

outcomes of macrolide-based treatment are generally poor and do not correlate well with in vitro susceptibilities^{119 129} potentially due to *erm*⁴¹-dependent inducible macrolide resistance and relative short duration of adequate regimens, which were often interrupted because of toxicity. Indeed, in the absence of a functional *erm*⁴¹ gene, response to macrolide-containing treatments has been good.⁹⁴ The CLSI has recommended routine testing for inducible macrolide resistance by performing extended incubation of isolates in the presence of clarithromycin, as inducible resistance may predict treatment failure.¹²⁰ For *M. simiae*, the role of DST is unknown, although the generally poor outcomes of treatment have been correlated with a lack of synergistic activity between rifampicin and ethambutol, an in vitro observation that still awaits clinical validation.¹³⁰ Some molecular methods to assess drug susceptibility exist, but are not yet routinely available. For example, sequencing of the 16S rRNA and 23S rRNA genes can reveal mutations associated with high-level resistance to aminoglycosides and macrolides, respectively.^{119 127}

DIAGNOSIS OF NTM-PD IN CF

Should the ATS/IDSA criteria for the diagnosis of NTM-PD be used in individuals with CF?

Recommendation 20: The CF Foundation and the ECFS recommend that ATS/IDSA criteria for the diagnosis of NTM-PD should be used in individuals with CF (ATS/IDSA 2007 Statement).

Recommendation 21: The CF Foundation and the ECFS recommend that other CF pathogens and comorbidities should be considered as potential contributors to a patient's symptoms and radiological features when determining the clinical significance of NTM-positive cultures.

Recommendation 22: The CF Foundation and the ECFS recommend that NTM treatment should be considered for individuals with CF who have ATS/IDSA defined NTM-PD.

Recommendation 23: The CF Foundation and the ECFS recommend that individuals receiving azithromycin as part of their CF medical regimen who have a positive NTM culture should not continue azithromycin treatment while evaluation for NTM disease is underway, as azithromycin monotherapy may lead to resistance. A macrolide agent may be included in a multidrug treatment regimen if criteria are met for NTM disease.

In contrast to *M. tuberculosis*, a single positive culture of NTM does not necessarily indicate that an individual has NTM-PD. To address the difficulty of making a diagnosis of NTM-PD, the ATS/IDSA proposed a set of clinical, radiological and microbiological criteria required to define an individual as having NTM-PD (ref 22; box 1). Although these criteria have not been validated for individuals with CF, they have been widely adopted by NTM specialists around the world and provide an operational definition for NTM-PD, which supports clinical decision-making and facilitates research. The Statements Committee therefore concluded that, in the absence of an alternate, CF-validated definition, the ATS/IDSA criteria should be used for the definition of NTM-PD in individuals with CF.

Microbiological criteria for NTM-PD

Individuals should have two or more positive sputum cultures of the same NTM species or one positive culture from bronchoscopic lavage or wash. The threshold for the number of positive sputum samples is derived from an observational study of individuals without CF with MAC in which 98% individuals with at least two positive sputum cultures developed progressive radiographic change compared to only 2% with one positive

Box 1 ATS/IDSA clinical and microbiologic criteria for diagnosing non-tuberculous mycobacterial pulmonary disease (NTM-PD) (based on ref 22)

Clinical (both required)

1. Pulmonary symptoms with nodular or cavitary opacities on chest radiograph, or a high-resolution CT scan that shows multifocal bronchiectasis with multiple small nodules.
2. Appropriate exclusion of other diagnoses.

Microbiologic (one of the following required)

1. Positive culture results from at least two expectorated sputum samples. If the results from samples are non-diagnostic, consider repeat sputum acid-fast bacilli (AFB) smears and cultures.
2. Positive culture results from at least one bronchial wash or lavage.
3. Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathological features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.
 - A. Expert consultation should be obtained when either infrequently encountered NTM or those usually representing environmental contamination are recovered.
 - B. Patients who are suspected of having NTM-PD but who do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded.
 - C. Making the diagnosis of NTM-PD does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients.

culture.¹³¹ The type of NTM species isolated is also important. Thus, isolation of *M. abscessus* is more likely to reflect NTM-PD than culturing usually non-pathogenic species such as *M. goodii* and *M. terrae* complex.

Radiological criteria for NTM-PD

In the context of CF-related lung disease, a chest radiograph is unlikely to be of use for the investigation of NTM-PD. High-resolution CT (HRCT) scan changes supporting a diagnosis of NTM-PD would include: inflammatory nodules, new tree-in-bud opacities (particularly in areas of mild underlying bronchiectasis) and cavitation.¹³² However, these changes are non-specific, particularly in individuals with severe CF-related lung disease, and may reflect infection with more common CF pathogens, inadequate airway clearance or the development of allergic bronchopulmonary aspergillosis (ABPA).

Clinical criteria for NTM-PD

NTM-PD should be suspected in individuals with worsening respiratory symptoms (breathlessness, increased cough and sputum production) and/or declining pulmonary function tests that do not respond to antibiotic therapy targeting conventional CF-associated bacteria and optimised airway clearance. Night sweats, fevers, chest pains and weight loss (although uncommon) may also suggest possible NTM-PD.

NTM treatment should be considered in individuals with CF who fulfil ATS/IDSA criteria for NTM-PD. However, the decision to start treatment is a clinical one based on an