대한결핵 및 호흡기학회 제124차 추계학술대회

- 일선진료의를 위한 결핵강좌 -

M. abscessus complex 폐질환의 치료

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울산의대 서울아산병원 호흡기내과

심 태 선

목 차

MABC lung disease의 치료

1. General practice
2. Experimental regimens
3. Anti-NTM drugs
    1) Conventional drugs
    2) Experimental drugs

Decision to Treat MABC* Lung Disease

올바른 NTM 질환 진단

올바른 원인균 진단

약제감수성 검사

치료시기 결정

- Underlying general conditions
- Severity of symptoms
- Rapidity of progression
- Radiologic type
- Severity of side effects

치료 약제 선정

* MABC = *Mycobacterium abscessus* complex

Predictors of disease progression

(Park et al., Clin Infect Dis 2017; 64:301-8)

Retrospective study
South Korea, 2006 – 2015
56 *M. abscessus* vs. 54 *M. massiliense* lung disease

Variable	Unadjusted Odds Ratio (95% CI)	*P* Value	Adjusted[a] Odds Ratio (95% CI)	*P* Value
BMI				
≥18.5 kg/m^2	1.00	<.001	1.00	.013
<18.5 kg/m^2	8.57 (2.85–25.73)		4.79 (1.39–16.48)	
Radiographic pattern				
Nodular bronchiectatic	1.00	.001	1.00	.046
Fibrocavitary	7.00 (2.31–21.20)		3.62 (1.02–12.82)	
Disease extent				
Unilateral	1.00	.039	1.00	.040
Bilateral	3.08 (1.06–8.99)		3.83 (1.06–13.82)	

Treatment of MABC lung disease

(Griffith et al. AJRCCM 1993)

- 1975 - 1991 yrs
- 154 patients with RGM lung disease

  M. abscessus complex 119 cases
- Drug regimen: amikacin (58%), cefoxitin (43%), EM (31%)

  sulfonamides or TMP/SMX (28%), clarithromycin (0%)

  anti-TB drugs (37%)
- Outcome

  Treatment success in 10/119 (8.4%) MABC lung disease

  7: antibiotics for 1-3 mo → surgical excision

  3: antibiotics alone
- Patient characteristics

  female (65%), upper lobe infiltration (88%)
- Mortality: 18/119 (15%)

Treatment of MABC lung disease

(ATS guidelines,1997)

- Susceptible to clarithromycin (100%), clofazimine, amikacin (90%), and cefoxitin (70%) and imipenem (50%).
- **Monotherapy** with the newer macrolides is not sufficient to produce microbiologic cure for MABC.
- **Combination therapy** of low-dose amikacin plus high-dose cefoxitin for **2–4 wk** almost invariably produces clinical and microbiologic improvement, but cost and morbidity prohibit potentially curative courses of treatment (probably 4–6 mo).
- **Surgical resection** for limited disease can be curative.
- **Suppressive therapy**, including periodic parenteral antibiotic or oral macrolide therapy.

Treatment of MABC lung disease

(Daley & Griffith. Clin Chest Med 2002;23: 623-32)

Drug[a]	Dose (maximum)	Frequency
Clarithromycin[b] *and*	1000 mg (1.0 g)	Once daily or in two divided doses
Amikacin[c] *and*	15 mg/kg	Once daily or in two divided doses
Cefoxitin *or*	200 mg/kg (12 g/d)	Daily in divided doses
Imipenem	750 mg	Three times daily

Duration: unknown.

Treatment of MABC lung disease

(ATS guidelines,2007)

- Goal: negative sputum culture for more than 12 months: **Unrealistic**
- Alternative goal: symptomatic improvement or short-term culture conversion

  - Amikacin + cefoxitin (or imipenem) for 2-4 months (+ clarithromycin)

    => clinical & microbiological improvement
- Suppressive therapy, including periodic parenteral antibiotic or oral macrolide therapy
- Curative therapy in limited disease:

  => surgical resection & medical treatment
- Underlying condition modification

Treatment of MABC lung disease

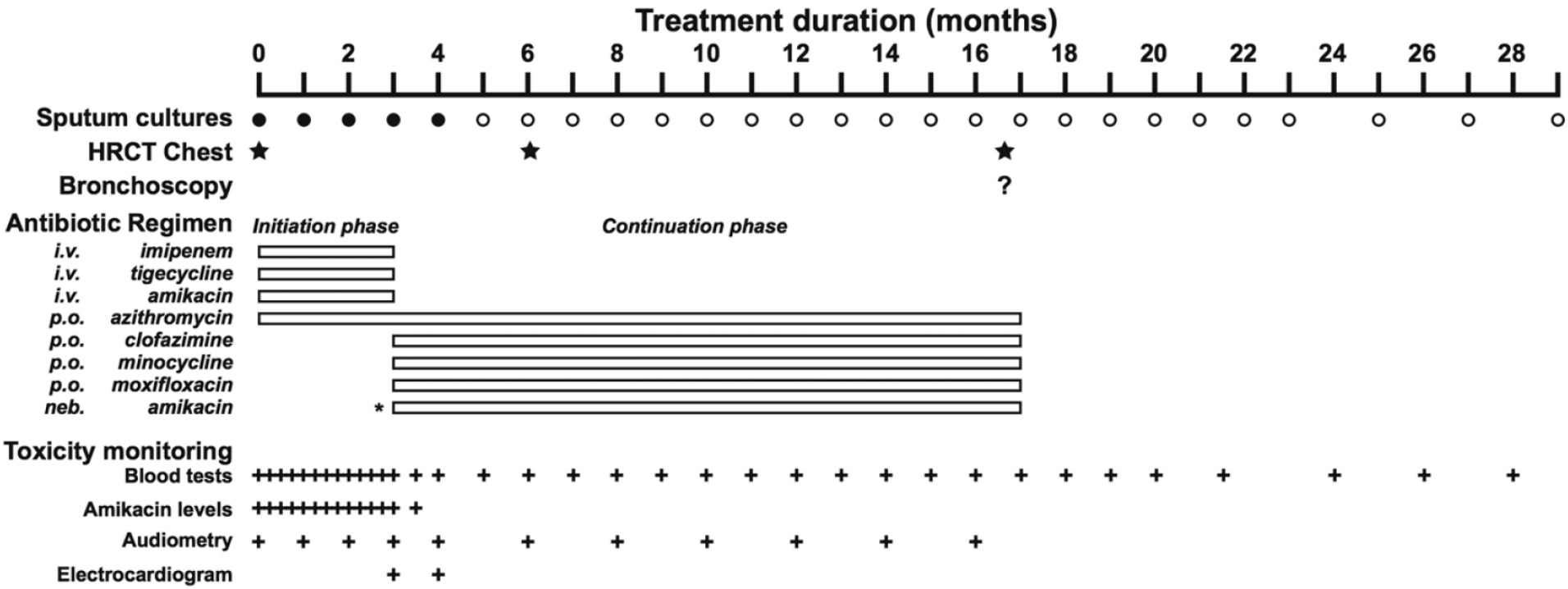
(De Groote et al. CID 2006;42: 1756 -63)

Most experts in the field practice intermittent intravenous therapy: intravenous imipenem or cefoxitin for 1 or 2 months plus a macrolide. Intravenous amikacin may also be used adjunctively in this pulsed fashion as long as there are no contraindications, such as renal insufficiency or evidence of damage to cranial nerve VIII. For the periods in between the pulsed intravenous therapy, "holding" regimens of a macrolide plus a quinolone may be helpful, even if in vitro susceptibility results reveal resistance to the quinolones.

Typical MABC treatment schedule in CF patients

(US CF Foundation and ECFS)

(Floto et al., Thorax 2016; 71:i1–i22)



Intensive (3–12 weeks): macrolide, iv amikacin + one or more.
Continuation: macrolide, inhaled amikacin + 2–3 drugs

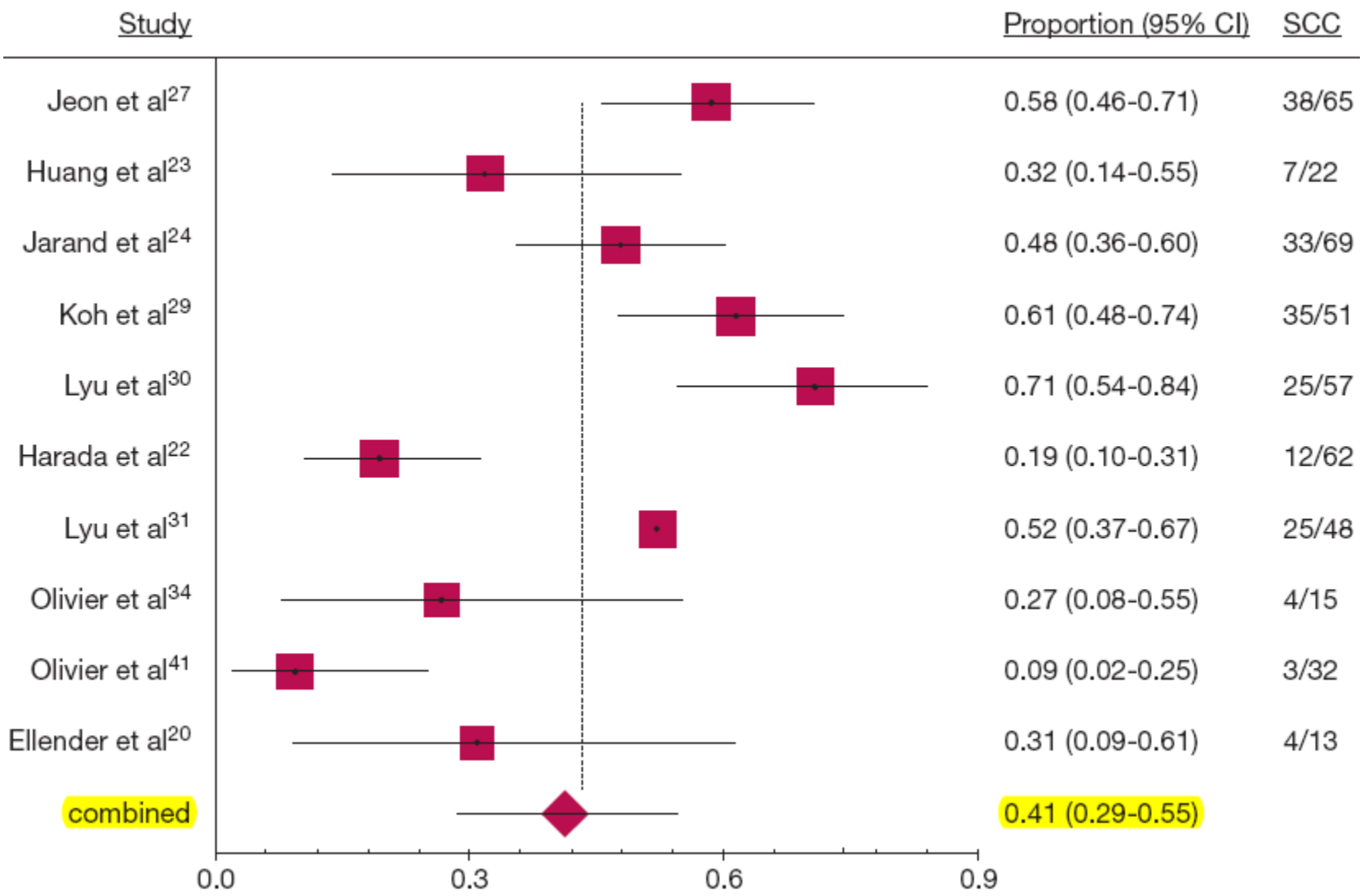
Treatment outcomes of MABC lung disease

(Koh et al., IJTLD 2014;18: 1141–1148)

Aetiology	Antibiotic treatment	Treatment duration (median or mean)		Combined surgery *n* (%)	Sputum conversion without relapse *n* (%)
		Parenteral antibiotics	Total		
M. abscessus complex*					
Jeon et al. ($n = 65$)[25]	AMK FOX CLM CPX DCX for 4 weeks' hospitalisation, followed by CLM CPX DCX[†]	4 weeks	24.4 months	14 (22)	38 (58)
Lyu et al. ($n = 41$)[26]	AMK FOX CLM (hospitalisation, $n = 24$, 59%) or AMK CLM (out-patient, $n = 17$, 41%)[‡]	7.7 months (12 weeks of hospitalisation)	17.0 months	13 (32)	29 (70)
Jarand et al. ($n = 69$)[27§]	CLM or AZM (97%) AMK (71%) IPM (55%) FOX (30%) CPX (43%) MFX (12%)	6 months	52 antibiotic-months	23 (33)	33 (48)

Overall treatment success for MABC lung disease

(Diel et al., Chest 2017; 152:120–42)



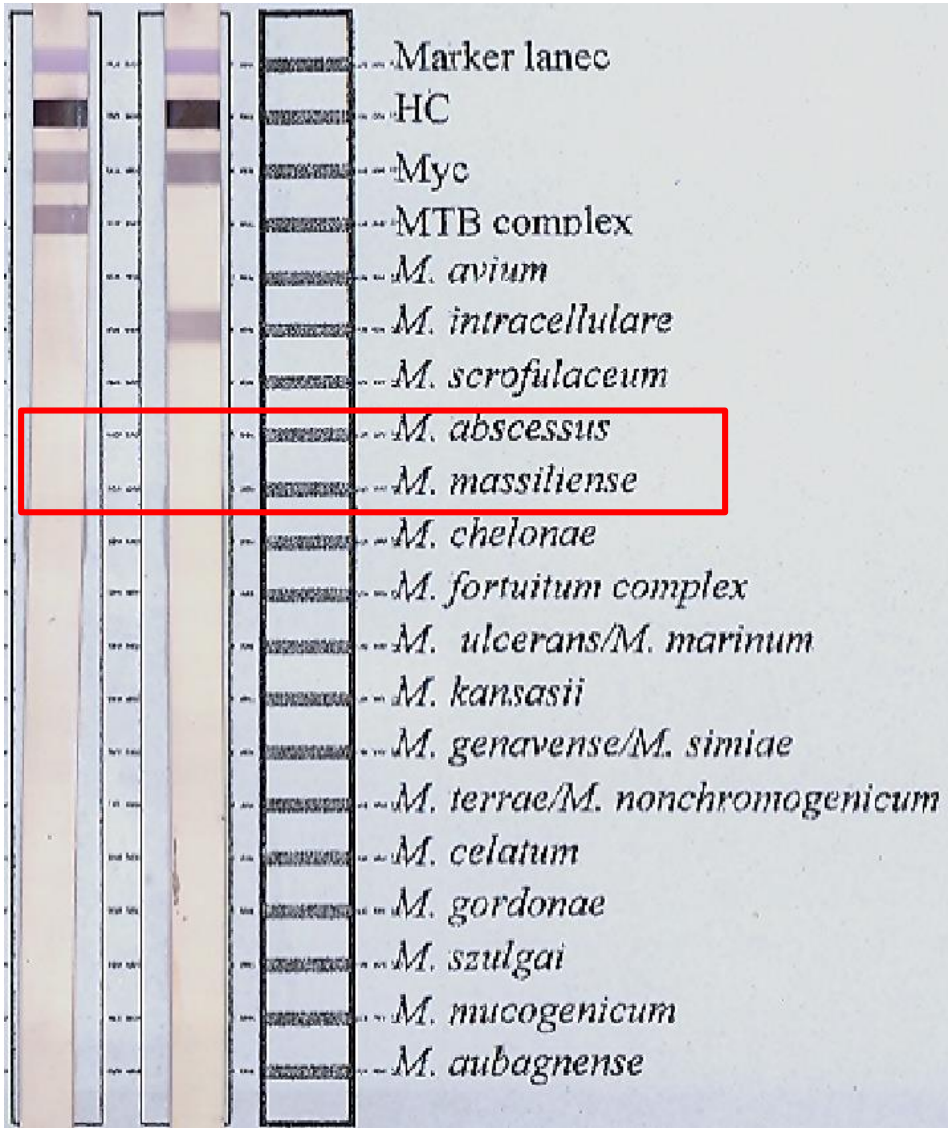
Taxonomy of *M. abscessus* complex

M. abscessus subsp. *abscessus*

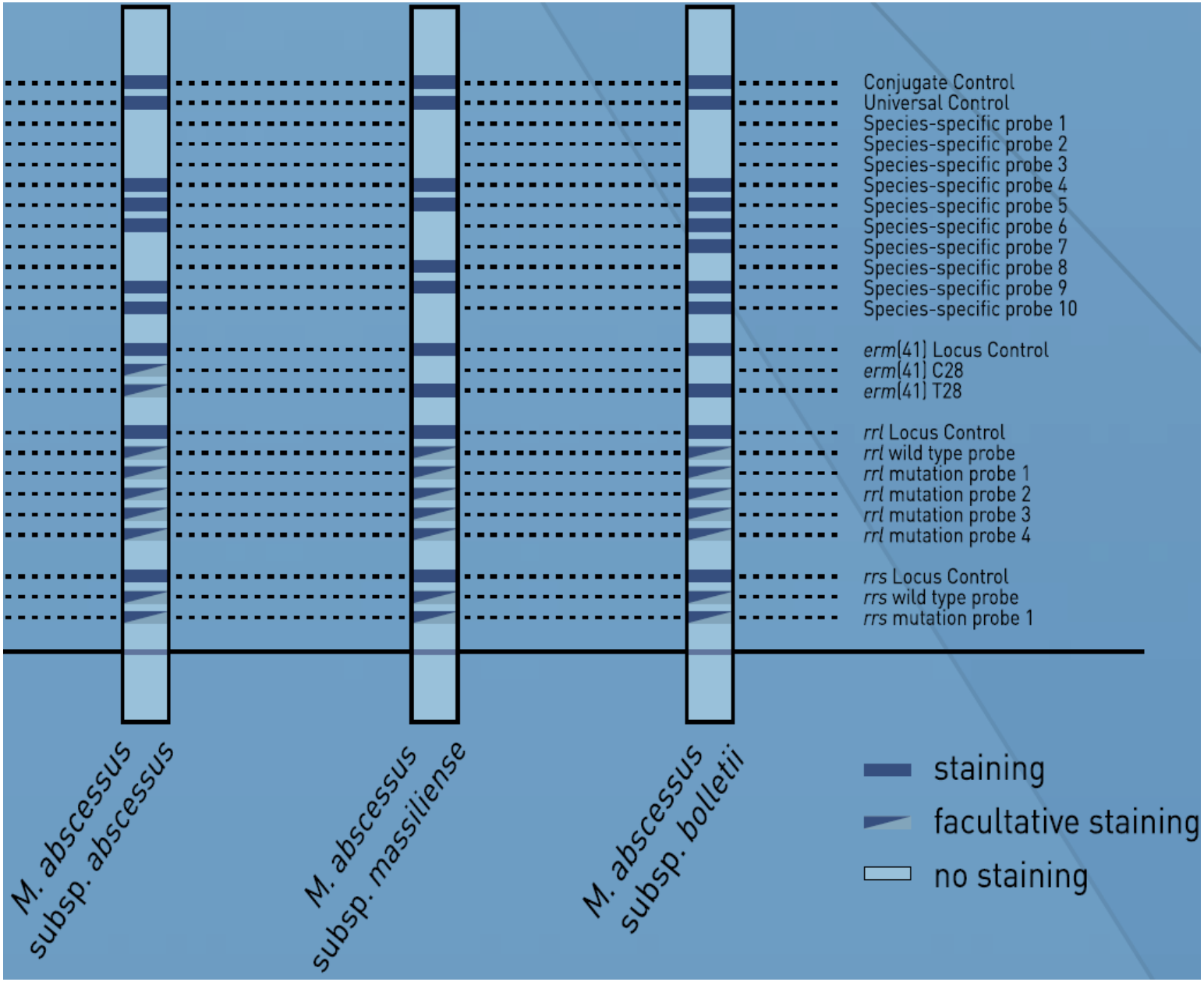
M. abscessus subsp. *massiliense*

M. abscessus subsp. *bolletii*

Subspecies differentiation of MABC (REBA Myco-ID, Korea)



GenoType NTM-DR



Geographic differences of proportion of MABC subspecies

(Koh et al., IJTLD 2014;18: 1141–1148)

Author, year, reference	Country	Total *n*	*M. abscessus* *n* (%)	*M. massiliense* *n* (%)	*M. bolletii* *n* (%)
Zelazny, 2009[16]	United States	40	27 (67.5)	11 (27.5)	2 (5)
van Ingen, 2009[17]	Netherlands	39	25 (64)	8 (21)	6 (15)
Roux, 2009[15]	France	50	30 (60)	11 (22)	9 (18)
Harada, 2012[18]	Japan	102	72 (71)	27 (26)	3 (3)
Yoshida, 2013[19]	Japan	143	90 (63)	50 (35)	3 (2)
Nakanaga, 2014[20]	Japan	115	69 (60)	43 (37)	3 (3)
Huang, 2013[21]	Taiwan	79	34 (43)	44 (56)	1 (1)
Kim, 2008[22]	Republic of Korea	126	67 (53)	57 (45)	2 (2)
Koh, 2011[23]	Republic of Korea	158	64 (44)	81 (55)	2 (1)
Lee, 2014[24]	Republic of Korea	404	202 (50)	199 (49)	3 (1)

Inducible macrolide resistance by functional *erm*(41)** gene

Subspecies	erm(41) function	Susceptibility to CLR	
		Baseline R (BR)* (Day 3)	Inducible R (IR) (Day 14)
M. abscessus	Yes	S	R
M. massiliense	No	S	S
M. bolletii	Yes	S	R

Some *M. abscessus*: T28C polymorphism (C28 sequevar)

⇒ IR to CLR (−) => susceptible to CLR

Some *M. massiliense*: functional *erm*(41) gene

⇒ IR to CLR (+) => resistant to CLR

* Some MABC have BR to CLR (23S rRNA mutations; *rrl* gene)

** *erm*: erythromycin resistance methylase

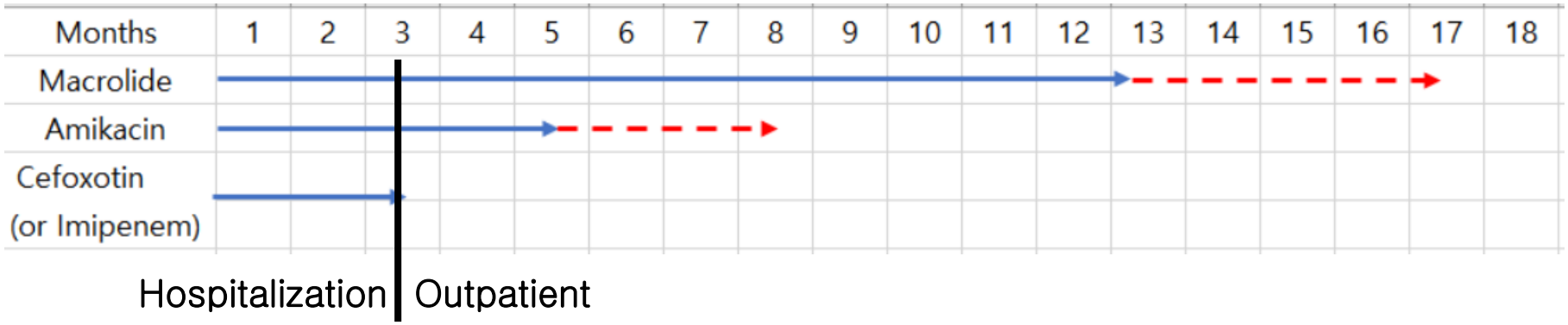
Treatment outcomes of MABC lung disease

(Koh et al., IJTLD 2014;18: 1141–1148)

Aetiology	Antibiotic treatment	Treatment duration (median or mean)		Combined surgery *n* (%)	Sputum conversion without relapse *n* (%)
		Parenteral antibiotics	Total		
M. abscessus					
Koh et al. ($n = 24$)[23]	AMK FOX CLM CPX DCX for 4 weeks' hospitalisation, followed by CLM CPX DCX	4 weeks	23.1 months	NA	6 (25)
M. massiliense					
Koh et al. ($n = 33$)[23]	AMK FOX CLM CPX DCX for 4 weeks' hospitalisation, followed by CLM CPX DCX	4 weeks	21.6 months	NA	29 (88)

Shorter treatment duration for *M. massiliense* lung disease

(Lyu et al., Respir Med 2014;108: 1706-12)



Retrospective study, Korea

M. massiliense (n=22 ⟶) vs. *M. abscessus* (n=26, - - →)

Parenteral treatment: 4.7 vs 7.4 months (p=0.006)

Total treatment: 12.1 vs 16.3 months (p=0.043)

Treatment success rate: 95.5% vs. 42.3% (p<0.01)

Relapse free, success rate: 77.3% vs. 30.8% (p<0.05)

F/U duration: mean 1087 days (range 52 – 2756)

Predictors of sustained culture conversion

(Park et al., Clin Infect Dis 2017; 64:301-8)

Retrospective study
South Korea, 2006 – 2015
36 *M. abscessus* or *M. 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)	

Microbiologic factors affecting treatment outcome in *M. abscessus* subsp. *abscessus* lung disease

(Koh et al., Clin Infect Dis 2017; 64:309-16)

Subspecies differentiation

Baseline DR, especially macrolide-R

Inducible macrolide-R

Smooth vs. rough colony

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			

Treatment outcomes of macrolide-R *M. massiliense* lung disease

(Choi et al., Antimicrob Agents Chemother 2017)

Retrospective study

South Korea, 2005 – 2015

15 patients

Favorable outcome in 7% (1/15): with concomitant surgery

Antibiotic therapy (no. [%])	
Amikacin	10 (67)
Cefoxitin or imipenem	10 (67)
Macrolide	15 (100)
Fluoroquinolone	5 (33)
Doxycycline	3 (20)
Linezolid	1 (7)
Trimethoprim-sulfamethoxazole	2 (13)
Clofazimine	7 (47)
Amikacin inhalation	5 (33)

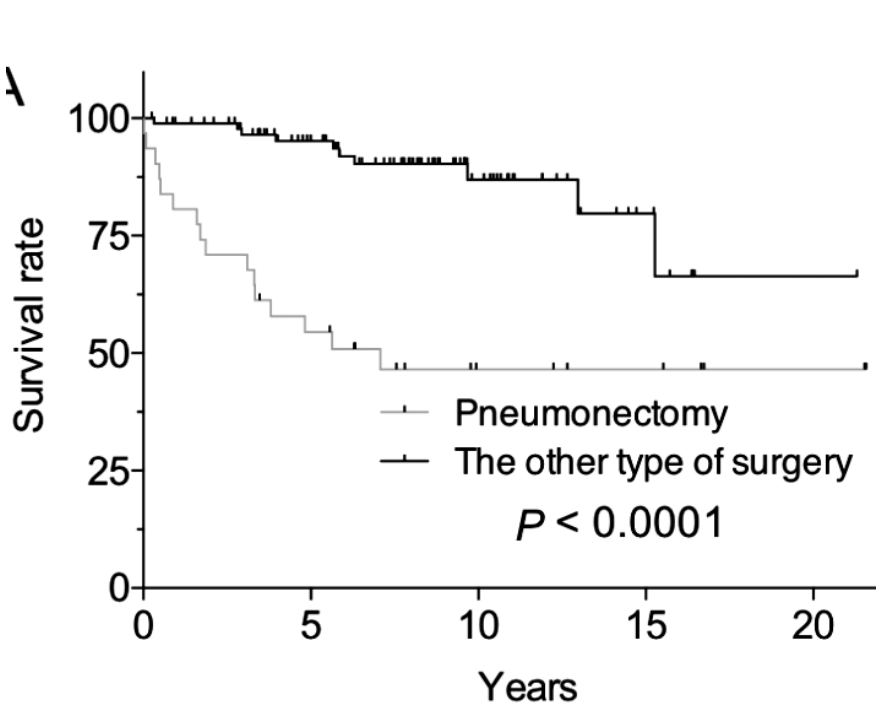
Surgical treatment of MABC lung disease

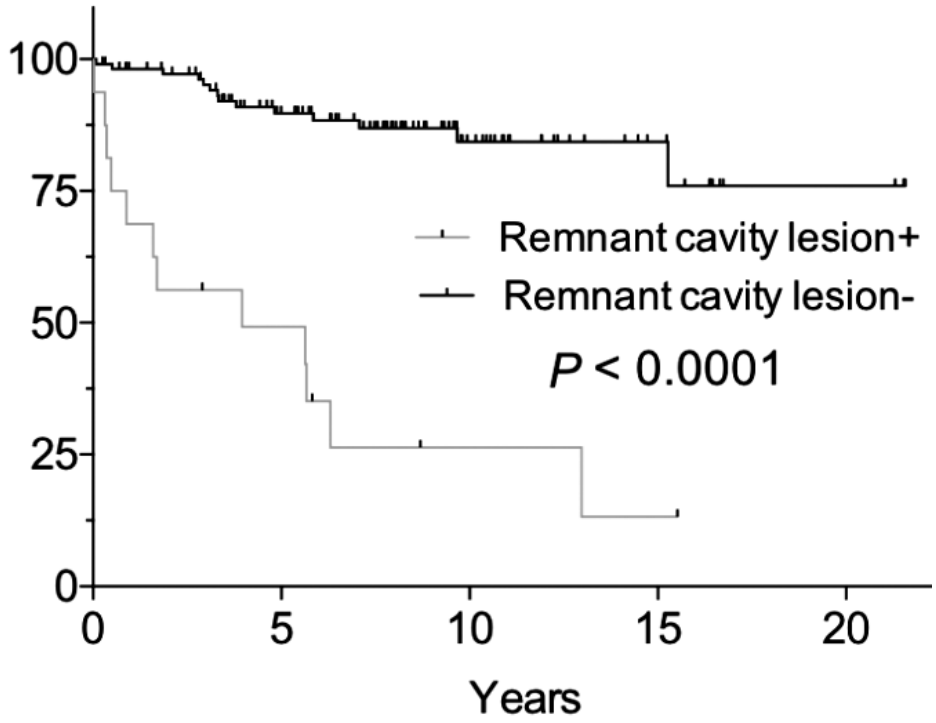
(Kang, et al. BMC Infect Dis 2015;15:76)

Authors	No. of Pts	Species	Sputum culture conversion (%)	Relapse (%)	Mortality/ Morbidity (%)	
Shiraishi, 2004	11	MAC (10), MABC (1)	100	9	18	36
Sherwood, 2005	26	MAC (15), MABC (1)	82	0	23	46
Koh, 2008	23	MAC (10), MABC (12)	91	0	4	35
Mitchell, 2008	236	MAC (189), MABC (32)	NA	NA	3	12
Yu, 2011	134	MAC (118), MABC (14)	84	7	0	7
Jarand, 2011	24	MABC (24)	57	NA	17	25
Mitchell, 2012	171	MAC (147), MABC (36)	NA	NA	0	9
Shiraishi, 2013	60	MAC (55), MABC (3)	100	3	0	12
Kang, 2015	70	MAC (45), MABC (23)	81	0	1	20

K-M survival curves after pulmonary resection in 125 patients with NTM lung disease

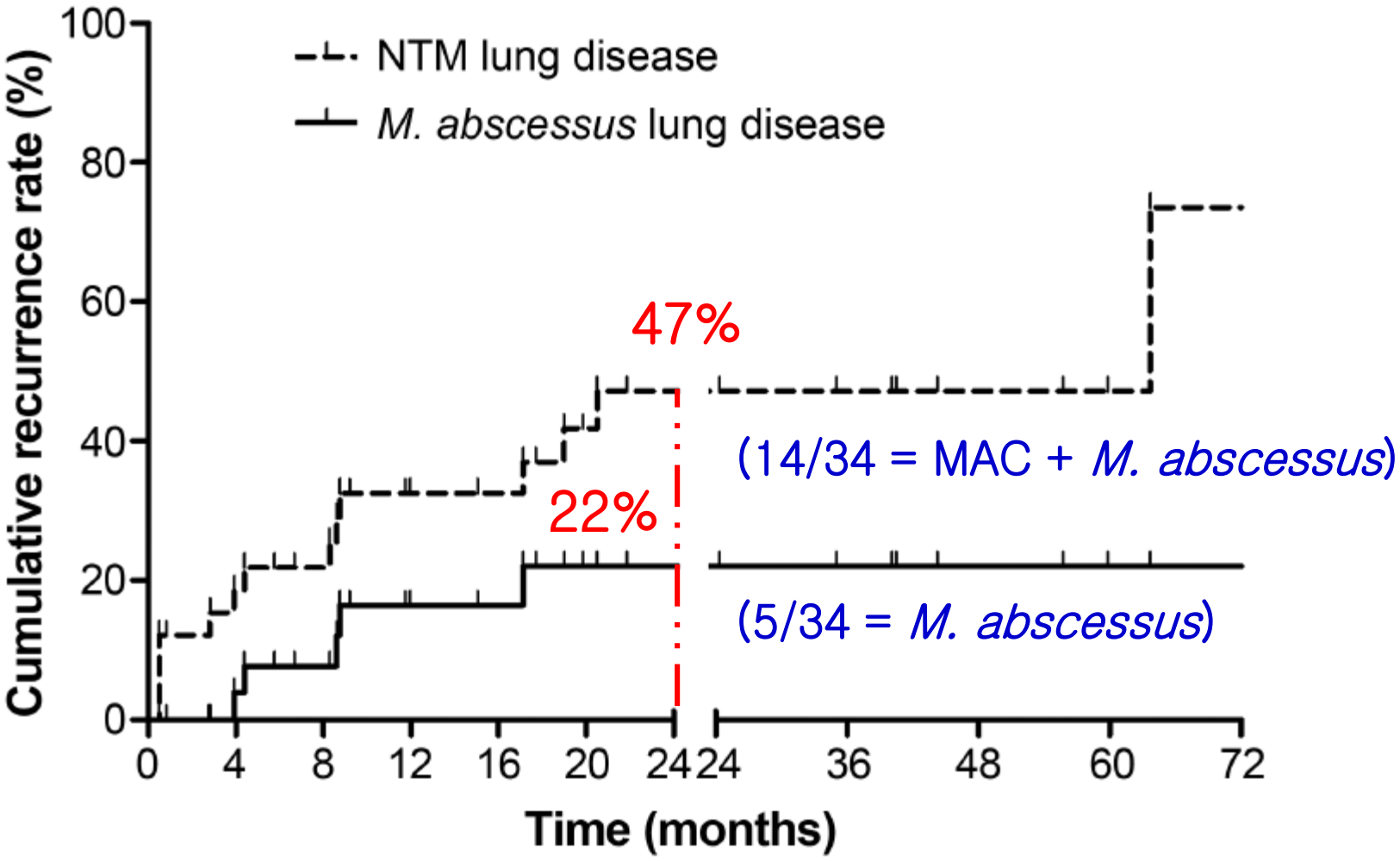
(Asakura et al., Clin Infect Dis 2017; 65:244-51)





Recurrence of NTM disease in 34 patients with *M. abscessus* lung disease

(Koh et al., Clin Infect Dis 2017; 64:309-16)



Controversies during treatment

수술적 절제술 시행 여부

주사제의 사용 기간: 외래 vs 입원치료

유지기 동반 약제의 선정

치료 기간(치료 종료의 결정)

치료결과(tretment outcome의 결정)

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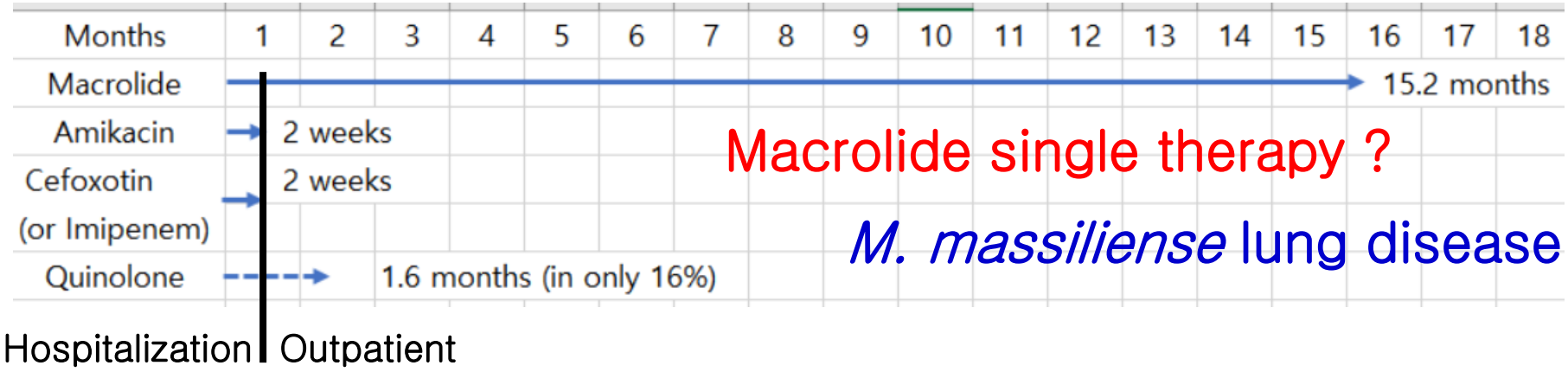
MABC lung disease

Oral macrolide therapy with initial 2 weeks' parenteral therapy

(Koh W-J et al., Chest 2016; 150:1211-21)



Retrospective study (n=43)

Treatment for at least 12 months after culture conversion

Total treatment duration = 15.2 months

The negative sputum culture rate after 12 months of treatment was 91%.

Acquired macrolide-R: 2 patients

(may induce CLR-R of co-isolated MAC)

Oral drug therapy alone

(Antimicrob Agents Chemother 2013;57:1098-1100)

Months	1	2	3	4	5	6	7	8	17	18	19	20	21	22	23	24
Macrolide	→															
Amikacin																
Cefoxotin	Outpatient												Moxifloxacin-R			
Moxifloxacin	→															

M. massiliense lung disease

Inhaled amikacin X
Clofazimine X

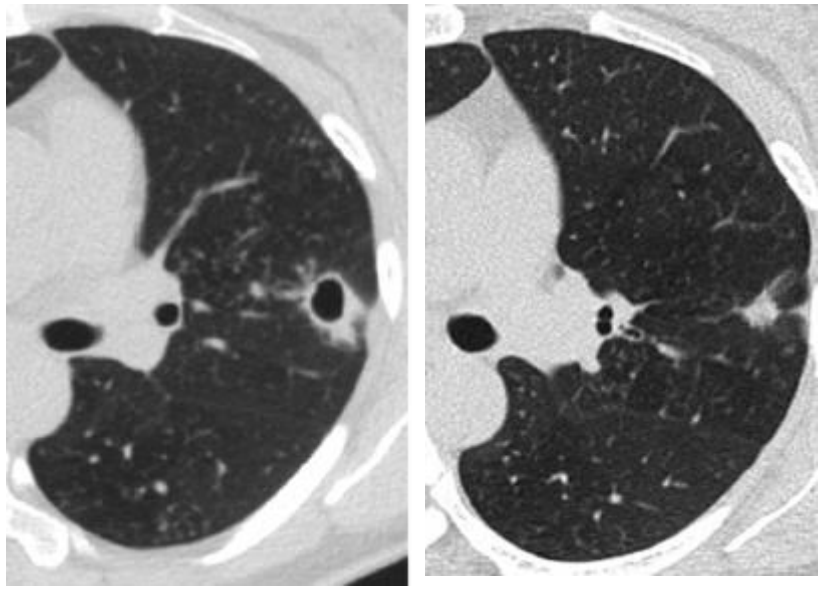
Macrolide + FQ ?

One case report (43/F)

AFB smear (+), cavity (+)

NB-type disease

CLR-S, Moxifloxacin-R



Outpatient treatment for *M. abscessus* lung disease

(Namkoong et al., BMC Infect Dis 2016; 16:396)

Retrospective study, Japan

13 *M. abscessus* subsp. *abscessus* patients, AFB (+) in all

Amikacin thrice weekly: median 12.5 mg/kg,

median 4 months (range 3-9 months)

CLR (13), Faropenem (10), imipenem/cilastatin (3), FQs (5)

Without cefoxitin

Sputum conversion 77% (10/13), 1Yr conversion 62% (8/13)

No SAEs

Outpatient treatment for MABC lung disease

(Lyu et al., Respir Med 2011; 105:781-7)

Retrospective study, Korea

17 MABC patients, AFB (+) in 88%

Amikacin (15mg/kg/day, maximum 1 g/day) + CLR

: median 230 (range 61 – 601) days, x5/weeks -> x3/weeks

Macrolides: 511 days (range 164 – 1249 days)

Surgical resection in 3

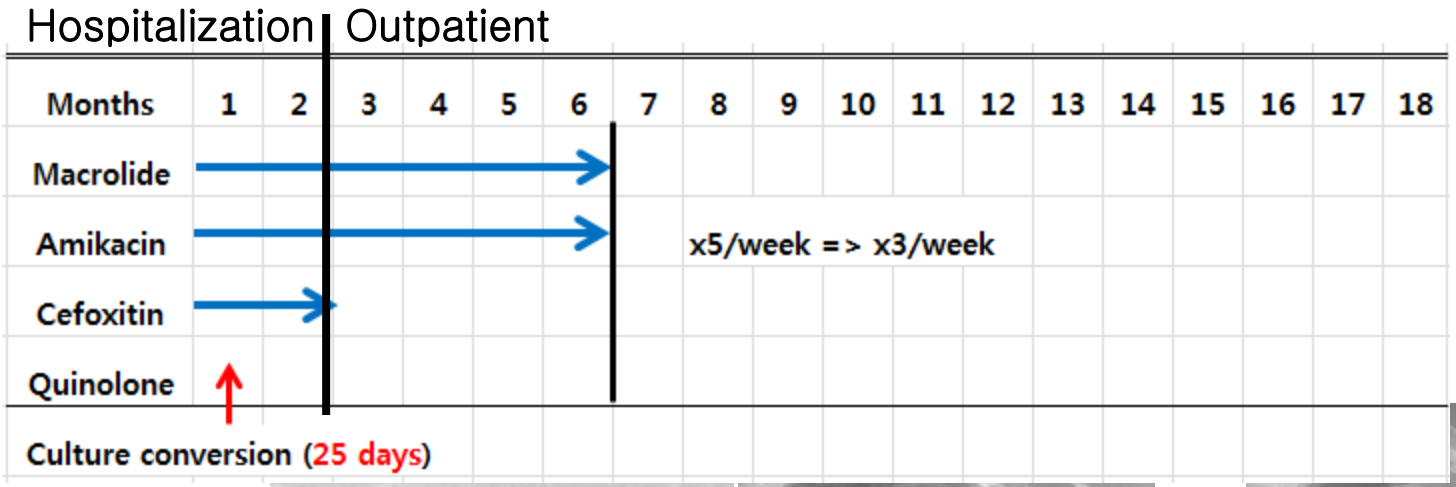
Treatment success: 76.5% (13/17)

Relapse-free success rate: 58.8% (10/17)

F/U duration: median 445 days

AE: total (17.6%), tinnitus/hearing difficulty (1/17, 5.9%)

Case: *M. massiliense* lung disease, 6 months treatment

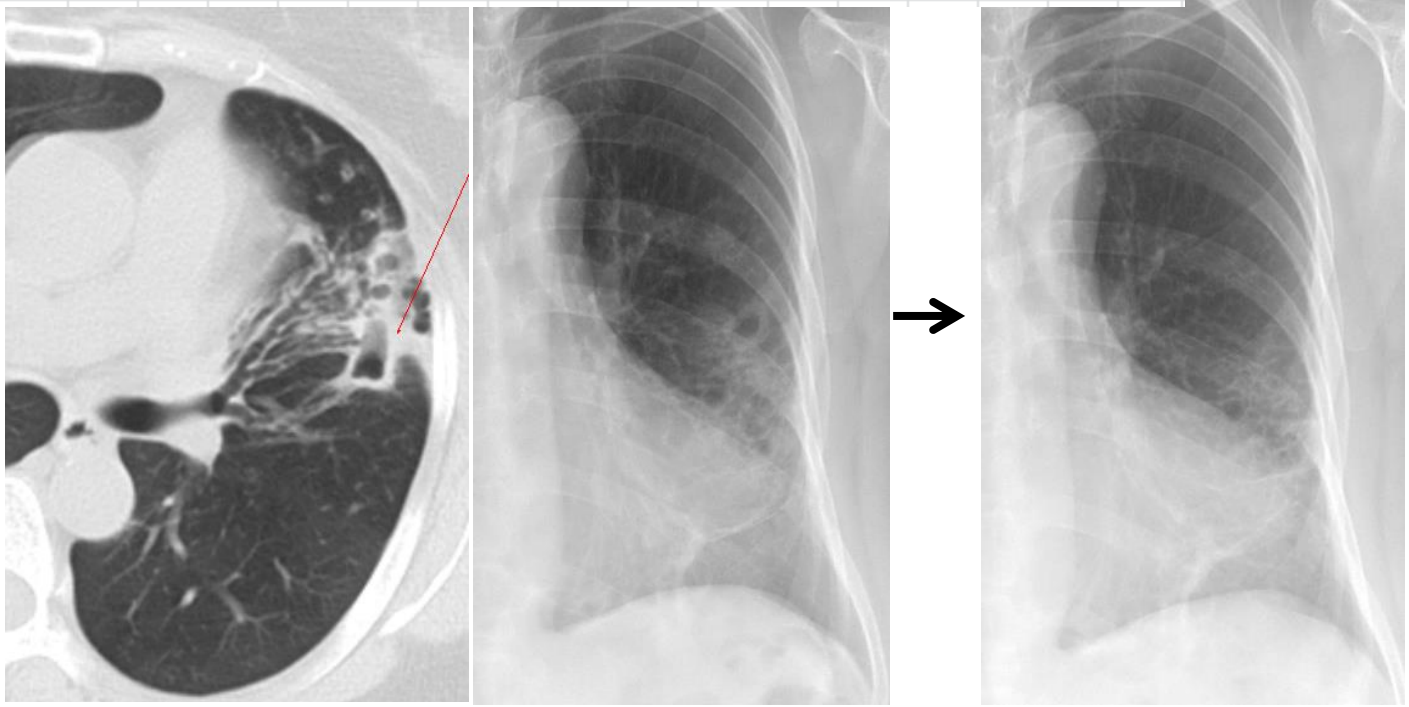


61/F

CLR-S; IR to CLR (-)

AFB smear (+)

Cavity (+)



Treatment initiation

6 month later
Tx completed

Summary: treatments of MABC lung disease

Baseline/inducible resistance to CLR

- **Long-term parenteral antibiotics (including inhaled amikacin or faropenem ??)**
- **Long-term total treatment duration**
- **New, effective drugs are needed**

Susceptible to CLR

- **Shorter total treatment duration**
- **Shorter duration of injectable drugs**
- **Oral (or inhalational) drug alone treatment ?**

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MABC lung disease

In vitro susceptibility of MABC

Drugs	*Daley et al*	*Griffith et al*	*Brown et al*
Amikacin	90%	100%	100%
Clarithromycin	100%		100%
Cefoxitin	70%	70%	99%
Imipenem	50%	60%	60%
Ciprofloxacin	0%	2%	< 5%
Sulfonamides	0%	6%	0%
Doxycycline	0%	0%	< 5%
Clofazimine	90%	-	-
Linezolid	50%	-	23%
Gatifloxacin	-	-	13%
Tigecycline	-	-	100%

Parenteral Amikacin (AMK)

(ATS guideline, 2007)

The most active of the parenteral agents is AMK.

Daily treatment with AMK is 10–15 mg/kg in two divided doses. Targeted Cmax is in the low 20 ug/ml range.

(Lee et al., IJTLD 2017; 21:818-24)

Once-daily AMK for 4 weeks with a target Cmax of 55–65 ug/ml can be used in patients with MABC lung disease, with careful monitoring of toxicity.

β-lactams and β-lactamase inhibitors

(Soroka D et al., J Antimicrob Chemother 2014; 69: 691–6)

Table 2. MICs of β-lactams for *M. abscessus* CIP104536

β-Lactam	MIC (mg/L)
Cephem	
cefalotin	>256
cefuroxime	>256
cefamandole	>256
ceftriaxone	>256
cefotaxime	>256
cefoxitin	32
ceftazidime	>256
Carbapenem	
imipenem	8
meropenem	16
ertapenem	256
doripenem	16

2007 ATS guidelines: For the majority of *M. abscessus and M. chelonae* isolates, imipenem is the preferred carbapenem over meropenem and ertapenem.

β-lactams and β-lactamase inhibitors

(Soroka D et al., J Antimicrob Chemother 2014; 69: 691-6)

MABC produce a β-lactamase (Bla_{Mab})
* BlaC in *M. tuberculosis*

β-lactamase inhibitors clavulanate, tazobactam and sulbactam did not inhibit Bla_{Mab}.

Cefoxitin was very slowly hydrolysed by Bla_{Mab}.

Bla_{Mab} hydrolysed imipenem more efficiently.

(Dubee V et al., J Antimicrob Chemother 2015; 70: 1051-8)

An inhibition of Bla_{Mab} by avibactam was observed in both infected macrophages and zebrafish.

β-lactams and β -lactamase inhibitors

(Soroka D et al., J Antimicrob Chemother 2014; 69: 691–6)

Inhibition of the β-Lactamase Bla_{Mab} by Avibactam Improves the *In Vitro* and *In Vivo* Efficacy of Imipenem against *Mycobacterium abscessus*

Anne-Laure Lefebvre,[a,b,c] Vincent Le Moigne,[d] Audrey Bernut,[e] Carole Veckerlé,[a,b,c] Fabrice Compain,[a,b,c,f] Jean-Louis Herrmann,[d] Laurent Kremer,[e,g] Michel Arthur,[a,b,c] Jean-Luc Mainardi[a,b,c,f]

In vivo efficacy of the drugs was tested by monitoring the survival of infected zebrafish embryos.

Combinations of avibactam and carbapenems

(Kaushik et al., Future Microbiol 2017’ 12:473–80)

Table 1. Minimum inhibitory concentrations (in µg/ml) of carbapenems with and without β-lactamase inhibitors against *Mycobacterium abscessus* ATCC 19977.

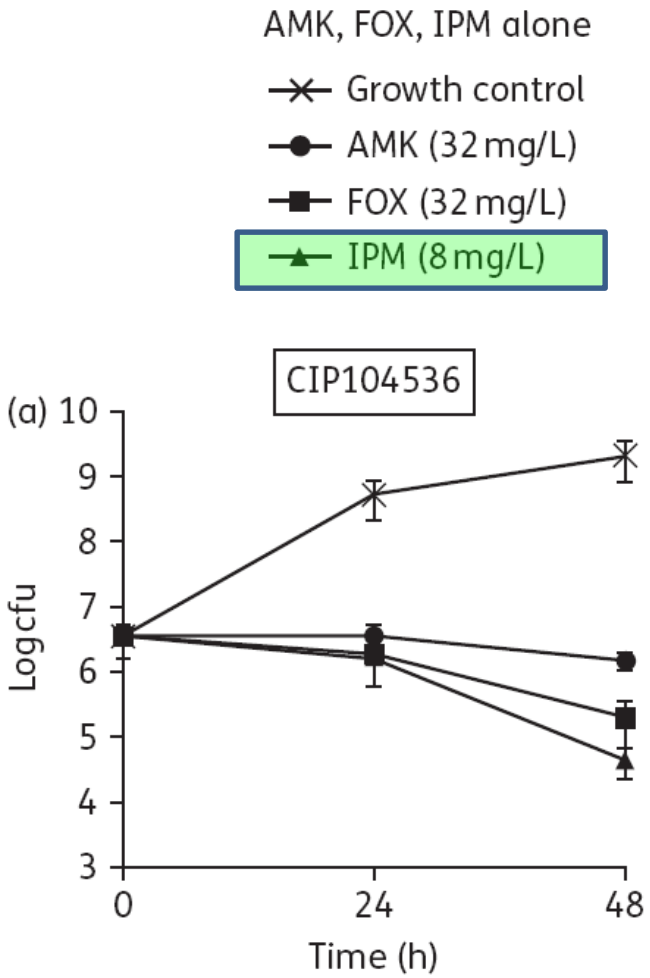
Drug	7H9 broth	7H9 + sulbactam	7H9 + tazobactam	7H9 + avibactam	CAMHB only	CAMHB + avibactam
Ertapenem	64–128	>64	32–64	4–8	128–256	8–16
Meropenem	8–16	8–16	8–16	2–4	32–64	4–8
Imipenem	4–8	4–8	2–4	2–4	8–16	4–8
Doripenem	8–16	8–16	8–16	2–4	16–32	4–8
Biapenem	8–16	4–8	8–16	2–4	16–32	8–16
Faropenem	32–64	16–32	32–64	8–16	64–128	16–32
Tebipenem	128–256	>64	>64	4–8	128–256	8–16
Panipenem	64–128	16–32	32–64	8–16	64–128	8–16
Sulbactam	>64	ND	ND	ND	ND	ND
Tazobactam	>64	ND	ND	ND	ND	ND
Avibactam	>256	ND	ND	ND	>256	ND

β-lactamase inhibitors sulbactam, tazobactam and avibactam were used at a fixed concentration of 4 µg/ml.
CAMHB: Cation-adjusted Mueller–Hinton broth; ND: Not determined.

Time-kill curve

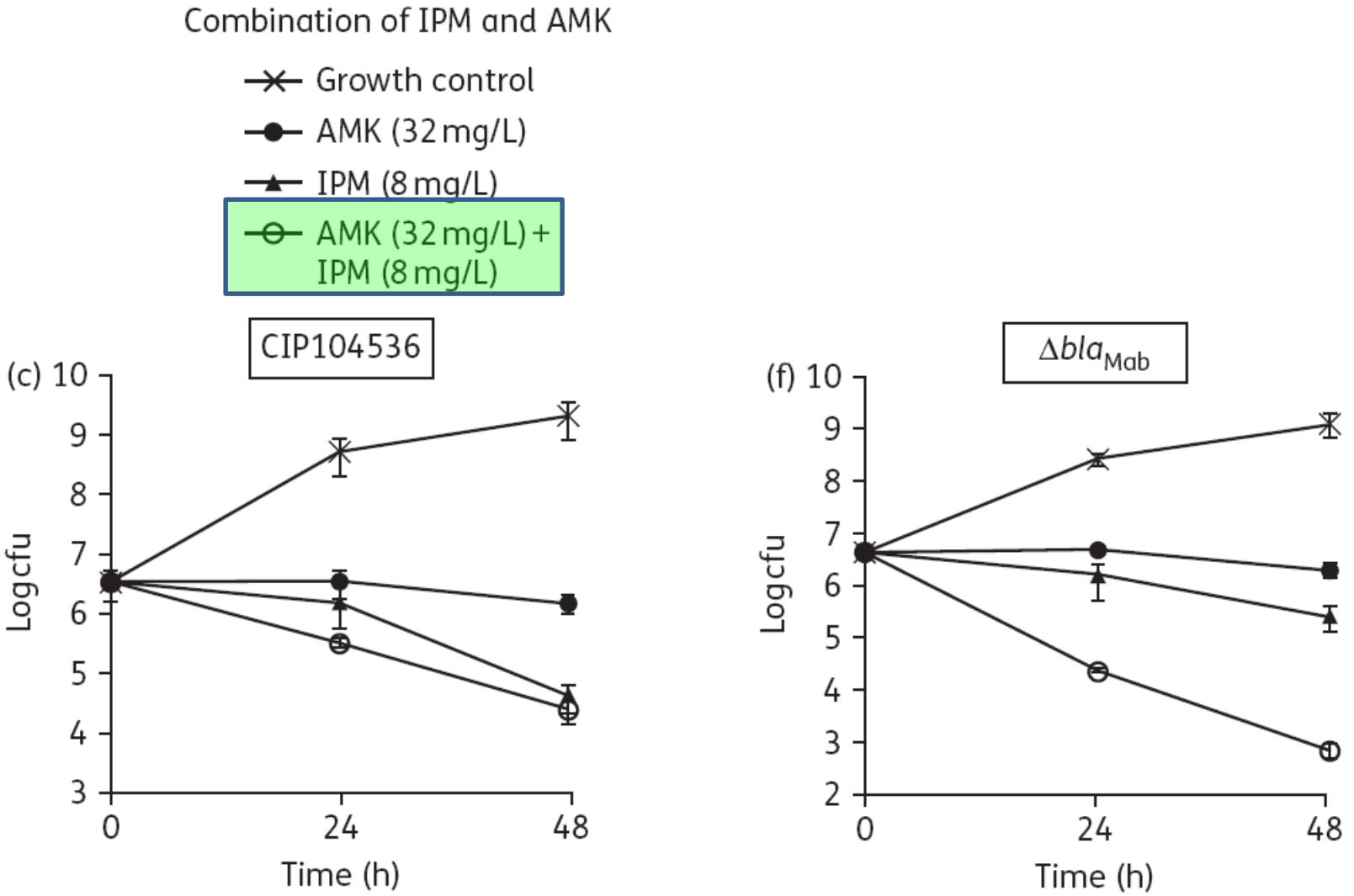
(Lefebvreet al., J Antimicrob Chemother 2016; 71: 1556-63)

Imipenem was more active than cefoxitin and amikacin.



Time-kill curve

(Lefebvreet al., J Antimicrob Chemother 2016; 71: 1556-63)



Evaluation of drug efficacy in a mouse model

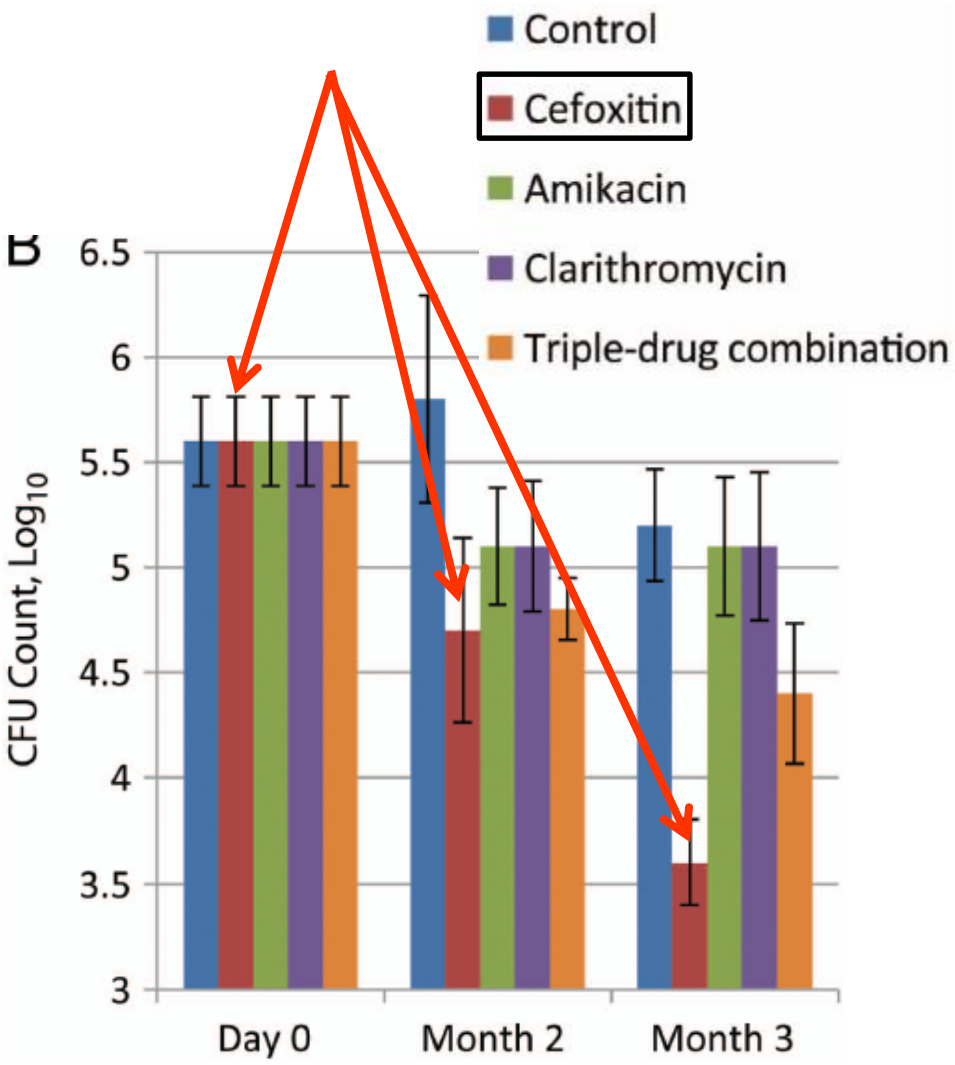
(Lerat et al., J Infect Dis 2014; 209:905–12)

M. abscessus ATCC 19977 strain

Among the 3 drugs,

Cefoxitin was the most active because it improved survival and reduced bacillary loads in spleen whereas CLR and AMK prevented death but had little impact on bacillary loads.

The triple-drug combination was not more active than cefoxitin alone.



목 차

MABC lung disease

Experimental drugs for MABC lung disease

Inhaled amikacin

Clofazimine

Fluoroquinolones

Linezolid

Tigecycline

Bedaquiline

Delamanid ?

Potential drugs

2006년 발표 자료

Linezolid

Tigecycline

Telithromycin

Interferon-gamma

등

Inhaled amikacin

(Olivier et al., Ann Am Thorac Soc 2014;11:30-35)

15 patients with CLR-R MABC

***M. abscessus* (n=10)**

***M. massiliense* (n=5)**

↓ **Addition of Inhaled amikacin**

Culture negative in 26% (4/15)

Liposomal amikacin inhalation (LAI)

(Olivier et al., Am J Respir Crit Care Med 2017; 195:814-23)

Phase II: randomized (OBR* + LAI or placebo)

Double-blind for 84 days -> 84 days open-label

Refractory MAC (64%) or MABC disease (36%)

mITT LAI=44, placebo=45

At least one negative culture at Day 84:

32% (14/44) vs 9% (4/45) (p=0.006)

Improvement in 6MWT: +20.6 m vs. -25.0 m (p=0.017)

SAE higher in the LAI group: 18.2% vs. 8.9%

*OBR: optimized background regimen

Clofazimine (CFZ)

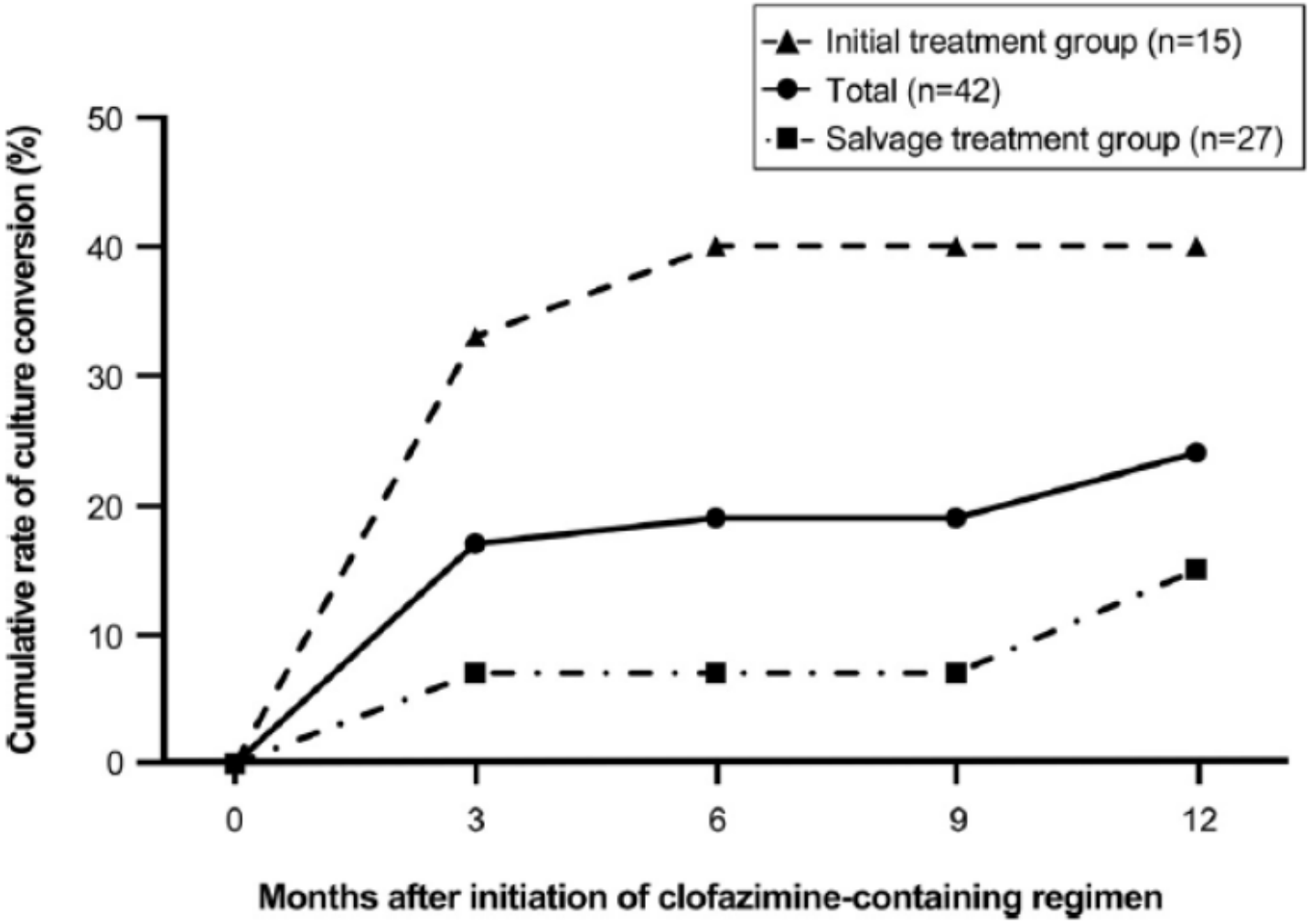
(Van Ingen et al., Antimicrob Agents Chemother 2012;56:6324-7)

In vitro synergy between CFZ and amikacin

- ***M. abscessus*: 82% (56/68)**
- ***M. massiliense*: 67% (6/9)**

Clofazimine (CFZ)

(Yang et al., Antimicrob Agents Chemother 2017;61:e02052)



Clofazimine (CFZ)

(Martiniano et al., Chest 2017)

112 patients with NTM-LD (median age 62 years)

21% (24): CF

78% (87): refractory disease with failure of prior therapy

MABC 48% (54), MAC 37% (41), 2 NTM species 14% (16)

Median duration of CFZ use: 383 days (range 3-2,419)

50% (42/82): negative culture conversion within 12 months

14% (16) stopped CFZ due to an ADR

In vitro susceptibility of MABC

Drugs	*Daley et al*	*Griffith et al*	*Brown et al*
Amikacin	90%	100%	100%
Clarithromycin	100%		100%
Cefoxitin	70%	70%	99%
Imipenem	50%	60%	60%
Ciprofloxacin	0%	2%	< 5%
Sulfonamides	0%	6%	0%
Doxycycline	0%	0%	< 5%
Clofazimine	90%	-	-
Linezolid	50%	-	23%
Gatifloxacin	-	-	13%
Tigecycline	-	-	100%

In vitro DST results of MABC

(Lee SH, et al. Ann Lab Med. 2014; 34:31)

404 MABC clinical isolates in Korea (KIT)

-50.0% *M. abscessus*, 49.3% *M. massiliense*, 0.7% *M. bolletii*

Strain (N)	Susceptibility	Ciprofloxacin N (%)	Moxifloxacin N (%)
M. abscessus (202)	Susceptible	4 (1.98)	14 (6.93)
	Intermediate	14 (6.93)	21 (10.39)
	Resistant	184 (91.09)	167 (82.68)
	Inducible resistant	-	-
M. massiliense (199)	Susceptible	9 (4.52)	17 (8.54)
	Intermediate	16 (8.04)	33 (16.58)
	Resistant	174 (87.44)	149 (74.88)
M. bolletii (3)	Susceptible	0 (0.00)	0 (0.00)
	Resistant	3 (100.00)	3 (100.00)
	Inducible resistant	-	-

In vitro DST for MABC

(Kim et al., Diag Microbiol Infect Dis 2014)

Two Korean Univ. hospital

Drug	Species	Total No.	No. (%) of isolates			*P*
			Susceptible	Intermediate	Resistant	
Amikacin	*M. abscessus*	34	31 (91.2)	3 (8.8)	0 (0)	0.255
	M. massiliense	25	25 (100)	0 (0)	0 (0)	
Cefoxitin	*M. abscessus*	33	20 (60.6)	13 (41.2)	0 (0)	0.015
	M. massiliense	24	6 (25.0)	18 (75.0)	0 (0)	
Ciprofloxacin	*M. abscessus*	35	5 (14.3)	16 (45.7)	14 (40.0)	0.305
	M. massiliense	26	2 (7.7)	17 (65.4	7 (26.9)	
Doxycycline	*M. abscessus*	33	0 (0)	0 (0)	33 (100.0)	0.103
	M. massiliense	23	1 (4.3)	2 (8.7)	20 (87.0)	
Moxifloxacin	*M. abscessus*	33	24 (72.7)	7 (21.2)	2 (6.1)	0.694
	M. massiliense	24	16 (66.7)	5 (20.8)	3 (12.5)	
Linezolid	*M. abscessus*	33	32 (97.0)	1 (3.0)	0 (0)	0.324
	M. massiliense	24	21 (87.5)	2 (8.3)	1 (4.2)	
Clofazimine	*M. abscessus*	33	29 (87.9)	2 (6.1)	2 (6.1)	0.439
	M. massiliense	24	23 (95.8)	0 (0)	1 (4.2)	
Tigecycline	*M. abscessus*	33	33 (100.0)	0 (0)	0 (0)	
	M. massiliense	24	24 (100.0)	0 (0)	0 (0)	

Antagonism btw CLR and FQ against MABC

(Choi et al., Antimicrob Agents Chemother 2012;56:3549-55)

TABLE 2 *In vitro* antimicrobial activities of the combinations of a macrolide and moxifloxacin against *M. abscessus* and *M. massiliense*

Species and agents	No. (%) of isolates with combination activity[a]		
	Synergism	Indifference	Antagonism
M. abscessus ($n = 26$)			
CLR-MXF	1 (3.8)	8 (30.8)	17 (65.4)
AZM-MXF	1 (3.8)	13 (50.0)	12 (46.2)
M. massiliense ($n = 28$)			
CLR-MXF	11 (39.3)	16 (57.1)	1 (3.6)
AZM-MXF	10 (35.7)	16 (57.1)	2 (7.1)

Moxifloxacin's Limited Efficacy in the Hollow-Fiber Model of *Mycobacterium abscessus* Disease

(Ferro et al., AAC 2016; 60:3779–85)

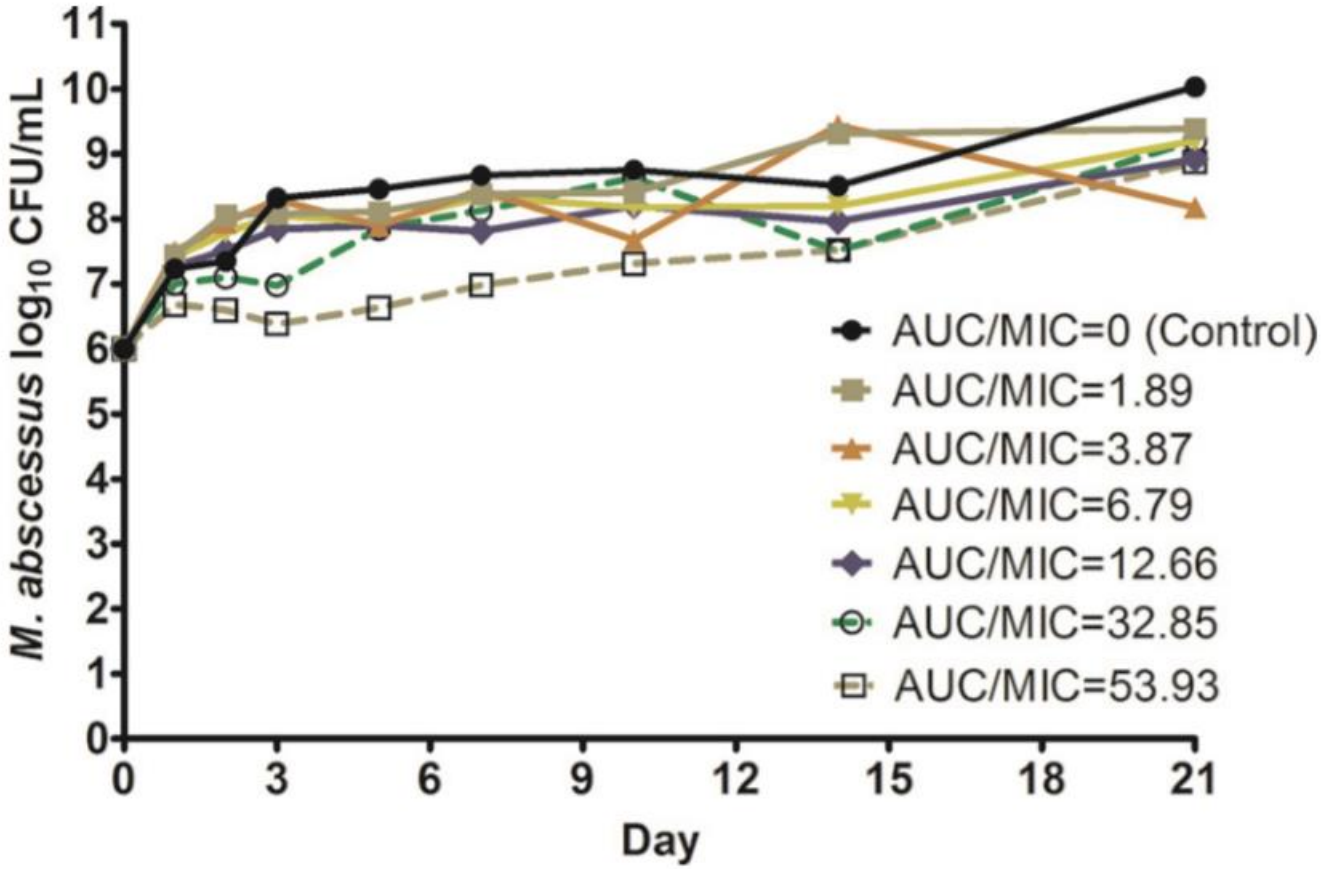


FIG 1 Moxifloxacin exposure-effect against *M. abscessus* in the HFS. None of the moxifloxacin exposures evaluated attained killing below the starting inoculum of 6.0 $\log_{10}$ CFU/ml at any point during the study. Regrowth was observed after day 3 in all systems.

Summary

1. MABC 폐질환 진단 자체가 치료를 의미하지는 않는다.
2. Conventional treatment는 macrolide + AMK + β-lactam (cefoxitin or imipenem) 이다.
3. 유지기의 치료 regimen 구성이 명확히 제시되어 있지 않다.
4. 권고 치료기간은 균배양 음전후 1년 더 치료이다.
5. Subspecies 종류, 약제내성 여부가 치료결과에 중요하므로, 세균학적 특성 검사가 중요하다.
6. 약제내성 원인균의 경우 장기간의 주사치료, experimental drug 의 추가가 필요하다.

감사합니다.

Clofazimine (CFZ)

(Yang et al., Antimicrob Agents Chemother 2017;61:e02052)

42 patients with *M. abscessus* lung disease in Korea

15 (36%): Initial treatment group

27 (64%): Salvage treatment group: CFZ was added to an existing antibiotic regimen for refractory disease

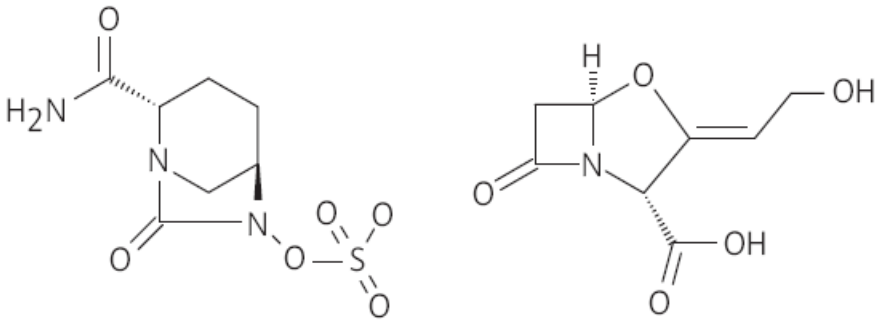


Figure 1. Structure of the β-lactamase inhibitors.

Table 3. Impact of the inhibition of β-lactamases by clavulanate or avibactam on the MIC of amoxicillin

		MIC (mg/L) of amoxicillin in the presence of the indicated inhibitor		
β-Lactamase	Residue 132	none	avibactam (4 mg/L)	clavulanate (4 mg/L)
None	NA	2	2	2
Bla_{Mab}	N	>512	4	>512
BlaC	G	512	64	8
Bla_{Mab} $N^{132}G$	G	>512	64	32
BlaC $G^{132}N$	N	512	2	64

In vitro DST results of MABC

92 isolates

	No. (%) of isolates		
	Susceptible	Intermediate	Resistant
Amikacin	88 (96)	0 (0)	4 (4)
Tobramycin[a]	25 (27)	39 (42)	28 (30)
Cefoxitin	3 (3)	85 (92)	4 (4)
Ciprofloxacin	3 (3)	2 (2)	87 (95)
Moxifloxacin[c]	7 (8)	10 (11)	75 (82)
Gatifloxacin[c]	6 (7)	16 (17)	70 (76)
Levofloxacin[c]	2 (2)	2 (2)	88 (96)
Clarithromycin	73 (79)	9 (10)	10 (11)
Azithromycin[c]	48 (52)	0 (0)	44 (48)
Telithromycin[c]	—	—	—
Doxycycline	0 (0)	7 (8)	85 (92)
Imipenem[b]	11 (12)	64 (70)	17 (18)
Meropenem[c]	0 (0)	1 (1)	9 (99)
TMP-SMZ[d]	1 (1)	—	91 (99)
Linezolid[e]	29 (32)	24 (26)	39 (42)

(Yang et al. AAC 2003;47: 1958 – 62)

M.abscessus complex 감수성 결과 (AMC)

Species	Clarithromycin			Minocycline			Tobramycin			Linezolid		
	S	I	R	S	I	R	S	I	R	S	I	R
M. abscessus (n=44)	42 (95.5)	0 (0)	2 (4.5)	0 (0)	5 (11.4)	39 (88.6)	0 (0)	6 (13.6)	38 (86.4)	25 (56.8)	10 (22.7)	9 (20.5)
M. massiliense (n=46)	45 (97.8)	1 (2.2)	0 (0)	1 (2.2)	6 (13)	39 (84.8)	0 (0)	4 (8.7)	42 (91.3)	32 (69.6)	10 (21.7)	4 (8.7)
Unidentified (n=48)	47 (97.9)	0 (0)	1 (2.1)	0 (0)	7 (14.6)	41 (85.4)	1 (2.1)	3 (6.2)	44 (91.7)	30 (62.5)	10 (20.8)	8 (16.7)
Total (n=138)	134 (97.1)	1 (0.7)	3 (2.2)	1 (0.7)	18 (13.1)	119 (86.2)	1 (0.7)	13 (9.4)	124 (89.9)	87 (63.1)	30 (21.7)	21 (15.2)

M.abscessus complex 감수성 결과(KIT)

Species	Amikacin			Cefoxitin			Ciprofloxacin			Moxifloxacin		
	S	I	R	S	I	R	S	I	R	S	I	R
M. abscessus	336	185	95	87	381	148	8	14	594		1	122
	(54.5)	(30)	(15.5)	(14.1)	(61.9)	(24)	(1.3)	(2.3)	(96.4)		(0.8)	(99.2)
M. masilliense	73	35	22	20	88	22		1	129		3	41
	(56.2)	(26.9)	(16.9)	(15.4)	(67.7)	(16.9)		(0.8)	(99.2)		(6.8)	(93.2)

Doxycycline			Linezolid		
S	I	R	S	I	R
7	16	593	29	43	51
(1.1)	(2.6)	(96.3)	(23.6)	(35)	(41.4)
	3	127	18	10	16
	(2.3)	(99.7)	(40.9)	(22.7)	(36.4)

MABC 감수성 결과 (AMC)

Species	Amikacin			Cefoxitin			Ciprofloxacin			Moxifloxacin		
	S	I	R	S	I	R	S	I	R	S	I	R
M. abscessus (n=44)	40	4	0	8/43	32/43	3/43	4	10	30	2/20	5/20	13/20
	(91)	(9)	(0)	(18.6)	(74.4)	(7)	(9)	(23)	(68)	(10)	(25)	(65)
M. massiliense (n=46)	42	4	0	4	38	4	3	7	36	3/22	5/22	14/22
	(91.3)	(8.7)	(0)	(8.7)	(82.6)	(8.7)	(6.5)	(15.2)	(78.3)	(13.7)	(22.7)	(63.6)
Unidentified (n=48)	43	5	0	8/47	36/47	3/47	8	4	36	7/19	5/19	7/19
	(89.6)	(10.4)	(0)	(17)	(76.6)	(6.4)	(16.7)	(8.3)	(75)	(36.8)	(26.3)	(36.9)
Total (n=138)	125	13	0	20/136	106/136	10/136	15	21	102	12/61	15/61	34/61
	(90.6)	(9.4)	(0)	(14.7)	(77.9)	(7.4)	(10.9)	(15.2)	(73.9)	(19.7)	(24.6)	(55.7)

신속 성장균에서 감수성 판독기준

(CLSI guidelines, 2011)

Antimicrobial agents	MIC (ug/mL) for category		
	S	I	R
Amikacin	≤16	32	≥64
Cefoxitin	≤16	32-64	≥128
Ciprofloxacin	≤1	2	≥4
Clarithromycin	≤2	4	≥8
Doxycycline (Minocycline)	≤1	2-4	≥8
Imipenem	≤4	8-16	≥32
Linezolid	≤8	16	≥32
Trimethoprim-sulfamethoxazole	≤2/38	-	≥4/76
Tobramycin	≤2	4	≥8
Meropenem	≤4	8-16	≥32
Moxifloxacin	≤1	2	≥4

Amikacin inhalation (LAI)

(Yagi K et al., BMC Infect Dis 2017; 17)

Japan, 2014 - 2016

Retrospective study

3 pulmonary MABC patients

Duration of amikacin therapy (n=2): 12 & 24 months

2/2 culture conversion

Subspecies not identified

Clofazimine Prevents the Regrowth of *Mycobacterium abscessus* and *Mycobacterium avium* Type Strains Exposed to Amikacin and Clarithromycin

Beatriz E. Ferro,[a] Joseph Meletiadis,[b,c] Melanie Wattenberg,[a] Arjan de Jong,[a] Dick van Soolingen,[a,d,e] Johan W. Mouton,[a,c] Jakko van Ingen[a]

- Clofazimine (CFZ) alone was bacteriostatic for both NTM. CFZ-amikacin (AMK) was synergistic against *M. abscessus* and *M. avium*.
- CFZ-clarithromycin (CLR) was also synergistic against *M. abscessus* and *M. avium*.
- CFZ prevented the regrowth observed with AMK or CLR alone. Target attainment rates of combination regimens were>60% higher than those of monotherapy regimens for *M. abscessus* and *M. avium*.
- This suggests a potential role for CFZ in treatment regimens that warrants further evaluation.

(Ferro BE, et al. Antimicrob Agents Chemother. 2016 Feb;60(2):1097)

Linezolid for MAB complex

CLSI M24-A2	MIC (ug/mL) for category		
	S	I	R
Linezolid	≤8	16	≥32

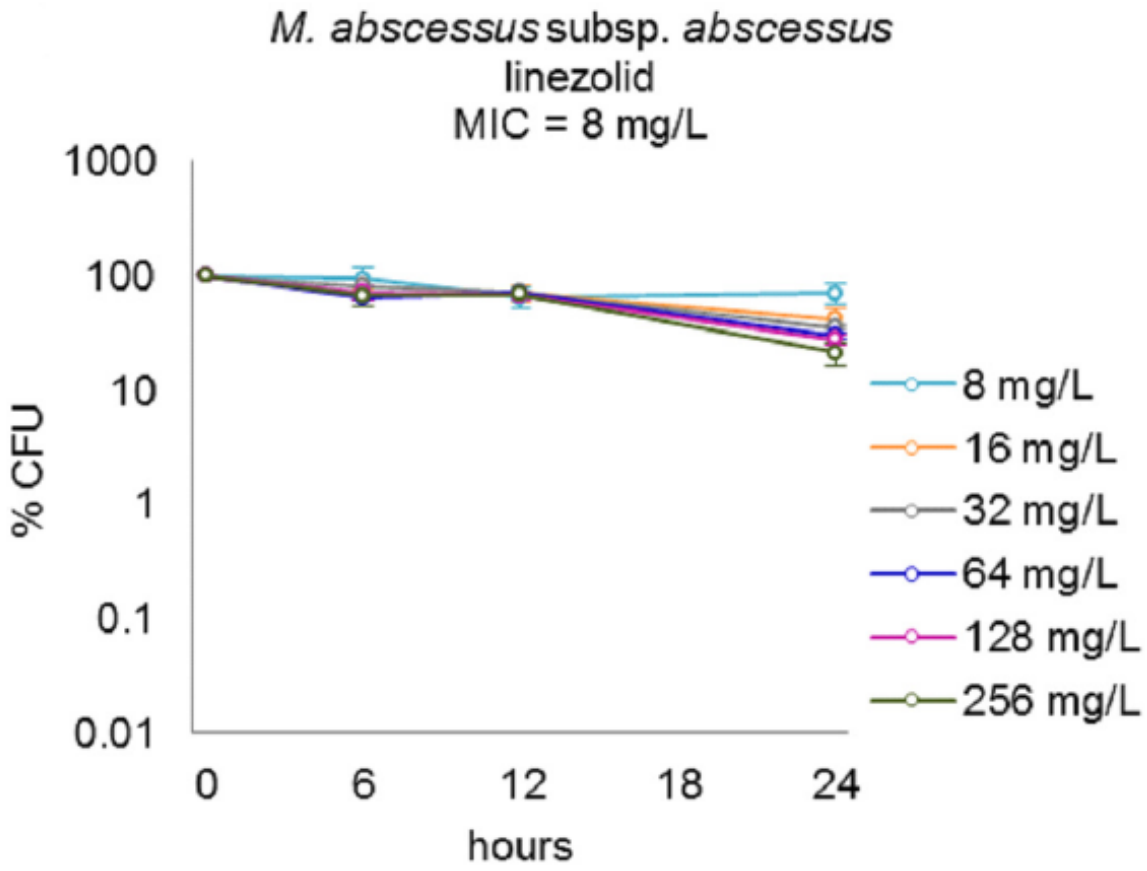
(Wallace Jr. et al., Antimicrob Agents Chemother 2001;45:764-767)

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

49.0% (48/98) susceptible or intermediate

Linezolid for *M. abscessus*

(Maurer et al., Antimicrob Agents Chemother 2014;58:3828-36)



Lack of antimicrobial bactericidal activity

Tolerability of Linezolid

(Winthrop et al., Eur Respir J 2015;45:1177-1179)

Retrospective study

102 NTM patients (27% [18/66] with cavity), 22% extrapulmonary

- ***M.abscessus*** **(44%), MAC (33%)**
- **concomitant drugs: Macrolide (80%), AG (45%), FQ (33%)**

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

45% (46/102) developed AEs after a median 19.9 weeks

→ 87% (40/46) stopped therapy → 43% resumed LZD

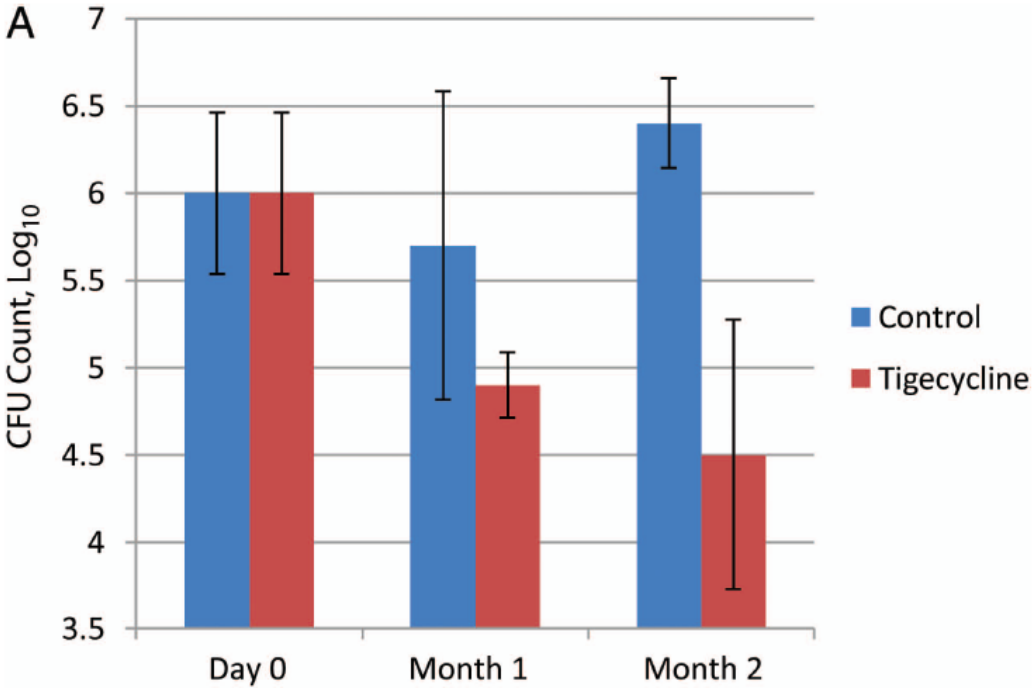
In vitro DST results of MABC

(Park et al. KJMS 2008;23: 49-52)

Drug	No.	No. (%) of isolates		
		Susceptible	Intermediate	Resistant
Amikacin	74	73 (99)	1 (1)	0 (0)
Cefoxitin	74	73 (99)	1 (1)	0 (0)
Imipenem	66	36 (55)	22 (33)	8 (12)
Tobramycin	74	27 (36)	25 (34)	22 (30)
Clarithromycin	74	67 (91)	5 (7)	2 (3)
Ciprofloxacin	74	42 (57)	19 (26)	13 (18)
Moxifloxacin	74	54 (73)	15 (20)	5 (7)
Doxycycline	74	5 (7)	9 (12)	60 (81)

Tigecycline in a mouse model

(Ierat et al., J Infect Dis 2014;209:905-912)



***M. abscessus* ATCC 19977**

Tigecycline, clinical study

(Wallace Jr. et al., J Antimicrob Chemother 2014;69:1945-53)

Retrospective study

30 MAB complex lung disease

Mean treatment of tigecycline duraiton: 165 ± 220 days

Macrolides (73.1%), amikacin (50.5%), linezolid (40.4%)

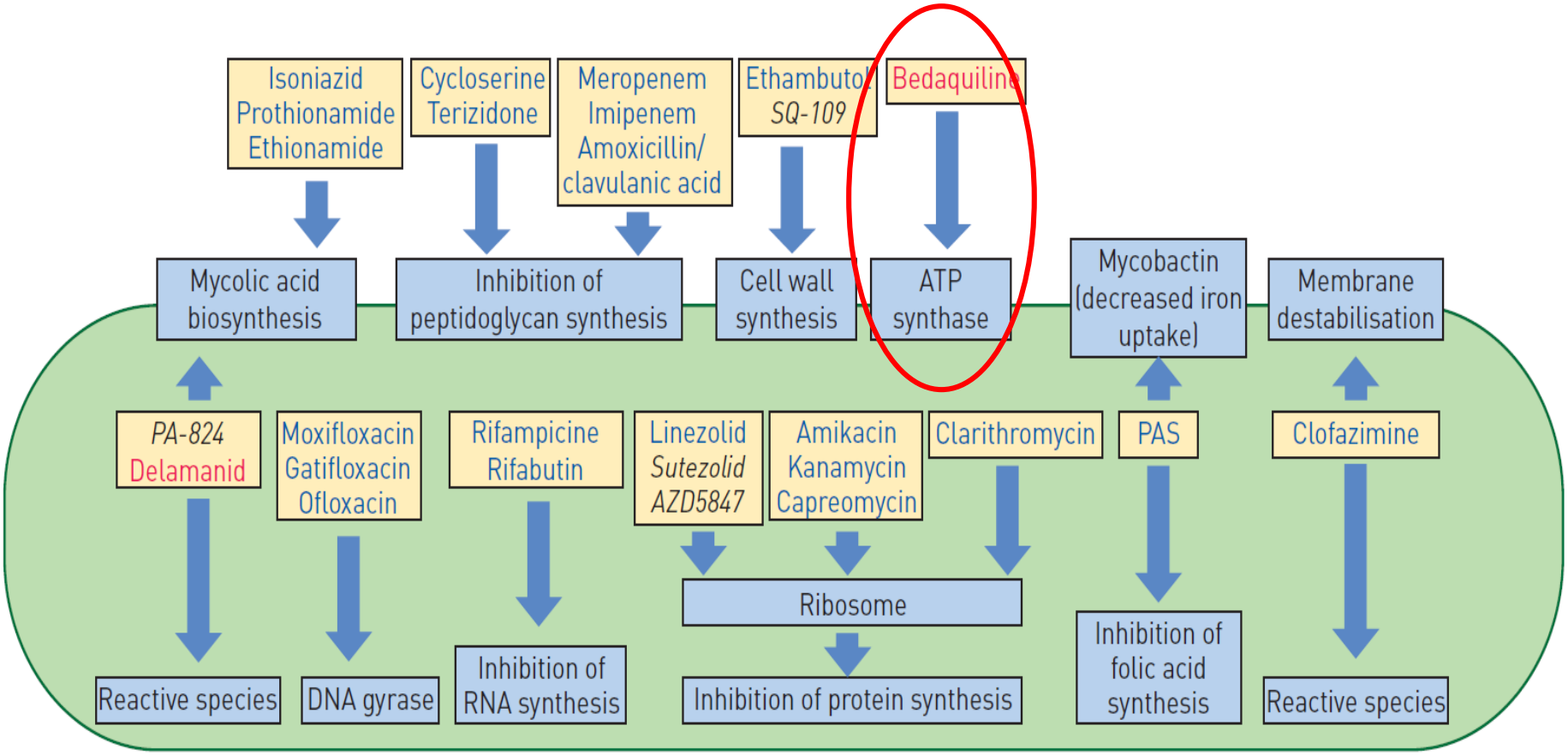
AE 94.2%, tigecycline-related SAE 23.1%

None of 8 deaths was related with tigecycline therapy

Infection site/organism	Improved, *n*	Failed, *n*	Indeterminate, *n*
Lung, total	16	11	9
M. abscessus complex	13	9	8
M. chelonae	1	1	0
M. abscessus complex/ *M. chelonae*	2	1	1

Bedaquiline

(Eur Respir J 2015;45:1119-1131)



Bedaquiline

(Philley et al., CHEST 2015;148:499-506)

Treatment failure lung disease caused by MAC or Mab (n=10)

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+
5 MAC	4+	3+	4+	4+	4+	4+	4+
6 MAC	4+	4+	Negative	Negative	2+	4+	3+
7 MAC	4+	4+	30 colonies	Negative	Negative	...[a]	...[a]
8 MAC	4+	1+	Negative	3+	4+	4+	4+
9 MAC	4+	2+	3+	1 colony	4 colonies	1+	4 colonies
10 MAC	30 colonies	8 colonies	Negative	1+	Negative	9 colonies	Negative

[a]Unable to produce sputum.

Some microbiologic responses, but no sustained culture conversion

Concomitant use of rifabutin and bedaquiline in 6 MAC patients

In vitro DST for MABC

(Kim et al., IJTLD 2016; 20:109-14)

53 MABC clinical isolates in Korea (AMC)
: 22 *M. abscessus*, 30 *M. massiliense*, 1 *M. bolletii*

Drug	Susceptible *n* (%)	Indeterminate *n* (%)	Resistant *n* (%)
Amikacin	53 (100)	0	0
Cefoxitin	8 (15.1)	45 (84.9)	0
Imipenem	14 (26.4)	35 (66.0)	4 (7.5)
Clarithromycin	53 (100)	0	0
Ciprofloxacin	10 (18.9)	14 (26.4)	29 (54.7)
Moxifloxacin	7 (13.2)	21 (39.6)	25 (47.2)
Doxycycline	0	1 (1.9)	52 (98.1)
Minocycline	1 (1.9)	15 (28.3)	37 (69.8)
Linezolid	44 (83.0)	9 (17.0)	0
Trimethoprim/ sulfamethoxazole	22 (41.5)	—	31 (58.5)

M. abscessus: Cfx-R 55%, Mfx-R 55%
M. massiliense: Cfx-R 57%, Mfx-R 43%

Synergy and antagonism

(Zhang et al., Intern J Antimicrob Agents 2017; 49:383-6)

Combination	Species	No. of isolates (%)			*P*-value
		Synergy	Indifference	Antagonism	
CLA + LZD	*M. abscessus*	0 (0.0)	15 (75.0)	5 (25.0)	0.229
	M. massiliense	2 (10.0)	11 (55.0)	7 (35.0)	
	Total	2 (5.0)	26 (65.0)	12 (30.0)	
CLA + MOX	*M. abscessus*	1 (5.0)	10 (50.0)	9 (45.0)	<0.001
	M. massiliense	17 (85.0)	3 (15.0)	0 (0.0)	
	Total	18 (45.0)	13 (32.5)	9 (22.5)	
CLA + AMK	*M. abscessus*	1 (5.0)	15 (75.0)	4 (20.0)	0.565
	M. massiliense	3 (15.0)	13 (65.0)	4 (20.0)	
	Total	4 (10.0)	28 (70.0)	8 (20.0)	
CLA + TGC	*M. abscessus*	5 (25.0)	12 (60.0)	3 (15.0)	0.038
	M. massiliense	13 (65.0)	6 (30.0)	1 (5.0)	
	Total	18 (45.0)	18 (45.0)	4 (10.0)	