The Treatment of Rapidly Growing Mycobacterial Infections

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KEYWORDS

• *Mycobacterium abscessus* • *Mycobacterium massiliense* • Antimicrobial therapy
• NTM lung diseases • Antimicrobial resistance • Drug susceptibility testing • Surgical therapy

KEY POINTS

- The *Mycobacterium abscessus* complex represent the most drug-resistant nontuberculous mycobacteria (NTM) and are the most difficult to treat.
- Treatment of rapidly growing mycobacterial infections is lengthy and expensive.
- Species-specific response to macrolides might explain improved outcomes in *M massiliense* lung disease.
- New drugs with bactericidal activity against NTM are needed.
- Preclinical in vivo testing models should mimic human disease presentation.

RAPIDLY GROWING MYCOBACTERIA AND NEW SEQUENCING TOOLS

Important pathogenic members of the rapidly growing mycobacteria (RGM) have undergone a series of taxonomic descriptions.[1–3] In the 1990s, many laboratories referred to the major RGM as *Mycobacterium chelonae* complex or *M fortuitum* complex until the appreciation that 2 major pathogens: *M abscessus* and *M chelonae* were unique. Although most clinicians have access to laboratories capable of identifying clinical isolates using the 16s rDNA sequencing, this methodology cannot reliably distinguish between these 2 closely related species. Later, we realized that *M abscessus* complex consisted of 3 subspecies: *M abscessus*, *M bolletii*, or *M massiliense*. However, currently a single official taxon unites *M massiliense* and *M bolletii as M abscessus* subsp. *bolletii* and *M abscessus subsp. abscessus*. Fortunately, these species are undergoing taxonomic reevaluation. Modern genomic tools are revolutionizing microbiology and the use of whole-genome sequencing is becoming less expensive and more readily accessible. Using these highly discriminatory new genomic techniques, it has become clear that 3 subspecies of the *M abscessus* group should be considered a separate species.[4,5] In addition to specific identification, these high-throughput genome sequencing datasets have been extremely useful in understanding the epidemiology of RGM infections in outbreak settings[6] and in understanding strain-specific disease pathogenesis.[7] Whole-genome sequencing and molecular epidemiology have recently shed light on a large global "outbreak" of a highly related strain of *M massiliense* occurring in the UK, the

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United State, and Brazil.[8] Strains from 2 cystic fibrosis clinics showed high-level relatedness with each other and major-level relatedness with strains that caused soft tissue infections during an epidemic in Brazil. Many of the isolates were highly drug resistant.[9,10] More work is necessary to identify the mechanisms of spread of this conserved strain. We will see the use of whole-genome sequencing for some time to come.

DOES THE SPECIES MATTER FOR OUTCOMES OF DISEASE AND TREATMENT?

Genetic tools can also play a role in differentiating patients with heterogeneous clinical presentation and prognoses. For instance, utilizing a development cohort (48 isolates) and validation cohort (63 isolates), Shin and colleagues[11] looked at predicting disease phenotype (stable nodular bronchiectatic disease vs those who had progressive forms and fibrocavitary disease) based on a bacterial typing scheme called variable number of tandem repeat loci (**Figs. 1** and **2**). Others have also shown drug susceptibility differences and clinical outcome measures between *M abscessus* and *M* massiliense,[12] supporting the need to identify to the species level.

DRUG SUSCEPTIBILITY IN RAPIDLY GROWING MYCOBACTERIA

It is recommended that drug susceptibility testing for the RGM be performed by broth microdilution. The species of the *M abscessus* complex are typically more drug resistant compared with *M chelonae* and *M fortuitum*. *M abscessus* is resistant to the first-line antituberculous mycobacterial agents, including rifampin, isoniazid, ethambutol, and pyrazinamide. In general, *M abscessus* is considered to be susceptible to amikacin, cefoxitin, and clarithromycin, and moderately susceptible to imipenem.[1] With the exception of the macrolide class, the correlation between in vitro susceptibility and clinical response for specific antimycobacterial drugs has not been established.[1,13] Therefore, the clinician should use the drug susceptibility report with an appreciation for its limitations.

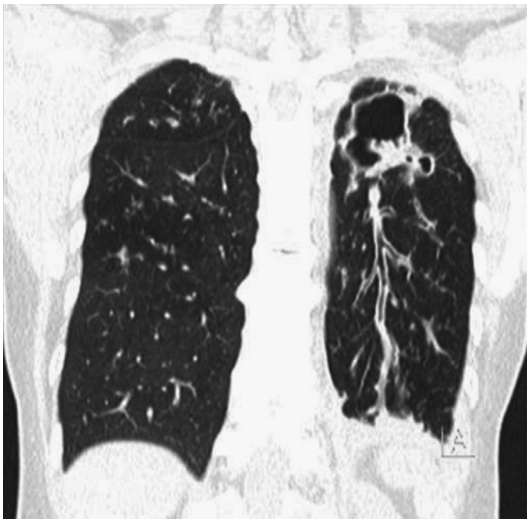

Fig. 1. Cavitary *M abscessus* pulmonary disease.

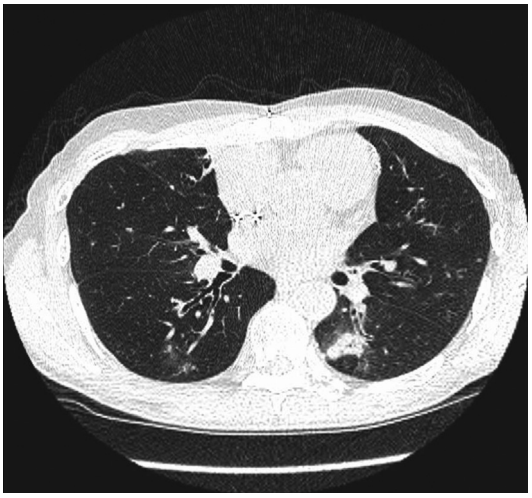

Fig. 2. Bronchiectatic nodular *M massiliense* pulmonary disease.

A study from Korea reported drug susceptibility testing for 74 isolates of *M abscessus*.[14] Identification of the species was performed using the polymerase chain reaction-restriction fragment length polymorphism method based on the *rpoB* gene. Most of the isolates were found to be susceptible to amikacin (99%) and cefoxitin (99%). Amikacin had much better activity compared with tobramycin (36%). Imipenem was found to have activity against 55% of isolates. Clarithromycin showed activity in most isolates (91%) and the fluoroquinolones showed moderate activity with moxifloxacin (73%), seeming to be more active in vitro than ciprofloxacin (57%). Doxycycline was only susceptible in 7% of isolates. This was one of the few studies that noted such high rates of susceptibility for the quinolones.

A study of 102 isolates from Japan noted *M abscessus* and *M massiliense* showed an high level of resistance to all antimicrobials, except for clarithromycin, kanamycin, and amikacin.[12] Resistance to clarithromycin was more frequent in *M abscessus* than *M massiliense* (16% vs 4%, respectively).