# Canadian Tuberculosis Standards

7th Edition

## Chapter 11: Nontuberculous Mycobacteria

Public Health Agency of Canada
Agence de la santé publique du Canada

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**Canadian Tuberculosis Standard, 7th edition**

Également disponible en français sous le titre :
**Normes canadiennes pour la lutte antituberculeuse, 7ième édition**

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PDF Cat.: HP40-18/2014E-PDF
ISBN: 978-1-100-23171-6
Pub.: 140206

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# CHAPTER 11

# NONTUBERCULOUS MYCOBACTERIA

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## KEY MESSAGES/POINTS

- Transmission of nontuberculous mycobacteria (NTM) between people is believed to be extremely rare. As such, NTM disease is not reportable, public health case management is not currently required, and treatment is not mandatory but, rather, determined on a case-by-case basis.
- There are many NTM species. Some species are associated with clinical diseases as well as a spectrum of clinical findings, whereas other species are rarely, if ever, associated with disease.
- Isolation of NTM organisms from nonsterile sites, such as sputum, does not necessarily indicate disease. It is recommended that pulmonary NTM disease only be diagnosed in the presence of suggestive clinical symptoms that are not otherwise explained and suggestive radiographic findings; diagnosis should be supported by isolation of NTM, ideally from multiple specimens.
- Treatment benefit/risk ratio is generally poorer than what is seen with TB. Therefore, even when the NTM are judged likely to be clinically significant, a careful assessment of the therapeutic goal and individual risks and benefits is recommended before initiating treatment.
- It is recommended that limited drug susceptibility testing be used to guide therapy of *M. avium-intracellulare* complex (MAC) (macrolide testing only) and *M. kansasii* (rifampin testing). For rapidly growing mycobacteria and other NTM, drug susceptibility results can be used but should be interpreted with caution, as data correlating *in vitro* susceptibility results with clinical outcomes are lacking.
- Therapy is generally species specific and involves multiple drugs for a prolonged duration.
- Clinical outcomes in lung disease are relatively poor, with high relapse rates requiring recurrent or ongoing drug therapy.
- Clinical outcomes in nonpulmonary disease are relatively good.

*Major Shifts in Recommendations: none*

# INTRODUCTION

Pulmonary nontuberculous mycobacterial disease is considered in the context of tuberculosis (TB) for two main reasons. First, lung disease associated with NTM is often characterized by cough, sputum, hemoptysis, a wasting illness, cavities on lung imaging and acid-fast organisms on sputum smear microscopy. Therefore, it can initially be mistaken for TB. Second, TB clinics are often asked to assess patients with known NTM disease because TB clinicians are experienced at prescribing and monitoring antituberculous drugs, many of which are also used to treat NTM disease. In addition, practitioners are not always aware that the provinces and territories do not require NTM disease to be reported, that case management is not mandated by public health, that treatment is not mandatory (rather, determined on a case-by-case basis) and, with some possible very rare exceptions,[1] that NTM disease is not contagious. This chapter provides some background information on NTM microbiology and epidemiology and is followed by a review and clinical recommendations regarding NTM disease.

Historically, the mycobacteriology laboratory served to isolate and speciate *Mycobacterium tuberculosis* complex organisms. This capacity to isolate known mycobacterial pathogens gradually enabled the laboratory to isolate other mycobacteria, of unknown or lesser pathogenicity.[2] These organisms have traditionally been grouped together by what they are not, and are now most often called NTM, a term used here for all mycobacterial species with the exception of *M. tuberculosis* complex organisms and *M. leprae*. At present, there are over 150 recognized mycobacterial species (http://www.bacterio.net/mycobacterium.html), the majority of which have little clinical relevance. This chapter will focus on the small number of NTM that are well associated with defined clinical syndromes.

The significance of an NTM isolate necessitates more deliberation by the clinician than is the case for *M. tuberculosis*, for which treatment is not optional. Certain NTM, such as *M. gordonae*, are rarely associated with clinical illness. It is generally accepted that when *M. gordonae* is found in a sample, treatment is not recommended.[3] At the other end of the spectrum, *M. kansasii* is usually associated with a *bona fide* clinical syndrome.[4] The severity of otherwise unexplained symptoms and suggestive abnormalities on chest imaging generally guide clinical decisions as to the relevance of the NTM isolate. Some patients lack attributable symptoms and chest imaging abnormalities, and the presence of the NTM might be termed colonization. In other patients, there may be a spectrum of findings ranging from minimal and nonprogressive symptoms to more extensive lung disease with chest imaging abnormalities. However, even in the presence of productive cough and radiographic abnormalities, it can still be difficult to judge whether the NTM is contributing to these findings, for instance when a patient also has chronic obstructive pulmonary disease (COPD) or pre-existing bronchiectasis. Suggested criteria for the diagnosis of pulmonary NTM disease are presented in Table 1. The Canadian Thoracic Society (CTS) recommends that, in the context of even a single NTM isolate from a normally sterile site (blood, pleural fluid, organ biopsy), NTM disease should be very strongly considered.

**Table 1. Recommended diagnostic criteria for pulmonary NTM disease[3]**

**1. Clinical**

a) Symptoms – pulmonary (such as cough, sputum production, hemoptysis, chest pain, dyspnea) and/or systemic (such as fatigue, weight loss, fever).

b) Other potential causes of symptoms should be excluded.

c) Progressive symptoms increase the likelihood of NTM disease, so that antimicrobial drug therapy may be necessary.

**2. Radiology**

a) Chest radiograph – nodular or cavitary opacities, or

b) Chest computed tomography – bronchiectasis with multiple small nodules or lung cavitation, or, in some cases, air space disease (consolidation or ground glass opacification).

**3. Microbiology**

a) Positive culture results from at least two separate sputum samples or

b) Positive culture result from at least one bronchial wash or lavage,* or

c) Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or acid-fast bacilli [AFB]) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.

* Sputum induction should be attempted before bronchoscopy. A single bronchoscopic isolate is acceptable for the diagnosis of pulmonary NTM disease when sputum (spontaneously expectorated or induced) cannot be obtained.

A bronchoscopic isolate should be corroborated with sputum results if both samples are available.

A single bronchoscopic isolate in the presence of repeatedly negative sputum samples should be interpreted cautiously.

A key reason to make the clinical determination of whether there is NTM colonization or NTM disease is that the former is not likely to benefit from treatment, while the latter may benefit from targeted therapy. Importantly, treatment of NTM disease, where indicated, benefits only the patient, in contrast to *M. tuberculosis*, for which there are also public health benefits of treatment. Furthermore, there is less urgency in deciding whether to treat NTM, as the clinical evolution of NTM is typically slower than that of TB, and the treatment is more complex (longer duration, greater toxicity). Where there is doubt about whether to treat or defer, one should obtain more specimens and consider further investigations before formulating a treatment plan and defining the therapeutic goal(s). Recommendations in this chapter are focused largely on therapy, and are summarized and rated in Table 2.[3] Ratings for the few remaining recommendations can be found in the text box.

## Table 2. Recommended treatment of nontuberculous mycobacterial disease[3]*

| Organism | Drugs | Duration |
|---|---|---|
| *M. avium* complex (MAC) lung disease (macrolide susceptible) | Daily Clarithromycin 500 mg bid or azithromycin 250 mg<br>Ethambutol (EMB) 15 mg/kg (may use 25 mg/kg for initial 2 months)<br>Rifampin (RMP) (450-600 mg) or rifabutin (RBT) (150-300 mg)<br>± aminoglycosides (streptomycin [SM] or amikacin) intermittently<br>*(Conditional recommendation, based on moderate evidence)*<br><br>Thrice weekly†<br>(may be considered for nonadvanced, nodular bronchiectatic pulmonary MAC)<br>Clarithromycin 500 mg bid or azithromycin 500 mg<br>EMB 25 mg/kg<br>RMP 600 mg<br>*(Conditional recommendation, based on moderate evidence)*<br><br>Clofazimine and fluoroquinolones (FQN) may be useful<br>*(Conditional recommendation, based on moderate evidence)* | 12 months after culture conversion to negative<br>*(Conditional recommendation, based on moderate evidence)* |
| MAC lymphadenitis (macrolide susceptible) | If antibacterial therapy is being considered (see text): daily or thrice weekly clarithromycin or azithromycin plus EMB ± RMP<br>*(Conditional recommendation, based on very weak evidence)* | 3-9 months<br>*(Conditional recommendation, based on very weak evidence)* |
| *M. xenopi* lung disease | Azithromycin or clarithromycin plus RMP plus EMB<br>Consider, in addition, moxifloxacin (or other FQN), isoniazid (INH), streptomycin (SM), amikacin<br>*(Conditional recommendation, based on very weak evidence)* | 12 months after culture-negative<br>*(Conditional recommendation, based on very weak evidence)* |
| *M. abscessus* complex lung disease | Clarithromycin or azithromycin + amikacin, cefoxitin or imipenem (+/- tigecycline, linezolid, clofazimine)<br>*(Conditional recommendation, based on moderate evidence)* | 2-6 months of combination IV and oral therapy<br>*(Conditional recommendation, based on weak evidence)* |
| *M. kansasii* lung disease | Daily RMP, EMB, INH<br>Consider clarithromycin or azithromycin, moxifloxacin, sulfamethoxazole and aminoglycosides<br>*(Strong recommendation, based on moderate evidence)* | 12 months after culture-negative<br>*(Conditional recommendation, based on weak evidence)* |
| *M. fortuitum* lung disease | Based on *in vitro* sensitivity testing:<br>azithromycin or clarithromycin and RMP or EMB<br>(+/- doxycycline, amikacin, imipenem, FQN, sulfonamides, cefoxitin)<br>*(Conditional recommendation, based on very weak evidence)* | 12 months after culture-negative for lung disease<br>*(Conditional recommendation, based on very weak evidence)* |
| *M. fortuitum* skin/soft tissue | Based on *in vitro* sensitivity testing:<br>azithromycin or clarithromycin and RMP or EMB<br>(+/- doxycycline, amikacin, imipenem, FQN, sulfonamides, cefoxitin)<br>*(Conditional recommendation, based on very weak evidence)* | 4 months for skin/soft tissue<br>(6 months for severe disease)<br>*(Conditional recommendation, based on weak evidence)* |
| *M. marinum* skin/soft tissue | Clarithromycin, EMB +/- RMP<br>*(Conditional recommendation, based on weak evidence)* | 3-6 months (consider longer if deep structures involved)<br>*(Conditional recommendation, based on weak evidence)* |

**Table 2. Recommended treatment of nontuberculous mycobacterial disease[3]* - *Continued***

| Organism | Drugs | Duration |
|---|---|---|
| Disseminated MAC in HIV-infected patients Treatment | ‡Clarithromycin 500 mg orally daily + EMB 15 mg/kg orally daily +/- RBT 300 mg orally daily<br>*(Strong recommendation, based on very strong evidence)* | Lifelong or until control of HIV viremia with rise of CD4 to >100 x $10^6$/L for at least 6 months and 12 months after culture-negative<br>*(Strong recommendation, based on strong evidence)* |
| Disseminated MAC in HIV-infected patients Prophylaxis<br>Patients with CD4 <50 x $10^6$/L | Azithromycin 1200 mg weekly<br>or<br>RBT 300 mg a day<br>or<br>clarithromycin 500 mg bid<br>*(Strong recommendation, based on very strong evidence)* | Lifelong or until control of HIV viremia with rise of CD4 to >100 x $10^6$/L for at least 6 months and 12 months after culture-negative<br>*(Strong recommendation, based on strong evidence)* |

Suggested regimens for initial therapy of NTM disease should be modified, if needed, depending upon clinical circumstances such as drug intolerance, the presence of macrolide-resistant MAC and a lack of efficacy.

*More detailed recommendations and treatment guidance regarding other NTM species may be found elsewhere.[3]

†Although directly observed therapy (DOT) is recommended for intermittent therapy of TB, this is not so in NTM disease, because there is no public health consideration of contagion. Intermittent therapy for pulmonary NTM has been suggested to reduce toxic effects and sometimes costs of therapy, and has been shown to be effective in many cases.

‡Doses may need to be adjusted according to interactions with concurrent antiretroviral therapy.

## LABORATORY METHODS

The typical mycobacteriology laboratory detects NTM using protocols and media that were optimized for the isolation of *M. tuberculosis* from sputum. If there is clinical suspicion of NTM disease, one should contact the laboratory so that it can modify the protocol, depending on what sample is provided and what organism is suspected.

Complete details on the laboratory handling of suspected NTM disease (and additional information for this section) can be found in the following three sources:

- http://www.asmscience.org/content/book/10.1128/9781555817435;
- http://mcm10.asmpress.org/;
- http://www.asmscience.org/content/book/10.1128/9781555817138.

Once an NTM has been isolated, in theory this is no longer a biosafety threat, as most NTM are harmless to humans and present a negligible risk to laboratory workers. In practice, NTM clinical work is done in the level 3 laboratory for two reasons. First, it is not known that the organism is NTM until after genetic or phenotypic tests have been conducted. Second, sputum is occasionally positive for both *M. tuberculosis* and NTM; thus, the demonstration of NTM does not guarantee the absence of *M. tuberculosis*. After selection of pure colonies from a culture that has been speciated, all other NTM work can be safely done outside of containment.

Characterization of an NTM isolate begins with a formal species designation, which in the molecular era often includes a combination of phentoypic anlaysis (growth rate, morphology, etc.) and molecular testing (specific probes for certain species and/or 16s rRNA sequence analysis). One consequence of the use of this highly discriminative technique is the identification of a "new" species from within a previously familiar species or group (e.g. *M. chimerae* as a variant of the *M. avium-intracellulare* complex [MAC][5]). This may confuse clinicians if there are new names for which the clinical information is limited to case reports or small case series, such that the clinical importance of the new designation is not immediately apparent.
In the case of antibiotic resistance testing it is relatively straightforward to grow organisms in the presence of various antibiotics and measure the minimum inhibitory concentration; however, the utility of these results for guiding therapeutic decisions remains largely unknown. For rapid-growing mycobacteria, antibiotic drug susceptibility (DS) testing is typically done in a manner comparable to the testing of common bacteria in the microbiology laboratory (e.g. *Staphylococcus aureus*). For slow-growing mycobacteria, there are laboratory issues with standardizing results (antibiotics may degrade during the time of testing) and clinical issues with interpreting results (antibiotics that do not appear effective in the laboratory have apparently provided benefit in the clinic). While there are many possible DS tests that could be requested for any given NTM isolate, the only good correlations between laboratory testing and clinical response to treatment are seen for macrolide resistance in MAC and rifampin resistance in *M. kansasii*.

## EPIDEMIOLOGY

The NTM that are most closely linked to human disease inhabit moist environments, both natural and engineered.[6] NTM have been recovered from all types of natural waters and soils from many parts of the world.[7,8] There has been a relatively high rate of NTM recovery from household water and plumbing fixture biofilms, but since NTM are common and NTM disease is rare, it is unclear whether environmental exposure in the home differs between people with and without NTM disease.[9,10] Transmission of NTM between patients is extremely rare and probably only occurs when an index patient with a large burden of NTM organisms comes into contact with someone who is particularly susceptible to NTM infection.[1] The mode of transmission, if it occurs at all, is unknown. For this reason, the CTS sees no public health concerns for the vast majority of patients with NTM disease.

It appears that a defect in pulmonary defences is the most common risk factor for pulmonary NTM disease. Structural lung diseases, especially COPD and bronchiectasis, are important risk factors for pulmonary NTM (30% of pulmonary NTM is associated with COPD).[11] However, the majority of patients do not have pre-existing structural lung disease.[3] In one series, approximately 30% of patients with apparently idiopathic MAC lung disease were found to carry at least one mutation for the cystic fibrosis transmembrane conductance regulator (CFTR) gene, without a prior diagnosis of cystic fibrosis (CF).[12] Cryptic abnormalities in pulmonary mucus and its clearance may represent a major risk factor for NTM lung disease. Both pediatric and adult patients with CF commonly have positive sputum cultures for NTM, ranging from 3.7% to 13%.[13-15] Systemic deficits in host defences are believed to be relatively uncommon in pulmonary NTM, and tumour necrosis factor alpha inhibitors have been inconsistently associated with elevated rates of NTM disease.[16,11] Increasing age is an important risk factor for pulmonary NTM: the prevalence of identified pulmonary MAC disease in Ontario was 1/100,000 in people <50 years old and 48/100,000 in people ≥80 years old.[11]

Historically, the epidemiology of NTM disease has not been well understood because of two key challenges. First, unlike TB, the provinces and territories do not require clinicians to report NTM disease to public health authorities, so there has not been any systematic collection of data regarding NTM disease. Second, the determination that someone has NTM disease, as opposed to simply a positive sputum culture, necessitates the integration of clinical, microbiological and radiological information.

Illustrating this, in 2008 in Ontario, the prevalence of pulmonary MAC isolation was 12.6/100,000, whereas the prevalence of disease was estimated to be 6.8/100,000.[11] Similarly, a British Columbia study reported an annual incidence of 6.7/100,000 for pulmonary NTM isolation and 1.6/100,000 for disease.[17] NTM isolation in Canada is more common than *M. tuberculosis* isolation, but there is great regional variability. In recent reports, the ratio of pulmonary NTM to *M. tuberculosis* was 5.3 in Ontario,[11] 2.7 in Alberta (personal communication: G. Tyrrell, University of Alberta, Edmonton, Alberta, 2011) and 1.4 in British Columbia.[17]

Most investigations into temporal trends of pulmonary NTM have observed increases. In Ontario, prevalence rates of MAC lung disease increased from 4.3 to 6.8/100,000 from 2003 to 2008 overall, and from 11.9 to 18.6/100,000 in people $\geq$50 years old.[11] Similar findings have been described in the United States.[18,19] Numerous factors have been postulated to contribute to these increases, including better laboratory detection and real changes in epidemiology. Improved sample collection practices and the use of liquid culture media, which are more sensitive for detection of NTM than conventional solid media in the TB laboratory, do not appear to completely explain the increase.[20] In addition, increases in at-risk populations (aged, immune suppressed, with chronic lung disease) are also not felt to be sufficiently important to explain the changing epidemiology of NTM disease.[11] "Cross-immunity" between *M. tuberculosis* and NTM has been hypothesized to be a contributing factor, since increases in NTM have usually been seen coincident with decreases in TB rates.[21] Finally increases in exposure to water aerosols, possibly through showering, have also been proposed as a potential contributing factor.[21]

Regional variations exist not only in rates of disease but also in the relative frequency of different NTM species causing disease.[22] For example, *M. xenopi* is common in Ontario and parts of Europe but relatively uncommon elsewhere; *M. kansasii* is common in the south and central United States, Asia and Eastern Europe but rare in most of Canada. The epidemiology of NTM infections is highly dependent upon the geographic region, likely reflecting the environmental NTM that are prevalent in patients' local environments.

# CLINICAL SYNDROMES

## LUNG DISEASE

### Diagnostic considerations

In adults, NTM disease is usually pulmonary; in Ontario between 2000 and 2007, 95% of people with NTM isolates had a pulmonary isolate. MAC represents the most common species group associated with NTM lung disease, followed variably by *M. xenopi* (second in Ontario), the rapid growers of the *M. fortuitum-chelonae-abscessus* complex (second in British Columbia and

Alberta) and *M. kansasii*.[22] As detailed in Table 1, at least two sputum isolates are recommended for the diagnosis of pulmonary NTM disease or, when sputum cannot be obtained (spontaneously expectorated or induced), a single bronchoscopic isolate or one biopsy isolate is suggested. In addition to isolating the organism, otherwise unexplained symptoms and chest imaging changes consistent with NTM infection are also recommended for the diagnosis.[3] In the case of *M. kansasii*, a single isolate is commonly considered to be diagnostic in the appropriate context.[3]

There are two traditionally described imaging patterns seen with pulmonary NTM disease, although overlap is common. The most common radiographic type is called "nodular bronchiectatic" based on a pattern of nodules, often "tree-in-bud," and bronchiectasis, with or without consolidation. This pattern occurs most often in patients without obvious underlying lung disease and has classically been described in a right middle lobe and lingular distribution in middle-aged to older women (Lady Windermere syndrome).[23] Such patients often share a phenotype that includes a tall slender habitus, scoliosis, pectus excavatum and mitral valve prolapse, and 36.5% have been found to have a mutation in at least one CFTR allele (versus 15.6% in controls).[12] The second pattern is one of predominant cavitation, often in the upper lobes in the setting of emphysema or pre-existing bronchiectasis – described as "fibrocavitary." The natural history and treatment response with nodular bronchiectatic disease appears to differ from fibrocavitary disease, with poorer treatment outcomes in the latter group.[24-26]

Screening for NTM is recommended in CF patients, with sputum (spontaneously expectorated or induced) collection at least yearly and during periods of clinical decline. The laboratory should be informed that the patient has CF, so that tailored protocols for decontamination of CF sputum can be employed. Patients being considered for chronic macrolide therapy should have sputum cultures for NTM before starting therapy and periodically thereafter, to avoid the risk of providing macrolide monotherapy (see below, Treatment). It is recommended that CF patients with repeated isolation of NTM not receive macrolide monotherapy without the potential risks of its use or its omission being carefully weighed. On the one hand, macrolide monotherapy is associated with the development of macrolide-resistant NTM disease, which is extremely difficult to treat.[27] On the other hand, azithromycin therapy has been shown to have clinically beneficial effects in CF patients.[28] In general, it is recommended that macrolide monotherapy be avoided in CF patients with repeated isolation of NTM who may have clinically significant NTM isolates. These recommendations may also be considered for patients with non-CF bronchiectasis and COPD if chronic macrolide therapy is being considered.

### Treatment (see Table 2)[3]

Fulfilling the diagnostic criteria for NTM-associated lung disease does not necessarily imply the need for treatment. Initiating therapy is a decision that should be made carefully, considering individual patient characteristics,[3] risk factors for treatment toxicities and the frustratingly low cure rates that are compounded by substantial recurrence rates after treatment completion.[29] Although there are no data to support this approach, anecdotal experience suggests that clinicians may wish to consider initiating therapy sequentially, adding a drug every 7-14 days, until a tolerable multidrug regimen is achieved. Staggered initiation may facilitate tolerance of a difficult drug regimen and does not appear to increase the risk of drug resistance using the scheme described above. Clinicians may also consider changes between drugs within a class (e.g. azithromycin versus clarithromycin), changes between drug classes, modification of frequency of administration (thrice weekly versus daily) and modifications of doses to achieve a tolerable and effective drug regimen. The initial regimen will usually require modification because of toxic effects[30] or inadequate efficacy, and the duration of therapy required can vary dramatically among patients.

Patients undergoing therapy for NTM lung disease should have careful clinical monitoring and regular sputum mycobacterial cultures. The frequency of clinical monitoring may be dictated by the need to make drug and dose changes and the presence of drug toxicities. The frequency of sputum assessment may depend upon whether results will lead to changes in management. In practice, sputum assessment every 1-3 months is often helpful. Consultation with physicians who have expertise in managing NTM lung disease should be considered as needed. Specific medication regimens and details regarding the recommendations are listed in Table 2.
Patients occasionally have a single or small number of incidental lung nodules found to be due to NTM. The diagnosis is usually made when nodules are biopsied or removed for diagnosis, usually to rule out malignancy. Such patients often are asymptomatic, and there are no robust data to direct clinical care in this context. It appears that in most cases medical therapy is not indicated[3] unless there is significant radiographic progression with the development of symptoms. A schedule of radiographic follow-up may often be determined, at least in part, to assess for the possibility of malignancy when there are residual nodules that were not biopsied. Occasionally, in patients with known NTM lung nodule(s) and risk factors for lung cancer, new and growing nodules raise the concern of possible malignancy. In such instances, instead of repeated biopsies of additional nodules, a trial of antimycobacterial drug therapy may occasionally be useful to demonstrate a reduction in the size or number of nodules.

### MAC lung disease

The treatment of MAC lung disease involves multiple antibacterial drugs, including, most importantly, a macrolide, either clarithromycin or azithromycin, and companion medications such as EMB, RMP and traditionally second-line agents such as clofazimine and FQN.[3] In noncomparative studies, regimens using macrolides have demonstrated far superior outcomes over those without macrolides.[29] However, there are very few data directly comparing macrolide versus non-macrolide based regimens.

In a large controlled trial comparing clarithromycin and ciprofloxacin (each combined with EMB and RMP), few differences were observed between the two regimens.[31] The study was complex, including patients with MAC, *M. malmoense* and *M. xenopi*, and it also included immunomodulatory therapy with *M. vaccae*. Patients were not treatment naïve (data regarding macrolide resistance were lacking), subgroups by species were small, and among MAC patients most had cavitary disease. Mortality was high (43%-44% overall), and the investigators could not conclude superiority of either regimen.

Other guidelines have recommended the combination of a macrolide, EMB and a rifamycin as daily or thrice weekly therapy, the former recommended for advanced or recurrent disease, including fibrocavitary disease, while the latter may be adequate for mild disease in treatment-naïve patients.[3] The addition of an injectable aminoglycoside (usually amikacin or SM), with appropriate monitoring, should be considered in advanced cases or if the possibility of surgical resection is being entertained.[32] Several additional or alternative antimicrobials may be considered, as noted above. Antimicrobial drug susceptibility testing is helpful for macrolides, as macrolide resistance predicts a poor response to therapy.[33,34] There are limited data regarding the utility of MAC susceptibility testing for other antimicrobial agents, although a correlation has been shown between good clinical outcomes and the number of drugs used to which the isolate is susceptible.[35] Favorable outcomes of macrolide-resistant MAC lung disease have been described in a retrospective study.[27] Treatment included discontinuation of the macrolide and initiation of EMB 25 mg/kg daily, RBT 300-450 mg daily, and either SM or amikacin. The injectable agent was continued for as long as could be tolerated, and surgical resection for cure or debulking was

considered in all cases. Sputum culture conversion was achieved in 11 of 14 patients (79%) who received aggressive combined medical and surgical therapy (including injectable drug), compared with 2 of 37 patients (5%) treated less aggressively.[27] On the basis of this information it is recommended that expert consultation should be considered for the treatment of macrolide-resistant MAC lung disease.

Where the defined therapeutic goal is cure, it is recommended that treatment of MAC lung disease should generally continue until sputum cultures have been culture-negative for at least 12 months.[3] In this setting, successful treatment outcomes may be expected in 56%, according to a systematic review.[29] However, many patients, because of advanced disease or difficulty in tolerating complex drug regimens, cannot attain sustained culture-negative sputum and achieve a "cure." [30] In such situations, tailoring the (often chronic) regimen is recommended to prevent progression of disease and minimize the adverse effects of therapy. Long-term follow-up is recommended, because recurrence rates approximate 40% in studies with follow-up exceeding 3 years, and many patients require ongoing or repeated therapy.[3] Treatment recommendations are summarized in Table 2.

### *M. kansasii* lung disease

*M. kansasii* is the most pathogenic of the NTM encountered in the lung and is characteristically associated with lung lesions similar to those seen in TB, including upper lobe involvement and cavitation.[4,37] Evidence for specific drug regimens in the treatment of *M. kansasii* is observational. Treatment for 9 months with RMP and EMB was evaluated in a prospective study in Britain and found to be successful in 88% of 155 subjects.[37] In North America, treatment regimens generally include standard doses of INH (despite frequent *in vitro* resistance to low concentrations of INH), with RMP and EMB. Treatment is generally continued for 12 months of negative sputum cultures.[3] RMP susceptibility testing should be sought routinely, as RMP resistance is associated with poorer outcome. In the event of RMP resistance or drug intolerance, additional susceptibility test results may be considered to help guide selection of a three-drug regimen from clarithromycin or azithromycin, moxifloxacin, EMB, sulfamethoxazole or streptomycin.[3] Alternatively, high dose INH (900 mg/day), EMB (25 mg/kg daily), sulfamethoxazole (1.0 g thrice daily) plus streptomycin or amikacin has been used in RMP-resistant *M. kansasii.*[3] Clarithromycin has been used with RMP and EMB in a thrice-weekly treatment regimen.[38] Treatment recommendations are summarized in Table 2.

### *M. xenopi* lung disease

*M. xenopi* disease may be manifest as cavities, nodules or infiltrates/consolidation on imaging.[39,40] The management of *M. xenopi* lung disease is controversial, and the available evidence is weak. In British and French studies, RMP and EMB appeared to be beneficial,[40,41] but a systematic review (performed before all of the French data were published) could not identify an advantage of any particular drug class.[39] North American guidelines have recommended azithromycin or clarithromycin, plus RMP, and EMB initially, with consideration of additional agents, including moxifloxacin, INH and amikacin or streptomycin.[3] *M. xenopi* lung disease is probably more difficult to treat than MAC lung disease, but it is unclear whether this is the because of differences among species or differences among patients (more patients with *M. xenopi* lung disease have architectural lung damage).[3] Treatment recommendations are summarized in Table 2.

### Rapidly growing mycobacterial lung disease

The clinical presentation and diagnosis of lung disease due to rapidly growing mycobacteria are similar to those of other NTM. Speciation of organisms is important to determine treatment and prognosis.[42] Most primary antituberculosis drugs are not active against rapidly growing mycobacteria. *M. fortuitum* is usually susceptible to newer macrolides, FQN, amikacin, doxycycline and sulfonamides.[3] It is recommended that for rapidly growing mycobacteria drug susceptibility results can be used, but interpreted with caution, as there are no published data correlating *in vitro* susceptibility results with clinical outcomes.

### *M. abscessus* lung disease

*M. abscessus* complex is the most common rapidly growing mycobacteria causing lung disease.[6] Molecular analyses have determined that *M. abscessus* is a complex consisting of three closely related subspecies (*M. abscessus*, *M. massiliense* and *M. bolletii*). One Korean study showed that treatment response rates were much higher in patients with *M. abscessus* subsp. *massiliense* than with *M. abscessus*.[43] *M. abscessus* complex is inherently resistant to RMP, EMB and INH, and therefore treatment is very challenging. Isolates are usually susceptible *in vitro* to parenteral agents (amikacin, imipenem, cefoxitin) and the macrolides.[3] Therapy typically requires 2-6 months of one or two intravenous antibiotics in combination with an oral macrolide. Macrolides were thought to be the only active oral agent, but the presence an inducible macrolide resistance (*erm)* gene likely diminishes their activity *in vivo.*[44] Choices of antibiotics are limited by drug toxicities and logistical difficulties administering the drugs.[3] Two retrospective studies of treatment, one with standardized and the other with individualized (i.e. tailored to drug susceptibility pattern and/or patient tolerability) antibiotic regimens, have shown that patients often respond clinically to therapy, but the degree and duration of response are variable. Microbiologic results were similar in both studies. Overall, outcomes are poor, and even in expert clinical programs approximately 25% of patients' sputum cultures never convert to negative; prolonged response and/or cure is uncommon. Surgical resection of localized disease may offer additional benefit to antibiotic therapy in select patients.[45,46]

### M. fortuitum

This is a relatively rare isolate that is uncommonly associated with lung disease. It is most often seen in patients with underlying lung disease or recurrent aspiration and/or gastroesophageal reflux disease. A Korean study (26 patients) suggests that clinical and radiologic findings may not be progressive, even without treatment (median follow-up 12.5 months).[47]

### Lymphadenopathy

NTM granulomatous lymphadenopathy is most commonly seen in children aged 6 months to 5 years.[48] A typical presentation is one of a persistent, unilateral cervical lymph node that may be fluctuant with overlying skin inflammation, which may give way to suppuration. In Canada, NTM account for more childhood granulomatous lymphadenopathy than *M. tuberculosis*.[49] However, TB should be considered in children in Canada who are from First Nations or Inuit communities (please refer to Chapter 14, Tuberculosis Prevention and Care in First Nations, Inuit and Métis Peoples) or whose parents were born in a country with a high incidence of TB.

Since TB is less likely than NTM in Canadian children without such risk factors, unless there is a suggestive history of TB contact it may be reasonable to withhold anti-TB treatment until the microbiologic results of surgically excised lymph node tissue are available. The majority of cases are caused by MAC followed variably by other species.[49-51]

Surgical excision has traditionally been considered to be curative without drug treatment in most cases. Recent studies in Canada and the United States both found that the majority of cases are being treated with surgery, usually followed by adjunctive antimycobacterial drugs.[49,52] When lymph node proximity to the facial nerve makes surgery difficult, successful treatment with antimycobacterial drugs (often clarithromycin and EMB) has been described. When antimicrobial drugs are employed, the species of NTM should be considered and drug susceptibility testing be utilized as appropriate. There are inadequate data to unequivocally support the use of antibiotics or surgery in all patients. With “advanced” disease, defined by overlying skin discoloration, a randomized trial of no therapy versus antibiotics alone (clarithromycin and RBT) found that the median time to resolution (40 weeks with no therapy versus 36 weeks with antibiotics) did not differ significantly between groups.[50] These data argue that specific therapy may not be needed in some cases and that perhaps more randomized trials including a "no therapy" control group are required to define the optimal therapeutic approach.

Currently, there are inadequate data to favour any one of 1) resection, 2) antibacterial drugs or 3) simple observation, as each option has been reported to offer good outcomes in various settings. If the diagnosis was made through an excisional biopsy of all involved nodal tissue, observation without antibacterial drug therapy is likely adequate for many cases. If, however, the diagnosis is made through a needle aspirate, one might consider antibacterial therapy with a macrolide and EMB, simple observation or surgery in the appropriate circumstances. However, the available data are inadequate to provide clear guidance in this regard.

### Skin and Soft-Tissue Infections (Bone and Joint Extension)

Skin and soft tissue NTM infections usually occur after trauma, surgery or other procedures.[53] Bone and joint infections are usually acquired by direct inoculation from an environmental source or a contiguous infection. Hands and wrists are the most frequently reported sites of NTM tenosynovitis. A long list of NTM have been reported to cause skin and/or soft-tissue infection, but the most common organisms are *M. marinum, M ulcerans, M. fortuitum*, *M. abscessus* and *M. chelonae.*[54] It is recommended that diagnosis be confirmed by culture of the specific pathogen from drainage material or tissue biopsy. Additional laboratory tasks may be required for recovery of fastidious organisms, therefore good communication between clinicians and laboratory staff is important to achieve timely diagnosis.[53] Clinical manifestations and the severity of disease depend on both the organism isolated and the host immune status.

*M. marinum* prefers 30 ˚C temperatures and consequently causes superficial peripheral ulcerative lesions after mild trauma, such as an abrasion, and exposure to fish or other aquatic animals. Clarithromycin combined with EMB or RMP may be the best therapy for these so-called fish tank or swimming pool granulomas.[3,55] Clarithromycin in combination with doxycycline, minocycline or cotrimoxazole has also been used with success. It is recommended that treatment should continue for at least 2 months after clinical resolution (usually 3-4 months' duration) or longer, depending on the severity of infection. Surgical debridement of the hand may need to be considered for severe and/or nonresponsive cases.[3,55]

*M. fortuitum* and *M. abscessus* complex are the most frequent cutaneous pathogens.[56] Approximately half of these cutaneous infections follow surgery or trauma, and they may be associated with the presence of a foreign body.[57] There is a strong association between *M. fortuitum* and prosthetic devices such as breast implants or peritoneal dialysis catheters. Patients with *M. chelonae* or *M. abscessus* complex are more likely than *M. fortuitum* patients to be taking immunosuppressive medications.[57] Treatment of cutaneous, rapidly growing mycobacterial infections may require surgical excision/debridement in addition to antibiotic therapy (with at least two drugs to which the organism is susceptible). Surgery is particularly successful for cutaneous infections associated with prosthetic devices.[3] In general, two active agents are recommended, for approximately 4-6 months, depending on severity of disease *(conditional recommendation, based on weak evidence)*.[58]

### Disseminated Infection

NTM infections may disseminate in hosts with impaired immunity.[59] Disseminated MAC was common in AIDS patients prior to the introduction of combination antiretroviral therapy in 1994. Since then, the rate of disseminated MAC in AIDS patients has decreased dramatically in the United States,[60] likely as a result of both the reduction in the number of people with advanced immune suppression because of antiretroviral therapy, and the use of MAC prophylaxis.[61,62] See Table 2 for treatment and prophylaxis of HIV-infected individuals with CD4 counts under $50 \times 10^6$/L.[63]

It is recommended that treatment of HIV-infected patients with disseminated MAC include concomitant anti-MAC and antiretroviral therapy; therefore, a regimen that minimizes drug-drug interactions is advised. Consultation with HIV and NTM experts and pharmacists is recommended. Patients with disseminated MAC are at risk of immune reconstitution syndromes, similar to that seen with TB, once they begin antiretroviral therapy.[64]

Disseminated NTM disease in non-HIV patients is uncommon but has been reported in patients who have had solid organ or bone marrow transplantation, chronic corticosteroid usage with or without other immunosuppressive agents (e.g. rheumatologic or sarcoidosis patients), hematologic malignancy and interferon-gamma receptor and interleukin-12 receptor abnormalities.[65] Apart from MAC, a variety of other NTMs can also cause disseminated infection, including *M. fortuitum* complex, *M. abcesssus* complex*, M. kansasii, M. gordonae, M. simiae, M. haemophilum, M. szulgai, M. genovense* and *M. smegmatis*.[3]

## CONCLUSION

The provinces and territories do not require NTM disease to be reported to local public health authorities and it is not generally considered contagious. Treatment is not mandatory but, rather, is determined on a case-by-case basis. NTM-related diseases are incompletely understood regarding the source of the infecting organism, natural history and indications, as well as optimal therapy. Diagnosis of NTM lung disease is complex, involving microbiological, clinical and radiological information, and is only one step in the decision to initiate therapy, wherein the relative risks and benefits of treatment versus observation should be considered.

Therapy for lung disease generally comprises multiple drugs for a prolonged duration, is often difficult to tolerate and is associated with suboptimal outcomes. In contrast, extrapulmonary NTM disease may be more easily treated and associated with better outcomes. The most recent guidelines prepared by the American Thoracic Society and Infectious Diseases Society of America[3] provide extensive and detailed information regarding the management of NTM disease. Consultation with an expert is suggested when treating NTM disease.

**SUMMARY OF MISCELLANEOUS RECOMMENDATIONS***

**Recommendations regarding patients with cystic fibrosis (and bronchiectasis from other causes):**

- Screening for NTM, with sputum (spontaneously expectorated or induced) collection, is advised at least yearly, and during periods of clinical decline.

  *(Conditional recommendation, based on very weak evidence)*

- Patients being considered for chronic macrolide therapy should have sputum cultures for NTM before starting therapy and periodically thereafter, to avoid the risk of macrolide monotherapy.

  *(Conditional recommendation, based on very weak evidence)*

- Patients with repeated isolation of NTM should not receive macrolide monotherapy.

  *(Conditional recommendation, based on very weak evidence)*

**Patients with COPD who are being considered for chronic macrolide therapy:**

- These patients should have sputum cultures for NTM before starting therapy and periodically thereafter, to avoid the risk of macrolide monotherapy for unrecognized NTM disease.

  *(Conditional recommendation, based on very weak evidence)*

- Patients with repeated isolation of NTM should not receive macrolide monotherapy.

  *(Conditional recommendation, based on very weak evidence)*

**Asymptomatic patients:**

- Asymptomatic patients with a single or a small number of randomly distributed, incidental lung nodules due to NTM generally should not be treated unless there is significant radiographic progression with the development of symptoms.

  *(Conditional recommendation, based on very weak evidence)*

**Other recommendations, relating to treatment, are summarized in Table 2.*

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