Pulmonary Non Tuberculous Mycobacteria Infections

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Non Tuberculous Mycobacteria

- Mycobacteria other than tuberculosis “MOTT” or “Atypical Mycobacteria”
  - Environmental Organisms
    - Soil, lakes, rivers, municipal water systems
    - Resistant to chlorine and most disinfectants
  - Biofilm
    - Live within amoeba, legionella, others
  - Animal pathogens, birds, swine

Laboratory Growth Characteristics

- “Slow” growers (> 2 weeks in AFB media, liquid media more quickly)
  - MAC, M. kansasii, M. marinum, M. xenopi
- “Rapid” growers (4-7 days in routine blood agar)
  - M. abscessus, M. chelonae, M. fortuitum
- “Need help” growing
  - M. marinum, M. haemophilum, M. ulcerans
  - M. genavense

NTM Disease- Clinical Manifestations

- Pulmonary (75%)
  - MAC
  - M. kansasii
  - M. xenopi
  - M. abscessus
  - M. malmoense
NTM Disease - Clinical Manifestations

- Skin and soft tissue (15%)
- Lymph node disease (5%)
- Disseminated (5%)
- Hypersensitivity Pneumonitis (0%)

Bug-Setting Associations

- Corneal Disease
  - M. chelonae
- Healthcare/Hygiene
  - M. chelonae
  - M. fortuitum
  - M. abscessus
- HIV setting
  - MAC, M. kansasi
  - M. genavense
  - M. haemophilum
- Tropical Setting
  - M. ulcerans (Buruli Ulcer)

Pearls Based on Species

- M. gordonae
  - Contaminant
- NTM are not communicable
  - EXCEPT M. massilense in CF
- M. immunogenicum, M. simiae
  - Pseudo-outbreaks
- M. szulgai, M. kansasi, M. marinum
  - Cross-react with IGRAs
- M. fortuitum lung disease
  - Aspiration
- M. marinum
  - Fish and fish tanks

A 72 y/o female with chronic cough, normal CXR and 1/3 sputum cultures grow MAC. Which of the following do you recommend?

- A. CT chest and additional sputum AFB cultures
- B. Empiric Therapy with Azithromycin, Ethambutol and Rifampin
- C. Additional sputum AFB cultures
- D. Wait for in vitro susceptibility data and then treat
Pulmonary NTM
2007 ATS/IDSA Diagnostic Criteria

- Patient has both radiologic evidence of disease and pulmonary symptoms
- At least 2 sputum cultures positive
  - OR:
  - One BAL or Tissue specimen with positive culture
  - OR:
  - Tissue with granulomatous histopathology in conjunction with positive culture (BAL or sputum)

Risk Factors
Associations reported for PNTM

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
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</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>44.187</td>
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<tr>
<td>Low body weight</td>
<td>9.0</td>
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<tr>
<td>Thoracic skeletal abnormalities</td>
<td>5.4</td>
</tr>
<tr>
<td>GE Reflux</td>
<td>5.3</td>
</tr>
<tr>
<td>COPD</td>
<td>2.10</td>
</tr>
<tr>
<td>Lung CA</td>
<td>3.4</td>
</tr>
<tr>
<td>Immunomodulatory Rx</td>
<td>2- infinite</td>
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<tr>
<td>Heritable genetic risk</td>
<td>?</td>
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</table>

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soil Exposure</td>
<td>5.9</td>
</tr>
<tr>
<td>Indoor Swimming Pool use</td>
<td>5.9</td>
</tr>
<tr>
<td>Proportion of environment on surface water</td>
<td>4.6</td>
</tr>
<tr>
<td>Mean daily potential evapotranspiration</td>
<td>4.0</td>
</tr>
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Pulmonary NTM Risk Factors

- Underlying lung architectural abnormalities
  - Bronchiectasis, CF, α-1, emphysema
  - Prior TB, GERD/Aspiration
- Exposure / transmission
  - Gardening/soil, Hot tubs
- Immunosuppressives
  - Prednisone, inhaled steroids, biologics

What are Tree in Bud Opacities?
The Dreaded Tree in Bud

- Original description endobronchial spread of TB
- Differential diagnosis: Not Just Mycobacteria
- Pathogenesis: Inflammatory obstruction of small airways, bronchiolitis
- Associations:
  - Infections: Viruses, Mycoplasma, Mycobacteria, Fungi
  - Aspiration
  - Neoplasia: Lymphoma, Lymphangitic Spread
  - Inflammation: Respiratory bronchiolitis interstitial lung disease (RBILD)
  - Idiopathic

PNTM are common in patients with bronchiectasis

- 2-10% of British patients with bronchiectasis grew NTM

Bronchiectasis vs. NTM

- 3-25% of CF patients grow NTM at some time, with 30-50% meeting ATS criteria for diagnosis

NTM Pulmonary Disease

- Diagnosis ≠ Decision to treat!
  - Observation vs. Suppression vs. Cure

Pulmonary NTM

- MAC is most common etiology (60-90%)
- M. kansasii and M. abscessus
  - M. kansasii primarily in the south
  - Recent M. abscessus increase in CF
- Other organisms of importance
  - M. xenopi (Northern US/Canada, Europe)
  - M. malmoense (Europe)

MAC Pulmonary Diseases—Two Types

- Older male, smoker, COPD
  - Atypical cavitary or fibronodular disease
  - More rapidly progressive
- Older Female ("Lady-Windermere")
  - Scoliosis, thin, pectus deformities, hypomastia
  - Nodular and interstitial nodular infiltrate
  - Bronchiectasis right middle lobe / lingula
  - Bronchiolitis ("tree and bud") on HRCT
  - Slowly progressive

MAC Cavitary Lesion (Rapidly Progressive)

"Lady Windermere"

Decision to treat Pulmonary MAC
Questions that every clinician should think

1. Colonization vs Infection?
2. Is infection causing significant pulmonary disease (clinical, imaging)?
3. How rapidly is that clinical or radiographic form of disease likely to progress without immediate treatment?
   - Underdiagnosis
   - Overdiagnosis
Decision to Treat Pulmonary MAC

- Early Treatment
  - Rapid progression clinically or radiographically any cavitation
  - Profoundly immunocompromised (AIDS, BMT, SOT, TNF inhibitor) to prevent dissemination
- Observation
  - Lack of above
  - Elderly with severe chronic illnesses
  - Alternate explanations for some symptoms
  - Responds to therapy for reflux / aspiration

REMEMBER ROLE OF BIOPSY

MAC Therapy - Options

- Treatment best defined for MAC
  - Start Macrolide, Rifampin, Ethambutol
  - Amikacin first 1-2 months for Cavitary disease
  - Duration 18-24 months (12 months culture negative)
  - Macrolide monotherapy contraindicated
  - Recommend to test susceptibility for macrolide
  - Three times a week therapy (TIW) okay if noncavitary disease or not re-infection

Clinical Relapse

"Repeat positive cultures in Mycobacterium Intracellulare Lung Disease after Macrolide therapy represent new infections in patients with nodular bronchiectasis"

Wallace, RJ et al, JID 2002

- After completion of therapy
  - 23 relapses
  - 17/20 (85%) were new strain

Bathrooms and MAC Reinfection?

In one study:

- Polyclonal MAC colonized bathtub inlets and / or shower heads in 52% of bathrooms of patients with PMAC
- 47% of these had strain with an identical PFGE pattern as the clinical isolate
- Some bathtubs and shower types and maintenance programs are associated with lower risk of colonization
- Aerosolization and inhalation more likely from shower head
- Hypersensitivity pneumonitis related to a MAC culture- Positive home shower reported

BMJ Case Reports 2011- Hankwitz, PE, et al.
Prevention of Infection or Reinfection

- Avoid pools, warm water lakes or thermals and hot tubs?
- Prefer bath or showers?
- Modify environments in bathtubs and showers and bathrooms?

Patient M.K.

- 65 y/o American born, ETOH use disorder, smoker
- 3 months of progressive cough, sputum production with blood streaking, low grade fevers and weight loss
- Exam: Normal temp, mild tachypnea, lungs clear
- HIV negative

Patient M.K.

2 sputum smears 2+ AFB, cultures pending, Direct probe on one sputum negative for Mycobacterium Tuberculosis, positive for?

- A. M. genavense
- B. M. chelonae
- C. M. Kansasii
- D. Lead poisoning

M. kansasii
Pulmonary M. kansasii- Therapy

- M. kansasii clinically more like TB
  - Thin-walled cavities, upper lobes
  - Treat with INH, Rifampin (RIF), Ethambutol (EMB)
  - TIW therapy okay
  - Duration: 12 months culture negativity
  - High treatment success rates! (90% +)
  - RIF is the key drug

Patient with RGM Infection

Which statement is true?

A. Agent(s) should be selected based on in vitro susceptibility testing
B. While they may test macrolide susceptibility, many contain an inducible erm gene which renders macrolide ineffective
C. Rapid identification from positive cultures can be done using MALDI-TOF is reported
D. All of the above

M. abscessus Pulmonary Infection

- Up to 80% of pulmonary disease from RGM
- Risk factors: CF, other bronchiectasis, prior mycobacterial infection, GE dismotility disorders
- 5-15% will have MAC or other NTM isolated from sputum concurrently
- Prognosis depends on subspecies, host factors and type/extent of infection
- Treatment has improved, but only curative treatment includes surgery

M. abscessus

3 Subspecies:

- M. abscessus subspecies abscessus
  - Chronic, incurable for most patients given the limited antimicrobial options
- M. abscessus subspecies massiliense
  - Better prognosis given absence of functional erm gene
- M. abscessus subspecies boletti
  - Erm gene may be nonfunctional
**M. abscessus Pulmonary Disease Treatment**

Updated Guidelines:
- Treat underlying conditions
- Evaluate for surgery
- Periodic administration of multidrug therapy, including a macrolide (if active) and one or more parenteral agents (amikacin, cefoxitin, or imipenem) or a combination of parenteral agents over several months may help control symptoms and progression.

**Pulmonary M. abscessus - Therapy**
- M. boletti, M. massiliense, M. abscessus
- Inducible macrolide resistance- erm (41) gene
- “Cure” is RARE
- More rapidly progressive than MAC
- 3-4 drugs for 18-24 months
- 4-6 month induction phase
- “Suppressive strategy” thereafter

**Mycobacterium abscessus Therapy**
- Parenteral agents
  - Tigecycline 50 mg Daily
  - Cefoxitin 2 gm TID
  - Imipenem 1 gm BiD
  - Amikacin 10 mg/kg TIW
- Oral agents
  - Clofazimine 50-100 mg Daily
  - Linezolid 600 mg Daily
  - Moxifloxacin 400 mg Daily (rarely susceptible)
- Surgical Resection

**Newer Treatment Paradigms**
- “Induction Therapy”, adding Linezolid once/day and Tigecycline to beta-lactam and Amikacin +/- Azithromycin
- Staggered start and aggressive management of side effects
- May need to rotate drugs based on tolerance & toxicity, always maintaining ≥ 3 active drugs
- Clofazimine often added or rotated
- No role for suppressive therapy. Once patient is intolerant to a combination, stop therapy and observe and retreat if needed
- Treatment requires clinical expertise
Potential Drugs
- IV Tigecycline
  - Salvage or initial therapy?
- Clofazimine
  - Salvage or initial therapy?
- Bedaquiline
- Inhaled Amikacin (liposomal)

Monitoring Therapy
Clinical, Laboratory, Microbiologic & Radiographic monitoring may include:
- **Efficacy**
  - Visits weeks 2, 4, 8 and then as needed: symptoms, exam including weight
  - If improvement in first days of therapy, may be bronchiectasis and not NTM
  - Sputum x 3 at baseline, then q 4-6 weeks
  - PFTs at baseline and then q 6-12 mths.
- **Toxicity**
  - Safety labs (renal, hepatic, CBC) at baseline, 2, 4, and 8 weeks; then as needed
  - Ethambutol: Ophthalmology baseline eval then 3 mos. (Ishihara plates at every visit)
  - Quinolone: QTc at baseline then 2-4 weeks
  - Audiogram if parenteral agent: baseline and q 3-4 weeks

Adjunctive Therapy in PNTM: Identify and Treat Concurrent Issues
- Role of GERD and aspiration
  - Mechanical, dietary and anti-acid therapies
- Treatment of bronchiectasis
  - Bronchial hygiene (improve airway clearance)
    - Aerobic exercise, devices (flutter or acapella or vests), nebulized hypertonic saline
    - Chest PT
- Identify and treat bronchiectasis flares, bronchitis, COPD or pneumonia (with drugs WITHOUT MAC activity, if possible)
- Appropriate vaccines and personal infection control measures

Guidelines for NTM Lung Disease
- **Pros:**
  - Consensus by experts reviewing “best available data”
- **Cons:**
  - No randomized trials
  - Not validated
  - Based on most common NTMs (MAC)
  - No natural history criteria (studies lack long term follow up, which is key in this infection)
  - CLINICAL JUDGEMENT IS PARAMOUNT!
NTM Conclusions: 1
- More pulmonary infections with NTM in the US than MTB
  - Incidence raising worldwide
- NTM may colonize or cause a spectrum of lung disease, most commonly fibronodular bronchiectasis in middle aged women
  - Pulmonary disease chronic or relapsing
- No validated guidelines for the diagnosis of NTM, use IDSA/ATS guidelines and clinical judgement
  - Guidelines are biased towards MAC and particular forms of infection
- Remember to diagnose and treat co-existing conditions, observe natural history and obtain tissue biopsy if picture is unclear

NTM Conclusions: 2
- NTM are important causes of extrapulmonary disease
  - High index of suspicion is key
    - Include AFB stains/cultures in your evaluation in appropriate settings
    - Alert micro to include cultures and potentially freeze tissue for 16 S RNA PCR
- Treatment for NTM is less effective and more toxic than TB
  - Remember adjunctive therapies, including surgery
  - Manage expectations: disease may relapse or infection recur

NTM Conclusions: 3
- RGM are increasingly important causes of PNTM infection
  - Treatment is more toxic and less effective, though newer drugs are helping
- Many unanswered questions in NTM infection, including whether we can do more to prevent it

Pulmonary NTM Adults
- Female predominance
- Caucasian predominance
- Post-menopausal
- "Lady Windermere Syndrome"
  - Tall, thin, pectus abnormalities
- Association with CFTR mutations
- Complex immunologic and somatic genetics

American Journal of Respiratory and Critical Care Medicine 2015
Remember...

Disseminated NTM means immunodeficiency

..Isolated Pulmonary NTM DOES NOT