BMJ Open

Efficacy and safety of ceftazidime–avibactam versus polymyxins in the treatment of carbapenem-resistant Enterobacteriaceae infection: a systematic review and meta-analysis

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To cite: Yang P, Li Y, Wang X, *et al*. Efficacy and safety of ceftazidime–avibactam versus polymyxins in the treatment of carbapenem-resistant Enterobacteriaceae infection: a systematic review and meta-analysis. *BMJ Open* 2023;**13**:e070491. doi:10.1136/bmjopen-2022-070491

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-070491).

Received 28 November 2022
Accepted 12 April 2023

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ABSTRACT

Objectives Carbapenem-resistant Enterobacteriaceae is increasingly recognised as a significant public health concern. Ceftazidime-avibactam (CAZ-AVI) and polymyxins are considered as the last therapeutic options worldwide. This is the first meta-analysis of recently published data to compare the clinical efficacy and safety of CAZ-AVI with polymyxins in the treatment of carbapenem-resistant Enterobacteriaceae infections.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase and the Cochrane Library were systematically searched, for publications in any language, from database inception to February 2023.

Eligibility criteria for selecting studies Studies comparing the clinical efficacy and safety of CAZ-AVI with polymyxins were included. Mortality, clinical success, microbiological eradication and nephrotoxicity were assessed as the main outcomes.

Data extraction and synthesis Literature screening, data extraction and the quality evaluation of studies were conducted by two researchers independently, with disagreements resolved by another researcher. The Newcastle–Ottawa Scale was used to assess the bias risk for the included studies. Review Manager V.5.3 was employed for the meta-analysis.

Results The meta-analysis included seven retrospective and four prospective cohort studies with 1111 patients enrolled. The CAZ-AVI groups demonstrated a lower 30-day mortality (risk ratio (RR)=0.48, 95% CI of 0.37 to 0.63, I^2=10%, p<0.0001) in nine studies with 766 patients; higher clinical success (RR=1.71, 95% CI 1.33 to 2.20, I^2=35%, p<0.0001) in four studies with 463 patients; and lower nephrotoxicity in seven studies with 696 patients (RR=0.42, 95% CI 0.23 to 0.77, I^2=35%, p<0.05). However, no significant difference in microbiological eradication rates was observed in 249 patients from two studies (RR=1.16, 95% CI 0.97 to 1.39, I^2=0, p>0.05).

Conclusion Available evidence suggested that CAZ-AVI treatment held a dominant position with respect to efficacy and safety compared with polymyxins in carbapenem-resistant Enterobacteriaceae infections. However, the analysis included only observational studies, and high-quality, large-scale, multicentre, double-blind randomised controlled trials are needed to confirm the advantage of CAZ-AVI.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Rigorous reviewing methods were used in this systematic review and meta-analysis, including a comprehensive search strategy, explicit eligibility criteria and the selection of studies by two independent reviewers.
- ⇒ No restrictions were implemented on the type of articles, study design, language or publication year, and the Newcastle–Ottawa Scale was used to evaluate the quality of the studies.
- ⇒ Subgroup analyses of diseases and strains were not performed due to the lack of some necessary information.
- ⇒ The included studies were all observational studies with limited sample sizes; high-quality and large-scale multicentre randomised controlled trials are needed to confirm our findings.

INTRODUCTION

Globally, bacterial resistance is becoming an increasingly serious problem owing to the use of antibacterial drugs. Carbapenem-resistant Enterobacteriaceae (CRE) infections have emerged throughout the world, posing a global public health threat and a formidable challenge to antimicrobial therapy.[1] Nonetheless, increased carbapenem use could lead to carbapenem resistance in gram-negative bacteria, which is the chief reason of antimicrobial resistance.[2] CRE infections have presented a particularly grave threat worldwide. In the past decades, tigecycline has been considered as one of the last lines of defence against severe CRE infections. However, suboptimal concentrations of tigecycline have been found in both serum and pulmonary epithelial lining fluid, and this observation has prompted many physicians to use either combination therapy or high-dose tigecycline to treat CRE infections. Severe coagulopathy with hypofibrinogenaemia and diarrhoea have recently been reported to be associated with high-dose tigecycline.[3 4] Therefore, the Food and Drug Administration (FDA) has warned against the off-label use of tigecycline to treat nosocomial pneumonia because of the increased mortality risk indicated in randomised trials.[5 6] Recently, some new antibiotics also show great advantages in the treatment of CRE infection, such as cefiderocol, meropenem/vaborbactam and imipenem/cilastatin/relebactam.[7–9] However, given the accessibility of drugs, the optimal treatment for CRE infection in China still involves either ceftazidime–avibactam (CAZ-AVI) or polymyxins-based regimens.

CAZ-AVI was approved by the European Medicines Agency for infections caused by gram-negative aerobic bacteria in adults with limited treatment options, including *Klebsiella pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*.[10] Recently, polymyxins were reintroduced into medical practice as one of the last resorts for treating extensively drug-resistant gram-negative bacteria. However, acute kidney injury was frequently experienced after conventional doses of polymyxins.[11]

Recent meta-analysis demonstrated that CAZ-AVI had a favourable pharmacological profile and might be an option for empirical therapy of CRE infection.[12] However, large-scale clinical trials comparing the safety and efficacy of CAZ-AVI with polymyxins in the treatment of CRE infection are still lacking.

Naturally, systematically assessing the results of the previous researches in multiple centres could provide important information. Therefore, we conducted a meta-analysis to further explore the efficacy and safety profile of CAZ-AVI relative to polymyxins in the treatment of CRE infection.

METHODS

Literature search

The PubMed, Embase and Cochrane Central Register of Controlled Trials electronic databases were independently searched by two authors, starting from the database inception to February 2023. The full search strategy aimed to include any clinical studies performed on patients with CRE infection treated with CAZ-AVI versus polymyxins. The PubMed search strategy was (‘ceftazidime-avibactam’) AND (‘polymyxin’ OR ‘polymyxins’ OR ‘colistin’) AND (‘carbapenem-resistant *klebsiella pneumoniae*’ OR ‘carbapenem resistant Enterobacter*’ OR ‘carbapenem resistant gram-negative bacteria’ OR ‘carbapenem resistant organism’ OR ‘multidrug-resistant gram-negative bacteria’) as applied on both the medical subject heading and free text. This search strategy was subsequently modified for searching in Embase and the Cochrane Central Register of Controlled Trials (online supplemental file 1). Previously published systematic reviews were also checked to identify any additional studies that might have been overlooked in our search strategy.

Study selection

Two authors independently screened the eligibility of the literature by examining the titles, abstracts and full-text of the retrieved articles. Eligible studies included all available published studies that compared CAZ-AVI with polymyxins for the treatment of CRE infections in adult patients (>18 years). CAZ-AVI or polymyxins-based combined administration schemes were allowed. Studies lacking quantitative or qualitative target outcome results were excluded. Disagreements between reviewers were settled by another researcher.

Data extraction

Data extraction was conducted by two authors independently. Each study was reviewed for the following information: (1) study author, publication year and the study regions; (2) study design and sample size; (3) patients’ characteristics (age, sex, drug administration regimen, infection site and causative pathogen); and (4) outcomes, such as mortality, clinical efficacy, bacterial eradication and adverse reactions.

Quality assessment

The risk of bias of the included studies in terms of patient selection, comparability between groups, outcome and exposure factors assessment was evaluated by the Newcastle–Ottawa Scale (NOS) or a modified NOS.[13] NOS scores ranged from 0 to 9, and the studies were then classified according to quality as poor (0–4), moderate (5–6) or high-quality (7–9) research. A consensus was reached between reviewers to resolve differences.

Statistical analysis

Review Manager V.5.3 was used to conduct the statistical analysis. Based on a random-effects model, dichotomous outcomes were represented as a risk ratio (RR) with a 95% CI. The Cochrane I^2 statistic was used to measure heterogeneity. Note that heterogeneity was significant if the I^2 value exceeded 50%. The model was considered robust if no significant difference was observed in the p value of the corresponding combined effect size. Moreover, publication biases were visually assessed using funnel plots.

Patient and public involvement

None.

RESULTS

Description of included studies

The retrieval strategy initially retrieved 580 articles. From those, 482 potentially useful studies were obtained after removing duplicates. The full texts of the remaining articles were evaluated for eligibility based on the inclusion and exclusion criteria. Finally, 11 cohort studies were included in the meta-analysis.[14–24] The detailed process was displayed in figure 1. table 1, 1a summarised the details of the included studies, including study year, author, region, design and participant information .

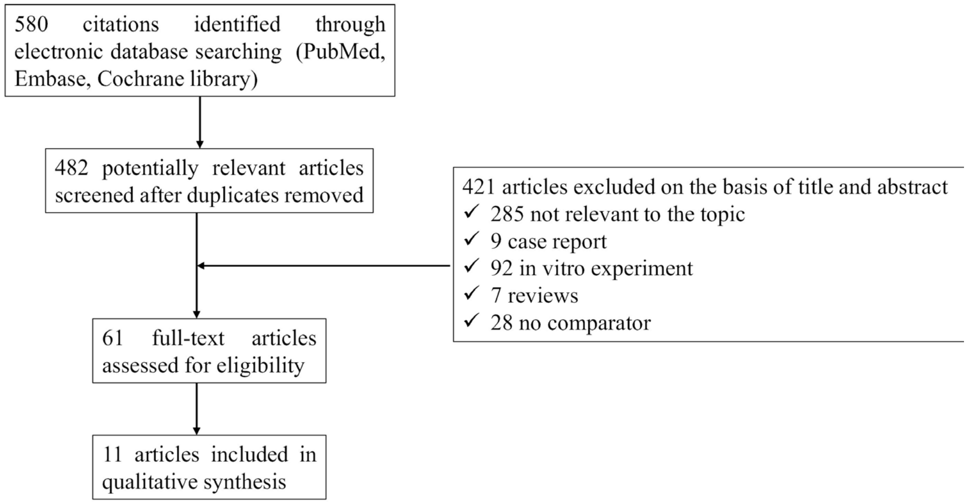

Figure 1 Flow chart of literature search process and review based on eligible criteria.

The included studies involved 467 patients for the CAZ-AVI group and 644 patients for polymyxins group. All study designs were available, and the eligible articles consisted of seven retrospective[15 16 18–22] and four prospective cohort studies.[14 17 23 24] One of them is a single-centre study,[19] while the other 10 are multicentre studies.[14–18 20–24] Three studies originated from the USA,[14 19 23] two studies were conducted in Saudi Arabia,[20 22] four studies were performed in China,[15 16 18 24] and two studies were conducted in Italy and Greece, respectively.[17 21] Among the 11 studies, 6 articles reported the patient age, with the mean age of 57–66 years in the CAV-AVI group and 49–67.5 years in the polymyxins group.[14 15 18–20 22] Further, six articles reported participant sex, with 31.7%–67.6% male patients. Based on our inclusion criteria, monotherapy or combination therapy was allowed. CAZ-AVI was provided as monotherapy in two studies[19 23] and polymyxins were provided as monotherapy in one study.[23] Only one study was conducted according to the combination of the above two drugs,[15] and all others were based on monotherapy or combination regimens (online supplemental table 1). The most common infection site in the enrolling studies was the bloodstream, followed by respiratory, abdominal and urinary tract. The studied strain included CRE[14 16 17 20 22–24] and carbapenem-resistant *K. pneumoniae*.[15 18 19 21] The outcomes involved 30-day mortality in nine studies,[14 16–19 21–24] clinical response in four studies,[16 19 20 22] microbiological response in two studies[20 22] and nephrotoxicity in seven studies.[14 17–20 22 23]

Assessment of study quality

As depicted in online supplemental table 2, all studies were evaluated by NOS. The NOS scores of all assessed studies were ≥7. Thus, all studies were considered to have low risk of bias.

Outcomes

Mortality

The 30-day mortality was reported in nine studies, including 766 patients.[14 16–19 21–24] As displayed in figure 2, the CAZ-AVI group showed a lower 30-day mortality rate compared with polymyxins group when random effects were employed (RR=0.48, 95% CI 0.37 to 0.63, I^2=10%, p<0.0001). Funnel plots of included studies showed that all plots exhibited roughly symmetrically inverted funnel shapes, indicating no publication bias (online supplemental figure 1).

Clinical success

Clinical success was reported in four studies, including 463 patients.[16 19 20 22] Compared with those in the polymyxins group, patients in the CAZ-AVI group had a significantly higher clinical cure rate as illustrated in figure 3 (RR=1.71, 95% CI 1.33 to 2.20, I^2=35%, p<0.0001).

Bacterial eradication

Two studies with 249 patients reported data on microbiological response.[20 22] As shown in figure 4, a pooled analysis with random-effects models revealed comparable potencies of CAZ-AVI with polymyxins in microbiological eradication abilities (RR=1.16, 95% CI 0.97 to 1.39, I^2=0, p>0.05).

Nephrotoxicity

Seven studies with 696 patients reported nephrotoxicity.[14 17–20 22 23] As shown in figure 5, pooled results from the included studies indicated a lower nephrotoxicity rate in the CAZ-AVI group relative to the polymyxins counterpart (RR=0.42, 95% CI 0.23 to 0.77; I^2=35%, p<0.05).

DISCUSSION

In this meta-analysis, seven retrospective and four prospective cohort studies with 1111 patients were included to compare the efficacy and safety of CAZ-AVI with polymyxins regimens in patients with CRE infection. Polymyxins-containing regimens had an increased risk of mortality, clinical failure and nephrotoxicity compared with CAZ-AVI. However, CAZ-AVI did not exhibit superior bacterial eradication ability over polymyxins. To date,

Table 1 Characteristics of the included studies

First author, year	Region	Design	No (C/P)	Mean age (years) (C/P)	Sex (% male) (C/P)	Most common infection site	Causative pathogen	Outcomes
Shields, 2017[19]	USA	Retrospective, single centre	13/30	66 (32–91)/59 (26–84)	54/60	Bloodstream, abdominal, respiratory, urinary tract, soft tissue	CRKP	Clinical success, mortality, bacterial eradication, nephrotoxicity
van Duin, 2018[14]	USA	Prospective, multicentre	38/99	57 (45–64)/63 (54–76)	61/42	Bloodstream, respiratory, urinary tract, wound	CRE	Mortality, nephrotoxicity
Hakeam, 2021[22]	Saudi Arabia	Retrospective, multicentre	32/29	58.0±17.9/49±19.9	56.2/62.1	Bloodstream, urinary tract, respiratory, intra-abdominal, skin and soft tissue, central line	CRE	Mortality, bacterial eradication, clinical success, nephrotoxicity
Fang, 2021[15]	China	Retrospective, multicentre	37/78	64 (47–72)/62.5 (52.5–70.5)	66.1%/67.6%	Respiratory, bloodstream, abdominal, urinary tract, other sites	CRKP	Mortality, microbiological eradication, clinical success
Almangour, 2022[20]	Saudi Arabia	Retrospective, multicentre	149/81	59±18/57.5±20	62/61	Respiratory, urinary tract, wound, intra-abdominal, bloodstream	CRE*	Mortality, clinical success, nephrotoxicity, microbiological eradication
Falcone, 2020[21]	Italy	Retrospective, multicentre	13/61	NA	NA	Bloodstream	CRKP	Mortality, a composite endpoint of mortality or nephrotoxicity
Falcone, 2021[17]	Italy and Greece	Prospective, multicentre	52/27	69 (49.75–77)/NA	69.2/NA	Bloodstream	CRE*	Mortality, clinical failure, length of hospital stays, nephrotoxicity
Zhou, 2021[24]	China	Prospective, multicentre	4/28	NA/NA	NA/NA	Bloodstream	CRE*	Mortality, clinical cure, sepsis/ septic shock incidence
Chen, 2021[16]	China	Retrospective, multicentre	26/103	NA/NA	NA/NA	Bloodstream	CRE*	Mortality, clinical failure
Satlin, 2022[23]	USA	Prospective, multicentre	21/26	NA/NA	NA/NA	Bloodstream	CRE*	Mortality, nephrotoxicity
Zheng, 2022[18]	China	Retrospective, multicentre	82/82	63.2±17/67.5±12.3	31.7/40.2	Respiratory, bloodstream	CRKP	Mortality, microbiological eradication, clinical safety, nephrotoxicity

*CRE=carbapenem-resistant Enterobacterales.
C/P, ceftazidime–avibactam group/polymyxins group; CRE, carbapenem-resistant Enterobacteriaceae; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; NA, not available.

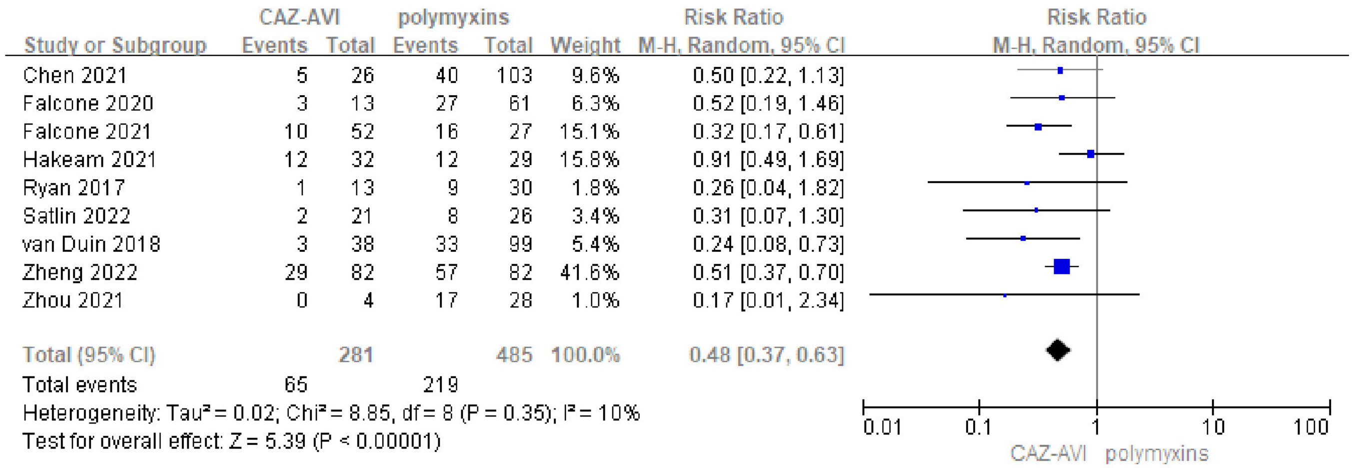

Figure 2 The 30-day mortality of the CAZ-AVI regimens compared with polymyxins regimens. CAZ-AVI, ceftazidime–avibactam.

this work remains the first meta-analysis to compare the efficacy and safety of CAZ-AVI with polymyxins in treating CRE infection.

CRE pathogens have spread alarmingly in recent years, showing marked correlations with a high risk of morbidity, mortality and considerable economic burden. Inactivated enzyme production, enhanced efflux activity and reduced cell permeability have been considered as the most frequent and important mechanisms of CRE prevalence. Until now, current antimicrobial therapy options for CRE infections are still very limited, including polymyxins and novel β-compound preparations of lactamase inhibitors, such as ceftazidime/avibactam, aztreonam/avibactam, meropenem/vaborbactam and imipenem/cilastatin/relebactam.[25] However, given the availability of such drugs, CAZ-AVI and polymyxins-containing regimens have been highly recommended as the frontline agents in the treatment of multidrug-resistant gram-negative bacterial infections in China. Polymyxins exert their antibacterial effect by increasing the permeability of the bacterial outer membrane through interaction with lipopolysaccharides in the outer membrane of gram-negative bacteria.[26] As a novel β-lactam/β-lactamase inhibitor combination, CAZ-AVI exhibits activity against various clinically important β-lactam-resistant bacteria producing class A and *K. pneumoniae* carbapenemases and class C and certain class D enzymes, but not against the metallo-β-lactamases (MBL) of class B enzymes.[27] Consequently, the distinct action mechanisms of the two drugs contribute different clinical effectiveness.

Early meta-analysis including three randomised controlled trials observed that CAZ-AVI was similar to carbapenem for the treatment of Enterobacteriaceae infections and could provide an alternative to carbapenem.[28] However, a recent meta-analysis demonstrated an advantage of CAZ-AVI to treat CRE bloodstream infections on efficacy and safety, and subgroup analysis revealed that the CAZ-AVI group had a significantly lower 30-day mortality than colistin-based regimens.[12] Moreover, previous studies indicated the incidence rate of polymyxins-related nephrotoxicity ranged from 11.8% to 50.6%.[29] Therefore, the safety advantage of CAZ-AVI compared with polymyxins was not surprising.

In our meta-analysis, most studies applied combination therapy, which was consistent with the current recommended guidelines, mainly because most CRE infections involved multidrug-resistant mechanisms. Therefore, most of the included studies were based on the combined administration of CAZ-AVI or polymyxins, and the combined administration plan also included other activity antibiotics. Given the heterogeneously resistant nature of polymyxins, the combination administration is recommended as the first-line treatment. However,

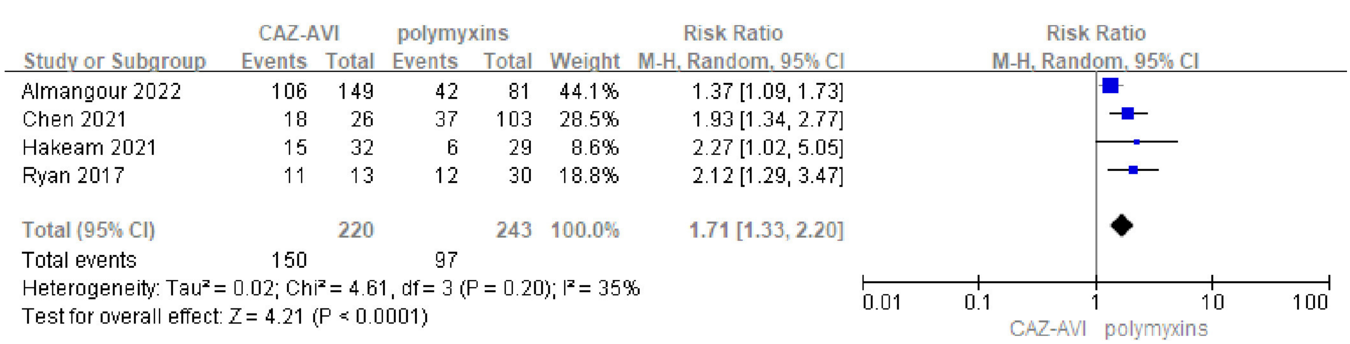

Figure 3 Clinical success of the CAZ-AVI regimens compared with polymyxins regimens. CAZ-AVI, ceftazidime–avibactam.

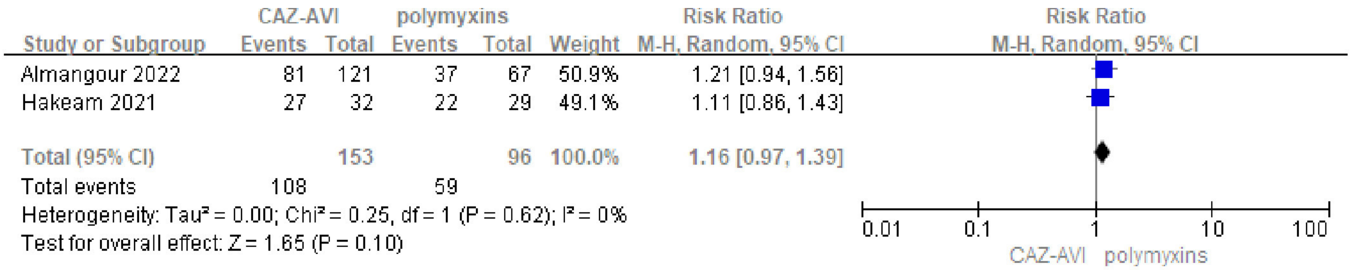

Figure 4 Bacterial eradication of the CAZ-AVI regimens compared with polymyxins regimens. CAZ-AVI, ceftazidime–avibactam.

a recent meta-analysis did not observe an advantage of polymyxins combination therapy on multidrug-resistant gram-negative bacterial infections.[30] In addition, another meta-analysis suggested that CAZ-AVI in monotherapy or combination therapy for CRE infections demonstrated similar effect on mortality and microbiological cure rates.[31] Therefore, both combined and single-drug regimens were included in our meta-analysis.

CAZ-AVI is the first new type β-lactamase inhibitor for the CRE infection treatment approved by FDA.[32] Moreover, CAZ-AVI has been approved for infections without additional therapeutic options, such as for complicated intra-abdominal infections, complicated urinary tract infections and hospital-acquired pneumonia/ventilator-associated pneumonia. CAZ-AVI shows low plasma protein binding and steady-state distribution volume, allowing it to maintain an adequate trough concentration to achieve the bactericidal effect. Additionally, CAZ-AVI is excreted almost exclusively through renal excretion, resulting in high urinary drug concentrations,[33] and its good blood concentration in the bronchial epithelial lining fluid endows CAZ-AVI with a favourable pharmacological profile for bloodstream, abdominal, respiratory and urinary tract infection. These infection sites were the most common in our meta-analysis. Regarding the causative pathogens, CAZ-AVI sustains excellent ability in the treatment of CRE infection except for the MBL-producing Enterobacteriaceae. Interestingly, the CAZ-AVI and aztreonam combination offers a therapeutic advantage on patients with bloodstream infection caused by MBL-producing Enterobacterales.[17] Although the types of bacteria and diseases were not limited in our studies, little heterogeneity was detected in our work. Considering the well-characterised pharmacokinetic parameters and pharmacological activity of CAZ-AVI, all CRE infections were included in our meta-analysis.

This review had some limitations that should be acknowledged. First, all included studies were observational in design, and the seven retrospective and four prospective cohort studies included only 1111 patients, resulting in a small sample size. Second, most studies did not provide antimicrobial resistance or enzyme production information; moreover, changes in the pathogen's resistance to antibiotic exposure and specific information of various diseases were not available in all included studies. Thus, subgroup analyses of diseases and strains were not performed given the lower heterogeneity. Finally, among these included studies, colistin was taken as a control group in six studies, while polymyxin B in four studies, and both two drugs were used as a control group in the other article, but the dosage was not reported in detail. Therefore, further subgroup analysis was not performed for the two drugs as a control group.

CONCLUSION

Overall, CAZ-AVI showed advantages over polymyxins in terms of mortality, clinical success and safety. In addition, similar bacterial eradication profiles were observed for CAZ-AVI and polymyxins groups. To the best of our knowledge, this work is the first meta-analysis to be conducted on this topic. However, given the small sample size and the

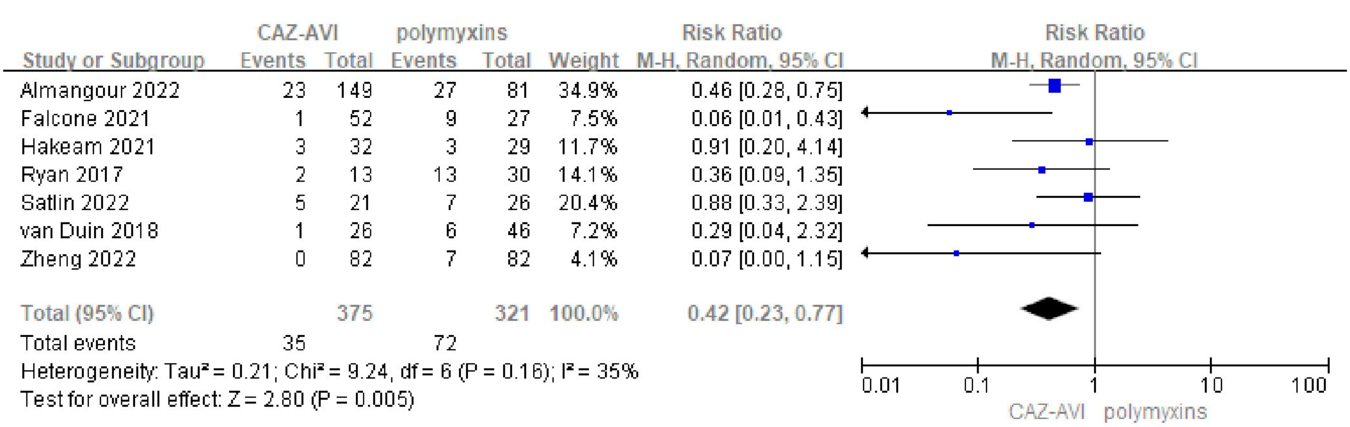

Figure 5 Nephrotoxicity of the CAZ-AVI regimens compared with polymyxins regimens. CAZ-AVI, ceftazidime–avibactam.

limitations of the studies included in the present work, large, high-quality, multicentre, randomised, double-blind, controlled trials should be conducted to establish the dominance of CAZ-ZVI over polymyxins in treating CRE infections.

Acknowledgements The authors gratefully acknowledge the suggestions given by Rong-Rong Wang on the manuscript.

Contributors YY-L and XJ-W are responsible for literature retrieval and data extraction. NC is responsible for handling disagreements and data analysis. PY is responsible for paper writing. XY-L is responsible for overall design and final approval of the manuscript.

Funding This work was funded by Zhejiang Pharmaceutical Association hospital pharmacy special scientific research funding project (2019ZYY11), Zhejiang Medical Association clinical research funding project (2020ZYC-A107), Zhejiang medical and health science technology project (2019RC168) and the Nature Science Foundation of Zhejiang province (LQ20H300003, LYY21H300004).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethics approval was not required as the study was based on existing publicly available data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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Table S1. Characteristics of the included studies

First author, year	Drug administration regimen (C/P)
Shields, 2017	CA monotherapy /COL[1]
van Duin, 2018	CA /COL[2]
Hakeam， 2021	CA/COL[3]
Fang, 2021	CA/PMB[4]
Almangour,2022	CA/COL[5]
Falcone, 2020	CA/COL[6]
Falcone, 2021	CA/COL[7]
Zhou, 2021	CA/PMB[8]
Chen, 2021	CA/PMB[9]
Satlin, 2022	CA monotherapy /Polymyxin monotherapy[10]
Zheng 2022	CA/PMB[11]

Abbreviations: C/P, Ceftazidime-avibactam group/Polymyxins group; CA, Ceftazidime-avibactam; COL, colistin; PMB, polymyxin B;

[1] All are combined administration schemes including carbapenem.

[2] 24 patients in CA group and 93 patients in colistin group received combined drug administration, the other combination drugs include that are effective for CRE, such

as tigecycline, amikacin, gentamicin, trimethoprim/sulfamethoxazole, carbapenem, or fosfomycin.

[3] 23 patients in CA group and all patients in colistin group received combined drug administration, the other combination drugs include carbapenem, aztreonam, cefepime, piperacillin/tazobactam, aminoglycosides, fluoroquinolones, tigecycline, or vancomycin.

[4] all CA and Polymyxin B groups were used in combination with carbapenems, aminoglycosides, tigecycline, fosfomycin, cephalosporins, quinolones, or trimethoprim/sulfamethoxazole.

[5] 34 in CA group and 57 patients in colistin group received combined drug administration, the other combination drugs include carbapenem, aztreonam, piperacillin/tazobactam, aminoglycosides, cephalosporin, fluoroquinolones, or tigecycline.

[6] CA group was monotherapy or in combination with fosfomycin or aminoglycosides, while the most frequent antibiotic regimen in COL group was colistin plus meropenem plus tigecycline ± gentamycin.

[7] All patients in CA group received the combined administration scheme of aztreonam, and 25 patients in colistin-group received combination administration, including fosfomycin, tigecycline, meropenem, aztreonam, piperacillin/tazobactam or cotrimoxazole

[8] 3 patients received combined drug administration (tigecycline or imipenem) in CA group while 25 patients in colistin group received combined drug administration (tigecycline, carbapenem or aminoglycosides)

[9] 13 patients received combined drug administration (tigecycline) in CA group while all patients received combination therapy in polymyxin B group (tigecycline, carbapenem or aminoglycosides)

[10] Polymyxin monotherapy consisted of polymyxin B (n = 24) and colistin (n = 2).

[11]49 patients received combined drug administration in CA group while 60 patients in PMB group, the other combination drugs include carbapenems, tigecycline, amikacin, fosfomycin, aztreonam, minocycline, moxifloxacin, sulfamethoxazole/trimethoprim.

Table S2. Quality scoring for included cohort studies using New castle-Ottawa Scale (NOS)

First author, year	Selection				Comparability		Outcome			
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	On basis of the design	On basis of the analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	Total scores
Shields, 2017	1	1	1	1	1	1	1	1	1	9
van Duin, 2018	1	1	1	1	1	1	1	1	1	9
Hakeam，2021	1	1	1	1	1	1	1	1	1	9
Fang, 2021	1	1	1	1	1	1	1	1	1	9
Almangour, 2022	1	1	1	1	1	1	1	1	1	9
Falcone, 2020	1	1	1	1	0	0	1	1	1	7
Falcone, 2021	1	1	1	1	1	0	1	1	1	8
Zhou, 2021	1	1	1	1	0	0	1	1	1	7
Chen, 2021	1	1	1	1	0	0	1	1	1	7
Satlin, 2022	1	1	1	1	0	0	1	1	1	7
Zheng 2022	1	1	1	1	1	0	1	1	1	9

Search strategy

PubMed 216

Search: (((colistin) OR (“polymyxin”)) AND (“ceftazidime avibactam”)) AND (“Carbapenem Resistant klebsiella pneumoniae” OR “Carbapenem Resistant Enterobacter*” OR “Carbapenem Resistant gram-negative bacteria” OR “Carbapenem resistant Organism” OR “multidrug-resistant Gram-negative bacteria”) Sort by: Publication Date

EMBASE 354

#1 polymyxin*

#2 colistin*

#3 ‘carbapenem resistant klebsiella pneumoniae'exp OR 'carbapenem resistant klebsiella pneumoniae'

#4 ‘carbapenem resistant enterobacterales'/exp OR 'carbapenem resistant enterobacterales'

#5 'carbapenem-resistant enterobacteriaceae'/exp OR 'carbapenem-resistant enterobacteriaceae'

#6 ‘carbapenem resistant gram-negative bacteria'

#7 ‘carbapenem resistant organism’

#8 'multidrug resistant gram negative bacterium'exp OR 'multidrug resistant gram-negative bacterium'

#9 #3 OR #4 OR#5 OR#6 OR #T OR #8

#10 #1 AND #2 AND #9

Cochrane 10

#1 (polymyxin) OR (colistin)

#2 ceftazidime avibactam

#3 (Carbapenem Resistant klebsiella pneumoniae) OR (Carbapenem Resistant Enterobacterales) OR (Carbapenem Resistant Enterobacteriaceae) OR (Carbapenem Resistant gram-negative bacteria) OR (Carbapenem resistant Organism) OR (multidrug-resistant Gram-negative bacteria)

#1 AND #2 AND#3

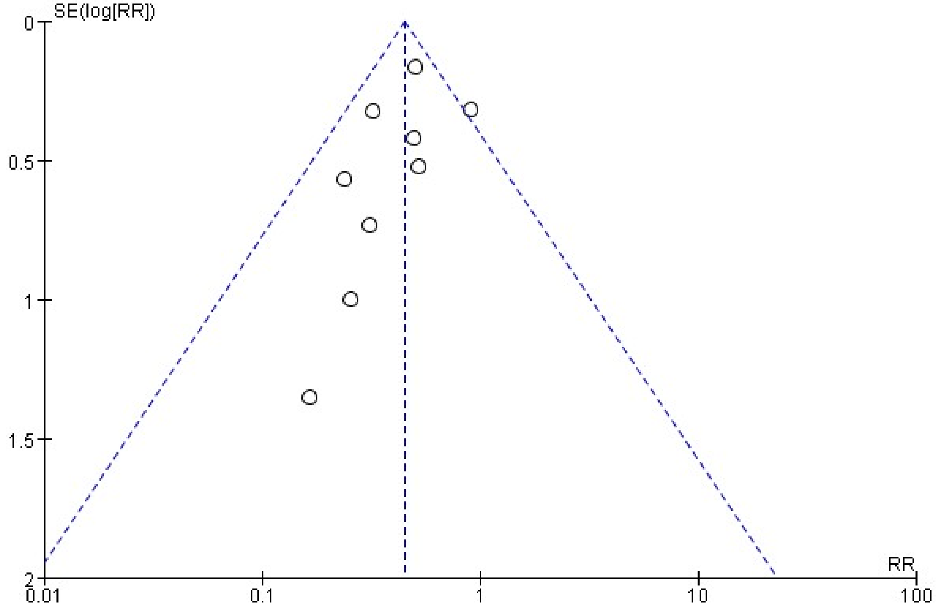

Fig S1. The funnel plot of publication bias