EDITORIAL COMMENTARY

The Talking Mycobacterium abscessus Blues

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(See the article by Jarand et al, on pages 565–571.)

You try so hard but you don’t understand … Something is happening but you don’t know what it is, do you Mr. Jones? (“Ballad of a thin man,” Bob Dylan)

I thought I knew what was happening, but then again, maybe I don’t. In 1993 we published our experience with 120 patients who had Mycobacterium abscessus lung disease [1]. Patients were followed up for an average of almost 5 years and received various antimicrobial agents including, amikacin, cefoxitin, erythromycin (most patients were treated prior to the availability of clarithromycin), or sulfonamides. Only 10 patients (8%) with M. abscessus lung disease were cured as defined by return of respiratory symptoms to baseline and reversion of sputum to AFB culture negative for at least 1 year. Of the 10 patients in whom M. abscessus was cured, 7 received amikacin and cefoxitin or imipenem followed by surgical excision, whereas only 3 subjects were successfully treated with antibiotics alone. Eighteen patients (15%) died as direct result of their lung disease.

In the interval between 1993 and 2010, few new studies were published that addressed the treatment of M. abscessus lung disease. In this issue of the Journal, however, Jarand et al [2] present a retrospective analysis of treatment outcomes for 107 patients with M. abscessus pulmonary disease from 2001 to 2008. Sixty-four percent of the patients were followed up for an average of 34 months. Antibiotic treatment was individualized based on drug susceptibility results and patient tolerance. Sixteen different antibiotics were used in 42 different combinations for an average of 4.6 drugs per patient over the course of therapy with a median of 6 intravenous antibiotic months. At least 1 drug was stopped due to side effects or toxicity in the majority of patients, most commonly amikacin or cefoxitin. Twenty-four patients had surgery in addition to medical therapy. Forty-nine patients converted sputum cultures to negative, but 16 relapsed. There were significantly more surgical patients who culture converted compared with medical patients. Seventeen (15.9%) deaths occurred in the study population.

Jeon et al [3] also recently published the results of antibiotic treatment for 65 patients with M. abscessus lung disease. Patients were initially hospitalized and treated with 4 weeks of parenteral amikacin and cefoxitin or imipenem followed by surgical excision, whereas only 3 subjects were successfully treated with antibiotics alone. Eighteen patients (15%) died as direct result of their lung disease.

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Now the rainman gave me 2 cures, then he said “jump right in”. The one was Texas medicine, the other was railroad gin. And like a fool I mixed them, and it strangled up my mind… (“Stuck inside of Mobile with the Memphis blues again,” Bob Dylan)

So, what has changed in the management of M. abscessus lung disease in the last 17 years? In the study by Jarand et al [2], the
major changes in therapy compared with 1993 appear to be the routine use of multiple agents including drugs that were not widely used prior to 1993, especially clarithromycin and azithromycin. Additionally, Jarand et al [2] used prolonged courses of parenteral agents and more aggressive use of adjunctive surgery. The microbiologic results are unquestionably better overall than in 1993, but it is yet to be determined what the long-term relapse rate will be. Jarand et al [2] certainly do not offer the promise of an easy way out of the M. abscessus treatment dilemma.

Perhaps the most important new development has been the discovery of an inducible macrolide resistance gene or *erm* gene in *M. abscessus* [4]. The presence or activity of this gene would not have been appreciated by standard in vitro susceptibility methods used in the studies cited above [1–3]. Rather, the effect of this gene on the macrolide minimum inhibitory concentration (MIC) for an *M. abscessus* isolate could only be revealed in vitro by determining the organism MIC after incubation of the isolate in media containing the macrolide. The discovery of the *erm* gene at least offers a window into one mechanism for *M. abscessus* antibiotic resistance and may have relevance to multiple other mycobacteria.

The recognition of this inducible macrolide resistance gene makes the generally poor results of macrolide-based regimens more comprehensible but conversely, this discovery makes the findings of Jeon et al [3] more difficult to understand. These patients were treated primarily with clarithromycin, ciprofloxacin, and doxycycline. With an active *erm* gene, they basically received only ciprofloxacin and doxycycline, which have very limited in vitro activity against *M. abscessus*. There are possible explanations for the results reported by Jeon et al [3]. First, this cohort of patients had generally mild disease as 83 (44%) of 188 patients did not require any therapy. The treatment cohort may have been a select group with mild disease and predisposed to favorable treatment response. Second, the *erm* gene in some *M. abscessus* isolates can be inactive and therefore not functional. Third, some *M. abscessus* isolates are now subtyped by molecular methods as *M. massiliense*, which apparently either does not carry the *erm* gene or the *erm* gene is inactive which would result in more favorable response to macrolide therapy [5]. Perhaps a significant number of these patients were infected by *M. massiliense* rather than *M. abscessus* (see below).

This newly identified species discrepancy is indeed ironic given the long (>20 years) and, sadly, ongoing battle to convince mycobacterial labs to identify isolates as *M. abscessus* rather than *M. something/abscessus* complex. This struggle is now further complicated because *M. massiliense* is apparently genetically identical to *M. bolletii* so that *M. massiliense* will soon be relegated to the taxonomic trashheap in favor of the name *M. abscessus* subspecies *bolletii* [6]. This dizzying taxonomy roller coaster offers one more compelling reason for all mycobacterial laboratories to offer routine molecular analyses for accurate, current mycobacterial species identification.

What is not new since 1993 is equally important to consider. The medical treatment of *M. abscessus* lung disease still cannot be reliably guided by in vitro drug susceptibility test results. Not even the macrolides, which have been the foundation of *M. abscessus* therapy, can be depended on to have in vivo activity in the wake of the *erm* gene discovery. There are still only a handful of drugs that have even modest activity against *M. abscessus* either in vitro or in vivo. On reflection, the lack of new effective antimicrobials over the last 17 years is perhaps the most discouraging aspect of *M. abscessus* disease. Both tigecycline and linezolid appeared promising, based on initial in vitro testing, but have subsequently joined the ranks of other under achieving agents in the pantheon of drugs used for *M. abscessus* [7, 8]. Surgical intervention, however, has been a consistently important and statistically significant treatment adjunct for selected patients [1–3]. Interestingly, the mortality of patients with *M. abscessus* lung disease was almost identical in the Jarand et al study compared with 1993 in spite of the improved clinical response rate [1, 2]. Fifteen percent mortality with this disease could be perceived as relatively low, given the generally poor microbiologic treatment response. Perhaps mortality is more related to underlying disease than microbiologic response to therapy.

The 2007 ATS/IDSA guidelines for treatment of NTM disease noted, “At present, there is no reliable or dependable antibiotic regimen, even based on in vitro susceptibilities, including parenteral agents, to produce cure for *M. abscessus* lung disease” [9], a sentiment echoed by Jeon et al [3], who noted, “The optimal therapeutic regimen and duration of treatment for *M. abscessus* lung disease has not been established.”

The choices of antimicrobial agents are limited by poor in vivo performance, difficulty administering the drugs, drug toxicities, and the unavoidable inconvenient truth that there is still no reliable correlation between in vitro susceptibility testing and in vivo response, except perhaps for macrolides when tested under conditions that reveal the presence of the *erm* gene. At present, the unfortunate clinician is left to contemplate an array of antibiotic choices for *M. abscessus* lung disease without a reliable guide.
At this juncture, I am not persuaded that most patients with *M. abscessus* lung disease should have therapy any less aggressive than that used by Jarand et al [2]. In my opinion, caution is warranted if the regimen outlined by Jeon et al is chosen [3]. I am concerned that it may not be appropriate for patients with severe or advanced disease, and it behooves clinicians prescribing this regimen to monitor patients closely for treatment response. A larger prospective trial of this regimen would be most helpful. Additionally, it simply cannot be ignored that surgery was an important adjunct to medical therapy in all 3 studies but, as cautioned by Jarand et al, should be performed preferentially in centers with mycobacterial disease surgery expertise [1–3].

Information provided to the clinician needs to reflect the recent advances in the mycobacteriology laboratory, specifically, clinicians need to know the species of each clinically significant isolate, whether it is *M. abscessus* or *M. abscessus* subspecies *bolletii* or even *M. chelonae* (which also does not contain the erm gene) and if *M. abscessus* is isolated, is the erm gene active? Lastly, new, more effective drugs are desperately needed. For instance, the diarylquinoline TMC207 has impressive in vitro activity against *M. abscessus* but has not been tested clinically in patients with *M. abscessus* lung disease [10]. While this drug appears to be a very important addition to the treatment of drug resistant tuberculosis (TB), a small carefully monitored trial to evaluate in vivo efficacy for *M. abscessus* disease should not jeopardize its role in treating TB.

I see my light come shining from the west unto the east. Any day now, any day now, I shall be released ("Any day now," Bob Dylan)

Progress has been painfully and frustratingly slow with *M. abscessus* disease, and the goal that this disease can be viewed as predictably curable is not in sight. Sometimes it seems that the question is not why some people improve with current therapy for *M. abscessus* disease, but rather, why does anyone improve with current therapy for *M. abscessus* disease. The work by Jarand et al is another step forward in that process, a process that I hope will culminate in the successful treatment of all patients with *M. abscessus* disease and one that will not include another 17 years of frustration [2].

Acknowledgments

With gratitude to my colleagues R. J. Wallace, Jr., MD, and Barbara Brown Elliott MS, MT (ASCP) S. M.

Financial support. Supported in part by the W. A. and E. B. Moncrief Distinguished Professorship.

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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