MORTALITY IN PATIENTS WITH MYCOBACTERIUM AVIUM COMPLEX LUNG DISEASE – A REVIEW OF PUBLISHED LITERATURE

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Background

- Nontuberculous mycobacteria (NTM) are ubiquitous environmental bacteria (Johnson 2014). Currently over 172 species of NTM have been identified with a variable geographical distribution. (Faria 2015, Hoefsloot 2013)
- Mycobacterium avium Complex (MAC) has been reported to be the most common causative agent in NTM lung disease. (Schönfeld 2013, Johnson 2014)
- Although it is a rare condition the incidence and prevalence of NTM lung disease is increasing worldwide. (Johnson 2014, Kwon 2016)

The objective of the analysis was to review the published literature on long-term mortality in patients with MAC lung disease, to explore study characteristics that may have contributed to variability in mortality reports, and to summarize documented predictors of mortality.

Methods

- Publications were searched in MEDLINE using search algorithm: "(mortality OR survival) AND (NTM OR nontuberculous mycobacteria OR nontuberculous mycobacterial OR mycobacterium avium Complex)". References of identified papers and review articles were also checked.
- Included were studies reporting 5-year all-cause mortality in patients with MAC lung disease. No restrictions were made with respect to study design, patient subpopulation, or data collection (prospective or retrospective). Studies with less than 10 patients with MAC lung disease were excluded.
- Heterogeneity in mortality rates reported was quantified in terms of the Q- and I2-statistics. The Q-statistics is based on the chi-squared test and assesses deviation between individual study effect and the pooled effect across studies. A large Q-value relative to its degree of freedom provides evidence of heterogeneity of outcome measured (variation in outcome estimates beyond chance). The I^2-statistics describes the percentage of the variability in outcome estimates that is due to heterogeneity rather than sampling error (chance).
- Key study characteristics, including patient population, sample size, setting, and therapies were extracted to identify potential reasons for variability in mortality reports.
- Predictors of all-cause mortality and proportions of deaths related to MAC lung disease were also analyzed.

Results

- We identified 13 published studies reporting 5-year mortality in patients with MAC lung disease. Ten studies were retrospective and three were prospective, including from 34 to 782 patients with MAC lung disease. Key characteristics of the identified studies are summarized in Table 1.

Table 1. Key characteristics of the studies included

Study	Type of study	Country	Patient population	Number of MAC patients	Demographics	Radiology	Therapy
Yeager 1973	Retrospective medical chart review	USA	MAC lung disease	45	Age: 49% above 50 years Male/Female: 100%/0%	Cavitation confirmed in 81% (7% none, 11% unknown), with multiple cavities in 50%	1 to 3 drugs: 53%, 4 or more drugs: 47%, adjunctive surgical treatment: 42%
BTS 2002	Prospective, randomized study	UK and Scandinavia	MAC lung disease	75	Age (mean): 64 years Male/Female: 53%/47%	Cavitation: 61%	Rifampicin and ethambutol, with or without isoniazid
Griffith 2006	Retrospective medical chart review	USA	Macrolide-resistant MAC lung disease	51	Age (mean): 64.7 ± 13.6 years Male/Female: 45%/55%	Cavities: 53% Nodules: 47%	Surgery + injectables (27.5%), Surgery, no injectables (3.9%), No surgery, injectables (15.7%), No surgery, no injectables (52.9%)
Jenkins 2008a*	Prospective, randomized study	UK, Denmark, Sweden and Italy	MAC lung disease	83	Age (mean): 65 years Male/Female: 48%/52%	Cavitation 69%	Rifampicin/ ethambutol/clarithromycin with or w/o immunotherapy
Jenkins 2008b*	Prospective, randomized study	UK, Denmark, Sweden and Italy	MAC lung disease	87	Age (mean): 65 years Male/Female: 51%/49%	Cavitation 66%	Rifampicin/ ethambutol/ciprofloxacin with or w/o immunotherapy
Andrejak 2010	Retrospective population registry analysis	Denmark	Prevalent NTM lung disease (MAC subgroup considered)	425	Age (mean): 61.2 ± 16.5 years Male/Female: 59%/41%	Not reported	Not reported
Hayashi 2012	Retrospective medical chart review	Japan	Newly diagnosed MAC lung disease patients	634	Age (mean): 68.9 ± 11.4 years Male/Female: 41.5%/58.5%	Nodular/bronchiectatic (NB): 82.9%, fibrocavitary lesions (FC): 11.5%, NB+FC: 3.3%, Unclassifiable: 2.3%	First-line antibiotic therapy was initiated in 30.9% of patients (one to five drug regimen)
Ito 2012	Retrospective medical chart review	Japan	Newly diagnosed MAC lung disease patients	78	Age (mean): 65.2 ± 12.6 years Male/Female: 39.7%/60.3%	Cavitary lesions: 26%, Bronchiectatic lesions: 59%	Treated patients-various regimens (69%), Untreated (31%)
Morimoto 2014	Retrospective medical chart review	Japan	MAC lung disease	309	Age (mean): 67 ± 13.7 years Male/Female: 35.3%/64.7%	Not reported	Standard 3-drug regimen including clarithromycin: 42.4%, pulmonary resection: 5.1%
Gochi 2015	Retrospective medical chart review	Japan	Nodular/ bronchiectatic MAC lung disease	782	Age (mean): 68.1 ± 11.1 years Male/Female: 31.5%/68.5%	Cavities: 15%	First-line antibiotic therapy was initiated in 19.6% of patients (one to five drug regimen)
Gommans 2015	Retrospective medical chart review	Netherlands	NTM lung disease (MAC subgroup considered)	42	Age (mean): 62 ± 14 years Male/Female: 70%/30%	Cavities:38%, Nodules+bronchiectasis: 4%, Consolidation: 33%	Antibiotic therapy was initiated in 41.1% patients
Kotilainen 2015	Retrospective medical chart review	Finland	NTM lung disease (MAC subgroup considered)	99	Age (mean): 65.6 ± 14.4 years Male/Female: 30%/70%	Infiltrates: 42%, Nodules: 34%, Cavities: 10%, Bronchiectasis: 31%, Missing information: 6%	Not reported
Moon 2016	Retrospective medical chart review	South Korea	Macrolide-resistant MAC lung disease	34	Age (mean): 65 years Male/Female: 68%/32%	Cavitary lesions: 80%	Different antibiotics (100%) plus surgery when suitable (6%)

** Note: Jenkins et al. 2008 provide mortality data for two differently treated cohorts of patients with MAC lung disease*

- Five-year all-cause mortality rates with 95% confidence intervals are presented in Figure 1. Five-year all-cause mortality ranged between 10% and 66%, and 10 of the 13 studies reported a rate exceeding 25% (Figure 1). A pooled estimate using random-effects model was 32% (95%CI 25%-39%).
- The Q-statistics (Q=172, degrees of freedom (df)=12) suggest substantial deviations of study-specific mortality from an aggregate mortality estimate. The I^2-statistic (I2=93%) indicates that 93% of the observed variability in mortality rates was likely due to true heterogeneity in mortality rates among the studies.
- In fact, mortality rates documented by studies in patients with predominantly nodular disease (Gochi 2015, Kotilainen 2015, Ito 2011) were lower than those reported by studies in patients with predominantly cavitary disease (Yeager 1973, Gommans 2015, Jenkins 2008). Mortality rates were high also in patients with macrolide-resistant MAC lung disease (Griffith 2006, Moon 2016). This is in line with what individual studies found on predictors of all-cause mortality, with commonly reported negative prognostic factors of the 5-year survival: presence of cavitary disease, high co-morbidity level, increased age, low body mass index, and male sex. (Table 2)

Results

Figure 1: Five-year all-cause mortality in MAC lung disease

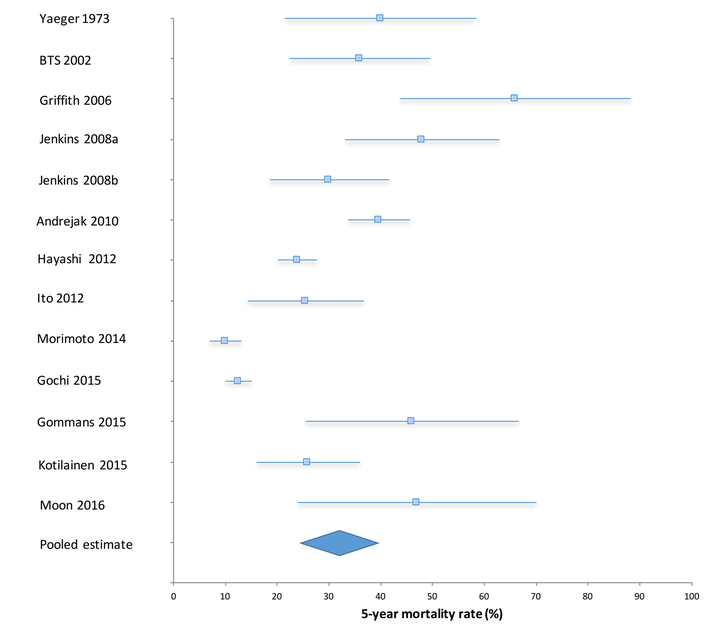


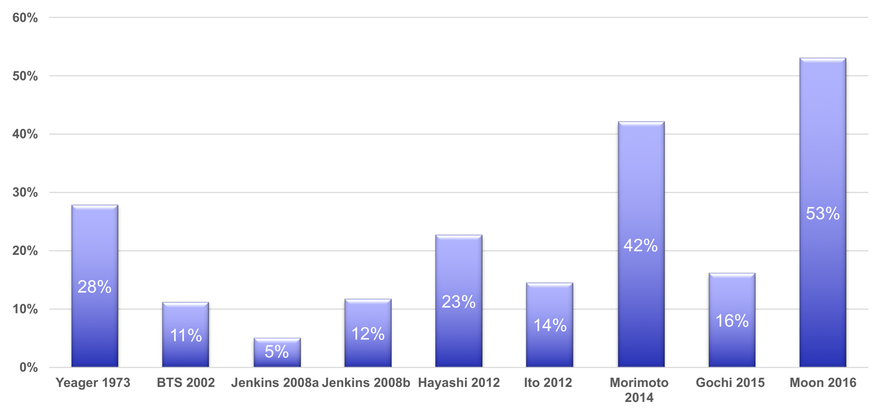
Table 2: Reported predictors of all-cause mortality in patients with MAC lung disease

Study	Predictors of all-cause mortality
Yeager 1973	(+): surgical treatment
BTS 2002	(-): increasing age, male sex, involvement of more than one lung zone, low initial body weight
Griffith 2006	(+): conversion to culture negative
Jenkins 2008	(+): adding clarithromycin vs. ciprofloxacin to rifampicin and ethambutol therapy regimen
Andrejak 2010	(-): high comorbidity level, age greater than or equal to 65 years, male sex, positive smear
Hayashi 2012	(-): male sex, older age (≥ 70 years), presence of systemic and/or respiratory comorbidity, presence of fibrocavities, body mass index < 18.5 kg/m2, anemia, hypoalbuminemia, erythrocyte sedimentation rate ≥ 50 mm/h
Ito 2012	(-): high Charlson comorbidity index, presence of cavitary lesions , malignancy
Gochi 2015	(-): male sex, older age (≥ 70 years), body mass index <18.5 kg/m2, absence of bloody sputum, hypoalbuminaemia, erythrocyte sedimentation rate >40 mm/h
Gommans 2015	(+): haemoptysis (-): consolidation on radiologic investigation at the moment of diagnosis, severe COPD, lung malignancy
Kotilainen 2015	(-): underlying ultimately or rapidly fatal disease (McCabe classification 3–4), increasing age, female sex
Moon 2016	(+): surgical treatment (-): sputum positivity at the time of detection of macrolide resistance

(+): positive prognostic factor, (-): negative prognostic factor

- MAC-specific deaths, i.e. deaths attributed to MAC infection, were reported by 9 studies. The proportion of all death assigned to be MAC-related varied from 5% to 53% (Figure 2).
- When cavities were present MAC-related deaths occurred far more frequently than when no cavities were observed - 5-year MAC-related mortality was 17.1% vs. 2.8% (Hayashi 2012) and 8.5% vs. 0.8% (Gochi 2015), respectively.

Figure 2: MAC-related deaths as proportion of all deaths reported



Discussion

- This research found that majority of the identified studies showed poor long-term survival in patients with MAC lung disease. Particularly in patients with cavities, MAC lung disease considerably contributed to the all-cause mortality.
- The wide range of mortality rates reported, however, suggests presence of heterogeneity in the rate of all-cause mortality, likely driven by differences in patient characteristics and patient management.
- Reported predictors of all-cause mortality are likely population-specific and thus have varying relevance for mortality. Also, not all factors found as predictors in one study were measured in other studies, thus making comparison across studies difficult. Nevertheless, some commonalities can be observed, particularly high co-morbidity levels and presence of cavities as negative prognostic factors.
- A limitation of the study is that we searched for studies included in the MEDLINE database only. Therefore, the identified list of relevant studies may not be fully comprehensive.
- Additionally, we did not exclude studies according to a set of stringent, pre-specified criteria, hence the results of this meta analysis are likely to be influenced by the study design and quality of the published reports.

Conclusions

- Risk of all-cause mortality in patients with MAC lung disease varies across studies. Most of the studies document a 5-year mortality rate greater than 25%, indicating a substantial health threat to people with the disease.

Disclosures

Dr. Roald van der Laan and Dr. Marko Obradovic are employees of Insmed Incorporated.

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