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

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INTRODUCTION

- Nontuberculous mycobacteria (NTM) are **ubiquitous** organisms responsible for **opportunistic** infections.
- They affect both the **immunocompromised** and the **immunocompetent**.
- The **incidence** and **prevalence** of NTM lung disease are **increasing** worldwide.

INCLUSION/EXCLUSION

Groups covered within the guideline

- Individuals without pre-existing lung disease
- COPD and other chronic inflammatory lung diseases
- Bronchiectasis
- Cystic fibrosis (CF)
- Primary or secondary immunodeficiency
- Lung transplantation.

Groups not covered

- Extrapulmonary NTM
- Neonates and infants
- Patients with HIV infection.

SCOPE OF THE GUIDELINE

- **Scope of the guideline**

  1) **Epidemiology**—incidence, prevalence and risk factors and diagnosis

  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** (DST)

6) **Non-antibiotic treatment**—interferon gamma, *M. vaccae*

7) **Investigation** to be undertaken during and after treatment

8) Role of **surgery**

9) Impact of NTM on **lung transplant eligibility**.

EVIDENCE LEVELS

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, for example, case reports, case series
4	Expert opinion

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+

EPIDEMIOLOGY

- NTM comprises of Mycobacterial species other than the Mycobacterium tuberculosis complex and those organisms causing leprosy.

SLOW GROWERS	RAPID GROWERS
• M. avium complex (M. avium, M.intracellulare, M.chimaera)	• M. abscessus (M. a. abscessus, M.a.massiliense, M. a. bolletii)
• M. Kansasii	• M. chelonae
• M. malmoense	• M. fortuitum
• M. xenopi	

- Found mostly in **soil** and **water** and cause lung, sinus, lymph node, joint, CNS, and catheter-related and disseminated infections in susceptible individuals.

- In USA the prevalence is currently between 1.4 and 6.6/100k while In UK the incidence has increased from 4.0/100k in 2007 to 6.1/100k in 2012

- Possible **causes for increase** in NTM infection rates include:

  Increases in environmental exposure to NTM.

  Increased long-term antibiotic usage.

  Potential impact of person-to-person transmission (Ex: CF)

  Declining rates of M. tuberculosis infection

- Increasing Host susceptibility

  Pre-existing lung disease

  Lady Windermere syndrome

  Immunodeficiency

- Medications

  Immunosuppression

  Azithromycin

  Inhaled antibiotics

  Proton pump inhibitors

RECOMMENDATION

- Adequate infection control policies to minimise risk of transmission of *Mycobacterium abscessus* in individuals with cystic fibrosis (CF). (Grade B)

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

- It is essential to distinguish transient or persistent colonisation from infection.

RECOMMENDATION

- The use of the ATS/IDSA 2007 definition of NTM-PD

  The management of coexisting lung conditions/infections should be optimised.

CLINICAL CRITERIA (BOTH REQUIRED)

- Pulmonary symptoms, 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.

MICROBIOLOGICAL

- Positive culture results from at least two separate expectorated sputum samples.
  Or
  Positive culture results from at least one bronchial wash or lavage.
  Or
  Transbronchial or other lung biopsy with mycobacterial HPE features (granulomatous inflammation or AFB)
  +
  Biopsy giving a positive NTM culture
  Or
  One or more sputum or bronchial washings that are culture-positive for NTM.

MICROBIOLOGY

RECOMMENDATIONS FOR SAMPLING

- Sputum, induced sputum, bronchial washings, bronchoalveolar lavage or transbronchial biopsy samples

- Less invasive. (Grade D)

- Samples should be processed within 24 hours of collection or refrigerated at **4°C** in case of delays. (Grade D)

- Oropharyngeal swab culture or serology testing is not recommended. (Grade D)

- If sputum cannot be collected then CT directed bronchial washings can be used.

  If individuals are taking antibiotics, consider discontinuing these antibiotics 2 weeks prior to collecting samples.

RECOMMENDATION FOR TESTS

- A validated rapid method should be used to detect TB in respiratory samples. (Grade D)

- Stained using auramine- phenol after liquefaction and concentration. (Grade B)

- Samples should be cultured (following decontamination) on solid and liquid media for 8 to 12 weeks. (Grade D)

- Routine use of non-culture-based detection methods is not recommended. (Grade D)

- If there is high clinical suspicion of NTM infection but negative sample cultures, consider:

  (1) the possibility of culture on alternative media, at different temperatures, and/or for extended durations

  (2) the utility of molecular detection methods

RECOMMENDATION FOR SPECIATION

- All NTM isolates should be identified to at least species level. (Grade B)

- M. abscessus should be subspeciated (Grade C)

- If person-to-person transmission is suspected, isolates should be typed, preferably using whole genome sequencing (Grade C).

DRUG SUSCEPTIBILITY TESTING

RECOMMENDATION

- Follow the **Clinical Laboratory Standards Institute** (CLSI) guidelines. (Grade D)

  Drug susceptibility testing should be performed on an isolate taken prior to initiation of treatment.

- Subsequent isolates if the patient fails to respond to treatment or re-cultures the bacterium after culture conversion. (Grade C)

The resistant isolates should be tested against a panel of antibiotics to guide, but not dictate, treatment regimens. (Grade D)

For M. avium complex (MAC) - Clarithromycin
Amikacin

M. kansasii – Rifampicin

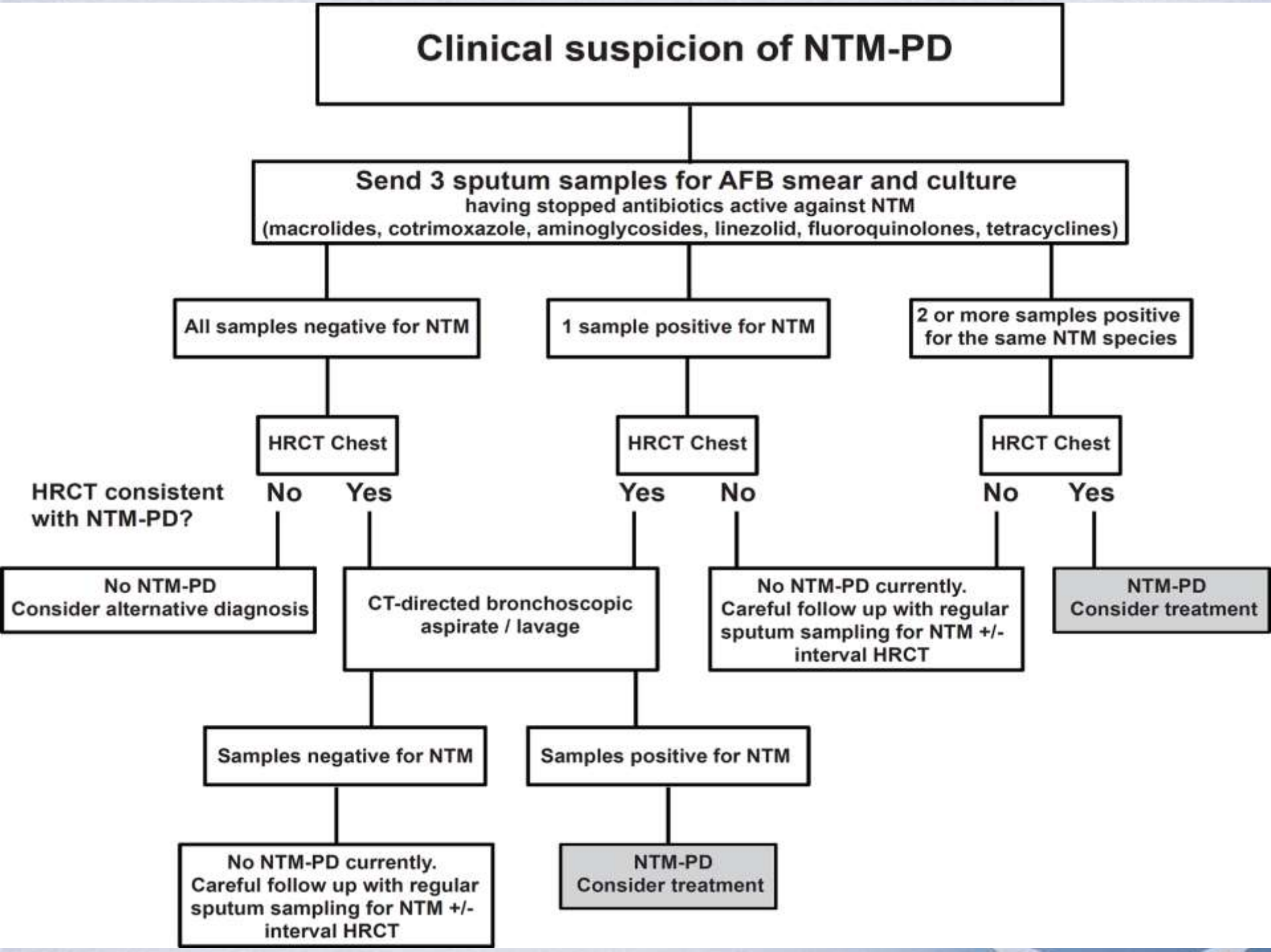
M. abscessus - clarithromycin, cefoxitin
amikacin ,
tigecycline, imipenem,
minocycline, doxycycline,
moxifloxacin, linezolid, co-trimoxazole and clofazimine

GOOD PRACTICE POINTS

Susceptibility testing should only done where there is clinical suspicion of disease .

Reporting of minimum inhibitory concentration (MIC) and critical concentration.

INVESTIGATIONS


Clinical suspicion of NTM-PD
Send 3 sputum samples for AFB smear and culture
having stopped antibiotics active against NTM
(macrolides, cotrimoxazole, aminoglycosides, linezolid, fluoroquinolones, tetracyclines)
All samples negative for NTM
1 sample positive for NTM
2 or more samples positive for the same NTM species
HRCT Chest
HRCT Chest
HRCT Chest
HRCT consistent with NTM-PD?
No
Yes
Yes
No
No
Yes
No NTM-PD
Consider alternative diagnosis
CT-directed bronchoscopic aspirate / lavage
No NTM-PD currently.
Careful follow up with regular sputum sampling for NTM +/- interval HRCT
NTM-PD
Consider treatment
Samples negative for NTM
Samples positive for NTM
No NTM-PD currently.
Careful follow up with regular sputum sampling for NTM +/- interval HRCT
NTM-PD
Consider treatment

RECOMMENDATION FOR CULTURES

- A minimum of two sputum samples collected on separate days should be sent for mycobacterial culture. (Grade D)
- Sputum induction. (Grade D)
- CT-directed bronchial washings. (Grade D)
- Transbronchial biopsies should not be performed routinely. (Grade D)

RECOMMENDATION FOR RADIOLOGY

- A **chest X-ray** should be performed. (Grade D)

- A **CT scan** should be performed. (Grade D)

RECOMMENDATIONS FOR OTHER INVESTIGATIONS

- There is insufficient evidence to recommend the routine use of serological testing. (Grade D)

- Positron emission scanning, skin testing and interferon gamma release assays should not be used in the evaluation. (Grade D)

FACTORS INFLUENCING TREATMENT

RECOMMENDATIONS

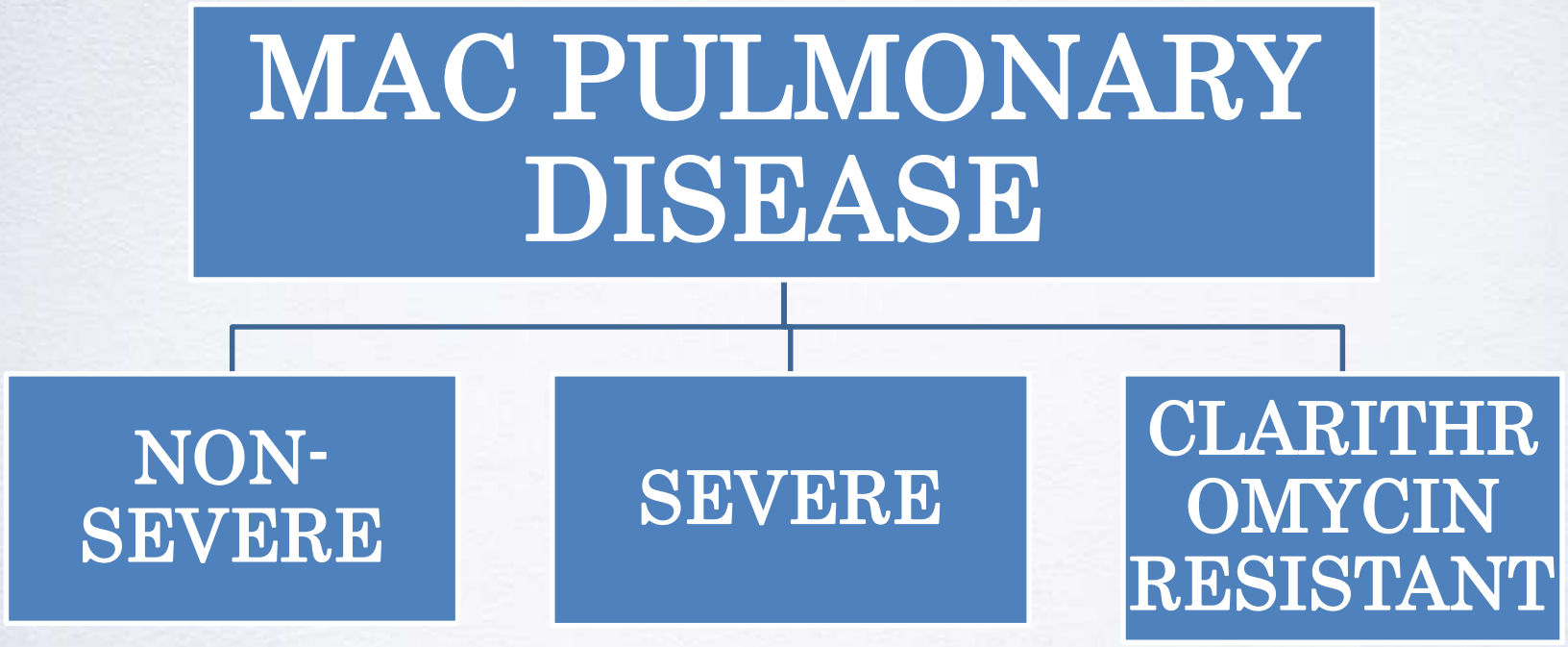
- Assesment of severity of disease, the risk of progressive disease, comorbidities and the goals of treatment. (Grade D)

- The views of the affected individual should be sought on the potential risks and benefits of starting NTM treatment versus observation.

ANTIBIOTIC TREATMENT

Antibiotic treatment should continue for a minimum of 12 months after culture conversion

MAC PULMONARY DISEASE



NON SEVERE MAC-PD

- **DEFINITION**

AFB smear-negative respiratory tract samples.

No radiological evidence of lung cavitation or severe infection.

Mild-moderate symptoms.

No signs of systemic illness.

- **REGIMEN**

Rifampicin 600 mg 3/week

+

Ethambutol 25 mg/kg 3/week

+

- Azithromycin 500 mg 3/week

OR

Clarithromycin 1 g in two divided doses 3/week

SEVERE MAC-PD

- **DEFINITION**

AFB smear-positive respiratory tract samples

Radiological evidence of lung cavitation/severe infection

Severe symptoms

Signs of systemic illness

- **REGIMEN**

Rifampicin 600 mg daily

+

Ethambutol 15 mg/kg daily and

+

Azithromycin 250 mg daily

OR

Clarithromycin 500 mg twice daily

Consider intravenous amikacin for up to 3 months or nebulised amikacin

CLARITHROMYCIN RESISTANT MAC PD

- Rifampicin 600 mg daily

  +

  Ethambutol 15 mg/kg daily

  +

- Isoniazid 300 mg (+pyridoxine 10 mg) daily

  OR

  Moxifloxacin 400 mg daily

  Consider intravenous amikacin for up to 3 months or nebulised amikacin.

MYCOBACTERIUM MALMOENSE PD

NON-SEVERE

- Rifampicin 600 mg daily
  +
  Ethambutol 15 mg/kg daily and
  +
  Azithromycin 250 mg daily
  OR
  Clarithromycin 500 mg twice daily

SEVERE

- Rifampicin 600 mg daily
  +
  Ethambutol 15 mg/kg daily and
  +
  Azithromycin 250 mg daily
  OR
  Clarithromycin 500 mg twice daily

- Consider intravenous amikacin for up to 3 months or nebulised amikacin

MYCOBACTERIUM XENOPI PD

NON-SEVERE

- Rifampicin 600 mg daily
  +
  Ethambutol 15 mg/kg daily
  +
  Azithromycin 250 mg daily
  OR
  Clarithromycin 500 mg twice daily
  +
  Moxifloxacin 400 mg daily
  OR
  Isoniazid 300 mg (with pyridoxine 10 mg) daily

SEVERE

- Rifampicin 600 mg daily
  +
  Ethambutol 15 mg/kg daily
  +
  Azithromycin 250 mg daily
  OR
  Clarithromycin 500 mg twice daily
  +
  Moxifloxacin 400 mg daily
  OR
  Isoniazid 300 mg (with pyridoxine 10 mg) daily

- Consider intravenous amikacin for up to 3 months or nebulised amikacin

MYCOBATERIUM KANSASII PD

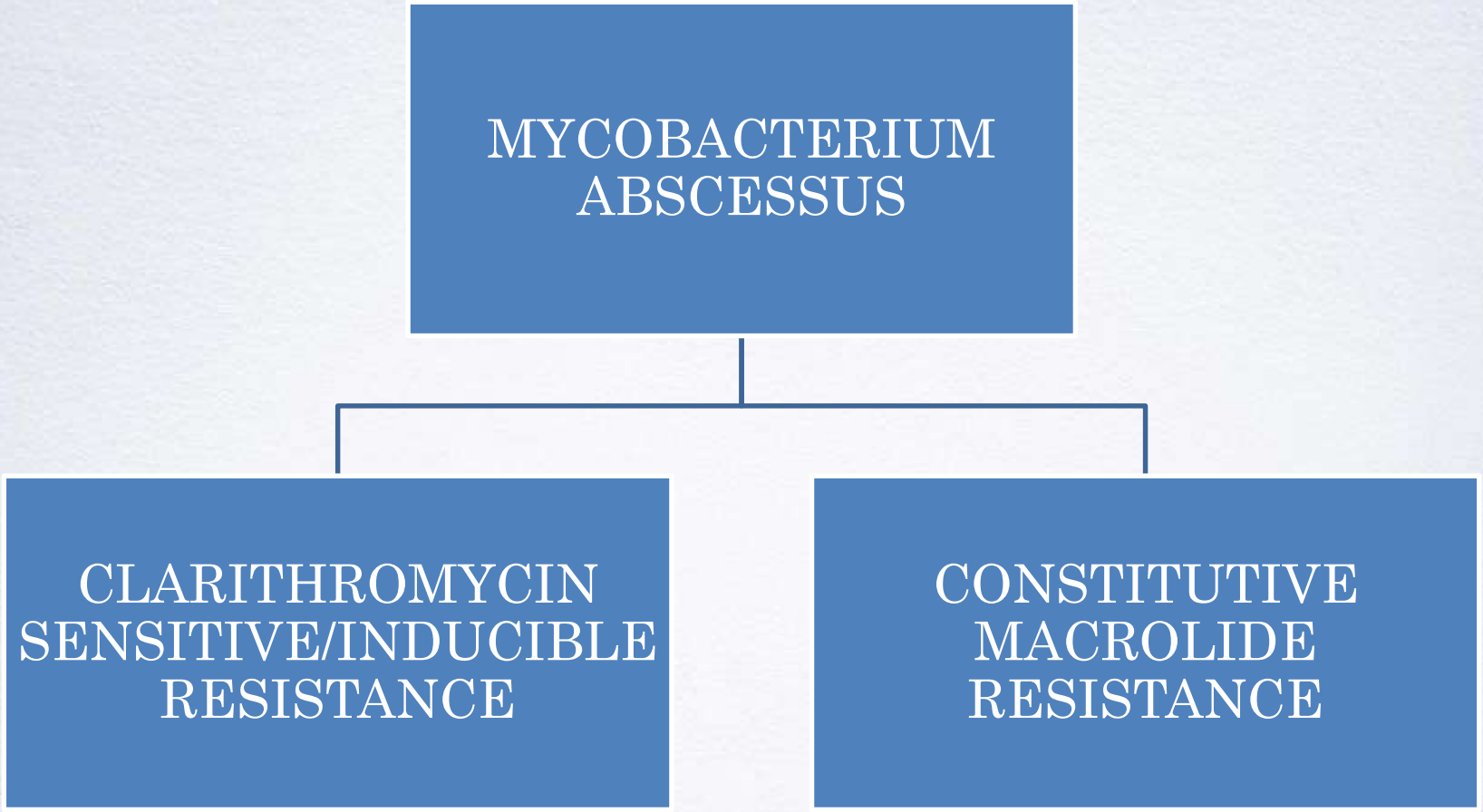
RIFAMPICIN SENSITIVE

- Rifampicin 600 mg daily
  +
  Ethambutol 15 mg/kg daily
  +
- Isoniazid 300 mg (with pyridoxine 10 mg) daily
  OR
  Azithromycin 250 mg daily/Clarithromycin 500 mg twice daily

RIFAMPICIN RESISTANT

- Three-drug regimen guided, but not dictated by, DST results using a daily oral regimen.

MYCOBACTERIUM ABSCESSUS PD



Initiation phase ≥ 1 month

Continuation phase minimum of 12 months after culture conversion

CLARITHROMYCIN SENSITIVE/INDUCIBLE RESISTANCE

- **INITIATION PHASE**

IV amikacin 15 mg/kg daily or 3 /week

+

IV tigecycline 50 mg twice daily

+

IV imipenem 1 g twice daily(where tolerated)

+

Oral clarithromycin 500 mg twice daily (where tolerated)

OR

Oral azithromycin 250–500 mg daily

- **CONTINUATION PHASE**

Nebulised amikacin

+

Oral Clarithromycin 500 mg twice daily

OR

Oral Azithromycin 250–500 mg daily

+

1–3 of the antibiotics guided by drug susceptibility results and patient tolerance

CONSTITUTIVE MACROLIDE RESISTANCE

- **INITIATION PHASE**

  IV amikacin 15 mg/kg daily or 3 /week

  +

  IV tigecycline 50 mg twice daily

  +

  IV imipenem 1 g twice daily(where tolerated)

- **CONTINUATION PHASE**

  Nebulised amikacin

  +

  2-4 of the 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 co-trimoxazole 960 mg twice daily

NON-ANTIBIOTIC TREATMENT

RECOMMENDATION

- Interferon gamma is not recommended as adjuvant therapy without a defined immunodeficiency. (Grade D)

- M. vaccae is not recommened as adjuvant therapy. (Grade D)

INVESTIGATION DURING TREATMENT AND FOLLOW-UP

MICROBIOLOGY RECOMMENDATION

- Sputum
- Expectorated sputum
- CT-directed bronchial washings
- cultured every 4–12 weeks during treatment and for 12 months after completing treatment. (Grade D)

RADIOLOGICAL RECOMMENDATION

- A **CT scan** should be performed shortly before starting NTM treatment and at the end of NTM treatment. (Grade D)

CLINICAL RECOMMENDATION

- A detailed clinical assessment should be done at each clinical review. (Grade D)

THERAPEUTIC DRUG MONITORING RECOMMENDATION

- Therapeutic drug monitoring should not be performed routinely. (Grade D)

- When aminoglycosides are administered, serum levels and the serum creatinine must be monitored. Audiometry should be considered before starting aminoglycosides. (Grade D)

- When Ethambutol is being administered, visual acuity and colour vision should be assessed. (Grade D)

- Serum ethambutol levels should be measured in patients with renal dysfunction. (Grade D)

  Audiometry and ECG before, and 2 weeks after should be considered before starting azithromycin or clarithromycin.

SPECIALIST vs NON-SPECIALIST TREATMENT

RECOMMENDATION

- NTM-PD should be managed in collaboration with a experienced physician. (Grade D)

ROLE OF SURGERY

RECOMMENDATION

- The role of lung resection surgery should be considered in refractory disease. (Grade D)
- Lung resection surgery may be indicated in localised areas of severe disease. (Grade D)
- Surgery should be performed following expert multidisciplinary assessment. (Grade D)

- Individuals should be on antibiotic treatment before surgery and should continue for 12 months after culture conversion. (Grade D).

- Following resection of a solitary NTM nodule with no other features, antibiotic treatment is not usually required. (Grade D)

- Assessment of cardiopulmonary status and nutritional status should be optimised prior to surgery.

LUNG TRANSPLANT ELIGIBILITY

RECOMMENDATION

- Individuals being considered for transplantation should be assessed for evidence of NTM-PD. (Grade D)

- Isolation of NTM should not preclude referral. (Grade D)

- When diagnosed it should be treated. (Grade D)

- Individuals should be counselled about the high postoperative risk. (Grade D)
- Individuals should be able to tolerate optimal antibiotic therapy.
- Progressive NTM-PD despite optimal antibiotic therapy is likely to be a contraindication for transplant.

TAKE HOME MESSAGE

- To have NTM-PD as a differential diagnosis in individuals with pre-existing Lung disease.
- NTM should ideally be identified at species and subspecies level to better guide the treatment.
- Treatment must be continued 12 months after culture conversion.
- Sputum sampling and cultures must be done every 4-12 weeks for monitoring the treatment effectiveness.
- Drug toxicity monitoring should ideally be a part of follow-up.

THANK YOU