Nontuberculous Mycobacterial Pulmonary Disease

Diagnosis and Management

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Calgary, Alberta

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SOCIÉTÉ CANADIENNE DE THORACOLOGIE
CANADIAN THORACIC SOCIETY

Disclosure of Conflict of Interest

(over the past 2 years)

- ❒ I have no conflict of interest.

CanMEDs Roles

This session will address the following CanMEDs roles:
(Please include all that apply)

- Medical Expert (the integrating role)
- Collaborator
- Scholar

Learning Objectives

At the end of this session, participants will be able to:

- Review the epidemiology of NTM
- Identify risk factors associated with NTM pulmonary disease;
- Recognize how to diagnose NTM pulmonary disease and which patients are candidates for treatment;
- Describe how to treat NTM pulmonary disease (in particular, *Mycobacterium avium* complex)

Taxonomy of Mycobacteria

- Genus: Mycobacterium
    - *Mycobacterium tuberculosis* complex
    - *Mycobacterium leprae*
    - Nontuberculous mycobacterium (NTM)

- >200 species and subspecies of NTM
    - http://www.bacterio.net/mycobacterium

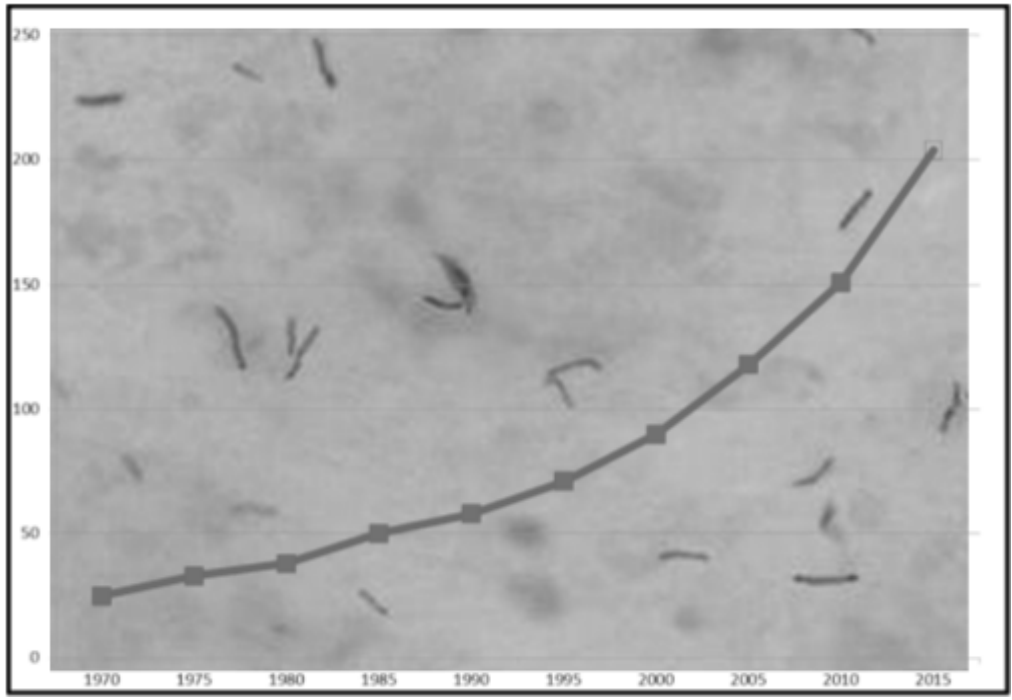


TABLE 1] Examples of Clinically Relevant Slow-Growing and Rapid-Growing NTM Species[1]

Slow-Growing NTM Species	Rapid-Growing NTM Species
M avium complex, comprising:	*M abscessus* complex, comprising:
M avium	*M abscessus* subspecies *abscessus*
M intracellulare	*M abscessus* subspecies *massiliense*
M chimaera	*M abscessus* subspecies *bolletii*
M kansasii	*M chelonae*
M malmoense	*M fortuitum*
M xenopi	

NTM = nontuberculous mycobacteria.

Kumar and Loebinger Chest March 2022

Epidemiology – NTM across the globe

- Regardless of differences in epidemiology data, the incidence and prevalence of NTM-PD are generally increasing worldwide; data from North America, UK, South Korea, Japan, New Zealand and Australia

- Prevalence of NTM-PD in the US and Europe is similar and appears to be lower than in Asia

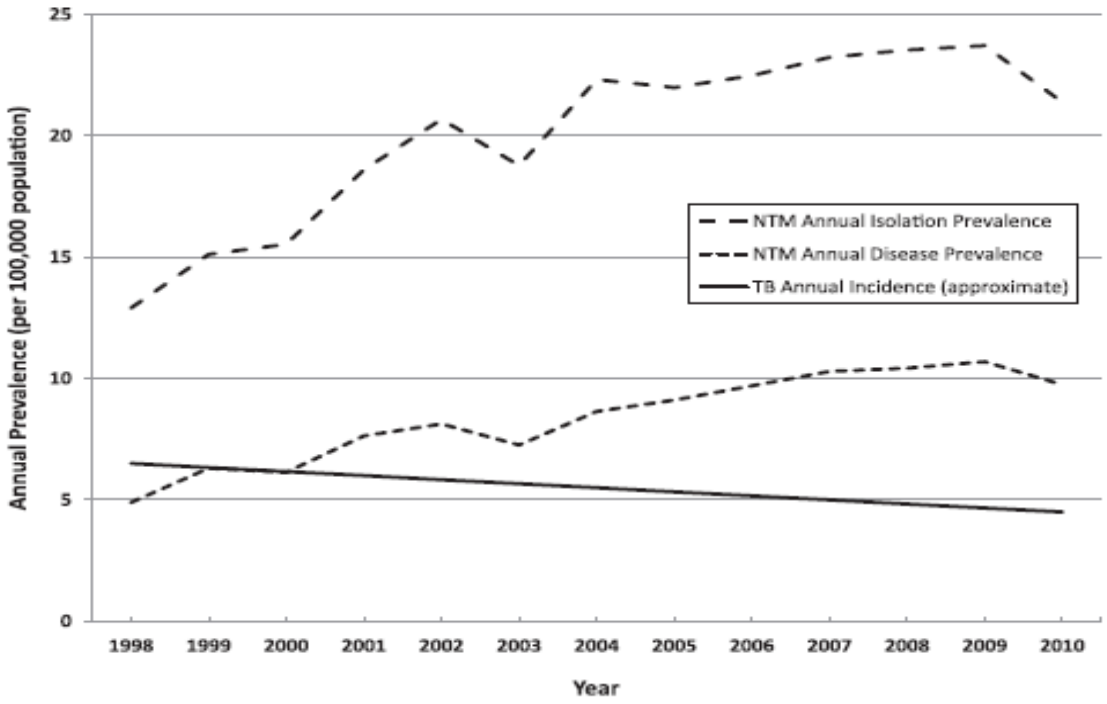


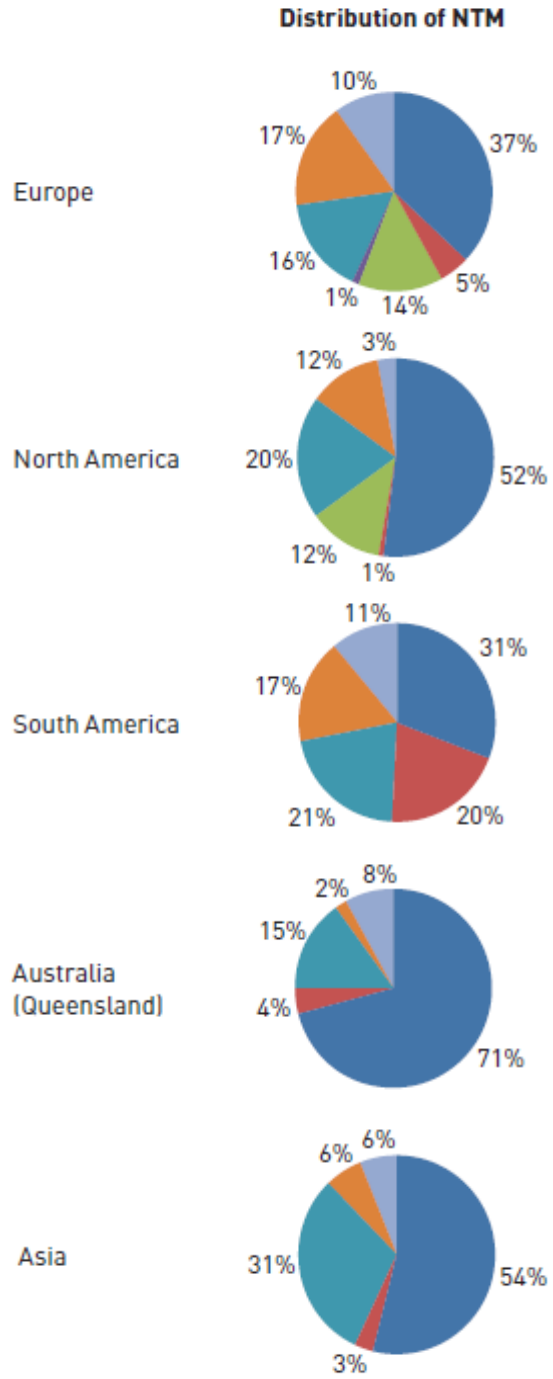
Fig. 2. Prevalence of nontuberculous mycobacteria (NTM) isolation and disease, and incidence of tuberculosis (TB), Canada, 1998 to 2010.

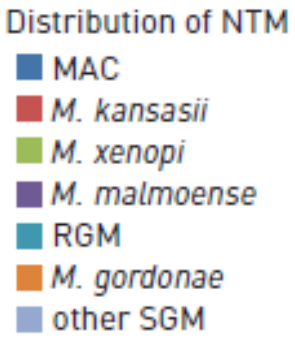
Marras Emerg Inf Dis 2013

Van Ingen Expert Review Resp Med 2021

Epidemiology - Microbiology

- Environmental mycobacteria
- Predominant NTM species is variable depending on geographic location





Hoefsloot ERJ 2013

Yearly Incidence of NTM-PD

Yearly Prevalence of NTM-PD

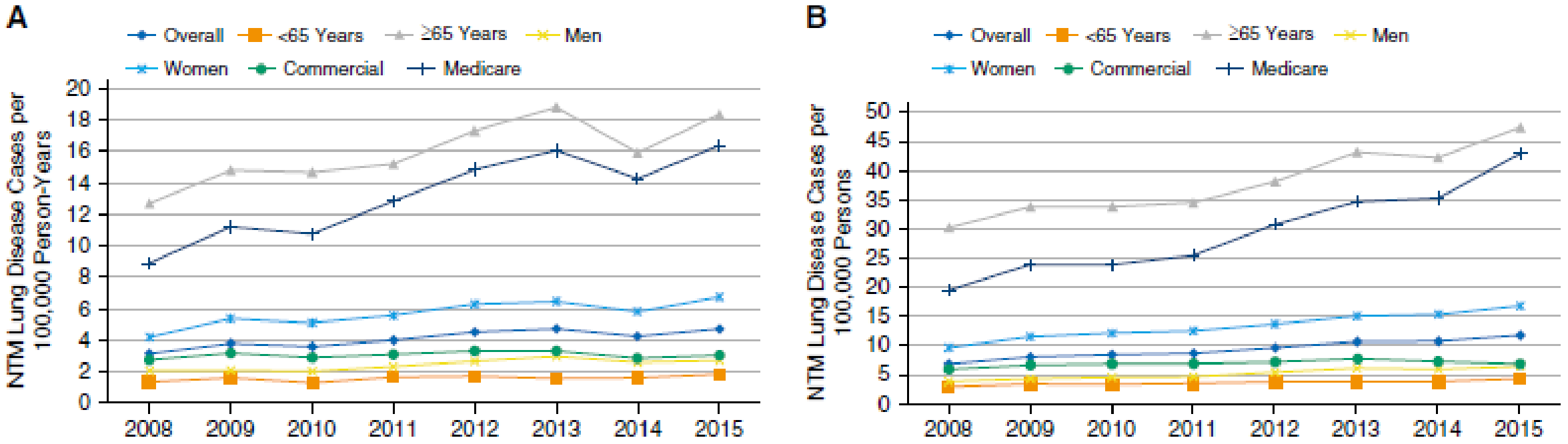


Figure 2. (*A*) Yearly incidence and (*B*) yearly prevalence of nontuberculous mycobacterial (NTM) lung disease (2008–2015) by select subgroups in a U.S. national health insurance plan.

NTM PD incidence – 4.7 per 100,000 (2015)
TB incidence - 2.7 per 100,000 (2019)

Average annual increase in prevalence of 7.5%

Winthrop Ann Am Thor Soc 2020

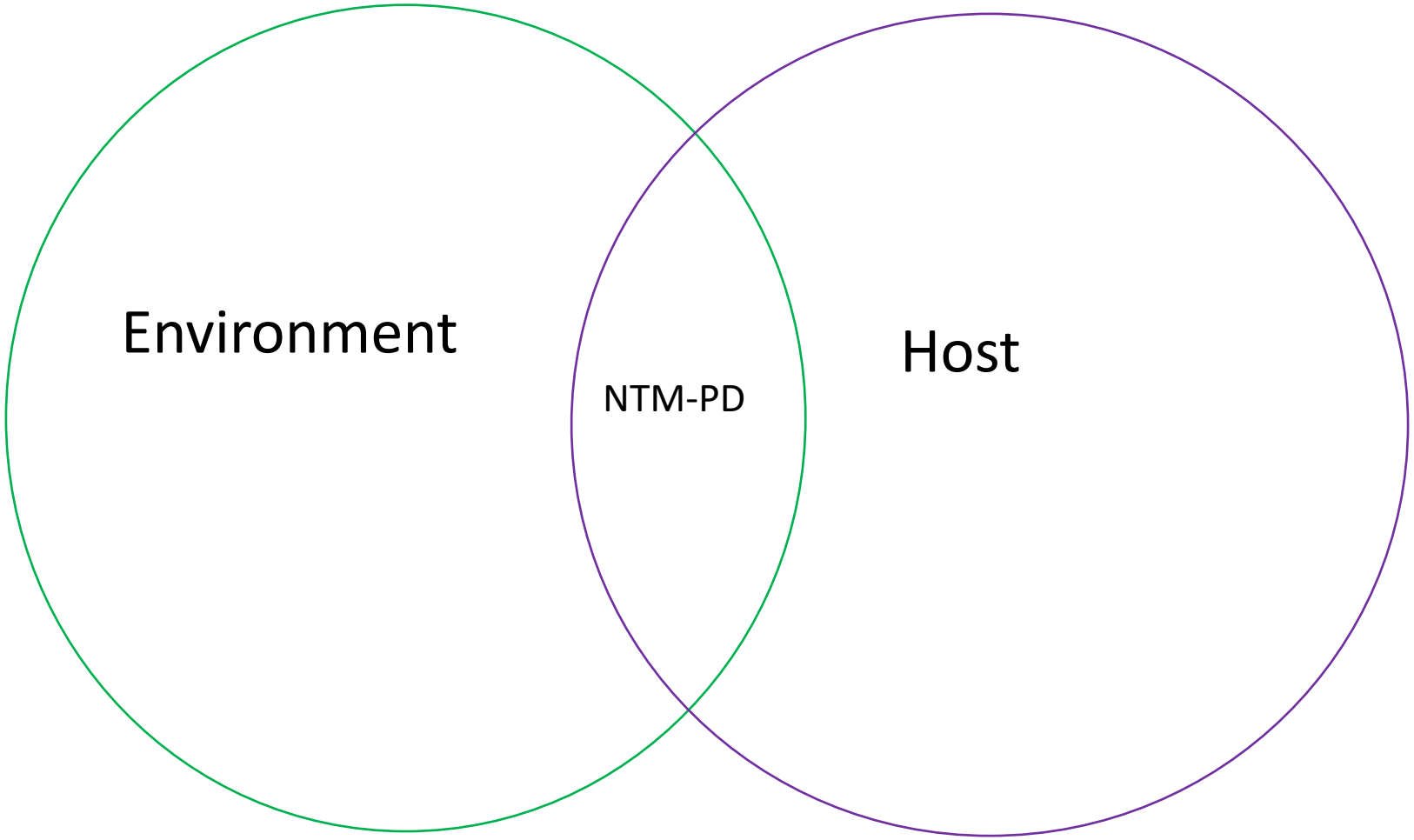
Increased Economic burden, Decreased Quality of Life and Increased Mortality

- Higher costs and hospitalization rates than matched controls
  - Ramsay Emerg Inf Dis 2020; Diel ERJ 2017

- Decreased Quality of Life
  - Mehta Respir Med 2011; Henkle ERJ 2020;Kwak BMC Pulm Med 2020,

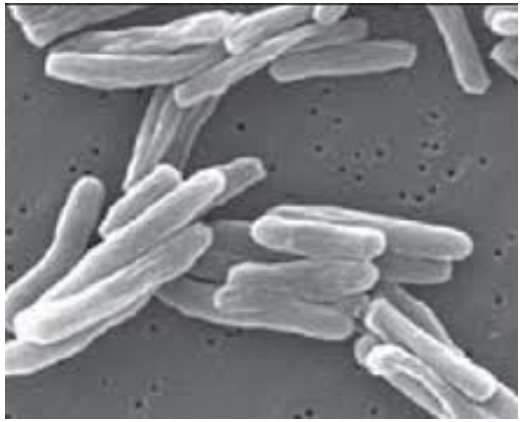
- Mortality risk is higher in patients with NTM-PD
  - 5 year all cause mortality 45% among patients with NTM-PD & comorbidities vs 25% with NTM-PD without comordities vs 6% in demographically matched general population cohort
    - Mourad CID 2021

Risk factors/Susceptibility



Risk factors for NTM-PD – The Environment

- Environmental factors
  - Exposure to NTM reservoirs ie. contaminated water supplies and soil and high levels of environmental humidity
  - Much more likely reinfection than relapse after treatment completion



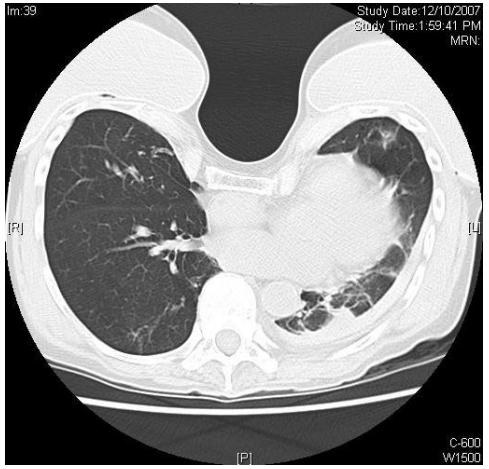
Risk factors for NTM-PD – The Host

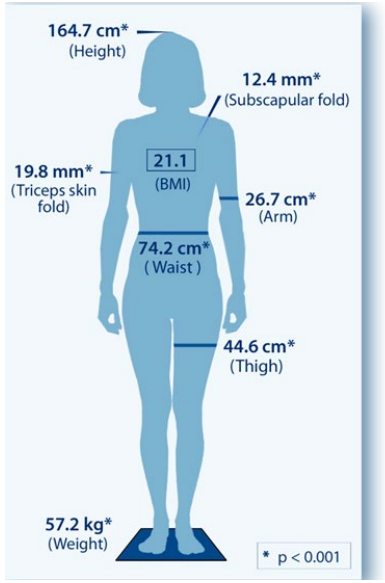
- Host factors
  - Structural lung disease – bronchiectasis, COPD, Asthma, IPF
  - Genetic disorders – CF/CFTR anomalies, Primary ciliary dyskinesia, Alpha-1 antitrypsin deficiency
  - Associated medical conditions – GERD, Rheumatoid arthritis, Sjogren's

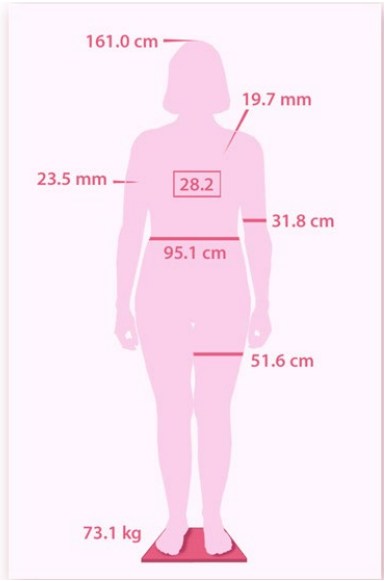
Kumar Chest 2022

Risk factors for NTM-PD – The Host

- Host factors
- Innate host phenotype
  - Postmenopausal women
  - Tall
  - Low BMI
  - Scoliosis, Mitral valve prolapse







Kim AJRCCM 2008

Risk factors for NTM-PD – The Host

- Impaired Immunity
  - Inherited immunodeficiency- CVID, STAT3 mutations (HyperIgE syndrome), GATA2 mutations
  - Acquired immunodeficiency
    - HIV/AIDS
    - Malignancy
    - Transplant
    - Interferon-gamma neutralizing antibody syndrome
    - Immunosuppressive medications
      - Corticosteroids – oral and inhaled (prednisone >15 mg or >800 mcg fluticasone)
      - Anti-TNF therapy (e.g. infliximab, etanercept, adalimumab)

Kumar Chest 2022

An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases

David E. Griffith, Timothy Aksamit, Barbara A. Brown-Elliott, Antonino Catanzaro, Charles Daley, Fred Gordin, Steven M. Holland, Robert Horsburgh, Gwen Huitt, Michael F. Iademarco, Michael Iseman, Kenneth Olivier, Stephen Ruoss, C. Fordham von Reyn, Richard J. Wallace, Jr., and Kevin Winthrop, on behalf of the ATS Mycobacterial Diseases Subcommittee

2007

Clinical Infectious Diseases

IDSA FEATURES

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

Charles L. Daley,[1,2,a] Jonathan M. Iaccarino,[3] Christoph Lange,[4,5,6,7,a] Emmanuelle Cambau,[8,a] Richard J. Wallace, Jr,[9,a] 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]

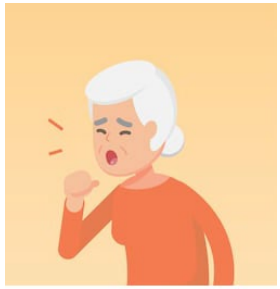
CID 2020

ATS/ERS/IDSA Diagnostic Criteria for NTM Pulmonary Disease

Clinical

Pulmonary and/or Systemic symptoms

eg. Cough, sputum production, weight loss, dyspnea, fatigue

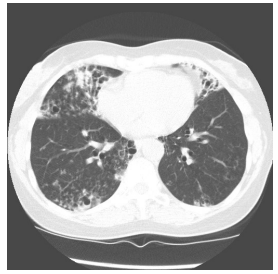


AND

Radiologic

CXR & CT chest

Bronchiectasis, tree-in-bud nodules, cavities



AND

Microbiologic

Positive cultures from at least 2 sputum samples

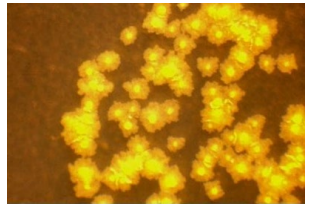
(of same species)

OR

Positive culture from BAL

OR

Positive culture from lung biopsy/TBBx

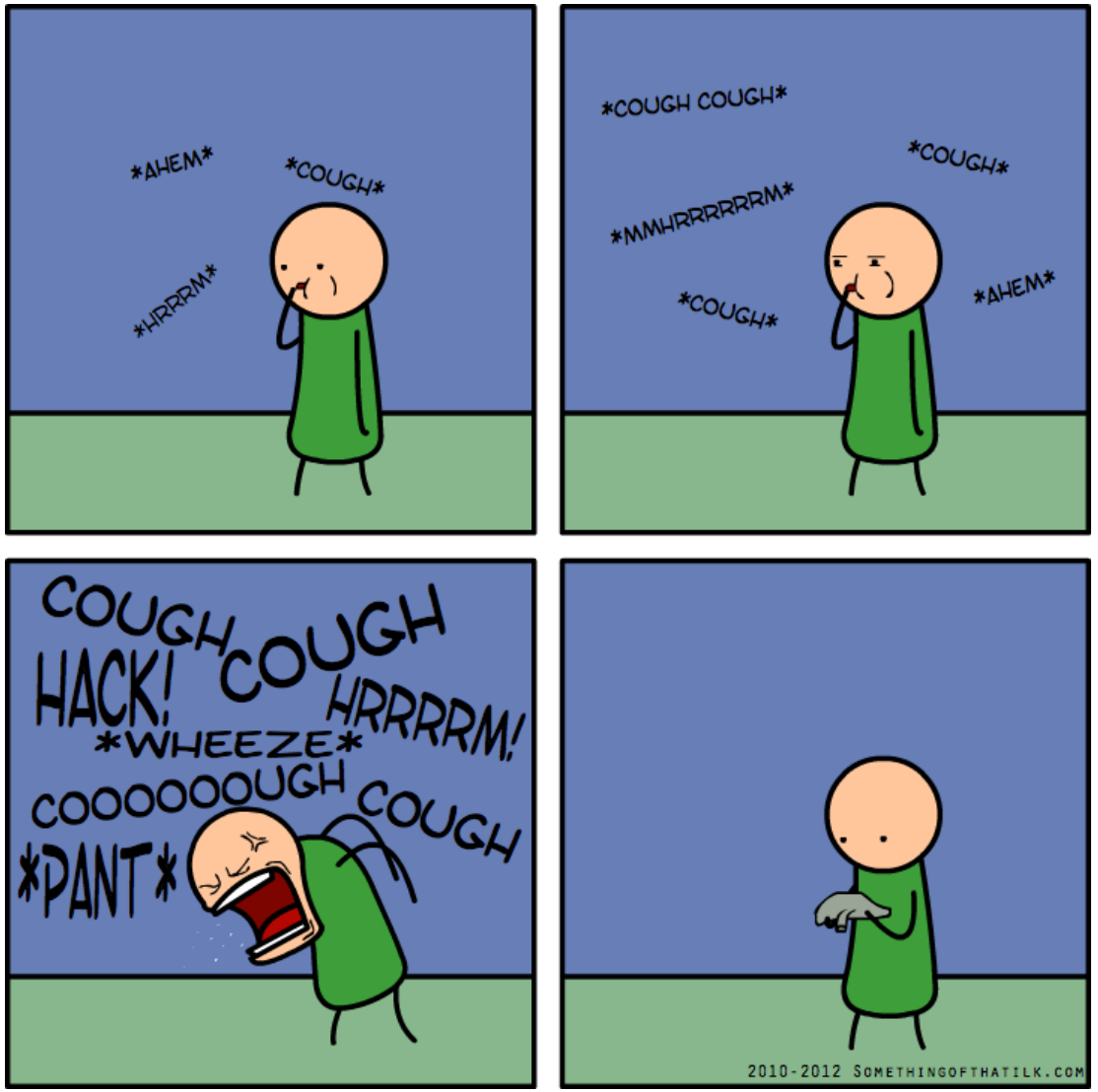


ATS/IDSA NTM guideline 2007 + 2020

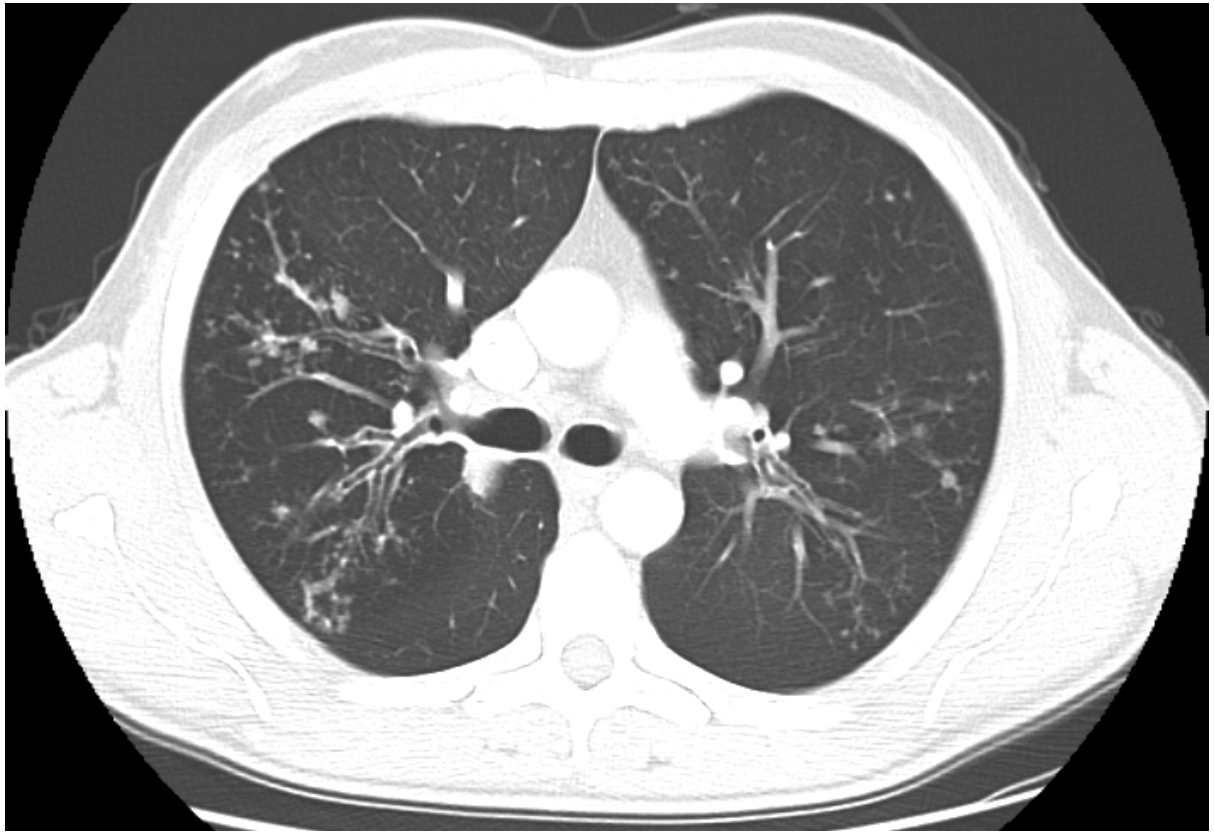
Clinical symptoms

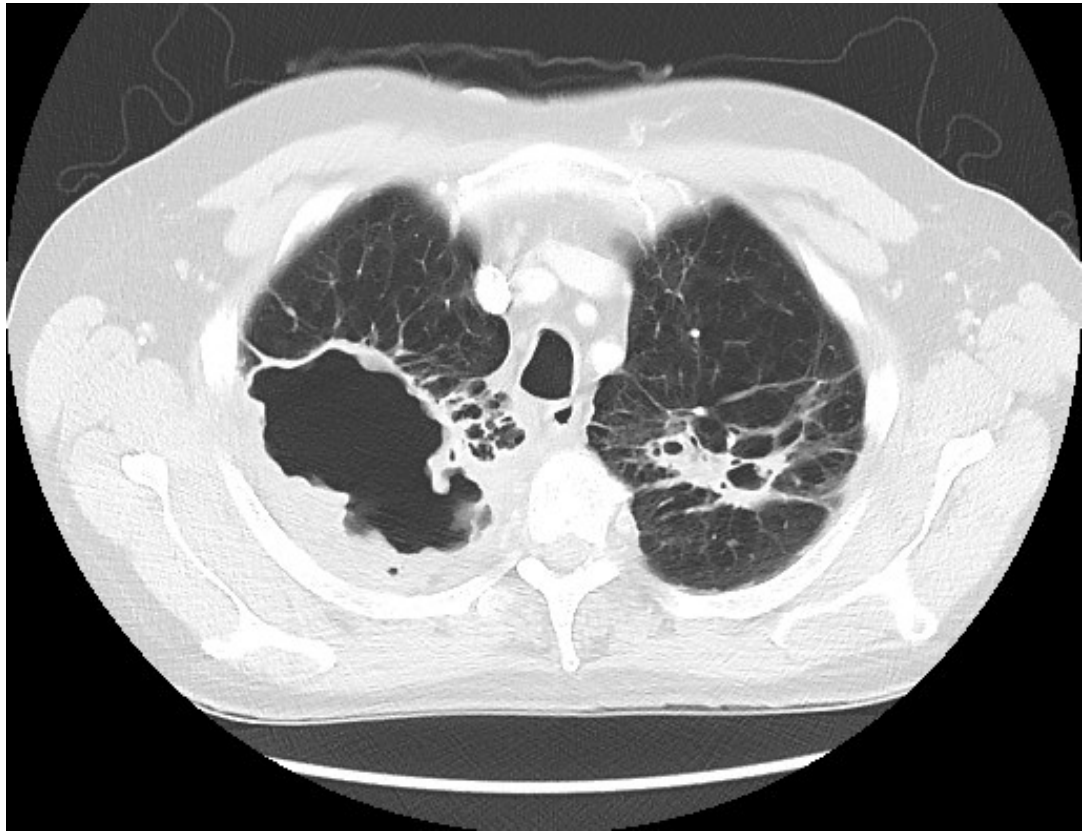
- Non- specific symptoms
  - Cough and sputum production
  - weight loss
  - Dyspnea
  - Fatigue
  - Fever/night sweats
  - Hemoptysis

- Diagnosis is often delayed



Radiologic pattern





Microbiologic diagnosis

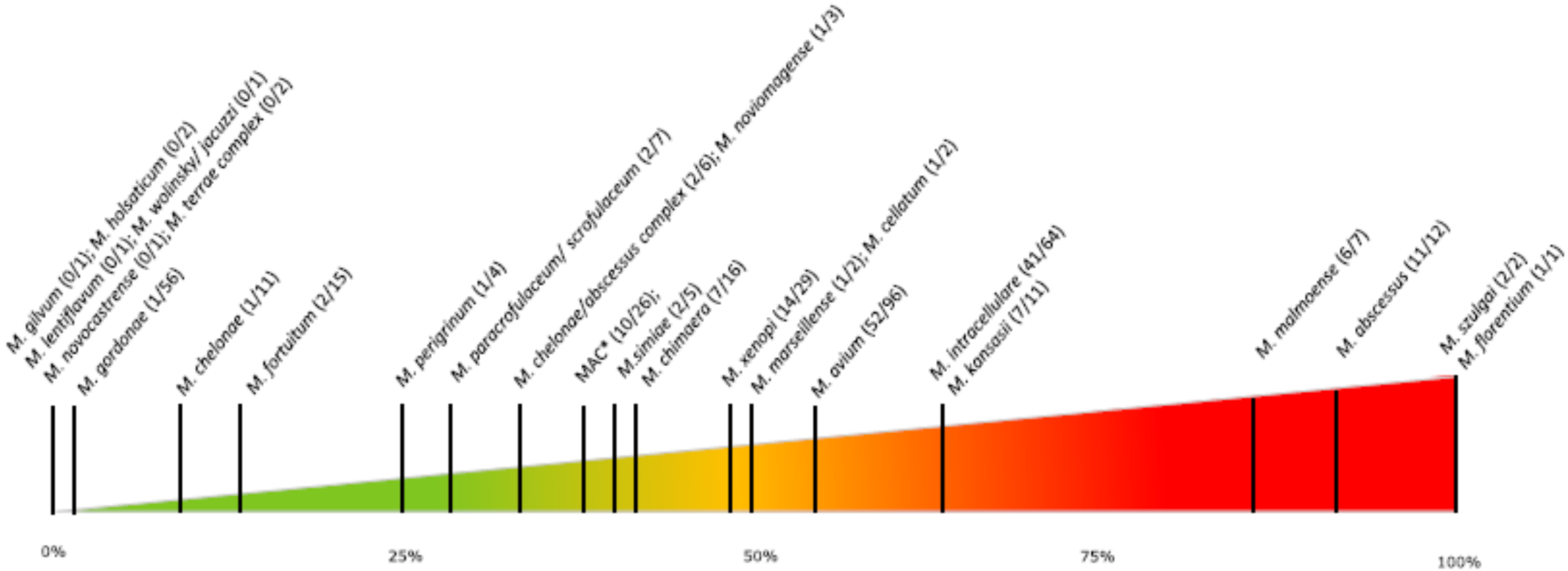
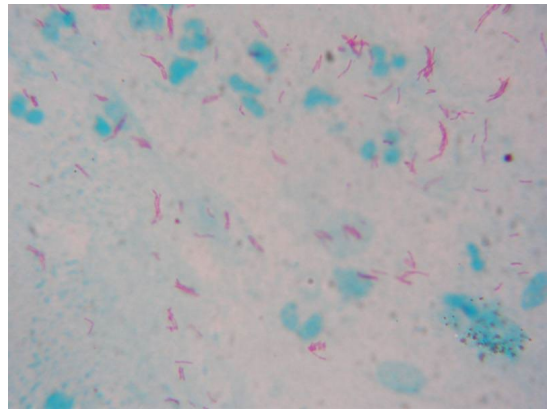


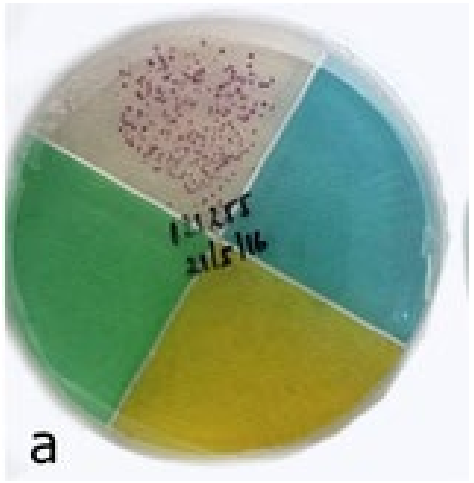
Fig. 4 Ratio of clinical significance. Clinical significance per species; presented as a percentage based on the number of cases meeting ATS/IDSA criteria for NTM-PD and the total number of isolates per species. MAC and *M. chelonae/abscessus* complex, not further specified, were regarded separately. On the left, species of low virulence are found and on the right the most pathogenic species. Figure concept van Ingen et al., Thorax 2009, with permission

Weygaerde BMC Infect Dis 2019

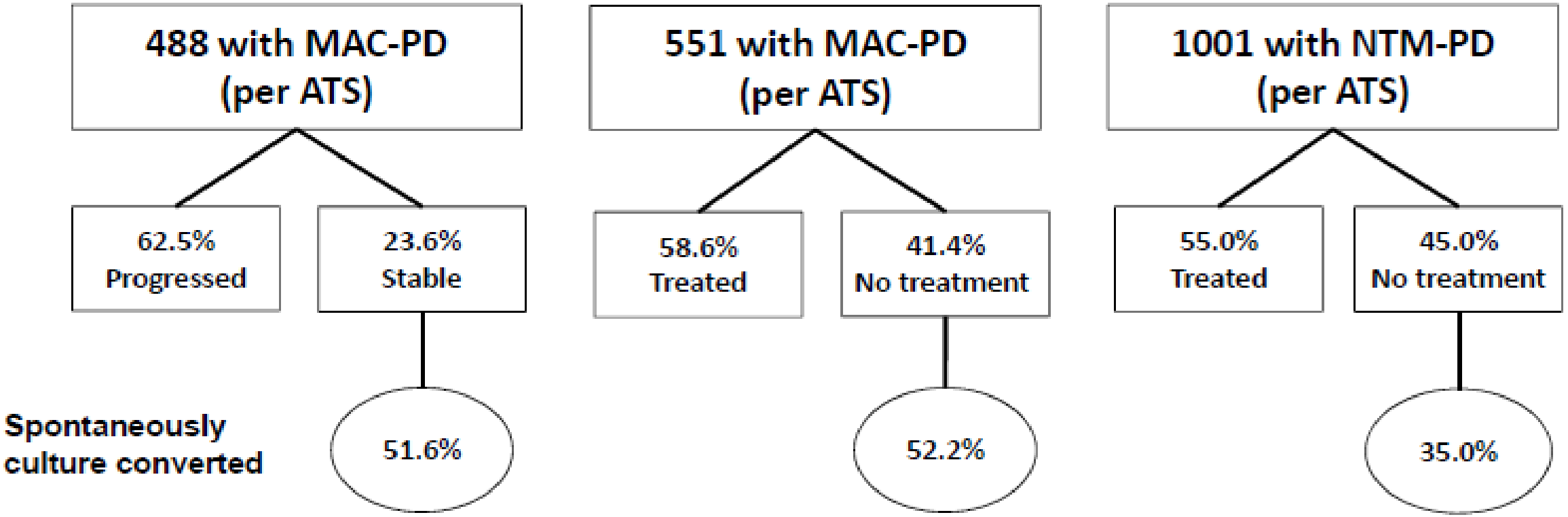
Microbiologic diagnosis



- Drug susceptibility testing
  - *M avium* complex – Macrolides, Amikacin
  - *M. abscessus* complex – Macrolides - inducible macrolide resistance
  - *M. kansasii* - Rifampin



Progression of NTM Pulmonary Disease in Those Who Meet ATS/IDSA Diagnostic Criteria



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

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

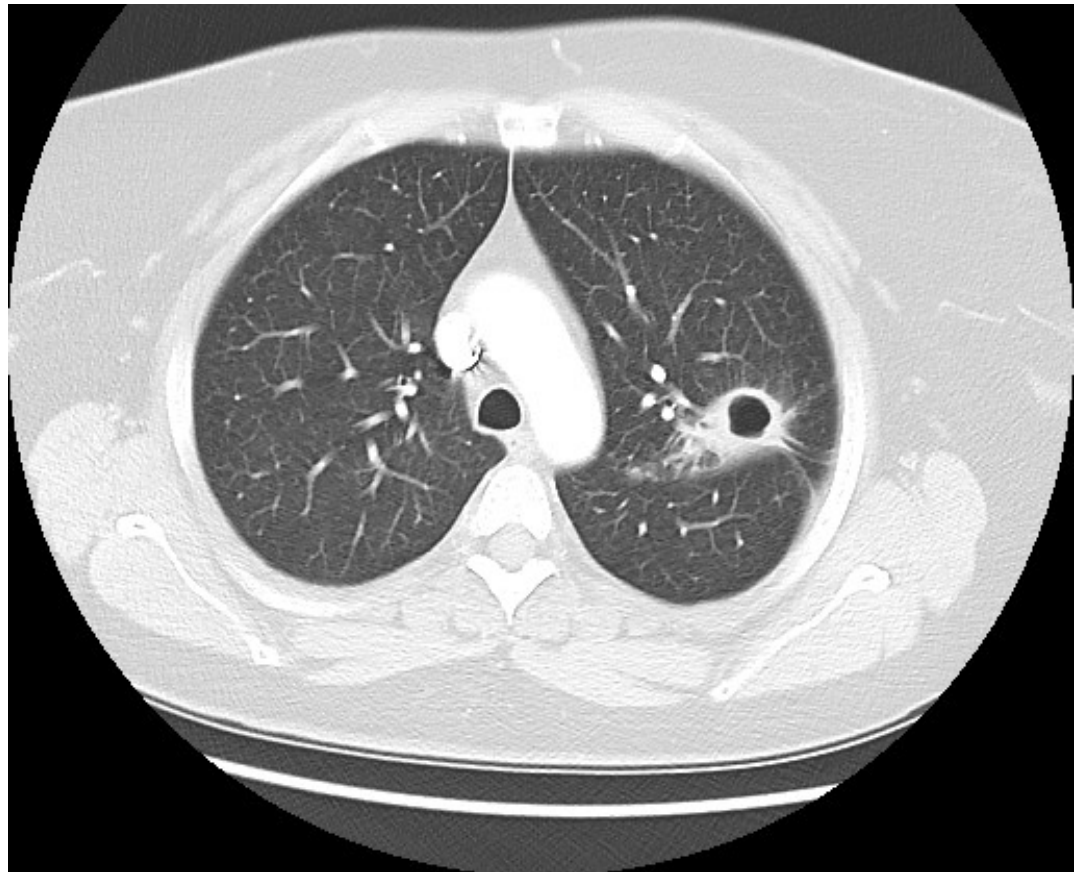
Moon SM, et al.
Resp Med 2019;151:1-7.

Risk factors associated with Progression

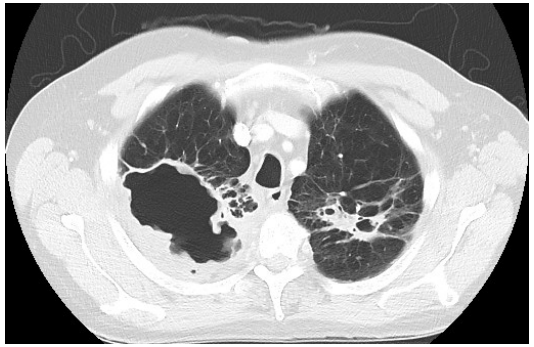
- **Host/Demographic factors**
  - Male gender
  - Older age
  - Low BMI
  - Presence of co-morbidities
- **Laboratory factors**
  - Elevated inflammatory indices (ESR, CRP)
  - Anemia
  - Hypoalbuminemia

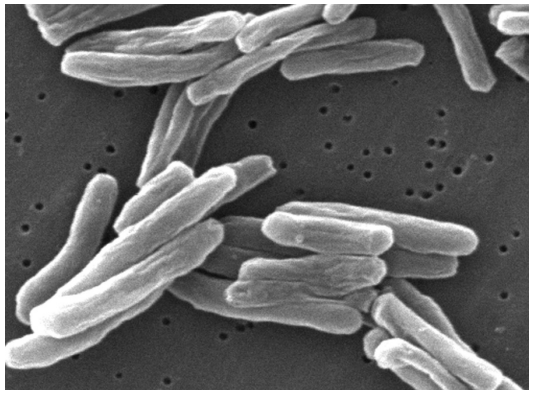
- **Radiographic**
  - Fibrocavitary
  - Extent of disease
- **Microbial**
  - Bacterial load
  - Species

Hwang Eur Resp J 2017
Byoung Resp Med 2019
Moon Resp Med 2019

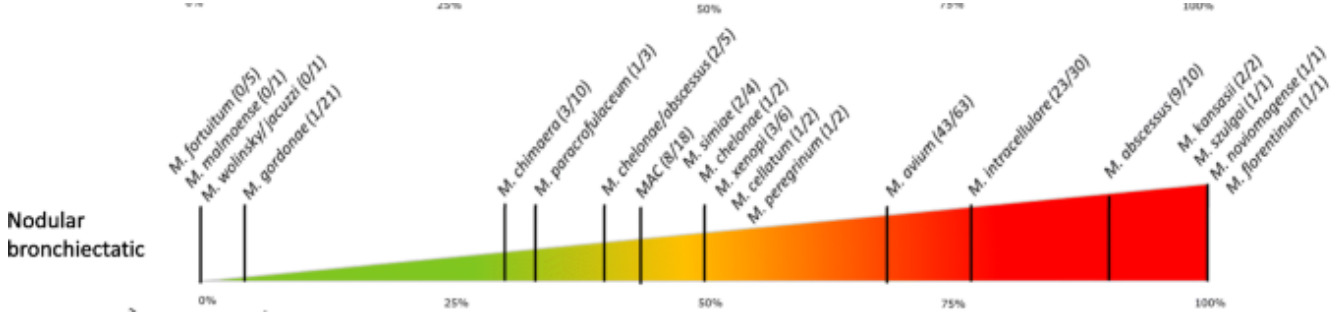


NTM Pulmonary Disease Whom to Treat





Increased susceptibility
Clinical symptoms and overall condition of the patient
Extent of radiographic abnormalities

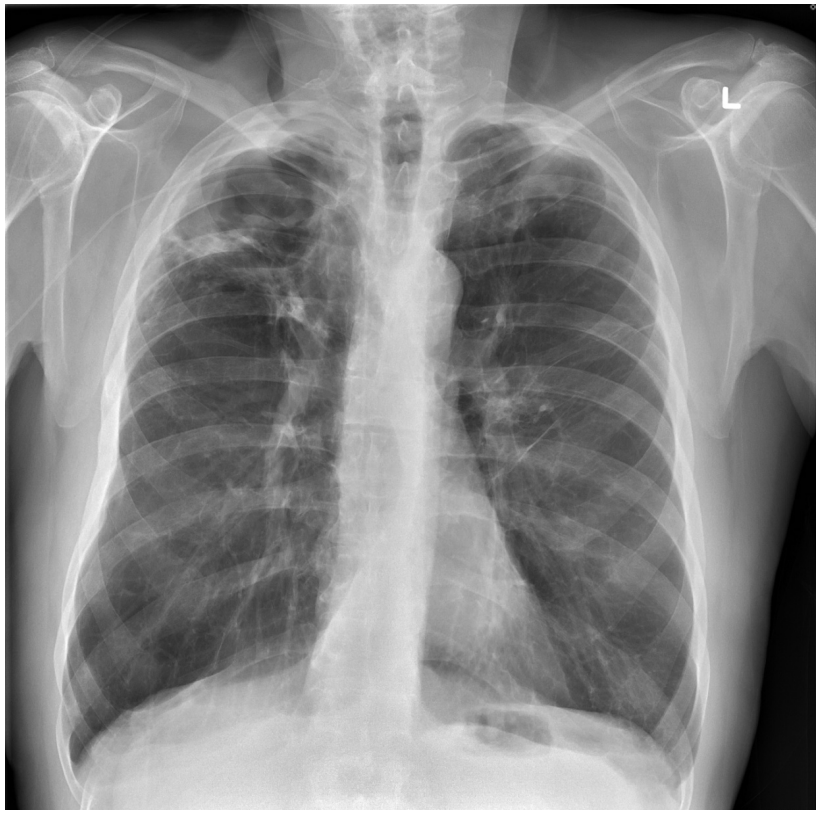


Cure, bacteriologic conversion, relief of symptoms, improved quality of life, prevention of progression

If NTM treatment is not started……

*AVOID MACROLIDES

*Screen for NTM if considering macrolides for another reason



Nonpharmacologic therapy

- Airway clearance/chest physiotherapy
- Assessing and treating GERD +/- aspiration
- Assessing for immune problems
- Identifying and treating other organisms that could be causing/contributing to symptoms
  - e.g. Pseudomonas, MSSA, Nocardia

Clinical Infectious Diseases

IDSA FEATURES

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

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CID August 2020

22 PICO questions
31 evidence based recommendations about treatment of NTM pulmonary disease

Treatment guidelines

- In patients who meet diagnostic criteria for NTM-PD, guidelines suggest initiation of treatment rather than watchful waiting, especially in the context of AFB smear positivity and/or cavitary lung disease (conditional recommendation, very low certainty in estimates of effects)

- Use 3 drugs (rather than 2 drugs and unclear risk of acquired drug resistance with 2 drug regimen)

- Refractory MAC-PD is defined as patients who remain culture positive after 6 months of guideline-based therapy (GBT)

Treatment of MAC pulmonary disease

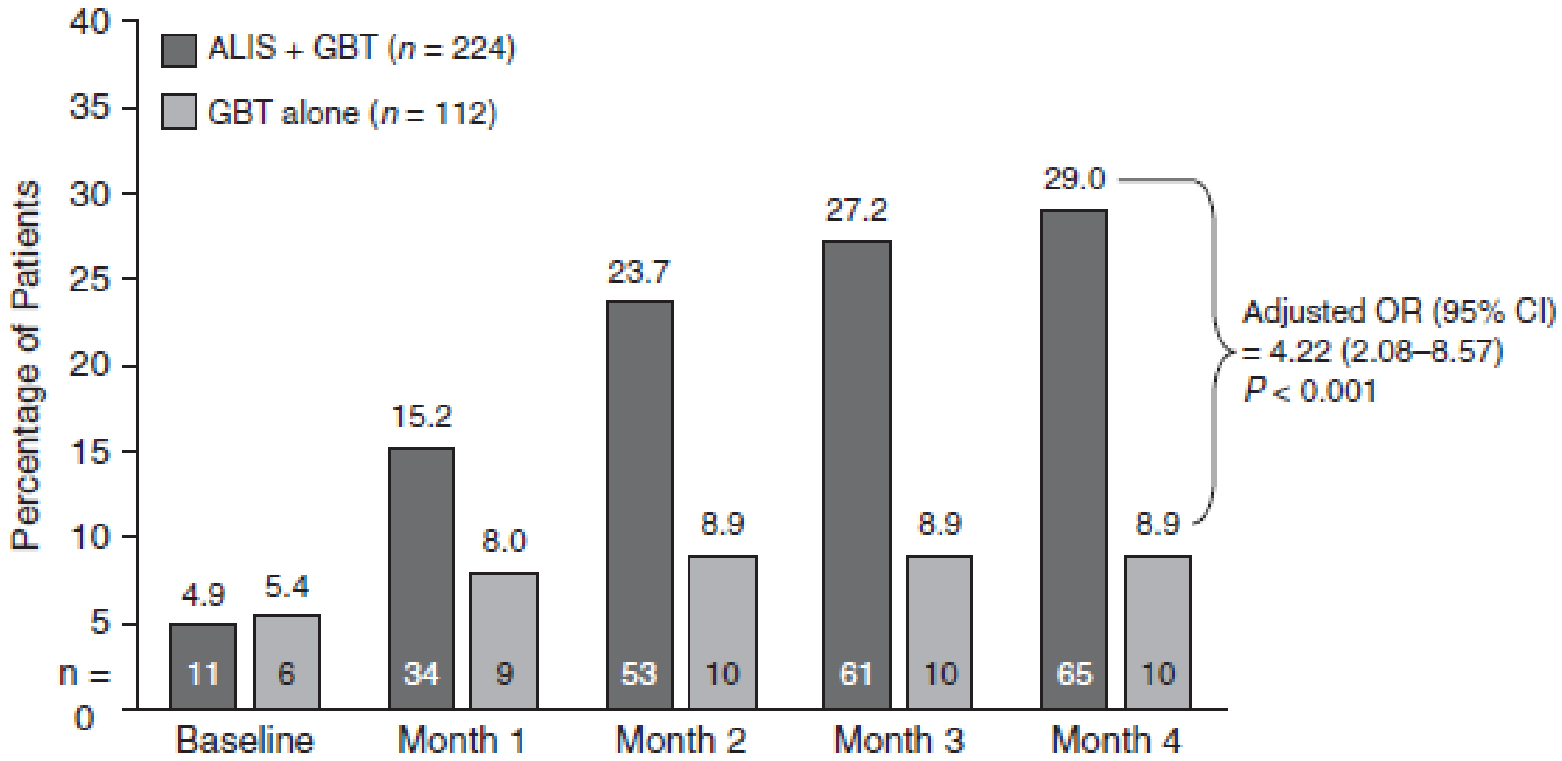
Table 4. Recommended Treatment Regimens for *Mycobacterium avium* complex, *M. kansasii*, and *M. xenopi* Pulmonary Disease

Organism	No. of Drugs	Preferred Drug Regimen[a]	Dosing Frequency
M. avium complex			
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
Cavitary	≥3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)[b]	Daily (3 times weekly may be used with aminoglycosides)
Refractory[c]	≥4	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin liposome inhalation suspension or amikacin IV (streptomycin)[b]	Daily (3 times weekly may be used with aminoglycosides)

Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by *Mycobacterium avium* Complex (CONVERT)

A Prospective, Open-Label, Randomized Study

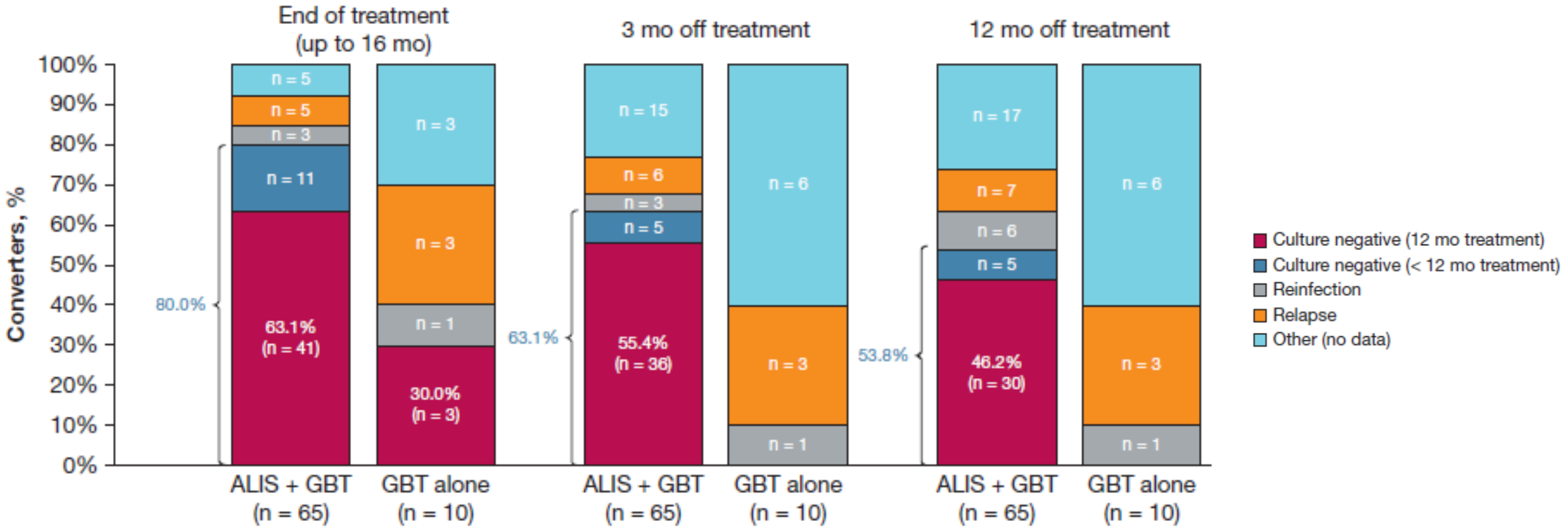
Griffith AJRCCM 2018



MAC LUNG DISEASE can feel like it gets in the way

It's time to talk to your doctor about ARIKAYCE

ALIS – CONVERT study extension



Griffith Chest 2021

Highlights from treatment guidelines

- MAC
    - Treat for at least 12 months after culture conversion (optimal duration of therapy not known)

- M. *kansasii*
    - Treat for at least 12 months, fixed duration (no trials with shorter regimens), rather than 12 months after culture conversion

Treatment Outcomes of M. avium complex Systematic Review and Meta-analysis

- 42 studies (2748 patients)
  - 18 retrospective, 18 prospective, 6 randomized
- Treatment success- sputum culture conversions after subtracting posttreatment microbiologic recurrence
- Treatment success
  - Overall for macrolide containing regimen – 52.8%
  - 3 drug ATS regimen – 61.4%
  - **Above taken for at least a year – 65.7%**

Diel R et al Chest 2018

Monitoring for response to therapy & toxicity

- Monitoring of drug toxicity
    - Bloodwork – CBC, liver function tests (electrolytes, creatinine, BUN)
    - Visual acuity and colour discrimination
    - ECG (QTc)
    - Audiogram
- Repeat sputum samples – every 1-2 months
- Repeat imaging (CXR +/- CT chest)
- Reassess clinical symptoms

Refractory MAC/Treatment failures

- ALIS is first choice

- Intermittent to daily dosing
- Additional drugs: clofazimine, moxifloxacin, linezolid
- New drugs: bedaquiline

- Consult an expert!

TABLE 1 Treatment regimens for *Mycobacterium avium* complex pulmonary disease and *M. abscessus* pulmonary disease

	Treatment regimen	Frequency
M. abscessus		
Macrolide susceptible	Initial phase At least 3 of: 1–2 parenteral: amikacin, imipenem (or cefoxitin), tigecycline 2 oral: macrolide (azithromycin or clarithromycin), clofazimine, linezolid Continuation phase At least 2 of: 2–3 oral or inhaled: macrolide (azithromycin or clarithromycin), clofazimine, linezolid, inhaled amikacin	Daily (or 3 times per week for parenteral aminoglycosides)
Inducible macrolide resistance	Initial phase At least 4 of 2–3 parenteral: amikacin, imipenem (or cefoxitin), tigecycline 2–3 oral: macrolide (azithromycin or clarithromycin), clofazimine, linezolid Continuation phase At least 2 of: 2–3 oral or inhaled: macrolide (azithromycin or clarithromycin), clofazimine, linezolid, inhaled amikacin	Daily (or 3 times per week for parenteral aminoglycosides)

Kumar Eur Resp Rev 2022
Griffith and Daley Chest 2022

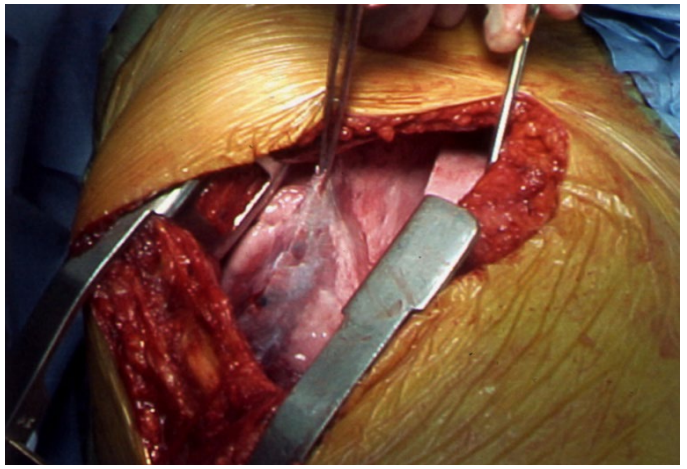
TABLE 2] Treatment Outcomes for Pulmonary *Mycobacterium abscessus* vs *Mycobacterium massiliense*

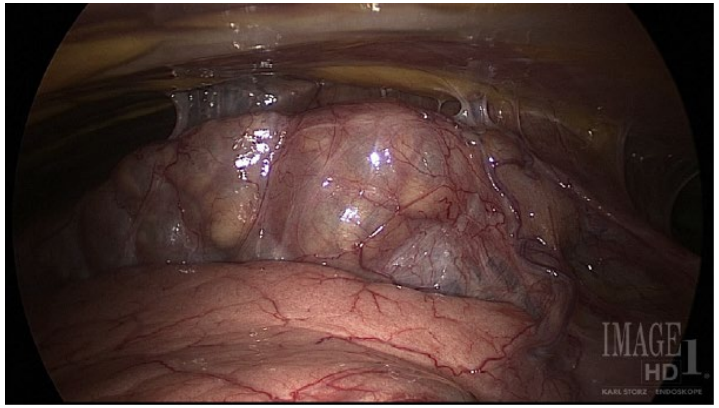
Study	Population	*M abscessus* Subspecies	No.	Sputum Conversion	Failure to Convert	Relapse
Koh et al,[12] 2011	Noncystic fibrosis	*M abscessus*	24	25%	58%	17%
		M massiliense	33	88%	3%	9%
Lyu et al,[13] 2014	Noncystic fibrosis	*M abscessus*	26	42%	27%	31%
		M massiliense	22	96%	0%	5%
Roux et al, [14] 2015	Cystic fibrosis	*M abscessus*	12	25%	…	…
		M massiliense	7	86%	…	…
Park et al,[15] 2017	Noncystic fibrosis	*M abscessus*	19	26%	74%	55%
		M massiliense	17	82%	18%	0%

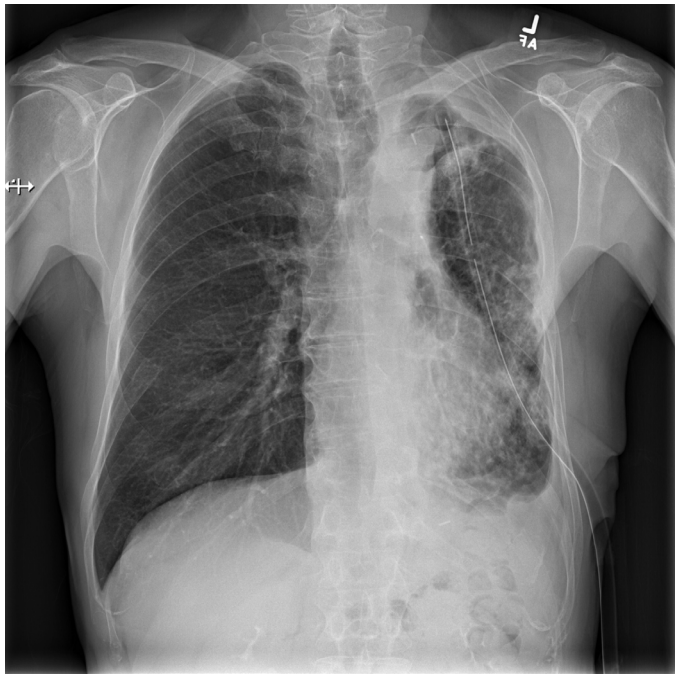
Griffith & Daley Chest 2022

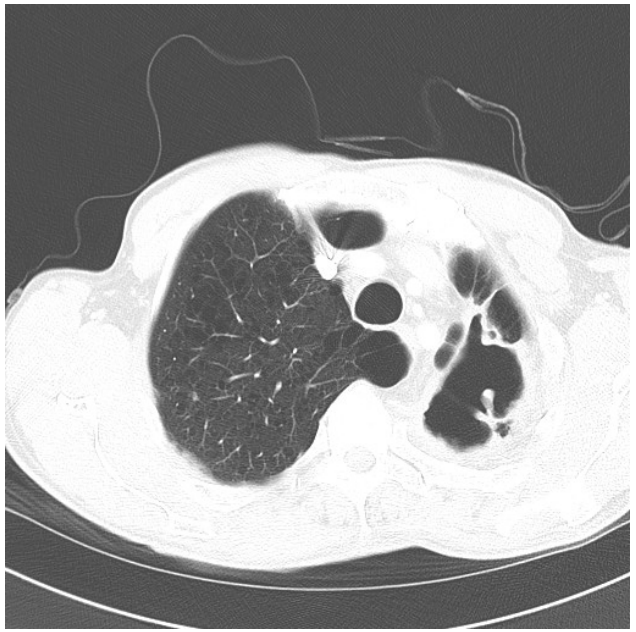
Role of surgery

- Consider in focal cavitary disease
- Failed therapy
- Macrolide resistance
- Collaborative approach (med+surg)









Mitchell Clin Chest Med 2015

Shared Decision Making

- Step 1 – Elicit info from patient first, including their treatment priorities
- Step 2 –Correct misinformation
- Step 3 –Review how he/she/thy does or does not meet NTM-LD diagnostic criteria
- Step 4 - Review risk factors (patient-specific & microbiologic)
- Step 5 – Propose a treatment plan
- Step 6 – Agree on a management plan
- Step 7 – Follow up at each visit regarding treatment plan

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Summary

- NTM-PD is a growing health concern associated with significant clinical and economic burden
- Consider NTM in respiratory/immunocompromised patients
- Diagnosis should consider the clinical and radiologic presentation as well as the species isolated
- The decision to treat should be individualized in patients who meet diagnostic criteria
- Treatment outcomes remain suboptimal and are associated with high rates of reinfection and poor tolerance
- Ongoing research is needed

Thank you!

Questions?