Mycobacterium abscessus pulmonary disease: individual patient data meta-analysis

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For *Mycobacterium abscessus* pulmonary disease in general, imipenem use is associated with improved outcome. For *M. abscessus* subsp. *abscessus*, the use of either azithromycin, amikacin or imipenem increases the likelihood of treatment success. http://ow.ly/w24n30nSakf

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ABSTRACT Treatment of *Mycobacterium abscessus* pulmonary disease (MAB-PD), caused by *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense* or *M. abscessus* subsp. *bolletii*, is challenging.

We conducted an individual patient data meta-analysis based on studies reporting treatment outcomes for MAB-PD to clarify treatment outcomes for MAB-PD and the impact of each drug on treatment outcomes. Treatment success was defined as culture conversion for ⩾12 months while on treatment or sustained culture conversion without relapse until the end of treatment.

Among 14 eligible studies, datasets from eight studies were provided and a total of 303 patients with MAB-PD were included in the analysis. The treatment success rate across all patients with MAB-PD was 45.6%. The specific treatment success rates were 33.0% for *M. abscessus* subsp. *abscessus* and 56.7% for *M. abscessus* subsp. *massiliense*. For MAB-PD overall, the use of imipenem was associated with treatment success (adjusted odds ratio (aOR) 2.65, 95% CI 1.36–5.10). For patients with *M. abscessus* subsp. *abscessus*, the use of azithromycin (aOR 3.29, 95% CI 1.26–8.62), parenteral amikacin (aOR 1.44, 95% CI 1.05–1.99) or imipenem (aOR 7.96, 95% CI 1.52–41.6) was related to treatment success. For patients with *M. abscessus* subsp. *massiliense*, the choice among these drugs was not associated with treatment outcomes.

Treatment outcomes for MAB-PD are unsatisfactory. The use of azithromycin, amikacin or imipenem was associated with better outcomes for patients with *M. abscessus* subsp. *abscessus*.

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Introduction

The incidence and prevalence of pulmonary disease caused by nontuberculous mycobacteria (NTM) are increasing globally [1–4]. *Mycobacterium abscessus*, comprising of three subspecies, *i.e. M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense* and *M. abscessus* subsp. *bolletii*, is the second most common NTM causing pulmonary disease, following *Mycobacterium avium* complex, in East Asia and the USA [2, 5–8].

Treatment for *M. abscessus* pulmonary disease (MAB-PD) is challenging because of the high frequency of mutational and acquired resistance to commonly used antibiotics [9]. Although macrolides are recommended as a cornerstone of chemotherapy [10, 11], mutations in the *rrl* gene of *M. abscessus*, which encodes 23S rRNA, lead to the acquisition of clarithromycin resistance [12, 13]. Moreover, the *erm*(41) gene, which encodes a ribosomal methylase, confers inducible resistance to macrolide antibiotics [14]. *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *bolletii* typically express a functional *erm*(41) gene, and hence demonstrate inducible resistance to macrolide antibiotics. Most *M. abscessus* subsp. *massiliense* harbours a mutation in the *erm*(41) gene that renders it nonfunctional, hence *M. abscessus* subsp. *massiliense* isolates are intrinsically susceptible to clarithromycin [12, 15].

For the treatment of MAB-PD, the American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) recommends multidrug therapy that includes a macrolide and one or more parenteral drugs (amikacin plus cefoxitin or imipenem) [10]. The British Thoracic Society (BTS) guidelines recommend an antibiotic regimen comprised of intravenous amikacin, tigecycline and imipenem with a macrolide for the initial treatment phase, followed by a continuation phase comprised of nebulised amikacin and a macrolide in combination with additional oral antibiotics [11].

However, the effectiveness of these treatment approaches has not yet been precisely determined, because different studies have adopted different definitions of treatment success [16, 17]. Some researchers defined sputum culture conversion and maintenance of conversion as treatment success [16], while others reported treatment outcomes based on clinical improvement in addition to sputum culture conversion [17]. Furthermore, the effect of individual drugs has not been elucidated.

Recently, two meta-analyses reporting treatment outcomes for MAB-PD were published [18, 19]. According to these analyses, the treatment success rates for *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* were 34.0–41.2% and 54.0–69.8%, respectively. However, accurate measurement of the outcomes and role of each drug in MAB-PD treatment could not be determined because these analyses were based on aggregated data provided in published articles.

In this study, we performed a meta-analysis based on individual patient data to clarify treatment outcomes of MAB-PD as well as the impact of each drug on these outcomes.

Methods

This study was performed in accordance with the PRISMA individual participant data statement [20]. The study protocol was registered with the PROSPERO database (identifier CRD42017070348). Exemption from ethical approval was confirmed by the Institutional Review Board of Seoul National University Hospital (Seoul, South Korea) (1707-007-864).

Search strategy and selection criteria

We conducted a literature search of the MEDLINE, Embase and Cochrane databases using Medical Subject Heading (MeSH) terms and text words associated with MAB-PD and its treatment. The search query was [(*Mycobacterium abscessus*) OR (*Mycobacterium massiliense*) OR (*Mycobacterium bolletii*)]

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AND [(Treat*) OR (Therapy)]. The literature search was restricted to articles published between January 1, 1987 and July 31, 2017. The abstracts were independently reviewed by two investigators (N.K. and J.P.). Randomised controlled studies and observational studies reporting treatment outcomes for MAB-PD were selected for a full-text review. The discrepancies were resolved by reaching a consensus with a third investigator (J-J.Y.).

We selected all studies of patients who were diagnosed as MAB-PD according to the criteria suggested by the ATS/IDSA or BTS [10, 11], who underwent chemotherapy, and for whom microbiological and clinical outcomes were reported. We excluded studies with case reports, with patients <15 years old and with insufficient reporting of treatment outcomes. Studies mainly comprising patients refractory to previous chemotherapy or patients with acquired mutational macrolide resistance were also excluded.

Data collection and quality assessment

The corresponding authors of eligible studies were contacted by e-mail and requested to provide the raw data. The following variables were collected: age, sex, body mass index (BMI), past medical history (previous NTM/tuberculosis (TB) treatment, chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis (CF), bronchiectasis, malignancy or HIV infection), subspecies identification results, radiographic features (nodular bronchiectatic, fibrocavitary or indeterminate), detailed medical treatment history, duration of parenteral drug(s) use, duration of total treatment, details of adjunctive surgery and treatment outcomes (microbiological, radiographic and symptomatic). If the reply from these authors could not be obtained, repeated contacts were attempted two times more.

The de-identified data provided by the corresponding authors were reviewed by two investigators. All data were merged and transformed into one common dataset. Methodological quality of the studies was evaluated with the Newcastle–Ottawa Scale [21]. The scale was modified with reference to previous reports that described treatment outcomes of single-arm studies [22, 23].

Definitions

Treatment success was defined as culture conversion for ⩾12 months while on treatment or sustained culture conversion without relapse until the end of treatment [10, 11, 23, 24]. Culture conversion was defined as three or more consecutive negative mycobacterial cultures of sputum. Symptomatic and radiographic improvements were decided based on evaluations by the treating physician at the completion of treatment.

Statistical analysis

Descriptive variables were summarised with median, interquartile ranges and proportions. These variables were compared between subspecies using Fisher's exact test and the Wilcoxon rank-sum test.

For the analysis of treatment outcomes, the proportions of patients with treatment success, symptomatic and radiographic improvement were calculated. The 95% confidence intervals for each proportion were obtained with the DerSimonian–Laird random effects model [25]. I^2 statistics were used to estimate heterogeneity across the studies [26]. The effect of excluded studies on treatment success rates was measured with meta-regression. The potential source of heterogeneity was also assessed with meta-regression [27]. Potential for publication bias was measured using the funnel plot and the Egger test [28].

As a small number of studies and small sample sizes were expected, the one-stage approach was adopted [29]. We used multilevel mixed effects logistic regression with a random intercepts model, and used the random effect parameter for each study and the fixed effect parameter for each intervention to estimate the adjusted odds ratios (aOR) and 95% confidence intervals of treatment outcomes. Estimates were adjusted for five covariates: age, sex, BMI, radiographic features and presence of respiratory comorbidity [30, 31]. Stata version 14.2 (StataCorp, College Station, TX, USA) was used for all statistical analyses.

Results

Study selection

We identified a total of 1600 records with our key word-directed literature search, and the titles and abstracts of 1529 articles remained after the removal of duplicates. Of these, 187 articles were selected for full-text review based on the criteria described in the Methods. Full-text reviews narrowed this number down to 14 and the authors were contacted for study participation (Cohen's κ for interrater agreement 0.76). The data could not be obtained from six studies [17, 32–36] owing to inaccessibility of the data from four studies, refusal from one study and absence of a response from the authors of one study. Finally, eight studies were the subject of the final analysis: one from Brazil [37], one from Australia [38], one from the USA [39], one from Japan [40], one from the Netherlands [41] and three from South Korea [42–44] (figure 1). Six [37–41, 44] out of the eight were retrospective observational studies, while the other two [42, 43] were prospective observational studies (table 1). Two studies [42, 43] were published by the same

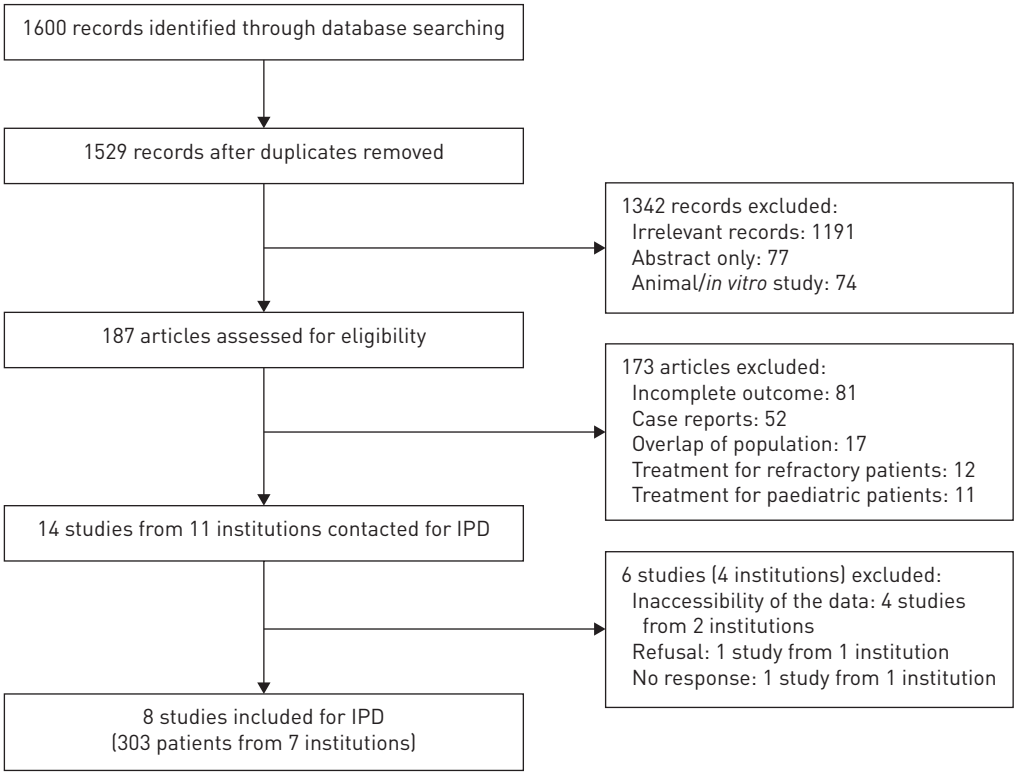

FIGURE 1 PRISMA individual patient data (IPD) flow diagram.

institution and the data from these studies were merged into a combined dataset. Requested and retrieved items from the authors are described in supplementary table E1. The updated data were collected from one study [41]. Four studies [37, 41–43] had a low risk of bias in all aspects, while the others had a risk of bias in terms of representativeness of MAB-PD patients [40], subspecies identification [39] and adequacy of follow-up after treatment [38, 40, 44] (supplementary table E2). The characteristics of the excluded studies are described in supplementary table E3.

Characteristics of study population

A total of 303 patients with MAB-PD were included: 126 patients with *M. abscessus* subsp. *abscessus*, 95 with *M. abscessus* subsp. *massiliense*, one with *M. abscessus* subsp. *bolletii* and 81 without subspecies identification. The subspecies identification was determined based on sequencing of *rpoB* [38, 40, 42–44], *hsp*65 [38–43], *erm*(41) [39, 41], *secA* [38] and the internal transcribed spacer region [40] or *hsp*65 PCR restriction enzyme analysis [37].

The median age of the patients was 59 years, 78.6% were female, 141 (46.5%) had a previous treatment history for NTM or TB and 12 (4.0%) had CF. Nodular bronchiectatic features were more prevalent among patients with *M. abscessus* subsp. *massiliense* (74.7%) than patients with *M. abscessus* subsp.

TABLE 1 Characteristics of the eight studies included in the analysis

First author [ref.]	Study design	Study period	Region	Sample size n	Clinical setting	Type of drug regimen
de Mello [37]	Retrospective, cohort	1993–2011	Brazil	26	Single centre	Individualised
Ellender [38]	Retrospective, cohort	2002–2012	Australia	13	Single centre	Individualised
Jarand [39]	Retrospective, cohort	2001–2004	USA	69	Single centre	Individualised
Koh [42]	Prospective, cohort	2007–2012	South Korea	71	Single centre	Standardised and individualised
Koh [43]	Prospective, cohort	2002–2012	South Korea	67	Single centre	Standardised and individualised
Namkoong [40]	Retrospective, cohort	2004–2013	Japan	13	Multicentre	Individualised
Park [44]	Retrospective, cohort	2006–2015	South Korea	36	Single centre	Individualised
van Ingen [41]	Retrospective cohort	1999–2005	The Netherlands	8	Single centre	Individualised

TABLE 2 Baseline characteristics of the 303 patients included in the analysis

	Total[#]	*M. abscessus* subsp. *abscessus* pulmonary disease	*M. abscessus* subsp. *massiliense* pulmonary disease	p-value[¶]
Patients	303	126	95	
Age years	59 (51–66)	59.5 (50–66)	57 (52–64)	0.817[+]
Female	238 (78.6)	91 (72.2)	79 (83.2)	0.076[§]
Body mass index kg·m^{-2}	20.5 (18.8–22.0)	20.0 (18.2–21.9)	20.6 (18.8–21.8)	0.385[+]
Current or ex-smoker	60 (19.8)	20 (15.9)	11 (11.6)	0.434[§]
Presence of respiratory comorbidities				
Previous history of treatment for NTM/TB	141 (46.5)	79 (62.7)	49 (51.6)	0.092[§]
COPD	20 (6.6)	10 (7.9)	5 (5.3)	0.591[§]
Asthma	9 (3.0)	2 (1.6)	4 (4.2)	0.406[§]
Cystic fibrosis	12 (4.0)	0	1 (1.1)	0.430[§]
Bronchiectasis	127 (41.9)	63 (50.0)	59 (62.1)	0.078[§]
Radiographic features prior to treatment				0.023[§]
Nodular bronchiectatic	195 (64.4)	80 (63.5)	71 (74.7)	
Fibrocavitary	63 (20.8)	35 (27.8)	23 (24.2)	
Indeterminate	45 (14.9)	11 (8.7)	1 (1.1)	

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. *M. abscessus*: *Mycobacterium abscessus*; NTM: nontuberculous mycobacterium; TB: tuberculosis; COPD: chronic obstructive pulmonary disease. Body mass index in 26 patients and smoking history in 13 patients were missing; these values were estimated using multivariate sequential imputation using chained equations. [#]: subspecies identifications of *M. abscessus* were missing in 81 patients (one patient was identified as having *M. abscessus* subsp. *bolletii*); [¶]: from comparison between patients with *M. abscessus* subsp. *abscessus* pulmonary disease and *M. abscessus* subsp. *massiliense* pulmonary disease; [+]: Wilcoxon rank-sum test; [§]: Fisher's exact test.

abscessus (63.5%; p=0.023) (table 2). Detailed characteristics of the included patients are provided in supplementary table E4.

Treatment outcomes and modalities

Among the 303 patients with MAB-PD, 164 patients met the criteria for treatment success. The weighted proportion of treatment success for MAB-PD overall was 45.6% (95% CI 26.7–64.4%), while the specific treatment success rates were 33.0% (95% CI 16.1–49.8%) for *M. abscessus* subsp. *abscessus* and 56.7% (95% CI 9.9–97.8%) for *M. abscessus* subsp. *massiliense* (figure 2). If we excluded studies comprising MAB-PD patients where subspeciation was not performed, the treatment success rates for *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* pulmonary disease were 27.2% (95% CI 10.8–43.5%) and 57.2% (95% CI 10.9–97.5%), respectively. For *M. abscessus* subsp. *abscessus* pulmonary disease, the patients with treatment success received azithromycin (p=0.037), parenteral amikacin (p=0.008) or imipenem (p=0.034) more frequently than patients without treatment success, but not cefoxitin (p=0.444). Among patients with MAB-PD as well as patients with *M. abscessus* subsp. *abscessus*, durations of total treatment were longer in the treatment failure group than in the success group (p<0.001 and p=0.044, respectively). Duration of parenteral drug(s) use was also longer in the treatment failure group among patients with MAB-PD (p<0.001) (table 3).

The weighted proportion of symptomatic improvement after treatment was 64.2% (95% CI 51.6–76.7%) among MAB-PD patients overall: 63.4% (95% CI 43.9–81.1%) for patients with *M. abscessus* subsp. *abscessus* and 63.6% (95% CI 15.9–99.6%) for patients with *M. abscessus* subsp. *massiliense* (supplementary figure E1). Parenteral amikacin was more frequently prescribed to patients with *M. abscessus* subsp. *abscessus* or *M. abscessus* subsp. *massiliense* who experienced symptomatic improvement (p=0.008 and p=0.001, respectively) (supplementary table E5).

The weighted proportion of radiographic improvement was 46.8% (95% CI 36.8–56.8%) among MAB-PD patients. Radiographic improvement was attained for 35.7% (95% CI 27.2–44.8%) of patients with *M. abscessus* subsp. *abscessus* and 70.5% (95% CI 33.6–98.0%) of patients with *M. abscessus* subsp. *massiliense* (supplementary figure E2). For *M. abscessus* subsp. *abscessus* pulmonary disease, azithromycin rather than clarithromycin was used more commonly in patients with radiographic improvement (p=0.006) (supplementary table E6).

Treatment outcomes according to age, sex, BMI, respiratory comorbidities and radiographic features are provided in supplementary table E7.

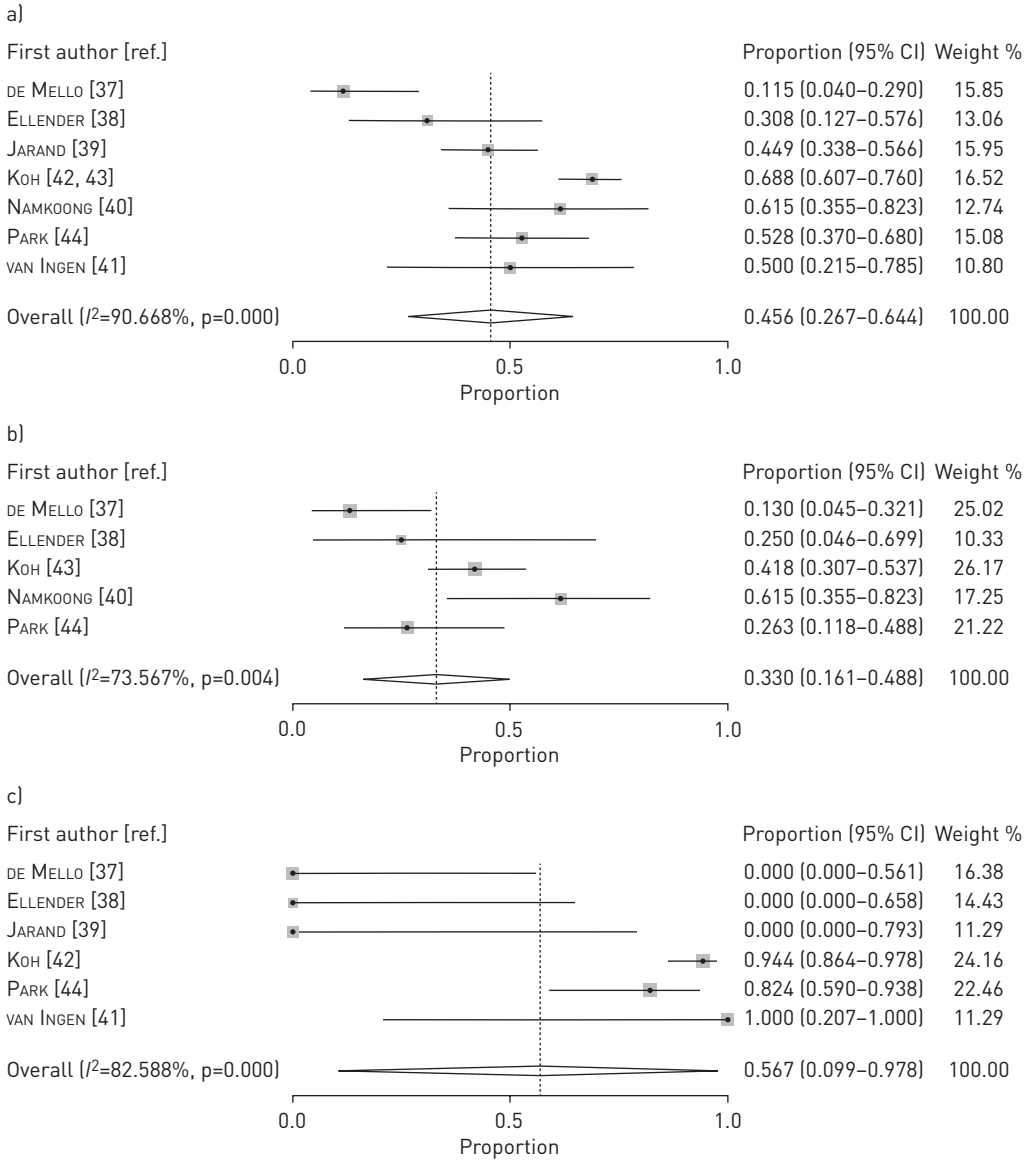

FIGURE 2 Weighted proportion of treatment success for selected studies: a) *Mycobacterium abscessus*, b) *M. abscessus* subsp. *abscessus* and c) *M. abscessus* subsp. *massiliense*.

Meta-regression and publication bias

The concordance of treatment outcomes between included and excluded studies was confirmed with meta-regression (coefficient −0.04, p=0.765). The ethnicity of the population (Asian *versus* non-Asian) (coefficient 0.31, p=0.052), design of studies (prospective *versus* retrospective) (coefficient 0.28, p=0.137) and study quality (low risk of bias *versus* medium to high risk of bias) (coefficient −0.02, p=0.922) did not contribute to the heterogeneity. The funnel plot showed asymmetry (supplementary figure E3), while the Egger test proved no evidence of publication bias (p=0.073).

Effect of individual drugs on treatment success

For patients with MAB-PD, the use of imipenem (aOR 2.65, 95% CI 1.36–5.10) was associated with treatment success, while the other drugs did not show any significant impact on treatment outcomes. For patients with *M. abscessus* subsp. *abscessus* specifically, the use of azithromycin (aOR 3.29, 95% CI 1.26–8.62), parenteral amikacin (aOR 1.44, 95% CI 1.05–1.99) or imipenem (aOR 7.96, 95% CI 1.52–41.6) was associated with higher treatment success, while the use of cefoxitin (aOR 1.22, 95% CI 0.53–2.86) was not. For patients with *M. abscessus* subsp. *massiliense*, the choice among these drugs and treatment outcomes did not show significant correlation (table 4).

TABLE 3 Comparison of treatment modalities between treatment success and treatment failure groups

	Total[#]			*M. abscessus* subsp. *abscessus* pulmonary disease[¶]			*M. abscessus* subsp. *massiliense* pulmonary disease[+]		
	Success	Failure	p-value	Success	Failure	p-value	Success	Failure	p-value
Patients	164	139		45	81		82	13	
Macrolides									
Clarithromycin[§]	99 (60.4)	87 (62.6)	0.813	27 (60.0)	63 (77.8)	0.041	51 (62.2)	7 (53.8)	0.552
Azithromycin[f]	61 (37.2)	41 (29.5)	0.144	18 (40.0)	17 (21.0)	0.037	31 (37.8)	5 (38.5)	>0.999
Parenteral drugs									
Cefoxitin[##]	48 (29.3)	48 (34.5)	0.323	19 (42.2)	28 (34.6)	0.444	20 (24.4)	5 (38.5)	0.321
Imipenem[¶¶]	43 (26.2)	22 (15.8)	0.036	7 (15.6)	3 (3.7)	0.034	19 (23.2)	1 (7.7)	0.288
Amikacin	153 (93.3)	116 (83.5)	0.010	45 (100.0)	71 (87.7)	0.008	77 (93.9)	10 (76.9)	0.075
Fluoroquinolones									
Ciprofloxacin	51 (31.1)	43 (30.9)	>0.999	14 (31.1)	26 (32.1)	>0.999	23 (28.0)	1 (7.7)	0.173
Levofloxacin	4 (2.4)	7 (5.0)	0.356	1 (2.2)	5 (6.2)	0.420	2 (2.4)	0	>0.999
Moxifloxacin	24 (14.6)	30 (21.6)	0.133	11 (24.4)	21 (25.9)	>0.999	12 (14.6)	1 (7.7)	0.687
Tetracycline									
Doxycycline	6 (3.7)	14 (10.1)	0.035	6 (13.3)	13 (16.0)	0.798	0	0	
Tigecycline	2 (1.2)	6 (4.3)	0.146	0	0		1 (1.2)	1 (7.7)	0.224
Minocycline	9 (5.5)	3 (2.2)	0.236	3 (6.7)	1 (1.2)	0.130	1 (1.2)	0	>0.999
Ethambutol	17 (10.4)	39 (28.1)	<0.001	7 (15.6)	22 (27.2)	0.189	1 (1.2)	2 (15.4)	0.048
Rifampicin	13 (7.9)	18 (12.9)	0.182	5 (11.1)	6 (7.4)	0.520	1 (1.2)	1 (7.7)	0.256
Linezolid	5 (3.0)	3 (2.2)	0.732	2 (4.4)	2 (2.5)	0.619	0	0	
Duration of treatment months[++]									
Total treatment	23.4 (15.3–27.8)	38.1 (20.0–83.1)	<0.001	24.1 (18.1–31.6)	36.0 (20.0–57.0)	0.044	18.5 (14.9–24.0)	21.4 (2.7–33.1)	0.971
Use of parenteral drug(s)	1.0 (0.5–4.0)	2.0 (1.0–8.0)	<0.001	1.0 (1.0–4.0)	1.0 (1.0–2.2)	0.485	1.0 (0.5–1.0)	1.4 (0.5–8.0)	0.082
Surgical resection[§§]	26 (17.0)	26 (25.5)	0.114	7 (17.1)	15 (25.9)	0.337	5 (6.1)	2 (25.0)	0.119

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. *M. abscessus*: *Mycobacterium abscessus*. [#]: n=303; [¶]: n=126; [+]: n=95; [§]: including patients who used clarithromycin first, then changed to use azithromycin; [f]: including patients who used azithromycin first, then changed to use clarithromycin; [##]: including patients who used cefoxitin first, then changed to use imipenem; [¶¶]: including patients who used imipenem first, then changed to use cefoxitin; [++]: information on treatment duration was not available in 18 patients; [§§]: information on surgical resection was not available in 48 patients.

Effect of individual drugs on symptomatic improvement

Among the 303 patients with MAB-PD, parenteral amikacin was associated with symptomatic improvement (aOR 2.95, 95% CI 1.26–6.91). For patients with *M. abscessus* subsp. *abscessus*, the use of azithromycin (aOR 4.58, 95% CI 1.48–14.2) or amikacin (aOR 19.5, 95% CI 2.01–189.7) was related to symptomatic improvement, while the use of clarithromycin (aOR 0.20, 95% CI 0.07–0.62) was not. For

TABLE 4 Association of individual drugs with treatment success

	Total[#]		*M. abscessus* subsp. *abscessus* pulmonary disease[¶]		*M. abscessus* subsp. *massiliense* pulmonary disease[+]	
	Adjusted OR[§] (95% CI)	p-value	Adjusted OR[§] (95% CI)	p-value	Adjusted OR[§] (95% CI)	p-value
Clarithromycin	0.81 (0.47–1.40)	0.438	0.33 (0.13–0.84)	0.020	3.85 (0.50–29.6)	0.190
Azithromycin	1.61 (0.93–2.78)	0.085	3.29 (1.26–8.62)	0.016	0.23 (0.02–2.42)	0.226
Cefoxitin	0.61 (0.35–1.07)	0.080	1.22 (0.53–2.86)	0.640	0.39 (0.04–4.12)	0.429
Imipenem	2.65 (1.36–5.10)	0.005	7.96 (1.52–41.6)	0.018	10.2 (0.08–1364.6)	0.353
Amikacin	2.03 (0.74–4.11)	0.181	1.44 (1.05–1.99)	0.020	0.38 (0.01–53.1)	0.698
Fluoroquinolone	0.62 (0.36–1.01)	0.076	1.24 (0.46–3.33)	0.680	3.12 (0.27–35.9)	0.362
Ethambutol	0.48 (0.23–1.02)	0.060	0.54 (0.15–1.96)	0.355	0.62 (0.01–556.3)	0.890
Rifampicin	0.70 (0.29–1.70)	0.425	1.21 (0.16–9.35)	0.904	0.67 (0.01–788.6)	0.912

[#]: n=303; [¶]: n=126; [+]: n=95; [§]: adjusted for age, sex, body mass index, initial radiographic finding and presence of respiratory comorbidity.

patients with *M. abscessus* subsp. *massiliense*, amikacin was associated with symptomatic improvement (aOR 31.7, 95% CI 3.70–271.6) (supplementary table E8).

Effect of individual drugs on radiographic improvement

For patients with MAB-PD overall, none of the individual drugs was related to radiographic improvement. However, the use of azithromycin (aOR 5.66, 95% CI 1.86–17.2) rather than clarithromycin (aOR 0.16, 95% CI 0.06–0.49) was related to the radiographic response for *M. abscessus* subsp. *abscessus*. Among patients with *M. abscessus* subsp. *massiliense*, no drugs showed significant correlation to radiographic improvement (supplementary table E9).

Discussion

We analysed treatment outcomes for MAB-PD and the predictors thereof based on the individual data of 303 patients from seven institutions across six countries. The two main findings of this analysis were: 1) the overall treatment outcomes for MAB-PD, irrespective of subspecies, were unsatisfactory, and 2) the use of azithromycin, amikacin and imipenem was associated with better treatment outcomes among patients with *M. abscessus* subsp. *abscessus* pulmonary disease. Previous studies have also reported poor treatment outcomes for MAB-PD, especially for *M. abscessus* subsp. *abscessus* [18, 19, 45]. According to a recent meta-analysis, the rates of sputum culture conversion were 54% for MAB-PD altogether, 35% for *M. abscessus* subsp. *abscessus* and 79% for *M. abscessus* subsp. *massiliense* [18]. Our study showed similar findings to these reports: the overall treatment success rate of MAB-PD was 45.6%. Specifically, 33.0% of patients with *M. abscessus* subsp. *abscessus* and 56.7% with *M. abscessus* subsp. *massiliense* achieved treatment success. Longer treatment duration in patients with MAB-PD, as well as patients with *M. abscessus* subsp. *abscessus* in whom treatments failed, might reflect the difficulties of treatment.

Which macrolide (clarithromycin or azithromycin) is better for the treatment of MAB-PD has not yet been proven and the results of *in vitro* studies on this issue have been mixed; these mixed results apply both to efficacy and to the differential ability to induce *erm*(41)-mediated macrolide resistance [38, 39]. One study that was included in the present meta-analysis reported a higher treatment success rate with azithromycin than clarithromycin for patients with MAB-PD [44]. This finding also emerged in our study. The use of azithromycin, rather than clarithromycin, was associated with better outcomes in terms of treatment success as well as the symptomatic and radiographic improvement of patients with *M. abscessus* subsp. *abscessus*.

Most clinical isolates of *M. abscessus* are susceptible to amikacin [46, 47]. In addition, imipenem has the highest *in vitro* activity among the carbapenems [48] and is preferred over meropenem or ertapenem for the treatment of MAB-PD [10]. In our analysis, the use of amikacin (aOR 1.44, 95% CI 1.05–1.99) or imipenem (aOR 7.96, 95% CI 1.52–41.6), but not cefoxitin (aOR 1.22, 95% CI 0.53–2.86), was associated with treatment success among patients with *M. abscessus* subsp. *abscessus*. The importance of the β-lactam antibiotics is supported by hollow fibre model simulations, which applied cefoxitin because imipenem is too unstable, in which the β-lactam antibiotic proved to be the main driver of the efficacy of the cefoxitin–amikacin–clarithromycin regimen [49]. The lower effectiveness of cefoxitin in clinical practice can be explained in two ways. First, cefoxitin has lower bactericidal and intracellular activity towards *M. abscessus* subsp. *abscessus* than imipenem [50]. Second, cefoxitin frequently causes adverse drug events, including leukopenia, thrombocytopenia or drug-induced hepatotoxicity. According to a previous report, 60% of patients cannot tolerate cefoxitin because of these adverse events [51]. Given the ineffectiveness observed in the current study, frequent adverse events and unavailability of the drug in some regions [11, 33], the use of imipenem rather than cefoxitin for the treatment of MAB-PD may be a reasonable approach.

As it is difficult to achieve long-term sputum culture conversion for MAB-PD, radiographic or symptomatic improvements are suggested as alternative goals of treatment [10]. Quality of life after treatment has also been suggested as a treatment measure [52]. In our study, treatment outcomes in terms of radiographic and symptomatic improvement were included in the analysis. Again, the use of azithromycin rather than clarithromycin was associated with radiographic and symptomatic improvement in *M. abscessus* subsp. *abscessus* pulmonary disease, although the two macrolides were comparable in *M. abscessus* subsp. *massiliense* pulmonary disease.

While azithromycin, amikacin and imipenem were associated with better treatment outcomes in *M. abscessus* subsp. *abscessus* pulmonary disease in our study, only amikacin was associated with improvement in symptoms of patients with *M. abscessus* subsp. *massiliense*. As most *M. abscessus* subsp. *massiliense* has intrinsic susceptibility towards clarithromycin [12], treatment outcomes of patients with *M. abscessus* subsp. *massiliense* are better than those with *M. abscessus* subsp. *abscessus* when using this drug [42, 44]. In our study, treatment success rates for *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* pulmonary disease were 27.2% and 57.2%, respectively, after the exclusion of studies

including MAB-PD patients without subspeciation. The higher success rate of *M. abscessus* subsp. *massiliense* pulmonary disease treatment in general may have otherwise masked the superiority of azithromycin over clarithromycin and the effectiveness of imipenem and amikacin.

Our study has several limitations. First, drug susceptibility test results were not available from some institutions and the impact of constitutive clarithromycin resistance could not be adjusted for in the analysis [13]. Second, individual patient data from only eight out of the 14 eligible studies could be obtained. This could limit the generalisability of our results. Third, the asymmetry of the funnel plot and the result of the Egger test suggested the possibility of publication bias, although the Egger test provided a nonsignificant p-value. Fourth, multiple comparisons resulting from the analysis of subspecies and a diverse range of drugs might lead to the risk of type I errors [53]. Fifth, the role of newly adopted drugs, such as tigecycline or the inhaled amikacin, could not be elucidated in our analysis because the numbers of patients using these drugs were too small. Finally, the causality between some drugs and outcomes may not have been fully elucidated because salvage regimens might be associated with poor outcomes regardless of their effectiveness. Despite these limitations, this study has several strengths. This is the first individual patient data meta-analysis of not only patients with MAB-PD but of patients across the whole NTM pulmonary disease spectrum. With the data of individual patients, we were able to evaluate treatment outcomes and the impact of each drug more accurately.

In conclusion, treatment outcomes for MAB-PD are unsatisfactory. For patients with *M. abscessus* subsp. *abscessus*, the use of azithromycin, imipenem and amikacin was associated with better treatment outcomes. For patients with *M. abscessus* subsp. *massiliense*, the choice among these drugs was not related to treatment outcomes. These findings may prove helpful to clinicians in the design of treatment regimens for patients with MAB-PD.

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