#1468

Culture Conversion and Mortality in Patients With *Mycobacterium abscessus* (MAB) Lung Disease: A Systematic Literature Review

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BACKGROUND

- MAB is a highly pathogenic group of NTM that can cause progressive and often life-threatening pulmonary disease[1]
- MAB complex includes 3 subspecies of rapidly growing NTM (*M abscessus, M massiliense, and M bolletii*) with different macrolide susceptibilities; MAB infections are among the most difficult to treat due to different mechanisms that can lead to drug resistance[1,2]
- Treatment outcomes for MAB pulmonary disease are highly variable, and patients are at significant risk for disease progression and mortality[3]
- Clinical data characterizing disease progression in patients with MAB pulmonary disease, as well as the association between sputum culture conversion (microbiological eradication) and mortality in these patients, are limited[3]

OBJECTIVES

- To examine the relationship between treatment, culture conversion, and mortality in patients with MAB pulmonary disease
- To examine disease progression in patients with MAB pulmonary disease

METHODS

- Two related systematic literature reviews were performed in accordance with the National Institute of Health and Care Evidence guidelines[4]
  - The first search (mortality focus) had a data cutoff of September 24, 2019
  - The second search (progression focus) had a data cutoff of March 4, 2020
- English-language MAB pulmonary disease studies with ≥10 patients reporting outcomes of interest were identified from EMBASE, PubMed, congress abstracts, and the Cochrane Library using the search strategy shown in **Table 1**
- The titles and abstracts from 1551 indexed records (**Figure 1**) were screened by 2 independent reviewers; 61 records were identified during the additional search period, all of which were excluded during screening
- 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, disease progression[a]

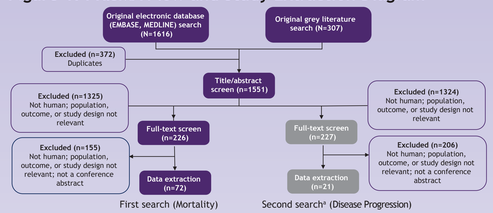
Inclusion Criteria	Exclusion Criteria
• Human studies in the English language • Examined MAB infections in the lung • First search focus » Reported mortality » Reported microbiological outcome • Second search focus[a] » Reported disease progression » Patients underwent treatment » Reported a worsening of outcomes	• Studies on NTM other than MAB • Case report on a single patient • Review article/opinion piece with no new data • Meta-analysis • Study population » <10 patients » Lung transplant recipients

[a] Additional criteria applied in search for MAB disease progression.

ABBREVIATIONS

CRP, C-reactive protein; MAB, *Mycobacterium abscessus*; NTM, nontuberculous mycobacteria; PRISMA, *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*; QOL, quality of life.

Figure 1. PRISMA Flow and Study Extraction Diagram



[a] An additional 61 sources were identified in the second search; all were excluded from full-text screening.

RESULTS

Treatment Regimen

- Treatment regimens were highly variable across studies with regards to type and number of antibiotics, treatment duration and schedules, and length of follow-up period
- Treatment duration ranged from 32 days to over 3 years and was often not reported precisely

Culture Conversion

- A total of 46 publications reported culture conversion; 44 studies were included in the analysis since 2 studies were metanalyses
- The mean culture conversion rate in 44 studies (population size, N=2237; range 11 to 244) was 46.7% (range, 0% to 98.6%)[5-48]
- Across 21 studies that reported culture conversion rates by MAB subspecies, 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)[7,9,10,12,14,17,19,25,27-30,32,35,36,38,39,42,47-49]

All-Cause Mortality and Culture Conversion

- Mean all-cause mortality across 17 studies that reported mortality data (population size, N = 1291) was 12.1% (range, 3.1% to 33.3%) (**Figure 2**)[8-10,16,20-23,35,41-43,49-53]; the length of follow-up was highly variable (range, 2 months to 20 years) and was not consistently reported
- Overall, 13 studies (population size, N = 1202; follow-up, 2 months to 20 years) reported all-cause mortality and culture conversion rates (**Figure 2**); a weak correlation was reported between all-cause mortality and culture conversion (r^2 = 0.16) (**Figure 3**), with a mean all-cause mortality of 11.9% (range, 3.1% to 33.3%) and a mean culture conversion rate of 45.8% (range, 0% to 93%)[8-10,16,20-23,35,41-43,49]

Figure 2. All-Cause Mortality and Culture Conversion Rates

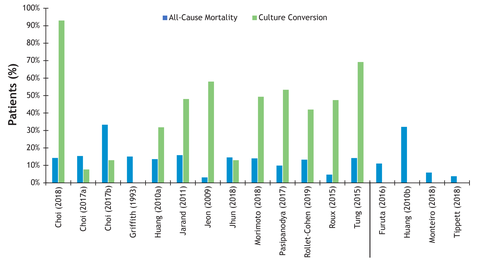
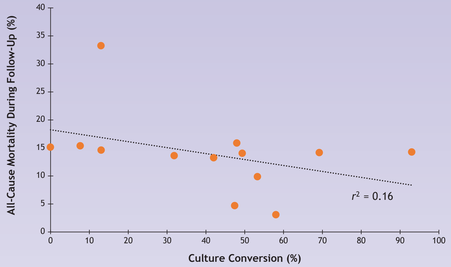


Figure 3. Correlation Between All-Cause Mortality and Culture Conversion



MAB-Attributed Mortality and Culture Conversion

- In 9 studies that reported MAB-attributed mortality and culture conversion rates (population size, N = 526; follow-up, 6 months to 20 years), mean MAB-attributed mortality was 7.6% (range, 0% to 26.7%), and mean culture conversion was 42.1% (range, 0% to 93%) (**Figure 4**)[8,10,16,20,22,35,41-43]
- A moderate correlation was found between MAB-attributed mortality and culture conversion (r^2= 0.60) (**Figure 5**)

Figure 4. MAB-Attributed Mortality and Culture Conversion

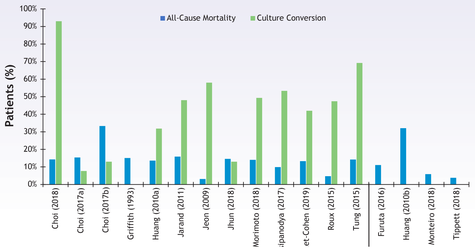
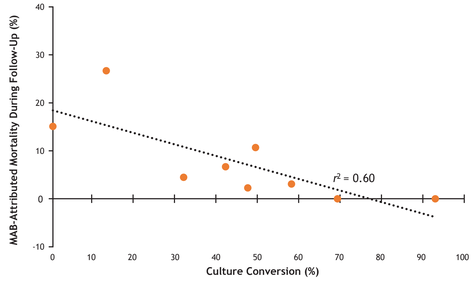


Figure 5. Correlation Between MAB-Attributed Mortality and Culture Conversion



Disease Progression

- In the second literature analysis that examined MAB pulmonary disease progression, data were extracted from 21 studies[17-18,20,22,25,28,31,32,36,39,43,44,47-48,51,54-59]
- Definitions of disease progression varied across studies; the most common definition/driver of disease progression was radiographic outcome, supported by persistent symptoms and/or positive cultures (**Table 2**)

Table 2: Outcomes Used to Define Disease Progression

Reference	Outcome							
	Radiology	Symptoms	Recurrent Infection	Lung Function	Death	QOL	Treatment Initiation < 24 months	CRP
Huang (2010a)								
Griffith (2015)								
Han (2003)								
Lyu (2011)								
Jeon (2009)								
Koh (2011)								
Esther (2010)[a]								
Huang (2010b)								
Verreghen (2012)[a]								
Czaja (2016)								
Shin (2013)								
Lyu (2014)								
Wallace (2014)								
Tung (2015)								
Yoon (2019)								
Daniel-Wayman (2019)								
Yoshida (2018)								
Park (2017)								
Namkoong (2016)								
Guo (2018)								
Kim (2012)								
	16	11	7	3	1	1	1	1

[a] Cystic fibrosis cohorts.

- Of 16 studies that reported radiographic outcomes in the definition of disease progression,[17-18,22,25,28,31-32,36,39,43,47-48,51,55,57,59] 8 studies (population size, N = 382) reported that 22.5% of patients (range, 13.8% to 61.5%) had progression while receiving treatment[18,22,25,28,32,36,47,51]
- In 8 studies (population size, N = 415) that reported overall disease progression using various composite definitions (including radiology, symptoms, recurrent infection, and timing of antibiotic treatment initiation), 35.2% of patients (range, 11.5% to 85.7%) experienced disease progression while receiving treatment[20,31,32,39,43,48,58-59]
- In 4 studies reporting subspecies-level data for overall disease progression,[32,39,48,58] fewer patients with *M massiliense* infection experienced disease progression with treatment (40.7%) than those with *M abscessus* (51.3%) (**Figure 6**)
- In 4 studies reporting subspecies-level data for radiographic disease progression,[25,28,32,51] the difference in progression by species was more pronounced with *M abscessus* (**Figure 7**)

Figure 6: Effect of Treatment on Overall Disease Progression by MAB Subspecies

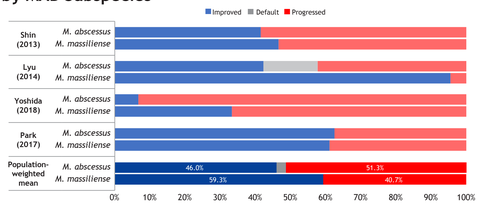
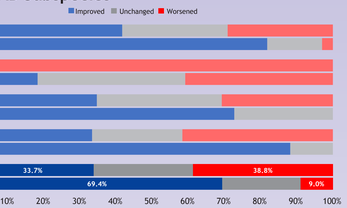


Figure 7. Effect of Treatment on Radiographic Disease Progression by MAB Subspecies



LIMITATIONS

- This systematic literature review revealed inconsistent treatment approaches, which may have led to variable rates of culture conversion
- No study directly correlated mortality and culture conversion
- Definitions of disease progression were inconsistent across studies
- Data were limited, and studies had small sample sizes and inconsistent or no methodology reporting

CONCLUSIONS

- Our systematic literature review highlights the inconsistencies in MAB pulmonary disease treatment approaches
- Overall, culture conversion rates were variable (< 50% overall) and twice as low in patients infected with subspecies *M abscessus* than in patients infected with *M massiliense* (35.8% vs 76.9%, respectively)
- Available indirect data suggest a weak inverse correlation between all-cause mortality and culture conversion (r^2 = 0.16) and a stronger inverse correlation between MAB-attributed mortality and culture conversion (r^2 = 0.60)
- Approximately one-third of patients had disease progression while receiving treatment
- Most studies reporting disease progression used a definition that included radiographic progression
  - In comparison with the use of a broader definition of disease progression, radiographic-specific progression was better aligned with overall differences in conversion rates among patients with *M abscessus* compared with *M massiliense*
- Although some data suggest lower MAB-attributed mortality with 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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