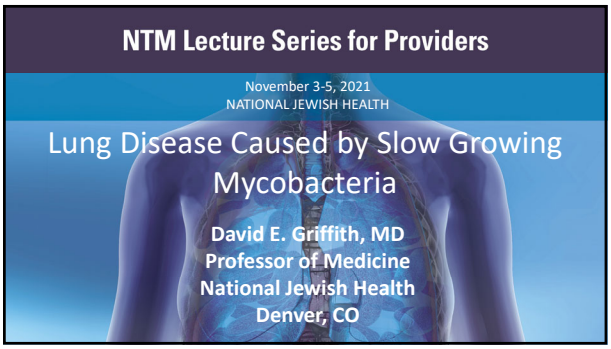


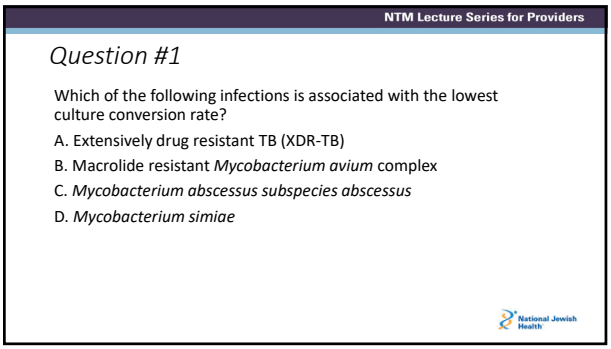


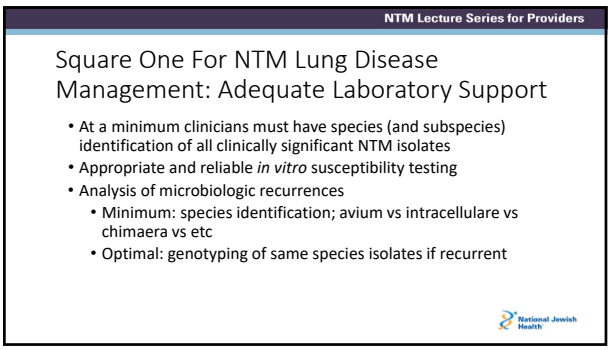

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## NTM That Have Been Reported to Cause Lung Disease

| Slowly Growing Mycobacteria | | Rapidly Growing Mycobacteria* | |
|---|---|---|---|
| *M. arupense* | *M. kubicae* | *M. abscessus* | *M. holsaticum* |
| *M asiaticum* | *M. lentiflavum* | *M. alvei* | *M. fortuitum* |
| *M. avium* | *M. malmoense* | *M. boenickei* | *M. mageritense* |
| *M. branderi* | *M. palustre* | *M. bolletii* | *M. massiliense* |
| *M. celatum* | *M. saskatchewanse* | *M. brumae* | *M. mucogenicum* |
| *M. chimaera* | *M. scrofulaceum* | *M. chelonae* | *M. peregrinum* |
| *M. florentinum* | *M. shimodei* | *M. confluentis* | *M. phocaicum* |
| *M. heckeshornense* | *M. simiae* | *M. elephantis* | *M. septicum* |
| *M. intermedium* | *M. szulgai* | *M. goodii* | *M. thermoresistible* |
| *M. interjectum* | *M. terrae* | | |
| *M. intracellulare* | *M. triplex* | | |
| *M. kansasii* | *M. xenopi* | * Growth in subculture within 7 days | |

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## Slow Growing Mycobacteria Species Discussed In This Presentation

- *Mycobacterium avium* complex (MAC)
- *Mycobacterium kansasii*
- *Mycobacterium xenopi*
- *Mycobacterium malmoense*
- *Mycobacterium szulgai*
- *Mycobacterium simiae*

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## NTM drug resistance: NTM species are (mostly) not like TB

- Innate or "natural" or "cryptic" drug resistance
- Not readily or predictably associated with *in vitro* measures of resistance such as MICs (minimum inhibitory concentration):
  - Inducible macrolide resistance (*erm*) gene, *M. abscessus*
- *In vitro* susceptibility results (MIC) do not reliably predict *in vivo* (clinical) treatment response for most NTM treatment

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## NTM drug resistance: NTM species are (mostly) not like TB

- *In vitro* susceptibility results (MIC) do not reliably predict *in vivo* (clinical) treatment response for most NTM treatment
- ***Three important exceptions:***
  - **MAC: Macrolide/Amikacin *in vitro* susceptibility results predict *in vivo* treatment response**
  - ***M. kansasii*: Rifampin *in vitro* susceptibility results predict *in vivo* treatment response**

- Van Ingen et al in Nontuberculous Mycobacterial Disease; Griffith DE (ED) 2019. Pg 61-88

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## Role of Antimicrobial Susceptibility Testing (AST): 2020 NTM Treatment Guidelines

| Species | Drugs |
|---|---|
| *M. kansasii* | Rifampicin |
| MAC | Macrolide<br>Amikacin |
| *M. abscessus* | Macrolide<br>(including *erm*(41) gene)<br>Amikacin |

**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. *Clin Infect Dis.* 2020;71(4):905-913.
Daley CL, et al. *Eur Respir J.* 2020;56(1):2000535.

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MAC, *Mycobacterium avium* complex

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## NTM drug resistance: NTM can *sometimes* be like TB, and it is important to know when that occurs

- Where *in vitro* susceptibility correlates with clinical outcome, clinically significant mutational resistance can occur as it does with TB (resistant isolates can be selected with suboptimal treatment regimens)
- *M. avium* complex (MAC):
  - 23S rRNA gene, *rrl*, (macrolides)
  - 16S rRNA gene *rrs,* (amikacin)
- *M. Kansasii*
  - *rpoB* gene (riampin)
  - ?Macrolide/amikacin/fluoroquinolone

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## NTM drug resistance: Bottom Line

- MIC values and cut points indicating "susceptibility" and "resistance" for most slow growing NTM are not validated and must be interpreted with caution (including 2020 NTM Treatment Guidelines based regimens)
- This lack of correlation between *in vitro* "susceptibility" and clinical response is a major reason for the inconsistent and frequently poor treatment response for many NTM
- Where correlation exists between *in vitro* MIC and clinical response (MAC, macrolide and amikacin; M. kansasii, rifampin), a high priority is preventing the emergence of acquired mutational resistance

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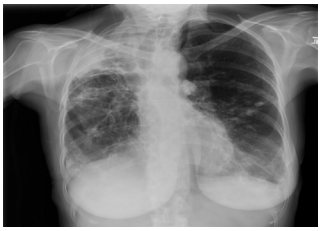
## 78 yo with MAC treated with AZI/FQ because she was EMB "resistant", now macrolide RESISTANT



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## Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline.

Daley CL and the 2020 NTM Treatment Guidelines Committee
*Clin Infect Dis*. 2020;71(4):905-913.
*Eur Respir J*. 2020 Jul 7;56(1):2000535

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## 2020 NTM Treatment Guidelines: "Watchful Waiting"

- Should patients with NTM pulmonary disease be treated with antimicrobial therapy or followed for evidence of progression ("watchful waiting")?
- 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).

- Daley CL, et al. *Eur Respir J*. 2020;56(1):2000535.

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## 2020 NTM Treatment Guidelines: "Watchful Waiting"

- Meeting diagnostic criteria does NOT automatically require initiating anti-mycobacterial therapy due to the limitations of NTM diagnostic criteria
  - NTM that are contaminants or unusual/rare respiratory pathogens: *M. gordonae*, *M. fortuitum*
  - Relatively non-virulent NTM respiratory pathogens: *M. chimaera*
- Patients with MAC who have stable, indolent or slowly progressive disease (Risk/benefit decision)
- Not appropriate for cavitary NTM disease or disease associated with AFB smear positivity

- Daley CL, et al. *Eur Respir J*. 2020;56(1):2000535.

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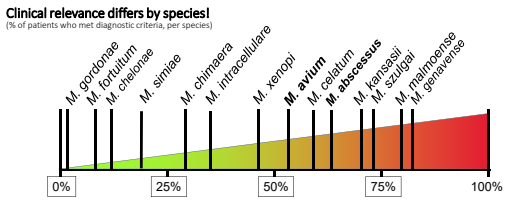
Clinical relevance of pulmonary NTM isolates in NL

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## Initiate Treatment or "Watchful Waiting"?

**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).

- Over 50% of patients who meet diagnostic criteria for NTM-LD progress within 3 to 5 years

| Host/demographic factors | Laboratory factors | Radiographic factors | Bacteriologic factors |
|---|---|---|---|
| • Male gender<br>• Older age<br>• Presence of co-morbidities<br>• Low body mass index | • Elevated inflammatory indices (ESR, CRP)<br>• Anemia<br>• Hypoalbuminemia | • Fibrocavitary<br>• Extent of disease | • Bacterial load<br>• NTM species |

Daley CL, et al. *Clin Infect Dis*. 2020;71(4):905-913.
Daley CL, et al. *Eur Respir J*. 2020;56(1):2000535.
Hwang JA, et al. *Eur Respir J*. 2017;49(3):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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## "Watchful waiting" is not a passive process, it is doing something

- Nodular/bronchiectatic MAC lung disease is in general a very indolent (glacial) process. There is usually time for appropriate data collection and a deliberate risk/benefit assessment about treatment
- Patients should be started on airway clearance for bronchiectasis which can be transformative symptomatically, 10%-15% cases have sputum AFB culture conversion (Moon et al, Resp Med; 2019 and Hwang et al ERJ; 2017)
- Airway clearance is likely a necessary element for any successful antibiotic therapy of nodular/bronchiectatic NTM/MAC lung disease
- Address other potentially contributing factors: GERD, sinus disease, bronchospasm, nutrition, fitness, etc.
- If not started on antimycobacterial therapy, patients are engaged with a physician who will manage bronchiectasis and evaluate status of NTM/MAC INDEFINITELY.

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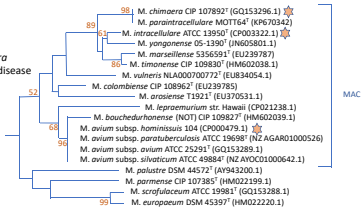
## *Mycobacterium avium* complex is the most common NTM pathogen

12 species of MAC

*M. avium*, *M. intracellulare*, and *M. chimaera* are the most common to cause pulmonary disease




Adapted from International journal of systematic and evolutionary microbiology. , 2018, Vol.68(11), p.3666-3677.

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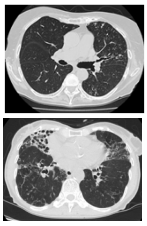
## Nodular/bronchiectatic MAC lung disease

**Epidemiology**
- Post-menopausal females (>60 yrs old)
- Scoliosis, mitral valve prolapse, low BMI
- No pre-existing lung disease, CFTR mutation

**Clinical course**
- Prolonged cough, fatigue, weight loss

**Microbiology**
- Frequently AFB smear negative with culture positivity on broth medium only.
- Collect multiple sputum specimens or BAL

**Radiology**: Requires chest CT scan
- Bronchiectasis w/ nodules, tree-in-bud
- Middle lobe and lingula worst affected



- Holt MR et al. In: Griffith DE (Ed), Nontuberculous Mycobacterial Disease; 2019. Pg 310-324.
  Cowman S et al. Eur Respir J. 2019 Jul 11;54.
  Griffith DE. Semin Respir Crit Care Med. 2018:351-361.

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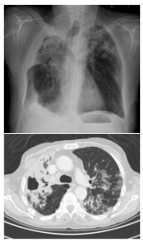
## Fibro-cavitary MAC lung disease

**Epidemiology**
- Mostly male, aged 50-70 yrs old
- Pre-existing COPD, silicosis, fibrosis

**Clinical course**
- TB-like, but slower

**Microbiology**
- Often AFB smear positive sputum
- High yield of broth and solid medium culture

**Radiology**
- Fibro-cavitary lesions, upper lobes:
- Diagnosis can usually be made on plain chest radiograph



- Holt MR et al. In: Griffith DE (Ed), Nontuberculous Mycobacterial Disease; 2019. Pg 310-324.
  Cowman S et al. Eur Respir J. 2019 Jul 11;54.
  Griffith DE. Semin Respir Crit Care Med. 2018:351-361.

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## Recommended Treatment Regimens for MAC-LD

| | No. of Drugs | Preferred Regimen[a] | Dosing Frequency | Duration |
|---|---|---|---|---|
| Nodular-bronchiectatic | 3 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol | 3 times weekly | 12 months after culture conversion |
| Cavitary | ≥3 | Azithromycin (clarithromycin)<br>Rifampicin (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

| | Culture Conversion |
|---|---|
| Macrolide susceptible | |
| Non-cavitary<br>Cavitary | 80%<br>50% to 80% |

Daley CL, et al. *Clin Infect Dis*. 2020;71(4):905-913.
Daley CL, et al. *Eur Respir J*. 2020;56(1):2000535.

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## Treatment Outcomes for MAC

| | Culture Conversion |
|---|---|
| **Macrolide susceptible** | |
| Non-cavitary | 80% |
| Cavitary | 50-80% |
| **Macrolide resistant** | |
| No surgery/aminoglycoside | 5% |
| Some surgery/aminoglycoside | 15% |
| Surgery + prolonged aminoglycoside* | 80% |

* ≥ 6 months IV aminoglycoside

Griffith DE, et al. AJRCCM 2006;174:928
Jeong BH, et al. AJRCCM 2015;191:96-103
Moon SM, et al. Antimicrob Agents Chemother; 2016
Wallace R, et al. Chest 2014;146:276-282
Koh WJ, et al. Eur Respir J 2017;50

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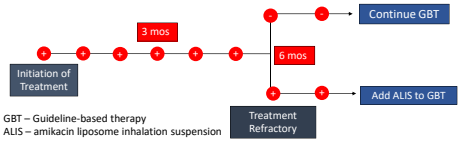
## Treatment Refractory MAC

- Treatment Refractory: Remains culture positive after at least 6 months of guideline-based therapy




GBT – Guideline-based therapy
ALIS – amikacin liposome inhalation suspension

Daley CL, et al. *Clin Infect Dis*. 2020;71(4):905-913.
Daley CL, et al. *Eur Respir J*. 2020;56(1):2000535.

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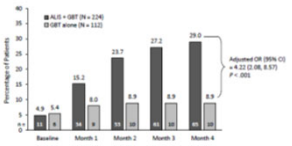
## Treatment for Refractory MAC Pulmonary Disease: Inhaled Amikacin

**Recommendation**

**In patients with MAC pulmonary disease who have failed therapy after at least 6 months of guideline-based therapy, we recommend the 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




Proportion of Patients With Negative Sputum Cultures for MAC

Daley CL, et al. *Clin Infect Dis*. 2020;71(4):905-913.
Daley CL, et al. *Eur Respir J*. 2020;56(1):2000535.
Griffith DE, et al. *Am J Respir Crit Care Med*. 2018;198(12):1559-1569.

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## Inhaled Generic Amikacin

- 5 observational studies over 12 years
- 61 patients with MAC lung disease treated with inhaled generic amikacin for variable periods of time (3-24 months)
- No amikacin susceptibility results, variable macrolide susceptibility
- Variable inhalation delivery systems
- Variable amikacin doses and treatment duration with variable amikacin tolerance and side effects
- Multiple and variable companion drugs
- Mixed (combined) data analysis
- Variable outcomes: 15-83% sputum conversion

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## Alternatives to "first line" antibiotics for MAC lung disease

- For Ethambutol (the most important drug in first line MAC therapy for preventing the emergence of macrolide resistance)
  - Parenteral amikacin
  - Inhaled liposomal amikacin
  - (Inhaled generic amikacin)
  - Clofazimine
- For rifampin
  - Rifabutin
  - Clofazimine

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## MAC Lung Disease Therapy

- Most experts recommend gradual introduction of MAC medications (One week at a time)
- Intermittent (TIW) therapy is better tolerated, in general, than daily therapy with the standard macrolide-based regimen
- There is no persuasive data that daily therapy is more effective than intermittent therapy, with the exception of cavitary disease
- Brief interruptions in therapy do not jeopardize the chances for clinical success
- Splitting doses or taking doses at night may improve medication tolerance
- Taking medications with food may not be optimal but if it allows the patient to tolerate the medication then it is acceptable


- Griffith et al. Chest. 2020 Epub ahead of print.
Holt MR et al. In: Griffith DE (Ed), Nontuberculous Mycobacterial Disease; 2019. Pg 310-324.
Cowman S et al. Eur Respir J. 2019 Jul 11;54.
Griffith DE. Semin Respir Crit Care Med. 2018:351-361.


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## Following MAC patients on therapy

- Monitoring for effectiveness:
  - Sputum AFB cultures: frequency 1 month until sputum conversion then 2-3 months (there is no such thing as collecting too many sputum AFB specimens)
  - Sputum AFB cultures necessary for determining if patients are failing therapy or for determining the treatment duration
  - Imaging frequency: patient-dependent, minimize chest CT use, ideally at the start and end of therapy but otherwise should be ordered to answer a specific question
  - Symptom response
- Treatment duration:
  - Continue therapy for 12 months past sputum conversion

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## MAC lung disease microbiologic recurrence
(Relapse vs Reinfection)

- Microbiologic recurrences are common during and after therapy for MAC lung disease
  - Occurs in approximately 15% of patients who convert sputum to AFB culture negative while on therapy
  - Occurs in approximately 50% of patients who convert sputum to AFB culture negative while on therapy
- 75% of microbiologic recurrences due to new MAC genotypes
- Can also be due to new MAC species that are reported as "MAC"
- No simple algorithm for management. Single smear negative, low culture positivity specimens not likely a harbinger of clinical failure/relapse


- 1. Wallace R, et al. Chest 2014;146:276-282
- 2. Boyle DP, et al. Ann Am Thorac Soc 2016
- 3. Koh WJ, et al. ERJ 2017;50 epub


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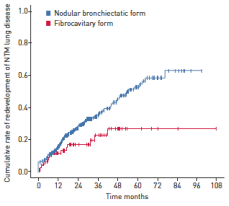
## Recurrence of MAC Based on Clinical Phenotype

Of 402 patients with favorable outcomes:

- 118 (29%) recurred
  - 55% same MAC species
    - 74% reinfection*
    - 26% relapse
- Recurrence occurred in
  - 33% of NB patients
  - 16% fibrocavitary patients

*based on rep-PCR




Koh WJ, et al. Eur Resp J 2017:50

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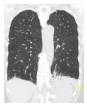
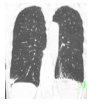
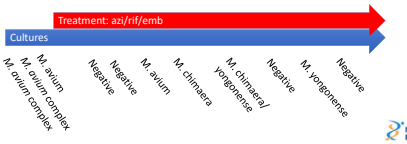
## Mixed Infection with Different MAC Species



62 y/o woman with fatigue and chronic cough



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## Macrolide and amikacin resistance

- Resistance to macrolides and amikacin emerges when they are not protected by adequate companion medications.
- Protection of macrolides to prevent the emergence of macrolide resistance is a well established priority for clinicians.
- Protection of amikacin is less well appreciated so clinicians must be reminded to use adequate companion medications to prevent the emergence of amikacin resistance.
- Macrolide and ethambutol should be adequate for protecting amikacin against the emergence of resistance.

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## Development of Macrolide Resistant MAC

- Risk Factors (Griffith 2007):
  - Macrolide mono-therapy, macrolide plus flouroquinolone
- Risk Factors (Morimoto 2016):
  - Macrolide mono-therapy, macrolide plus fluoroquinolone, macrolide plus rifampin, deviation from standard treatment due to adverse effects of ethambutol
- Risk Factors (Koh et al 2016):
  - One-, three-, and five-year mortality: 9, 24 and 47% respectively
  - 65% treated with guidelines recommended regimens including macrolide/emb/rifamycin

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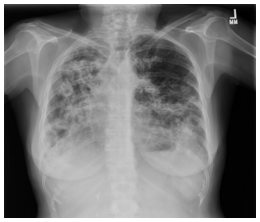
64 yo female with macrolide resistant MAC
Multiple courses of antibiotics
Chronic respiratory failure



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## Therapy for macrolide resistant MAC

- Ethambutol and rifabutin
- **Injectable + surgery** (Griffith et al 2007, Morimoto et al 2016)
- Inhaled liposomal amikacin
- Clofazimine
- Bedaquiline
- Oxazalidinones
- Mucinex, Doritos (CR), and Preparation H
- New drugs (?)

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## Treatment Outcomes for MAC

| | Culture Conversion |
|---|---|
| **Macrolide susceptible** | |
| Non-cavitary | 80% |
| Cavitary | 50-80% |
| **Macrolide resistant** | |
| No surgery/aminoglycoside | 5% |
| Some surgery/aminoglycoside | 15% |
| Surgery + prolonged aminoglycoside* | 80% |

* ≥ 6 months IV aminoglycoside

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Moon SM, et al. Antimicrob Agents Chemother; 2016
Wallace R, et al. Chest 2014;146:276-282
Koh WJ, et al. Eur Respir J 2017;50

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## *Question #2*

- *Mycobacterium kansasii* was described in:
  - A) Arkansas
  - B) Arkansasii
  - C) Kansas
  - D) Kansasii
  - E) Brooklyn, NYC

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## *Mycobacterium kansasii*

- The only known environmental reservoir for *M. kansasii* is municipal or household water
- 5-7 strain types identified by DNA-based analysis, the majority of human isolates subtype I.
- Phylogenic analyses suggest that, among all NTM species, is most closely related to *M. tuberculosis*
- Clinically and radiographically the NTM most closely related to tuberculosis
  - Apical fibrocavitary disease
  - Nodular/bronchictatic disease

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## *Mycobacterium kansasii*

- High rates of pulmonary disease reported in Southern and Midwestern US, Europe, East Asia, Australia, parts of the Middle East
- Risk factors include COPD, prior TB, bronchiectasis and silicosis.
- Single *M. kansasii* isolates are likely to reflect clinically significant infection but confirmation still required according to diagnostic guidelines.
- "Watchful waiting" risky

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## Recommended Treatment Regimen
## *M. kansasii*

| Organism | Drugs (n) | Preferred Regimen | Dosing Frequency | Duration |
|---|---|---|---|---|
| ***M. kansasii*** | | | | |
| Nodular-bronchiectatic or cavitary | 3 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol | Daily | 12 months |
| Nodular-bronchiectatic | 3 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol | 3 times weekly | |

Daley CL, et al. *Clin Infect Dis.* 2020;71(4):905-913.
Daley CL, et al. *Eur Respir J.* 2020;56(1):2000535.

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## Recommended Treatment Regimen
## *M. kansasii* Lung Disease

| Organism | Drugs (n) | Preferred Regimen | Dosing Frequency | Duration |
|---|---|---|---|---|
| ***M. kansasii*** | | | | |
| Nodular-bronchiectatic or cavitary | 3 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol | Daily | 12 months |
| Nodular-bronchiectatic | 3 | Azithromycin (clarithromycin)<br>Rifampicin (rifabutin)<br>Ethambutol | 3 times weekly | |
| Nodular-bronchiectatic or cavitary | 3 | Isoniazid<br>Rifampicin (rifabutin)<br>Ethambutol | Daily | |

Daley CL, et al. *Clin Infect Dis.* 2020;71(4):905-913.
Daley CL, et al. *Eur Respir J.* 2020;56(1):2000535.

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## *Question #3*

- Mycobacterium xenopi was first discovered in:
  A. Spam
  B. North American prairie dog
  C. A South African toad
  D. A South American sloth
  E. A Himalayan three-toed xenopi

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## *Mycobacterium xenopi*

- *M. xenopi* which has been isolated from household water systems among patients with *M. xenopi* disease and hospital water systems associated with outbreaks and pseudo-outbreaks of *M. xenopi* disease
- *M xenopi* is tolerant of higher water temperatures than MAC (?selected by raising hot water heater temperatures)
- Highest rates of disease reported in parts of Western Europe and Ontario, Canada, and the NE US.
- *M xenopi* lung disease highly associated with COPD, frequent cavitation and high mortality

- Marras T and Brode S. in Nontuberculous Mycobacterial Disease, Springer Nature, 2019: 325-368
- Daley CL, et al. *Clin Infect Dis.* 2020;71(4):905-913

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## *Mycobacterium xenopi*

- *M. xenopi* pulmonary disease is difficult to treat and associated with high all-cause mortality higher than other NTM species
- 5-year mortality of 51% and 43% in studies from Denmark and Canada respectively
- Elevated mortality may be due to underlying lung disease, frequent concomitant pulmonary aspergillosis, as well as frequent cavitation.

- Marras T and Brode S. in Nontuberculous Mycobacterial Disease, Springer Nature, 2019: 325-368
- Daley CL, et al. *Clin Infect Dis.* 2020;71(4):905-913

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## *Mycobacterium xenopi*

- *In vitro* activity of moxifloxacin is equal to that of clarithromycin
- One randomized clinical trial compared ciprofloxacin with clarithromycin added to ethambutol/rifampin regimen in 34 patients
- No significant differences found between the two regimens with regard to death, cure, recurrence of adverse events
- Preliminary data from ongoing study in France in which patients randomized to either moxifloxacin or clarithromycin plus ethambutol-rifampin shows no difference in treatment success between the two arms

- Marras T and Brode S. in Nontuberculous Mycobacterial Disease, Springer Nature, 2019: 325-368
- Daley CL, et al. *Clin Infect Dis.* 2020;71(4):905-913

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## *Mycobacterium Xenopi* Treatment Recommendations (2020 NTM Treatment Guidelines)

- A daily regimen that includes at least 3 drugs, rifampin, ethambutol, and either a macrolide and/or fluoroquinolone (e.g. moxifloxacin)
- In patients with cavitary or advanced/severe bronchiectatic *M. xenopi* pulmonary disease, we suggest adding parenteral amikacin to the treatment regimen and obtaining expert consultation
- Treatment should be continued for at least 12 months beyond culture conversion, acknowledging that the optimal duration of treatment is unknown

- Daley CL, et al. *Clin Infect Dis.* 2020;71(4):905-913

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## Consensus management recommendations for additional non-tuberculous mycobacterial pulmonary diseases

Christoph Lange and 2020 NTM Guidelines Committee, in press, Lancet Infectious Disease, 2021

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## *Question #4*

- *Mycobacterium szulgai* was named after
  A. Dr. Mike O. Bacterium, Tyler, TX
  B. Dr. T. Szulgai, Poland
  C. Lake Szulgai, Romania
  D. Dr. V. Szulgai, Brooklyn, NYC
  E. The Szulgai thermal spa, Iceland

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## *Mycobacterium szulgai*

- Rarely isolated from the environment
- Because of the scarcity of reports of environmental isolation, respiratory isolates have generally been regarded as indicative of disease assuming environmental contamination unlikely
- Recent data suggest variable association between *M. szulgai* isolates and disease so diagnostic criteria should still be applied
- *M. szulgai* lung disease is rare (0.1% of NTM disease in one report from Canada). No clear geographic predilection
- Lung disease resembles TB with fibro-cavitary radiographic changes, male predominance, associated with COPD, prior TB

- Marras T and Brode S. in Nontuberculous Mycobacterial Disease, Springer Nature, 2019: 325-368

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## *Mycobacterium szulgai*

- *In vitro* drug susceptibility testing suggests frequent susceptibility to rifampin, ethambutol, amikacin and macrolide
- Treatment not addressed in 2020 NTM Guidelines but recent consensus document recommends at least 3 agents to which the organism shows *in vitro* susceptibility, typically daily macrolide, rifampin, ethambutol.
- Parenteral amikacin for cavitary and/or severe disease. No experience with flouroquinolones.
- Treatment duration to include 12 months of sputum culture negativity while on therapy after sputum conversion

- Marras T and Brode S. in Nontuberculous Mycobacterial Disease, Springer Nature, 2019: 325-368

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## *Question #5*

- *Mycobacterium malmoense* was first described in
  A. Malmo, Denmark
  B. Malmo, Norway
  C. Malmo, Sweden
  D. Malmo, Finland
  E. Malmo, Brooklyn, NYC

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## *Mycobacterium malmoense*

- *M. malmoense* rarely isolated from the environment (reported in natural water and soil)
- A common NTM species causing lung disease in Northern Europe
- Often mimics TB clinically with fibro-cavitary disease
- Male predominance, associated with COPD and/or history of prior TB
- Isolation from sputum usually associated with clinically significant disease although application of diagnostic guidelines still necessary

- Marras T and Brode S. in Nontuberculous Mycobacterial Disease, Springer Nature, 2019: 325-368

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## *Mycobacterium malmoense*

- *In vitro* susceptibility results vary but drugs with some evidence of clinical efficacy include rifampin, ethambutol, INH, macrolides and fluoroquinolones
- Two randomized trials from BTS
  - Rifampin/ethambutol vs rifampin/ethambutol/INH
  - Rifampin/ethambutol clarithromycin vs rifampin/ethambutol/ciprofloxacin
- No significant differences in clinical outcome in either study AND the proportion of patients alive and cured at 5 years in the second trial the same as the rifampin/ethambutol arm of the first trial

- Marras T and Brode S. in Nontuberculous Mycobacterial Disease, Springer Nature, 2019: 325-368

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## *Mycobacterium malmoense*

- Treatment not addressed in 2020 NTM Guidelines but recent consensus document recommends at least 3 agents including macrolide, ethambutol and rifampin given daily.
- Additional drugs might include moxifloxacin or clofazimine
- Consider parenteral amikacin for cavitary disease or severe nodular/bronchiectatic disease
- Duration of therapy at least 12 months after sputum conversion

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## *Question #6*

- *Mycobacterium simiae* was first described in
  A. Rhesus macaque
  B. Chimpanze
  C. Spider monkey
  D. Baboon
  E. Gorilla

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## *Mycobacterium simiae*

- *Mycobacterium simiae* has been isolated from fresh water, various animals, milk from dairy animals, and potable (municipal) water
  - Associated with nosocomial outbreaks and pseudo-outbreaks
- Uncommon in most regions, extensively described in Israel and the American Southwest (Arizona, Texas)
- Respiratory *M. simiae* isolates usually not associated with clinically significant disease (4%-21%).
- Because most *M. simiae* respiratory isolates are contaminants, and because it is so difficult to treat, there is a high bar for diagnosis of disease and initiating therapy

- Marras T and Brode S. in Nontuberculous Mycobacterial Disease, Springer Nature, 2019: 325-368

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## *Mycobacterium simiae*

- *In vitro* susceptibility results for most *M. simiae* isolates "bleak"
- *M. simiae* isolates may show *in vitro* susceptibility to amikacin, Bactrim, moxifloxacin, clofazimine, linezolid and clarithromycin.
  - "Results may not correlate with clinical outcome"
- Treatment not addressed in 2020 NTM Guidelines but recent consensus document recommends at least 3 drugs including, macrolide, Bactrim, moxifloxacin, amikacin, or clofazimine.
- Anecdotally, macrolide susceptible *M. simiae* with best outcomes
- Surgical resection of affected lung should be considered

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## Surgery for NTM Lung Disease

- Indications for surgery: medication unresponsive disease (drug resistance, large cavities), uncontrolled symptoms, hemoptysis, destroyed lung
- Most published experience with MAC and M. abscessus
- In uncontrolled case series, surgery for NTM lung disease associated with better microbiologic outcomes than medical management alone (selected patients with adequate cardio-pulmonary reserve and focal disease)
- In general, the more drug resistant the NTM species, the more necessary surgery becomes for favorable microbiologic outcome

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## Dave's (NTM Treatment) Frustration Index (DFI) 1-10 Scale (Scores +/- "1")

1: *M. fortuitum*
2: *M. kansasii*
4: *M. Szulgai*
5: *Mycobacterium avium* complex (MAC)
6: *M. xenopi*
7: *M. malmoense*
9 : *M. abscessus* subsp *abscessus*
12: *M. simiae*

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## Question #7

If you had to have a mycobacterial lung infection, which of the following would you want?

A. *M. avium complex (MAC)*
B. *M. kansasii*
C. *M. simiae*
D. *M. xenopi*
E. *M. tuberculosis*

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