Assessment of mortality-related risk factors and effective antimicrobial regimens for the treatment of bloodstream infections caused by carbapenem-resistant Enterobacterales

Liang Chen (chenliang1995@sina.com)
Beijing jishuitan Hospital https://orcid.org/0000-0002-3147-5688
Xiudi Han
Qingdao Municipal Hospital Group
YanLi Li
Beijing Chao-Yang Hospital: Beijing Chaoyang Hospital

Research

Keywords: Bloodstream infection, Carbapenem-resistant Enterobacterales, Mortality, Risk factor, Antimicrobial

Posted Date: April 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-397946/v1

Version of Record: A version of this preprint was published at Antimicrobial Agents and Chemotherapy on August 17th, 2021. See the published version at https://doi.org/10.1128/AAC.00698-21.

Abstract

Background

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 efficacy of different antimicrobial treatment regimens in affected individuals.

Methods

Data pertaining to 187 CRE-BSI cases from three teaching hospitals in China collected between January 2018 and June 2020 were retrospectively analyzed.

Results

For the 187 analyzed patients in this study, the 30-day mortality of CRE-BSI was 41.7% (78/187). Multivariate logistic regression analyses revealed that Pitt score [odd ratio (*OR)* 5.313, *95% confidence interval (CI)* 3.209–8.797, *P*< 0.001], immunocompromised status (*OR* 4.605, *95% CI* 1.629–13.020, *P* = 0.004), meropenem minimum inhibitory concentration (MIC) ≥ 8 mg/L (*OR* 3.736, *95% CI* 1.091–12.795, P = 0.036), source control of infection (*OR* 0.316, *95% CI* 0.117–0.854, P = 0.023), and appropriate empirical therapy (*OR* 0.129, *95% CI* 0.027–0.625, P = 0.011) 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 (*OR* 1.287, *95% CI* 0.124–13.403, P = 0.833) were not related to any significant change in patient mortality risk, whereas 30-day mortality risk was higher for patients administered other antimicrobial regimens (*OR* 12.407, *95% CI* 1.684–31.430, P = 0.011). When patients were treated with antimicrobial regimens not containing CAZ-AVI, combination therapy (*OR* 0.239, *95% CI* 0.077–0.741, P = 0.013) was related to a decreased 30-day mortality risk relative to monotherapy treatment.

Conclusion

The mortality-related risk factors and relative antimicrobial regimen efficacy data demonstrated in this study may guide the management of CRE-BSI patients.

Background

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 US National Healthcare Safety Network (NHSN) in 2006–2007 indicated that an estimated 4.0% and 10.8% of *E. coli* and *K. pneumoniae* isolates, respectively, were resistant to carbapenems [3]. Similarly, following initial reports in 2007 of carbapenemase-generating *K. pneumoniae* in Zhejiang Province, China, 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, respectively, with CRE infections having been reported in almost all Chinese

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

The most effective antimicrobial regimens for treating CRE-BSI patients remain to be defined, as few alternative antimicrobials remain for these patients 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 *in vitro* susceptibility testing or the experience of the attending clinician. Ceftazidime-avibactam (CAZ-AVI) regimens were approved in 2015 by the US 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 Gram0negative bacteria that produce antimicrobial resistance genes such as extended-spectrum β-lactamases (ESBL), 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.

Methods

Study design and patient selection

Medical records for hospitalized patients at three teaching hospitals in China (Supplementary Material 1) with positive CRE blood cultures between January 1, 2018 and June 30, 2020 were retrospectively reviewed. 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; (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 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 end.

Microbiology

The Vitek 2 system (bioMérieux, Marcy l'Etoile, France) or MALDI-TOF mass spectrometry (MALDI Biotyper, Bruker Daltonics GmbH, Leipzig, Germany, or Vitek-MS, bioMérieux) were employed for isolate identification. Testing for antibiotic susceptibility was conducted as per the standard protocols of each hospital, with most utilizing the Vitek 2 system or a broth microdilution method (BMD). Minimum inhibitory concentrations (MICs) for tigecycline, colistin, and CAZ-AVI were determined via standard BMD and were interpreted as per Clinical and Laboratory Standards

Institute (CLSI) breakpoints. In accordance with the 2018 CLSI guidelines, carbapenem resistance was defined by an MIC ≥ 2 μg/mL for ertapenem or ≥ 4 μg/mL for meropenem or imipenem [14]. The tigecycline (≥ 8 μg/ml) and colistin (> 2 μg/ml) breakpoints were defined as per the US FDA [15] and European Committee on Antibiotic Susceptibility Testing guidelines [16], 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. 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 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 bacteria 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 [17].

Data Collection

Data pertaining to patient demographics (age and sex), comorbidities (see Supplementary Material 2 for definitions of underlying conditions), ward, prior antibiotic exposure, invasive procedures (mechanical ventilation, urinary catheterization, gastric catheterization, and central venous catheterization), Acute Physiology and Chronic Health Evaluation (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 retrospectively analyzed.

Statistical analysis

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

Baseline features between patients that were and were not alive at the 30-day time point were compared, with those variables yielding a $P < 0.1$ 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 efficacy of different antimicrobial regimens was assessed by treating these risk factors as confounding variables in a multivariate backward stepwise logistic regression model analysis.

Results

Patient overview

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

Analyzed patients exhibited a mean age of 67.0 years old (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). 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 healthcare-associated infections. Appropriate empirical antimicrobial treatments were administered to 13.9% (26/187) of patients within 48 h following BIS onset, as detailed in Supplementary Material 4. 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) (Table 1).

Antimicrobial susceptibility testing results

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. 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. Resistance rates to other tested antimicrobial agents were over 90% (Supplementary Material 3).

Risk factors associated with CRE-BSI patient 30-day mortality

Relative to surviving CRE-BSI patients, those that were deceased at the end of the 30-day period exhibited higher APACHE II scores (median, 13.0 vs 10.0, P < 0.001) and Pitt scores (median, 3.0 vs 1.5, P < 0.001) at the time of BSI. Deceased patients also exhibited higher incidence of immunocompromising conditions (42.3%, vs 17.4%, P < 0.001), primary BSI (11.5% vs 2.8%, P = 0.016), and ICU hospitalization at time of BSI onset 42.3% vs 26.6%, P = 0.025). The number of days of appropriate antimicrobial treatment was also decreased for deceased patients relative to survivors (median, 10.0 vs 12.0, P = 0.049) (Table 1).

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

The impact of definitive antimicrobial treatment on CRE-BSI patient mortality

After controlling for Pitt scores, meropenem MICs ≥ 8 mg/L, 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 + tigecycline (OR 1.645, 95% CI 0.106 - 25.422, P = 0.722), and CAZ-AVI + tigecycline + polymyxin B sulfate (OR 0.606, 95% CI 0.016 - 23.056, P = 0.788) were related to a comparable 30-day mortality risk in CRE-BSI patients. Other definitive regimens not containing CAZ-AVI (*OR* 12.407, *95% CI* 1.684 - 31.430, P = 0.011), in contrast, were associated with a higher 30-day mortality risk, including specific regimens composed of tigecycline + polymyxin B sulfate (*OR* 13.674, *95% CI* 1.160 - 26.148, P = 0.040), carbapenem + tigecycline + polymyxin B sulfate (*OR* 8.295, *95% CI* 1.041 - 16.123, P = 0.046), carbapenem + polymyxin B sulfate + aminoglycoside (*OR* 13.564, *95% CI* 1.160 - 26.148, P = 0.038), carbapenem +

tigecycline (*OR* 29.810, *95% CI* 1.835 - 69.751, P = 0.037), tigecycline (*OR* 33.121, *95% CI* 3.322 - 69.322, P = 0.005), and carbapenem + aminoglycoside (*OR* 24.250, *95% CI* 1.989 - 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 - 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 - 5.956, P = 0.092), tigecycline (*OR* 1.139, *95% CI* 0.410 - 3.166, P = 0.802), polymyxin B sulfate (*OR* 1.020, *95% CI* 0.394 - 2.642, P = 0.968), and aminoglycosides (*OR* 2.259, *95% CI* 0.741 - 7.143, P = 0.165) exhibited similar 30-day mortality risk profiles relative to regimens not including these respective drugs (Supplementary Material 5).

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 + tigecycline (*OR* 2.044, *95% CI* 0.324 - 12.900, P = 0.447) and CAZ-AVI + tigecycline + polymyxin B sulfate (*OR* 0.899, *95% CI* 0.099 - 8.170, P = 0.925) were related to a comparable risk of clinical failure, whereas other definitive regimens n to containing CAZ-AVI (*OR* 8.047, *95% CI* 1.896 - 34.151, p = 0.005) were associated with a higher risk of clinical failure even after adjustment for Pitt score, meropenem MIC ≥ 8 mg/L, immunocompromised status, source control of infection, appropriate empirical therapy, possible source of BSI, and days of appropriate antimicrobial therapy (Supplementary Material 6).

The impact of monotherapy and combination therapy regimens on CRE-BSI patient mortality

After adjusting for Pitt score, meropenem MIC ≥ 8 mg/L, 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 - 13.403, P = 0.833) was linked to comparable 30-day mortality risk 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 - 0.745, p = 0.014) was related to a lower 30-day mortality risk relative to monotherapy (Table 4).

Consistent with the above 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 efficacy 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 30–80% [6–8]. Much as with other infections, CRE-BSI infection outcomes are influenced by pathogen type, host factors, and medical interventions [18]. In previous studies, patients infected with CRE isolates exhibiting a meropenem MIC ≤ 8 mg/L were found to better survive when administered antimicrobial regimens containing a high-dose carbapenem, particularly when they underwent combination or

prolonged-effusion treatment [19–21]. Daikos et al. [19] further found that patients with BSIs attributable to strains with a meropenem MIC ≤ 4 mg/L were more likely to benefit from regimens to which carbapenems were aged relative to patients infected by bacteria exhibiting a meropenem MIC ≥ 8 mg/L. This relationship remained detectable even following adjustment for meropenem dosing or MIC. Xiao et al. [20] also observed significantly higher mortality rates in patients infected with bacteria exhibiting an imipenem MIC ≥ 8 mg/L relative to those with an imipenem MIC of < 8 mg/L (57.9% vs. 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 analyzed isolated exhibited a meropenem MIC ≥ 8 mg/L, possibly due to limited therapeutic options, 85% of empirical antimicrobial regimens and 47% of definitive regimens nonetheless contained a carbapenem. We further confirmed that a meropenem MIC ≥ 8 mg/L was an independent predictor of mortality in CRE-BSI patients.

In addition to being a previously reported risk factor for CRE infection [22], 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 [23]. Even when effectively treated with antibiotics, immunocompromised patients suffer from infections and exhibit higher death rates relative to 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, 25–26]. 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. [27], 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.

Owing to its relatively recent introduction to the Chinese market and its 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% vs 47.4%, P < 0.001), with comparable differences in rates of clinical failure (28.6% vs 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 [28–30]. Van Duin et al. [29] previously examined the relative efficacy of CAZ-AVI and colistin for the treatment of CRE infections. After 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 64% (*95% CI*, 57% − 71%). In a retrospective analysis conducted by Shields et al. [30] clinical success was observed to be more common among patients treated with CAZ-AVI-containing regimens (85% [11/13]) relative to 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* 1.61–43.39, P < 0.01).

Prior reports indicate that combination therapies are associated with lower mortality rates than monotherapies when used to treat CRE infections [17, 19–20, 23]. Indeed, one prior meta-analysis of 44 observational studies incorporating 3195 patients with CRKP infections found monotherapy to be linked to a higher mortality risk relative to combination therapy (*OR* 1.45, *95% CI* 1.18–1.78%) [31]. Herein, 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. [28] and Mario Tumbarello et al. [32] 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 [19, 23, 33–34]. Most isolates in this study exhibited a high carbapenem MIC (> 8 mg/L), 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 [35–36]. Tigecycline monotherapy has even been attributed to increased CRE-BSI patient mortality in prior studies [37]. As polymixins exhibit a narrow therapeutic window and highly variable pharmacokinetics, their optimal dosage range also remains poorly understood [25].

There are several potential limitations to this analysis. First, our study had a retrospective design and is thus susceptible to selection bias and recall bias. Second, other factors beyond the categories of utilized antimicrobial agents 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. 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.

Conclusions

In summary, the analysis of mortality-related risk factors and antimicrobial agent efficacy in CRE-BSI patients conducted 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.

Abbreviations

BSI: bloodstream infection; CRE: carbapenem-resistant Enterobacterales; OR: odd ratio; CI: confidence interval; MIC: minimum inhibitory concentration; CAZ-AVI: ceftazidime-avibactam; CRKP: carbapenem resistant *K. pneumoniae*; BMD: broth microdilution method; APACHE: Acute Physiology and Chronic Health Evaluation; SD: standard deviation; IQR: interquartile range; CVC: central venous catheter; ICU: intensive care unit.

Declarations

Ethics approval and consent to participate

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 an informed consent was not necessary.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was founded by Beijing JST research (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.

Authors' contributions

Study concept and design: LC, XdH. Acquisition of data: LC, XdH, YlL, CxZ, XqX. Statistical analysis of data: LC. Drafting of the manuscript: LC. Critical revision of the manuscript for important intellectual content: XdH, XqX. All authors agree with the article submission. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to express their gratitude to BMCSCI (http://www.bmcscience.com/) for the expert linguistic services provided.

References

1. E Durante-Mangoni, R Andini, R Zampino. Management of carbapenem-resistant Enterobacteriaceae infections. Clin Microbiol Infect. 2019;25(8):943-950. doi: 10.1016/j.cmi.2019.04.013.
2. Joseph D Lutgring. Carbapenem-resistant Enterobacteriaceae: An emerging bacterial threat. Semin Diagn Pathol. 2019;36(3):182-186. doi: 10.1053/j.semdp.2019.04.011.
3. Alicia I Hidron, Jonathan R Edwards, Jean Patel, Teresa C Horan, Dawn M Sievert, Daniel A Pollock, et al. 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. 2008;29(11):996-1011. doi: 10.1086/591861.
4. Nordmann P, Naas T, Poirel L. 2011. Global spread of carbapenemaseproducing Enterobacteriaceae. Emerg Infect Dis 17:1791–1798. org/10.3201/eid1710.110655.
5. Zhang Y, Wang Q, Yin Y, et al. Epidemiology of carbapenem-resistant Enterobacteriaceae infections: report from the China CRE network. Antimicrob Agents Chemother. 2018;62. doi:10.1128/aac.01882-17
6. Marco Falcone, Giusy Tiseo, Alberto Antonelli, Cesira Giordano, Vincenzo Di Pilato, Pietro Bertolucci, et al. Clinical Features and Outcomes of Bloodstream Infections Caused by New Delhi Metallo-β-Lactamase-Producing Enterobacterales During a Regional Outbreak. Open Forum Infect Dis. 2020;7(2):ofaa011. doi: 10.1093/ofid/ofaa011.
7. Liangfei Xu, Xiaoxi Sun, Xiaoling Ma. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant Klebsiella pneumoniae. Ann Clin Microbiol Antimicrob. 2017;16(1):18. doi:

10.1186/s12941-017-0191-3.

8. Seo H, Lee SC, Chung H, et al. Clinical and Microbiological Analysis of Risk Factors for Mortality in Patients with Carbapenem-Resistant Enterobacteriaceae Bacteremia. Int J Antimicrob Agents. 2020;56 (4):106126. doi:10.1016/j.ijantimicag.2020.106126.
9. Reenu Thomas, Sithembiso Velaphi, Sally Ellis, A Sarah Walker, Joseph F Standing, Paul Heath, et al. The use of polymyxins to treat carbapenem resistant infections in neonates and children. Expert Opin. Pharmacother. Expert Opin Pharmacother. 2019;20(4):415-422. doi: 10.1080/14656566.2018.1559817.
10. E Durante-Mangoni, R Andini, R Zampino. Management of carbapenem-resistant Enterobacteriaceae infections. Clin Microbiol Infect. 2019;25(8):943-950. doi: 10.1016/j.cmi.2019.04.013.
11. John E Mazuski, Leanne B Gasink, Jon Armstrong, Helen Broadhurst, Greg G Stone, Douglas Rank, et al. Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program. Clin Infect Dis. 2016;62(11):1380-1389. doi: 10.1093/cid/ciw133.
12. Antoni Torres, Nanshan Zhong, Jan Pachl, Jean-François Timsit, Marin Kollef, Zhangjing Chen, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis. 2018;18(3):285-295. doi: 10.1016/S1473-3099(17)30747-8.
13. Roopali Sharma, Tae Eun Park, Stanley Moy. Ceftazidime-Avibactam: A Novel Cephalosporin/β-Lactamase Inhibitor Combination for the Treatment of Resistant Gram-negative Organisms. Clin Ther. 2016;38(3):431-44. doi: 10.1016/j.clinthera.2016.01.018.
14. Clinical and Laboratory Standards Institute. 2018. M100-S28. Performance Standards for Antimicrobial Susceptibility Testing: 28th Informational Supplement. Wayne, PA: Clinical and Laboratory Standards Institute.
15. 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.European Committee on
16. Antimicrobial Susceptibility Testing. 2013. Breakpoint tables for interpretation of MICs and zone diameters, version 3.1, 2013. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpoint_table_v_3.1.pdf.
17. Chaoe Zhou, Longyang Jin, Qi Wang, Xiaojuan Wang, Fengning Chen, Yue Gao, et al. Bloodstream Infections Caused by Carbapenem-Resistant Enterobacterales: Risk Factors for Mortality, Antimicrobial Therapy and Treatment Outcomes from a Prospective Multicenter Study. Infect Drug Resist. 2021;14:731-742. doi: 10.2147/IDR.S294282.
18. Steven Y C Tong 1, Luke F Chen, Vance G Fowler Jr. Colonization, pathogenicity, host susceptibility, and therapeutics for Staphylococcus aureus: what is the clinical relevance? Semin Immunopathol. 2012;34(2):185-200. doi: 10.1007/s00281-011-0300-x.
19. George L Daikos, Sophia Tsaousi, Leonidas S Tzouvelekis, Ioannis Anyfantis, Mina Psichogiou, Athina Argyropoulou, et al. Carbapenemase-producing Klebsiella pneumoniae bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother. 2014;58(4):2322-8. doi: 10.1128/AAC.02166-13.
20. Xiaojuan Wang, Qi Wang , Bin Cao, Shijun Sun, Yawei Zhang, Bing Gu, et al. Retrospective Observational Study from a Chinese Network of the Impact of Combination Therapy versus Monotherapy on Mortality from

Carbapenem-Resistant Enterobacteriaceae Bacteremia. Antimicrob Agents Chemother. 2018;63(1):e01511-18. doi: 10.1128/AAC.01511-1

21. I Karaiskos, G L Daikos, A Gkoufa, G Adamis, A Stefos, S Symbardi, et al.Ceftazidime/avibactam in the era of carbapenemase-producing Klebsiella pneumoniae: experience from a national registry study. J Antimicrob Chemother. 2021;76(3):775-783. doi: 10.1093/jac/dkaa503.
22. Michael J Satlin, Stephen G Jenkins, Thomas J Walsh. The global challenge of carbapenem-resistant Enterobacteriaceae in transplant recipients and patients with hematologic malignancies. Clin Infect Dis. 2014;58(9):1274-83. doi: 10.1093/cid/ciu052.
23. A Gomez-Simmonds, B Nelson, D P Eiras, A Loo, S G Jenkins, S Whittier, et al. Combination Regimens for Treatment of Carbapenem-Resistant Klebsiella pneumoniae Bloodstream Infections. Antimicrob Agents Chemother. 2016;60(6):3601-7. doi: 10.1128/AAC.03007-15.
24. Lesia K Dropulic, Howard M Lederman. Overview of Infections in the Immunocompromised Host. Microbiol Spectr. 2016;4(4). doi: 10.1128/microbiolspec.DMIH2-0026-2016.
25. Tingting Xiao, Yunying Zhu, Shuntian Zhang, Yuan Wang, Ping Shen, Yanzi Zhou, et al. A Retrospective Analysis of Risk Factors and Outcomes of Carbapenem-Resistant Klebsiella pneumoniae Bacteremia in Nontransplant Patients. J Infect Dis. 2020;221(Suppl 2):S174-S183. doi: 10.1093/infdis/jiz559.
26. George L Daikos, Panayiotis Petrikkos, Mina Psichogiou, Chris Kosmidis, Evangelos Vryonis, Athanasios Skoutelis, et al. 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. 2009;53(5):1868-73. doi: 10.1128/AAC.00782-08.
27. Marco Falcone, Matteo Bassetti, Giusy Tiseo, Cesira Giordano, Elia Nencini, Alessandro Russo, et al. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing Klebsiella pneumoniae. Crit Care. 2020;24(1):29. doi: 10.1186/s13054-020-2742-9.
28. Juan José Castón, Marina Gallo, Manuel García, Angela Cano, Antonio Escribano, Isabel Machuca, et al. 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. 2020;56(3):106075. doi: 10.1016/j.ijantimicag.2020.106075.
29. David van Duin, Judith J Lok, Michelle Earley2, Eric Cober, Sandra S Richter, Federico Perez, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis. 2018;66(2):163-171. doi: 10.1093/cid/cix783.
30. Ryan K Shields, M Hong Nguyen, Liang Chen , Ellen G Press, Brian A Potoski, Rachel V Marini, et al. Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia. Antimicrob Agents Chemother. 2017;61(8):e00883-17. doi: 10.1128/AAC.00883-17.
31. Akosua A Agyeman, Phillip J Bergen, Gauri G Rao, Roger L Nation, Cornelia B Landersdorfer. A systematic review and meta-analysis of treatment outcomes following antibiotic therapy among patients with carbapenem-resistant Klebsiella pneumoniae infections. Int J Antimicrob Agents. 2020;55(1):105833. doi: 10.1016/j.ijantimicag.2019.10.014.
32. Mario Tumbarello, Francesca Raffaelli, Maddalena Giannella, Elisabetta Mantengoli, Alessandra Mularoni, Mario Venditti, et al. Ceftazidime-avibactam use for KPC-Kp infections: a retrospective observational multicenter study. Clin Infect Dis. 2021;ciab176. doi: 10.1093/cid/ciab176.
33. Akosua A Agyeman, Phillip J Bergen, Gauri G Rao, Roger L Nation, Cornelia B Landersdorfer. A systematic review and meta-analysis of treatment outcomes following antibiotic therapy among patients with carbapenem-

resistant Klebsiella pneumoniae infections. Int J Antimicrob Agents. 2020;55(1):105833. doi: 10.1016/j.ijantimicag.2019.10.014.

34. Renato Pascale, Maddalena Giannella, Michele Bartoletti, Pierluigi Viale, Federico Pea. Use of meropenem in treating carbapenem-resistant Enterobacteriaceae infections. Expert Rev Anti Infect Ther. 2019;17(10):819-827. doi: 10.1080/14787210.2019.1673731.
35. Wentao Ni, Yuliang Han, Jie Liu, Chuanqi Wei, Jin Zhao, Junchang Cui, et al. Tigecycline Treatment for CarbapenemResistant Enterobacteriaceae Infections: A Systematic Review and Meta-Analysis. Medicine (Baltimore). 2016;95(11):e3126. doi: 10.1097/MD.0000000000003126.
36. Nikolas J Onufrak, Alan Forrest, Daniel Gonzalez. Pharmacokinetic and Pharmacodynamic Principles of Anti-infective Dosing. Clin Ther. 2016;38(9):1930-47. doi: 10.1016/j.clinthera.2016.06.015.
37. Thien B Tran, Tony Velkov, Roger L Nation, Alan Forrest, Brian T Tsuji, Phillip J Bergen, et al. Pharmacokinetics/pharmacodynamics of colistin and polymyxin B: are we there yet? Int J Antimicrob Agents. 2016;48(6):592-597. doi: 10.1016/j.ijantimicag.2016.09.010

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial1.docx