Mycobacterium avium complex lung disease: more patients, multiple bacteria

Eric Houpt MD
Professor and Chief
Division of Infectious Diseases and International Health
University of Virginia
Outline

• Epidemiology
• Clinical presentation
• Diagnosis and treatment
• UVA research findings
Epidemiology

- Nontuberculous lung disease
- Medicare: 8% increase in prevalence per year
- 20K-80K cases annually in the US (9K TB)
- 1.4x Female predominance
- Higher in certain geographies, such as SE US
Epidemiology

- UVA

“Nontuberculous Mycobacteria” on CT scan reports

Satyanarayana et al., BMC ID 2011
Epidemiology

- UVA

"Nontuberculous Mycobacteria" on CT scan reports

Satyanarayana et al., BMC ID 2011
Epidemiology – NTM lung disease

- Morbidity/Mortality
- 1.4-2x higher mortality than similarly aged patients without NTM (Adjemian, AJRCCM 2012)
- Esp males, elderly
- May relate to comorbidities (die with it > from it)
- Generally a slowly progressive disease, with progressive symptoms and lung function decline
Clinical phenotype 1: male smoker cavitary lung disease

• 50 y.o. male former smoker

• Therapy with azithromycin, ethambutol, rifampin (Rif) for over a year, plus amikacin and clofazimine, yet experienced symptomatic, radiographic, and microbiologic failure.

• Required lobectomy which demonstrated caseating necrosis with abundant extracellular MAC.

• Died from the infection.
Classic phenotype 2 (more common): thin female with nodular bronchiectasis

- 71 y.o. female
- Cough for years prior to diagnosis
- Consistently worsening dyspnea, severe disease on chest imaging, and persistently positive sputum cultures.

- Has been on therapy for years, including standard triple therapy (Azi, Rif, Emb) plus adjunctive IV Amik (with hearing loss), followed by inhaled liposomal Amik, followed by Clofazimine, with essentially no improvement.
### 71 y.o. female timeline

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
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<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
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<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>Clari,Rif,Emb +IV Streptomycin</td>
<td>Off</td>
<td>Azi,Rif,Emb +IV Amik</td>
<td>Azi,Rif,Emb +inhaled liposomal-Amik</td>
<td>Azi,Rif,Emb +Clofaz</td>
<td>Azi500qd,Rif,Emb +Clofaz</td>
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<tr>
<td><strong>MAC culture results</strong></td>
<td>+ + - - -</td>
<td>- -</td>
<td>+</td>
<td>+ + + -</td>
<td>- + +</td>
<td>+</td>
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<td><strong>Susceptibility testing</strong></td>
<td>Clarithro S</td>
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- Only Clarithromycin matters
- Only drug with in vitro/in vivo correlation
- Generally ignore the others
- Clarithro (S) means use standard Azi/Clari regimens
- Clarithro (R) rare
Clinical phenotype 2: thin female with nodular bronchiectasis

Has been described for a long time

Reich et al., Chest 1992 …we offer the hypothesis that habitual voluntary suppression of cough may have led to the development of nonspecific inflammatory processes in these poorly draining lung regions (L lingula, RML), upon which MAC engrafted. We offer the term, Lady Windermere's syndrome, to describe this pattern among elderly women and to suggest that their fastidiousness may be its root cause....
Phenotype 2b: thin female with nodular bronchiectasis with minimal or no symptoms

Often CT scan performed for other reasons, often with subtle changes years prior
ATS/IDSA guidelines for NTM

• Dx NTM lung disease =

• Pulm symptoms (cough, sputum, fatigue, weight loss) and/or consistent imaging

• Exclusion of other diagnoses

• Positive sputum cultures x 2 (or 1 bronchoscopic)

• First question with any patient: Dx Y or N
ATS/IDSA guidelines for NTM

If Yes, Question 2: To treat or not to treat?

Minimal symptoms:

- May observe.
- “...one with minimal symptoms and radiographic findings such that the treatment seems worse than the disease, follow closely with collecting respiratory specimens for AFB analysis as well as follow-up radiographic studies, usually HRCT scans, over a long period of time as the MAC disease will likely progress at some time and the patient’s symptoms and chest radiographs will likely worsen.”
ATS/IDSA guidelines for NTM

- If treatment – at least 12 months (post-culture conversion)
- Azithromycin (or clarithromycin) – if ”Clari S”
- Plus rifampin (or rifabutin) – regardless of Rif S/R result
- Plus ethambutol – regardless of EMB S/R result
- M-W-F if nodular bronchiectasis
- Daily, plus IV amikacin if cavitary (if can tolerate)
- Long term efficacy about 50% - high relapse/reinfection rate, drug tolerability an issue
Relapse or reinfection?

- Known to occur in 15-50% of patients (especially with bronchiectasis form of disease)
- Molecular analysis (PFGE, etc) of strains traditionally has shown more reinfection (new strain – 80%) than relapse (same strain – 20%)

Wallace, AJRCCM 1998
Clinical microbiology of NTM

DNA probe to identify "M. Avium complex" vs. M. Tuberculosis

Step 1: Microbiology culture plate
Step 2: Sonicate for 15 minutes
Step 3: Heat at 95°C for 10 minutes
Step 4: Add DNA probe reagent

Storage
MAC = Mycobacterium avium complex
UVA study: 2010-2017

- 35 patients that met criteria for MAC LD with multiple longitudinal isolates available (n=95)
- Mostly nodular bronchiectasis

Table 1. Clinical and Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>All (N = 35)</th>
<th>Off Therapy (n = 16)</th>
<th>On Therapy (n = 11)</th>
<th>Relapse/Reinfection (n = 8)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M</td>
<td>17 (49%)</td>
<td>8 (50%)</td>
<td>4 (36%)</td>
<td>5 (63%)</td>
<td>NS</td>
</tr>
<tr>
<td>Median age at first culture (range), yr</td>
<td>60 (10–87)</td>
<td>35 (10–80)</td>
<td>66 (34–87)</td>
<td>62 (31–86)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Median BMI (IQR)</td>
<td>24 (20–27)</td>
<td>22 (21–28)</td>
<td>21 (20–23)</td>
<td>26 (24–27)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Current or former</td>
<td>14 (40%)</td>
<td>2 (13%)</td>
<td>7 (64%)</td>
<td>5 (63%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>21 (60%)</td>
<td>14 (87%)</td>
<td>4 (36%)</td>
<td>3 (37%)</td>
<td></td>
</tr>
<tr>
<td>MAC disease type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Cavity present</td>
<td>8 (23%)</td>
<td>3 (19%)</td>
<td>4 (36%)</td>
<td>1 (13%)</td>
<td></td>
</tr>
<tr>
<td>Noncavitary-nodular bronchiectasis</td>
<td>27 (77%)</td>
<td>13 (81%)</td>
<td>7 (64%)</td>
<td>7 (87%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Underlying conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>11 (31%)</td>
<td>1 (6%)</td>
<td>6 (55%)</td>
<td>4 (50%)</td>
<td></td>
</tr>
<tr>
<td>CF</td>
<td>12 (34%)</td>
<td>9 (56%)</td>
<td>2 (18%)</td>
<td>1 (13%)</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>5 (14%)</td>
<td>2 (13%)</td>
<td>3 (27%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other lung disease</td>
<td>6 (17%)</td>
<td>4 (25%)</td>
<td>0</td>
<td>3 (38%)</td>
<td></td>
</tr>
</tbody>
</table>
Whole genome sequencing

MAC ~ 5MB
Isolate # | Species composition
--- | ---
S01 - S05 | Mycobacterium avium
S06 - S09 | Mycobacterium marinum
S10 - S13 | Mycobacterium intrathoracica
S14 - S17 | Mycobacterium phlei
S18 - S21 | Mycobacterium chelonae
S22 - S25 | Mycobacterium abscessus
S26 - S29 | Mycobacterium fortuitum
S30 - S33 | Mycobacterium gordonae
S34 - S37 | Mycobacterium smegmatis
S38 - S41 | Mycobacterium avium subsp. avium
S42 - S45 | Mycobacterium avium subsp. intracellulare
S46 - S49 | Mycobacterium avium subsp. hominis
S50 - S53 | Mycobacterium avium subsp. paratuberculosis
S54 - S57 | Mycobacterium avium subsp. avium
S58 - S61 | Mycobacterium avium subsp. intracellulare
S62 - S65 | Mycobacterium avium subsp. hominis
S66 - S69 | Mycobacterium avium subsp. paratuberculosis
S70 - S73 | Mycobacterium avium subsp. avium
S74 - S77 | Mycobacterium avium subsp. intracellulare
S78 - S81 | Mycobacterium avium subsp. hominis
S82 - S85 | Mycobacterium avium subsp. paratuberculosis
S86 - S89 | Mycobacterium avium subsp. avium
S90 - S93 | Mycobacterium avium subsp. intracellulare
S94 - S97 | Mycobacterium avium subsp. hominis
S98 - S00 | Mycobacterium avium subsp. paratuberculosis
S01 - S05 | Other Species

95 isolates
Isolate # | Species composition
--- | ---

Patients #1 through 35

Off Rx | On Rx | Relapse

Cluster

M. Avium

M. intracellulare

M. chimaera

Other MAC, mixtures
Prior studies of MAC LD:
Mostly *M. avium* in Japan/Korea
70% *M. intracellulare* in Texas
25% of MAC LD in Illinois
Isolate #

Species composition

Patients #1 through 35

Cluster

M. Avium

- M. Avium
- M. intracellulare
- M. chimaera
- Other MAC, mixtures
Isolate #
Patients #1 through 35
Species composition

Hypothesis: patients not being treated (minimal dz), early on rx, or with relapse, would have the same strain
Isolate #

Patients #1 through 35

Species composition

Cluster

M. Avium

M. intracellulare

M. chimaera

Other MAC, mixtures

Hypothesis:

patients not being treated (minimal dz), early on rx, or with relapse, would have the same strain

Those with re-infection would have a distant strain
Hypothesis:
patients not being treated (minimal dz), early on rx, or with relapse, would have the same strain
Those with re-infection would have a distant strain

Generally false:
All groups had substantial MAC isolate diversity over time

Am J Respir Crit Care Med. 2019 Aug 1;200(3):393-396.
Mixtures and changes over time has been noted before:

Am J Respir Crit Care Med. 2019 Aug 1;200(3):393-396.
Some possible explanations

• MAC LD often reflects a polymicrobial infection, with shifts in bacteria or different sampling among sputa over time. “Biofilm”

• There is an extremely high reinfection rate from the environment in these susceptible hosts
**MAC in the environment**

- *M. avium* and *chimaera* are found in drinking water, more than *M. intracellulare*
- However, *M. intracellulare* (and avium, and others) are found in plumbing biofilms
- Soil:
  - Thus, some recommend water treatments to patients:
    - Drain and refill the hot water heater every 2 wk.
    - **Raise hot water heater temperatures (> 130F).**
    - **Remove and clean showerheads (full-strength household bleach for 30 min).**
    - Replace showerhead with one that produces streams (holes . 1 mm diameter) and not a fine mist.
    - Reduce aerosol exposures in bathrooms (fan and window).
    - Install shower and tap filters that remove bacteria (> 0.45 μm pore size).
    - Replace granular activated carbon filters every 2 wk.
    - **Get rid of any and all humidifiers.**
    - Avoid dusts from potting soils (wet potting soil).

Falkinham, AEM. 2001
Aim 1
- All ~200 Virginia MAC LD cases/yr = ~600 overall
- WGS to discern relapse vs. reinfection (n ~120)
- WGS to discern environment-patient MAC are similar or distinct (n ~ 500)

Aim 2
- All ~100 NEW Virginia MAC LD cases/yr = ~300 overall
- ~200 will be treated and complete 2 yr follow-up
- Follow for clinical outcomes and in vitro/in vivo correlations (MIC, PK/PD, Biofilm, MAC species)
Summary

- MAC lung disease is a growing problem at UVA and the US, particularly in thin white post-menopausal women.
- Most patients warrant treatment but a few do not – depends on symptoms, radiography, and microbiology.
- Treatment moderately effective but is long and difficult and often not durable - relapse/reinfection is common.
- MAC lung disease not simply one infection “MAC” lung disease – speciation probably important.
- Appears to reflect polymicrobial infection or frequent environmental reinfection into a bronchiectatic lung (which has poor clearance) : “Biofilm”
- We need better treatments.
1 new drug - Liposomal Inhaled Amikacin (Arikayce)

• Dose: One vial (590 mg) daily
• Indication: treatment refractory MAC LD
• Primary endpoint was microbiological reduction over 12 weeks: not achieved.
• However, a greater proportion of the LAI group demonstrated at least one negative sputum culture 32% vs. 9%; and improvement in 6-minute-walk test at week 12. > FDA approval
• 39% cough, 16% stopped rx
Lifecycle of Research

• Careful descriptive epidemiology of an important clinical problem

• Apply new thinking and new research tools to the leading questions

• Interventional study
Thank you

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• Scott Heysell