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

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Background
- Non tuberculosis mycobacteria (NTM) are ubiquitous environmental bacteria (Johnson 2014). Currently over 172 species of NTM have been identified with a variable geographical distribution. (Farna 2015, Hoellstorf 2013)
- Mycobacterium avium Complex (MAC) has been reported to be the most common causative agent in NTM lung disease. (Schliep 2010, Johnson 2014)
- Although it is a rare condition the incidence and prevalence of NTM lung disease is increasing worldwide. (Johnson 2014, Newberry 2015)

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 non tuberculosis mycobacteria OR non tuberculosis 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 population, 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 I^2-statistic. The I^2-statistic is based on the chi-squared test and assesses deviation between individual study results and the pooled effect according to 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 (Figure 1).
- 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Country</th>
<th>Population source</th>
<th>Number of patients</th>
<th>Demographics</th>
<th>Rationale</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTS 2002</td>
<td>Prospective, randomized controlled trial</td>
<td>USA</td>
<td>Thoracic imaging</td>
<td>75</td>
<td>Male/Female: 47%/53%</td>
<td>60% (7%) none, 11% unknown, with multiple cavities in 50%</td>
<td>MAC infection, treatment with or without immunotherapy</td>
</tr>
<tr>
<td>Jenkins 2008a</td>
<td>Retrospective, single center study</td>
<td>Denmark, Sweden</td>
<td>Medical chart</td>
<td>80</td>
<td>Male/Female: 55%/45%</td>
<td>No surgery, no medications (37.5%), no surgery, no medications (58%)</td>
<td>Rifampicin/etambutol/macrolide combination</td>
</tr>
<tr>
<td>Jenkins 2008b*</td>
<td>Retrospective, single center study</td>
<td>Sweden</td>
<td>Medical chart</td>
<td>87</td>
<td>Male/Female: 50%/50%</td>
<td>No surgery, no medications (50.1%), no surgery, no medications (39.7%)</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Andrejak02010</td>
<td>Retrospective, population-based registry analysis</td>
<td>Japan</td>
<td>Medical chart</td>
<td>495</td>
<td>Male/Female: 77%/23%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hayashi02012</td>
<td>Retrospective, single center study</td>
<td>Japan</td>
<td>Medical chart</td>
<td>133</td>
<td>Male/Female: 68%/32%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Muffling2014</td>
<td>Observational cohort study</td>
<td>Germany</td>
<td>Medical chart</td>
<td>200</td>
<td>Male/Female: 38%/62%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Goldi2015</td>
<td>Retrospective, single center study</td>
<td>Norway</td>
<td>Medical chart</td>
<td>782</td>
<td>Male/Female: 70%/30%</td>
<td>No surgery, no medications (32.9%), no surgery, no medications (37.6%)</td>
<td>Rifampicin/moxifloxacin combination treatment</td>
</tr>
<tr>
<td>Goulet2014</td>
<td>Retrospective, single center study</td>
<td>Canada</td>
<td>Medical chart</td>
<td>42</td>
<td>Male/Female: 54%/46%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kalia2016</td>
<td>Retrospective, single center study</td>
<td>Canada</td>
<td>Medical chart</td>
<td>44</td>
<td>Male/Female: 47%/53%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Discussions
- 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. Nonetheless, some comorbidities 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.

References:

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

Table 2: Predicted cause of mortality in patients with MAC lung disease

<table>
<thead>
<tr>
<th>Year</th>
<th>Disease death</th>
<th>Other death</th>
<th>Total death</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>20%</td>
<td>30%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>2014</td>
<td>25%</td>
<td>25%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>2015</td>
<td>30%</td>
<td>20%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>2016</td>
<td>35%</td>
<td>15%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>2017</td>
<td>40%</td>
<td>10%</td>
<td>50%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Note: Jansen et al. (2002) provide mortality data for two different treated cohorts of patients with MAC lung disease

- Five-year all-cause mortality rates with 95% confidence intervals are presented in Figure 1. One pooled estimate using random-effects model was 32% (95%-CI 25%-39%).
- The Q-statistics (Q=12.7; degrees of freedom =9) (p=0.01) suggest substantial deviations of study-specific mortality from an aggregate mortality estimate. The I^2-statistic (I^2=55%) indicates that 50% 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 (Griffith 2015, Kalia 2015, Jo 2011) were lower than those reported by studies in patients with predominantly cavitary disease (Yager 1973, Griffith 2008). Mortality rates were high in patients with multidrug-resistant MAC lung disease (Ghigna 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).