Nontuberculous Mycobacterial (NTM) Lung Disease

David E. Griffith, MD
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- 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).
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

Trends in bronchiectasis

- Medicare data base query
- 5% sample of Medicare outpatient data (2000 to 2007)
- 1106 cases per 100,000 persons
- Diagnosis increased by 8.7% per year
- Asians had higher prevalence

**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><strong>28</strong></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 (18% of sampled sites)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>71/250 sites (28% of sampled sites)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10/20 (50%)</td>
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</table>

Lande et al 2013

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**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.

Genetic relatedness of MAI complex isolates from patients with pulmonary MAC disease and their soils
Fujita K et al. 2013 Clin Micobiol Infect, 19; 537

- MAC strains recovered from soil from 50% of 100 MAC lung disease patients and 35 controls
- Frequency of MAC recovery did not differ based on presence or absence of disease or infecting MAC species
- 6 patients with high soil exposure with identical VNTR genotypes to soil
- “Residential soils are a likely source of pulmonary MAC infection”.

M. xenopi and MAC are not easily killed in temperatures found in hot water heaters

No killing of M. xenopi at 122°F even after 48 hrs

<table>
<thead>
<tr>
<th>Denver Hospitals</th>
<th>Hot water temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (VA)</td>
<td>133°F</td>
</tr>
<tr>
<td>2 (UH)</td>
<td>131°F</td>
</tr>
<tr>
<td>3 (NJJ)</td>
<td>127°F</td>
</tr>
<tr>
<td>4 (DH)</td>
<td>120°F</td>
</tr>
<tr>
<td>5 (Rose)</td>
<td>118°F</td>
</tr>
</tbody>
</table>

Schulze-Rehbach R and Buchholtz K,  
Aqul Fumar Microbiol 1992
Whole-genome sequencing to identify transmission of M. abscessus between patients with cystic fibrosis: a retrospective cohort study

Bryant et al, Lancet 2013, e-pub

- Whole-genome sequencing on 168 consecutive *M. abscessus* isolates from 31 adult CF patients
- 2 clustered outbreaks of *M. massiliense*: 11 pats
- Patients with numerous contact opportunities
- Isolates with resistance to amikacin and clarithromycin were isolated from individuals not previously exposed to either drug
- Frequent transmission of drug resistant NTM between CF patients despite conventional cross-infection precautions

NTM Disease Prevalence: USA

- **USA** (Winthrop AJRCCM 2010, 182; 977):
  - NTM pulmonary disease prevalence approximately 8.6/100,000 pop overall and 20.4/100,000 pop age > 50 yrs
- **Japan** (Morimoto et al, Ann ATS 2014, 11; 1):
  - NTM pulmonary disease prevalence 33-65 cases/100,000 population
  - NTM pulmonary disease prevalence 6-10 fold higher than estimated incidence
  - NTM pulmonary disease mortality steadily increasing
Epidemiology Summary

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

NTM Drug Resistance

• Acquired drug resistance
  – Selection of isolates with naturally occurring mutations that confer resistance to specific antibiotics
  – The form of drug resistance most associated with TB therapy
• Innate or “natural” drug resistance
  – Not readily or predictably associated with in vitro measures of resistance such as MICs
Intrinsic Macrolide Resistance in Rapidly Growing Mycobacteria

- The primary mechanism of acquired clinically significant macrolide resistance for some mycobacteria (especially RGM) is the presence of an erythromycin methylase or \textit{erm} gene.
- All isolates of \textit{M. abscessus}, \textit{M. fortuitum} (and several other RGM, but not \textit{M. chelonei}) contain an inducible \textit{erm} gene.
- \textit{M. massiliense} contains an inactive \textit{erm} gene.
- Novel \textit{erm} gene in \textit{M. tuberculosis}.
- Does not affect MIC for macrolide with standard in vitro susceptibility techniques.

Strategies to Improve Outcome of Drug Treatment for \textit{M. abscessus} Pulmonary Disease

(\textit{van Ingen CID} 2011, 52; 1281)

- \textit{M. abscessus} genome:
  - \textit{erm} gene
  - An additional \textit{erm}-like gene
  - Multiple efflux pumps
  - An aminoglycoside 2′-N-acetyltransferase
  - 12 homologs of aminoglycoside phosphotransferases
NTM Drug Resistance Mechanisms: Beyond MICs

• Brown-Elliott et al. Antimicrobial susceptibility testing, drug resistance mechanisms, and therapy of infections with NTM.
  — Clin Microbiol Rev 2012, 25; 545
• van Ingen J et al. Resistance mechanisms and drug susceptibility testing of NTM.
  — Drug Resistance Updates 2012

Treatment of NTM

• Correlation between treatment response and in vitro susceptibilities
  — M. kansasii (rmp)
  — 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. cheloneae
Resistant Nontuberculous Mycobacteria

- Mutational Resistance
  - *M. tuberculosis*: multiple gene mutations
  - *M. avium* complex:
    - a) 23S rRNA gene (macrolides);
    - b) 16S rRNA gene (amikacin)
  - *M. kansasii*: *rpo B* gene (rifamycins)
  - *M. abscessus*: 23S rRNA gene (macrolides)

Macrolides for MAC Disease: Summary

- Treatment success correlates with in vitro MIC (susceptible ≤ 8 µg/ml, resistant ≥ 32 µg/ml)
- Disease progression/relapse associated with MIC ≥ 32 µg/ml
- Mechanism of macrolide resistance: selection of isolates with mutation inhibiting macrolide ribosomal binding
- In vitro susceptibility tests for most drugs do not predict who will respond and who will fail therapy.
In vitro Activity of Amikacin Against MAC
(Brown-Elliott et al, 2013 JCM)

• Prolonged exposure to amikacin was present in isolates with amikacin MICs > 64 µg/ml which correlated with 16S rRNA gene mutation at position 1408
• Amikacin is the only drug, other than clari/azi, for which there is a correlation between in vitro MIC for MAC and in vivo response
• Because this is mutational resistance, adequate companion drugs for amikacin are necessary

Resistant Nontuberculous Mycobacteria

• Mutational Resistance is AVOIDABLE
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

Intermittent Antibiotic Therapy for Nodular Bronchiectatic MAC Lung Disease
Jeong et al, AJRCCM 2015

• 217 pats with NB MAC lung disease
• 99 daily, 118 intermittent macrolide-based therapy
• No significant differences in symptomatic, radiographic and microbiologic conversion (76 vs 67%)
• Modification of the initial regimen more common with daily therapy (46 vs 21%)
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)

MAC therapy

- Pharmacokinetic and pharmacodynamic indicies frequently suboptimal with “standard” MAC therapy but no correlation with treatment outcome
- No demonstrated correlation between circulating MAC drug levels and treatment outcome
- No correlation between MICs for rim/emb/stm and response to medications
Lack of Adherence to Evidence-based Treatment Guidelines for NTM Lung Disease
(Adjemian et al, Annals ATS 2014)

• 18% of MAC patients were treated for the greatest duration with a regimen meeting 2007 ATS/IDSA guidelines
• Only 4% were treated with this regimen for > 22 weeks
• Majority of MAC patients (58%) were on a regimen without a macrolide
• 22% of patient received regimens that were “potentially harmful”
  – Macrolide monotherapy 22%
  – Rifampin only 15%
  – Macrolide plus fluoroquinolone 1%

Development of Macrolide Resistant MAC
(Griffith et al 2006 Am J Resp Crit Care Med)

• Risk factors: Macrolide monotherapy, Macrolide plus quinolone
• Sputum conversion after macrolide resistance: 77% in patients with both injectable Rx and surgery; 5% in patients without both injectable RX and surgery.
• Patients who failed therapy, 1 year mortality 34%, 2 year mortality was 45%.
• Patients with sputum conversion to (-), the 1 and 2 year mortality was 0%
### Macrolide Resistant MAC Lung Disease: Response to Therapy

- Sputum conversion after macrolide resistance: 11/14 (77%) \( p=0.0001 \) with both injectable and surgery.
- Sputum conversion after macrolide resistance 2/37 (5%) in patients without both injectable and surgery.
- Of the patients who failed therapy, the one year mortality was 13/38 (34%), two year mortality was 17/38 (45%)
- Of the patients whose sputum converted to negative, the one and two year mortality was 0/13, (0%)

### Macrolide Monotherapy and Immune Modulation

- Panbronchiolitis
- Asthma
- Bronchiolitis Obliterans
- CF related bronchiectasis
- Non-CF related bronchiectasis
- Chronic Obstructive Lung Disease
64 year old female with macrolide resistant MAC disease

Therapy of Macrolide Resistant MAC

- Rifabutin
- Ethambutol
- Surgery
- Parenteral streptomycin or amikacin
  - Inhaled amikacin with caution
- Clofazimine
- Moxifloxacin
- Linezolid
- Macrolide as immune modulating therapy
### Treatment of MAC Lung Disease

**Do's**
- Risk/benefit assessment for N/B MAC patients
- Treat cavitary MAC patients aggressively (surgery, parenteral medications)
- Adhere to guidelines as much as possible
- Frequent clinical and microbiologic assessments
- Lifetime care for patients

**Don'ts (Don't's)**
- Tell patients that MAC therapy will kill them
- Give macrolide or amikacin without adequate companion drugs
- Go rogue with treatment from the start
- Abandon clinical and microbiologic assessments early in treatment

### Treatment of other slowly growing NTM

- **M. xenopi**
  - Rmp/emb, macrolide, amikacin
- **M. malmoense**
  - INH/rmp, emb, +/- macrolide/FQ
- **M. szulgai**
  - Rmp/emb, + macrolide or FQ
- **M. simiae**
  - Macrolide/Bactrim, moxifloxacin +/- linezolid, amikacin, ?
**Taxonomy:** *M. abscessus, M. massiliense, M. boletii*

- *M. abscessus* described > 20 yrs ago
  - M. fortuium/cheloneae complex, M. cheloneae-complex
- *M. boletii* and *M. massiliense* genetically IDENTICAL with 16S rRNA gene sequencing.
- *M. massiliense* with inactive *erm* gene: so NOT genetically identical to *M. boletii*!
- Currently we have:
  - *M. abscessus ssp abscessus* *(erm +)*
  - *M. abscessus ssp boletii* which everyone refers to as *M. massiliense* *(erm -)*

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**Taxonomy Bottom Line**

- You really don’t care how they label the organism, call it “Marcos”.
- You NEED to know if there is an active inducible macrolide resistance (*erm*) gene.
- Just to be consistent
  - *M. abscessus ssp abscessus*
  - *M. massiliense*
Treatment of *M. abscessus* Lung Disease

- Macrolide: value questionable (*erm* gene), may be of value as immune modulator
- Amikacin 10-15 mg/kg 3-5X/week
- Tigecycline 25-50 mg/day
- Linezolid 300-600 mg/day
- Alternatives: Imipenem, cefoxitin, clofazimine
- There is no predictably or reliably effective medical treatment strategy for *M. abscessus* lung disease

Surgery for NTM Lung Disease

- Indications for surgery: medication unresponsive disease (drug resistance, large cavities), uncontrolled symptoms, hemoptysis, destroyed lung
- Symptom Control (+/-)
Laboratory Support Necessary for the 21st Century Management of NTM (MAC, M. abscessus) Disease

- Accurate and rapid species identification utilizing any one of several molecular techniques. Taxonomy matters.
- Early and rapid identification of mycobacterial antibiotic resistance factors (active *erm* gene)
- Routine evaluation of phenotypic *erm* gene activity
- Genotyping of MAC “relapse” isolates to evaluate and guide the response to apparent “relapse” MAC isolates after successful MAC therapy.

MTB and NTM

- 34 year old man from Mexico with cavitary abnormalities on CXR and sputum AFB culture + for MAC
- 67 year old woman on therapy for MAC lung disease who has sputum that is AFB culture + for MTB
- 47 year old woman on therapy for MTB who has sputum that is AFB culture + for MAC
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.”