#1488

Relationship Between Culture Conversion and Clinical Outcomes in Patients With *Mycobacterium abscessus* (MAB) Lung Disease: A Systematic Literature Review

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BACKGROUND

- MAB is one of the most common and highly pathogenic group of NTM that can cause chronic pulmonary disease[1]
- As with all NTM pulmonary disease, the goals of treatment are to achieve microbiological eradication (sputum culture conversion), reduce symptoms, improve quality of life, and prevent respiratory failure; however, MAB infection is among the most difficult NTM infections to treat due to various mechanisms of antibiotic resistance[1,2]
- Treatment of MAB pulmonary disease involves complicated and lengthy multidrug regimens, which contribute to low adherence to treatment guidelines[1,3]
- Updated guidelines have been published for MAB pulmonary disease treatment, yet limited clinical evidence is available regarding the association of sputum culture conversion and clinical outcomes[1,4]

OBJECTIVE

- To examine the relationship between treatment, culture conversion, and clinical outcomes among patients with MAB pulmonary disease reported in the medical literature

METHODS

- A systematic literature review was performed in accordance with the National Institute of Health and Care Evidence guidelines[5]
- English-language MAB pulmonary disease studies with ≥ 10 patients reporting an outcome of interest were identified from EMBASE, PubMed, congress abstracts, and the Cochrane Library (data cutoff, September 24, 2019) using the search strategy shown in **Table 1**
- The titles and abstracts from 1551 indexed records (**Figure 1**) were screened by 2 independent reviewers; data from relevant full-text reports of studies were extracted and are expressed as population-weighted means

Table 1. Search Strategy

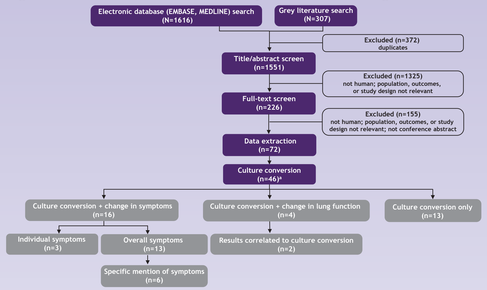
Search Topics: disease area, infection type, mortality, symptoms, QOL/burden of illness, lung infection, radiologic outcomes, microbiologic outcomes

Inclusion Criteria	Exclusion Criteria
• Human studies in the English language	• Study on NTM other than MAB
• Examined MAB infections in the lung	• Case report on a single patient
• Reported an outcome of interest	• Review article/opinion piece with no new data
» Symptoms	• Meta-analysis
» Quality of life/burden of illness	• Study population
» Lung function	» < 10 patients
» Radiological changes	» Lung transplant recipients
» Microbiological outcomes	

ABBREVIATIONS

CI, confidence interval; FVC, forced vital capacity; MAB, *Mycobacterium abscessus*; MCID, minimal clinically important difference; NTM, non-tuberculous mycobacteria; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QOL, quality of life; SGRQ, St George's Respiratory Questionnaire.

Figure 1. PRISMA Flow and Study Extraction Diagram



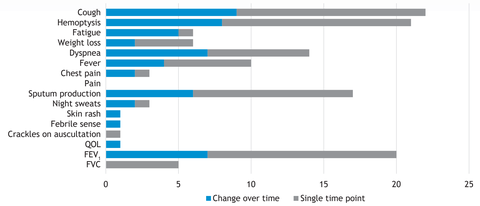
*Two studies were meta-analyses and thus are not included in the analysis; 13 studies reported culture conversion and mortality (presented separately; see poster #1468).

RESULTS

Culture Conversion

- Of 72 studies that reported a clinical or biological outcome associated with MAB pulmonary disease, 53 papers reported data from multiple time points allowing for comparisons of results before and after treatment (**Figure 2**); papers that reported outcomes at a single time point were excluded from the analysis
- Overall, 46 publications reported culture conversion data; 44 studies were included in the analysis (2 meta-analyses were excluded)
- The mean culture conversion rate in 44 studies (population size, N=2237; range 11 to 244) was 46.7% (range, 0% to 98.6%)[6-49]
- Across 21 studies that reported subspecies culture conversion rates, lower rates of conversion were reported among patients with infection due to *M abscessus* (35.8%; population size, N = 834) than *M massiliense* (76.9%; population size, N = 507) [8,10,11,13,15,18,20,26,28-31,33,36,37,39,40,43,48-50]

Figure 2. Number of Papers Reporting Symptoms or Lung Function



Overall Symptoms and Culture Conversion

- Although no studies directly correlated overall symptoms with culture conversion, indirect evidence from 10 studies (population size, N = 869) (**Figure 3**) revealed that 56.5% of patients (range, 13.0% to 98.6%) achieved culture conversion and 72.5% (range, 36.3% to 95.8%) experienced overall symptom improvement (r^2 = 0.36) (**Figure 4**)[9,15, 21,23,29,30,33,44,47,51]
- In 3 studies (population size, N = 106) that reported overall symptomatic improvement and culture conversion as a single measurement, 49.6% of patients (range, 25.0% to 80.5%) experienced symptomatic improvement[32,46,49]

Figure 3. Overall Symptoms and Culture Conversion Studies

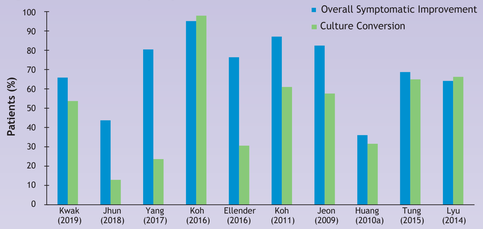
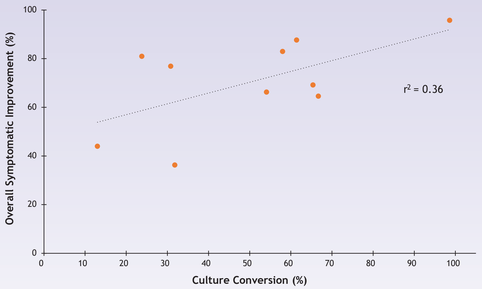


Figure 4. Correlation Between Overall Symptoms and Culture Conversion



Individual Symptoms and Culture Conversion

- The most common disease symptoms (prevalence ≥ 25%) at baseline were:
  - Cough, 88.4% (population size, N = 569)
  - Sputum production, 85.8% (population size, N = 422)
  - Fatigue, 49.9% (population size, N = 225)
  - Hemoptysis, 38.2% (population size, N = 462)
  - Dyspnea, 34% (population size, N = 317)
- No studies reported a direct correlation between an individual symptom and culture conversion

Cough and Fatigue

- Two studies (population size, N = 120) reported an indirect correlation between both cough and culture conversion and fatigue and culture conversion[22,37]
  - Absolute improvements in cough (23.1% and 77.6% of patients in each study) and fatigue (7.7% and 60.0% of patients in each study) were reported, with culture conversion occurring in 62.0% and 48.0% of patients (**Figure 5**)
- In 6 studies (population size, N = 433) that reported an improvement in overall symptoms and specifically mentioned cough, absolute improvement in symptoms was observed in 59.0% of patients (range, 31.3% to 82.2%), and 59.2% of patients (range, 31.8% to 80.5%) achieved culture conversion[21,23,29,32,33,44]
- In 2 studies (population size, N = 89) that reported symptom improvement and specifically mentioned fatigue, absolute improvement in symptoms was observed in 30.2% of patients (range, 21.5% to 31.4%), and 64.3% of patients (range, 66.7% to 80.5%) achieved culture conversion[32,33]

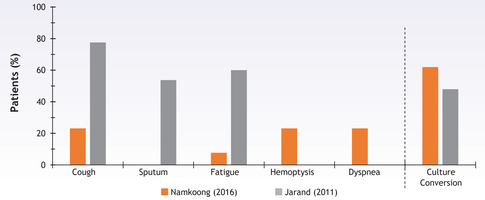
Sputum Production

- One study (N = 107) reported an absolute improvement in sputum production in 53.7% of patients and culture conversion in 48.0% of patients (**Figure 5**)[22]
- In 4 studies (population size, N = 299) that reported an improvement in overall symptoms and specifically mentioned change in sputum production, absolute improvement in symptoms was observed in 65.1% of patients (range, 52.5% to 78.0%), and 62.9% of patients (range, 58.0% to 80.5%) achieved culture conversion[23,29,32,33]

Hemoptysis and Dyspnea

- An indirect correlation between both hemoptysis and culture conversion and dyspnea and culture conversion was reported in 1 study (N = 13),[37] with absolute improvement in hemoptysis and dyspnea each reported among 23.1% of patients and culture conversion in 62.0% of patients (**Figure 5**)
- In 6 studies that reported an improvement in overall symptoms and specifically mentioned hemoptysis (population size, N = 433), absolute improvement in symptoms was observed in 29.0% of patients (range, 11.5% to 44.8%), and 60.8% of patients (range, 31.8% to 80.5%) achieved culture conversion[21,23,29,32,33,44]
- In 5 studies that reported an improvement in overall symptoms and specifically mentioned dyspnea (population size, N = 288), absolute improvement in symptoms was observed in 23.5% of patients (range, 1.6% to 41.1%), and 60.7% of patients (range, 31.8% to 80.5%) achieved culture conversion[21,23,32,33,44]

Figure 5. Absolute Symptom Improvement and Culture Conversion

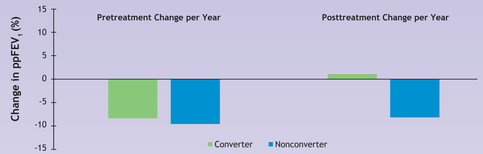


Lung Function and Culture Conversion

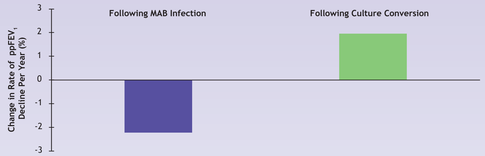
- Two studies directly correlated lung function and changes in MAB culture conversion[7,41]; both reported the negative impact of MAB infection on $ppFEV_1$
  - In the first study (N = 18), $ppFEV_1$ improved in converters (9.6%/year [95% CI, 5.99% to 13.23%]; $P < 0.0001$ for the 2-year posttreatment period vs the 2-year pretreatment period) but did not significantly change in nonconverters (1.5%/year [95% CI, −1.61% to 4.51%]; $P = 0.352$) (**Figure 6A**)[7]
  - The second study (N = 44) found that MAB infection hastened the decline in $ppFEV_1$ (by 2.22%; 95% CI, −3.21% to −1.23%) and that culture conversion slowed $ppFEV_1$ decline (1.95%; 95% CI, 0.64% to 3.27%), similar to the preinfection rate (**Figure 6B**)[41]
- In 2 studies (population size, N = 46), patients with MAB infections experienced a greater decline in FEV_1 compared with patients without MAB infections; patients with MAB infections had a 2.4% and 7.9% decline in FEV_1 compared with 1.6% and 1.0% in patients without infection, respectively[52,53]

Figure 6. Lung Function and Culture Conversion

A. Change in $ppFEV_1$ Between Converters and Nonconverters[7]



B. Change in Rate of $ppFEV_1$ Before and After Culture Conversion[41]



QOL and Culture Conversion

- One study (N = 47) indirectly correlated an improvement in QOL (measured by SGRQ) and culture conversion[54]
  - SGRQ mean score improved from 35 at baseline to 30 at 24 months, which is greater than the MCID of 4 points
  - The percent of patients with negative sputum culture increased from 26% at baseline to 66% at 12 months

LIMITATIONS

- This systematic literature review revealed limited data from published studies correlating culture conversion and clinical outcomes among patients with MAB pulmonary disease; no studies directly correlated individual symptoms and culture conversion
- Most indirect correlations between individual symptoms and culture conversion were derived from 2 studies[22,37]
- Limited data, small study size, and inconsistent or lack of methodology reporting may have influenced reported outcomes

CONCLUSIONS

- Indirect evidence suggests that symptom improvement is more likely in patients who achieve culture conversion
- Few studies have reported relationships between culture conversion and individual disease symptoms (cough, dyspnea, fatigue, hemoptysis, and sputum), although the limited data available suggest an improvement in individual symptoms with culture conversion
- Studies suggest that lung function decline increases in the presence of MAB infection, with a return to preinfection rates of decline after culture conversion
- Although indirect data suggest a weak correlation between symptom improvement and culture conversion, more evidence is needed to directly demonstrate the clinical benefits associated with culture conversion

DISCLOSURES

This systematic literature review was conducted by ApotheCom (London, UK) and funded by Insmed Incorporated (Bridgewater, NJ, US). Editorial support was provided by MediTech Media, Ltd (Hamilton, NJ, US), funded by Insmed Incorporated.

REFERENCES

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