NTM PULMONARY DISEASE IN NON-HIV: SPECTRUM AND CHALLENGES

WHO DAT MOTT?
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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
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

<table>
<thead>
<tr>
<th>Pulmonary conditions</th>
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<tbody>
<tr>
<td>Cystic Fibrosis</td>
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<tr>
<td>COPD</td>
</tr>
<tr>
<td>Prior TB</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Silicosis/Fibrosis</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Lung cancer</td>
</tr>
</tbody>
</table>

### GERD

- Persons living with HIV/AIDS
- Soil exposure
- Alcohol abuse
- Smoking
- Low body weight
- Steroid use/Immune suppression

### TB Risk Factor

<table>
<thead>
<tr>
<th>Persons living with HIV/AIDS</th>
<th>50–170&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant recipients</td>
<td>20–74&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Silicosis</td>
<td>30&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chronic renal failure/hemodialysis</td>
<td>10–25.3&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Recent TB infection (within prior 2 years)</td>
<td>15&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carcinoma of the head and neck</td>
<td>16&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Radiographic evidence of prior healed TB</td>
<td>6–19&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>TNF-alpha blockers</td>
<td>1.7–9.0&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glucocorticoid treatment</td>
<td>4.9&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infants and children &lt; 5 years of age</td>
<td>2.2–5&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2–3.6&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Low body weight</td>
<td>2–3&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cigarette smoker (1 pack/day)</td>
<td>2–3&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>2–5&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Jejunoileal bypass</td>
<td>27–63&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>2.0–5.9&lt;sup&gt;3&lt;/sup&gt;</td>
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WORLDWIDE NTM DISTRIBUTION (RESPIRATORY)

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

**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.
• 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
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
**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***

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**Environmental Sources of NTM**

<table>
<thead>
<tr>
<th>Soils, acidic pine forest or coastal swamp soils</th>
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<tbody>
<tr>
<td>Dusts from agriculture, garden &amp; potting soils</td>
</tr>
<tr>
<td>Drainage waters from acidic pine forests or coastal swamps</td>
</tr>
<tr>
<td>Natural waters</td>
</tr>
<tr>
<td>Drinking water</td>
</tr>
<tr>
<td>Water / ice from refrigerators</td>
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<tr>
<td>Water from granular activated charcoal filters</td>
</tr>
<tr>
<td>Aerosols from natural &amp; drinking waters</td>
</tr>
<tr>
<td><strong>Aerosols from indoor humidifiers</strong></td>
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<tr>
<td>Mist from indoor swimming pools</td>
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</tbody>
</table>
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**


“Pulmonary Nontuberculous Mycobacterial Infection: A Multisystem, Multigenic Disease.” Szymanski et al
PATHOGENESIS

M.malmoense
M.szulgai
M.kansasii
M.abscessus
M.xenopi
M.avium
Others

NTM
Pathogenicity species

Exposure
Infecting load duration of exposure

Host
Chronic lung disease
Immunosuppression
Genetic predisposition

Possible outcomes
Transient colonisation
Persistent colonisation
Indolent infection
Active disease

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 a 10 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"
Defense mechanisms of the respiratory tract

**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)
Defense mechanisms of the respiratory tract

**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

Researchgate.net
Defense mechanisms of the respiratory tract

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)
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
THE MICROBE
I. 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
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 Neutrophilic serine proteinases NSP activity*
2. Oxygen intermediates
3. Inflammatory cytokines

- Blocked by AIAT
- Could be blocked by inhibitor agents

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

In Non CF:
- CFTR variants with single mutations
- Association with Vit D deficiency
If the question refers to *chicken* eggs specifically, the answer is still the egg, 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*).

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."

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. 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.

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

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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

• 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

- 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 = 0.53
  - 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

- **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/hrs (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)
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
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?

#### Discovery
- **LCB01-0371**
  - Target 50S ribosome
  - For M. abs

- **PIPD**
  - Target MmpL3
  - For M. abs

- **Indole-2-carboxamides**
  - Target MmpL3
  - For M. abs

- **Thiacetazone derivatives**
  - Target FAS-II dehydratase
  - For M. avium and M. abs

- **Clotazoline*^**
  - Target NOH-2
  - For M. abs

- **Tedizolid*^**
  - Target 50S ribosome
  - For NTM

- **Bedaquiline*^**
  - Target ATP synthase
  - For NTM

- **β-lactams with avibactam*^**
  - Target penicillin-binding protein
  - For M. abs and M. avium

- **Rifabutin*^**
  - Target RNA polymerase
  - For M. abs

#### Phase I/II
- **Clotazoline**
  - Target NOH-2
  - For M. avium PD

- **Liposomal amikacin for inhalation (LAI)**
  - Target 30S ribosome
  - For M. abs PD

- **Nitric oxide**
  - Enhance host defense
  - Produce reactive nitrogen intermediates
  - For CF patients with NTM (especially M. abs)
  - From AIT therapeutics

- **Gaseous nitric oxide (gNO)*^**
  - Enhance host defense
  - Produce reactive nitrogen intermediates
  - For NTM
  - Thiolance® from novartis

#### Phase III
- **Liposomal amikacin for inhalation (LAI)**
  - Target 30S ribosome
  - For refractory MAC PD

- **Nitric oxide**
  - Enhance host defense
  - Produce reactive nitrogen intermediates
  - For NTM
  - Thiolance® from novartis

#### Phase IV
- **Linezolid**
  - Target 50S ribosome
  - For NTM disease

- **Clarithromycin vs azithromycin**
  - Target 50S ribosome
  - For MAC PD

- **Clarithromycin vs moxifloxacin**
  - Target DNA gyrase
  - For M. xeropl PD

#### Mechanism of action
- Inhibition of cell wall synthesis
- Inhibition of protein synthesis
- Inhibition of nucleic acid synthesis
- Other mechanisms
PARADIGM FOR NOVEL TREATMENT

- Primary single-point whole-cell screen for growth inhibitors against M. abscessus and M. avium
  - Hit confirmation (MIC determination)
  - Activity (MIC) in different media
    - Activity (MIC) against subspecies panel
    - Bactericidal activity
  - In vitro ADME
  - Mouse PK
  - Drug penetration into infection sites (in vitro)
    - Activity (MIC) against collection of clinical isolates
    - Mouse tolerability
    - Mouse dose escalation PK
  - Mouse efficacy

- Selection of resistant mutants, target identification via whole-genome sequencing and biochemical assays
- Iterative medicinal chemistry cycles during hit-to-lead and lead optimization
- Preclinical development compound

Drug Discovery Today
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 remain **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.