of clinical success (Table 3).

Survival rates at 30 and 90 days were 92% (12/13) among patients receiving C-A regimens versus 69% (66/96) and 55% (53/96), respectively, among patients receiving

TABLE 1 Patient characteristics and clinical outcomes across treatment groups

Characteristic[a]	Treatment group[b]				*P* value
	C-A (*n* = 13)	CB+AG (*n* = 25)	CB+COL (*n* = 30)	Other[c] (*n* = 41)	
Patient demographics					
Male (*n* [%])	7 (54)	16 (64)	18 (60)	21 (51)	0.75
Age (median [range])	66 (32–91)	57 (32–87)	59 (26–84)	62 (25–90)	0.63
Underlying disease					
Diabetes (*n* [%])	4 (31)	8 (32)	8 (27)	15 (37)	0.85
Chronic liver disease (*n* [%])	0 (0)	9 (36)	9 (30)	13 (32)	0.11
Chronic respiratory disease (*n* [%])	5 (38)	5 (20)	8 (27)	8 (20)	0.51
Immunocompromised (*n* [%])	5 (38)	13 (52)	14 (47)	22 (54)	0.78
Solid-organ transplant recipient (*n* [%])	3 (23)	11 (44)	9 (30)	17 (41)	0.46
Severity of illness					
ICU at time of bacteremia (*n* [%])	6 (46)	13 (52)	12 (40)	25 (61)	0.36
RRT (*n* [%])	2 (15)	7 (28)	7 (23)	8 (20)	0.79
Pitt bacteremia score (median [range])	4 (1–6)	4 (0–9)	4 (0–9)	4 (0–9)	0.74
APACHE II score (median [range])	20 (16–33)	17 (8–38)	16 (7–36)	19 (4–34)	0.46
Strain characteristic					
Presence of KPC (*n* [%])	13 (100)	24 (96)	30 (100)	39 (95)	0.56
KPC-2	9	19	24	29	
KPC-3	4	5	6	10	
Primary bacteremia (*n* [%])	3 (23)	6 (24)	5 (17)	14 (34)	0.41
Secondary bacteremia (*n* [%])	10 (77)	19 (76)	25 (83)	27 (66)	0.41
Abdominal	2	12	16	20	
Respiratory	3	2	6	3	
Urinary tract	5	2	2	4	
Soft tissue	0	3	1	0	
Treatment characteristic					
≥2 active agents[d] (*n* [%])	5 (38)[e]	10 (40)[f]	9 (30)	8 (20)	0.28
Time to active treatment (median [IQR])	55.7 (25–67)	52.5 (28–64)	67.9 (30–133)	65.0 (35–95)	0.23
Duration of treatment (median days [range])	13 (5–23)	12 (3–28)	14 (3–96)	10 (3–47)	0.31
Patient outcome					
Clinical success (*n* [%])	11 (85)	12 (48)	12 (40)	15 (37)	0.02[g]
30-Day survival (*n* [%])	12 (92)	17 (68)	21 (70)	28 (68)	0.37
90-Day survival (*n* [%])	12 (92)	14 (56)	19 (63)	20 (49)	0.04[h]
Persistent bacteremia (*n* [%])	0 (0)	1 (4)	5 (17)	8 (20)	0.13
Recurrent bacteremia (*n* [%])	2 (15)	5 (20)	3 (10)	9 (22)	0.60
Drug toxicity[i]					
Acute kidney injury at 48 h (*n* [%])	1 (9)	0 (0)	7 (30)	4 (12)	0.10
Acute kidney injury at 7 days (*n* [%])	1 (9)	3 (17)	10 (43)	4 (12)	0.02
Acute kidney injury at end of treatment (*n* [%])	2 (18)	8 (44)	13 (57)	6 (18)	0.01
Initiation of renal replacement therapy (*n* [%])	0 (0)	0 (0)	5 (22)	3 (9)	
Time to start of RRT (median days [range])			5 (2–8)	8 (5–8)	

[a]ICU, intensive care unit; IQR, interquartile range; RRT, renal replacement therapy.

[b]AG, aminoglycoside; C-A, ceftazidime-avibactam; CB, carbapenem; COL, colistin.

[c]Other regimens included patients treated with monotherapy (*n* = 29) or combination therapy (*n* = 12). Monotherapy consisted of an AG (*n* = 11), CB (*n* = 8), COL (*n* = 4), tigecycline (*n* = 4), and ciprofloxacin (*n* = 2). Combination regimens were COL+tigecycline (*n* = 3), AG+tigecycline (*n* = 2), and 1 each of AG+cefepime, AG+COL+tigecycline, COL+aztreonam, COL+cefepime, COL+ciprofloxacin, CB+doxycycline, and CB+tigecycline.

[d]Active agents were defined by *in vitro* susceptibility according to CLSI interpretive criteria for all agents except the carbapenems, which were defined as active *in vitro* if the MIC was ≤8 μg/ml.

[e]Five patients received gentamicin in combination with C-A.

[f]Six patients received CB+AG+COL.

[g]Patients treated with C-A had higher rates of clinical success than those treated with CB+AG (*P* = 0.04), CB+COL (*P* = 0.009), or other regimens (*P* = 0.004). Clinical success rates were higher among patients treated with C-A than in those treated with all other regimens (*P* = 0.006).

[h]Patients treated with C-A had higher rates of 90-day survival than those treated with CB+AG (*P* = 0.03) or other regimens (*P* = 0.008); there was a trend toward higher 90-day survival for C-A compared with CB+COL (*P* = 0.07). The 90-day survival rates were higher among patients treated with C-A than in those treated with all other regimens (*P* = 0.01).

[i]Among patients not requiring RRT at baseline, which included those receiving CA (*n* = 11), CB+AG (*n* = 18), CB+COL (*n* = 23), or other regimens (*n* = 33). Acute kidney injury was defined by KDIGO criteria as a ≥0.3-mg/dl increase in serum creatinine from baseline at 48 h and as a 1.5× increase in serum creatinine from baseline at 7 days or the end of treatment.

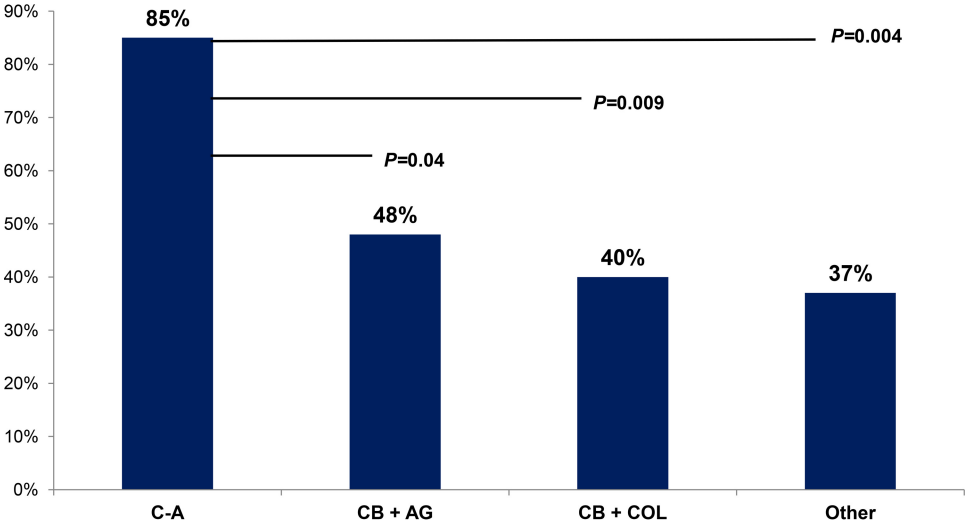

FIG 1 Rates of 30-day clinical success across treatment regimens. Among patients with carbapenem-resistant *Klebsiella pneumoniae* bacteremia, rates of clinical success were significantly higher among patients receiving ceftazidime-avibactam than among those who received a carbapenem plus aminoglycoside ($P = 0.04$) or colistin ($P = 0.009$) or other regimens ($P = 0.004$). Other regimens included aminoglycoside ($n = 11$), carbapenem ($n = 8$), colistin ($n = 4$), tigecycline ($n = 4$), and ciprofloxacin ($n = 2$) monotherapy, as well as combination regimens of colistin plus tigecycline ($n = 3$), aminoglycoside plus tigecycline ($n = 2$), and 1 each of aminoglycoside plus cefepime, aminoglycoside plus colistin plus tigecycline, colistin plus aztreonam, colistin plus cefepime, colistin plus ciprofloxacin, carbapenem plus doxycycline, and carbapenem plus tigecycline.

any other regimen ($P = 0.10$ and 0.01, respectively). Survival rates were 87.5% (7/8) and 100% (5/5) among patients receiving C-A alone or in combination with gentamicin, respectively.

Twenty-two percent (24/109) of the patients required renal replacement therapy at baseline. Among the remaining patients, 21% (18/85) and 34% (29/85) developed acute kidney injury (AKI) by 7 days and end of treatment (EOT), respectively (Table 1). At EOT, AKI rates were 18% (2/11), 44% (8/18), 57% (13/23), and 18% (6/33) for C-A, CB+AG, CB+COL, and other regimens, respectively. EOT AKI rates were 25% (1/4) and 14% (1/7) for patients receiving C-A with and without an AG, respectively. Across groups, EOT AKI rates were significantly higher among patients receiving an AG or COL (42% [28/66]) than among patients not receiving these agents (5% [1/19]; $P = 0.002$). AKI rates were 26% (8/31), 55% (16/29), and 80% (4/5) for patients receiving an AG, COL, or both, respectively. AKI was significantly more common with COL-containing than with AG-containing regimens at 7 days (38% [11/29] versus 10% [3/31]; $P = 0.01$) and EOT (55% [16/29] versus 26% [8/31]; $P = 0.03$).

To our knowledge, this is the first study to compare the clinical outcomes of CRE-infected patients treated with C-A with those of patients treated with other regimens. Our most noteworthy finding is that clinical success and survival were significantly improved for patients with CR-Kp bacteremia who received C-A. These data build on findings from early observational reports, in which overall clinical response rates with C-A ranged from 53% to 68% across CRE infection types (6–8). Among previously reported patients with CRE bacteremia, the composite success rate was 69% (48/70) (6–9). This figure and our experience compare favorably with those reported for patients with bacteremia treated with ≥2 *in vitro* active agents, where survival rates ranged from 60% to 82% (3, 10). Compared to AG and COL, C-A demonstrates more reliable *in vitro* activity against KPC-producing CRE, exhibits more favorable PK characteristics, and is well tolerated. Indeed, rates of AKI were significantly higher among our patients who received AG- or COL-containing regimens (Table 1). Taken together, the data from this study and others establish that C-A is an important advance in the treatment of CRE infections.

TABLE 2 Clinical characteristics of patients with CR-Kp bacteremia treated with ceftazidime-avibactam

Age[a] (sex)	Underlying disease[a]	KPC variant	C-A MIC (μg/ml)	Creatinine clearance (ml/min)[b]	Source of bacteremia	Treatment regimen (days duration)	Clinical outcome at 30 days	Clinical outcome at 90 days
47 (M)	Renal transplantation	KPC-2	1	64	Urine	C-A (16)	Clinical success	Alive
68 (F)	Stem cell transplantation	KPC-2	0.5	25	Urine	C-A (19) plus gentamicin (5)	Clinical success	Alive
75 (F)	Seizure disorder, chronic PEG/trach	KPC-2	0.25	47	Urine	C-A (13) plus gentamicin (4)	Clinical success	Alive
33 (M)	Paraplegia s/p hemorrhagic stroke	KPC-2	0.5	>120	Central venous catheter	C-A (8) plus gentamicin (3)	Clinical success	Alive
79 (M)	Trauma leading to splenectomy	KPC-3	1	46	Respiratory	C-A (13)	Recurrent pneumonia and death	Dead
60 (F)	Double lung transplantation	KPC-3	1	iHD	Central venous catheter	C-A (24)	Clinical success	Alive
67 (M)	Short-gut syndrome	KPC-3	2	51	Abdominal	C-A (4) plus gentamicin (7)	Clinical success	Alive
91 (F)	Dementia	KPC-2	1	48	Urine	C-A (7) followed by doripenem and gentamicin (7)[c]	Clinical success	Alive
66 (M)	Charcot-Marie-Tooth disease	KPC-2	1	>120	Respiratory	C-A (14)	Recurrent bacteremia and survived	Alive
68 (F)	Intracranial hemorrhage	KPC-2	1	56	Urine	C-A (21)	Clinical success	Alive
65 (F)	Schizophrenia	KPC-2	1	14	Abdominal	C-A (15)	Clinical success	Recurrent bacteremia and survived
52 (M)	Renal and pancreas transplantation	KPC-3	2	iHD	Central venous catheter	C-A (13) plus gentamicin (3)	Clinical success	Alive
32 (M)	Intravenous drug user	KPC-2	0.5	63	Respiratory	C-A (13)	Clinical success	Alive

[a]F, female; iHD, intermittent hemodialysis; M, male; PEG, percutaneous endoscopic gastrostomy; s/p, status post.
[b]All ceftazidime-avibactam doses were adjusted according to manufacturer recommendations.
[c]Patient was treated successfully with C-A for 7 days but switched to doripenem plus gentamicin on discharge due to an ongoing national shortage of C-A.

The improved outcomes we observed following the introduction of C-A in 2015 stand in contrast to data from a recent multicenter study at hospitals in regions of New York/New Jersey where CRE is endemic. At these centers, mortality rates for CRE bacteremia in 2013 (before availability of C-A) were unchanged from those a decade earlier (11). Notably, time to receipt of active treatment in our study was not an independent predictor of clinical success or survival. Indeed, the rather lengthy times to receipt of an *in vitro* active agent (median, 58 h [IQR, 29.5 to 92 h]) or C-A specifically

TABLE 3 Multivariable analysis of factors associated with clinical success at 30 days

Factor[a]	Treatment outcome		*P* value	Multivariate *P* value (OR, 95% CI)[a]
	Success (n = 50)	Failure (n = 59)		
Male (n [%])	26 (52)	36 (61)	0.34	
Age (median [range])	59 (26–91)	61 (25–85)	0.49	
Diabetes (n [%])	13 (26)	22 (37)	0.21	
Chronic liver disease (n [%])	11 (22)	20 (34)	0.17	
Chronic respiratory disease (n [%])	14 (28)	12 (20)	0.35	
Immunocompromised (n [%])	25 (50)	29 (49)	0.93	
Any malignancy (n [%])	7 (14)	17 (29)	0.06	0.10
Solid-organ transplant recipient (n [%])	18 (36)	22 (37)	0.89	
Primary bacteremia (n [%])	19 (38)	9 (15)	0.007	0.006 (4.50, 1.53–13.21)
Renal replacement therapy (n [%])	6 (12)	18 (31)	0.02	0.20
Pitt bacteremia score (median [range])	3 (0–9)	5 (0–9)	0.003	0.15
APACHE II score (median [range])	17 (7–38)	21 (4–36)	0.02	Excluded for confounding
ICU (n [%])	21 (42)	35 (59)	0.07	0.24
Treatment with ≥2 active agents (n [%])	21 (42)	11 (19)	0.008	Excluded for confounding
Time to active treatment (median [IQR])	55.6 (23.5–74.6)	66 (34.3–105)	0.08	0.28
Treatment with C-A (n [%])	11 (22)	2 (3)	0.003	0.01 (8.64, 1.61–46.39)

[a]CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio.

(median, 55.7 h [IQR, 25 to 67 h]) suggest an area for future improvement. In this regard, it will be important to determine whether rapid CRE detection assays can shorten times to appropriate treatment and improve outcomes.

To date, clinical response rates have been similar for CRE-infected patients treated with C-A monotherapy or combination therapy (6–8). However, as in our experience here, sample sizes in earlier reports were small, and indication biases cannot be excluded. We used combination therapy with short-course gentamicin followed by deescalation to C-A alone in five patients, which may represent a strategy for maximizing treatment effectiveness while limiting toxicity. In fact, AKI occurred at 7 days in only 10% of patients receiving an AG. Clearly, the roles of combination regimens in treating various types of CRE infections merit further investigation. In particular, it will be important to determine if combination therapy (and shorter time to active treatment) can improve outcomes among patients with CRE pneumonia, in whom success rates with C-A have been consistently lower than for patients with bacteremia (6, 7), and suppress the emergence of C-A resistance, which has been noted after short courses of treatment (12).

Because our study was not a randomized controlled trial (RCT), bias in selection of therapy existed. Furthermore, treatment regimens were not blinded to investigators at the time of review. Nevertheless, we provide evidence to support C-A as the frontline agent for treatment of CR-Kp bacteremia. C-A treatment failures, particularly for infections such as pneumonia, and reports of emerging resistance among CRE isolates attest to the ongoing need for new drugs. Along these lines, recently completed RCTs of two antibiotics in development, meropenem-vaborbactam and plazomicin, may provide further clarity on the efficacy of newer agents compared with traditional CRE treatment regimens.

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We declare no conflicts of interest.

REFERENCES

1. Centers for Disease Control and Prevention. 2016. Healthcare-associated infections (HAIs): FAQs about choosing and implementing a CRE definition. https://www.cdc.gov/hai/organisms/cre/definition.html. Accessed 6 April 6.
2. Daikos GL, Tsaousi S, Tzouvelekis LS, Anyfantis I, Psichogiou M, Argyropoulou A, Stefanou I, Sypsa V, Miriagou V, Nepka M, Georgiadou S, Markogiannakis A, Goukos D, Skoutelis A. 2014. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother 58:2322–2328. https://doi.org/10.1128/AAC.02166-13.
3. Tzouvelekis LS, Markogiannakis A, Piperaki E, Souli M, Daikos GL. 2014. Treating infections caused by carbapenemase-producing *Enterobacteriaceae*. Clin Microbiol Infect 20:862–872. https://doi.org/10.1111/1469-0691.12697.
4. Clancy CJ, Chen L, Hong JH, Cheng S, Hao B, Shields RK, Farrell AN, Doi Y, Zhao Y, Perlin DS, Kreiswirth BN, Nguyen MH. 2013. Mutations of the *ompK36* porin gene and promoter impact responses of sequence type 258, KPC-2-producing *Klebsiella pneumoniae* strains to doripenem and doripenem-colistin. Antimicrob Agents Chemother 57:5258–5265. https://doi.org/10.1128/AAC.01069-13.
5. Clancy CJ, Chen L, Shields RK, Zhao Y, Cheng S, Chavda KD, Hao B, Hong JH, Doi Y, Kwak EJ, Silveira FP, Abdel-Massih R, Bogdanovich T, Humar A, Perlin DS, Kreiswirth BN, Hong Nguyen M. 2013. Epidemiology and molecular characterization of bacteremia due to carbapenem-resistant Klebsiella pneumoniae in transplant recipients. Am J Transplant 13:2619–2633. https://doi.org/10.1111/ajt.12424.
6. Temkin E, Torre-Cisneros J, Beovic B, Benito N, Giannella M, Gilarranz R, Jeremiah C, Loeches B, Machuca I, Jimenez-Martin MJ, Martinez JA, Mora-Rillo M, Navas E, Osthoff M, Pozo JC, Ramos Ramos JC, Rodriguez M, Sanchez-Garcia M, Viale P, Wolff M, Carmeli Y. 2017. Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms. Antimicrob Agents Chemother 61:e01964-16. https://doi.org/10.1128/AAC.01964-16.
7. Shields RK, Potoski BA, Haidar G, Hao B, Doi Y, Chen L, Press EG, Kreiswirth BN, Clancy CJ, Nguyen MH. 2016. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant *Enterobacteriaceae* infections. Clin Infect Dis 63:1615–1618. https://doi.org/10.1093/cid/ciw636.
8. King M, Heil E, Kuriakose S, Bias T, Huang V, El-Beyrouty C, McCoy D, Hiles J, Richards L, Gardner J, Harrington N, Biason K, Gallagher JC. 2016. Outcomes of ceftazidime/avibactam in patients with carbapenem-resistant Enterobacteriaceae (CRE) infections: a multi-center study, abstr. 2034. Abstr ID Week 2016.
9. Wu G, Abraham T, Lee S. 2016. ceftazidime-avibactam for treatment of carbapenem-resistant *Enterobacteriaceae* bacteremia. Clin Infect Dis 63:1147–1148. https://doi.org/10.1093/cid/ciw491.
10. Tumbarello M, Trecarichi EM, De Rosa FG, Giannella M, Giacobbe DR, Bassetti M, Losito AR, Bartoletti M, Del Bono V, Corcione S, Maiuro G, Tedeschi S, Celani L, Cardellino CS, Spanu T, Marchese A, Ambretti S, Cauda R, Viscoli C, Viale P, Isgri S. 2015. Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study. J Antimicrob Chemother 70:2133–2143. https://doi.org/10.1093/jac/dkv086.
11. Satlin MJ, Chen L, Patel G, Gomez-Simmonds A, Weston G, Kim AC, Seo SK, Rosenthal ME, Sperber SJ, Jenkins SG, Hamula CL, Uhlemann AC, Levi

MH, Fries BC, Tang YW, Juretschko S, Rojtman AD, Hong T, Mathema B, Jacobs MR, Walsh TJ, Bonomo RA, Kreiswirth BN. 2017. Multicenter clinical and molecular epidemiological analysis of bacteremia due to carbapenem-resistant *Enterobacteriaceae* (CRE) in the CRE epicenter of the United States. Antimicrob Agents Chemother 61:e02349-16. https://doi.org/10.1128/AAC.02349-16.

12. Shields RK, Chen L, Cheng S, Chavda KD, Press EG, Snyder A, Pandey R, Doi Y, Kreiswirth BN, Nguyen MH, Clancy CJ. 2017. Emergence of ceftazidime-avibactam resistance due to plasmid-borne bla_{KPC-3} mutations during treatment of carbapenem-resistant *Klebsiella pneumoniae* infections. Antimicrob Agents Chemother 61:e02097-16. https://doi.org/10.1128/AAC.02097-16.