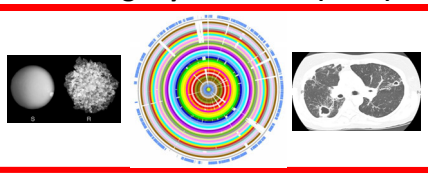
Treatment of Rapidly Growing Mycobacteria (RGM)



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Research Grant
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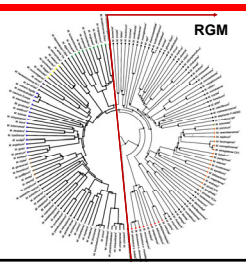
What is a Rapid Grower?

"Rapidly growing mycobacteria," defined by Runyon as mycobacteria that form mature colonies on solid agar in 7 days (from subculture)



Runyon EH. Med Clin North Am, 1959;43:273-90.
Runyon EH. Am J Clin Pathol, 1970;54:578-86.
Clin Infect Dis, 2006;42:1756–1763
Tortoli E, et al. Infect Genetics Evol 2017;56:19-25

Question

- Which of the following is not a rapidly growing mycobacteria?
  a) Mycobacterium wolinskyi
  b) Mycobacterium goodii
  c) Mycobacterium franklinii
  d) Mycobacterium iranicum
  e) All are rapidly growing mycobacteria

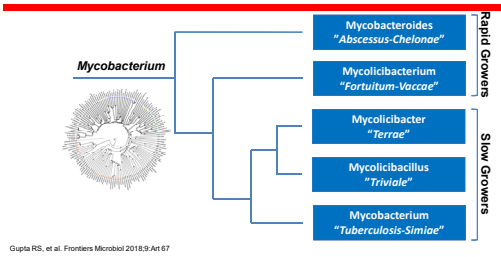
Rapidly Growing NTM

Pathogen type	Nonpigmented species	Pigmented species
Common	*M. abscessus* subsp. *abscessus*,[a] *M. abscessus* subsp. *massiliense*, *M. chelonae*, *M. fortuitum*, *M. porcinum*	None
Infrequent but proven	*M. abscessus* subsp. *bolletii*, *M. fortuitum* group[b] (*M. boenickei*, *M. houstonense*, *M. peregrinum*, *M. senegalense*), *M. franklinii*, *M. immunogenum*, *M. mageritense*, *M. mucogenicum*,[c] *M. wolinskyi*	*M. bacteremicum*, *M. canariasense*,[c] *M. celeriflavum*, *M. cosmeticum*, *M. goodii*,[c] *M. iranicum*, *M. necaurum*, *M. smegmatis* (formerly *sensu stricto*)[c]
Rare or unproven	*M. agri*,[d] *M. algericum*,[d] *M. alvei*,[d] *M. anyangense*[d] (cattle), *M. arabiense*,[d] *M. aubagnense*,[d] *M. barrassiae*,[d] *M. bourgelatii*[d] (cattle), *M. brisbanense*,[d] *M. brumae*,[d] *M. chitae*,[d] *M. confluentis*,[d] *M. diernhoferi*, *M. fallax*,[d] *M. fluoranthenivorans*,[d] *M. insubricum*,[d] *M. litorale*,[d] *M. lutetiense*,[d] *M. moriokaense*,[d] *M. neworleansense*,[d] *M. phocacium*,[d] *M. salmoniphilum* (fish), *M. sediminis*,[d] *M. septicum*,[d] *M. setense*[d]	*M. aichiense*,[d] *M. aromaticivorans*,[d] *M. aurum*,[d] *M. austroafricanum*,[d] *M. chlorophenolicum*,[d] *M. chubuense*,[d] *M. crocinum*,[d] *M. duvalii*,[d] *M. elephantis*,[d] *M. flavescens*,[d] *M. frederiksbergense*,[d] *M. gadium*,[d] *M. gilvum*,[d] *M. hassiacum*,[d] *M. hippocampi*[d] (seahorse), *M. hodleri*,[d] *M. holsaticum*,[d] *M. komossense*,[d] *M. madagascariense*,[d] *M. monacense*,[d] *M. murale*,[d] *M. novocastrense*,[d] *M. obuense*,[d] *M. pallens*,[d] *M. paraffinicum*,[d] *M. phlei*,[d] *M. pontiense*,[d] *M. psychrotolerans*,[d] *M. pyrenivorans*,[d] *M. rhodesiae*,[d] *M. rufum*,[d] *M. rutilum*,[d] *M. sphagni*,[d] *M. thermoresistibile*,[d] *M. tokaiense*,[d] *M. vaccae*,[d] *M. vanbaalenii*[d]

[a]Formerly *M. abscessus* (46).
[b]The *M. mucogenicum* group is composed of *M. mucogenicum*, *M. aubagnense*, and *M. phocaicum*.
[c]Late pigmentation.
[d]Associated with human disease, but fewer than five cases.
[e]No established clinical significance in humans.
[f]Late brown/black pigment develops after several weeks.

Brown-Elliott BA, et al. Microbiology Spectrum. 2017;TNM17-0027-2016

Division of Genus *Mycobacterium* into Emended Genus *Mycobacterium* and Four Novel Genera



Gupta RS, et al. Frontiers Microbiol 2018;9:Art 67

NTM Pulmonary Disease by Species and Region

Region	Country	*M. abscessus*	*M. fortuitum*
North America	USA	4-12%	1-8%
	Canada	3%	3%
Europe	France	9%	-
	Greece	8%	5%
	Italy	-	6%
Australia & New Zealand	Australia	5-7%	-
	New Zealand	9%	-
East Asia	South Korea	18-33%	2-11%
	Taiwan	30-44%	10-23%
Middle East and South Asia	Israel	-	9%
	Saudi Arabia	31%	29%

Prevots and Marras. Clin Chest Med 2015;36:13

Underlying Disease in Patients with Pulmonary Disease due to RGM

- **154 patients with pulmonary disease due to RGM at the University of Texas Health Center, Tyler and Baylor College of Medicine (1976-1991)**

TABLE 4
SPECIES AND SUBGROUP OF RGM RELATED TO THE TYPE OF UNDERLYING DISEASE

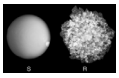
Identified Species/Subgroup	Cystic Fibrosis (*n* = 9)	Gastro-esophageal Disease (*n* = 10)	Prior Granulomatous Disease (*n* = 24)	No Associated Disease (*n* = 49)	UTHCT* Cases (*n* = 33)	All Cases (*n* = 146)
M. abscessus, %	100	40	83	82	88	82
M. fortuitum, %		40	17	16	12	13
M. fortuitum-third biovar, %		10				2
M. peregrinum, %						1
M. smegmatis, %		10				1
M. chelonae, %				2		
M. chelonae-like (MCLO), %						
Unknown species/subgroup, n			3	1		8

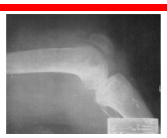
* University of Texas Health Center hospital.

Griffith D, et al. Am Rev Respir Dis 1993;147:1271-1278

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
- Smooth and rough morphotypes – R morphotype was virulent

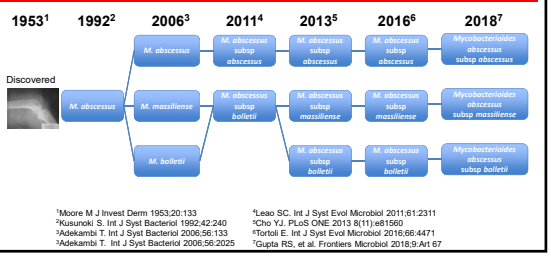




Isolated in 1950 from synovial fluid and buttock lesions in a 63 year old woman

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

Mycobacterium abscessus An Evolving Taxonomy



[1]Moore M J Invest Derm 1953;20:133
[2]Kusunoki S. Int J Syst Bacteriol 1992;42:240
[3]Adekambi T. Int J Syst Bacteriol 2006;56:133
[3]Adekambi T. Int J Syst Bacteriol 2006;56:2025
[4]Leao SC. Int J Syst Evol Microbiol 2011;61:2311
[5]Cho YJ. PLoS ONE 2013 8(11):e81560
[6]Tortoli E. Int J Syst Evol Microbiol 2016;66:4471
[7]Gupta RS, et al. Frontiers Microbiol 2018;9:Art 67

Proportions of *M. abscessus* complex subspecies

Study	Country	Total	M. abscessus	M. massiliense	M. bolletii
Zelazny, 2009	US	40	27 (68)	11 (28)	2 (5)
Van Ingen, 2009	Netherlands	39	25 (64)	8 (21)	6 (15)
Roux, 2009	France	50	30 (60)	11 (22)	9 (18)
Harada, 2012	Japan	102	72 (71)	27 (26)	3 (3)
Yoshida, 2013	Japan	143	90 (63)	50 (35)	3 (2)
Nakanaga, 2014	Japan	115	69 (60)	43 (37)	3 (3)
Huang, 2013	Taiwan	79	34 (43)	44 (56)	1 (1)
Kim, 2008	Korea	126	67 (53)	57 (45)	2 (2)
Kim, 2011	Korea	158	64 (44)	81 (55)	2 (1)
Lee, 2014	Korea	404	202 (50)	199 (49)	3 (1)

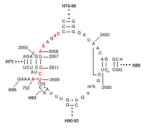
Koh WJ, et al. Int J Tuberc Lung Dis 2014;18:1141

In Vitro Macrolide Resistance in *M. abscessus*

Constitutive (mutational) resistance

- Mutation in region of the *rrl* gene encoding the peptidyltransferase domain of 23S rRNA
- Results in increased MIC as measured on day 3 of incubation

23S rRNA, domain V



Inducible resistance

- Erythromycin ribosomal methylase gene, *erm*(41) modifies the binding site for macrolides resulting in resistance in presence of macrolide
- Functional gene present in most *M. abscessus* subspecies *abscessus* and *bolletii*
  - However, approximately 15-20% of subspecies *abscessus* have a nonfunctional gene (T to C substitution at position 28)
- Truncated, nonfunctional gene in *M. abscessus* subspecies *massiliense*

Wallace RJ, et al. AAC 1996;40:1676
Nash KA, et al. AAC 2009;53:1367

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

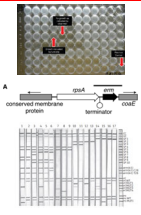
Presence of Inducible Resistance to Clarithromycin

Isolates	Clarithromycin resistance (MIC, μg/mL)		Day 3	Day 7
M. abscessus (n=19)	Susceptible	≤0.5 1 2	9 (46%) 6 (32%) 4 (21%)	- - -
	Intermediate	4	-	-
	Resistant	8 16 32 ≥64	- - - -	1 (5%) 8 (42%) 4 (21%) 6 (32%)
M. massiliense (n=28)	Susceptible	≤0.5 1 2	20 (71%) 8 (29%) -	20 (71%) 8 (29%) -
	Intermediate	4	-	-
	Resistant	≥8	-	-

Koh WJ et al. AJRCCM. 2011;183:405

Detection of Macrolide Resistance

- Mutational resistance
  - 3 day incubation
  - Sequencing
  - Line probe assay
- Inducible resistance
  - 14 day incubation
  - PCR (length of gene)
  - Sequencing
  - Line probe assay



Brown-Elliott, et al. J Clin Micro. 2015;53:1211
Shallom SJ, et al. J Clin Micro 2015;53:3430
Mougari F, et al. AAC 2017;72:1669
Nash KA, et al. AAC 2009;53:1367

Macrolide Resistance: Implications for Treatment

Clarithromycin susceptibility results					
Days 3-5	Day 14	Genetics	Subspecies	Susceptibility Phenotype	Use Macrolide
Susceptible	Susceptible	Dysfunctional *erm*(41) gene	*M. massiliense*	Macrolide susceptible	Yes
Susceptible	Resistant	Functional *erm*(41) gene	*M. abscessus** *M. bolletii*	Inducible macrolide resistance	Possibly but don't count as active
Resistant	Resistant	23S rRNA point mutation	Any	Constitutive macrolide resistance	Only for anti-inflam purposes

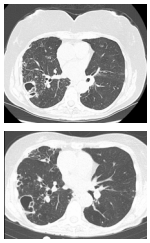
* 10-15% have nonfunctional *erm*(41) gene due T to C substitution at position 28

Haworth C. et al Thorax 2017;72ii1-ii64

Clinical Case

79 year old woman with remote history of pulmonary TB with right upper lobe ant. and post. Segmentectomies

- 11/17 – sputum grew MAC
- 12/17 – BAL grew *M. abscessus*
- Started on 3 drug MAC regimen
- Culture converted 3/2018
- Treatment stopped 5/2019
- Continued to grow *M. abscessus*



12/17

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M. abscessus – Whom to Treat

- 241 patients with *M. abscessus* pulmonary disease (2012-2017)
- 126 with persistent sputum positivity for > 6 months without treatment were enrolled and followed for mean of 3-4 years
- 33 (26.2%) received treatment within 2 years of diagnosis
- 93 (73.8%) did not receive treatment
  - 24 (25.8%) spontaneously culture converted
    - 27.8% reverted to positive within a median of 18.2 months
- Co-morbid malignancy and lower number of lobes involved were predictors of spontaneous conversion to negative

Jo KW, et al. PLoS ONE 2020;15:e0232161

Question

- You have decided to treat our patient with *M. abscessus* pulmonary disease. Which of the following regimens would you start?
  a) Azithromycin, rifampin, ethambutol, amikacin
  b) Azithromycin, moxifloxacin, doxycycline
  c) Imipenem, amikacin, clofazimine, linezolid
  d) Cefoxitin, amikacin, linezolid, trimethoprim-sulfamethoxazole

Guideline-based Treatment Recommendations

Question XIX - In patients with *M. abscessus* pulmonary disease should a macrolide-based regimen or a regimen without a macrolide be used for treatment?

Question XX - In patients with *M. abscessus* pulmonary disease how many antibiotics should be included within multidrug regimens?

Question XXI - In patients with *M. abscessus* pulmonary disease should shorter or longer duration therapy be used for treatment?

M. abscessus Pulmonary Disease
Should a macrolide-based regimen be used for treatment?

Recommendation

In *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 *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)

- No studies were identified that compared macrolide-containing regimens with non macrolide-containing regimens
- Systematic reviews (N = 2) reported higher culture conversion with macrolide-containing regimens:
  - Pooled sustained culture conversion of 34% with *M. abscessus* vs. 54% with *M. massiliense*
  - Good treatment outcomes of 23% with *M. abscessus* vs. 84% with *M. massiliense*
- Patients with macrolide-resistant *M. massiliense* have poor outcomes

Daley CL, et al. *Eur Respir J* 2020; 56: 2000535

M. abscessus Pulmonary Disease

How many antibiotics should be included within regimens?

Recommendation

In patients with *M. abscessus* pulmonary disease, we suggest a multidrug regimen that includes at least 3 active drugs (guided by *in vitro* susceptibility) in the initial phase of treatment (conditional recommendation, very low certainty in estimates of effect)

- No studies have directly compared the efficacy or safety of different multidrug regimens
- The few cases series that have described treatment outcomes all used multidrug regimens with ≥ 3 drugs
- Treatment outcomes are significantly worse for macrolide-resistant *M. abscessus* infections so ≥ 4 drugs are recommended, when possible

Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

M. abscessus Pulmonary Disease

Should shorter or longer duration therapy be used for treatment?

Recommendation

In patients with *M. abscessus* pulmonary disease, we suggest that either a shorter or longer treatment regimen be used and expert consultation obtained (conditional recommendation for either the intervention or the comparison, very low certainty in estimates of effect)

- Two systematic reviews noted that most patients had been treated for > 12 months with multidrug regimens including a minimum of 4 weeks of ≥ 1 parenteral agent
- It may be possible to treat *M. massiliense* pulmonary disease with shorter regimens but the optimal duration is not known
- Expert consultation is advised prior to the initiation of therapy

Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

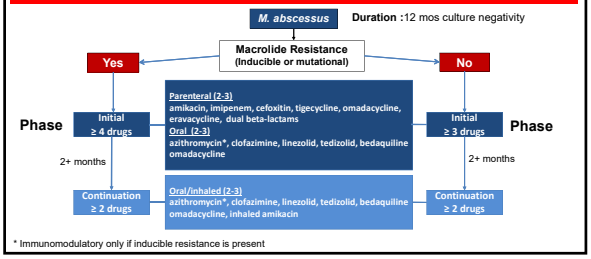
Recommended Treatment Regimens *M. abscessus*

Macrolide Susceptibility				
Mutational	Inducible	No. of Drugs	Preferred Drugs	Frequency of Dosing
Susceptible	Susceptible	Initial Phase ≥3	*Parenteral (choose 1-2)* Amikacin Imipenem (or cefoxitin) Tigecycline *Oral (choose 2)* Azithromycin* Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides
		Continuation Phase ≥ 2	*Oral/inhaled (choose 2-3)* Azithromycin* Clofazimine Linezolid Inhaled amikacin	
Susceptible	Resistant	Initial Phase ≥ 4	*Parenteral (choose 2-3)* Amikacin Imipenem (or cefoxitin) Tigecycline *Oral (choose 2-3)* Azithromycin** Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides
		Continuation Phase ≥ 2	*Oral/inhaled (choose 2-3)* Azithromycin** Clofazimine Linezolid Inhaled amikacin	
Resistant	Susceptible or Resistant	As above		

*Azithromycin is active
**Azithromycin is unlikely to be active

Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

Treatment of *M. abscessus* Pulmonary Disease



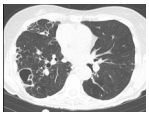
* Immunomodulatory only if inducible resistance is present

Clinical Case

Cultures grew *M. abscessus* subspecies *abscessus* with functional erm(41) gene
Amikacin MIC ≤8 (S)
Imipenem MIC 8 (I)
Clofazimine MIC ≤0.5
Cefoxitin MIC ≤16 (S)
Tigecycline MIC 1
Linezolid MIC16 (I)

She was started on:
Amikacin (IV) 500 mg MWF
Imipenem (IV) 500 mg twice daily
Clofazimine 100 mg daily

After 2 months she was changed to inhaled amikacin and continued clofazimine



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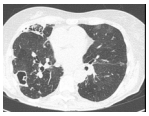

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Other Treatment Options for RGM

- Dual-beta lactams (±beta-lactamase inhibitors)
- Oxazolidinones (tedizolid > linezolid)
- Cyclines (eravacycline > tigecycline = omadacycline)
- Bacteriophages
- Inhaled nitric oxide
- Intravenous gallium
- Rifabutin

Clinical Case

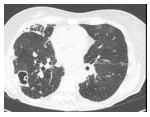
She was still culture positive and losing weight

She was re-started on therapy (10/19):
Amikacin (IV) 500 mg MWF
Imipenem (IV) 500 mg twice daily
Clofazimine 100 mg daily

Ceftaroline 600 mg twice daily was added 12/19

Gained 5 kg, normalized CRP and albumin and converted cultures to negative

Completed therapy 3/20



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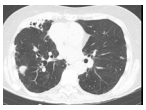

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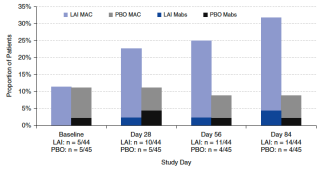
Treatment of *M. abscessus* Pulmonary Disease with Amikacin Liposome Inhalation Suspension

Randomized, placebo-controlled trial of amikacin liposome inhalation suspension in treatment refractory NTM – 90 patients enrolled

- 32 (36%) subjects had predominantly *M. abscessus*
- 4 culture converted
  - 3 after receiving ALIS
  - 1 on placebo



Olivier K. Am J Resp Crit Care Med. 2017;195:814-823

Inhaled Amikacin for Treatment of *M. abscessus* Pulmonary Disease

- 82 treatment-naïve patients with *M. abscessus* pulmonary disease (2015-2018)
- Initial treatment regimen: amikacin (IV), imipenem (or cefoxitin) and oral azithromycin
  - Clofazimine was added if macrolide resistant or in *M. massiliense* patients, if cavities were present
  - 4 weeks for *M. abscessus* and 2 weeks for *M. massiliense*
- Continuation phase regimen: amikacin (inhaled 500 mg once daily three times weekly), azithromycin and clofazimine as above
- **Results:** Status 12 months after initiation of treatment
  - Cure: 91% of *M. massiliense* and 31% of *M. abscessus*
  - Adverse effects: 19 of 82 (23%) discontinued inhaled amikacin, 79% due to ototoxicity

Kang N, et al. Chest 2021;160:436-445

Treatment Outcomes for *M. abscessus* vs. *M. massiliense*

Study	Population	Treatment	N	Sputum conversion	Failure to convert	Relapse
Koh, 2011	Non Cystic Fibrosis	*M. abscessus*	24	25%	58%	17%
		M. massiliense	33	**88%**	**3%**	**9%**
Lyu, 2014	Non Cystic Fibrosis	*M. abscessus*	26	42%	27%	31%
		M. massiliense	22	**96%**	**0%**	**5%**
Roux, 2015	Cystic Fibrosis	*M. abscessus*	12	25%	-	-
		M. massiliense	7	**86%**	-	-
Park, 2017	Non Cystic Fibrosis	*M. abscessus*	19	**26%**	74%	55%
		M. massiliense	17	**82%**	**18%**	**0%**

Koh WJ, et al. Am J Respir Crit Care Med 2011;183:405-10
Lyu J, et al. Respir Med. 2014;108:1706-12
Roux AL, et al. Cyst Fibros. 2015 Jan;14(1):63-9
Park J, et al. CID 2017;64:301-8
Choi H, et al. Antimicrob Agents Chemother 2016 epub

Impact of Macrolide-resistance on Treatment Outcomes

- Macrolide-susceptible *M. abscessus* subsp *abscessus*
  - 14 patients: 93% achieved culture conversion
- Macrolide-resistant (mutational) *M. abscessus* subsp *abscessus*
  - 13 patients: 0% treatment success
  - 1 converted after surgery
- Macrolide-resistant *M. abscessus* subsp *massiliense*
  - 15 patients: 1 patient (7%) cured (had resectional surgery)

Choi H, et al. Antimicrob Agents Chemother. 2017;61:e01146.
Choi H. et al. Antimicrob Agents Chemother. 2017;61:e02189.
Choi H, et al. Diagnostic Microbiology and Infectious Disease. 2018;90:293–295

Predictors of Culture Conversion/Treatment Success

Host Factors

- **BMI ≥ 18.5**
- **Less radiographic involvement**
- **Noncavitary**
- **Previous NTM lung disease**

Microbial Factors

- ***M. massiliense***
- **Macrolide susceptible**
- **Smooth morphotype**

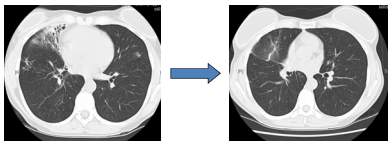
Antimicrobial Factors

- **Use of:**
  - **azithromycin**
  - **imipenem**
  - **amikacin**

Park J, et al. Clin Infect Dis. 2017;64:301-308
Park J, et al. Resp Med. 2021;187:106549

Treatment of *M. abscessus*
Surgery

56 year old Caucasian woman cleared her MAC but not the *M. abscessus*

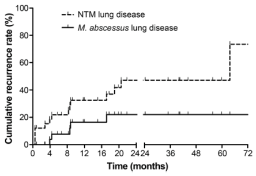


Treatment Success

Jeon, 2009	58% (med) vs 88% (med+surg)
Jarand, 2011	39% (med) vs 65% (med+surg)

Recurrence and Reinfection

77 consecutive patients with *M. abscessus* pulmonary disease



All recurrences had a different genotype pattern (rep PCR)

Koh WJ, et al. CID 2017;64:309-16

Question

- Where was *M. chelonae* first isolated? From a…
  a) Human
  b) Elephant
  c) Turtle
  d) Bird

Mycobacterium chelonae

- *M. chelonae* was isolated in 1903 from a turtle by Friedmann who referred to it as the "turtle tubercle bacillus"
- *M. chelonae* and *M. abscessus* were thought to be identical until 1992 when *M. chelonae* was elevated to its own species
- *M. chelonae* does not possess an erm gene so macrolides are usually active

Bergey DH. Manual of Determinative Bacteriology, 1923

Drug Susceptibility Results for *M. fortuitum* and *M. chelonae*

Agent	*M. fortuitum*	*M. chelonae*
Parenteral		
Amikacin	100%	80%
Imipenem	100%	60%
Cefoxitin	80%	0%
Oral		
Moxi	100%	75%
Doxycycline	50%	25%
Minocycline	50%	25%
Clarithromycin	50% (beware inducible resistance)	100% (no inducible resistance)
Tobramycin	-	100%

Griffith D. Up To Date

Treatment of *M. chelonae*

No. of drugs	Oral Drugs	Parenteral Drugs	Comments
Initial phase: ≥3 (2) Continuation phase: ≥2	Azithromycin (Clarithromycin)	Tobramycin (i.v.)	• Drugs should be selected according to DST results, when available • Caution about oto-vestibular and nephrotoxicity of aminoglycosides • For mild-to-moderate disease an oral two-drug regimen could suffice, provided that DST has proven 2 such drugs to be active.
	Moxifloxacin/or Levofloxacin/or Ciprofloxacin	Imipenem/Cilastatin	
	Linezolid		
	Clofazimine		

IV – intravenous, DST - drug susceptibility testing

Example regimen: imipenem + tobramycin + azithromycin + another oral drug guided by DST

Lange C, et al. Lance Infect Dis, in press

Mycobacterium fortuitum

- *Mycobacterium fortuitum* (formerly *Mycobacterium ranae*), was originally recovered from frogs in 1905.
- In 1938, da Costa Cruz gave the name *M. fortuitum* to an isolate that he thought was a new mycobacterial species isolated from a patient with a skin abscess following local vitamin injections.
- Currently, the MFC includes:
  - *M. fortuitum*, *M. peregrinum*, *M. porcinum*, *M. septicum*, *M. conceptionense*, *M. boenickei*, *M. houstonense*, *M. neworleansense*, *M. brisbanense*, *M. farcinogenes*, *M. senegalense*, and *M. setense*
- Variable frequency of inducible macrolide resistance:
  - 85% of *M. fortuitum* has *erm(38)* gene

da Costa Cruz JC. 1938. Acta Med Rio Janeiro 1938;1:298–301.
Kim SY, et al. Antimicrob Agents Chemother 2019;63: e02331-18

Clinical Significance of *Mycobacterium fortuitum*

- **All patients whose respiratory specimens were positive for *M. fortuitum* between January 2003 and December 2005.**
- **Samsung Medical Center (a 1250-bed tertiary referral hospital in Seoul, Korea)**

	N (%)
≥ 1 positive cultures	182
≥ 2 positive cultures	26 (14)
≥ 2	15/26 (58)
≥ 3	11/26 (42)
Started on treatment	1/26 (4)
Clinical progression (median f/u 12.5 mos)	0

Park S, et al. Resp Medicine. 2008;102:437-442

Treatment of *M. fortuitum*

No. of drugs	Oral Drugs	Parenteral Drugs	Comments
Initial phase: ≥3 (2)	Moxifloxacin/or Levofloxacin/or Ciprofloxacin	Amikacin (i.v.)	• Drugs should be selected according to DST results, when available • The detection and management of underlying esophageal disorders and/or aspiration is critical • Active erm gene • Caution about oto-vestibular and nephrotoxicity of aminoglycosides • For mild-to-moderate disease an oral two-drug regimen could suffice, provided that DST has proven 2 such drugs to be active.
	Linezolid	Imipenem/Cilastatin	
Continuation phase: ≥2	Trimethoprim/ Sulfamethoxazole	Cefoxitin	
	Clofazimine		
	Doxycycline		

Example regimen: imipenem + moxi + another oral drug guided by DST
Add amikacin for more severe disease

IV – intravenous, DST - drug susceptibility testing

Lange C, et al. Lance Infect Dis, in press

Summary

- *M. abscessus* should be sub-speciated and the status of the *erm*(41) gene determined
- Patients with *M. massiliense* have better treatment outcomes than subspecies *abscessus*.
- A combination of oral and IV antibiotics should be used for 2+ months followed by an oral/inhaled regimen until 12 months of cx negativity
- Recurrence and reinfection are common
- Surgical resection should be considered for more focal disease
- *M. chelonae* and *M. fortuitum* are uncommon causes of pulmonary disease.
  - Evaluate for esophageal disease/vomiting when *M. fortuitim* is isolated