Therapy for lung infection by agent other that bacteria

Mycobacteria in cystic fibrosis

Code: 122 **Updated:** July 1, 2022

Background

Nontuberculous mycobacteria (NTM) are ubiquitous environmental mycobacteria that have the potential to cause respiratory disease, particularly in compromised patients. Although generally low, NTM virulence does differ between individual species (Weiss CH et al, 2012) . Recently (Faverio P et al, 2021)a review outlined the relevance of an integrated approach to NTM-PD including not only antibiotic therapy, but also the impact of exposure to environments where mycobacteria are present and careful evaluation of lifestyle , a personalised pulmonary rehabilitation plan and airway clearance techniques to improve symptoms, exercise capacity, health-related quality of life (QoL), nutritional approach, management of comorbidities that affect disease outcomes, including structural lung diseases, immune status evaluation and psychological support.

NTM have a particular affinity for patients with CF. Recent studies suggest a possible relationship between acquiring NTM and the level of environmental water in a given area. A retrospective chart review was performed on 150 children with CF in Florida. Inclusion criteria required regular follow-up, at least two acid-fast bacilli cultures, and a consistent home address over a 3-year period, defining the distance from each patient's home to the nearest body of water. Of the 150 CF patients, 65 met inclusion criteria and 21 (32.3%) tested positive for NTM. On the logistic regression, results showed that CF patients who lived within 500 meters of water were 9.4 times more likely to acquire NTM (p=0.013). Other significant predictors included a history of Aspergillus fumigatus (OR 7.9, p=0.011) isolation and a recent history of Pseudomonas aeruginosa acquisition (OR 2.5, p=0.007) (Bouso JM et al, 2017).

An australian study demonstrated that cross-infection of NTM occurs in CF hospital patients suggesting to implement hospital infection control practices (Jan J et al, 2019).

The prevalence of Mycobacteria (M) organisms in patients with CF is highly variable, ranging from 5% to 20% (Park IK et al, 2015) (Bar-On O et al, 2015). It is unclear if this represents increasing rates of infection or improved surveillance.

A study including 48 CF adults and children attending the CF center of Lyon from 2009 to 2014, having at least one positive NTM isolate matched by age and gender with 96 CF patients with no NTM isolate (controls), showed that the age group for whom incident NTM was higher was composed by young adolescents aged 13 to 17 years. A significant association for NTM positivity was found with Staphylococcus aureus in multivariate analysis and with allergic bronchopulmonary aspergillosis, corticosteroid and itraconazole in univariate analysis. Mean annual FEV1 decline was faster for NTM-positive patients compared to controls (Cavalli Z et al , 2017).

Conflicting data are underway regarding the NTM pathogenicity in respiratory tract infection in CF. The recent discovery of functional impairment of autophagy in CF provides a new basis for understanding susceptibility to CF-associated bacterial and fungal pathogens, suggesting that autophagy restoration therapy may improve pathogen clearance and mitigate lung inflammation in CF airways (Rovetta Al et al, 2014).

NTM infection is defined as “at least two respiratory specimens positive by culture for NTM” (Griffith DE et al, 2007).

NTM can cause lung disease in people with CF leading to a more rapid decline in lung function and even death in certain circumstances. The infection may remain indolent in some people with CF, without evidence of clinical consequence, whereas other patients suffer significant morbidity and mortality (Martiniano SL et al, 2016). Factors including the steady aging of the CF population, the apparent increase of NTM in the environment, and the potential for patient-to-patient transmission, may contribute to increased acquisition. Comprehensive care of the CF patient must be optimized to assess the clinical impact of the NTM (indolent versus active), and to improve response to treatment. A CF-specific approach to the diagnosis and treatment of NTM infection is a priority research for the CF community (Martiniano SL et al, 2015). The dilemma faced by clinicians is to accurately identify those patients who are likely to benefit from therapy, while avoiding unnecessary treatment in those with indolent infection (Nick JA et al, 2017).

NTM are found in approximately 10 up to 20% of CF patients, but only a portion will develop NTM disease. CF lung disease therapy should be optimized, including antibiotic therapy targeted to the individual's usual airway bacteria, prior to considering treatment for NTM lung disease. Those who meet criteria for NTM lung disease may not necessarily require treatment and could be monitored if symptoms and radiographic findings are minimal. However, the presence of *Mycobacterium abscessus* complex (MABSC), severe lung disease, and/or anticipated lung transplant should prompt NTM therapy initiation. For CF patients with *Mycobacterium avium* complex (MAC), recommended treatment includes triple antibiotic therapy with a macrolide, rifampin, and ethambutol. Azithromycin is generally the preferred macrolide in CF, as it is better tolerated and has fewer drug to drug interactions. MABSC treatment is more complex and requires an induction phase (oral macrolide and two IV agents including amikacin), as well as a maintenance phase (nebulized amikacin and two to three oral antibiotics including a macrolide). The induction phase may range from one to three months (depending on infection severity, treatment response, and medication tolerability). For both MAC and MABSC, treatment duration is extended 1-year post-culture conversion. However, in patients who do not achieve culture negative status but tolerate therapy, ongoing treatment for mycobacterial suppression and prevention of disease progression has to be considered (Skolnik K et al, 2016).

Anecdotal reports show that the decline in respiratory function has been correlated with the persistence of specific Mycobacteria species complex as M. avium, abscessus, chimaera.

Patients with CF who have M. avium complex are older, have better lung function, have a higher rate of Staphylococcus aureus and a lower rate of Pseudomonas aeruginosa infection (Roux AL et al, 2009). In contrast, M. abscessus infection is more prevalent than M. avium complex in children with CF and may lead to more deleterious clinical outcome (Catherinot E et al, 2012).

In the past the use of low-dose azithromycin with antiinflammatory properties was associated with development of infection with NTM, by impairing autophagic and phagosomal degradation and consequently inhibiting intracellular killing of NTM within macrophages. These results failed to be demonstrated in an other paper (Catherinot E et al, 2012).

Generally, microbiology laboratories do not routinely process CF respiratory tract specimens for identifying emerging pathogens as mycobacteria. Recently (Preece CI et al, 2015) a simple and effective culture method for the isolation of rapidly-growing mycobacteria from sputum samples from patients with CF has been developed. A further novel selective agar (RGM medium) has been recommended for the isolation of rapidly growing mycobacteria from the sputa of CF patients by MALDI-TOF MS (Stephenson D et al, 2019). Extended incubation of RGM medium for 28 days facilitates the isolation of slow-growing species, including members of the *Mycobacterium avium* complex (Plongla R et al, 2017).

Previously (Lobo LJ et al, 2013) a retrospective study examined CF patients transplanted at the University of North Carolina from 1992 to 2012 that met microbiological criteria for disease pre-transplant and with at least one respiratory sample positive for M. abscessus prior to transplantation in order to evaluate survival post-transplant. Survival data showed no statistically significant difference compared with a contemporaneously transplanted population of CF patients without M. abscessus.

Guidelines are available for the antimicrobial treatment of NTM lung disease (Weiss CH et al, 2012).

ATS have summarized the approach to infections with NTM (Chmiel JF et al, 2014). Treatment requires prolonged periods of multiple drugs and varies depending on NTM species, resistance pattern, and extent of disease.

In general, in order to assist clinicians for diagnosis and treatment of NTM, a panel of experts from the US Cystic Fibrosis Foundation (CFF) and the European Cystic Fibrosis Society (ECFS) generated a series of pragmatic, evidence-based for the screening, investigation, diagnosis and management of NTM-PD in individuals with CF (Floto RA et al , 2016).

Issues

- To compare antibiotic treatment to no antibiotic treatment, or to compare different combinations of antibiotic treatment, when lung disease is linked to NTM colonization;
- to define the best choice of antibiotics or route of antibiotic administration (oral, intravenous or inhaled) with which to treat patients with CF and NTM infection;
- to evaluate the effectiveness of early antibiotic therapy to eradicate NTM;
- to assess treatment effects on lung function and pulmonary exacerbations and to quantify adverse events;
- to assess treatment effects on the amount of bacteria in the sputum, quality of life, mortality, nutritional parameters, hospitalizations and use of oral antibiotics;
- to evaluate chronic antimicrobial suppressive treatment of NTM to prevent lung function decline in CF patients.

What is known

A CDSR (Waters V and Ratjen F, 2020) outlined a comparison between antibiotic treatment and no antibiotic treatment, as well as different combinations of antibiotic treatment, for NTM lung infections in people with CF, evaluating as primary outcomes the effect of treatment on lung function and pulmonary exacerbations and to quantify adverse events, while the amount of bacteria in the sputum, quality of life, mortality, nutritional parameters, hospitalization and use of oral antibiotics have been evaluated as secondary outcomes. No completed clinical trials are available for this analysis in order to identify the type of antibiotic and treatment regimen for NTM that are conversely available for NTM in non-CF patients. These data are comparable with previous data of a CDSR performed in 2016.

Currently, NTM antimicrobial therapy is generally guided by old recommendations of the ATS and the IDSA (Griffith DE et al, 2007) in people with no CF. In CF for M. avium complex clarithromycin and azithromycin could represent an alternative to the first-line anti-tuberculosis drugs. Multi-drug therapy as a macrolide, amikacin and cefoxitin or imipenem are recommended concerning M. abscessus infection based on expert opinion (Griffith DE et al, 2007)(Chmiel JF et al, 2014).

A phase II randomized, double-blind, placebo-controlled trial (NCT01315236) Arikayce for Non Tuberculous Mycobacteria) has been completed, in collaboration with the National Institute of Allergy and Infectious Diseases, in order to evaluate inhaled liposomal amikacin for the treatment of recalcitrant NTM lung disease due to either M. avium complex or M. abscessus and who have received at least six months of antibiotic therapy. Among enrolled patients people with CF were included and results have been stratified also by the presence of CF in the final analysis.

An observational-cohort study of clofazimine used for pediatric and adult CF and non-CF patients with pulmonary and extrapulmonary NTM infection as part of a multidrug regimen from 2006-2014 has been completed including 112 subjects (median age 62 years); 24 subjects (21%) had CF. Clofazimine was safe, tolerated, and active for NTM infection in this heterogeneous population of pediatric and adult CF and non-CF patients. It should be considered as an alternative drug for treatment of NTM disease (Martiniano SL et al, 2017).

More recently clofazimine inhalation suspension (CIS) was developed to determine the efficacy, minimum inhibitory concentrations in vitro, and tolerability in naïve mouse models infected with both Mycobacterium avium and M. abscessus, showing tolerability and efficacy in vitro as in mice models (Banaschewski B et al, 2019).

Recently, microbiological data by collection of more than 2,700 approved drugs screened at a single-point concentration against a *M. abscessus* clinical isolate showed that rifabutin was active, in contrast to rifampin, against the *Mycobacterium abscessus* complex bacteria *in vitro,* and also against clarithromycin-resistant strains and may be considered for treatment of *M. abscessus*

lung disease (Aziz DB et al. 2017).

Very recently (Laudone TW et al. 2021) new treatment options have been summarized as alternative regimens in patients that show antibiotic resistance and toxicity, as bedaquiline, tetracycline derivatives, eravacycline, tedizolid, as well as inhaled antibiotics or GM-CSF, up to bacteriophage therapyincluding benefits and side effects of each drug.

Unresolved questions

Large prospective studies are required to provide further information for attending diagnosis and treatment of NTM in CF. There is a need to assess the efficacy and safety of antibiotic therapy. Yet standardization of microbiological assays for detecting NTM is required. More selective surveillance for NTM has to be routinely recommended.

Until evidence becomes available, it is reasonable for clinicians to follow recommendations sugested by CFF and ECFS (Floto RA et al. 2016) or by a review (Martiniano SL et al. 2017) o more recentle by ATS/ERS/ESCMID/IDSA clinical practice guidelines (Daley CL et al. 2020) that provide new insights into current NTM diagnosis and treatment guidelines, highlighting new treatment options, discussing what future research projects will aim to better define which patients affected by NMT infection to treat and timing and duration of treatment (Lu M et al. 2019), especially in children with CF.

Keywords

Mycobacteriosis; Drugs against mycobacteria;