

# *Mycobacterium abscessus* subsp *abscessus* lung disease: ‘trouble ahead, trouble behind...’

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## Abstract

*Mycobacterium abscessus* subsp *abscessus* is the most common respiratory pathogen among the rapidly growing non-tuberculous mycobacteria (NTM) and is also the most feared due to its well-deserved reputation for being refractory to antibiotic therapy. *M. abscessus* subsp *abscessus* has multiple innate antibiotic resistance mechanisms, but the most important one described so far is an inducible erythromycin methylase (*erm*) gene. *M. abscessus* subsp *abscessus* isolates may appear macrolide susceptible on initial *in vitro* testing but become macrolide resistant after exposure to macrolide. It is therefore very important to test clinically significant *M. abscessus* subsp *abscessus* isolates for *erm* gene activity. Remarkably, controversy still exists about the taxonomy and nomenclature of *M. abscessus* subspecies including subsp *abscessus*, subsp *massiliense* and subsp *bolletii*. Identification of these subspecies is not moot as *M. abscessus* subsp *massiliense* does not have an active *erm* gene resulting in both *in vitro* and *in vivo* susceptibility to macrolide. It is imperative from the clinician’s perspective that mycobacterial laboratories correctly and rapidly identify *M. abscessus* to the subspecies level. Unfortunately, there are no reliably or predictably effective treatment regimens for *M. abscessus* subsp *abscessus* and better, more effective antimicrobial agents are badly needed. Surgical resection of involved lung tissue as an adjunct to antibiotic therapy is beneficial in selected patients but cannot be broadly applied. Overall, *M. abscessus* subsp *abscessus* remains a formidable respiratory mycobacterial pathogen, one that we are only beginning to understand microbiologically and one that as yet consistently evades our best efforts at successful therapeutic outcomes.

‘trouble ahead, trouble behind, and you know that notion just crossed my mind’.

Casey Jones, Grateful Dead (1970)

## Introduction

Of the non-tuberculous mycobacteria (NTM) commonly isolated from clinical respiratory specimens, *Mycobacterium abscessus* subsp *abscessus* is neither the most common nor the most virulent NTM human pathogen [1]. However, because it is notoriously refractory to therapy, it has achieved a well-deserved status as one of the most feared and difficult-to-manage NTM pathogens. *M. abscessus* subsp *abscessus* is part of a group of NTM—along with *M. chelonae*, *M. fortuitum*, and others—termed the rapidly growing mycobacteria (RGM) on the basis of *in vitro* growth characteristics. For the purposes of this article, *M. abscessus* refers to organisms not further subspeciated.

*M. abscessus* was recognized as a distinct species over 20 years ago when it was separated from the *M. chelonae/abscessus* or *M. fortuitum/chelonae* complexes. Sadly, even after two decades, many laboratories still report *M. abscessus* isolates as part of a complex rather than by species.

## Taxonomic uncertainty

The uncertainty and confusion about the identification and reporting of RGM clinical isolates are largely due to the inability of most microbiology laboratories to make species and subspecies identifications that require molecular laboratory techniques not widely available largely due to financial constraints. It is unfortunate that many,

if not most, microbiology laboratories will not have the capability to make species and subspecies identifications of RGM isolates in the near future. These identifications are not moot. For instance, *M. chelonae* and *M. fortuitum* are uncommon causes of NTM lung disease and might be viewed with appropriate skepticism as true pathogens if only a single clinical isolate is obtained [2,3]. More importantly, RGM species identification helps guide therapeutic decision making.

Further confounding the RGM taxonomic complexity is the recent recognition that *M. abscessus* can be split further into subspecies on the basis of the activity, or lack of activity, of an inducible macrolide resistance gene. Macrolide antimicrobial agents act by binding to the 50S ribosomal subunit and inhibiting peptide synthesis. Erythromycin methylase (*erm*) genes, a diverse collection of methylases that impair binding of macrolides to ribosomes, reduce the inhibitory activity of these agents. The primary mechanism of innate clinically significant macrolide resistance for RGM is the presence of an inducible *erm* gene (*erm* 41) [4,5]. Most isolates of *M. abscessus* subsp *abscessus*, *M. fortuitum*, and several other RGM, but not *M. chelonae*, contain an active inducible *erm* gene. Parenthetically, there is also a novel *erm* gene in *M. tuberculosis*, which explains the poor response of *M. tuberculosis* to macrolide antibiotics. The most interesting aspect of this inducible gene is that, if an *M. abscessus* subsp *abscessus* isolate is exposed to macrolide, the *erm* gene activity is induced with subsequent *in vivo* macrolide resistance, which may not be reflected by the initial *in vitro* minimal inhibitory concentration (MIC) of the organism for the macrolide. Stated another way, the organism may appear to be susceptible *in vitro* to the macrolide but will not respond to the macrolide *in vivo*. This *in vivo* macrolide resistance that does not affect the initial *in vitro* MIC for macrolide has been termed 'cryptic resistance' and requires incubation of an NTM isolate with macrolide prior to determining an MIC for the macrolide. It appears to be one mechanism for the discrepancy between *in vitro* susceptibility results and *in vivo* responses for *M. abscessus* subsp *abscessus*. An *M. abscessus* subsp *abscessus* isolate may have a mutation inactivating the *erm* gene, resulting in retention of *in vitro* and *in vivo* macrolide susceptibility, so that both molecular identification of the *erm* gene and phenotypic analysis of macrolide susceptibility are necessary.

Mycobacterial isolates previously identified as *M. abscessus* have undergone a taxonomic split with the designation of three subspecies: *M. abscessus* subsp *massiliense*, *M. abscessus* subsp *bolletii*, and *M. abscessus* subsp *abscessus*. *M. abscessus* subsp *bolletii* and *M. abscessus* subsp *massiliense* are regarded as identical by the widely adopted mycobacterial technique for speciation using 16S ribosomal RNA gene sequencing [6–8]. This gene is highly conserved in the mycobacterial

genome such that very small sequence differences can usually define a new mycobacterial species. However, it was subsequently shown that, elsewhere in the genome, the organism identified as *M. abscessus* subsp *massiliense* had a smaller, inactive *erm* gene compared with *M. abscessus* subsp *bolletii* [9]. In a confusing twist, the name *M. abscessus* subsp *bolletii* was first proposed as a designation for the organisms with identical 16S ribosomal RNA gene sequences presumed to be the same *M. abscessus* subspecies [10]. After further analysis, however, these organisms have subsequently been identified as two subspecies [9,11]. *M. abscessus* subsp *massiliense* is the consensus taxonomic designation for the *M. abscessus* subspecies with an inactive *erm* gene, whereas the designation *M. abscessus* subsp *bolletii* is applied to the *M. abscessus* subspecies with an active *erm* gene [11]. As noted, *M. abscessus* subsp *abscessus* also usually has an active *erm* gene. Hopefully, these taxonomic designations will soon be formally proposed and accepted.

The implications of the taxonomic uncertainty for clinicians are at least two-fold. First, in perhaps an esoteric vein for clinicians, 16S ribosomal RNA gene sequencing may not be useful for comparing closely related mycobacterial species. Second, and more importantly, contemporary microbiology labs that depend on traditional microbiological techniques for species identification do not have adequate technology for separating NTM species or subspecies. Organism identification facilitates informed decision making by the clinician. If the species identified from a patient is *M. abscessus* subsp *massiliense*, then the *erm* gene is inactive so that macrolides should be effective *in vivo* for this organism. Conversely, the identification of an *M. abscessus* subsp *abscessus* isolate means the almost certain presence of an active *erm* gene and therefore less chance of response with macrolide-containing regimens.

### Antibiotic resistance

Although species identification may be helpful to clinicians for presumptive antibiotic choices, the most important laboratory determination is whether or not an RGM species has an active or functioning *erm* gene, which absolutely dictates therapeutic choices regardless of the taxonomic designation of an organism. The determination of *erm* gene activity can be accomplished by non-molecular techniques that are within the capabilities of most microbiology laboratories that do *in vitro* drug susceptibility testing for NTM isolates. The isolate in question is incubated for a period of time in the presence of macrolide prior to measuring the MIC of the organism for macrolide. This information is not only invaluable for managing the patient's antibiotic regimen; just as taxonomic designation informs presumptive *erm* gene activity, knowing *erm* gene activity informs likely taxonomic identity. For instance, *M. chelonae* and *M. abscessus* subsp

*massiliense* do not have active *erm* genes, so macrolide incubation would have no effect on the MIC of the organism for macrolides. Conversely, *M. abscessus* subsp *abscessus* isolates usually possess an active *erm* gene (in the absence of an inactivating 28 T→C *erm* gene mutation) and would be expected to promote a significant rise in MIC for macrolide following macrolide incubation.

The problems of effectively treating *M. abscessus* subsp *abscessus* infections result primarily from the presence of the inducible macrolide resistance (*erm*) but are also the consequence of many other antibiotic resistance mechanisms of the organism. The *M. abscessus* subsp *abscessus* genome includes some other disconcerting features such as an additional *erm*-like gene, multiple efflux pumps, an aminoglycoside 2'-N-acetyltransferase, and 12 homologs of aminoglycoside phosphotransferases [12]. These antibiotic resistance mechanisms are likely explanations for the frequent failure of antibiotic treatment of *M. abscessus* subsp *abscessus* disease. Van Ingen and colleagues hypothesized that *M. abscessus* subsp *abscessus* has acquired *erm* genes, aminoglycoside-converting enzymes, and other armaments, not because of antibiotics but as protective mechanisms against the antimicrobial molecules secreted by the micro-organisms with which *M. abscessus* subsp *abscessus* shares its environmental habitats such as soil and water [13]. It shares these habitats with micro-organisms, including *Streptomyces* and closely related genera that are the source of aminoglycoside and macrolide antibiotics. The close contact is illustrated by the large number of genes that *M. abscessus* subsp *abscessus* has acquired from *Streptomyces* and related genera by lateral gene transfer. Perhaps drug susceptibility in mycobacteria is acquired and reflects the low level of competition in, and adaptation to, a closer-to-human environmental niche. In turn, mycobacteria that inhabit the most competitive environmental niches are the least adapted to humans, thus are of low clinical significance, but are most tolerant to antibiotics derived from microbes with which they share their habitat, lowering the chances of cure in case of infection [13].

Aside from these innate resistance mechanisms, acquired macrolide resistance can occur as a result of mutation(s) in the 23S rRNA gene, which is usually the consequence of macrolide monotherapy for an *M. abscessus* subsp *abscessus* organism and can occur in the presence or absence of an active *erm* gene [14]. This is the mechanism of mycobacterial resistance familiar to clinicians managing tuberculosis patients. The possible emergence of acquired macrolide mutational resistance again underscores the importance of both molecular and phenotypic drug susceptibility analysis.

The multiple innate mechanisms of antibiotic resistance, especially *erm* gene activity, displayed by *M. abscessus* subsp

*abscessus* at least partially explain in retrospect the long-recognized discordance between apparent *in vitro* susceptibility and poor *in vivo* response to the agent with putative susceptibility. Perhaps not surprisingly, there are many other NTM species and pathogens that share this frustrating property with *M. abscessus* subsp *abscessus* (including *M. avium* complex, *M. xenopi*, *M. malmoense*, and *M. simiae*) and although the explanations are not yet forthcoming (these non-RGM organisms do not possess *erm* genes, for instance), the recent work with *M. abscessus* subsp *abscessus* may offer a window into the complex relationship between *in vitro* susceptibility results and *in vivo* effect of antibiotics for NTM.

### Treatment

In the context of the extensive innate drug resistance, the treatment of *M. abscessus* subsp *abscessus* lung disease remains difficult, and results are inconsistent as reflected in two very different recently published studies. Jarand and colleagues reported a retrospective analysis of treatment outcomes for 107 patients with *M. abscessus* pulmonary disease [15]. Antibiotic treatment was individualized on the basis of 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 one drug, most commonly amikacin or cefoxitin, was stopped because of side effects or toxicity in the majority of patients. 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, a number similar to that found in a study of RGM lung disease published 20 years ago [2].

Jeon and colleagues published the results of antibiotic treatment for 65 patients with *M. abscessus* lung disease [16]. Patients were initially hospitalized and treated with 4 weeks of parenteral amikacin and cefoxitin in combination with oral drugs, including clarithromycin, ciprofloxacin, and doxycycline. Patients tolerated the cefoxitin for an average of only 22 days. Sputum conversion and maintenance of negative sputum cultures for more than 12 months were achieved in 58% of patients. Surgical resection was performed in 22% of patients. Seven (88%) of eight patients with preoperative culture-positive sputum achieved and maintained culture negativity post-operatively. Sputum conversion with macrolide-resistant strains occurred in 27% of patients versus 71% with macrolide-susceptible strains (*erm* gene activity was not determined). Treatment success was associated with *in vitro* susceptibility to clarithromycin but not with any of the

other antimicrobial agents used. These sputum conversion rates are surprisingly high given the *in vitro* susceptibility pattern of *M. abscessus* previously reported for fluoroquinolones and doxycycline and the relatively short period of parenteral therapy. One explanation for these surprisingly good results is the presence of a high percentage of isolates that were really *M. abscessus* subsp *massiliense*, without an active *erm* gene, in the study population.

Subsequent work has shown that patients with *M. abscessus* subsp *massiliense* infection have a much more favorable response to macrolide-based therapy, presumably due to an inactive *erm* gene, than patients infected with *M. abscessus* subsp *abscessus* [17,18]. It was reported that clarithromycin induces greater *erm* gene activity than azithromycin and thus higher macrolide resistance than azithromycin [19]. A more recent report refuted this observation, however, so there is no clear clinically relevant advantage of azithromycin over clarithromycin in the treatment of *M. abscessus* subsp *abscessus* [20]. The two macrolides appear to be equally effective against *M. abscessus* subsp *massiliense* [19].

For unclear reasons, in the US but not in Korea, there appears to be more lung disease caused by *M. abscessus* subsp *abscessus* than *M. abscessus* subsp *massiliense*. However, there is a clear treatment advantage with macrolide-based regimens for *M. abscessus* organisms without an active *erm* gene. Even if a laboratory is unable to identify *M. abscessus* isolates to the subspecies level, any laboratory should be capable of determining the MIC for macrolide for an *M. abscessus* isolate after incubation of that isolate in the presence of macrolide.

### Newer antimicrobial agents

Newer antimicrobial agents such as linezolid and tigecycline are tantalizingly active *in vitro* against *M. abscessus* but rather disappointing, at least so far, for treating *M. abscessus* subsp *abscessus* lung disease *in vivo* [21,22]. In a study of 52 patients receiving tigecycline for emergency/compassionate use for *M. abscessus* infections, most patients with pulmonary or skin and soft tissue infections clinically improved [23]. However, 90% of the patients reported adverse events, primarily nausea and vomiting. To date, there are only preliminary or anecdotal reports of linezolid activity for *M. abscessus* subsp *abscessus* lung disease. It is perhaps informative that adverse events for tuberculosis patients treated with linezolid occur with a frequency similar to that noted for tigecycline [24].

In a recent study of time-kill curves for tigecycline and linezolid with *M. abscessus* subsp *abscessus*, it was found that neither agent was bactericidal against *M. abscessus* subsp *abscessus* [25]. The authors concluded that the lack

of bacteriocidal antibiotics in currently recommended treatment regimens provides a reasonable explanation for the poor therapeutic outcomes in *M. abscessus* subsp *abscessus* infection. This observation appears to be one more example of innate antibiotic resistance exhibited by this organism. Given the toxicity and expense of these antibiotics and given the context of (apparently) sub-optimal *in vitro* and *in vivo* activity, these drugs have not proven to be the 'silver bullets' in the management of *M. abscessus* subsp *abscessus* lung disease.

### Conclusion

The optimal therapy for *M. abscessus* subsp *abscessus* lung disease remains problematic and elusive and usually requires one or more parenteral agents. Antibiotic choices are usually made on the basis of *in vitro* susceptibility results, but as already noted, there is poor correlation between *in vitro* susceptibility for a specific antibiotic and *in vivo* response to that antibiotic. The net result is a lack of a reliable or predictable treatment response even with therapy guided by *in vitro* susceptibilities. *M. abscessus* subsp *massiliense* responds in a more predictably favorable manner to macrolide-containing regimens than *M. abscessus* subsp *abscessus*, and it remains unclear whether there is a significant role to play for macrolide in most *M. abscessus* subsp *abscessus* lung infections. My own practice is to routinely use parenteral amikacin and tigecycline with oral linezolid, but I cannot point to support of that regimen in the medical literature. Surgery for limited *M. abscessus* subsp *abscessus* lung disease, combined with antibiotic agents, also clearly offers an improved treatment outcome but is an option for only a minority of selected patients [2,18,19]. Clearly, better, more effective agents for treating *M. abscessus* subsp *abscessus* are much needed. Perhaps the new diarylquinoline, bedaquiline, will improve therapeutic outcomes with *M. abscessus* subsp *abscessus* [26]. Van Ingen and colleagues have pointed out that, because of the unique mechanism of action of the diarylquinolines, it is possible that *M. abscessus* subsp *abscessus* would not have significant innate resistance to this drug, but it is so far untested in the treatment of patients infected with *M. abscessus* subsp *abscessus* [12].

Progress with *M. abscessus* subsp *abscessus* disease remains frustratingly slow and incremental. Laboratory support for clinicians is all too commonly suboptimal, and treatment strategies remain frustratingly ineffective. However, in the midst of this generally unsatisfactory scenario, new and important insights into the mechanisms of antibiotic resistance exhibited by *M. abscessus* subsp *abscessus* have been discovered and will undoubtedly lead to more successful treatment outcomes in the future.



## Abbreviations

*erm*, erythromycin methylase; MIC, minimal inhibitory concentration; NTM, non-tuberculous mycobacteria; RGM, rapidly growing mycobacteria.

## Disclosures

The author declares that he has no disclosures.

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