The Lung Health Foundation's

Ontario Thoracic Reviews

Ontario Thoracic Society | Autumn 2020 Volume 32 Issue 2

EDITORIAL

Herculean but not Sisyphean: Challenges in Nontuberculous Mycobacterial Disease

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In this issue of the Ontario Thoracic Review (OTR), Brode presents an excellent summary of contemporary guidelines for the treatment of *Mycobacterium avium* complex pulmonary disease (MAC-PD). The implementation and uptake of the new guidelines into clinical practice remains to be seen. Historical adherence to nontuberculous mycobacterial (NTM) guidelines has been poor,(1-3) possibly due to the tremendous challenges in treating this group of infections, including managing co-existing lung disease, uncertainties regarding treatment initiation, antimicrobial drug intolerance, prolonged treatment duration, inadequate response to therapy and high recurrence rates. Despite the daunting challenges, thoughtful clinical care leads to important improvements in patients' lives. The excellent review stresses some of the most important aspects of managing MAC-PD, and in the current editorial, additional reflections are provided regarding surveillance for treatment decisions, antimicrobial drug selection and treatment failure.

Although some patients obviously require the initiation of therapy at the first clinical encounter with a specialist, deciding to initiate therapy in MAC-PD is usually made after some period of follow-up. The suggested frequency of follow-up reviewed by Brode rightly focuses on detecting NTM progression, but most patients with MAC-PD also have bronchiectasis and often have COPD. The complexity of managing these patients' lung disease includes selecting appropriate treatments for pulmonary exacerbations. Recognizing which pathogens may be present and prescribing appropriate antimicrobial therapies is aided through the periodic collection of sputum for comprehensive microbiological testing and considering the presence and role of other chronic pathogens like Aspergillus and Pseudomonas species. Systemic corticosteroids should generally be reserved for the treatment of exacerbations of COPD, asthma or other non-infectious inflammatory conditions, although the distinction may be extremely difficult. Ensuring avoidance of macrolide monotherapy (in the absence of ethambutol) during exacerbations is important to reduce the risk of macrolide resistance, and requires education of both patients and other care providers.(4) Inhaled corticosteroids should also be

judiciously minimized to reduce the potential risks of superimposed infections and MAC progression.(5) In most patients with MAC-PD, these issues translate into the need for more frequent follow-up than that needed to detect the progression of MAC-PD.

Regarding the selection of a treatment regimen, it is difficult to overstate the importance of including ethambutol in a macrolide-based regimen for MAC-PD. Ethambutol is the most important drug in preventing the development of macrolide resistance, which heralds a transition from an often curable infection to one that is usually incurable and not infrequently fatal despite more complex and toxic regimens.(4, 6) It goes without saying that knowing whether a MAC isolate is macrolide susceptible is critical for treatment decisions. As described by Brode in her review, the latest guidelines again stress the importance of macrolide drug susceptibility testing (DST) and add to this that the clinical relevance of amikacin DST has been established. It is instructive to consider the DST utilization for MAC-PD in Ontario from 2010-2015. In our province, where DST is performed upon clinicians' requests, only 6.3% of incident MAC-PD cases had DST performed, despite the fact that 24% were treated.(7) Furthermore, macrolide resistance was identified in a surprisingly high proportion - 8% of MAC isolates.(7) These observations demonstrate that DST was underutilized, and that clinicians reserved DST for more challenging situations. Clinicians should obtain DST for all patients who require treatment for MAC-PD and consider repeating DST in treatment-refractory situations. Evidence-based recommendations for MAC DST can only be made for the macrolide and amikacin MICs. Temptations to exclude other standard recommended drugs based on a perception of high MICs must be avoided.

Unfortunately, persistently or recurrently culture positive sputum is often encountered. Brode reminds us of the microbiologically-based consensus definition of treatment failure, and provides appropriate therapeutic considerations. Additional consideration should be given to our limitations in defining outcomes in MAC-PD. NTM disease is defined by symptoms, imaging and microbiology, while outcomes are usually described only microbiologically. This may be reasonable since numerous factors could affect symptoms or imaging abnormalities. However, exclusive reliance on microbiology may be misleading and is an imperfect correlate of clinical status. Microbiological treatment success is sub-optimal - 52-60% in systematic reviews,(8, 9) and 71-86% for mild disease treated in expert settings.(10, 11) Microbiological recurrence after treatment completion is very common - 30% at 14 months(12) and 48% at 4 years.(11) In patients with nodular bronchiectatic MAC-PD, recurrence is usually reinfection with a new strain.(11, 13) Even during uninterrupted treatment, sputum reversion from negative to positive and the persistence of positive sputum (both generally considered indicative of treatment failure) are largely due to new strains, presumably reflecting ongoing acquisition of NTM from the environment.(11, 13) Given the absence of genotyping in routine clinical practice, a high frequency of new strain acquisition confounds the ability to determine whether treatment is effective at clearing the causative strain, giving a perception of treatment failure or recurrence. In addition to the useful advice provided in Brode's excellent review, treatment failure or recurrence should prompt careful consideration of symptoms and chest imaging with antimicrobial therapy. If these factors suggest disease control, then it could be that apparently refractory disease is explained by ongoing exposure with continuous "reinfection" or "re-colonization" (with or without original strain eradication) or that the burden of organism has been reduced to a clinically meaningful extent. In the absence of strain typing, possible exposures should be considered. If NTM disease is to be controlled long-term, patients should completely avoid hot tubs and probably indoor swimming pools, and consider other measures as outlined in the review and other sources(14). Given the near-ubiquitous presence of *M. avium* in engineered water systems, complete avoidance is not feasible and likely impossible, so attempting to

mitigate highest risk exposures is probably most appropriate. Unfortunately, data are minimal in this area. Additionally, airway clearance measures, as described in the review, are critical when addressing treatment failure.

Treating MAC-PD is often daunting but never impossible. Clinicians should take advice from guidelines, employ antimicrobial and ancillary treatment measures, and use all available clinical evidence in making therapeutic decisions.

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FEATURE

Treatment of Mycobacterium avium complex (MAC) Pulmonary Disease: Incorporating the New Guidelines into Clinical Practice

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Introduction

Mycobacterium avium complex (including *M. avium*, *M. intracellulare* and *M. chimera*) pulmonary disease (MAC-PD) is by far the most common type of nontuberculous mycobacteria (NTM) infection in humans. MAC-PD is increasing in prevalence (1), and is associated with significant morbidity (2) and mortality (2, 3). Clinically, patients present with chronic respiratory and/or constitutional symptoms, and radiologic abnormalities typically falling within two broad categories; fibro-cavitary disease, usually in current/former smokers and presenting as upper lobe cavities that resemble tuberculosis; and nodular-bronchiectasis, presenting more often in non-smoking women without prior lung disease.

The 2007 American Thoracic Society(ATS)/Infectious Diseases Society of America (IDSA) treatment guidelines provide recommendations for the diagnosis of NTM-PD, based upon clinical, radiographic, and microbiologic criteria (Table 1) (4).

Table 1. Diagnostic criteria for NTM-PD: All must be met

Clinical criteria	Radiographic criteria	Microbiologic criteria
Compatible symptoms (ie. cough, sputum, hemoptysis, dyspnea, chest pain, fever, night sweats, weight loss, and/or fatigue) AND appropriate exclusion of other diagnoses	Nodular or cavitary opacities on chest radiography OR computed tomography scan showing multifocal bronchiectasis with multiple small nodules	At least 2 sputa culture positive for the same NTM species OR 1 bronchoscopy culture positive OR 1 lung biopsy with mycobacterial histopathologic features and 1 positive culture (from lung biopsy or sputum or bronchoscopy)

Adapted from Griffith *et al*.(4)

These diagnostic criteria are useful in practice to assist the clinician in distinguishing colonization from infection, and have been adopted in research settings. They have also been endorsed by the British Thoracic Society (BTS) treatment guidelines (5), and the new ATS/ERS/ESCMID/IDSA guidelines(6) (abbreviated in this document as the ATS guidelines).

While occasionally the diagnosis of MAC-PD can pose a challenge to clinicians, much more often the challenge lies in the management of MAC-PD; deciding when to treat, how to treat, and how to address treatment failure and intolerance. This review will focus on the treatment of MAC-PD, incorporating recent recommendations from the new ATS and BTS treatment guidelines.

Initial patient evaluation

The decision to treat involves a risk benefit analysis that is best made jointly by provider and patient. Multiple factors must be considered, including the presence of symptoms and their impact on the patient's quality of life, microbiologic results (greater number of positive sputum cultures and positive acid fast bacilli [AFB] smears indicate greater disease burden and increased likelihood of progression (7)), radiologic findings (presence of cavities, extensive disease, and progression on serial imaging favor treatment), presence and severity of underlying lung disease, patient comorbidities, immune function and ability to tolerate therapy, and the overall goal of treatment. With respect to radiologic findings, fibro-cavitary disease is a risk factor for disease progression (7), and greater all-cause (7, 8) and MAC-specific mortality (9), and therefore this form of disease should almost always be treated. The new ATS guidelines provide a conditional recommendation for initiation of treatment rather than watchful waiting in patients who meet diagnostic criteria for NTM-PD, especially in patients with AFB smear positive and/or cavitary disease, but also note that this decision should be individualized (6).

Patients who are not initially treated should be followed longitudinally, as treatment may be needed in the future. The natural history of MAC-PD is variable, likely due to both patient and microbial factors. The proportion of MAC-PD patients receiving antibiotic treatment has varied in studies from 24% in a population-based study of Ontario seniors (10), to 63% within 3 years of diagnosis in a South Korean specialty clinic-based study (7). In the latter study, among patients who had stable disease and were not treated for at least 3 years, 19% were later started on treatment, while 52% had spontaneous sputum culture conversion (7). There are no guidelines on how these patients should be followed. Some experts recommend symptom assessments, sputum microbiologic testing, and lung imaging every 3-6 months for the initial 2 years, and if treatment is not started in that timeframe, then at least yearly thereafter (11). Serial pulmonary function testing may also be useful.

When treatment is being considered, drug susceptibility testing should be performed for macrolides and amikacin, with treatment guided by the results (5, 6). The Clinical and Laboratory Standards Institute (CLSI) provides breakpoint concentrations to interpret minimum inhibitory concentrations (MICs) as susceptible or resistant for both of these drugs (12, 13). Regarding macrolides, the presence of macrolide resistance (clarithromycin MIC ≥32 mcg/ml) predicts worse clinical outcomes, including treatment failure, need for treatment augmentation, and mortality (14-16). Regarding amikacin, the CLSI has recommended distinct breakpoints defining resistance for intravenous (MIC ≥64 mcg/ml) and inhaled liposomal (MIC ≥128 mcg/ml) preparations. One retrospective study of 462 consecutive clinical MAC isolates demonstrated that only 7 isolates (1.5%) repeatedly had an MIC >64 mcg/ml, and these were associated with mutations in the 16S rRNA gene, extensive prior exposure to aminoglycosides, and treatment failure (17). Additionally, a randomized trial of amikacin liposome inhalation suspension (ALIS) showed that culture conversion was not achieved in patients with isolates with an MIC >64 mcg/ml who received ALIS (whereas 32% of all patients receiving ALIS achieved culture conversion), and these isolates were more often associated with amikacin resistance mutations (18). In addition to being performed prior to treatment initiation, drug susceptibility testing for macrolides and amikacin is also recommended for patients with treatment failure and recurrence (5). Importantly, many clinical laboratories routinely perform drug susceptibility testing for other antibiotics on MAC isolates, however, outside of macrolides and amikacin, there is no evidence correlating *in vitro* drug activity with treatment outcomes, and therefore it is not clear how these results should be interpreted.

Pharmacologic treatment options

For most patients with MAC-PD, the recommended first line therapy still consists of the three-drug combination of a macrolide, ethambutol, and rifampin, supported by both the ATS and BTS guidelines (5, 6) (Table 2).

Table 2. Suggested treatment regimens for MAC-PD

Disease category	Antibiotic regimen
Nodular-bronchiectatic	Azithromycin 500 mg thrice weekly and Ethambutol 25 mg/kg thrice weekly and Rifampin 600 mg thrice weekly
Fibro-cavitary	Azithromycin 250-500 mg daily and Ethambutol 15 mg/kg daily and Rifampin 10 mg/kg (450 or 600 mg) daily and Amikacin 8-15 mg/kg IV thrice weekly for first ≥2 months*
Refractory	Azithromycin 250-500 mg daily and Ethambutol 15 mg/kg daily and Rifampin 10 mg/kg (450 or 600 mg) daily and ALIS 590 mg inhaled daily or amikacin 250-500 mg inhaled daily or thrice weekly† or amikacin 8-15 mg/kg IV thrice weekly*

Adapted from Daley et al.(6)

**Our centre generally prefers parenteral amikacin over streptomycin to avoid painful injections, and because it is easier to perform drug level monitoring. Dosing of IV amikacin in MAC-PD is controversial. The ATS guidelines recommend higher doses (10-15 mg/kg daily or 15-25 mg/kg thrice weekly) than shown in this table, however the ATS recommended dosing is known to cause permanent ototoxicity in approximately one third of patients after 15 weeks (58). We use doses at the lower end of the range shown here, adjusted according to drug level monitoring; targeting a peak serum level of 20-25 mg/L (59).*

† The largest case series suggested that 500 mg thrice weekly of nebulized parenteral amikacin may be the best dose to optimize efficacy and limit toxicity (43)

In the absence of macrolide resistance, the macrolide remains the cornerstone of treatment for MAC-PD, based mainly on observational study data. Only two randomized controlled trials have compared regimens with and without a macrolide, but neither had conclusive results (19, 20). However, a meta-analysis of 21 studies including 2534 patients showed that the pooled sustained sputum culture conversion incidence ratio (IR) was numerically higher in patients receiving a macrolide-containing regimen (IR 0.54, 95% CI 0.45-0.63) than those receiving a macrolide-free regimen (IR 0.38, 95% CI 0.25-0.52), and that this difference was significant when only good quality studies were examined (21).

Additionally, the value of the macrolide can be inferred from the fact that patients with macrolide-resistant disease have poorer treatment outcomes (14, 15). Regarding the choice of macrolide, the same meta-analysis showed no significant difference with respect to sputum culture conversion comparing azithromycin- and clarithromycin- based regimens (21). However, the ATS guidelines recommend azithromycin over clarithromycin because of the increased potential for drug interactions with clarithromycin (particularly important with respect to rifamycins), the perception that azithromycin is better tolerated, and the need for once rather than twice daily dosing (6).

In terms of companion drugs, both ethambutol and rifampin are recommended by BTS guidelines (5), and 'preferred' by ATS guidelines, although the ATS guidelines provide more emphasis on the use of at least 3 drugs, including macrolide and ethambutol (6). Ethambutol is a key drug for preventing the development of macrolide resistance (14, 15). The role of rifampin, or an alternative third drug, is less clear, but much of the outcome data that has accumulated over the past two decades has studied this three-drug combination (21). It is possible that rifampin adds to ethambutol's activity in the prevention of macrolide resistance, as was suggested in one trial of disseminated MAC infection (22). However, one open label randomized trial of 119 patients in Japan compared treatment with 12 months of a two-drug regimen (clarithromycin-ethambutol) to the standard three-drug regimen (clarithromycin-ethambutol-rifampin) and found that the two-drug regimen was non-inferior in intention to treat analysis; sputum culture conversion 55% versus 41%, respectively (difference: 14% [95%CI: -32 to 3%]) (23). Limitations of this study include the large number of patients who did not complete treatment, lower than standard doses of drugs used, and the small number of isolates from non-converters that were tested for macrolide resistance. Given these limitations, this regimen is not currently guidelines-recommended (6), however a multi-centre randomized trial of this comparison is ongoing.

Regarding the medication administration schedule, there have been two large case series that have evaluated outcomes associated with thrice weekly and daily macrolide-ethambutol-rifamycin regimens. The first study from Texas included 180 patients with nodular bronchiectatic MAC-PD who were treated for at least 12 months; the choice of administration schedule was at the discretion of the treating physician (24). They found similar rates of sputum culture conversion; 85% of patients on thrice weekly therapy throughout, and 88% on daily therapy. Additionally, significantly fewer patients receiving thrice weekly therapy required regimen modification than those receiving daily (71% versus 3% of treatment episodes; $p<0.001$). The second study from Korea evaluated 217 patients with nodular bronchiectatic MAC; 118 initiated thrice weekly therapy and 99 initiated daily therapy (25). There was no significant difference in symptomatic, radiologic, or microbiologic response to treatment between the two groups (sputum culture conversion rate 67% in thrice weekly group versus 76% in daily group, $p=0.154$). However, modification of therapy was less common in the thrice weekly group (21 versus 46%, $p<0.001$). Similarly, a meta-analysis of macrolide-containing regimens for MAC-PD showed that 19% (95% CI 13-25%) on daily therapy defaulted, compared to 12% (95% CI 9-15%) on thrice weekly therapy (26). Importantly, the two case series included only patients with nodular bronchiectatic disease. Prior work has shown that patients with cavitary disease have poorer outcomes with intermittent therapy; one prospective series of 91 patients treated with thrice weekly therapy for 1 year showed that patients with cavitary disease had a lower rate of culture conversion (4 vs 24%), culture improvement (sustained reduction in colony count; 20 vs 71%,) and CT improvement (46 vs 77%) than patients with non-cavitary disease, with a hazard ratio for culture improvement for noncavitary disease (vs cavitary) of 4.00 (95% CI 1.74-9.19) (27). Based on these data, the new ATS guidelines recommend that

treatment be given daily in patients with fibro-cavitary disease, and thrice weekly in patients with nodular-bronchiectatic disease (6). The BTS guidelines are slightly different, in that they recommend daily therapy in patients with *severe* disease (AFB smear positive, radiological evidence of cavitary/severe infection, or severe symptoms), and thrice weekly therapy in non-severe disease (5).

Patients with severe disease may also benefit from the addition of an aminoglycoside to their therapy in the first several months. One randomized trial from Japan studied the addition of streptomycin (15 mg/kg intramuscularly thrice weekly) versus placebo for the initial 3 months to clarithromycin-ethambutol-rifampin given for at least 24 months, and found that patients in the streptomycin arm were significantly more likely to achieve sputum culture conversion (71% versus 51%, $p<0.05$), although there was no difference in recurrence rates or clinical response (28). Additionally, two retrospective case series have shown that patients with macrolide-resistant MAC who receive aminoglycosides (amikacin, kanamycin, or streptomycin) have better treatment outcomes than those that do not (14, 15). The ATS guidelines suggest that parenteral amikacin or streptomycin, typically given for at least 2 months, be included in the initial treatment regimen for patients with fibro-cavitary or advanced/severe macrolide susceptible MAC-PD (6), and the BTS guidelines recommend that up to 3 months of parenteral amikacin be *considered* in patients with severe MAC-PD (5). The two guidelines disagree with respect to the role of inhaled amikacin in this setting; the ATS suggests that neither inhaled parenteral amikacin or amikacin liposome inhalational suspension (ALIS) be used as part of the initial treatment regimen, because of lack of data (6), however the BTS recommends that nebulized amikacin may be considered in place of parenteral when "IV/IM administration is impractical, contraindicated, or longer term treatment with an aminoglycoside is required" (5).

The current guidelines-recommended duration of therapy for MAC-PD is still 12 months after sputum culture conversion (5, 6), although data supporting this recommendation are limited (16). Some studies have shown better treatment outcomes in patients treated for at least 12 months, compared to < 12 months (24, 29).

Nonpharmacologic treatment options

It is believed that susceptible individuals contract MAC-PD (and other forms of NTM-PD) through environmental exposure to aerosolized water or soil. It therefore seems logical that attempts to reduce environmental exposure to MAC should improve the likelihood of eradication and reduce the risk of recurrence, and for this reason, avoidance measures are sometimes recommended by experts (30). However, there is currently no evidence that supports specific exposure avoidance measures, and the most recent ATS/BTS guidelines do not address this issue. Some experts recommend minimizing exposure to hot tubs, humidifiers, and indoor swimming pools, avoiding water dispenser systems that could promote growth of NTM and lead to NTM-PD through aspiration (such as carbon filter pitchers and ice/water dispensers), and avoiding working with dry soil (30). Changing or cleaning shower heads at regular intervals, use of in-line antimicrobial filters in showers or water taps, and increasing the temperature of the hot water tank to ≥54.4◦C (31) might also be helpful. NTM Info & Research Inc. (32) provides avoidance recommendations, and may be a useful resource for patients.

Patients with MAC-PD often have concomitant bronchiectasis, chronic obstructive pulmonary disease, and/or asthma, and treatment recommendations for these conditions should also be followed. Of particular note are airway clearance techniques, which are recommended in treatment guidelines for all

patients with bronchiectasis (33), and which have been shown in one small case series to improve symptoms and lung function in patients with NTM-PD who were not receiving antibiotics (34).

Treatment failure

The definition of treatment failure in NTM-PD is "The re-emergence of multiple positive cultures or persistence of positive cultures with the causative species from respiratory samples after ⩾12 months of antimycobacterial treatment, while the patient is still on treatment" (35). However, recent data suggests that failure to convert at 6 months of treatment is a reliable predictor of treatment failure at 12 months (36, 37), so an approach should be considered in patients with refractory disease after 6 months of treatment. When this occurs, one of the first items that should be explored is the possibility of treatment non-adherence, although there is no data specific to MAC-PD elucidating how often this occurs. The possibility of emergent macrolide resistance should also be considered, with drug susceptibility testing requested (6). In the absence of these two possibilities, there are several therapeutic options to consider.

The most evidence supported approach, in patients with amikacin-susceptible MAC-PD, is the addition of amikacin liposome inhalation suspension (ALIS). There have been two randomized trials evaluating the addition of ALIS in refractory MAC-PD. The first, a phase II double blind placebo controlled study, randomized patients with either refractory MAC or *M. abscessus*-PD, despite at least 6 months of guidelines-based therapy (GBT), to either ALIS 590 mg inhaled once daily for 84 days, or placebo (18). In the modified intention-to-treat analysis, including 44 patients on ALIS and 45 on placebo, the primary endpoint of change from baseline to day 84 in semiquantitative sputum culture results was not achieved (p=0.072). However, a greater proportion of patients in the ALIS group achieved sputum culture conversion by day 84 (32% versus 9% in placebo group, p=0.006), with the treatment effect seen mainly in patients with MAC-PD. The second trial, a phase III study, randomized patients with amikacin-susceptible refractory MAC-PD despite 6 months of GBT to ALIS+GBT or GBT alone (38). More patients in the ALIS+GBT group achieved sputum culture conversion by month 6 (the primary endpoint) than patients receiving GBT alone (29% vs. 9%; odds ratio 4.22, 95% CI 2.8-8.57, p=0.001). Respiratory adverse events, including dysphonia, cough, and dyspnea, were more common in the ALIS+GBT group (87% vs 50%), however, the rate of serious adverse events was comparable in each arm (20% vs 18%). Unfortunately, ALIS is not currently licenced in Canada, and can only be obtained through Compassionate Use from the manufacturer combined with Health Canada Special Access Program approval. Until ALIS has licensure in Canada, another consideration is the use of parenteral amikacin by inhalation. Five small case series, including a total of 55 patients with MAC-PD, found that 18-67% of patients with refractory disease achieved sputum culture conversion after the addition of inhaled amikacin to their oral antibiotic regimen (39-43). Amikacin was given daily, twice daily, or intermittently, at doses ranging from 250-1000 mg daily. Side effects were seen in 8-38%, and included ototoxicty, nephrotoxicity, hemoptysis, dysphonia, throat irritation, bitter taste, and thrush. The ATS guidelines suggest that inhaled parenteral amikacin is a reasonable alternative to ALIS for refractory MAC-PD in areas where ALIS is not yet available (6). Parenteral amikacin for nebulization is not covered by the Ontario Drug Benefits program, but coverage can be obtained through an Exceptional Access Program request, or through many private insurers. The addition of parenteral (IV) amikacin for treatment failure is another option that is commonly pursued in practice and is anecdotally sometimes successful, but it has not been formally evaluated.

Other medical options for intensifying therapy in the face of treatment failure, supported by less evidence than ALIS, are several. If the patient is on intermittent therapy, a switch to daily therapy may be helpful, with one small case series showing that 30% of patients who failed to convert after 12 months of intermittent therapy did so after switching to daily (44). Another consideration is the addition of moxifloxacin, with a small series demonstrating that 30% of patients who failed to convert after 6 months of treatment did so after the addition of moxifloxacin (45). The addition of clofazimine may also be considered, with one series finding that 42% of patients, the majority of whom had refractory disease, achieved sputum culture conversion with its addition (46). Clofazimine is not licenced in Canada, but it can be obtained through the Health Canada Special Access Program.

Adjuvant surgical resection should also be considered for select patients with refractory disease (6). Despite limited evidence to guide patient selection, the BTS guidelines suggest consideration of surgical resection in patients with refractory NTM-PD despite 6-12 months of appropriate therapy or those who have recurrence after treatment completion, who have localized areas of severe disease, and who have sufficient physiological reserve to tolerate the resection (5). The ATS guidelines suggest adjuvant surgical resection in select patients, after expert consultation, but they do not provide advice regarding patient selection (6). Segmentectomy, lobectomy, or bi-lobectomy, employed to remove areas of cavitation or bronchiectasis, are generally preferred, but pneumonectomy may be appropriate in select cases (5). Multiple retrospective cases series, including one involving 236 patients (47), and a series from Toronto (48), have reported sputum culture conversion rates of >80% and recurrence rates of <20% after surgical resection (47-54). However, post-operative complications, including prolonged air leak, bronchopleural fistula, empyema, respiratory failure, and arrythmia, among others, have been reported in 7-35% of patients (12% in the largest series (47) and 20% in the Toronto series (48)) and post-operative mortality in 0-9%. Post-operative mortality decreases with increased surgical experience (47), and given the potential for morbidity, it is recommended that surgery be performed at expert centers with surgical and medical expertise in NTM-PD (5). At our centre, in addition to standard antibiotic therapy, we typically treat patients with parenteral amikacin for at least 1 month pre- and post-operatively, and we try to achieve at least smear conversion before surgery. Patients who undergo surgical resection are usually treated for at least 12 months post-surgery, if culture conversion is achieved at the time of surgery.

Finally, when confronted with treatment failure, the goals of therapy should always be re-visited. While augmenting therapy may increase the likelihood of sputum culture conversion, it may also be associated with drug toxicity. This may make a goal of eradication less desirable than a goal of symptom control or preventing progression for some patients, particularly in light of the high rates of recurrence (ranging from 25-48% (24, 55, 56)) seen in successfully treated MAC-PD patients.

Drug intolerance and macrolide-resistant MAC

A full approach to these topics is beyond the scope of this review. However, when faced with intolerance, the clinician should try to maintain as many “first-line” drugs as possible. Macrolides are the most important drug in the treatment of MAC-PD, and patients who do not tolerate one macrolide may tolerate the other (6). Adequate companion drugs must be included in the regimen to prevent the development of macrolide resistance. In this regard, ethambutol appears to be the most important drug (14, 15). If ethambutol cannot be used, current expert opinion supports replacement with clofazimine or amikacin to prevent macrolide resistance (11), however there is no data to support this practice. If

rifampin cannot be used, there is some data to suggest that macrolide-ethambutol-clofazimine is a reasonable alternative with comparable outcomes (57). It is not advisable to treat patients with macrolide-fluoroquinolone (+/- rifamycin), or just macrolide+rifamycin, because these regimens are known to foster macrolide resistance (14, 15). In the face of macrolide-resistant MAC, expert consultation is advised.

Patient evaluation during and after treatment

Sputum for AFB should be collected every 1-2 months during treatment to assess for therapeutic response (6). Symptom assessments and chest imaging should also be used to assess for response to treatment. While there are no guidelines, our centre typically performs chest CT scans before starting treatment, approximately 3-6 months into treatment, and at the end of treatment. Chest x-rays are often performed at other clinic visits. More frequent chest CTs may also be helpful for patients with severe/destructive disease. After treatment completion, patients should continue to be followed with clinical assessments, sputum cultures and chest imaging for recurrence.

Summary

The decision to treat MAC-PD involves a complex risk-benefit assessment, except in the case of fibro-cavitary disease, which should usually be treated. MAC-PD should be treated with azithromycin-ethambutol-rifampin, given thrice weekly in nodular bronchiectatic disease and daily in fibro-cavitary disease, with IV amikacin for at least the initial 2 months considered in the latter. Treatment should be given for 12 months post-sputum culture conversion. Patients with refractory MAC-PD should be considered for the addition of ALIS, or parenteral amikacin until ALIS becomes available, in addition to surgical resection.

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2020-2021 Lung Health Foundation Funded Projects

Lung Health Foundation Team Breathe Research Awards and Lung Health Foundation Breathing As One Research Awards 2020-2021

The Ontario Thoracic Society (OTS) is pleased to announce that funding from the Lung Health Foundation has been awarded to the following recipients:

A) Lung Health Foundation Team Breathe Research Awards

Primary Investigator: Vanessa D'Costa
(Breathe New Life Award for highest scoring Young Investigator*)
Title: *Investigating the Pathogenesis of the Multidrug-resistant Lung Pathogen Acinetobacter baumannii*
Amount: $50,000

Primary Investigator: Azadeh Yadollahi
(Asthma Champion**)
Title: *How Does Obstructive Sleep Apnea Worsen Asthma?*
Amount: $50,000

Primary Investigator: Denis E. O'Donnell
(COPD Champion**)
Title: *The Effect of Inhaled Nitric Oxide (iNO) on Inspiratory Neural Drive and Dyspnea during Exercise in Mild Chronic Obstructive Pulmonary Disease*
Amount: $12,605

Primary Investigator: Dawn Bowdish
Title: *Early Life Adversity Increases the Risk of Invasive Pneumococcal Infection*
Amount: $50,000

Primary Investigator: Chris Verschoor
Title: *Chronic Inflammation as a Determinant of Influenza Vaccine Efficacy and Respiratory Outcomes in Older Adults*
Amount: $49,786

Primary Investigator: Mauricio Terebiznik
Title: *Asbestos Phagocytosis by Alveolar Macrophages: Disruption of Phagosomal Morphogenesis and Function*
Amount: $50,000

Primary Investigator: Kjetil Ask
Title: *Investigating the Role of Myeloid-derived Macrophages in Fibrotic Lung Disease*
Amount: $50,000

Primary Investigator: Ruud Veldhuizen
Title: *Anti-inflammatory Exogenous Surfactant for ARDS*
Amount: $50,000

Primary Investigator: Sean Gill
Title: *The Role of Extracellular Matrix-Pulmonary Microvascular Endothelial Cell Interaction in Regulation of Microvascular Permeability during Lung Injury*
Amount: $50,000

Primary Investigator: Gaspard Montandon
Title: *Identification of New Molecular Pathways Regulating Opioid-induced Respiratory Depression and Safe Opioid Pain Therapies using Zebrafish Models*
Amount: $49,000

Primary Investigator: Chung-Wai Chow
Title: *Airway Oscillometry for Early Detection of Allograft Dysfunction Following Lung Transplant*
Amount: $50,000

Primary Investigator: Theodore Marras
Title: *Pilot Study of Point-of-Use Microbial Water Filters as Adjunctive Management in Patients with Mycobacterium Avium Pulmonary Disease*
Amount: $49,219

Primary Investigator: Laurent Brochard
Title: *Correlation Between Sleep-Wakefulness Continuum, Sedation and Patient-Ventilator Asynchronies*
Amount: $50,000

Primary Investigator: Indra Narang
Title: *The Use of Heated High Flow Nasal Cannula Therapy for the Management of Obstructive Sleep Apnea in Obese Adolescents*
Amount: $49,787

Primary Investigator: Samir Gupta
Title: *Shared Decision-making in Mild Asthma: Developing a Patient Decision Aid for a New Therapeutic Paradigm*
Amount: $43,535

Primary Investigator: Tetyana Kendzerska
Title: *Air Pollution and Control of Obstructive Sleep Apnea by Positive Airway Pressure Therapy*
Amount: $35,000

Primary Investigator: Ewan Goligher
Title: *Extracorporeal Life Support and Ventilator-Induced Diaphragm Dysfunction*
Amount: $49,588

Primary Investigator: Melanie Chin
Title: *Evaluating the Impact of Patient Activation on Clinical Outcomes in CF*
Amount: $27,530

Primary Investigator: Miranda Kirby
Title: *Computed Tomography Imaging of Lung Structure in Cannabis Users*
Amount: $47,400

B) Lung Health Foundation/Pfizer Canada Team Breathe Research Award for Infectious Disease**

Primary Investigator: Jim Sun
Title: *Targeting PPM1A In Vivo for Host-directed Tuberculosis Therapy*
Amount: $50,000

C) Lung Health Foundation Breathing as One Awards

Lung Health Foundation Breathing as One Young Investigator Research Awards (4):

Primary Investigator: Chris Verschoor
Title: *Examining the Relationship Between Biological Age and Influenza Vaccine Responses in Older Adults*
Amount: $15,000

Primary Investigator: Geneviève Digby
Title: *Characterizing and Overcoming Barriers to Access of Specialty Care for Patients with Lung Cancer in Southeastern Ontario*
Amount: $15,000

Primary Investigator: Sunita Mulpuru
Title: *Validating the Use of Frailty Measurements to Predict Deteriorations in Quality of Life and Care Expectations Among People with COPD: A Prospective Cohort Study*
Amount: $15,000

Primary Investigator: Miranda Kirby
Title: *Quantitative Computed Tomography Imaging of Lung Disease*
Amount: $15,000

Lung Health Foundation Breathing as One Non-Small Cell Lung Cancer Research Award:

Primary Investigator: Natasha Leighl
Title: *Accelerating Lung Cancer Diagnosis through Liquid Biopsies*
Amount: $40,000

Lung Health Foundation Breathing as One Kayla Baker LHF Staff & Volunteer Pediatric Research Award:

Primary Investigator: Amy Plint
Title: *Risk of Asthma in Children Diagnosed With Bronchiolitis During Infancy: A Longitudinal Study Linking Emergency Department-Based Clinical Data to Provincial Health Administrative Databases*
Amount: $26,316

Lung Health Foundation Breathing as One Health Disciplines Training Bursary Awards (2):

Primary Investigator: Joyce Wu
Title: *Characterize Idiopathic Pulmonary Fibrosis using Respiratory Oscillometry*
Amount: $2,500

Primary Investigator: Shirley Quach
Title: *Common Pediatric Ventilation Practices Across Canada*
Amount: $2,500

The launch of the application process for 2021-2022 funding opportunities has been delayed due to COVID-19. OTS and ORCS members will receive advanced notice of the new launch dates via an email from societies@lunghealth.ca at such time as the Lung Health Foundation is ready to proceed. Alternatively, you can check https://hcp.lunghealth.ca/apply-for-a-grant-or-fellowship periodically for updates.

**The Breathe New Life Award was developed to highlight excellence amongst upcoming researchers. Each year, it is awarded to the new investigator with the highest score, as determined by the review panel. The award is partially or fully funded by donations made to the "Top It Up!" campaign, a specific fundraiser for respiratory health research.*

***In keeping with the new strategic plan of the Lung Health Foundation, researchers working in one of the five foci (Asthma, COPD, Lung Cancer, Immunization/Infectious Disease, Smoking/Vaping Prevention & Cessation) will be highlighted and promoted for their work in advancing the Lung Health Foundation's specific goals in these foci.*

The winner of these award will be featured in various marketing and communications vehicles produced by the Lung Health Foundation as a means of promoting research and how it translates to better lung health within the larger community.

WHAT'S HAPPENING
RESPIRATORY TRAINING & EDUCATOR COURSES

For a list of upcoming online courses, please click on either of the two logos below:

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You can find out more about upcoming events or view archived webinars at any time by clicking on items under the "**Education**" tab at https://hcp.lunghealth.ca , the Lung Health Foundation's website dedicated specifically to healthcare professionals.

And don't forget that the Ontario Thoracic Society also has a dedicated area which can be found under the "**Societies**" tab.

Feel free to explore the various options under the other tabs to familiarize yourself with additional resources offered by the Lung Health Foundation.

If you have any feedback you would like to give about the new website, please direct it to societies@lunghealth.ca. We would love to hear from you!

PUBLICATIONS ARISING FROM PREVIOUS RESEARCH AWARDS

1) Humayun M, Chow CW, Young EWK. **Microfluidic Lung Airway-on-a-Chip with Arrayable Suspended Gels for Studying Epithelial and Smooth Muscle Cell Interactions**. Lab on a Chip, 18: 1298-1309 (2018). https://pubs.rsc.org/lv/content/articlehtml/2018/lc/c7lc01357d

   (This article is part of the themed collections: Lab on a Chip Emerging Investigators and Organ-, body- and disease-on-a-chip systems)

2) McHugh J, Duong M, Ma J, Dales RE, Bassim CW, Verschoor CP. **A comprehensive analysis of factors related to lung function in older adults: Cross-sectional findings from the Canadian Longitudinal Study on Aging**. Respir Med. 2020 Sep 23;173:106157.

doi: 10.1016/j.rmed.2020.106157. Epub ahead of print. PMID: 33010732.
https://www.resmedjournal.com/article/S0954-6111(20)30297-3/fulltext

Do you have research updates, new publications or achievements to share?
Send your news to societies@lunghealth.ca

HAVE YOU RENEWED YOUR OTS MEMBERSHIP?

Ontario Thoracic Society (OTS) members include academic and community respirologists and researchers who are local and national leaders in their fields. The society manages a suite of educational and research programs, and works closely with the Lung Health Foundation to advocate for lung health initiatives in the province.

The current OTS membership term runs from April 1, 2020 to March 31, 2021.

OTS Active membership is open to individuals with a medical degree and scientists holding a PhD or equivalent degree of training. The 2020-2021 fee is $95.00.

The OTS Associate Membership is available to interns, residents or graduate students in medical science or the health disciplines, and to fellows during their period of training. Associate members do not pay fees and may not vote or hold office in the society, but enjoy all the benefits of a membership.

To join the OTS or renew your membership for 2020-2021, please go to
https://lunghealth.member365.com

If you experience any difficulties in signing up or renewing, please email societies@lunghealth.ca and an administrator will get back to you shortly.

The Ontario Thoracic Review is the official publication of the Ontario Thoracic Society, a medical section of the Lung Health Foundation.

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