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Antimicrobial Activity of Aztreonam-Avibactam and Comparator Agents When Tested against a Large Collection of Contemporary *Stenotrophomonas maltophilia* Isolates from Medical Centers Worldwide

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ABSTRACT Aztreonam-avibactam was tested against 1,839 *Stenotrophomonas maltophilia* isolates collected worldwide and demonstrated potent activity against isolates from all geographic regions and infection types (overall $MIC_{50/90}$, 4/4 mg/liter; 97.8% inhibited at ≤8 mg/liter). Trimethoprim-sulfamethoxazole (TMP-SMX) ($MIC_{50/90}$, ≤0.5/1 mg/liter; 95.4% susceptible) and minocycline ($MIC_{50/90}$, 0.5/2 mg/liter; 99.5% susceptible) were also very active. Aztreonam-avibactam inhibited 84.7% of non-TMP-SMX-susceptible isolates at ≤8 mg/liter. Aztreonam-avibactam may represent a valuable option for the treatment of *S. maltophilia* infections, addressing a major unmet medical need.

KEYWORDS Gram-negative bacteria, *Stenotrophomonas maltophilia*, aztreonam-avibactam, bloodstream infections, nonfermentative, trimethoprim-sulfamethoxazole

The occurrence of *Stenotrophomonas maltophilia* infections has increased continuously in recent years, becoming a major cause of hospital-acquired pneumonia (HAP) and bloodstream infections (BSI) and an increasingly frequent colonizer of the lungs of cystic fibrosis patients (1–3). Moreover, the selection of an appropriate antimicrobial regimen for the treatment of *S. maltophilia* infections is complicated by the high level of intrinsic resistance and uncertainties related to breakpoint criteria for susceptibility testing (2, 4). Thus, *S. maltophilia* is recognized by the World Health Organization as one of the leading multidrug-resistant organisms in hospital settings for which disease prevention and treatment strategies must be developed (5).

S. maltophilia displays decreased susceptibility to many antimicrobial agents, including agents used empirically to treat pneumonia and bloodstream infections, the two most common types of *S. maltophilia* infections. Low membrane permeability, chromosomally encoded multidrug resistance efflux pumps, and the production of two inducible β-lactamases (L1 and L2) contribute to the intrinsic resistance of *S. maltophilia* to most β-lactam agents currently available for clinical use (6, 7). L1 is a class B3 metallo-β-lactamase (MBL) that hydrolyzes carbapenems and other β-lactams but not the monobactam aztreonam. L1 is resistant to all clinically available β-lactamase inhibitors. L2 is a class A cephalosporinase that confers resistance to broad-spectrum cephalosporins and aztreonam but is inhibited by commercially available serine-β-lactamase inhibitors, such as tazobactam and avibactam (8). Results of steady-state kinetics and electrospray ionization mass spectrometry experiments have demonstrated that avibactam competitively and reversibly inhibits L2, and the carbamylation rates (k_2/K) for L2 are comparable to those results published for the avibactam inactivation of KPC-2 (9). The most recent Food and Drug Administration (FDA)-approved β-lactam–β-lactamase inhibitor combinations—such as ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, and imipenem-relebac-

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tam—are potent inhibitors of class A carbapenemases but are ineffective against L1 MBL produced by *S. maltophilia* (10). Therefore, it is crucial to develop new agents to treat *S. maltophilia* infections.

Aztreonam-avibactam is a drug combination currently undergoing clinical trials to assess its efficacy in treating infections caused by Gram-negative organisms, including those organisms producing MBLs. Aztreonam, the only clinically available monobactam, is a β-lactam antibiotic that was approved for treatment of Gram-negative infections by the U.S. FDA in 1986. Aztreonam is stable to hydrolysis by MBLs, a feature unique among β-lactams; however, it is hydrolyzed by most clinically relevant serine β-lactamases (11). Avibactam is a non-β-lactam β-lactamase inhibitor that inhibits Ambler class A (including L2 produced by *S. maltophilia*), class C, and some class D enzymes (12). Thus, the aztreonam-avibactam combination has demonstrated activity against Gram-negative bacteria producing most clinically relevant β-lactamases, including MBLs (13), and is being developed to treat serious infections caused by MBL-producing Gram-negative bacteria (ClinicalTrials registration no. NCT03580044). In this study, we evaluated the *in vitro* activity of 1,839 clinical *S. maltophilia* isolates collected worldwide from 2016 to 2019.

A total of 1,839 *S. maltophilia* isolates were collected from 145 medical centers located in Western Europe (W-EU; $n = 388$; 24 centers in 9 nations [Belgium, France, Germany, Ireland, Italy, Portugal, Spain, Sweden, and the United Kingdom]), Eastern Europe and Mediterranean region (E-EU; $n = 156$; 15 centers in 12 nations [Belarus, Croatia, Czech Republic, Greece, Hungary, Israel, Poland, Romania, Russia, Slovakia, Slovenia, and Turkey]), North America (NA; $n = 1,095$; 75 centers in the United States and 2 in Canada), Latin America (LATAM; $n = 92$; 12 centers in 9 nations [Argentina, Brazil, Chile, Costa Rica, Ecuador, Mexico, Panama, Peru, and Venezuela]), and the Asia-Pacific region (APAC; $n = 108$; 17 centers in 8 nations [Australia, Japan, Malaysia, New Zealand, Philippines, Singapore, South Korea, and Taiwan]) as part of the SENTRY Antimicrobial Surveillance Program. All bacterial species were consecutively collected by infection type. Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program. The criteria used to categorize a bacterial isolate as "clinically significant" were not defined in the study protocol, but they were based on local algorithms, which may vary among participating medical centers. Species identification was confirmed by using standard biochemical tests and/or a MALDI Biotyper (Bruker Daltonics, Billerica, MA, USA) when necessary.

Isolates were tested against aztreonam-avibactam and >25 comparator agents by the broth microdilution method, according to CLSI guidelines (14). All tests were conducted in a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA). Aztreonam-avibactam was tested with avibactam at a fixed concentration of 4 mg/liter based on the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of avibactam, the known spectrum of β-lactamase inhibition by avibactam, and the fact that avibactam alone has no antibacterial activity at a clinically relevant concentration (15, 16).

A cutoff of $\leq$8 mg/liter, which indicates the aztreonam susceptible breakpoint published by CLSI for *Pseudomonas aeruginosa* and the aztreonam-avibactam tentative PK/PD susceptible breakpoint, was applied to aztreonam-avibactam for comparison purposes (17–19). CLSI breakpoints were applied for the following comparator agents: trimethoprim-sulfamethoxazole (TMP-SMX; susceptible at $\leq$2 mg/liter and resistant at $\geq$4 mg/liter), minocycline (susceptible at $\leq$4 mg/liter and resistant at $\geq$16 mg/liter), levofloxacin (susceptible at $\leq$2 mg/liter and resistant at $\geq$8 mg/liter), and ceftazidime (susceptible at $\leq$8 mg/liter and resistant at $\geq$32 mg/liter) (17). The only published EUCAST breakpoints are for TMP-SMX (susceptible at $\leq$0.001 mg/liter and resistant at >4 mg/liter) (20). Colistin breakpoints published by the CLSI for *P. aeruginosa* (susceptible at $\leq$2 mg/liter) and tigecycline breakpoints published by the U.S. FDA for *Enterobacterales* (susceptible at $\leq$2 mg/liter) were applied for comparison purposes (17, 21). Concurrent quality control (QC) testing was performed to ensure proper test conditions and procedures.

These isolates mostly came from patients with pneumonia (70.4%) and BSI (12.6%).

TABLE 1 MIC distributions of aztreonam-avibactam and comparator agents tested against *Stenotrophomonas maltophilia* isolates collected worldwide (2016–2019)

Antimicrobial agent	No. of isolates (cumulative %) inhibited at a MIC (mg/liter) of:											MIC (mg/liter)	
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>[a]	50%	90%
Aztreonam-avibactam	0 (0.0)	1 (0.1)	3 (0.2)	12 (0.9)	132 (8.0)	766 (49.7)	780 (92.1)	105 (97.8)	16 (98.7)		24 (100.0)	4	4
Ceftazidime	0 (0.0)	1 (0.1)	0 (0.1)	0 (0.1)	26 (1.4)	113 (7.6)	115 (13.8)	131 (20.9)	148 (29.0)	240 (42.0)	1,066 (100.0)	>32	>32
Colistin	8 (0.4)	77 (4.6)	194 (15.2)	164 (24.1)	159 (32.7)	160 (41.4)	257 (55.4)	287 (71.0)			533 (100.0)	4	>8
Levofloxacin	0 (0.0)	1 (0.1)	45 (2.5)	326 (20.2)	709 (58.8)	354 (78.0)	173 (87.4)				231 (100.0)	1	>4
Moxifloxacin			736 (42.9)	404 (66.5)	238 (80.3)	132 (88.0)	94 (93.5)				111 (100.0)	0.5	4
Minocycline	0 (0.0)	1 (1.0)	11 (11.7)	65 (74.8)	15 (89.3)	5 (94.2)	5 (99.0)	1 (100.0)				0.5	2
Tigecycline	1 (0.1)	5 (0.3)	94 (5.4)	464 (30.7)	633 (65.1)	366 (85.0)	179 (94.8)	85 (99.4)			11 (100.0)	1	2
TMP-SMX[b]				1,646 (89.7)	60 (92.9)	45 (95.4)	29 (96.9)				56 (100.0)	≤0.5	1

[a]Greater than the highest dilution tested.
[b]TMP-SMX, trimethoprim-sulfamethoxazole.

Other infection sites included skin and soft tissue (9.3%), intra-abdominal sites (3.3%), the urinary tract (2.4%), and other locations (2.1%).

Aztreonam-avibactam was very active against isolates from all geographic regions and infection types, with overall $MIC_{50/90}$ values of 4/4 mg/liter and 97.8% of isolates inhibited at ≤8 mg/liter (Table 1). Aztreonam-avibactam activity was consistent across regions, with the highest percentage of isolates inhibited at ≤8 mg/liter observed in LATAM (100.0%), followed by E-EU (98.7%), NA (98.1%), W-EU (96.6%), and APAC (96.3%) (Table 2). Moreover, aztreonam-avibactam inhibited 97.6% of isolates from pneumonia and 99.1% of isolates from BSI at ≤8 mg/liter (data not shown) and retained good activity against non-TMP-SMX-susceptible isolates, inhibiting 84.7% at ≤8 mg/liter (Table 2).

TMP-SMX ($MIC_{50/90}$, ≤0.5/1 mg/liter) and minocycline ($MIC_{50/90}$, 0.5/2 mg/liter) also were active against *S. maltophilia*. The percentage of isolates inhibited at the TMP-SMX susceptible breakpoint (≤2 mg/liter; CLSI) ranged from 93.5% in E-EU to 96.9% in W-EU. The percentage of isolates inhibited at the minocycline susceptible breakpoint (≤4 mg/liter; CLSI) was 99.0% in APAC and 100.0% in W-EU, E-EU, and LATAM (Tables 1 and 2). Furthermore, minocycline retained activity against 92.4% of non-TMP-SMX-susceptible isolates (Table 2).

The fluoroquinolones levofloxacin ($MIC_{50/90}$, 1/>4 mg/liter) and moxifloxacin ($MIC_{50/90}$, 0.5/4 mg/liter) exhibited moderate *in vitro* activity against *S. maltophilia*. Levofloxacin inhibited 78.0% of isolates at the current CLSI susceptible breakpoint for *S. maltophilia* (≤2 mg/liter) but only 58.8% at ≤1 mg/liter, which is the current levofloxacin breakpoint for *P. aeruginosa* according to the CLSI (17). Levofloxacin susceptibility rates were higher in LATAM (88.0%), APAC (87.0%), and W-EU (84.3%) than in E-EU (78.8%) and NA (74.0%) (Table 2). Moxifloxacin was approximately 2-fold less

TABLE 2 Aztreonam-avibactam and comparator agents tested against clinical isolates of *S. maltophilia* collected worldwide and stratified by geographic region (2016–2019)

Region or characteristic[a] (no. of isolates)	% of isolates susceptible[b] to:						
	ATM-AVI	TMP-SMX	Minocycline	Levofloxacin	Ceftazidime	Tigecycline	Colistin
All (1,839)	97.8	95.4	99.5	78.0	20.9	85.0	41.4
W-EU (388)	96.6	96.9	100.0	84.3	17.3	88.9	42.8
E-EU (156)	98.7	93.5	100.0	78.8	16.7	84.0	42.9
NA (1,095)	98.1	95.0	99.2	74.0	22.0	83.0	41.6
LATAM (92)	100.0	96.7	100.0	88.0	30.4	88.0	29.3
APAC (108)	96.3	95.3	99.0	87.0	21.3	90.7	42.6
TMP-SMX-NS (85)	84.7	0.0	92.4	30.6	14.1	66.7	40.0

[a]W-EU, Western Europe; E-EU, Eastern Europe; NA, North America; LATAM, Latin America; APAC, Asia-Pacific region; TMP-SMX-NS, isolates not susceptible to trimethoprim-sulfamethoxazole (17).
[b]For TMP-SMX, minocycline, levofloxacin, and ceftazidime, the percentage of isolates susceptible by CLSI criteria is shown. For aztreonam-avibactam (ATM-AVI), the percentage inhibited at ≤8 mg/liter is shown for purposes of comparison (18). For tigecycline, the percentage inhibited at ≤2 mg/liter, the U.S. FDA susceptible breakpoint for *Enterobacterales*, is shown (21). For colistin, the percentage inhibited at ≤2 mg/liter, the CLSI susceptible breakpoint for *P. aeruginosa*, is shown (17) for comparison.

active than levofloxacin and inhibited 80.3% of isolates at ≤1 mg/liter, but inhibited only 42.9% at ≤0.25 mg/liter, which is the current EUCAST breakpoint for *Enterobacterales* (66.5% inhibited at ≤0.5 mg/liter) (Table 1) (20). Ciprofloxacin ($MIC_{50/90}$, 2/>4 mg/liter) was the least active of the fluoroquinolones tested; it inhibited only 2.8% of isolates at ≤0.5 mg/liter, which is the current CLSI breakpoint for *P. aeruginosa* (data not shown).

Evaluation of the *in vitro* activity of tigecycline depends greatly on the cutoff applied. Overall, 85.0% of isolates were inhibited at ≤2 mg/liter, which is the susceptible breakpoint published by the U.S. FDA for *Enterobacterales* (21). However, only 30.7% of isolates were inhibited at ≤0.5 mg/liter, which is the breakpoint currently published by EUCAST for *Escherichia coli* and *Citrobacter koseri* (Table 1) (20). Ceftazidime ($MIC_{50/90}$, >32/>32 mg/liter; 20.9% susceptible at ≤8 mg/liter) (17) and colistin ($MIC_{50/90}$, 4/>8 mg/liter; 41.4% inhibited at ≤2 mg/liter) showed limited activity against *S. maltophilia* (Tables 1 and 2). Other compounds that demonstrated limited activity were ceftazidime-avibactam ($MIC_{50/90}$, 32/>32 mg/liter) and ceftolozane-tazobactam ($MIC_{50/90}$, >16/>16 mg/liter).

The main limitation of this study is that other new compounds that may be active against *S. maltophilia*, such as eravacycline and cefiderocol, could not be included as comparators.

The selection of proper antibiotic treatment for *S. maltophilia* infections poses a challenge due to the lack of controlled clinical trials evaluating treatment regimens. Current treatment recommendations are based on historical evidence, cases series, case reports, and *in vitro* susceptibility test studies (22, 23). TMP-SMX is considered the first-line agent for *S. maltophilia* infections due to historically high susceptibility rates and large clinical experience. However, adverse effects, such as nephrotoxicity and hyperkalemia, allergic reactions, intolerance, and resistance, can limit its usage. Fluoroquinolones also may be used, but there is limited information on their effectiveness (24–26). Minocycline has emerged as a potential treatment for *S. maltophilia* infection due to high susceptibility rates, excellent penetration into the lungs, high oral bioavailability, and a favorable safety profile; however, clinical data are scarce (27). In summary, the availability of drugs with *in vitro* activity against this organism that have demonstrated clinical efficacy is very limited; therefore, new treatment options are clearly needed.

We evaluated the *in vitro* activity of a large collection of contemporary clinical isolates of *S. maltophilia*. Our results indicated that aztreonam-avibactam, TMP-SMX, and minocycline are the most active compounds against this organism. It should be noted that PK/PD and clinical studies evaluating *S. maltophilia* infections are very limited and that currently available breakpoint criteria for susceptibility testing are dated and were mostly based only on *in vitro* susceptibility testing results (MIC distributions) and/or on PK/PD data generated with other nonfermentative Gram-negative species more frequently isolated in the clinical setting (28).

Based on the tentative PK/PD susceptible breakpoint for aztreonam-avibactam, which agrees with the current aztreonam susceptible breakpoint published by the CLSI for *P. aeruginosa* (≤8 mg/liter), aztreonam-avibactam was active against 97.8% of isolates. This percentage is slightly higher than the percentage of isolates susceptible to TMP-SMX (95.4%) and slightly lower than the percentage of isolates susceptible to minocycline (99.5%) based on current CLSI criteria for these agents (17). Notably, if one applied a breakpoint 1 doubling dilution lower, these three agents would still remain active against >90% of isolates (Table 1). Levofloxacin and moxifloxacin were the most active of the fluoroquinolones, but both agents exhibited low susceptibility rates when the breakpoints currently published by the CLSI and EUCAST for *P. aeruginosa* and *Enterobacterales* were applied (17, 20). It is important, however, that the treatment cost be carefully weighed when other agents are also active against *S. maltophilia*.

In summary, aztreonam-avibactam demonstrated potent *in vitro* activity against a large worldwide collection of contemporary *S. maltophilia* isolates collected from patients with pneumonia, bloodstream infections, and other systemic infections. The

results of this investigation indicate that aztreonam-avibactam may represent a valuable option for the treatment of *S. maltophilia* infections, addressing a major unmet medical need. These findings support the clinical development of aztreonam-avibactam to treat infections caused by this organism.

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