Activity of Potential Alternative Treatment Agents for *Stenotrophomonas maltophilia* Isolates Nonsusceptible to Levofloxacin and/or Trimethoprim-Sulfamethoxazole

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ABSTRACT *Stenotrophomonas maltophilia* is difficult to treat due to the production of multiple intrinsic and acquired mechanisms of resistance. Trimethoprim-sulfamethoxazole (TMP-SMZ) and the fluoroquinolones have traditionally been considered the drugs of choice but are plagued by increasing resistance and adverse drug effects. The objective of this study was to evaluate the *in vitro* activities of 12 clinically relevant antimicrobials against clinical *S. maltophilia* isolates nonsusceptible to levofloxacin and/or TMP-SMZ. A diverse panel of 41 clinical *S. maltophilia* isolates collected through the SENTRY Antimicrobial Surveillance Program from 2008 to 2018 was evaluated against ceftazidime, ceftazidime-avibactam, chloramphenicol, delafloxacin, levofloxacin, moxifloxacin, eravacycline, minocycline, omadacycline, polymyxin B, and tigecycline. MICs were determined in triplicate via reference broth microdilution and interpreted according to CLSI guidelines where available. MIC distributions and susceptibilities were also compared across infection type, acquisition setting, and geographic origin. Susceptibilities to levofloxacin and TMP-SMZ were 29.3% and 36.6%, respectively. Minocycline displayed the highest susceptibility rate overall (92.7%) and the lowest MIC₉₀ value (4 mg/liter) of any of the 12 agents tested. Only 3 isolates were resistant to levofloxacin, TMP-SMZ, and minocycline. Polymyxin B and tigecycline were the second most active agents. No significant differences were observed in MIC distributions across the 3 strata evaluated. These data demonstrate that few antimicrobials, old or new, maintain reliable activity against resistant *S. maltophilia*. The role of minocycline in the treatment of infections due to *S. maltophilia* warrants further clinical investigation given its potent *in vitro* activity and favorable adverse effect profile.

KEYWORDS delafloxacin, eravacycline, levofloxacin, minocycline, omadacycline, trimethoprim-sulfamethoxazole, *Stenotrophomonas maltophilia*

On the brink of the postantibiotic era, clinicians frequently encounter multidrug-resistant (MDR) pathogens for which there is no known optimal treatment. One such organism is *Stenotrophomonas maltophilia*, an opportunistic pathogen often overshadowed by other MDR Gram-negative organisms such as carbapenem-resistant *Enterobacteriaceae* (CRE), *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. However, *S. maltophilia* is the most prevalent carbapenem-resistant Gram-negative pathogen among bloodstream infections in U.S. hospitals (1) and is associated with significant morbidity and mortality (2–4). Furthermore, treatment is particularly challenging due to the production of multiple intrinsic and acquired mechanisms of resistance that render many first-line antimicrobials, particularly the β -lactams, ineffective (5).

Trimethoprim-sulfamethoxazole (TMP-SMZ) has traditionally been considered the

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treatment of choice for *S. maltophilia*, as it displays predictably high rates of *in vitro* susceptibility (6–8). However, increasing reports of resistance and adverse drug effects and a lack of robust pharmacokinetic-pharmacodynamic (PK-PD) data for which to optimize dosing limit its clinical utility (9–14). The fluoroquinolones are generally considered preferred alternatives to TMP-SMZ, with the majority of data existing for levofloxacin (11, 15, 16). However, the role of fluoroquinolones, including levofloxacin, is also limited by baseline and treatment-emergent resistance, growing safety concerns, and drug-drug interactions (7, 11, 15, 17, 18).

Additional agents with reliably high susceptibility rates against *S. maltophilia* include tetracycline derivatives like minocycline and tigecycline. Minocycline displays susceptibility rates similar to those of TMP-SMZ, and anecdotal data suggest that clinical outcomes with minocycline and TMP-SMZ monotherapy do not significantly differ (12, 15, 17, 19, 20). Despite these data and availability of interpretive susceptibility criteria (21), minocycline is rarely used clinically for the treatment of *S. maltophilia* due in large part to the fact that many clinical microbiology labs do not specifically perform susceptibility testing for minocycline (22). Tigecycline displays reliable *in vitro* activity against *S. maltophilia*, but clinical use is hampered by lack of an oral formulation, dose-limiting gastrointestinal toxicities, and reports of increased clinical failure and mortality (7, 23). Finally, the *in vitro* activities of recently approved tetracycline derivatives, eravacycline and omadacycline, have been reported for *S. maltophilia* (24–29), but no studies to date have simultaneously assessed the activity of both agents or either agent specifically against *S. maltophilia* isolates resistant to levofloxacin and/or TMP-SMZ, and no clinical data exist to support their use.

Taking into consideration the numerous limitations of these currently available agents, there is an urgent need to identify alternatives with meaningful activity against *S. maltophilia*. The objective of this study was to evaluate the *in vitro* activities of 12 clinically relevant comparator agents against *S. maltophilia* isolates nonsusceptible to levofloxacin and/or TMP-SMZ.

(Results of this study were presented in part at ECCMID 2019 as abstract 6182.)

MATERIALS AND METHODS

Bacteria and susceptibility testing. A diverse panel of 41 clinical *S. maltophilia* isolates collected through the SENTRY Antimicrobial Surveillance Program (2008 to 2018) nonsusceptible to levofloxacin and/or TMP-SMZ was evaluated. These 41 isolates were selected randomly from the collection of JMI Laboratories *S. maltophilia* isolates nonsusceptible to levofloxacin, TMP-SMZ, or both. Species identification was confirmed at JMI Laboratories by standard biochemical tests and via matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Billerica, MA). Among isolates with available data, strains were acquired either in the community ($n = 17$) or in a nosocomial setting ($n = 16$) and were cultured from patients with the following infection types: pneumonia ($n = 32$), bacteremia ($n = 4$), skin/soft tissue infection ($n = 4$), and urinary tract infection ($n = 1$). Isolates were collected primarily from sites in North America ($n = 17$) and Europe ($n = 14$), followed by Asia ($n = 4$), Australia ($n = 3$), and South America ($n = 3$). Isolates were maintained at -80°C in cation-adjusted Mueller-Hinton broth (CAMHB) with 20% glycerol and were subcultured twice on tryptic soy agar plates with 5% sheep blood prior to use.

Analytical-grade avibactam, ceftazidime, chloramphenicol, delafloxacin, levofloxacin, minocycline, moxifloxacin, polymyxin B, sulfamethoxazole, tigecycline, and trimethoprim powders were obtained commercially (Sigma-Aldrich, St. Louis, MO), along with eravacycline and omadacycline powders (MedChemExpress, Monmouth Junction, NJ). Stock solutions of each agent were freshly prepared as single-use aliquots at the beginning of each week and kept frozen at -80°C . MICs were determined in triplicate by reference broth microdilution at a standard inoculum according to Clinical and Laboratory Standards Institute (CLSI) guidelines using the same 0.5 McFarland suspension (30). Modal MIC values are reported. Susceptibility testing for omadacycline and tigecycline was performed using CAMHB freshly prepared the same day as MIC testing, as recommended. *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were included as quality control (QC) organisms. Susceptibility interpretations were based on current CLSI interpretive categories for agents with available criteria against *S. maltophilia* (21) unless otherwise noted for the purpose of comparison. MIC distributions and susceptibilities were compared across three strata: infection type (pneumonia versus nonpneumonia), acquisition setting (community versus nosocomial), and geographic origin (U.S. versus non-U.S.) via Mann-Whitney U test. A 2-tailed P value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL).

RESULTS

The MIC₅₀, MIC₉₀, and MIC range of each agent against each phenotypic subset of isolates (1, all isolates [*n* = 41]; 2, levofloxacin-nonsusceptible [NS] isolates [*n* = 29]; 3, TMP-SMZ-resistant isolates [*n* = 26]; and 4, levofloxacin-NS and TMP-SMZ-resistant isolates [*n* = 14]) are summarized in Table 1.

Twelve of the 41 isolates (29.3%) and 15/41 (36.6%) isolates were susceptible to levofloxacin and TMP-SMZ, respectively. Delafloxacin showed activity similar to that of levofloxacin, while the MIC₅₀/MIC₉₀ for moxifloxacin were ≥ 1 log₂ dilution less than those for the other fluoroquinolones tested. Ceftazidime, ceftazidime-avibactam, and chloramphenicol all demonstrated susceptibility rates of <25%. Evaluating polymyxin B and tigecycline using interpretive criteria against *P. aeruginosa* and *Enterobacteriaceae*, respectively, revealed susceptibility rates of 73.2% for each. Minocycline demonstrated the highest rate of susceptibility overall (at 92.7%), the lowest MIC₉₀ value of any of the 12 agents tested, and improved potency over the other tetracycline derivatives eravacycline and omadacycline.

Just over half (51.7%) of the 29 levofloxacin-NS isolates were susceptible to TMP-SMZ (Table 1). The MIC₅₀/MIC₉₀ for delafloxacin and moxifloxacin were within 1 log₂ dilution of those from the first phenotypic subset once the 12 levofloxacin-susceptible isolates were removed in phenogroup 2. Susceptibilities to ceftazidime, ceftazidime-avibactam, and chloramphenicol remained under 25%, while those to polymyxin B and tigecycline dropped below 70%. Minocycline again retained the highest susceptibility rate, at 89.7%, although MIC₅₀/MIC₉₀ values were similar to those of eravacycline but were ≥ 8 -fold lower than those of omadacycline. Figure 1 demonstrates the shift in MIC distributions for the tetracycline compounds against the levofloxacin-NS isolates compared to those against the isolates that were levofloxacin susceptible.

Similarly, approximately half (46.2%) of the TMP-SMZ-resistant isolates were susceptible to levofloxacin (Table 1). The activity of delafloxacin and moxifloxacin again remained largely unchanged. Ceftazidime, ceftazidime-avibactam, polymyxin B, and tigecycline were all below 70% susceptibility. Minocycline continued to be the only agent with >80% susceptibility, and MIC₅₀/MIC₉₀ values were comparable to those of eravacycline and tigecycline but less than that of omadacycline.

Finally, against the most resistant phenotypic subset of isolates nonsusceptible to both levofloxacin and TMP-SMZ, none of the agents with applicable interpretive criteria maintained susceptibility rates above 43% except minocycline (78.6%). Analogous to the previous groups, potency as determined by the MIC₅₀/MIC₉₀ was congruent among the tetracycline derivatives other than omadacycline.

Table 2 displays the MIC₅₀, MIC₉₀, and MIC range of each agent against all 41 isolates stratified across infection type, acquisition setting, and geographic origin. No statistically significant differences were observed for any drug across any stratum.

DISCUSSION

S. maltophilia is an opportunistic pathogen that primarily infects vulnerable hosts and is resistant to many first-line antimicrobials. Long considered the drugs of choice for *S. maltophilia*, TMP-SMZ and the fluoroquinolones have recently come under increased scrutiny due to reports of resistance, lack of established efficacy in controlled trials, and high toxicity (18, 31, 32). Consequently, there is an urgent need to identify alternative treatment strategies for this difficult-to-treat pathogen.

This study demonstrated that the tetracyclines as a class maintain the most reliable *in vitro* activity against *S. maltophilia*, regardless of resistance phenotype. Among the tetracyclines, minocycline was as active as or more active than tigecycline, eravacycline, and omadacycline and demonstrated the highest susceptibility (78.6%) against the most difficult-to-treat group of isolates nonsusceptible to both levofloxacin and TMP-SMZ. These results are consistent with those of a recent study by Flamm et al., who reported that 64/69 (92.8%) TMP-SMZ-resistant *S. maltophilia* isolates (including 54/69 levofloxacin-NS isolates) were susceptible to minocycline (20). While rare in the clinical setting, we did identify three *S. maltophilia* isolates nonsusceptible to levofloxacin,

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

Isolate group and drug	MIC (mg/liter)			Susceptibility (%) ^a		
	50%	90%	Range	S	I	R
All isolates (<i>n</i> = 41)						
Ceftazidime	64	>128	1 to >128	17.1	7.3	75.6
Ceftazidime-avibactam ^b	64	128	0.125 to >128	19.5	4.9	75.6
Chloramphenicol	16	>64	2 to >64	24.4	24.4	51.2
Delafloxacin	8	16	0.5 to 32			
Eravacycline	2	8	0.5 to 16			
Levofloxacin	8	>16	0.25 to >16	29.3	12.2	58.5
Minocycline	2	4	0.125 to 8	92.7	7.3	0
Moxifloxacin	4	8	0.125 to 16			
Omadacycline	8	32	0.5 to >64			
Polymyxin B ^c	0.5	>8	0.03 to >8	73.2	7.3	19.5
Tigecycline ^d	1	8	0.125 to >8	73.2	9.7	17.1
TMP-SMZ ^e	8	>8	0.03 to >8	36.6		63.4
Levofloxacin nonsusceptible (<i>n</i> = 29)						
Ceftazidime	128	>128	1 to >128	20.7	10.3	69.0
Ceftazidime-avibactam ^b	64	>128	0.125 to >8	24.1	6.9	69.0
Chloramphenicol	32	>64	2 to >64	10.3	24.1	65.5
Delafloxacin	8	16	2 to 32			
Eravacycline	4	8	0.5 to 8			
Levofloxacin	8	>16	4 to >16	0.0	17.2	82.8
Minocycline	2	8	0.125 to 8	89.7	10.3	0.0
Moxifloxacin	4	16	0.5 to 16			
Omadacycline	16	64	0.5 to >64			
Polymyxin B ^c	0.25	>8	0.03 to >8	69.0	3.4	27.6
Tigecycline ^d	2	8	0.125 to 8	62.1	13.8	24.1
TMP-SMZ ^e	2	8	0.03 to >8	51.7		48.3
TMP-SMZ resistant (<i>n</i> = 26)						
Ceftazidime	64	>128	1 to >128	7.7	7.7	84.6
Ceftazidime-avibactam ^b	64	>128	0.125 to >128	11.5	3.8	84.6
Chloramphenicol	16	>64	2 to >64	38.4	30.8	30.8
Delafloxacin	4	16	0.5 to 32			
Eravacycline	2	4	0.5 to 8			
Levofloxacin	8	>16	0.25 to >16	46.2	0.0	53.8
Minocycline	2	8	1 to 8	88.5	11.5	0.0
Moxifloxacin	2	16	0.125 to 16			
Omadacycline	4	32	2 to >64			
Polymyxin B ^c	2	>8	0.06 to >8	57.7	11.5	30.8
Tigecycline ^d	1	8	0.125 to >8	69.2	11.5	19.2
TMP-SMZ ^e	8	>8	8 to >8	0.0		100.0
Levofloxacin nonsusceptible, TMP-SMZ resistant (<i>n</i> = 14)						
Ceftazidime	128	>128	1 to >128	7.1	14.3	78.6
Ceftazidime-avibactam ^b	64	>128	0.125 to >128	14.3	7.3	78.6
Chloramphenicol	16	>64	2 to >64	21.4	35.7	42.9
Delafloxacin	8	16	4 to 32			
Eravacycline	2	8	0.5 to 8			
Levofloxacin	16	>16	8 to >16	0	0	100
Minocycline	2	8	1 to 8	78.6	21.4	0
Moxifloxacin	8	16	2 to 16			
Omadacycline	16	64	4 to >64			
Polymyxin B ^c	8	>8	0.06 to >8	35.7	7.2	57.1
Tigecycline ^d	4	8	1 to >8	42.9	21.4	35.7
TMP-SMZ ^e	8	8	8 to >8	0		100

^aS, susceptible; I, intermediate; R, resistant.^bSusceptibility interpretations based on CLSI-approved breakpoints for ceftazidime alone.^cBased on CLSI breakpoints for *Pseudomonas aeruginosa*.^dBased on FDA breakpoints for *Enterobacteriaceae*.^eTMP-SMZ, trimethoprim-sulfamethoxazole. Value reflects MIC of trimethoprim component only.

FIG 1 MIC distributions of eravacycline, minocycline, omadacycline, and tigecycline against levofloxacin-susceptible (solid bars; $n = 12$) and -nonsusceptible (hatched bars; $n = 29$) *Stenotrophomonas maltophilia* isolates.

minocycline, and TMP-SMZ, and no agent tested in this study was active against all three of these isolates.

Other notable findings from this work include the following. First, we observed an association between levofloxacin and/or TMP-SMZ resistance and decreased activity of other agents outside these two classes. For example, the MIC_{50}/MIC_{90} of polymyxin B seemed to correlate with TMP-SMZ susceptibility. Against TMP-SMZ-susceptible isolates, the MIC_{50}/MIC_{90} were 0.125/0.5 mg/liter, compared to 2/>8 mg/liter against TMP-SMZ-resistant isolates. Second, we observed a correlation between levofloxacin susceptibilities and the activities of the tetracyclines other than minocycline (eravacycline, omadacycline, and tigecycline) (Fig. 1). The MIC_{50} and MIC_{90} values for eravacycline, omadacycline, and tigecycline were consistently higher against levofloxacin-NS isolates than against those that were levofloxacin susceptible, irrespective of susceptibility to TMP-SMZ (data not shown). This correlation may be due to expression of the SmeDEF efflux pump, which is known to be associated with both levofloxacin and tigecycline susceptibilities in *S. maltophilia* (33). Third, we observed improved potency of moxifloxacin over levofloxacin and delafloxacin against all 41 isolates. Cumulatively, delafloxacin was the least active fluoroquinolone, while moxifloxacin demonstrated the lowest MIC_{50}/MIC_{90} . Although the improved potency of moxifloxacin has been previously reported (34–36), the most recent CLSI guidelines (37) continue to provide only interpretive criteria for levofloxacin against *S. maltophilia* despite its decreased activity and the overall lack of supporting clinical data for either agent. As discussed, many clinical microbiology laboratories do not routinely test susceptibility of *S. maltophilia* to agents other than those recommended by the CLSI, so the between-class associations observed in this study may be useful clinically in the absence of an MIC or approved interpretive criteria.

Strengths of this study include the use of clinical isolates from a wide geographic distribution and from many different infection types and acquisition settings. Importantly, no significant differences in MIC distributions were observed across these three strata, suggesting that these results are applicable regardless of patient- or location-specific factors. Bacterial isolates were specifically chosen by their phenotypic resistance to first-line agents to elucidate potential alternative treatment options, although this obviously enriched the sample with isolates outside the normal MIC distribution, which may not accurately reflect the activity of the antimicrobial agents tested in routine clinical practice (17, 38). A recent evaluation of 1,289 isolates of *S. maltophilia*

TABLE 2 Activities of selected agents against clinical *Stenotrophomonas maltophilia* isolates nonsusceptible to levofloxacin and/or TMP-SMZ stratified according to infection type, acquisition setting, and geographic origin^a

	MIC (mg/liter)			
Parameter and drug	50%	90%	Range	% susceptible
Infection type				
Pneumonia (n = 32)				
Ceftazidime	64	>128	1 to >128	15.6
Ceftazidime-avibactam ^b	64	128	0.125 to >128	18.2
Chloramphenicol	16	>64	2 to >64	28.1
Delafloxacin	8	16	0.5 to 16	
Eravacycline	2	8	0.5 to 8	
Levofloxacin	8	>16	0.25 to >16	28.1
Minocycline	2	4	0.125 to 8	93.8
Moxifloxacin	4	8	0.125 to 16	
Omadacycline	8	32	0.5 to 64	
Polymyxin B ^c	0.25	>8	0.06 to >8	75.0
Tigecycline ^d	1	8	0.125 to 8	71.9
TMP-SMZ ^e	8	>8	0.03 to >8	37.5
Nonpneumonia (n = 9)				
Ceftazidime	64		1 to >128	22.2
Ceftazidime-avibactam ^b	64		1 to >128	22.2
Chloramphenicol	32		8 to >64	11.1
Delafloxacin	8		1 to 32	
Eravacycline	2		0.5 to 16	
Levofloxacin	8		0.5 to >16	33.3
Minocycline	2		1 to 8	88.8
Moxifloxacin	4		0.5 to 16	
Omadacycline	16		2 to >64	
Polymyxin B ^c	2		0.03 to >8	66.7
Tigecycline ^d	1		0.125 to >8	77.7
TMP-SMZ ^e	8		1 to >8	33.3
Acquisition setting				
Community (n = 17)				
Ceftazidime	64	>128	1 to >128	23.5
Ceftazidime-avibactam ^b	64	>128	0.125 to >128	29.4
Chloramphenicol	16	64	2 to 64	35.3
Delafloxacin	8	16	1 to 16	
Eravacycline	2	8	0.5 to 16	
Levofloxacin	4	16	0.5 to >16	35.3
Minocycline	2	8	0.5 to 8	82.4
Moxifloxacin	2	8	0.25 to 16	
Omadacycline	8	64	0.5 to >64	
Polymyxin B ^c	0.25	4	0.03 to 8	82.3
Tigecycline ^d	1	8	0.125 to >8	82.3
TMP-SMZ ^e	8	>8	0.25 to >8	35.3
Nosocomial (n = 16)				
Ceftazidime	64	>128	1 to >128	12.5
Ceftazidime-avibactam ^b	64	128	1 to >128	12.5
Chloramphenicol	32	>64	8 to >64	6.3
Delafloxacin	8	16	0.5 to 32	
Eravacycline	2	8	1 to 8	
Levofloxacin	16	>16	0.25 to >16	18.8
Minocycline	2	4	0.125 to 4	100
Moxifloxacin	4	16	0.125 to 16	
Omadacycline	16	64	2 to 64	
Polymyxin B ^c	0.5	>8	0.06 to >8	68.8
Tigecycline ^d	2	8	0.5 to 8	62.5
TMP-SMZ ^e	8	>8	0.5 to >8	37.5
Geographic origin				
U.S. (n = 17)				
Ceftazidime	128	>128	1 to >128	17.6
Ceftazidime-avibactam ^b	64	128	0.125 to >128	23.5
Chloramphenicol	16	32	2 to 64	35.3
Delafloxacin	8	16	0.5 to 16	

(Continued on next page)

TABLE 2 (Continued)

Parameter and drug	MIC (mg/liter)			% susceptible
	50%	90%	Range	
Eravacycline	2	8	0.5 to 8	
Levofloxacin	8	>16	0.25 to >16	35.3
Minocycline	2	8	0.5 to 8	88.2
Moxifloxacin	4	16	0.125 to 16	
Omadacycline	8	64	1 to 64	
Polymyxin B ^c	0.5	>8	0.03 to >8	70.6
Tigecycline ^d	1	8	0.25 to 8	76.5
TMP-SMZ ^e	8	>8	0.03 to >8	29.4
Non-U.S. (n = 24)				
Ceftazidime	64	>128	1 to >128	16.7
Ceftazidime-avibactam ^b	64	>128	1 to >128	16.7
Chloramphenicol	32	>64	4 to >64	16.7
Delafloxacin	8	16	1 to 32	
Eravacycline	2	8	0.5 to 16	
Levofloxacin	8	>16	0.5 to >16	25.0
Minocycline	2	4	0.125 to 8	95.8
Moxifloxacin	4	8	0.5 to 16	
Omadacycline	16	32	0.5 to >64	
Polymyxin B ^c	0.5	>8	0.06 to >8	75.0
Tigecycline ^d	1	8	0.125 to >8	70.8
TMP-SMZ ^e	8	>8	0.25 to >8	41.7

^aNo statistically significant differences in MIC distribution were present for any agent based on infection type, acquisition setting, or location using the Mann-Whitney U test.

^bSusceptibility interpretations based on CLSI-approved breakpoints for ceftazidime alone.

^cBased on CLSI breakpoints for *Pseudomonas aeruginosa*.

^dBased on FDA breakpoints for *Enterobacteriaceae*.

^eReflects MIC of trimethoprim component only.

collected in the United States via the SENTRY program from 2014 to 2018 demonstrated MIC₅₀, MIC₉₀, and percent susceptibility for levofloxacin and TMP-SMZ of 1 mg/liter, >4 mg/liter, and 75.8% and ≤0.5 mg/liter, 1 mg/liter, and 94.6%, respectively (20). Additional limitations include the number of isolates, lack of molecular analysis of all isolates, and exclusion of pipeline agents that may have activity against MDR *S. maltophilia* (e.g., cefiderocol and aztreonam-avibactam). Further studies evaluating the genotypic mechanisms of resistance among *S. maltophilia*, particularly to the tetracyclines, are needed in order to elucidate the within-class differences in phenotypes observed in this study. Finally, the susceptibility rates reported for agents without approved interpretive criteria for *S. maltophilia* (e.g., tigecycline and polymyxin B) should be interpreted with caution, as they may over- or undercall true resistance rates.

In summary, these data demonstrate how few antimicrobial agents, old or new, have reliable activity against *S. maltophilia*, particularly against strains resistant to one or both current first-line agents. Minocycline demonstrated the most reliable *in vitro* activity, and its role in the clinical arena for the treatment of infections due to *S. maltophilia* warrants further investigation given its favorable adverse event profile, minimal drug-drug interactions, extensive body site penetration, and the availability of both intravenous (i.v.) and oral formulations.

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REFERENCES

1. Lodise TP, Jr, Echols R, Wang W, Corvino F, Cai B. 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:S360. <https://doi.org/10.1093/ofid/ofy210.1024>.

2. 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>.
3. Falagas ME, Kastoris AC, Vouloumanou EK, Dimopoulos G. 2009. Community-acquired *Stenotrophomonas maltophilia* infections: a systematic review. *Eur J Clin Microbiol Infect Dis* 28:719–730. <https://doi.org/10.1007/s10096-009-0709-5>.
4. Waters V, Atenafu EG, Lu A, Yau Y, Tullis E, Ratjen F. 2013. Chronic *Stenotrophomonas maltophilia* infection and mortality or lung transplantation in cystic fibrosis patients. *J Cyst Fibros* 12:482–486. <https://doi.org/10.1016/j.jcf.2012.12.006>.
5. Adegoke AA, Stenstrom TA, Okoh AI. 2017. *Stenotrophomonas maltophilia* as an emerging ubiquitous pathogen: looking beyond contemporary antibiotic therapy. *Front Microbiol* 8:2276. <https://doi.org/10.3389/fmicb.2017.02276>.
6. Gales AC, Jones RN, Forward KR, Linares J, Sader HS, Verhoef J. 2001. Emerging importance of multidrug-resistant *Acinetobacter* species and *Stenotrophomonas maltophilia* as pathogens in seriously ill patients: geographic patterns, epidemiological features, and trends in the SENTRY Antimicrobial Surveillance Program (1997–1999). *Clin Infect Dis* 32(Suppl 2):S104–S113. <https://doi.org/10.1086/320183>.
7. Farrell DJ, Sader HS, Jones RN. 2010. Antimicrobial susceptibilities of a worldwide collection of *Stenotrophomonas maltophilia* isolates tested against tigecycline and agents commonly used for *S. maltophilia* infections. *Antimicrob Agents Chemother* 54:2735–2737. <https://doi.org/10.1128/AAC.01774-09>.
8. Nicodemo AC, Paez JL. 2007. Antimicrobial therapy for *Stenotrophomonas maltophilia* infections. *Eur J Clin Microbiol Infect Dis* 26:229–237. <https://doi.org/10.1007/s10096-007-0279-3>.
9. Toleman MA, Bennett PM, Bennett DM, Jones RN, Walsh TR. 2007. Global emergence of trimethoprim/sulfamethoxazole resistance in *Stenotrophomonas maltophilia* mediated by acquisition of sul genes. *Emerg Infect Dis* 13:559–565. <https://doi.org/10.3201/eid1304.061378>.
10. Wang WS, Liu CP, Lee CM, Huang FY. 2004. *Stenotrophomonas maltophilia* bacteremia in adults: four years' experience in a medical center in northern Taiwan. *J Microbiol Immunol Infect* 37:359–365.
11. 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>.
12. 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>.
13. Bostanghadiri N, Ghalavand Z, Fallah F, Yadegar A, Ardebili A, Tarashi S, Pournajaf A, Mardaneh J, Shams S, Hashemi A. 2019. Characterization of phenotypic and genotypic diversity of *Stenotrophomonas maltophilia* strains isolated from selected hospitals in Iran. *Front Microbiol* 10:1191. <https://doi.org/10.3389/fmicb.2019.01191>.
14. Gajdacs M, Urban E. 2019. Prevalence and antibiotic resistance of *Stenotrophomonas maltophilia* in respiratory tract samples: a 10-year epidemiological snapshot. *Health Serv Res Manag Epidemiol* 6:233339. <https://doi.org/10.1186/s13023-019-00774-7>.
15. 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>.
16. 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>.
17. Flamm RK, Castanheira M, Streit JM, Jones RN. 2016. Minocycline activity tested against *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* species complex isolates from a global surveillance program (2013). *Diagn Microbiol Infect Dis* 85: 352–355. <https://doi.org/10.1016/j.diagmicrobio.2016.03.019>.
18. Nys C, Cherabuddi K, Venugopalan V, Klinker KP. 2019. Clinical and microbiologic outcomes in patients with monomicrobial *Stenotrophomonas maltophilia* infections. *Antimicrob Agents Chemother* 63: e00788-19. <https://doi.org/10.1128/aac.00788-19>.
19. Badwal J, Traugott K, Hand E. 2018. 2419. Standard vs. alternative therapy for *Stenotrophomonas maltophilia* infections: focus on trimethoprim-sulfamethoxazole, minocycline, and moxifloxacin monotherapy. *Open Forum Infect Dis* 5:S723. <https://doi.org/10.1093/ofid/ofy210.2072>.
20. Flamm RK, Shortridge D, Castanheira M, Sader HS, Pfaller MA. 2019. *In vitro* activity of minocycline against U.S. isolates of *Acinetobacter baumannii*-*Acinetobacter calcoaceticus* species complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* complex: results from the SENTRY Antimicrobial Surveillance Program (2014–2018). *Antimicrob Agents Chemother* 63:e01154-19. <https://doi.org/10.1128/aac.01154-19>.
21. CLSI. 2019. Performance standards for antimicrobial susceptibility testing. CLSI document M100-S29. Clinical and Laboratory Standards Institute, Wayne, PA.
22. Cai B, Echols R, Morgan G, Marcella S, Ariyasu M, Sawada T, Nagata T. 2019. Prevalence and treatment of *Stenotrophomonas maltophilia* among adult patients in United States hospitals between 2010 and 2015, poster 0911. *Abstr 29th Eur Clin Conf Microbiol Infect Dis*.
23. Yahav D, Lador A, Paul M, Leibovici L. 2011. Efficacy and safety of tigecycline: a systematic review and meta-analysis. *J Antimicrob Chemother* 66:1963–1971. <https://doi.org/10.1093/jac/dkr242>.
24. Sutcliffe JA, O'Brien W, Fyfe C, Grossman TH. 2013. Antibacterial activity of eravacycline (TP-434), a novel fluorocycline, against hospital and community pathogens. *Antimicrob Agents Chemother* 57:5548–5558. <https://doi.org/10.1128/AAC.01288-13>.
25. Morrissey I, Bassetti M, Magnet S, Hawser S, Olesky M, Fyfe C. 2017. *In vitro* activity of eravacycline and comparator agents against *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and *Enterobacteriaceae*, including carbapenem-resistant and ESBL phenotype subgroups, collected from European hospitals in 2015, poster P1260. 27th Eur Congr Clin Microbiol Infect Dis, Vienna, Austria.
26. Bassetti M, Corey R, Doi Y, Morrissey I, Grossman T, Olesky M, Sutcliffe J. 2016. *In vitro* global surveillance of eravacycline and comparators against *Enterobacteriaceae*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, including multidrug-resistant (MDR) isolates, over a three-year period (2013–15), poster 1825. ID Week 2016, 26 to 30 October 2016, New Orleans, LA.
27. Pfaller MA, Huband MD, Rhomberg PR, Flamm RK. 2017. Surveillance of omadacycline activity against clinical isolates from a global collection (North America, Europe, Latin America, Asia-Western Pacific), 2010–2011. *Antimicrob Agents Chemother* 61:e00018-17. <https://doi.org/10.1128/AAC.00018-17>.
28. Pfaller MA, Huband MD, Shortridge D, Flamm RK. 2018. Surveillance of omadacycline activity tested against clinical isolates from the United States and Europe as part of the 2016 SENTRY Antimicrobial Surveillance Program. *Antimicrob Agents Chemother* 62:e02327-17. <https://doi.org/10.1128/AAC.02327-17>.
29. Huband M, Rhomberg P, Sader H, Schuchert J, Flamm R. 2017. *In vitro* activity of omadacycline and comparators against Gram-negative bacterial isolates collected from patients in European medical centres (2016): results from the SENTRY antimicrobial surveillance program, poster P1253. 27th Eur Congr Clin Microbiol Infect Dis, 22 to 25 April 2017, Vienna, Austria.
30. CLSI. 2012. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. CLSI document M07-A9. Clinical and Laboratory Standards Institute, Wayne, PA.
31. 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>.
32. Ko J-H, Kang C-I, Cornejo-Juárez P, Yeh K-M, Wang C-H, Cho SY, Gözel MG, Kim S-H, Hsueh P-R, Sekiya N, Matsumura Y, Lee D-G, Cho S-Y, Shiratori S, Kim Y-J, Chung DR, Peck KR. 2019. Fluoroquinolones versus trimethoprim-sulfamethoxazole for the treatment of *Stenotrophomonas maltophilia* infections: a systematic review and meta-analysis. *Clin Microbiol Infect* 25:546–554. <https://doi.org/10.1016/j.cmi.2018.11.008>.
33. Zhao J, Liu Y, Liu Y, Wang D, Ni W, Wang R, Liu Y, Zhang B. 2018. Frequency and genetic determinants of tigecycline resistance in clinically isolated *Stenotrophomonas maltophilia* in Beijing, China. *Front Microbiol* 9:549. <https://doi.org/10.3389/fmicb.2018.00549>.
34. Wei C, Ni W, Cai X, Cui J. 2015. A Monte Carlo pharmacokinetic/pharmacodynamic simulation to evaluate the efficacy of minocycline, tigecycline, moxifloxacin, and levofloxacin in the treatment of hospital-acquired pneumonia caused by *Stenotrophomonas maltophilia*. *Infect Dis (Lond)* 47:846–851. <https://doi.org/10.3109/23744235.2015.1064542>.
35. Chung HS, Hong SG, Lee Y, Kim M, Yong D, Jeong SH, Lee K, Chong Y. 2012. Antimicrobial susceptibility of *Stenotrophomonas maltophilia* iso-

- lates from a Korean tertiary care hospital. *Yonsei Med J* 53:439–441. <https://doi.org/10.3349/ymj.2012.53.2.439>.
36. Grillon A, Schramm F, Kleinberg M, Jehl F. 2016. Comparative activity of ciprofloxacin, levofloxacin and moxifloxacin against *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* assessed by minimum inhibitory concentrations and time-kill studies. *PLoS One* 11:e0156690. <https://doi.org/10.1371/journal.pone.0156690>.
37. Rodriguez-Martinez JM, Poirel L, Nordmann P. 2009. Molecular epidemiology and mechanisms of carbapenem resistance in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 53:4783–4788. <https://doi.org/10.1128/AAC.00574-09>.
38. Shortridge D, Arends SJR, Streit JM, Castanheira M, Flamm RK. 2019. Minocycline activity against *Stenotrophomonas maltophilia* isolates from patients in US hospitals, poster 1584. ID Week 2019, Washington, DC, 2 to 6 October 2019.