Slowly Growing Nontuberculous Mycobacterial Infections

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University of Colorado, Denver
Disclosures

• Advisory Board – Horizon, Johnson and Johnson, Otsuka and Spero
• Investigator – Insmed
Objectives

After participating in this lecture, you should be able to:

1. Describe the epidemiology of NTM infections
2. Describe an approach to deciding whom to treat
3. Describe treatment regimens for MAC and *M. kansasii* infections
Questions

• What are nontuberculous mycobacteria?
• Are NTM infections increasing?
• How do you diagnosis pulmonary NTM infections?
• How do you decide whom to treat?
• How do you treat *M. kansasii* infection?
• How do you treat MAC infection?
Nontuberculous Mycobacteria (NTM)

- NTM represent all mycobacteria except *M. tuberculosis* and *M. leprae*
- Over 170 species of NTM
  - Many (~80) have been reported to cause disease in humans
- Also referred to as:
  - Atypical mycobacteria
  - Mycobacteria other than tuberculosis (MOTT)
  - Environmental mycobacteria
## NTM That Have Been Reported to Cause Lung Disease

<table>
<thead>
<tr>
<th>Slowly Growing Mycobacteria</th>
<th>Rapidly Growing Mycobacteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. arupense</em></td>
<td><em>M. kubicae</em></td>
</tr>
<tr>
<td><em>M. asiaticum</em></td>
<td><em>M. abscessus</em></td>
</tr>
<tr>
<td><em>M. avium</em></td>
<td><em>M. lentiflavum</em></td>
</tr>
<tr>
<td><em>M. avium</em></td>
<td><em>M. malmoense</em></td>
</tr>
<tr>
<td><em>M. branderi</em></td>
<td><em>M. boenickei</em></td>
</tr>
<tr>
<td><em>M. celatum</em></td>
<td><em>M. boenickei</em></td>
</tr>
<tr>
<td><em>M. chimaera</em></td>
<td><em>M. brumae</em></td>
</tr>
<tr>
<td><em>M. florentinum</em></td>
<td><em>M. cheloneae</em></td>
</tr>
<tr>
<td><em>M. heckeshornense</em></td>
<td><em>M. confluentis</em></td>
</tr>
<tr>
<td><em>M. intermedius</em></td>
<td><em>M. elephantis</em></td>
</tr>
<tr>
<td><em>M. intracellular</em></td>
<td><em>M. goodii</em></td>
</tr>
<tr>
<td><em>M. intracellulare</em></td>
<td><em>M. thermoresistible</em></td>
</tr>
<tr>
<td><em>M. kansasii</em></td>
<td><em>M. xenopi</em></td>
</tr>
<tr>
<td><em>M. kansasii</em></td>
<td></td>
</tr>
<tr>
<td><em>M. kansasii</em></td>
<td></td>
</tr>
</tbody>
</table>

* Growth in subculture within 7 days
Questions

- What are nontuberculous mycobacteria?
- **Are NTM infections increasing?**
- How do you diagnosis pulmonary NTM infections?
- How do you decide whom to treat?
- How do you treat M. kansasii infection?
- How do you treat MAC infection?
## Annual Rates and Trends of NTM
### North America, Population Based

<table>
<thead>
<tr>
<th>Region</th>
<th>Period</th>
<th>Isolation</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>US HMO (4)</td>
<td>1994-2006</td>
<td>11.8</td>
<td>5.5</td>
</tr>
<tr>
<td>USA Medicare (≥65yrs)</td>
<td>1997-2007</td>
<td>NR</td>
<td>∼ 47</td>
</tr>
<tr>
<td>Ontario, Canada</td>
<td>1998-2010</td>
<td>22.2</td>
<td>9.8</td>
</tr>
<tr>
<td>Oregon, state-wide</td>
<td>2005-2006</td>
<td>12.7</td>
<td>5.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td>12.7 (11.8-22.2)</td>
<td>5.6 (5.5-9.8)</td>
</tr>
</tbody>
</table>

*Annualized (per 100,000 population/year): overall average or final year of study (generally excludes *M. gordonae*)

Courtesy: Ted Marras
Audience Response Question #1

Which state has the highest rate of pulmonary nontuberculous mycobacterial infections in the United States?

A. Florida
B. New Mexico
C. Hawaii
D. Mississippi
Prevalence of Pulmonary NTM Among Medicare Part B Enrollees by State

- A national representative 5% sample of Medicare Part B beneficiaries, 1997-2007
- All subjects were ≥ 65 yrs

Prevalence of Pulmonary NTM Infection by Race/Ethnicity

Overall – 112 cases/100,000
Women 1.4 X more likely than men

Incidence of Pulmonary Nontuberculous Mycobacterial Infection Over Time

Questions

• What are nontuberculous mycobacteria?
• Are NTM infections increasing?
• How do you diagnosis pulmonary NTM infections?
• How do you decide whom to treat?
• How do you treat M. kansasii infection?
• How do you treat MAC infection?
# Clinical Presentation

<table>
<thead>
<tr>
<th>Symptoms/Signs</th>
<th>Underlying Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough (chronic)</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Fatigue</td>
<td>COPD</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Pneumoconiosis</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>Alveolar proteinosis</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Esophageal disorders</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disorders</td>
</tr>
<tr>
<td></td>
<td>Immunocompromised</td>
</tr>
</tbody>
</table>
Radiographic Presentations

Nodular Bronchiectatic  Fibrocvavitary
Culture Techniques

- Cultures for mycobacteria should include both solid and liquid media
- Broth media have a higher yield and provide results more rapidly
- Solid media allow observation of colony morphology, growth rates, recognition of mixed cultures, and quantitation
- **Speciation should be done with sequencing**
Susceptibility Testing for NTM Slowly Growing Mycobacteria

- Method: broth-based with both microdilution or macrodilution acceptable
- MAC - Test all initial isolates, failures, relapses to clarithromycin
- *M. kansasii* - Test all initial isolates, failures, and relapses to rifampin
  - If rifampin resistant tests amikacin, ciprofloxacin, clarithromycin, ethambutol, rifabutin, sulfonamides, isoniazid, moxifloxacin

ATS/IDSA AJRCCM 2007;175:367
# ATS Diagnostic Criteria For NTM Lung Disease

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Cough, fatigue, weight loss</th>
</tr>
</thead>
</table>
| Radiograph | • Nodular or cavitary opacities on chest radiograph  
  or  
  • CT showing multifocal bronchiectasis with multiple small nodules |
| Bacteriology | • Positive cultures from at least two separate expectorated sputum samples  
  or  
  • Positive culture from at least one bronchial wash or lavage  
  or  
  • Transbronchial biopsy or other lung biopsy with mycobacterial histopathologic features and positive culture |
Questions

• What are nontuberculous mycobacteria?
• Are NTM infections increasing?
• How do you diagnosis pulmonary NTM infections?
• **How do you decide whom to treat?**
• How do you treat M. kansasii infection?
• How do you treat MAC infection?
NTM Pulmonary Infections
Who to Treat?

- The Patient
  - Increased susceptibility?
  - Clinical symptoms and overall condition of patient
  - Extent of radiograph abnormalities and whether there is evidence of progression

- The Organism
  - Species that has been isolated
  - Bacteriologic load (smear + vs. smear -)

- Overall goal of therapy?
  - Cure, bacteriologic conversion, relief of symptoms, prevention of progression
The Host
Risk Factors for NTM Infection

Underlying Conditions
- CF/CFTR anomalies
- AAT anomalies
- COPD
- Pneumoconiosis
- Collagen vascular disease
- Bronchiectasis
- TNF alpha antagonists
- Alveolar proteinosis

Significant exposures
- Aerosolized water
- Aerosolized soil
- Residence in endemic areas

Innate host issues
- Postmenopausal women
- Thin women with distinct body habitus
- Predisposition to hypersensitivity

Adapted from Chan E and Iseman MD. Gender Med 2010;7:5-18
Lady Windermere’s Syndrome


Iseman MD, et al. ARR 1991;144:914
Kim, et al. AJRCCM 2008;178:1066
Clinical Relevance of Different Species: Netherlands and S. Korea

Van Ingen J, Koh WJ, Daley CL, unpublished
## Correlation with Positive Cultures and Progression

<table>
<thead>
<tr>
<th>Positive cultures</th>
<th>N</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>114</td>
<td>2</td>
</tr>
<tr>
<td>Two</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>Three</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>≥ Four</td>
<td>116</td>
<td>116</td>
</tr>
</tbody>
</table>

Tsukamura M. Chest 1991;99:667
# NTM
## Treatment Regimens – Goals

<table>
<thead>
<tr>
<th>NTM</th>
<th>Drugs</th>
<th>Duration</th>
<th>Expected Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. kansasii</em></td>
<td>Isoniazid (macrolide)</td>
<td>&gt;12 mo</td>
<td>≥ 95%</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rifamycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAC*</td>
<td>Macrolide (azithromycin)</td>
<td>&gt;12 mo</td>
<td>56% to 85%</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rifamycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. abscessus</em></td>
<td>Macrolide (azithromycin)</td>
<td>&gt;12 mo</td>
<td>&lt;50%</td>
</tr>
<tr>
<td></td>
<td>Cefoxitin or imipenem (IV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amikacin (IV or inhaled)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other oral drugs?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Three times weekly for nodular bronchiectatic MAC without cavitation

Note: aminoglycoside for cavitary disease
Questions

- What are nontuberculous mycobacteria?
- Are NTM infections increasing?
- How do you diagnosis pulmonary NTM infections?
- How do you decide whom to treat?
- How do you treat M. kansasii infection?
- How do you treat MAC infection?
Mycobacterium kansasii

- First described by Buhler and Pollack as the “yellow bacilli” in 1953 and later named in 1955 by Hauduroy.
- Most cases are associated with progressive disease.
Mycobacterium kansasii

- 45 year old Caucasian woman with chronic cough
- Chest x-ray - abnormal
- Three sputum specimens obtained
- She was started on a 4-drug TB treatment regimen
- Sputum cultures grew *M. kansasii*
Treatment Regimen

*M. kansasii*

**MK**

Rifampin sensitive

- **Yes**
  - Cavities Present
    - **No**
      - 3X/WEEK Isoniazid (or macrolide) Rifampin Ethambutol
    - **Yes**
      - DAILY Isoniazid (or macrolide) Rifampin Ethambutol

- **No**
  - DAILY Isoniazid Ethambutol Other drug

Azithromycin Clarithromycin Moxifloxacin Clofazimine

Add IV Amikacin
# Mycobacterium kansasii
## Outcomes of Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimen</th>
<th>Duration mos</th>
<th>Conversion</th>
<th>Cure*</th>
<th>Failure</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahn, 1983</td>
<td>40</td>
<td>H/R/E SM biw for 3 mo</td>
<td>12</td>
<td>Median – 5.5 weeks</td>
<td>ND</td>
<td>0</td>
<td>2.5%</td>
</tr>
<tr>
<td>Santin, 2009</td>
<td>75</td>
<td>H/R/E SM for 2-3 mo</td>
<td>12</td>
<td>ND</td>
<td>83%</td>
<td>0</td>
<td>6.6%</td>
</tr>
<tr>
<td>Evans, 1996</td>
<td>47</td>
<td>H/R/E ± Z</td>
<td>Mean-10</td>
<td>ND</td>
<td>79%</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td>Sauret, 1995</td>
<td>14</td>
<td>H/R/E</td>
<td>12, 18</td>
<td>100%, mean-4.5±2.0</td>
<td>93%</td>
<td>0</td>
<td>3.5%</td>
</tr>
<tr>
<td>Park, 2010</td>
<td>31</td>
<td>H/R/E</td>
<td>Median-16</td>
<td>Median – 1 mo 95% by 12 mo</td>
<td>52%</td>
<td>0</td>
<td>6%</td>
</tr>
<tr>
<td>BTS, 1994</td>
<td>173</td>
<td>R/E</td>
<td>9</td>
<td>89% by 3 mo</td>
<td>89%</td>
<td>1</td>
<td>9.7%</td>
</tr>
</tbody>
</table>

*Cure was nearly 100% when non-mycobacterial deaths and lost to follow-up patients are excluded*
Outcomes With Clarithromycin-based Regimen

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimen</th>
<th>Mean Duration, months*</th>
<th>Mean Culture Conversion, months</th>
<th>Cure n (%)</th>
<th>Failure n (%)</th>
<th>Relapse n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffith D, 2003</td>
<td>18</td>
<td>Clarithromycin Ethambutol Rifampin, given tiw</td>
<td>13</td>
<td>1</td>
<td>14** (78)</td>
<td>0</td>
<td>0***</td>
</tr>
<tr>
<td>Shitrit D, 2006</td>
<td>56</td>
<td>Clarithromycin Ethambutol Rifampin, given daily</td>
<td>21</td>
<td>9</td>
<td>56 (100)</td>
<td>0</td>
<td>ND</td>
</tr>
</tbody>
</table>

*At least 12 months of culture negativity
**Among completers, 100% cure rate
***Mean duration of follow-up was 46±8.0 mos

Questions

• What are nontuberculous mycobacteria?
• Are NTM infections increasing?
• How do you diagnosis pulmonary NTM infections?
• How do you decide whom to treat?
• How do you treat M. kansasii infection?
• How do you treat MAC infection?
Mycobacterium avium Complex

FIG 5 Phylogenetic tree, based on the 16S rRNA gene, for the species belonging to the M. avium complex.
Treatment
*M. avium* complex

MAC

- **Yes**
  - Macrolide sensitive
    - **Yes**
      - Cavities Present
        - **No**
          - 3X/WEEK Azithromycin, Rifampin, Ethambutol
        - **Yes**
          - DAILY Azithromycin, Rifampin, Ethambutol
    - **No**
      - DAILY Rifampin, Ethambutol, Other drug
  - **No**
    - Add IV Amikacin

- **No**
  - New drug?
# Treatment Outcomes for MAC

<table>
<thead>
<tr>
<th></th>
<th>Culture Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolide susceptible</strong></td>
<td></td>
</tr>
<tr>
<td>Non cavitary</td>
<td>80%</td>
</tr>
<tr>
<td>Cavitary</td>
<td>&lt;50%</td>
</tr>
<tr>
<td><strong>Macrolide resistant</strong></td>
<td></td>
</tr>
<tr>
<td>No surgery/aminoglycoside</td>
<td>5%</td>
</tr>
<tr>
<td>Surgery + aminoglycoside*</td>
<td>80%</td>
</tr>
</tbody>
</table>

* ≥ 6 months IV aminoglycoside

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Griffith DE, et al. AJRCCM 2006;174:928  
# Three-times Weekly Therapy for Pulmonary MAC

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Conversion</th>
<th>Regimen Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallace, 2014</td>
<td>180</td>
<td>Daily: 7/8 (88%)</td>
<td>Daily: 24/34 (80%)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIW: 147/172 (85%)</td>
<td>TIW: 5/180 (3%)*</td>
</tr>
<tr>
<td>Jeong, 2015</td>
<td>217</td>
<td>Daily: 75/99 (76%)</td>
<td>Daily: 46/99 (46%)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIW: 79/118 (67%)</td>
<td>TIW: 25/118 (21%)*</td>
</tr>
</tbody>
</table>

*P < 0.001

Jeong BH et al. AJRCCM 2015; 191:96-103
### MAC Recurrences
#### Relapse vs reinfection

<table>
<thead>
<tr>
<th>Measure</th>
<th>University of Texas, Tyler ¹</th>
<th>Northwestern ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still on Therapy</td>
<td>25/180 (14%)</td>
<td>46/190 (25%)</td>
</tr>
<tr>
<td>After Completion of Therapy</td>
<td>74/155 (48%)</td>
<td></td>
</tr>
</tbody>
</table>

- **Microbiologic recurrence after sputum conversion**
- **New infection***: 48% | 75% | 46%
- **True Relapse**: 52% | 25% | 54%

* Determined by pulse field electrophoresis

A 67 year old women with chronic Pseudomonas infection and bronchiectasis is treated with azithromycin monotherapy for 12 months. She is now diagnosed with macrolide resistant MAC pulmonary disease. Which of the following factors is associated with a better prognosis?

A. use of an aminoglycoside
B. continued use of a macrolide
C. surgical resection
D. use of a later generation fluoroquinolone
E. A and C
Inhaled Amikacin for Treatment of Refractory Pulmonary NTM

Olivier KN, et al. Annal ATS 2014;11:30

Cultures

- 8 achieved negative cultures
- 5 persistently negative

<table>
<thead>
<tr>
<th>Reason</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ototoxicity</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Nephrotoxicity*</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Persistent dysphonia</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Mo on inhaled amikacin, median (range)

<table>
<thead>
<tr>
<th>Dose</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg daily</td>
<td>10 (50)</td>
</tr>
<tr>
<td>250 mg twice daily</td>
<td>4 (20)</td>
</tr>
<tr>
<td>250 mg thrice weekly</td>
<td>3 (15)</td>
</tr>
<tr>
<td>250 mg every other d</td>
<td>1 (5)</td>
</tr>
<tr>
<td>500 mg daily</td>
<td>1 (5)</td>
</tr>
<tr>
<td>125 mg twice daily</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

*Exceeded normal creatinine levels (1.2 mg/dl) at two visits (1.43, 1.42 mg/dl).
Inhaled Liposomal Amikacin (Insmed)

Proportion of Patients With Negative Sputum Cultures for NTM in the Double-blind Phase

Baseline
LAI: n = 5/44
PBO: n = 5/45

Day 28
LAI: n = 10/42
PBO: n = 5/45

Day 56
LAI: n = 11/42
PBO: n = 4/45

Day 84
LAI: n = 14/41
PBO: n = 4/45

P = 0.006

LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; NTM, nontuberculous mycobacteria; PBO, placebo.

Olivier K, et al. AJRCCM 2016;epub
Clofazimine in the Treatment of Pulmonary MAC

Culture Conversion, Microbiologic Relapse, and Re-treatment Rates

- Calgary, Canada
- Retrospective study
- Pulmonary MAC
  - 54% AFB sm +
- 107 patients
  - 90 clofaz + EMB/AZI
  - 14 rifampin + EMB/AZI
  - 3 clofaz + rifampin + EMB/AZI

Summary

• NTM infections appear to be increasing
• Diagnosis should consider the clinical and radiographic presentation
• The decision to treat should be based on at least three factors; patient, organism (species and bacterial load) and goals of treatment
• Treatment of *M. kansasii* is with INH, rifampin, ethambutol (macrolides may be substituted for INH)
• Treatment of *M. avium* complex is with azithromycin, rifampin, and ethambutol (± amikacin)