Therapy for lung infection by agent other that bacteria

Mycobacteria in cystic fibrosis

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Background

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 whether this represents increasing rates of infection or improved surveillance.

Nontuberculous mycobacteria (NTM) are ubiquitous environmental mycobacteria that have the potential to cause respiratory disease, particularly in compromised patients. More than 30 species of NTM are known to cause human infections. 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 infection is defined as “at least two respiratory specimens positive by culture for NTM” (Griffith DE et al, 2007).

Generally, microbiology laboratories do not routinely process CF respiratory tract specimens for identifying emerging pathogens as mycobacteria. A simple and effective culture method for the isolation of rapidly-growing mycobacteria from sputum samples from patients with CF has been developed (Preece CI et al, 2015). 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).

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. Among 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).

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 outcomes (Catherinot E et al, 2012).

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 AI et al, 2014).

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).

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).

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.

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).

Guidelines are available for the antimicrobial treatment of NTM lung disease. 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 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).

A recent review aimed to provide an overview of the latest ongoing findings to fight M. abscessus infections. Alternative treatments as nitric oxide, phage therapy and antivirulence therapy, new drugs including antimicrobial peptides, and innovative molecules to treat Mab infections via nanoparticles and nanocarriers may represent new opportunities in the future (Recchia D et al, 2023).

Recently a study aimed to determine how Bacille Calmette-Guérin (BCG) vaccination may impact NTM infection, using a murine model of *Mycobacterium abscessus* infection and observational data from a non-BCG vaccinated CF cohort in Sydney, Australia and a BCG-vaccinated CF cohort in Cape Town, South Africa. In mice, BCG vaccination induced multifunctional antigen-specific $CD4^+$ T cells circulating in the blood and was protective against dissemination of bacteria to the spleen. In the clinical CF cohorts, the overall rates of NTM sampling during a three-year period were equivalent; however, rates of NTM colonisation were significantly lower in the BCG-vaccinated (Cape Town) cohort, which was most apparent for *M. abscessus*. This study provides evidence that routine BCG vaccination may reduce *M. abscessus* colonisation in individuals with CF, which correlates with the ability of BCG to induce multifunctional $CD4^+$ T cells recognising *M. abscessus* in a murine model (Warner S et al, 2023).

A series of three workshops were organized in 2023 by the Cystic Fibrosis Foundation (CFF) and the National Institute of Allergy and Infectious Diseases (NIAID) to review the current murine models of M. abscessus infections, discussing current challenges and priorities toward establishing validated and globally harmonized preclinical models with the aim to facilitate the implementation of informative murine models of therapeutic efficacy testing across laboratories, improve reproducibility from lab-to-lab and accelerate preclinical-to-clinical translation (Dartois V et al, 2024).

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;
- to evaluate the NTM infection on survival post-transplant.

What is known

A CDSR (Jahncke et al, 2025) updated of a previous review in order to compare antibiotic treatment to no antibiotic treatment, or to compare different combinations of antibiotic treatment, for eradicating NTM lung infections in people with CF. Clinicaltrials: gov and the World Health Organization International Clinical Trials Registry) were evaluated for searching list of (RCTs) or quasi-RCTs with a parallel design; non-randomised studies of interventions (NRSIs) that compared antibiotic treatment to no antibiotic treatment, or different combinations of antibiotic treatment, in people with CF of any age with NTM pulmonary infection. Outcomes of microbiological clearance of NTM in sputum, quality of life, adverse events, lung function and pulmonary exacerbations were assessed, as well as outcomes of mortality, nutritional parameters, hospitalisations and use of additional oral antibiotics . Only a single retrospective case review conducted in Sweden in 2003 was included, which presented data as the change from baseline for some outcomes in 11 participants with CF and NTM infection (three males) aged between 10 and 36 years. Based on in vitro susceptibility testing antibiotics isoniazid, ethambutol, rifampicin (or rifabutin), amikacin, clarithromycin, ciprofloxacin, streptomycin and clofazimine were evaluated. Main results showed that antimicrobial treatment may lead to sputum clearance of NTM in people with CF, but clinical response was

variable in terms of lung function. Adverse events may be common, necessitating close monitoring. Larger studiesd are needed.

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 previous 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).

Therapeutic drug monitoring is recommended to reduce toxicity, particularly from intravenous amikacin use. The absorption and pharmacokinetics of antibiotics as tiygeciclin, amikacin, clofazimine may vary for people with CF. The ongoing FORMaT trial (Finding the Optimal Regimen for *M. abscessus* treatment (NCT04310930) will determine the best regimen for *M. abscessus* eradication, with tolerance of adverse effects.

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 89 (LAI = 44; placebo = 45) enrolled patients people with CF were included and results have been stratified also by the presence of CF in the final analysis.The average age of the sample was 59 years; 88% were female; 92% were white; and 80 and 59 patients completed study drug dosing during the double-blind and open-label phases, respectively. Patients were randomly assigned to LAI (590 mg) or placebo once daily added to their multidrug regimen for 84 days. Both groups could receive open-label LAI for 84 additional days. The primary endpoint was change from baseline to Day 84 on a semiquantitative mycobacterial growth scale. Other endpoints included sputum conversion, 6-minute-walk distance, and adverse events. The primary endpoint was not achieved (P = 0.072); however, a greater proportion of the LAI group demonstrated at least one negative sputum culture (14 [32%] of 44 vs. 4 [9%] of 45; P = 0.006) and improvement in 6-minute-walk test (+20.6 m vs. -25.0 m; P = 0.017) at Day 84. A treatment effect was seen predominantly in patients without CF with MAC and was sustained 1 year after LAI. Most adverse events were respiratory, and in some patients it led to drug discontinuation. The primary endpoint was not reached; however, LAI added to a multidrug regimen produced improvements in sputum conversion and 6-minute-walk distance versus placebo with limited systemic toxicity in patients with refractory MAC lung disease (Olivier KN et al, 2017).

An observational-cohort study to evaluate clofazimine using 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).

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).

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).

New treatment options (Laudone TW et al, 2021) have been recently 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 therapy outlining benefits and side effects of each drug.

Recently (Dedrick RM, et al, 2023) 20 patients with symptomatic disease by mycobacteria susceptible to one or more lytic phages were treated intravenously, by aerosolization, or both on a compassionate use basis. No adverse reactions were registered in any patient regardless of the pathogen, phages administered, or the route of delivery. Challenge with phage treatment of Mycobacterium infections may represent an adjuntive treatment option for some mycobacterial infections.

More recntly a retrospective multicenter cohort study was performed (Wiesel V et al, 2024), including patients with CF from five CF centers in Israel aged older than 6 who had at least one positive NTM airway culture in the past two years and treated with ETI for at least one year. The annual NTM and bacterial isolations, pulmonary function tests, and body mass index were analyzed before and after ETI treatment. Fifteen pwCF were included (median age 20.9 years, 73.3% females, 80% pancreatic insufficient). In nine patients (66%) NTM isolations were eradicated following treatment with ETI. Seven of them had MABC. The median time between the first NTM isolation and treatment with ETI was 2.71 years (0.27-10.35 years). Eradication of NTM was associated with improved pulmonary function tests ($p<0.05$). Results are encouraging. Further studies are needed to assess whether treatment with ETI can result in the long-term eradication of NTM.

Until evidence becomes available, it is reasonable for clinicians to follow recommendations suggested by CFF and ECFS (Floto RA et al, 2016) or by a review (Martiniano SL et al, 2017) or more recently 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 as timing and duration of treatment (Lu M et al, 2019), especially in children with CF.

Recent standards of care (Burgel PR et al, 2024) summarizes statements which were reviewed by a Delphi consultation on monitoring

and treating NTM, as well other conditions of CF disease.

The use of highly effective modulator therapy in a large cohort of subjects with CF may further reduce clinical signs and symptoms of NTM disease, as well as sensitivity of sputum cultures (Martiniano SL et al, 2022) (Burke A et al, 2023).

Unresolved questions

Large prospective studies are required to provide further information for attending diagnosis and treatment of NTM in CF developing a disease-specific approach to the diagnosis and treatment of NTM infection. There is a need to assess the efficacy and safety of antibiotic therapy. Standardization of microbiological assays for detecting NTM is still required. More selective surveillance for NTM has to be routinely recommended. A lifelong strategy is needed for this high-risk population.

Keywords

Mycobacteriosis; Drugs against mycobacteria;