

# In vitro Susceptibility of Nontuberculous Mycobacteria to Tedizolid

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**Objective:** Nontuberculous mycobacteria (NTM) can cause pulmonary and extrapulmonary diseases. Tedizolid (TZD) is a new oxazolidinone with in vitro activity against NTM such as *Mycobacterium avium* complex (MAC), *Mycobacterium fortuitum*, and *Mycobacterium abscessus* complex. The aim of this study was to evaluate the TZD susceptibility profiles of clinical isolates of NTM.

**Methods:** The microdilution method was used to identify the minimum inhibitory concentration (MIC) of TZD and linezolid (LZD) for 133 clinical NTM isolates. Broth microdilution chequerboard assays were used to investigate the synergistic effects of TZD and three antibiotics on two reference isolates and eleven clinical isolates of NTM.

**Results:** The TZD MIC<sub>50</sub> and MIC<sub>90</sub> for *M. abscessus* complex were 2 and 4 µg/mL, 16 and >32 µg/mL for MAC, respectively. TZD exhibited lower MICs than that of LZD for most NTM, which were positively correlated. Due to the high MIC values of TZD against MAC, it is necessary to conduct drug sensitivity tests before TZD administration. TZD-clarithromycin combination had synergistic response on *M. abscessus* complex in 3 of the 8 isolates, which lasted only 3–5 days. TZD-cefoxitin had synergistic effect against all five *M. fortuitum* isolates.

**Conclusion:** Our study demonstrates that TZD had greater in vitro potency than LZD, and synergy studies suggested that TZD may be an important component of multi-drug treatment regimen.

**Keywords:** tedizolid, susceptibility testing, nontuberculous mycobacteria, linezolid, oxazolidinone

## Introduction

Nontuberculous mycobacteria (NTM) are opportunistic pathogens particularly in susceptible populations of all ages that infect pulmonary and extrapulmonary sites including the skin, soft tissues, lymph nodes, bones, and joints.<sup>1</sup> In 2010, it was reported that the prevalence of pulmonary NTM in the United States exceeds that of tuberculosis,<sup>2</sup> raising public awareness. The most common NTM pathogens are *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium xenopi*, among the slowly growing NTM (SGM), and *Mycobacterium abscessus* complex, among the rapidly growing NTM (RGM).<sup>1</sup> Many species of NTM are naturally multidrug resistant;<sup>2</sup> the infections caused by them are difficult to treat and usually require long-term combination therapy.

Linezolid (LZD), an oxazolidinone antibiotic, has been recommended as a first-line drug in the treatment of *M. abscessus* complex disease and as the second-line drug in the treatment of MAC pulmonary disease, due to its strong antibacterial activity.<sup>3</sup> However, its high recommended dosage of 600 mg once or twice per day incurs many adverse events such as cytopenia, and neuropathy restricts its long-term usage in clinical applications.<sup>4</sup> Tedizolid (TZD) has many of the same structural features as LZD, and inhibits protein synthesis by binding to the 23S rRNA of the 50S subunit, thereby blocking the formation of the 70S initiation complex.<sup>5,6</sup> Tedizolid phosphate is a prodrug that is rapidly converted by endogenous phosphatases to TZD.<sup>6</sup> This structural difference confers higher aqueous solubility and bioavailability, and less steric

hindrance than that of LZD.<sup>7,8</sup> TZD has been approved by the US Food and Drug Administration (FDA) in 2014, and the European Medicine Agency in 2015 for the treatment of acute bacterial skin and soft tissue infections. TZD has presented high activity against *Mycobacterium tuberculosis* and exhibited greater potency than that of LZD.<sup>9</sup> In the hollow-fiber system model of intracellular MAC, TZD showed bactericidal activity, and is the backbone of short-course anti-MAC.<sup>10</sup> The recommended therapeutic dose of TZD has greater in vitro potency than that of LZD against inhibition of mitochondrial protein synthesis for a shorter duration, indicating its potent effect and fewer adverse reactions.<sup>11</sup> Furthermore, Yuste et al published the first clinical case of pulmonary NTM infection that shifted to prolonged treatment with TZD after hematological toxicity and gastrointestinal intolerance with LZD, and the patient tolerated the full course of TZD with no nausea or other side effects during this time.<sup>12</sup> TZD was recommended in the 2020 ATS/ERS/ESCMID/IDSA clinical practice guidelines for the treatment of NTM pulmonary disease when patients are intolerant or whose isolate is resistant to first-line drugs including clofazimine, moxifloxacin, and LZD.<sup>1</sup> However, further studies are required to elucidate the activity of TZD against NTM.

Nonetheless, the time-kill assays of TZD did not show any bactericidal activity against *M. abscessus* complex.<sup>13</sup> Due to little clinical data, the in vitro effects of TZD on other NTMs are still vague. Additionally, TZD was reported to have a synergistic interaction with some antibiotics against NTM. The combination of TZD with clarithromycin showed an initial synergistic effect against *M. abscessus* complex, whereas indifferent interactions were noted when TZD was combined with tigecycline, ciprofloxacin, doxycycline, ceftioxin, and amikacin.<sup>13–15</sup> In another report, the combination of TZD with imipenem showed a moderate synergistic effect against *M. abscessus* ATCC 19977.<sup>16</sup> The combination of TZD and ceftioxin showed significant synergistic interaction against *M. fortuitum*.<sup>15</sup> TZD exhibited no notable synergistic interaction with other commonly used antimycobacterial drugs against MAC including clarithromycin, rifampicin, ethambutol, amikacin, and minocycline.<sup>15</sup> However, the strains included in these synergistic studies are limited.

Hence, in our study, we investigated the drug susceptibility status of TZD compared to that of LZD against a total of 133 clinical NTM strains in vitro, particularly those isolates have the high MIC values of LZD. Additionally, we evaluated the synergistic effect of TZD with other antibiotics that are effective against these clinical isolates.

## Material and Methods

### Isolates and Antibiotics

In total, 133 clinical isolates were collected by our laboratory from Huashan Hospital, Fudan University (Shanghai, China) between 2016 and 2021, including 64 respiratory isolates, 33 tissue samples (skin, puncture fluid, pus and wound), 5 blood system isolates, 3 urinary tract isolates, 1 central system isolate. Regrettably, the rest 27 isolates source records are missing. All NTM isolates collected between 2016 and 2021 except for MAC previously reported or *Mycobacterium marinum* were selected in this study. For *M. marinum*, we randomly selected 10 isolates of *M. marinum* collected in 2021. If a patient had multiple isolates, only the earliest isolate was included.

*M. abscessus* ATCC 19977, *M. fortuitum* ATCC 6841, *Mycobacterium mucogenicum* ATCC 49650, *Mycobacterium smegmatis* ATCC 700084, *Mycobacterium peregrinum* ATCC 700686, *Mycobacterium intracellulare* ATCC 13950, and *M. kansasii* ATCC 12478 were used as reference strains (Table 1) performed in each round of drug susceptibility test that were purchased from the American Type Culture Collection (ATCC). All isolates were thawed and recovered in cation-adjusted Mueller-Hinton Broth (CAMHB) (Oxoid, Hampshire, UK) or 7H9 liquid medium (Difco, Becton Dickinson, Sparks, MD).

**Table 1** The Drug Susceptibility Results of 7 Reference NTM Isolates

Organism	MICs of Tedizolid (mg/L)	MICs of Linezolid (mg/L)
<i>M. abscessus</i> ATCC 19977	4	32
<i>M. fortuitum</i> ATCC 6841	4	16
<i>M. mucogenicum</i> ATCC 49650	<0.125	<0.5
<i>M. smegmatis</i> ATCC 700084	0.5	1
<i>M. peregrinum</i> ATCC 700686	1	4
<i>M. intracellulare</i> ATCC 13950	16	64
<i>M. kansasii</i> ATCC 12478	0.5	2

TZD, LZD and ceftiofur sodium salt were purchased from Aladdin (Shanghai, China). Imipenem and clarithromycin powders were purchased from Meilunbio (Shanghai, China).

All NTM isolates were identified at the species level using polymerase chain reaction (PCR) amplification and Sanger sequencing of 16S rRNA according to a previous study.<sup>17</sup> The subspecies of the 35 *M. abscessus* complex clinical isolates was identified by multi-locus sequencing of the *rpoB*, *hsp65* and *secA* genes as reported.<sup>26,19</sup>

## Drug Susceptibility Tests

The drug susceptibility tests of SGM were performed by using the broth microdilution method in 96-well plates according to the CLSI guidelines M24-A2.<sup>18</sup> We tested the TZD concentrations ranging from 0.125 to 32 mg/L and LZD from 0.5 to 128 mg/L in 2-fold serial dilutions in all 140 NTM isolates. The minimum inhibitory concentration (MIC) was defined as the concentration of antibiotic at which there was no visible growth. MIC<sub>50</sub> and MIC<sub>90</sub> values were, respectively, defined as drug concentrations that inhibited 50% and 90% of the isolates. All experiments were performed at least twice with the reference strains as the control. To obtain sufficient growth for the SGM isolates, we used 7H9 liquid medium supplemented with 0.05% Tween<sup>®</sup> 80 and 10% bovine serum albumin-dextrose-catalase (ADC) enrichment instead of CAMHB at 37°C for 14 days as the previous studies recommended,<sup>25</sup> and bacteria (McFarland standard of 1.0) were inoculated into 7H9 containing antibiotics. After 14–21 days of incubation at 37°C (30°C for *M. marinum*), the MIC was determined. The RGM bacteria (McFarland standard of 0.5) were inoculated in CAMHB containing antibiotics. For some RGM isolates, the growth is insufficient in the growth control well; therefore, MICs for RGM bacteria were determined after incubating at 37°C instead of 30°C for 3–5 days, depending on the growth of the positive control wells containing no antibiotic. As showed in a previous study to explore the relationship between LZD and TZD MIC,<sup>15</sup> we also  $\ln(x+1)$  transformed the MIC values and performed a Spearman's  $\rho$  two-tailed correlation test using a Gaussian approximation by the SPSS software version 20.

The normality of MIC distribution of *M. abscessus* complex, *M. fortuitum*, MAC and *M. kansasii* was evaluated by Shapiro–Wilk test using SPSS. The comparison between *M. abscessus* complex subspecies was analyzed by Kruskal–Wallis test, with  $P \leq 0.05$  as statistically significant.

## Synergy Studies and Genotype of *erm(41)*

Synergy testing was performed using the broth microdilution checkerboard method.<sup>20</sup> According to the MIC of TZD in our experiments, clinical isolates whose drug concentrations ranged around the MIC<sub>50</sub> of its species used in the drug synergy test. TZD was evaluated in combination with clarithromycin and imipenem against 7 clinical isolates of *M. abscessus* complex and the reference strain ATCC 19977. The result of TZD–clarithromycin combination was read at both day 3 and day 14. The *erm(41)* genotype of all 7 clinical strains were sequenced as previous study.<sup>27</sup>

TZD in combination with ceftiofur was evaluated against 4 clinical isolates of *M. fortuitum* and the reference strain ATCC 6841. The fractional inhibitory concentration index (FICI) was calculated as follows:

$$\text{FICI} = \frac{\text{MIC drug A in combination}}{\text{MIC drug A alone}} + \frac{\text{MIC drug B in combination}}{\text{MIC drug B alone}}$$

Interaction was classified as synergistic, indifferent, and antagonistic when the FICI value was  $\leq 0.5$ , 0.5–4, and  $>4$ , respectively.

## Results

### MICs of LZD and TZD

The RGM species included *M. abscessus* complex (n = 35), *M. fortuitum* (n = 21), *M. mucogenicum* (n = 4), *M. chelonae* (n = 1), and *M. Itetiense* (n = 1). Among the 35 *M. abscessus* complex strains, there were 24 *M. abscessus* isolates, 11 *M. massiliense* isolates and no *M. bolletii* identified by multi-locus sequencing. The SGM species included MAC (n = 40), *M. kansasii* (n = 18), *M. marinum* (n = 10), *M. virginianse* (n = 1), and *M. gordonae* (n = 2).

The MICs of TZD for clinical isolates of NTM are given in Table 2. The detailed MICs of each strain are given in Supplementary Table 1. The MIC<sub>50</sub> and MIC<sub>90</sub> of *M. abscessus* complex are 2 and 4  $\mu\text{g/mL}$  for TZD, respectively. There was no significant difference between the 2 subspecies of the *M. abscessus* complex ( $P = 0.142$  for TZD and 0.182 for

**Table 2** The Drug Susceptibility Results of 133 Clinical NTM Isolates

Organism	n	Antimicrobial Agent	MIC (mg/L)		
			Range	MIC <sub>50</sub>	MIC <sub>90</sub>
<b>RGM</b>					
<i>M. abscessus</i> complex	35	Tedizolid	0.125–8	2	4
		Linezolid	0.5–32	16	16
<i>M. fortuitum</i>	21	Tedizolid	0.25–8	4	8
		Linezolid	1–32	16	32
<i>M. mucogenicum</i>	4	Tedizolid	<0.125–0.5		
		Linezolid	<0.5–2		
<i>M. chelonae</i>	1	Tedizolid	0.5		
		Linezolid	4		
<i>M. itetiense</i>	1	Tedizolid	4		
		Linezolid	16		
<b>SGM</b>					
<i>M. avium</i> complex	40	Tedizolid	1 - >32	16	>32
		Linezolid	4 - >128	64	128
<i>M. kansasii</i>	18	Tedizolid	0.25–8	1	8
		Linezolid	2–64	8	32
<i>M. marinum</i>	10	Tedizolid	<0.125–2		
		Linezolid	<0.5–16		
<i>M. virginiense</i>	1	Tedizolid	4		
		Linezolid	64		
<i>M. goodii</i>	2	Tedizolid	0.125–4		
		Linezolid	4–16		

LZD). The susceptibilities of the TZD MIC<sub>50</sub> and MIC<sub>90</sub> of *M. fortuitum* are 4 and 8 µg/mL, respectively, which are 4 times lower than those of LZD. The 40 MAC isolates had MIC<sub>50</sub> and MIC<sub>90</sub> values of 16 and >32 µg/mL for TZD, and 64 and 128 µg/mL for LZD, respectively. Analysis showed that MICs of TZD and LZD are strongly correlated for *M. abscessus* complex (Spearman's  $\rho = 0.692$ ,  $P < 0.001$ ), *M. fortuitum* (Spearman's  $\rho = 0.617$ ,  $P < 0.05$ ), and *M. kansasii* (Spearman's  $\rho = 0.811$ ,  $P < 0.001$ ), and moderately correlated for MAC (Spearman's  $\rho = 0.564$ ,  $P < 0.001$ ). The gaussian distribution was showed in the MIC distribution of TZD for *M. abscessus* complex ( $P = 0.265$ ), *M. fortuitum* ( $P = 0.096$ ) and *M. kansasii* ( $P = 0.32$ ) in Figure 1, except for MAC ( $P = 0.025$ ).

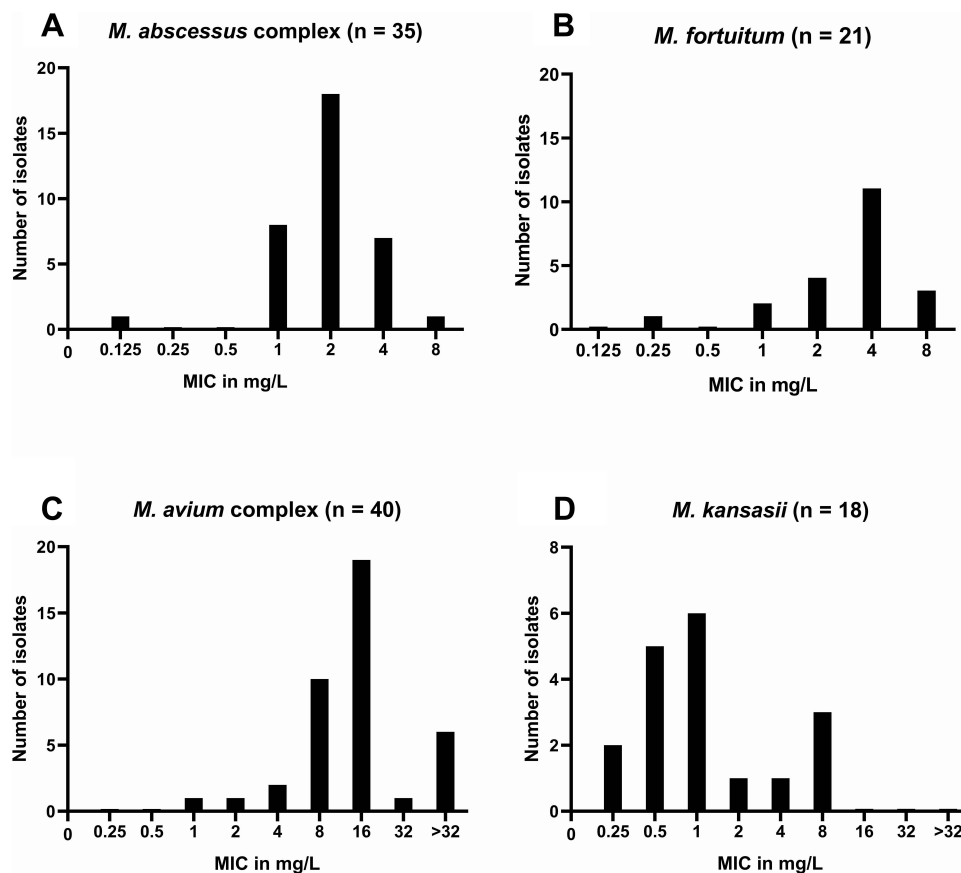
## TZD Synergy Response with Other Antimicrobials

For the 7 clinical isolates of *M. abscessus* complex tested in TZD-clarithromycin combination, the *erm*(41) PCR product of the *M. massiliense* ( $n = 3$ ) was shorter (~350 bp) than that of the *M. abscessus* ( $n = 4$ ) (~700 bp), consistent with the previous study.<sup>27</sup> Among the 4 clinical isolates of *M. abscessus* which had longer *erm*(41), one isolate had a nonfunctional T28C mutation in it, while the other 3 isolates had a wildtype *erm*(41).

The synergistic response of TZD-clarithromycin combination was observed in 3 clinical isolates of the *M. abscessus* and this synergistic response of TZD-clarithromycin lasted 3–5 days, but rapidly showed inducible clarithromycin resistance. As for the other 4 isolates susceptible to clarithromycin, we did not observe the synergistic response on day 3 (Average FICI = 0.84) or day 14 (Average FICI = 1.016). The FIC and *erm*(41) genotype of each *M. abscessus* complex isolate is shown in Table 3.

The combination of TZD and TZD-imipenem showed indifferent interactions (FICI = 0.82) (Table 4) against 4 isolates of *M. abscessus* complex, and the other 4 clinical isolates were highly resistant to imipenem.

For *M. fortuitum*, TZD-cefoxitin exhibited a synergistic effect against all five isolates (average FICI = 0.36).



**Figure 1** MIC distributions of tedizolid for clinical isolates of (A) *M. abscessus* complex (n = 35), (B) *M. fortuitum* (n = 21), (C) *M. avium* complex (n = 40) and (D) *M. kansasii* (n = 18).

## Discussion

The drug susceptibility of NTM clinical strains is important for evaluating the effect of TZD. In this study, the MIC<sub>50</sub> and MIC<sub>90</sub> of TZD for *M. abscessus* complex were 2 and 4 µg/mL, respectively. This result is consistent with previous studies in which the TZD MIC<sub>50</sub> and MIC<sub>90</sub> were 1–4 and 2–8 µg/mL, respectively.<sup>13,15,21–23</sup>

The TZD MIC<sub>50</sub> and MIC<sub>90</sub> for MAC were relatively high at 16 and 32 µg/mL, respectively (Table 2). In a previous study, both the TZD MIC<sub>50</sub> and MIC<sub>90</sub> for MAC were 8 µg/mL.<sup>21</sup> Similarly, another study showed the TZD MIC<sub>50</sub> and MIC<sub>90</sub> for *M. avium* were 2 and 16 µg/mL, respectively, and the MIC ranged from 4 to 8 µg/mL for *M. intracellulare*.<sup>15</sup>

**Table 3** FICs of Tedizolid in Combination with Clarithromycin Against *M. abscessus* complex (n = 8)

Isolate ID	Subspecies	FICI		<i>erm(41)</i>
		TZD/Clarithromycin (Day 3) <sup>a</sup>	TZD/Clarithromycin (Day 14)	
ATCC 19977	<i>M. abscessus</i>	0.625	Induced resistant	Wildtype
18-T2394-2	<i>M. massiliense</i>	1	1.016	Truncated
18-T2449-2	<i>M. massiliense</i>	0.75	1.016	Truncated
BY1802	<i>M. massiliense</i>	1.016	1.016	Truncated
18-T1911	<i>M. abscessus</i>	0.625	1.016	Nonfunction T28C mutant
HS20072	<i>M. abscessus</i>	<b>0.5</b>	Induced resistant	Wildtype
HS19011	<i>M. abscessus</i>	<b>0.5</b>	Induced resistant	Wildtype
BY1803	<i>M. abscessus</i>	<b>0.5</b>	Induced resistant	Wildtype

**Note:** <sup>a</sup>Bold style indicates synergy according to FIC.

**Table 4** FICIs of Tedizolid in Combination with Clarithromycin and Imipenem for *M. abscessus* complex, and Tedizolid in Combination with Cefoxitin for *M. fortuitum*

Organism	Combination	Average FICI	FICI Range (Min–Max)
<i>M. abscessus</i> complex (n=8)	TZD/clarithromycin (day 3)	0.69	0.5–1.016
<i>M. abscessus</i> complex (n=4)	TZD/clarithromycin (day 14)	1.016	1.016
<i>M. abscessus</i> complex (n=4)	TZD/imipenem	0.82	0.75–1.03
<i>M. fortuitum</i> (n=5)	TZD/cefoxitin	0.36	0.3125–0.375

However, a previous study from Beijing, China, showed high-level MIC values to TZD, in which the TZD MIC<sub>50</sub> and MIC<sub>90</sub> for *M. avium* and *M. intracellulare* were 32 and >32 µg/mL, respectively.<sup>23</sup> Therefore, the relative higher MIC values for MAC isolates in our study could have national and geographical reasons such as the high use of antibiotics in China. Furthermore, all studies including ours showed the high MIC values of TZD against MAC; thus, it is necessary to carry out drug sensitivity tests before TZD administration. Meanwhile, TZD MIC distribution in our study was unimodal for *M. abscessus* complex and *M. fortuitum*, nearly bimodal for *M. kansasii* and MAC, which was consistent with the previous study.<sup>15</sup> The breakpoint for TZD was set as 1mg/L in a previous study in 2017, in which the exposure–response experiment in the hollow-fiber system model of intracellular MAC was performed at the TZD dose of 200mg/day.<sup>10</sup> However, we did not use the recommended breakpoint, because 1mg/L is exactly on the first peak of MIC distribution for *M. kansasii*, MAC, and *M. abscessus* complex, that may divide the wild type population and subsequently leads to once as susceptible and once as resistant in the resistance replicate test, which usually not identical and lay within a relatively small range. As there is insufficient basis for setting breakpoint based on current data, the setting of breakpoint still requires more clinical data and further study.

A previous study showed that TZD's penetration into lung epithelial lining fluid and alveolar macrophages is greater than that of LZD.<sup>24</sup> Additionally, TZD had stronger potency against NTM, which may be an effective substitute for LZD in the treatment of NTM-related infectious diseases. Furthermore, we found the MICs of TZD and LZD were positively correlated for *M. abscessus* complex, *M. fortuitum*, *M. kansasii*, and MAC; this observation is partially consistent with those in a study by Ruth et al<sup>15</sup> wherein TZD and LZD MICs were correlated for MAC but not for *M. abscessus* complex. This may be because >10% *M. abscessus* complex had an MIC >32 µg/mL in LZD and a limited number of isolates in their study; therefore, there was no significant difference (Spearman's  $\rho = 0.2304$ ,  $P = 0.1192$ ). Due to the correlation between TZD and LZD, we do not recommend directly replacing LZD with TZD in the treatment of drug-resistant strains without first verifying the susceptibility of TZD.

Synergy tests showed that TZD exhibited significant interactions with cefoxitin against *M. fortuitum*, which was consistent with the results of a previous study.<sup>15</sup> Although the combination of TZD with imipenem showed a moderate synergistic effect against *M. abscessus* ATCC 19977,<sup>16</sup> this synergy was not observed in our clinical strains. In addition to the broth microdilution checkerboard method, TZD-amikacin combination showed modest, concentration-dependent synergy against MAC relative to the Bliss independence model by time–kill kinetics assays, whereas TZD-ethambutol combination was synergistic for *M. avium* at lower concentrations.<sup>15</sup> TZD showed concentration-dependent bactericidal activity against *M. avium* and bacteriostatic activity against *M. abscessus* in time-kill experiments, and the Bliss independent model focused on the superposition of doses. In the hollow-fiber system model of intracellular MAC, Deshpande et al identified a novel four-drug combination (ceftazidime/avibactam, rifabutin, TZD, and moxifloxacin) exhibiting kill rates better than that of standard therapy.<sup>16</sup> Similarly, the results of synergy tests in the current study suggested that TZD may be an important component of multi-drug treatment regimen, although further research on exposure dosages is required.

However, our study has several limitations. First, probably since most of our NTM isolates were from patients who had been on antimicrobial therapy, a large amount of RGM isolates were not growing well in 30°C although we tried to perform the drug susceptibility tests in 30°C. The MICs for all RGM bacteria in our study uniformly grew and were determined after incubating at 37°C for 3–5 days, depending on the growth of the positive control wells containing no

antibiotic. We recorded the MICs timely and included the standard strains as quality controls in each batch. Although we changed the incubation temperature to 37°C, the TZD and LZD MIC of our quality control strains were comparable to the previous studies,<sup>15,22</sup> therefore, the results still have reference value. Second, the isolates were collected from a geographically limited group of patients who visited Shanghai. Additionally, a limited number of NTM isolates were collected. Hence, the drug susceptibility and synergic combination results should be verified in more clinical strains.

In conclusion, our results showed that TZD has lower MICs than those of LZD when tested against NTM-related diseases, which indicated that TZD had greater in vitro potency than LZD. Furthermore, the results of MICs of TZD and LZD were correlated in vitro, based on the synergistic interactions with ceftioxin and clarithromycin against *M. fortuitum* and only initially 3/7 of the clinical isolates of *M. abscessus* complex, respectively.

## Ethics Approval and Informed Consent

The research for the current study has been approved by the Institutional Review Board (IRB) of Huashan Hospital, Fudan University (Number: 2022-291). Our study is a retrospective study without direct contact with the patient, and did not involve personal privacy or commercial interests, so the informed consent was waived. This study is in accordance with the Helsinki Declaration and the information of all patients included in the study remained confidential.

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## Disclosure

The authors declare no conflicts of interest in this work.

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