TB Intensive
San Antonio, Texas
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Nontuberculous Mycobacterial
Lung Disease
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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
Nontuberculous Mycobacterial Lung Disease

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NTM Incidence and Prevalence

- Why it is difficult to know the exact incidence and prevalence of NTM disease
  - Not all NTM isolates are pathogenic, some isolates represent specimen contamination
    - *M. gordonae*
    - NTM in tap water (*M. kansasii, M. simiae, M. abscessus, M. xenopi*)
  - Even pathogenic NTM are not always associated with progressive disease

NOT ALL NTM ISOLATED ARE CLINICALLY SIGNIFICANT
NTM Disease Prevalence
Winthrop et al

- NTM pulmonary disease more common than TB
- MAC the predominant isolate (RGM 2nd)
- The prevalence of NTM pulmonary disease rose with age and in females
- A positive respiratory culture for a non- *M. gordonae* NTM signified NTM pulmonary disease in approximately 50% of patients
- NTM epidemiology possible in “small” populations with closed laboratory systems
- Isolation prevalence a fair predictor

Evidence for environmental transmission of NTM to humans

- “Opportunistic pathogens enriched in showerhead biofilms” Feazel et al. PNAS 2009, 106; 16393. MAC genetic sequences found in 20% of 45 showerheads from 9 cities
Nontuberculous Mycobacterial infections and antitumor necrosis factor therapy
Winthrop et al, 2009: 15: 1556

- Data from U.S. FDA Med-watch database
- 105 reports met NTM disease criteria
  - 65% female, X age = 62, majority with RA
- All available TNF-α blockers implicated
- MAC most common NTM implicated
  - 44% extrapulmonary disease, 9% died time of reporting
- TNF-α blockers are clearly an important predisposing factor for serious, sometimes fatal, NTM infection.

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
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)
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.

**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

ATS Diagnostic Guidelines for NTM Lung Disease

- More than 160 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 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

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<th>Under diagnosis</th>
<th>Over diagnosis</th>
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<td>Untreated disease</td>
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Usually enough time for a careful assessment of patients with bronchiectasis and possible NTM disease
Diagnosis of NTM Lung Disease: Microbiologic Criteria

• A single positive culture from any source (sputum or bronchoscopy) 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*

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.
NTM Diagnostic Guidelines

- Current diagnostic guidelines are inadequate, but will continue to evolve
- Diagnostic evaluation influenced by:
  - The virulence of the isolated NTM: *M. kansasii*, *M. gordonae*
  - The host (immune suppression, airway abnormalities, body morphotype): MAC, *M. mucogenicum*, *M. abscessus*
  - The clinical source (setting) of the organism: blood, soft tissue, sputum
- It is imperative that clinicians evaluating patients with NTM lung disease are familiar with characteristics of individual NTM species.

Factors Influencing the Decision to Treat NTM Lung Disease

- **MAKING THE DIAGNOSIS OF NTM LUNG DISEASE DOES NOT, PER SE, NECESSITATE THE INSTITUTION OF THERAPY.**
- The decision to initiate treatment for patients with NTM lung disease is ultimately a decision based on risk/benefit analysis taking into account patient symptoms, radiographic findings (progression) and microbiologic results vs. the adverse effects of multiple potentially toxic and relatively weak drugs.
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**Patient Name:**
**DOB:** 07/28/1955
**Sex:** F
**County:** TX
**Address:** 12345

**Contributor:**
**Name:** GRIFITHS, DAVID MD

**Reported by:**
**Date:** 04/13/06
Mycobacterium avium complex (MAC) Lung Disease

AKA Mycobacterium avium-intracellulare (MAI) disease
State of the Art: Nontuberculous Mycobacteria and Associated Diseases (Wolinsky, ARRD 1979;119: 107)

- “Chronic pulmonary disease resembling TB represents the most important clinical problem associated with NTM…”
- “The average case of *M. kansasii* or MAI disease would be a 48-year-old man with long-standing lung disease...with a 3-month history of increasingly productive cough, night sweats, a low-grade fever, and moderate weight loss.”
- “The chest roentgenogram shows fibrosis and a thin-walled cavity in the right upper lobe.”
**M. avium Complex (MAC) Lung Disease**

Clinical presentations:
- Fibronodular cavitary or "tuberculosis" type
  - <50% cases
  - Heavy smoker, male predominance, alcoholism, onset <60 years age
  - Diagnosed initially as TB suspects

**MAC Lung Disease with Nodules and Bronchiectasis: Clinical Features**
- > 50% of 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
Nodular/Bronchiectasis MAC Lung Disease: Radiographic Features

- Predominantly involve RML and lingula
- Cavities are unusual (typically in mid lung)
- On CT or HRCT have:
  a) Cylindrical bronchiectasis and/or
  b) Small nodules ≤5mm usually in the same lung segments
  c) Rarely neither
- Radiographic progression is usually slow (years)
Nontuberculous Mycobacterial Diseases: Pulmonary Disease

- **Usual clinical presentation:** chronic cough (“recurrent pneumonia”), debilitating fatigue, weight loss, fever, hemoptysis
- **Variable disease progression:** frequent bronchiectasis-related symptoms
- **Prevalence:** ?1/3-500 women over age 65
  - ? Most common cause of cough and abnormal chest radiograph in this population

Pathogenesis of NTM Lung Disease
Kim et al. AJRCCM 2008, 178; 1066

- Characteristic morphotype (body habitus) in 63 patients with NTM lung disease evaluated at the NIH:
  - BMI significantly lower and height significantly greater than matched controls
  - High rates of scoliosis (51%), pectus excavatum (11%) and mitral valve prolapse (9%), CFTR mutations (36%)
  - No recognized immune defects (cell mediated dysfunction or cytokine pathway abnormalities)

Pathophysiologic consequences of this constellation of findings currently unknown. Does not explain disease in majority of patients
Pathogenesis of NTM Lung Disease

- Bronchiectasis and pulmonary NTM infection inextricably linked
- 20% of cystic fibrosis patients and 15% of primary ciliary dyskinesia patients have NTM recovered from respiratory specimens
  - difficult to determine clinical significance, effect on prognosis, MAC vs *M. abscessus*
- Strongly suggests, at least for some patients, a predisposing alteration in airway surface defenses
Therapy of MAC Lung Disease
New 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

*Not indicated for severe and/or cavitary disease
Treatment of NTM Lung Disease

• Controversies in the treatment of patients with NTM lung disease
  – Role of in vitro susceptibility testing
  – Consequences of ineffective therapy:
    Diminishing treatment response with successive treatment efforts
  – Disease Relapse vs Reinfection
Increasing numbers of patients receiving therapy for NTM (MAC) lung disease magnify these controversies

In Vitro Susceptibility Testing
**M. tuberculosis**
The “ideal” for mycobacterial response to therapy

- **INH and Rifampin**
  - Highly active bacteriocidal drugs
  - Achievable blood levels 10-100X MIC’s of susceptible organisms
  - Penetrate all tissues
  - Clear association between MIC and resistance

- **EMB and PZA:** not all TB drugs are created equal

**PULMONARY DISEASE CAUSED BY MAC IN HIV-NEGATIVE PATIENTS: FIVE-YEAR FOLLOW-UP OF PATIENTS RECEIVING STANDARDISED TREATMENT**
(BTS Int J Tuberc Lung Dis 2002; 6: 628)

- 75 patients with MAC lung disease
- 40 (53%) M, 46 (61%) cavitation
- 37 RE vs 38 REH for 24 mos
PULMONARY DISEASE CAUSED BY MAC IN HIV-NEGATIVE PATIENTS: FIVE-YEAR FOLLOW-UP OF PATIENTS RECEIVING STANDARDISED TREATMENT
(BTS Int J Tuberc Lung Dis 2002; 6: 628)

- 23 (31%) patients alive and cured
- 21 (28%) treatment failures/relapses
- MAC Susceptibility: 14%R, 32%E, 0%H

No correlation between in vitro resistance and treatment failure/relapse

MAC and In Vitro Susceptibility Testing (Kobashi et al. J Infect Chemother 2006, 12; 195)

- 52 patients with pulmonary MAC treated with Rmp, Emb, Clari, and Stm
- No relationship between clinical response and MICs for Rmp, Emb and Stm (similar findings BTS study IJTL 2002, 6; 628)
Macrolides for MAC Disease: Summary

• Treatment success correlates with in vitro MIC (susceptible < 8 μg/ml, intermediate 16 μg/ml, resistant > 32 μg/ml)
• Disease progression/relapse associated with MIC > 32 μg/ml
• There are no drugs, other than the macrolides for which there is a correlation between in vitro susceptibility (MIC) and in vivo response for disseminated or pulmonary MAC disease.

Macrolides for MAC Disease: Summary

• The designation of “susceptible” must be used with caution for all drugs other than macrolides in MAC disease.
• In vitro susceptibility tests for most drugs do not predict who will respond and who will fail therapy.
MAC In Vitro Susceptibility Testing: 2007 NTM Guidelines

- Clarithromycin susceptibility testing only is recommended for new MAC isolates
- Clarithromycin is the “class agent” for macrolide susceptibility testing
- No other drugs are recommended for susceptibility testing of new MAC isolates
- Clarithromycin susceptibility should be performed for MAC isolates from patients who fail macrolide therapy

Nontuberculous mycobacteria for which there is not an established correlation between in vitro susceptibility and in vivo response

- *M. malmoense*
- *M. scrofulaceum*
- *M. simiae*
- *M. xenopi*
- *M. abscessus*
- *M. immunogenum*
- *Etc.*
NTM for which there is an established correlation between in vitro susceptibility and in vivo response

- *M. kansasii*
- *M. marinum*
- *M. szulgai*
- *M. fortuitum* (except macrolides)

Consequences of Macrolide Resistance
Possible Risk Factors for the Development of Macrolide Resistance
(Griffith et al 2006 Am J Resp Crit Care Med)

• Macrolide Monotherapy: 28/51 (55%)
• Macrolide plus quinolone: 11/51 (22%)
• Combined, regimens without ethambutol: 39/51 (76%)
• Other risk factors: 12/51 (23%)
• No difference in macrolide resistance based on macrolide (azi or clari) or dosing interval (daily or intermittent)

Macrolide Resistant MAC Lung Disease: Response to Therapy

• Sputum conversion after macrolide resistance: 11/14 (77%) \( p=0.0001 \) in patients who had both injectable therapy and surgery.
• Sputum conversion after macrolide resistance 2/37 (5%) in patients without both injectable therapy and surgery.
• No difference in response between cavitary and nodular disease
Macrolide Resistant MAC Lung Disease: Response to Therapy

- 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%)
Significance of Multiple (+) Sputum Cultures After 10-12 Months (-) Cultures on Rx:

1. Occurs in the setting of nodular bronchiectasis
2. May be seen at any time during therapy or after stopping therapy
3. Approximately 90% will be new infections, and often involve multiple strains
4. Reinfection isolates usually macrolide susceptible
5. True clinical/microbiologic relapses are unusual

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.”
MAC: Hypersensitivity-Like Lung Disease

- Clinically, radiographically, histologically resembles hypersensitivity lung disease (subacute onset)
- Associated with standing water sources ("hot tub lung")
- Infectious, inflammatory, ?both
- Identical MAC genotypes recovered from water source, patient
- Inconsistent attention to manufacturers recommended specifications for hot tub maintenance procedures

MAC: Hypersensitivity-Like Lung Disease ("Hot tub lung")

(Hanak et al Respir Med 2006, 100; 610)

- Prognosis generally excellent: most patients recover spontaneously
- Most benefit gained by removing patient from antigen exposure
- Steroids may hasten symptomatic/physiologic recovery
- MAC antimicrobials of unclear benefit
M. kansasii

- Clinical presentation, in vitro susceptibilities and response to medications similar to M. tuberculosis
- Rifampin, INH, Ethambutol effective
- Multiple medications with activity against M. kansasii: clari, azi, moxi, sulfa, strep, etc.
- Expect treatment for cure
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 *erm* gene

• All isolates of *M. abscessus*, *M. fortuitum* (and several other RGM, but not *M. chelonae*) contain an inducible *erm* gene.

• Novel *erm* gene in *M. tuberculosis*.

• Bottom line for *M. abscessus* and *M. fortuitum*
  – Macrolides should not be used as monotherapy
  – No empiric macrolide therapy for *M. fortuitum*
  – “cryptic” resistance difficult (impossible) to detect in the laboratory
  – Macrolides should be used with caution with MIC >4mcg/L (for *M. fortuitum*)

• Kevin Nash USC, Richard Wallace and Barbara Elliott UTHSCT (JAC 2005, 55; 170 and AAC 2006, 50; 3476, AAC 2009, 53; 1367)
**Mycobacterium abscessus** LUNG DISEASE

1. Female, non-smokers, 60 years or older
2. Mid and lower lung field nodules/bronchiectasis
3. Lung disease resembles, non-cavitary Mycobacterium *avium* complex (MAC) lung disease
4. No consistently identified immune defect (unusual pathogen in AIDS)

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**Treatment of *M. abscessus* Lung Disease**

- Macrolide: value uncertain, no other oral agents of proven value
- Amikacin 10-15 mg/kg 3-5X/week
- Cefoxitin 8-12g/day in divided doses
- Imipenem 500 mg 2-4X/day
- Tigecycline 25-50 mg/day
- There is no predictably or reliably effective medical treatment strategy for *M. abscessus* lung disease
Healthcare Associated NTM Disease

- NTM transmission in the healthcare setting most frequently linked to exposure to tap (municipal) water (MAC, *M. kansasii*, *M. simiae*, *M. xenopi*, *M. fortuitum*, *M. abscessus*)
- Even with potent disinfectants, NTM organisms can persist on equipment or devices.
Healthcare Associated NTM Disease

- Infections and Pseudoinfections: median sternotomy, liposuction, LASIK, catheters (IV and peritoneal), prosthetic heart valves, prosthetic joints, ocular lenses, pedicures, etc.
- **Complete avoidance of tap water for specimen collection, instrument cleaning and wound cleaning is absolutely necessary!**