NON-TUBERCULOUS MYCOBACTERIA: UPDATE ON MANAGEMENT

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Financial Disclosures

- PI for clinical trials with Insmed/Aradigm/Novartis/Chiltern (all bronchiectasis/NTM related)
- Consultant (ended 9/2018)
  - AIT Therapeutics
  - Insmed

About NTM

- NTM lung disease is a chronic condition that can significantly increase patient morbidity and mortality.
- The signs and symptoms of NTM lung disease often overlap with the underlying pulmonary condition. Patients with bronchiectasis, COPD, and and other chronic pulmonary disorders are at risk for NTM infection.
- Among the almost 200 different species of NTM identified, the most common pathogens for lung disease are *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium abscessus*.
- **MAC** accounts for more than **80%** of all NTM lung disease cases in the US.
- NTM bacteria are most commonly classified by **growth rate**—either slowly growing (eg, MAC, *Mycobacterium kansasii*, *Mycobacterium xenopi*) or rapidly growing (eg, *Mycobacterium abscessus*, *Mycobacterium fortuitum*, *Mycobacterium chelonae*)

Incidence of NTM

- NTM is rising In the US it is increasing 8%/year. In 2018, it is estimated that 75,000–105,000 patients were diagnosed with NTM lung disease.
- NTM infections are increasing among patients aged 65 and older, a population that's expected to nearly double by 2030
- NTM is now more prevalent than tuberculosis (TB) in the US.
- A US study across 25 states showed that NTM bacteria were found in **nearly 8 out of 10 water samples**
- NTM lung disease varies by geographic area: coastal regions, including Gulf States, have higher rates of infection, accounting for 70% of annual NTM cases in the US

The Epidemiology of Pulmonary Nontuberculous Mycobacteria: Data from a General Hospital in Athens, Greece, 2007–2013

Marios Panagiotou, Andriana I. Papaioannou, Konstantinos Kostikas, Maria Paraskeua,Ekaterini Velentza, Maria Kanellopoulou, Vasiliki Filaditaki, and Napoleon Karagiannidis

- A retrospective review of the demographic, microbiological, and clinical characteristics of patients with NTM culture-positive respiratory specimens from January 2007 to May 2013
- A total of 120 patients were identified with at least one respiratory NTM isolate and 56 patients (46%) fulfilled the microbiological ATS/IDSA criteria for NTM disease.
- Of patients with adequate data, 16% fulfilled the complete ATS/IDSA criteria for NTM disease

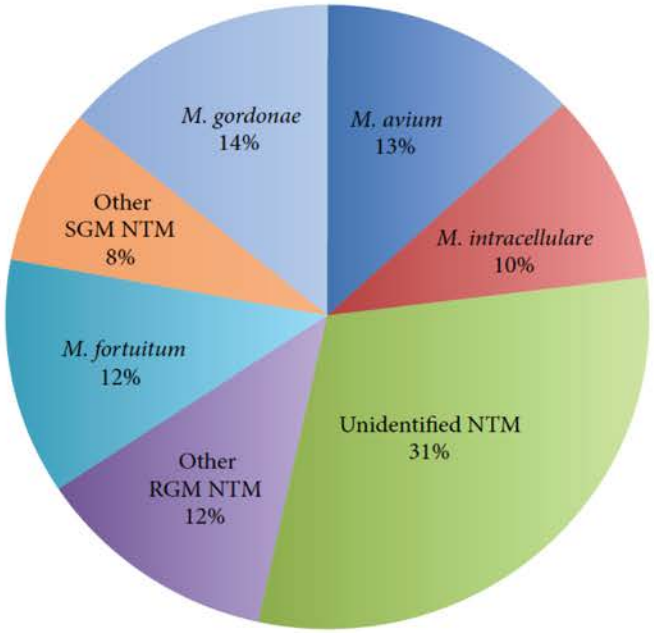


FIGURE 2: Diversity of isolated nontuberculous mycobacteria (NTM). RGM: rapidly growing, SGM: slowly growing.

Incidence of NTM in Greece

The Epidemiology of Pulmonary Mycobacteria:
Data from a General Hospital in Athens, Greece, 2007–2013

- The incidence of pulmonary NTM infection and disease was 18.9 and 8.8 per 100.000 inpatients and outpatients, respectively.
- NTM infection is common in patients with chronic respiratory disease
- However, only a significantly smaller proportion of patients fulfill the criteria for NTM disease

- US rates --A population-based study conducted at Oregon, USA, for 2005-2006 reported the estimated annual pulmonary NTM disease prevalence to be 5.6/100,000 statewide but as high as 15.5/100,000 for those over 50 years of age.
- f/u study- the upper limit 2-year prevalence estimate in those at least 50 years old was 25.7/100,000.

K. L. Winthrop, et al., AJRCCM vol. 182, no.7, pp. 977–982, 2010 and Clin Infect Diseases, vol. 49, no. 12, pp. e124–e129, 2009.

Risk Factors for NTM

Risk Factors	Examples
Pre-existing disease	Non-CF bronchiectasis, CF, COPD, other chronic lung disease
Immunodeficiency syndromes	ALPHA-1 antitrypsin deficiency, immunoglobulin G (IgG) deficiency
Phenotype	Age >65 years, female, low BMI, taller height, vitamin D deficiency, asymptomatic GERD, mitral valve prolapse, thoracic anomalies
Drug treatment	TNF inhibitors, immunosuppressants (e.g. azathioprine, cyclophosphamide, cyclosporine)

Bronchiectasis

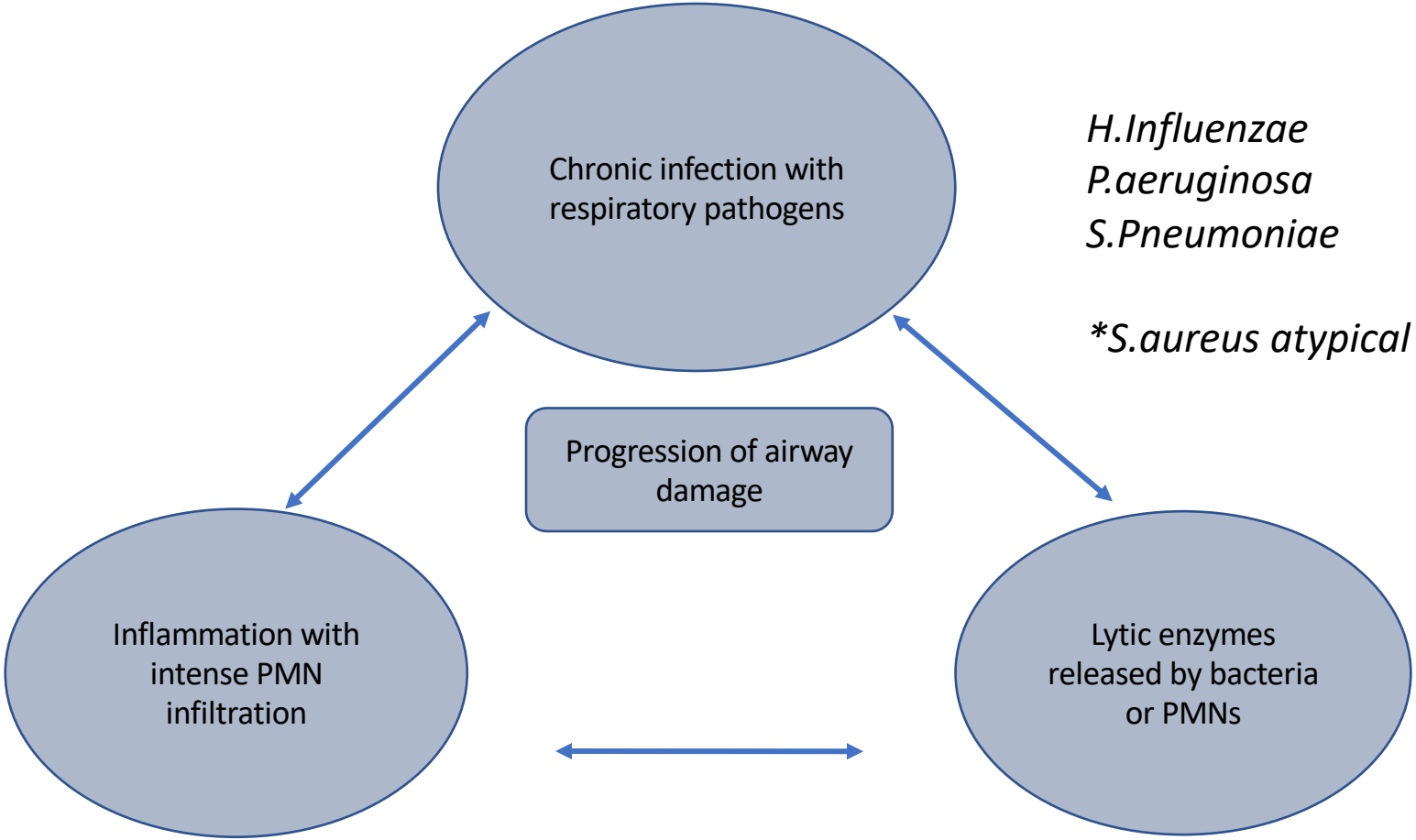
Bronchiectasis

- Syndrome
  - Irreversible dilatation and destruction of bronchi &
  - Inadequate clearance and pooling of mucus in the airways

- Characterized by
  - Persistent microbial infection and inflammatory response
  - Divided into Cystic Fibrosis (CF) and Non-CF forms

Bronchiectasis

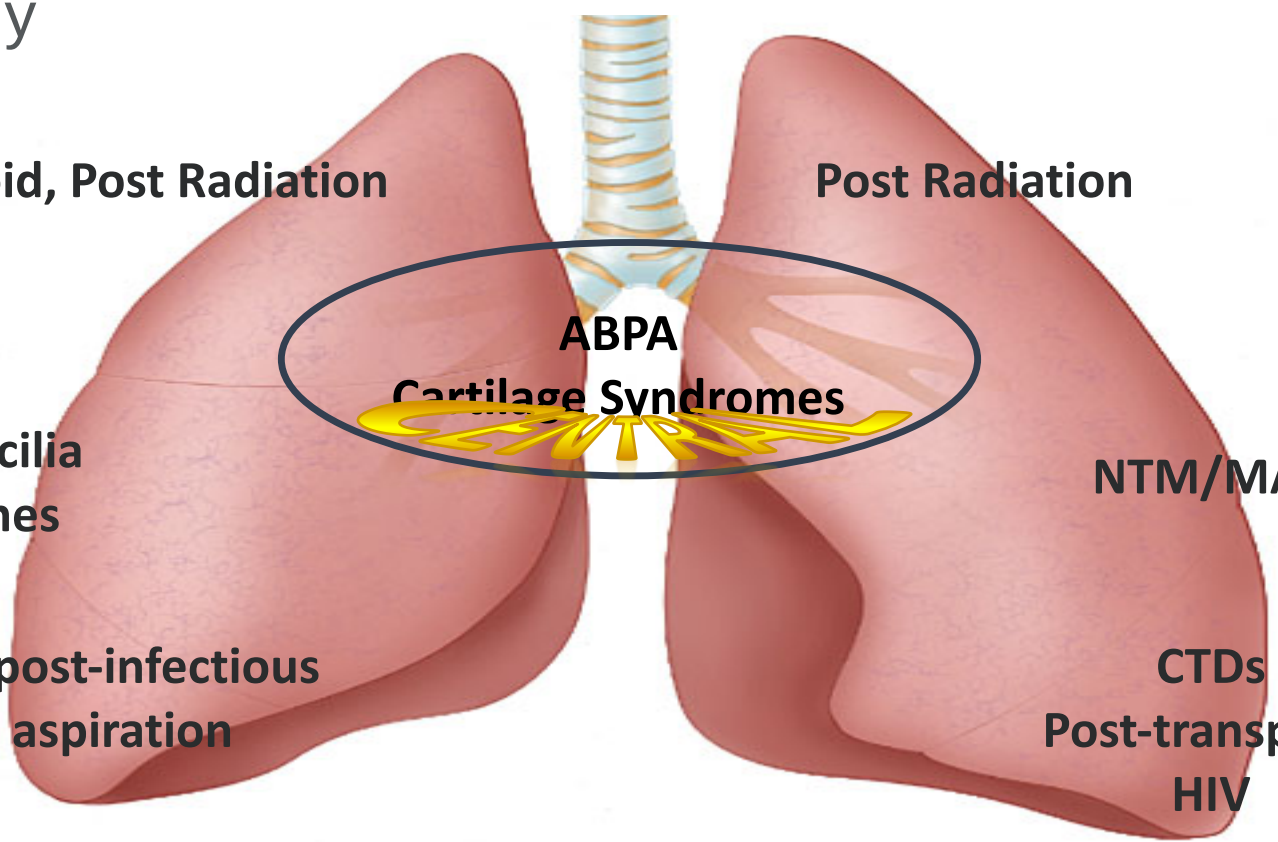
- Final common pathway of a variety of infectious, genetic, autoimmune, developmental and allergic disorders
- Characterized clinically by syndrome of cough, sputum production and recurrent respiratory infections
- Highly heterogeneous in etiology, impact, and prognosis
  - Clinical phenotypes important for treatment strategies
- And radiographically by permanent dilatation of the bronchi


Chronic infection with respiratory pathogens
H.Influenzae
P.aeruginosa
S.Pneumoniae
*S.aureus atypical
Progression of airway damage
Inflammation with intense PMN infiltration
Lytic enzymes released by bacteria or PMNs
Non-CF Bronchiectasis

Etiology

CF, Sarcoid, Post Radiation

Post Radiation



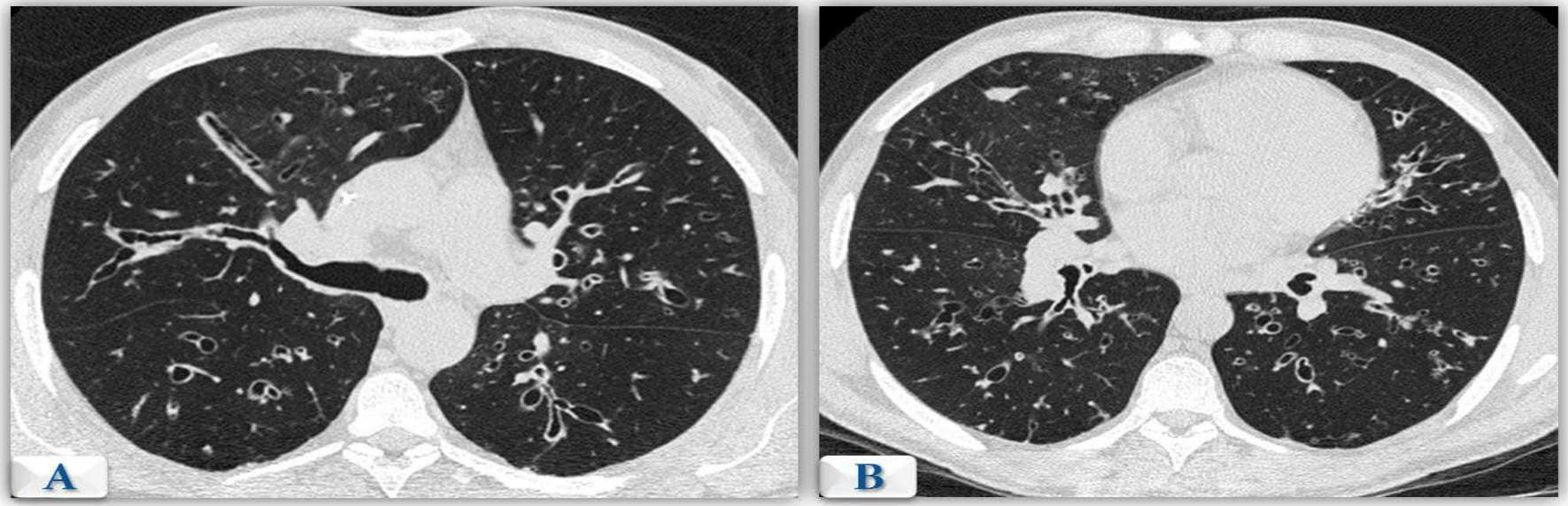
Immotile cilia syndromes

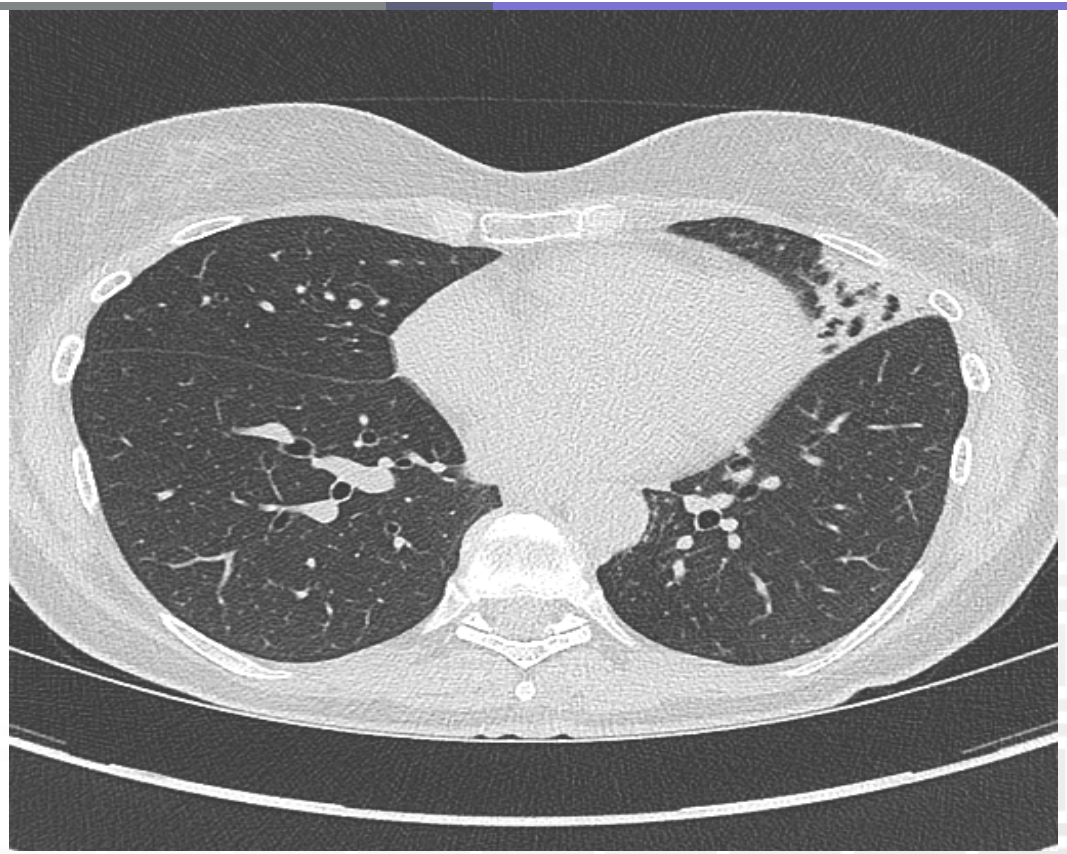
NTM/MAC

Idiopathic, post-infectious
Chronic aspiration

CTDs
Post-transplant
HIV

High-Resolution Computed Tomographic Images of Lungs with Bronchiectasis

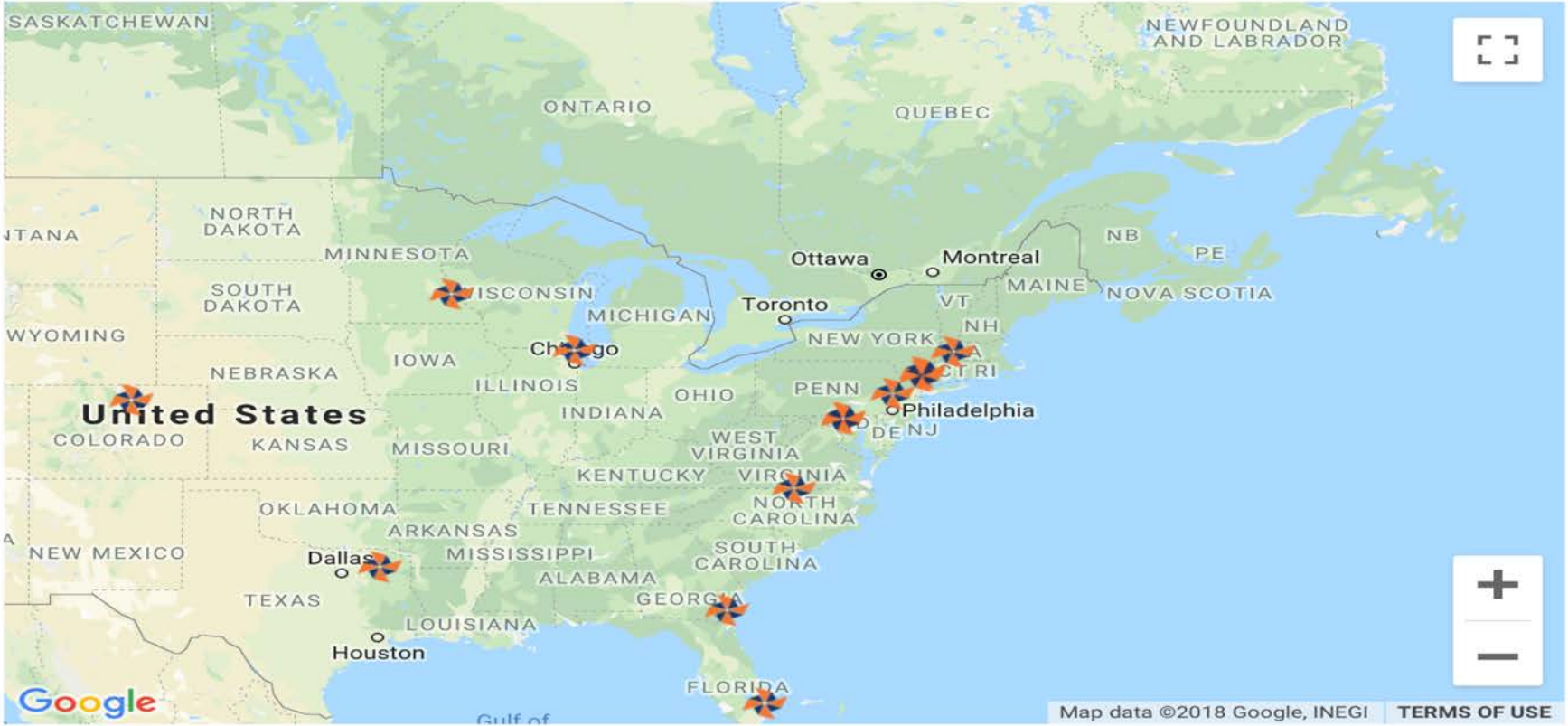




Adult Patient with Bronchiectasis -- A First Look at the US Bronchiectasis Research Registry: Aksamit et al, Chest May 2017

- US Bronchiectasis Research Registry (BRR)
  - 13 sites; Non-CF bronchiectasis patients
  - 1826 patients between 2008-2014; greater than 2500
  - 79% women; 89% white; 60% never smokers
  - Mean age 64
  - 63% with NTM disease

BRONCHIECTASIS RESEARCH CONSORTIUM SITE LISTINGS



*Click the pinwheel on the map to view more information about the site listing.

The EMBARC European Bronchiectasis Registry: protocol for an international observational study

Chalmers, et al ERJ open research 2016

- EMBARC
  - European Multicenter Bronchiectasis Audit and Research Collaboration
  - A Pan-European registry of patients with non-CF bronchiectasis.
  - Goal is to enroll 10,000 patients from across at least 20 European countries by March 2020.
  - Much lower rate of NTM; often lower than 20% in many countries

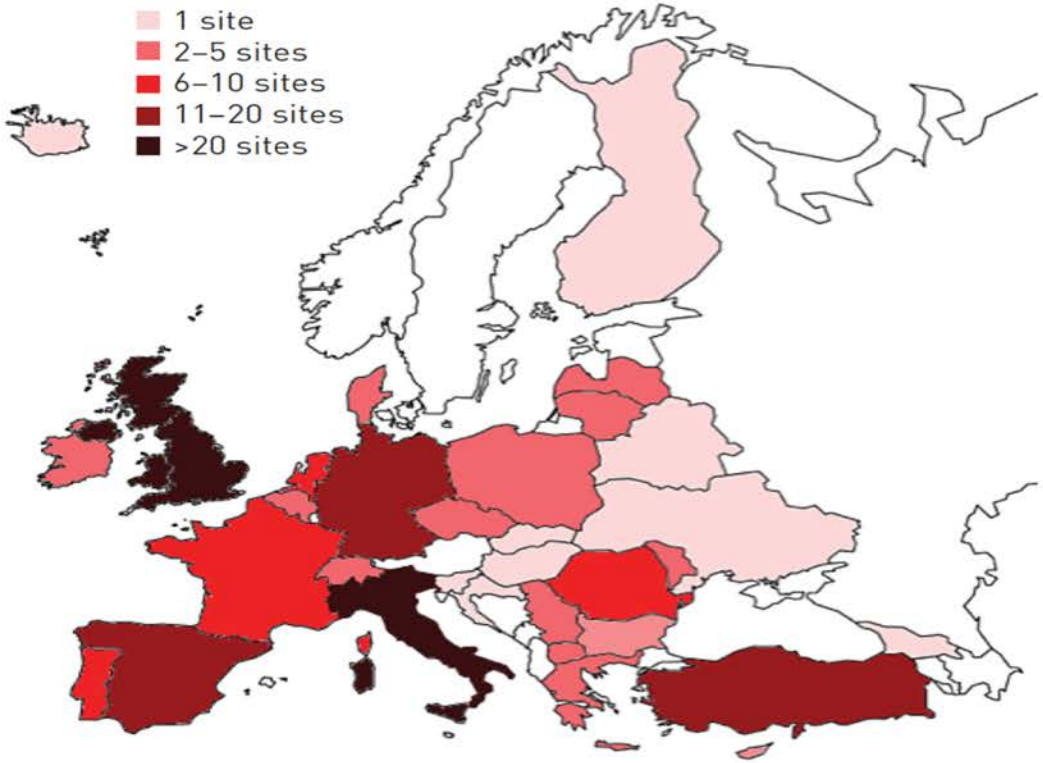


FIGURE 3 Distribution of EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration) sites across Europe.

Question 1

In order to have a diagnosis of NTM disease vs infection you need a chest CT with bronchiectasis and/or nodular disease and/ or cavitary findings and:

a. One positive sputum cultures for NTM
b. Two positive sputum cultures for NTM
c. Any bronchoscopy specimen showing AFB on smear
d. Any of the above

Question 1

In order to have a diagnosis of NTM disease vs infection you need a chest CT with bronchiectasis and/or nodular disease and/ or cavitary findings and:

a. **One positive sputum cultures for NTM**
b. **Two positive sputum cultures for NTM (or one bronchoscopy culture for NTM)**
c. **Any bronchoscopy specimen showing AFB on smear**
d. **Any of the above**

Griffith, et al AJRCCM 2007

NTM: Does Everyone with Disease Require Treatment?

Variables to Consider:

-Age of patient/Causative species of NTM

-Comorbidities/underlying conditions

-Severity of symptoms

-Chest CT scan findings

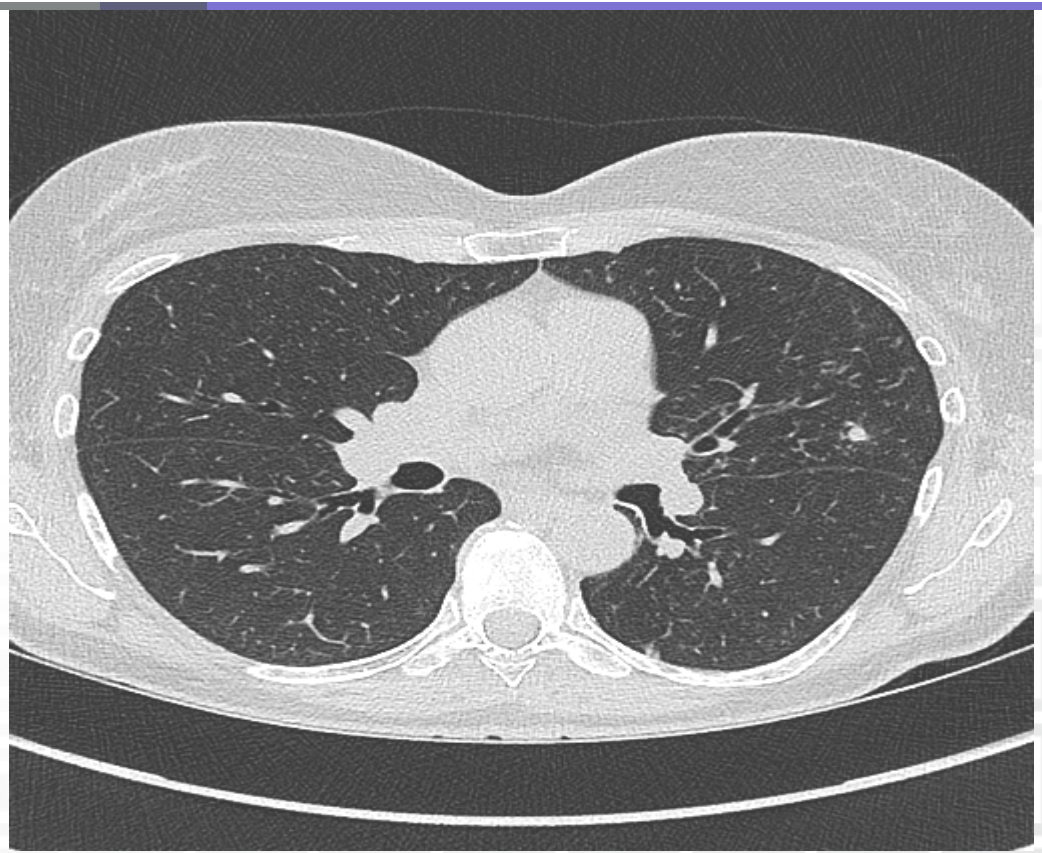
-Patient preferences

Choice of Therapeutic Regimen:

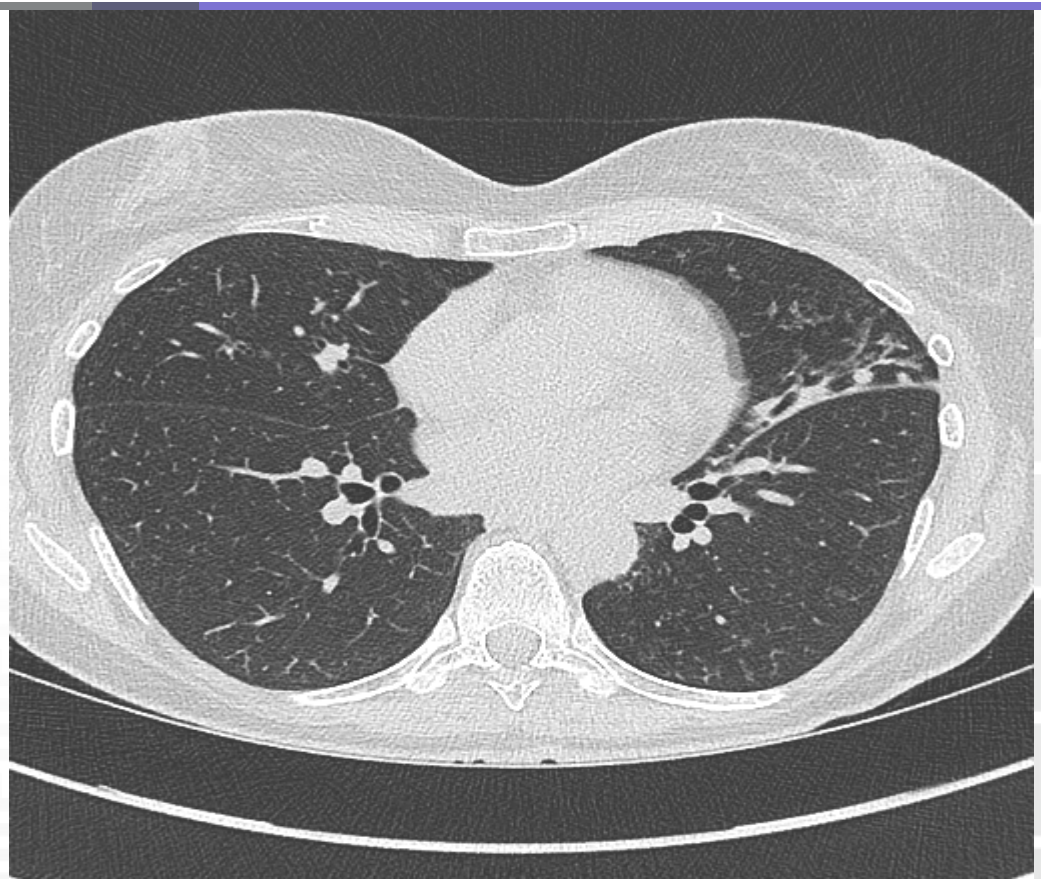
- Nodular vs. cavitary disease
- Patient comorbidities
- Drug-drug interactions and/or intolerance

- 71 year old woman referred for evaluation of bronchiectasis and MAI
- History of CAP in 2014/ scoliosis/GERD
  - CT revealed bronchiectasis and bronchiolitis in lingula and LLL
- **No chronic cough/weight loss/NS or fevers**
- Another episode of PNA in 2017
  - Sputum AFB testing done
  - **Smear +**, culture + for MAC
- **Good functional status**
  - Enjoys dancing and playing tennis
  - Uses an Acapella for airway clearance

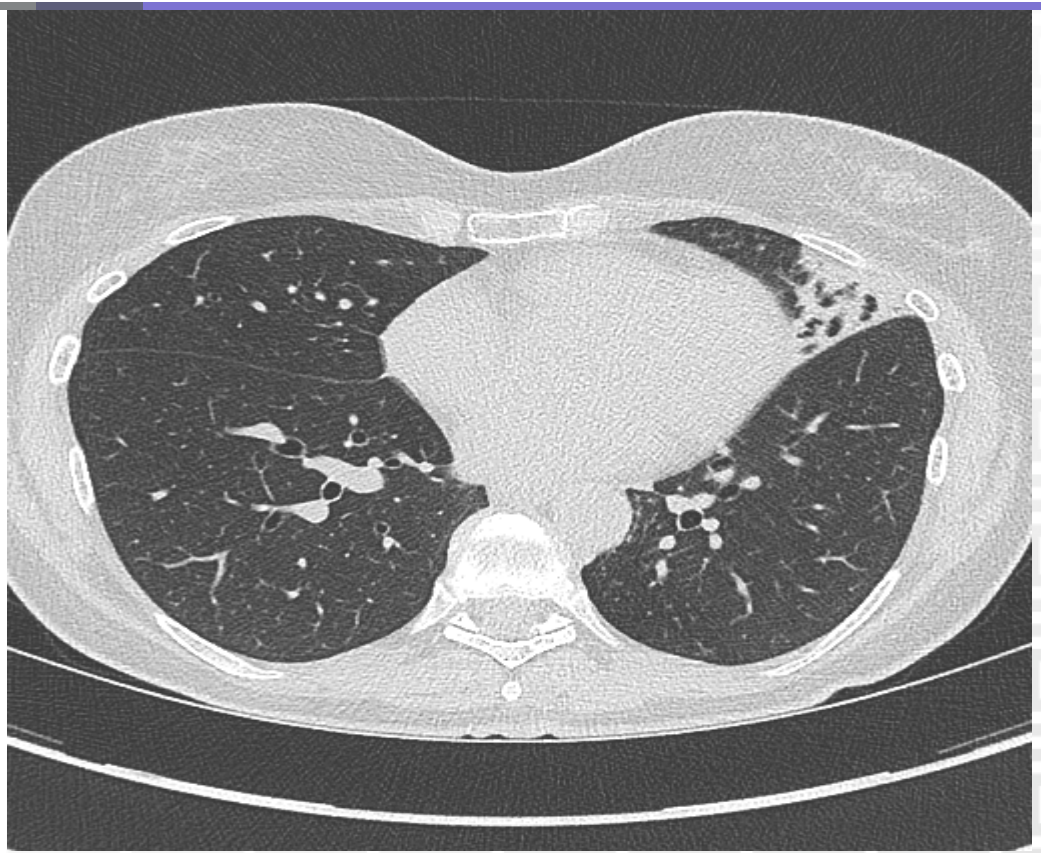
CT in 2014

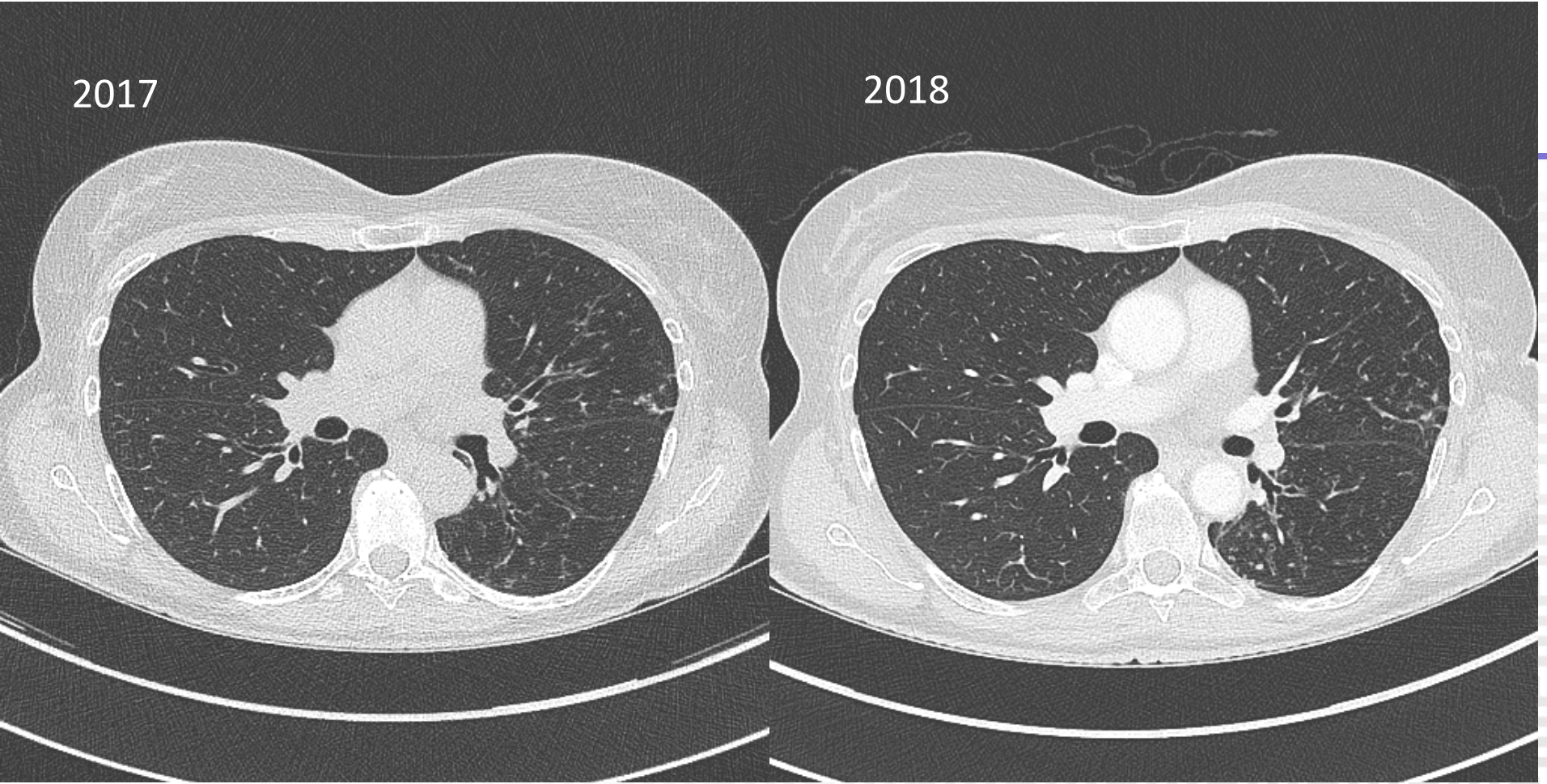


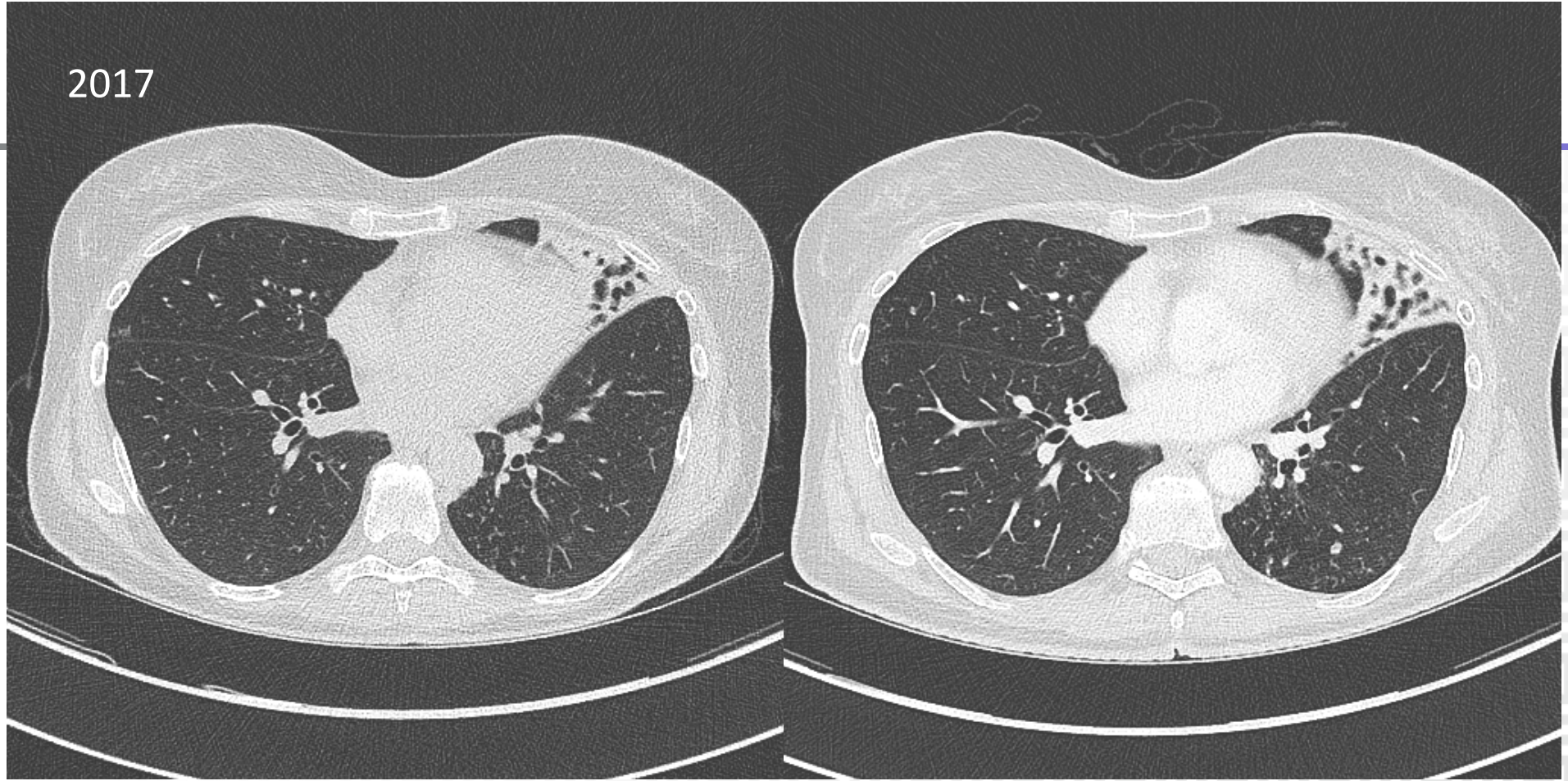
CT in 2014



CT in 2014




2017
2018


2017

Case 1 (cont'd)

- Patient developed mild, productive cough
- Continues to exercise
- Sputum AFB testing still positive
  - Smear +
  - Culture + for MAC

Question 2 – What would you do now?

a) Begin daily treatment with azithromycin, rifampin and ethambutol
b) Begin three times a week treatment
c) Add daily hypertonic nebs and continue Acapella use
d) Refer for surgical resection

Question 2 – What would you do now?

a) Begin daily treatment with azithromycin, rifampin, ethambutol
b) Begin three times a week treatment with azithromycin, rifampin, ethambutol and inhaled amikacin
c) Add daily hypertonic nebs and continue Acapella use
d) Refer for surgical resection

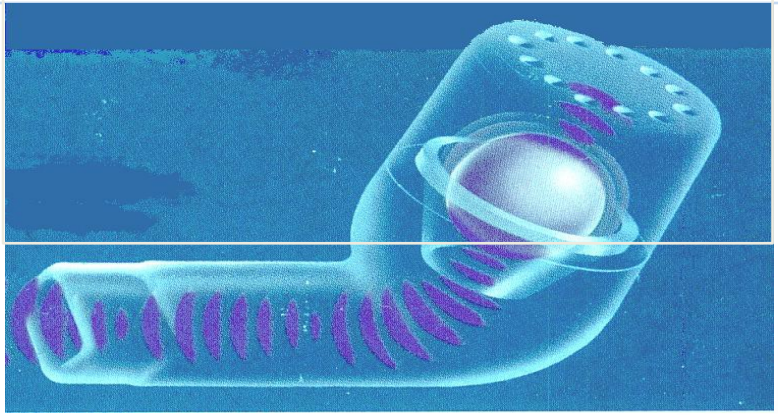
Effects of Chest Physical Therapy in patients with Non-tuberculous mycobacteria. Basavaraj et al 2017

Airway Clearance

- Exercise
- Nebulized Solutions
  - Hyertonic Saline 7%; 3%; normal saline
- Chest percussion Therapy
- Breathing Exercises
- Vibratory PEP (Positive Expiratory Pressure) Devices
- Vest Therapy
- Key is Patient Education and Choice

- **Treating Cough Due to Non-CF and CF Bronchiectasis With Nonpharmacological Airway Clearance– A CHEST Expert Panel Report** **Hill et al., CHEST 2018; 153(4)**

Vibratory PEP



Flutter® Device

Aerobika ™ Device

Acapella™ Device

High Frequency Chest Wall Oscillation (HFCWO)

- **Which is the most appropriate treatment of this symptomatic patient with pulmonary *M. avium* disease based on the ATS/IDSA guidelines?**

- **Question 3**

a. Daily therapy with a macrolide/ethambutol/rifamycin
b. Daily therapy with a macrolide and ethambutol
c. Intermittent 3x/week therapy with macrolide/ethambutol/rifamycin
d. No anti-microbial therapy at this time

- **Question 3**

a. Daily therapy with a macrolide/ethambutol/rifamycin
b. Daily therapy with a macrolide and ethambutol
c. Intermittent 3x/week therapy with macrolide/ethambutol/rifamycin
d. No anti-microbial therapy at this time

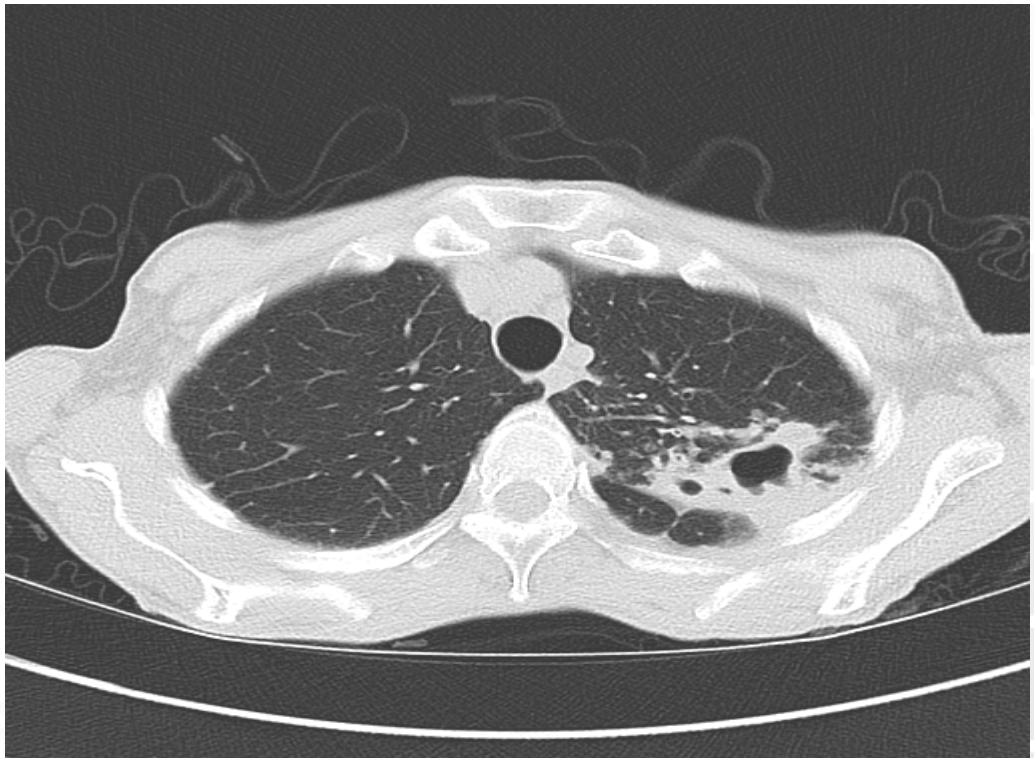
Fibronodular bronchiectasis (Macrolide sensitive)

Medication	dosage	frequency
macrolide	Clari 1000 mg OR azithro 500mg	Three days per week
ethambutol	25mg/kg	Three days per week
rifampin	600mg	Three days per week
aminoglycoside	N/A	

MAC Fibro-nodular Lung Disease: Treatment

- 180 patients
  - Completed > 12 Months of guideline based therapy
  - No differences in clarithromycin vs azithromycin
  - Treatment modification increased in daily (80%) vs intermittent (1%)
  - Treatment success achieved in 84% of patients
  - Microbiologic recurrences in 48% after completion of therapy – 75% reinfection isolates/25% true relapse
    - » Wallace RJ, et al Chest 2014 Aug 146:276-82

- **Which is the most appropriate treatment for *M. Avium* in this patient?**



- **Question 4**

a. Daily therapy with a macrolide/ethambutol/rifamycin
b. Daily therapy with a macrolide/ethambutol/rifamycin + inhaled amikacin
c. Daily therapy with a macrolide/ethambutol/rifamycin + IV amikacin
d. Daily therapy with a macrolide/ethambutol/rifamycin + IV amikacin + surgical resection

- **Question 4**

a. Daily therapy with a macrolide/ethambutol/rifamycin
b. Daily therapy with a macrolide/ethambutol/rifamycin + inhaled amikacin
c. Daily therapy with a macrolide/ethambutol/rifamycin + IV amikacin
d. Daily therapy with a macrolide/ethambutol/rifamycin + IV amikacin + surgical resection

MAC Fibrocavitary

medication	dosage	frequency
macrolide	Clari 500mg/BID Azithro 250 mg	daily
ethambutol	15 mg/kg	daily
rifampin	600 mg	daily
Aminoglycoside Localized	amikacin IV Surgery	uncertain

Question 5

- **Which of the following antibiotics sensitivity/MIC profiles are important when treating patients with pulmonary mycobacterium avium disease?**

a. azithromycin
b. amikacin
c. Rifampin
d. A and B
e. A, B and C

Question 5

- **Which of the following antibiotics sensitivity/MIC profiles are important when treating patients with pulmonary mycobacterium avium disease?**

a. azithromycin
b. amikacin
c. Rifampin
d. A and B
e. A, B and C

- Griffith et al., Clinical and molecular analysis of macrolide resistance In MAI lung disease Am J Respir Crit Care Med 2006
- Moon et al., Clinical characteristics, treatment and outcomes, and resistance mutations associated with macrolide-resistance MAC lung disease Antimicrob Agents Chemother 2016
- Brown-Elliott, et al., In vitro activity of amikacin against isolates of MAC with proposed breakpoints and finding of a 16S r RNA gene mutation in treatd isolates J Clin Microbiol 2013

Question 6

- **Which of the following regimens has been shown to promote macrolide resistance?**

a. Azithromycin/ethambutol/rifamycin
b. Azithromycin/ethambutol
c. Azithromycin/quinolone
d. Azithromycin/ethambutol/clofazimine

Question 6

- **Which of the following regimens has been shown to promote macrolide resistance?**

a. Azithromycin/ethambutol/rifamycin
b. Azithromycin/ethambutol
c. Azithromycin/quinolone
d. Azithromycin/ethambutol/clofazimine

- Development of macrolide resistance with macrolide- quinolone regimens, Griffith, et al Am J resp Crit Care Med 2006
  - Fluoroquinolone usage-despite lack of in vitro or in vivo efficacy
- Poor adherence to management guidelines in NTM pulmonary disease van Ingen, et al Eur Respir J 2017 Research letter
  - Survey 6 countries- France, Germany, Italy, Spain, UK and Japan
  - Only 16.9% of all the 746 treated MAC-PD patients received greater than 6 months of a macrolide-rifamycin-ethambutol regimen.
  - For MAC-PD, patients received macrolides (76%), rifamycins (67%), ethambutol (56%) and quinolones (56%)
- US experience " Lack of adherence to evidence-based treatment guidelines for NTM lung disease" Adjemian, et al Ann Am Thoracic Soc 2014;11:9-16
  - 13% received guideline compliant treatment

Question 7

Treatment for NTM infection should be continued for how long following a negative sputum AFB culture?

- 3 months
- 6 months
- 12 months
- 24 months

Question 7

Treatment for NTM infection should be continued for how long following a negative sputum AFB culture?

- 3 months
- 6 months
- 12 months
- 24 months

Other Options for Treatment in Recalcitrant or Difficult to Treat Patients

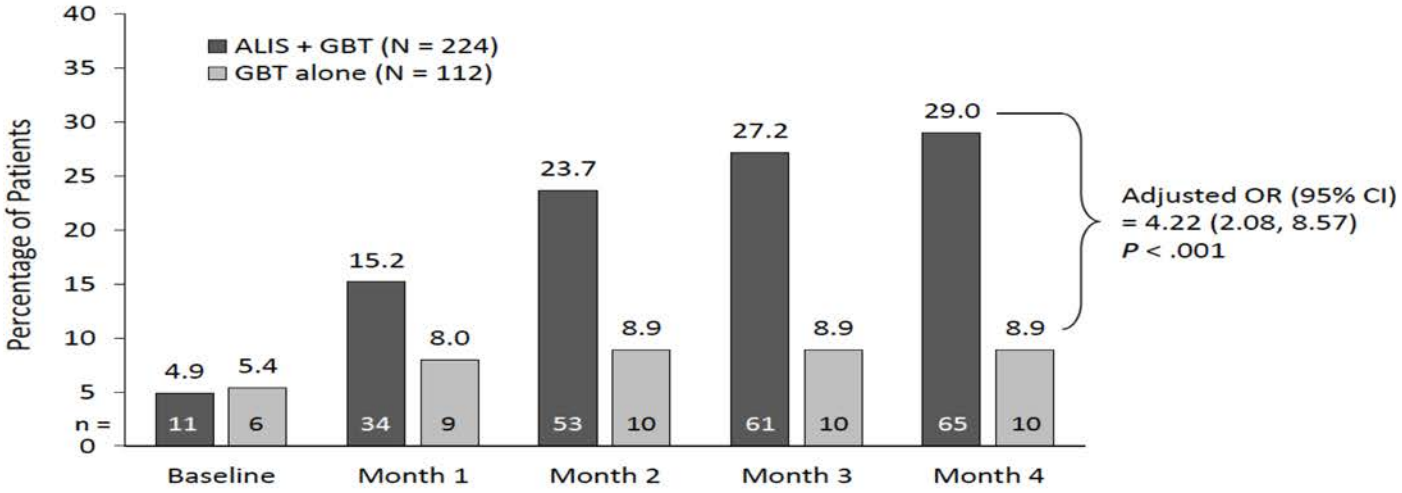
- **Liposomal Amikacin (ALIS)**
- **Clofazimine**
- **Bedaquiline**
- **Oxazolidinones**
- **Avibactams**
- **Surgery**
- **? Inhaled Nitric Oxide**
- **? Phage Therapy**

Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by Mycobacterium avium Complex (CONVERT): A Prospective, Open-Label, Randomized Study

Griffith, et al Am J Resp Crit Care Med Sept 2018

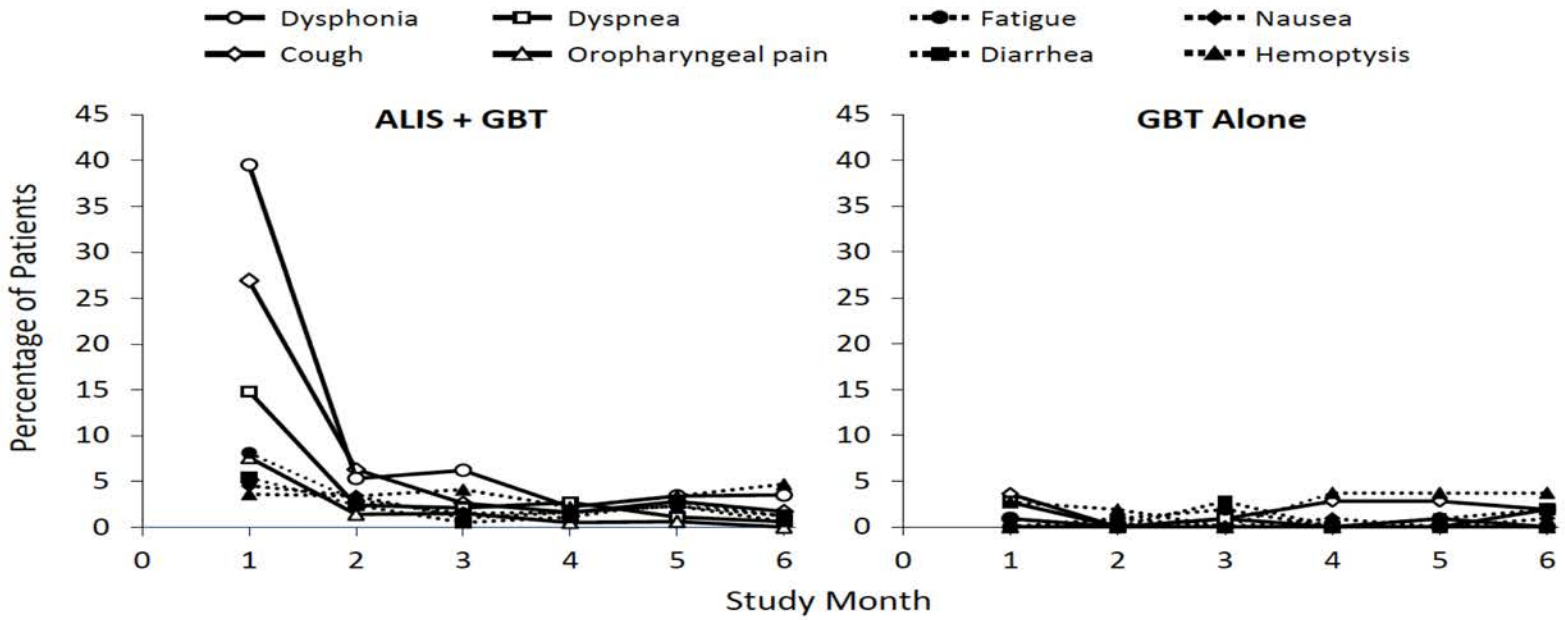
- 336 adults with amikacin-susceptible MAC lung disease and MAC-positive sputum cultures despite >/= 6 months of stable guideline based therapy(GBT)
- Assigned 2:1 to receive ALIS +GBT vs GBT alone
- Daily therapy of ALIS 590mg
- Primary endpoint was culture conversion defined as 3 consecutive monthly MAC-negative sputum cultures by month

Sputum Culture Conversion by Study Month – ITT Population



Griffith, et al Am J Resp Crit Care Med Sept 2018

Figure 5. Onset of the Most Frequent Adverse Events Over Time – Safety Population



Griffith, et al Am J Resp Crit Care Med Sept 2018

Question 8

- **Addition of clofazimine to a multi-drug regimen for pulmonary NTM disease results in:**

a. A significant increase in side effects
b. Decreased sputum conversion rates
c. Competitive outcomes compared to standard therapy
d. Cardiac adverse events related to Qt prolongation

Question 8

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Jarand J, et al. CHEST 2016

Martinino, et al CHEST 2017

Surgery

- **Indications for surgery**: medication unresponsive (drug resistant; large cavities); hemoptysis; uncontrolled symptoms; ? Debulking of disease
- **Safety** -- Mitchell, J Ann Thorac Surg 2008; Eur Journ CV surg 2011
- **Microbiologic efficacy –** Griffith AJRCCM 2006; Nelson Ann Thor Surg 1998; Griffith AJRCCM 1993

  - ***M abscessus* disease treatment success**
    - Jeon 2009 -- 58% (med) vs 88% (med + surg)
    - Jarand 2011 – 39% (med) vs 65% (med +surg)

M. abscessus group

Mycobacterium abscessus

"Pleased to Meet You, Hope You Guess My Name..."

David E. Griffith[1], Barbara A. Brown-Elliott[2], Jeana L. Benwill[1,2], and Richard J. Wallace, Jr.[1,2]

Ann Am Thorac Soc. 2015 Mar;12(3):436-439

M. abscessus group

Table 1. Taxonomic/nomenclature designations for "*Mycobacterium abscessus*" and associated genetic and phenotypic features

Name	Complete 16S rRNA Gene Sequence	*rpo β* Gene Sequence	*erm*(41) Gene Sequence	*erm* (41) Functional	Whole-Genome Sequence
M. abscessus or *M. abscessus* subsp. *abscessus* or *M. abscessus sensu stricto*	Identical to *M. bolletii* and *M. massiliense*	Unique to *M. abscessus*	Unique to *M. abscessus*	Yes*	Unique to *M. abscessus*
M. bolletii or *M. abscessus* subsp. *bolletii*	Identical to *M. abscessus* and *M. massiliense*	Unique to *M. bolletii*	Unique to *M. bolletii*	Yes	Unique to *M. bolletii*
M. massiliense or *M. abscessus* subsp. *massiliense*	Identical to *M. abscessus* and *M. bolletii*	Unique to *M. massiliense*	Unique to *M. massiliense*	No	Unique to *M. massiliense*

Question 9 – In addition to identification of subspecies, what pharmacokinetic and/or pharmacogenomic info must be confirmed when treating *M. abscessus*?

a) Duration of incubation for macrolide sensitivity testing
b) Presence of A1408G point mutation in the 16S rRNA gene
c) Presence of *erm*(41) gene
d) Cefoxitin MIC level
e) a) and c)
f) b) and d)

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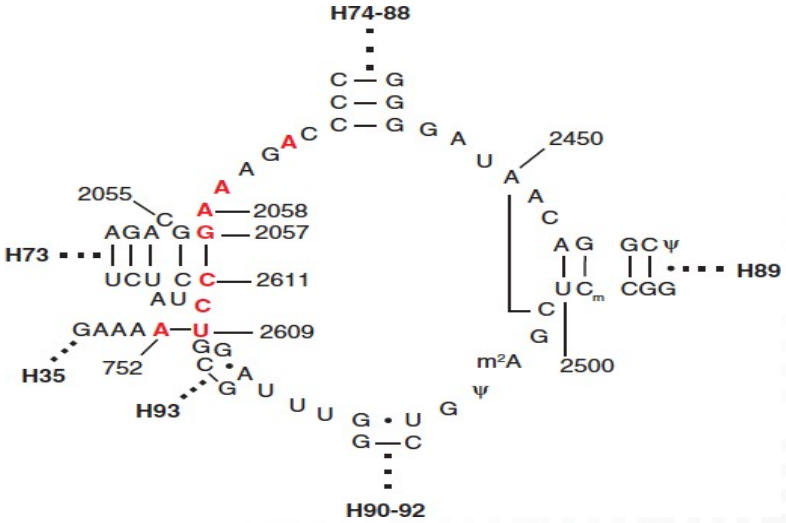
e) a) and c)
f) b) and d)

Constitutive (mutational) macrolide resistance



23S rRNA, domain V

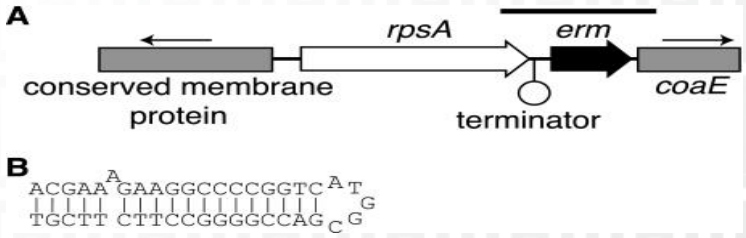
- Mutation in region of the *rrl* gene encoding the peptidyltransferase domain of 23S rRNA
- Results in increased MIC as measured on day 3 of incubation

Wallace RJ, et al. AAC 1996;40:1676
Nash KA, et al. AAC 2009;53:1367

Inducible macrolide resistance

Wallace RJ, et al. AAC 1996;40:1676; Nash KA, et al. AAC 2009;53:1367

- Erythromycin ribosomal methylase gene, *erm*(41) modifies the binding site for macrolides resulting in resistance in presence of macrolide
- Functional gene present in most *M. abscessus* subspecies *abscessus* and *bolletii*
  - Approximately 10-20% of subspecies *abscessus* also have a nonfunctional gene (T to C substitution at position 28)
- Truncated, nonfunctional gene in *M. abscessus* subspecies *massiliense*

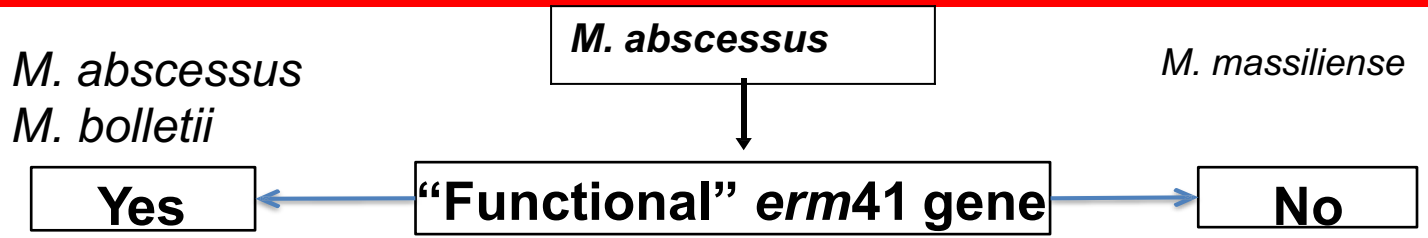


M. abscessus

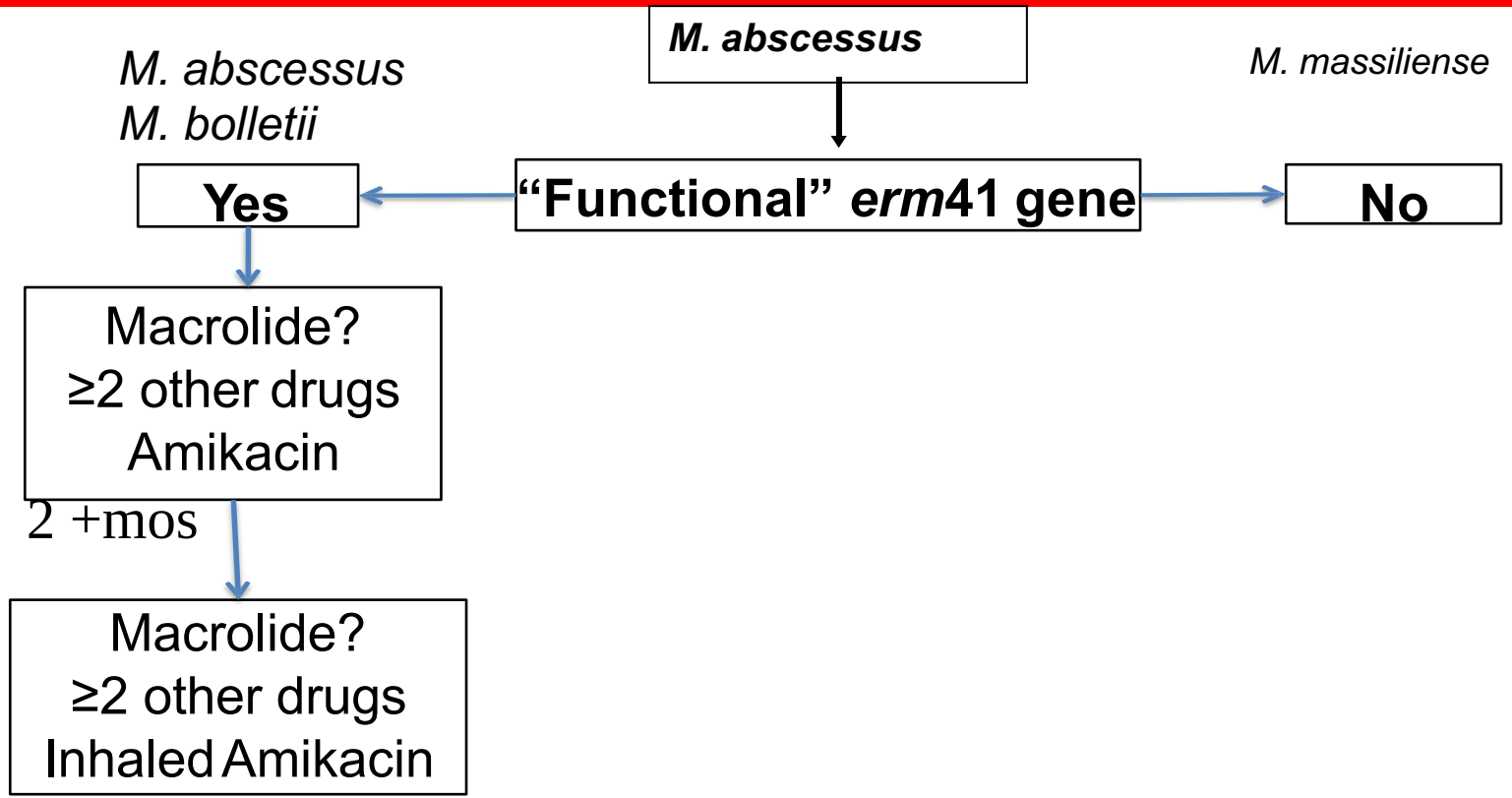
Drug	MIC Range	MIC50	MIC90	Susceptibility
Amikacin	0.125-64	4	816	90-98%
Cefoxitin	16-256	32	32	32-99%
Ciprofloxacin	0.064-64	4-32	16-32	1-57%
Clarithromycin	0.032-64	0.25-1	2-16	78-100%
Clofazimine	<0.25-1	≤0.5	1.0	82-90%
Imipenem	<0.5-256	4-16	8-128	13-73%
Linezolid	0.5-64	16	32	43%
Moxifloxacin	0.064-32	2-32	2-32	6-73%
Tigecycline	0.064-24	0.5-3	2-12	24-100%

Park S, et al. J Korean Med Sci 2008;23:49-52 Nie W, et al. Int J Infect Dis 2014;25:170-174
Huang YC et al. J Micro, Immunol Infect 2010;43:401-406
Yoshida S, et al. Int J Infect 2013;42:226-231

Treatment of *M. abscessus*

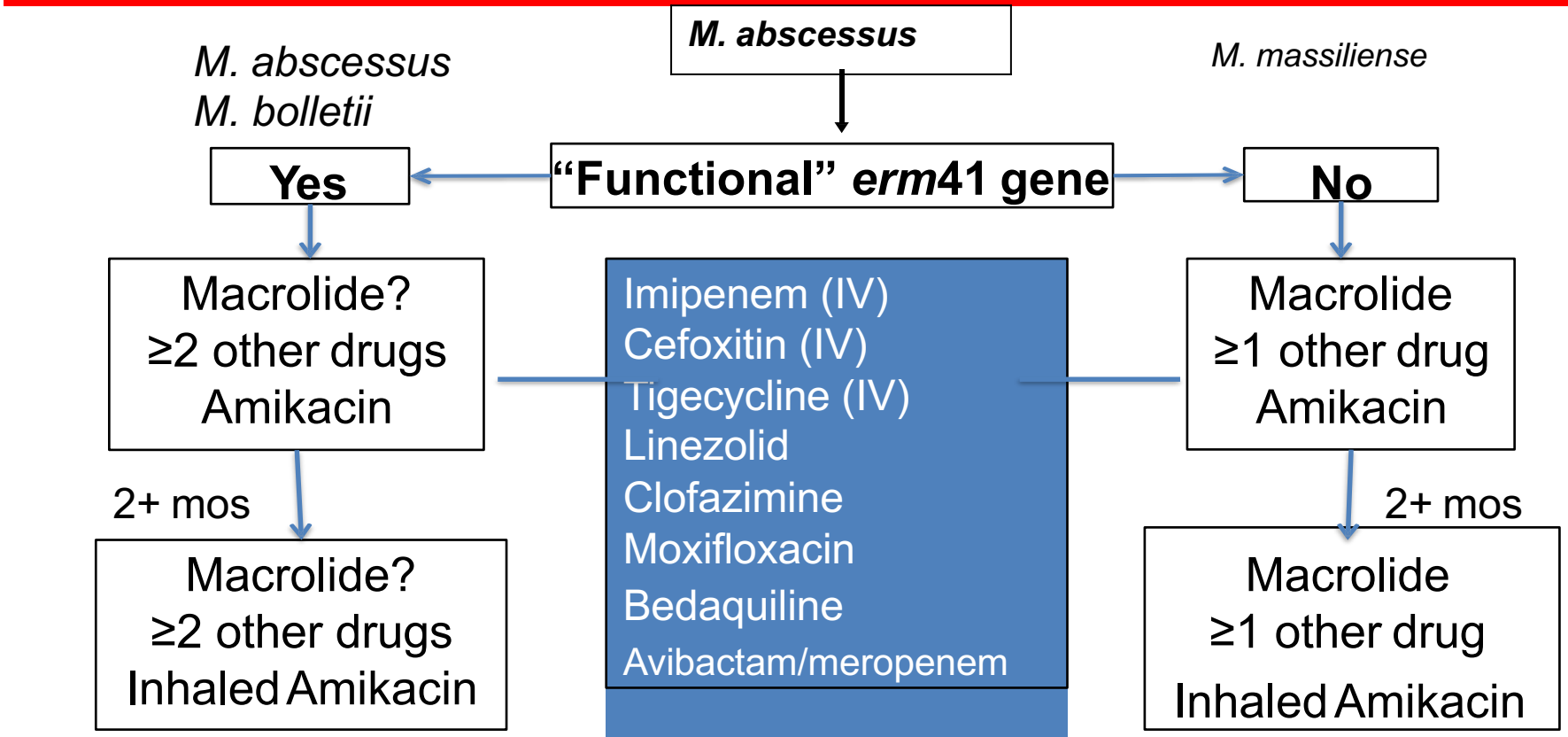


Treatment of *M. abscessus*



Treatment of *M. abscessus*

(Duration 12 months culture negativity)



Question 10 – In addition to a GI work-up for silent aspiration, what testing for an underlying cause of bronchiectasis should be considered in a young adult without a history of recurrent/severe lung infections?

a) Aspergillus IgE and/or IgG titers
b) Sweat chloride level measurement
c) Immunoglobulin level measurement
d) Ciliary function testing
e) All of the above

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Points To Remember

- NTM lung disease is increasing
- Diagnosis and treatment of disease relies on symptoms; CT scan and respiratory culture analysis
- Basis of therapy in patients with NTM/bronchiectasis is airway clearance followed by
  - Intermittent therapy with macrolide/ethambutol/rifamycin for nodular disease and daily therapy for more severe disease/cavitary disease
- Sensitivity data for macrolides and amikacin is important in patients with MAC disease; recurrences can be relapses or reinfections

Points To Remember

- In recalcitrant disease consider additional therapies such as ALIS or clofazimine.
- Consider surgery early on in localized disease
- Monitor sputums regularly and treat for one year after culture negativity
- For cases of *M abscessus* be sure to know your species, erm gene status and sensitivities
- Refer cases to experienced centers for consultation early in the treatment plan

NYU Langone Health

Division of Pulmonary, Critical Care, and Sleep Medicine

THANK YOU!