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 Adolescent: 10-15 mg/kg/dose OD (Max dose 1500mg daily and max. 15g per course)	10-30 mg/kg OD or 15/mg/day in 2 divided doses daily or x3/wk. doses. Max. 1.5 g per day; and max. 15 g per course.
Amikacin	Neb	250-500 mg/dose OD or BD	250-500mg/dose OD or BD
Azithromycin	PO	Child: 10-12 mg/kg/dose (max. 500mg) OD Adolescent: see adult dose	250-500mg OD
Cefoxitin	IV	50 mg/kg/dose TDS (Max dose 12 g/day – max. single dose 4g)	200 mg/kg/day in 3 divided doses (Max dose 12 g/day – max. single dose 4g)
Clarithromycin	PO	7.5 mg/kg/dose BD (max. single dose 500mg)	500mg BD
Clarithromycin	IV	Child 1 month–11 years: 7.5 mg/kg every 12 hours (max. per dose 500 mg every 12 hours). Child 12–17 years: 500 mg every 12 hours	500mg every 12hrs
Co-trimoxazole	PO	Child 6 mths–5 years: 240 mg twice daily. Child 6–11 years: 480 mg twice daily Child 12–17 years: 960 mg twice daily	960mg BD
Co-trimoxazole	IV	18-27 mg/kg/dose BD	1.44 g every 12hrs.
Ethambutol	PO	Child & Adolescent: 20 mg/kg/dose OD	15 mg/kg/dose OD
Linezolid	PO	Neonates >7days old to <12 years old: 10mg/kg/dose TDS ≥12 years old: 10 mg/kg/dose OD or BD (Max dose 600mg)	600mg OD or BD

Antibiotic	Route	Paediatric Dose	Adult Dose
Linezolid	IV	Neonates >7days old to <12 years old: 10mg/kg/dose TDS ≥12 years old: 10 mg/kg/dose OD or BD (Max dose 600mg)	600mg OD or BD
Moxifloxacin	PO	10mg/kg (max 400mg) OD	400mg OD
Minocycline	PO	12 yrs: 100mg BD	100mg BD
Rifampicin	PO	10-20 mg/kg/dose OD (max. dose 600mg)	<50 kg: 450mg OD >50 kg: 600mg OD
Rifabutin	PO	5-10 mg/kg/dose OD (Max dose 1g)	150-300 mg OD 150 mg if on CYP3A4 inhibitor 450-600 mg if on CYP3A4 inducer
Streptomycin	IM/IV	IM injection, 15mg/kg OD (maximum dose 1g).	15 mg/kg (max. dose 1g) OD
Tigecycline	IV	8-11 years: 1.2 mg/kg/dose BD (Max dose 50 mg) ≥12 years old: 100mg loading dose then 50mg BD, reduced to 50mg OD if not tolerated	100mg loading dose then 50mg BD

8. Side-effects and Monitoring

Antibiotic (class)	Side Effects (common/very common)	Monitoring
Amikacin (aminoglycoside)	Nephrotoxicity Auditory-vestibular toxicity. Common/very common: dysphonia (hoarseness); tinnitus; vomiting.	Serum amikacin levels, UEs Audiograms
Azithromycin (macrolide)	Common/very common: Appetite decreased; diarrhoea; dizziness; GI discomfort and/or disorders (prokinetic effect); headache; hearing impairment; insomnia; nausea; pancreatitis; paraesthesia (tingling, numbness or "pins and needles); skin reactions; taste altered; vasodilation; vision disorders; vomiting. Prolonged QT interval risk.	Symptoms Audiograms ECG
Cefoxitin (2nd gen cephalosporin)	Common/very common: abdominal pain; diarrhoea; dizziness; eosinophilia; headache; leucopenia; nausea; neutropenia; pseudomembranous enterocolitis; skin reactions; thrombocytopenia; vomiting; vulvovaginal candidiasis. ↓WCC, ↓plt, ↓Hb	Symptoms FBC Renal function should be monitored if using with a nephrotoxic drug.
Clarithromycin (macrolide)	Hepatitis Taste disturbance Inhibits hepatic metabolism of rifabutin (increased concentration of rifabutin) and rifabutin decreases concentration of clarithromycin (dose adjustment may be needed)..	LFTs Symptoms Consider dose adjustment
Co-trimoxazole (trimethoprim and sulfamethoxazole)	Diarrhoea; electrolyte imbalance; fungal overgrowth; headache; nausea; skin reactions (including Stevens-Johnson syndrome [SJS] or toxic epidermal necrolysis). Trimethoprim a folate antagonist (risk of low folate but folate supplementation may counteract antibacterial effect) ↓WCC, ↓plt, ↓Hb	Monitor serum potassium and sodium in patients at risk of hyperkalaemia or hyponatraemia. Monitor blood counts (FBCs) on prolonged treatment. Plasma concentration monitoring may be required with high doses.
Ethambutol (bacteriostatic)	Hyperuricaemia; nerve disorders; visual impairment	Renal function should be checked before treatment. Visual acuity should be tested by Snellen chart before treatment with ethambutol. In young children, routine ophthalmological monitoring recommended.

Antibiotic (class)	Side Effects (common/very common)	Monitoring
Imipenem (carbapenem) with cilastatin (competitive, reversible and specific inhibitor of dehydropeptidase – not an antibiotic)	Diarrhoea; eosinophilia; nausea; skin reactions; thrombophlebitis; vomiting. Rare/very rare: hepatitis.	LFTs
Linezolid (oxazolidinone)	Anaemia; constipation; diarrhoea; dizziness; gastrointestinal discomfort; headache; hypertension; increased risk of infection; insomnia; localised pain; nausea; skin reactions; taste altered; vomiting. Other: ↓WCC, ↓plt, ↓Hb Optic neuritis Peripheral neuropathy, myelosuppression, diarrhoea, nausea, headache.	Monitor full blood count (including platelet count) weekly. Severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days. The CHM recommends that: patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect, changes in visual acuity and colour vision) immediately. patients experiencing new visual symptoms (regardless of treatment duration) should be evaluated promptly and referred to an ophthalmologist if necessary. visual function should be monitored regularly if treatment is required for longer than 28 days.
Moxifloxacin (quinolone)	Diarrhoea; eye discomfort; eye disorders; fungal infection; headache; nausea; skin reactions; taste altered; vision disorders; vomiting. Other: Drowsiness; heart valve incompetence; hypoglycaemic coma; increased risk of aortic aneurysm; increased risk of aortic dissection; polyneuropathy; QT interval prolongation.	Symptoms Symptoms Symptoms Symptoms ECG
Minocycline (tetracycline)	Angioedema; diarrhoea; headache; Henoch-Schönlein purpura; hypersensitivity; nausea; pericarditis; photosensitivity reaction; skin reactions; systemic lupus erythematosus exacerbated; vomiting.	If treatment continued for longer than 6 months, monitor every 3 months for hepatotoxicity, pigmentation and for systemic lupus erythematosus—discontinue if these develop or if pre-existing systemic lupus erythematosus worsens.
Rifampicin (rifamycin)	Nausea; thrombocytopenia; vomiting Other: orange discolouration to bodily fluids Hepatitis Fever, chills Renal failure Increased hepatic metabolism of drugs.	• Renal function should be checked before treatment. • Hepatic function should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. However, liver function should be monitored on prolonged therapy. Blood counts (FBCs) should be monitored in patients on prolonged therapy.
Rifabutin (rifamycin)	Frequency not known: agranulocytosis; anaemia; arthralgia; bronchospasm; chest pain; corneal	Renal function should be checked before treatment.

Antibiotic (class)	Side Effects (common/very common)	Monitoring
	deposits; decreased leucocytes; dyspnoea; eosinophilia; fever; haemolysis; hepatic disorders; influenza like illness; myalgia; nausea; neutropenia; pancytopenia; skin reactions; thrombocytopenia; urine discolouration; uveitis (more common following high doses or concomitant use with drugs that increase plasma concentration); vomiting.	Hepatic function should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. However, hepatic function should be monitored on prolonged therapy. Blood counts should be monitored on prolonged therapy.
Streptomycin (aminoglycoside)	Dysphonia (hoarseness); tinnitus; vomiting. Other: nephrotoxicity Auditory-vestibular toxicity	Serum streptomycin levels, U+Es Audiograms
Tigecycline (tetracycline)	Common or very common: abscess; appetite decreased; diarrhoea; dizziness; gastrointestinal discomfort; headache; healing impaired; hyperbilirubinaemia; hypoglycaemia; hypoproteinaemia; increased risk of infection; nausea; sepsis; skin reactions; vomiting.	Symptoms. LFTs, amylase, lipase, coagulation and haematology parameters before starting treatment, and regularly during treatment.

9. References

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