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Best Practices for Pulmonary Nontuberculous Mycobacteria

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PIDAC Provincial Infectious Diseases Advisory Committee
Communicable diseases

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Provincial Infectious Diseases Advisory Committee (PIDAC)

Tel: 647-260-7100 Email: pidac@oahpp.ca

Authors/Contributors

Nontuberculous Mycobacteria Working Group Members:

Dr. Theodore Marras, Chair
Respirologist, Toronto Western Hospital
Associate Professor of Medicine,
University of Toronto

Dr. Anne Stephenson
Clinician Scientist, Division of Respirology
St. Michael's Hospital

Dr. Gonzalo Alvarez
Respirologist
Divisions of Respirology and Infectious Diseases
Department of Medicine
The Ottawa Hospital

Julia Lechner
TB Program Manager
Toronto Public Health

Dr. Martha Fulford
Chief of Medicine, Division of Infectious Diseases
McMaster University Medical Centre

Dr. Peter Jessamine
Medical Microbiologist & Infectious Diseases
Departments of Pathology & Laboratory Medicine & Medicine
The Ottawa Hospital

Dr. Sarah Brode
Respirologist
Toronto Western Hospital and West Park Healthcare Centre

Dr. Scott Weese
Professor, Department of Pathobiology
University of Guelph

Dr. Valerie Waters
Staff Physician, Infectious Diseases
Hospital for Sick Children

Ex-officio Members:

Dr. Catherine Filejski
Public Health Veterinarian
Ministry of Health and Long-Term Care

Dr. Doug Sider
Public Health Physician
Public Health Ontario

Dr. Frances Jamieson
Medical Microbiologist
Public Health Ontario

Dr. Jin Hee Kim
Public Health Physician
Public Health Ontario

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Abbreviations

CF	Cystic fibrosis
DST	Drug susceptibility testing
MIC	Minimal inhibitory concentration
NTM	Nontuberculous mycobacteria
NTM-PD	Nontuberculous mycobacteria pulmonary disease

Introduction

Nontuberculous mycobacteria (NTM) comprise over 170 species that are widespread environmental organisms found in soil and water, including treated drinking water distribution systems, and may be concentrated in showerheads and faucets.[1] Human NTM infections are most often pulmonary and typically cause slowly progressive respiratory and systemic symptoms. Pulmonary NTM infections are increasingly common and difficult to treat.[2,3] Less common non-pulmonary NTM infections may include: localized infections of skin and soft tissue, lymph nodes, joints or other sites and disseminated disease.[3] Disseminated disease occurs almost exclusively in the presence of systemic immune deficiency.

Objective

The objective of this document is to provide an overview of human NTM infections for clinicians, including:

- epidemiology and clinical presentations
- diagnosis
- overview of treatments
- potential opportunities for prevention of infections

Sample collection and microbiology

Specimen quality and proper transport to the laboratory are critical for successful isolation of mycobacteria. For respiratory specimens (e.g., sputa), individuals should not rinse their mouths with tap water or other fluids (e.g., mouthwash) prior to obtaining specimens because of the potential for specimen contamination with environmental NTM. Three early morning specimens collected on three consecutive days are optimal; however, specimens collected on the same day, at least one hour apart, are acceptable.[4]

See specimen collection instructions:

- Mycobacterium — Respiratory specimen requirements, handling and testing information
- Additional specimen collection details — Mycobacterium

The most common NTM species isolated in Ontario are: *Mycobacterium avium, M. xenopi, M. gordonae, M. intracellulare, M. fortuitum* and *M. abscessus*. It is important to recognize that some NTM species are frequently associated with disease (e.g., *M. avium, M. xenopi*, and *M. abscessus*); when they are identified in sputum samples, their significance should be carefully considered. On the other hand, *M. fortuitum* is an uncommon cause of significant lung disease and *M. gordonae* is very rarely a cause of significant lung disease.[3-5]

Disease versus colonization

For several reasons it may be difficult to determine whether a NTM isolated from a respiratory specimen is clinically significant. Because NTM are widely distributed in the environment, they may contaminate clinical specimens. Widespread exposure to NTM from drinking water may lead to their transient presence in the pharynx /upper airway tract and may result in false-positive cultures. Individuals with abnormal lungs who have impaired airway clearance (e.g., bronchiectasis with or without cystic fibrosis, emphysema /chronic obstructive pulmonary disease) may not spontaneously clear inhaled NTM, as would be expected in the healthy state. The presence of NTM in the lungs in these individuals does not necessarily indicate disease. NTM that is chronically present in the lungs without causing disease is often referred to as "colonization".[3] When NTM are present and causing significant infection, NTM pulmonary disease (NTM-PD) is said to be present. The distinction between disease and colonization is not always easy and guidelines have been developed to assist in this regard.[3] Specifically, to determine that NTM-PD is present, at least two sputum specimens must yield the same species of NTM (see diagnostic and treatment criteria). Therefore, a single sputum specimen that yields NTM should prompt the collection of additional samples. If sputum cannot be obtained, a single bronchoscopic or lung biopsy sample can be diagnostic if other diagnostic criteria are satisfied (see recommended diagnostic criteria for NTM pulmonary disease).

Diagnostic and treatment criteria for NTM-PD

Established diagnostic criteria may help determine whether an individual with respiratory NTM isolates has NTM-PD.[3-5]

Clinical, radiological and microbiological criteria have been identified and all three need to be considered.

Recommended diagnostic criteria for NTM pulmonary disease

1. **Clinical**
    a. symptoms: pulmonary (such as cough, sputum production, hemoptysis, chest pain, dyspnea) and/or systemic (such as fatigue, weight loss, fever), **and**
    b. other potential causes of symptoms are excluded. Note: progressive symptoms increase the likelihood of NTM-PD, so that antimicrobial drug therapy may be necessary.
2. **Radiological**
    a. chest radiograph: nodular or cavitary opacities, **or**
    b. chest computed tomography (CT): bronchiectasis with multiple small nodules (including tree-in-bud/centri-lobular nodules) or lung cavitation, or, in some cases, air space disease (consolidation or ground glass opacification)

3. **Microbiological**

    a. Positive culture results from at least two separate sputum samples, **or**

    b. Positive culture results from at least one bronchial wash or lavage. Note: sputum induction should be attempted before bronchoscopy. A single bronchoscopic isolate is acceptable for the diagnosis of pulmonary NTM-PD 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 with caution, and in conjunction with clinical and radiological data. **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.

In addition to the appropriate microbiologic investigations (usually multiple sputum samples), a diagnosis of NTM-PD requires a careful history and a chest x-ray (CXR). Although given superior sensitivity, a thoracic CT scan is preferred to identify the radiographic abnormalities of NTM-PD.

Although the presence of characteristic symptoms and radiographic findings in the context of multiple positive sputa defines NTM-PD, the presence of NTM lung disease *per se* does not necessitate the institution of therapy. Therapy for NTM-PD comprises multiple antibiotics, typically for 18 months, with sub-optimal rates of both response to therapy and recurrence after treatment completion. As a result, the decision to treat is determined based on the individual risks and benefits for each patient.[3-5]

Typically, individuals are offered treatment in the setting of progressively symptomatic disease, with additional emphasis placed on the extent and severity of lung involvement on CXR or CT scan (especially cavitation) and the burden of organisms in the sputum (especially heavily positive acid-fast smear). Severe cough, the expectoration of blood and systemic symptoms of fever, sweats, weight loss, and fatigue are common factors leading to treatment initiation.

Regardless of treatment status, because the rate of progression cannot be predicted, individuals with NTM-PD require lifelong follow-up to assess for progression and/or recurrence.

Most common clinical presentations

NTM-PD typically presents in one of a few clinical situations, with the common feature of impaired bronchopulmonary clearance.[3]

Known bronchiectasis, including cystic fibrosis

Cystic fibrosis (CF) is a prototypical disease state of impaired bronchopulmonary clearance, which can result in retention of inhaled matter, including environmental micro-organisms. Similarly, non-CF bronchiectasis is a very common chronic lung disease in which NTM-PD occurs.[3] Patients with CF should

be tested for NTM annually as a routine and at times of unexplained worsening of symptoms.[5] A similar approach is likely appropriate for symptomatic patients with non-CF bronchiectasis. The most common clinical scenarios are further described below.

Chronic unexplained cough in middle-aged to older patients

Most commonly, NTM-PD occurs in middle-aged to older people with a chronic unexplained variably productive cough that has usually not responded to typical empiric approaches, including inhalers (bronchodilators and/or corticosteroids). These individuals tend to be female, but both men and women may be affected.[3] People with chronic unexplained cough should be investigated with a complete medical history and appropriate tests. Spirometry and other lung function tests may lead to a diagnosis of asthma or chronic obstructive pulmonary disease (COPD). We recommend that individuals with persistently unexplained cough after lung function assessment and all older people or smokers with persistent cough should have chest imaging performed and sputum specimens collected for microbiologic analyses, including submission for acid-fast microscopy and mycobacterial culture.

Unexplained persistent worsening of pre-existing COPD or asthma

Another very common scenario is an unexplained worsening of symptoms in individuals with COPD.[3] We recommend that unexplained persistent worsening of COPD should prompt chest imaging and sputum specimen collection for microbiologic analyses, including submission for acid-fast microscopy and mycobacterial culture.

A less common but still important presentation is among people with unexplained persistent worsening of asthma.[6] If no alternative cause is identified after reviewing common causes for persistent worsening asthma, individuals should be investigated with chest imaging and sputum collection for microbiologic analyses, including submission for acid-fast microscopy and mycobacterial culture.

Other

Non-pulmonary NTM infection is much less common and presents with symptoms and signs specific to the involved organ/system.

Public health implications

NTM-PD is not reportable in Ontario. Although NTM-PD rates have increased over the past decade, it is not clear that there is an effective and timely public health response to these infections, given the widespread exposure to NTM from the environment and the likelihood that individual host susceptibility is the determining factor for developing the disease. In Queensland, Australia, an active microbiological surveillance system, including the routine analysis of case numbers and geographic distribution, has been felt to be helpful in understanding environmental sources of pulmonary NTM.[7] Respiratory outbreaks in institutions are reportable, regardless of the causative organism. Additionally, health care providers with concerns about potential community outbreaks should contact public health.

Non-pulmonary NTM infections continue to occur with a low and stable frequency in Ontario. Skin and soft tissue NTM infections usually occur after direct inoculation, although the recent attention focused

on risks of exposure to *M. chimaera* from heater-cooler units involved in cardiac surgery indicate that other routes of exposure are possible.[8] Direct inoculation may occur during medical procedures, esthetic procedures such as pedicures after soaking in foot baths containing high NTM concentrations, tattooing with contaminated inks, or from working with contaminated fish or aquaria. Although NTM infections are not reportable, identifying the source of non-pulmonary NTM infections may enable prevention of additional cases from contaminated sources. There is very limited literature on the public health response to clusters of non-pulmonary NTM infections given that few jurisdictions have designated these infections reportable, with the notable exception of recently published experience from Oregon.[9]

NTM infections in animals

There is no evidence of transmission of NTM between humans and domestic animals. However, NTM colonization and infection can occur in animals, including infections with the same species that cause disease in people. This likely represents coincidental infection with commonly encountered environmental NTM species (e.g., *M. avium* from waters).

NTM and TB co-isolation

NTM species are frequently isolated from individuals with pulmonary TB. This is not surprising considering that TB patients have lung disease, so colonization or infection with environmental organisms is possible. Individuals with TB also usually have numerous sputum samples collected, some of which may become contaminated with NTM. In the presence of co-isolation with NTM and TB, the TB isolate must take priority in diagnostic and treatment considerations. Among individuals on therapy for proven TB, whose specimens subsequently are found to yield NTM, an adequate curative course of TB therapy remains the priority. It is generally best practice to continue TB therapy without modification, and to assume that the NTM is not clinically significant. Exceptions exist and should be reviewed with an experienced clinician if there is uncertainty as to whether the NTM isolation may be clinically significant.

Treatment

Treatment for NTM must be overseen by a specialist, usually a respirologist or an infectious diseases physician. In some cases additional input from a NTM specialist is required. Antibiotic treatment involves multiple drugs and prolonged therapy with careful monitoring for toxicity and benefits. Therapy is often not curative, and there are high recurrence rates. Individuals with NTM-PD require lifelong follow-up.[3-5]

Drug susceptibility testing (DST) in the setting of NTM infections is of relatively limited utility. However, in some circumstances, it is recommended as outlined below. It should be noted that appropriate minimal inhibitory concentration (MIC) breakpoints have not been identified for most drugs used for the treatment of NTM. However, using Clinical and Laboratory Standards Institute (CLSI) MIC thresholds, DST results are clinically useful for *M. avium/M. intracellulare* and *M. abscessus* for the drugs clarithromycin/azithromycin and amikacin. For *M. abscessus*, it is believed that established MIC thresholds are of some relevance for some additional agents. For more information regarding DST, please visit the Public Health Ontario (PHO) website or read PHO's Labstract: Tuberculosis and

Mycobacteriology: Identification of *M. abscessus* subspecies and molecular detection of macrolide resistance.

For *M. avium/M. intracellulare,* the clinician should very strongly consider obtaining DST for clarithromycin and amikacin before initiating therapy (especially if there is history of prior macrolide use) and in cases of non-responding or recurrent infection.[3-5] First-line antibiotic drug combinations for *M. avium/M. intracellulare* and *M. xenopi* pulmonary disease are listed in Table 1.

For all cases of *M. abscessus* disease, DST results should be obtained to assist with drug selection. Therapy for *M. abscessus* is very complex. It involves a minimum of two intravenous (IV) agents plus at least one oral agent. Specific drug selection and duration of therapy are not well defined. Detailed information regarding antibiotic treatment for NTM-PD is provided elsewhere.[3-5]

Table 1: First line* antibiotic drug combinations for *M. avium/M. intracellulare and M. xenopi* pulmonary disease

Species	Dose	Dose timing
M. avium/M. intracellulare†	Azithromycin 250 mg or clarithromycin 500 mg bid **and** ethambutol 15-17 mg/kg **and** rifampin 300-600 mg or rifabutin 150-300 mg	Daily
	Azithromycin 500 mg or clarithromycin 500 mg bid **and** ethambutol 20-25 mg/kg **and** rifampin 450-600 mg or rifabutin 150-300 mg	Thrice weekly
M. xenopi‡	azithromycin 250 mg or clarithromycin 500 mg bid **and** ethambutol 15-17 mg/kg **and** rifampin 450-600 mg or rifabutin 150-300 mg	Daily

* Treatment frequently requires adjustments including addition of an injectable agent (usually amikacin, and usually in the case of severe disease) or substitution/addition of other drugs

† The macrolide (azithromycin or clarithromycin) forms the cornerstone of therapy. Macrolide resistance is likely to develop if a macrolide is used in the absence of appropriate "companion" drugs. If

macrolide resistance develops, disease becomes extremely difficult to treat. It is therefore critical to avoid the use of macrolides without adequate companion drugs in patients with *M. avium/intracellulare* lung disease. The ideal companion drugs are believed to be ethambutol and rifampin/rifabutin. Rifampin has less toxicity and is therefore generally preferred over rifabutin.

‡ Fluoroquinolones, especially moxifloxacin, are more often judged to be useful for *M. xenopi* therapy than for M. *avium /M. intracellulare;* although expert opinion differs, compared with the regimen presented, the substitution of moxifloxacin for a macrolide or the addition of moxifloxacin may be appropriate.

NTM-PD transmission between people

NTM are widely found in the environment and infected individuals pose limited risk to others. Person-to-person spread of NTM is not a concern in the vast majority of situations. Individuals with NTM pulmonary disease do not need to observe any isolation precautions in general. There have been situations where *M. abscessus* appears to have been transmitted between individuals within CF clinics and across vast geographic distances.[10,11] However, direct person-to-person transmission has not been confirmed. Other possibilities include transmission from a shared environment. The US Cystic Fibrosis Foundation has put forth recommendation specifically related to individuals with CF.[5]

There is no evidence of transmission between individuals without CF or for other NTM species.

Environmental sources and avoidance of exposure

Although no data supports specific exposure avoidance measures, for individuals with prior NTM-PD or CF who may be susceptible to NTM-PD, it is likely appropriate to minimize potential exposures. The inhalation of water aerosols carrying NTM organisms could cause lung infection. Hot tubs, showers and humidifiers all generate aerosols containing NTM that may be inhaled. Use of indoor swimming pools (possibly due to the lack of ventilation compared with outdoor pools) has been associated with NTM-PD among individuals with CF.[12] Although drinking water is likely associated with lower risk than these activities, aspiration (with or without reflux) may lead to lung infection with organisms in drinking water. Among people at risk of aspiration, avoidance of dispenser systems that could promote reproduction of NTM (e.g., refrigerated filter pitchers, ice dispensers, water dispensers through refrigerators) might reduce exposure. Minimizing inhalation of soil aerosols may reduce the risk of infection with species like *M. intracellulare*, thought to be primarily contracted from soils. Avoiding "turning over" soil and working with dry soil (which may be associated with higher aerosol generation) may reduce inhalation of soil aerosols. Suggested measures have been offered by NTM Info & Research, Inc.

As described above, although NTM infections are not reportable, identifying the source of non-pulmonary infections may enable prevention of additional cases from contaminated sources, including but not limited to such sources as nail salon foot baths, tattoo inks and surgical equipment.[7-9] Because potential exposures for pulmonary infections (inhalation of drinking water or soil aerosols) is near ubiquitous, the belief that host susceptibility is the major determinant of disease development and the uncertainties as to the effectiveness of the public health outcomes in response to cases or clusters,

reportability for pulmonary disease would appear to be less relevant. Additional work is required to understand in which circumstances public health investigations and interventions may be useful when cases of NTM-PD are identified.

Helpful resources

- American Thoracic Society/Infectious Diseases Society of America Guidelines for the Diagnosis and Management of NTM Disease
- Canadian Thoracic Society/Public Health Agency of Canada Nontuberculous Mycobacteria Guidelines
- NTM Info and Research – a non-profit organization providing patient support, medical education, and research funding for NTM
- US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for managing NTM in individuals with CF

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Public Health Ontario
480 University Avenue, Suite 300
Toronto, Ontario
M5G 1V2

647.260.7100
communications@oahpp.ca
www.publichealthontario.ca