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Efficacy of ceftazidime/avibactam in monotherapy or combination therapy against carbapenem-resistant Gram-negative bacteria: A meta-analysis

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ABSTRACT

Clinicians may use ceftazidime/avibactam in combination with other active agents to treat infections due to carbapenem-resistant organisms, although no conclusive data support this practice. This meta-analysis compared the efficacy of ceftazidime/avibactam as monotherapy or combination therapy against infections due to carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPa). An online literature search was conducted to identify observational studies published as full papers and indexed up to February 2019 comparing the efficacy, in terms of mortality and microbiological cure rates, of ceftazidime/avibactam monotherapy or combination therapy with other active agents for infections due to CRE or CRPa. The relative risk (RR) of mortality and microbiological eradication was estimated based on pooled data from all eligible studies. Eleven studies were included in the meta-analysis accounting for 396 subjects, of whom 202 received combination therapy. The mortality rate was 38.1% for combination therapy and 30.9% for monotherapy (RR = 1.18, 95% CI 0.88–1.58; $P = 0.259$). Similarly, no difference was found between the two groups when analysing the rate of microbiological cure (64.9% for combination therapy vs. 63.4% for monotherapy; RR = 1.04, 95% CI 0.85–1.28, $P = 0.705$). Moreover, no difference was observed for both outcomes when patients infected with *P. aeruginosa* were excluded from the analysis. This meta-analysis suggests that use of ceftazidime/avibactam in monotherapy or combination therapy for infections due to CRE or CRPa could show a similar effect on mortality and microbiological cure rates. Studies on larger samples are needed to address this important issue.

1. Introduction

During the last few decades, the spread of antimicrobial resistance has become a global health problem, with infection by multidrug-resistant micro-organisms representing one of the main causes of hospital morbidity and mortality [1].

Ceftazidime/avibactam, a novel β-lactam/β-lactamase inhibitor combination, displays in vitro activity against bacteria producing class A [including *Klebsiella pneumoniae* carbapenemase (KPC)] as well as some class D carbapenemases and has been approved by the European Medicines Agency (EMA) for infections due to Gram-negative bacteria with limited treatment options [2]. However, no conclusive data are available in the literature regarding whether ceftazidime/avibactam can be used alone or in combination therapy against carbapenem-resistant Gram-negative bacteria. In fact, although combination therapy may be associated with a greater selective pressure and thus the development of antimicrobial resistance, in clinical practice several clinicians have used it in combination, also considering recent data on the selection of mutations in bla_{KPC} genes conferring resistance to ceftazidime/avibactam [3].

The aim of this meta-analysis was to compare the efficacy, in term of survival and microbiological eradication, of ceftazidime/avibactam as monotherapy or combination therapy against infections due to carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPa).

2. Methods

2.1. Search strategy and selection criteria

Two researchers (LO and GDC) conducted a comprehensive computerised literature search using Medline, Google Scholar and

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the Cochrane Library until February 2019, involving both Medical Subject Headings (MeSH) terminology and relevant keywords for search strings, to identify original reports published as full papers comparing the efficacy of ceftazidime/avibactam used in monotherapy or combination therapy with other agents displaying in vitro activity against the isolated strains for infections due to CRE or CRPa. The following items were used to search for relevant studies: 'ceftazidime' and 'avibactam'. In addition, the reference lists of all studies meeting the inclusion criteria as well as published review articles were manually searched to identify any other study that might merit inclusion in the meta-analysis.

All included studies had to fulfil the following characteristics and inclusion criteria: (i) reported sufficient data to calculate the relative risk (RR) and 95% confidence interval (CI) for the occurrence of the endpoint evaluated (mortality or microbiological failure) in patients treated with ceftazidime/avibactam as monotherapy or combination therapy for infections due to CRE or CRPa; (ii) case–control studies, cohort studies or case series; (iii) available as full-text; (iv) in English language; and (v) published online and indexed up to February 2019. Meta-analyses, letters, reviews, meeting abstracts and editorial comments were excluded. The authors of studies not reporting separate data for patients who received monotherapy or combination therapy were contacted to retrieve the information.

Two reviewers (LO and GDC) independently screened the title, abstract and key words from all citations identified in the search to select relevant articles. Studies that satisfied the inclusion criteria were retrieved for a full-text evaluation performed independently by the same reviewers.

2.2. Data extraction

Two reviewers (LO and GDC) independently extracted the data according to the inclusion criteria. The following relevant information was collected from each article: name of first author; year of publication; country; study design; sample size; participant's characteristics (age, sex, type of infection, clinical isolate); hospital, 30-day or 90-day mortality rate; and microbiological eradication rate (defined as the presence of negative cultures at any time during treatment, after ≥7 days of treatment or at the end of therapy).

2.3. Quality assessment

Two reviewers (LO and GDC) independently determined the methodological quality of each study. For case–control and cohort studies, quality was assessed according to the Newcastle–Ottawa Scale for non-randomised studies [4], whilst for case series a tool proposed by Murad et al. was used [5]. A description of these tools is provided in the Supplementary material.

Any discrepancies in assessing the risk of bias scores between the reviewers were addressed with a joint re-evaluation of the original article. If a consensus was not reached, it was determined by a third reviewer (NC).

2.4. Statistical analysis

The primary outcome measure for the meta-analysis was the mortality rate and the secondary endpoint was the rate of microbiological cure. RRs were used as the meta-analytic measure of association between therapy and the incidence of events. Further details are provided in the Supplementary material.

3. Results

3.1. Literature search

A flow diagram of the process of identification and selection of the articles included in the meta-analysis is shown in Supplementary Fig. S1. A total of 388 potentially relevant articles were identified from the electronic database search, of which 367 were excluded after the first screening based on the title and abstracts. Thus, 21 articles were considered potentially relevant and the full-texts were retrieved for detailed evaluation. Following further evaluation, 11 articles [6–16] were included in the meta-analysis.

3.2. Study characteristics

The main characteristics of the 11 studies included in the meta-analysis are summarised in Table 1. All 11 studies were retrospective studies and 3 were case series [6–8]. The studies were published between 2017–2019 and the number of patients per study ranged from 6 to 104, for a total of 396 subjects (202 in the combination therapy group and 194 in the monotherapy group). Four studies were conducted in the USA [7,9–11], three in Spain [12–14], one in Italy [15], one in Saudi Arabia [6], one included centres from both Spain and Israel [16] and one included centres from six countries [8]. Seven studies included only patients infected with CRE [9–12,14–16], one included only patients infected with CRPa [13] and three reported infections due to both aetiologies [6–8]. The clinical characteristics of the enrolled patients are shown in Supplementary Table S1. Regarding the site of infection, 105 patients had pneumonia, 222 had bacteraemia, 65 had an intra-abdominal infection, 55 had a urinary tract infection, 33 had a skin and soft-tissue infection, 8 had a bone and joint infection and 14 had an infection at another site; some subjects had multiple sites of infection. The percentage of patients admitted to the intensive care unit varied between studies (range 12.5–62.5%). The Charlson comorbidity index was reported in six studies [9,11,12,14–16].

Regarding mortality, five studies evaluated in-hospital mortality [6–10], four studies evaluated 30-day mortality [11,14–16] and two studies evaluated 90-day mortality [12,13]. Data regarding 30-day mortality in the two treatment groups were not available in the text of one study [16] but the authors were contacted and provided the information.

Regarding microbiological outcome, two studies defined microbiological cure as the presence of negative cultures at the end of therapy [6,9], three studies as the presence of at least one negative culture during treatment [7,8,10] and two studies as the presence of negative cultures after ≥7 days of treatment [11,14].

The antimicrobial agents most frequently used in combination with ceftazidime/avibactam included colistin, tigecycline, aminoglycosides, fosfomycin and ciprofloxacin. The median duration of treatment ranged from 13–21 days (range 4–71 days).

Regarding mechanisms of carbapenem resistance, 198 patients in six studies were infected with a KPC-producing strain [7,8,10,11,15,16], 102 patients in five studies were infected with an OXA-48-producing strain [6,8,12,14,16], whilst the mechanism of resistance was not known in the remaining 96 cases.

A detailed description of the quality assessment is reported in Supplementary Table S2 and the Supplementary material.

3.3. Analysis of the data

The results of the meta-analysis are shown in Table 2. Considering all 396 included patients, a mortality rate of 38.1% in the combination therapy group and 30.9% in the monotherapy group was observed. The mortality rate was similar in patients treated with monotherapy or combination therapy (RR = 1.18, 95% CI 0.88–1.58; $P = 0.259$). Similarly, the mortality rate was similar in the two groups of patients considering the five studies [6–10] evaluating in-hospital mortality (RR = 1.37, 95% CI 0.80–2.34; $P = 0.256$), the four studies [11,14–16] assessing 30-day mortality (RR = 1.07, 95%

Table 1
Characteristics of studies included in the meta-analysis.

First author, year [ref.]	No. of pts	Enrolment period	Country	Study design	Age (years) [median (IQR)]	Male sex [*n* (%)]	CCI [median (IQR)]	Pts with bacteraemia [*n* (%)]	Clinical isolates [*n* (%)]				Combination therapy [*n* (%)]	Outcome [*n* (%)]	
									K. pneumoniae	*P. aeruginosa*	Polymicrobial	Other		Mortality	Microbiological cure
King, 2017 [9]	60	May 2015–April 16	USA	RS	60 (51–69)	36 (60)	4.5 (3–7)	23 (38.3)	50 (83.3)	0 (0)	32 (53.3)	12 (20.0)	27 (45.0)	19 (31.6)*	32 (53.3)[a]
Krapp, 2017 [10]	6	August–December 2015	USA	RS	53 (41.2–60.2)	3 (50.0)	NR	0 (0)	6 (100)	0 (0)	0 (0)	0 (0)	4 (66.7)	2 (33.3)*	3 (100)[b,$]
Temkin, 2017 [8]	38	2013–2016	Different countries[^]	CS	61 (47–67)	25 (65.8)	NR	26 (68.4)	34 (89.5)	2 (5.3)	11 (28.9)	2 (5.3)	25 (65.8)	15 (39.5)*	24 (63.2)[b]
Castón, 2017 [16]	8	June 2012–March 2016	Spain/Israel	RS	61 (42)[°°]	4 (50.0)	2.5 (0–7)	8 (100)	6 (75.0)	0 (0)	0 (0)	2 (25.0)	7 (87.5)	2 (25.0)**	NR
Shields, 2018 [11]	77	April 2015–April 2017	USA	RS	62 (19–91)[°]	47 (61.0)	4 (0–10)[°]	20 (26.0)	60 (77.9)	0 (0)	0 (0)	17 (22.1)	24 (31.2)	15 (19.5) **	52 (67.5)[c]
Algwizani, 2018 [6]	6	NR	Saudi Arabia	CS	38.5 (15.7–65.7)	6 (100)	NR	3 (50.0)	3 (50.0)	3 (50.0)	0 (0)	0 (0)	3 (50.0)	1 (16.7)*	5 (83.3)[a]
De la Calle, 2019 [12]	24	October 2014–December 2016	Spain	RS	58.8 (16)[°°]	19 (82.6)	4.3 (2.9)[°°]	8 (33.3)	23 (95.8)	0 (0)	0 (0)	1 (4.2)	10 (41.7)	5 (20.8)***	NR
Rodríguez-Núñez, 2018 [13]	8	January 2016–May 2017	Spain	RS	64.5 (62.5–69.2)	7 (87.5)	NR	2 (25.0)	1 (12.5)	8 (100)	1 (12.5)	0 (0)	6 (75.0)	3 (37.5)***	NR
Sousa, 2018 [14]	57	April 2016–December 2017	Spain	RS	64 (26–86)	44 (77.2)	3 (0–13)	26 (45.6)	54 (94.7)	0 (0)	0 (0)	3 (5.3)	11 (19.3)	13 (22.8)**	37 (64.9)[c]
Santevecchi, 2018 [7]	8	July 2015–July 2016	USA	CS	53 (32–74)[°]	5 (62.5)	NR	2 (25.0)	1 (12.5)	6 (75.0)	6 (75.0)	1 (12.5)	3 (37.5)	2 (25.0)*	5 (71.4)[b,$$]
Tumbarello, 2019 [15]	104	April 2016–December 2017	Italy	RS	61 (27–79)	68 (65.4)	CCI > 3, *n* (%): 38 (36.5)	104 (100)	104 (100)	0 (0)	2 (1.9)	0 (0)	82 (78.8)	38 (36.5)**	NR

pts, patients; IQR, interquartile range; CCI, Charlson comorbidity index; RS, retrospective; NR, not reported; CS, case series.
* In-hospital mortality.
** 30-day mortality.
*** 90-day mortality.
[a] Negative cultures at end of therapy.
[b] At least one negative culture during treatment.
[c] Negative cultures after ≥7 days of treatment.
[^] Israel, Spain, Italy, France, Australia and Switzerland.
[$] Data reported for three patients.
[$$] Data reported for seven patients.
[°] Median (range).
[°°] Mean (standard deviation).

Table 2
Meta-analysis data on the relative risk (RR) of mortality and microbiological cure in patients treated with ceftazidime/avibactam monotherapy or combination therapy.

Outcome (subjects)	No. of studies	Combination therapy [events/total (%)]	Monotherapy [events/total (%)]	Risk ratio (95% CI)	*P*-value	Heterogeneity test (*P*-value)	I^2
Mortality (all patients)	11 [6–16]	77/202 (38.1)	60/194 (30.9)	1.18 (0.88–1.58)	0.259	0.987	0%
Microbiological cure (all patients)	7 [6–11,14]	61/94 (64.9)	97/153 (63.4)	1.04 (0.85–1.28)	0.705	0.883	0%
Mortality (excluding patients infected with *Pseudomonas*)	9 [7–12,14–16]	74/191 (38.7)	58/186 (31.2)	1.20 (0.89–1.61)	0.229	0.923	0%
Microbiological cure (excluding patients infected with *Pseudomonas*)	6 [7–11,14]	57/90 (63.3)	91/147 (61.9)	1.05 (0.84–1.31)	0.653	0.687	0%

CI, confidence interval.

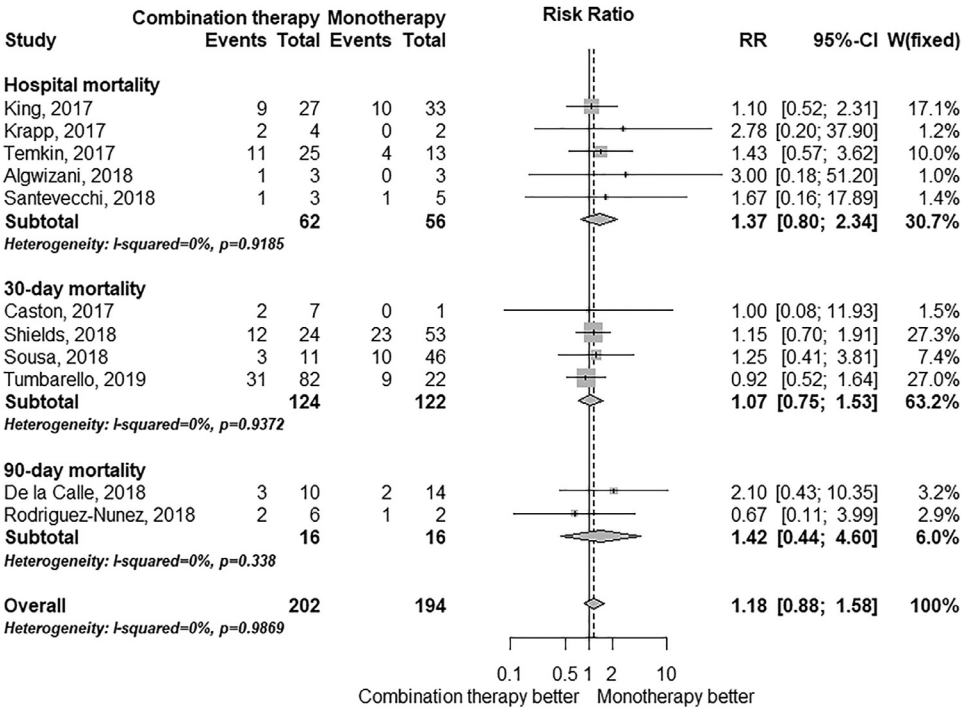

Fig. 1. Meta-analysis of clinical outcomes in the overall population. RR, risk ratio; CI, confidence interval.

CI 0.75–1.53; $P = 0.714$) and the two studies [12,13] reporting 90-day mortality (RR = 1.42, 95% CI 0.44–4.60; $P = 0.557$) (Fig. 1).

When the 19 patients infected with CRPa were excluded from the analysis, no difference between patients treated with ceftazidime/avibactam monotherapy or combination therapy was observed in overall mortality (RR = 1.20, 95% CI 0.89–1.61; $P = 0.229$) (Table 2).

Regarding microbiological outcome, among the 247 patients included, microbiological cure was achieved in 63.4% of patients treated with ceftazidime/avibactam alone and in 64.9% of those treated with combination therapy. Thus, no difference was observed between combination therapy and monotherapy (RR = 1.04, 95% CI 0.85–1.28; $P = 0.705$) (Table 2; Supplementary Fig. S2). Similarly, no difference was observed between treatment groups in the three studies [7,8,10] where microbiological outcome was defined as the presence of at least one negative culture during therapy (RR = 1.02, 95% CI 0.67–1.56; $P = 0.917$), in the two studies [11,14] where microbiological outcome was defined as negative cultures after ≥7 days of treatment (RR = 0.92, 95% CI 0.69–1.24; $P = 0.588$) or in the two studies [6,9] evaluating the negativity of cultures at the end of therapy (RR = 1.31, 95% CI 0.87–1.97; $P = 0.201$) (Supplementary Fig. S2). Moreover, no difference between the two treatment groups was observed when patients infected with CRPa were excluded (Table 2).

All studies except one [16] reported data on the emergence of resistance to ceftazidime/avibactam, with a total of 8 patients (4.1%) in the monotherapy and 6 patients (3.0%) in the combination group developing ceftazidime/avibactam resistance.

Finally, data on adverse events were not reported in three studies [6,10,15]. Twenty patients showed a clinically relevant adverse event, but whether they were treated with monotherapy or combination therapy was not available.

There was no evidence of between-study heterogeneity for all clinical and microbiological outcomes considered ($I^2 = 0\%$) (Table 2) or for all pre-planned subgroups. The shape of the funnel plots showed asymmetry for the mortality outcome, and the Egger's test showed statistical evidence of publication bias ($P = 0.096$). The trim-and-fill method indicated that this publication bias did not change the statistical significance of the estimate (RR = 1.10, 95% CI 0.83–1.45).

Finally, a sensitivity analysis was performed excluding studies with <10 subjects enrolled. Again, no differences in mortality and microbiological cure rates were observed between the treatment groups in the population of patients infected with all aetiologies

(Supplementary Figs S3 and S4) and in the subanalysis including only CRE-infected subjects.

4. Discussion

The aim of this meta-analysis was to compare the efficacy, in terms of mortality and microbiological cure rates, of ceftazidime/avibactam used as monotherapy or in combination with other active agents against infections due to carbapenem-resistant Gram-negative organisms, particularly CRE and CRPa.

Although the phase III studies that led to the registration of the drug did not aim to evaluate the efficacy of the drug against multidrug-resistant organisms, real-life studies including patients infected with carbapenem-resistant Gram-negative strains reported a significantly lower mortality rate in subjects treated with ceftazidime/avibactam compared with colistin-based regimens [15]. However, an increasing amount of evidence has demonstrated the selection of resistance during exposure to ceftazidime/avibactam, most frequently due to point mutations of the bla_{KPC} gene [3]. Moreover, it has been demonstrated that ceftazidime/avibactam has in vitro synergistic activity in combination with carbapenems, colistin, tigecycline and aminoglycosides against carbapenem-resistant organisms [17]. Finally, it has been shown that some bla_{KPC-3} mutations induced by ceftazidime can reduce the enzymatic activity of KPC-3 and restore susceptibility to carbapenems [18]. All of these data have encouraged several clinicians to use ceftazidime/avibactam in combination with carbapenems or other antibiotic classes in order to exploit the synergistic activity displayed in vitro and to prevent the selection of resistance. However, no data are available in the literature regarding the superiority of ceftazidime/avibactam in combination therapy over monotherapy for the treatment of carbapenem-resistant Gram-negative bacteria; moreover, combination therapy can possibly expose patients to a higher risk of adverse events and further selection of resistance.

This meta-analysis of 11 eligible studies, for a total of 396 patients, found a similar mortality rate among 202 patients who received combination therapy and 194 patients who received monotherapy (38.1% and 30.9%, respectively). Since *P. aeruginosa* displays different resistance mechanisms and prevalence compared with Enterobacteriaceae [19], a subanalysis was performed excluding patients infected with CRPa, but again no significant difference was observed between the treatment groups. Also, considering the microbiological cure rate, no difference was found between monotherapy and combination therapy. To our knowledge, the only meta-analysis reporting an advantage of combination therapy compared with monotherapy for carbapenem-resistant Gram-negative infections was conducted by Paul et al. [20], but this superiority was limited only to studies comparing colistin alone versus any colistin-based combination.

This meta-analysis has several strengths. First, a comprehensive literature search strategy was applied to minimise identification and selection bias, and a sufficient number of studies was enrolled. Second, the outcomes used (mortality and microbiological cure) can be considered significant in clinical practice and to evaluate the superiority of an antibiotic regimen in the treatment of an infection. Third, no between-study heterogeneity was observed; heterogeneity is a potential problem when interpreting the results of all meta-analyses, and finding the sources of heterogeneity is one of the most important goals. The absence of heterogeneity demonstrates the reliability of the results obtained.

However, this study also has several limitations. First, the sample of patients enrolled in the studies included in the meta-analysis was small (<400). Second, no randomised controlled trials or prospective observational studies comparing ceftazidime/avibactam monotherapy and combination therapy were identified. All of the data included in the analysis derived from retrospective studies, for most of which it is not possible to demonstrate a clear comparability among the treatment groups in terms of severity of illness, source of infection and other clinically relevant features. Third, the definitions of the outcomes evaluated, i.e. mortality and microbiological cure, varied in the different studies. Finally, we could not evaluate other potentially relevant outcomes, such as selection of ceftazidime/avibactam resistance or adverse events, observed during treatment in each group because most of the studies did not include these data.

5. Conclusions

The current meta-analysis demonstrated no significant difference in mortality and microbiological cure rates between ceftazidime/avibactam monotherapy and combination therapy for the treatment of infections due to carbapenem-resistant Gram-negative organisms, including CRE and *P. aeruginosa.* However, given the limited number of patients included, no definitive conclusion can be drawn. Further prospective studies conducted on larger samples are needed to address the role of this antimicrobial agent in the management of such difficult-to-treat infections.

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Ethical approval: Not required. All procedures used in the study were in accordance with current international guidelines, with the standards on human experimentation of the Ethics Committee of the Azienda Ospedaliera of the University of Campania (Naples, Italy) and with the Helsinki Declaration of 1975, revised in 1983.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.08.025.

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