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

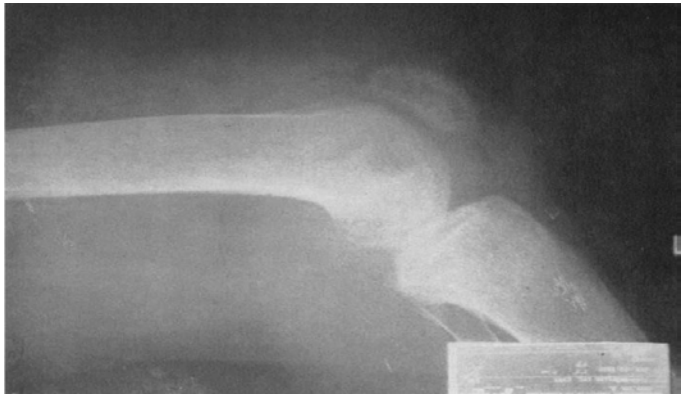
- And back on IV and then oral and back and forth…….....

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

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M. abscessus group

Table 1. Taxonomic/nomenclature designations for "*Mycobacterium abscessus*" and associated genetic and phenotypic features

Name	Complete 16S rRNA Gene Sequence	*rpo β* Gene Sequence	*erm*(41) Gene Sequence	*erm* (41) Functional	Whole-Genome Sequence
M. abscessus or *M. abscessus* subsp. *abscessus* or *M. abscessus sensu stricto*	Identical to *M. bolletii* and *M. massiliense*	Unique to *M. abscessus*	Unique to *M. abscessus*	Yes*	Unique to *M. abscessus*
M. bolletii or *M. abscessus* subsp. *bolletii*	Identical to *M. abscessus* and *M. massiliense*	Unique to *M. bolletii*	Unique to *M. bolletii*	Yes	Unique to *M. bolletii*
M. massiliense or *M. abscessus* subsp. *massiliense*	Identical to *M. abscessus* and *M. bolletii*	Unique to *M. massiliense*	Unique to *M. massiliense*	No	Unique to *M. massiliense*

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

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

Park S, et al. J Korean Med Sci 2008;23:49-52 Nie W, et al. Int J Infect Dis 2014;25:170-174
Huang YC et al. J Micro, Immunol Infect 2010;43:401-406
Yoshida S, et al. Int J Infect 2013;42:226-231

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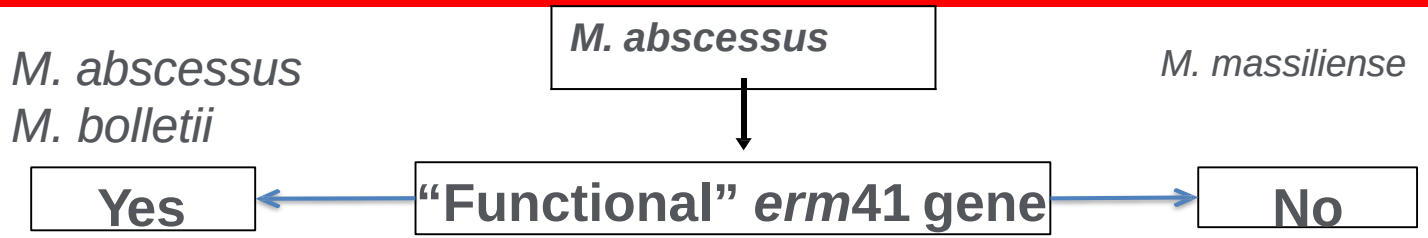
Treatment of *M. abscessus*



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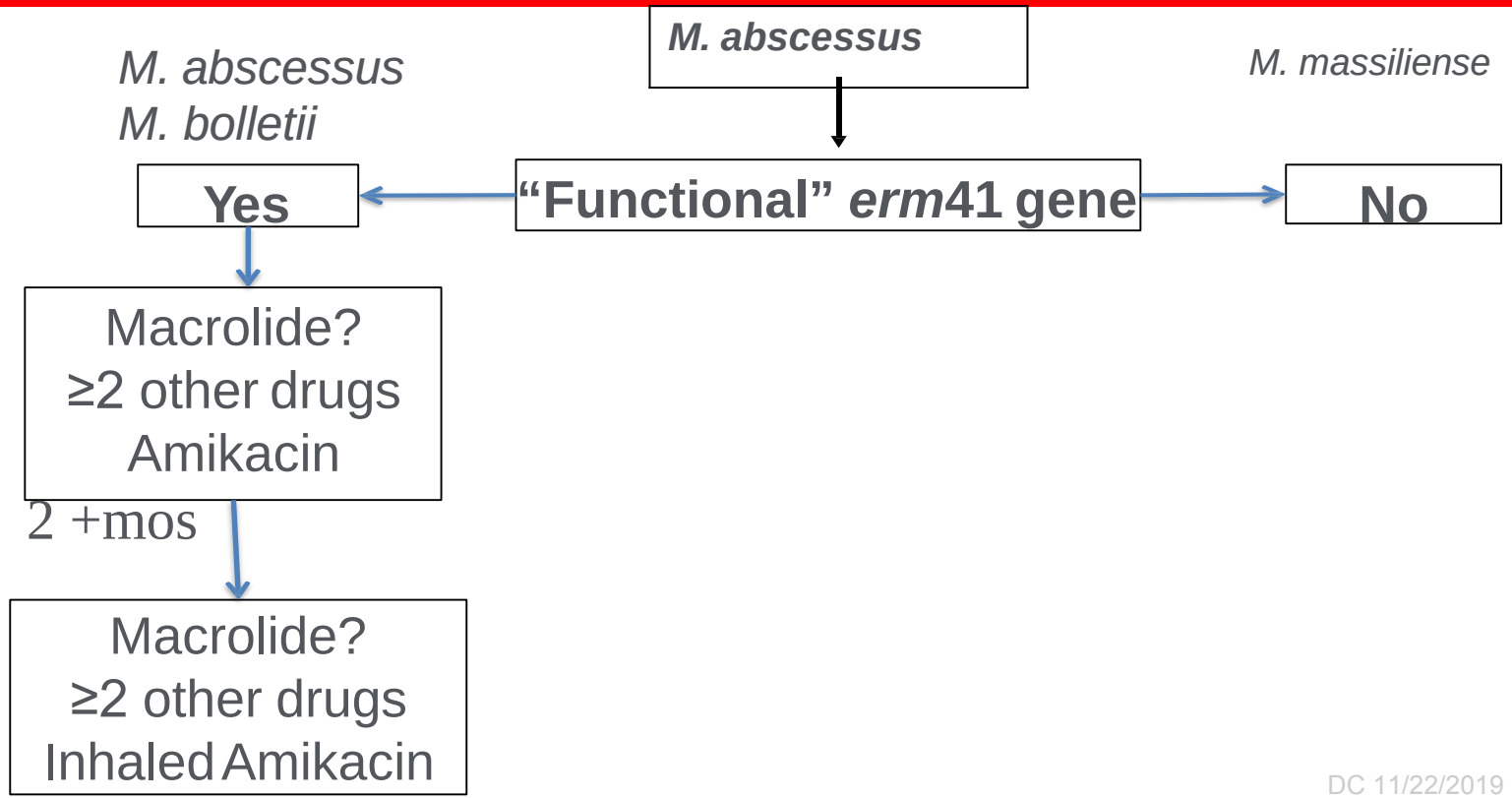
Treatment of *M. abscessus*



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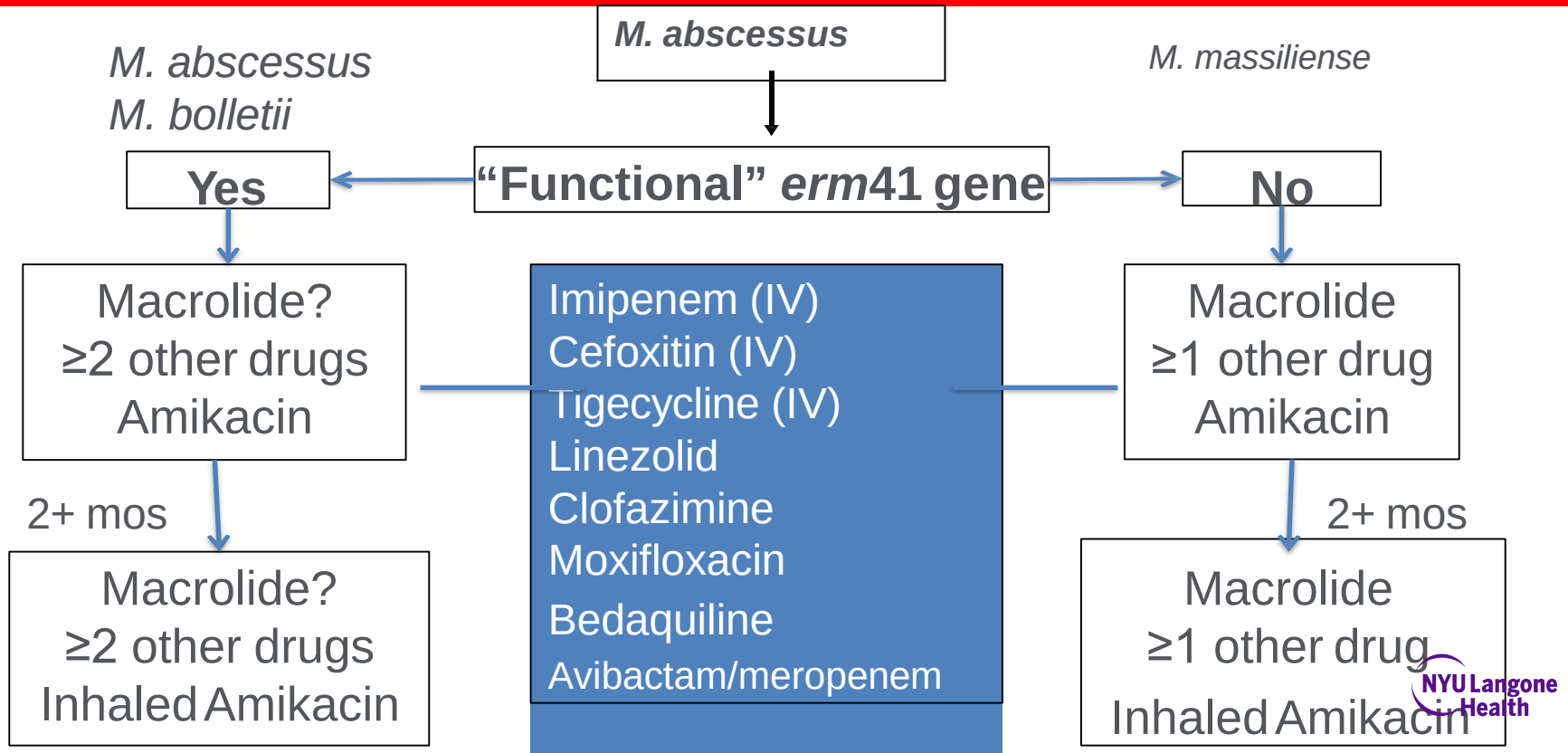
Treatment of *M. abscessus*

(*Duration 12 months culture negativity)*



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DOES BEDAQUILINE WORK?

- **Preliminary Results of Bedaquiline as Salvage Therapy for Patients With Nontuberculous Mycobacterial Lung Disease**
  Philley, J, et al *CHEST* 2015; 148(2):499-506.

- Bedaquiline is an oral antimycobacterial agent belonging to the diarlylquinolines 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 anaologs

Bax H, et al. J Antimicrob Chemother 2019 (Netherlands)
Kaushi, A, et al Antimicrobial Agents and Chemotherapy 2019 (Hopkins)

- **New Tetracycline Analogs**
  - **Omadacycline (oral) / Eravacycline (IV)**
  - **In vitro data against drug resistant *M. Abscessus***
  - **Promising alternative to IV Tigecycline**
  - **Favorable MICs**
  - **Lower toxicity**

Isolate or MIC	*M. abscessus* subspecies	MIC (μg/ml)		
		Tigecycline	Omadacycline	Eravacycline
Isolates				
Strain ATCC 19977[a]	*abscessus*	1	1	0.5
1N	*abscessus*	1	1	0.5
2N	*massiliense-bolletii*[b]	1	1	0.25
3N	*abscessus*	2	2	1
4N	*massiliense*	1	1	0.25
5N	*massiliense*	1	0.5	0.25
6N	*abscessus*	2	4	1
11N	*abscessus*	1	2	2
12N	*abscessus*	1	0.5	0.25
13N	*massiliense-bolletii*	1	2	0.5
14N	*massiliense-bolletii*	2	2	1
19N	*abscessus*	1	0.5	0.25
201	*abscessus*	1	0.5	0.25
202	*abscessus*	1	2	0.5
203	*massiliense-bolletii*	1	2	0.5
204	*massiliense*	1	1	0.5
206	*massiliense*	0.5	0.5	0.125
208	*massiliense*	2	2	0.5
210	*abscessus*	2	2	0.5
211	*abscessus*	2	2	0.5
212	*massiliense-bolletii*	1	1	0.25
214	*massiliense*	1	1	0.5
215	*abscessus*	1	1	0.25
216	*massiliense*	1	1	0.25
218	*abscessus*	4	4	2
JHH2	*abscessus*	1	1	0.25
JHH4	*abscessus*	1	1	0.25
JHH9	*abscessus*	2	2	0.5
JHHKB	*abscessus*	2	2	0.5

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Surgery

- **Indications for surgery**: medication unresponsive (drug resistant; large cavities); hemoptysis; uncontrolled symptoms; ? Debulking of disease
- **Safety** -- Mitchell, J Ann Thorac Surg 2008; Eur Journ CV surg 2011
- **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!