

UPDATE ON M. ABSCESSUS AND NEW THERAPIES FOR NTM

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- PI for clinical trials with Insmed/Zambone/Hill Rom (all bronchiectasis/NTM related)

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- 3 subspecies

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. abscessus 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. bolletii	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. massiliense	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
 - Clofazimine
 - Oxazolidinones

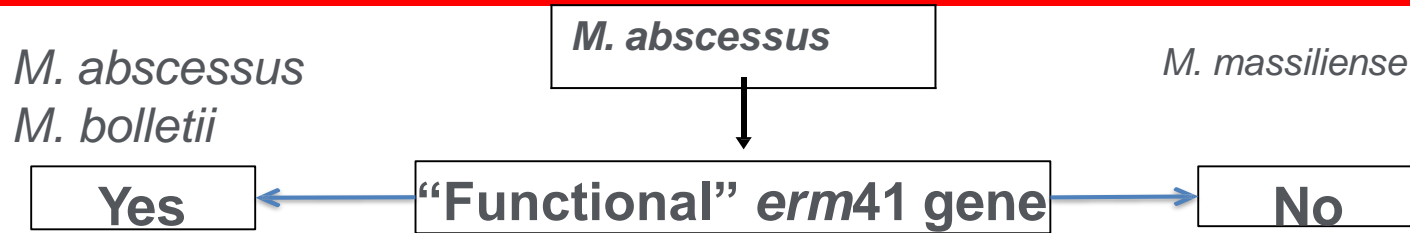
Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline

Charles L. Daley,^{1,2,a} Jonathan M. Iaccarino,³ Christoph Lange,^{4,5,6,7,a} Emmanuelle Cambau,^{8,a} Richard J. Wallace, Jr.,^{9,a} Claire Andrejak,^{10,11} Erik C. Böttger,¹² Jan Brozek,¹³ David E. Griffith,¹⁴ Lorenzo Guglielmetti,^{8,15} Gwen A. Huitt,^{1,2} Shandra L. Knight,¹⁶ Philip Leitman,¹⁷ Theodore K. Marras,¹⁸ Kenneth N. Olivier,¹⁹ Miguel Santin,²⁰ Jason E. Stout,²¹ Enrico Tortoli,²² Jakko van Ingen,²³ Dirk Wagner,²⁴ and Kevin L. Winthrop²⁵

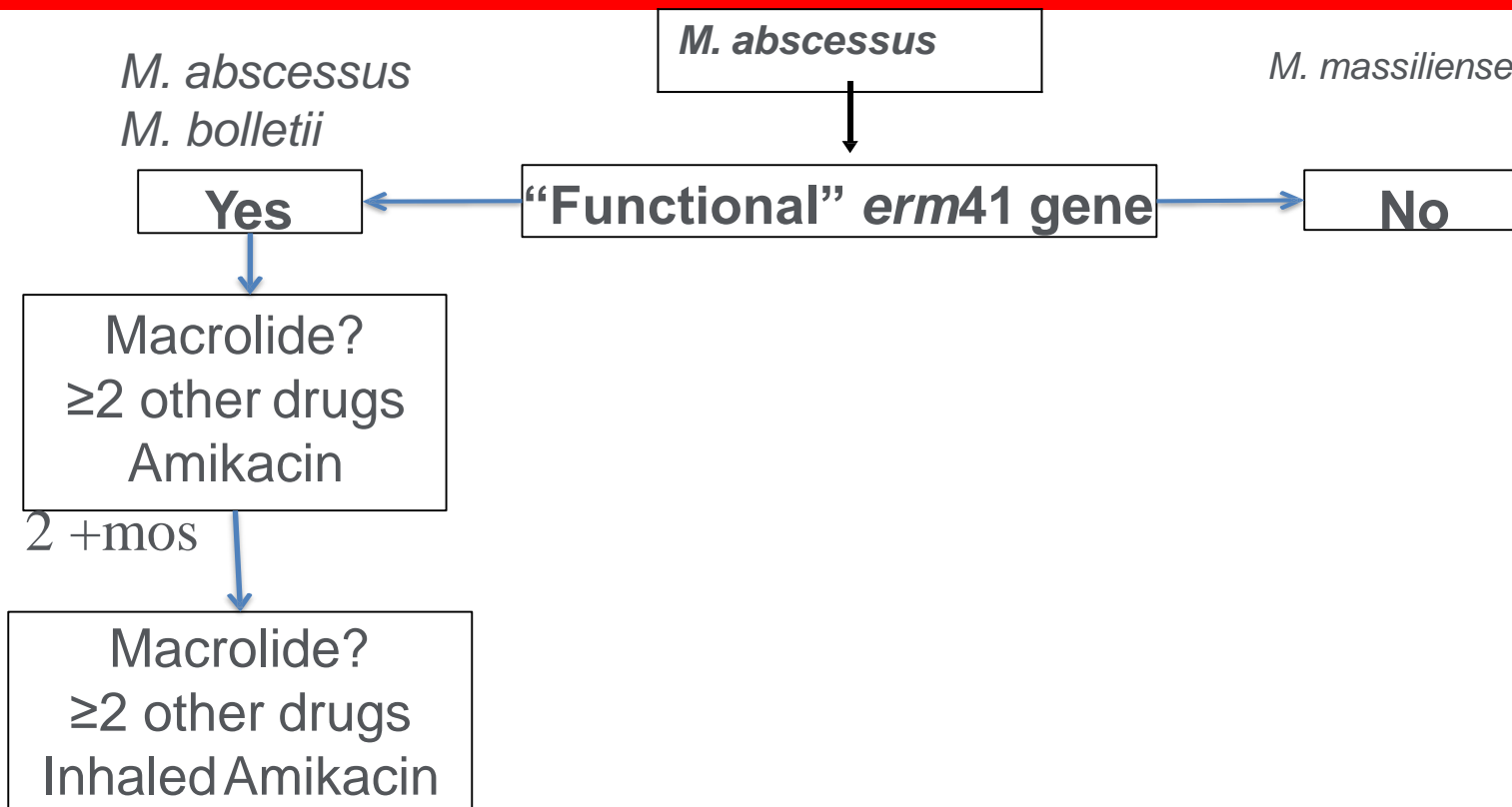
Mycobacterium abscessus

- In patients with *m.abscessus* pulmonary disease caused by strains **without inducible** or mutational resistance, **we recommend a macrolide-containing** multidrug treatment regimen (*strong recommendation, very low certainty in estimates of effect*).
- In patients with *m.abscessus* pulmonary disease caused by strains **with inducible** or mutational macrolide resistance, **we suggest a macrolide-containing** regimen if the drug is being used for its **immunomodulatory** properties although the macrolide is not counted as an active drug in the multidrug regimen (*conditional recommendation, very low certainty in estimates of effect*).
- In selected patients with NTM pulmonary disease, **we suggest surgical resection** as an adjuvant to medical therapy after expert consultation (*conditional recommendation, very low certainty in estimates of effect*).

Treatment of *M. abscessus*

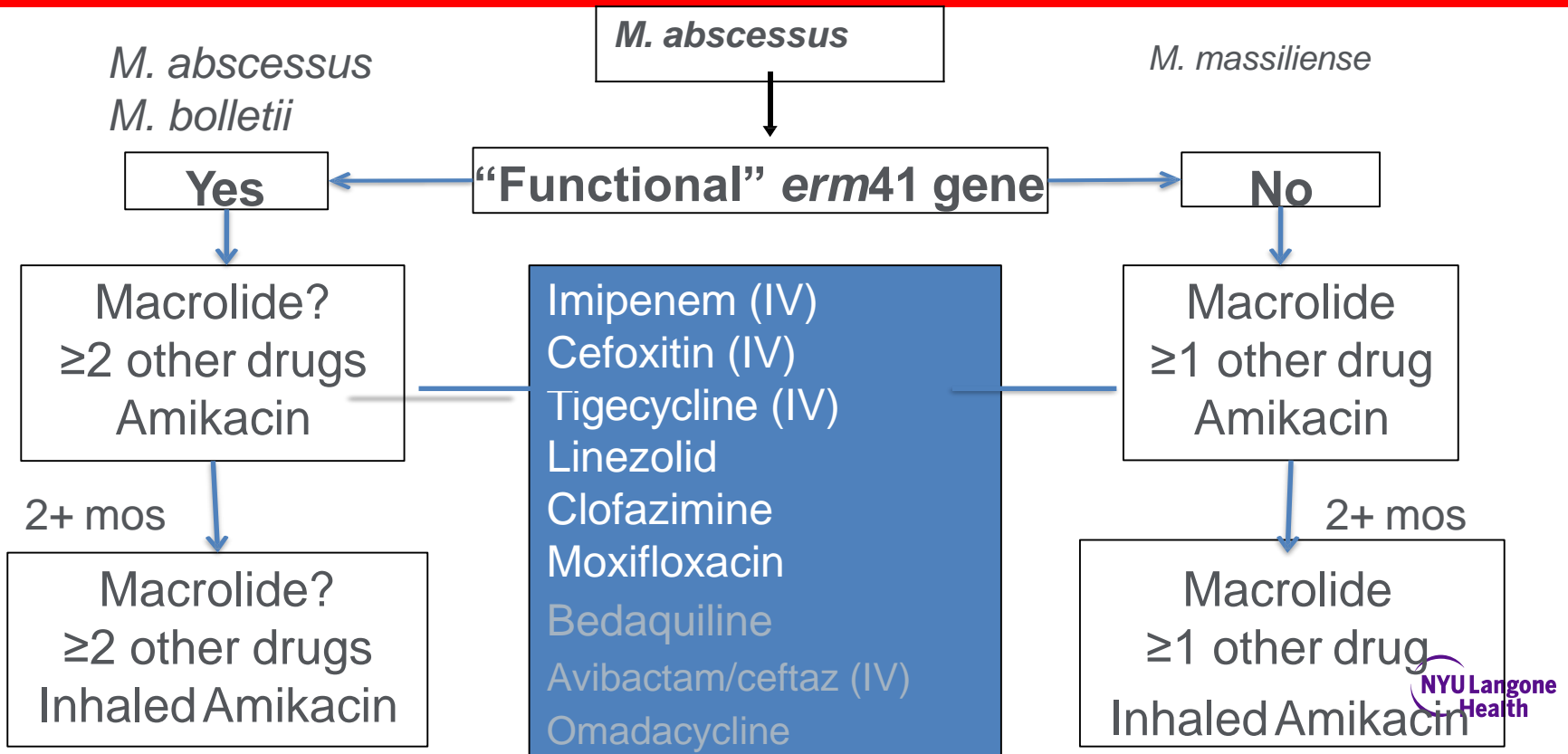


Treatment of *M. abscessus*



Treatment of *M. abscessus*

(Duration 12 months culture negativity)



- **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
 - (**Robotic Surgery in NTM:** Abstract in preparation on NYU experience)
- **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)

Possible Future Treatments

- *New antimicrobial formulations*
 - Oral amikacin
 - Inhaled clofazimine
- *Non antimicrobial drugs*
 - Inhaled GS-CMF
 - Inhaled nitric oxide
- *Other*
 - Bacteriophage

THANK YOU!

