Bronchiectasis and Nontuberculous Mycobacterial Disease

David E. Griffith, MD\textsuperscript{a,}*, Timothy R. Aksamit, MD\textsuperscript{b}

KEYWORDS
- Nontuberculous mycobacteria • Bronchiectasis • Mycobacterium avium complex • Mycobacterium abscessus

KEY POINTS
- Bronchiectasis and nontuberculous mycobacterial (NTM) lung disease are inextricably linked pathophysiologically.
- Mycobacterium avium complex (MAC) is the most frequently encountered NTM respiratory pathogen in bronchiectasis patients.
- Therapy for NTM respiratory pathogens in bronchiectasis patients should be guided by published guidelines.
- Diagnosis of NTM lung disease in bronchiectasis patients does not always necessitate therapy directed against the NTM pathogen.
- Optimal management of patients with bronchiectasis and NTM lung disease requires carefully considered treatment of both conditions.

To paraphrase that underappreciated philosopher Forrest Gump, nontuberculous mycobacterial (NTM) lung infections and bronchiectasis “goes together like peas and carrots.”\textsuperscript{1} Although this assertion may seem self-evident now, it has in fact only recently become widely accepted. As a corollary, it is also axiomatic that many patients with NTM lung disease have at least one additional lung disease, either bronchiectasis or chronic obstructive pulmonary disease (or both), necessitating treatment of more than one disease process in most patients with NTM lung disease. The interplay between NTM lung infections and bronchiectasis is growing progressively more complex and encompasses fundamental pathophysiologic and management considerations, including assessment of which is the primary disease process, which disease is a predisposition to the other, when and how should NTM disease be treated in the presence of bronchiectasis, and what are the optimal management strategies for bronchiectasis. In the relatively brief time that has elapsed since the recognition that these 2 diseases are intimately related, a deepening appreciation is evolving for the complex interaction between them. There is, however, little lingering doubt that NTM infections and bronchiectasis are inextricably linked (Fig. 1).

Two impediments had to be overcome before the association of NTM disease and bronchiectasis would be widely embraced. The first, and most important, was the description of NTM lung disease in patients who did not present with the expected...
radiographic findings typical of reactivation tuberculosis (TB) and traditionally accepted to be also typical of NTM lung disease. Credit for this observation is generally attributed to Prince and colleagues, who published a seminal article describing Mycobacterium avium complex (MAC) lung infection in older women without underlying lung disease other than bronchiectasis. In retrospect, there was some anticipation for this observation evident in previous work. In 1979, as part of the first comprehensive description of NTM diseases, Emanuel Wolinsky wrote, “The average case of M kansasii or M avium-intracellulare disease would be a 48-year-old white man with longstanding lung disease, such as chronic obstructive pulmonary disease or silicosis... The chest roentgenogram shows fibrosis and a thin walled cavity in the right upper lobe and sputum is positive for AFB on smear.” Wolinsky added, “It must be emphasized, however, that cases do occur in women, in younger men, and in middle aged men without apparent lung disease or deficiency of cellular immunity” and that bronchiectasis was among the “most common predisposing conditions...” for NTM pulmonary disease.

Also in 1979, Rosenzweig published the findings from a series of 100 consecutive patients with MAC lung disease in Wisconsin. Although there is limited detail about the radiographic abnormalities in this cohort, 24 patient radiographs were described as either “minimal” or “moderate noncavitary.” Of additional interest, all but 1 of the women in this series older than 50 years were Caucasian, whereas in other age groups, for both men and women, there was a more diverse racial distribution. In a statement all too familiar today, Rosenzweig noted, “While the tuberculosis caseload has declined steadily in the past 10–15 years in our clinic, cases of atypical mycobacterial infection, especially with M intracellulare-avium, have grown from a trickle to numbers which currently rival those of tuberculosis.” In 1982, Ahn and colleagues described a group of 66 patients with sputum cultures that were repeatedly positive for MAC or Mycobacterium kansasii, who also had

Fig. 1. (A) P/A chest radiograph of a 62-year-old woman with bronchiectasis and M avium complex lung disease, showing bilateral primarily midlung nodular and reticulonodular densities. (B, C) HRCT images of the same patient demonstrating bronchiectasis, nodular densities, and tree-in-bud densities. (D) Posteroanterior (P/A) chest radiograph of a 74-year-old woman with bronchiectasis and Mycobacterium avium complex lung disease, showing bilateral primarily midlung nodular and reticulonodular densities. (E, F) High-resolution chest CT (HRCT) images of the same patient demonstrating bronchiectasis with destruction of the right middle lobe and lingula, nodular densities, and tree-in-bud densities characteristic of mycobacterial lung infection.
noncavitary radiographic changes described as “...changes resembling infiltration of some type, mostly fibrotic.” These patients were noted to attain more rapid conversion of sputum to acid-fast bacilli (AFB) culture negativity with therapy when compared with patients with cavitary radiographic abnormalities, although the apparent rapid microbiological response to therapy was not associated with significant radiographic improvement. Longitudinal follow-up of these patients, a step necessary to show convincingly that they had MAC infection and disease rather than “colonization,” was unfortunately not reported. That important step was, however, accomplished by Prince and colleagues, who described patients with noncavitary MAC lung disease including a subpopulation who had progressive lung disease resulting in death. It subsequently became clear that this form of MAC lung disease, henceforth referred to as the nodular-bronchiectatic form of NTM lung disease, could be seen not only with MAC, but with essentially any NTM respiratory pathogen, albeit most commonly with MAC.\(^6\)\(^-\)\(^9\)

The second and perhaps less well appreciated barrier that was overcome was a technological one. Until approximately 25 years ago, the diagnostic proof for bronchiectasis required the performance of bronchography (bronchograms), a rather medieval radiographic procedure that requires instillation of radiographic dye into the tracheobronchial tree, an experience that few patients would voluntarily repeat. The technological advance was the advent of computed tomography (CT) of the chest and, specifically, high-resolution chest CT (HRCT) scanning.\(^10\),\(^11\)

It is interesting that widespread acceptance of CT scanning of the chest as a reliable diagnostic test for bronchiectasis was not immediate, and as late as the mid-1990s some reviewers were hesitant to accept CT abnormalities alone as diagnostic for bronchiectasis.\(^12\) At present, HRCT scanning is the standard for diagnosing bronchiectasis, as well as following the course of the disease and related comorbidities such as NTM infections.

With the advent of better diagnostic tools, bronchiectasis has emerged as a much more readily recognized and more frequently diagnosed disease entity, perhaps not coincidentally in tandem with increased recognition of NTM lung disease. As previously noted, this association was not immediately demonstrated or widely appreciated. In some initial studies assessing the microbiological findings from patients with bronchiectasis, the isolation prevalence of NTM ranged from 0% to 40%.\(^12\)\(^-\)\(^16\) Some of this discrepancy might be explained by geographic differences, particularly between the United States and Europe, but it is also possible that the application of uniform and rigorous microbiological methodology would yield more consistent NTM isolation from patients in disparate geographic locations.

PATHOPHYSIOLOGY: CHICKEN AND EGG

Is NTM pulmonary disease a consequence or the cause (or both) of bronchiectasis? There are lines of evidence that support both contentions. First, it is clear that patients with severe generalized bronchiectasis, for whatever reason, are predisposed to acquiring NTM infection and in some instances progressive NTM disease. The best-described bronchiectasis-associated disease that is recognized as a predisposition for NTM infection is cystic fibrosis (CF). Olivier and colleagues\(^17\),\(^18\) reported the results of a multicenter study evaluating the prevalence of NTM respiratory isolates in CF patients. These studies found that 13% of the CF patients had NTM respiratory isolates, including 72% MAC and 16% *Mycobacterium abscessus*. A reliable algorithm that can predict which CF patients with NTM respiratory isolates will have progressive NTM disease and which patients, especially those with MAC respiratory isolates, require therapy directed against the NTM pathogen, has not emerged to date. The pathogen of most concern is *M abscessus*, because of case reports describing rapid clinical deterioration and even death in some CF patients infected by *M abscessus*.\(^19\) This concern is unfortunately confounded by the difficulty in effectively treating *M abscessus*, resulting in a complicated risk/benefit decision in the absence of a mechanism for accurately predicting those patients who will have disease progression and those likely to have satisfactory treatment response. In addition to CF patients, NTM respiratory isolates have been reported in 10% of patients with ciliary dyskinesia syndromes and bronchiectasis.\(^20\)

It has long been postulated that prior TB is a risk factor for NTM respiratory disease, and it has been assumed that postinflammatory bronchiectasis was likely responsible for this association.\(^2\),\(^21\) A question that is still debated is whether mycobacterial pathogens other than *M tuberculosis* can cause postinflammatory bronchiectasis. For a pathogen such as *M kansasii*, which is the NTM that causes lung disease clinically and radiographically most similar to reactivation TB, it is perhaps easier to accept this association than with a less virulent NTM pathogen such as MAC. In a series of reports from Japan, Fujita and colleagues\(^22\),\(^23\)
described the pathologic findings after partial lung resections from a small number of patients diagnosed with MAC lung disease. All patients had presurgical cavitary MAC lung disease radiographically. Pathologic findings from these patients included bronchiectasis, bronchiolitis, nodules, and extensive granuloma formation throughout the airways. These findings suggested that at least for cavitary MAC lung disease, bronchiectasis was a common and expected pathologic consequence of MAC infection.

It is perhaps relatively easy to accept that cavitary NTM disease caused by any NTM pathogen might result in postinflammatory bronchiectasis. It is clear, however, that the nodular/bronchiectatic form of the disease is more difficult to accept in this role. In a brief but tantalizing report, Tanaka and colleagues reported a small group of patients with nodular/bronchiectatic MAC disease who appeared to have the initial appearance of nodules followed temporally by bronchiectasis formation in the bronchi subtending these nodules. Unfortunately, aside from this incomplete and inconclusive report, there is little current evidence to support the evolution of bronchiectasis in patients with nodular/bronchiectatic lung disease resulting from an initial peripheral MAC infection, granulomatous inflammation, and nodule formation.

The debate has recently been intensified by the demonstration of a disproportionately large prevalence of NTM lung disease patients with primarily nodular/bronchiectatic NTM lung disease who are heterozygous for CF or $\alpha_1$-antitrypsin (AAT) mutations. Kim and colleagues recently reported a characteristic body habitus in 63 patients with nodular/bronchiectatic NTM lung disease evaluated at the National Institutes of Health. In this population of mostly postmenopausal Caucasian women, the body mass index was significantly lower and the height significantly greater than in matched controls. There were no recognized immune defects, cell-mediated dysfunction, or cytokine-pathway abnormalities identified in these patients, and no significant or unusual correlations regarding environmental water exposure. This population did have higher rates of scoliosis, pectus excavatum, and mitral valve prolapse, compared with a matched control population. In this select population, cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations were found significantly more commonly than in the general population but with no consistent correlation between sweat chloride concentrations and CFTR variants. It has also recently been noted in a study from Japan that patients presenting with pulmonary NTM disease have mutations in the CFTR gene significantly more frequently than in the general population.

Prior dogma has suggested that patients with single CFTR mutations do not have sufficient bronchial mucosal ion and water-transport disturbance to cause clinically detectable CF with abnormal chloride test results for sweat. Recent data, however, suggest that even heterozygous CFTR mutations may be associated with abnormalities of bronchial epithelial ion transport. Patients with bronchiectasis without CF mutations, patients heterozygous for CFTR mutations, and patients with homozygous CFTR mutations were found to have a continuum of nasal mucosal potential differences compatible with a spectrum of abnormalities related to mucosal ion transport. This apparent bronchial mucosal ion and water-transport abnormality seems plausible as a possible mechanism for bronchiectasis development and a potential explanation for why an apparently high percentage of women with nodular/bronchiectatic disease have CFTR mutations without frank CF. An alternative explanation might be that these patients are not truly heterozygous for CFTR mutations but have an additional unidentified CFTR mutation or polymorphism that would indicate actual CF, and more readily explain a pathway to bronchiectasis development. To date, no clear mechanistic connections have been discovered between the characteristic body habitus described earlier, single CFTR mutations, and the pathogenesis of bronchiectasis. These patients are undeniably intriguing, and may provide clues to the pathogenesis of NTM lung disease in at least a subset of patients.

These data also beg 2 important questions. First, should all patients with bronchiectasis and NTM disease be screened for genetic or hereditary predispositions for bronchiectasis, such as CF, AAT deficiency, or immune globulin deficiency? It is arguable that immune globulin deficiency and AAT deficiency are treatable and, even if rarely identified, would lead to a specific therapeutic intervention. The CF evaluation, however, is expensive, and even with a 20% to 30% yield in selected populations may not be a cost-effective strategy other than as a guide for genetic counseling for a patient’s family. Outside of research settings this remains an unsettled question, although there is some agreement among experts that younger patients with bilateral and/or diffuse bronchiectasis are the population most likely to yield positive results with these analyses. The second question is perhaps somewhat less controversial: should all patients with bronchiectasis be screened for NTM pathogens? This question takes on perhaps even more urgency with
the current recommendation for the use of a macrolide as an immune-modulating agent in patients with CF, and the recent suggestion that macrolide might also benefit some patients with frequent exacerbations of chronic obstructive pulmonary disease (COPD). \(^{31,32}\) The use of macrolide monotherapy for patients also at risk for NTM lung disease raises the specter that macrolide-resistant NTM isolates, especially MAC isolates, might emerge in a patient with occult or unrecognized NTM (MAC) lung disease. It seems reasonable that any patient with bronchiectasis considered for macrolide monotherapy should have sputum collected for AFB analysis initially and then intermittently afterward, as recommended for CF patients. \(^ {30}\) In addition, it also seems reasonable that sputum should be evaluated for NTM in any patient with bronchiectasis with unexplained clinical deterioration or new and unexplained radiographic abnormalities.

**PATHOPHYSIOLOGY: NTM ACQUISITION**

The source of NTM respiratory pathogens is still assumed to be the environment, with increasing concern that biofilms that form in municipal water sources may be a significant source for NTM. Feazel and colleagues \(^ {33}\) recently analyzed rRNA gene sequences from 45 showerhead biofilm sites around the United States. Sequences indicating *M. avium* were identified in 20% of showerhead swabs. Using a quantitative polymerase chain reaction with *M. avium*-specific primers, *M. avium* DNA was detected in 20 additional biofilm swab samples in which *M. avium* was not encountered in their RNA gene libraries.

Using microbiological techniques, Nishiuchi and colleagues \(^ {34}\) reported the recovery of MAC from residential bathrooms of patients in Japan with pulmonary MAC disease. MAC was isolated from 10 of 371 patient residence cultures versus 1 of 33 control households. Two patients with MAC lung disease were found to have identical sputum and bathroom MAC genotypes. Falkingham \(^ {35}\) recently reported that NTM were isolated from the household water systems of 59% of patients with NTM lung disease. In 7 households, the patient isolate and 1 plumbing isolate showed similar genotype patterns. Two additional reports have demonstrated identical genotypes of MAC isolated from plumbing and MAC isolates obtained from humans with MAC lung disease, including one with conventional MAC lung infection and one with hypersensitivity-like lung disease. \(^ {36,37}\)

Even in the context of this provocative data, it is still unknown how much of a risk NTM in plumbing presents and whether municipal plumbing in general, and showerheads specifically, represent a significant or common source of NTM for patients with NTM lung disease. The ubiquity of the organisms in the environment, along with what appears to be inevitable and universal environmental exposure and the seemingly endless variety of NTM (especially MAC) genotypes, makes the task of matching environmental and patient NTM isolate genotypes challenging to say the least. In the context of this daunting task, patients inevitably ask if they should continue to take showers, knowing that NTM are part of the flora of modern municipal water systems. In the opinion of the authors there is likely some risk of NTM infection and disease transmission via this route, but NTM organisms are ubiquitous and exposure is unavoidable even if patients abstain from showering or bathing, also an unsavory public health prospect.

**DIAGNOSIS: NTM LUNG DISEASE IN BRONCHIECTASIS PATIENTS**

The diagnosis of NTM lung disease is dependent on 3 components: patient symptoms, radiographic findings, and microbiological results. In the setting of bronchiectasis, symptom evaluation is complicated because of the shared symptoms of bronchiectasis and NTM lung disease, including cough, sputum production, fatigue, and weight loss. A change or progression of symptoms may presage the diagnosis of NTM lung disease. Similarly, the radiographic abnormalities of bronchiectasis may mask or confuse radiographic changes associated with NTM disease and infection. Again, new or progressive radiographic abnormalities, not thought to be due to an acute bacterial process such as pneumonitis or bronchiectatic exacerbation, would provide a clue to possible NTM infection and disease. Certainly some radiographic patterns such as tree-in-bud abnormalities, nodules, and cavitation would raise suspicion for NTM lung disease, even in the absence of symptomatic change (see Fig. 1). \(^ {38–41}\)

Ultimately the microbiological evaluation will be the final arbiter of NTM disease diagnosis in patients with bronchiectasis. The NTM are all found in 1 or multiple niches in the environment so that isolation of any NTM species can be the consequence of environmental contamination, especially contamination by nonsterile (tap) water sources. Hence, diagnostic criteria for respiratory NTM isolates are necessary to aid in the determination of which NTM isolates are clinically significant (Box 1). \(^ {21}\) It is readily conceded that one set of diagnostic criteria could not be and is not appropriate or applicable to more than 100
species of NTM. A clinician evaluating these patients cannot uncritically apply these diagnostic criteria, and must have knowledge about the virulence of the NTM species isolated and the host from which the organism was isolated.

The diagnosis of NTM lung disease based on a single positive NTM culture from a bronchoscopic specimen merits particular attention (see Box 1). This criterion was adopted specifically for application to patients with nodular/bronchiectatic NTM disease who are frequently unable to produce sputum for AFB analysis and for whom serial bronchoscopies would be either impractical or risky. The important caveat for this recommendation is that common NTM pathogens such as MAC, M kansasii, Mycobacterium simiae, Mycobacterium fortuitum, and M abscessus can be found in municipal (tap) water so that contamination of a bronchoscopic specimen with tap water can result in a false-positive bronchoscopic culture (pseudoinfection), triggering unnecessary and potentially toxic therapy. Again, uncritical application of the diagnostic guidelines may cause more harm than benefit.

There are NTM species such as M kansasii and Mycobacterium szulgaii that are almost always associated with significant disease when isolated from respiratory specimens. In some cases, lung disease might be diagnosed on the basis of one positive culture for these organisms (especially M kansasii). Conversely, there are NTM such M simiae and M fortuitum that are usually not respiratory pathogens, even if the NTM diagnostic criteria are met. Lastly there are NTM species such as Mycobacterium gordonae and Mycobacterium terrae complex, which almost always represent contamination of respiratory specimens.

Other diagnostic techniques to augment the current diagnostic criteria remain under investigation but are not currently recommended for general use. Skin testing with NTM antigens has been of interest for many years, especially in the context of NTM disease prevalence, but the role of skin testing for diagnosing NTM disease in individual patients is not established. Another novel approach is a serologic test based on an enzyme immunoassay (ELISA) kit detecting serum immunoglobulin A (IgA) antibody to glycopeptidolipid core antigen specific for MAC. This technique offers promise in identifying patients with MAC lung disease and differentiating patients with MAC lung disease from TB patients. There is, however, considerable overlap in serum IgA antibody levels between the patient groups. It remains to be determined as to where this test will fit in the overall evaluation of patients with suspected MAC lung disease. Certainly in this population of sometimes frail, elderly individuals with bronchiectasis and NTM lung disease who have difficulty producing sputum for AFB analysis, some type of noninvasive, nonmicrobiological-based diagnostic test would be of great value.

Time and patience are perhaps the only two luxuries in the diagnostic evaluation of these patients, owing to the indolence of nodular/bronchiectatic NTM disease. Careful evaluation of the microbiological and radiographic data over time in conjunction with the patient’s symptoms is invaluable and can boost the diagnostic confidence of the physician and patient who is, after all, facing many months of potentially toxic therapy. It cannot be overstressed, however, that making the diagnosis of NTM lung disease in a bronchiectasis patient does not, per se, necessitate the institution of therapy. Alternatively, the coexistence of bronchiectasis and NTM infection does not in any way preclude treatment of the NTM, as some patients may experience an accelerated respiratory decline without such therapy. The decision to initiate treatment for patients with

Box 1
Suggested microbiological diagnostic criteria for NTM lung disease

1. Pulmonary symptoms associated with either cavitary or nodular/bronchiectatic radiographic (chest radiograph or HRCT scan) abnormalities.
2. Exclusion of other diagnoses such as tuberculosis
3. Positive AFB culture results from at least 2 separate expectorated sputum samples
4. Positive culture result from at least one bronchial wash or lavage
5. Transbronchial or other lung biopsy with compatible histopathologic features (granulomatous inflammation or AFB smear positive) and positive AFB culture for NTM, OR biopsy showing compatible histopathologic features and one or more sputum or bronchial washings that are culture positive for NTM


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Mycobacterium terrae complex, which almost always represent contamination of respiratory specimens.
NTM lung disease is ultimately a decision based on risk/benefit analysis, taking into account patient symptoms, radiographic findings (progression), and microbiological results versus the adverse effects of multiple potentially toxic and relatively weak drugs. In addition, the authors do not recommend empiric treatment of suspected NTM lung disease in the absence of isolation and identification of an NTM pathogen.

**THERAPY FOR NTM LUNG DISEASE**

It has been approximately 25 years since the newer macrolides, clarithromycin and the closely related azalide azithromycin, were recognized as the key element in successful treatment regimens for multiple NTM species, especially MAC. The limitations of macrolide-containing regimens for NTM pathogens are now abundantly clear, and it is equally clear that new, more potent medications are needed to improve therapy for NTM disease.

An especially frustrating problem in the management of patients with NTM lung disease is the observation that in vitro susceptibility testing may not be a reliable predictor for in vivo response to antibiotics, as it is in the therapy for TB. The most clinically vexing example is MAC, where there is, so far, only evidence to support a correlation between in vitro macrolide susceptibility and in vivo clinical response.21,44–47 Both the Clinical and Laboratory Standard Institute and the American Thoracic Society (ATS) recommend that new MAC isolates should be tested in vitro only for susceptibility to macrolides.21 Understandably, clinicians still cling to in vitro susceptibility reports for MAC isolates that list multiple agents as either “susceptible” or “resistant” based on in vitro minimum inhibitory concentrations (MICs), even though those MICs have not been shown to correlate with in vivo response to the antibiotics tested. Perhaps not surprisingly, there are multiple other NTM species and pathogens that share this frustrating property with MAC, including, among many others, *M simiae*, *Mycobacterium xenopi*, *Mycobacterium malmoense*, and *M abscessus*.21

It should be noted as well that there are several species for which in vitro susceptibility testing can be a reliable guide for successful therapy, including *M kansasii*, *Mycobacterium marinum*, *Mycobacterium szulgai*, and *M fortuitum*.21

The explanation for this somewhat inconvenient aspect of NTM behavior is not yet clear, but recent work with rapidly growing mycobacteria (RGM) may offer a window into the complex relationship between in vitro responses and the in vivo effect of antibiotics for NTM. 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 acquired clinically significant macrolide resistance for some mycobacteria, especially RGM, is the presence of an inducible *erm* gene (*erm 41*).48 All isolates of *M abscessus* and *M fortuitum*, but not *Mycobacterium chelonae*, contain an inducible *erm* gene. The most interesting and frustrating aspect of this inducible gene is that if an *M fortuitum* or *M abscessus* isolate is exposed to macrolide, the *erm* gene activity is induced, with subsequent in vivo macrolide resistance that may not be reflected by the initial in vitro MIC of the organism for the macrolide! In other words, the organism may appear to be susceptible in vitro to the macrolide but will not respond to the macrolide in vivo.

To expose this inducible macrolide resistance, termed cryptic resistance, requires incubation of an NTM isolate with macrolide before determining an MIC for the macrolide. This discovery offers one explanation for the discrepancy between in vitro susceptibility results and in vivo responses for *M abscessus* and *M fortuitum*. There is no *erm* gene in MAC, and the primary mechanism for the emergence of macrolide-resistant MAC strains is still the selection of 23S rRNA gene mutations with macrolide monotherapy. It is important to ask, however, if there could be other inducible genes that confer in vivo resistance to antibiotics for MAC. It is an intriguing, if unproved, possibility.

### Mycobacterium avium Complex Lung Disease

The decision to treat patients with MAC lung disease, especially the nodular/bronchiectatic form of MAC lung disease, should be based on potential risks and benefits of therapy for individual patients. Treatment of MAC lung disease is long, expensive, frequently associated with drug-related toxicities, and requires considerable commitment on the part of the patient and physician. Clinical improvement and sputum conversion to AFB-culture negativity for 12 months while on therapy are the main treatment goals, but for many patients may not be attainable. Recent guidelines suggest that MAC treatment regimens should include a rifamycin (rifampicin or rifabutin), ethambutol, and a macrolide (azithromycin or clarithromycin).21 An example of successful MAC therapy with a macrolide-based regimen is illustrated in Fig. 2. Multidrug regimens can be given daily or intermittently, depending on the disease type and severity. Cavitary disease and disease caused by documented relapse after previous
successful therapy should be treated with daily drug dosing, as intermittent therapy is frequently not effective in these patients. For moderate or severe disease, or for patients not responding to standard oral drug regimens, parenteral agents such as streptomycin or amikacin can be included in the treatment regimen. The optimal duration for parenteral therapy is not established, but in the authors’ experience, patients may require these drugs for 6 months or longer to determine their efficacy. The inclusion of parenteral agents in MAC treatment regimens increases culture conversion rates, but does not appear to improve long-term outcome.

A critical element in the management of patients with MAC lung disease is prevention of the emergence of macrolide-resistant MAC. While the role of in vitro susceptibility for other agents remains controversial, it is clear that the development of macrolide resistance in a MAC isolate (MIC >16 μg/mL) is strongly associated with treatment failure and increased mortality. The most important risk factors for developing macrolide-resistant MAC are macrolide monotherapy and the combination of a macrolide and fluoroquinolone without an effective third companion drug. It is a therapeutic imperative that clinicians protect patients from the emergence of macrolide-resistant MAC isolates.

Several aspects of therapy for MAC lung disease remain controversial, including the roles of clofazimine, fluoroquinolones, and inhaled amikacin. There are limited data that suggest a possible role for clofazimine and nebulized amikacin in the treatment of MAC lung disease, but no large or convincing trials that would support routine or first-line use of these agents. There are essentially no data demonstrating the efficacy of fluoroquinolones for the treatment of MAC lung disease.

Other inconvenient aspects of the treatment of MAC lung disease include the observation that after an initial treatment failure, even if a MAC isolate remains macrolide susceptible, subsequent treatment efforts will be less effective. In addition, patients who are successfully treated with sputum conversion to AFB-culture negativity are likely to have new MAC genotypes (strains) if the sputum again becomes culture-positive for MAC as opposed to recurrence of the original MAC genotype (disease relapse). It has been proposed that this phenomenon can be explained by reinfection of the patient by a new MAC genotype, although polyclonal infections cannot be completely discounted. These “reinfection” MAC isolates are uniformly macrolide susceptible. Some patients with bronchiectasis and NTM infections do not respond, for unclear reasons, to what seem to be appropriate multidrug regimens.

Mycobacterium abscessus Lung Disease

Jeon and colleagues recently reported the results of therapy in a series of 69 patients, 84% female, with M abscessus lung disease. The patients were treated with a regimen consisting of an initial 1 month of parenteral therapy with amikacin and cefoxitin while hospitalized, in combination with oral medications including clarithromycin, ciprofloxacin, and doxycycline for a median of 24 months. Forty-seven of 69 patients (68%)
converted sputum to negative, with a median time to sputum conversion of 1 month. Nine of 47 patients (19%) relapsed after a median of 12 months. Sputum conversion with macrolide-resistant strains occurred in 27% of patients versus 71% with macrolide-susceptible strains, while relapse occurred in 100% of patients with macrolide-resistant strains. These sputum-conversion rates and the rapidity of sputum conversion are surprising, given the very poor in vitro susceptibility pattern of \textit{M. abscessus} previously reported with fluoroquinolones and doxycycline, and the relatively short period of parenteral therapy administered to patients in this study.\textsuperscript{20,56}

Jarand and colleagues\textsuperscript{57} published a retrospective analysis of treatment outcomes for 107 patients with \textit{M. abscessus} lung disease. Sixty-four percent of the patients were followed 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 months on intravenous antibiotics. At least 1 drug was stopped because of side effects or toxicity in most 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 became culture negative compared with medically treated patients. Seventeen (15.9%) deaths occurred in the study population, remarkably similar to results

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\caption{(A) HRCT image of a 62-year-old woman with bronchiectasis and one cystic fibrosis transmembrane regulator (CFTR) gene mutation diagnosed with MAC lung disease before initiation of therapy. (B) Comparable HRCT image after 24 months of treatment for MAC lung disease including 12 months’ therapy with a parenteral agent and right middle lobe lobectomy, and with persistently positive sputum AFB cultures for MAC. (C) P/A chest radiograph of a 64-year-old woman with minimal mid-lung field densities before initiating multidrug MAC therapy with a macrolide-based regimen. (D) HRCT image showing minimal right middle lobe tree-in-bud abnormalities from the same patient after 12 months of multidrug macrolide-containing therapy, with sputum still AFB-culture-positive for MAC.}
\end{figure}
of a previous study of *M abscessus* lung disease from 1993.

The bottom line for therapy for *M abscessus* is murky at best. To date, there is no predictably or reliably effective regimen with or without parenteral agents or guided by in vitro susceptibility results. In the authors’ opinion, if the regimen suggested by Jeon and colleagues\(^5\) is chosen then patients must be followed very closely for evidence of disease progression and treatment failure.

### Treatment of Bronchiectasis in Patients with NTM Lung Disease

Because chronic lung disease is inevitably and unavoidably present in patients with NTM lung disease, management of the underlying or concomitant chronic lung disease is an inevitable and unavoidable complicating aspect of the overall care of patients with NTM lung disease, and can sometimes be the most important and effective therapy for the patient. The comprehensive management of bronchiectasis is beyond the scope of this manuscript so that comments in this section are focused on the bronchiectasis management specifically for patients with NTM pulmonary disease.

First, and perhaps most importantly, bronchiectasis is literally a separate disease and presents its own treatment challenges that often arise unexpectedly during the course of therapy for NTM lung disease. Symptoms of bronchiectasis including...
cough, sputum production, fatigue, weight loss, and bronchospasm are not just nuisances but also significantly overlap with symptoms caused by NTM lung infection, complicating the interpretation of NTM treatment response.

Bronchiectasis is also associated with its own sometimes severe complications and exacerbating factors, such as infectious exacerbation of bronchiectasis (frequently due to drug-resistant bacteria such as Pseudomonas), pneumonia, hemoptysis (±mycetoma) and bronchospastic exacerbations of bronchiectasis, all of which require either adjustments to therapy or introduction of new therapeutic strategies in a patient already on 2 to 3 antibiotics. Infectious (bacterial) processes, either exacerbation of underlying bronchiectasis or frank pneumonitis, are perhaps the most common and troublesome bronchiectasis sequelae, partly because of the symptomatic and radiographic overlap with NTM lung disease (Fig. 4). Usually the time course of these infections provides a major clue to their origins, with relatively acute symptom or radiographic changes being caused by bronchiectasis rather than NTM infection, but careful clinical judgment is still necessary to ensure that a worsening of the NTM infection is not overlooked or that symptoms are inappropriately attributed to NTM disease. Based on clinical observations, the acute onset of purulent sputum with increased respiratory symptoms in those with NTM lung disease and bronchiectasis most often heralds an exacerbation of bronchiectasis rather than a flare of NTM lung disease. The use of oral fluoroquinolones in the management of bronchiectactic exacerbations caused by Pseudomonas is a frequent occurrence and has been conditionally recommended by the British Thoracic Society. Because fluoroquinolones have limited activity against MAC and an unclear association between in vitro susceptibility and in vivo response, there does not appear to be a risk, as seen with Mycobacterium tuberculosis, that fluoroquinolone therapy for bronchiectasis exacerbations will result in delayed diagnosis of MAC disease or induce fluoroquinolone MAC resistance, although these possibilities have not been rigorously tested.

Airway-clearance therapies such as inhaled hypertonic saline or mannitol, as well as sputum clearance devices, chest percussion with postural drainage, and use of a percussion vest can also have a significant, if somewhat unpredictable, beneficial effect (Fig. 5). Prolonged administration of inhaled antipseudomonal antibiotics can also offer symptomatic improvement to some patients. The pros and cons of macrolide monotherapy in this patient population was discussed earlier.

However, the authors wish to emphasize the importance of addressing treatment opportunities and strategies for bronchiectasis as well as NTM disease.

**SUMMARY**

The challenges for the clinician managing patients with NTM lung disease with bronchiectasis were summarized eloquently in a recent editorial.

Thus, the decision is made by the clinician, who may, in view of sometimes rather uncomfortable effects the drugs can have, be wise enough to keep under observation even some of those patients who fulfill consensus criteria for mycobacterial disease. Optimal conservative treatment of underlying disease should not be underestimated, either in this or other contexts, despite the fact that drug treatment has improved over the decades, and patients with bronchiectasis and chronic bronchitis...should profit from such an approach.

The insightful commentator added, “Is this a mere opinion? The ATS statement is full of opinions, and rightly so!” Major challenges for the future include better, more effective treatment modalities for both NTM and bronchiectasis, better understood disease pathophysiology, and better strategies for disease prevention.

**REFERENCES**


