# DISEASE IN NON-HIV : SPECTRUM AND CHALLENGES

*"WHO DAT MOTT"*

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# DISCLOSURES

- Consultant / Speaker's Forum : Oxford Immunotec
- Consultant / Advisory Board / Speaker : 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 prepared by Dr Nicole Lapinel, Asst Prof LSUHSC –Co-Director Wetmore-NTM Program

# 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 with the "ABCDEFG pathway"
- Be able to gauge the importance of programmatic multi-disciplinary approach in management
-

# A ‘BUG’ BY (M)ANY OTHER NAME(S)

## WHO DAT MOTT ?


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

## Challenges in management of NTM Pulmonary Disease

1. Awareness and lack there of
2. Significance related to cost of HealthCare
3. Myriads of Presentations
4. Management strategies ABCDEFG towards Connecting the Partners in Care
5. Mycobacterial ID,  Culture/Sen Complexities
6. GBT background
7. Use of Secondary Drugs and issues thereof
8. Injectables and AG use and logistics thereof
9. Response / Tolerance Ratio
10. Judicious use of the “New kid/s on the Block”

# NTM PULMONARY DISEASE IN THE UNITED STATES

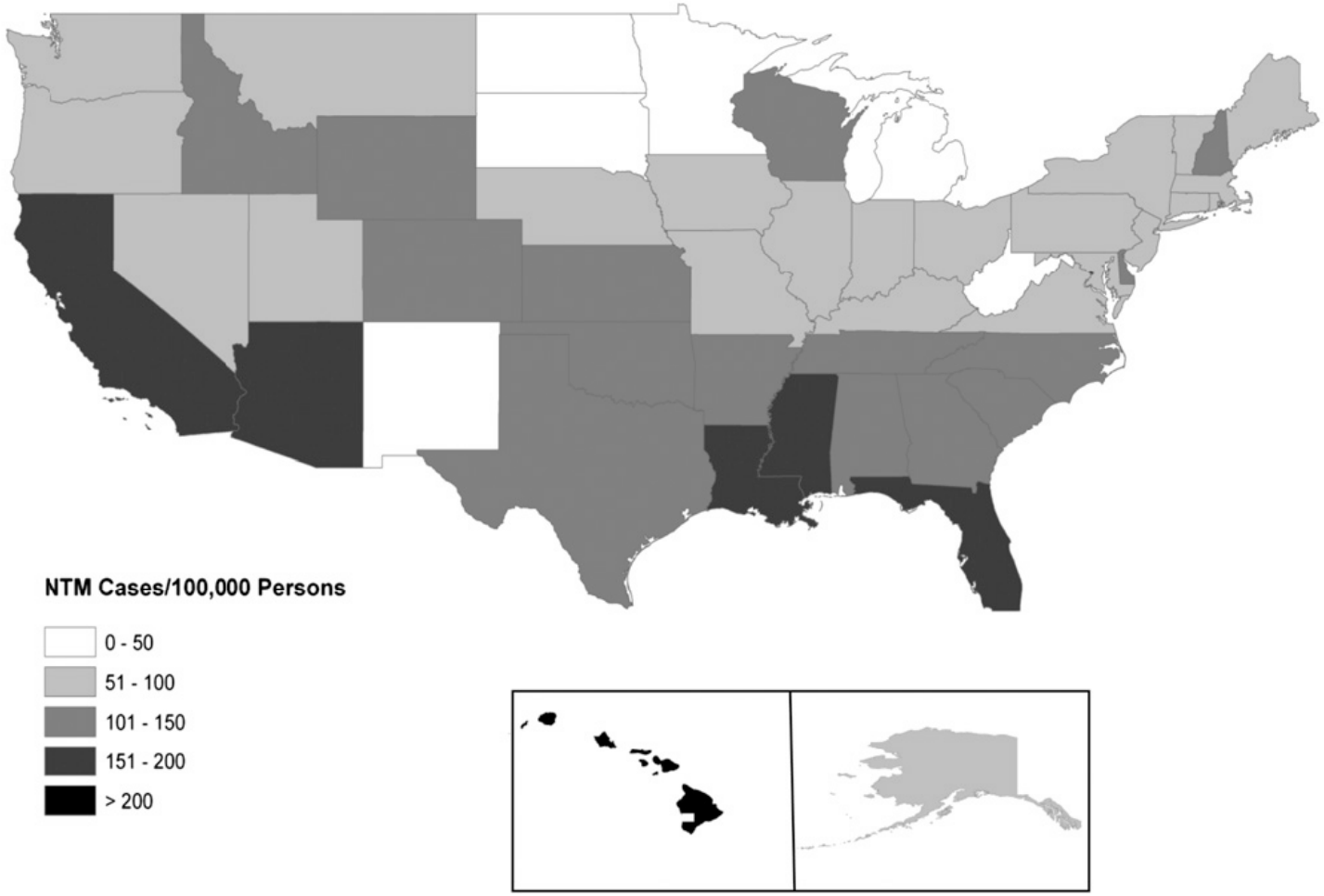



***Figure 1.*** Prevalence of pulmonary nontuberculous mycobacteria cases among a sample of U.S. Medicare Part B enrollees aged 65 and older, 1997 to 2007. NTM = nontuberculous mycobacteria.

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

**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**

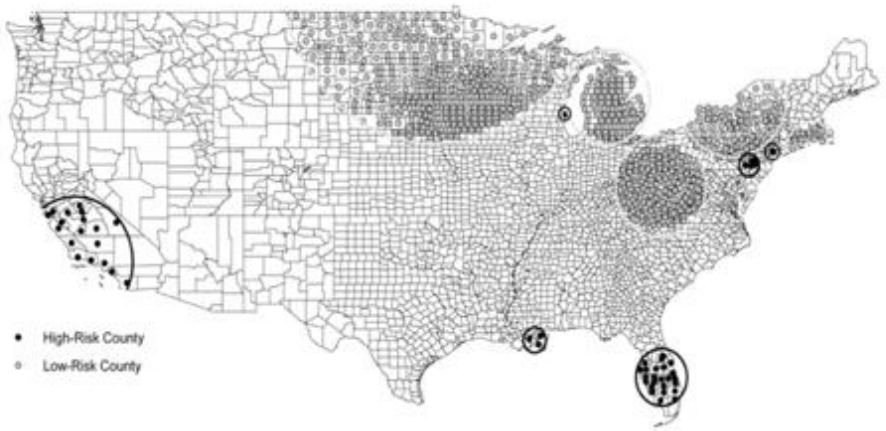



*Figure 1.* Significant clusters of counties identified by SaTScan as being at either high or low risk for pulmonary nontuberculous mycobacterial (PNTM) disease among U.S. Medicare beneficiaries 65 years of age and older.

# 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

# 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.

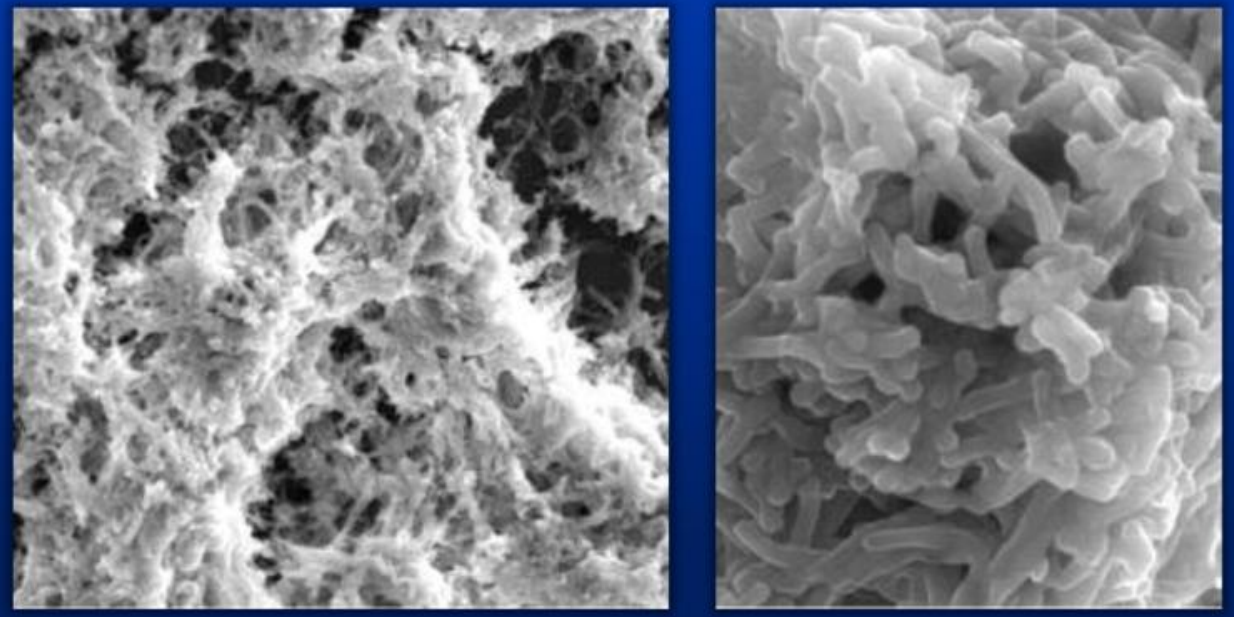
# HOW BIG A PROBLEM IS THIS?

- 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

# NTM Can Live as Planktonic Mycobacteria or in Biofilm Colonies

- NTM exist in the planktonic state and form biofilms on various surfaces (eg, pipes, catheter films, rubber surfaces)[1-4]
- The ability to attach to pipe surfaces as biofilm prevents NTM from being washed out of municipal drinking water systems[5]
- NTM grown in catheter biofilms are significantly more resistant to antibiotics than those grown in suspension[3]

**SEM view of *Mycobacterium smegmatis* biofilm[6]**



SEM, scanning electron microscopy.

**1.** Feazel LM et al. *Proc Natl Acad Sci USA*. 2009;106(38):16393-16399. **2.** Falkinham JO III et al. *Appl Environ Microbiol*. 2001;67(3):1225-1231. **3.** Falkinham JO III. *J Med Microbiol*. 2007;56(pt 2):250-254. **4.** Schulze-Röbbecke R et al. *Tuber Lung Dis*. 1992;73(3):141-144. **5.** Falkinham JO III. *Clin Chest Med*. 2015;36(1):35-41. **6.** Sousa S et al.

# Surrounded by Mycobacteria:
## NTM in the Environment[1,2]

- Soils, especially acidic pine forest and coastal swamp soils
- Dusts from agriculture, garden, and potting soils
- Drainage waters from acidic pine forest and coastal swamp soils
- Natural waters
- Drinking waters
- Water and ice from refrigerators
- Water from granular-activated charcoal filters
- Aerosols from natural and drinking waters
- Shower aerosols
- Spas and hot tubs
- Aerosols from indoor humidifiers
- Mist from indoor swimming pools



**1.** Falkinham JO III. *Clin Chest Med*. 2015;36(1):35-41. **2.** Falkinham JO III. *Curr Environ Health Rep*. 2016;3(2):161-167.

# 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

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

# 1. WHY SURVIVAL AND IMMUNE EVASION ?
## THE MICROBE

- 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

# NTM MGM & 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/bronchiectasis disease pattern and NTM cross migration)
  - **Adaptive** resistance due to continual exposure

## 2. Why survival and immune evasion?*

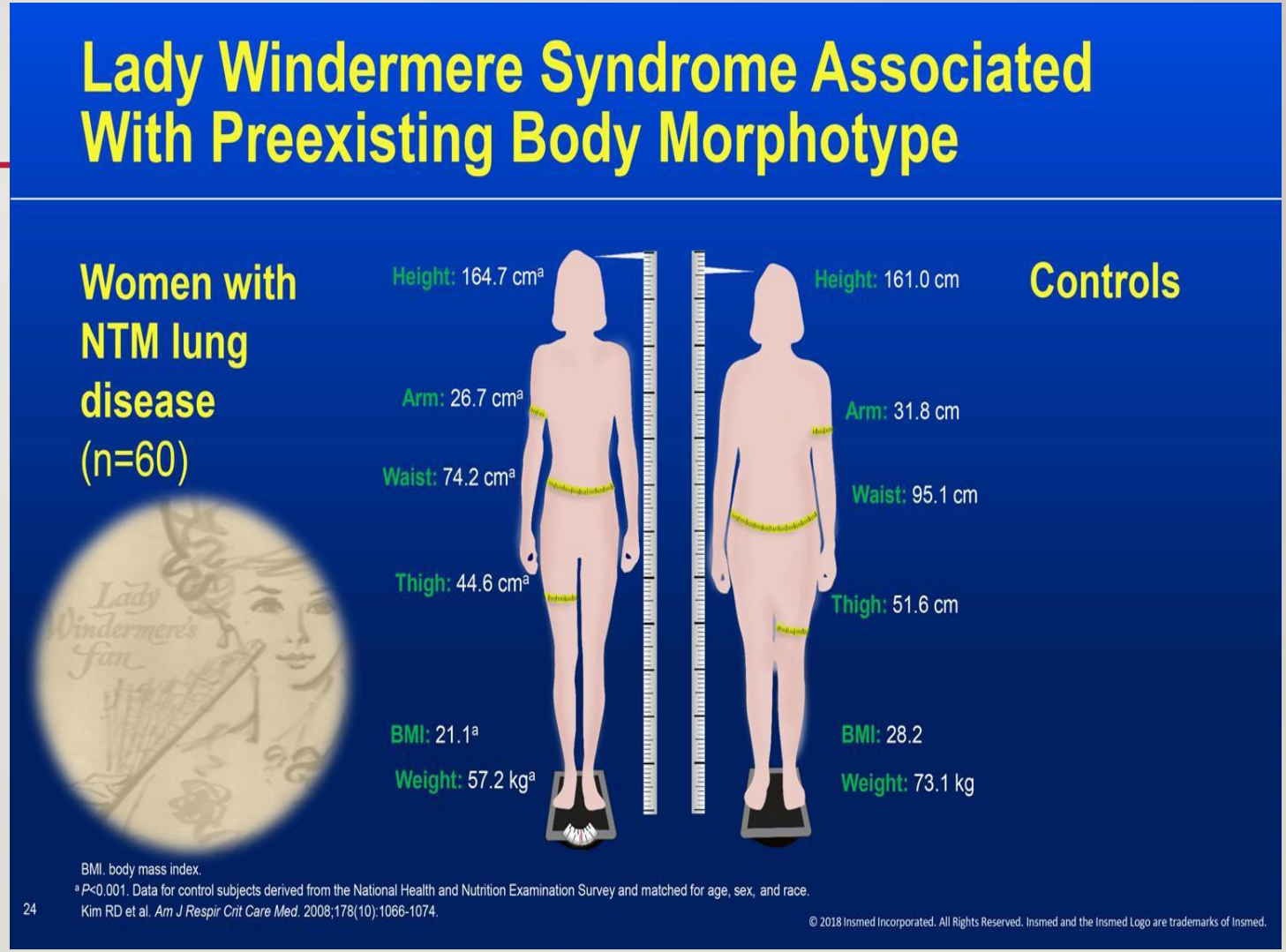
## The HOST FACTORS

Induction of macrophage apoptosis by down regulation of Bcl-2 gene

Absence of or sluggishness of the T helper lymphocyte or NK innate immunity

# PULMONARY DISEASE RISK : HOST FACTORS

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



# Host Susceptibility Factors for NTM Lung Disease

| Study description | RR, OR, or relative prevalence |
|---|---|
| **Bronchiectasis** | 44.0-187.5 |
| **Low body weight** | 9.09[a] |
| **Thoracic skeletal abnormalities** | 5.4 |
| **Lung cancer** (neoplasms of larynx, trachea, and bronchus) | 3.4 |
| **Immunomodulatory drugs/anti-TNF agents** | 1.3 (undefined)<br>2.2 (anti-TNF agents) |
| **COPD** | 2.0-10.0 |
| **Steroid use** | 1.6-8.0 |
| **RA** | 1.5-1.9[b] |
| **GERD** | 1.5[a]-5.3[b] |

GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus; OR, odds ratio; RA, rheumatoid arthritis; RR, relative risk; TNF, tumor necrosis factor.

[a] Estimated from data in paper.

[b] Hazard ratio, fully adjusted for age, sex, income, rurality, and comorbidities for NTM (HIV, COPD, asthma, and GERD).

Prevots DR, Marras TK. *Clin Chest Med*. 2015;36(1):13-34.

# PERSPECTIVE : NTM 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 :

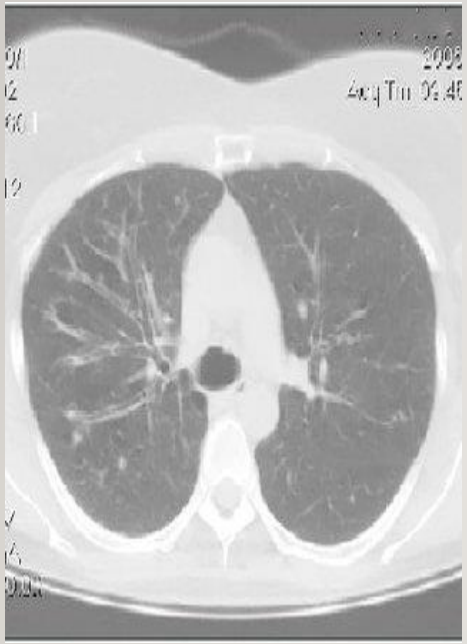
" Houston : we have a problem"

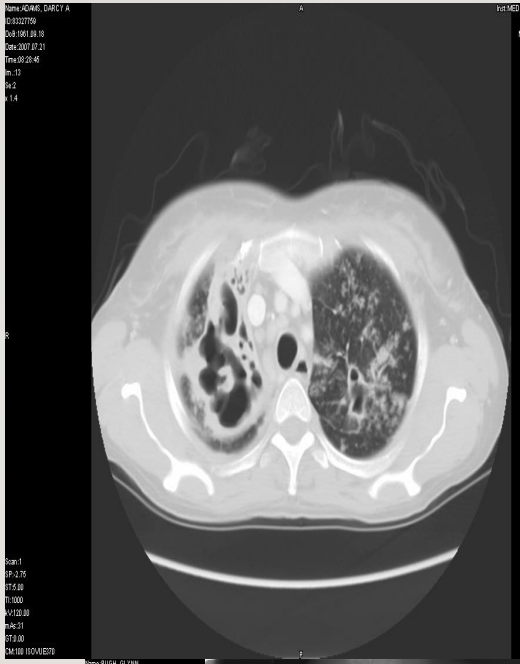
# RESULT / SEQUELAE LEADING TO THE MANY FACES OF NTM PULM DISEASE

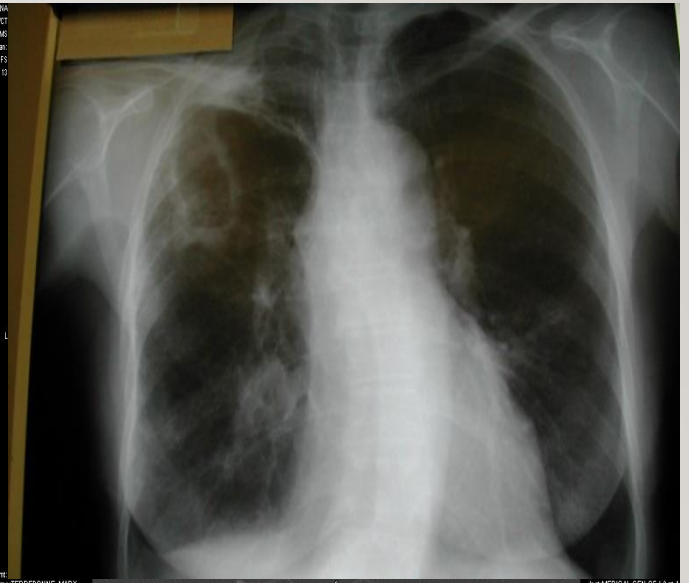
- Resultant Granuloma formation
- Release of cytolytic and cytotoxic enzymes to form either a cavity, necrotic nodules

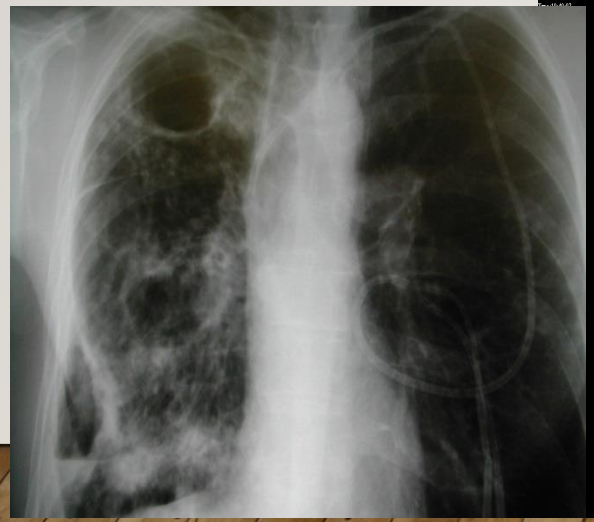
Resulting in PRIMARY BRONCHIECTASIS / F/C disease

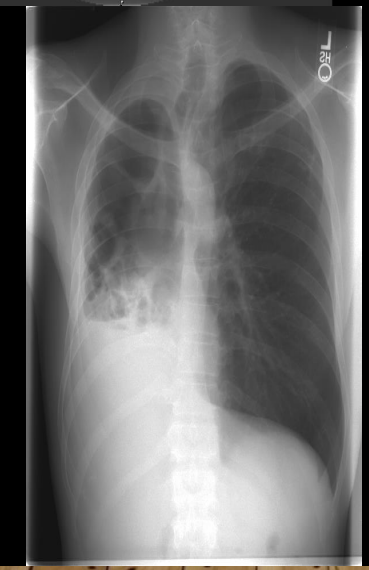
or F/N disease with traction like cylindrical bronchiectasis

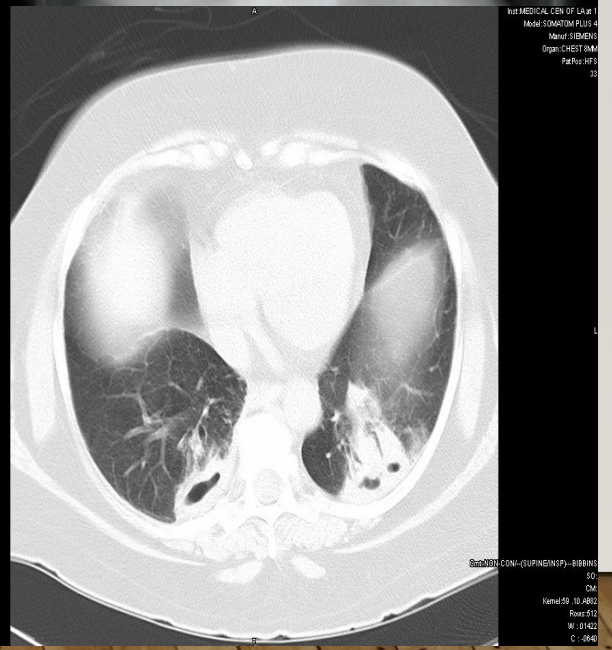













If the question refers to *chicken* eggs specifically, the answer is still the egg,[7] but the explanation is more complicated. The process by which the chicken arose through the interbreeding and domestication of multiple species of wild jungle fowl is poorly understood, and the point at which this 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 .**

Thus some known or unknown insult or continuum of insult
or an immune or airway deficiency (Aka Jungle Fowl)

Lead to Bronchiectasis ( chicken with OC 17 protein)

Leading to NTM ( Thickened Egg shell)

# UNDERSTANDING THE MANAGEMENT PATHWAY "ABCDEFG"

- A: AIRWAYS EVALUATION & CLEARANCE
- B: BRONCHIECTASIS
- C: CO-MORBID UNDERLYING ASSOCIATED CONDITIONS
- D: DISEASE INFECTION ITSELF
- E: ENVIRONMENTAL FACTORS
- F: $$ CONNECTING THE PPPs
- G: GI ISSUES CONTRIBUTING

# THE HOST

Defense mechanisms of the respiratory tract 1

**Upper respiratory tract (nose, oropharynx, laryn**

Mechanical

Nasal hairs and sneezing

Nasal, oropharyngeal and sinuses ciliated epitheliu

Saliva, **mucus**

Vocal cords

Innate immunity

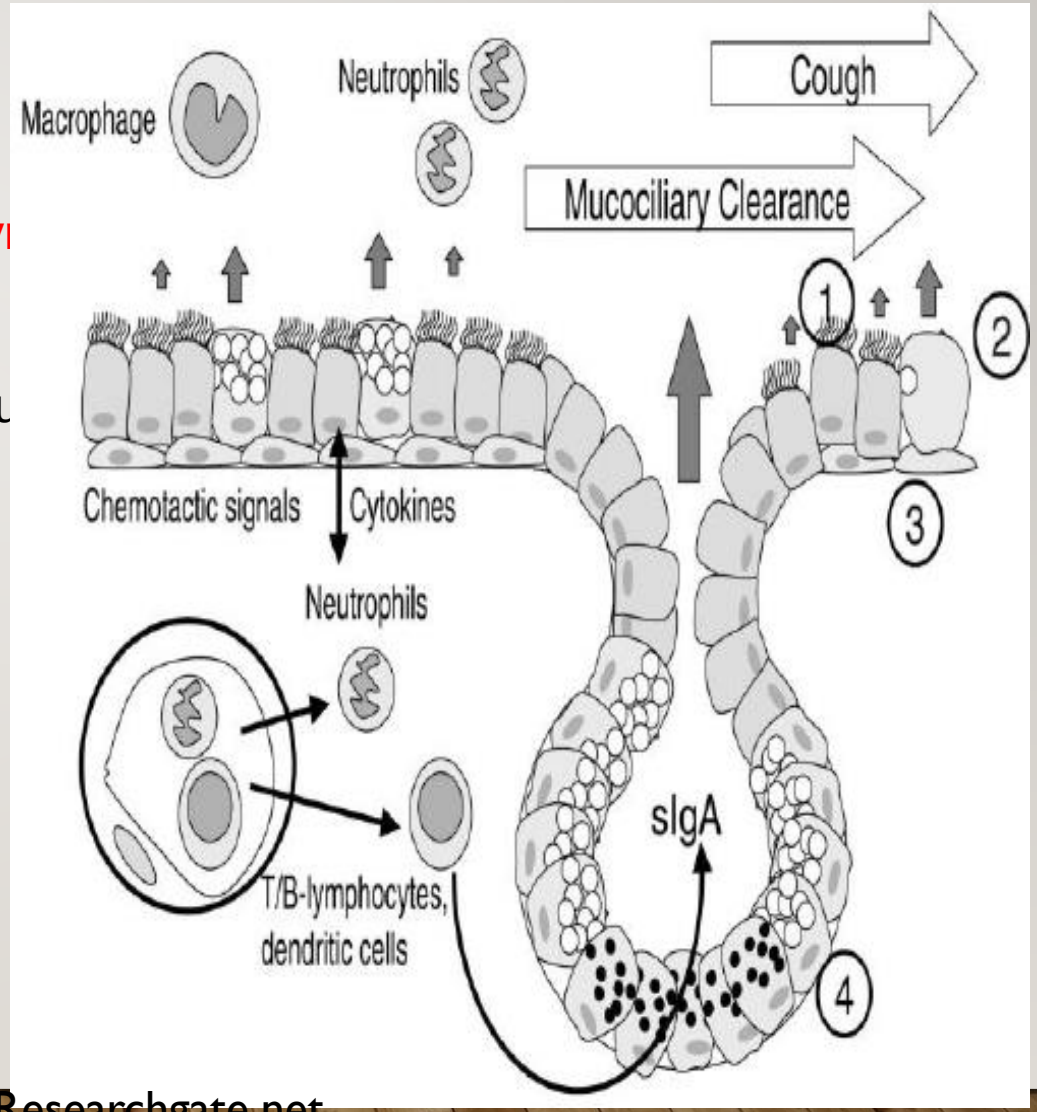
**Complement**

**Proteases**

Lactoferrin

Acquired humoral immunity

Secretory immunoglobulin (Ig-A and IgM)

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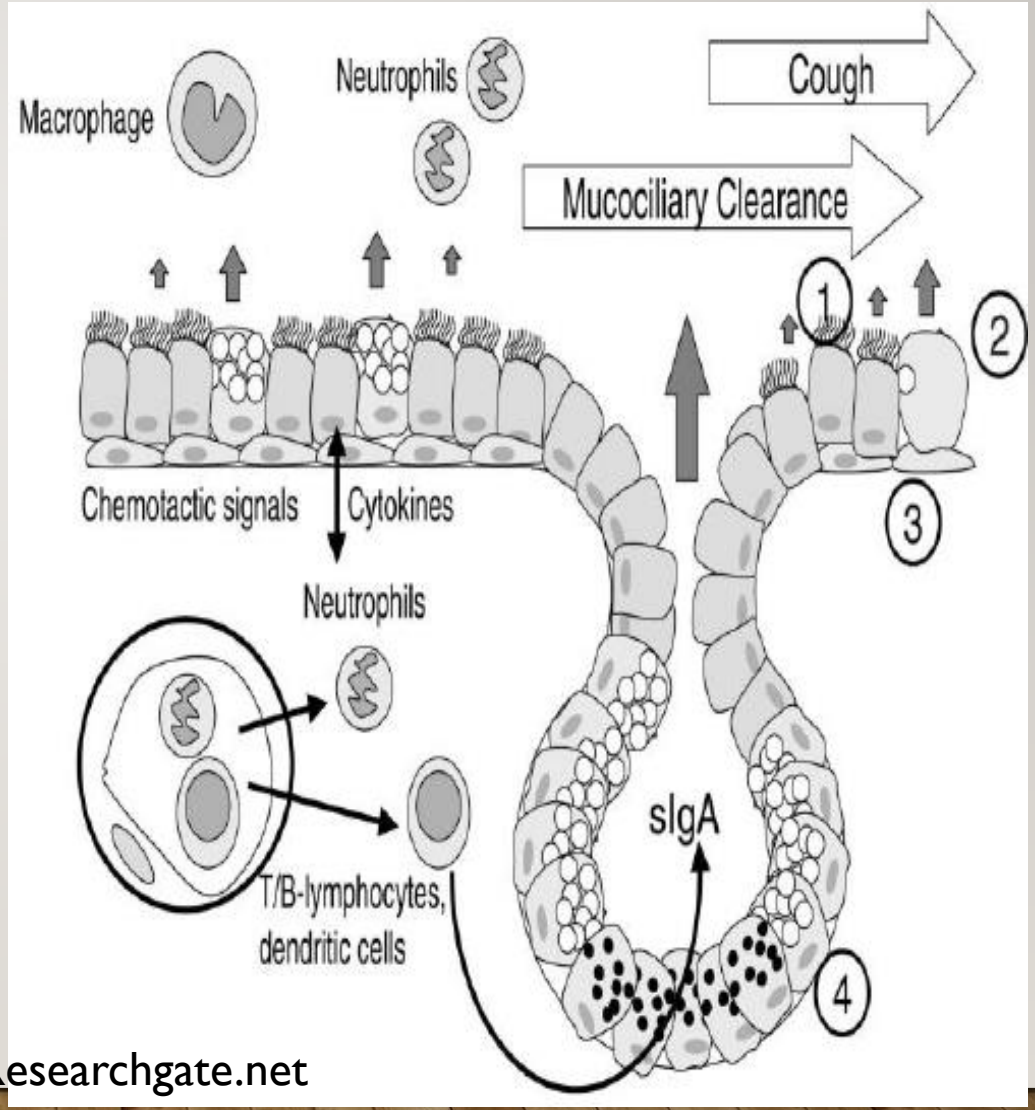
Defense mechanisms of the respiratory tract 2
Lower respiratory tract (tracheobronchial tree)

Upper airway dysfunction
Mechanical
**Mucociliary clearance**
**Cough and impaction on bronchial branching**
**Acquired cellular immunity**
**Blunted phagocyte response**
Bronchial-associated lymphoid tissue (BALT)
Humoral immunity
**Secretory IgA and IgM**

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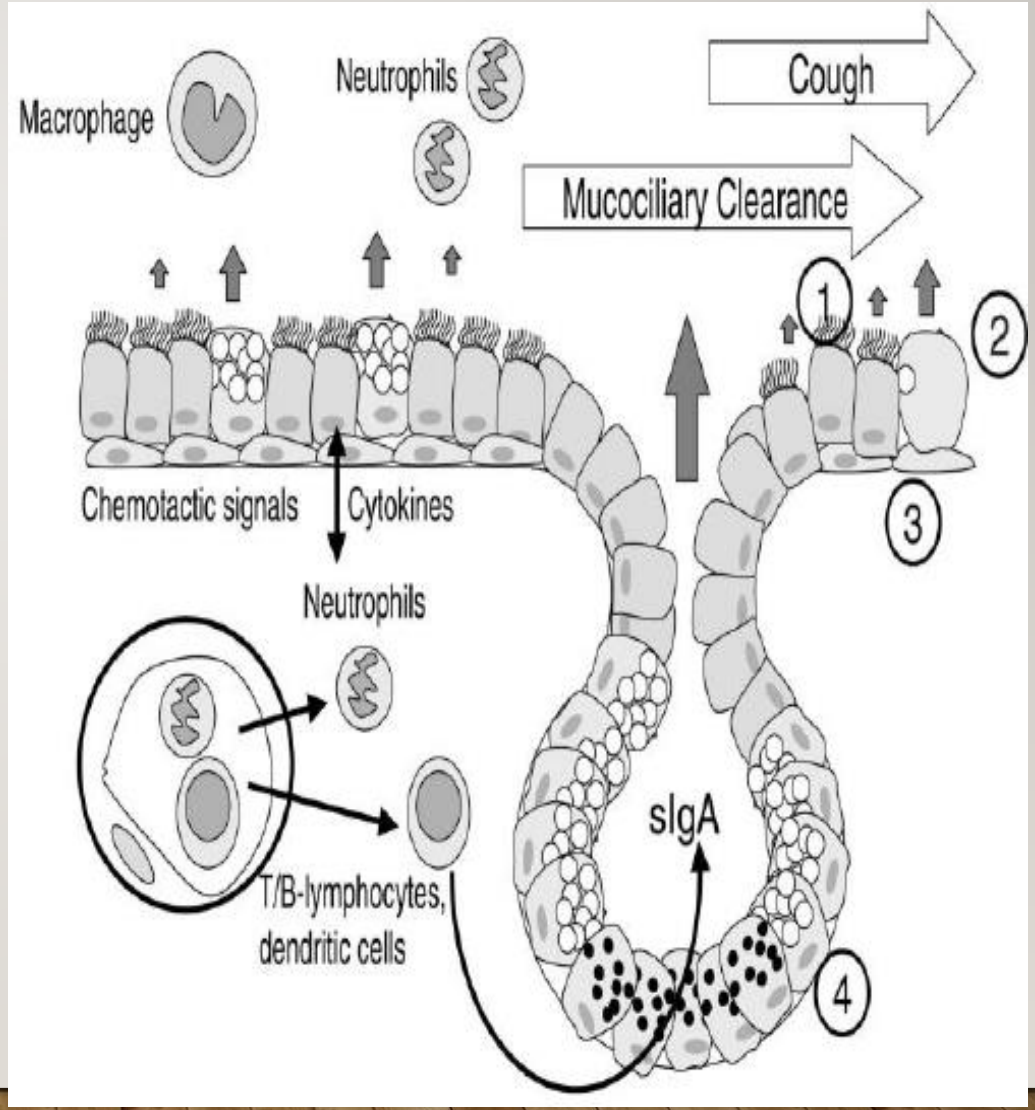
Defense mechanisms of the respiratory tract 3

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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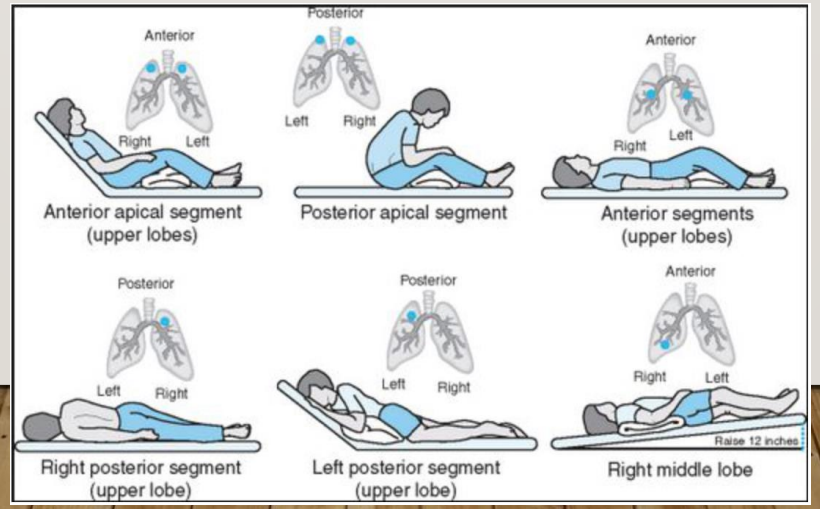
# UNDER THE CLOUD OF INCIPIENT OR OVERT BRONCHIECTASIS: PRINCIPLES OF MANAGEMENT

- GOALS
  - Reduce symptoms
  - Maintain lung function
  - Prevent exacerbations
  - Watch for red alerts monitoring BSI scores etc

- TREATMENT OPTIONS
  - Antibiotic therapy
  - Airway Clearance / Mucolytics
  - Anti-inflammatory agents with caution
  - Respiratory conditioning
  - Surgery in selected cases ( localized )

# AIRWAY CLEARANCE


- Options
  - Traditional CPT/postural drainage
  - Oscillatory positive expiratory pressure (PEP) (i.e. Aerobika, Acapella)
  - High frequency chest wall oscillation (The VEST)
  - Autogenic drainage
  - Active cycle breathing with huff coughs




# 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[illegible]lic 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

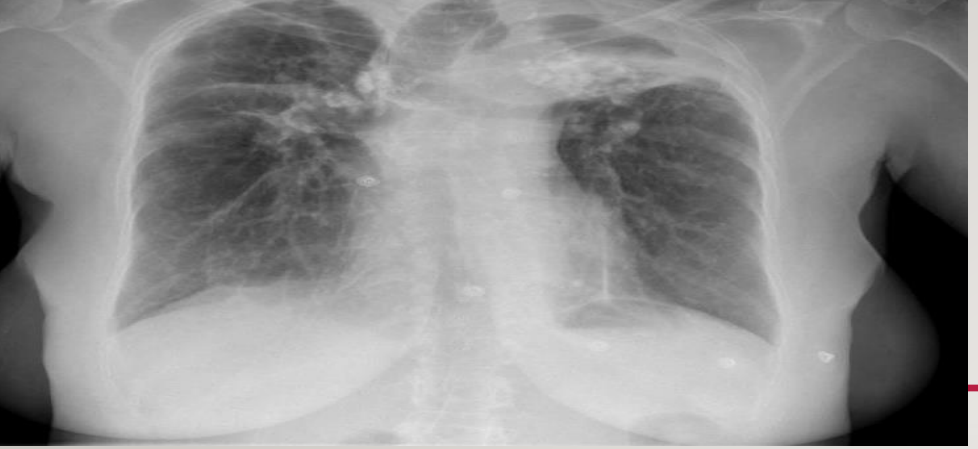
**Add to the mix the underlying structural disease/co-morbid state**

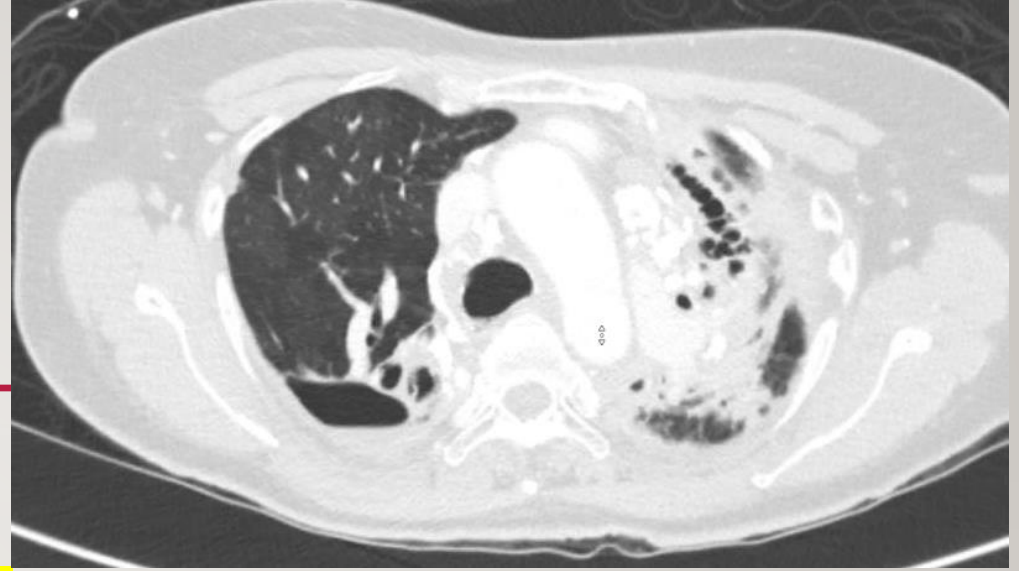
Type 3-4 Sarcoid/ IPF / COPD /Old TB

With its anatomical distortion and secondary bronchiectasis

.....

**…….and we have…Case # 1 ..**





# Case # 1

- CC: Dyspnea
- 63 yo F with progressive **shortness of breath, fatigue** and unintentional **weight loss** of 15 lbs. Also complains of intermittent nonproductive cough.

Hx: Sarcoidosis (Type 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 #1

- **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 (10-50 CFU)

# CASE #1

- 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
  - Action item : Limited options/ Specific SE / second line drugs ? vs Suppressive Rx ?

# COMMON CLINICAL RX 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?

# CASE #2

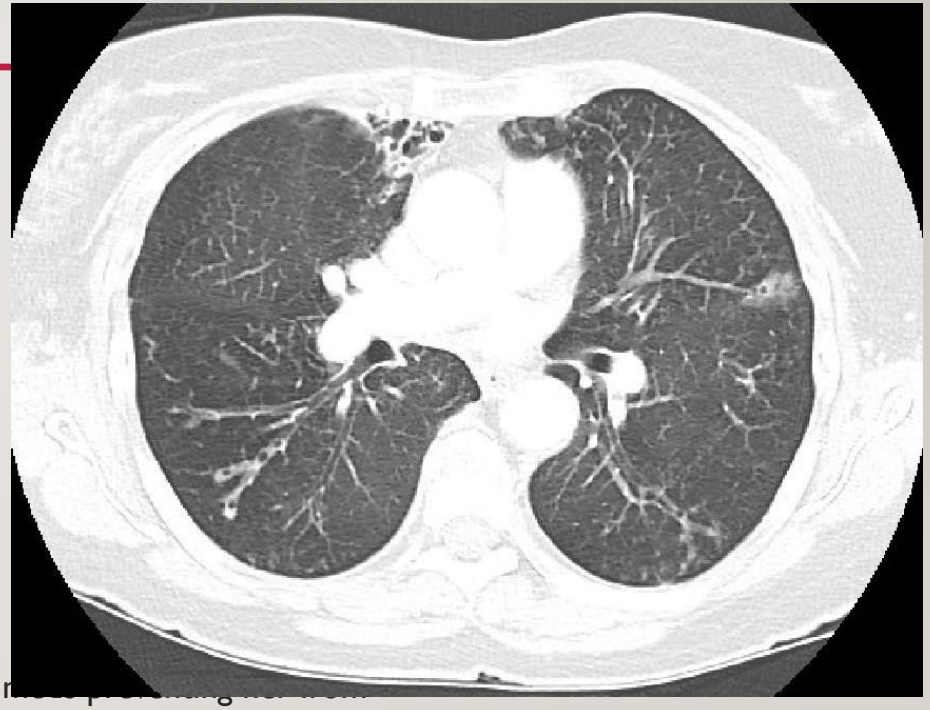
- CC: Chronic cough and fatigue
- 79 yo Caucasian F with **chronic cough** productive of whitish sputum present since 2003. Cough had been worse at night. She always noticed intermittent PND but not significant rhinorrhea; also with heartburn symptoms. She uses her Albuterol nebulizer 1-2x/day noting 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 #2

- **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 post BD 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 #2

- Diagnosis: classic **"Lady Windermere Syndrome"**

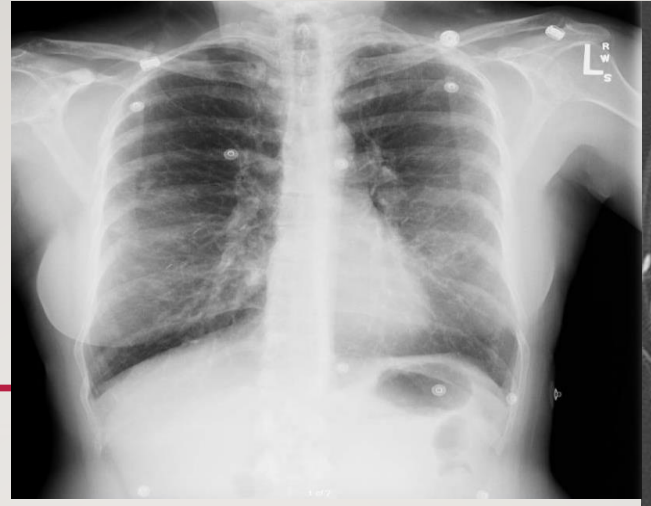


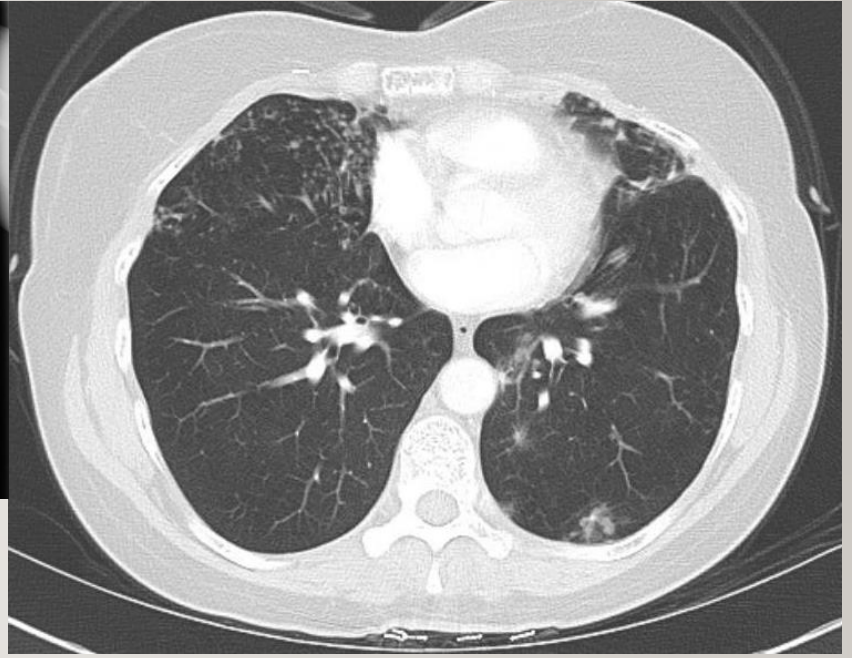
- Recommended Treatment:
  - Rifampin / Ethambutol / Azithromycin three times weekly
  - Albuterol nebulizer 2-3x daily for airway clearance
  - Rhinitis: Flonase/Antihistamine
  - GERD: H2B


Challenges:

- Patient complained of nausea and diarrhea on days she would take her [illegible] leaving the house
- Advised: Azithromycin AM, Ethambutol qhs, Rifampin qhs
- ACTION ITEM: TAILOR THERAPY ADMINISTRATION

# CASE #3





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

# CASE #3

- **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.**

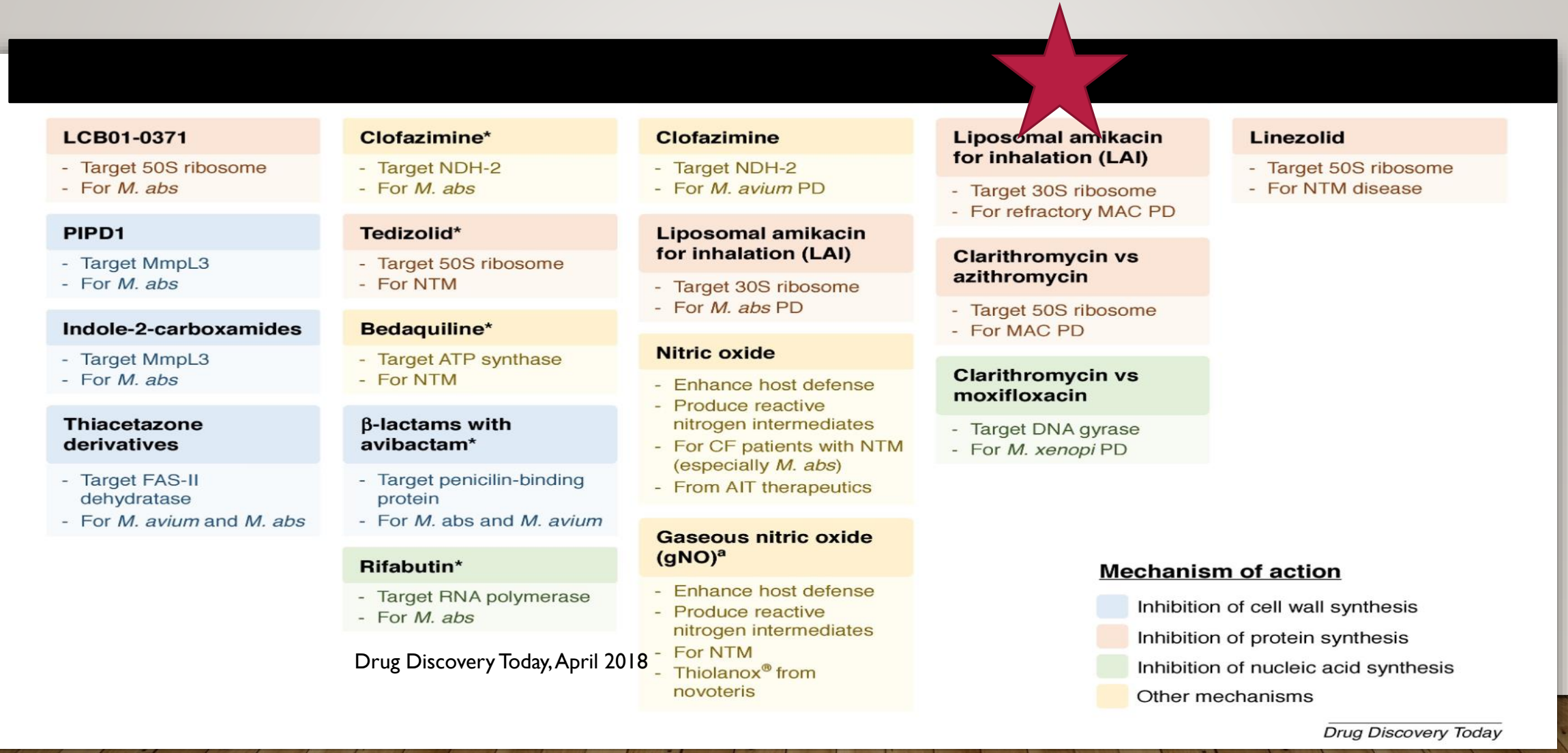
- **Microbiology:** BAL AFB smear 1+, Culture = MAC; all other micro and cytology negative

# CASE #3

DIAGNOSIS = Mild nodular bronchiectasis disease due to MAC with BAL positive

- To TREAT or NOT TO TREAT?…
- .. Recommended Treatment:
  - Rifabutin/Rif / Ethambutol / Azithromycin THREE times weekly
- Considerations:
  - DDI with Chemotherapy regimen (Rifampin vs Rifabutin)
- Challenges:
  - Adverse rx to Rifabutin: High fever, N/V/D, 5lb weight loss, arthralgia/myalgias, debilitating fatigue
  - Action item: Rx worse than problem : Rifamycin s/e
  - Options Rif vs RB/ vs non RIF regimen

# TREATMENT OPTIONS
# GBT AND/ OR




Drug Discovery Today, April 2018

# MULTI-FACETED MANAGEMENT PRINCIPLES : THE "ABCDEFG" PATHWAY AND SPECIFIC CHECKLIST

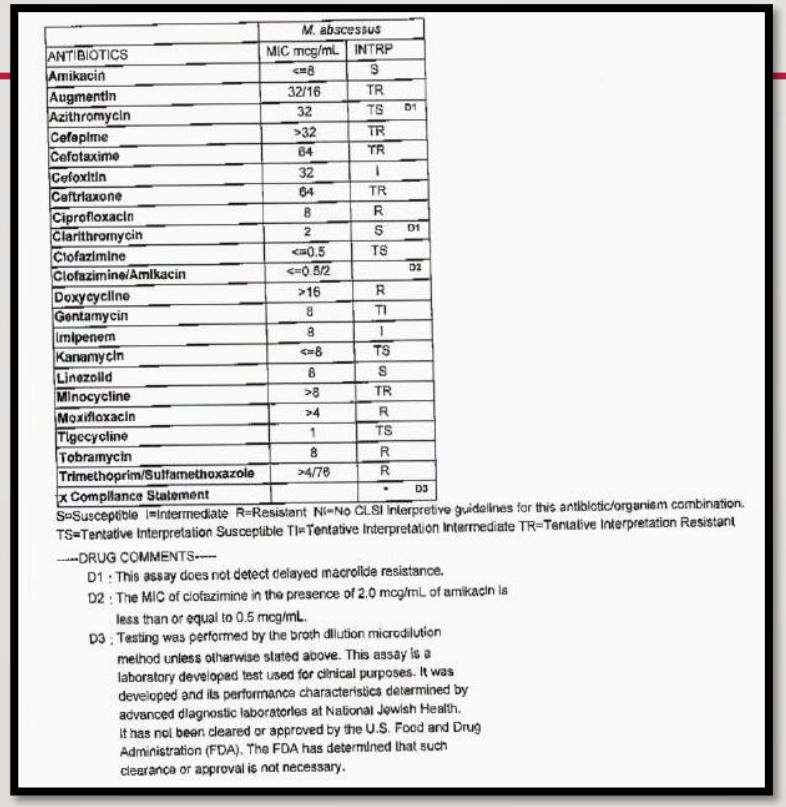
- Immune status & Rx thereof
- Triggers and Associated Confounders : Avoid Steroids /ICS if possible
- Environmental /"Eco check" Yes and No but never hurts
- Contribution of underlying disease and sift out symptoms & causes related to these co morbid states
- Evaluation of degree of infection and specific treatment plan including outlying patient expectations and agreement about cautious waiting
- Overarching : BRONCHIECTASIS & Management thereof
- Watch for progression and red alert danger signs

# CASE #4

- CC: intermittent cough/fever
- 64 yo Asian M presents as a referral for history of NTM & Pseudomonas 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 |
| Compliance Statement | | * D3 |

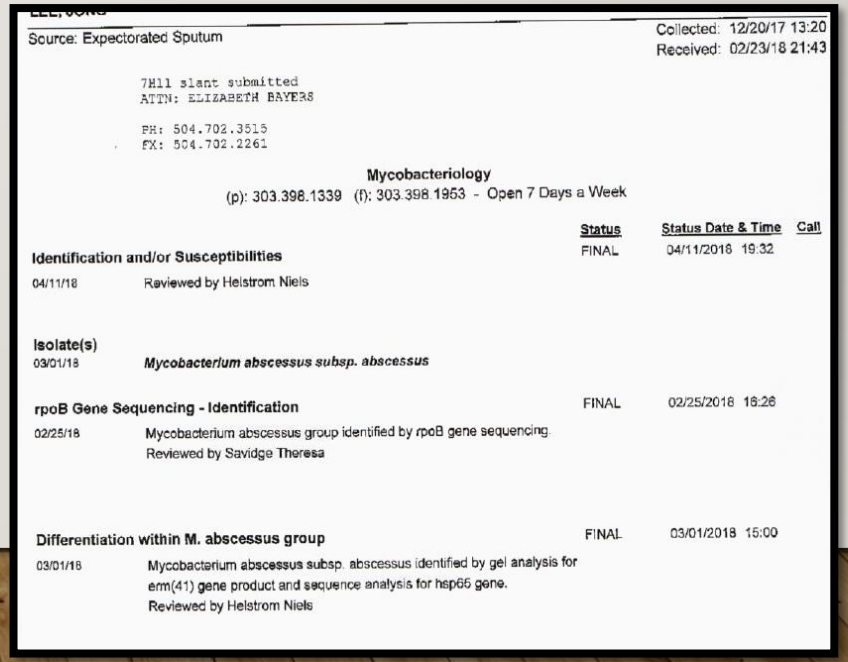
S=Susceptible I=Intermediate R=Resistant NI=No CLSI interpretive guidelines for this antibiotic/organism combination.
TS=Tentative Interpretation Susceptible TI=Tentative Interpretation Intermediate TR=Tentative Interpretation Resistant

-----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

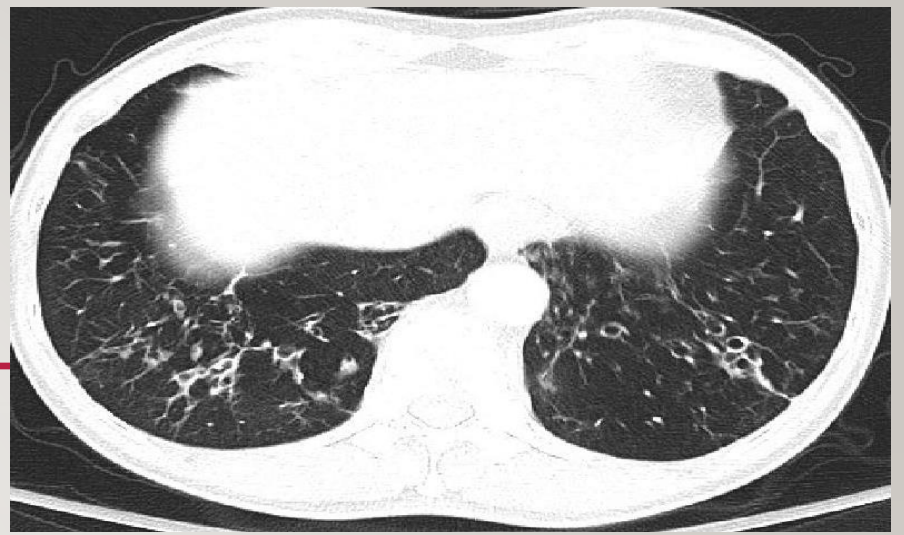
| | | Status | Status Date & Time | Call |
|---|---|---|---|---|
| **Identification and/or Susceptibilities** | | FINAL | 04/11/2018 19:32 | |
| 04/11/18 | Reviewed by Helstrom Niels | | | |
| **Isolate(s)** | | | | |
| 03/01/18 | ***Mycobacterium abscessus subsp. abscessus*** | | | |
| **rpoB Gene Sequencing - 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

- DIAGNOSIS: Nodular bronchiectasis 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???**

# CASE #4



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  - Pulmonary toileting: Vest/Acapella/CPT
  - Monthly IVIG
  - To begin NEW regimen: Clofazimine / Linezolid / Azithromycin ( did not tolerate Linezolid )
- Challenges:
  - **Variable + DELAYED** identification & susceptibility reporting
  - Intensive regimen requiring IV therapy
  - Polymicrobial infections
  - **Recurrence vs relapse vs reinfection???**
  - **Action item : Modified treatment / Burden of disease ? What next ?**

# MULTIDISCIPLINARY MANAGEMENT APPROACH 1

- **Laboratory**
  - Speciation / colony count /Susceptibility testing
- **Nutritional support** **Watch weight loss**
- **Respiratory therapy**
  - Education/Goals/Expectation/Practical implementation
  - Airway clearance techniques (Nebulizer / PEP devices / P
    Postural drainage)
- **Psychological support**
  - Patient outreach /Caregiver support
  - Support groups


CYSTIC FIBROSIS FOUNDATION

# MULTIDISCIPLINARY MANAGEMENT APPROACH 2

- **Specific therapy /phasic ID/PULM OPTIONS**
  - Surveillance
  - Suppressive treatment
  - Regular GBT
  - Inhaled AG
  - Regular with Inhaled
  - Intensive with inhaled
  - Intensive with IV
  - SURGERY
- **Underlying non-pulmonary/pulmonary disease**
  - Autoimmune: Co-mgmt with Immunologist/ Rheumatologist
  - Chronic rhinitis / sinusitis: Referral to ENT
  - GERD/Esophageal motility d/o: Referral to GI
  - Bronchiectasis/ IPF/COPD/Sarcoidosis/TB Pulm

CYSTIC FIBROSIS FOUNDATION

# 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 management requires communication and coordination between pulmonologists/ID specialists, radiologists and microbiologists and PATIENTS with set goals and expectations. Awareness of " Red flag alert points"
- NTM causes various forms of pulmonary disease (i.e. nodular, bronchiectatic, cavitary) inn different settings and requiring different management approaches
- Management of co-morbid conditions and associated pulmonary diagnosis and contributing/associated TRIGGERS ( Immune state , naso-sinusitis /GERD/Aspiration/Environmental /Constitutional )
- Treatment options remains limited and are encumbered by long, ill-tolerated multi-drug regimens. With logistical challenges. Engagement of patients/caregivers/ Goals of Rx / Limitations/ Outcomes well understood
- **THUS : NEED FOR COORDINATED EFFORTS/ REGISTRIES* / STUDIES/PARTNERSHIPS**
- **Thank you. Juzar Ali with *NL/JA LSUHSC program**