Disease Caused by *Mycobacterium Abscessus* and Other Rapidly Growing Mycobacteria (RGM)

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Taxonomy

Historical Background and Current RGM Classification

The term rapidly growing mycobacteria (RGM) was originally used to describe mycobacterial organisms with growth on subculture in less than 7 days. The first rapidly growing mycobacterium was described in the early twentieth century when *Mycobacterium chelonae* was recovered from the lungs of sea turtles [1]. *Mycobacterium fortuitum* was originally recovered from frogs in 1905 and dubbed *Mycobacterium rana*e later to become *M. fortuitum* at the suggestion of Ernest Runyon [2]. In 1953 *Mycobacterium abscessus* was first reported as a cause of human skin and soft tissue infection in a patient with multiple soft tissue abscesses [3].

There are now more than 75 recognized RGM species, representing approximately 50% of all mycobacterial species. (Table 1) [4–11]. The three most clinically important pathogenic species that represent more than 80% of clinical RGM isolates are *M. fortuitum*, *M. chelonae*, and *M. abscessus*. *Mycobacterium abscessus* was separated from *M. chelonae* more than 20 years ago, but some mycobacterial laboratories still utilize anachronistic nomenclature labeling *M. abscessus* isolates with a group label, "*M. chelonae/abscessus* complex," rather than species or subspecies identification. This approach is not adequate or acceptable for contemporary RGM disease management.

Unfortunately, even the advent of molecular organism identification methods has not eliminated nomenclature confusion as illustrated by the recent controversies surrounding *M. abscessus* species and subspecies taxonomic designations.

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Table 1 RGM species associated with human disease

Common	*M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*
Infrequent	*M. chelonae*, *M. fortuitum*, *M. porcinum*, *M. abscessus* subsp. *bolletii*
Rare but proven pathogens	*M. fortuitum* group (*M. boenickei*, *M. houstonense*, *M. peregrinum*, *M. senegalense*), *M. franklinii*, *M. immunogenum*, *M. mageritense*, *M. mucogenicum*[a], *M. wolinskyi*, *M. bacteremicum*, *M. canariasense*[c], *M. celeriflavum*, *M. cosmeticum*, *M. goodii*[c], *M. iranicum*, *M. neoaurum*, *M. smegmatis*

[a]*M. mucogenicum* group is composed of *M. mucogenicum*, *M. aubagnense*, and *M. phocaicum*
[c]Late pigmentation

Mycobacterium bolletii and *M massiliense* were originally described as unique species distinct from *M abscessus* in 2004 and 2006, respectively, but were subsequently found to be indistinguishable based on 16S rRNA sequence analysis [5, 12–15]. This latter finding suggested that the putatively unique species were in fact the same species [12–15]. In 2011, a proposal was made that the two organisms should be combined as one species and reclassified as *M. bolletii* [14]. Subsequently, with multigene and whole genome sequencing, it became apparent that the two organisms are in fact distinct species with an extremely important genetic difference [15, 16]. One organism has an active erythromycin ribosomal resistance methylase (*erm*) gene and one does not. The *erm* gene results in methylation of the 23S rRNA macrolide binding site and inducible loss of macrolide activity/function, discussed in detail below.

Adoption of the 2011 proposal would have created significant confusion because the taxonomic designation *M. massiliense* had already been widely accepted in the medical literature to describe the "*M. abscessus*" organism without an active *erm* gene, while the term *M. bolletii* was used to describe the other similar organism with an active *erm* gene. There was a clear need to standardize the nomenclature for the three closely related *M. abscessus* organisms, two with active *erm* genes and one with an inactive *erm* gene.

In an effort to clarify this situation, Tortoli et al. recently proposed that the three organisms in the *M. abscessus* complex should be emended to three subspecies: *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *bolletii* with active *erm* genes and *M. abscessus* subsp. *massiliense* with an inactive *erm* gene [16, 17]. The Tortoli proposal is not without controversy as universally accepted criteria for species and subspecies designations does not exist. A counter proposal has recently been advocated to grant species designations for the three *M. abscessus* organisms [18]. It should be emphasized that the M *abscessus* subsp. *massiliense*, or *M. massiliense* as sometimes cited, remains the generally accepted name for the *M. abscessus* organism with an inactive *erm* gene which remains the most clinically important aspect of the taxonomy debate [16, 17, 19, 20]. From a nihilistic standpoint, the clinician may not care what an organism is named but absolutely must know the status of the *erm* gene and in vitro macrolide susceptibility of the organism.

For this chapter we have adopted the *M abscessus* nomenclature suggested by Tortoli et al. with *M. abscessus* subspecies designations [16]. Where possible, an *M. abscessus* subspecies is identified in the text. When the term *M. abscessus* without a subspecies designation is used, it was not possible to tease out a particular subspecies designation. The term *M. abscessus* without a subspecies designation is not, therefore, synonymous with *M. abscessus* subspecies *abscessus* but indicates a lack of subspecies differentiation in the cited references.

Identifying RGM

Laboratory techniques for identifying RGM are briefly summarized here. A detailed discussion is beyond the scope of this chapter. For a more in-depth discussion, please see chapter "Laboratory Diagnosis and Antimicrobial Susceptibility Testing of Nontuberculous Mycobacteria".

Phenotypic laboratory identification of RGM was previously based on growth in subculture in less than 7 days, colony morphology, and biochemical growth requirements. While the group of organisms categorized as RGM can be identified in this manner, definitive RGM identification is not possible. High-performance liquid chromatography (HPLC) of mycolic acids can identify only a few RGM species. HPLC may be useful for separating organisms into complexes or groups but lacks the specificity needed for full species-level identification [11, 21].

Lipid and ribosomal protein analyses by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) is a method currently being used to identify the NTM including RGM [21–23]. Although MALDI-TOF MS has been successful in the identification of many species of NTM, several clinically significant species and subspecies of RGM, including *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*, *and M. abscessus* subsp. *bolletii*, have been difficult to differentiate by MALDI-TOF.

Currently, the only nucleic acid probe available for identification of the RGM is the INNO-LiPA multiplex probe assay (Innogenetics, Ghent, Belgium). The major advantage is that a large variety of species can be identified by a single probe without necessitating the selection of a specific probe for each species. Disadvantages include cross-reactivity among closely related *M. fortuitum* groups and the inability to differentiate isolates of *M. chelonae* from *M. abscessus* [24, 25].

The primary gene target of molecular taxonomic studies has been the 16S rRNA gene which is a highly conserved gene within mycobacterial species [26]. Differentiation of *M. chelonae* and *M. abscessus* and some species within the *M. fortuitum* group requires complete 16S rRNA sequence analysis for species identification unless other gene targets are sequenced. The limitations of complete 16S rRNA sequencing for RGM species and subspecies differentiation were exposed by the recent *M. abscessus* subspecies controversy described above.

The 65-kDa heat shock protein gene (*hsp*65) is also useful for species-level RGM isolates such as *M. abscessus* and *M. chelonae* and for most of the common RGM species [27, 28]. Some RGM species, including *M. fortuitum*, are more readily discriminated with the *hsp*65 gene analysis than by 16S rRNA gene analysis [29]. The *rpo*β gene has been used recently in the identification of RGM, including the identification of several new species [5, 12, 30–33].

Multiple different *erm* genes have been recognized in RGM species, including *erm* (*M. fortuitum*) and *erm* (*M. abscessus* subsp. *abscessus*). Some RGM species such as *M. chelonae* have no detectable *erm* gene which allows reliable identification of this organism.

Whole genome sequencing (WGS) and phylogenomic analysis are the most recently utilized methods for studying genetic variations and population studies in mycobacteria. Whole genome sequencing enables the study of multiple genetic regions which may be associated with pathogenicity, antibiotic resistance, virulence, and/or host relationships to the NTM. [34–38]. As previously noted, there are no universally accepted WGS criteria for defining NTM species and subspecies. Recent publications in cystic fibrosis literature have revealed *M. abscessus* subsp. *massiliense* isolates from patients in different countries including the United Kingdom, Brazil, and the United States, to have high levels of genetic relatedness by WGS and thus provided the first suggestion of possible person-to-person RGM transmission [17, 39, 40]. The future of NTM identification and epidemiological studies will likely be based upon WGS findings.

Clinicians must be familiar with the laboratory methods used for RGM identification including the limitations of the specific methods available to them. Clinicians should clearly communicate to laboratorians that optimal management of RGM disease patients requires timely and accurate organism identification. Clinicians face many challenges impeding successful treatment of these patients, and the laboratory should not be one of them.

Clinical Disease

The RGM are frequently isolated in the environment and have been found in 30% to 78% of soil samples from various geographical regions in the United States [11, 41, 42]. Although it is a much less common occurrence than with *Mycobacterium avium* complex (MAC), *M. abscessus* has also been isolated from municipal water [43]. Until recently, the majority of reported cases were from the United States, with a strong disease geographic localization in the southern United States [11, 44]. Human infections have now been reported from most areas of the developed world (see chapters "Epidemiology of Nontuberculous Mycobacterial Pulmonary Disease (NTM PD) in the USA" and "Global Epidemiology of NTM Disease (Except Northern America)"). The route of organism acquisition for RGM pulmonary disease is presumably inhalation of contaminated aerosols, similar to MAC [44]. Community-acquired localized

skin, soft tissue, and/or bone disease usually follows a traumatic injury with potential soil contamination. Nosocomial infections are strongly associated with tap water exposure or contamination.

Chronic Pulmonary Infections

Chronic RGM pulmonary infections are most often associated with *M. abscessus* subspecies [11, 42, 44] (Tables 2 and 3). The majority are due to either *M. abscessus* subsp. *abscessus* or *M. abscessus* subsp. *massiliense*. These infections are typically

Table 2 Rapidly growing mycobacterial (RGM) species and their common clinical diseases

M. fortuitum group	M. chelonae	M. abscessus
Localized posttraumatic infections	Disseminated skin infections	Chronic lung infections
Catheter infections	Localized posttraumatic wound infections	Localized posttraumatic wound infections
Surgical wound infections	Catheter infections	Catheter infections
Augmentation mammaplasty	Sinusitis	Disseminated skin infections
Cardiac surgery	Corneal infections	Corneal infections

Table 3 Pulmonary syndromes associated with positive respiratory cultures for RGM

Finding	Interpretation	Most common RGM involved
Single AFB smear-negative culture-positive specimen	Transient infection or specimen contamination	M. abscessus
Multiple culture-positive specimens		
Elderly nonsmoking patients, usually female, with nonspecific radiographic findings consistent with bronchiectasis and multiple sputum AFB-positive cultures	Probable nodular bronchiectasis disease: confirm by HRCT[a]	M. abscessus
Cavitary radiographic changes either apical typical of fibrocavitary mycobacterial disease, usually male, or mid and lower lung field associated with bronchiectasis, usually female	Possible association with prior granulomatous disease (TB) or due to progressive nodular/bronchiectatic disease	M. abscessus
Achalasia with chronic vomiting and bilateral interstitial/alveolar infiltrates or known lipoid pneumonia	Chronic pneumonitis, reversal of underlying GI problem essential for adequate therapy	M. fortuitum any RGM
Cystic fibrosis	Focal pneumonitis, transient infection or progressive disease (HRCT may be helpful in determination)	M. abscessus

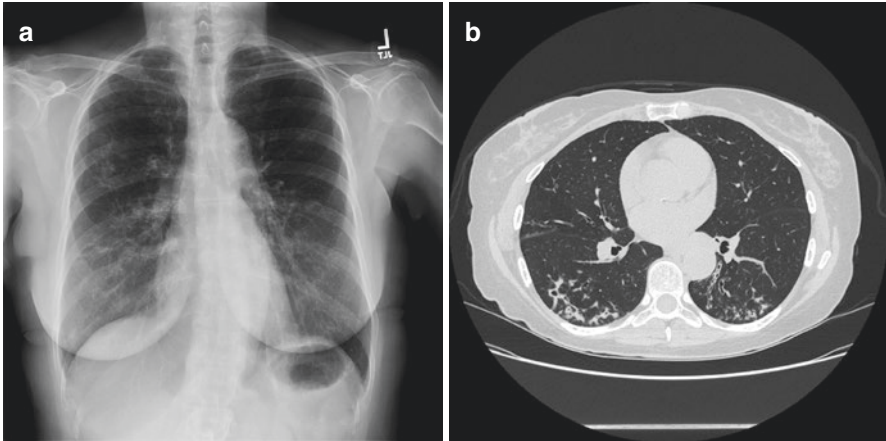[a]HRCT, high-resolution computerized tomography

Fig. 1 *M. abscessus* lung disease with nodular bronchiectasis

found in postmenopausal nonsmoking females who present with chronic cough, weight loss, fatigue, and sometimes hemoptysis. By high-resolution computerized tomography (HRCT) of the chest, most patients have patchy cylindrical bronchiectasis and small nodules involving the right middle lobe and lingua (Fig. 1a, b). This radiographic pattern is referred to as nodular bronchiectatic (NB) disease and is also typical of patients with *Mycobacterium avium* complex (MAC) lung disease. Chronic NB lung disease caused by MAC and *M. abscessus* are radiographically and clinically indistinguishable. RGM lung disease tends to be slowly progressive, with indolent symptomatic and radiographic progression [42, 44].

Patients undergoing therapy for MAC lung disease sometimes have co-isolation of *M. abscessu*s from respiratory specimens. The clinical significance of these isolates is variable and must be determined with longitudinal evaluation [45]. In one recent series of MAC patients with co-isolation of *M. abscessus*, most *M. abscessus* isolates did not appear to be clinically significant when they occurred only once or twice without clinical and radiographic impact [45]. For some patients, however, *M. abscessus* was isolated from multiple specimens over time and was associated with radiographic progression, especially new or expanding lung cavitation. In these patients *M. abscessus* appeared to be a significant pathogen requiring therapeutic intervention. This latter consideration is not inconsequential as there are few antibiotic agents with activity against both MAC and *M. abscessus* subspecies with an active *erm* gene and therefore little overlap in treatment regimens for *M. abscessus* and MAC.

Cavitary lung disease that occurs with *M. abscessus* subspecies is a more aggressive disease than the NB form. Patients with long-standing NB RGM lung disease, either untreated or refractory to treatment, can evolve from NB lung disease to a mixed NB and cavitary lung disease (Fig. 2). Patients with primary cavitary disease are similar clinically to cavitary MAC lung disease patients, usually male with a history of cigarette smoking and COPD. *Mycobacterium abscessus* infection is also

Fig. 2 Bronchiectasis with cavitary lesions in a patient with M. *abscessus* spp. *abscessus*

sometimes associated with other lung diseases and infections that leave residual areas of bronchiectasis and scarring such as tuberculosis.

Pulmonary infections with the *M. fortuitum* group are rare and most often seen in patients with achalasia, chronic vomiting, and other forms of gastrointestinal disturbances associated with chronic aspiration [42]. *Mycobacterium fortuitum* is a relatively non-virulent pathogen and a rare cause of lung disease outside of these conditions [42, 46]. *Mycobacterium mucogenicum* is sometimes a significant pathogen in the setting of chronic obstructive lung disease but overall is rarely associated with progressive chronic pulmonary infection [42]. *Mycobacterium fortuitum* and *M. mucogenicum* are examples of the poor specificity of the current NTM diagnostic guidelines in that patients with multiple sputum AFB cultures positive for *M. fortuitum* or *M. mucogenicum* are unlikely to develop progressive disease and require therapy. In the absence of a specific predisposition, such as chronic aspiration, clinicians are urged to use more rigorous diagnostic criteria for *M. fortuitum* and *M. mucogenicum* isolates than for other more common NTM respiratory pathogens.

Chronic pulmonary infections with *M. abscessus* also are seen in patients with cystic fibrosis (CF) (chapter "Non-tuberculous Mycobacteria in Cystic Fibrosis") [47–49]. Patients with CF have aggressive and rapidly progressive bronchiectasis in addition to chronic recurrent airway and parenchymal infections due to *Pseudomonas aeruginosa* and other bacterial pathogens [48, 49]. Nontuberculous mycobacteria were previously thought not transmissible between humans. Recently, however, geographically widely dispersed cases associated with *M. abscessus* subsp. *massiliense* isolates that are indistinguishable by DNA analysis have been identified, suggesting direct or indirect spread of identical infections that can occur at least in this highly vulnerable population [17, 50].

The most common pathogens associated with CF lung disease in some series have been members of the *M. abscessus* group. One-half of 104 NTM isolates recovered in a multicenter study involving 1582 CF patients in France were *M. abscessus* [51]. A 3-year longitudinal clinical study from Brazil recovered NTM from 8% of 129 children with the majority of RGM isolates *M. abscessus* [52]. An early large study from US CF centers found that *M. abscessus* isolates were second in prevalence to those of the MAC [49]. Although some patients appear to have transient carriage, other patients remain culture positive, with significant symptoms and high morbidity and mortality [49].

The difficulty effectively treating *M. abscessus* lung infections in CF patients adds an additional layer of complexity to their management. Because of resistance to antibiotic therapy and the specter of postoperative infections with poor wound healing, isolation of *M. abscessus* can preclude lung transplant for CF patients in some centers.

Localized Posttraumatic Wound Infections

Wound infections are typically associated with accidental penetrating trauma with soft tissue infection sometimes followed by osteomyelitis [11] (Fig. 3). Patients with this type of infection are usually healthy without systemic immune suppression. After an incubation period of 3–6 weeks, local redness and swelling with spontaneous drainage typically occurs. Systemic symptoms such as fever, chills, malaise, and fatigue are infrequent. The drainage is usually thin and clear but occasionally can be thick and purulent. Sinus tract formations with intermittent drainage are common.

The most common pathogens in these settings are the *M. fortuitum* group including *M. fortuitum*, *M. porcinum*, and *M. houstonense*, but almost any of the pathogenic

Fig. 3 *M. abscessus* subsp. *abscessus* skin and soft tissue infection following penetrating trauma to the finger demonstrating characteristic purple discoloration associated with purulent drainage

RGM species can cause disease in patients with infected open fractures [4, 8, 11]. Furthermore, these infections may be polymicrobial, reflecting environmental contamination with more than one species of mycobacteria or a combination of bacteria and mycobacteria. Timely diagnosis requires clinical suspicion in a patient who is not responding to or improving with standard antibacterial antibiotics.

Surgical Wound Infections

Most outbreaks of healthcare-associated RGM infections or pseudo-infections have been associated epidemiologically with various water sources, including water-based solutions, distilled water, tap water, ice, and ice water [11, 52, 53]. The utilization of pulsed-field gel electrophoresis and randomly amplified polymorphic DNA PCR methods for analyzing genomic DNA has improved the investigation of nosocomial outbreaks [11, 54, 55]. DNA fingerprinting for some of these outbreaks has confirmed molecular identity between water and human isolates. One study of hemodialysis centers in the United States showed that 55% of incoming city water contained mycobacteria, of which RGM species were the most common [56]. Biofilms, which are the lipid-rich layers that form at water-solid interfaces, are present in most water transport pipes. Up to 90% of these from community-piped water systems contain mycobacteria [57]. Compared with free-living mycobacteria, mycobacteria associated with biofilms are more resistant to water treatment [58].

Surgical wound infections, including cataract excision, corneal graft, laser surgery, extremity amputations, dacryocystorhinostomy, plastic surgery of the face, prosthetic hip or knee insertions, coronary artery bypass, excision of basal cell carcinoma, augmentation mammaplasty, and cosmetic surgeries including liposuction and liposculpture, clinically present in a similar fashion to accidental trauma [11, 59–64]. After an incubation period of 2–8 weeks, the healing wound will develop serous drainage and redness. Localized nodular areas adjacent to the incision may develop which are often painful and may require incision and drainage. Isolates of the *M. fortuitum* group are most commonly recovered in these settings, but other species may also be involved [11, 64]. Rare cases of *M. wolinskyi* infection have been reported, mainly skin and soft tissue infection following surgery including cosmetic procedures [65–68]. Additionally, pseudo-outbreaks of *M. abscessus* or *M. immunogenum* related to contaminated automated bronchoscope disinfection machines, contaminated gastric endoscopes, and laboratory contamination have been described [11, 69, 70].

A recent large nosocomial outbreak of *M. abscessus* subspecies in lung transplant patients was associated with positive cultures for *M. abscessus* from patients, biofilms, and water sources obtained from hospital water outlets [71]. Using pulsed-field gel electrophoresis (PFGE), 4 of 10 patients and 8 of 12 environmen-

tal cultures showed the same strain of *M. abscessus*. Multiple interventions were made, and the incidence rate of *M. abscessus* decreased from 3.9 cases/month during the outbreak period to 1 case/month during the intervention period. This decrease in incidence showed that the outbreak of clonally related pulmonary *M. abscessus* was epidemiologically linked to the water sources and amenable to targeted infection control efforts [71]. Please see chapter "Environmental Niches for NTM and Their Impact on NTM Disease" for a more extensive discussion of nosocomial RGM disease.

Catheter-Related Infections

The most common healthcare-associated NTM disease since the 1990s has been central venous catheter infections. These may manifest as occult bacteremia, granulomatous hepatitis, septic lung infiltrates, tunnel infections, or exit site infections [11]. The timing of these infections usually involves catheters that have been in place at least several months. The most frequent etiologic agent is *M. fortuitum*, although pigmented species such as *M. neoaurum* and *M. bacteremicum* have also been associated with catheter sepsis [72–75]. Other long-term catheters, including chronic peritoneal dialysis catheters, hemodialysis catheters, nasolacrimal duct catheters, and ventriculoperitoneal shunts also have been associated with RGM infection [4, 76, 77]. Removal of catheters is necessary for successful treatment.

Disseminated Cutaneous Infections

One type of RGM skin involvement occurs in patients who require chronic steroid therapy and is characterized by the presence of multiple noncontiguous nodules with spontaneous drainage on one or more extremities. These multiple skin lesions develop without life-threatening sequelae and almost always involve the lower extremity and are typically due to *M. chelonae* [11]. Steroid doses may be as low as 5–10 mg of prednisone daily. The most common underlying disease is rheumatoid arthritis but may also include organ transplants and chronic autoimmune disorders [11]. The patients are frequently asymptomatic except for the local discomfort of the lesions.

A second type of disseminated skin disease is seen in immune-compromised patients, some with rapidly fatal disorders such as poorly controlled hematologic malignancies [11, 77, 78]. This type of infection is usually systemic, with positive cultures of the blood and bone marrow. A portal of entry for the organism is rarely identified, although central catheters may be involved. It is usually caused by *M. abscessus* and, combined with the underlying disease, was often fatal in the era before current antimicrobial therapy was available. Interestingly, members of the *M. fortuitum* and *M. mucogenicum* groups are rarely associated with either type of disseminated disease [11, 79]. As with most infections associated with immune sup-

pression, reversal of the immune suppression is necessary for adequate treatment response for the RGM pathogen.

Ophthalmic Infections

A recent study of 100 patients with nontuberculous mycobacterial ophthalmic infections showed that 95% of the infections were due to RGM, commonly *M. chelonae* and *M. abscessus* [80]. Ophthalmic infections due to RGM are often associated with poor visual outcomes despite aggressive treatment [81–83].

Nail Salon/Footbath-Associated Folliculitis

RGM lower extremity skin infections involving *M. fortuitum*, *M. mageritense*, and a newly described species, *M. cosmeticum*, is associated with the use of contaminated nail salon whirlpool footbaths [81–83]. Patients were salon customers with persistent skin infections below the knee [83]. Most often the infections involved a furunculosis of the lower leg hair follicles [82]. The disease pathogenesis likely results from microtrauma caused by shaving the legs prior to pedicures and footbath water that is heavily contaminated with RGM due to failure to routinely clear the footbath filters [82–84].

Anti-TNF-α Therapy-Associated Infections

NTM infections associated with the use of biologic therapies that inhibit tumor necrosis factor alpha (TNF-α) have been reported and are discussed in detail in chapters "Vulnerability to Nontuberculous Mycobacterial Lung Disease or Systemic Infection Due to Genetic/Heritable Disorders and Immune Dysfunction and Nontuberculous Mycobacterial Disease". Patients receiving anti-TNF-α therapy are at high risk for activation of tuberculosis and appear to have some increase in disease risk or difference in clinical manifestation for NTM as well [85]. A recent review of the US Food and Drug Administration MedWatch database reports identified 239 possible cases of NTM disease associated with TNF-α inhibitor use from 1999 to 2006 of which 105 cases (44%) met NTM disease criteria. NTM infections were associated with immunosuppressive therapies including infliximab, etanercept, and adalimumab, while 65% and 55% of patients were also taking prednisone and methotrexate, respectively. Infections with MAC were most commonly reported, while 20/105 cases (20%) involved RGM species including *M. abscessus*, *M. chelonae*, and *M. fortuitum* [85].

Interferon-Gamma/Interleukin 12 (IFN- γ/IL-12)- Associated Infections

IFN-γ/IL12 is an immunological pathway designed for intracellular killing of mycobacteria and is discussed in more detail in chapter "Vulnerability to Nontuberculous Mycobacterial Lung Disease or Systemic Infection Due to Genetic/ Heritable Disorders". An apparently acquired autoantibody-mediated immunodeficiency was recently described and found to be almost exclusively among Asian-born women [86, 87]. Most cases related to NTM were associated with MAC; however, recent reports suggest that approximately 45% of the NTM cases are due to RGM including *M. abscessus* (32%) and *M. fortuitum* (12%). Infections were typically multifocal affecting lymph nodes, osteoarticular tissue, lungs, skin, and/or soft tissues. IFN-γ autoantibodies should be considered in cases of unexplained disseminated NTM infection, especially in the Asian-born population. [86, 87].

Drug Therapy/Drug Resistance

Antimicrobial Susceptibility

Antimicrobial regimens for disease caused by the RGM are usually based upon their in vitro susceptibility patterns. While this approach is appealing from a traditional infectious diseases perspective, it is frequently frustrating with limited practical applicability [11, 42, 88–94]. Recognizing those limitations is a prerequisite for successful RGM patient treatment. RGM isolates are not susceptible to the first-line antituberculous drugs and require in vitro susceptibility testing in specialized laboratories that are experienced in processing RGM. The current drugs that should be tested for susceptibility include amikacin, cefoxitin, imipenem, moxifloxacin, meropenem, sulfamethoxazole or trimethoprim-sulfamethoxazole, clarithromycin, ciprofloxacin, doxycycline/minocycline, linezolid, and tobramycin (the latter only for isolates of *M. chelonae*) [90]. Tigecycline is frequently included in routine testing, but no minimum inhibitory concentration (MIC) breakpoints have been determined [88, 89].

Clarithromycin inhibits all RGM isolates with no functional *erm* gene, including *M. chelonae* and *M. abscessus* subsp. *massiliense* at a concentration of 4 µg/ml at 3 days [90]. The MICs for several species, including *M. abscessus* subsp. *abscessus*, *M abscessus* subsp. *bolletii*, and *M. fortuitum* may be in the susceptible range with only 3 days of incubation but due to the presence of the *erm* gene become resistant with a 14-day macrolide incubation. Most RGM species that have late intrinsic resistance to clarithromycin contain an inducible *erm* gene [91–94]. The finding of the *erm* gene in the RGM helps explain the lack of effectiveness for macrolide therapy despite ostensibly "susceptible" routine in vitro MICs with standard (3 days) incubation times.

It cannot be overemphasized that routine in vitro macrolide susceptibility testing that does not include macrolide preincubation of the RGM isolate for 14 days is not reliable and cannot be used for basing treatment decisions [92]. In 2011, the Clinical and Laboratory Standards Institute (CLSI) recommended the final reading of the clarithromycin MICs for RGM at 14 days, to detect inducible resistance [88]. Alternatively, the need for extended incubation could be eliminated for isolates where *erm* gene functionality has been molecularly determined by *erm* gene sequencing [89].

Multiple studies have shown that patients with RGM lung disease due to an *erm* gene inactive isolate respond significantly more favorably to therapy than patients with an *erm* gene active RGM [95, 96]. Because of the impact on treatment response, determining the *erm* gene functionality of clinically significant RGM isolates is absolutely essential, either with preincubation of the RGM isolate in the presence of macrolide or by molecular methods. Clinicians can also be confident that RGM isolates accurately identified as *M. chelonae* or *M. abscessus* subsp. *massiliense* do not have an active *erm* gene and will respond to macrolide-containing regimens.

For antibiotics other than the macrolides, the terms "susceptible" and "resistant" have limited meaning as treatment regimens based on these designations are not predictably effective. In general, isolates of *M. abscessus* (all subspecies) and *M. chelonae* are more resistant to antibiotics than other RGM species and are usually susceptible or intermediate only to amikacin, imipenem, and clarithromycin, in the absence of an active *erm* gene [11]. Isolates of *M. abscessus* (all subspecies) are moderately susceptible (intermediate) to cefoxitin (MIC ≤64 μg/mL), whereas isolates of *M. chelonae* are highly resistant (MIC ≥256 μg/mL). Additionally, MICs of tobramycin for *M. chelonae* are lower than those of amikacin, so that

Table 4 Antimicrobials used for treatment of commonly encountered species of RGM

Species	Drugs[a]
M. fortuitum	Oral: ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, moxifloxacin, clarithromycin[b] (80%), doxycycline (50%), linezolid (86%)
	Parenteral: amikacin, cefoxitin, imipenem,[c] tigecycline[d]
M. abscessus subspecies	Oral: clarithromycin or azithromycin in isolates with nonfunctional *erm* genes (i.e., approximately 20% *M. abscessus* subsp. *abscessus*, 100% *M. abscessus* subsp. *massiliense*), doxycycline (<5%), ciprofloxacin (<5%), moxifloxacin (<15%), linezolid (23%)
	Parenteral: amikacin, tigecycline,[d] cefoxitin (70%), imipenem
M. chelonae	Oral: doxycycline (25%), ciprofloxacin (25%), linezolid (54%), clarithromycin or azithromycin
	Parenteral: tobramycin, amikacin (70%), imipenem, tigecycline[d]

[a]Untreated strains are 100% susceptible unless otherwise noted
[b]Does not include inducible (*erm*) resistance determination. *M. fortuitum* isolates must be assumed to be macrolide resistant. No studies have yet addressed specific percentage of inducible *erm* genes present in the *M. fortuitum* group
[c]Susceptible or intermediate
[d]No breakpoints are currently available for tigecycline with RGM, but most MICs for *M. fortuitum*, *M. abscessus*, and *M. chelonae* have been ≤1 μg/mL

M. chelonae is the only species of RGM for which amikacin is not the preferred aminoglycoside. Approximately 20% of the strains of *M. chelonae* are also susceptible to achievable serum levels of ciprofloxacin and/or doxycycline or minocycline [11, 97] (Table 4).

Amikacin is an important antibiotic in RGM treatment regimens. An amikacin resistance breakpoint MIC of >64 μg/mL (compared to ≥64 μg/mL for IV amikacin) has been proposed to the CLSI for inhaled amikacin and has been correlated with the finding of a mutation in the 23S rRNA gene [89, 98]. A recent randomized placebo controlled trial of inhaled liposomal amikacin in patients with MAC and *M. abscessus* lung disease demonstrated the efficacy of inhaled amikacin in *Mycobacterium avium* complex (MAC), but only a small number of conversions occurred in patients with *M. abscessus* [99].

Among the oxazolidinones, linezolid has in vitro activity against the *M. fortuitum* group and *M. chelonae* [100]. Linezolid has been used subsequently in the treatment of infections due to RGM, including disseminated *M. chelonae* with acquired mutational resistance to clarithromycin [101]. Isolates of *M. abscessus* have variable susceptibility to linezolid. Recently a new oxazolidinone, tedizolid, has shown early in vitro activity among isolates of RGM [102]. No clinical experience in the treatment of RGM disease has been reported so far with this antibiotic.

Tigecycline, a glycylcycline derivative of minocycline, has shown excellent in vitro activity against all species of RGM, including *M. chelonae*, *M. abscessus*, and *M. fortuitum* group with MICs of <1 μg/mL [97]. A clinical trial of patients treated with tigecycline showed limited efficacy of the drug for salvage therapy of patients with respiratory *M. abscessus* infections [103]. However, MIC breakpoints for this agent with the RGM have not been established so that tigecycline MICs are reported without interpretation [89].

Clofazimine, a riminophenazine antibiotic, has been used in the treatment of *M. leprae* and multidrug-resistant (MDR) *M. tuberculosis*. Recently there has been a revival of interest in its efficacy against RGM, especially *M. chelonae* and *M. abscessus.* Synergism between clofazimine and amikacin against *M. abscessus* was demonstrated in vitro [104, 105]. Clofazimine may also act to increase exposure to other important antimicrobials including macrolides. There are no CLSI breakpoints available yet for the interpretation of clofazimine MICs, and large prospective clinical studies have not been done. A recent retrospective study of 42 patients treated with clofazimine as part of multidrug treatment regimens for *M. abscessus* subsp. *abscessus* found a 24% sputum conversion rate and 81% treatment response rate based on symptoms with 31% radiographic response [106]. Although clofazimine MICs are frequently reported and the drug appears to be widely used, the clinical efficacy of clofazimine for treating *M. abscessus* subsp. *abscessus* remains unclear and its role in this context not yet established. As with most aspects of this difficult process, further studies are necessary.

The new diarylquinolone antibiotic, bedaquiline, was recently approved by the FDA to treat multidrug-resistant (MDR) tuberculosis. It causes disruption of ATP synthesis and has impressive in vitro activity against isolates of NTM including *M. abscessus* subspecies. In a study of four patients with *M. abscessus* lung infection,

two patients had microbiologic improvement (i.e., decrease in semiquantitative colony counts), and all but one patient showed symptomatic improvement [107]. Large clinical studies along with in vitro susceptibility studies, however, remain to be performed.

A 2014 in vitro study showed the lack of bactericidal antibiotics, including amikacin, in the currently recommended treatment regimens for *M. abscessus* [108]. This finding was hypothesized to be due to the presence of functional aminoglycoside-modifying enzymes encoded by specific genes in the *M. abscessus* chromosome [108]. In vitro studies, such as this, emphasize the need for novel antibiotics and/or therapeutic options to improve the therapeutic outcome of patients with RGM, especially *M. abscessus* [108, 109].

Isolates of the *M. fortuitum* group, *M. smegmatis* group, and *M. mucogenicum* group are generally the most susceptible of the commonly encountered RGM species [6, 11]. In vitro, they are usually susceptible or intermediate to amikacin, cefoxitin, imipenem, ciprofloxacin, sulfonamides, and moxifloxacin, with about 50% of the isolates of *M. fortuitum* susceptible to doxycycline (Table 4). Both minocycline and doxycycline are preferred over tetracycline because of greater in vitro activity of the former two antimicrobials in previous studies of the RGM [97].

Treatment of RGM Disease

Therapy for most RGM infections has not been established from clinical trials. Current recommendations are generally based on uncontrolled case series and clinical experience. There is a clear dichotomy in the anticipated response of RGM pathogens to therapy. Infections caused by *M. fortuitum* group pathogens are usually responsive to antibiotic therapy, while infections due to *M. abscessus* subsp. are usually less responsive to antibiotic therapy.

Effective therapy for many RGM, especially *M. abscessus* subsp. *abscessus*, is thwarted by two major mechanisms of drug resistance. The first is innate or natural drug resistance best illustrated by the *erm* gene whereby initial, routine, MICs for macrolides appear susceptible, but subsequent MICs after macrolide exposure show resistance consistent with the activation of the inducible macrolide resistance gene [91–94, 109]. While the description of the *erm* gene has opened windows into the perplexing and complicated realm of innate antibiotic resistance, it is by no means the end of the story. *M. abscessus* subsp. *abscessus* possesses multiple innate drug resistance mechanisms that frustrate antibiotic therapy [109].

Patients infected with *M. abscessus* with a nonfunctional *erm*(41) gene, primarily those due to *M. abscessus* subsp. *massiliense*, have the best prognosis as they are macrolide susceptible [96, 109]. The prognostic difference between an RGM pathogen with an active versus an inactive *erm* gene is so critical that it necessitates a pause at this point in the narrative to explicitly emphasize this concept. When a clinician is faced with an RGM infection, especially one due to an organism identified as "*M. abscessus*," the clinician must know the functional status of the *erm* gene

from that organism. The *erm* gene status can usually be deduced from the identification of the organism but must be corroborated after incubation of the organism in the presence of macrolide for 14 days. Identification of an organism as *M. abscessus* subsp. *massiliense* will inevitably mean the organism does not have an active *erm* gene. Identification of an organism as *M. abscessus* subsp. *abscessus* does not inevitably mean that the organism will have an active *erm* gene as approximately 20% of these isolates will have an *erm* gene mutation that renders it nonfunctional [110]. The clinician must have both taxonomic and *erm* gene functional status for all clinically significant RGM isolates. It is imperative that the clinician is familiar with the method used to determine in vitro macrolide susceptibility.

The second mechanism of resistance is through acquired mutational drug resistance in isolates that do not have an active *erm* gene such as *Mycobacterium abscessus* subsp. *massiliense*, *M. chelonae*, and approximately 20% of *M. abscessus* subsp. *abscessus* isolates [109]. Mutational drug resistance can develop on therapy and is a concern for ribosomal active drugs, such as clarithromycin (23S rRNA gene) and amikacin (16S rRNA gene). The mechanism of acquired mutational resistance for these organisms is the same as for all mycobacteria, inadequate companion medications to prevent the emergence of isolates with naturally occurring ribosomal gene mutations. The recognition that clinically significant RGM isolates without *erm* gene activity can subsequently develop acquired mutational macrolide resistance dictates that these isolates must be treated with adequate companion medications for macrolide to prevent the emergence of acquired mutational macrolide resistance.

The difference in clinical response for *M. abscessus* subspecies with and without active *erm* genes is profound [95, 111–114]. It would be extraordinarily disappointing for a patient with *M. abscessus* subsp. *abscessus* disease who was fortunate enough to have an inactive *erm* gene to become macrolide resistant because of inappropriate therapy resulting in acquired mutational macrolide resistance. Protection against the emergence of acquired mutational amikacin resistance is equally as important. Physicians must treat these patients with adequate aggressiveness to prevent acquired mutational resistance. This is, yet again, another reminder that there are no shortcuts in the management of these infections.

Mutational resistance is also a concern for the quinolones. Hence, therapy with these agents for organisms such as *M. chelonae* and *M. fortuitum* should include combination therapy, especially for extensive disease with large numbers of organisms. Acquired mutational resistance with the tetracyclines and sulfonamide monotherapy has not been described.

Treatment of *M. abscessus* lung disease is impeded not only by the antibiotic resistance of the organisms but by the complexity, expense, and toxicity of the required antibiotics [42]. See Tables 4 and 5 for a summary of drugs and suggested therapeutic approaches.

A critical evaluation, comparison, and summary of the literature reporting treatment outcomes for "*M. abscessus*" are impossible for studies done prior to knowledge and demonstration of *erm* gene activity. Prior to *erm* gene analysis, published *M. abscessus* case series included variable numbers of patients with *erm* gene active

Table 5 General principles of therapy of RGM disease

Clinical setting	Drug treatment[a]
Pulmonary disease	
M. fortuitum.	Short-term parenteral treatment (4–6 wks.) and then multiple (at least 2) oral antibiotics with in vitro activity for minimum of 6 mos.
M. abscessus subsp. *abscessus,* and *M. abscessus* subsp. *bolletii*	Isolates with functional *erm*(41) gene will be difficult to treat effectively, relatively low-dose amikacin (single daily dose with peaks in low- to mid-20 range), cefoxitin, and/or tigecycline or imipenem. Consider linezolid and/or clofazimine. We recommend a minimum of three antibiotics initially. Consider inhaled amikacin after microbiologic conversion. Initial therapeutic attempt should be to attain sputum culture negativity for 12 months
	For isolates with nonfunctional *erm* genes (i.e., approximately 20% *M. abscessus* subsp. *abscessus*, 100% *M. abscessus* subsp. *massiliense*), best oral antimicrobials are clarithromycin or azithromycin and linezolid with addition of pyridoxine (to potentially reduce risk of peripheral neuropathy). In addition to oral drugs, begin with relatively low-dose amikacin (single daily dose with peaks in low- to mid-20 range) and consider inhaled amikacin after microbiologic conversion
Localized skin/soft tissue/bone disease	
M. fortuitum, *M. chelonae,* *M. abscessus*	Initial (4–8 weeks) parenteral antibiotics for extensive disease followed by oral medicines as guided by in vitro susceptibility; for minor disease, oral antibiotics only. Essential to remove catheter or foreign body. Treat 6 mos. total for significant disease, including all cases with osteomyelitis
	Linezolid (oral or parenteral) with pyridoxine has also been successful for treatment of *M. chelonae*
Disseminated (cutaneous) disease	
M. chelonae	Once-daily low-dose tobramycin or intermittent daily imipenem plus clarithromycin for first 2–4 wks and then clarithromycin only to complete 6 mos.; linezolid with pyridoxine may also be effective
M. abscessus subsp. *abscessus*	Same as for *M. chelonae* except use of amikacin in place of tobramycin and cefoxitin may replace imipenem; 80% of the isolates will be macrolide resistant, 20% macrolide susceptible
M. abscessus subsp. *massiliense*	Best oral antimicrobials are clarithromycin or azithromycin and linezolid with pyridoxine

[a]Guided by in vitro susceptibility results

(*M. abscessus* subsp. *abscessus*) and *erm* gene inactive (*M abscessus* subsp. *massiliense*) patients which explains the wide variability in reported treatment responses. For instance, in one study from the United States, 69 *M. abscessus* lung disease patients without subspecies identification or reported *erm* gene activity were aggressively treated for 52 antibiotic months, including 6 months parenteral antibiotic therapy and surgery in 33% of cases [115]. Forty-eight percent of patients were AFB culture negative by the end of the study including 57% of the patients who had surgery [115]. In a retrospective study from the Republic of Korea, 65 patients with *M. abscessus* lung disease were treated with 1 month parenteral and oral antibiotics followed by 24 months oral antibiotics usually including a macrolide [116]. Sputum conversion and maintenance of negative sputum cultures for ≥12 months were

achieved in 58%. In another study from the Republic of Korea 41 patients, 41% received macrolide and one parenteral agent while 59% received a macrolide and 2 parenteral agents [117]. Sputum conversion was achieved in 81% of patients without a difference between the two groups. It is clear that the improved outcomes in the Korean studies cited above were due to a much higher prevalence of *M. abscessus* subsp. *massiliense* patients in the study cohorts compared to the US cohorts.

In a subsequent study from the Republic of South Korea with subspecies organism identification, sputum conversion and maintenance of culture negativity occurred in 88% of 33 patients with *M. massiliense* lung disease compared with only 25% of 24 patients with *M. abscessus* subsp. *abscessus* infection [95]. Similar results were reported in a Japanese study that evaluated 62 patients and found higher sputum conversion rates (50% vs 31%) and lower relapse rates (30% vs 65%) in patients with *M. abscessus* subsp. *massiliense* lung disease compared with *M. abscessus* subsp. *abscessus* lung disease [118]. In a prospective cohort of 16 *M. abscessus* subsp. *massiliense* and 27 *M. abscessus* subsp. *abscessus* lung infection cases with CF, clarithromycin-based combination therapies led to mycobacterial eradication in 100% of *M. massiliense* cases but only in 27% of *M. abscessus* cases [119].

The preponderance of patients with *erm* gene inactive *M. abscessus* subsp. *massiliense* not only explains the improved treatment outcomes reported in the Republic of Korea compared with the United States but also the success of less aggressive treatment regimens with only brief exposure to parenteral medications and long-term oral antibiotic therapy including macrolide monotherapy [120]. While attractive from the standpoint of patient convenience and avoidance of drug toxicity, this approach has been reported to result in acquired macrolide resistance and is not recommended [95, 111–114].

It cannot be emphasized too strongly that patients with macrolide susceptible *M. abscessus* subsp. *abscessus* isolates because of an inactive *erm* gene are vulnerable to acquired mutational macrolide resistance due to mutations in the 23S rRNA gene. These mutations emerge during therapy with inadequate companion medications for the macrolides. This development is especially pernicious because it signals a significant decline in the chances for successful therapy of the patient [95, 111–114]. We are concerned by the recommendations for oral drugs of uncertain, even dubious, activity as companions for macrolides against *M. abscessus* isolates that do not have an active *erm* gene, and we strongly disagree with this approach [121]. It perhaps doesn't matter what oral drugs are used with *erm* gene active *M. abscessus* subsp. *abscessus*, but the creation of acquired mutational macrolide resistance for these difficult to treat organisms is an incalculable disservice to the patient. Expert consultation for management of RGM lung disease patients should occur prior to the advent of acquired mutational macrolide resistance.

So far, there is no consensus on the optimal composition of multidrug therapy for *M. abscessus* subsp. *abscessus* with the exception of the necessity for including a macrolide for patients with an inactive *erm* gene. The therapy of the patient is directed by the *erm* gene activity analysis and in vitro macrolide susceptibility status. Patients who are macrolide susceptible unquestionably have a much greater

chance of completing successful therapy than those patients with macrolide-resistant isolates. For *erm* gene active isolates, there is also consensus that amikacin is an important element in the therapeutic regimen.
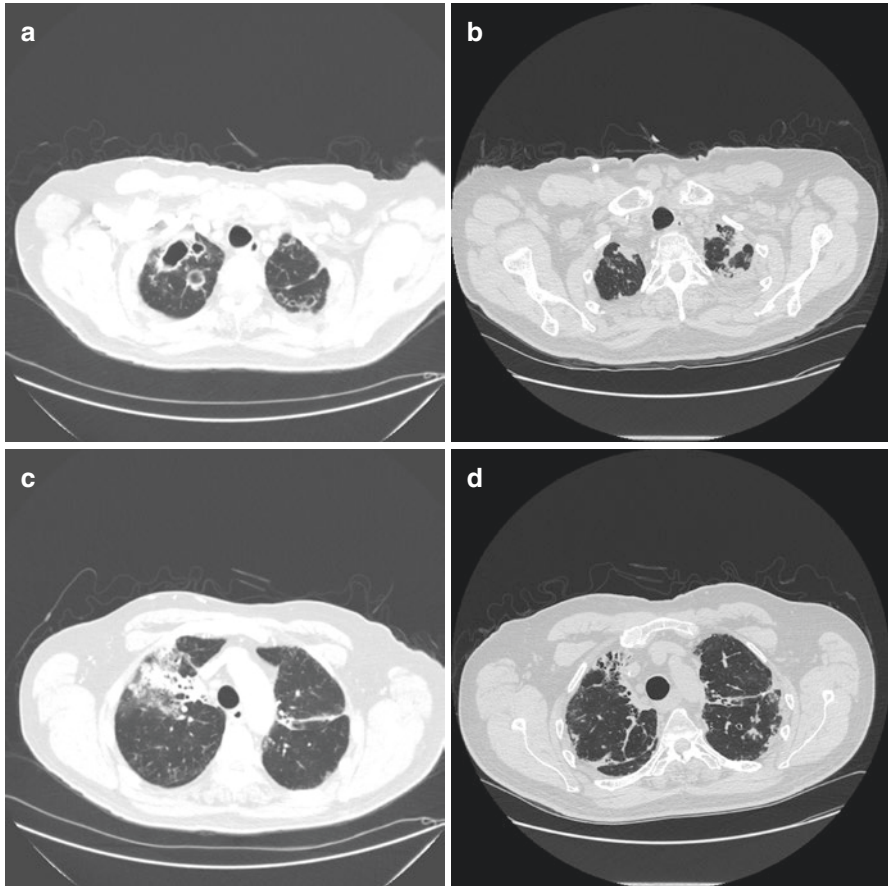

Fig. 4 (**a**) Chest CT cut from 71-year-old man with *M. abscessus* subsp. *abscessus* lung disease and right apical cavitation. (**b**) Chest CT cut from the same patient showing extensive right upper lobe inflammatory density. (**c**) Chest CT cut at same level as Fig. 4a showing improvement in cavitary lesions after extended therapy with tigecycline, tedizolid switched to linezolid, and amikacin switched to imipenem for a duration including 12 months sputum culture negativity. (**d**) Chest CT cut a same level as Fig. 4b showing improvement in extensive inflammatory densities after therapy. (**e**) Chest CT cut from 62-year-old patient with *M. abscessus* subsp. *abscessus* lung disease. Her *M. abscessus* subsp. *abscessus* isolate was macrolide susceptible in vitro because the isolate had an *erm* gene mutation rendering it inactive. (**f**) Chest CT cut from the same patient at the same level showing closure of the cavity associated with 12 months sputum culture negativity while on therapy. Her treatment consisted of 6 months oral azithromycin and linezolid with intravenous amikacin followed by 8 months oral azithromycin and linezolid with inhaled amikacin
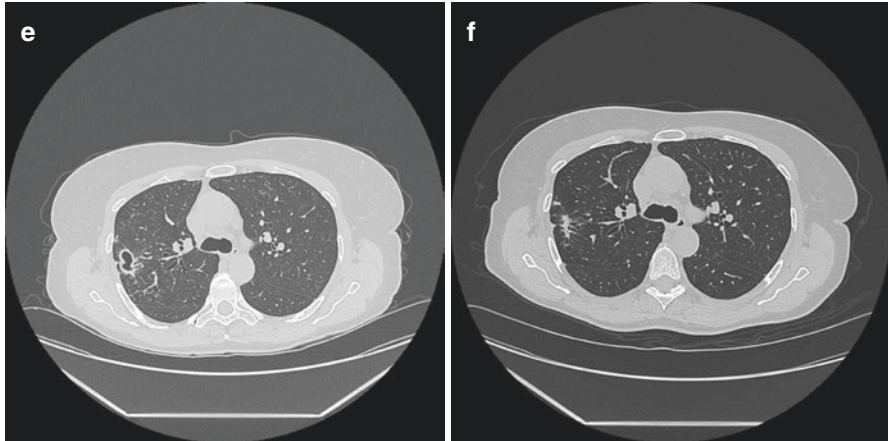
Fig. 4 (continued)

Our approach to patients with RGM diseases including lung disease is to treat with the intent to eradicate the infection (Fig. 4a–d). We recognize that this approach is not universally accepted due to extensive RBM drug resistance and the need for potentially toxic parenteral medications in a prolonged multidrug treatment regimen. We also do not promote the concept of "induction" and "maintenance" therapy for RGM in general and *M. abscessus* subsp. *abscessus* in particular. First, those concepts make pathophysiologic sense for tuberculosis, but we are not aware of information that supports similar pathophysiology for RGM lung disease. Second, also in contrast to TB, there are not a plethora of oral medications with activity against *M. abscessus* subsp. *abscessus* to choose from which brings into play the possibility that an *erm* gene inactive macrolide susceptible *M. abscessus* subsp. *abscessus* isolate might undergo macrolide therapy with oral drugs of questionable activity resulting in acquired mutational macrolide resistance.

We are also aware that some clinicians, as a result of multiple obstacles, toxicity, and complexities presented by parenteral medication administration, choose to treat patients with relatively short and intermittent regimens. Given the lack of a predictably favorable response to current antibiotic choices, it is hard to argue vehemently against this approach which should be left to the discretion of the patient and treating physician.

We base initial therapy on in vitro susceptibility results, which is clearly not optimal but is the best default approach available in our view. Obviously, an inactive *erm* gene isolate should be treated with a macrolide (Fig. 4e, f). For *M. abscessus* subsp. *abscessus* and *M. massiliense*, we would then choose at least one parenteral agent, usually amikacin. The next choice would depend on disease severity. For cavitary disease we would choose a second parenteral agent, such as tigecycline, imipenem, or cefoxitin. If the isolate was susceptible in vitro to linezolid, that would be a reasonable third drug choice as well. Some experts would use clofazimine in this situation. As noted, our goal initially is eradication of the organism. We do not a priori assume that
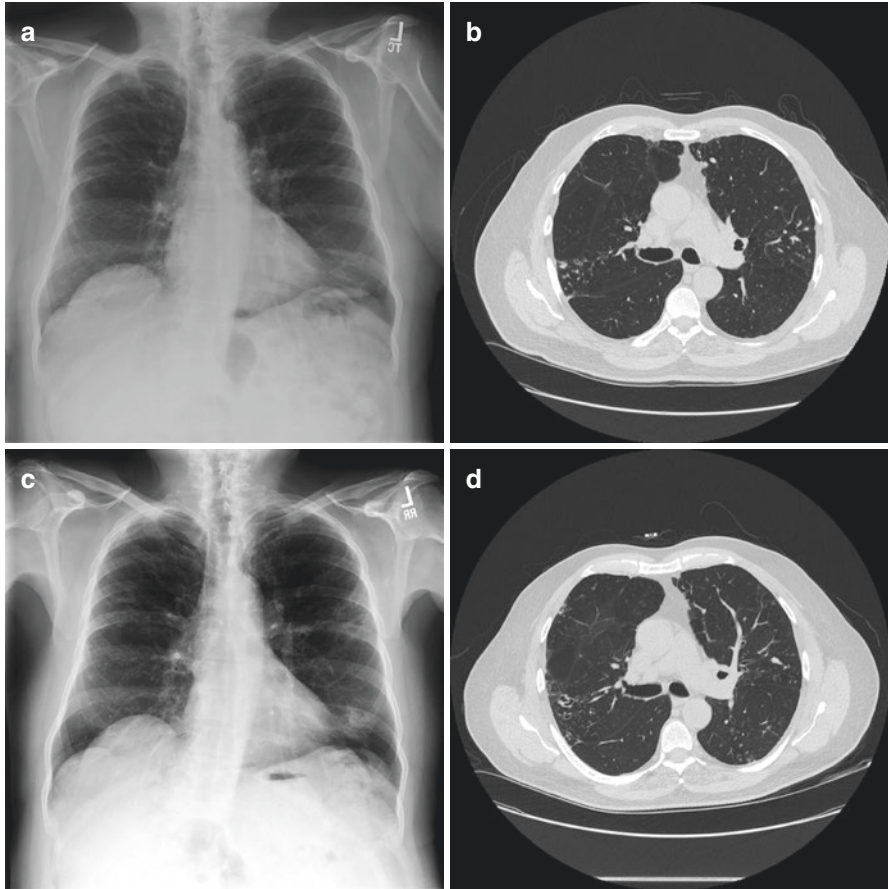
Fig. 5 (**a**) Chest radiograph from 76-year-old patient with *M. abscessus* subsp. *abscessus* lung disease showing nonspecific bilateral densities consistent with bronchiectasis and nontuberculous mycobacterial disease. (**b**) Chest CT cut from the same patient showing bronchiectasis and nodular densities with tree-in-bud pattern. (**c**) Chest radiograph showing progressive right lower lung field densities associated with persistently positive sputum cultures for *M. abscessus* subsp. *abscessus* in spite of treatment with amikacin, imipenem, and tedizolid switched to linezolid and azithromycin. (**d**) Chest CT cut at same level as Fig. 5b at same time as chest radiograph in Fig. 5c showing bronchiectasis with increased peribronchial inflammation and early cavitation

any patient is untreatable, although regrettably, a significant proportion of these patients will turn out to be refractory to even aggressive therapeutic efforts (Fig. 5a–d). Our recommendation for a specific treatment strategy is outlined in Table 5.

For *erm* gene active *M. abscessus* subsp. *abscessus* isolates, we recommend at least two parenteral agents including amikacin plus oral linezolid or clofazimine (Table 5). We do not believe that the inclusion of a macrolide favorably influences the outcome of therapy for these organisms, but the macrolide may have a beneficial effect on bronchiectasis as an immune modulating agent. *Mycobacterium bolletii*
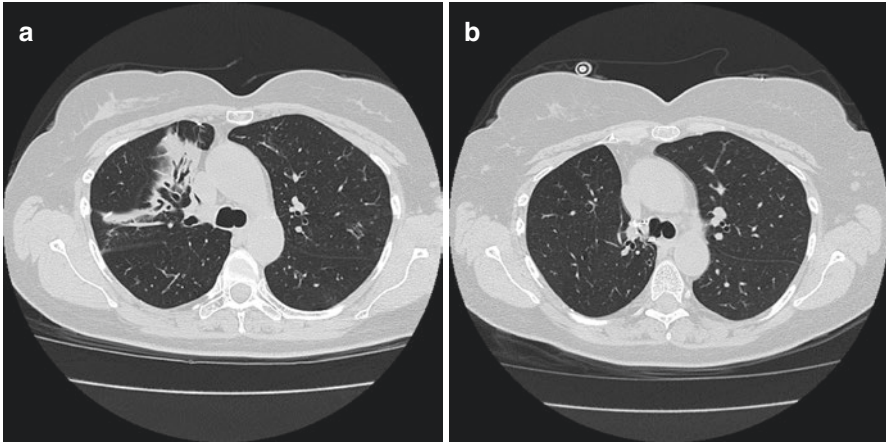
Fig. 6 (**a**) Chest CT cut from 64-year-old female with *M. abscessus* subsp. *abscessus* lung disease and persistently positive sputum cultures in spite of aggressive therapy including parenteral antibiotics. (**b**) Chest CT cut from the same patient at a comparable level to Fig. 6b after right middle lobe lobectomy and 12 months sputum culture negativity following surgery and antibiotic therapy including tigecycline and amikacin

isolates would be treated identically to *M. abscessus* subsp. abscessus isolates, guided by *erm* gene activity. As with other NTM respiratory pathogens, the target duration of therapy is 12 months of sputum culture negativity while on therapy.

In the (hopefully) rare situation where a clinician is faced with an *M. abscessus* isolate of unknown *erm* gene activity, then we believe it would be reasonable to include a macrolide in the regimen on the small chance that the isolate had an inactive *erm* gene.

Surgery is an important option for selected patients with *M. abscessus* disease, especially those with macrolide resistance from any mechanism, and is covered in detail in chapter "Surgical Management of NTM Diseases". For an organism that is so difficult to eradicate with medication alone, surgery is associated with improved clinical outcomes [115] (Fig. 6a, b). While a minority of patients will be appropriate candidates for adjunctive surgery, for various reasons, we feel that the surgical option should be considered for all *M. abscessus* patients, even if only briefly to confirm a patient's non-suitability.

Fortunately, *M. fortuitum* is usually susceptible in vitro to multiple oral antibiotics with the exception of macrolides due to the presence of an active *erm* gene. We recommend treatment of *M. fortuitum* disease with at least two agents to which the organism is susceptible in vitro. Parenteral agents may be necessary for severe or refractory disease. Removal of any foreign body is also essential for successful therapy of extrapulmonary or disseminated *M. fortuitum* infection associated with foreign material.

M. chelonae does not have an active *erm* gene and is also frequently more susceptible to oral antibiotics than *M. abscessus* subsp. *abscessus*, including macrolide, which offers opportunities for therapy without parenteral agents. It must be empha-

Table 6 Essentials for evaluation of an RGM clinical isolate

Accurate Organism Identification, Do Not Accept "Group" Designation or Nomenclature	
For in vitrosusceptibility testing, all clinically significant RGM isolates[a] must be preincubated with macrolide to determine *erm* gene activity;do not accept any in vitrosusceptibility result without this step	
Preincubation step must be done even if the isolate is identified as *M. abscessus* subsp. *abscessus* because 20% of these isolates will have mutations inactivating the *erm* gene	
erm Gene Active	
YES	NO
Therapy without macrolide	Therapy with macrolide-based regimen and adequate companion drugs to prevent acquired macrolide resistance

[a]With the exceptions of *M. chelonae* and *M. abscessus* subsp. *massiliense* because they do not have an active *erm* gene

sized again that monotherapy with macrolide can result in acquired macrolide resistance and worse prognosis.

The general recommendation for serious wound infections is combination therapy with initial parenteral therapy for *M. chelonae* and *M. abscessus* until clinically improved, followed by oral therapy for a total treatment duration of at least 6 months. Development of new skin lesions on therapy is not necessarily indicative of treatment failure. Cultures should be obtained, and antibiotic therapy should be continued. In most cases, cultures are sterile following approximately 6–8 weeks of proper treatment. The new skin lesions likely represent a paradoxical immunological response rather than microbiological persistence or relapse. New lesions on therapy are not unexpected but should be aggressively evaluated including new AFB cultures. As long as cultures of these new lesions remain negative, treatment should be continued for a minimum of 4 months for less serious infections and 6 months for more serious infections. Abscess drainage and surgical debridement are essential. Surgical debridement may be necessary more than once. Cultures for AFB must be sent with each biopsy and debridement procedure. Sadly, this simple requirement is not always met.

In summary, the management of RGM infections in general and *M. abscessus* infections, specifically, remains challenging. There are many confounding aspects to RGM disease from nomenclature to drug resistance mechanisms that confuse or intimidate clinicians caring for these patients. Given those unfavorable circumstances, there is no other group of NTM organism that require as much knowledge by the clinician for optimal patient management. The clinician must have accurate organism identification and must know the significance of in vitro susceptibility results. With that knowledge, the clinician must craft drug treatment regimens that, at a minimum, do not make the patient's status worse. There is simply no substitute for an in-depth understanding by the clinician of the nuances and idiosyncrasies of RGM disease and no short cuts in the management of these patients (Table 6).

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