Assessment of Mortality-Related Risk Factors and Effective Antimicrobial Regimens for Treatment of Bloodstream Infections Caused by Carbapenem-Resistant *Enterobacterales*

Liang Chen,a,b Xiudi Han,c YanLi Li,d Minghui Li,a

aDepartment of Infectious Diseases, Nanjing Lishui People’s Hospital, Nanjing City, China
bDepartment of Infectious Diseases, Beijing Jishuitan Hospital, 4th Medical College of Peking University, Beijing, China
cDepartment of Pulmonary and Critical Care Medicine, Qingdao Municipal Hospital, Qingdao City, China
dDepartment of Infectious Diseases and Clinical Microbiology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China
eDepartment of Infectious Diseases, Shaoxing People’s Hospital, Shaoxing Hospital of Zhejiang University, Shaoxing City, China

ABSTRACT
Bloodstream infections (BSIs) attributable to carbapenem-resistant *Enterobacterales* (CRE-BSIs) are dangerous and a major cause of mortality in clinical settings. This study was therefore designed to define risk factors linked to 30-day mortality in CRE-BSI patients and to examine the relative efficacies of different antimicrobial treatment regimens in affected individuals. Data pertaining to 187 CRE-BSI cases from four teaching hospitals in China collected between January 2018 and December 2020 were retrospectively analyzed. For the 187 patients analyzed in this study, the 30-day mortality of CRE-BSI was 41.7% (78/187). Multivariate logistic regression analyses revealed that Pitt bacteremia score, immunocompromised status, meropenem MIC of $\geq 8 \text{mg/liter}$, absence of source control of infection, and appropriate empirical therapy were independent predictors of CRE-BSI patient 30-day mortality. After controlling for potential confounding factors relative to ceftazidime-avibactam (CAZ-AVI) treatment, combination therapies including CAZ-AVI (odds ratio [OR], 1.287; 95% confidence interval [CI], 0.124 to 13.403; $P=0.833$) were not related to any significant change in patient mortality risk, whereas the 30-day mortality risk was higher for patients administered other antimicrobial regimens (OR, 12.407; 95% CI, 1.684 to 31.430; $P=0.011$). When patients were treated with antimicrobial regimens not containing CAZ-AVI, combination therapy (OR, 0.239; 95% CI, 0.077 to 0.741; $P=0.013$) was related to a decreased 30-day mortality risk relative to monotherapy treatment. The mortality-related risk factors and relative antimicrobial regimen efficacy data demonstrated in this study may guide the management of CRE-BSI patients.

KEYWORDS
bloodstream infection, carbapenem-resistant *Enterobacterales*, mortality, risk factor, antimicrobial

Carbapenems are antibiotics that are typically reserved as a last-resort therapy for high-risk multidrug-resistant Gram-negative bacterial infections. However, as the clinical utilization of carbapenems has grown over the past 10 years, so too has the incidence of carbapenem-resistant *Enterobacteriaceae* (CRE) infections, which represent a major public health threat (1–3). A study conducted by the U.S. National Healthcare Safety Network (NHSN) in 2006 to 2007 indicated that an estimated 4% and 10.8% of *Escherichia coli* and *Klebsiella pneumoniae* isolates, respectively, were resistant to carbapenems (3). Similarly, following initial reports of carbapenemase-generating *K. pneumoniae* isolates in Zhejiang Province of China in 2007, the relative rates of *E. coli* and *K. pneumoniae* carbapenem resistance have risen from 0% and 0.7% (in 2004) to 1.0% and 13.4% (in 2014). CRE infections have also been reported in almost all Chinese
provinces (4). At present, CRE infections are associated with approximately 4.0 in every 10,000 hospital discharges in China (5).

Bloodstream infections (BSIs) caused by CRE (CRE-BSIs) are related to extremely high 14- and 30-day mortality rates, ranging from 30 to 80% in affected patients (6–8). One systematic review of 62 studies recently estimated that CRE-BSIs associated with carbapenem-resistant \textit{K. pneumoniae} (CRKP) found these infections to exhibit a mortality rate of 54.3% (95% confidence interval [CI], 47.5 to 61.0) (7), with such carbapenem resistance being linked to a 3-fold increase in the risk of death among patients suffering from \textit{K. pneumoniae} BSIs (8). The risk factors associated with mortality among CRE-BSI patients, however, are not well understood (3–8).

The most effective antimicrobial regimens for treating CRE-BSI patients remain to be defined, as few alternative antimicrobials remain for these patients in China, including carbapenems, colistins, aminoglycosides, and tigecycline (9, 10). Typically, one or more of these antibiotics are used for the clinical treatment of patients based upon either \textit{in vitro} susceptibility testing or the experience of the attending clinician. Ceftazidime-avibactam (CAZ-AVI) regimens were approved in 2015 by the U.S. Food and Drug Administration (FDA) to treat complex abdominal, urinary, and hospital-acquired-pneumonia infections (11, 12). In 2019, CAZ-AVI injections were approved in China. These CAZ-AVI formulations represent a novel combination antimicrobial treatment that is effective against Gram-negative bacteria that produce antimicrobial resistance genes such as extended-spectrum \(\beta\)-lactamases (ESBLs), AmpC, KPC, and certain class D enzymes (13). CRE infections, however, were not well represented in CAZ-AVI clinical trials, and while preliminary evidence suggests that CAZ-AVI may be an effective means of treating CRKP infections, clinical experience in this context remains limited in China.

Herein, we performed a multicenter retrospective analysis in order to identify risk factors associated with CRE-BSI patient 30-day mortality and to compare the relative effects of different antimicrobial treatment regimens on the clinical outcomes (30-day mortality and clinical failure) of patients hospitalized with CRE-BSIs.

RESULTS

Patient overview. In total, 226 hospitalized patients with blood cultures positive for CRE were screened for this study, with 187 nonduplicate patients ultimately being enrolled in our analysis (Fig. 1), including 164, 21, 1, and 1 CRE-BSI cases caused by \textit{K. pneumoniae}, \textit{E. coli}, \textit{Enterobacter cloacae}, and \textit{Citrobacter freundii}, respectively.

The patients analyzed exhibited a mean age of 67.0 years (standard deviation [SD], 14.5) and were 61.5% (115/187) male. The most prevalent comorbid conditions in these individuals were cardiovascular disease (26.2%, 49/187), cerebrovascular disease (21.4%, 40/187), and chronic obstructive pulmonary disease (19.8%, 37/187), and 27.8% (52/187) of these individuals were immunocompromised. The most common suspected sources of CRE-BSIs were central venous catheter (CVC)-related infections (28.3%, 53/187), lower respiratory tract (LRT) infections (24.1%, 45/187), and abdominal infections (23.0%, 43/187). Source control of infection was conducted in 38.0% (71/187) of patients. Of these patients, 33.2% (62/187) were hospitalized in the intensive care unit (ICU) at the time of BSI development, while just 4.3% (8/187) of cases were community onset health care-associated infections. Appropriate empirical antimicrobial treatments were administered to 13.9% (26/187) of patients within 48 h following BSI onset, as detailed in Table S2 in the supplemental material. The all-cause 30-day mortality rate for these patients was 41.7% (78/187), and the 30-day clinical failure rate was 61.0% (114/187), while the 30-day mortality rate in immunocompromised patients was 63.5% (33/52) (Table 1).

Antimicrobial susceptibility testing results. The susceptibility rates of tested isolates to tigecycline and polymyxin B were excellent at over 90%, whereas just 73 isolates were tested for CAZ-AVI susceptibility, revealing a 78.1% (57/73) susceptibility rate. The respective rates of isolate susceptibility to sulfamethoxazole, amikacin, and
gentamicin were 30.5% (57/187), 54.5% (102/187), and 26.7% (50/187), respectively. The resistance rates to other antimicrobial agents tested were over 90% (Table S3).

Risk factors associated with CRE-BSI patient 30-day mortality. Relative to the surviving CRE-BSI patients, those that were deceased at the end of the 30-day period exhibited higher acute physiology and chronic health evaluation (APACHE II) scores (median scores, 13.0 versus 10.0; $P < 0.001$) and Pitt scores (median scores, 3.0 versus 1.5; $P < 0.001$) at the time of BSI. Deceased patients also exhibited higher incidences of immunocompromising conditions (42.3% versus 17.4%; $P < 0.001$), primary BSI (11.5% versus 2.8%; $P = 0.016$), and ICU hospitalization at time of BSI onset (42.3% versus 26.6%; $P = 0.025$). The number of days of appropriate antimicrobial treatment was also decreased for deceased patients relative to survivors (median numbers of days, 10.0 versus 12.0; $P = 0.049$) (Table 1).

Multivariate backward stepwise logistic regression analysis indicated that Pitt score (odds ratio [OR], 5.313; 95% CI, 3.209 to 8.797; $P < 0.001$), immunocompromised status (OR, 4.605; 95% CI, 1.629 to 13.020; $P = 0.004$), and a meropenem MIC of $\geq 8$ mg/liter (OR, 3.736; 95% CI, 1.091 to 12.795; $P = 0.036$) were positively associated with 30-day mortality, whereas source control of infection (OR, 0.316; 95% CI, 0.117 to 0.854; $P = 0.023$) and appropriate empirical therapy (OR, 0.129; 95% CI, 0.027 to 0.625; $P = 0.011$) were negatively correlated with 30-day mortality in these CRE-BSI patients (Table 2).

The impact of definitive antimicrobial treatment on CRE-BSI patient mortality. The dosages of definitive antimicrobials are shown in Table S4, and dosages were adjusted to creatinine clearance when indicated.

After controlling for Pitt score, meropenem MIC of $\geq 8$ mg/liter, immunocompromised status, source control of infection, and the administration of appropriate empirical therapy, an additional multivariate backward stepwise logistic regression analysis revealed that definitive therapy with CAZ-AVI alone, CAZ-AVI plus tigecycline (OR, 1.645; 95% CI, 0.106 to 25.422; $P = 0.722$), and CAZ-AVI plus tigecycline plus polymyxin B sulfate (OR, 0.606; 95% CI, 0.016 to 23.056; $P = 0.788$) were related to comparable 30-day mortality risks in CRE-BSI patients. Other definitive regimens not containing CAZ-AVI (OR, 12.407; 95% CI, 1.684 to 31.430; $P = 0.011$), in contrast, were associated with higher 30-day mortality risks, including specific regimens composed of tigecycline plus polymyxin B sulfate (OR, 13.674; 95% CI, 1.160 to 26.148; $P = 0.040$), carbapenem plus tigecycline plus polymyxin B sulfate (OR, 8.295;
TABLE 1 Comparison of clinical characteristics and treatment between deceased and surviving patients with CRE-BSI

| Variablea | Mean no. of patients ± SD or indicated value |
|-----------|---------------------------------------------|
|           | Total (n = 187) | Deceased (n = 78) | Survived (n = 109) | P valueb |
| Mean age (yr) | 67.0 ± 14.5 | 66.7 ± 15.2 | 67.3 ± 14.0 | 0.797 |
| Male | 115 (61.5) | 47 (60.3) | 68 (62.4) | 0.468 |
| Comorbidities | | | | |
| Cardiovascular disease | 49 (26.2) | 22 (28.2) | 27 (24.8) | 0.598 |
| Cerebrovascular disease | 40 (21.4) | 20 (25.6) | 20 (18.3) | 0.230 |
| COPD | 37 (19.8) | 16 (20.5) | 21 (19.3) | 0.833 |
| Diabetes mellitus | 34 (18.2) | 12 (15.4) | 22 (20.2) | 0.543 |
| Chronic kidney disease | 11 (5.9) | 6 (7.7) | 5 (4.6) | 0.566 |
| Immunocompromised statusc | 52 (27.8) | 33 (42.3) | 19 (17.4) | <0.001 |
| Infected by isolate with meropenem MIC of ≥8 mg/literc | 141 (75.4) | 64 (82.1) | 77 (70.6) | 0.074 |
| Illness severity at time of BSI | | | | |
| APACHE II scorec | 12.0 (9.0, 15.0) | 13.0 (12.0, 16.3) | 10.0 (8.0, 14.0) | <0.001 |
| Pitt scorec | 2.0 (1.0, 3.0) | 3.0 (2.0, 5.0) | 1.5 (1.0, 2.0) | <0.001 |
| Possible source of BSI | | | | |
| CVC-related infection | 53 (28.3) | 20 (25.6) | 33 (30.3) | 0.488 |
| LRT infectionc | 45 (24.1) | 24 (30.8) | 21 (19.3) | 0.310 |
| Abdominal infection | 43 (23.0) | 15 (19.2) | 28 (25.7) | 0.596 |
| Urinary infection | 34 (18.2) | 10 (12.8) | 24 (22.0) | 0.016 |
| Primary BSIc | 12 (6.4) | 9 (11.5) | 3 (2.8) | 0.086 |
| Source control of infection | 71 (38.0) | 24 (30.8) | 47 (43.1) | 0.066 |
| Prior exposure to antibiotics within 30 days | | | | |
| Cephalosporins | 80 (42.8) | 31 (39.7) | 49 (45.0) | 0.478 |
| Carbapenems | 49 (26.2) | 23 (29.5) | 26 (23.9) | 0.388 |
| Quinolones | 32 (17.1) | 12 (15.4) | 20 (18.3) | 0.596 |
| Aminoglycosides | 21 (11.2) | 9 (11.5) | 12 (11.0) | 0.910 |
| Tigecycline | 5 (2.7) | 2 (2.6) | 3 (2.8) | 0.001 |
| Prior invasive procedures within 30 days | | | | |
| Central venous catheterization | 65 (34.8) | 24 (30.8) | 41 (37.6) | 0.332 |
| Urinary catheterization | 41 (21.9) | 15 (19.2) | 26 (23.9) | 0.451 |
| Gastric catheterization | 25 (13.4) | 7 (9.0) | 18 (16.5) | 0.135 |
| Mechanical ventilation | 7 (3.7) | 1 (1.3) | 6 (5.5) | 0.267 |
| Epidemiology | | | | |
| Community-onset healthcare-associated infection | 8 (4.3) | 4 (5.1) | 4 (3.7) | 0.905 |
| ICU at time of BSI onsetc | 62 (33.2) | 33 (42.3) | 29 (26.6) | 0.025 |
| Median no. of days from BSI onset to ICU admission (IQR) | 14.0 (8.0, 19.0) | 14.0 (8.5, 17.3) | 14.0 (8.0, 19.5) | 0.961 |
| Appropriate empirical therapyc | 26 (13.9) | 7 (9.0) | 19 (17.4) | 0.099 |
| Duration from BSI onset to appropriate therapy of ≥24 h | 7 (3.7) | 5 (6.4) | 2 (1.8) | 0.217 |
| Combination therapy | 7 (3.7) | 2 (2.6) | 5 (4.6) | 0.963 |
| Definitive therapy | | | | |
| Combination therapyc | 137 (73.3) | 52 (66.7) | 85 (78.0) | 0.085 |
| Median no. of days of appropriate antimicrobial therapy (IQR)c | 10.0 (7.5–13.5) | 10.0 (5.0–17.3) | 12.0 (8.5–18.0) | 0.049 |

95% CI, 1.041 to 16.123; P = 0.046), carbapenem plus polymyxin B sulfate plus aminoglycoside (OR, 13.564; 95% CI, 1.160 to 26.148; P = 0.038), carbapenem plus tigecycline (OR, 29.810; 95% CI, 1.835 to 69.751; P = 0.037), tigecycline (OR, 33.121; 95% CI, 3.322 to 69.322; P = 0.005), and carbapenem plus aminoglycoside (OR, 24.250; 95% CI, 1.989 to 52.579; P = 0.012) (Table 3 and Fig. 2).

After controlling for potential confounding variables, definitive CAZ-AVI therapy (OR, 0.088; 95% CI, 0.020 to 0.379; P = 0.001) was associated with a lower risk of 30-day...
mortality relative to definitive therapy without CAZ-AVI. Regimens containing carbapenems (OR, 2.281; 95% CI, 0.874 to 5.956; \(P = 0.092\)), tigecycline (OR, 1.139; 95% CI, 0.410 to 3.166; \(P = 0.802\)), polymyxin B sulfate (OR, 1.020; 95% CI, 0.394 to 2.642; \(P = 0.968\)), and aminoglycosides (OR, 2.259; 95% CI, 0.741 to 7.143; \(P = 0.165\)) exhibited 30-day mortality risk profiles similar to those of regimens not including these respective drugs (Table S5).

The impact of definitive antimicrobial regimens on clinical failure rates in CRE-BSI patients. Multivariate backward stepwise logistic regression analyses additionally indicated that, relative to definitive therapy with CAZ-AVI alone, CAZ-AVI plus tigecycline (OR, 2.044; 95% CI, 0.324 to 12.900; \(P = 0.447\)) and CAZ-AVI plus tigecycline plus polymyxin B sulfate (OR, 0.899; 95% CI, 0.099 to 8.170; \(P = 0.925\)) were related to comparable risks of clinical failure, whereas other definitive regimens not containing CAZ-AVI (OR, 8.047; 95% CI, 1.896 to 34.151; \(P = 0.005\)) were associated with higher risks of clinical failure even after adjustment for Pitt score, meropenem MIC of \(\geq 8\) mg/liter, immunocompromised status, source control of infection, appropriate empirical therapy, possible source of BSI, and days of appropriate antimicrobial therapy (Table S6).

The impact of monotherapy and combination therapy regimens on CRE-BSI patient mortality. After adjusting for Pitt score, meropenem MIC of \(\geq 8\) mg/liter, immunocompromised status, source control of infection, and appropriate empirical therapy administration, an additional multivariate backward stepwise logistic regression analysis indicated that, compared with definitive CAZ-AVI monotherapy, treatment with combination therapies containing CAZ-AVI (OR, 1.287; 95% CI, 0.124 to 13.403; \(P = 0.833\)) was linked to comparable 30-day mortality risks among CRE-BSI patients. In contrast, when patients were administered definitive antimicrobial regimens not containing CAZ-AVI, combination therapy (OR, 0.240; 95% CI, 0.077 to 0.745; \(P = 0.014\)) was related to lower 30-day mortality risks than was monotherapy (Table 4).

Consistent with the above-described data, Cox regression survival curves indicated that CAZ-AVI monotherapy-treated-patient 30-day mortality rates were similar to those of patients treated with a combination of antimicrobial agents including CAZ-AVI, whereas the 30-day mortality for patients that underwent monotherapy treatment was significantly higher than that of patients administered combination therapies not containing CAZ-AVI (Fig. 3).

**DISCUSSION**

The present multicenter real-world study enabled us to successfully identify certain predictors of CRE-BSI patient mortality and to compare the relative efficacies of different antimicrobial regimens used to treat CRE-BSI patients in China. Together, our data highlight the most promising therapeutic options available at present to treat BSIs caused by CRE.

We found that CRE-BSI patients in the present study cohort exhibited a 30-day mortality rate of 41.7%, which was consistent with prior reported rates ranging from 30 to 80% (6–8). Much as with other infections, CRE-BSI infection outcomes are influenced by pathogen type, host factors, and medical interventions (14). In previous studies, patients infected with CRE isolates exhibiting a meropenem MIC of \(\leq 8\) mg/liter were found to have better survival when administered antimicrobial regimens containing a high-dose carbapenem, particularly when they underwent combination or prolonged-

**TABLE 2** Risk factors for mortality in patients with CRE-BSI

| Variable                        | OR (95% CI)          | \(P\) value |
|---------------------------------|----------------------|-------------|
| Pitt score                      | 5.313 (2.209–8.797)  | <0.001      |
| Immunocompromised status        | 4.605 (1.629–13.020) | 0.004       |
| Isolate with meropenem MIC of \(\geq 8\) mg/liter | 3.736 (1.091–12.795) | 0.036       |
| Source control of infection     | 0.316 (0.117–0.854)  | 0.023       |
| Appropriate empirical therapy   | 0.129 (0.027–0.625)  | 0.011       |

\(^a\)OR, odds ratio; CI, confidence interval.
effusion treatment (15–17). Daikos et al. (15) further found that patients with BSIs attributable to strains with a meropenem MIC of $\geq$8 mg/liter were more likely to benefit from regimens to which carbapenems were added than were patients infected by bacteria exhibiting a meropenem MIC of $\geq$8 mg/liter. This relationship remained detectable even following adjustment for meropenem dosing or MIC. Xiao et al. (16) also observed significantly higher mortality rates in patients infected with bacteria exhibiting an imipenem MIC of $\geq$8 mg/liter than in those with an imipenem MIC of $<\!8$ mg/liter (57.9% versus 14.5%; $P < 0.001$) when evaluating CRE-BSI patients infected with CRKP treated by carbapenems alone or together with other antimicrobial agents. In the present study, while 75% of the isolates analyzed exhibited meropenem MICs of $\geq$8 mg/liter, 85% of empirical antimicrobial regimens and 47% of definitive regimens nonetheless contained a carbapenem, possibly due to limited therapeutic options. We further confirmed that a meropenem MIC of $\geq$8 mg/liter was an independent predictor of mortality in CRE-BSI patients.

In addition to being a previously reported risk factor for CRE infection (18), immunocompromised status was identified as a risk factor associated with increased CRE-BSI patient mortality in our study, in line with the work of Gomez-Simmonds et al. (19). Even when effectively treated with antibiotics, immunocompromised patients suffer from infections more and exhibit higher death rates than immunocompetent individuals. As 95% of the cases in our study were of secondary BSIs, the source control of infections via abscess drainage, urinary catheterization, CVC removal or replacement, and related techniques was critical. Appropriate empirical therapy has previously been reported to be associated with better CRE-BSI patient prognosis, and prompt treatment within 48 h of BSI onset with such empirical antibiotics is agreed to be associated with better severe infection outcomes (8, 20, 21). We did not confirm whether BSI patients can benefit from treatment within a shorter duration, such as the 24-h period proposed by Falcone et al. (22), potentially due to the limited sample size in the present report. Future large-scale studies will be required to further examine the association between the timing of treatment and patient outcomes.

Due to its relatively recent introduction to the Chinese market, high price, and restricted clinical indications, only 35 patients in the present study were treated with CAZ-AVI. We found that patients treated with CAZ-AVI-containing regimens exhibited reduced 30-day mortality relative to patients treated without CAZ-AVI (17.1% versus 47.4%; $P < 0.001$), with comparable differences in rates of clinical failure (28.6% versus 68.4%; $P < 0.001$). Even after controlling for confounding variables, regimens containing CAZ-AVI were associated with increased survival rates and lower clinical failure rates, consistent with prior reports (23–25). van Duin et al. (24) previously examined the relative efficacies of CAZ-AVI and colistin for the treatment of CRE infections. After

### TABLE 3 The impacts of definitive antimicrobial regimens on the mortality of patients with CRE-BSI

| Antimicrobial regimen | No. of deceased patients/total no. of patients (%) | Logistic regression |
|-----------------------|-----------------------------|---------------------|
|                       |                             | Univariate          | Multivariate        |
|                       |                             | OR (95% CI)         | $P$ value           | OR (95% CI)          | $P$ value           |
| CAZ-AVI               | 3/13 (23.1)                | Reference           | Reference           |
| CAZ-AVI + tigecycline | 2/13 (15.4)                | 0.606 (0.083–4.405) | 0.621              | 1.645 (0.106–25.422) | 0.722              |
| CAZ-AVI + tigecycline + polymyxin B sulfate | 1/9 (11.1) | 0.417 (0.036–4.813) | 0.483              | 0.606 (0.016–23.056) | 0.788              |
| Other regimens        |                             |                     |                    |
| Tigecycline + polymyxin B sulfate | 19/46 (41.3) | 2.346 (0.568–9.679) | 0.238              | 13.674 (1.160–26.148) | 0.040              |
| Carbapenem + tigecycline + polymyxin B sulfate | 16/44 (36.4) | 1.905 (0.456–7.951) | 0.377              | 8.295 (1.041–16.123) | 0.046              |
| Carbapenem + polymyxin B sulfate + aminoglycoside | 5/13 (38.5) | 2.083 (0.378–11.482) | 0.399              | 13.564 (1.160–26.148) | 0.038              |
| Carbapenem + tigecycline | 11/14 (78.6) | 7.222 (1.444–16.444) | 0.016              | 29.810 (1.835–69.751) | 0.037              |
| Tigecycline           | 13/19 (68.4)               | 12.222 (1.990–25.060) | 0.007              | 33.121 (3.322–69.322) | 0.005              |
| Carbapenem + aminoglycoside | 8/16 (50.0) | 3.333 (0.660–16.847) | 0.145              | 24.250 (1.989–52.579) | 0.012              |

*CAZ-AVI, ceftazidime-avibactam.*

*Adjusted for Pitt score, meropenem MIC of $\leq$8 mg/liter, immunocompromised status, source control of infection, and appropriate empirical therapy.*
adjusting for the inverse probability of treatment weighting (IPTW), these authors found that the all-cause mortality in patients treated with CAZ-AVI \((n = 38)\) was just 9%, as opposed to 32% for patients treated with colistin \((n = 99)\), with CAZ-AVI-treated patients having IPTW-adjusted odds of good clinical outcomes at 30 days of 64% (95% CI, 57% to 71%). In a retrospective analysis conducted by Shields et al. (25), clinical success was observed to be more common among patients treated with CAZ-AVI-containing regimens (85% [11/13]) than among patients treated with other regimens \((P = 0.006)\), including those composed of ≥2 agents exhibiting in vitro activity (44% [12/27]; \(P = 0.02)\), with CAZ-AVI administration being an independent predictor of successful clinical outcomes in their multivariate logistic regression analysis (OR, 8.64; 95% CI, 1.61 to 43.39; \(P < 0.01)\). In our study, all 35 isolates from cases treated with CAZ-AVI were susceptible to CAZ-AVI. The development of CAZ-AVI resistance among CRE during treatment has been reported previously (26, 27). Potential impacts of this on clinical outcomes need to be further studied.

Prior reports indicate that combination therapies are associated with lower mortality rates than monotherapies when used to treat CRE infections (15, 16, 19, 28). Indeed, one prior meta-analysis of 44 observational studies incorporating 3,195 patients with CRKP infections found monotherapy to be linked to a higher mortality risk than combination therapy (OR, 1.45; 95% CI, 1.18 to 1.78%) (29). Here, we found that combination therapy benefits were only evident for therapeutic regimens not containing CAZ-AVI, whereas no differences were observed in patient survival when comparing CAZ-AVI monotherapy and combination regimens incorporating CAZ-AVI. Caston et al. (23) and Tumbarello et al. (30) similarly found that CAZ-AVI-containing combination therapies were not linked to any improvements in the success of clinical treatment compared...
with CAZ-AVI monotherapy. As such, we posit that CAZ-AVI is a more promising therapeutic choice for treating patients infected with susceptible CRE isolates, even when used as a monotherapy.

We found that there were no significant differences among different antimicrobial regimens that did or did not contain carbapenems, polymyxins, tigecycline, or aminoglycosides with respect to CRE-BSI patient 30-day mortality. Using carbapenems to treat CRE infections remains a matter of controversy, with the relative benefits of including these antibiotics being dependent upon the carbapenem-specific MIC of the infecting pathogen (15, 19, 29, 31). Most isolates in this study exhibited a high carbapenem MIC (>8 mg/liter), indicating that carbapenem-containing regimens were unlikely to be effective. While isolates herein exhibited high rates of susceptibility to tigecycline, polymyxins, and aminoglycosides in vitro, the treatment of patients with these agents largely failed to improve survival outcomes, likely due to their low concentrations in serum and sites of infection, such as the LRT, following administration (32, 33). Tigecycline monotherapy has even been implicated in increased CRE-BSI patient mortality in prior studies (34). As polymyxins exhibit

### TABLE 4 The impacts of monotherapy and combination therapy on the mortality of patients with CRE-BSI

| Antimicrobial regimen | No. of deceased patients/total no. of patients (%) | Logistic regression |  |  |
|----------------------|-----------------------------------------------|-------------------|---|---|
|                      |                                               | Univariate        | Multivariate |  |
|                      |                                               | OR (95% CI)       | P value      | Adjusted OR (95% CI)<sup>a</sup> | P value |
| With CAZ-AVI         |                                               |                   |              |                                     |         |
| Monotherapy          | 3/13 (23.1)                                  | Reference         | 0.526 (0.089–3.103) | 0.478 | 1.287 (0.124–13.403) | 0.833 |
| Combination therapy  | 3/22 (13.6)                                  |                   |              |                                     |         |
|                      |                                               |                   |          |                                     |         |
| Without CAZ-AVI      |                                               |                   |              |                                     |         |
| Monotherapy          | 32/49 (65.3)                                 | Reference         | 0.337 (0.166–0.686) | 0.003 | 0.240 (0.077–0.745) | 0.014 |
| Combination therapy  | 40/103 (38.8)                                |                   |              |                                     |         |

<sup>a</sup>Adjusted for Pitt score, meropenem MIC of ≥8 mg/liter, immunocompromised status, source control of infection, and appropriate empirical therapy.
a narrow therapeutic window and highly variable pharmacokinetics, their optimal dosage range also remains poorly understood (20).

There are several potential limitations to this analysis. First, our study had a retrospective design and was thus susceptible to selection bias and recall bias. Second, other factors beyond the categories of antimicrobial agents utilized, such as their doses and the duration of effusion, can influence treatment efficacy. As our study was retrospective and sample subgroups were limited, we were not able to analyze these data. The punctual meropenem MIC value may be an important tool for understanding the response or absence of response to therapy. However, it was possible to measure the punctual MIC value. Additional analyses of drug resistance genes in the bacteria isolated from these patients would also be of value as a means of further exploring drug resistance-related characteristics and related treatments.

In summary, the analysis of mortality-related risk factors and antimicrobial agent efficacies in CRE-BSI patients reported herein has the potential to guide the management of these critically ill patients. However, future prospective cohort studies or randomized trials are urgently needed to validate and expand upon the findings of the present study.

MATERIALS AND METHODS

Study design and patient selection. Medical records for hospitalized patients at four teaching hospitals in China (Table S1) with positive CRE blood cultures between 1 January 2018 and 31 December 2020 were reviewed retrospectively. Patients were excluded if they (i) were <14 years old, (ii) exhibited polymicrobial bacteremia, (iii) did not have medical records that were fully available, (iv) did not exhibit clinical manifestations consistent with bacteremia, or (v) experienced more than one CRE-BSI, in which case only the first positive blood culture report was included.

The primary study outcome was 30-day mortality following BSI onset, while the secondary outcome was clinical failure, including (i) death, (ii) symptom persistence or evidence of infection at day 30, and (iii) the recurrence of symptoms or evidence of infection after treatment ended.

The study design was approved by the Ethics Committee of Beijing Jishuitan Hospital (no. 201911-15). Given the retrospective nature of the study, the Ethics Committee determined that informed consent was not necessary.

Microbiology. The Vitek 2 system (bioMérieux, Marcy l’Etoile, France) or matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (MALDI Biotyper [Bruker Daltonics GmbH, Leipzig, Germany] or Vitek-MS [bioMérieux]) was employed for isolate identification. Testing for antibiotic susceptibility was conducted according to the standard protocols of each hospital, with most utilizing the Vitek 2 system or a broth microdilution (BMD) method. MICs for tigecycline, colistin, and CAZ-AVI were determined via standard BMD and were interpreted according to Clinical and Laboratory Standards Institute (CLSI) breakpoints. In accordance with the 2018 CLSI guidelines, carbapenem resistance was defined as a MIC of ≥2 μg/ml for ertapenem or ≥4 μg/ml for meropenem or imipenem (35). The tigecycline (≥8 μg/ml) and colistin (≥2 μg/ml) breakpoints were defined according to the U.S. FDA (36) and European Committee on Antibiotic Susceptibility Testing guidelines (37), respectively.

Study definitions. Bacteremia was defined by the detection of a minimum of one blood culture positive for a known pathogen that coincided with consistent clinical features. Immunocompromised status included primary immune deficiency diseases, active malignancy, human immunodeficiency virus infection with a CD4 T-lymphocyte count of <200 cells/ml or percentage of <14%, immunosuppressive therapy, solid organ transplantation, hematopoietic stem cell transplantation, and splenectomy. Antimicrobial drug exposure was defined as utilizing any antibiotics for >72 h within 30 days prior to CRE-BSI diagnosis. Empirical therapy was defined by the administration of antimicrobial agents before blood culture reports were available, while definitive therapy was defined by antimicrobial therapy administration following susceptibility testing result availability. Regimens were considered to be “appropriate” when they consisted of a minimum of one drug to which the causative bacterium was noted to be susceptible upon in vitro susceptibility testing, whereas they were otherwise deemed “inappropriate.” Combination therapy was the administration of more than one antimicrobial treatment exhibiting in vitro activity, whereas monotherapy was the administration of just one antimicrobial agent exhibiting in vitro activity (28).

Data collection. Data pertaining to patient demographics (age and sex), comorbidities (see Text S1 for definitions of underlying conditions), hospital wards, prior antibiotic exposure, invasive procedures (mechanical ventilation, urinary catheterization, gastric catheterization, and central venous catheterization); APACHE II scores at BSI onset, Pitt bacteremia scores at BSI onset, empirical and definitive antimicrobial treatments administered, and 30-day all-cause mortality rates were obtained from patient medical records and analyzed retrospectively.

Statistical analysis. Kolmogorov-Smirnov tests were used to assess data normality. Normally distributed data are given as mean values ± standard deviations (SD), while other data are given as median values and interquartile ranges. Categorical variables were analyzed with the chi-square test or Fisher’s exact test, whereas continuous data were evaluated via Student’s t test or the Mann-Whitney U test. A
two-tailed P value of <0.05 was the significance threshold for all studies, and all analyses were conducted using SPSS 22.0 (IBM, Armonk, NY, USA).

Baseline features were compared between patients that were and were not alive at the 30-day time point, with those variables yielding a P value of <0.1 in univariate analyses being incorporated into a multivariate backward stepwise logistic regression model to establish independent predictors of CRE-BSI patient 30-day mortality. The relative efficacies of different antimicrobial regimens were assessed by treating these risk factors as confounding variables in a multivariate backward stepwise logistic regression model analysis.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.

ACKNOWLEDGMENTS

We express our gratitude to BMSCI for the expert linguistic services provided. We declare that we have no competing interests.

This study was funded by Beijing JST research (grant number ZR-201921). The sponsor had no role in study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the article for publication.

REFERENCES

1. Durante-Mangoni E, Andini R, Zampino R. 2019. Management of carbapenem-resistant Enterobacteriaceae infections. Clin Microbiol Infect 25:943–950. https://doi.org/10.1016/j.cmi.2019.04.013.

2. Lutgring JD. 2019. Carbapenem-resistant Enterobacteriaceae: an emerging bacterial threat. Semin Diagn Pathol 36:182–186. https://doi.org/10.1053/j.semdp.2019.04.011.

3. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, Fridkin SK, National Healthcare Safety Network Team, Participating National Healthcare Safety Network Facilities. 2019. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. Infect Control Hosp Epidemiol 29:996–1011. https://doi.org/10.1089/ice.2008.05816.

4. Nordmann P, Naas T, Poirel L. 2011. Global spread of carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis 17:1791–1798. https://doi.org/10.3201/eid1710.110655.

5. Zhang Y, Wang Q, Yin Y, Chen H, Jin L, Gu B, Xie L, Yang C, Ma X, Li H, Li W, Zhang X, Liao K, Man S, Wang S, Wen H, Li B, Guo Z, Tian J, Pei F, Liu L, Zhang L, Zou C, Hu T, Cai J, Yang H, Huang J, Jia X, Huang W, Cao B, Wang W. 2018. Epidemiology of carbapenem-resistant Enterobacteriaceae infections: report from the China CRE Network. Antimicrob Agents Chemother 62:e01882-17. https://doi.org/10.1128/AAC.01882-17.

6. Falcone M, Tiseo G, Antonelli A, Giordano C, Di Pilato V, Bertolucci P, Parisio EM, Leonildi A, Aiezza N, Baccani I, Tagliaferri E, Righi L, Forni S, Parisio G. 2019. The use of polymyxins to treat carbapenem-resistant infections in neonates and children. Expert Opin Pharmacother 20:415–422. https://doi.org/10.1080/14656566.2018.1559817.

7. Adekunle R, Gbadegesin R, Adekunle O, Aderemi S, Okoju K, Osuntokun O, Ojikutu A, Akinboye A, Akinbile J. 2021. Ceftazidime/avibactam in the era of carbapenem-producing Klebsiella pneumoniae: experience from a national registry study. J Antimicrob Chemother 76:775–783. https://doi.org/10.1093/jac/dkaa503.

8. Satlin MJ, Jenkins SG, Walsh TJ. 2014. The global challenge of carbapenem-resistant Enterobacteriaceae bacteremia. Antimicrob Agents Chemother 63:e00151-18. https://doi.org/10.1128/AAC.01511-18.

9. Karaiskos I, Daikos GL, Gkoufa A, Adamis G, Stafanos A, Petraki M, Papadimitriou E, Galani I, Poulakou G, Routsi C, Giannarellou H, Hellenic Ceftazidime/Avibactam Registry Study Group. 2020. Ceftazidime/avibactam in the era of carbapenem-producing Klebsiella pneumoniae: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother 65:e01511-18. https://doi.org/10.1128/AAC.01511-18.

10. Gomez-Simmonds A, Nelson B, Eiras DP, Loo A, Jenkins SG, Whittier S, Calfee DP, Satlin MJ, Kubin CJ, Furuya EY. 2016. Combination regimens for treatment of carbapenem-resistant Klebsiella pneumoniae bloodstream infections. Anti- microb Agents Chemother 60:3601–3607. https://doi.org/10.1128/AAC.03007-15.

11. Xiao T, Zhu Y, Zhang S, Wang Y, Shen P, Zhou Y, Yu X, Xiao Y. 2020. A retrospective analysis of risk factors and outcomes of carbapenem-resistant
Klebsiella pneumoniae bacteremia in nontransplant patients. J Infect Dis 221:S174–S183. https://doi.org/10.1093/infdis/jiz559.

21. Daikos GL, Petrikkos P, Psychogiou M, Kosmidis C, Vryonis E, Skoutelis A, Georgousi K, Tzouvelekis LS, Tassios PT, Bama C, Petrikkos G. 2009. Prospective observational study of the impact of VIM-1 metallo-beta-lactamase on the outcome of patients with Klebsiella pneumoniae bloodstream infections. Antimicrob Agents Chemother 53:1868–1873. https://doi.org/10.1128/AAC.00782-08.

22. Falcone M, Bassetti M, Tiseo G, Giordano C, Nencini E, Russo A, Graziano E, Tagliaferri E, Leonardi A, Bannini S, Farcomeni A, Menichetti F. 2020. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing Klebsiella pneumoniae. Crit Care 24:29. https://doi.org/10.1186/s13054-020-2742-9.

23. Caston JJ, Gallo M, Garcia M, Cano A, Escribano A, Machuca I, Gracia-Aufinger J, Guzman-Puche J, Perez-Nadales E, Recio M, Munoz M, Martinez-Martinez L, Torre-Cisneros J. Spanish Network for Research in Infectious Diseases. 2020. Ceftazidime-avibactam in the treatment of infections caused by KPC-producing Klebsiella pneumoniae: factors associated with clinical efficacy in a single-center cohort. Int J Antimicrob Agents 56:106075. https://doi.org/10.1016/j.ijantimicag.2020.106075.

24. van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, Salata RA, Katayian RC, Watkins RR, Doi Y, Kaye KS, Fowler VG, Paterson DL, Bonomo RA, Evans S. Antibacterial Resistance Leadership Group. 2018. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clin Infect Dis 57:163–171. https://doi.org/10.1093/cid/cix783.

25. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marin RV, Doi Y, Kreiswirth BN, Clancy CJ. 2017. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant Klebsiella pneumoniae bacteremia. Antimicrob Agents Chemother 61:e00883-17. https://doi.org/10.1128/AAC.00883-17.

26. Shields RK, Chen L, Cheng S, Chauda 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 blaKPC-3 mutations during treatment of carbapenem-resistant Klebsiella pneumoniae infections. Antimicrob Agents Chemother 61:e02097-16. https://doi.org/10.1128/AAC.02097-16.

27. Raasikinen K, Koivula J, Ilmavirta H, Puranen S, Kallonen T, Lyytikainen O, Jalava J. 2019. Emergence of ceftazidime-avibactam-resistant Klebsiella pneumoniae during treatment, Finland, December 2018. Euro Surveill 24:1900256. https://doi.org/10.2807/1560-7917.ES.2019.24.19.1900256.

28. Zhou C, Jin L, Wang Q, Wang X, Chen F, Gao Y, Zhao C, Chen H, Cao B, Wang H. 2021. Bloodstream infections caused by carbapenem-resistant Enterobacteriales: risk factors for mortality, antimicrobial therapy and treatment outcomes from a prospective multicenter study. Infect Drug Resist 14:731–742. https://doi.org/10.2147/IDR.S294282.

29. Agreyman AA, Bergen PJ, Rao GG, Nation RL, Landersdorfer CB. 2020. A systematic review and meta-analysis of treatment outcomes following antibiotic therapy among patients with carbapenem-resistant Klebsiella pneumoniae infections. Int J Antimicrob Agents 55:105833. https://doi.org/10.1016/j.ijantimicag.2019.10.014.

30. Tumbarello M, Raffaelli F, Giannella M, Mantegoni E, Mularoni A, Venditti M, De Rosa FG, Sarmati L, Bassetti M, Brindicci G, Rossi M, Luzzati R, Grossi PA, Corona A, Capone A, Falcone A, Mussini C, Trecarichi EM, Casco A, Guffanti E, Russo A, De Pascale G, Tascini C, Gentile I, Losito AR, Bussini L, Conti G, Ceccarelli G, Coricone S, Compagno M, Giacobbe DR, Saracino A, Fantoni M, Antinori S, Peghin M, Bonfanti P, Oliva A, De Gasperi A, Tiseo G, Rovelli C, Meschiari M, Shbakto N, Spanu T, Cauda R, Viale P. 22 February 2021. Ceftazidime-avibactam use for KPC-Kp infections: a retrospective observational multicenter study. Clin Infect Dis https://doi.org/10.1093/cid/ciab176.

31. Pascale R, Giannella M, Bartoletti M, Viale P, Pea F. 2019. Use of meropenem in treating carbapenem-resistant Enterobacteriaceae infections. Expert Rev Anti Infect Ther 17:819–827. https://doi.org/10.1080/14787210.2019.1673731.

32. Ni W, Han Y, Liu J, Wei C, Zhao J, Cui J, Wang R, Liu Y. 2016. Tigecycline treatment for carbapenem-resistant Enterobacteriaceae Infections: a systematic review and meta-analysis. Medicine (Baltimore) 95:e3126. https://doi.org/10.1097/MD.0000000000031326.

33. Onufraf NJ, Forrest A, Gonzalez D. 2016. Pharmacokinetic and pharmacodynamic principles of anti-infective dosing. Clin Ther 39:1930–1947. https://doi.org/10.1016/j.clinthera.2016.06.015.

34. Tran TB, Velkov T, Nation RL, Forrest A, Tsuji BT, Bergen PJ, Li J. 2016. Pharmacokinetics/pharmacodynamics of colistin and polymyxin B: are we there yet? Int J Antimicrob Agents 48:592–597. https://doi.org/10.1016/j.ijantimicag.2016.09.014.

35. Clinical and Laboratory Standards Institute. 2018. M100-S28. Performance Standards for Antimicrobial Susceptibility Testing: 28th Informational Supplement. CLSI, Wayne, PA.

36. Food and Drug Administration. Highlights of prescribing information: Tygacil. Food and Drug Administration, Silver Spring, MD. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021821s021lbl.pdf.

37. European Committee on Antimicrobial Susceptibility Testing. 2013. Breakpoint tables for interpretation of MICs and zone diameters, version 3.11, valid from 2013-02-11.http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpoint_table_v_3.11.pdf.

38. Dropulic LK, Lederman HM. 2016. Overview of infections in the immunocompromised host. Microbiol Spectr 4:4.4.43. https://doi.org/10.1128/microbiolspec.DM12-0026-2016.