Infection and Drug Resistance

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ORIGINAL RESEARCH

In vitro Antimicrobial Activity and Dose Optimization of Eravacycline and Other Tetracycline Derivatives Against Levofloxacin-Non-Susceptible and/or Trimethoprim-Sulfamethoxazole-Resistant *Stenotrophomonas maltophilia*

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Purpose: To better guide clinical use, we determined the in vitro antimicrobial activity of the new drug eravacycline and other tetracycline derivatives against levofloxacin (LVFX)-non-susceptible and/or trimethoprim-sulfamethoxazole (TMP-SMZ)-resistant *Stenotrophomonas maltophilia* and evaluated their dosing regimens.

Methods: Seventy-seven unique strains of *S. maltophilia* were isolated from sputa samples and airway aspirate samples that were either LVFX-non-susceptible and/or TMP-SMZ-resistant. Monte Carlo simulations were performed for different dosing regimens according to the population pharmacokinetic parameters of antibiotics in patients with respiratory tract infections at the minimum inhibitory concentration (MIC).

Results: Eravacycline had excellent in vitro antibacterial activity against LVFX-non-susceptible and/or TMP-SMZ-resistant *S. maltophilia*. Monte Carlo simulations showed that for LVFX-non-susceptible strains, the cumulative fraction of response (CFR) of minocycline at the conventional recommended dose of 100 mg q12 h was 90.90%; for TMP-SMZ-resistant strains, the CFR of minocycline at a high dose of 200 mg q12 h was only 91.64%. For strains resistant to both LVFX and TMP-SMZ, the CFR of minocycline at a high dose of 200 mg q12 h was 89.81%. In contrast, the CFR of tigecycline was less than 40%, even at a dose of 100 mg q12 h.

Conclusion: For pneumonia, minocycline is better for *S. maltophilia* that is non-susceptible to LVFX; for TMP-SMZ-resistant strains and strains that are not susceptible to either LVFX or TMP-SMZ, the efficiency of eravacycline requires further evaluation. Eravacycline may be a better choice for extremely resistant *S. maltophilia* strains that are non-susceptible to LVFX, TMP-SMZ, and minocycline.

Keywords: eravacycline, tetracyclines, levofloxacin, trimethoprim, sulfamethoxazole drug combination, *Stenotrophomonas maltophilia*, Monte Carlo method

Introduction

With the beginning of the postantibiotic era, *Stenotrophomonas maltophilia*, an opportunistic pathogen, has begun to develop a significant increase in resistance to commonly used first-line drugs by intrinsic and acquired resistance mechanisms, making the optimal clinical treatment option difficult to determine. Increasingly, resistant isolates to drugs with historically good susceptibility, such as levofloxacin (LVFX), trimethoprim-sulfamethoxazole (TMP-SMZ), and minocycline, are being reported.[1–4] A resistance study in China comparing 300 *S. maltophilia* strains collected over

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two periods, 2005–2009 and 2010–2014, showed a significant increase in rates of resistance, with TMP-SMZ-resistance increasing from 29.7% to 47.1%, ceftazidime-resistance increasing from 28.9% to 52.3%, and a decrease in the percentage of minocycline-susceptible strains from 13.5% to 10.9%.[5] In addition to increasing resistance rates, multiple adverse drug reactions and a lack of definitive pharmacokinetic/pharmacodynamic (PK/PD) data have limited the use of these antibiotics.[6,7] Tetracycline derivatives, including minocycline, tigecycline, and eravacycline, are currently drugs to which strains have high sensitivity in vitro and show promise as an important option for treating non-susceptible *S. maltophilia*.[8–11] National/global surveillance programs have been conducted to compare the in vitro minimum inhibitory concentration (MIC) of tetracycline derivatives against *S. maltophilia*. These surveillance programs suggest that our new drug, eravacycline, has potential for treating extremely drug-resistant strains. In vitro, the efficacy of eravacycline is superior to or similar to that of minocycline and tigecycline, especially for strains that are non-susceptible to LVFX, resistant to TMP-SMZ or non-susceptible to both.[9,11,12] With respect to clinical dosing regimens for tetracycline derivatives, Zidaru et al suggests minocycline (the agent with the greatest $fAUC_{24h}$ /MIC_{90}) be preferentially used in critically ill patients with bacteremia and/or sepsis. The f in $fAUC_{24h}$ /MIC_{90} represents the free fraction of the drug, and the AUC_{24h} is the area under the plasma concentration-time curve from 0 to 24 h (mg ·h /L). Eravacycline can be used (alone or in combination with other drugs) for infections caused by resistant *S. maltophilia* when conventional therapy has failed.[13]

S. maltophilia infections are mainly associated with respiratory systems, such as pneumonia and acute exacerbations of chronic obstructive pulmonary disease (COPD).[14–17] However, *S. maltophilia* is not covered by empirical antibiotic regimens for respiratory tract infections.[16] In a joint guideline from the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) published in 2016, clinicians should adopt dosing regimens and administered doses based on the PK/PD of antimicrobial drugs rather than relying solely on drug instructions.[18] Although the findings of Zidaru et al provide a good guide for clinical drug selection for *S. maltophilia* bloodstream infections, their sample included only 11 blood isolates, they did not specify whether the strains were drug resistant, and no specific dosing regimen was indicated.[13] In this study, we compared the in vitro MIC values of LVFX-non-susceptible and/or TMP-SMZ -resistant *S. maltophilia* to that of various tetracycline derivatives, performed PK/PD evaluation of the dosing regimen of tetracycline derivatives for the treatment of respiratory tract infection using Monte Carlo simulation (MCS), and calculated the probability of the reaching target to identify the optimal regimen for the treatment of non-susceptible *S. maltophilia* infection.

Materials and Methods

Bacterial Strains

In this work, a total of 77 strains of *S. maltophilia* non-susceptible to LVFX and/or resistant to TMP-SMZ, isolated from sputa samples and airway aspirate samples between June 2020 and August 2022, were collected from the Clinical Microbiology Laboratory of the First Medical Center of the Chinese People's Liberation Army General Hospital (Table 1). Susceptibility to clinically relevant antibiotics was determined using the VITEK 2 Compact automated microbiological analysis system (bioMérieux, Marcy-l'Étoile, France). After we screened the drug-resistant strains that met the requirements from the clinical strain database, we used the gold standard of drug sensitivity determination, the micro broth dilution method, to determine their MIC values, and further screened the strains that met the requirements according to the Clinical and Laboratory Standards Institute (CLSI) document M100-Ed32 (2022).[19] Seventy-seven strains isolated in the clinic were non-susceptible to LVFX, resistant to TMP-SMZ, or non-susceptible to both of these substances. Non-susceptible strains included intermediate and drug-resistant strains according to CLSI. However, CLSI did not define intermediates susceptibility for TMP-SMZ, and only resistant strains were considered in this study. Strains that were not susceptible to LVFX were those with MICs ≥ 4 mg/L, including intermediate and resistant strains, for a total of 71 strains; strains that were resistant to TMP-SMZ were those with MICs ≥ 4/76 mg/L, for a total of 34 strains; and strains that were not susceptible to either were those that were not susceptible to LVFX with MICs ≥ 4 mg/L and resistant to TMP-SMZ with MICs ≥ 4/76 mg/L, a total of 28 strains. In addition, 7 strains were not susceptible to minocycline (MICs ≥ 8 mg/L). Because of the small number of strains that were not susceptible to a single drug, they

Table 1 Type and Features of Isolated Strains

Observation Indicators	All Isolates	LVFX-Non-Susceptible Isolates	TMP-SMZ-Resistant Isolates	LVFX-Non-Susceptible and TMP-SMZ Resistant Isolates	LVFX-Non-Susceptible, TMP-SMZ-Resistant, and Minocycline-Non-Susceptible Isolates
Totals (n)	77	71	34	28	7
Average age (years)	74.23±17.12	74.15±17.22	76.00±16.92	76.17±16.97	73.71±16.82
Gender (n)					
Male	55	52	23	20	5
Female	22	19	11	8	2
Hospital ward (n)					
General ward	63	58	28	23	6
Intensive care unit	14	13	6	5	1
Comorbidities (n)					
Malignant tumor	24	22	6	4	1
Hematologic diseases	11	10	4	3	1
Transplant status	6	7	2	2	1
Lung disease	73	68	31	26	7
Severe infection	37	35	13	11	3
Chronic renal disease	21	18	13	10	3
Liver disease	24	21	11	8	2

were not grouped and statistically analyzed. Species-appropriate quality control strains were used to ensure that isolates met the standards recommended by the CLSI document M07-Ed11 (2018).[20] *Escherichia coli* ATCC 25922 was used as the experimental quality control strain for minocycline and TMP-SMZ, and *Pseudomonas aeruginosa* ATCC 27853 was used as the control for the other drugs.

Antimicrobial Susceptibility Testing

Eravacycline was purchased from MedChemExpress (USA), tigecycline was purchased from Shanghai Yuanye Technology & Biology Co., Ltd. (China), minocycline and doxycycline were purchased from the National Institutes for Food and Drug Control (China), and Mueller-Hinton Broth (MHB) lot 212322 medium was purchased from Becton, Dickinson and Company (USA). Stock solutions of each agent were prepared fresh in individual aliquots at the beginning of each week and stored frozen at −80°C. Cation-adjusted MHB was used within 12 hours after preparation. The MICs of minocycline, tigecycline, doxycycline, and eravacycline against *S. maltophilia* were determined by the microbroth dilution method, and the test was performed in strict accordance with the criteria of CLSI document M07-Ed11 (2018).[20] Minocycline, tigecycline and doxycycline were diluted in a gradient of 10 concentrations with a concentration range of 0.5 mg/L-256 mg/L. Eravacycline was diluted in a gradient of 11 concentrations, and the concentration range was 0.03 mg/L-32 mg/L. The colonies were picked after reviving the strains. The colonies were inoculated in fresh sterilized broth, and enriched at 37°C for 6–8 hours. After the turbidity of the cultured bacteria solution was 0.5 McF, the bacterial suspension was inoculated in the drug susceptibility testing plate. The drug susceptibility testing plates were incubated for 20–24 hours in a constant temperature incubator at 37°C in an air environment.

Pharmacokinetic/Pharmacodynamic (PK/PD) Model

All pharmacokinetic parameters, associated standard deviations (SD), and protein binding indices were referenced from published studies (Table 2). The pharmacokinetic parameters for minocycline were from 12 patients with respiratory bacterial infections and those for tigecycline were from 89 patients with hospital-acquired pneumonia.[21–26] Minocycline 100 mg q12 h and tigecycline 50 mg q12 h are the recommended dosing regimens based on treatment instructions

Table 2 Summary of PK Parameters and PK/PD Target Level

Antibiotic	PK CL±SD	Unbound Fraction	PK/PD Target Level	References
Minocycline	1.14±0.4 (L/h)	0.35	8.75	[24–26]
Tigecycline	19.2±7.76 (L/h)	0.2	0.9	[21–23]
Eravacycline	0.16±0.027 (L/h/kg)	0.18	–	[34,35]

Abbreviations: CL, total body clearance; PK, pharmacokinetic; PD, pharmacodynamic; SD, standard deviation.

Table 3 CFR for Achieving PK/PD Indices with Different Antimicrobial Regimens Against 71 Isolates of LVFX-Non-Susceptible Strains, 34 Isolates of TMP-SMZ-Resistant Strains and 28 Isolates of LVFX-Non-Susceptible and TMP-SMZ-Resistant Strains

Antibiotic	Dosing Regimen	CFR of Strains (%)		
		LVFX-Non-Susceptible	TMP-SMZ-Resistant	LVFX-Non-Susceptible and TMP-SMZ-Resistant
Minocycline	100 mg q12 h	90.90	83.11	79.49
	150 mg q12 h	94.07	88.10	85.59
	200 mg q12 h	95.94	91.64	89.81
Tigecycline	50 mg q12 h	12.43	19.50	14.87
	75 mg q12 h	21.08	35.28	28.57
	100 mg q12 h	27.29	39.17	32.51

Abbreviations: CFR, cumulative fraction of response; PD, pharmacodynamic; PK, pharmacokinetic.

(Table 3). For tetracycline derivatives, the chosen PK/PD ratio f AUC_{0-24h}/MIC, which is considered the most likely predictor of efficacy,[23,25] can be calculated by the following equation:

$$f\ AUC_{24h}/MIC = f\ dose_{24h}/(CL \times MIC)$$

where $dose_{24h}$ is the dose administered over 24 h (mg), CL represents the total body clearance (L/h) and MIC is the minimum inhibitory concentration (mg/L).

Monte Carlo Simulation

In this study, MCSs were performed using Oracle Crystal Ball software (version: Oracle Crystal Ball 11.1.24) based on the PK/PD parameters and dosing regimens for minocycline and tigecycline. Simulations were performed assuming a random distribution for MICs, a log-normal distribution for pharmacokinetic parameters, and a uniform distribution for f, with 10,000 run calculations and confidence intervals set at 95%. The MCS results were generally expressed as the probability target attainment (PTA) for a given MIC and the cumulative fraction of response (CFR) for reaching a given target for the MIC population was calculated using the following equation:

$$CFR = \sum_{i=1}^{n} PTAi \times Fi$$

where PTAi represents the probability of target attainment for each MIC value and Fi is the proportion of strains with this MIC in the population (i). A dosing regimen with a CFR greater than 90% is generally considered optimal for an antimicrobial drug against that bacterium.[27]

Results

Antimicrobial Susceptibility Testing

Table 4 displays the MIC_{50}, MIC_{90}, and MIC range of each agent against all 77 isolates. According to the drug sensitivity breakpoints from CLSI document M100-Ed32 (2022),[19] 69 of the 77 strains (89.6%) were susceptible to minocycline,

Table 4 Activities of Selected Agents Against Clinical *S. maltophilia* Isolates Non-Susceptible to Levofloxacin and/or Trimethoprim-Sulfamethoxazole

Isolate Group and Drug	MIC (mg/L)			Susceptibility (%)		
	50%	90%	Range	S	I	R
All isolates (n=77)						
Doxycycline	4	16	1–128	-	-	-
Minocycline	1	8	0.5–32	89.60	5.19	5.19
Tigecycline	2	4	0.03–16	-	-	-
Eravacycline	2	4	0.03–16	-	-	-
Levofloxacin	16	32	0.5–64	7.79	7.79	84.42
TMP-SMZ	2/38	32/608	0.06/1.2–32/608	55.84	NA	44.16
LVFX-non-susceptible (n=71)						
Doxycycline	4	16	1–128	-	-	-
Minocycline	2	8	0.03–32	88.73	5.63	5.63
Tigecycline	4	4	0.03–16	-	-	-
Eravacycline	2	4	0.03–16	-	-	-
Levofloxacin	16	32	4–64	0	8.45	91.55
TMP-SMZ	1/19	32/608	0.06/1.2–32/608	61.54	NA	38.46
TMP-SMZ-resistant (n=34)						
Doxycycline	4	64	1–128	-	-	-
Minocycline	1	16	0.03–32	79.41	8.82	11.76
Tigecycline	2	8	0.03–16	-	-	-
Eravacycline	2	4	0.03–16	-	-	-
Levofloxacin	16	64	0.5–64	17.65	8.82	73.5
TMP-SMZ	32/608	32/608	4/76–32/608	0	NA	100
LVFX-non-susceptible, TMP-SMZ-resistant (n=28)						
Doxycycline	4	64	1–128	-	-	-
Minocycline	2	16	0.5–32	75.00	10.71	14.29
Tigecycline	4	8	0.03–16	-	-	-
Eravacycline	2	4	0.25–16	-	-	-
Levofloxacin	16	64	4–64	0	10.71	89.29
TMP-SMZ	32/608	32/608	4/76–32/608	0	NA	100
LVFX-non-susceptible, TMP-SMZ-resistant, minocycline-non-susceptible (n=7)						
Doxycycline	64	128	8–128	-	-	-
Minocycline	16	32	8–32	0	42.86	57.14
Tigecycline	4	16	1–16	-	-	-
Eravacycline	4	16	0.5–16	-	-	-
Levofloxacin	16	64	4–64	0	14.29	85.71
TMP-SMZ	32/608	32/608	4/76–32/608	0	NA	100

Abbreviations: MIC, minimum inhibitory concentration; S, susceptible; I, intermediate; R, resistant; Susceptibility interpretations based on CLSI-approved breakpoints for minocycline, levofloxacin, and trimethoprim-sulfamethoxazole; TMP-SMZ, trimethoprim-sulfamethoxazole; NA, not applicable.

and there were no defined breakpoints for the remaining the drugs. In each bacterial subgroup, eravacycline showed the highest in vitro efficacy with $MIC_{50/90}$ values of 2/4 mg/L. The results of tigecycline were similar to that of eravacycline, but it had $MIC_{50/90}$ values of 2/8 mg/L for the TMP-SMZ-resistant strains. Although minocycline had MIC_{50} values of 1–2 mg/L, its MIC_{90} was one to two gradients higher than that of eravacycline due to the presence of a minocycline-resistant strain. For LVFX-non-susceptible, TMP-SMZ-resistant, minocycline-non-susceptible strains, the $MIC_{50/90}$ values were 4/16 mg/L.

Probability Target Attainment

Due to the lower in vitro efficacy of doxycycline compared to the other three drugs and the lack of pharmacokinetic parameters associated with eravacycline for the treatment of respiratory tract infections, MCSs were performed in this study for only minocycline and tigecycline (Figure 1A and B). When simulating the recommended dose of minocycline

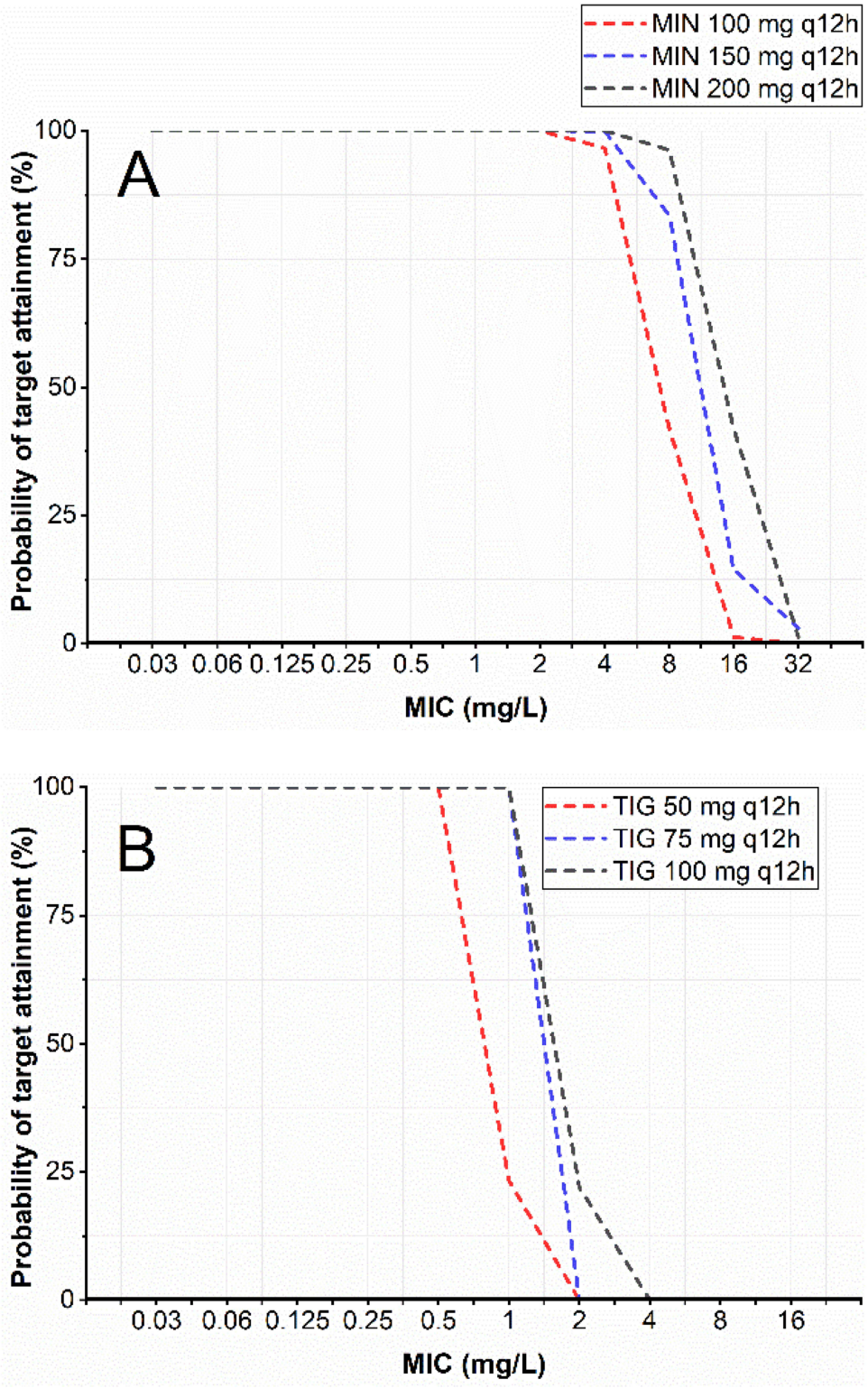

Figure 1 Probability of target attainment in 10,000 simulated patients given two antibiotics at different regimens. (**A**) The simulated probability of target attainment of minocycline on 100, 150, and 200 mg q12h regimens. (**B**) The simulated probability of target attainment of tigecycline on 50, 75, and 100 mg q12h regimens.

(100 mg q12 h), the PTA with MIC ≤ 4 mg/L was 96.58%; at an MIC value up to 8 mg/L, the PTA decreased rapidly to 41.82%; and at an MIC of 16 mg/L, the PTA was only 1.31%. The recommended dose of tigecycline (50 mg q12 h) had a PTA greater than 99% at an MIC ≤ 0.5 mg/L; when the MIC increased to 1 mg/L, the PTA was 71.83%; and at an MIC of 2 mg/L, the PTA was 11.6%. We increased the simulated dose of administration and found that the PTA in each MIC group also increased. When the simulated minocycline dose was increased to the maximum recommended dose of 200 mg q12 h, the PTA for the MIC of 8 mg/L was almost 2.3 times higher than the recommended dose, reaching 96.27%. For tigecycline simulation at a dose of 75 mg q12 h, the PTA for the MIC of 1 mg/L was elevated nearly 4.3 times higher than the recommended dose, and it reached 100%.

Cumulative Fraction of Response

According to the calculation formula, combined with the frequency of MIC distribution (Figure 2A–F) and the corresponding PTA (Figure 1A and B), we calculated the CFRs for different dosing regimens (Table 3). First, for LVFX-non-susceptible strains, the CFR of minocycline at 100 mg q12 h reached 90.90%, while the CFR of tigecycline at 100 mg q12 h was only 27.29%. Second, for TMP-SMZ-resistant strains, it was necessary to increase the minocycline dose to 200 mg q12 h to achieve a CFR of 91.64%, but the CFR of tigecycline at a dose of 100 mg q12 h was only 39.17%. Third, for LVFX-non-susceptible and TMP-SMZ-resistant strains, the CFR of minocycline at 200 mg q12 h reached 89.81%, while the CFR of tigecycline at 100 mg q12 h was only 32.51%.

Discussion

Respiratory infections caused by *S. maltophilia* strains that are non-susceptible to LVFX and/or resistant to TMP-SMZ pose a serious threat to immunocompromised patients. Tetracycline derivatives are increasingly used in clinical therapy, but there are fewer data related to drug-resistant bacteria. This study examined the MIC values of tetracycline derivatives against our LVFX-non-susceptible and/or TMP-SMZ-resistant *S. maltophilia* and evaluated their treatment regimens for respiratory infections based on MCSs with PK/PD parameters.

For tetracyclines, the pH, calcium ion and magnesium ion content of the MHB affects the final MIC value. For tigecycline, whether the MHB is freshly prepared or not will also affect the drug sensitivity results, and nonfreshly prepared MHB will make the MIC value higher.[19] Therefore, we required that the MIC values of quality control bacteria were within the quality control range to ensure the validity of the experiments. In this study, among the four tetracycline derivatives, eravacycline showed the highest in vitro activity, followed by tigecycline, minocycline, and doxycycline, especially in TMP-SMZ-resistant strains of *S. maltophilia*. The MIC of eravacycline reported in this study is slightly lower than the MICs of the 41 LVFX-non-susceptible and/or TMP-SMZ-resistant *S. maltophilia* strains that were assessed by Biagi et al (MIC_{50}, 2 mg/L, MIC_{90}, 8 mg/L), but the MIC_{90} results for minocycline reported here are higher than what was reported in their study (MIC_{50}, 2 mg/L, MIC_{90}, 4 mg/L).[9] In the absence of specific CLSI or EUCAST breakpoints for eravacycline, the level of resistance was not interpreted to avoid misestimation of the true resistance rate. However, the low MIC values (≤4 mg/L) suggest that eravacycline is highly effective against the strains in our collection, which indicates that eravacycline may be an acceptable therapeutic choice against LVFX-non-susceptible and/or TMP-SMZ-resistant *S. maltophilia* infections; eravacycline should also be considered for routine susceptibility screening in clinical microbiology laboratories. The IDSA recommends minocycline as a first line agent,[28] and the rate of susceptibility to minocycline in this study agrees with the results of Biagi et al and Flamm et al;[9,10] however, minocycline-non-susceptible strains are rapidly emerging. We identified seven clinical strains that were not susceptible to LVFX, TMP-SMZ, or minocycline, and eravacycline showed good in vitro activity (MIC ≤ 4 mg/L) against 5 of these strains. Only one strain with a high eravacycline MIC (MIC 16 mg/L) was collected in our strain set, and such specific resistant strains are rarely collected based on the literature, so the exact mechanism of resistance should be further investigated.

Eravacycline is a new fluorocycline drug with a broad antimicrobial spectrum that overcomes the common mechanisms of tetracycline resistance; however, studies on the efficacy of this drug against non-susceptible *S. maltophilia* infections are rarely reported.[12,29,30] The results of this study demonstrate that eravacycline effectively inhibits the growth of non-susceptible *S. maltophilia* in vitro, and clinical trial results have shown good clinical efficacy of eravacycline in the treatment of severe intra-abdominal infections, including infections caused by extended-spectrum β-

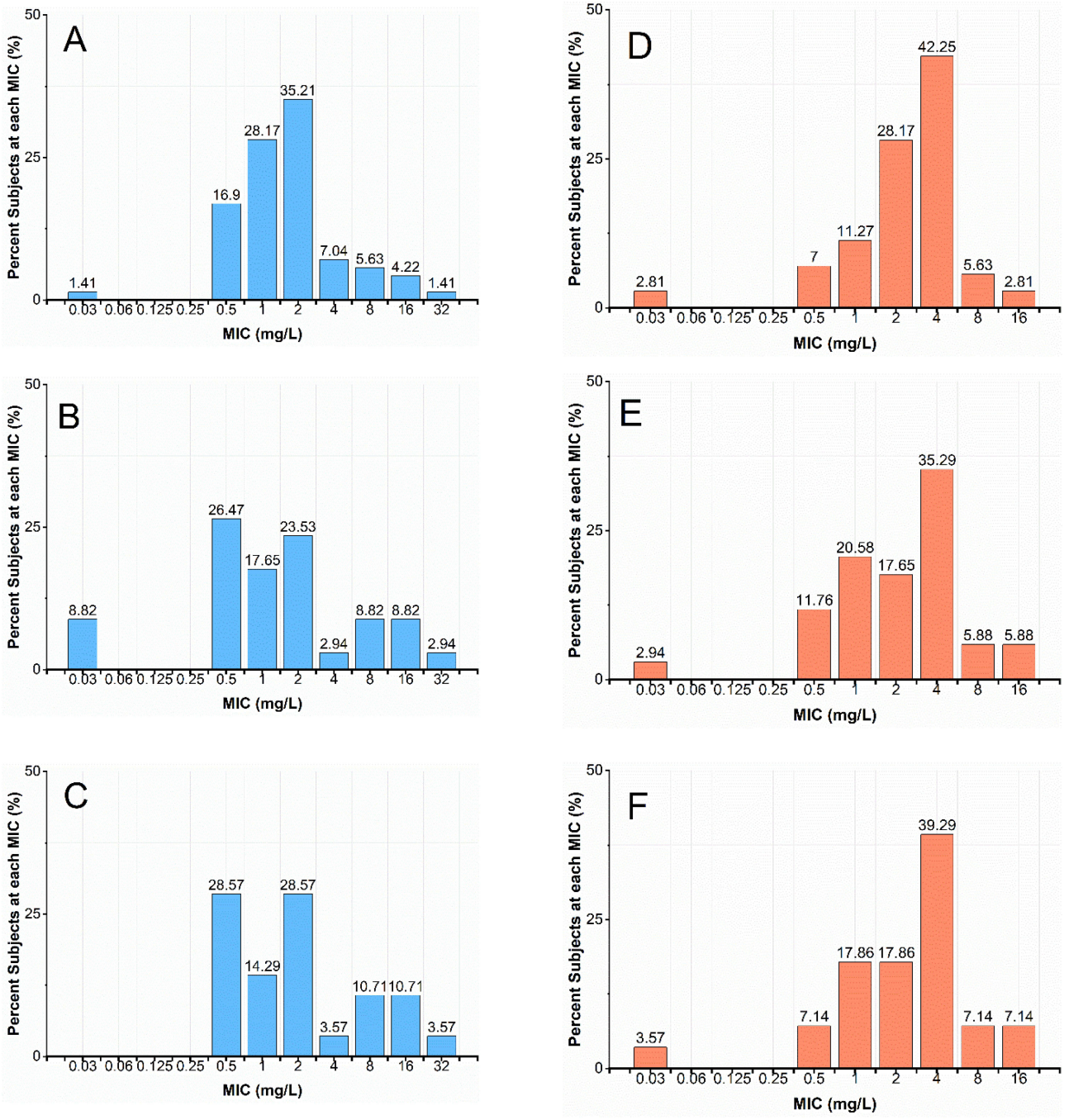

Figure 2 MIC distribution frequency for various types of strains. MIC distribution frequency of minocycline for various types of strains: (**A**) LVFX-non-susceptible strains, (**B**) TMP-SMZ-resistant strains, (**C**) LVFX-non-susceptible and TMP-SMZ resistant strains. MIC distribution frequency of tigecycline for various types of strains: (**D**) LVFX-non-susceptible strains, (**E**) TMP-SMZ-resistant strains, (**F**) LVFX-non-susceptible and TMP-SMZ resistant strains.

lactamase (ESBL)-producing bacteria.[31–33] This suggests that in the face of increasing drug resistance, eravacycline holds promise as an emerging drug for the treatment of non-susceptible *S. maltophilia* respiratory tract infections. Clinical PK/PD targets are generally used as targets for optimal efficacy. If clinical PK/PD targets are not available, animal PK/PD targets are preferred and are calculated by measuring blood concentrations in animal models of infections with different MIC values treated by different administration methods. However, only PK/PD targets obtained for eravacycline in a mouse model of thigh infection have been examined,[31] and no animal model of respiratory tract infection is available. Meanwhile, studies have only provided pharmacokinetic parameters for eravacycline in healthy humans,[34,35] without

clinical data for patients with respiratory tract infections. The feasibility of performing efficacy simulations for the administration regimen of eravacycline is low and the confidence level is poor. Studies clarified drug clearance and protein binding in healthy volunteers receiving an infusion of 1 mg/kg q12h eravacycline (Table 2). Additionally, for the non-susceptible bacteria, the MIC of eravacycline measured in this study was close to that of tigecycline. According to the results calculated by the PK/PD formula, the infusion of 1 mg/kg q12h of eravacycline in healthy volunteers closely resembled that of patients with respiratory tract infections using the recommended tigecycline regimen. Combined with the PK/PD target values for the comparable drug tigecycline, it is reasonable to assume that the clinical efficacy achieved by these two regimens is similar and that adequate pharmacodynamic exposure cannot be achieved. The correlation coefficients of AUC_{24h}/MIC and Cmax/MIC with antibacterial response are greater than 0.8, suggesting that both parameters are highly correlated with antibacterial response;[36] therefore, when the AUC_{24h}/MIC is difficult to determine, the C_{max} value combined with in vitro drug sensitivity results can be used to assess in vivo drug efficacy. The C_{max} for the recommended dose of eravacycline was 2.125 ± 0.36 mg/L in healthy volunteers and 9.793 ± 16.4 mg/L for a single injection of 3 mg/kg;[35] the C_{max} for the recommended dose of minocycline was 7.22 ± 3.53 mg/L in patients with respiratory tract infections.[24] Based on the MCS results of minocycline, the C_{max} values of the drugs, and with reference to the lower MIC values for eravacycline than minocycline, we infer that a single injection of 3 mg/kg eravacycline is likely to achieve similar effects as multiple injections of 100 mg minocycline q12 h when treating patients with respiratory infections of *S. maltophilia* that are non-susceptible to LVFX. In addition, drug concentrations are determined based on blood samples, and minocycline and eravacycline have been shown to have higher concentrations in the lungs,[37–39] making both 100 mg q12 h minocycline or a single injection of 3 mg/kg eravacycline highly effective in the treatment of respiratory infections caused by these strains.

This study has some limitations. First, the host sources of the 77 non-susceptible strains are mainly concentrated in northern China and may not be representative of the MIC distribution in other regions. Second, the sample size taken for the simulation is small due to the small number of TMP-SMZ-resistant strains collected clinically, especially LVFX-non-susceptible strains that are also resistant to TMP-SMZ. The larger the sampling volume of MCS is, the more accurate the results. Third, although some studies have shown that minocycline is well tolerated at single intravenous doses of up to 600 mg in healthy adult subjects, with a maximum tolerated multiple dose of 300 mg q12 h intravenously,[40] treatment of pneumonia with high doses of minocycline is also very infrequent. Therefore, high doses are not recommended for the treatment of respiratory infections. There have also been studies in healthy volunteers in which the incidence of adverse reactions was lower with single injections of eravacycline than with multiple injections, but the incidence of nausea and vomiting was higher with a single intravenous injection of 2 mg/kg and 3 mg/kg eravacycline than with the recommended dose (1 mg/kg).[35] In addition, there are no clinical trials of eravacycline for the treatment of respiratory tract infections, and a detailed risk-benefit assessment needs to be completed in patients with clinical pneumonia before clinical dosing can be guided. Fourth, the pharmacokinetic studies of minocycline in patients with respiratory tract infections are rare, thus, this study only used parameters with earlier publication times and smaller sample sizes.

In summary, in this study, eravacycline was the most effective in vitro agent for pneumonia caused by either LVFX-non-susceptible or TMP-SMZ-resistant *S. maltophilia*. MCS analysis combining PK/PD parameters showed that the recommended dose of minocycline for LVFX-non-susceptible *S. maltophilia* pneumonia could achieve a high CFR. Good simulated clinical efficacy could also be achieved by doubling the dose of minocycline for TMP-SMZ-resistant strains, and for strains non-susceptible to LVFX and resistant to TMP-SMZ. Although there is no definitive evidence that eravacycline can be used in LVFX-non-susceptible and/or TMP-SMZ-resistant pneumonia caused by *S. maltophilia*, this study suggests that eravacycline can combat the increase in drug resistance, with satisfactory clinical efficacy seen at high doses. To treat *S. maltophilia* first-line with eravacycline, more preliminary work needs to be done by domestic and foreign scholars. We look forward to many clinical studies on this important new antibiotic in the next few years.

Ethics Statement

The study was approved by the Ethics Committee of Chinese People's Liberation Army General Hospital. The study confirmed that informed consent was obtained from the study participants (for clinical sample collection) and the

guidelines outlined in the Declaration of Helsinki were followed. The approval number of the study is S2023-064-01.

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Disclosure

The authors report no conflicts of interest in this work.

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