ERJ Express. Published on March 17, 2019 as doi: 10.1183/13993003.01991-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

ORIGINAL ARTICLE

Mycobacterium abscessus pulmonary disease: individual patient data meta-analysis

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Please cite this article as: Kwak N, Dalcolmo MP, Daley CL, *et al*. *Mycobacterium abscessus* pulmonary disease: individual patient data meta-analysis. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.01991-2018).

Mycobacterium abscessus pulmonary disease: individual patient data meta-analysis

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Authors' contribution

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, were fully responsible for all content, and were involved at all stages of manuscript development. Study conception and design: N.K and J-J.Y; Data collection: N.K, M.P.D, C.L.D, G.E, R.G, N.H, B.W.J, W-J.K, H.N, J.P, J.I, S.M.Z and J-J.Y; and Data Interpretation: N.K, M.P.D, C.L.D, G.E, R.G, N.H, B.W.J, W-J.K, H.N, J.P, J.I, S.M.Z and J-J.Y.

Financial Grants

This work was supported by the Seoul National University College of Medicine Research Fund (grant number 2320170050).

Running head

Outcomes for *M. abscessus* pulmonary disease

Take home message

For *M. abscessus* pulmonary disease in general, imipenem use was shown to be associated with improved outcome. For *M. abscessus* subspecies *abscessus*, the use of either azithromycin, amikacin, or imipenem increased the likelihood of treatment success.

Abstract

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

We conducted an individual patient data meta-analysis based on studies reporting treatment outcomes for MAB-PD to clarify the 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* subspecies *abscessus* and 56.7% for *M. abscessus* subspecies *massiliense*. For MAB-PD overall, the use of imipenem was associated with treatment success (adjusted odds ratio [aOR], 2.65; 95% confidence interval [CI], 1.36–5.10). For patients with *M. abscessus* subspecies *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* subspecies *massiliense*, the choice among these drugs was not associated with the 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* subspecies *abscessus*.

Keywords: *Mycobacterium abscessus*; *Mycobacterium abscessus* subspecies *massiliense*; azithromycin; amikacin; imipenem

Introduction

The incidence and prevalence of pulmonary disease caused by non-tuberculous mycobacteria (NTM) are increasing globally[1-4]. *Mycobacterium abscessus* (MAB), comprising *M. abscessus* subspecies (subsp.) *abscessus*, *M. abscessus* subsp. *massiliense*, and *M. abscessus* subsp. *bolletii*, is the second most common NTM causing pulmonary disease, following the *M. avium* complex in East Asia and the United States[2, 5-8].

Treatment for MAB pulmonary disease (MAB-PD) is challenging because of the high frequency of mutational and acquired resistance to commonly used antibiotics[9]. Though macrolides are recommended as a cornerstone of chemotherapy[10, 11], mutations in the *rrl* gene of MAB, which encodes 23S rRNA, leads 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* harbors a mutation in the *erm*(41) gene which renders it non-functional, 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 nebulized 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 meta-analysis based on individual patient data to clarify the 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 Preferred Reporting Items for a Systematic review and Meta-analysis of Individual Participant Data statement[20]. The study protocol was registered with the PROSPERO database (CRD42017070348). The exemption from ethical approval was confirmed by the Seoul National University Hospital Institutional Review Board (1707-007-864).

Search strategy and selection criteria

We conducted a literature search of the Medline, Embase, and Cochrane databases using

Medical Subject Heading terms and text words associated with MAB-PD and its treatment. The search query was [(*Mycobacterium abscessus*) OR (*Mycobacterium massiliense*) OR (*Mycobacterium bolletii*)] AND [(Treat*) OR (Therapy)]. The literature search was restricted to articles published between 1 January 1987 and 31 July 2017. The abstracts were independently reviewed by two investigators (N.K and J.P). Randomized controlled studies and observational studies reporting the 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 ATS/IDSA or BTS[10, 11], who underwent chemotherapy, and for whom the microbiological and clinical outcomes were reported. We excluded studies with case reports, with patients < 15 years old, and 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 ≥ 3 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 summarized 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 (CIs) for each proportion were obtained with the DerSimonian and Laird random-effects model[25]. I^2 statistics[26] were used to estimate heterogeneity across the studies. 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 funnel plot and Egger test[28].

Because 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% CIs 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 1,600 records with our keyword-directed literature search and the titles and abstracts of 1,529 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 kappa for inter-rater agreement; 0.76). The data could not be obtained from six studies[17, 32-36] owing to inaccessibility to the data from four studies, the refusal from one study, and the 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 United States[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 institution and the data from these studies were merged into a combined dataset. Requested and retrieved items from the authors are described in Table E1 in the online data supplement. The updated data was 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] (Table E2). The characteristics of the excluded studies are described in 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 ITS region[40] or *hsp*65 PCR restriction enzyme analysis[37].

The median age of the patients was 59 years, 78.6% were female, 141 patients (46.5%) had a previous treatment history for NTM or TB, and 12 patients (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. *abscessus* (63.5%, P=0.023; Table 2). Detailed characteristics of the included patients are provided in 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 patients where sub-speciation 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 treatment failure group than in success group (P < 0.001 and 0.044, respectively). Duration of parenteral drug(s) use was also longer in 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* (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) (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) patients with *M. abscessus* subsp. *abscessus* and 70.5% (95% CI, 33.6–98.0) patients with *M. abscessus* subsp. *massiliense* (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) (Table E6).

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

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 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 (Figure E3) while 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 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 a 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 the treatment outcomes did not show significant correlation (Table 4).

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 patients with *M. abscessus* subsp. *massiliense*, amikacin was associated with symptomatic improvement (aOR, 31.7; 95% CI, 3.70–271.6) (Tables 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 (Table E9).

Discussion

We analyzed the treatment outcomes for MAB-PD and the predictors thereof based on the individual data of 303 patients from seven institutions across six countries. Two main findings of this analysis were: First, the overall treatment outcomes for MAB-PD, irrespective of subspecies, were unsatisfactory. Secondly, 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 with 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 were 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 their 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 MAB 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 fiber 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 lesser 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, 52], the use of imipenem rather than cefoxitin for the treatment of MAB-PD may be a reasonable approach.

Because 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[53]. 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 in *M. abscessus* subsp. *massiliense* pulmonary disease, the two macrolides were comparable.

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 sub-speciation. 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 fourteen eligible studies could be obtained. This could limit the generalizability of our results. Third, the asymmetry of funnel plot and the result of the Egger test suggested the possibility of publication bias, although the Egger test provided a non-significant 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 [54]. 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-PD spectrum. With the data of individual patients, we were able to evaluate the treatment outcomes and 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 the treatment outcomes. These findings may prove helpful to clinicians in the design of treatment regimens for patients with MAB-PD.

Acknowledgments

This work was supported by the Seoul National University College of Medicine Research Fund (grant number 2320170050).

Conflicts of Interest

Charles L. Daley reports grants and personal fees from Insmed, personal fees from Horizon, personal fees from Spero, personal fees from Johnson and Johnson, outside the submitted work. Naoki Hasegawa reports grants and personal fees from Insmed Incorporated, during the conduct of the study; grants from Nikon Corporation, grants from Taisho-Toyama Pharmaceutical Co., Ltd., grants from Eisai Co.,Ltd., grants from Daiichi Sankyo Co.,Ltd., grants from MSD K.K. a subsidiary of Merck & Co.Inc., grants from Sumitomo Dainippon Pharma Co.,Ltd., grants from Pfizer Inc., grants from Astellas Pharma Inc., grants from Cepheid Inc.Ð grants from Presision System Science Co., Ltd., grants from Medical &

Biological Laboatories Co., Ltd., outside the submitted work. Won-Jung Koh reports personal fees from Insmed Inc., outside the submitted work. Rachel Thomson reports personal fees from INSMED, personal fees from SAVARA, personal fees from MENARINI, personal fees from ASTRA ZENECA, outside the submitted work. Jakko van Ingen reports personal fees from Insmed, Johnson and Johnson and Spero outside the submitted work. Sanne M.H. Zweijpfenning reports personal fees and non-financial support from insmed and novartis outside the submitted work.

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Table 1. Characteristics of 8 studies included for the analysis

	Study design	Study period	Region	Sample size	Clinical setting	Type of drug regimen
de Mello *et al.* [37]	Retrospective, cohort	1993-2011	Brazil	26	Single center	Individualized
Ellender *et al.* [38]	Retrospective, cohort	2002-2012	Australia	13	Single center	Individualized
Jarand *et al.* [39]	Retrospective, cohort	2001-2004	United States	69	Single center	Individualized
Koh *et al.* 2016 [42]	Prospective, cohort	2007-2012	South Korea	71	Single center	Standardized and individualized
Koh *et al.* 2017 [43]	Prospective, cohort	2002-2012	South Korea	67	Single center	Standardized and individualized
Namkoong *et al.* [40]	Retrospective, cohort	2004-2013	Japan	13	Multicenter	Individualized
Park *et al.*[44]	Retrospective, cohort	2006-2015	South Korea	36	Single center	Individualized
van Ingen *et al.* [41]	Retrospective cohort	1999-2005	Netherland	8	Single center	Individualized

Table 2. Baseline characteristics of 303 patients included for the analysis

	Total[*] (n=303)	*M. abscessus* subsp. *abscessus* pulmonary disease (n=126)	*M. abscessus* subsp. *massiliense* pulmonary disease (n=95)	P-value[†]
Age, years, median[IQR]	59 [51-66]	59.5 [50-66]	57 [52-64]	0.817[‡]
Sex, female, n (%)	238 (78.6)	91 (72.2)	79 (83.2)	0.076[§]
Body mass index, kg/m^2, median [IQR]	20.5 [18.8-22.0]	20.0 [18.2-21.9]	20.6 [18.8-21.8]	0.385[‡]
Current or previous smoker, n (%)	60 (19.8)	20 (15.9)	11 (11.6)	0.434[§]
Presence of respiratory comorbidities, n (%)				
Previous history of treatment for NTM/TB	141 (46.5)	79 (62.7)	49 (51.6)	0.092[§]
Chronic obstructive pulmonary disease	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, n (%)				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)	

Abbreviation: subsp., subspecies; IQR, Interquartile range; NTM, Nontuberculous mycobacterium; TB, tuberculosis

[*]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 and [§] Fisher's exact test were used.

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.

Table 3. Comparison of treatment modalities between treatment success and treatment failure group

	Total (n=303)			*M. abscessus* subsp. *abscessus* pulmonary disease (n=126)			*M. abscessus* subsp. *massiliense* pulmonary disease (n=95)		
	Success (n=164)	Failure (n=139)	P-value	Success (n=45)	Failure (n=81)	P-value	Success (n=82)	Failure (n=13)	P-value
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†	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, median [IQR]¶									

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

Abbreviation: subsp., subspecies; IQR, Interquartile range.

[*]Including patient who used clarithromycin first, then changed to use azithromycin.

[†]Including patient who used azithromycin first, then changed to use clarithromycin.

[‡]Including patient who used cefoxitin first, then changed to use imipenem.[§] Including patient 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.

Table 4. Association of individual drugs with treatment success

	Total (n=303)			*M. abscessus* subsp. *abscessus* pulmonary disease (n=126)			*M. abscessus* subsp. *massiliense* pulmonary disease (n=95)		
	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

Abbreviation: subsp., subspecies; OR, odds ratio.

*Adjusted for age, sex, body mass index, initial radiographic finding, and presence of respiratory comorbidity

Figure legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for Individual Patient Data (IPD) flow diagram.

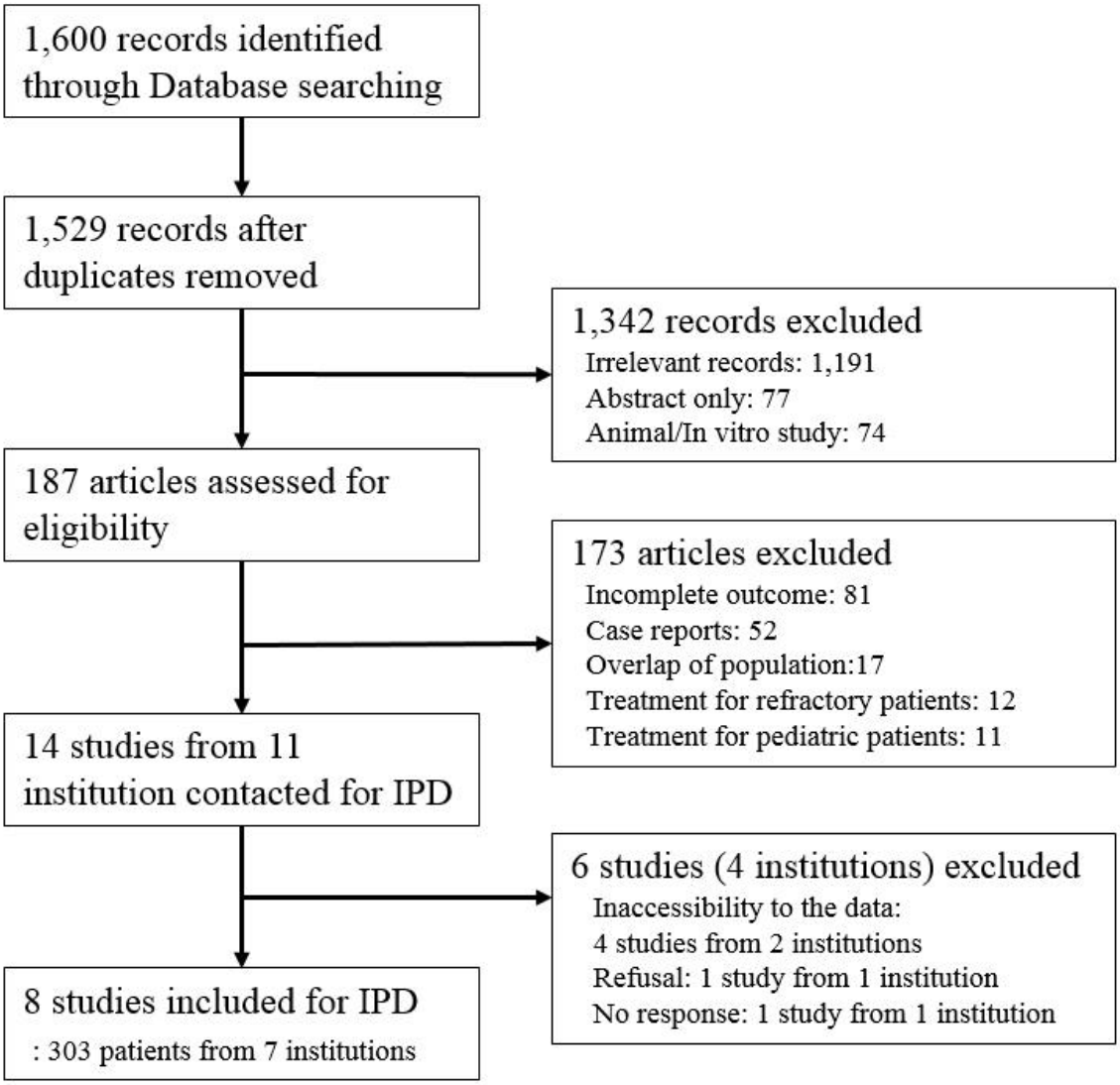
Figure 2. Weighted proportion of treatment success for selected studies.

(A) *Mycobacterium abscessus* (B) *Mycobacterium abscessus* subspecies *abscessus* (C) *Mycobacterium abscessus* subspecies *massiliense.* Abbreviation: CI, confidence interval.

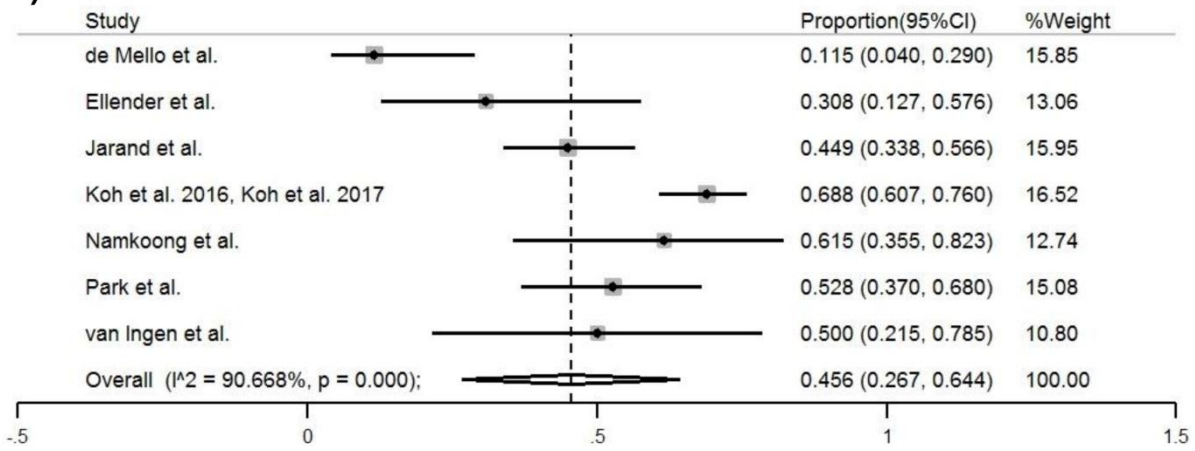
Figure E1. Weighted proportion of symptomatic improvement after treatment for selected studies. (A) *Mycobacterium abscessus* (B) *Mycobacterium abscessus* subspecies *abscessus* (C) *Mycobacterium abscessus* subspecies *massiliense.* Abbreviation: CI, confidence interval.

Figure E2. Weighted proportion of radiographic improvement after treatment for selected studies. (A) *Mycobacterium abscessus* (B) *Mycobacterium abscessus* subspecies *abscessus* (C) *Mycobacterium abscessus* subspecies *massiliense.* Abbreviation: CI, confidence interval.

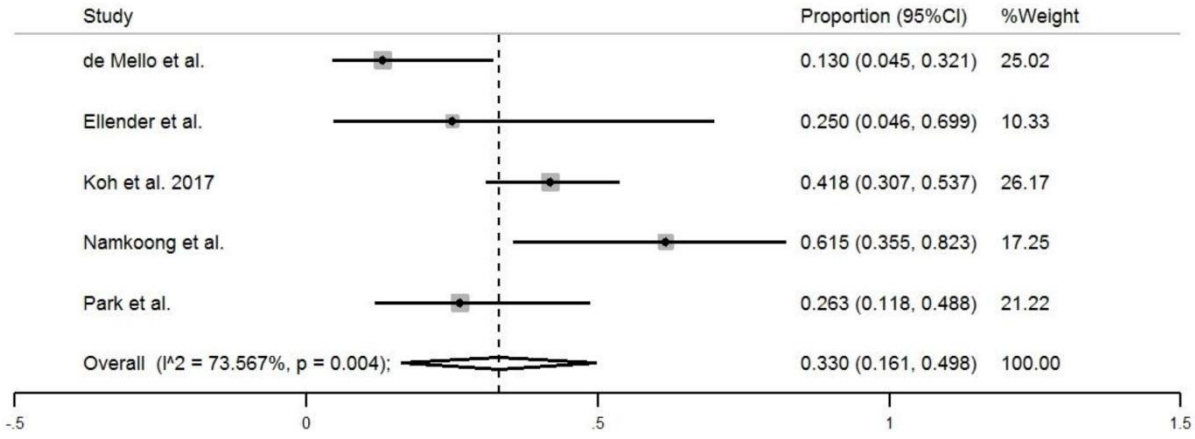
Figure E3. Funnel plot assessing symmetry of effect estimates for included studies.


1,600 records identified through Database searching
1,529 records after duplicates removed
1,342 records excluded
Irrelevant records: 1,191
Abstract only: 77
Animal/In vitro study: 74
187 articles assessed for eligibility
173 articles excluded
Incomplete outcome: 81
Case reports: 52
Overlap of population:17
Treatment for refractory patients: 12
Treatment for pediatric patients: 11
14 studies from 11 institution contacted for IPD
6 studies (4 institutions) excluded
Inaccessibility to the data:
4 studies from 2 institutions
Refusal: 1 study from 1 institution
No response: 1 study from 1 institution
8 studies included for IPD
: 303 patients from 7 institutions

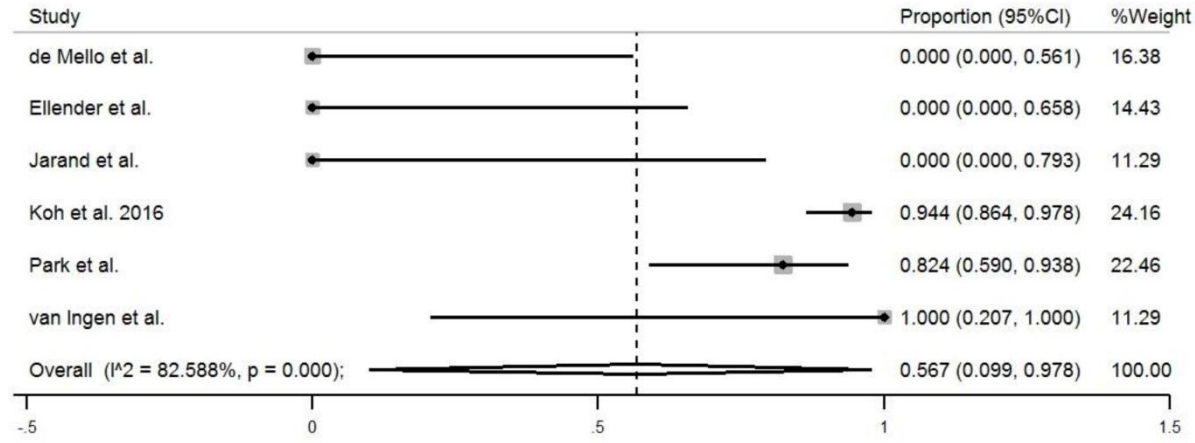
a)


Study
Proportion(95%CI)
%Weight
de Mello et al.
0.115 (0.040, 0.290)
15.85
Ellender et al.
0.308 (0.127, 0.576)
13.06
Jarand et al.
0.449 (0.338, 0.566)
15.95
Koh et al. 2016, Koh et al. 2017
0.688 (0.607, 0.760)
16.52
Namkoong et al.
0.615 (0.355, 0.823)
12.74
Park et al.
0.528 (0.370, 0.680)
15.08
van Ingen et al.
0.500 (0.215, 0.785)
10.80
Overall (I^2 = 90.668%, p = 0.000);
0.456 (0.267, 0.644)
100.00
-.5
0
.5
1
1.5

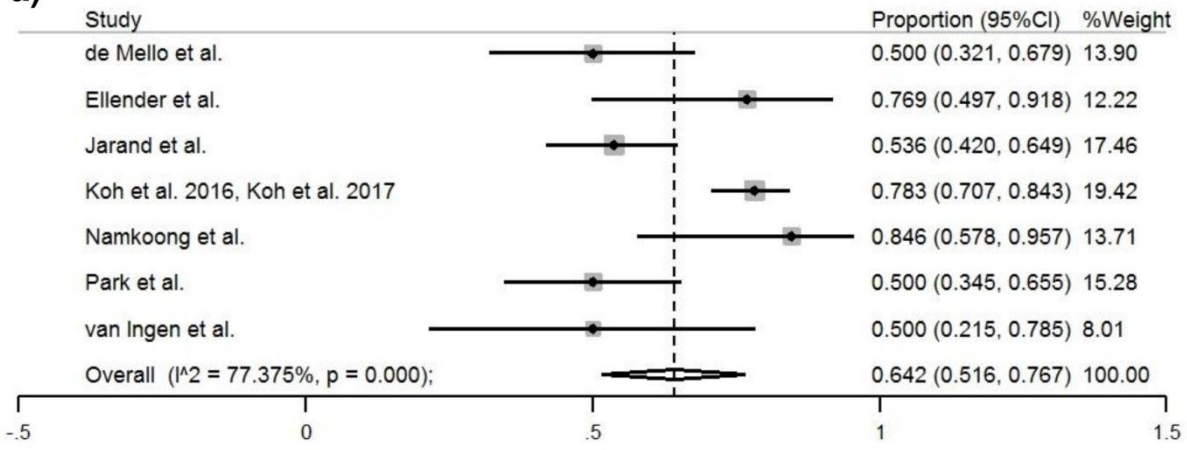
b)


Study
Proportion (95%CI)
%Weight
de Mello et al.
0.130 (0.045, 0.321)
25.02
Ellender et al.
0.250 (0.046, 0.699)
10.33
Koh et al. 2017
0.418 (0.307, 0.537)
26.17
Namkoong et al.
0.615 (0.355, 0.823)
17.25
Park et al.
0.263 (0.118, 0.488)
21.22
Overall (I^2 = 73.567%, p = 0.004);
0.330 (0.161, 0.498)
100.00
-.5
0
.5
1
1.5

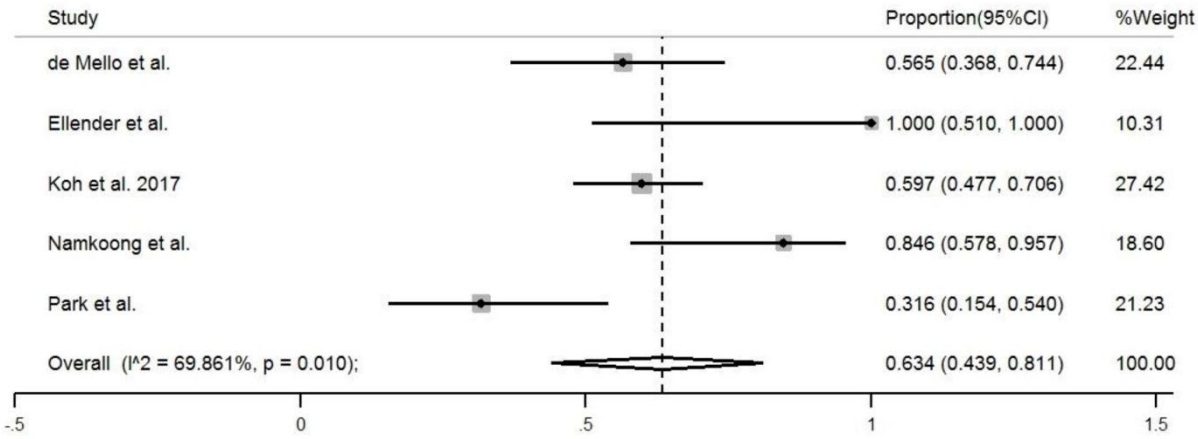
c)


Study
Proportion (95%CI)
%Weight
de Mello et al.
0.000 (0.000, 0.561)
16.38
Ellender et al.
0.000 (0.000, 0.658)
14.43
Jarand et al.
0.000 (0.000, 0.793)
11.29
Koh et al. 2016
0.944 (0.864, 0.978)
24.16
Park et al.
0.824 (0.590, 0.938)
22.46
van Ingen et al.
1.000 (0.207, 1.000)
11.29
Overall (I^2 = 82.588%, p = 0.000);
0.567 (0.099, 0.978)
100.00
-.5
0
.5
1
1.5

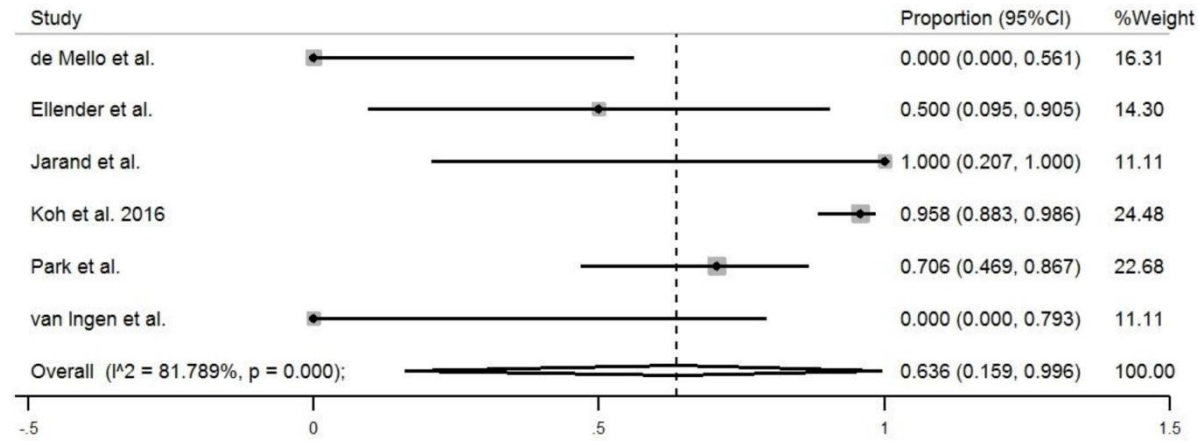
a)


Study
Proportion (95%CI)
%Weight
de Mello et al.
0.500 (0.321, 0.679) 13.90
Ellender et al.
0.769 (0.497, 0.918) 12.22
Jarand et al.
0.536 (0.420, 0.649) 17.46
Koh et al. 2016, Koh et al. 2017
0.783 (0.707, 0.843) 19.42
Namkoong et al.
0.846 (0.578, 0.957) 13.71
Park et al.
0.500 (0.345, 0.655) 15.28
van Ingen et al.
0.500 (0.215, 0.785) 8.01
Overall (I^2 = 77.375%, p = 0.000);
0.642 (0.516, 0.767) 100.00
-.5
0
.5
1
1.5

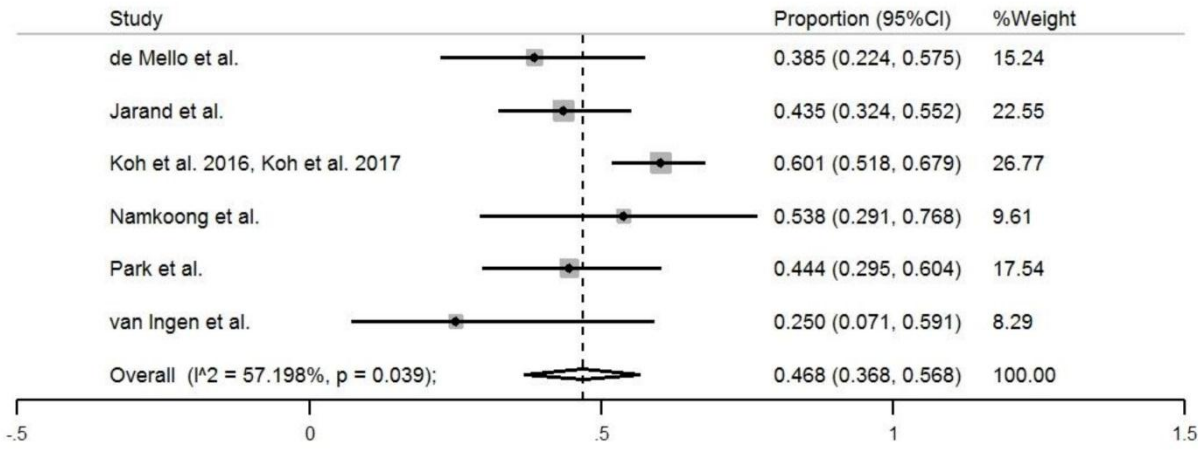
b)


Study
Proportion(95%CI)
%Weight
de Mello et al.
0.565 (0.368, 0.744)
22.44
Ellender et al.
1.000 (0.510, 1.000)
10.31
Koh et al. 2017
0.597 (0.477, 0.706)
27.42
Namkoong et al.
0.846 (0.578, 0.957)
18.60
Park et al.
0.316 (0.154, 0.540)
21.23
Overall (I^2 = 69.861%, p = 0.010);
0.634 (0.439, 0.811)
100.00
-.5
0
.5
1
1.5

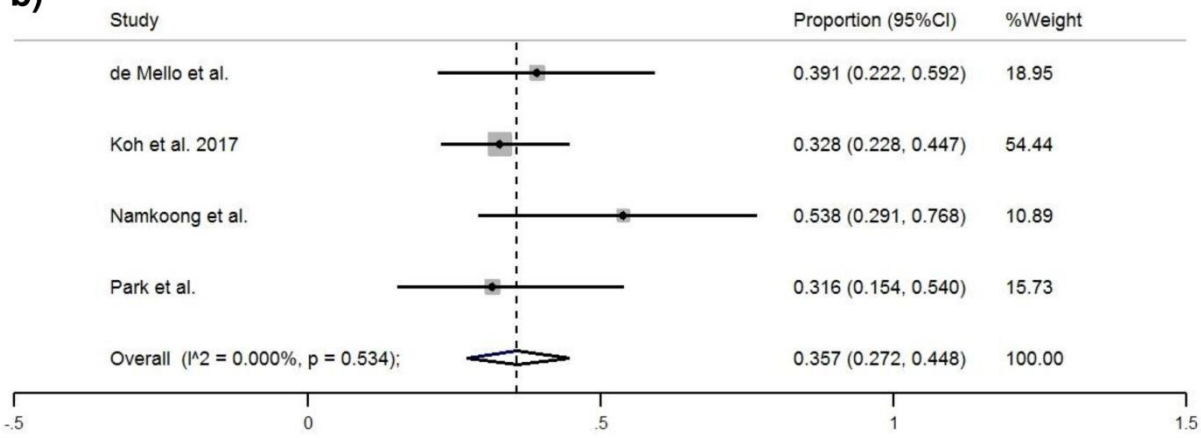
c)


Study
Proportion (95%CI)
%Weight
de Mello et al.
0.000 (0.000, 0.561)
16.31
Ellender et al.
0.500 (0.095, 0.905)
14.30
Jarand et al.
1.000 (0.207, 1.000)
11.11
Koh et al. 2016
0.958 (0.883, 0.986)
24.48
Park et al.
0.706 (0.469, 0.867)
22.68
van Ingen et al.
0.000 (0.000, 0.793)
11.11
Overall (I^2 = 81.789%, p = 0.000);
0.636 (0.159, 0.996)
100.00
-.5
0
.5
1
1.5

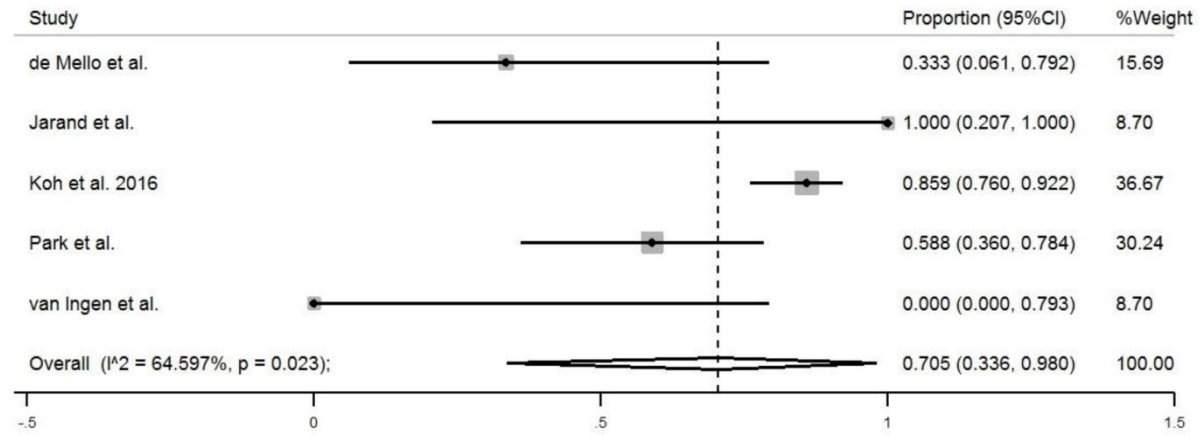
a)


Study
Proportion (95%CI)
%Weight
de Mello et al.
0.385 (0.224, 0.575)
15.24
Jarand et al.
0.435 (0.324, 0.552)
22.55
Koh et al. 2016, Koh et al. 2017
0.601 (0.518, 0.679)
26.77
Namkoong et al.
0.538 (0.291, 0.768)
9.61
Park et al.
0.444 (0.295, 0.604)
17.54
van Ingen et al.
0.250 (0.071, 0.591)
8.29
Overall (I^2 = 57.198%, p = 0.039);
0.468 (0.368, 0.568)
100.00
-.5
0
.5
1
1.5

b)


Study
Proportion (95%CI)
%Weight
de Mello et al.
0.391 (0.222, 0.592)
18.95
Koh et al. 2017
0.328 (0.228, 0.447)
54.44
Namkoong et al.
0.538 (0.291, 0.768)
10.89
Park et al.
0.316 (0.154, 0.540)
15.73
Overall (I^2 = 0.000%, p = 0.534);
0.357 (0.272, 0.448)
100.00
-.5
0
.5
1
1.5

c)


Study
Proportion (95%CI)
%Weight
de Mello et al.
0.333 (0.061, 0.792)
15.69
Jarand et al.
1.000 (0.207, 1.000)
8.70
Koh et al. 2016
0.859 (0.760, 0.922)
36.67
Park et al.
0.588 (0.360, 0.784)
30.24
van Ingen et al.
0.000 (0.000, 0.793)
8.70
Overall (I^2 = 64.597%, p = 0.023);
0.705 (0.336, 0.980)
100.00
-.5
0
.5
1
1.5

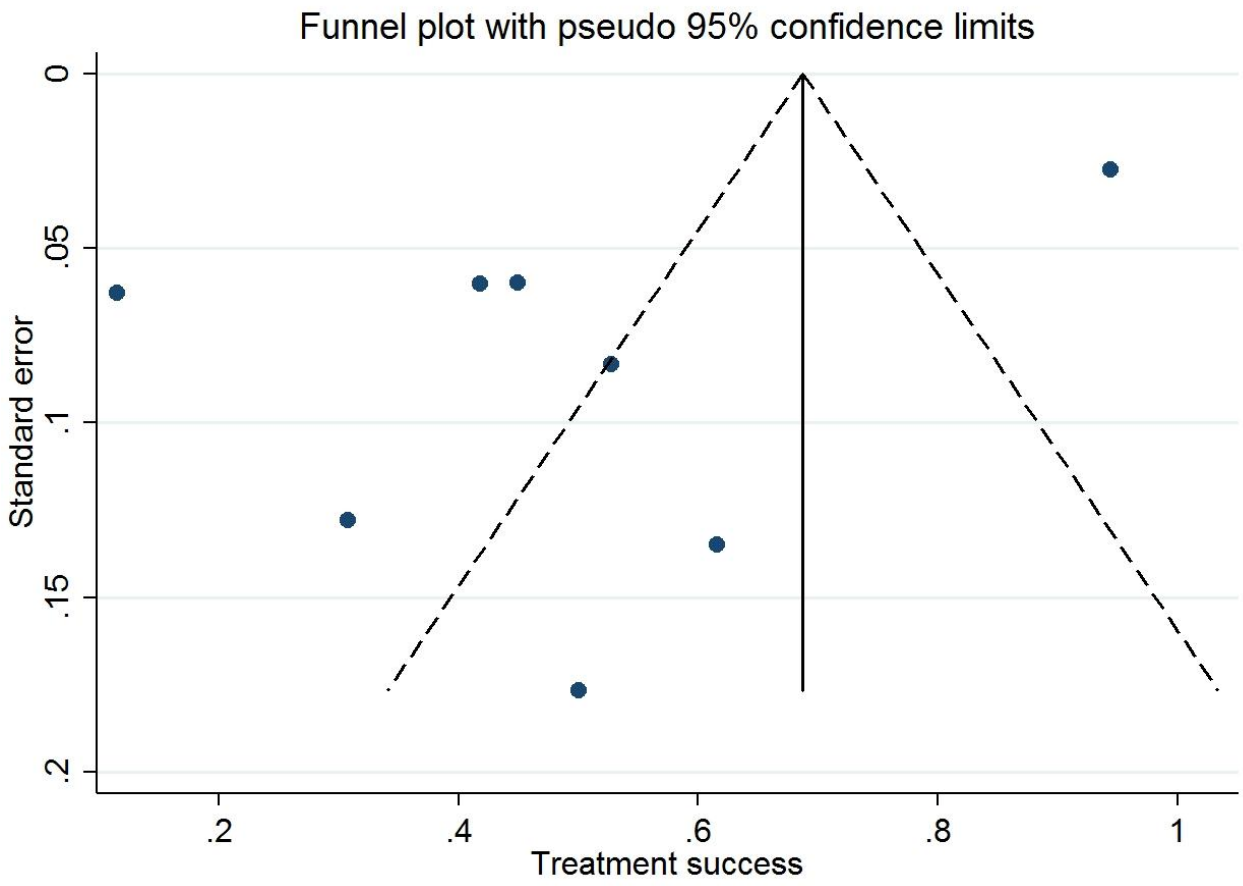

Funnel plot with pseudo 95% confidence limits
Standard error
0
.05
.1
.15
.2
.2
.4
.6
.8
1
Treatment success

Table E1. Requested to and retrieved items from contact authors

	de Mello *et al.*(37)	Ellender *et al.*(38)	Jarand *et al.*(39)	Koh *et al.* 2016(42)	Koh *et al.* 2017(43)	Namkoong *et al.*(40)	Park *et al.*(44)	van Ingen *et al.* (41)
Demography								
Age	*	*	*	*	*	*	*	*
Sex	*	*	*	*	*	*	*	*
Body mass index	-	*	*	*	*	*	*	*
Smoking status	*	-	*	*	*	*	*	*
Medical history								
Previous history of treatment for NTM/TB	*	-	*	*	*	*	*	*
Chronic obstructive pulmonary disease	*	*	*	*	*	*	*	*
Asthma	*	-	*	*	*	*	*	*
Cystic fibrosis	*	*	*	*	*	*	*	-
Bronchiectasis	*	*	*	*	*	*	*	*
Malignancy	*	-	*	*	*	*	*	*
Chronic kidney disease	*	-	*	*	*	*	*	-
Chronic liver disease	*	-	*	*	*	*	*	-
Diabetes mellitus	*	-	*	*	*	*	*	*
HIV infection	*	-	*	*	*	*	*	*
Immune-suppressive agent or steroid use	*	-	*	*	*	*	*	*
AFB smear and culture								
AFB smear positivity (or quantification)	-	*	-	*	*	*	*	*
Culture sample origin (sputum/bronchial washing/BAL/tissue)	*	*	-	*	*	*	*	*
Drug susceptibility test results (MIC)								
Clarithromycin (day 3, 7, and 14)	-	-	-	*	*	*	*	*
Amikacin	-	-	-	*	*	*	*	*
Cefoxitin	-	-	-	*	*	-	*	*
Ciprofloxacin	-	-	-	*	*	-	*	*
Moxifloxacin	-	-	-	*	*	-	*	*

Imipenem	-	-	-	*	*	-	*	*
Linezolid	-	-	-	*	*	-	*	*
Tigecycline	-	-	-	*	*	-	*	*
Symptoms present prior to treatment								
Hemoptysis	-	*	*	*	*	*	*	*
Cough	-	-	*	*	*	*	*	*
Sputum	-	-	*	*	*	*	*	*
Dyspnea	-	-	*	-	-	*	*	*
Weight loss	-	*	*	*	*	*	*	*
Fever	-	-	*	*	*	*	*	*
Night sweat	-	*	*	-	-	*	*	*
Malaise	-	-	*	-	-	*	*	*
Radiographic features prior to treatment								
Nodular bronchiectatic	*	*	*	*	*	*	*	*
Fibrocavitary	*	*	*	*	*	*	*	*
Indeterminate	*	*	*	*	*	*	*	*
Extent of disease (number of involved lobes or bilateral/unilateral involvement)	*	-	*	-	-	*	*	*
Medical treatment								
Clarithromycin	*	*	*	*	*	*	*	*
Azithromycin	*	*	*	*	*	*	*	*
Amikacin	*	*	*	*	*	*	*	*
Cefoxitin	*	*	*	*	*	*	*	*
Imipenem	*	*	*	*	*	*	*	*
Moxifloxacin or levofloxacin	*	*	*	*	*	*	*	*
Linezolid	-	-	*	*	*	*	*	*
Tigecycline	*	-	*	*	*	*	*	*
Clofazimine	-	*	*	*	*	*	*	*
Other	*	*	*	*	*	*	*	*
Detailed treatment history								
Subspecies identification result	*	*	-	*	*	*	*	*

Time from diagnosis to treatment	-	-	-	-	-	*	*	*
Duration of total treatment	*	*	*	*	*	*	*	*
Duration of intravenous treatment	-	*	*	*	*	*	*	-
Daily or thrice weekly treatment	-	-	-	*	*	*	*	-
Hospitalization (or outpatient setting)	-	-	-	*	*	*	*	-
Surgical resection								
Segmentectomy/lobectomy/pneumonectomy	-	-	*	*	*	*	*	-
Treatment outcomes								
Culture conversion for 12 months while on treatment or till the end of treatment	*	*	*	*	*	*	*	*
AFB smear and culture results at each clinic visit	-	*	*	*	*	*	*	*
Symptom improvement or worsening after treatment	*	*	*	*	*	*	*	*
Radiographic improvement or worsening after treatment	*	-	*	*	*	*	*	*
Death prior to planned treatment completion	*	*	*	*	*	*	*	*
Loss to follow-up or discontinuation prior to planned treatment completion	*	*	*	-	-	*	*	*
Adverse drug reactions								
Allergic reaction or anaphylaxis	-	-	*	*	*	*	*	*
Skin irritation	-	-	*	*	*	*	*	*
Gastro-intestinal disturbance	-	-	*	*	*	*	*	*
Abnormal liver function test	-	-	*	*	*	*	*	*
Acute kidney injury	-	*	*	*	*	*	*	*
Ototoxicity	-	*	*	*	*	*	*	*
Ocular toxicity	-	*	*	*	*	*	*	*
Neuropathy	-	-	*	*	*	*	*	*
Others	-	-	*	-	-	*	*	*
Follow-up after treatment								
Total duration of follow-up after treatment	-	-	*	*	*	-	*	*

Recurrence or relapse during follow-up	-	-	*	*	*	*	*	*
Co-infection with other NTM species while on treatment and during follow-up	-	-	*	-	-	*	*	*

Abbreviation: NTM, nontuberculous mycobacterium; TB, tuberculosis; HIV, human immuno-deficiency virus; AFB, acid-fast bacilli; BAL, bronchial alveolar lavage; MIC, minimal inhibitory concentration

Asterisk and dash mean the presence and absence of the items, respectively

Table E2. Quality assessment of included studies

Study [Ref.]	Selection				Measurement		Outcome			
	Representativ-eness of MAB-PD patients	Ascertainm-ent of treatment regimens	Confirmation of MAB through mycobacterial culture	Risk of bias	Subspecies identification	Risk of bias	Explicit treatment outcome assessment by culture results	Adequate treatment duration (Intention to treat for more than 12 months)	Adequacy of follow-up after treatment	Risk of bias
de Mello *et al.*(37)	*	*	*	low	*	low	*	*	*	low
Ellender *et al.*(38)	*	*	*	low	*	low	*	*	-	medium
Jarand *et al.*(39)	*	*	*	low	-	high	*	*	*	low
Koh *et al.* 2016(42)	*	*	*	low	*	low	*	*	*	low
Koh *et al.* 2017(43)	*	*	*	low	*	low	*	*	*	low
Namkoong *et al.*(40)	-	*	*	medium	*	low	*	*	-	medium
Park *et al.*(44)	*	*	*	low	*	low	*	*	-	medium
van Ingen *et al.* (41)	*	*	*	low	*	low	*	*	*	low

Abbreviation: MAB, *Mycobacterium abscessus*; PD, pulmonary disease.

Asterisk and dash mean the presence and absence of the items, respectively

Table E3. Overview of six studies excluded from the analysis (references are below the table)

Author	Study period (years)	Region	Subspecies identification	Total patients (n)	Definition for treatment outcomes
Jo (32)[*]	1996-2003	South Korea	No	29	Cure was defined as three or more consecutive negative cultures for 12 months while on treatment and completion of treatment for at least 12 months
Lyu, 2011 (17)[*]	2003-2008	South Korea	No	41	Treatment success was defined to satisfy all of the followings: (1) culture conversion, (2) clinical improvement (3) minimum duration of treatment at least 6 months, (4) completion of treatment according to the physician's decision
Harada (33)	1990-2010	Japan	Yes	102	Treatment response was assessed as followings: (1) radiological improvement (2) initial sputum conversion to negativity (3) relapse after sputum conversion
Lyu, 2014 (34)[*]	2006-2012	South Korea	Yes	48	Treatment success was defined to satisfy all of the followings: (1) culture conversion, (2) clinical improvement (3) minimum duration of treatment at least 6 months, (4) completion of treatment according to the physician's decision
Roux (36)[†]	2001-2004	France	Yes	43	Response to treatment was measured in terms of mycobacterial eradication.
Martiniano (35)[‡]	2006-2014	United States	Yes	54	Subjects with culture conversion (defined as having at least 2 consecutive negative cultures) to negative were classified as "responders"

[*]Population overlap between these studies was estimated.

[†]All patients had cystic fibrosis. The vast majority of patients were estimated to be non-adults.

[‡]The patients with refractoriness to previous treatments were included.

Table E4. Detailed characteristics of patients with *M. abscessus* pulmonary disease included in the analysis

	de Mello *et al.*(37)	Ellender *et al.*(38)	Jarand *et al.*(39)	Koh *et al.* 2016(42)	Koh *et al.* 2017(43)	Namkoong *et al.*(40)	Park *et al.*(44)	van Ingen *et al*. (41)
Number of patients	26	13	69	71	67	13	36	8
Age, years, median[IQR]	54 [46-67]	65[59-67]	59 [53-68]	57 [52-64]	57 [48-64]	65 [59-67]	62 [54-68]	59 [51-68]
Sex, female, n (%)	11 (42.3)	12 (92.3)	59 (85.5)	61 (85.9)	52 (77.6)	11 (84.6)	28 (77.8)	4 (50.0)
Body mass index, kg/m^2, median [IQR]	n/a	21.0 [19.0-22.0]	21.0 [20.0-23.0]	20.7 [19.1-21.9]	20.3 [18.5-22.0]	19.1 [17.4-21.0]	18.9 [17.7-21.2]	19.9 [18.3-22.7]
Current or previous smoker, n (%)	7 (26.9)	n/a	24 (34.8)	7 (9.9)	9 (13.4)	2 (15.4)	5 (13.9)	6 (75.0)
Presence of respiratory comorbidities, n (%)	11 (42.3)	9 (69.2)	42 (60.9)	68 (95.8)	64 (95.5)	5 (38.5)	15 (41.7)	7 (87.5)
Radiographic findings, n (%)								
Nodular-bronchiectatic	14 (53.8)	0	42 (60.9)	57 (80.3)	53 (79.1)	3 (23.1)	23 (63.9)	3 (37.5)
Fibro-cavitary	12 (46.2)	2 (15.4)	0	14 (19.7)	11 (16.4)	6 (46.2)	13 (36.1)	5 (62.5)
Indeterminate	0	11 (84.6)	27 (39.1)	0	3 (4.5)	4 (30.7)	0	0
Subspecies identification results								
subspecies *abscessus*	23 (88.5)	4 (30.8)	0	0	67 (100.0)	13 (100.0)	19 (52.8)	0
subspecies *massiliense*	3 (11.5)	2 (15.4)	1 (1.4)	71 (100.0)	0	0	17 (47.2)	1 (12.5)
subspecies *bolletii*	0	1 (7.6)	0	0	0	0	0	0
unidentified	0	6 (46.2)	68 (98.6)	0	0	0	0	7 (87.5)
Specification of medical treatment, n (%)								
Clarithromycin	25 (96.2)	8 (61.5)	16 (23.2)	34 (47.9)	40 (59.7)	13 (100)	8 (22.2)	2 (25.0)
Clarithromycin followed by azithromycin	0	0	8 (11.6)	15 (21.1)	12 (17.9)	0	5 (13.9)	
Azithromycin	0	5 (38.5)	32 (46.4)	21 (29.6)	15 (22.4)	0	21 (58.3)	4 (50.0)
Azithromycin followed by clarithromycin	0	0	1 (1.5)	1 (1.4)	0	0	2 (5.6)	

Intravenous amikacin	18 (69.2)	13 (100.0)	52 (75.4)	71 (100.0)	67 (100.0)	13 (100.0)	28 (77.8)	7 (87.5)
Cefoxitin	0	10 (76.9)	12 (17.4)	12 (16.9)	1 (1.5)	0	14 (38.9)	1 (12.5)
Cefoxitin followed by imipenem	0	0	5 (7.2)	0	32 (47.8)	0	9 (25.0)	
Imipenem	1 (3.9)	0	30 (43.5)	17 (23.9)	0	4 (30.8)	6 (16.7)	5 (62.5)
Imipenem followed by cefoxitin	0	0	1 (1.5)	0	0	0	1 (2.8)	
Ciprofloxacin	3 (11.5)	1 (7.7)	29 (42.0)	24 (33.8)	33 (49.3)	0	4 (11.1)	0
Levofloxacin	0	0	3 (4.4)	0	2 (3.0)	1 (7.7)	5 (13.9)	0
Moxifloxacin	0	1 (7.7)	8 (11.6)	12 (16.9)	29 (43.3)	0	3 (8.3)	1 (12.5)
Doxycycline	2 (7.7)	0	1 (1.5)	0	17 (25.4)	0	0	0
Linezolid	0	0	3 (4.4)	0	3 (4.5)	0	1 (2.8)	1 (12.5)
Tigecycline	1 (3.9)	0	3 (4.4)	0	0	0	0	4 (50.0)
Clofazimine	1 (3.9)	2 (15.4)	6 (8.7)	2 (2.8)	12 (17.9)	0	0	7 (87.5)
Minocycline	1 (3.9)	0	4 (5.8)	0	0	3 (23.1)	0	4 (50.0)
Ethambutol	18 (69.2)	2 (15.4)	23 (33.3)	0	0	9 (69.2)	4 (11.1)	0
Rifampicin	0	2 (15.4)	17 (24.6)	0	0	9 (69.2)	3 (8.3)	0
Trimethoprim/sulfamethoxazole	0	0	3 (4.4)	0	0	0	0	0
Surgical resection, n (%)	n/a	n/a	23 (33.3)	5 (7.0)	19 (28.4)	0	5 (13.9)	n/a
Treatment outcome, n (%)								
Microbiologic success	3 (11.5)	4 (30.8)	31 (44.9)	67 (94.4)	28 (41.8)	8 (61.5)	19 (52.8)	4 (50.0)
Symptomatic improvement	13 (50.0)	10 (76.9)	37 (53.6)	68 (95.8)	40 (59.7)	11 (84.6)	18 (50.0)	4 (50.0)
Radiographic improvement	10 (38.5)	n/a	30 (43.5)	61 (85.9)	22 (32.8)	7 (53.8)	16 (44.4)	2 (25.0)

Abbreviation: IQR, Interquartile range; n/a, not applicable.

Table E5. Comparison of treatment modalities between patients who achieved symptomatic improvement and not.

	Total (n=303)			*M. abscessus* subsp. *abscessus* pulmonary disease (n=126)			*M. abscessus* subsp. *massiliense* pulmonary disease (n=95)		
	with symptom improvement (n=201)	without symptom improvement (n=102)	P-value	with symptom improvement (n=74)	without symptom improvement (n=52)	P-value	with symptom improvement (n=82)	without symptom improvement (n=13)	P-value
Macrolides									
Clarithromycin*	124 (61.7)	62 (60.8)	0.803	48 (64.9)	42 (80.8)	0.071	49 (59.8)	9 (69.2)	0.761
Azithromycin†	71 (35.3)	31 (30.4)	0.371	25 (33.8)	10 (19.2)	0.072	32 (39.0)	4 (30.8)	0.760
Parenteral drugs									
Cefoxitin‡	59 (29.4)	37 (36.3)	0.242	27 (36.5)	20 (38.5)	0.853	21 (25.6)	4 (30.8)	0.739
Imipenem§	40 (19.9)	25 (24.5)	0.375	5 (6.8)	5 (9.6)	0.740	15 (18.3)	5 (38.5)	0.138
Amikacin	188 (93.5)	81 (79.4)	<0.001	73 (98.6)	43 (82.7)	0.008	79 (96.3)	8 (61.5)	0.001
Fluoroquinolone									
Ciprofloxacin	60 (29.9)	34 (33.3)	0.599	19 (25.7)	21 (40.4)	0.119	23 (28.0)	1 (7.7)	0.173
Levofloxacin	5 (2.5)	6 (5.9)	0.191	2 (2.7)	4 (7.7)	0.229	2 (2.4)	0	>0.999
Moxifloxacin	30 (14.9)	24 (23.5)	0.080	16 (21.6)	16 (30.8)	0.300	11 (13.4)	2 (15.4)	>0.999
Tetracycline									
Doxycycline	10 (5.0)	10 (9.8)	0.141	9 (12.2)	10 (19.2)	0.317	0	0	
Tigecycline	1 (0.5)	7 (6.9)	0.003	0	0		0	2 (15.4)	0.015
Minocycline	8 (4.0)	4 (3.9)	>0.999	4 (5.4)	0	0.142	0	1 (7.7)	0.137
Ethambutol	32 (15.9)	24 (23.5)	0.114	16 (21.6)	13 (25.0)	0.673	1 (1.2)	2 (15.4)	0.048
Rifampicin	17 (8.5)	14(13.7)	0.159	8 (10.8)	3 (5.8)	0.523	1 (1.2)	1 (7.7)	0.256
Linezolid	5 (2.5)	3 (2.9)	>0.999	1 (1.4)	3 (5.8)	0.311	0	0	

Duration of treatment, months, median [IQR] ¶									
Total treatment	24.1 [16.0-43.1]	24.7 [16.0-61.0]	0.422	28.7 [23.7-60.0]	23.9 [15.8-42.3]	0.034	18.2 [14.9-24.0]	22.2 [10.6-25.2]	0.559
Use of parenteral drug(s)	1.0 [0.5-4.0]	1.3 [1.0-9.0]	0.005	1.0 [1.0-4.0]	1.0 [1.0-1.5]	0.183	0.5 [0.5-1.0]	1.0 [0.6-1.6]	0.208
Surgical resection ‖	36 (20.7)	16 (19.8)	>0.999	13 (22.8)	9 (21.4)	>0.999	7 (8.5)	0	>0.999

Abbreviation: subsp., subspecies; IQR, Interquartile range.

*Including patient who used clarithromycin first, then changed to use azithromycin. †Including patient who used azithromycin first, then changed to use clarithromycin.

‡Including patient who used cefoxitin first, then changed to use imipenem. § Including patient 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.

Symptomatic improvement was determined at the completion of treatment based on the duty physicians' judgement.

Table E6. Comparison of treatment modalities between patients who achieved radiographic improvement and not.

	Total (n=290)			*M. abscessus* subsp. *abscessus* pulmonary disease (n=122)			*M. abscessus* subsp. *massiliense* pulmonary disease (n=93)		
	with radiographic improvement (n=148)	without radiographic improvement (n=142)	P-value	with radiographic improvement (n=44)	without radiographic improvement (n=78)	P-value	with radiographic improvement (n=73)	without radiographic improvement (n=20)	P-value
Macrolides									
Clarithromycin[*]	87 (58.8)	91 (64.1)	0.396	24 (54.5)	63 (80.8)	0.003	46 (63.0)	11 (55.0)	0.607
Azithromycin[†]	54 (36.5)	40 (28.2)	0.318	19 (43.2)	15 (19.2)	0.006	26 (35.6)	9 (45.0)	0.448
Parenteral drugs									
Cefoxitin[‡]	39 (26.4)	47 (33.1)	0.201	17 (38.6)	27 (34.6)	0.697	17 (23.3)	7 (35.0)	0.387
Imipenem[§]	36 (24.3)	29 (20.4)	0.484	5 (11.4)	5 (6.4)	0.493	15 (20.5)	5 (25.0)	0.760
Amikacin	134 (90.5)	122 (85.9)	0.274	42 (95.5)	70 (89.7)	0.744	69 (94.5)	16 (80.0)	0.062
Fluoroquinolone									
Ciprofloxacin	41 (27.7)	52 (36.6)	0.131	10 (22.7)	30 (38.5)	0.108	19 (26.0)	5 (25.0)	>0.999
Levofloxacin	2 (1.4)	9 (6.3)	0.032	1 (2.3)	5 (6.4)	0.417	0	2 (10.0)	0.044
Moxifloxacin	22 (14.9)	31 (21.8)	0.132	8 (18.2)	24 (30.8)	0.141	10 (13.7)	2 (10.0)	>0.999
Tetracycline									
Doxycycline	5 (3.4)	15 (10.6)	0.020	5 (11.4)	14 (17.9)	0.439	0	0	
Tigecycline	1 (0.7)	7 (4.9)	0.033	0	0		1 (1.4)	1 (5.0)	0.386
Minocycline	5 (3.4)	7 (4.9)	0.566	4 (9.1)	0	0.015	0	1 (5.0)	0.215
Ethambutol	16 (10.8)	38 (26.8)	<0.001	10 (22.7)	19 (24.4)	>0.999	0	2 (10.0)	0.044
Rifampicin	10 (6.8)	19 (13.4)	0.053	4 (9.1)	7 (9.0)	>0.999	0	1 (5.0)	0.215
Linezolid	3 (2.0)	5 (3.5)	0.494	1 (2.3)	3 (3.8)	>0.999	0	0	

Duration of treatment, months, median [IQR] ¶									
Total treatment	23.6 [15.1-35.0]	30.0 [18.7-67.6]	<0.001	26.4 [18.2-54.0	25.9 [19.0-50.1]	0.812	18.2 [14.8-24.0]	20.1 [14.0-24.2]	0.599
Use of parenteral drug(s)	1.0 [0.5-3.2]	1.0 [1.0-7.0]	<0.001	1.0 [1.0-4.0]	1.0 [1.0-1.0]	0.089	0.5 [0.5-1.0]	1.0 [0.5-1.6]	0.105
Surgical resection ‖	21 (15.4)	31 (26.1)	0.043	6 (17.1)	16 (25.0)	0.453	5 (6.9)	2 (11.8)	0.615

Abbreviation: subsp., subspecies; IQR, Interquartile range.

*Including patient who used clarithromycin first, then changed to use azithromycin. †Including patient who used azithromycin first, then changed to use clarithromycin.

‡Including patient who used cefoxitin first, then changed to use imipenem. § Including patient who used imipenem first, then changed to use cefoxitin.

¶ Information on treatment duration was not available in 5 patients

‖Information on surgical resection was not available in 35 patients.

Radiographic improvement was determined at the completion of treatment based on the duty physicians' judgement. Radiographic records of thirteen patients were not retrieved.

Table E7. Pooled treatment success rates according to the baseline characteristics

		Total (n=303)				*M. abscessus* subsp. *abscessus* pulmonary disease (n=126)				*M. abscessus* subsp. *massiliense* pulmonary disease (n=95)			
		Events /Total	Treatment success rates	95% CI	I^2	Events /Total	Treatment success rates	95% CI	I^2	Events /Total	Treatment success rates	95% CI	I^2
Age	≥60	77/144	43.1	228-63.4	84.2	23/63	33.5	14.6-52.4	61.9	36/40	69.4	6.5-100.0	84.4
	<60	87/159	49.7	30.2-69.5	81.0	22/63	34.9	13.6-56.1	66.4	46/55	70.2	23.8-100.0	58.8
Sex	Female	135/238	45.8	27.3-64.2	86.5	33/91	31.9	16.9-48.7	43.9	71/79	89.5	52.3-100.0	59.2
	Male	29/65	40.0	16.6-63.4	74.2	12/35	36.6	11.8-64.9	48.4	11/16	45.4	0.0-100.0	83.0
BMI	≥20.5	86/153	60.1	45.6-74.6	56.5	18/56	42.3	27.5-57.1	2.1	45/49	74.5	15.3-100.0	75.1
	<20.5	78/150	44.5	29.7-59.2	64.9	27/70	36.4	23.2-50.5	0.0	37/46	65.0	16.2-100.0	69.5
Respiratory comorbidities	Absence	37/82	50.1	29.1-71.1	76.5	11/35	34.1	9.1-59.1	65.5	11/14	82.1	30.4-100.0	2.5
	Presence	127/221	45.6	23.8-67.4	90.0	34/91	34.3	15.9-52.6	59.8	71/81	57.1	6.2-99.7	78.6
Radiographic features prior to treatment	Nodular bronchiectatic	114/196	50.4	25.3-75.4	91.3	29/80	32.7	12.3-53.2	70.2	63/71	64.3	9.9-100.0	84.5
	Fibrocavitary or indeterminate	50/108	42.9	26.7-59.1	68.7	16/46	29.0	8.0-55.0	62.0	19/24	75.0	26.2-100.0	62.8

Abbreviation: BMI, Body mass index

Table E8. Association of individual drugs with symptomatic improvement

	Total (n=303)			*M. abscessus* subsp. *abscessus* pulmonary disease (n=126)			*M. abscessus* subsp. *massiliense* pulmonary disease (n=95)		
	Adjusted OR*	95% CI	P-value	Adjusted OR*	95% CI	P-value	Adjusted OR*	95% CI	P-value
Clarithromycin	0.78	0.43-1.41	0.408	0.20	0.07-0.62	0.005	0.16	0.02-1.41	0.096
Azithromycin	1.67	0.92-3.05	0.093	4.58	1.48-14.2	0.007	6.82	0.81-87.6	0.075
Cefoxitin	0.72	0.41-1.27	0.255	1.12	0.45-2.77	0.810	3.55	0.29-43.0	0.306
Imipenem	0.93	0.50-1.76	0.833	0.74	0.15-3.54	0.711	0.21	0.03-1.37	0.113
Amikacin	2.95	1.26-6.91	0.007	19.5	2.01-189.7	0.003	31.7	3.70-271.6	0.002

Abbreviation: subsp., subspecies; OR, odds ratio.

*Adjusted for age, sex, body mass index, initial radiographic finding, and presence of respiratory comorbidity

Table E9. Association of individual drugs with radiographic improvement

	Total (n=290)			*M. abscessus* subsp. *abscessus* pulmonary disease (n=122)			*M. abscessus* subsp. *massiliense* pulmonary disease (n=93)		
	Adjusted OR*	95% CI	P-value	Adjusted OR*	95% CI	P-value	Adjusted OR*	95% CI	P-value
Clarithromycin	0.67	0.39-1.16	0.159	0.16	0.06-0.49	0.011	1.39	0.45-4.31	0.568
Azithromycin	1.46	0.85-2.46	0.172	5.66	1.86-17.2	0.005	0.96	0.30-3.09	0.942
Cefoxitin	0.69	0.41-1.17	0.171	1.24	0.56-2.75	0.600	0.52	0.14-1.98	0.340
Imipenem	1.48	0.81-2.71	0.201	2.06	0.52-8.20	0.312	0.87	0.22-3.53	0.848
Amikacin	1.37	0.59-3.16	0.470	2.65	0.50-14.2	0.251	3.19	0.54-18.7	0.198

Abbreviation: subsp., subspecies; OR, odds ratio.

*Adjusted for age, sex, body mass index, initial radiographic finding, and presence of respiratory comorbidity