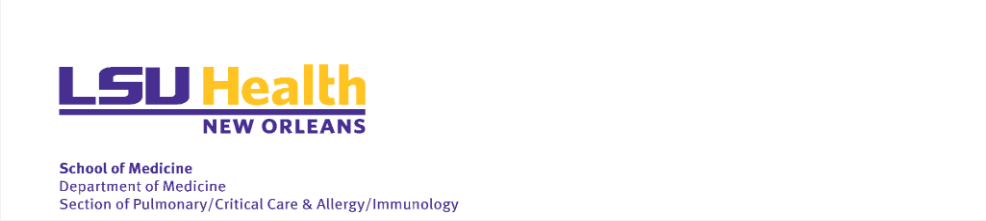
NTM PULMONARY DISEASE IN NON-HIV : SPECTRUM AND CHALLENGES

WHO DAT MOTT?

Juzar Ali MD, FRCP(C), FCCP
LSU Health Sciences Center - Alumni Klein Professor of Medicine
Section Pulmonary/Critical Care & Allergy/Immunology
Director LSUHSC -Wetmore Mycobacterial Disease/NTM Program
University Medical Center - NTM (Non-Tuberculosis Mycobacterial) Disease Clinic

Nicole Lapinel MD
LSU Health Sciences Center - Assistant Professor of Medicine
Co-Director LSUHSC-Wetmore Mycobacterial Disease/NTM Program
University Medical Center - NTM Disease Clinic



www.lsudocs.com **www.lsuhsc.edu**
http://www.medschool.lsuhsc.edu/tb/
http://ntm.lsuhsc.edu

DISCLOSURES

- Consultant / Speaker's Forum : Oxford Immunotec
- Consultant / Advisory Board : INSMED

- Study PI /Co-PI: INSMED 212/312 (Inhaled Liposomal Amikacin for refractory MAC)
- Study PI / Co-PI: INSMED Willow Study (Non-CF Bronchiectasis)

- Acknowledgment: Some slides by Dr NL

OBJECTIVES

At the end of the presentation, the participants will:

- Have an overview of the spectrum of NTM presentations in clinical practice
- Appreciate the challenges clinicians encounter in management of NTM Pulmonary Disease
- Understand the importance of programmatic multi-dimensional approach in management

- SECTION A : JA SECTION B NL

A ‘BUG’ BY (M)ANY OTHER NAME(S)

- Anonymous
- Atypical
- Unclassified
- Unknown
- Tuberculoid
- Environmental
- Opportunistic
- MOTT

PULMONARY NTM CONSIDERATIONS BY PATHOGEN

M. avium-intracellulare Complex

- Most common
- Traditionally diagnosed in middle-aged or older white men
  - usually with a history of cigarette smoking and underlying lung disease
- Most patients have cavitary changes, some with nodules associated with bronchiectasis or nodular/bronchiectatic disease
- Heterogenous clinical presentation
  - particularly in older female nonsmokers with no underlying lung disease

M. kansasii

- Closely parallels clinical disease caused by *M. tuberculosis*
  - radiographic findings similar to re-activated pulmonary TB
    - upper lobe predilection and cavitation in ~90% of patients
    - although some patients with non-cavitary disease also confirmed to have *M. kansasii* disease
- Characteristically older men from urban environments who are cigarette smokers with one or more underlying lung diseases

M. abscessus

- Typically older nonsmoking females with no known underlying or predisposing lung disease
- Clinically and radiographically resembles non-cavitary (nodular bronchiectatic) pulmonary MAIC disease

DIFFERENTIATING PULMONARY TB FROM NTM

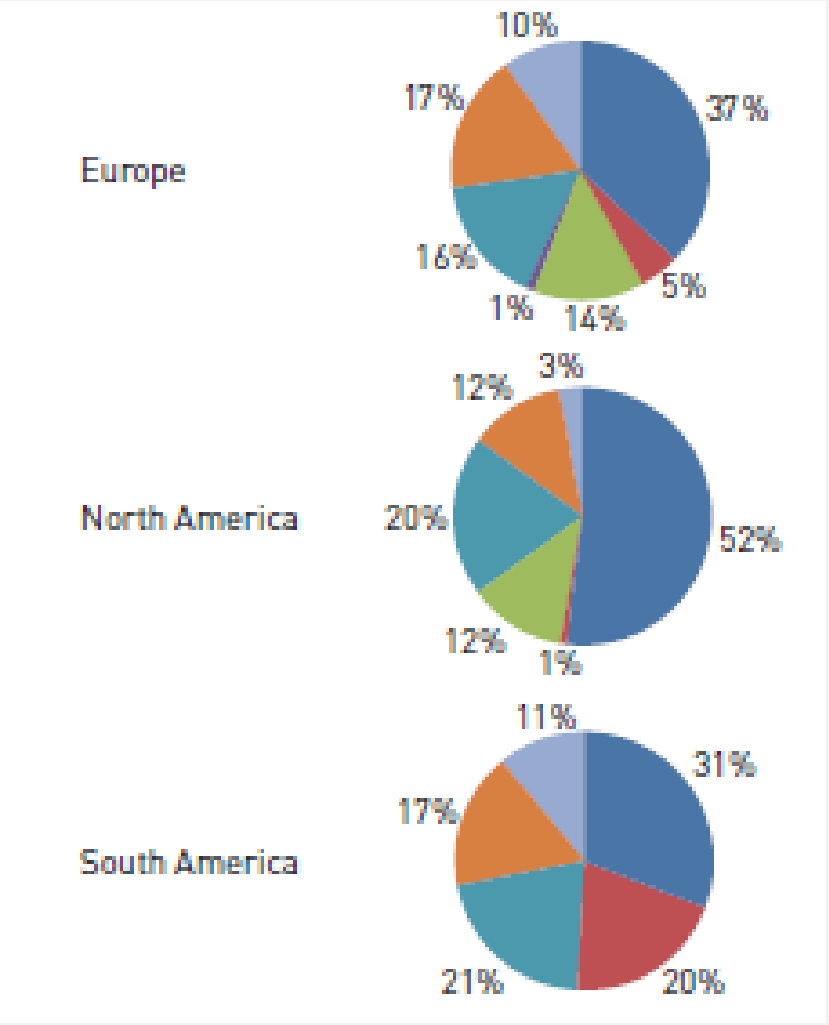
- Importance
  - Infection control
    - NTMs are not contagious
    - TB is contagious and requires isolation
  - Smear positive patients often placed in isolation and started on an anti-TB regimen
  - Isolating and treating non-TB patients:
    - inappropriate treatment regimens
    - drain on resources
    - patient burden
- Why it's difficult in the absence of culture results…
  - overlapping clinical presentation (symptoms, radiographic findings)

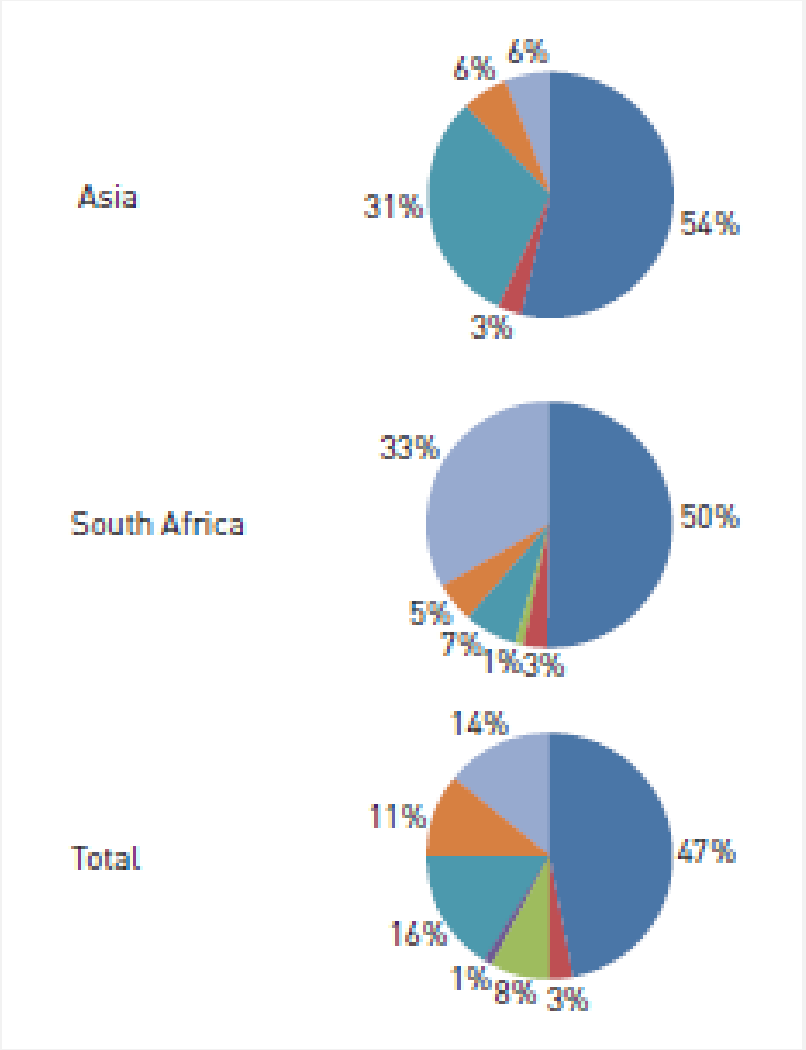
PULMONARY DISEASE RISK FACTORS

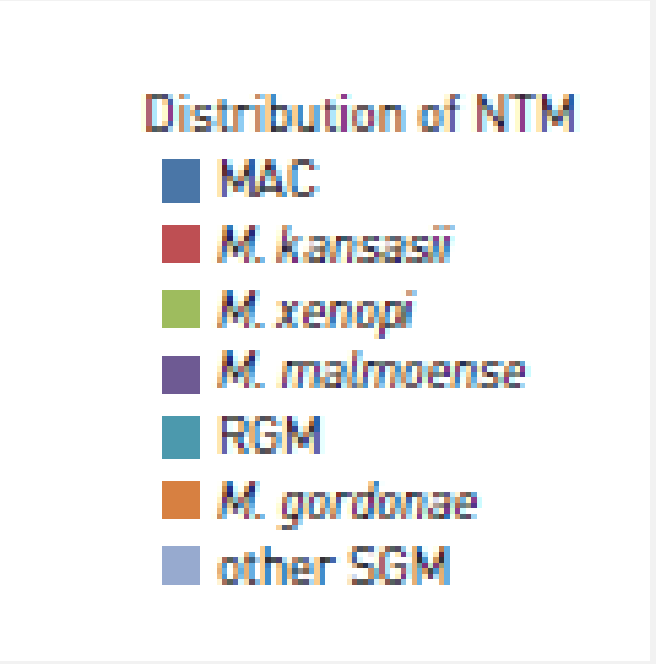
NTM Risk Factor
Pulmonary conditions
Cystic Fibrosis
COPD
Prior TB
Bronchiectasis
Silicosis/Fibrosis
Asthma
Lung cancer
GERD
Persons living with HIV/AIDS
Soil exposure
Alcohol abuse
Smoking
Low body weight
Steroid use/Immune suppression

TB Risk Factor	Relative Risk
Persons living with HIV/AIDS	50–170[1]
Transplant recipients	20–74[1]
Silicosis	30[1]
Chronic renal failure/hemodialysis	10–25.3[1]
Recent TB infection (within prior 2 years)	15[2]
Carcinoma of the head and neck	16[2]
Radiographic evidence of prior healed TB	6–19[2]
TNF-alpha blockers	1.7–9.0[2]
Glucocorticoid treatment	4.9[2]
Infants and children < 5 years of age	2.2–5[2]
Diabetes mellitus	2–3.6[2]
Low body weight	2–3[2]
Cigarette smoker (1 pack/day)	2–3[2]
Gastrectomy	2–5[1]
Jejunoileal bypass	27–63[1]
Alcohol abuse	2.0–5.9[3]

WORLDWIDE NTM DISTRIBUTION (RESPIRATORY)







Hoefsloot W, van Ingen J, Andrejak C, et al. *Eur Respir J*. 2013;42(6):1604-1613.

NTM PULMONARY DISEASE IN THE UNITED STATES

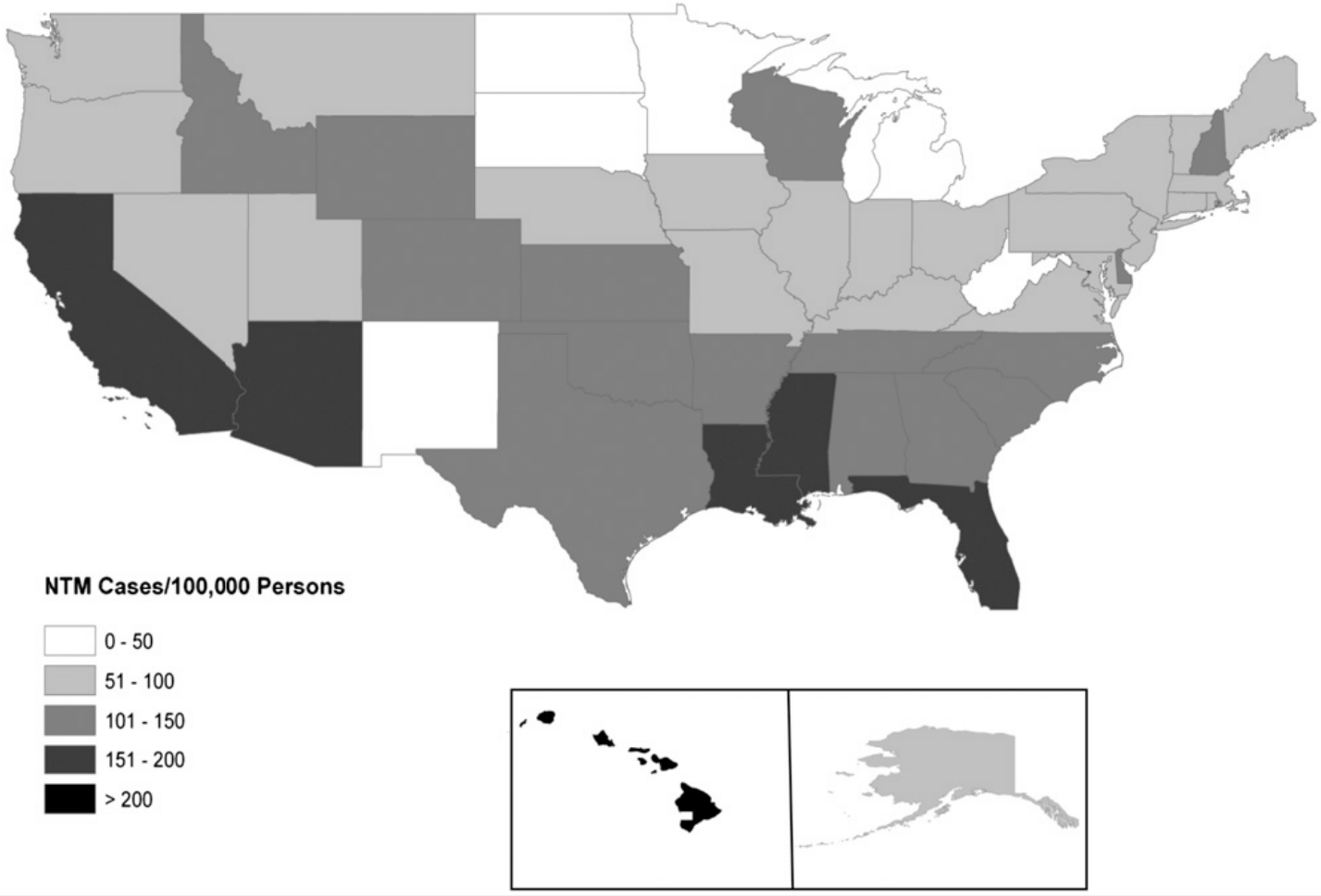


Figure 1. Prevalence of pulmonary nontuberculous mycobacteria cases among a sample of U.S. Medicare Part B enrollees aged 65 and older, 1997 to 2007. NTM = nontuberculous mycobacteria.

Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. *Am J Respir Crit Care Med*. 2012;185(8):881-886.

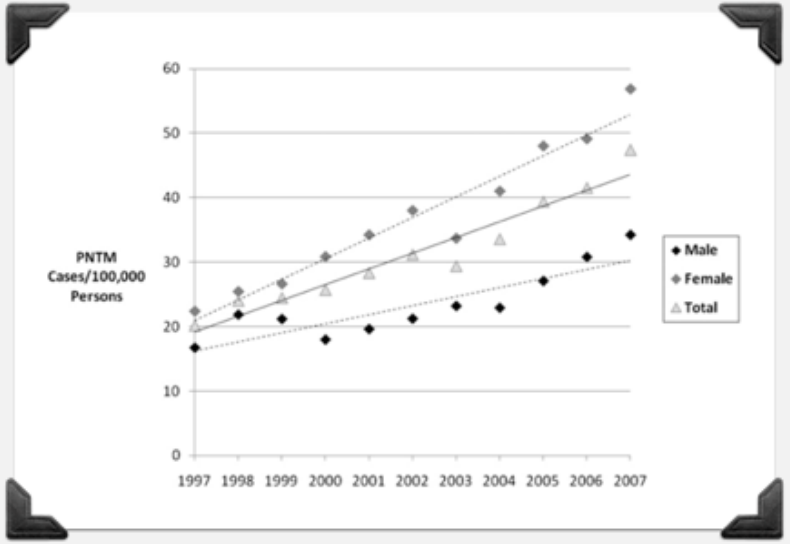
BURDEN OF PULMONARY NTM IN THE UNITED STATES

- Based on 2003 – 2007 Medicare data
- Projected 8% annual increase in prevalence
- Estimated 86,244 cases in 2010 at an annual cost $815 million; 87% inpatient
- 70% of NTM disease cases occurred in oceanic coast line & gulf states
- Medication cost: 76% of all total cost

Strollo SE, Adjemian J, Adjemian MK, Prevots DR. The Burden of Pulmonary Nontuberculous Mycobacterial Disease in the United States. *Annals ATS*. 2015;12(10):1458-1464.

NTM PREVALENCE (SNAPSHOT)

- **Medicare beneficiaries 1997-2007 (Adjemian et al):** Annual prevalence of NTM among those > 65 years old significantly increased from 20 cases/100,000 persons in 1997 to 47 cases/100,000 persons in 2007



- **Oregon 2007-2012 (Henkle et al):** Identified 1,146 incident pulmonary NTM cases; median age 69. Cases were more likely female (56%). Most were MAC (86%) and 6% were M. abscessus/chelonae. Incidence increased from 4.8/100,000 (2007) to 5.6/100,000 (2012) (p = 0.21). In patients > 80 yrs incidence increased to more than 25/100,000.

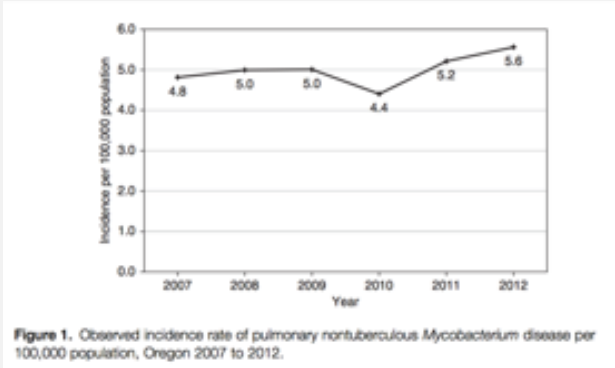


Figure 1. Observed incidence rate of pulmonary nontuberculous *Mycobacterium* disease per 100,000 population, Oregon 2007 to 2012.

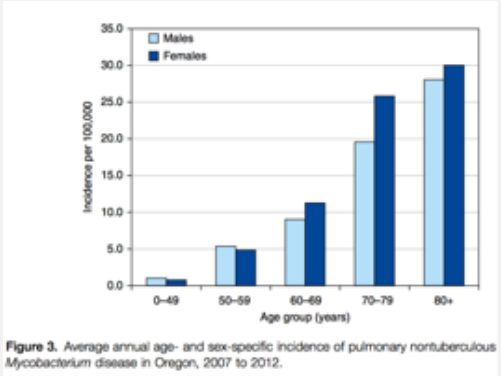


Figure 3. Average annual age- and sex-specific incidence of pulmonary nontuberculous *Mycobacterium* disease in Oregon, 2007 to 2012.

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

- 1st study describing **environmental/socioeconomic determinants** of PNTM disease clustering by county
- 5% sample of > 65 yo Medicare Part B beneficiaries, 1997-2007
- Included 2.3 million individuals: 16,508 PNTM claims representing 2,548 unique cases (~6.5 NTM claim/case)
- **Counties located in clusters had:**
  - greater population densities
  - higher median household income levels
  - higher max/min temperatures
  - greater proportion of area as surface water
  - higher daily evapotranspiration

TABLE 1. SUMMARY OF ALL SIGNIFICANT CLUSTERS IDENTIFIED BY SaTScan OF PULMONARY NONTUBERCULOUS MYCOBACTERIAL DISEASE AMONG U.S. MEDICARE BENEFICIARIES 65 YEARS OF AGE AND OLDER

Cluster Type	Centroid County and State	No. of Counties (Radius, km)	Relative Risk	*P* Value
High risk	Highlands, FL	24 (159.4)	1.9	<0.0001
	Santa Barbara, CA	18 (344.5)	2.0	<0.0001
	Montgomery, PA	5 (42.2)	2.2	0.0001
	New York, NY	1 (0)	2.7	0.002
	Milwaukee, WI	1 (0)	3.6	<0.0001
	Kalawao, HI	3 (114.8)	3.7	<0.0001
	Plaquemines, LA	3 (70.2)	6.5	<0.0001
Low risk	Washington, RI	16 (106.7)	0.5	0.02
	Iosco, MI	93 (351.4)	0.4	<0.0001
	Roane, WV	208 (268.5)	0.4	<0.0001
	Polk, MN	247 (689.7)	0.4	<0.0001
	Cayuga, NY	95 (289.0)	0.3	<0.0001

7 significant HIGH-risk clusters

- 3 Southern Coastal Parishes identified within the cluster in **Louisiana**:
  - **Plaquemines**
  - **Jefferson**
  - **St. Bernard**

- Previous nationwide study on NTM in CF patients:
  - **Orleans Parish = highest NTM prevalence among 21 sites**

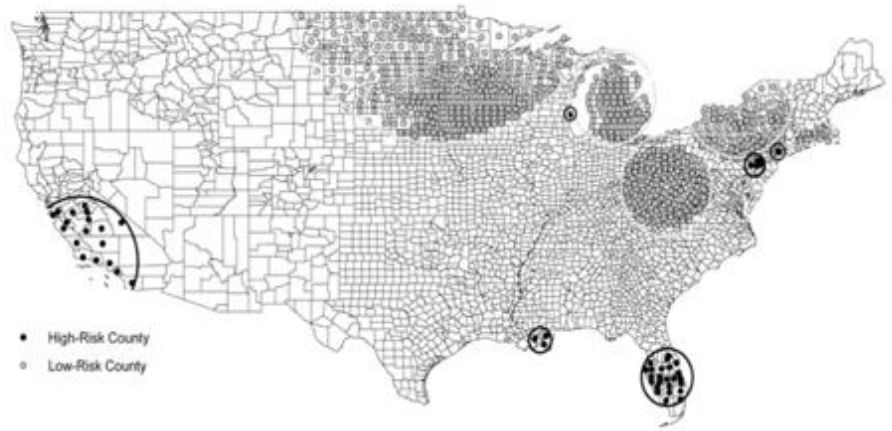


Figure 1. Significant clusters of counties identified by SaTScan as being at either high or low risk for pulmonary nontuberculous mycobacterial (PNTM) disease among U.S. Medicare beneficiaries 65 years of age and older.

TRANSMISSION

- **Environment = major source of human NTM infections**
- **Routes of exposure:**
  - 1) Aerosolization and inhalation
  - 2) Swallowing and aspiration
  - 3) Introduction into wounds (injury/surgical)
  - 4) Zoonotic (pigs, birds, cattle)
- Rarely transmitted from patient to patient***

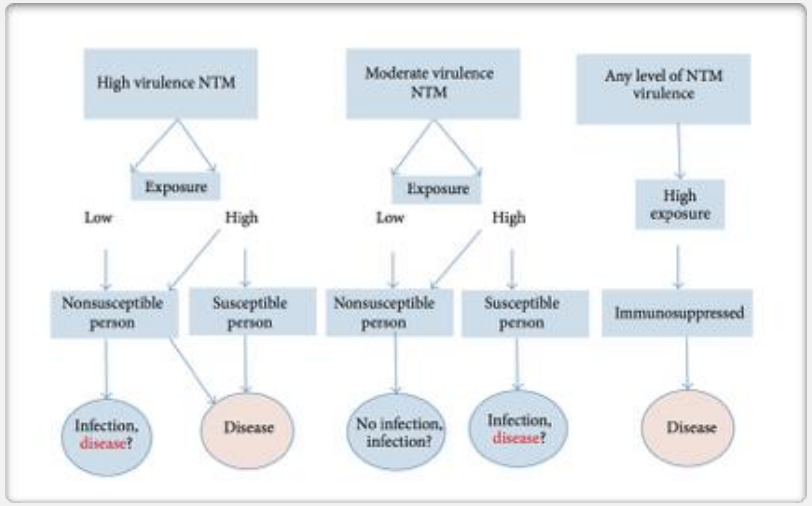
Environmental Sources of NTM
Soils, acidic pine forest or coastal swamp soils
Dusts from agriculture, garden & potting soils
Drainage waters from acidic pine forests or coastal swamps
Natural waters
Drinking water
Water / ice from refrigerators
Water from granular activated charcoal filters
Aerosols from natural & drinking waters
Aerosols from indoor humidifiers
Mist from indoor swimming pools

PROVEN ROUTES OF NTM INFECTION

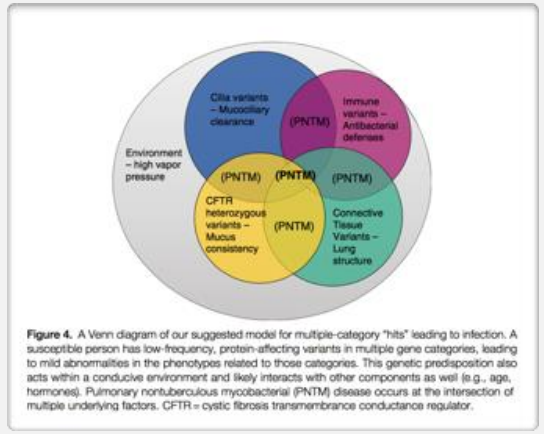
- 1) Matching **pulsed field gel electrophoresis patterns** of M. avium isolates from AIDS patients, Charles River water & drinking water in Boston
- 2) Matching **rep-PCR patterns** of M. avium isolates from a patient & their showerhead
- 3) M. avium infected patients & isolates from their household plumbing
- 4) Identical **16S rRNA sequences** of NTM isolates from patients & their potting soils
- 5) Similarity of **RFLP patterns** among human & porcine isolates indicates close genetic relatedness, suggesting that *M. avium* is transmitted between pigs and humans

PROPOSED MECHANISMS OF PATHOGENESIS

- **Susceptible patient:**
  - Chest wall abnormality
  - Anatomical lung abnormality
  - Mendelian abnormality***
  - Immunosuppressed
    - Autoimmune on anti-TNF-alpha
    - HIV/AIDS
    - Active malignancy on chemo/radiation
    - Steroids
    - Primary immunodeficiency



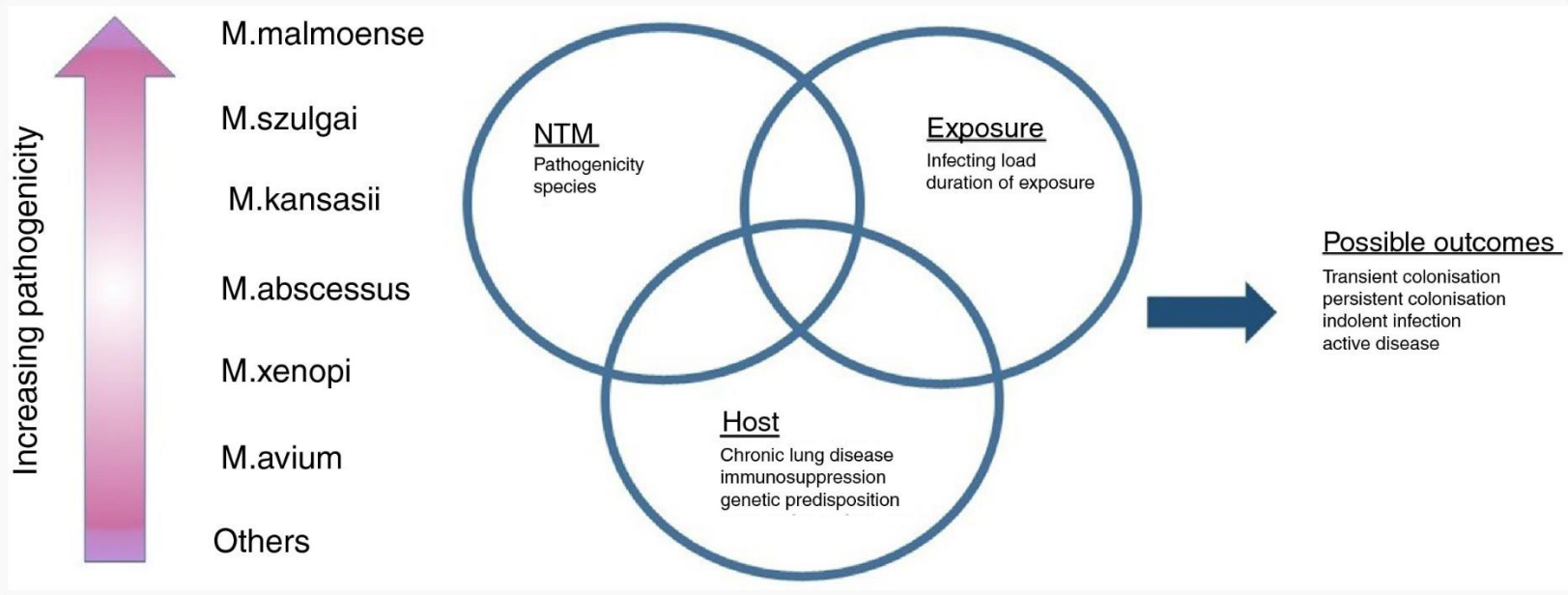
Highlight on Advances in Nontuberculous Mycobacterial Disease in North America. BioMed Research International Volume 2014 (2014)



"Pulmonary Nontuberculous Mycobacterial Infection: A Multisystem, Multigenic Disease." Szymanski et al

- **PULMONARY NTM DISEASE = Gene Variants + Environmental Exposure + Susceptibility**

PATHOGENESIS



Pneumol 2018; 24:120-131.

HOW BIG A PROBLEM IS THIS?

- Based on high prevalence of PPD reactivity to MAC : High
- Based on culture ID in lab specimens : High* increased prevalence from 20 to 47/100K in a10 year period ending 2007; Increased in the western and SE states ; more in Asian Pacific Islanders
- 40 % more likely to die if associated with co-morbid conditions** ***That is the key***
- Based on reportability : Unknown

PERSPECTIVE : NOT A BIG DEAL?**

- **Thus: either the bug is stupid or the host is smart ?

*** Yes it is seen more ….

- *** The bug is not stupid and if we combine the smart bug with the inadequate host response :

" Houston : we have a problem"

THE HOST

Defense mechanisms of the respiratory tract 1

Upper respiratory tract (nose, oropharynx, larynx)

Mechanical

Nasal hairs and sneezing

Nasal, oropharyngeal and sinuses ciliated epithelium

Saliva, **mucus**

Vocal cords

Innate immunity

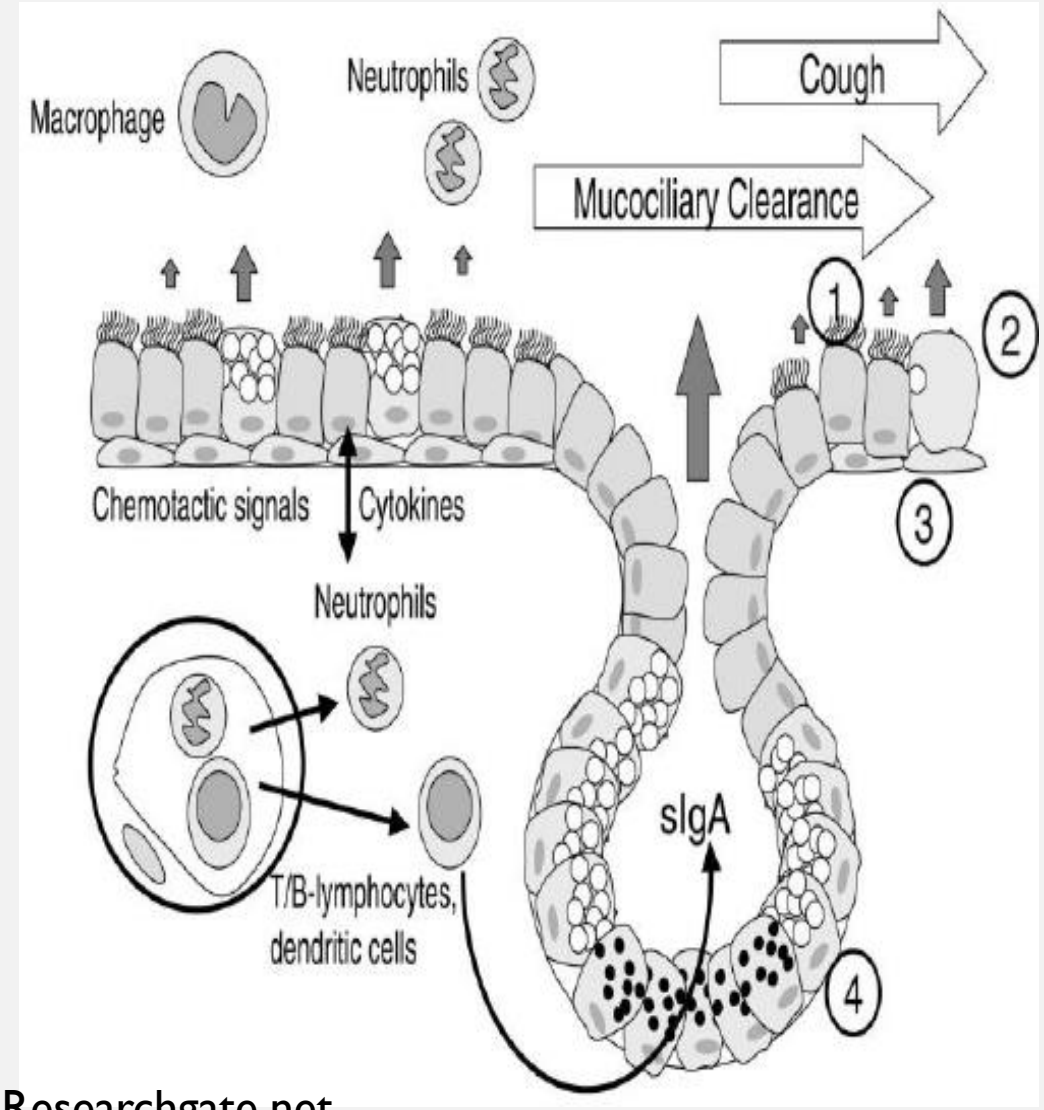
Complement

Proteases

Lactoferrin

Acquired humoral immunity

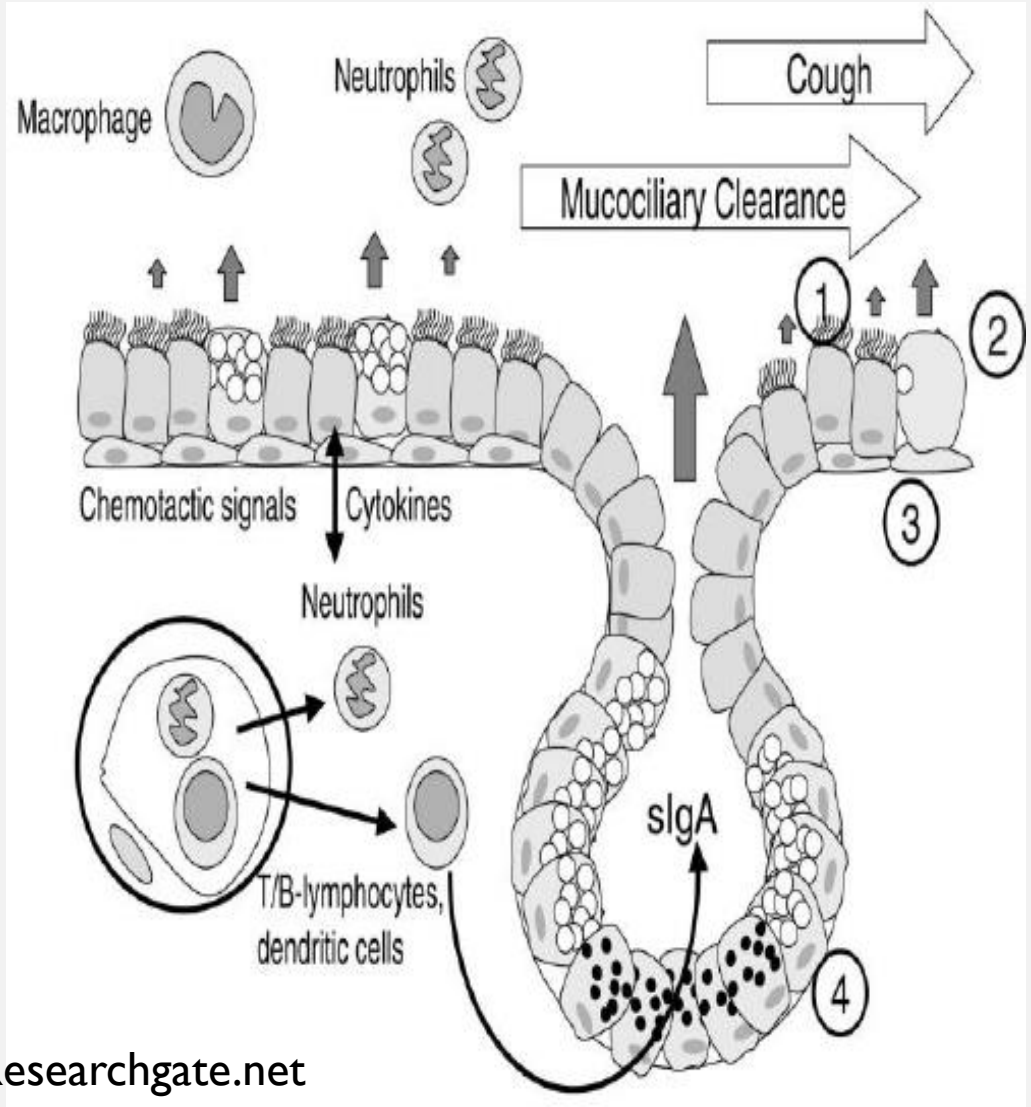
Secretory immunoglobulin (Ig-A and IgM



Researchgate.net

Defense mechanisms of the respiratory tract 2

Lower respiratory tract (tracheobronchial tree)
Mechanical
Mucociliary clearance
Cough and impaction on bronchial branching
Acquired cellular immunity
Bronchial-associated lymphoid tissue (BALT)
Humoral immunity
Secretory IgA and IgM



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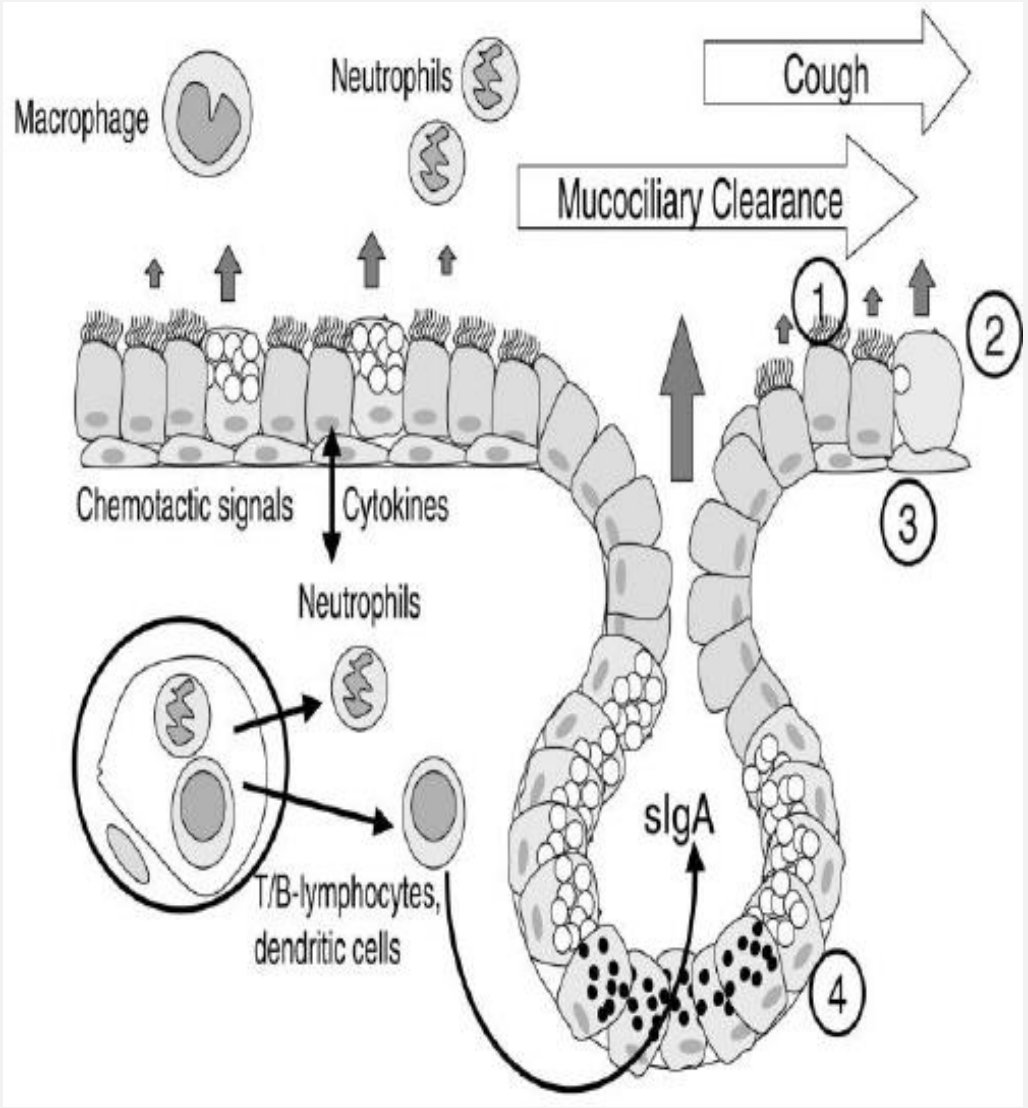
Defense mechanisms of the respiratory tract 3

Lung parenchyma (alveoli and lung interstitium)
Surfactant products (SP-A, SP-B, SP-D)
Phagocytic cellular mechanisms
Resident alveolar macrophages
Phagocytosis
Oxygen and nitrogen metabolites
Lysozyme, acid hydrolases
Recruited polymorphonuclear neutrophils (from pulmonary microvessels)
Phagocytosis
Oxygen and nitrogen metabolites
Lactoferrin, defensins (human neutrophil peptides 1–4)
Bacterial/permeability increasing protein
Cationic antimicrobial protein (CAP/azurocidin)



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PATHWAY OF PATHOGENESIS IN NON-IMMUNE COMPROMISED PATIENTS WITH A CONNECTION AND YET A DISCONNECT BETWEEN INFECTION, IMMUNE RESPONSE AND STAGES OF DISEASE

- Inhalation from soil/water/ Role of Aspiration
- Macrophage phagocytosis and binding through fibronectin receptors for cell wall moieties and through Complement.
- Vacuolar persistence/survival of MAC
- Shedding and macrophage turnover
- Alveolar Dendritic Cell migration to regional LN
- Differentiate into INF-G, TNF TH1 or cytotoxic Tc1 cells respectively IL-17, 21, 22
- DTH Reaction
- TH2 response with central caseation and necrosis

Mack U, Migliori GB, Sester M, et al. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. *Eur Respir J*. 2009;33(5):956-973. doi:10.1183/09031936.00120908

THE MICROBE
1. WHY SURVIVAL AND IMMUNE EVASION?*

- Biofilm formation, Cell wall characteristics blocking vacuolar acidification
- Inhibition of phagosome-lysosome fusion
- Anaerobic intracellular environment
- Induction of NTM related genes that enhance replication
- Inhibition of the host macrophage function and lymphocyte proliferation

THE GPL* DIFFERENCE : MICROBE

- Produced by NTM and not MTB
- Impacts colony morphology
- Smooth variants with nsGPL are cleared but rough variants without nsGPL evolve and persists
- The severity and persistence of disease depends upon the transition between smooth and rough variants .The variation and presence or absence of nsGPL and ssGPL dictates intracellular survival
- Serovariable oligosaccharides contribute to species specific pathogenesis.
- This coupled with biofilm formation dictates Immune evasion and survival of NTM

*The Gycopeptolipids

2. Why survival and immune evasion?*
The HOST FACTORS

Induction of macrophage apoptosis by down regulation of Bcl-2 gene
Absence of or sluggishness of the T helper lymphocyte or NK innate immunity

INFECTION, INSULT PLUS IMPAIRED HOST*

Impaired host
1. Defect in host defense**
2. Defect in clearance
3. Defect in flow (OAD)

Host response
1. Unopposed Neutrophilic elastase and Neutr ilic serine proteinases NSP activity*
2. Oxygen intermediates
3. Inflammatory cytokines

Blocked by A1AT
Could be blocked by inhibitor agents

-
-

In Non CF :
CFTR variants with single mutations
Association with Vit D deficiency

At an anatomic level
inflammation /edema/ulceration/neovascularization
Irreversible bronchiolar dilatation and tissue destruction
At the cytokine level
Increased mucus secretions
Inhibition of mucociliary clearance

If the question refers to *chicken* eggs specifically, the answer is still the egg,[7] but the explanation is more complicated. The process by which the chicken arose through the interbreeding and domestication of multiple species of wild jungle fowl is poorly understood, and the point at which this evolving organism became a chicken is a somewhat arbitrary distinction. Whatever criteria one chooses, an animal nearly identical to the modern chicken (i.e., a proto-chicken) laid a fertilized egg that had DNA identical to the modern chicken (due to mutations in the mother's ovum, the father's sperm, or the fertilized zygote).[8][4][9][10]
Put more simply by Neil deGrasse Tyson:
"Which came first: the chicken or the egg? The egg — laid by a bird that was not a chicken."[11]

Alternatively, if the question refers specifically to the chicken egg as it exists today, the answer may be different. Chickens produce a protein, ovocleidin-17 (OC-17), that is expressed in the uterus and causes the formation of the thickened calcium carbonate shell around modern chicken eggs. Because OC-17 is expressed by the hen and not the egg, the bird in which the protein first arose, though having hatched from a non-reinforced egg, would then have laid the first egg having such a reinforced shell: the chicken would have preceded this first 'modern' chicken egg.[9][12] This is only the case, however, if OC-17 arose after the domestication of their wild-fowl ancestors gave rise to chickens.

JUNGLE FOWL LEAD TO A CHICKEN ; CHICKEN PRODUCED OC-17 AND THE EGG

RESULT / SEQUELAE

- Resultant Granuloma formation
- Release of cytolytic and cytotoxic enzymes to form either a cavity, necrotic nodules

  Resulting in PRIMARY BRONCHIECTASIS / F/C disease

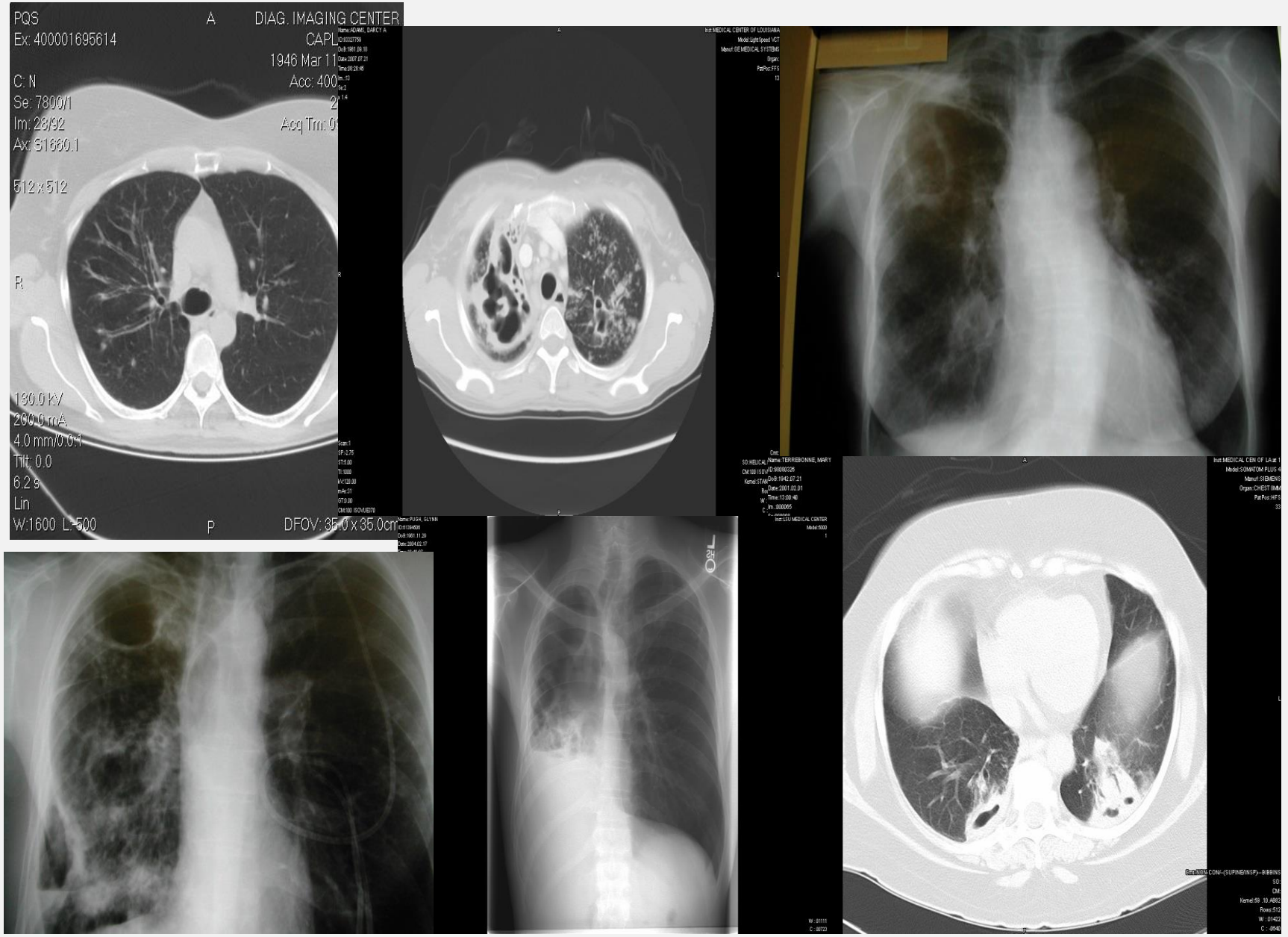
  or F/N disease with traction like cylindrical bronchiectasis

Add to the mix the underlying disease:

Type 3-4 Sarcoid/ IPF / COPD /Old TB

With its anatomical distortion

and secondary bronchiectasis



Over to You,
Dr Lapinel

PULMONARY DISEASE CT FINDINGS

Summary of features in pulmonary nontuberculous mycobacterial infection and *M. tuberculosis* infection

No imaging finding is sufficiently specific to exclude the diagnosis of tuberculosis.

NTM and TB	More common in TB	More common in NTM
Cavitary lesion or nodules	Thick walled cavity	Thin walled cavity
Multiple or single cavities	Cavity consolidation	Cavity & satellite nodules
Nodular infiltration	Bronchiectasis with upper lobe predominance.	Bronchiectasis with middle and upper lobe predominance
Tree-in-bud	Fibrodestruction	Bronchiectasis with cystic changes
Bronchiectasis	Volume loss	
Peribronchial wall thickening	Unilateral disease	
Interlobular septal thickening	Randomly distributed nodules	
Consolidation	Calcified parenchyma	
Atelectasis	Calcified lymph node	
Lymphadenopathy	Pleural effusion	
Pleural calcification	Pleural thickening	

Lim, Joel. Pictorial essay on CT imaging manifestations of pulmonary nontuberculous mycobacterial infection. 2015. doi:10.1594/ecr2015/C-2401.

CASE PRESENTATIONS

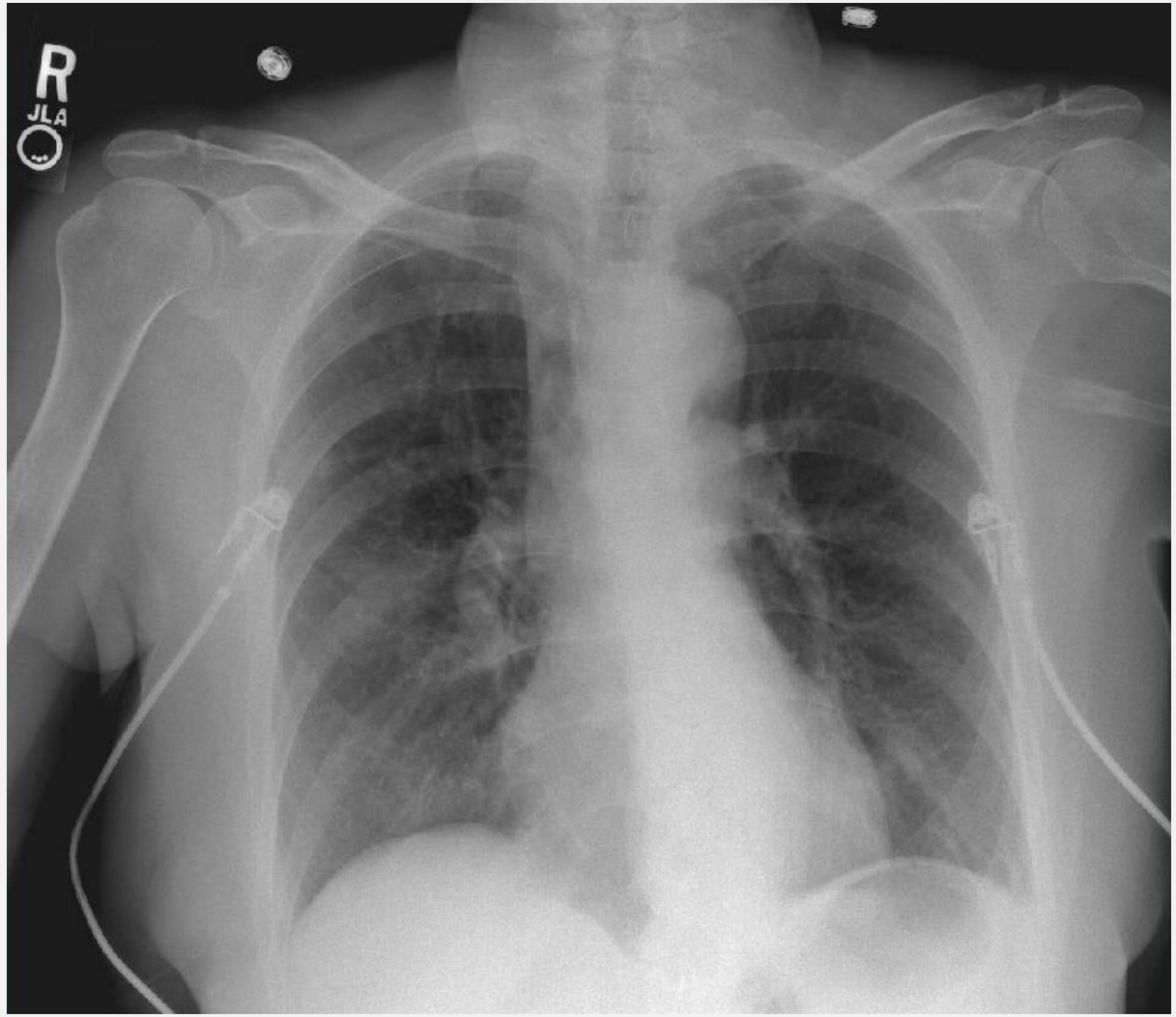
CASE #1

- CC: Chronic cough and fatigue
- 79 yo Caucasian F with **chronic cough** productive of whitish sputum present since 2003. Cough had been worse at night. She always noticed intermittent PND but not significant rhinorrhea; also with heartburn symptoms. She uses her Albuterol nebulizer 1-2x/day noting significant improvement in airway clearance. She denies fever, chills, N/V/D or night sweats. She reports 5 lb weight loss over 3-5 months despite decent appetite. She denies SOB at baseline but is no longer able to play tennis due to significant dyspnea and fatigue.
- PMHx: Chronic rhinitis, GERD, HTN, Osteopenia
- Social Hx: Never smoker; **Former gardener** (noting "I avoid the dirt now because of all the germs.")
- Meds: Flonase NS, Protonix, Singulair, Albuterol inh/nebulizer
- PE: **thin, asthenic elderly female**, bronchial BS LLL, rales RLL

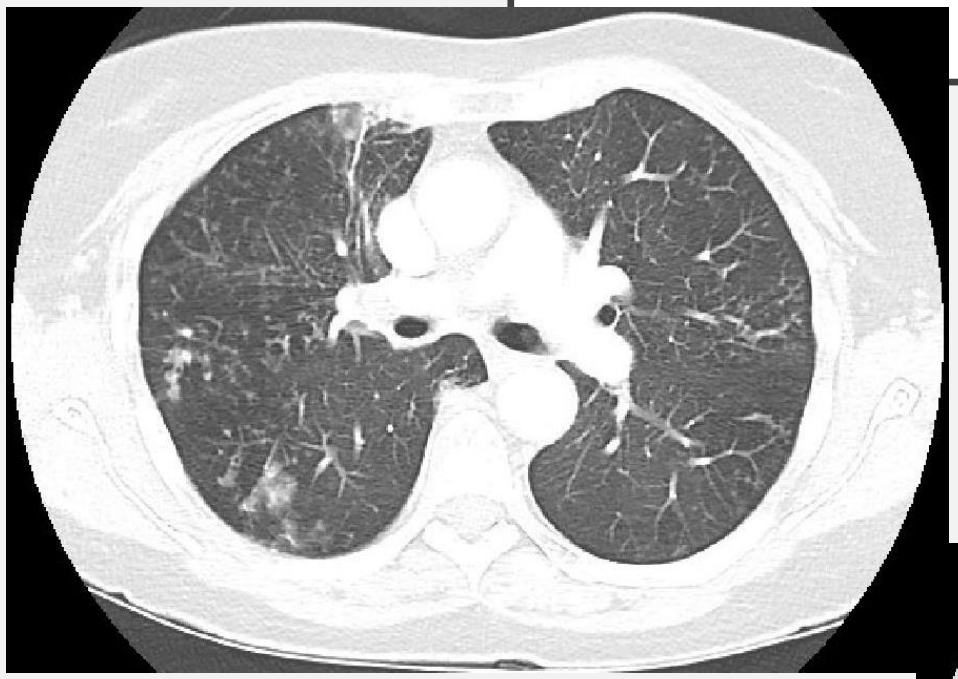
CASE #1

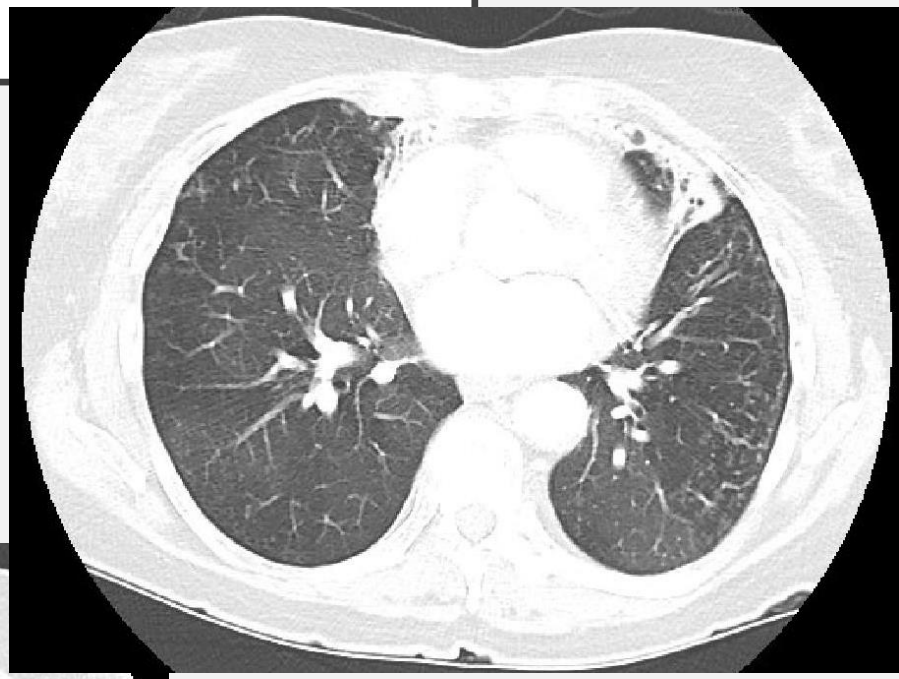
- **Pulmonary Function Test**
  - FEV1/FVC = .57
  - FEV1 = 1.02 (60%) → 1.15 post BD
  - FEF25-75% = 0.38 (25%)
  - TLC = 115%, RV = 162%
  - DLCO = 88%
  - **Moderate obstruction with significant postBD response and air trapping.**
- **Microbiology**
  - 2017: Sputum AFB x 3 = smear negative; MAC via liquid culture
  - 2017: Sputum Bacterial culture = negative
  - 2013: BAL = MAC; Pseudomonas

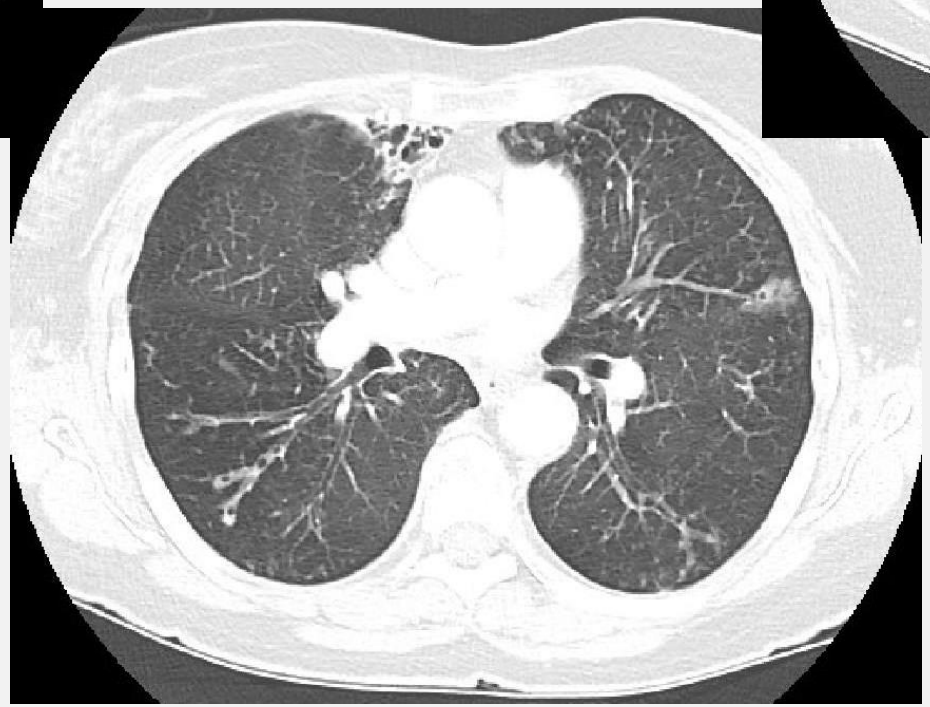
CASE #1



CASE #1







CASE #1

- Diagnosis: classic **"Lady Windermere Syndrome"**
- Recommended Treatment:
  - Rifampin / Ethambutol / Azithromycin three times weekly
  - Albuterol nebulizer 2-3x daily for airway clearance
  - Rhinitis: Flonase/Antihistamine
  - GERD: H2B
- Challenges:
  - Patient complained of nausea and diarrhea on days she would take her meds preventing her from leaving the house
  - Advised: Azithromycin AM, Ethambutol qhs, Rifampin qhs

CASE #2

- CC: Abnormal Chest CT + chronic cough
- 57 yo Caucasian F with **nonproductive cough** intermittently for "a few years" – worse in Spring/Fall. Had episode of scant **hemoptysis**, spontaneously resolved, but prompted bronchoscopy for further evaluation. Cough somewhat more productive of clear/white sputum since bronch. No shortness of breath. Some postnasal drip. No fever, chills, night sweats, weight loss. No established pulm history but recalls repeated episodes of bronchitis in early adulthood.

- PMHx: Breast ca s/p mastectomy/Chemo/XRT with metastatic recurrence

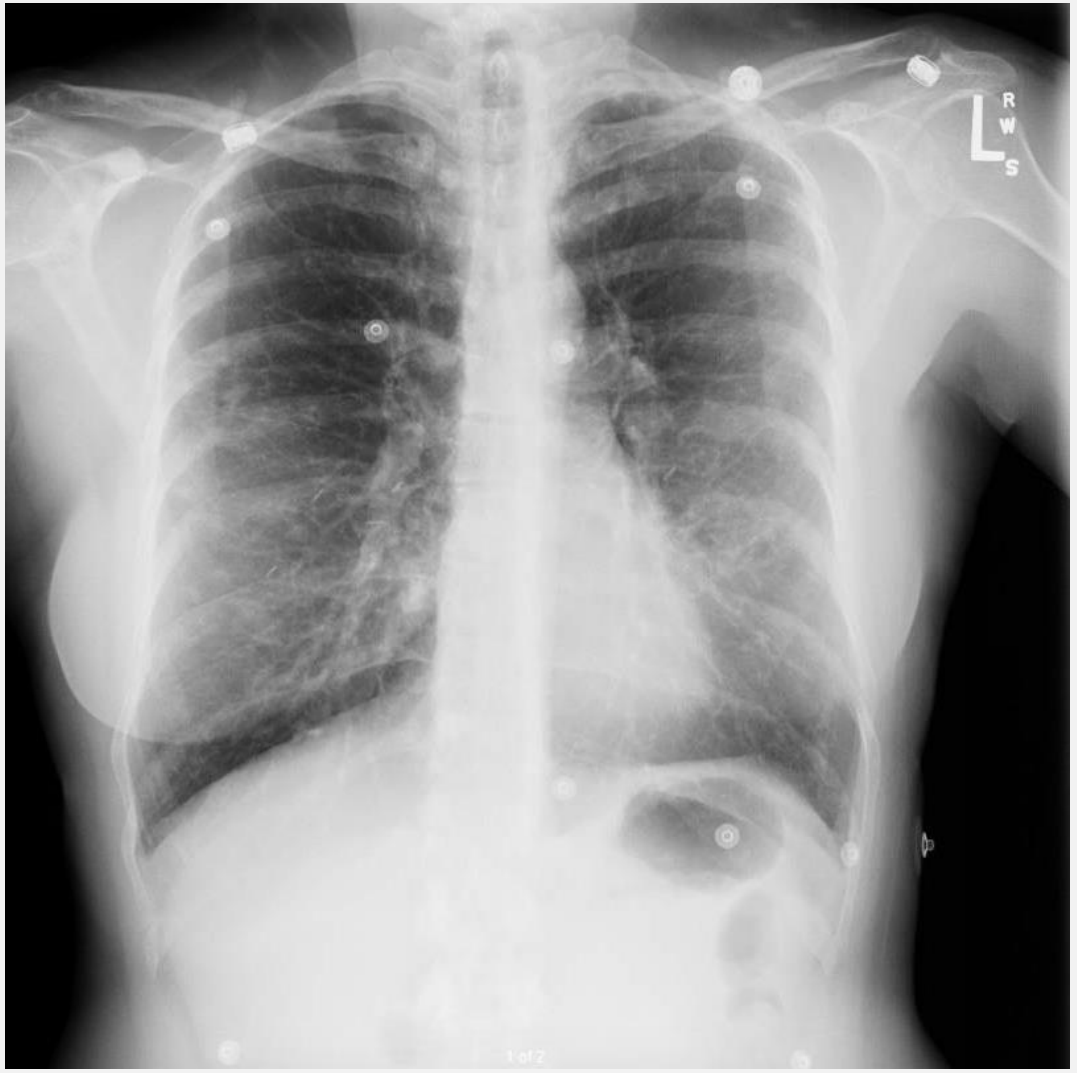
- Social hx: never smoker; **gardener** spring/fall; accountant

CASE #2

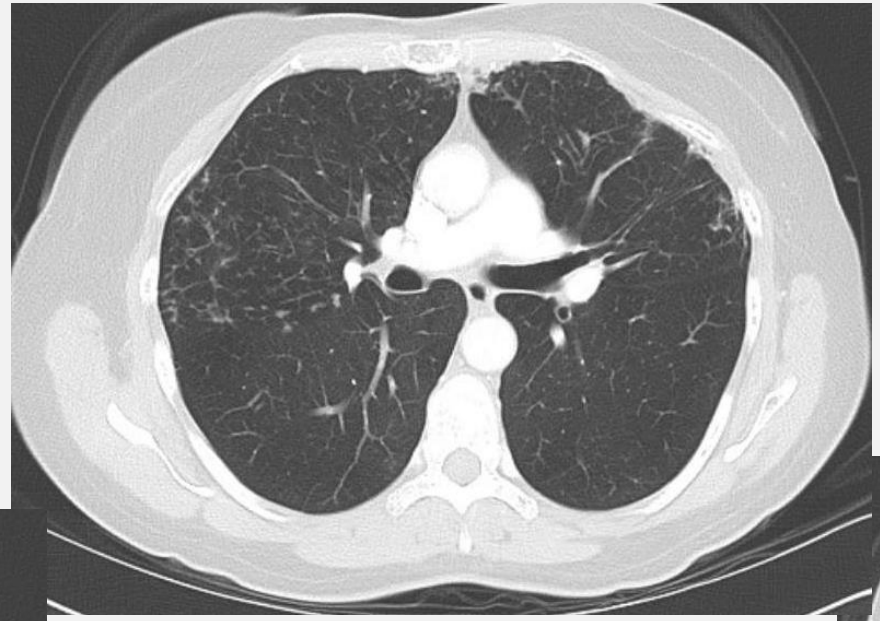
- **Pulmonary Function Test**
  - FEV1/FVC = .72
  - FEV1 = 2.06 (80%)
  - FEF25-75% = 1.46 (60%)
  - TLC = 104%, RV = 123%
  - DLCO = 69%
  - **No obstruction, gas trapping with mildly reduced DLCO.**

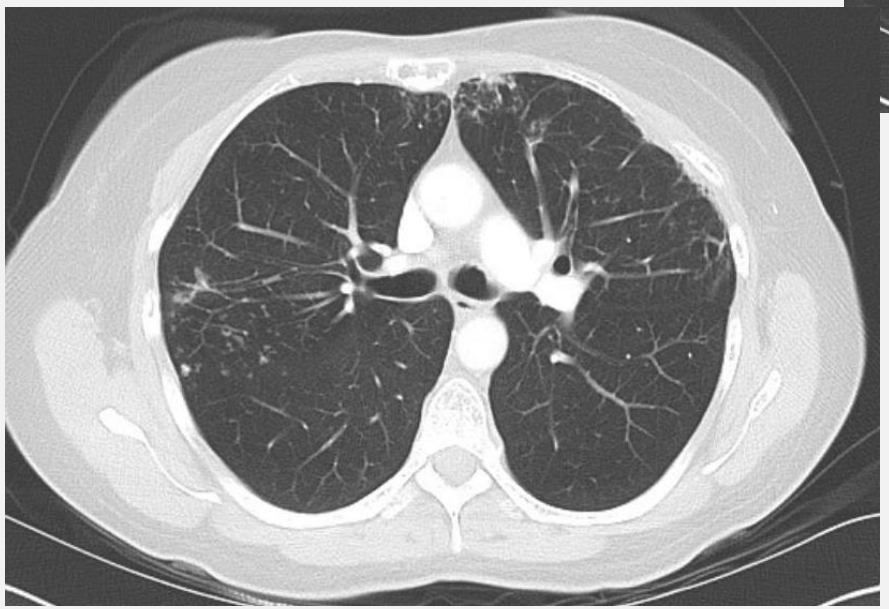
- **Microbiology:** BAL AFB smear 1+, Culture = MAC; all other micro and cytology negative

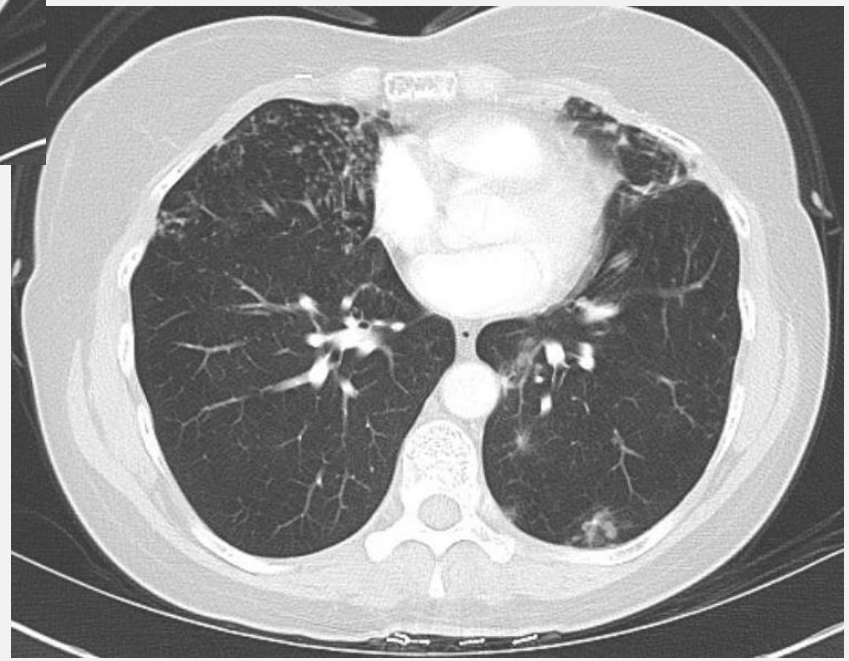
CASE #2



CASE #2







CASE #2

- What next?.....
- DIAGNOSIS = Mild nodular bronchiectatic disease due to MAC
- To TREAT or NOT TO TREAT?…..

CASE #2

- Recommended Treatment:
  - Rifabutin / Ethambutol / Azithromycin THREE times weekly
- Considerations:
  - DDI with Chemotherapy regimen (Rifampin vs Rifabutin)
- Challenges:
  - Adverse rxn to Rifabutin: High fever, N/V/D, 5lb weight loss, arthralgia/myalgias, debilitating fatigue

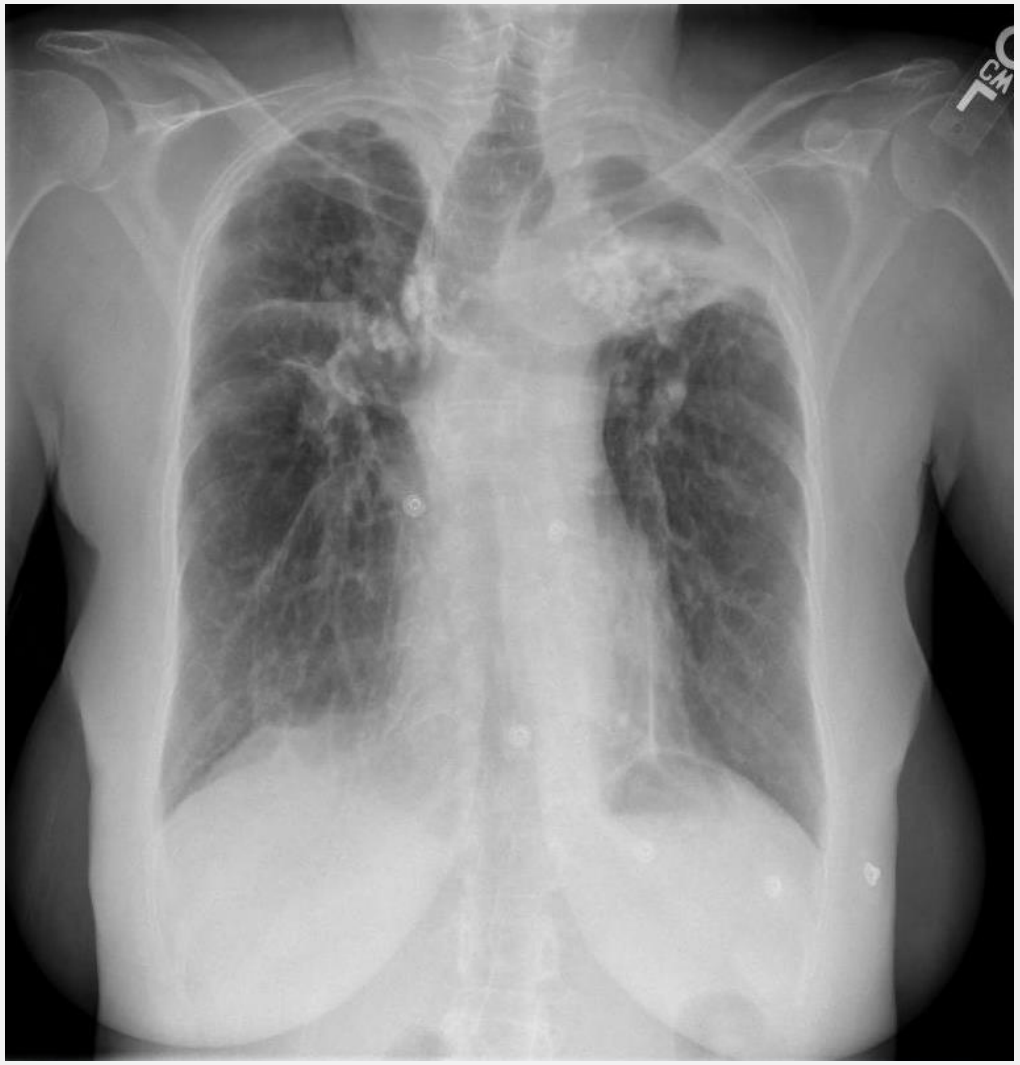
CASE #3

- CC: Dyspnea
- 63 yo F with progressive **shortness of breath, fatigue** and unintentional **weight loss** of 15 lbs. Also complains of intermittent nonproductive cough.
- PMHx: Sarcoidosis (stage V), Pneumothorax, Chronic hypoxemic resp failure, DM, pancreatic& adrenal insufficiency, HTN, Pulm MAC (tx 1990s)
- Social Hx: 10pk/yrs (quit 30yrs ago)
- Meds: Methotrexate, Hydrocortisone, Insulin

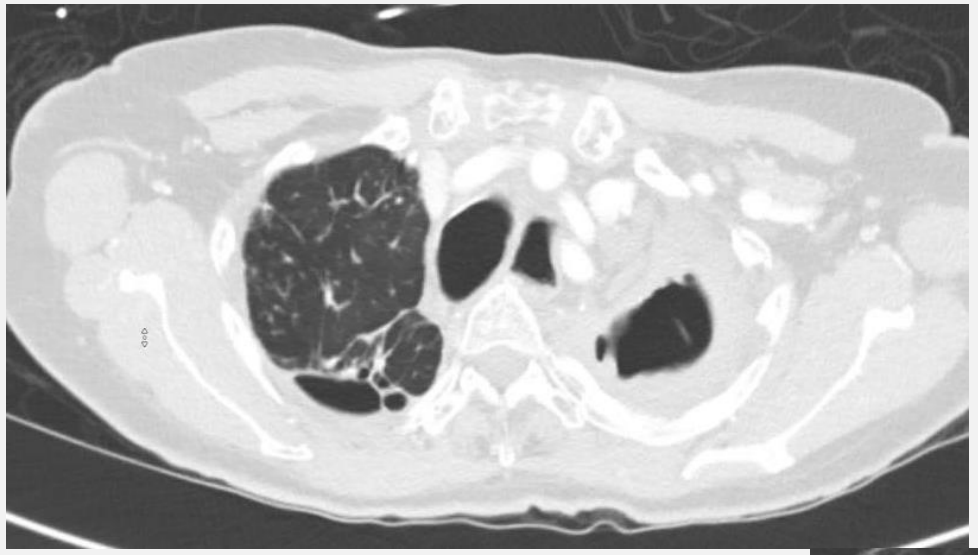
CASE #3

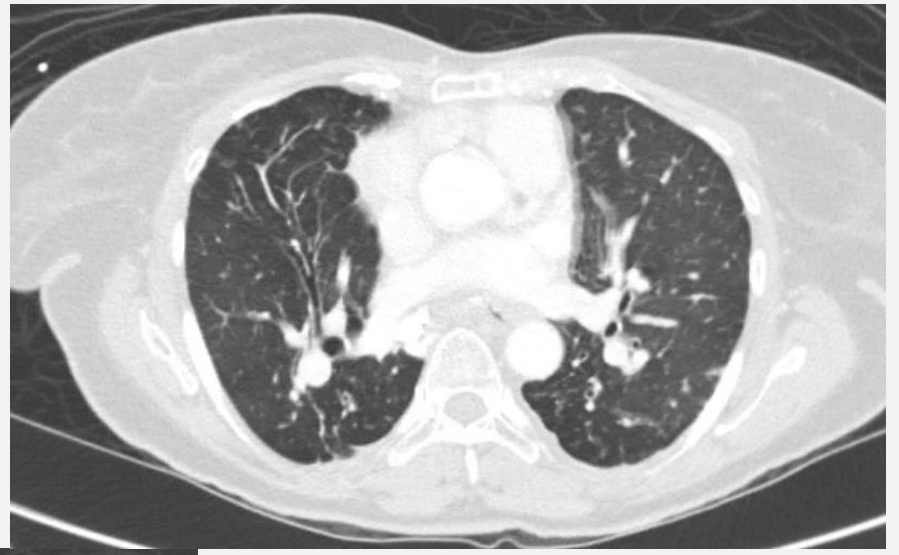
- **Pulmonary Function Test**
  - FEV1/FVC = .53
  - FEV1 = 0.55 (26%)
  - FEF25-75% = 0.26 (13%)
  - TLC = 59%, RV = 91%
  - DLCO = 19%
  - **Very severe obstruction with moderate restrictive lung disease and severely reduced DLCO.**
- **Microbiology**
  - 11/2013: Smear (-), Group IV RGM
  - 7/2017: Smear (-), M. abscessus
  - 8/2017: Smear 1+, MAC
  - 9/2/17: Smear 2+, M. abscessus (1 CFU) + ESBL Klebsiella pneumonia
  - 9/3/17: Smear 2+, M. abscessus (<10 CFU)
  - 9/23/17: Smear (-), negative
  - 5/2018: Smear 2+, M. abscessus (<10 CFU)

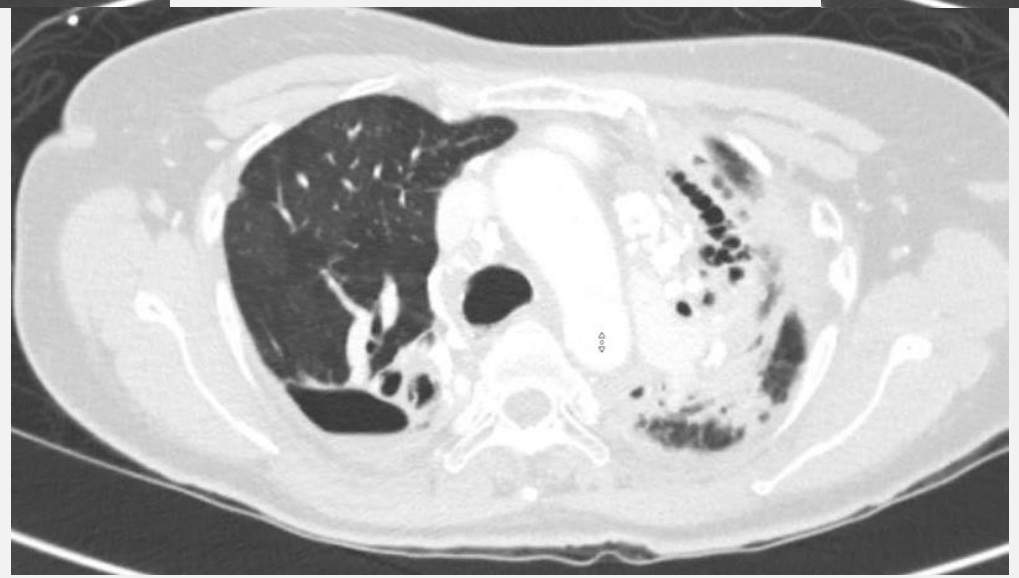
CASE #3



CASE #3







CASE #3

- DIAGNOSIS: **Fibrocavitary disease** due to MAC + M. Abscessus

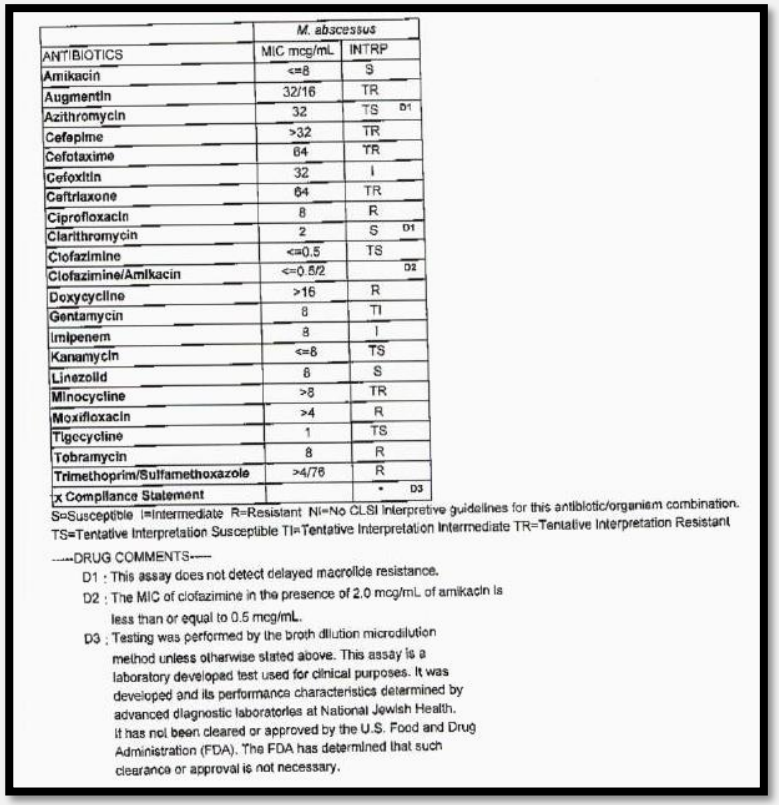
- Treatment Course
  - IV Ertapenem for ESBL Kleb
  - Started on **DAILY Rifampin / Ethambutol / Azithromycin + IV Amikacin**
  - IV Amikacin discontinued after 2 weeks
  - REA held after 4 months
- Challenges
  - Cellulitis d/t PICC line
  - Weight loss - down 25lbs from baseline
  - Tinnitus;Vision changes – adverse rxn to meds?
  - Cholecystitis req surgical intervention

CASE #4

- CC: intermittent cough/fever
- 64 yo Asian M presents as a referral for history of NTM & Pseudomonal infection with progressive bronchiectasis. No overt pulmonary symptoms. No dyspnea. **Intermittent cough** and **fever**. Unintentional **weight loss** of 5 lbs.
- PMHx: Immunoglobulin deficiency (low IgM, IgG4); Bronchiectasis (Dx 2002); Pulmonary MAC + M. Kansasii (s/p tx with RIPE x 14 mos 2014)
- Social Hx: 5pk/yrs (quit 4yrs ago)
- Meds: monthly IVIG

CASE #4

- **Pulmonary Function Test:**
  - FEV1/FVC = 64
  - FEV1 = 2.60 (93%)
  - TLC = 116%, RV = 116%
  - DLCO = 103%
  - **Mild obstruction.**
- **Microbiology:**
  - 11/2014 x 2: smear 2+; M. kansasii
  - 5/2017 (BAL): 2+; M. abscessus
  - 9/2017 x 2: smear (-); Group IV RGM
  - 11/2017 = smear (-); M. abscessus (>50 CFU)
  - 12/2017 = smear (-); M. abscessus (>50 CFU)



	M. abscessus	
ANTIBIOTICS	MIC mcg/mL	INTRP
Amikacin	<=8	S
Augmentin	32/16	TR
Azithromycin	32	TS D1
Cefepime	>32	TR
Cefotaxime	64	TR
Cefoxitin	32	I
Ceftriaxone	64	TR
Ciprofloxacin	8	R
Clarithromycin	2	S D1
Clofazimine	<=0.5	TS
Clofazimine/Amikacin	<=0.5/2	D2
Doxycycline	>16	R
Gentamycin	8	TI
Imipenem	8	I
Kanamycin	<=8	TS
Linezolid	8	S
Minocycline	>8	TR
Moxifloxacin	>4	R
Tigecycline	1	TS
Tobramycin	8	R
Trimethoprim/Sulfamethoxazole	>4/76	R
x Compliance Statement		* D3

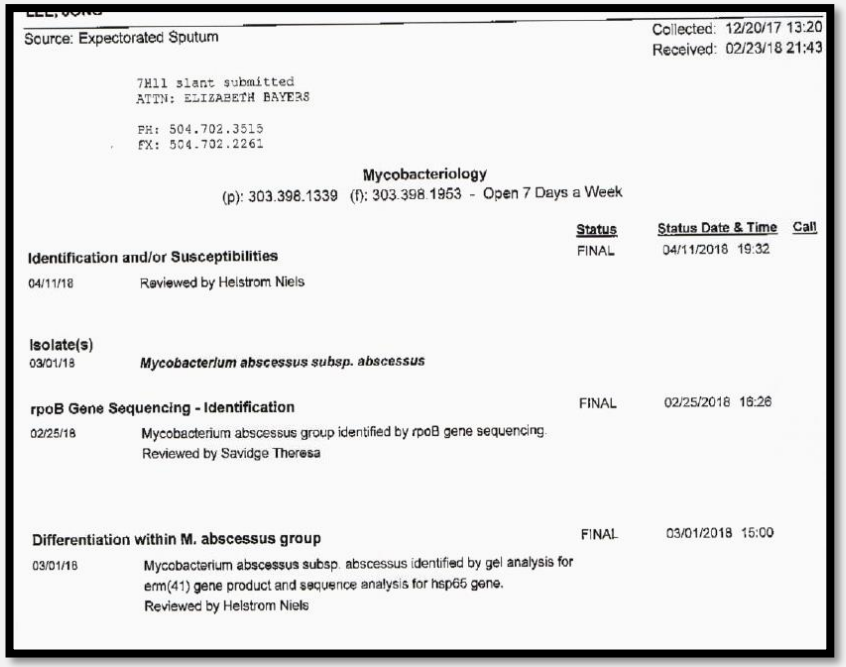
S=Susceptible I=Intermediate R=Resistant NI=No CLSI interpretive guidelines for this antibiotic/organism combination.
TS=Tentative Interpretation Susceptible TI=Tentative Interpretation Intermediate TR=Tentative Interpretation Resistant

-----DRUG COMMENTS-----

D1 : This assay does not detect delayed macrolide resistance.

D2 : The MIC of clofazimine in the presence of 2.0 mcg/mL of amikacin is less than or equal to 0.5 mcg/mL.

D3 : Testing was performed by the broth dilution microdilution method unless otherwise stated above. This assay is a laboratory developed test used for clinical purposes. It was developed and its performance characteristics determined by advanced diagnostic laboratories at National Jewish Health. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.



Source: Expectorated Sputum

Collected: 12/20/17 13:20
Received: 02/23/18 21:43

7H11 slant submitted
ATTN: ELIZABETH BAYERS

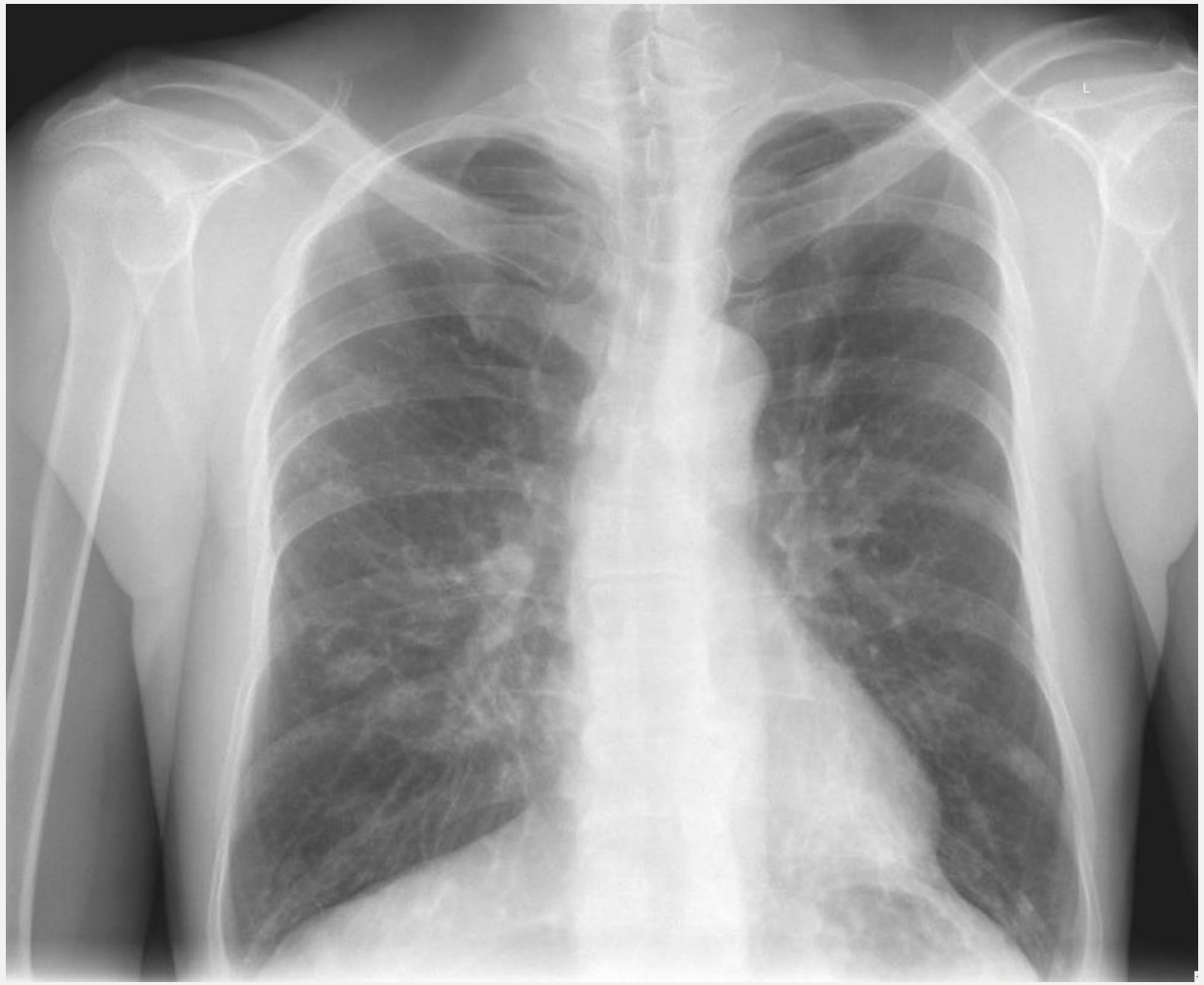
PH: 504.702.3515
FX: 504.702.2261

Mycobacteriology

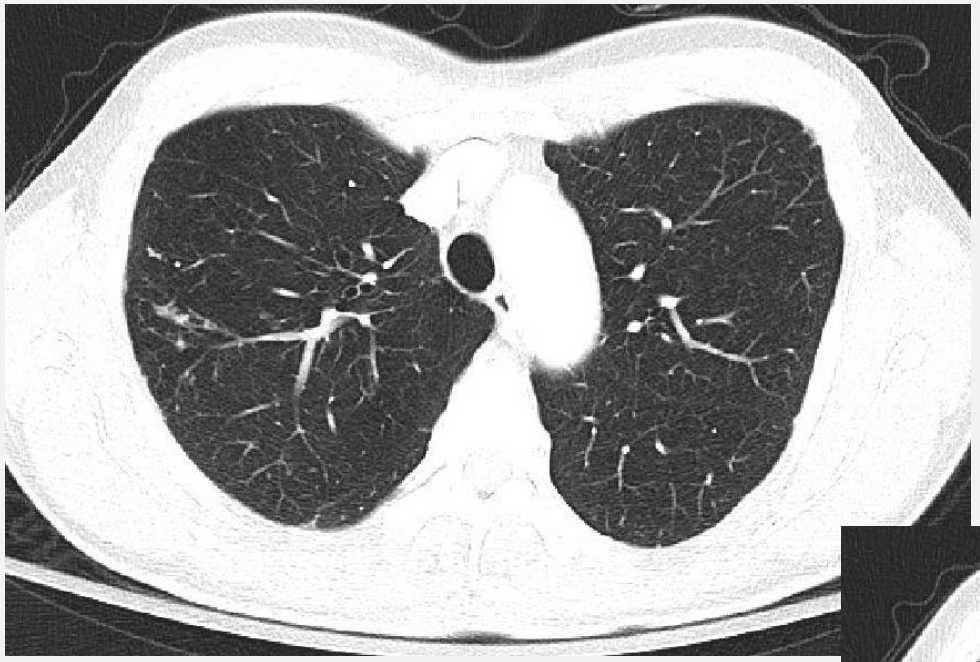
(p): 303.398.1339 (f): 303.398.1953 - Open 7 Days a Week

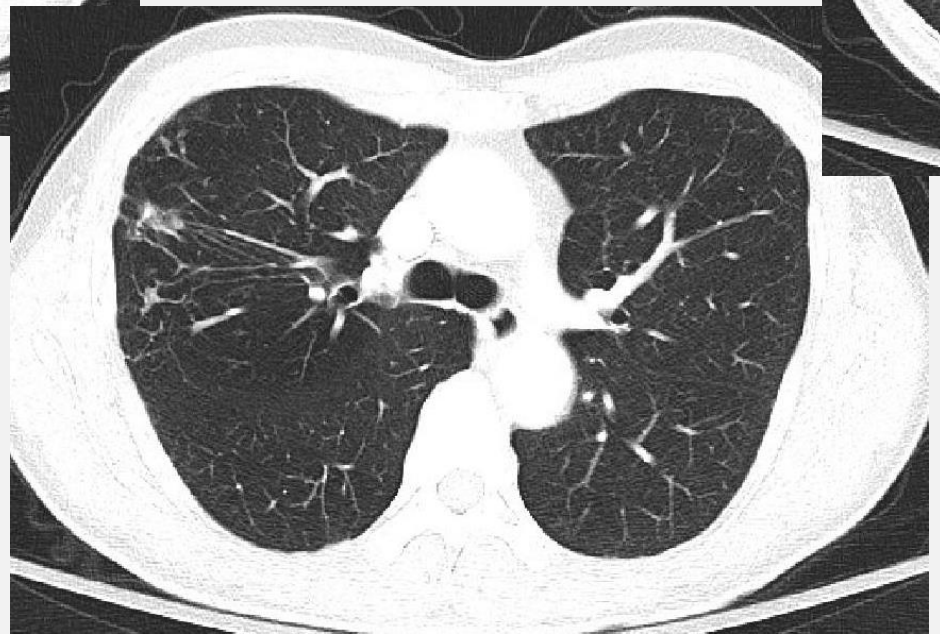
		Status	Status Date & Time	Call
Identification and/or Susceptibilities		FINAL	04/11/2018 19:32	
04/11/18	Reviewed by Helstrom Niels			
Isolate(s)				
03/01/18	***Mycobacterium abscessus subsp. abscessus***			
rpoB Gene Sequencing - Identification		FINAL	02/25/2018 16:26	
02/25/18	Mycobacterium abscessus group identified by rpoB gene sequencing. Reviewed by Savidge Theresa			
Differentiation within M. abscessus group		FINAL	03/01/2018 15:00	
03/01/18	Mycobacterium abscessus subsp. abscessus identified by gel analysis for erm(41) gene product and sequence analysis for hsp65 gene. Reviewed by Helstrom Niels			

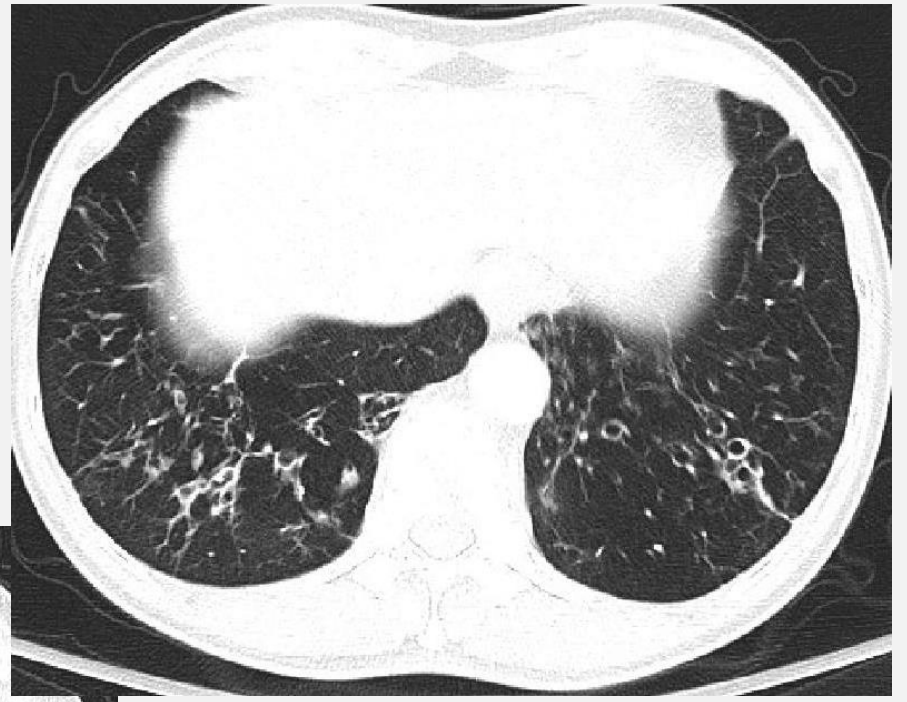
CASE #4



CASE #4







CASE #4

- DIAGNOSIS: Nodular bronchiectatic disease due to M. abscessus (prior MAC, m. kansasii)

- Treatment Course:
  - 3 month course of DAILY IV Amikacin / Imipenem / Azithromycin
  - Pulmonary toileting: Vest/Acapella/CPT
  - Monthly IVIG
  - To begin NEW regimen: Clofazimine / Linezolid / Azithromycin
- Challenges:
  - **Variable + DELAYED** identification & susceptibility reporting
  - Intensive regimen requiring IV therapy
  - Polymicrobial infections
  - **Recurrence vs relapse vs reinfection???**

MULTIDISCIPLINARY MANAGEMENT APPROACH

- **Antimicrobial therapy**
  - Surveillance
  - Suppressive treatment
  - Active treatment (minimum 3 abx simultaneously)
- **Underlying disease**
  - Autoimmune: Co-mgmt with Rheumatology specialist
  - Chronic rhinitis / sinusitis: Referral to ENT
  - GERD/Esophageal motility d/o: Referral to GI
- **Laboratory**
  - Speciation / Susceptibility testing
- **Nutritional support**
- **Respiratory therapy**
  - Education
  - Airway clearance techniques (Nebulizer / PEP devices / Percussive vests / Postural drainage)
- **Psychological support**
  - Patient outreach (internet resources)
  - Support groups

CYSTIC FIBROSIS FOUNDATION

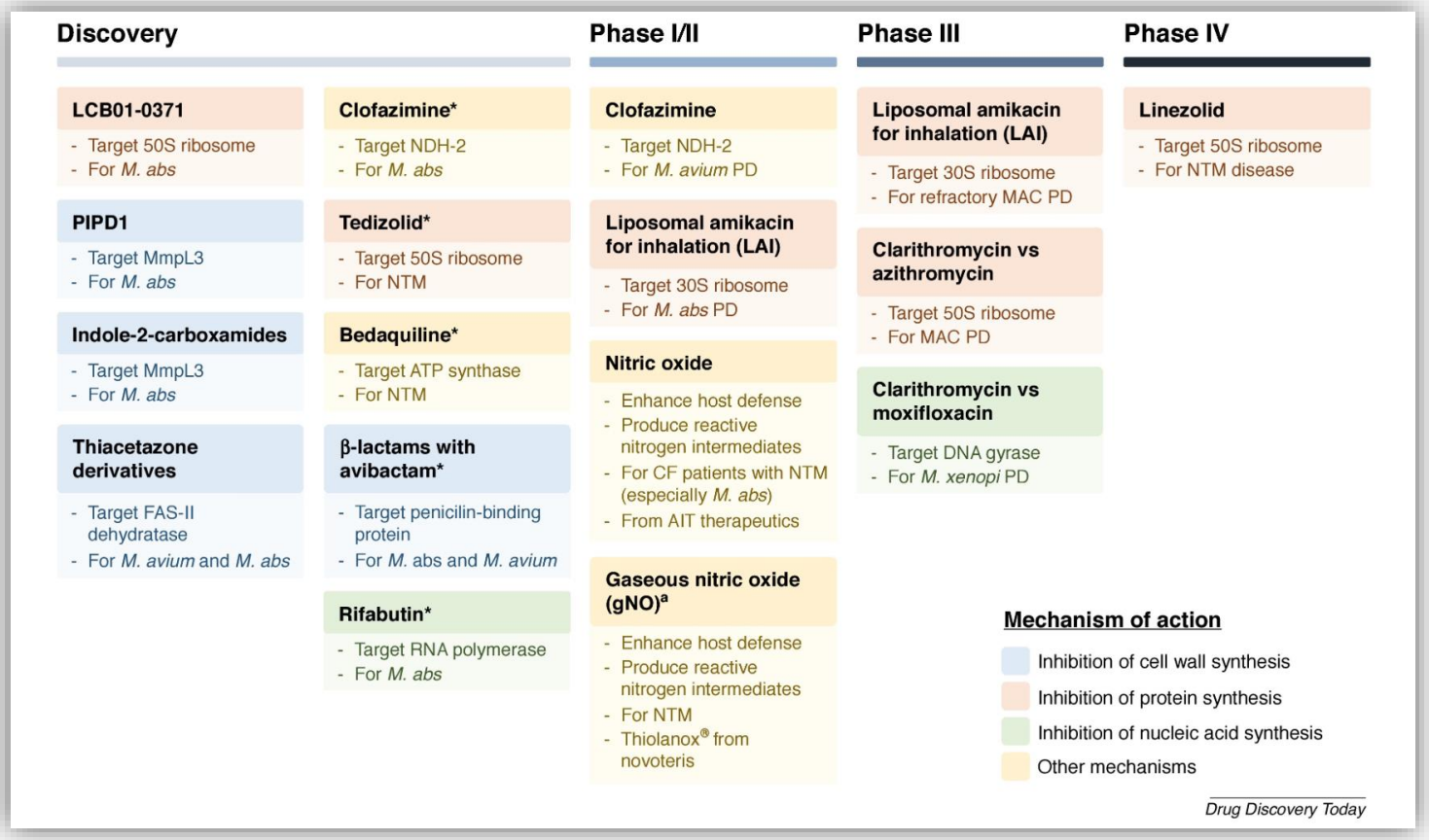
COMMON CLINICAL CHALLENGES

- Who to treat?
- How long to treat?
- Which regimen is ideal?
  - Drug intolerance
  - Drug side effects
  - Drug-drug interactions
- How do patients afford their lengthy/complicated medication regimen?
- Are susceptibility data reliable?

NTM TREATMENT LIMITATIONS

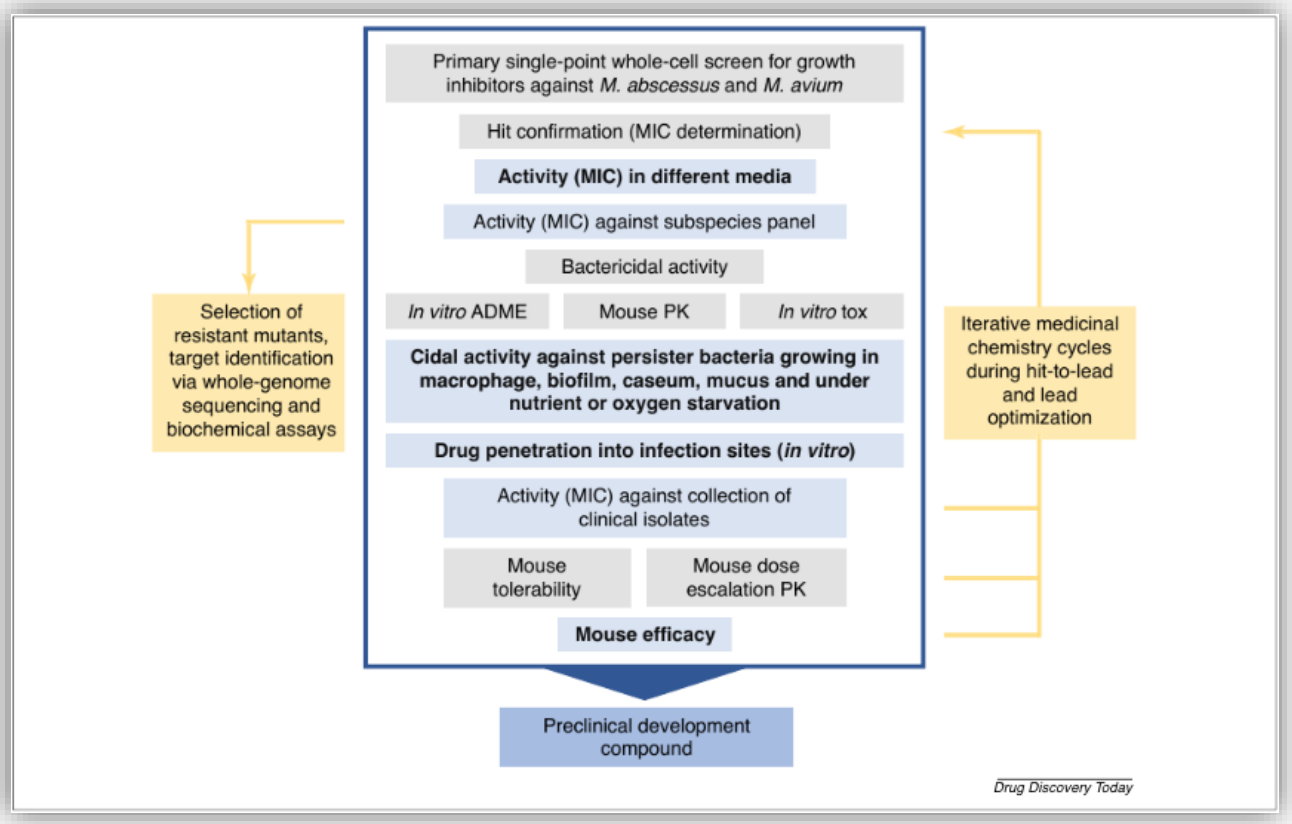
- Methods of identification (accuracy, timeliness, availability)
- Not a reportable disease
- Mycobacterial evasion / inefficient treatment options:
  - **Intrinsic** resistance
    - **Macrophage** barrier (intracellular) to Rx
    - **Hydrophobicity** of NTM with drugs being hydrophilic in nature(e.g. more hydrophobic drugs - rifabutin as opposed to rifampin)
    - **Cell wall associated permeability** barrier (e.g. *M. Chelonei ;* hence ethambutol in combination a better choice)
    - **Caseum growth** & nonreplicating state of persistence
    - **Mucus growth** (e.g. M. abscessus undergo phenotypic switch in mucus niche)
    - **Biofilm growth** (NTM in biofilms are ten times less susceptible)
  - Poor correlation between in vitro and therapeutic efficacy
  - Multi strain sero-variance (e.g. AIDS patients; subjects with nodular/bronchiectatic disease pattern AND NTM migration)
  - **Adaptive** resistance due to continual exposure

FUTURE TREATMENT OPTIONS?



Drug Discovery Today, April 2018

PARADIGM FOR NOVEL TREATMENT



IN SUMMARY…

- Pulmonary disease due to NTM is increasing in prevalence worldwide, particularly among the elderly
- NTM is ubiquitous in the environment with important geographic predilections or "hot spots"
- For NTM disease to progress it requires a complex interplay between host susceptibility, inoculum size/frequency and mycobacterial evasion techniques
- Diagnosis of NTM disease is complex and requires communication and coordination between pulmonologists/ID specialists, radiologists and microbiologists
- NTM causes various forms of pulmonary disease (i.e. nodular, bronchiectatic, cavitary) requiring different management approaches
- Treatment options remains limited and are encumbered by long, ill-tolerated multi-drug regimens. Engagement of patients/caregivers/ Goals of Rx / Limitations/ Outcomes well understood
- **THUS : NEED FOR COORDINATED EFFORTS/ REGISTRIES / STUDIES/PARTNERSHIPS**
- **We welcome that approach Thank you,** *NL / JA*