Nontuberculous Mycobacteria:
Ubiquitous Environmental Pathogens
for Predisposed Hosts

History, Epidemiology, Spectrum of Disease
Diagnosis, Treatment and Predictors of Treatment Outcome

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History of NTM Disease in the U.S.

- **1943** - Feldman et al. Amer Rev of Tuberculosis 48:82
- ‘50s - ’60s - Patients in TB sanitoria (1-2%) w/ poor resp. to Rx
- ‘70s - ‘80s - Increasing case reports
- ‘70s - ‘80s - Isolation from hospital water; Nosocomial cases
- ‘80s - ‘90s - AIDS - dissem. MAC recognized commonly
- ‘80s - ‘90s - NTM assoc. with CF (Frederic Chopin’s dis.?)
- ‘90s - present - NTM - females / others with lung disease
Nontuberculous Mycobacteria (NTM)

Pathogenic Mycobacteria

TB
M. tuberculosis

Nontuberculous Mycobacteria
(Runyon Classification)

Group I
(Photochromogens)
M. kansasii
M. marinum
M. simiae

Group II
(Scotochromogens)
M. xenopi
M. scrofulaceum
M. szulgai
M. celatum
M. gordonaec?

Group III
(Nonphotochromogens)
M. avium
M. intracellulare
M. malmoense
M. terrae
M. hemophilum

Group IV
(Rapid Growers)
M. abscessus
M. chelonae
M. fortuitum

> 60 species and growing

Most common
Less common
Contaminant

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Epidemiology
As the TB incidence fell, NTM disease “appeared” on the radar
Changing NTM Epidemiology

- **TB:**NTM ratio has changed:
  - 1900  >95:1  TB:NTM
  - 1980s  2:1  TB:NTM - ↓TB incidence, ↑DMAC/AIDS
  - 1990s  1:3  TB:NTM
  - 2000s  <1:20  Suburbia; mostly MAI and RGM; very little TB

- **The patient gender ratio has changed:**
  - 1950s  > 80% male – mostly smokers w/cavitary disease
  - now  >80% female – mostly nonsmokers w/ bronchiectasis

- **Geographic prevalence of NTM infections (MAI > RGM > variable species)**
  - M. kansasi M. Middle U.S., UK (England, Wales)
  - M. xenopii M. Canada, northern U.S., UK (southeastern England)
  - M. simiae M. Texas, New Mexico, Arizona, Cuba, Israel
  - M. malmoense M. UK (Scotland), northern Europe
  - M. ulcerans M. Tropics
Environmental Sources of NTM Infection

• Soil: ~ 80% of soil samples positive  ARRD 97:1032, ’68

• Water – Joe Falkinham at Virginia Tech  ARRD 128:652, ’83
  - Almost any water source: fresh, salt, domestic, hot tubs, swimming pools, hospital water supplies, CAPD, metal workers cooling fluids
  - NTM are chlorine-resistant: (NTM > fungi > viruses > E. coli) Zentralbl Bakt Microbiol Hyg [B] 171:6, ‘80

• Nosocomial sources
  - Rapid growers - most common pathogens
  - MAC, M. xenopi - hospital hot water supplies
  - M. gordonae - clinical laboratory contaminant
Numerous Opportunities for Infection with Environmental NTM

- Cosmetic facial surgery
- Ophthalmic trauma or surgery
- Augmentation mammoplasty
- Median sternotomy; valve heterografts
- Cardiac pacer or TENS unit pockets or wires
- Chronic ambulatory peritoneal dialysis
- Orthopedics: prosthetic joint placement; spine hardware
- Injection-associated abscesses
- Transmission by bronchoscopy
- Soil or water contaminated trauma ± residual foreign body
Spectrum of Presentation of Pulmonary NTM Disease
X-ray and CT Findings in NTM Pulmonary Disease

- Pre-existing lung abnormalities
- Nodular infiltrates in the context of bronchiectasis
- Patchy densities
- Cavitary lesions
- Bronchiolitis / hazy, irregular HSP-like changes
Most Common Presentation
Female nonsmokers with subtle bronchiectasis; MAI > M. abscessus disease

- 58 yo white female, never-smoker
- Persistent cough following URI
- Fatigue, scant hemoptysis
- Serial sputums:
  - AFB smear-negative
  - 2 of 5 cultures positive for MAI

“tree-in-bud”
How MAI disease might start
Localized infection in an area of pre-existing bronchiectasis
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Localized infection in an area of pre-existing bronchiectasis
Emphysema and Cavitary MAI disease

• 72 yo white male. >100 pk years cigarettes.
• Cough and fatigue. Sputums: AFB smear-positive.
• Initial diagnosis = TB. Cultures all positive for MAI.
• Disease progressed despite oral antibiotic therapy.
Infection of Other Pre-Existing, Structural Lung Abnormalities

- 16 y.o. black female with DOE
- No previous symps or Ch. X-ray
- Repeated AFB+ and MAI cult.+  

- 6 months after anti-MAI Rx and RUL ectomy
Mass-Like Presentation of NTM Disease — or Lung Cancer?

60-70 y.o. patients with remote smoking history

Male, 50 pk-yrs
Female, 60 pk-yrs
Male, 30 pk-yrs

Web image adenoCa

1 yr follow-up on anti-MAI therapy
4 mo follow-up CT Needle bx = adenoCa (stage IV)
MAI-induced Hypersensitivity Pneumonitis

Inhaled Bioaerosol

12 yo male with dyspnea and cyanosis with exertion
Bronchoscopy – AFB smear-negative, culture positive for MAI
Predisposing Conditions for NTM Pulmonary Disease

• Underlying lung disease – the great majority of NTM cases:
  – Bronchiectasis - past bronchitis/pneumonia, CF, old TB
  – COPD (upper lobe cavitary disease)
  – ILD/Idiopathic pulmonary fibrosis
  – Adult-onset cystic fibrosis
  – Chest radiotherapy/fibrosis (e.g., for breast Ca)
  – Congenital / acquired cystic lung abnormalities
  – Pulmonary infarction / scarring
  – Recurrent aspiration → basilar bronchiectasis
Diagnosis
The 3 Elements of Diagnosis of NTM Disease

• Symptoms:
  – Cough, fatigue, +/- hemoptysis, sweats, weight loss
  – “Hard to improve an asymptomatic patient.” Andy Deiss, MD

• Culture data:
  – Beware of the perils of Rx’ing a single positive culture!
  – Require multiple positive cultures

• Radiology / Chest Imaging data
  – Clusters of nodules; patchy/hazy consolidation; cavitation
  – Look at your patient’s X-rays / CTs -- don’t rely on reports!
Apply all 3 elements of diagnosis, **before** treating. (case example)

- 61 yr. old male; 50 pk-yr smoker
- Initial productive cough
- Bronch’d Jan 2013 → AFB-neg, but cult-pos for MAI; not Rx’d
- 6 mos later, **cough had resolved**
- Follow-up chest CT → “evidence of disease progression with cavitating lung nodules” (radiol. report)
- Based upon that report → started on Rifampin/Ethambutol/Azithromycin
- Developed fever, chills, joint and back aches and visual problems.
- Sent for consultation for Rx recs.
Be Sure of the Diagnosis
Before Launching Anti-NTM Therapy

MARY BESSESON, MD
FIRST DIAGNOSE
THEN TREAT

www.tombstonebuilder.com
Beware of a single positive AFB smear
Confirm with repeated studies, before proceeding with Rx
Remember Other Causes of Chronic Cavitary Lung Disease
Even when AFB smears are positive

- 4/5 sputums pos for MAI
  - Responded slowly to rifampin/ethambutol and clarithromycin therapy

- Only 1/5 sputums pos for MAI
  - Treated anyway → severe nausea and vomiting from multidrug anti-MAI therapy
  - VATS lung biopsy → positive for Histoplasma
  - Responded well to itraconazole therapy
Beware of a single positive culture for NTM

- 80 y.o. white female with progressive dyspnea.
- Minimal cough, no fever, sweats or hemoptysis
- Multiple sputums negative for routine bacteria and AFB
- BAL positive for few colonies of MAI

VATS biopsy:
Bronchoalveolar Ca
Treatment
“Begin with the end in mind”

- “If you don’t know where you’re going, then you probably won’t end up there.”  Forrest Gump

- What are the goals of therapy?
  - Cure of NTM infection (always good, not always possible)
  - Preparation for surgery (judicious aminoglycoside Rx)
  - Long-term suppression (especially with Rx failures)
  - Palliation (e.g., in the elderly; for end-stage disease)
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<tr>
<th><strong>NTM Classification</strong></th>
<th><strong>Concepts regarding therapy</strong></th>
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<tr>
<td><strong>Slowly Growing NTM</strong></td>
<td>1. Clarithromycin (azithromycin)-based regimens recommended for most infections</td>
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<td>(e.g., MAI, M. kansasii, M. xenopi)</td>
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<td>2. Ethambutol added as an “enhancing” drug</td>
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<td>3. Rifampin or rifabutin added as a third drug</td>
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<td>4. Parenteral aminoglycoside (e.g., amikacin) may be added initially (1-3 mos.) for severe illness or cavitary disease.</td>
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<td>5. Dosing frequency: Uncertain whether daily or intermittent dosing is preferable, but the latter can be effective and has reduced cost and toxicity.</td>
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<td>6. Treatment duration: Initial goal = 12 mos. therapy beyond sputum conversion to smear-negative. Re-assessment of disease status at the end of this period of therapy is important.</td>
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**NTM—Treatment Essentials**


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| Rapidly Growing NTM (e.g., M. abscessus, M. chelonae, M. fortuitum) | 7. Different regimens than for slowly growing NTM disease.  
Initial therapy may include several months of parenteral therapy with cefoxitin-amikacin or imipenem-amikacin.  
Long-term therapy usually requires two-drug oral Rx with a macrolide and a fluoroquinolone.  
Relapse is common.  
Cycles of therapy: parenteral ↔ oral therapy may be needed for long-term disease suppression. |
Treatment Monitoring - Drug-Related Side Effects

• **Amikacin**
  - Baseline electrolytes, serum magnesium and renal function
  - Baseline audiometry and repeat every two weeks → high-freq hearing loss
  - Patient watch for subjective hearing changes
  - Weekly blood studies and audiometry every two weeks during therapy

• **Clarithromycin / Azithromycin**
  - Baseline and every three month audiometry → pan-frequency hearing loss
  - Patient watch for subjective hearing changes

• **Rifampin / Rifabutin**
  - Baseline CBC w/ diff and plats; LFTs
  - Repeat weekly during the first month and then Q3 months or prn

• **Ethambutol**
  - Baseline and every three month check for ethambutol-related ocular toxicity
  - Patient watch for subjective changes in vision
Treatment - Ancillary Measures

• Optimize pulmonary hygiene
  – Goal = improved respiratory secretion clearance
  – Fluttering devices - e.g., Acapella choice, Vibrator vest
  – Hypertonic saline inhalation
  – Postural drainage, as appropriate for involved lung areas

• Reduce / discontinue immunosuppression, if possible
  – Discontinue all non-critical immunosuppressive therapy, including high-dose, inhaled corticosteroid therapy.

• Discontinue iron therapy, unless critical (not for anemia of chronic disease)
  – Iron stimulates mycobacterial growth:
    • Iron is a key mycobacterial growth factor (mycobactins; 40 diff enzymes)
    • Increased serum iron → Increased susceptibility to MAI infection in mice
  – Increased iron reduces macrophage defense against mycobacteria
Whether to treat? When to treat? When not to treat?

- Single positive culture – sputum vs. bronchoscopy or “sterile site”
- Colonization? – many patients will eventually progress
- Therapeutic decision vs. mycobacterial species isolated
  - M. kansasii, M. xenopi, M. simiae → usually treat
  - M. gordonae → almost never treat
  - MAI, rapidly growing mycobacteria → clinical decision
- Consider withholding therapy or treating with minimal regimen when:
  - No disease progression
  - Elderly patient with severe drug side effects
  - End-stage mycobacterial disease – palliative care
Outcome
Pulmonary NTM Disease: Predictors of Treatment Outcome

Suzanne Templer, Rashmi Baragi and James L. Cook

• Introduction:
  – Intuitive predictors of poor treatment outcome:
    • Antibiotic-resistance
    • Previous treatment failure
  – No reported data to assess predictions

• Purpose: Identify predictors of disease persistence among patients previously treated for pulmonary NTM disease

• Goal: Early recognition of patients who may fail therapy, so that treatment goals can be reviewed and adjusted.
Demographics, Definitions, General Observations

• Retrospective review – 202 pts referred for consultation

• “Persister” = culture-positive NTM disease despite therapy
  – ~1/3 of patients “Persisters”
  – ~2/3 of patients “Others” = cured; culture-negative

• Gender: ~80% female

• Age: no difference between Persisters and Others:
  – Persisters: median 63 yrs range 24-81 yrs
  – Others: median 66 yrs range 16-93 yrs
Greater Duration of Illness Among Persisters

Increased Time from Diagnosis to Consultation

P < 0.001

Median

24 months

Others w/Rx

6 months
More Courses of Previous Therapy AmongPersisters

- Persisters: 2.12 ± 0.31 courses
- Others w/Rx: 0.76 ± 0.08 courses

$P < 0.001$
Increased Drug Exposure Among Persisters

% Previously Treated

Persisters
Others
* P < 0.001

Clari = clarithromycin; Azi = azithromycin
FQ = any fluoroquinolone
More Cavities Among Persisters

- Persisters: 1.2 ± 0.4 cavities/pt
- Others: 0.3 ± 0.3 cavities/pt

P = 0.04
Greater Extent of Bronchiectasis

More Lung Regions Involved in Persisters

% of Lung Regions w/ B'ect

Persisters
82 ± 5%
of regions

Others
58 ± 4%
of regions

6 Lung Regions Scored:
RUL, RML, RLL
LUL, Lingula, LLL

P < 0.001
Distinguishing Persisters by Regions of Lung Involvement with Bronchiectasis

Increased LLL and LUL Bronchiectasis
Predictors of Persistent NTM Disease

- History
  - Cavitary Dis hx: $P = 0.001$
  - Smoking
  - Bronchiectasis
  - Gender
  - COPD hx
  - Pneumonia hx
- Previous Therapy
  - >1 course Rx: $P < 0.001$
  - Prev Clari-Azi Rx: $P = 0.002$
- Micro
  - Rapid Grower Infection: $P < 0.001$
  - Dual MAI+RGM Infection: $P = 0.001$
  - AFB smear-pos
  - MAI Infection
Predictors of NTM Disease Persistence

- More than one previous course of therapy
- Previous Rx with clarithromycin or azithromycin
- Cavitary lung disease
- RGM or dual / serial infection with MAC-RGM
Persistent NTM Disease: Adjusting Treatment Goals

- Adjust treatment expectations, goals and strategies
- Suppressive therapy and disease palliation
- Aggressive management of bronchiectasis
- Nutritional support
- Psychosocial support for chronic illness issues
- Family support – education; care giver issues
Pulmonary NTM Infections - Summary

- NTM are environmental pathogens
- Not communicable
- Pre-existing pulmonary abnormalities are common / “necessary”? 
- Antibiotic susceptibility testing for selected cases
- Drug treatment usually requires multiple antibiotics
- Lung resection surgery in highly selected cases
- Disease persistence \(\rightarrow\) redefine treatment goals and supportive Rx
  <idsociety.org/Organism>  FREE


  <bmb.oxfordjournals.org/content/96/1/45.full.pdf>  FREE