International Journal of Antimicrobial Agents 52 (2018) 443–450

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

# Evaluation of the efficacy and safety of ceftazidime/avibactam in the treatment of Gram-negative bacterial infections: a systematic review and meta-analysis

Han Zhong[a,1], Xian-Yuan Zhao[b,1], Zai-Li Zhang[a], Zhi-Chun Gu[a], Chi Zhang[a], Yuan Gao[b,*], Min Cui[a,*]

[a] Department of Pharmacy, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, 160 Pujian Road, Shanghai 200127, China
[b] Department of Critical Care, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, 160 Pujian Road, Shanghai 200127, China

ARTICLE INFO

*Article history:*
Received 21 February 2018
Accepted 7 July 2018

Editor: Dr Jim Gray

*Keywords:*
Avibactam
Gram-negative bacteria
Carbapenem-resistant Enterobacteriaceae
Clinical response
Microbiological response
Safety

ABSTRACT

Data on the efficacy and safety of ceftazidime/avibactam (CAZ-AVI) are limited. A systematic review and meta-analysis was conducted to clarify the role of CAZ-AVI for patients with serious Gram-negative bacterial infections. The PubMed, EMBASE and Cochrane Library databases were searched for randomised controlled trials (RCTs) and cohort studies involving CAZ-AVI. Summary risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using a fixed- or random-effects model. Twelve articles (4951 patients) were included, consisting of nine RCTs and three observational studies comparing CAZ-AVI with other regimens, e.g. carbapenems or colistin. CAZ-AVI showed a comparable clinical response (RR = 0.99, 95% CI 0.96–1.02; $I^2 = 0\%$) and non-inferior bacterial eradication (RR = 1.04, 95% CI 0.93–1.17; $I^2 = 79.1\%$) to carbapenems. No significant difference was detected between groups regarding mortality and adverse events. Moreover, subgroup analyses demonstrated that CAZ-AVI improved the clinical response (RR = 1.61, 95% CI 1.13–2.29) with reduced mortality (RR = 0.29, 95% CI 0.13–0.63) in patients infected by carbapenem-resistant Enterobacteriaceae versus comparators. Likewise, CAZ-AVI improved the clinical cure rate of bloodstream infections (RR = 2.11, 95% CI 1.54–2.88). An improved ability of CAZ-AVI in microbiological eradication was also detected in patients with complicated urinary tract infections (RR = 1.13, 95% CI 1.05–1.21). CAZ-AVI exhibited comparable efficacy and safety with carbapenems. Therefore, this agent might be a potential powerful agent for patients with serious Gram-negative bacterial infections.



## 1. Introduction

The increasing prevalence of resistance to currently available antimicrobial agents for bacterial infections, especially for complicated infections caused by Gram-negative bacteria (GNB), is still a challenge [1]. Currently, carbapenems are the first-line recommended therapy for patients with severe infections [2]. However, there is concern that the extensive utilisation of carbapenems may result in an increasing incidence of resistant strains, in particular carbapenem-resistant Enterobacteriaceae (CRE) [3,4]. Hence, it is important to use carbapenems selectively and to develop more effective agents [5].

Avibactam (AVI) is a non-$\beta$-lactam $\beta$-lactamase inhibitor with potent ability in inhibiting most of the Ambler classes A, C and some D serine $\beta$-lactamases, including extended-spectrum $\beta$-lactamases (ESBLs) and *Klebsiella pneumoniae* carbapenemases (KPCs), which may address the demand for a weapon against resistant GNB [6,7]. Nowadays, numerous studies are investigating the combination of AVI with ceftaroline fosamil [8], aztreonam (ATM) [9,10] and ceftazidime (CAZ) [11]. The combination CAZ-AVI was recently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for infections without additional therapeutic options in adults, including complicated intra-abdominal infections (cIAIs), complicated urinary tract infection (cUTIs) and hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP) (Europe only). However, the most important characteristic of this combination is its potential activity against carbapenemase-producing bacteria [5,12].

Previous systematic reviews have demonstrated that CAZ-AVI has a favourable pharmacological profile and may be an option for empirical therapy of severe GNB infections. However, neither statistical analysis nor quality validation was performed in those reviews [2,13]. Recently, a meta-analysis reported the potential

* Corresponding authors. Tel.: +86 21 6838 3162, fax: +86 21 6838 3162 (Y. Gao); tel.: +86 21 6838 3427, fax: +86 21 6838 3427 (M. Cui).
*E-mail addresses:* gaoyuan@renji.com (Y. Gao), cuimin@renji.com (M. Cui).
[1] These two authors contributed equally to this article.

https://doi.org/10.1016/j.ijantimicag.2018.07.004
0924-8579/

benefit of novel β-lactam/β-lactamase inhibitor combinations, including CAZ-AVI, in cUTI and cIAI, whilst no other indication is referred to [14]. Likewise, another meta-analysis including six randomised controlled trials (RCTs) documented the efficacy of CAZ-AVI in cUTI and cIAI [15]. Considering that a number of studies have demonstrated the impact of CAZ-AVI in infectious diseases, especially those caused by CRE [16–18], here we conducted a systematic review and meta-analysis to better understand the activity and safety profile of this newly approved drug combination.

## 2. Methods

### 2.1. Literature search

The PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases were searched by two authors (HZ and X-YZ) independently from inception to 9 February 2018 without language restriction.

The PubMed search strategy was 'avibactam' or 'AVE1330A' or 'NXL104' searched both in Medical Subject Headings (MeSH) and free text. The search strategy was then adapted for EMBASE and CENTRAL.

The two authors also conducted complementary searches by screening all of the reference lists of included articles to identify any other potentially relevant articles. The ClinicalTrials.gov website of the US National Library of Medicine (http://clinicaltrials.gov/) was also searched for completed and ongoing trials.

### 2.2. Selection of studies

The titles, abstracts and full-text of articles from the retrieved literature were screened by two authors (HZ and X-YZ) independently to identify their eligibility (Fig. 1). Studies that (i) evaluated the impact of AVI or AVE1330A or NXL104 and (ii) were conducted among patients with infectious diseases compared with other treatments were considered eligible for inclusion. In addition, the following studies were excluded: (i) case reports or case series without a control group; and (ii) studies lacking quantitative or qualitative target outcome results. Any disagreements were resolved by discussion.

Target outcomes of interest in these studies were clinical response, microbiological response, mortality, adverse events (AEs) and serious adverse events (SAEs).

### 2.3. Data extraction and management

Data extraction was performed independently by two authors (HZ and X-YZ). The following information was extracted from each study: (i) study author and year of publication as well as the region(s) where the study was conducted; (ii) study characteristics (including study design and sample size); (iii) characteristics of the patients (including age, sex, infection type and causative pathogen); (iv) characteristics of the treatment (including dosage of avibactam, concomitant therapy and antimicrobial duration); (v) characteristics of the control group; and (vi) types of outcome measures.

### 2.4. Assessment of risk of bias in the included studies

The risk of bias of the included RCTs in the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting was assessed by two authors (HZ and X-YZ) using the Cochrane Risk of Bias Tool (Supplementary Table S1) [19]. For each item, the quality characteristics of each study were rated as (i) low risk of bias, (ii) unclear or (iii) high risk of bias. When observational studies were considered, the Newcastle–Ottawa Scale (NOS) was used to assess the risk of bias in patient selection, comparability between groups, and outcome and exposure factors assessment. NOS scores range from 0–9, with scores ≥7 indicating good quality (Supplementary Table S2) [20]. Disagreements between the reviewers were resolved by an open discussion to develop a consensus.

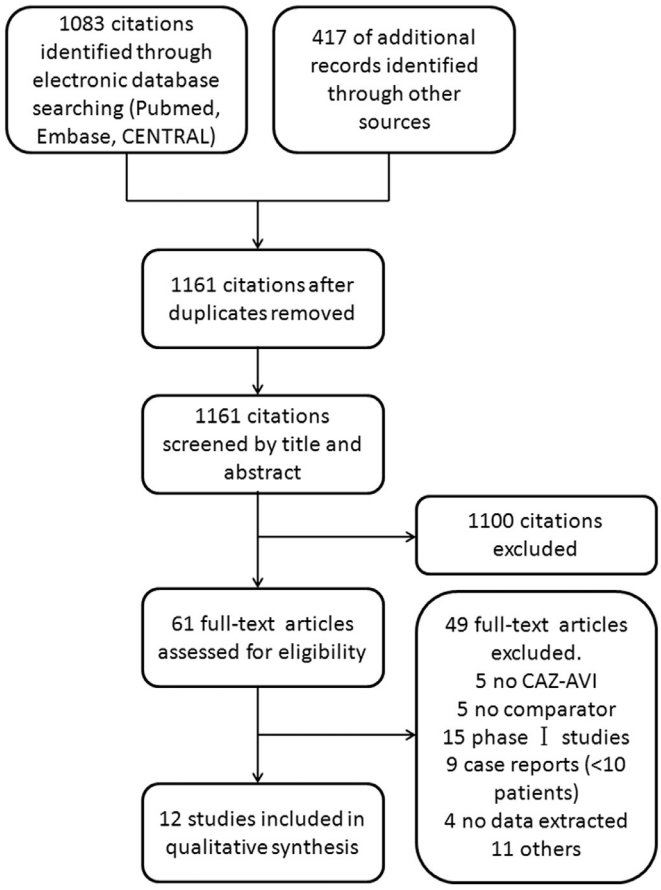


**Fig. 1.** Flow diagram of assessed and included studies. CENTRAL, Cochrane Central Register of Controlled Trials; CAZ-AVI, ceftazidime/avibactam.

### 2.5. Statistical analysis

Statistical analyses were performed according to the *Cochrane handbook for systematic reviews of interventions* [21]. Data were analysed using Stata 13.1 (StataCorp LP, College Station, TX). Treatment effects were calculated as risk ratio (RR) with 95% confidence interval (CI) for dichotomous data using a fixed- or random-effects model according to heterogeneity among studies. Heterogeneity was identified using the Cochrane $I^2$ statistic. An $I^2$ statistic of >50% was considered to indicate statistically significant heterogeneity. Subgroup analysis for clinical response, microbiological response and mortality were performed for different causative pathogens, infection types, renal status and illness severity levels. Sensitivity analyses were also conducted by excluding each study to investigate the confidence of the outcomes.

## 3. Results

Electronic and manual searches identified 1500 potential studies, from which 339 duplicates were removed. After the initial screening of titles and abstracts, 1100 studies were excluded. Thus, 61 full-text articles were assessed for eligibility. Finally, 12 studies

met the inclusion criteria. A total of 49 studies were excluded for the following criteria: no AVI (5 studies); no comparator (5 studies); phase 1 studies (15 studies); case reports (<10 patients) (9 studies); and other exclusion criteria (Fig. 1).

### 3.1. Description of the included studies

The characteristics of the 12 retrieved studies are described in Table 1, including 9 RCTs and 3 observational studies [16–18,22–30]. The outcomes were clinical response in 12 studies (4951 patients) [16–18,22–30], microbiological response in 7 studies (3426 patients) [17,18,26–30], mortality in 8 studies (3484 patients) [16–18,22,23,25,27,29], AEs in 9 studies (3921 patients) [16–18,22,23,27–30] and SAEs in 8 studies (3784 patients) [17,18,22,23,27–30].

The included studies involved 4951 patients with an age range of 43–68 years and proportion female ranged from 21–75%. The studies were multicentre studies (11 studies) [16–18,23–30] or single-centre (1 study) [22] studies. Meanwhile, nine studies were international [17,18,24–30], two studies originated from the USA [16,22] and one study was performed in Asia [23].

Nine studies involved CAZ 2000 mg + AVI 500 mg [17,18,23–29] and two studies involved CAZ 500 mg + AVI 125 mg [26,30]. Seven studies included concomitant therapy with CAZ-AVI [16,22–24,26,27,29], which were metronidazole (five studies) [23,24,26,27,29], gentamicin (two studies) [16,22] and additional anti-CRE agents including tigecycline, amikacin, trimethoprim/sulfamethoxazole, carbapenems or fosfomycin (one study) [16]. The duration of antimicrobial therapy was 5–14 days in most studies. The comparators were carbapenems, colistin, tigecycline, fosfomycin, aminoglycosides, $\beta$-lactamase-inhibiting $\beta$-lactams, carbapenem + aminoglycosides and carbapenem + colistin (Table 1).

### 3.2. Methodological quality of the included studies

Among the RCTs, allocation concealment and blinding to the outcome assessors were absent only in one study [28]. Considering observational studies, all of the NOS scores were >7, thus most of the studies were of low risk of bias (Supplementary Table S1).

### 3.3. Effect of interventions

Table 2 describes the evaluation of the quality of evidence generated using GRADEpro software [31], which is a modified table summarising the findings regarding the outcomes related to clinical response, microbiological response, mortality, AEs and SAEs.

### 3.4. Outcome measures

#### 3.4.1. Clinical response

When the causative pathogen and infection type were not taken into account, five studies [18,23,27,29,30] reported clinical response of CAZ-AVI compared with carbapenems in the clinical evaluable (CE) population at the test-of-cure (TOC) visit. Result of the meta-analysis by fixed-effect showed a non-inferior effect of CAZ-AVI (RR = 0.99, 95% CI 0.96–1.02) with no significant heterogeneity ($I^2 = 0\%$) (Fig. 2A). This outcome was consistent with clinical response reported in the CE population, the microbiological modified intent-to-treat (mMITT) population and the modified intent-to-treat population at TOC, at end-of-treatment (EOT) and at late follow-up (LFU) (Supplementary Fig. S1). In the subgroup analysis by causative pathogen, CRE infections treated with CAZ-AVI (four studies, 281 patients) [16,22,24,25] showed a significant benefit in clinical response (RR = 1.61, 95% CI 1.13–2.29; $I^2 = 61.7\%$). Moreover, in the analysis by infection type, two studies (140 patients) reported data on bloodstream infection (BSI) [22,25] and a notable difference in clinical response between the CAZ-AVI therapy group and the control group was documented (RR = 2.11, 95% CI 1.54–2.88; $I^2 = 0$). However, in patients with other types of infection and other pathogens (including ESBL-positive organisms and CAZ-non-susceptible organisms), regardless of renal function and illness severity level, comparable efficacy was seen between the CAZ-AVI group and the control group (Table 3).

#### 3.4.2. Microbiological response

Five studies [17,18,27,28,30] reported data on microbiological response when the causative pathogen was not considered. To pool these five trials, the variable for number of patients with microbiological response in the mMITT population at TOC was entered into Stata 13.1 software yielding a RR of 1.04 (95% CI 0.93–1.17) by random-effects model (Fig. 2B). This pooled analysis showed that the microbiological eradication ability of CAZ-AVI was as potent as carbapenems. However, significant heterogeneity was observed ($I^2 = 79.1\%$). A pooled analysis was also conducted in the mMITT population at EOT and LFU, revealing similar results to the TOC visit (Supplementary Fig. S2). In subgroup analysis by infection type, CAZ-AVI appeared to show a superior ability in microbiological eradication in cUTI: three studies (1186 patients) [17,28,30] generated a RR of 1.13 (95% CI 1.05–1.21; $I^2 = 43.6\%$) (Table 3).

#### 3.4.3. Mortality

A meta-analysis of the four studies [17,18,23,29] reporting data on mortality in the safety population was performed. However, this analysis indicated that mortality was equal in the CAZ-AVI group and the carbapenem group (RR = 1.30, 95% CI 0.84–2.01; $I^2 = 0$) (Fig. 3). Remarkably, CAZ-AVI demonstrated lower mortality than controls for infections caused by CRE (RR = 0.29, 95% CI 0.13–0.63; $I^2 = 0$) (Table 3).

#### 3.4.4. Safety

There were no significant difference in AEs and SAEs across the CAZ-AVI and control groups. Six studies (3656 patients) [17,18,23,27,29,30] reported AEs with a pooled RR of 1.05 (95% CI 0.99–1.12; $I^2 = 8.4\%$). Meanwhile, five studies (3521 patients) [17,18,23,27,29] reported SAEs with a pooled RR of 1.22 (95% CI 0.98–1.52; $I^2 = 0$) (Fig. 3).

### 3.5. Sensitivity analyses

To assess the influence of each included study, a sensitivity analysis was performed. After exclusion of each study, similar results for clinical response, microbiological response, mortality and safety were observed (Supplementary Table S3).

### 3.6. Publication bias

Funnel plots of reported studies showed that all plots exhibited roughly symmetrical inverted funnel shapes, indicating that publication bias was not a concern (Supplementary Fig. S3).

## 4. Discussion

This systematic review, which identified 12 studies including 4591 patients, supports the hypothesis that CAZ-AVI is as effective as carbapenems in the treatment of GNB infections. In particular, the investigations revealed significantly increased effects in the cure of infections caused by resistant organism, cUTI and BSI. Meanwhile, these published studies also suggested equivalent safety between CAZ-AVI and carbapenems.

**Table 1**
Characteristics of the included studies

| Source | Region | Design | No. (I/C) | Mean age (years) (I/C) | Sex (% female) | Type of infection | Causative pathogen(s) | Concomitant therapy | Dosage | Comparator/dosage | Antimicrobial duration | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vazquez et al., 2012 [30] | Multicentre (global) | RCT | 68/67 | 46/48 | 75/73 | cUTI | Mix | None | CAZ 500 mg + AVI 125 mg q8h | IPM-CIL 500 mg q6h | 7–14 days | Clinical response, microbiological response, AEs and SAEs |
| Lucasti et al., 2013 [29] | Multicentre (global) | RCT | 101/102 | 43/43 | 31/21 | cIAI | Mix | MTR | CAZ 2000 mg + AVI 500 mg q8h | MEM 1000 mg q8h | 5–14 days | Clinical response, microbiological response, AEs, SAEs and mortality |
| Carmeli et al., 2016 [28] | Multicentre (global) | RCT | 165/168 | 63/62 | 45/45 | cUTI and cIAI | CAZ-NS Enterobacteriaceae and PA | None | CAZ 2000 mg + AVI 500 mg q8h | Best available therapy (CB, COL and TIG, combination) | 5–21 days | Clinical response, microbiological response, AEs and SAEs |
| Wagenlehner et al,. 2016 [17] | Multicentre (global) | RCT | 393/417 | 51/53 | 69/70 | cUTI | Mix | None | CAZ 2000 mg + AVI 500 mg q8h | DOR 500 mg q8h | 5–14 days | Clinical response, microbiological response, AEs, SAEs and mortality |
| Mendes et al., 2016 [26] | Multicentre (global) | RCT | 86/90 | N/A | N/A | cUTI and cIAI | GNB | MTR for cIAI | CAZ 500 mg + AVI 125 mg q8h for cUTI; CAZ 2000 mg + AVI 500 mg q8h for cIAI | IPM-CIL 500 mg q6h; MEM 1000 mg q8h | 5–14 days | Clinical response, microbiological response |
| Mazuski et al., 2016 [27] | Multicentre (global) | RCT | 520/523 | 50/50 | 37/36 | cIAI | Mix | MTR | CAZ 2000 mg + AVI 500 mg q8h | MEM 1000 mg q8h | 5–14 days | Clinical response, microbiological response, AEs, SAEs and mortality |
| Mendes et al., 2017 [24] | Multicentre (global) | RCT | 413/410 | N/A | N/A | cIAI | Aerobic GNB | MTR | CAZ 2000 mg + AVI 500 mg q8h | MEM 1000 mg q8h | 5–14 days | Clinical response |
| Qin et al., 2017 [23] | Multicentre (Asia) | RCT | 214/217 | 48/48 | 34/30 | cIAI | Mix | MTR | CAZ 2000 mg + AVI 500 mg q8h | MEM 1000 mg q8h | 5–14 days | Clinical response, AEs, SAEs and mortality |
| Torres et al., 2018 [18] | Multicentre (global) | RCT | 356/370 | 62/62 | 25/26 | HAP | Mix | None | CAZ 2000 mg + AVI 500 mg q8h | MEM 1000 mg q8h | 7–14 days | Clinical response, microbiological response, AEs, SAEs and mortality |
| Castón et al., 2017 [25] | Multicentre (global) | Retrospective study | 8/23 | 61/59 | 50/35 | Bacteraemia | CRE | N/A | CAZ 2000 mg + AVI 500 mg q8h, doses adjusted according to renal function | Other treatments (CB, AG, BLIBL, TIG, FOS, COL) | N/A | Clinical response and mortality |
| Shields et al., 2017 [22] | Single centre (USA) | Retrospective study | 13/90 | 66/60 | 46/43 | Bacteraemia | CRKP | GEN | N/A | CB+AG, CB+COL, other treatments | N/A | Clinical response, AEs, SAEs and mortality |
| van Duin et al., 2018 [16] | Multicentre (USA) | Prospective observational study | 38/99 | 57/63 | 39/58 | Mix | CRE | TIG, AG, GEN, CB, FOS, SXT | N/A | COL | N/A | Clinical response, AEs and mortality |

I/C, intervention/control; RCT, randomised controlled trial; cUTI, complicated urinary tract infection; CAZ, ceftazidime; AVI, avibactam; q8h, every 8 h; IPM-CIL, imipenem/cilastatin; q6h, every 6 h; AEs, adverse events; SAEs, serious adverse events; cIAI, complicated intra-abdominal infection; MTR, metronidazole; MEM, meropenem; CAZ-NS, ceftazidime-non-susceptible; PA, *Pseudomonas aeruginosa*; CB, carbapenems; COL, colistin; TIG, tigecycline; DOR, doripenem; N/A, not available; GNB, Gram-negative bacteria; HAP, nosocomial pneumonia; CRE, carbapenem-resistant Enterobacteriaceae; AG, aminoglycosides; BLIBL, $\beta$-lactamase-inhibiting $\beta$-lactams; FOS, fosfomycin; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; GEN, gentamicin; SXT, trimethoprim/sulfamethoxazole.

**Table 2**
Summary of the outcome findings for ceftazidime/avibactam (CAZ-AVI) versus other treatment for patients with infectious diseases

| Outcome | RR (95% CI) | No. of participants (no. of studies) | Quality of evidence (GRADE) [a] |
|---|---|---|---|
| Clinical response | 0.99 (0.96–1.02) | 1955 (5 studies) | ⊕⊕⊕⊕, high [b] |
| Microbiological response | 1.04 (0.93–1.17) | 2364 (5 studies) | ⊕⊕⊕⊖, moderate [b,c,d] |
| Mortality | 1.3 (0.84–2.01) | 2463 (4 studies) | ⊕⊕⊕⊕, high [b] |
| AEs | 1.05 (0.99–1.12) | 3656 (6 studies) | ⊕⊕⊕⊕, high [b] |
| SAEs | 1.22 (0.98–1.52) | 3521 (5 studies) | ⊕⊕⊕⊕, high [b] |

RR, risk ratio; CI, confidence interval; AE, adverse event; SAE, serious adverse event.

[a] GRADE Working Group grades of evidence: high quality, further research is very unlikely to change confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; very low quality, very uncertain about the estimate.

[b] Most of the studies included were funded by AstraZeneca, which may lead to publication bias. None the less, the quality of the evidence was not downgraded considering the overall risk of bias was low.

[c] The intervention group allocation was not concealed, whilst the outcome assessment was not blinded in some included studies. However, the overall risk of bias was considered low.

[d] There was serious heterogeneity among the studies included in the analysis of microbiological response ($I^2 = 79.1\%$). Overall, we decided to downgrade by one level when considering these issues along with inconsistency.

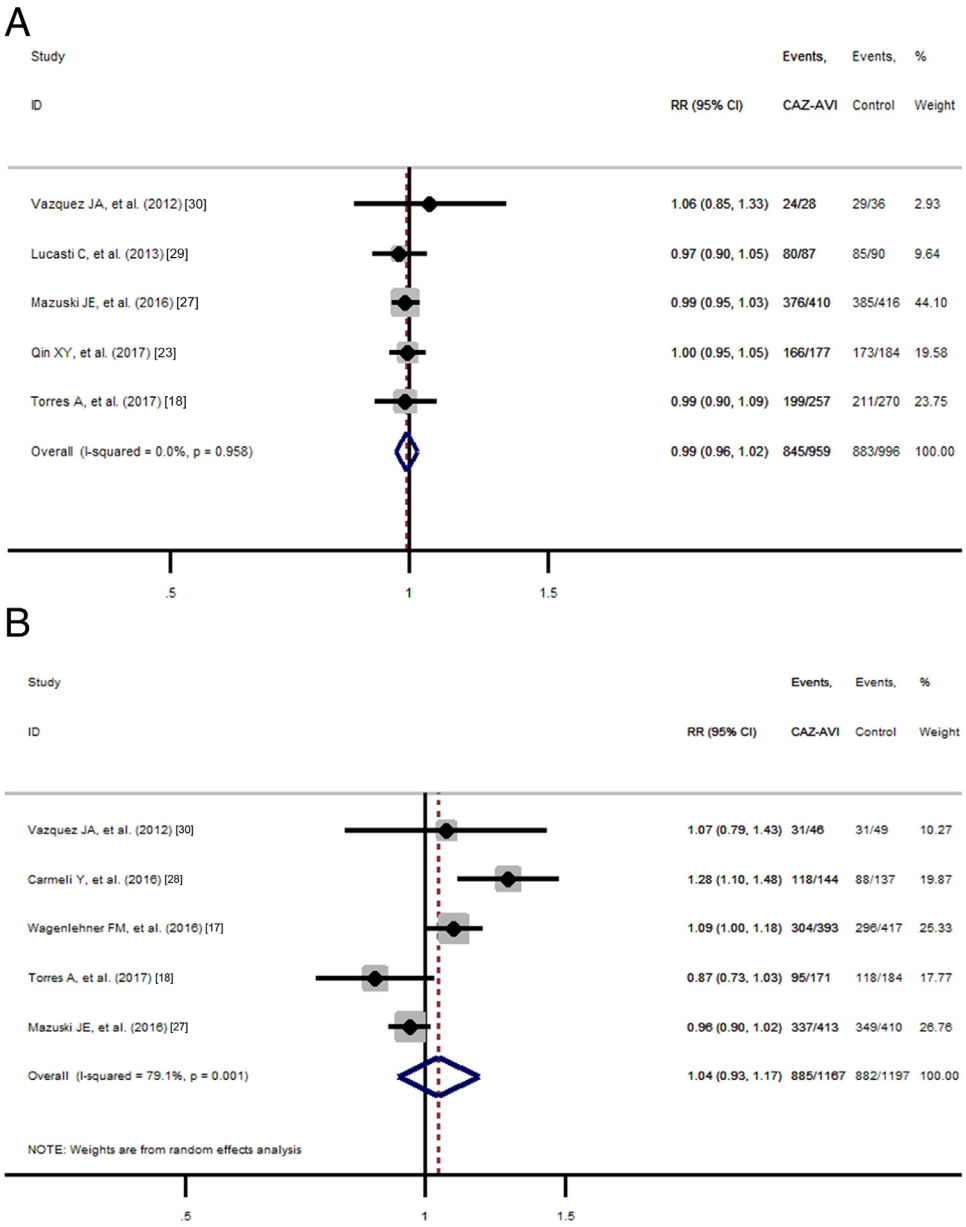


**Fig. 2.** Effects of ceftazidime/avibactam (CAZ-AVI) compared with other treatments at test-of-cure visit: (A) clinical response of CAZ-AVI in clinically evaluable population; and (B) microbiological response of CAZ-AVI in microbiologically modified intent-to-treat population. RR, risk ratio; CI, confidence interval.

**Table 3**
Subgroup analysis of clinical response, microbiological response and mortality in the ceftazidime/avibactam (CAZ-AVI)-treated group compared with other treatments

| Subgroup | Clinical response | | | Microbiological response | | | Mortality | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR (95% CI) | No. of participants (no. of studies) | $I^2$ | RR (95% CI) | No. of participants (no. of studies) | $I^2$ | RR (95% CI) | No. of participants (no. of studies) | $I^2$ |
| Pathogens | | | | | | | | | |
| CRE | **1.61 (1.13–2.29)** | 281 (4) | 61.7 | – | – | – | **0.29 (0.13–0.63)** | 277 (3) | 0 |
| ESBL-positive organisms | 1.00 (0.90–1.12) | 172 (2) | 0 | 1.18 (0.67–2.07) | 24 (1) | 0 | – | – | – |
| CAZ-NS organisms | 0.99 (0.91–1.07) | 319 (3) | 0 | 1.00 (0.88–1.13) | 332 (4) | 0 | – | – | – |
| Infections | | | | | | | | | |
| cIAI | 0.95 (0.91–1.00) | 1313 (4) | 0 | 0.96 (0.91–1.01) | 967 (2) | 0 | 1.68 (0.41–6.96) | 1693 (3) | 0 |
| cUTI | 1 (0.96–1.03) | 1155 (3) | 0 | **1.13 (1.05–1.21)** | 1186 (3) | 43.6 | – | – | – |
| BSI | **2.11 (1.54–2.88)** | 140 (2) | 0 | – | – | – | 0.35 (0.12–1.05) | 140 (2) | 0 |
| HAP/VAP | 0.943 (0.859–1.035) | 726 (1) | 0 | 0.8669 (0.729–1.029) | 355 (1) | 0 | 1.26 (0.797–1.993) | 808 (1) | 0 |
| Renal status [a] | | | | | | | | | |
| Normal renal function | 0.98 (0.95–1.01) | 2622 (4) | 0 | – | – | – | – | – | – |
| Moderate renal function | 0.82 (0.60–1.11) | 209 (4) | 65.9 | – | – | – | – | – | – |
| Augmented renal function | 1.04 (0.88–1.22) | 108 (1) | 0 | – | – | – | – | – | – |
| APACHE II score | | | | | | | | | |
| <10 | 0.99 (0.94–1.04) | 462 (2) | 0 | – | – | – | – | – | – |
| 10–30 | 1.13 (0.81–1.56) | 876 (4) | 85.3 | – | – | – | – | – | – |

RR, risk ratio; CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum $\beta$-lactamase; CAZ-NS, ceftazidime-non-susceptible; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; BSI, bloodstream infection; HAP, hospital-acquired pneumonia; VAP, ventilator-acquired pneumonia; APACHE, Acute Physiology and Chronic Health Evaluation.

[a] Normal renal function, creatinine clearance ($CL_{Cr}$) >50 mL/min; moderate renal function, $CL_{Cr}$ >16 to ≤50 mL/min; and augmented renal function, $CL_{Cr}$ ≥150 mL/min.

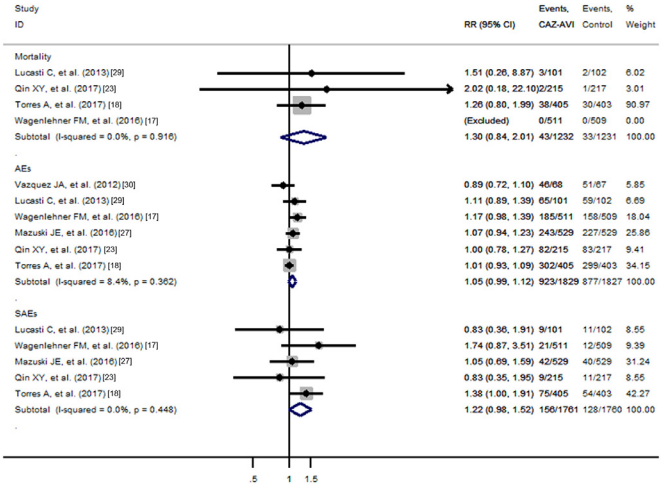


**Fig. 3.** Safety of ceftazidime/avibactam (CAZ-AVI) compared with other treatments in the safety population, including mortality, adverse events (AEs) and serious adverse events (SAEs). RR, risk ratio; CI, confidence interval.

GNB are a common cause of complicated infectious diseases, including cUTI, cIAI, pneumonia and BSI [32–34]. Nevertheless, resistance to carbapenems in GNB has increased dramatically, probably correlated with extensive carbapenem use [35,36]. CRE are one of the most important menaces to global health owing to poor clinical outcomes, including mortality rates as high as 40–65% [5,37,38]. Frankly, multiple currently available agents are not feasible, such as colistin and tigecycline [39,40]. It is therefore important to find more efficacious and safer alternatives to manage this emerging need.

Responding to this threat, three novel carbapenemase inhibitors have been developed to support current antimicrobial agents [41]. These inhibitors are AVI, relebactam and vaborbactam, with high affinity for carbapenemases except metallo-$\beta$-lactamases [35]. Numerous trials have demonstrated favourable outcomes with new $\beta$-lactamase inhibitor co-formulations, including CAZ-AVI, imipenem/relebactam and meropenem/vaborbactam [23,42,43]. The present review focused on studies of CAZ-AVI, the first approved antimicrobial combination to utilise AVI.

In the present meta-analysis, CAZ-AVI was shown to possess comparable ability to carbapenems in the cure of serious GNB infections, consistent with previous findings [14,17,18,27]. As AVI is mainly excreted unchanged in the urine, resulting in high urinary drug concentrations [44], the bacterial eradication ability of CAZ-AVI is superior to carbapenems when cUTIs are taken into consideration [28]. Likewise, for patients with BSI, the CAZ-AVI treatment group also showed a favourable clinical outcome despite the small sample size, leading to a low quality of evidence to make a recommendation. Moreover, a non-inferior result in patients with HAP/VAP may be explained by the fact that penetration of CAZ-AVI in the epithelial lining fluid is only 30% of the plasma concentration, whilst penetration of meropenem ranges from 3.7–178% [45,46]. Across the causative pathogens, CAZ-AVI sustains comparable ability to carbapenems in the treatment of ESBL-positive and CAZ-non-susceptible organisms. In particular, the CAZ-AVI group showed superior outcomes in the treatment of CRE compared with other therapies owing to the high affinity and expanded spectrum of AVI for carbapenemases [13,47]. Therefore, CAZ-AVI can be used as a salvage therapy after carbapenems in treating complicated GNB infections.

The present review found that AE and SAE rates in the CAZ-AVI-treated group were generally similar to comparators, consistent with previous studies reporting that AVI was well tolerated at multiple dose ranges [48,49]. Consequently, AVI brought no extra harm to patients.

Currently, numerous studies have been completed without results available to date. Amongst these studies, NCT01281462 investigated ceftaroline fosamil and NXL104 in adults with cUTI [50], and NCT02655419 determined the pharmacokinetics and safety of

ATM-AVI in hospitalised adults with cIAI [10], whilst NCT02497781 [51] and NCT02475733 [52] evaluated the efficacy of CAZ-AVI in adolescents and infants. Furthermore, one study (NCT03329092) is ongoing to determine the efficacy of ATM-AVI for the treatment of serious GNB infections [53]. It will be necessary to update this review over the next 2 years as these projects are completed.

This review process should have minimal bias. An extremely broad search strategy was used in conjunction with the ClinicalTrial.gov website to capture as many studies as possible. This methodology indicated that both completed and ongoing RCTs and cohort studies regarding AVI co-formulations have been found. Two authors then independently selected relevant articles from this list and met to discuss a final list of included studies. Overall, the entire risk of methodological bias was low.

The present review has some limitations that should be considered. First, the methodology utilised to evaluate clinical success and microbiological eradication was distinct in each study, e.g. Vazquez et al. reported clinical response analysed in the CE population [30], whilst Carmeli et al. presented clinical response analysed in the mMITT population [28]. Therefore, it was not possible to generate meta-analysis results from these two studies. Second, confounding by indications was also a potential issue, resulting in recommended indications of CAZ-AVI being hard to interpret. Third, as there were variations in concomitant therapy and duration, a standard regimen was therefore impossible to perform. Finally, data on CRE were mainly hampered by a few cohort studies. The lack of RCTs on this issue was obvious, calling for future research efforts to fill these gaps.

## 5. Conclusion

Overall, CAZ-AVI showed comparable efficacy to carbapenems in complicated infectious diseases such as cUTI, cIAIs and HAP/VAP, with a similar safety profile. This agent replenishes the current candidate therapy for multidrug-resistant GNB pathogens, particularly ESBL-producing organisms and CRE, which is likely to be its principal role in therapy. Nevertheless, it will be vital to conduct more clinical trials to explore indications other than those approved, such as BSI, in order to identify whether this co-formulation will be a feasible option for these infections. Conclusively, it is promising to promote CAZ-AVI in treating patients with complicated infectious illnesses, especially those caused by multidrug-resistant bacteria.

## Acknowledgments

The authors thank Jun Xia of the ‘Cochrane Schizophrenia Group for support and advice. The authors are also grateful to Yu-Xiao Deng (Surgical Intensive Care Unit, Shanghai Jiao Tong University, Shanghai, China) for drug information. In addition, the authors appreciate all of the authors of the original articles.

## Funding

This work was supported by the Program for Key Discipline of Clinical Pharmacy of Shanghai [2016-40044-002] and the Program for Key but Weak Discipline of Shanghai Municipal Commission of Health and Family Planning [2016ZB0304].

## Competing interests

None declared.

## Ethical approval

Not required.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.07.004.

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