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Tuberculosis Physician Manual

Section 12: Pulmonary Non-Tuberculous Mycobacteria (NTM)

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A research and teaching centre affiliated with UBC

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Introduction

This section of the BC Centre for Disease Control (BCCDC) tuberculosis (TB) physician manual:

1. Supports the care of pulmonary Non-Tuberculous Mycobacteria (NTM) patients by outlining care pathways.
2. Is a resource for BC physicians managing the care of patients with pulmonary NTM in outpatient clinics.

The current care model for NTM patients in BC is in evolution as Provincial TB Services are no longer accepting new NTM client referrals at the BCCDC TB clinics. However, TB Services physicians are able provide support with NTM management upon request. Please refer to the updated BCCDC NTM Referral Form.

Many NTM patients require coordinated, multi-disciplinary expert care. For example, pediatric patients are managed exclusively through BC Children's Hospital. Adult Cystic Fibrosis patients are managed at St. Paul's Hospital, and the Transplant Infectious Disease physicians support the management of NTM disease in solid organ and bone marrow transplant. Many other subspecialty physicians manage their NTM patients in their outpatient clinics in the Lower Mainland and beyond. Any BC physician who wishes to establish their patient on NTM therapy is encouraged to do so.

If there is a need for BCCDC Pharmacy Services to supply medications, the referring physician can fax a copy of the requested prescription to (604) 707-2583. Currently, some NTM medications (e.g. rifampin, ethambutol) are provided free of charge to the patient by the BCCDC Pharmacy, but this is subject to change. Macrolides are not provided to the patients from the provincial pharmacy and must be purchased independently.

Prescription requests will be entered into Panorama (subject to change) and medications will be supplied for pill pick up or shipping through the BCCDC pharmacy. All care and follow-up is at the discretion of the most responsible provider (MRP). The only role of the BCCDC TB physician is to facilitate the prescription as need be and clearly outline the follow-up plan in a physician's note (e.g. "Dr. X will be managing all clinical and biochemical monitoring of this patient. TB Services is only involved in medication access. A prescription has been entered into Panorama"). TB Services and the Provincial Pharmacy are exploring ways to further streamline this process to optimize access to medications and limit delays in treatment starts.

Patients not actively on treatment for pulmonary NTM disease are being discharged from TB Services back to the care of the referring provider or MRP. The TB Clinic does not have the capacity to follow NTM patients long term off treatment (e.g. repeat CT scanning, surveillance sputum etc). In the future, the role of the BCCDC and care pathways for NTM patients in BC will change again with the creation of a much needed provincial NTM Clinic.

Key Recommendations

DIAGNOSIS

- The diagnosis of pulmonary NTM disease is based on clinical, radiographic and microbiologic evidence of disease.
- Microbiologic diagnosis requires at least two positive sputum cultures for the same pathogenic organism, or a single positive culture from a bronchial wash or lavage
- Patients with relapsed or recurrent MAC disease, or patients who fail to convert sputum cultures on treatment, should have macrolide and clofazimine drug susceptibility testing to guide therapy.
- *M. abscessus* should be identified to the subspecies level and drug susceptibility testing should be performed at baseline.
- Drug susceptibility testing for Rifampin should be performed for *M. kansasii* at baseline.

TREATMENT

- First-line therapy for pulmonary MAC is a three drug combination of a macrolide, rifampin and ethambutol daily or three times weekly for at least 12 months post-culture conversion.
- First-line therapy for *M. kansasii* is rifampin, ethambutol and *either* isoniazid *or* a macrolide daily for 12 months.
- First-line therapy for *M. abscessus* should include a minimum of three drugs with demonstrated in vitro activity and a minimum of four drugs if macrolide resistance is present.

Background

Non-Tuberculous Mycobacteria (NTM) are a diverse group of over 190 species and subspecies of environmental mycobacteria, the majority of which are non-pathogenic. Human disease is most often chronic pulmonary infection in older patients, usually associated with underlying structural lung damage, bronchiectasis and chronic obstructive pulmonary disease (COPD). By far the most common cause of pulmonary NTM disease is *Mycobacterium avium complex* (MAC), followed by *M. abscessus* and M. *kansasii*. Extra-pulmonary NTM disease in children is primarily cervical lymphadenitis caused by MAC or *M. scrofulaceum*. In adults, rapidly growing mycobacteria (RGM) such as *M. abscessus*, *M. chelonae* and *M. fortuitum* can cause skin and soft-tissue disease, including nosocomial surgical site infections. Severe extra-pulmonary or disseminated NTM infections in adults are almost invariably found in immune suppressed individuals such as HIV, post-transplant or other defects in cell-mediated immunity.

The incidence and prevalence of NTM infection is increasing worldwide and in Canada. In British Columbia (BC), the median incidence of NTM isolated from pulmonary specimens between 1990-2006 was 6.7 per 100,000, with MAC accounting for 77% of isolates (Hernandez-Garduno, 2009). The prevalence of pulmonary NTM isolates increased significantly from 10.47 per 100,000 in 2006 to 11.92 per 100,000 in 2013 (p=0.001) (BCCDC Lab). Increasing trends are likely multifactorial

including enhanced provider awareness and testing, and an aging population with a higher degree of immune suppression.

The diagnosis and treatment of NTM infections is challenging. Diagnosis rests on a combination of clinical, radiographic and microbiological tests. Even after diagnosis the decision to begin treatment in patients with pulmonary disease is not always straight forward, and patients may be monitored with a "watchful waiting" approach. Treatment requires multiple antimicrobial agents, few with predictable in vivo activity, all with associated toxicity or adverse reactions that require regular monitoring. The duration of treatment is typically 12-18 months with recurrence common. Thus, NTM infections have typically been managed by respiratory or infectious diseases specialists.

The following recommendations regarding the diagnosis and treatment of NTM is intended for physicians treating the most common pulmonary NTM pathogens, particularly MAC*, M. abscessus*, and *M. kansasii*. The management of NTM infection in children and cystic fibrosis is beyond the scope of this guideline. Similarly, disseminated MAC disease in HIV is a specific syndrome with a large evidence base and is well-described elsewhere.

Diagnosis

The diagnosis of NTM pulmonary disease includes three criteria:

1. Clinical
2. Radiographic
3. Microbiologic (see Table 1)

CLINICAL CRITERIA

Symptoms associated with pulmonary NTM disease are variable and depend on the stage of infection and the presence of underlying lung disease or other co-morbid conditions. Cough, which may be dry or productive, is most common. Occasionally patients may present with hemoptysis. Dyspnea, fatigue, weight loss and malaise are frequent. Fever and night sweats may be present, but are less common than with TB.

Two clinical syndromes are characteristic of pulmonary NTM disease:

1. **Disease with known underlying lung disease.** This syndrome occurs in patients with chronic bronchiectasis, most commonly due to cystic fibrosis, COPD, prior TB or smoking. The most common pathogen is MAC, followed by *M. abscessus and M. kansasii.*

2. **Disease without known underlying lung disease**. This syndrome occurs primarily in non-smoking women over the age of 50, with undiagnosed bronchiectasis. These patients often have a gradually progressive cough and dyspnea over months to years. By far, the most common pathogen in this scenario is MAC.

RADIOGRAPHIC CRITERIA

The radiographic features of pulmonary NTM are variable and can be indistinguishable from TB, although progression is usually more indolent. Classically, two radiographic appearances occur:

1. **Fibrocavitary Disease**
   Imaging is similar to post-primary TB with predominant upper lobe involvement, cavities and heterogeneous linear and nodular opacities with or without calcification. Progressive fibrosis, volume loss and traction bronchiectasis may occur. Lower lobe disease is less common.

2. **Nodular bronchiectatic Disease**
   Imaging shows multifocal cylindrical bronchiectasis and 1-3 mm centrilobular nodules in a "tree in bud" like pattern. High resolution CT scan has superior diagnostic sensitivity. Findings may be most prominent in the right middle lobe and lingula.

MICROBIOLOGIC CRITERIA

The isolation of NTM from the respiratory tract can represent either contamination or infection. Some NTM organisms, such as *M. gordonae*, have low pathogenicity and are most likely to be contaminants when isolated from a respiratory specimen. The isolation of *M. kansasii,* however is more likely to represent disease (van Ingen, 2009). While MAC disease is unlikely with a single positive sputum culture, patients with ≥ 2 positive MAC sputum cultures are highly likely to have disease (Tsukamura, 1991).

To reduce the likelihood of contamination, three sputum samples should be collected over at least one week. **The diagnosis of pulmonary NTM disease requires at least two positive sputum cultures for the same pathogenic organism**. Bronchoscopy should be considered in all patients who cannot produce a sputum sample either spontaneously or through induction. Bronchoscopy may also be more sensitive than sputum collection for patients with nodular bronchiectatic disease (Sugihara, 2003). A single positive culture from a bronchial wash or lavage is adequate for diagnosis when clinical and radiographic criteria are present.

TABLE 1. DIAGNOSTIC CRITERIA FOR PULMONARY NTM DISEASE

Clinical	Pulmonary and/or Systemic symptoms consistent with NTM infection
Radiographic	Nodular and/or cavitary opacities on chest radiograph, or a high resolution CT scan that shows bronchiectasis with multiple small nodules.
Microbiologic	Positive culture results from at least two separate expectorated sputum samples. If the results are non-diagnostic, repeat sputum smears and culture or Positive culture results from at least one bronchial wash or lavage or Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive tissue culture for NTM or Biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.

Laboratory Tests

Some hospitals (e.g. Vancouver General Hospital, St. Paul's Hospital and sites in Island Health) do their own inpatient cultures. Otherwise, sputum and bronchial specimens are processed at the BCCDC Public Health lab. Smear microscopy, culture and molecular testing is performed inhouse, while drug susceptibility testing is outsourced.

AFB smear

The sensitivity of sputum smear is low and positive results suggest a higher mycobacterial burden. Positive results are graded 1+ to 4+ (e.g. Gaffky score).

Molecular methods

- **PCR**-Performed on all smear positive results from respiratory samples to rapidly identify MAC vs. MTB. The sensitivity for MAC is 87%.
- **MAC Accuprobe**-Performed on all positive culture results with initial morphology suggestive of NTM. This test only identifies MAC.
- **HSP65 Sequencing**-Performed on all MAC Accuprobe negative specimens to identify the species and subspecies of NTM.

Culture

The gold standard for NTM diagnosis and monitoring, and necessary for drug susceptibility testing (DST). Both liquid and solid media culture is performed.

DRUG-SUSCEPTIBILITY TESTING

All NTM drug-susceptibility testing (DST) is sent out to the National Microbiology Lab (NML) in Winnipeg. The return time varies between two to six weeks depending upon whether the sample is fresh or frozen, or a slow or rapidly growing mycobacteria. NTM positive samples from sterile sites are automatically sent to the NML, while NTM DST from respiratory samples must be requested by a physician using a Public Health Agency of Canada form. For more information, see the National Reference Centre for Mycobacteriology (NRCM) service page.

DST for NTM is performed at the NRCM (Winnipeg) including clofazimine. The National Jewish Health Advanced Diagnostic Laboratories (Denver CO), does clofazimine testing for MTB. Interpretation of DST for NTM is challenging due to the lack of established MIC breakpoints for many drugs and, for drugs with breakpoints, an unclear correlation between in vitro susceptibility and in vivo outcomes.

- Susceptibility breakpoints for the most common anti-microbials to treat pulmonary NTM pathogens (see Table 2)
- The antibiotics included on DST panels (see Table 3)

At initial diagnosis, DST is recommended only for M. kansasii and M. abscessus subsp. DST is not automatically done nor recommended for all MAC isolates, as between 2016 and 2020 only 10% of all MAC isolates tested had macrolide resistance.

MAC isolates from patients who have relapsed, recurred or failed to culture convert should have DST. The most recent isolate should be used for DST. DST should also be sent for patients with adverse events or toxicities to first-line drugs in whom it is necessary to choose an alternative regimen.

Treating physicians are encouraged to connect with the TB Laboratory if they have questions regarding NTM DST. Completed requisitions should be faxed to the TB Lab (Fax: 604-707-2672).

CLOFAZIMINE

Clofazimine susceptibility is not automatically performed and must be specifically requested from NML. Clofazimine DST results are required in order for the drug to be released by Health Canada's Special Access Program (SAP). Request a drug:

- Telephone: (613) 941-2108
- Fax: (613) 941-3194
- E-mail: hc.sapd-pasm.sc@canada.ca

MAC - MACROLIDE AND AMIKACIN

A correlation between in vitro susceptibility and clinical outcome is only clear for two antibiotics: macrolides and amikacin. Susceptible MAC isolates to clarithromycin have an MIC ≤ 8 mcg/ml, and resistance is defined by an MIC ≥ 32 mcg/ml. Susceptibility to clarithromycin predicts susceptibility to azithromycin. Resistance to parenteral amikacin is defined by an MIC ≥ 64 mcg/ml and ≥ 128 mcg/ml for inhaled amikacin liposomal solution. Although tentative breakpoints have been established for Linezolid and Moxifloxacin, the impact on clinical outcome is unknown.

Macrolide resistance in patients with no prior MAC treatment is unlikely, and routine DST is not necessary at initial diagnosis. Estimates of macrolide resistance in all MAC isolates is ~10%. However, the likelihood of acquired resistance increases with exposure to macrolide therapy. **Therefore, all patients with relapse or recurrent disease, or patients who fail to convert sputum cultures after six months on treatment, should have DST performed.** Patients with underlying lung disease who receive or have received frequent or continuous macrolide therapy for treatment of lung infections or inflammation should also have baseline DST.

Between 2016 and 2020, 55% of MAC isolates tested in BC had either resistance or intermediate susceptibility to Amikacin. Therefore if Amikacin is to be used in the initial treatment regimen, baseline DST should be performed to ensure susceptibility. Baseline susceptibility can be done on the initial isolate and need not impact treatment start although regimen may require adjustment pending results.

M. KANSASII

The correlation between in vitro susceptibility and clinical outcome is established only for rifampin. Rifampin resistance should be determined at baseline and is done automatically by the PH Lab. Resistance to rifampin is defined by an MIC ≥ 2 mcg/ml and is associated with treatment failure. Rifampin susceptibility predicts rifabutin susceptibility. Clarithromycin has excellent in vitro activity for *M. kansasii* although correlation with clinical outcome is lacking. All isolates with an MIC ≥ 1 mcg/ml to rifampin should have second-line DST performed to amikacin, ciprofloxacin, linezolid, moxifloxacin, doxycycline, rifabutin, and trimethoprim-sulfamethoxazole (TMP-SMX) if treatment is being considered. DST for isoniazid and ethambutol are not reliable for *M. kansaii,* do not predict clinical response, and should not be performed.

M. ABSCESSUS

M. abscessus has three important subspecies:

1. subsp. abscessus
2. subsp. massiliense
3. subsp. bolletii

Because drug susceptibility may vary between subspecies, it is critical to identify this organism to the subspecies level.

Most importantly, subsp. abscessus and subsp. bolletii commonly have an inducible erythromycin resistance methylase (erm) gene, which confers macrolide resistance. The erm gene is activated only in the presence of the macrolide and the initial MIC may indicate susceptibility. Typically the laboratory will prolong the DST microdilution incubation period to detect phenotypic inducible resistance. Subsp. massiliense remains susceptible to macrolides due to a large deletion in the erm gene. All three subspecies can develop acquired macrolide resistance through mutation in the 23S RNA gene.

Similar to MAC, macrolide, and to a lesser extent amikacin, susceptibility is strongly correlated with treatment success in M. abscessus disease. Initial DST also includes cefoxitin, ciprofloxacin, doxycycline (or minocycline), imipenem, linezolid, moxifloxacin, and trimethoprim-sulfamethoxazole. Tigecycline and clofazimine may be tested, but there are insufficient data to establish MIC breakpoints. However, in vitro clofazimine is synergistic with macrolides and amikacin, and prevents the emergence of amikacin resistance (Ferro, 2016).

TABLE 2. SUSCEPTIBILITY BREAKPOINTS FOR NTM PULMONARY PATHOGENS * $

Species	MIC (mcg/ml)			Comments
	Susceptible	Intermediate	Resistant	
M. avium complex First line (if failing treatment or increased risk for macrolide resistance)				
Clarithromycin	≤ 8	16	≥ 32	Results match azithromycin
Amikacin (IV)	≤ 16	32	≥ 64	
Amikacin (liposomal Inhaled)	≤ 64		≥ 128	
M. avium complex Second line				
Moxifloxacin	≤ 1	2	≥ 4	Clinical efficacy of these drugs for MAC remains uncertain
Linezolid	≤ 8	16	≥ 32	
Clofazimine				Insufficient data to establish MIC breakpoints
M. kansasil First line (at baseline)				
Clarithromycin	≤ 8	16	≥ 32	
Rifampin	≤ 1		≥ 2	
Ethambutol/Isoniazid				Unreliable so not done
M. kansasil Second line				
Amikacin	≤ 16	32	≥ 64	
Ciprofloxacin	≤ 1	2	≥ 4	Ciprofloxacin and levofloxacin are interchangeable but both are less active than moxifloxacin
Doxycycline	≤ 1	2 - 4	≥ 8	
Linezolid	≤ 8	16	≥ 32	
Moxifloxacin	≤ 1	2	≥ 4	
Rifabutin	≤ 2		≥ 4	
TMP-SMX (trimethoprim-sulfamethoxazole)	≤ 2/38		≥ 4/76	

Continued Table 2. Susceptibility Breakpoints for NTM Pulmonary Pathogens * $

Species	MIC (mcg/ml)			Comments
	Susceptible	Intermediate	Resistant	
M. abscessus First Line (at baseline)				
Clarithromycin	≤ 2	4	≥ 8	
Amikacin	≤ 16	32	≥ 64	*M. abscessus* isolates with MIC of ≥ 64 mcg/ml should be retested and/or the 16S rRNA gene sequenced to check for mutation
Cefoxitin	≤ 16	32 - 64	≥ 128	
Ciprofloxacin	≤ 1	2	≥ 4	Ciprofloxacin and levofloxacin are interchangeable but both are less active than moxifloxacin
Doxycycline	≤ 1	2-4	≥ 8	
Imipenem	≤ 4	8 -16	≥ 32	
Linezolid	≤ 8	16	≥ 32	
TMP-SMX (trimethoprim-sulfamethoxazole)	≤ 2/38		≥ 4/76	
Clofazimine				Insufficient data to establish MIC breakpoints
Tigecycline				Insufficient data to establish MIC breakpoints

* Adapted from Clinical and Laboratory Standards Institute (CLSI) 3rd edition, 2018.

$ There is no DST available for bedaquiline (BDQ) in North America.

TABLE 3. DRUG-SUSCEPTIBILITY PANELS FOR NTM

Initial Drug Susceptibility Report		
MAC	***M. Kansasii***	***M. abscessus subsp.***
Amikacin	Clarithromycin	Amikacin
Clarithromycin	Rifampin	Cefoxitin
		Ciprofloxacin
		Moxifloxacin
		Clarithromycin (inducible resistance will be automatically set up)
		Linezolid
		SXT
		Tigecycline*
		Doxycycline
		Imipenem
Not reported in DST panel. MIC and interpretations can be requested from NML		
MAC	***M. Kansasii***	***M. abscessus subsp.***
Ciprofloxacin	Amikacin	
Doxycycline	Ciprofloxacin	
Linezolid	Doxycycline	
Minocycline	Linezolid	
Moxifloxacin	Minocycline	
Rifabutin	Moxifloxacin	
Rifampin	Rifabutin	
Streptomycin	Streptomycin	
TMP-SMX	TMP-SMX	
Clofazamine $ *		
$ Clofazimine can be done in initial DST panel but must be specifically requested. * No interpretations, but MIC can be requested.		

TESTING FOR INTERFERON-GAMMA AUTO-ANTIBODIES

Over the past decade disseminated NTM disease has been increasingly described in otherwise healthy adults, usually of Southeast Asian ancestry. Occasionally patients will have a history of other infections associated with defects in cell-mediated immunity such as herpes zoster and disseminated salmonellosis. Such patients have been found to have acquired auto-antibodies to IFN-gamma, a critical component of host immunity to mycobacterial infections. Treatment of mycobacterial disease in this context requires both prolonged antimicrobial therapy and rituximab, however appropriate duration of therapy is unknown and relapse is common.

For patients with disseminated NTM and no obvious immune deficiency, an IFN-gamma auto-antibody level should be ordered to confirm the diagnosis and provide the rationale for rituximab therapy. The only lab in North America currently performing this is the US National Institutes of Health (NIH). Permission is required from the NIH lab before sending samples. If you have further questions, please contact TB Services.

Treatment

Not all patients that meet criteria for pulmonary NTM diagnosis will develop progressive disease, and some will experience spontaneous sputum conversion in the absence of treatment (Hwang, 2017). Patients who initiate therapy face a long treatment course with drugs that have significant adverse events and toxicities. Cure is not guaranteed and persistent infection, re-infection and relapse are common. Therefore a period of "watchful waiting" is a reasonable decision in selected patients. This may include repeat respiratory specimens and imaging.

Risk factors for progression include fibrocavitary disease, extensive disease on radiographic imaging, low body mass index and low albumin. These patients are more likely to benefit from treatment, as are those with immune suppression or in whom quality of life is poor due to symptoms. The decision to treat may also be influenced by the specific organism; *M. kansasii* is relatively easy to treat, whereas *M. abscessus* is less responsive to antimicrobial therapy.

All treatment decisions should be made after a discussion with the patient in which the benefits and risks are clearly outlined. Attempts should be made to outline realistic goals of care with each patient (e.g. symptom improvement vs. culture conversion or normalization of chest imaging). However, once the decision to treat is made, it is critical to optimize the initial drug regimen, as this choice will have the biggest impact on treatment outcome. See Table 4 for pulmonary NTM Treatment regimens.

MAC

Standard first-line therapy for pulmonary MAC is a three drug combination of a macrolide, rifampin and ethambutol. Although a two drug combination of a macrolide and ethambutol has equivalent clinical response rates, the addition of rifampin results in less macrolide resistance (Gordon, 1999). For this reason, two drug regimens should be avoided and attempts should be made to explore other options (e.g. clofazimine). For patients with nodular bronchiectatic disease the three drug regimen

may be given daily or three times per week. Intermittent dosing has been shown to have equivalent sputum culture conversion, with less toxicity and no increase in macrolide resistance (Daley, 2020). However, patients with fibrocavitary or extensive disease should receive daily dosing of a three drug regimen.

There is limited data about the optimal length of therapy for pulmonary MAC. A duration of at least 12 months results in higher treatment success than a shorter course, however duration of therapy post-culture conversion has not been well-studied. Therefore, **patients with macrolide-susceptible disease should be treated for a minimum of 12 months after sputum culture conversion.** Patients who cannot produce a sputum sample, but have otherwise improved clinically and radiographically, should be treated for a minimum of 12 months. A repeat bronchoscopy to establish negative cultures is not recommended.

MACROLIDES: AZITHROMYCIN AND CLARITHROMYCIN

The cornerstone of pulmonary MAC treatment is a macrolide. Treatment success is highest (65.7%) in patients who receive a macrolide as a component of a three-drug regimen for at least 12 months (Diel, 2018). Macrolide resistance is a dreaded complication of MAC treatment. Sputum conversion in macrolide-susceptible patients is 80%, compared to 11-13% in patients with macrolide resistance (Wallace, 2014; Morimoto, 2016; Griffith, 2006). **To prevent resistance, two companion drugs should be used with a macrolide throughout treatment in a three-drug regimen.** Ethambutol and either rifampin or clofazimine are the only regimens shown to be effective in protecting against macrolide resistance.

Studies have not shown any difference between clarithromycin and azithromycin in terms efficacy, culture conversion, or development of macrolide resistance (Pasipanodya, 2017). However, drug-drug interactions are more significant with clarithromycin than azithromycin, particularly with the rifamycins (Daley, 2020). Azithromycin is also available in single daily dosing and may be better tolerated than clarithromycin. While either macrolide is acceptable and may be substituted in cases of intolerance, azithromycin is favoured by consensus guidelines (Daley, 2020). Rifabutin may be substituted for rifampin if significant medication interaction or toxicity is anticipated.

AMIKACIN: PARENTERAL AND INHALED LIPOSOMAL

The role of amikacin in treating pulmonary MAC is to intensify the regimen in cases of extensive, fibrocavitary disease or macrolide resistance. Limited data suggests improved sputum culture conversion in patients who received streptomycin three times weekly for the initial three months of treatment (Kobashi, 2012). The use of amikacin for six months, in combination with surgery, has also been associated with better outcomes in patients with macrolide resistance (Morimoto, 2016; Griffith, 2006).

However, amikacin is parenteral and has significant oto and nephrotoxicity requiring close monitoring. The risk of acute kidney injury increases with age, concomitant nephrotoxic medications and co-morbidities common in elderly patients. Therefore the use of amikacin should be individualized and reserved for patients with a high burden of disease such as extensive bilateral or

cavitary disease, or as salvage therapy for macrolide resistance. To limit toxicity, amikacin should be used for short periods, such as the initial three to six months of treatment or until culture conversion.

Inhaled liposomal amikacin is a salvage medication in MAC and *M. abscessus* treatment. Clinical trials of patients who fail to convert sputum cultures at 6 months with a standard macrolide-based treatment demonstrate three times higher culture conversion rates with inhaled liposomal amikacin compared to placebo, although amikacin resistance occurred in 10% of patients (Olivier, 2017; Griffith, 2018). Therefore inhaled liposomal amikacin may be added to the regimen for patients with amikacin susceptible MAC isolates (MIC ≤ 64 mcg/ml) who have failed standard oral therapy after 6 months.

If possible, an additional companion drug should be added at the same time to prevent amikacin resistance. Inhaled amikacin shares a similar toxicity profile to parenteral amikacin – monitoring for nephrotoxicity, ototoxicity and vestibular toxicity is required. In addition, some patients have bronchospasm related to the mode of therapy. Access to inhaled liposomal amikacin involves SAP and links to the drug company. Currently access is extremely limited in BC due to issues of cost.

CLOFAZIMINE

Clofazimine is an oral antimicrobial originally developed for leprosy and more recently used for drug-resistant TB. For pulmonary MAC disease, it has shown to be equally effective to rifampin when substituted in macrolide-based regimens (Jarand, 2016; Filed, 2003) and safe when used in salvage regimens (Cariello, 2015). Thus, the role for Clofazimine in MAC lung disease is as a substitution drug for rifampin in cases of intolerance, or as a salvage drug.

Special Access for Clofazimine

Physicians should apply for clofazimine independently following the steps below:

1. Test for HIV (patients must be HIV negative for Health Canada (HC) approval).
2. Order clofazimine DST using NRCM requisition (see page 8).
3. If susceptible, request clofazimine prescription (see page 3).
4. Liase with the local pharmacist as needed to fill out HC Special Access Program (SAP) Form; you will need to sign and date the form, and in some clinic locations, fill out the rationale for use section. BCCDC pharmacy is available for support/trouble-shooting.
5. If approved by Health Canada, the clinician must complete relevant forms online so that Novartis will release clofazimine. This step must be done promptly to avoid delays in receiving clofazimine.
6. When clofazimine is received, it will be shipped to referring physician or pharmacy as directed.

M. KANSASII

Treatment of M. kansasii lung disease is highly successful compared with other pulmonary NTM. **Standard first-line therapy is rifampin, ethambutol and *either* isoniazid *or* a macrolide.**

Because isoniazid is associated with fewer side effects and drug interactions than macrolides, we recommend starting with isoniazid and switching to a macrolide if necessary. This recommendation is based on overall good tolerability of INH, lack of drug-drug interactions and QTc potentiation if other QTc agents are used, and anti-microbial stewardship concerns. Treatment should be daily for at least 12 months. Because treatment outcomes are excellent with a fixed duration of 12 months, there is no reason to base length of therapy on culture conversion.

Rifampin is the cornerstone of treatment for pulmonary *M. kansasii* disease. The presence of rifampin in the regimen results in higher sputum culture conversion and lower relapse rates (Ahn, 1981). Although DST for both ethambutol and isoniazid are unreliable, long clinical experience has reinforced the in vivo efficacy of these drugs. More recently, studies have shown equivalent outcomes when clarithromycin is substituted for isoniazid in the regimen. Moxifloxacin also has excellent in vitro activity against *M. kansasii* and is the best substitute drug in cases of rifampin resistance or intolerance to one of the first-line drugs.

M. ABSCESSUS COMPLEX

The M. abscessus complex includes several subspecies –subsp abscessus, massilense and bolletii. *M. abscessus* lung disease is associated with high rates of morbidity and mortality. Treatment is challenging due to limited antibiotic options; most oral drugs show in vitro resistance and the only parenteral options are Tigecycline, Imipenem, Amikacin and Cefoxitin. **Standard first-line therapy should include a minimum of three drugs with demonstrated in vitro activity.**

In patients with macrolide resistance, four drugs should be used, particularly in the first months of treatment when mycobacterial burden and risk of resistance development is highest. Treatment should be daily and for a minimum of 12 months, although longer or periodic treatment courses may be necessary in subgroups of patients. Due to the complexity of treating *M. abscessus* lung disease, particularly in subsp *abscessus* and *bolletii*, patients will require individualized treatment plans.

Similar to MAC, successful treatment of *M. abscessus* pulmonary disease is highly dependent on macrolides. Inducible (*erm*) or mutational (23S RNA) macrolide resistance dramatically reduces sputum culture conversion rates. Multiple studies have shown far better treatment outcomes for patients with *M. abscessus* subsp *massilense,* which carries a non-functional *erm* gene, compared to patients with subsp *abscessus*, supporting the critical importance of macrolide-based therapy (Daley 2020). Therefore, ***M. abscessus* must be identified to the subspecies level and DST for clarithromycin, including inducible resistance determination, should be performed to determine macrolide susceptibility.**

Macrolides also have an immunomodulatory effect, likely through reduced neutrophilic inflammation, and are commonly used in the treatment of chronic lung disease such as COPD, cystic fibrosis and

bronchiectasis. If a macrolide is used for immunomodulatory effect in a patient with macrolide resistant *M. abscessus* disease, it should not be counted as an active drug in the regimen. Sputum monitoring every three months should also be done to rapidly identify the development of a new NTM infection, particularly MAC, to prevent the development of macrolide resistance. If MAC co-infection is identified, the macrolide should be held until the results of DST are available.

Clofazimine has good in vitro activity against *M. abscessus*, and is synergistic with clarithromycin, amikacin and tigecycline (Shen, 2010). In *M. abscessus* lung disease, clofazimine has been shown to be moderately effective at improving sputum conversion rates, especially when used at the initiation of treatment (Yang, 2017). Thus, clofazimine may be a good initial component of a three-four drug macrolide-based regimen. (For M. abscessus treatment options see Table 4) and if possible, treatment should be deferred until DST is available to guide therapy.

Adjunctive Treatment Options

BRONCHIECTASIS CARE

Bronchiectasis is both a precursor and a consequence of NTM infection, and the importance of airway clearance in the treatment of pulmonary NTM disease cannot be overstated. Patients with extensive disease, mucus plugging on CT scan and/or chronic productive cough should engage in an airway clearance technique once or twice daily. These patients should be referred to a respiratory specialist for lung function testing and airway management, as well as a chest physiotherapy program as necessary. These patients also need optimal nutrition, GERD treatment, hemoptysis management, activity levels and vaccinations. The referring respirologist should continue playing a key role in the support of NTM patients on therapy.

BEDAQUILINE

Bedaquiline is an oral antibiotic developed for multi-drug resistant TB (MDR-TB). It has bacteriostatic activity against both MAC and M. abscessus, with an MIC lower for MAC than M. tuberculosis. However, the clinical efficacy of Bedaquiline for pulmonary NTM infection has only been evaluated in a single small study to date (Philley, 2015). Ten patients with refractory MAC or M. abscessus infection were treated with six months of Bedaquiline in addition to an optimised background regimen of ≥ 5 drugs. While 60% of patients had a reduction of mycobacterial burden, no patient achieved culture conversion at six months. At this time, Bedaquiline is only approved in Canada for the treatment of MDR-TB and is not available for NTM infection.

SURGERY

The role of surgical resection in NTM pulmonary disease is unclear. Patients most likely to benefit from surgery are those with unilateral or segmental cavitary disease, drug resistance and/or complications such as severe bronchiectasis or hemoptysis. At the very least a surgical candidate will have failed medical management, but ideally will achieve smear conversion prior to surgery. The decision to pursue surgical resection should be made after careful evaluation of the benefits and risks with the patient, surgeon and respiratory or infectious diseases specialist. Pulmonary NTM patients should be referred for thoracic surgery opinion early into treatment.

NITRIC OXIDE

Nitric oxide (NO) has broad-spectrum antimicrobial activity including against mycobacteria both in vitro and in vivo. It has been used in small trials to successfully reduce the burden of M. abscessus in cystic fibrosis patients and improve lung function in the short term (Yaacoby-Bianu, 2018, Bentur 2020), although its impact on culture conversion in unknown.

- NO treatment is challenging, requiring hospitalization, dosing schedules of up to five times daily, and monitoring for safety.
- NO should be reserved for patients with refractory M. abscessus infection as adjunctive therapy.
- Currently, there is no local NO trial actively recruiting.

TABLE 4. RECOMMENDED TREATMENT REGIMENS FOR PULMONARY NTM *

Pathogen	Drugs	Preferred Regimen	Daily Dose	
MAC				
Nodular-bronchiectatic	**3**	Azithromycin	250-500mg	500 mg
		Clarithromycin	500 mg twice daily	
		Rifampin	450-600 mg (10 mg/kg)	600 mg
		Rifabutin	150-300 mg (150 mg with Clarithomycin)	300 mg
		Ethambutol	15 mg/kg	25 mg/kg
Cavitary	**≥ 3**	Azithromycin	250-500mg	500 mg
		Clarithromycin	500 mg twice daily	
		Rifampin	450-600 mg (10 mg/kg)	600 mg
		Rifabutin	150-300 mg (150 mg with Clarithomycin)	300 mg
		Ethambutol	15 mg/kg	25 mg/kg
		Amikacin IV	10-15 mg/kg	15-25 mg/kg
Alternative/Salvage		Amikacin inhaled liposomal	590 mg	
		Clofazimine	100 mg	
M. kansasii				
Option 1	**3**	Rifampin (Rifabutin)	450-600 mg (10 mg/kg)	
		Ethambutol	15 mg/kg	
		Isoniazid	300 mg	
Option 2		Rifampin (Rifabutin)	450-600 mg (10 mg/kg)	
		Ethambutol	15 mg/kg	
		Azithromycin	250-500 mg	

* Adapted from Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ECMID/IDSA Clinical Practice Guideline (2020).

TABLE 4. RECOMMENDED TREATMENT REGIMENS FOR PULMONARY NTM CONT.

Pathogen	Drugs	Preferred Regimen	Daily Dose	3 times per week
M. abscessus				
Macrolide susceptible	**≥ 3**	Azithromycin (Clarithromycin)	250-500mg	
		AND **Choose 2-3:**		
		Amikacin IV	10-15 mg/kg	15-25 mg/kg
		Cefoxitin	2-4 g BID-TID (max 12 g/day)	
		Imipenem	500-1000 mg BID-TID	
		Tigecycline	25-50 mg QD-BID	
		Clofazimine	100 mg	
		Linezolid	600 mg QD-BID	
Macrolide resistant	**≥ 4**	**Choose 4-6:**		
		Amikacin IV	10-15 mg/kg	15-25 mg/kg
		Cefoxitin	2-4 g BID-TID (max 12 g/day)	
		Imipenem	500-1000 mg BID-TID	
		Tigecycline	25-50 mg QD-BID	
		Clofazimine	100 mg	
		Linezolid	600 mg QD-BID	
		Amikacin inhaled liposomal	590 mg	
		Azithromycin (Clarithromycin) #	250-500mg	

Macrolide should not be considered an active drug, but can be used or maintained for its immunomodulatory effect.

Monitoring During Treatment

The same criteria used for diagnosis (clinical, radiographic and microbiologic) should be used to gauge response to treatment. After initiation of treatment, patients should be seen monthly to assess both clinical response and medication tolerance.

Patients should have sputum collected spontaneously or through induction every one to two months until culture conversion. Thereafter, stable patients who are tolerating medication can be evaluated every two to three months for the duration of therapy. Bronchoscopy is not necessary to document culture conversion in patients who cannot produce sputum and have otherwise improved.

Radiographic changes can occur slowly if ever. It is not unusual to see CT images with evidence for improvement, deterioration and stability all on the same scan. In patients who are clinically improving there is no need to repeat chest imaging more frequently than every six to twelve months. However repeat imaging is warranted in patients with clinical progression and/or failure to convert sputum culture if a treatment change is planned. Repeat imaging may also be considered at the discontinuation of therapy to determine a new baseline.

Adverse events are very common during the treatment of NTM infections. Medication regimens should be chosen after reviewing the "Best Possible Medication History" to limit the risk of significant medication interactions. (See Table 5 for the most significant medication side effects and recommendations for monitoring).

PROLONGED QTC

Three medications used in the treatment of pulmonary NTM are associated with prolongation of the QTc interval: Azithromycin, Moxifloxacin and Clofazamine. Before starting treatment, a careful review of the patient's medication list is critical to identify other medications that prolong the QTc and determine their necessity. A baseline ECG should be performed.

If the baseline is abnormal (> 450 ms in males, > 470 ms in females) the ECG should be repeated within two weeks of starting Azithromycin, Moxifloxacin or Clofazimine. If the difference between baseline and follow-up QTc is < 60 ms, and the patient is on only one QTc prolonging antibiotic, no further ECG monitoring is required. If the patient is taking two or more QTc prolonging medications, ECG should be monitored monthly. If the difference between baseline and follow-up QTc is > 60 ms, or QTc is > 500 ms, Cardiology consultation is recommended to review the ECG and advise on continuing therapy.

AMIKACIN TOXICITY

Amikacin has concentration dependent bactericidal activity against mycobacteria and is an important component of treatment of *M. abscessus* and cavitary MAC infections. However clinicians are often reluctant to use this drug due to toxicity. Rates of ototoxicity in long-term mycobacterial treatment in highly controlled settings are as high as 37%, with risk increasing with age and cumulative dose

(Peloquin, 2004), and particularly after six months of therapy (Modongo, 2014). Vestibular toxicity occurs in 9% and reversible nephrotoxicity in 15% (Peloquin, 2004). There is no difference in rates of toxicity with dose, dosing frequency or serum trough levels (Peloquin, Modongo). The most important interventions to reduce toxicity include maintaining adequate hydration, replacing calcium, magnesium and potassium as needed, and ensuring appropriate weight-based dosing for renal function. Parenteral Amikacin should be reserved for the initial three to six months of therapy or until culture conversion is achieved. Inhaled liposomal Amikacin, which has lower rates of toxicity, can be continued if necessary for the duration of treatment.

DRUG-DRUG INTERACTIONS

Of all the drugs used to treat pulmonary NTM, Rifampin is the most likely to cause drug-drug interactions due to its potent induction of the hepatic cytochrome P-450 (CYP) enzyme system and the P-glycoprotein (P-gp) transport system. Some of the most common interactions include warfarin, oral contraceptives, cyclosporine, glucocorticoids, and opioids. A thorough review of the patient's medication list is essential before starting NTM therapy to identify and plan for interactions. Rifabutin is a less potent P450 inhibitor and can be used in place of Rifampin to minimize drug interactions during pulmonary NTM therapy.

THERAPEUTIC DRUG MONITORING

Therapeutic Drug Monitoring (TDM) is recommended in situations where drug-drug interactions or malabsorption may be causing sub-therapeutic drugs levels. Patients who fail to have clinical improvement or culture conversion despite good adherence and drug susceptible isolates should have TDM performed. There is no indication for collecting routine drug levels for all patients during the treatment of pulmonary NTM disease.

TDM (two hour and six hour) is available for Azithromycin, Clarithromycin, Ciprofloxacin, Moxifloxacin, Clofazimine, Linezolid, Rifabutin, Rifampin and Ethambutol. Repeat levels are discouraged especially if there was no intervention with initial results.

TABLE 5. SIGNIFICANT ADVERSE EVENTS AND MONITORING RECOMMENDATIONS

Drug	Most Common Reaction	Monitoring	Action
Azithromycin Clarithromycin	Gastrointestinal	Clinical	Anti-emetics Change to Azithromycin If MAC, reduce dose/frequency
	Prolonged QTc	ECG baseline, 2 weeks after starting treatment, and then every 2-4 weeks if ≥ 2 drugs that prolong the QTc and/or the QTc increase is > 60 ms.	Stop if QTc > 500 ms
	Ototoxicity	Consider audiogram at baseline and monthly	Stop if change in audiogram
Rifampin Rifabutin	Pruritis/Rash	Clinical	Anti-histamines, topical lotion Stop only if severe or evidence of IgE mediated reaction
	Hepatotoxicity	AST and T. Bili at baseline, 2 weeks and monthly	Stop if AST or T. Bili 3x ULN, restart when levels normal
	Cytopenias	CBC at baseline, 2 weeks and monthly	Stop if severe, attempt to restart when levels normal
	Body Fluid Discoloration	Clinical	Inform patient prior to start
	Uveitis (Rifabutin)	Visual acuity testing monthly	If documented change in VA stop drug and refer to ophthalmology
Ethambutol	Ocular Toxicity	Visual acuity and color discrimination testing at baseline and monthly; referral to ophthalmology	If documented change on eye exam stop drug and refer to ophthalmology
Amikacin IV	Nephrotoxicity	Cr/GFR at baseline, 2 weeks and monthly	Maintain hydration Replace electrolyte depletion Stop if 50% increase Cr from baseline
	Ototoxicity	Audiogram at baseline and monthly; ask about vestibular concerns (e.g. balance)	Maintain hydration Replace electrolyte depletion Stop if change in audiogram
Amikacin, Inhaled Liposomal	Cough/Dyspnea Dysphonia	Clinical	Stop if severe
	Nephrotoxicity	Cr/GFR at baseline, 2 weeks and monthly	Maintain hydration Replace electrolyte depletion Stop if 50% increase Cr from baseline
	Ototoxicity	Audiogram at baseline and monthly; ask about vestibular concerns (e.g. balance)	Maintain hydration Replace electrolyte depletion Stop if change in audiogram

TABLE 5. SIGNIFICANT ADVERSE EVENTS AND MONITORING RECOMMENDATIONS CONT.

Drug	Most Common Reaction	Monitoring	Action
Clofazimine	Skin discoloration and dryness	Clinical	Inform patient prior to start
	Hepatotoxicity	AST and T. Bili at baseline, 2 weeks and monthly	Stop if AST or T. Bili 3x ULN, restart when levels normal
	Prolonged QTc	ECG baseline, 2 weeks after starting treatment, and then every 2-4 weeks if ≥ 2 drugs that prolong the QTc and/or the QTc increase is > 60 ms.	Stop if QTc > 500 ms
Linezolid	Cytopenias	CBC at baseline, 2 weeks and monthly	Stop if severe, restart at 300 - 600 mg QD or 600 mg QOD
	Peripheral Neuropathy	Clinical	Stop if severe
	Optic neuritis	Visual acuity and color discrimination testing at baseline and monthly	If documented change on eye exam stop drug and refer to ophthalmology
Moxifloxacin	Prolonged QTc	ECG baseline, 2 weeks after starting treatment, and then every 2-4 weeks if ≥ 2 drugs that prolong the QTc and/or the QTc increase is > 60 ms.	Stop if QTc > 500 ms
	Tendinopathy	Clinical	Stop if suspected
	CNS (dizziness, delirium, tremor)	Clinical	Stop if suspected
	C. difficile Infection	Clinical	Send stool for *C. difficile* testing
	Hepatotoxicity	AST and T. Bili at baseline, 2 weeks and monthly	Stop if AST or T. Bili 3x ULN, restart when levels normal
Cefoxitin	Cytopenias	CBC at baseline, 2 weeks and monthly	Stop if severe, attempt to restart when levels normal
	Nephrotoxicity	Cr/GFR at baseline, 2 weeks and monthly	Maintain hydration Stop if 50% increase Cr from baseline
Imipenem	Cytopenias	CBC at baseline, 2 weeks and monthly	Stop if severe, attempt to restart when levels normal
	Nephrotoxicity	Cr/GFR at baseline, 2 weeks and monthly	Maintain hydration Stop if 50% increase Cr from baseline
Tigecycline	Gastrointestinal	Clinical	Anti-emetics
	Hepatotoxicity	AST and T. Bili at baseline, 2 weeks and monthly	Stop if AST or T. Bili 3x ULN, restart when levels normal

End of Treatment

The decision to end treatment is an individualized one. Patients who have had symptom resolution, radiographic improvement or stability, and have achieved culture conversion are candidates to stop treatment after a minimum of 12 months. For MAC and *M. abscessus*, patients should be treated for a minimum of 12 months after culture conversion. Almost half (48%) of patients with nodular bronchiectatic MAC will have recurrence after treatment, primarily as re-infection (Wallace, 2014), and patients should be informed about this possibility.

Some patients may not achieve culture conversion and this is common in cases of extensive disease, macrolide resistance and *M. abscessus* infection. In such cases the likelihood of cure is low and goals of care are to reduce or limit further worsening of symptoms and slow disease progression in order to maximize quality of life. The risks and benefits of continuing or intensifying therapy should be discussed with patients, their families and primary care providers. Some patients may choose to stop therapy in order to reassess symptoms and quality of life off therapy (e.g. drug holiday).

In many instances, NTM management is complicated with suboptimal treatment response. In the event of treatment non-response or the need for non-standard regimen, a second opinion may be warranted. Complex Patient Referrals can be made to the National Jewish Health Advanced Diagnostic Laboratories in Denver, CO.

Suggested Readings

Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline (2020).

Pharmacotherapy Approaches in Nontuberculous Mycobacteria Infections, Mayo Clinic Proceedings (2019).

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