FDA Public Meeting on
Nontuberculous Mycobacterial Lung Infection:
Patient-Focused Drug Development

Epidemiology & Natural History of NTM Lung Infections

Kenneth N Olivier, MD, MPH
Cardiovascular & Pulmonary Branch/NHLBI
Oct 15, 2015

National Heart, Lung, and Blood Institute

NTM Epid…historic

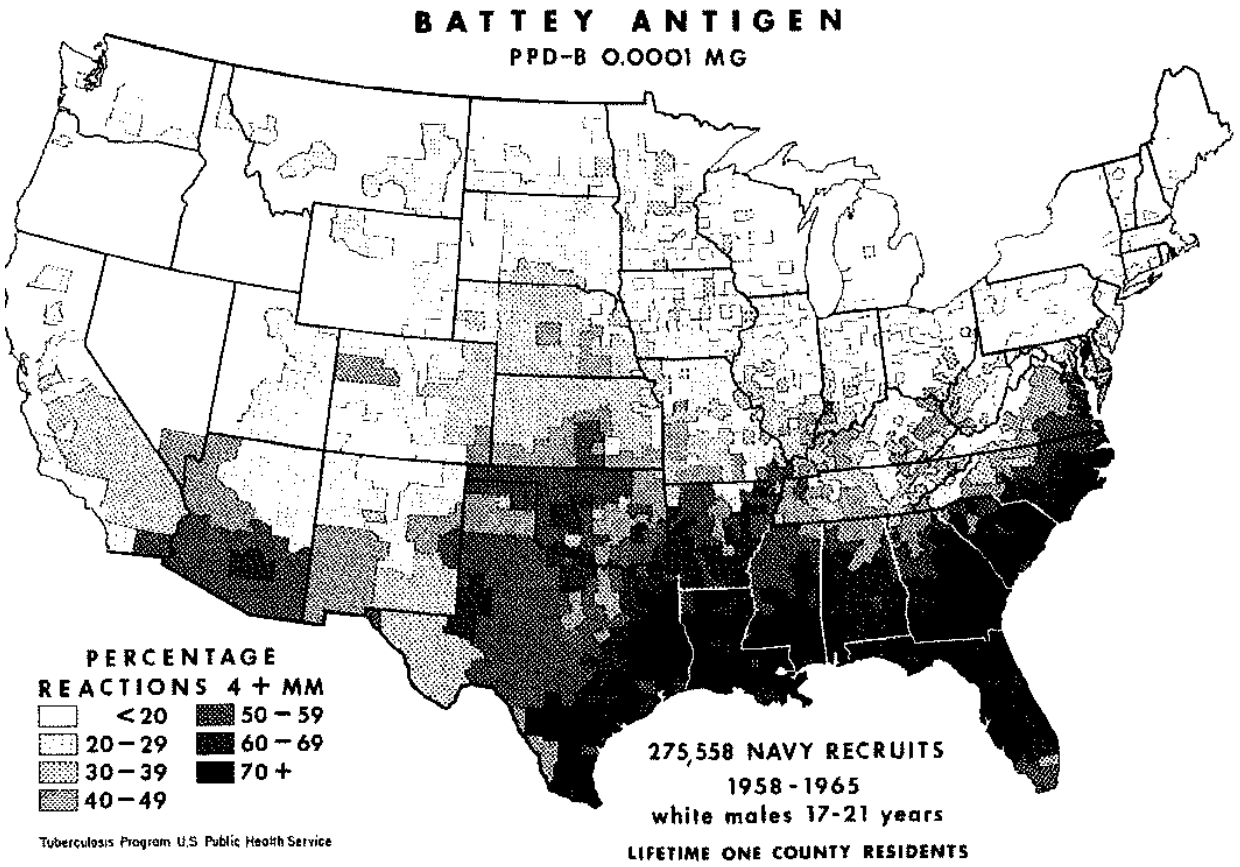
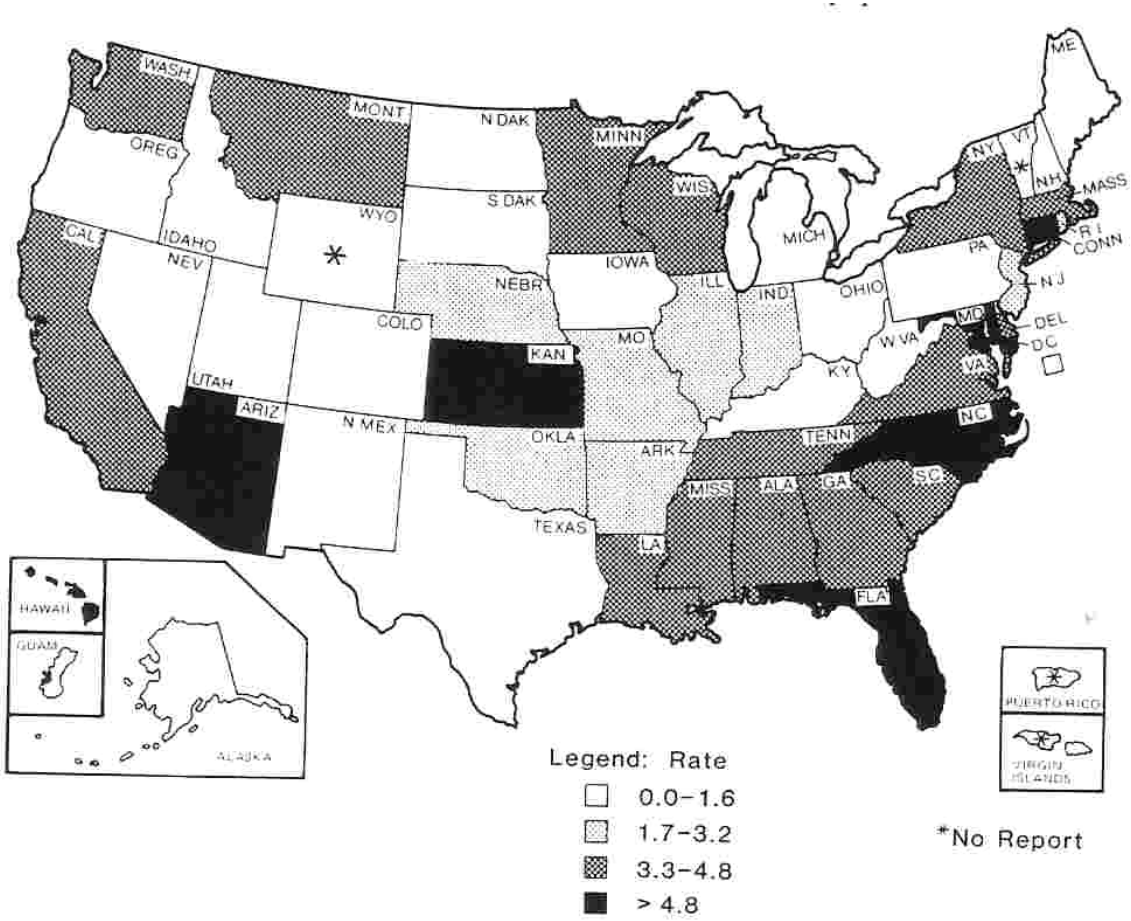


FIG. 11. Geographic variation in the frequency of reactors to 0.0001 mg PPD-B.

Edwards. *Am Rev Respir Dis* 1969;99:1–132

NTM Epid…historic



Prevalence *M. avium* complex/100,000 by state
Good. J Infect Dis 1982; 146:829-833

Nontuberculous Mycobacterial Lung Disease Prevalence at Four Integrated Health Care Delivery Systems

D. Rebecca Prevots[1], Pamela A. Shaw[2], Daniel Strickland[3], Lisa A. Jackson[4], Marsha A. Raebel[5], Mary Ann Blosky[6], Ruben Montes de Oca[1], Yvonne R. Shea[7], Amy E. Seitz[1], Steven M. Holland[1], and Kenneth N. Olivier[1]

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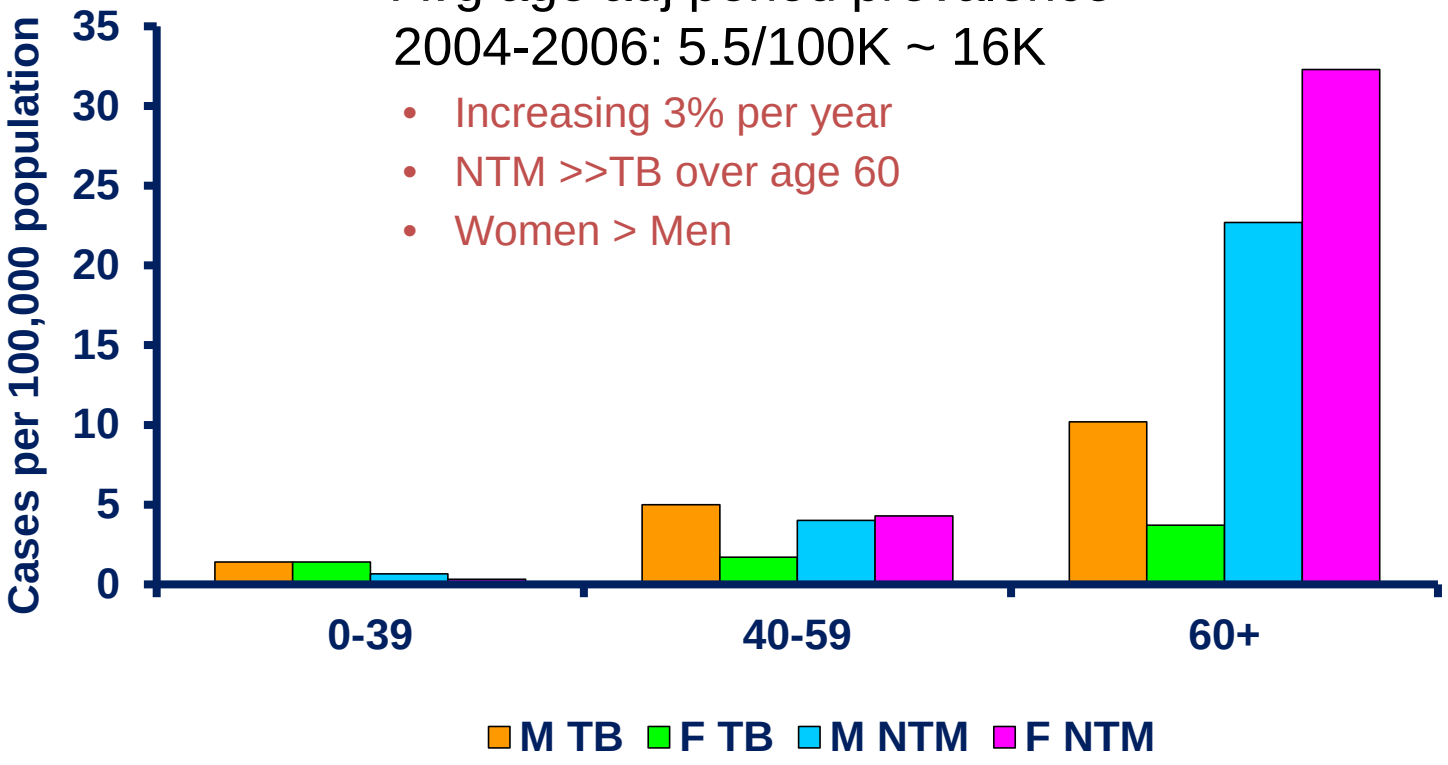
  - Increasing 3% per year
  - NTM >>TB over age 60
  - Women > Men

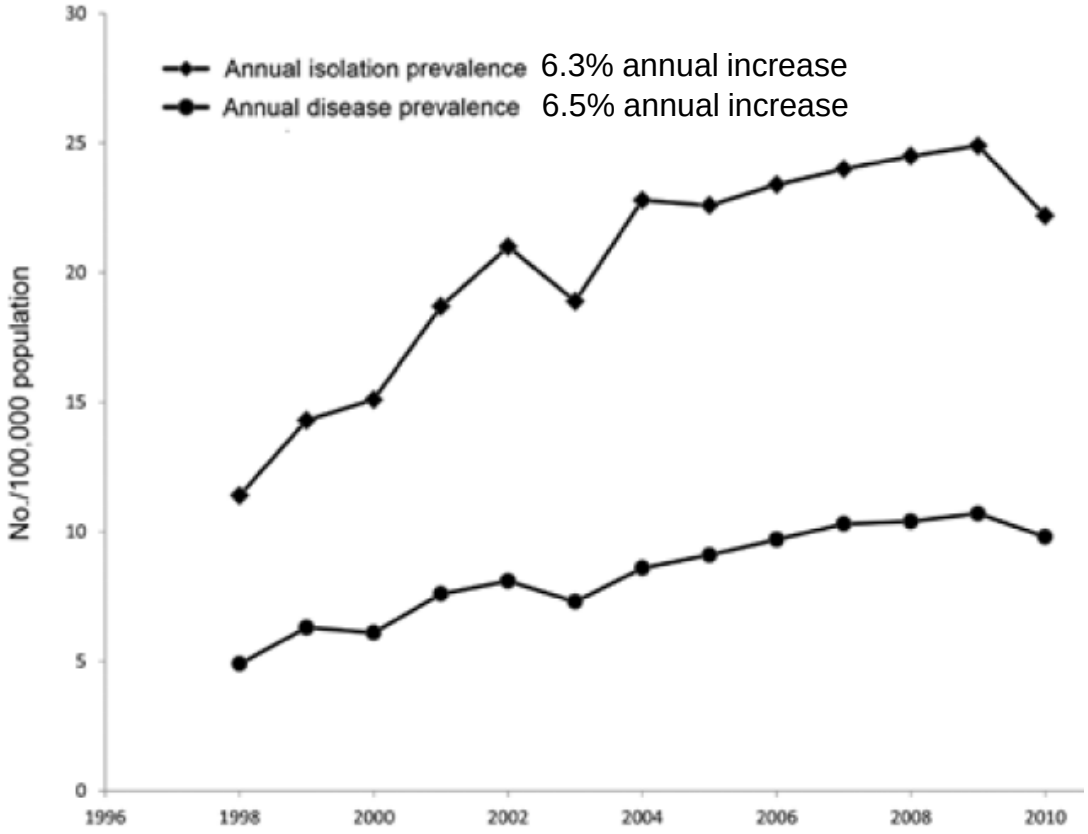


Am J Respir Crit Care Med 2010

Pulmonary Nontuberculous Mycobacterial Disease, Ontario, Canada, 1998–2010

Theodore K. Marras, David Mendelson, Alex Marchand-Austin, Kevin May, and Frances B. Jamieson

- Retrospective study Ontario
- Case = ≥2 pos sputum or 1 bronch/bx
- Species in 2010
  - Mac 12.2/100K
  - M. xenopi 3.9/100K
  - M. abscessus 0.6/100K



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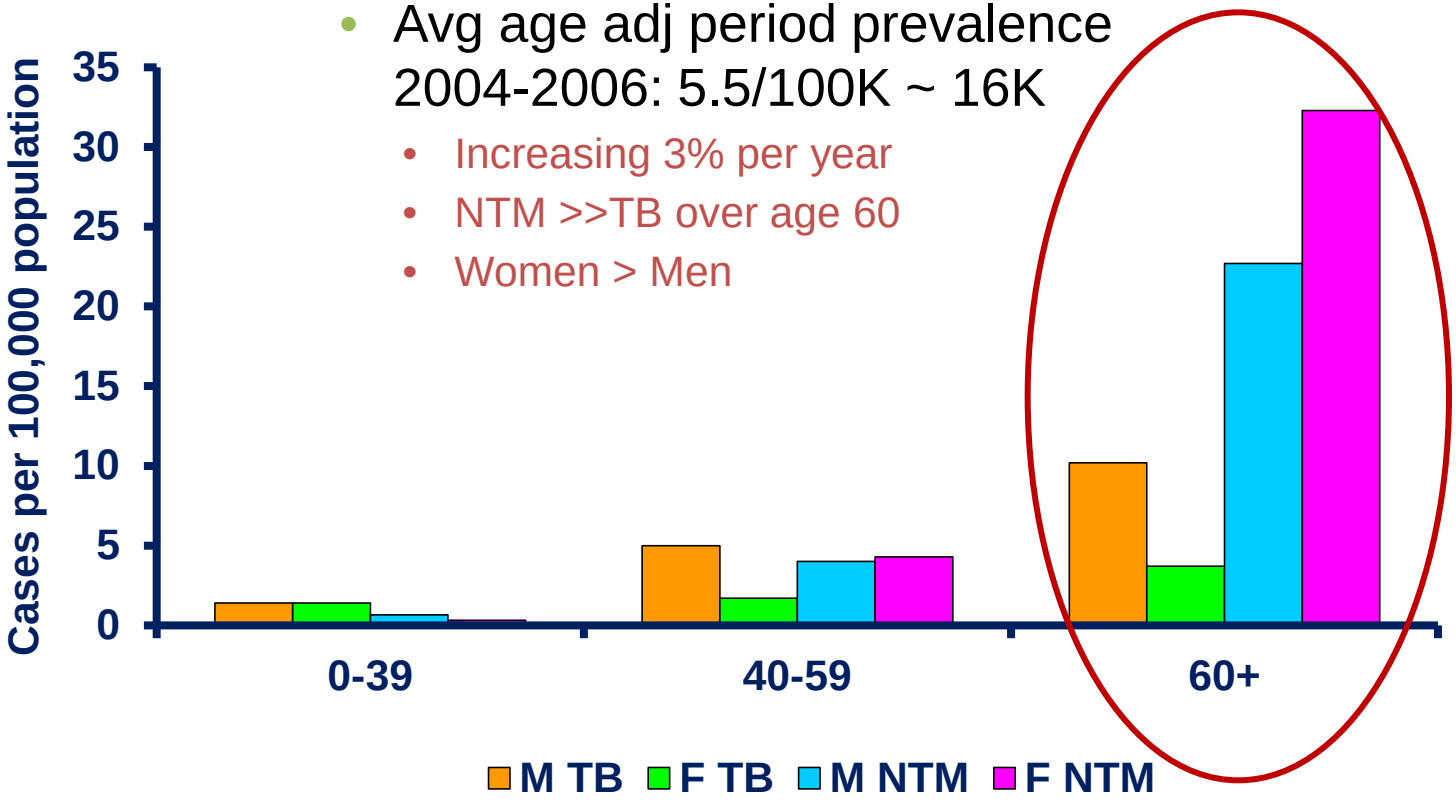
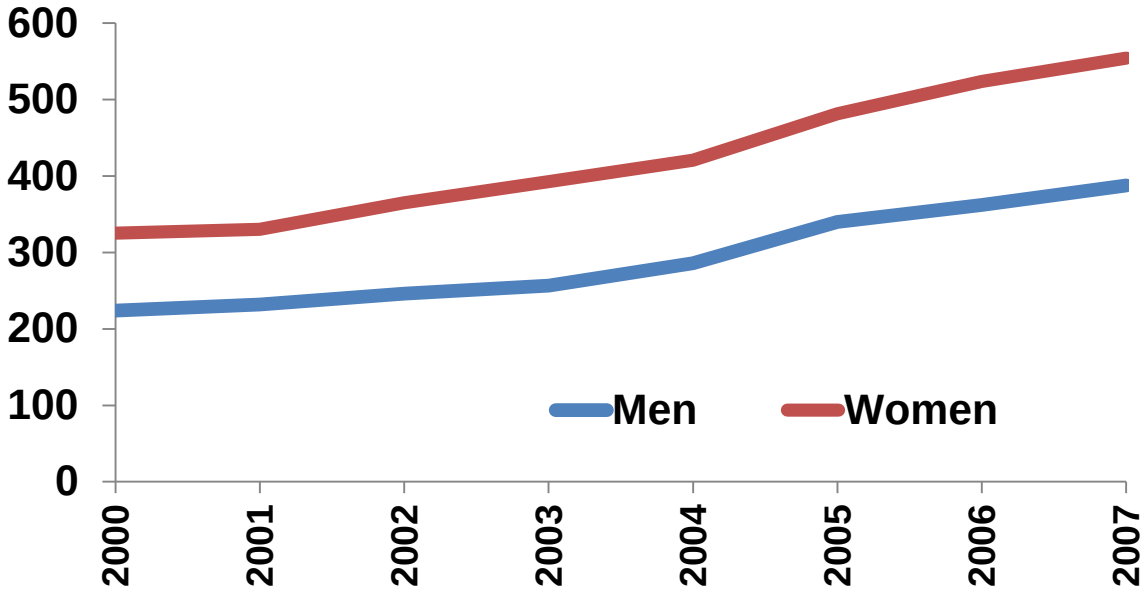
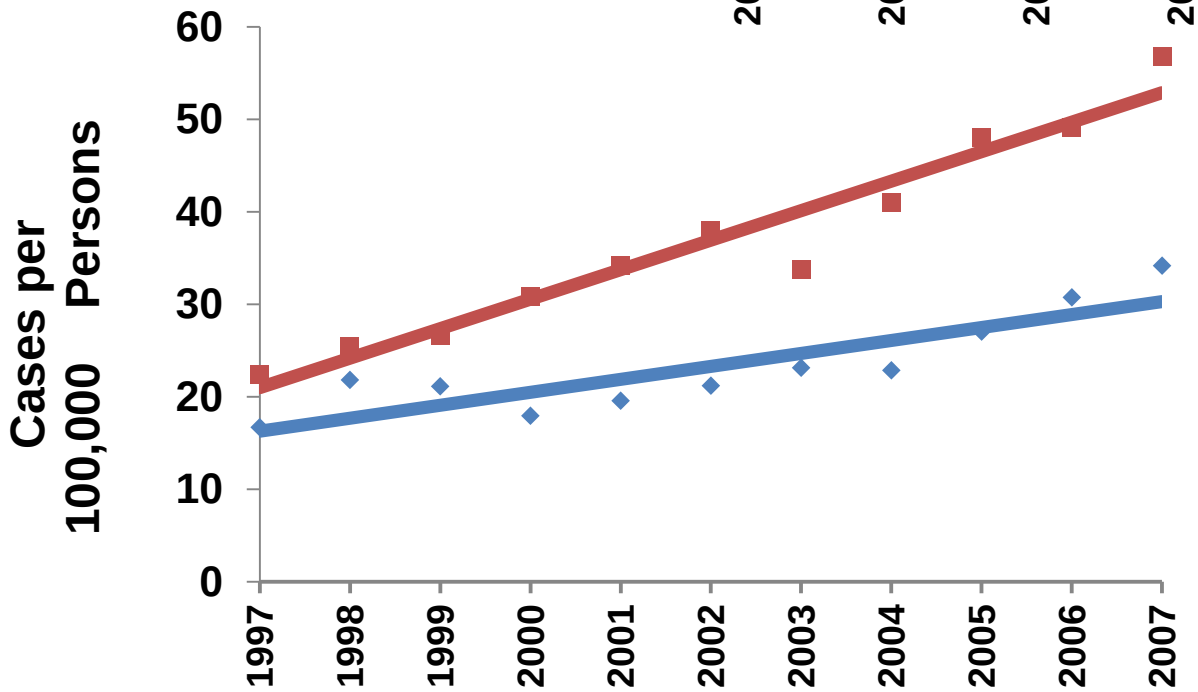


Am J Respir Crit Care Med 2010

US Medicare: Bronchiectasis Prevalence

Seitz A. Chest 2012





US Medicare: NTM Prevalence

Adjemian J. AJRCCM 2012

National Heart, Lung, and Blood Institute

The Burden of Pulmonary Nontuberculous Mycobacterial Disease in the United States

Sara E. Strollo[1], Jennifer Adjemian[1,2], Michael K. Adjemian[3], and D. Rebecca Prevots[1]

[1]Epidemiology Unit, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; [2]Commissioned Corps, United States Public Health Service, Rockville, Maryland; and [3]Market and Trade Economics Division, Economic Research Service, United States Department of Agriculture, Washington, DC

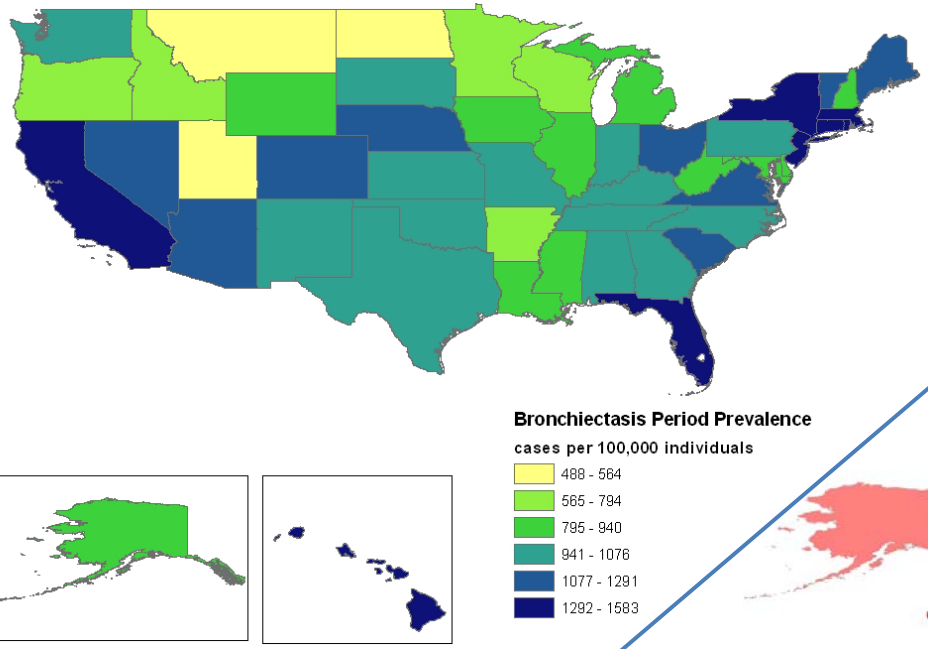
- Estimated annual medical costs
  - Extrapolated data from US Medicare and practice survey studies
  - Assumed
    - 73% cases missed based on ICD9 coding
    - 31% NTM cases are younger than age 65
    - 8.2% annual increase in prevalence
  - 2010 US Census Bureau data

	National Nontuberculous Mycobacterial Disease Estimates	National Nontuberculous Mycobacterial Disease Estimates Assuming 1 Additional Outpatient Visit per Year	National Nontuberculous Mycobacterial Disease Estimates Assuming 2 Additional Outpatient Visits per Year	National Nontuberculous Mycobacterial Disease Estimates Assuming 3 Additional Outpatient Visits per Year
Annual medical encounters*	86,244	172,487	258,731	344,974
Annual cost†	$815,098,690	$937,491,959	$1,059,885,228	$1,182,278,496

  - 80% costs attributed to prescription medication costs

Strollo. Ann Am Thorac Soc 2015

NIH National Heart, Lung, and Blood Institute

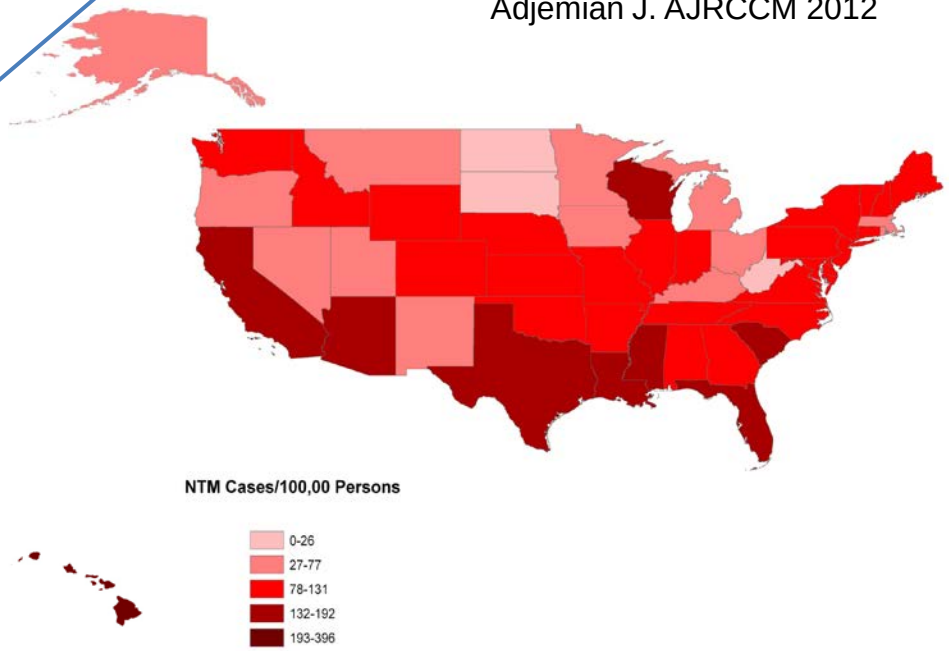


Bronchiectasis

Seitz A. Chest 2012

NTM

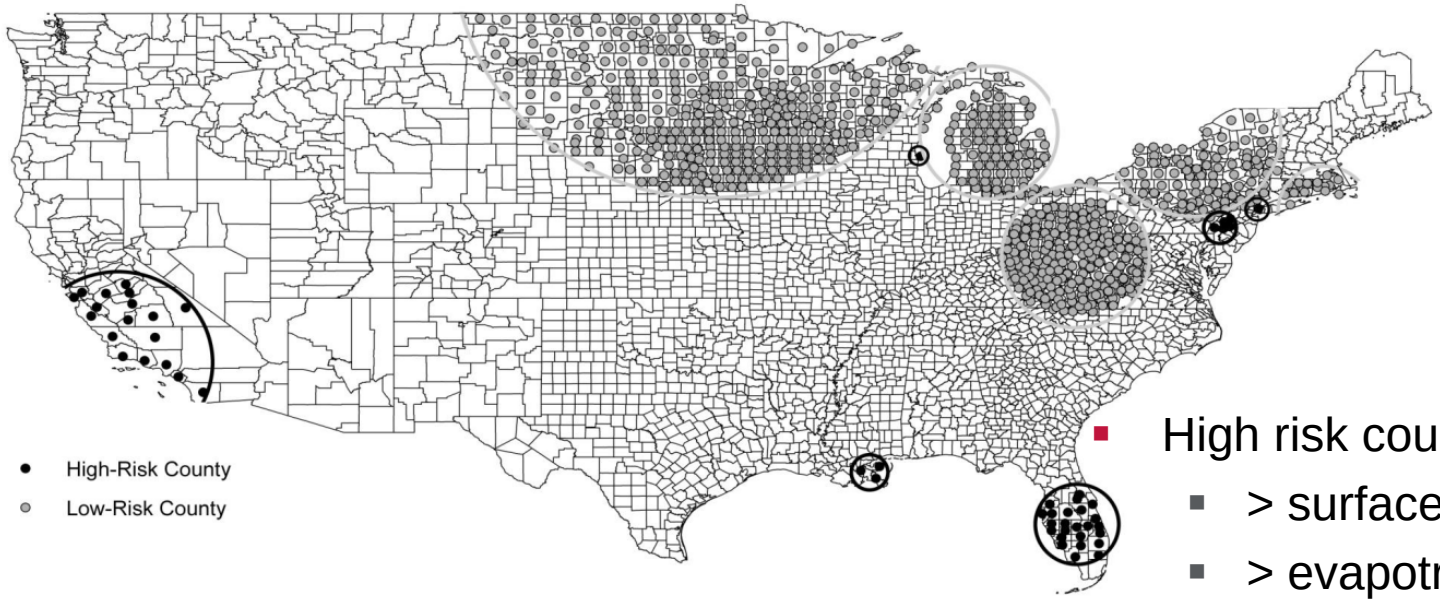
Adjemian J. AJRCCM 2012



Spatial Clusters of Nontuberculous Mycobacterial Lung Disease in the United States

Jennifer Adjemian[1,2], Kenneth N. Olivier[2], Amy E. Seitz[1,2], Joseph O. Falkinham III[3], Steven M. Holland[2], and D. Rebecca Prevots[1,2]

[1]Epidemiology Unit and [2]Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and [3]Virginia Polytechnic Institute and State University, Blacksburg, Virginia



- High risk counties
  - > surface water (OR 4.6)
  - > evapotranspiration (4.0)
  - > copper (1.2) & Na^+ (1.9)
  - < manganese (0.7)

Adjemian. AJRCCM 2012; 186:553-8

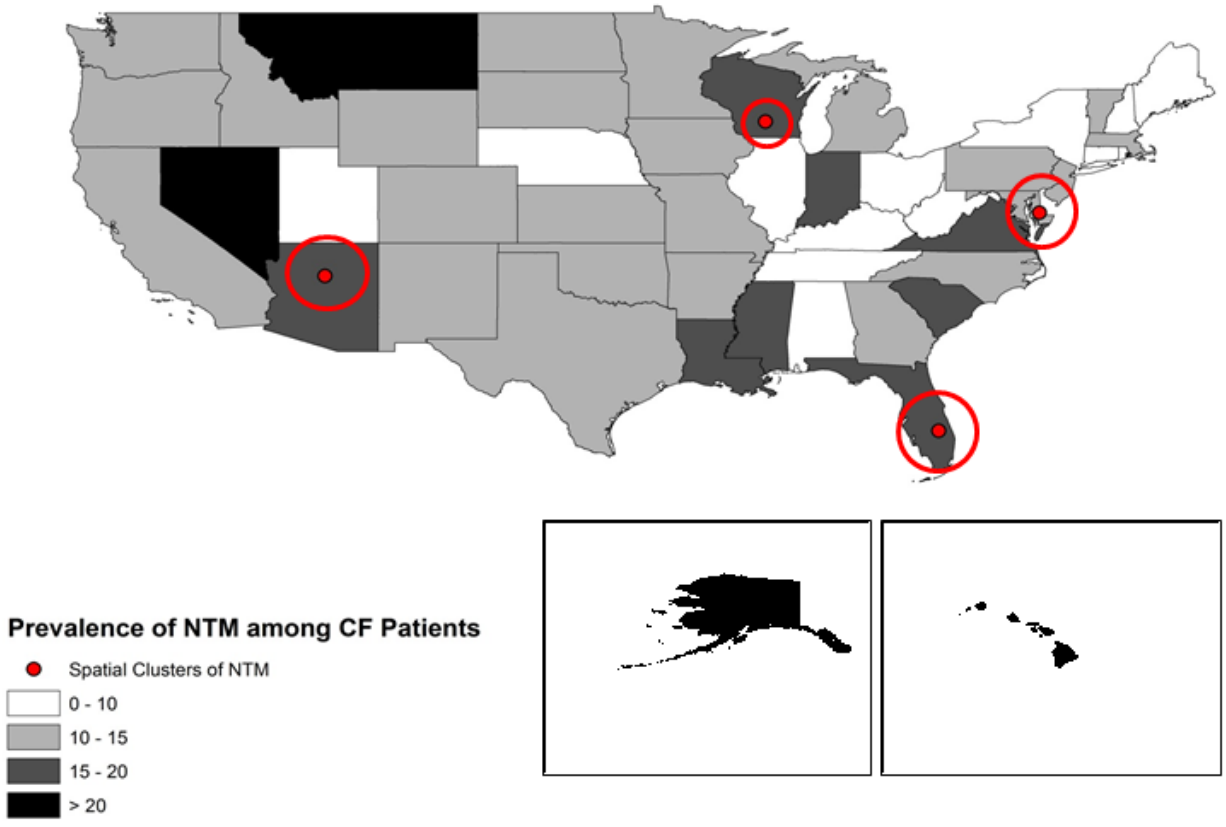
NIH National Heart, Lung, and Blood Institute

Nontuberculous Mycobacteria among Patients with Cystic Fibrosis in the United States

Screening Practices and Environmental Risk

Jennifer Adjemian[1,2], Kenneth N. Olivier[3], and D. Rebecca Prevots[1]

[1]Epidemiology Unit and [3]Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and [2]United States Public Health Service, Rockville, Maryland

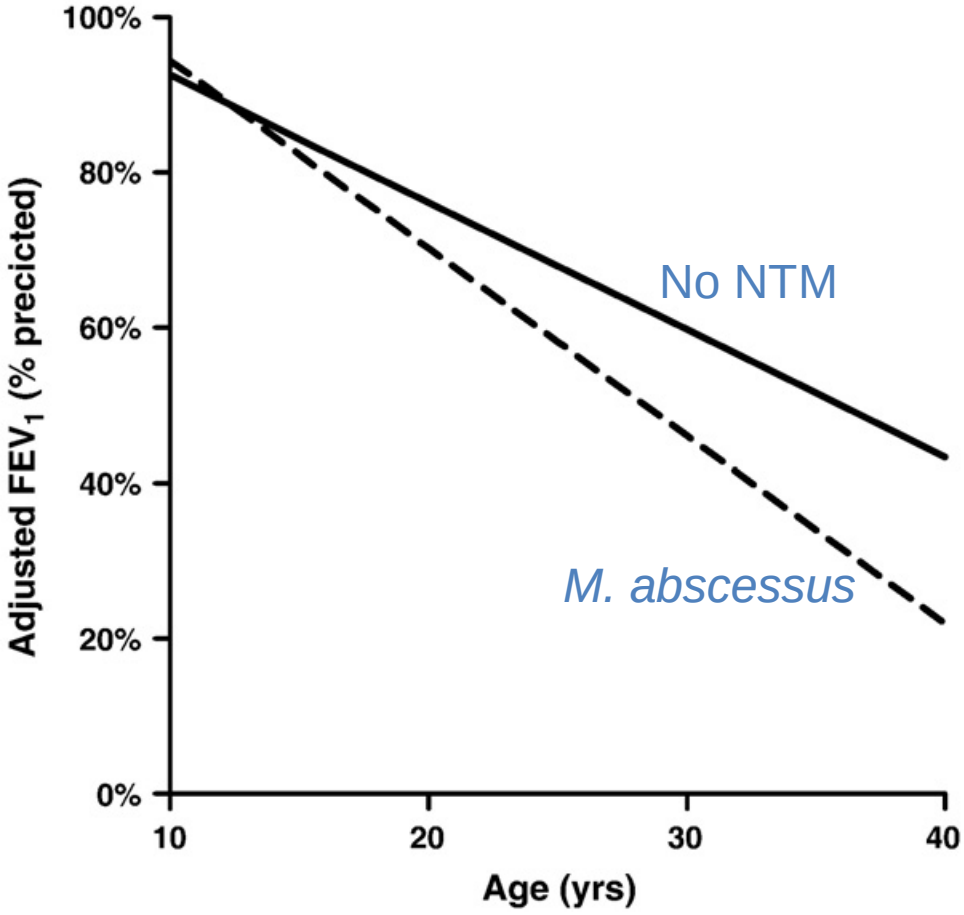


- CF Patient Registry 2010 & 2011
- 18,003 pts >12 yrs
  - 14% pos Mac/Mab
  - 4 significant geospatial clusters
    - **Saturated vapor pressure** specific climatic risk

Adjemian. Am J Respir Crit Care Med 2014

Significance of *M. abscessus*

- *M. abscessus* excess decline of -0.78% per year vs no NTM (p=0.02)
- Other NTM were intermediate between *M. abscessus* and no NTM

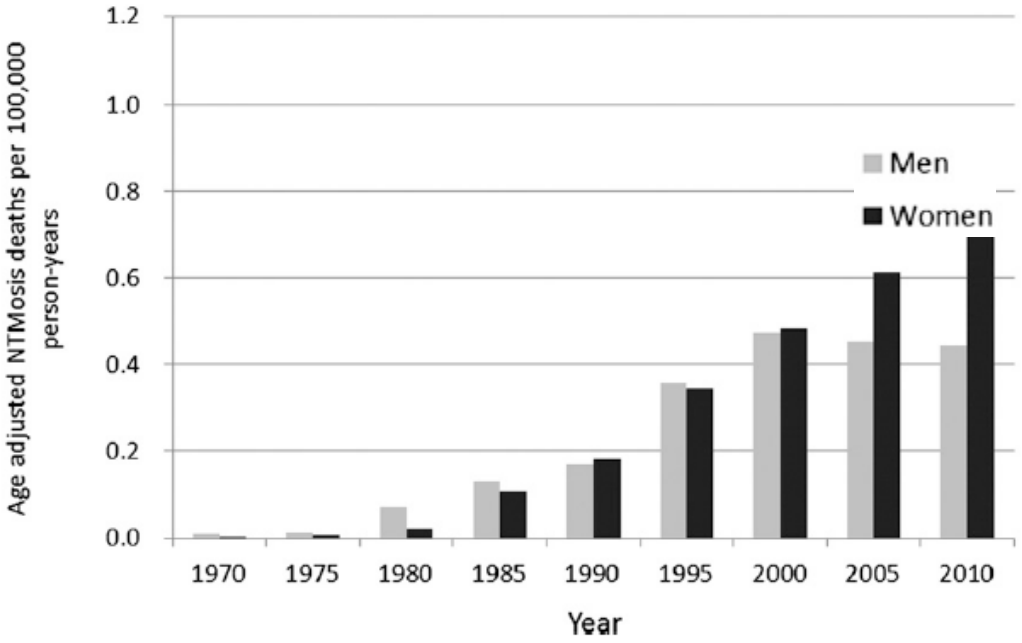


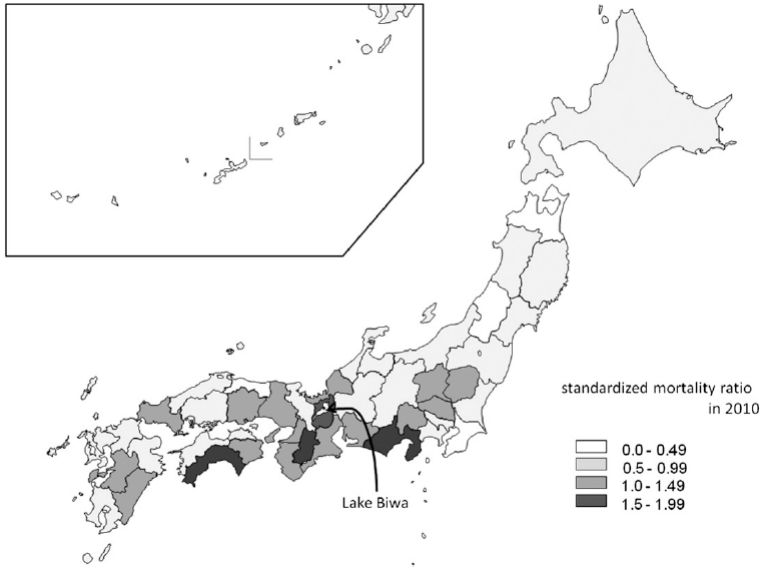
Esther. J Cyst Fibros 2010

A Steady Increase in Nontuberculous Mycobacteriosis Mortality and Estimated Prevalence in Japan

Kozo Morimoto[1], Kazuro Iwai[2], Kazuhiro Uchimura[2], Masao Okumura[1], Takashi Yoshiyama[1], Kozo Yoshimori[1], Hideo Ogata[1], Atsuyuki Kurashima[1], Akihiko Gemma[3], and Shoji Kudoh[1]

[1]Respiratory Disease Center, Fukujuji Hospital, Japan Anti-Tuberculosis Association, [2]Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, and [3]Division of Pulmonary Medicine, Infectious Diseases, and Oncology, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan





- Increasing mortality for both sexes through 2000, then only in women
  - Increased in warm areas, high rainfall
- Estimated prevalence 33-65/100K
  - >50% dx with Mac remained cx pos at 2yr; 36% cx pos at 5 yr

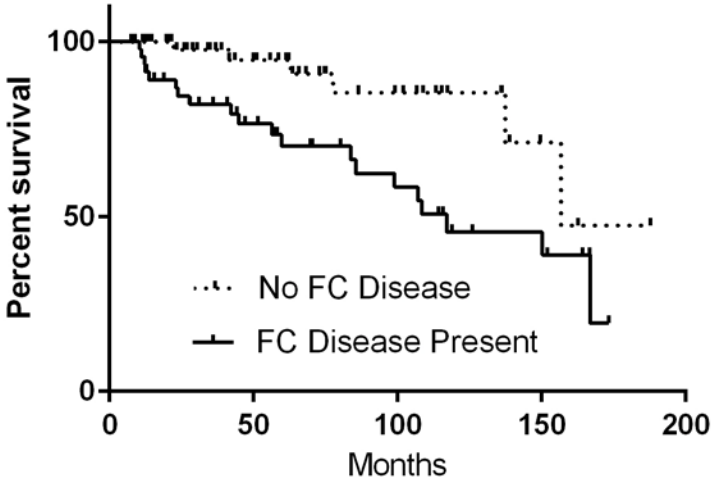
Morimoto. Ann Am Thorac Soc 2014

Mortality in NTM

- Several studies have reported 5-year mortality
  - Hayashi AJRCCM 2012 – Japan: 25%
  - Ito IJTLD 2012 – Japan: 28%
  - Andrejak AJRCCM 2010 – Denmark: 40%
  - Kotilainen SJID 2013 – Finland: 28% (4yr)
  - Strollo (unpub 2015) – NIH cohort: 25%

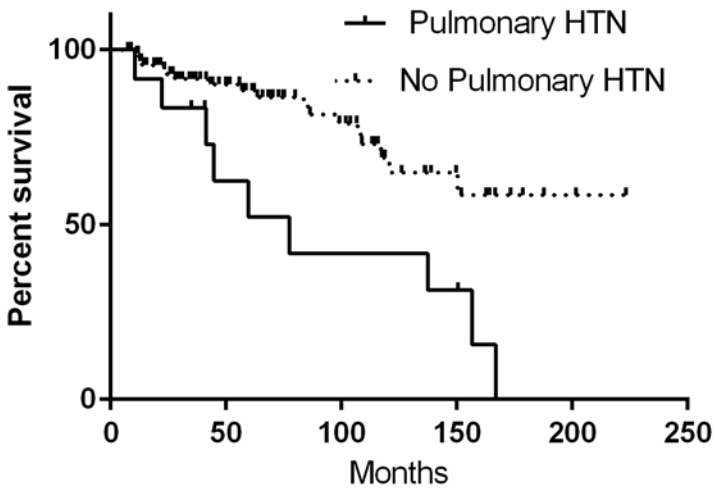
Mortality risk factors

Fibrocavitary Disease



- Median survival
  - FCD = 9.0 years
  - No FCD = 13.1 years
  - p = 0.006

Pulmonary Hypertension



- Median survival
  - PH = 6.8 years
  - No PH = >18 years
  - p = 0.48

Fleshner. *Submitted* 2015

NIH National Heart, Lung, and Blood Institute

Summary

- US prevalence difficult to assess
  - ~16K – 84K
- Increased in women and age >60
- Considerable geographic variability
  - Likely reflects environmental influences
- Disease burden and costs are substantial
- Adversely effects lung function
- Associated with increased mortality

Nontuberculous Mycobacterial (NTM) Lung Disease: Diagnosis and Treatment Guidelines

David E. Griffith, MD

Professor of Medicine

University of Texas Health Science Center, Tyler, TX

Potential COI Statement

* I was a co-investigator on a recent multi-center trial of inhaled liposomal amikacin (Arykace) sponsored by Insmed
* I am a co-investigator on a new multi-center trial of inhaled liposomal amikacin (Arykace) sponsored by Insmed

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

* Diagnosis and treatment of disease caused by NTM. ARRD, 1990; 142: 940-953
* Diagnosis and treatment of disease caused by NTM. AJRCCM. 1997;156:S1-25.
* An official ATS/IDSA Statement: Diagnosis, treatment and prevention of NTM diseases. AJRCCM, 2007: 175: 367-416

Why do we need NTM diagnosis and treatment guidelines (NTMDTG)?

* This ain't TB
* Let me rephrase that: This ain't TB
* NTMDTG are actually sometimes helpful for diagnosing NTM lung disease with specific pathogens
* NTMDTG are actually sometimes helpful for guiding successful therapy of NTM lung disease
* NTMDTG usually do not make things worse
* NTMDTG can be instructive for clinicians unfamiliar with NTM

NTM Diagnostic Guidelines

* Current diagnostic guidelines are inadequate for 160 mycobacterial species, but will hopefully continue to evolve
* Diagnostic evaluation influenced by:
  * The virulence of the isolated NTM: *M. kansasii, M. gordonae*
  * The host (immune suppression, airway abnormalities, body morphotype): MAC, *M. mucogenicum, M. abscessus, M. simiae*
  * The clinical source (setting) of the organism: blood, soft tissue, sputum
* It is imperative that clinicians evaluating patients with NTM lung disease are familiar with characteristics of individual NTM species.

Diagnosis of NTM Lung Disease: Microbiologic Criteria

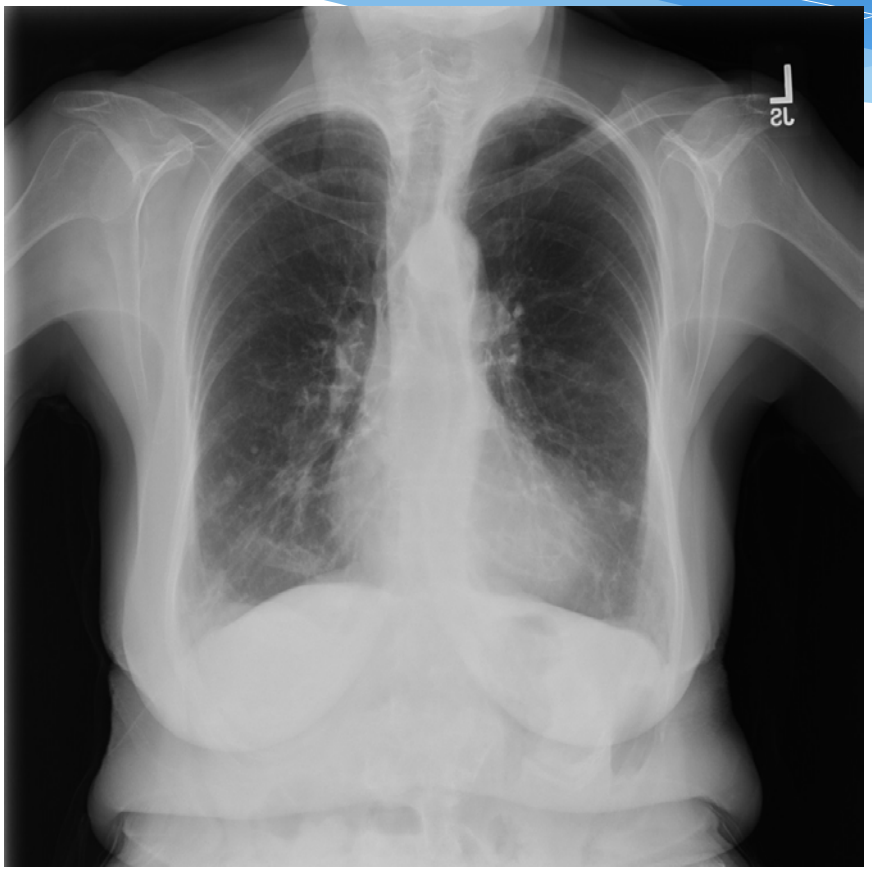
* A single positive culture from any source (sputum or bronchoscopy) is regarded as indeterminate for diagnosis of NTM lung disease:
  * Frequent contaminants, *M. gordonae*, *M. terrae* complex, *M. mucogenicum*
  * NTM species known to be present in tap water, *M. simiae*, *M. lentiflavum*, *M. abscessus*, *M. kansasii*, *M. xenopi*
  * NTM isolated from respiratory specimens are frequently NOT associated with progressive disease

Factors Influencing the Decision to Treat NTM Lung Disease

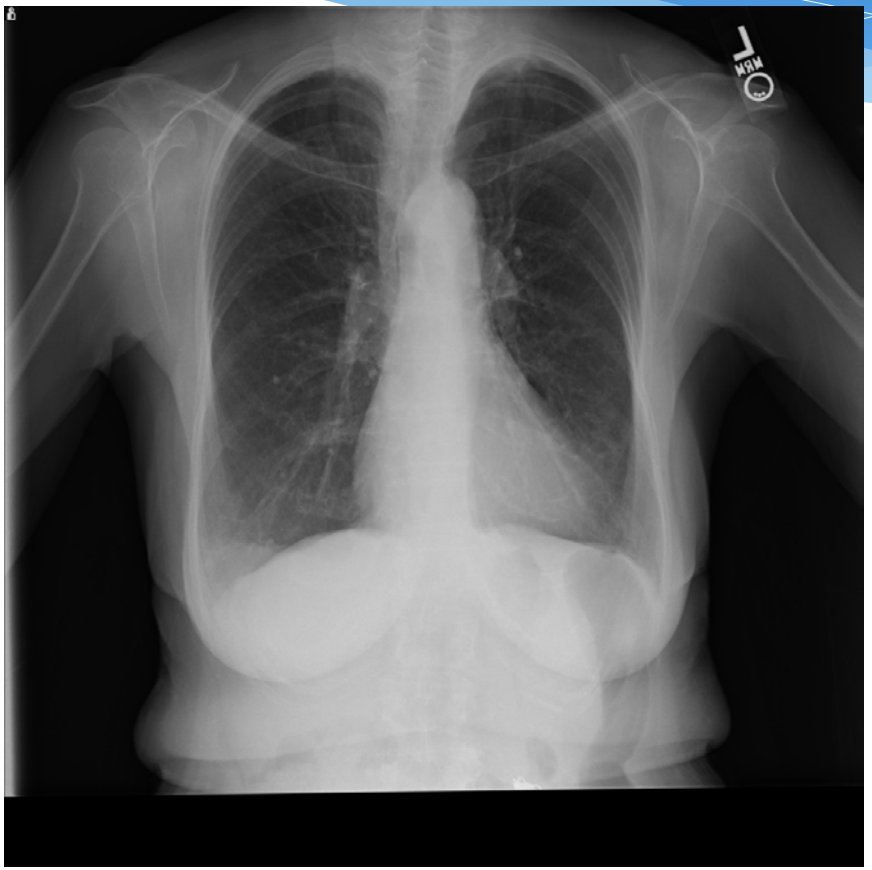
* Making the diagnosis of NTM disease does not by itself necessitate the initiation of therapy. The decision to start therapy for NTM lung disease is based on a careful risk/benefit analysis for the individual patient.

* Is the NTM disease cavitary?
* How symptomatic is the patient and how do the symptoms impact QOL?
* What are the patient's pulmonary co-morbidities and are they compensated?
* What systemic co-morbidities does the patient have and do they impact NTM disease? What is the patient's short and long term prognosis?
* What are the short term (mos) trends in symptoms, radiographic appearance and culture results?
* What does the patient want to do?

75 year old woman with sputum AFB culture + for MAC



(75 + 12) year old woman with 35/70 sputum AFB culture + for MAC, no therapy



Therapy of MAC Lung Disease 2007 ATS NTM Guidelines

* Nodular/bronchiectatic disease: macrolide/EMB/rifamycin: INTERMITTENT*
* Cavitary disease: macrolide/EMB/rifamycin ± injectable: DAILY
* Severe or previously treated disease: macrolide/EMB/rifamycin/injectable: DAILY
* Duration: 12 months sputum culture negativity while on therapy
* Surgery for selected patients

*Not indicated for severe and/or cavitary disease

Macrolide/Azalide Therapy for Nodular/Bronchiectatic *Mycobacterium avium* Complex Lung Disease

(Wallace et al Chest 2014)

* 180 patients with NB MAC lung disease with ≥ 12 months macrolide/azalide-based therapy
* 150/180 (86%) sputum conversion
  * No difference between azi and clari
  * Regimen modification common with daily RX
  * Microbiologic recurrence 14% (73% new genotype)
* Treatment success 83%
* Microbiologic recurrence 74/155 (48%)
  * 75% new genotypes

Intermittent Antibiotic Therapy for Nodular Bronchiectatic MAC Lung Disease

Jeong et al, AJRCCM 2015

* 217 pats with NB MAC lung disease
* 99 daily, 118 intermittent macrolide-based therapy
* No significant differences in symptomatic, radiographic and microbiologic conversion (76 vs 67%)
* Modification of the initial regimen more common with daily therapy (46 vs 21%)

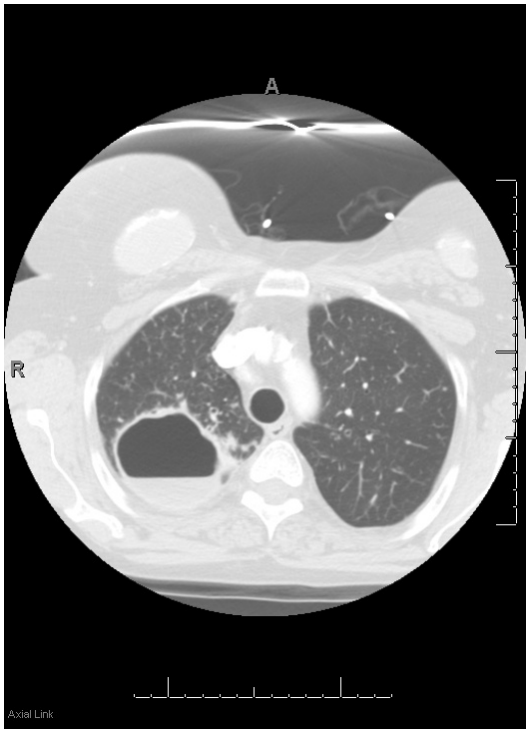
Macrolide/Azalide Therapy for Nodular/Bronchiectatic MAC Lung Disease

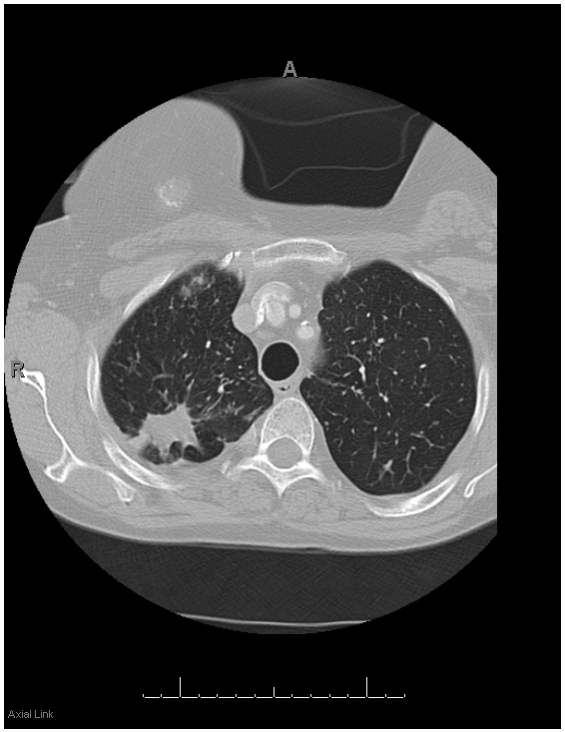
* Current guidelines for macrolide/azalide-based regimens for NB MAC lung disease result in favorable microbiologic outcomes for most patients
* These regimens do not promote macrolide resistance
* Intermittent regimens as effective as daily regimens with fewer side effects, therefore TIW therapy preferred
* Microbiologic recurrences common, most due to unique MAC genotypes ("reinfection")

Cavitary MAC (NTM) Lung Disease

* Pathophysiologically a smoking related disease
* Smoking likely inhibits favorable treatment response
* Likely associated with long term respiratory impairment
* Associated with high all cause mortality, greater than NB MAC lung disease
* Requires aggressive and appropriate therapy
  * Parenteral agents
  * Surgery
  * Smoking cessation
  * Avoidance of macrolide resistance (fatal disease)

56 yo female, sputum 4+ AFB pos for MAC 19 mos daily azi/emb/rmp + 6 mos TIW amk > 12 mos sputum culture negative



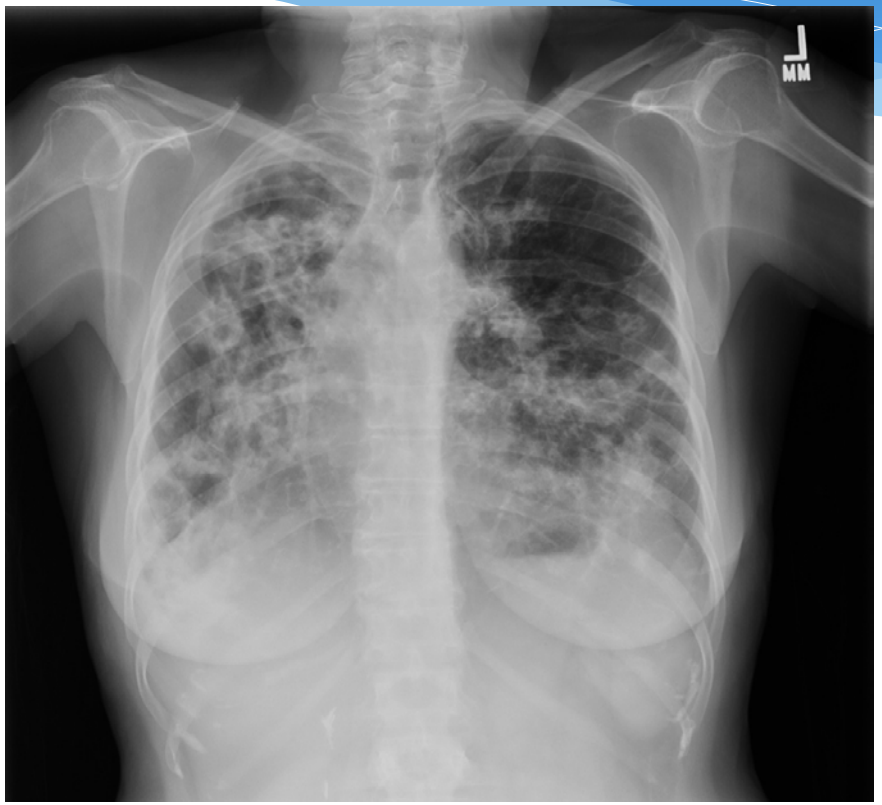


Development of Macrolide Resistant MAC

(Griffith et al 2006 Am J Resp Crit Care Med)

* Risk factors: Macrolide monotherapy, Macrolide plus quinolone
* Sputum conversion after macrolide resistance: 77% in patients with both injectable Rx and surgery; 5% in patients without both injectable RX and surgery.
* Patients who failed therapy, 1 year mortality 34%, 2 year mortality was 45%,
* Patients with sputum conversion to (-), the 1 and 2 year mortality was 0%

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



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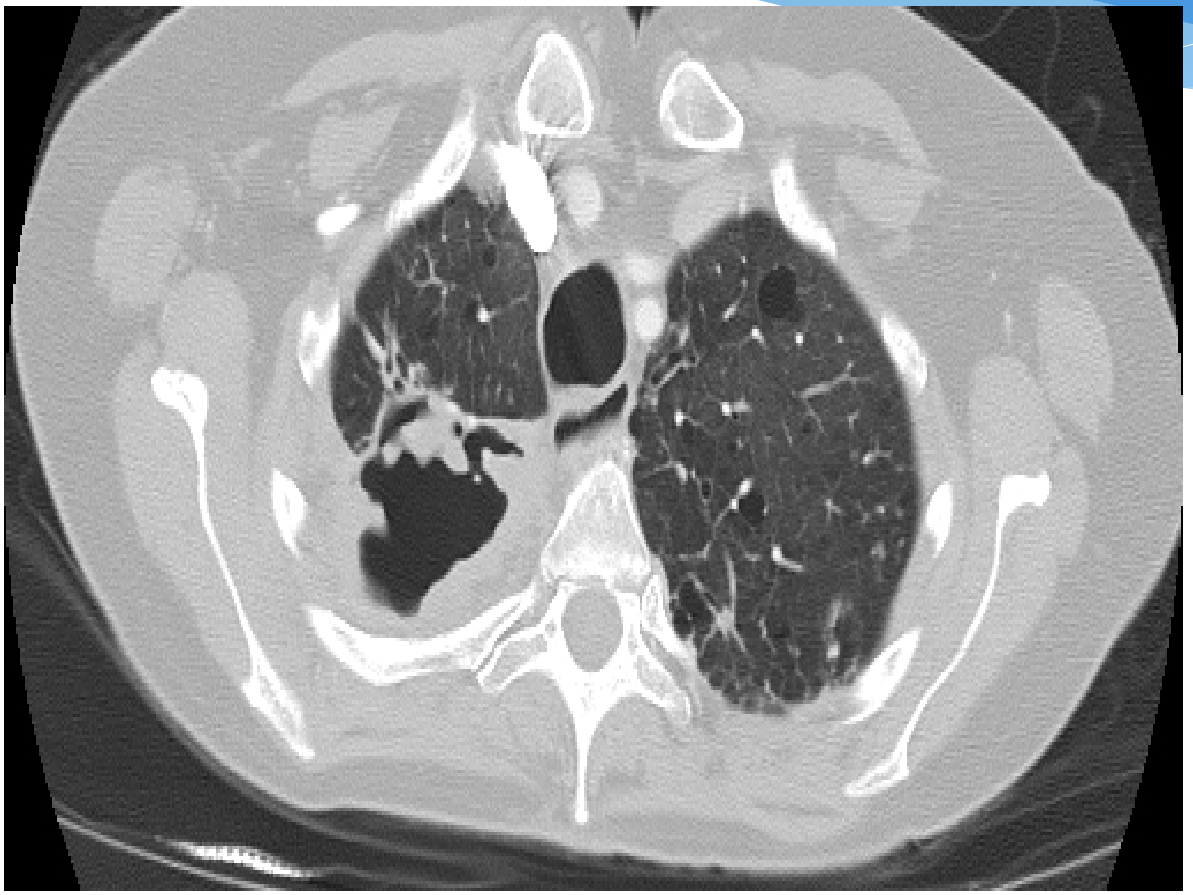
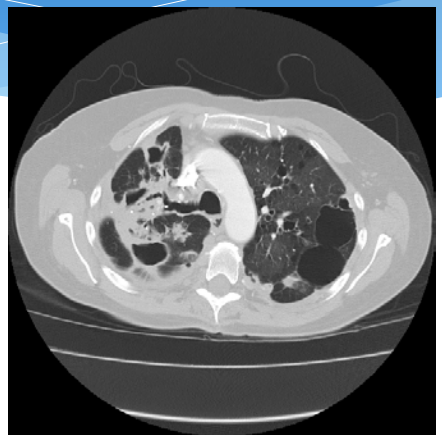
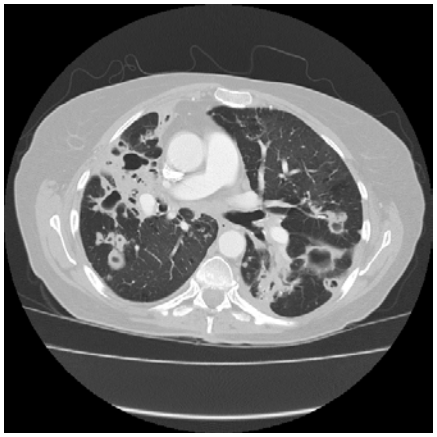






Therapy of Macrolide Resistant MAC

* Rifabutin
* Ethambutol
* Surgery
* Parenteral streptomycin or amikacin
  * Inhaled amikacin with caution
* Clofazimine
* Moxifloxacin
* Linezolid
* Macrolide as immune modulating therapy

NTM Drug Resistance

* Innate or "natural" drug resistance
  * Not readily or predictably associated with in vitro measures of resistance such as MICs
  * Inducible macrolide resistance (*erm*) gene
* Acquired drug resistance
  * Selection of isolates with naturally occuring mutations that confer resistance to specific antibiotics
  * The form of drug resistance most associated with TB therapy

Resistant Nontuberculous Mycobacteria

* Mutational Resistance
  * *M. tuberculosis:* multiple gene mutations
  * *M. avium* complex:
    a) 23S rRNA gene (macrolides);
    b) 16S rRNA gene (amikacin)
  * *M. kansasii*: rpo β gene (rifamycins)
  * *M. abscessus:* 23S rRNA gene (macrolides)

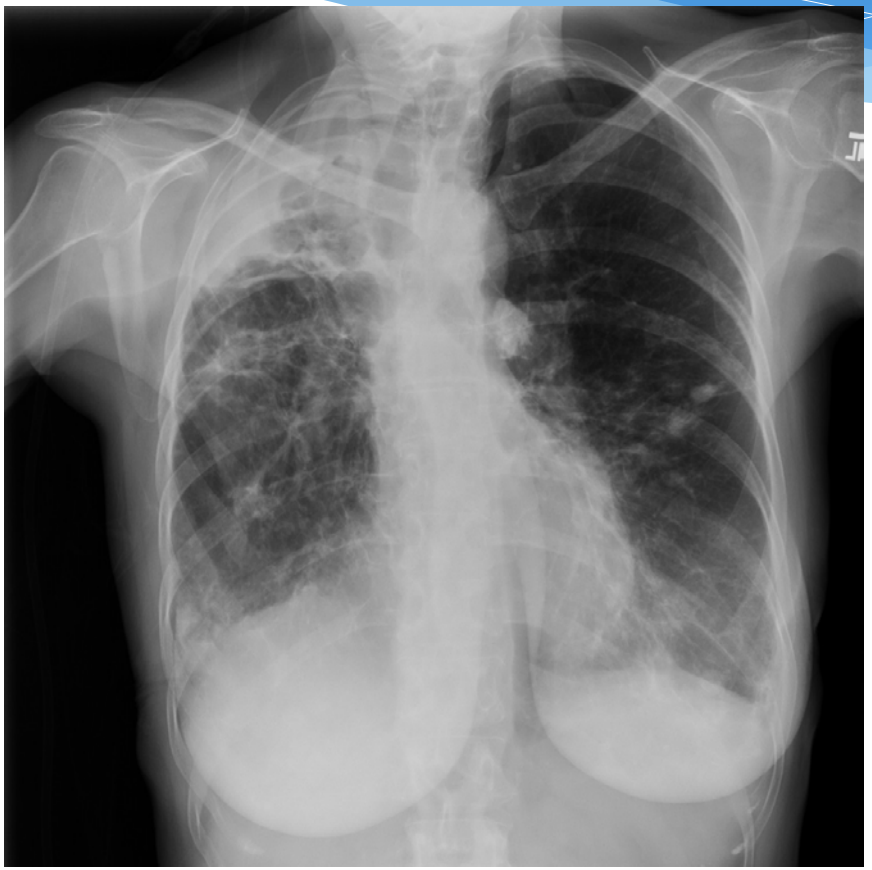
Resistant Nontuberculous Mycobacteria

* Innate Resistance in Inevitable
* Mutational Resistance is AVOIDABLE

MAC therapy

* Pharmacokinetic and pharmacodynamic indicies frequently suboptimal with "standard" MAC therapy but no correlation with treatment outcome
* No demonstrated correlation between circulating MAC drug levels and treatment outcome
* No correlation between MICs for rim/emb/stm and response to medications

78 yo with MAC treated with azi/FQ because she was emb “resistant”, now macrolide resistant



Lack of Adherence to Evidence-based Treatment Guidelines for NTM Lung Disease

(Adjemian et al, Annals ATS 2014)

* 18% of MAC patients were treated for the greatest duration with a regimen meeting 2007 ATS/IDSA guidelines
* Only 4% were treated with this regimen for > 22 weeks
* Majority of MAC patients (58%) were on a regimen without a macrolide
* 22% of patient received regimens that were "potentially harmful"
  * Macolide monotherapy 22%
  * Rifampin only 15%
  * Macrolide plus fluoroquinolone 1%

NTM Guidelines

* Last ATS/IDSA NTM guidelines published 2007
* NTM guidelines 2014
  * ATS
  * IDSA
  * ERS
  * ESCMID
  * Non-member Japanese observers

PICO-Based Key Questions/Process (Population, Intervention, Comparator, Outcome)

* The panel should be predominantly (> 50%) free of relevant COI's. Individuals with moderate conflicts can be selected.
* Funding: there is no industry funding
* The panel drafts key clinical questions that frontline clinician agree would proved important guidance for stakeholders
* Searches are conducted from multiple databases for systemic reviews (if available) and primary literature
* Quality is assessed for individual studies (RCT's, observational studies)
* Recommendations (when the body of evidence permits an evidence-based guideline methodology) and suggestions (consensus based-not graded).

An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of IPF: Executive Summary Questions

AJRCCM, 2015, 192; 238-248

* Should patients with IPF be treated with:
  * #1: anticoagulation?
  * #2: Imatinib, a tyrosine kinase inhibitor (TKI)?
  * #3: combination prednisone, azathioprine and N-acetylcysteine?
  * #4: ambrisentan, a selective ER-A endothelin receptor antagonist?
  * #5: nintedanib, a TKI?
  * #6: pirfenidone?
  * #7: sildenafil, a phosphodiesterase-5 inhibitor?
  * #8: bosentan or macitentan, dual endothelin receptor antagonists (ER-A and ER-B)?

State of the Art: Nontuberculous Mycobacteria and Associated Diseases

(Wolinsky, ARRD 1979;119: 107)

* "Proper management requires greater expertise than is needed for treatment of TB, first, to decide who needs to be treated, and second, to determine which drug regimens to use."

We still need help!

Review Considerations for New Drugs

Patient Focused Drug Development

NTM Lung Infections

October 15, 2015

Outline

- Adequate and Well Controlled Clinical Trials
- Drugs in Combination
- Trial Endpoints

Drug Development

- Non-Clinical
  - Chemistry and Manufacturing
  - Toxicology
  - Pharmacology
  - In vitro activity
  - Animal models of infection (if any)

Clinical Trials

- For market authorization/approval, drug must show substantial evidence of efficacy
  - Section 505(d) of the FD&C act: adequate and well-controlled investigations

- 21 CFR 314.126
  - Adequate and well controlled clinical trials
  - To distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo-effect, or biased observation.

Types of A &WC Clinical Trials

- Placebo concurrent control
  - Randomized trial in which test drug is compared to inactive drug that is similar in appearance
- No treatment concurrent control
  - Randomized trial in which test drug is compared to no treatment
- Dose-comparison concurrent control
  - Randomized trial in which two or more doses of the test drug are compared

Types of A &WC Clinical Trials

- Active treatment concurrent control
  - Randomized trial in which test drug is compared to known effective therapy (active control)

- Historical control
  - Test drug is compared to historical experience
  - Reserved for special circumstances (e.g., disease with high mortality, course of illness predictable, or where drug effect is self-evident such as in general anesthetics)

Types of Clinical Trials

- Superiority Trials: test drug better than comparator
  - Placebo, no treatment, dose-comparison, active control or historical trials

- Advantage: Can assess any outcome of interest regardless of what previous trials had assessed

Clinical Trials

- Non-inferiority trials: test drug no worse than an active comparator by a certain pre-specified degree (non-inferiority margin)
- Disadvantages
  - The effect of the active comparator compared to placebo needs to be estimated in the particular population and for the particular outcome of interest
  - May limit choice of study population and study outcome measures
  - Possible that study cannot support efficacy if no historical evidence of active comparator exists

NTM Lung Infection Trials

- Monotherapy is not recommended
- Complicates trial design for a new regimen; For diseases that require use of drugs in combination, the new drug(s) must be demonstrated to make a contribution to the overall regimen
  - The contribution may be additive treatment effect, prevention of emergence of resistance or mitigation of toxicity
  - Demonstrating the contribution of a drug in a combination regimen may be difficult unless the clinical trial is an add-on trial
- In some instances, drugs in a combination regimen can be co-developed.

Drugs in Combination

- Guidance for Industry – Co-development of two or more new investigational drugs for use in combination
  - Treatment of serious disease (lung NTM is)
  - Compelling reasons why the drugs cannot be developed independently (monotherapy is not recommended)
  - Strong biologic rationale for the combination (e.g., drugs act on different microbial targets)
  - Nonclinical evidence that combination provides significant therapeutic advance over available therapy and is superior to the individual drugs (in vitro synergy or prevention of resistance; effects in animal model)

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf

NTM Lung Infection Trials

- Superiority trials
  - Add-on trials: Test drug or test drug combination added to background regimen (BR) compared to placebo or no treatment added to BR
    - Test drug plus BR vs. BR used in TB trials
  - New Regimen
    - Test drug combination compared to placebo or no treatment (no BR) in patients in whom delaying treatment may be clinically acceptable
    - Test combination regimen compared to another combination that does not include the same drugs
    - Contribution of each component may be demonstrated in vitro or animal model

NTM Lung Infection Trials

- Non-inferiority trials
  - Test drug substitutes for a drug in the BR (has been used in TB to allow treatment shortening)
  - If feasible, compare new combination regimen to another combination regimen for treatment shortening or mitigation of toxicities
- NI trials are likely to be extremely challenging
  - Treatment effect of single drug substitution for efficacy or to allow shorter treatment duration is not known to allow derivation of NI margin

Trial Endpoints (Outcome Measures)

- Assess a clinically meaningful endpoint that is a direct measure of how a patient feels, functions or survives
  - Federal Register/Vol. 57, No.73/April 15, 1992
- Include:
  - Improved survival
  - Improvement of symptoms or functional capacity
  - Prevention of disease complication (e.g., treatment of latent TB)

Biomarkers and Surrogates

- Biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention.
  - Biomarkers Definitions Working Group 2001 & IOM Report 2011

- A surrogate is a laboratory measurement or physical sign that is used as a substitute for a clinically meaningful outcome
  - Reasonably likely to predict clinical benefit [21 CFR 314.500 (subpart H)]
  - Examples: BP, HIV viral load

Surrogate Endpoints

- A surrogate is a biomarker, but not every biomarker is a surrogate
- However, for a biomarker to be established as a surrogate that is predictive of clinical outcome, evidence that changes in the biomarker correlate with changes in the clinical outcome should be established.
- Once established, surrogates allow faster drug development
- If accelerated approval on the basis of surrogate biomarker, a confirmatory trial that assesses the clinical outcome is required
  - Example: TB drugs may receive accelerated approval based on culture conversion to negative but a confirmatory trial showing relapse free survival is required

Endpoints in NTM Lung Infections Trials

- Endpoints under consideration in NTM lung infection trials

1. Survival
2. Measures of symptoms or function
   - Clinician reported outcomes: may be difficult for some symptoms
   - Patient reported outcomes (PRO): require validation
   - 6MWT or other functional assessment: degree of change that is meaningful to the patient should be defined

Endpoints in NTM Lung Infections Trials

3. Surrogate biomarkers to consider
   - Microbiologic: Sputum culture conversion to negative
     - Similar to TB trials, but
       - Number of consecutive negative cultures not established
       - Timing of determining conversion during therapy not established
       - Correlation with clinical outcomes needs to be established
   - Other surrogates? (e.g., radiologic – same considerations as microbiologic endpoints):

Conclusions

- Drugs need to show evidence of *efficacy for a clinically meaningful outcome* evaluated in *adequate and well controlled trials*
- Surrogate markers can be used for approval if the surrogate has been shown to *predict/correlate with* a meaningful clinical outcome
- PROs, if validated, can be used for approval
- Co-development of a new test drug combination may be possible in certain situations

The Road from Patient-Focused Drug Development Public Meetings to Clinical Study Endpoints

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Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

PATIENT-FOCUSED DRUG DEVELOPMENT (PFDD) MEETINGS

WHERE DO WE GO FROM HERE

PATIENTS' VOICE


I need a valid assessment.

Two Pathways for FDA Clinical Outcome Assessment Review & Advice

1

Within an individual drug development program

- Investigational New Drug (IND) submissions to FDA
- Potential to result in labeling claims

2

Within the Drug Development Tool (DDT) qualification program; **outside** of an individual drug development program

- Potential to result in qualification*

**In the future, we anticipate there will be tools that are both qualified and in labeling.*

Key Takeaways

- PFDD meetings are a "starting point" for developing patient-focused outcome measures and endpoints
- The outcomes of PFDD meetings will support and guide FDA risk-benefit assessments in drug reviews
- Patients' input ultimately helps determine:
  - WHAT is measured to provide evidence of treatment benefit
  - HOW best to measure concepts in a clinical study
  - WHAT a meaningful improvement is in treatment benefit

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Quality of Life-NTM Module

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UNIVERSITY OF MIAMI

ACKNOWLEDGEMENTS: KEN OLIVIER, KEVIN WINTHROP, MATTHIAS SALATHE

Quittner A, Madan A, Saez-Flores E, Olivier K, Fennelly K, Schmid A, & Salathe M. Development of the quality of life module for nontuberculous mycobacteria (NTM). ***European Respiratory Journal, 2015; 46, Supp. 59, No. 275. (Abstract)***

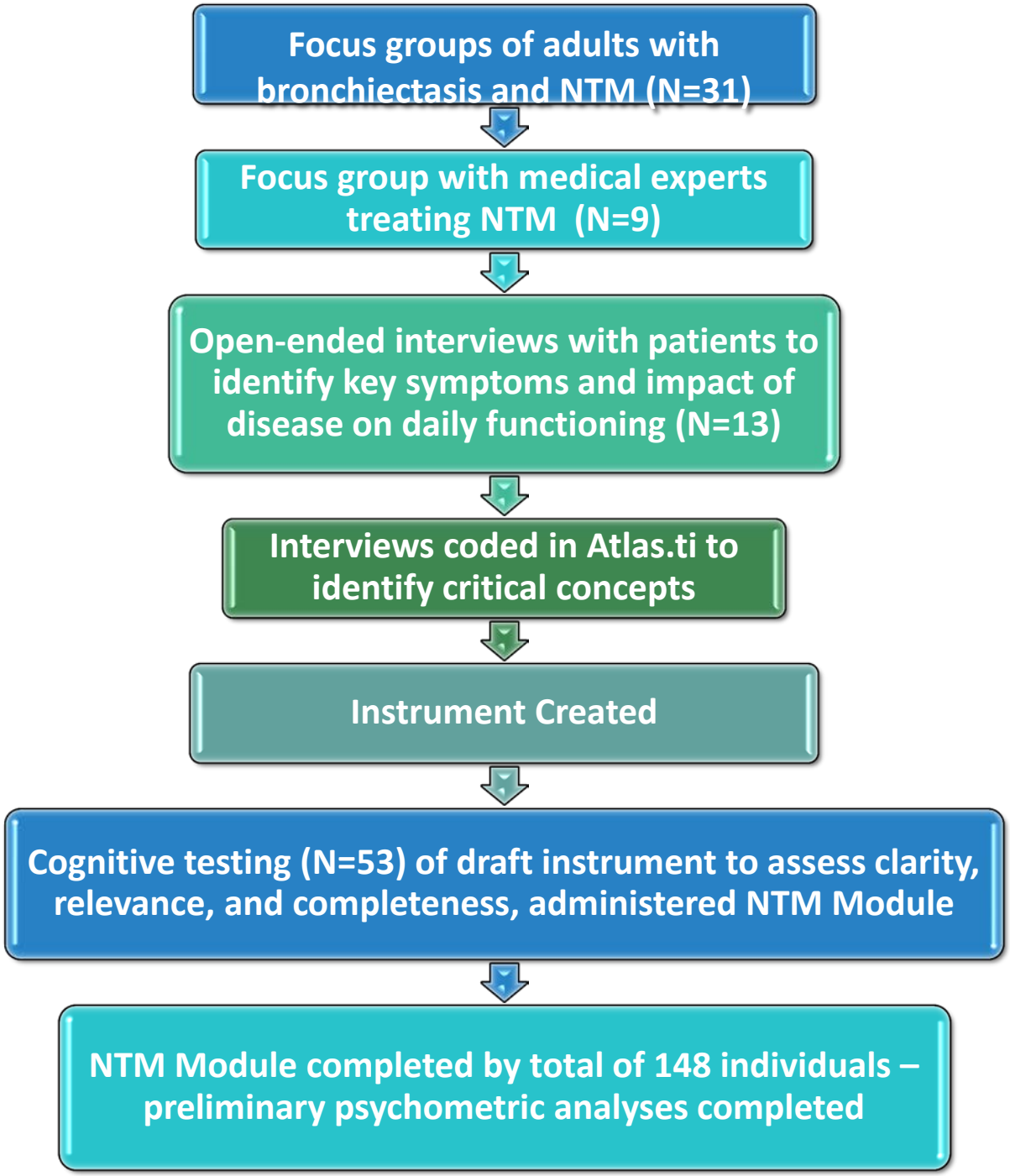
Objectives

- **Nontuberculous mycobacteria (NTM) is a substantial cause of pulmonary infections and can affect those with chronic respiratory diseases, such as cystic fibrosis (CF) and bronchiectasis.**
- **NTM is rare, poorly understood, and difficult to treat, with few clear identified endpoints to evaluate new medications in randomized, controlled trials.**
- **We are developing a patient-reported outcome (PRO) that identifies key symptoms, tracks the progression of disease, and can serve as an important end-point in clinical trials of new therapies (FDA Guidance, 2009)**
- **The aim of this study was to develop an instrument for NTM symptoms; this can be used with existing PROs measures for CF (CFQ-R) and bronchiectasis (QOL-B)**

Methods

- **We followed the FDA Guidance on PROs (2009)**
- **Reviewed published literature on NTM to identify critical symptoms and challenges of living with NTM**
- **Focus groups, moderated by a psychologist, were conducted with adults with NTM + bronchiectasis at 2 sites, N=31**
- **A consensus panel of 9 pulmonologists with expertise in NTM provided input on how NTM and its treatment affects their patients**
- **Open-ended interviews were conducted with 13 patients: asked how NTM affects their daily lives; including frequent and difficult symptoms, effects on physical, emotional, and social functioning. Patients then completed the QOL-B; coded in Atlas.ti**
- **Cognitive testing, using a standard "think aloud" procedure conducted with 53 adults; input on the preliminary items & rating scale options**
- **We completed an initial psychometric validation of the module in 148 patients**

Measurement Development Process



Patient Demographics

	Focus Groups (N=31)	Open-Ended Interviews (N=13)	Cognitive Testing (N=53)
Gender			
N (%)			
Female	**29 (93.5%)**	**12 (92.3%)**	**45 (83.3%)**
Male	**2 (6.5%)**	**1 (7.7%)**	**8 (14.8%)**
Ethnicity/Race			
Caucasian	**31 (100%)**	**13 (100%)**	**47 (87%)**
Hispanic	**0**	**0**	**5 (9.3%)**
Not reported	**0**	**0**	**2 (3.8%)**
Age			
Mean	**67.8 years**	**65.9 years**	**66.3 years**
(Range)	**(54.9 – 91.1 years)**	**(42 – 82 years)**	**(28 – 86 years)**

Key Themes

Main themes from Focus Groups (N=31)
• Frequent pain (dull, aches, pressure in chest) • Metal taste in mouth
• Fever • Lack of sleep

Main themes from Open-Ended Interviews (N=13)
• Fatigue • Sensitivity to smell
• Sensitivity to cold/chills • Hot flashes/sweats

Main themes from Physician Panel (N=9)
• Memory loss • Body Image issues
• Side effects from medications: GI problems • Weight loss with greater disease severity

Results

- **Focus groups and open-ended interviews identified eating issues, sleep quality, fever, and chills; physicians also identified body image as a concern**
- **The new NTM Module consists of eight unique symptoms; administered to 148 patients (α = .73); very good reliability**

Sample items from NTM module

"Bothered by cold weather?"

"Have you experienced problems with memory?"

Internal consistency of NTM module (N = 148)

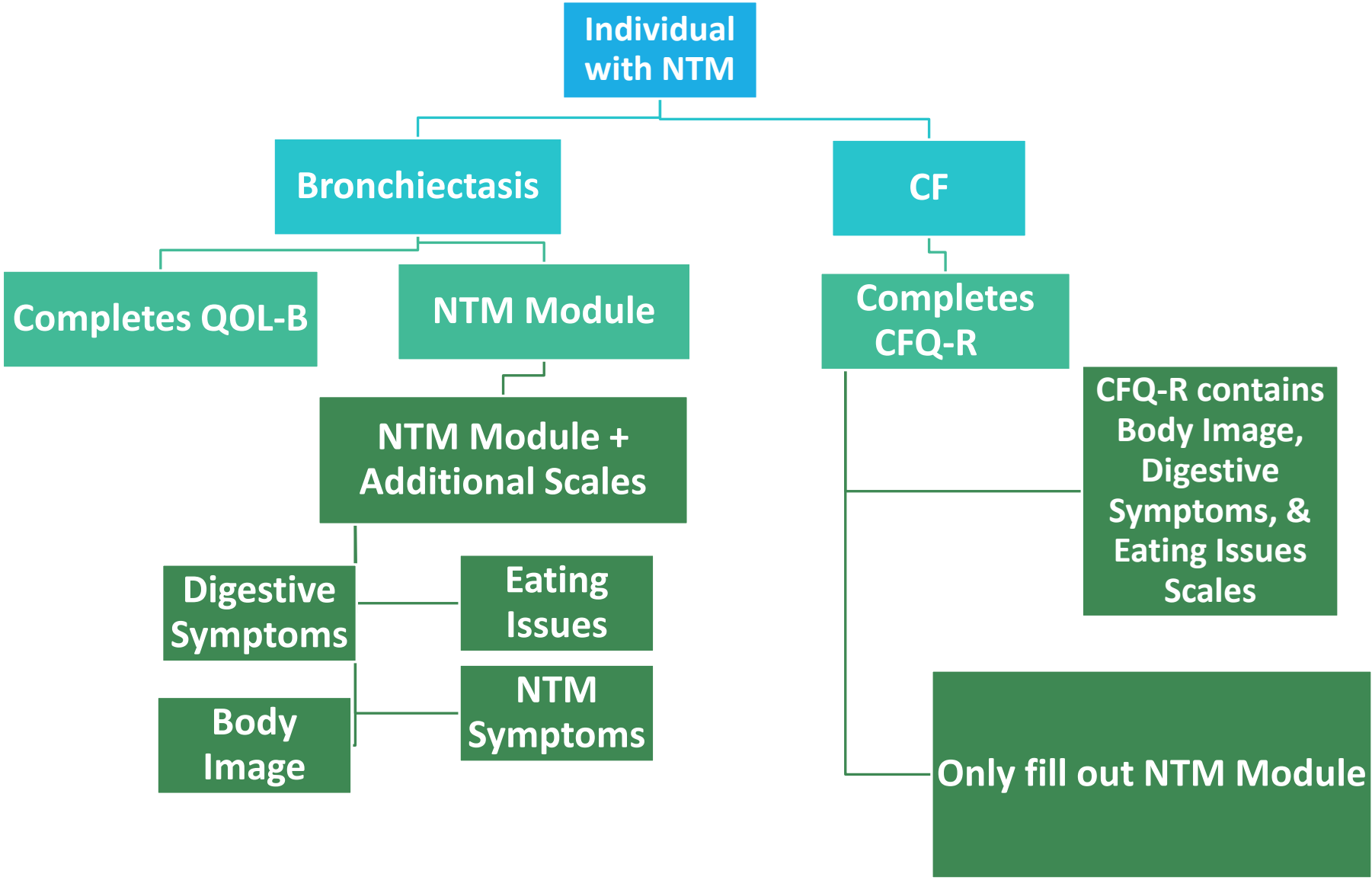
Scale Name	Cronbach's Alpha
NTM Symptoms	0.73
Body Image	0.76
Eating Problems	0.89
Digestive Symptoms	0.75

Multitrait analysis of NTM module (N = 148)

Item	Abbreviated Item Content	*NTM Symptoms*
NTM48	Feverish (chills, sweating)	0.42[a]
NTM49	Problems sleeping	0.39[a,b]
NTM50	Pain	0.41[a]
NTM51	Bothered by cold weather	0.51[a]
NTM52	Sensitivity to smell	0.37[a,b]
NTM53	Sensitivity to taste	0.39[a]
NTM54	Bad taste in mouth	0.48[a]
NTM55	Memory problems	0.45[a]

[a]Item-scale correlation adjusted for overlap (item removed from its scale for correlation)
[b]Item-scale correlation is <.40

Algorithm for administering NTM module with QOL-B or CFQ-R



Summary & Future Directions

- **Cognitive testing indicated that the draft items were relevant, clear, and easy to understand**
- **Strong reliability**
- **When utilizing NTM module with non-CF bronchiectasis: use module + Body Image, Eating Issues, & Digestive Symptoms scale (elicited from those with bronchiectasis)**
- **Next steps include additional psychometric testing, and identification of the meaningful change on this instrument**

Challenges in design of clinical trials for NTM lung infections

Anne E. O'Donnell MD

October 15, 2015

GEORGETOWN UNIVERSITY

Disclosures

- Principal Investigator/Grant support to GU for clinical trials
  - Insmed (inhaled liposomal amikacin)
- Foundation support to GU for Bronchiectasis Registry
  - COPD Foundation
- Consultant/Advisor
  - Insmed (inhaled liposomal amikacin): in Jan 2014
  - Xellia Pharmaceuticals (manufactures amikacin and colistin)

- No FDA approved therapies

NTM and clinical trials

In a perfect world

- Medications are simple
- Medications are tolerable
- Results are easy to evaluate:
  - Patient feels better
  - Infection is cured
  - Lung damage reversed
- Infection never recurs

Reality

- Regimen is complex
- Side effects are troublesome
- What constitutes response?
  - Microbiology
  - Imaging
  - Lung function
  - Patient's symptoms
- "Cure" is elusive

NTM and clinical trials

- Microbiologic results
  - Reduction in organism counts
  - Eradication of organism
  - Duration of response
  - Presence or development of resistance
- Imaging results
- Lung function results
- Patient reported outcomes
  - Exacerbations are not a clinical feature in NTM

NTM and clinical trials
Microbiology

- Current “gold standard”
  - 12 months of negative cultures while receiving Rx
- How are cultures processed?
  - Routine practice
    - Haphazard, standard lab evaluation
  - Tyler
    - Monthly
    - Semiquanititative cultures
    - Macrolide susceptibility testing
    - Genotyping

- ***Griffith DE et al. Am J Respir Crit Care Med 2015;192:754-760***

NTM and clinical trials Microbiology

- Tyler results
  - 180 patients with MAC and nodular bronchiectasis
  - Greater than 12 months of three drug therapy
    - 82% had culture conversion to negative
    - Microbiologic recurrences during therapy in 14%
      - 73% reinfection
      - 27% true relapse
    - Microbiologic recurrences after therapy in 48%
      - 75% reinfection
      - 25% true relapse
        - ***Wallace RJ et al. Chest 2014;146:276-282***

NTM and clinical trials Microbiology

- South Korean results
  - 217 patients with MAC and nodular bronchiectasis
  - Daily or intermittent three drug therapy
    - 71-72% sputum culture conversion to negative
    - Only 4 patients had recurrence while on therapy
    - No post therapy results
      - ***Jeong B et al. Am J Respir Crit Care Med 2015;191:96-103***
- Cavitary MAC disease
  - 49 subjects with MAC and cavitary disease
    - Thrice weekly regimen
    - 4.1% culture conversion
      - ***Lam PK et al. Am J Respir Crit Care Med 2006;173:1283-1289***

NTM and clinical trials Microbiology

- MAC and M. abscessus refractory to treatment
  - Salvage with bedaquiline
    - 10 subjects
      - 8 macrolide resistance
      - 6/10 had microbiologic response
        - ***Philley JV et al. Chest 2015;148:499-506***
  - Salvage with inhaled liposomal amikacin
    - 90 patients: MAC 64%, m. abscessus 36%
      - 10/44 MAC patients converted at day 56; 11/44 at day 84
      - 0/15 M. abscessus converted at day 56; 1/15 at day 84
        - ***Biller JA et al. Am J Respir Crit Care Med 2015;191:A6295***

NTM and clinical trials
Microbiology endpoint

- Advantages
  - Hard end point
  - Reproducible if done in advanced mycobacterial lab
- Problems
  - How to define success?
    - Three negative cultures while on therapy
    - One positive culture “doesn’t count”
    - What about after the conclusion of therapy
      - Defining relapse vs new infection
      - How long to monitor

NTM and clinical trials
Imaging

- Heterogeneous findings
- Nodular vs cavitary disease
  - Waxing and waning bronchiolitis
- Lack of standardized CXR or CT scoring
- Radiation dosing and exposure
  - ***McCunney RJ. Chest 2015;147:872***
  - ***Doss M. Chest 2015;147:874***
- Two trials that reported serial imaging findings
  - ***Jeong B et al. Am J Respir Crit Care Med 2015;191:96-103***
  - ***Lam PK et al Am J Respir Crit Care Med 2006;173:1283-89***

NTM and clinical trials
Lung function testing

- Lung function results
  - Pulmonary function tests
  - 6 min walk test
- Paucity of published data
- Heterogeneous patient population
- Probably only helpful for monitoring adverse effects of inhaled medications

NTM and clinical trials
Patient reported outcomes

- Mortality
  - Fortunately, a rare outcome
- Morbidity
  - Fatigue
  - Fever
  - Cough
  - Hemoptysis
  - Weight loss
  - Night sweats
  - Shortness of breath
  - Sputum production
    - ***Olivier KN et al. Annals ATS 2014;11:30-35***

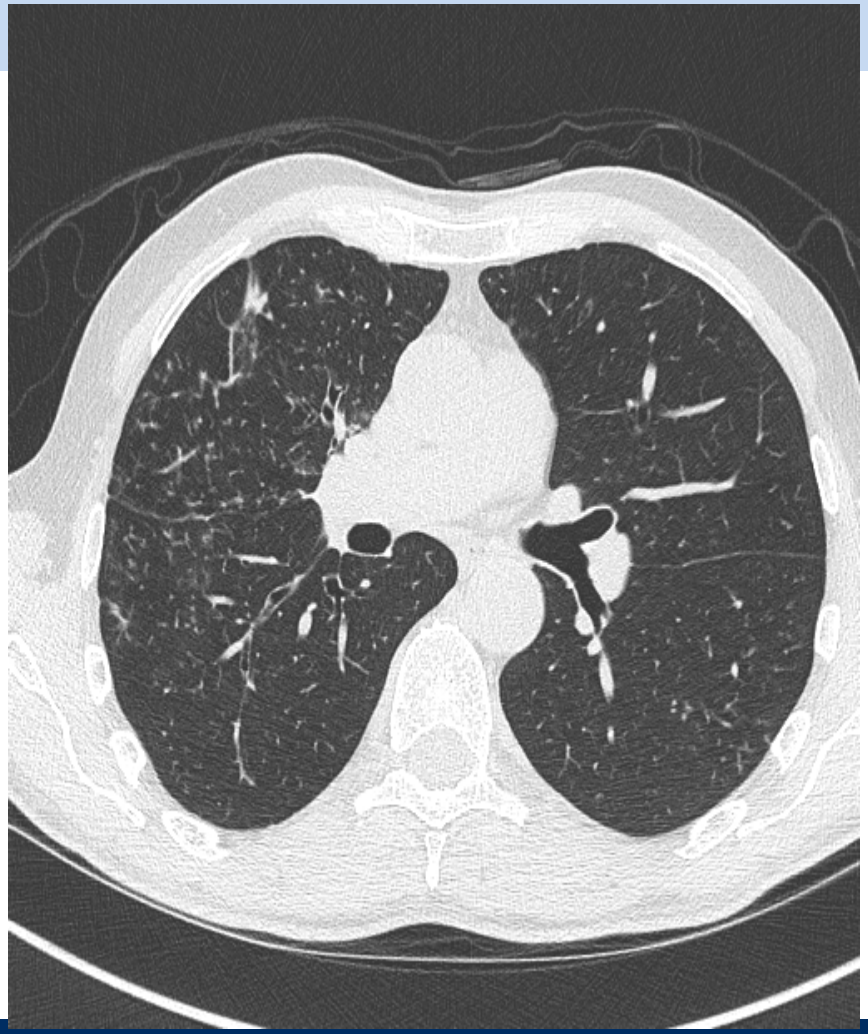
NTM and clinical trials
Patient reported outcomes

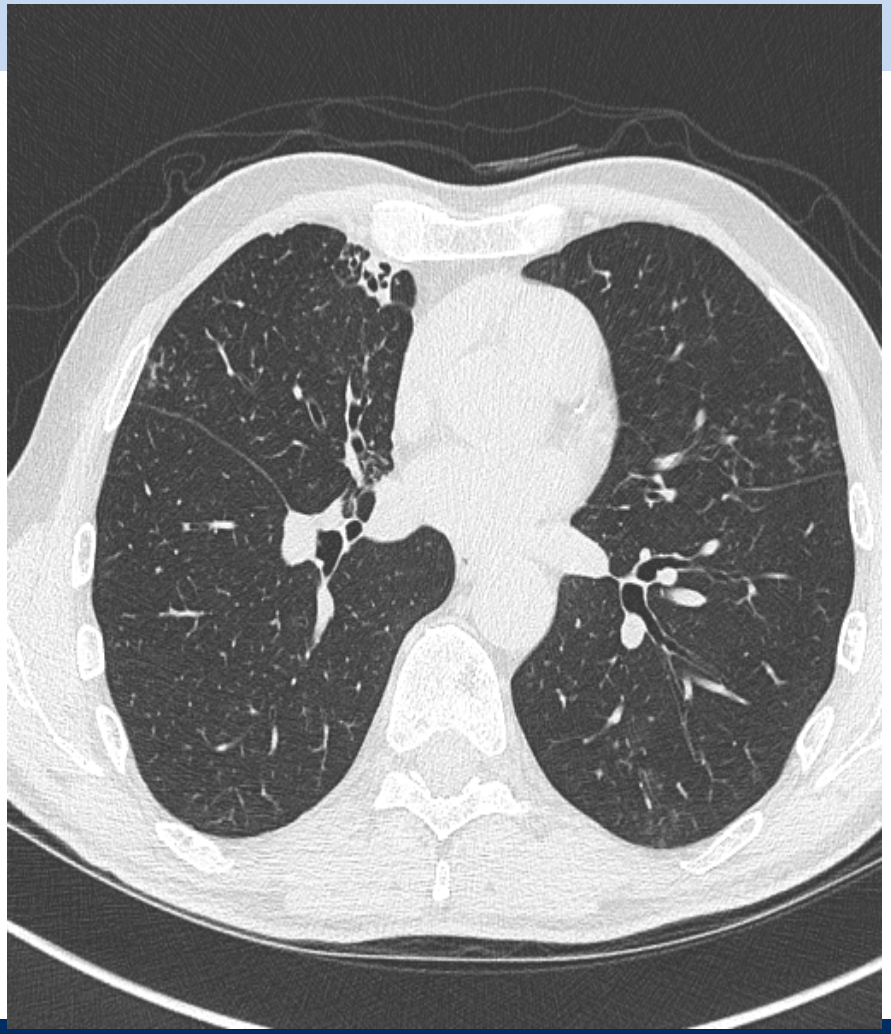
- 20 patients with refractory NTM infection
  - 15 m. abscessus, 5 MAC
  - Inhaled amikacin added to regimen
    - 8/20 had at least one negative culture
    - 5/20 had persistently negative cultures
    - 9/20 had improved symptom scores
    - 7 unchanged, 4 worsened symptom scores
      - » ***Olivier KN et al. Annals ATS 2015;11:30-35***
- Quality of life bronchiectasis with NTM specific questions
  - » ***Quittner A et al. ERJ 2015;46:A2635***

NTM and clinical trials
Confounding factors

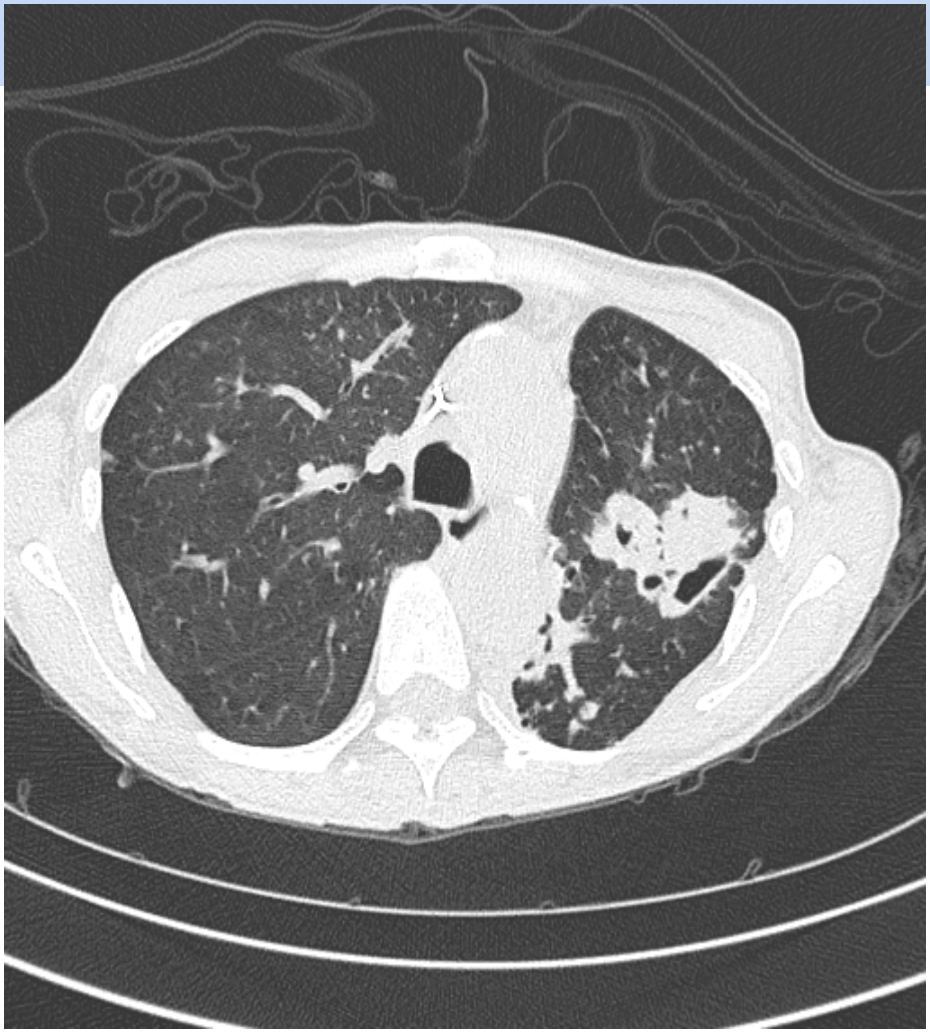
- Heterogeneous disease
  - MAC vs M. abscessus
  - Nodular bronchiectasis vs cavitary disease
    - NTM causing the structural damage
      - Female predominant
    - NTM superimposed on chronic disease
      - Males and females affected
      - Cystic fibrosis
      - Emphysema
- Co-infections with other bacteria
  - Pseudomonas, staphyloccus, nocardia, aspergillus

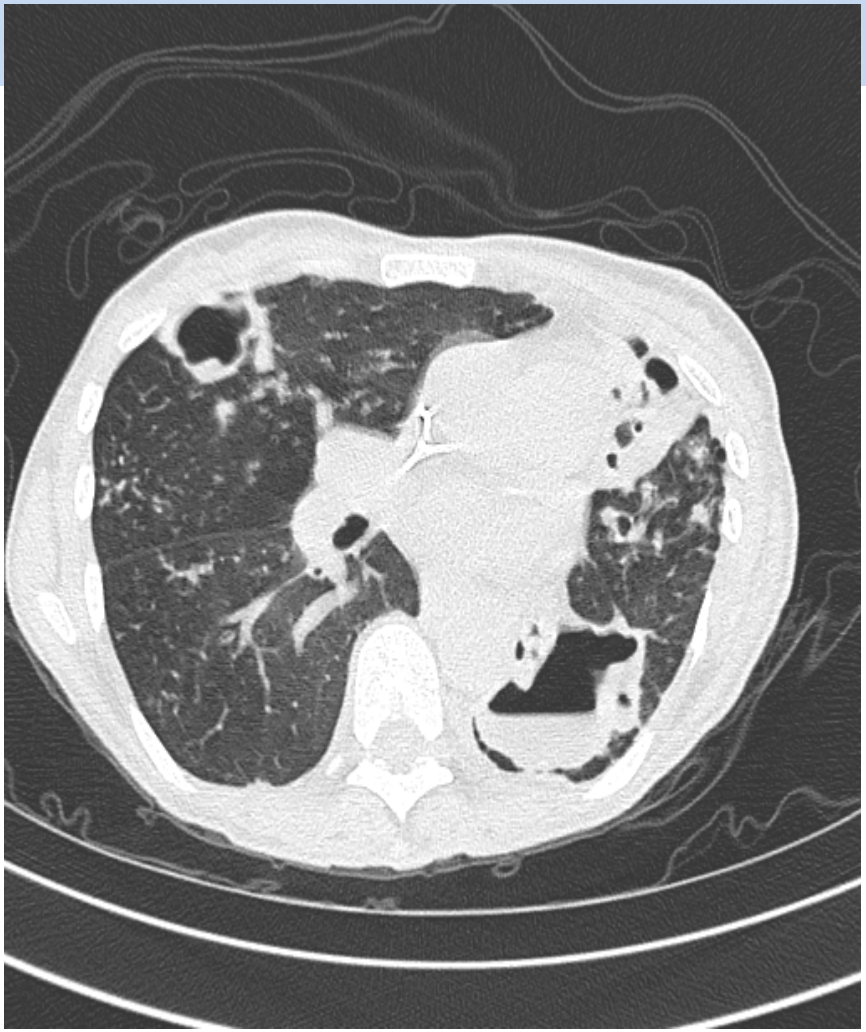
65 year old male with MAC and pseudomonas aeruginosa



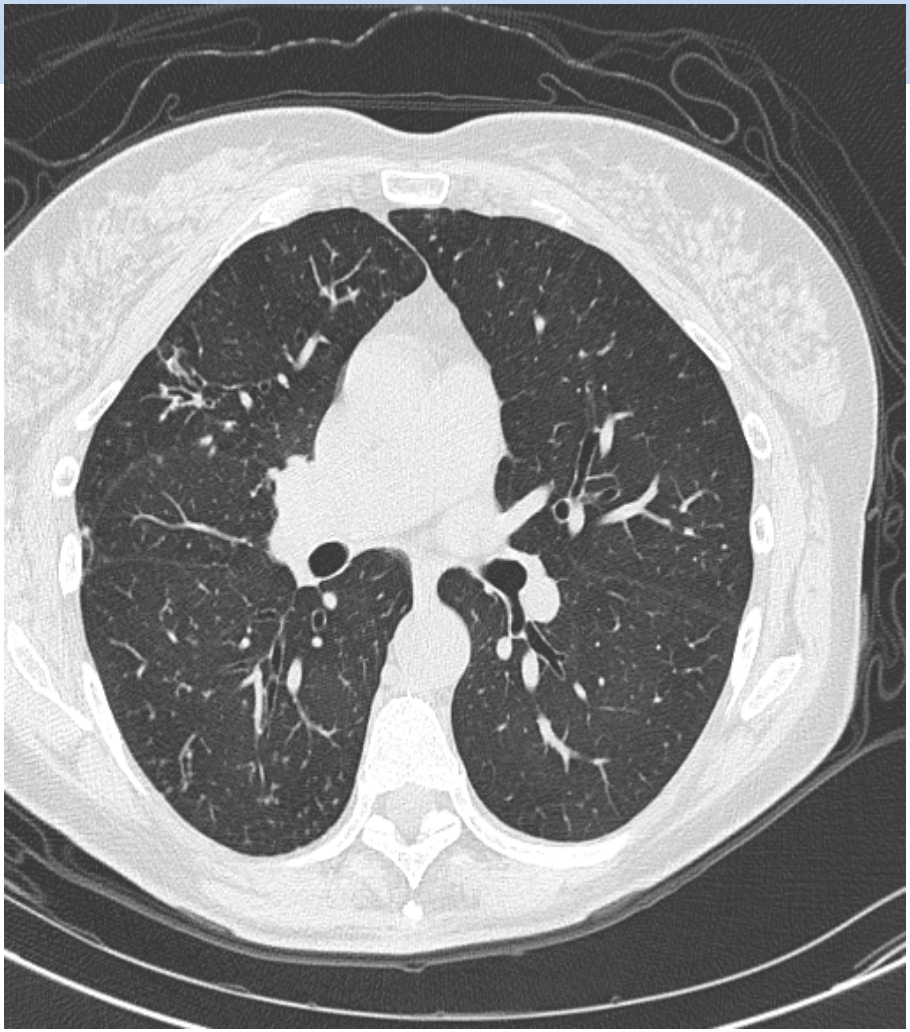


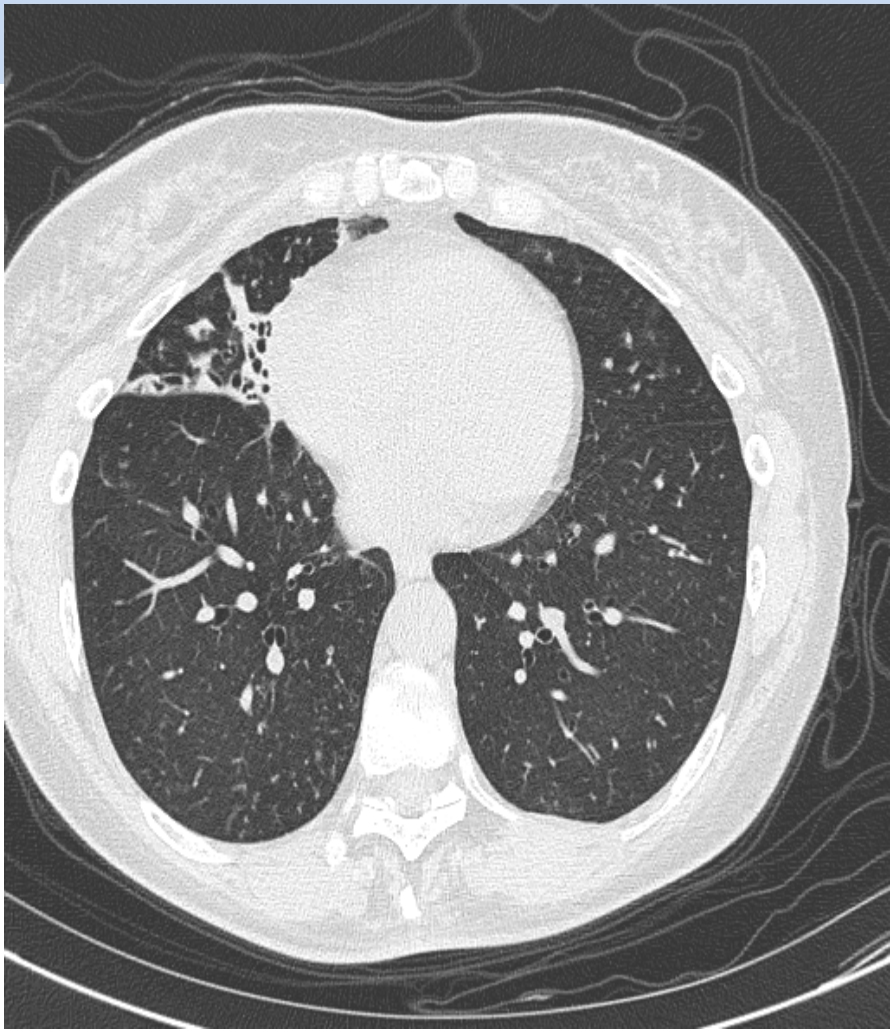
59 year old female with MAC



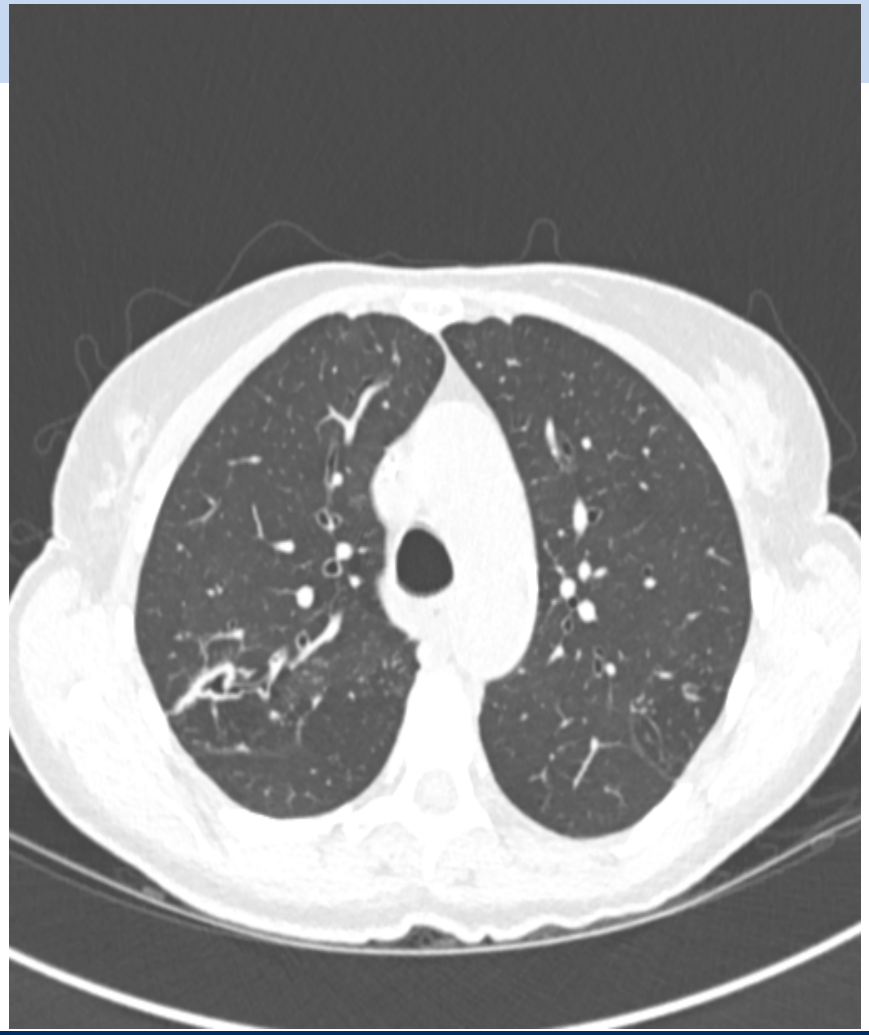


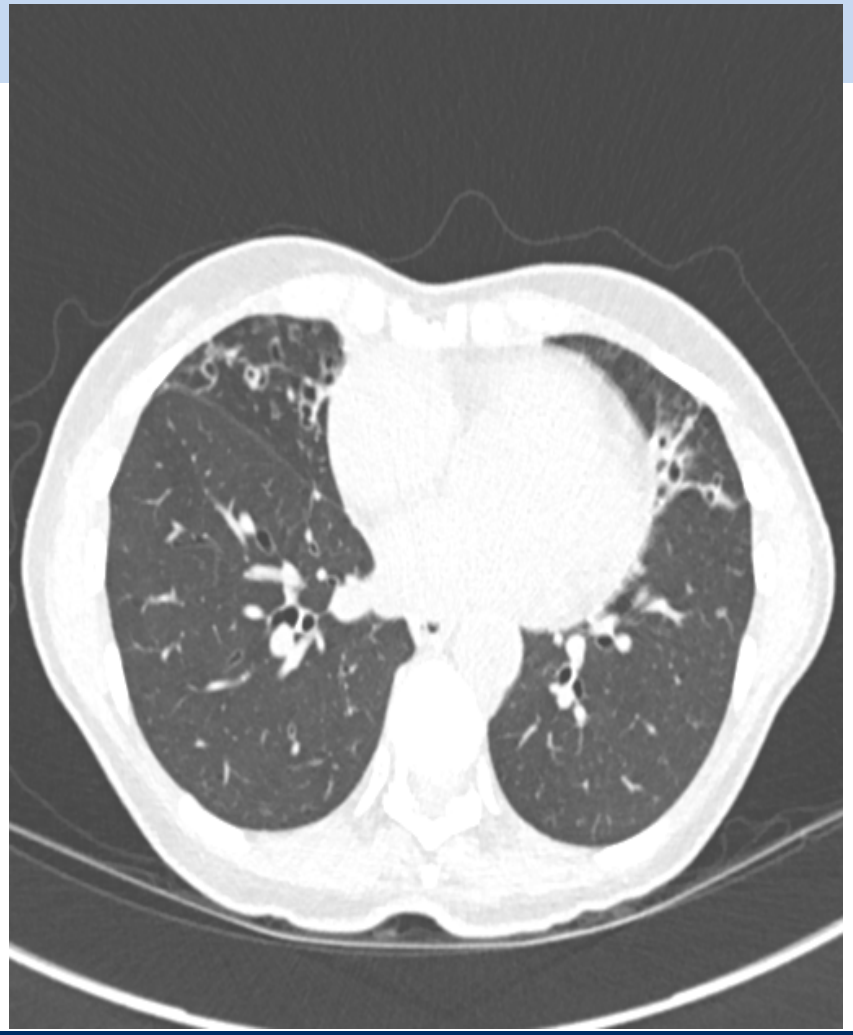
56 year old female with MAC





72 year old female with m. abscessus





NTM and clinical trials
Conclusions/Discussion

- Imaging endpoints
  - Not currently feasible
- Pulmonary function endpoints
  - Not predictive of overall outcomes
  - Helpful for monitoring inhaled antibiotic toxicity
- Patient reported outcomes
  - Vital, need to be in all trials
  - Need to continue after conclusion of therapy
  - Assess adverse treatment effects vs disease effects

NTM and clinical trials Conclusions/Discussion

- Microbiologic endpoint probably best
  - Standardization of culture collection and processing
  - Consider Stratifying trials
    - MAC only: M. avium vs M. intracellulare vs others
      - Virulence issues
        - ***Koh W et al. Chest 2012;142:1486-1488***
        - ***Boyle DP et al. Am J Respir Crit Care Med 2015;191:1310-1317***
    - M. abscessus only: M. abscessus abscessus vs others
      - ***Griffith DE et al. Annals ATS 2015;12:436-439***
    - Nodular vs cavitary disease
    - Evaluate impact on co-infecting organisms, if present
  - Prolonged microbiologic follow up after therapy

NTM and clinical trials
Serological monitoring?

- Serodiagnosis of MAC reported from Japan
  - IgA antibodies against mycobacterial gycopeptidolipid
    - Potentially supportive for confirming diagnosis
    - Possibly helpful for monitoring response to disease
  - Not commercially available in US
  - Not validated as a diagnostic or monitoring tool
  - May be helpful in the future/may warrant further evaluation
    - ***Kobayashi K. Jpn J Infect Dis 2014;67:329-332***
    - ***Shigeki K et al. Eur Respir J 2015;46:PA2675***

NTM and clinical trials

- Questions for the panel and the FDA
  - Microbiologic endpoint AND clinical outcome
- Acknowledgments:
  - Work done to date
  - FDA and pharma
  - Patients
    - NTM Info and Research
    - US Bronchiectasis Registry