

In Vitro Activity of Cefiderocol Against a Broad Range of Clinically Important Gram-negative Bacteria

Yoshinori Yamano

Pharmaceutical Research Division, Shionogi & Co, Ltd, Osaka, Japan

Carbapenem-resistant gram-negative bacteria including Enterobacteriaceae as well as nonfermenters, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, have emerged as significant global clinical threats. Although new agents have recently been approved, none are active across the entire range of resistance mechanisms presented by carbapenem-resistant gram-negative bacteria. Cefiderocol, a novel siderophore cephalosporin, has been shown in large surveillance programs and independent in vitro studies to be highly active against all key gram-negative causative pathogens isolated from patients with hospital-acquired or ventilator-associated pneumonia, bloodstream infections, or complicated urinary tract infections. The improved structure, the novel mode of entry into bacteria, and its stability against carbapenemases enables cefiderocol to exhibit high potency against isolates that produce carbapenemases of all classes or are resistant due to porin channel mutations and/or efflux pump overexpression. Resistance to cefiderocol is uncommon and appears to be multifactorial.

Keywords. carbapenem-resistant *Acinetobacter*; carbapenem-resistant Enterobacteriaceae; carbapenem-resistant *Pseudomonas*; cefiderocol; *Stenotrophomonas maltophilia*.

The alarming spread of antimicrobial-resistant pathogens is a significant public health issue. Most importantly, carbapenem-resistant Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* have been designated by the World Health Organization as high-priority pathogens for which new antimicrobials are urgently needed [1, 2]. In addition, *Stenotrophomonas maltophilia*, which is now being recognized as more prevalent in immunocompromised patients, is another difficult-to-treat nonfermenting gram-negative species owing to its intrinsic resistance to carbapenems and other β -lactam antibiotics [3–6].

Recently, several new antimicrobials, such as ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, plazomicin, and eravacycline, have been approved, and their use will help to address globally increased antimicrobial resistance [7–9]. All of these antimicrobials belong to well-established classes of antibiotics such as β -lactams, aminoglycosides, and tetracyclines, with unique features that overcome some of the resistance mechanisms identified in multidrug-resistant gram-negative pathogens. However, these compounds still have certain gaps in their

spectrum of activity against carbapenem-resistant gram-negative bacteria; the new β -lactam- β -lactamase inhibitor (BL-BLI) combinations only restore the activity of the parent antibiotic against some serine-carbapenemases (eg, *Klebsiella pneumoniae* carbapenemase [KPC], oxacillin carbapenemases [OXA]) but not metallo- β -carbapenemases (eg, New Delhi metallo- β -lactamase [NDM]), and the non- β -lactam compounds have limited activity against the nonfermenters [10]. As reported by Nordmann and Poirel, the incidences of different types of enzymes vary greatly in different geographical locations [11].

Cefiderocol is a novel siderophore cephalosporin in development, with activity against a broad range of carbapenem-resistant gram-negative bacteria. Its broad activity is explained by its distinctive mechanism of penetration using active iron transporters and its high stability against all classes of carbapenemases, including serine-carbapenemases (KPC and OXA) but importantly also metallo- β -lactamases (MBLs) such as NDM, Verona integron-encoded metallo- β -lactamase (VIM), imipenemase metallo- β -lactamase (IMP), and L1 [12–14]. The combination of active transport and stability against all β -lactamases provides a uniquely broad spectrum of activity against gram-negative bacteria, including almost all Enterobacteriaceae and nonfermenter species [15].

Correspondence: Y. Yamano, Pharmaceutical Research Division, Shionogi & Co, Ltd, 3-1-1 Futaba-cho, Toyonaka, Osaka 561-0825, Japan (yoshinori.yamano@shionogi.co.jp).

Clinical Infectious Diseases® 2019;69(S7):S544–51

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 DOI: 10.1093/cid/ciz827

MINIMUM INHIBITORY CONCENTRATION DETERMINATION UNDER IRON-DEPLETED CONDITIONS

Cefiderocol mimics the action of natural siderophore molecules and forms a chelate complex with ferric iron at the site of infection, which is followed by binding to the iron transporters

embedded into the outer bacterial membrane [12]. The natural bacterial iron transporters are upregulated under iron-depleted conditions that occur during acute infections. Thus, iron concentration needs to be taken into account when determining the in vitro activity of such antibiotics.

The iron concentration in standard culture media (eg, cation-adjusted Mueller-Hinton broth [CAMHB]) is neither controlled nor limited, and it can vary depending on the manufacturer [16]. To test the in vitro activity of siderophore antibiotic conjugates, iron-depleted media are required to provide reproducible minimum inhibitory concentrations (MICs) that predict in vivo efficacy [17, 18]. The Clinical and Laboratory Standards Institute (CLSI) has approved the use of iron-depleted CAMHB to determine cefiderocol MICs. The growth medium is prepared by removing all cations from the Mueller-Hinton broth through incubation with a cation-binding resin, followed by replenishment of Mg²⁺, Ca²⁺, and Zn⁺ [19].

Based on the preclinical in vivo efficacy and pharmacokinetic/pharmacodynamic (PK/PD) analyses using this MIC testing methodology, provisional susceptible, intermediate, and resistant cefiderocol breakpoints of 4, 8, and 16 µg/mL, respectively, have been approved by CLSI for Enterobacteriaceae, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia* [19]. This was the first case of breakpoints being approved by CLSI prior to approval of a new drug based on in vitro activity and preclinical in vivo PK/PD data.

ACTIVITY AGAINST CLINICAL ISOLATES IN MULTINATIONAL STUDIES

The in vitro activity of cefiderocol has been investigated in small independent and large-scale multinational surveillance

studies. As part of the preclinical development of cefiderocol, large multinational surveillance studies (ie, SIDERO-WT studies) were initiated in North America and Europe [20–22]. In parallel, carbapenem-resistant isolates collected in Europe, North America, South America, and the Asia-Pacific region are being tested in the SIDERO-CR program [23]. In addition, several independent studies to determine cefiderocol activity have included collections of difficult-to-treat carbapenem-resistant pathogens gathered from various countries. The activity of cefiderocol in these studies was compared with that of the recently approved BL-BLI combinations, such as ceftolozane-tazobactam and ceftazidime-avibactam.

In the SIDERO-WT program [20, 21, 24–26], 3 consecutive multinational surveillance studies tested a total of 9205 gram-negative bacterial clinical isolates in 2014–2015, 8954 in 2015–2016, and 10 470 in 2016–2017. The isolates were randomly collected from approximately 100 hospitals in North America (~50) and Europe (~50). The results showed that cefiderocol MICs were low for a range of gram-negative bacterial species (Table 1). Of note, >99% of isolates had low cefiderocol MIC values in each testing period. For Enterobacteriaceae, the minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC₉₀) ranged from 0.25 to 1 µg/mL for *Escherichia coli*, *Klebsiella* spp, *Citrobacter* spp, *Enterobacter* spp, and *Serratia* spp. For the nonfermenters, the MIC₉₀ ranged from 0.03 to 1 µg/mL against *P. aeruginosa*, *Burkholderia cepacia*, and *S. maltophilia*, and from 1 to 4 µg/mL against *A. baumannii*. Importantly, the MIC distribution range of cefiderocol showed peak MIC values between 0.06 µg/mL and 0.12 µg/mL for most of the Enterobacteriaceae, *P. aeruginosa*,

Table 1. Minimum Inhibitory Concentration Required to Inhibit the Growth of 90% of Organisms Against Each Bacterial Species From 3 Annual Consecutive SIDERO-WT Studies

Bacterial Species	SIDERO-WT-2014		SIDERO-WT-2015		SIDERO-WT-2016	
	No. of Test Strains	MIC ₉₀ , µg/mL	No. of Test Strains	MIC ₉₀ , µg/mL	No. of Test Strains	MIC ₉₀ , µg/mL
Enterobacteriaceae	6087	0.5	6013	1	7019	1
<i>Escherichia coli</i>	1529	0.5	1830	1	1780	1
<i>Klebsiella pneumoniae</i>	1526	1	1528	1	1573	1
<i>Klebsiella oxytoca</i>	505	0.25	389	0.5	540	0.25
<i>Citrobacter freundii</i>	303	0.5	252	1	273	0.5
<i>Citrobacter koseri</i>	172	0.5	169	0.5	176	1
<i>Enterobacter cloacae</i>	514	1	594	1	692	1
<i>Enterobacter aerogenes</i>	442	0.5	244	0.5	331	0.5
<i>Serratia marcescens</i>	927	0.25	776	0.5	679	0.5
<i>Serratia</i> spp	996	0.25	794	0.5	718	0.5
<i>Morganella morganii</i>	NT	NT	NT	NT	195	0.25
<i>Proteus vulgaris</i>	NT	NT	NT	NT	40	0.12
<i>Proteus mirabilis</i>	NT	NT	NT	NT	329	0.25
<i>Pseudomonas aeruginosa</i>	1530	0.5	1540	0.5	1872	0.5
<i>Acinetobacter baumannii</i>	1148	1	837	2	911	4
<i>Burkholderia cepacia</i>	12	1	45	0.12	37	0.03
<i>Stenotrophomonas maltophilia</i>	428	0.25	340	0.5	405	0.25

Source: Adapted from [20, 21, 25, 26].

Abbreviations: MIC₉₀, minimum inhibitory concentration required to inhibit the growth of 90% of organisms; NT, not tested.

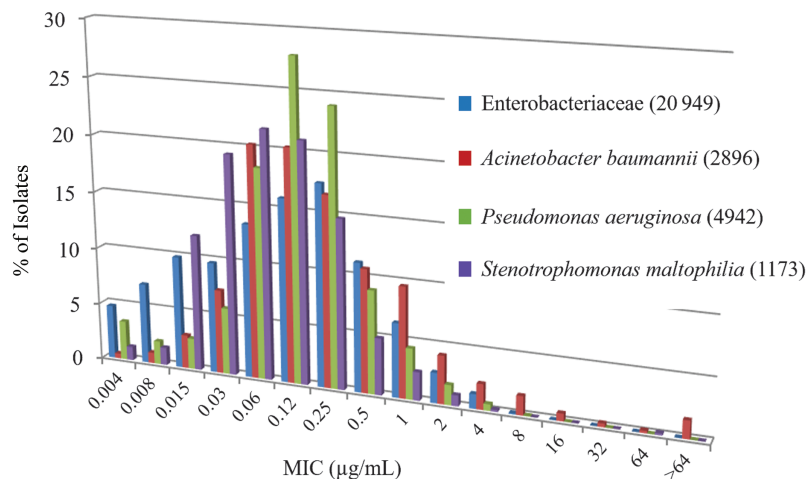


Figure 1. Minimum inhibitory concentration distribution of Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* combined from 3 annual consecutive SIDERO-WT studies. Adapted from [20, 21, 24–40]. Abbreviation: MIC, minimum inhibitory concentration.

A. baumannii, and *S. maltophilia* isolates (Figure 1). These results demonstrate that ceftiderocol has potent activity against a wide variety of gram-negative bacterial species. The surveillance program also demonstrated that ceftiderocol was highly active even against the carbapenem-resistant gram-negative strains of Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii* [20–22, 24–40].

Analysis of the subpopulation of meropenem-nonsusceptible isolates of the SIDERO-WT studies [20–22, 35, 38] showed that, in the 3 sequential collection periods, ceftiderocol was also active against meropenem-nonsusceptible strains of Enterobacteriaceae with MIC₉₀ values of 1/4/4 µg/mL, with MIC₉₀ values of 0.5/1/1 µg/mL against strains of *P. aeruginosa*, and with MIC₉₀ values of 1/2/4 µg/mL against strains of *A. baumannii*, respectively. Furthermore, ceftiderocol demonstrated activity against meropenem-susceptible strains of Enterobacteriaceae with MIC₉₀ values of 0.5/1/1 µg/mL, with MIC₉₀ values of 0.5/0.5/0.5 µg/mL against strains of *P. aeruginosa*, and with MIC₉₀ values of 1/2/4 µg/mL against strains of *A. baumannii*, respectively in the same periods. These results showed that no significant increase of MIC was observed in the presence of meropenem resistance. Of note, ceftiderocol suppressed the growth of 97.0%/99.6%/98.7% of meropenem-nonsusceptible strains of Enterobacteriaceae, 100%/99.7%/100% of *P. aeruginosa*, 96.9%/96.1%/91.0% of *A. baumannii*, and 100%/99.4%/100% of *S. maltophilia* at ≤4 µg/mL in the 3 consecutive collection periods [20, 21, 24, 35, 38, 40].

The SIDERO-CR-2014/2016 program collected carbapenem-nonsusceptible clinical isolates, including carbapenem-nonsusceptible Enterobacteriaceae, multidrug-resistant (MDR) *A. baumannii*, MDR *P. aeruginosa*, and *S. maltophilia*, from 52 countries (in North America, South America, Europe, Asia-Pacific, and Africa) between 2014 and 2016 [23, 41, 42].

The studies showed that ceftiderocol suppressed the growth of 96.2% of these isolates at ≤4 µg/mL [23]. Against 1022 strains of carbapenem-nonsusceptible Enterobacteriaceae, including 23.0% ceftazidime-avibactam-resistant strains and 22.2% colistin-resistant isolates, ceftiderocol MIC₉₀ was 4 µg/mL and it suppressed the growth of 97.0% of the isolates at ≤4 µg/mL [23, 41]. Against 368 MDR *A. baumannii*, 262 MDR *P. aeruginosa*, and 217 *S. maltophilia* isolates, ceftiderocol MIC₉₀ values were 8, 1, and 0.25 µg/mL, respectively, and it inhibited the growth of 90.9%, 99.2%, and 100% of the isolates at ≤4 µg/mL, respectively [23]. It should be noted that 71.4% of MDR *P. aeruginosa* strains were ceftolozane-tazobactam resistant and 5.4% of MDR *A. baumannii* strains were colistin resistant. The susceptibility ratios of ceftiderocol against these isolates were significantly larger than those of the comparators, such as ceftazidime-avibactam, ceftolozane-tazobactam, and colistin (Table 2) [23].

In vitro activity of ceftiderocol has been demonstrated in a multinational randomized phase 2 clinical study that enrolled patients with complicated urinary tract infections, and a small proportion with acute uncomplicated pyelonephritis [43]. The majority of causative pathogens were Enterobacteriaceae spp, although a small proportion of patients were infected with *P. aeruginosa*. All species had ceftiderocol MIC₉₀ values of ≤4 µg/mL, and only a small number of *K. pneumoniae* had a ceftiderocol MIC of 8 µg/mL, suggesting a very high susceptibility rate among clinically relevant pathogens of urinary tract infections [43].

ACTIVITY AGAINST CARBAPENEMASE PRODUCERS

The recently approved BL-BLI combination drugs, such as ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam, have been shown to be active against only KPC and/or OXA-48 producers, and not against

Table 2. Susceptibility Ratio to Cefiderocol and Comparators of Carbapenem-resistant Isolates From the SIDERO-CR-2014/2016 Study

Species (No. of Strains)	Ratio of Susceptible Strains ^a , (%)				
	Cefiderocol	Ceftazidime-avibactam	Ceftolozane-tazobactam	Ciprofloxacin	Colistin
Carbapenem-nonsusceptible strains ^b					
Enterobacteriaceae (1022)	97.0	77.0	1.7	11.5	77.8 ^c
<i>Pseudomonas aeruginosa</i> (262)	99.2	36.3	24.1	1.2	99.6
<i>Acinetobacter baumannii</i> (368)	90.9	NA	NA	0	94.6
<i>Stenotrophomonas maltophilia</i> (217)	100 ^e	NA	NA	NA	NA

Source: Adapted from [23].

Abbreviation: NA, susceptibility breakpoints not available.

^aRatio of susceptible strains (%) was calculated using the following minimum inhibitory concentration (MIC) criteria: cefiderocol MIC $\leq 4 \mu\text{g/mL}$; ceftazidime-avibactam MIC $\leq 8 \mu\text{g/mL}$; ceftolozane-tazobactam MIC $\leq 2 \mu\text{g/mL}$ for Enterobacteriaceae, $\leq 4 \mu\text{g/mL}$ for nonfermenters; ciprofloxacin MIC $\leq 1 \mu\text{g/mL}$; colistin MIC $\leq 2 \mu\text{g/mL}$.

^bCarbapenem-nonsusceptible strain was defined as meropenem MIC $\geq 2 \mu\text{g/mL}$ for Enterobacteriaceae, $\geq 4 \mu\text{g/mL}$ for nonfermenters.

^cIncludes 39 *Serratia* species that are intrinsically resistant to colistin.

other carbapenemase-producing organisms, suggesting that rapid diagnosis of specific carbapenemase enzymes using molecular methods will be important in guiding antibiotic selection. Investigation of the carbapenemase production profile of the isolates from the SIDERO-CR-2014/2016 study showed some variation in the carbapenemase enzymes between regions (Figure 2A) and countries (Figure 2B) [38, 44].

These new results from the SIDERO-CR study [44] showed that cefiderocol had potent activity against each carbapenemase-producing organism, irrespective of the bacterial species and the carbapenemase molecular types (class A such as KPC and Guiana extended-spectrum β -lactamase [GES]; class B such as VIM, NDM, and IMP; and class D such as OXA-23, -24/40, -48, and -58) with MIC₉₀ values of 0.5–8 $\mu\text{g/mL}$ (Figure 3). One feature was that cefiderocol was active against class B MBL producers such as NDM, VIM, and IMP; this finding is in contrast to the profile of the recently approved BL-BLI combination drugs [22]. The activity of cefiderocol against a broad range of pathogens

harboring carbapenemases could be due to the unique mode of action of cefiderocol, which is described in detail by Sato and Yamawaki [45].

ACTIVITY AGAINST COLLECTIONS OF DIFFICULT-TO-TREAT PATHOGENS

Among multiple independent studies, Rolston et al reported that cefiderocol showed activity against 478 gram-negative clinical isolates from the MD Anderson Cancer Center [46]. In this study, composed mostly of blood culture isolates, 97% had a cefiderocol MIC of $\leq 4 \mu\text{g/mL}$. Cefiderocol was shown to be active against less common pathogens such as *Achromobacter* spp. (MIC₉₀ of 0.125 $\mu\text{g/mL}$), as well as MDR *P. aeruginosa*, *Acinetobacter* spp, and *S. maltophilia*, with MIC₉₀ values of 1, 4, and 0.25 $\mu\text{g/mL}$, respectively [46]. The authors also found that cefiderocol inhibited the growth at $\leq 8 \mu\text{g/mL}$ against clinical isolates of *Pantoea* spp, *Sphingomonas paucimobilis*, *Rhizobium radiobacter*, and *Elizabethkingia meningoseptica*. Separately, Robertson et al

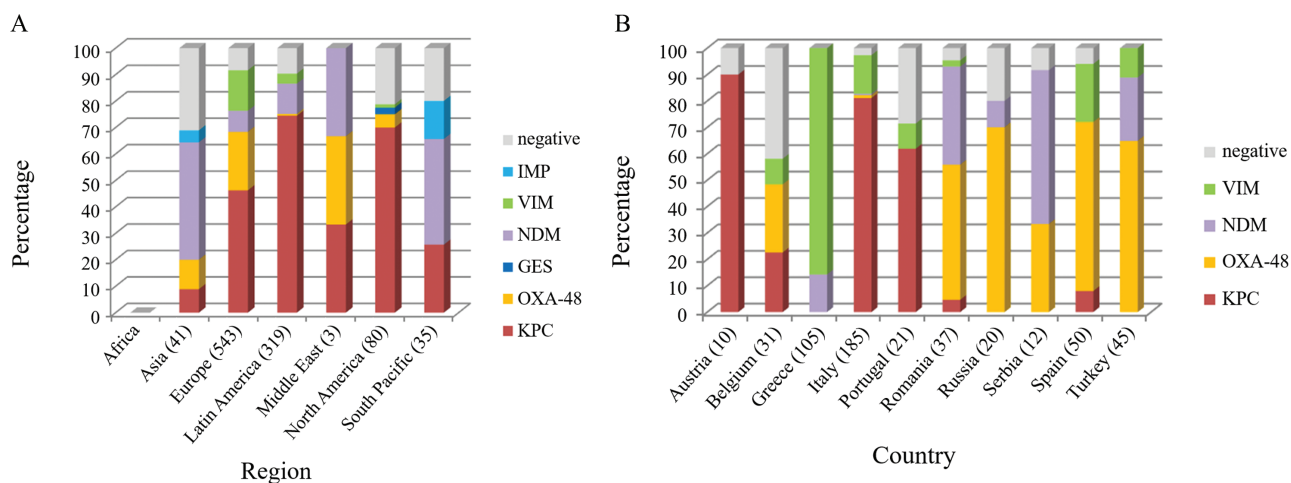


Figure 2. Distribution of carbapenemases produced by carbapenem-resistant Enterobacteriaceae, from the SIDERO-CR study between regions (A) and countries (B). Adapted from [38, 44]. Abbreviations: GES, Guiana extended-spectrum β -lactamase; IMP, imipenemase metallo- β -lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo- β -lactamase; OXA, oxacillin carbapenemase; VIM, Verona integron-encoded metallo- β -lactamase.

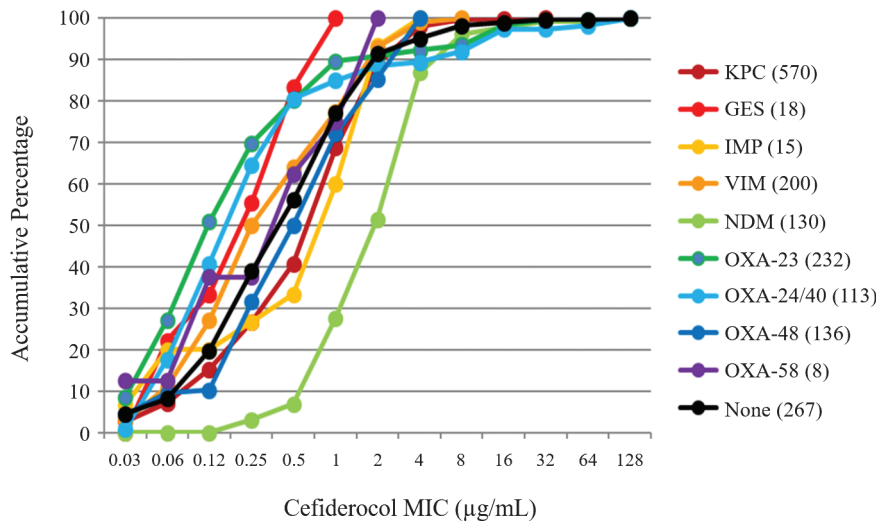


Figure 3. In vitro activity of cefiderocol against various carbapenemase producers from the SIDERO-CR study. Adapted from [23, 44]. Abbreviations: GES, Guiana extended-spectrum β -lactamase; IMP, imipenemase metallo- β -lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimum inhibitory concentration; NDM, New Delhi metallo- β -lactamase; OXA, oxacillin carbapenemase; VIM, Verona integron-encoded metallo- β -lactamase.

reported that cefiderocol was active against 185 clinical isolates of a biothreat pathogen, *Burkholderia pseudomallei*, which was isolated in Northern Australia, with an MIC₉₀ of 0.125 μ g/mL [47]. These results show that cefiderocol has in vitro activity against a wide variety of gram-negative bacteria including carbapenem-resistant Enterobacteriaceae and nonfermenters.

The potent activity of cefiderocol against carbapenem-resistant gram-negative bacteria including various carbapenemase producers was also demonstrated separately by external investigators who conducted multiple independent studies using a collection of difficult-to-treat carbapenem-resistant pathogens. Cefiderocol was shown to be effective against a collection of carbapenem-resistant gram-negative pathogens from Greek hospitals. Activity against *A. baumannii* (n = 107), *P. aeruginosa* (n = 82), *K. pneumoniae* (n = 244), and *Enterobacter cloacae* (n = 14) was demonstrated by MIC₉₀ values of 0.5, 0.5, 1, and 1 μ g/mL, respectively [48]. In a study that investigated a worldwide collection of isolates from hospitalized patients, cefiderocol was shown to be active with an MIC₉₀ of 2 μ g/mL against 753 MDR gram-negative bacteria, including 164 *E. coli*, 298 *K. pneumoniae*, 159 *Enterobacter* species, 45 *P. aeruginosa*, and 87 *A. baumannii* isolates. These also included 127 KPC-producing Enterobacteriaceae, 154 OXA-48 producing Enterobacteriaceae, 134 MBL-producing Enterobacteriaceae (NDM, VIM, or IMP), 74 colistin-resistant Enterobacteriaceae (15 mobilized colistin resistance [MCR]-1 producers), 30 carbapenemase-producing *P. aeruginosa* (IMP, KPC, VIM, São Paulo metallo- β -lactamase [SPM], or German imipenemase [GIM]), and 85 OXA-producing *A. baumannii* (OXA-23, -40, -58, or -72). Cefiderocol suppressed the growth of 733 of 753 isolates at concentrations of ≤ 4 μ g/mL [49].

The in vitro activity of cefiderocol against carbapenem-resistant gram-negative pathogens was also investigated by the Antibacterial Resistance Leadership Group. The results of this independent study showed that the MIC₉₀ values against *A. baumannii*, *S. maltophilia*, and *P. aeruginosa* were 1, 0.25, and 0.5 μ g/mL, respectively [50]. For Enterobacteriaceae, the MIC₉₀ was 1 μ g/mL in isolates harboring OXA-48 carbapenemase, 2 μ g/mL in isolates with KPC-3, and 8 μ g/mL for the group of isolates harboring Temoneira class A extended-spectrum β -lactamase (TEM)/sulfhydryl variant of the TEM enzyme extended-spectrum β -lactamase (SHV), NDM, and KPC-2 [50].

A recent study conducted by Public Health England investigated the activity of cefiderocol against 210 carbapenem-resistant nonfermenting clinical isolates from the United Kingdom with diverse carbapenemase production profiles [51]. Against 111 carbapenem-resistant *P. aeruginosa* clinical isolates from the United Kingdom, cefiderocol inhibited 86.5% of all isolates at ≤ 4 μ g/mL, except for those with NDM (72.7%) and Pseudomonas extended resistant (PER) (73.3%) β -lactamases. Against 99 carbapenem-resistant *A. baumannii* clinical isolates, cefiderocol inhibited 88.9% of all isolates at ≤ 4 μ g/mL, except for those with NDM (80.0%) [51]. Cefiderocol was also shown to be effective against well-characterized carbapenem-resistant Enterobacteriaceae, including the isolates with the mutation in KPC genes involving the Ω -loop insertion, which has been reported to occur in patients during treatment with ceftazidime-avibactam. In this collection of isolates, cefiderocol showed an MIC₉₀ of 4 μ g/mL and an 8% resistance rate, whereas ceftazidime-avibactam showed an MIC₉₀ of >8 μ g/mL and a 14% resistance rate [52].

In summary, ceftiderocol has been shown to have potent antimicrobial activity against a wide variety of carbapenemase-producing carbapenem-resistant bacterial species that were collected globally or from selected countries. The acquisition of resistance to ceftiderocol mediated by specific carbapenemase production has not been observed, although the susceptibility rate was lower for NDM producers than for other carbapenemase-producing organisms.

RESISTANCE MECHANISMS TO CEFTIDEROCOL

In the ongoing SIDERO-WT surveillance program, a low proportion of ceftiderocol-nonsusceptible isolates, with an MIC of >4 $\mu\text{g/mL}$, was observed (ie, 0.4% in 2014–2015; 0.6% in 2015–2016; and 0.7% in 2016–2017, respectively). Among a total of 161 isolates with a ceftiderocol MIC of >4 $\mu\text{g/mL}$, the most frequent species was *A. baumannii* ($n = 127$), followed by Enterobacteriaceae ($n = 28$) [20–22]. In the SIDERO-CR program ($N = 1873$ isolates), 3.8% ($n = 72$ isolates) were ceftiderocol-nonsusceptible, and the most frequent species were *A. baumannii* ($n = 38$) and Enterobacteriaceae ($n = 31$) [23].

Whole genome nucleotide sequence analysis of 111 isolates with ceftiderocol MIC >4 $\mu\text{g/mL}$ from the SIDERO-WT-2014 [20] and SIDERO-CR [23] studies showed that the most common isolates were 57 PER-producing *A. baumannii* (most frequently in Russia [$n = 33$], and Turkey [$n = 12$]) and 25 NDM-producing Enterobacteriaceae (including *E. cloacae* and *K. pneumoniae*; 8 from Guatemala, 5 from Turkey) [27, 53], and interestingly, these isolates were found only in specific countries.

Further investigations have revealed that ceftiderocol resistance could be reverted in the presence of BLIs, suggesting that the production of β -lactamases might have been responsible for the elevated ceftiderocol MICs in almost all cases. In MBL-producing organisms, including NDM-producing Enterobacteriaceae, the elevated ceftiderocol MIC was not decreased in the presence of metallo- β -lactamase inhibitors, although the MIC was decreased when both metallo- and serine- β -lactamases were inhibited. These results suggest that not only NDM production but also the simultaneous production of NDM and some serine- β -lactamases could lead to ceftiderocol resistance.

Against all non-NDM/VIM producers, mainly PER-producing *A. baumannii*, ceftiderocol resistance was suppressed by the addition of avibactam. This suggests that combination with avibactam could be effective against ceftiderocol-resistant isolates without MBL production. However, ceftiderocol showed an MIC₉₀ of 1 $\mu\text{g/mL}$ against other PER-producing bacteria, suggesting that PER expression alone might not be the cause of ceftiderocol resistance.

From these results, ceftiderocol resistance in clinical isolates was mainly due to the production of β -lactamases, and PER and

NDM could be important factors responsible for ceftiderocol resistance, although NDM or PER production alone might not be sufficient to cause ceftiderocol resistance [27, 53].

CONCLUSIONS

Ceftiderocol shows potent activity against both carbapenem-susceptible and nonsusceptible/resistant gram-negative bacteria, almost irrespective of the type of carbapenemases, although some NDM producers showed an elevated MIC. The enhanced activity of ceftiderocol against gram-negative bacteria could be due to the combination of rapid penetration via iron transport channels and high stability to both serine- and metallo-carbapenemases. The ongoing SIDERO-WT and SIDERO-CR surveillance studies will continue to monitor resistance rates to ceftiderocol globally.

Notes

Acknowledgments. The authors thank M. Hackel, D. F. Sahm, K. M. Kazmierczak, and colleagues, International Health Management Associates Inc (Schaumburg, Illinois), for their ongoing contribution to the SIDERO surveillance programs. Editorial support was provided by Highfield (Oxford, United Kingdom), sponsored by Shionogi Inc (Florham Park, New Jersey).

Financial support. This review article is sponsored by Shionogi & Co, Ltd (Osaka, Japan).

Supplement sponsorship. This supplement is sponsored by Shionogi & Co., Ltd.

Potential conflicts of interest. Y. Y. is an employee of Shionogi & Co, Ltd. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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