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Microbiological and Clinical Outcomes of Treating Non-*Mycobacterium Avium* Complex Nontuberculous Mycobacterial Pulmonary Disease

A Systematic Review and Meta-Analysis

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BACKGROUND: Pulmonary disease caused by nontuberculous mycobacteria (NTM) is steadily increasing worldwide.

METHODS: A systematic review of non-*Mycobacterium avium* complex studies published prior to October 2016 was conducted with respect to microbiological and clinical outcomes of current treatment regimens.

RESULTS: We retrieved 352 citations, which yielded 24 studies eligible for evaluation. Sixteen studies were retrospective chart reviews, three studies were prospective, and only five studies were randomized. The weighted average proportion of sputum culture conversion (SCC) after subtracting posttreatment relapses for patients with *M abscessus* was 41.2% (95% CI, 28.6%-54.5%) but was 69.8% (95% CI, 41.0%-91.9%) with subspecies *M massiliense* in macrolide-containing regimens, 80.2% (95% CI, 58.4%-95.2%) in patients with *M kansasii*, 32.0% (95% CI, 16.5%-49.8%) for *M xenopi* (MX) and 54.4% (95% CI, 34.7%-73.4%) for *M malmoense*. SCCs in the total of 55 patients who underwent lung resection and had MX or *M abscessus* was high at 75.9%.

The risk of bias was low in four of five randomized studies. However, heterogeneous use of outcome parameters (eight definitions of "relapse," eight of "treatment success," and four of "cure") hampered comparison of nonrandomized studies as well as producing possible bias by a posteriori exclusion (13.3%) and uncompleted treatment of participants (25.3%).

CONCLUSIONS: As a sustained microbiological response without surgery is unsatisfactory in treating *M abscessus*, MX, and *M malmoense*, functional and quality of life aspects should be given more emphasis in the individual evaluation of treatment outcome. Further, properly planned studies with sufficient power are needed, as are new drugs or better-tolerated application of current antibiotics, or both. CHEST 2017; 152(1):120-142

KEY WORDS: meta-analysis; nontuberculous mycobacteria; systematic review; treatment outcome

ABBREVIATIONS: 6MWT = 6-min walk test; AMX = amikacin; ATS = American Thoracic Society; AZT = azithromycin; BTS = British Thoracic Society; CLARI = clarithromycin; IDSA = Infectious Diseases Society of America; INH = isoniazid; IQR = interquartile range; LAI = liposomal amikacin for inhalation; MAC = *Mycobacterium avium* complex; MK = *Mycobacterium kansasii*; MX = *Mycobacterium xenopi*; NTM = nontuberculous mycobacteria; PD = pulmonary disease; QOL = quality of life; RIF = rifampicin; SCC = sputum culture conversion; SGRQ = St. George's Respiratory Questionnaire

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The frequency of pulmonary disease caused by nontuberculous mycobacteria (NTM)[1] has been recognized as steadily increasing.[2-4] A few species account for the majority of isolated cases of NTM: *Mycobacterium avium* and *M intracellulare,* a subspecies of the slowly growing *M avium* complex (MAC), have been reported to be the predominant species in both patients with CF and patients without CF worldwide.[5]

However, with respect to pathogenicity, the next most frequent "other" species in the United States, *M kansasii* (MK) and *M abscessus*, can be considered at least equivalent.[6,7] *M abscessus* can be differentiated into three subspecies: *M abscessus* subspecies *abscessus*, *M abscessus* subspecies *massiliense,* and the rarely isolated *M abscessus* subspecies *bolletii.*[8] Pulmonary disease caused by *M abscessus* subspecies *abscessus* is often associated with a poor outcome.[9,10]

M xenopi (MX) is rarely found in the United States but is common in Europe, usually in patients with impaired immunity, and the isolation of *M malmoense,* the most serious pathogen after MAC in Europe, has been reported to be clinically relevant in 70% to 80% of patients with pulmonary disease.[11]

Although updates of the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines of 2007[2] or the older British Thoracic Society (BTS) guidelines[12] for management and treatment of NTM pulmonary disease (NTM-PD) are expected to be released in 2017, there was only one systematic review on therapeutic success in non-MAC disease published in 2009, which is restricted to the investigation of patients with MX.[13] We conducted an up-to-date systematic review that includes the most recently published studies on microbiological and clinical outcomes of treating non-MAC NTM-PD.

Methods

Study Search

We searched studies published in English, French, German, Italian, or Spanish through September 30, 2016 (see e-Appendix 1 for details). Initially, all NTM species were included in our search criteria; our final selection, however, included only articles concerning individual non-MAC species for which a microbiological treatment outcome was reported.

Assessment of Study Quality

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14] Risk of bias in randomized studies was assessed using the Cochrane risk of bias tool[15] and classified across nonrandomized observational studies using the Grading of Recommendations Assessment, Development, and Evaluation system[16] (see e-Appendix 1 for details).

Results

Figure 1 presents a flow diagram of the literature search results: In the selection process, 352 abstracts were identified, 87 of which were read in full text (Fig 1). Finally, 24 studies published in peer-reviewed journals could be included in the review.[17-25,37-41] Two BTS studies on MX[25] and *M malmoense*[33] provide additional information on cases reported in an earlier (2001) BTS study.[36] To avoid double counting, the 2001 publication was not included.

Origin of Studies

The studies came from a total of 10 countries. Most were from the United Kingdom (7 of 24 [29.2%]), the United States (6 of 24 [25.0%]), and South Korea (4 of 22 [18.2%]). There was only a single study each from France, Canada, Japan, Taiwan, Spain, Australia, and the Netherlands (Tables 1 and 2).

Study Participants

The outcome of treatment could be evaluated in a total of 1,224 study participants (mean, 51.0 participants; interquartile range [IQR], 31.5 participants).
M abscessus was addressed in 10 studies comprising 424 patients (34.6%), followed by MK (six studies; 279 patients [22.8%]), MX (six studies; 233 patients [19.0%]), *M malmoense* (three studies; 287 patients [23.4%]), and *M fortuitum* (one study; one patient).

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FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

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DOI: http://dx.doi.org/10.1016/j.chest.2017.04.166