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Review

Prospective role of cefiderocol in the management of carbapenem-resistant *Acinetobacter baumannii* infections: Review of the evidence

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ABSTRACT

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) has been classified by the World Health Organization as being in the critical category of pathogens requiring urgent new antibiotic treatment options. Cefiderocol, the first approved siderophore cephalosporin, was designed for the treatment of carbapenem-resistant Gram-negative pathogens, particularly the non-fermenting species *A. baumannii* and *Pseudomonas aeruginosa*. Cefiderocol is mostly stable against hydrolysis by serine β-lactamases and metallo-β-lactamases, which are leading causes of carbapenem resistance. This review collates the available evidence on the in vitro activity, pharmacokinetics/pharmacodynamics, and efficacy and safety of cefiderocol, and outlines its current role in the management of CRAB infections. In vitro surveillance data show susceptibility rates of >90% for cefiderocol against CRAB isolates as well as in vitro synergism with a variety of antibiotics recommended in guidelines. Clinical efficacy of cefiderocol monotherapy against CRAB infections has been demonstrated in the descriptive, open-label CREDIBLE-CR and the non-inferiority, double-blind APEKS-NP randomised clinical trials as well as in real-world cases in patients with underlying health problems. To date, the frequency of on-therapy development of cefiderocol resistance in *A. baumannii* appears to be low, but monitoring is highly recommended. Within current treatment guidelines for moderate-to-severe CRAB infections, cefiderocol is recommended for infections in which other antibiotics failed and in combination with other active antibiotics. In vivo pre-clinical data support the combination of sulbactam or avibactam with cefiderocol to enhance efficacy and to suppress the emergence of cefiderocol resistance. The benefit of combination therapy in the clinical setting is yet to be determined in prospective studies.

1. Introduction

Acinetobacter baumannii complex is an opportunistic pathogen that has successfully developed multiple antibiotic resistance mechanisms and frequently causes outbreaks in healthcare institutions and hospitals [1]. The World Health Organization (WHO) has classified carbapenem-resistant *A. baumannii* (CRAB) under the critical category requiring urgent new antibiotic treatments [2].

The prognosis of critically ill patients infected by CRAB is often very poor and mortality rates are higher than for infections caused by carbapenem-susceptible *A. baumannii* [3,4]. Studies have shown that host factors (e.g. immunosuppression, higher Charlson comorbidity index), severity of illness [e.g. severe sepsis or

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septic shock, Pitt bacteraemia score, Sequential Organ Failure Assessment (SOFA) score], specific clone types, infection source and inappropriate antibiotics for multidrug-resistant (MDR) *A. baumannii* or CRAB are independently associated with increased all-cause mortality [1,5,6]. There is an urgent need for newer, more-effective antibiotics for infections caused by CRAB [2]. Despite administration of active antibiotics, high 28-day mortality rates have been shown in large randomised controlled trials (RCTs) in patients with nosocomial pneumonia (NP) and bloodstream infection (BSI) caused by CRAB [7]. Furthermore, the risk of 28-day mortality was not reduced by treatment with combinations of colistin with meropenem, rifampicin or fosfomycin (42–52.2%) compared with colistin alone (42.9–57.4%) [7,8]. As the activity of generic agents (e.g. polymyxins, aminoglycosides, tetracyclines and ampicillin/sulbactam) against CRAB varies across regions, new potent antibiotics with favourable safety profiles are required [9,10].

Cefiderocol is the first approved siderophore cephalosporin and was designed for the treatment of carbapenem-resistant Gram-negative pathogens, including Enterobacterales but particularly the non-fermenting species *A. baumannii* and *Pseudomonas aeruginosa*. Cefiderocol does not have in vitro activity against Gram-positive bacteria or anaerobes. Cefiderocol is intrinsically stable against hydrolysis by most extended-spectrum β-lactamases (ESBLs), class A, B and D carbapenemases and class C cephalosporinases. As cefiderocol enters bacteria mainly through iron transport channels via siderophore receptors, with a smaller fraction entering via porin channels, mutations in porin genes have a minimal impact on cefiderocol minimum inhibitory concentrations (MICs) [11,12]. Recent reports have shown the potent in vitro activity and efficacy of cefiderocol against carbapenem-resistant Enterobacterales (CRE), both of which have been confirmed in clinical studies [13]. These data suggest that patients with NP, BSI or complicated urinary tract infection (cUTI) caused by CRE harbouring metallo-β-lactamases, OXA-48 oxacillinase, or *Klebsiella pneumoniae* carbapenemase (KPC) could benefit from cefiderocol treatment [13].

In this article, we aim to review the evidence on the in vitro activity, pharmacokinetics/pharmacodynamics (PK/PD), and efficacy and safety of cefiderocol, along with its role in the management of CRAB infections.

2. Cefiderocol

2.1. In vitro activity and synergism with other antibiotics

Susceptibility data for cefiderocol against CRAB and carbapenem-susceptible *A. baumannii* are shown in Table 1, and the current susceptibility breakpoints for cefiderocol by the US Food and Drug Administration (FDA), Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) against *A. baumannii* are given in Table 2. The multinational SIDERO surveillance programme, conducted between 2014 and 2019, systematically collected non-consecutive Gram-negative bacterial isolates from hospitalised patients with BSI, respiratory tract infection, UTI, intra-abdominal infection or wound infection in North America and European countries [14–19]. Susceptibility testing was performed consistently by the CLSI-approved reference broth microdilution (BMD) method using iron-depleted cation-adjusted Mueller–Hinton broth (ID-CAMHB) [14–19]. Cefiderocol MICs against *A. baumannii* overall or against CRAB ranged between ≤0.002 μg/mL and >256 μg/mL, with MIC_{90} values (MIC required to inhibit 90% of the isolates) of 1–2 μg/mL (Table 1) [14–19]. In the SENTRY surveillance programme, the cefiderocol MIC_{90} was similar to that in the 5-year SIDERO surveillance programme against 306 meropenem-resistant *A. baumannii* isolates collected in 2020 [20]. Cefiderocol susceptibility rates were >90% according to both CLSI and EUCAST criteria in the USA and Europe [20]. Susceptibility rates for carbapenem-non-susceptible *A. baumannii* were between 77.9% and 97.2% across different countries and regions (Table 1).

Of 5225 CRAB isolates collected in the SIDERO surveillance programme, 204 (3.9%) had high (i.e. ≥8 μg/mL) cefiderocol MICs without prior exposure to this antibiotic. The ESBL *Pseudomonas*-extended resistance (PER) enzyme, which is involved in mediating cefiderocol resistance when combined with other factors [21], was detected in most of these isolates [22–26]. PER-expressing isolates were found mainly in Russia, with a small number in Sweden and Turkey, but also in Taiwan, China, Bangladesh, Egypt and Saudi Arabia, in regions without access to cefiderocol [22–29]. However, PER-harbouring *A. baumannii* isolates are rarely found in North America or Europe [26,30–33].

Heteroresistance in *A. baumannii* has been described for a number of antibiotic classes, including cefiderocol [34], although the clinical significance is not clear. In an in vitro study of ten different *A. baumannii* strains with different susceptibilities to cefiderocol, including strains resistant to colistin and/or meropenem, bactericidal activity was followed by re-growth in four strains with 10^3 CFU/mL at the highest cefiderocol concentration (32 μg/mL). Heteroresistant populations (those with ratio ≥$1/10^6$ colonies at 32 μg/mL of cefiderocol concentration compared with those growing on antibiotic-free plates) were unstable and returned to initial MIC values in antibiotic-free media. The addition of serine-β-lactamase inhibitors, such as avibactam, to cefiderocol restored cefiderocol antimicrobial activity against resistant and heteroresistant strains [34]. A high level of in vitro cefiderocol heteroresistance, recently described in 108 US CRAB isolates, has been proposed as a potential contributing factor to the observed increased mortality in the CREDIBLE-CR study [35,36]. However, a recent analysis of baseline CRAB isolates collected in the CREDIBLE-CR study did not confirm this hypothesis [37]. Of 38 CRAB isolates in the cefiderocol arm, nearly one-half (47%) displayed heteroresistance by population analysis profiling method, despite nearly all isolates being susceptible by the BMD method [36,37]. However, most heteroresistant CRAB isolates collected at randomisation were found in patients who survived by end of study, and no correlation was found between heteroresistance and mortality [37].

In vitro synergism has been demonstrated between cefiderocol and other antibiotics against *A. baumannii*. Using humanised doses against isolates with increased cefiderocol MICs (i.e. 16 μg/mL) in the chemostat model, sustained bactericidal activity against PER-1-producing *A. baumannii* was found with the combination of cefiderocol and each of avibactam, sulbactam, meropenem and amikacin [38]. In another study, using disk stacking methodology, synergism between cefiderocol and ceftazidime/avibactam against cefiderocol-resistant strains of *A. baumannii* was demonstrated by the increase in zone diameter irrespective of PER production [39]. The synergy of cefiderocol plus avibactam at a fixed concentration of 4 μg/mL was confirmed using the BMD method, with a 64–512-fold reduction in cefiderocol MIC values [39]. Another series of experiments in *A. baumannii* strains with cefiderocol MICs of 16–32 μg/mL confirmed the synergism between cefiderocol and avibactam, sulbactam, amikacin and minocycline, but not colistin or ceftazidime [40]. Avibactam does not lead to a reduction in cefiderocol MICs against cefiderocol-susceptible *A. baumannii* isolates [41].

Currently, the CLSI has a warning about the reproducibility and accuracy of the BMD method and the disk diffusion (DD) method for susceptibility testing against *Acinetobacter* spp. [42]. These concerns emerged due to difficult-to-interpret MICs and DD endpoints caused by trailing with BMD or emerging colonies within the predominant zones of growth inhibition, respectively, for isolates with cefiderocol MIC ≥ 2 μg/mL. In addition, minor variability in

Table 1
Regional in vitro activity of cefiderocol against carbapenem-susceptible or -non-susceptible *Acinetobacter baumannii*

Surveillance programme or region	Collection period	*N*	MIC range (μg/mL)	MIC_{90} (μg/mL)	% with MIC ≤4 μg/mL	%S	Susceptibility criteria	Reference
SIDERO – overall	2014–2015 (North America)	309	≤0.002–8	1	99.0	N/A	N/A	[14]
SIDERO [a]	2014–2015 (North America)	173	≤0.002–8	1	98.3	N/A	N/A	[14]
SIDERO – overall	2014–2015 (Europe)	839	0.004–64	1	97.0	N/A	N/A	[14]
SIDERO [a]	2014–2015 (Europe)	595	0.004–64	1	96.5	N/A	N/A	[14]
SIDERO – overall	2014–2019 (North America + Europe)	5225	≤0.002 to >256	1	96.0	96.0 94.1	CLSI EUCAST	[19]
SIDERO [a]	2014–2019 (North America + Europe)	2810	≤0.002 to >256	2	94.2	94.2 91.1	CLSI EUCAST [b]	[19]
SENTRY – overall	2020	650	≤0.004 to >64	1	97.7	97.7 95.7	CLSI EUCAST [b]	[20]
SENTRY [c]	2020	306	0.015 to >64	2	95.8	95.8 91.5	CLSI EUCAST [b]	[20]
Greece [c]	2010–2016	107	≤0.03–2	0.5	100	N/A	N/A	[113]
Switzerland [d]	2000–2016	85	0.03–64	4	N/A	N/A	N/A	[114]
Canada [e]	2015–2017	11	≤0.03–0.25	N/A	100	100	CLSI	[115]
Taiwan [f]	2016–2017	100	0.06 to >64	8	88	N/A	N/A	[116]
Taiwan [g]	2018–2020	255	0.06 to >64	2	N/A	94.9	CLSI	[117]
Germany [h]	2013–2014	13	0.06–0.12	0.12	100	N/A	N/A	[118]
Germany [i]	2014–2021	39	0.016–24	N/A	84.6	77.9	EUCAST [b]	[119]
UK (England) [j]	2014–2018	70	0.008 to >256	1	94.3	94.3	EUCAST [b]	[15]
France [c]	2014–2018	16	0.008–8	2	N/A	93.8	EUCAST [b]	[16]
Spain [c]	2014–2018	175	0.015–4	1	100	96.6	EUCAST [b]	[17]
Italy [c]	2014–2018	354	<0.004 to >256	2	N/A	95.2	EUCAST [b]	[18]
Italy [k]	2019–2021	70	N/A	1	N/A	97.2	EUCAST [b]	[120]

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; MIC_{90}, MIC required to inhibit 90% of the isolates; N/A, not available; %S, percent susceptible.
[a] All meropenem-non-susceptible.
[b] EUCAST species-independent pharmacokinetic-pharmacodynamic (PK/PD) breakpoint.
[c] All meropenem-resistant.
[d] All carbapenemase producers.
[e] All meropenem-susceptible.
[f] All imipenem-resistant.
[g] 99.2% carbapenem-resistant.
[h] 38.5% meropenem-resistant.
[i] 76.9% carbapenem-non-susceptible.
[j] 12.9% meropenem-non-susceptible.
[k] 95.7% imipenem-resistant.

Table 2
Cefiderocol susceptibility breakpoints by US Food and Drug Administration (FDA), Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST)

	MIC (μg/mL)			Disk zone diameter (mm) (for 30 μg disk)		
	S	I	R	S	I	R
FDA [121]	≤1	2	≥4	≥19	12–18	≤11
CLSI [122]	≤4	8	≥16	≥15	–	–
EUCAST [44]	IE	–	IE	IE	–	IE
EUCAST PK/PD (non-species related) breakpoints [a] [44]	≤2	–	>2	–	–	–

I, intermediate; IE, insufficient evidence; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; R, resistant; S, susceptible.
[a] Broth microdilution MIC determination must be performed in iron-depleted Mueller–Hinton broth, and specific reading instructions must be followed.

the inoculum level caused major differences in cefiderocol MICs. They recommend the use of a nephelometer to confirm the colony counts [42]. For Enterobacterales and *Pseudomonas*, EUCAST recommends starting susceptibility testing with DD, and if the zone diameter falls within the area of technical uncertainty (ATU) range, another test should be performed [43]. However, EUCAST has not yet established clinical breakpoints or ATU for *Acinetobacter* spp. [44], but zone diameters ≥17 mm by DD corresponded with MICs of ≤2 μg/mL for all but one isolate [43], which is equivalent with the PK/PD breakpoint [44]. Thus, isolates showing ambiguous results by DD should be re-tested by disk or a broth-based method, which could be the reference ID-CAMHB method or commercial broth tests such as ComASP® (Liofilchem) or UMIC (Bruker). Both of these commercial broth tests use ID-CAMHB and seem to provide reliable MIC values, which correlate with the zone diameters provided by the DD method [45]. Currently, other commercially available methods such as gradient strips are not reliable to confirm cefiderocol susceptibility for *Acinetobacter* spp.

Although data are limited currently, cefiderocol appears to have in vitro activity in the biofilm setting for a number of Gram-negative pathogens, including *A. baumannii* [46]. At a concentration of 4 μg/mL, cefiderocol reduced biofilm mass formation by 67–80% against *A. baumannii* and the effect was comparable with that of other tested antibiotics [46]. However, a retrospective, multicentre study conducted in Taiwan has shown that there was no difference in all-cause mortality (ACM) rates or carbapenem susceptibility status between patient populations infected by biofilm-forming and non-biofilm-forming forms of *A. baumannii*, but it highlighted some important differences in the clinical characteristics of patients between these two populations [47]. Thus, currently the role of biofilm formation in the clinical setting regarding patient outcomes remains unclear.

2.2. Pre-clinical in vivo effectiveness and combination treatment

The bactericidal activity of cefiderocol was investigated in several pre-clinical infection models. Dose fractionation studies in neutropenic murine thigh and lung infection models showed that the percentage of the dosing interval during which the free cefiderocol concentration remains above the MIC (%$fT_{>MIC}$) is the main PD driver of carbapenem-resistant Gram-negative bacteria killing [48]. Using the neutropenic murine lung infection model caused by three different *A. baumannii* isolates, the mean %$fT_{>MIC}$ of the dosing interval required to achieve a 1 log reduction in the growth of CRAB isolates was 88% [48]. In an immunocompetent rat lung infection model, humanised cefiderocol exposure with 3-h infusions every 8 h over 96 h resulted in bactericidal effects against CRAB strains, with at least a 3 $\log_{10}$ reduction in bacterial load [49].

The susceptibility breakpoint for cefiderocol was suggested as 4 μg/mL based on results from a neutropenic murine thigh infection model under 24-h humanised exposure of cefiderocol, which was applicable to all Gram-negative species tested, including *A. baumannii*. Across 35 *A. baumannii* strains with cefiderocol MICs ranging from 0.12 μg/mL to >256 μg/mL, bacterial stasis or ≥1 log CFU reduction in growth was achieved for 87% of isolates with cefiderocol MICs of ≤2 μg/mL and 88% of isolates with cefiderocol MICs of ≤4 μg/mL. In contrast, growth of isolates with cefiderocol MICs of ≥8 μg/mL was not reduced over 24 h [50]. In a subsequent investigation in the same pre-clinical PD model, sustained bacterial kill or stasis over 72 h was demonstrated against CRAB isolates with cefiderocol MICs of 0.5, 1 and 4 μg/mL, but not 16 μg/mL [51].

In vivo efficacy was also investigated for seven *A. baumannii* strains that showed re-growth and resistance development in the in vitro chemostat model [52]. While post-exposure MICs of these isolates were elevated (from 1–2 μg/mL to 8–128 μg/mL) in the in vitro system, clinically relevant exposures of cefiderocol that simulated the 2 g every 8 h 3-h infusion regimen in the in vivo translational murine thigh model did not display MIC elevations, and sustained bacterial killing was found over 72 h for five of seven strains [52]. The resistance to cefiderocol observed in vitro was linked to mutations emerging in the *tonB* gene and a reduction in mRNA levels of *exbB* and *exbD*, genes that are linked to iron transport [52]. Importantly, an investigation in the neutropenic murine thigh infection model previously demonstrated that the in vivo efficacy and bactericidal effects of cefiderocol humanised exposures against *A. baumannii* are not diminished under iron overload conditions compared with standard iron level conditions [53]. Furthermore, cefiderocol in combination with meropenem, ceftazidime/avibactam or ampicillin/sulbactam more effectively reduced the bacterial load in vivo against three cefiderocol-susceptible *A. baumannii* isolates (MIC 2 μg/mL) than cefiderocol alone at humanised exposures. Additionally, cefiderocol combined with ceftazidime/avibactam or ampicillin/sulbactam also prevented the development of resistance [54].

Among *A. baumannii* defined as non-susceptible to cefiderocol (MIC 8 μg/mL or >32 μg/mL), humanised exposures of cefiderocol in combination with ceftazidime/avibactam and ampicillin/sulbactam resulted in profound in vivo bactericidal activity (mean changes in $\log_{10}$ CFU/thigh of up to −5.55) in all 12 isolates tested, whereas synergistic activity was observed in 8/12 isolates with the cefiderocol–meropenem combination regimen [54,55].

2.3. Cefiderocol pharmacokinetics, population pharmacokinetics and exposure

In healthy subjects, a linear PK profile has been demonstrated for ascending single doses of cefiderocol between 100 mg and 4000 mg [56,57]. Following multiple dosing of cefiderocol up to 2000 mg in 1-h infusions in healthy subjects, there was no accumulation of cefiderocol and the terminal elimination half-life ranged from 2 h to 3 h [56]. Protein binding was ∼60% in healthy subjects [58].

The majority of cefiderocol in plasma is excreted via the kidneys [59] and no clinically relevant metabolites have been identified [59]. Compared with subjects with normal renal function, subjects with mild, moderate or severe renal impairment as well as with end-stage renal disease without haemodialysis showed an increase in cefiderocol area under the concentration–time curve (AUC) (from 212.0 μg·h/mL to 872.5 μg·h/mL) and half-life (from 2.8 h to 9.6 h) and a decrease in renal clearance (from 4.7 L/h to 1.1 L/h) [58]. Additionally, the volume of distribution ranged between 13.5 L and 16.4 L [58]. Thus, cefiderocol dose adjustment is required for patients with renal impairment. The standard dosing of cefiderocol is 2 g infused over 3 h every 8 h in patients with creatinine clearance of 60–89 mL/min (mild impairment) and 90–119 mL/min (normal renal function). Cefiderocol dosing for patients with moderate and severe renal impairment is 1.5 g infused over 3 h every 8 h and 1 g infused over 3 h every 8 h, respectively. For patients with end-stage renal disease, the cefiderocol dose is reduced to 0.75 g infused over 3 h every 12 h [60]. Critically ill patients who require continuous renal replacement therapy (CRRT) are at risk of suboptimal antibiotic dosing and therefore potential treatment failure. A recent analysis identified effluent flow rate during CRRT as the covariate requiring adjustment by cefiderocol dosing regimen [61]; thus, FDA-validated recommendations have been incorporated into the cefiderocol prescribing information [62,63]. Cefiderocol dosing for patients with augmented renal clearance (ARC) is 2 g infused over 3 h every 6 h [60], and this was confirmed in the phase 3 clinical trials and incorporated into the product label.

Effective lung penetration of cefiderocol has been demonstrated both in healthy subjects and in patients with pneumonia requiring mechanical ventilation [64,65]. Population PK modelling, based on healthy subjects and patients with Gram-negative cUTI, NP or BSI receiving approved doses of cefiderocol in phase 2 and phase 3 studies, adequately described cefiderocol plasma concentrations, with creatinine clearance as the most significant covariate [60]. The probability of target attainment (PTA) for 100% $fT_{>MIC}$ was >90% across all infection sites and renal function groups for pathogens with cefiderocol MICs of ≤4 μg/mL, with the exception of those with BSI and normal renal function, in whom the PTA was 85% [60]. The estimated free minimum plasma concentration in patients with ARC was >4 μg/mL, making the current approved dosing regimen adequate for the treatment of such patients [60]. Interesting findings from a PK/PD study reported no correlation between clinical outcome, microbiological outcome or vital status and PD target levels (i.e. 100% $fT_{>MIC}$) [60] and showed that a more conservative target (%$fT_{>4 \times MIC}$) was achieved by 83% of patients in the two cefiderocol phase 3 RCTs, namely CREDIBLE-CR and APEKS-NP [36,60,66]. Among patients with pneumonia, the estimated maximum concentrations of cefiderocol and the AUC were similar in ventilated and non-ventilated patients [60], and the epithelial lining fluid to plasma penetration ratio was 34%, with a PTA of 100%$fT_{>MIC}$ being estimated in most patients; ≥99.5% for Gram-negative pathogens with cefiderocol MIC ≤ 2 μg/mL and ≥87% with cefiderocol MIC ≤ 4 μg/mL across all renal function groups [67].

3. Clinical evidence

3.1. Randomised controlled trials

To date, two phase 3 RCTs have been conducted in critically ill patients with NP, BSI or cUTI that included patients with carbapenem-susceptible *A. baumannii* or CRAB [36,66].

The CREDIBLE-CR study was an open-label, international, descriptive (i.e. no inferential hypothesis testing), parallel-group, phase 3 study that enrolled hospitalised patients with serious carbapenem-resistant Gram-negative bacterial infections, including NP, BSI or cUTI [36]. The exclusion criteria were very limited, enabling enrolment of patients with carbapenem-resistant Gram-negative bacterial infections or with prior treatment failure and serious underlying medical co-morbidities. Patients were stratified at the time of randomisation for infection site, Acute Physiology and Chronic Health Evaluation (APACHE) II score and region, but not for specific pathogens. Nearly one-half of the patient population had pneumonia and ~30% had BSI, which were caused primarily by CRAB [NP: cefiderocol 65%, best available therapy (BAT) 53%; BSI: cefiderocol 44%, BAT 50%) [36].

Clinical cure (NP: cefiderocol 50%, BAT 60%; BSI: cefiderocol 30%, BAT 43%) and microbiological eradication (NP: cefiderocol 31%, BAT 30%; BSI: cefiderocol 20%, BAT 29%) rates at test of cure (i.e. 7 ± 2 days following end of treatment) were generally similar in the cefiderocol and BAT arms for patients with CRAB [36]. Although administration of a second agent in combination with cefiderocol was permitted for patients with NP and BSI, ~78% of these patients received cefiderocol monotherapy. In the BAT arm, 76% of these patients with CRAB infections received combination therapy, which was usually colistin-based [7,36].

Bassetti et al. reported a numerically increased ACM in the cefiderocol arm at each study visit, mainly among patients with NP or BSI caused by *Acinetobacter* spp.; Day 28 ACM was 38% in the cefiderocol arm and 18% in the BAT arm [7,36]. The ACM rate with cefiderocol was within the range seen in other randomised, controlled and retrospective observational studies (i.e. 15–52%) [7,8,68–71], possibly due to similarities in the vulnerability, host factors and site of infection of the enrolled patient populations [7]. Among patients with CRAB and other *Acinetobacter* spp. at randomisation in the CREDIBLE-CR study, patients in the cefiderocol arm were generally older, with slightly higher median APACHE II score, and moderate or severe renal impairment and a Charlson comorbidity index ≥6 were more frequent [36]. Perhaps most importantly, there were substantial numerical differences in patients with ongoing/prior shock and intensive care unit (ICU) admission (cefiderocol 26% and 81% and BAT 6% and 47%, respectively) [36]. The severity of illness was reflected by multiple underlying co-morbidities (e.g. pulmonary or cerebral haemorrhage, burns, malignancy, cirrhosis) in all patients who died [36].

APEKS-NP was a registrational, double-blind, international, non-inferiority, controlled RCT in patients with ventilator-associated pneumonia (VAP), hospital-acquired pneumonia or healthcare-associated pneumonia comparing cefiderocol 2 g by 3-h infusion every 8 h with meropenem 2 g by 3-h infusion every 8 h [66]. The study tested the null hypothesis that cefiderocol was non-inferior to meropenem for ACM at Day 14 with a non-inferiority margin of 12.5% [66]. Exclusion criteria included cystic fibrosis, bronchiectasis, refractory septic shock, concomitant central nervous system (CNS) infection or mould infection, APACHE II score ≥35 and knowledge that a baseline qualifying Gram-negative pathogen at randomisation was carbapenem-resistant [66].

High-dose, extended-infusion meropenem was selected as the comparator arm to treat Gram-negative pathogens, including *A. baumannii*, with meropenem MIC up to 8 μg/mL, which is the EUCAST high-dose meropenem susceptibility breakpoint [44]. A recent pre-clinical study, combined with PD modelling, demonstrated that meropenem 2 g every 8 h infused over 3 h could provide adequate/sufficient exposure against *A. baumannii* isolates with meropenem MICs up to 16 μg/mL [72]. Monte Carlo simulations confirmed that meropenem at higher doses (i.e. 2 g every 8 h in continuous infusion) would achieve a PTA of 100%$fT_{>3\times MIC}$ for Gram-negative pathogens with meropenem MICs of 8 μg/mL for patients with ARC, a PTA of 100%$fT_{>2\times MIC}$ up to 16 μg/mL for patients with normal renal function, and a PTA of 100%$fT_{>2\times MIC}$ up to 32 μg/mL for patients with severe renal impairment [73].

The baseline characteristics in APEKS-NP in the two treatment arms were balanced at randomisation both among ventilated and non-ventilated patients, including those with *Acinetobacter* spp.; approximately 70% and 66% were being treated in the ICU, 33% and 32% had empirical treatment failure, and <10 patients per treatment arm had shock [66]. *Acinetobacter baumannii* and other *Acinetobacter* spp. at randomisation were isolated in 26 (18%) and 27 (18%) patients in the cefiderocol and meropenem arms, respectively [66].

The study met the primary endpoint, with ACM rates at Day 14 of 12.4% in the cefiderocol arm and 11.6% in the meropenem arm [treatment difference 0.8, 95% confidence interval (CI) −6.6 to 8.2] [66]. Among patients with *A. baumannii*, 5 (22%) of 23 patients and 4 (17%) of 24 patients died by Day 14 (treatment difference 5.1, 95% CI −17.4 to 27.6). By Day 28, 7 (32%) of 22 patients and 6 (25%) of 24 patients had died (treatment difference 6.8, 95% CI −19.2 to 32.9) [66]. Rates of clinical cure (cefiderocol 52%, meropenem 58%) and microbiological eradication (cefiderocol 39%, meropenem 33%) were similar between treatment arms at test of cure among patients with *A. baumannii* [66]. A post-hoc analysis showed that Day 28 ACM was comparable (cefiderocol 33%, meropenem 39%) for patients who had meropenem-resistant (i.e. meropenem MIC > 8 μg/mL) *Acinetobacter* spp., however mortality tended to be higher for the meropenem arm when meropenem MICs were ≥32 μg/mL [66].

3.2. Controlled observational studies and case reports

Since approval in 2019 by the FDA and in 2020 by the European Medicines Agency (EMA), cefiderocol has been used for the treatment of MDR, carbapenem-resistant or extensively drug-resistant (XDR) Gram-negative infections, including patients with *A. baumannii*, mainly during the period of the COVID-19 (coronavirus disease 2019) pandemic. Some patients have been treated as part of the pre-regulatory approval, compassionate-use programme in the USA, Canada and Europe.

In a retrospective, multicentre, observational, cohort study of ICU patients who developed CRAB infections between January 2020 and April 2021, a total of 46 received cefiderocol as compassionate use (i.e. patients had no alternative treatment option due to prior treatment failure or toxicity) and 82 patients received colistin-based treatment [74]. Most patients had COVID-19 pneumonia (cefiderocol 42, colistin-based treatment 65), who were the basis of the analysis, and required mechanical ventilation (cefiderocol 42, colistin-based treatment 63) during this period. Patients had lower respiratory tract infection or BSI caused by CRAB. Median SOFA scores were similar at admission (cefiderocol 9, other antibiotics 8), and septic shock was present in 46% and 38% of patients receiving cefiderocol or colistin-based treatment, respectively [74]. Clinical cure within 14 days was reported for 40% and 36% of patients, with a reduction in median SOFA score to 1 and 0, in patients receiving cefiderocol or colistin-based treatment, respectively [74]. Despite clinical improvement, at Day 14 40% of cefiderocol-treated patients and 51% of patients receiving other antibiotics had died; at Day 28, mortality had increased to 55% and 58%, respectively [74].

The second retrospective, observational cohort study enrolled 124 consecutive critically ill patients with CRAB infection, mainly BSI or VAP, between June 2019 and August 2021 [75]. Among 47 patients receiving cefiderocol, ~68% received it in combination with other antibiotics (including tigecycline, fosfomycin, ampicillin/sulbactam, meropenem/vaborbactam or ertapenem, and excluding colistin). Similarly, among 77 patients receiving colistin-

based regimens, 83% received combination therapy [75]. Illness severity was reflected by high SOFA and APACHE II scores, ~40% with underlying COVID-19 pneumonia, 60% with septic shock and 25% with acute kidney injury at the time of sepsis. Extracorporeal membrane oxygenation was significantly more frequent among cefiderocol-treated patients (14.9% and 2.6%, respectively), who also had a significantly longer duration of hospital stay (median 28 days and 13 days, respectively). By Day 30, 34% of patients receiving cefiderocol and 56% receiving colistin-based treatment had died [75]. The authors reported more frequent microbiological failure among patients receiving cefiderocol than patients receiving colistin-based regimens [17.4% (8/46) and 6.8% (5/74); not significant], 4 of whom developed resistance on therapy [75]. ACM at Day 14 was significantly lower with cefiderocol for BSI patients (7.4% and 42.3%; $P = 0.001$) but not VAP patients (33.3% and 52.2%). In multivariate analysis, septic shock, SOFA score and age were independent predictors of Day 30 mortality, and cefiderocol treatment was an independent protective factor [75].

In a single-centre, retrospective, observational study, outcomes were compared following cefiderocol- or colistin-containing treatment in patients with COVID-19 pneumonia requiring mechanical ventilation and who developed VAP and secondary bacteraemia caused by XDR or pandrug-resistant *A. baumannii* [76]. Patients hospitalised in the ICU between March 2020 and August 2022 were included. Nearly all (91.7%) of the 73 patients had septic shock, but baseline clinical characteristics were generally similar between the two treatment groups. For all 19 patients treated with cefiderocol, also fosfomycin, tigecycline and/or meropenem was applied in combination therapy [76]. In this study, cefiderocol-containing treatment, particularly in combination with fosfomycin, was independently associated with 30-day survival [76]. Another single-centre, retrospective investigation in patients with CRAB infections, either pneumonia or BSI, found similar clinical cure, microbiological eradication and mortality rates between cefiderocol- and colistin-based therapies; however, 30 of 60 patients received cefiderocol as monotherapy [77].

Cefiderocol has also been used in a number of case reports/case series as a last-resort antibiotic in 150 patients with serious infections involving XDR *A. baumannii*, MDR *A. baumannii*, CRAB or difficult-to-treat resistance (DTR) *A. baumannii* (Table 3) [78–100]. Cefiderocol monotherapy or combination therapy was used successfully in patients aged between 18 years and 92 years with a variety of infection types, including NP, BSI, meningitis and prosthetic joint infection, which were complicated by sepsis, COVID-19 pneumonia or other co-morbidities. Among these reported cases, one patient had CNS infection [90], but to date no paediatric cases were reported with *A. baumannii* or CRAB infections. Most patients were successfully treated with cefiderocol (approximately 55–65%), although clinical or microbiological failure and deaths due to any cause were also reported (Table 3) in concordance with previous reports [7,8,68,69].

4. Emergence of on-therapy resistance

On-therapy resistance development in the phase 3 RCTs was monitored by central laboratory confirmation of cefiderocol MICs in cultures collected at randomisation and during and following treatment. In the CREDIBLE-CR study, 5 (12.8%) of 39 patients with CRAB had isolates with 4–16-fold on-treatment increases in cefiderocol MICs, although post-treatment isolates remained susceptible by CLSI criteria (MICs 1, 1 and 4 μg/mL) for three patients and had MICs of 8 μg/mL in two patients [36]. In the BAT arm, 2 (11.8%) of 17 patients with CRAB showed ≥16-fold increases in the MICs of the antibiotics they were receiving (colistin and tigecycline) [36]. Only three of the five baseline isolates were genetically linked to the post-treatment isolates with higher cefiderocol MICs, and whole-genome sequencing identified a point mutation in penicillin-binding protein 3 ($n = 1$), two point mutations in OXA-23 ($n = 1$) and no mutations in the third CRAB isolate [101]. On-therapy resistance among patients receiving cefiderocol monotherapy was also reported in four patients in an Italian observational retrospective study [during ($n = 2$) or following ($n = 2$) cefiderocol treatment] [75], in one critically ill patient in an Italian case series [82], and in one patient in a burn ICU that led to an outbreak of cefiderocol-resistant CRAB isolates with mutations in *piuA*, a TonB-dependent siderophore receptor, or *pirA*, a siderophore gene [102]. Russo et al. have recently reported that cefiderocol resistance emerged during therapy in two patients who received cefiderocol in combination therapy [76].

5. Role of cefiderocol in the management of carbapenem-resistant Acinetobacter baumannii infections

Management of patients with CRAB infections is challenging due to limited treatment options [10,103,104] combined with the multiplicity of host factors. The most frequently used agents include colistin, polymyxin B, tigecycline, minocycline, ampicillin/sulbactam and meropenem in extended infusion at high dose if the meropenem MIC is <8 μg/mL for CRAB (Fig. 1); however, important limitations of some of these agents regarding safety and tissue levels have been recognised [10].

Several studies have highlighted that ICU patients with CRAB infections can be highly vulnerable [68,70,71,105]; thus, the safety profile of antibiotics selected for treatment is critical. Among the treatment options, colistin and polymyxin B use are often associated with acute kidney injury within 14 days in 30–50% of patients [8,68–70,106]. Colistin use also led to the emergence of other adverse events such as hyponatraemia, hypomagnesaemia, hypokalaemia and hypophosphataemia [106]. Tigecycline use is not recommended for patients with BSI because of the low plasma concentrations and lack of established susceptibility breakpoints [10]. Both the polymyxins and some tetracyclines have limited penetration into certain infections sites (e.g. lung or urine). Cefiderocol is a siderophore cephalosporin with a safety profile similar to that of other β-lactams and achieves appropriate drug exposure for use in critically ill patients [36,66,107].

Therapeutic drug monitoring has been investigated for infections caused by CRAB or MDR *A. baumannii* for a more optimal application of tigecycline [108], colistin [106] and meropenem [109]. According to these studies, treatment with an initial loading dose of tigecycline or colistin followed by a maintenance dose, or continuous infusion of high-dose meropenem was necessary to achieve more favourable clinical outcomes and to obtain antibiotic exposures for these antibiotics above target MIC values. However, use of a colistin loading dose was associated with increased nephrotoxicity [106]. Routine therapeutic drug monitoring for β-lactam antibiotics has been proposed to support adequate plasma concentrations [110], however correct dosing for the right antibiotic appears to be a more practical approach in the management of critically ill patients [111]. Cefiderocol dosing recommendations (in monotherapy) have been extensively investigated, including patients with ARC or severe renal impairment requiring CRRT, and PK data derived from clinical trials suggest that cefiderocol dosing recommendations in the label provide coverage against all Gram-negative pathogens with MICs up to 4 μg/mL [58,60,64,65,67].

Among generic antibiotics, ampicillin/sulbactam is currently the preferred agent of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Infectious Diseases Society of America (IDSA) and the Society of Infectious Diseases Pharmacists (SIDP) (Fig. 1) [10,103,104,112]. For moderate-to-severe CRAB infections, the IDSA and SIDP recommend combination treatment, which could include high-dose ampicillin/sulbactam and minocy-

Table 3
Outcomes with cefiderocol treatment for extensively drug-resistant (XDR) *Acinetobacter baumannii*, carbapenem-resistant *A. baumannii* (CRAB) and difficult-to-treat resistance *A. baumannii* (DTR-AB) infections in 150 real-world cases

Reference	No. of patients, age/underlying conditions	Infection type(s)	Combination therapy and duration of treatment	Clinical outcome	Microbiological outcome	Note
[91]	13 patients, 35–79 years COPD, obesity, hypertension, and other types of co-morbidities, 12/13 with COVID-19 pneumonia and 1/13 with recurrent pneumonia	Polymicrobial HAP/VAP for 12 patients caused by CRAB [plus *Pseudomonas aeruginosa* (6), *Klebsiella pneumoniae* (6), other Enterobacterales (4)]	5 patients received combination treatment Cefiderocol: median 10 days (range 7–27 days)	7 patients had cure 6 patients died	N/R	No adverse events reported 46% died by Day 30 Nearly all patients had COVID-19 pneumonia at baseline
[88]	13 patients (8 male, 5 female) Severe COVID-19 pneumonia, mechanical ventilation	13 patients with VAP and/or BSI caused by XDR *A. baumannii*; all 13 patients had monomicrobial infection 6 patients with VAP + BSI; 2 patients with BSI; 5 patients with VAP	3 patients received combination treatment (colistin + AMP/SUL; fosfomycin; AMP/SUL) Cefiderocol: median duration 10 days	9 patients survived, 4 patients died by Day 30	All BSI patients achieved eradication, except 1, 4 VAP patients achieved eradication 7 patients had microbiological failure	$fC_{min>MIC}$ was the PD parameter associated with outcomes
[84]	10 patients (8 male, 2 female), 25–78 years Multiple co-morbidities, COVID-19 in 7 patients	CRAB infections included: monomicrobial BSI (7 patients), monomicrobial VAP (1 patient), monomicrobial VAP + BSI (1 patient), polymicrobial perihepatic abscess (with MDR *Enterobacter cloacae* complex, *Morganella morganii, Enterococcus faecium*; 1 patient)	10 patients received combination treatment (with colistin, tigecycline, fosfomycin, meropenem) Duration 5–21 days	7 patients had success, 3 deaths	All 10 patients had eradication	2 patients (1 immunocompromised) died from COVID-19 pneumonia 1 immunocompromised patient died from new Gram-positive bacterial and fungal infection
[82]	8 patients (3 male, 5 female), 33–82 years Burns in 4 patients, COVID-19 in 3 patients, hypertension in 6 patients, ICU and mechanical ventilation for 8 patients	Monomicrobial BSI (6), monomicrobial VAP (2) caused by CRAB	1 patient received combination treatment (plus fosfomycin) Cefiderocol: median duration 14 days	5 patients with clinical cure, 1 death and 2 relapses	2 patients had microbiological failure due to skin and rectal persistence	1 patient died by Day 30
[80]	Male, 29 years SSI	Polymicrobial osteomyelitis caused by CRAB (plus *E. cloacae, P. aeruginosa*)	Yes (colistin, CAZ/AVI) Cefiderocol: 2 weeks	Cure	No persistence	Polytrauma occurred to the patient prior to infection
[80]	Male, 64 years Post-operative implant-associated infection	Monomicrobial osteomyelitis caused by XDR *A. baumannii*	Yes (colistin, CAZ/AVI) Cefiderocol: 6 weeks	Cure	No recurrent infection	Polytrauma occurred to the patient prior to infection, colistin-associated AKI occurred
[80]	Male, 62 years Haemothorax and rib fractures	Polymicrobial HAP caused by XDR *A. baumannii* (plus *K. pneumoniae*), and subsequent osteomyelitis, UTI caused by XDR *A. baumannii*	Yes (colistin) Cefiderocol: 8 weeks	Cure	Eradication	Thoracic trauma Two courses of cefiderocol were administered due to recurrent XDR *A. baumannii*
[81]	Male, 60 years Hypertension and haemorrhagic tamponade	VAP caused by CAZ-resistant *K. pneumoniae*; secondary bacteraemia caused by PDR *A. baumannii*	No Cefiderocol: 2 weeks	Favourable response	Favourable response	Death due to non-infectious cause 30 days following discharge

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Table 3 (*continued*)

Reference	No. of patients, age/underlying conditions	Infection type(s)	Combination therapy and duration of treatment	Clinical outcome	Microbiological outcome	Note
[81]	Female, 70 years DM, septic shock, pyelonephritis	Polymicrobial BSI caused by XDR *A. baumannii* (plus XDR *P. aeruginosa*)	No Cefiderocol: 2 weeks	Failure	Eradication for XDR *A. baumannii*, persistence for *P. aeruginosa*	Death due to disseminated HSV-1 infection on Day 14
[81]	Female, 55 years Severe scoliosis	Monomicrobial spondylodiscitis caused by XDR *A. baumannii*	No Cefiderocol: 3 weeks	Clinical improvement and no relapse	Eradication	Minocycline oral treatment was given for 6 weeks
[93]	3 male patients (56, 71 and 45 years) (i) lung transplant, (ii) COVID-19 and (iii) pneumonia, hypertension All patients received CVVHDF	(i) Monomicrobial sepsis caused by DTR-AB VAP, (ii) polymicrobial BSI caused by DTR-AB, *Enterococcus faecalis, E. faecium,* monomicrobial VAP due to DTR-AB and (iii) polymicrobial VAP due to DTR-AB and MRSA, and monomicrobial BSI due to DTR-AB	(i) No, (ii) yes (fosfomycin) and (iii) yes (colistin and linezolid) Cefiderocol: 7 days	(i) Clinical improvement, (ii) cure and (iii) cure	Microbiological eradication in all cases	No patients died by Day 30 Patient (iii) developed significant maculopapular rash, which resolved followed antibiotic discontinuation. Cefiderocol was administered at 2g q8h, and TDM showed high plasma concentrations ($>100\%fT_{>MIC}$ for DTR-AB) in two patients
[83]	1 patient, 37 years 1 patient, 54 years Not provided	(i) Monomicrobial catheter-related BSI caused by XDR *A. baumannii* and (ii) monomicrobial RTI + IAI + catheter-related BSI caused by XDR *A. baumannii*	(i) No and (ii) yes (plus colistin, tigecycline) Duration not clearly specified	(i) Cure and (ii) cure	N/R	Both cases were caused by XDR *A. baumannii*
[78]	Adult male Acute influenza and ventilator-associated bilateral pneumonia, BSI, ECMO	Polymicrobial BSI, VAP caused by XDR *A. baumannii* (plus KPC-*K. pneumoniae*)	No Cefiderocol: 2 weeks	Complete resolution, discharge	N/R	Prior treatment failure and colistin-associated acute kidney failure
[79]	Male, 57 years Tibia and fibula fractures, surgical debridements	Polymicrobial osteomyelitis caused by XDR *A. baumannii* (plus *E. faecalis, Corynebacterium striatum*)	No Cefiderocol: 109 days	Cure	Eradication	Prior treatment failure and side effects on polymyxin B, vancomycin, minocycline and daptomycin therapy
[85]	Female, 81 years Asthma, hypertension, osteoporosis	Polymicrobial hardware-associated wound infection caused by XDR *A. baumannii* (plus pan-sensitive *P. aeruginosa*)	Yes (oral ciprofloxacin for *P. aeruginosa*) Cefiderocol: 32 days	Clinical improvement, cure, wound healing complete	N/R	Acute interstitial nephritis and peripheral eosinophilia as adverse events emerged, resolved after discontinuation of treatment after 32 days
[86]	Female, 66 years Fracture, hypertension, hypothyroidism	Monomicrobial prosthetic joint infection caused by CRAB	Yes (tigecycline) Cefiderocol: 25 days	Clinical cure, wound healing	N/R	No toxicity was reported
[87]	Female, 55 years Metabolic syndrome, obesity, acute COVID-19 infection, ARDS, pneumothorax	Polymicrobial VAP and septic shock caused by XDR *A. baumannii* (plus pan-sensitive *P. aeruginosa*)	Yes (sulbactam/durlobactam) Cefiderocol: 14 days	Clinical cure, fever resolved	N/R	Hospitalised with COVID-19 pneumonia and developed XDR *A. baumannii* superinfection under mechanical ventilation

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Table 3 (*continued*)

Reference	No. of patients, age/underlying conditions	Infection type(s)	Combination therapy and duration of treatment	Clinical outcome	Microbiological outcome	Note
[89]	Male, 50 years Paraplegia, wound, right hip dislocation, UTI, decubitus ulcer	Polymicrobial osteomyelitis caused by MDR *A. baumannii* (plus *Proteus mirabilis, P. aeruginosa*)	Yes (daptomycin) Cefiderocol: 109 days	Clinical improvement	N/R	Repeated debridement was performed *Candida albicans* superinfection in the wound
[90]	Female, 61 years Epilepsy, schizophrenia, tracheostomy, hypertension	Monomicrobial meningitis caused by CRAB	Yes (intraventricular gentamicin) Cefiderocol: 21 days	Cure	Eradication	CSF concentration measurement indicated penetration into the CSF
[92]	Male, 65 years Hypertension, COPD, aortic aneurysm repair	Polymicrobial pneumonia caused by XDR *A. baumannii* (plus pan-susceptible *Escherichia coli*)	Yes (minocycline, and tigecycline + AMP/SUL) Cefiderocol: 8 days in first course	Eradication and re-infection	N/R	XDR *A. baumannii*, PK-driven analysis, CVVHDF was received Synergistic effects between cefiderocol, sulbactam and tigecycline
[102]	11 patients (6 male, 5 female), 18–67 years	Burn patients with VAP, BSI or ventilator-associated tracheobronchitis caused by CRAB	Yes (2 patients received polymyxin B)	Clinical improvement in 64% of patients and success in 36% of patients	Microbiological failure in 7 patients	Outbreak due to on-therapy resistance Relapse or respiratory colonisation within 90 days occurred in 7 patients 3 patients died
[94]	28 patients (22 male, 6 female), 25–83 years Myocardial infarction, COPD, DM, CKD	13 patients with MDR *A. baumannii* (plus *P. aeruginosa* 9, *Stenotrophomonas maltophilia* 7, Enterobacterales 14), overall RTI 38%, UTI 22%, IAI 20%, BSI 24.4%, SSI 15.5%, infection in >1 sites 42%	Yes, 6 patients (colistin 2, amikacin 2, CAZ/AVI 2, tigecycline 1, fosfomycin 1) Cefiderocol: 10 days	Overall clinical success 64.3% at Day 7, 50% at Day 14 Clinical improvement in 6/13 patients with *A. baumannii* infections	Overall 77.8% (14/18) among patients with follow-up samples, and 87.5% (7/8) among patients with follow-up samples among *A. baumannii* infections	3 patients had COVID-19 9 patients had Gram-positive or fungal co-infection Median duration of cefiderocol treatment was 10 (range 1–32) days 11 patients (39.3%) died
[95]	24 patients (17 male, 7 female), 32–92 years	14 MDR *A. baumannii* (plus *P. aeruginosa* 3, *K. pneumoniae* 1, *S. maltophilia* + *K. pneumoniae* 1), pneumonia 10, BSI + pneumonia 2, BSI + wound 1, UTI 1	Yes, 6 *A. baumannii* patients (colistin 1, tigecycline 4, minocycline 1) Cefiderocol: 4.9–17.6 days	Clinical success in 5 patients (35.7%) among *A. baumannii* infections	7 patients had recurrence	Patients were treated with cefiderocol due to documented resistance of *A. baumannii*, or treatment failure, or history of CR infection Mortality 6 patients (42.9%) among MDR *A. baumannii* infections
[96]	1 patient, 44 years No co-morbidities reported	VAP caused by XDR/DTR *A. baumannii*, ESBL-NDM *K. pneumoniae* and *Candida auris*	Yes (nebulised colistin, nebulised tobramycin), Cefiderocol: 25 days	Clinical cure	Microbiological cure No recurrence	Haemodialysis, ECMO support was given No adverse event during treatment Survival at Day 30 and died by Day 90
[97]	Male, 76 years	VAP + BSI due to MDR *A. baumannii*	Yes (tigecycline + colistin). Cefiderocol duration: not clearly specified	Clinical failure	Microbiological failure	CVVH, COVID-19 pneumonia, ARDS Death on Day 15

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Table 3 (*continued*)

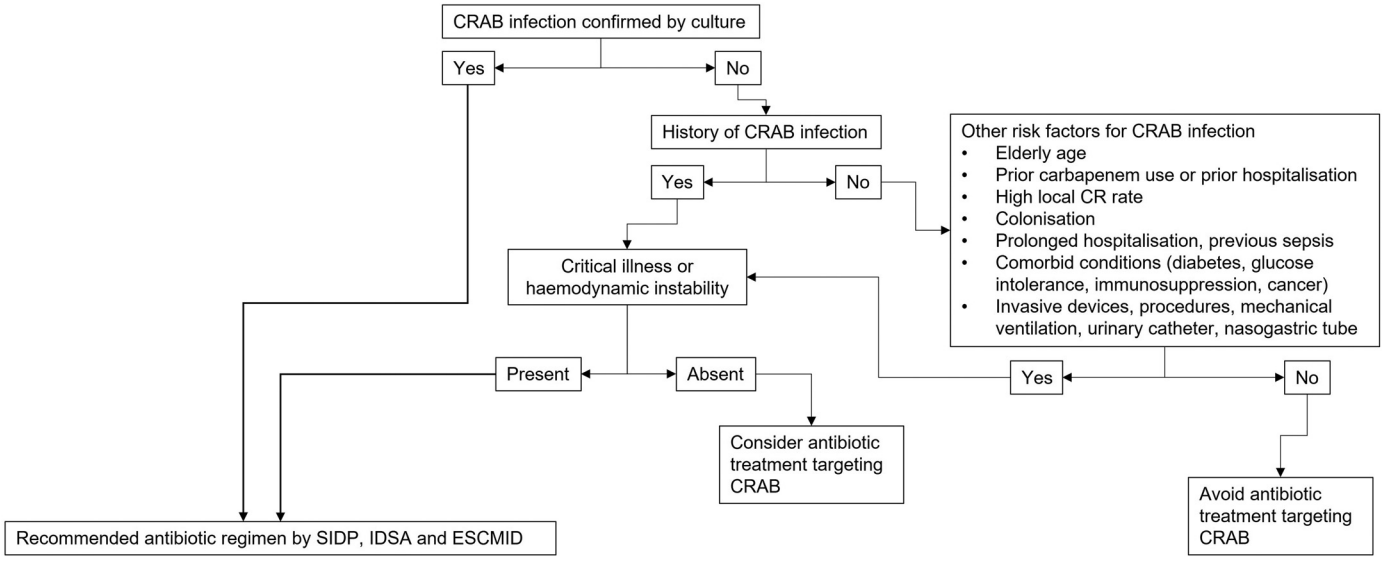
Reference	No. of patients, age/underlying conditions	Infection type(s)	Combination therapy and duration of treatment	Clinical outcome	Microbiological outcome	Note
[98]	18 patients (15 male, 3 female), median age 57 years Multiple co-morbidities (DM, smoking, malignancy, obesity, cardiovascular disease)	15 patients with CRAB (VAP, BSI or Fournier gangrene)	Yes, 14 patients [colistin-sparing agents 8, colistin 6 (aerosolised colistin 4)] Cefiderocol: median 9.5 days	Overall clinical cure 66.7% (12/18)	Overall microbiological failure 22.2% (4/18)	Nearly all patients in the ICU, 6 patients received haemodialysis, 3 patients received ECMO support Mortality at Day 30: 27.8% (monotherapy 25%, combination therapy 28.6%)
[99]	Female, 49 years Smoker, drug abuser, HIV infection	VAP + BSI caused by MDR/CR *A. baumannii*	Yes (colistin) Cefiderocol: 3 weeks	Clinical success	Microbiological eradication	HIV-positive without antiretroviral treatment COVID-19 pneumonia – unvaccinated at the time of hospitalisation
[100]	41 patients (20 male, 21 female), median age 70 years Median CCI, 5	31 patients with CRAB (HAP, cIAI, cUTI, SSTI, CNS infection, osteomyelitis, secondary bacteraemia)	Yes, 6 patients with CRAB (fosfomycin or colistin); monotherapy for 80.6% of patients Cefiderocol median duration: 9 (IQR 7–21) days	Among patients with CRAB, clinical response within 72 h: 90.4%; clinical cure at EOT: 64.5%	Among patients with CRAB, microbiological eradication at EOT: 80.6%	30-day mortality was 35.5% among patients with CRAB Resistance on therapy was not reported

AKI, acute kidney injury; AMP/SUL, ampicillin/sulbactam; ARDS, acute respiratory distress syndrome; BSI, bloodstream infection; CAZ/AVI, ceftazidime/avibactam; CCI, Charlson comorbidity index; cIAI, complicated intra-abdominal infection; CKD, chronic kidney disease; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CR, carbapenem-resistant; CSF, cerebrospinal fluid; CVVH, continuous venovenous haemofiltration; CVVHDF, continuous venovenous haemodiafiltration; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; EOT end of therapy; ESBL, extended-spectrum β-lactamase; $fC_{min>MIC}$, fraction of time that the minimum concentration of the free drug was above the MIC; $\%fT_{>MIC}$, percentage of the dosing interval during which the free cefiderocol concentration remains above the MIC; HAP, hospital-acquired pneumonia; HSV-1, herpes simplex virus type 1; HIV, human immunodeficiency virus; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; N/R, not reported; PD, pharmacodynamic; PDR, pandrug-resistant; PK, pharmacokinetic; q8h, every 8 h; RTI, respiratory tract infection; SSI, surgical site infection; SSTI, skin and soft-tissue infection; TDM, therapeutic drug monitoring; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

cline, tigecycline or polymyxin B, or cefiderocol depending on in vitro activity [10,103]. Cefiderocol use is suggested for infections in which other antibiotics resulted in treatment failure and only in combination with other antibiotics that are active in vitro [103]. The SIDP recommend a combination of meropenem, polymyxin B and ampicillin/sulbactam for the treatment of CRAB pneumonia, with either meropenem plus minocycline or combination treatment with cefiderocol as alternative options [10]. Currently, there is no evidence on the efficacy of cefiderocol in combination therapy from randomised, prospective trials; however, future clinical studies are needed, which include other agents that demonstrated synergism with cefiderocol, such as sulbactam or avibactam, as part of cefiderocol combination therapy to address this point.

Local susceptibility testing for antibiotics is recommended prior to selecting combination therapy for at-risk patients with CRAB infections. In the SENTRY surveillance programme, contemporary susceptibility rates to ampicillin/sulbactam, minocycline, amikacin and ciprofloxacin for CRAB range between 2% and 56% in North America and between 0% and 32% Europe (Supplementary Tables S1 and S2), suggesting that the use of many conventional antibiotics may fail to provide benefit in approximately one-half of cases. The SENTRY surveillance data also showed that cefiderocol has potent in vitro activity against >90% of carbapenem-resistant, colistin-resistant and ampicillin/sulbactam-resistant *A. baumannii* isolates (Supplementary Table S3). In one study, the cefiderocol MIC_{90} was 0.5 μg/mL both for colistin-resistant and colistin-susceptible *A. baumannii* isolates [113]. Since prospective clinical studies of specific cefiderocol combination treatments are needed, selection of cefiderocol as part of combination therapy for moderate-to-severe infections seems reasonable based on in vitro potency and the enhanced in vivo bactericidal activity observed both with cefiderocol-susceptible and -non-susceptible *A. baumannii*. The added benefit has been demonstrated in the translational murine model infected with CRAB and exposed to humanised plasma profiles in combination with ampicillin/sulbactam, ceftazidime/avibactam or meropenem [54,55,112]. Thus, future prospective clinical studies may build on the results of these investigations to employ combination of cefiderocol with agents showing synergism in animal models, such as ampicillin/sulbactam or ceftazidime/avibactam, or other agents showing high susceptibility rates, such as sulbactam/durlobactam [112]. Clinical data on combination therapy are limited to retrospective observational studies, however some combinations show promising results in terms of clinical cure and/or mortality (e.g. cefiderocol plus fosfomycin) [76].

Finally, the clinical efficacy data for cefiderocol, not just from phase 3 clinical trials but also from published data of 318 patients treated in the real-world setting to date, provides valuable information suggesting both efficacy and safety benefits for seriously ill patients with XDR *A. baumannii*, DTR *A. baumannii* and CRAB infections.



Site of infection	SIDP [10]	IDSA [103]	ESCMID [104]
HAP, VAP	Preferred: MEM + PMXB ± AMP/SUL Alternative: MEM + MINO or CFDC in combination *Consider inhaled colistin on a case by case basis* *Avoid monotherapy with any agent*	For *mild* infections (e.g., cUTI, SSSI): Preferred: AMP/SUL Alternative: MINO or TIG or PMXB/COL or CFDC	For *mild* infections: High-dose AMP/SUL (if active *in vitro*) PMX or high-dose TIG (if AMP/SUL not active *in vitro*)
BSI	Preferred: MEM + PMXB ± AMP/SUL Alternative: MEM + MINO ± AMP/SUL or CFDC in combination *Avoid TIG, ERAV*	For *moderate or severe infections* (e.g., pneumonia, bloodstream infections, intra-abdominal infections):	For *severe and high-risk* infections:
cUTI	AG or COL or CFDC *Avoid TIG, ERAV*	Combination of high-dose AMP/SUL plus MINO or TIG or PMXB or extended-infusion meropenem or CFDC	Combination of 2 *in vitro* active antibiotics: PMX, AG, TIG, AMP/SUL High-dose meropenem to be used for CRAB with meropenem MIC ≤8 µg/mL
cIAI	TIG ± MEM or ERAV ± MEM *Avoid AG*		
CNS	MEM + PMXB + AMP/SUL MEM + TIG + AMP/SUL *Avoid AG*	*Avoid combination of meropenem + colistin or rifampicin + colistin* *Inhaled or nebulized antibiotics are not recommended*	*Avoid combination of meropenem + colistin or rifampicin + colistin*

Figure 1. Treatment algorithm for carbapenem-resistant *Acinetobacter baumannii* (CRAB) based on culture and susceptibility, risk factors, and comparison of antibiotic recommendations by US and European professional societies [10,103,104]. AG, aminoglycoside; AMP/SUL, ampicillin/sulbactam; BSI, bloodstream infection; CFDC, cefiderocol; cIAI, complicated intra-abdominal infection; CNS, central nervous system; COL, colistin; CR, carbapenem resistance; cUTI, complicated urinary tract infection; ERAV, eravacycline; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HAP, hospital-acquired pneumonia; IDSA, Infectious Diseases Society of America; MEM, meropenem; MIC, minimum inhibitory concentration; MINO, minocycline; PMX, polymyxin; PMXB, polymyxin B; SIDP, Society of Infectious Diseases Pharmacists; SSSI, skin and skin-structure infection; TIG, tigecycline; VAP, ventilator-associated pneumonia.

6. Conclusions

Cefiderocol represents an important treatment option for CRAB infections in critically ill patients. Notable for its stability against hydrolysis by ESBLs, class A and D carbapenemases, class C cephalosporinases and class B metallo-β-lactamases, cefiderocol demonstrates potent in vitro activity against CRAB isolates from a variety of infection sources, with susceptibility rates of >90%. It has a well-defined PK/PD profile, with effective tissue penetration in healthy subjects and in patients with infections, and has shown a target attainment for 100%$fT_{>MIC}$ of >90% across infection sites and renal function groups for pathogens with cefiderocol MICs of ≤4 µg/mL. Cefiderocol monotherapy has established efficacy in CRAB infections, as shown in randomised clinical trials and real-world investigations. Furthermore, its safety profile, which is similar to that of other β-lactam antibiotics, is commensurate with its use for the treatment of critically ill patients. Cefiderocol shows enhanced killing in vitro with some guideline-recommended antibiotics (e.g. tigecycline, meropenem) and also in in vivo studies incorporating exposures achievable in humans using the currently approved dosing regimen for ampicillin/sulbactam and ceftazidime/avibactam. While in vivo enhancements in bactericidal activity and resistance suppression have been demonstrated both for cefiderocol-susceptible and -non-susceptible *A. baumannii* using the translational murine thigh model with meropenem or certain β-lactam/β-lactamase inhibitors (e.g. clinically achievable plasma profiles of cefiderocol in combination with ampicillin/sulbactam, ceftazidime/avibactam), these antibiotics are not usually active in vitro. Clinical studies are needed to corroborate the potential of such combination therapy in the future, potentially expanding the investigations with currently approved or investigational agents with a more favourable safety profile. Finally, since on-therapy resistance has been reported in only a few cases, continuous monitoring of emerging resistance should be considered as part of routine clinical practice and antibiotic stewardship to prevent outbreaks and to preserve its potent in vitro activity.

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Supplementary materials

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