2018.10.5, 1st KATRD TB/NTM international symposium

M. avium complex pulmonary disease, update

Division of Pulmonology
University of Ulsan College of Medicine
Asan Medical Center
Kyung-Wook Jo

Natural history of MAC lung disease

Cavitary MAC lung disease

Antimicrobial susceptibility testing

Treatment of refractory MAC lung disease

Environmental sources

Recurrence

Natural history of MAC lung disease

Cavitary MAC lung disease

Antimicrobial susceptibility testing

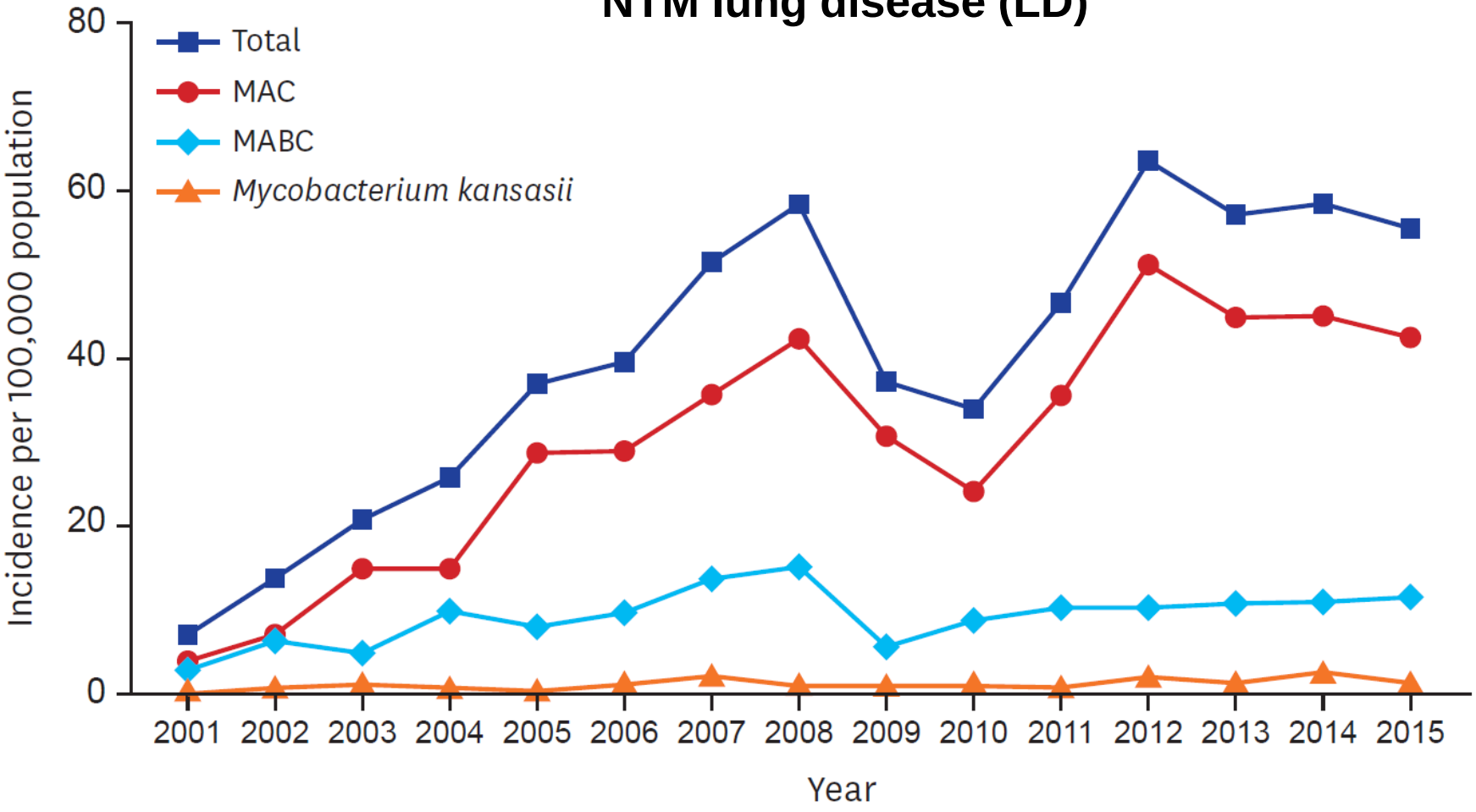
Treatment of refractory MAC lung disease

Environmental sources

Recurrence

2001-2015, Samsung Medical Center

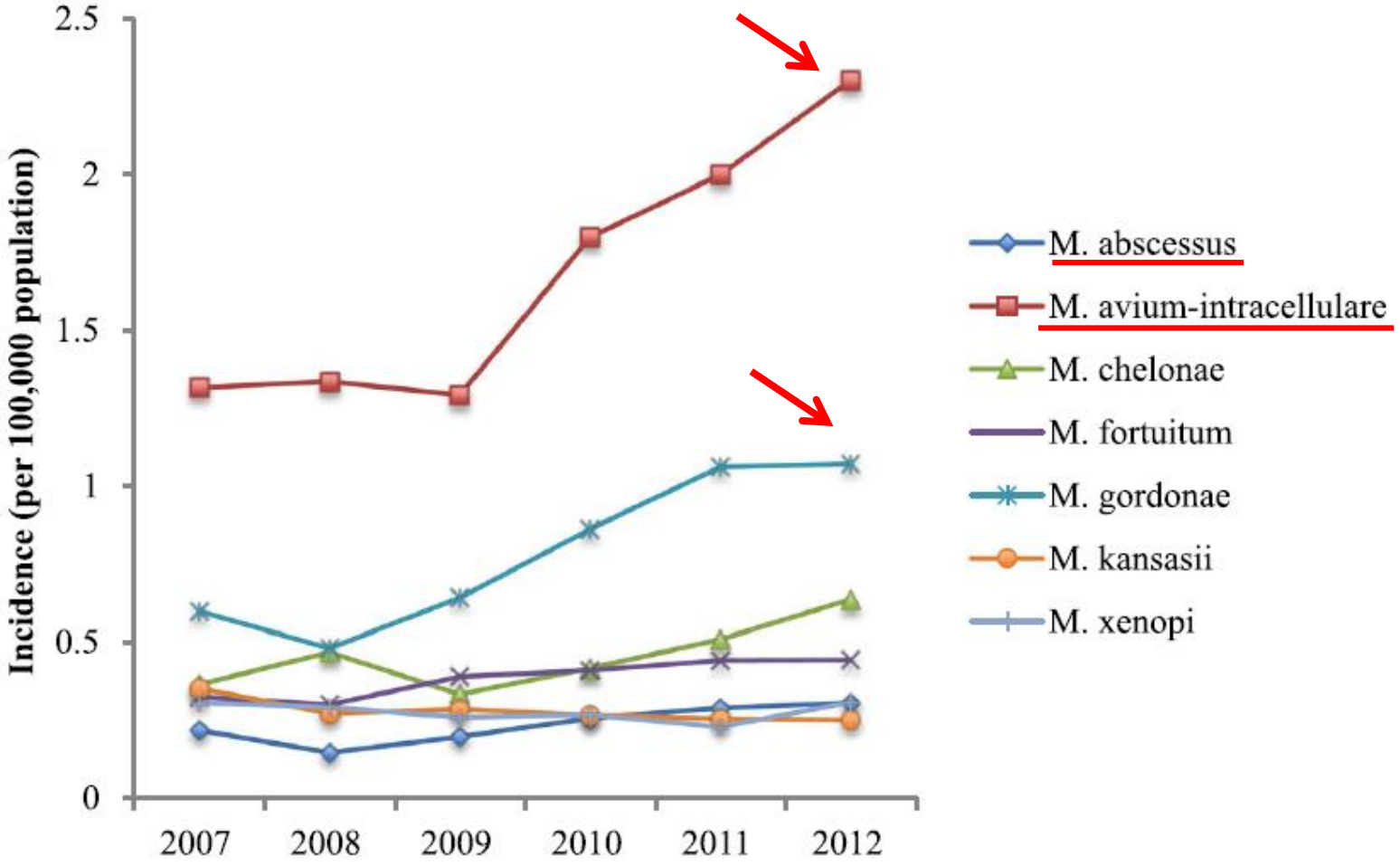
NTM lung disease (LD)



J Korean Med Sci 2018;33:e65

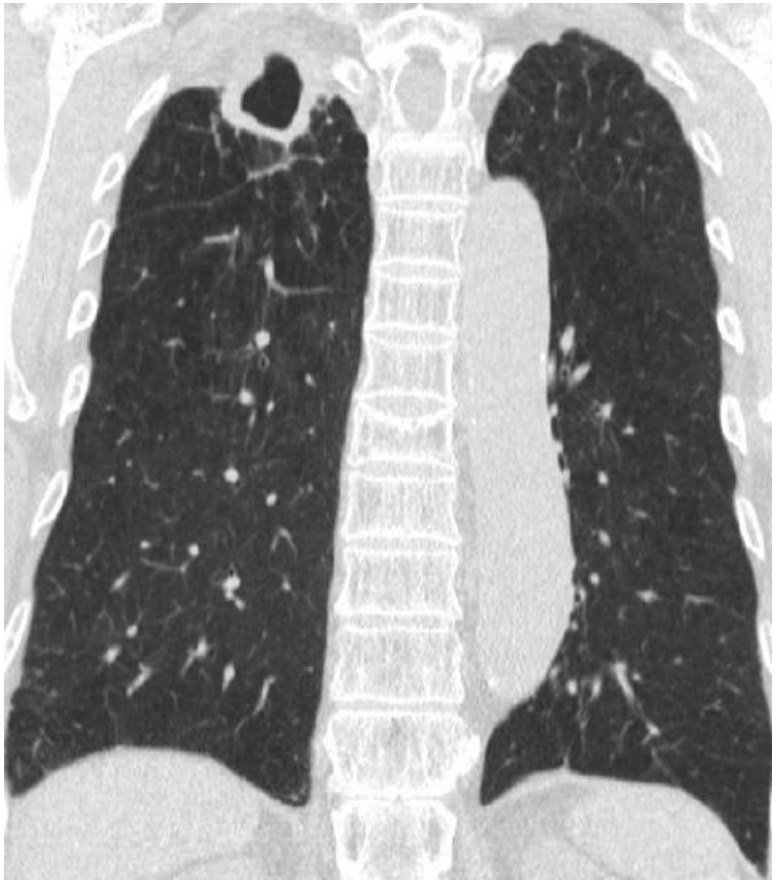
Public Health England, 2007-2012,

21,118 NTM culture positive isolate

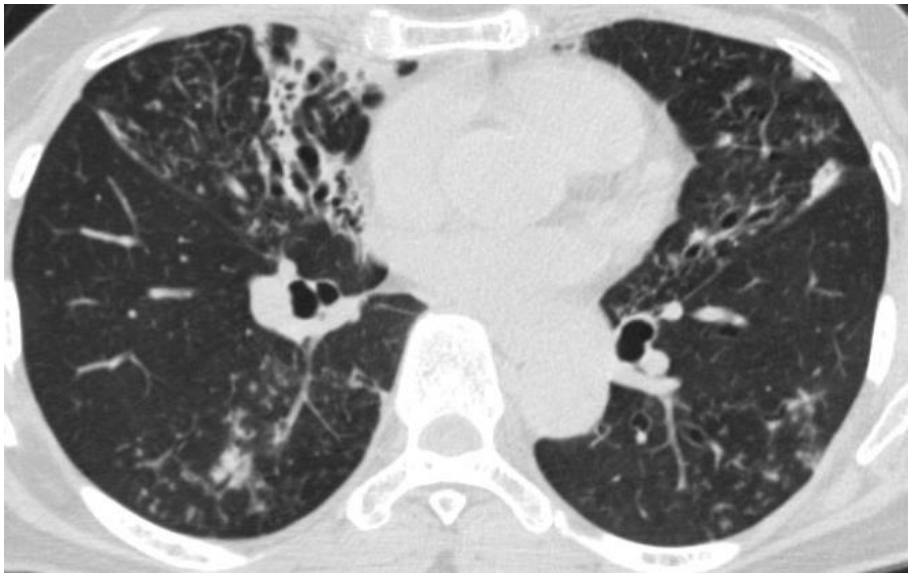


BMC Infectious Diseases 2016;16:195

The fibrocavitary (FC) form



The nodular bronchiectatic (NB) form



Tuberc Respir Dis 2016;79:74–84

MAC LD patients with FC disease

: usually require immediate treatment

: rapid progression

: because cavitary disease is associated with a higher rate of mortality

Int J Infect Dis 2016;45:123–134

NB form

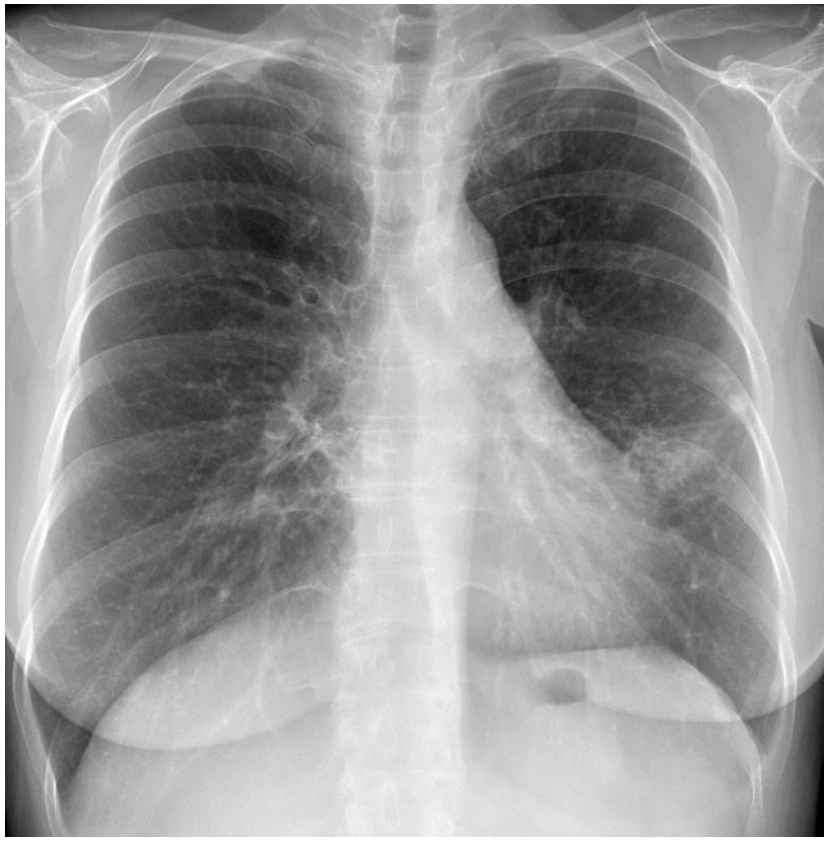
: Often progresses slowly

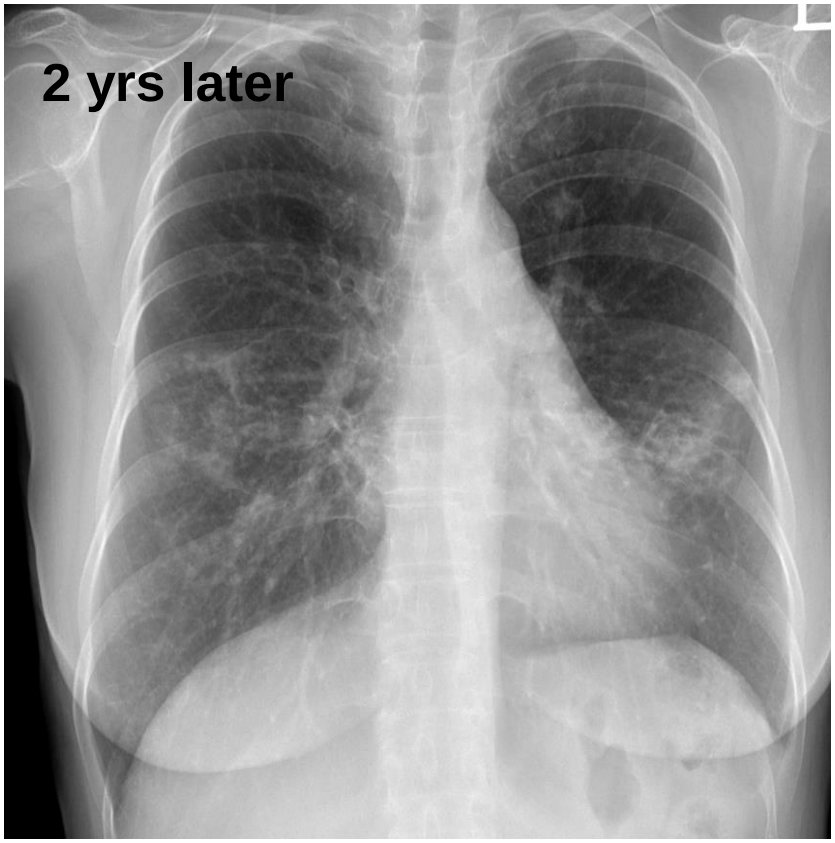
: Early treatment of mild and indolent nodular bronchiectatic disease may not be advisable

Int J Infect Dis 2016;45:123–134

59/F

Cough with sputum ↑





L411906	Sputum, AFB Stain	1-9/10F 2+		
L411952	AFB culture, 액체배지	AFB growth		
L411953	AFB culture, 고체배지	AFB growth colony : 1+		
BNTM	Nontuberculous mycobacterium	Non-yellow pig, 균주번호: 79929	→	***M. avium***
L411905	Broncheal aspirates, AFB Stain	1-9/100F 1+		
L411952	AFB culture, 액체배지	AFB growth		
L411953	AFB culture, 고체배지	AFB growth colony : 1+		
BNTM	Nontuberculous mycobacterium	Non-yellow pig, 균주번호: 79926	→	***M. avium***
L411905	Broncheal aspirates, AFB Stain	1-2/300F +/-		
L411952	AFB culture, 액체배지	AFB growth		
L411953	AFB culture, 고체배지	AFB growth colony : 5		
BNTM	Nontuberculous mycobacterium	Non-yellow pig, 균주번호: 79925	→	***M. avium***

Identification

Natural history of *Mycobacterium avium* complex lung disease in untreated patients with stable course

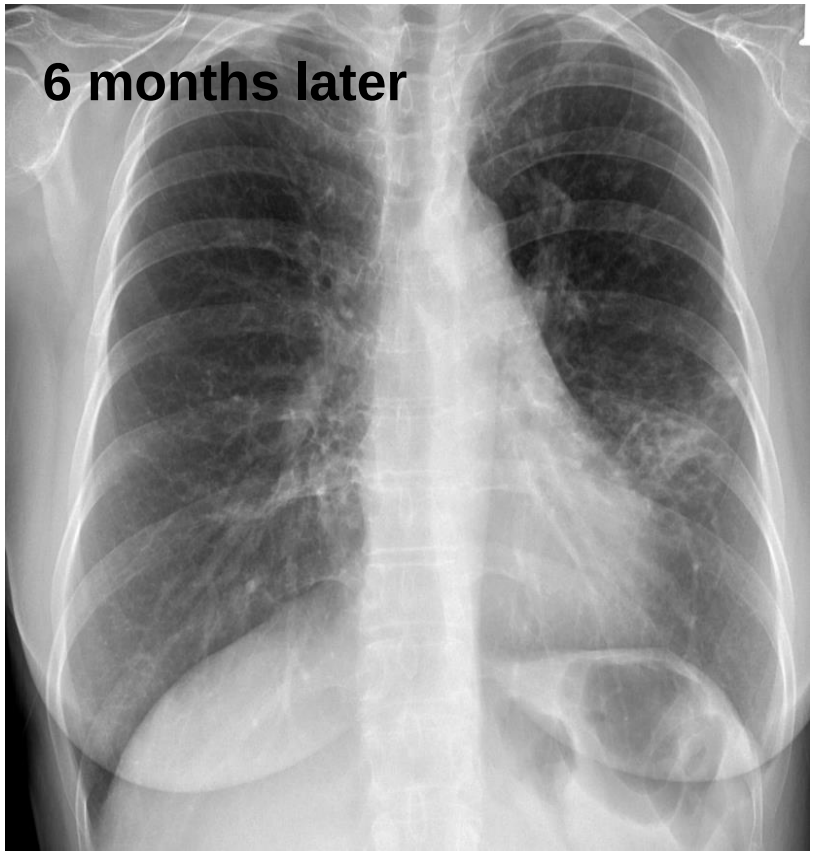
Ji An Hwang[1,3], Sunyoung Kim[2,3], Kyung-Wook Jo[1] and Tae Sun Shim[1]

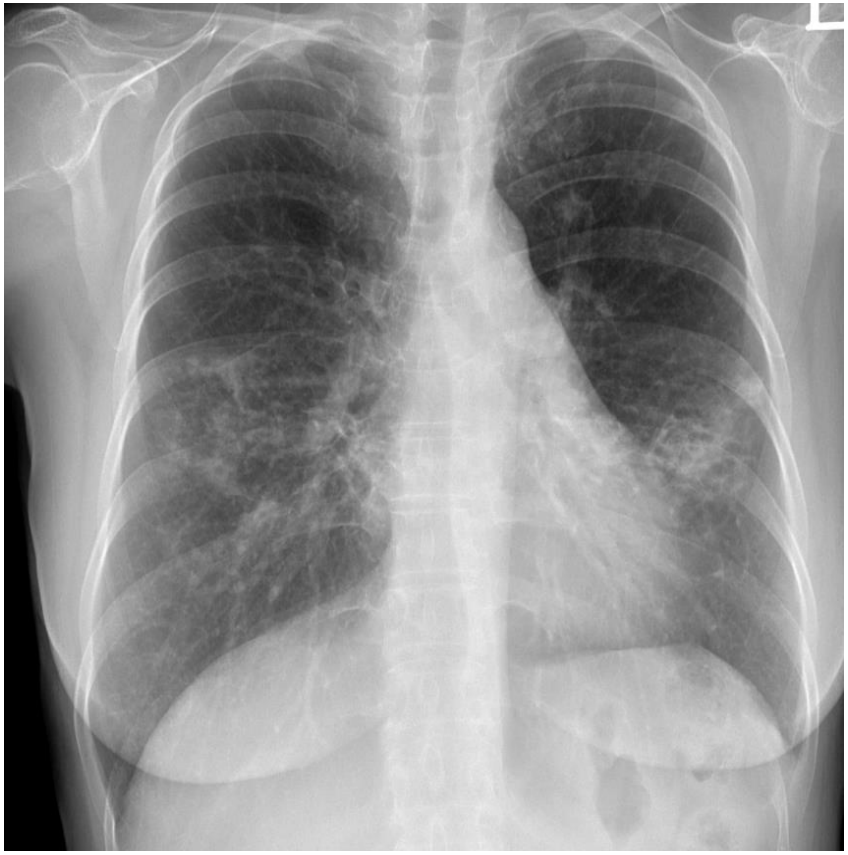
Eur Respir J 2017;49:1600537

1998-2011, 488 patients with MAC-LD

Of the 93 untreated patients with stable MAC-LD

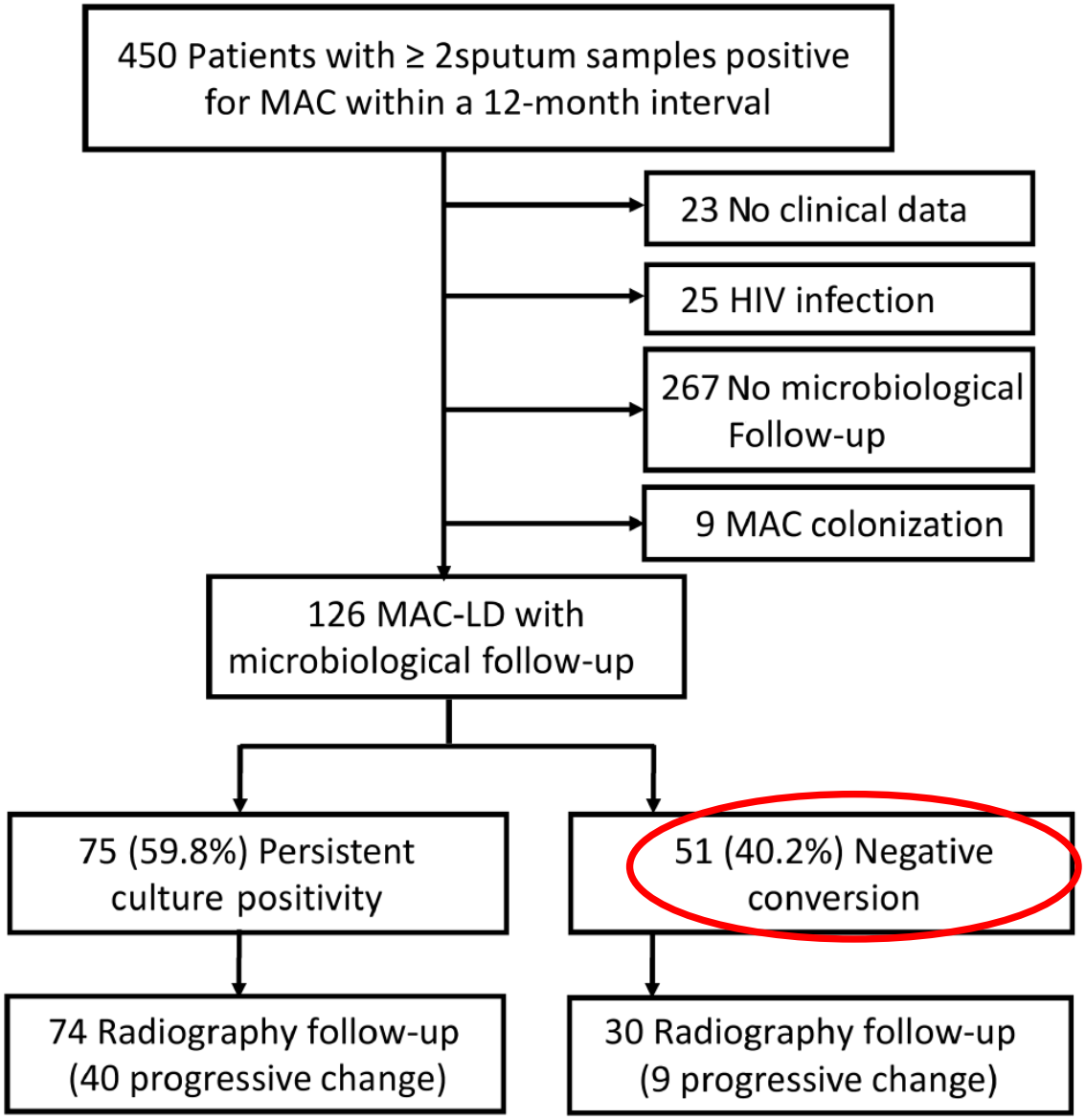
Spontaneous sputum conversion – 51.6% (48/93)


6 months later



Taiwan

2011-2016



Clin Infect Dis 2017;65:927–934

Natural history of MAC lung disease

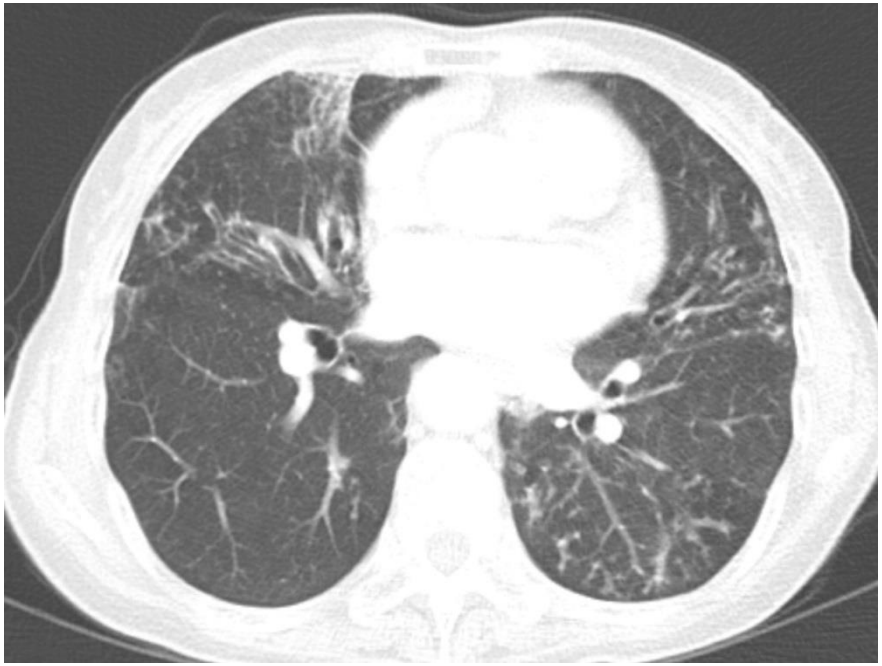
Cavitary MAC lung disease

Antimicrobial susceptibility testing

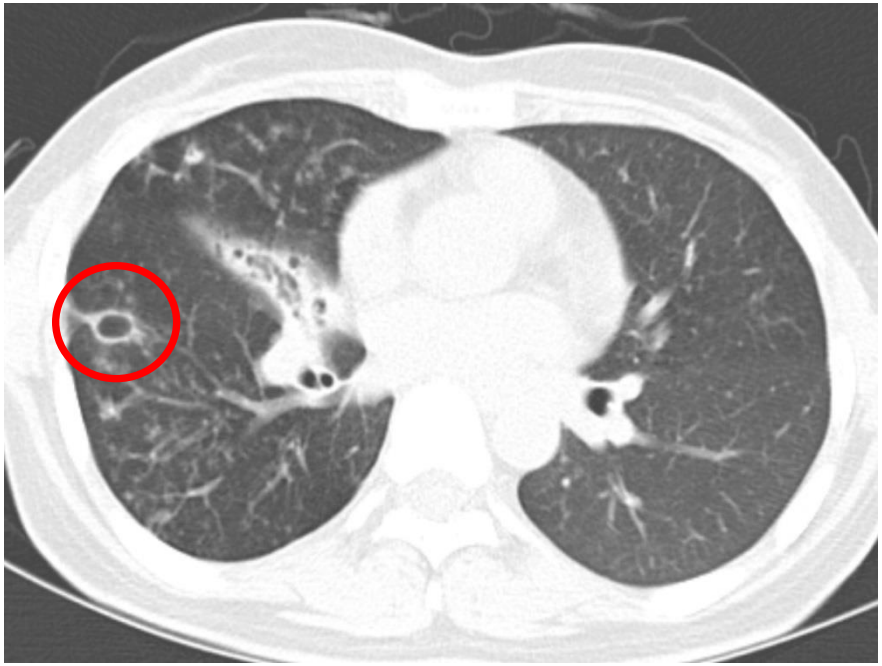
Treatment of refractory MAC lung disease

Environmental sources

Recurrence



NB form



Cavitary NB form

Mycobacterial burden ↑

Outcomes of *Mycobacterium avium* complex lung disease based on clinical phenotype

Won-Jung Koh[1,7], Seong Mi Moon[1,7], Su-Young Kim[1], Min-Ah Woo[2], Seonwoo Kim[2], Byung Woo Jhun[1], Hye Yun Park[1], Kyeongman Jeon[1], Hee Jae Huh[3], Chang-Seok Ki[3], Nam Yong Lee[3], Myung Jin Chung[4], Kyung Soo Lee[4], Sung Jae Shin[5], Charles L. Daley[6], Hojoong Kim[1] and O Jung Kwon[1]

2002-2013, Samsung Medical Center, South Korea

481 MAC-LD who received treatment for ≥ 12 month

- **FC form, 25% (n = 123)**
- **NB form, 75% (n = 358)**
  - **Cavitary NB form (n = 80)**
  - **Noncavitary NB form (n = 278)**

Eur Respir J 2017;50:1602503

	Noncavitary NB	Cavitary NB	Fibrocavitary
Subjects	278 (58)	80 (17)	123 (25)
Time interval between diagnosis and treatment months	7.0 (2.2–23.2)	5.8 (1.5–16.6)	1.5 (0.5–5.4)
Treatment regimen[¶]			
Daily	135 (49)	80 (100)	123 (100)
Intermittent	143 (51)	0 (0)	0 (0)
Streptomycin	72 (26)	48 (60)	90 (73)
Duration months	3.0 (2.3–5.1)	3.2 (2.8–5.7)	4.0 (3.0–6.2)
Surgical resection[+]	11 (4)	5 (6)	20 (16)
Time from treatment start to resection months	21.9 (19.6–24.5)	12.7 (11.9–18.3)	12.6 (7.0–18.8)
Treatment duration months	19.7 (15.9–24.1)	24.0 (18.2–24.8)	24.1 (19.6–27.5)
Treatment outcomes			
Favourable	246 (88)	62 (78)	94 (76)
Unfavourable	32 (12)	18 (22)	29 (24)

Eur Respir J 2017;50:1602503

Treatment regimen for MAC LD

Non-cavitary NB form

Clarithromycin 1000mg or azithromycin 500mg TIW

Ethambutol 25mg/Kg TIW

Rifampin 450-600mg TIW

Cavitary NB or FC form

Clarithromycin 1000mg or azithromycin 250mg daily

Ethambutol 15mg/Kg daily

Rifampin 450-600mg daily

Streptomycin or amikacin 10-15mg/Kg

Int J Infect Dis 2016;45:123–134

Treatment regimen for MAC LD

Non-cavitary NB form

Clarithromycin 1000mg or azithromycin 500mg *TIW*

Ethambutol 25mg/Kg *TIW*

Rifampin 450-600mg *TIW*

Cavitary NB or FC form

Clarithromycin 1000mg or azithromycin 250mg *daily*

Ethambutol 15mg/Kg *daily*

Rifampin 450-600mg *daily*

Streptomycin or amikacin 10-15mg/Kg

Int J Infect Dis 2016;45:123–134

Treatment regimen for MAC LD

Non-cavitary NB form

Clarithromycin 1000mg or azithromycin 500mg TIW

Ethambutol 25mg/Kg TIW

Rifampin 450-600mg TIW

Cavitary NB or FC form

Clarithromycin 1000mg or azithromycin 250mg daily

Ethambutol 15mg/Kg daily

Rifampin 450-600mg daily

Streptomycin or amikacin 10-15mg/Kg

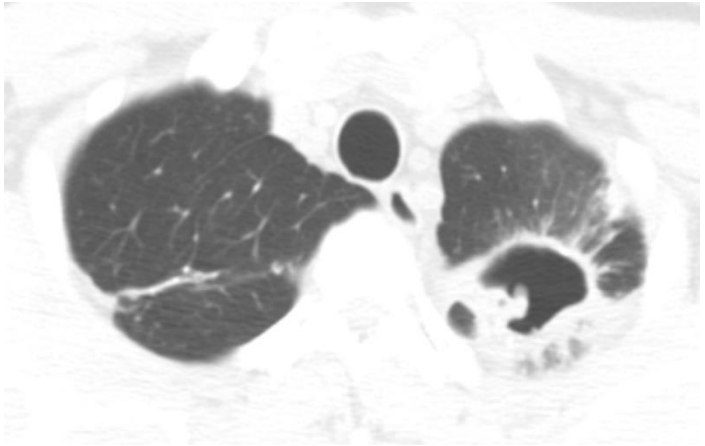
Int J Infect Dis 2016;45:123–134

British Thoracic Society guideline

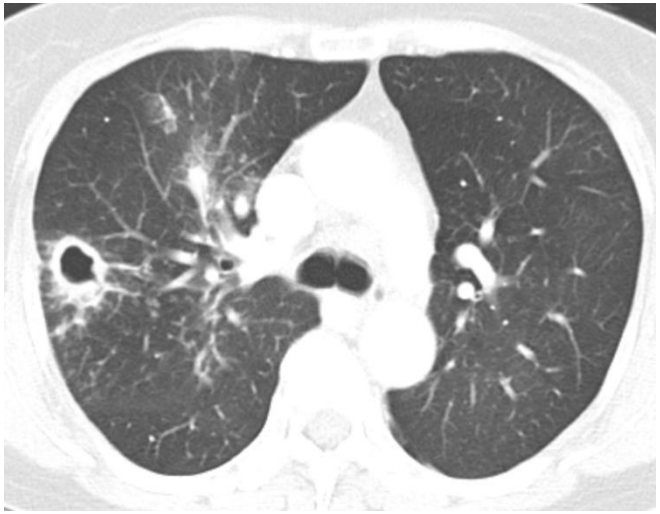
M. avium complex-pulmonary disease	Antibiotic regimen
Non-severe MAC-pulmonary disease (ie, AFB smear-negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-moderate symptoms, no signs of systemic illness)	Rifampicin 600 mg 3× per week and Ethambutol 25 mg/kg 3× per week and Azithromycin 500 mg 3× per week or clarithromycin 1 g in two divided doses 3× per week Antibiotic treatment should continue for a minimum of 12 months after culture conversion.
Severe MAC-pulmonary disease (ie, AFB smear-positive respiratory tract samples, radiological evidence of lung cavitation/severe infection, or severe symptoms/signs of systemic illness)	Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or clarithromycin 500 mg twice daily and consider intravenous amikacin for up to 3 months or nebulised amikacin Antibiotic treatment should continue for a minimum of 12 months after culture conversion.

Thorax 2017;72:ii1–ii64

FC form



Cavitary NB form



High mycobacterial burden

Limited drug penetration

Poor blood supply

→ **Aminoglycoside treatment duration,**

longer than recommended?

Duration of aminoglycoside (AG) treatment and outcome of cavitary MAC lung disease

Asan Medical Center, cavitary MAC-LD, 2000-2013

101 patients treated with regimen containing AGs

Median (IQR) duration of AG treatment: 126 (86-196) days

Overall treatment success: 63.4%

AGs for **≥3 months (median duration 164 days): 69.3%**

vs. **<3 months (median duration 59 days): 46.2%** (*P* = 0.035)

AG for ≥3 months: adjusted OR 3.602 (95% CI 1.249-10.39)

Clin Infect Dis 2018, doi: 10.1093/cid/ciy804

Natural history of MAC lung disease

Cavitary MAC lung disease

Antimicrobial susceptibility testing

Treatment of refractory MAC lung disease

Environmental sources

Recurrence

Antimicrobial susceptibility testing (AST) of MAC isolates

Antimicrobial agents	Method (pH)	MIC (μg/mL) for category		
		S	I	R
Primary				
Clarithromycin	Broth microdilution	≤8	16	**≥32**
	Radiometric method	≤16	32	≥64
Secondary				
Moxifloxacin	Broth microdilution	≤1	2	≥4
Linezolid	Broth microdilution	≤8	16	≥32

CLSI (Clinical and Laboratory Standards Institute) 2011

In vitro MIC data for RIF, EMB

→ **Poor correlation between the MIC and the outcome**

→ **AST of MAC isolates for RIF and EMB is not recommended**

Am J Respir Crit Care Med 2007;175:367–416

Respir Med 2014;108:417–425

Recommendation based on studies

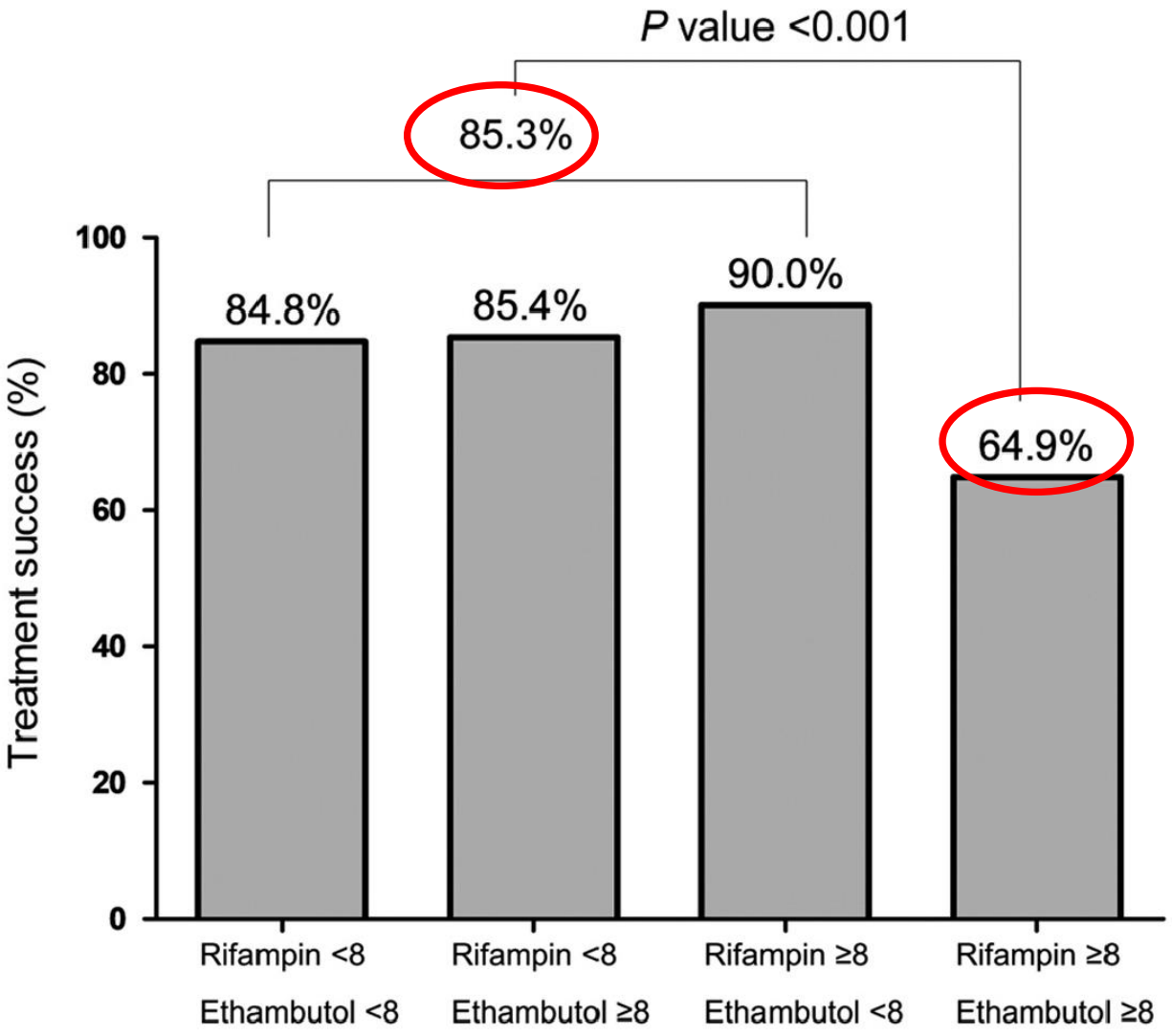
with a limited number of patients and the adequacy of treatment

2008-2013, 274 MAC isolates, Asan Medical Center

Broth microdilution method using the Sensititre Myco susceptibility plate

	Rifampin		Ethambutol	
MIC (μg/ml)	No. (%) of isolates	Treatment success rate (%)	No. (%) of isolates	Treatment success rate (%)
0.25	1 (0.4)	100		
0.5	10 (3.6)	90.0		
1	47 (17.2)	89.4		
2	75 (27.4)	85.3	16 (5.8)	87.5
4	54 (19.7)	79.6	99 (36.1)	84.8
8 ←	86 (31.4)	67.4	84 (30.7)	77.4
16	1 (0.4)	100	55 (20.1)	74.5
32			20 (7.3)	70.0

Antimicrob Agents Chemother. doi:10.1128/AAC.00491-18



Total no. of patients	105	82	10	77
No. of patients treatment success	89	70	9	50

Antimicrob Agents Chemother. doi:10.1128/AAC.00491-18

Natural history of MAC lung disease

Cavitary MAC lung disease

Antimicrobial susceptibility testing

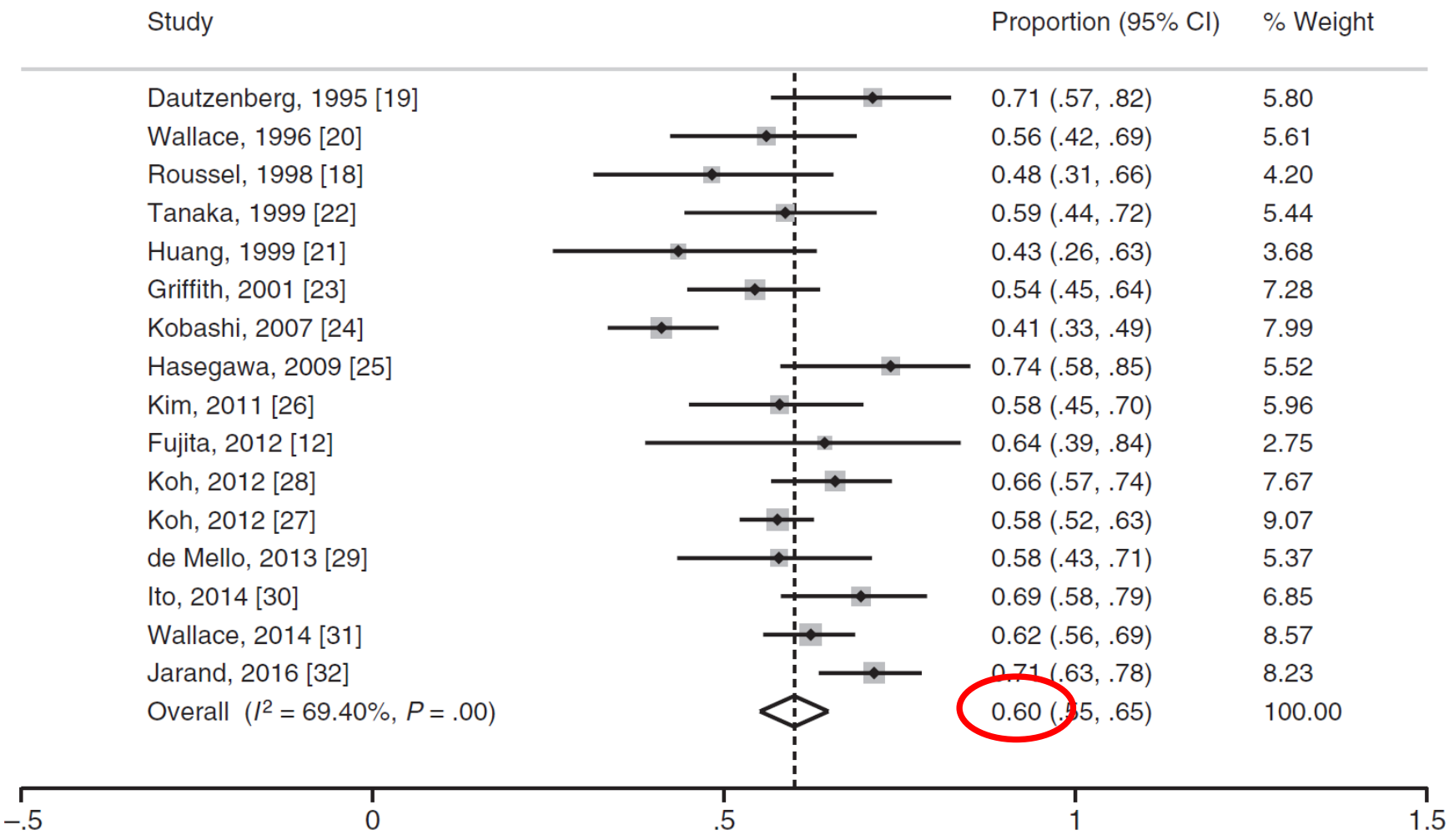
Treatment of refractory MAC lung disease

Environmental sources

Recurrence

Systematic review and meta-analysis, MAC-LD

16 studies involving 1462 patients, Treatment success rate



Clin Infect Dis 2017;65:1077–1084

Antimicrobial susceptibility testing (AST) of MAC isolates

Antimicrobial agents	Method (pH)	MIC (μg/mL) for category		
		S	I	R
Primary				
Clarithromycin	Broth microdilution	≤8	16	≥32
	Radiometric method	≤16	32	≥64
Secondary				
Moxifloxacin	Broth microdilution	≤1	2	≥4
Linezolid	Broth microdilution	≤8	16	≥32

CLSI (Clinical and Laboratory Standards Institute) 2011

Germany, a tertiary referral center, 2002-2012
***in vitro* MIC of linezolid (LZD) against 148 *M. tuberculosis* isolates**

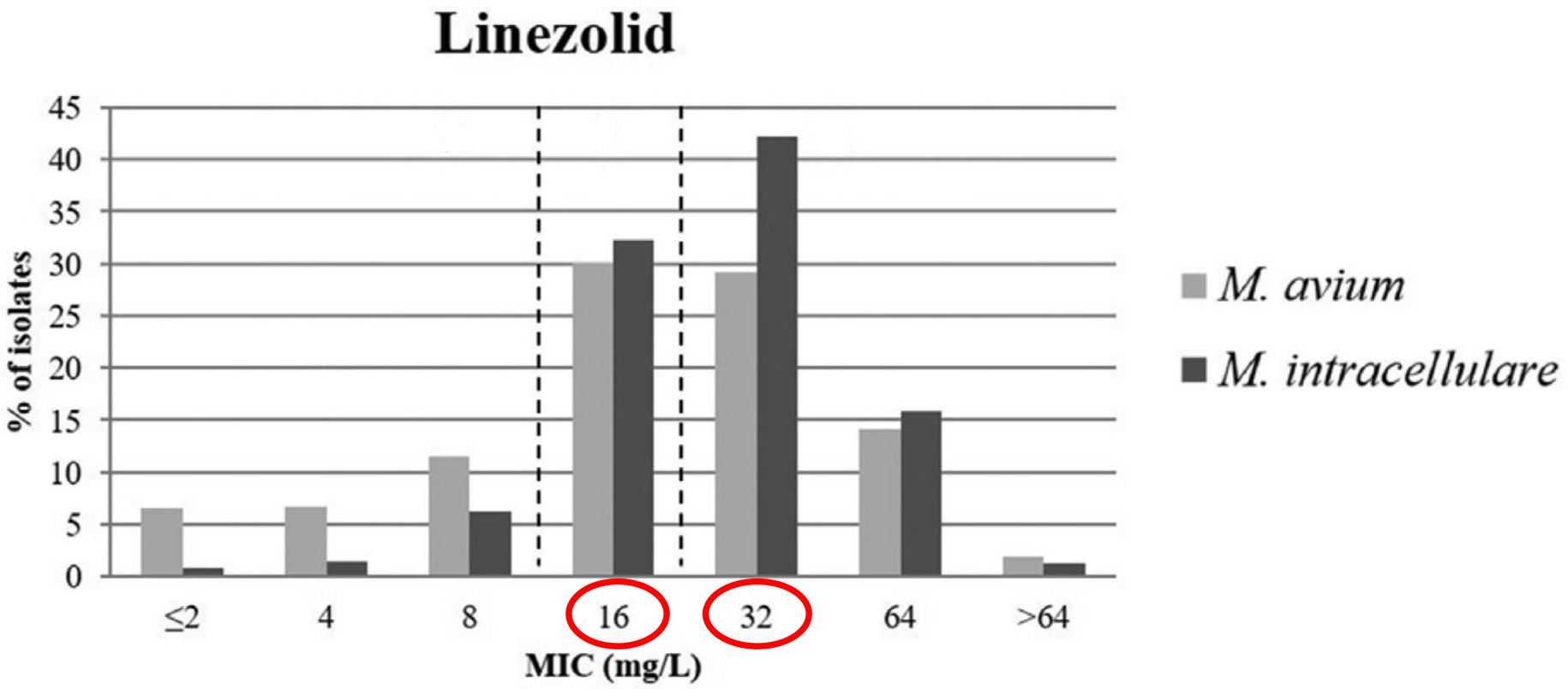
TABLE 1 Minimal inhibitory concentrations (MIC) for the multidrug-resistant (MDR) tuberculosis (TB) and non-MDR-TB strains found in the study

Bacterial strain	Patients	MIC $\mu g \cdot L^{-1}$			
		0.125	0.25	0.5	1.0
MDR-TB	18	0	10	8	0
Non-MDR-TB	130	4	121	5	0

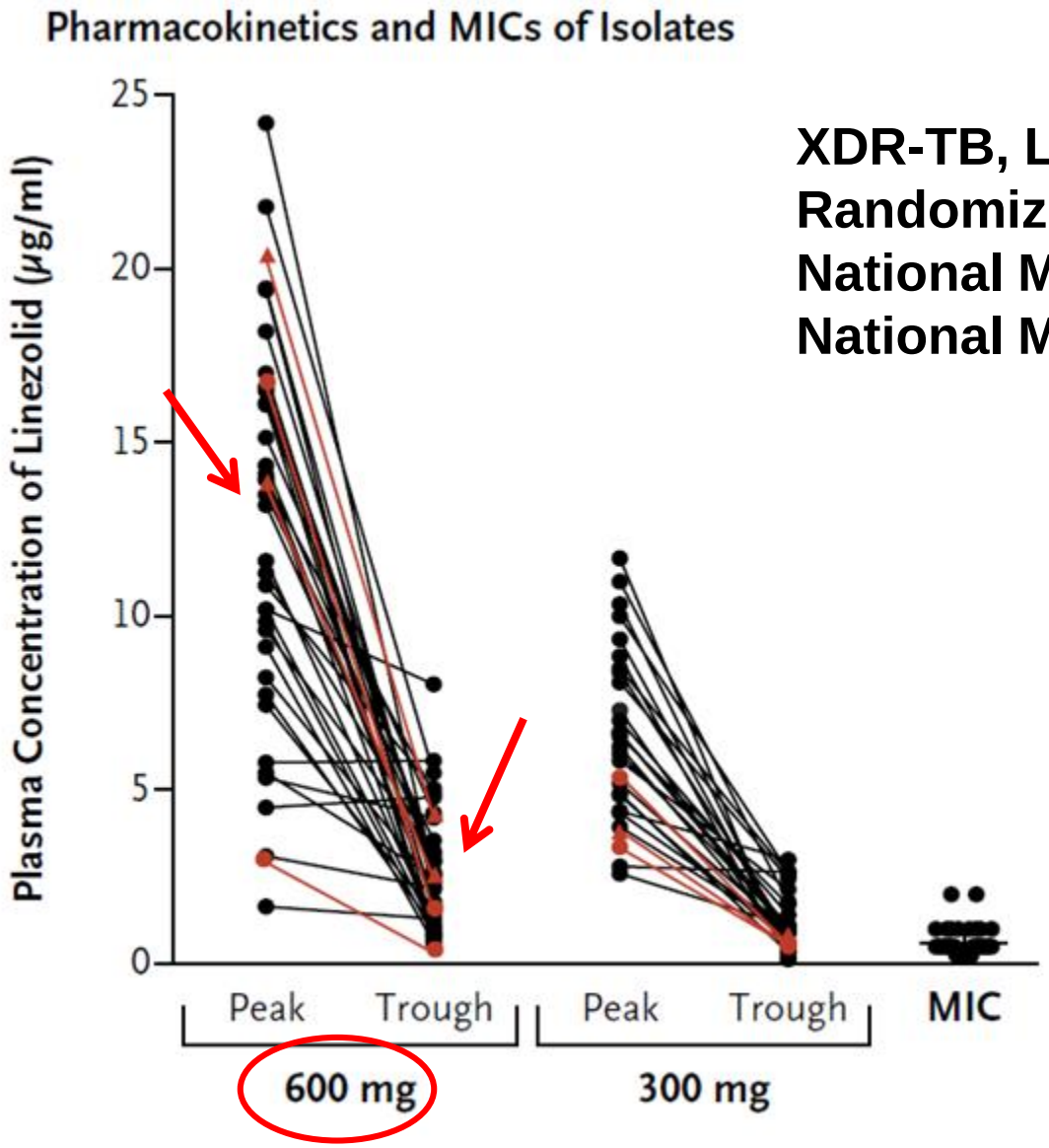
Data are presented as n.

Eur Respir J 2015;45:285–287

Samsung Medical Center, 2011–2016
1060 *M. avium*, 823 *M. intracellulare* isolates
MIC, broth microdilution method



J Infect Chemother 2018;24:315–318



XDR-TB, Linezolid, Randomized trial, South Korea National Masan Hospital and National Medical Center

N Engl J Med 2012;367:1508–1518

The tolerability of linezolid in the treatment of nontuberculous mycobacterial disease

Kevin L. Winthrop[1], Jennifer H. Ku[1], Theodore K. Marras[2], David E. Griffith[3], Charles L. Daley[4], Kenneth N. Olivier[5], Timothy R. Aksamit[6], Cara D. Varley[1], Katherine Mackey[1] and D. Rebecca Prevots[5]

Eur Respir J 2015;45:1177–1179

102 NTM patients (27% with cavity)

- **MAC (33%)**
- **Macrolide (80%), AG (45%), FQ (33%)**

LZD – median 21.4 weeks , 600mg once daily (79%)

45% developed adverse events after a median 19.9 weeks

→ 87% stopped therapy

→ 43% resumed LZD

Safety and Effectiveness of Clofazimine for Primary and Refractory Nontuberculous Mycobacterial Infection

Stacey L. Martiniano, MD; Brandie D. Wagner, PhD; Adrah Levin, MPH; Jerry A. Nick, MD; Scott D. Sagel, MD, PhD; and Charles L. Daley, MD

RESULTS: A total of 112 patients were included (median age, 62 years); 24 patients (21%) had CF. Eighty-seven (78%) had refractory disease with failure of previous therapy. Fifty-four patients (48%) had *Mycobacterium abscessus* complex, 41 (37%) had *Mycobacterium avium* complex, and 16 (14%) had two NTM species. The median duration of clofazimine use was 383 days (range, 3-2,419 days). Sixteen patients (14%) stopped clofazimine due to an ADR after a median of 101 days (95% CI, 63-119). Forty-one of 82 patients (50%) with pulmonary disease converted to negative NTM cultures within 12 months.

CHEST 2017;152:800–809

Frequency of Reported Clinical Adverse Drug Reactions While Taking Clofazimine

Adverse Drug Reaction	Non-CF (n = 88)	CF (n = 24)
Skin related		
Skin discoloration	55 (63)	13 (54)
Dry skin	28 (32)	5 (21)
Sun hypersensitivity	18 (20)	3 (13)
GI		
Nausea	32 (36)	5 (21)
Diarrhea	27 (31)	1 (4)
Abdominal pain	19 (22)	6 (25)
Anorexia	17 (19)	4 (17)
Vomiting	17 (19)	1 (4)

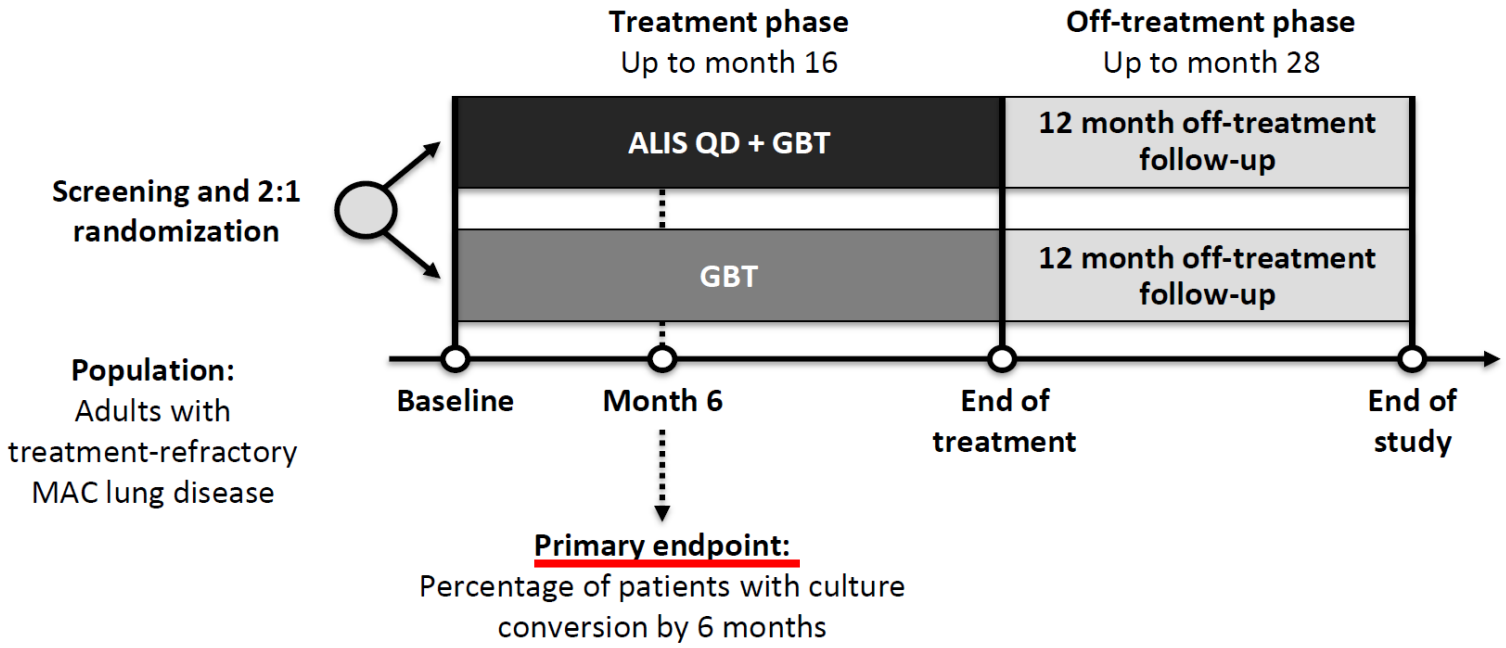
CHEST 2017;152:800–809

Prospective, open-label, randomized trial

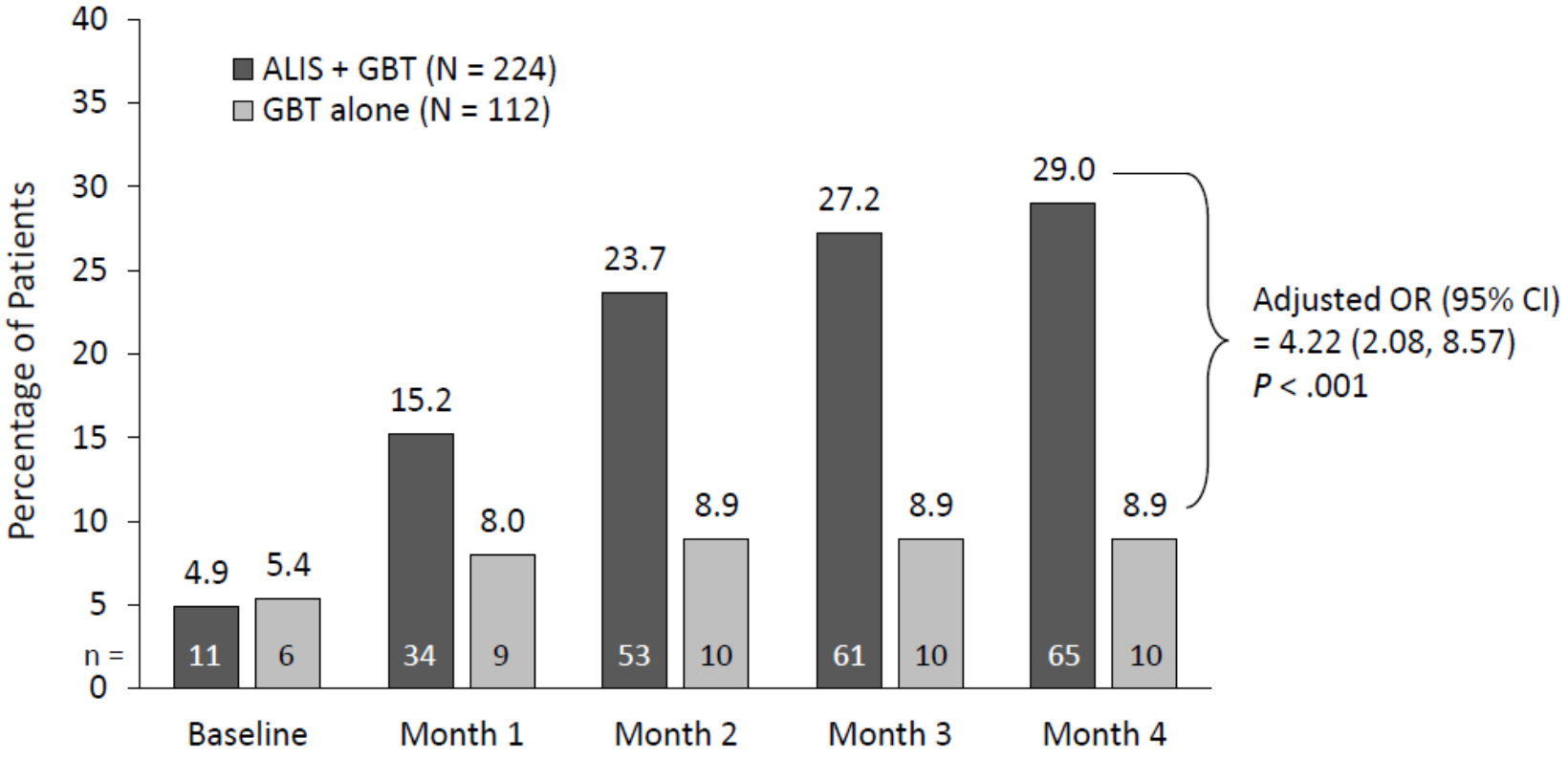
Treatment refractory MAC lung disease (n = 336)

Guideline-based therapy (GBT)

***vs* GBT + Amikacin Liposomal Inhalation Suspension (ALIS)**



AJRCCM in press, doi: 10.1164/rccm.201807-1318OC



AJRCCM in press, doi: 10.1164/rccm.201807-1318OC

FDA News Release

FDA approves a new antibacterial drug to treat a serious lung disease using a novel pathway to spur innovation

First drug granted approval under FDA's Limited Population Pathway for Antibacterial and Antifungal Drugs, instituted to spur development of antibiotics for unmet medical needs

For Immediate Release September 28, 2018

Release

The U.S. Food and Drug Administration today approved a new drug, Arikayce (amikacin liposome inhalation suspension), for the treatment of lung disease caused by a group of bacteria, Mycobacterium avium complex (MAC) in a limited population of patients with the disease who do not respond to conventional treatment (refractory disease).

“Refractory” ?

Persistent positive sputum cultures after at least 6 months of treatment

Antimicrob Agent Chemother 2018;62 e00011–18

Am J Respir Crit Care Med 2017;195:814–823

Persistent positive sputum cultures after at least 12 months of treatment

AJRCCM 2018; doi: 10.1164/rccm.201802-0321OC

“***Persistence of the original strain***”

Samsung Medical Center, 49 patients with refractory MAC lung disease

Genotyping analysis **73% → reinfection with new strains**

Table 4. Summary of Genotyping Analyses of Isolates from the 49 Patients with Stored Pre- and Post-treatment Isolates

	Patients with serial clinical isolates (n = 49)*			*P*-value
	Persistent infection (n = 13, 27%)	Mixed infection (n = 12, 24%)	New infection (n = 24, 49%)	
Etiology				0.171
M. avium	3 (23)	4 (33)	13 (54)	
M. intracellulare	10 (77)	8 (67)	11 (46)	
Type				0.493
Nodular bronchiectatic form	8 (62)	9 (75)	19 (79)	
Fibrocavitary form	5 (38)	3 (25)	5 (21)	
Development of macrolide resistance	3 (23)	5 (42)	4 (17)	0.269

AJRCCM 2018; doi: 10.1164/rccm.201802-0321OC

Natural history of MAC lung disease

Cavitary MAC lung disease

Antimicrobial susceptibility testing

Treatment of refractory MAC lung disease

Environmental sources

Recurrence

Environmental Sources of Nontuberculous Mycobacteria

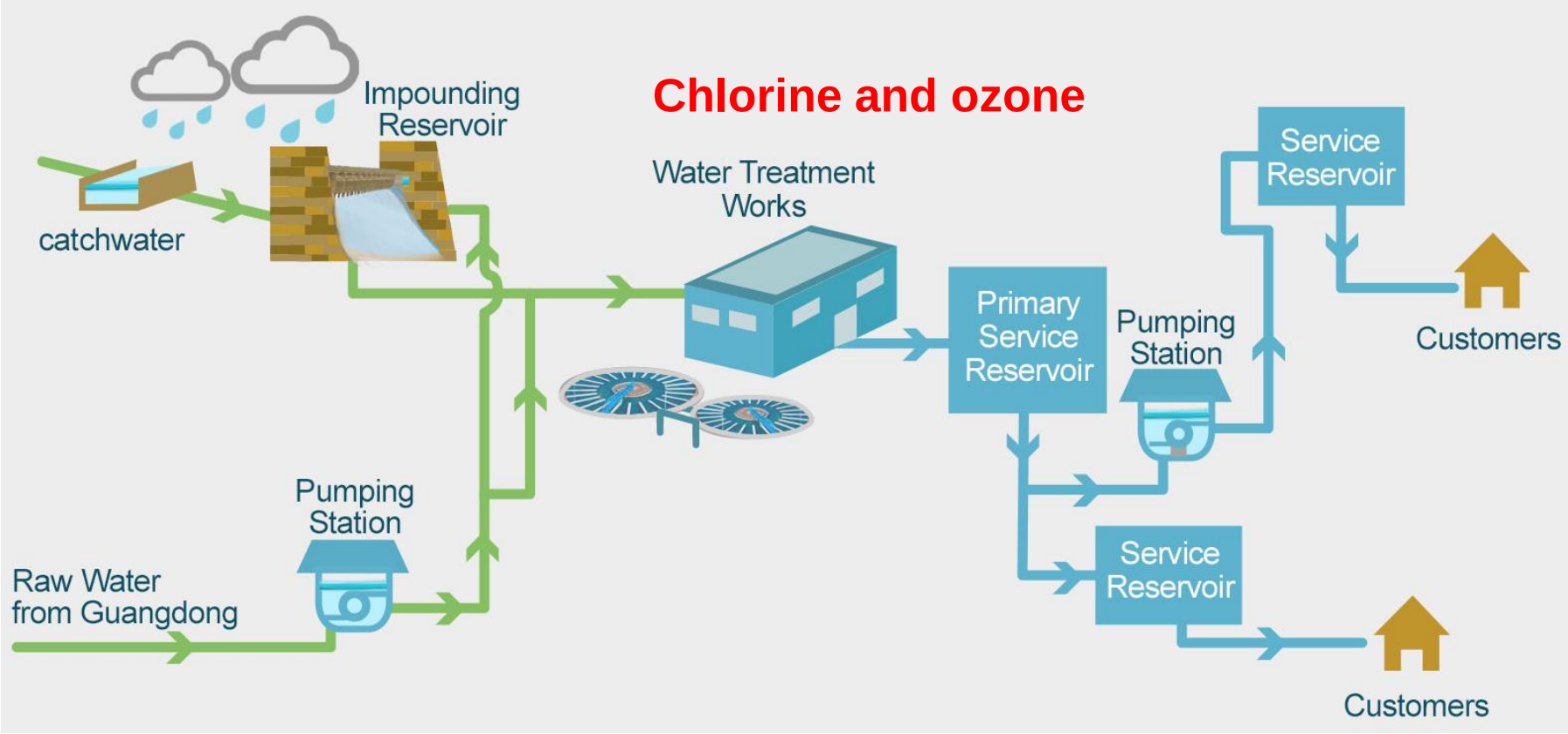
Joseph O. Falkinham III, PhD

Box 1
Environmental sources of nontuberculous mycobacteria

- Soils, especially acidic pine forest or coastal swamp soils
- Dusts from agriculture, garden, and potting soils
- Drainage waters from acidic pine forests or coastal swamps
- Natural waters
- Drinking water
- Water and ice from refrigerators
- Water from granular-activated charcoal filters
- Aerosols from natural and drinking waters
- Aerosols from indoor humidifiers
- Mist from indoor swimming pools

Clin Chest Med 2015;36:35–41

Water distribution system



Chlorine, Chloramine, Chlorine Dioxide, and Ozone Susceptibility of *Mycobacterium avium*

ROBERT H. TAYLOR,[1] JOSEPH O. FALKINHAM III,[1]* CHERYL D. NORTON,[2] AND MARK W. LeCHEVALLIER[2]

Most of the *M. avium* strains were highly resistant to chlorine and ozone

than *E. coli* (500 fold)

than *Pseudomonas* (40 fold)

Appl Environ Microbiol 2000;66:1702–1705

Showerhead

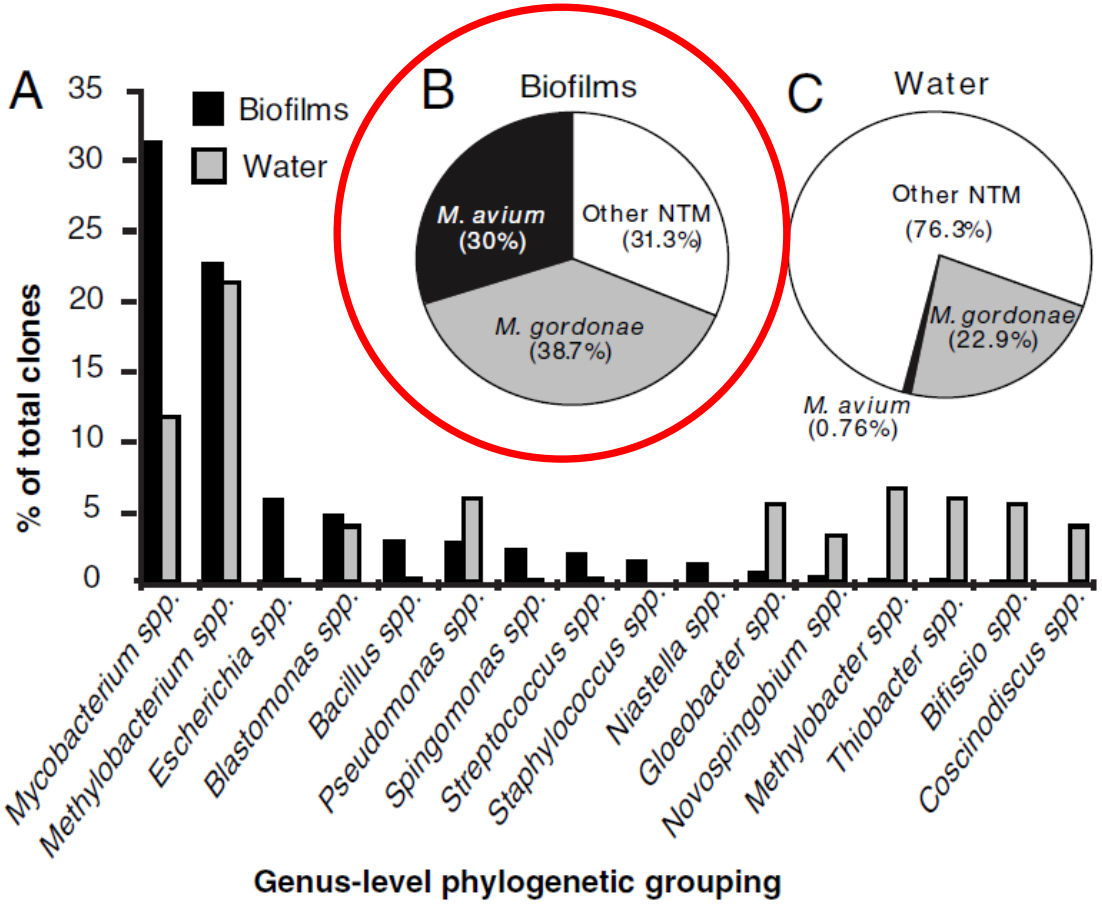
Showerhead – specific niche

- **moist**
- **warm**
- **frequently replenished with low-level nutrient**

PNAS 2009;106:16393–16399

Opportunistic pathogens enriched in showerhead biofilms

Leah M. Feazel[a], Laura K. Baumgartner[a], Kristen L. Peterson[a], Daniel N. Frank[a], J. Kirk Harris[b], and Norman R. Pace[a,1]



PNAS 2009;106:16393–16399

Aerosolization

Mycobacteria

- **Hydrophobic (lipid rich, mycolic acid)**
- **Waxy**
- **Resistant to shear force**

PNAS 2009;106:16393–16399

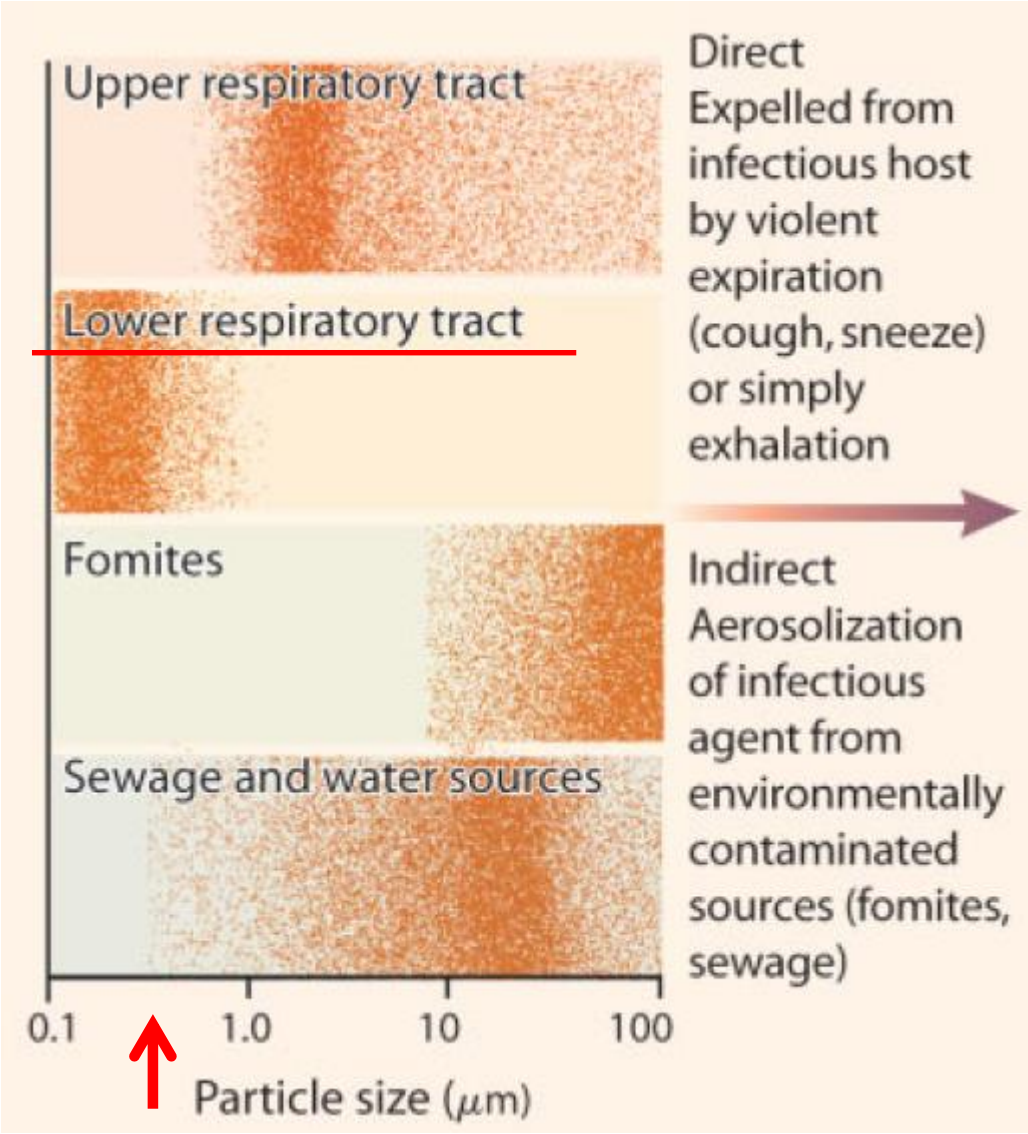
Mycobacterial Aerosols and Respiratory Disease

Joseph O. Falkinham, III*

Aerosolization can result in > 1,000 fold increase in numbers of viable mycobacterial cells

Less than 0.5 µm

Emerg Infect Dis 2003;9:763–767



N Engl J Med 2004;350:1710–1712

The global increase in NTM infections may reflect

the use of showers rather than bathing

Int J Mycobacteriol 2015;4:81–91

Refractory MAC lung disease

Persistent positive sputum cultures despite ≥ 6-12 months of treatment

Genotyping

Persistent infection with the original strain

→ Clofazimine, inhaled AK, moxifloxacin...

Reinfection with new strains

→ Avoid environmental exposure

Table 3 Measures to reduce NTM exposure

Drain water heater
Increase water heater temperature to 55 °C (130 °F)
Switch from piped to well water
Install microbiological filters (≤0.2-μm pore size)
Do not use granular activated carbon filters
Replace showerhead with one having large holes
Disinfect showerhead monthly
Reduce bathroom aerosols
Remove aerators from all taps
Get rid of all humidifiers
Avoid dusts from potting soils
Boiling water for 10 min kills NTM

Curr Environ Health Rep. 2016;3:161–7

“Pink Slime”

Pink-pigmented *Methylobacterium*

Clin Chest Med 2015;36:35–41

Natural history of MAC lung disease

Cavitary MAC lung disease

Antimicrobial susceptibility testing

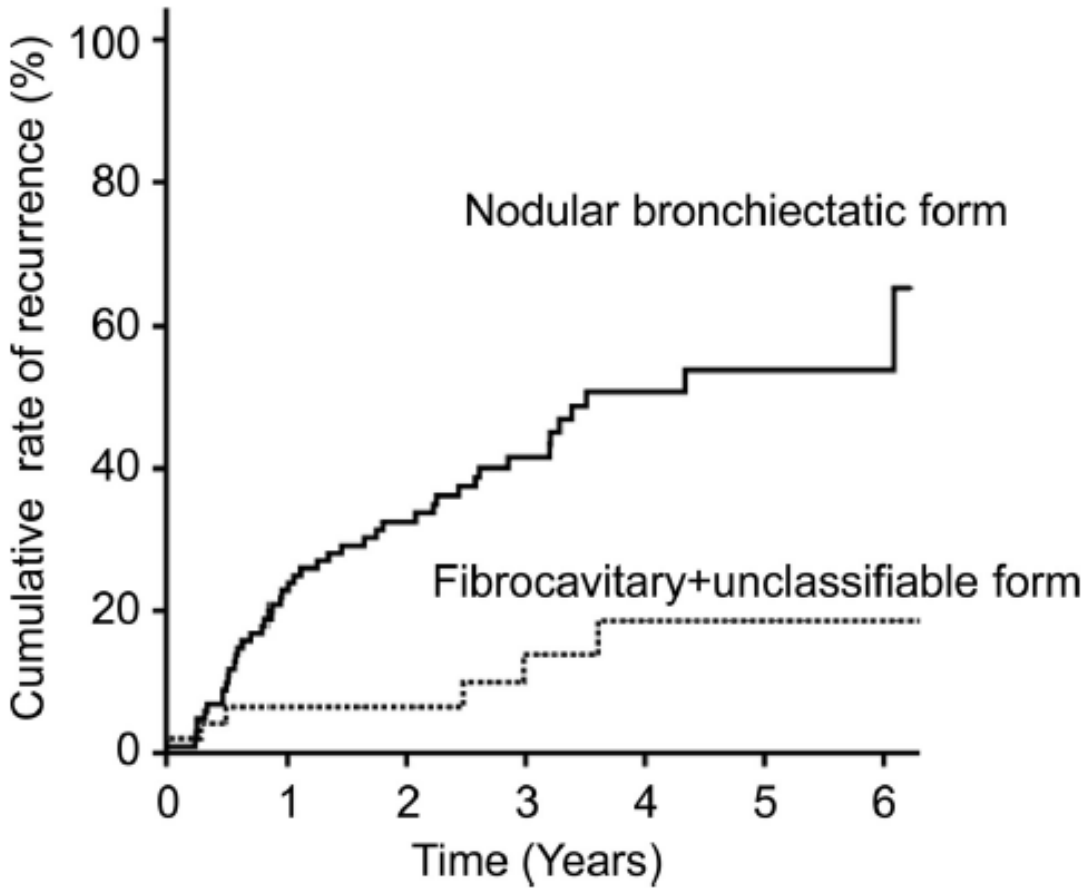
Treatment of refractory MAC lung disease

Environmental sources

Recurrence

158 successfully treated MAC-LD patients.

31.6% recurrence was noted, during a median follow-up of 43.8 mo



Antimicrob Agent Chemother 2015;59:2972

Relapse versus Reinfection of *Mycobacterium avium* Complex Pulmonary Disease

Patient Characteristics and Macrolide Susceptibility

Daniel P. Boyle[1], Teresa R. Zembower[1], and Chao Qi[2,3]

Measurements and Main Results: In our cohort, 25% of patients suffered a clinical recurrence. Of the 46 included patients, 25 (54%) suffered a true relapse and 21 (46%) had a reinfection. Median time between completion of therapy and clinical recurrence was significantly lower in the relapse group compared with the reinfection group (210 d vs. 671 d; $P = 0.004$). The measured convalescent macrolide minimum inhibitory concentrations were significantly more likely to increase in the relapse group compared with the reinfection group (80 vs. 33%; $P = 0.002$). No differences in clinical outcomes were observed between the two groups at conclusion of the study.

Ann Am Thorac Soc 2016;13:1956–1961

TABLE 6 Genotyping results of paired clinical isolates from patients with recurrent *Mycobacterium avium* complex (MAC) lung disease[#]

	Total	Reinfection[¶]	Relapse[¶]	p-value
Subjects	27 (100)	20 (74)	7 (26)	
Type of disease				0.091
NB	22 (81)	18 (82)	4 (18)	
Noncavitary NB	17	14	3	
Cavitary NB	5	4	1	
Fibrocavitary form	5 (19)	2 (40)	3 (60)	
Aetiology				0.091
M. avium	12 (44)	11 (92)	1 (8)	
M. intracellulare	15 (56)	9 (60)	6 (40)	
Time interval between treatment completion and recurrence months	10.6 (5.5–18.3)	13.0 (6.0–23.7)	6.0 (4.8–8.5)	0.040

Eur Respir J 2017;50:1602503

British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD)

- Recurrence: two positive mycobacterial cultures following culture conversion. If available, genotyping may help distinguish relapse from reinfection.

Thorax 2017;72:ii1–ii64

Natural history of MAC lung disease

Cavitary MAC lung disease

Antimicrobial susceptibility testing

Treatment of refractory MAC lung disease

Environmental sources

Recurrence

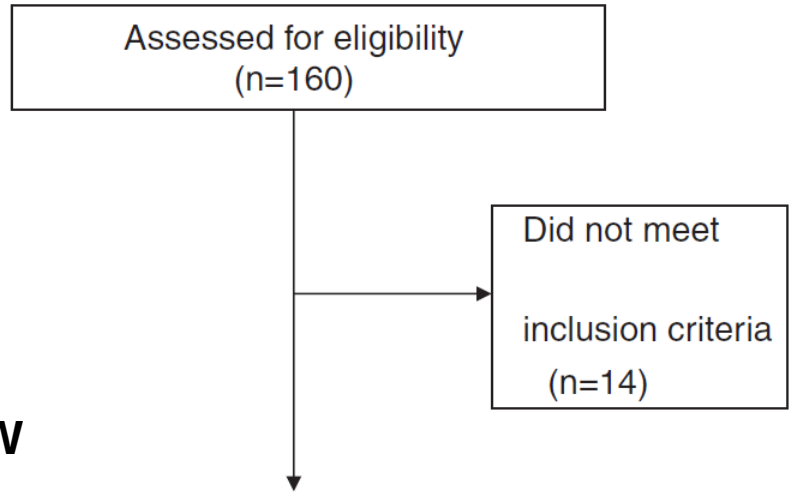
TABLE 3 Predictors of spontaneous sputum conversion in the untreated stationary group of 93 patients

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age years	0.969 (0.945–0.994)	0.015	0.973 (0.948–0.999)	0.043
Male	1.087 (0.612–1.929)	0.776	0.885 (0.484–1.621)	0.693
BMI kg·m^{-2}	1.108 (1.018–1.205)	0.017	1.101 (1.007–1.205)	0.035
Nonsmoker	0.961 (0.542–1.704)	0.892		
Presence of comorbidity[#]	1.309 (0.730–2.345)	0.366		
Positive sputum AFB smear	0.536 (0.259–1.110)	0.093	0.377 (0.156–0.912)	0.030
Causative organism		0.817		
Mycobacterium avium	1			
Mycobacterium intracellulare	0.932 (0.514–1.691)			
Radiological type: nodular bronchiectatic	1.246 (0.634–2.450)	0.524		
Involved lobes	1.012 (0.770–1.329)	0.934		
FVC % pred <80%	1.165 (0.655–2.072)	0.604		
Transient anti-TB medication (⩾1 month)[¶]	2.091 (0.974–4.490)	0.059	3.769 (1.505–9.435)	0.005

Multicenter

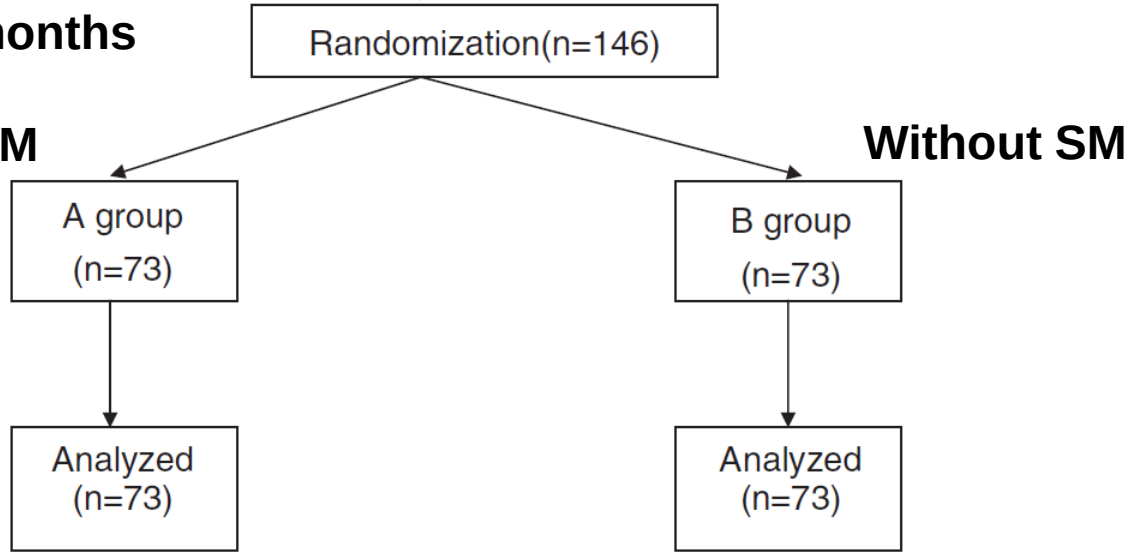
Prospective study, Japan

1998-2004



15mg/Kg/TIW

for 3 months



With SM

Without SM

Sputum conversion: 71.2%

Sputum conversion: 50.7%

Respiratory Medicine 2007;101:130-138

RESEARCH ARTICLE Open Access

The efficacy, safety, and feasibility of inhaled amikacin for the treatment of difficult-to-treat non-tuberculous mycobacterial lung diseases

Kazuma Yagi[1], Makoto Ishii[1*], Ho Namkoong[1], Takahiro Asami[1], Osamu Iketani[2], Takanori Asakura[1], Shoji Suzuki[1], Hiroaki Sugiura[3], Yoshitake Yamada[3], Tomoyasu Nishimura[4], Hiroshi Fujiwara[5], Yohei Funatsu[1], Yoshifumi Uwamino[5], Tetsuro Kamo[1], Sadatomo Tasaka[1], Tomoko Betsuyaku[1] and Naoki Hasegawa[5]

Injectable amikacin sulfate solution, 15mg/Kg/day for 30 min

Commercial available compressor nebulizer

26 patients with NTM lung disease

43.5% - sputum culture conversion

No serious adverse events

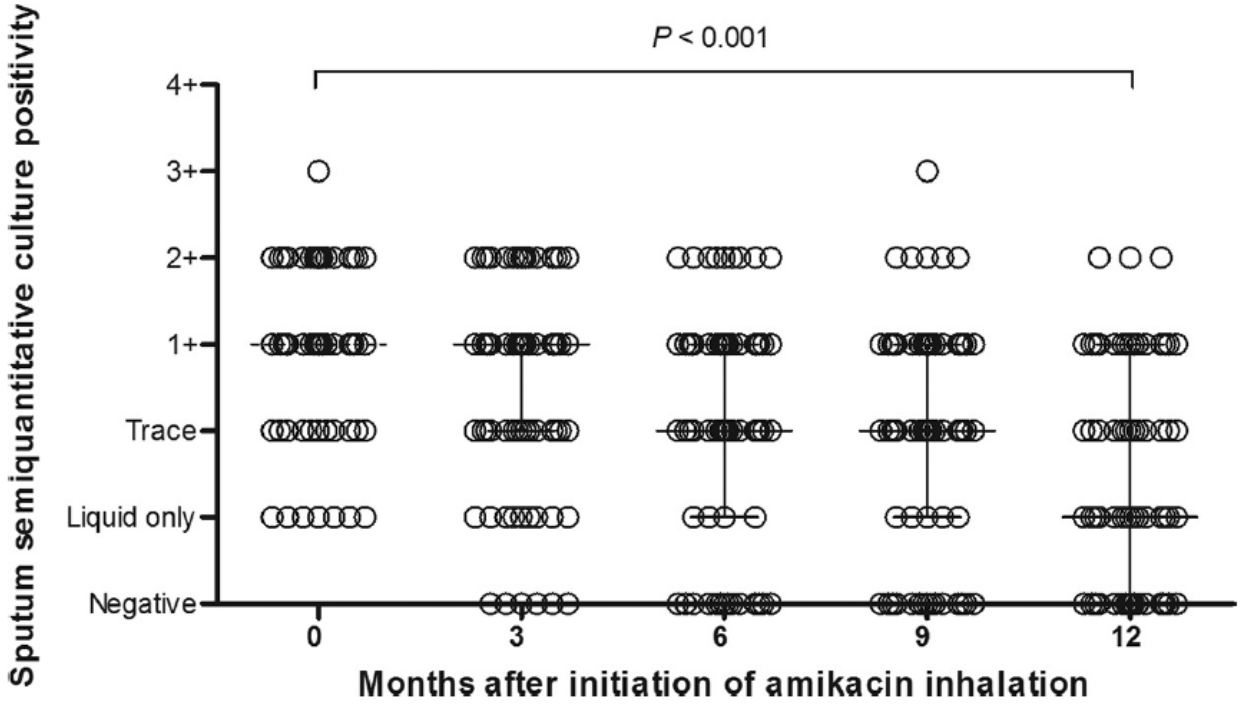
BMC Infect Dis 2017;17:558

2015-2016, Samsung Medical Center

77 patients with refractory NTM lung disease

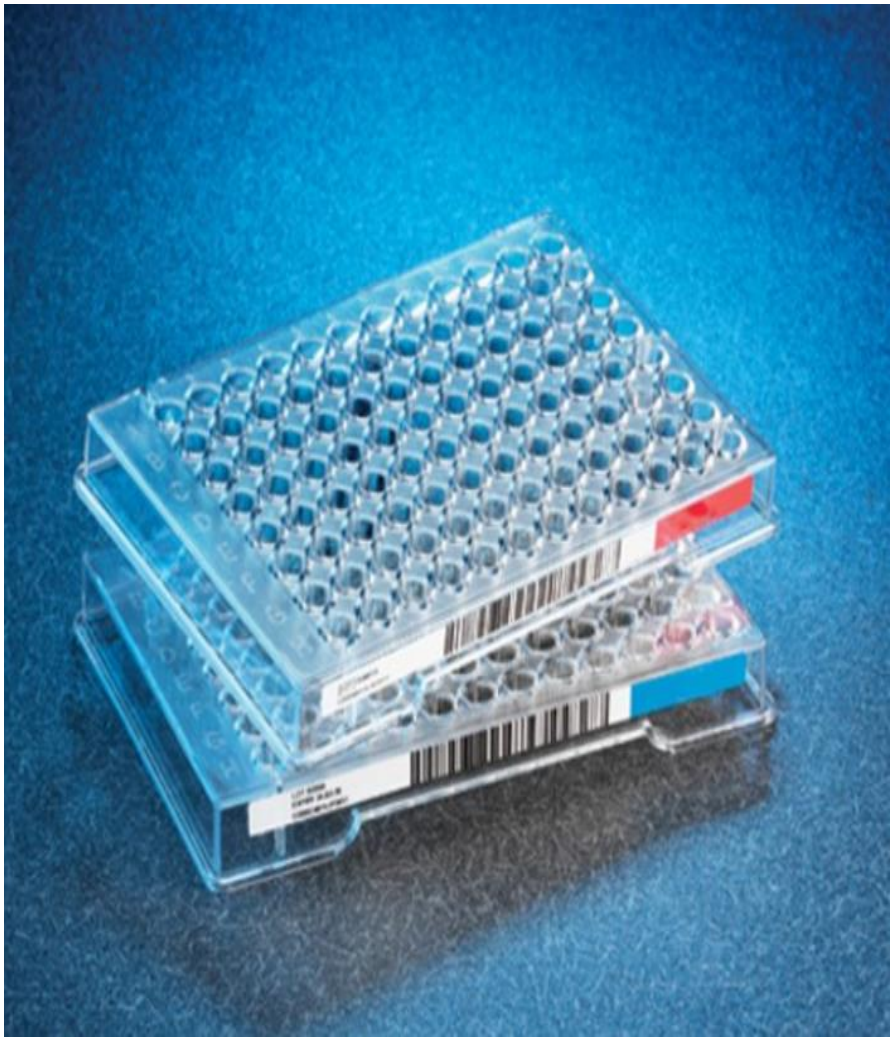
Injectable amikacin sulfate solution

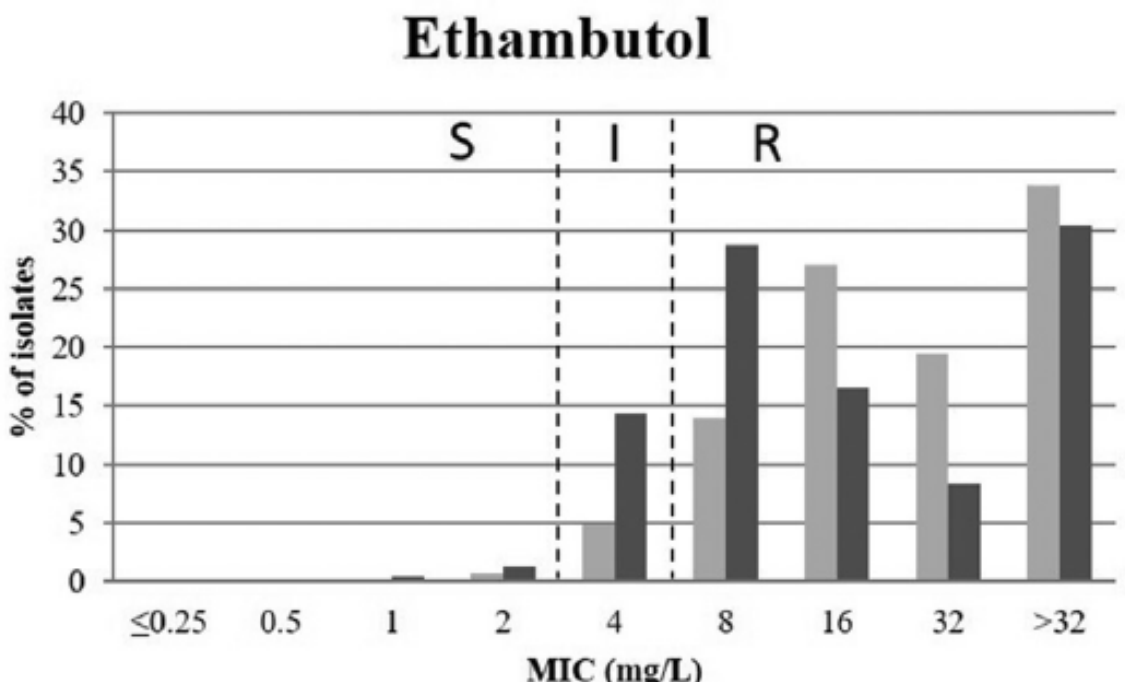
Sputum culture conversion, 18%

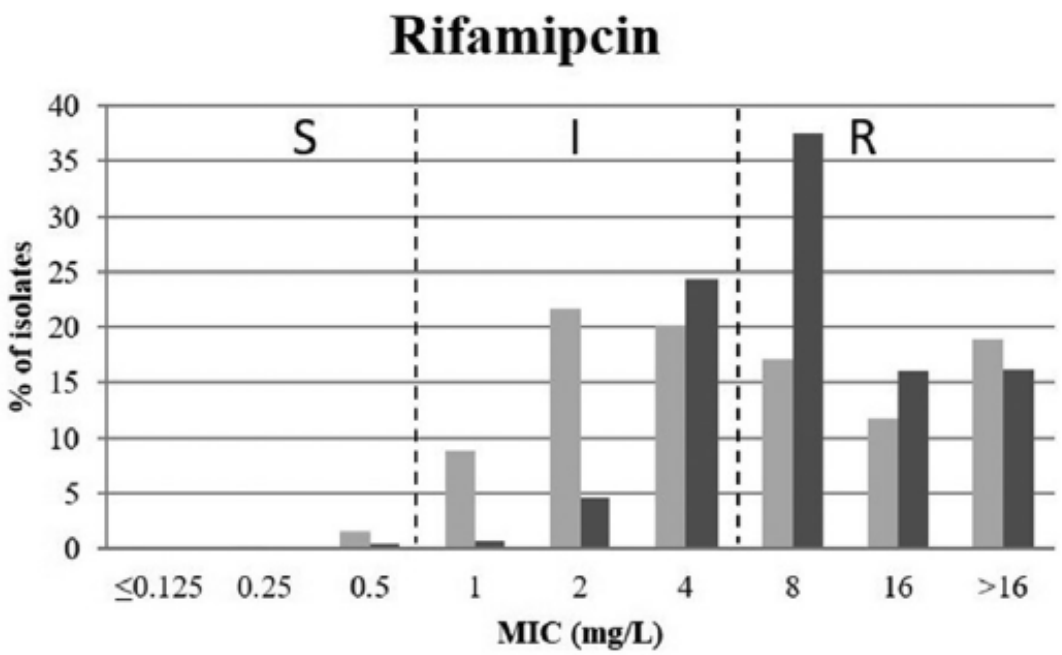


Antimicrob Agent Chemother 2018;62 e00011–18

Sensititre™ Myco Susceptibility Plate for Slow Growing Mycobacteria (Thermo Fisher Scientific Inc., Waltham, Massachusetts, USA)







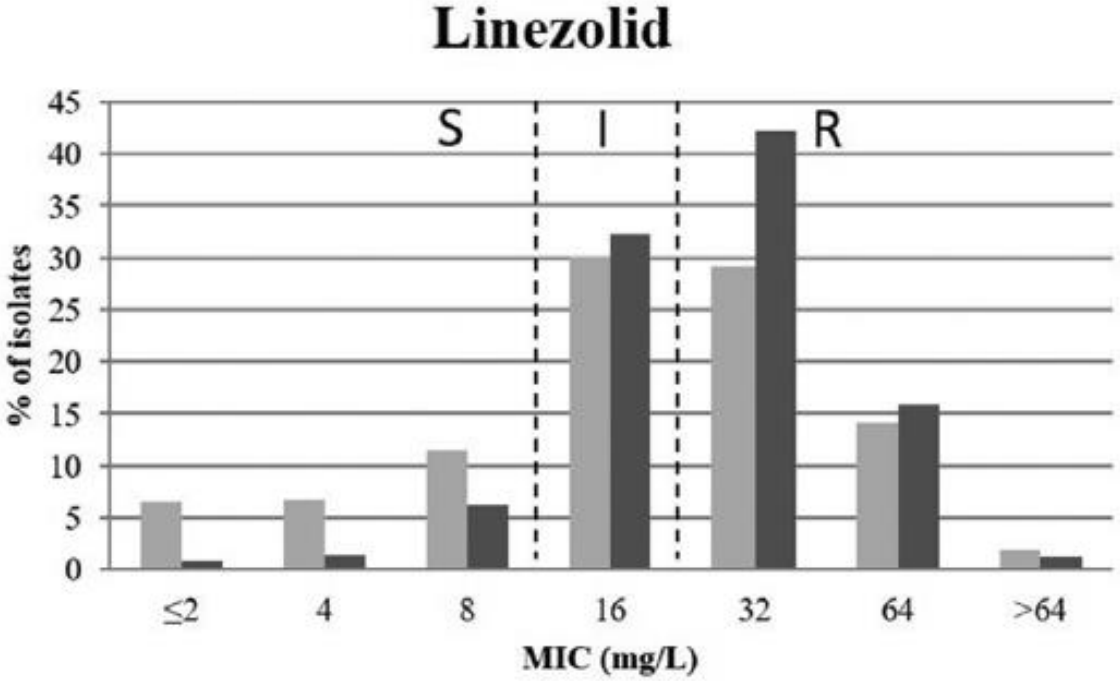
M. avium

M. intracellulare

University of Texas, 189 MAC isolates
Inhibition of MAC by LZD at specified MICs

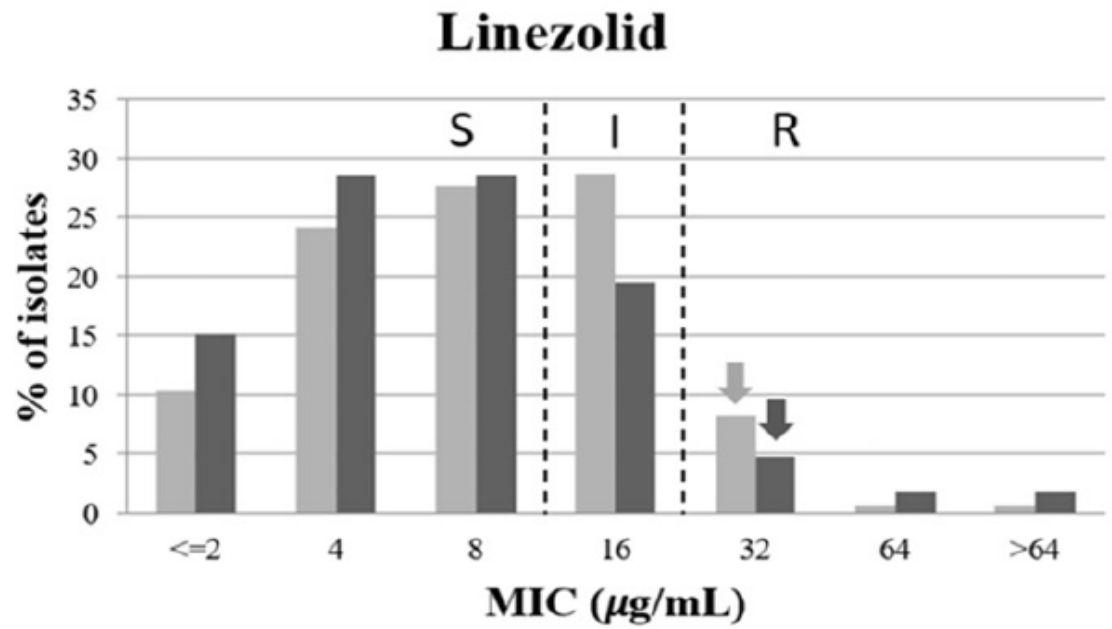
	No. of isolates susceptible at indicated MIC (ug/ml) (cumulative % susceptible)						
	1	2	4	8	16	32	> 32
MAC		2 (2)	3 (4)	17 (13)	50 (39)	63 (72)	52 (100)

Antimicrob Agents Chemother 2003;47:1736–1738



M. avium

M. intracellulare



M. abscessus

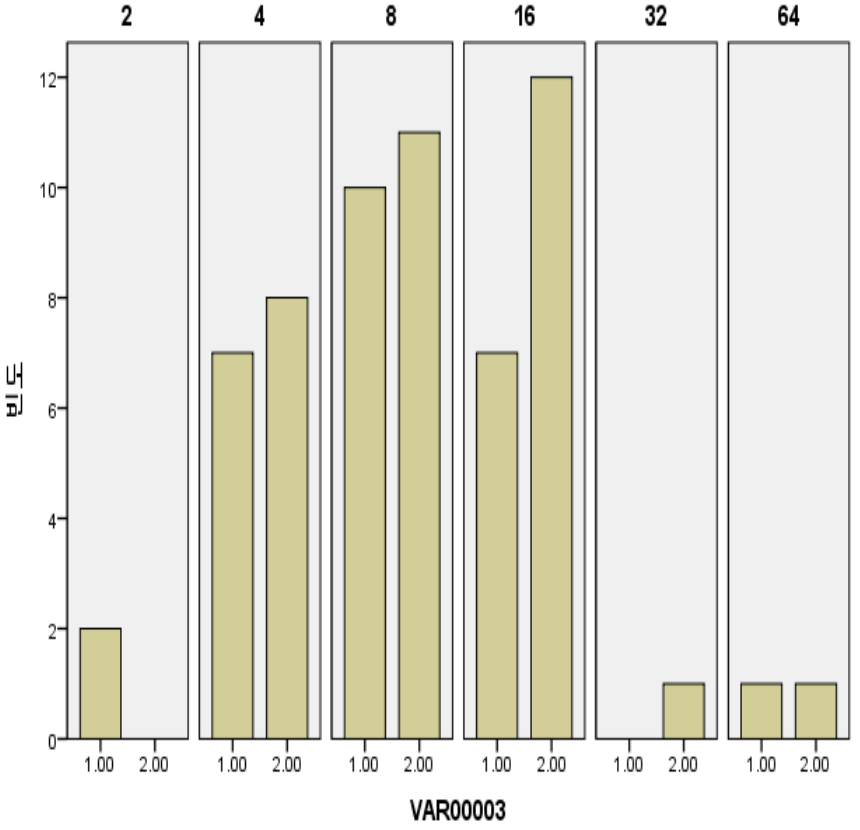
M. massiliense

TABLE 1. Susceptibility of 249 clinical isolates of seven species or taxa of rapidly growing mycobacteria to linezolid as determined by broth microdilution

Species	No. (cumulative %) of isolates inhibited by MIC (μg/ml) of:										No. of isolates tested
	0.25	≤0.5	1	2	4	8	16	32	64	≥128	
M. fortuitum group[a]	0 (0)	0 (0)	4 (5)	15 (26)	26 (61)	19 (86)	7 (96)	3 (100)	0 (100)	0	74
M. fortuitum third biovariant complex	0 (0)	0 (0)	0 (0)	1 (10)	6 (70)	3 (100)	0	0	0	0	10
M. abscessus	0 (0)	2 (2)	0 (2)	1 (3)	6 (9)	14 (23)	24 (48)	39 (88)	10 (98)	2 (100)	98
M. chelonae	0 (0)	0 (0)	1 (2)	0 (0)	5 (12)	21 (54)	20 (94)	2 (98)	1 (100)	0 (100)	50
M. mucogenicum	0 (0)	2 (20)	4 (60)	1 (70)	2 (90)	1 (100)	0	0	0	0	10
M. smegmatis group[b]	0 (0)	1 (33)	0 (33)	1 (67)	1 (100)	0	0	0	0	0	3
M. immunogenum	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (50)	2 (100)	0	0	4

Antimicrob Agents Chemother 2001;45:764-767

Linezolid MIC	*M. avium* (n = 27)	*M. Intracellulare* (n = 33)
2	2	0
4	7	8
8	10	11
16	7	12
32	0	1
64	1	1



1: *M. avium*
2: *M. intracellulare*

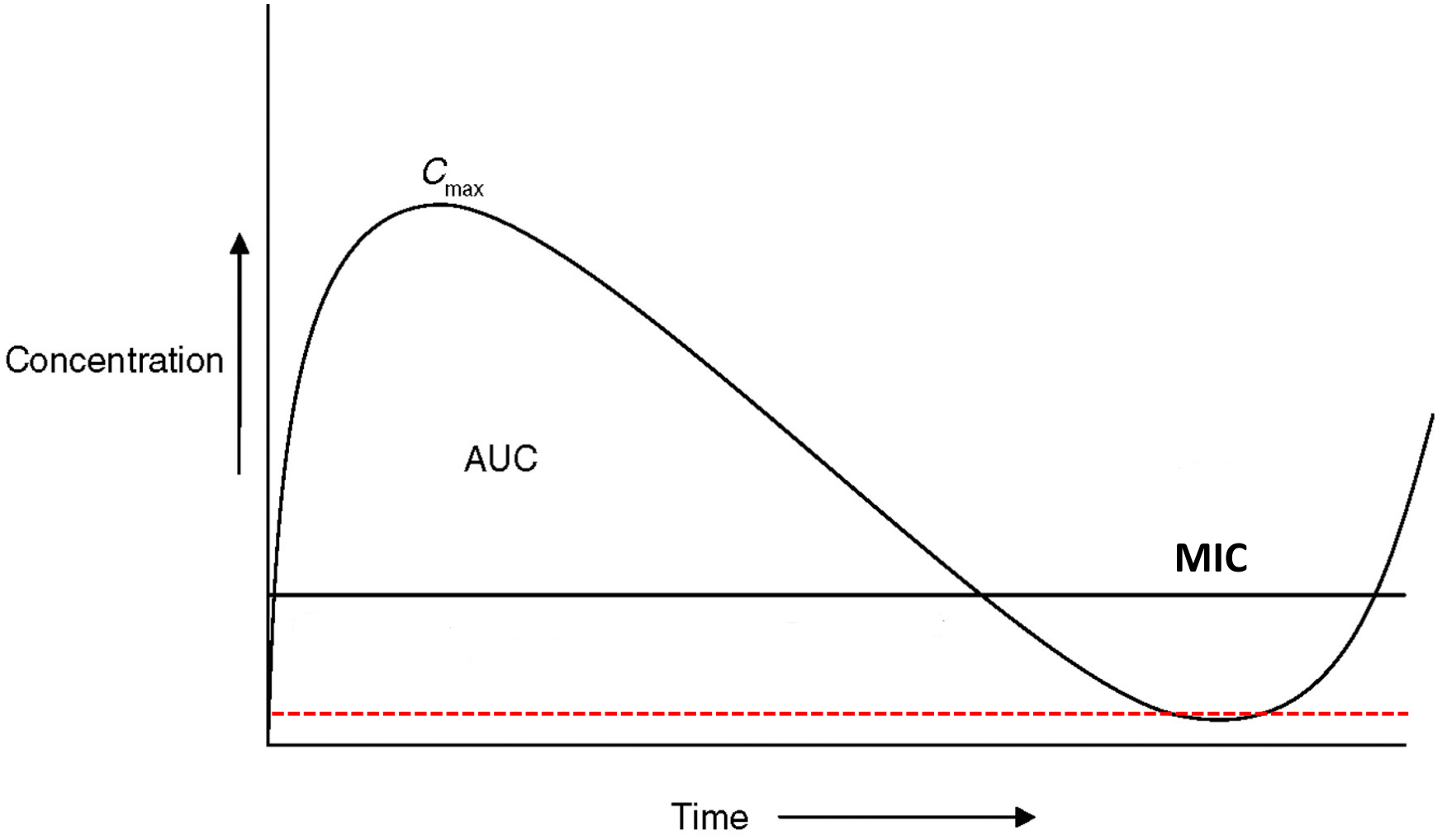
J Antimicrob Chemother 2017; **72** Suppl 2: ii24–ii29
doi:10.1093/jac/dkx304

Journal of Antimicrobial Chemotherapy

Linezolid as treatment for pulmonary *Mycobacterium avium* disease

Devyani Deshpande, Shashikant Srivastava, Jotam G. Pasipanodya and Tawanda Gumbo*

Results: Linezolid achieved a hitherto unprecedented feat of at least 1.0 $\log_{10}$ cfu/mL reduction. Efficacy was most closely linked to the AUC_{0-24}/MIC ratio. The AUC_{0-24}/MIC ratio associated with no change in bacterial burden or bacteriostasis was 7.82, while that associated with 1.0 $\log_{10}$ cfu/mL kill was 42.06. The clinical dose of 600 mg/day achieved or exceeded the bacteriostasis exposure in 98.73% of patients. The proportion of 10000 patients treated with the standard 1200 mg/day who achieved the exposure for 1.0 $\log_{10}$ cfu/mL kill was 70.64%, but was 90% for 1800 mg/day. The proposed MIC breakpoint for linezolid is 16 mg/L, with which 49%–80% of clinical isolates would be considered resistant.


C_{max}
Concentration
AUC
MIC
Time

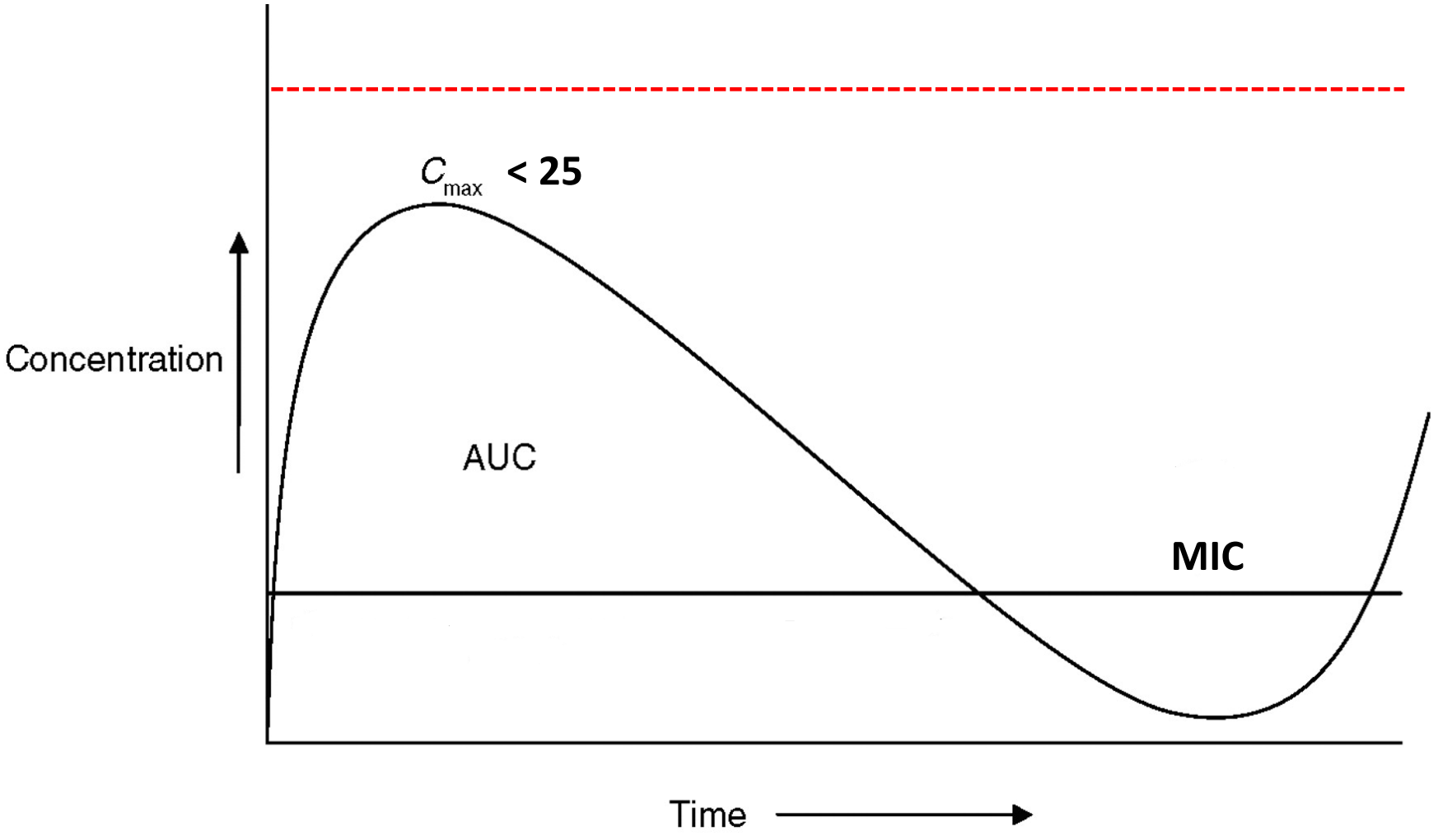

C_{max} < 25
Concentration
AUC
MIC
Time

Table 4. Association of duration of treatment with injectable aminoglycosides with treatment success

Duration of treatment (mo)	n	Multivariate analysis	
		Adjusted OR (95% CI)	*P* Value
0–1.4	8	1.0 (reference)	
1.5–2.9	18	3.793 (0.504–28.546)	0.195
3.0–4.4	28	10.560 (1.489–74.867)	0.018
4.5–5.9	18	24.534 (2.733–220.261)	0.004
6.0–7.4	14	15.481 (1.651–145.186)	0.016
7.5–30	15	1.520 (0.180–12.835)	0.700

Treatment

All patients received clofazimine in combination with other antimycobacterial drugs (e-Table 2). On average, patients with MAC or MABSC used clofazimine as part of a regimen that included three additional drugs during the treatment course. Patients with $>$ 1 NTM species used an average of four additional drugs. Almost all patients (90%) were treated with a macrolide. The majority of patients were prescribed clofazimine 100 mg once daily; six patients started at 50 mg once daily.

Proposal for a standardised treatment regimen to manage pre- and extensively drug-resistant tuberculosis cases

Jose A. Caminero[1,2], Alberto Piubello[2,3], Anna Scardigli[4] and Giovanni Battista Migliori[5]

TABLE 2 Recommended doses for the drugs used in the proposed pre-XDR and XDR-TB regimen

Drug	Body weight kg				
	30–35	36–45	46–55	56–70	>70
Linezolid 600 mg	1 pill	1 pill	1 pill	1 pill	1 pill
Bedaquiline 100 mg	4 pills/24 h during 2 weeks, followed by 2 pills 3 times weekly until the end of the treatment				
Delamanid 50 mg	2 pills/12 h				
Clofazimine 100 mg	1 pill				
Meropenem/imipenem	500 mg/12 h	500 mg/12 h	1 gr/12 h	1 gr/12 h	1,5 gr/12 h
Amoxicillin/clavulanate	1000 mg/12 h				
Amikacin/kanamycin/capreomycin	0.5 g	0.750 g	0.750 g	1 g	1 g
Moxifloxacin	400 mg	600 mg	600 mg	800 mg	800 mg
Levofloxacin	500 mg	750 mg	1 gr	1 gr	1 gr
PAS 4 g	1+1 pill	1+1 pill	1+1 pill	1+1 pill	1+1+1 pill
Isoniazid 300 mg	2 pills	2.5 pills	3 pills	3.5 pills	4 pills

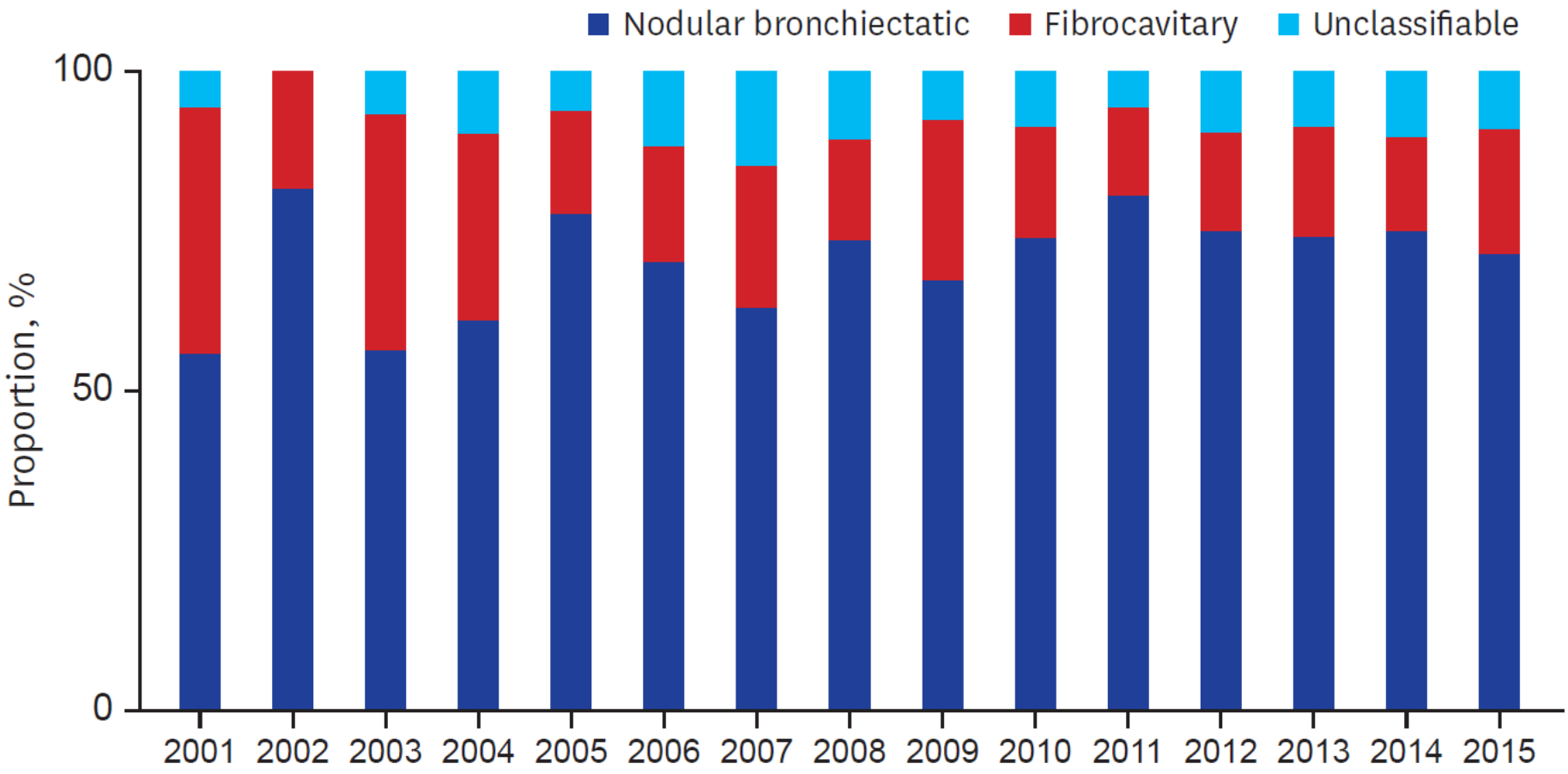
endTB

Clinical and Programmatic Guide for Patient Management with New TB Drugs

Version 3.3

Cfz (50, 100 mg tablets)	200 mg once daily for 2 months, followed by 100 mg daily for duration of treatment

The proportion of NB form > FC form

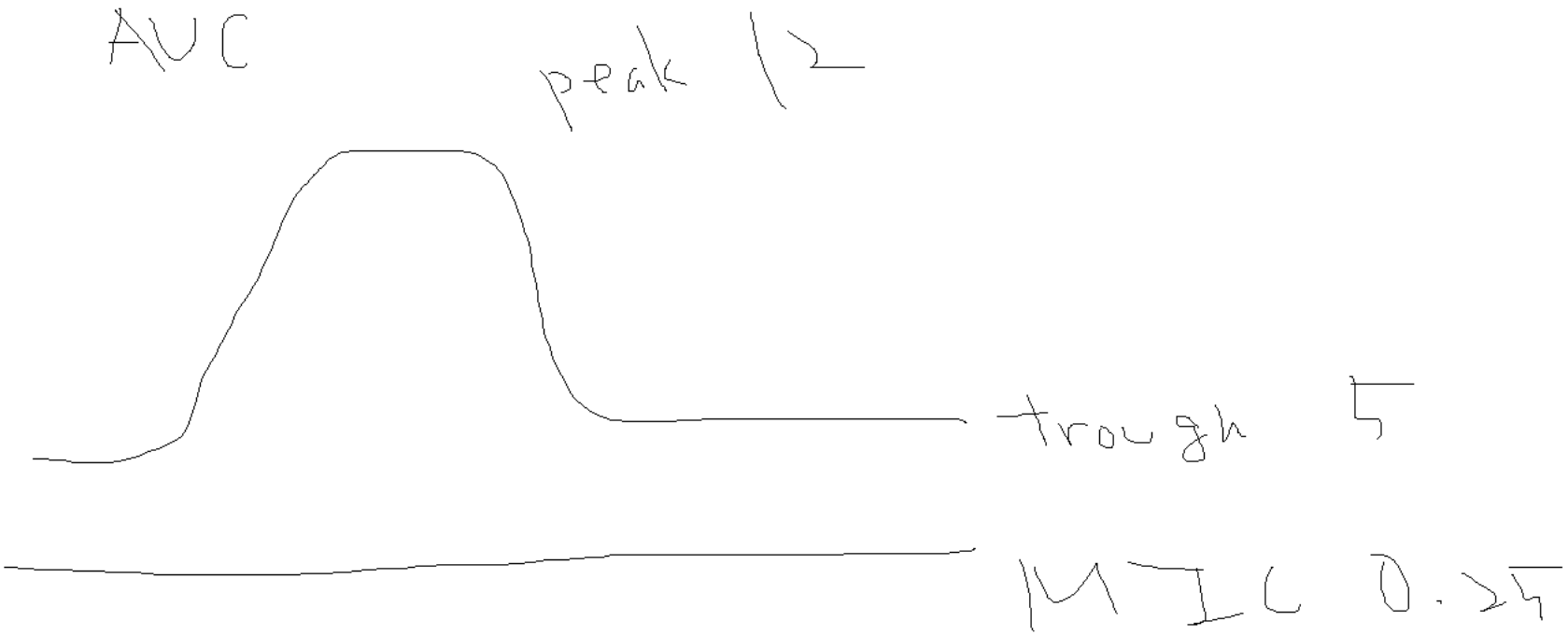


J Korean Med Sci 2018;33:e65

Odds ratio of treatment success in MDR-TB

Duration of intensive phase of treatment		
Duration (months)	Observations	Adjusted[b] odds ratio (95% CLs)
1–2.5	308	1.0 (ref)
2.6–4.0	1406	1.2 (0.5–2.9)
4.1–5.5	481	2.4 (1.3–4.3)
5.6–7.0	377	3.7 (1.9–7.1)
7.1–8.5	172	5.1 (2.1–12.7)
8.6–20	792	2.2 (1.2–3.9)

WHO MDR-TB guideline, 2011



LZD는 AUC/MIC에 비례해서 약효가 있다.
LZD 600mg qd 투여시 peak가 12, trough가 5라면
결핵균 MIC 0.25 보다는 무조건 높음

LZD 600mg qd 투여시 peak가 12, trough가 5라면
MAC MIC 16 보다는 무조건 낮다 → 아무 효과가 없음