İstanbul Journal of Pharmacy
Istanbul J Pharm2024, 54 (3): 395–402
DOI: 10.26650/IstanbulJPharm.2024.1536403

Original Article

Efficacy of aztreonam/avibactam against *Stenotrophomonas maltophilia* alone and in combination with tigecycline

Özlem Oyardı[1], Gülbeyaz Altunboğa[1], Fatima Nur Olcay[2], Zayre Erturan[3]

[1]Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Microbiology, Ankara, Türkiye
[2]İstanbul University, Faculty of Pharmacy, Department of Pharmaceutical Microbiology, İstanbul Türkiye
[3]İstanbul University, Istanbul Faculty of Medicine, Department of Medical Microbiology, İstanbul, Türkiye

ABSTRACT

Background and Aims: *Stenotrophomonas maltophilia* is a multidrug-resistant opportunistic pathogen that threatens human and public health because of its widespread intrinsic and acquired antibiotic resistance. These bacteria become resistant to aztreonam by degrading it using the beta-lactamases. The aim of this study was to evaluate the effect of aztreonam/avibactam on aztreonam resistance in clinical strains of *S. maltophilia* and to assess the synergistic potential of aztreonam in combination with tigecycline.

Methods: Minimum Inhibitory Concentrations (MICs) of aztreonam, aztreonam/avibactam, tigecycline, and doxycycline were determined using broth microdilution in sixty-six *S. maltophilia* isolates. Additionally, six isolates with the most common MICs of aztreonam/avibactam against the strains, 2 µg/ml and 4 µg/ml were selected from among the sixty-six tested strains, and the effectiveness of the combination of aztreonam/avibactam with tigecycline was determined using both the checkerboard test and the time-dependent killing method.

Results: Aztreonam/avibactam restored aztreonam activity in 96.9% of resistant *S. maltophilia* isolates. Half of the isolates were susceptible to tigecycline, whereas all were susceptible to doxycycline. The combination of aztreonam/avibactam with tigecycline was found to have an additive effect against all isolates in the checkerboard experiment in which the activity of aztreonam/avibactam in combination with tigecycline was investigated against six isolates. In the time-dependent killing experiment, the combination exerted a synergistic effect against two isolates.

Conclusion: Aztreonam/avibactam appears to be an important alternative for reversing aztreonam resistance in *S. maltophilia*. Additionally, tetracyclines, such as tigecycline and doxycycline, are highly effective against these bacteria. To confirm these promising findings, further *in vitro*, *in vivo*, and clinical studies are required.

Keywords: *Stenotrophomonas maltophilia*, Aztreonam/avibactam, Tigecycline, Combination

INTRODUCTION

Stenotrophomonas maltophilia is a multidrug-resistant Gram-negative pathogen that causes life-threatening infections, especially in immunocompromised and intensive care patients (Liu, Xiang, & Zhang, 2024; Mojica et al., 2022). Natural resistance and multidrug resistance, which occur through the transfer of antibiotic resistance genes via gene transfer mechanisms such as plasmids, cause the treatment options for Gram-negative pathogens to gradually decrease and place an important focus on health studies related to the discovery of new antibiotics. *S. maltophilia* is particularly notable for causing respiratory tract infections, but it can also be encountered as the causative agent of bacteremia, skin and soft tissue infections, osteomyelitis, meningitis, endocarditis, and urinary tract infections (Brooke, 2021). *S. maltophilia* respiratory tract infections can have a mortality rate of almost 50%. In the case of septic shock, this rate can increase (Hafiz et al., 2022). *S. maltophilia* is naturally resistant to antibiotics such as carbapenems and aminoglycosides, which are critical in infections with multidrug-resistant Gram-negative pathogens. Resistance to antibiotics occurs especially in the presence of genes encoding efflux pumps and enzymes that degrade antibiotics (Gil-Gil, Martínez, & Blanco, 2020). Additionally, acquired resistance is common due to the large number of antibiotic resistance genes and gene mutations. The empirical antibiotic treatment approach preferred for other Gram-negative pathogen infections may not be applicable for *S. maltophilia*. In order to prevent unnecessary antibiotic use and

Corresponding Author: Özlem Oyardı **E-mail:** ozlemyrd@gmail.com
Submitted: 20.08.2024 • **Revision Requested:** 20.09.2024 • **Last Revision Received:** 22.09.2024 • **Accepted:** 23.09.2024

not contribute to antibiotic resistance, the treatment regimen should be evaluated after reviewing factors such as bacterial culture results, the patient's general condition, and risk factors (Tamma et al., 2023). It has been observed that a history of previous broad-spectrum antibiotic use increases the risk of *S. maltophilia* infections in hospitalised patients (Hafiz et al., 2022; Brooke, 2021).

Efflux pump-mediated resistance is observed against trimethoprim/sulfamethoxazole, which is considered the first step in the treatment of *S. maltophilia*. Similarly, resistance to levofloxacin and minocycline is also transmitted through the presence of various resistance genes and can be transferred between bacteria (Mojica, Bonomo, & Van Duin, 2023; Tamma et al., 2023). A meta-analysis reported that *S. maltophilia* resistance to levofloxacin, trimethoprim/sulfamethoxazole, and minocycline can be observed worldwide (Dadashi et al., 2023).

Serine β-lactamases and metallo β-lactamases, which cleave the β-lactam rings necessary for the antimicrobial activity, inactivate the beta-lactam antibiotics. In order to overcome this critical challenge, β-lactamase inhibitors that inhibit β-lactamases have been synthesized and combined with β-lactam antibiotics. L1 metallo β-lactamase and L2 serine β-lactamase are responsible for the β-lactam resistance observed in *S. maltophilia*. L1 β-lactamases hydrolyse penicillins, cephalosporins, and carbapenems, while L2 serine β-lactamases are responsible for the hydrolysis of aztreonam and extended-spectrum cephalosporins. L2 serine β-lactamases can be inactivated by the β-lactamase inhibitors clavulanic acid and avibactam (Mojita et al., 2022). With the approval of avibactam, a new serine β-lactamase inhibitor, in 2016, its combination with ceftazidime was approved and introduce to increase the effectiveness of ceftazidime (Tyers & Wright, 2019). The combination of aztreonam, a monobactam, and avibactam has been the subject of research in recent years and has been found to be an effective combination (Sader, Carvalhaes, Arends, Castanheira, & Mendes, 2021; Sader, Castanheira, Kimbrough, Kantro, & Mendes, 2023; Cornely et al., 2020). In 2024, aztreonam/avibactam was approved by the European Medicines Agency (EMA) for the treatment of Gram-negative bacterial infections, such as complicated intra-abdominal and urinary tract infections and hospital-acquired pneumonia. Furthermore, EUCAST has published aztreonam/avibactam clinical cut-off values for Enterobacterales (EUCAST, 2024b). In light of new studies, in cases of resistance to other antibiotics, the combination of aztreonam and ceftazidime/avibactam should be used, as recommended in the 2023 report by the Infectious Diseases Society of America (IDSA) (Tamma et al., 2023).

The most important problem with antibiotic susceptibility testing for *S. maltophilia* is that breakpoints are available for only a few antibiotics because of insufficient in vitro and clinical data (CLSI, 2023). In addition, given antibiotic resistance, there appears to be insufficient data to assess the effectiveness of alternative antibiotics. The IDSA recommends that combination therapy be preferred for *S. maltophilia* infections to increase the chance of treatment success. The use of minocycline in combination with other treatment regimens is recommended to accelerate clinical improvement. Although breakpoints for minocycline have been established by the CLSI, no data on tigecycline are available. Although minocycline is preferred because it has some advantages, such as better tolerance to it than tigecycline, it is also known that tigecycline is an important alternative (Tamma et al., 2023; CLSI, 2023). The aim of this study was to evaluate the efficacy of new drugs/combinations, primarily aztreonam/avibactam, for which CLSI breakpoints have not yet been determined. These drugs may be alternatives in the treatment of *S. maltophilia* infections.

MATERIALS AND METHODS

Bacteria and antibiotics

Sixty-six *S. maltophilia* strains included in the study were isolated from clinical samples collected from Istanbul University, Faculty of Medicine, Istanbul, Turkey between 2005 and 2009. *Pseudomonas aeruginosa* ATCC 27853 was used as a quality control strain to verify the accuracy of the experiments. Tryptic soy agar (TSA-BD DIFCO™) and cation-adjusted Muller–Hinton Broth (MHB-BD BBL™) were used for the growth of bacteria. In this study, aztreonam (Sigma–Aldrich), avibactam (Sigma–Aldrich), doxycycline (Sigma–Aldrich), and tigecycline (Pfizer Inc.) were tested for their effectiveness against these strains. Antibiotics were prepared in accordance with the CLSI recommendations and stored at - 20°C for a maximum of 6 months. For this purpose, aztreonam was dissolved in saturated sodium bicarbonate solution and diluted with sterile distilled water. All other antibiotics were dissolved in sterile distilled water. The aztreonam/avibactam combination was studied in accordance with the CLSI recommendations, with the avibactam concentration fixed at 4 µg/ml in all experiments (CLSI, 2023).

Broth microdilution

Minimum Inhibitory Concentrations (MICs) of aztreonam, tigecycline, doxycycline, and aztreonam/avibactam against the isolates were determined using the broth microdilution method recommended by the CLSI (CLSI, 2006). Bacterial suspensions at a final concentration of 5x105 were added to two-fold serial dilutions of antibiotics (128-0.06 µg/ml) prepared in 96-well U-bottom microplates. After incubating the microplate at 37°C for 24 hours, MICs were determined as the lowest antibiotic concentration at which no growth was observed. In the aztreonam/avibactam combination, the final concentration of avibactam was fixed at 4 µg/ml in all wells. Experiments were repeated three times.

Checkerboard Assay

A checkerboard assay was performed to determine the effects of the aztreonam/avibactam combination with tigecycline on *S. maltophilia* isolates (Eliopoulos & Moellering, 1996). For this purpose, six isolates with the most common MICs of aztreonam/avibactam against the strains, 2 µg/ml and 4 µg/ml were selected from among the 66 tested strains, and the experiments were continued with these isolates. After the MIC values of aztreonam/avibactam and tigecycline were determined separately, two-fold serial dilutions of the antibiotics between 8xMIC and MIC/8 were prepared, and each of these concentrations was added to the microplate to match each other. For this purpose, aztreonam/avibactam was added to the horizontal plane of the microplate, and tigecycline was added to the vertical plane of the microplate at increasing concentrations. Then, bacterial suspensions were added to the microplate to a final concentration of $5x10^5$ and incubated at 37°C for 24 h. The next day, 30 µl of resazurin solution (0.1 mg/ml) was added to all wells, and the mixture was kept for 3 h. Wells with no bacterial growth were identified, and the lowest concentrations of the two antibiotics in these wells were determined. The fractional inhibitory concentration (FIC) index was determined by considering the concentrations. The FIC value for each antibiotic was determined by dividing the lowest antimicrobial concentration in wells with no bacterial growth by the MIC value of that antibiotic alone against the same isolate. The FIC index was obtained by summing the FIC values of both antibiotics. According to the FIC index results, combinations were evaluated as synergistic (values ≤ 0.5), additive (values 0.5-4) or antagonist (values ≥ 4.0) (Odds, 2003).

Time-Kill Assay

A time-kill assay was used to determine the time-dependent effects of the combination of aztreonam/avibactam with tigecycline on six *S. maltophilia* isolates (NCCLS, 2002). After the antibiotics were prepared to have final concentrations corresponding to their MICs, they were added either alone or in combination to bacterial inocula at a final concentration of 10^6 CFU/ml. Samples were taken from these suspensions at 0, 2, 4, 6, and 24 h, dilutions were made, and the plates were then incubated at 37°C for 24 h. The number of bacterial colonies formed the next day was counted and determined. The obtained data were used to create time-kill curves, with time on the x-axis and bacterial counts expressed logarithmically on the y-axis. The results were then evaluated as synergistic, additive, or antagonistic based on the National Committee for Clinical Laboratory Standards (NCCLS) criteria (NCCLS, 2002). Bactericidal activity was defined as a decrease of ≥3log10 cfu/mL in the number of viable bacteria in the initial inoculum. Antibiotic combinations were evaluated by comparing the effects of each combination with those of the individual antibiotics. Synergy and antagonism were determined by changes in colony numbers. A ≥ 2log10 decrease was considered to indicate synergy and a ≥ 2log10 increase for antagonism. If no 2log10 change was observed, the effect of the combination was considered additive.

Statistical analysis

The graphs were generated using GraphPad Prism version 8.0.0 (GraphPad Software, San Diego, CA, USA). Statistical analysis was performed on the time-kill data using two-way analysis of variance followed by Tukey's post-hoc test, with p-values of < 0.05 considered statistically significant.

RESULTS

Antibiotic susceptibility test results

The MICs (µg/ml) of the antibiotics against sixty-six *S. maltophilia* isolates are provided in Supplementary 1. MIC_{50} and MIC_{90} values (µg/ml), representing the lowest MICs that inhibited 50% and 90% of the isolates, respectively, are presented in Table 1.. As the breakpoints, the susceptibility breakpoint for aztreonam published by CLSI for *P. aeruginosa*, which is ≤8 µg/ml, was applied (CLSI, 2023); for aztreonam-avibactam, the provisional PK/PD susceptibility breakpoint of ≤8/4 µg/ml was used (Singh et al., 2015). According to the results, all isolates except one (n:65) were determined to be aztreonam-resistant. When aztreonam is used together with avibactam, MIC values decreased significantly. All strains, except two, were evaluated as susceptible to aztreonam/avibactam. Although the MIC50 and MIC90 values for aztreonam were found to be >128 µg/ml, these values for aztreonam/avibactam were 4/4 and 8/4 µg/ml, respectively. All isolates tested were susceptible to doxycycline according to the breakpoints for *Enterobacterales* (CLSI, 2023). The tigecycline susceptibility breakpoint, ≤2 µg/ml, determined by the US Food and Drug Administration (FDA) (2023) for *Enterobacterales*, was applied. As a result, 9 of 66 isolates were found to be resistant to tigecycline, 24 were intermediately susceptible, and 33 were susceptible to tigecycline.

Table 1. MIC_{50} and MIC_{90} values of antibiotics

Antibiotics	*MIC_{50} (µg/ml)*	*MIC_{90} (µg/ml)*
Doxycycline	1	2
Tigecycline	2	8
Aztreonam	>128	>128
Aztreonam/Avibactam	4/4	8/4

MIC breakpoints (µg/ml): Dox: S≤4 I=8 R≥16; Tig: S≤2 I=4 R≥8; Azt: S≤8 I=16 R≥32; Azt/Avi: S≤8 I=16 R≥32

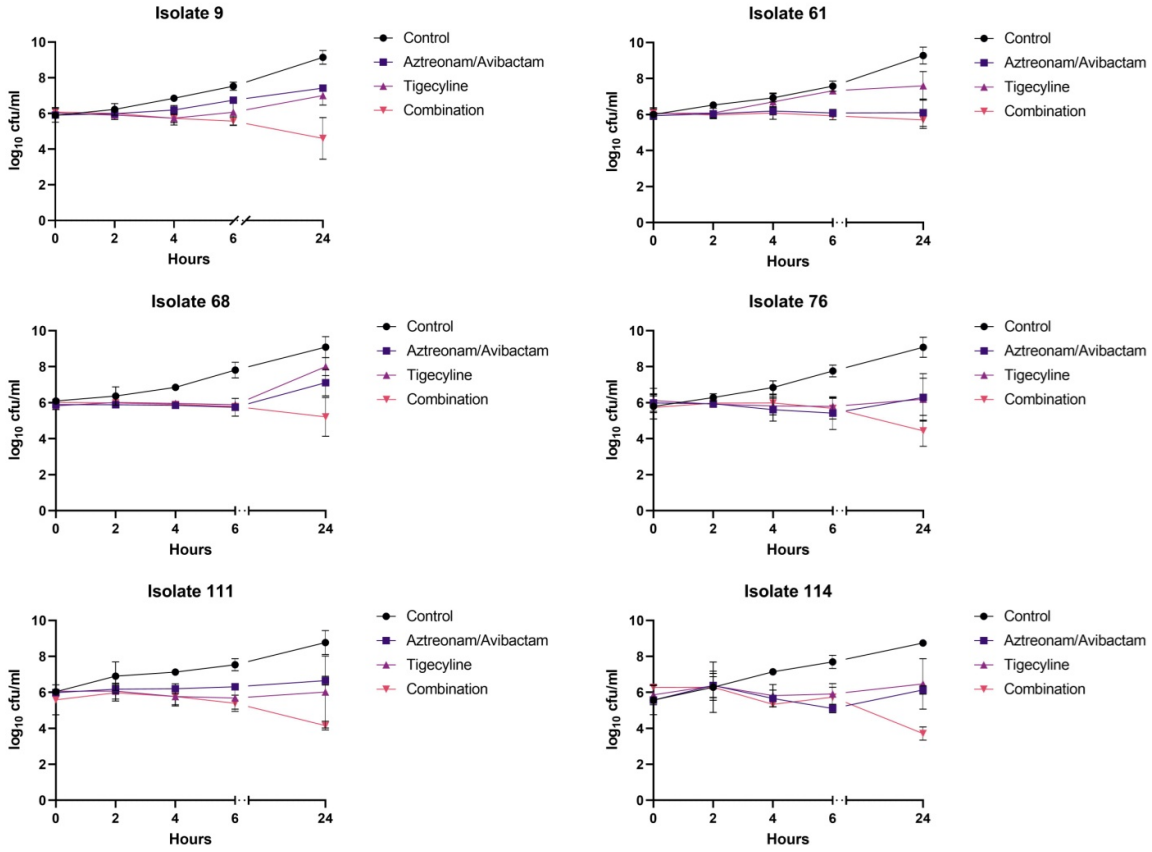

Figure 1. Time-kill curves of antibiotics and combination

Checkerboard assay results

To determine the effect of the combination of aztreonam/avibactam with tigecycline, three of the six selected isolates had MIC values of 4/4 µg/ml for aztreonam/avibactam, and the other three had 2/4 µg/ml. The isolates used in the combination experiments are described in Table 2.

Table 2. MIC values of isolates used in combinations

Isolate number	*Antibiotics*	
	Aztreonam/avibactam	**Tigecycline**
	MICs (µg/ml)	
9	2/4	4
61	2/4	2
68	4/4	4
76	4/4	4
111	2/4	4
114	4/4	4

The combination experiments were repeated three times, and the results are shown in Table 3. According to the FIC index values, the combination of aztreonam/avibactam and tigecycline had additive effects on all six isolates tested. Synergism or antagonism was not observed.

Table 3. FIC index values of the aztreonam/avibactam and tigecycline combinations

Isolate number	*FIC index of aztreonam/avibactam and tigecycline combination therapy*
9	0.75
61	0.625
68	0.75
76	0.625
111	0.625
114	0.75

Time-kill results

Time-dependent killing results showed that aztreonam/avibactam and tigecycline alone or in combination did not cause a 3log reduction in initial bacterial counts. These antibiotics inhibited bacterial growth for most of the

tested isolates at all-time intervals compared with the control group. The effectiveness of the combination was observed at the end of 24-h, and statistical significance was determined between the control and combination groups for all tested isolates ($p < 0.05$). For isolates 9 and 114, the combination of aztreonam/avibactam and tigecycline was found to have at least a 2-log reduction in bacterial counts at the end of the 24th hour compared with the most effective antibiotic alone; therefore, the combination was evaluated as synergistic. For isolates 68, 76, and 111, the combination caused a 1 log decrease in the number of bacteria at the end of the 24th hour compared with the most effective antibiotic alone. No significant effect was observed for isolate 61. The effects of the combination were evaluated as additives for isolates 61, 68, 76, and 111.

DISCUSSION

S. maltophilia is a Gram-negative pathogen that poses a health risk due to its widespread antibiotic resistance and severe mortality and morbidity in immunocompromised patients. Treatment options for *S. maltophilia* are quite limited, and besides clinical data, information on clinical breakpoints for antibiotic efficacy as defined by reference sources, such as CLSI and EUCAST, is also limited (CLSI, 2023; EUCAST, 2024a). The three antibiotics recommended by the CLSI for first-line therapy are trimethoprim/sulfamethoxazole, levofloxacin, and minocycline. However, studies conducted worldwide have shown that clinical *S. maltophilia* isolates may exhibit resistance to these three antibiotics (Dadashi et al., 2023). In addition to these three antibiotics, IDSA's 2023 guide also recommends antibiotics such as aztreonam, tigecycline, ceftazidime/avibactam (Tamma et al., 2023). Results of a study examining 486 patients treated for bloodstream infections caused by *S. maltophilia* showed that levofloxacin was the most commonly used antibiotic. Trimethoprim/sulfamethoxazole was largely preferred as definitive treatment after empirical treatment. The study results also showed that aztreonam, tigecycline, and doxycycline were not widely preferred (Cai, Tillotson, Benjumea, Callahan, & Echols, 2020). Additionally, studies have revealed the existence of tigecycline resistance. Among the 450 *S. maltophilia* strains isolated between 2012 and 2015, tigecycline resistance was 22.22% and doxycycline resistance was 18.67% (Zhao et al., 2018). In our study, half of the 66 *S. maltophilia* strains isolated from respiratory tract samples from patients with cystic fibrosis were found to be susceptible to tigecycline. All isolates were found to be susceptible to doxycycline. These results indicate that in addition to minocycline, other tetracyclines is an important treatment option. Studies evaluating the efficacy of doxycycline against *S. maltophilia* are limited. In a clinical study comparing tetracyclines (minocycline and doxycycline) with trimethoprim/sulfamethoxazole, similar clinical (28.6% vs. 25.4%) and microbiological success rates (55.6% vs. 66.4%) were determined for these two antibiotic groups (Alhayani, Philpott, Liao, Gentene, & Mueller, 2024). Tigecycline has been tested in many studies for *S. maltophilia*, and resistance rates have been reported to be between 11.8% and 28.1% (Banar et al., 2023; Biagi et al., 2020a; Su et al., 2023; Wang, Yu, Hsu, & Wu, 2020). It was determined that minocycline and tigecycline had bacteriostatic effects on *S. maltophilia* isolates carrying the dihydropteroate synthase (*sul*) gene (Zhao et al., 2022). Similarly, the results of the time-dependent killing assay conducted with 6 strains in our study revealed that tigecycline had a bacteriostatic effect on these strains. It is thought that these strains may carry the sul gene, and genetic studies are required to confirm this. According to the results of a study conducted by Gülmez et al. (2010), the most effective antibiotics against 25 tested *S. maltophilia* isolates were trimethoprim/sulfamethoxazole, tigecycline, and doxycycline. In the results of this study, resistance percentages were determined as 4% and 0% for tigecycline and doxycycline, respectively. In our study, the resistance percentages were the same for doxycycline but higher for tigecycline (13.6%) (Gülmez, Cakar, Şener, Hasçelik, & Karakaya, 2010).

The efficacy of aztreonam/avibactam against *Enterobacterales* has been demonstrated in numerous studies, and broth microdilution breakpoints have been published by EUCAST (EUCAST, 2024b). Results from a large surveillance study involving 63 countries determined that aztreonam/avibactam was 99.4% potent against metallo β-lactamase positive *Enterobacterales* isolates (Rossolini, Arhin, & Kantecki, 2024). The combination of ceftazidime/avibactam with aztreonam has been recommended in the guidelines published by IDSA, as its effectiveness has been proven in the treatment of *S. maltophilia* (Tamma et al., 2023; de Almeida Torres, Junior, Lopes, Zeigler, & Uip, 2023; Ranieri et al., 2023; Emeraud et al., 2019). Avibactam enhances the in vitro activities of both ceftazidime and aztreonam when combined with them in *S. maltophilia* isolates (Lin et al., 2020).

Aztreonam resistance is common among *S. maltophilia* isolates (Anđelković et al., 2019). Avibactam has been reported to competitively and reversibly inhibit *S. maltophilia* L2 β-lactamases, thus restoring the susceptibility of this bacteria to aztreonam (Mojica et al., 2017). Other β-lactamase inhibitors, when combined with aztreonam, restored activity to a lesser extent than avibactam. Following avibactam (98%), relebactam (71%), clavulanate (61%) and vaborbactam (15%) were determined as effective β-lactamases, respectively (Biagi et al., 2020b). Similarly, another large-scale study examining 1,839 *S. maltophilia* isolates from different geographic regions and infection types showed that aztreonam/avibactam was effective against 97.8% of the isolates. The same study determined that the sensitivity of the isolates to tigecycline was 85% (Sader et al., 2020). Our study demonstrated that aztreonam resistance was eliminated by aztreonam/avibactam in *S. maltophilia* strains isolated from Türkiye. Additionally, 86.4% of the iso-

lates were found to be susceptible or intermediate to tigecycline in our study.

Antibiotic combinations are frequently preferred in situations that require rapid and effective treatment to achieve broad-spectrum effects, reduce the risk of resistance development, decrease the efficacy of existing resistance, target heterogeneous bacterial populations by combining different antibiotics, and enhance clinical efficacy in cases in which in vitro synergism is observed (Roemhild, Bollenbach, & Andersson, 2022). However, it is possible that antibiotics may interact with each other, resulting in synergism or antagonism. Synergism between antibiotics used in combination is preferable for treatment, but antagonism can make treatment unsuccessful. Therefore, when making antibiotic combinations, this possibility should be considered, and appropriate studies should be conducted. Combination studies on aztreonam/avibactam have been limited to testing combinations of ceftazidime/avibactam and aztreonam. Hence, it is important to test the efficacy of aztreonam/avibactam along with another highly effective antibiotic with a different mechanism of action, such as tigecycline. A previous study determined that combinations of tigecycline with cefoperazone-sulbactam and levofloxacin had a synergistic effect (Karamanlıoğlu & Dizbay, 2019). Although many methods are used in the literature to test the effectiveness of combinations, the most frequently used are the checkerboard assay and the time-kill method. Both of these methods have advantages and disadvantages. While the checkerboard method is a more static method that examines the effects of antibiotics on the growth of bacteria, the time-kill method is a dynamic method based on the principle that antibiotics kill bacteria in a time-dependent manner (White, Burgess, Manduru, & Bosso, 1996). This fundamental difference between them may have caused some inconsistencies in the results of the two tests. In our study, although the checkerboard assay results indicated that the combination was additive in all isolates, the time-kill experiment results indicated that the combination of tigecycline and aztreonam/avibactam, a β-lactam-β-lactamase inhibitor, showed synergism for two isolates. A meta-analysis showed that synergisms detected by the time-kill method were greater than those detected using the checkerboard method (Zusman et al., 2013). Similarly, previous studies have reported that the time-kill method is more sensitive in detecting synergism (Visalli, Jacobs, & Appelbaum, 1998; Rizvi, Ahmed, Khan, Shukla, & Malik, 2013). In parallel with these findings, synergism was observed in two isolates using the time-dependent killing method in our study.

CONCLUSION

The results obtained from this study, in parallel with the literature, showed that aztreonam/avibactam restored aztreonam activity in *S. maltophilia* isolates that were isolated from Türkiye and resistant to aztreonam. In addition, the effectiveness of tigecycline and doxycycline against *S. maltophilia* isolates indicated that they could be important alternatives for treating these infections, and further studies are therefore necessary. According to the results of the time-kill experiment performed to determine the efficacy of the combination of aztreonam/avibactam with tigecycline, the observation of synergism in the two isolates was interpreted as promising for the combined use of these antibiotics. However, clinical studies are needed to confirm the results.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study: Ö.O., F.N.O.; Data Acquisition: Ö.O., G.A., F.N.O.; Data Analysis/Interpretation: Ö.O., Z.E.; Drafting Manuscript: Ö.O., G.A., F.N.O.; Critical Revision of Manuscript: Z.E.; Final Approval and Accountability: Ö.O., G.A., F.N.O., Z.E.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The research is financed by Gazi University Scientific Research Projects Unit with project number TKB-2023-8817.

ORCID IDs of the authors

Özlem Oyardı 0000-0001-9992-7225
Gülbeyaz Altunboğa 0000-0001-7562-7842
Fatima Nur Olcay 0000-0001-8442-8538
Zayre Erturan 0000-0002-6427-3046

REFERENCES

Alhayani, T., Philpott, C. D., Liao, S., Gentene, A. J., & Mueller, E. W. (2024). Comparison of doxycycline or minocycline to sulfamethoxazole-trimethoprim for treatment of *Stenotrophomonas maltophilia pneumonia. Annals of Pharmacotherapy, 58*(1), 21-27.

Anđelković, M. V., Janković, S. M., Kostić, M. J., Živković Zarić, R. S., Opančina, V. D., Živić, M. Ž., ... & Pejčić, A. V. (2019). Antimicrobial treatment of *Stenotrophomonas maltophilia* invasive infections: systematic review. *Journal of Chemotherapy, 31*(6), 297-306.

Banar, M., Sattari-Maraji, A., Bayatinejad, G., Ebrahimi, E., Jabalameli, L., Beigverdi R, & Jabalameli, F. (2023). Global prevalence and antibiotic resistance in clinical isolates of *Stenotrophomonas maltophilia*: a systematic review and meta-analysis. *Frontiers in Medicine, 10*, 1163439.

Biagi, M., Lamm, D., Meyer, K., Vialichka, A., Jurkovic, M., Patel S, & Wenzler, E. (2020b). Activity of aztreonam in combination with avibactam, clavulanate, relebactam, and vaborbactam against multidrug-resistant *Stenotrophomonas maltophilia. Antimicrobial Agents and Chemotheraphy 64*(12), e00297-20. https://doi.org/10.1128/AAC.00297-20

Biagi, M., Tan, X., Wu, T., Jurkovic, M., Vialichka, A., Meyer K. & Wenzler, E. (2020a). Activity of potential alternative treatment

agents for Stenotrophomonas maltophilia isolates nonsusceptible to levofloxacin and/or trimethoprim-sulfamethoxazole. *Journal of Clinical Microbiology, 58*(2), e01603-19. https://doi.org/10.1128/JCM.01603-19

Brooke, J. S. (2021). Advances in the microbiology of *Stenotrophomonas maltophilia. Clinical Microbiology Reviews, 34*(3), e00030-19. https://doi.org/10.1128/CMR.00030-19

Cai, B., Tillotson, G., Benjumea, D., Callahan, P., & Echols, R. (2020). The burden of bloodstream infections due to *Stenotrophomonas maltophilia* in the United States: a large, retrospective database study. In Open Forum on Infectious Diseases (Vol. 7, No. 5, p. ofaa141). US: Oxford University Press.

CLSI (Clinical and Laboratory Standards Institute). (2006). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically—seventh edition: M07. Wayne, PA, USA: CLSI

CLSI (Clinical and Laboratory Standards Institute). (2023). Performance standards for antimicrobial susceptibility testing. 33rd ed. CLSI M100. Wayne, PA, USA: CLSI.

Cornely, O. A., Cisneros, J. M., Torre-Cisneros, J., Rodríguez-Hernández, M. J., Tallón-Aguilar, L., Calbo, E., ... & Luckey, A. (2020). Pharmacokinetics and safety of aztreonam/avibactam for the treatment of complicated intra-abdominal infections in hospitalized adults: results from the REJUVENATE study. *Journal of Antimicrobial Chemotherapy, 75*(3), 618-627.

Dadashi, M., Hajikhani, B., Nazarinejad, N., Noorisepehr, N., Yazdani, S., Hashemi, A., ... & Fatemeh, S. (2023). Global prevalence and distribution of antibiotic resistance among clinical isolates of *Stenotrophomonas maltophilia*: a systematic review and meta-analysis. *Journal of Global Antimicrobial Resistance 34*, 253-267. https://doi.org/10.1016/j.jgar.2023.02.018

de Almeida Torres, N., Junior, R. M., Lopes, L. F. B., Zeigler, R., & Uip, D. E. (2023). Synergistic combination of aztreonam and ceftazidime/avibactam against resistant Stenotrophomonas maltophilia on pancreatitis. *The Journal of Infection in Developing Countries, 17*(06), 881-885.

Eliopoulos, G. & Moellering Jr., R.C. (1996). Antimicrobial Combinations. In: Lorian, V., (Ed.), *Antibiotics in Laboratory Medicine* (pp. 330-396), Baltimore, USA, The Williams & Wilkins Co.

Emeraud, C., Escaut, L., Boucly, A., Fortineau, N., Bonnin, R. A., Naas, T., & Dortet, L. (2019). Aztreonam plus clavulanate, tazobactam, or avibactam for treatment of infections caused by metallo-β-lactamase-producing Gram-negative bacteria. *Antimicrobial Agents and Chemotherapy, 63*(5), e00010-19.

EUCAST (The European Committee on Antimicrobial Susceptibility Testing). (2024a). Breakpoint tables for interpretation of MICs and zone diameters. Version 14.0, 2024. Retrieved from https://www.eucast.org.

EUCAST (The European Committee on Antimicrobial Susceptibility Testing). (2024b). Breakpoints for aztreonam-avibactam May 2024. Retrieved from https://www.eucast.org/clinical_breakpoints

Gil-Gil, T., Martínez, J. L., & Blanco, P. (2020). Mechanisms of antimicrobial resistance in Stenotrophomonas maltophilia: a review of current knowledge. *Expert Review of Anti-infective Therapy, 18*(4), 335-347.

Gülmez, D., Cakar, A., Şener, B., Hasçelik, G., & Karakaya, J. (2010). Comparison of different antimicrobial susceptibility testing methods for *Stenotrophomonas maltophilia* and results of synergy testing. *Journal of Infection and Chemotherapy, 16*(5), 322-328.

Hafiz, T. A., Aldawood, E., Albloshi, A., Alghamdi, S. S., Mubaraki, M. A., Alyami, A. S., & Aldriwesh, M. G. (2022). *Stenotrophomonas maltophilia* epidemiology, resistance characteristics, and clinical outcomes: understanding of the recent three years' trends. *Microorganisms, 10*(12), 2506.

Karamanlıoğlu, D., & Dizbay, M. (2019). In vitro combination of tigecycline with other antibiotics in *Stenotrophomonas maltophilia* isolates. *Turkish Journal of Medical Sciences, 49*(2), 683-686.

Lin, Q., Zou, H., Chen, X., Wu, M., Ma, D., Yu, H., ... & Huang, S. (2021). Avibactam potentiated the activity of both ceftazidime and aztreonam against *S. maltophilia* clinical isolates *in vitro*. *BMC Microbiology, 21*, 1-6.

Liu, J., Xiang, Y., & Zhang, Y. (2024). *Stenotrophomonas maltophilia*: An urgent threat with increasing antibiotic resistance. *Current Microbiology, 81*(1), 6.

Mojica, M. F., Bonomo, R. A., & Van Duin, D. (2023). Treatment approaches for severe Stenotrophomonas maltophilia infections. *Current Opinion in Infectious Diseases, 36*(6), 572-584.

Mojica, M. F., Humphries, R., Lipuma, J. J., Mathers, A. J., Rao, G. G., Shelburne, S. A., ... & Bonomo, R. A. (2022). Clinical challenges treating *Stenotrophomonas maltophilia* infections: an update. *JAC-Antimicrobial Resistance, 4*(3), dlac040.

Mojica, M. F., Papp-Wallace, K. M., Taracila, M. A., Barnes, M. D., Rutter, J. D., Jacobs, M. R., ... & Bonomo, R. A. (2017). Avibactam restores the susceptibility of clinical isolates of *Stenotrophomonas maltophilia* to aztreonam. *Antimicrobial* Agents and Chemotherapy, 61(10), e00777-17. https://doi.org/10.1128/aac.00777-17

Odds, F.C. (2003). Synergy, antagonism, and what the chequerboard puts between them. *Journal of Antimicrobial Chemotherapy, 52*, 1. https://dx.doi.org/10.1093/jac/dkg301

Ranieri, E. M., Denicolò, S., Stolfa, S., Dalfino, L., Bavaro, D. F., Saracino, A., ... & Mosca, A. (2023). Looking for *Stenotrophomonas maltophilia* treatment: *in vitro* activity of ceftazidime/avibactam alone and in combination with aztreonam. *Journal of Chemotherapy, 35*(7), 610-613.

Rizvi, M., Ahmed, J., Khan, F., Shukla, I., & Malik, A. (2013). Assessment of combination therapy by time kill curve analysis and chequerboard assay for treatment of multi-drug resistant *Pseudomonas aeruginosa isolates. Journal of Global Antimicrobial Resistance, 1*(2), 103-108.

Roemhild, R., Bollenbach, T., & Andersson, D. I. (2022). The physiology and genetics of bacterial responses to antibiotic combinations. *Nature Reviews Microbiology, 20*(8), 478-490.

Rossolini, G. M., Arhin, F. F., & Kantecki, M. (2024). In vitro activity of aztreonam-avibactam and comparators against Metallo-β-Lactamase-producing *Enterobacterales* from ATLAS Global Surveillance Program, 2016–2020. *Journal of Global Antimicrobial Resistance, 36*, 123-131.

Sader, H. S., Carvalhaes, C. G., Arends, S. R., Castanheira, M., & Mendes, R. E. (2021). Aztreonam/avibactam activity against clinical isolates of *Enterobacterales* collected in Europe, Asia and Latin America in 2019. *Journal of Antimicrobial Chemotherapy, 76*(3), 659-666.

Sader, H. S., Castanheira, M., Kimbrough, J. H., Kantro, V., & Mendes, R. E. (2023). Aztreonam/avibactam activity against a large collection of carbapenem-resistant *Enterobacterales* (CRE) collected in hospitals from Europe, Asia and Latin America (2019–21). *JAC-Antimicrobial Resistance, 5*(2), dlad032.

Sader, H. S., Duncan, L. R., Arends, S. R., Carvalhaes, C. G., & Castanheira, M. (2020). Antimicrobial activity of aztreonam-avibactam and comparator agents when tested against a large collection of contemporary *Stenotrophomonas maltophilia* isolates from medical centers worldwide. *Antimicrobial Agents and Chemotherapy, 64*(11), e01433-20. https://doi.org/10.1128/aac.01433-20

Singh, R., Kim, A., Tanudra, M. A., Harris, J. J., McLaughlin,

R. E., Patey, S., ... & Eakin, A. E. (2015). Pharmacokinetics/pharmacodynamics of a β-lactam and β-lactamase inhibitor combination: a novel approach for aztreonam/avibactam. *Journal of Antimicrobial Chemotherapy, 70*(9), 2618-2626.

Su, B. A., Chen, C. C., Chen, H. J., Lai, H. Y., Tsai, C. H., Lai, C. C., ... & Chao, C. M. (2023). In vitro activities of antimicrobial combinations against planktonic and biofilm forms of *Stenotrophomonas maltophilia. Frontiers in Microbiology, 14*, 1186669.

Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., & Clancy, C. J. (2023). Infectious Diseases Society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. *Clinical Infectious Diseases*, ciad428.

Tyers, M., & Wright, G. D. (2019). Drug combinations: a strategy to extend the life of antibiotics in the 21st century. *Nature Reviews Microbiology, 17*(3), 141-155

U.S. Food and Drug Administration. 2023. https://www.fda.gov/drugs/development-resources/tigecycline-injection-products. Accessed 21 September 2024.Visalli, M. A., Jacobs, M. R., & Appelbaum, P. C. (1998). Activities of three quinolones, alone and in combination with extended-spectrum cephalosporins or gentamicin, against *Stenotrophomonas maltophilia. Antimicrobial Agents and Chemotherapy, 4*2(8), 2002-2005.

Wang, C. H., Yu, C. M., Hsu, S. T., & Wu, R. X. (2020). Levofloxacin-resistant *Stenotrophomonas maltophilia:* risk factors and antibiotic susceptibility patterns in hospitalized patients. *Journal of Hospital Infection, 104*(1), 46-52.

White, R. L., Burgess, D. S., Manduru, M., & Bosso, J. A. (1996). Comparison of three different in vitro methods of detecting synergy: time-kill, checkerboard, and E test. *Antimicrobial Agents and Chemotherapy, 40*(8), 1914-1918.

Zhao, J., Huang, Y., Li, J., Zhang, B., Dong, Z., & Wang, D. (2022). *In vitro* antibacterial activity and resistance prevention of antimicrobial combinations for dihydropteroate synthase-carrying *Stenotrophomonas maltophilia. Infection and Drug Resistance, 15*, 3039-3046.

Zhao, J., Liu, Y., Liu, Y., Wang, D., Ni, W., Wang, R., ... & Zhang, B. (2018). Frequency and genetic determinants of tigecycline resistance in clinically isolated *Stenotrophomonas maltophilia* in Beijing, China. Frontiers in Microbiology, 9, 549.

Zusman, O., Avni, T., Leibovici, L., Adler, A., Friberg, L., Stergiopoulou, T., ... & Paul, M. (2013). Systematic review and meta-analysis of in vitro synergy of polymyxins and carbapenems. Antimicrobial Agents and Chemotherapy, 57(10), 5104-5111.

How cite this article

Oyardı, Ö., Altunboğa, G., Olcay, F.N., & Erturan, Z. (2024). Efficacy of aztreonam/avibactam against *Stenotrophomonas maltophilia* alone and in combination with tigecycline. *İstanbul Journal of Pharmacy, 54*(3): 395–402. DOI: 10.26650/IstanbulJPharm.2024.1536403