Nontuberculous Mycobacteria Clinical Care Guidelines

Nontuberculous mycobacteria can cause chronic pulmonary infection or can reside in the lungs without causing progressive disease. Challenges include making decisions on when and how to initiate treatment.

Nontuberculous Mycobacteria Clinical Care Guidelines: Executive Summary

Floto RA, Olivier KN, Saiman L, Daley CL, Herrmann JL, Nick JA, Noone PG, Bilton D, Corris P, Gibson RL, Hempstead SE, Koetz K, Sabadosa KA, Sermet-Gaudelus I, Smyth AR, van Ingen J, Wallace RJ, Winthrop KL, Marshall BC, Haworth CS, U.S. Cystic Fibrosis Foundation and European Cystic Fibrosis Society. U.S. Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of nontuberculous mycobacteria in individuals with cystic fibrosis. *Thorax*. 2016;71:i1-i22.

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms that can cause chronic pulmonary infection, particularly in individuals with pre-existing lung disease, such as cystic fibrosis. NTM lung disease in CF is emerging as a significant threat to these individuals, although there is limited data on diagnosis and treatment.

To better provide guidance for this challenging disease, the U.S. Cystic Fibrosis Foundation and the European Cystic Fibrosis Society (ECFS) convened a committee of experts to address the specific issues surrounding NTM pulmonary disease (NTM-PD) in individuals with CF. This summary highlights a comprehensive list of questions associated with screening, microbiology, diagnosis, treatment, and issues regarding transplantation.

Nontuberculous mycobacteria are increasingly being isolated from the sputum of individuals with CF with estimates of prevalence increasing from 1.3 percent in 1984 to 12 percent in 2012. The most commonly isolated organism is *Mycobacterium avium* complex comprising 72 percent of NTM positive cultures, followed by *M. abscessus*.

NTM-PD is defined by microbiological, clinical, and radiographic features; although it is clear that NTM can reside in the lungs of individuals with CF without causing progressive disease, making decisions on when to initiate treatment is challenging. Other challenges exist in knowing how best to identify NTM, how to initiate treatment, and how NTM-PD affects lung transplantation consideration. The CF Foundation and ECFS created these consensus guidelines to help standardize the approach to NTM-PD.

Methodology

The CF Foundation and ECFS convened a 19-member committee of adult and pediatric experts in CF and NTM-related lung disease. Using the PICO (population, intervention, comparison, and outcome) format, questions were developed and systematic literature searches were conducted. The committee drafted and voted on the recommendations accepting a recommendation if 80 percent of the committee agreed. The committee included 50 statements in the final consensus recommendations.

Recommendations

Screening

Recommendations	Evaluation of the Evidence
1. Cultures for NTM should be performed annually in spontaneously expectorating individuals with a stable clinical course.	Consensus
2. Oropharyngeal swabs should not be used for NTM screening.	Consensus

Microbiology

Recommendations	Evaluation of the Evidence
3. Cultures and smears for acid-fast bacilli (AFB) from sputum, induced sputum, bronchial wash, or broncho-alveolar lavage samples can be used to evaluate individuals with CF for NTM pulmonary disease.	Consensus
4. Nonculture-based methods should not be used for detecting NTM in respiratory tract samples.	Consensus
5. For *M. avium* complex, clarithromycin susceptibility testing should be performed on an isolate recovered prior to initiation of treatment.	Consensus
6. For *M. abscessus* complex, susceptibility testing should include at least clarithromycin, cefoxitin, and amikacin (and preferably also tigecycline, imipenem, minocycline, moxifloxacin, and linezolid).	Consensus

Diagnosis

Recommendations	Evaluation of the Evidence
7. NTM treatment should be considered for individuals with CF who have pulmonary disease as defined by the American Thoracic Society and the Infectious Diseases Society of America.	Consensus
8. Individuals receiving azithromycin as part of their CF medical regimen who have a positive NTM culture should not continue azithromycin while evaluation for NTM disease is underway.	Consensus

Treatment

Recommendations	Evaluation of the Evidence
9. Treatment of *M. abscessus* complex pulmonary disease should involve an intensive phase and a continuation phase.	Consensus
10. The intensive phase should include daily oral macrolide (preferably azithromycin) in conjunction with 3-12 weeks of intravenous (IV) amikacin and one or more of the following: IV tigecycline, imipenem, or cefoxitin, guided but not dictated by drug susceptibility testing. The duration of the intensive phase of therapy should be determined by the severity of infection, the response to treatment, and the tolerability of the regimen.	Consensus
11. The continuation phase should include a daily oral macrolide (preferably azithromycin), and inhaled amikacin, in conjunction with 2-3 of the following additional oral antibiotics: minocycline, clofazimine, moxifloxacin, and linezolid, guided but not directed by susceptibility testing.	Consensus
12. Monotherapy with a macrolide or other antimicrobial should never be used in the treatment of *M. abscessus* complex or *M. avium* complex pulmonary disease.	Consensus
13. Clarithromycin-sensitive *M. avium* complex pulmonary disease should be treated with a daily oral antibiotic regimen containing a macrolide (preferably azithromycin), rifampin, and ethambutol.	Consensus
14. An initial course of IV amikacin should be considered in the treatment of *M. avium* complex pulmonary disease in the presence of one or more of the following: a. AFB smear positive respiratory tract samples b. Radiological evidence of lung cavitation or severe infection c. Systematic signs of illness	Consensus
15. Individuals with CF receiving NTM treatment should have expectorated or induced sputum samples sent for NTM culture every 4-8 weeks throughout the entire course of treatment to assess microbiological response.	Consensus
16. A schedule for detecting drug toxicity (including hearing loss, visual loss, renal impairment, and liver function test abnormalities) should be set in place at the time of treatment initiation and implemented throughout treatment based on the specific drugs prescribed.	Consensus
17. A high-resolution computed tomography scan of the lungs should be performed shortly before starting NTM treatment and at the end of NTM treatment to assess radiological response.	Consensus
18. NTM antibiotic therapy should be prescribed for 12 months beyond culture conversion (defined as three consecutive negative cultures, with the time of conversion being the date of the first of the three cultures) as long as no positive cultures are obtained during these 12 months.	Consensus
19. When amikacin is given intravenously or when streptomycin is given intravenously or intramuscularly, serum levels should be monitored and dosing adjusted to minimize ototoxicity and nephrotoxicity.	Consensus

Transplantation

Recommendations	Evaluation of the Evidence

20.	The presence of current or previous respiratory tract samples for positive NTM should not preclude individuals being considered for lung transplantation.	Consensus
21.	Individuals with CF who have NTM pulmonary disease and are being evaluated for transplantation should commence treatment prior to transplant listing.	Consensus
22.	The presence of persistent *M. abscessus* complex or *M. avium* complex infection despite optimal therapy is not an absolute contraindication to lung transplant.	Consensus

Unanswered Questions

- Who is at risk for NTM-PD?
- What is the optimal screening method to identify NTM?
- What factors determine if a specific CF individual will develop pulmonary disease related to NTM versus asymptomatic colonization?
- How do we define NTM-PD in the CF population?
- What is the best treatment paradigm for NTM-PD in the CF population?
- How will CFTR modulator therapy alter NTM colonization and pulmonary disease?

Further Reading

Relevant manuscripts published after the original guidelines are listed below. These manuscripts have not been reviewed or endorsed by the guidelines committee.

1. Viviani L, Harrison MJ, Zolin A, Haworth CS, Floto RA. Epidemiology of nontuberculous mycobacteria (NTM) amongst individuals with cystic fibrosis (CF). *J Cyst Fibros*. 2016 Sep; 15(5): 610-23.
2. Salsgiver EL, Fink AK, Knapp EA, LiPuma JJ, Olivier KN, Marshall BC, Saiman L. Changing epidemiology of the respiratory bacteriology of patients with cystic fibrosis. *Chest* 2016 Feb; 149(2): 390-400.
3. Qvist T, Gilljam M, Jönsson B, Taylor-Robinson D, Jensen-Fangel S, Wang M, Svahn A, Kötz K, Hansson L, Hollsing A, Hansen CR, Finstad PL, Pressler T, Høiby N, Katzenstein TL; Scandinavian Cystic Fibrosis Study Consortium (SCFSC). Epidemiology of nontuberculous mycobacteria among patients with cystic fibrosis in Scandinavia. *J Cyst Fibros*. 2015 Jan; 14(1): 46-52.
4. Caverly LJ, Carmody LA, Haig SJ, Kotlarz N, Kalikin LM, Raskin L, LiPuma JJ. Culture-Independent identification of nontuberculous mycobacteria in cystic fibrosis respiratory samples. *PLoS One*. 2016; 11(4): e0153876.

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