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Review

Cefiderocol in clinical practice: From randomised trials to real-world evidence in the management of multidrug-resistant Gram-negative bacterial infections

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ABSTRACT

Objectives: Multidrug-resistant Gram-negative bacteria (MDR-GNB) represent a major global health threat, with limited therapeutic options and high morbidity and mortality. Cefiderocol, a novel siderophore cephalosporin, has emerged as a potential treatment for MDR-GNB infections. This narrative review aims to critically appraise evidence from randomised controlled trials (RCTs) and real-world studies to clarify the clinical effectiveness, safety, and optimal place-in-therapy of cefiderocol in the management of MDR-GNB infections.

Methods: A narrative review of phase 2 and 3 RCTs and available real-world observational studies was performed. Evidence was synthesised focusing on mechanism of action, pharmacokinetic/pharmacodynamic properties, resistance mechanisms, and clinical outcomes across different infection sites, pathogens, and treatment strategies.

Results: RCTs demonstrated non-inferiority of cefiderocol compared with standard-of-care therapies in complicated urinary tract infections, nosocomial pneumonia, and bloodstream infections sustained by GNB. However, heterogeneous outcomes and mortality imbalances were observed in specific subgroups, particularly in Acinetobacter baumannii and metallo-β-lactamase (MBL)-producing pathogens. Real-world studies support cefiderocol use in critically ill patients, ventilator-associated pneumonia, and bloodstream infections, with more consistent benefits observed for Pseudomonas aeruginosa and carbapenem-resistant Enterobacterales. Outcomes in carbapenem-resistant A. baumannii infections remain variable. Early initiation of therapy appears associated with improved outcomes, while no clear superiority of combination therapy over monotherapy has been established.

Conclusions: Cefiderocol represents a valuable option for the treatment of MDR-GNB infections. Its optimal use requires careful patient and pathogen selection, early administration, and integration within antimicrobial stewardship strategies. Further pathogen- and infection-specific trials are needed to better define its role, particularly in carbapenem-resistant A. baumannii and MBL-producing infections.

Introduction

Multidrug-resistant Gram-negative bacteria (MDR-GNB) represent an increasing challenge in modern clinical practice, resulting in high morbidity and mortality as well as substantial healthcare costs. The rapid emergence and global spread of carbapenem-resistant strains, along with resistance to last-line agents, have limited available therapeutic options. For this reason, the World Health Organisation considers pathogens such as carbapenem-resistant Enterobacterales (CRE), *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* as critical-priority organisms[1].

Cefiderocol is a novel siderophore cephalosporin designed to overcome major resistance mechanisms in MDR-GNB. With its distinctive “Trojan horse” mechanism, it exploits bacterial iron transport systems, penetrating the outer membrane and reaching the periplasmic space, where it inhibits cell wall synthesis. This strategy enables activity against pathogens with porin mutations, efflux pump overexpression, and β-lactamases, including carbapenemases, and provides a potent bactericidal activity and an effective option against MDR-GNB[2,3]. From a regulatory standpoint, cefiderocol received U.S. Food and Drug Administration (FDA)

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approval between 2019 and 2020 for the treatment of complicated urinary tract infections (cUTI), as well as hospital-acquired and ventilator-associated pneumonia (HAP/VAP). In 2020, the European Medicines Agency (EMA) authorised its use for difficult-to-treat Gram-negative bacterial infections in adults with limited therapeutic options. Pivotal phase 3 randomised controlled trials (RCTs) demonstrated non-inferiority to standard-of-care (SOC) therapy across a spectrum of infections, although an imbalance in all-cause mortality was observed in certain subgroups, particularly in *A. baumannii* infections[4–6].

Despite its potential, the precise place-in-therapy of cefiderocol remains incompletely defined to date, and robust data are still needed to clarify areas in which RCTs evidence remains limited. In this context, multicentre observational studies have been designed to define the demographic and clinical characteristics of patients receiving the drug, to evaluate clinical outcomes, and to identify predictors of mortality[7–10]. Emerging real-world evidence suggests a potential benefit of cefiderocol in critically ill patients with bloodstream infections (BSIs) and VAP, especially in intensive care settings, although therapeutic effectiveness appears to be influenced by infection type and pathogen[11,12]. Observational data further support its use both as monotherapy and in combination regimens, although no clear superiority of either approach has been established[7,12].

This narrative review provides a critical evaluation of cefiderocol by integrating evidence from RCTs and real-world studies to address key uncertainties, with a focus on defining its clinical effectiveness and appropriate use. Emphasis is placed on identifying both the strengths and limitations of the available evidence to clarify the current and future role of cefiderocol in the management of MDR-GNB infections.

Mechanism of action, pharmacokinetics/pharmacodynamics, and resistance

Cefiderocol is a next-generation siderophore cephalosporin, developed to overcome the principal resistance mechanisms in Gram-negative bacteria. Through an innovative iron-dependent uptake mechanism, it exploits bacterial siderophore-mediated iron transport systems to achieve active cellular penetration and high periplasmic accumulation. Its strong affinity for penicillin-binding protein 3 (PBP3) and stability against all β-lactamase classes, including metallo-β-lactamases (MBLs), provide a high barrier to resistance development[13] and allow to retain activity against pathogens with compromised outer-membrane permeability or upregulated efflux pumps[14,15]. Extensive surveillance studies have consistently demonstrated robust bactericidal activity against Enterobacterales, *P. aeruginosa*, *A. baumannii*, and *Stenotrophomonas maltophilia*, including carbapenemase-producing and multidrug-resistant isolates[13,16,17].

Cefiderocol is administered intravenously at a standard dose of 2 g every 8 h as a prolonged 3-hour infusion, optimising exposure against pathogens with minimum inhibitory concentrations (MICs) up to 4 μg/mL[3]. Its pharmacokinetic (PK) profile features predominantly renal elimination, a moderate volume of distribution (13.5–26.6 L), and approximately 58% plasma protein binding. In patients with normal renal function, the elimination half-life ranges from 2 to 3 h, while in those with severe renal impairment it is prolonged to 6–8 h, thereby necessitating dose adjustment in the presence of renal dysfunction[3,18]. Drug exposure during continuous renal replacement therapy (CRRT) is generally adequate, although interindividual variability supports the selective use of therapeutic drug monitoring (TDM) in complex clinical scenarios or severe infections[19]. Similarly, in critically ill patients supported with extracorporeal membrane oxygenation (ECMO), cefiderocol pharmacokinetics appear largely preserved, with minimal circuit adsorption and standard dosing regimens achieving pharmacokinetic/pharmacodynamic (PK/PD) targets in most cases[20]. Regarding intrapulmonary PK for VAP treatment, the siderophore-mediated active transport mechanism enables cefiderocol to achieve therapeutic concentrations in epithelial lining fluid (ELF)[21]. In line with its β-lactam pharmacodynamic (PD) profile, cefiderocol exhibits time-dependent antibacterial activity, with efficacy driven by percentage of free drug concentration above the MIC (%fT > MIC). Preclinical models, population PK analyses, and real-world clinical data consistently demonstrated that standard dosing regimens achieve PD targets of ≥75–100% fT > MIC[19,22].

Resistance to cefiderocol remains uncommon, predominantly involving alterations in bacterial iron transport systems, including mutations or downregulation of siderophore receptors[23–26]. Notably, resistance emergence typically results from multiple concurrent mechanisms rather than from a single genetic alteration[27]. Reduced susceptibility may arise from the synergistic effect of β-lactamase production – particularly MBLs and certain serine β-lactamases – combined with compromised iron-mediated entry[28–30]. In contrast, target-site modification *via* alterations in penicillin-binding proteins appears to be rare and of limited clinical relevance[31,32]. Heteroresistance has been described in *A. baumannii*, with bacterial subpopulations exhibiting elevated MICs. However, this phenotype is often unstable, reversible, and inconsistently associated with clinical failure[22,33,34]. Overall, global rates of cefiderocol non-susceptibility remain low (< 5%) among Enterobacterales and *P. aeruginosa*, with higher rates (8–10%) reported in carbapenem-resistant *A. baumannii* (CRAB) and in MBL-producing isolates[33,34].

Evidence from randomised controlled trials (RCTs)

Registration trials have established the efficacy and safety of cefiderocol in adults with infections caused by GNB (Table 1). In the phase 2 randomised APEKS-cUTI study, cefiderocol was noninferior to imipenem-cilastatin in patients with cUTI, including immunocompromised patients and renal transplant recipients[35]. Clinical and microbiological responses at the end of therapy confirmed its efficacy in complex cases. However, concomitant severe conditions (*e.g.*, bacteraemia, septic shock, ICU admission) were not addressed, and cefiderocol was evaluated only as monotherapy. The phase 3 APEKS-NP trial assessed cefiderocol in patients with nosocomial pneumonia (NP), predominantly critically ill, demonstrating non-inferiority to high-dose meropenem for 14-day all-cause mortality and clinical response[4]. It is worth noting that the concomitant 5-day linezolid administration in all patients complicates the interpretation of cefiderocol efficacy as truly monotherapy, given the presence of mixed infections involving both Gram-positive and Gram-negative pathogens in 15% of patients receiving meropenem and 8% of those receiving cefiderocol. Besides, in both these trials, carbapenem-resistant pathogens were excluded, limiting applicability to more challenging settings such as infections sustained by CRAB, MBL-producing organisms, and non-fermenter pathogens. The open-label CREDIBLE-CR trial compared cefiderocol with best available therapy – primarily colistin-based regimens – in 150 patients with severe infections, including HAP/VAP, BSI, and cUTI, with the most common pathogens being carbapenem-resistant *Acinetobacter* spp., *K. pneumoniae*, and *P. aeruginosa*[5]. While clinical and microbiological outcomes were similar between groups, mortality was numerically higher with cefiderocol at day 28 and at the end of the study, particularly in *Acinetobacter* infections. Baseline imbalances in disease severity and pathogen distribution limit interpretation, and it remains unclear whether excess mortality reflects reduced efficacy against *A. baumannii* or confounding by pathogen virulence. In a *post hoc* analysis of the APEKS-NP and CREDIBLE-CR trials, Timsit *et al.* reported cefiderocol activity against MBL-producing pathogens[36]: pooled data from both trials showed clinical cure and microbiological eradication rates of 70.8% and 58.3%,

Table 1
Overview of the randomised controlled trials which evaluated efficacy and safety of cefiderocol.

Study (year), country	Study design, centres	Number of patients	Population and setting	Main pathogens	Type of infection	Comparator	Key efficacy results	Safety	Comments
APEKS-UTI (2018), multinational[35]	Phase 2, double-blind, non-inferiority, multicentre	452 (CFDC: 303, IMIc: 149)	Adults with complicated urinary tract infection (cUTI) ± pyelonephritis	Enterobacterales	cUTI	Imipenem-cilastatin	Composite clinical and microbiological response: 73% (CFDC) *vs.* 55% (IMIc)	Well tolerated; AE profile similar to imipenem	Non-inferiority of cefiderocol
APEKS-NP (2020), multinational[4]	Phase 3, double-blind, non-inferiority, multicentre	301 (CFDC: 148, MER: 152)	Adults with nosocomial pneumonia (NP), including VAP	Gram-negative pathogens (Enterobacterales, *P. aeruginosa*)	NP/VAP	Meropenem	14-day mortality: 12.4% (CFDC) *vs.* 11.6% (MER)	Comparable safety profile; few serious AEs	Non-inferiority of cefiderocol
CREDIBLE-CR (2021), multinational[5]	Phase 3, open-label, descriptive, multicentre	152 (CFDC: 101, BAT: 51)	Adults with serious carbapenem-resistant Gram-negative infections (BSI, NP, cUTI)	CRAB, CRPA, CRE	BSI, NP, cUTI	Best available therapy (BAT)	Clinical cure: 50% (CFDC) *vs.* 53% (BAT)	Well tolerated; some AEs related to infections	Numerically more deaths in the cefiderocol group, primarily in the patient subset with *Acinetobacter* spp.
GAME CHANGER (2025), multinational[37]	Phase 3, open-label, non-inferiority, multicentre	504 (CFDC: 256, SOC: 257)	Adults with bloodstream infections due to Gram-negative bacteria	CRAB, CRPA, CRE	BSI	Standard of care (SOC)	14-day mortality: 8% (CFDC) *vs.* 7% (SOC)	Five serious AEs	Non-inferiority of cefiderocol

Legend: *CFDC*, cefiderocol; *IMIc*, imipenem-cilastatin; *MER*, meropenem; *cUTI*, complicated urinary tract infection; *NP*, nosocomial pneumonia; *VAP*, ventilator-associated pneumonia; *BSI*, bloodstream infection; *AE*, adverse events; *BAT*, best available therapy; *SOC*, standard of care; *CRAB*, carbapenem-resistant *Acinetobacter baumannii*; *CRPA*, carbapenem-resistant *Pseudomonas aeruginosa*; *CRE*, carbapenem-resistant Enterobacterales.

respectively. However, the small sample size (*n*=24), limits the strength and generalisability of these findings.

Recent evidence from the open-label, randomised GAME CHANGER trial evaluated cefiderocol in hospital-acquired and healthcare-associated GN-BSIs[6]. In a previous *post hoc* analysis of phase 2 and phase 3 RCTs, Paterson *et al.* evaluated cefiderocol in patients with GN-BSIs, showing efficacy and safety comparable to standard treatment, along with higher rates of bacterial clearance[37]. This latest trial similarly evaluated more than 500 patients, mainly from Southeast Asia and Australia, randomised to receive cefiderocol or investigator-selected SOC therapy. The study met its primary endpoint, demonstrating noninferiority of cefiderocol compared with standard treatment for 14-day all-cause mortality. Subgroup analyses showed pathogen-specific heterogeneity: in *A. baumannii* BSIs, cefiderocol was associated with lower 14-day mortality compared with SOC (9% *versus* 21%). In contrast, higher mortality was observed with cefiderocol in infections caused by MBL-producing Enterobacterales, predominantly New Delhi metallo-β-lactamase (NDM) producers (*n*=28).

Several issues remain unresolved or uncertain based on RCTs, including the efficacy of cefiderocol against CRAB, its optimal use as monotherapy *versus* in combination regimens, and its role in infection subgroups that have been underrepresented in clinical trials. In this context, evidence derived from real-world clinical experience is essential to better define the positioning of cefiderocol in routine practice and to address gaps left by RCTs (Table 2).

Evidence from real-world studies

Site of infection

Large cohorts consistently reported respiratory infections as the most frequent indication for cefiderocol use in the real-world practice, reflecting both the underlying disease severity and the high burden of ICU admission[38–40]. Smaller observational studies highlight substantial variability in outcomes according to the infection site, with inferior effectiveness reported in VAP[12,41]. Comparison with colistin-based regimens suggested a possible survival benefit of cefiderocol in CRAB infections overall; however, subgroup analyses focusing on VAP were underpowered and therefore failed to provide informative insights[41,42]. In this context, a single-centre study in critically ill COVID-19 patients with CRAB bacteraemic VAP reported improved 30-day survival with cefiderocol-containing regimens, although interpretation is limited by investigation design, including the relatively small sample size, the selection of antibiotic therapies based on clinical judgement, and the limited use of adjunctive inhaled colistin in addition to intravenous administration, as instead recommended by current international guidelines[11]. More recently, Cascio *et al.* recommended cefiderocol in combination therapy with high-dose ampicillin/sulbactam as second-line option for CRAB VAP[43], consistent with IDSA guidelines, which support sulbactam/durlobactam combined with imipenem/cilastatin as first-line therapy[44]. Clinical and preclinical evidence demonstrated lower mortality rates and more favourable clinical outcomes with this combination, particularly in CRAB-related pulmonary infections, albeit indirectly compared with data reported for cefiderocol[45–48]. Expert consensus increasingly recommends early initiation and optimised dosing of cefiderocol for MDR VAP infections to ensure maximal pulmonary exposure, despite the scarcity of robust comparative data[49].

Real-world evidence also supports the use of cefiderocol in cUTIs, including those caused by MDR-GNB. Although cUTIs have generally been represented as subgroups within larger, heterogeneous cohorts, available data suggest more favourable outcomes than those observed in other infection sites. Retrospective data from both monocentre and multicentre studies demonstrated robust efficacy of

Table 2
Overview of observational studies that evaluated the real-world use of cefiderocol.

Study (year), country	Study design, centres	Number of patients	Setting and population	Main pathogens	Type of infection	Cefiderocol use	Clinical outcome and mortality	Safety	Comments
Zingg *et al.* (2020), Switzerland[56]	Case series, multicentre	8	Critically ill patients	CRAB (*n*=4); *P. aeruginosa* (*n*=3, with 1 CRPA); *K. pneumoniae* (*n*=1, MBL-producing)	Various infections	Rescue therapy	Dead wad reported in one patient (due to complicating infections with vancomycin-resistant enterococci, *Candida glabrata*, and *Clostridoides difficile*)	Well tolerated	–
Bleibtreu *et al.* (2021), France[64]	Retrospective, multicentre	13	Hospitalised patients	P. aeruginosa (*n*=12 with 9 CRPA), CRAB (*n*=2), CRE (*n*=2)	RTI, others	Rescue therapy	Overall clinical cure: 53.8%	Two AEs	–
Falcone *et al.* (2022), Italy[41]	Observational retrospective study, single centre	124 (CFDC 47, COL regimens 77)	Nosocomial CRAB infections	CRAB (*n*=124)	BSI, VAP, others	Combination therapy (*n*=32), monotherapy (*n*=15)	Overall all-cause 30-day mortality: 47.6% [55.8% (COL) *vs.* 34% (CFDC)]	Well tolerated	Mortality difference confirmed in BSI but not in VAP. The rate of microbiological failure was signicantly higher in patients who received monotherapy compared to those who received combination therapy [6/14 (42.9%) *versus* 2/32 (6.3%), *P* = 0.006]
Piccica *et al.* (2023), Italy[40]	Retrospective, multicentre	142	Hospitalised patients, frequent ICU admission	*A. baumannii* (*n*=89, unspecified number of CRAB], *P. aeruginosa* (*n*=27, with 9 CRPA), Enterobacterales (*n*=26, with 23 CRE)	VAP, BSI, SSTI, cUTI, cIAI, others	Rescue therapy; monotherapy (*n*=70) and combination therapy (*n*=72)	All-cause 30-day mortality: 37%	AEs uncommon	No differences in mortality between monotherapy and combination therapy
Palermo *et al.* (2023), Italy[51]	Retrospective, single centre	41	High-complexity patients	CRAB (*n*=31), *P. aeruginosa* (*n*=5, unspecified number of CRPA), Enterobacterales (unspecified numbers)	Pneumonia, BSI	Rescue therapy; monotherapy (*n*=31), combination therapy (*n*=10)	Clinical cure EOT: 56.1% All-cause 30-day mortality: 36.6%	No severe AEs reported	Septic shock was an independent factor associated with mortality. No difference in CFDC effectiveness between monotherapy and combination therapy
Karruli *et al.* (2023), Italy[50]	Observational retrospective study, single centre	28	Hospitalised patients	CRAB [*n*=14 (31.1%)], CRPA [*n*=9 (20%)], *S. maltophilia [n*=7 (16%)], others Enterobacterales (unspecified number of CRE)	RTI, BSI, cIAI, cUTI	Rescue therapy; monotherapy (*n*=22), combination therapy (*n*=6)	Therapeutic success in 64.3% of cases at 7 days and 50% at 14 days	Well tolerated	Option for infections due to colistin-resistant pathogens, when other regimens fail or in cases at risk of kidney dysfunction. The use in monotherapy *vs.* combination therapy did not affect hospital mortality (31.8% *versus* 66.6%, *P*= 0.174)
Clancy *et al.*, PROVE *interim* analysis (2024), USA[39]	Retrospective, multicentre	244	Hospitalised/ICU patients	CRAB, CRE, CRPA [unspecified number, overall 209 (85.7%) were carbapenem-resistant]	RTI, BSI, SSTI, cUTI, BJI, other	Rescue therapy; combination therapy frequently used (*n*=171, 70%)	Overall clinical cure: 64.8% All-cause 30-day mortality: 18.4%	Favourable tolerability profile	Cefiderocol had similar clinical cure and response rates to previous retrospective studies, and lower mortality
Oliva *et al.* (2024), Italy[52]	Observational, single centre	104 (CFDC: 50, COL: 54)	Adults with CRAB BSI	CRAB (*n*=104)	BSI, HAP/VAP	Mostly combination therapy (*n*=78, 75%)	Overall 30-day mortality: 39.4% (CFDC: 36%)	Limited AEs	Clinical cure was higher in CFDC than COL group. Difference between monotherapy and

(*continued on next page*)

Table 2 (*continued*)

Study (year), country	Study design, centres	Number of patients	Setting and population	Main pathogens	Type of infection	Cefiderocol use	Clinical outcome and mortality	Safety	Comments
									combination therapy was not evaluated due to the small sample size
Sollima *et al.* (2024), Italy[61]	Case series	5	CNS infections	CRAB (*n*=1), CRPA (*n*=3), CRE (*n*=1)	CNS infections (meningitis/ ventriculitis)	Combination therapy frequently used (*n*=3)	Dead was reported in one patient (for another fungal infection of the CNS)	Rare AEs	Cefiderocol might be a promising candidate for the treatment of CNS infections
Torre-Cisneros *et al.*, PERSEUS (2025), Spain[38]	Retrospective, multicentre	261	Hospitalised, high-complexity patients	*P. aeruginosa* [*n*=174 (66.7%), including MBL-producers (42%)], Enterobacterales (including CRE), other non-fermenters (unspecified numbers); *Acinetobacter* spp. excluded	RTI, VAP, cIAI, cUTI	Mainly rescue therapy; monotherapy (*n*=170, 65.1%) and combination therapy (*n*=91, 34.9%)	Overall clinical success: 84.3% All-cause 28-day mortality: 21.5%	Rare AEs, low discontinuation rate	Prior antibiotic treatment for > 7 days and mechanical ventilation were independent negative predictive factors for clinical cure. Clinical cure rates were numerically higher among patients receiving monotherapy *versus* those receiving combination therapy (not statistically significant)
Rauch *et al.* (2025), USA[66]	Retrospective, single centre	76	Hospitalised patients	DTR *P. aeruginosa* [*n*=13 (17%)]; CRAB [*n*=9 (12%)]; Enterobacterales [*n*=58 (78%), with 48 CRE], others	VAP, BSI, SSTI, cUTI, cIAI, others	Rescue therapy	Overall 30-day mortality: 20%	Favourable safety profile	Poorer outcomes in *A. baumannii* infections
Augello *et al.*, CEFI-BAC (2025), Italy[7]	Observational retrospective study, multicentre	239	Hospitalised patients, frequent ICU admission	*A. baumannii* [*n*=155 (64.9%), with 153 CRAB], *P. aeruginosa* [*n*=42 (17.6%), with 38 CRPA], *Klebsiella* spp. [*n*=55 (23%), all carbapenemase-producing]; *S. maltophilia* [*n*=21 (8.8%)]; other Enterobacterales	BSI, HAP/VAP, others	Monotherapy (*n*=105) *vs.* combination therapy (*n*=134)	Overall 30-day survival: 71%	Well tolerated	No significant differences in mortality between monotherapy and combination therapy. Independent predictors of higher 30-day mortality were: having received 2 or 3 previous lines of antibiotic therapy, SARS-CoV-2 coinfection and isolation of NDM-producing *Klebsiella* spp.

Legend: *MBL*, metallo-β-lactamase; *CRAB*, carbapenem-resistant *Acinetobacter baumannii*; *CRPA*, carbapenem-resistant *Pseudomonas aeruginosa*; *CRE*, carbapenem-resistant Enterobacterales; *RTI*, respiratory tract infections; *HAP*, hospital-acquired pneumonia; *VAP*, ventilator-associated pneumonia; *cIAI*, complicated intra-abdominal infection; *cUTI*, complicated urinary tract infection; *BJI*, bones and joints infection; *SSTI*, skin and soft tissue infection; *BSI*, bloodstream infection; *EOT*, end of treatment; *AE*, adverse events; *CFDC*, cefiderocol, *COL*, colistin; *CNS*, central nervous system; *ICU*, intensive care unit.

cefiderocol in cUTI treatment[38,40,50,51]. Notably, findings from the PROVE registry reported high clinical response (93.3%) and a remarkably low 30-day mortality (6.7%) in this subgroup, highlighting more favourable outcomes compared with other infections sites[39].

Beyond its approved indications, cefiderocol has been increasingly used in BSIs. Preliminary data from the international PROVE cohort supported its potential role in this context[39]. Likewise, real-world experience from the Italian multicentre CEFI-BAC study recently showed that approximately half of the treated infections were BSIs, with no significant impact of infection site on 30-day survival[7]. Similar findings were observed in a single-centre cohort from Palermo *et al.*, where BSIs accounted for 43.9% of cases and overall clinical efficacy remained favourable[51]. In specific settings, such as CRAB-BSIs, data from Oliva *et al.* suggested that cefiderocol may be associated with lower mortality and higher clinical cure rates than colistin, although these differences did not reach statistical significance[52].

Notably, cefiderocol has been also employed in off-label, compassionate-use settings for selected difficult-to-treat infections, including central nervous system (CNS) infections, osteomyelitis, intra-abdominal infections (IAI), skin and soft tissue infections (SSTI), and endocarditis. However, the evidence base in these clinical scenarios remains predominantly limited to small case series and isolated observational reports, which preclude definitive conclusions. Among patients with IAI included in the cohort by Marino *et al.* (n=8), the overall treatment success rate was 50%[12]. Case reports have also documented the efficacy of cefiderocol in tertiary peritonitis attributable to multidrug-resistant *P. aeruginosa* and complex polymicrobial postoperative IAI[53,54]. Cefiderocol has also shown promise in treating MDR-GNB bone and joint infections. In this context, Babidhan *et al.* documented favourable clinical outcomes and good tolerability in a real-world cohort[55]. Zingg *et al.* reported two cases of acute and post-operative bone and joint infections, demonstrating clinical success with cefiderocol administered as part of combination therapy for polymicrobial infections including CRAB[56]. Alamarat *et al.* further described a successfully treated case of chronic bone infection[57]. Evidence supporting cefiderocol in MDR-GNB endocarditis is also limited to case reports, which document successful outcomes in native and prosthetic valve infections, as well as device-associated endocarditis, particularly when used in combination regimens and alongside appropriate source control[58–60]. Data on CNS penetration and clinical efficacy in Gram-negative meningitis remain scarce. Current evidence is restricted to case reports and preclinical models, suggesting that cefiderocol may achieve therapeutic concentrations in the cerebrospinal fluid, particularly in the presence of meningeal inflammation. While *in vitro* activity against MDR pathogens is promising, robust clinical data supporting its routine use in CNS infections are still lacking[61–63]. Available clinical experiences have primarily described its use in combination with intrathecal or intraventricular polymyxins, reporting favourable results in microbiological and clinical cure outcomes[43]. In the context of SSTI, while sparse real-world data and case reports suggest potential clinical benefit in severe infections caused by MDR-GNB[55,64], solid evidence from prospective studies is lacking.

Type of pathogen

Cefiderocol has emerged as a valuable therapeutic option for treating infections caused by MDR *P. aeruginosa*. While clinical experience remains limited and resistance can emerge during therapy[65], recent guidelines endorse its use for MBL-producing isolates[44]. Real-world studies provide supportive, though non-definitive, evidence. In the PERSEUS study, *P. aeruginosa* accounted for 66.7% of isolates, with cefiderocol achieving a clinical cure rate of 84.5% and 28-day mortality of 17.2%[38]. Similarly, the PROVE study reported an overall cure rate of 70%, including strains resistant to conventional β-lactam/β-lactamase inhibitor combinations[39].

For carbapenem-resistant Enterobacterales, retrospective analyses report high susceptibility rates and clinical outcomes comparable to those observed with other MDR pathogens, highlighting cefiderocol as a valid option when conventional therapies are limited[7,66]. Real-world data demonstrate that cefiderocol maintains *in vitro* activity against NDM-producing isolates, albeit with considerable heterogeneity in susceptibility profiles. Activity is attenuated in a substantial proportion of strains, and documented resistance is frequently associated with elevated MICs[67–70]. Notably, a recent study showed that, among MBLs, the NDM-1 and NDM-5 enzymes are able to hydrolyse cefiderocol at levels sufficient to drive clinically meaningful resistance[28]. This microbiological variability may translate into inferior clinical outcomes, as highlighted by the CEFI-BAC study, in which the isolation of NDM-producing *Klebsiella* spp. was associated with a 6-fold higher risk of 30-day mortality[7]. Recent results suggest that PK/PD-guided dosing optimisation may partially overcome these limitations, further underscoring the potential role of individualised dosing strategies, especially in high-risk populations[71].

Evidence for other difficult-to-treat pathogens remains less robust. In the cohort by Augello *et al.*, CRAB accounted for 64.9% of infections, with an overall favourable 30-day survival (71%); despite the absence of pathogen-specific subanalyses, the microbiological isolate did not appear to influence the mortality, supporting the effectiveness of cefiderocol for the treatment of infections sustained by this pathogen[7]. Piccica *et al.* reported a similar prevalence of *A. baumannii* (62.7%) and found no association between bacterial species and mortality, despite a substantial proportion of isolates exhibiting *in vitro* resistance[40]. Smaller cohorts revealed considerable heterogeneity: Calò *et al.* observed high 30-day mortality (45.7%) among 38 patients with CRAB BSIs and pneumonia[8], whereas Campogiani *et al.* reported a 72.7% clinical success rate and 27.3% mortality in a single-centre series[72]. Collectively, these findings underscore the variability of outcomes in CRAB infections and highlight that, although cefiderocol may achieve meaningful clinical responses in selected patients, its effectiveness is influenced by patient factors, infection severity, and local microbiological characteristics, warranting cautious, individualised use.

Data on *S. maltophilia* infections are limited and heterogeneous. Subgroup analyses from the PERSEUS study reported an overall clinical cure rate of 70%, with lower cure rates and higher mortality among patients with respiratory tract infections[73]. Real-world case series of BSIs have shown clinical success in 62.5% of patients treated with cefiderocol[74]. From a microbiological perspective, a retrospective cohort evaluated cefiderocol use in routine clinical practice, and reported 100% *in vitro* susceptibility among *S. maltophilia* isolates, although the number of cases was limited[66]. Nonetheless, small real-world series and multicentre cohorts report variable clinical outcomes, including relatively high relapse rates and occasional emergence of resistance during therapy[10].

Clinical use of cefiderocol: empirical therapy, timing, and combination strategies

Several studies have investigated the use of cefiderocol both as empirical and targeted therapy in the management of MDR-GNB infections. Large real-world cohorts suggest that empirical administration of cefiderocol may be associated with greater clinical benefit. When compared to the use as targeted therapy, clinical cure rates with cefiderocol used as empirical therapy were numerically higher in both PROVE and PERSEUS cohorts (77.8% *versus* 64.6%, and 90.5% *versus* 78.5%, respectively)[38,39]. Nevertheless, clear criteria or guideline-based recommendations for empirical use are still lacking. Although expert consensus documents provide practical

recommendations[75], real-life decision-making is primarily driven by clinical severity and a history of colonisation or previous infection with MDR-GNB[9]. From an antimicrobial stewardship perspective, identifying patients most likely to benefit from early cefiderocol initiation is crucial to improve clinical outcomes[7], while preserving the activity of this agent and minimising unnecessary exposure, selective pressure, and the potential emergence of resistance. The development and validation of standardised risk stratification tools may help optimise empirical cefiderocol use and ensure its incorporation into clinical practice in compliance with the antimicrobial stewardship principles.

The timing of cefiderocol initiation represents another critical determinant of outcome. Early initiation of therapy has generally been associated with improved clinical outcomes; however, a consistent benefit on 30-day mortality has not been conclusively demonstrated[39,55]. Notably, this concept is further supported by several monocentre and multicentre real-world studies, which have consistently shown that delays in cefiderocol initiation are associated with increased mortality. In the CEFI-BAC study, prior exposure to 2 or 3 previous lines of antibiotic therapy before cefiderocol initiation was associated with a 4- to 7-fold increased risk of 30-day mortality[7]. Similar findings were reported by Rauch *et al.* and Riccobene *et al.*[7,66,76], highlighting the prognostic relevance of early cefiderocol initiation in severe infections caused by MDR-GNB.

No clear consensus or guideline-based recommendation is provided regarding the optimal use of cefiderocol as monotherapy or in combination therapy. A recent expert consensus recommends its use in combination therapy for CRAB BSIs, for instance with ampicillin/sulbactam or fosfomycin, due to their *in vitro* synergic activity[43]. In a meta-analysis by Onorato *et al.*, cefiderocol monotherapy was associated with lower mortality, while no significant differences were observed in clinical or microbiological failure[77]. However, these observations should be interpreted with caution, as they refer to retrospective studies and are therefore subject to relevant selection biases. Additional data from retrospective multicentre cohort studies further reflect the lack of robust evidence. Combination therapy appears to be more frequently employed in patients with CRAB infections and in highly immunocompromised populations, such as haematopoietic stem cell transplant recipients, with no significant advantage in clinical outcomes[8,9]. Similarly, the cohort study by Piccica *et al.* did not identify differences in 30-day mortality, nor in baseline demographic or clinical characteristics, between the two approaches[40]. The CEFI-BAC study provided additional real-world insights: although combination regimens were preferentially used in patients with septic shock and in those colonised with MDR bacteria or who previously stayed in ICU, no differences in clinical outcomes were observed between the two approaches, highlighting a preference of clinicians for combination therapy in patients with more severe infections and in those with risk factors for MDR infections[7]. Pathogen-driven differences were also observed in the same study: cefiderocol monotherapy was more commonly prescribed for CRAB infections, whereas combination regimens were favoured in infections caused by *P. aeruginosa* and *S. maltophilia*. These findings are consistent with observations from other real-world studies[51], but contrast with current guidelines. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) conditionally advises against its routine use due to limited efficacy and safety data[78], while the Infectious Diseases Society of America (IDSA) recommends cefiderocol for CRAB infections only when other treatments fail or are not tolerated, preferably in combination regimens, citing higher recurrence rates (17% *versus* 7% with colistin), frequent resistance emergence (up to 50% of recurrent isolates), and uncertain outcomes in trials[44]. Overall, current evidence suggests that cefiderocol use in clinical practice is primarily guided by clinical severity, host factors, and microbiological considerations, rather than by evidence of differences in efficacy.

Future directions

Cefiderocol represents a relevant therapeutic option in the management of MDR-GNB infections, particularly in clinical contexts with limited treatment alternatives. Data from RCTs and real-world studies suggests that its effectiveness is driven not only by its extensive antimicrobial spectrum against GNB, but mostly by the identification of selected clinical scenarios in which standard therapies are ineffective, poorly tolerated, or associated with toxicity. However, clinical outcomes appear strongly influenced by host-related factors, infection severity, causative pathogen, and timing of treatment initiation, underscoring the importance of tailored approaches. Real-world data have provided further insights into pathogen-driven use of cefiderocol. It has emerged as an effective and viable option for *P. aeruginosa* and CRE, with favourable clinical and microbiological outcomes. In contrast, its therapeutic role in CRAB infections remains controversial due to variable clinical outcomes and limited evidence; therefore, it should be reserved for cases where alternative agents are unavailable or unsuitable. Decisions between monotherapy *versus* combination therapy should be guided by clinical context, with combination regimens typically considered in patients with septic shock, significant bacterial load, or infections caused by pathogens associated with poorer outcomes.

Despite these promising findings, several critical questions remain unsolved. First, there is a need for RCTs that better reflect the complexity of patient populations across different clinical scenarios, including critically ill patients, BSIs, and infections caused by MBL producers. Endpoints should be carefully selected to include infection site and pathogen-specific mortality, ideally with stratification according to underlying resistance mechanisms. Comparative studies of cefiderocol *versus* current SOC regimens could further help to define its therapeutic role. Moreover, key uncertainties persist regarding the clinical relevance of heteroresistance, the potential development of on-therapy resistance, and the optimal use and management of cefiderocol in off-label indications. Addressing these gaps will be essential to fully define the place-in-therapy of cefiderocol in the contemporary antimicrobial landscape.

Conclusions

Cefiderocol should be considered a valuable option for the treatment of MDR-GNB infections. Its efficacy depends largely on appropriate patient selection, early initiation, and strategies guided by antimicrobial stewardship principles. When applied in the proper clinical context, cefiderocol can provide meaningful benefit, but its role still needs to be refined through high-quality clinical trials and real-world evidence.

Declaration of Competing Interest

The authors have no conflicts of interest related to this work to disclose.

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