

**Mycobacterium abscessus subsp. abscessus Lung Disease: Drug Susceptibility Testing in Sputum Culture Negative Conversion**

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**Abstract**

**Background:** Among Mycobacterium abscessus complex infections, patients with *M. abscessus* subsp. *abscessus* (MAA) lung disease are difficult to treat and no standard therapy has been established. Few reports have investigated the drug susceptibility of these strains. We retrospectively investigated how *in vitro* drug susceptibility testing (DST) of MAA affects the induction of sputum conversion using pharmacotherapy. **Methods:** Patients with MAA lung disease diagnosed and treated between 2010 and 2014 at our hospital were enrolled and divided into Group A (sputum conversion without relapse within 1 year) and Group B (persistent positive cultured or negative conversion with relapse). MAA was identified in *M. abscessus* using sequence with genotyping, and DST of MAA was performed. **Results:** We assessed 23 patients (9 males and 14 females). There were 8 patients in Group A and 15 in Group B. Higher prevalence of susceptible isolates for clarithromycin (CAM) susceptibility on day 14 was noted in Group A than in Group B (*P* = 0.03) and no significant difference observed in the two groups for other drugs. **Conclusions:** *In vitro* DST of MAA, especially CAM susceptibility on day 14, affected the results of negative conversion. No other drugs were found to affect sputum culture negative conversion.

**Keywords:** Drug susceptibility testing, erythromycin resistance methylase gene *erm* (41), inducible resistance, *Mycobacterium abscessus* subsp. *abscessus*, minimal inhibitory concentration

**Introduction**

The *Mycobacterium abscessus* complex (MabC) comprises a group of rapidly growing mycobacteria (RGM) that represent the most common etiological agents of lung disease.¹⁻³ MabC bacteria are resistant to many antibiotics *in vitro*,¹⁴⁻⁵ leading to unfavorable treatment results.⁶ Recently, it was reported that ⁷⁻⁹ the MabC is differentiated into three subspecies: *M. abscessus* subsp. *abscessus* (MAA), *M. abscessus* subsp. *massiliense* (MAM), and *M. abscessus* subsp. *bolletii*.⁹ In particular, MAA lung disease has poorer treatment outcomes than MAM because of macrolide resistance induced by *M. abscessus* erythromycin resistance methylase gene *erm* (41). When a T or C polymorphism occurs at position 28 of the gene, the mutation generates a loss of function of the *erm* (41) gene (C28 sequvar); isolates of the C28 sequvar are usually susceptible to macrolides. In addition to inducible macrolide resistance, acquired macrolide resistance can develop during antibiotic treatment due to mutations in the 23S rRNA gene (*rrl*).¹⁰

Current treatment recommendations are based on retrospective case series.¹¹ The treatment regimen for MabC lung disease usually involves an initial combination of macrolide therapy and parenteral agents for at least 2 weeks and up to several months, followed by oral macrolide-based therapy.

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Clarithromycin (CAM) susceptibility may influence the prognosis and severity of MabC lung disease.\textsuperscript{12-15} However, drug susceptibility testing (DST) of MAA isolates from patients is currently not well documented, but it may predict outcomes in patients with MAA lung disease.\textsuperscript{13,15}

This study aimed to evaluate the in vitro drug susceptibility of several antibiotics and to assess the influence of in vitro drug susceptibility of pathogens on MAA lung disease outcomes.

**Methods**

**Study design**

In this retrospective, single-institution study, files from all consecutive patients referred to National Hospital Organization Kinki Chuo Chest Medical Center, a 385-bed center in Southern Osaka that specializes in pulmonary disease, from January 1, 2010, to December 31, 2014 were reviewed. Patients with MabC lung disease were included if they met the American Thoracic Society (ATS) diagnostic criteria: presence of at least two positive sputum cultures or one bronchoalveolar lavage culture or one lung tissue biopsy specimen culture positive for MabC, along with pulmonary symptoms and chest computed tomography (CT) findings.\textsuperscript{16} In addition, patients were included if their isolates were available (in storage) and if they were followed up at least for 1 year until January 2015. This study was approved by the Ethics Committee of Kinki Chuo Chest Medical Center (No. 502, date of approval: July 25, 2015). Informed consent was waived because of the retrospective nature of the study.

**Data collection**

Information on patient history was obtained at admission or during an outpatient visit. Height and weight were measured. Data on comorbidities and the course of antituberculous mycobacteria (NTM) treatment were collected from the medical records. Patients were diagnosed with MAA of sputum isolates which were identified by \textit{hsp65}, \textit{rpoB}, and \textit{erm} (41).\textsuperscript{17} Patients received combination antibiotic therapy as recommended by the ATS and Infectious Diseases Society of America. In addition, patients were diagnosed with NTM coinfection if NTM species other than the MabC was isolated at least twice.

Disease progression was determined in the time interval between the time of making the diagnosis and the 1-year follow-up. After 12 months of treatment, sputum culture conversion or relapse was periodically assessed. Sputum culture negative conversion was defined as two consecutive negative cultures within 3 months after therapy for 12 months. If a patient could not expectorate sputum even after sputum induction, sputum conversion from positive to negative was considered to have occurred. Relapse was defined when there was at least one positive sputum culture during the study period and the positive sputum culture became negative. The enrolled patients were classified into three groups: Group A (favorable response), which comprised patients with MAA lung disease in the negative conversion group; Group B (unfavorable response), which comprised patients with persistently positive cultures or negative conversion with relapse; and Group C (no treatment intervention), which comprised patients with follow-up for at least 1 year without any antibiotics.

**Microbiological examination**

We performed DST in vitro before the treatment. The interpretative breakpoints used were those recommended by the Clinical and Laboratory Standards Institute (CLSI).\textsuperscript{18} The minimal inhibitory concentration (MIC) was defined as the lowest concentration of drug that inhibited visible growth. MICs in CAM were determined in cation-adjusted Mueller–Hinton medium using the broth microdilution method (pH 7.35–7.40). Plates were evaluated after 3 days and then incubated for 14 days to obtain a final reading to ensure the detection of inducible resistance. The MIC of CAM was determined on day 3 and day 14 after incubation; MAA isolates were considered susceptible (MIC ≤2 µg/mL on day 3 and day 14) or resistant (MIC ≥8 µg/mL on day 3). Susceptibilities to other antibiotics (kanamycin [KM], amikacin [AMK], linezolid [LZD], and imipenem [IPM]) were also evaluated according to previous reports.\textsuperscript{14,19} The breakpoint of sitafloxacin hydrate (STFX) was complained with it of moxifloxacin and ciprofloxacin for RGM in CLSI.\textsuperscript{10}

**Genetic analyses**

To extract DNA, a loopful of colonies of each strain was used; and the extracted DNA was suspended in 300 ml 16 Tris-ethylenediaminetetraacetic acid buffer and boiled for 10 min. The polymerase chain reaction (PCR) cycling conditions were as follows: initial denaturation at 95°C for 2 min; 35 cycles of denaturation at 95°C for 1 min, annealing at 62°C for 1 min, and extension at 72°C for 1.5 min, and a final extension at 72°C for 10 min. Genetic analyses, such as the presence of \textit{erm} (41) or 23S rRNA gene (\textit{rrl}) mutations, were performed by PCR sequencing as previously described.\textsuperscript{17,20,21}

**Statistical analysis**

Categorical variables were analyzed using the Chi-square or Fisher’s exact test. Continuous variables were analyzed using the Mann–Whitney U-test or t-test. All \textit{P} values are two-sided. \textit{P} < 0.05 indicates statistical significance. Statistical analyses were performed using the JMP statistical software (12\textsuperscript{th} version, SAS Institute Inc., Cary, NC, USA). Proportions and medians were used to describe demographic, clinical, and radiographic characteristics.

**Results**

**Clinical information of patients**

Among 79 patients with at least one respiratory sputum culture containing an MabC isolate, 38 had the MAA isolate, and in 3 patients, the isolate could not be confirmed.
because their isolate cultures did not develop. None were identified as having *M. abscessus* subsp. *bolletii* or MAA/ MAM mixed lung disease. Of the 38 patients with at least one respiratory sputum culture of the MAA isolate, there were 30 with MAA lung disease who met ATS diagnostic criteria[16] [Figure 1].

The characteristics of the 30 patients with MAA lung disease are summarized in Table 1. Their median age was 75 (range, 52–87) years; there were 11 (36.7%) males and 19 (63.3%) females. Cavitary findings were observed in the chest CT findings in 12 patients (40%). There were 5 patients (16.7%) with prior pulmonary tuberculosis and 13 (43.3%) with infections by other NTM species. Treatment for MAA lung disease was administered for at least 1 year in 23 patients (76.6%) [Tables 2 and 3]. Negative conversion occurred in 8 patients (34.8%) (8 patients in Group A [negative conversion group]; 15 in Group B [persistently positive cultures: 12, negative conversion with relapse: 3]; 7 in Group C [follow-up without any antibiotics for at least 1 year]).

Susceptibilities to each drug (CAM day 3, CAM day 14, KM, AMK, STFX, LZD, and IPM) were 87.5, 37.5, 100.0, 100.0, 62.5, 50.0, and 50.0, respectively, in Group A and 73.3, 0.0, 93.3, 86.7, 60.0, 33.3, and 26.7, respectively, in Group B. MAA isolates from the 8 patients in Group A more frequently exhibited susceptibility to CAM on day 14 than patients in Group B (Group A: 3 patients [37.5%] vs. Group B: 0 patients [0.0%], *P* = 0.03) [Table 3]. Two isolates of the C28 sequevar for *erm* (41) and one isolate of the T28 sequevar in Group A exhibited CAM susceptibility on day 14. In contrast, two isolates of the *rrl* gene were observed only in Group B. There was not significantly relationship between susceptibility to other antibiotics (KM, AMK, STFX, LZD, and IPM) and biological outcomes [Table 3].

One of the seven patients had the isolate of the C28 sequevar, and no patient in Group C had the isolate with *rrl* mutation [Table 3].

### Discussion

This study demonstrated two important findings. First, *in vitro* DST of MAA isolates greatly affects negative conversion in patients with MAA lung disease. Our findings indicated that CAM susceptibility on day 14 is of particular importance. No clear relationships were shown indicating whether the other drugs affected negative conversion. Second, patients with MAA lung disease having the C28 sequevar in their isolate tended to exhibit negative conversion.

MAA is known to have poorer treatment outcome because of drug resistance to many antibiotics even among other types of nontuberculous mycobacteria. Susceptibility to CAM, AMK, and IPM is usually maintained.[22] It has been proposed that rather than *in vitro* DST with a standard culture period of 3 days, CAM should be cultured for 14 days because of inducible resistance due to the *erm* (41) gene.[23] The guidelines[16] recommend selecting the treatment regimen based on *in vitro* DST of MAA. Our investigation of the

### Table 1: Characteristics of patients with *M. abscessus* subsp. *abscessus* lung disease

| Total (n=30) |
|-------------|
| Age, years  | 75 (52-87) |
| Male, n (%) | 11 (36.7) |
| Body mass index (kg/m²) | 18.9 (14.1-24.7) |
| Smoking habits |
| Never smoker, n (%) | 15 (50.0) |
| Current smoker, n (%) | 3 (10.0) |
| Ex-smoker, n (%) | 7 (23.3) |
| Unknown, n (%) | 5 (16.7) |
| Initial symptoms |
| Dyspnea on exertion, n (%) | 7 (23.3) |
| Hemoptysis, n (%) | 11 (36.7) |
| Sputum, n (%) | 11 (36.7) |
| Cough, n (%) | 11 (36.7) |
| Fever, n (%) | 7 (23.3) |
| Comorbidities |
| Prior pulmonary tuberculosis, n (%) | 5 (16.7) |
| Aspergillosis, n (%) | 1 (3.3) |
| Interstitial pneumonitis, n (%) | 1 (3.3) |
| DM, n (%) | 0 (0.0) |
| RA, n (%) | 1 (3.3) |
| Lung cancer, n (%) | 2 (6.7) |
| COPD, n (%) | 4 (13.3) |
| BA, n (%) | 1 (3.3) |
| Other NTM lung disease |
| MAC lung disease | 12 (40.0) |
| *M. kansasii* lung disease | 1 (3.3) |
| Cavitary lesion on chest CT | 12 (40.0) |
| Initial chemotherapy | 23 (76.7) |
| Parenteral agents with oral agents | 15 (50.0) |
| Oral agents | 8 (26.7) |

**Figure 1:** Study flowchart

**Table 1:** Characteristics of patients with *M. abscessus* subsp. *abscessus* lung disease

**Table 2:** Characteristics of patients with MAA lung disease

**Table 3:** Characteristics of patients with MAA lung disease

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**Figure 1:** Study flowchart
not cause rapid progression and that treatment intervention might be unnecessary. Current recommendations for MAA lung disease treatment are based on case series studies with no comparison cases or on individual experience. Moreover, an inappropriate regimen can induce CAM resistance. Many patients with MAA lung disease have a history of receiving chemotherapy including CAM for MAC lung disease. Having already underwent treatment for MAC lung disease, which is a common comorbidity, may affect the results of DST of MAA lung disease and ultimately affect negative conversion in patients MAA lung disease. The importance of CAM susceptibility is similar in patients with M. avium complex lung disease, indicating that CAM susceptibility is related to the treatment response rate. No effective treatment regimen has been established for CAM-resistant MAC lung disease, and the prognosis is poor. Moreover, an inappropriate regimen can induce CAM resistance. Many patients with MAA lung disease have a history of receiving chemotherapy including CAM for MAC lung disease. Having already underwent treatment for MAC lung disease, which is a common comorbidity, may affect the results of DST of MAA lung disease and ultimately affect negative conversion in patients MAA lung disease. The limitations of this study were the fact that it was a single-institution study with a small sample size; further, it was a retrospective cohort study. The treatment regimens were decided by physicians. Oral agents (CAM, EB, RFP, and STFX) as the initial treatment were received because some patients refused the admission. In terms of sputum conversion, we could not divide our analysis according to cases of reinfection and continued infection. Although parenteral agents such as AMK and IPM are considered necessary for CAM-resistant MAC lung disease, current recommended regimens are limited by factors such as toxicity. In the present study, LZD and KM were rarely used to treat MAA lung disease because of the moderate-to-severe side effects in Japan. In the future, multicenter prospective studies with a unified regimen need to be conducted to investigate this research topic further.

Conclusions

In vitro DST of MAA isolates greatly affects sputum conversion. This study revealed that CAM susceptibility on
### Table 3: Mycobacterium abscessus subsp. abscessus lung disease

|                      | Group A (favorable response) | Group B (unfavorable response) | Group C (follow-up without treatment) | Group A versus Group B (P) |
|----------------------|------------------------------|-------------------------------|---------------------------------------|----------------------------|
| n (%)                | 8                            | 15                            | 12                                    | 3                         | 7                        | 0.65                     |
| Age (years)          | 73 (52-82)                   | 75 (62-85)                    | 76 (62-85)                            | 66 (64-68)                | 78 (68-91)               | 0.4                      |
| Male, n (%)          | 2 (25.0)                     | 7 (46.7)                      | 6 (50.0)                              | 1 (33.3)                  | 2 (28.6)                 | 0.08                     |
| BMI (kg/m²)          | 17.1 (14.1-21.2)             | 19.4 (16.4-22.7)              | 19.6 (16.9-22.7)                      | 17.8 (16.4-20.1)          | 19.5 (14.2-24.7)         | 0.08                     |
| Smoking habits, n (%)|                              |                               |                                       |                           |                          |                          |
| Never smoker         | 4 (50.0) s                   | 7 (46.7)                      | 6 (50.0)                              | 1 (33.3)                  | 4 (57.1)                 | 0.61                     |
| Current smoker       | 1 (12.5)                     | 1 (6.7)                       | 1 (8.3)                               | 0                         | 1 (14.3)                 |                          |
| Ex-smoker            | 2 (25.0)                     | 3 (20.0)                      | 2 (16.7)                              | 1 (33.3)                  | 2 (28.6)                 |                          |
| Unknown              | 1 (12.5)                     | 4 (26.7)                      | 3 (25.0)                              | 1 (33.3)                  | 0                        |                          |
| Comorbidity, n (%)   |                              |                               |                                       |                           |                          |                          |
| Prior pulmonary tuberculosis | 1 (12.5) | 2 (13.3)              | 2 (16.7)                              | 0                         | 2 (28.6)                 | 1.0                      |
| Aspergillosis        | 0                            | 1 (6.7)                       | 1 (8.3)                               | 0                         | 0                        | 1.0                      |
| Interstitial pneumonitis | 0                  | 0                              | 0                                     | 0                         | 0                        | 1.0                      |
| DM                   | 0                            | 0                              | 0                                     | 0                         | 0                        | 1.0                      |
| RA                   | 1 (12.5)                     | 0                              | 0                                     | 1 (14.3)                  | 0.35                     |
| Lung cancer          | 0                            | 0                              | 0                                     | 2 (28.6)                  | 1.0                      |
| COPD                 | 2 (25.0)                     | 1 (6.7)                       | 1 (8.3)                               | 0                         | 1 (14.3)                 | 0.27                     |
| BA                   | 1 (12.5)                     | 0                              | 0                                     | 0                         | 0                        | 0.35                     |
| Other NTM species    |                              |                               |                                       |                           |                          |                          |
| MAC                  | 4 (50.0)                     | 6 (40.0)                      | 4 (33.3)                              | 2 (66.7)                  | 2 (28.6)                 | 0.49                     |
| Mycobacterium kansasii | 0                | 1 (6.7)                       | 1 (8.3)                               | 0                         | 0                        | 0.65                     |
| NB/FC pattern, n (%) |                              |                               |                                       |                           |                          |                          |
| NB pattern           | 2 (25.0)                     | 8 (53.3)                      | 7 (58.3)                              | 1 (33.3)                  | 1 (14.3)                 | 0.38                     |
| FC pattern           | 6 (75.0)                     | 7 (46.7)                      | 5 (41.7)                              | 2 (66.7)                  | 6 (85.7)                 |                          |
| Cavitary lesion on chest CT | 3 (37.5) | 7 (46.7)                      | 5 (41.7)                              | 2 (66.7)                  | 2 (28.6)                 | 0.51                     |
| Initial chemotherapy |                              |                               |                                       |                           |                          |                          |
| Parenteral agents with oral agents | 5 (62.5) | 10 (66.7) | 8 (66.7) | 2 (66.7) | 0 | 1.0 |
| Oral agents          | 3 (37.5)                     | 5 (33.3)                      | 4 (33.3)                              | 1 (33.3)                  | 0                        |                          |
| Serum albumin (g/dL) | 3.6 (2.6-4.2)                | 3.8 (3.2-4.6)                 | 3.9 (3.2-4.6)                         | 3.6 (3.6-4.2)             | 3.3 (3.1-3.9)            | 0.35                     |
| C28 sequevar in the isolate | 2 (25.0) | 0 | 0 | 0 | 1 (14.3) | 0.11 |
| rrl mutation         | 0                            | 2 (13.3)                      | 2 (16.7)                              | 0                         | 0                        | 0.11                     |
| CAM susceptibility   |                               |                               |                                       |                           |                          |                          |
| Day 3                |                               |                               |                                       |                           |                          |                          |
| S                    | 7 (87.5)                     | 11 (73.3)                     | 9 (75.0)                              | 2 (66.7)                  | 6 (85.7)                 | 0.62                     |
| I                    | 0                            | 2 (13.3)                      | 2 (16.7)                              | 0                         | 0                        |                          |
| R                    | 1 (12.5)                     | 2 (13.3)                      | 1 (8.3)                               | 1 (33.3)                  | 1 (14.3)                 |                          |
| Day 14               |                               |                               |                                       |                           |                          |                          |
| S                    | 3 (37.5)                     | 0                              | 0                                     | 0                         | 1 (14.3)                 | 0.03                     |
| I                    | 0                            | 0                              | 0                                     | 0                         | 1 (14.3)                 |                          |
| R                    | 5 (62.5)                     | 15 (100.0)                    | 12 (100.0)                            | 3 (100.0)                 | 5 (71.4)                 |                          |
| KM susceptibility    |                               |                               |                                       |                           |                          |                          |
| S                    | 8 (100.0)                    | 14 (93.3)                     | 11 (91.7)                             | 3 (100.0)                 | 7 (100.0)                | 0.65                     |
| I                    | 0                            | 1 (6.7)                       | 1 (8.3)                               | 0                         | 0                        |                          |
| R                    | 0                            | 0                              | 0                                     | 0                         | 0                        |                          |
| AMK susceptibility   |                               |                               |                                       |                           |                          |                          |
| S                    | 8 (100.0)                    | 13 (86.7)                     | 10 (91.7)                             | 3 (100.0)                 | 7 (100.0)                | 0.53                     |
| I                    | 0                            | 1 (6.7)                       | 1 (8.3)                               | 0                         | 0                        |                          |
| R                    | 0                            | 0                              | 0                                     | 0                         | 0                        |                          |

Contd...
Table 3: Contd...

|                      | Group A (favorable response) | Group B (unfavorable response) | Group C | Group A versus Group B (P) |
|----------------------|------------------------------|--------------------------------|---------|---------------------------|
|                      | Persistently positive | Negative conversion with relapse |         |                           |
| STFX susceptibility   |                              |                                |         |                           |
| S                    | 5 (62.5)                    | 9 (60.0)                       | 7 (58.3) | 2 (66.7)                  | 6 (85.7) | 1.0|
| I                    | 3 (37.5)                    | 4 (26.7)                       | 3 (8.3)  | 1 (33.3)                  | 0        |    |
| R                    | 0                            | 2 (13.3)                       | 2 (16.7) | 0                         | 1 (14.3) |    |
| LZD susceptibility    |                              |                                |         |                           |
| S                    | 4 (50.0)                    | 5 (33.3)                       | 3 (25.0) | 2 (66.7)                  | 4 (57.1) | 0.37|
| I                    | 3 (37.5)                    | 7 (46.7)                       | 6 (50.0) | 1 (33.3)                  | 3 (42.9) |    |
| R                    | 1 (12.5)                    | 3 (20.0)                       | 3 (25.0) | 0                         | 0        |    |
| IPM susceptibility    |                              |                                |         |                           |
| S                    | 4 (50.0)                    | 4 (26.7)                       | 4 (33.3) | 0                         | 2 (28.6) | 0.25|
| I                    | 4 (50.0)                    | 6 (40.0)                       | 4 (33.3) | 2 (66.7)                  | 2 (28.6) |    |
| R                    | 0                            | 5 (33.3)                       | 4 (33.3) | 1 (33.3)                  | 3 (42.9) |    |
| Radiological outcomes |                              |                                |         |                           |
| Deterioration        | 2 (25.0)                    | 10 (66.7)                      | 8 (66.7) | 2 (66.7)                  | 0        | 0.08|
| No deterioration     | 6 (75.0)                    | 5 (33.3)                       | 4 (33.3) | 1 (33.3)                  | 7 (100.0)|    |

MAC: Mycobacterium avium complex, DM: Diabetes mellitus, RA: Rheumatoid arthritis, COPD: Chronic obstructive pulmonary disease, BA: Bronchial asthma, CT: Computed tomography, CAM: Clarithromycin, KM: Kanamycin, AMK: Amikacin, STFX: Sitafloxacin hydrate, LZD: Linezolid, IPM: Imipenem, S: Susceptible, I: Intermediate, R: Resistant, NB: Nodular bronchiectasis, FC: Fibrocavitary, BMI: Body mass index, NTM: Nontuberculous mycobacteria

day 14 in MAA isolates is of particular importance. There was no association between susceptibility to other drugs (KM, IPM, AMK, and STFX) and biological outcomes.

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Conflicts of interest
There are no conflicts of interest.

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