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Short Communication

Ceftazidime/avibactam versus carbapenems for the treatment of infections caused by Enterobacteriaceae: A meta-analysis of randomised controlled trials

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ABSTRACT

Objectives: Enterobacteriaceae are the most common pathogens in nosocomial and community infections. Carbapenems are widely used as the most effective antibacterial agents against Enterobacteriaceae. However, increasing use of carbapenems has accelerated the emergence of carbapenem-resistant Enterobacteriaceae. This was a systematic review of recently published data to compare the clinical efficacy and safety of ceftazidime/avibactam (CAZ-AVI) and carbapenems in the treatment of Enterobacteriaceae infections. Moreover, we also attempted to assess whether it is feasible to treat Enterobacteriaceae infections with CAZ-AVI instead of carbapenems.

Methods: A comprehensive search was performed using Medline, Embase and Cochrane Library for randomised controlled trials (RCTs) comparing the efficacy and safety of CAZ-AVI and carbapenems for the treatment of Enterobacteriaceae infections. Clinical success, microbiological success, adverse events (AEs), serious adverse events (SAEs) and mortality were assessed as the main outcomes.

Results: Three RCTs (1186 patients) were included in the meta-analysis. The meta-analysis showed that there were no significant differences between CAZ-AVI and carbapenems in clinical success [risk difference (RD) = 0.00, 95% confidence interval (CI) −0.06 to 0.06; $P = 0.99$], microbiological success (RD = 0.07, 95% CI −0.04 to 0.18; $P = 0.21$) or AEs (RD = 0.00, 95% CI −0.02 to 0.03; $P = 0.81$). SAEs with CAZ-AVI were numerically higher than with carbapenems (RD = 0.02, 95% CI −0.00 to 0.04; $P = 0.06$).

Conclusion: CAZ-AVI is comparable with carbapenems in efficacy and safety for Enterobacteriaceae infections. More high-quality and large-scale RCTs are needed to further confirm the safety of CAZ-AVI. [PROSPERO ID: CRD42019116685.]

1. Introduction

The family Enterobacteriaceae is a group of Gram-negative, facultative anaerobes and non-spore-forming bacilli including *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae* and *Proteus mirabilis*, among others. Carbapenems such as imipenem and meropenem are first-line antimicrobial agents for the treatment of serious nosocomial infections caused by multidrug-resistant clinical bacterial isolates belonging to the family Enterobacteriaceae [1]. Carbapenems bind to critical penicillin-binding proteins, disrupting the growth and structural integrity of the bacterial cell wall. The enhanced Gram-negative coverage and stability of carbapenems against extended-spectrum β-lactamases (ESBLs) make them an effective treatment option [2]. However, increasing use of carbapenems has resulted in selection pressure for carbapenem resistance. Previous studies have reported the correlation between carbapenem exposure and antimicrobial resistance [3]. Carbapenem-resistant Enterobacteriaceae (CRE) have spread widely in a short time, and infections caused by these organisms are associated with crude mortality rates of up to 70% [4]. As an important medical problem, the spread of CRE has become a major global public-health threat. Therefore, it is urgently required to develop emerging therapies and alternative agents in order to prevent the spread of antimicrobial resistance.

The β-lactam antibiotics have gradually lost their value against CRE. However, β-lactams are still therapeutically effective owing to the complementary advantage in structural biology of β-lactam/β-lactamase inhibitors (BL/BLIs). To deal with the rise in resistance, one strategy is to re-evaluate BL/BLI combinations such

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as amoxicillin/clavulanic acid, piperacillin/tazobactam and ceftazidime/avibactam (CAZ-AVI). Avibactam is a novel non-β-lactam β-lactamase inhibitor that restores the activity of ceftazidime against the majority of organisms producing β-lactamases, except metallo-β-lactamases. CAZ-AVI has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of complicated intra-abdominal infections, complicated urinary tract infections (cUTIs), pneumonia (EMA only), and infections due to aerobic Gram-negative organisms in adult patients with limited treatment options [5,6]. An increasing number of experts have supported that BL/BLIs can be used for the treatment of carbapenem-resistant Gram-negative pathogens [7], and various combination regimens are in the process of being evaluated [8]. However, the therapeutic effects of BL/BLI combinations against infections caused by Enterobacteriaceae remain largely unexplored, especially for CAZ-AVI.

In the present study, a meta-analysis of available randomised controlled trials (RCTs) was conducted to further explore the feasibility of using CAZ-AVI as an alternative antibiotic to carbapenems for the treatment of Enterobacteriaceae infections.

2. Materials and methods

2.1. Data sources

All RCTs comparing BL/BLI combinations versus carbapenems for the treatment of Enterobacteriaceae infections were searched from the PubMed, Embase and Cochrane Library databases, starting from their inception to December 2018. Articles published in languages other than English were not included in the present review. Search terms were combined as follows: ('carbapenem' OR 'meropenem' OR 'imipenem' OR 'ertapenem' OR 'doripenem' OR 'biapenem' OR 'panipenem') AND ('β-lactamase inhibitor' OR 'beta-lactamase inhibitor' OR 'tazobactam' OR 'avibactam' OR 'relebactam' OR 'sulbactam' OR 'clavulanate') AND ('Enterobacteriaceae' OR 'Gram-negative bacilli' OR '*Enterobacter*' OR '*Klebsiella*' OR '*Serratia*' OR '*Escherichia*' OR '*Citrobacter*'). Any published articles reporting patients with Enterobacteriaceae infections were considered eligible. The reference lists of all included articles and other relevant reviews commenting on novel BL/BLIs were also searched for possibly eligible trials. Previously published systematic reviews were reviewed to identify any additional studies that might have been missed in the primary literature search.

2.2. Study selection

Eligible studies included all available published RCTs that compared CAZ-AVI with carbapenems for the treatment of Enterobacteriaceae infections or mixed infections based on Enterobacteriaceae (Enterobacteriaceae bacteria infecting >90% of the population) in adult patients (>18 years), with carbapenems and CAZ-AVI both administered as monotherapy. Studies on paediatric patients, combination therapy and non-Enterobacteriaceae infections were excluded.

2.3. Qualitative assessment

The Cochrane Collaboration 'risk of bias' tool was used to assess the methodological quality of included RCTs, including the following seven modules: sequence generation (selection bias); allocation sequence concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other potential sources of bias. The risk of bias was assessed by classifying each item separately as low, unclear or high risk.

2.4. Data extraction

Two investigators (HYC and JW) independently performed the literature search and extracted the data to ensure the reliability of data. Any disagreement was resolved by discussion, and was decided by the lead author (YC) if necessary. All data were recorded in a pre-designed table. The following data were extracted and recorded: name of first author; publication year; types of primary infection; bloodstream infection (BSI) or not; population size; treatment regimens; organisms; resistance phenotypes; β-lactamase production; and outcome.

2.5. Outcome analysis

The main outcomes of this meta-analysis were efficacy outcomes, including clinical success (defined as complete resolution or substantial improvement of signs and symptoms of the index infection, such that no further antibacterial therapy was required) and microbiological success (defined as pathogen eradication), and safety outcomes, including adverse events (AEs), serious adverse events (SAEs) and mortality.

2.6. Data analysis and statistical methods

Data were analysed using Review Manager (RevMan) 5.3. The risk difference (RD) with 95% confidence interval (CI) was used for overall effect and statistical heterogeneity. A P-value of <0.05 was considered statistically significant, indicating that the intervention factor studied was either protective or harmful. Heterogeneity was identified using the Cochrane I^2 statistic, and a P-value <0.10 or I^2 value $>50\%$ was considered to indicate statistically significant heterogeneity. A random-effects model was selected to analyse the data extracted from published reports.

3. Results

3.1. Study identification

A total of 2674 articles were initially retrieved from the literature search. Following removal of duplicates and excluding studies that did not meet the inclusion criteria, only three studies were included in the meta-analysis [9–11]. Table 1 summarises the basic characteristics of the included studies. All included studies were RCTs comprising 1186 patients. CAZ-AVI was administrated at CAZ doses ranging from 0.5 g to 2 g given by infusion every 8 h. For individuals with kidney injury, the dosage was adjusted based on creatinine clearance. The three RCTs included patients with cUTIs or/and acute pyelonephritis, and the vast majority of pathogens (90%) were Enterobacteriaceae.

3.2. Assessment of study quality

The Cochrane Collaboration 'risk of bias' tool was used to assess the quality of the studies. All RCTs [9–11] were designed with a low risk of random sequence generation. Two trials [10,11] were designed in a double-blind model with low risks for performance bias and detection bias. Regarding attrition bias, one study [11] possessed a high risk with a relatively large amount of missing population data and the other two trials [9,10] were assessed as low risk. All included studies [9–11] were registered with clinical trial registration numbers.

3.3. Clinical and microbiological success

Meta-analysis of the three studies including 1186 patients [9–11] demonstrated that there was no significant difference in the

Table 1
Basic characteristics of the included randomised controlled trials (RCTs).

First author/year	Primary infection(s)	BSI (*n*)	Organism	Resistance phenotype	β-Lactamase	Sample		Mean age (years)		Treatment regimen		Outcomes
						BL/BLI	Carb	BL/BLI	Carb	BL/BLI	Carb	
Wagenlehner, 2016 [10]	cUTIs	NA	Enterobacteriaceae Non-Enterobacteriaceae (4.8% *)	NA	NA	393	417	51.4	53.3	CAZ-AVI	DOR	[b,c,e]
Carmeli, 2016 [9]	cUTIs	BSI (10) Non-BSI (271)	Enterobacteriaceae Non-Enterobacteriaceae (6.8% *)	CAZ-resistant	NA	144	137	64.3	61.3	2000 mg CAZ plus 500 mg AVI q8h i.v.	DOR (11), ETP (1), ETP sodium (2), IPM (76), MEM (57), other (6)	[a,b,c,d]
Vazquez, 2012 [11]	Acute pyelonephritis/cUTIs	BSI (7) Non-BSI (128)	*Escherichia coli* *Enterobacter cloacae* *Proteus mirabilis* *Citrobacter koseri* Non-Enterobacteriaceae (1.5% *)	NA	NA	46	49	46.4	48.2	CAZ 500 mg plus vi 125 mg q8h i.v.	IPM-CIL 500 mg q6h iv	[b,c,d,e]

BSI, bloodstream infection; BL/BLI, β-lactam/β-lactamase inhibitor; Carb, carbapenem; cUTI, complicated urinary tract infection; NA, not available; CAZ, ceftazidime; AVI, avibactam; DOR, doripenem; q8h, every 8 h; i.v., intravenous; ETP, ertapenem; IPM, imipenem; MEM, meropenem; CIL, clastatin; q6h, every 6 h.

* Proportion of patients infected with non-Enterobacteriaceae.

[a] Mortality.

[b] Clinical success.

[c] Microbiological success.

[d] Adverse events.

[e] Serious adverse events.

rate of clinical success between the two groups treated with CAZ-AVI versus carbapenems (RD = 0.00, 95% CI −0.06 to 0.06; $P = 0.99$) (Fig. 1a). Microbiological success of treatment was provided in three trials comprising 1186 subjects [9–11]. Result of the meta-analysis by random-effects model also showed no statistically significant difference in microbiological success (RD = 0.07, 95% CI −0.04 to 0.18; $P = 0.21$) (Fig. 1b).

3.4. Adverse events and serious adverse events

Meta-analysis of two trials comprising 467 subjects [9,11] demonstrated no difference in AEs (RD = 0.00, 95% CI −0.02 to 0.03; $P = 0.81$) (Fig. 2a). SAEs were reported in two studies comprising 1153 subjects [10,11] and there was no statistically significant difference in the incidence of SAEs between two groups (RD = 0.02, 95% CI −0.00 to 0.04; $P = 0.06$) (Fig. 2b).

3.5. Mortality

Only one study comprising 332 patients [9] reported mortality and showed no statistically significant difference between the two groups (RD = 0.00, 95% CI −0.03 to 0.03; $P = 0.98$).

4. Discussion

In this systematic review, three studies including 1186 patients [9–11] were analysed to compare the efficacy and safety of CAZ-AVI with classic carbapenem regimens for the treatment of infections caused by Enterobacteriaceae.

With respect to the efficacy indicators, including clinical and microbiological success, there was no significant difference detected between the two groups. These results show that, at least in terms of effectiveness, CAZ-AVI is similar to carbapenems for the treatment of Enterobacteriaceae infections and could provide an alternative to carbapenems. The classical β-lactamase inhibitors are generally active against class A β-lactamase enzymes, whereas they do not have activity against carbapenemases and have no clinically useful activity against class C enzymes such as AmpC. In addition, they do not have activity against most class B or D enzymes. The emergence of inhibitor-resistant bacterial strains and the inefficient inhibitory activity of traditional β-lactam inhibitors against carbapenems lead to the development of the 'second-generation' β-lactamase inhibitors. The newer generations of β-lactamase inhibitors, including avibactam, were developed based on non-β-lactam structures and their spectrum of inhibition is extended to *K. pneumoniae* carbapenemase (KPC), an important class A carbapenemase [12]. Chen et al. demonstrated that the efficacy of CAZ-AVI is comparable with alternative antibiotics, including carbapenems, in various infections [13].

Regarding safety, there was no statistically significant difference between CAZ-AVI and carbapenems when mortality and the incidence of AEs and SAEs were assessed. Avibactam has a low potential for drug–drug interactions and its safety and tolerability have been established in multiple clinical studies during the development of CAZ-AVI, including in subjects with renal impairment and receiving drug combinations [14]. However, we found that although there was no statistically significant difference in safety between CAZ-AVI and carbapenem regimens, the incidence of SAEs with CAZ-AVI was numerically higher than with carbapenems. Even in some studies that support CAZ-AVI as an alternative to carbapenems, increased AEs have also been reported [14,15]. Sternbach et al. conducted a systematic review and meta-analysis of the efficacy and safety of CAZ-AVI and showed that CAZ-AVI was microbiologically as effective as carbapenems for the treatment of infections in a setting in which ~25% of Enterobacteriaceae were

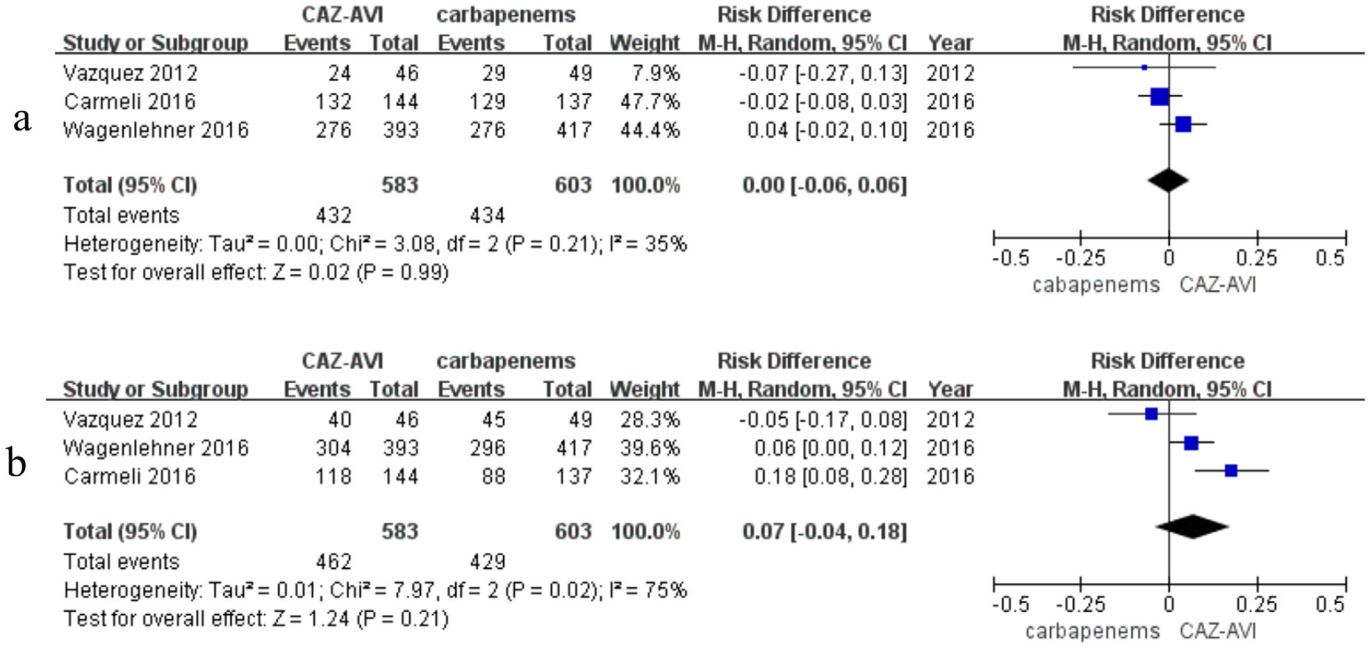

Fig. 1. Forest plots showing risk difference with 95% confidence interval (CI) of efficacy outcomes in a random-effects model for (a) clinical success; and (b) microbiological success of ceftazidime/avibactam (CAZ-AVI) versus carbapenems.

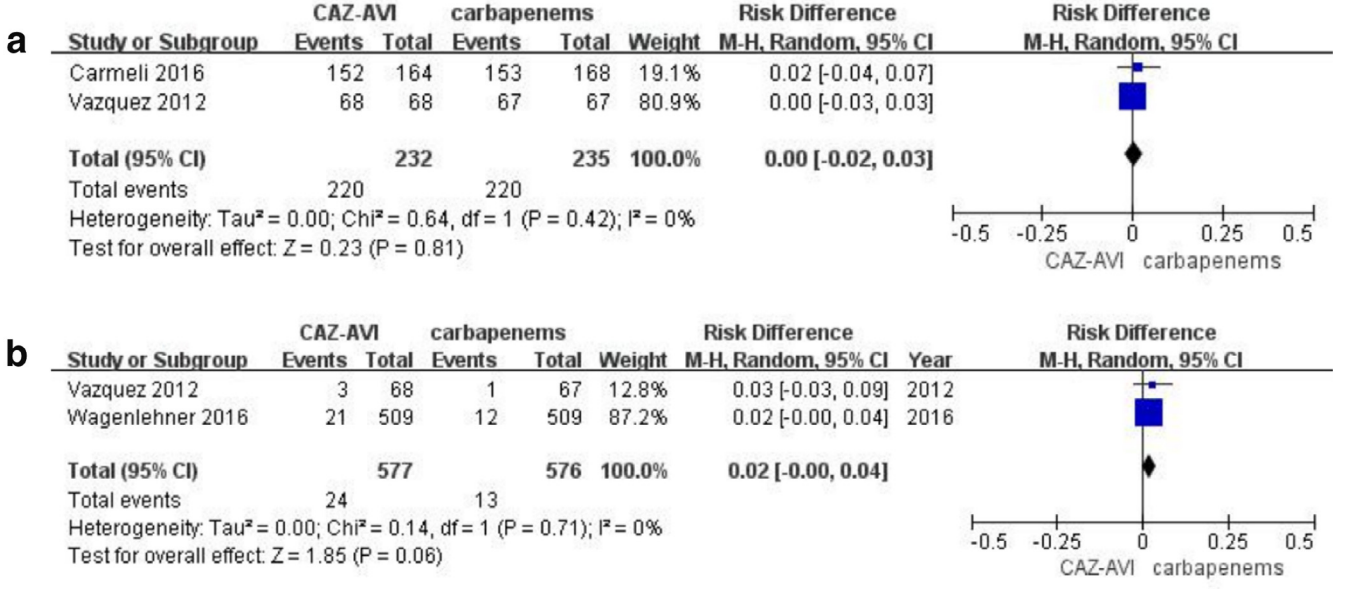

Fig. 2. Forest plots showing risk difference with 95% confidence interval (CI) of safety outcomes in a random-effects model for (a) adverse events and (b) serious adverse events with ceftazidime/avibactam (CAZ-AVI) versus carbapenems.

ESBL-positive, whilst the safety of the drug should be further evaluated owing to a higher rate of SAEs compared with carbapenems [16].

Several limitations should be taken into consideration when interpreting the results of this meta-analysis. First, although the included three studies involved patients with the same primary infection type, i.e. UTI, a few patients developed BSI; 10/281 (3.6%) in the study by Carmeli et al. [9] and 7/135 (5.2%) in the study by Vazquez et al [11]. Due to lack of original data, we were unable to compare the efficacy and safety of CAZ-AVI with carbapenems for these BSI patients. Second, since most studies did not provide information regarding antimicrobial resistance or enzyme production, the effect of CAZ-AVI and carbapenems against Enterobacteriaceae with different resistance phenotypes cannot be evaluated. Finally, changes in the resistance of pathogens following antibiotic exposure were not available from all of the included studies. Therefore, we were unable to assess the impact of CAZ-AVI and carbapenems on resistance.

Collectively, the present meta-analysis showed that CAZ-AVI is comparable with carbapenems in efficacy and safety for the treatment of Enterobacteriaceae infections. In addition, although the difference was not significant, CAZ-AVI showed a numerically higher risk of SAEs compared with carbapenems. Until more RCTs become available, the higher risk of AEs should be taken into account when CAZ-AVI is applied as an alternative regimen for the treatment of Enterobacteriaceae infections.

Declarations

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Ethical approval: Not required.

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