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REVIEW

Evaluating Cefiderocol in the Treatment of Multidrug-Resistant Gram-Negative Bacilli: A Review of the Emerging Data

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Abstract: Infections due to multidrug-resistant Gram-negative bacteria (MDR-GNB), especially when carbapenem resistant, have been very difficult to manage in the last fifteen years, owing to the paucity of dependable therapeutic options. Cefiderocol is a siderophore cephalosporin recently approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) that may have the potential to fill some of the remaining gaps in the treatment of MDR-GNB infections. Among others, cefiderocol demonstrated in vitro activity against carbapenem-resistant *Acinetobacter baumannii* and metallo-β-lactamases producers. Clinical data from both registrative studies and post-marketing experiences are essential to confirm whether these promises from in vitro studies could readily translate into clinical practice, as well as to delineate the precise place in therapy for cefiderocol for the treatment of MDR-GNB in the near future. Because of its unique potential, it is essential to provide both randomized controlled trials (RCT) and real-life data to improve the ability of clinicians to exploit its benefit in both empirical and targeted treatment of MDR-GNB infections. In this narrative review, we discuss the emerging data from pivotal RCT and initial real-life experiences on the use of cefiderocol for the treatment of MDR-GNB infections.

Keywords: cefiderocol, siderophore, *Pseudomonas*, *Acinetobacter*, *Enterobacterales*, antimicrobial resistance

Introduction

Infections due to multidrug-resistant Gram-negative bacteria (MDR-GNB), especially when carbapenem resistant, have been very difficult to manage in the past fifteen years, owing to the paucity of therapeutic options.[1–5] Furthermore, available options such as polymyxins, aminoglycosides, and/or glycylcyclines, although certainly useful in presence or resistance to all other classes, have some disadvantages that clinicians would like to avoid, including nonnegligible toxicity and possible suboptimal pharmacokinetics in some sites of infection.[6–8]

Some precious additions to the antibiotic armamentarium such as ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam, and imipenem/relebactam have recently allowed to renew the availability of β-lactam antibiotics (that usually display good safety profiles and pharmacokinetics) for treating some MDR-GNB.[9–12] However, some gaps still need to be filled, for example, restoring the activity of β-lactams against metallo-β-lactamases (MBL)-producing GNB and carbapenem-resistant *Acinetobacter baumannii*.

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In this narrative review, we discuss the available antimicrobial, pharmacological, and clinical data for cefiderocol, a siderophore cephalosporin recently approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) that may have the potential to fill some of the remaining gaps in the treatment of MDR-GNB infections.

Methods

The structure of the present narrative review was agreed by all authors and articulated in the following sections: (i) antimicrobial properties; (ii) pharmacological properties; (iii) results of randomized clinical trials: efficacy; (iv) safety of cefiderocol; (v) case reports and case series; (vi) place in therapy. Then, the authors were divided in small groups in order to draft the different sections, supported by inductive PubMed searches for relevant publications. Eventually, the different drafts were merged into a final manuscript that was approved by all authors.

Antimicrobial Properties

Cefiderocol is a novel siderophore cephalosporin active against GNB, including strains of *Enterobacterales* and nonfermenters that exhibit difficult-to-treat (DTR) resistance phenotypes (ie, resistant to fluoroquinolones and older β-lactams including carbapenems).[13,14] This notable and thus far unique spectrum of activity is dependent on the following features: i) uptake across the bacterial outer membrane also via iron transporters, thus enhancing accumulation of the drug in the periplasmic space and overriding resistance mechanisms such as efflux pumps and porin alterations; and ii) remarkable stability, likely conferred by modifications in the C-7 and C-3 side chains, against all classes of beta-lactamases, including carbapenemases (both serine carbapenemases, such as KPC and OXA-types, and metalloenzymes such as NDM, VIM, IMP and the intrinsic L1 carbapenemase of *Stenotrophomonas maltophilia*).[15–18]

Similar to cefepime, cefiderocol carries a pyrrolidinium group on the C3 side chain, which enhances stability to β-lactamases and antimicrobial activity. Moreover, similar to ceftazidime, cefiderocol carries an aminothiazole ring and a carboxypropyl-oxyimino group on the C7 side chain, which also enhances stability to β-lactamases and activity against Gram-negative bacilli, including *Pseudomonas aeruginosa*. In addition, cefiderocol harbors a chlorocatechol group at the end of the C3 side chain, which is able to chelate ferric iron and confers siderophore activity: the complex cefiderocol-Fe^{3+} can thus be actively transported into the periplasmic space by specific iron-transporters, such as PiuA in *P. aeruginosa*, unlike other beta-lactams which only enter by passive diffusion across porin channels.[14,18] Indeed, resistance acquisition studies revealed that mutations causing increased levels of pyoverdine production or higher level of FecA expression (both involved in the iron transport system) were associated with increased cefiderocol minimum inhibitory concentration (MIC) values in *P. aeruginosa*.[19] Once in the periplasmic space, cefiderocol exerts its antimicrobial activity by inhibition of the penicillin-binding proteins (PBP)-mediated cell wall synthesis, leading to cell death.[14,18] Cefiderocol was shown to have high affinity for PBP3 in clinically relevant Gram-negative rods (eg, *Klebsiella pneumoniae, Escherichia coli, P. aeruginosa*, and *Acinetobacter baumannii*), and also for PBP2 in *K. pneumoniae* and for PBP1a in *P. aeruginosa*.[20,21]

Similar to cefepime, cefiderocol is a weak AmpC inducer (possibly due to low PBP4 binding) with low affinity for chromosomal AmpC-type β-lactamases,[22] which account for its overall good activity also against AmpC overproducing strains. Mutations causing alteration or loss of porin channels, such as OmpK35 and OmpK36 in *K. pneumoniae*, are associated with a marginal decrease of cefiderocol antimicrobial activity,[18] while inactivation of the MexAB-OprM efflux pump only causes a slight cefiderocol MIC decrease in *P. aeruginosa*, suggesting that this mechanism is unable to efficiently expel the molecule outside the microbial cell.[20]

During infections, an iron depleted-milieu is expected to be encountered in the host tissues in response to which the bacterial iron transporters are up-regulated.[23] This should be accounted for when testing in vitro susceptibility to cefiderocol, which must be carried out using iron-depleted media when using reference broth microdilution. The growth medium is prepared by treating conventional cation-adjusted Mueller-Hinton broth with a cation-binding resin in order to remove all the cations, and subsequently replenishing the cation-depleted broth with adequate concentrations of Mg^{2+}, Zn^{2+} and Ca^{2+}.[24–26]

For cefiderocol, the Clinical and Laboratory Standards Institute (CLSI) has set clinical breakpoints (CB) for *Enterobacterales, P. aeruginosa, S. maltophilia,* and *A. baumannii*, with MIC values of ≤4, 8, and ≥16 mg/L for susceptible, intermediate, and resistant categories, respectively.[24] However, these breakpoints were not accepted by FDA for *A. baumannii* and *S. maltophilia*,

since these two species were not included in the Apeks-UTI clinical trial that was designed for the approval of the drug in the USA.[27] In Europe, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has set cefiderocol CB with MIC values of ≤2 mg/L and >2 mg/L for susceptible and resistant categories, respectively, for both *Enterobacterales* and *Pseudomonas* spp., and also apharmacokinetic/pharmacodynamic (PK/PD) breakpoint MIC value of ≤2 mg/L for susceptibility, while CB was not set for *A. baumannii* and *S. maltophilia* due to insufficient clinical evidence.[25] Epidemiological cut-off (ECOFF) values were also defined by the EUCAST as follows: 0.25 mg/L for *E. coli, K. pneumoniae,* and *A. baumannii*; 0.5 mg/L for *P. aeruginosa*, and 0.06 mg/L for *S. maltophilia*.[25]

Cefiderocol susceptibility has been investigated in large international surveillance studies carried out since 2014 (SIDERO-WT studies), covering over 28,000 Gram-negative isolates.[13] Overall, the MIC_{90} for *Enterobacterales* (including *E. coli, Klebsiella* spp., *Citrobacter* spp., *Enterobacter* spp., *Serratia* spp., *Morganella morganii,* and *Proteus* spp.) ranged from 0.25 to 1 mg/L, with no significant geographical or temporal differences. Cumulative activity against *Enterobacterales* from surveillance studies revealed that >98% and >99% of isolates were inhibited at concentrations of 2 mg/L and 4 mg/L, respectively. Activity was retained against most isolates resistant to expanded-spectrum cephalosporins and carbapenems, including those producing different types of serine carbapenemases and metallo-β-lactamases. The MIC_{90} of *Enterobacterales* was 2–16 mg/L for strains producing different types of carbapenemases (Table 1). Against 1022 carbapenem-nonsusceptible *Enterobacterales*, of which 23% ceftazidime/avibactam resistant and 22% colistin resistant, cefiderocol MIC_{90} was 4 mg/L and 97% of the isolates were inhibited at a concentration of 4 mg/L.[28]

Data for Gram-negative nonfermenters from the international surveillance studies (see Table 1) reported MIC_{90} values of 0.5–2 mg/L for *P. aeruginosa*, 1–2 mg/L for *Acinetobacter* spp., 0.25–0.5 mg/L for *S. maltophilia*, and 0.12–0.5 mg/L for *Burkholderia cepacia* complex, underscoring the remarkable activity of cefiderocol against these difficult-to-treat pathogens. Cumulative activity data revealed that >99%, >95%, and >95% of isolates of *P. aeruginosa, A. baumannii,* and *B. cepacia* complex from surveillance studies, respectively, were inhibited at a concentration of 4 mg/L, while >99% of isolates of *S. maltophilia* were inhibited at a concentration of 2 mg/L. Activity was retained against most *P. aeruginosa* isolates resistant to carbapenems (>98% inhibited at 2 mg/L), including those resistant to ceftolozane/tazobactam and producing metalloenzymes. A notable activity was also retained against carbapenem-resistant *A. baumannii*, with an MIC_{90} of 1 mg/L for isolates producing OXA-type carbapenemases (Table 1).

Few isolates with elevated cefiderocol MIC values (≥8 mg/L) were detected from large surveillance studies. Some of these isolates were NDM-1 metallo-β-lactamase or PER-1 extended-spectrum β-lactamase producers; in such cases, the addition of enzyme inhibitors (eg, dipicolinic acid and/or avibactam) was capable of reducing cefiderocol MIC values, suggesting that production of these β-lactamases may contribute to increased cefiderocol MICs. However, cefiderocol exhibited good activity against several isolates producing these enzymes,[29] suggesting that the presence of additional resistance mechanisms is likely necessary to increase MIC values above the susceptibility breakpoint.

Concerning other pathogens, cefiderocol was shown to be active in vitro against *Vibrio* spp. *Haemophilus influenzae, Moraxella catarrhalis,* and *Bordetella parapertussis*,[20] and also against less common Gram-negative pathogens including *Pantoea* spp., *Sphingomonas paucimobilis*, and *Elizabethkingia meningoseptica*.[30] On the other hand, activity is variable against anaerobes, likely due to the variable importance of the siderophore-iron transport systems for growth under anaerobic conditions.[20]

In conclusion, cefiderocol is a new antibiotic with a unique mechanism of cell entry in Gram-negative pathogens, while being stable to most beta-lactamases. It is a potentially useful drug for treating infections caused by carbapenemase-producing *Enterobacterales* and non-fermenters. As such, cefiderocol appears to be one of the most innovative antibiotics among those recently approved.

Pharmacological Properties

Pharmacokinetic Properties

The pharmacokinetic profile of cefiderocol was studied in healthy subjects both after single-ascending dose (100 to 1000 mg) and multiple-ascending dose (1000 mg q8h and 2000 mg q8h).[31] Overall, cefiderocol showed a linear pharmacokinetic behavior with ascending doses and a mean elimination half-life of 2.0–2.7h. The mean total clearance was of 4.6–6.0 L/h and the fraction excreted unchanged

Table 1 Susceptibility to Cefiderocol of Gram-Negative Isolates from Selected Surveillance Studies

Order/Genus/Species[a]	(No. Isolates)	Source[b] (Years)	MIC (mg/L)		% Inhibited at 4 mg/L[c]	% Inhibited at 2 mg/L[d]	References
			Range	MIC_{90}			
Enterobacterales	3007	NAm (2014–15)	≤0.002–8	0.5	NR[e]	NR	[73]
Enterobacterales	3080	EU (2014–15)	≤0.002–8	1	NR	NR	[73]
Enterobacterales	2470	NAm (2015)	≤0.002–128	0.5	NR	NR	[74]
Enterobacterales	3543	EU (2015)	≤0.002–8	1	NR	NR	[74]
Enterobacterales	20,949	Cumulative (2014–16)	≤0.002–>256	NR	99.4	98.6	[71]
P. aeruginosa	1530	NAm/EU (2014–15)	≤0.002–8	0.5	NR	NR	[73]
P. aeruginosa	1540	NAm/EU (2015)	≤0.002–8	0.5	NR	NR	[74]
P. aeruginosa	4942	Cumulative (2014–16)	≤0.002–8	2	99.9	NR	[71]
A. baumannii	1148	NAm/EU (2014–15)	≤0.002–64	1	NR	NR	[73]
Acinetobacter spp.	308	NAm (2015)	≤0.002–>256	1	NR	NR	[74]
Acinetobacter spp.	664	EU (2015)	≤0.002–>256	2	NR	NR	[74]
A. baumannii	2896	Cumulative (2014–16)	≤0.002–256	2	95.6	NR	[71]
S. maltophilia	152	NAm (2014–15)	≤0.002–4	0.5	100	NR	[73]
S. maltophilia	276	EU (2014–15)	0.004–2	0.25	100	100	[73]
S. maltophilia	165	NAm (2015)	0.004–64	0.5	NR	NR	[74]
S. maltophilia	175	EU (2015)	≤0.002–64	0.25	NR	NR	[74]
S. maltophilia	217	Global (2014–16)	0.004–2	0.25	100	100	[28]
S. maltophilia	1173	Cumulative (2014–16)	≤0.002–64	0.25	99.8	99.6	[71]
B. cepacia complex	40	NAm (2015)	≤0.002–32	0.5	NR	NR	[74]
B. cepacia complex	49	EU (2015)	≤0.002–32	0.12	NR	NR	[74]
B. cepacia complex	164	Cumulative (2014–16)	≤0.002–64	0.25	95.7	NR	[71]
Enterobacterales Carba-NS	1020	Global (2014–16)	0.004–32	4	NR	NR	[28]
Enterobacterales KPC+	75	NAm/EU (2014–15)	0.03–4	2	NR	NR	[75]
Enterobacterales KPC-2^+	355	NR	≤0.03–32	8	NR	NR	[76]
Enterobacterales KPC-3^+	380	NR	≤0.03–64	2	NR	NR	[76]
Enterobacterales OXA-48^+	154	Global (2000–16)	0.03–64	2	NR	NR	[77]
Enterobacterales MBL (VIM, NDM, IMP)$^+$	69	Global (2000–11)	≤0.12–>16	16	89.8	86.9	[78]
Enterobacterales MBL (VIM, NDM, IMP)$^+$	134	Global (2000–16)	0.03–64	4	NR	NR	[77]
Enterobacterales ESCR	2547	Cumulative (2014–16)	NR	NR	99.1	91.3	[71]
P. aeruginosa Carba-NS and CTZ-NS	1005	Global (2014–16)	0.004–32	4	NR	NR	[28]
P. aeruginosa Carba-NS	1154	Cumulative (2014–16)	NR	NR	99.9	98.5	[71]
P. aeruginosa Carba-NS MBL$^+$	30	NAm/EU (2014–15)	0.008–2	2	NR	NR	[75]
A. baumannii Carba-NS OXA-23/24/58$^+$	681	NAm/EU (2014–15)	≤0.002–64	1	NR	NR	[75]
A. baumannii Carba-NS	1891	Cumulative (2014–16)	NR	NR	94.8	91.8	[71]

Notes: [a]Carba-NS, carbapenem nonsusceptible; CTZ-NS, ceftolozane-tazobactam nonsusceptible; ESCR, resistant to expanded-spectrum cephalosporins (cefepime MIC >4 mg/L). [b]NAm, North America; EU, Europe. [c]CLSI susceptibility breakpoint for *Enterobacterales*, *P. aeruginosa*, *Acinetobacter* spp., and *S. maltophilia*. [d]EUCAST susceptibility breakpoint for *Enterobacterales* and *P. aeruginosa*. [e]NR, not reported.

into urine was of 60–70%. The pharmacokinetic characteristics of cefiderocol at the dose of 2000 mg q8h over 1 h in healthy subjects are summarized in Table 2.[31]

The pharmacokinetics of cefiderocol was compared in healthy subjects with those in subjects with mild [estimated glomerular filtration rate (eGFR) 60-<90 mL/min/

Table 2 Dosage Regimens of Cefiderocol Focused at Achieving 90% of PTAs of 75% T>MIC Against Pathogens with an MIC Up to 4 mg/L in Patients with Different Classes of Renal Function[44]

CLCr	Dosage Regimen
≥ 120 mL/min° (ARC)	2g q6h over 3h
≥ 90 mL/min/1.73 m^{2*}	2g q8h over 3h
60-<90 mL/min/1.73 m^{2*}	2g q8h over 3h
30-<60 mL/min/1.73 m^{2*}	1.5 g q8h over 3h
15 to 30 mL/min/1.73 m^{2*}	1 g q8h over 3h
< 15 mL/min/1.73 m^{2*}	0.75 g q12h over 3h
IHD**	0.75 g q12h over 3h

Notes: °Estimated by means of the Cockcroft and Gault formula. *Estimated by means of the modified diet renal diseases (MDRD) formula. **A supplemental dose of 0.75g over 3h should be administered after completion of IHD on the dialysis day.
Abbreviations: ARC, augmented renal clearance; CLCr, creatinine clearance; IHD, intermittent hemodialysis.

1.73 m^2], moderate (eGFR 30-<60 mL/min/1.73 m^2) and severe impairment of renal function (eGFR <30 mL/min/1.73 m^2) after a single dose of 1000 mg.[32] Overall, total drug clearance and elimination half-life were inversely and linearly related with renal dysfunction. The mean ratio of drug exposure, in terms of area under the concentration–time curve from zero-to-infinity ($AUC_{0-\infty}$), in subjects with mild, moderate, and severe renal impairment compared with those with normal renal function was 1.0, 1.5, and 2.5. The volume of distribution (Vd) and the fraction unbound (fu) to the plasma proteins were very similar between groups (mean Vd ranged from 13.5 to 16.4 L; mean fu ranged from 0.42 to 0.35).[32]

The potential for drug–drug interaction of cefiderocol with different human drug transporters [organic anion transporter (OAT) 1 and 3, organic cation transporter (OCT) 1 and 2, multidrug and toxin extrusion (MATE) 2-K and organic anion transporting polypeptide (OATP) 1B3] was assessed in three cohorts of healthy subjects.[33] Substrates of these transporters were administered concomitantly to cefiderocol for assessing whether cefiderocol might or not inhibit drug transport. Overall, the study did not show any clinically significant drug–drug interaction of cefiderocol via drug transporters.[33]

The intrapulmonary pharmacokinetics of cefiderocol was assessed in healthy adult subjects after administration of a single 2000 mg dose infused over 1 h.[34] The mean epithelial lining fluid (ELF)-to-plasma ratio was of 0.101 and 0.239 based on total drug in plasma and on free drug in plasma, respectively, similar to other cephalosporins.[34]

A recent study assessed the concentration-time profile of total radioactivity equivalent and unchanged cefiderocol after administration of 1000 mg [^{14}C] cefiderocol over 1 h in healthy subjects.[35] The findings showed that cefiderocol accounted for 92.3% of total radioactivity in plasma and for 90.6% of the administered dose into urine, thus confirming that metabolism is a minor route of elimination of cefiderocol.[35]

Pharmacodynamic Properties

Cefiderocol is a beta-lactam antibiotic for which the pharmacodynamic determinant of efficacy is the time that the plasma concentration exceeds the MIC of the pathogen (t>MIC) during the dosing interval.[36] Experimental animal models of infections showed that a t>MIC of around 75% is associated with an effective microbiological response to cefiderocol in terms of 1–2 log of bacterial killing.[36,37] In a *P. aeruginosa* neutropenic murine model, the t>MIC targets needed for stasis, 1 log and 2 log decrease in bacterial burden against strains with MICs of 0.064–0.5 mg/L ranged 44.4–94.7%, 50.2–97.5%, and 62.1–100%, respectively.[36] In murine thigh and lung infection models, the mean t>MIC needed for 1-log reduction in bacterial burden against various Gram-negative bacteria (*E. coli, K. pneumoniae, P. aeruginosa, A. baumannii*, and *S. maltophilia*) differed according to the site of infection and to the pathogen.[37] In the thigh infection model, the mean t>MIC was of 73.3% and 77.2% against *Enterobacterales* and *P. aeruginosa*, respectively; in the lung infection model, it was of 64.4%, 70.3%, 88.1%, and 53.9% against *Enterobacterales, P. aeruginosa, A. baumannii,* and *S. maltophilia*, respectively.

Matsumoto et al assessed in an immunocompetent rat respiratory tract infection model the influence that infusion time of administration (3 h vs 1 h) may have on the efficacy of humanized cefiderocol exposure (2g q8h) against carbapenem-resistant Gram-negative bacilli (*P. aeruginosa, A. baumannii* and *K. pneumoniae*). Administration by extended infusion (EI) over 3 h resulted in more sustained reduction in lung bacterial burden (3.04–4.41 log_{10}) compared with intermittent infusion (II) over 1 h (0.7–3.7 log_{10}).[38] This provided the rationale for considering the use of EI for ameliorating t>MIC with cefiderocol.

Consistently, the efficacy of humanized exposures of 2g q8h EI over 3 h cefiderocol was assessed against various species of Gram-negative bacteria with variable patterns of susceptibility to other antibiotics in several murine neutropenic thigh infection models.[39–43] Monogue

and colleagues assessed the efficacy of cefiderocol against a collection of 15 *P. aeruginosa, A. baumannii,* and *Enterobacterales* isolates. They found that the humanized exposures of cefiderocol were able to cause a ≥1-log drop in bacterial burden against all pathogens with an MIC up to 4 mg/L.[42] Similar findings were observed also by Ghazi and colleagues who assessed the efficacy of humanized exposures of cefiderocol against eight different strains of *P. aeruginosa* with an MIC ranging from 0.063 to 0.5 mg/L for cefiderocol, from 2 to 64 mg/L for cefepime, and from 1 to 32 mg/L for levofloxacin.[40] Stainton and colleagues assessed the sustainability of humanized exposure of cefiderocol over 72 h against a collection of 12 *P. aeruginosa, A. baumannii,* and *Enterobacterales* isolates. Sustained kill was observed at 72 h against 9 out of 11 strains with an MIC ranging from 0.5 and 8 mg/L, and no adaptive resistance was observed during therapy.[43] In another study, the effect of cefiderocol human-simulated exposures was compared with that of ceftazidime human-simulated exposures (2g q8h over 2 h) against 24 *S. maltophilia* strains that were fully susceptible to cefiderocol (MICs 0.015–0.5 mg/L) and either ceftazidime-susceptible (10/24) or ceftazidime-nonsusceptible (14/24). For cefiderocol bacterial killing was potent against all strains (mean ± SD bacterial burden $\log_{10}$ reduction at 24 h - 2.76 ± 0.68; ≥2 log in 87.5% and ≥1 log in the remaining 12.5% of isolates) whereas for ceftazidime it was present but less potent against the 10 ceftazidime-susceptible strains (- 1.38 ± 1.49) and absent against the 14 ceftazidime-nonsusceptible strains (mean ± SD bacterial growth of 0.64 ± 0.79).[39] Recently, a neutropenic thigh infection model confirmed that the efficacy of humanized cefiderocol exposure at 72 h against *Enterobacterales, P. aeruginosa,* and *A. baumannii* isolates is unaltered even by host iron overload (mean ± SD $\log_{10}$ bacterial decrease – 2.5 ± 1.5 vs – 2.5 ± 1.4 in standard and iron-overloaded models, respectively).[41] Consistently with these findings, the dosage regimens proposed for cefiderocol were focused at predicting by means of Monte Carlo simulations a high probability of success (≥90% of PTAs of 75% t>MIC) against pathogens with an MIC up to 4 mg/L in patients belonging to all of the different classes of renal function (Table 2).[44]

Noteworthy is that cefiderocol is one of the few antibiotics in the therapeutic armamentarium with a well-defined dosing strategy specified in the manufacturer's fact sheet also for patients with augmented renal clearance (ARC). ARC is defined as a CLCr >120–130 mL/min/1.73 m^2 and is a pathophysiological condition that may accelerate the elimination of beta-lactams like cefiderocol, thus theoretically causing underexposure if standard dosages are administered.[45] The strategy of a more intensified dosage is extremely relevant in preventing the risk of therapeutic failure associated with drug underexposure when using cefiderocol in populations of critically ill patients at high prevalence of ARC, like those with febrile neutropenia (16.4%), sepsis (39.5–56%), burns (65%), trauma (85%), and subarachnoid hemorrhage (100%).[45]

The strategy of administering cefiderocol by EI among all patients irrespective of the degree of renal function may be helpful also at minimizing the development of multidrug antimicrobial resistance. Administering beta-lactams by EI rather than by II may represent a step forward in suppressing resistance amplification, as it may ensure better exposures in terms of t>MIC compared with II.[46]

Results of Randomized Clinical Trials: Efficacy

The efficacy of cefiderocol in complicated urinary tract infections (cUTI) was evaluated in a randomized (2:1), Phase II, double-blind, parallel-group, non-inferiority trial (APEKS-cUTI), started in 2014. In this trial, cefiderocol was compared with imipenem-cilastatin. Patients infected by carbapenem-resistant organisms were not enrolled. The primary endpoint was clinical cure/microbiological eradication (as a composite endpoint) at the test of cure (TOC), which was set at 7±2 days after the end of treatment (EOT). The study was planned with a non-inferiority margin of 20%. However, following discussion with the FDA on the possible decrease of the non-inferiority margin to 15% and the increase of the sample size, the study protocol was amended accordingly.[47]

The APEKS-cUTI study was conducted in 67 hospitals in 15 countries, from February 2015 to August 2016. Only individuals aged ≥18 years and with a diagnosis of cUTI (with or without pyelonephritis) or acute uncomplicated pyelonephritis (30% of the total sample size) were recruited. A one/two-week intravenous therapy was planned in the study protocol: cefiderocol (2 g) q8h vs imipenem-cilastatin (1g) q8h. Dosages were adjusted depending on renal function and body weight. The high dose of imipenem was chosen to allow inclusion of patients with *P. aeruginosa* infection.

A total of 371 patients were enrolled in the primary study population (modified intention-to-treat [mITT]).

More than half of patients were aged ≥65 years (in both arms) and complicated patients were more frequent than in contemporary studies. The most frequent uropathogens were *E. coli* and *K. pneumoniae*, whereas *P. aeruginosa* was isolated from 7% and 4% of patients treated with cefiderocol and imipenem-cilastatin, respectively. Several bacterial isolates were resistant to cefepime and levofloxacin. The primary endpoint was achieved by 73% (183/252) and 55% (65/119) of the patients enrolled in the cefiderocol and imipenem-cilastatin arms, respectively (adjusted difference: 18.6%; 95% confidence interval [CI] 8.2 to 28.9, thereby demonstrating not only non-inferiority but also superiority of cefiderocol as a post hoc result). When analyzing the single components of the composite endpoint, microbiological response was higher in patients treated with cefiderocol (73% [184/252]) as opposed to those treated with imipenem-cilastatin (56% [67/119]), with an adjusted difference of 17.3% (95% CI 6.9 to 27.6). Conversely, clinical response was similar in the two arms (90% [226/252] in cefiderocol-treated patients vs 87% [104/119] in the imipenem-cilastatin treated-patients; adjusted difference 2.4%, 95% CI −4.7 to 9.4).

The efficacy of cefiderocol in patients with hospital-acquired bacterial pneumoniae (HABP), ventilator-associated bacterial pneumonia (VABP), or healthcare-associated bacterial pneumonia (HCABP) caused by GNB was evaluated in the study APEKS-NP, a Phase III, double-blind, randomized, non-inferiority trial. The results of the APEKS-NP trial have been recently published.[48,49] The patients were randomized to cefiderocol 2 g every 8 h or to meropenem 2 g every 8 h, both as a 3-h infusion. Linezolid was administered in both arms for a duration of at least 5 days while cefiderocol or meropenem was administered for 7–14 days. The primary endpoint was all-cause mortality at day 14 for the mITT population, with a non-inferiority margin of 12.5%. Cefiderocol was non-inferior to meropenem with respect to all-cause mortality at day 14 (12.4% [18/145] in cefiderocol arm vs 11.6% [17/146] in meropenem arm; difference 0.8%; 95% CI −6.6 to 8.2).[48]

The CREDIBLE-CR study was an open-label, international, multicenter, Phase 3 RCT that was pathogen-oriented rather than indication oriented:[50,51] this was a descriptive study, not powered for inferential testing. Indeed, cefiderocol was compared with best available therapy (BAT) for the treatment of severe infections (HCABP, HABP, VABP, cUTI, or bloodstream infections [BSI]/sepsis) due to carbapenem-resistant (CR) GNB. The results of the CREDIBLE-CR study have also been recently published.[52] Cefiderocol 2 g every 8 h was given as a 3-h infusion and BAT was chosen by the investigator and consisted of up to three antibiotics. Patients were randomized 2:1 to receive cefiderocol or BAT. Duration of therapy (either with cefiderocol or with BAT) was 7 to 14 days, possibly extended up to 21 days based on reasonable explanation. In patients with cUTI, a minimum length of therapy of 5 days was allowed. The primary efficacy endpoint for patients with HABP/VABP/HCABP and for those with BSI/sepsis was clinical cure at TOC visit. For patients with cUTI, the primary efficacy endpoint was microbiological cure (eradication) at TOC. In the CR-mITT population (primary study population) clinical cure rates at TOC were comparable between groups, overall (52.5% [42/80] in cefiderocol-treated vs 50% [19/38] in BAT-treated patients) and in subgroups of patients with HABP/VABP/HCABP (50% [20/40] in cefiderocol-treated vs 52.6% [10/19] in BAT-treated patients), and patients with BSI/sepsis (43.5% [10/23] in cefiderocol-treated vs 42.9% [6/14] in BAT-treated patients). Microbiological cure in patients with cUTI was 52.9% (9/17) and 20% (1/5) in cefiderocol-treated and BAT-treated patients, respectively. However, all-cause mortality at day 14, day 28, and day 49 was numerically higher in the cefiderocol group (19%, 25%, 34%, respectively) compared to BAT (12%, 18%, 18%, respectively). This mortality imbalance was greatest at days 14, 28, and 49 for patients with HABP/VABP/HCABP (cefiderocol 24%, 31%, and 42% vs BAT 14%, 18%, and 18%). It is worth noting that, in the safety population, a greater number of deaths occurring up to day 3 were reported in the cefiderocol arm (cefiderocol 4% vs 0% BAT), which may be considered unrelated to study drug efficacy. Moreover, a greater number of deaths were reported in the cefiderocol arm (9% cefiderocol vs 0% BAT) after day 28 through the end of study as opposed to BAT, whereas proportions were similar from day 4 to day 28 (21% and 18% in cefiderocol and BAT arms, respectively).

Of note, the difference in 49-day mortality stratified for pathogen was the highest for *Acinetobacter* spp. (50% [21/42] vs 18% [3/17] in cefiderocol and BAT-treated patients, respectively), although it is of note that some variables indicating severity of presentation or of baseline diseases (ICU at randomization, severe renal dysfunction, ongoing shock, and shock within 31 days before randomization)

were more frequent in the cefiderocol than BAT arms in patients with *Acinetobacter* spp. infections.[52]

Safety of Cefiderocol

Two Phase 1 studies showed mild, clinically not significant adverse events mainly represented by diarrhea and skin reactions (maculopapular rash, urticarial) in less than 20% of patients, with only one treatment discontinuation due to urticaria.[31,32] In another phase 1 study in healthy adult subjects, cefiderocol in normal doses (2 g) and supratherapeutic doses (3–4 g) had no apparent clinically significant effect on QT and corrected QT (QTcF) interval.[53]

Phase 2 and phase 3 studies confirmed that cefiderocol is comparable to other cephalosporins in terms of tolerability and safety profile. In the APEKS-cUTI RCT, safety was assessed in all randomly assigned individuals who received at least one dose of study drug.[47] Adverse events occurred in 41% (122/300) and 51% (76/148) of patients in the cefiderocol and in the imipenem-cilastatin groups, respectively, with the majority being mild or moderate. Overall, diarrhea and constipation were observed in 7.7% of patients in the cefiderocol group and in 10.1% of those in the imipenem-cilastatin group. Serious adverse events were reported in 5% and 8% of patients in the cefiderocol and imipenem-cilastatin groups, respectively. Among serious adverse events, *Clostridioides difficile* infection (CDI) occurred in one patient in the cefiderocol group and in two patients in the imipenem-cilastatin group. One death due to cardiac arrest, considered unrelated to study drug by the investigator, was reported in the cefiderocol group.

In the APEKS-NP study, adverse events were observed in 88% (130/148) and 86% (129/150) in cefiderocol and meropenem groups, respectively.[48] In both arms, urinary tract infections (15.5% and 10.7% in cefiderocol and meropenem arms, respectively) and hypokalemia (10.8% and 15.3% in cefiderocol and meropenem arms, respectively) were the most frequently observed adverse events. Serious adverse events were observed in 36% (54/148, of which 3 drug-related) and 30% (45/150, of which 5 drug-related) in cefiderocol and meropenem groups, respectively. Among patients treated with cefiderocol and meropenem, 4/148 (3%) and 4/150 (3%) developed *C. difficile* infection.[48]

According to the results of the CREDIBLE-CR study, the rate of adverse events (evaluated in 101 patients who received cefiderocol and 49 patients who received BAT) was similar in the two arms, with over 90% of patients experiencing at least one adverse event.[52] Diarrhea, pyrexia, septic shock, vomiting, and hypokalemia were the most frequently observed adverse events in both groups and diarrhea (19% vs 12%), ALT increased (7% vs 0%), AST increased (8% vs 2%), pleural effusion (8% vs 2%), and chest pain (6% vs 0%) were observed more frequently in the cefiderocol than in the BAT groups. The majority of chest pain episodes reported in the cefiderocol group were considered to be of non-cardiovascular origin and not related to cefiderocol. Most adverse events occurred at a low frequency and were considered manifestations of the patients' underlying disease. Indeed, the frequency of adverse events considered to be treatment-related by the investigator was 15% (15/101) in the cefiderocol arm and 22% (11/49) in the BAT arm. Diarrhea (2%), abnormal liver function tests (2%), ALT increased (3%), and AST increased (3%) were the most frequently reported treatment-related, treatment-emergent adverse events in the cefiderocol group; while acute kidney injury (8%) was the most frequently reported treatment-related, treatment-emergent adverse event in the BAT group. Serious adverse events were reported for 50% and 47% of patients in cefiderocol group and BAT group, respectively. Septic shock was the most frequently reported serious adverse event in both cefiderocol (12%) and BAT (12%) groups. Overall, only 1/101 patient in the cefiderocol group (1%) experienced a treatment-related serious adverse event, that is, an increase in transaminases levels which led to study drug discontinuation and resolved in 30 days. Conversely, treatment-related serious adverse events were observed in 5/49 patients in the BAT group (10%). Discontinuation due to treatment-related adverse events occurred in 3% and 4% of patients in the cefiderocol group and BAT group, respectively.

Case Reports and Case Series

Case reports and case series of patients with severe GNB infections treated with cefiderocol in compassionate use are detailed in Table 3.[54–66] All these cases highlight unique challenges in managing patients infected by MDR-GNB including MBL-producing GNB.

Place in Therapy

Cefiderocol is a first-in-class antibiotic, a siderophore intravenous cephalosporin that binds ferric iron and is actively transported into the periplasm of GNB.[14,67,68] Beyond its novel mechanism of action, from a practical standpoint what makes it attractive for clinicians is the

Table 3 Published Case Reports and Case Series of Compassionate Use of Cefiderocol

Age, Sex (Reference)	Underlying Condition of the Patient	Type of Infection Pathogen (in vitro Susceptibility)	Antimicrobial Therapy History	Outcome
46, Male[57]	Partial right great toe amputation treated with daptomycin and levofloxacin for a vancomycin-resistant *Enterococcus faecium* and *Pseudomonas aeruginosa* stump infection with residual osteomyelitis. Hemodialysis-dependent for end-stage renal disease, diabetes mellitus, coronary disease.	Perforation of the colon with intraabdominal abscess. End ileostomy and right hemicolectomy. *Pseudomonas aeruginosa* (carbapenem-resistant, cefiderocol susceptible), *Escherichia coli, Bacteroides fragilis*.	**First line:** Meropenem, daptomycin, linezolid. **Second line:** Ceftazidime/avibactam, polymyxin B, metronidazole. polymyxin B was discontinued due to suspect of neurotoxicity. **Third line:** cefiderocol plus metronidazole.	Decrease in size of intraabdominal abscess on day 5 of cefiderocol therapy. Complete resolution of paracolic gutter abscess on day 19 of therapy. Discontinuation of treatment after 28 days therapy.
Adult, male[58]	Severe H1N1 influenza complicated by bilateral pneumonia and respiratory failure. Intubation and extracorporeal membrane oxygenation.	Bacteremia. *Acinetobacter baumannii* (extensively drug-resistant, susceptible to colistin); *Klebsiella pneumoniae* (carbapenem resistant; colistin, gentamicin, ceftazidime/avibactam, and cefiderocol susceptible).	**First line empiric:** piperacillin-tazobactam, clarithromycin, linezolid, zanamivir. **Second line:** meropenem, vancomycin, anidulafungin. **Third line:** colistin, fosfomycin, tigecycline, daptomycin. Fourth line: cefiderocol, linezolid	Patient conditions rapidly improved with resolution of fever and normalization of procalcitonin levels after start of cefiderocol therapy. After 14 days of cefiderocol treatment, chest X-rays showed complete resolution of lung infiltrates.
78, female[56]	Hydronephrosis secondary to a spontaneous ureteric hematoma. She had a past medical history of aortic stenosis, ischemic heart disease, and cerebral infarction and was in remission from breast cancer. Thickened aortic valve.	Bacteremia complicated by aortic valve endocarditis, *Pseudomonas aeruginosa* (susceptible only to colistin, gentamicin and amikacin); (resistant also to ceftazidime/avibactam and ceftolozane/tazobactam. No synergy between antipseudomonal agents and fosfomycin and rifampicin).	**First line:** colistin plus gentamicin. **Second line:** colistin plus meropenem **Third line:** colistin plus meropenem plus cefiderocol for one week followed by colistin plus cefiderocol for an additional 3 weeks.	Aortic valve replacement was performed on day 2 of cefiderocol. Blood culture taken the day of surgery was negative and persisted negative up to day 275.
68, female[55]	End-stage renal disease secondary to diabetes who had been on hemodialysis for 8 years. Renal transplant complicated by cardiac arrest with pulseless electronic activity, requiring initiation of extracorporeal membrane oxygenation and continuous renal replacement therapy. Hematoma surrounding the kidney allograft and placement of abdominal drains	Isolation from peritoneal drain cultures and blood. *Klebsiella pneumoniae* positive for both NDM-1 and OXA-48 group enzymes (resistant to carbapenems, ceftazidime/avibactam, meropenem/vaborbactam, and gentamycin; susceptible to colistin, tigecycline, eravacycline, and cefiderocol).	**First line:** polymyxin B plus tigecycline. **Second line:** polymyxin B, ceftazidime/avibactam, aztreonam. **Third line:** polymyxin B, ceftazidime/avibactam, cefiderocol (1.5 g/12h)	Subsequent blood cultures and peritoneal fluid culture were all negative after cefiderocol was started, with clinical improvement. The patient developed vancomycin-resistant *Enterococcus faecium* bacteremia, invasive candidiasis due to *Candida glabrata*, and *Clostridioides difficile*-infection, which were treated with daptomycin, caspofungin, and oral vancomycin, respectively. Eventually the patient developed fatal ischemic colitis.
15, male[54]	Femur fracture after a motor vehicle accident, intramedullary pin placement.	Recurrent wound infection treated with various antibiotics (details not available). Chronic osteomyelitis of the left femur, with phlegmonous changes extending to the skin. *Pseudomonas aeruginosa* (extensively drug resistant, susceptible only to colistin and cefiderocol), Extended-spectrum β-lactamases-producing *Klebsiella pneumoniae* (susceptible to carbapenem, ceftazidime/avibactam, colistin, cefiderocol, aminoglycosides).	**First line empiric:** levofloxacin, metronidazole, trimethoprim-sulfamethoxazole, antibiotic-cement nail containing tobramycin and vancomycin. **Second line:** cefepime, vancomycin, metronidazole. **Third line:** ceftazidime/avibactam plus aztreonam **Fourth line:** polymyxin B, aztreonam, tigecycline. **Fifth line:** cefiderocol plus aztreonam. Aztreonam discontinued after two weeks. Bone graft and antibiotic nail exchange. Cefiderocol was administered for a total of 14 weeks.	After 9 weeks of cefiderocol therapy bone cultures were sterile, and a histopathology report showed benign bone without associated acute or chronic inflammation.

(*Continued*)

Table 3 (Continued).

Age, Sex (Reference)	Underlying Condition of the Patient	Type of Infection Pathogen (in vitro Susceptibility)	Antimicrobial Therapy History	Outcome
84, male[59]	Diabetes mellitus, chronic renal failure, previous non-Hodgkin's lymphoma, vascular diseases, hallux amputation.	BSI secondary to an infected, wet gangrenous left foot, caused by OXA- and NDM-producing *K. pneumoniae* (susceptible to colistin, tigecycline, and cefiderocol).	**First line empiric:** piperacillin-tazobactam, clindamycin, and amikacin, in addition to surgical debridement **Second line:** colistin, tigecycline **Third line:** cefiderocol plus colistin, then de-escalated to cefiderocol monotherapy. Treated with cefiderocol for 14 days	Improvement and discharge from ICU, subsequent death in a medical ward without signs of infection relapse
63, male[60]	Obesity, diabetes mellitus, cardiac ischemic disease, gout arthritis.	Para-duodenal pancreatic collection with extensively drug resistant (XDR) *P. aeruginosa* (susceptible to colistin and cefiderocol) isolated from pancreatic pus.	**First line:** colistin, meropenem **Second line:** cefiderocol	Favorable resolution after 6 weeks of treatment. Subsequent isolation of a cefiderocol-resistant strain from ischial eschar. Subsequent death due to XDR *P. aeruginosa* pneumonia
65, male 70, female 56, female[61]	Patient 1: hypertension, cardiac tamponade, septic thrombosis due to carbapenemase-producing *K. pneumoniae* Patient 2: diabetes mellitus, *K. oxytoca* septic shock with bacteraemic pyelonephritis Patient 3: *Staphylococcus aureus* spinal implant infection.	Patient 1: BSI due to pan-drug resistant *Acinetobacter baumannii* Patient 2: BSI due to colistin-susceptible *Acinetobacter baumannii*, complicated by XDR *P. aeruginosa* bacteremia Patient 3: wound superinfection and spondylodiscitis due to XDR *A. baumannii* (bone culture positive)	Patient 1: **First line empiric:** trimethoprim/sulfamethoxazole **Second line:** cefiderocol Patient 2: **First line:** colistin **Second line:** cefiderocol Patient 3: **First line:** colistin, tigecycline **Second line:** cefiderocol	Patient 1: Improvement and discharge from ICU, subsequent death in a medical ward without signs of infection relapse Patient 2: Resolution of *A. baumannii* but not *P. aeruginosa* BSI. Subsequent death due to intercurrent HSV-1 disseminated infection Patient 3: Bone culture negative after 21 days of cefiderocol treatment. Subsequent completion of a 6-week treatment with oral minocycline and no signs of relapse at 9-week follow-up
10 patients (4 males and 6 females) with a mean age of 69 years[62]	Hypertension (9/10), COVID-19 (5/10), burns (4/10), obesity (2/10), bipolar disorder (1/10), bladder cancer (1/10), colonic perforation (1/10), intravenous drug use (1/10).	Six BSI and 4 ventilator-associated pneumonia (VAP) due carbapenem-resistant organisms (7 *A. baumannii*, 1 NDM-producing *Stenotrophomonas maltophilia*, 1 NDM-producing *K. pneumoniae*, 1 *A. baumannii* plus NDM-producing *K. pneumoniae)*	**First line:** 7 colistin-based combination, 1 colistin monotherapy, 1 tigecycline plus ampicillin-sulbactam, 1 ceftazidime/avibactam plus aztreonam plus fosfomycin **Second line:** cefiderocol (9 monotherapy, 1 combined with fosfomycin)	Clinical outcome at day 30 was favorable in 7/10 cases (70%), 30-day mortality was 10% (1/10)
67, male[63]	Atrial fibrillation, chronic Glaucoma, previous left knee replacement, aortic stent, right knee replacement.	Acute prosthetic joint infection of the right knee managed with debridement, antibiotics and implant retention (DAIR). Isolation from intraoperative material of XDR *Enterobacter hormaechei* (susceptible to colistin and tigecycline).	**First line empirical:** vancomycin, piperacillin/tazobactam **Second line:** colistin, tigecycline **Third line:** cefiderocol	Improved, discharged, and treated for 12 weeks (including 10 weeks of cefiderocol monotherapy). Follow-up at 12 weeks after end of antibiotic treatment showed full recovery.
45, female[64]	Hemangioblastoma requiring multiple neurosurgical interventions, esophageal-pleural fistula, esophageal perforation repaired with jejunostomy and gastrostomy tube placement.	Esophageal leak with fistula and growth of cefiderocol-susceptible XDR *P. aeruginosa* from plural fluid culture, treated surgically and with antibiotic therapy.	**First line:** ceftazidime/avibactam, polymyxin B **Second line:** cefiderocol	Full recovery after 3 weeks of cefiderocol treatment. Subsequent respiratory colonization by cefiderocol-resistant XDR *P. aeruginosa*, without infection and need for antibiotic therapy.

(*Continued*)

Table 3 (Continued).

Age, Sex (Reference)	Underlying Condition of the Patient	Type of Infection Pathogen (in vitro Susceptibility)	Antimicrobial Therapy History	Outcome
29, male 64, male 62, male[65]	Patient 1: polytrauma with external fixation of an open fracture of the tibia Patient 2: polytrauma Patient 3: blunt thoracic trauma with lung injury, hemothorax, rib fractures.	Patient 1: early postoperative, polymicrobial, implant-associated wound infection due to VIM-producing *P. aeruginosa*, OXA-23-producing *A. baumannii*, and KPC-producing *Enterobacter cloacae* Patient 2: postoperative implant-associated spine infection due to OXA-40 and NDM- producing *A. baumannii* Patient 3: pleural empyema due to XDR *A. baumannii* and subsequent acute osteomyelitis and urinary tract infection due to XDR *A. baumannii*.	Patient 1: **Treatment:** multiple surgeries plus cefiderocol for 2 weeks and colistin and ceftazidime-avibactam for 4 weeks Patient 2: **Treatment:** removal of osteosynthesis and colistin plus cefiderocol for 14 days, then cefiderocol monotherapy for a total of 6 weeks Patient 3: **Treatment:** cefiderocol plus colistin (for 14 days) for pleural empyema and cefiderocol (6 weeks) for osteomyelitis	Patient 1: Definite implantation and not signs of relapse at 8 weeks of follow-up Patient 2: Novel osteosynthesis with no signs of relapse at 13 weeks of follow-up Patient 3: No signs of relapse at 6 weeks of follow-up
57, male[66]	Hypertension, diabetes mellitus, left tibia and fibula fracture with external fixation followed by two surgical debridements.	Osteomyelitis of left leg with intraoperative cultures positive for *Enterococcus faecalis, Corynebacterium striatum*, And XDR A. *baumannii*.	**First line empirical:** piperacillin/tazobactam with subsequent addition of vancomycin **Second line:** Polymyxin B, minocycline, and vancomycin (the latter subsequently substituted by daptomycin) **Third line:** Daptomycin, meropenem, tigecycline **Fourth line:** Daptomycin, cefiderocol	Cefiderocol discontinued after 102 days and no signs of relapse at 128 days after antibiotics discontinuation.

displayed in vitro activity against carbapenem-resistant *A. baumannii* and MBL-producing GNB, ie, those MDR-GNB for which there are currently no marketed active β-lactams (without forgetting its in vitro activity against *Stenotrophomonas* spp. and *Burkholderia* spp.).[69] Therefore, clinical data from both registrative studies and post-marketing experiences are essential to confirm whether these promises from in vitro studies could readily translate into clinical practice, as well as to delineate a precise place in therapy for cefiderocol for the treatment of MDR-GNB in the near future. Real-life data would also be important for further delineating the safety of cefiderocol through Phase 4 surveillance studies.

While the results of the APEKS-cUTI and APEKS-NP studies have eventually led to the FDA approval of cefiderocol for cUTI and HABP/VABP,[47,48] the recent EMA approval of cefiderocol for the treatment of infections due to Gram-negative bacteria in adults with limited treatment options[70,71] opens doors to its use also for other pressing priorities, such as BSI caused by carbapenem-resistant *A. baumannii* or MBL producers, or for its empirical use in endemic settings or in colonized patients with severe infection. In this regard, it would be critical to clarify the remaining issue of the increased mortality in cefiderocol-treated patients in the CREDIBLE-CR study, especially in the case of infections due to non-fermenting GNB. In our opinion, this could be achieved in two different, complementary ways: (i) through conduction of further RCT (the open-label GAMECHANGER RCT, which is comparing cefiderocol vs BAT for the treatment of BSI due to GNB, is currently recruiting patients [NCT03869437]); (ii) through post-marketing observational experiences, which, although unable to provide high-quality evidence for guiding treatment due to the inherent limitations of observational studies (even when properly adjusting for confounding variables) may provide useful hypothesis-generating data and clinical success/mortality rates for fine-tuning the design of future RCT (perhaps by identifying those categories of patients that may benefit the most from

cefiderocol administration) should also the GAMECHANGER study provide inconclusive evidence.

Until then, some uncertainties in delineating the precise place in therapy of cefiderocol for the treatment of MDR-GNB infections will remain. Indeed, on the one hand, we now have a β-lactam that, at least in vitro, fills the gaps against some high-priority MDR-GNB, taking also into account the consideration that the increased mortality observed in the CREDIBLE-CR study may be merely due to chance alone in view of the low power related to the small sample size (especially in subgroups) of the CREDIBLE-CR study and the current lack of a clear explanation for the observed result. On the other hand, further studies remain necessary to verify this hypothesis, and cefiderocol should not be used indiscriminately. In our opinion, the potential advantages of having restored β-lactam activity against highly resistant *A. baumannii* and MBL producers should not be wasted while waiting for further evidence. What remains largely unclear is whether cefiderocol should be used alone or in combination with BAT (eg, polymyxins) until more solid evidence is provided. There is still no clear answer to this question, which, notably, does not involve the classical (and still unresolved) dilemma of the general comparison of monotherapy vs combinations for MDR-GNB infections in terms of efficacy, but the novel one of not using cefiderocol alone considering the possible imbalance in mortality registered in the CREDIBLE-CR study. In our opinion, it could be ultimately reasonable to consider using cefiderocol-including combinations in the case of severe clinical presentations, in which a de-escalation rather than escalation strategy could be more indicated (authors opinion only, not supported by published evidence at the present time). The same may apply to the inclusion of cefiderocol in empirical regimens in patients with severe infections and hospital-level or patient-level risk factors for infections due to carbapenem-resistant *A. baumannii* and/or MBL producers. Of note, in this scenario reliable and rapid microbiological tests for the detection of causative agents and involved resistance mechanisms will increasingly play a crucial role in the optimization of the empirical use of cefiderocol (initiation/discontinuation) according to antimicrobial and diagnostic stewardship principles.[72]

In conclusion, cefiderocol expands the spectrum of MDR-GNB that can be treated again with β-lactams and will likely offer a precious addition to the clinician armamentarium. Because of this unique potential, it remains essential to provide both RCT (eg, GAMECHANGER) and real-life data to improve the clinicians' ability to exploit its benefit in both empirical and targeted treatment of MDR-GNB infections.

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