Why Do I (and so many others) Have NTM Lung Infections?

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Disclosures

- No conflict of interest disclosures
- No discussion of nonFDA approved drugs
Overview – Why so much NTM disease?

- We’re looking for it more
- The bug
- The environment
- The host
Overview – Why so much NTM disease?

- We’re looking for it more
- The bug
- The environment
- The host
Nontuberculous Mycobacteria

- Common environmental bugs
  - Water including potable, soil
- >150 species
  - *M. avium* complex
  - *M. abscessus* group
  - *M. kansasii*

- Clinical
  - Lung (85%)
  - Skin, soft tissues
  - Disseminated
“Unusual dose” vs. “Susceptible host”

“Hot Tub Lung” vs. “Lady Windermere”
NTM Host Risk Factors

Adapted from:
Lake. BMC Medicine 2016
Wu. Lancet Infect Dis 2015
Host Susceptibility

- Varies by organism & anatomic location of infection

\[\begin{array}{c}
\text{Disease Severity or} \\
\text{Treatment Refractory} \\
\neq \\
\text{Immunodeficiency}
\end{array}\]
<table>
<thead>
<tr>
<th>Impaired local defenses</th>
<th>Clinical history, chest imaging, pulmonary function tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis, COPD, coal/gold miners, sand blasters, previous cavitary tuberculosis</td>
<td></td>
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<tr>
<td>Alpha-1 antitrypsin deficiency</td>
<td>A1AT phenotype, level, genetic testing</td>
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<tr>
<td>Cystic fibrosis</td>
<td>Sweat chloride test, genetic testing</td>
</tr>
<tr>
<td>Alveolar proteinosis</td>
<td>Chest imaging, bronchoscopy or biopsy, anti-GMCSF antibody levels</td>
</tr>
<tr>
<td>Primary ciliary dyskinesia</td>
<td>Measurement of nasal nitric oxide, cardinal clinical features, biopsy for electron microscopy (cilia structure), genetic testing (38+ genes)</td>
</tr>
</tbody>
</table>

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<tr>
<th>Impaired systemic immunity</th>
<th>Total IgE, cardinal clinical features &amp; family history, genetic testing</th>
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<tbody>
<tr>
<td>Job’s syndrome</td>
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<th>Immunosuppressant use</th>
<th>Drug history</th>
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<td>Tumor necrosis factor-α blockers</td>
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<th>Lady Windermere syndrome</th>
<th>Clinical history with exclusion of above risk factors, unique physical features</th>
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</table>

Adapted from Wu. Lancet Infect Dis 2015
Lady Windermere Dissected: More Form Than Fastidious

Kenneth N. Olivier
Ann Am Thorac Soc 2016

Genetic diseases
- Cystic fibrosis
- Marfan syndrome
- Nontuberculous mycobacteria
  - Idiopathic nodular bronchiectasis
- Primary ciliary dyskinesia
- Job’s syndrome

Genetic connective tissue diseases
Genetic immune diseases

Genetic diseases affecting airway clearance
## Physical Features


<table>
<thead>
<tr>
<th>Measurement</th>
<th>% PNTM (n=63)</th>
<th>% General Population</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoliosis</td>
<td>51 (23)</td>
<td>1.9</td>
<td>&lt;0.001</td>
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<tr>
<td>Pectus excavatum</td>
<td>11 (7)</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>9 (5/56)</td>
<td>2.4</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Pulmonary Nontuberculous Mycobacterial Disease

NHANES Controls
Familial traits

- 14 (12.8%) at least 1 relative with PNTM
  - 8 sibling pairs
  - 4 parent-child
  - 2 aunt-niece

- 13 (11.9%) had relatives with bronchiectasis
PNTM Exome Sequencing Study*

*Looking for rare, protein-altering gene changes that may increase risk of developing PNTM disease

1. CF
2. Cilia
3. Connective tissue
4. Immune
Whole Exome Analysis Results

- PNTM patients & unaffected family members vs. controls
  - More changes in CF, cilia, & connective tissue genes
  - No difference - PNTM patients & unaffected family members
- What about “unaffected” family members?
  - Many had bronchiectasis and/or overlapping physical features
- More immune gene changes only in PNTM affected
- Whole exome data support
  - “Susceptible persons” model of PNTM disease
  - The more “mild” changes you have in relevant gene categories, the greater risk of developing bronchiectasis and PNTM

Szymanski EP. Am J Respir Crit Care Med 2015
Host-Environment-Pathogen

**Host**
- Structural\genetic\ immunologic
- Bronchiectasis
- COPD
- Cystic fibrosis
- Anti-TNF agents

**Environment**
- Vapor pressure
- pH of water
- Temperature
- Chlorination
- Biofilms\ piping material

**Pathogen**
- Virulence, drug resistance