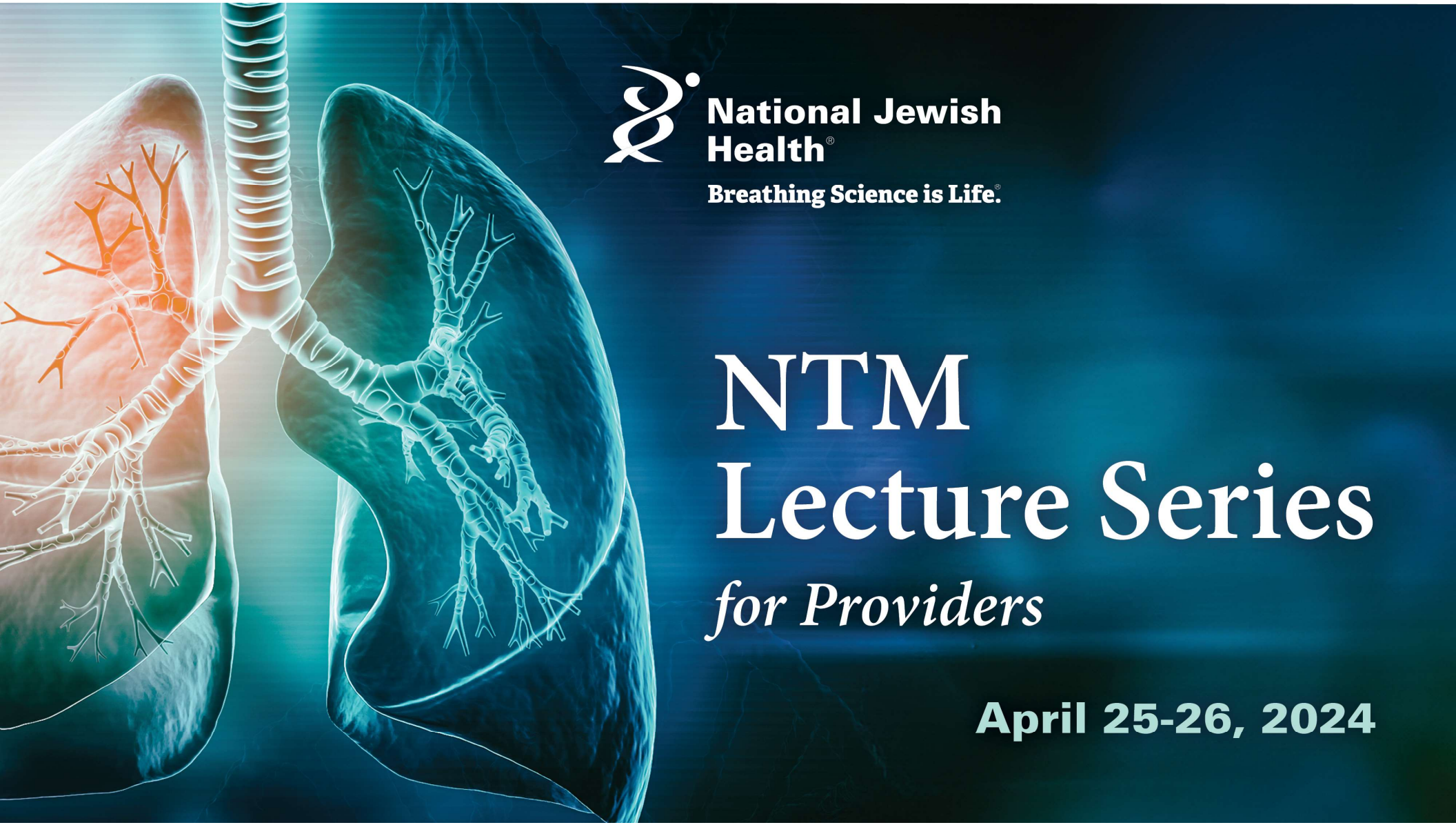
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# Treatment of Slow Growing Mycobacteria

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# Disclosures

**Consultant:** Genentech, Pfizer

**Advisory Board Member**: AN2, Hyfe, Insmed, MannKind, Matinas BioPharma Holdings, Inc., Nob Hill, Paratek Pharmaceuticals, Spero Therapeutics, Zambon

**Data Monitoring Committee**: Ostuka Pharmaceutical, Eli Lilly and Company, Bill and Melinda Gates Foundation

**Contracted Research**: AN2 Therapeutics, Bugworks, Insmed, Juvabis, Paratek Pharmaceuticals

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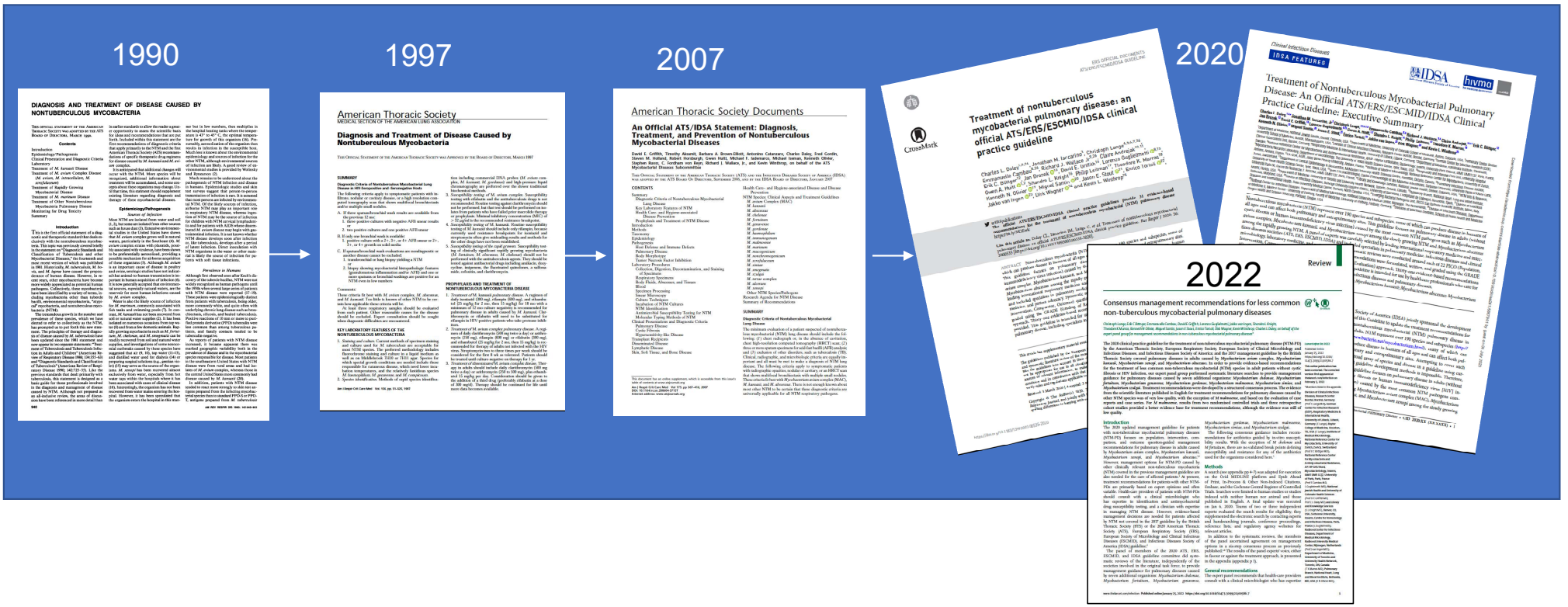
# NTM Treatment Guidelines




Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535
Lange C, et al. Lancet Infect Dis 2022;22:e178-190

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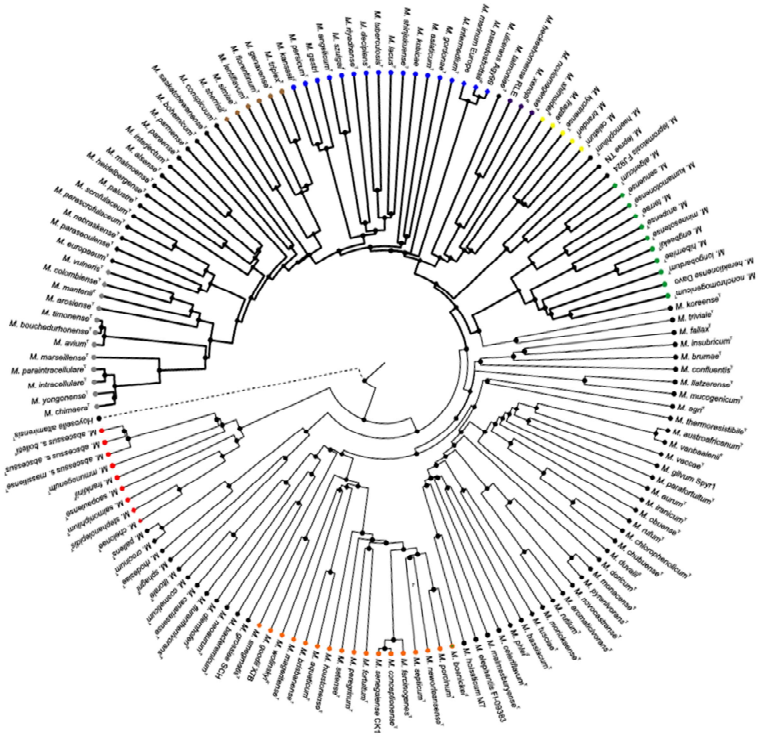
# NTM Treatment Guidelines – The Species Included


***M. avium* complex**
***M. kansasii***
***M. xenopi***



Tortoli E, et al. Inf Gen Evol 2017;56:19


***M. malmoense***
***M. simiae***
***M. szulgai***
*M. genevense*
*M. gordonae*

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# NTM-LD: Diagnostic Criteria

| | | |
|---|---|---|
| **Clinical** | Pulmonary or systemic symptoms | Both required |
| **Radiological** | Nodular or cavitary opacities on chest radiograph or high-resolution CT (HRCT) that shows bronchiectasis with multiple small nodules | |
| **Appropriate exclusion of other diagnoses** | | |
| **Microbiological** | 1. Positive cultures from ≥ 2 separate sputum samples. If results are non-diagnostic, consider repeat sputum AFB smears and cultures<br>OR<br>2. Positive cultures from ≥ 1 bronchial wash or lavage<br>OR<br>3. Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM OR biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and ≥ 1 sputum or bronchial washings that are culture-positive for NTM | |

Daley CL, et al. *CID* 2020;71:5-913; *Euro Respir J* 2020;56:2000535

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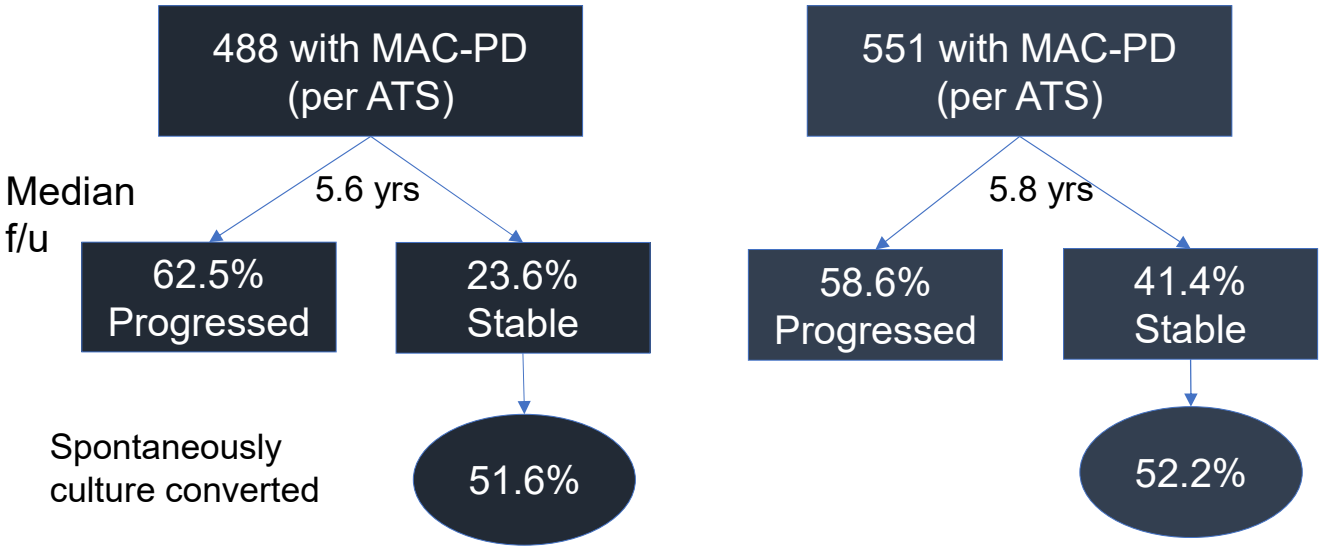
# Watchful waiting or initiation of treatment?

## Guideline recommendation

In patients who meet the diagnostic criteria for NTM pulmonary disease, we suggest initiation of treatment rather than watchful waiting, especially in the context of positive acid-fast bacilli sputum smears and/or cavitary lung disease (conditional recommendation, very low certainty in estimates of effect).




Hwang JA, et al. Eur Respir J 2017;49:1600537

Kwon BS, et al. Resp Med 2019;150:45-50

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Daley CL, et al. *CID* 2020;71:5-913; *Euro Respir J* 2020;56:2000535

# Risk Factors for Progression

| Host/Demographic Factors | Laboratory Factors | Radiographic Factors | Microbial Factors |
|---|---|---|---|
| • Male gender<br>• Older age<br>• Presence of co-morbidities<br>• Low body mass index | • Elevated inflammatory indices (ESR, CRP)<br>• Anemia<br>• Low albumin | • Fibrocavitary<br>• Extent of disease | • Bacterial load<br>• Species |

Hwang JA, et al. Eur Respir J 2017;49:1600537
Kwon BS, et al. Resp Med 2019;150:45-50
Moon SM, et al. Resp Med 2019;151:1-7.

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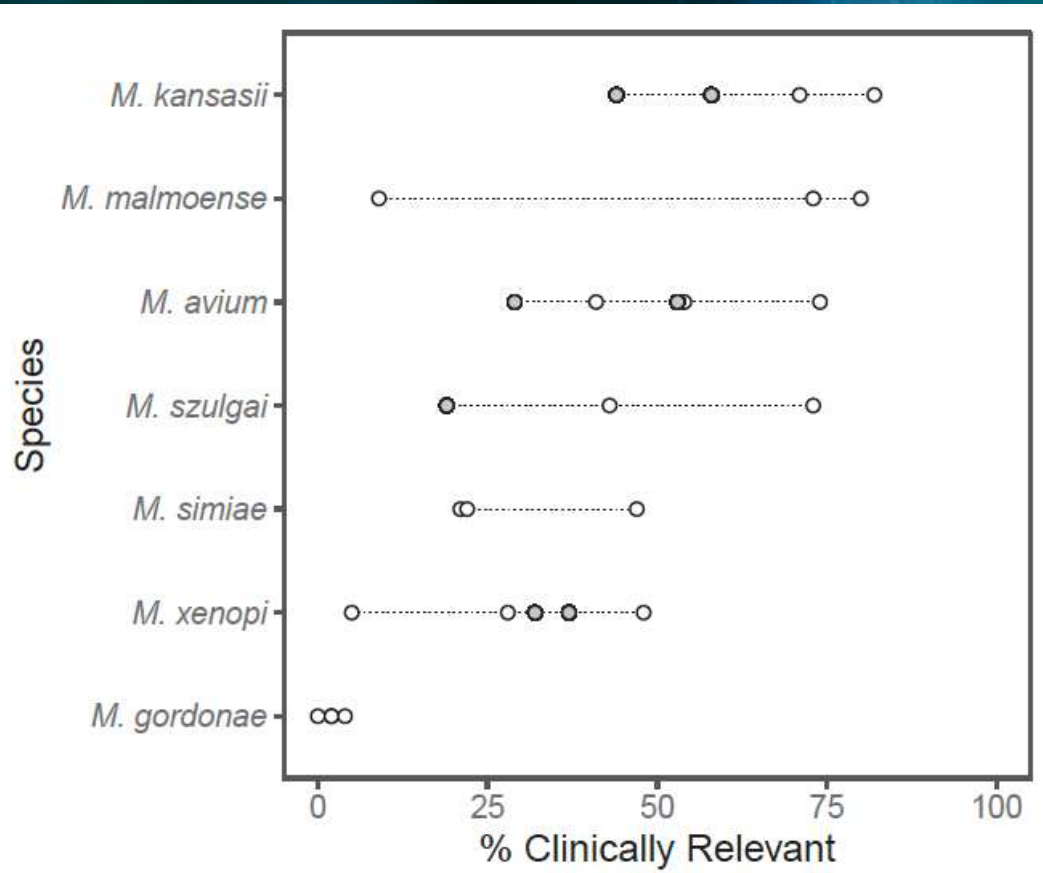
# Clinical Relevance of Different NTM Species




Circle – a study that described "clinical relevance" of NTM
White circle – met full ATS/IDSA diagnostic criteria
Gray circle – met microbiologic definition

Yan M, et al. Clin Chest Med 2023;44:799-813

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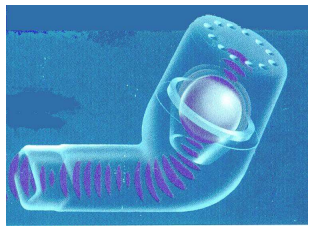
# Nonpharmacologic Therapy

- **Airway Clearance**
  - Regular exercise
  - Vibratory PEP
  - Chest percussion
  - Nebulized hypertonic saline
  - Chest wall oscillation
  - Autogenic drainage
  - Active cycle of breathing
- **Pulmonary rehabilitation**
- **Nutrition**
- **GERD**
  - Lifestyle modifications




Best choice is what the patient will do

- Education
- Time commitment

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# Question: Which of the following animals gets the same subspecies of *M. avium* as humans?

A. 

C. 

B. 

D. 

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# *Mycobacterium avium* complex –the most common species/subspecies

| Species | Subspecies | Comments |
|---|---|---|
| ***M. avium*** | *avium* | Primarily in birds |
| | *hominissuis* | Most common to cause disease in humans |
| | *paratuberculosis* | Rarely causes human disease<br>Cause of Johne's disease in cattle |
| | *silvaticum* | Rarely causes human disease |
| ***M. intracellulare*** | *intracellulare* | Most common ssp of *M. intracellulare* to cause human pulmonary disease |
| | *chimaera* | Second most common ssp of *M. intracellulare* to cause human disease; Cause of disseminated disease associated with heater cooler units |
| | *yongonense* | Third most common ssp of *M. intracellulare* to cause of pulmonary disease |

Vu MV, Daley CL. Clin Chest Med 2023;44:771-783

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# *Mycobacterium avium* complex –the rest

| Species | Subspecies | Comments |
|---|---|---|
| ***M. arosiense*** | – | Uncommon cause of human disease |
| ***M. bouchedurhonense*** | – | Uncommon cause of human disease |
| ***M. colombiense*** | – | Uncommon cause of human disease |
| ***M. lepraemurium*** | – | Cause of murine and feline leprosy |
| ***M. marseillense*** | – | Uncommon cause of human disease |
| ***M. paraintracellulare*** | – | Uncommon cause of human disease |
| ***M. timonense*** | – | Uncommon cause of human disease |
| ***M. vulneris*** | – | Uncommon cause of human disease |

Vu MV, Daley CL. Clin Chest Med 2023;44:771-783

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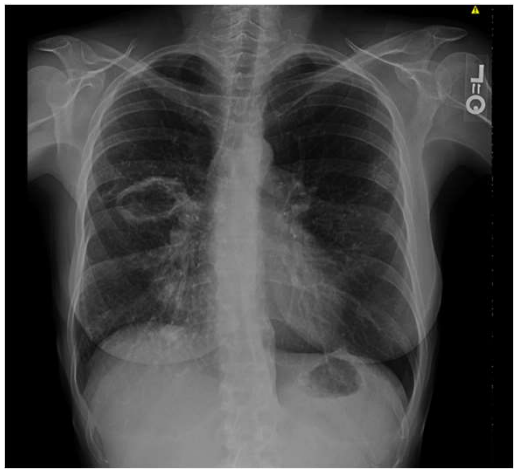
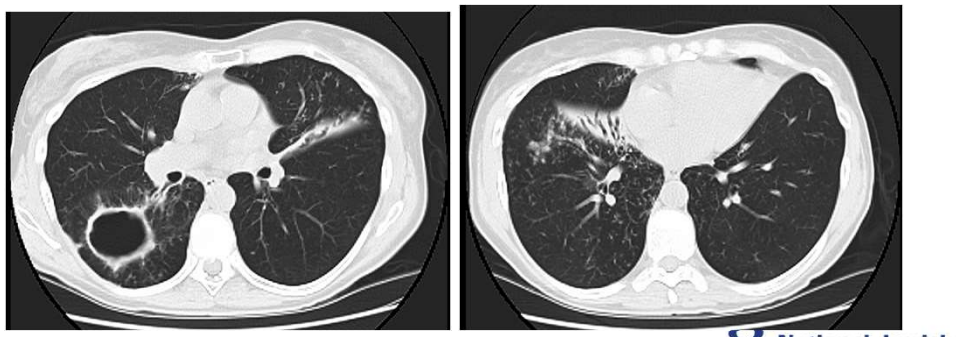
# *Mycobacterium avium* complex

- 65 year old Caucasian woman treated for *Mycobacterium avium* complex on two previous occasions with macrolide, rifampin, and ethambutol

- Now with AFB smear positive sputum specimen and culture positive for *M. intracellulare*





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# *Mycobacterium avium* complex-resistance cut-points

| Complex | Drugs to Test | Drugs to Consider Testing |
|---|---|---|
| MAC | Macrolide<br>Amikacin | Moxifloxacin<br>Linezolid |

AST for MAC

| Antimicrobial Agent | MIC, ug/ml | | |
|---|---|---|---|
| | S | I | R |
| Clarithromycin | ≤ 8 | 16 | ≥ 32 |
| Amikacin (IV) | ≤ 16 | 32 | ≥64 |
| Amikacin (liposomal inhaled) | ≤ 64 | - | ≥ 128 |

CLSI. M62 Performance Standards for Susceptibility Testing, 2018

Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

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# Treatment Regimens for MAC Pulmonary Disease

| | No. of Drugs | Preferred Regimen[a] | Dosing Frequency | Duration |
|---|---|---|---|---|
| Nodular-bronchiectatic | 3 | Azithromycin (clarithromycin)<br>Rifampin (rifabutin)<br>Ethambutol | 3 times weekly | 12 months beyond culture conversion |
| Cavitary | ≥ 3 | Azithromycin (clarithromycin)<br>Rifampin (rifabutin)<br>Ethambutol<br>Amikacin IV (streptomycin)[b] | Daily (IV aminoglycoside may be used 3 times weekly) | |

a. Alternative drugs could include clofazimine, moxifloxacin, linezolid (tedizolid), bedaquiline
b. Consider for cavitary, extensive nodular bronchiectatic or macrolide resistant disease

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Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

# Question: Which of the following infections is associated with the lowest culture conversion rate?

A. Extensively drug resistant TB (XDR-TB)

B. Macrolide resistant *Mycobacterium avium* complex

C. *Mycobacterium abscessus subspecies abscessus*

D. *Mycobacterium simiae*

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# Treatment Outcomes for MAC Pulmonary Disease

| | Culture Conversion | Microbiologic Recurrence | Reinfection |
|---|---|---|---|
| Macrolide susceptible | | | |
| Non cavitary<br>Cavitary | 70% - 80%<br>50% - 80% | 25-48% | 46-75% |
| Macrolide resistant | | | |
| No surgery/aminoglycoside*<br>Some surgery/aminoglycoside<br>Surgery + prolonged aminoglycoside* | 5%<br>15%<br>80% | – | – |

* ≥ 6 months parenteral aminoglycoside


Griffith DE et al. *Am J Respir Crit Care Med.* 2006;174:928-934.
Jeong BH et al. *Am J Respir Crit Care Med.* 2015;191:96-103.
Moon SM et al. *Eur Respir J.* 2016;50:1602503.

Wallace R et al. *Chest.* 2014;146:276-282.
Koh WJ et al. *Eur Respir J.* 2017;50.
Morimoto K et al. *Ann Am Thorac Soc.* 2016;11:1904.

Boyle DP et al. *Ann Am Thorac Soc.* 2016;13:1956-1961


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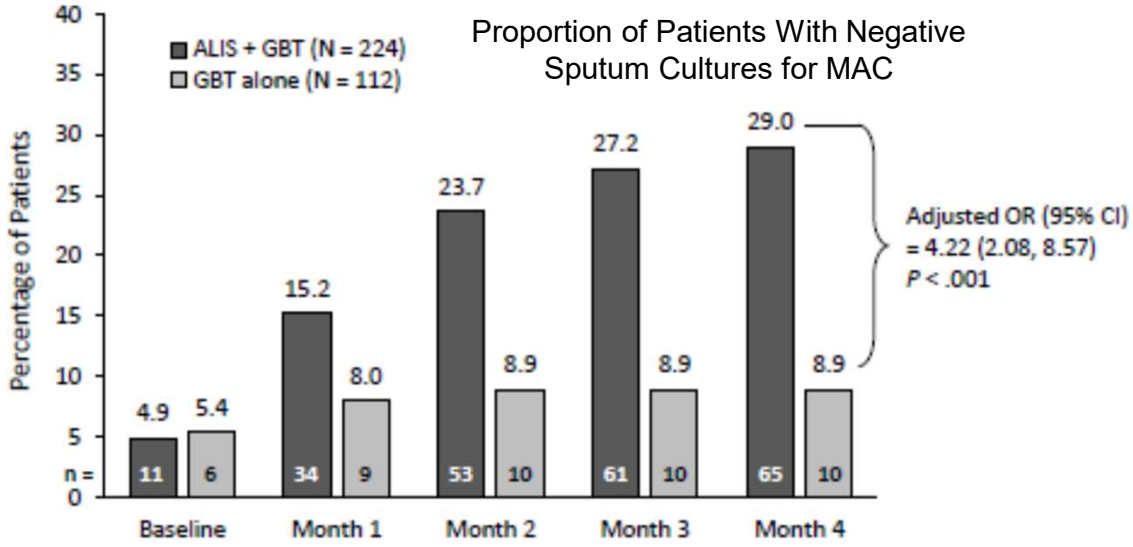
# Treatment Refractory MAC Pulmonary Disease

## Guideline recommendation

In patients with MAC pulmonary disease who have failed therapy after at least six months of guideline-based therapy, we recommend addition of amikacin liposome inhalation suspension (ALIS) to the treatment regimen rather than a standard oral regimen only. (strong recommendation, moderate certainty in estimates of effect).

CONVERT Study – Randomized, controlled study of ALIS in treatment refractory MAC pulmonary disease




Griffith D, et al. AJRCCM 2018;198:1559-1569

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# Sustainability and Durability of Culture Conversion

In patients who achieved culture conversion by month 6 in CONVERT:

- Was conversion **sustained** (negative results for 12 mos on treatment)
- Was conversion **durable** (negative results for 3 mos and 12 mos after treatment)

| | | % Remaining Culture Negative | | |
|---|---|---|---|---|
| Condition | Time of Measurement | ALIS +GBT | GBT | P-value |
| Sustained | 12 months on therapy | 63.1% | 30.0% | 0.064 |
| Durable | 3 months after therapy | 55.4% | 0% | 0.0017 |
| | 12 months after therapy | 46.2% | 0% | < 0.0001 |

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Griffith D, et al. *Chest* 2021;160:831-842

# Recommended Treatment Regimens for MAC Pulmonary Disease

| | No. of Drugs | Preferred Regimen[a] | Dosing Frequency |
|---|---|---|---|
| Nodular-bronchiectatic | 3 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol | 3 times weekly |
| Cavitary | ≥ 3 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol<br>Amikacin IV (streptomycin)[b] | Daily (IV aminoglycoside may be used 3 times weekly) |
| Refractory[c] | ≥ 4 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol<br>Amikacin liposome inhalation suspension or IV (streptomycin)[b] | Daily (IV aminoglycoside may be used 3 times weekly) |

a. Alternative drugs could include clofazimine, moxifloxacin, linezolid (tedizolid), bedaquiline
b. Consider for cavitary, extensive nodular bronchiectatic or macrolide resistant disease
c. Sputum culture positive after 6 months of guideline-based therapy

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Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

# Other Interventions for Treatment Refractory MAC Pulmonary Disease

- Switching from intermittent therapy to daily therapy
- Adding additional medications
  - Clofazimine
  - Bedaquiline
  - Oxazolidinones (linezolid, tedizolid)
  - Omadacycline
- Substituting medications
  - Rifabutin (substituting for rifampin)
- Surgery

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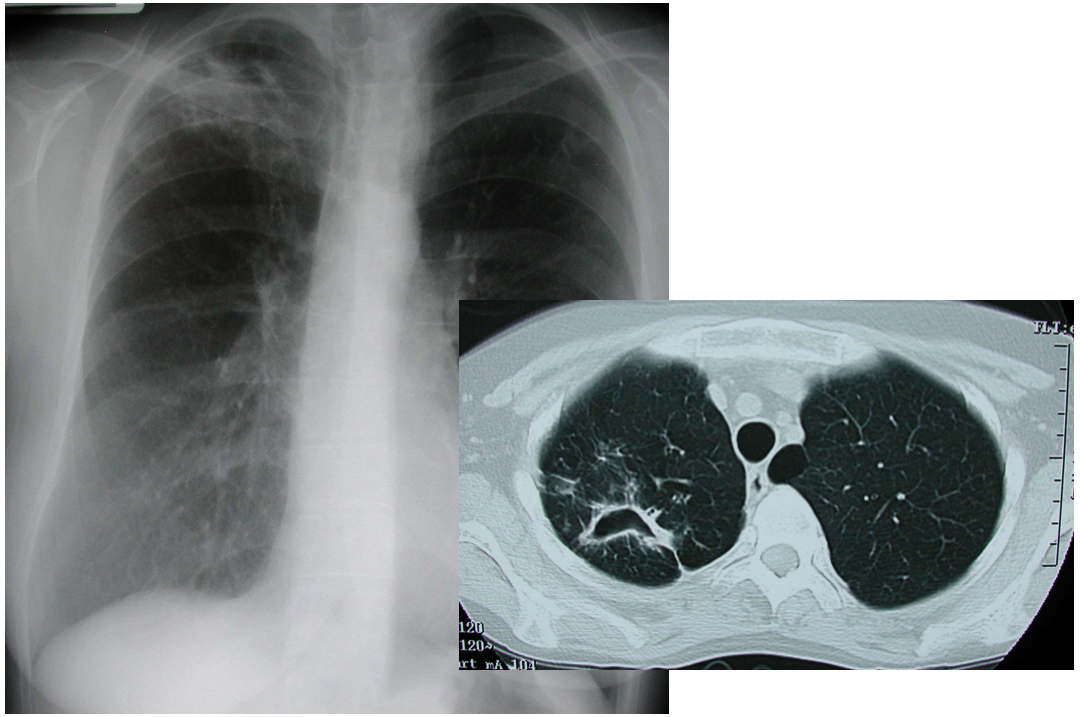
Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

# Clinical Case

- 45 year old Caucasian woman with chronic cough
- Chest x-ray - abnormal
- Three sputum specimens obtained that were AFB smear negative
- She was started on a 4-drug TB treatment regimen



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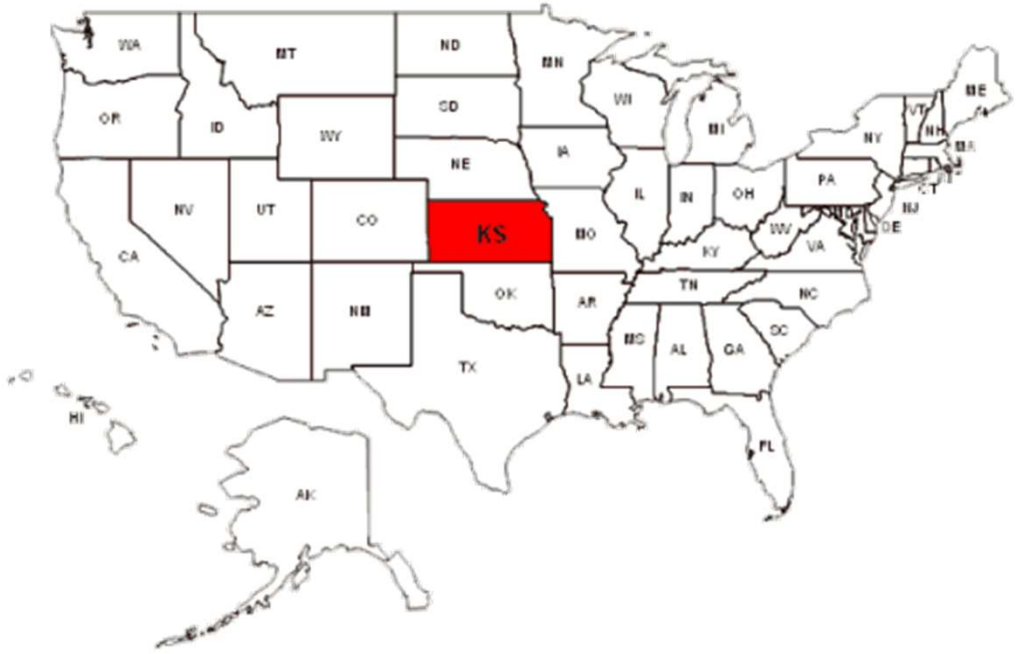
# *Mycobacterium kansasii*




- First described by Buhler and Pollack as the “yellow bacilli” in 1953 and later named in 1955 by Hauduroy
- Genomically, close to *M. tuberculosis*
- High pathogenicity
- Infection likely from tap water
- 44% to >90% have fibrocavitary disease
- Often associated with pre-existing lung disease, including pneumoconiosis
- Most cases are associated with progressive disease

Buhler VB, Pollack A. Am J Clin Pathol 1953;23:363-74

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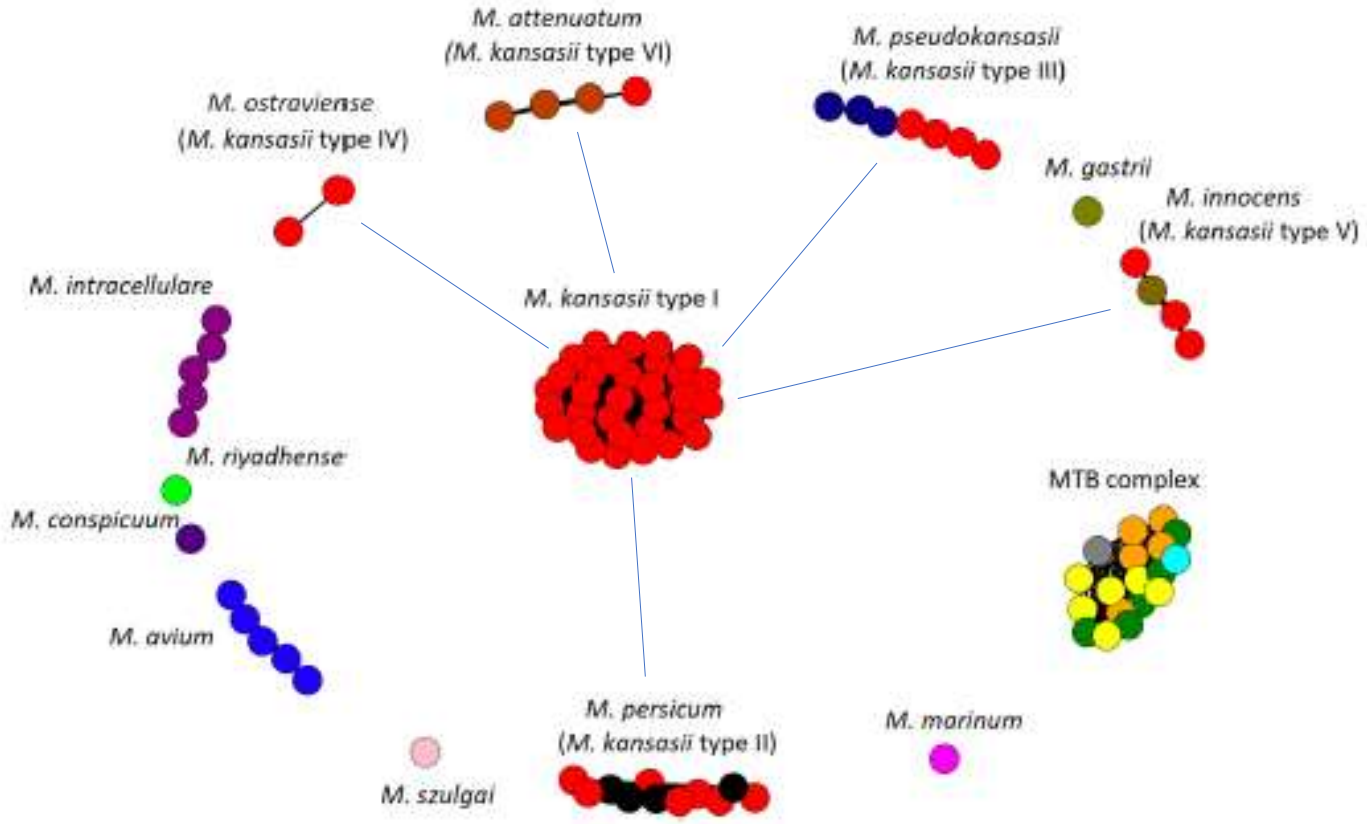
# *Mycobacterium kansasii* complex




Jagielski T, et al. Frontiers Micro 2020;10:2918

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# *Mycobacterium kansasii* complex
# Outcomes of Treatment

| Study | N | Regimen | Duration mos | Conversion | Cure* | Failure | Recurrence |
|---|---|---|---|---|---|---|---|
| Ahn, 1983 | 40 | H/R/E<br>SM biw for 3 mo | 12 | Median – 5.5 weeks | ND | 0 | 2.5% |
| Santin, 2009 | 75 | H/R/E<br>SM for 2-3 mo | 12 | ND | 83% | 0 | 6.6% |
| Sauret, 1995 | 14<br>14 | H/R/E<br>H/R/E | 12<br>18 | 100%, mean-4.5±2.0 | 93%<br>100% | 0 | 3.5%<br>0 |
| Evans, 1996 | 47 | H/R/E±Z | Mean-10.3 | ND | 79% | ND | 0 |
| BTS, 1994 | 173 | R/E | 9 | 89% by 3 mo | 89% | 1 | 9.7% |

H - INH, R – rifampin, E – ethambutol, Z - pyrazinamide, S - streptomycin

*Cure was nearly 100% when non-mycobacterial deaths and lost to follow-up patients are excluded

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# *Mycobacterium kansasii* complex
# Outcomes with Clarithromycin-based Regimens

| Study | N | Regimen | Mean Duration, months* | Mean Culture Conversion, months | Cure n (%) ** | Failure n (%) | Recurrence n (%) |
|---|---|---|---|---|---|---|---|
| Griffith D, 2003 | 18 | Clarithromycin Ethambutol Rifampin, given tiw | 13.3±0.8 | 1.0 ± 0.9 | 14** (78) | 0 | 0*** |
| Shitrit D, 2006 | 56 | Clarithromycin Ethambutol Rifampin, given daily | 21.0±7.2 | 8.9 ± 10.3 | 56 (100) | 0 | ND |

*At least 12 months of culture negativity
**Among completers, 100% cure rate
***Mean duration of follow-up was 46±8.0 mos

Griffith D, et al. CID 2003;37:1178-82
Shitrit D, et al. Chest 2006;129:771-76

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# Recommended Treatment Regimens for *Mycobacterium kansasii* complex

| Phenotype | No. of Drugs | Preferred Regimen* | Dosing Frequency |
|---|---|---|---|
| Nodular-bronchiectatic | 3 | **Azithromycin** (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol | 3 times weekly |
| Nodular-bronchiectatic or cavitary | 3 | **Azithromycin** (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol | Daily |
| Nodular-bronchiectatic or cavitary | 3 | **Isoniazid**<br>Rifampicin (rifabutin)<br>Ethambutol | Daily |

*Alternative drugs: clofazimine, moxifloxacin

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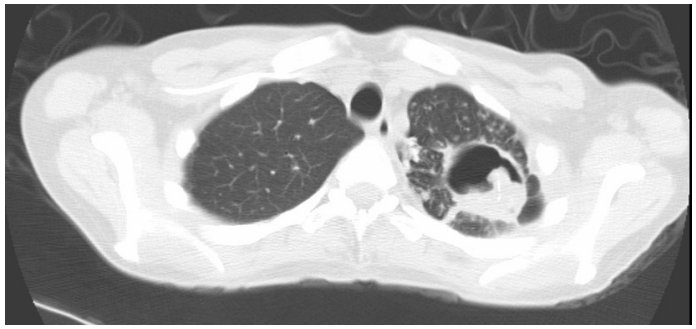
Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

# Clinical Case

- 35 year old physician who developed cough, fever and progressive dyspnea
- Sputum specimens grew an NTM and *Aspergillus fumigatus*
- She was treated with azithromycin, moxifloxacin, rifampin, and amikacin
- Her fungal infection was treated with posaconazole
- She eventually underwent left upper lobe resection



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# *Mycobacterium xenopi*

- Identified in 1959 from lesions on the skin of a South African toad, *Xenopus laevis*
- *M. xenopi* grows optimally at 45° C (113° F)
- Most patients are men, with underlying COPD or previous TB
- Fibrocavitary disease is more common than with MAC
- 28% to 51% of isolates reflect true disease
- All-cause 5-year mortality of 43% to 69%

van Igen J. Emerg Infect Dis 2008;14:385

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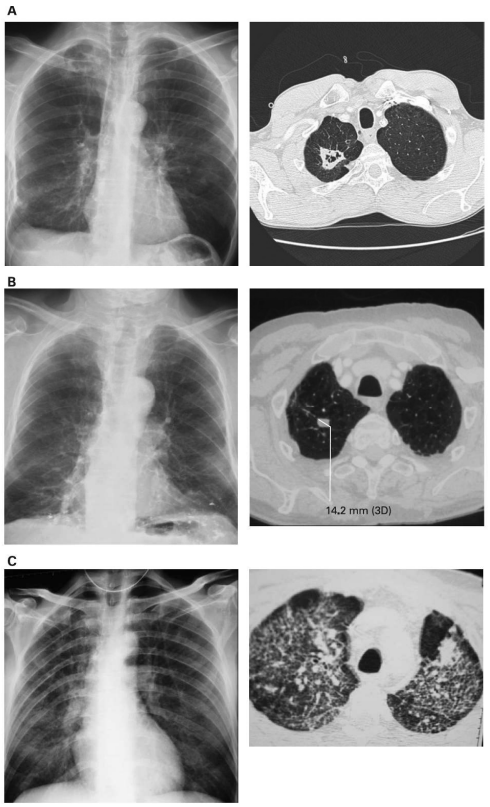
# *M. xenopi* Pulmonary Infections in North-East France

- 13 hospitals in NE France (1983-2003)
- 136 patients
  - Cavitary – 39 (31%)
  - Solitary nodule – 41 (33%)
  - Infiltrative – 45 (36%)




- 80 (59%) patients were treated
- Rifamycin, ethambutol, INH, clarithromycin, fluoroquinolones
- After 36 mos, 69% had died
  - Acute infiltrative form associated with poor prognosis (p=0.001)
  - **Rifamycin**-containing regimens were associated with better prognosis (p=0.006)

Andrejak C, et al. Thorax 2009;64:291-296

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# Mean $Log_{10}$ CFU/lung of *M. xenopi* in Nude Mice

| | Timepoint Relative to the Start of Treatment | | | |
|---|---|---|---|---|
| Group | Week 2 | Week 4 | Week 8 | Week 12 |
| Untreated | 6.95 | 6.93 | 7.76 | 7.79 |
| CLR/EMB/RIF | 5.75 | 6.57 | 5.68 | 4.69 |
| CLR/EMB/RIF/AMK | 5.86 | 5.22 | 4.83 | 4.58 |
| MXF/EMB/RIF | 6.42 | 6.19 | 5.97 | 5.57 |
| MXF/EMB/RIF/AMK | 5.67 | 5.25 | 4.49 | 4.23 |
| MXF/CLR | | 6.07 | | 5.23 |

CLR-clarithromycin, EMB-ethambutol, RIF-rifampicin, AMK-amikacin, MXF-moxifloxacin

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Andrejak C, et al. J Antimicrob Chemother 2013;68:659-665

# *M. xenopi* Pulmonary Infections in North-East France

- Randomized, controlled trial in France
  - **Clarithromycin**, ethambutol, rifampin vs.
  - **Moxifloxacin**, ethambutol, rifampin
- Enrolled 72 patients with *M. xenopi* pulmonary disease
- Results
  - Culture conversion at 6 months:
    - 30/39 patients (76.9%) with clarithromycin
    - 25/33 patients (75.8%) with moxifloxacin
  - No difference between regimens

Andrejak C, et al. AJRCCM 2016;193:A3733
Andrejak C, et al. Rev Malad Respir Actual 2021;13:25.

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# Recommended Treatment Regimens for *Mycobacterium xenopi*

| Phenotype | No. of Drugs | Preferred Regimen* | Dosing Frequency |
|---|---|---|---|
| Nodular bronchiectatic | ≥ 3 | Azithromycin and/or moxifloxacin<br>Rifampicin (rifabutin)<br>Ethambutol | Daily (aminoglycoside may be used 3 times weekly) |
| Cavitary | ≥ 3 | Azithromycin and/or moxifloxacin<br>Rifampicin (rifabutin)<br>Ethambutol<br>**Amikacin IV (cavitary)** | Daily (aminoglycoside may be used 3 times weekly) |

*Alternative drugs: clofazimine, moxifloxacin

Treatment duration: 12 months after culture conversion

Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

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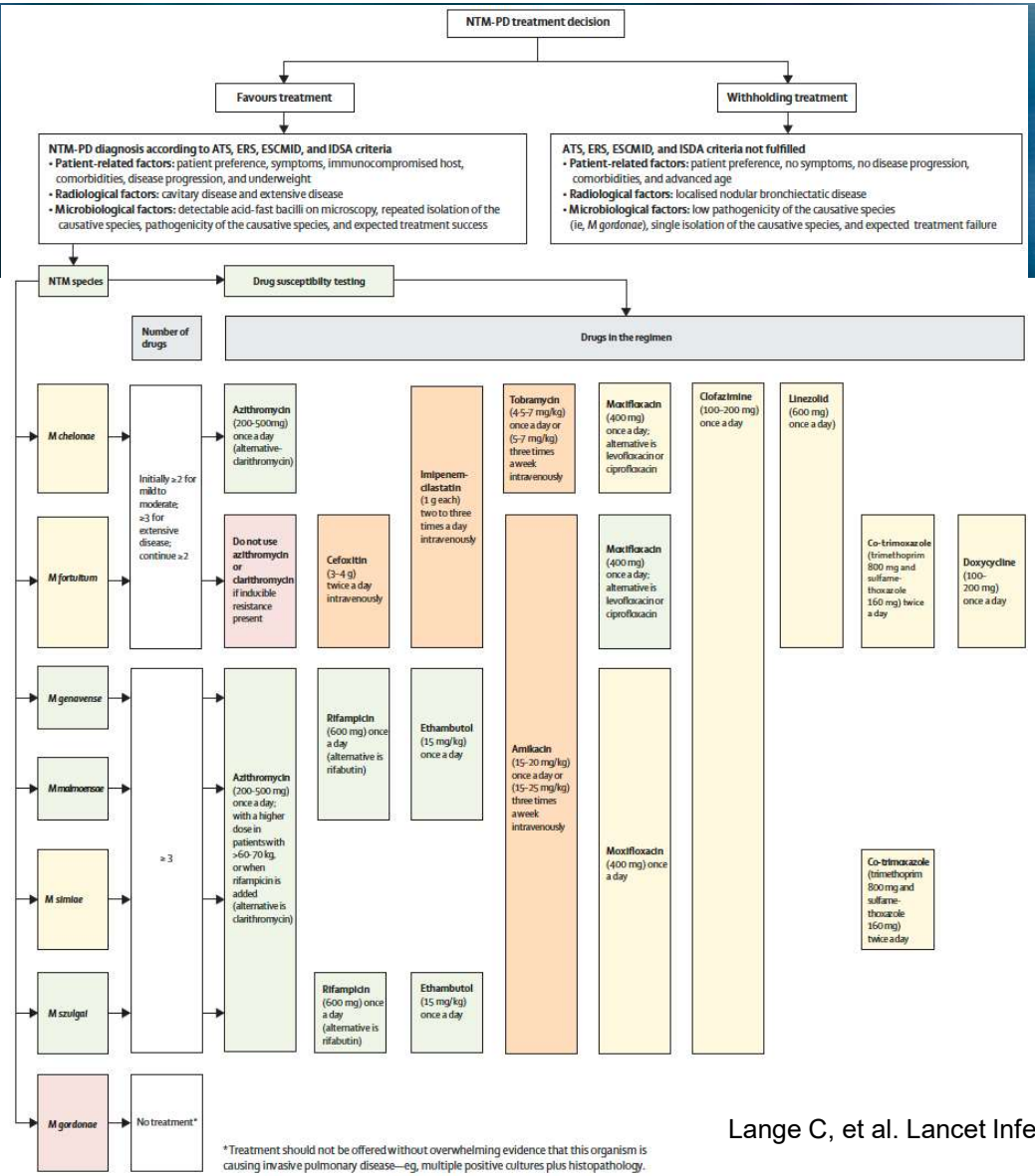
# Treatment Algorithm for Other NTM




**NTM species:**
Green- high pathogenicity
Yellow – less pathogenic
Red – likely contaminant

**Drug recommendations:**
Green – drugs that are recommended
Yellow – drugs with less certainty
Orange – intravenous
Red - should not be used

Lange C, et al. Lancet Infect Dis 2022;22.e178-90

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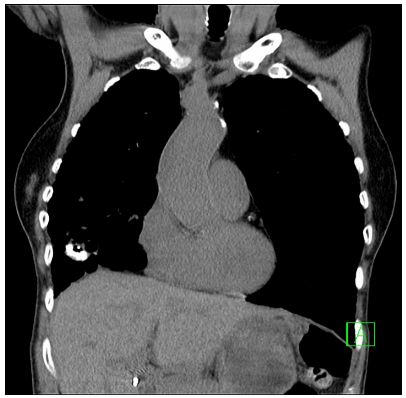
# Clinical Case

- 68 year old women with Sjogren's syndrome and rheumatoid arthritis
- Presented with fatigue, minimal dry cough
- BAL grew an NTM
- Attempts at treatment unsuccessful due to drug-related toxicity
- Followed for over 5 years with no evidence of progression



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# *Mycobacterium malmoense*

- **Etymology:** mal.mo.en'se. N.L. neut. adj. *malmoense*, of or belonging to Malmö, Sweden, the source of the strains on which the original description is based
- **Effective publication:** Schröder KH, Juhlin I. *Mycobacterium malmoense* sp. nov. *International Journal of Systematic Bacteriology* 1977; **27**:241-246
  - First described in 4 patients from Malmo and Lund, Sweden
- **Systematic review:** two randomized controlled trials and three retrospective cohort studies. In addition, two systematic reviews were identified that addressed treatment outcomes or treatment recommendations for *M. malmoense* pulmonary disease.
- **Source:** Isolated from fresh water and soil
- **Distribution:** One of the most common NTM in northern Europe
- **Clinical forms:** Mainly pulmonary disease. Extrapulmonary and disseminated disease have also been described. 32/40 (80%) met ATS criteria for disease in the Netherlands
- **Risk factors for pulmonary disease:** Underlying pulmonary disease

https://www.bacterio.net/genus/mycobacterium

Lange C, et al. Lancet Infect Dis 2022;22.e178-90; Hoefsloot W, Eur Respir J, 2009; 34:926-931

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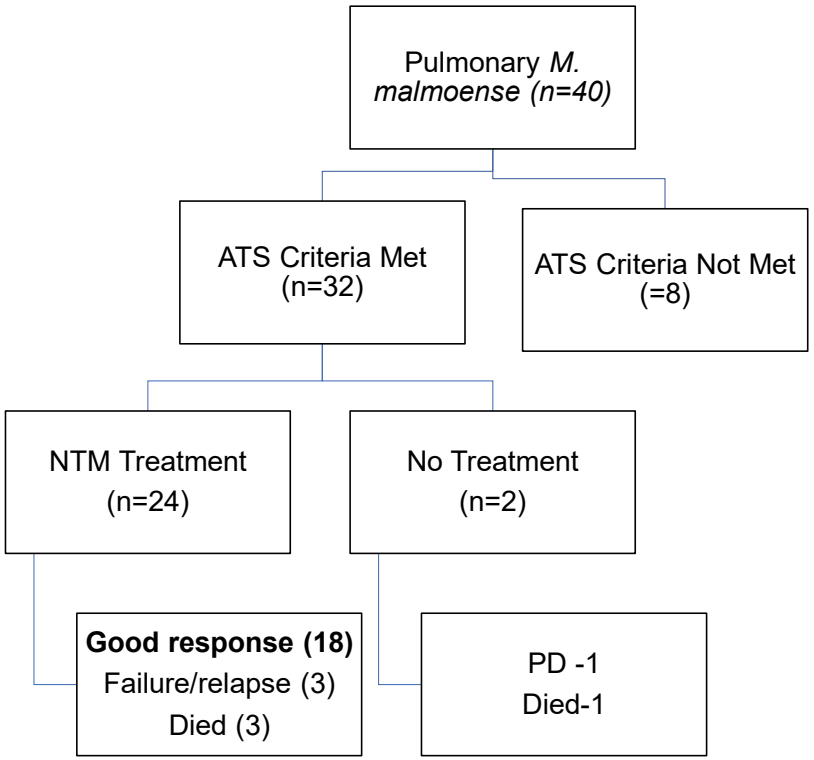
# Treatment Outcomes for M. malmoense

- Patients with pulmonary *M. malmosense* in the Netherlands
- Retrospective design
- Regimens included various combinations including macrolides and fluoroquinolones
- Mean duration of therapy – 12 months (1-26)




Hoefsloot W, et al. Eur Respir J 2009;34:926-931

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# Treatment Regimens for *M. malmoense*

| Phenotype | No. of Drugs | Preferred Regimen* | Dosing Frequency |
|---|---|---|---|
| Nodular-bronchiectatic | 3 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol | Daily |
| Cavitary | ≥3 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol<br>**Amikacin (IV)** | Daily (IV aminoglycoside may be used 3 times weekly) |

*Alternative drugs: clofazimine, moxifloxacin

Treatment duration: 12 months after culture conversion

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Lange C, et al. Lancet Infect Dis 2022;22.e178-90

# Question #2

A 65 year old woman with chronic cough and nodular bronchiectasis has two sputum specimens which grow *Mycobacterium simiae*. What would be the most appropriate next step?

A. Initiate azithromycin, ethambutol, rifampin

B. Initiate moxifloxacin, clofazimine and trimethoprim-sulfamethoxazole

C. Follow without treatment for evidence of progressive disease

D. Discharge the patient as *M. simiae* is a water contaminant.

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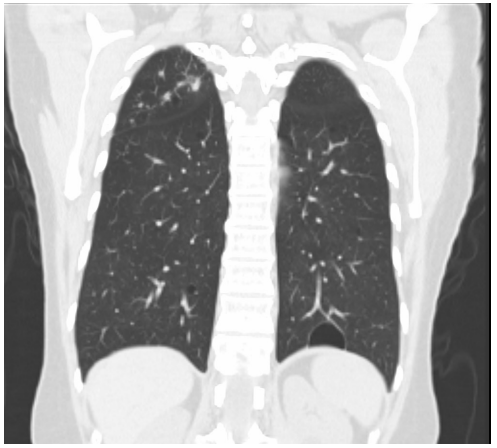
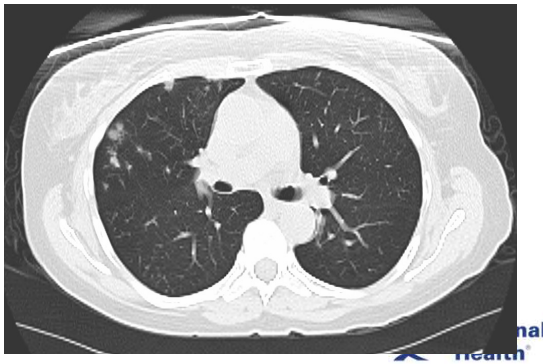
# Clinical Case

- 66 year old woman from Alaska
- Presented with myalgias, night sweats, fatigue, jaw pain and cough
- Sputum cultures grew MAC so she was treated with azithromycin, rifampicin, and ethambutol
- After two months of therapy, all cultures positive for a different NTM
- Still culture positive after 6 months so 8 weeks of IV amikacin given
- Despite 18 months of therapy all cultures remained positive





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# *Mycobacterium simiae*

- **Etymology:** si'mi.ae. L. masc./fem. n. *simia*, an ape; L. gen. masc./fem. n. *simiae*, of an ape
- **Effective publication:** Karassova V, Weissfeiler J, Krasznay E. Occurrence of atypical mycobacteria in Macacus rhesus. *Acta Microbiol Acad Sci Hung* 1965; **12**:275-282.
  - First isolated from rhesus macaques in 1965
- **Systematic review:** 11 case reports and case series - 197 patients with *M. simiae* pulmonary disease.
- **Source:** Isolated from water and soil. Found in water networks.
- **Distribution:** Worldwide. Particularly common in Isolated arid regions (Israel, Lebanon, Iran, India, Cuba, desert SW of US)
- **Clinical forms:** Pulmonary and extrapulmonary disease. Less than 20% of isolates are deemed clinically relevant
- **Risk factors for pulmonary disease:** COPD, bronchiectasis, smoking

https://www.bacterio.net/genus/mycobacterium
Lange C, et al. Lancet Infect Dis 2022;22.e178-90

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# $MIC_{50}$ and $MIC_{90}$ for *M. simiae*

| Drug | *M. simiae (n=21)* |
|---|---|
| Clarithromycin | **4/8** |
| Ciprofloxacin | 16/>16 |
| Moxifloxacin | **2/>8** |
| Linezolid | 16/32 |
| Clofazimine | **<0.12/0.25** |
| Amikacin | **8/16** |
| Tobramycin | NT |
| Co-trimoxazole | **4/>8** |
| Doxycyline | 16/16 |

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Lange C, et al. Lancet Infect Dis 2022;22.e178-90

# Treatment Outcomes for *M. simiae*

| Study | Country | N | Regimen | Outcomes |
|---|---|---|---|---|
| Barzilai A, 1998 | Israel | 3 | **Clarithromycin**<br>Ciprofloxacin<br>Ethambutol | Successful in AIDS patients with disseminated *M. simiae* after 24 months f/u.<br>Also started on ART |
| Van Ingen J, 2008 | Netherlands | 3 | **Macrolide**<br>Ethambutol<br>Other | One improved, One relapsed<br>One died |
| Qvist T, 2013 | Denmark | 1 | **Clarithromycin**<br>Moxifloxacin<br>Trim-Sulfa | Negative cultures at one year in bilateral lung transplant recipient |
| Shitrit D, 2008 | Israel | 102 | **Clarithromycin**<br>Ethambutol<br>Rifampin | No failures/relapses during median of 24 mos f/u |
| Baghaei P, 2012 | Iran | 26 | **Clarithromycin**<br>Ofloxacin<br>Trim-Sulfa | 24 (92%) “cured”<br>No recurrences over 2 yrs f/u |

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# Recommended Treatment Regimens for *M. simiae*

| Phenotype | No. of Drugs | Preferred Regimen* | Dosing Frequency |
|---|---|---|---|
| Nodular-bronchiectatic | 3 | Azithromycin (clarithromycin)<br>Moxifloxacin<br>Clofazimine<br>Trim/sulfa | Daily |
| Cavitary | ≥3 | Azithromycin (clarithromycin)<br>Moxifloxacin<br>Clofazimine<br>Trim/sulfa<br>Amikacin (IV) | Daily (IV aminoglycoside may be used 3 times weekly) |

*Alternative drugs: clofazimine, moxifloxacin

Treatment duration: 12 months after culture conversion

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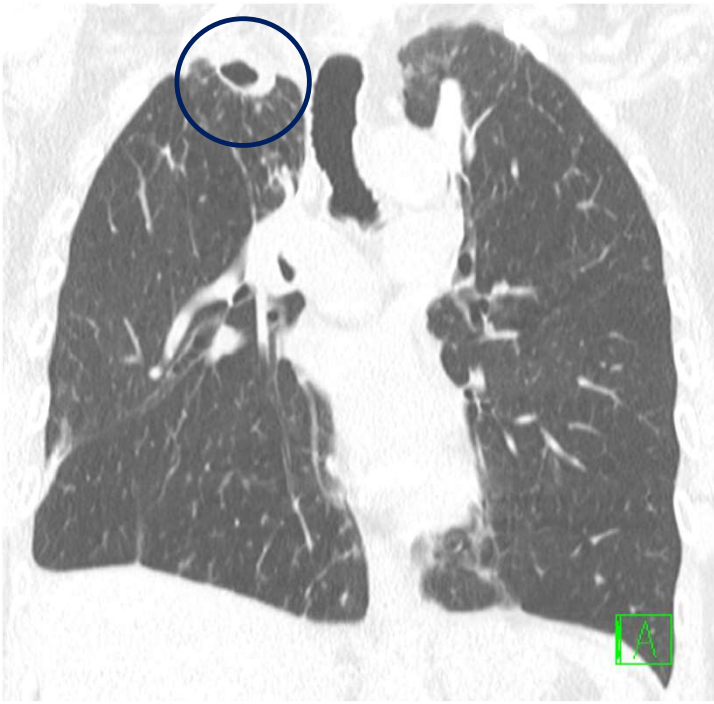
Lange C, et al. Lancet Infect Dis 2022;22.e178-90

# Clinical Case


- 82 year old woman with chronic cough but otherwise very active and healthy
- Previously treated for macrolide resistant, cavitary, MAC pulmonary disease with VATS right upper lobectomy
- Now growing another NTM



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# *Mycobacterium szulgai*


- **Etymology:** szul'ga.i. N.L. gen. masc. n. *szulgai*, of Szulga, named after T. Szulga, a Polish microbiologist
- **Effective publication:** Marks J, Jenkins PA, Tsukamura M. *Mycobacterium szulgai*--a new pathogen. *Tubercle* 1972; **53**:210-214.
  - First described in 1972 seven patients with pulmonary and extrapulmonary disease
- **Systematic review:** 25 retrospective case reports and case series - 44 patients with *M. szulgai* pulmonary disease.
- **Source:** Rarely isolated from water supply networks and soil. Accounts for <1% of NTM isolates
- **Distribution:** Worldwide.
- **Clinical forms:** Mainly caused pulmonary disease mimicking TB. 43-76% meet the American Thoracic Society diagnostic criteria and were thus likely to have *M. szulgai* disease.
- **Risk factors for pulmonary disease:** COPD, smoking

https://www.bacterio.net/genus/mycobacterium
Lange C, et al. Lancet Infect Dis 2022;22.e178-90
Yoo H, et al. Scand J Infect Dis 2014:46:169-74
Van Ingen J, Clin Infect Dis 2008;46:1200-5

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# Treatment Outcomes for *M. szulgai*

- Systematic review: 25 retrospective case reports and case series, including a total of 44 patients with *M szulgai* pulmonary disease
- Regimens: Most patients were treated with a combination of rifampicin, ethambutol, and clarithromycin or azithromycin.
- Treatment duration: Variable; 12 months was most frequently used (range 5–18 months).
- Outcomes: Favorable in 85% of patients treated with rifampicin and macrolide (clarithromycin or azithromycin) combination regimens; no relapses were observed among the five (11%) patients that post-treatment follow-up was available for.
  - The cure rate was 81% among 21 patients not treated with macrolide-based regimen

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Lange C, et al. Lancet Infect Dis. 2022;22:e178-e190

# Treatment Regimen for *M. szulgai*

| Phenotype | No. of Drugs | Preferred Regimen* | Dosing Frequency |
|---|---|---|---|
| Nodular-bronchiectatic | 3 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol | Daily |
| Cavitary | ≥3 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol<br>**Amikacin (IV)** | Daily (IV aminoglycoside may be used 3 times weekly) |

*Alternative drugs: clofazimine, moxifloxacin

Treatment duration: 12 months

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Lange C, et al. Lancet Infect Dis 2022;22.e178-90

# Surgery Plus Medical Therapy or Medical Therapy Alone?

**Recommendation**

**In selected patients with NTM pulmonary disease, we suggest surgical resection as an adjuvant to medical therapy after expert consultation** (conditional recommendation, very low certainty in estimates of effect)

- 15 observational studies including approximately 700 patients who underwent surgical resection including 3 studies (296 patients) that compared outcomes in those who had surgery plus antimicrobial therapy vs antimicrobial therapy alone
  - Culture conversion more common in those who underwent surgery
  - Complications in 7-35%
  - No operative mortality
  - 0-9% post-operative mortality
  - Beware of selection bias

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Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

# Summary: Treatment Recommendations

| Organism | Regimen* | Duration |
|---|---|---|
| *M. avium* complex | azithromycin, ethambutol, rifampin | 12 mos after conversion |
| *M. kansasii* complex | | 12 months |
| *M. malmoense* | | 12 mos after conversion |
| *M. szulgai* | | 12 months |
| *M. simiae* | azithromycin, moxifloxacin, clofazimine, trim/sulfa | 12 mos after conversion |
| *M. xenopi* | azithromycin ± moxifloxacin, ethambutol, rifampin | 12 mos after conversion |

*IV amikacin three times weekly for 1-2 months, except for *M. kansasii*

Lange C, et al. Lancet Infect Dis 2022;22.e178-90
Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

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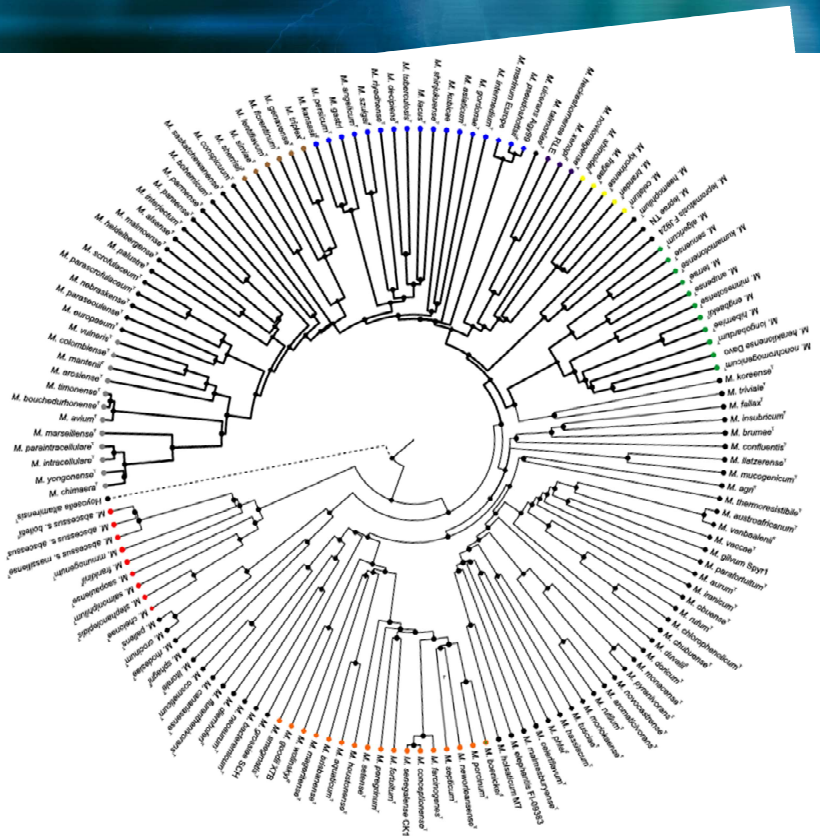
# What about all the rest…



http://www.bacterio.net/mycobacterium.html
Tortoli E, et al. Inf Gen Evol 2017;56:19

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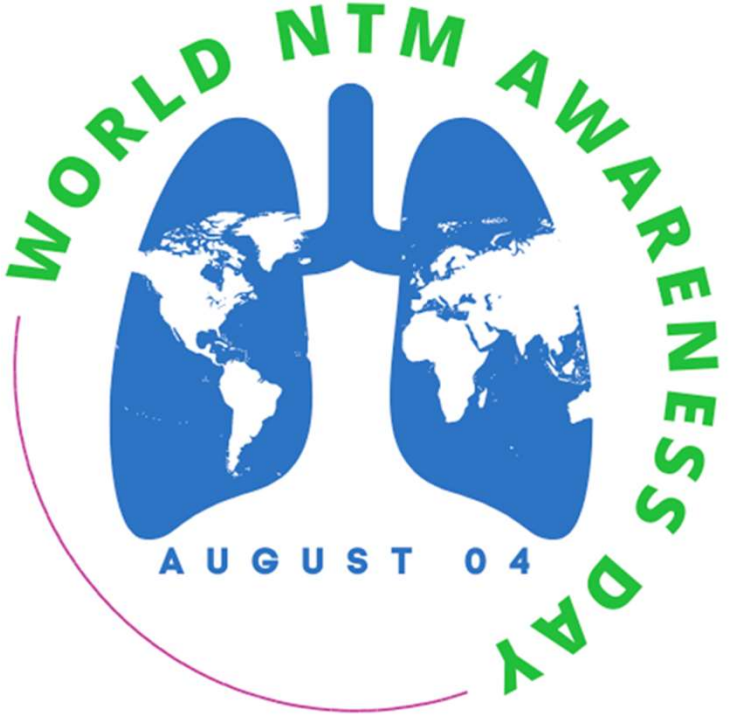
# World NTM Awareness Day!

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