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REVIEW

Cefiderocol, a Siderophore Cephalosporin, as a Treatment Option for Infections Caused by Carbapenem-Resistant Enterobacterales

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ABSTRACT

Carbapenem-resistant Enterobacterales (CRE) remain a significant public health threat, and, despite recent approvals, new antibiotics are needed. Severe infections caused by CRE, such as nosocomial pneumonia and bloodstream infections, are associated with a relatively high risk of morbidity and mortality. The recent approval of ceftazidime–avibactam, imipenem–relebactam, meropenem–vaborbactam, plazomicin, eravacycline and cefiderocol has broadened the armamentarium for the treatment of patients with CRE infections. Cefiderocol is a siderophore cephalosporin with overall potent in vitro activity against CRE. It is taken up via iron transport channels through active transport, with some entry into bacteria through traditional porin channels. Cefiderocol is relatively stable against hydrolysis by most serine- and metallo-beta-lactamases, including KPC, NDM, VIM, IMP and OXA carbapenemases—the most frequent carbapenemases detected in CRE. The efficacy and safety of cefiderocol has been demonstrated in three randomised, prospective, parallel group or controlled clinical studies in patients at risk of being infected by multidrug-resistant or carbapenem-resistant Gram-negative bacteria. This paper reviews the in vitro activity, emergence of resistance, preclinical effectiveness, and clinical experience for cefiderocol, and its role in the management of patients with CRE infections.

Keywords: Carbapenem resistance; Carbapenemase; Cefiderocol; Enterobacterales; *Klebsiella pneumoniae*; Resistance

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Key Summary Points

Infections caused by carbapenem-resistant Enterobacterales (CRE) remain a challenging threat to public health, despite recent achievements in antibiotic development.

A range of resistance mechanisms exist in CRE, which makes antibiotic development challenging, as new antibiotics may overcome only some mechanisms and emerging resistance could also hinder their long-term use.

Cefiderocol is a siderophore cephalosporin with a unique mode of entry into Gram-negative bacteria, which has shown potent in vitro activity against CRE with any of the major carbapenem-resistance mechanisms from global collections.

Cefiderocol was efficacious in the treatment of Gram-negative bacterial infections caused by CRE strains producing metallo-beta-lactamases, *Klebsiella pneumoniae* carbapenemase and OXA-48 enzymes.

Cefiderocol has been approved in the USA for the treatment of adult patients with ventilator-associated bacterial pneumonia, hospital-acquired bacterial pneumonia, and complicated urinary tract infections, and in Europe for the treatment of adult patients with infections caused by susceptible Gram-negative bacteria with limited treatment options.

INTRODUCTION

Burden of Carbapenem-Resistant Enterobacterales

Carbapenem-resistant (CR) Enterobacterales (CRE), particularly CR *Klebsiella pneumoniae* and CR *Escherichia coli*, constitute a major global health threat [1–3]. According to the World Health Organization (WHO), between 2016 and 2020 there was a significantly increasing trend in the carbapenem resistance rate among *E. coli* and *K. pneumoniae* [2], with some countries reporting prevalence as high as ≥ 50% for CR *K. pneumoniae* [2]. CRE infections may emerge among patients hospitalised in acute care hospitals, in long-term care facilities, and in patients in community settings [4–7]. Data from prospective studies in the US ($n = 1040$) and China ($n = 128$) report that, among hospitalised patients, CRE most commonly cause urinary tract infections (UTI) and lower respiratory tract infections, followed by bloodstream infections (BSI), wound infections and, less frequently, intra-abdominal infections (IAI) [7, 8]. Colonisation by CRE of mucosal surfaces is one of the risk factors for acquiring subsequent infections; thus, active screening may play a role not only in infection control but also for appropriate patient management and antibiotic stewardship [7–9].

Risk factors for CRE colonisation and/or infection are similar to those identified for all CR Gram-negative infections [10], being associated with the host (e.g., older age), hospitalisation (e.g., number of previous hospitalisations, emergency department stay > 2 days prior to intensive care unit admission), treatment (e.g., previous exposure to antibiotics) and procedures (e.g., invasive procedures/indwelling devices), recent surgery, immunocompromised status and organ transplantation [11–25], chronic skin ulcers [13], along with mechanical ventilation and patient movement between hospital departments [26].

Evidence suggests that delay in appropriate antibiotic treatment of CRE infections increases the risk of morbidity and mortality [27]. The prospective, multicentre, CRACKLE-2 cohort study found that the mortality rate among 449 US hospitalised patients with CRE infections was 24% [7], although earlier studies have shown mortality rates > 40% [28, 29]. More vulnerable patient populations, such as those undergoing solid organ transplantation, may be at a higher risk of CRE-related recurrent

infections and hospitalisations, increasing the risk of morbidity and mortality [30].

The main mechanism of carbapenem resistance in Enterobacterales is due to the production of various carbapenem-hydrolysing enzymes: also called carbapenemases. The proportion of carbapenemase-producing (CP) strains among CRE varies between regions (i.e., 76.2–90%) and a smaller proportion are non-CP CRE [7, 31, 32]. However, in certain geographical areas, non-CP CRE may yet be more prevalent (e.g., Texas) [33], while an increasing spread of carbapenemases was found in Europe between 2013 and 2017 [34]. Mortality findings for infections due to CP-CRE versus non-CP CRE are equivocal. Some investigators have reported a higher likelihood of mortality for non-CP CRE compared with CP CRE infections [26, 32], whereas others have reported a higher mortality rate with CP CRE versus non-CP CRE bacteraemia [35], and still others have found no difference in mortality rates [7].

Mechanisms of Carbapenem Resistance

CRE may harbour a range of mechanisms that render these pathogens resistant to carbapenems, including: (1) production of serine-carbapenemases or metallo-carbapenemases; and (2) expression of extended-spectrum beta-lactamases (ESBLs) and/or AmpC, which weakly hydrolyse carbapenems, in association with impaired drug uptake due to loss or modification of porin channels and/or upregulation of efflux pumps [36–39]. This variety of CRE resistance mechanisms poses a challenge to the selection of even novel antibiotics, most of which are not active against all mechanisms.

Carbapenemase production is the most widespread mechanism of carbapenem resistance owing to the high transmission rates via mobile elements (e.g., plasmids, transposons) and their frequent association with high-risk clones, which are particularly efficient in spreading. Carbapenemases may belong to distinct molecular classes of beta-lactamases [40–43]: Class A and Class D enzymes, which have a serine in their catalytic domain and exhibit variable hydrolytic activities towards carbapenems, and Class B enzymes [the metallo-beta-lactamases (MBLs)], which readily hydrolyse these antibiotics [36, 41]. The most notable plasmid-encoded Class A carbapenemase, *Klebsiella pneumoniae* carbapenemase (KPC), emerged over 25 years ago [44]. The Class D oxacillinase OXA-48 and its variants (e.g., OXA-162, -181, -204, -232, -244, and others) have been associated with CRE in the presence of permeability defects. Because Enterobacterales isolates can be reported as carbapenem susceptible when expressing OXA-48, their prevalence (and their spread) may be underestimated [45]. The most frequent MBLs include New Delhi (NDM), Verona integron-encoded (VIM), imipenemase MBL (IMP), and variants thereof [46, 47]. Class C serine-beta-lactamases (AmpC-type) primarily hydrolyse cephalosporins and only very weakly carbapenems; however, isolates expressing these plasmid-encoded enzymes or overproducing chromosomal AmpC in the presence of porin channel mutations or upregulated efflux pumps may become CR [41, 48]. Notable major porin channels are OmpC and OmpF in *E. coli*, and OmpK35 and OmpK36 in *K. pneumoniae* [49].

METHODS

Literature Search Strategy

A literature search for this narrative review was conducted in PubMed for relevant published papers and in conference abstracts with the search terms “cefiderocol”, “carbapenem-resistant”, “CRE”, “Enterobacterales”, “Enterobacteriaceae”, “*Klebsiella pneumoniae*” and “*Escherichia coli*”. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Current Treatment Options for CRE

Historically, treatment options for infections caused by CRE included polymyxins,

tigecycline, carbapenems, aminoglycosides and fosfomycin, as monotherapy or more frequently in combination therapy. It is concerning that resistance to colistin is spreading, and that approximately 20% of CRE isolates are resistant to colistin, according to surveillance studies involving isolates from the USA, Europe (i.e., 21.3%) and Japan (i.e., 20.4%) [50, 51]. Among the newer agents, ceftazidime–avibactam, meropenem–vaborbactam, imipenem–relebactam, plazomicin [for complicated UTI (cUTI) only in the USA], eravacycline [for complicated IAI (cIAI) only] and cefiderocol are approved for the treatment of patients with CRE infections when isolates are susceptible to these agents [52–61]. The effectiveness of these treatment options is related to specific CR mechanisms [37, 62–64].

Randomised, double-blind, non-inferiority, controlled studies enrolling patients with cUTI, cIAI, or nosocomial pneumonia (NP), and secondary bacteraemia have demonstrated the efficacy and safety of these antibiotics in certain patient populations, although these studies did not specifically target CRE infections [65–72]. On the other hand, data on the efficacy of these antibiotics in CRE infections were provided by smaller prospective, open-label or retrospective observational studies, or by small pathogen-focused, prospective, descriptive studies, which specifically targeted CR infections. The efficacies of meropenem–vaborbactam in TANGO II [73], plazomicin in CARE [74] and imipenem–relebactam in RESTORE-IMI 1 [75] were demonstrated and compared with either best available therapy (BAT) or colistin-based therapy, although the RESTORE-IMI 1 study only included six patients with CRE infections, limiting the evaluation of imipenem–relebactam efficacy against these pathogens [75]. These studies enrolled a limited number of patients due to the low prevalence of CRE globally and to the challenges related to enrolling such a medically complex patient population [2, 76]. Considering all clinical evidence [56, 73, 75, 77–83] and current in vitro activity [49, 50, 76, 84–88], the recently published European Society of Clinical Microbiology and Infectious Diseases (ESCMID) treatment guidelines and the Infectious Diseases Society of America (IDSA) guidance provide recommendations for use of these antibiotics in various infections complicated by each of the CR mechanisms [89, 90]. Additionally, country-specific recommendations in Europe may be considered according to local epidemiology [63, 64]. Further clinical evidence on the latest antibiotics is needed to strengthen the recommendations.

Cefiderocol

Cefiderocol is the first approved siderophore cephalosporin. It targets penicillin-binding proteins (PBPs), mainly PBP-3 [91]. The structure inherently enhances the stability of cefiderocol against hydrolysis by various beta-lactamases, including MBLs and other carbapenemases, thus enabling potential in vitro activity even in the absence of a beta-lactamase inhibitor [91]. The structure also allows iron chelation via the linked chlorocatechol group on the C-3 side chain, which consequently promotes the uptake of cefiderocol into the periplasmic space via active siderophore transport systems in Gram-negative bacteria [91]. The siderophore moiety of cefiderocol mimics natural siderophore molecules released by bacteria to facilitate iron uptake, which is essential for bacterial growth. Thus, cefiderocol predominantly enters the cell via active transport through iron transport systems, and a relatively small amount via traditional porins [91, 92]. Because cell entry is mediated by active transport during iron uptake by the bacteria, either porin channel loss or modification, or efflux pump upregulation has very limited impact on its in vitro activity [91, 92].

In Vitro Activity of Cefiderocol: Susceptibility Testing and Breakpoints, and Global Epidemiology

The reference method for in vitro susceptibility testing of cefiderocol is broth microdilution in iron-depleted cation-adjusted Mueller–Hinton medium [93, 94]. According to current European Committee for Antimicrobial Susceptibility Testing (EUCAST), clinical breakpoints for cefiderocol against Enterobacterales,

susceptibility is a minimum inhibitory concentration (MIC) ≤ 2 μg/mL (or a ≥ 22-mm zone diameter for a 30-μg disk) and resistance is an MIC > 2 μg/mL (or a < 22-mm zone diameter for a 30-μg disk) [93]. The Clinical and Laboratory Standards Institute (CLSI) and Food and Drug Administration define susceptibility as ≤ 4 μg/mL (or a ≥ 16-mm zone diameter for a 30-μg disk), intermediate as 8 μg/mL (a 9- to 15-mm zone diameter for a 30-μg disk) and resistance as ≥ 16 μg/mL (or a ≤ 8-mm zone diameter for a 30-μg disk) [94]. Various commercial systems for cefiderocol susceptibility testing have also been developed, but they have been affected by major accuracy issues [95], resulting in a recent warning by EUCAST [96].

Cefiderocol is active against a broad range of aerobic Gram-negative bacteria, including Enterobacterales and non-fermenters, but lacks activity against Gram-positive and anaerobic bacteria. In an in vitro study, cefiderocol MIC values were found to be between ≤ 0.031 and 8 μg/mL for *E. coli* and *K. pneumoniae* clinical isolates that expressed ESBLs (MIC range 0.125–2 μg/mL), KPC (MIC range 2–8 μg/mL), NDM (MIC range 2–4 μg/mL), IMP (MIC range 0.125–1 μg/mL), OXA-48 (MIC ≤ 0.031 μg/mL) and acquired AmpC enzymes (MIC range 0.063–1 μg/mL) (Table 1) [92]. In the same study, deletion in iron transport proteins in *E. coli* strains led to an increase in cefiderocol MIC values; however, these isolates remained susceptible to cefiderocol based on current EUCAST and CLSI susceptibility breakpoints [92]. Similar findings were observed with mutations in porin channel *ompK35/36* genes in *K. pneumoniae*, where two- to four-fold increases in cefiderocol MIC values were observed and the highest MIC value was 0.125 μg/mL [92].

The in vitro activity of cefiderocol was investigated in the multinational SIDERO-WT and SIDERO-CR surveillance programmes in clinical isolates collected between 2014 and 2020 (Table 1) [76, 97–103]. These surveillance programmes investigated the susceptibility of Gram-negative bacteria to cefiderocol and comparator antibiotics, including carbapenem-susceptible Enterobacterales, CRE and Enterobacterales isolates that were non-susceptible to ceftazidime–avibactam or ceftolozane–tazobactam (Table 1) [97–103]. Among meropenem-non-susceptible Enterobacterales, cefiderocol demonstrated a MIC_{90} value of 4 μg/mL in 2014–2015 [97], with regional variance (North America 1 μg/mL; Europe 4 μg/mL) [97]. The annual cefiderocol susceptibility rate among all Enterobacterales in the SIDERO programme according to CLSI criteria ranged between 99.6 and 100% in North America, and between 99.3 and 99.9% in Europe, with very small variations [76]. Among 1021 meropenem-non-susceptible Enterobacterales collected over 5 years, 96.7% (CLSI) and 79.9% (EUCAST) were susceptible to cefiderocol (i.e., the difference is due to EUCAST breakpoints categorising isolates with cefiderocol MICs of 4 μg/mL as resistant [~ 17%)] [76]. Additionally, 91.6% of isolates non-susceptible to ceftazidime–avibactam and 97.7% of isolates non-susceptible to ceftolozane–tazobactam were susceptible to cefiderocol based on CLSI breakpoints [76]. Among difficult-to-treat resistant Enterobacterales, 98.3% were susceptible to cefiderocol based on CLSI breakpoints (Table 1) [101].

Against 120 MBL-producing CRE isolates (including NDM and VIM) collected between 2014 and 2017 in the SIDERO-WT programme, the cefiderocol MIC_{90} was 4 μg/mL [102]. Against 45 NDM-producing CREs, MIC_{90} was 8 μg/mL (84% of isolates were inhibited at 4 μg/mL) and against 75 VIM-producing CREs, MIC_{90} was 4 μg/mL (100% of isolates were inhibited at 4 μg/mL) (Table 1) [102]. Additional data for 151 CRE isolates collected between 2014 and 2015 showed that the cefiderocol MIC_{90} values were 2 μg/mL for KPC-producing CRE, 2 μg/mL for carbapenemase-negative CRE, 4 μg/mL for VIM-producing CRE, 4 μg/mL for OXA-48-producing CRE and 8 μg/mL for NDM-producing CRE (Table 1) [100]. These isolates also had a high rate of colistin resistance (i.e., 30.5%) [100]. A European subset of the carbapenemase-producing (i.e., KPC, VIM, OXA-48 and NDM-1) strains collected in SIDERO-CR between 2014 and 2016 showed that, among 107 ceftazidime–avibactam-resistant Enterobacterales isolates, cefiderocol MIC values were ≤ 2 μg/mL (EUCAST breakpoint) for 66.4% of the isolates, approximately 30% had a MIC value of 4 μg/mL

Table 1 In vitro activity of cefiderocol against Enterobacterales and CRE

Enterobacterales phenotypic profile or carbapenemase production	*N*	Surveillance programme	Collection period	MIC_{90} (µg/mL)	% S by CLSI interpretation (or % inhibited at susceptibility breakpoint [i.e., ≤ 4 µg/mL])	% S by EUCAST interpretation (or % inhibited at susceptibility breakpoint [i.e., ≤ 2 µg/mL])	References
Overall (North America + Europe)	31,896	SIDERO-WT	2014–2019	1	99.8	98.3	[76]
Meropenem-non-susceptible	1021	SIDERO-WT	2014–2019	4	96.7	79.9	[76]
Ceftazidime–avibactam non-susceptible	263	SIDERO-WT	2014–2019	4	91.6	NR	[76]
Ceftolozane–tazobactam non-susceptible	2658	SIDERO-WT	2014–2019	4	97.7	NR	[76]
DTR Enterobacterales	573	SIDERO-WT	2014–2017	4	98.3	NR	[101]
Overall (USA + Europe)	8047	SENTRY	2020	0.5	99.8	99.1	[50]
Carbapenem-resistant	169	SENTRY	2020	4	98.2	87.6	[50]
Ceftazidime–avibactam non-susceptible	37	SENTRY	2020	8	89.2	54.1	[50]
Imipenem–relebactam non-susceptible	49	SENTRY	2020	4	95.9	69.4	[50]
Meropenem–vaborbactam non-susceptible	41	SENTRY	2020	4	95.1	70.7	[50]
Carbapenem-non-susceptible (global)	1022	SIDERO-CR	2014–2016	4	(97.0)	NR	[98]
Carbapenem-non-susceptible and ceftazidime–avibactam non-susceptible	235	SIDERO-CR	2014–2016	4	(91.9)	NR	[98]

Table 1 continued

Enterobacterales phenotypic profile or carbapenemase production	*N*	Surveillance programme	Collection period	MIC_{90} (µg/mL)	% S by CLSI interpretation (or % inhibited at susceptibility breakpoint [i.e., ≤ 4 µg/mL])	% S by EUCAST interpretation (or % inhibited at susceptibility breakpoint [i.e., ≤ 2 µg/mL])	References
Carbapenem-non-susceptible and ceftolozane–tazobactam non-susceptible	1005	SIDERO-CR	2014–2016	4	(96.7)	NR	[98]
Carbapenem-non-susceptible (Europe)	457	SIDERO-CR	2014–2016	4	NR	81.6	[103]
KPC-producing	238	SIDERO-CR	2014–2016	4	NR	83.6	[103]
NDM-producing	37	SIDERO-CR	2014–2016	4	NR	51.4	[103]
VIM-producing	62	SIDERO-CR	2014–2016	4	NR	79	[103]
OXA-48-producing	85	SIDERO-CR	2014–2016	4	NR	88.2	[103]
Meropenem-resistant (North America + Europe)	151	SIDERO-WT	2014–2015	4	NR	NR	[100]
KPC-producing	75	SIDERO-WT	2014–2015	2	(100)	(90.7)	[100]
NDM-producing	12	SIDERO-WT	2014–2015	8	NR	NR	[100]
VIM-producing	27	SIDERO-WT	2014–2015	4	NR	NR	[100]
OXA-48-producing	32	SIDERO-WT	2014–2015	4	(100)	(84.4)	[100]
Carbapenemase-negative	13	SIDERO-WT	2014–2015	2	NR	NR	[100]

Table 1 continued

Enterobacterales phenotypic profile or carbapenemase production	*N*	Surveillance programme	Collection period	MIC_{90} (µg/mL)	% S by CLSI interpretation (or % inhibited at susceptibility breakpoint [i.e., ≤ 4 µg/mL])	% S by EUCAST interpretation (or % inhibited at susceptibility breakpoint [i.e., ≤ 2 µg/mL])	References
MBL-producing meropenem-non-susceptible	120	SIDERO-WT	2014–2017	4	NR	NR	[102]
NDM-producing	45	SIDERO-WT	2014–2017	8	(84)	NR	[102]
VIM-producing	75	SIDERO-WT	2014–2017	4	(100)	NR	[102]
				MIC range (µg/mL)			
Carbapenem-susceptible and carbapenem-non-susceptible Enterobacterales							
ESBL-producing	7	In vitro study	Na	0.125–2	Na	Na	[92]
KPC-producing	3	In vitro study	Na	2–8	Na	Na	[92]
NDM-producing	3	In vitro study	Na	2–4	Na	Na	[92]
IMP-producing	2	In vitro study	Na	0.125–1	Na	Na	[92]
OXA-48-producing	1	In vitro study	Na	≤ 0.031	Na	Na	[92]
Acquired or constitutive AmpC-producing	5	In vitro study	Na	0.063–1	Na	Na	[92]
Porin channel mutations (*ompK-35*, *ompK-36*)	4	In vitro study	Na	0.031–0.125	Na	Na	[92]
Iron transport channel mutations (*cirA*, *fiu*)	4	In vitro study	Na	0.063–1	Na	Na	[92]

Table 1 continued

Enterobacterales phenotypic profile or carbapenemase production	*N*	Surveillance programme	Collection period	MIC_{90} (µg/mL)	% S by CLSI interpretation (or % inhibited at susceptibility breakpoint [i.e., ≤ 4 µg/mL])	% S by EUCAST interpretation (or % inhibited at susceptibility breakpoint [i.e., ≤ 2 µg/mL])	References
Carbapenemase-producing CRE	222	In vitro study	2012–2019	≤ 0.03–> 64	(93)	81	[104]
KPC-producing	24	In vitro study	2012–2019	0.12–8	(96)	92	[104]
NDM-producing	21	In vitro study	2012–2019	0.5–> 64	(81)	48	[104]
VIM-producing	17	In vitro study	2012–2019	0.25–> 64	(88)	76	[104]
IMP-producing	13	In vitro study	2012–2019	0.03–4	(100)	85	[104]
OXA-48-like producing	51	In vitro study	2012–2019	≤ 0.03–8	(96)	90	[104]

CLSI Clinical and Laboratory Standards Institute, *CR* carbapenem-resistant, *CRE* carbapenem-resistant Enterobacterales, *DTR* difficult-to-treat resistant (defined as isolates not susceptible to fluoroquinolones, extended-spectrum cephalosporins and carbapenems according to CLSI M100-Ed28; 2018), *EUCAST* European Committee on Antimicrobial Susceptibility Testing, *IMP* imipenemase metallo-beta-lactamase, *KPC Klebsiella pneumoniae* carbapenemase, *MBL* metallo-beta-lactamase, *MIC* minimum inhibitory concentration, *Na* not applicable, *NDM* New Delhi metallo-beta-lactamase, *NR* not reported, *OXA* oxacillinase, *S* susceptible; *VIM* Verona integron-encoded metallo-beta-lactamase, *WT* wild-type

and only a few isolates were detected with MICs of 8 and 32 μg/mL [103]. The overall MIC_{90} value was 4 μg/mL for each carbapenemase type, suggesting a high cefiderocol susceptibility rate among CRE, including ceftazidime–avibactam-resistant strains (Table 1) [103].

Similarly, a very high susceptibility rate to cefiderocol was found in the SENTRY surveillance programme in CRE isolates collected in 2020 (Table 1) [50]. Overall, for Enterobacterales, cefiderocol demonstrated MIC_{50}/MIC_{90} values of 0.06/0.5 μg/mL, with susceptibility rates of 99.8% and 99.1% according to CLSI and EUCAST criteria, respectively [50]. Corresponding values for CRE were MIC_{50}/MIC_{90} values of 0.5/4 μg/mL and susceptibility rates of 98.2% (CLSI) and 87.6% (EUCAST) [50] (Table 1). No regional differences were found in susceptibility rates between the USA and Europe for Enterobacterales. The majority of CRE were CR *K. pneumoniae* [50]. Cefiderocol susceptibility rates of isolates resistant to ceftazidime–avibactam, imipenem–relebactam and meropenem–vaborbactam were 89.2%, 95.9% and 95.1%, respectively, according to CLSI criteria, and 54.1%, 69.4% and 70.7%, respectively, according to EUCAST criteria [50].

Susceptibility rates to cefiderocol were determined against a collection of CRE from two national reference centres in France and Belgium, representing part of the CR Gram-negative isolates in these two countries. Cefiderocol susceptibility rates against 222 CRE isolates based on CLSI and EUCAST breakpoints were 93% and 81%, respectively. The susceptibility rate varied by the expressed carbapenemase enzyme between 81 and 100% by CLSI and between 48 and 92% by EUCAST breakpoints (Table 1) [104].

Cefiderocol Resistance Mechanisms in Enterobacterales: On-Therapy Emergent and Pre-existing Resistance

Mechanisms that can reduce cefiderocol susceptibility in Enterobacterales have been recently reviewed [105] and may include enhanced production of some beta-lactamases (especially NDM and some KPC variants among carbapenemases), modification of siderophore uptake systems, and rarely mutations in PBP targets. When present alone, these mechanisms modestly increase MICs and are usually not sufficient to confer clinically relevant resistance, especially when considering the higher CLSI susceptibility breakpoint of 4 μg/mL. Their combination, however, can eventually increase cefiderocol MICs beyond the clinical breakpoint for resistance [105].

There are a number of reports on the emergence of resistance to cefiderocol. These reports describe resistance either associated with cefiderocol exposure in clinical settings or in vitro (in serial passage experiments), or without cefiderocol exposure in isolates with resistance to other beta-lactams, such as ceftazidime or cefepime, following prior treatment with these agents (Table 2).

To date, two case reports have been published on cefiderocol resistance emerging during therapy [86, 87]. According to these reports, in NDM-producing CRE, cefiderocol exposure may select for mutations in the siderophore receptor *cirA* gene, or increased NDM enzyme production, leading to cefiderocol resistance [86, 87]. One of these two patients had an NDM- and OXA-48-producing *E. cloacae* and the second patient had an NDM-5-producing *E. coli*; both patients had serious comorbidities (i.e., liver transplantation and acute myeloid leukaemia) [86, 87]. The patient with NDM-producing *E. cloacae* had IAI and BSI, and, although follow-up blood samples became negative, the bile samples remained positive for *E. cloacae* after 21 days of cefiderocol treatment, and the isolates tested resistant to cefiderocol (MIC > 256 μg/mL) with *cirA* mutations [86]. The second patient received 19 days of cefiderocol treatment; the mutant *E. coli* isolates resistant to cefiderocol had an increased copy number and expression of NDM-5 gene and also, in some cases, mutations in the *envZ* gene [87]. In vitro serial passage experiments in NDM-producing *K. pneumoniae* strains resulted in similar findings; however, loss of fitness was also described for the mutant strains [106, 107].

While on-therapy, ≥ 4-fold increases in MIC occurred in seven Enterobacterales isolates in cefiderocol-treated patients and in seven

Table 2 On-therapy emergence of and prior resistance to cefiderocol

Species	Cefiderocol MIC values (μg/mL)	Findings
Resistance emerged while on therapy		
CR *Enterobacter cloacae*	> 256	CFDC resistance development during therapy in NDM- and OXA-48-producing *E. cloacae*, with emerging mutation in *cirA* gene [86]
CR *E. coli*	> 32	On-therapy resistance due to increased copy number and expression of NDM-5 (and, possibly, to *envZ* mutations) in CR *E. coli* [87]
E. cloacae	8[a]	ACT-17 identified at baseline with ACT-17-like post-baseline; ACT-17-like post-treatment mutation (A313P) identified [108]
Resistance emerged following in vitro exposure		
CR *E. coli*	> 128	Serial passage of *E. coli* under CFDC pressure; NDM increases the propensity of resistance development via *cirA* mutations; the effect on resistance could be inhibited by dipicolinic acid, which inhibits the NDM enzyme [106]
CR *K. pneumoniae*	> 128	Serial passage of NDM *K. pneumoniae* under CFDC pressure; high-level resistant mutants selected with *cirA* mutations; high fitness cost [107]
Resistance observed in absence of previous cefiderocol exposure		
CR *E. cloacae*	≥ 16	AmpC deletion mutant *E. cloacae* showed resistance to cephalosporins following treatment with meropenem and cefepime [110]
CR *E. cloacae*	> 16	AmpC with R2 loop deletion showed reduced susceptibility to CFDC and CZA, and increased hydrolysis of these agents without prior exposure to either agent [88]
KPC-producing *K. pneumoniae*	8, 16	KPC-3 variant (KPC-31) *K. pneumoniae* with D179Y mutation was resistant to CFDC after CZA treatment [84]
KPC-producing *K. pneumoniae*	Up to 64	Cross-resistance with CZA in CZA-resistant KPC-*K. pneumoniae* with D179Y or KPC-Δ242-GT-243 mutations [111]
K. pneumoniae N435 KPC-41 *K. pneumoniae* N859 KPC-50	4–8 16	KPC-3 variants of Enterobacterales (e.g., KPC-41, KPC-50), which are resistant to CZA, show resistance to CFDC – cross-resistance [112]
E. coli, E. cloacae, K. pneumoniae	Up to 4–> 32	Cross-resistance to CZA in KPC variants only at high bacterial inoculum level [113]
Enterobacterales	Disk zone: 5–15 mm	No in vitro activity of cefiderocol against OXA-427-producing Enterobacterales [114]

Table 2 continued

Species	Cefiderocol MIC values (μg/mL)	Findings
P. rettgeri	> 32	Resistance in pan-drug-resistant isolate with 10 different resistance genes [115]
CR *E. coli*	> 32	Resistance likely occurred without prior exposure due to *cirA* gene mutation [116]
CR *K. pneumoniae*	8–> 256	Resistance occurred in the presence of NDM-1 or NDM-5 and *cirA* gene mutation [117]
CR *E. coli*	256	NDM-35, YRIN insertion in PBP-3, truncated *cirA* gene [121]
CR *E. coli* (n = 26), CR *K. pneumoniae* (n = 2), CR *E. cloacae* (n = 2)	≥ 16–128	Resistance occurred in the presence of NDM-5, YRIN or YRIK, and *cirA* gene mutation [120]
Various CRE		Combination of heterogeneous mechanisms contribute to resistance in non-wild-type CRE isolates [124]
K. pneumoniae	4–32	
Enterobacter hormaechei	64	
Enterobacter asburiae	16	
Enterobacter kobei	4	
Citrobacter freundii	8	

CFDC cefiderocol, *CR* carbapenem resistant, *CRE* carbapenem-resistant Enterobacterales, *CZA* ceftazidime–avibactam, *KPC Klebsiella pneumoniae* carbapenemase, *NDM* New Delhi metallo-beta-lactamase, *OXA* oxacillinase
[a]Median MIC (of 3 measurements)

isolates from patients in the control arms of two randomised clinical studies (i.e., cefiderocol MICs increased in cefiderocol-treated patients, while meropenem or BAT agents MICs increased in meropenem- or BAT-treated patients in APEKS-NP and CREDIBLE-CR studies, respectively) [82, 108, 109]. Cefiderocol resistance developed in only one *E. cloacae* isolate based on EUCAST criteria and had intermediate susceptibility based on CLSI and FDA criteria. In this isolate a mutation in the gene for the ACT-17 enzyme had occurred, and cloning experiments in *E. coli* confirmed the role of this mutation in increasing cefiderocol MIC twofold [108]. The other six post-treatment isolates with ≥ 4-fold increases in cefiderocol MIC remained susceptible according to EUCAST, CLSI, and FDA criteria [108]. No mutations in iron transport-related genes were found [108]. In the control arms, six of seven isolates became resistant to the antibiotic used for treatment [82, 109].

There are some reports on cefiderocol resistance without prior drug exposure. Shields et al. described a patient without previous exposure to cefiderocol who had necrotising pancreatitis and septic shock, complicated by ventilator-associated pneumonia (VAP), who received piperacillin-tazobactam, meropenem (23 days), cefepime (11 days), and ceftazidime–avibactam (1 day) sequentially [110]. *E. cloacae-hormaechei* isolates developed mutations in porin channels leading to carbapenem resistance and a mutation in *ampC* (deletion of two amino acids) that conferred resistance to cefepime, ceftazidime–avibactam and cefiderocol. Neither carbapenemases nor ESBLs were present in parental and mutant *E. cloacae* isolates. It was

postulated that the identified A292_L293del AmpC mutation was responsible for resistance to the cephalosporin class rather than one agent alone [110]. In another case, Kawai et al. showed that *E. cloacae* with reduced susceptibility or resistance to ceftazidime–avibactam and cefiderocol harboured a mutant form of AmpC with deletion of two amino acids, which significantly altered the structure of the enzyme in the R2 loop, leading to increased hydrolysis of these antibiotics [88]. The hydrolytic efficiency towards ceftazidime increased ~ 1000-fold, whereas, for cefiderocol, it was increased by ~ 20-fold. It was postulated that cefiderocol resistance with an MIC value of > 16 μg/mL could be the result of increased expression of mutant AmpC in *E. cloacae* [88].

Tiseo et al. showed that a mutation in the gene encoding the KPC-3 enzyme resulted in a CR KPC-*K. pneumoniae* isolate developing resistance to ceftazidime–avibactam (following exposure) and cefiderocol (without exposure to cefiderocol), while restoring susceptibility to meropenem and imipenem [84]. Similar findings were reported by Bianco et al. [111]. In their investigation, following treatment of patients with ceftazidime–avibactam, mutations in KPC were detected among ceftazidime–avibactam-resistant KPC-producing CRE, and a high rate of cefiderocol resistance was also observed [111]. In contrast, these isolates demonstrated impaired carbapenemase activity and low rates of carbapenem resistance [111]. Among ceftazidime–avibactam-susceptible KPC-producing isolates, the cefiderocol susceptibility rate was high, whereas the carbapenem susceptibility rate was low [111].

The role of mutations in KPC in the development of cefiderocol resistance was investigated in additional in vitro studies. Poirel et al. showed that two different mutations in KPC-3 in CR *K. pneumoniae* strains, resulting in KPC-41 and KPC-50 variants under in vitro antibiotic pressure, had cross-resistance between ceftazidime–avibactam and cefiderocol based on EUCAST breakpoints [112]. These CR *K. pneumoniae* variants had mutations in porin genes; however, susceptibility to meropenem was restored [112]. Hobson et al. showed that CR KPC-*K. pneumoniae* with mutations in KPC had increased cefiderocol MIC (highest MIC, 4 μg/mL) and developed resistance to ceftazidime–avibactam. All isolates growing at a high inoculum level had cefiderocol resistance (MICs 4 to > 32 μg/mL) [113].

Jacob et al. showed that a recently identified OXA variant (OXA-427) in Enterobacterales conferred cefiderocol resistance (zone diameters 5–15 mm), although the exact mechanism has not been confirmed [114]. Mc Gann et al. found an NDM- and *Pseudomonas* extended-resistant (PER) beta-lactamase-producing pan-drug-resistant *Providencia rettgeri* that was resistant to several antibiotics, including cefiderocol [115].

Price et al. identified an NDM-5-producing CR *E. coli* strain that was resistant to cefiderocol without prior exposure to cefiderocol (zone diameter 7 mm) [116]. Comparing this strain with other genetically similar (equivalent sequence type, NDM-producing) cefiderocol-susceptible and cefiderocol-resistant CR *E. coli* strains, the authors suggested that a mutation in the *cirA* gene (via truncation and premature stop codon) was likely to be responsible for cefiderocol resistance [116]. Similar findings were reported on the role of NDM enzyme by Lan et al. [117] and Jousset et al. [118]. Previous work by Ito et al. suggested that *E. coli* isolates with mutations in *cirA* and *fiu* genes resulted in a 16-fold increase in cefiderocol MIC values, although the isolates remained susceptible [92]. Sato et al. also showed that YRIN mutations in PBP-3 may contribute to reduced susceptibility to cephalosporins and monobactams [119]. The observations on the role of NDM enzyme, *cirA* mutation, and YRIN insertion were similar to those by the in vitro susceptibility studies conducted in China on 1158 CRE isolates without prior exposure to cefiderocol [120] and in Switzerland in one CR *E. coli* isolate [121], showing resistance to cefiderocol when these mechanisms are jointly present. These investigations describing cefiderocol-resistant NDM-producing CRE suggest that such strains emerged prior to clinical use of cefiderocol. Moreover, a nosocomial outbreak of NDM-producing *K. pneumoniae* resistant to cefiderocol, mostly caused by a mutant clone with a *cirA* mutation, was recently reported. The resistant clone was able to spread in the absence of

significant selective pressure by cefiderocol, suggesting that similar mutants do not necessarily exhibit a fitness defect [122]. Infection control to prevent outbreaks linked to such strains is essential to preserve the activity and utility of cefiderocol for the treatment of CRE infections [122, 123].

Simner et al. investigated in detail the potential mechanisms of cefiderocol resistance in 56 CRE using whole-genome sequencing and found that isolates with increased cefiderocol MIC values had a heterogeneous mechanism profile [124]. Fourteen isolates (25%) with cefiderocol MICs ≥ 4 μg/mL were found, but no consistent mechanism across these isolates could be confirmed. The expression of beta-lactamases, including carbapenemases, in combination with permeability defects might have explained the increased cefiderocol MICs [124].

It is worth noting that the addition of both the serine beta-lactamase inhibitor, avibactam, and the MBL inhibitor, dipicolinic acid, reduced the MICs of cefiderocol against previously non-susceptible Enterobacterales isolates [125, 126].

Pharmacokinetics/Pharmacodynamics, and Effectiveness of Cefiderocol in Preclinical Models

Early pharmacokinetic and pharmacodynamic (PK/PD) preclinical studies in various infection models have established that cefiderocol is a time-dependent cephalosporin, and that the fraction of time (i.e., dosing period) that the unbound drug concentration exceeds the MIC (% $fT_{>MIC}$) is the PD driver of its antibacterial effect in vivo. The preclinical dose-finding experiments in murine models supported the administration of cefiderocol 2 g every 8 h in 3-h infusions, which achieved bactericidal effects against Gram-negative bacteria with cefiderocol MIC values up to 4 μg/mL [127]. The in vivo efficacy of cefiderocol against *E. coli* and *K. pneumoniae* has been demonstrated in neutropenic murine thigh infection and lung infection models, as well as in an immunocompetent rat lung infection model and in an in vitro chemostat model [128–132].

Cefiderocol administration at humanised dosing achieved stasis or a ≥ 1-$\log_{10}$ reduction in bacterial density against CR *E. coli* and CR *K. pneumoniae* [128]; this was achieved against 77% of tested Enterobacterales strains, which had cefiderocol MIC values up to ≤ 4 μg/mL. Growth of Enterobacterales strains with cefiderocol MIC values of ≥ 8 μg/mL was not inhibited in this model [128]. Similar inhibitory effects were shown by Stainton et al. in a murine thigh infection model against AmpC-producing *E. coli* and CR KPC-producing *K. pneumoniae* strains for up to 72 h [129]. Nakamura et al. demonstrated that a 1-$\log_{10}$ reduction in bacterial density would be achieved at ~ 73% $fT_{>MIC}$ in a murine thigh infection model and at ~ 64% $fT_{>MIC}$ in a murine lung infection model, suggesting a PD target of ~ 75% $fT_{>MIC}$ for Enterobacterales infections [130]. In a rat lung infection model, humanised dosing of cefiderocol, simulating 3-h infusions every 8 h, resulted in bactericidal effects against both KPC-producing CR *K. pneumoniae* and NDM-producing *K. pneumoniae* [131]. In these experiments, one NDM-producing CR *K. pneumoniae* strain had a cefiderocol MIC of 8 μg/mL; however, reduction in bacterial growth was achieved [131].

Further investigations in the in vitro chemostat model confirmed the bactericidal activity of cefiderocol with humanised dosing, 2 g every 8 h as a 3-h infusion, against CR *K. pneumoniae* and CR *E. coli* producing carbapenemases (NDM, KPC), ESBLs (SHV-11, CTX-M-15) and acquired AmpC (CMY-2) enzymes, with cefiderocol MIC values of 2–4 μg/mL [132].

To justify the dosing recommendation from the preclinical studies with CR infections, Monte-Carlo simulations for various patient populations were performed and showed that cefiderocol 2 g every 8 h over a 3-h infusion period would reach a > 90% probability of target attainment (PTA) to achieve 75% $fT_{>MIC}$ for isolates with cefiderocol MIC values up to 4 μg/mL [133]. The optimised population PK modelling following incorporation of PK data from Phase 3 clinical studies from patients with NP, BSI/sepsis and cUTI confirmed that cefiderocol 2 g every 8 h in a 3-h infusion provided > 90% PTA for 100% $fT_{>MIC}$ against MICs of ≤ 4 μg/mL

for all infection sites across all renal function groups, including patients with augmented renal clearance, except for patients with BSI and normal renal function (> 85% PTA) [134].

Cefiderocol demonstrated a linear PK profile at ascending doses, and its plasma levels correlate with renal function [135–138]. Renal impairment decreases its clearance and increases the plasma area under the concentration-time curve; therefore, dose adjustment is recommended for patients with renal impairment, including patients with continuous renal replacement therapy [138, 139]. A Phase 1b study in pneumonia patients who underwent broncho alveolar lavage to estimate lung penetration of cefiderocol following multiple doses demonstrated that cefiderocol penetrates the epithelial lining fluid (ELF) [81]. Application of PK modelling in seven patients with nosocomial pneumonia who received cefiderocol 2 g every 8 h in a 3-h infusion reported ≥ 99.5% PTA for 100% $fT_{>MIC,ELF}$ against MICs of ≤ 2 μg/mL and ≥ 87.0% against MICs of ≤ 4 μg/mL regardless of renal function [140].

Clinical Efficacy of Cefiderocol

To date, three prospective, randomised clinical studies have been conducted in a total of 906 patients. The efficacy and safety of cefiderocol was investigated in infections caused by Enterobacterales in > 350 patients with cUTI, NP and BSI/sepsis across three randomised controlled studies (i.e., CREDIBLE-CR, APEKS-NP, and APEKS-cUTI) [82, 109, 141]. Most patients with Enterobacterales were enrolled in the double-blind Phase 2 APEKS-cUTI study, in which *E. coli* (60.3%) and *K. pneumoniae* (19.0%) were the two most frequent species [141], and only a small proportion had CRE infections receiving cefiderocol [(2.4% (6/252)] [142]. The APEKS-cUTI study was not designed to enrol patients with CR infections as imipenem–cilastatin was the comparator agent. However, patients had underlying risk factors for multidrug-resistant Gram-negative pathogens [141]. The overall results of the APEKS-cUTI study showed that the composite endpoint of clinical response and microbiological response at test of cure was achieved in 73% of patients in the cefiderocol arm versus 55% of patients in the imipenem–cilastatin arm [adjusted difference 18.6%, 95% confidence interval (CI) 8.2; 28.9] [141]. Similar results were found for patients with *E. coli* (cefiderocol 74%, imipenem–cilastatin 58%) and *K. pneumoniae* (cefiderocol 74%, imipenem–cilastatin 48%) (Table 3) [141]. Among six patients with NDM- and/or OXA-48-producing CR *K. pneumoniae*, clinical cure (100%) and microbiological eradication (83.3%) rates at test of cure were high in cefiderocol-treated patients (Table 3) [142]. Only one patient had CR KPC-producing *K. pneumoniae* in the imipenem–cilastatin arm, and this patient achieved clinical cure and eradication by test of cure. None of the patients with CRE cUTI died in this study [142].

Patients with suspected Gram-negative bacterial NP were randomised in the double-blind, controlled, non-inferiority Phase 3 APEKS-NP study to receive either cefiderocol 2 g every 8 h in 3-h infusions or high-dose, extended-infusion meropenem for 7–14 days [109]. Among 292 pneumonia patients in the modified intention-to-treat population, 58.6% (85/145) and 58.5% (86/147) had Enterobacterales identified as a pathogen in the cefiderocol and meropenem arms, respectively, with *K. pneumoniae* being the most frequent species, followed by *E. coli* and *E. cloacae* in both arms [109]. This study was not designed to enrol patients with CR pathogens; however, 16.5% (14/85) and 8.1% (7/86) had at least one CRE at randomisation in the cefiderocol and meropenem arms, respectively [142]. The CRE isolates in this study expressed a variety of beta-lactamases, including ESBLs, NDM and OXA-48 carbapenemases. In these CRE isolates, porin mutations were also detected and some isolates were non-CP CRE [142]. The study met the overall primary endpoint of non-inferiority for all-cause mortality (ACM) at Day 14 [109]. Among patients with pneumonia caused by *K. pneumoniae* and *E. coli* overall, comparable clinical cure (cefiderocol 65% and 63%, meropenem 66% and 59%, respectively) and microbiological eradication (cefiderocol 44% and 53%, meropenem 50% and 50%, respectively) rates were achieved (Table 3) [109].

Table 3 Overview of the clinical efficacy of cefiderocol and comparator agents in the treatment of Enterobacterales and CRE infections in clinical studies

Clinical study	APEKS-cUTI [141, 142]	APEKS-NP [109, 142]	CREDIBLE-CR [82, 83, 142]	MBL-CRE infections [47, 145]
Dosing of cefiderocol and comparators	Cefiderocol: 2 g, 1-h infusion, q8h, or renal function-adjusted dosing	Cefiderocol: 2 g, 3-h infusion, q8h, or renal function-adjusted dosing	Cefiderocol: 2 g, 3-h infusion, q8h, or renal function-adjusted dosing	
	Comparator: imipenem–cilastatin 1 g/1 g, 1-h infusion, q8h, or renal function-adjusted dosing	Comparator: meropenem 2 g, 3-h infusion, q8h, or renal function-adjusted dosing	Comparator: best available therapy, dosing was applied according to local labels	
Efficacy in Enterobacterales infections	*E. coli* cUTI [141]	*E. coli* NP [109]		
	Composite endpoint at TOC: cefiderocol (108/146) 74% and I/C (45/77) 58%	Clinical cure rate at TOC: cefiderocol (12/19) 63% and meropenem (13/22) 59%		
	Clinical cure rate at TOC: cefiderocol (131/146) 90% and I/C (68/77) 88%	Microbiological eradication rate at TOC: cefiderocol (10/19) 53% and meropenem (11/22 (50%)		
	Microbiological eradication rate at TOC: cefiderocol (114/152) 75% and I/C (46/79) 58%	Day 28 ACM rate: cefiderocol (6/19) 32% and meropenem (4/22) 18%		
	K. pneumoniae cUTI [141]	*K. pneumoniae* NP [109]		
	Composite endpoint at TOC: cefiderocol (34/46) 74% and I/C (12/25) 48%	Clinical cure rate at TOC: cefiderocol (31/48) 65% and meropenem (29/44) 66%		
	Clinical cure rate at TOC: cefiderocol (41/46) 89% and I/C (21/25) 84%	Microbiological eradication rate at TOC: cefiderocol (21/48) 44% and meropenem (22/44) 50%		
	Microbiological eradication rate at TOC: cefiderocol (36/48) 75% and I/C (13/25) 52%	Day 28 ACM rate: cefiderocol (11/48) 23% and meropenem (12/44) 27%		
	1 patient with CSE receiving cefiderocol died in the study and none receiving I/C [141, 142]			

Table 3 continued

Clinical study	APEKS-cUTI [141, 142]	APEKS-NP [109, 142]	CREDIBLE-CR [82, 83, 142]	MBL-CRE infections [47, 145]
Efficacy in CRE infections	7 patients with CRE cUTI [142]	21 patients with CRE NP [142]	40 patients with CRE infections overall [82, 83]	APEKS-NP [47]
	Clinical cure rate at TOC: cefiderocol (6/6) 100% and I/C (1/1) 100%	Clinical cure rate at TOC: cefiderocol (8/14) 57% and meropenem (5/7) 71% Clinical cure rate at TOC: cefiderocol (8/14) 57% and meropenem (5/7) 71%	Clinical cure rate at TOC: cefiderocol (19/29) 66% and BAT (5/11) 45%	Clinical cure rate at TOC: cefiderocol (3/5) 60% and meropenem (1/1) 100%
	Microbiological eradication rate at TOC: cefiderocol (5/6) 83% and I/C (1/1) 100%	Microbiological eradication rate at TOC: cefiderocol (5/14) 36% and meropenem (4/7) 57%	Microbiological eradication rate at TOC: cefiderocol (14/29) 48% and BAT (2/11) 18%	Microbiological eradication rate at EOT: cefiderocol (3/5) 60% and meropenem (1/1) 100%
	No deaths for patients with CRE [142]	Day 28 ACM rate: cefiderocol (3/13) 23% and meropenem (1/7) 14%	Day 28 ACM rate: cefiderocol (4/29) 14% and BAT (3/11) 27%	Day 28 ACM rate: cefiderocol (1/5) 20% and meropenem (0/1) 0%
			CRE pneumonia [142]	CREDIBLE-CR [47]
			Clinical cure rate at TOC: cefiderocol (5/8) 63% and BAT (3/8) 38%	Clinical cure rate at TOC: cefiderocol (8/10) 80% and BAT (0/4) 0%
			Microbiological eradication rate at TOC: cefiderocol (1/8) 12.5% and BAT (2/8) 25%	Microbiological eradication rate at EOT: cefiderocol (7/10) 70% and BAT (0/4) 0%
			Day 28 ACM rate: cefiderocol (1/8) 12.5% and BAT (2/8) 25%	Day 28 ACM rate: cefiderocol (1/10) 10% and BAT (3/4) 75%
			CRE cUTI [142]	Case series: 18 cefiderocol-treated patients [145]
			Clinical cure rate at TOC: cefiderocol (10/12) 83% and BAT (2/3) 67%	Clinical cure rate at TOC: cefiderocol (13/18) 72%
			Microbiological eradication rate at TOC: cefiderocol (9/12) 75% and BAT (0/3) 0%	Microbiological eradication rate at EOT: cefiderocol (14/18) 78%
			Day 28 ACM rate: cefiderocol (1/12) 8% and BAT (1/3) 33%	Day 28 ACM rate: cefiderocol (4/18) 22%

ACM all-cause mortality, *BAT* best available therapy, *CRE* carbapenem-resistant Enterobacterales, *CSE* carbapenem-susceptible Enterobacterales, *(c)UTI* (complicated) urinary tract infection, *EOT* end of treatment, *I/C* imipenem–cilastatin, *MBL* metallo-beta-lactamase, *NP* nosocomial pneumonia, *TOC* test of cure

Among patients with CRE infections, clinical cure [cefiderocol 57.1% (8/14), meropenem 71.4% (5/7)] was observed in similar proportion of patients, although these patient numbers were relatively small [142] (Table 3). For Enterobacterales infections, the overall ACM rates at Day 14 [cefiderocol 12%, meropenem 10% (treatment difference 1.1%, 95% CI −9.4; 11.7) and at Day 28 [cefiderocol 22%, meropenem 19% (treatment difference 2.7, 95% CI −11.0; 16.3)] were similar between treatment arms [109]. Among patients with CRE pneumonia by Day 28, three died in the cefiderocol arm and one died in the meropenem arm [142].

The third clinical study was specifically designed to enrol patients with infections caused by CR Gram-negative pathogens, including CRE, and only a limited number of exclusion criteria were specified in order to facilitate patient enrolment. The pathogen-focused, open-label, randomised (2:1), descriptive Phase 3 CREDIBLE-CR study assessed the efficacy of cefiderocol, 2 g every 8 h in a 3-h infusion, and BAT in 150 hospitalised patients with serious CR Gram-negative infections [82]. Nearly half (45%) of the patient population had NP, 25% had BSI/sepsis and 30% had cUTI. Most patients received cefiderocol in monotherapy, and the majority of patients in the BAT arm received colistin-based combination therapy [82]. The primary endpoint was clinical cure in patients with NP and BSI/sepsis, and microbiological eradication in patients with cUTI. The overall clinical cure rates were 52.5% (42/80) for cefiderocol and 50.0% (19/38) for BAT. Clinical cure rates at test of cure in the cefiderocol and the BAT arms were: 50.0% (20/40) and 52.6% (10/19), respectively, in patients with pneumonia; 43.5% (10/23) and 42.9% (6/14), respectively, in patients with BSI/sepsis; and 70.6% (12/17) and 60.0% (3/5), respectively, in patients with cUTI [82]. A range of molecular mechanisms behind carbapenem resistance, often in parallel, were present in CRE, and included expression of KPC, OXA-48, NDM, OXA-48 + NDM, VIM carbapenemases, porin channel mutations and expression of ESBLs [47, 142, 143]. For CRE infections across all diagnoses, the overall clinical cure rate was 66% with cefiderocol and 45% with BAT, and the microbiological eradication rate was 48% with cefiderocol and 18% with BAT (Table 3). In the subset of patients with CRE pneumonia, 62.5% (5/8) of patients with cefiderocol and 37.5% (3/8) of patients with BAT had clinical cure [142]. In the subgroup of patients with cUTI caused by CRE, 83.3% (10/12) of patients with cefiderocol and 66.7% (2/3) with BAT had clinical cure [142]. ACM rates at Day 28 in cefiderocol-treated patients with NP [cefiderocol 12.5% (1/8); BAT 25.0% (2/8)] or cUTI (cefiderocol 8.3%; BAT 33.3%) remained low [142]. Across the APEKS-NP and CREDIBLE-CR studies, 10 patients had OXA-48-positive Enterobacterales isolates, all of which were *K. pneumoniae*. Clinical cure was achieved in seven of these patients, with one clinical failure and two indeterminate outcomes [144].

A post-hoc analysis of 84 patients with bacteraemia enrolled into the APEKS-cUTI, APEKS-NP and CREDIBLE-CR studies demonstrated that cefiderocol eradicated the baseline pathogens, including CRE, by days 3–4 in a large proportion of patients, and persistence or recurrence rates were low [143]. A total of 62 Enterobacterales isolates were grown from blood cultures across the three studies. Most CRE blood isolates were identified in the CREDIBLE-CR study, including patients with BSI/sepsis, NP and cUTI. The highest eradication rates of Enterobacterales with cefiderocol treatment [100% (18/18)] was found in the APEKS-cUTI study. In the CREDIBLE-CR study, within 3–4 days, 75.0% (9/12) of CRE were eradicated with cefiderocol treatment and 50.0% (3/6) with BAT. This analysis also showed that eradication rates at this early time point were similar by various resistance mechanisms [75.0% (3/4) for MBL-producing CRE, 75.0% (6/8) for serine-carbapenemase-producing CRE, and 71.4% (5/7) for ESBL-producing CRE] [143]. Corresponding clinical cure rates at test of cure were 75.0% (3/4), 50.0% (4/8) and 57.1% (4/7), respectively, in the cefiderocol arm [143].

In another post hoc analysis, looking solely at infections caused by MBL-producing pathogens in the CREDIBLE-CR and APEKS-NP studies, most CRE expressed an NDM enzyme, and a smaller proportion expressed a VIM enzyme [47]. These isolates were highly resistant to

meropenem. Cefiderocol treatment eradicated MBL-expressing CRE in 7 of 10 patients by the end of treatment, and 8 of 10 patients had clinical cure at test of cure in the CREDIBLE-CR study [47] (Table 3). In the APEKS-NP study, 60% of the MBL-producing CRE were eradicated and 60% of patients had clinical cure (Table 3). In a case series of 18 Italian patients with MBL-producing CRE infections, who were treated with cefiderocol in combination therapy, the clinical cure rate (72.2%) at test of cure, the eradication rate (77.8%) at end of cefiderocol treatment and the ACM rate (22.2%) at Day 28 (Table 3) were similar to the outcomes in cefiderocol-treated patients in the analysis by Timsit et al. [47, 145]. Most CRE in the case series expressed NDM, and 76% of patients received cefiderocol in combination therapy [145].

In addition to case reports of resistance [86, 87], eight case reports of CRE infections treated with cefiderocol have been published. Cefiderocol treatment for 14 days resulted in successful eradication of an OXA-48+NDM-1-producing CR *K. pneumoniae* in a patient with BSI, although the patient later died due to hospital-acquired pneumonia [146]. Cefiderocol treatment for 14 days in a patient with VAP and BSI led to a successful outcome in a polymicrobial infection of extensively drug-resistant *A. baumannii* and KPC-producing CR *K. pneumoniae* [147]. In the compassionate use programme, patients with CR Gram-negative pathogens and life-threatening conditions were treated with cefiderocol. Thus, patients with osteomyelitis or prosthetic joint infection caused by pathogens that lack active treatment options were treated long term. In two such cases, (1) ESBL- and ACT-5-producing *E. hormaechei*, and (2) ESBL-positive *K. pneumoniae* with extensively drug-resistant *P. aeruginosa*, cefiderocol treatment given for 10 and 14 weeks resulted in successful outcomes [148, 149]. However, for one patient with respiratory tract infection due to OXA-48-producing *K. pneumoniae* with NDM-1-producing *P. aeruginosa*, cefiderocol treatment did not result in a favourable outcome [150]. Furthermore, a diabetic kidney transplant patient, who was infected by a CR *K. pneumoniae* expressing NDM-1 and OXA-232 enzymes, had a fatal outcome despite eradication of the blood isolate with cefiderocol-containing combination treatment [151]. According to a recent case report of a 44-year-old male patient, who developed meningitis due to KPC-producing *K. pneumoniae*, 14-day treatment with cefiderocol plus trimethoprim-sulfamethoxazole resulted in eradication of *K. pneumoniae* from the cerebrospinal fluid and clinical success [152]. In a paediatric case report of BSI caused by VIM-producing *K. pneumoniae*, cefiderocol treatment resulted in clinical improvement and clearance of the blood isolate, although paediatric dosing for cefiderocol has yet to be established in clinical studies [153].

DISCUSSION

Since the latest call by the WHO for urgent development of new antibiotics against the priority pathogens, CR *A. baumannii*, CR *P. aeruginosa* and CRE, research has been intensified, with some success. Despite the latest approvals of new antibiotics, such as ceftazidime–avibactam, cefiderocol, meropenem–vaborbactam, imipenem–relebactam, eravacycline and plazomicin, more clinical research is needed to establish their role in the management of CRE infections. Pathogen-focused descriptive clinical studies with these new antibiotics, which prospectively enrolled patients with CRE infections, have found clinical cure (59.4–65.5%, except plazomicin 35.3%) and ACM (11.8–15.6%) rates that were relatively similar across studies [73, 74, 82, 83]. Of note, these new agents were administered in monotherapy in these clinical studies and comparators were frequently colistin-based regimens. Only one retrospective study compared two new agents head-to-head (i.e., ceftazidime–avibactam and meropenem–vaborbactam) [154]. Data on imipenem–relebactam are very limited in CRE infections (i.e., only six patients with CRE in RESTORE-IMI 1), although the RESTORE-IMI 2 study enrolled 178 patients with Enterobacterales pneumonia [72]. Nevertheless, these are notable outcomes for the new antibiotics

compared with historical mortality rates of more than 40% [28, 29].

Enterobacterales frequently express ESBLs, which are responsible for resistance to extended spectrum cephalosporins. For the treatment of critically ill patients with severe infections, carbapenems are the preferred option. Previously hospitalised patients with recurrent infections often require alternative treatment options, as prior carbapenem use and use of indwelling catheters are risk factors for colonisation and subsequent infections by CRE. Similarly, patients repatriated or having visited countries with high rates of CP Gram-negative pathogens are at increased risk for carriage and thus infections by these pathogens. For such patients and for those who are critically ill or have comorbidities that may be associated with poor outcomes, such as immunosuppression, cancer or renal impairment, the newer agents are preferred. The older antibiotics, such as colistin, amikacin and tigecycline, are known to increase the risk of toxicity or are associated with inadequate plasma levels, as reported in several studies [155–158]. The safety profile of the newer agents is a key benefit for the treatment of patients with CRE infections. Beta-lactams are preferred over polymyxins or aminoglycosides, which may be nephrotoxic [159].

The recent IDSA guidance and ESCMID guidelines provide recommendations on when and how to use the new agents [89, 90]. Neither of them recommends a second agent to be used in combination with the new antibiotics for the treatment of CRE infections. Resistance has been reported for each of the new agents; however, these agents still have high susceptibility rates globally, with some regional variations. Overall susceptibility rates are reduced for ceftazidime–avibactam, meropenem–vaborbactam, and imipenem–relebactam in regions where MBLs are prevalent, while cefiderocol MICs are higher where NDM-producing CRE are more prevalent, but many MBL producers remain susceptible to it. Rapid molecular diagnostic testing for resistance mechanisms should lead to the improved surveillance and diagnosis of CRE and, hence, to the selection of the most appropriate antibiotic agent [160]. Indeed, in addition to the recommendations [89, 90], rapid diagnostics is one of the issues that will guide the optimal use of newer antibiotics against CRE. Other considerations include those related to the hospital formulary (such as local epidemiology and drug acquisition costs) and the development of criteria for use, as part of antimicrobial stewardship [161]. Another major limiting factor for the treatment of infections caused by CRE may be a lack of availability of newer agents along with susceptibility testing methods in countries with locally relevant enzymatic epidemiology, the very regions where these agents may be of most benefit.

The most therapeutically challenging carbapenemases are the MBLs, among which NDM, VIM and IMP (in South-East Asia) enzymes are the MBLs most commonly produced by CRE. None of the new beta-lactam–beta-lactamase inhibitor agents alone has activity; the combination of ceftazidime–avibactam with aztreonam, even in the absence of in vitro activity separately, may be effective [162]. Aztreonam–avibactam combination is currently under Phase 3 clinical development and may be available in the future [163].

In addition to aztreonam–avibactam, cefiderocol is the only other beta-lactam with activity against MBL-producing CRE. In vitro studies and surveillance studies showed that cefiderocol MIC values are higher against NDM-producing isolates than VIM-producing isolates. Nevertheless, clinical studies demonstrated that NDM-producing CRE infections with cefiderocol MICs of 4 μg/mL, which corresponds to the CLSI susceptibility breakpoint, could be successfully treated with cefiderocol [47]. Based on resistance reports, an increased copy number of NDM may increase cefiderocol MIC values beyond the resistance breakpoint [87]. Moreover, mutations affecting siderophore uptake systems (especially the CirA siderophore receptor) can confer high-level resistance to cefiderocol in NDM-producing strains [86]. Emergence of these mutants has been occasionally reported under cefiderocol treatment [86, 87], and was also observed in vitro, although loss of fitness was observed in these isolates [107]. Of note, the combination of mutations in iron transport genes and

expression of NDM enzyme was found in CRE in China, where cefiderocol has not been used in clinical practice [117, 120]; thus, resistance to cefiderocol by this mechanism may occur as a collateral damage driven by other, so far unknown mechanisms of selection [113].

In CRE, the development of resistance to cefiderocol treatment appears infrequent and, based on case reports, no consistent mechanisms or mutations are associated with reduced cefiderocol susceptibility. To date, cefiderocol resistance following treatment was demonstrated for two patients in case reports and one patient in Phase 3 clinical studies [82, 108, 109]. Of note, pre-existing resistance to cefiderocol, without exposure to the drug, has been described in some case reports. These patients were treated with other beta-lactam antibiotics and developed resistance to ceftazidime–avibactam with cross-resistance to cefiderocol as a result of certain mutations emerging in KPC-2, KPC-3 or AmpC [84, 88, 110]. Cross-resistance may emerge for the cephalosporin class with specific mutations in AmpC [88, 110]. The combination of the expression of the NDM enzyme and mutation in the *cirA* gene has been reported in other case reports of cefiderocol resistance [86]. However, NDM MBLs or *cirA* mutations have not been reported in cases with KPC or AmpC mutations. Thus, the reports suggest that, rather than a single mutation causing resistance, the presence of different mechanisms or mutations in parallel is necessary to develop clinically relevant cefiderocol resistance [87, 105].

The efficacy of cefiderocol in monotherapy was established in a large number of patients with carbapenem-susceptible Enterobacterales infections in two randomised controlled trials, and in a smaller number of patients with CRE in the CREDIBLE-CR study. The mortality rates with cefiderocol treatment in patients with CRE infections were similar to those seen in other pathogen-focused clinical studies with other newer antibiotics [83]. One limitation of all these pathogen-focused studies was the relatively low number of randomised patients [83]. In patients with CRE infections in CREDIBLE-CR, an overall benefit was seen with cefiderocol treatment. In cUTI patients with CRE, high rates of clinical and microbiological favourable cure rates were seen in both APEKS-cUTI and CREDIBLE-CR studies. In pneumonia patients, the clinical cure rates were similar in APEKS-NP (57%) and CREDIBLE-CR studies (62%), and these rates were also within the range seen for patients with carbapenem-susceptible Enterobacterales (64% and 56%, respectively) and in other pneumonia studies for Enterobacterales (RESTORE-IMI 2: imipenem–relebactam 61%, piperacillin-tazobactam 55.8% [72]). Early eradication of CRE harbouring Class A ESBLs, MBLs and other carbapenemases was confirmed from blood samples with cefiderocol treatment in patients with bacteraemia, and persistence and recurrence rates were low [143].

CONCLUSIONS

Cefiderocol is a potent beta-lactam (siderophore) antibiotic against CRE producing serine- or metallo-carbapenemases, ESBLs and/or AmpC enzymes. As a siderophore cephalosporin, cefiderocol has a unique and efficient mode of cell entry in Gram-negative pathogens, which may overcome resistance mechanisms involving alterations of porin channels and upregulation of efflux pumps. The efficacy and safety of cefiderocol was demonstrated in patients infected by various Enterobacterales species, including CRE producing KPC, MBL or OXA-48-type enzymes, across different infection sites. There is a need for additional comparative effectiveness clinical data to establish the value of cefiderocol in the management of CRE infections for seriously ill patient populations. Furthermore, continued surveillance is imperative to monitor emergence of resistance under cefiderocol treatment among pathogens in the clinical setting.

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