M. ABSCESSUS: UPDATE ON MANAGEMENT

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Financial Disclosures

• PI for clinical trials with Insmed/Aradigm/Novartis/Chiltern/Hill Rom (all bronchiectasis/NTM related)

• Consultant (ended 9/2018)
  – AIT Therapeutics
  – Insmed
Case

- 59 y/o F without significant PMH
- Recurrent respiratory infections over 3 years;
- CXR revealed mild increase in airways disease;
- CT finally performed after 3 years of cough
CT Chest from 2016
Case

- *M. Abscessus* subspecies *abscessus*
- Recurrent courses of combination of oral antibiotics with IV therapy for weeks to months
- IV tigecycline and IV amikacin with clofazimine and tedizolid for 3 months
- Then on oral therapy bedaquiline, clofazimine and inhaled amikacin
- And back on IV and then oral and back and forth.................
**Mycobacterium abscessus**

- *Mycobacterium abscessus* was first identified in a patient with a knee infection and SQ abscesses.

- *M. abscessus* is the 2nd-3rd most common cause of lung disease due to NTM and the most common cause of lung disease due to a rapid grower.

- The organism is highly resistant to antibiotics with current *in vitro* methods.

Isolated in 1950 from synovial fluid and buttock lesions in a 63 year old woman.

Moore M et al. J Invest Derm. 1953;20:133
# M. abscessus group

## Table 1. Taxonomic/nomenclature designations for “Mycobacterium abscessus” and associated genetic and phenotypic features

<table>
<thead>
<tr>
<th>Name</th>
<th>Complete 16S rRNA Gene Sequence</th>
<th>rpo β Gene Sequence</th>
<th>erm(41) Gene Sequence</th>
<th>erm (41) Functional</th>
<th>Whole-Genome Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. abscessus or M. abscessus subsp. abscessus or M. abscessus sensu stricto</td>
<td>Identical to M. bolletii and M. massiliense</td>
<td>Unique to M. abscessus</td>
<td>Unique to M. abscessus</td>
<td>Yes*</td>
<td>Unique to M. abscessus</td>
</tr>
<tr>
<td>M. bolletii or M. abscessus subsp. bolletii</td>
<td>Identical to M. abscessus and M. massiliense</td>
<td>Unique to M. bolletii</td>
<td>Unique to M. bolletii</td>
<td>Yes</td>
<td>Unique to M. bolletii</td>
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<tr>
<td>M. massiliense or M. abscessus subsp. massiliense</td>
<td>Identical to M. abscessus and M. bolletii</td>
<td>Unique to M. massiliense</td>
<td>Unique to M. massiliense</td>
<td>No</td>
<td>Unique to M. massiliense</td>
</tr>
</tbody>
</table>
Current Common Options for Treatment

• Tigecycline IV
• Amikacin IV
• Cefoxitin IV
• Imipenem IV
• Moxifloxacin PO or IV
• Along with oral options
  • Clofazamine
  • Oxazolidinones (??)
**In vitro Drug Susceptibility, M. abscessus**

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC Range</th>
<th>MIC50</th>
<th>MIC90</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>0.125-64</td>
<td>4</td>
<td>816</td>
<td>90-98%</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>16-256</td>
<td>32</td>
<td>32</td>
<td>32-99%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.064-64</td>
<td>4-32</td>
<td>16-32</td>
<td>1-57%</td>
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<tr>
<td>Clarithromycin</td>
<td>0.032-64</td>
<td>0.25-1</td>
<td>2-16</td>
<td>78-100%</td>
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<tr>
<td>Clofazimine</td>
<td>≤0.25-1</td>
<td>≤0.5</td>
<td>1.0</td>
<td>82-90%</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&lt;0.5-256</td>
<td>4-16</td>
<td>8-128</td>
<td>13-73%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0.5-64</td>
<td>16</td>
<td>32</td>
<td>43%</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.064-32</td>
<td>2-32</td>
<td>2-32</td>
<td>6-73%</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>0.064-24</td>
<td>0.5-3</td>
<td>2-12</td>
<td>24-100%</td>
</tr>
</tbody>
</table>

Treatment of *M. abscessus*

- **Yes**
- “Functional” *erm41* gene
- **No**

- *M. abscessus*
- *M. bolletii*
- *M. abscessus*
- *M. massiliense*
Treatment of *M. abscessus*

- **M. abscessus**
  - **M. bolletii**
  - Yes
  - “Functional” *erm*41 gene
    - Yes
      - Macrolide? ≥2 other drugs
        - Amikacin
  - No
    - 2 +mos
      - Macrolide? ≥2 other drugs
        - Inhaled Amikacin

- **M. massiliense**
Treatment of *M. abscessus*

*(Duration 12 months culture negativity)*

- **M. abscessus**
  - **Yes**
    - Macrolide? ≥2 other drugs
      - Amikacin
    - 2+ mos
    - Macrolide? ≥2 other drugs
      - Inhaled Amikacin
  - **“Functional” erm41 gene**
    - Imipenem (IV)
    - Cefoxitin (IV)
    - Tigecycline (IV)
    - Linezolid
    - Clofazimine
    - Moxifloxacin
    - Bedaquiline
    - Avibactam/meropenem
  - **No**
    - Macrolide ≥1 other drug
      - Amikacin
    - 2+ mos
    - Macrolide ≥1 other drug
      - Inhaled Amikacin

- **M. bolletii**
  - Macrolide? ≥2 other drugs
  - Amikacin
  - 2+ mos

- **M. massiliense**
DOES BEDAQUILINE WORK?

Preliminary Results of Bedaquiline as Salvage Therapy for Patients With Nontuberculous Mycobacterial Lung Disease

- Bedaquiline is an oral antimycobacterial agent belonging to the diarylquinolines class
- It appears to be effective for the treatment of MDRTB but has not been tested for NTM disease
• Preliminary Results of Bedaquiline as Salvage Therapy for Patients With Nontuberculous Mycobacterial Lung Disease  Philley, J, et al  CHEST 2015; 148(2):499-506

• A case series of off-label use of bedaquiline caused by MAC or Mab.
• 10 patients were reviewed (6 MAC, 4 Mab)
• Patients had refractory disease and were treated for 1-8 years prior to starting bedaquiline
• 80% had macrolide resistant isolates
• Dose was 400mg daily with food for 2 weeks followed by 200mg TIW.
• All patients completed 6 months of therapy with bedaquiline and remain on therapy.
• Preliminary Results of Bedaquiline as Salvage Therapy for Patients With Nontuberculous Mycobacterial Lung Disease  Philley, J, et al  CHEST 2015; 148(2):499-506

• After 6 months of therapy, 60% (6/10) had a microbiologic response with 50% (5/10) having one or more negative cultures.

• Side effects-
  – Nausea (60%)
  – Arthralgias (40%)
  – Anorexia and subjective fever (30%)

• No abnormal ECG changes were observed.

• A small preliminary study that highlights the potential clinical and microbiologic activity of bedaquiline in patients with advance MAC/Mab.
Emerging Pharmacologic Therapies -- Bedaquiline

A bedaquiline/clofazimine combination regimen might add activity to the treatment of clinically relevant non-tuberculous mycobacteria

Ruth M, J Antimicrob Chemother 2019; Ijakko van Ingen

In TK assays, bedaquiline showed a bacteriostatic effect. Clofazimine extended the bacteriostatic activity of bedaquiline against MAB and yielded a slight bactericidal effect against M. avium.

A bedaquiline/clofazimine combination might add activity to MAB and MAC treatment. The bedaquiline/clarithromycin combination might have lower activity compared with bedaquiline alone for MAC treatment.
A New Approach – Avibactam with Carbapenems??

- Combination of avibactam and carbapenems exhibit enhanced potencies against drug resistant *Mycobacterium abscessus*.
  - Kaushik, A et al Future Microbiol 2017

- 28 resistant isolates of *M abscessus*
  - Avibactam was able to restore the MICs of tebipenem, ertapenem, and panipenem against *M abscessus* to therapeutically achievable concentrations
Emerging Pharmacologic Therapies – tetracycline analogs


• New Tetracycline Analogs
  • Omadacycline (oral) / Eravacycline (IV)
  • In vitro data against drug resistant *M. Abscessus*
  • Promising alternative to IV Tigecycline
  • Favorable MICs
  • Lower toxicity
<table>
<thead>
<tr>
<th>Isolate or MIC</th>
<th>M. abscessus subspecies</th>
<th>MIC (µg/ml)</th>
<th>Tigecycline</th>
<th>Omadacycline</th>
<th>Eravacycline</th>
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</tr>
</tbody>
</table>
Surgery

- **Indications for surgery:** medication unresponsive (drug resistant; large cavities); hemoptysis; uncontrolled symptoms; ? Debulking of disease


- **Microbiologic efficacy** – Griffith AJRCCM 2006; Nelson Ann Thor Surg 1998; Griffith AJRCCM 1993

  - *M abscessus* disease treatment success
    - Jeon 2009 -- 58% (med) vs 88% (med + surg)
    - Jarand 2011 – 39% (med) vs 65% (med + surg)
THANK YOU!