4.3.6 Non-Tuberculous Mycobacteria

Authors: Jesica Mazza-Stalder, Oriol Manuel, Elizabeth Tullis, Laurent P Nicod

1. INTRODUCTION

- Non-tuberculous mycobacteria (NTM) are frequently found in CF patients. NTM were previously considered innocent bystanders but, nowadays, their presence in the airways of CF patients is worrisome, and considered to cause potentially serious lung damage. They emerged as some of the most difficult and challenging pathogens to treat in CF.
- NTM are ubiquitous in soil and water. They can be found in all types of water such as drinking water distribution systems, hot recirculating water in jacuzzis, swimming pools, and particularly in nebulizers, showerheads and bronchoscopes.
- Unlike *M. tuberculosis*, NTM need the presence of structural lung damage to cause disease and, in this regard, the CF lung is an ideal host for opportunistic infection.
  - In addition to the impaired mucociliary clearance and the continuous airway inflammation that favor the development of NTM infection, CFTR dysfunction itself may predispose to NTM infection.
- The diagnosis of NTM-pulmonary disease (NTM-PD) is based on specific clinical, radiological and microbiological criteria.
- **Table 1** summarizes some important points concerning NTM in CF.

Table 1: Important points concerning NTM in CF

With the aging of the CF population, NTM have become more prevalent.
Routine screening for NTM in sputum samples should be performed at least annually in all CF patients.
NTM should be searched specifically: - in cases of unexpected clinical or functional decline, or when NTM-PD is suspected on imaging studies - before prescribing long-term azithromycin - before listing for lung transplantation
It is important to identify *M. abscessus* correctly at the subspecies level because susceptibility to antibiotics differs.
Recognition of inducible macrolide resistance conferred by expression of a novel *erm* gene may help adapt antibiotic regimens.
Chronic use of azithromycin as part of the CF regimen should be avoided in patients with NTM, to prevent the emergence of resistance (although a macrolide may be used as part of a multidrug regimen for NTM-PD).

(continued)

No evidence is available on the long-term benefits of eradication regimens for recently acquired *M. abscessus* in an asymptomatic patient. Eradication should be considered on a case-by-case basis, balancing the potential adverse effects of anti-NTM treatment and the risks of chronic NTM colonization.
Making the diagnosis of NTM-PD does not necessarily mean that anti-NTM therapy should start. For an individual patient, the decision should be based on the potential risks and benefits.
Presence of NTM-PD in CF is not an absolute contraindication for lung transplantation referral but, before listing, it is recommended to treat NTM and attempt to decrease the bacterial load.
Concerning isolation policies in CF centers, and while awaiting more research results regarding NTM transmission, it is recommended to apply cross-infection control measures according to infection control CF guidelines.

2. PREVALENCE

- In the recent years, prevalence of NTM in sputum samples of CF patients has increased. This may represent true increase in prevalence and/or increased detection rates due to routine, standardized screening.
- In the 80s the prevalence was rather low (around 1.3%) and by the 90s the reported prevalence was already increasing to 6.6%. Since 2010, the CF Foundation Patient Registry has tracked NTM prevalence which was estimated at around 10% in 2010 and 10.8% in 2011.

3. NTM SPECIES IN CF

- The NTM species found more frequently among CF patients are Mycobacterium Avium Complex (MAC) *and M. abscessus* (with most frequent subspecies: *abscessus, massiliense* and *bolletii)*.
- *M. xenopi*, *M. kansasii* and *M. szulgai* are found in CF patients less frequently. If present, they should be considered pathogens.
- Among the other NTM species found in CF some are nonpathogenic:
  - *M. gordonae* can represent contamination rather than colonization.
  - *M. fortuitum* rarely affects the lungs and more frequently affects the skin, soft tissue and bones.
  - *M. terrae* and *M. simiae* have been described in Israeli CF patients.

4. RISK FACTORS FOR NTM ACQUISITION

- Potential risk factors for NTM acquisition in CF are summarized in **Table 2.**
- The only clear link between CF and NTM acquisition is **older age**. A French study shows a relatively low prevalence of NTM (about 5%) until 14 years of age, a sharp increase after this age and a higher prevalence (about 15%) at older ages (15 to 24 years). Prolonged exposure to mycobacteria from the environment may be a possible explanation.
- Evidence for the role of other factors in NTM acquisition is inconclusive.

Table 2: Potential risk factors for NTM acquisition in CF

Risk factor	Evidence	Comment / Suggested mechanism
Older age (notably for MAC)	Consistent	Prolonged exposure to environmental NTM
CFTR dysfunction	Inconclusive	High rate of CFTR mutation heterozygocity in non-CF patients with NTM
Aspergillus fumigatus ABPA	Inconclusive	The presence of *A. fumigatus* has been associated with NTM-positive cultures Use of systemic corticosteroids in ABPA
St. aureus, *Ps. aeruginosa,* *S. maltophilia*	Inconclusive	Some studies have shown that NTM-positive patients were colonized more often by *S. aureus* and less often with *P. aeruginosa.* However, other studies showed higher rates of *P. aeruginosa* infection in NTM-positive patients. Data for *S. maltophilia* are also inconclusive.
Corticosteroids (oral)	Inconclusive	Data showing a positive, a negative or no association with NTM acquisition
Corticosteroids (inhaled)	Inconclusive	Data from non-CF patients suggest that inhaled corticosteroids may predispose to NTM acquisition
Macrolides (long-term use)	Inconclusive	One in vitro study showed that azithromycin could impair the intracellular killing of mycobacteria within macrophages by inhibiting autophagy. However, epidemiological data showed a lower prevalence of NTM infection among patients receiving chronic macrolides
Inhaled antibiotics	Inconclusive	Changes in lung flora
GERD and acid suppression treatment	Inconclusive	High prevalence of GERD in non-CF patients with MAC disease. High prevalence of GERD in CF.
Cross infection	Limited but strong	Reported for *M. abscessus* (see below)

ABPA: Allergic bronchopulmonary aspergillosis, GERD: gastroesophageal reflux disease

5. TRANSMISSION

- Traditionally, we used to believe that transmission from person to person did not exist and, until recently, segregation was not necessary.
- However, recent data came to challenge this dogma.
  - Strong evidence of transmission of *M. abscessus* subsp. *massiliense* among CF patients was reported in a UK CF center. Among 31 patients, 9 shared a genetically near identical strain of *M. massiliense*.

- The CF Foundation and the European CF Society (ECFS) recommend **implementation of infection control guidelines to minimize the potential microbial (including NTM) cross-infection among individuals with CF** (see also Chapter "*Infection Control*")**.**

6. SCREENING FOR NTM

- **Table 3** summarizes screening recommendations for NTM.

Table 3: Screening recommendations for NTM

When to perform	Annually in all CF patients
	Before starting immunomodulatory treatment with macrolides (i.e. NTM presence should always be excluded before introducing long-term azithromycin)
	Before listing for lung transplantation
How to perform	Acid Fast Bacilli (AFB) smear and cultures from spontaneous sputum is the standard screening method Information on the "diagnosis of CF" should be transmitted to the laboratory (different processing compared to non-CF samples, to prevent overgrowth of common CF pathogens on the plate).
Comments on other diagnostic approaches (not recommended for screening)	Hypertonic saline induced sputum is not necessary, unless the patient does not expectorate spontaneously and has evidence of NTM-PD*
	Bronchoscopy, bronchoalveolar lavage and bronchial aspirates are valid tools in patients suspected of having NTM-PD*
	Transbronchial biopsies are NOT recommended because they can cause bleeding or pneumothorax
	Skin testing, serological assays or swabs are NOT recommended

*NTM-PD: NTM-pulmonary disease

7. NTM-PULMONARY DISEASE (NTM-PD)

7.1 Diagnosis of NTM-pulmonary disease

- The diagnostic criteria for NTM-PD are summarized in **Table 4**. According to the recent guidelines published by the CF Foundation and the ECFS, the ATS/IDSA criteria for diagnosis of NTM-PD used in non-CF patients can also be applied in individuals with CF.
- The symptoms of mycobacterial lung disease in CF patients may be subtle, insidious and often confounded with other bacterial, viral or fungal infections. Night sweats, minor hemoptysis, low-grade recurrent fever and a rapid decline of lung function associated with repeated microbiological documentation of mycobacteria in sputum samples may indicate that symptoms are due to mycobacterial infection.
- Not all CF patients infected with NTM react the same way: in some patients, the presence of NTM may lead to severe lung function decline with invasive disease, whereas in others it may be associated with little clinical deterioration.

- High-resolution CT (HRCT) findings of NTM-PD may overlap with CF-related pulmonary lesions. Although not specific for NTM, cavities accompanied with areas of consolidation, peripheral micronodules, tree in bud branching zones or progressive fibrosis and atelectasis may be observed in NTM-pulmonary disease. In this regard comparison with a previous HRCT may be helpful **(Figure 1)**.

Figure 1: HRCT scan showing multiple upper lobe cavities in a CF patient with *M. abscessus*

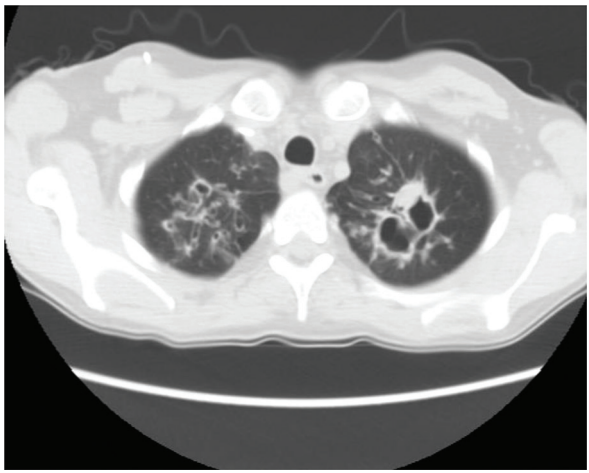

Table 4: Diagnostic criteria for NTM-pulmonary disease and suggested strategies (adapted from[1,2])

Diagnostic criteria
1) Clinical (all required)
a) Compatible symptoms*[a]
b) Compatible HRCT findings*[b]
c) Exclusion of other diagnoses
2) Microbiological (one of the following required):
a) positive culture results from at least two expectorated sputum samples OR
b) positive culture results from at least one bronchial wash or lavage OR
c) lung biopsy with mycobacterial histopathological features (i.e. granulomatous inflammation or AFB) and at least one NTM-positive sputum or bronchial wash culture OR
d) lung biopsy with mycobacterial histopathological features (i.e. granulomatous inflammation or AFB) and NTM-positive culture

(continued)

Strategies

A) Specialized advice should be obtained when infrequently encountered NTM or NTM usually representing environmental contamination are recovered

B) If the patient doesn't fulfill the diagnosis of NTM-PD, consider follow-up until diagnosis is confirmed or ruled out

C) If the patient fulfills the diagnosis of NTM-PD, consider treatment

AFB: acid-fast bacilli, NTM-PD: NTM-pulmonary disease

*a Such as night sweats, minor hemoptysis, low-grade recurrent fever and a rapid decline of lung function (they are not specific for NTM)

*b Such as cavities accompanied with areas of consolidation, peripheral micronodules, tree in bud branching zones or progressive fibrosis and atelectasis of the affected areas (they are not specific for NTM)

7.2 Decision to treat

- In patients with recently acquired NTM or in those who are colonized with NTM but who do not fulfill the criteria for NTM-PD, it is challenging to define which patient will deteriorate and may benefit of a treatment. For this reason, eradication treatment is usually not recommended (lack of evidence).
- Patients fulfilling the diagnosis of NTM-PD or present a decline of FEV_1 attributed to NTM-PD and not other diagnoses should be treated in the light of potential risks and benefits.
- **The decision to treat must include an analysis of the following elements (see Table 4):**
  - **Positive samples for NTM** especially if the mycobacterial load increases
  - **Clinical symptoms, decline of FEV_1 and radiological progression (with appearance of cavitation, bronchiectasis or micronodules) not attributed to an alternative diagnosis.** The later may be challenging to exclude due to the similar symptoms observed during a CF exacerbation by other pathogens such as *P. aeruginosa*, *S. aureus, B. cepacia*, fungi or viruses.
- **The optimal time-point for anti-NTM treatment initiation may be challenging** and needs clinical expertise in both CF and mycobacterial lung diseases.

7.3 Treatment of NTM-PD

- No randomized controlled trials exist to guide NTM treatment in CF patients. Thus, most treatment recommendations are not evidence-based but rather reflect expert opinion.
- **Tables 5-7** summarize recommended treatment regimens. Drug doses and pharmacological considerations are summarized in **Table 8**.
- **Standard therapy must include 3 or more drugs to prevent the development of drug resistance.**
- **The recommended treatment duration for NTM-PD is 1 year after culture conversion but patients who fail to convert and lung transplant patients may benefit from long-term suppressive antibiotic treatment.** If cultures remain positive after 1year of anti-NTM treatment (culture non-conversion), pausing of NTM treatment can be considered under a close clinical follow-up.

- **Antimicrobial resistance should be assessed with in vitro drug susceptibility testing (DST).** This applies particularly for macrolide susceptibility of MAC, since certain species of *M. abscessus* can show inducible resistance to macrolides (*M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *bolletii*). The presence of macrolide resistance is predictive of worse clinical outcomes.
- There is a risk of subtherapeutic drug levels in CF patients and adjustments with therapeutic drug monitoring (TDM) may be helpful **(see also Chapter "*Therapeutic drug monitoring*")**.

7.3.1 Treatment of Mycobacterium avium complex (MAC) (Tables 5 and 8)

- **MAC includes *M. intracellulare, M. chimaera and M. avium***. It represents the most common species isolated in CF (72% of the isolates).
- MAC pulmonary disease in CF patients can present with two distinct types:

  a) the bronchiectatic type with micronodules, bronchiectasis and tree in bud infiltrates or

  b) the more severe, fibro-cavitary type with extensive, large lung cavities.

7.3.2 Treatment of Mycobacterium abscessus (Tables 6 and 8)

- Rates of multidrug resistant *M. abscessus* are increasing and, in some centers, they are surpassing MAC.
- New evidence shows that rapidly growing mycobacteria, like *M. abscessus*, can produce a biofilm with a "cord formation growth pattern" and conversion into a "rough variant" which has a more aggressive character, similar to that found in *M. tuberculosis* (TB).
- **It is important to identify *M. abscessus* correctly at the subspecies level because susceptibility to antibiotics differs.**
  - **The new taxonomy divides *M. abscessus* in 3 different subspecies: 1) *M. abscessus* subsp. *massiliense*, 2) *M. abscessus* subsp. *bolletii*, 3) *M. abscessus* subsp. *abscessus*.**

Table 5: Treatment options for MAC in adult CF patients (adapted from[1-3])

1) Clarithromycin or azithromycin
2) Rifampicin or Rifabutin
3) Ethambutol
4) For extended cavitary disease, in patients with smear positive respiratory tract infections, in severely ill patients or in MAC resistant to macrolides: consider adding IV amikacin (for 6 months if tolerated for macrolide resistant MAC). If IV amikacin is not well tolerated, after the first month of treatment, aerosolized amikacin may be considered.
5) Liposomal encapsulated amikacin therapy is under study for MAC disease refractory to macrolide treatment

Treatment duration: 1 year after culture conversion (i.e. until cultures remain negative for 12 months). If cultures remain positive after 1year of anti-NTM treatment (culture non-conversion), pausing of NTM treatment can be considered under a close clinical follow-up.

- A deletion in the erm41 gene of *M. abscessus* subsp. *massiliense* confers to this subspecies susceptibility to macrolides, whereas *M. abscessus* subsp. *abscessus* and *M. abscessus* supsp. *bolletii* have a full length functional erm41 gene that confers inducible resistance to macrolides.

Table 6: Treatment options for M. abcessus in adult CF patients (adapted from[1-3])

Intensive Phase

1) Clarithromycin or azithromycin
2) Amikacin IV
3) One or more of the following (guided by in-vitro susceptibility testing):
   a) Imipenem
   b) Cefoxitin
   c) Tigecycline
   d) Clofazimine (may be considered during the intensive phase since it is administered orally and is generally well tolerated)

Treatment duration: 3-12 weeks determined by the severity of infection, the response to treatment and the tolerability of the regimen

Continuation Phase*

1) Clarithromycin or azithromycin
2) Amikacin inhaled
3) Two or more of the following (guided by in-vitro susceptibility testing):
   a) Moxifloxacine
   b) Minocycline
   c) Linezolid / tedizolid
   d) Clofazimine

Treatment duration: 1 year after culture conversion. Patients who fail to convert and lung transplant patients may benefit from long-term suppressive antibiotic treatment. If cultures remain positive after 1year of anti-NTM treatment (culture non-conversion), pausing of NTM treatment can be considered under a close clinical follow-up.

IV: intravenously

* ***M. abscessus* pulmonary disease:** *M. abscessus* isolates having a functional ***erm41*** gene or a **23S RNA mutation,** present a high level of macrolide resistance (erm41 acquired point mutations confer inducible macrolide resistance). There is growing concern that switching to oral treatment after an intensive IV phase, may compromise treatment success. In these cases, continuous IV therapy with two or more effective antibiotics for prolonged time should be considered. In addition to amikacin, imipenem is probably the best choice; the use of cefoxitin and tigecycline is limited due to their toxicity.

7.3.3 Treatment of Mycobacterium kansasii (Tables 7 and 8)

- *Mycobacterium kansasii* is rarely found in CF patients.
- Nevertheless, when present it must always be considered a pathogen (isolation invariably means real infection rather than colonization).
- *M. kansasii* may cause extensive cavitary upper lobes disease, similar to *M. tuberculosis* and must be treated aggressively.

Table 7: Treatment options for *M. kansasii* in adult CF patients (adapted from1-3)

1) Isoniazid and vitB6 (pyridoxine)
2) Rifampicin
3) Ethambutol

Treatment duration: 1 year following culture conversion. Patients who fail to convert and lung transplant patients may benefit from long-term suppressive antibiotic treatment. If cultures remain positive after 1year of anti-NTM treatment (culture non-conversion), pausing of NTM treatment can be considered under a close clinical follow-up.

Table 8: Pharmacological considerations for specific antibiotics used in adult CF patients with MAC, *M. abscessus* or *M. kansassi pulmonary* disease (adapted from[1,2])

Drug	Route	Dose in adults	Main side effects	Monitoring approach
Amikacin	IV	15-30 mg/kg 1x/day (dose max 1500 mg/day) Alternative: 25 mg/kg 3x/week (e.g. Mo, Wed, Fri)*[a]	Nephrotoxicity Ototoxicity	Creatinine levels Baseline and interval audiograms **TDM:** -For 1x/day dose: aim for peak levels 35-55 µg/ml and trough levels ≤1.5 µg/ml -For 3x/week dose (no literature data for TDM target): suggested peak levels 60-90 µg/ml and trough levels ≤1.5 µg/ml
	Inhaled	Usually start with 500 mg 2x/day (diluted in 3ml of NaCl 0.9%) Minimal dose 250 mg 1x/day	Bronchospasm	Administration of bronchodilators before each dose. Spirometry before and after administration of the first dose.
Azithromycin	Oral	10 mg/kg 1x/day (max. 500 mg)	GI Ototoxicity QT prolongation	Audiogram ECG

(continued)

Cefoxitin	IV	200 mg/kg/day divided in 3 doses (max 12 g/day)	Fever, rash Hematological Interference with Creat measuring assays	CBC
Clarithromycin	Oral	500 mg 2x/day	Hepatotoxicity QT prolongation	Liver function tests ECG
	IV	500 mg 2x/day (usually not recommended)		
Clofazimine	Oral	100 mg 1x/day	Skin discoloration GI	
Doxycycline	Oral	100mg 2x/day	Hepatotoxicity Hypersensitivity reactions, serum sickness, drug induced lupus	Liver function tests Determine antinuclear antibodies at baseline and repeat if dermatological symptoms
Ethambutol	Oral	15 mg/kg 1x/day	Optic neuritis	Baseline and interval opthalmology assessment
Imipenem	IV	1 g 2x/day	Hepatotoxicity	Liver function tests
Isoniazide	Oral, IM, IV	5 mg/kg 1x/day (maximum 300 mg daily) (½ -1h before or 2h after a meal) Add VitB6 (pyridoxine) 40mg orally 1x/day	Polyneuropathy Hepatotoxicity Hematological Urticaria	Symptoms, vitB6 for prevention of isoniazide-induced polyneurophathy Liver function tests CBC
Linezolid	Oral	600 mg 1-2x/day For patients receiving 2x/day consider to decrease if toxicity or after 6 months of treatment to 300 mg 2x/day or 600 mg 1x/day	Hematological Peripheral neuropathy Optic neuritis	CBC Baseline and interval opthalmology assessment Risk of interaction with serotonergic agents
	IV	10 mg/kg /dose 1-2x/day (max 600 mg/dose)		

Moxifloxacin	Oral	400 mg 1x/day	GI Tendonitis Photosensitivity QT prolongation	ECG
Minocycline	Oral	100 mg 2x/day	GI Photosensitivity Drug induced lupus Serum sickness Hypersensitivity	Consider testing anti-nuclear antibodies at baseline if long term minocycline
Rifampicin	Oral	<50 kg : 450 mg 1x/day >50 kg: 600 mg 1x/day (½ -1h before a meal)	Orange color of body fluids Hepatotoxicity GI Hematological Renal failure Drug interactions	Inform patient (can stain contact lenses) Liver function tests CBC Creatinine levels Dose adjustment, TDM when applicable
Rifabutin	Oral	150-300 mg 1x/day 150 mg in patients taking a strong CYP3A4 inhibitor 450-600 mg in patients taking a strong CYP3A4 inducer	Orange color of body fluids Hepatotoxicity GI Hematological Drug interactions	Inform patient (can stain contact lenses) Liver function tests CBC Dose adjustment, TDM when applicable
Tigecycline	IV	50 mg 2x/day*[b]	GI Photosensitivity Prolonged pro-thrombin time Hypoglycemia Dizziness Headache	Baseline and interval PT measurement Inform patient for hypoglycemia risk
TMP/SMX	Oral	960 mg 2x/day	Hematological GI Fever, rash, Stevens-Johnson syndrome	CBC
	IV	1.44 g 2x/day		

CBC=complete blood count, GI=gastrointestinal, TDM=therapeutic drug monitoring
For more details see product information (www.swissmedicinfo.ch)
*[a] Limited evidence
*[b] For tigecycline, a dose of 100mg 2x/day has a better pharmacokinetic and pharmacodynamic profile but lower tolerability (mainly GI secondary effects)

8. CONSIDERATIONS FOR SPECIFIC ANTIBIOTICS

- **Linezolid** shows in vitro activity in approximately 50% of *M. abscessus* but prolonged administration is limited by hematological and neurological toxicity, particularly when high doses are used (600 mg 2x/day). As in multidrug resistant TB (MDR-TB), lower levels of linezolid (600 mg 1x/day or 300mg 1x/day) may be used with less toxicity for long-term treatment in combination with other drugs.
- **Tedizolid**, a new oxazolidinone administered at a dose of 200 mg once daily orally or IV, has shown a greater in vitro potency and a better tolerability profile than linezolid, however published data are limited (case report evidence). The pharmacokinetics of tedizolid in CF is the subject of an ongoing trial (clinicaltrials.gov NCT02444234).
- **Clofazimine** was once developed for leprosy and is currently used for MDR-TB. Clofazimine and amikacin have synergistic properties *in vitro* and the addition of clofazimine to amikacin-containing regimens has been studied in clinical trials. An interesting regimen for MAC-PD using a combination of ethambutol, clofazimine and a macrolide showed a conversion rate of 87% and treatment success of 67%.
- **Bedaquiline** has been recently added to 5-drug containing regimens for patients treated for MAC and *M. abscessus* and who have previously failed to respond to other drug combinations (salvage therapy, 400 mg 1x/day for 2 weeks followed by 200 mg 3x/week). A small preliminary report demonstrates potential clinical and microbiological activity in this patient population but requires confirmation with larger studies.
- **Amikacin (inhaled)**
  - Inhaled amikacine is used in the continuation phase of therapy against *M. abscessus.* There are no studies, so doses vary from 250mg 1x/day to 500mg 2x/day. However, the starting dose is usually 500 mg 2x/day.
  - Currently, there is an increased interest and trials are ongoing in multidrug regimens combined with a new liposomal formulation of amikacin, which may improve drug delivery to the infected macrophages in MAC-PD and *M. abscessus*-PD patients.
- **Co-trimoxazole (TMP/SMX) and doxycycline**
  - In case of intolerance to minocycline, doxycycline or co-trimoxazole should be considerd.

8.1 Surgery

- Some studies, suggest that localized resections (lobectomy or segmentectomy) may be considered for severe unilateral NTM-PD that have failed to respond to conventional antibiotic therapy. However, in the context of CF, localized bronchiectasis is extremely rare and the place for surgery is very limited.

8.2 Interferon γ (INF-γ)

- INF-γ is considered to be an important component of the immune response against NTM.
  - Impaired INF-γ-mediated immunity increases susceptibility to NTM.
  - In vitro addition of IFN-γ to human macrophages infected with NTM enhances intracellular killing and autophagy.

- Although data are limited, use of adjuvant INF-γ in non-CF patients with disseminated, refractory NTM infection was associated with a greater response rate.
- In the context of CF, evidence is lacking regarding the efficacy of IFN-γ, hence this drug cannot be recommended. However, adjuvant IFN-γ therapy may be considered in particularly difficult-to-treat cases of disseminated, refractory NTM infection.

8.3 Granulocyte-macrophage colony-stimulating factor (GM-CSF)

- Case report evidence suggests that nebulized GM-CSF may improve host response to *M. abscessus* in CF and could lead to clinical improvement. At the moment of writing, a clinical trial is lacking.

9. TRANSPLANTATION

- NTM-PD or isolation of *M. abscessus* in the sputum is not considered an absolute contraindication for lung transplantation.
  - Although NTM disease may cause severe complications and significant morbidity after lung transplantation, it may be successfully controlled and not lead to attributable mortality.
  - However, progressive pulmonary or extra-pulmonary disease due to NTM (despite optimal therapy or due to inability of the patient to tolerate therapy) is usually a contraindication for transplant listing **(see also Chapter "*Transplantation*").**
  - Treatment in this context should be provided in collaboration with the lung transplant center.
- Although, NTM eradication may not be realistic particularly for *M. abscessus*, attempts to treat NTM should be implemented before lung transplantation
  - to reduce the mycobacterial load
  - to avoid complications
  - to delay further lung function deterioration while waiting on the transplant list
- After transplantation, the risk of complications is increased with *M. abscessus*, particularly among patients that have positive smears at the time of transplantation. Despite aggressive anti-mycobacterial treatment before, peri-operatively and after lung transplantation, complications such as skin, muscular and soft tissue abscesses may occur. Colonization of graft anastomosis with associated mycobacterial mediastinitis and death has been described.

10. REFERENCES

1. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175:367-416.
2. Floto RA, Olivier KN, Saiman L, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis: executive summary. Thorax 2016;71:88-90.

3. Leung JM, Olivier KN. Nontuberculous mycobacteria: the changing epidemiology and treatment challenges in cystic fibrosis. Current opinion in pulmonary medicine 2013;19:662-9.
4. Howard ST, Rhoades E, Recht J, et al. Spontaneous reversion of Mycobacterium abscessus from a smooth to a rough morphotype is associated with reduced expression of glycopeptidolipid and reacquisition of an invasive phenotype. Microbiology 2006;152:1581-90.
5. Smith MJ, Efthimiou J, Hodson ME, Batten JC. Mycobacterial isolations in young adults with cystic fibrosis. Thorax 1984;39:369-75.
6. Fauroux B, Delaisi B, Clement A, et al. Mycobacterial lung disease in cystic fibrosis: a prospective study. Pediatr Infect Dis J 1997;16:354-8.
7. Olivier KN, Weber DJ, Wallace RJ, Jr., et al. Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. Am J Respir Crit Care Med 2003;167:828-34.
8. Levy I, Grisaru-Soen G, Lerner-Geva L, et al. Multicenter cross-sectional study of nontuberculous mycobacterial infections among cystic fibrosis patients, Israel. Emerg Infect Dis 2008;14:378-84.
9. Qvist T, Gilljam M, Jonsson B, et al. Epidemiology of nontuberculous mycobacteria among patients with cystic fibrosis in Scandinavia. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2015;14:46-52.
10. Pierre-Audigier C, Ferroni A, Sermet-Gaudelus I, et al. Age-related prevalence and distribution of nontuberculous mycobacterial species among patients with cystic fibrosis. J Clin Microbiol 2005;43:3467-70.
11. Mussaffi H, Rivlin J, Shalit I, Ephros M, Blau H. Nontuberculous mycobacteria in cystic fibrosis associated with allergic bronchopulmonary aspergillosis and steroid therapy. The European respiratory journal 2005;25:324-8.
12. Renna M, Schaffner C, Brown K, et al. Azithromycin blocks autophagy and may predispose cystic fibrosis patients to mycobacterial infection. The Journal of clinical investigation 2011;121:3554-63.
13. Binder AM, Adjemian J, Olivier KN, Prevots DR. Epidemiology of nontuberculous mycobacterial infections and associated chronic macrolide use among persons with cystic fibrosis. Am J Respir Crit Care Med 2013;188:807-12.
14. Andrejak C, Nielsen R, Thomsen VO, Duhaut P, Sorensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. Thorax 2013;68:256-62.
15. Thomson RM, Armstrong JG, Looke DF. Gastroesophageal reflux disease, acid suppression, and Mycobacterium avium complex pulmonary disease. Chest 2007;131:1166-72.
16. Bryant JM, Grogono DM, Greaves D, et al. Whole-genome sequencing to identify transmission of Mycobacterium abscessus between patients with cystic fibrosis: a retrospective cohort study. Lancet 2013;381:1551-60.
17. Gilljam M, Berning SE, Peloquin CA, Strandvik B, Larsson LO. Therapeutic drug monitoring in patients with cystic fibrosis and mycobacterial disease. The European respiratory journal 1999;14:347-51.

18. van Ingen J, Totten SE, Helstrom NK, Heifets LB, Boeree MJ, Daley CL. In vitro synergy between clofazimine and amikacin in treatment of nontuberculous mycobacterial disease. Antimicrob Agents Chemother 2012;56:6324-7.
19. Field SK, Cowie RL. Treatment of Mycobacterium avium-intracellulare complex lung disease with a macrolide, ethambutol, and clofazimine. Chest 2003;124:1482-6.
20. Philley JV, Wallace RJ, Jr., Benwill JL, et al. Preliminary Results of Bedaquiline as Salvage Therapy for Patients With Nontuberculous Mycobacterial Lung Disease. Chest 2015;148:499-506.
21. Milanes-Virelles MT, Garcia-Garcia I, Santos-Herrera Y, et al. Adjuvant interferon gamma in patients with pulmonary atypical Mycobacteriosis: a randomized, double-blind, placebo-controlled study. BMC Infect Dis 2008;8:17.
22. Chernenko SM, Humar A, Hutcheon M, et al. Mycobacterium abscessus infections in lung transplant recipients: the international experience. J Heart Lung Transplant 2006;25:1447-55.
23. Qvist T, Pressler T, Thomsen VO, Skov M, Iversen M, Katzenstein TL. Nontuberculous mycobacterial disease is not a contraindication to lung transplantation in patients with cystic fibrosis: a retrospective analysis in a Danish patient population. Transplant Proc 2013;45:342-5.
24. Peloquin CA, Berning SE, Nitta AT, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis 2004;38:1538-44.
25. Chalermskulrat W, Sood N, Neuringer IP, et al. Non-tuberculous mycobacteria in end stage cystic fibrosis: implications for lung transplantation. Thorax 2006;61:507-13.
26. Scott JP, Yinduo Ji, Kannan M, Wylam ME. Inhaled granulocyte-macrophage colony-stimulating factor for *Mycobacterium abscessus* in cystic fibrosis. ERJ 2018;51:1702127