

***M. ABSCESSUS:* UPDATE ON MANAGEMENT**

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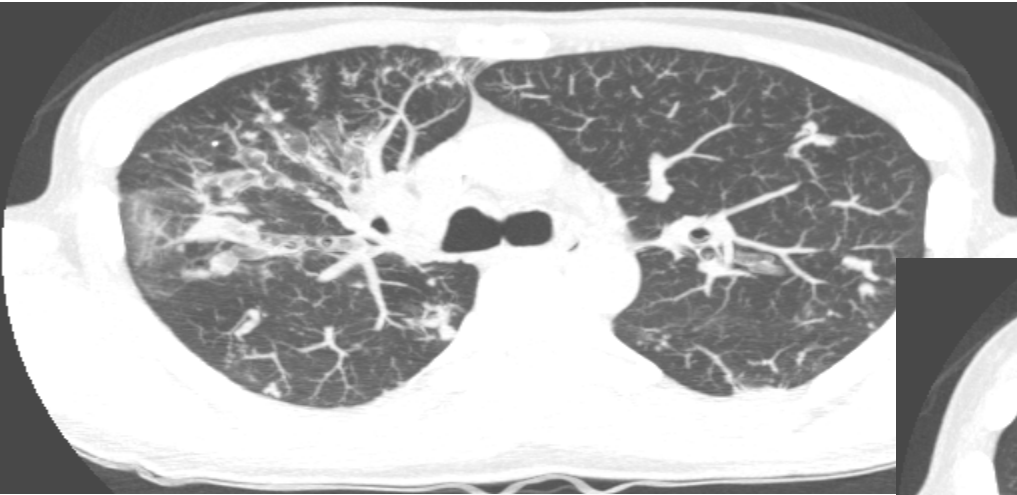
Financial Disclosures

- 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

M. abscessus group

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

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

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%

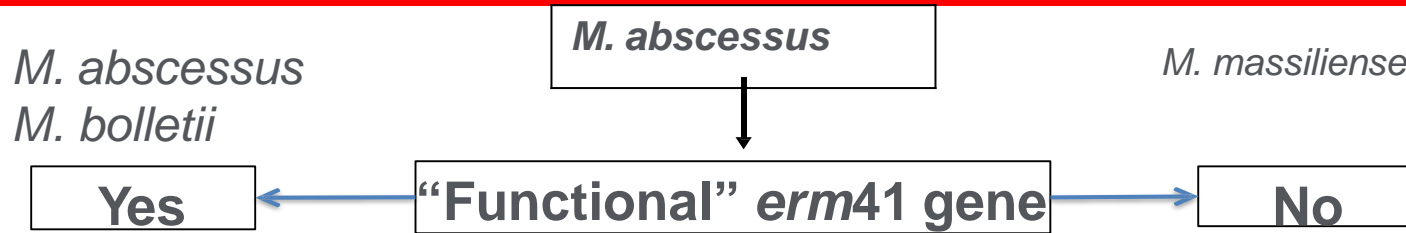
Park S, et al. J Korean Med Sci 2008;23:49-52 Nie

W, et al. Int J Infect Dis 2014;25:170-174

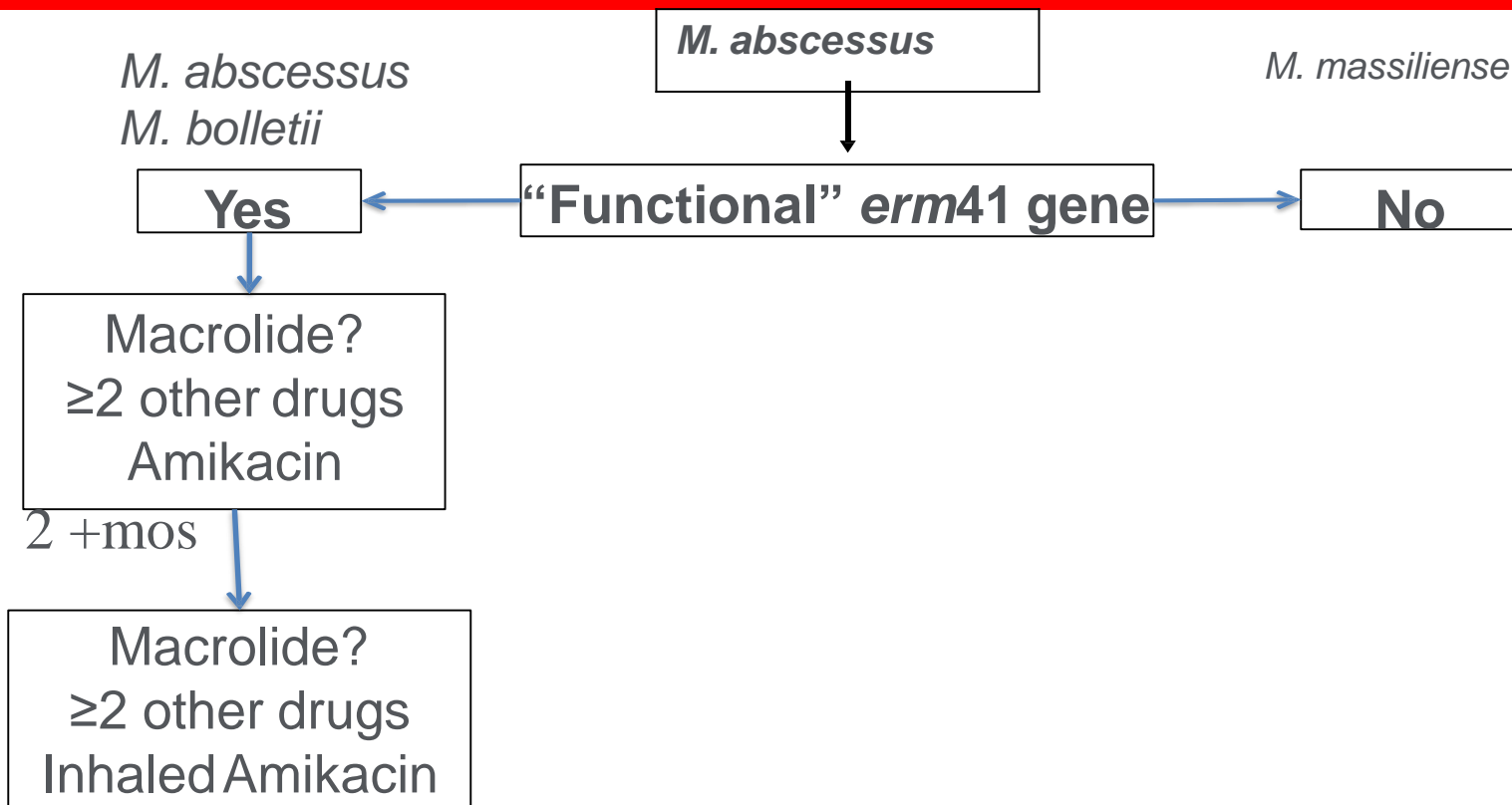
Huang YC et al. J Micro, Immunol Infect 2010;43:401-406

Yoshida S, et al. Int J Infect 2013;42:226-231

Treatment of *M. abscessus*

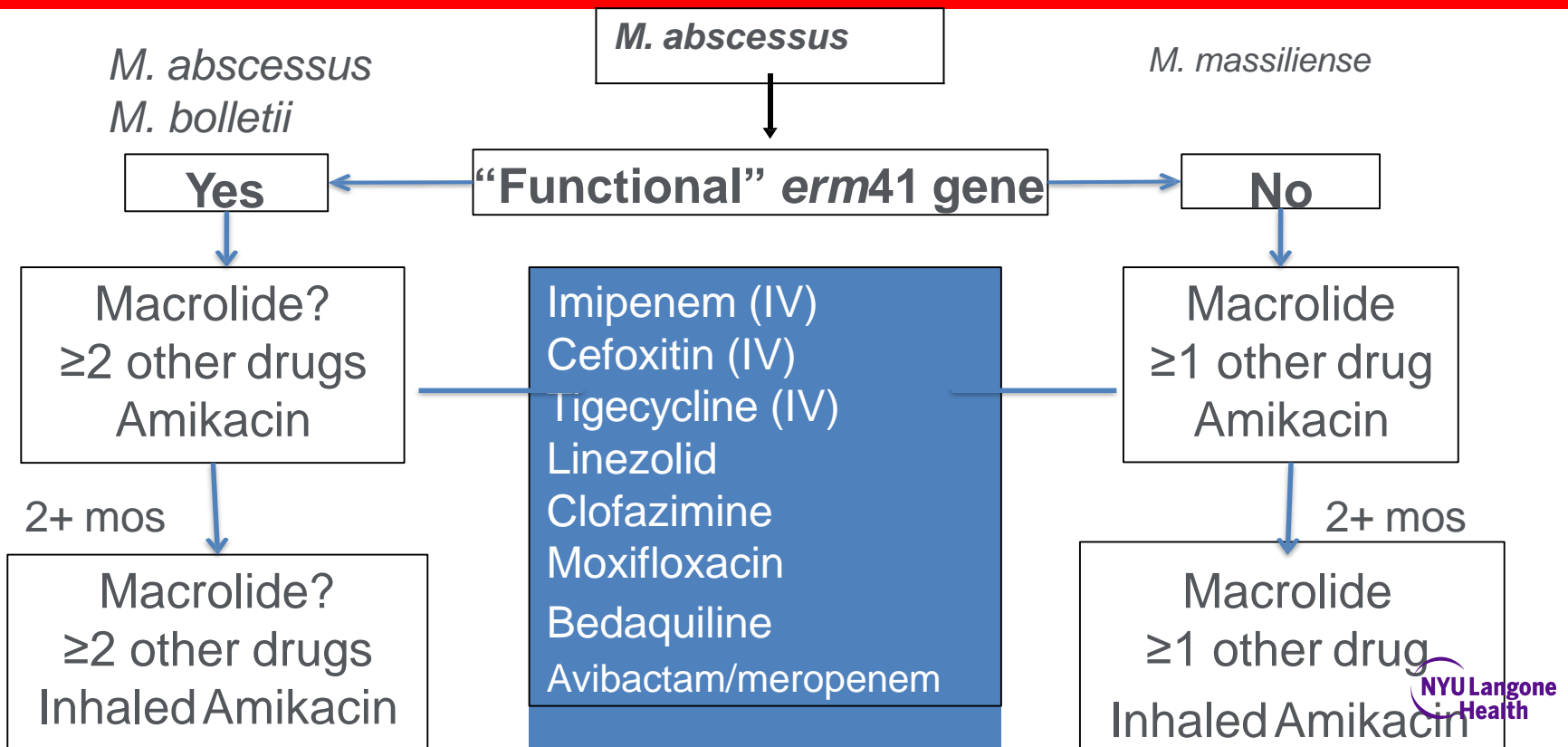


Treatment of *M. abscessus*



Treatment of *M. abscessus*

(Duration 12 months culture negativity)



■ DOES BEDAQUILINE WORK?

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

Phillely, J, et al *CHEST* 2015; 148(2):499-506.

- 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

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	<i>M. abscessus</i> subspecies	MIC ($\mu\text{g/ml}$)		
		Tigecycline	Omadacycline	Eravacycline
Isolates				
Strain ATCC 19977 ^a	<i>abscessus</i>	1	1	0.5
1N	<i>abscessus</i>	1	1	0.5
2N	<i>massiliense-bolletii</i> ^b	1	1	0.25
3N	<i>abscessus</i>	2	2	1
4N	<i>massiliense</i>	1	1	0.25
5N	<i>massiliense</i>	1	0.5	0.25
6N	<i>abscessus</i>	2	4	1
11N	<i>abscessus</i>	1	2	2
12N	<i>abscessus</i>	1	0.5	0.25
13N	<i>massiliense-bolletii</i>	1	2	0.5
14N	<i>massiliense-bolletii</i>	2	2	1
19N	<i>abscessus</i>	1	0.5	0.25
201	<i>abscessus</i>	1	0.5	0.25
202	<i>abscessus</i>	1	2	0.5
203	<i>massiliense-bolletii</i>	1	2	0.5
204	<i>massiliense</i>	1	1	0.5
206	<i>massiliense</i>	0.5	0.5	0.125
208	<i>massiliense</i>	2	2	0.5
210	<i>abscessus</i>	2	2	0.5
211	<i>abscessus</i>	2	2	0.5
212	<i>massiliense-bolletii</i>	1	1	0.25
214	<i>massiliense</i>	1	1	0.5
215	<i>abscessus</i>	1	1	0.25
216	<i>massiliense</i>	1	1	0.25
218	<i>abscessus</i>	4	4	2
JHH2	<i>abscessus</i>	1	1	0.25
JHH4	<i>abscessus</i>	1	1	0.25
JHH9	<i>abscessus</i>	2	2	0.5
JHHKB	<i>abscessus</i>	2	2	0.5

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!

