Mycobacterium chimaera
Disseminated Infections

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Outline

• What's in a name – *Mycobacterium chimaera*
• Clinical Presentation - When to suspect disseminated disease
• Diagnosis – A Clinical Laboratory Perspective
• Treatment – Challenging under any circumstance
Conflict of Interest Disclosures

- Investigator in multicenter randomized placebo controlled clinical trial of inhaled liposomal amikacin in pulmonary NTM infections (Insmed)
- Investigator in Bronchiectasis and NTM Research Registry (COPD Foundation)
- Investigator, Colorado CF/NTM Research Development Program (Cystic Fibrosis Foundation)
174 Species and 13 Subspecies in genus *Mycobacterium* as of March 29, 2016

Source: [http://www.bacterio.net/mycobacterium.html](http://www.bacterio.net/mycobacterium.html)
Mycobacterium avium Complex

FIG 5 Phylogenetic tree, based on the 16S rRNA gene, for the species belonging to the M. avium complex.

Tortoli E. Clin Micro Rev 2014;27:727-752
Occurrence and Clinical Relevance of *M. chimaera*, Germany

- 97 patients from Charité University Hospital between 2002-2006 and
- 69 isolated provided by National Reference Laboratory (Borstel, Germany)
  - 166 *Mycobacterium intracellulare* strains identified by 16s rRNA-based methods
  - 143 (86%) were *Mycobacterium chimaera* by sequencing 16S-23S ITS region

> 8,800 isolates were analyzed using *rpoB* gene sequencing

Seven *Mycobacterium* species accounted for ~80% of all isolates tested

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.4%</td>
<td><em>M. abscessus</em> group</td>
</tr>
<tr>
<td>19.9%</td>
<td><em>M. avium</em></td>
</tr>
<tr>
<td>16.4%</td>
<td><em>M. intracellulare</em></td>
</tr>
<tr>
<td>6.0%</td>
<td><em>M. chimaera</em></td>
</tr>
<tr>
<td>5.1%</td>
<td><em>M. fortuitum</em></td>
</tr>
<tr>
<td>3.8%</td>
<td><em>M. gordonae</em></td>
</tr>
<tr>
<td>3.7%</td>
<td><em>M. chelonae</em></td>
</tr>
</tbody>
</table>

42.3%

Source: Max Salfinger, MD
Mycobacterium avium Complex

What's in a Name?

- **Acquisition of infection**
  - *M. avium* and *M. chimaera* are found in water. *M. intracellulare*?

- **Pathogenicity**
  - *M. intracellulare* ≥ *M. avium* > *M. chimaera*

- **Clinical Presentation**
  - *M. intracellulare* presents with more advanced disease

- **Treatment outcomes**
  - *M. chimaera* and *M. avium* may have a higher rate of clinical recurrence than *M. intracellulare*

## Clinical Presentation

### Pulmonary Infection

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Chronic cough Fatigue, Fever, Weight loss, Shortness of breath</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs</td>
<td>Thin in stature Adventitious breath sounds</td>
</tr>
<tr>
<td>Laboratory Values</td>
<td>Lymphocytopenia, Elevated CRP Normal immunological tests (immunoglobulins, lymphocyte phenotyping)</td>
</tr>
</tbody>
</table>

Dissemination outside of the lung does not occur unless severely immunocompromised.
### Clinical Presentation

**Disseminated Infection**

#### Time to Presentation – median 21 months (5-40)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Fever, Fatigue, Weight loss, Shortness of breath</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs</td>
<td>Splenomegaly, Chorioretinitis</td>
</tr>
<tr>
<td>Laboratory Values</td>
<td>Anemia, Lymphocytopenia, Thrombocytopenia, Elevated CRP, Elevated transaminases, Elevated creatinine</td>
</tr>
</tbody>
</table>

Manifestation of Infections

- Prosthetic valve endocarditis
- Vascular graft infection
- Manifestations of disseminated disease:
  - Emboli
  - Bone marrow involvement
  - Splenomegaly
  - Nephritis
  - Myocarditis
  - Osteomyelitis

Delays in Diagnosis

• Long period from index surgery to clinical presentation
• Various clinical manifestations
• Lack of appropriate cultures at presentation
• Slow growth of *M. chimaera*
• Disbelief on behalf of provider
Diagnosis of NTM Infections
Routine Methods Take a Long Time!

Think about it!

Collect a specimen
Microscopic examination
Culture (liquid and solid media)
Identification
Drug susceptibility
Diagnosis
8 weeks
Molecular Methods of Identification/Speciation

In-solution hybridization probes

Line Probe

(MAC, M. avium, M. intracellulare, M. gordonae, M. kansasii, Mtb)

Sequencing

rpoB

hsp65
Sequencing For Identification

- Many clinical laboratories nationwide do not use sequencing nor provide final identification for NTM species: expertise in NTM identification is not common in the US
- Using rpoB sequencing NJH is able to produce final identification for the vast majority of NTM species (methods are validated by CLIA standards)
  - Once a positive culture is received, turn-around time is typically between 3-5 days for identification to species level: *M. abscessus* may require an additional 2-3 days to identify subspecies and erm41 mutations
- Testing is routinely performed at NJH 7 days a week to improve turn around times and capacity can be increased by addition of staff in order to meet turn-around time expectations
Antimicrobial Susceptibility Testing

Slowly growing NTM

- NTM10: 10-Drug MIC (CLF, CIP, MXF, AMK, STR, RFB, LZD, CLR, RIF, EMB, RIF/EMB)

- Single Drug MIC: (CLF, CIP, MXF, AMK, STR, RFB, LZD, CLR, RIF, EMB, ETH, LVX, AZM, OFX, CS)
Treatment

*M. avium* complex Pulmonary Infection

**MAC**

Duration: 12 mos culture negativity

Macrolide sensitive

Cavities Present

- Yes
- No

3X/WEEK
- Azithromycin
- Rifampin
- Ethambutol

DAILY
- Azithromycin
- Rifampin
- Ethambutol

Yes

- Add IV Amikacin

No

- Clofazimine
- Moxifloxacin
- Ciprofloxacin
- Bedaquiline
- DAILY
- Rifampin
- Ethambutol
- Other drug
# Treatment Outcomes for Pulmonary MAC

<table>
<thead>
<tr>
<th></th>
<th>Culture Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolide susceptible</strong></td>
<td></td>
</tr>
<tr>
<td>Non cavitary</td>
<td>80%</td>
</tr>
<tr>
<td>Cavitary</td>
<td>&lt;50%</td>
</tr>
<tr>
<td><strong>Macrolide resistant</strong></td>
<td></td>
</tr>
<tr>
<td>No surgery/aminoglycoside</td>
<td>5%</td>
</tr>
<tr>
<td>Surgery + aminoglycoside*</td>
<td>80%</td>
</tr>
</tbody>
</table>

* ≥ 6 months IV aminoglycoside

Griffith DE, et al. AJRCCM 2006;174:928
Treatment
Disseminated *M. chimaera*

**MAC**
- Yes: DAILY Azithromycin, Rifampin, Ethambutol
- No: Clofazimine, Moxifloxacin, Ciprofloxacin, Bedaquiline

Duration: ????

Add IV Amikacin
3 months?
Clinical Outcomes of Disseminated *M. chimaera* Infections

Why so Difficult to Treat?

- Delay in diagnosis resulting in widespread disseminated infection
- Endovascular infection involving foreign material (biofilm)
- Largely bacteriostatic drugs
- Low serum drug concentrations
- Co-morbidities
Summary

- Disseminated *M. chimaera* infections post-cardiac surgery presents with evidence of endovascular and disseminated disease
- Diagnosis should be considered when such a patient presents with the typical signs, symptoms, and laboratory values described to date
- Delays in diagnosis and treatment are multifactorial in nature
- Precise speciation should be performed and antimicrobial susceptibility testing performed to at least the macrolides and amikacin
- Treatment should include a macrolide-based regimen and addition of intravenous amikacin if possible
- Surgery to removed infected valves/grafts should be considered as mortality is high (we need additional data on impact of surgery)
- Hopefully earlier diagnosis and initiation of treatment will improve outcomes