Non–Tuberculosis Mycobacterium (NTM) in Cystic Fibrosis

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Cystic Fibrosis (CF)

- Defect in the CFTR gene
  - Sinuses
  - Lungs
  - Pancreas (Endocrine/Exocrine)
  - Liver
  - Absorption/Nutrition
  - Bowel health/digestive transit
  - Reproductive System
  - Bones/Joints
One of the most common genetic diseases
- ~30,000 US (~70,000 worldwide)
- ~1,000 new cases per year
- >70% of patients are diagnosed by age two.
- >45% of the patient population is >18 years old!

Dramatic improvement in survival over the past 50 years
- Predicted median age early 40s.
Other Pathogenic organisms

- *Burkholderia cepacia*
- *Stenotrophomonas maltophilia*
- *Achromobacter (Alcaligenes xylooxidans)*
- Nontuberculous mycobacteria (NTM)
What are mycobacteria?

- *M. tuberculosis* complex
  - TB
- *M. leprae* and *M. lepromatosis*
  - Hansen’s disease or leprosy
- NTM – also known as:
  - Environmental mycobacteria (Water and soil)
  - Atypical mycobacteria
  - Mycobacteria other than tuberculosis (MOTT)

[www.waterscan.rs](http://www.waterscan.rs)
NTM – Microscopic
NTM – Acid Fast Bacilli (AFB)
NTM Species

- M. avium Complex
- M. kansasii
- M. abscessus
- M. haemophilium
- M. immunogenum
- M. malmoense
- M. smeegmatis
- M. szulgai
- M. terrae Complex
- M. chelonae
- M. fortuitum
- M. genavense
- M. gordonae
- M. marinum
- M. mucogenicum
- M. scrofulaceum
- M. simiae
- M. ulcerans
- M. xenopi
- Other NTM*

* Complete list can be found at http://www.bacterio.cict.fr/m/mycobacterium.html
Common NTM species

- Slow growers
  - *M. avium* complex (MAC)
  - *M. kansasii*

- Rapid growers (RGM)
  - *M. abscessus* complex
  - *M. chelonae*
  - *M. fortuitum*
Common NTM species

- M. avium complex (MAC)
  - M. avium
  - M. intracellulare
  - M. chimaera

- M. abscessus complex
  - M. abscessus
  - M. massiliense
  - M. bolletii
Before 1990 rarely reported
  - No routine AFB testing
  - Poor culture technique
  - Younger CF population

1990s–2000: 2–28% N. America/Europe
  - Based on single sputum sample
  - Poor culture techniques
  - Only screened patients when ill
  - No adult data

Olivier, et al. AJRCCM. 2003
Prevalence in Cystic Fibrosis

United States overall prevalence ~13%
- MAC (75%)
- *M. abscessus* (21%)
- Mac and *M. abscessus* (2%)
- Other species (2%)

Olivier, et al. AJRCCM. 2003
Martiniano et al., AATS. 2014
Associated Risk Factors

- NTM Associated with
  - More frequent in adults; lower age (median 32 yrs)
  - Higher baseline FEV–1
  - Lower frequency of *P. aeruginosa*
  - Higher frequency of *S. aureus*
  - Coinfection with *Stenotrophomonas maltophilia* and *Aspergillus fumigatus*

Olivier, et al. AJRCCM. 2003
Martiniano et al., AATS. 2014
NTM Transmission

- No Person-to-person transmission
- No nosocomial acquisition

- Most patients had unique bacterial strains
- Only cases of same strain laboratory cross-contamination
- No correlation between NTM culture status and
  - Number of hospitalizations
  - Days in the hospital
  - Outpatient visits

Olivier, et al. AJRCCM, 2003
Relevance of Positive Culture

- Single positive culture
  - Clears spontaneously

- Recurrent, no disease
  - ≥ 2+ cultures
  - No symptomatic progression
  - No radiographic progression

- NTM disease
  - ≥ 2+ cultures and
  - Symptomatic progression and
  - Radiographic progression

Martiniano et al., AATS. 2014
Diagnosing NTM Disease

- Symptoms: Overlapping
- Radiology: Overlapping
  - Difficult to interpret in CF
  - Cannot account for all NTM species
- Microbiology: Bacterial overgrowth
  - Distinguishing treatment failure/reinfection
- Appropriate exclusion of other diagnoses
Diagnosis: Symptoms

- Single or recurrent infections (61.5%)
  - no significant difference in decline in FEV1 before or after 1\textsuperscript{st} + NTM culture.

- Active NTM disease (38.5%)
  - lower baseline FEV1 at first positive culture
  - FEV\textsubscript{1} decline in year before 1\textsuperscript{st} + culture
  - FEV\textsubscript{1} decline 3 years after 1\textsuperscript{st} + culture 
    - 5.8\% predicted/yr
    - 4.1\% predicted/yr

- Not linked to other clinical characteristics
  - Gender/age
  - Azithromycin use/resistance
  - CF genotype
  - Co–infection with other CF pathogens

Martiniano et al., AATS, 2014
Diagnosis: Symptoms

[Graph showing percent predicted FEV₁ over time (years) around first positive NTM culture, with lines labeled 'Persistent', 'Transient', and 'Active'.]
Diagnosis: Radiology

http://synapse.koreamed.org
Diagnosis: Radiology
**Diagnosis: Radiology**

- MAC recovered from 299 non–CF patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>MAC Isolates</th>
<th>New cavitation or infiltrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>114</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>29</td>
<td>2</td>
<td>90%</td>
</tr>
<tr>
<td>40</td>
<td>3</td>
<td>98%</td>
</tr>
<tr>
<td>116</td>
<td>≥ 4</td>
<td>100%</td>
</tr>
</tbody>
</table>

- 98% of patient with ≥ 2 isolates showed radiographic progression.

Diagnosis: Radiology

- NTM in CF patients
- Entry HRCT:

- Progression on exit HRCT:
  - 38% control subjects
  - 22% \( \leq 2 \) NTM+ culture
  - 100% \( \geq 3 \) NTM+ cultures

Olivier, et al. AJRCCM. 2003
Diagnosis: Microbiology

- Initial MAC isolate
  - 24% grew 2nd NTM (primarily *M. abscessus*)

- Initial *M. abscessus*
  - 34% grew 2nd NTM (primarily MAC)

- Overall
  - 5 years: 26% with second NTM species
  - 10 years: 36% with second NTM species
In the setting of CF, documented deterioration from baseline and “reasonable exclusion of other disease to explain (the patient’s) condition” is an essential component.

- Suboptimal CF care
- Pulmonary exacerbation (usual pathogens)
- New bacterial infection (*B. cepacia*, etc)
- Poorly controlled sinus disease
- ABPA
- CFRD
- Poorly controlled sinusitis
- Chronic aspiration
Clinical Criteria for diagnosis

- Symptoms – Overlapping
- Radiology – non specific
- Microbiology – difficult
- Appropriate exclusion of other diagnoses

Despite these limitations, and given the most recent data, the ATS definition appears most appropriate for CF.
ATS/IDSA 2007 Definition of NTM Pulmonary Disease

- **Pulmonary Symptoms**
  - Increased Cough/SOB
  - Massive hemoptysis

- **Radiology**
  - CXR with nodular or cavitary opacities
  - In absence of cavitation, HRCT with multifocal bronchiectasis*** with multiple small nodules.

- **Microbiology**
  - + AFB > 2 separated sputum samples, or
  - + AFB from ≥ BAL, or
  - TBBx with mycobacterial histopathologic feature +
  - One or more sputum or BAL +ve for NTM

- **Appropriate exclusion of other diagnoses**
  - Underlying CF lung disease ***
  - Tuberculosis (TB)
ATS/IDSA 2007 Definition of NTM Pulmonary Disease

- Expert consultation once NTM recovered

- Close follow up of patients with suspected NTM lung disease who don’t meet ATS criteria

- NTM lung disease ≠ initiation of therapy
  - Risk vs benefit
Diagnosis of NTM in CF: CFF and ECFS Recommendations

- ATS/IDSA criteria should be used in individuals with CF
- Rule out other CF pathogens and co-morbidities with decline in symptoms and radiological changes with 1st + NTM cultures.
- Discontinue azithromycin treatment while evaluation for NTM disease is underway.
- Minimum annual sputum AFB cultures in Non-sputum producers: if no clinical/radiologic features resembling NTM pulmonary disease, do not require screening cultures for NTM.
Stanford NTM Surveillance Protocol

- Follow CFF guidelines: biannual AFB cultures
- If positive, monthly AFB
- If 2–3 persistent positive, CT of chest
- If FEV–1 stable and no disease on CT
  - Cont monitoring AFB
  - Annual chest CT or sooner if increase in symptoms or decline in FEV–1
When Should NTM Therapy Start?

- Under treat
- Disease Progression
- Over treat
- Drug Toxicity
When Should NTM Therapy Start?

- The patient
  - Symptoms, overall condition of patient
  - Imaging progression
  - Transplant listed or post transplant

- The organism
  - Species
  - Bacterial load

- Treatment goals?
  - Eradication
  - Prevent progression
  - Symptoms relief
The CFF and the ECFS recommend that NTM treatment should be considered for individuals with CF who have ATS/IDSA defined NTM pulmonary disease.

**Treatment Goals:**
- Symptomatic improvement
- Radiographic improvement
- Microbiological improvement:
  - Conversion to negative cultures
  - 12 months negative cultures **ON** Rx
Treatment Success

- 43% DID NOT clear NTM after 1st + culture

**MAC**
- N = 25
  - 32% Converted to Negative
  - 60% Converted, Recurred
  - 8% Never Converted

**M. abscessus**
- N = 11
  - 55% Converted to Negative
  - 45% Converted, Recurred

Martiniano et al., AATS, 2014
Common MAC Treatment

- Azithromycin
  - HIGH DAILY DOSING ONLY.
  - NEVER USE AS MONOTHERAPY

- IV/IH Amikacin

- Other agents
  - in collaboration with experts in CF/NTM
Common M. Abspessus Therapy

- **Intensive phase:**
  - Daily oral macrolide + IV amikacin
  - And one or more of:
    - Tigecycline
    - Imipenem
    - Cefoxitin (?)

- **Continuation phase:**
  - Daily oral macrolide + IH amikacin
  - And 2–3 of the following:
    - Moxifloxacin
    - Linezolid
    - Minocycline (?)
    - Clofazimine (?)

- Guided but not dictated by susceptibility results

3–12 weeks

ATS Statement AJRCCM 2007
# Drug Toxicities

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicities</th>
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| Clarithromycin | - GI (metallic taste, nausea, diarrhea  
|            |   - Rare: REVERSIBLE vestibular and hearing impairment       |
| Azithromycin  | - GI (diarrhea, nausea)  
|            |   - Rare: REVERSIBLE vestibular and hearing impairment       |
| Rifampin     | - Orange discoloration of secretions and urine  
|            |   - GI (Nausea, vomiting)  
|            |   - Hypersensitivity reactions (fever/rash)                   |
| Rifabutin    | - GI (Nausea, vomiting)  
|            |   - Neutropenia  
|            |   - Myalgia and arthralgia                                    |
| Ethambutol   | - Ocular toxicity/optic neuritis (loss of acuity, red-green discrimination)  
|            |   - Peripheral neuropathy, headache, disorientation           |
| Amikacin     | - Hearing impairment  
|            |   - Renal impairment  
|            |   - Vestibular impairment                                     |
| Tigecycline  | - GI (nausea, vomiting, diarrhea)  
|            |   - Renal impairment                                          |
| Linezolid    | - Bone marrow suppression  
|            |   - Peripheral neuropathy                                     |

ATS Statement AJRCCM 2007
Management of NTM in CF patients is complex/difficult

- Validated CF-specific diagnostic criteria
- Standardize treatment protocols
- Understanding NTM species/behavior
- Analysis of standard antimicrobial agents
- NTM-specific antibiotics for prolonged treatment
- Defined rates of treatment response
- Markers of response and treatment endpoints specific to CF
- MORE DATA, MORE RESEARCH!!!
References