THE STORY OF MYCOBACTERIUM ABSCESSUS

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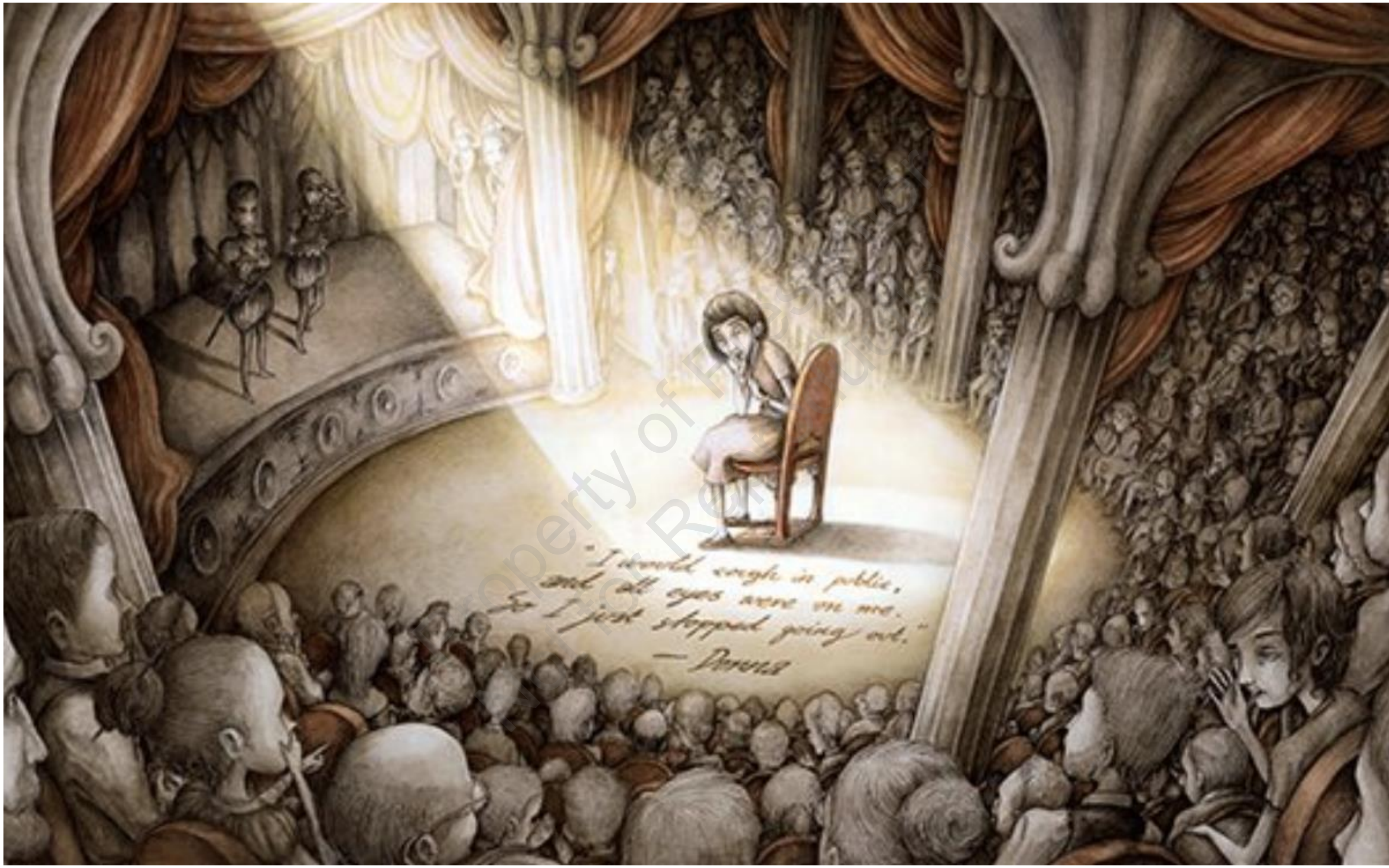
DISCLOSURE

- Consultant: Johnson and Johnson
- Speaker/consultant: Insmed

LEARNING OBJECTIVES

- Examine characteristics of the RGM
- Define the main characters
- Review the epidemiology
- Illustrate clinical manifestations
- Consider therapeutic options, challenges and predictors of outcomes



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RGM: CULTURE

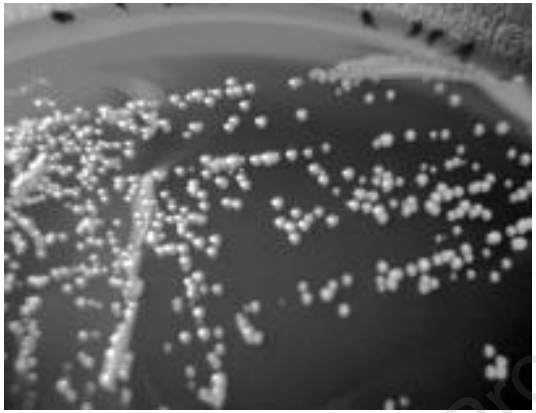
- *In vitro* rapid growth in subculture (usually 3 to 10 days)

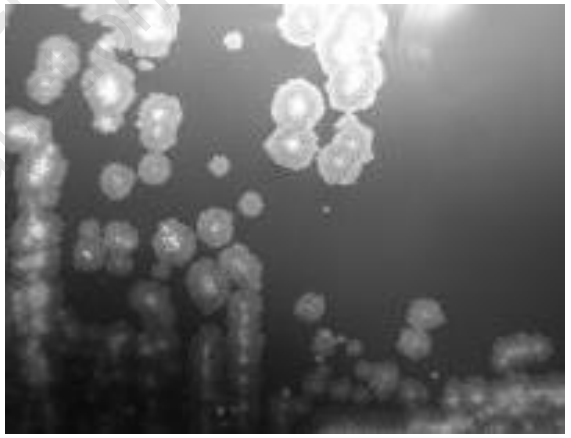
COMMON RAPIDLY GROWING MYCOBACTERIA

- *M. abscessus* complex
  - *M. abscessus*
  - *M. massiliense*
  - *M. bolletii*
- *M. chelonae*
- *M. fortuitum* complex
  - *M. fortuitum*
  - *M. peregrinum*
  - *M. porcinum*

Int J Syst Evol Microbiol. 2017 Aug;67(8):2726-2730

M. ABSCESSUS COMPLEX





Smooth phenotype

Rough phenotype

J Clin Microbiol 2007;45;1497-1504.

M. ABSCESSUS VIRULENCE

Deletion of a dehydratase important for intracellular growth and cording renders rough *Mycobacterium abscessus* avirulent

Iman Halloum[a], Séverine Carrère-Kremer[b,c], Mickael Blaise[a], Albertus Viljoen[a], Audrey Bernut[a], Vincent Le Moigne[d], Catherine Vilchèze[e,f], Yann Guérardel[g], Georges Lutfalla[h], Jean-Louis Herrmann[d], William R. Jacobs Jr.[e,f,1], and Laurent Kremer[a,i,1]

Proc Natl Acad Sci U S A. 2014;111(10):E943-52

Proc Natl Acad Sci U S A. 2016 Jul 19;113(29):E4228-37

MACROLIDE RESISTANCE

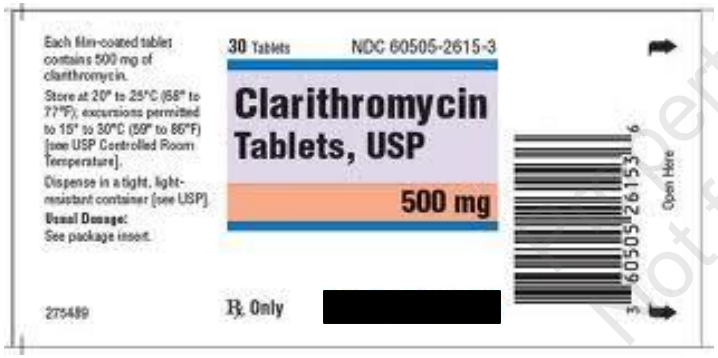
- **Inducible macrolide resistance: R at 14 days incubation**
  - **Ribosomal methylases (erm genes)**
    - *MTB* (erm 37), *M. fortuitum* (erm 39)
    - *M. abscessus* and *M. bolletii* (erm41)

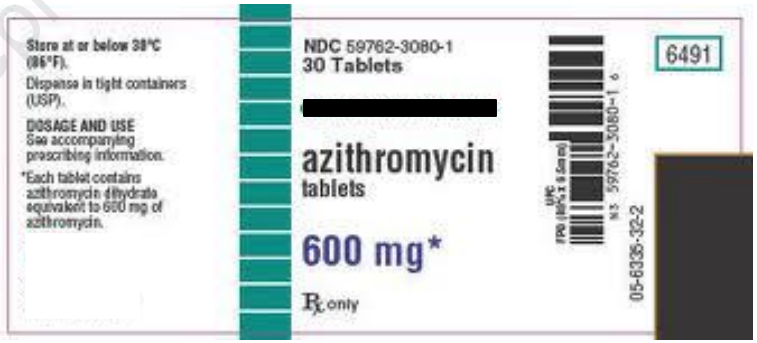
- **Acquired macrolide resistance: R at 3 days incubation**
  - Mutation in the 23S rRNA gene (*rrl*) (infrequent)
  - 17% sputum conversion rate (Koh 2009)

Am Rev Resp Dis 1993;147:A917
Antimicrob Agents Chemother. 2009; 53 :1367-76

MACROLIDE RESISTANCE

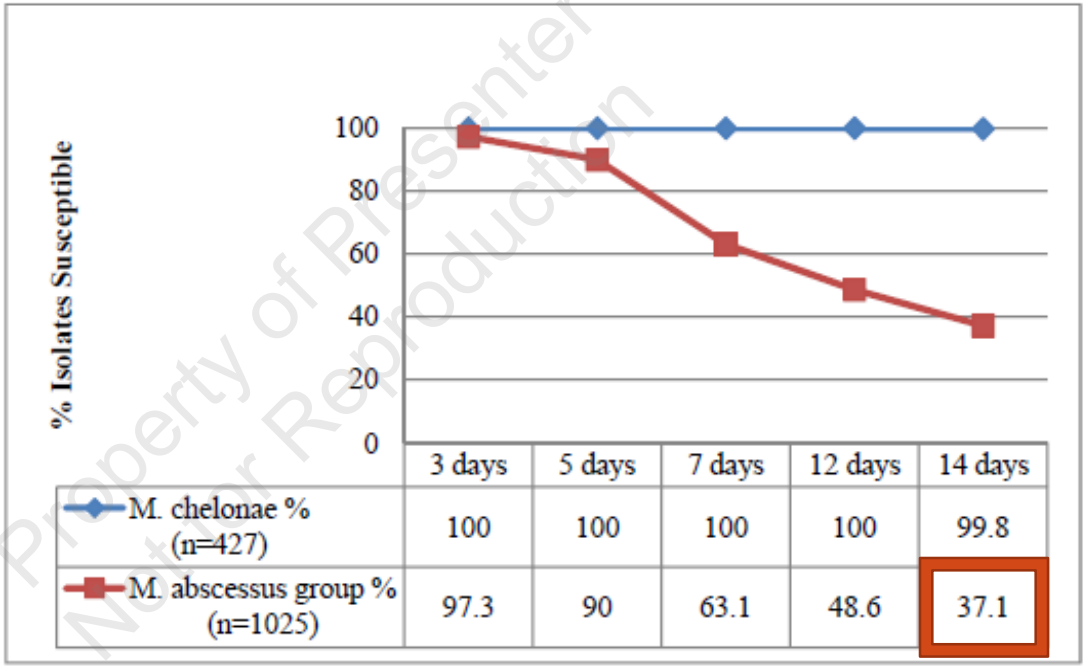
- Not all macrolides are the same…
- Clarithromycin was noted to induce a higher level of macrolide resistance compared to azithromycin with *M. abscessus* isolates





AJRCCM 2012; 186(9):917–925.

CLARITHROMYCIN SUSCEPTIBILITY ARUP DATA



	3 days	5 days	7 days	12 days	14 days
M. chelonae % (n=427)	100	100	100	100	99.8
M. abscessus group % (n=1025)	97.3	90	63.1	48.6	37.1

Summary:

- *Erm*(41) sequencing of MAB compared to 14 day susceptibility
- Agreement was 98.9%

J Clin Microbiol. 2014 May;52(5):1705-7

CLARITHROMYCIN SUSCEPTIBILITY

157 *M. ABSCESSUS SUBSPECIES ABSCESSUS* CLINICAL STRAINS

***M. abscessus* (N 157)**	**N**	**%**
Clarithromycin Susceptible	17	10.8%
Clarithromycin Resistant	35	22.9%
Clarithromycin Inducible Resistance	105	66.88%

J Clin Lab Anal. 2014 Sep;28(5):409-14.

JCM
Journals.ASM.org

Utility of Sequencing the *erm*(41) Gene in Isolates of *Mycobacterium abscessus* subsp. *abscessus* with Low and Intermediate Clarithromycin MICs

Barbara A. Brown-Elliott,[a] Sruthi Vasireddy,[a] Ravikiran Vasireddy,[a] Elena Iakhiaeva,[a] Susan T. Howard,[a] Kevin Nash,[b] Nicholas Parodi,[a] Anita Strong,[a] Martha Gee,[a] Terry Smith,[a] Richard J. Wallace, Jr.[a]

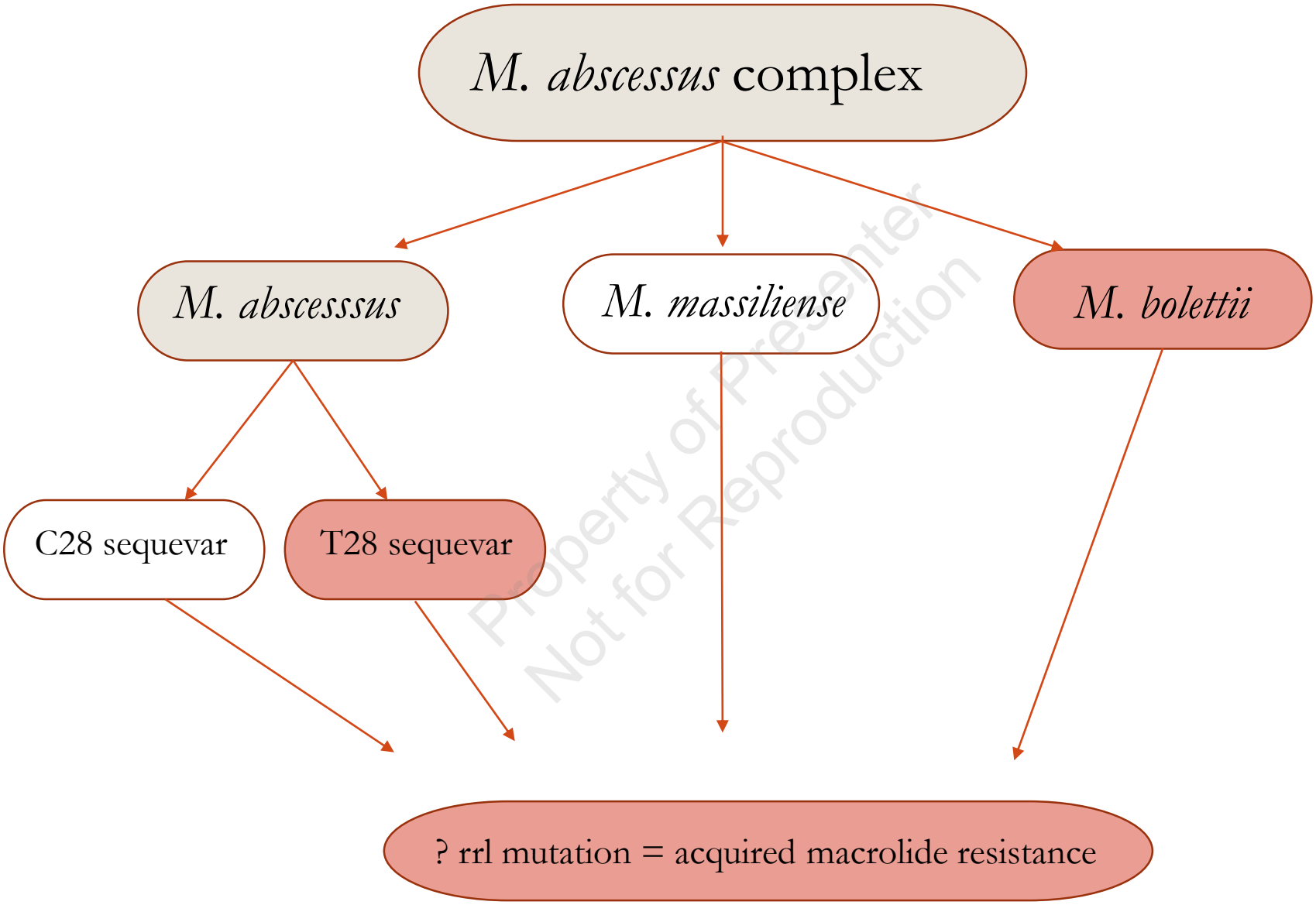
Mycobacteria/Nocardia Laboratory, University of Texas Health Science Center at Tyler, Tyler, Texas, USA[a]; Department of Pathology, Keck School of Medicine of USC, Los Angeles, California, USA[b]

349 clinical *M. abscessus* isolates

Summary of findings

- The T28C substitution in erm(41), associated with macrolide susceptibility, was identified in 62 isolates (18%)

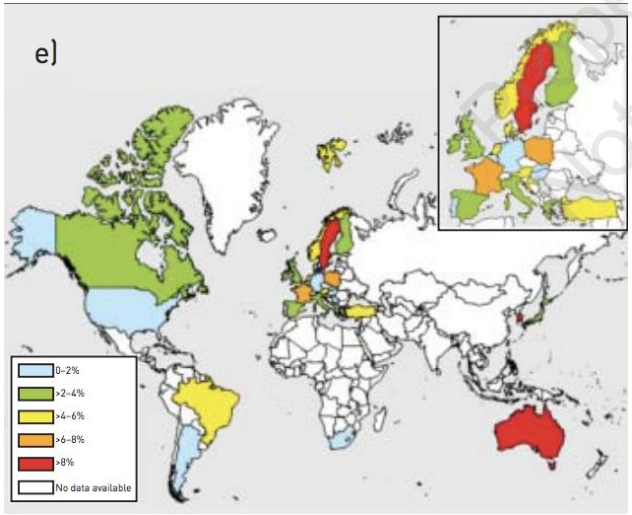
J Clin Microbiol. 2015 Apr;53(4):1211-5



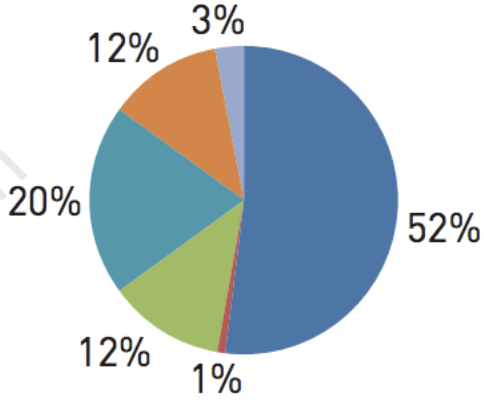
AAC 2009;53:1367-76.

GEOGRAPHIC DISTRIBUTION OF NTM ISOLATES: 2008

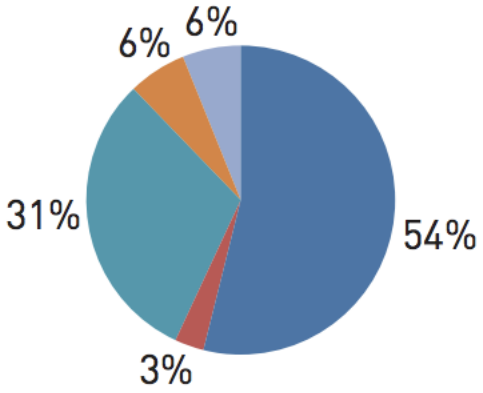
Distribution of NTM
- MAC
- *M. kansasii*
- *M. xenopi*
- *M. malmoense*
- RGM
- *M. gordonae*
- other SGM



North America



Asia



Eur Respir J. 2013 Dec;42(6):1604-13.

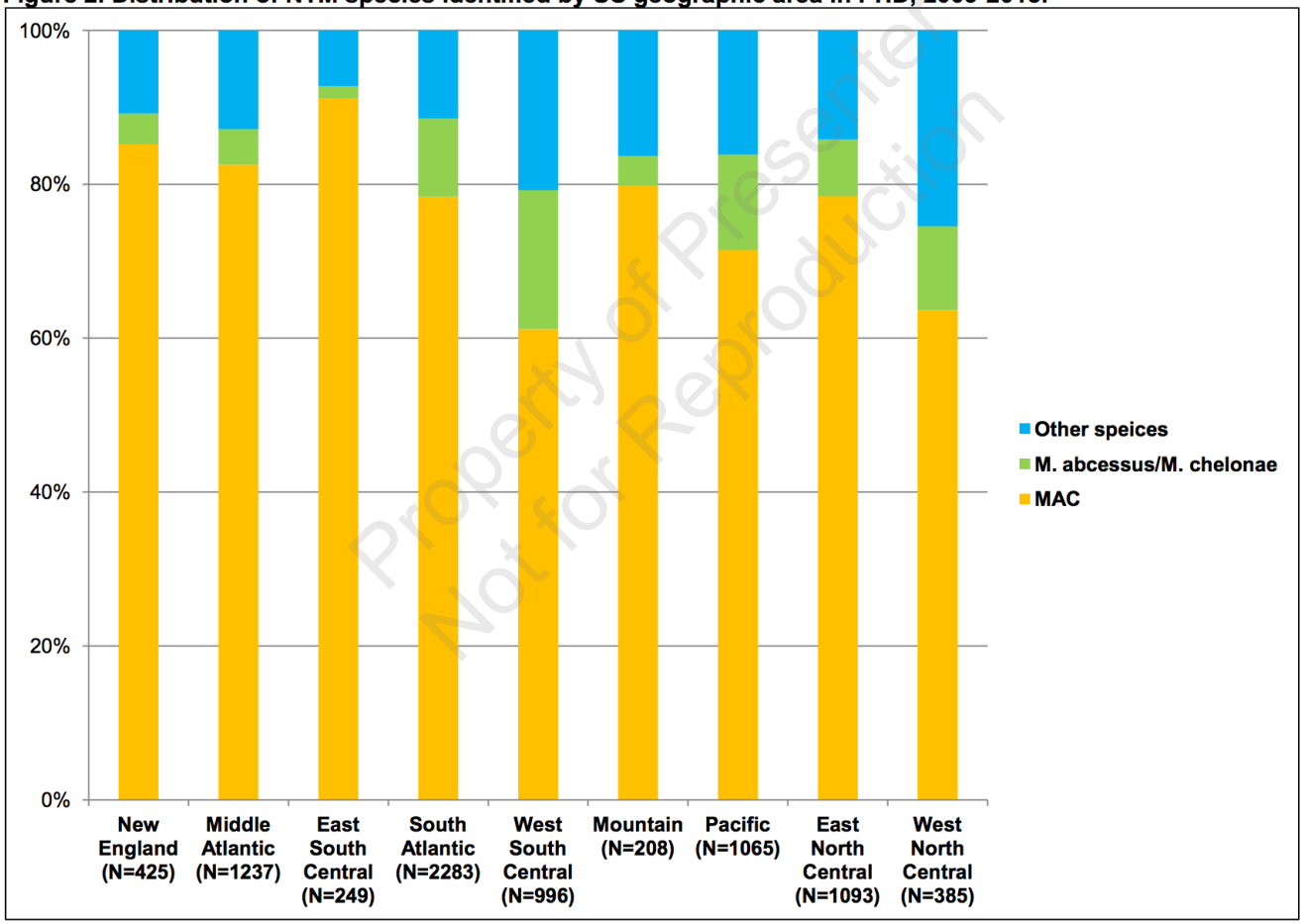
EPIDEMIOLOGY

Location		N	MAC	M.ab/chel	Other
Oregon, USA [1]	2005-2006	407	85%	4%	
New York, USA[2]	2005-2006	81	80%	13%	
Toronto, Canada [3]	2002-2003	255	69%	7%	*M. xenopi* 21%
USA [4]	1994-2006	1865	80%	12%	*M. fortuitum* 6%, *M. kansasii* 6%
Seoul, South Korea [5]	2002-2003	195	48%	33%	*M. fortuitum* 11%

1. CID 2009;49:e124-9.
2. Emerg Infect Dis 2008;14:390-6.
3. Lung 2010;188: 289-99.
4. Am J Respir Crit Care Med 2010; 182:970-6.
5. Chest 2006;129:341-8.

US DISTRIBUTION OF NTM

Figure 2. Distribution of NTM species identified by US geographic area in PHD, 2009-2013.



Ann ATS 2017 Nov;14(11):1655-1661.

EPIDEMIOLOGY IN CYSTIC FIBROSIS

Location	Year	N	Prevalence	MAC	MABSC
France [5]	1996-99	29	9.8%	21%	52%
USA [1]	2003	128	13%	72%	9%
France [2]	2004	104	6.6%	22%	48%
North Carolina, USA [3]	2000-2007	166	11%	59%	41%
Scandinavia [4]	2000-2012	157	11%	32%	45%
UK [6]	2007-2009		3.3-5%	68-62%	27-28%

MABSC: *M. abscessus* complex

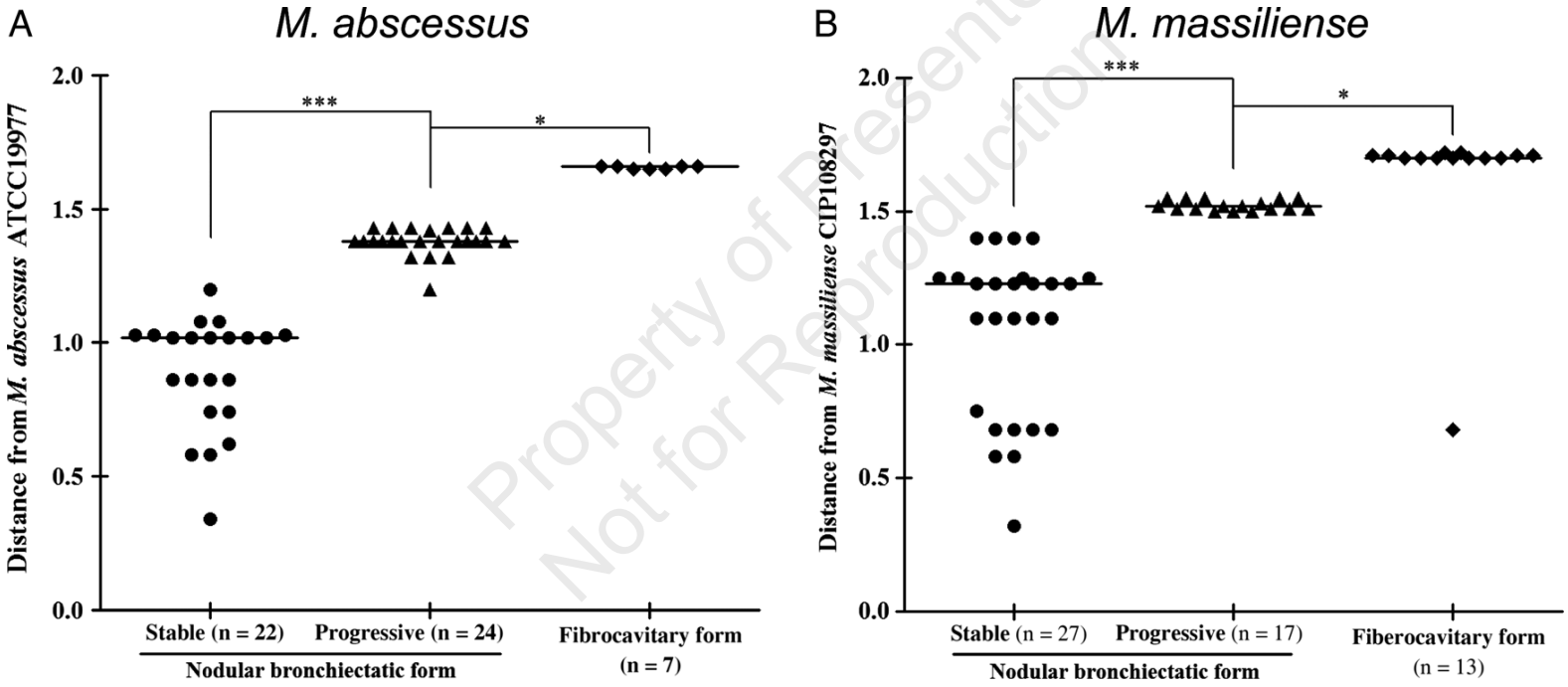
1. Am J Respir Crit Care Med 2003;167:828–834.
2. J Clin Microbiol 2009;47:4124-8.
3. J Cyst Fibros 2010;9:117-23.
4. J Cyst Fibros. 2015 Jan;14(1):46-52.
5. Emerg Infect Dis 2003;9:1587-91.
6. Emerg Infect Dis 2013;19:1128-30.

CLINICAL RELEVANCE OF ISOLATION

- N= 95
- *M. abscessus*
  - 50% (9/18) met ATS criteria
- *M. massiliense*
  - 29% (2/7) met ATS criteria
- *M. bolletii*
  - 20% (1/5) met ATS criteria

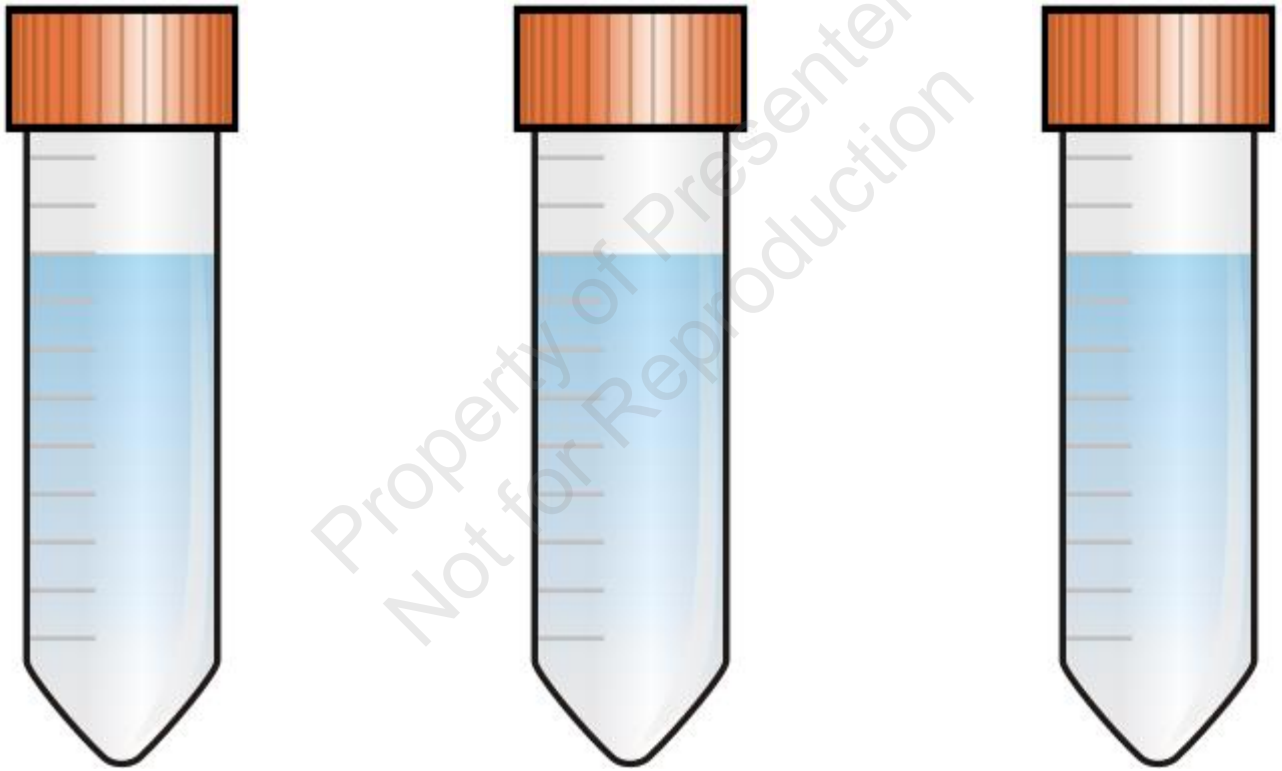
J Infect 2009;59:324-331.

GENOTYPING TO PREDICT RELEVANCE



J Clin Microbiol. 2012;50(9):3084-3088
Clin Infect Dis. 2013;57(1):32-39
Clin Microbiol Infect. 2013;19(10):E473-E482.

DIAGNOSIS



Three separate early morning sputum specimens. Expectorated-**Induced**-BAL

DIAGNOSIS

- Smear nonspecific
- No commercial DNA probes
- HPLC not species specific
- Biochemical testing
  - (salt tolerance, citrate utilization)
- Drug susceptibility testing
  - (MAB: usually Cefoxitin S)

- **Molecular methods**
  - rpoB
  - ERM 41

DIAGNOSIS

- Drug Susceptibility testing
  - Broth micro dilution
    - All clinically significant isolates
    - Any isolate from treatment failure/relapse

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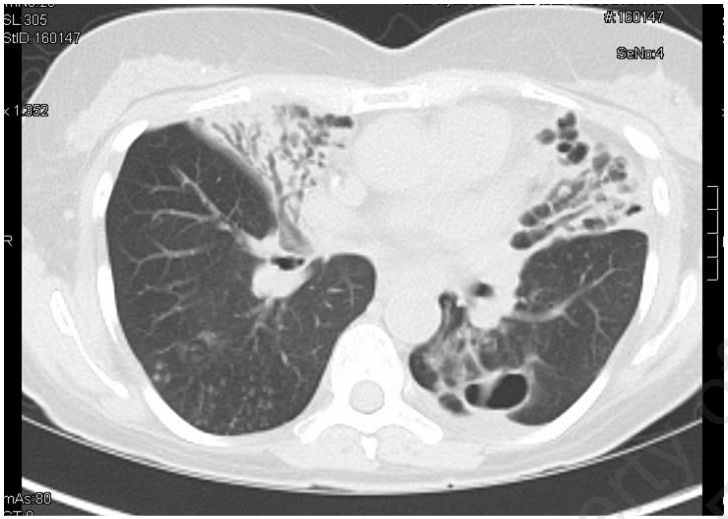
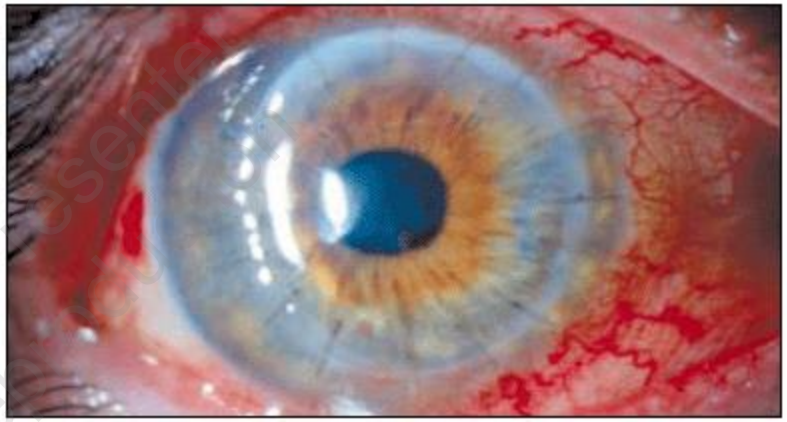
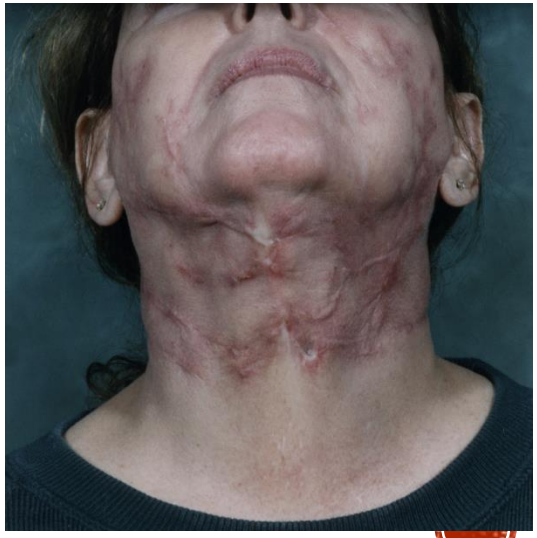
CLINICAL MANIFESTATIONS

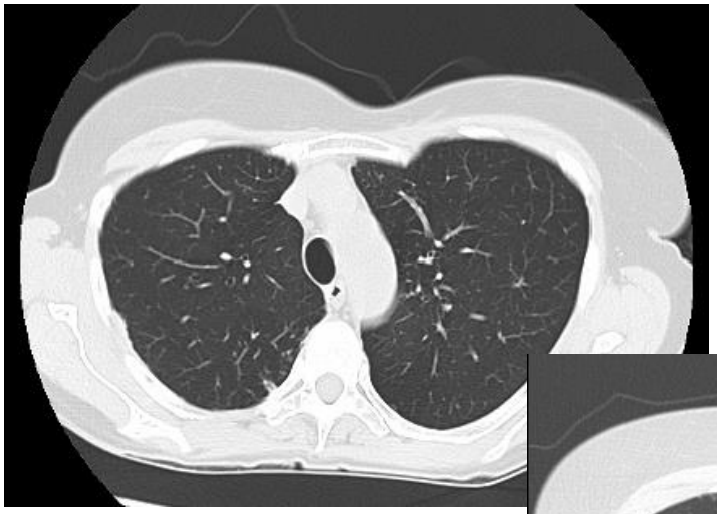






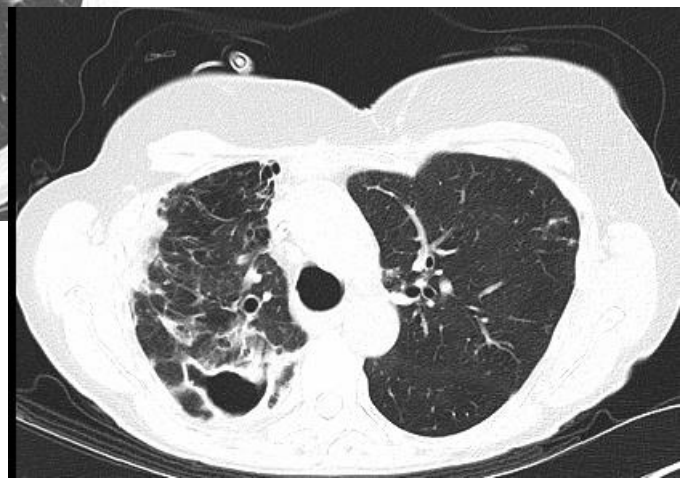
CLINICAL MANIFESTATIONS

2003



2013

2017




"WHEN YOU CAN'T GET A GOOD NIGHT'S SLEEP FOR YEARS, YOUR WHOLE LIFE CHANGES"
-MARILYNN

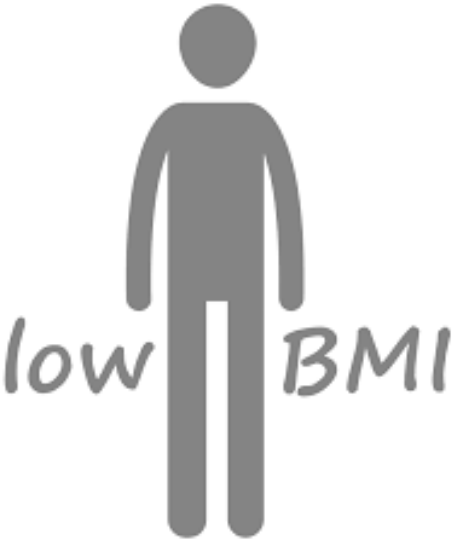
CLINICAL MANIFESTATIONS

Table 1. Baseline characteristics of patients infected with CLA-resistant and -sensitive *M. abscessus* genotypes[a]

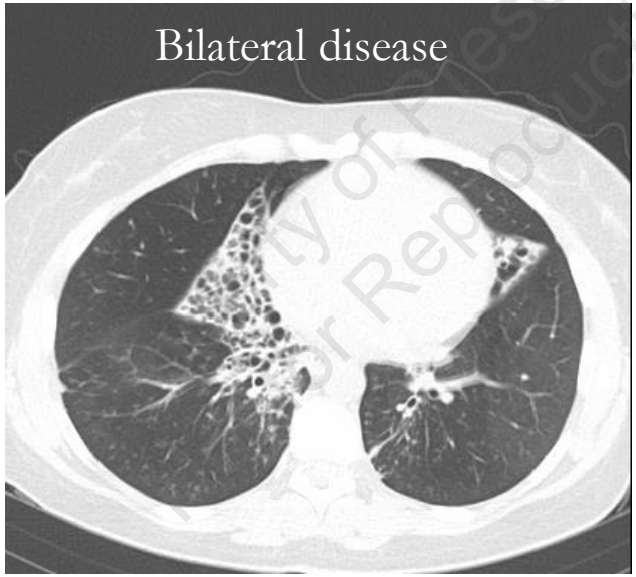
Characteristic	Resistant group (n=69)	Sensitive group (n=31)	*P* value
Age, median (IQR, years)	58 (44-66)	56 (32-64)	0.562
Males, n (%)	26 (37.7)	17 (54.8)	0.107
BMI, mean ± SD (kg/㎡)	19.93 ± 0.37	19.69 ± 0.57	0.729
Symptoms			
Cough, n (%)	55 (79.7)	25 (80.6)	0.914
Sputum, n (%)	69 (100.0)	31 (100.0)	1
Fever, n (%)	15 (21.7)	4 (12.9)	0.298
Hemoptysis, n (%)	22 (31.9)	4 (12.9)	0.045
Disease pattern			
Bronchiectasis	66 (95.7)	29 (93.4)	0.655
Cavity	50 (72.5)	8 (25.8)	<0.001
Nodules (d < 1 cm)	38 (55.0)	19 (61.3)	0.561
Nodules (d>1cm)	39 (56.5)	16 (51.6)	0.648
Tree-in-bud pattern	16 (23.2)	14 (45.2)	0.027

Guo et al. Antimicrob Agents Chemother 2018, Feb 26 epub

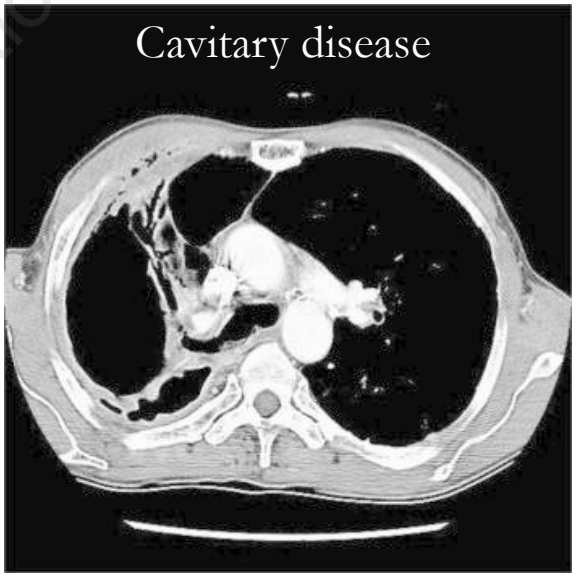
PREDICTORS OF PROGRESSION



OR 4.79 (1.39–16.48)
p 0.13



OR 3.83 (1.06–13.82)
p 0.04



OR 3.62 (1.02–12.82)
p 0.46

CID 2017;64(3):301–8.

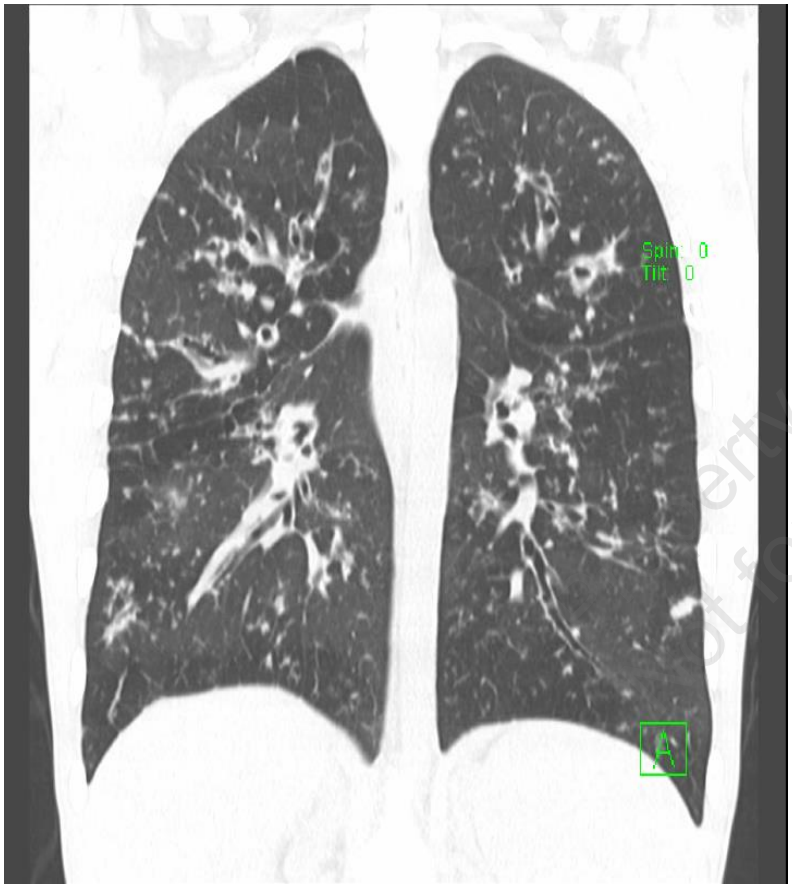
Clinical Manifestations of NTM Isolation in Cystic Fibrosis

Prospective, Case Controlled

- 60 incident NTM positive patients
  - *M. abscessus* (n=7)
- 99 matched controls
- Followed patients for 15 months
  - Rate of FEV1 decline was the same
  - Rate of progression of CT findings was higher in the group that met ATS criteria for pNTM

AJRCCM 2003;167;835-840.

M. ABSCESSUS IN CYSTIC FIBROSIS



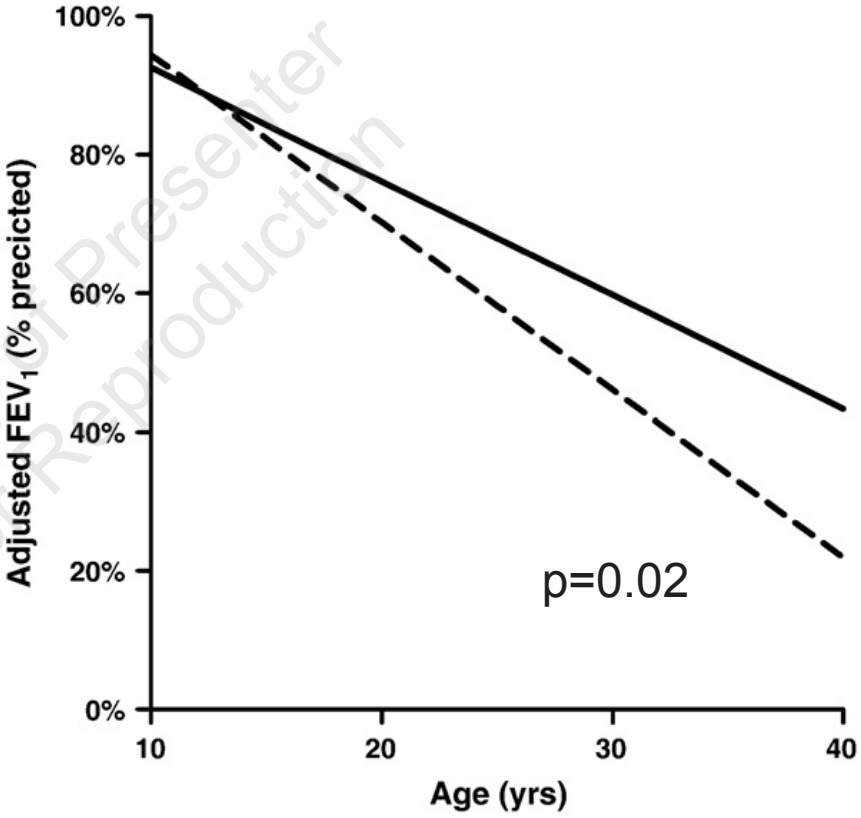
6/2009

8/2010

CLINICAL MANIFESTATIONS OF NTM INFECTION: CF

RETROSPECTIVE ANALYSIS AT UNC

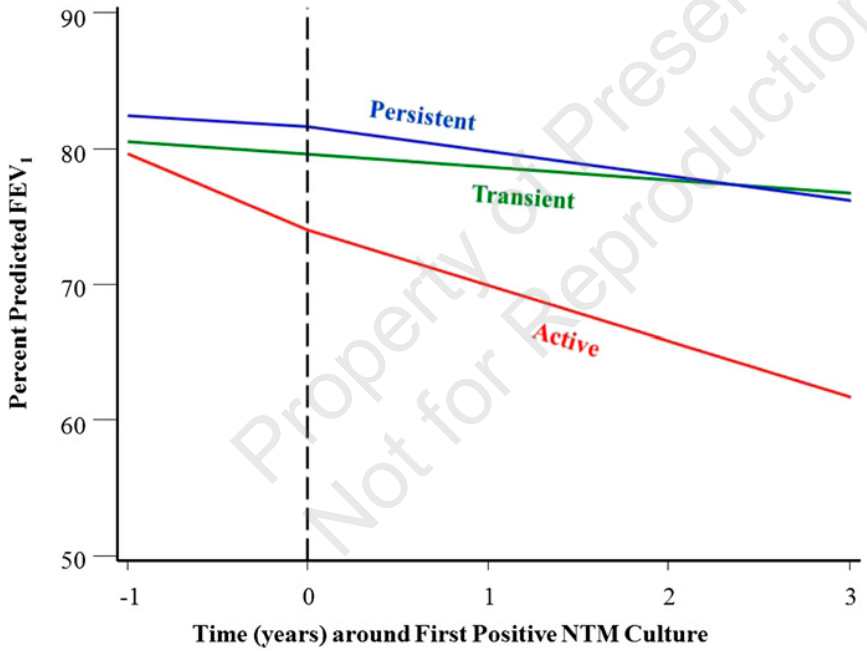
- 1216 CF pts over 8years
  - changes in FEV1 % adjusted for confounders.
  - No NTM infection
    - (solid line)
  - Chronic *M. abscessus*
    - (dashed line n=23)



J Cyst Fibros 2010: 9(2): 117-123.

CLINICAL IMPACT OF NTM INFECTION: CF

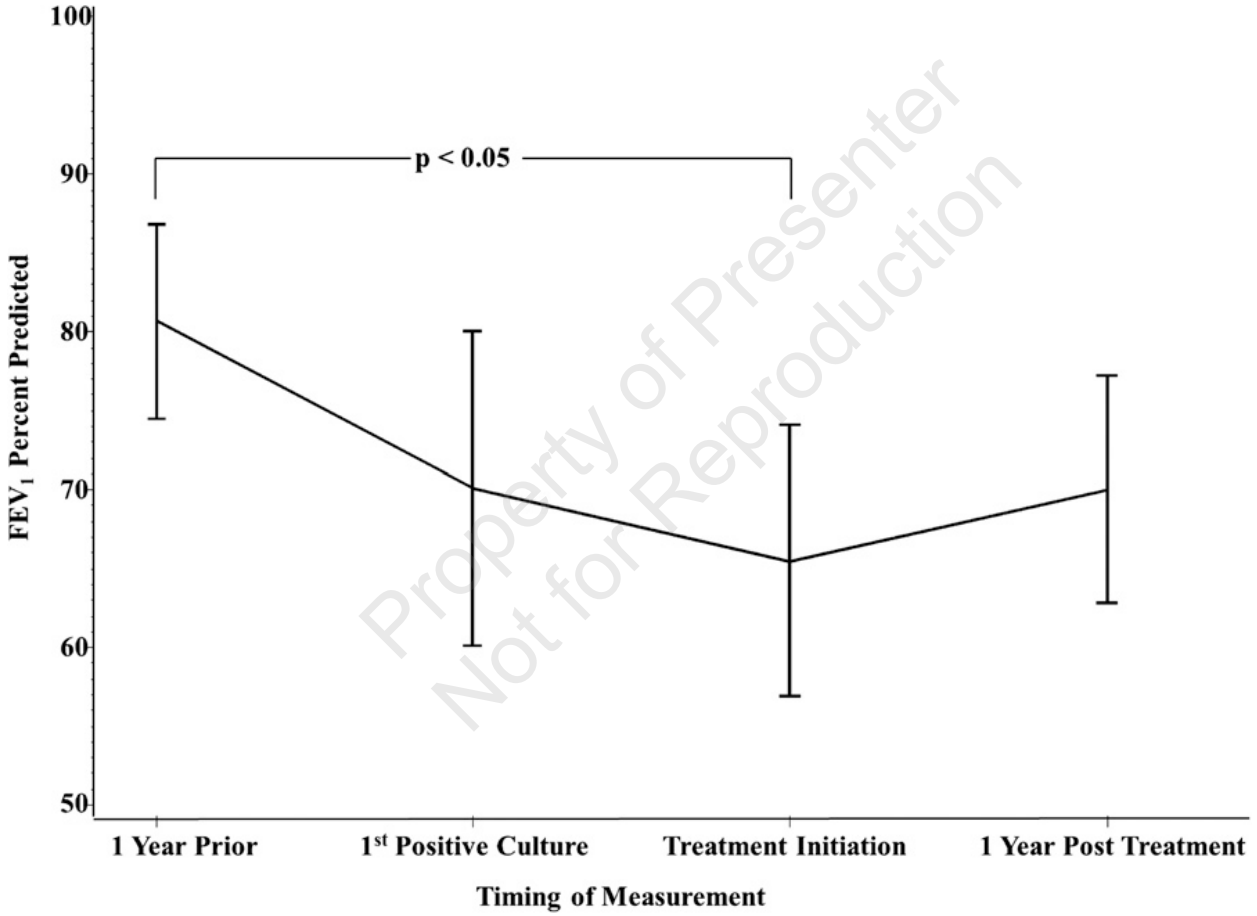
- N:150 pediatric and adult CF patients 2000-2010
- MAC 69-75%, MABSC 21-27%



- Adults: lower FEV1, higher rates of pseudomonas
- 26% had a second NTM at 5 years, 36% at 10 years

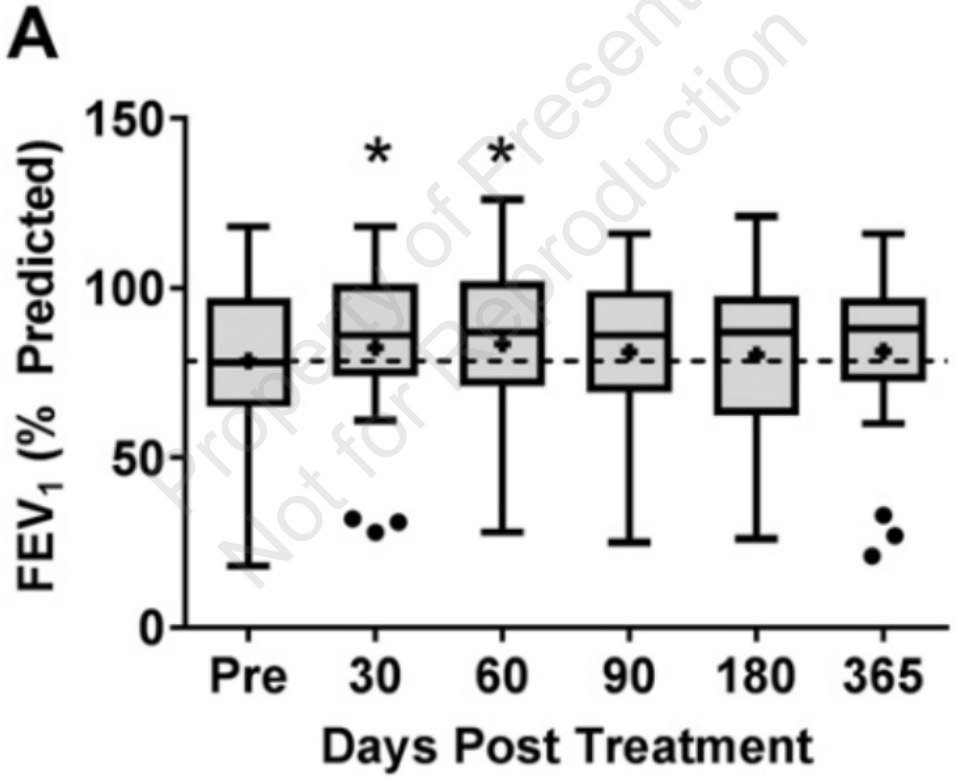
Ann Am Thorac Soc 2014;11:36-44.

CLINICAL IMPACT OF NTM INFECTION IN CF



Ann Am Thorac Soc 2014;11:36-44.

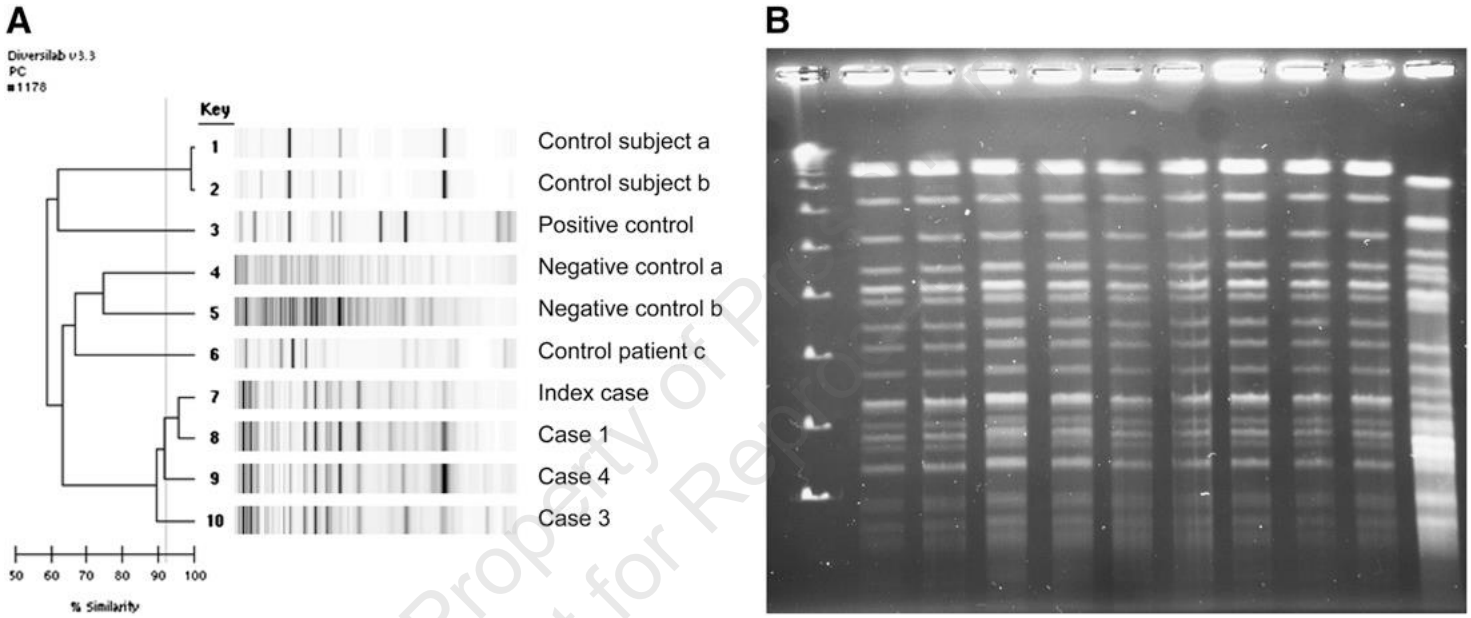
UNC: RETROSPECTIVE STUDY OF CF AND M. ABSCESSUS (N=41)



J of Cyst Fibros 16 (2017) 483–487.

"The patient in the next bed is highly infectious. Thank God for these curtains."

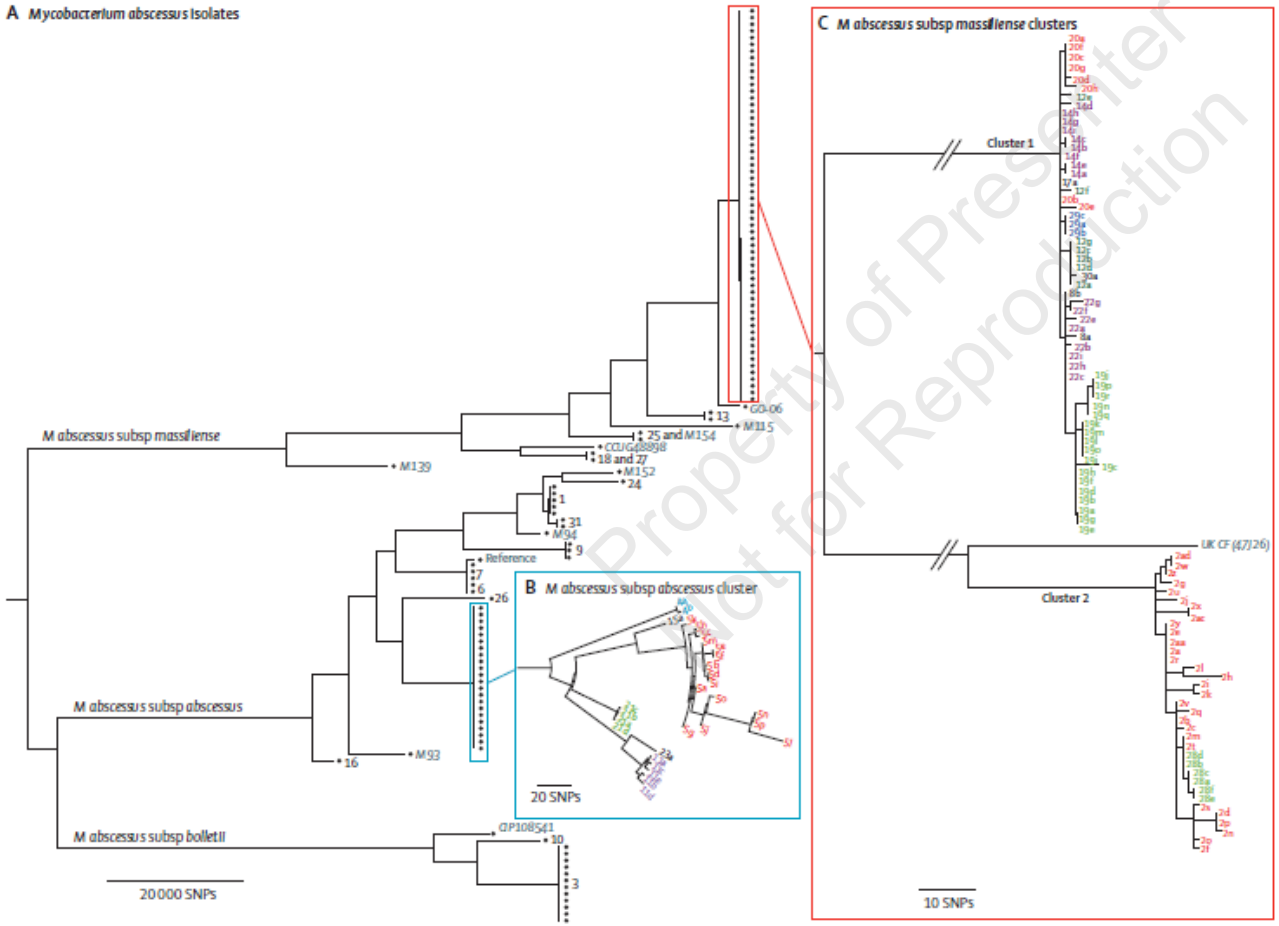
OUTBREAK OF *M. MASSILIENSE* IN A CF CLINIC



- Index case: 4+ smear positive
- 8 months later 4 additional cases were identified
- 3/5 patients died due to mycobacterial infection

AJRCCM 2012; 185: 231-32.

CLUSTERS OF IDENTICAL *M. MASSILIENSE* IN CF CLINIC IN UK



- Whole genome sequencing
- 168 isolates
- 31 patients
- 2007-2011
- Parallel environmental testing
- 2 cluster outbreaks from 11 patients

Lancet 2013:381:1551-60

RGM DRUG SUSCEPTIBILITY PROFILE

Table 1. MIC_{50} and MIC_{90} (mg/L) of 15 antibiotics (determined at the ERT) for 165 clinical isolates of *M. abscessus* with regard to the s

	M. abscessus (n=165)			*abscessus* C28 (n=18)		*abscessus* T28 (n=94)	
Antibiotic	MIC_{50}	MIC_{90}	MIC range (mg/L)	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Clarithromycin	0.25	8	0.06 to >16	0.25	0.5	0.5	>16
Amikacin	16	32	2 to >64	16	64	16	64
Tobramycin	16	>16	4 to >16	>16	>16	16	>16
Cefoxitin	32	64	8 to 128	32	64	32	64
Imipenem	16	>64	4 to >64	16	64	16	≥64
Linezolid	16	32	≤1 to >32	32	32	16	32
Tigecycline	0.25	1	0.015 to ≥4	0.25	1	0.5	1
Doxycycline	>16	>16	1 to >16	>16	>16	>16	>16
Minocycline	>8	>8	2 to >8	>8	>8	>8	>8
Ciprofloxacin	>4	>4	0.5 to >4	>4	>4	>4	>4
Moxifloxacin	>8	>8	1 to >8	8	>8	8	>8
Trimethoprim/sulfamethoxazole	>8/152	>8/152	<0.25/4.75 to >8/152	>8/152	>8/152	>8/152	>8/152
Cefepime	>32	>32	16 to >32	>32	>32	>32	>32
Ceftriaxone	>64	>64	8 to >64	>64	>64	>64	>64
Co-amoxiclav	>64/32	>64/32	2/1 to >64/32	>64/32	>64/32	>64/32	>64/32

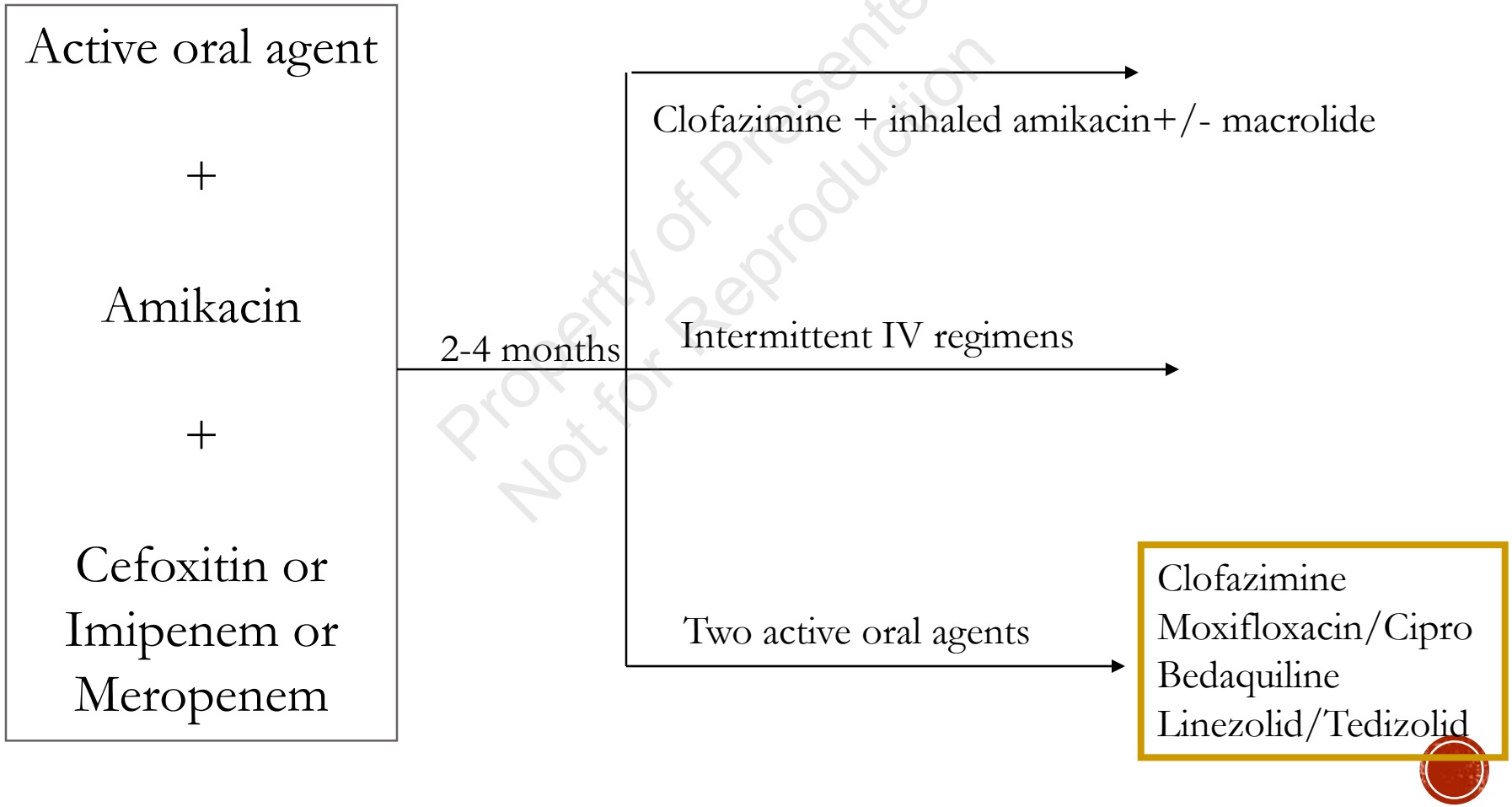
MICs were determined using RAPMYCO sensititre plates (see the text).
ERT was defined as the first day when the growth control was positive (median=5 days).
Sequevars are those of the subspecies *M. abscessus* subsp. *abscessus* (*abscessus*), *M. abscessus* subsp. *bolletii* (*bolletii*) and *M. abscessus* s
erm41 sequevars are distinguished among *M. abscessus* subsp. *abscessus* isolates: one containing a T nucleotide at position 28 (*absce*
position 28 (*abscessus* C28).

J Antimicrob Chemother 2016; 71: 2208–2212.

TREATMENT OF RGM

www.pinsdaddy.com

TREATMENT OF *M. ABSCESSUS COMPLEX* LONG-TERM TREATMENT REGIMENS



TREATMENT OUTCOMES

Location	U of Texas	National Jewish Health	Samsung Medical
N	154 [1]	69 [2]	65 [3]
Medical alone	147	46	
Median duration of Rx		50 mo.	24 mo.
Medical + Surgery	7	23	14 (22%)
Conversion without relapse	10 (6%)	33 (48%)	**88% MMA** **25% MAB**
Failure	144(94%)	36 (52%)	12%MMA 75% MAB
Mean follow up		34 mo	36 mo (32)

1.Am Rev Respir Dis. 1993;147(5):1271-8.
2.CID 2011 Mar 1;52(5):565-71.
3. AJRCCM. 2009 180:896-902.

TREATMENT OUTCOMES: KOREAN EXPERIENCE ASAN MEDICAL CENTER

N	41[1]	48[2]	
	MAG	MAB	MMA
Medical	41	26	22
Median duration antibiotics (mo)	17	16.3	12.1
Medical + Surgery	13 (31.7%)	8 (30.7%)	1 (4.5%)
Conversion without relapse	**29 (70.7%)**	**8 (30.7%)**	**17 (77.3%)**
Failure	9 (21.9 %)	11 (42.3%)	1 (4.5%)
Default	3 (7.3%)	4	0
Median f/u after Rx (mo)	14.8	48.2	48.2

MAG: *M abscessus* group
MAB: *M. abscessus*
MMA: *M. massiliense*

Respiratory Medicine 2011; 105: 781-787
Respiratory Medicine 2014; 108: 1706-1712

TREATMENT OUTCOMES: SHANGHAI HOSPITAL

Table 4. Treatment outcomes of CLA-resistant and -sensitive genotype groups

	Resistant group (n=69)	Sensitive group (n=31)	*P* value
Median duration of treatment, mo (IQR)	18 (9-30)	15 (9-22)	0.260
Sputum result			0.013
Conversion to stable negative	21 (30.4)	19 (61.3)	
Failure to convert	39 (56.5)	9 (29.0)	
Relapse after conversion to negative	9 (13.0)	3 (9.7)	
Initial smear/culture conversion			
Number of patients who initially convert	30 (43.5)	22 (71.0)	0.011
Median time to initial conversion, mo (IQR)	12 (6-23)	7 (5-11)	0.004
Radiological result			
Improved	25 (36.2)	22 (71.0)	0.006
No change	24 (34.8)	5 (16.1)	
Progressed	20 (30.0)	4 (12.9)	
Final treatment response			
Effective	30 (43.5)	26 (83.9)	<0.001
Failure	39 (56.5)	5 (16.1)	

Guo et al. Antimicrob Agents Chemother 2018, Feb 26 epub

PREDICTORS OF FAVORABLE OUTCOME

Table 5. Predictors of Sustained Culture Conversion Among the 36 Patients Treated for *Mycobacterium abscessus* or *Mycobacterium massiliense* Lung Disease

Variable	Unadjusted Odds Ratio (95% CI)	*P* Value	Adjusted[a] Odds Ratio (95% CI)	*P* Value
BMI[b]				
≥18.5 kg/m^2	1.00	.011	1.00	.021
<18.5 kg/m^2	0.15 (.03–.64)		0.08 (.01–.69)	
NTM species				
M. abscessus	1.00	.002	1.00	.007
M. massiliense	13.07 (2.61–65.48)		17.23 (2.17–136.85)	
Initial macrolide				
Clarithromycin	1.00	.053	1.00	.041
Azithromycin	4.00 (.98–16.31)		9.03 (1.09–74.70)	
Susceptibility to clarithromycin				
Not susceptible	1.00	.001		
Susceptible	27.5 (3.91–193.49)			

- Higher BMI
- *M. massiliense*
- Azithromycin use
- Macrolide susceptible

CID 2017;64(3):301–8.

PROSPECTIVE OBSERVATIONAL STUDY OF 4 WK VS. 2 WK IV THERAPY IN M. MASSILIENSE

TABLE 3] Treatment Outcomes

Treatment Outcome Data	4-Week IV Group (n = 28)	2-Week IV Group (n = 43)	*P* Value
After 12 mo of treatment, No. (%)			
Symptomatic improvement	25 (89)	43 (100)	.057
HRCT scan improvement	22 (79)	39 (91)	.177
Sputum culture conversion	28 (100)	39 (91)	.148
Sputum culture conversion at the end of treatment, No. (%)	28 (100)	42 (98)	1.000
Follow-up duration after treatment completion, mo	33.8 (12.3-50.3)	14.7 (0.5-29.5)[a]	.006
Microbiologic recurrence, No. (%)	2 of 28 (7)	3 of 42 (7)[a]	1.000

CHEST 2016; 150(6):1211-1221

PREDICTORS OF FAVORABLE OUTCOMES

Table 3. Comparison of the Mycobacterial Characteristics of Pretreatment *Mycobacterium abscessus* Isolates According to Treatment Outcomes

Mycobacterial Characteristics	Patients With Final Negative Conversion (n = 20)	Patients With Persistently Positive Cultures (n = 24)	*P* Value
Initial morphotype			
Smooth	9 (45)	2 (8)	.020
Mixed (smooth + rough)	4 (20)	8 (33)	
Rough	7 (35)	14 (58)	
Initial susceptibility to clarithromycin			
Susceptible	7 (35)	1 (4)	.015
Inducible resistance	13 (65)	23 (96)	
Resistant	0	0	
Initial 28th sequevar of *erm*(41)			
C28	6 (30)	1 (4)	.035
T28	14 (70)[a]	23 (96)	
Initial *rrl* mutation			

Data are presented as medians (interquartile ranges) or numbers (%).

[a] An isolate from 1 patient had a C19→T point mutation in the *erm*(41) gene, and this isolate was susceptible to clarithromycin [16].

- Smooth phenotype
- Susceptible to clarithromycin
- C28 sequevar of the ERM 41
- 13/14 (93%) culture conversion in C28 sequevar *

CID 2017;64(3):309–16.
*Diagn Microbiol Infect Dis. 2017

OUTCOMES WITH ACQUIRED MACROLIDE RESISTANCE IN M. ABSCESSUS (N=13)

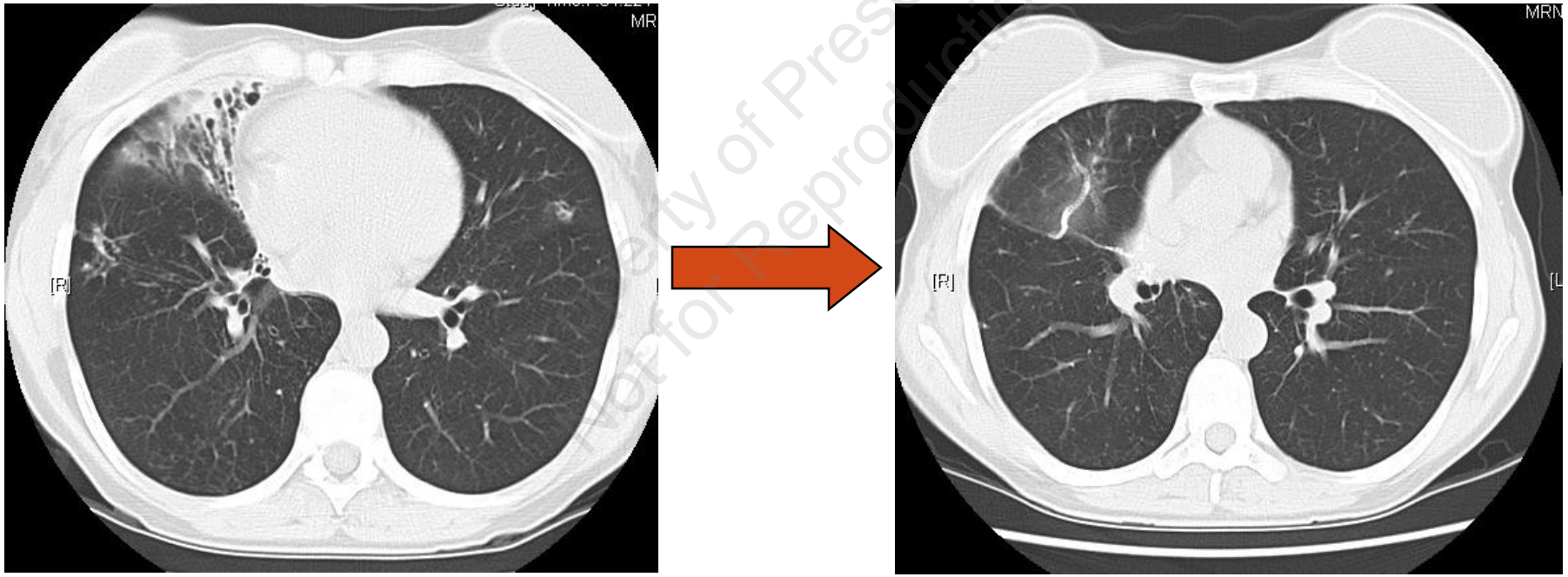
TABLE 3 Treatment modalities and outcomes after detection of macrolide-resistant *M. abscessus* subsp. *abscessus* lung disease[a,b]

Treatment modality	Value
Antibiotic therapy	
Amikacin	6 (46)
Cefoxitin or imipenem	6 (46)
Macrolide	11 (85)
Fluoroquinolone	1 (8)
Clofazimine	10 (77)
Amikacin inhalation	7 (54)
Surgical resection	2 (15)
Total treatment duration, mo	24.0 (16.0–43.0)
Treatment outcome	
Favorable outcome	0
Sputum culture conversion after surgery	1 (8)

[a]The total number of patients in the study was 13.
[b]Data are presented as number (percent) or as median (interquartile range).

Antimicrob Agents Chemother. 2017 Sep 22;61(10).

TREATMENT OF *M. ABSCESSUS*
SURGERY



TREATMENT OUTCOMES FOR *M. ABSCESSUS* LUNG DISEASE NATIONAL JEWISH HEALTH

Culture Conversion	Total N (%)	Medical N (%)	Surgical + Medical N (%)	P-value
Converted, no relapse	33 (48%)	18 (39%)	15 (65%)	0.049
Never converted or converted then relapsed	36 (52%)	28 (61%)	8 (35%)	

CID 2011 Mar 1;52(5):565-71

ALTERNATIVE THERAPY: CLOFAZIMINE
CLOFAZIMINE + AMIKACIN= SYNERGY

Species	N	Clofazimine		Amikacin		% (n) Synergy	MIC for combination
		MIC50	MIC90	MIC50	MIC90		Clofazimine / amikacin
M.abscessus	133	≤0.5	2.0	16.0	32.0	85 (46)	≤0.5 / 2.0 (MIC50) 1.0 / 2.0 (MIC90)
M. chelonae	17	≤0.5	1.0	8.0	32.0	100 (3)	≤0.5 / 2.0
M. fortuitum	42	≤0.5	≤0.5	≤2.0	16.0	50 (2)	≤0.5 / 2.0

CFZ: MIC ≤0.5 and 1.0 (S), 2.0 (I), >4 (R)
AMK: MIC ≤16 (S), 32 (I), >64 (R)

Antimicrob Agents Chemother. 2012;56(12):6324-7.

CULTURE CONVERSION WITH CLOFAZIMINE

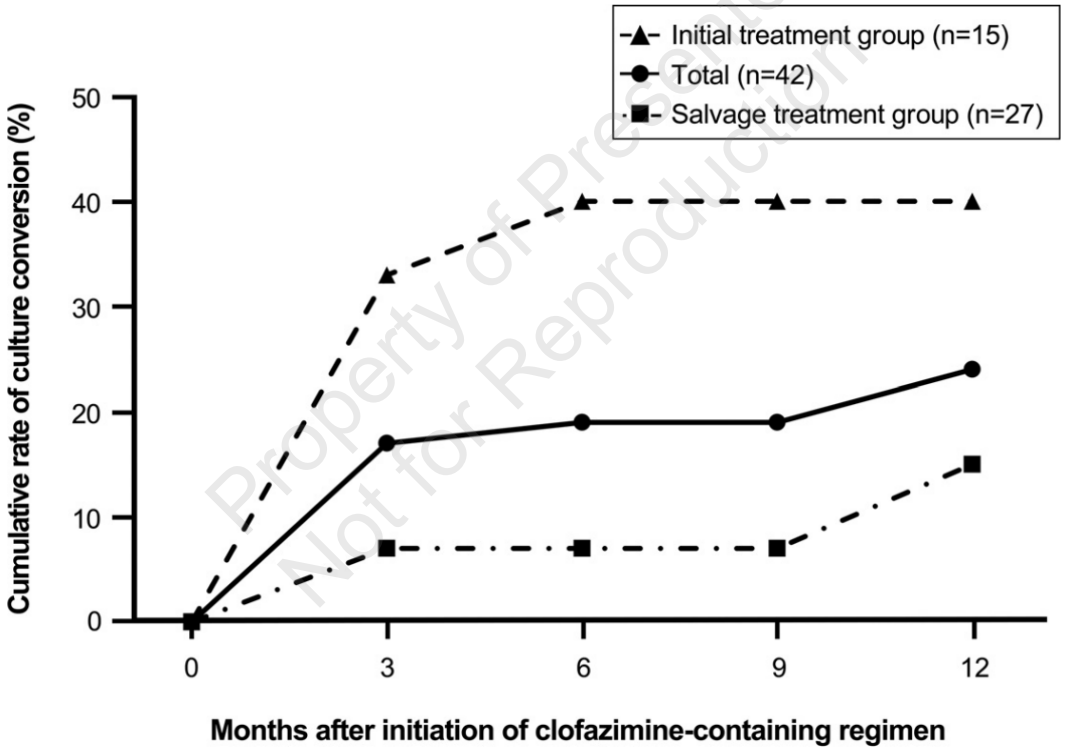
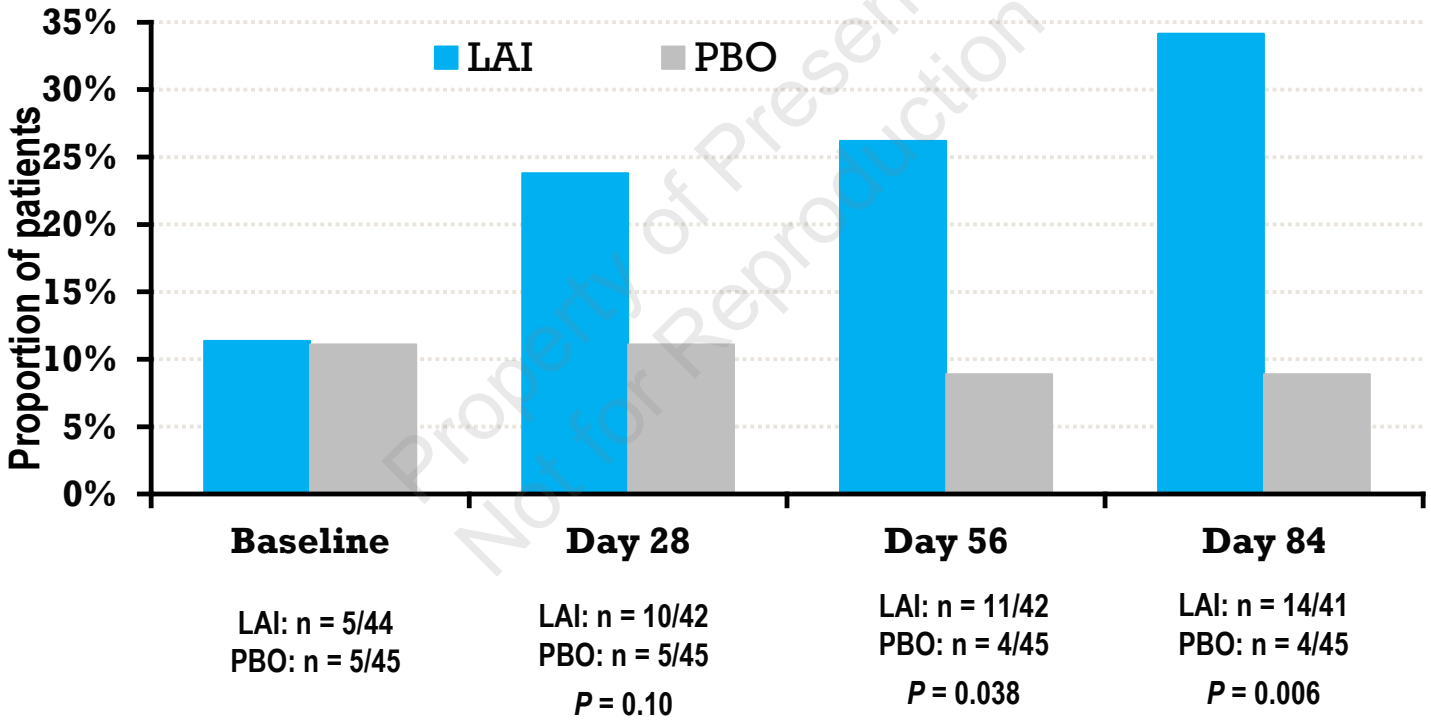


FIG 1 Cumulative sputum culture conversion rates after patients started a clofazimine-containing regimen.

Antimicrob Agents Chemother 2017: 61(6) e02052-16.

INHALED LIPOSOMAL AMIKACIN

Proportion of Patients With Negative Sputum Cultures for NTM



LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; NTM, nontuberculous mycobacteria; PBO, placebo.

Olivier KN, et al. Am J Respir Crit Care Med 2017;195:814

ALTERNATIVE THERAPY: TIGECYCLINE

Baseline Characteristics	Pulmonary (36)
Age (years) mean	35.2
Female sex	80.6%
Cystic fibrosis	58.3%
Prior M. abscessus antibiotic therapy	88.5%
Tigecycline < 1 month	10 (27%)
Tigecycline >1 month	26 (72%)
Median duration	161 days

J Antimicrob Chemother. 2014 Mar 14

ALTERNATIVE THERAPY: TIGECYCLINE

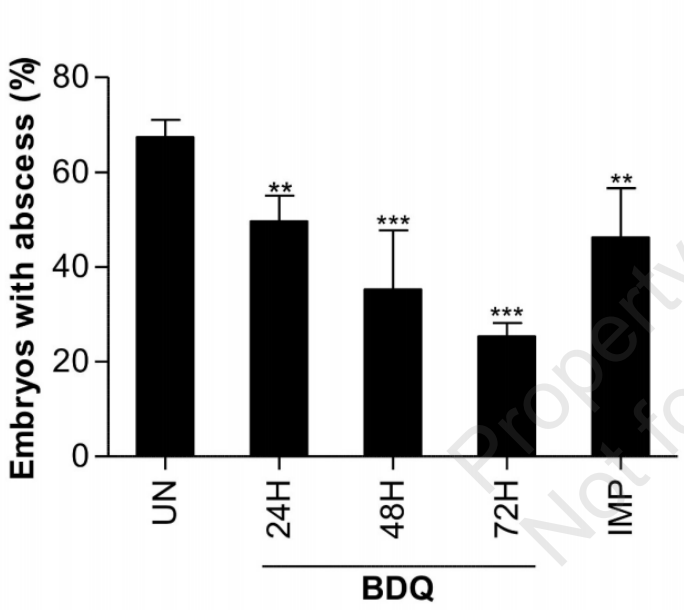
Therapy duration	Improved	Failed	Indeterminate
< 1 month			
CF n=6	-	3 (50%)	3 (50%)
No CF n=4	-	3 (75%)	1 (25%)
> 1 month			
CF n=15	10 (66.7%)	3 (20%)	2 (13.3%)
Non CF n=11	6 (54.5%)	4 (36.4%)	1 (9.1%)

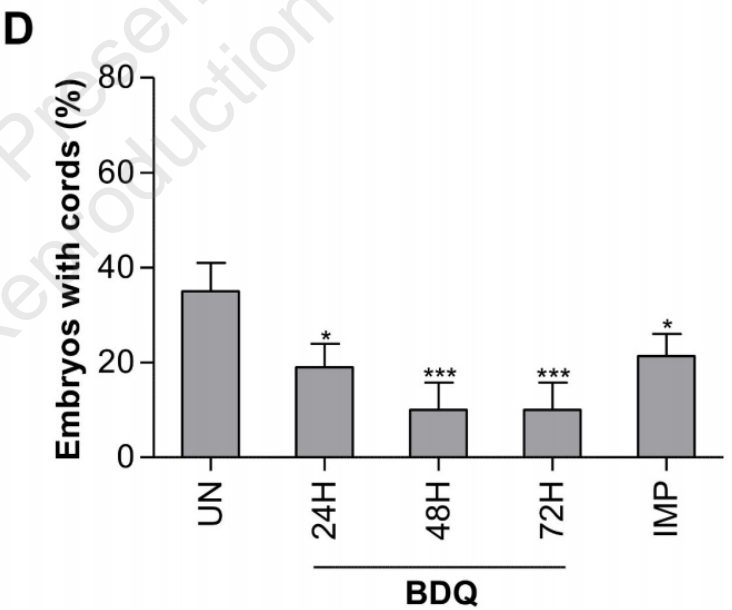
Summary:

- Clinical improvement was evident in 48.1% of patients.
- Occurred in spite of a history of prior drug therapy in 90% of these patients

J Antimicrob Chemother. 2014 Jul;69(7):1945-53.

ALTERNATIVE THERAPY: BEDAQUILINE ACTIVITY AGAINST MAB IN ZEBRAFISH MODEL





Antimicrob Agents Chemother. 2017 Aug 14

ALTERNATIVE THERAPY: BEDAQUILINE TREATMENT IN NTM

TABLE 1] Semiquantitative Monthly Sputum Cultures of 10 Patients on a Bedaquiline-Containing Regimen

Patient No.	Baseline (at the Start of Therapy)	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
1 Mab	4+	3+	1+	2+	3+	1+	2+
2 Mab	1+	3+	1+	35 colonies	37 colonies	16 colonies	3+
3 Mab	4+	28 colonies	Negative	8 colonies	Negative	Negative	32 colonies
4 Mab	4+	4+	4+	4+	4+	4+	4+

TABLE 3] Monthly Clinical Symptom Response of 10 Patients to a Bedaquiline-Containing Regimen

Patient No.	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
1	Unchanged	Worse	Improved	Unchanged	Worse	Unchanged
2	Improved	Improved	Improved	Worse	Unchanged	Unchanged
3	Improved	Improved	Improved	Improved	Improved	Unchanged
4	Unchanged	Improved	Improved	Improved	Improved	Improved

CHEST 2015; 148(2):499-506

ALTERNATIVE THERAPY: OXAZOLIDINONE IN VITRO DATA

Species	Intermediate Breakpoint (ug/ml)	Antibiotic	MIC(ug/ml)		
			Range	50%	90%
M. abscessus (81)	--	Tedozolid	0.12-32	4	8
	16	Linezolid	0.25-128	16	32
M. massiliense (12)	--	Tedizolid	0.12-32	2	4
	16	Linezolid	0.5-32	8	32

J Clin Microbiol. 2017;55(6):1747-54

ALTERNATIVE THERAPY: B LACTAMASE INHIBITORS

BLA_{MAB} = BROAD SPECTRUM BETA-LACTAMASE

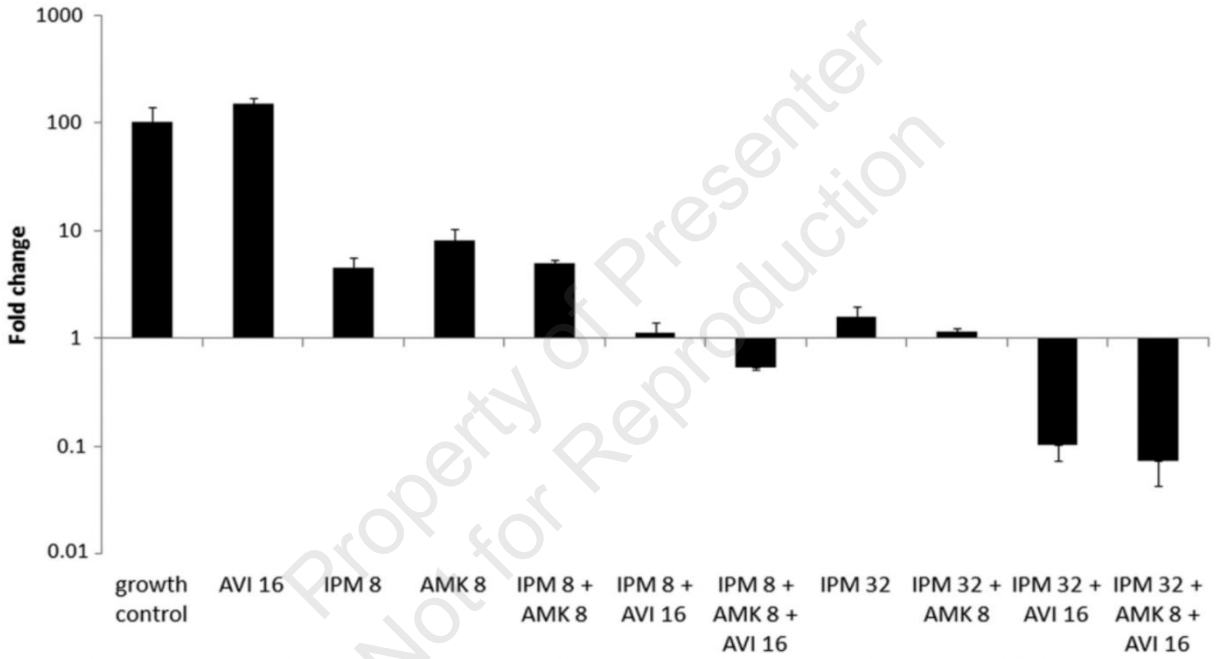


FIG 2 Intracellular activity of imipenem (IPM; 8 μg/ml and 32 μg/ml) alone or in combination with the β-lactamase inhibitor avibactam (AVI; 16 μg/ml) and amikacin (AMK; 8 μg/ml) against *M. abscessus* CIP104536 S. Intracellular bacteria were enumerated, and the fold change in the number of CFU was determined at between days 0 and 2 postinfection. Bars represent standard deviations.

- Not inactivated by clavulanate, sulbactam, and tazobactam
- Efficiently inhibited by avibactam, ? relebactam, vaborbactam

Antimicrob Agents Chemother. 2017 Mar 24;61(4).
J Antimicrob Chemother. 2015 Apr;70(4):1051-8.

TREATMENT

- *M. abscessus/chelonae*
  - Pulmonary
    - IV + oral therapy for 12 months of culture negativity
- *M. fortuitum*
  - Pulmonary
    - Treat with two active agents for 12 months of culture negativity
- Surgical Indications
  - In limited pulmonary disease, surgery may be curative
  - Poor response to drug therapy
  - Significant complications, such as hemoptysis