Two drugs (macrolide and ethambutol) are enough for non-cavitary nodular bronchiectatic MAC-PD
2. Con

건양대학교병원 호흡기내과 권선중

2024년 4월 13일

1. Clinical practice guidelines and Clinical evidence of 3-drug regimen

ATS/ERS/ESCMID/IDSA guideline,2020

VII: In patients with macrolide-susceptible MAC pulmonary disease, should a 3-drug or a 2-drug macrolide-containing regimen be used for treatment?

Recommendation

1. In patients with macrolide-susceptible MAC pulmonary disease, we suggest a treatment regimen with at least 3 drugs (including a macrolide and ethambutol) over a regimen with 2 drugs (a macrolide and ethambutol alone) (conditional recommendation, very low certainty in estimates of effect).

Remarks: A priority in MAC pulmonary disease therapy is preventing the development of macrolide resistance. The panel members were concerned that the currently available data [21] were insufficient to determine the risk of acquired macrolide resistance with a 2-drug regimen and therefore suggest a 3 drug macrolide-containing regimen.

→ *Miwa S, 2014*

ATS/ERS/ESCMID/IDSA guideline, CID, 2020

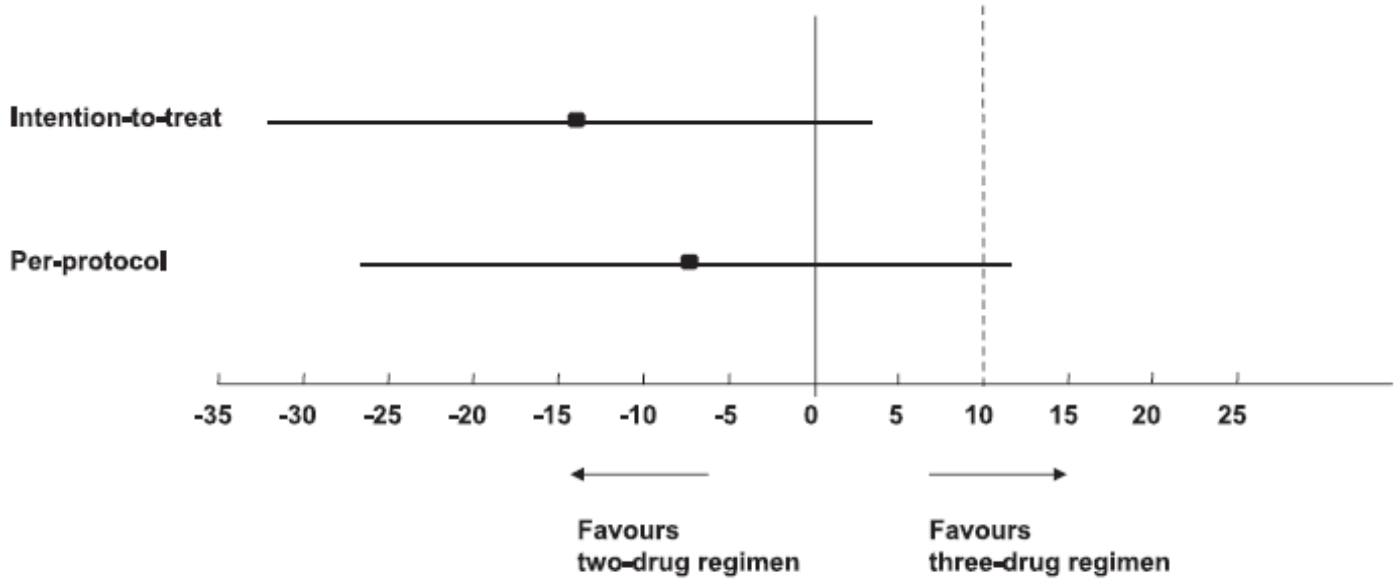
3 drug or 2-drug regimen in MAC disease

- Unblinded RCT in Japan, Preliminary study
- Noninferiority of a 2-drug regimen

	3-drug (n=59)	2-drug (n=60)
BMI	19.1	19.1
cavitation	49.2%	31.1%
Bronchiectasis on HRCT	71.2%	73.3%
Extension of lesion (⅓of unilateral lung field)	52.5%	53.3%
Sputum smear	?	?
Drop out	45.7%	33.3%
Discontinuation d/t adverse events	37.2%	26.6%

Miwa S, AnnalsATS; 2014; 11; 23

3 drug or 2-drug regimen in MAC disease



- 2-drug is not inferior to 3-drug
- Limitation ; unblinded

  small sample size

  significant drop out

  use of low doses clarithromycin

Miwa S, AnnalsATS; 2014; 11; 23

3-drug regimen; BTS guideline,2017

SECTION 12A: WHAT ANTIBIOTIC REGIMEN SHOULD BE USED TO TREAT MAC-PULMONARY DISEASE?

Recommendations

- Clarithromycin-sensitive MAC-pulmonary disease should be treated with rifampicin, ethambutol and clarithromycin or azithromycin using an intermittent (three times per week) or daily oral regimen. The choice of regimen should be based on the severity of disease (as defined in table 3) and treatment tolerance. (Grade D)
- An intermittent (three times per week) oral antibiotic regimen should not be used in individuals with severe MAC-pulmonary disease (as defined in table 3) or in individuals with a history of treatment failure. (Grade D)

BTS guideline, Thorax, 2017
Miwa S, AnnalsATS; 2014; 11; 23

BTS guideline,2017

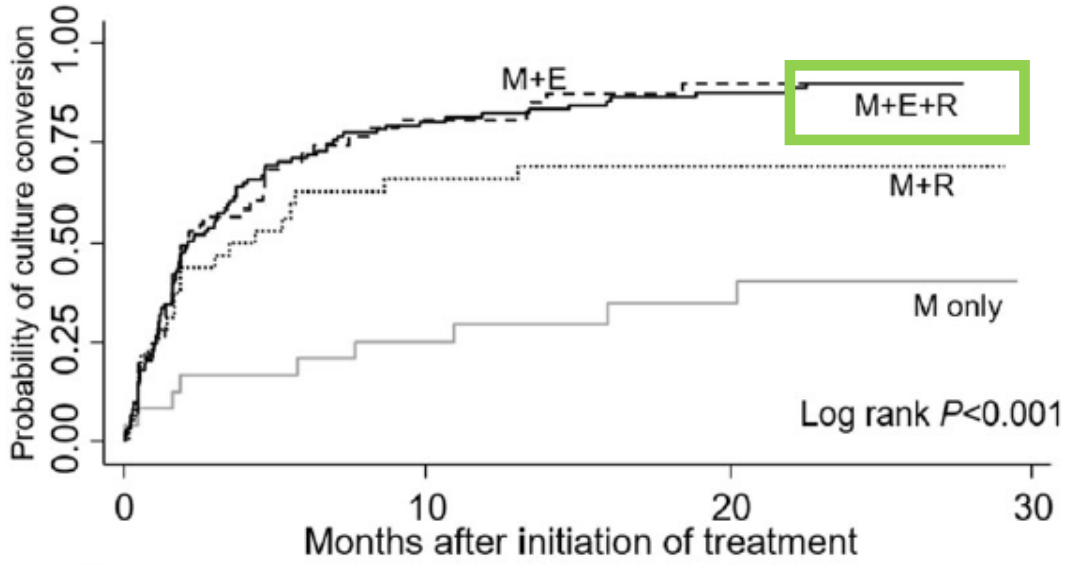
M. avium complex-pulmonary disease	Antibiotic regimen
Non-severe MAC-pulmonary disease (ie, AFB smear-negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-moderate symptoms, no signs of systemic illness)	Rifampicin 600 mg 3× per week and Ethambutol 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.

- Evidence 부족으로 2-drug에 대한 언급은 없음

BTS guideline, Thorax, 2017

3 drug; most favorable treatment outcomes

- Retrospective, 237 patients
- 9year study period
- AIDS (x)
- Nodular bronchiectatic ; 79.8%
- 2007 ATS/IDSA guidelines
- Companion drugs; adverse events 로 중단 (EMB)



Number at risk				
M	25	17	12	7
M + E	57	9	3	0
M + R	32	11	8	5
M + E + R	113	20	11	6

(Probability of culture conversion)

Kim HJ, BMC Pulmonary Medicine 2019;19

Table 6 Predictors for treatment failure among patients with ≥12 months of antimycobacterial treatment

Variables	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Maintenance of antibiotics (≥6mo)				
M only	Reference		Reference	
M + E	0.28 (0.09–0.82)	0.021	0.17 (0.03–1.09)	0.061
M + R	0.57 (0.18–1.82)	0.344	0.13 (0.01–1.13)	0.064
M + E + R	0.19 (0.07–0.50)	0.001	0.09 (0.01–0.53)	0.008

- Synergic effects of RIF and EMB on MAC (in vitro)
- Treatment failure; 32.4%
- macrolide resistance의 획득 : 5 patients
- **Adverse event**; deterioration of visual acuity (31.6%), AST elevation (5.9%)
- 약제 중단의 주 원인; 시력 저하 (4명), 구토, 약물 상호작용
- **EMB**; 41.1% 에서 부작용 경험, 35명은 조기 중단

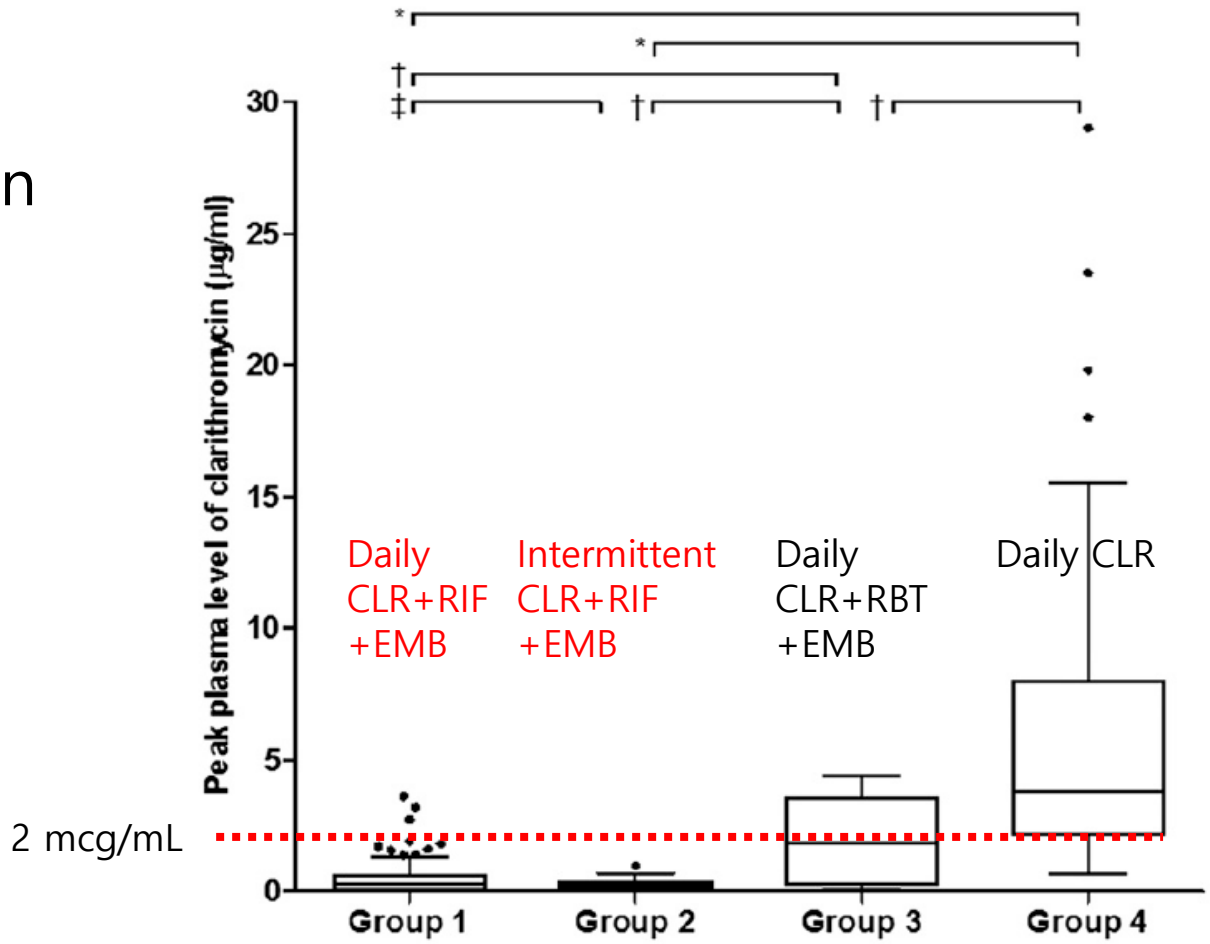
Kim HJ, BMC Pulmonary Medicine 2019;19

2. Serum concentration of macrolide and clinical outcomes

Lowered serum level of macrolide by rifampicin ?

- Through induction of cytochrome p450 by rifampicin
- Plasma concentration of CLR (companion drug RIF, EMB) in MAC disease

  vs CLR in *M.abscessus* (control group)



	Group 1	Group 2	Group 3	Group 4
Peak plasma level of clarithromycin (μg/ml)	0.3 (0.1–0.6)	0.2 (0.1–0.3)	1.8 (0.3–3.5)	3.8 (2.1–8.0)
Peak plasma level of clarithromycin <2.0 μg/ml	96/99 (97%)	21/21 (100%)	6/10 (60%)	14/60 (23%)

Go WJ, Am J Respir Crit Care Med. 2012

	Patients with Favorable Microbiological Responses ($n = 75$)	Patients with Unfavorable Microbiological Responses ($n = 26$)	*P* Value
Plasma drug levels, μg/ml			
CLR	0.30 (0.10–0.70)	0.32 (0.17–0.74)	0.299
RIF	6.40 (1.85–10.93)	8.76 (2.45–15.06)	0.340
EMB	3.22 (2.21–4.98)	2.70 (2.29–3.86)	0.393
MIC, μg/ml			
CLR	1.0 (0.5–2.0)	1.0 (0.5–2.0)	0.354
RIF	8.0 (4.0–16.0)	8.0 (8.0–16.0)	0.543
EMB	32.0 (16.0–32.0)	32.0 (16.0–32.0)	0.721
Plasma drug level/MIC ratio			
CLR	0.23 (0.12–0.64)	0.35 (0.08–1.39)	0.756
RIF	0.73 (0.29–1.56)	0.61 (0.23–1.27)	0.870
EMB	0.15 (0.08–0.33)	0.14 (0.08–0.21)	0.395

Patient Characteristics	Favorable Responses ($n = 75$)	Unfavorable Responses ($n = 26$)	Univariable Analysis *P* Value	Multivariable Logistic Regression Adjusted OR (95% CI)	Multivariable Logistic Regression *P* Value
Peak plasma levels, μg/ml*					
CLR	0.30 (0.10–0.70)	0.32 (0.17–0.74)	0.299	0.66 (0.11–4.12)	0.658
RIF	6.40 (1.85–10.93)	8.76 (2.45–15.06)	0.340	3.64 (0.92–14.47)	0.066
EMB	3.22 (2.21–4.98)	2.70 (2.29–3.86)	0.393	0.32 (0.02–4.82)	0.411

- Plasma CLR concentration ≠ treatment outcomes
- Tissue concentrations: 2-20 times than plasma concentration, alveolar macrophage concentration: 400 times

Go WJ, Am J Respir Crit Care Med. 2012

3. Adverse drug reactions, inappropriate regimen and macrolide resistance

1 or 2-Drugs in MAC pulmonary disease

Macrolide

Ethambutol

Rifampicin

Macrolide resistance

Drugs intolerance

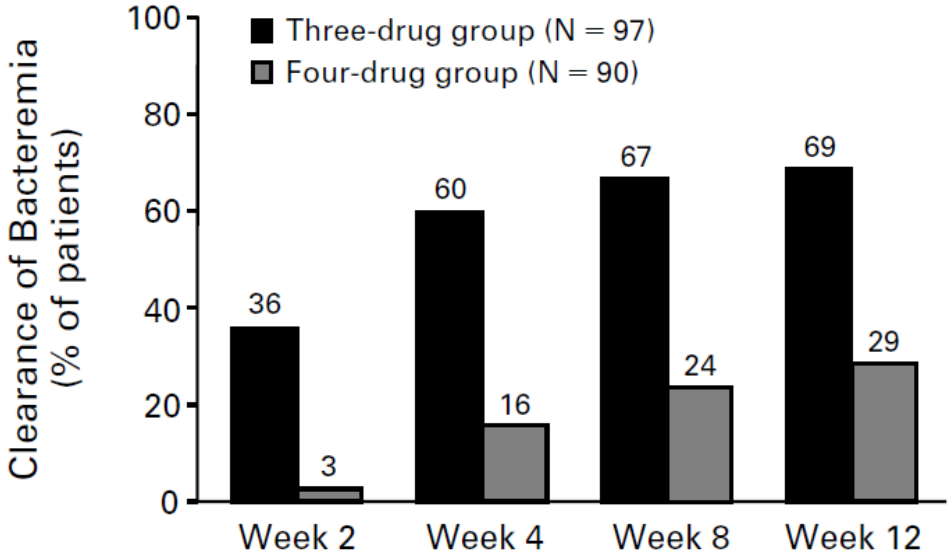
2-drugs without Macrolide
: Ethambutol + Rifampicin

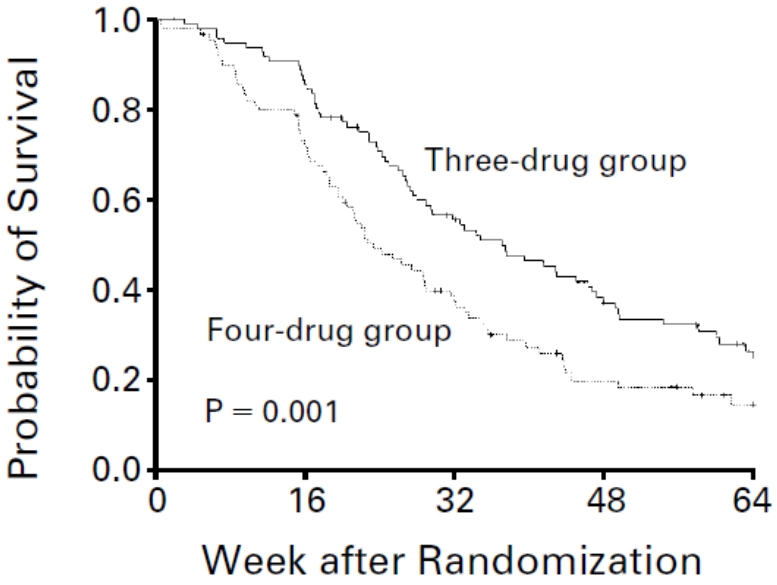
Macrolide
+
Ethambutol or Rifampicin

Macrolide Monotherapy

Macrolide-based regimen

- AIDS + MAC bacteremia
- 3-drug (macrolide containing)
  Clarithromycin + EMB+RIF
  vs 4-drug:
  clofazimine +ciprofloxacin + EMB+RIF
- No relapse in macrolide containing group





Shafran SD, N Eng J Med 1996; 355: 377

ATS/ERS/ESCMID/IDSA guideline,2020

Clinical Infectious Diseases

IDSA FEATURES

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

Charles L. Daley,[1,2,a] Jonathan M. Iaccarino,[3] Christoph Lange,[4] Jan Brozek,[13] David E. Griffith,[14] Lorenzo Guglielmetti,[8,15] Gwen Kenneth N. Olivier,[19] Miguel Santin,[20] Jason E. Stout,[21] Enrico

Mycobacterium avium Complex (Questions III–IX)

III: Should patients with macrolide-susceptible MAC pulmonary disease be treated with a 3-drug regimen with a macrolide or without a macrolide?

Recommendation

1. In patients with macrolide-susceptible MAC pulmonary disease, we recommend a 3-drug regimen that includes a macrolide over a 3-drug regimen without a macrolide (strong recommendation, very low certainty in estimates of effect).

ATS/ERS/ESCMID/IDSA guideline, CID, 2020

Drug intolerance: Adverse reactions

- A recent randomized clinical trial reported that >90% of subjects in each arm reported a treatment emergent adverse reaction

Drug	Adverse Reactions	Monitoring
Azithromycin	Gastrointestinal	Clinical monitoring
	Tinnitus/hearing loss	Audiogram
	Hepatotoxicity	Liver function tests
	Prolonged QTc	ECG (QTc)
Clarithromycin	Gastrointestinal	Clinical monitoring
	Tinnitus/hearing loss	Audiogram
	Hepatotoxicity	Liver function tests
	Prolonged QTc	ECG (QTc)
Ethambutol	Ocular toxicity	Visual acuity and color discrimination
	Neuropathy	Clinical monitoring
Rifabutin	Hepatotoxicity	Liver function test
	Cytopenias	Complete blood count
	Uveitis	Visual acuity
	Hypersensitivity	Clinical monitoring
	Orange discoloration of secretions	
Rifampicin (rifampin)	Hepatotoxicity	Liver function test
	Cytopenias	Complete blood count
	Hypersensitivity	Clinical monitoring
	Orange discoloration of secretions	
Amikacin, Streptomycin, Tobramycin	Vestibular toxicity	Clinical monitoring
	Ototoxicity	Audiograms
	Nephrotoxicity	BUN, creatinine
	Electrolyte disturbances	Calcium, magnesium, potassium

+

Long duration : ≥12 months of treatments after culture negative

ATS/ERS/ESCMID/IDSA guideline, CID, 2020

Inappropriate regimens d/t adverse reactions

Table 6 Predictors for treatment failure among patients with ≥12 months of antimycobacterial treatment

Variables	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Maintenance of antibiotics (≥6mo)				
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M + E	0.28 (0.09–0.82)	0.021	0.17 (0.03–1.09)	0.061
M + R	0.57 (0.18–1.82)	0.344	0.13 (0.01–1.13)	0.064
M + E + R	0.19 (0.07–0.50)	0.001		

Macrolide

+

- Synergic effects of RIF and EMB on MAC (in v
- Treatment failure; 32.4%
- macrolide resistance의 획득 : 5 patients
- **Adverse event**; deterioration of visual acuity (31.6%), AST elevation (5.9%)
- 약제 중단의 주 원인; 시력 저하 (4명), 구토, 약물 상호작용
- **EMB**; 41.1% 에서 부작용 경험, 35명은 조기 중단

Kim HJ, BMC Pulmonary Medicine 2019;19

3rd drug; Preventing the emergency of Macrolide resistance

	Rifabutin+ Clarithromycin +Ethambutol	Clarithromycin +Ethambutol	P-value
Week 16			
bacteriologic response	44/70(63%)	42/69(61%)	0.81
Clarithromycin resistance during therapy	1/44(2%)	6/42(14%)	0.05

- Rifamycin 동반 사용 시 macrolide resistance 발생 빈도 감소
- Clarithromycin and rifabutin; synergistic in vitro

Gordon FM, Clin Infect Dis 1999;28:1080

Protecting effect of Companion drugs

- Retrospective chart review, macrolide-resistance MAC-PD

Study Group	No. Developed Resistance/Enrolled	
	First 6 mo	All of Therapy
1. Initial 4-mo monotherapy, then three drugs (daily)		
Clarithromycin	5/30	6/30
Azithromycin	0/29	6/29
Totals for group 1	5/59 (8.5%)	12/59 (20.3%)
2. No initial monotherapy		
A. Initial three drugs (daily)		
Clarithromycin	1/95	5/95
Azithromycin	1/46	1/46
Totals	2/141 (1.4%)	6/141 (4.25%)

- Macrolide resistance; rarely in receiving EMB and rifamycin

  → RIF and EMB: **Protecting against** macrolide resistance

Griffith DE, Am J Respir Crit Care Med, 2006
Wallace RJ, Am J Respir Crit Care Med, 1996

Inappropriate regimens d/t adverse reactions; main cause of macrolide resistance

Treatment	No. (*n* = 90)	%
CLR monotherapy	29	32.2
Monotherapy from the beginning	17	18.9
Discontinuation of both EMB and RIP	7	7.8
CLR monotherapy for other disease	5	5.6
CLR plus fluoroquinolone	6	6.7
CLR plus RIP	23	25.6
Without EMB from the beginning	2	2.2
Discontinuation of EMB	21	23.3
CLR plus EMB (discontinuation of RIP)	5	5.6
Other causes	25	27.8
More than three courses of treatment	4	4.4
Unidentified treatment period	7	7.8
Desensitization	2	2.2
Unknown (three drugs only)	12	13.3
Macrolide resistance before the first treatment	2	2.2

- Macrolide-resistance MAC-PD, retrospective
- 60.2% of macrolide-resistance MAC-PD
  ; inappropriate first-line regimen(not standard treatment, ATS 2007)
- Cause of inappropriate regimen; frequent adverse events of **EMB** (34.4%)

Morimoto K, AnnalsATS, 2016; 13;1904

Macrolide resistance and Poor clinical outcomes

- Macrolide는 MAC 폐질환에서 가장 중요한 약제로서 단독사용이나 부적절한 약제조합을 사용하게 되는 경우에는 마크로라이드 내성이 발생
- **Poor clinical and radiologic outcome of Clarithromycin-resistant** MAC-PD
  - companion drug; rifampicin, ethambutol, fluoroquinolone, aminoglycoside, isoniazid
  - sputum culture conversion; 36%, radiologic worsening; 55%

regimen [161]. Until additional evidence is provided showing that acquired macrolide resistance is equally common among macrolide containing 3-drug and 2 drug regimens, the panel prefers a 3-drug regimen. A PCORI-funded randomized con-

Jhun BW, JKMS, 2024
Kadota T, BMC Infectious Diseases 2016
ATS/ERS/ESCMID/IDSA guideline, CID, 2020

Relationship between In vitro activity of rifampicin/ethambutol and Clinical outcomes

- Macrolide-susceptible MAC-PD with 3-drug regimen
  nodular bronchiectactic without cavity; 69%
- EMB, RIF resistance; MICs ≥ 8mcg/mL

	Ethambutol			Rifampin		
MIC (μg/mL)	No. (%) of patients	No. with culture conversion at 12 mo after treatment/ total no. (%)	No. with treatment success with microbiological cure/total no. (%)	No. (%) of patients	No. with culture conversion at 12 mo after treatment/total no. (%)	No. with treatment success with microbiological cure/total no. (%)
0.5				1 (1)	1/1 (100)	1/1 (100)
1	1 (1)	1/1 (100)	1/1 (100)	5 (3)	4/5 (80)	4/5 (80)
2	2 (1)	2/2 (100)	2/2 (100)	27 (17)	24/27 (89)	26/27 (96)
4	17 (11)	15/17 (88)	13/17 (77)	31 (20)	26/31 (84)	26/31 (84)
8	24 (15)	18/24 (75)	17/24 (71)	48 (30)	41/48 (86)	39/48 (81)
16	35 (22)	29/35 (83)	29/35 (83)	28 (18)	25/28 (89)	24/28 (86)
32	21 (13)	20/21 (95)	20/21 (95)	18 (11)	12/18 (67)	13/18 (72)
>32	58 (37)	48/58 (83)	51/58 (88)			

- Only clarithromycin susceptibility correlates with treatment outcomes
- TB처럼 *In vitro* 결과로 regimen을 구성하는 것은 무리

Moon SM, Antimicrobial Agents and Chemotherapy, 2022
ATS/ERS/ESCMID/IDSA guideline, CID, 2020

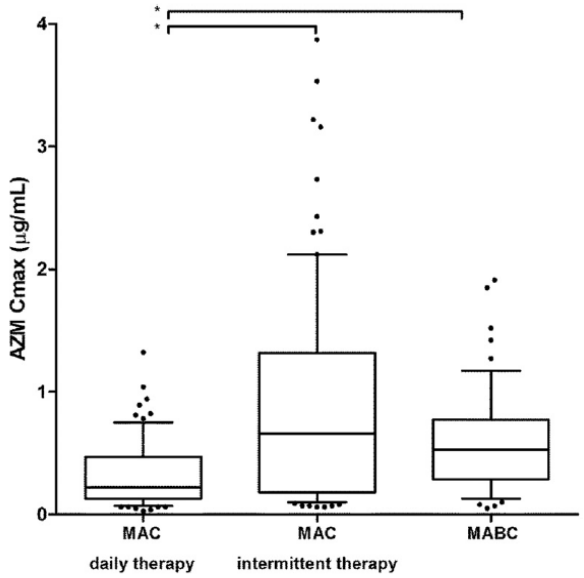
Summary

- Noncavitary nodular bronchiectactic disease를 대상으로 2-drug regimen과 3-drug regimen과 직접 비교한 임상 연구가 없다. 전향적인 연구와 새로운 동반약제에 대한 연구가 많이 필요하다
- RIF이 macrolide의 혈중농도를 낮추지만 MAC-PD에서 임상적 치료결과의 차이는 없다.
- Macrolide 내성은 불량한 예후임이 분명하고, 동반약제가 획득 내성을 감소시킨다는 직접적 증거는 없지만, 동반약제의 부작용 등으로 중단 시 부적절한 regimen이 될 수 있다.

반론

Lowered concentration of macrolide by rifampicin and unfavorable clinical outcomes ?

Characteristic	MAC			
	Total (n=166)	Daily AZM (250mg qd) (n=77)	Intermittent AZM (500mg 3 times/week) (n=89)	P-value
Fibrocavity	15.7%	33.8%	0	<0.001
Nodulo-bronchiectactic	79.5%	61%	95.5%	
unclassified	4.8%	5.2%	4.5%	<0.001
Cavity on HRCT	39.8%	85.7%	0	<0.001
Smear positive	45.8%	68.8%	25.8%	<0.001

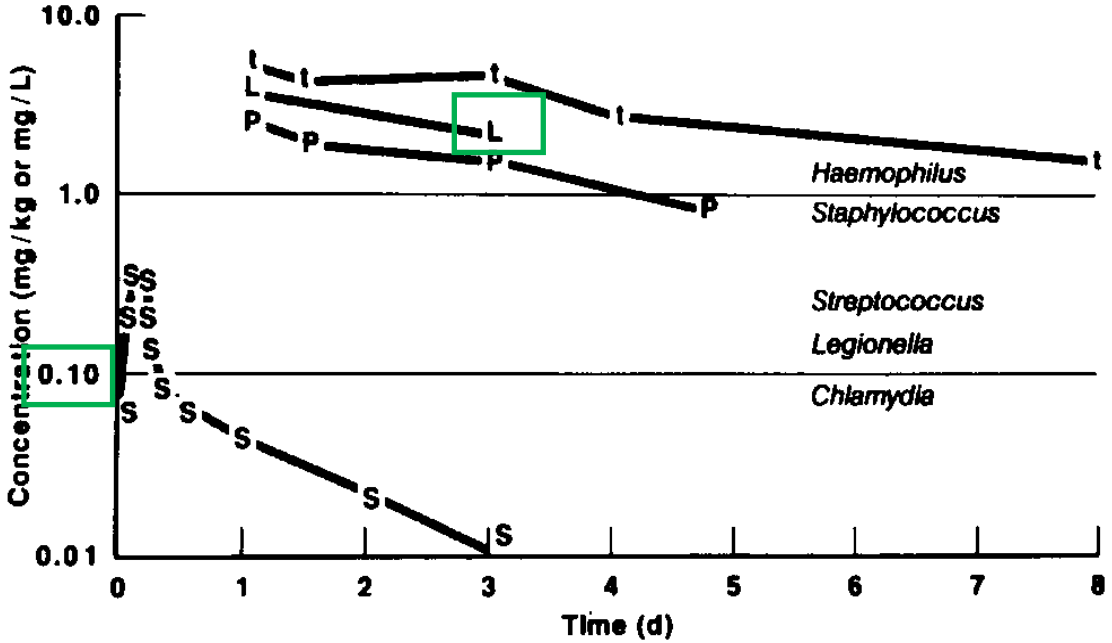


	MAC daily therapy	MAC intermittent therapy	MABC
AZM Cmax (μg/mL)†	0.22 (0.13-0.47)	0.66 (0.18-1.32)	0.53 (0.29-0.77)
AZM Cmax < 0.2 μg/mL	36/77 (46.8%)	23/89 (25.8%)	9/55 (16.4%)

sponses. The results also suggested that the addition of rifampin may lower AZM C_{max}. When a daily AZM-based multidrug regimen is used for treating severe MAC-LD, such as cavitary disease, the currently recommended AZM dose might be suboptimal. (This study has been registered at ClinicalTrials.gov under identifier NCT00970801.)

Jung BH, Antimicrobial Agents and Chemotherapy, 2016

Lung concentration of Azithromycin; Higher than serum



- Cmax, Cmax/MIC ratio로 효과를 예측할 수는 없어 TDM이 아직 유용할 수 없음.
- 2018 CLSI에서는 molecular methods를 추가함: in Korea?

  - 23S rRNA gene at adenine position 2058 or 2059

Species/complex	MIC (μg/ml) Susceptible	Intermediate	Resistant	Comment
M. avium complex				
First line				
Clarithromycin	≤8	16	≥32	Clarithromycin is class drug for macrolides
Amikacin (IV)	≤16	32	≥64	
Amikacin (liposomal inhaled)	≤64		≥128	
Second line				
Moxifloxacin	≤1	2	≥4	The clinical efficacy of these agents for
Linezolid	≤8	16	≥32	MAC disease remains uncertain

Ballow CH, The Annals of Pharmacotherapy, 1992
Elliott BA, J Clic Micro 2019, CLSI 2018

Low adverse events and drug tolerance; Intermittent therapy

- Noncavitary nodular bronchiectatic MAC-PD, 3 drug-regimen
- AFB smear positive; 40-47%

	Daily Therapy (*n* = 99)	Intermittent Therapy (*n* = 118)	*P* Value
Early discontinuation of antibiotic treatment	15 (15%)	13 (11%)	0.366
Dose reduction of CLR	11/95 (12%)	1/26 (4%)	0.458
Change from AZM to CLR	0/12 (0%)	3/116 (3%)	NA
Discontinuation of RIF or RFB	4/99 (4%)	7/118 (6%)	0.527
Discontinuation of EMB	24/99 (24%)	1/118 (1%)	<0.001
Discontinuation of streptomycin	4/60 (7%)	—	NA
Total	46/99 (46%)*	25/118 (21%)	<0.001
Improvement of symptom	74 (75%)	97 (82%)	0.181
Improvement of HRCT	67 (68%)	86 (73%)	0.402
Sputum culture conversion	75 (76%)	79 (67%)	0.154
Time of sputum culture conversion, d	34 (27–68)	35 (28–85)	0.149

Jeong BH, Am J Respir Crit Care Med. 2015
Wallace RJ, Chest, 2014

3-drug regimen with intermittent treatment (3 times/week)

1. In patients with noncavitary nodular/bronchiectatic macrolide-susceptible MAC pulmonary disease, we suggest a 3 times per week macrolide-based regimen rather than a daily macrolide-based regimen (conditional recommendation, very low certainty in estimates of effect).
2. In patients with cavitary macrolide-susceptible MAC pulmonary disease we suggest a daily macrolide-based regimen rather than 3 times per week macrolide-based regimen (conditional recommendation, very low certainty in estimates of effect)

ATS/ERS/ESCMID/IDSA guideline, CID, 2020

Other companion drug and Clofazimine in MAC-PD

- Other companion drugs: Amikacin liposomal inhalation suspension: not commercial in Korea, Clofazimine, Moxifloxacin, Linezolid, Bedaquiline
- Nonblinded, RCT, 40 patients, noninferior

	Rifampicin +Macrolide+EMB (n=19)	Clofazimine +Macrolide+EMB (n=21)
Nodular-bronchiectatic	42.1%	42.9%
MAC	63.1%	61.9%
Sputum culture conversion after 6 months	57.9%	61.9%
Discontinuation of trial	26.3%	33.3%
Adverse events	26%	33%

Sanne MH, Chest, 2024

경청해 주셔서 감사합니다!