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Note

Differences in drug susceptibility pattern between *Mycobacterium avium* and *Mycobacterium intracellulare* isolated in respiratory specimens☆

Eun Hye Cho [a, 1], Hee Jae Huh [a, 1], Dong Joon Song [a], Seong Mi Moon [b], Seung-Heon Lee [c], So Youn Shin [c], Chang Ki Kim [d], Chang-Seok Ki [a], Won-Jung Koh [b, **], Nam Yong Lee [a, *]

[a] Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[b] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[c] Korean Institute of Tuberculosis, Cheongju, South Korea
[d] Seoul Clinical Laboratories, Seoul, South Korea

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ABSTRACT

Mycobacterium avium complex (MAC) is the most common etiologic organisms of nontuberculous mycobacteria (NTM) lung disease. In this study, we aimed to retrospectively investigate the differences in drug susceptibility patterns of two major MAC species; *Mycobacterium avium* and *Mycobacterium intracellulare*. A total of 1883 major two MAC isolates (1060 *M. avium* and 823 *M. intracellulare*) from respiratory specimens were included in this study during the period 2011–2016. The minimum inhibitory concentrations (MICs) were determined by broth microdilution method and MIC_{50}/MIC_{90} values were derived from MIC distribution. *M. intracellulare* had generally low susceptible rates than *M. avium* for almost all tested antimicrobials except ethambutol and amikacin. The susceptible rate to clarithromycin was >94% of the MAC without significant differences between the two species. The MIC_{50} values of ciprofloxacin, clarithromycin, linezolid, moxifloxacin, and rifampicin were higher in *M. intracellulare* than in *M. avium*, contrary to the results of ethambutol with a higher MIC_{50} in *M. avium*. In general, *M. intracellulare* showed a higher resistance rate and higher MIC_{50} values than *M. avium*. Differences between this study and previous reports suggest regional differences in drug susceptibility profile of MAC species.

Mycobacterium avium complex (MAC), which is divided into two major species including *Mycobacterium avium* and *Mycobacterium intracellulare*, is the most common etiologic cause of nontuberculous mycobacterial (NTM) lung disease [1]. Some studies have demonstrated that drug susceptibility patterns and treatment outcomes were different between *M. avium* and *M. intracellulare* lung disease [2–5]. These findings raise the need for comprehensive studies about the drug susceptibility pattern of MAC species to establish optimal treatment strategy. Thus, we aimed to provide information about epidemiologic data with MIC distribution and to evaluate the differences in drug susceptibility patterns between *M. avium* and *M. intracellulare* isolated from a large number of patients with MAC pulmonary infections.

Drug susceptibility test (DST) results of respiratory MAC isolates were obtained from mycobacteriology laboratory reports between January 2011 and December 2016 at Samsung Medical Center (a 1979-bed referral hospital in Seoul, South Korea). This retrospective study was approved by the Samsung Medical Center Institutional Review Board. Species identification was conducted by a PCR and reverse hybridization assay targeting the *rpoB* gene or internal

☆ All authors meet the above ICMJE authorship criteria.

* Corresponding author. Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-Gu, Seoul 06351, South Korea.
** Corresponding author. Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-Gu, Seoul 06351, South Korea
E-mail addresses: wjkoh@skku.edu (W.-J. Koh), micro.lee@samsung.com (N.Y. Lee).

[1] These authors contributed equally to this work.

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transcribed spacer region [6]. DST was performed at the Korean Institute of Tuberculosis using the broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) [7]. Seven antimicrobial agents including clarithromycin, ethambutol, rifampicin, amikacin, ciprofloxacin, moxifloxacin, and linezolid were tested. The tested concentration ranges are listed in Supplemental Table 1. The minimum inhibitory concentrations (MICs) for clarithromycin, moxifloxacin, and linezolid were interpreted according to the CLSI M24-A2 protocol [7]. The suggested breakpoints based on pharmacokinetic/pharmacodynamic (PK/PD) data were applied for ethambutol and rifampicin [8]. For amikacin, the proposed breakpoint of Brown-Elliott et al. was used, which was derived from the mutation study for 16S rRNA gene (Supplemental Table 2) [9]. MIC_{50} and MIC_{90} values were derived from MIC distribution. The Pearson χ^2-test for categorical variables and the Mann-Whitney U test for continuous variables was performed using IBM SPSS version 23 (IBM, Armonk, NY).

After the exclusion of duplicates, a total of 1883 MAC isolates (1060 *M. avium* and 823 *M. intracellulare*) from 1883 patients with MAC pulmonary disease were studied. The drug susceptibility patterns including MIC_{50} and MIC_{90} values are presented in Table 1. For clarithromycin, the vast majority of the isolates were susceptible without significant difference in susceptible rate (94.4% for *M. avium* versus 94.2% for *M. intracellulare*, respectively; $p = 0.804$). When applying the suggested PK/PD-derived breakpoints for ethambutol and rifampicin [8], resistance to ethambutol was noted in 89.8% of MAC isolates and was more frequent in *M. avium* (94.3%) than in *M. intracellulare* (84.0%, $p < 0.001$). Resistance to rifampicin was noted in 57.4% of MAC isolates and was more frequent in *M. intracellulare* than in *M. avium* ($p < 0.001$). Applying the breakpoint of Brown-Elliott et al. [9], the majority of MAC isolates were susceptible or intermediate to amikacin. Resistance rates to amikacin were higher in *M. avium* compared to *M. intracellulare* ($p = 0.007$). For moxifloxacin and linezolid, about half of the MAC isolates (55.9% and 51.3%, respectively) were resistant and *M. intracellulare* was more resistant than *M. avium* ($p < 0.001$). Drug susceptibility distributions are detailed in Fig. 1. MIC distribution for all antimicrobial agents was significantly different between the two species. The MIC_{50} values of ciprofloxacin, clarithromycin, linezolid, moxifloxacin, and rifampicin were higher in *M. intracellulare* than in *M. avium*, contrary to the results of ethambutol with a higher MIC_{50} in *M. avium*.

Our group previously demonstrated that *M. intracellulare* infection had severe clinical features and poor treatment outcome resulting in poor prognosis relative to *M. avium* infection [3]. In the present study, which included 1883 MAC clinical isolates, *M. intracellulare* had generally lower susceptible rates and higher MIC_{50}/MIC_{90} values than *M. avium* except amikacin and ethambutol. These findings may explain the poor prognosis in *M. intracellulare* cases, although the correlation between clinical outcomes and DST results has not been demonstrated.

We found that most MAC isolates were susceptible to clarithromycin, as previously reported [10,11]. The two species showed similar resistance rates and the MIC_{50} was higher in *M. intracellulare* than in *M. avium*, which was opposite to previous studies that showed higher resistance rates in *M. avium* than in *M. intracellulare* [4,5,12,13].

The CLSI suggests the tentative breakpoints for moxifloxacin and linezolid, the secondary agents for macrolide-resistant MAC isolates or isolates from patients who cannot tolerate macrolide therapy [7]. We previously reported the clinical efficacy of a moxifloxacin-containing regimen for MAC lung disease, and the treatment success rate did not correlate with the *in vitro* MICs, albeit the study contained a small number of patients [14]. For linezolid, there are few studies that have addressed the clinical efficacy and drug susceptibility pattern. One study in Sweden reported that the percentage of moxifloxacin-resistant and linezolid-resistant MAC isolates was more or less 50%, consistent with our study [10]. In studies in China, however, the resistance rates to the two drugs were lower than those of ours, although the same DST method and breakpoints were used. Furthermore, in contrast to our findings, they reported that *M. avium* was more resistant to moxifloxacin and linezolid than *M. intracellulare* [5,13]. These findings suggest regional differences in drug susceptibility patterns of MAC isolates, not only the overall susceptibility but the susceptibility profile between *M. avium* and *M. intracellulare* as well.

The present study has several limitations. First, a clinical outcome cannot be derived from our results, since the correlation between the clinical outcomes of MAC infections and DST results other than for the macrolides has not been clearly demonstrated [1]. Second, patient treatment histories were unknown. Third, the reverse hybridization assay, which was used for the species identification in the present study, was unable to identify several new species that are closely related to *M. intracellulare*, such as *M. chimaera*. However, *M. chimaera* appears to be relatively rare in South Korea [15].

In conclusion, there are differences in drug susceptibility patterns between *M. avium* and *M. intracellulare*. Differences between this study and previous reports on the susceptibility profile for MAC

Table 1
Drug susceptibility profiles of *Mycobacterium avium* complex.

Antibiotics	No. of isolates (%)[a]							MIC_{50}/MIC_{90}		
	Susceptible		Intermediate		Resistant					
	M. avium	*M. intracellulare*	*M. avium*	*M. intracellulare*	*M. avium*	*M. intracellulare*	*p*-value	*M. avium*	*M. intracellulare*	*p*-value
Clarithromycin	1001 (94.4)	775 (94.2)	9 (0.8)	3 (0.4)	50 (4.7)	45 (5.5)	0.460	1/4	2/4	0.046
Ethambutol	9 (0.8)	14 (1.7)	51 (4.8)	118 (14.3)	1000 (94.3)	691 (84.0)	<0.001	32/>32	16/>32	<0.001
Rifampicin	19 (1.8)	5 (0.6)	535 (50.5)	244 (29.6)	506 (47.7)	574 (69.7)	<0.001	4/>16	8/>16	<0.001
Amikacin	558 (52.6)	475 (57.7)	392 (37.0)	292 (35.5)	110 (10.4)	56 (6.8)	0.007	16/64	16/32	0.017
Ciprofloxacin	69 (6.5)	8 (1.0)	125 (11.8)	11 (1.3)	866 (81.7)	804 (97.7)	<0.001	8/>16	>16/>16	<0.001
Moxifloxacin	240 (22.6)	45 (5.5)	293 (27.6)	251 (30.5)	527 (49.7)	527 (64.0)	<0.001	2/16	4/8	<0.001
Linezolid[b]	219 (24.7)	58 (8.5)	267 (30.2)	221 (32.3)	399 (45.1)	406 (59.3)	<0.001	16/64	32/64	<0.001

MIC, minimum inhibitory concentration.
[a] A total of 1060 *M. avium* and 823 *M. intracellulare* isolates were included.
[b] For linezolid, 885 *M. avium* and 685 *M. intracellulare* were studied.

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