Non-tuberculous Mycobacterial (NTM) Lung Disease

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April 6, 2016

Tuberculosis Intensive
April 5-8, 2016
San Antonio, TX

David Griffith, MD has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
NTM are commonly found in the environment

- NTM are found mostly in soil, dust, water (fresh, salt, natural, potable), biofilms, and their aerosols.

- **NTM are built to survive in harsh environments**
  - **Slow growth** → Greater resistance to antibiotics and disinfectants
  - **Lipid-rich cell wall** → Less permeable, hydrophobic
  - **Hydrophobic** → Concentration at air-water interface (bubbles) and biofilms
  - **Oligotrophic** → Grow at low nutrient concentrations
  - **Microaerobic** → Grow at 6% oxygen (in "swampy" areas)
  - **Acidophilic** → Grow at pH 5-6 (in “brackish” water)

How do we get NTM?

- Direct inhalation of NTM-contaminated water aerosols and dust.

- Microaspiration of NTM-contaminated water from the oropharynx to the lungs.

- Gastroesophageal reflux from swallowed NTM that survive in the stomach (I wonder whether β₂-agonists or “antacids” contributes…)

- For skin and soft-tissue infections, direct inoculation of NTM from NTM-contaminated water, soil, or medications (iatrogenic).
## Comparison between Home and Respiratory NTM Isolates

<table>
<thead>
<tr>
<th>Total # Patients</th>
<th>Patient isolates growing M. avium</th>
<th>Patient isolates growing M. intracellulare</th>
<th># Home Water Samples with M. avium</th>
<th>Matching rep-PCR and VNTR type between home and patient M. avium isolate</th>
<th># Home Water Samples with M. chelonae</th>
<th># Home Water Samples with M. intracellulare</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>20/28 (71%)</td>
<td>4/28 (14%)</td>
<td>250</td>
<td>24/28 homes (28 homes; avg 9 sites per home)</td>
<td>17/28 homes (28% of sampled sites)</td>
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<td>10/20 (50%)</td>
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<td>71/250 sites (28% of sampled sites)</td>
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Lande et al 2013

### Why is potable water not safe from NTM (MAC)?

- *Mycobacterium avium* complex (MAC) is 1,000-10,000X more resistant to chlorine than *E. coli*.

- MAC is more resistant to chlorine than *M. scrofulaceum*.

- *M. xenopi* and MAC are particularly resistant to temperatures seen in home hot water heaters.
Known risk factors for NTM disease
(isolated lung disease vs. disseminated)

**Underlying conditions**
- Cystic fibrosis, CFTR anomalies
- Alpha-1-antitrypsin anomalies
- Emphysema
- Pneumoconiosis / CVD
- Chronic aspiration
- Previous bronchiectasis
- Pulmonary alveolar proteinosis
- Calcified chest adenopathy
- Partial deficiency in IFNγ
- MonoMAC (QGATA)
- CGD (CYBB)
- ARS-15, AIP6S
- TNFα antagonists
- HIV
- Anti-IFNγ antibody
- Absolute defects in IL-12, IFNγ, or NEMO bioactivity

**Innate host characteristics**
- Slender individuals with thoracic cage abnormalities such as scoliosis & pectus excavatum (Marfanoid features)

**Significant environmental exposure**
- Aerosolized water (hot tubs, showerheads)
- Aerosolized soil exposure
- Residence in SE United States

**Diversity of NTM Pulmonary Disease**

- Associated with disseminated disease and immune suppression
  - HIV
  - Defects in IFNγ and IL-12 pathways
  - Tumor necrosis factor α blockers
- Tuberculosis-like disease
- Disease associated with nodules/bronchiectasis
  - Disease associated with genetic airway abnormalities and abnormal airways clearance (cystic fibrosis, primary ciliary dyskinesia)
- Esophageal motility disorders
- Hypersensitivity-like lung disease
Pathogenesis of NTM Lung Disease

• Bronchiectasis and pulmonary NTM infection inextricably linked
• 20% of CF patients and 15% of PCD patients have NTM in respiratory specimens
• Strongly suggests, at least for some patients, a predisposing alteration in airway surface defenses
• Bronchiectasis/NTM: ?Chicken vs Egg
• Routine AFB evaluation for bronchiectasis in the age of macrolide immune modulation: YES!
• ? Routine evaluation for etiology of bronchiectasis

Pathogenesis of NTM Lung Disease

Kim et al, AJRCCM 2008, 178; 1066; Kartalija et al, AJRCCM 2013 187; 197

• Characteristic morphotype (body habitus) in 166 patients with NTM lung disease evaluated at the NIH and NJH:
  – BMI significantly lower and height significantly greater than matched controls
  – High rates of scoliosis, pectus excavatum, and mitral valve prolapse, CFTR mutations
  – NIH: no recognized immune defects (cell mediated dysfunction or cytokine pathway abnormalities)
  – NJH: IFN-gamma and IL-10 levels were significantly suppressed in stimulated whole blood of patients with NTM lung disease

Pathophysiologic consequences of this constellation of findings currently unknown. Does not explain disease in majority of patients
1. Prevalence of NTM pulmonary disease is increasing globally, in some countries NTM disease significantly more common than TB
2. MAC the predominant isolate (RGM 2nd)
3. The prevalence of NTM pulmonary disease increases with age especially in females
4. ? The most common cause of chronic cough in older women?
5. Different species have different clinical relevance and different ecologic reservoirs: better data needed on environmental distribution and risk factors by species

Epidemiology Summary

Is it TB or NTM Disease?

- NTM Disease
  - Indolent, Milder Symptoms
  - Thin walled cavities
  - Contiguous spread
  - > Pleural reaction
  - Pleural effusion rare
  - Frequent nodules/bronchiectasis

- Tuberculosis
  - Rapidly Progressive Severe Symptoms
  - Variable cavity shape
  - Bronchogenic spread
  - < Pleural reaction
  - Pleural effusion common
  - N/B disease unusual
Is there any one radiographic finding or combination of findings that distinguishes NTM disease from TB?

NO

Clinically distinguishing NTM disease from TB

• Scenario #1
  – 35 yo male from Mexico
  – History of TB in family
  – Several months cough, sweats, weight loss
  – (+) PPD
  – CXR: apical cavitary consolidation
  – 1st sputum AFB culture (+) for MAC
Clinically distinguishing NTM disease from TB

• Scenario #1:
  – Pulmonary MAC disease unusual in a 35 yo male
  – Multiple risk factors for TB
  – Clinical presentation typical for TB
  – Patient subsequently grew multiple (+) cultures for *M. tuberculosis*
  – Empiric therapy for TB ok in this setting, may occur frequently

Clinically distinguishing NTM disease from TB

• Scenario #2:
  – Patient with established diagnosis of TB on antituberculosis therapy
  – Sputum AFB culture (+) for NTM (especially MAC) during course of TB therapy
  – Does therapy need to be altered?
Nontuberculous mycobacteria isolated during the treatment of pulmonary tuberculosis
Jun et al, 2009; 103: 1936

• 958 patients with tuberculosis: 68 (7.1%) had NTM isolated during TB therapy
• 71% had only one positive NTM culture
• Only two patients (3%) both with *M. abscessus* isolates were felt to have progressive NTM disease after completion of TB therapy
• Progressive NTM disease rare after completion of TB therapy but patients require follow-up after completion of TB therapy, especially with isolation of *M. abscessus*.

Clinically distinguishing NTM disease from TB

• Scenario #2:
  – Therapy does not need to be altered
  – NTM in sputum will complicate therapy especially if specimens also AFB smear (+)
  – Complete therapy for TB then evaluate significance of NTM isolate
  – In our experience, most patients do not have progressive NTM disease in this setting
Clinically distinguishing NTM disease from TB

• Scenario #3:
  – Patient with established NTM disease and multiple AFB culture (+) specimens for NTM
  – While on therapy for NTM disease, AFB culture (+) specimen for *M. tuberculosis*
  – Does this patient have NTM disease and TB?
Clinically distinguishing NTM disease from TB

- 66 yo female with longstanding MAC lung disease
- Unresponsive microbiologically to MAC medication
- Patient’s son, living in household, diagnosed with tuberculosis
- Patient with *M. tuberculosis* isolate, same genotype as her son’s isolate.
Clinically distinguishing NTM disease from TB

• Scenario #3:
  – Very rare occurrence
  – In our experience, (+) AFB culture for *M. tuberculosis* usually due to specimen contamination
  – Need genotyping of *M. tuberculosis* isolate to exclude specimen contamination
  – May need to treat TB pending evaluation

Clinically distinguishing NTM disease from TB

• What do you do with the elderly female patient who has a clinical course and radiographic changes characteristic of nodular/bronchiectatic MAC disease and a sputum smear (+) for AFB?
  • Start antituberculosis therapy or wait for culture results?
    – Start antituberculosis therapy in most cases
An Official ATS/IDSA Statement: Diagnosis, Treatment and Prevention of Nontuberculous Mycobacterial Diseases

American Journal of Respiratory and Critical Care Medicine
2007, 175; 367-416

Diagnosis of NTM Lung Disease
Minimum Evaluation

• Compatible Symptoms
• Radiographic Evaluation
  – Chest radiograph (cavitary disease) or,
  – HRCT of chest (nodular/bronchiectatic disease)
• Microbiologic Evaluation
  – 3 or more sputum for AFB analysis
  – Bronchoscopic evaluation
• Exclusion of other diagnoses (TB)
Diagnosis of NTM Lung Disease: Microbiologic Criteria 2007

- 3 sputum results: 2 positive cultures regardless of AFB smear results
- Single available bronchial wash or lavage: One positive culture regardless of smear results
- Tissue biopsy:
  - Compatible histopathology and (+) culture
  - Compatible histopathology and (+) sputum or bronchial wash culture

ATS Diagnostic Guidelines for NTM Lung Disease

- More than 140 NTM species with a spectrum of virulence for humans
- NTM lung disease diagnostic criteria are based on experience with common and well-described respiratory pathogens such as *Mycobacterium avium* complex, *M. kansasii* and *M. abscessus*
- It is extremely unlikely that a single set of diagnostic criteria would be useful or accurate for all NTM species in all clinical circumstances.
Diagnosis of NTM Lung Disease: Microbiologic Criteria

• A single positive culture from any source (sputum or bronchoscopy) is is regarded as indeterminate for diagnosis of NTM lung disease:
  – Frequent contaminants, *M. gordonae, M. terrae* complex, *M. mucogenicum*
  – NTM species known to be present in tap water, *M. simiae, M. lentiflavum, M. abscessus, M. kansasii, M. xenopi*

Factors Influencing the Decision to Treat NTM Lung Disease

• Making the diagnosis of NTM disease does not by itself necessitate the initiation of therapy. The decision to start therapy for NTM lung disease is based on a careful risk/benefit analysis for the individual patient.

  • Is the NTM disease cavitary?
  • How symptomatic is the patient and how do the symptoms impact QOL?
  • What are the patient’s pulmonary co-morbidities and are they compensated?
  • What systemic co-morbidities does the patient have and do they impact NTM disease? What is the patient’s short and long term prognosis?
  • What are the short term (mos) trends in symptoms, radiographic appearance and culture results?
  • What does the patient want to do?
Diagnostic Criteria for NTM Lung Disease

- PATIENTS WHO ARE SUSPECTED OF HAVING NTM LUNG DISEASE BUT DO NOT MEET THE DIAGNOSTIC CRITERIA SHOULD BE FOLLOWED UNTIL THE DIAGNOSIS IS FIRMLY ESTABLISHED OR EXCLUDED.

75 year old woman with sputum AFB culture + for MAC
(75 + 12) year old woman with 35/70 sputum AFB culture + for MAC, no therapy

Treatment of NTM

- Correlation between treatment response and in vitro susceptibilities
  - M. kansasii (rpm)
  - M. marinum
  - M. szulgai
  - M. fortuitum (erm gene)

- Limited or no correlation between treatment response and in vitro susceptibility
  - MAC
  - M. xenopi
  - M. malmoense
  - M. simiae
  - M. abscessus
  - M. chelonae
Therapy of MAC Lung Disease
2007 ATS NTM Guidelines

• Cavitary disease: macrolide/EMB/rifamycin ± injectable: DAILY
• Nodular/bronchiectatic disease:
  macrolide/EMB/rifamycin: INTERMITTENT*
• Severe or previously treated disease:
  macrolide/EMB/rifamycin/injectable: DAILY
• Duration: 12 months sputum culture negativity while on therapy
• Surgery for selected patients
  *Not indicated for severe and/or cavitary disease
Macrolide/Azalide Therapy for Nodular/Bronchiectatic Mycobacterium avium Complex Lung Disease

(Wallace et al Chest 2014)

• 180 patients with NB MAC lung disease with ≥ 12 months macrolide/azalide-based therapy
• 150/180 (86%) sputum conversion
  – No difference between azi and clari
  – Regimen modification common with daily RX
  – Microbiologic recurrence 14% (73% new genotyope)
• Treatment success 83%
• Microbiologic recurrence 74/155 (48%)
  – 75% new genotypes
• “Intermittent antibiotic therapy for nodular bronchiectatic MAC lung disease” Jeong et al AJRCCM 2014 e-pub

Macrolide/Azalide Therapy for Nodular/Bronchiectatic MAC Lung Disease

• Current guidelines for macrolide/azalide-based regimens for NB MAC lung disease result in favorable microbiologic outcomes for most patients
• These regimens do not promote macrolide resistance
• Intermittent regimens as effective as daily regimens with fewer side effects, therefore TIW therapy preferred
• Microbiologic recurrences common, most due to unique MAC genotypes (“reinfection”)
Cavitary MAC (NTM) Lung Disease

• Pathophysiologically a smoking related disease
• Smoking likely inhibits favorable treatment response
• Likely associated with long term respiratory impairment
• Associated with high all cause mortality, greater than NB MAC lung disease
• Requires aggressive and appropriate therapy
  – Parenteral agents
  – Surgery
  – Smoking cessation
  – Avoidance of macrolide resistance (fatal disease)
64 year old female with macrolide resistant MAC disease

State of the Art: Nontuberculous Mycobacteria and Associated Diseases
(Wolinsky, ARRD 1979;119: 107)

• “Proper management requires greater expertise than is needed for treatment of TB, first, to decide who needs to be treated, and second, to determine which drug regimens to use.”