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Infection by Non Tuberculous Mycobacteria in Cystic Fibrosis

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1. Introduction

Cystic fibrosis (CF) is a common autosomal recessive genetic condition affecting white population with an approximate incidence of 1 per 2500 live births (Davis et al., 1996), nearly 30,000 people in the USA (Olivier et al., 2003). Patients with this life-shortening disease have abnormally thickened secretions that facilitate chronic infection of the airways, bronchiectasis and early death. The respiratory pathogens most frequently isolated in these patients are *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

As the survival of this group of patients has been improved by better nutrition, intensive therapy to clear airway secretions and more aggressive use of antibiotics (FitzSimmons, 1993, Ramsey, 1996), new pathogens such as *Stenotrophomonas maltophilia, Burkholderia cepacia, Alkaligenes xylosoxidans, Nocardia* spp., fungi and non tuberculous mycobacteria (NTM) are evolving (Burns et al., 1998; Burns & Saiman, 1999; Olivier et al., 1996)

NTM have increasingly been reported in the world as pulmonary pathogens not only in immunosuppressed but also in non immunocompromised persons, mainly in patients with lung disease (bronchiectasis, hypersensitivity, pneumonitis, chest wall disorders, previous mycobacteriosis and CF) (Huang et al., 1999; Prince et al., 1989; Hjelte et al., 1990; Fauroux et al., 1997)

Two important issues to consider are: 1) the clinical significance of isolation of a NTM (contamination, colonization or disease) (Hayes, 2005); and 2) bacterial overgrowth, especially with *P. aeruginosa*, leading to difficulty in the isolation of the mycobacterium from sputum samples.

NTM produce insidious infections that require several months of combined antibiotic therapy, difficult eradication and frequent relapses with progressive lung function deterioration (Esther et al., 2010). They represent an important social and health problem (Olivier et al., 2003), with not well defined and unsolved aspects, such as mode of infection, pathogenic role, standardized treatment or prophylaxis.

In this chapter we will review the main epidemiological, clinical, diagnostic, therapeutic and prophylactic aspects of NTM infections in CF patients.

2. Epidemiology and pathogenesis

2.1 General aspects

The term NTM refers to *Mycobacterium* spp. different to *M. tuberculosis complex* and *M. leprae*. These microorganisms are widely distributed in the environment (water, soil, dust, animals and food). Almost all NTM are less virulent and contagious than *M. tuberculosis* (Runyon, 1959; Brown-Elliot et al., 2002). There are more than 100 described species, of which only 15-20 produce infections in humans.

NTM are resistant to chlorination and ozonation (Prim et al., 2004) and to multiple antiseptics and antibiotics. They are opportunistic microorganisms capable of causing disease in a different range of locations (skin and soft tissues, lymph nodes and lung) as well as disseminated diseases.

The extent and severity of infection depends on the anatomic and immune integrity of the host. These bacteria can adhere to biomedical materials (catheters, prosthesis, filters or membranes of inhalation systems) forming a biofilm that may complicate the pharmacological treatment of such infections (Williams et al., 2009).

Infection by NTM was first reported in a patient with CF in 1980 (Boxerbaum, 1980). Few infections were described before 1990, but in the last 20 years, NTM have emerged as new pathogens in CF (Griffith, 2003; Olivier et al., 1996). This increase may be due to several factors: greater survival of patients with CF, increasing their environmental exposure; more aggressive therapies, which facilitate susceptibility to infection; improved microbiological diagnostic methods; and better interaction between clinicians and microbiologists. In 1997, the American Thoracic Society (ATS) published a Consensus Statement that identified CF as a risk factor for NTM pulmonary disease in HIV-seronegative patients and provided recommendations for laboratory and clinical diagnosis of NTM infection (Official Statement ATS, 1997).

In summary, NTM are common in patients with CF but neither person to person nor nosocomial acquisition explain their high prevalence. Clinical significance of NTM is incompletely defined but patients with these organisms should be monitored with repeated sample cultures (Olivier et al., 2003).

2.2 Pathogenesis

Patients with CF have abnormally viscous and thickened airway and gastrointestinal secretions as a result of a defect or decrease in the transmembrane conductance regulator protein or gene product which regulates chloride and liquid secretions across epithelial surfaces and resorption of sodium and liquid. These thick respiratory secretions occlude the airways and ductal lumens leading to recurrent pulmonary infections, pancreatic insufficiency and intestinal obstruction (Welsh, 1990).

NTM, which enter mainly through the respiratory tract, are phagocytosed by macrophages and survive and reproduce within patients until symptomatic infection occurs. The disease manifestations depend on the immune cellular response and the possible granulome formation; hence, its difficult eradication and its tendency to persistence or recurrence (Morales et al., 2011).

2.3 Frequency and distribution

Prevalence rates of NTM infections in patients with CF are variable, due mainly to the few multicenter studies (Olivier et al., 2003; Roux et al., 2009; Mussaffi, et al., 2005; Levy et al., 2008) and their diversity in the methodology used, since some refer to patients who had at least one positive culture and others to those who met disease criteria following the ATS recommendations from 1997 (Official Statement ATS, 1997) or 2007 (Griffith et al., 2007), obtaining fewer cases.

Infection data vary between 2 and 30%, with an average of 13 to 15%. These differences are due to the number of cases reported in each study - the most numerous being Olivier et al, 1186 and Roux et al, 1582-, the geographical location - with differences between continents (America greater reports) and within countries (the highest prevalence values were those reported for coastal states) - and the age of the patients included. In general, more isolates may be found in teenagers (10-20%) and young adults with CF (American Academy of Paediatrics, 2006).

Regarding age, both multicenter studies and general observations, suggest that NTM infections occur as a complication in adolescents and young adults (10 to 25 years old) although with small differences between mycobacteria, since the rapidly growing can be acquired at almost any age and *M. avium complex* (MAC) in older patients (Roux et al., 2009). Some do not find significant differences among sex (Olivier et al., 2003), while as others describe more cases in women than men (Roux et al., 2009).

2.4 Isolated NTM

In relation to the isolated species of NTM, most authors agree that both, MAC and the rapidly growing mycobacteria (RGM), are the most frequent, accounting around 80% (Roux et al., 2009). Infection is usually caused by a single species and exceptionally by a mixture of two mycobacteria.

MAC is composed of a group of slow, fastidiously growing mycobacteria that includes *M. avium*, *M. intracellulare* and unnamed genetically related species. It ranks first in North America with 72% of the isolates, mainly *M. avium* (Olivier et al., 2003) but is second and third in frequency in other series. *M. abscessus*, a member of the RGM (culture growth in less than 7 days) seems to prevail in Western Europe (Roux et al., 2009; Jönsson et al., 2007; Sermet-Gaudelus et al., 2003) and Israel (Levy et al., 2008), where *M. simiae* is also frequent. (Figure 1).

M. abscessus may be confused due to its different classification in time, since it was first included within *M. chelonae* group, then as a different species by itself, and more recently as part of the *M. abscessus complex* (MABSC), together with *M. massiliense* (Adékambi et al., 2004) and *M. bolletii* (Adékambi et al., 2006).

The prevalence of these two groups - MAC and MABSC - varies with age. MABSC may appear at any age, but most frequently in teenagers age 11 to 15 years old, while as MAC is more common in young adults aged 20 to 25 (Pierre-Audigier et al., 2005; Rodman et al., 2005). In all series, there is a minority group of varied mycobacteria named "others", which includes *M. gordonae* (possible contaminant), *M. fortuitum*, *M. kansasii*, *M. simiae*, *M. peregrinum*, *M. malmoense*, all of them infrequent and poorly representative.

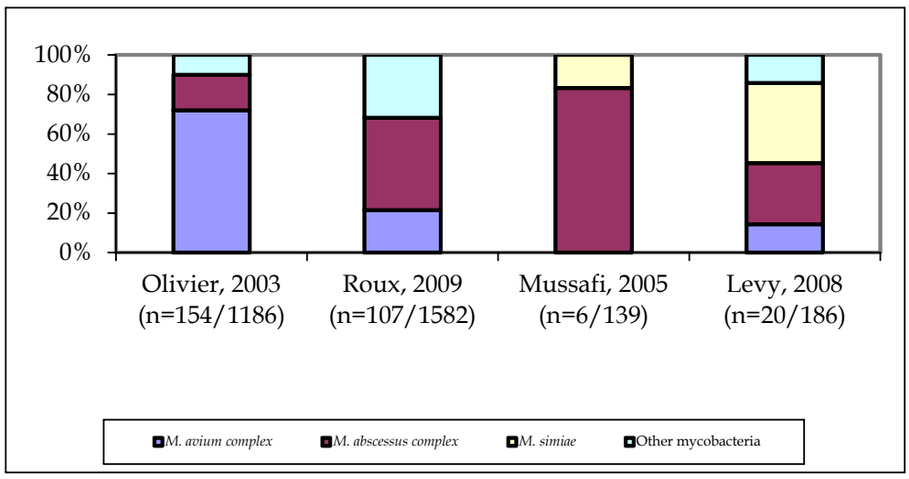

Fig. 1. Frequency of NTM species isolated in CF patients according to several studies (Olivier et al., 2003; Roux et al., 2009; Mussaffi et al., 2005; Levy et al., 2008).

2.5 Transmission

Given the ubiquitous nature of NTM, the port of entry for infection may be diverse: cutaneous, oropharyngeal mucosa, digestive or respiratory. NTM are frequently present in tap water and shower heads, where they remain viable in aerosols (Parker et al., 1983). Some, such as MAC, are resistant to chlorine and ozone, as already mentioned. Most infections remain near the port of entry but may also disseminate to other organs if the patient is immunocompromised. There is no evidence of person-to-person transmission of NTM infection. Therefore, no patient isolation but only universal precautions are necessary. Infections usually present as single cases, but outbreaks have also been reported, some of them by molecular techniques, secondary to a common focus neither identified nor corrected (Wallace et al., 1998; Kim et al., 2007; Viana-Niero et al, 2008).

2.6 Risk factors

In the last ten years, several authors have sought the relationship between NTM infection and different aspects of the patients, the disease or the microorganisms involved, describing some predisposing or risk factors (Table 1). (Olivier et al., 2003; Roux et al., 2009; Mussafi et al., 2005; Levy et al., 2008).

Age	Sweat chloride	*P. aeruginosa*
Race	Insulin-requiring diabetes	*S. aureus*
Sex	Pancreatic enzymes use	*Aspergillus spp.*
BMI	Steroids	Sputums cultured
Place of residence	Severe genotypes	FEV1

BMI, body mass index; FEV1, forced espiratory volume in the 1st second.

Table 1. Predictors of NTM infection in CF patients

Olivier et al, compared CF patients with and without positive culture for NTM. The culture-positive patients were significantly older (26 versus 22, p<0,001), had higher FEV1 (60% versus 54%), higher frequency of *S. aureus* (43% versus 31%) and lower frequency of *P. aeruginosa* co-infection (71% versus 82%). Another related factor was the body mass index (BMI). There were no significant differences between *M. abscessus* and *MAC*. When several risk factors are present (for example, age, FEV1 and *S. aureus* co-infection) the probability of having NTM is 50-fold higher.

Roux et al, found nuances in age between the two groups of mycobacteria, as previously mentioned, suggesting that this difference may be due to the different degree of virulence of these mycobacteria. Women were more frequently affected, a fact not previously referenced. Little is known about the clinical significance and the risk factors of the new species of RGM, apart from their tendency to produce cutaneous lesions. A recent study has also found clinical differences between *M. maxiliense* and *M. abscessus* infection (Zelazny et al., 2009).

Levy et al, found that the presence of *Aspergillus* spp. in sputum and the number of the sputum specimens processed for mycobacteria were the most significant predictors for isolation of NTM.

Mussafi et al, have found a relationship between pulmonary *M. abscessus* disease and allergic bronchopulmonary aspergillosis and corticosteroid therapy. Eradication of infection was more difficult in these circumstances.

In addition to the risk factors analyzed, we must not forget that, back in 1997, the ATS published a consensus document identifying CF as a risk factor itself for NTM infection, providing extensive information about it.

3. Clinical manifestations and radiology

Clinical manifestations, together with radiological findings and the microbiological cultures that will be commented further on, constitute the three basic pillars for the diagnosis of NTM disease (Table 2) (Griffith et al., 2007**)**.

CATEGORY	REQUIREMENTS
Clinical findings	Pulmonary symptoms Exclusion of other diagnoses
Radiological findings	Chest X-ray: nodular or cavitary images; or HRCT: multifocal bronchiectasis with multiple small nodules.
Bacteriological findings	Sputum: 2 or more positive cultures or BAS or BAL: ≥ 1 positive culture or lung biopsy: granulomatous inflammation or positive staining for AFB together with one or more positive cultures (biopsy, sputum, BAS; BAL)

Table 2. ATS / IDSA criteria for the diagnosis of lung disease caused by NTM

Diagnosis requires: all the clinical criteria + 1 radiological criterion + 1 bacteriological criterion. ATS: American Thoracic Society; IDSA: Infectious Diseases Society of America; NTM: Non-tuberculous Mycobacteria; HRCT: high-resolution computerized tomography; BAS: bronchoalveolar secretions (aspirate); BAL: bronchoalveolar lavage; AFB: acid-alcohol resistant bacilli.

Lung infections in general tend to have non specific symptoms (cough, dyspnea, weight loss, increased expectoration, sometimes hemoptysis) and chest radiographic findings that vary from innocuous or no findings, to infiltrates or nodules, sometimes cavitated, (Morales et al., 2007) with HRCT scanning chest abnormalities - nodules and/or multifocal bronchiectasis (Hayes, 2005).

The chest radiography in NTM pulmonary disease caused by RGM is likely to show multilobular, patchy, reticulonodular or mixed interstitial and alveolar infiltrates with upper lobe predominance and cavitation in only 15% of cases (Griffith et al., 1993, Daley & Griffith, 2002) (Figure 2).

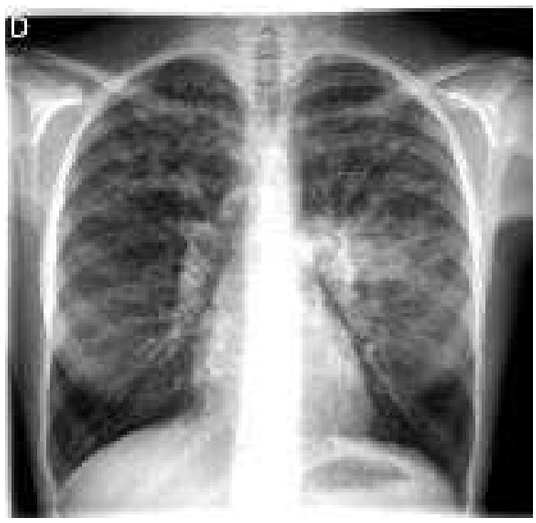

Fig. 2. Chest radiography of *M. abscessus* infection in CF patient.

The most common radiographic changes in MAC infection are cavitary disease and fibronodular bronchiectasis (Goo & Im, 2002). Cavities are finer and surrounded by less parenchymal opacification than in the case of tuberculosis (TB) (Erasmus et al., 1999). Bronchiectasis appear preferentially in the middle lobe and lingula (Lynch et al., 1995). Pleural effusion is not common. In HRCT scanning, the presence of bronchiectasis and multiple small nodules are predictive of MAC lung disease (Maycher et al., 2000).

Cutaneous manifestations may vary from small single nodes to ulcers, sometimes coincident with skin disruptions such as wounds, burns, surgical incisions, catheter implantation sites and so forth. These cutaneous lesions are very important in lung transplant recipients (LTx), since they can be the first sign of dissemination (Taylor & Palmer, 2006, Morales et al., 2007).

In isolated cases and, especially, in immunossuppressed patients, including transplant recipients, infection may diseminate to other organs, like from skin to lungs, intestine or other sites.

3.1 Clinical course and evolution

Clinical course is similar to that of TB, with insidious and slow progression that requires combined treatment for various months. This is difficult to comply due to its adverse effects and interactions with other drugs. Initial clinical and microbiological response is usually good but, even after complete compliance, with apparently successful therapy, there is a tendency to persistance and relapse (Mussaffi et al., 2005). NTM affects pulmonary function and chronic lung infection in CF patients is the main cause of morbidity and mortality (Esther et al., 2010). There is no data of mortality directly associated to mycobaterial infection, since these patients usually suffer simultaneous infections by different microorganisms (Figure 3).

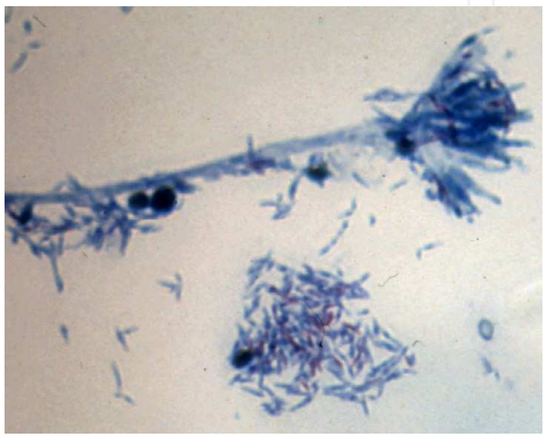

Fig. 3. Modified Ziehl-Neelsen stain showing co-infection of *Mycobacterium* spp. with *Aspergillus* spp. in a CF patient.

4. Microbiological diagnosis

Samples that reach the laboratory are mainly of respiratory origin (sputum, pleural fluid or its biopsy specimen, BAL and lung biopsy specimen). They can also be from skin or other locations if infection is disseminated.

With the staining methods - Ziehl-Neelsen or auramine fluorescence -, there are features on the AFB in terms of their number, shape, and grouping, that characterize the different NTM.

Bacterial overgrowth, especially with *P. aeruginosa*, is problematic and leads to difficulties in isolating mycobacteria from respiratory secretions and sputum. Therefore, together with the classical decontamination process using 0.25% N-acetylcysteine and 1% NaOH, addition of 5% oxalic acid is recommended (Whittier et al., S. 1997)

Samples are cultured in solid (Löwenstein-Jenssen or other) and liquid media (radiometric BACTEC 460 and nonradiometric BACTEC 9050 and 960, Becton Dickinson, or other). Some NTM have specific requirements for culture, such as temperature (MAC 42ºC) and time (RGM grow in less than 7 days, whereas others in 10-14 days).

Colonies may be identified phenotypically in most cases (Kent & Kubica, 1983, Metchock et al., 1999) and be confirmed by molecular typing methods, using commercial RNA/DNA probes (AccuProbe, GenProbe, San Diego, Ca) (Cousins et al.,1996, Wallace et al., 1998) and

other techniques (Zhang et al., 1997). The different species included in the MABSC are distinguished by *rpoB* sequencing (AdéKambi et al., 2003). Molecular identification of the mycobacteria also helps in differentiating between relapse and reinfection, and in determining whether an outbreak is secondary to a common origin or not.

Chromatography techniques (Butler & Guthertz, 2001) are less used, since they are more complex and less precise (Leite et al., 2005). Serologic diagnosis, such as determining the presence of IgG immunoglobulin against antigen A 60 (Oliver et al., 2001), has been discarded due to its low sensitivity and specificity (Pottumarthy et al., 2000). Tuberculin skin testing may be positive in patients infected with NTM, since *M. tuberculosis* shares antigens with various species, but generally the induration induced is less than 10 mm in diameter (Field & Cowie, 2006). Techniques based on lymphocyte interferon gamma (IFN-γ) production have been developed and can be useful in distinguishing between infection by *M. tuberculosis*, NTM, or BCG vaccination (Scholvink et al., 2004).

There is controversy over the systematic use of susceptibility testing of NTM, since there is no clear correlation to the clinical therapeutic response. At least for clarithromycin in the case of MAC disease there are some recommendations (Wayne, 2000). RGM are intrinsically resistant to classic antituberculous drugs and have variable antimicrobial susceptibility profile. Clinically significant isolates should be tested against amikacin, cefoxitine, ciprofloxacin, clarithromycin, doxycycline, imipenem, trimethoprim/sulfamethoxazole and recently, linezolid (Woods, 2000). Synergy studies with two or more antibiotics can also be done. Methods used include dilution, diffussion (E-test) and automated techniques.

5. Treatment and evolution

5.1 General aspects

No guidelines exist for the treatment of NTM pulmonary diseases in the CF population. Given the natural tendency of these bacteria to seek refuge in macrophages and to the fact that *in vitro* susceptibility tests do not show true antibiotic concentration, combined therapy may favour synergy and minimize the appearance of resistance. It is difficult to determine a treatment of choice since experience is limited and results are variable, and *in vitro* tests do not always correlate to *in vivo* response. Duration of treatment is also variable, depending on the NTM to be treated, the severity and extent of disease, and the clinical and immune status of the patient. In any case, treatment compliance is difficult since it is long lasting, antibiotics have adverse effects and interactions with other drugs, in particular with immunesuppressors in the case of transplant recipients. A close clinical and microbiological surveillance of the patients is necessary, to watch out for possible relapses, dissemination or risk of graft rejection in the case of transplantation (Morales et al, 2007; Morales et al., 2011).

We will focus on the treatment of MAC and *M. abscessus*, the most frequent NTM in CF patients. Treatment of the less common mycobacteria requires individualized considerations, keeping as a basic principle the combination of two or three active drugs.

5.2 Treatment of MAC

Transmission of the mycobacteria included in the MAC is varied, but mainly through birds and water (Marras et al., 2005). Infection has been related to recreational hot-tubs and can

cause a hypersensitivity pneumonitis like syndrome in exposed patients (Embril et al., 1997; Rickman et al., 2002; Hanak et al., 2006).

Mycobacteria included in the MAC are resistant to first-line antituberculous drugs – rifampicin, isoniazid and streptomycin - except for ethambutol, and are usually susceptible to amikacin and macrolides, in particular clarithromycin.

Initial treatment includes ethambutol, clarithromycin or azithromycin and a third drug according to susceptibility test results. Duration of treatment is from 6 to 9 months for small lesions and up to 12-24 months in case of dissemination. Combination of ethambutol, a macrolide and rifampicin has been used successfully due to their synergism and good tolerance (Field & Cowie, 2003). Some authors recommend maintenance of the macrolide 12 more months once patients convert to negative, thus reducing the number of relapses (ATS, 1997). The importance of macrolides relies on the intracellular penetrance of both, the antibiotic and the bacteria. First recommendations included clarithromycin (Field & Cowie, 2003) and then azithromycin (Griffith et al., 2001), but always in combination and not in monotherapy as initial drugs.

M. avium is the most common cause of immune reconstitution inflammatory syndrome caused by NTM (Field & Cowie, 2006). IFN-γ is a macrophage activator in response to mycobacteria. Patients with disseminated MAC infection, with relapses or poor prognosis, respond favorably to inhaled IFN-γ (Holland et al., 1994; Hallstrand et al., 2004).

In exceptional cases, when infection is localized and with persistent lung affection, surgery has been applied. Post-operative morbidity and complications that include hemorrhages, bronchopleural fistula and empyema are possible.

5.3 Treatment of *M. abscessus* and other RGM

This group of mycobacteria is ubiquitous and can survive in adverse conditions. They can grow in any culture media used in bacteriology in less than 7 days, with the risk of not being evaluated or being considered as contaminants. Although it includes various species, the most relevant and virulent in CF patients is *M. abscessus*. This mycobacterium can cause skin infection, lung disease or even disseminate. Its treatment is difficult due to its multiresistance, not only to the classic, already mentioned antituberculous drugs, including ethambutol, but also to ampicillin, amoxicillin-clavulanate, cefoxitin, ciprofloxacin, erythromycin, sulfamethoxazole and tobramycin. It is universally susceptible to amikacin, and a recommended treatment is the combination of amikacin, clarithromycin and imipenem for 6 to 9 months (Yang et al., 2003). There can be initial improvement, but relapses are very frequent, in which case, therapy should be extended and/or a drug should be changed according to susceptibility testing. Other alternative therapeutic agents include the new oxazolidinone, linezolid, that is active against RGM (Wallace et al., 2001) with good therapeutic results (Morales et al, 2007). An open line includes the new quinolones gatifloxacin and moxifloxacin.

In the presence of big lung abscesses, a very rare presentation, surgical drainage might be necessary and can potentially lead to extrapulmonary seeding of the infecting mycobacteria and be an added risk if lung transplantation is needed.

Recommended suppressive therapy includes oral clarithromycin and aerosolized amikacin (Cullen et al., 2000; Colin AA, 2000). Monotherapy must always be avoided, since the most common cause of macrolide resistance is the use of clarithromycin as single drug in patients with CF and disseminated cutaneous infection (Wallace et al., 1996).

6. Prophylaxis

Given the extensive and varied presence of NTM in the environment and their variable susceptibility to antibiotics, the inevitable environmental exposure of CF patients and the lack of person-to-person transmission, primary chemoprophylaxis is not indicated. The only situation in which clarithromycin or azithromycin would be recommended is in HIV positive patients over 6 years of age and with a CD4 count of less than 50/μL, with risk of MAC infection (American Academy of Pediatrics, 2006).

Clinical and radiological monitoring is important, including intensive and selective search for NTM, in pulmonary samples from suspected foci, especially in young adults with impaired lung disease, *Aspergillus* spp. and steroid treatment.

On the other hand, it is important to take into consideration the life style of the patient, with a watchful attitude towards surrounding environment, being aware that it constitutes an unavoidable but reducible risk. Recently, a practical and excellent guideline in this regard has been published (Avery et al., 2009)

7. Peri-transplant considerations

7.1 Pre-transplant

As has been discussed, NTM infections must be kept in mind in the differential diagnosis of any lung disease in CF patients, especially when approaching an indication of LTx. Identification and *in vitro* susceptibility of the mycobacteria are required to ensure proper treatment and to achieve complete recovery before transplantation.

In particular, so difficult is the treatment of *M. abscessus* infection, that it has been considered a strong relative contraindication to LTx (Orens et al., 2006). Recently, Gilljama et al., reported their experience in three double LTx CF patients with ongoing therapy, and a fourth with recent treatment for *M. abscessus* lung infection. The first three developed skin infection and abscesses. Recovery was finally accomplished and pulmonary function was re-established after a prolonged 7 years long follow-up. With this, they conclude that LTx is feasible but may involve severe complications.

7.2 Post-Transplant

Infection and graft rejection in organ recipients are the two main causes of morbidity and mortality. Transplant may lead to the reactivation of a previously undetected infection, to its dissemination or to its initial onset. NTM have emerged as important pathogens in these patients, especially in LTx, causing pulmonary and extrapulmonary infections (Malouf & Glanville, 1999). These bacteria have also been identified as a potential cause of graft dysfunction and mortality by themselves or together with other opportunistic pathogens, which is a very common situation. In particular, infection by *M. abscessus* may be fatal

(Sanguinetti et al., 2001; Fairhurst et al., 2002) or resolve even when disseminated (Morales et al, 2007)

7.3 Donor

Even though we have not found any documented case of NTM infection in the organ donor, mycobacteriosis would be hypothetically a relative contraindication for transplantation. Systematic search of NTM in the bronchoaspirate of donors must be done to introduce treatment as soon as possible.

8. Final considerations

- Life expectancy and quality of life have improved in CF patients and their treatments have turned/become more aggressive.
- NTM cause frequent pulmonary infection especially related to advancing age and lung function deterioration. *M. abscessus* and MAC are the most frequently isolated NTM.
- Early clinical suspicion is important. The routine or selective mycobacterial search according to known risk factors is an important decision. No comparative studies indicate which option is the most effective.
- NTM must be decontaminated, cultured and typified thoroughly, since species identification is crucial for treatment and other clinical considerations.
- When a NTM is isolated from a sputum sample, both clinician and microbiologist will determine whether it should be considered a contaminant, colonization or infective agent, with the consequent attitude.
- It is important to perform correctly the *in vitro* susceptibility tests and to try new antibiotics against NTM.
- Ensure treatment compliance, since it will prevent the emergence of antibiotic resistance, infection relapse and poor outcome.
- Since there are no primary chemoprophylaxis recommendations, patients should be oriented to a healthy life style.
- If the moment for the lung transplant arrives, all the previously mentioned considerations should be taken very seriously, since the probability for infection and dissemination are greater due to the immunosuppressive therapy.
- These processes pose significant social and health burdens (school absenteeism, work and family limitations, doctor visits, hospitalization, diagnostic testing and treatment) with the resulting economic impact.

Future should rely on early suspicion and adequate search for NTM, the use of modern microbiological techniques applied directly on the sample, safer and more active antibiotics, research of mycobacterial virulence factors and the determinants for persistence of infection.

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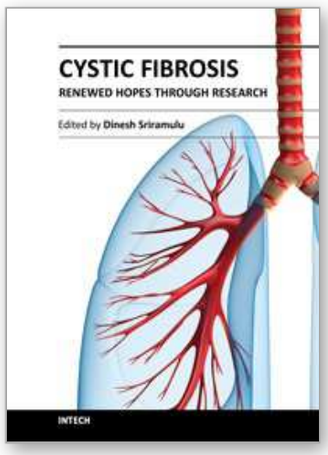

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Living healthy is all one wants, but the genetics behind creation of every human is different. As a curse or human agony, some are born with congenital defects in their menu of the genome. Just one has to live with that! The complexity of cystic fibrosis condition, which is rather a slow-killer, affects various organ systems of the human body complicating further with secondary infections. That's what makes the disease so puzzling for which scientists around the world are trying to understand better and to find a cure. Though they narrowed down to a single target gene, the tentacles of the disease reach many unknown corners of the human body. Decades of scientific research in the field of chronic illnesses like this one surely increased the level of life expectancy. This book is the compilation of interesting chapters contributed by eminent interdisciplinary scientists around the world trying to make the life of cystic fibrosis patients better.

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