# Treatment of *Mycobacterium abscessus*

## All Macrolides Are Equal, but Perhaps Some Are More Equal than Others

*Mycobacterium abscessus* is a challenging pathogen causing chronic respiratory infections in patients with underlying inflammatory lung diseases (such as cystic fibrosis, non–cystic fibrosis bronchiectasis, and chronic obstructive pulmonary disease) as well as in individuals with poorly defined susceptibility factors (1). This rapid growing nontuberculous mycobacterium (NTM) is in fact a complex of three subspecies—*M. abscessus*, *M. massiliense*, and *M. bolletii*—that are not currently distinguished by hospital laboratories but may have different clinical behaviors. For unclear reasons, infections with *M. abscessus* complex (MABSC) have become more common recently. Studies from Taiwan, the United States, and Australia have all reported significant increases in the prevalence of MABSC pulmonary infection over the past decade (2–4), which is of particular concern because this organism is resistant to many antimicrobial agents and responds poorly to treatment. For example, one of the larger studies of pulmonary MABSC infection examined 69 patients treated at National Jewish Health between 2001 and 2004 (5). Patients received intensive therapy that included an average of 6 months of intravenous antibiotics as well as oral antibiotics, and 24 (35%) also had surgical resection of affected lung tissue. Despite this intensive treatment, only 33 (48%) had sustained culture conversion to negative for at least 1 year after antibiotics were discontinued.

The second-generation macrolides clarithromycin and azithromycin are key components of MABSC treatment. The current American Thoracic Society/Infectious Diseases Society of America guidelines for treatment of NTM recommend use of one of these agents as part of a multidrug regimen, with no stated preference for one macrolide or the other (6). In the absence of head-to-head clinical trials, the choice of macrolide is driven by clinician preference and the potential for drug interactions. The report by Choi and colleagues (7) in this issue of the *Journal* (pp. 917–925) provides some interesting insights into why MABSC pulmonary infection responds suboptimally to antibiotic therapy, how the two subspecies *M. abscessus* and *M. massiliense* behave differently *in vitro* and *in vivo*, and how clarithromycin and azithromycin may differentially influence the development of macrolide resistance.

Macrolides function as antibiotics by binding to the 23S ribosomal RNA to block bacterial protein synthesis (Figure 1). Many bacteria can sense macrolides, usually through direct or indirect detection of ribosomal stalling, and express "*erm*" methyl transferases (*erythromycin resistance methylase*) that modify the ribosomal binding site for macrolides causing antibiotic resistance. In the case of *M. abscessus*, erythromycin resistance methylase is expressed by a novel gene, named "*erm*(41)," in response to low-level exposure to erythromycin or clarithromycin and mediates high-level macrolide resistance (8).

Choi and colleagues examined the role of the *erm*(41) gene in macrolide resistance and the differential effects of clarithromycin and azithromycin in induction of *erm*(41)-mediated resistance using a number of complementary approaches. First, macrolide resistance was assessed, using broth microdilution, at baseline and over 14-day incubation with either clarithromycin or azithromycin for 23 *M. abscessus* and 24 *M. massiliense* clinical isolates. Inducible macrolide resistance was observed in all *M. abscessus* isolates and was significantly greater after exposure to clarithromycin than to azithromycin. In contrast, none of the isolates of *M. massiliense* (which has a nonfunctional *erm*(41) gene) demonstrated any inducible resistance to either antibiotic. The authors then examined *erm*(41) mRNA induction in response to incubation with

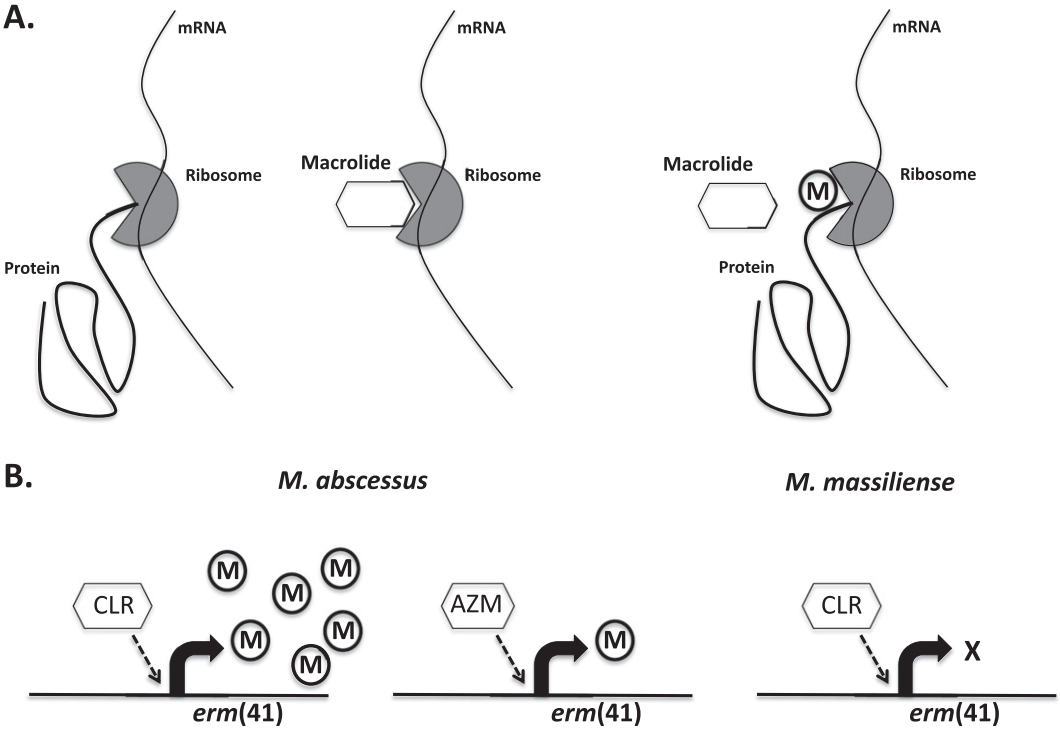


***Figure 1.*** Mechanism of macrolide action and inducible macrolide resistance. (*A*) Macrolide antibiotics bind to the 23S ribosomal RNA, preventing bacterial protein synthesis. Expression of erm (*erythromycin resistance methylase*) proteins in response to macrolides leads to modification of their ribosomal binding site and induction of macrolide resistance. (*B*) Induction of *erm*(41) and subsequent macrolide resistance is greater after exposure to clarithromycin (CLR) than to azithromycin (AZM) in *Mycobacterium abscessus* subspecies. However, neither macrolide can induce resistance in *M. massiliense*, because it carries a defective *erm*(41) gene.

macrolides. As expected, clarithromycin induced far higher *erm* (41) mRNA levels in *M. abscessus* than did azithromycin. Knocking out the *erm*(41) gene in *M. abscessus* eliminated the inducible macrolide resistance, whereas adding a functional *erm*(41) gene to *M. massiliense* bestowed inducible resistance to that subspecies. The authors then tested azithromycin and clarithromycin in a murine bone marrow–derived macrophage system, where azithromycin reduced *M. abscessus* colony-forming units significantly more than clarithromycin, but the two drugs were similarly effective for *M. massiliense*. Finally, the authors tested the two drugs in a murine lung infection model. Although both macrolides reduced the burden of *M. abscessus* organisms in the mouse lungs, azithromycin reduced the colony counts significantly more than clarithromycin. Conversely, both macrolides were equally effective when mice were infected with *M. massiliense*.

Although there is uncertainty about how relative increases in *erm*(41) mRNA induction by the two macrolides and subsequent resistance profiles detected *in vitro* translate to clinical outcomes and the fidelity of mouse infection model in studying human NTM disease, the results presented by Choi and coworkers arrive at the same conclusions using a number of complementary approaches: (*1*) inducible macrolide resistance mediated by *erm*(41) is important in modulating the effectiveness of macrolide treatment for *M. abscessus*; and (*2*) clarithromycin induces *erm*(41) to a significantly greater extent than azithromycin. The one available human study comparing treatment outcomes of *M. abscessus* with *M. massiliense* lung disease provides support to the authors' conclusions. In that study, patients with *M. abscessus* infection had significantly lower rates of sputum culture conversion in response to clarithromycin-based therapy than patients with *M. massiliense* despite similar baseline characteristics (9). Why azithromycin should induce *erm*(41) to a lesser extent than clarithromycin is unclear but may relate to antibiotic-specific (and possibly multiple) ribosomal binding sites (10) or differential activation of stress pathways, similar to *whiB7* in *M. tuberculosis* (11), which may regulate *erm*(41) transcription in *M. abscessus*.

Although sorely needed, no randomized clinical trials of treatment for *M. abscessus* lung infection are, to our knowledge, on the immediate horizon. Pending such studies, the work of Choi and colleagues suggests that azithromycin should be the macrolide of choice in treatment of *M. abscessus* pulmonary disease and that accurate subspeciation of MABSC may have important clinical implications for the management of this difficult infection.

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

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**DOI: 10.1164/rccm.201208-1500ED**