MANAGEMENT OF NON-TUBERCULOUS MYCOBACTERIAL PULMONARY DISEASE

NTM DIALOGUE

April 2021; MED-00476

NON-TUBERCULOUS MYCOBACTERIAL PULMONARY DISEASE

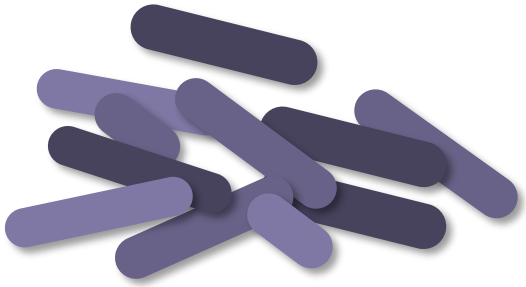
Non-tuberculous mycobacterial pulmonary disease (NTM-PD)

Non-tuberculous mycobacteria (NTM)

Over 190 species and subspecies[1]

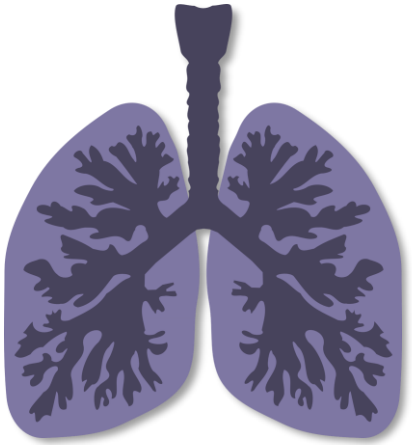
Can produce opportunistic infections in humans of all ages[1,2]

Affect both pulmonary and extrapulmonary sites[1]



Clinical presentation:[3, 4]

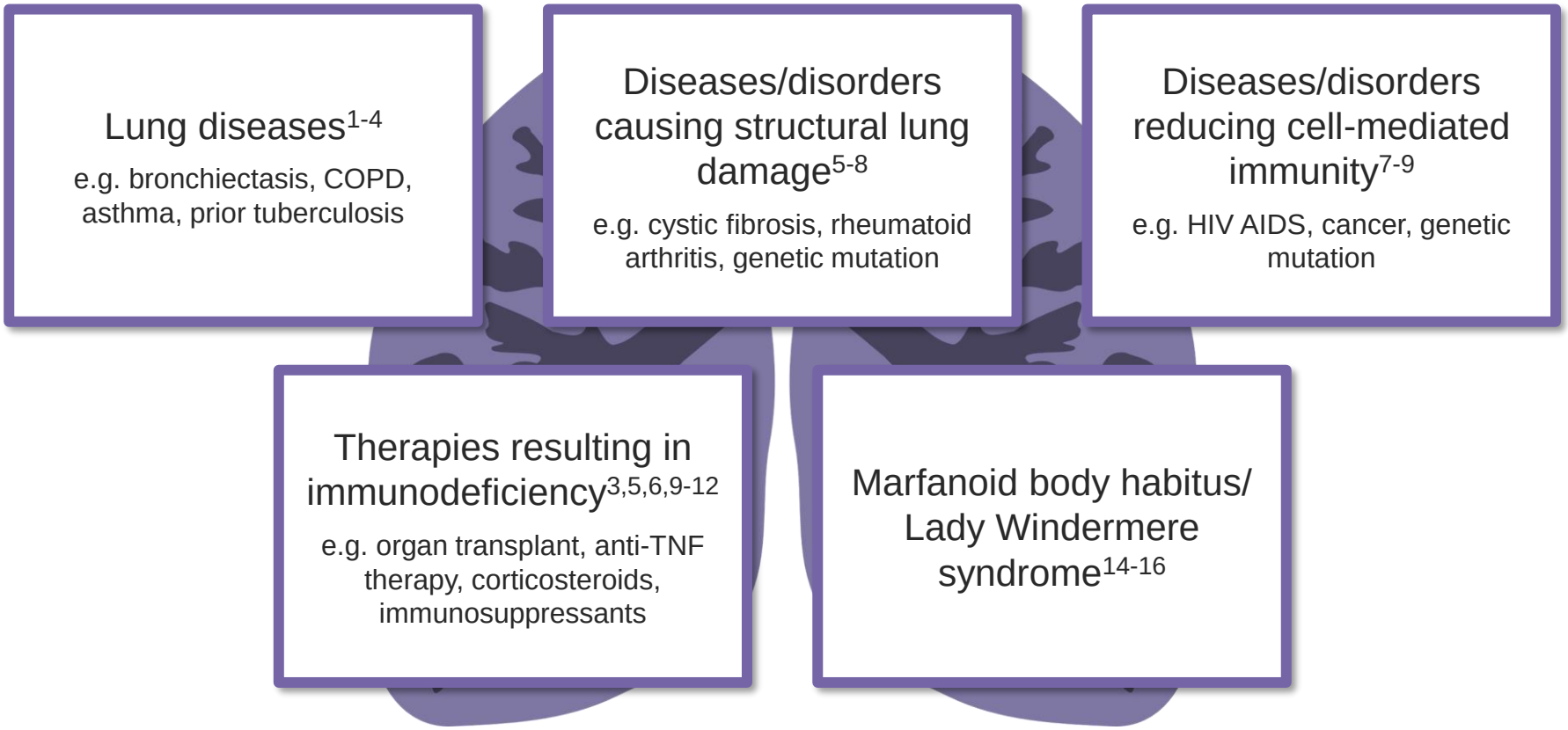
- ✓ Productive cough
- ✓ Rhonchi
- ✓ Crackles
- ✓ Wheezes
- ✓ Constitutional symptoms
- ✓ Haemoptysis



NTM, non-tuberculous mycobacteria; NTM-PD, non-tuberculous mycobacterial pulmonary disease

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36; 3. van Ingen J, et al. Eur Respir J 2018;51:1-6; 4. Griffith DE, et al. Am J Respir Crit Care Med 2007;175:367-416

Risk factors for NTM-PD



AIDS, acquired immune deficiency syndrome ; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus infection; NTM-PD, non-tuberculous mycobacterial pulmonary disease; TNF, tumour necrosis factor

1. Andrejak C, et al. Thorax 2013;68:256-62; 2. Jones MM, et al. PLoS One 2018;13:0197976; 3. Dirac MA, et al. Am J Respir Crit Care Med 2012;186:684-91; 4. Aksamit TR, et al. Chest 2017;151:982-92; 5. Winthrop KL, et al. Ann Rheum Dis 2013;72:37-42; 6. Brode SK, et al. Thorax 2015;70:677-82; 7. Wu UI, Holland SM. Lancet Infect Dis 2015;15:968-80; 8. Szymanski EP, et al. Am J Respir Crit Care Med 2015;192:618-28; 9. Henkle E, et al. Clin Chest Med 2015;36:91-9; 10. Ose N, et al. Surg Case Rep 2019;5:11; 11. Friedman DZP, et al. Transpl Infect Dis 2020;22:e13229; 12. Chao WC, et al. BMC Infect Dis 2017;17:796; 1 3. Liu VX, et al. Ann Am Thorac Soc 2018;15:1169-76; 14. Kim RD, et al. Am J Respir Crit Care Med 2008;178:1066-74; 15. Holt MR, et al. Eur Respir J 2019;54:1900252; 16. Ku JH et al. Diagn Microbiol Infect Dis 2020;96:114916

Prevalence of NTM-PD

The incidence and prevalence of NTM-PD is increasing in many parts of the world[1-4]

This may reflect increases in:

- Awareness of the importance of NTM[1]
- Incidence of risk factors such as COPD and bronchiectasis[5,6]
- Use of immunosuppressive treatments[7]
- Testing for NTM-PD and effectiveness of diagnostic tools[1,7,8]

Rates of NTM-PD are particularly high in:[3,4]

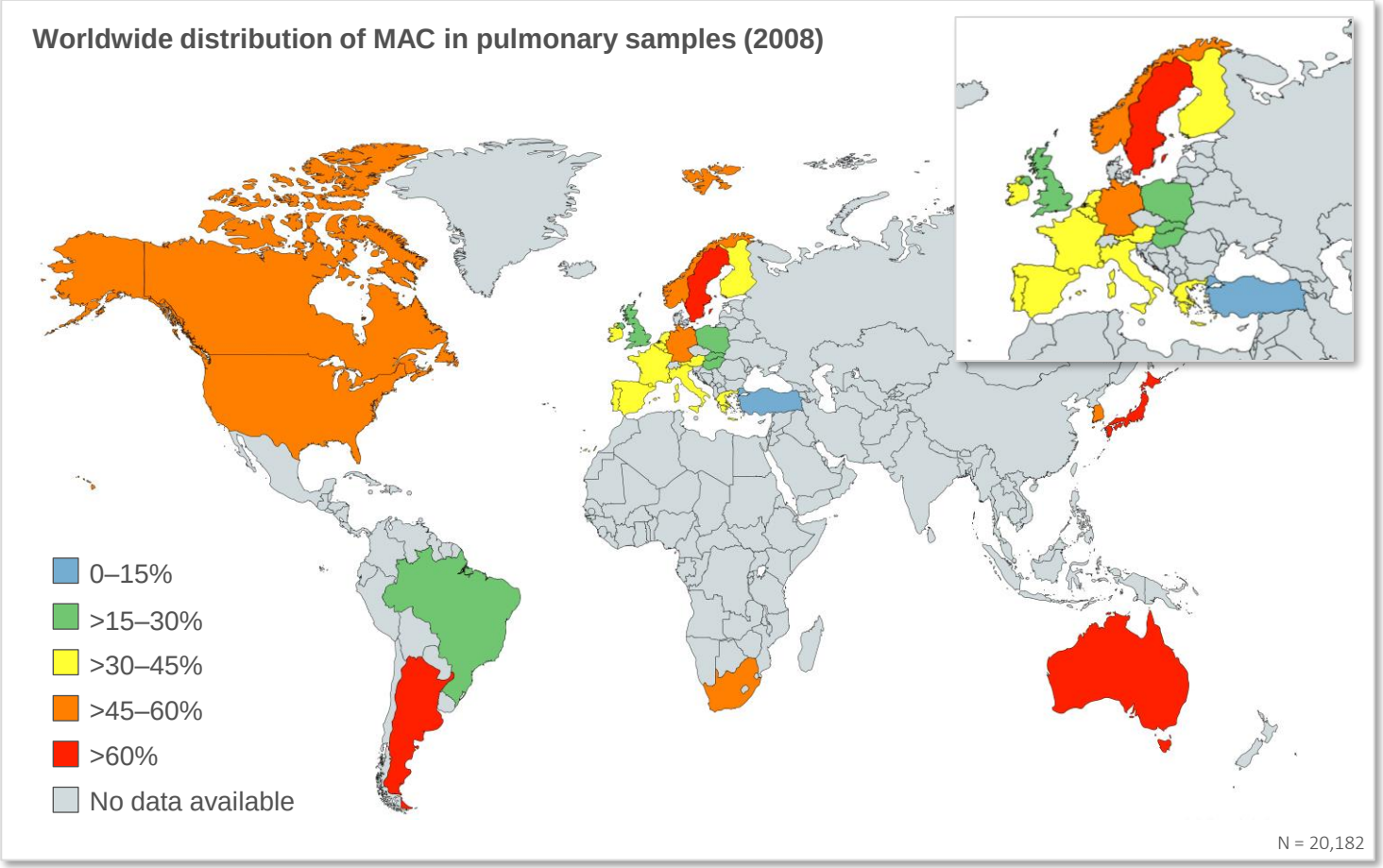
- Older individuals
- Individuals with underlying bronchiectasis

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus infection; NTM, non-tuberculous mycobacteria; NTM-PD, non-tuberculous mycobacterial pulmonary disease

1. Griffith DE, et al. Am J Respir Crit Care Med 2007;175:367-416; 2. Diel R, et al. BMC Infect Dis 2018;18:206; 3. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 4. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36; 5. Terzikhan N, et al. Eur J Epidemiol 2016;31:785-92; 6. Snell N, et al. Respir Med 2019;158:21-23; 7. Chalmers JD, et al. Pulmonol 2018;24:120-31; 8. Park TY, et al. PLoS One 2017;12:1-11

Mycobacterium avium complex (MAC)

MAC is the predominant NTM species causing lung disease in most countries worldwide[1]



Adapted from Hoefsloot W, et al. Eur Respir J 2013;42:1604-13

MAC, *Mycobacterium avium* complex; NTM, non-tuberculous mycobacteria

1.. Hoefsloot W, et al. Eur Respir J 2013;42:1604-13

Disease progression in MAC-PD

MAC-PD is associated with progressive decline in lung function and radiologic deterioration, although some patients remain stable[1-5]

Patients may experience exacerbation of symptoms which may require hospitalization for their management[5]

Correct, early diagnosis and treatment are paramount to prevent disease progression[6-9]

MAC-PD, *Mycobacterium avium* complex pulmonary disease

1. Hwang JA, et al. Eur Respir J 2017;49:1600537; 2. Park TY, et al. PLoS One 2017;12:1-11; 3. Kobayashi T, et al. J Clin Tuberc Other Mycobact Dis 2018;11:17-21;
4. Lee MR, et al. PLoS One 2013;8:e58214; 5. Huang CT, et al. Int J Tuberc Lung Dis 2012;16:539-45; 6. Maiga M, et al. PLoS One 2012;7:e36902;
7. Eikhani MS, et al. BMC Infect Dis 2018;18:311; 8. Wagner D et al. Poster presented at: ERS Annual Congress; 2014; Munich, Germany;
9. Griffith DE, et al. Am J Respir Crit Care Med 2007;175:367-416

TREATMENT OF NON-TUBERCULOUS MYCOBACTERIAL PULMONARY DISEASE: AN OFFICIAL ATS/ERS/ESCMID/IDSA CLINICAL PRACTICE GUIDELINE

Treatment of NTM-PD: an official ATS/ERS/ESCMID/IDSA clinical practice guideline 2020[1,2]

Makes recommendations based on PICO questions regarding:

- Diagnostic procedures
- Diagnostic criteria
- Drug susceptibility testing
- When to start therapy
- Regimens for treatment of MAC-PD
- Regimens for treatment of lung disease associated with *M. kansasii*, *M. xenopi* and *M. abscessus*

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus infection; NTM, non-tuberculous mycobacteria; NTM-PD, non-tuberculous mycobacterial pulmonary disease; MAC-PD, *Mycobacterium avium* complex pulmonary disease; PICO, Population, Intervention, Comparators, Outcomes

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

Summary of guideline recommendations for diagnosis of MAC-PD

	ATS/IDSA 2007 guidelines[1]	ATS/ERS/ESCMID/IDSA 2020 guidelines[2,3]
Clinical/ radiologic	Pulmonary symptoms OR chest X-ray OR CT scan	Pulmonary or systemic symptoms AND Chest X-ray OR CT scan
Microbiologic	Minimum of two sputum samples Bronchoalveolar lavage, bronchial washing and transbronchial biopsy samples may also be used	Minimum of two sputum samples of the same NTM species Bronchoalveolar lavage, bronchial washing and transbronchial biopsy samples may also be used
Susceptibility testing	Clarithromycin	Macrolides (preferentially azithromycin) and amikacin

National guidelines are available from national societies in Germany, Japan and UK[4-6]

Purple text indicates updates to 2007 guidelines

ATS, American Thoracic Society; BTS, British Thoracic Society; CT, computed tomography; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America; MAC-PD, *Mycobacterium avium* complex pulmonary disease; NTM, non-tuberculous mycobacteria

1. Griffith DE, et al. Am J Respir Crit Care Med 2007;175:367-416; 2. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 3. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36; 4. Schönfeld N, et al. Pneumologie 2016;70:250-76; 5. Nontuberculous Mycobacteriosis Control Committee of the Japanese Society for Tuberculosis; Scientific Assembly for Infection and Tuberculosis of the Japanese Respiratory Society. Kekkaku. 2013 Jan;88(1):29-32. PMID: 23513566. 6. Haworth CS et al. Thorax 2017;72(Suppl 2):ii1-ii64

Criteria for diagnosis of MAC-PD

	Criteria from 2020 guidelines[1,2]
Clinical	Pulmonary symptoms (e.g. cough, sputum production, haemoptysis, dyspnoea, chest pain)[3] Appropriate exclusion of other diagnoses
AND	
Radiologic	Nodular or cavitary opacities on chest radiograph, or bronchiectasis with multiple small nodules on high-resolution CT scan
AND	
Microbiologic	One of the following: • Positive culture results from at least two sputum samples* • Positive culture results from at least one bronchial wash or lavage • Transbronchial or other lung biopsy with mycobacterial histologic features† and positive culture for NTM • Transbronchial or other lung biopsy with mycobacterial histologic features† and one or more sputum or bronchial washings culture positive for NTM

*When 2 positive cultures are obtained, the isolates should be the same NTM species in order to meet disease criteria; †granulomatous inflammation or acid-fast bacilli
CT, computed tomography ; MAC-PD, *Mycobacterium avium* complex pulmonary disease; NTM, non-tuberculous mycobacteria

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36;
3. Griffith DE, et al. Am J Respir Crit Care Med 2007;175:367-416

Microbiologic evidence for MAC-PD

Recommendations from 2020 guidelines[1,2]

- **>1 positive sputum culture** is required (to avoid spurious results from environmental contamination)
- **>3 respiratory samples** should be collected over 1 week (to distinguish MAC-PD from occasional presence of MAC in the tracheobronchial tract)
- **Sputum samples** are often suitable to diagnose cavitary disease
- **Bronchoalveolar lavage fluid/bronchial washing cultures** may be used to diagnose nodular/bronchiectatic NTM disease
- **Bronchoscopy** is performed only if sputum specimens are not obtainable

Where the same species is isolated in ≥2 sputum cultures over an interval of ≥1 week, there is a 98% likelihood of clinically significant MAC

Low pathogenicity species (e.g. *Mycobacteriurm gordonae*): several repeated positive cultures over months plus strong clinical and radiological evidence required to determine if it is causing disease

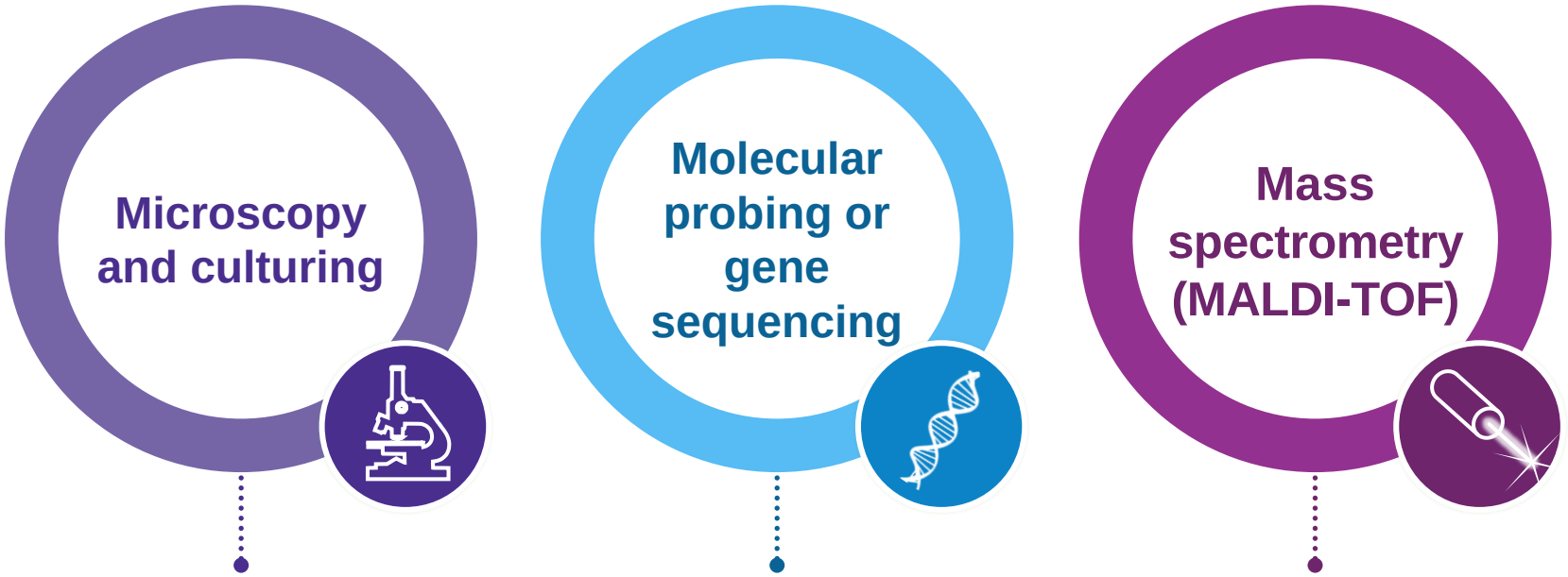
Pathogenic species (e.g. *Mycobacteriurm kansasii*): single positive culture may be enough evidence to initiate treatment

MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease; NTM, non-tuberculous mycobacteria

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

Identification of pathogen species

Species identification helps determine clinical relevance and treatment selection[1,2]



Staining and examination by microscopy and culturing on both solid and liquid media

Sequencing is more accurate but not available in all centres

Probe-based assays are easier to perform and implement but lack discriminatory power

Not able to differentiate all species/subspecies

Culture on solid media required for good results

- **Isolates from patients undergoing treatment should be frozen to allow reinfection/relapse to be distinguished if recurrence occurs and to obtain differences in drug susceptibility testing patterns**

MALDI-TOF, matrix-assisted laser desorption ionization-time of flight

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

Drug susceptibility testing

The 2020 guidelines recommend susceptibility testing for macrolides and amikacin over empirical therapy for MAC[1,2]

Acquired macrolide resistance in MAC is due to point mutations in the 23S rRNA (*rrl*) gene

Acquired amikacin resistance is due to mutations in the 16S rRNA (*rrs*) gene

For MAC, there is a clear correlation between ***in vitro* susceptibility** of the causative strain and the **outcome of treatment** with some antibiotic regimens

The Clinical and Laboratory Standards Institute (CSLI) provides **guidelines for test procedures[3]**

The CLSI breakpoints for resistance are MIC ≥32 µg/mL for clarithromycin and ≥64 µg/mL for parenteral amikacin and ≥128 µg/mL for ALIS[3]

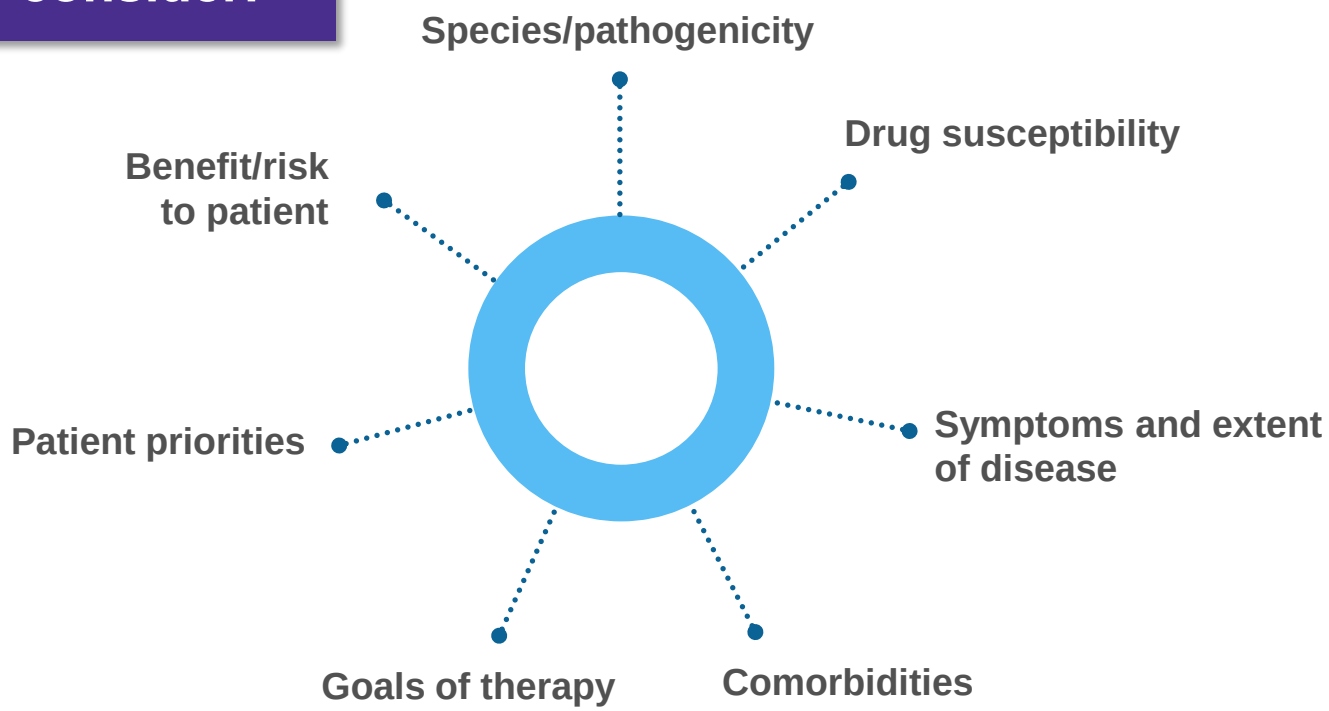
ALIS, amikacin liposome inhalation suspension; CLSI, Clinical and Laboratory Standards Institute; MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease; MIC, minimum inhibitory concentration; NTM, non-tuberculous mycobacteria

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36;
3. CLSI. Performance standards for susceptibility testing of mycobacteria, Nocardia spp, and other aerobic actinomyces. 1st Edn. Vol. M62. Clinical and Laboratory Standards Institute, 2018.

Factors determining treatment approach

The decision to initiate antibiotic therapy should not be based on diagnostic criteria alone[1,2]

Also consider:[1,2]



MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease; NTM, non-tuberculous mycobacteria

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

Challenges of treatment

- Require multi-agent regimens
- Often associated with clinically significant adverse reactions
- Need for prolonged therapy
- Treatment outcomes are often suboptimal
- Reinfection with another strain/species common

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

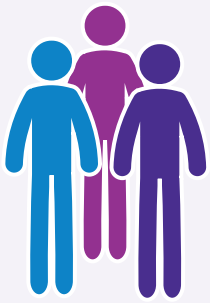
When to initiate treatment

In patients who meet the diagnostic criteria for NTM-PD, initiation of treatment is recommended over watchful waiting, especially in the context of positive AFB sputum smears and/or cavitary lung disease[1,2]

The decision should be individualised, based on potential risks and benefits of therapy for individual patients

Evidence

- In a study of **488 patients with MAC-PD** who were followed **for at least 1 year**, progression was more likely to occur in those who were **AFB smear positive, had fibrocavitary disease or more extensive radiographic disease**[3]



Factors favouring treatment[1,2]

- Features associated with poor prognosis:
  - Cavitary disease
  - Low BMI
  - Low albumin
  - Elevated inflammatory markers
- Isolation of a species that is virulent and/or responsive to antimicrobial therapy
- Underlying immune suppression
- Major symptoms causing decreased health-related quality of life (e.g. fatigue)

AFB, acid-fast bacilli; MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease; NTM-PD, non-tuberculous mycobacteria pulmonary disease

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36;
3. Hwang JA, et al. Eur Respir J 2017;49:1-10

Summary of guideline recommendations for when to initiate therapy

	ATS/ERS/ESCMID/IDSA 2020 guidelines[1,2]
Initiation of therapy	Decision based on potential risks and benefits of therapy for individual patients Patients who meet diagnostic criteria should be treated, especially if AFB-positive sputum or cavitary disease present

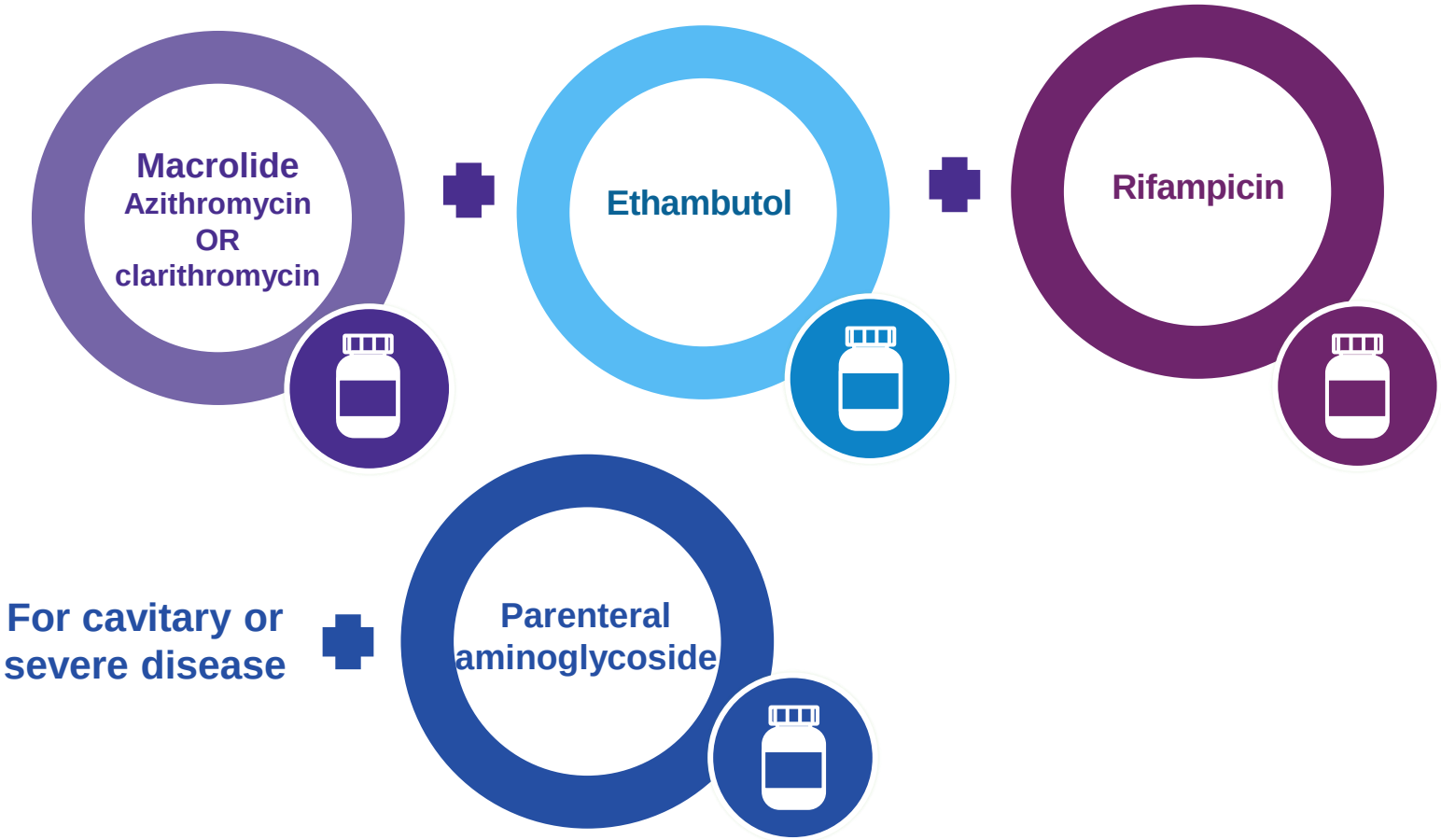
Purple text indicates updates to 2007 guidelines

AFB, acid-fast bacilli; ATS, American Thoracic Society; BTS, British Thoracic Society; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America;

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

Recommended classes of antibiotics for management of MAC-PD

Oral guideline-based therapy (GBT) consists of:[1,2]



GBT, guideline-based therapy; MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease; NTM, non-tuberculous mycobacteria

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

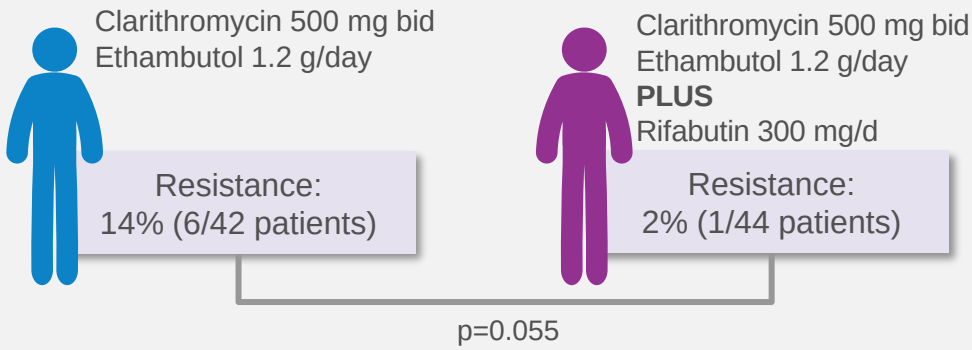
Triple-agent regimens

A treatment regimen with at least three drugs (including a macrolide and ethambutol) is recommended over a regimen with 2 drugs (a macrolide and ethambutol alone) in patients with macrolide-susceptible MAC-PD[1,2]

- Reducing the risk of development of macrolide resistance is a priority in MAC-PD therapy

Evidence

- In a randomized controlled trial of rifabutin added to clarithromycin and ethambutol for treatment of disseminated MAC infection, response rates were equivalent with or without rifabutin but development of macrolide resistance was lower (p=0.055) in patients on the 3-drug regimen[3]
- A randomized controlled trial to evaluate the safety and efficacy of a 2 versus 3 drug regimen is currently underway, funded by the Patient-Centered Outcomes Research Institute[4]



MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36; 3. Gordin FM, et al. Clin Infect Dis 1999;28:1080-5; 4. PCORI Available at: https://www.pcori.org/research-results/2018/using-two-versus-three-antibiotics-treat-mac-lung-infections [Accessed April 2021]

Inclusion of a macrolide in triple-agent regimens

Macrolide-susceptible MAC-PD should be treated using a three-drug regimen including a macrolide (clarithromycin or azithromycin) in preference to a regimen without a macrolide[1,2]

Evidence

Two randomized controlled trials have compared a macrolide regimen with a nonmacrolide regimen[3,4]

In 170 patients with primarily cavitary MAC-PD randomized to receive clarithromycin or ciprofloxacin with standard doses of rifampicin and ethambutol, **the clarithromycin group had a lower failure/relapse rate than the ciprofloxacin group** (13% versus 23%)[3]

In 27 patients with MAC-PD treated for 1 year with rifampicin and ethambutol plus either gatifloxacin or low dose clarithromycin, **treatment outcomes were not significantly different between study arms**: 85% of patients in the gatifloxacin group and 64% in the clarithromycin group achieved sputum culture conversion[4]

In macrolide-resistant disease, sputum culture conversion rates fall from approximately 80% to only 5–36%[1,2]

MAC-PD, *Mycobacterium avium* complex pulmonary disease

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36; 3. Jenkins PA, et al. Thorax 2008;63:627–34; 4. Fujita M, et al. J Infect Chemother 2012;18:146-51

Choice of macrolide

In macrolide-susceptible MAC-PD, azithromycin is recommended over clarithromycin[1,2]

Evidence

- Both macrolides demonstrate similar efficacy in terms of culture conversion[1,2]
- However, azithromycin may have benefits over clarithromycin:[1,2]
  - ✓ Fewer drug-drug interactions
  - ✓ Potential better tolerability
  - ✓ Lower pill burden
  - ✓ Once daily dosing
  - ✓ Possibly lower costs

- **Switching from one agent to the other may be considered in case of intolerance[1,2]**

MAC-PD, *Mycobacterium avium* complex pulmonary disease

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

Frequency of treatment

3-times per week macrolide-based regimen recommended in noncavitary nodular/bronchiectatic macrolide-susceptible MAC-PD[1,2]

Daily macrolide-based regimen recommended in patients with cavitary macrolide-susceptible MAC-PD[1,2]

Evidence

- Several noncomparative case series with consistent microbiologic results demonstrate that intermittent therapy is similar in efficacy to daily therapy, but is better tolerated than daily therapy for nodular/bronchiectatic MAC-PD
- Importantly, the evidence suggests no development of macrolide resistance with intermittent therapy
- Similar evidence to justify or support intermittent therapy for cavitary MAC-PD is not available and it is not recommended

MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease; NTM, non-tuberculous mycobacteria

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

Adding amikacin or streptomycin

Parenteral aminoglycosides are recommended for inclusion in the initial treatment of cavitary MAC, advanced/severe MAC-PD and macrolide-resistant MAC-PD[1,2]

- Macrolide-resistant MAC-PD may arise through prolonged use, e.g. in treatment of asthma to reduce exacerbation frequency, however, macrolides can exert effects through immunomodulatory mechanisms as well as via direct antibacterial action[3]

Evidence

A randomized controlled trial which evaluated the impact of adding streptomycin to macrolide-based oral therapy for the initial three months of therapy found a **significantly higher sputum culture conversion rate for patients who received streptomycin** than for those who received oral therapy only (71.2% versus 50.7%)[4]

Retrospective studies have suggested that the inclusion of **a parenteral aminoglycoside administered for ≥6 months** in addition to adjunctive surgery improves outcomes for patients with macrolide-resistant MAC-PD[5,6]

- **Administration of an aminoglycoside for at least 2–3 months is considered the best balance between risks and benefits[1,2]**

MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36; 3. Smith D, et al. BMJ Open Resp Res 2020;7:e000489; 4. Kobashi Y, et al. Respir Med 2007;101:130–8; 5. Griffith DE, et al. Am J Respir Crit Care Med 2006;174:928-34; 6. Morimoto K, et al. Ann Am Thorac Soc 2016;13:1904-11

Testing for culture conversion

The aim of treatment is to achieve an improvement in symptoms and culture conversion, leading to a microbiological cure[1]

? NTM-NET definition

Culture conversion

≥3 consecutive negative mycobacterial cultures from respiratory samples, **collected ≥4 weeks apart**, during antimycobacterial treatment[2]

? NTM-NET definition

Microbiological cure

Multiple consecutive negative but no positive cultures with the causative species from respiratory samples **after culture conversion and until the end of antimycobacterial treatment**[2]

- Improvements in symptoms should be observed within 3–6 months of initiating therapy and culture conversion should be seen within 12 months[1]

MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease; NTM, non-tuberculous mycobacteria

1. Griffith DE, et al. Am J Respir Crit Care Med 2007;175:367-416; 2. van Ingen J, et al. Eur Respir J 2018;51:1-6

Summary of guideline recommendations for management of MAC-PD (1)

	ATS/ERS/ESCMID/IDSA 2020 guidelines[1,2]
Treatment regimen (1)	*Macrolide susceptible* Three-drug regimen containing a macrolide azithromycin OR clarithromycin (azithromycin is preferred over clarithromycin to reduce drug-drug interaction), ethambutol and rifampicin
Treatment regimen (2)	*Cavitary disease/macrolide resistant* Azithromycin OR clarithromycin plus ethambutol and rifampicin – plus parenteral amikacin or streptomycin as initial therapy for 2–3 month
Treatment regimen (3)	*Refractory (6 months)* Azithromycin, rifampicin, ethambutol, ALIS*
Treatment recommendations	Treatment regimen should contain AT LEAST 3 antimicrobials (macrolide plus ethambutol)

ALIS (amikacin liposome inhalation suspension) is known in Europe as ARIKAYCE liposomal 590 mg nebuliser dispersion

Purple text indicates updates to 2007 guidelines. ALIS, amikacin liposome inhalation suspension; ATS, American Thoracic Society; BTS, British Thoracic Society; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America; MAC-PD, *Mycobacterium avium* complex pulmonary disease

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

Summary of guideline recommendations for management of MAC-PD (2)

	ATS/ERS/ESCMID/IDSA 2020 guidelines[1,2]
Implementation	*Nodular/bronchiectatic:* intermittent *Severe or cavitary disease:* daily
Use of aminoglycosides	*Cavitary or advanced disease/macrolide resistant* Parenteral amikacin or streptomycin for 2–3 months Amikacin (inhaled or ALIS) not recommended for patients as part of initial treatment Patients not responsive to treatment after 6 months add ALIS to current treatment regimen
Duration	12 months AFTER culture conversion

Purple text indicates updates to 2007 guidelines. ALIS, amikacin liposome inhalation suspension; ATS, American Thoracic Society; BTS, British Thoracic Society; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America; MAC-PD, *Mycobacterium avium* complex pulmonary disease

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

Management of refractory MAC-PD

The 2020 guidelines strongly recommend* adding ALIS to oral GBT triple therapy in patients with treatment-refractory disease†[1,2]

- Systemic use of parenteral amikacin has been associated with a high frequency of renal, auditory, and vestibular toxicity[1,2]
- Delivery of amikacin by hand-held nebulization may be a potential way to improve efficacy and decrease drug-related toxicity[1,2]

Evidence

Five case series (N=138, 55 patients with MAC), in which clinical responses were reported in 20–100% and sputum conversion was reported in 18–67% of treatment refractory MAC-PD[1-7]

CONVERT Phase 3 trial of ALIS versus oral GBT in patients failed on oral GBT compared with oral GBT alone (see next slide)[8]

- There is insufficient evidence to support the use of inhaled antibiotics as an **initial** treatment option[1,2]

*In patients with MAC-PD who have failed at least 6 months GBT, guidelines recommend the additional of ALIS to the treatment regimen (strong recommendation, moderate certainty in estimates of effect;[1,2]
†defined as culture positivity after at least 6 months of GBT[1,2]

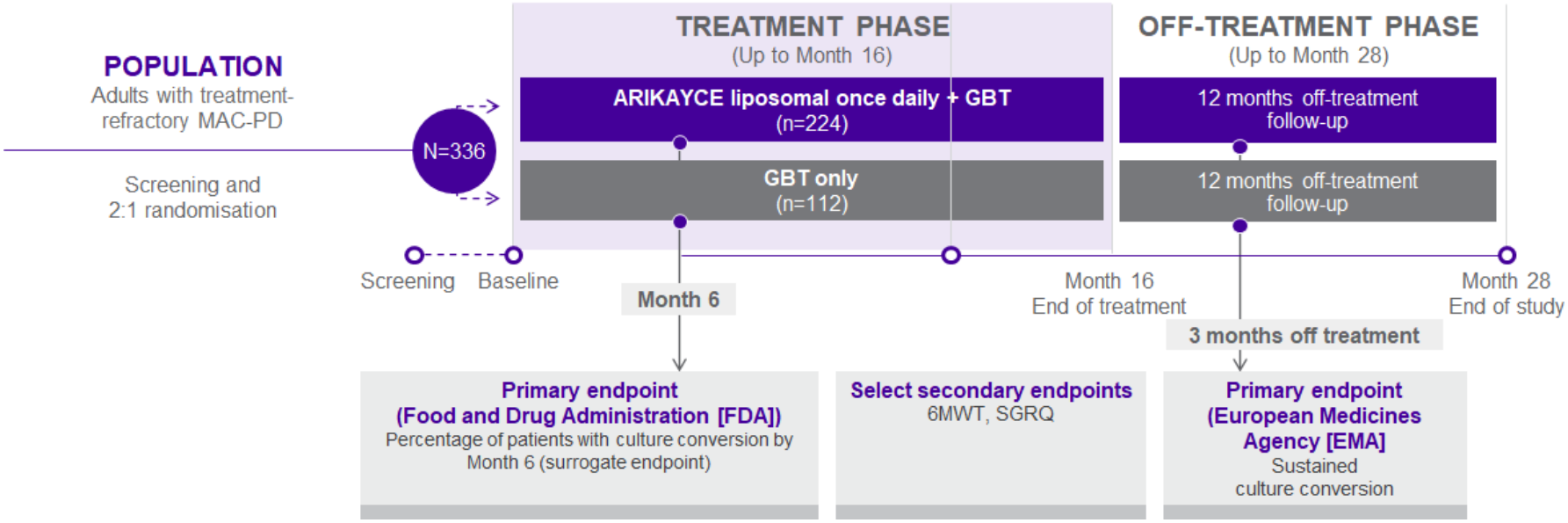
ALIS, amikacin liposome inhalation suspension; GBT, guideline-based therapy; MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36; 3. Davis KK, et al. BMC Pulm Med 2007;7:2; 4. Safdar A. Eur J Clin Microbiol Infect Dis 2012;31:1883-7; 5. Olivier KN, et al. Ann Am Thorac Soc 2014;11:30-5; 6. Jhun BW, et al. Antimicrob Agents Chemother 2018;62:e00011-18; 7. Yagi K, et al. BMC Infect Dis 2017;17:558; 8. Griffith DE, et al. Am J Respir Crit Care Med 2018;198:1559-69

CONVERT: ALIS for treatment-refractory MAC-PD

Study design and primary endpoints[1,2]

- **CONVERT was a prospective, open-label, randomized Phase 3 study in which adults with treatment-refractory MAC-PD were randomly assigned (2:1) to receive ALIS with oral GBT or oral GBT alone**



ALIS, amikacin liposome inhalation suspension; CI, confidence interval; GBT, guideline-based therapy; MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease; OR, odds ratio

1. Griffith DE, et al. Am J Respir Crit Care Med 2018;198:1559-69; 2. European Medicines Agency Available at: https://www.ema.europa.eu/en/documents/assessment-report/arikayce-liposomal-epar-public-assessment-report_en.pdf Accessed April 2021

CONVERT: ALIS for treatment-refractory MAC-PD

Primary endpoint outcomes[1]

Primary endpoint (FDA)

Culture conversion: 3 months consecutive MAC-negative sputum cultures by Month 6

Results of FDA primary endpoint at 6 months[1,2]

Culture conversion achieved by:

- **29%** (65/224 patients) with ALIS plus oral GBT
- **9%** (10/112 patients) with oral GBT alone

(adjusted OR [95% CI] = 4.22 [2.08–8.57], p<0.001)

Primary endpoint (EMA)

Durable culture conversion: maintenance of culture conversion after 12 months treatment and following withdrawal of all antibiotic therapy for 3 months

Results of EMA primary endpoint at 3 months off all therapy, following 12-month treatment[2]

Durable culture conversion achieved by:

- **16%** (36/224 patients) with ALIS plus oral GBT
- **0%** (0/112 patients) with oral GBT alone

(p<0.001)

ALIS, amikacin liposome inhalation suspension; CI, confidence interval; GBT, guideline-based therapy; MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease; OR, odds ratio

1. Griffith DE, et al. Am J Respir Crit Care Med 2018;198:1559-69; 2. ARIKAYCE liposomal, Summary of Product Characteristics October 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/arikayce-liposomal-product-information_en.pdf [Accessed April 2021]

CONVERT: ALIS for treatment-refractory MAC-PD

Secondary endpoints[1,2]

	Results at 6 months
Change from baseline in the distance achieved in the **6-minute-walk test**	No significant difference between treatment arms (least squares mean difference [SE], -3.0 [9.0]; 95% CI, 220.64 to 14.65; p=0.74)
Change from baseline in **St George's Respiratory Questionnaire**	No statistical difference between treatment arms, only a numerical difference favouring the GBT-alone arm (least squares mean difference [SE], 3.8 [1.6]; 95% CI, 0.67–6.94)

	ALIS plus oral GBT % (n)	Oral GBT % (n)	p value
Culture conversion at 6 months[1,3]	29.0 (65/224)	8.9 (10/112)	0.0001
Sustained culture conversion at 12 months on-treatment (ITT)[2]	18.3 (41/224)	2.7 (3/112)	0.0644
Durable conversion off-treatment at 3 months (ITT)[3]	16.1 (36/224)	0 (0)	0.0001

ALIS, amikacin liposome inhalation suspension; CI, confidence interval; GBT, guideline-based therapy; MAC-PD, *Mycobacterium avium* complex pulmonary disease; SE, standard error

1. Griffith DE, et al. Am J Respir Crit Care Med 2018;198:1559-69; 2. Griffith DE, et al. Eur Resp J 2019;54:Suppl. 63, OA4951; 3. ARIKAYCE liposomal, Summary of Product Characteristics October 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/arikayce-liposomal-product-information_en.pdf [Accessed April 2021]

CONVERT: ALIS for treatment-refractory MAC-PD

Safety outcomes[1]

TEAEs were reported in **98.2%** of patients in the ALIS + oral GBT arm and **91.1%** in the oral GBT alone arm

Serious TEAEs occurred in 20.2% and 17.9% of patients, respectively

Respiratory adverse events (primarily dysphonia, cough, and dyspnea) were reported in **87.4%** of patients receiving ALIS plus oral GBT and **50.0%** receiving oral GBT alone

Adverse events, if they occur are most frequent in the first month; new onset of adverse events declined thereafter

	ALIS plus oral GBT (n=223)	GBT alone (n=112)
Dysphonia	102 (45.7)	1 (0.9
Cough	102 (45.7)	17 (15.2
Dyspnoea	83 (37.2)	10 (8.9)
Haemoptysis	39 (17.5)	15 (13.4)
Diarrhoea	28 (12.6)	5 (4.5)
Fatigue	36 (16.1)	8 (7.1)
Nausea	25 (11.2)	4 (3.6)
Tinnitus	17 (7.6)	10 (8.9)
Dizziness	14 (6.3)	3 (2.7)
Hypoacusis	5 (2.2)	6 (5.4)
Renal/urinary disorders	6 (2.7)	6 (5.4)

There was no difference between groups in the incidence of hearing loss or renal impairment

ALIS, amikacin liposome inhalation suspension; GBT, guideline-based therapy; MAC-PD, *Mycobacterium avium* complex pulmonary disease; TEAE, treatment-emergent adverse events

1. Griffith DE, et al. Am J Respir Crit Care Med 2018;198:1559-69

Duration of therapy

Patients with macrolide-susceptible MAC pulmonary disease should receive treatment for at least 12 months after culture conversion[1,2]

Evidence

This recommendation is based on limited evidence, since the optimal duration of therapy for pulmonary MAC disease is not currently known and has not been evaluated in a prospective randomized clinical trial

- In a single centre retrospective observational cohort study, culture conversion was observed in 22% of who received treatment for <12 months, compared with 86% of patients who completed at least 12 months of therapy (p<0.001)[3]
- A systematic review reported that treatment success was higher in persons who received at least 12 months of macrolide-based therapy compared with <12 months[4]

However, these studies didn't evaluate treatment outcomes by duration of treatment after culture conversion

- In a postmarketing study from Japan, bacteriologic relapse was noted in 5% of patients when treatment was continued for <15 months after sputum culture conversion and in 0 patients who continued treatment for >15 months[5]

MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease; NTM, non-tuberculous mycobacteria

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36; 3. Wallace RJ Jr, et al. Chest 2014;146:276–82; 4. Diel R, et al. Chest 2018;153: 888-921; 5. Kadota JI, et al. J Infect Chemother 2017;23:293–300

SUMMARY

Summary of 2020 guidelines for NTM-PD

- **New 2020 guidelines for MAC-PD** refine management from NTM identification to treatment of refractory disease[1,2]
- **Clinical**, **radiographic**, and **microbiologic** criteria are required for diagnosis, including ≥2 sputum samples of the same NTM species[1,2]
- **Susceptibility testing** should be performed for macrolides (preferentially azithromycin) and amikacin[1,2]
- In appropriate patients diagnosed with NTM-PD, **initiation of treatment** is recommended over watchful waiting[1,2]

MAC, *Mycobacterium avium* complex; MAC-PD, *Mycobacterium avium* complex pulmonary disease; NTM, non-tuberculous mycobacteria; NTM-PD, non-tuberculous mycobacteria pulmonary disease

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36

Summary of 2020 guidelines for MAC-PD

- The aim of treatment is to achieve an **improvement in symptoms and culture conversion**, leading to a **microbiological cure**[1,2]
- In macrolide-susceptible MAC-PD, a **3-drug regimen** should be used, containing a macrolide (azithromycin or clarithromycin), ethambutol and rifampicin[1,2]
- In cavitary disease or macrolide resistant MAC-PD, **parenteral amikacin or streptomycin should be added** as initial therapy for 2–3 months[1,2]
- In treatment-refractory disease, **ALIS should be added** to oral GBT[1,2]
- Patients should receive treatment for **at least 12 months** after culture conversion[1,2]

GBT, guideline-based therapy; MAC-PD, *Mycobacterium avium* complex pulmonary disease

1. Daley CL, et al. Eur Respir J 2020 ;56:2000535; 2. Daley CL, et al. Clin Infect Dis 2020;71:e1-e36


Thank you