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Drug susceptibility patterns of *Mycobacterium abscessus* and *Mycobacterium massiliense* isolated from respiratory specimens

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ABSTRACT

In this study, we aimed to retrospectively investigate and compare the drug susceptibility patterns of two major *Mycobacterium abscessus* complex (MABC) species; *M. abscessus* and *M. massiliense*. A total of 546 MABC respiratory isolates (277 *M. abscessus* and 269 *M. massiliense*) from 2011 to 2016 were analyzed in this study. We estimated minimum inhibitory concentrations (MICs) using the broth microdilution method, and we calculated MIC_{50} and MIC_{90} values from the MIC distribution. Both *M. abscessus* and *M. massiliense* were highly susceptible to amikacin and linezolid. For *M. abscessus*, the proportions of inducible and acquired resistance to clarithromycin were 68.6% and 12.3%, respectively. Only 15.2% of *M. abscessus* remained susceptible at day 14. On the other hand, none of the *M. massiliense* showed inducible resistance and 6.3% showed acquired resistance to clarithromycin. A total of 92.6% of the *M. massiliense* remained susceptible at day 14. The resistance rate of *M. abscessus* to moxifloxacin (90.3%) was significantly higher than that of *M. massiliense* (83.3%; $p = 0.016$). These susceptibility differences may explain the divergent treatment outcomes between patients with pulmonary disease caused by these two species.

1. Introduction

Mycobacterium abscessus complex (MABC) is the most common etiology of pulmonary infection caused by rapidly growing mycobacteria worldwide (Griffith et al., 2007; Koh et al., 2014). MABC is divided into three species: *M. abscessus*, *M. massiliense*, and *M. bolletii*. Among them, *M. abscessus* is the most common, followed by *M. massiliense*. *M. bolletii*, in comparison, is a relatively rare pathogen (Koh et al., 2014, 2017). According to a previous study, *M. massiliense* lung disease was associated with a favorable treatment outcome, contrary to *M. abscessus* lung disease (Koh et al., 2011). Inducible macrolide resistance, which means susceptible at Day 3 but resistant at Day 14 of drug susceptibility tests (DSTs), is the most important factor for determining treatment outcome. While *M. abscessus* has a high inducible resistance rate to macrolides, *M. massiliense* does not (Kim et al., 2015; Koh et al., 2011). Inducible resistance to macrolides is due to a functional erythromycin ribosome methyltransferase (*erm*) (41) gene (Nash et al., 2009). Approximately 9% to 17% of *M. abscessus* strains are macrolide susceptible because of a nonfunctional C28 sequevar of the *erm* (41) gene (Brown-Elliott et al., 2015; Lee et al., 2014; Mougari et al., 2016; Yoshida et al., 2013).

To investigate other factors affecting treatment outcomes, comprehensive analysis of DSTs of *M. abscessus* and *M. massiliense* isolates is required. However, precise species differentiation between *M. abscessus* and *M. massiliense* has not been conducted in many clinical laboratories, and only a few studies to date have compared DST results between these two species. Thus, we aimed to retrospectively review the DST results of *M. abscessus* and *M. massiliense* and compare the drug susceptibility pattern of the two species from respiratory specimens isolated in a tertiary referral hospital in South Korea over a six-year period.

2. Materials and methods

2.1. Nontuberculous mycobacteria isolates

A total of 1878 DST results from respiratory MABC isolates (1320 *M. abscessus* and 558 *M. massiliense*) collected at Samsung Medical Center (a 1979-bed referral hospital in Seoul, South Korea) from January 2011 to December 2016 were included. For patients with

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multiple DST results, only the first DST result was analyzed. This study was approved by the institutional review board of Samsung Medical Center. From January 2011 to May 2014, the REBA Myco-ID® (YD Diagnostics, Yongin, South Korea), a diagnostic kit based on polymerase chain reaction (PCR)-reverse-blot hybridization of the *rpoB* gene, was used for species identification of nontuberculous mycobacteria (NTM). From June 2014 to December 2016, species identification of NTM was conducted via nested multiplex PCR and a reverse-hybridization assay of the internal transcribed spacer region (AdvanSure™ Mycobacteria GenoBlot Assay; LG Life Sciences, Seoul, South Korea), followed by real-time PCR with species-specific primers and probes targeting the *erm* (41) gene to differentiate between *M. abscessus* and *M. massiliense*.

2.2. Drug susceptibility test

All DSTs were performed at the Korean Institute of Tuberculosis, a World Health Organization-designated supranational reference laboratory, using the broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) (Clinical Laboratory Standards Institute, 2011). The nine antimicrobial agents – amikacin, cefoxitin, imipenem, clarithromycin, moxifloxacin, ciprofloxacin, doxycycline, linezolid, and trimethoprim/sulfamethoxazole (TMP/SMX) – were tested. In the case of clarithromycin, the minimum inhibitory concentration (MIC) was determined on both day 3 and day 14 to assess the inducible resistance. The antimicrobial concentration ranges for DST are listed in Table 1. Two different steps for quality control were conducted. For media production quality control, *M. peregrinum* American Type Culture Collection (ATCC) 700,686, *M. kansasii* ATCC 12478 and six different *M. abscessus* and *M. fortuitum* complex clinical isolates with distinguishing DST characteristics were used. For every batch of tests, *M. peregrinum* ATCC 700686, *M. kansasii* ATCC 12478 and *M. avium* ATCC 700898 were used for quality control.

The MICs determined with broth microdilution were interpreted according to the CLSI M24-A2 protocol (Clinical Laboratory Standards Institute, 2011). Additionally, MIC_{50} and MIC_{90} values were derived from the MIC distribution. The 95% epidemiological cutoff values (ECOFFs) were estimated using ECOFFinder (Turnidge et al., 2006).

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS version 23 (IBM, Armonk, NY, USA). The Pearson chi-squared test was used for categorical variables, and the Mann–Whitney test was used for continuous variables. A *p*-value of <0.05 was considered significant.

3. Results

After excluding duplicates, 546 MABC isolates (277 *M. abscessus* and 269 *M. massiliense*) from 546 patients with MABC lung disease were studied. The drug susceptibility patterns of MABC, including the MIC_{50}/MIC_{90} values and 95% ECOFFs, are presented in Table 2 and Fig. 1. Amikacin was the most active drug for MABC. The resistance rate to amikacin was 4.7% (13/277) for *M. abscessus* and 5.9% (16/269) for *M. massiliense* without a significant difference between the two species ($P = 0.513$). Resistance rate to cefoxitin was higher in *M. abscessus* (13.4%, 37/277) than in *M. massiliense* (7.1%, 19/269; $P = 0.015$). For imipenem, resistance rates were not different between the two species ($P = 0.403$).

For clarithromycin, 15.2% (42/277) of *M. abscessus* was susceptible at both day 3 and day 14. A total of 68.6% (190/277) of *M. abscessus* was susceptible at day 3 but resistant at day 14, which corresponded to inducible resistance for clarithromycin, while 12.3% (34/277) of *M. abscessus* was resistant at day 3, which corresponded to acquired resistance to clarithromycin. On the other hand, all *M. massiliense* isolates showed the same susceptibility results at day 3 and day 14: none of the *M. massiliense* isolates exhibited inducible resistance. The vast majority of *M. massiliense* isolates (92.6%, 249/269) were susceptible to clarithromycin, and 6.3% (17/269) of *M. massiliense* were resistant to clarithromycin at day 3, which indicated acquired resistance to clarithromycin.

Resistance rates to moxifloxacin and ciprofloxacin were high in both *M. abscessus* and *M. massiliense*. The resistance rate to moxifloxacin was significantly higher in *M. abscessus* (90.3%, 250/277) than in *M. massiliense* (83.3%, 224/269; $p = 0.016$), while there was no significant difference seen in the resistance rate to ciprofloxacin (94.2% [261/277] for *M. abscessus* versus 90.0% [242/269] for *M. massiliense*, $P = 0.065$). Almost all isolates were resistant to doxycycline, and there was no significant difference in the resistance rates between *M. abscessus* and *M. massiliense* (97.8% [271/277] for *M. abscessus* versus 98.1% [264/269] for *M. massiliense*; $p = 0.798$). The resistance rate to linezolid was less than 10% for both *M. massiliense* and *M. abscessus*.

Table 1
Antimicrobial concentration ranges (μg/mL) for DSTs and suggested breakpoints (μg/mL) of the antimicrobial agents.

Antimicrobial	Tested concentration ranges (μg/mL)	Breakpoints suggested by CLSI		
		Susceptible	Intermediate	Resistant
Amikacin	1–128	≤16	32	≥64
Cefoxitin	2–256	≤16	32–64	≥128
Imipenem	0.5–64	≤4	8–16	≥32
Clarithromycin	0.5–64	≤2	4	≥8
Moxifloxacin	0.125–16	≤1	2	≥4
Ciprofloxacin	0.125–16	≤1	2	≥4
Doxycycline	0.25–32	≤1	2–4	≥8
Linezolid	2–64	≤8	16	≥32
TMP/SMX	0.25/475–32/608	≤2/38	-	≥4/76

CLSI: Clinical Laboratory Standards Institute, TMP/SMX: trimethoprim/sulfamethoxazole.

4. Discussion

To the best of our knowledge, this is the largest evaluation of DST patterns of MABC species, which included about 550 clinical isolates from respiratory specimens. Herein, the proportions of *M. abscessus* (50.7%) and *M. massiliense* (49.3%) in our clinical dataset were similar, which was consistent with previous studies in South Korea (Koh et al., 2011; Lee et al., 2014).

Inducible macrolide resistance is considered to be a key factor affecting treatment outcome differences between *M. abscessus* and *M. massiliense*. Because inducible resistance to macrolides is often observed in *M. abscessus* but not in *M. massiliense*, *M. abscessus* may jeopardize the effectiveness of standard therapy and delay treatment, leading to poorer treatment outcomes as compared with *M. massiliense* (Koh et al., 2011). The inducible resistance to macrolides of *M. abscessus* is associated with a functional *erm* (41) gene (Nash et al., 2009). *M. massiliense* does not show inducible resistance to macrolides, since *M. massiliense* has a nonfunctional *erm* (41) gene with a deletion (Bastian et al., 2011). Meanwhile, *M. abscessus* isolates with a C28 sequevar of the *erm* (41) gene were susceptible to macrolides and showed a better treatment outcome than did T28 sequevar isolates (Bastian et al., 2011; Koh et al., 2017).

We found that *M. abscessus* had a 68.6% inducible resistance rate and a 12.3% acquired resistance rate for clarithromycin. A total of 15.2% of *M. abscessus* was susceptible to clarithromycin, which was consistent with previous studies' findings (Brown-Elliott et al., 2015; Lee et al., 2014; Mougari et al., 2016; Yoshida et al., 2013). Although a genetic analysis of the *erm* (41) gene was not performed in this study, these isolates may have a C28 sequevar of the *erm* (41) gene. Contrary to the low susceptibility to clarithromycin observed in *M. abscessus*, 92.6% of *M. massiliense* isolates were susceptible to clarithromycin. These findings highlight the importance of using different treatment strategies for *M. abscessus* and *M. massiliense* and the consequent need

Table 2
Drug susceptibility profiles of *M. abscessus* and *M. massiliense*.

Antibiotics	No. of isolates (%)[a]							MIC_{50}/MIC_{90}		
	Susceptible		Intermediate		Resistant					
	M. abscessus	*M. massiliense*	*M. abscessus*	*M. massiliense*	*M. abscessus*	*M. massiliense*	*p*-value	*M. abscessus*	*M. massiliense*	*p*-value
Amikacin	207 (74.7)	208 (77.3)	57 (20.6)	45 (16.7)	13 (4.7)	16 (5.9)	0.513	16/32	16/32	0.185
Cefoxitin	71 (25.6)	59 (21.9)	169 (61.0)	191 (71.0)	37 (13.4)	19 (7.1)	0.015	32/128	32/64	0.981
Imipenem	60 (21.7)	53 (19.7)	150 (54.2)	159 (59.1)	67 (24.2)	57 (21.2)	0.403	8/64	8/32	0.897
Clarithromycin (D3)	232 (83.8)	249 (92.6)	11 (4.0)	3 (1.1)	34 (12.3)	17 (6.3)	0.017	1/8	≤0.5/1	<0.001
Clarithromycin (D14)	42 (15.2)	249 (92.6)	2 (0.7)	3 (1.1)	233 (84.1)	17 (6.3)	<0.001	64/>64	≤0.5/1	<0.001
Moxifloxacin	5 (1.8)	12 (4.5)	22 (7.9)	33 (12.3)	250 (90.3)	224 (83.3)	0.016	8/>16	8/>16	0.171
Ciprofloxacin	5 (1.8)	4 (1.5)	11 (4.0)	23 (8.6)	261 (94.2)	242 (90.0)	0.065	16/>16	16/>16	0.011
Doxycycline	4 (1.4)	1 (0.4)	2 (0.7)	4 (1.5)	271 (97.8)	264 (98.1)	0.798	>32/>32	>32/>32	0.002
Linezolid[b]	121 (62.1)	167 (72.3)	56 (28.7)	45 (19.5)	18 (9.2)	19 (8.2)	0.713	8/16	8/16	0.023
TMP/SMX	16 (8.2)	26 (11.3)	-	-	179 (91.8)	205 (88.7)	0.293	8/152 / 32/608	8/152 / 32/608	0.080

MIC = minimum inhibitory concentration, TMP/SMX: trimethoprim/sulfamethoxazole.
[a] A total of 277 *M. abscessus* and 269 *M. massiliense* were included.
[b] For TMP/SMX and linezolid, 195 *M. abscessus* and 231 *M. massiliense* were studied.

for precise differentiation between causative species among MABC clinical isolates.

However, according to recently published guidelines, including the British Thoracic Society (BTS) guidelines for the management of NTM pulmonary disease and the United States Cystic Fibrosis Foundation (US CFF) and the European Cystic Fibrosis Society (ECFS) consensus recommendations for the management of NTM in individuals with cystic fibrosis, similar treatment regimens have been recommended for *M. abscessus* and *M. massiliense* lung disease (Floto et al., 2016; Haworth et al., 2017). The BTS guidelines recommend applying different treatment regimens to macrolide-susceptible or inducible resistant isolates and acquired resistant isolates, respectively. These guidelines suggest the implementation of an initial phase antibiotic regimen with intravenous amikacin, tigecycline, and/or imipenem with or without oral macrolides (according to macrolide susceptibility) for at least 4 weeks, followed by a continuation phase regimen with nebulized amikacin and oral macrolides with one to three oral antibiotics (clofazimine, linezolid, minocycline or doxycycline, moxifloxacin or ciprofloxacin, and co-trimoxazole) (Haworth et al., 2017). Meanwhile, the US CFF and ECFS consensus recommendations suggest initial oral macrolide and intravenous amikacin with one or more intravenous antibiotics (tigecycline, imipenem, cefoxitin) for 3 to 12 weeks, followed by a continuation phase of oral macrolide with inhaled amikacin and 2 to 3 additional oral antibiotics (minocycline, clofazimine, moxifloxacin, and linezolid) (Floto et al., 2016). Although macrolides are a key drug in MABC treatment, *M. abscessus*, with the exception of approximately 15% of susceptible isolates, have acquired or inducible resistance to them, according to findings from the present and previous studies (Bastian et al., 2011; Brown-Elliott et al., 2015; Lee et al., 2014; Mougari et al., 2016). Therefore, the majority of *M. abscessus* isolates may not be responsive to this treatment regimen, including macrolides. Furthermore, based on the high resistance rate to doxycycline, ciprofloxacin, and moxifloxacin that we observed in this study, the use of these antibiotics in the continuation phase may not be appropriate for both *M. abscessus* and *M. massiliense*. Therefore, precise differentiation between causative species among MABC clinical isolates and the use of different treatment strategies for *M. abscessus* and *M. massiliense* should be considered to improve treatment outcomes in MABC lung disease.

In this study, amikacin was the most active antimicrobial agent against MABC species, showing a 76.0% overall susceptibility rate. However, several other studies found an overall susceptible rate of more than 90% (Chua et al., 2015; Pang et al., 2015; Yang et al., 2003). After amikacin, linezolid was the second most effective antimicrobial agent against MABC, with a 67.6% susceptibility rate. Although prior studies have reported a variable susceptibility rate for linezolid, ranging from 32.0% to 97.0% (Chua et al., 2015; Kim et al., 2015;Yang et al., 2003; Yoshida et al., 2013), the majority of MABC species are susceptible to linezolid. Therefore, linezolid could be used as an alternative choice, especially against isolates with inducible resistance to macrolides, although there is a lack of research about the in vivo activity of linezolid.

The resistance rate of MABC species to imipenem was 22.7%, and there was no significant difference between *M. abscessus* and *M. massiliense* resistance rates (24.1% versus 21.2%, respectively; $P =$ .403). Our findings are consistent with those from previous studies conducted in Japan and Taiwan (Yang et al., 2003; Yoshida et al., 2013). However, resistance rates were higher among MABC specimens isolated in the United Kingdom and Australia, ranging from 68.4% to 98.0% (Broda et al., 2013; Chua et al., 2015). The resistance rate to cefoxitin was two times higher in *M. abscessus* (13.4%) than in *M. massiliense* (7.1%; $P =$ .015). Contrary to our results, one Australian study reported that *M. massiliense* (27.8%) was more resistant to cefoxitin than *M. abscessus* was (10.0%) (Chua et al., 2015). These findings suggest regional differences in the drug susceptibility patterns of MABC.

The vast majority of MABC isolates were resistant to moxifloxacin and ciprofloxacin, as previously reported (Chua et al., 2015; van Ingen et al., 2010; Yang et al., 2003; Yoshida et al., 2013). Only a study from China found a relatively high susceptible rate to ciprofloxacin and moxifloxacin (Pang et al., 2015). In South Korea, prior research reported that almost all MABC isolates were resistant to ciprofloxacin and moxifloxacin (Jeong et al., 2017; Lee et al., 2014). Based on these findings, the treatment effects of moxifloxacin and ciprofloxacin seem to be limited.

The present study has several limitations. First, patient treatment histories were unknown. Second, a genetic analysis of the *erm* (41) gene for inducible clarithromycin resistance could not be performed due to the retrospective nature of this study. Third, the NTM identification methods used in this study were unable to differentiate between *M. abscessus* and *M. bolletii*, which might affect the DST results of *M. abscessus*. However, *M. bolletii* appears to be very rare (<1% of MABC) in South Korea (Koh et al., 2011, 2017; Lee et al., 2014).

In conclusion, there are significant differences in the drug susceptibility patterns of *M. abscessus* and *M. massiliense*, which could explain the different treatment outcomes between the two subspecies. Prospective studies of individual MABC species are needed to understand the association between different DST results and clinical outcomes.

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Competing interests

None declared.

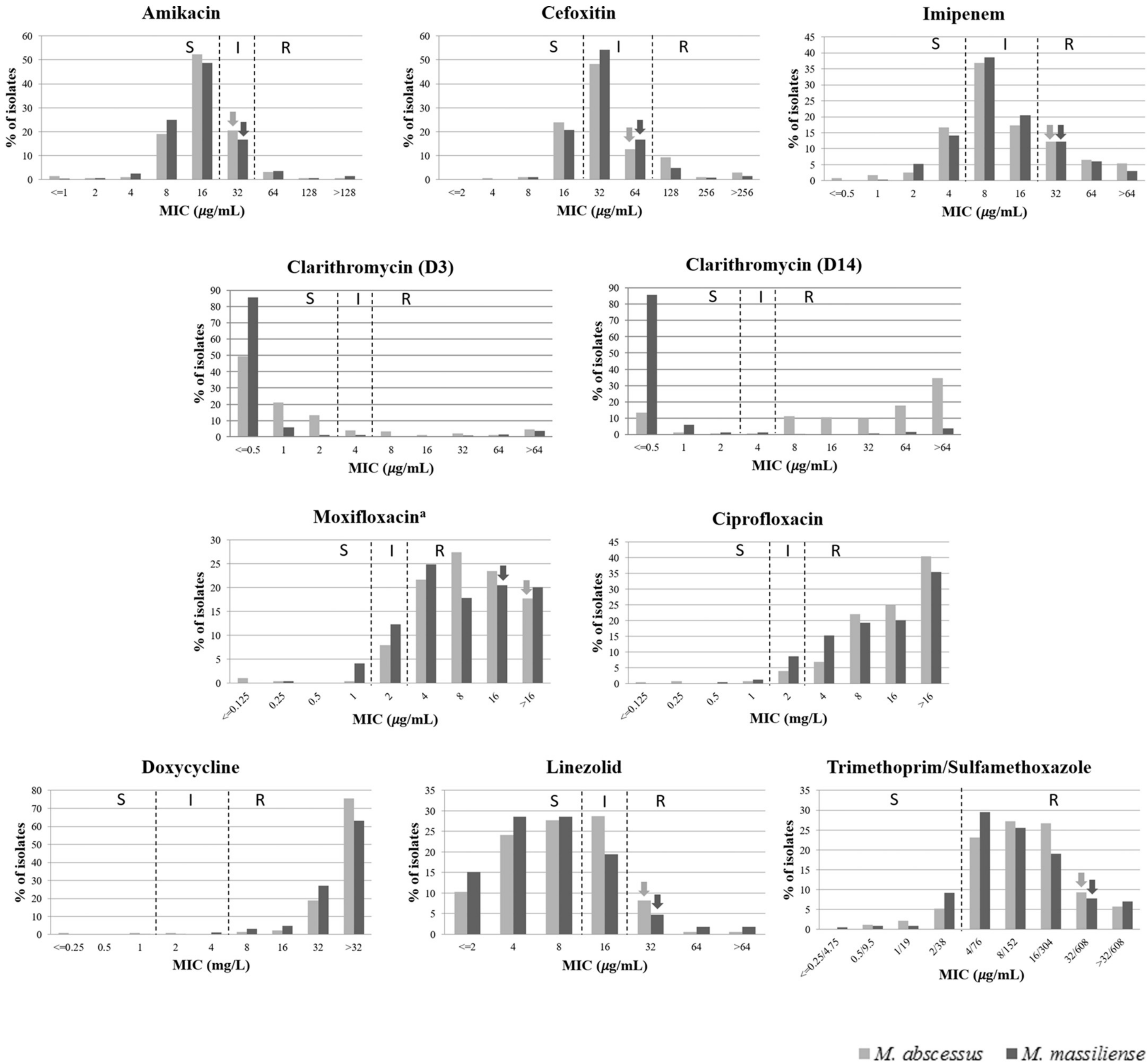

Fig. 1. MIC distribution for *M. abscessus* and *M. massiliense*. The gray and black arrows indicate the 95% ECOFFs for *M. abscessus* and for *M. massiliense*, respectively. [a]The 95% ECOFF for *M. abscessus* is 64 μg/mL.

Ethical approval

This study was approved by the institutional review board of Samsung Medical Center [2016–12-130].

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