“You Can’t Always Get What You Want...” The *Mycobacterium abscessus* Issue

Name versus Function

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The article in this month’s issue of *AnnalsATS* by Griffith and colleagues (pp. 436–439) regarding *Mycobacterium abscessus* taxonomy illustrates the classic lag between scientific discovery and clinical practice (1). The molecular microbiology laboratory is commonplace in research settings and is contributing significantly both to the exploding dendrograms of mycobacterial taxonomy and to real advances in understanding virulence and treatment response that may be virtually unrecognizable if functionally dissimilar organisms are lumped together. However, the capability for molecular discrimination between species or for separating species and subspecies is lacking in many commercial and even public health laboratories in which clinical mycobacterial isolates are identified. There are likely multiple reasons for this, including a lack of recognition of the significance of disease caused by these organisms and, among those who may recognize the significance, a feeling of futility with regard to treatment, especially for *M. abscessus*, regardless of what the organism is called.

The reported relative prevalence of *M. abscessus* is increasing. In a recent retrospective, multiyear, isolate-based assessment of prevalence within integrated health systems, the annual prevalence of nontuberculous mycobacteria pulmonary disease was steadily increasing by 3% per

year, and rapid-grower mycobacteria was the second most prevalent group behind *Mycobacterium avium* complex (2). It is likely the vast majority of these infections were caused by *M. abscessus*, but they were reported under a variety of names with no ability to distinguish species or subspecies within that complex.

Cystic fibrosis (CF) has served as a particularly vulnerable population heralding trends seen in the broader susceptible population with nontuberculous mycobacteria lung disease. The reported relative prevalence of *M. abscessus* has increased in patients with CF, going from around 20% of isolates in the mid 1990s to around 50% in recent studies (3). In many countries, it is the most frequent cause of nontuberculous mycobacteria lung disease in patients with CF. It appears to affect younger patients and contributes to accelerated deterioration in lung function (3).

Although there have been relatively few reported treatment trials for *M. abscessus*, recent studies have shown beneficial response to treatment. By far the most striking information to come from these recent studies is the differential response to macrolide-based regimens based on the grouping within the *M. abscessus* complex. Those patients infected with *M. abscessus* subspecies *massiliense* with no evidence of inducible macrolide resistance related to

a functional *erm(41)* gene had excellent treatment responses compared with the dismal response seen in patients with *M. abscessus* subspecies *abscessus* and a functional *erm(41)* (4).

Although *M. abscessus* subspecies *massiliense* may be more treatment-responsive, some strains have been increasingly associated with respiratory outbreaks in CF centers and soft tissue postsurgical infections. The genomic similarity among these outbreak strains raised different hypotheses, such as independent emergence of global strains or strain transmission (5). These organisms are increasingly prevalent, cause significant disease, may respond to treatment, and may be associated with apparent outbreaks of disease, and the clinical mycobacteriology laboratory could tell us quite a bit about prognosis and level of concern. That should be significant incentive to get this right.

You can’t always get what you want
But if you try sometimes well you
just might find
You get what you need. (6)

The ideal solution as suggested by Griffith and colleagues is to advance all laboratories performing clinical mycobacterial isolate identification into the molecular era with the capability to perform multilocus sequencing for subspecies-level

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identification within the *M. abscessus* complex and for inferring *erm(41)* gene functionality, using genomic sequencing and also using phenotypic induction of resistance on extended incubation with clarithromycin, as recommended by the Clinical and Laboratory Standards Institute (7).

The implementation of polyphasic approaches involving phenotypic and molecular methods has unveiled novel species closely related to well-known entities and increased the use of “species complex” for selected microorganisms such as the *Acinetobacter calcoaceticus*–*Acinetobacter baumannii* complex, the *Burkholderia cepacia* complex, and the *Mycobacterium tuberculosis* complex. The members of these complexes may show distinct epidemiology, pathogenicity, and susceptibility, making their precise identification critical (8). *Burkholderia cepacia* complex (formerly *Pseudomonas cepacia*) includes at least 18 different species (including *B. cepacia*, *B. multivorans*, and *B. cenocepacia*) (9) and can cause pneumonia in immunocompromised individuals with underlying lung disease such as CF or chronic granulomatous disease. *B. cepacia* complex infections in CF range from mild disease to the serious “cepacia syndrome,” characterized by rapidly progressing radiological and clinical signs of necrotizing pneumonia, pyrexia, and death. Cepacia syndrome has most frequently been associated with *Burkholderia cenocepacia*, the species of the highly transmissible ET-12 epidemic strain (10, 11).

The increased use of matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) has

revolutionized the clinical microbiology laboratory (12). Commercial and homemade databases most commonly identify *M. abscessus* complex but do not distinguish the subspecies *M. abscessus* subspecies *abscessus*, *M. abscessus* subspecies *massiliense*, and *M. abscessus* subspecies *bolletii* (13). Interestingly, recent studies suggest the ability of MALDI-TOF MS to discriminate among the subspecies of *M. abscessus* complex, using cluster analysis or the presence or absence of specific peaks (14). Although promising, these new approaches still require additional expertise and software beyond the standard applications of MALDI-TOF MS for microbial identification.

The proposed definitions of Griffith and colleagues for *M. abscessus*, *M. massiliense*, and *M. bolletii* (recommendations 3, 4, and 5) will likely simplify the interpretation of clinical microbiology reports and lead clinicians to appropriate drug choices even though they may misclassify or be inconclusive with some strains because of possible horizontal gene transfer events (15, 16).

We propose to have the entity “*M. abscessus* complex” encompass all three subspecies when identification methods used do not provide subspecies-level identification. We suggest that a minimum acceptable standard for clinical microbiology laboratories is the identification of *M. abscessus* complex clearly separated from *M. chelonae*, followed by phenotypic testing for inducible clarithromycin resistance and detection of full-size or truncated (inactive) *erm(41)* gene by polymerase chain reaction. Specific instances in which subspecies

level may be important are for suspected outbreaks or in the CF population.

M. abscessus subspecies-level identification could be performed using standardized multilocus gene sequencing, validated polymerase chain reaction–based assays, and/or validated MALDI TOF protocols for subspecies-level identification. A group of mycobacterial experts convened to discuss *M. abscessus* taxonomy (recommendation 7) should also address methods for species or subspecies identification.

The increasing number of whole-genome sequences of *M. abscessus* complex may shed light on specific genes and virulence factors favoring infections of specific organs or patient populations. For the cases in which more detailed molecular testing is required, isolates should be referred to reference laboratories at academic centers at which experience and technological capability exist. This model has worked well in the CF community for referral of isolates of *B. cepacia* complex or even *Pseudomonas aeruginosa* for more detailed analysis. Finally, clinicians need to insist the laboratories that process their mycobacterial specimens bank these isolates so they remain available for more detailed molecular analysis dictated by clinical severity, need for treatment, or treatment response. This will be increasingly important as we move beyond culture-based susceptibility testing for macrolides and realize the goal of having rapidly available, clinically relevant molecular susceptibility testing, as is now being recognized for amikacin (17). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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