DIAGNOSIS AND MANAGEMENT OF NONTUBERCULOUS MYCOBACTERIAL INFECTIONS

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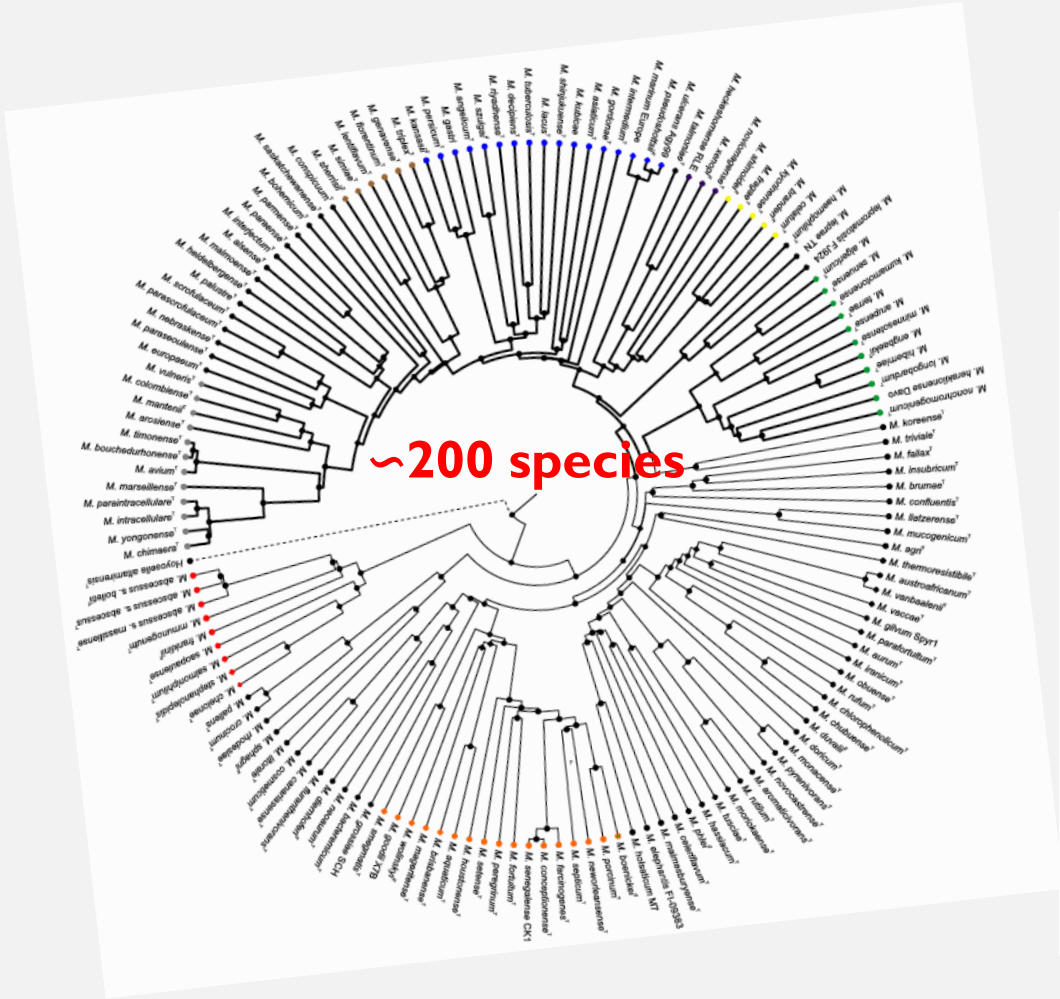
DISCLOSURES

- Insmed: speaker, consultant, investigator
- AN2: consultant
- Paratek: speaker, consultant
- Zambon: consultant

OBJECTIVES

- Overview of NTM Pulmonary disease
- Guideline update
- Review management of MAC Pulmonary Disease
- Review management of *M. abscessus* Pulmonary Disease

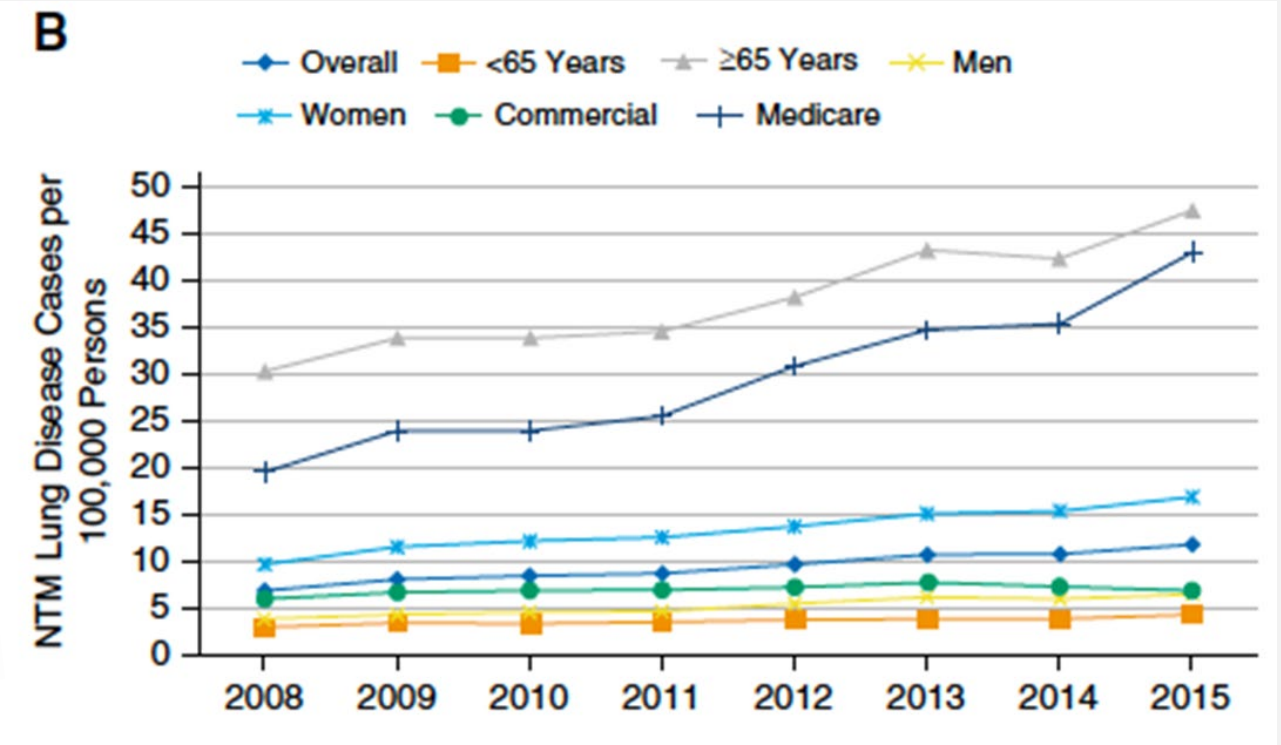
NONTUBERCULOUS MYCOBACTERIA (NTM) AN INCREASING CAUSE OF PULMONARY DISEASE



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

National Managed Care Claims Database – 27 million people annually

Prevalence (per 100,000)



Winthrop KL, et al. *Ann Am Thorac Soc.* 2020;17(2):178-185.

INCREASING TRENDS IN NTM MEDICARE DATA 2010-2019

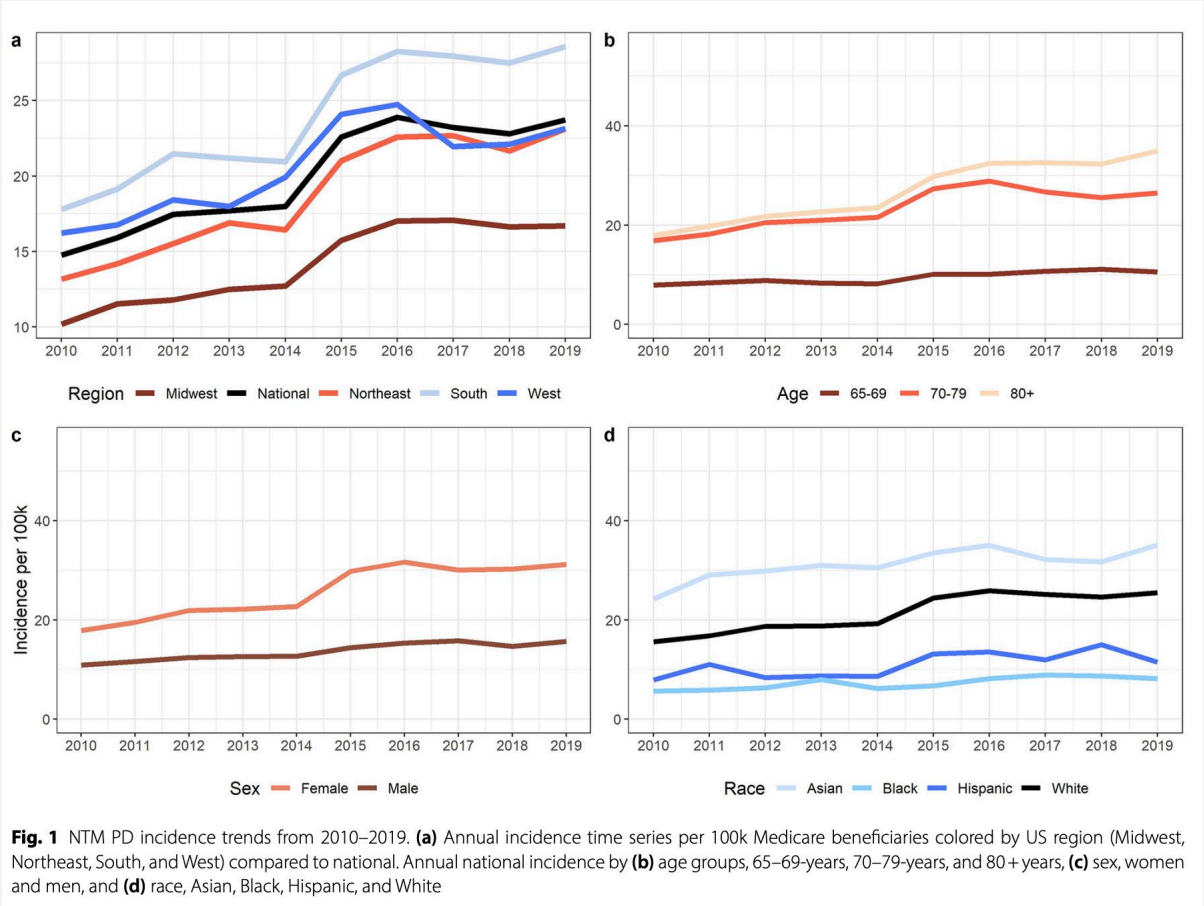
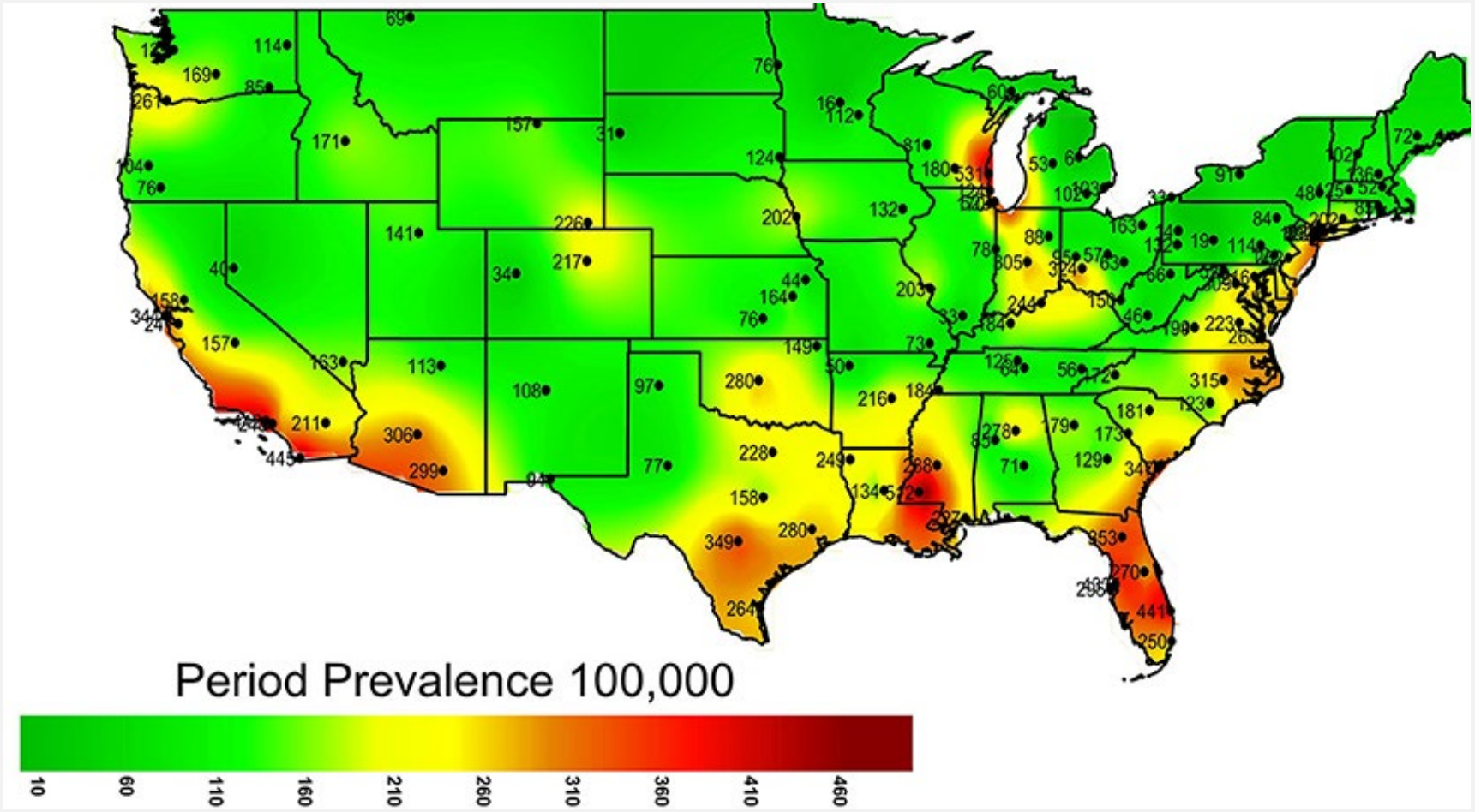


Fig. 1 NTM PD incidence trends from 2010–2019. **(a)** Annual incidence time series per 100k Medicare beneficiaries colored by US region (Midwest, Northeast, South, and West) compared to national. Annual national incidence by **(b)** age groups, 65–69-years, 70–79-years, and 80 + years, **(c)** sex, women and men, and **(d)** race, Asian, Black, Hispanic, and White

Bents et al. BMC Infectious Diseases (2024) 24:1094

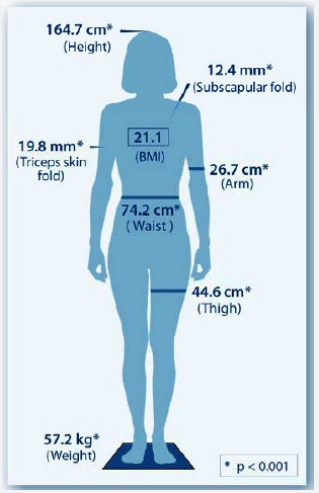
COASTAL REGIONS SEE HIGHER PREVALENCE OF NTM-PD VETERANS DATABASE, INCIDENCE OF NTM-PD IN COPD

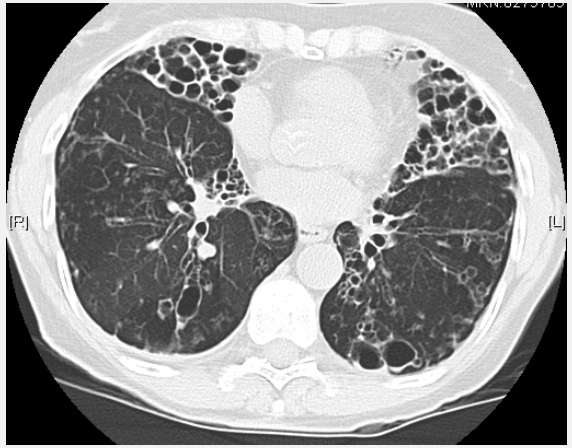


Pyarali FF et al. *Front Med* (Lausanne). 2018 Nov 6;5:311.

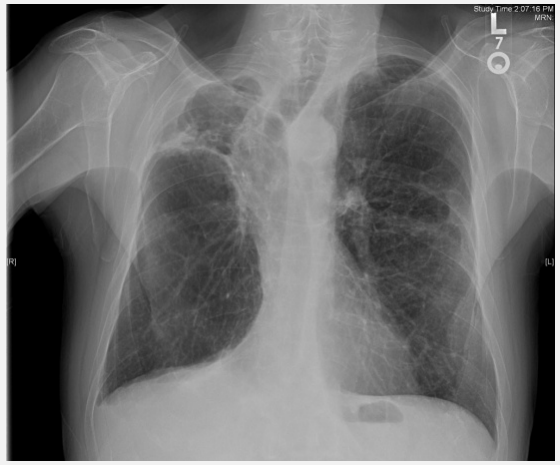
CLINICAL PHENOTYPES

- Nodular / bronchiectatic disease
  - Women
  - Older
  - Nonsmokers
  - Tall, thin, low body mass index





- Fibrocavitary disease
  - Male
  - Older
  - Smokers
  - Various body builds

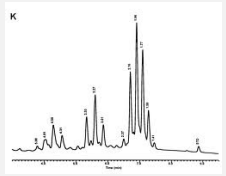


Kim RD, et al. AJRCCM 2008;178:1066-1074

DIAGNOSTIC APPROACHES TO NTM-LD AND REDUCING TIME TO TREATMENT

Think about it!

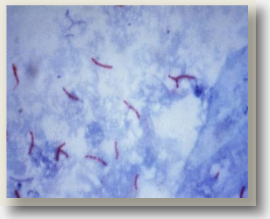
Drug susceptibility



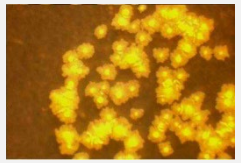
Identification

Diagnosis
8-12 weeks!

Collect a specimen

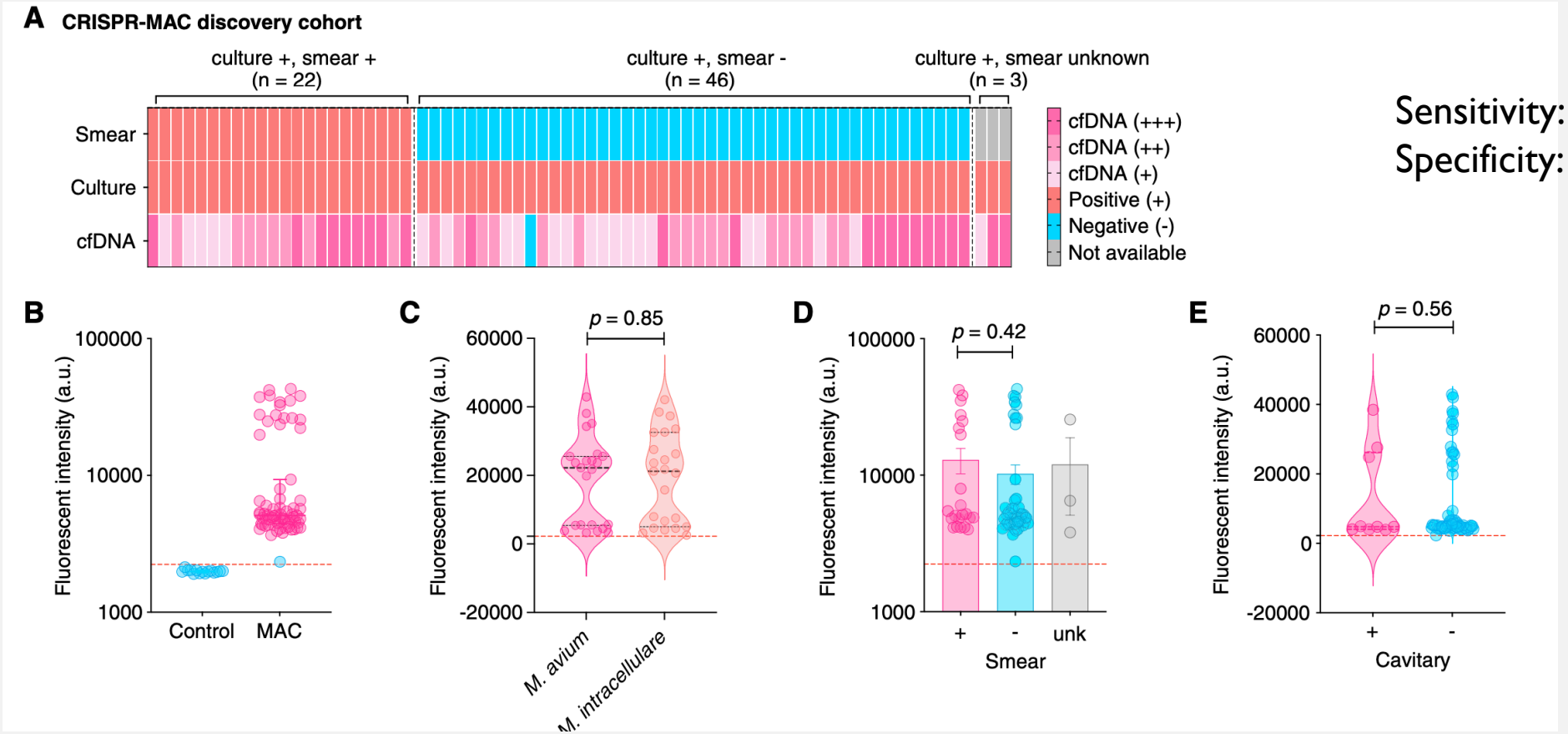


Microscopic examination



Culture (liquid and solid media)

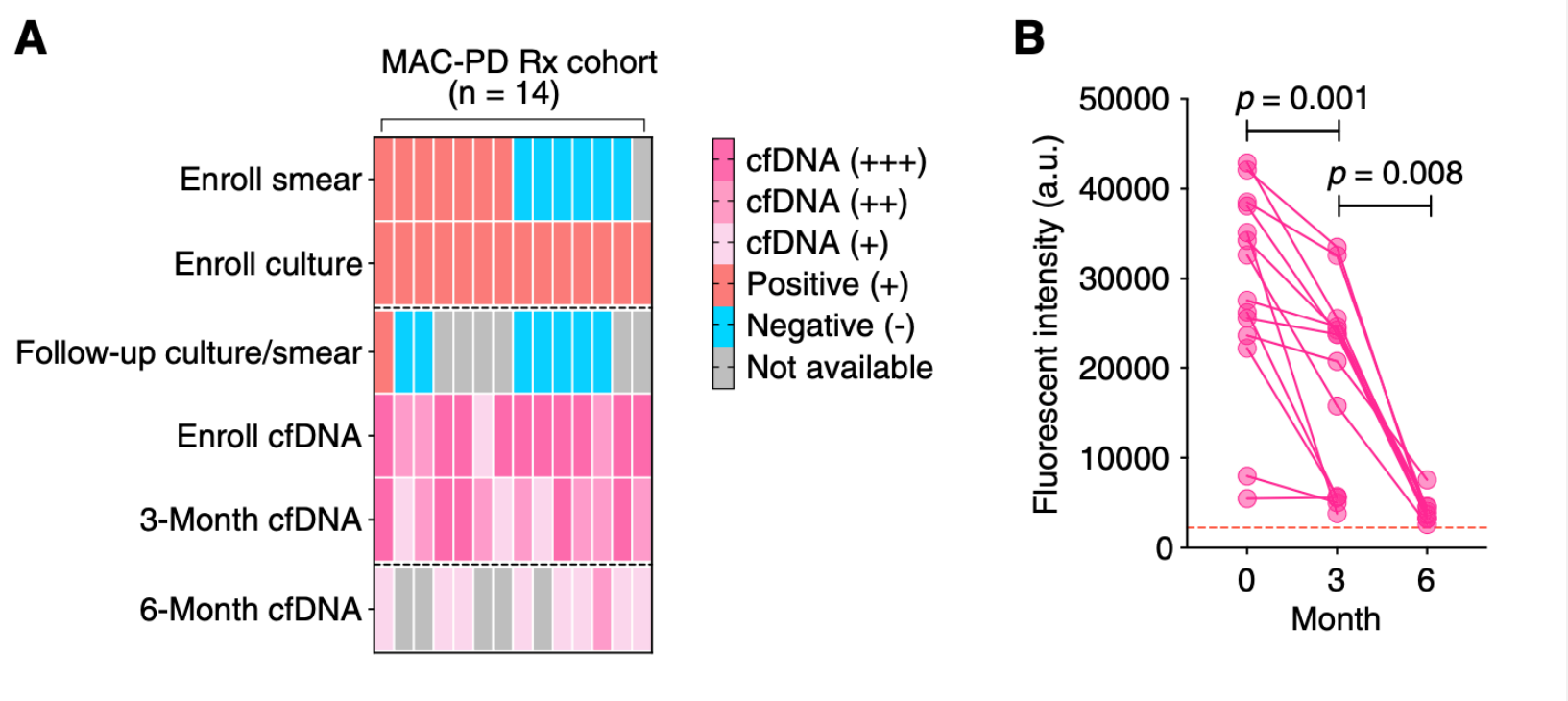
SERUM CELL-FREE DNA-BASED DETECTION OF MYCOBACTERIUM AVIUM COMPLEX INFECTION



Sensitivity: 98.6% (CI 92.4-100)
Specificity: 100% (CI 78.2-100)

Li, Lin et al. Am J Respir Crit Care Med 2024 May 15;209(10):1246-1254.

SERUM CELL-FREE DNA CHANGES AFTER TREATMENT INITIATION



Li, Lin et al. Am J Respir Crit Care Med 2024 May 15;209(10):1246-1254.

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 with 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% than in controls: mortality higher in untreated MAC than treated (33% v 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

2020 NTM Diagnostic Guidelines

Disease Criteria (unchanged from 2007 guidelines)	
Clinical	Pulmonary/systemic symptoms
Radiology	CXR-nodules, cavities, or CT-bronchiectasis with multiple small nodules
Micro	With ≥ 2 sputa → 2 positive cultures, or With 1 BAL/wash → 1 positive bronchial wash, or With biopsy → positive biopsy culture, or 1 positive culture and biopsy evidence of disease

Symptoms + Imaging findings + Microbiology = Disease

Deciding to initiate antimicrobial therapy should be individualized based on

- clinical factors,
- the infecting species, and
- individual patient priorities

Daley CL, et al. CID 2020;71:5-913

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

The factors to consider when initiating treatment

NTM species
- Likelihood of pathogenicity
- Resistance pattern

Severity of disease
- Smear positivity
- Cavitary

Host predictors for progression
- BMI of the patient
- Immune competency

Drugs
- Multiple drugs, long duration

Short term outcomes
- MAC "success"
  - 60% (Kwak et al, CID 2017)
  - 71-86% (Jeong et al, AJRCCM 2015; Wallace, Chest 2014)

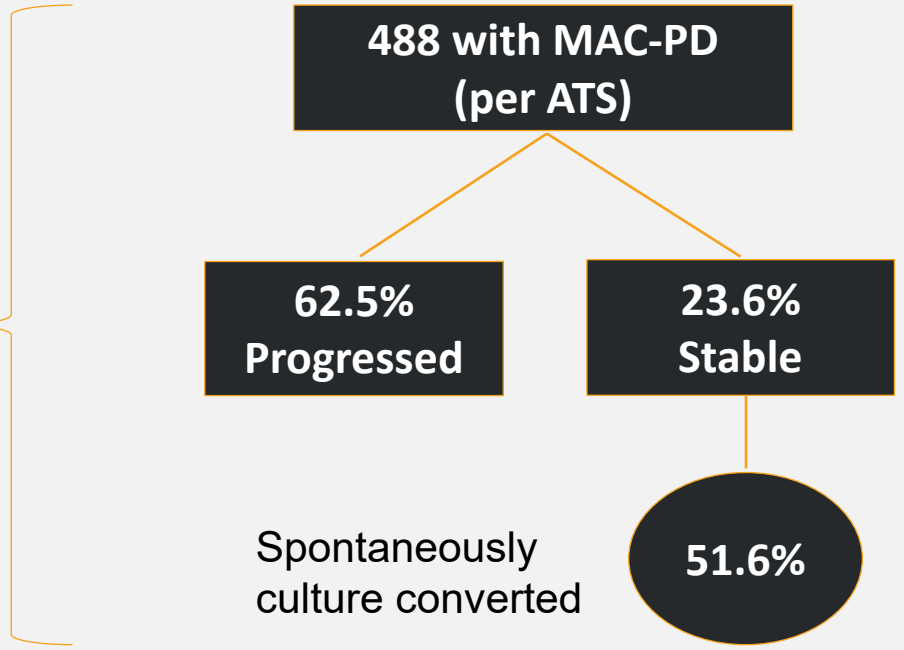
Recurrence
- 30% - 14 mo (Koh et al, 2017)
- 50% - 4 years (Wallace et al, 2014)

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

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

QUESTION

In vitro susceptibility testing for MAC is recommended for which 2 antibiotics?

1. Ethambutol and rifampin
2. Azithromycin and ethambutol
3. Azithromycin and amikacin
4. Ethambutol and moxifloxacin

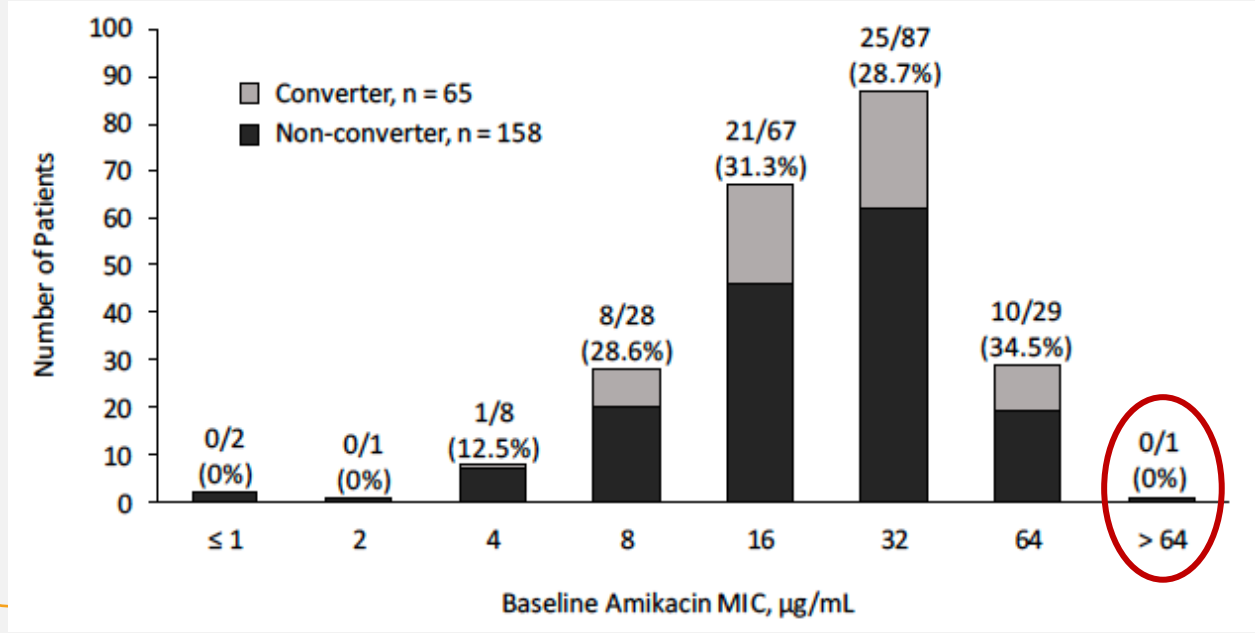
COMPOSITION OF TREATMENT REGIMEN EMPIRIC TREATMENT VS SUSCEPTIBILITY-BASED?

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

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



Daley CL, et al. CID 2020;71:5-913

Olivier KN, et al. Am J Respir Crit Care Med 2017;195:814-823

ROLE OF ANTIMICROBIAL SUSCEPTIBILITY TESTING (AST)

Species	Drugs
M. kansasii	Macrolide Rifampicin
MAC	Macrolide Amikacin
M. abscessus	Macrolide (including *erm*(41) gene) 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. CID 2020;71:5-913

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

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

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

Daley CL, et al. CID 2020;71:905-913

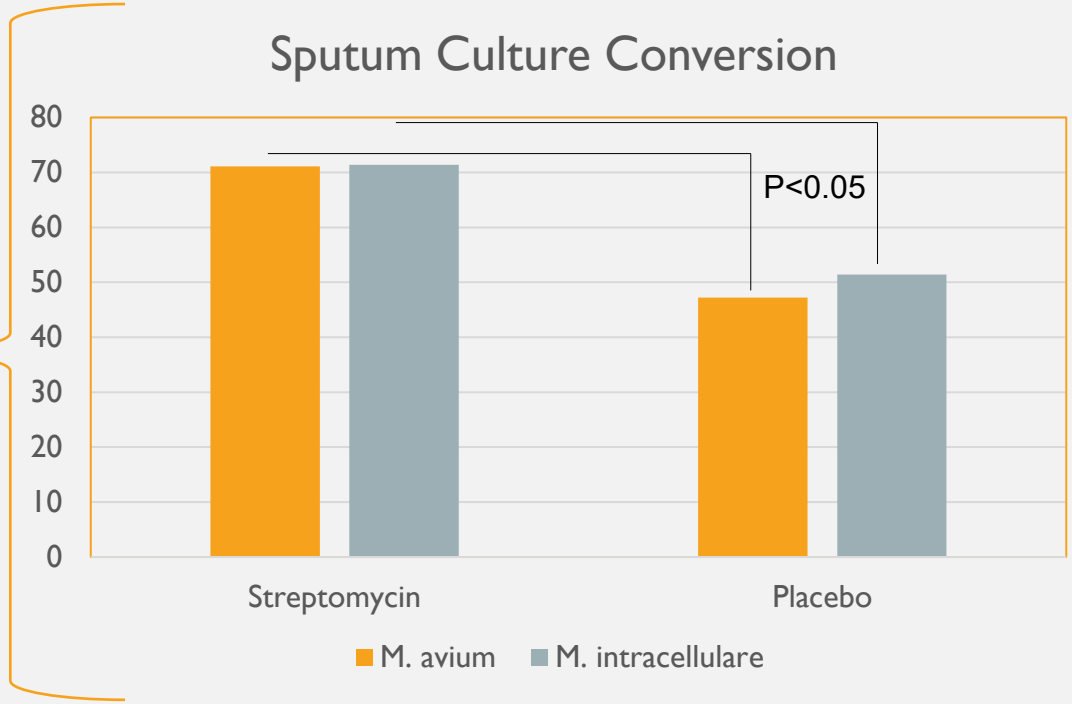
Pasipanodya JG, et al. J Anti Chemother 2017;72:i3-19

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 mos
- 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

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

QUESTION

In patients with refractory MAC lung disease defined as persistently positive sputum cultures for MAC after at least 6 months of guideline-based therapy, what is the FDA approved recommendation for augmenting therapy according to the 2020 multi-society NTM treatment guidelines?

1. Add daily oral moxifloxacin
2. Add daily amikacin liposomal inhalation suspension (ALIS)
3. Add intravenous amikacin three times weekly
4. Add daily oral clofazimine

COMPOSITION OF TREATMENT REGIMEN INHALED AMIKACIN?

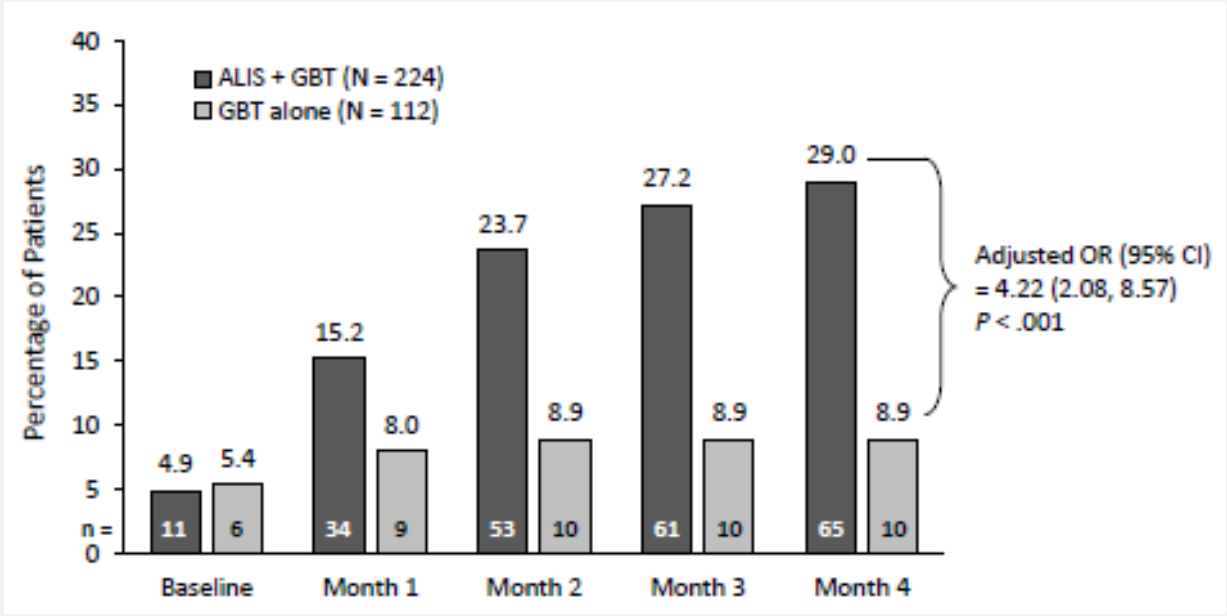
Recommendation 6

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, 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

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



Proportion of Patients With Negative Sputum Cultures for MAC

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

Recruiting

Study to Evaluate ALIS (Amikacin Liposome Inhalation Suspension) in Participants With Nontuberculous Mycobacterial Lung Infection Caused by Mycobacterium Avium Complex (ENCORE)

ClinicalTrials.gov ID NCT04677569

- RCT in patients with newly diagnosed pulmonary MAC
  - ALIS (amikacin liposome inhalation suspension) + background regimen (azithromycin [AZI] + ethambutol [ETH]) compared to the ELC (empty liposome control) + background regimen
- ARISE: Validation of PRO tool (QOL-B respiratory domain)
- ENCORE: efficacy between groups (PRO) at 13 months

- TOPLINE RESULTS (ARISE)
- 43.8% improvement in QOL-B respiratory score vs. 33.3% in the comparator arm
- significantly higher culture conversion rates (mo 7) vs comparator arm (78.8% vs. 47.1%, p=0.0010)

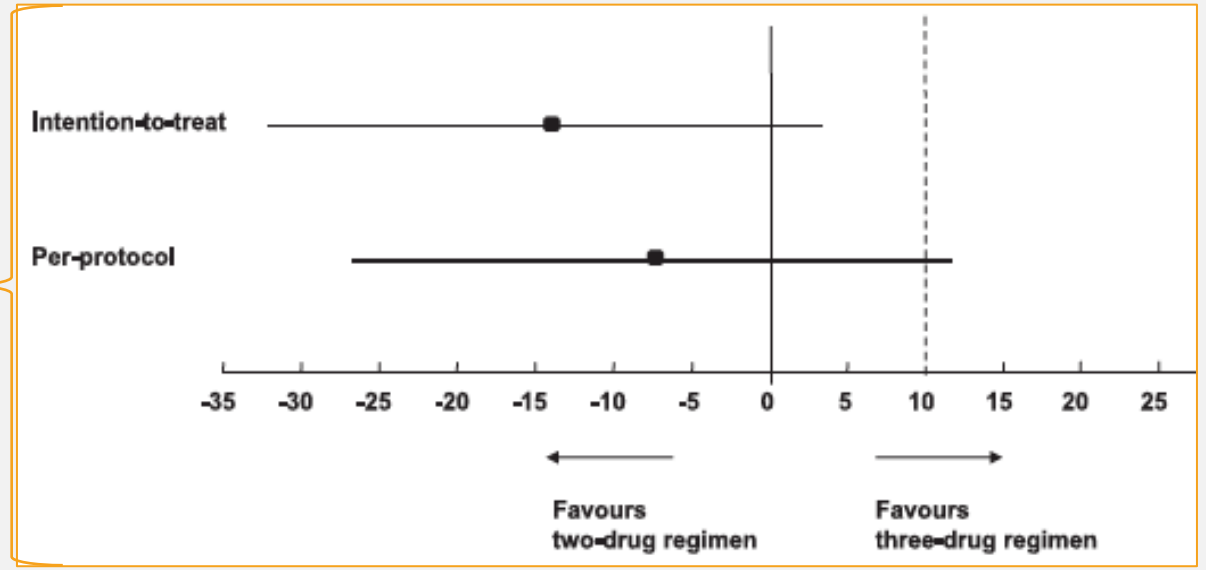
COMPOSITION OF TREATMENT REGIMEN
3 VS 2 DRUG REGIMEN?

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

Randomized trial of 2 vs 3 drug



Daley CL, et al. CID 2020;71:905-913

Miwa S, et al. Ann Am Thorac Soc 2014;11:23-29

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 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

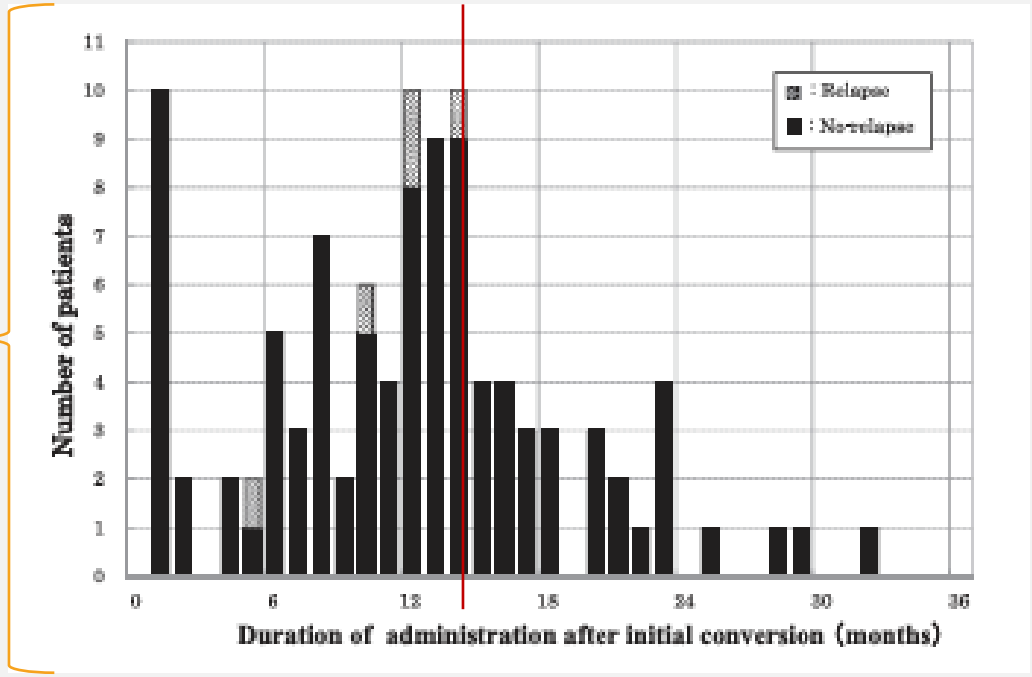
Daley CL, et al. CID 2020;71:905-913

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

Kadota JI, et al. Infect Chemother 2017;23:293-300

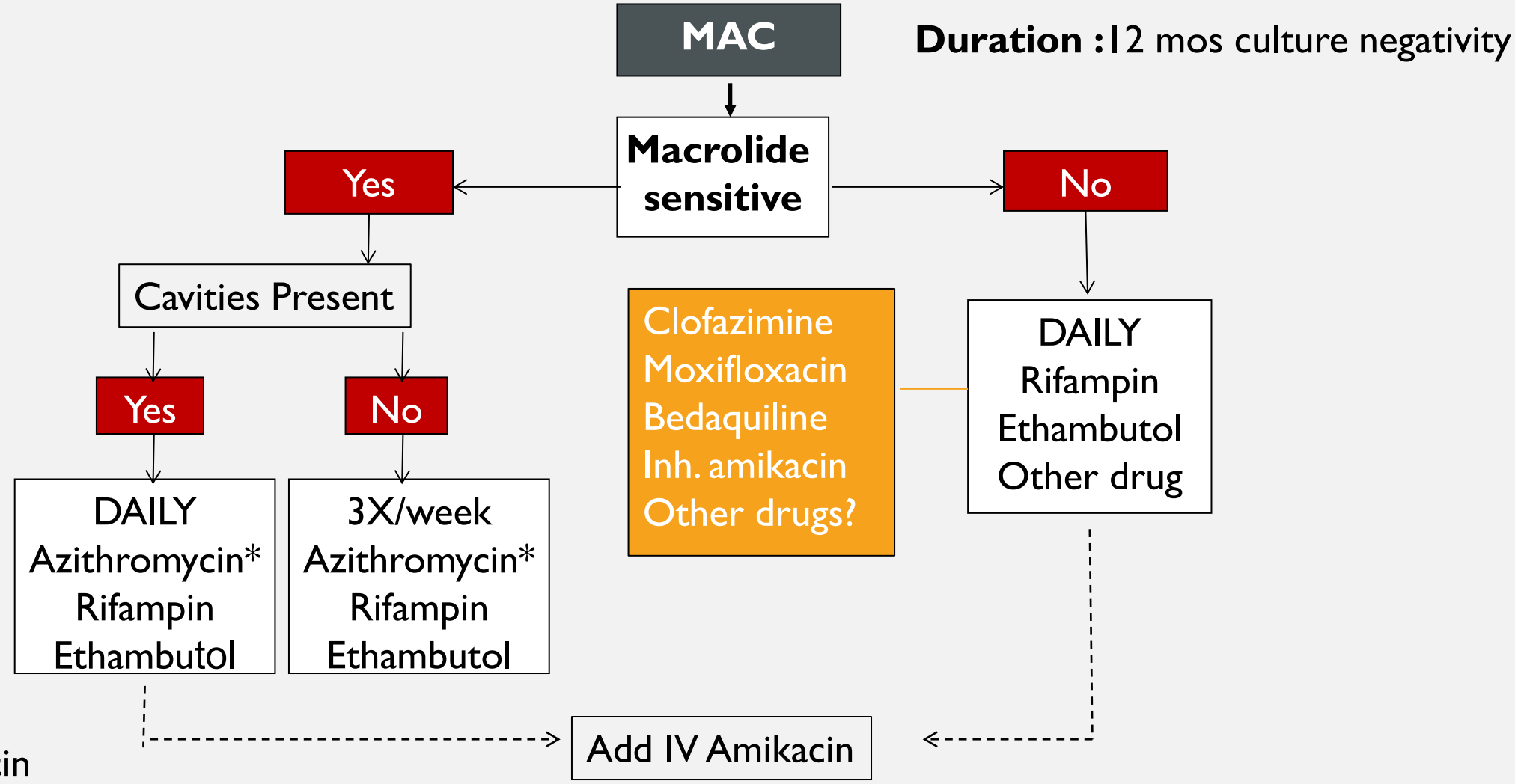
RECOMMENDED TREATMENT REGIMENS MAC

	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

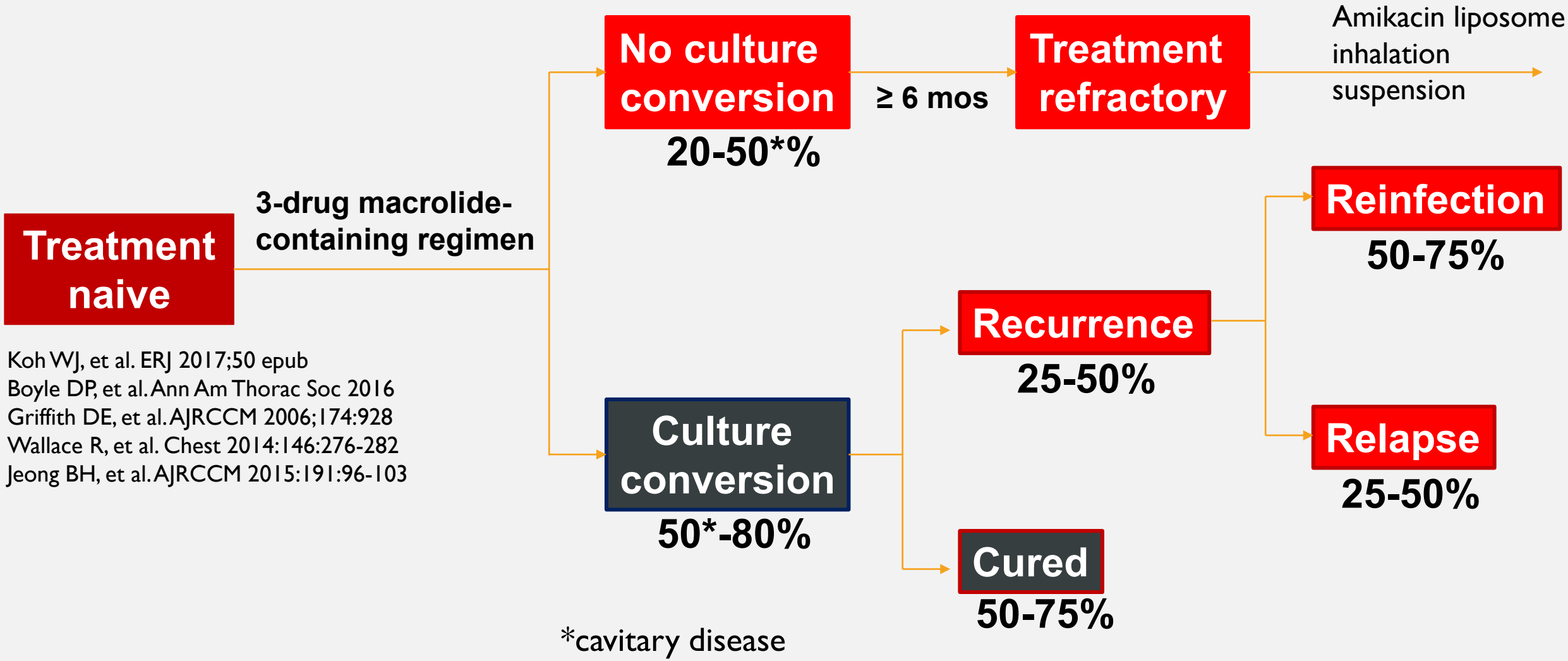
Daley CL, et al. CID 2020;71:905-913

TREATMENT OF MAC PULMONARY DISEASE



* clarithromycin

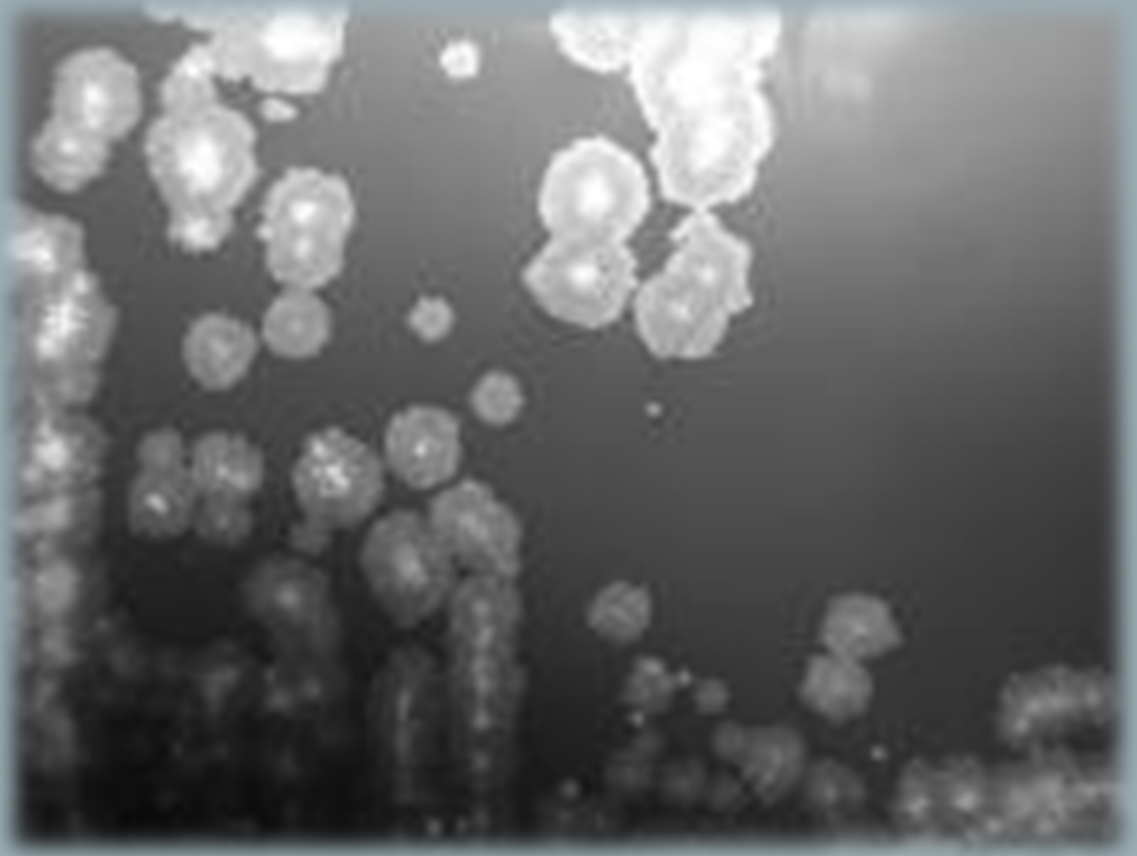
TREATMENT OF MAC PULMONARY DISEASE



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

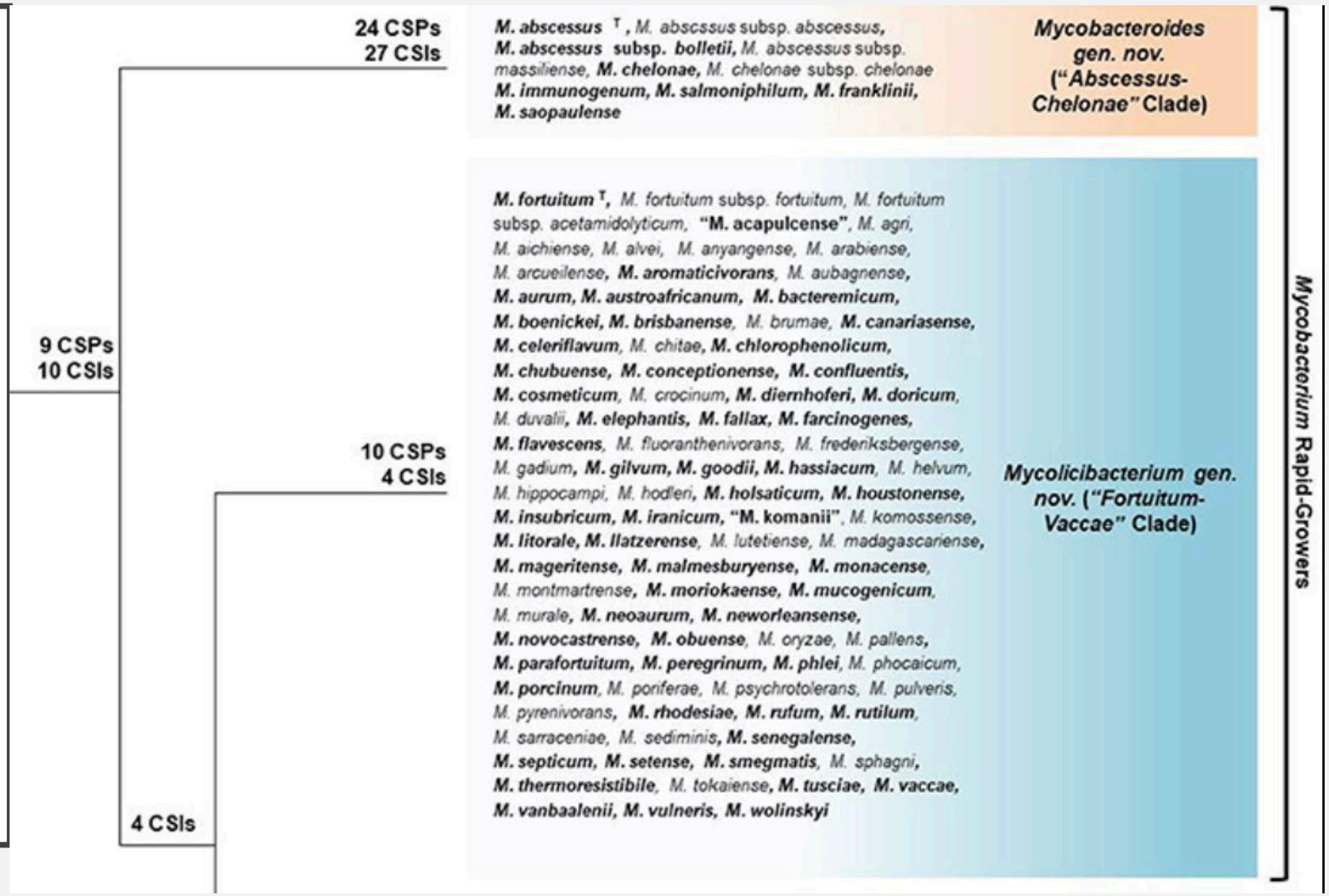
*cavitary disease

MYCOBACTERIUM ABSCESSUS



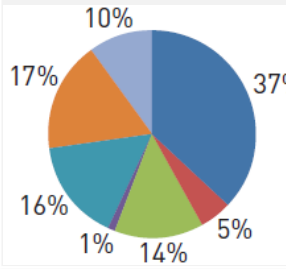
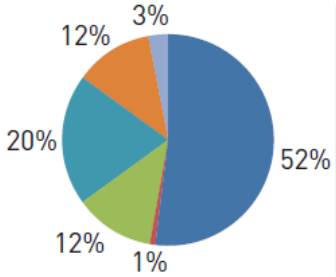
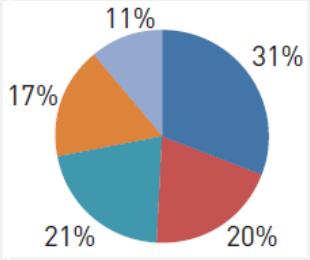
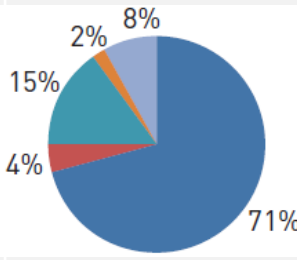
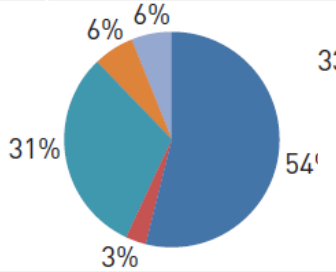
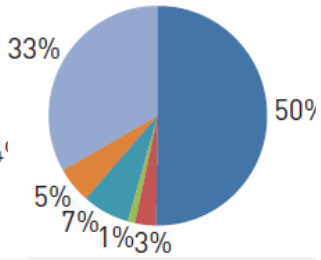
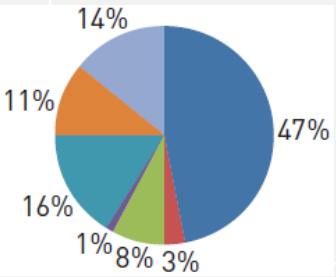
Phylogenomics and Comparative Genomic Study

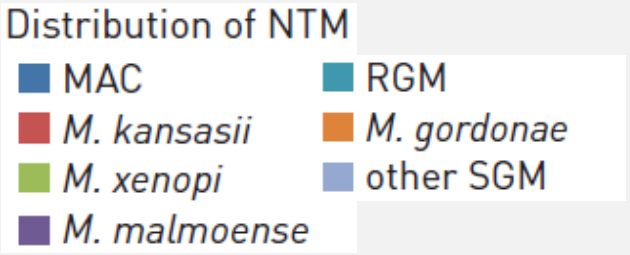
MYCOBACTERIUM ABSCESSUS ~~COMPLEX~~



Gupta RS, et al. Front Microbiol. 2018 Feb 13;9:67.

DISTRIBUTION OF NTM DISEASE

Distribution	Europe	North America	South America	Australia	Asia	South Africa	TOTAL
NTM							



Hoefsloot W, et al. Eur Respir J. 2013;42:1604-1613.

MACROLIDE SUSCEPTIBILITY DIFFERS BETWEEN SUBSPECIES

M. abscessus subspecies	CLR susceptibility days 3–5	CLR susceptibility day 14	Macrolide susceptibility phenotype	Genetic implication	Macrolide Effect
massiliense (abscessus)*	Susceptible	Susceptible	Macrolide susceptible	dysfunctional *erm*(41) gene	Anti-mycobacterial
abscessus 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 subsp.abscessus* have a dysfunctional ERM41 (C28)
CLR: Clarithromycin

Haworth C, et al. Thorax 2017;72(Suppl 2):ii1

PATIENT CHARACTERISTICS DIFFER BASED ON MACROLIDE RESISTANCE

Characteristic	Resistant group (69)	Sensitive group (31)	P value
Age, median (IQR)	58 (44-66)	56 (32-64)	0.562
Males, n (%)	26 (37.7)	17(54.8)	0.107
BMI, mean	19.93	19.69	0.729
Bronchiectasis	66 (95.7)	29 (93.4)	0.655
Cavity	**50 (72.5)**	**8 (25.8)**	**<0.001**
Nodules	38 (55.0)	19 (61.3)	0.648
Tree in bud	**16 (23.2)**	**14 (45.2)**	**0.027**
Cough, n (%)	55 (79.7)	25 (80.6)	0.914
Sputum, n (%)	69 (100.0)	31 (100.0)	1
Fever, n (%)	15 (21.7)	4 (12.9)	0.298
Hemoptysis, n (%)	**22 (31.9)**	**4 (12.9)**	**0.045**

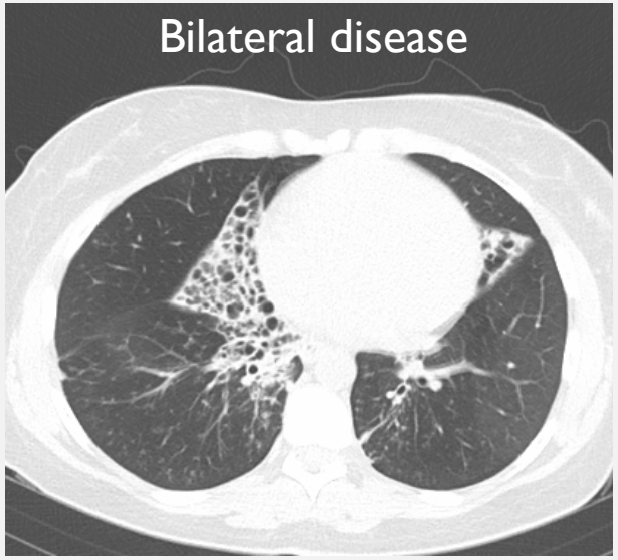
Guo Q, et al. Antimicrob Agents Chemother. 2018 Apr 26;62(5):e02360-17.

PREDICTORS OF PROGRESSION

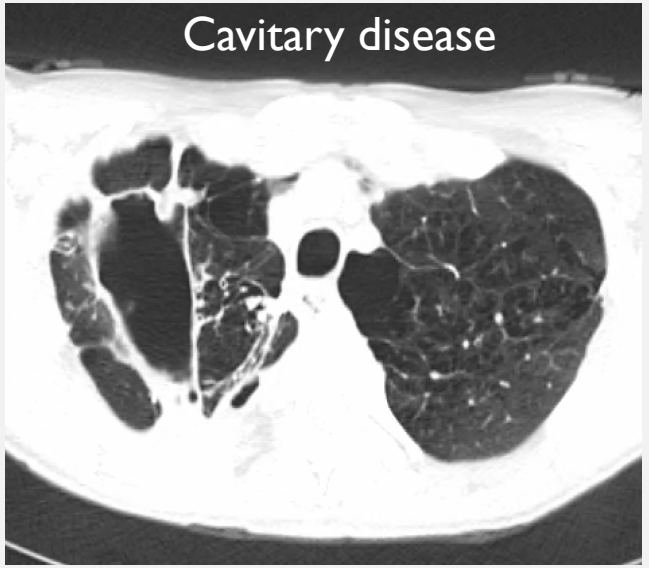
N=113 median follow up 3.4 years, Seoul National University

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

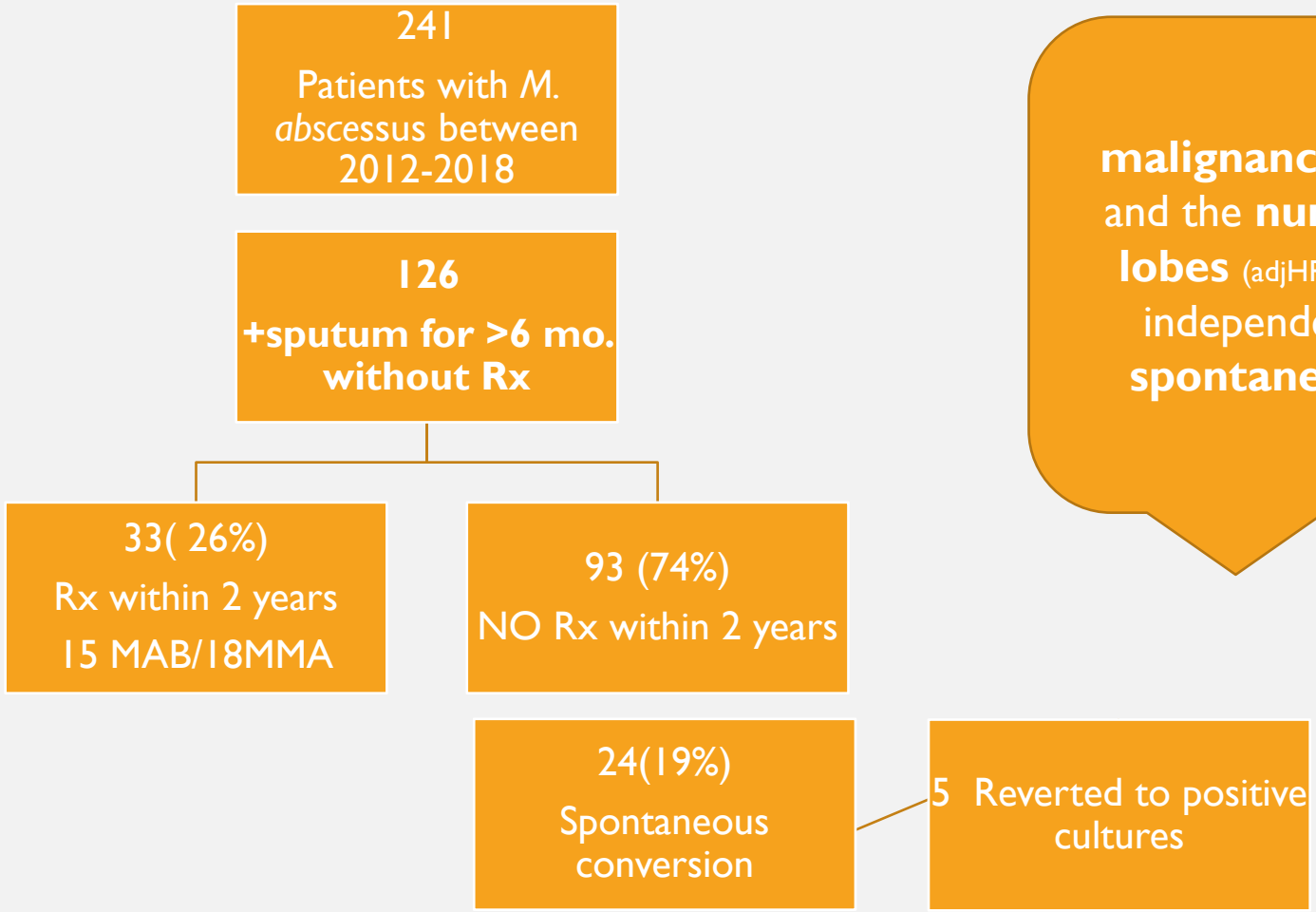


OR 3.62 (1.02–12.82)
p 0.46

MAB: *M. abscessus* subspecies *abscessus* MMA: *M. abscessus* subspecies *massiliense*

Park J, et al. CID. 2017 Feb 1;64(3):301-308.

SPONTANEOUS CONVERSION IN *M. ABSCESSUS* LUNG DISEASE OCCURRED IN 15%

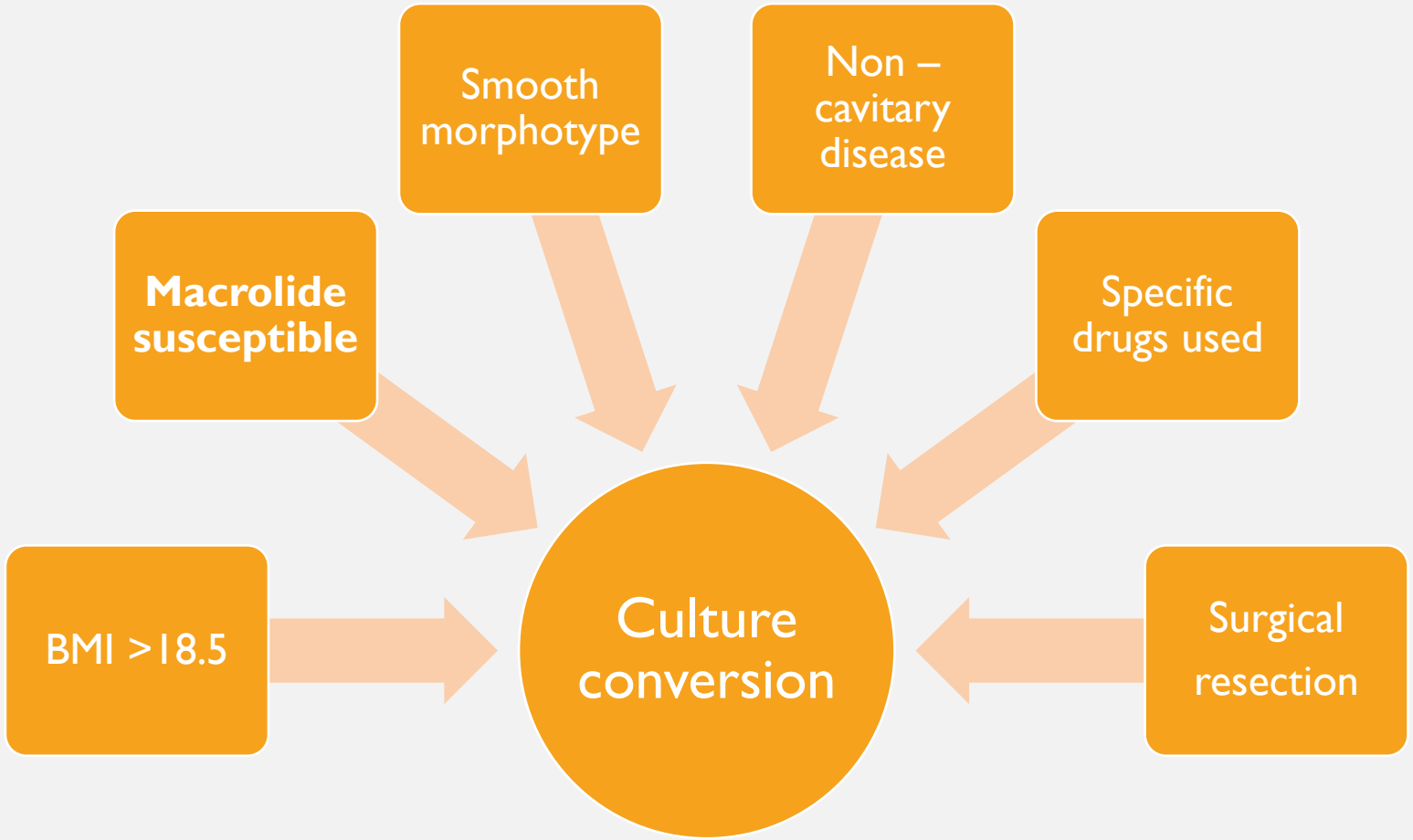


malignancy (adj HR, 2.664; P = 0.042) and the **number of involved lobes** (adjHR, 0.677; P = 0.019) were independent predictors of **spontaneous conversion**

MAB: *subsp abscessus*. MMA: *subsp. massiliense*

Jo KW et al. PLoS One. 2020 Apr 27;15(4):e0232161

PREDICTORS OF A FAVORABLE OUTCOME



Park J, et al. Clin Infect Dis. 2017 Feb 1;64(3):301-308
Park J, et al. Respir Med. 2021 Oct;187:106549

2020 MULTI-SOCIETY CLINICAL PRACTICE GUIDELINE

Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline: Executive Summary FREE

Charles L Daley ✉, Jonathan M Iaccarino, Jr, Christoph Lange, Emmanuelle Cambau, Richard J Wallace, Claire Andrejak, Erik C Böttger, Jan Brozek, David E Griffith, Lorenzo Guglielmetti, Gwen A Huitt, Shandra L Knight, Philip Leitman, Theodore K Marras, Kenneth N Olivier, Miguel Santin, Jason E Stout, Enrico Tortoli, Jakko van Ingen, Dirk Wagner, Kevin L Winthrop

Author Notes

Clinical Infectious Diseases, ciaa241, https://doi.org/10.1093/cid/ciaa241

Published: 06 July 2020 **Article history** ▾

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

Charles L. Daley[1,2,26], Jonathan M. Iaccarino[3], Christoph Lange[4,5,6,7,26], Emmanuelle Cambau[8,26], Richard J. Wallace Jr[9,26], Claire Andrejak[10,11], Erik C. Böttger[12], Jan Brozek[13], David E. Griffith[14], Lorenzo Guglielmetti[8,15], Gwen A. Huitt[1,2], Shandra L. Knight[16], Philip Leitman[17], Theodore K. Marras[18], Kenneth N. Olivier[19], Miguel Santin[20], Jason E. Stout[21], Enrico Tortoli[22], Jakko van Ingen[23], Dirk Wagner[24] and Kevin L. Winthrop[25]

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

SHOULD A REGIMEN WITH OR WITHOUT A MACROLIDE BE USED IN *M. ABSCESSUS* PD?

Recommendation	Strength	Certainty
In patients with *M. abscessus* PD caused by strains ***without* inducible or mutational resistance**, we recommend a macrolide-containing multidrug treatment regimen.	Strong	Very low
In patients with *M. abscessus* PD 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	Very low

- No studies were identified that compared macrolide-containing regimens with non macrolide-containing regimens
- Systematic reviews (N = 2) reported higher culture conversion with macrolide-containing regimens with macrolide susceptible infection
- Patients with macrolide-resistant *M.massiliense* have poor outcomes

Daley CL, et al. *CID*. 2020;71(4):e1-e36.

TREATMENT OF RGM: SYSTEMATIC REVIEW

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

Antimicrob Agents Chemother 2017; Oct 24;61(11).

HOW MANY ANTIBIOTICS SHOULD BE INCLUDED WITHIN MULTIDRUG REGIMENS FOR *M. ABSCESSUS* PD?

Recommendation	Strength	Certainty
In patients with *M. abscessus* PD, we suggest a multidrug regimen that includes **at least 3 active drugs** (guided by *in vitro* susceptibility) in the initial phase of treatment.	Conditional	Very low

- No studies 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
- Treatment outcomes are significantly worse for macrolide-resistant *M. abscessus* infections so ≥ 4 drugs are recommended, when possible

Daley CL, et al. *Clin Infect Dis*. 2020;71(4):e1-e36.

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

SHOULD SHORTER OR LONGER DURATION THERAPY BE USED FOR TREATMENT IN *M. ABSCESSUS* PD?

Recommendation	Strength	Certainty
In patients with *M. abscessus* PD, we suggest that either a shorter or longer treatment regimen be used and expert consultation obtained.	Conditional	Very low

- Two systematic reviews noted that most patients had been treated for > 12 months with multidrug regimens including a minimum of 4 weeks of ≥ 1 parenteral agent
- It may be possible to treat *M. massiliense* pulmonary disease with shorter regimens but the optimal duration is not known
- Expert consultation is advised prior to the initiation of therapy

Daley CL, et al. *Clin Infect Dis*. 2020;71(4):e1-e36.

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

TREATMENT REGIMENS FOR *M. ABSCESSUS*

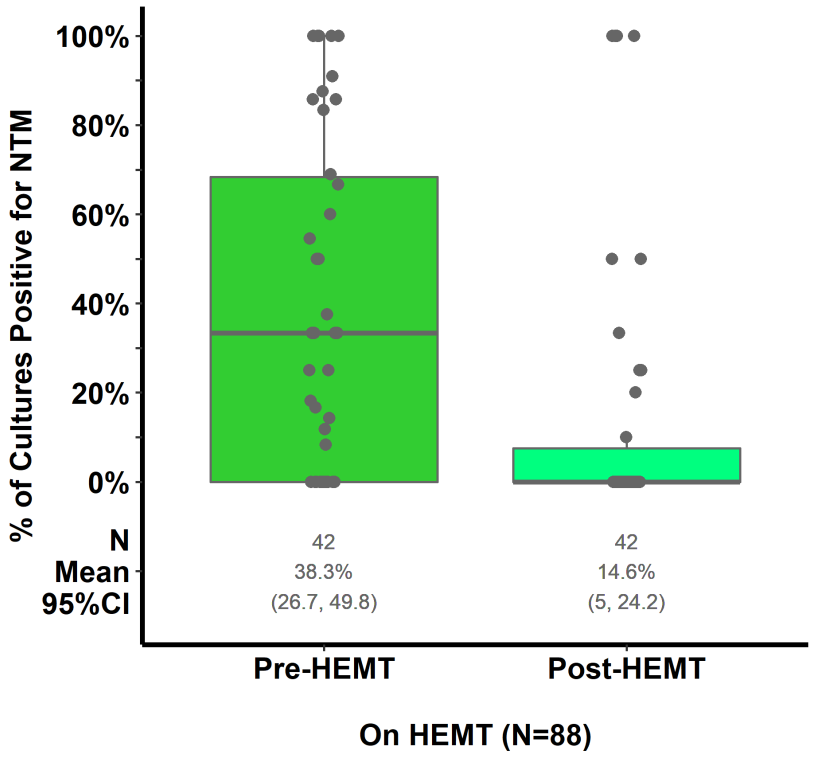
Macrolide susceptibility	No. of Drugs	Preferred Drugs		Dosing Frequency
Susceptible	Initial phase ≥3	Parenteral (choose 1-2) • Amikacin • Imipenem (or cefoxitin) • Tigecycline	Oral (choose 2) • Azithromycin (clarithromycin) • Clofazimine • Linezolid	Daily (3 times weekly may be used for aminoglycosides)
	Continuation phase ≥2	Oral/Inhaled (choose 2-3) • Azithromycin (Clarithromycin) • Clofazimine • Linezolid • Inhaled amikacin		
Resistant	Initial phase ≥4	Parenteral (choose 2-3) • Amikacin • Imipenem (or cefoxitin) • Tigecycline	Oral (choose 2-3) • Azithromycin (clarithromycin)* • Clofazimine • Linezolid	
	Continuation phase ≥2	Oral/Inhaled (choose 2-3) • Azithromycin (Clarithromycin)* • Clofazimine • Linezolid • Inhaled amikacin		

* macrolide is not counted as an active drug

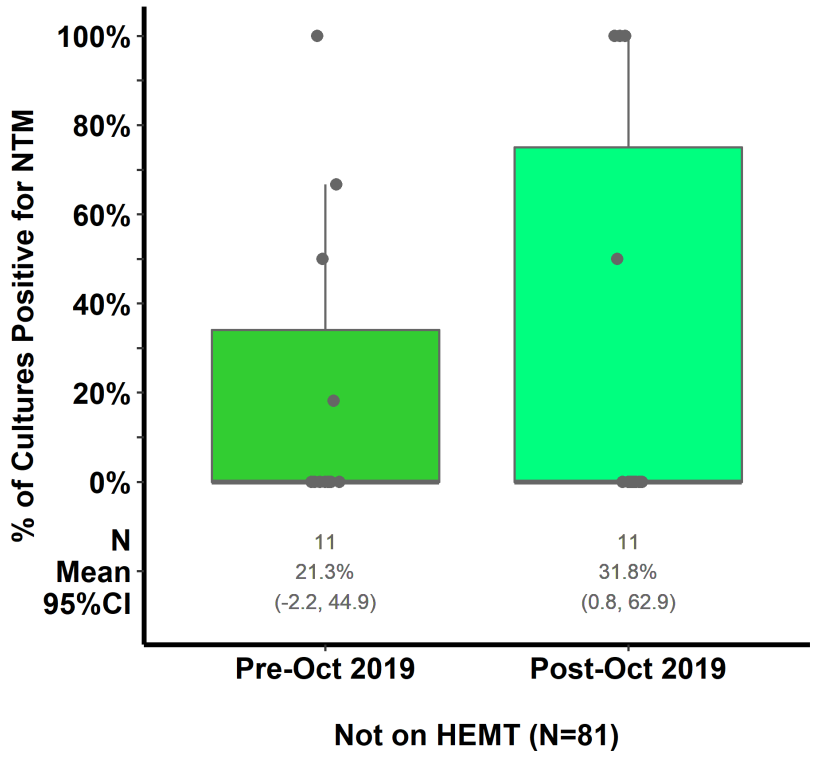
Daley CL, et al. Eur Respir J 2020; 56: 2000535

MODULATOR THERAPY HAS A SIGNIFICANT IMPACT ON NTM CULTURE % POSITIVITY

Mean Diff: -24% (P-value <0.001)



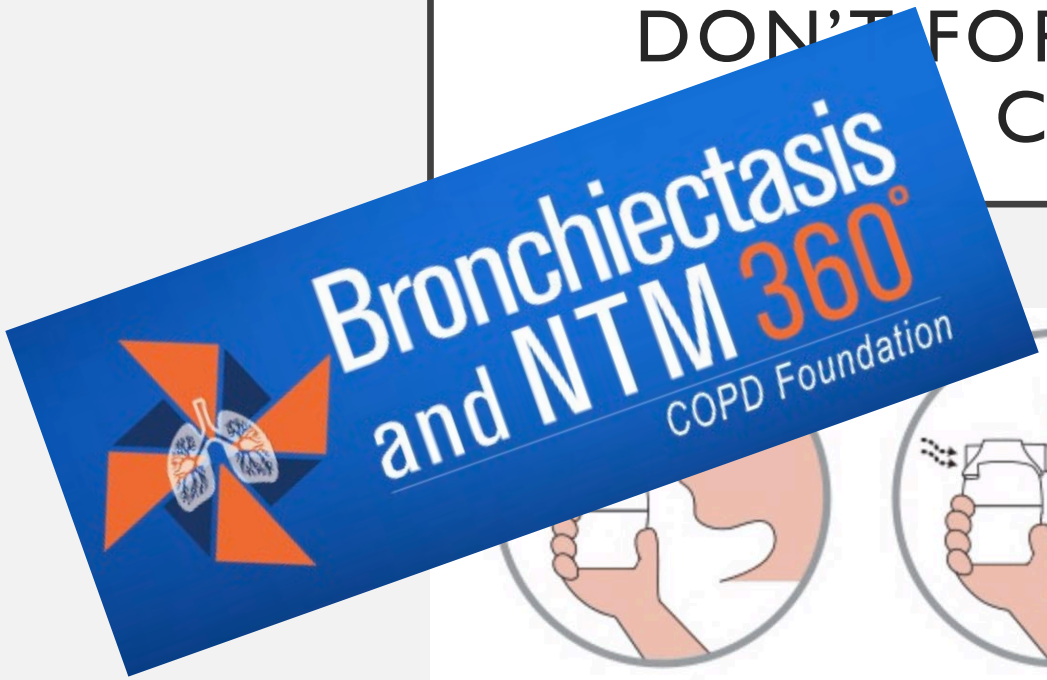
Mean Diff: +10% (P-value 0.439)



HEMT: highly effective modulator therapy

Unpublished data, courtesy of S. Martiniano M.D.

DON'T FORGET ABOU CLEARANC




Respirology

INVITED REVIEW SERIES:
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Airway clearance, mucoactive therapies and pulmonary rehabilitation in bronchiectasis

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ABSTRACT

This paper aims to provide physiological rationale for airway clearance, mucoactive therapy and pulmonary rehabilitation (PR) (or exercise interventions) in bronchiectasis. There is increasing emphasis on the role of airway clearance techniques (ACT) in the management of bronchiectasis. No single ACT has currently shown superior effect over another. Given the large range of different techniques available, consideration of the physiological effects underpinning a technique including expiratory flow, ventilation and oscillation, is essential to effectively personalize ACT. Key clinical trials of mucoactives in bronchiectasis are underway and will provide clarity on the role of these agents in the management of patients with bronchiectasis. Prescription of mucoactive therapies should be done in conjunction with ACT and therefore the mechanism of action of mucoactive drugs and their timing with ACT should be taken into consideration. PR and/or exercise training are recommended in all current bronchiectasis guidelines. There is a clear physiological rationale that muscle weakness and physical inactivity may play a role in disease progression as well as impacting health-related quality of life, frequency of pulmonary exacerbations and ability to mobilize sputum. However, there are residual unanswered questions surrounding the delivery and accessibility to PR. This review summarizes the physiological principles and supporting evidence for airway clearance, mucoactive medication and PR, which are key components in the management of bronchiectasis.

Key words: airway clearance, bronchiectasis, mucoactives, pulmonary rehabilitation.

INTRODUCTION

Chronic cough, sputum production as well as decreased exercise capacity and inactivity are some of the main clinical manifestations reported in patients with bronchiectasis.[1–3] These symptoms worsen during exacerbations and impact negatively on health-related quality of life (HRQoL).[4] This paper summarizes the physiological rationale for airway clearance including mucoactive therapy as well as pulmonary rehabilitation (PR) (or exercise interventions) in bronchiectasis.

AIRWAY CLEARANCE IN BRONCHIECTASIS

Airway clearance techniques (ACT) are non-pharmacological strategies to improve symptoms and HRQoL and reduce exacerbation frequency.[5,6] Short-term goals are to provide more effective sputum clearance that improves ventilation and reduces cough impact and breathlessness. Longer term goals are reducing further airway damage by halting the vicious cycle of bacterial colonization and subsequent inflammation, reducing the number of pulmonary exacerbations and hospitalizations and improving HRQoL.[7–9] Published guidelines agree that ACT are a key component in the management of bronchiectasis and that all patients with bronchiectasis should be taught ACT by a respiratory physiotherapist. ACT which can be performed independently are recommended in these guidelines.[7,9] Patients with a chronic productive cough or difficulty expectorating sputum may benefit from regular twice daily ACT as recommended in current guidelines.[9] In addition, the physiotherapist can discuss step up and step down ACT in managing exacerbations.[9] In practice, ACT remain significantly underutilized. Data from the European Bronchiectasis Data Registry (EMBARC) report that only 45% of data registrants perform an ACT regularly.[10] Furthermore, airway clearance has very low rates of adherence.[11]

ACT rely on two overriding physiological principles. First, a mechanism to allow air to move behind the obstruction and ventilate the regions distally and second, modulation of expiratory airflow to propel secretions proximally up the airways. in vitro flow models suggest two conditions that improve airway clearance: (i) the peak expiratory flow rate should be greater than the peak

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www.bronchiectasisandntminitiative.org
www.bronchiectasis.com.au
www.rethinkbronchiectasis.com
www.impact-be.com

O'Neill K et al. Respirology (2019) 24, 227–237doi: 10.1111/resp.13459

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