

British Thoracic Society Guideline for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD)

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ABSTRACT

The full guideline for the management of non-tuberculous mycobacterial pulmonary disease is published in *Thorax*. The following is a summary of the recommendations and good practice points. The sections referred to in the summary refer to the full guideline.

INTRODUCTION

The full guideline for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD) is published in *Thorax*.¹ The key features of the guideline are highlighted in a short article published to accompany the full guideline.² The following is a summary of the recommendations and good practice points. The sections referred to in the summary refer to the full guideline.

BACKGROUND

Since the publication of the British Thoracic Society (BTS) Guideline on the 'Management of opportunistic mycobacterial infections'³ in 2000, our understanding of the epidemiology, microbiology and management of NTM-PD has advanced. The incidence and prevalence of NTM-PD is increasing and is most likely explained by improved clinician awareness and enhanced detection methods, as well as a variety of changing environmental, mycobacterial and host factors. Technological advances in molecular microbiology have revolutionised our understanding of NTM taxonomy and it is now appreciated that species and subspecies often differ in their pathogenicity and treatment response. While there remains a dearth of contemporary randomised controlled trial data to inform practice, the Guideline Development Group have sought to combine the

best available evidence with clinical experience to create a pragmatic management guideline.

Target audience for the guideline

This guideline is aimed at healthcare practitioners who are involved in the care of individuals with NTM-PD, which will include hospital specialists in respiratory medicine, infectious diseases, paediatrics, microbiology, immunology and radiology.

Groups covered within the guideline include: (a) individuals without pre-existing lung disease (de novo NTM infection); (b) individuals with chronic obstructive pulmonary disease and other chronic inflammatory lung diseases; (c) individuals with bronchiectasis; (d) individuals with cystic fibrosis; (e) individuals with a primary or secondary immunodeficiency; (f) individuals being considered for and following lung transplantation. Groups not covered within the guideline are patients with extrapulmonary NTM disease, neonates (birth to 28 days), infants (1–12 months), and patients with HIV infection.

Scope of the guideline

1. Epidemiology—incidence, prevalence and risk factors
2. Microbiology—types of samples, detection and speciation
3. Definition of NTM-PD and indications for treatment
4. Antibiotic treatment regimens for specific NTM species
5. Role of drug susceptibility testing
6. Non-antibiotic treatment—interferon-gamma, *Mycobacterium vaccae*



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Table 1 Key to evidence statements

| Grade | Evidence |
|-------|---|
| 1++ | High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias |
| 1+ | Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias |
| 1– | Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias |
| 2++ | High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal |
| 2+ | Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal |
| 2– | Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal |
| 3 | Non-analytic studies, eg, case reports, case series |
| 4 | Expert opinion |

RCT, randomised controlled trial.

7. Investigation of individuals suspected of having NTM-PD and investigations to be undertaken during and after treatment
8. Role of thoracic surgery
9. Impact of NTM on lung transplant eligibility

METHODOLOGY

This guideline is based on the best available evidence. The methodology used to write the guideline adheres strictly to the criteria as set by the AGREE (Appraisal of Guidelines for Research and Evaluation) collaboration, which is available online www.agreertrust.org/resource-centre/agree-ii/. The BTS Standards of Care Committee guideline production manual is available at <http://www.brit-thoracic.org.uk/guidelines-and-quality-standards/>.

Clinical questions, literature search and appraisal of the literature

Clinical questions were structured in the Population, Intervention, Comparison, Outcome format (see online

appendix 1 in the full guideline), to define the scope of the guideline and inform the literature search.

The searches were first run in November 2012 and updated in June 2015 (see full guideline online appendix 1).

Appraisal was performed to be compliant with the AGREE collaboration. Please see the full guideline for further details.

Considered judgement and grading of evidence

The Guideline Development Group used the evidence tables (see full guideline online appendix 2) to judge the body of evidence and grade recommendations for this guideline (tables 1 and 2). Where evidence was lacking to answer the formulated clinical questions, expert opinions were obtained through consensus. The following were considered in grading of the recommendations:

- ▶ The available volume of the body of evidence.

Table 2 Grades of recommendations

| Grade | Type of evidence |
|-------|--|
| A | At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results |
| B | A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 1++ or 1+ |
| C | A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 2++ |
| D | Evidence level 3 or 4 or Extrapolated evidence from studies rated as 2+ |
| ✓ | Important practical points for which there is no research evidence, nor is there likely to be any research evidence. The guideline committee wishes to emphasise these as good practice points. |

RCT, randomised controlled trial.

- ▶ How applicable the obtained evidence was in making recommendations for the defined target audience of this guideline.
- ▶ Whether the evidence was generalisable to the target population for the guideline.
- ▶ Whether there was a clear consistency in the evidence obtained to support recommendations.
- ▶ What the implications of recommendations would be on clinical practice in terms of resources and skilled expertise.
- ▶ Cost-effectiveness was not reviewed in detail as in-depth economic analysis of recommendations falls beyond the scope of this guideline.

Recommendations were graded from A to D as indicated by the strength of the evidence as shown in [table 2](#). In line with the Scottish Intercollegiate Guideline Network (SIGN) guidance, ‘minus’ evidence was considered in context but in the absence of other ‘plus’ supporting evidence, it was discussed among the Guideline Development Group regarding that point and any recommendation hence made was grade D. Important practical points lacking any research evidence, nor likely to be research evidence in the future were highlighted as ‘good practice points’.

Drafting the guideline

The Guideline Development Group corresponded regularly by email and meetings of the full group were held in

Box 1 Clinical and microbiological criteria for diagnosing non-tuberculous mycobacterial lung disease (modified with permission from reference ⁴)

Clinical (both required)

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

Microbiological

1. Positive culture results from at least two separate expectorated sputum samples. If the results are non-diagnostic, consider repeat sputum AFB smears and cultures. or
2. Positive culture result from at least one bronchial wash or lavage. or
3. Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.

AFB, acid-fast bacilli; NTM, non-tuberculous mycobacteria.

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May and July 2012, July and September 2013, January, April and November 2014 and June 2015 as well as a number of teleconferences. The Guideline Development Group were asked if they agreed or disagreed with the draft recommendations and good practice points in an anonymous electronic survey administered by the BTS project co-ordinator in Spring 2016. The Guideline Development Group had agreed at the start of the guideline development process that 80% or more agreement would be the threshold for acceptance. Although not always unanimous, 80% or greater agreement was achieved for all recommendations and good practice points in the first round of voting.

The BTS Standards of Care Committee (SOCC) reviewed the draft guideline in November 2016. The draft guideline was made available online in February 2017 for public consultation and circulated to all the relevant stakeholders. The BTS SOCC rereviewed the revised draft guideline in June 2017 and final SOCC approval for publication was granted in July 2017.

This BTS Guideline will be reviewed within 5 years from publication date.

SUMMARY OF RECOMMENDATIONS AND GOOD PRACTICE POINTS

Section 4: What is the evidence for transmission of NTM between individuals?

Recommendation

- ▶ Adequate infection control policies need to be implemented in both inpatient and outpatient settings to minimise risks of person-to-person transmission of *Mycobacterium abscessus* in individuals with cystic fibrosis (grade B).

Section 5: How should the lung disease attributable to NTM infection be defined?

Recommendation

- ▶ In the absence of robust evidence to support an alternative definition and due to the clinical and research benefits of having a uniform definition, use of the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) 2007 definition of NTM-PD is recommended ([box 1](#)) (grade D).

Good practice point

- ✓ The management of coexisting lung conditions/infections should be optimised before ascribing clinical decline to NTM-PD.

Section 6: What samples should be used to detect pulmonary non-tuberculous mycobacterial infection?

Recommendations

- ▶ Sputum, induced sputum, bronchial washings, bronchoalveolar lavage or transbronchial biopsy samples can be used to evaluate individuals suspected to have NTM-PD (grade D).

- ▶ Whenever possible, less invasive sampling should be attempted first to minimise procedural risks (grade D).
- ▶ Respiratory samples should be processed within 24 hours of collection (or refrigerated at 4°C if delays are anticipated) (grade D).
- ▶ Oropharyngeal swab culture or serology testing should not be used to diagnose NTM-PD (grade D).

Good practice points

- ✓ Respiratory specimens should be collected with appropriate infection control precautions, including personal protective equipment, given the frequent differential diagnosis of *Mycobacterium tuberculosis* infection.
- ✓ If sputum cultures are negative but clinical suspicion of NTM infection is high, consider performing CT-directed bronchial washings to obtain targeted samples.
- ✓ If individuals undergoing diagnostic evaluation for NTM infection are taking antibiotics that may impair NTM growth (such as aminoglycosides, macrolides, tetracyclines, cotrimoxazole, linezolid), consider discontinuing these antibiotics 2 weeks prior to collecting samples.

Section 7: What microbiological tests should be used to detect NTM in respiratory samples?

Recommendations

- ▶ A validated rapid method should be used to detect NTM in respiratory samples (grade D).
- ▶ All respiratory samples should be stained using auramine-phenol after liquefaction and concentration and then examined by microscopy (grade B).
- ▶ Respiratory tract samples should be cultured (following decontamination) on solid and liquid media in a ISO15189 accredited clinical laboratory for 8 weeks extending to 12 weeks if necessary (grade D).
- ▶ Routine use of non-culture-based detection methods is not recommended at the present time (grade D).

Good practice point

- ✓ If there is high clinical suspicion of NTM infection but negative sample cultures, consider discussing with a mycobacterial reference laboratory about (i) the possibility of culture on alternative media, at different temperatures, and/or for extended durations or (ii) the utility of molecular detection methods.

Section 8: What microbiological tests should be used to speciate and type NTM from respiratory samples?

Recommendations

- ▶ All NTM isolates from respiratory samples should be identified to at least species level using validated molecular or mass spectrometry techniques (grade B).
- ▶ Isolates of *M. abscessus* should be subspeciated using appropriate molecular techniques (grade C).

- ▶ If person-to-person transmission of *M. abscessus* is suspected, isolates should be typed, preferably using whole genome sequencing (grade C).

Section 9: Does in vitro drug susceptibility testing predict response to antibiotic treatment in people with NTM pulmonary infection?

Recommendations

- ▶ Drug susceptibility testing and reporting should follow the Clinical Laboratory Standards Institute guidelines (grade D).
- ▶ For *Mycobacterium avium* complex (MAC), clarithromycin and amikacin susceptibility testing should be performed on an isolate taken prior to initiation of treatment and on subsequent isolates if the patient fails to respond to treatment or recultures MAC after culture conversion (grade C).
- ▶ Macrolide-resistant MAC isolates should be tested against a wider panel of antibiotics to guide, but not dictate, treatment regimens (grade D).
- ▶ For *Mycobacterium kansasii*, rifampicin susceptibility testing should be performed on an isolate prior to initiation of treatment and on subsequent isolates if the patient fails to respond to treatment or recultures *M. kansasii* after culture conversion (grade D).
- ▶ Rifampicin-resistant *M. kansasii* isolates should be tested against a wider panel of antibiotics to guide, but not dictate, treatment regimens (grade D).
- ▶ Susceptibility testing for *M. abscessus* should include at least clarithromycin, cefoxitin and amikacin (and preferably also tigecycline, imipenem, minocycline, doxycycline, moxifloxacin, linezolid, cotrimoxazole and clofazimine if a validated method is available) to guide, but not dictate, treatment regimens (grade D).

Good practice points

- ✓ Susceptibility testing should only be carried out on isolates where there is clinical suspicion of disease (to avoid unnecessary cost and conserve laboratory resources).
- ✓ Reporting of minimum inhibitory concentration (MIC) and critical concentration rather than susceptible or resistant may be more appropriate in the belief that a drug that has a very high MIC is unlikely to be active in vivo, whereas one just above a putative 'critical concentration' may have some activity, especially if combined with additive or synergistic agents.

Section 10: What investigations should be performed in patients suspected of having NTM-PD? (see figure 1)

Respiratory tract cultures

Recommendations

- ▶ A minimum of two sputum samples collected on separate days should be sent for mycobacterial culture when investigating an individual suspected of having NTM-PD (grade D) (see figure 1).

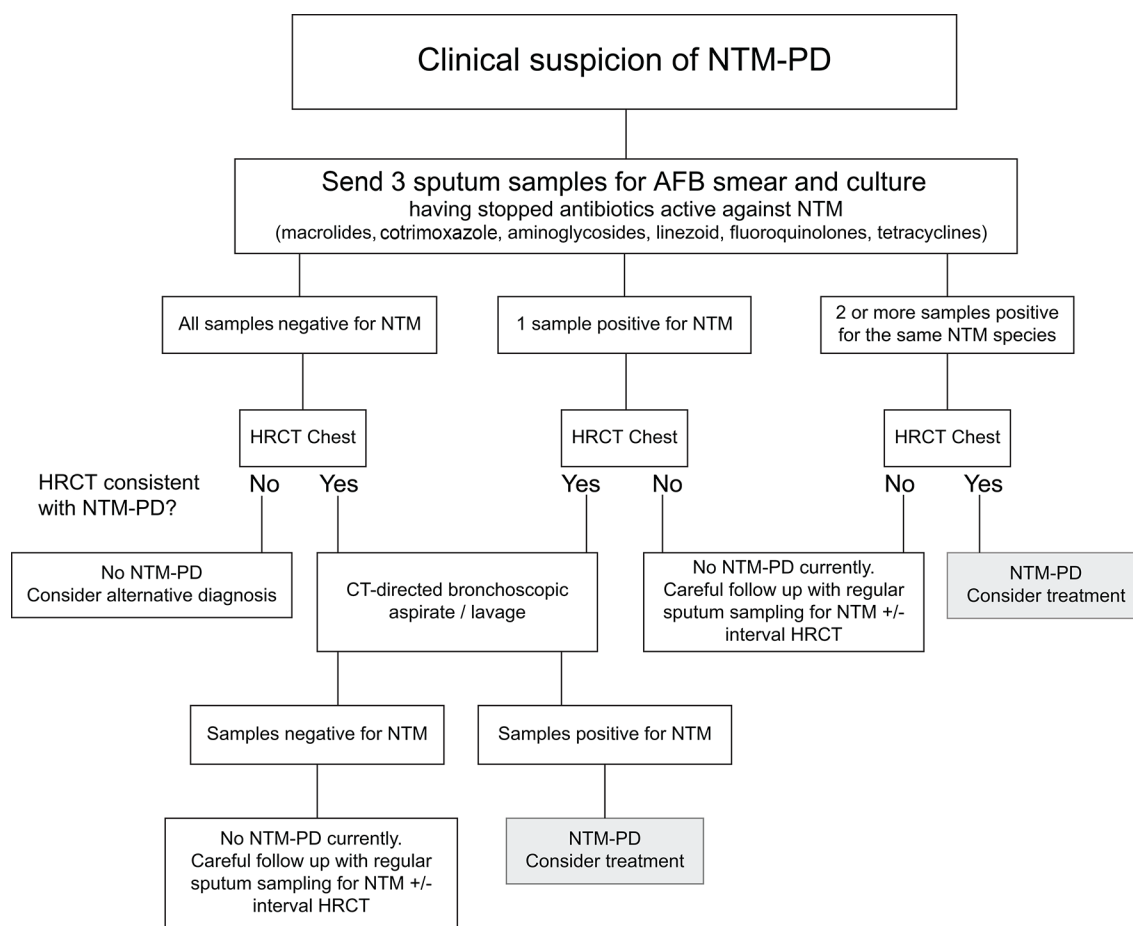


Figure 1 A suggested algorithm for the investigation of individuals with clinical suspicion of NTM-PD. AFB, acid-fast bacilli; HRCT, high-resolution CT; NTM-PD, non-tuberculous mycobacterial pulmonary disease.

- ▶ Individuals suspected of having NTM-PD whose sputum samples are consistently culture negative for mycobacteria should have CT-directed bronchial washings sent for mycobacterial culture (grade D).
- ▶ Individuals suspected of having NTM-PD who are unable to expectorate sputum should have CT-directed bronchial washings sent for mycobacterial culture (grade D).
- ▶ Transbronchial biopsies should not be performed routinely in individuals suspected of having NTM-PD (grade D).

Good practice points

- ✓ Sputum induction resulting in a positive culture may avoid the need for CT-directed bronchial washings in individuals who are unable to spontaneously expectorate sputum.
- ✓ Sputum induction should be considered in individuals suspected of having NTM-PD who are unable to spontaneously expectorate sputum and in whom CT-directed bronchial washings are considered inappropriate

Radiology

Recommendations

- ▶ A chest X-ray should be performed in individuals suspected of having NTM-PD (grade D).
- ▶ A CT scan should be performed in individuals suspected of having NTM-PD (grade D).

OTHER INVESTIGATIONS

Recommendations

- ▶ There is insufficient evidence to recommend the routine use of serological testing for diagnosis and monitoring of individuals with NTM-PD (grade D).
- ▶ Positron emission scanning, skin testing and interferon-gamma release assays should not be used in the evaluation of individuals suspected of having NTM-PD (grade D).

Section 11: What factors influence when NTM treatment should be started?

Recommendations

- ▶ The decision to start treatment should be influenced by the severity of NTM-PD, the risk of progressive

Table 3 Suggested antibiotic regimens for adults with *Mycobacterium avium* complex (MAC)-pulmonary disease

| MAC-pulmonary disease | Antibiotic regimen |
|---|---|
| Non-severe MAC-pulmonary disease (ie, AFB smear negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-to-moderate symptoms, no signs of systemic illness) | Rifampicin 600 mg 3×per week and Ethambutol 25 mg/kg 3×per week and Azithromycin 500 mg 3×per week or Clarithromycin 1 g in two divided doses 3 x per week. Antibiotic treatment should continue for a minimum of 12 months after culture conversion. |
| Severe MAC-pulmonary disease (ie, AFB smear positive respiratory tract samples, radiological evidence of lung cavitation/severe infection, or severe symptoms/signs of systemic illness) | Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or Clarithromycin 500 mg twice daily and Consider intravenous amikacin for up to 3 months or nebulised amikacin. Antibiotic treatment should continue for a minimum of 12 months after culture conversion. |
| Clarithromycin-resistant MAC-pulmonary disease | Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Isoniazid 300 mg (+pyridoxine 10 mg) daily or moxifloxacin 400 mg daily and Consider intravenous amikacin for up to 3 months or nebulised amikacin. Antibiotic treatment should continue for a minimum of 12 months after culture conversion. |

AFB, acid-fast bacilli; NTM, non-tuberculous mycobacteria.

NTM-PD, the presence of comorbidity and the goals of treatment (grade D).

- ▶ Individuals may require a period of longitudinal assessment (symptoms, radiological change and mycobacterial culture results) to inform NTM treatment decisions (grade D).

Good practice point

- ✓ The views of the affected individual should be sought on the potential risks and benefits of starting NTM treatment versus observation (ie, longitudinal assessment of symptoms, radiological change and mycobacterial culture results).

Section 12a: What antibiotic regimen should be used to treat MAC-PD?

Recommendations

- ▶ Clarithromycin-sensitive MAC-PD should be treated with rifampicin, ethambutol and clarithromycin or azithromycin using an intermittent (3×per week) or daily oral regimen. The choice of regimen should be based on the severity of disease (as defined in table 3) and treatment tolerance (grade D).
- ▶ An intermittent (3×per week) oral antibiotic regimen should not be used in individuals with severe MAC-PD (as defined in table 3) or in individuals with a history of treatment failure (grade D).

- ▶ An injectable aminoglycoside (amikacin or streptomycin) should be considered in individuals with severe MAC-PD (as defined in table 3) (grade D).
- ▶ Clarithromycin-resistant MAC-PD should be treated with rifampicin, ethambutol and isoniazid or a quinolone, and consider an injectable aminoglycoside (amikacin or streptomycin) (grade D).
- ▶ Nebulised amikacin may be considered in place of an injectable aminoglycoside when intravenous/intramuscular administration is impractical, contraindicated or long-term treatment with an aminoglycoside is required for the treatment of MAC-PD (grade D).
- ▶ Macrolide monotherapy or macrolide/quinolone dual therapy regimens should not be used for the treatment of MAC-PD (grade D).
- ▶ Antibiotic treatment for MAC-PD should continue for a minimum of 12 months after culture conversion (grade D).

Good practice points

- ✓ Individuals with clarithromycin-resistant MAC-PD should be managed in collaboration with a physician experienced in managing NTM-PD.
- ✓ Individuals with a history of treatment intolerance or treatment failure should be managed in collaboration with a physician experienced in managing NTM-PD.

Table 4 Suggested antibiotic regimen for adults with *Mycobacterium kansasii*-pulmonary disease

| <i>M. kansasii</i> -pulmonary disease | Antibiotic regimen |
|--|---|
| Rifampicin-sensitive <i>M. kansasii</i>-pulmonary disease | Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Isoniazid 300 mg (with pyridoxine 10 mg) daily or azithromycin 250 mg daily or clarithromycin 500 mg twice daily. Antibiotic treatment should continue for a minimum of 12 months after culture conversion. |

Section 12b: What antibiotic regimen should be used to treat *M. kansasii*-PD?

Recommendations

- ▶ Rifampicin-sensitive *M. kansasii*-PD should be treated with rifampicin, ethambutol and isoniazid or a macrolide (clarithromycin or azithromycin) using a daily oral regimen (grade D) (see table 4).
- ▶ Rifampicin-resistant *M. kansasii*-PD should be treated with a three-drug regimen guided, but not dictated by, drug susceptibility test results using a daily oral regimen (grade D).
- ▶ Antibiotic treatment for *M. kansasii*-PD should continue for a minimum of 12 months after culture conversion (grade D).

Good practice points

- ✓ Individuals with rifampicin-resistant *M. kansasii*-PD should be managed in collaboration with a physician experienced in managing NTM-PD.
- ✓ Individuals with a history of treatment intolerance or treatment failure should be managed in collaboration

with a physician experienced in managing NTM-PD.

Section 12c: What antibiotic regimen should be used to treat *Mycobacterium malmoense*-PD?

Recommendations

- ▶ *M. malmoense*-PD should be treated with rifampicin, ethambutol and a macrolide (clarithromycin or azithromycin) using a daily oral regimen (grade D). (see Table 5)
- ▶ An injectable aminoglycoside (amikacin or streptomycin) should be considered in individuals with severe *M. malmoense*-PD (ie, AFB smear positive respiratory tract samples, radiological evidence of lung cavitation/severe infection or severe symptoms/signs of systemic illness) (grade D).
- ▶ Nebulised amikacin may be considered in place of an injectable aminoglycoside when intravenous/intramuscular administration is impractical, contraindicated or long-term treatment with an aminoglycoside is

Table 5 Suggested antibiotic regimens for adults with *Mycobacterium malmoense*-pulmonary disease.

| <i>M. malmoense</i> -pulmonary disease | Antibiotic regimen |
|--|--|
| Non-severe <i>M. malmoense</i>-pulmonary disease (ie, AFB smear negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-to-moderate symptoms, no signs of systemic illness) | Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or Clarithromycin 500 mg twice daily. Antibiotic treatment should continue for a minimum of 12 months after culture conversion. |
| Severe <i>M. malmoense</i>-pulmonary disease (ie, AFB smear positive respiratory tract samples, radiological evidence of lung cavitation/severe infection or severe symptoms/signs of systemic illness) | Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or Clarithromycin 500 mg twice daily and Consider intravenous amikacin for up to 3 months or nebulised amikacin. Antibiotic treatment should continue for a minimum of 12 months after culture conversion. |

AFB, acid-fast bacilli.

Table 6 Suggested antibiotic regimens for adults with *Mycobacterium xenopi*-pulmonary disease

| <i>M. xenopi</i> -pulmonary disease | Antibiotic regimen |
|--|--|
| Non-severe <i>M. xenopi</i>-pulmonary disease (ie, AFB smear negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-to-moderate symptoms, no signs of systemic illness) | Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or Clarithromycin 500 mg twice daily and Moxifloxacin 400 mg daily or Isoniazid 300 mg (+pyridoxine 10 mg) daily. Antibiotic treatment should continue for a minimum of 12 months after culture conversion. |
| Severe <i>M. xenopi</i>-pulmonary disease (ie, AFB smear positive respiratory tract samples, radiological evidence of lung cavitation/severe infection or severe symptoms/signs of systemic illness) | Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or Clarithromycin 500 mg twice daily and Moxifloxacin 400 mg daily or Isoniazid 300 mg (+pyridoxine 10 mg) daily and Consider intravenous amikacin for up to 3 months or nebulised amikacin. Antibiotic treatment should continue for a minimum of 12 months after culture conversion. |

AFB, acid-fast bacilli.

required in the treatment of *M. malmoense*-PD (grade D).

- ▶ Antibiotic treatment for *M. malmoense*-PD should continue for a minimum of 12 months after culture conversion (grade D).

Good practice points

- ✓ Individuals with a history of treatment intolerance or treatment failure should be managed in collaboration with a physician experienced in managing NTM-PD.

Section 12d: What antibiotic regimen should be used to treat *M. xenopi*-PD?

Recommendations

- ▶ *M. xenopi*-PD should be treated with a four-drug regimen (where tolerated) comprising rifampicin, ethambutol and a macrolide (clarithromycin or azithromycin), with either a quinolone (ciprofloxacin or moxifloxacin) or isoniazid (grade D) (see table 6).
- ▶ An injectable aminoglycoside (amikacin or streptomycin) should be considered in individuals with severe *M. xenopi*-PD (ie, AFB smear positive respiratory tract samples, radiological evidence of lung cavitation/severe infection or severe symptoms/signs of systemic illness) (grade D).
- ▶ Nebulised amikacin may be considered in place of an injectable aminoglycoside when intravenous/intramuscular administration is impractical, contraindicated or long-term treatment with an aminoglycoside is required in the treatment of *M. xenopi*-PD (grade D).
- ▶ Antibiotic treatment for *M. xenopi*-PD should continue for a minimum of 12 months after culture conversion (grade D).

Good practice points

- ✓ Individuals with a history of treatment intolerance or treatment failure should be managed in collaboration with a physician experienced in managing NTM-PD.

Section 12e: What antibiotic regimen should be used to treat *M. abscessus*-PD?

Recommendations

- ▶ *M. abscessus*-PD treatment should comprise an initial phase antibiotic regimen (including intravenous and oral antibiotics) followed by a continuation phase antibiotic regimen (including inhaled and/or oral antibiotics) (grade D).

Initial phase

- ▶ For individuals with *M. abscessus* isolates that are clarithromycin sensitive or demonstrate inducible macrolide resistance (see tables 7 and 8), the initial phase antibiotic regimen should include at least a 4-week course of intravenous amikacin, intravenous tigecycline and (where tolerated) intravenous imipenem, and (where tolerated) oral clarithromycin or oral azithromycin (grade D).
- ▶ For individuals with *M. abscessus* complex isolates that demonstrate constitutive macrolide resistance (see tables 7 and 8), the initial phase antibiotic regimen should include a minimum 4-week course of intravenous amikacin, intravenous tigecycline and (where tolerated) intravenous imipenem (grade D).
- ▶ The duration of intravenous treatment should be influenced by the severity of infection, treatment response and tolerance of the regimen (grade D).
- ▶ To reduce the likelihood of treatment-related nausea and vomiting, antiemetic medication such as ondansetron should be considered (grade D).

Table 7 Interpretation of extended clarithromycin susceptibility results for *Mycobacterium abscessus*

| Clarithromycin susceptibility days 3–5 | Clarithromycin susceptibility day 14 | Genetic implication | <i>M. abscessus</i> subspecies | Macrolide susceptibility phenotype |
|--|--------------------------------------|------------------------------------|---|--|
| Susceptible | Susceptible | Dysfunctional <i>erm</i> (41) gene | <i>M. a. massiliense</i> | Macrolide susceptible |
| Susceptible | Resistant | Functional <i>erm</i> (41) gene | <i>M. a. abscessus</i> <i>M. a. bolletii</i> | Inducible macrolide resistance |
| Resistant | Resistant | 23S ribosomal RNA point mutation | Any | High-level constitutive macrolide resistance |

setron (note potential for QT interval prolongation) and/or aprepitant should be prescribed to individuals receiving tigecycline and/or imipenem (grade D).

► Nebulised amikacin may be considered in place of intravenous amikacin when intravenous administration is impractical, contraindicated or long-term treat-

Table 8 Suggested antibiotic regimens for adults with *Mycobacterium abscessus*-pulmonary disease -

| <i>M. abscessus</i> | Antibiotic regimen |
|--|---|
| Clarithromycin-sensitive isolates or inducible macrolide-resistant isolates | <p>Initial phase: ≥1 month* intravenous amikacin 15 mg/kg daily or 3×per week† and intravenous tigecycline 50 mg twice daily and where tolerated intravenous imipenem 1 g twice daily and where tolerated oral clarithromycin 500 mg twice daily or oral azithromycin 250–500 mg daily</p> <p>Continuation phase: nebulised amikacin† and oral clarithromycin 500 mg twice daily or azithromycin 250–500 mg daily and 1–3 of the following antibiotics guided by drug susceptibility results and patient tolerance: oral clofazimine 50–100 mg daily‡ oral linezolid 600 mg daily or twice daily oral minocycline 100 mg twice daily oral moxifloxacin 400 mg daily oral cotrimoxazole 960 mg twice daily</p> |
| Constitutive macrolide-resistant isolates | <p>Initial phase: ≥1 month* intravenous amikacin 15 mg/kg daily or 3×per week† and intravenous tigecycline 50 mg twice daily and where tolerated intravenous imipenem 1 g twice daily</p> <p>Continuation phase: nebulised amikacin† and 2–4 of the following antibiotics guided by drug susceptibility results and patient tolerance: oral clofazimine 50–100 mg daily‡ oral linezolid 600 mg daily or twice daily oral minocycline 100 mg twice daily oral moxifloxacin 400 mg daily oral cotrimoxazole 960 mg twice daily</p> |

*Due to the poorer response rates in patients with inducible or constitutive macrolide-resistant isolates and the greater efficacy of antibiotics administered through the intravenous route, -extending the duration of intravenous antibiotic therapy to 3–6 months in those that can tolerate it may be the most appropriate treatment strategy in this subgroup of patients.

†Substitute intravenous/nebulised amikacin with an alternative antibiotic if the *M. abscessus* is resistant to amikacin (ie, MIC >64 mg/L or known to have a 16S rRNA gene mutation conferring constitutive amikacin resistance).

‡Start clofazimine during the initial phase of treatment if tolerated as steady state serum concentrations may not be reached until ≥30 days of treatment.

ment with an aminoglycoside is required in individuals with *M. abscessus*-PD (grade D).

- ▶ In the context of amikacin-resistant *M. abscessus* (ie, MIC >64mg/L or the isolate is known to have a 16S rRNA gene mutation conferring constitutive amikacin resistance), intravenous/nebulised amikacin should be substituted with an alternative intravenous/oral antibiotic (grade D).

Continuation phase

- ▶ For individuals with *M. abscessus* isolates that are clarithromycin sensitive or demonstrate inducible macrolide resistance (see tables 7 and 8), the continuation phase antibiotic regimen should include nebulised amikacin and a macrolide (oral azithromycin or clarithromycin), in combination with one to three of the following oral antibiotics guided by drug susceptibility and patient tolerance: clofazimine, linezolid, minocycline or doxycycline, moxifloxacin or ciprofloxacin and cotrimoxazole (grade D).
- ▶ For individuals with *M. abscessus* complex isolates that demonstrate constitutive macrolide resistance (see tables 7 and 8), the continuation phase antibiotic regimen should include nebulised amikacin in combination with two to four of the following oral antibiotics guided by drug susceptibility and patient tolerance: clofazimine, linezolid, minocycline or doxycycline, moxifloxacin or ciprofloxacin and cotrimoxazole (grade D).
- ▶ In the context of amikacin-resistant *M. abscessus* (ie, MIC >64mg/L or the isolate is known to have a 16S rRNA gene mutation conferring constitutive amikacin resistance), nebulised amikacin should be substituted with an alternative oral antibiotic (grade D).
- ▶ Antibiotic treatment for *M. abscessus*-PD should continue for a minimum of 12 months after culture conversion. However, individuals who fail to culture convert may benefit from a long-term suppressive antibiotic regimen (grade D).

Good practice point

- ✓ Individuals with *M. abscessus*-PD should be managed in collaboration with a physician experienced in managing NTM-PD.

Section 13: Is there a role for adjuvant therapies in the management of NTM-PD?

Recommendations

- ▶ Interferon-gamma is not recommended as adjuvant therapy in individuals with NTM-PD without a defined immunodeficiency affecting intrinsic interferon-gamma signalling (grade D).
- ▶ *M. vaccae* is not recommended as adjuvant therapy in individuals with NTM-PD (grade D).

Section 14: What investigations should be performed during treatment or following treatment for NTM-PD?

Box 2 Definitions for microbiological outcomes

- ▶ Culture conversion: three consecutive negative mycobacterial sputum cultures collected over a minimum of 3 months, with the time of conversion being the date of the first of the three negative mycobacterial cultures. In patients unable to expectorate sputum, a single negative mycobacterial culture of a CT-directed bronchial wash is indicative of culture conversion.
- ▶ Recurrence: two positive mycobacterial cultures following culture conversion. If available, genotyping may help distinguish relapse from reinfection.
- ▶ Refractory disease: failure to culture convert after 12 months of non-tuberculous mycobacterial treatment.

Microbiological outcomes

Recommendations

- ▶ Sputum samples should be sent for mycobacterial culture every 4–12 weeks during treatment and for 12 months after completing treatment to assess the microbiological response (grade D) (see box 2).
- ▶ If there is doubt about persisting NTM infection despite negative sputum cultures, a CT-directed bronchial wash should be performed to assess the microbiological response to treatment (grade D).
- ▶ In individuals who are unable to expectorate sputum, a CT scan followed by a CT-directed bronchial wash after 6 and 12 months treatment can be used to assess the microbiological response to treatment (grade D).

Good practice point

- ✓ In individuals who are unable to spontaneously expectorate sputum and in whom CT-directed bronchial washings are not feasible, induced sputum samples should be sent for mycobacterial culture every 4–12 weeks during treatment and for 12 months after completing treatment to assess the microbiological response.

RADIOLOGICAL OUTCOMES

Recommendation

- ▶ A CT scan should be performed shortly before starting NTM treatment and at the end of NTM treatment to document the radiological response to treatment (grade D).

Good practice point

- ✓ During the course of treatment for NTM-PD, more frequent radiological monitoring may be indicated in selected individuals.

CLINICAL OUTCOMES

Recommendation

- ▶ A detailed assessment of pulmonary and systemic symptoms should be recorded at each clinical review (grade D).

Good practice point

- ✓ A more detailed clinical assessment may include measurements of body weight, spirometry and systemic inflammatory markers (ESR and CRP).

THERAPEUTIC DRUG MONITORING**Recommendations**

- ▶ Therapeutic drug monitoring (other than for aminoglycosides) should not be performed routinely in individuals' prescribed antibiotic therapy for NTM-PD (grade D).
- ▶ When aminoglycosides are administered, serum levels and the serum creatinine must be monitored and aminoglycoside dosing adjusted according to local policies (grade D).

Good practice point

- ✓ Therapeutic drug monitoring can be considered in individuals in whom gastrointestinal malabsorption, drug-drug interactions or suboptimal adherence may be adversely affecting treatment response.

MONITORING FOR DRUG TOXICITY**Recommendations**

- ▶ When aminoglycosides are administered, serum levels and the serum creatinine must be monitored and aminoglycoside dosing adjusted according to local policies (grade D).
- ▶ Audiometry should be considered before starting aminoglycosides and intermittently during treatment (frequency according to perceived risk and symptoms). Patients should be informed to stop aminoglycoside treatment immediately and to inform the prescriber if they develop tinnitus, vestibular disturbance or hearing loss (grade D).
- ▶ Assess visual acuity and colour vision before starting ethambutol and advise patients to stop treatment immediately and inform the prescriber if changes in visual acuity or colour vision occur (grade D).
- ▶ Serum ethambutol levels should be measured in patients with renal dysfunction (grade D).

Good practice points

- ✓ The frequency/type of toxicity monitoring required during NTM treatment is dependent on the drug regimen. Treatment-related adverse events and suggested toxicity monitoring protocols are outlined in the NTM antibiotic treatment monograph (section 18).
- ✓ Audiometry should be considered before starting azithromycin or clarithromycin and intermittently during treatment (frequency according to perceived risk and symptoms) and advise individuals to stop treatment immediately and inform the prescriber if they develop tinnitus, vestibular disturbance or hearing loss.

- ✓ Perform an ECG before, and 2 weeks after, starting drugs (such as azithromycin or clarithromycin) that are known to prolong the QT interval.

Section 15: Are there differences in outcome between patients with NTM-PD treated in specialist versus non-specialist care settings?**Recommendation**

- ▶ Individuals with NTM-PD should be managed in collaboration with a physician experienced in managing NTM-PD (grade D).

Section 16: What is the role of surgery in the treatment of NTM-PD?**Recommendations**

- ▶ The role of lung resection surgery in the management of NTM-PD should be considered at the time of diagnosis and revisited in individuals who develop refractory disease (grade D).
- ▶ Lung resection surgery for NTM-PD may be indicated in individuals with localised areas of severe disease (grade D).
- ▶ Lung resection surgery for NTM-PD should only be performed following expert multidisciplinary assessment in a centre experienced in managing individuals with NTM-PD (grade D).
- ▶ Individuals with NTM-PD should be established on antibiotic treatment prior to lung resection surgery and should continue treatment for 12 months after culture conversion (grade D).
- ▶ Following resection of a solitary NTM nodule in an individual with no other features of NTM-PD, antibiotic treatment is not usually required (grade D).

Good practice points

- ✓ Individuals with NTM-PD in whom lung resection surgery is being considered should have a comprehensive assessment of cardiopulmonary status in line with current guidance for lung cancer resection.
- ✓ Nutritional status should be optimised prior to lung resection surgery.

Section 17: Does NTM infection affect an individual's suitability for lung transplantation?**Recommendations**

- ▶ Individuals being considered for lung transplantation referral should be assessed for evidence of NTM-PD (grade D).
- ▶ Isolation of NTM organisms including *M. abscessus* in potential lung transplant candidates should not preclude referral and assessment for lung transplantation (grade D).
- ▶ Potential lung transplant candidates with evidence of NTM-PD should be treated whenever possible prior to listing to either eradicate the organism or lower bacterial load (grade D).
- ▶ Individuals with previous or current *M. abscessus* infection or disease who are listed for lung transplan-

tation should be counselled about the high postoperative risk of developing invasive and disseminated NTM disease which causes significant morbidity and necessitates prolonged treatment with a multidrug antibiotic regimen (grade D).

Good practice points

- ✓ Individuals with NTM-PD should demonstrate an ability to tolerate optimal antibiotic therapy before listing for lung transplantation.
- ✓ Progressive NTM-PD despite optimal antibiotic therapy is likely to be a contraindication to listing for lung transplantation.

Section 18: NTM drug monograph

The treatment of NTM-PD involves complex drug regimens that are commonly associated with intolerance and toxicity. The purpose of this monograph is to facilitate antibiotic prescribing in people with NTM-PD, but it should only be used in conjunction with, and not as a substitute for, local/national prescribing formularies. The monograph also provides guidance on the type and frequency of monitoring for drug toxicity which must, however, be determined on a case-by-case basis, informed by patient symptoms at each clinical encounter, and adjusted according to existing comorbidities. The information in this section of the guideline is provided as an aid to monitoring adverse effects and is correct at the time of publication. Readers are advised to confirm the latest information with their pharmacy colleagues.

The NTM drug monograph can be found as section 18 of the full guideline and also on the BTS website at: www.brit-thoracic.org.uk/.

ONLINE APPENDICES

Available at: <https://www.brit-thoracic.org.uk/standards-of-care/guidelines/bts-guidelines-for-non-tuberculous-mycobacteria/>

Appendix 1: Clinical questions and literature search strategy

Appendix 2: Evidence tables

Appendix 3: Patient information

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