What is So Atypical About the Atypicals (Mycobacteria)?
Or
When is a “Community Acquired Pneumonia (CAP)” not CAP?

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“TB or Not TB” (“What’s in a name? That which we call a Rose…”)
• Atypical Mycobacteria-used to emphasize the fact that they were mycobacteria but term did not acknowledge features of typical mycobacteria tuberculosis
• Mycobacteria other than tuberculosis (MOTT)-
• Environmental Opportunistic mycobacteria-emphasize recovered from natural and human-influenced environments and can infect and cause disease in humans, animals and birds
• Nontuberculous mycobacteria (NTM)-this term currently has broad support

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NTM Epidemiology in US
• NTM disease is not a reportable disease in the US
  – ?? the incidence and prevalence
• Two national surveys in early 1980’s
  – a survey of State Labs : 1/3 of 32,000 mycobacterial isolates were NTM
  – a survey of TB Programs : estimated prevalence of pulmonary NTM disease to be 1.8 per 100,000 population
  – Southeast US had a higher prevalence of disease (56% of army recruits from Southeast US skin tested positive for MAC compared to 15-25% from other areas of US)

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NTM Epidemiology
• 1993, CDC survey of State Labs :
  – TB accounting for only 26% of cultures, with the rest being NTM-mainly MAC
  – ?? to HIV or better culture techniques

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FL AHCA Data 1999-2000
Patients Discharge Diagnoses (Dx)

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<tr>
<th></th>
<th>1st Dx</th>
<th>2nd Dx</th>
<th>Total</th>
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<tr>
<td>TB</td>
<td>38</td>
<td>16</td>
<td>2144</td>
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<tr>
<td>MAC</td>
<td>310</td>
<td>729</td>
<td>?</td>
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LAB Results

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<tr>
<th>Specimens</th>
<th>MTB</th>
<th>NTM</th>
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<tbody>
<tr>
<td>Sent to State Lab Directly</td>
<td>2891</td>
<td>4329</td>
</tr>
<tr>
<td>Sent to State Lab from Community Hospitals</td>
<td>364</td>
<td>2848</td>
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</table>
US Epidemiology
- 2 more recent studies utilizing large healthcare databases revealed:
  - In the Integrated Healthcare Delivery System in S Calif, Seattle, Denver and Pennsylvania the incidence of Lung Dx due to NTM was 5.5/100,000 and seems to be increasing.
  - In Oregon using a population based surveillance study 5.6/100,000
- 86% of pts who met microbiologic criteria for dx also met ATS criteria
- ~50% of patients who had respiratory cultures positive for non M. gordonae NTM had disease

NTM among Medicare Recipients
- 65% of cases were female
- Over case rate 110/100,000 population
- Asian/Pacific Islanders 2 fold increased risk compared to whites
- One third of all cases were in the Southeast US with case rate of 131/100,000
- Case rates were increasing 8.2%/yr from 1997-2007
- Pulmonary NTM pts were 40% more likely to die over this period

NTM Epidemiology
- Seems to be associated with atmospheric high water vapor pressures (humidity)
- Associated with warmer climate
- Florida patients most likely to have M. abscessus

Classification (Partial List)
Over 140 different mycobacterial species
Slow Growing Mycobacteria
- Mycobacterium avium
- Mycobacterium intracellulare
- Mycobacterium kansasi
- Mycobacterium genavense
- Mycobacterium tuberculosis
- Mycobacterium bovis
- Mycobacterium marinum
- Mycobacterium scrofulaceum
- Mycobacterium fortuitum
- Mycobacterium ulcerans
- Mycobacterium abscessus

Rapid Growing Mycobacterium
- Mycobacterium fortuitum
- Mycobacterium chelonae

Epidemiology Among Medicare Recipients

Cluster Epidemiology Among Medicare Recipients
Runyon Classification

- Group I-Photochromogens (slow growers, yellow pigment on exposure to light but not in dark-M. tuberculosis, M. kansasii or M. marinum)
- Group II-scotochromogens (slow growers, produce pigment in light and dark-M. scrofulaceum, M. gordonae, M. szulgai)
- Group III-nonphotochromogens (extremely slow growers, non-pigmented-MAC, M. xenopi, M. terrae)
- Group IV-rapid growers (grow < 7 days, smooth colonies, +/- pigments-M. fortuitum, M. abscessus, M. chelonae)

Habitats for NTM

- NTM are extremely robust organisms
- Water-highest number found in acid brown-water swamps of southeastern coastal US. Changes in water sources have occurred and while M. scrofulaceum used to be commonly found in water, it no longer is coinciding with decrease of disease from this organism
- Drinking Water-MAC and M. kansasii recovered (but not from bottled water c/w NTM not in ground water)
- When present in water or soil samples they are not contaminants but capable of persistence through growth

Transmission

- Unlike TB, no evidence of person-to-person spread
- ? Exactly how individuals become exposed to organisms
- Not evidence for infection stage

Proposed Pathways of Infection for Patients with Pulmonary NTM

- Ingestion of water or exposure to mycobacterial-laden aerosols

“Are Showers the culprit?”

- Increased number of individuals have switched from baths to showers with increased aerosolized water, made worse by shower enclosures which retain and concentrate aerosols
- Lowering of water temperature for energy conservation-MAC lives in 45°C temp (>130°F kills NTM)
- Chlorination of water selected for MAC
- Switch to PVC indoor plumbing-increased biofilms

? Pathogenesis

One Theory

A G Holley Hospital and The Florida Bureau of TB Control and Refugee Health
Habitats for NTM Biofilms

- Mycobacteria readily form biofilms and because of their hydrophobicity and metal-resistance may have been the “pioneers” of biofilms

Habitats for NTM Biofilms

- May be an important source of NTM and perhaps basis for their persistence in drinking water systems.
- MAC has been isolated from biofilms of drinking water distribution systems. The number of MAC in biofilms can be as high as 10,000-100,000 cfu.
- Disinfection will reduce NTM numbers but considering the hundreds of miles of pipes it may be considerable.
- This is consistent with the findings that even water systems that use ground water still have mycobacteria.
- Cases of NTM have been linked to water ingested as well as from biofilms of indwelling catheters

Association Conditions with Pulmonary NTM

| Associated Risk Factors in Patients with Bronchiectasis (BRX) with or without NTM |
|----------------------------------|------------------|
| GERD                             | 37%              |
| Swallowing Disorders             | 80%              |
| CF gene Mutation                 | 12%              |
| Abnormal AAT phenotype           | 23% (most common)|
| Abnormal MS phenotype            | 4.5%             |

BRX + NTM (36 pts)  BRX (33 pts)

- Variable and nonspecific
  - Chronic cough
  - Sputum production
  - Fatigue
  - Less commonly malaise, dyspnea, fever, hemoptysis, weight loss
- Evaluation often complicated by symptoms of underlying lung disease

Risk Factors for Developing Pulmonary NTM Disease

- Malignancy
- Immunosuppression
- HIV infection
- Transplantation
- ? Alcohol abuse
- ? Smoking
- Male Sex
- Increasing Age
- No Risk Factors (Elderly, slight woman???)

Criteria used to establish diagnosis of pulmonary disease caused by NTM (ATS Guidelines 2007)

Clinical.
1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules.

and
2. Appropriate exclusion of other diagnoses.
Criteria for diagnosis of pulmonary NTM

Microbiologic.
1. Positive culture results from at least two separate expectorated sputum samples. (If the results from the initial sputum samples are nondiagnostic, consider repeat sputum AFB smears and cultures.) or
2. Positive culture results from at least one bronchial wash or lavage. or
3. Trambronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and 1 or more sputum or bronchial washings that are culture (+) for NTM.
4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination.
5. Patients who are suspected of having NTM lung disease but who do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded.
6. Making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients.

Pulmonary Disease Associated with MAC

- Includes both M. avium and M. intracellulare
- The most commonly isolated group of mycobacteria in most labs
- The most common NTM responsible for Pulmonary Disease
- An increasingly important respiratory pathogen in “immunocompetent” patients

Pulmonary Disease Associated with MAC

1) Upper lobe disease that radiographically resembles TB (“Classic MAC”)
   - usually older white males, smoking history with COPD
   - Most Common

2) MAC which develops as a complication of bronchiectasis
   - common in pts with history of TB
   - presents with recurrence of symptoms and worsening infiltrate on radiographs areas of previous disease
   - tend to be older individuals but no sex or smoking relation
Pulmonary Disease Associated with MAC (con’t)
3) Disease in individuals with no prior history of Lung Disease
- Predominantly Caucasian Women, in 6th decade of life
- Non-smokers
- Have interstitial rather than cavitary radiographic changes, usually confined to the lingula and middle lobes (“Lady Windermere Syndrome”)
- Studies suggest that the development of bronchiectasis in these patients is due to pathologic disease caused by MAC
  - *not “colonization”*
  - *some may progress to respiratory failure*

“Lady Windermere Syndrome”
- Based on the main characters fastidious nature to voluntarily suppress her cough
- Original cases included patients who suppressed their coughs and may be unable to clear airway secretions

Nodular Bronchiectasis MAC Lung Clinical Features

PATIENTS

- 50% / cases
- 80% of patients are women
- 95% of patients are Caucasian
- 60% are lifelong non-smokers, no alcohol
- mean age is 70 years
- most have no serious underlying disease

Thoracic Cage Abnormalities
70% of patients with MAC had either scoliosis or narrowing of A/P diameter (<10.2 cm for males and <9.2 cm for females from anterior vertebral body to sternum. Also more common to have pectus excavatum and mitral prolapse. (Iseman et. al ARRD 1991;914-6)
High Resolution CT (HRCT) Appearance of NTM

- HRCT has shown >90% of patients with mid and lower lung field noncavitary disease with MAC have associated multifocal bronchiectasis, with many patients having clusters of small (<5mm) nodules in associated areas of the lung ("Tree in Bud"-centrolobular nodules).
- The combination of bronchiectasis and nodules have been shown to have an overall sensitivity of 80% and specificity of 87% in patients with MAC.

Treatment of MAC

- Routine susceptibility testing for macrolides recommended.
- Natural history of the disease not clear inferential data suggests benefit for those with cavitary (classic) disease. Less known about bronchiectatic form and response to therapy.
- Macrolides have improved the chances of successful Rx (>85% cured but ~40% will develop reinfection\(^1\)).
- Usually macrolide (e.g. clarithromycin or azithromycin) with rifampicin and ethambutol (+/- amikacin) for at least 1 year (usually 18-24 months) after culture conversion can give TW-less side effects and better tolerated\(^1\) but not cavitary or severe disease.
- Period of observation in asymptomatic or minimal symptoms is often appropriate but must closely follow.

\(^1\)Wallace et al CHEST 2014; 146(2):276-282.
MAC Treatment Approach

- First need to decide if MAC is responsible for disease
- Then need to decide if need to treat (given side effects esp in elderly) and if so give a trial of therapy
- Adjust dose to age and weight and try to minimize number of doses and pick drugs which decrease interactions
- Monitor for side effects
- Assure no other conditions causing symptoms and address these (e.g. GERD, malignancy)
- Consider adjunctive medications (eg nausea) and modalities (flutter valve, secondary superinfections)
- Due to drug adverse effects, some cases use intermittent therapy to suppress disease rather than cure

CYSTIC FIBROSIS AND NTM INFECTION

(Adjemian et al. AJRCCM 9/14)

- Cystic Fibrosis Foundation registry has helped define the scope of the disease since 2010
- (+) cultures for NTM common in CF patients (~10-26% of pts>12 yo, >20% in FL)
- NTM recognized as a cause of clinical decline and morbidity in patients with CF esp. M. abscessus
- Difficult to diagnose using ATS criteria given lung abnormalities
- Role of chronic macrolide suppression for pseudomonas unclear on NTM

“Hot Tub Lung”

- Rare, subacute presentation of young pts with subacute presentation of SOB and dry cough
- Diffuse infiltrates with ground glass appearance on CT
- 96% grew MAC, with non necrotizing granulomas (but not discrete or compact) found c/w hypersensitivity pneumonitis
- Disease vs hypersensitivity pneumonitis
- Most respond to corticosteroids with or without MAC Rx after discontinuation of hot tub use

Hypersensitivity Pneumonitis

M. Kansaii

- Second most common lung disease caused by NTM
- Spread by aerosol route with tap water probably most likely source
- Occurs in geographic clusters-“inverted T” distribution in US (Southern states of Texas, Louisiana, Florida, and central states of Illinois, Kansas and Nebraska)-more likely in urban vs rural (tap water)

M. Kansaii

- Resembles TB in symptoms and radiographs
M. Kansasi

A.G Holley Hospital and The Florida Bureau of TB Control and Tuberculosis Health

M. Kansasi

- Most M. Kansasi respiratory isolates are clinically significant (though may occur in asymptomatic pts with normal CXRs but must follow these closely for progression).
- Probably easiest NTM to treat due to similarity to TB and effectiveness of TB meds-rifampin most effective then ethambutol. Relatively less sensitive to INH compared to TB but still felt to be effective. Resistant to PZA.
- I/R/E for 18 months-can treat TIW
- Must monitor with serial sputums to assure culture negative

Rapid Growing Mycobacteria (RGM)

- M. abscessus and M. fortuitum most likely to cause pulmonary disease
- M. abscessus third most common NTM cause of pulmonary disease
- Aspiration of gastric contents is the most important potentially reversible underlying condition predisposing patients to RGM
- Also seen in CF patients
- Most patients with lung disease caused by RGM are white, female non smokers, at least 60 years of age
- Insidious onset of symptoms

Rapid Growing Mycobacteria (RGM)

- Radiographs similar to MAC pts
- Susceptibility testing should be done on all clinically significant RGM patients who fail therapy or relapse-test for amikacin, cefoxitin, cipro, clarithro, doxycycline, imipenim and sulfamethoxazole
- Usually resistant to all first line TB meds
- M. abscessus is usually resistant to oral meds and 20% die, most cured with addition of surgery. ATS recommend Clari/cefoxitin (12g/day)/Amik-usually does not cure. Patients with M. fortuitum may do better with meds alone
- Inducible erm gene confers macrolide resistance (M. massiliense macrolide susceptible)-need to test in presence of Macrolide
- Tigecycline may be effective >60% but 90% adverse effects (N/V)
- Since RGM disease usually progresses slowly may want to observe especially in elderly

When is a “Community Acquired Pneumonia (CAP)” not CAP?

- Chronic Cough with systemic features or recurrent pneumonia that has not resolved with “traditional” therapy especially if:
- Atypical Radiologic Findings (e.g. increased interstitial markings and nodules)
- History of Bronchiectasis
- Patients on Chronic Antibiotic Therapy
- Middle age Caucasian females without other clear etiology elucidated

When is a “Community Acquired Pneumonia (CAP)” not CAP? What to do?

- Consider the possibility of NTM and collect sputum for AFB and send to Lab (Preferably one that has experience with isolation and identification of NTM)
- If considering NTM, try to avoid macrolide of quinolone monotherapy
Summary

- NTM are common environmental organisms
- Infection and disease due to NTM is increasing
- Disease is seen in individuals with impaired systemic and local pulmonary immunity
- Diagnosis and treatment is challenging
- NTM will likely account for increasing amounts of human morbidity and mortality

TB Hotline
1-800-4TB-INFO