Improving Outcomes in NTM-LD:

Strategies for Diagnosis, Individualized Treatment Plans and Patient Adherence

Supported by an educational grant from Insmed.

BEST HOSPITALS U.S.News NATIONAL PULMONOLOGY & LUNG SURGERY 2020-21

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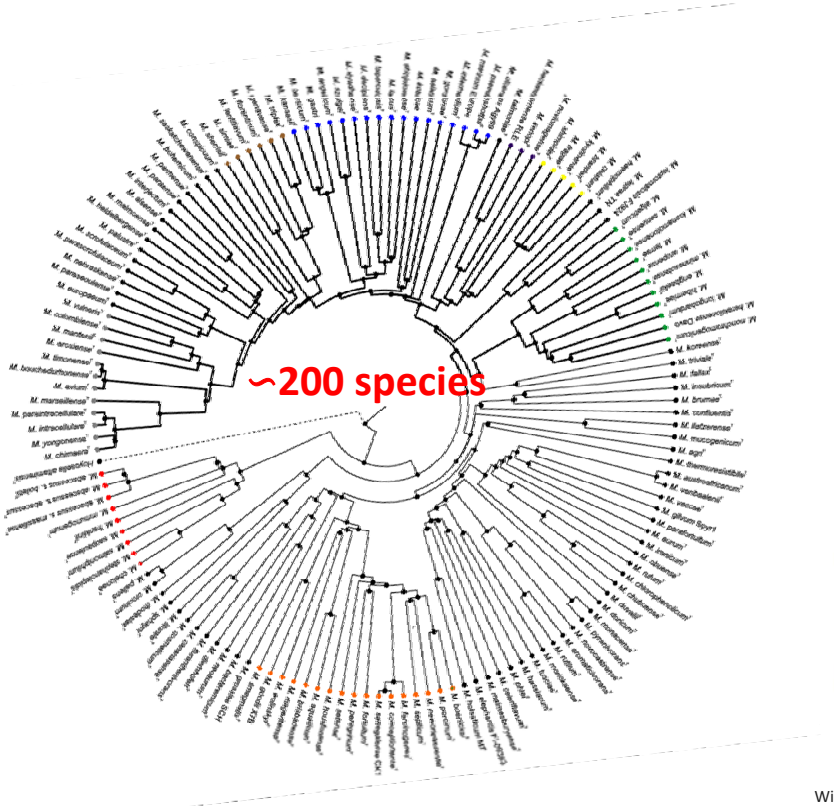
This program is provided by National Jewish Health and supported by an educational grant from Insmed.

The Learning Objectives for this program are:

- Apply strategies to reduce time to diagnosis and initiation of evidence-based treatment of NTM-LD.
- Use a patient-centered approach for communications related to diagnosis and development of individualized treatment plans in NTM-LD.
- Integrate strategies to manage adverse events and improve adherence to promote the completion of treatment regimens and improved patient outcomes in NTM-LD.

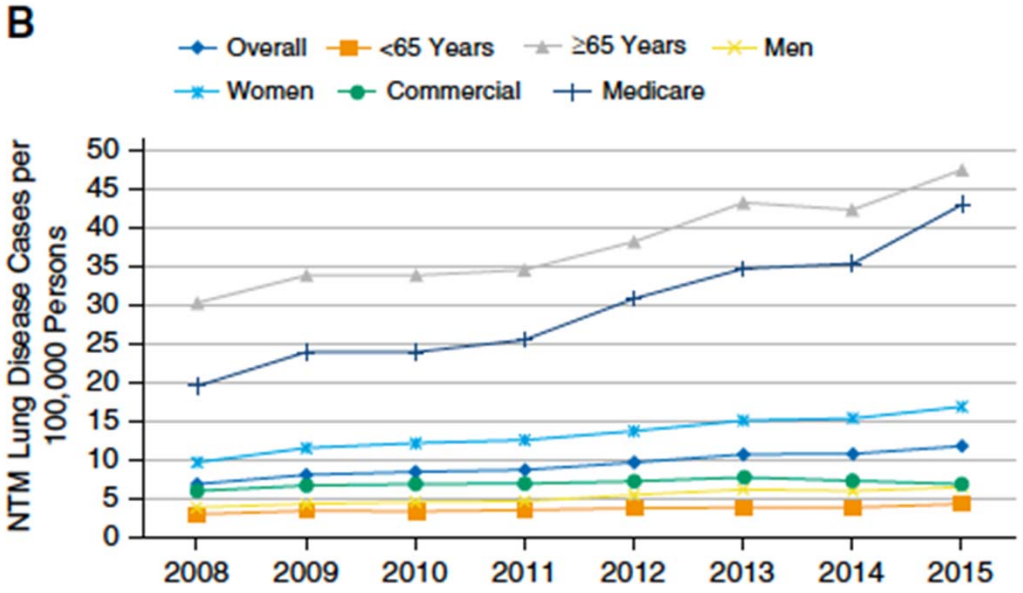
Nontuberculous Mycobacteria (NTM)
An Increasing Cause of Lung Disease



Tortoli E, Fedrizzi T, Meehan CJ, et al. The new phylogeny of the genus Mycobacterium: The old and the news. Infect Genet Evol. 2017;56:19-25.

National Managed Care Claims Database – 27 million people annually

Prevalence (per 100,000)



Winthrop KL, Marras TK, Adjemian J, Zhang H, Wang P, Zhang Q. Incidence and Prevalence of Nontuberculous Mycobacterial Lung Disease in a Large U.S. Managed Care Health Plan, 2008-2015. *Ann Am Thorac Soc*. 2020;17(2):178-185. doi:10.1513/AnnalsATS.201804-236OC

Why Early Diagnosis and Reducing Time to Treatment is Important

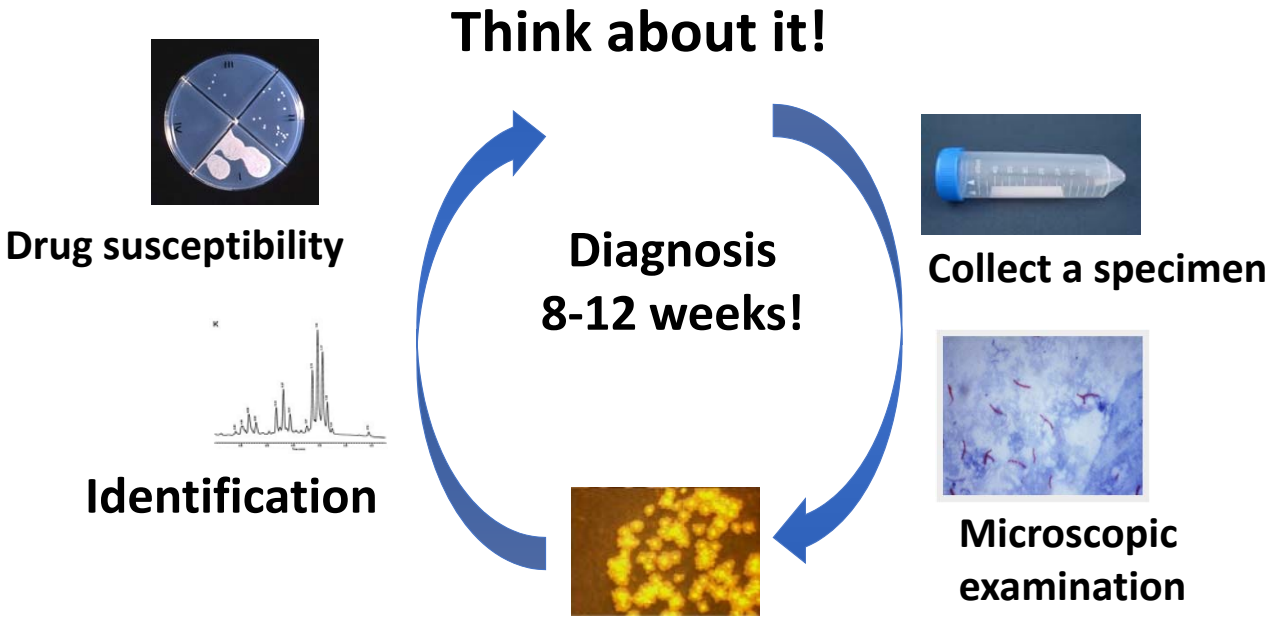
- Disease progression occurs in ∽ 60% of persons who meet ATS/IDSA diagnostic criteria for disease within 3-5 years
  - Hwang JA, et al. Eur Respir J, 2017;49:1600537
  - Kwon BS, et al. Respir Med 2019;150:45-50
  - Moon SM, et al. Respir Med 2019;151:1-7
- Lung function declines
  - Park HY, et al. Chest 2016;150:1222-1232
  - Kimuzuka Y, et al. PLoS ONE 2019;14:e0216034
- 5-year all-cause mortality can be as high as 10-33% and higher than general population: mortality higher in untreated MAC than treated (33% vs 22%)
  - Ito Y, et al. Int J Tuberc Lung Dis 2012;16:408-14
  - Diel R, et al. BMC Infect Dis 2018;18:206
  - Jhun BW, et al. Eur Respir J 2020;55:1900798

NTM Pulmonary Disease Diagnostic Criteria

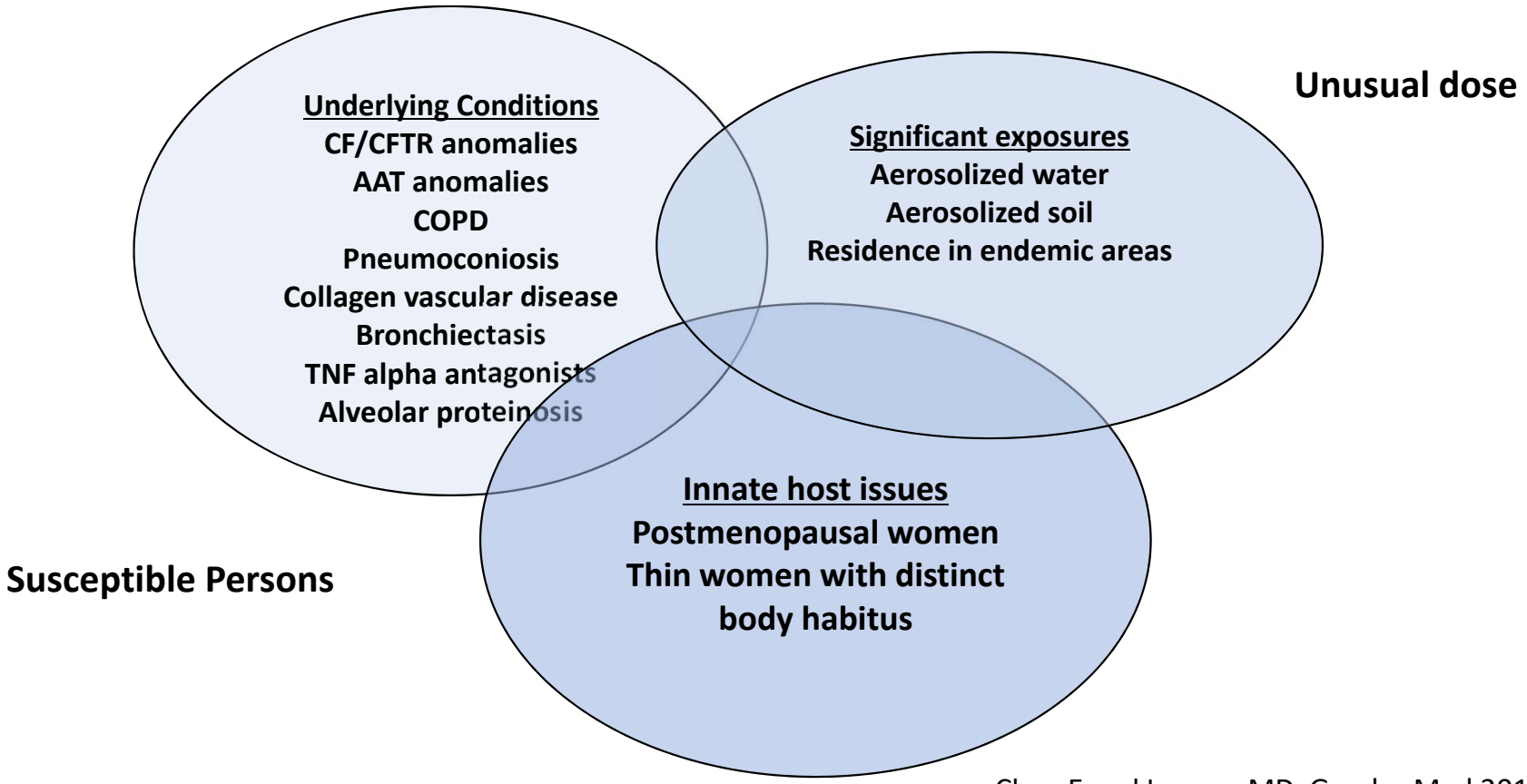
Clinical	Pulmonary or Systemic Symptoms	Both required
Radiological	Nodular or cavitary opacities on chest radiograph or HRCT that shows bronchiectasis with multiple small nodules	
Appropriate exclusion of other diagnoses		
Microbiological	1. Positive cultures from at least **two** separate sputum samples. If the results are non-diagnostic, consider repeat sputum AFB smears and cultures **or** 2. Positive cultures from at least **one** bronchial wash or lavage **or** 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 one or more sputum or bronchial washings that are culture positive for NTM	

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

Diagnostic Approaches to NTM-LD and Reducing Time to Treatment



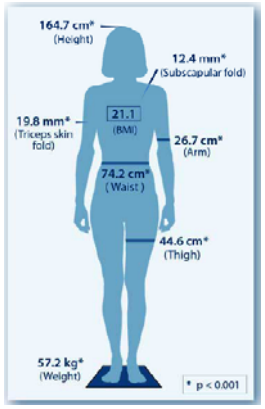
Risk Factors for NTM Pulmonary Disease

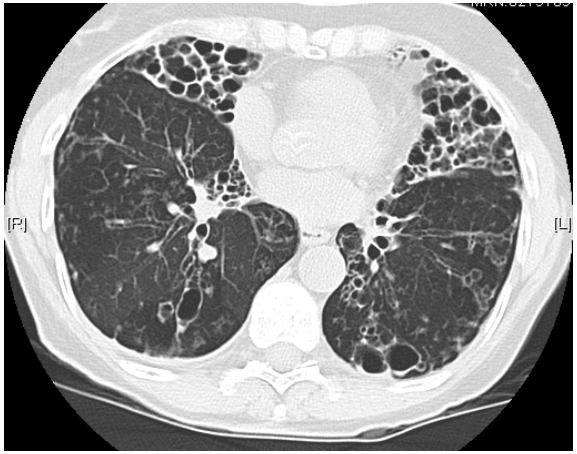


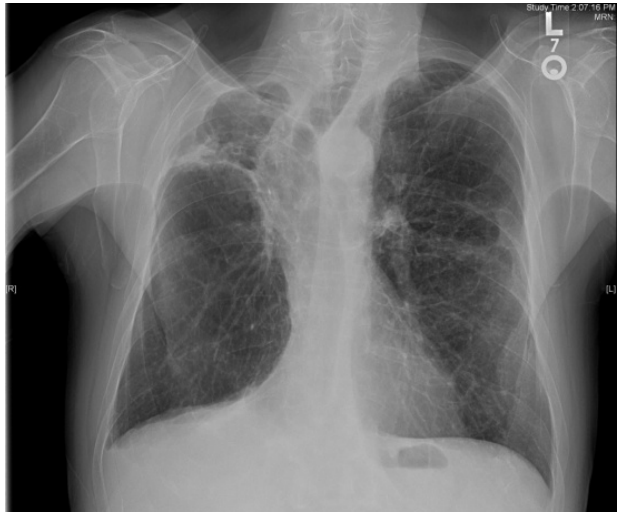
Chan E and Iseman MD. Gender Med 2010;7:5-18
Kim, et al. AJRCCM 2008;178:1066

Clinical Phenotypes

- Nodular / bronchiectatic disease
  - Women
  - Older
  - Nonsmokers
  - Tall, thin, low body mass index
- Fibrocavitary disease
  - Male
  - Older
  - Smokers
  - Various body builds







Kim RD, Greenberg DE, Ehrmantraut ME, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. *Am J Respir Crit Care Med*. 2008;178(10):1066-1074. doi:10.1164/rccm.200805-686OC
The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

Symptoms of MAC Pulmonary Disease

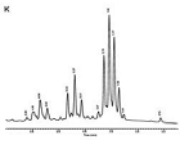
Symptom	Frequency (n = 63)
Fatigue, n (%)	52 (83%)
Cough	49 (78%)
Phlegm	42 (67%)
Shortness of breath	41 (65%)
Night sweats	43 (54%)
Fever	28 (44%)
Hemoptysis	18 (29%)
Weight loss	3.7 kg ± 5.2

Median time from symptom onset to diagnosis = 10 months (1 month to 6 years)

Huang JH, et al. Chest 1999;115:1033-1040.

Diagnostic Approaches to NTM-LD and Reducing Time to Treatment

Drug susceptibility

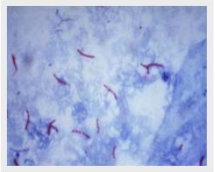


Identification

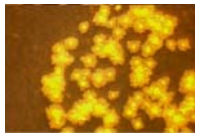
Think about it!

Diagnosis
8-12 weeks!

Collect a specimen



Microscopic examination



Culture (liquid and solid media)

Specimen Collection

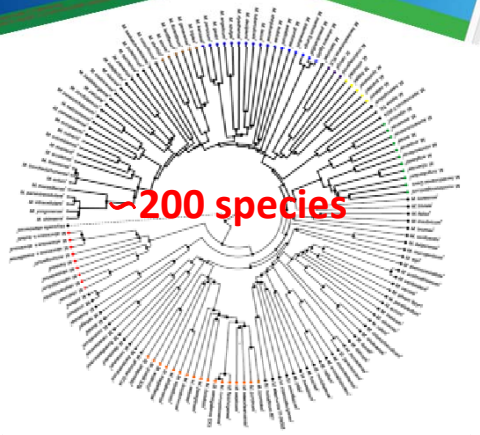
Bronchoscopy specimens

- Not as good as you think
  - Lidocaine is bacteriostatic
  - Specimen is dilute
  - Sampling error
  - Unable to determine bacterial load
  - Risks
  - Costs

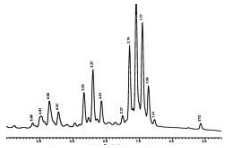
Sputum

- Better than you think
  - Multiple specimens – 3 over at least one week, preferably over weeks
  - Sputum AFB smear positivity and number of cultures are associated with progression of NTM disease
  - Similar culture yield as bronchoscopy in TB and NTM
  - Induction with hypertonic saline is easy! Patients can do it at home

Diagnosis of NTM Infections
Laboratory Diagnosis



Drug susceptibility

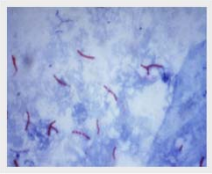


Identification

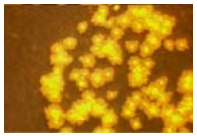
Think about it!

Diagnosis
8 weeks

Collect a specimen



Microscopic examination



Culture (liquid and solid media)

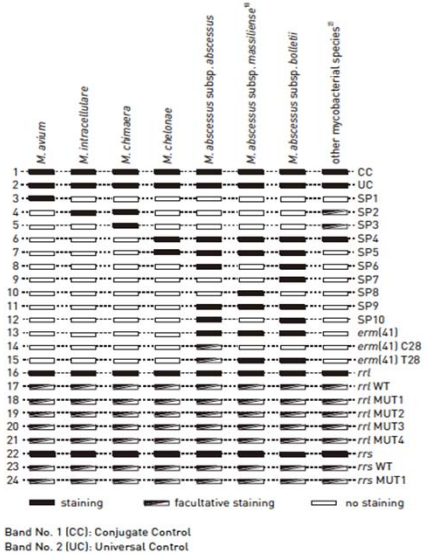
Antimicrobial Susceptibility Testing (AST) for *Mycobacterium avium* complex

Phenotypic Testing (weeks)

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

Genotypic Testing (hours/days)



<u>rrl mutations (macrolide)</u>

Sensitivity - 96.3%
Specificity - 100%

<u>rrs mutations (aminoglycoside)</u>

Sensitivity - 50+%
Specificity - 100%

Huh HJ, Kim SY, Shim HJ, et al. GenoType NTM-DR Performance Evaluation for Identification of Mycobacterium avium Complex and Mycobacterium abscessus and Determination of Clarithromycin and Amikacin Resistance. J Clin Microbiol. 2019;57(8)

Key Points Summary

- NTM, including MAC, are increasing in prevalence
- The most common symptoms are cough and fatigue
- Two clinical phenotypes are recognized; however there is a great deal of overlap
- Laboratory diagnosis should include precise speciation and determination of *in vitro* susceptibility testing to at least the macrolides and amikacin
- Diagnosis of NTM-related disease includes synthesis of clinical, radiographic and microbiologic information

Development of an Individualized Treatment Plan and Patient-Centered Approach - MAC

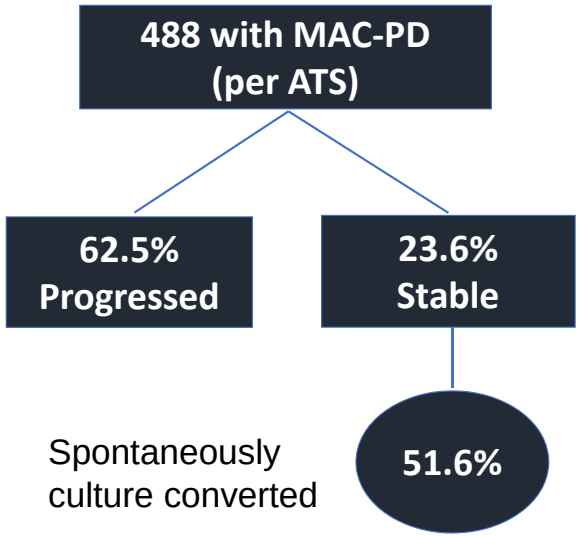
- Scope of Guidelines
  - Pulmonary disease in adults (without HIV or CF)
  - *M. avium* complex*, M. kansasii, M. xenopi, M. abscessus*
- GRADE methodology
- 22 PICO questions and 31 recommendations
  - 7 MAC recommendations

Initiate Treatment or "Watchful Waiting?"

Recommendation 1

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)**.**

- Host and organism factors are related to progression of disease
  - Some NTM species are more pathogenic than others
  - Immunocompromised at greater risk
- Cohort studies have reported that **bacterial load** (i.e., smear positive) and **radiographic extent of disease** (i.e. cavitary) are predictors of progression
- Other predictors are older age, low body mass index (<18.5), co-morbidities, low albumin, anemia, elevated inflammatory indices



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

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

Composition of Treatment Regimen
Empiric Treatment vs Susceptibility-based?

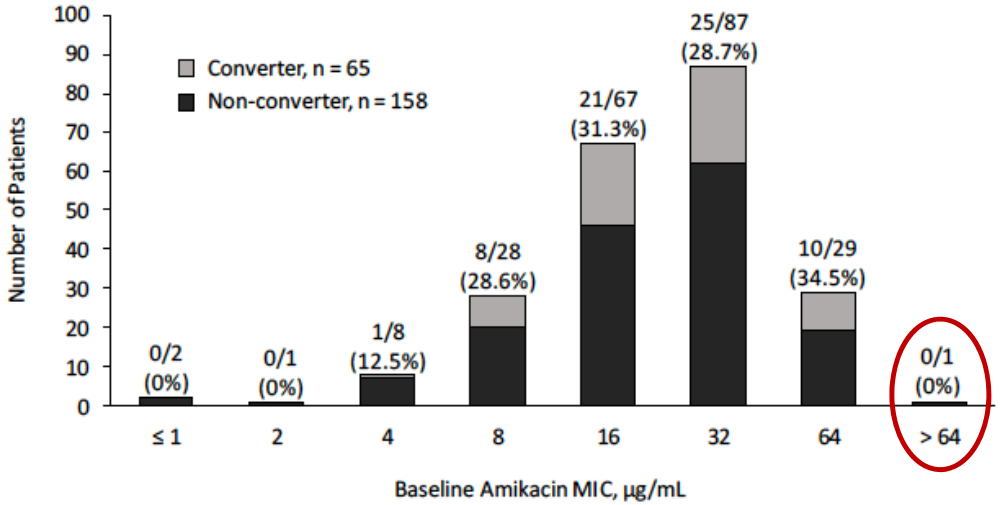
Recommendation 2

In patients with MAC pulmonary disease, we suggest susceptibility-based treatment for macrolides and amikacin over empiric therapy (conditional recommendation, very low certainty in estimates of effect).

- Macrolide resistance correlates with poor treatment outcomes.
  - Monotherapy trials in HIV-related disseminated MAC
  - Retrospective studies in non-HIV-related pulmonary disease
- Amikacin resistance associated with specific mutation and worse outcomes
- No evidence for other drugs

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

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



Olivier KN, Griffith DE, Eagle G, et al. Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease. Am J Respir Crit Care Med. 2017;195(6):814-823. https://doi.org/10.1164/rccm.201604-0700OC. *The American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Composition of Treatment Regimen Macrolide vs no macrolide?

Recommendation 3

In patients with MAC pulmonary disease, we recommend a 3-drug regimen that includes a macrolide over a 3-drug regimen without a macrolide (strong recommendation, very low certainty in estimates of effect).

- No well designed studies have addressed this issue
- Macrolide susceptibility has been a strong predictor of treatment success
- Loss of the macrolide is associated with a markedly reduced rate of sputum culture conversion (5-36%)

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

Systematic review (21 studies)

Sustained culture conversion incidence rate ratio:

Macrolide-containing	0.54 (0.45-0.63)
Macrolide-free	0.38 (0.25-0.52)

Sputum culture conversion increased in macrolide-containing vs macrolide-free regimens as study quality improved

Pasipanodya JG, et al. J Anti Chemother 2017;72:i3-19

Composition of Treatment Regimen azithromycin vs clarithromycin?

Recommendation 4

In patients with macrolide-susceptible MAC pulmonary disease we suggest azithromycin-based treatment regimens rather than clarithromycin-based regimens. (conditional recommendation, very low certainty in estimates of effect).

- Equal efficacy in cohort studies
- Better tolerated with azithromycin
- Less drug interactions
- Lower pill burden
- Single daily dosing

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

Systematic review (21 studies)

- No difference in sputum culture conversion at:
  - 6 months
  - End of therapy (EOT)
  - Sustained (12 months)
- No difference in acquired macrolide resistance

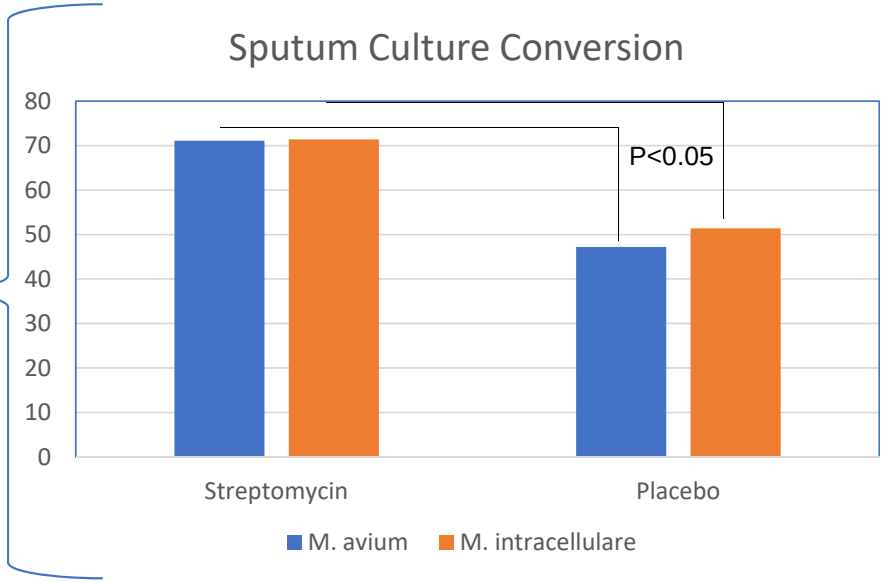
Pasipanodya JG, et al. J Anti Chemother 2017;72:i3-19

Composition of Treatment Regimen Aminoglycoside vs no aminoglycoside?

Recommendation 5

For patients with cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC pulmonary disease, we suggest that parenteral amikacin or streptomycin be included in the initial treatment regimen (conditional recommendation, moderate certainty in estimates of effect).

- Randomized placebo controlled study compared macrolide-based 3 drug regimen with IM streptomycin vs placebo
  - Higher rate of culture conversion with streptomycin for first 3 months
- Higher culture conversion in those with macrolide resistant disease when an aminoglycoside is included in regimen



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

Kobashi Y, et al. Resp Med 2007;101:130-138

Composition of Treatment Regimen
Inhaled amikacin?

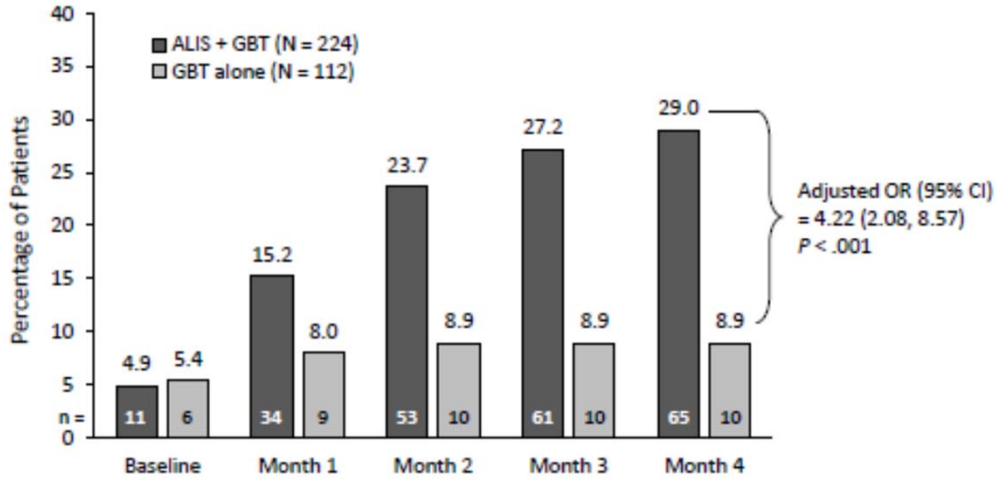
Recommendation 6

In patients with newly diagnosed MAC pulmonary disease, we suggest neither inhaled amikacin (parenteral formulation) nor amikacin liposome inhalation suspension (ALIS) be used as part of the initial treatment regimen. (conditional recommendation, very low certainty in estimates of effect).

In patients with MAC pulmonary disease who have failed therapy after at least six months of guideline-based therapy (GBT), 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).

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

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



Proportion of Patients With Negative Sputum Cultures for MAC

Griffith DE, Eagle G, Thomson R, et al. Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by Complex (CONVERT). A Prospective, Open-Label, Randomized Study. Am J Respir Crit Care Med. 2018;198(12):1559-1569. https://doi.org/10.1164/rccm.201807-1318OC. *The American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Composition of Treatment Regimen
3 vs 2 drug regimen?

Recommendation 7

In patients with macrolide-susceptible MAC pulmonary disease, we suggest a treatment regimen with at least three drugs (including a macrolide and ethambutol) over a regimen with two drugs (a macrolide and ethambutol alone). (conditional recommendation, very low certainty in estimates of effect).

- Most studies have evaluated three drug regimens
- Only one randomized study of 2 vs 3 drugs: underpowered with several methodologic weaknesses
- Concern about acquired macrolide resistance with 2 drugs

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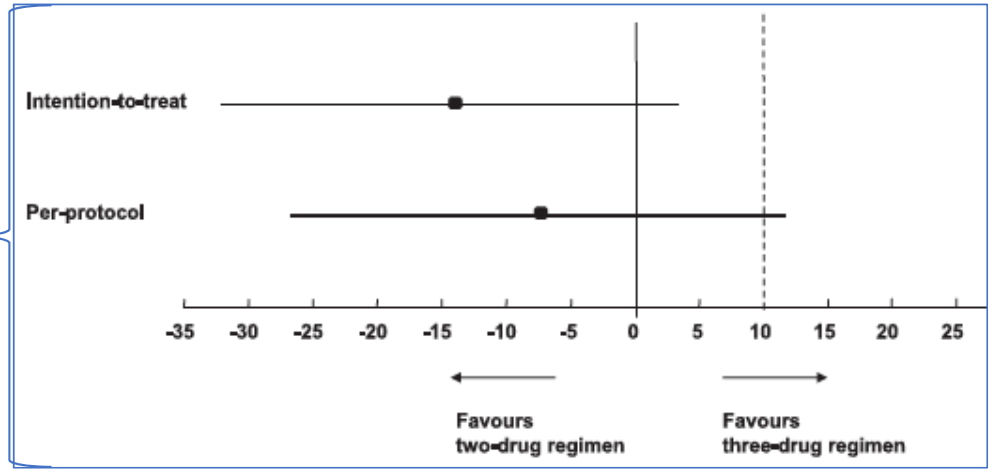
Euro Respir J 2020;56:2000535

Randomized trial of 2 vs 3 drug



Miwa S, Shirai M, Toyoshima M, et al. Efficacy of clarithromycin and ethambutol for Mycobacterium avium complex pulmonary disease. A preliminary study. *Ann Am Thorac Soc*. 2014;11(1):23-29. doi:10.1513/AnnalsATS.201308-266OC
Annals of the American Thoracic Society is an official journal of the American Thoracic Society.

Administration of the Regimen Intermittent vs Daily Therapy?

Recommendation 8

In patients with noncavitary nodular/bronchiectatic macrolide-susceptible MAC pulmonary disease, we suggest a three times per week macrolide-based regimen rather than a daily macrolide-based regimen. (conditional recommendation, very low certainty in estimates of effect).

In patients with cavitary or severe/advanced nodular bronchiectatic macrolide-susceptible MAC pulmonary disease, we suggest a daily macrolide-based regimen rather than three times per week macrolide-based regimen. (conditional recommendation, very low certainty in estimates of effect).

- Cohort studies have demonstrated similar culture conversion rates with intermittent vs daily therapy
- Intermittent therapy has less adverse effects (AEs) and better completion rate
- No evidence of increased risk of macrolide resistance
- Very low rate of culture conversion with intermittent therapy in cavitary MAC

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

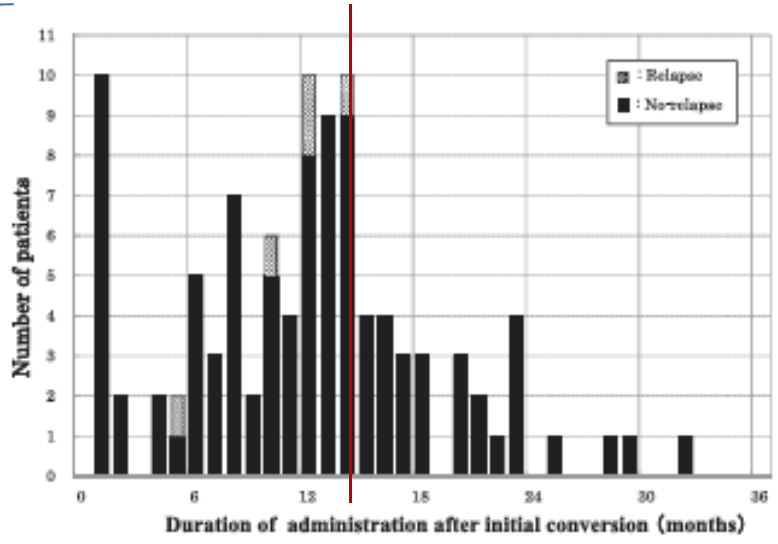
Duration of Therapy?

Recommendation 9

In patients with macrolide-susceptible MAC pulmonary disease, we suggest that patients receive treatment for at least 12 months after culture conversion. (conditional recommendation, very low certainty in estimates of effect).

- No randomized studies have evaluated the optimum duration of therapy
- Treatment success higher in persons who received at ≥ 12 mos of macrolide-based therapy compared with < 12 mos
- Bacteriologic relapse in Japan
  - 5% when treatment for < 15 mos after sputum culture conversion *vs*
  - 0% when treatment for > 15 mos after sputum culture conversion

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



Reprinted from Kadota JI, Kurashima A, Suzuki K. The clinical efficacy of a clarithromycin-based regimen for Mycobacterium avium complex disease: A nationwide post-marketing study. *J Infect Chemother*. 2017;23(5):293-300. doi:10.1016/j.jiac.2017.01.007

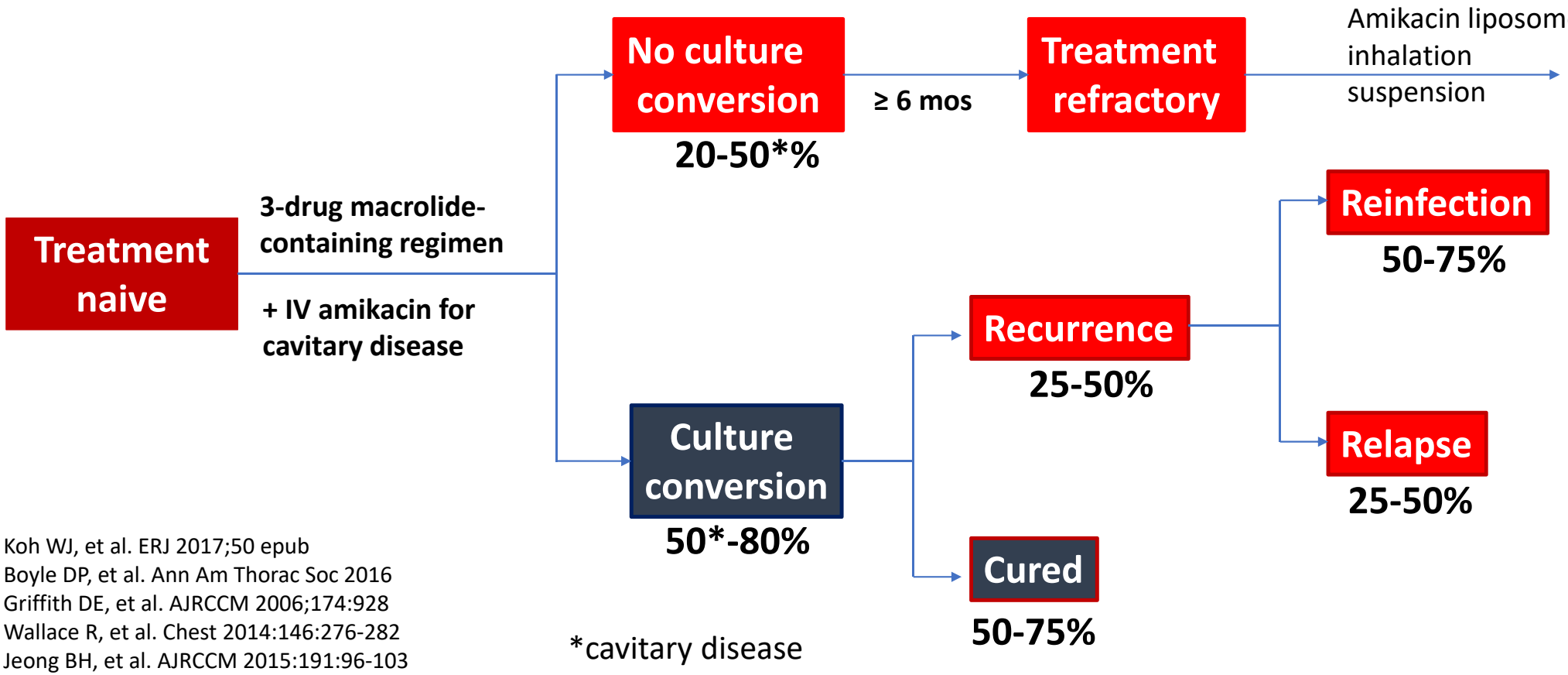
Recommended Treatment Regimens
MAC

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

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

Treatment of MAC Pulmonary Disease



Koh WJ, et al. ERJ 2017;50 epub
Boyle DP, et al. Ann Am Thorac Soc 2016
Griffith DE, et al. AJRCCM 2006;174:928
Wallace R, et al. Chest 2014:146:276-282
Jeong BH, et al. AJRCCM 2015:191:96-103

*cavitary disease

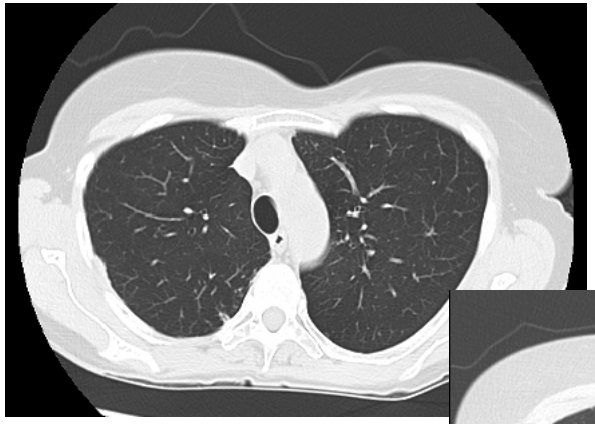
Key Points Summary

- New guideline for treatment of NTM pulmonary disease
- For those who meet diagnostic criteria, initiation of therapy is preferred, especially for those with higher bacterial load and extensive radiographic disease
- MAC should be treated with a 3-drug macrolide-containing regimen for 12 months after culture conversion to negative
  - Nodular-bronchiectatic disease can be treated 3X/week
  - Cavitary disease should be treated daily and parenteral aminoglycoside considered for first 2-3 months
- Treatment refractory MAC pulmonary disease should have ALIS added to guideline-based therapy

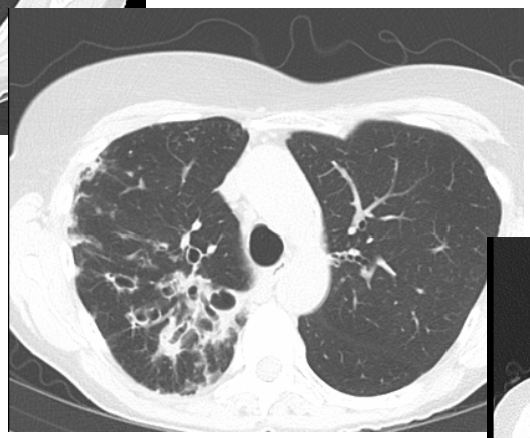
Development of an Individualized Treatment Plan and Patient-Centered Approach – *M. abscessus*

Chronic Pulmonary Disease

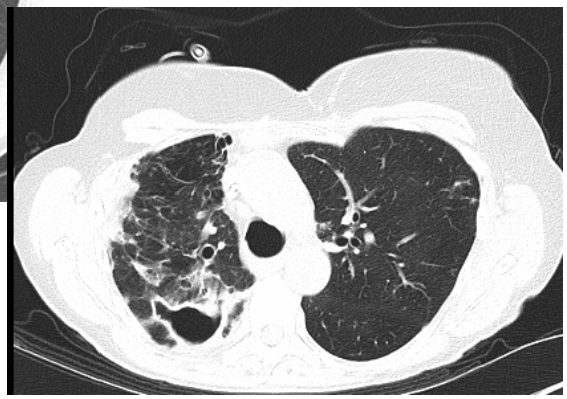
2003



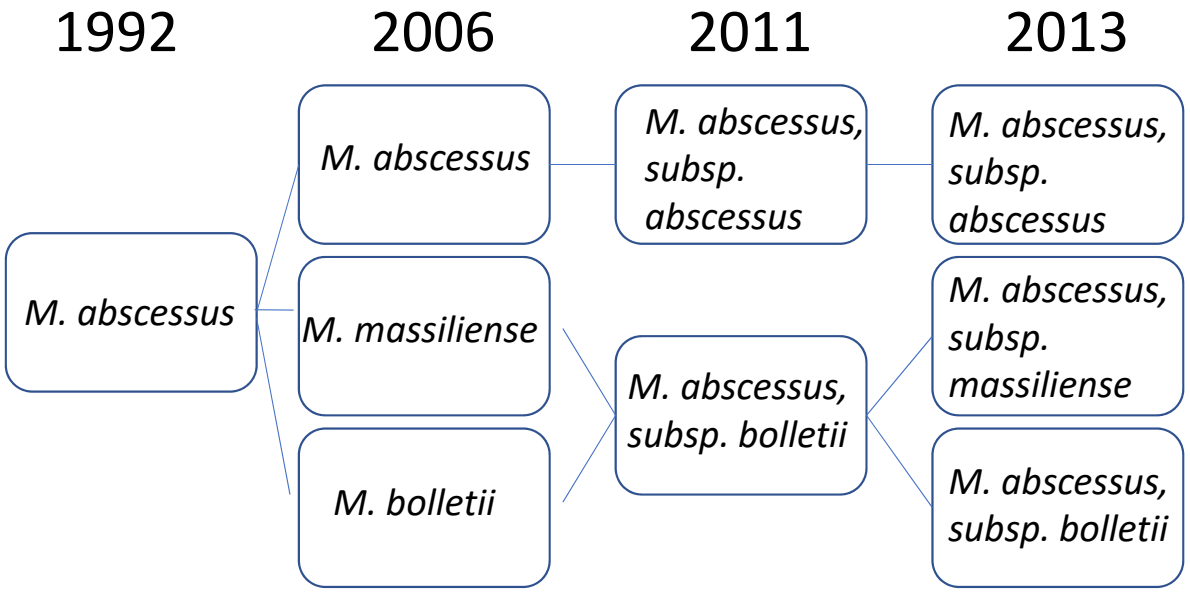
2013



2017



Evolution of Taxonomy



Emerg Infect Dis 2015;21:1638

Mycobacterium abscessus complex Characteristics: Macrolide resistance

M. Abscessus (MAB) subspecies	Clarithromycin (CLR) susceptibility days 3–5	Clarithromycin (CLR) susceptibility day 14	Macrolide susceptibility phenotype	Genetic implication	Macrolide Effect
M. massiliense *(M. abscessus*)*	Susceptible	Susceptible	Macrolide susceptible	dysfunctional *erm*(41) gene	Anti-mycobacterial
M. abscessus *M. bolletii*	Susceptible	Resistant	Inducible macrolide resistance	functional *erm*(41) gene	Immuno-modulatory
Any	Resistant	Resistant	High-level constitutive macrolide resistance	23S ribosomal RNA point mutation	Immuno-modulatory

*15-20% of *M.abscessus* have a dysfunctional ERM41 (C28)

Thorax 2017;72(Suppl 2):ii1

In *M. abscessus* pulmonary disease, should a macrolide-based regimen be used for treatment?

Recommendation

In *M. abscessus* pulmonary disease caused by strains without inducible or mutational resistance, we recommend a macrolide-containing multidrug treatment regimen

(strong recommendation, very low certainty in estimates of effect)

In *M. abscessus* pulmonary disease caused by strains with inducible or mutational macrolide resistance, we suggest a macrolide-containing regimen if the drug is being used for its immunomodulatory properties although the macrolide is not counted as an active drug in the multidrug regimen

(conditional recommendation, very low certainty in estimates of effect)

- no studies identified that compared macrolide-containing regimens with non macrolide-containing regimens

Daley CL, et al. *Eur Respir J* 2020; 56: 2000535

Clinical Significance of Differentiation of *M. massiliense* from *M. abscessus*

- 57 patients received a standardized combination regimen, macrolide containing with a 4-week course of cefoxitin and amikacin (12+ mo)
  - 24 with *M. abscessus* and 33 with *M. massiliense*
  - Cure in *M. massiliense* (88%) vs. *M. abscessus* (25%; P , 0.001)

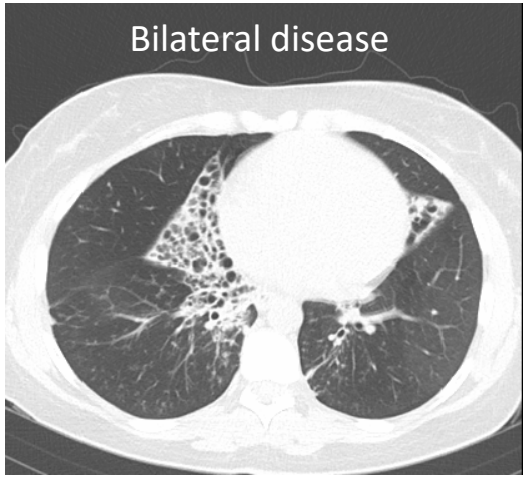
Treatment Naive				
Species	N	Sustained culture conversion	Sustained culture conversion without relapse	Recurrence rate
M. abscessus	233	77/233 (34%)	52/223 (23%)	40%
M. massiliense	141	117/141 (83%)	118/141 (84%)	7%

Jeon K et al. *Am J Respir Crit Care Med* 2009; 180: 896–902.
Koh WJ et al. *Am J Respir Crit Care Med* 2011; 183: 405–410.
Pasipanodya JG et al. *Antimicrob Agents Chemother* 2017; Oct 24:61(11). e01206-17.

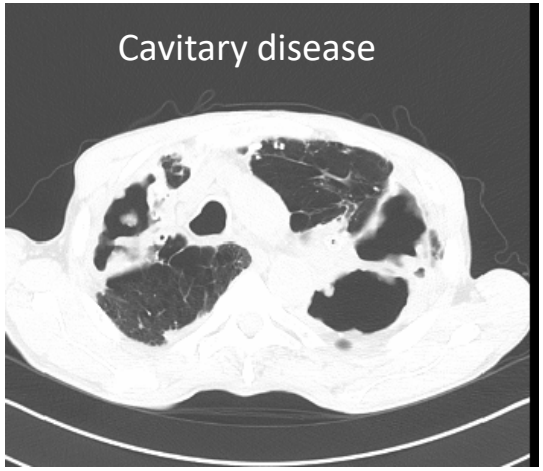
Predictors of Progression

N=113 median follow up 3.4 years, Seoul National University
37% of MAB group and 38% of MMA group progressed requiring treatment.

OR 4.79 (1.39–16.48)
p 0.13



OR 3.83 (1.06–13.82)
p 0.04



OR 3.62 (1.02–12.82)
p 0.46

CID 2017;64(3):301-308.

In *M. abscessus* complex pulmonary disease, how many antibiotics should be included within regimens?

Recommendation

In patients with *M. abscessus* pulmonary disease, we suggest a multidrug regimen that includes at least 3 active drugs (guided by *in vitro* susceptibility) in the initial phase of treatment

(conditional recommendation, very low certainty in estimates of effect)

- No studies that have directly compared the efficacy or safety of different multidrug regimens.
- The few cases series that have described treatment outcomes all used multidrug regimens with ⩾3 drugs

Daley CL, et al. *Eur Respir J* 2020; 56: 2000535

In *M. abscessus* pulmonary disease, should shorter or longer duration therapy be used for treatment?

Recommendation

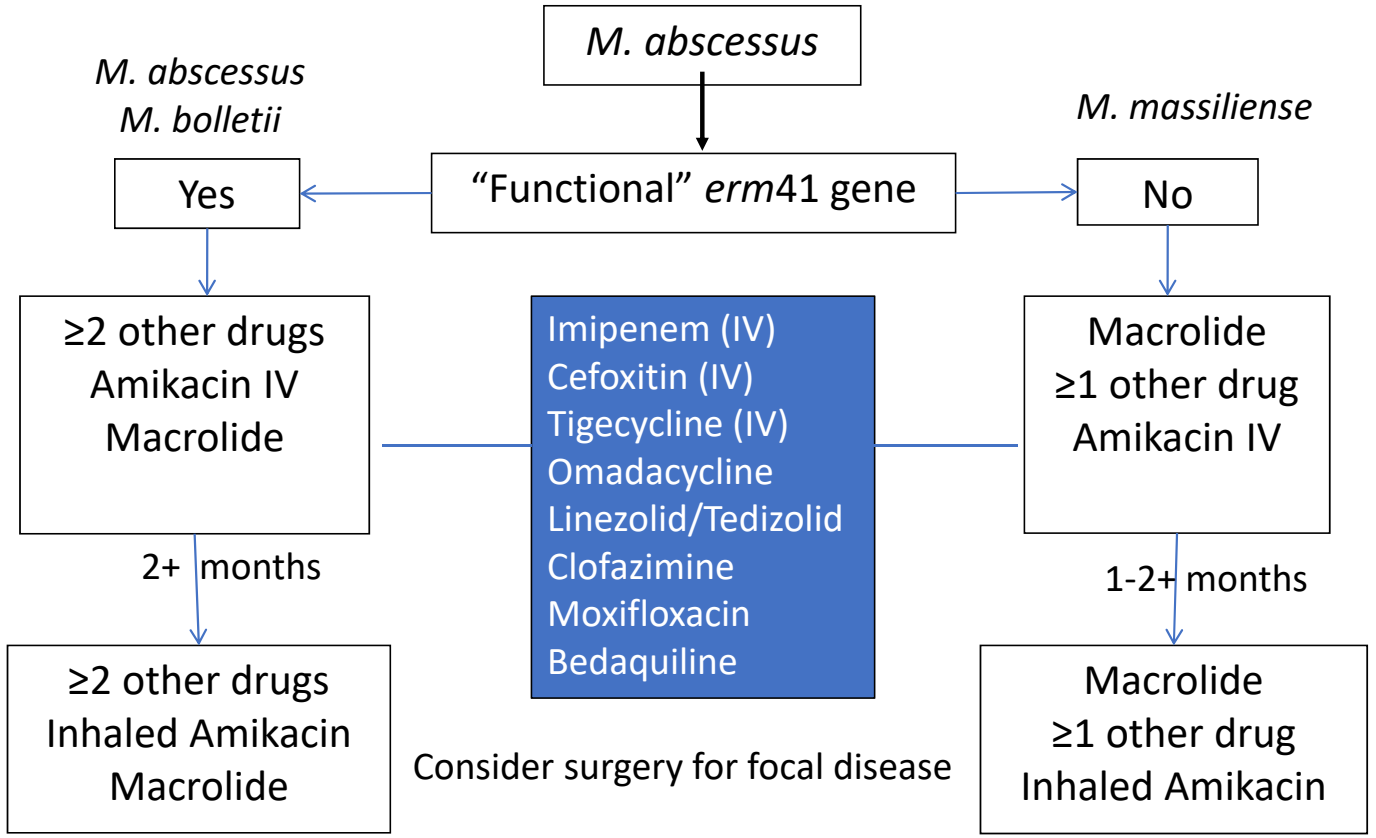
In patients with *M. abscessus* pulmonary disease, we suggest that either a shorter or longer treatment regimen be used and expert consultation obtained

(conditional recommendation for either the intervention or the comparison, very low certainty in estimates of effect)

- 1 observational retrospective study identified had a very small sample size, only indirectly addressed this question, and was felt to be of too low quality to form the basis of a recommendation

Daley CL, et al. *Eur Respir J* 2020; 56: 2000535

Treatment of *M. abscessus* complex



Should surgery plus medical therapy or medical therapy alone be used to treat NTM pulmonary disease?

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)

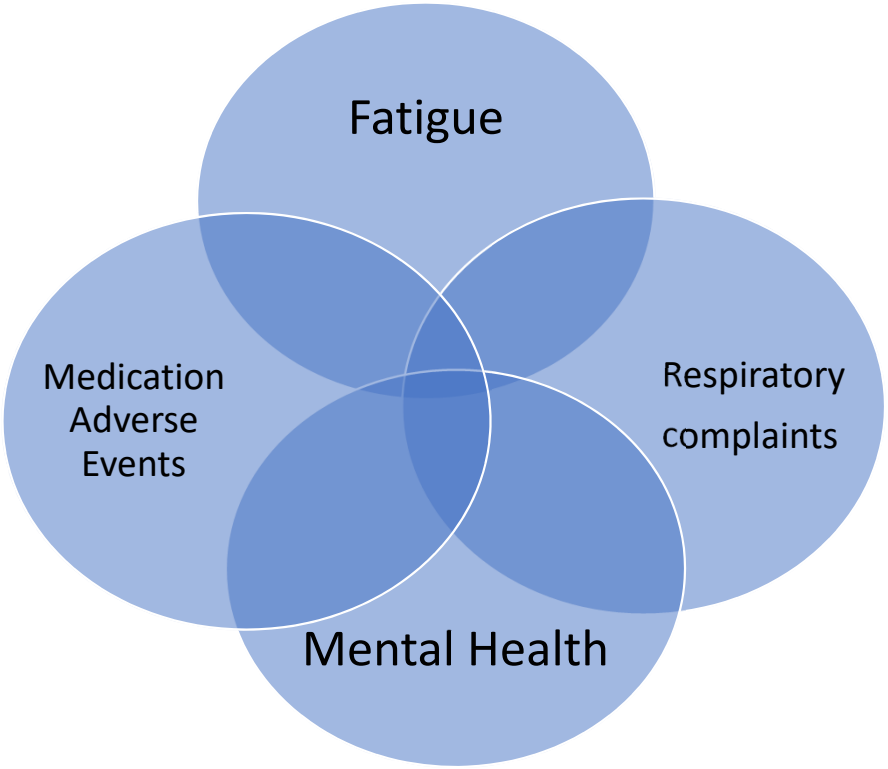
- In 107 patients with *M. abscessus* pulmonary disease there were significantly more surgical patients than medical patients whose culture converted and remained negative for at least 1 year (57% vs 28%; P = .022).

  Jarand J et al. Clin Infect Dis. 2011 Mar 1;52(5):565-71.

Key Points Summary

- *M. abscessus* complex is comprised of three subspecies with different degrees of susceptibility to the macrolides
- Differentiation of these subspecies is critical to the management and prognosis of the patient
- Macrolides should be used in the treatment of a macrolide susceptible infection
- At least 3 active drugs should be used to treat *M. abscessus* infection
- The optimal duration of IV or oral therapy is unknown and we would recommend expert consultation

Strategies to Manage Adverse Events and Improve Adherence
A Patient Centered Approach



Macrolides

- Azithromycin and clarithromycin are essential drugs used in the treatment of patients with MAC disease
- Experience suggest that azithromycin is better tolerated
- The most common adverse drug reactions associated with macrolides are:
  - Gastrointestinal
  - Tinnitus/hearing loss
  - Hepatotoxicity
  - Prolonged QTc

Strategies for monitoring and improving adherence

Drug	Adverse Reactions	Monitoring	Strategy
Azithromycin/clarithromycin	• Gastrointestinal	• Clinical monitoring	• Change clarithromycin to azithromycin • Move administration to bedtime • Take with small starch
	• Metallic taste • Dysgeusia	• Clinical monitoring	• Change clarithromycin to azithromycin
	• Tinnitus/hearing loss	• Audiogram	• Interruption/change to thrice weekly
	• Hepatotoxicity	• Liver function tests	• Hold medication, re-challenge to determine etiology
	• Prolonged QTc	• ECG (QTc)	• Stop concomitant QT prolonging medications

*Provided in the clinical reference aid handout

Ethambutol

- Ethambutol is a relatively well tolerated medication, that when paired with a macrolide, decreases the risk of acquired macrolide resistance
- Treatment failure was significantly higher in those who discontinued ethambutol (39.1% vs 19.3%, p=0.045)
- The most common adverse drug reactions associated with ethambutol are:
  - Ocular toxicity
  - Neuropathy

Kwon YS, et al. *J Korean Med Sci* 2020;9:e59

Ethambutol Ocular Toxicity in MAC Pulmonary Disease

- 229 patients with MAC pulmonary disease (1996-2000)
  - Mean of 16.1 +/- 10.8 months on ethambutol
- EMB administered either
  - Daily (25 mg/kg/day for 2 months then 15 mg/kg/day)
  - Three times weekly (25 mg/kg/day)
- Results
  - 91 (40%) of patients had ocular symptoms not related to ethambutol
  - Daily therapy – 8/139 (6%) developed optic neuritis
  - Three times weekly– 0/90 (0%)
- All returned to baseline
- All developed symptoms between appointments

Griffith DE, et al. AJRCCM 2005;172:250-253

Strategies for monitoring and improving adherence

Drug	Adverse Reactions	Monitoring	Strategy
Ethambutol	• Ocular toxicity	• Visual acuity/color discrimination • Read fine print every day of the same font	• Stop medication immediately and see an ophthalmologist • Rate limiting toxicity
	• Neuropathy	• Clinical monitoring	• Rate limiting toxicity

*Provided in the clinical reference aid handout

Rifamycins

- Rifampin or rifabutin are used as the 3rd drug in a standard 3 drug macrolide regimen
- Rifampin is an inducer of CYP3 and rifabutin is both an inducer and substrate
- The most common adverse drug reactions associated with rifamycins are:
  - Hepatotoxicity
  - Cytopenias
  - Hypersensitivity
  - Orange discoloration of secretions
  - Uveitis (rifabutin)

Strategies for monitoring and improving adherence

Drug	Adverse Reactions	Monitoring	Strategy
Rifampin/rifabutin	• Hepatotoxicity	• Liver function test	• Stop medication and consider re-challenge to determine etiology
	• Cytopenia	• Complete blood count	• Continue if WBC remains above 2.0 • Stop if the platelet count drops significantly (ITP)
	• Hypersensitivity	• Clinical monitoring	• Stop medication
	• Orange discoloration	• Clinical monitoring	• Reassure patient orange discoloration of secretions is expected
	• Uveitis (rifabutin)	• Visual acuity	• Rate limiting toxicity • Consider re-challenging with rifampin

*Provided in the clinical reference aid handout

Aminoglycosides

- Aminoglycosides are potent drugs against MAC organisms
- Amikacin is the most commonly used aminoglycoside for MAC and comes in parenteral and inhaled formulations
- The most common adverse drug reactions associated with amikacin are:
  - Oto/vestibular toxicity
  - Nephrotoxicity
  - Electrolyte disturbances
  - Dysphonia (ALIS)
  - Cough (ALIS)
  - Dyspnea (ALIS)

Strategies for monitoring and improving adherence

Drug	Adverse Reactions	Monitoring	Strategy
Amikacin (parenteral)	• Ototoxicity	• Audiogram	• May be rate limiting
	• Tinnitus	• Clinical monitoring	• Stop other medications that can cause tinnitus • May be rate limiting
	• Vestibular toxicity	• Clinical monitoring	• Rate limiting toxicity
	• Nephrotoxicity	• BUN, creatinine	• Maintain hydration • Stop unnecessary medications that may affect renal function
	• Electrolyte disturbances	• Metabolic panel	• Correct electrolyte abnormalities prior to initiation

*Provided in the clinical reference aid handout

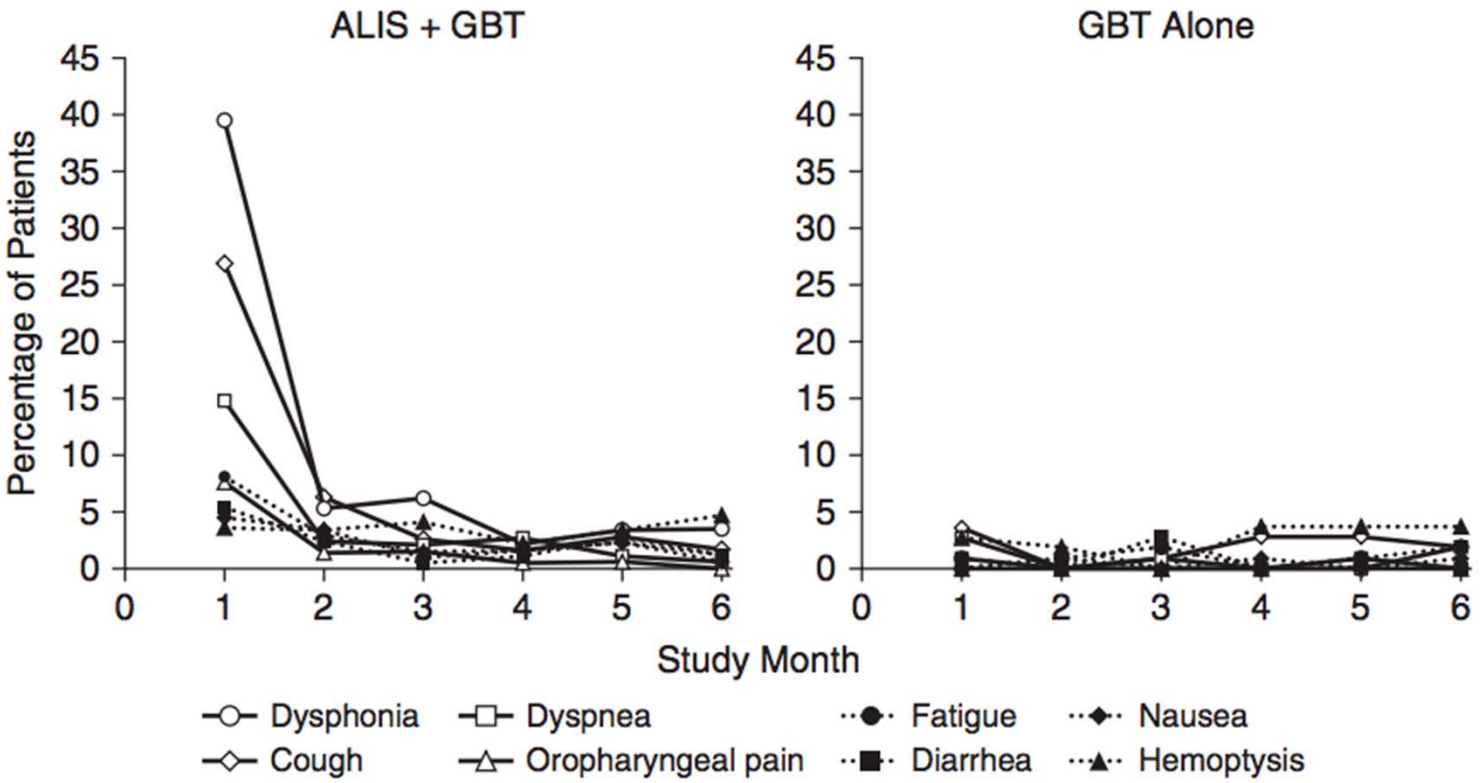
CONVERT STUDY
Treatment Emergent Adverse Events (TEAE)

Adverse Event	GBT	GBT + ALIS
Respiratory-related AEs		
Dysphonia	0.9%	45.7%
Cough	15.2%	37.2%
Dyspnea	8.9%	21.5%
Hemoptysis	13.4%	17.5%
Oropharyngeal pain	1.8%	10.8%
Audiological AEs		
Tinnitus	0.9%	7.6%
Dizziness	2.7%	6.3%
Hearing loss	6.3%	4.5%
Serious adverse events	17.9%	20.2%
Discontinuation of ALIS	–	17.5%

GBT= guideline-based therapy
ALIS = amikacin liposome inhalation suspension

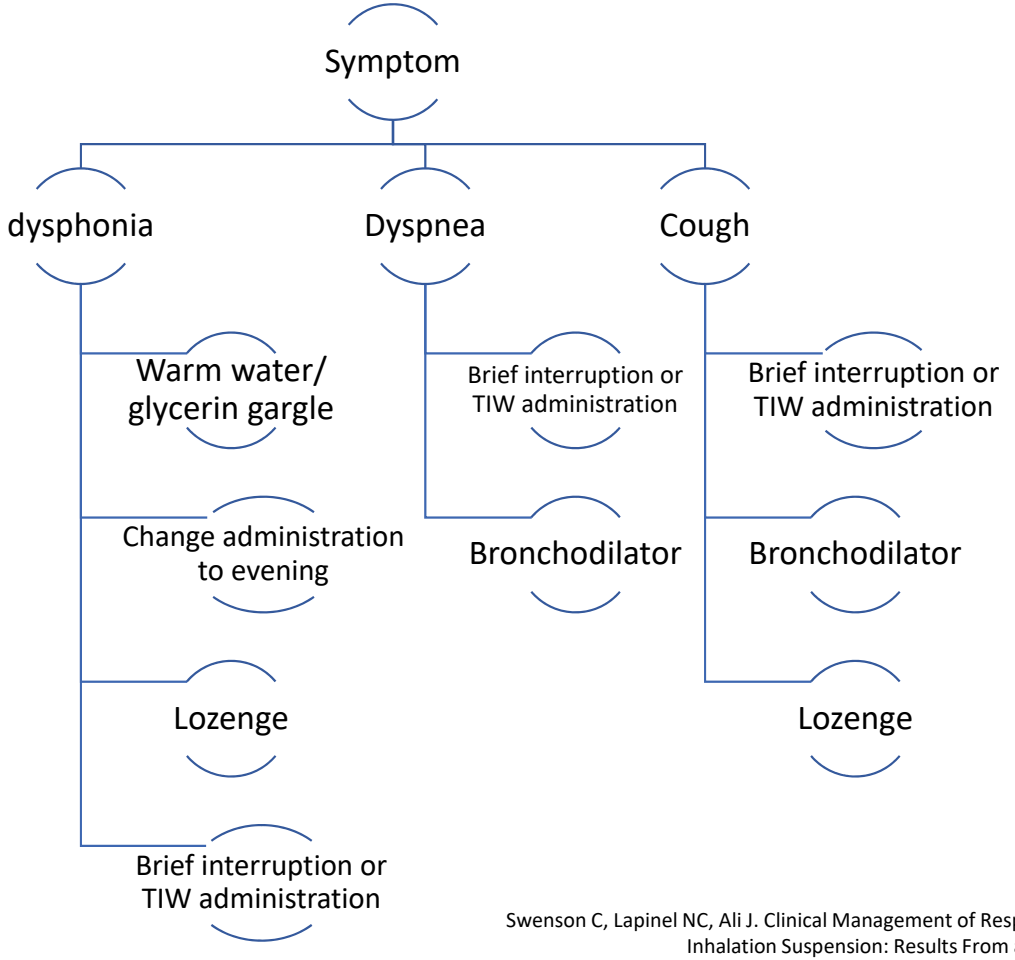
Griffith DE et al. *Am J Respir Crit Care Med* Vol 2018; 198(12): 1559–1569

Amikacin liposome inhalation solution
Respiratory adverse events decrease by 2 months



Griffith DE, Eagle G, Thomson R, et al. Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by Complex (CONVERT). A Prospective, Open-Label, Randomized Study. Am J Respir Crit Care Med. 2018;198(12):1559-1569. https://doi.org/10.1164/rccm.201807-1318OC. *The American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

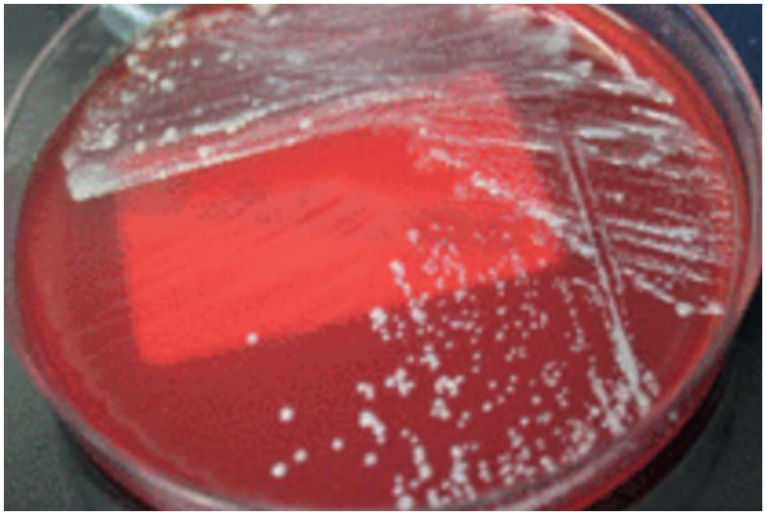
Amikacin liposome inhalation solution
Management of adverse events



Swenson C, Lapinel NC, Ali J. Clinical Management of Respiratory Adverse Events Associated With Amikacin Liposome Inhalation Suspension: Results From a Patient Survey. Open Forum Infect Dis. 2020;7(4):ofaa079.

If your treatment could change one thing about your NTM lung infection what would that be?

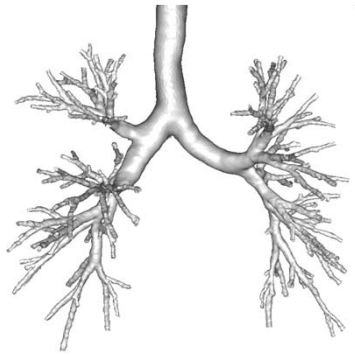
1. Culture conversion
2. Less coughing
3. Less fatigue

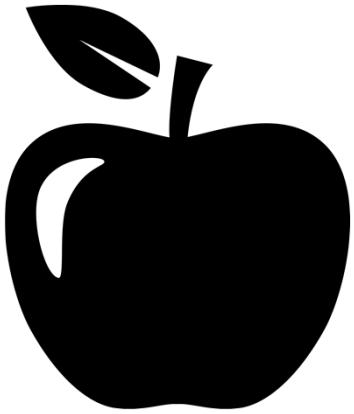


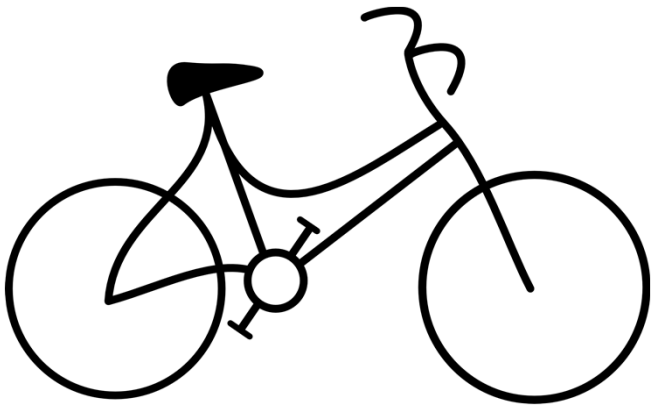
NTM patient survey March 2019
Courtesy of Amy Leitman

How to optimize wellness with NTM lung disease

This requires a multidisciplinary team

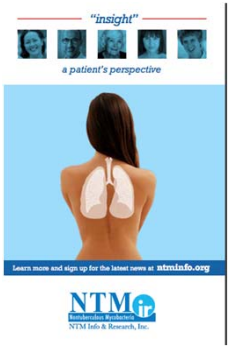






Effective Communication Strategies

- Plan two visits around initial diagnosis
  - First to discuss bronchiectasis, airway clearance and the NTM infection
  - Second to discuss results of bronchiectasis evaluation, airway clearance adherence and whether NTM treatment is needed
- Follow up with treated patients frequently
  - i.e. at 4 weeks, then every 3 months thereafter
  - Monthly labs/sputum cultures (nursing call with results to check in)
- Use “airway clearance action plan” www.impact-be.com
- Resources and connectivity for patient and family members
  - NTMinfo.org, BronchandNTM360social.org, AboutNTM.com



Key Points Summary

- Adverse drug reactions occur in the majority of patients during the course of treatment for MAC
- It is important to detect ADRs early, manage appropriately and try to keep patients on the most effective treatment regimen
- Management strategies include aggressive treatment of side effects, short drug “holidays”, intermittent administration where appropriate

Key Points Summary

- NTM lung disease is a chronic condition that affects individuals on multiple levels, both physical and emotional
- Fatigue is the highest reported symptom which is likely multifactorial
- Effective treatment of the whole individual requires a multidisciplinary team (respiratory therapy (RT), nutrition, psychotherapy, rehab)
- Set up regular follow up with patients and encourage the use of online resources referenced