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REVIEW

Ceftazidime-Avibactam for the Treatment of Serious Gram-Negative Infections with Limited Treatment Options: A Systematic Literature Review

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ABSTRACT

Introduction: A systematic literature review was undertaken to evaluate real-world use of ceftazidime-avibactam for infections due to aerobic Gram-negative organisms in adults with limited treatment options.
Methods: Literature searches retrieved peer-reviewed publications and abstracts from major international infectious disease congresses from January 2015 to February 2021. Results were screened using pre-defined criteria to limit the dataset to relevant publications (notable exclusions were paediatric data and outcomes data for bacteria intrinsically resistant to ceftazidime-avibactam). Data for included publications were subjected to qualitative synthesis.
Results: Seventy-three relevant publications (62 peer-reviewed articles; 10 abstracts) comprising 1926 patients treated with ceftazidime-avibactam (either alone or combined with other antimicrobials) and 1114 comparator/control patients were identified. All patients were hospitalised for serious illness and most had multiple comorbidities. The most common infections were pneumonia, bacteraemia, and skin/soft tissue, urinary tract, or abdominal infections; smaller numbers of patients with

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meningitis, febrile neutropenia, osteomyelitis, and cystic fibrosis were also included. Carbapenem-resistant or carbapenemase-producing Enterobacterales (CRE; $n = 1718$) and carbapenem-resistant, multidrug-resistant (MDR), and extensively drug-resistant *Pseudomonas aeruginosa* ($n = 150$) were the most common pathogens. Most publications reported positive outcomes for ceftazidime-avibactam treatment (clinical success rates ranged from 45 to 100% and reported 30-day mortality from 0 to 63%), which were statistically superior versus comparators in some studies. ceftazidime-avibactam resistance emergence occurred infrequently and mostly in *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* strains.
Conclusion: This review provides qualitative evidence of successful use of ceftazidime-avibactam for the treatment of hospitalised patients with CRE and MDR *P. aeruginosa* infections with limited treatment options.

Keywords: Ceftazidime-avibactam; Gram-negative bacteria; Limited treatment options; Carbapenem-resistant Enterobacterales; Carbapenem-producing Enterobacterales; *Pseudomonas aeruginosa*

Key Summary Points

Why carry out this study?

Antimicrobial resistance among Gram-negative bacteria, including Acinetobacter species, Enterobacterales, and Pseudomonas aeruginosa, represents a significant problem for healthcare systems worldwide. For regions with high local prevalence of extended-spectrum β-lactamase (ESBL)- and carbapenemase-producing organisms, treatment options for infections caused by such pathogens can be severely limited.

A systematic literature review was undertaken to evaluate real-world use of ceftazidime-avibactam for infections due to aerobic Gram-negative organisms in adults with limited treatment options.

What was learned from the study?

Literature searches identified 73 publications reporting data for 1926 patients treated with ceftazidime-avibactam and 1114 comparator/control patients, including 26 case reports, 17 case series, 15 retrospective cohort/chart review studies, 12 retrospective comparative/case-control studies and 2 prospective observational studies.

This review provides important insights into how ceftazidime-avibactam is being used in practice for the treatment of serious Gram-negative infections with limited treatment options, in particular, those caused by non-MBL-producing CRE and *P. aeruginosa*.

INTRODUCTION

Antimicrobial resistance among Gram-negative bacteria, including *Acinetobacter* species, Enterobacterales, and *Pseudomonas aeruginosa*, represents a significant problem for healthcare systems worldwide, in particular for resistance epicentres with high local prevalence of extended-spectrum β-lactamase (ESBL)- and carbapenemase-producing organisms, where treatment options for infections caused by such pathogens can be severely limited [1]. The need for antimicrobial development to address third-generation cephalosporin-resistant and carbapenem-resistant Enterobacterales (CRE) and *P. aeruginosa* has been designated a critical priority by the World Health Organization [2].

Ceftazidime-avibactam, a combination of the anti-pseudomonal cephalosporin ceftazidime and the novel β-lactamase inhibitor avibactam, has in vitro activity against a broad range of Gram-negative bacteria, including highly resistant strains, such as ESBL-, AmpC-, and serine carbapenemase-producing Enterobacterales (CPE) and *P. aeruginosa*, but not against metallo-β-lactamase (MBL) producers [3, 4]. In an extensive phase 2 and 3 randomised controlled trial (RCT) programme, ceftazidime-

avibactam has demonstrated efficacy generally comparable to carbapenem-based comparator regimens in the primary indications of complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI; including pyelonephritis), and hospital-acquired pneumonia (HAP/HABP; including ventilator-associated pneumonia [VAP/VABP]) [5–11], including against ceftazidime non-susceptible and multidrug-resistant (MDR) Enterobacterales and *P. aeruginosa* [6, 12]. Ceftazidime-avibactam (standard dose 2.5 g by 2-h intravenous infusions every 8 h [q8h], adjusted for patients with creatinine clearance [CrCL] $\geq$ 50 ml/min) is approved in the US for the treatment of adults with cIAI (co-administered with metronidazole), cUTI (including pyelonephritis) and HABP (including VABP), and cIAI or cUTI (including pyelonephritis) in children aged $\geq$ 3 months [13]. In Europe it is approved for cUTI (including pyelonephritis), cIAI, and HAP/VAP in adults, including for cases of bacteraemia associated with these infections, and for the treatment of infections due to aerobic Gram-negative organisms with limited treatment options [14]. It is also approved for children aged $\geq$ 3 months with cUTI (including pyelonephritis), cIAI, HAP/VAP, and infections due to aerobic Gram-negative organisms with limited treatment options [14]. Approval of ceftazidime-avibactam for the 'limited treatment options' indication in adults was based on microbiological data, demonstration of clinical efficacy in patients with cIAI and cUTI, and population pharmacokinetic (PK) data demonstrating adequate PK/pharmacodynamic (PD) target attainment with approved dosages [15]. By definition, there is a lack of RCT data describing outcomes of treatment for this diverse patient population. However, there is a growing body of published (predominantly retrospective and observational) data on the use of ceftazidime-avibactam in indications for which there are limited treatment options. This systematic literature review provides a qualitative synthesis of the clinical and microbiological outcomes of ceftazidime-avibactam treatment of infections caused by aerobic Gram-negative organisms in adult patients with limited treatment options. This article is based on published literature and does not contain any previously unreported studies with human participants or animals.

METHODS

Definition of 'Infections due to Aerobic Gram-Negative Organisms with Limited Treatment Options'

For the purposes of this review, a working definition of publications describing 'aerobic Gram-negative infections in adult patients with limited treatment options' was formulated. Publications reporting outcomes for patients with any of the approved 'primary' indications for ceftazidime-avibactam (cIAI, cUTI, HAP/HABP, or VAP/VABP) were only included if the infection(s) involved microbiological confirmation/suspicion of ESBL- and/or carbapenemase-producing Gram-negative organisms, excluding MBL producers. Other acute infections included in the working definition of 'limited treatment options' were those with microbiological confirmation/suspicion of involvement of ceftazidime-avibactam-susceptible Gram-negative bacteria (i.e., non-MBL-producing Enterobacterales or *P. aeruginosa*), such as primary or secondary bacteraemia/bloodstream infections including sepsis/toxic shock, bacterial meningitis, febrile neutropenia, device-related infections, transplant-related infections, bone and joint infections, cystic fibrosis-related bronchopulmonary infections, and skin and soft tissue infections (SSTI).

Literature Search

Methodology for conducting literature searches followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and guidance [16, 17]. A PubMed search using the search terms 'ceftazidime AND avibactam' (filters: none) was conducted in February 2021 to include publications from 2015 onwards. Additional searches were conducted to retrieve abstracts from major international infectious disease congresses

[European Congress of Clinical Microbiology and Infectious Diseases, American Society for Microbiology (ASM) Microbe/International Conference on Antimicrobial Agents and Chemotherapy, and Infectious Diseases Society of America IDWeek] from 2015 to 2019.

All retrieved publication search results were screened by two researchers by titles and abstracts. The following publication types were excluded, with reasons for exclusion documented in each case: RCT data for any of the primary indications for ceftazidime-avibactam; in vitro/animal study data, including microbiological surveillance or population PK and PK/PD modelling; review articles, guidelines, commentaries/opinion pieces, and editorials not reporting original outcomes data for patients treated with ceftazidime-avibactam; publications primarily reporting outcomes of treatment for infections caused by pathogens not susceptible to ceftazidime-avibactam as defined in the European Summary of Product Characteristics [i.e., *Staphylococcus aureus* (methicillin-resistant and methicillin-sensitive), anaerobes, *Enterococcus* spp., *Stenotrophomonas maltophilia*, and *Acinetobacter* spp.] [14], or those describing outcomes of MBL-producing Gram-negative infections. Meta-analyses of published literature were also excluded from the analysis to avoid duplication of data; however, the source data/references within such articles were reviewed to ensure all relevant primary data were included.

Data Extraction

Included publications were tabulated in Microsoft Excel for data extraction. In addition to author/citation details, the following data (where reported) were extracted for each included publication: country/region; study design; number of sites (single or multiple); number of ceftazidime-avibactam and control/comparator participants and their characteristics [age, sex, type of infection, clinical isolate(s) and resistance mechanism(s), renal status, and intensive care unit (ICU) admittance]; primary/index infection and proportion of patients with bacteraemia; duration of ceftazidime-avibactam treatment and use of prior and concomitant antibiotics; timing relative to index infection and duration of ceftazidime-avibactam treatment; clinical and microbiological outcomes (for example, hospital, 30-day, or 90-day mortality), and rates of eradication, recurrence, and emergence of resistance.

RESULTS

Literature Search

The literature search identified a total of 1262 publications, from which initial screening and further exclusion identified 73 relevant publications (Fig. 1). The included publications (63 journal articles and 10 congress abstracts) reported data for a total of 1926 patients treated with ceftazidime-avibactam and 1114 comparator/control patients and comprised 26 case reports, 17 case series, 16 retrospective cohort/chart review studies, 12 retrospective comparative/case-control studies, and 2 prospective observational studies (Table 1).

Most publications were from Europe (34; 47%) and North America (29; 40%), with five from China (7%) and two each from Latin America (3%) and the Middle East (3%). One publication (1%) included patients from Europe and Australia. Included publications involved patients with a variety of infections, including IAI, HAP/VAP, UTI, SSTI, primary and secondary bacteraemia, meningitis, osteomyelitis, and febrile neutropenia. Five publications (44 patients) included haematology/oncology patients; seven (35 patients) involved solid organ transplant (SOT) patients; six (14 patients) involved treatment of bronchopulmonary infections in patients with cystic fibrosis. Ten case studies (10 patients) included surgical and trauma patients. The most frequently identified pathogens were Enterobacterales (1718 patients), including CPE and CRE strains, and *P. aeruginosa* (150 patients), including carbapenem-resistant, MDR, and extensively drug-resistant (XDR) strains; 74 patients had other Gram-negative pathogens, including *Burkholderia cepacia* complex, *Burkholderia multivorans*, and *Raoultella planticola*.

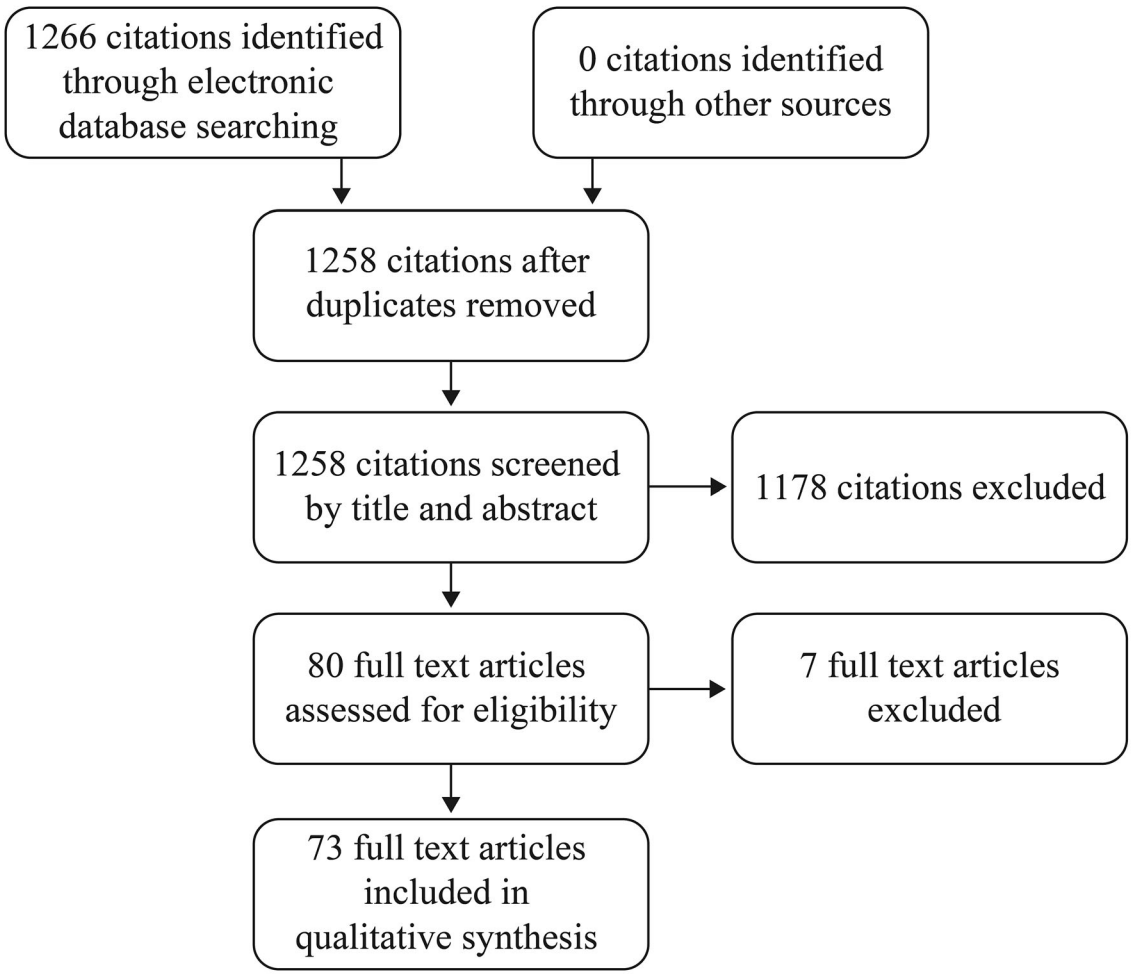

Fig. 1 Overview of the publications search results

Prospective Observational Studies

Data for 95 patients treated with ceftazidime-avibactam from two prospective studies were included [18, 19]. Both studies included patients with CRE infections; no decreased susceptibility/ceftazidime-avibactam resistance emergence was reported in either study.

Sousa et al. (2018) prospectively collected data on outcomes of ceftazidime-avibactam salvage therapy for 57 patients with OXA-48-producing *K. pneumoniae* infections during an outbreak caused by this pathogen at a Spanish hospital [18]. The most common primary infections were intra-abdominal [16 patients (28%)] or respiratory tract [15 patients (26%)]; 26 patients (57%) had bacteraemia and 51 (89%) had received prior antibiotics. All-cause mortality rates were 14% at 14 days and 22% at 30 days.

In a US prospective, multicentre observational study in patients with CRE bacteraemia (ceftazidime-avibactam, $n = 38$; colistin, $n = 99$), Van Duin et al. (2018) reported that inverse probability of treatment weighting (IPTW)-adjusted all-cause 30-day hospital mortality was significantly lower in the ceftazidime-avibactam group (9%) compared with the colistin group [32%; difference 23%, 95% confidence interval (CI) 9–35; $P = 0.001$]. Based on desirability of outcome ranking (DOOR) analysis, patients treated with ceftazidime-avibactam had an IPTW-adjusted probability of a better outcome of 64% (95% CI, 57–71) [19].

Table 1 Publications included in the analysis

Publication	Type of study	Patient population	Country	Number of patients		Pathogens isolated from patients treated with ceftazidime-avibactam		
				Ceftazidime-avibactam	Comparator	CRE or CPE	*Pseudomonas aeruginosa*	Other
Algwizani 2018 [48]	Case series	Mixed	Saudi Arabia	6	–	3	1	0
Alraddadi 2019 [20]	Retrospective comparative/case control	Mixed	Saudi Arabia	10	28	10	0	0
Amore 2020 [63]	Case series	Transplant	Italy	4	3	3	1	0
Bandali 2018 [21]	Retrospective comparative/case control	Mixed	US	25	125	25	0	0
Barlow 2018 [66]	Case report	Cystic fibrosis	UK	1	–	0	0	1
Borjan 2019 [22]	Retrospective comparative/case control	Haematology/oncology	US	24	19	24	0	0
Bulbin 2017 [67]	Case report	Surgical	US	1	–	1	0	0
Camargo 2015 [68]	Case report	Surgical	US	1	–	1	0	0
Cantón-Bulnes 2019 [69]	Case report	Cystic fibrosis	Spain	1	–	0	0	1
Carannante 2018 [70]	Case report	Other	Italy	1	–	1	0	0
Caravaca-Fontan 2015 [71]	Case report	Transplant	Spain	1	–	1	0	0
Castón 2017 [23]	Retrospective comparative/case control	Haematology/oncology	Spain, Israel	8	23	8	0	0

Table 1 continued

Publication	Type of study	Patient population	Country	Number of patients		Pathogens isolated from patients treated with ceftazidime-avibactam		
				Ceftazidime-avibactam	Comparator	CRE or CPE	*Pseudomonas aeruginosa*	Other
Castón 2020 [33]	Retrospective cohort/chart review	Mixed	Spain	47	–	47	0	0
Chen 2020 [64]	Case series	Transplant	China	10	–	9	1	0
Daccò 2019 [72]	Case report	Cystic fibrosis	Italy	1	–	0	0	1
De la Calle 2019 [49]	Case series	Mixed	Spain	23	–	24	0	0
De León-Borrás 2018 [73]	Case report	Bone/joint	Puerto Rico	1	–	1	0	0
Gallagher 2016 [50]	Case series	Mixed	US	15	–	14	1	0
Gofman 2018 [74]	Case report	Other	US	1	–	1	1	0
Gonzales Zamora 2018 [77]	Case report	Trauma	US	1	–	0	0	1
Guedes 2020 [76]	Case report	Surgical	Portugal	1	–	1	0	0
Gugliandolo 2017 [75]	Case report	Trauma	Italy	1	–	1	0	0
Guimarães 2019 [51]	Case series	Mixed	Brazil	29	–	29	0	0
Holyk 2018 [78]	Case report	Other	US	1	–	1	0	0
Iacovelli 2018 [79]	Case report	Other	Italy	1	–	1	0	0
Iannaccone 2020 [46]	Retrospective cohort/chart review	Mixed	Italy	23	–	23	0	0
Jacobs 2016 [80]	Case report	Transplant	US	1	–	1	0	0

Table 1 continued

Publication	Type of study	Patient population	Country	Number of patients		Pathogens isolated from patients treated with ceftazidime-avibactam		
				Ceftazidime-avibactam	Comparator	CRE or CPE	*Pseudomonas aeruginosa*	Other
John 2019 [24]	Retrospective comparative/case control	Mixed	US	42	75	42	0	0
Jorgensen 2019 [34]	Retrospective cohort/chart review	Mixed	US	203	–	117	63	23
Karaiskos 2021 [25]	Retrospective comparative/case control	Mixed	Greece	147	71	147	0	0
Katchanov 2018 [35]	Retrospective cohort/chart review	Mixed	Germany	5	114	5	0	0
King 2016 [36]	Retrospective cohort/chart review	Mixed	US	10	–	0	10	0
King 2017 [37]	Retrospective cohort/chart review	Mixed	US	60	–	60	0	0
Krapp 2017 [38]	Retrospective cohort/chart review	Mixed	US	6	38	6	0	0
Kuang 2020 [44]	Retrospective cohort/chart review	Mixed	China	20	–	21	3	9
Los-Arcos 2019 [52]	Case series	Cystic fibrosis	Spain	2	–	0	0	1
Meschiari 2020 [61]	Case series	Mixed	Italy	2	1	1	3	0
Metafuni 2019 [53]	Case series	Haematology/oncology	Italy	3	–	1	1	0

Table 1 continued

Publication	Type of study	Patient population	Country	Number of patients		Pathogens isolated from patients treated with ceftazidime-avibactam		
				Ceftazidime-avibactam	Comparator	CRE or CPE	*Pseudomonas aeruginosa*	Other
Micozzi 2018 [54]	Case series	Haematology/oncology	Italy	8	–	8	0	0
Nguyen 2020 [81]	Case report	Cystic fibrosis	US	1	–	0	0	1
Nwankwo 2021 [45]	Retrospective cohort/chart review	Mixed	UK	28	–	NR	NR	NR
Papadimitriou-Olivgeris 2021 [43]	Retrospective cohort/chart review	Mixed	Greece	1	114	115	0	0
Park 2019 [82]	Case report	Other	US	1	–	0	0	1
Parruti 2019 [83]	Case report	Surgical	Italy	1	–	1	0	0
Pillinger 2017 [26]	Retrospective comparative/case control	Mixed	US	8	65	8	0	0
Pingue 2020 [84]	Case report	Surgical	Italy	1	–	1	0	0
Rahmati 2017 [39]	Retrospective cohort/chart review	Mixed	US	11	–	11	0	0
Räisänen 2019 [85]	Case report	Trauma	Finland, Greece	1	–	1	0	0
Rico-Nieto 2018 [86]	Case report	Trauma	Spain	1	–	1	0	0
Rodríguez-Núñez 2018 [40]	Retrospective cohort/chart review	Mixed	Spain	8	–	0	8	0
Samuel 2016 [87]	Case report	Trauma	US	1	–	1	0	0

Table 1 continued

Publication	Type of study	Patient population	Country	Number of patients		Pathogens isolated from patients treated with ceftazidime-avibactam		
				Ceftazidime-avibactam	Comparator	CRE or CPE	*Pseudomonas aeruginosa*	Other
Santevecchi 2018 [55]	Case series	Mixed	US	10	–	6	6	4
Shen 2021 [27]	Retrospective comparative/case control	Mixed	China	9	89	9	0	0
Schimmenti 2018 [88]	Case report	Bone/joint	Italy	1	–	1	0	0
Shields 2018 [32]	Retrospective cohort/chart review	Mixed	US	77	–	77	0	0
Shields 2017 [28]	Retrospective comparative/case control	Mixed	US	13	96	13	0	0
Shields 2017 [89]	Case report	Haematology/oncology	US	1	–	1	0	0
Shields 2016 [56]	Case series	Mixed	US	37	–	37	0	0
Sousa 2018 [18]	Prospective observational	Mixed	Spain	57	–	57	0	0
Spoletini 2019 [57]	Case series	Cystic fibrosis	Italy	8	–	0	6	4
Sun 2019 [29]	Retrospective comparative/case control	Transplant	US	16	19	16	0	0
Temkin 2017 [41]	Retrospective cohort/chart review	Mixed	Australia, France, Israel, Italy, Spain, Switzerland	38	–	36	2	0

Table 1 continued

Publication	Type of study	Patient population	Country	Number of patients		Pathogens isolated from patients treated with ceftazidime-avibactam		
				Ceftazidime-avibactam	Comparator	CRE or CPE	*Pseudomonas aeruginosa*	Other
Tsolaki 2020 [31]	Retrospective comparative/case control	Mixed	Greece	41	36	41	0	0
Tumbarello 2019 [30]	Retrospective comparative/case control	Mixed	Italy	138	104	138	0	0
Tumbarello 2021 [47]	Retrospective cohort/chart review	Mixed	Italy	577	0	577	0	0
van Asten 2021 [60]	Case series	Mixed	Italy, The Netherlands	5	–	5	0	0
van Duin 2018 [19]	Prospective observational	Mixed	US	38	99	38	0	0
Vena et al. [42]	Retrospective cohort/chart review	Mixed	Italy	41	–	0	38	7
Wang 2020 [62]	Case series	Transplant	China	2	4	2	0	0
Wang 2020 [90]	Case report	Transplant	China	1	0	1	0	0
Wu 2016 [58]	Case series	Mixed	US	3	–	3	0	0
Xipell 2017 [59]	Case series	Mixed	Spain	2	–	0	2	0
Yasmin 2020 [91]	Case report	Surgical	US	1	0	1	0	0

CPE carbapenemase-producing Enterobacterales, *CRE* carbapenem-resistant Enterobacterales

Table 2 Overview of retrospective comparative/case-control studies involving ceftazidime-avibactam for the treatment of CRE infections

Publication	Patient population	Number of patients (% with bacteraemia)		Baseline pathogens (resistance mechanisms)	Reported outcomes (ceftazidime-avibactam vs. comparator)			
		Ceftazidime-avibactam	Comparator		Clinical cure	30-day mortality	90-day mortality	Adverse events/safety
Alraddadi 2019 [20]	38 patients with CRE infections treated with ceftazidime-avibactam or other agents, 2017–2018	10 (70%)	28 (54%)	CRE (80% OXA-48; 10% NDM-1; 10% none identified)	4/10 (40%) vs. 11/28 (39%)	5/10 (50%) vs. 16/28 (57%)	NR	NR
Bandali 2018 [21]	150 patients with CRE infections treated with ceftazidime-avibactam or other agents, 2009–2017	25 (24%)	125 (18%)	CRE (NR)	20/25 (80%) vs. 90/125 (72%); $P = 0.469$	All-cause: 6/25 (24%) vs. 91/125 (73%); $P = 0.006$ Infection related: 1/25 (4%) vs. 33/125 (26%); $P = 0.017$	NR	NR
Borjan 2019 [22]	43 patients with cancer with CRE bacteraemia treated with ceftazidime-avibactam or polymyxin-based regimens (dates NR)	24 (100%)	19 (100%)	CRE (44% non-carbapenemase producing; 56% unknown)	NR	NR[a]	NR[a]	Patients treated with ceftazidime-avibactam had an 81% reduction in IPTW-adjusted odds of a worse DOOR (OR 0.19, 95% CI 0.05–0.76; $P = 0.02$)
Castón 2017 [23]	31 haematological patients with CPE bacteraemia treated with ceftazidime-avibactam or other agents, 2012–2016	8 (100%)	23 (100%)	CPE (61% OXA-48; 39% KPC)	6/8 (75%) vs. 8/23 (35%); $P = 0.031$	2/8 (25%) vs. 12/23 (52%); $P = 0.19$	NR	In no case was ceftazidime-avibactam discontinued due to adverse effects. In 2 patients (25%) who developed renal failure during treatment, the dosing was adjusted
John 2019 [24]	117 patients with CRE infections treated with ceftazidime-avibactam or polymyxin B, 2010–2018	42 (NR[b])	75 (NR[b])	CRE (NR)	NR	9/42 (21%) vs. 19/75 (25%); $P = 0.653$	NR	Polymixin B was associated with a higher incidence of nephrotoxicity (19% vs. 43%; $P = 0.048$)
Karaiskos 2021 [25]	147 patients with KPC- or OXA-48-KP infections treated with ceftazidime-avibactam, 2018–2019; 71 matched bacteraemic controls treated with other regimens, 2018–2019	147 (48%)	71 (100%)	CRE (95% KPC; 5% OXA-48)	Day 14 clinical success was observed in 119/147 patients (81%)	NR[c]	NR[c]	Emergence of resistance to ceftazidime-avibactam during therapy was observed in 2/147 patients (1%) Relapse of infection after discontinuation of ceftazidime-avibactam occurred in 6/147 patients (4%)
Pillinger 2017 [26]	73 patients with CRE bacteraemia treated with ceftazidime-avibactam or other agents, 2010–2016	8 (100%)	65 (100%)	CRE (NR)	NR	NR[d]	NR	NR

Table 2 continued

Publication	Patient population	Number of patients (% with bacteraemia)		Baseline pathogens (resistance mechanisms)	Reported outcomes (ceftazidime-avibactam vs. comparator)			
		Ceftazidime-avibactam	Comparator		Clinical cure	30-day mortality	90-day mortality	Adverse events/safety
Shen 2021 [27]	89 patients with CRKP BSI; 9 treated with ceftazidime-avibactam, 2018	9 (100%)	80 (100%)	CRKP (NR)	NR	NR[e]	NR	NR
Shields 2017 [28]	109 patients with CRKP bacteraemia treated with ceftazidime-avibactam or other regimens, 2009–2017	13 (100%)	96 (100%)	CRKP (97% KPC)	NR	1/13 (8%) vs. 30/96 (31%); $P = 0.10$	1/13 (8%) vs. 43/96 (45%); $P = 0.01$	Aminoglycoside- and colistin-containing regimens were associated with increased rates of nephrotoxicity ($P = 0.002$)
Sun 2019 [29]	235 solid organ transplant recipients with CRE infections treated with ceftazidime-avibactam or salvage agents, 2012–2019	16 (NR[f])	19 (NR[f])	CRE (NR)	NR	0/16 (0%) vs. 5/19 (26%); $P = 0.049$	1/16 (6%) vs. 7/19 (37%); $P = 0.047$	Among patents who survived 90 days, recurrent CRE infections were diagnosed in 53% and 17% of those treated with ceftazidime-avibactam and a salvage regimen, respectively ($P = 0.10$) Ceftazidime-avibactam resistance developed in 3/8 (38%) patients with recurrent infections
Tsolaki 2020 [31]	77 critically ill mechanically ventilated patients with CRE infections (40-month period; dates NR)	41 (54%)	36 (78%)	CRE (100% KPC)	Overall: 33/41 (80%) vs. 19/36 (53%); $P < 0.05$ Patients with bacteraemia: 18/22 (82%) vs. 15/28 (54%);$P < 0.05$	NR[g]	NR	No significant adverse events reported

Table 2 continued

Publication	Patient population	Number of patients (% with bacteraemia)		Baseline pathogens (resistance mechanisms)	Reported outcomes (ceftazidime-avibactam vs. comparator)			
		Ceftazidime-avibactam	Comparator		Clinical cure	30-day mortality	90-day mortality	Adverse events/safety
Tumbarello 2019 [30]	138 patients with KPC-KP infections treated with ceftazidime-avibactam in compassionate use programmes, 2016–2017; 104 matched controls for bacteraemia cohort	138 (75%)	104 (100%)	*K. pneumoniae* (100% KPC)	NR	Patients with bacteraemia: 37% vs. 56%; $P = 0.005$	NR	NR

CI confidence interval, *CPE* carbapenemase-producing Enterobacterales, *CRE* carbapenem-resistant Enterobacterales, *CRKP* carbapenem-resistant *Klebsiella pneumoniae*, *DOOR* desirability of outcome ranking, *IPTW* inverse probability of treatment weighted, *KPC Klebsiella pneumoniae* carbapenemase, *KPC-KP K. pneumoniae* carbapenemase- producing *K. pneumoniae*, *NDM-1* New Delhi metallo-β-lactamase 1, *NR* not reported, *OR* odds ratio

[a] Fourteen-day mortality was 2/24 (8%) for patients receiving ceftazidime-avibactam vs. 5/19 (26%) for patients treated with polymyxin-containing regimens (IPTW-adjusted OR 0.12, 95% CI 0.02, 0.82; $P = 0.03$)

[b] Bacteraemia reported for 45/117 patients (36%) overall

[c] Fourteen- and 28-day mortality rates were 9% and 20%, respectively. For 71 matched patients with KPC-KP BSIs, 28-day mortality was 8% and 41% for ceftazidime-avibactam-based regimens and for other agents, respectively ($P = 0.005$)

[d] Overall 28-day mortality was 42/89 patients (47%); 7/9 patients (78%) treated with ceftazidime-avibactam survived

[e] Twenty-eight-day mortality was 1/8 (13%) vs. 18/65 (28%)

[f] Bacteraemia reported for 20/35 patients (57%) overall

[g] Twenty-eight-day survival was 85% vs. 61% ($P < 0.05$) overall and 82% vs. 57% for patients with bacteraemia

Retrospective Comparative/Case–Control Studies

Data for 481 patients treated with ceftazidime-avibactam from 12 retrospective comparative/case-control studies (Table 2) were retrieved from the literature search [20–31]. Each of these studies involved infections caused by CRE and most of the patients were bacteraemic; some included patients treated on a 'compassionate use' basis before the commercial availability of ceftazidime-avibactam (the drug was first approved in the US in 2015). Comparator treatments comprised best available therapy (BAT) and included polymyxin B, colistin, aminoglycosides and tigecycline alone or in combination with carbapenems and unspecified 'salvage agents' (Table 2). Clinical outcomes included clinical cure and 30- and 90-day mortality rates. Across these studies, efficacy outcomes for ceftazidime-avibactam (where reported) were in general numerically similar or superior to those reported for comparator treatments (Table 2). Emergence of resistance to ceftazidime-avibactam in three of eight patients with recurrent infections (38%) was reported in one congress abstract involving 35 solid organ transplant (SOT) patients with CRE infections (predominantly bacteraemia or pneumonia); however, the duration of ceftazidime-avibactam treatment, resistance mechanism(s), and timing of resistance emergence were not reported [29]. Of note, a non-comparative retrospective analysis by the same investigators (see below) reported an overall rate of ceftazidime-avibactam resistance emergence of 10% among 77 patients infected with CRE, of whom 4 were SOT recipients [32]. A separate study among 147 patients treated with KPC- or OXA-48-producing *K. pneumoniae* infections treated with ceftazidime-avibactam reported a lower rate of resistance emergence of 1% (2/147 patients); details of timings and mechanism(s) were not reported [25].

Retrospective Cohort/Chart Review Studies

Data for 1155 patients treated with ceftazidime-avibactam from 16 retrospective non-comparative cohort/chart review studies were identified (Table 3) [32–46], the majority of which involved CRE/CPE infections (981 patients); six publications included data for *P. aeruginosa* infections (124 patients). Emergence of resistance and/or reduced susceptibility to ceftazidime-avibactam was reported in seven of these publications, including one OXA-48-producing *K. pneumoniae* in a single patient [35]; in the remaining cases, the resistant strains were either *K. pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* or carbapenem-resistant *K. pneumoniae* (CRKP) with unreported resistance mechanisms [32–35, 46, 47]. Decreased sensitivity to ceftazidime-avibactam was reported in one patient with KPC-producing *K. pneumoniae* [39].

The largest retrospective cohort study, reported by Tumbarello et al. (2021), included 577 patients with KPC-producing *K. pneumoniae* infections, including 391 patients with bacteraemia. In this analysis, there was no difference in 30-day mortality for patients who received ceftazidime-avibactam combination or monotherapy regimens (26% vs. 25%, $P = 0.79$), and rates of resistance development and adverse events were low (both 3%) [47].

Another large retrospective cohort study, reported by Jorgensen et al. (2019), included 203 patients who received ceftazidime-avibactam for $\geq$ 72 h at six US hospitals (2015–2019) and included data for 117 patients with CRE and 63 with *P. aeruginosa* as well as infections with other Gram-negative and gram-positive pathogens [34]. In the overall cohort, clinical failure, 30-day mortality and 30-day recurrence occurred in 59 (29%), 35 (17%) and 12 (6%) patients, respectively, and outcomes were similar for patients infected with CRE or *P. aeruginosa*. Of note, ceftazidime-avibactam dosage adjustments for renal function were made for 92 patients but were considered inappropriate for 11 patients (effectively resulting in underdosing); among these patients, five (46%) experienced clinical failure and three (27%) died by day 30. Moreover, only 50 of 74 CRKP isolates underwent baseline testing for ceftazidime-avibactam susceptibility, of which 48 were susceptible [two isolates were ceftazidime-avibactam-resistant, one with New Delhi

Table 3 Overview of retrospective cohort/chart review studies involving ceftazidime-avibactam for the treatment of infections caused by Gram-negative organisms with limited treatment options

Publication	Patient characteristics	Patients with bacteraemia, n/N (%)	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Concomitant antibiotics, n/N (%)	Reported outcomes			
						Clinical and/or microbiological cure	30-day mortality	90-day mortality	Adverse events/safety
Castón 2020 [33]	47 patients, median age 70 years, median CCI 4	25/47 (53%) had septic shock	KPC-KP	Dose NR, median duration 14 days	13/47 (28%)	14-day clinical response rate was 28/147 (60%)	11/47 (23%)	NR	Resistance emergence to ceftazidime-avibactam reported in 6/47 patients (13%)
Iannaccone 2020 [46]	23 patients, ages 18–80 years, 87% male	23/23 (100%)	KPC-KP	Dose NR, duration 4–34 days	20/23 (90%)	17/23 patients (74%) recovered from the infection; 6/23 patients (26%) died during hospitalisation	NR	NR	Resistance emergence to ceftazidime-avibactam reported in 2/23 patients (9%)
Jorgensen 2019 [34]	203 patients who received ceftazidime-avibactam for > 72 h, median age 62 years, 62% male. Infection sources included respiratory tract (n = 76), urinary tract (n = 40), intra-abdominal (n = 38), skin and soft tissue (n = 18), osteoarticular (n = 14)	22/203 (11%)	CRE (58%); *Pseudomonas* spp. (31%); others (23%)	92/203 patients (45%) required renal dose adjustments; median duration 9 days	68/203 (34%)	Clinical failure: 59/203 (29.1%) 30-day recurrence occurred in and 12/203 (5.9%)	35/203 (17%)	NR	17/203 patients (8.4%) experienced a potential drug-related adverse effect Resistance emergence to ceftazidime-avibactam reported in 1/62 patients (2%) with repeat testing
Katchanov 2018 [35]	119 patients colonized or infected with CR MDR-Gram-negative bacteria; 5 patients with severe HAP (and bacteraemia in 1 case) treated with ceftazidime-avibactam during an outbreak of OXA-48 and CTX-M-14 producing *K. pneumoniae*	1/5 (20%)	CRKP (OXA-48)	NR	NR	NR	NR	NR	Ceftolozane/tazobactam and ceftazidime-avibactam were administered to 3 and 5 patients, respectively (in-hospital mortality: 66% and 100%). Development of drug-resistance under therapy was observed for both antimicrobials
King 2016 [36]	10 patients, mean age 73 years, 70% male, median CCI 6	1/10 (10%)	*P. aeruginosa* (MDR and XDR)	NR	5/10 (50%)	Microbiological cure 9/10 (90%) Clinical success 8/10 (80%)	NR[a]	NR	NR
King 2017 [37]	60 patients, median age 60 years, 60% male. Infection sources: bacteraemia (37%), UTI (11%), wound (19%), intra-abdominal (15%), pneumonia (30%), bone/joint (4%)	22/60 (37%)	CRE (83% *K. pneumoniae*)	33/60 patients (55%) required renal dose adjustments; duration NR	27/60 (45%)	Microbiological cure 32/60 (53%) Clinical success 39/60 (65%)	NR[b]	NR	No drug-related adverse events were reported

Table 3 continued

Publication	Patient characteristics	Patients with bacteraemia, n/N (%)	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Concomitant antibiotics, n/N (%)	Reported outcomes			
						Clinical and/or microbiological cure	30-day mortality	90-day mortality	Adverse events/safety
Krapp 2017 [38]	6 patients treated with ceftazidime-avibactam, ages 29–67 years, 50% male. 5/6 patients had severe renal dysfunction, and 4/6 patients required dialysis	2/6 (33%)	*K. pneumoniae* (KPC-3, OXA-9)	NR	4/6 (67%)	5/6 patients (83%) achieved clinical cure	NR	NR	2 patients relapsed with the same CRKP strain within 3 weeks of end of ceftazidime-avibactam treatment, and subsequently died due to persistent sepsis
Kuang 2020 [44]	20 patients, mean age 55 years, 70% male, mean CCI 4	7/20 (35%)	*K. pneumoniae* (n = 18; 12 CRKP) *P. aeruginosa* (n = 3; 2 carbapenem-resistant) *Escherichia coli* (n = 3; all ESBL-producing strains) Others (n = 9)	Standard dose, adjusted for renal function	NR	14-day clinical cure rate: 9/20 (45%)	11/20 (55%)[c]	NR	Adverse effects reported in 3/20 patients (15%)
Nwankwo 2021 [45]	28 patients, ages 10–70 years, 43% male 31 courses of ceftazidime-avibactam	NR	*Pseudomonas, Klebsiella, Burkholderia, Enterobacter* and *Achromobacter* spp. (n = 27) Non-tuberculous mycobacteria (n = 5)	Dose NR, 2/11 patients (18%) required renal dose adjustments; mean duration 20 days	28/28 (100%)	NR	NR[d]	NR	Adverse effects reported in 2/28 patients (7%) No resistance emergence among 7 patients with persistent infections
Papadimitriou-Olivgeris 2021 [43]	115 critically ill patients with CR bloodstream infections; 1 treated with ceftazidime-avibactam	1/1 (100%)	*K. pneumoniae* (KPC-2, KPC-3)	NR	1/1 (100%)	NR[e]	NR[e]	NR	NR
Rahmati 2017 [39]	11 patients, median age 49 years, 73% female 27% solid organ transplant recipients	6/11 (55%)	*K. pneumoniae* (KPC-2, KPC-3)	Dose NR, median (range) duration 15 (3–43) days	2/11 (18%)	Clinical success 8/11 (73%)	2/11 (18%)[f]		Recurrence occurred in 2/11 patients (18%) Decreased sensitivity to ceftazidime-avibactam noted in 1/11 patients (9%) 3/11 patients (27%) had CRE isolated after ≥ 7 days treatment
Rodríguez-Núñez 2018 [40]	8 patients, ages 51–71 years, 88% male Infection sources included respiratory tract (n = 5), osteomyelitis (n = 1), meningitis (n = 1), catheter-related bacteraemia (n = 1)	1/8 (13%)	*P. aeruginosa* (MDR and XDR)	Dose NR, range 7–34 days	6/8 (75%)	Clinical cure achieved in 4/8 (50%) patients	1/8 (13%)	3/8 (38%)	1 patient (13%) developed encephalopathy that improved with drug discontinuation

Table 3 continued

Publication	Patient characteristics	Patients with bacteraemia, n/N (%)	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Concomitant antibiotics, n/N (%)	Reported outcomes			
						Clinical and/or microbiological cure	30-day mortality	90-day mortality	Adverse events/safety
Shields 2018 [32]	77 consecutive patients with CRE infections treated with ceftazidime-avibactam for ≥ 72 h; mean age 62 years, 61% male	20/77 (26%)	KPC-KP	Standard dose, median (range) 14 (4–71) days	24/77 (31%)	Clinical success was achieved for 55% of patients but differed by the site of infection. Success rates were lowest for pneumonia (36%) and highest for bacteraemia (75%) and UTI (88%)	81%	69%	Resistance emergence to ceftazidime-avibactam reported in 8/77 patients (10%)
Temkin 2017 [41]	38 patients who received ceftazidime-avibactam salvage therapy on a compassionate-use basis, median age 61 years, 66% male	26/38 (68%)	CRE (n = 36); *P. aeruginosa* (n = 2)	Standard dose for 24 patients; adjusted for renal function in 14 patients, median 16 days	25/38 (66%)	28 patients (74%) experienced clinical and/or microbiological cure	NR	NR	5 patients (21%) with documented microbiological cure died, 10 patients (71%) with no documented microbiological cure died
Tumbarello 2021 [47]	55 patients who received ceftazidime-avibactam for > 72 h, median age 66 years, 67% male	391/577 (68%)	KPC-KP	Dose NR, median 12 days	412/577 (71%)	Infection relapse: 63/577 (11%)	146/577 (25%)	NR	Resistance emergence to ceftazidime-avibactam reported in 20 patients (3%) Adverse events reported in 20 patients (3%)
Vena et al. [42]	41 patients with non-CRE MDR Gram-negative, median age 62 years, 68% male	14/41 (34%)	*P. aeruginosa* (n = 38) ESBL-positive Enterobacterales (n = 7) > 50% of isolates XDR	Dose NR, median 12 days	33/41 (80%)	Clinical success at the end of the follow-up period was 37/ 41 (91%) 1 patient (2%) had recurrent infection	NR	NR	No adverse events related to ceftazidime-avibactam treatment No resistance development was documented in any patient

CCI Charlson Comorbidity Index score, *CRKP* carbapenem-resistant *Klebsiella pneumoniae*, *CRRT* continuous renal replacement therapy, *CT* computed tomography, *KPC-KP K. pneumoniae* carbapenemase-producing *K. pneumoniae*, *MDR* multidrug-resistant, *MIC* minimum inhibitory concentration, *MRI* magnetic resonance imaging, *NR* not reported, *q8h* every 8 h, *UTI* urinary tract infection, *XDR* extensively drug resistant

[a] In-hospital mortality 2/10 (20%) patients

[b] In-hospital mortality 19/60 (32%) patients

[c] Fourteen-day and 30-day mortality rates were 4/20 (25%) and 11/20 (55%), respectively. No significant difference was found in 30-day mortality between treatment with CAZ/AVI monotherapy and combination regimens ($P > 0.05$)

[d] Eight of 28 (29%) deaths occurred during the course of the 18-month study; of the 8 deaths, 3 were due to the patient succumbing to overwhelming infection and the others were unrelated to the infection

[e] Overall 30-day mortality was 39.1%; among 51 patients with septic shock, 30-day mortality was 54.9%. Multivariate analysis identified the development of septic shock, Charlson comorbidity index, and bacteraemia other than primary or catheter related as independent predictors of mortality, while a combination of at least three antimicrobials was identified as an independent predictor of survival. Thirty-day mortality was 0/1 for a combination regimen of ceftazidime-avibactam + colistin + tigecycline

[f] In-hospital mortality for 3/11 (27%) patients. Three of four patients (75%) receiving CRRT or haemodialysis died ($P = 0.02$)

Table 4 Overview of case series involving ceftazidime-avibactam for the treatment of infections caused by Gram-negative organisms with limited treatment options

Publication	Patient characteristics	Patients with bacteraemia, n/N (%)	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Concomitant antibiotics, n/N (%)	Reported outcomes			
						Clinical and/or microbiological cure	30-day mortality	90-day mortality	Adverse events/safety
Algwizani 2018 [48]	6 male patients, age 15–87 years 3 patients were on mechanical ventilation, 1 was on CRRT	2/6 (33%)	CRPA (*n* = 3) CRKP (*n* = 3; 2 with OXA-48, 1 with NDM and OXA-48)	2.5 g q8h, adjusted for renal function, Range 9–30 days	3/6 (50%)	5/6 (83%)	1/6 (17%)	NR	1 patient (17%) died 9 days after starting ceftazidime-avibactam treatment (NDM and OXA-48 *K. pneumoniae* CLABSI and VAP)
Amore 2020 [63]	7 lung transplant patients had *P. aeruginosa* and *K. pneumoniae* MDR isolated from BAL; 3 received ceftazidime-avibactam, 3 received ceftolozane-tazobactam, 1 received both agents	0	*P. aeruginosa* (*n* = 1) *K. pneumoniae* MDR (*n* = 3)	2.5 g q8h (no renal adjustments required) Range 8–24 days	1/4 (25%)	NR	NR	NR	1 patient (14%) died of primary graft dysfunction 15 days after LTx (treatment group NR); BAL performed 10 days after start of therapy was sterile
Chen 2020 [64]	10 male lung transplant recipients (age 31–68 years); infections after Tx included pneumonia and/or tracheobronchitis (*n* = 9), cholecystitis and BSI (*n* = 1)	1/10 (10%)	CRKP (*n* = 9) CRPA (*n* = 1)	2.5 g q8h, 8–24 days 6 patients (60%) started ceftazidime-avibactam as salvage therapy after a first-line treatment with other antimicrobials	8/10 (80%)	9 patients (90%) achieved negative microbiological culture of CRKP/CRPA, within a median (range) of 6.7 (1–15) days	0	1/10 (10%)	5 patients (50%) had relapse of CRKP/CRPA infections in the respiratory tract
De la Calle 2019 [49]	24 episodes of infection in 23 patients, mean (SD) age 59 (16) years, 83% male	8/24 (33%)	CPE (*n* = 24; all OXA-48)	Doses NR Median (IQR) 14 (8.5–30) days	10/24 (42%)	Clinical success: 63% Recurrence: 35%	2/24 (8%)	5/24 (21%)	4/23 patients (19%) experienced adverse events attributed to ceftazidime-avibactam
Gallagher 2016 [50]	15 patients, median (range) age 61 (31–92) years, 47% male	10/15 (67%)	CRKP (*n* = 12) Other CRE (*n* = 2)[a] CRPA (*n* = 1)	NR	NR	Clinical success: 5/11 (45%) Microbiological success: 13/15 (87%)	In hospital: 10/15 (67%)	NR	Hypersensitivity reaction in 1 patient (7%); transient LFT elevations in 2 patients (13%)
Guimarães 2019	29 patients, mean age 51 years, 62% male	12/29 (41%)	CRKP (*n* = 28) *S. marcescens* (*n* = 2)	2.5 g q8h adjusted for renal function Mean (range) 12 (2–24) days	14/29 (48%)	Clinical success: 24/29 (83%) overall; 8/12 (75%) for bacteraemic cases	15 (52%)	NR	4/29 patients (14%) experienced adverse events

Table 4 continued

Publication	Patient characteristics	Patients with bacteraemia, n/N (%)	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Concomitant antibiotics, n/N (%)	Reported outcomes			
						Clinical and/or microbiological cure	30-day mortality	90-day mortality	Adverse events/safety
Los-Arcos 2019 [52]	2 patients with CF, ages 30 and 32 years, both male Ceftazidime-avibactam prophylaxis during lung transplant and for post-operative relapse of respiratory infection	1/2 (50%)	PDR *B. cepacia* complex (*n* = 2) MRSA (*n* = 1)	2.5 g q8h (prophylaxis; lung transplant) 2.5 g q8h, 15 days (post-transplant)	2/2 (100%)	2/2 (100%)	NR	NR	1/2 patients (50%) died after 10 months due to severe *B. cepacia* sinusitis with intracranial invasion
Meschiari 2020 [61]	3 patients (age 29–66 years, 2 male) with neurosurgical infections Patients 1 and 3 (both male) were treated with ceftazidime-avibactam (patient 1 after switching from ceftolozane-tazobactam)	0	XDR *P. aeruginosa* (*n* = 2) KPC-KP (*n* = 1)	Patient 1: 2.5 g q6h extended infusion (off-label dose) Patient 3: 2.5 g q8h	Patient 1: aztreonam 2 g q6h for 6 weeks Patient 3: colistin then switch to aztreonam 2 g q6h for 8 weeks	Patient 1: complete resolution of vertebral osteomyelitis by MRI after 100 days Patient 3: complete resolution of vertebral osteomyelitis by CT after 60 days	NR	NR	Patient 1: NR Patient 3: Rectal swab performed for routinely screening at the end of treatment yielded XDR PA with acquired resistance to ceftazidime-avibactam (MIC = 16 mg/l)
Metafuni 2019 [53]	3 patients, ages 52–69 years, all male	3/3 (100%)	KPC-KP (*n* = 2) MDR *P. aeruginosa* (*n* = 1)	2.5 g q8h, added to current antibiotics combination Median (range) 15 (12–16) days	3/3 (100%)	2/3 (67%)	1/3 (33%)	NR	1/3 patients (33%) had resolution of fever but died after 12 days of treatment (respiratory failure and massive bleeding)
Micozzi 2018[54]	8 colistin-resistant CRKP rectal carriers (age/sex NR) developed fever during profound neutropenia and received empiric ceftazidime-avibactam treatment	6/8 (50%)	KPC-KP (*n* = 2) CoNS (*n* = 3) *K. oxytoca* (*n* = 1)	Doses NR Mean (range) 13.6 (10–28) days; 9.8 (6–17) days during profound neutropenia	2/8 (25%)	1 patient (13%) developed pneumonia No Gram-negative breakthrough bacteraemia occurred	NR	NR	NR
Santevecchi 2018 [55]	10 patients, ages 32–74 years, 50% male 8 patients had renal impairment, including 4 undergoing CRRT	2/10 (20%)	MDR *P. aeruginosa* (*n* = 8) CRE (*n* = 9) Other (*n* = 4)[b]	Doses NR, adjusted for renal function Median (range) 16 (4–50) days	5/10 (50%)	Clinical success: 7/10 (70%); 2/4 CRRT patients (50%) Microbiological cure: 6/9 (67%); 3/4 (75%) CRRT patients	3/10 (30%)	NR	2/10 patients (20%) developed emergence of resistance while on therapy with ceftazidime-avibactam

Table 4 continued

Publication	Patient characteristics	Patients with bacteraemia, n/N (%)	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Concomitant antibiotics, n/N (%)	Reported outcomes			
						Clinical and/or microbiological cure	30-day mortality	90-day mortality	Adverse events/safety
Shields 2016 [56]	37 consecutive patients; median (range) age: 64 (26–78) years; 57% male	12/37 (32%)	CRKP (n = 31; 90% harboured a *blaKPC* gene) Other CRE (n = 6)[c]	2.5 g q8h adjusted for renal function Median (range) 14 (4–71) days	11/37 (30%)	22/37 (59%)	9/37 (24%)	14/37 (38%)	Ceftazidime-avibactam resistance emergence occurred in 3/10 of microbiological failures (30%)
Spoletini 2019 [57]	8 patients with CF (63% female, ages 22–41 years) received 15 courses of ceftazidime-avibactam (1–4 courses/patient)	1/8 (13%)	MDR *P. aeruginosa* (n = 6) Other (n = 4)[d]	Doses NR Range 12–145 days	8/8 (100%)	Effective clinical response seen in 13/15 courses (87%)	NR	NR	2/8 patients (25%) with a very poor prognosis died owing to complex underlying lung pathology
van Asten 2021 [60]	5 patients (age 42–69 years, 60% male) with KPC-KP infections and phenotypic development of ceftazidime-avibactam resistance	3/5 (60%)	KPC-KP (n = 5)	Dose NR Range 12–145 days	4/5 (80%)	4/5 patients (80%) were alive after a range of 64–138 days	NR	NR	Ceftazidime-avibactam resistance was identified after 21–42 days In vitro restoration of carbapenem susceptibility during treatment was observed in 3 isolates
Wang 2020 [62]	6 patients (age 37–55 years, 3 male) with donor-related CRKP infection following renal transplant; 3 were treated with ceftazidime-avibactam ± other antibiotics	1/3 (33%)	CRKP (n = 3)	Dose NR Range 12–145 days	3/3 (100%)	Patients 4 and 5 were cured at Days 28 and 56 respectively Patient 6 achieved microbiological clearance at Day 30	0	1/3 (33%)	Patient 6 died at Day 60
Wu 2016 [58]	3 female patients (UTI, n = 2, endocarditis n = 1) with secondary bacteraemia; 1 patient was in septic shock and 2 had CKD	3/3 (100%)	CRE (n = 3)	Doses NR, adjusted for renal function Range 10–42 days	NR	3/3 (100%)	NR	NR	NR

Table 4 continued

Publication	Patient characteristics	Patients with bacteraemia, n/N (%)	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Concomitant antibiotics, n/N (%)	Reported outcomes			
						Clinical and/or microbiological cure	30-day mortality	90-day mortality	Adverse events/safety
Xipell 2017 [59]	2 patients (69-year-old male and 56-year-old female) with severe XDR *P. aeruginosa* infections	1/2 (50%)	XDR *P. aeruginosa* ($n = 2$)	2.5 g q8h Range 18–30 days	2/2 (100%)	2/2 (100%)	NR	NR	NR

BAL bronchoalveolar lavage, *CF* cystic fibrosis, *CI* confidence interval, *CKD* chronic kidney disease, *CLABSI* central line-associated bloodstream infection, *CoNS* coagulase-negative *Staphylococci*, *CPE* carbapenemase-producing Enterobacterales, *CR* carbapenem resistant, *CRE* carbapenem-resistant Enterobacterales, *CRKP* carbapenem-resistant *Klebsiella pneumoniae*, *CRP* C-reactive protein, *CRRT* continuous renal replacement therapy, *CT* computed tomography, *IQR* interquartile range, *KPC-KP K. pneumoniae* carbapenemase-producing *K. pneumoniae*, *LFT* liver function test, *MDR* multidrug resistant, *MIC* minimum inhibitory concentration, *MRI* magnetic resonance imaging, *MRSA* methicillin resistant *Staphylococcus aureus*, *NR* not reported, *PDR* pan-drug resistant, *q6h* every 6 h, *q8h* every 8 h, *SD* standard deviation, *UTI* urinary tract infection, *VAP* ventilator-associated pneumonia, *XDR* extensively drug-resistant

[a] *Escherichia coli* ($n = 1$); *Enterobacter aerogenes* ($n = 1$)

[b] *Stenotrophomonas maltophilia* ($n = 2$); *Achromobacter xylosoxidans* ($n = 1$); *Acinetobacter* spp. ($n = 1$)

[c] *Escherichia coli* ($n = 3$); *Enterobacter cloacae* ($n = 2$); *Enterobacter aerogenes* ($n = 1$)

[d] *Burkholderia cenocepacia* ($n = 2$); *Burkholderia multivorans* ($n = 1$); *Burkholderia vietnamiensis* ($n = 1$)

metallo-β-lactamase (NDM) and OXA-48 and a second with an unknown mechanism]. Similarly, only 27 of 63 *P. aeruginosa* isolates underwent baseline testing for ceftazidime-avibactam susceptibility, of which 26 were susceptible and one was resistant with NDM and OXA-type carbapenemases. Ceftazidime-avibactam resistance development on treatment was not detected in any of the 61 patients (30%) with available follow-up cultures. In total, 17 patients (8%) experienced potential drug-related adverse effects [34].

Shields et al. (2018) reported an analysis of 77 consecutive patients with CRE infections treated with ceftazidime-avibactam for ≥ 3 days in a US hospital [32]. Thirty- and 90-day survival rates were 81% and 69%, respectively. Clinical success was 55% overall but differed by infection site (pneumonia, 36%; bacteraemia, 75%; UTI, 88%). Pneumonia ($P = 0.045$) and receipt of renal replacement therapy [either intermittent haemodialysis or continuous renal replacement therapy (CRRT); $P = 0.046$] were associated with clinical failure in multivariate analysis. Microbiological failure occurred in 32% of patients and was more common among patients with KPC-3-producing CRE versus KPC-2-producing CRE infections ($P = 0.002$). Pneumonia was an independent predictor of microbiological failure ($P = 0.007$). Ceftazidime-avibactam resistance (all in *K. pneumoniae* harbouring variant KPC-3 enzymes) emerged in eight (10%) patients. Renal replacement therapy was an independent predictor of resistance development ($P = 0.009$). Importantly, the authors noted that 'optimal dosing of ceftazidime-avibactam in patients with renal insufficiency, particularly those receiving CRRT, is an ongoing challenge for clinicians'. Of note, appropriate ceftazidime-avibactam dosage regimens for patients receiving CRRT have not been established, and there are currently no approved dose recommendations for such patients. Similar rates of resistance emergence were reported in a Spanish study of 47 patients with CRKP infections (Castón et al. 2020) and in an Italian study (Iannacone et al. 2020) of 23 patients with CRE infections [46] (Table 3).

In a further US retrospective, multicentre study in 60 severely ill patients with CRE

Table 5 Overview of case reports involving ceftazidime-avibactam for the treatment of Gram-negative infections with limited treatment options

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Barlow 2018 [66]	Young adult patient (age/sex NR) with ΔF508-homozygous CF, chronic airflow limitation, pancreatic insufficiency, and frequent respiratory exacerbations presented with increasing shortness of breath and cough productive of green sputum severe enough for hospital admission	No	XDR *B. multivorans*	2.5 g q8h, 2 weeks	FEV1 improved from a baseline of 0.9 to 1.24 l (39% of predicted), the patient's best spirometric values for 3 years; patient was not readmitted to hospital in the 5 months since treatment
Bulbin 2017 [67]	66-year-old male, bacterial isolates in lumbar wound and blood culture following elective L2-pelvis posterior spinal fusion Comorbidities including spinal stenosis, chronic back pain, remote L4-L5 laminectomy, diabetes, and hypertension	Yes	KPC-KP	1.25 g q8h, 6 weeks	During the 6 weeks of treatment, the patient's back pain improved CT showed no evidence of discitis or osteomyelitis, approximately 9 weeks after second surgery. Fluid aspirated from a thecal sac at L5 level was sterile Steady clinical improvement was reported at 6, 12, and 18 months after discharge
Camargo 2015 [68]	64-year-old female, bacteraemia following IAI and bowel transplant	Yes	CRKP	1.25 g q8h, 2 weeks	The patient responded well, and blood cultures were negative 24 h after initiating ceftazidime-avibactam + ertapenem

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Cantón-Bulnes 2019 [69]	27-year-old male, lung transplantation due to CF; bacteraemic pneumonia	Yes	*B. cepacia* complex (PDR)	2.5 g q8h, 26 days	Blood cultures negative 72 h after the start of combined antibiotic treatment. On day 4, vasopressor support was stopped. On day 7, renal function was recovered and CRRT was stopped. On day 15, BAL fluid was culture-negative. The patient was transferred to the ward 3 weeks after his second ICU admission and was discharged home 10 days later
Carannante 2018 [70]	Bangladeshi male migrant from Libya (age NR), cellulitis with KPC-KP	No	KPC-KP	Dose NR, 10 days	After 10 days of treatment, cultures and molecular tests resulted negative both from ulcers and rectal swabs
Caravaca-Fontán 2015 [71]	78-year-old male kidney transplant recipient, recurring UTI	No	KPC-KP	1.25 g q12h, 2 weeks	Definitive eradication of the urinary infection as well as the KPC carrier state
Daccò 2019 [72]	32-year-old female with lung transplantation due to CF, post-surgery bacteraemia and brain abscesses Comorbidities including diabetes, ESRD on HD	Yes	*B. multivorans*	2.5 g q24h (after HD), added on day 19, increased to 2.5 g q12h on day 33, continued to day 129	The patient was discharged on day 135. Brain MRIs 1 and 4 months later documented an almost complete resolution of the parenchymal abscesses. No adverse events were reported throughout the entire treatment period

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
De León-Borrás 2018 [73]	36-year-old male; refractory bacteraemia with KPC-KP. Also, vertebral L1-L2 diskitis and osteomyelitis with pre-vertebral abscess and bilateral psoas pyomyositis; admitted to hospital with diabetic ketoacidosis and pneumonia; persistent bacteraemia was unsuccessfully treated with amikacin + carbapenems + polymyxin B	Yes	KPC-KP	Dose NR, 6 weeks	Fever subsided 6 days after starting ceftazidime-avibactam and blood cultures on day 13 were negative; polymyxin B and amikacin were discontinued The patient completed 6 weeks of ceftazidime-avibactam, attaining complete resolution of the infectious processes. No adverse effects were reported and the patient was discharged home
Gofman 2018 [74]	32-year-old male with intracranial haemorrhage due to traumatic injury; ventriculitis and sepsis	No	*P. aeruginosa* CRKP *Streptococcus viridans*	2.5 g q8h, 6 weeks	CSF cultures were sterile after 3 days' treatment with ceftazidime-avibactam + intrathecal amikacin, with treatment continued for 4 and 6 weeks, respectively. The patient did not experience any seizures or neurological deficits and was transferred to a long-term care facility for rehabilitation

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Gugliandolo 2017 [75]	27-year-old male; LRTI following traumatic brain injury and chest trauma. No known comorbidities	Yes	*K. pneumoniae* (KPC-3)	2.5 g q8h, 2 weeks	Resolution of fever and improvement in WBC/inflammatory markers within 2 days. A week after the end of the therapy, urine and blood cultures were negative, oropharyngeal bacterial flora was normal. Only rectal swab was still positive for *K. pneumonia*e. A month later rectal swabs were also culture-negative for *K. pneumoniae*
Guedes 2020 [76]	61-year-old male with secondary peritonitis and IAI, initially managed with piperacillin/tazobactam and surgical debridement; 1 week later, patient presented with clinical deterioration and was admitted to ICU with nosocomial pneumonia	No	KPC-KP	Dose NR, 13 days	Prior antibiotics included vancomycin, meropenem, colistin and gentamicin; switched to ceftazidime-avibactam + tigecycline followed by colistin + high dose tigecycline 13 days of ceftazidime-avibactam + tigecycline was completed without any adverse events. Inflammatory markers and abdominal CT scan showed resolution of IAI. The patient was discharged 3 months after hospital admission without clinical signs of IAI

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Gonzales Zamora 2018 [77]	85-year-old female, nosocomial pneumonia and bacteraemia; intubated and in ICU; 1st- and 2nd-degree burns and CVVH After 12 days of antibiotic treatment for MRSA pneumonia, developed *Enterococcus faecalis* bacteraemia, and 3 days later endotracheal aspirates and blood cultures were positive for *Raoultella planticola*	Yes	*Enterococcus faecalis* *Raoultella planticola* (KPC) *Morganella morganii* MRSA	Dose NR, 2 weeks	Follow-up blood cultures were negative, the patient's respiratory status improved over the following days, and she was transferred to a long-term acute care facility to complete 2 weeks of antibiotic therapy
Holyk 2018 [78]	Elderly patient (age/sex NR), intubated with intraventricular haemorrhage and post-neurosurgical meningitis with CRKP identified in BAL fluid and EVD cultures	No	*K. pneumoniae* (MDR/CRE)	2.5 g q8h (days 26–29 and 31–52)	All repeat cultures after day 31 were negative. Treatment concluded after 21 days of ceftazidime-avibactam and 15 days of intraventricular gentamicin. 1-day post-completion of ceftazidime-avibactam, the EVD was removed and a ventriculoperitoneal shunt was placed. Throughout the hospital stay, the patient remained largely unchanged neurologically. On day 74, the patient was discharged to a long-term care facility

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Iacovelli 2018 [79]	49-year-old male with septic thrombophlebitis and right atrial endocarditis, developed VAP due to KPC-KP	Yes	KPC-KP	2.5 g q8h, 47 days	There was an apparent discrepancy between clinical and microbiological courses: the patient became rapidly afebrile; haemodynamically stable and his procalcitonin levels improved. Nevertheless, blood cultures remained persistently positive until day 80. Patient was clinically stable for 5 months with no signs of infection recurrence but died suddenly 6 months after discharge
Jacobs 2016 [80]	47-year-old female kidney transplant recipient; admitted to ICU with post-transplant complications; abdominal abscess and CRKP bacteraemia developed on day 6; CRRT initiated due to AKI secondary to sepsis	Yes	CRKP	2.5 g q8h (4-h extended infusions), 32 days	Bacteraemia was cleared after femoral line exchange. Patient died on day 37 post-surgery

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Park 2019 [82]	35-year-old male with cirrhosis, colonised with both blaKPC- and blaOXA-48-carrying organisms; intubated and undergoing CRRT	Yes	*Raoultella planticola* (OXA-48)	2.5 g q8h for 14 days	Blood cultures on hospital Days 21 and 26 were negative. His treatment course was complicated by another MICU readmission for intubation and CRRT due to worsening kidney injury and respiratory failure. Patient was transferred back to the floor unit on day 39 but returned to the MICU on Day 43. The patient/his family decided to pursue comfort measures only, and he died shortly afterwards
Parruti 2019 [83]	53-year-old male with paraplegia due to RTA; multiple vertebral fractures Multiple sepsis episodes due to skin and soft tissue infection	Yes	KPC-KP	Dose NR, 16 days	Patient was discharged on Day 31 to a local rehabilitation facility and finally discharged home after 56 days. His procalcitonin, CRP, and blood cultures were all negative 40 days after discharge. At his last follow-up visit (nearly a year after discharge), the patient had persistently normal clinical and laboratory parameters

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Pingue 2020 [84]	~ 70-year-old female, post neurosurgical complications, including sepsis and possible cUTI	Yes	*P. aeruginosa* KPC-KP	2.5 g q8h, 2 weeks	Patient had normal renal function on admission. Initially treated with empiric vancomycin and meropenem. Following positive blood culture for KPC-KP, switched to ceftazidime-avibactam + fosfomycin with positive clinical course. On Day 6, patient developed focal seizures and progressive impaired awareness (indicative of neurotoxicity associated with cephalosporins); blood creatine levels remained normal. Investigations revealed aseptic meningeal inflammation and damage to blood brain barrier Ceftazidime-avibactam was discontinued on Day 15 with sepsis resolution, and the patient's neurological status improved; 2 weeks later, brain CT confirmed resolution of meningeal involvement

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Nguyen 2020 [81]	16-year-old female with CF; admitted with acute pulmonary exacerbation caused by *B. cepacia* complex	No	*B. cepacia* complex (MDR)	2.5 g q8h, 2 weeks; 36 days before resistance identified	Initially treated with tobramycin, meropenem and minocycline. On Day 7, minocycline was switched to ceftazidime-avibactam based on culture/susceptibility results. Following stabilisation of lung function, patient discharged home on Day 12 to complete an additional 7 days of ceftazidime-avibactam + meropenem. On day 50, patient was readmitted and cultures showed an increase in ceftazidime-avibactam MIC from 1 to 3 mg/l
Räisänen 2019 [85]	Patient in Finland (age/sex NR) transferred from a hospital in Greece who had been colonised with blaKPC-2-producing *K. pneumoniae* ST39 Bacteraemia developed 16 days after initial infection	Yes	*K. pneumoniae* (KPC-2, ST39)	Dose NR, 34 days before resistance identified	Patient recovered from the infection following discontinuation of ceftazidime-avibactam and subsequent 12 days administration of sulfamethoxazole-trimethoprim and colistin Ceftazidime-avibactam resistance was observed after 34 days of treatment. The strain isolated after ceftazidime-avibactam treatment had a mutated *blaKPC-2* gene encoding KPC-2 protein with 15 amino acid insertion; the observed mutation in *blaKPC-2* gene has not been described previously

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Rico-Nieto 2018 [86]	29-year-old female with infection of a lumbar instrumentation	No	*K. pneumoniae* (OXA-48)	2.5 g q8h, 8 weeks	The patient improved clinically after 8 weeks and without toxicity. After 1 year, she remained stable and without further infection or need for surgery. Implanted osteosynthesis material has remained in situ without the need for removal/modification
Samuel 2016 [87]	27-year-old male with post-neurosurgical meningitis	No	*K. pneumoniae* (KPC)	2.5 g q6h, 2 weeks	The patient was treated successfully with ceftazidime-avibactam monotherapy (NB non-approved dosage regimen)
Schimmenti 2018 [88]	26-year-old male with prosthetic joint infection; right knee replacement following multiple fractures due to a fall. Previous fracture of left femur, Von Willebrand disease and depressive disorder	No	*K. pneumoniae* (KPC)	2.5 g q8h, 2 weeks	No signs and symptoms of infection 32 days after commencement of ceftazidime-avibactam. During the latest orthopaedic follow-up visit, the patient had no signs and symptoms of infection, was walking with the help of crutches, and continued being treated with physical therapy

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Shields 2017 [89]	67-year-old male with oesophageal cancer underwent esophagectomy, complicated by kidney injury necessitating CRRT, developed VAP (treated with ceftazidime-avibactam) and subsequently intra-abdominal abscess and bacteraemia with ceftazidime-avibactam-resistant *K. pneumoniae*	Yes	*K. pneumoniae* (KPC-3, ST258)	1.25 g q8h, 15 days	VAP treated successfully with ceftazidime-avibactam + inhaled gentamicin 10 days later, patient developed leucocytosis. CT scan revealed an intra-abdominal abscess. Ceftazidime-avibactam was restarted empirically. Drainage culture grew ceftazidime-avibactam-resistant meropenem-susceptible *K pneumoniae*. Ceftazidime-avibactam was continued for 15 days, the abscess was surgically drained, and the patient improved. Several weeks later, the patient developed ceftazidime-avibactam-resistant meropenem-susceptible *K pneumoniae* bacteraemia. He was treated successfully with meropenem for 18 days and subsequently discharged

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Wang 2020 [90]	Renal transplant patient; initial prophylactic tigecycline discontinued at post-transplant Day 10; on Day 15, patient developed multisite CRKP infection involving the bloodstream, urinary tract, and lungs, indicating probable transmission from the donor	Yes	CRKP	2.5 g q12h, 15 days	Infection was controlled quickly and effectively with a combination therapy consisting of ceftazidime-avibactam + meropenem However, the CRKP infection reappeared in the bloodstream and urinary tract soon after the treatment of acute rejection. Ceftazidime-avibactam + meropenem was continued for 15 days, and the patient ultimately recovered. On Day 40, another recurrence of infection was treated with ceftazidime-avibactam + imipenem (15 days) followed by meropenem. During the following 15 months of observation, the patient's renal graft function remained stable, without recurrence of the CRKP infection

Table 5 continued

Publication	Patient history and comorbidities	Bacteraemia	Baseline pathogens (resistance mechanisms)	Ceftazidime-avibactam dose and duration	Reported outcomes
Yasmin 2020 [91]	38-year-old male with head trauma requiring surgery; prolonged hospitalisation requiring MV and intrathecal pump; readmitted with acute pyogenic meningitis	Yes	*K. pneumoniae* (KPC-3)	2.5 g q8h, 10 days	Prior antibiotics included meropenem, vancomycin, meropenem-vaborbactam and ciprofloxacin Following initiation of ceftazidime-avibactam + intrathecal amikacin, patient had microbiological clearance after 10 days and showed gradual clinical improvement

AKI acute kidney injury, *BAL* bronchoalveolar lavage, *CF* cystic fibrosis, *CRE* carbapenem-resistant Enterobacterales, *CRKP* carbapenem-resistant *K. pneumoniae, CRP* C-reactive protein, *CRRT* continuous renal replacement therapy, *CSF* cerebrospinal fluid, *CT* computerised tomography, *CVVH* continuous veno-venous haemofiltration, *ESRD* end-stage renal disease, *EVD* external ventricular drain, *FEV1* forced expiratory volume in 1 s, *HD* haemodialysis, *IAI* intra-abdominal infection, *ICU* intensive care unit, *KPC K. pneumoniae* carbapenemase, *KPC-KP K. pneumoniae* carbapenemase-producing *K. pneumoniae*, *LRTI* lower respiratory tract infection, *MDR* multidrug-resistant, *MICU* medical intensive care unit, *MRI* magnetic resonance imaging, *MRSA* methicillin-resistant *Staphylococcus aureus*, *NR* not reported, *q6h* every 6 h, *q8h* every 8 h, *q12h* every 12 h, *q24h* every 24 h, *RTA* road traffic accident, *ST* sequence type, *UTI* urinary tract infection, *VAP* ventilator-associated pneumonia, *WBC* white blood cell, *XDR* extensively drug resistant

infections treated with ceftazidime-avibactam, King el al. (2017) reported that in-hospital mortality, microbiological cure, and clinical success occurred in 32%, 53%, and 65% of patients, respectively; there were no documented cases of drug-related adverse events or on-therapy resistance emergence [37].

Vena et al. (2020) reviewed outcomes for 41 patients treated with ceftazidime-avibactam for infections [predominantly nosocomial pneumonia (NP) and primary bacteraemia] caused by non-CRE MDR Gram-negative bacteria (38 isolates of *P. aeruginosa* and 7 ESBL-positive Enterobacterales, with > 50% of isolates classified as XDR), including 4 patients with polymicrobial infections, in 13 Italian hospitals [42]. Most patients received ceftazidime-avibactam as part of a combination regimen following resistance emergence or failure of initial antibiotic treatments; despite relatively severe baseline disease status (median Charlson Comorbidity Index score of 4; 24% of patients admitted to ICU and 59% with sepsis/septic shock), clinical success occurred in 37 patients (90%). Three of the four patients who were clinical failures were undergoing CRRT; all received ceftazidime-avibactam 1.25 g q8h (as noted above, there are no approved ceftazidime-avibactam dosing recommendations for patients on CRRT). No adverse events related to ceftazidime-avibactam treatment occurred, and resistance development was not documented in any patient [42].

Temkin et al. (2017) analysed outcomes for 38 patients in Europe and Australia with infections caused by carbapenem-resistant organisms (36 with CRE and two with *P. aeruginosa*), 95% of whom received ceftazidime-avibactam as salvage therapy [41]. Clinical and/or microbiological cure occurred in 28 patients (74%). Five patients (21%) with documented microbiological cure died versus ten patients (71%) with no documented microbiological cure ($P = 0.01$).

Rahmati et al. (2017) and Krapp et al. (2017) reported outcomes for 11 and 6 patients, respectively, with KPC-producing *K. pneumoniae* infections treated with ceftazidime-avibactam in the US [38, 39]. In the cohort of 11 patients, the clinical success rate was 73%, 30-day survival was 82%, 90-day survival was 73%, and in-hospital mortality was 27% [39]. Mortality was 75% among four patients receiving CRRT or haemodialysis ($P = 0.02$); however, as noted above, approved ceftazidime-avibactam dosing recommendations are not currently available for patients on CRRT (moreover, ceftazidime-avibactam dosages were not reported in this congress abstract). Recurrence occurred in two patients (18%). Decreased sensitivity to ceftazidime-avibactam was noted in one patient (9%), and three patients (27%) had CRE isolated after ≥ 7 days of treatment [39]. In the cohort of six patients, five achieved clinical cure; however, two relapsed with the same KPC-3-producing *K. pneumoniae* strain within 3 weeks of completing ceftazidime-avibactam treatment [38]. One patient with pneumonia experienced clinical failure, despite having a documented ceftazidime-avibactam-susceptible CRKP strain [minimum inhibitory concentration (MIC) = 2 mg/l]. Thus, the overall clinical success rate in this small cohort was 50% [38].

In two retrospective cohort studies involving MDR or XDR *P. aeruginosa* infections (in 8 and 10 patients in Spain and the US, respectively) in various locations (including respiratory, blood, bone/joint, skin/wound, and meningitis), clinical success rates with ceftazidime-avibactam treatment were 50–80% [36, 40]. In the Spanish study, 30- and 90-day mortality rates were 13% and 38%, respectively [40]. In-hospital mortality in the US study was 20% [36]. Kuang et al. (2021) and Nwankwo et al. (2020) reported outcomes for 21 and 28 patients with a variety of MDR Gram-negative infections treated with ceftazidime-avibactam in the UK and China, respectively; Papadimitriou-Olivgeris et al. (2021) included a single patient treated with ceftazidime-avibactam in a wider analysis of 115 critically ill patients with *K. pneumoniae* bloodstream infections (Table 3).

Finally, Katchanov et al. (2018) described a prevalence study of patients infected or colonised with MDR Gram-negative bacteria in a German tertiary care hospital, in which ceftazidime-avibactam was administered to five patients with severe HAP (and bacteraemia in one case) during an outbreak of OXA-48- and CTX-M-14-producing *K. pneumoniae* [35]. In-hospital mortality occurred in all five patients

(100%), and ceftazidime-avibactam resistance emergence on therapy was documented in one patient (three patients were not assessed for resistance emergence), prompting the authors to note that 'novel β-lactam/β-lactamase inhibitor combinations are of limited usefulness in our setting because of the high prevalence of Ambler class B carbapenemases (in *Pseudomonas* spp. and *Escherichia coli* but not in *Klebsiella* spp.) and the emergence of non-susceptibility under therapy'. Of note, the five patients received 2, 57, 86, 8, and 61 days, respectively, of ceftazidime-avibactam therapy, implying a 30-day mortality rate of 2/5 (i.e., 40%) [35].

Case Series and Case Reports

Data for 169 patients treated with ceftazidime-avibactam from 17 case series (Table 4) were identified from the literature search [48–64]. One case series of three patients (Shields et al. 2017 [65]) was excluded from the literature search results because clinical outcomes for these patients are included in another larger case series published by the same group (Shields et al. 2016 [56]); data for the latter publication are summarised in Table 4. Most of the included case series involved CRE/CPE infections (141 patients); 10 publications included data for *P. aeruginosa* infections (24 patients). Three case series reported emergence of ceftazidime-avibactam resistance on therapy in two of ten patients (20%; one *P. aeruginosa*; one *Citrobacter freundii* with KPC detected in initial isolate and undetermined mechanism of ceftazidime-avibactam resistance) [55]; 3 of 37 patients (8%; all initial isolates were KPC-3-producing *K. pneumoniae*) [56] and one of two patients (50%) were treated for XDR *P. aeruginosa* infections [61].

The literature search identified 26 case reports with data for 26 patients (Table 5) treated with ceftazidime-avibactam [66–91]. As with the other included publications, most of the case reports involved CRE/CPE infections (16 patients, of which 1 was also infected with *P. aeruginosa*). Emergence of ceftazidime-avibactam resistance on treatment was reported in one patient each in two case reports involving *K. pneumoniae* bloodstream infections (one KPC-2; one KPC-3) [85, 89], and an increase in ceftazidime-avibactam MIC was reported for a paediatric patient with cystic fibrosis and acute pulmonary exacerbation caused by *B. cepacia* complex [81].

DISCUSSION

This systematic review provides important insights into the real-world use of ceftazidime-avibactam treatment for adults with serious Gram-negative infections with limited treatment options. Although limited by potential publication bias (the tendency for positive results to be more likely to be published than negative results) and the qualitative approach necessitated by the inclusion of heterogenous data representing multiple patient populations, infection types, and bacterial pathogens, the included data are consistent with the broad definition of 'limited treatment options' in the European Summary of Product Characteristics for ceftazidime-avibactam [14] and generally reflect the expected usage of ceftazidime-avibactam in this setting.

As expected, most of the included publications involved severely ill patients with significant comorbidities; the main pathogens were CRE/CPE and *P. aeruginosa*. A large proportion of reported cases treated with ceftazidime-avibactam included either primary or secondary bacteraemia, and many involved combination treatment with other antibiotics. The relatively wide inclusion criteria for literature in the current analysis [notable exclusions were paediatric data and studies involving pathogens listed in the European Summary of Product Characteristics as non-susceptible to ceftazidime-avibactam (e.g., *Acinetobacter* spp. or MBL-producing isolates)] and the resulting large number of publications encompassing multiple patient populations, infection types, and various endpoints and definitions limit the possibility for quantitative analysis and warrant caution in generalising the findings. However, an advantage of this broad scope is the inevitable inclusion of several publications that have been subject to more formal analysis. Onorato et al. (2019) reported a meta-analysis of 11 studies

including 396 patients with CRE or carbapenem-resistant *P. aeruginosa* infections treated with ceftazidime-avibactam [92]; these 11 studies were all included in the current review. The meta-analysis by Onorato et al. was designed to assess the impact of ceftazidime-avibactam monotherapy versus combination therapy with other antibiotics. Rates of mortality [38% for combination therapy and 31% for monotherapy; risk ratio (RR) 1.18, 95% CI 0.88–1.58; $P = 0.259$] and microbiological cure (65% vs. 63%, respectively; RR 1.04, 95% CI 0.85–1.28, $P = 0.705$) were comparable for ceftazidime-avibactam as monotherapy or as part of a combination regimen [92]. A similar network meta-analysis by Fiore et al. (2020) [93] included six observational studies, all of which are also included in the current review [18, 20, 23, 28, 30, 37]. Similarly, Dietl et al. (2020) reviewed 11 observational and comparative studies of ceftazidime-avibactam in patients with CPE infections (including 8 in patients with KPC- and 3 in patients with OXA-48-producing Enterobacterales) [94], all of which were also included in the current review [18, 19, 23, 28, 30, 31, 34, 38, 41, 49, 56]. Finally, a systematic review of severe infectious complications among patients with haematological malignancies identified three studies of ceftazidime-avibactam [95], of which two were included in the current review (the third was excluded as it involved treatment of an infection caused by an MBL-producing organism) [23, 53].

The current qualitative analysis is an attempt to complement, rather than replicate, the meta-analyses and RCTs that were excluded from our dataset [92–100]. Although lacking the statistical robustness of RCTs or meta-analyses, advantages of our qualitative approach include the broad inclusion criteria and focus on observational data, in contrast to the relatively selective inclusion criteria inherent in meta-analyses and RCTs. Given these broad inclusion criteria, our dataset inevitably included a varied and heterogeneous patient population and a mixture of different assessments and outcome measures; as such, we are unable to provide overall or aggregated efficacy data for ceftazidime-avibactam across the different publications that we included. Nevertheless, this review provides important insights into how ceftazidime-avibactam is being used in practice for the treatment of serious Gram-negative infections with limited treatment options, in particular, those caused by non-MBL-producing CRE and *P. aeruginosa*. In some cases, positive clinical outcomes were reported with documented reductions in renal toxicity compared with other possible treatment options (e.g., aminoglycosides and/or colistin/polymixins). The accumulating data from RCTs and real-world clinical experience with ceftazidime-avibactam have prompted its inclusion in various national and regional guidance documents and management protocols [101–107]. For example, guidance by the Infectious Diseases Society of America for the management antimicrobial-resistant Gram-negative infections recommends ceftazidime-avibactam as a preferred treatment option for CRE and *P. aeruginosa* infections both within and outside of the urinary tract [107].

The review also highlights areas in which further research may help elucidate optimal use of ceftazidime-avibactam (for example, in patients undergoing CRRT). In addition, and not unexpectedly given the nature of the limited treatment options setting (including complicated infections and extensive and complex comorbidities), the analysis included several publications reporting resistance emergence and/or reduced susceptibility during therapy with ceftazidime-avibactam [29, 32–35, 39, 47, 55, 56, 61, 85, 89]. A further study specifically evaluated outcomes for five patients with documented resistance ceftazidime-avibactam emergence [60]. Of note, information on the timing of resistance emergence relative to initiation of ceftazidime-avibactam therapy was reported inconsistently. As with all antimicrobial agents, use of ceftazidime-avibactam should be guided, wherever possible, by pathogen culture/phenotypic susceptibility results (ideally supported by genotypic detection and characterisation of any carbapenemases identified) and local resistance patterns. In cases where patients show signs of deterioration or failure to improve, it is important that purposeful microbiological sampling is undertaken

to enable early detection of potential resistance development on therapy.

An important point to highlight regarding the inclusion criteria and data extraction is that although we endeavoured to exclude publications reporting off-label use of ceftazidime-avibactam, in some instances, we did include publications reporting data on the use of ceftazidime-avibactam outside of the approved European Summary of Product Characteristics. For example, some reported studies included patients undergoing CRRT [32, 42, 48, 50, 55], although there are no approved ceftazidime-avibactam dosing recommendations for such patients; similarly, some studies reported the use of doses of ceftazidime-avibactam (including adjustments for renal function) outside of the dosing recommendations in the European Summary of Product Characteristics. One case series reported on the use of ceftazidime-avibactam in surgical prophylaxis in two patients with cystic fibrosis undergoing lung transplantation [52] (this publication was nonetheless included because both patients also subsequently received ceftazidime-avibactam postoperatively for infections consistent with the 'limited treatment options' definition). Moreover, a few studies reported on the use of ceftazidime-avibactam in combination with other agents to treat infections caused by MBL-producing bacteria or species listed in the European Summary of Product Characteristics as inherently resistant to ceftazidime-avibactam (for example *Acinetobacter* species); we excluded such publications, except in a few instances where the data were reported alongside/within a larger patient group in which the reported use of ceftazidime-avibactam was otherwise consistent with approved labelling. A case series of three patients with XDR *P. aeruginosa* infections reported use of an off-label dose of ceftazidime-avibactam alongside aztreonam [61]; we nevertheless included these data since a second patient in the series received standard-dose ceftazidime-avibactam (plus colistin then aztreonam) and was reported to have on-therapy resistance emergence after 60 days of treatment.

Although it has been anecdotally reported that the standard ceftazidime-avibactam dosage regimen for patients with CrCL $\geq$ 50 ml/min (i.e., 2.5 g by 2-h intravenous infusions q8h) may be suitable for patients with pneumonia undergoing continuous venovenous haemodiafiltration [108, 109], it is important to note that appropriate ceftazidime-avibactam dosage regimens for patients receiving CRRT have not been established. In the retrospective study of 77 patients with CRE infections by Shields et al. (2018), 3 patients required CRRT, including 2 of the 5 patients with pneumonia [32]. Ceftazidime-avibactam doses for these three patients ranged from 0.94 g every 12 h (q12h) to 2.5 g q8h. The link between ceftazidime-avibactam underdosing and clinical failure in renal impairment was identified in the phase 3 RECLAIM trial [5] and has been further reviewed by Li et al. (2020) [110]. Considering the small sample size and variable ceftazidime-avibactam dosing in the CRRT subset in the analysis by Shields et al. [32], the reported statistical association between pneumonia and treatment failure should be interpreted with caution.

In conclusion, the data reviewed here demonstrate qualitative evidence of successful use of ceftazidime-avibactam for treatment of hospitalised patients with Gram-negative infections with limited treatment options, based on clinical and microbiological cure outcomes and mortality, including evidence of effectiveness against CRE and MDR *P. aeruginosa*. The review also highlights areas where further data are needed, for example, on the use of ceftazidime-avibactam in patients undergoing CRRT.

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