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MAJOR ARTICLE

Impact of Susceptibility to Injectable Antibiotics on the Treatment Outcomes of *Mycobacterium abscessus* Pulmonary Disease

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Background. Current guidelines recommend a susceptibility-based regimen for *Mycobacterium abscessus* subspecies *abscessus* pulmonary disease (MAB-PD), but the evidence is weak. We aimed to investigate the association between treatment outcomes and in vitro drug susceptibility to injectable antibiotics in MAB-PD patients.

Methods. We enrolled MAB-PD patients treated with intravenous amikacin and beta-lactams for ≥4 weeks at 4 referral hospitals in Seoul, South Korea. Culture conversion and microbiological cure at 1 year were evaluated based on susceptibility to injectable antibiotics among patients treated with those antibiotics for ≥2 weeks.

Results. A total of 82 patients were analyzed. The mean age was 58.7 years, and 65.9% were women. Sputum culture conversion and microbiological cure were achieved in 52.4% and 41.5% of patients, respectively. Amikacin was the most common agent to which the *M. abscessus* subspecies *abscessus* isolates were susceptible (81.7%); 9.8% and 24.0% of the isolates were resistant to cefoxitin and imipenem, respectively. The clarithromycin-inducible resistance (IR) group (n = 65) had a lower microbiological cure rate than the clarithromycin-susceptible group (35.4% vs 64.7%). The treatment outcomes appeared to be similar regardless of in vitro susceptibility results with regard to intravenous amikacin, cefoxitin, imipenem, and moxifloxacin. In the subgroup analysis of the clarithromycin-IR group, the treatment outcomes did not differ according to antibiotic susceptibility.

Conclusions. We did not find evidence supporting the use of susceptibility-based treatment with intravenous amikacin and beta-lactams in patients with MAB-PD. Further research is required.

Keywords. amikacin; beta-lactams; microbial sensitivity tests; *Mycobacterium abscessus*; nontuberculous mycobacteria; treatment outcome.

The incidence of nontuberculous mycobacterial pulmonary disease has increased worldwide in recent decades [1, 2]. The *Mycobacterium abscessus* complex is one of the most important causative organisms of nontuberculous mycobacterial pulmonary disease and comprises 3 distinct subspecies: *M. abscessus* subspecies *abscessus*, *M. abscessus* subspecies *bolletii*, and *M. abscessus* subspecies *massiliense* [3].

Treatment for *M. abscessus* subspecies *abscessus* pulmonary disease (MAB-PD) is challenging because of the frequency of intrinsic resistance to common antibiotics. According to a recent meta-analysis, the treatment success rate in patients with MAB-PD was only 30%–40% [4, 5]. Macrolide resistance due to either mutational or inducible resistance (IR) related to the presence of a functional *erm*(41) gene in *M. abscessus* subspecies *abscessus* is associated with worse treatment outcomes in patients with MAB-PD [3, 6].

For the treatment of MAB-PD, recent guidelines have suggested a multidrug regimen, including at least 3 or 4 active drugs guided by in vitro drug susceptibility results [7, 8]. Especially in the initial phase, the administration of 2 or 3 intravenous antibiotics for at least 1 month is recommended [7, 8]. However, the drug susceptibility test (DST) of *M. abscessus* subspecies *abscessus* is difficult and controversial. Macrolides are the only oral agents that show a correlation between in vitro susceptibility and treatment response in patients with MAB-PD. For other antimicrobial agents, there is no established correlation between susceptibility and the clinical response [9, 10]. Therefore, we aimed to investigate the impact of in vitro testing of susceptibility to intravenous antibiotics on treatment outcomes in patients with MAB-PD.

Received 8 February 2021; editorial decision 20 April 2021; accepted 22 April 2021.

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Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofab215

METHODS

Study Design and Population

This was a multicenter retrospective cohort study. We integrated the medical records of patients with MAB-PD from the 4 tertiary referral centers in Seoul, South Korea (Asan Medical Centre [AMC], Samsung Medical Centre [SMC], Seoul National University Hospital [SNUH], and Severance Hospital). The study population met the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) diagnostic criteria [11].

Previously published data from the 2 referral centers were obtained first: Clinical data of patients diagnosed between January 2002 and December 2012 were obtained from a prospective, observational cohort at the SMC [12], and the data of patients diagnosed between January 2006 and June 2015 were obtained from a retrospective cohort study at the SNUH [13]. Additional cohort data from the other 2 referral centers were retrospectively reviewed: Data of patients diagnosed between March 2012 and December 2018 at Severance Hospital were collected, and data of patients diagnosed between July 2012 and December 2019 at AMC were collected.

Patients with MAB-PD treated with intravenous amikacin and beta-lactams for ≥4 weeks were included. We excluded the following patients: those with clarithromycin-resistant *M. abscessus* subspecies *abscessus* isolates, those treated with amikacin nebulizers, those who had no DST results for intravenous antibiotics, and those with insufficient data. According to the previously defined categories, radiographic abnormalities were measured based on chest computed tomography at initial diagnosis [12]. A positive result on the acid-fast bacilli (AFB) smear or the presence of cavitary lung lesions was considered to indicate extensive disease.

The primary outcome measures were culture conversion and microbiological cure according to susceptibility to injectable antibiotics in patients with MAB-PD. Secondary outcome measures were treatment outcomes according to antibiotic susceptibility in subgroups based on disease severity, macrolide susceptibility, and treatment duration.

Microbiological Examination

According to the standard guidelines, we performed AFB smears and mycobacterial cultures of respiratory specimens [7, 14]. Sputum or bronchoscopy samples were cultured in solid medium (Ogawa medium; Korean Institute of Tuberculosis, Cheongju, South Korea) and liquid medium (BACTEC 960 Mycobacterial Growth Indicator Tube; Becton Dickinson, Sparks, MD, USA). The species of NTM isolates were identified by polymerase chain reaction and restriction fragment length polymorphism methods based on the *rpoB* gene or sequencing of the *rpoB* and *tuf* genes [15, 16]. Species differentiation between *M. abscessus* subspecies *abscessus* and *M. massiliense* subspecies *massiliense* was performed based on the *erm*(41) gene detected by polymerase chain reaction [17] or multilocus sequencing analysis of the *rrs*, *hsp65*, and *rpoB* genes [18].

Three centers (SMC, SNUH, and Severance) sent samples to the Korean Institute of Tuberculosis, a supranational reference laboratory, for antibiotic susceptibility testing. AMC sent samples to the same laboratory between December 1, 2015, and January 4, 2019; otherwise, the in-house laboratory performed the DSTs using the Sensititre RAPMYCO or RAPMYCOI plate (Thermo Fisher Scientific, Waltham, MA, USA). The broth microdilution method was used for all tests, and the cutoff points for antibiotic susceptibility were those set by the Clinical and Laboratory Standards Institute guidelines [19, 20].

The first reported minimal inhibitory concentration (MIC) for *M. abscessus* subspecies *abscessus* strains was used in this study. The MIC of clarithromycin was measured on days 3 and 14 after incubation. *M. abscessus* subspecies *abscessus* isolates were regarded as macrolide susceptible if the clarithromycin MIC was ≤2 μg/mL on days 3 and 14 or as macrolide resistant if the clarithromycin MIC was ≥8 μg/mL on day 3. If the isolates were susceptible on day 3 but resistant on day 14 of incubation, we considered them clarithromycin-IR. Genetic analysis was conducted for *M. abscessus* subspecies *abscessus* strains of the SMC, and those with the presence of the C28 sequevar in the *erm*(41) gene were regarded as clarithromycin susceptible [12, 21]. We conducted subgroup analyses with the clarithromycin-IR group because macrolide susceptibility affects treatment outcomes [21–23]. Follow-up DST results were compared with the initial test result when available.

Treatment Modalities and Outcomes

Treatment modalities varied among the centers. All patients at SMC were hospitalized and received treatment with a 4-week fixed course of amikacin and cefoxitin with oral macrolide, fluoroquinolone, and doxycycline [12]. After discharge, patients maintained an oral regimen for at least 12 months after sputum culture conversion. In the other 3 centers, the treatment duration of intravenous antibiotics was determined by the attending physician. Combination therapy with oral macrolide and at least 2 intravenous amikacin and beta-lactam antibiotics was prescribed for 3 or 4 weeks during the initial hospitalization. After discharge, a macrolide-based regimen with optional outpatient-based intravenous amikacin 3–5 times a week was maintained. The total duration of intravenous antibiotic administration was decided by the attending physicians at each center based on the occurrence of clinico-radiological improvement or drug-related adverse events.

We used the NTM-NET consensus statement to define the treatment outcomes in this study [24]. Culture conversion was defined as 3 consecutive negative cultures from respiratory samples during treatment. Microbiological cure was defined as the absence of positive cultures of NTM

after achieving culture conversion and maintaining that for 1 year after treatment initiation. In addition, radiographic responses were evaluated at 1 year after treatment. We analyzed patients who received the antibiotics of interest for ≥2 weeks to investigate the association between antibiotic susceptibility and treatment outcomes.

Statistical Analysis

Continuous variables were compared using the Student *t* test or the Mann-Whitney *U* test; categorical variables were analyzed using the Pearson χ^2 test or Fisher exact test. All statistical analyses were performed with R software, version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed *P* value <.05 was considered statistically significant for all analyses.

Patient Consent Statement

The institutional review board of each center, including Severance Hospital (4-2020-0952), approved the study protocol. The need for patient consent was waived because the study was based on a retrospective analysis and previously published data.

RESULTS

Baseline Characteristics and Overall Treatment Outcomes

A total of 127 patients (AMC, 39; SMC, 67; SNUH, 9; Severance, 12) were initially enrolled from the 4 referral centers; eligibility screening identified 82 patients (AMC, 37; SMC, 35; SNUH, 6; Severance, 4) (Figure 1). The mean age was 58.7 years, and 65.9% were women (Table 1). There were 65 participants with MAB-PD who were infected with clarithromycin-IR strains.

Table 2 shows the treatment regimens and outcomes in the study population. The median treatment duration was 15.4 months, and the treatment durations and modalities were similar between the clarithromycin-IR and clarithromycin-susceptible groups. All participants were treated with intravenous amikacin and beta-lactams for ≥4 weeks combined with an oral macrolide. Among them, approximately one-third of participants took oral clofazimine or moxifloxacin. Radiologic improvements were observed in 42.7% of patients, and sputum culture conversion and microbiological cure were achieved in 52.4% and 41.5%, respectively. The presence of clarithromycin-IR was related to a lower microbiological cure rate with marginal statistical significance (35.4% vs 64.7%; *P* = .056).

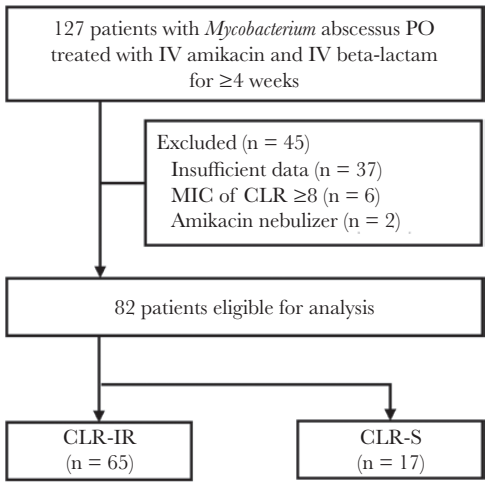

Figure 1. Study population. Abbreviations: CLR, clarithromycin; CLR-IR, clarithromycin inducible resistance; CLR-S, clarithromycin susceptible; MIC, minimal inhibitory concentration; PD, pulmonary disease.

Antibiotic Susceptibility and Treatment Outcomes

Supplementary Table 1 presents the antibiotic susceptibility profile of the entire population. Amikacin was the most common agent to which the isolates were susceptible (81.7%), followed by linezolid (60.7%). In total, 9.8% and 24.0% of the isolates were resistant to cefoxitin and imipenem, respectively.

Figure 2 and Table 3 show the antibiotic susceptibility and treatment outcomes in patients treated with the agents of interest for at least 2 weeks. The overall sputum culture conversion rate and microbiological cure rate were similar regardless of the susceptibility to injectable antibiotics.

We performed subgroup analyses based on disease severity, treatment duration, and clarithromycin susceptibility. In patients with cavitary lesions and patients with positive smears and cavitary lesions, antibiotic susceptibility to amikacin seemed to be related to the treatment outcomes, but this finding should be interpreted with caution as the number of isolates in the resistant group was small (Supplementary Table 2). Among patients treated for ≥1 year, the microbiological cure rate was related to the cefoxitin susceptibility pattern (*P* = .025) (Supplementary Table 3). The microbiological cure rate was also different based on cefoxitin susceptibility in patients with positive smear results (*P* = .021).

When we analyzed 65 patients with clarithromycin-IR strains, treatment outcomes were similar regardless of whether the strains were susceptible to amikacin, cefoxitin, imipenem, or moxifloxacin (Table 4). In patients with cavitary lesions, amikacin susceptibility seemed to be related to the treatment outcomes, but the amikacin-resistant group was small.

There were 43 patients with a median follow-up DST of 19.6 months. We compared the results of amikacin susceptibility from the 2 DSTs to assess resistance emergence (Supplementary Table 4). There were 13 patients with an increased MIC and 15 patients with a decreased MIC for amikacin; the culture conversion rates were similar between the 2 groups (*P* = .699). Among the 34 patients with amikacin-susceptible isolates on the initial test, 4 showed intermediate susceptibility and 2 showed resistance to amikacin on the follow-up test. The intermediate and resistant groups on the initial test also showed a similar

Table 1. Baseline Characteristics

	Total (n = 82)	CLR-S (n = 17)	CLR-IR (n = 65)	*P* Value
Age, y	58.7 ± 11.4	60.5 ± 13.8	58.2 ± 10.8	.452
Sex, female	54 (65.9)	12 (70.6)	42 (64.6)	.861
BMI, kg/m^2	20.4 ± 2.8	21.3 ± 1.6	20.2 ± 3.0	.038
BMI <18.5 kg/m^2	22 (26.8)	1 (5.9)	21 (32.3)	.060
Smoking, current or past	18 (22.0)	4 (23.5)	14 (21.5)	>.999
History of tuberculosis	39 (47.6)	6 (35.3)	33 (50.8)	.387
History of NTM treatment	9 (11.0)	1 (5.9)	8 (12.3)	.750
Comorbidities				
Bronchiectasis	73 (89.0)	16 (94.1)	57 (87.7)	.750
COPD	5 (6.1)	3 (17.6)	2 (3.1)	.096
Diabetes mellitus	9 (11.0)	1 (5.9)	8 (12.3)	.750
Chronic kidney disease	2 (2.4)	2 (11.8)	0 (0.0)	.055
Radiological type				.446
Fibrocavitary	14 (17.1)	1 (5.9)	13 (20.0)	
Cavitary NB	20 (24.4)	6 (35.3)	14 (21.5)	
Noncavitary NB	44 (53.7)	9 (52.9)	35 (53.8)	
Unclassifiable	4 (4.9)	1 (5.9)	3 (4.6)	
Smear, positive	65 (79.3)	13 (76.5)	52 (80.0)	>.999
Presence of cavity	35 (42.7)	7 (41.2)	28 (43.1)	>.999
Follow-up after treatment, median (IQR), mo	13.7 (3.0–36.0)	8.4 (3.3–34.1)	15.9 (2.8–41.9)	.499

Data are presented as No. (%) or mean ± SD, unless otherwise indicated.

Abbreviations: BMI, body mass index; CLR-IR, clarithromycin inducible resistant; CLR-S, clarithromycin susceptible; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NB, nodular bronchiectatic; NTM, nontuberculous mycobacteria.

pattern on the follow-up test. The culture conversion rates according to the initial and follow-up DST results were similar (Supplementary Table 5).

Adverse Drug Events

Adverse drug events related to intravenous antibiotics are presented in Table 5. Among 82 participants, 41 patients (50%)

Table 2. Treatment Regimen and Outcomes

	Total (n = 82)	CLR-S (n = 17)	CLR-IR (n = 65)	*P* Value
Treatment duration, mo	15.4 (9.5–24.5)	14.7 (7.5–24.1)	15.7 (10.6–24.8)	.430
IV amikacin duration, wk	8.9 (4.0–27.1)	14.7 (4.0–27.1)	7.3 (4.0–27.1)	.638
IV beta-lactam duration, wk	5.3 (4.0–9.4)	5.4 (4.0–10.4)	5.1 (4.0–9.4)	>.999
IV beta-lactam, type	82 (100.0)	17 (100.0)	65 (100.0)	.109
Cefoxitin	33 (40.2)	9 (52.9)	24 (36.9)	
Cefoxitin to imipenem	37 (45.1)	6 (35.3)	31 (47.7)	
Imipenem	11 (13.4)	1 (5.9)	10 (15.4)	
Imipenem to cefoxitin	1 (1.2)	1 (5.9)	0 (0.0)	
Macrolide	82 (100.0)	17 (100.0)	65 (100.0)	.336
AZT	50 (61.0)	10 (58.8)	40 (61.5)	
AZT to CLR	11 (13.4)	4 (23.5)	7 (10.8)	
CLR	21 (25.6)	3 (17.6)	18 (27.7)	
CLR to AZT	0 (0.0)	0 (0.0)	0 (0.0)	
Other drugs				
Clofazimine	23 (28.0)	2 (11.8)	21 (32.3)	.169
Moxifloxacin	26 (31.7)	5 (29.4)	21 (32.3)	>.999
Linezolid	4 (4.9)	0 (0.0)	4 (6.2)	.677
Surgical resection within 1 y	6 (7.3)	0 (0.0)	6 (9.2)	.436
Radiographic response				
Improved	35 (42.7)	8 (47.1)	27 (41.5)	.776
Unchanged	31(37.8)	7 (7.0)	24 (36.9)	
Worsened	16 (19.5)	2 (11.8)	14 (21.5)	
Culture conversion	43 (52.4)	12 (70.6)	31 (47.7)	.158
Microbiological cure	34 (41.5)	11 (64.7)	23 (35.4)	.056

Data are presented as No. (%) or median (interquartile range).

Abbreviations: AZT, azithromycin; CLR, clarithromycin; CLR-IR, clarithromycin inducible resistant; CLR-S, clarithromycin susceptible.

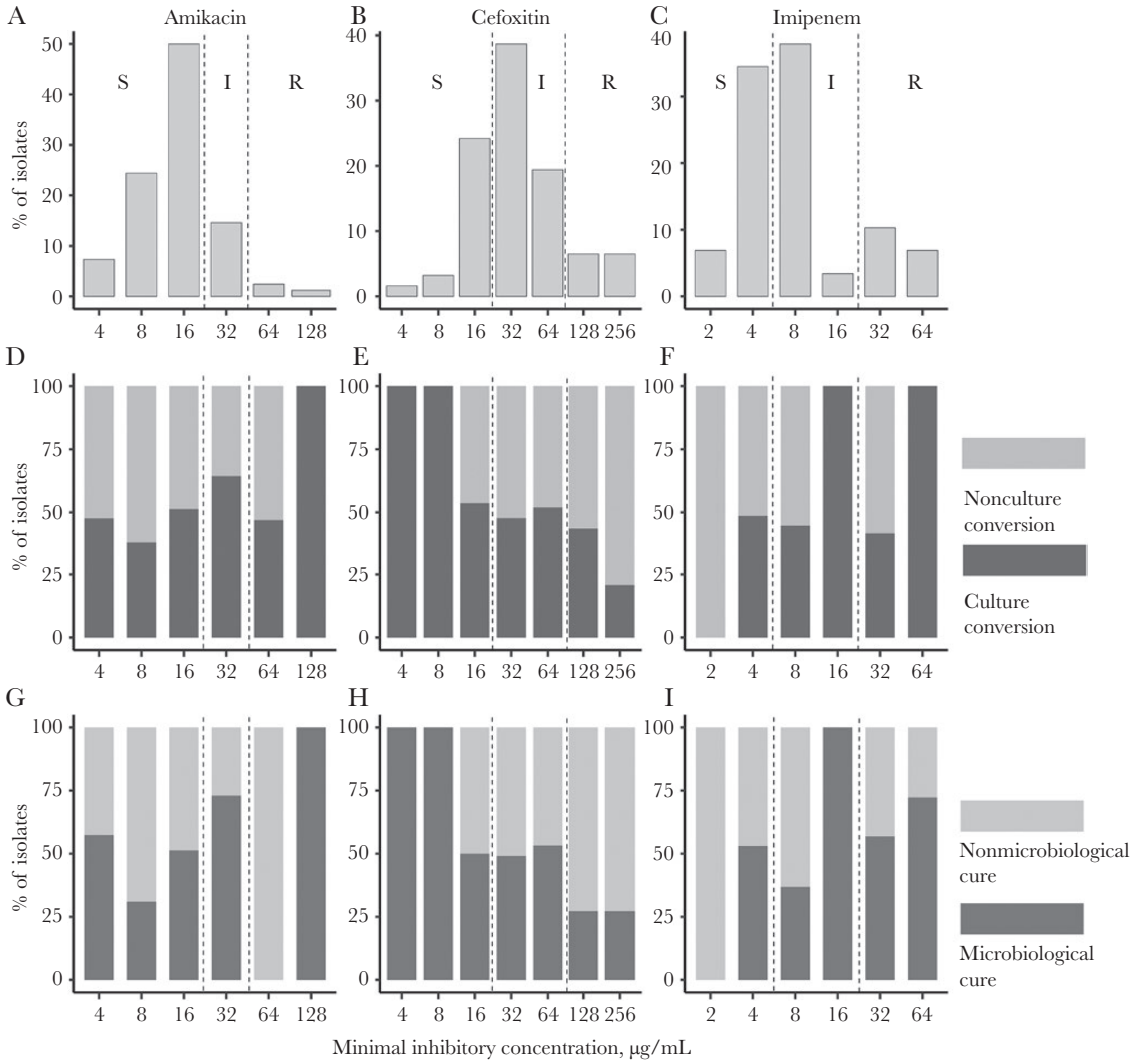

Figure 2. Antibiotic susceptibility profile and treatment outcomes in patients treated with the intravenous antibiotics of interest for ≥2 weeks. The upper panel shows the minimal inhibitory concentration of (A) amikacin, (B) cefoxitin, and (C) imipenem. The middle panel shows the sputum culture conversion rate according to the minimal inhibitory concentration of (D) amikacin, (E) cefoxitin, and (F) imipenem. The lower panel shows the microbiological cure rate according to the minimal inhibitory concentration of (G) amikacin, (H) cefoxitin, and (I) imipenem. Abbreviations: I, intermediate; R, resistant; S, susceptible.

experienced an adverse event related to intravenous antibiotics. Four patients (4.9%) experienced ototoxicity due to amikacin, and 19 patients (27.1%) developed hematologic abnormalities, such as leukopenia, due to cefoxitin. Hematologic abnormalities were the most frequent adverse reactions to imipenem usage (10.2%).

DISCUSSION

Current guidelines suggest susceptibility-based treatment rather than empirical therapy for patients with MAB-PD [7, 8]. However, it is currently unknown whether a susceptibility-based regimen results in better treatment outcomes. To the best of our knowledge, this is the first study investigating this aspect of the treatment of MAB-PD; the evidence supporting the use of susceptibility-based treatment is inconclusive with regard to injectable antibiotics.

MAB-PD is often considered an incurable chronic disease because *M. abscessus* subspecies *abscessus* is highly virulent and chemo-resistant [25]. Several research groups have investigated the association between macrolide susceptibility and treatment outcomes in patients with MAB-PD. It is well known that macrolide-based therapy is useful for cases of infection with macrolide-susceptible strains [21–23]. Previous reports stated that ~20% of *M. abscessus* subspecies *abscessus* isolates were macrolide susceptible due to a C28 sequevar of the *erm*(41) gene [26–28]. In the present study, 20.7% of the patients were infected with clarithromycin-susceptible isolates, and those patients had more favorable outcomes than the patients with clarithromycin-IR isolates.

Table 3. Antibiotic Susceptibility Profile and Treatment Outcomes in Patients Treated With the Antibiotics of Interest for ≥2 Weeks

	Susceptible	Intermediate	Resistant	*P* Value[a]	*P* Value[b]
Amikacin (n = 82)	67 (81.7)	12 (14.6)	3 (3.7)		
Culture conversion	33 (49.3)	8 (66.7)	2 (66.7)	.513	>.999
Microbiological cure	25 (37.3)	8 (66.7)	1 (33.3)	.170	>.999
Cefoxitin (n = 62)	18 (29.0)	36 (58.1)	8 (12.9)		
Culture conversion	12 (66.7)	20 (55.6)	3 (37.5)	.384	.279
Microbiological cure	11 (61.1)	15 (41.7)	2 (25.0)	.223	.276
Ciprofloxacin (n = 17)			17 (100.0)		
Culture conversion			11 (64.7)	NA	NA
Microbiological cure			10 (58.8)	NA	NA
Clarithromycin (n = 82)	17 (20.7)		65 (79.3)[c]		
Culture conversion	12 (70.6)		31 (47.7)	NA	.159
Microbiological cure	11 (64.7)		23 (35.4)	NA	.056
Imipenem (n = 29)	12 (41.4)	12 (41.4)	5 (17.2)		
Culture conversion	4 (33.3)	5 (41.7)	3 (60.0)	.703	.622
Microbiological cure	3 (25.0)	3 (25.0)	2 (40.0)	.746	.597
Moxifloxacin (n = 26)	1 (3.8)	2 (7.7)	23 (88.5)		
Culture conversion	1 (100.0)	0 (0.0)	9 (39.1)	.292	>.999
Microbiological cure	1 (100.0)	0 (0.0)	7 (30.4)	.372	>.999

Data are presented as No. (%). We omitted antibiotic subgroups with <10 patients taking those antibiotics for ≥2 weeks.

Abbreviation: NA, not available.

[a] *P* value among the susceptible, intermediate, and resistant groups.

[b] *P* value between the susceptible plus intermediate group and the resistant group.

[c] Inducible resistance.

However, most patients were infected with clarithromycin-IR strains in this study, as in previous reports [27, 28]. Although macrolides could be used for their immunomodulatory properties or antimicrobial effects against co-infecting organisms, they are not considered active antibiotics against macrolide-IR or macrolide-resistant strains [7]. Therefore, the use of at least 4 drugs other than macrolides is recommended in the initial phase, including intravenous amikacin, imipenem (or cefoxitin), and tigecycline [7].

Most isolates of *M. abscessus* subspecies *abscessus* are susceptible or intermediately susceptible to amikacin [27, 28]. Although intravenous amikacin was administered for a median of 8.9 weeks in this study and although every patient maintained treatment with amikacin for at least 4 weeks in the initial phase, the overall treatment success rate was unsatisfactory irrespective of the amikacin susceptibility results (Tables 3 and 4). This implies that the impact of in vitro amikacin susceptibility on treatment outcomes is limited. For clinicians, great concerns regarding the long-term use of amikacin include the occurrence of adverse drug events and the emergence of resistant strains. Similar to a previous report [29], ototoxicity and nephrotoxicity were the main adverse events in the present study.

Data on the emergence of resistance to amikacin during treatment are scarce. In the CONVERT study of refractory *M. avium* complex pulmonary disease, 23 (10.3%) of 224 patients in the inhaled liposomal amikacin group had isolates with a postbaseline amikacin MIC >64 mcg/mL, but 21.7% of these subsequently had isolates with an MIC <64 mcg/mL [30]. In addition, there is the issue of frequent reinfection in NTM-PD [31, 32]. Thus, we did not determine the effect of amikacin use on the emergence of resistant strains in our study.

Kwak et al. found that treatment with imipenem was associated with better results in patients with MAB-PD [4]. In our study, the overall microbiological cure rate was 43.5% in patients treated with cefoxitin and 27.6% in those treated with imipenem ($P = .230$, calculated from Table 3). Adverse reactions seemed to be frequent in patients treated with cefoxitin. In a large-scale study in Korea, 24% and 13% of clinically isolated *M. abscessus* subspecies *abscessus* strains had in vitro resistance to imipenem and cefoxitin, respectively [28]. The results in our study were similar: Cefoxitin resistance was identified in 9.8%, and imipenem resistance was identified in 24.0%. However, beta-lactam susceptibility was not related to the treatment success rate in this study, except for the microbiological cure rate in those treated for ≥1 year (Supplementary Table 3). It is noteworthy that 7 out of 82 patients (8.5%) had strains that were resistant to both imipenem and cefoxitin, 2 of whom achieved a microbiological cure with cefoxitin and imipenem. Therefore, we should not merely rely on susceptibility results to guide the selection of beta-lactams but should consider diverse aspects, such as the patient's other medical conditions or adverse drug events.

We do not suggest that there is no need to consider antibiotic susceptibility when selecting the treatment regimen for MAB-PD. In contrast, we strongly suggest further research on

Table 4. Antibiotic Susceptibility Profile and Treatment Outcomes in 65 Patients With CLR-IR *M. abscessus* Subspecies *abscessus* Strains

	Susceptible	Intermediate	Resistant	*P* Value[a]	*P* Value[b]
CLR-IR					
Amikacin (n = 65)	52 (80.0)	11 (16.9)	2 (3.1)		
Culture conversion	23 (44.2)	7 (63.6)	1 (50.0)	.503	>.999
Microbiological cure	15 (28.8)	7 (63.6)	1 (50.0)	.082	>.999
Cefoxitin (n = 47)	13 (27.7)	27 (57.4)	7 (14.9)		
Culture conversion	8 (61.5)	14 (51.9)	2 (28.6)	.369	.379
Microbiological cure	7 (53.8)	9 (33.3)	2 (28.6)	.388	.692
Imipenem (n = 26)	10 (38.5)	12 (46.2)	4 (15.4)		
Culture conversion	3 (30.0)	5 (41.7)	2 (50.0)	.748	>.999
Microbiological cure	2 (20.0)	3 (25.0)	2 (50.0)	.509	.604
Moxifloxacin (n = 21)		2 (9.5)	19 (90.5)		
Culture conversion		0 (0.0)	7 (36.8)	NA	.793
Microbiological cure		0 (0.0)	6 (31.6)	NA	.906
CLR-IR & positive smear					
Amikacin (n = 52)	43 (82.7)	8 (15.4)	1 (1.9)		
Culture conversion	17 (39.5)	5 (62.5)	0 (0.0)	.332	>.999
Microbiological cure	10 (23.3)	5 (62.5)	0 (0.0)	.065	>.999
Cefoxitin (n = 37)	9 (24.3)	23 (62.2)	5 (13.5)		
Culture conversion	5 (55.6)	11 (47.8)	1 (20.0)	.423	.442
Microbiological cure	5 (55.6)	6 (26.1)	1 (20.0)	.226	.901
Imipenem (n = 20)	6 (30.0)	11 (55.0)	3 (15.0)		
Culture conversion	1 (16.7)	4 (36.4)	1 (33.3)	.692	>.999
Microbiological cure	1 (16.7)	2 (18.2)	1 (33.3)	.820	>.999
Moxifloxacin (n = 18)		2 (11.1)	16 (88.9)		
Culture conversion		0 (0.0)	5 (31.2)	NA	.926
Microbiological cure		0 (0.0)	4 (25.0)	NA	>.999
CLR-IR & cavitary lesions					
Amikacin (n = 28)	22 (78.6)	5 (17.9)	1 (3.6)		
Culture conversion	9 (40.9)	5 (100.0)	0 (0.0)	.035	>.999
Microbiological cure	7 (31.8)	5 (100.0)	0 (0.0)	.014	>.999
Cefoxitin (n = 23)	7 (30.4)	13 (56.5)	3 (13.0)		
Culture conversion	3 (42.9)	8 (61.5)	1 (33.3)	.569	.936
Microbiological cure	3 (42.9)	7 (53.8)	1 (33.3)	.775	>.999
Moxifloxacin (n = 10)		1 (10.0)	9 (90.0)		
Culture conversion		0 (0.0)	3 (33.3)	NA	>.999
Microbiological cure		0 (0.0)	3 (33.3)	NA	>.999
CLR-IR & treatment ≥1 y					
Amikacin (n = 44)	32 (72.7)	10 (22.7)	2 (4.5)		
Culture conversion	17 (53.1)	6 (60.0)	1 (50.0)	.922	>.999
Microbiological cure	11 (34.4)	6 (60.0)	1 (50.0)	.343	>.999
Cefoxitin (n = 32)	8 (25.0)	17 (53.1)	7 (21.9)		
Culture conversion	6 (75.0)	11 (64.7)	2 (28.6)	.152	.149
Microbiological cure	6 (75.0)	7 (41.2)	2 (28.6)	.157	.503
Imipenem (n = 15)	5 (33.3)	7 (46.7)	3 (20.0)		
Culture conversion	2 (40.0)	3 (42.9)	2 (66.7)	.736	.897
Microbiological cure	2 (40.0)	1 (14.3)	2 (66.7)	.254	.494
Moxifloxacin (n = 16)		1 (6.2)	15 (93.8)		
Culture conversion		0 (0.0)	6 (40.0)	NA	>.999
Microbiological cure		0 (0.0)	5 (33.3)	NA	>.999

Data are presented as No. (%). We omitted antibiotic subgroups with <10 patients taking those antibiotics for ≥2 weeks.

Abbreviations: CLR-IR, clarithromycin inducible resistance; NA, not available.

[a] *P* value among the susceptible, intermediate, and resistant groups.

[b] *P* value between the susceptible plus intermediate group and the resistant group, unless otherwise indicated.

this issue for the following reasons. First, large-scale multinational data are needed to determine the clinical implications of DST and enable generalization of the results. Although we enrolled patients with MAB-PD from the 4 largest referral centers in Korea, the number of cases was insufficient. Only 3 patients were infected with amikacin-resistant strains, which

Table 5. Adverse Drug Events Related to Intravenous Antibiotics

	Total (n = 82)	Amikacin (n = 82)	Cefoxitin (n = 71)	Imipenem (n = 49)
Any adverse events	41 (50.0)	9 (11.0)	27 (38.0)	7 (14.3)
Dermatologic abnormalities	4 (4.9)	0 (0.0)	4 (5.6)	1 (2.0)
Fever	6 (7.3)	1 (1.2)	5 (7.0)	0 (0.0)
Gastrointestinal abnormalities	2 (2.4)	0 (0.0)	1 (1.4)	1 (2.0)
Haematologic abnormalities	21 (25.6)	0 (0.0)	19 (27.1)	5 (10.2)
Hepatotoxicity	8 (9.8)	0 (0.0)	8 (11.2)	0 (0.0)
Nephrotoxicity	3 (3.7)	3 (3.7)	0 (0.0)	0 (0.0)
Ototoxicity	4 (4.9)	4 (4.9)	0 (0.0)	0 (0.0)
Peripheral neuropathy	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)

Data are presented as No. (%).

limited the statistical power. Second, the stability of the antibiotics used in the DST should be considered with care because it has been reported that imipenem instability affects MIC results [33, 34]. Third, the relationship between susceptibility to other antimycobacterial drugs and the treatment success rate needs to be evaluated. In this study, linezolid seemed to be the second most effective drug against *M. abscessus* subspecies *abscessus* after amikacin, but a very small number of patients were treated with it. Frequent adverse events associated with linezolid might be a barrier to its prescription [35]. Additionally, inhaled amikacin was also excluded from this analysis; therefore, we could not evaluate the additive effects of inhaled antibiotics. Fourth, it would be helpful to conduct additional studies with expanded susceptibility tests for other antibiotics. Tigecycline has been recommended as an initial choice in recent guidelines [7, 8]. A lower MIC of clofazimine was associated with negative sputum culture conversion [36]. However, tigecycline and clofazimine susceptibility are not routinely tested at the Korean Institute of Tuberculosis, a supranational reference laboratory. Therefore, a wide range of DSTs should be performed in future studies. Fifth, treatment outcomes other than the rate of sputum culture conversion or microbiological cure need to be measured. As MAB-PD is considered an incurable disease, symptomatic improvements could be a new target. A susceptibility-based regimen might slow disease progression or improve quality of life. Finally, a standardized treatment modality is needed to measure treatment outcomes.

In conclusion, we did not find evidence supporting the use of susceptibility-based treatment with injectable amikacin and beta-lactams for MAB-PD patients. Further research is needed to clarify this issue and help physicians choose effective antimycobacterial agents for this chronic incurable disease.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgements

Financial support. None.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. Concept and design: K.W.J., Y.A.K.; data acquisition: Y.P., Y.E.P., B.W.J., J.P.; analysis and interpretation: B.W.J., N.K., K.W.J., J.J.Y., T.S.S., Y.A.K.; drafting of the manuscript for important intellectual content: Y.P.; critical revision and final approval: all authors.

Access to data. The data sets used during the current study are available from the corresponding author on reasonable request.

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