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Antimicrobial Activity of Aztreonam-Avibactam and Comparator Agents against a Large Collection of *Stenotrophomonas maltophilia* Isolates Collected in Europe, Asia, and Latin America (2018–2023)

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Introduction

- Aztreonam-avibactam is under development to treat infections caused by Gram-negative bacteria, including metallo-β-lactamase (MBL) producers.
- Aztreonam is a monobactam stable to hydrolysis by MBLs, including those intrinsically produced by *S. maltophilia*.
- Avibactam is a non–β-lactam β-lactamase inhibitor that inhibits most clinically relevant serine β-lactamases, such as extended-spectrum β-lactamases (ESBLs), KPCs, AmpCs, and some OXAs.
- The occurrence of *S. maltophilia* infections has increased continuously in the last few years.
- We evaluated the *in vitro* activities of aztreonam-avibactam (avibactam fixed at 4 mg/L) and comparators against a large collection of *S. maltophilia*.

Methods

- 1,078 clinical isolates were collected from 57 medical centres as part of the SENTRY Antimicrobial Surveillance Program. Centres were located in:
  - Western Europe (W-EU; n=589), 28 centres in 10 countries: Belgium, France, Germany, Ireland, Italy, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.
  - Eastern Europe (E-EU; n=251), 12 centres in 8 countries: Czech Republic, Greece, Hungary, Israel, Poland, Romania, Slovenia, and Turkey.
  - Asia-Pacific region (APAC; n=154), 10 centres in 6 countries: Australia, Malaysia, New Zealand, Philippines, South Korea, and Taiwan.
  - Latin America (LATAM; n=84), 7 centres in 4 countries: Brazil, Chile, Mexico, and Panama.
- Infection sites included pneumonia (n=671), bacteraemia (n=201), and others (n=206).
- Isolates were susceptibility tested by CLSI M07 (2018) broth microdilution method.
- An aztreonam-avibactam pharmacodynamic/pharmacokinetic (PK/PD) susceptible breakpoint of ≤8 mg/L was applied for comparison.
- EUCAST and CLSI/US FDA breakpoints were applied when available.

Results

- *S. maltophilia* isolates were collected mostly from patients with pneumonia and bloodstream infection (Figure 1).
- Aztreonam-avibactam demonstrated potent activity against isolates from all geographic regions and infection types ($MIC_{50/90}$, 4/4 mg/L; 98.2% inhibited at ≤8 mg/L; Tables 1 and 2 and Figure 2).
- Aztreonam-avibactam activity remained stable during the study period (Table 1).
- The percentage inhibited at ≤8 mg/L ranged from 97.4% in APAC to 100.0% in LATAM (Table 2).
- Aztreonam-avibactam inhibited 98.1% of isolates from pneumonia and 99.0% of isolates from bloodstream infection at ≤8 mg/L (Table 2).
- Aztreonam-avibactam retained potent activity against trimethoprim-sulfamethoxazole–nonsusceptible isolates, inhibiting 90.9% at ≤8 mg/L (Table 2).
- Trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.12/0.5 mg/L; 95.9% susceptible), minocycline ($MIC_{50/90}$, 0.5/1 mg/L; 99.5% susceptible), and moxifloxacin ($MIC_{50/90}$, 0.5/2 mg/L; 92.6% inhibited at ≤2 mg/L) also were very active against *S. maltophilia* based on current breakpoint criteria (Figure 3).
- Levofloxacin and ceftazidime were active against 84.1% and 17.8% of isolates at their respective CLSI breakpoints (Figure 3).

Conclusions

- Aztreonam-avibactam demonstrated potent *in vitro* activity against *S. maltophilia* from Europe, Asia, and Latin America and may represent a valuable option to treat *S. maltophilia* infections, addressing a major unmet medical need.
- Clinical studies are urgently warranted to evaluate the efficacy of aztreonam-avibactam against infection caused by *S. maltophilia*.
- Although *S. maltophilia* exhibited high susceptibility rates for some antimicrobial agents based on current breakpoint criteria, these results should be interpreted with caution since those breakpoints were established in the 1980s, i.e., before the knowledge of PK/PD parameters that are currently used to establish breakpoints.

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Table 1. Aztreonam-avibactam activity stratified by region and year

Region (no. isolates)	Aztreonam-avibactam MIC_{50}/MIC_{90} (% inhibited at ≤8 mg/L) by year (no. of isolates)						
	2018 (162)	2019 (159)	2020 (179)	2021 (179)	2022 (273)	2023 (126)	All (1,078)
All (1,078)	4/4 (96.9)	2/4 (96.2)	4/4 (97.2)	2/4 (99.4)	2/4 (100.0)	2/4 (98.4)	4/4 (98.2)
W-EU (589)	4/4 (94.6)	2/4 (97.2)	4/4 (97.8)	4/4 (100.0)	2/4 (100.0)	2/4 (97.6)	2/4 (98.1)
E-EU (251)	4/8 (100.0)	2/4 (98.0)	4/8 (95.3)	2/4 (97.6)	4/4 (100.0)	2/8 (100.0)	4/4 (98.4)
APAC (154)	2/4 (100.0)	2/16 (89.7)	4/4 (96.3)	2/4 (100.0)	4/4 (100.0)	2/4 (100.0)	2/4 (97.4)
LATAM (84)	4/4 (100.0)	4/4 (100.0)	4/4 (100.0)	2/8 (100.0)	4/4 (100.0)	4/— (100.0)	4/4 (100.0)

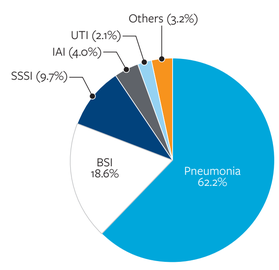
Abbreviations: W-EU, Western Europe; E-EU, Eastern Europe; APAC, Asia-Pacific region; LATAM, Latin America.

Table 2. Activity of aztreonam-avibactam and comparator agents stratified by region and infection type

Region / Infection Type (no. isolates)	% susceptible per EUCAST or CLSI criteria					
	ATM-AVI[a]	TMP-SMX[b]	Minocycline[c]	Levofloxacin[c]	Ceftazidime[c]	Tigecycline[d]
All Regions (1,078)	98.2	95.9	92.1	84.1	17.8	91.6
W-EU (589)	98.1	97.4	93.5	85.2	16.5	92.2
E-EU (251)	98.4	95.2	89.6	81.6	17.1	90.0
APAC (108)	97.4	94.1	91.6	86.4	18.8	91.6
LATAM (92)	100.0	90.5	90.5	79.8	27.4	91.7
Pneumonia (671)	98.1	96.3	92.4	84.6	15.2	92.5
BSI (201)	99.0	97.0	94.0	85.1	22.9	92.0
Others (206)	98.1	93.7	89.2	81.6	21.4	87.9
TMP-SMX-NS (44)[e]	90.9	0.0	61.4	52.3	6.8	81.8

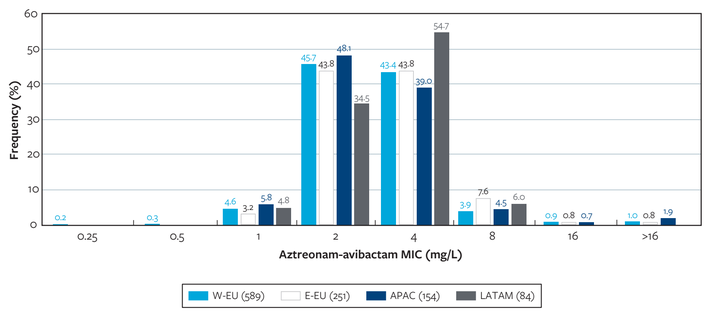
[a] % inhibited at ≤8 mg/L for comparison purpose.
[b] % susceptible per EUCAST criteria.
[c] % susceptible per 2024 CLSI criteria, except ceftazidime, for which 2023 CLSI criteria were applied.
[d] % inhibited at ≤2 mg/L, which is the US FDA susceptible breakpoint for Enterobacterales for comparison.
[e] Isolates not susceptible to trimethoprim-sulfamethoxazole per EUCAST criteria.
Abbreviations: ATM-AVI, aztreonam-avibactam; TMP-SMX, trimethoprim-sulfamethoxazole; W-EU, Western Europe; E-EU, Eastern Europe; APAC, Asia-Pacific region; LATAM, Latin America; BSI, bloodstream infection; NS, nonsusceptible.

Figure 1. Distribution of *S. maltophilia* isolates by infection type



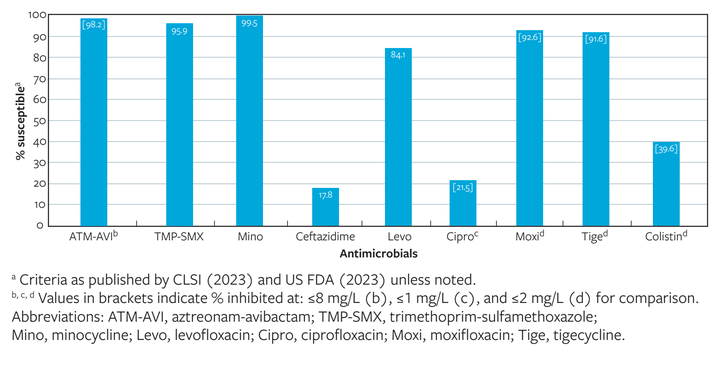
Abbreviations: BSI, bloodstream infection; SSSI, skin and skin structure infection; IAI, intraabdominal infection; UTI, urinary tract infection.

Figure 2. Aztreonam-avibactam MIC distributions stratified by region



Abbreviations: W-EU, Western Europe; E-EU, Eastern Europe; APAC, Asia-Pacific region; LATAM, Latin America.

Figure 3. Antimicrobial susceptibility of *S. maltophilia* (*n*=1,078) from Europe, Asia, and Latin America (2018–2023)



[a] Criteria as published by CLSI (2023) and US FDA (2023) unless noted.
[b, c, d] Values in brackets indicate % inhibited at: ≤8 mg/L (b), ≤1 mg/L (c), and ≤2 mg/L (d) for comparison.
Abbreviations: ATM-AVI, aztreonam-avibactam; TMP-SMX, trimethoprim-sulfamethoxazole; Mino, minocycline; Levo, levofloxacin; Cipro, ciprofloxacin; Moxi, moxifloxacin; Tige, tigecycline.

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