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NTM-TB INSIGHTS

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# Nontuberculous Mycobacterial Infections in Cystic Fibrosis Patients

***Introduction and Epidemiology***

Over the past two decades, nontuberculous mycobacteria (NTM) have emerged as important pathogens in the setting of cystic fibrosis (CF) lung disease (1). While historically CF was considered a fatal disease of childhood, improvements in therapy have resulted in a steady increase in expected lifespan, with a current projected median survival of 37 years (2). The American Thoracic Society has identified the CF population as having both an especially high risk for NTM, with a reported prevalence of positive cultures and/or NTM infection between 6-13% (3-7). There is widespread agreement that the prevalence of NTM infection is increasing within the CF population (1, 3, 6, 8-10), as has been reported within the general population as well (11, 12).

The overwhelming majority of NTM species recovered in CF samples are from either *Mycobacterium avium* complex or *M. abscessus* group (7). *M. avium* complex has historically been the most common NTM isolated (13, 14), and in the largest U.S. survey, it was present in up to 72% of patients with NTM-positive sputum cultures (3). The percentage of *M. abscessus* group reported in CF patients with NTM-positive sputum cultures has ranged between 16 to 68% (3, 6, 15, 16), and it does appear that the proportion of *M. abscessus* group is increasing (9, 17, 18). This effect may be due to geographic factors, as *M. abscessus* group appears especially prevalent in Europe, and *M. simiae* and *M. abscessus* group are the most common species isolated in Israel (19). *M. avium* complex is more often associated with older CF patients, often diagnosed in adulthood, while *M. abscessus* group is frequently seen in younger patients and those with more severe lung disease (6, 20). Less frequently isolated species include *M. kansasii* and *M. fortuitum*.

***Risk factors for NTM in CF***

Our understanding of risk factors for NTM in CF patients is incomplete, but the most worrisome trend is that increased prevalence of NTM is strongly linked to older age and relatively milder lung disease (3). A very high prevalence has been recorded in patients with an adult diagnosis (13, 21), which is typically associated with the "nonclassic" form of CF resulting from less severe CF mutations (13, 22). The presence of the fungus *Aspergillus fumigatus* (9, 23, 24) has also been associated with increased risk for NTM, as has allergic bronchopulmonary aspergillosis (25, 26).

It has been suggested that various medications and CF treatment strategies have contributed to the apparent increase in NTM prevalence, including systemic steroids, high dose ibuprofen, azithromycin and anti-pseudomonal antibiotics (19, 24-30). However, these reports are for the most part retrospective and their conclusions have been disputed by other researchers (4, 19, 31-34). More recently, the potential for patient-to-patient spread of *M. abscessus* group within CF Centers has been described (35-38).

***Screening for NTM in CF***

Historically, recovery of NTM from CF sputum samples was difficult due to co-infection with *Pseudomonas aeruginosa* and other microbes, which overgrow the culture long before detection of slower growing NTM (39, 40). Effective sample decontamination protocols have now allowed for improved culture-based detection of mycobacteria in CF samples (41, 42). Frequently, NTM is first detected in a CF sputum sample in the absence of clinical suspicion, thus screening for NTM

with an acid-fast bacilli smear and culture on an annual basis has been recommended (43). More frequent screening may be considered in various patients deemed to be at higher risk for acquiring the infection, or in which the infection could have more severe consequence.

***CF-specific Diagnostic Considerations***

NTM species require repeated isolation prior to confirming the diagnosis of NTM lung disease. Even for pathogenic NTM species isolated on more than one occasion, clinical sequelae can range from nondetectable to severe (44-46). Guidelines developed under the sponsorship of the United States Cystic Fibrosis Foundation and the European Cystic Fibrosis Society require the presence of >1 positive culture, in the setting of characteristic clinical symptoms and radiographic findings, with exclusion of other CF-related comorbidities (43). These guidelines have not been validated, and are particularly challenging as radiographic signs suggestive of NTM are common in CF, and identical clinical symptoms can occur due to co-infections with *P. aeruginosa* and *Staphylococcus aureus*. Patients who are acid-fast bacilli smear positive for NTM are more likely to have NTM disease (14, 19), as well as those who demonstrate progression by high-resolution computed tomography of typical findings associated with NTM (45). Unexpectedly rapid decline in forced expiratory volume (FEV1) is frequently associated with NTM disease (47-49). In a recent retrospective study, a cohort of patients with NTM disease demonstrated a mean decline in $FEV_1$ for a year prior to initial recovery of NTM in their sputum, whereas patients with indolent infection or patients who apparently cleared the infection after a single positive culture demonstrated a stable $FEV_1$ for a year prior, and three years after, the initial positive culture (44).

***Treatment considerations***

There have been no completed trials evaluating antibiotic treatment regimens for NTM lung infection in CF (50). Initial treatment of NTM pulmonary disease in CF should broadly be based on current guidelines from the United States CF Foundation and European Cystic Fibrosis Society (43). Standard treatment regimens typically include at least 3 drugs directed against the specific NTM pathogen, in oral, inhaled and/or intravenous form. Routine monitoring of drug toxicity is required, and a plan for monitoring should be set in place at the initiation of treatment. In addition to pharmacologic treatment of NTM infection, nonpharmacologic therapies for underlying CF lung disease that primarily target clearance of airway mucus obstruction and bronchoconstriction are essential. All NTM treatment regimens need to be part of a comprehensive CF care plan that is most effectively delivered at a CF Care Center, utilizing a multidisciplinary approach.

***Clinical Response***

To date, reports of therapeutic response to the treatment of NTM disease in both CF and non-CF patient cohorts have focused on rates of eradication of the organism (51). In CF-lung disease, eradication often may not be achieved. However, within the individual patient, other clinical benefit may be appreciated from suppressive treatment of NTM disease. Regardless of response to treatment, close follow-up is needed in patients previously infected with an NTM or treated for NTM pulmonary disease, as the presence of a second NTM is a relatively common occurrence. In patients from the Colorado CF Center, 26% of subjects were identified with a second NTM species at 5 years and 36% at 10 years (44). These findings support the need for lifelong strategies for NTM surveillance and management in CF patients who present with a positive NTM culture.

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## Treatment of Pulmonary NTM Infections: the Consideration of Surgery

Although recognized with increasing frequency in the United States, the treatment of pulmonary infection related to nontuberculous mycobacteria (NTM) can admittedly be difficult. The recommended drug regimen (when prescribed correctly) is arduous and prolonged, and may be complicated by drug intolerance, toxicity, or resistance. Patients may experience repeated recurrence of the infection, often associated with progressive symptoms and dwindling therapeutic options. In these situations, the use of surgical resection has been proposed as an adjunct (or addition) to medical therapy to improve outcomes. The rationale for adding surgery to the treatment of affected patients is that the areas of damaged lung are poorly penetrated by the antibiotic therapy, thus serving as a reservoir for organisms to trigger recurrent infection. In this article, we explore the use of surgery in patients with pulmonary NTM infection.

***Initial Considerations***

At the outset, several points about the use of surgical resection in this patient group should be emphasized. First, the use of surgery must be seen as an adjunct to, and not a replacement for, conventional medical treatment. The appropriate drug regimen remains the mainstay of therapy, and should be continued for several months after (apparently) successful surgical intervention. This fact is often lost on patients undergoing therapy for years with recurrent treatment failure. Further, one should recognize that not all patients are candidates for surgery; in our program, only a small proportion of evaluated pulmonary NTM patients are considered for surgical intervention. Individuals invariably describe a pattern of recurrent infections, usually in the setting of significant drug intolerance or resistance. In addition, they must possess focal lung damage – typically end-stage bronchiectasis or persistent cavitary lung disease – to serve as surgical "targets" for removal. Finally, the decision for surgical intervention is best made in a multidisciplinary setting, carefully weighing all treatment alternatives. At our institution, all prospective candidates for surgery are discussed in detail within our multidisciplinary group, including the timing and extent of surgical resection and the use of other procedures such as muscle flap transposition. We strongly feel this improves patient outcomes.

***What is the Goal?***

When considering surgery in patients with NTM infection, it is important to identify the *goals* of the proposed operative intervention. What do we hope to accomplish by operating on this patient? In most cases, the goal is to eradicate the infection – render the patient culture negative, off antibiotic therapy. Unfortunately, this is not possible in all cases due to the extent of lung disease. However, we have found surgery may be helpful in two additional situations. First, the presence of disabling or life-threatening symptoms, such as intractable cough or significant hemoptysis, may be alleviated with surgical intervention. Second, in some patients surgery may be able to slow down or even halt the progression of the disease by "debulking" or removing large areas of significant tissue damage. These areas, if left *in situ*, can soil uninvolved areas of the lungs. An example of this would be the patient with a cavitated, completely destroyed lung and limited disease in the contralateral lung; removal of the destroyed side will limit ongoing contamination to the remaining lung.

***Preparation for Surgery***

The *timing* of surgical intervention is important. The medical regimen should be optimized with the collection of new cultures and drug susceptibility testing when appropriate. Surgery is usually planned 8 to 12 weeks later, at a time when the mycobacterial counts could be anticipated to be at a low point. Occasionally, the final decision regarding extent of surgical resection may hinge on updated imaging after initiation of the improved regimen. Factors which may alter this traditional approach include: the presence of an adequate medical regimen on presentation, which may accelerate the

path to surgery; or a poorly controlled infection, heavy burden of disease or poor nutritional status, which may slow the path to surgery.

Of course, patients must be acceptable candidates for surgical resection in the traditional sense – adequate pulmonary reserve, and a general lack of disqualifying medical problems. Interestingly, what constitutes "adequate pulmonary reserve" in this patient cohort often differs from the typical thoracic patient undergoing surgery for cancer. In pulmonary NTM infection the targets of surgical resection, due to significant cavitary disease or bronchiectasis, have very little function and thus may cause little decrement in the patient's pulmonary status once removed. Thus, in the absence of other mitigating factors, a NTM patient with borderline function (e.g. FEV1 ~ 35%) and a destroyed left lung remains a candidate for pneumonectomy.

***Surgical Approach***

An open thoracotomy approach has traditionally been utilized in patients with bronchiectasis and cavitary lung disease, producing excellent results with acceptable morbidity and mortality in several published studies. Within the past decade, though, it has become increasingly clear that many (if not most) of these operations may be accomplished through a minimally invasive, or VATS (video-assisted thoracoscopic surgery) approach. The key, as with so many surgical techniques, lies with proper patient selection. The degree of pleural symphysis and the extent of cavitary lung disease on the computed tomography images are the crucial elements to assess to decide if a VATS approach is feasible. Regardless of the approach, we favor anatomic lung resection whenever possible in this patient population, believing that this produces the best clearance of diseased lung tissue. However, lobectomy or segmentectomy for bronchiectasis or cavitary lung disease poses several technical challenges when compared with a similar procedure for thoracic malignancy. With this in mind, it should be understood that surgical success in this patient population can be difficult to come by, and as with so many other endeavors, experience counts.

***Outcomes***

Our institution has enjoyed considerable success in the use of surgery in selected patients with pulmonary NTM infection. In addition, several other retrospective studies have demonstrated excellent results following surgery for pulmonary NTM disease, with very low morbidity and mortality and high sputum conversion rates. Understandably, there is considerable bias in these reports involving selected patient populations, and in general there is limited data regarding patient selection and long-term outcomes in this field. Clearly, further research is needed.

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## Recent Staff Publications

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## Meetings

- **20th Annual Conference of the International Union Against Tuberculosis and Lung Disease – North American Region**, February 24-27, 2016. Sheraton Denver Downtown Hotel, Denver, CO
- **Advances in the Science and Practice in Tuberculosis Control,** Post-Graduate Course, February 24, 2016, 2:00 to 6:00PM, Sheraton Denver Downtown Hotel, Denver, CO
- **National Tuberculosis Controllers Association Meeting**, February 24-27, 2016, Sheraton Denver Downtown Hotel, Denver, CO
- **Tuberculosis Co-Morbidities and Immunopathogenesis**, February 28-March 3, 2016, Keystone Resort, Keystone, CO
- **World Tuberculosis Day,** March 24, 2016
- **The 53rd Semi-Annual Denver TB Course**, April 6-9, 2016; Molly Blank Conference Center at National Jewish Health Main Campus. Click here for more information and registration.
- **Front Range Mycobacteriology**, June 7-10, 2016, Colorado State University, Fort Collins, CO

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