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Aminoglycoside susceptibility and treatment outcomes in *Mycobacterium avium* complex pulmonary disease

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ABSTRACT

Background: Treatment with parenteral aminoglycosides is recommended for patients with advanced *Mycobacterium avium* complex pulmonary disease (MAC-PD). However, the evidence supporting susceptibility-based treatment with aminoglycosides is limited.

Methods: We retrospectively reviewed patients with MAC-PD treated with aminoglycosides for at least eight weeks between October 2005 and December 2018 at a tertiary referral center in South Korea. Patients without drug susceptibility test (DST) results were excluded.

Results: Among 951 patients diagnosed with MAC-PD, 46 received at least six months of treatment, including aminoglycosides. Thirty patients with DST results were enrolled in this study.

The median age was 57 years (interquartile range [IQR], 50–62 years), with 70 % female. Four patients had received prior treatment for MAC-PD. *M. intracellulare* was the most common causative species (46.7 %), followed by *M. avium* (43.3 %). The median duration of follow-up was 41.3 months (IQR 7.6–68.7 months) after treatment initiation.

Sputum acid-fast bacilli smear was positive in 43.3 %; cavities were present in 73.3 % of patients. The median treatment duration was 16.4 months (IQR 13.5–27.0 months). Culture conversion and all-cause mortality rates were 60.0 % and 20.0 %, respectively. Amikacin was susceptible in 80.0 % of the patients; however, culture conversion rates did not differ based on susceptibility. Amikacin-susceptible patients had a higher, but insignificant, odds of culture conversion (odds ratio 1.667, 95 % confidence interval 0.275–10.094, $p = 0.578$)

Conclusion: Our findings suggest that DST is not correlated with efficacy of aminoglycosides in MAC-PD. Further research is required to clarify its role in treatment decisions.

1. Introduction

Nontuberculous mycobacteria (NTM) are widely present in the environment and comprise approximately 200 species; however, only some cause disease in humans.[1] In humans, the most common site of infection is the lungs. NTM pulmonary disease (PD) is increasing in incidence and prevalence worldwide.[2] Among the NTM species with clinical significance in humans, the most common etiology of NTM-PD is *Mycobacterium avium* complex (MAC), which comprises *M. avium* and *M. intracellulare*.[2,3]

Recent guidelines suggest a macrolide-based regimen of at least three drugs for treating MAC-PD, with the addition of a parenteral aminoglycoside for cavitary, advanced to severe bronchiectatic, or macrolide-resistant disease.[1,4] Susceptibility-based treatment of MAC-PD is recommended for macrolides and amikacin (AMK). Drug susceptibility test (DST) may guide therapy if a clear correlation exists between *in vitro* activity of a drug and clinical outcomes.[1,5] This correlation has been demonstrated for macrolides,[6,7] however, not for other oral agents, such

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as rifampin or ethambutol.[8,9]

Considerable evidence suggests that DST may be useful in guiding aminoglycoside use in patients with MAC-PD. *In vitro* studies have shown that AMK is potent against MAC.[10] Recent studies on inhaled liposomal AMK have reported poor clinical response in MAC isolates with high minimal inhibitory concentration (MIC) for AMK of >64 mg/L or mutations to 16S ribosomal RNA (rRNA).[11,12] One randomized controlled trial in 2007 showed higher rates of clinical improvement, including sputum conversion rates, in MAC-PD patients with streptomycin (SM) than in those without.[13] However, studies assessing the efficacy of DST in guiding the use of aminoglycosides are limited. Therefore, we aimed to investigate the effects of DST on aminoglycoside treatment outcomes in patients with MAC-PD.

2. Methods

2.1. Study design and population

We retrospectively reviewed the electronic health records of patients diagnosed with MAC-PD between October 2005 and December 2018 at a tertiary referral center in Seoul, South Korea. The diagnosis of MAC-PD was based on the criteria from American Thoracic Society/Infectious Disease Society of America guidelines.[14]

We restricted the review to patients treated for at least six months and administered aminoglycosides for at least eight weeks. Patients were excluded if they lacked initial DST results or had a history of aminoglycoside use. We collected electronic health record data on clinical history, laboratory and imaging tests, including DST results, treatment regimens, and treatment outcomes. Adverse drug reactions were assessed through medical records documented by the attending physician, regardless of whether the patient had been referred to another specialist for further evaluation.

The primary outcome measure was culture conversion based on aminoglycoside susceptibility. The secondary outcome measures were treatment outcomes according to susceptibility to other antibiotics, including macrolides, ethambutol, rifampicin, and fluoroquinolones.

2.2. Microbiological examination

Acid-fast bacilli smears and mycobacterial cultures of respiratory specimens were performed according to standard guidelines.[1]

For DST, samples were sent to the Korean Institute of Tuberculosis, a supranational reference laboratory. The broth microdilution method was used for all tests, and the cutoff points for antibiotic susceptibility were those prescribed by the Clinical and Laboratory Standards Institute (CLSI) guidelines.[15,16] For AMK, isolates were considered susceptible if MIC ≤16 μg/mL, resistant if MIC ≥64 μg/mL, and intermediate if MIC = 32 μg/mL. For clarithromycin, isolates were considered susceptible if MIC ≤8 μg/mL, resistant if MIC ≥32 μg/mL, and intermediate if MIC = 16 μg/mL. For moxifloxacin, isolates were considered susceptible if MIC ≤1 μg/mL, resistant if MIC ≥4 μg/mL, and intermediate if MIC = 2 μg/mL.

When the attending physician decided to treat a patient with aminoglycoside, it was administered three to five times a week, in addition to macrolide-containing oral regimen. The attending physician determined the total duration of aminoglycoside use based on the course of each patient. We used the NTM-NET consensus statement to define the treatment outcomes of this study.[17] Culture conversion was defined as three or more consecutive negative cultures from respiratory tract samples during treatment.

2.3. Statistical analyses

Pearson's chi-square test or Fisher's exact test was used to analyze categorical variables. Mann-Whitney *U* test was used to compare continuous variables. Logistic regression analysis was performed to determine the odds ratio of culture conversion according to DST results. Additional analyses were performed after adjusting for other clinical variables. Statistical analyses were performed using SPSS statistics version 23.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a two-tailed *P*-value <0.05.

2.4. Ethics statement

The study protocol was approved by the institutional review board of Severance Hospital (4-2023-0113). The requirement for patient consent was waived because of the retrospective nature of this study.

3. Results

3.1. Baseline characteristics and overall treatment outcomes

Among the 951 patients diagnosed with MAC-PD during the study period, 306 patients received treatment for at least six months. Aminoglycosides were administered to 46 patients for at least eight weeks, and 30 patients were included in the final analysis (Fig. 1). As summarized in Table 1, the median age at diagnosis was 57 years [interquartile range (IQR), 50–62 years], and 70 % of the patients were females. Four patients had a history of NTM treatment (13.3 %). Cavities were observed in 22 patients (73.3 %). Patients were classified based on BACS score (range from 0 to 4, calculated by assigning a point for each of body mass index <18.5 kg/m^2, age of 65 years or older, presence of cavities, and male sex), which is adopted from a risk score from a previous study predicting mortality of NTM-PD.[18] Median BACS score for all patients was 1 (IQR 1–2). AMK and SM were administered in nine and 21 patients, respectively. Baseline characteristics were largely similar between the two groups of patients.

Table 2 shows the treatment regimens and patient outcomes in the study population. The median duration of treatment was 16.4 months (IQR 13.5–27.0 months). The median time to initial aminoglycoside administration was 0.0 weeks (IQR 0.0–4.9 weeks). Patients on AMK were treated longer with aminoglycosides (median 38.9 weeks, IQR 15.1–51.0 weeks) than those treated with SM (median 15.0 weeks, IQR

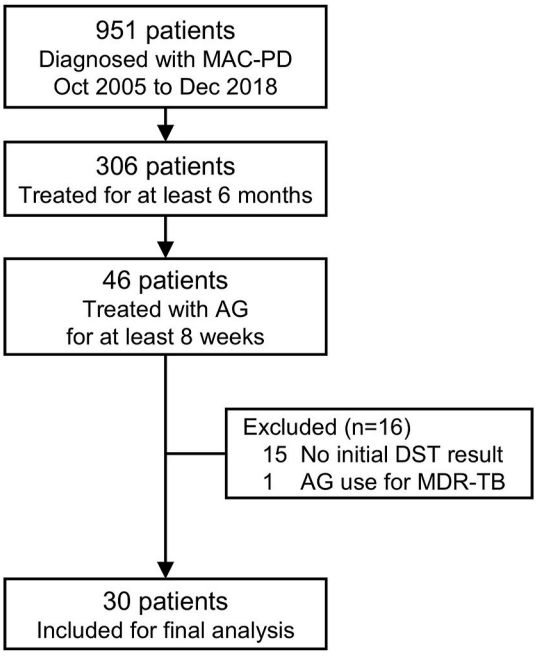

Fig. 1. Flowchart of the study population. Abbreviations: AG, aminoglycosides; DST, drug susceptibility test; MAC-PD, *Mycobacterium avium* complex pulmonary disease; MDR-TB, multidrug-resistant tuberculosis.

Table 1
Baseline characteristics.

	All patients (n = 30)	Streptomycin (n = 21)	Amikacin (n = 9)	*P*-value
Age, year	57 (50–62)	60 (50–68)	57 (48–61)	0.867
Sex, female	21 (70.0)	15 (71.4)	6 (66.7)	1.000
BMI, kg/m^2	20.3 (18.6–21.6)	20.0 (18.3–22.2)	20.6 (18.3–22.8)	0.976
BMI <18.5 kg/m^2	6 (20.0)	4 (19.0)	2 (22.2)	1.000
Smoking, current or past	9 (30.0)	7 (33.3)	2 (22.2)	0.537
History of tuberculosis	23 (76.7)	16 (76.2)	7 (77.8)	1.000
History of NTM treatment	4 (13.3)	3 (14.3)	1 (11.1)	1.000
Comorbidity				
Bronchiectasis	22 (73.3)	15 (71.4)	7 (77.8)	1.000
COPD	10 (33.3)	8 (38.1)	2 (22.2)	0.675
Chronic kidney disease	1 (3.3)	1 (4.8)	0 (0.0)	1.000
Diabetes mellitus	3 (10.0)	2 (9.5)	1 (11.1)	1.000
Malignancy	4 (13.3)	3 (14.3)	1 (11.1)	1.000
Causative species				0.442
M. avium	13 (43.3)	10 (47.6)	3 (33.3)	
M. intracellulare	14 (46.7)	10 (47.6)	4 (44.4)	
MAC[a]	3 (10.0)	1 (4.8)	2 (22.2)	
Radiologic type				0.533
Fibrocavitary	10 (33.3)	6 (28.6)	4 (44.4)	
Cavitary NB	12 (40.0)	8 (38.1)	4 (44.4)	
Non-cavitary NB	8 (26.7)	7 (33.3)	1 (11.1)	
Smear, positive	13 (43.3)	8 (38.1)	5 (55.6)	0.443
Presence of cavity	22 (73.3)	14 (66.7)	8 (88.9)	0.374
Follow-up after treatment, months	41.3 (7.6–68.7)	10.0 (1.4–15.4)	50.6 (23.3–74.8)	0.001
BACS[b] score	1 (1–2)	1 (0.5–2.5)	1 (1–2)	1.000
0	6 (20.0)	5 (23.8)	1 (11.1)	0.961
1	11 (36.7)	7 (33.3)	4 (44.4)	
2	6 (20.0)	4 (19.0)	2 (22.2)	
3	6 (20.0)	4 (19.0)	2 (22.2)	
4	1 (3.3)	1 (4.8)	0 (0.0)	

Data are presented as n (%) or median (interquartile range) unless indicated otherwise. *P*-value compared patients treated with streptomycin vs. those treated with amikacin. [a] Concurrent isolation of *M. avium* and *M. intracellulare*. [b] BACS score calculated by adding a point for each of the following: (1) Body mass index <18.5kg/m2, (2) Age ≥65 years, (3) presence of cavity, and (4) Male sex. Abbreviations: BACS, body mass index, age, cavity, and sex; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MAC, *Mycobacterium avium* complex; NB, nodular bronchiectatic; NTM, nontuberculous mycobacteria.

12.9–28.0 weeks, $p = 0.049$). Macrolides were used for all participants except for one patient who had clarithromycin resistance. The overall sputum culture conversion rate was 60.0 %; patients treated with SM (61.9 %) and with AMK (55.6 %) have similar rates of sputum culture conversion ($p = 1.000$). Six patients (20 %) died of all causes.

For patients treated with AMK, the most common dosage was 5–10 mg/kg twice to three times weekly (77.8 %), and the drug was most commonly administered intramuscularly (77.8 %, Supplementary Table 1). For patients treated with SM, the most common dosage was 15–20 mg/kg three times weekly (61.9 %), and the drug was exclusively administered intramuscularly (100.0 %).

3.2. Outcomes based on antibiotic susceptibility

Fig. 2 and Table 3 show the DST profiles and treatment outcomes of patients treated with each antibiotic. AMK susceptibility was observed in 80.0 % of the patients. Culture conversion rates for AMK-susceptible and AMK-non-susceptible (including intermediate or resistant) individuals were 62.5 % and 50.0 %, respectively. This difference in culture conversion rates with respect to DST results was statistically insignificant ($p = 0.926$). Logistic regression analysis (Table 4) shows that patients infected with AMK-susceptible MAC strains have a higher,

Table 2
Treatment regimens and outcomes.

Variable	All patients (n = 30)	Streptomycin (n = 21)	Amikacin (n = 9)	*P*-value
Treatment duration, months	16.4 (13.5–27.0)	15.8 (13.2–26.1)	16.8 (13.0–31.8)	0.734
Time from treatment initiation and AG administration, weeks	0.0 (0.0–4.9)	0.0 (0.0–4.9)	0.0 (0.0–69.9)	0.940
AG use	30 (100.0)	21 (100.0)	9 (100.0)	
Duration of AG use, weeks	16.8 (13.2–35.4)	15.0 (12.9–28.0)	38.9 (15.1–51.0)	0.049
Intramuscular administration	28 (93.3)	21 (100.0)	7 (77.8)	0.083
Intravenous administration	2 (6.7)	0 (0.0)	2 (22.2)	
Macrolide	29 (96.6)	21 (100.0)	8 (88.9)	0.300
Azithromycin	15 (50.0)	10 (47.6)	5 (55.6)	1.000
Azithromycin to Clarithromycin	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Clarithromycin	4 (13.3)	4 (19.0)	0 (0.0)	0.287
Clarithromycin to Azithromycin	10 (33.3)	7 (33.3)	3 (33.3)	1.000
Other drugs				
Rifampin	28 (93.3)	19 (90.5)	9 (100.0)	1.000
Ethambutol	26 (86.7)	19 (90.5)	7 (77.8)	0.220
Surgical resection within one year of treatment initiation	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Sputum culture conversion	18 (60.0)	13 (61.9)	5 (55.6)	1.000
All-cause mortality	6 (20.0)	5 (23.8)	1 (11.1)	0.637

Data are presented as n (%) or median (interquartile range). *P*-value compared patients treated with streptomycin vs. those treated with amikacin. Abbreviations: AG, aminoglycoside.

but statistically insignificant, odds of culture conversion [crude odds ratio (OR) 1.667, 95 % confidence interval (CI) 0.275–10.094, $p = 0.578$] than those infected with non-susceptible MAC strains. Results are similar for additional analyses that adjust for age and sex (adjusted OR 2.112, 95 % CI 0.288–15.469, $p = 0.462$), and for BACS score (adjusted OR 1.714, 95 % CI 0.269–10.927, $p = 0.569$).

Clarithromycin susceptibility was observed in 89.6 % of the patients treated with macrolides (n = 29, Table 3). Culture conversion rates for patients susceptible and non-susceptible to clarithromycin were 57.6 % and 100 %, respectively. Similar to AMK, this difference in culture conversion rates was statistically insignificant ($p = 0.423$). Detailed DST profiles are summarized in Supplementary Fig. 1 and Supplementary Table 2.

For 21 patients with two follow-up DST results, the median interval between two DST results was 23.6 months (IQR 14.3–45.2 months, Supplementary Table 3). Despite the changes in AMK susceptibility patterns in these patients (Supplementary Fig. 2), neither the initial nor follow-up DST results revealed any differences in the culture conversion rates based on AMK susceptibility (Supplementary Table 4).

3.3. Adverse drug reactions related to aminoglycosides

Adverse drug reactions to aminoglycosides were observed in 11 patients (36.7 %, Table 5). No differences in rates of adverse events were observed between patients treated with SM and those treated with AMK ($p = 0.687$ for any adverse events). The most common reaction was ototoxicity (n = 8, 26.7 %), which was observed in two patients treated with AMK (22.2 %) and six patients treated with SM (28.6 %). Other documented events included gastrointestinal abnormalities (n = 2), generalized weakness (n = 1), and peripheral neuropathy (n = 1).

When compared by age, the rate of any adverse events for patients younger than 65 years of age (n = 23, 34.8 %) was similar to that for patients of and older than 65 years of age (n = 7, 42.9 %, $p = 1.000$,

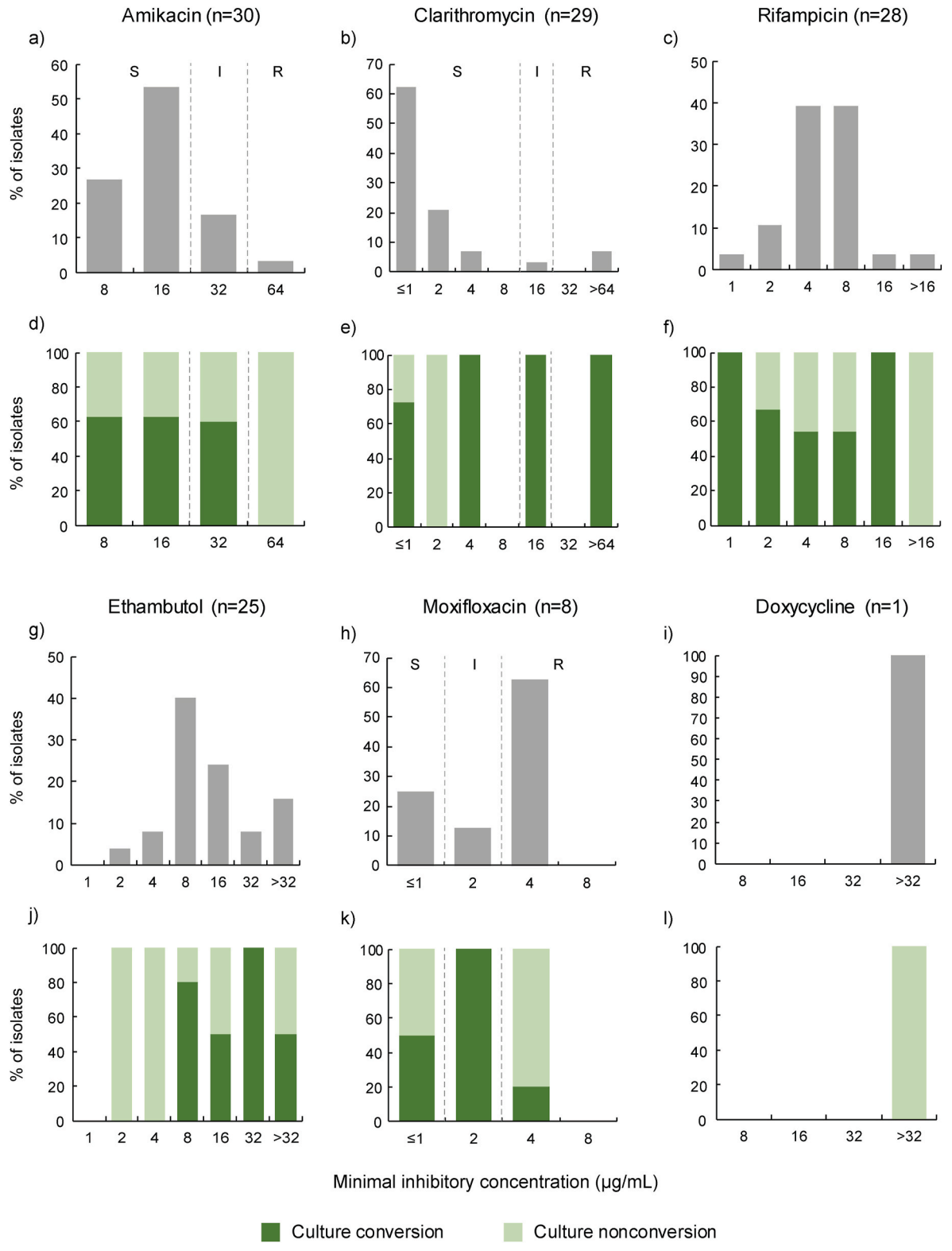

Fig. 2. Antibiotic susceptibility profiles and treatment outcomes for respective drugs. For each drug, the upper panels show the proportion of isolates with corresponding minimal inhibitory concentrations for (a) amikacin, (b) clarithromycin, (c) rifampicin, (g) ethambutol, (h) moxifloxacin, and (i) doxycycline, respectively. Lower panels show rates of culture conversion according to the minimal inhibitory concentrations for (d) amikacin, (e) clarithromycin, (f) rifampicin, (j) ethambutol, (k) moxifloxacin, and (l) doxycycline, respectively. For antibiotics with Clinical and Laboratory Standards Institute susceptibility breakpoints[16] (amikacin, clarithromycin, moxifloxacin), breakpoints are indicated in each respective panel. Abbreviations: I, intermediate; R, resistant; S, susceptible.

Table 3
Antibiotic susceptibility profile and treatment outcomes among patients treated with the corresponding antibiotic.

	Susceptible	Intermediate	Resistant	*P*-value
Amikacin (n = 30)	24 (80.0)	5 (16.7)	1 (3.3)	
Culture conversion	15 (62.5)	3 (60.0)	0 (0.0)	0.926
Clarithromycin (n = 29)	26 (89.6)	1 (3.4)	2 (6.9)	
Culture conversion	15 (57.6)	1 (100.0)	2 (100.0)	0.423

Data are presented as n (%). *P*-value compared susceptible patients vs. intermediate and resistant patients.

Table 4
Logistic regression analysis of culture conversion rates according to amikacin sensitivity.

	Odds ratio (95 % confidence interval)	*P*-value
Crude	1.667 (0.275–10.094)	0.578
Adjusted for age, sex	2.112 (0.288–15.469)	0.462
Adjusted for BACS score	1.714 (0.269–10.927)	0.569

Abbreviation: BACS, body mass index, age, cavity and male sex.

Table 5
Adverse drug reactions related to aminoglycosides.

	All patients (n = 30)	Streptomycin (n = 21)	Amikacin (n = 9)	*P*-value
Any adverse events	11 (36.6)	7 (33.3)	4 (44.4)	0.687
Ototoxicity	8 (26.7)	6 (28.6)	2 (22.2)	1.000
Generalized weakness	2 (6.7)	1 (4.8)	1 (11.1)	0.517
Gastrointestinal abnormalities	1 (3.3)	0 (0.0)	1 (11.1)	0.300
Peripheral neuropathy	1 (3.3)	1 (4.8)	0 (0.0)	1.000
Dermatologic abnormalities	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Fever	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Hematologic abnormalities	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Hepatotoxicity	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Nephrotoxicity	0 (0.0)	0 (0.0)	0 (0.0)	N/A

Data are presented as n (%). *P*-value compared patients treated with streptomycin vs. those treated with amikacin.

Supplementary Table 5). Similar results were observed for rates of ototoxicity (age younger than 65, 26.1 % vs. age at least 65, 28.6 %, $p = 1.000$).

Among the patients with documented ototoxicity (n = 8, Supplementary Table 6), four patients were referred to an otorhinolaryngology specialist and received audiometry. Audiometry was performed before AG use in one patient, who eventually developed ototoxicity during treatment. Of the three patients in whom audiometry was performed during treatment, two patients terminated AG administration based on abnormal results.

4. Discussion

In this study, we report a sputum culture conversion rate of 60.0 % in patients with MAC-PD who had received aminoglycosides for at least eight weeks as part of their treatment regimen. AMK susceptibility was observed in 80.0 % of the patients, with only one patient showing development of AMK resistance (4.8 %) among the 21 patients with at least two DST results. However, we observed no differences in culture conversion rates based on AMK susceptibility. Adverse events occurred in 36.7 % of all patients, similar to those in previous studies on inhaled or liposomal AMK.[11,12,19,20]

Despite the growing body of research to improve NTM-PD treatment, the latest treatment guidelines provide weak recommendations with low-quality evidence.[1,4] While many studies demonstrate clinical benefit from addition of aminoglycosides in MAC-PD treatment, they do not define a subpopulation of patients that can expect this benefit from adding aminoglycosides.

One of the most poorly understood issues of NTM-PD treatment is the relationship between *in vitro* DST and *in vivo* antibiotic response.[21] For macrolides, the correlation between *in vitro* DST results and clinical efficacy in patients with MAC-PD[6,7] has led to the recommendation of susceptibility-based treatment.[1] However, the role of DST in guiding ethambutol and rifampin use is largely unclear,[7,9,22] with some studies suggesting ethambutol as an important companion drug that prevents macrolide resistance.[23,24] A study on the *in vitro* activity of clofazimine suggested that lower MIC was associated with sputum culture conversion in MAC-PD, although the MIC values varied widely among isolates.[25]

Our study reports a higher, but statistically insignificant, rate of culture conversion (crude OR 1.667, 95 % CI 0.275–10.094, $p = 0.578$) among MAC-PD patients infected with susceptible isolates. This indicates that the DST results are poorly correlated with the clinical efficacy of aminoglycosides. Although recent consensus recommends susceptibility-based treatment for AMK use,[1] it is largely based on *in vitro* studies of AMK efficacy and not on clinical trials.[26] Similar to our findings, those of previous studies on the efficacy of aminoglycosides in treating MAC-PD do not support this recommendation.

The evidence investigating the correlation between DST and AMK efficacy is scarce. One *in vitro* study utilized clinical MAC isolates to propose MIC breakpoints for AMK.[10] Although the results of this study have been the basis of the recent CLSI guidelines for DST in MAC isolates,[16] this study did not include clinical data to inform treatment decisions. Another retrospective study of patients with MAC-PD demonstrated higher rates of microbiologic cure with the addition of AMK and clofazimine to macrolide, rifampin, and ethambutol, however, reported no DST results.[27]

Recent evidence on AMK use is mostly based on studies of inhaled AMK formulations. Adding liposomal AMK inhalation to guideline therapy has shown greater sputum culture conversion in treatment-refractory patients with MAC-PD infected with isolates susceptible to AMK.[11,12] One of these studies found that no patient with mutational resistance to AMK or MIC ≥64 μg/mL to AMK has shown culture conversion.[11] Previous studies on adding inhaled AMK in treatment-refractory NTM-PD have suggested greater treatment responses with inhaled AMK use despite common adverse effects, such as nephrotoxicity, ototoxicity, or dysphonia.[19,20,28] However, these studies include patients infected with *Mycobacterium abscessus* and did not include DST results for AMK, as they were all conducted before AMK breakpoints were introduced in CLSI guidelines. A real-world study of six refractory patients with MAC-PD showed limited efficacy of adding inhaled AMK, although all patients were infected with strains susceptible to AMK (MIC 4–16 μg/mL).[29]

Evidence of using *in vitro* DST to guide the use of SM in NTM-PD treatment is limited. An early prospective study examining the efficacy of a four-drug regimen (consisting of clarithromycin, ethambutol, rifampin, and SM) showed a poor correlation between the efficacy of SM and *in vitro* susceptibility.[6] One randomized controlled trial on the efficacy of adding SM to a three-drug regimen (clarithromycin, ethambutol, and rifampin) in patients with MAC-PD demonstrated better outcomes, such as culture conversion and clinical improvement (evaluated by both clinical symptoms, radiologic findings, and expert opinion).[13] The study found cases where the MIC and clinical efficacy were discordant, suggesting that a possible additive or synergistic effect of SM with other drugs may explain the results.

The poor correlation between DST and clinical efficacy can be attributed to multiple factors. Various resistance mechanisms – mutational resistance, biofilm formation, or metabolic changes – reduce susceptibility to AMK.[26] Synergistic activity between AMK and clofazimine has been observed against many NTM strains.[30] To determine the

optimal dose for treatment and resistance suppression, pharmacokinetic (PK) and pharmacodynamic (PD) studies are need for MAC. In *M. abscessus*, PK/PD data suggest that the recommended AMK dose of 10–15 mg/kg may be insufficient to reach the required therapeutic plasma concentrations.[26]

To improve our understanding of the utility of DST in guiding treatment decisions, we believe that future large-scale clinical trials should address the following issues: 1) identification of specific populations that benefit from adding aminoglycoside to treatment, 2) the association between DST results and clinical outcomes, and 3) optimal dosing and regimen based on PK/PD profiles.

Our study is limited in demonstrating a correlation between DST results and the treatment effect of aminoglycoside, possibly because of the following reasons. First, it was performed in a small patient group from a single center. Second, although we included patients treated with either AMK or SM in the study, we only obtained DST results for AMK. Additionally, we did not assess the effect of pharmacokinetic and pharmacodynamic data [such as therapeutic drug monitoring (TDM)] on clinical outcomes because only one of nine patients treated with AMK had TDM data. Furthermore, while 73.3 % of the patients had cavitary disease, most were macrolide-susceptible (89.6 %, Table 3) and treatment-naïve (86.7 % without a previous NTM treatment history, Table 1) with a relatively low risk of mortality (median BACS score of 1), which may not represent a true treatment-refractory population that could benefit from the addition of a parenteral drug. We also did not investigate the potential synergism among antibiotics, such as between AMK and clofazimine.[30] Finally, no data were available on 16S rRNA mutations, which exhibit *in vivo* resistance to AMK.[11]

In conclusion, based on the DST results, we observed no differences in the culture conversion rates of patients with MAC-PD treated with aminoglycosides. Despite these results, our findings highlight the need for further research on this issue. Similar to the findings of our study, much of the existing evidence[21,23,31] does not sufficiently support using DST to guide therapy. Large-scale multinational studies are necessary to determine the clinical effect of DST on MAC-PD treatment.

CRediT authorship contribution statement

Shihwan Chang: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Han Sung Kang:** Formal analysis, Conceptualization. **Young Ae Kang:** Supervision, Methodology, Conceptualization. **Moo Suk Park:** Writing – review & editing, Supervision. **Youngmok Park:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

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Declaration of competing interest

The authors declare no conflicts of interest, either financial or non-financial, that could influence the outcome or interpretation of this manuscript.

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Appendix A. Supplementary data

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