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PERSPECTIVE

New Perspectives on Antimicrobial Agents: Cefiderocol

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ABSTRACT Bacterial resistance to carbapenem agents has reached alarming levels. Accordingly, collaborative efforts between national and international organizations and the pharmaceutical industry have led to an impressive expansion of commercially available β-lactam agents in recent years. No available agent comes close to the broad range of activity afforded by cefiderocol, a novel siderophore-cephalosporin conjugate. The novelty of and need for cefiderocol are clear, but available clinical data are conflicting, leaving infectious diseases specialists puzzled as to when to prescribe this agent in clinical practice. After a brief overview of cefiderocol pharmacokinetics and pharmacodynamics, safety data, cefiderocol susceptibility testing, and putative mechanisms of cefiderocol resistance, this review focuses on determining cefiderocol's role in the management of specific pathogens, including carbapenem-resistant *Acinetobacter baumannii* complex, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Enterobacterales*, and less commonly identified glucose-nonfermenting organisms such as *Stenotrophomonas maltophilia*, *Burkholderia* species, and *Achromobacter* species. Available preclinical, clinical trial, and postmarketing data are summarized for each organism, and each section concludes with our opinions on where to position cefiderocol as a clinical therapeutic.

KEYWORDS multidrug resistant, Gram negative, *Acinetobacter baumannii* complex, metallo-β-lactamase, *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*

Antibiotic-resistant bacteria are among the most significant threats to public health. Accordingly, efforts by national and international organizations have led to an impressive expansion of commercially available therapeutic agents in recent years, including several targeting carbapenem-resistant pathogens (1). These are welcome additions to the anti-infective arsenal. However, some notable deficiencies remain, including effective therapies for metallo-β-lactamase (MBL)-producing *Enterobacterales* and several glucose-nonfermenting Gram-negative organisms (e.g., *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* complex).

Cefiderocol (formerly S-649266) received U.S. Food and Drug Administration (FDA) approval in October 2019 for the treatment of urinary tract infections (UTIs) and in September 2020 to include hospital-acquired pneumonia and ventilator-associated bacterial pneumonia. Cefiderocol is a synthetic conjugate composed of a cephalosporin moiety and a catechol-type siderophore, which binds to iron and facilitates bacterial cell entry using active iron transporters. Once inside the periplasmic space, it dissociates from iron and the cephalosporin moiety binds primarily to penicillin binding protein 3 to inhibit bacterial cell wall synthesis (2). Cefiderocol's unique chemical structure and mechanism of cell entry may afford it enhanced protection against loss of porin channels, overexpression of efflux pumps, and inactivation by carbapenemases.

Previous siderophore antibiotic candidates failed to demonstrate *in vivo* efficacy despite *in vitro* potency. This is potentially a consequence of downregulation of iron transport

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receptors due to the competition between siderophore-antibiotic conjugates and native siderophore production, which become upregulated in the presence of a threat (3–6). After an overview of cefiderocol pharmacokinetics/pharmacodynamics (PK/PD), safety data, cefiderocol susceptibility testing, and putative mechanisms of resistance to cefiderocol, this review is organized by pathogen. Available preclinical, clinical trial, and postmarketing data are summarized to assist clinicians in determining how best to position cefiderocol for the treatmen7t of carbapenem-resistant infections. Each section concludes with our opinions on prescribing cefiderocol for specific pathogens.

CEFIDEROCOL PK/PD

Similar to other cephalosporins, the PK/PD index for cefiderocol is the percentage of time free drug concentrations exceed the organism MIC during the dosing interval (%$fT>_{MIC}$). The standard dose of cefiderocol is 2 g administered every 8 h as a 3-h infusion with dose adjustments recommended for patients with a creatinine clearance of ≤60 ml/min and an increase in frequency to every 6 h for patients with augmented renal clearance (CL_{CR} ≥120 ml/min). Cefiderocol PK/PD was described in a population PK model developed from 91 uninfected patients and 425 infected patients enrolled in clinical trials (7). The probability of target attainment (PTA) for 100% $fT>_{MIC}$ was >90% against MICs of ≤4 μg/ml across all infection sites (e.g., pneumonia, bloodstream, and urinary tract) and renal function groups, except patients with normal renal function and bloodstream infections where PTA was 85%. Nevertheless, these clinical exposures exceed the PD target of $fT>_{MIC}$ 64 to 77% for 1-$\log_{10}$ growth reduction of *Enterobacterales* and *Pseudomonas aeruginosa* determined by murine thigh and lung infection models (8). High rates of target attainment were also observed for pulmonary epithelial lining fluid in an analysis of critically ill patients with pneumonia (9).

Clinical outcomes of infected patients treated with cefiderocol do not appear to correlate with cefiderocol MIC values. As an example, when evaluating mortality in patients with carbapenem-resistant *Enterobacterales* infections in a phase 3 clinical trial, cefiderocol MICs of 0.06, 0.12, 0.25, 0.5, 1, 2, and 4 μg/ml were associated with 30-day mortalities of 40, 0, 29, 0, 50, 33, and 0%, respectively (10, 11). Although the numbers of isolates in all of these MIC categories were low, no clear trend between cefiderocol MIC and poor outcomes is observed. The impressive exposures achieved with recommended cefiderocol dosing make it unlikely that inadequate PK/PD optimization contribute to clinical failures associated with this agent. Cefiderocol susceptibility criteria recommended by various agencies and committees are provided in Table 1.

CEFIDEROCOL SAFETY

Similar to other beta-lactam antibiotics, cefiderocol is generally well tolerated. In phase 1 evaluations, the most common adverse events reported in clinical trials were increases in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (12). In a phase 3 trial of patients with carbapenem-resistant infections, transaminase elevations were more common in cefiderocol-treated patients compared to best available therapy (30% versus 14%); however, no case met criteria for drug-induced liver injury (11). In a phase 3 trial of patients with nosocomial pneumonia, the proportions of ALT and AST increase between patients receiving cefiderocol and high-dose, extended-infusion meropenem were 13 and 8%, respectively (13). These findings suggest periodic monitoring of liver enzymes should be considered in patients receiving cefiderocol therapy. Considering the unique mechanism of transport into bacterial cells, concerns about adverse events related to iron homeostasis in humans have been raised. In the three published clinical trials to date, anemia-related adverse events and variables related to iron homeostasis (i.e., total iron binding capacity, transferrin concentration) were similar between cefiderocol and comparator arms (11, 13, 14).

CEFIDEROCOL SUSCEPTIBILITY TESTING

Obtaining accurate cefiderocol MICs using broth microdilution (BMD), the reference standard, requires the use of iron-depleted cation-adjusted Mueller-Hinton broth, since

TABLE 1 Cefiderocol susceptibility interpretative criteria, as of February 2021[a]

Organism	CLSI		FDA		EUCAST		USCAST	
	MIC (mg/liter)	Zone diam (mm)	MIC (mg/liter)	Zone diam (mm)	MIC (mg/liter)	Zone diam (mm)	MIC (mg/liter)	Zone diam (mm)
Enterobacterales spp.								
Pneumonia	≤4	≥16	≤4	≥16	≤2	≥22	≤2	–
Nonpneumonia	≤4	≥16	≤4	≥16	≤2	≥22	≤4	–
P. aeruginosa								
Pneumonia	≤4	≥18	≤1	≥22	≤ 2	≥22	≤2	–
Nonpneumonia	≤4	≥18	≤1	≥22	≤ 2	≥22	≤4	–
Acinetobacter spp.	≤4	≥15	≤1	≥19	IE	–	IE	–
S. maltophilia								
Pneumonia	≤1	≥15	–	–	IE	–	IE, ≤2	–
Nonpneumonia	≤1	≥15	–	–	IE	–	IE, ≤4	–

[a]CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, Food and Drug Administration; USCAST, U.S. Committee on Antimicrobial Susceptibility Testing; –, no breakpoint listed; IE, clinical efficacy data are limited, but *in vitro* and pharmacokinetic/pharmacodynamic activity support use in difficult-to-treat cases.

standard cation-adjusted Mueller-Hinton broth does not provide reproducible cefiderocol MICs that reflect anticipated *in vivo* activity (15–17). To elaborate further, the human innate immune system minimizes available free iron during acute bacterial infections. To survive under iron-depleted conditions, bacterial iron transporters are upregulated, which is advantageous for cefiderocol to gain entry into bacterial cells (18). Iron concentrations in laboratory media also need to mimic the *in vivo* state to appropriately determine cefiderocol *in vitro* susceptibility (19). Alternative FDA-cleared cefiderocol antibiotic susceptibility testing approaches are available, including the Sensititre lyophilized broth microdilution panel (Thermo Fisher Scientific, Waltham, MA) and 30-μg cefiderocol HardyDisks (Hardy Diagnostics, Santa Maria, CA). The Sensititre panel includes cefiderocol with an iron chelator embedded in wells, allowing for reconstitution of the panel with standard cation-adjusted Mueller-Hinton broth. Similarly, disk diffusion testing on Mueller-Hinton agar does not require iron depletion, since iron remains sufficiently bound to the agar (20).

Challenges still remain with cefiderocol susceptibility testing. *A. baumannii* susceptibility testing to cefiderocol has proven especially challenging; disk diffusion results have been associated with major errors (20), and BMD interpretation can be difficult due to the existence of trailing endpoints (16, 19, 21). For detailed guidance on interpreting cefiderocol disk and BMD results, we refer the reader to the Clinical and Laboratory Standards Institute (CLSI) M-100 document (10). MIC test strips and the addition of cefiderocol to automated susceptibility testing panels are under development and will facilitate clinical laboratory efforts in timely cefiderocol MIC determination.

CEFIDEROCOL RESISTANCE

Resistance to cefiderocol is complex and not well characterized. Previous experiences describing mutants in the TonB-dependent iron transporter pathway for other siderophore-antibiotic conjugates inform potential resistance targets for cefiderocol. TonB-dependent transporters are bacterial outer membrane proteins that enable the transport of siderophore-iron complexes. They depend on three inner membrane proteins, TonB-ExbB-ExbD, to transduce the necessary energy to the outer membrane for transportation to occur (22). The expression of TonB-dependent receptors is regulated by two-component systems comprising transcriptional regulators (23). Mutations leading to decreased function of components of this pathway can result in MIC increases of siderophore-antibiotic compounds, including cefiderocol (24).

Mutations in the iron transport pathway have been investigated more thoroughly in *A. baumannii* and *P. aeruginosa*, compared to the *Enterobacterales*. The deletion of

TonB-dependent receptors PiuA and PirA in *A. baumannii* decreased the susceptibility of BAL30072 and MC-1, earlier siderophore-conjugated antibiotics, by 4- to 8-fold (23, 25). Frameshift mutations in components of the inner membrane protein complex in *exbD3* or *tonB3 genes* led to significant increases in the MICs of BAL30072 and MC-1 (25). Overexpression of proteins such as the FecIRA operon—a regulator of iron transporter proteins—has been associated with a 4-fold or greater increase in cefiderocol MICs (23, 26–28). Variations in affinities of compounds for specific receptors in this pathway and/or differences in receptor expression levels likely exist; *pirA* deletions in *P. aeruginosa* led to 8 to 16-fold MIC increases for BAL30072 and MC-1, but only a 2-fold increase in cefiderocol MICs (29). However, the deletion of *piuD* led to 2- to 4-fold increases in BAL30072 MICs but increased cefiderocol MICs by 32-fold.

Mutations in the TonB-dependent transporter pathway for the *Enterobacterales* are less defined. Modifications to the *tonB* gene as well as deletions in both *cirA* and *fiu*, which encode two iron transporters specific to *E. coli*, reduced susceptibility to several earlier siderophore conjugated antibiotic candidates (30–33). Similarly, Ito et al. demonstrated that deletions of both *cirA* and *fiu* led to a 16-fold increase in elevations in cefiderocol MICs (2). Significant increases in cefiderocol MICs against *K. pneumoniae* due to mutations in the *baeS* gene, responsible for encoding a sensor kinase protein of the two-component BaeSR signal transduction system, have also been described (26).

Mutations in the *ampC* gene have also been identified as contributing to increased cefiderocol MICs. Shields and colleagues demonstrated a two amino acid deletion in the R2 loop of the AmpC β-lactamase (i.e., a deletion of alanine and leucine at positions 292 and 293) in two *Enterobacter hormaechei* isolates from distinct patients, resulting in cefiderocol nonsusceptibility (34). In another patient with *E. cloacae* complex recovered from a respiratory specimen with a cefiderocol MIC $>16\,\mu$g/ml, an alanine-proline deletion at positions 294 and 295 and a leucine-to-valine substitution at position 296 in AmpC were identified (35). Conformation changes in the R2 loop of AmpC β-lactamases can widen the substrate binding site and trap cephalosporins with bulkier R2 side chains (such as cefiderocol or ceftazidime-avibactam), limiting their effectiveness (36). Shields and colleagues have also shown that median cefiderocol MICs are higher among ceftazidime-avibactam-resistant carbapenem-resistant *Enterobacterales* (CRE) (37). The relative role of deletions, insertions, and amino acid substitutions in AmpC contributing to cefiderocol resistance to *P. aeruginosa* is still being explored. At least one case report describes a patient infected with a *P. aeruginosa* strain with elevated cefiderocol MICs (24). The isolate had mutations in *piuD* and *pirR*, in addition to a leucine-to-phenylalanine change at amino acid position 147 in the AmpC enzyme, making the relative contribution of the amino acid substitution unclear.

Another observation warranting further investigation is that cefiderocol MICs are higher at baseline for NDM-producing isolates compared to other carbapenemases (15). In one surveillance study including 151 international CRE isolates, cefiderocol was active against 98% of isolates (38). On closer inspection, it was active against 100% of 75 KPC-producing *Enterobacterales* isolates, 100% of 32 OXA-48-like isolates, but only 58% of the 12 NDM-producing *Enterobacterales* isolates, using cefiderocol MICs of $\leq 4\,\mu$g/ml as indicative of susceptibility.

Estimates of the frequency of acquired resistance to cefiderocol are currently unknown. Approximately 4 to 15% of isolates (including both *Enterobacterales* and glucose-nonfermenting isolates) from patients in large, randomized trials experienced a $\geq$4-fold increase in cefiderocol MICs after cefiderocol exposure; although these MIC increases did not necessarily translate into frank resistance, using current CLSI criteria (11, 14, 39). Indeed, of the 25 patients who experienced at least a 4-fold increase in MIC, only 3 (12%) isolates had a cefiderocol MIC of >4 mg/liter. It is unclear if an MIC shift that results in an isolate remaining in the susceptible range (e.g., 0.06 mg/liter to 0.25 mg/liter) has clinical relevance. We currently do not have evidence that cefiderocol MIC "creeps" that remain in the susceptible range are associated with treatment failure.

CARBAPENEM-RESISTANT *ACINETOBACTER BAUMANNII*

Carbapenem-resistant *A. baumannii* (CRAB) infections are among the most challenging infections to treat. CRAB is notorious for infecting vulnerable patients such as those requiring mechanical ventilation or with significant loss of skin integrity from burns, natural disasters, or combat-associated wounds (40). Approximately 80% of CRAB produce carbapenemases, including OXA-23-like, OXA-51-like, or OXA-58-like carbapenemases (41–43). Moreover, their multidrug-resistant phenotype is generally due to several mechanisms of resistance occurring in concert: increased AmpC expression, porin mutations, *gyrA* and *parC* mutations, production of aminoglycoside-modifying enzymes, increased expression of RND-type efflux pumps, and β-lactamase production (41). None of the novel, commercially available β-lactam-β-lactamase inhibitor agents (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, meropenem-vaborbactam) provide expanded coverage for CRAB.

***In vitro* data.** Although a number of large surveillance studies investigating the *in vitro* activity of cefiderocol against *A. baumannii* are available, few provide insight on cefiderocol susceptibility data specifically for CRAB (38, 44–50). Together, the available data indicate that of approximately 1,900 carbapenem-nonsusceptible *A. baumannii* isolates, 95% had cefiderocol MICs of $\leq$4 μg/ml (i.e., the CLSI susceptibility breakpoint). Notably, the FDA established a susceptibility breakpoint of $\leq$1 μg/ml, and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) did not establish a susceptibility breakpoint for *A. baumannii* due to a concern for suboptimal clinical outcomes data (Table 1).

Clinical trial data. The efficacy and safety of cefiderocol was investigated in three randomized clinical trials. The first was a phase 2 trial of 251 patients with complicated UTIs that did not include patients with CRAB infections (14).

The second trial (CREDIBLE-CR) was a phase 3, open-label study where 152 patients were randomized to cefiderocol or best available therapy (BAT), the later consisting mostly of polymyxin-based therapy (11). It included 54 critically ill hospitalized patients with CRAB infections, predominantly bacteremia and pneumonia. Patients infected with CRAB composed 46% of the study population, therefore the overall findings of the trial were largely reflective of the subgroup with CRAB infections. End-of-study mortality was 34 and 18% in the cefiderocol and best available therapy arms, respectively. More specifically, in the CRAB subgroup, end-of-study mortality was 50% in the cefiderocol arm versus 18% in the BAT arm. Of note, mortality rates in the best available therapy group were lower than in previously published trials for CRAB, and patients with CRAB had a higher proportion of septic shock in the cefiderocol arm compared to the BAT arm (51–54). Regardless, the findings of the CREDIBLE-CR trial suggest cefiderocol may be associated with poorer outcomes than polymyxin-based regimens for CRAB infections.

The third trial (APEKS-NP) was a phase 3 investigation of 300 patients with nosocomial pneumonia randomized to cefiderocol or high-dose, extended-infusion meropenem (i.e., 2 g intravenously every 8 h, as a 3-h infusion) (39). APEKS-NP included 36 patients with *Acinetobacter* spp. with meropenem MICs of $>$8 μg/ml, with 18 patients receiving cefiderocol and 18 patients receiving meropenem. Overall outcomes between the two arms were similar with a 14-day mortality of 28%, making cefiderocol's role as a therapeutic agent for CRAB pneumonia unclear. The best interpretation of these data is that cefiderocol is as good as an antibiotic with questionable activity against CRAB.

Postmarketing experience. Prior to FDA approval, cefiderocol was available through an expanded access (i.e., compassionate use) pathway, of which 251 requests were granted (10). Thirty-five patients infected with CRAB were included and several of these patient experiences have been published (55–60). The cases describe variable success of cefiderocol for the treatment of CRAB from multiple sites, including osteomyelitis, pneumonia, and bacteremia, often after failures or toxicities associated with polymyxin-based regimens (61, 62). A few cases describe the success of cefiderocol for the treatment of complex hardware-associated infections. This may be related to its

unique mechanism of uptake through the bacterial iron-transport system. Iron is critical for the formation of biofilms, and siderophore production is therefore upregulated in biofilm-forming infections (58–60).

Understanding the contribution of cefiderocol to clinical responses observed in reported cases is challenging as cefiderocol use has generally been limited to recalcitrant infections, often as combination therapy, and generally after most other antibiotic options have been exhausted. In addition, there is likely bias in the cases submitted for publication and their generally favorable clinical outcomes may not be completely representative of real-world clinical cases. Furthermore, critical details such as source control measures and organism susceptibility to other agents administered are often missing in reported cases.

Expert opinion on role in therapy. Despite highly favorable *in vitro* susceptibility data and promising case reports, the position of cefiderocol for CRAB infections remains unclear. There is no "standard care" antibiotic regimen for CRAB against which to measure the effectiveness of other treatment regimens. The "optimal" agent(s) or combination of agents are unknown and supportive data are generally limited to *in vitro* models (63–65). We believe cefiderocol should be limited to salvage therapy for CRAB infections that are refractory to high-intensity combination regimens or if intolerance precludes a combination of other agents. It is unknown whether cefiderocol should be used as monotherapy or combination therapy for CRAB infections. Our preference would be to use it as part of a combination regimen, considering the disappointing clinical trial results for invasive CRAB infections.

Four randomized controlled trials have investigated the role of combination therapy for CRAB infections (51–54). Two trials, with a total of 253 patients, compared colistin monotherapy versus colistin in combination with rifampin for adults with CRAB infections and found no difference in clinical outcomes (53, 54). *In vitro* and animal data indicate rifabutin may be more potent than rifampin (66–68). Clinical outcomes data are needed to determine whether the positive experimental findings observed with rifabutin translate to improved patient outcomes. Despite promising synergy data with rifamycin-based regimens against CRAB isolates, when combining the clinical trial results with their known toxicities and drug interactions, we do not favor these combinations in the absence of more encouraging clinical data (68). Another trial randomized 94 adults with CRAB infections to colistin alone or colistin with intravenous fosfomycin also found no difference in clinical outcomes (51). The unavailability of intravenous fosfomycin in many parts of the world precludes it as an option for many patients. A fourth trial included 312 patients with CRAB infections randomized to colistin versus colistin and high-dose meropenem (52). No difference in outcomes were observed between monotherapy and combination therapy, although 97% of isolates had meropenem MICs of at least 16 μg/ml.

Sulbactam has potent *in vitro* activity against *A. baumannii*, particularly when administered as high doses (i.e., ampicillin-sulbactam daily dosages of at least 27 g per day) (64, 65, 69). For non-severe CRAB infections, we believe high-dose ampicillin-sulbactam (e.g., 9 g intravenously every 8 h [4-h infusion]) is reasonable for isolates with ampicillin-sulbactam MICs of $\leq$16/8 mg/liter. For severe CRAB infections, we favor high-dose ampicillin-sulbactam (regardless of the ampicillin-sulbactam MICs) in combination with a second or third agent which could include polymyxin B, a tetracycline derivative (e.g., minocycline, tigecycline, and eravacycline) or high-dose, extended-infusion carbapenem therapy (e.g., 2 g meropenem administered over 3 h every 8 h) as informed by isolate susceptibility results and patient-specific considerations of drug toxicities and interactions. We favor dose-optimized combination therapy despite the lack of supportive clinical trial data because of the compelling *in vitro* synergy data with sulbactam-based regimens, the limited clinical efficacy data for any individual agent, the likelihood of CRAB to acquire new resistance mechanisms during therapy, and the complex and critically ill patient population at risk for CRAB infections.

Each of the adjunctive therapy options have important concerns. Systemically administered polymyxins do not achieve adequate organism killing in the lungs and

the therapeutic index for non-pulmonary infections is extremely narrow (i.e., ~2 mg/liter may be required to achieve 1-$\log_{10}$ reductions in bacterial growth but this is also the threshold associated with nephrotoxicity) (70–72). Tetracycline-derivatives, such as high-dose tigecycline, high-dose minocycline, or eravacycline, may be reasonable adjunctive therapies, but clinical trial data demonstrating their effectiveness for CRAB infections are lacking. Despite displaying *in vitro* activity, there are no data describing the pharmacodynamic target or optimal dosing regimen for eravacycline for serious CRAB infections.

CARBAPENEM-RESISTANT *PSEUDOMONAS AERUGINOSA*

Similar to CRAB, carbapenem-resistant *Pseudomonas aeruginosa* (CR-*P. aeruginosa*) infections are associated with significant morbidity and mortality, particularly in patients with malignancies, solid organ or hematopoietic stem cell transplants, cystic fibrosis, severe burns, or indwelling hardware (73). Treatment options for CR-*P. aeruginosa* include ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol.

CR-*P. aeruginosa* strains generally evolve because of an interplay of multiple complex resistance mechanisms, including loss or mutations in OprD porins, hyperproduction of AmpC enzymes, upregulation of efflux pumps, and mutations in penicillin-binding protein targets (74, 75). Carbapenemase production rarely contributes to carbapenem-resistance in *P. aeruginosa* in the United States but is identified in upwards of 20% in CR-*P. aeruginosa* in other regions of the world such as Europe, Asia, and Latin America (76–78).

***In vitro* data.** Although large surveillance studies investigating the *in vitro* activity of cefiderocol against *P. aeruginosa* are available, specific susceptibility data for CR-*P. aeruginosa* are limited. The combined data, including more than 1,500 carbapenem-nonsusceptible *P. aeruginosa* isolates, indicate that more than 97% of isolates had cefiderocol MICs of $\leq 4\,\mu$g/ml (38, 44–47, 49, 50). The percentage of cefiderocol-nonsusceptible *P. aeruginosa* isolates differs depending on the susceptibility criteria used (Table 1). Importantly, virtually no patients in these surveillance studies had prior exposure to cefiderocol and susceptibility estimates will need to be reexamined after widespread use of cefiderocol.

Clinical trial data. In the phase 2 trial of cefiderocol versus imipenem-cilastatin for the treatment of adults with complicated UTIs, 23 patients were infected with *P. aeruginosa* of which only four *P. aeruginosa* isolates were carbapenem resistant, leaving us unable to draw meaningful conclusions from this study (14). The small numbers of patients with CR-*P. aeruginosa* in APEKS-NP also limits this trial's ability to address the role of cefiderocol for CR-*P. aeruginosa* pneumonia (39). CREDIBLE-CR included 22 unique patients with 29 total CR-*P. aeruginosa* infections, including six patients with UTIs, 17 patients with pneumonia, and 6 patients with bloodstream infections (11). Mortality at the end of therapy was 18% in both the cefiderocol and best available therapy arms, when limiting the evaluation to CR-*P. aeruginosa*. The CREDIBLE-CR study indicates that cefiderocol performs as well as agents that were the mainstay of treatment against CR-*P. aeruginosa* in the past, such as combinations of extended-infusion meropenem, polymyxins, and aminoglycosides. Since only four patients were exposed to newer β-lactam agents in the CREDIBLE-CR trial, the results do not shed any light on the comparative effectiveness of cefiderocol versus other β-lactams with activity against CR-*P. aeruginosa* (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam).

Postmarketing experience. Seventy-one patients with *P. aeruginosa* infections received cefiderocol via an expanded access pathway, several of which are published in the peer-reviewed literature (10). A number of case reports indicate the successful treatment of CR-*P. aeruginosa* infections with cefiderocol therapy, generally in combination with other agents such as polymyxins (21, 56, 79–83).

Expert opinion on role in therapy. Unlike CRAB infections, there are several β-lactam agents which may be active against CR-*P. aeruginosa*, including ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-cilastatin-relebactam. There are no

comparative effectiveness studies to inform the decision of which of these agents are most effective for treating CR-*P. aeruginosa* infections and how they compare with cefiderocol. In settings where resistance or intolerance to these agents is present or these agents are unavailable, we recommend cefiderocol over polymyxin-based therapy. Although studies comparing cefiderocol monotherapy versus cefiderocol as part of a combination regimen are not available, we favor the addition of a second agent, at least initially, when cefiderocol is prescribed for critically ill patients or for infections where the bacterial burden is expected to be high.

We favor the novel β-lactam-β-lactamase inhibitors over cefiderocol as first-line therapy for CR-*P. aeruginosa* based on available clinical outcomes data. An observational study including 200 patients with drug-resistant *P. aeruginosa* compared the outcomes of patients receiving ceftolozane-tazobactam versus polymyxin or aminoglycoside-based therapy (84). Favorable clinical outcomes were observed in 81% of patients receiving ceftolozane-tazobactam versus 61% of patients receiving polymyxin or aminoglycoside-based therapy. A randomized clinical trial including 24 patients with imipenem-nonsusceptible *P. aeruginosa* identified a favorable clinical response in 81% of patients receiving imipenem-cilastatin-relebactam compared to 63% receiving imipenem-cilastatin in combination with colistin (85). In contrast, in the CREDIBLE-CR study, clinical outcomes for CR-*P. aeruginosa* were not improved when comparing cefiderocol or best available therapy.

CARBAPENEM-RESISTANT *ENTEROBACTERALES*

The *Enterobacterales* are a diverse order of Gram-negative bacilli that cause a variety of infections. The relative proportions of carbapenemase-producing and non-carbapenemase-producing *Enterobacterales* and the distribution of specific carbapenemase gene families vary regionally (86). In the United States, carbapenemase production contributes to slightly less than 50% of carbapenem-resistant *Enterobacterales* (CRE) strains (87–89). Of carbapenemase-producing CRE in the United States, approximately 95% are caused by serine *Klebsiella pneumoniae* carbapenemases (KPCs), and the remainder belong to the MBL or oxacillinase (e.g., OXA-48-like) carbapenemase group (90). Non-carbapenemase-producing CRE generally harbor β-lactamases (e.g., ESBL genes or *ampC* genes) in combination with reduced porin expression (e.g., Ompk35 mutation) or the overexpression of efflux pumps (e.g., the AcrAB-TolC efflux pump) (91). Recent antibiotics have filled critical gaps in the treatment of KPC-producing CRE. However, MBL-producing *Enterobacterales* (which include New Delhi metallo-β-lactamases [NDMs], Verona integron-encoded metallo-β-lactamases [VIMs], and imipenem-hydrolyzing metallo-β-lactamases [IMPs]) continue to have limited treatment options. Unlike all other novel β-lactam agents, cefiderocol is generally active against CRE regardless of whether carbapenemase producing or not and regardless of the presence of serine carbapenemases or MBLs.

***In vitro* data.** Several surveillance studies have investigated the activity of cefiderocol against carbapenem non-susceptible *Enterobacterales*. Overall, evaluating approximately 1,900 carbapenem non-susceptible *Enterobacterales*, cefiderocol MICs were $\leq$4 μg/ml for about 97% of isolates (38, 44–47, 49). In one of these studies, where carbapenemase gene data were included, cefiderocol MICs were $\leq$4 μg/ml against the following CRE: bla_{KPC} ($n = 75$, 100%), bla_{NDM} ($n = 14$, 64%), bla_{VIM} ($n = 53$, 100%), bla_{IMP} ($n = 4$, 100%), and $bla_{OXA\text{-}48\text{-}like}$ ($n = 32$, 100%) and carbapenemase-negative isolates ($n = 420$, 99%) (38).

Clinical trial data. There were too few patients (<3%) with CRE infections in the phase 2 UTI trial to provide meaningful insight into the role of cefiderocol for CRE UTIs (14). In CREDIBLE-CR, CRE was isolated from 44 patients from a variety of specimen sources (respiratory [32%], blood [34%], and urine [34%]) (11). Clinical cure was observed in 66% of patients with CRE infections receiving cefiderocol versus 45% receiving best available therapy. In the 23 patients with MBL-producing infections, 75% (12/16) versus 29% (2/7) achieved clinical cure comparing cefiderocol and best available therapy, respectively. While numbers are small, these data are encouraging.

Unfortunately, this trial does not provide insight into the relative effectiveness of cefiderocol compared to other novel β-lactams for the treatment of CRE infections. APEKS-NP did not include sufficient numbers of patients to further define the role of cefiderocol for CRE infections (39).

Postmarketing experience. Through the expanded access pathway, two of three patients infected with KPC-producing *Enterobacterales*, one of three patients infected with MBL-producing *Enterobacterales*, and two of three patients infected with non-carbapenemase-producing CRE recovered following cefiderocol treatment (10). A few of these experiences have been published along with additional cases that demonstrate the potential role of cefiderocol for treatment of CRE, particularly MBL-producing pathogens (62, 92–94).

Expert opinion on role in therapy. Unlike CRAB or CR-*P. aeruginosa*, there are often several treatment options available for CRE infections. Depending on the specific resistance phenotype, source of infection, severity of illness, and underlying host factors, a variety of agents other than the novel β-lactams may be effective treatment options for CRE infections. For a more nuanced discussion of alternative agents, we refer the reader to the Infectious Diseases Society of America guidance on the treatment of extended-spectrum β-lactamase producing *Enterobacterales*, carbapenem-resistant *Enterobacterales*, and *Pseudomonas aeruginosa* with difficult-to-treat resistance (95).

For severe CRE infections (that are not MBL producing), we favor ceftazidime-avibactam or meropenem-vaborbactam, depending on susceptibility results. Fewer clinical data are available for imipenem-cilastatin-relebactam, but when *in vitro* activity is demonstrated, it is also a consideration. As susceptibility results may not be readily available at the time an organism is identified as a CRE, cefiderocol, is a reasonable alternative when resistance or intolerance to other novel β-lactam agents is demonstrated. This may change as more data become available demonstrating the clinical effectiveness of cefiderocol for the treatment of CRE infections.

For MBL-producing infections, β-lactam options are limited to either cefiderocol or the combination of ceftazidime-avibactam and aztreonam (96). No studies comparing the clinical outcomes between these regimens are available and we believe both are reasonable treatment options.

STENOTROPHOMONAS MALTOPHILIA, BURKHOLDERIA SPECIES, AND *ACHROMOBACTER* SPECIES

Stenotrophomonas maltophilia, *Burkholderia* spp., *Achromobacter* spp., and other glucose-nonfermenting Gram-negative pathogens are rarely recovered in the general population but not uncommonly cause infection in patients with cystic fibrosis, ventilator dependency, or immunocompromising conditions (97). These organisms pose several challenges. First, they are often extensively drug resistant, even in their wild-type form, due to a broad range of resistance mechanisms that vary by species, generally resulting in limited treatment options (97). Second, these organisms are most commonly recovered from respiratory specimens or wounds, and often in polymicrobial specimens. It is not always clear if they represent colonizing organisms and function as "bystanders" in patients who are ill for reasons more attributable to their underlying host status, or if they represent true pathogens, leading to uncertainty about the need for antibiotic therapy and making interpretation of the available, although limited, clinical outcomes data challenging. Third, robust data on the comparative effectiveness of agents commonly used to treat these organisms are virtually nonexistent. Finally, susceptibility criteria to define agents as active against these nonfermenting organisms are outdated because of the rarity of contemporary PK/PD and clinical data to inform updated antibiotic breakpoints.

***In vitro* data.** The numbers of less common nonfermenters included in surveillance studies are limited. As cefiderocol susceptibility criteria are not available for these organisms, interpreting MICs poses challenges (Table 1). A summary of multinational surveillance studies included 94 *Burkholderia cepacia* complex isolates, none of which were

previously exposed to cefiderocol, with the MIC_{90} ranging from 0.03 to 1 μg/ml (15). This collection also included 1,173 *S. maltophilia* isolates with MIC_{90} ranging from 0.25 to 0.5 μg/ml. An evaluation of 246 *Burkholderia pseudomallei* clinical isolates from Australia demonstrated an MIC_{90} of 0.125 mg/liter and cefiderocol MICs ranging from $\leq$0.03 to 16 μg/ml (98). A U.S. study included several nonfermenter species from cancer patients with inhibition by cefiderocol demonstrated at the following concentrations: 100% of 7 *B. cepacia* complex isolates at $\leq$0.25 μg/ml, 100% of 50 *S. maltophilia* isolates at $\leq$4 μg/ml, 100% of 7 *Pantoea* isolates at $\leq$1 μg/ml, 100% of 7 *Sphingomonas paucimobilis* isolates at $\leq$0.5 μg/ml, 100% of 3 *Elizabethkingia meningoseptica* isolates at $\leq$4 μg/ml, and 88% of 8 *Rhizobium radiobacter* isolates at $\leq$4 μg/ml (44).

Clinical trial data. No patients in the cefiderocol phase 2 UTI study were infected with an uncommon glucose-nonfermenting organism (14). In CREDIBLE-CR, five patients were infected with *S. maltophilia*; two of the five were coinfected with CRAB (11). All 5 patients received cefiderocol and four of the five patients did not survive. Four patients in APEKS-NP had *S. maltophilia*, but their outcomes are not described (39). No patients in CREDIBLE-CR or APEKS-NP were infected with *Burkholderia* spp. or *Achromobacter* spp.

Postmarketing experience. There were 27 cases of the less common nonfermenters in the expanded access program (11 *Achromobacter* spp., 13 *B. cepacia* complex, and 3 *S. maltophilia*) (10). Some of these cases have been published. A 79-year-old patient with a ventilator-associated pneumonia with both *S. maltophilia* and NDM-producing *K. pneumoniae* recovered in respiratory specimens achieved clinical success with the use of cefiderocol (62). A 10-year-old female with cystic fibrosis and panresistant *Achromobacter* spp. was successfully treated with 2 weeks of cefiderocol (MIC 32 μg/ml) in addition to bacteriophage therapy (99). Eight cystic fibrosis patients infected with *Achromobacter xylosoxidans* received 12 courses of cefiderocol, mostly as part of a combination regimen, and an appropriate clinical response was observed for 11 of 12 episodes (100). Microbiological clearance was only achieved for one of the 12 patients, although this is not uncommon for cystic fibrosis patients. This patient also received bacteriophage therapy. Finally, a 66-year-old man with *A. xylosoxidans* bacteremia in the setting of a left ventricular assist device received cefiderocol, tigecycline, and piperacillin-tazobactam therapy (80). Cefiderocol was discontinued within 14 days due to thrombocytopenia, with platelet count recovery soon after discontinuation of this agent.

Expert opinion on role in therapy. There are very limited treatment options for all of the less common nonfermenters. Treatment options vary by species. The lack of robust comparative effectiveness studies underscores the difficulty with prioritizing any one regimen. For *S. maltophilia*, commonly used agents for which CLSI susceptibility criteria are available include trimethoprim-sulfamethoxazole (TMP-SMX), minocycline, or levofloxacin. Because ceftazidime is likely to be inactivated by intrinsic L1 and L2 β-lactamases produced by *S. maltophilia*, we do not recommend this agent for the treatment of *S. maltophilia* infections (95). We preferentially select TMP-SMX if *in vitro* susceptibility is demonstrated for *S. maltophilia*, with or without the addition of a second agent based on site of infection, severity of illness, and underlying host factors. We do not have sufficient data to suggest that cefiderocol would be more or less effective than these historically prescribed regimens. For extensively drug-resistant *S. maltophilia*, ceftazidime-avibactam plus aztreonam holds promise as a therapeutic option due to inhibition of its intrinsic L1 metallo- and L2 serine-β-lactamases (96, 101).

Potential treatment options are even more limited for other nonfermenters such as *B. cepacia* complex and *Achromobacter* spp. (102–104). Although there are very little supportive clinical data and virtually no comparative effectiveness studies, we believe cefiderocol is reasonable to consider as first-line therapy, either alone or in combination, for the treatment of rare non-glucose-fermenting Gram-negative pathogens, inferring susceptibility based on *S. maltophilia* CLSI susceptibility criteria (i.e., $\leq$1 μg/ml).

CONCLUSIONS

Cefiderocol is a welcome addition to the antibiotic arsenal. Despite *in vitro* potency and outstanding *in vivo* exposures, more clinical data are needed to determine where to position cefiderocol relative to other agents for the treatment of carbapenem-resistant infections. For MBL-producing infections and less-common nonfermenters, cefiderocol may emerge as preferred therapy. For CR-*P. aeruginosa*, cefiderocol is a reasonable alternative when β-lactam-β-lactamase inhibitors cannot be used (positioned ahead of polymyxin-based regimens in these settings). Finally, for CRAB, cefiderocol is likely to remain as salvage therapy in settings precluding the use of other agents.

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