Current Management Strategies for *Stenotrophomonas maltophilia*

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KEYWORDS

• *Stenotrophomonas maltophilia* • Treatment • Combination therapy • Monotherapy • Pharmacokinetic • Pharmacodynamic • Breakpoint

KEY POINTS

- For critically-ill or immunocompromised patients with *Stenotrophomonas maltophilia* infections, combination therapy is recommended.
- Current susceptibility breakpoints should be interpreted with caution, regimen adjustment based on clinical response is paramount.
- Cefiderocol and aztreonam-avibactam demonstrate potent in vitro activity and represent promising therapeutic options; however, clinical data are needed to establish their impact on treatment outcomes.

INTRODUCTION

Stenotrophomonas maltophilia, a nonfermenting gram-negative bacterium (NFGNB) ubiquitous in the environment, has emerged as an opportunistic pathogen increasingly implicated nosocomial infections, particularly among immunocompromised patients. *S maltophilia* ranks among the top 10 pathogens isolated from hospitalized and intensive care unit patients with pneumonia[1,2] and has garnered increased attention following the coronavirus disease 2019 pandemic.[3] It is also associated with various health care-related scenarios, including catheter-associated infections, institutional outbreaks, and is recognized as a notorious multidrug-resistant (MDR) pathogen in patients with cystic fibrosis.[2] Trailing behind *Pseudomonas aeruginosa* and

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Abbreviations	
ARC	augmented renal clearance
BAL	bronchoalveolar lavage
CFR	cumulative fraction of response
CI	confidence interval
CLSI	The Clinical & Laboratory Standards Institute
Co-ticarclav	ticarcillin-clavulanic acid
EUCAST	European Committee on Antimicrobial Susceptibility Testing
ID	insufficient data
MDR	multidrug-resistant
MIC	minimum inhibitory concentration
NFGNB	nonfermenting gram-negative bacterium
OR	odds ratio
PTA	probability of target attainment
RCTs	randomized controlled trials
TMP-SMX	trimethoprim-sulfamethoxazole
VAP	ventilator-associated pneumonia

Acinetobacter baumannii, *S maltophilia* has become one the prominent pathogens among the difficult-to-treat NFGNB.

Despite of decades of clinical experiences, optimal treatment strategies remain undetermined. No randomized controlled trials (RCTs) have been conducted to date, and most available evidence is derived from observational studies. Clinical breakpoints remain largely undefined: European Committee on Antimicrobial Susceptibility Testing (EUCAST) currently provides breakpoints only for trimethoprim-sulfamethoxazole (TMP-SMX), while the Clinical & Laboratory Standards Institute (CLSI) has established breakpoints for 6 agents (TMP-SMX, minocycline, levofloxacin, cefiderocol, ticarcillin-clavulanate, and chloramphenicol). Only 2 existing guidelines, from the United States (Infectious Diseases Society of America [IDSA])[4] and Spain (Spanish Society of Infectious Diseases and Clinical Microbiology [SEIMC]),[5] offer therapeutic recommendations for *S maltophilia* infections. The IDSA guidance suggests combination therapy for moderate to severe *S maltophilia* infections, using either (1) any 2 agents among cefiderocol, minocycline, TMP-SMX, and levofloxacin or (2) ceftazidime-avibactam plus aztreonam. The SEIMC consensus document also endorses combination regimens for severe infections, designating TMP-SMX as the first-line agent and levofloxacin as an alternative. However, these recommendations are based on limited and inconclusive evidence.

MEDICAL TREATMENT OPTIONS

Treatment options for *S maltophilia* are inherently limited due to its intrinsic β-lactam resistance, mediated by 2 chromosomally encoded β-lactamases. L1 is a class B3 metallo-β-lactamase that hydrolyzes virtually all β-lactams (including carbapenems and β-lactamase inhibitors), with the notable exception of aztreonam. L2 is a class A cephalosporinase capable of inactivating broad-spectrum cephalosporins and aztreonam, but is inhibited by clavulanic acid and avibactam.[2] In the following discussion, several agents—ceftazidime, ticarcillin-clavulanate, chloramphenicol, and polymyxins—are not included. Ticarcillin-clavulanate and ceftazidime are considered unreliable given their β-lactam structure; notably, CLSI removed ceftazidime breakpoints in 2024. Chloramphenicol is omitted due to its significant toxicity compared to other agents. Although *S maltophilia* is not intrinsically resistant to polymyxins, the in vitro activity is inconsistent, breakpoints are lacking, and susceptibility results are difficult to interpret.[6]

Trimethoprim-Sulfamethoxazole

TMP-SMX was long considered the drug of choice for *S maltophilia* mainly due to its favorable in vitro susceptibility. However, in the 2024 IDSA guidance, while treatment with TMP-SMX is still regarded as a treatment option, it is only recommended to be used in combination. Concerns were raised from a pharmacokinetic/pharmacodynamic (PK/PD) perspective that TMP-SMX only achieves bacteriostasis (rather than cidality) against *S maltophilia*, and that clinical data supporting its effectiveness are lacking.[4] EUCAST has also raised concerns about TMP-SMX and lowered the breakpoint for resistance from 4 to 2 mg/L in 2025 (**Table 1**).[7]

In large-scale surveillance programs over nearly 3 decades, TMP-SMX has consistently demonstrated high susceptibility rates. The (SENTRY Antimicrobial Surveillance Program [SENTRY]) Antimicrobial Surveillance Program has provided the most comprehensive longitudinal reports on TMP-SMX against *S maltophilia* since 1997, consistently reporting susceptibility rates above 90% for this organism.[8–11] These findings are comparable with other large global surveillance programs such as SIDERO-WT (2014–2019)[12] and (The International Network for Optimal Resistance Monitoring [INFORM]),[13,14] although higher resistance rates have been observed in cohort studies.[15]

Despite the potentially favorable susceptibility data, PK/PD evidence confirming efficacy or guiding optimal dosing remains limited. In vitro studies show that TMP-SMX is at best bacteriostatic against *S maltophilia* while used alone. A 1-log bacteria reduction at 24 hours was only achieved when combined with fluoroquinolone, ceftazidime, and aminoglycoside.[16,17] A time-kill study using a TMP-SMX concentration equivalent to 20 mg/kg/d of the TMP moiety showed no reduction in any *S maltophilia* isolates regardless of minimum inhibitory concentration (MIC), while demonstrating significant killing against *Escherichia coli*.[18] Another chemostat model testing TMP-SMX at 10, 20, 50,100 mg/kg/d (TMP moiety) found only 13% of susceptible isolates could attain 1-log or greater reduction at 24 hours, with 56% showing bacteriostasis.[19] Intriguingly, even at supraphysiological exposures doses (50 and 100 mg/kg/d), the target of 1-log bacterial reduction was not achieved. A rabbit pneumonia model showed that TMP-SMX failed to eradicate bacteria from bronchoalveolar lavage (BAL) fluid and lung tissue, resulting in only 25% survival, compared to 87% for cefiderocol.[20]

No RCTs have been performed comparing TMP-SMX with other antibiotics for *S maltophilia* infections. The most recent and comprehensive meta-analysis and systematic review concluded that fluoroquinolone monotherapy was associated with significantly lower overall mortality than TMP-SMX (odds ratio [OR], 1.46; 95% confidence interval [CI], 1.15–1.86; 2407 patients).[21] TMP-SMX was also associated with higher mortality compared to tetracycline derivatives, but not statistically significant (OR, 0.71; 95% CI, 0.41–1.22; 3 studies, 346 patients). Notably, the significant effect toward fluoroquinolones was not evident after omitting the largest study (1581 patients) by Sarzynsk and colleagues (OR, 1.65; 95% CI, 0.98–2.78). Four additional comparative studies were published after this meta-analysis, comparing TMP-SMX versus minocycline,[22,23] tetracyclines,[24] and levofloxacin.[25] Three reported no significant differences across assessed outcomes. The most recent study (93 pneumonia patients) compared TMP-SMX and minocycline, finding higher in-hospital mortality with TMP-SMX and more recurrent pneumonia with minocycline, but no differences in clinical cure, infection-related in-hospital mortality, or complications.[22] It must be noted that observational studies comparing effectiveness of different regimens are prone to confounding and bias. Furthermore, different study designs limit comparability, including varying definition of clinical cure/failure, heterogeneous populations

Table 1
Summary of breakpoints and adult dosing recommendations

Antimicrobial Agents (Adult Dosing Recommendations)	CLSI MIC (mg/L)			EUCAST MIC (mg/L)			PK/PD BP[a]	History of Breakpoints Revisions			
	S	I	R	S	R	(T)ECOFF[b]		Year[c]	S	I	R
TMP-SMX: 10–15 mg/kg/d (TMP component), divided q8h-q6h	≤2	—	≥4	≤0.001[d]	>2	2	0.5[30]	(E) ∼2019	≤4		>4
								(E) 2020∼2024	≤0.001		>4
								(E) 2025∼	≤0.001		>2
Minocycline: 200 mg q12 h	≤1	2	≥4	—[e]	—	2	1[30]	(C) ∼2023	≤4	8	≥16
								(C) 2024∼	≤1	2	≥4
Levofloxacin: 750 mg q24 h	≤2	4	≥8	—[e]	—	4	0.25[30] 1[37]				
Cefiderocol[f]: 2g q8h; 2g q6h for ARC	≤1	—	—	—[e]	—	0.125		(C) 2019∼2021	≤4	8	≥16
								(C) 2022∼	≤1	—	—
Co-ticarclav	≤16	32–64	≥128	—	—	ID					
Chloramphenicol	≤8	4	≥32	—	—	NA					
Tigecycline: 200 mg loading, then 100 mg q12 h	—	—	—	—[e]	—	4	1[30,70]				
ATM-AVI[f]: 2.67 g loading, then 2g q6h	—	—	—	—[e]	—	8	2[30]				

Abbreviations: ARC, augmented renal clearance; ATM-AVI, aztreonam-avibactam; BP, breakpoints; Co-ticarclav, ticarcillin-clavulanic acid; ID, insufficient data; NA, not available; q6/8/12/24h, every 6/8/12/24 hours; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] The doses simulated for the proposed PK/PD breakpoints: minocycline, 200 mg q12 h; levofloxacin 750 mg q24 h; tigecycline, 100 mg q12 h; ATM-AVI, 2g q6h.

[b] (T)ECOFF: (tentative) epidemiologic cut-off value.

[c] (E): EUCAST, European Committee on Antimicrobial Susceptibility Testing; (C): CLSI, The Clinical & Laboratory Standards Institute.

[d] Arbitrary "off-the-scale" breakpoint of EUCAST to make sure no susceptible result reported.

[e] EUCAST published guidance document in November 2024.

[f] Administration details: *Cefiderocol*: 2g q8h or q6h infused over 3 h; *ceftazidime-avibactam plus aztreonam*: 2.5 g (2/0.5) q8h plus 2g q8h, infused simultaneously via Y-site over 3 h; *ATM-AVI*: 2.67 g (2/0.67) loading over 3 h, followed by 2g (1.5/0.5) q6h infusion over 3 h.

with differing mortality rates, inclusion of polymicrobial infections, and dosing variations ranging from 7 to 10 mg/kg/d[26,27] to 15 to 20 mg/kg/d,[22,28] or fixed doses.[29]

Evidence remains too scarce to determine the optimal dose range. The 2024 IDSA guidance recommends 10 to 15 mg/kg/d (trimethoprim moiety) as part of the combination therapy.[4] A PK/PD study based on targets for critically ill patients found that TMP/SMX at doses of 960 and 1280 mg/d (for a 70 kg body weight) achieved greater than 90% of cumulative fraction of response (CFR) for US isolates.[30] However, the finding cannot be extrapolated to general population or geographic regions with different susceptibility patterns. Two retrospective cohort studies found no significant differences in clinical success or adverse events between high-dose and low-dose TMP-SMX. One study compared less than 15 versus 15 mg/kg/d or greater, with median doses of 12 and 16 mg/kg/d.[31] The other evaluated 8 to 12 versus greater than 12 mg/kg/d, with median doses of 10.2 versus 14.8 mg/kg/d.[32]

To summarize the current evidence on TMP-SMX: (1) increasing in vitro and in vivo data suggest that TMP-SMX lacks bactericidal activity as monotherapy, despite consistently good susceptibility in surveillance studies; (2) observational clinical studies and systematic reviews do not support TMP-SMX as the preferred monotherapy agent; and (3) the optimal dosing remains uncertain, though most recommendations and median doses fall between 10 and 15 mg/kg/d, in line with current IDSA suggestion.

Fluoroquinolones

Fluoroquinolones are frequently used as alternative agents for *S maltophilia* infections, particularly when TMP-SMX is precluded by common issues like sulfonamide allergy, myelosuppression, nephrotoxicity, or hyperkalemia. Since CLSI breakpoints are available only for levofloxacin, it remains the fluoroquinolone with the most clinical use and supporting data. In contrast to the consistently high susceptibility observed with TMP-SMX, resistance to levofloxacin is notably more prevalent, with a global rate of approximately 14.4% reported across studies.[15] Marked geographic variation exists, with the highest resistance rates reported in Asia (44.1%), followed by America (27.9%) and Europe (26.4%).[15] In terms of in vitro activity, moxifloxacin generally demonstrates greater potency than levofloxacin, whereas ciprofloxacin exhibits the weakest activity among the 3.[33] In a neutropenic mouse lung model, levofloxacin achieved significantly greater bacterial reduction at doses of 30 and 100 mg/kg compared to cefiderocol.[34] However, time-kill studies have reported inconsistent bactericidal effects for fluoroquinolones, and regrowth of *S maltophilia* has been observed.[16,33] Moreover, Monte Carlo simulations for hospital-acquired pneumonia[35] and the critically-ill[30] failed to demonstrate satisfactory CFR for levofloxacin or moxifloxacin, even at levofloxacin dose up to 1000 mg daily. A 2 compartment model further showed selection of resistant mutants and bacterial regrowth, simulating equivalence to oral moxifloxacin 400 mg every 24 hours and ciprofloxacin 750 mg every 12 hours (q12 h).[36]

As a common predicament in *S maltophilia* treatment, the CLSI breakpoint for levofloxacin (susceptible at $\leq$2 mg/L) lacks robust clinical correlation or PK/PD validation. In a neutropenic murine thigh model simulating human exposure to intravenous levofloxacin 750 mg daily, isolates with an MIC of 2 mg/L exhibited poor probability of target attainment (PTA) for 1-log kill (26.6%) and stasis (47.6%). Only isolates with MIC 1 mg/L or less consistently demonstrated cidal or static effects.[37] Furthermore, a recent cohort study of 851 patients across 109 hospitals found no association between lower levofloxacin MICs and improved mortality outcomes.[38]

To date, 2 meta-analyses have evaluated comparative outcomes of antimicrobial therapies for *S maltophilia* infections. Most included studies compared fluoroquinolones with TMP-SMX, while only a few assessed tetracyclines. Both meta-analyses

concluded that fluoroquinolone monotherapy was associated with a survival benefit over TMP-SMX[21,39]; however, the findings were limited by the observational nature of the included studies. In contrast, fluoroquinolones did not show a significantly reduced mortality compared to tetracyclines.[21] Taken together, fluoroquinolones may be considered a reasonable treatment option for *S maltophilia* infections when in vitro susceptibility is confirmed. However, due to variably reported bactericidal activity and the potential for bacterial regrowth and emergence of resistance, combination therapy should be considered in severe infections. Among the fluoroquinolones, moxifloxacin and levofloxacin are preferred over ciprofloxacin, with recommended daily doses of 400 and 750 mg, respectively. Importantly, cautious clinical monitoring is warranted when treating isolates with "borderline susceptibility" (ie, MIC = 2 mg/L for levofloxacin), given the limited clinical validation supporting the current CLSI breakpoint.

Tetracyclines

Minocycline is the only tetracycline with an established CLSI clinical breakpoint; the susceptible breakpoint was revised to 1 or less in 2024 (see **Table 1**). Prior to this revision, prevalence studies consistently reported high in vitro susceptibility rates for minocycline, generally above 98%.[8,11,15,40,41] However, with the application of updated breakpoints in studies published in 2025, susceptibility rates for isolates from 2018 to 2023 declined to 89.2% to 93.5%.[9,13,14] The MIC distribution of eravacycline is similar to that of minocycline, typically exhibiting MIC_{50} or MIC_{90} one dilution higher than minocycline and one dilution lower than tigecycline.[41,42] In *S maltophilia* isolates nonsusceptible to TMP-SMX and/or levofloxacin, eravacycline and tigecycline demonstrated comparable or slightly superior in vitro activity relative to minocycline, whereas omadacycline exhibited the poorest activity.[43,44]

Despite promising in vitro activity, PK/PD modeling has raised concerns regarding tigecycline efficacy against *S maltophilia.* Monte Carlo simulations revealed suboptimal CFR (27.3%–39.2%) across various resistant strains, even with high-dose tigecycline (100 mg q12 h). In contrast, minocycline achieved markedly higher CFRs (89.81%–95.94%) with the high-dose regimen of 200 mg q12 h.[44] Similar results were observed in simulations for hospital-acquired pneumonia: tigecycline failed to reach adequate CFR (75.4% with 100 mg twice daily), whereas minocycline achieved a 96.2% CFR with 100 mg twice daily.[35] However, minocycline monotherapy is not without concerns. Time-kill assays demonstrated inadequate killing with monotherapy, while bactericidal activity was observed when combined with moxifloxacin against susceptible isolates.[16] Furthermore, a neutropenic murine infection model challenged the current breakpoint under standard dosing conditions. Minocycline achieved less than 10% PTA for 1-log bacterial kill at 100 mg q12 h against isolates with a MIC of 1 mg/L, whereas a high-dose regimen of 200 mg q12 h achieved a PTA of 97% for stasis and 51.7% for 1-log kill at the same MIC.[45] No PK/PD data are currently available for eravacycline and omadacycline.

Clinical data comparing tetracyclines to other agents remain limited. As discussed previously, few clinical studies or systemic reviews evaluated minocycline (or tetracyclines) versus TMP-SMX or fluoroquinolones. Regarding tigecycline, one study comparing standard-dose tigecycline with TMP-SMX across various infections, found no significant differences in treatment response or mortality.[29] However, another study focused on ventilator-associated pneumonia (VAP) reported significantly worse clinical and microbiological cure with tigecycline compared to fluoroquinolones, and therefore advised against using standard-dose tigecycline for *S maltophilia* VAP.[46] Thus far, the only report of eravacycline treatment of *S maltophilia* infections is a retrospective

multicenter cohort including 41 patients.[47] The clinical cure rate (73.2%) and 30 day survival rate (68.3%) were comparable to observational outcomes from TMP-SMX, levofloxacin, or minocycline, while only 10% of the patients received combination therapy.

Although definitive conclusions regarding the efficacy of tetracycline monotherapy are lacking, current evidence suggests that high-dose minocycline holds the most therapeutic promise among tetracyclines, while tigecycline has the least reliable profile. Data on eravacycline remain insufficient to support specific recommendations. Nonetheless, given their consistently high in vitro activity, tetracyclines remain valuable treatment options for *S maltophilia* infections resistant to TMP-SMX and/or levofloxacin.

Cefiderocol

Similar to tetracyclines, cefiderocol has demonstrated good in vitro activity against *S maltophilia*. Following the revised CLSI breakpoint in 2022 (see **Table 1**), cefiderocol maintained high susceptibility rates in both the 5 year multinational (SIDERO-WT surveillance studies [SIDERO-WT]) (98.6%)[12] and the recent SENTRY program (97.9%).[10] PK/PD studies have shown favorable results for cefiderocol, including simulations involving critically ill patients.[30] In the lung infection model by Nakamura and colleagues,[48] the mean percentage of free drug time above the MIC (%fT > MIC) required for a 1-log or greater bacterial reduction against *S maltophilia* was 53%, which was 11% to 16% lower than Enterobacterales and *P aeruginosa*. In a neutropenic murine thigh model, cefiderocol achieved 1-log or greater reduction at 24 hours in 100% of isolates (n = 24) and 2-log or greater in 87.5% (n = 21).[49] In a neutropenic rabbit model of *S maltophilia* pneumonia, cefiderocol showed a superior survival rate (87%) compared with TMP-SMX (25%), with no residual bacteria in lung tissue or BAL fluid.[20] So far, only one time-kill study has evaluated the activity of cefiderocol monotherapy versus combination therapy against MDR *S maltophilia*. Synergy was observed in over 50% of the combinations tested (including minocycline, TMP-SMX, and polymyxin B), except levofloxacin (44.4%). The overall bactericidal activity was low (11.1%); however, extrapolation to clinical settings is constrained by the use of resistant isolates and subtherapeutic cefiderocol concentrations.[50]

Data from RCTs are sparse. In the (efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria [CREDIBLE-CR]) trial, only 5 patients with *S maltophilia* nosocomial pneumonia (13%) were included, all treated in the cefiderocol arm. The all-cause mortality was 80% (4 out of 5), decreasing to 67% (2 out of 3) when cases with concurrent *Acinetobacter* spp infection were excluded.[51] In the GAME CHANGER trial, 5 patients were randomized to cefiderocol and 3 to standard of care antibiotics. No patient in either arm died by 14 days. All-cause 28 day mortality was 40% (2 out of 5 died) in the cefiderocol arm and 0% (0 out of 3 died) for standard of care.[52] The 2 largest retrospective cohorts evaluating cefiderocol in *S maltophilia* infections to date are the PERSEUS (20 patients)[53] and (real-world multicentre study of cefiderocol treatment of immunocompromised patients with infections caused by multidrug-resistant Gram-negative bacteria [CEFI-ID]) (24 strains)[54] studies, which reported clinical cure rates of 53.5% to 70% and 28 day all-cause mortality rates of 30% to 37.7%. It is worth noting that close monitoring of resistance emergence is warranted. Three out of 24 cases in CEFI-ID experienced infection relapse within 90 days, with one strain confirmed as resistant. In CREDIBLE-CR, 1 of the 5 isolates showed at least 4 fold increase in cefiderocol MIC. This was not observed in the GAME CHANGER trial however.

Cefiderocol nonsusceptibility remained very low, with rates ranging from 0% to 5% and an overall average of approximately 1.3%.[10,12,55] However, higher nonsusceptible rates have been observed in isolates from patients with cystic fibrosis and

bronchiectasis.[56] Multiple mechanisms are presumed to contribute to cefiderocol resistance in *S maltophilia*, including mutations of the membrane receptor (*tonB*) or transporters (*tolQ, smlt1418*) for siderophore conjugates; overexpression of efflux pump (*smeDEF*) and its transcriptional regulator (*smeT*); and direct or indirect effects of β-lactamases, type-1 fimbriae, iron transporters, and core metabolic proteins.[55] Additionally, intrinsic cefiderocol resistance has recently been identified in *S maltophilia* genogroup 4.[57] Overall, cefiderocol represents a therapeutic option for critically-ill patients with MDR *S maltophilia* infection owing to its novel mode of action. It is not clear if there is an advantage to its use in combination therapy.

Ceftazidime-Avibactam Plus Aztreonam and Aztreonam-Avibactam

The combination of ceftazidime-avibactam and aztreonam (CZA-ATM) orchestrates a coordinated action against the 2 β-lactamases responsible for intrinsic β-lactam resistance in *S maltophilia*. Aztreonam remains active against the L1 metallo-β-lactamase, which hydrolyzes carbapenems and other β-lactams (including ceftazidime), while avibactam protects aztreonam from hydrolysis by the L2 cephalosporinase and restores aztreonam activity.[2] Among β-lactamase inhibitors added to aztreonam against MDR *S maltophilia* isolates, avibactam showed the greatest effect, restoring 98% of aztreonam susceptibility, compared to 61%, 71%, and 15% with clavulanate, relebactam, and vaborbactam, respectively; time-kill assay demonstrated bactericidal activity for aztreonam-avibactam at 24 hours against 83.3% (5 out of 6) of isolates.[58] The in vitro activity of aztreonam-avibactam has been excellent worldwide (97.8%–99.6% at MIC $\leq$8 mg/L, 2016–2023); it also retained great activity against isolates nonsusceptible to TMP-SMX (84.7%–100%), minocycline (99.3%), and levofloxacin (99.3%).[9,13]

Nevertheless, fixed-dose aztreonam-avibactam has been approved only in Europe and the United States at the time of writing, while clinicians in other regions could only rely on the combination of CZA-ATM when both agents are available. In a phase 1 study, the incidence of elevated hepatic aminotransferases was similar between the CZA-ATM and aztreonam-alone group. However, caution is warranted with continuous infusion of avibactam, as 2 out of 8 subjects experienced severe but reversible elevations in aminotransferases.[59] For aztreonam-avibactam, population PK/PD modeling incorporating data from phase 1, 2a, and 3 trials showed that the approved clinical regimen—a 2.67 g loading dose followed by 2g q6h maintenance, infused over 3 hours—achieved PTA from 89 to greater than 99% across all infection types and renal function categories.[60] In contrast, the proposed regimen combining CZA-ATM (2.5 g q8h plus 2g q8h, administered concurrently over 3 hours), resulted in PTA less than 85% for avibactam as aztreonam remained comparable to that of the fix-dose formulation. The lack of a loading dose and the lower daily dose of avibactam (1.5 g) may have contributed to the suboptimal PD target attainment for avibactam.

Clinical experience with the combination of aztreonam and avibactam for *S maltophilia* infections remains limited. In the 2 phase 3 trials for avibactam-aztreonam, REVISIT[61] and ASSEMBLE,[62] only 4 patients with *S maltophilia* infections were included. Among them, 2 of 4 achieved clinical response/cure and 3 were alive at 28 days. While aztreonam-avibactam represents a promising treatment option for *S maltophilia* infections, further clinical data are needed to correlate in vitro activity with clinical outcomes. Additionally, future studies are required to determine whether a loading dose, continuous infusion, or dosing adjustment is necessary for the CAZ-AVI regimen.

Combination Therapies

Combination therapy with TMP-SMX for treating *S maltophilia* bacteremia was first proposed in 1996, particularly for immunocompromised, neutropenic, or critically-ill

patients.[63] As discussed previously, the lack of consistent bactericidal activity from any single agent, alongside generally favorable or synergistic results observed from in vitro studies, has contributed to the current preference for combination therapy. Nevertheless, no single combination regimen has demonstrated clear superiority, and clinical data to support combination therapy remain inconclusive. To date, no RCTs have been conducted, and outcomes from cohort or comparative[64–67] studies are heterogeneous. Only 2 meta-analyses have specifically evaluated combination versus monotherapy for *S maltophilia* infections.[21,68] Prawang and colleagues[68] included 2 pneumonia cohorts (534 patient, I^2 = 0%) and 2 bacteremia studies (111 patients, I^2 = 55%). Their analysis found that monotherapy was associated with decreased mortality in hospital-acquired pneumonia (hazard ratio, 1.42; 95% CI, 1.04–1.94), while no statistical significance was observed in the bacteremia subgroup. Maraolo and colleagues[21] included 3 bacteremia and 1 pneumonia study. Two of the bacteremia studies were conducted in pediatric populations (136 patients), while the other 2 involved adults (347 patients). This analysis showed that monotherapy was associated with a trend toward reduced mortality compared to combination therapy, although the difference was not statistically significant (OR 0.71, 95% CI 0.41–1.22).

Definitive recommendations regarding the necessity and timing for combination therapy for *S maltophilia* infections remain elusive, owing to divergent findings across in vitro, in vivo, and clinical studies. Although existing guidelines advocate for combination therapy, evidence derived from observational studies is subject to confounding and bias, underscoring the urgent need for RCTs. Given the considerable challenges of conducting RCTs for relatively uncommon opportunistic pathogens like *S maltophilia*, several innovative trial designs and analytical approaches, such as target trial emulation and Bayesian analytical frameworks, have been employed.[69]

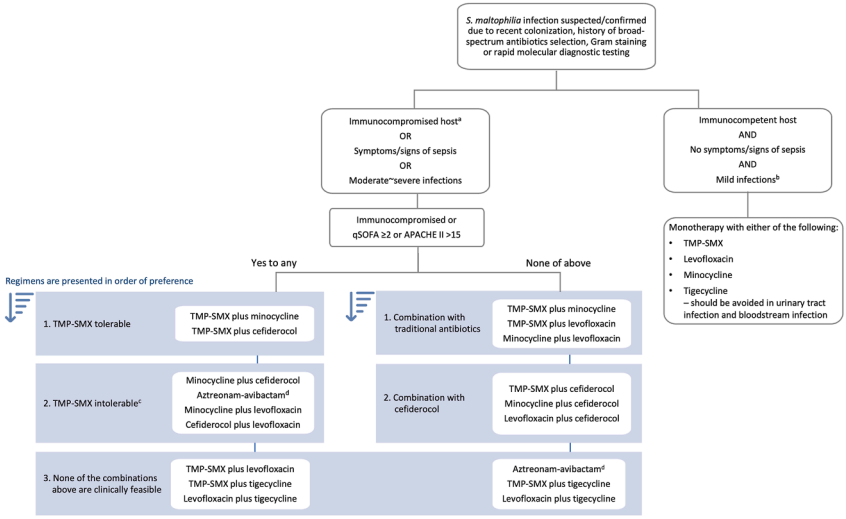

Fig. 1. Proposed algorithm for empiric treatment. [a]Defined as individuals with a quantitative or functional immune disorder.[71] [b]For example, uncomplicated skin and soft tissue infection, catheter-associated urinary tract infection, uncomplicated catheter-related bloodstream infection with a removable temporary catheter. [c]Including allergy, adverse effects and clinical conditions that preclude its use. [d]Represents both fix-dosed aztreaonam-avibactam and the combination of ceftazidime-avibactam plus aztreonam.

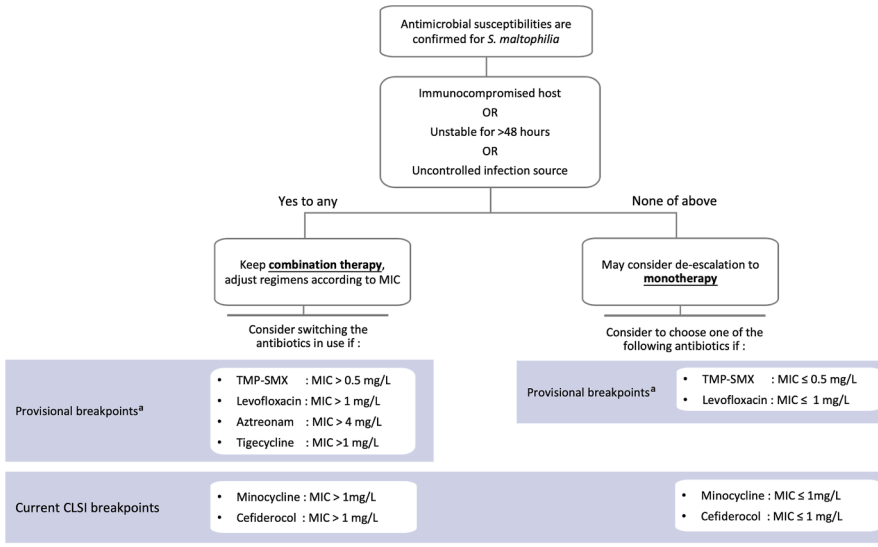

Fig. 2. Recommended algorithm for targeted therapy. [a]Provisional breakpoints based on updated pharmacokinetic/pharmacodynamic evidence (see Table 1).

SUMMARY AND FUTURE DIRECTIONS

Despite growing attention, optimal therapeutic strategies for *S maltophilia* remain undefined. Recent PK/PD data question the efficacy of monotherapy and the long-standing reliance on TMP-SMX. Population heterogeneity further complicates the correlation between MICs and clinical outcomes, posing challenges for clinical breakpoint validation. In the absence of RCTs, treatment decisions rely on observational studies that are often confounded and difficult to generalize. Current evidence tentatively supports combination therapy in vulnerable hosts and severe infections, yet no specific regimen has been proven superior. Figs. 1 and 2 present proposed treatment algorithms for empiric and targeted therapy based on updated PK/PD data and existing guidelines, while incorporating host factors, clinical severity, antimicrobial stewardship considerations, and contemporary concerns regarding susceptibility breakpoints (see Table 1).

Further studies incorporating patient stratification by clinical severity and MICs, may help identify candidates for monotherapy or de-escalation strategies, potentially reducing unnecessary antibiotics use. Ultimately, for relatively uncommon but emerging pathogens as *S maltophilia*, well-designed RCTs are essential to inform optimal treatment. Innovative trial methodologies may offer more feasible and cost-effective pathways to resolving these long-standing therapeutic dilemmas.

CLINICS CARE POINTS

- For *S maltophilia* infections in critically-ill or immunocompromised patients, combination therapy is recommended, as no single agent reliably provides bactericidal activity. However, no specific combination regimen has been proved superior to others.
- Among recommended agents, fluoroquinolones (mainly levofloxacin) exhibit the most variable in vitro susceptibility, with significant concerns regarding resistance emergence and

bacterial regrowth. Nevertheless, meta-analyses based on observational studies have suggested a survival benefit over TMP-SMX monotherapy.

- Despite favorable in vitro activity, tigecycline is not preferred from a PK/PD perspective; minocycline should be used instead whenever available.
- There may be discrepancies in avibactam exposure between aztreonam-avibactam and ceftazidime-avibactam plus aztreonam, based on current dosing strategies. Further data are needed to optimize dosing approaches.

DISCLOSURE

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