AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

EXPERIMENTAL THERAPEUTICS

Activity of Cefiderocol Alone and in Combination with Levofloxacin, Minocycline, Polymyxin B, or Trimethoprim-Sulfamethoxazole against Multidrug-Resistant *Stenotrophomonas maltophilia*

M. Biagi,[a] A. Vialichka,[a] M. Jurkovic,[a] T. Wu,[a] A. Shajee,[a] M. Lee,[a] S. Patel,[a] R. E. Mendes,[b] E. Wenzler[a]

[a]College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, USA
[b]JMI Laboratories, North Liberty, Iowa, USA

ABSTRACT The production of an L1 metallo-β-lactamase and an L2 serine active-site β-lactamase precludes the use of β-lactams for the treatment of *Stenotrophomonas maltophilia* infections. Preclinical data suggest that cefiderocol is the first approved β-lactam with reliable activity against *S. maltophilia*, but data on strains resistant to current first-line agents are limited, and no studies have assessed cefiderocol-based combinations. The objective of this study was to evaluate and compare the *in vitro* activity of cefiderocol alone and in combination with levofloxacin, minocycline, polymyxin B, or trimethoprim-sulfamethoxazole (TMP-SMZ) against a collection of highly resistant clinical *S. maltophilia* isolates. For this purpose, the MICs of cefiderocol, ceftazidime, levofloxacin, minocycline, polymyxin B, and TMP-SMZ for 37 *S. maltophilia* isolates not susceptible to levofloxacin and/or TMP-SMZ were determined. Nine strains with various cefiderocol MICs were then tested in time-kill experiments with cefiderocol alone and in combination with comparators. The only agents for which susceptibility rates exceeded 40% were cefiderocol (100%) and minocycline (97.3%). Cefiderocol displayed the lowest MIC_{50} and MIC_{90} values (0.125 and 0.5 mg/liter, respectively). In time-kill experiments, synergy was observed when cefiderocol was combined with levofloxacin, minocycline, polymyxin B, or TMP-SMZ against 4/9 (44.4%), 6/9 (66.7%), 5/9 (55.5%), and 6/9 (66.7%) isolates, respectively. These data suggest that cefiderocol displays potent *in vitro* activity against *S. maltophilia*, including strains resistant to currently preferred agents. Future dynamic and *in vivo* studies of cefiderocol alone and in combination are warranted to further define cefiderocol's synergistic capabilities and its place in therapy for *S. maltophilia* infections.

KEYWORDS cefiderocol, *Stenotrophomonas maltophilia*, synergy, antimicrobial combinations

The development of novel antimicrobials has improved the efficacy and reduced the toxicity associated with treating some important multidrug-resistant (MDR) Gram-negative pathogens, such as carbapenem-resistant *Enterobacterales* (1–3) and *Pseudomonas aeruginosa* (4–6). However, although *Stenotrophomonas maltophilia* is the most prevalent carbapenem-resistant Gram-negative bloodstream pathogen in the United States and is associated with significant morbidity and mortality (7, 8), treatment strategies for this pathogen have not advanced in more than a decade (9). This is due in large part to the myriad resistance mechanisms possessed by *S. maltophilia*, including aminoglycoside-modifying enzymes, multidrug efflux pumps, and two intrinsic, inducible β-lactamase enzymes, the L1 metallo-β-lactamase and the L2 serine active-site β-lactamase (9). This broad array of resistance mechanisms has confined treatment

Citation Biagi M, Vialichka A, Jurkovic M, Wu T, Shajee A, Lee M, Patel S, Mendes RE, Wenzler E. 2020. Activity of cefiderocol alone and in combination with levofloxacin, minocycline, polymyxin B, or trimethoprim-sulfamethoxazole against multidrug-resistant *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 64:e00559-20. https://doi.org/10.1128/AAC.00559-20.

Address correspondence to E. Wenzler, wenzler@uic.edu.

Received 23 March 2020
Returned for modification 21 April 2020
Accepted 13 June 2020
Accepted manuscript posted online 22 June 2020
Published 20 August 2020

TABLE 1 Activities of cefiderocol and comparator agents against 37 clinical *Stenotrophomonas maltophilia* isolates nonsusceptible to levofloxacin and/or trimethoprim-sulfamethoxazole

	MIC (mg/liter)			Susceptibility[a] (%)		
Agent	50%	90%	Range	S	I	R
Cefiderocol	0.125	0.5	<0.03 to 1	100	0	0
Ceftazidime	64	>128	1 to >128	16.2	2.7	81.1
Levofloxacin	8	>16	0.25 to >16	35.1	13.5	51.4
Minocycline	2	4	0.125 to 8	97.3	2.7	0
Polymyxin B[b]	0.5	>8	0.03 to >8	0	75.7	24.3
TMP-SMZ[c]	8	>8	0.03 to >8	37.8	0	62.2

[a]S, susceptible; I, intermediate; R, resistant.
[b]Based on CLSI interpretive criteria for *Pseudomonas aeruginosa*.
[c]Values given reflect the MIC of the trimethoprim component only.

to agents with increasing reports of resistance, high toxicity, and limited data with which to guide optimal dosing strategies (10–15).

Cefiderocol is a novel catechol-substituted siderophore cephalosporin with potent activity against MDR Gram-negative pathogens producing an array of β-lactamases, including both serine enzymes and metalloenzymes (16). Multiple studies including approximately 1,000 isolates have reported promising results on the *in vitro* activity of cefiderocol against *S. maltophilia*, consistently demonstrating MIC_{90} values from 0.12 to 0.5 mg/liter (17–21). Additionally, *in vivo* murine thigh and lung infection models confirm the potent efficacy of cefiderocol against *S. maltophilia* (22, 23). Unfortunately, these *in vivo* analyses included few levofloxacin- and/or trimethoprim-sulfamethoxazole (TMP-SMZ)-resistant isolates and no minocycline-resistant isolates, and they did not evaluate the activity of cefiderocol relative to that of clinically relevant comparators such as levofloxacin, minocycline, or TMP-SMZ. Additionally, the role of cefiderocol-based combination regimens has not been explored to assess the potential for *in vitro* synergy against this difficult-to-treat pathogen. As such, the objective of this study was to evaluate and compare the *in vitro* activity of cefiderocol alone and its activity in combination with levofloxacin, minocycline, polymyxin B, or TMP-SMZ against a global collection of highly resistant clinical *S. maltophilia* isolates.

RESULTS

The MIC_{50}, MIC_{90}, and MIC range of each agent against all 37 isolates are summarized in Table 1. All isolates (100%) were susceptible to cefiderocol, and its MIC_{50} and MIC_{90} values were the lowest among those of all agents, at 0.125 and 0.5 mg/liter, respectively. Minocycline was the only other agent to which ≥40% of isolates were susceptible, at 97.3%. Based on CLSI interpretative criteria for *P. aeruginosa*, 28/37 (75.7%) isolates were intermediate to polymyxin B and 9/37 (24.3%) were resistant. Only 6/37 (16.2%), 13/37 (35.1%), and 14/37 (37.8%) isolates were susceptible to ceftazidime, levofloxacin, and TMP-SMZ, respectively.

Table 2 displays the MIC values of cefiderocol and comparator agents against the nine *S. maltophilia* isolates selected for time-kill experiments. Cefiderocol MICs spanned nearly every doubling dilution, from 0.03 to 1 mg/liter, and there was an adequate distribution of resistant phenotypes across the other four comparators. Five (55.5%) isolates were susceptible to levofloxacin (MIC range, 1 to >16 mg/liter), 8 (88.9%) were susceptible to minocycline (MIC range, 0.125 to 8 mg/liter), 6 (66.7%) were intermediate to polymyxin B (MIC range, 0.125 to >8 mg/liter), and 3/9 (33.3%) were susceptible to TMP-SMZ (MIC ranges, 0.25 and 4.75 to >8 and 152 mg/liter for TMP and SMZ, respectively). No cross-resistance between cefiderocol and the comparator agents was observed, since none of the nine isolates were susceptible to all five agents, and the isolate that was least susceptible to cefiderocol (SM-7) was not resistant to any other agent, while the isolate that was most resistant to the four comparators (SM-9) demonstrated the lowest cefiderocol MIC (0.03 mg/liter).

The results of monotherapy time-kill experiments with each agent alone at the

TABLE 2 MICs of cefiderocol and comparator agents against nine *S. maltophilia* isolates included in time-kill experiments

Isolate	MIC (mg/liter)				
	Cefiderocol	Levofloxacin	Minocycline	Polymyxin B	TMP-SMZ[a]
SM-1	0.25	2	2	2	>8
SM-2	0.5	1	1	4	>8
SM-3	0.03	4	0.125	0.25	0.5
SM-4	0.125	8	0.5	0.125	0.25
SM-5	0.5	1	4	0.25	>8
SM-6	0.25	>16	2	>8	8
SM-7	1	4	2	0.25	0.5
SM-8	0.125	>16	8	2	8
SM-9	0.03	>16	4	>8	8

[a]Values reflect the MIC of the trimethoprim component only.

highest concentration tested (4× MIC or the maximum concentration of the free, unbound fraction of the drug in serum [fC_{max}]) are displayed in Fig. 1. Cefiderocol alone was bactericidal against 2/9 (22.2%) isolates (Fig. 1E and H). The mean (± standard deviation [SD]) decrease in the bacterial concentration from 0 to 24 h across all nine isolates exposed to cefiderocol at 4× MIC or fC_{max} was 0.05 ± 2.16 $\log_{10}$ CFU/ml.

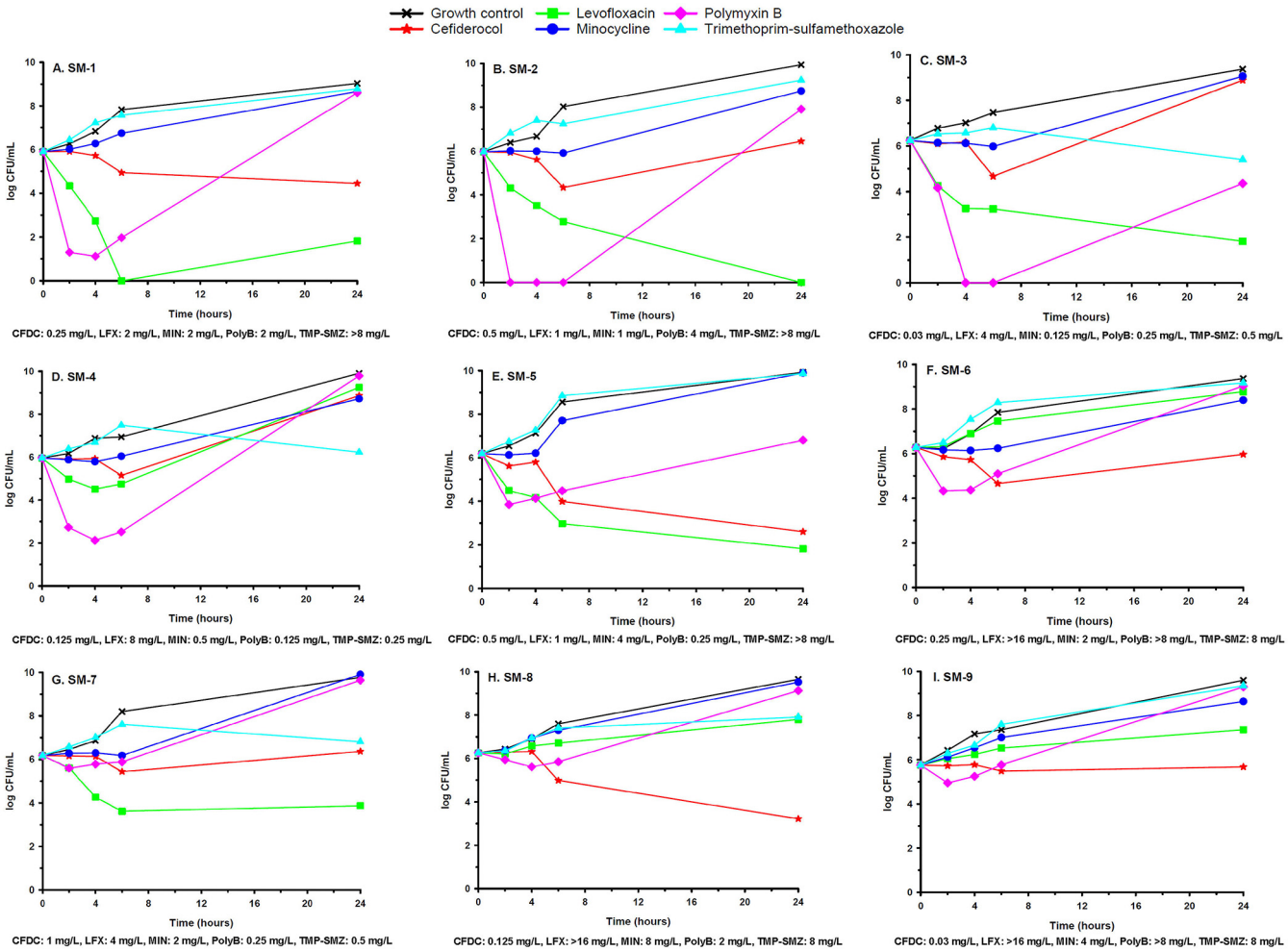

FIG 1 Mean bacterial concentration (expressed as $\log_{10}$ CFU per milliliter)-versus-time profiles for cefiderocol (4× MIC in all panels) and each comparator against nine *S. maltophilia* strains. Levofloxacin is shown at fC_{max} except in panels B and E (4× MIC). Minocycline is shown at fC_{max} except in panel C (4× MIC). Polymyxin B is shown at fC_{max} except in panels C, D, E, and G (4× MIC). TMP-SMZ is shown at fC_{max} except in panels C, D, and G (4× MIC). Curves represent average concentrations from triplicate experiments.

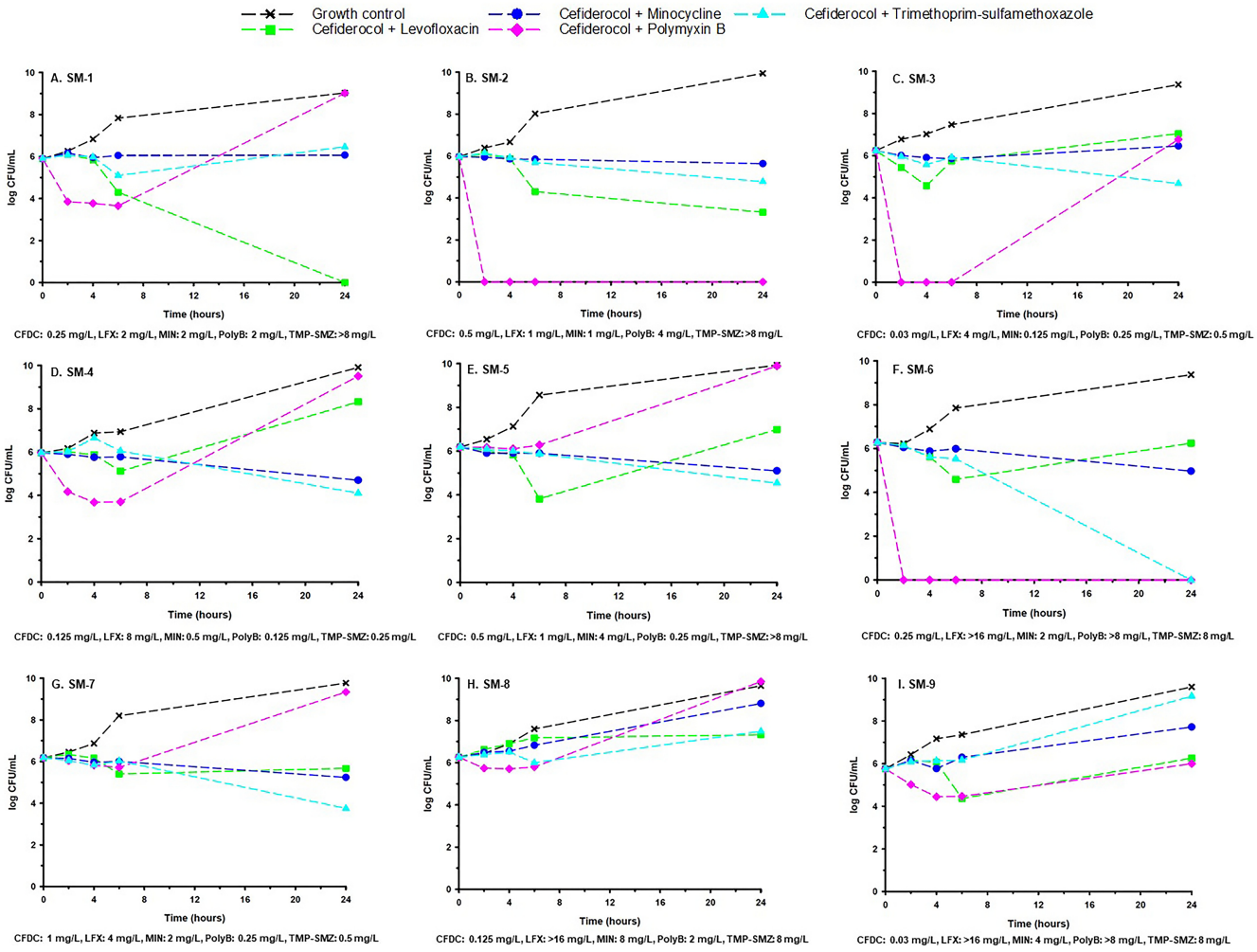

FIG 2 Mean bacterial concentration (expressed as $\log_{10}$ CFU per milliliter)-versus-time profiles for cefiderocol (1/2× MIC in all panels) in combination with each comparator against nine *S. maltophilia* strains. Levofloxacin is shown at either 1/4× MIC (A to E and G) or fC_{max} (F, H, and I). Minocycline is shown at fC_{max} in all panels except C (4× MIC). Polymyxin B is shown at either fC_{max} (A, B, F, H, and I) or 4× MIC (C to E and G). TMP-SMZ is shown at fC_{max} in all panels except D (4× MIC). Curves represent average concentrations from triplicate experiments.

Levofloxacin alone was bactericidal against 4/9 (44%) isolates (Fig. 1A to C and E), and the mean (± SD) decrease from 0 to 24 h across all nine isolates was 1.36 ± 3.56 $\log_{10}$ CFU/ml. Minocycline, polymyxin B, and TMP-SMZ were not bactericidal against any isolate, regardless of the concentration tested.

Based on results from individual time-kill experiments, a concentration of 1/2× MIC of cefiderocol was combined with 1/4× MIC or fC_{max} of levofloxacin and either 4× MIC or fC_{max} of minocycline, polymyxin B, or TMP-SMZ (Fig. 2). The combination of cefiderocol plus levofloxacin was synergistic and bactericidal against 4/9 (44.4%) and 1/9 (11.1%) isolates, respectively (Fig. 2A, B, F, and G). The mean (± SD) decrease in the bacterial concentration after exposure to the combination from 0 to 24 h across all nine isolates was 0.39 ± 2.47 $\log_{10}$ CFU/ml. Synergy was observed in 2/3 (66.7%) levofloxacin-susceptible isolates and 2/6 (33.3%) levofloxacin-intermediate or -resistant isolates. The cefiderocol-plus-minocycline combination was synergistic against 6/9 (66.7%) isolates but was not bactericidal against any isolate (Fig. 2B to G). The mean (± SD) decrease after exposure to the combination from 0 to 24 h across all nine isolates was 0.0 ± 1.41 $\log_{10}$ CFU/ml. Cefiderocol combined with polymyxin B was synergistic and bactericidal against 5/9 (55.5%) and 2/9 (22.2%) isolates, respectively (Fig. 2B, C, E, F, and I), although the mean (± SD) bacterial concentration increased 0.67 ± 4.09 $\log_{10}$ CFU/ml from 0 to 24 h. Finally, cefiderocol combined with TMP-SMZ was synergistic and

bactericidal against 6/9 (66.7%) and 1/9 (11.1%) isolates, respectively (Fig. 2B to G). Synergy was observed in 3/3 (100%) and 3/6 (50%) isolates susceptible or resistant to TMP-SMZ, respectively, and the mean (± SD) decrease from 0 to 24 h was 1.09 ± 2.70 $\log_{10}$ CFU/ml.

DISCUSSION

The prevalence of serious infections due to *S. maltophilia* continues to increase concomitantly with its almost inescapable resistance, while the number of viable treatment options with reliable activity and acceptable safety profiles continues to decline. Cefiderocol is the first and only approved β-lactam agent to demonstrate reliable *in vitro* activity against Gram-negative pathogens expressing serine β-lactamase and metallo-β-lactamase enzymes. As such, there is a growing interest in the potential use of cefiderocol against *S. maltophilia* infections, although thorough evaluation of its activity against resistant isolates alone and in combination with other agents is crucial to establishing its role in this arena.

In the present study, the activity of cefiderocol was assessed alone and in combination against a unique panel of *S. maltophilia* isolates resistant to one or more currently preferred first-line treatment options. Susceptibility testing demonstrated that cefiderocol was highly potent against MDR *S. maltophilia*. Despite widespread resistance to other agents included in this study, the maximum cefiderocol MIC observed was 1 mg/liter, 2 $\log_2$ dilutions below the CLSI provisional susceptibility breakpoint of 4 mg/liter (24). Notwithstanding the fact that our sample was intentionally enriched with isolates resistant to levofloxacin and/or TMP-SMZ, these results are consistent with those of previous studies evaluating the *in vitro* susceptibility of *S. maltophilia* to cefiderocol (25–28).

This is the first study to directly compare the antibacterial activity of cefiderocol to those of currently preferred treatment options for *S. maltophilia* using time-kill experiments. Bactericidal activity was rarely observed in either monotherapy or combination time-kill experiments regardless of the agent(s) or concentration(s) tested, and strain-to-strain variability was visible across the nine isolates included. This is likely due to the slow-growing nature of *S. maltophilia*, the inherently static nature of time-kill experiments, and the drug concentrations utilized. Although supratherapeutic concentrations of cefiderocol as high as 4× MIC were utilized, these concentrations are still ≥10-fold lower than the fC_{max} values observed after a 2-g dose administered to healthy volunteers over 3 h (~45 mg/liter) (29). Since the primary objective of this study was to evaluate synergy in combination with cefiderocol, drugs were utilized at concentrations multiplicative of the MIC for the respective isolate rather than at human physiologic concentrations. This approach allows for the evaluation of true synergy while maintaining a constant concentration-to-MIC ratio across pathogens (30), although it may underestimate the killing capacity possible at concentrations achievable in serum. Regardless, the inability of monotherapy to achieve bactericidal activity against *S. maltophilia in vitro* is consistent with the previous literature (31–33) and further supports the need to evaluate combination regimens against this difficult-to-treat pathogen.

Cefiderocol-based combinations were tested in 36 separate time-kill experiments (4 per isolate), and cefiderocol acted synergistically with another agent in 21/36 (58.3%) experiments but was bactericidal in just 4/36 (11.1%) combination experiments. In a majority of time-kill experiments, synergy was observed when cefiderocol was combined with either minocycline (66.7%), TMP-SMZ (66.7%), or polymyxin B (55.5%). Cefiderocol plus levofloxacin was the only combination for which synergy was not observed in at least 50% of experiments (44.4%). Further, although interstrain variability was high, cefiderocol in combination with TMP-SMZ achieved the largest average decrease in bacterial concentrations over the 24-h experiments, at 1.09 $\log_{10}$ CFU/ml, followed by polymyxin B at 0.67 $\log_{10}$ CFU/ml, levofloxacin at 0.39 $\log_{10}$ CFU/ml, and minocycline at 0.0 $\log_{10}$ CFU/ml. Although there appeared to be some correlation between susceptibility to the agent used in combination with cefiderocol and the

achievement of synergy, the factors predictive of synergism with cefiderocol require further study. Additionally, the spectrum of synergy observed in this study warrants further investigation of these combinations in dynamic pharmacokinetic (PK)/pharmacodynamic (PD) models that can mimic humanized PK, elucidate dose-exposure-response relationships, and discover dosing regimens and/or combinations capable of achieving bactericidal activity against this elusive pathogen.

The strengths of our study include the use of a global collection of clinical isolates with resistance to levofloxacin and/or TMP-SMZ and the evaluation of cefiderocol both alone and in combination with currently preferred agents. Since we intentionally enriched our panel with resistant isolates, the rates of susceptibility to levofloxacin and TMP-SMZ in this study are not reflective of those encountered in routine clinical practice. Additional limitations of this study include the inherently static nature of 24-h time-kill experiments and the use of cefiderocol concentrations well below those that are clinically achievable.

In summary, cefiderocol displays potent *in vitro* activity against *S. maltophilia*, including strains resistant to current first-line agents. In time-kill experiments, minocycline, polymyxin B, and TMP-SMZ acted synergistically with cefiderocol against a majority of isolates. These results support the further investigation of cefiderocol both alone and in combination with these agents against *S. maltophilia* in more-complex *in vitro* and *in vivo* models in order to further define its place in therapy for this pathogen.

MATERIALS AND METHODS

Bacteria and susceptibility testing. A panel of 37 clinical *S. maltophilia* isolates not susceptible to levofloxacin and/or TMP-SMZ collected through the SENTRY Antimicrobial Surveillance Program from 2017 to 2018 was included in all experiments (34). Species identification was confirmed at JMI Laboratories (North Liberty, IA) by standard biochemical tests and via matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Billerica, MA). Isolates included community- and nosocomially acquired strains collected from patients with various disease states across multiple continents (35). All isolates were maintained at −80°C in cation-adjusted Mueller-Hinton broth (CAMHB) (Teknova, Hollister, CA) with 20% glycerol and were subcultured twice on tryptic soy agar plates with 5% sheep blood prior to use.

Analytical-grade ceftazidime, levofloxacin, minocycline, polymyxin B, sulfamethoxazole, and trimethoprim powders were obtained commercially (Sigma-Aldrich, St. Louis, MO), and analytical-grade cefiderocol powder was provided by the manufacturer (Shionogi & Co., Ltd.). Stock solutions of each agent were freshly prepared as single-use aliquots at the beginning of each week and were kept frozen at −80°C. MICs were determined in triplicate via reference broth microdilution according to Clinical and Laboratory Standards Institute (CLSI) guidelines using the same 0.5 McFarland standard suspension (36). Cefiderocol MICs were determined using iron-depleted CAMHB (ID-CAMHB) as recommended elsewhere (24, 37) in custom-prepared MIC panels (International Health Management Associates, Schaumburg, IL). Modal MIC values are reported as MIC_{50}, MIC_{90}, and MIC range. *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control organisms. Susceptibility interpretations were based on 2020 CLSI interpretative criteria (document M100-S30) for activity against *S. maltophilia* for all agents except polymyxin B, for which results were interpreted on the basis of CLSI interpretative criteria for *P. aeruginosa* (24). Susceptibility breakpoints were as follows: for cefiderocol, ≤4 mg/liter; for ceftazidime, ≤8 mg/liter; for levofloxacin, ≤2 mg/liter; for minocycline, ≤4 mg/liter; and for TMP-SMZ, ≤2 and 38 mg/liter, respectively. A polymyxin B MIC of ≤2 mg/liter was considered intermediate given the lack of a susceptible category in CLSI document M100-S30.

Time-kill experiments. Time-kill experiments were performed in triplicate on the same day against a subset of nine *S. maltophilia* isolates selected to provide a range of cefiderocol MICs and a variety of phenotypic susceptibilities across comparator agents. Experiments were performed according to CLSI guidelines (38) modified using a final volume of 2 ml in deep-well, non-tissue-treated plates. A starting inoculum of ~10^6 CFU/ml was prepared by suspending 3 to 4 isolated colonies selected from a pure overnight culture in 5 ml of sterile saline and adjusting to a 0.5 McFarland standard; the suspension was subsequently incubated with agitation to ensure log-phase growth and was then diluted 1:100 in CAMHB. Colony counts were performed to ensure final inoculum densities. Time-kill experiments were performed stepwise as follows: cefiderocol, levofloxacin, minocycline, polymyxin B, and TMP-SMZ were tested alone at ¼, ½, 1, 2, and 4× MIC, unless any of these concentrations exceeded the respective drug's fC_{max} value, in which case the fC_{max} was used. Additionally, if the MIC value was below the limit of quantitation (e.g., <0.03 mg/liter), then the lowest observed value was used (0.03 mg/liter). The fC_{max} values utilized simulated single doses of 750 mg levofloxacin (6.5 mg/liter) (39), 200 mg minocycline given intravenously (1 mg/liter) (40), 1.5 mg polymyxin B/kg of body weight (2.5 mg/liter) (41), and 400 and 2,000 mg TMP-SMZ, respectively, given intravenously (5 and 35 mg/liter) (42). The fC_{max} of TMP-SMZ simulated a 5-mg/kg dose of TMP administered to an 80-kg patient (42). Next, cefiderocol was tested at ½× MIC in combination with each comparator agent using the highest concentration of each individual agent from step 1 that displayed no meaningful activity compared to the drug-free control strain

($\leq$1-$\log_{10}$ CFU/ml decrease from the starting inoculum at 24 h). A growth control without any antibiotic was included with each experiment. All cefiderocol-based experiments were performed using ID-CAMHB, including combination experiments, after an initial evaluation via MICs and time-kill analyses to ensure that the use of ID-CAMHB did not affect the activity of any comparator agent (data not shown). At the prespecified time points of 0, 2, 4, 6, and 24 h, aliquots of 20 μl were removed from the suspensions and serially diluted in $\log_{10}$ dilutions. A 50-μl aliquot was then plated onto MH agar plates using an automated spiral plater (Don Whitley WASP Touch; Microbiology International, Frederick, MD) and was incubated at 35°C for at least 24 h prior to enumeration. Colony counts were performed using an automated colony counter (ProtoCOL 3 Plus; Synbiosis, Frederick, MD). The theoretical lower limit of quantitation was 100 CFU/ml. Time-kill curves were generated by plotting the average bacterial concentration (expressed as $\log_{10}$ CFU per milliliter) against time to compare the 24-h killing effects of single agents alone and in combination. Bactericidal activity was defined as a $\geq$3-$\log_{10}$ CFU/ml reduction at 24 h from the starting inoculum, and synergy was defined as a $\geq$2-$\log_{10}$ CFU/ml difference between the combination and the most active single agent alone (38).

ACKNOWLEDGMENTS

This study was supported by an investigator-initiated grant awarded to E.W. by Shionogi Inc. (Florham Park, NJ).

E.W. serves on the speaker's bureau for Astellas Pharma, Melinta Therapeutics, and Allergan Plc and on the advisory board for GenMark Diagnostics and Shionogi. All other authors certify no potential conflicts of interest.

REFERENCES

1. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, Doi Y, Kreiswirth BN, Clancy CJ. 2017. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant Klebsiella pneumoniae bacteremia. Antimicrob Agents Chemother 61:e00883-17. https://doi.org/10.1128/AAC.00883-17.
2. van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, Salata RA, Kalayjian RC, Watkins RR, Doi Y, Kaye KS, Fowler VG, Jr, Paterson DL, Bonomo RA, Evans S, Antibacterial Resistance Leadership Group. 2018. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clin Infect Dis 66:163–171. https://doi.org/10.1093/cid/cix783.
3. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, Mathers AJ, Bassetti M, Vazquez J, Cornely OA, Solomkin J, Bhowmick T, Bishara J, Daikos GL, Felton T, Furst MJL, Kwak EJ, Menichetti F, Oren I, Alexander EL, Griffith D, Lomovskaya O, Loutit J, Zhang S, Dudley MN, Kaye KS. 2018. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: the TANGO II Randomized Clinical Trial. Infect Dis Ther 7:439–455. https://doi.org/10.1007/s40121-018-0214-1.
4. Motsch J, Murta de Oliveira C, Stus V, Koksal I, Lyulko O, Boucher HW, Kaye KS, File TM, Brown ML, Khan I, Du J, Joeng HK, Tipping RW, Aggrey A, Young K, Kartsonis NA, Butterton JR, Paschke A. 2019. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. Clin Infect Dis 70:1799–1808. https://doi.org/10.1093/cid/ciz530.
5. Kollef MH, Novacek M, Kivistik U, Rea-Neto A, Shime N, Martin-Loeches I, Timsit JF, Wunderink RG, Bruno CJ, Huntington JA, Lin G, Yu B, Butterton JR, Rhee EG. 2019. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis 19:1299–1311. https://doi.org/10.1016/S1473-3099(19)30403-7.
6. Pogue JM, Kaye KS, Veve MP, Patel TS, Gerlach AT, Davis SL, Puzniak LA, File TM, Olson S, Dhar S, Bonomo RA, Perez F. 23 September 2019. Ceftolozane/tazobactam vs polymyxin or aminoglycoside-based regimens for the treatment of drug-resistant Pseudomonas aeruginosa. Clin Infect Dis https://doi.org/10.1093/cid/ciz816.
7. Lodise TP, Jr., Echols R, Wang W, Corvino F, Cai B. 26 November 2018. 1191. Prevalence and microbiology of carbapenem resistance among six Gram-negative pathogens in bloodstream infections in US hospitals, 2010–2015. Open Forum Infect Dis 5(Suppl 1):S360. https://doi.org/10.1093/ofid/ofy210.1024.
8. Falagas ME, Kastoris AC, Vouloumanou EK, Rafailidis PI, Kapaskelis AM, Dimopoulos G. 2009. Attributable mortality of Stenotrophomonas maltophilia infections: a systematic review of the literature. Future Microbiol 4:1103–1109. https://doi.org/10.2217/fmb.09.84.
9. Chang YT, Lin CY, Chen YH, Hsueh PR. 2015. Update on infections caused by Stenotrophomonas maltophilia with particular attention to resistance mechanisms and therapeutic options. Front Microbiol 6:893. https://doi.org/10.3389/fmicb.2015.00893.
10. Cho SY, Kang CI, Kim J, Ha YE, Chung DR, Lee NY, Peck KR, Song JH. 2014. Can levofloxacin be a useful alternative to trimethoprim-sulfamethoxazole for treating Stenotrophomonas maltophilia bacteremia? Antimicrob Agents Chemother 58:581–583. https://doi.org/10.1128/AAC.01682-13.
11. Wang YL, Scipione MR, Dubrovskaya Y, Papadopoulos J. 2014. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of Stenotrophomonas maltophilia infections. Antimicrob Agents Chemother 58:176–182. https://doi.org/10.1128/AAC.01324-13.
12. Watson L, Esterly J, Jensen AO, Postelnick M, Aguirre A, McLaughlin M. 2018. Sulfamethoxazole/trimethoprim versus fluoroquinolones for the treatment of Stenotrophomonas maltophilia bloodstream infections. J Glob Antimicrob Resist 12:104–106. https://doi.org/10.1016/j.jgar.2017.09.015.
13. Hand E, Davis H, Kim T, Duhon B. 2016. Monotherapy with minocycline or trimethoprim/sulfamethoxazole for treatment of Stenotrophomonas maltophilia infections. J Antimicrob Chemother 71:1071–1075. https://doi.org/10.1093/jac/dkv456.
14. Badwal J, Traugott K, Hand E. 26 November 2018. 2419. Standard vs. alternative therapy for Stenotrophomonas maltophilia infections: focus on trimethoprim-sulfamethoxazole, minocycline, and moxifloxacin monotherapy. Open Forum Infect Dis 5(Suppl 1):S723. https://doi.org/10.1093/ofid/ofy210.2072.
15. Tekce YT, Erbay A, Cabadak H, Sen S. 2012. Tigecycline as a therapeutic option in Stenotrophomonas maltophilia infections. J Chemother 24:150–154. https://doi.org/10.1179/1120009X12Z.00000000022.
16. Ito A, Nishikawa T, Matsumoto S, Yoshizawa H, Sato T, Nakamura R, Tsuji M, Yamano Y. 2016. Siderophore cephalosporin cefiderocol utilizes ferric iron transporter systems for antibacterial activity against Pseudomonas aeruginosa. Antimicrob Agents Chemother 60:7396–7401. https://doi.org/10.1128/AAC.01405-16.
17. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. 2017. In vitro activity of the siderophore cephalosporin, cefiderocol, against a recent collection of clinically relevant Gram-negative bacilli from North America and Europe, including carbapenem-nonsusceptible isolates (SIDERO-WT-2014 Study). Antimicrob Agents Chemother 61:e00093-17. https://doi.org/10.1128/AAC.00093-17.
18. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. 2018. In vitro activity of the siderophore cephalosporin, cefiderocol, against carbapenem-nonsusceptible and multidrug-resistant isolates of Gram-negative bacilli collected worldwide in 2014 to 2016. Antimicrob Agents Chemother 62:e01968-17. https://doi.org/10.1128/AAC.01968-17.

19. Yamano Y. 2019. In vitro activity of cefiderocol against a broad range of clinically important Gram-negative bacteria. Clin Infect Dis 69: S544–S551. https://doi.org/10.1093/cid/ciz827.
20. Karlowsky JA, Hackel MA, Tsuji M, Yamano Y, Echols R, Sahm DF. 2019. In vitro activity of cefiderocol, a siderophore cephalosporin, against Gram-negative bacilli isolated by clinical laboratories in North America and Europe in 2015–2016: SIDERO-WT-2015. Int J Antimicrob Agents 53:456–466. https://doi.org/10.1016/j.ijantimicag.2018.11.007.
21. Tsuji M, Hackel M, Echols R, Yamano Y, Sahm D. 2019. In vitro antibacterial activity of cefiderocol against gram-negative clinical strains collected in North America and Europe, SIDERO-WT-2016, poster AAR-767. Microbe 2019, San Francisco, CA, 20 to 24 June 2019.
22. Chen IH, Kidd JM, Abdelraouf K, Nicolau DP. 2019. Comparative in vivo antibacterial activity of human-simulated exposures of cefiderocol and ceftazidime against Stenotrophomonas maltophilia in the murine thigh model. Antimicrob Agents Chemother 63:e01558-19. https://doi.org/10.1128/AAC.01558-19.
23. Nakamura R, Ito-Horiyama T, Takemura M, Toba S, Matsumoto S, Ikehara T, Tsuji M, Sato T, Yamano Y. 2019. In vivo pharmacodynamic study of cefiderocol, a novel parenteral siderophore cephalosporin, in murine thigh and lung infection models. Antimicrob Agents Chemother 63: e02031-18. https://doi.org/10.1128/AAC.02031-18.
24. CLSI. 2020. Performance standards for antimicrobial susceptibility testing. Thirtieth informational supplement, M100-S30. CLSI, Wayne, PA.
25. Ito A, Kohira N, Bouchillon SK, West J, Rittenhouse S, Sader HS, Rhomberg PR, Jones RN, Yoshizawa H, Nakamura R, Tsuji M, Yamano Y. 2016. In vitro antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting Gram-negative bacteria. J Antimicrob Chemother 71:670–677. https://doi.org/10.1093/jac/dkv402.
26. Ito A, Ota M, Nakamura R, Tsuji M, Sato T, Yamano Y. 2018. 1366. In vitro and in vivo activity of cefiderocol against Stenotrophomonas maltophilia clinical isolates. Open Forum Infect Dis 5:S418. https://doi.org/10.1093/ofid/ofy210.1197.
27. Hsueh SC, Lee YJ, Huang YT, Liao CH, Tsuji M, Hsueh PR. 2019. In vitro activities of cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam and other comparative drugs against imipenem-resistant Pseudomonas aeruginosa and Acinetobacter baumannii, and Stenotrophomonas maltophilia, all associated with bloodstream infections in Taiwan. J Antimicrob Chemother 74:380–386. https://doi.org/10.1093/jac/dky425.
28. Rolston KVI, Gerges B, Shelburne S, Aitken SL, Raad I, Prince RA. 2020. Activity of cefiderocol and comparators against isolates from cancer patients. Antimicrob Agents Chemother 64:e01955-19. https://doi.org/10.1128/AAC.01955-19.
29. Sanabria C, Migoya E, Mason JW, Stanworth SH, Katsube T, Machida M, Narukawa Y, Den Nagata T. 2019. Effect of cefiderocol, a siderophore cephalosporin, on QT/QTc interval in healthy adult subjects. Clin Ther 41:1724–1736.e4. https://doi.org/10.1016/j.clinthera.2019.07.006.
30. Doern CD. 2014. When does 2 plus 2 equal 5? A review of antimicrobial synergy testing. J Clin Microbiol 52:4124–4128. https://doi.org/10.1128/JCM.01121-14.
31. Wei C, Ni W, Cai X, Zhao J, Cui J. 2016. Evaluation of trimethoprim/sulfamethoxazole (SXT), minocycline, tigecycline, moxifloxacin, and ceftazidime alone and in combinations for SXT-susceptible and SXT-resistant Stenotrophomonas maltophilia by in vitro time-kill experiments. PLoS One 11:e0152132. https://doi.org/10.1371/journal.pone.0152132.
32. Giamarellos-Bourboulis EJ, Karnesis L, Giamarellou H. 2002. Synergy of colistin with rifampin and trimethoprim/sulfamethoxazole on multidrug-resistant Stenotrophomonas maltophilia. Diagn Microbiol Infect Dis 44: 259–263. https://doi.org/10.1016/s0732-8893(02)00443-1.
33. Zelenitsky SA, Iacovides H, Ariano RE, Harding GK. 2005. Antibiotic combinations significantly more active than monotherapy in an in vitro infection model of Stenotrophomonas maltophilia. Diagn Microbiol Infect Dis 51:39–43. https://doi.org/10.1016/j.diagmicrobio.2004.09.002.
34. Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. 2019. Antimicrobial susceptibility of Acinetobacter calcoaceticus-Acinetobacter baumannii complex and Stenotrophomonas maltophilia clinical isolates: results from the SENTRY Antimicrobial Surveillance Program (1997–2016). Open Forum Infect Dis 6:S34–S46. https://doi.org/10.1093/ofid/ofy293.
35. Biagi M, Tan X, Wu T, Jurkovic M, Vialichka A, Meyer K, Mendes RE, Wenzler E. 2019. Activity of potential alternative treatment agents for Stenotrophomonas maltophilia isolates nonsusceptible to levofloxacin and/or trimethoprim-sulfamethoxazole. J Clin Microbiol 58:e01603-19. https://doi.org/10.1128/JCM.01603-19.
36. Luster MI, Gerberick GF. 2010. Immunotoxicology testing: past and future. Methods Mol Biol 598:3–13. https://doi.org/10.1007/978-1-60761-401-2_1.
37. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. 2019. Reproducibility of broth microdilution MICs for the novel siderophore cephalosporin, cefiderocol, determined using iron-depleted cation-adjusted Mueller-Hinton broth. Diagn Microbiol Infect Dis 94:321–325. https://doi.org/10.1016/j.diagmicrobio.2019.03.003.
38. CLSI. 1999. Methods for determining bactericidal activity of antimicrobial agents. CLSI document M26-A. CLSI, Wayne, PA.
39. Craig W, Andes D. 2004. Activity of oritavancin (O) versus vancomycin (V) in the neutropenic murine thigh- and lung-infection models, abstr A-1863. Abstr 44th Intersci Conf Antimicrob Agents Chemother. American Society for Microbiology, Washington, DC.
40. Macdonald H, Kelly RG, Allen ES, Noble JF, Kanegis LA. 1973. Pharmacokinetic studies on minocycline in man. Clin Pharmacol Ther 14: 852–861. https://doi.org/10.1002/cpt1973145852.
41. Sandri AM, Landersdorfer CB, Jacob J, Boniatti MM, Dalarosa MG, Falci DR, Behle TF, Bordinhao RC, Wang J, Forrest A, Nation RL, Li J, Zavascki AP. 2013. Population pharmacokinetics of intravenous polymyxin B in critically ill patients: implications for selection of dosage regimens. Clin Infect Dis 57:524–531. https://doi.org/10.1093/cid/cit334.
42. Grose WE, Bodey GP, Loo TL. 1979. Clinical pharmacology of intravenously administered trimethoprim-sulfamethoxazole. Antimicrob Agents Chemother 15:447–451. https://doi.org/10.1128/aac.15.3.447.