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| **Title** | Non-Tuberculous Mycobacteria (NTM) |
| **Version** | 1.1 |


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## 1. Introduction

NTM are ubiquitous environmental organisms that can cause chronic pulmonary infection, particularly in individuals with pre-existing inflammatory lung disease such as CF. Pulmonary disease caused by NTM has emerged as a major threat to the health of individuals with CF but remains difficult to diagnose and problematic to treat.

## 2. Screening

**2.1.** Sputum or BAL samples can be used for NTM screening. Oropharyngeal swabs are not appropriate.
**2.2.** Cultures for NTM should be performed annually in spontaneously expectorating individuals with a stable clinical course.
**2.3.** In the absence of clinical features suggestive of NTM-PD, individuals who are not capable of spontaneously producing sputum do not require screening cultures for NTM.
**2.4.** When undertaking flexible bronchoscopy with lavage to obtain a definitive microbiological diagnosis, one of the lavage samples should be sent for NTM culture.

## 3. Identification of NTM

All cultured NTM isolates should undergo molecular identification and antibiotic susceptibility testing.

## 4. Who Should Receive Treatment?

**4.1.** NTM treatment should be considered for individuals with CF who have ATS defined NTM pulmonary disease (NTM-PD).
**4.2.** During evaluation for NTM disease, azithromycin should be discontinued as monotherapy may cause antibiotic resistance.

## 5. ATS Criteria for Diagnosing NTM Pulmonary Disease

**5.1. Clinical** (both parts required)
5.1.1. Pulmonary symptoms with nodular or cavitary opacities on chest radiograph, or a high-resolution CT scan that shows multifocal bronchiectasis with multiple small nodules.
5.1.2. Appropriate exclusion of other diagnoses.
**5.2. Microbiologic** (one of the following required)
5.2.1. 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.
5.2.2. Positive culture results from at least one bronchial wash or lavage.

5.2.3. 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.

**5.3.** Expert consultation should be obtained when either infrequently encountered NTM or those usually representing environmental contamination are recovered.

**5.4.** 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.

**5.5.** 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

## 6. Treatment Regimes

### 6.1. Mycobacterium Abscessus Complex

6.1.1. Intensive Phase (3-12 weeks) - Daily oral macrolide (preferably azithromycin) in conjunction with intravenous (IV) amikacin and one or more of the following: IV tigecycline, imipenem or cefoxitin [guided but not dictated by antibiotic testing].

6.1.2. Continuation Phase - 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 dictated by antibiotic testing].

### 6.2. Mycobacterium Avium Complex

6.2.1. Daily oral antibiotic regimen containing a macrolide (preferably azithromycin), rifampicin and ethambutol.

6.2.2. Consider an initial course of IV amikacin if: (i) smear positive, (ii) radiological evidence of lung cavitation / severe infection or (iii) systemic signs of illness.

**6.3. 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 negative cultures).

## 7. Antibiotic Doses

| Antibiotic | Route | Paediatric Dose | Adult Dose |
|---|---|---|---|
| Amikacin | IV | Child: 15-30 mg/kg/dose OD<br>Adolescent: 10-15 mg/kg/dose OD<br>(Max dose 1500mg daily) | 10-30 mg/kg OD or<br>15/mg/day in 2 divided doses<br>daily or x3/wk. doses |
| Amikacin | Neb | 250-500 mg/dose OD or BD | 250-500 mg/dose OD or BD |
| Azithromycin | PO | Child: 10-12 mg/kg/dose OD<br>Adolescent: see adult dose | 250-500 mg OD |
| Cefoxitin | IV | 50 mg/kg/dose TDS<br>(Max dose 12 g/day) | 200 mg/kg/day in 3 divided doses<br>(Max dose 12 g/day) |
| Clarithromycin | PO | 7.5 mg/kg/dose BD (Max dose 500 mg) | 500mg BD |
| Clarithromycin | IV | Not recommended | 500 mg BD |
| Co-trimoxazole | PO | 10-20 mg/kg/dose BD | 960 mg BD |
| Co-trimoxazole | IV | 10-20 mg/kg/dose BD | 1.44 g BD |
| Ethambutol | PO | Child & Adolescent: 15 mg/kg/dose OD | 15 mg/kg/dose OD |
| Imipenem | IV | 15-20 mg/kg/dose BD (Max dose 1g) | 1g BD |
| Linezolid | PO | <12 years old: 10mg/kg/dose TDS<br>≥12 years old: 10 mg/kg/dose OD or BD<br>(Max dose 600mg) | 600 mg OD or BD |
| Linezolid | IV | <12 years old: 10mg/kg/dose TDS<br>≥12 years old: 10 mg/kg/dose OD or BD<br>(Max dose 600mg) | 600 mg OD or BD |
| Moxifloxacin | PO | 7.5-10 mg/kg/dose<br>(Max dose 400mg daily) | 400 mg OD |
| Minocycline | PO | 2 mg/kg/dose OD (Max dose 200 mg) | 100 mg BD |
| Rifampicin | PO | 10-20 mg/kg/dose (Max dose 600mg) | <50 kg: 450 mg OD<br>>50 kg: 600 mg OD |
| Rifabutin | PO | 5-10 mg/kg/dose OD (Max dose 1g) | 150-300 mg OD |

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| | | | 150 mg if on CYP3A4 inhibitor<br>450-600 mg if on CYP3A4 inducer |
| Streptomycin | IM/IV | 20-40 mg/kg/dose (Max dose 1g) | 15 mg/kg (Max dose 1g) |
| Tigecycline | IV | 8-11 years: 1.2 mg/kg/dose BD<br>(Max dose 50 mg)<br>≥12 years old: 100mg loading dose then 50mg OD or BD | 100mg loading dose then 50mg OD or BD |

## 8. Side-effects and Monitoring

| Antibiotic | Side Effects | Monitoring |
|---|---|---|
| Amikacin | Nephrotoxicity<br>Auditory-vestibular toxicity | Serum amikacin levels, UEs<br>Audiograms |
| Azithromycin | Nausea, vomiting, diarrhoea<br>Auditory-vestibular toxicity<br>Prolonged QT | Symptoms<br>Audiograms<br>ECG |
| Cefoxitin | Fever, rash<br>↓WCC, ↓plt, ↓Hb | Symptoms<br>FBC |
| Clarithromycin | Hepatitis<br>Taste disturbance<br>Inhibited hepatic metabolism of rifabutin | LFTs<br>Symptoms<br>Consider dose adjustment |
| Co-trimoxazole | Nausea, vomiting, diarrhoea<br>↓WCC, ↓plt, ↓Hb<br>Fever, rash Steven-Johnson syndrome | Symptoms<br>FBC<br>Symptoms |
| Ethambutol | Optic neuritis<br>Peripheral neuropathy | Symptoms / ophthalmology review<br>Symptoms / nerve conduction studies |
| Imipenem | Hepatitis | LFTs |
| Linezolid | ↓WCC, ↓plt, ↓Hb<br>Optic neuritis<br>Peripheral neuropathy | FBC<br>Symptoms / ophthalmology review<br>Symptoms / nerve conduction studies |
| Moxifloxacin | Nausea, vomiting, diarrhoea<br>Insomnia, agitation, anxiety<br>Tendonitis<br>Photosensitivity<br>Prolonged QT | Symptoms<br>Symptoms<br>Symptoms<br>Symptoms<br>ECG |
| Minocycline | Photosensitivity<br>Nausea, vomiting, diarrhoea<br>Vertigo<br>Skin discolouration | Symptoms<br>Symptoms<br>Symptoms<br>Symptoms |
| Rifampicin & rifabutin | Orange discolouration to bodily fluids<br>Hepatitis<br>Fever, chills<br>↓plt<br>Renal failure<br>Increased hepatic metabolism of drugs | Symptoms<br>LFTs<br>Symptoms<br>FBC<br>UEs<br>Consider dose adjustment |
| Rifabutin | ↓WCC<br>Anterior uveitis<br>Polyarthralgia, polymyalgia | FBC<br>Symptoms<br>Symptoms |
| Streptomycin | Nephrotoxicity<br>Auditory-vestibular toxicity | Serum streptomycin levels, UEs<br>Audiograms |
| Tigecycline | Nausea, vomiting, diarrhoea<br>Pancreatitis<br>Hypoproteinaemia<br>Bilirubinaemia | Symptoms<br>Serum amylase<br>Serum albumin<br>Serum bilirubin |

## 9. Reference

RA Floto 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. Thorax 2016; 71:i1–i22. doi:10.1136/thoraxjnl-2015-207360