PRO

Early treatment for Mycobacterium Avium Complex(MAC) disease

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김 양 기

비결핵 항산균의 특징

- 자연수와 토양 등 자연환경에 널리 분포

  ▶**Environmental mycobacteria**

- **낮은** 병원성
- 사람과 사람 사이에서의 **전염이 없어** 격리할 필요는 없음
- NTM 폐질환은 **주위 환경에 존재하는 균**이 **공기를 통해** 호흡기에 감염되어 발생
- **소아**에서 주로 발생하는 NTM 림프절염과 **AIDS** 환자에서 발생하는 파종성 질환은 **경구**를 통한 오염된 물의 섭취가 원인으로 추정

진단은 어떻게 하나요?

임상적 기준

호흡기 증상,

흉부 엑스레이에서 **결절**성 병변 또는 **공동**성 병변의 존재, 혹은

HRCT에서 다병소의 기관지확장증과 동반된 다발성 결절의 존재

AND

다른 질환이 적절히 **배제**되어야 함

미생물학적 기준

최소한 **2회 이상의 객담**에서 **배양 양성** 또는 **기관지세척액 1회에서 배양 양성**

OR

경기관지 폐생검 등 조직배양이 양성이거나 또는 조직검사에서 육아종

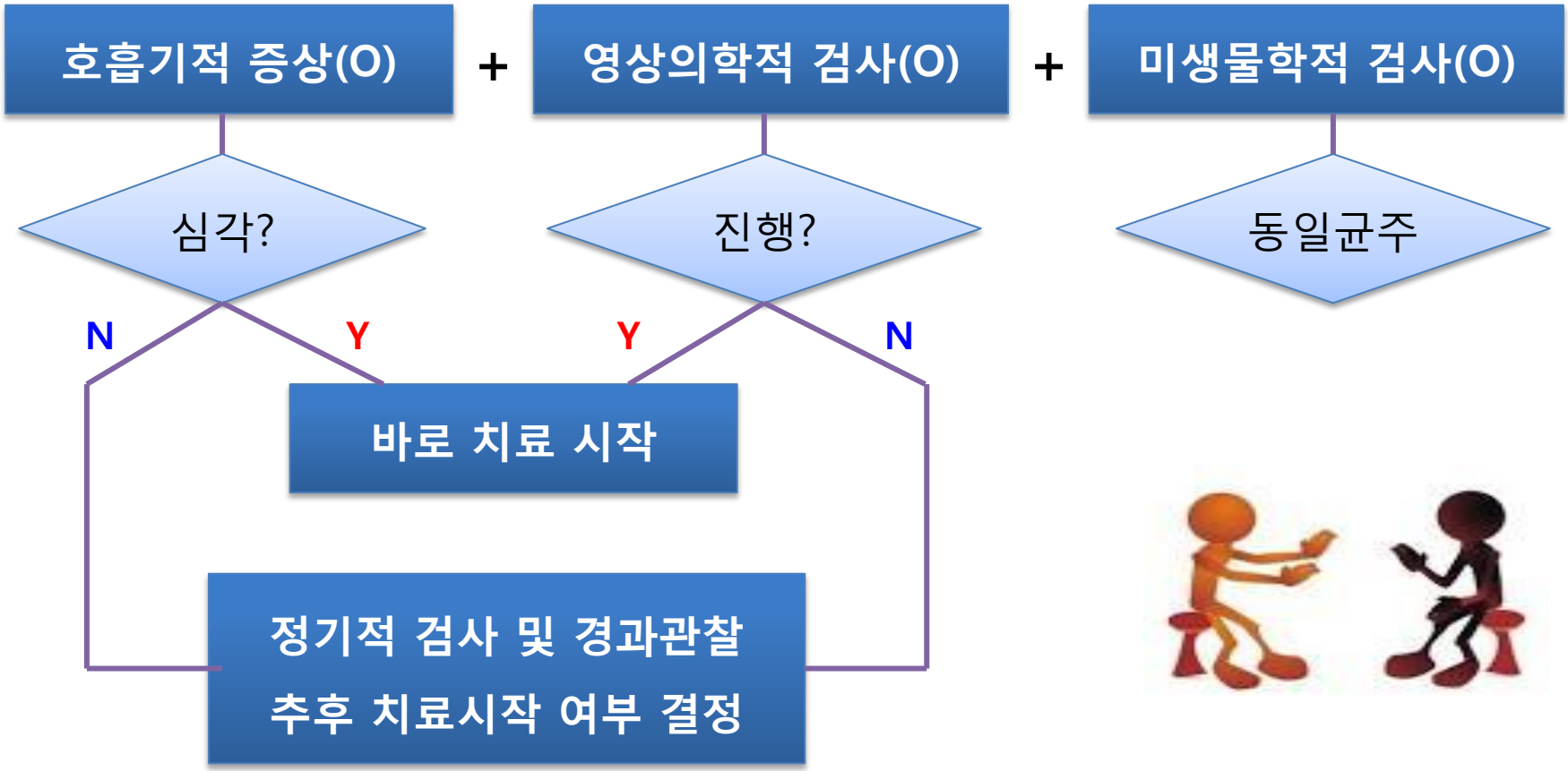
(granuloma) 등 마이코박테리아 감염의 병리학적 증거가 있으면서

1회 이상 객담 또는 기관지 세척액에서 배양이 양성

2007 미국흉부학회/미국감염학회의 진단기준

진단 후 치료시작 여부는 어떻게 결정하나요?

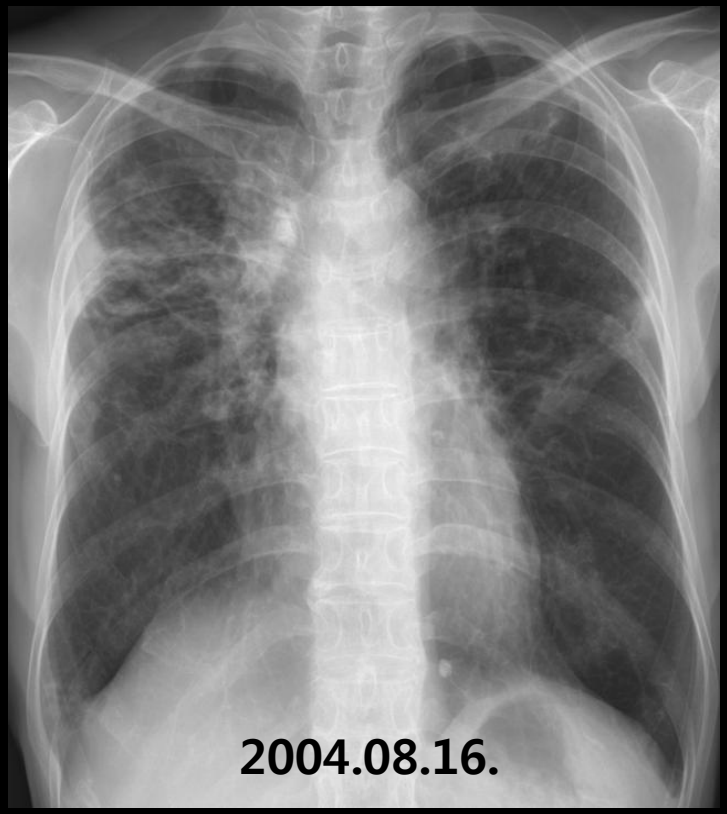
- 객담에서 NTM이 분리된 환자 중 약 **10-25%**만이 NTM 폐질환.
  - NTM 폐질환은 **진단 자체가 치료를 의미하지는 않음.**
- 치료에 따른 득실을 고려하여 모든 환자에서 **개별적으로** 결정



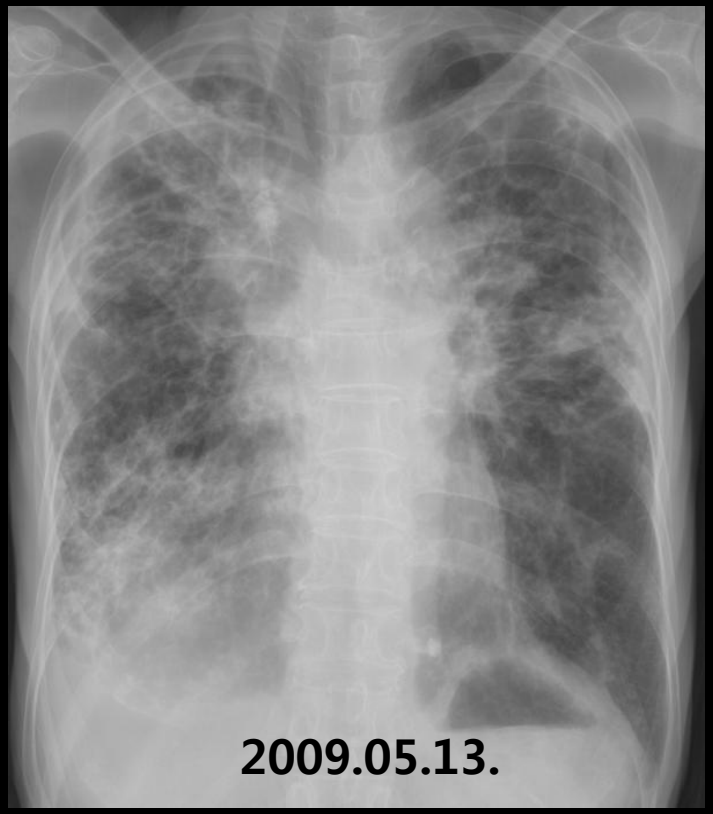
과거로의 여행

F/60, cough, sputum, weight loss

onset : 6개월



2004.08.16.



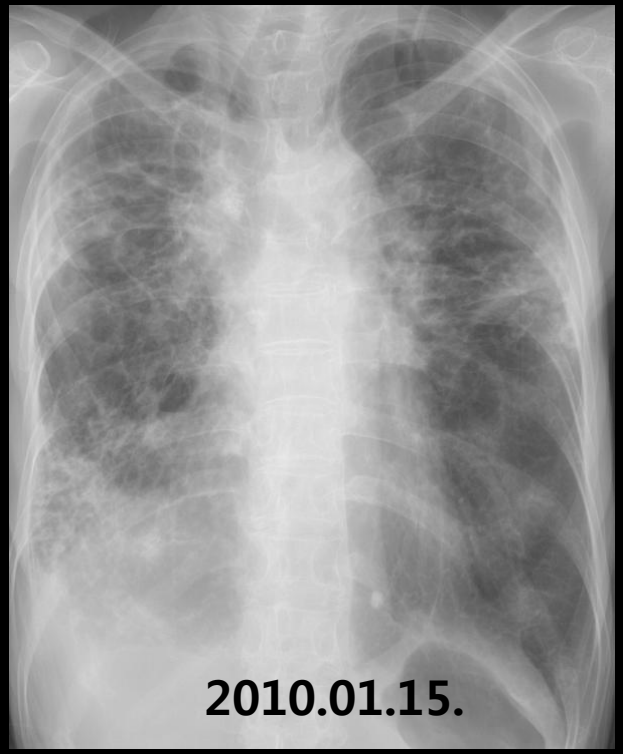
2009.05.13.

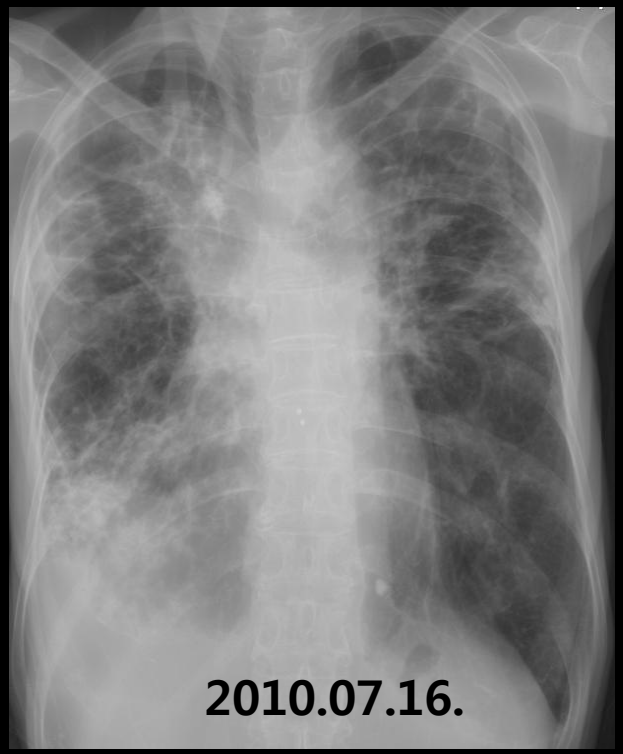
결핵협회에 문의결과 2004년부터 매년 각기 다른 병원에서 시행한 객담검사에서 M. intracellulare 가 자랐다고 함.

-> 2009년 M. intracellulare

미래로의 여행

F/60, dyspnea





2009년 5월 Clarithromycin + myambutol + rifampin + streptomycin 시작

본 환자에서 early treatment 란?

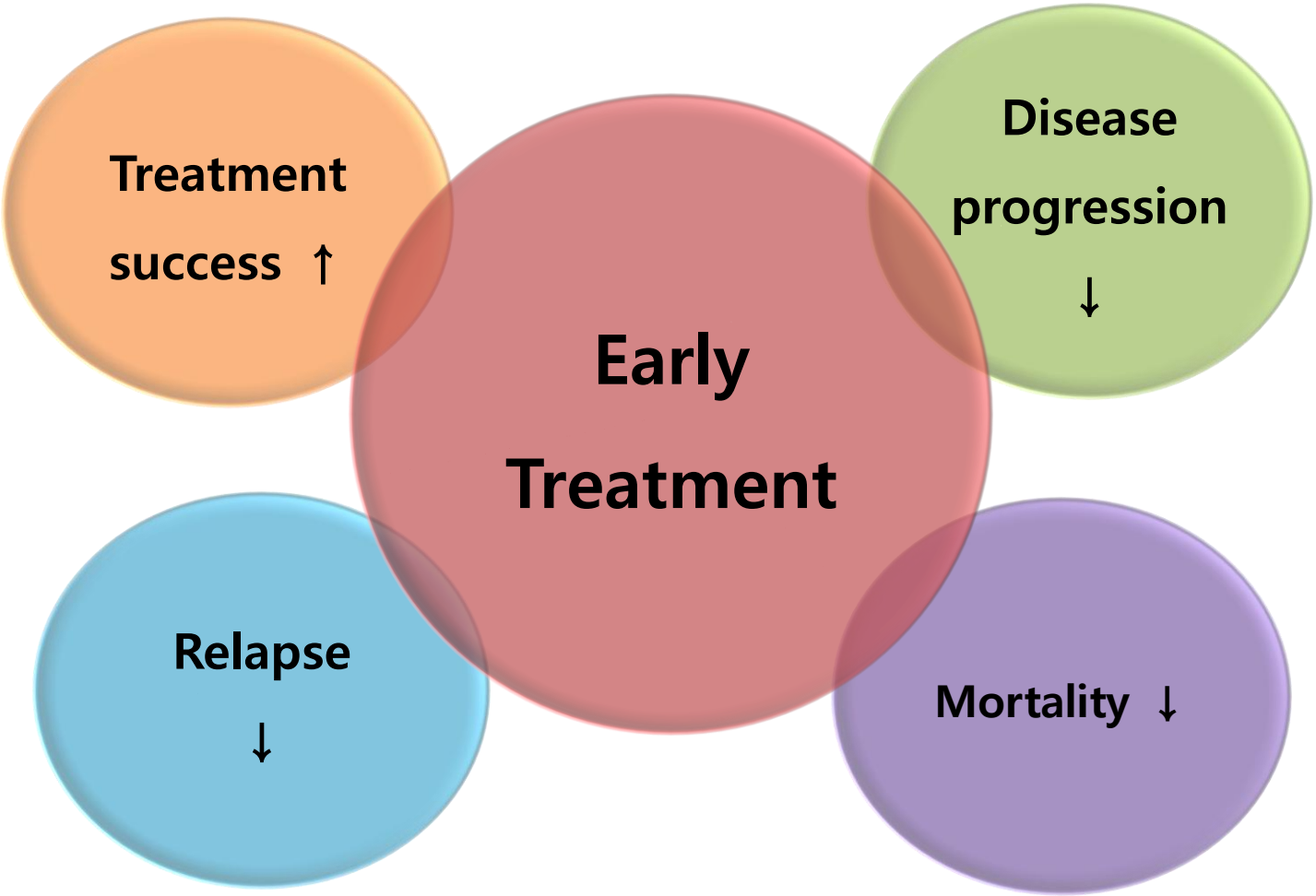
MAC에서 Early treatment 란 무엇을 말하나요?

❖ 임상적, 영상의학적, 미생물학적 MAC 진단기준을 만족하는 가장 빠른 시기에 치료를 시작?

▶ early treatment = not to delay treatment

❖ 폐기능 손상이 진행되기 전 혹은 심각한 호흡기적 장애가 진행되기 전 치료시작?

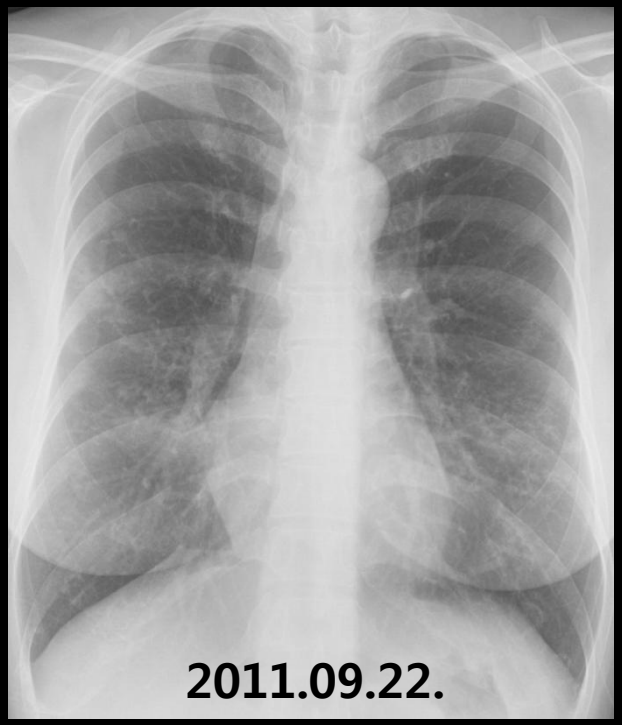
MAC에서 Early treatment 의 목적?

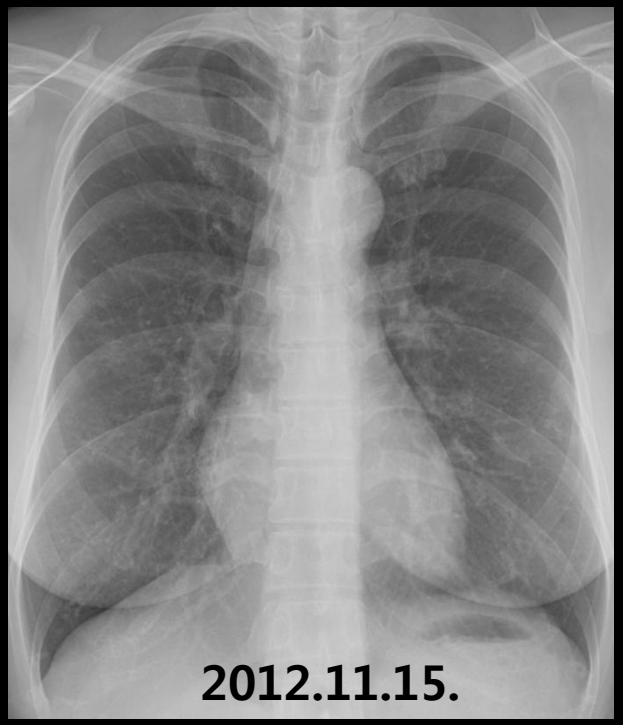


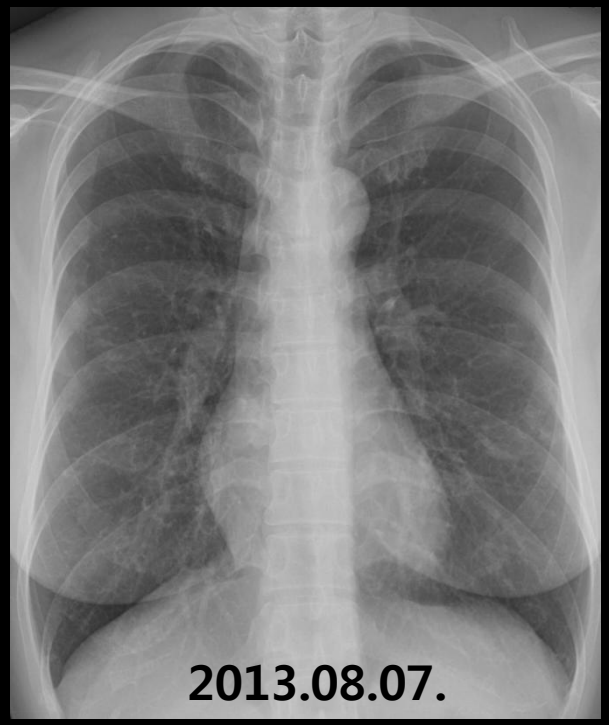
Nodular bronchiectatic form

F/45, 객담

onset : 3년





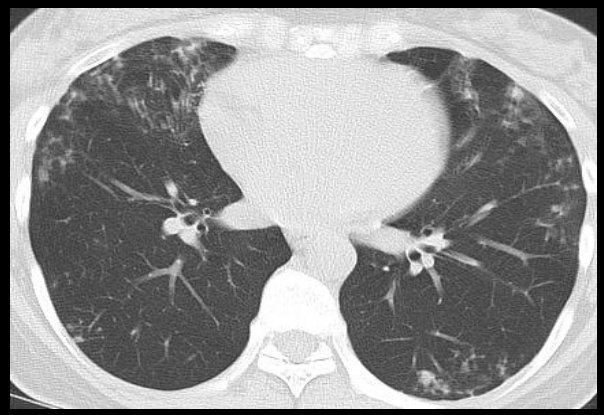


M. intracellulare ▶ MAC 로 2011년 9월부터 치료

중년 이상의 여성으로 기저질환이 없음

양측 폐에 다발성 결절, 우중엽과 좌상엽의 설상분절에 국한되거나 가장 심함

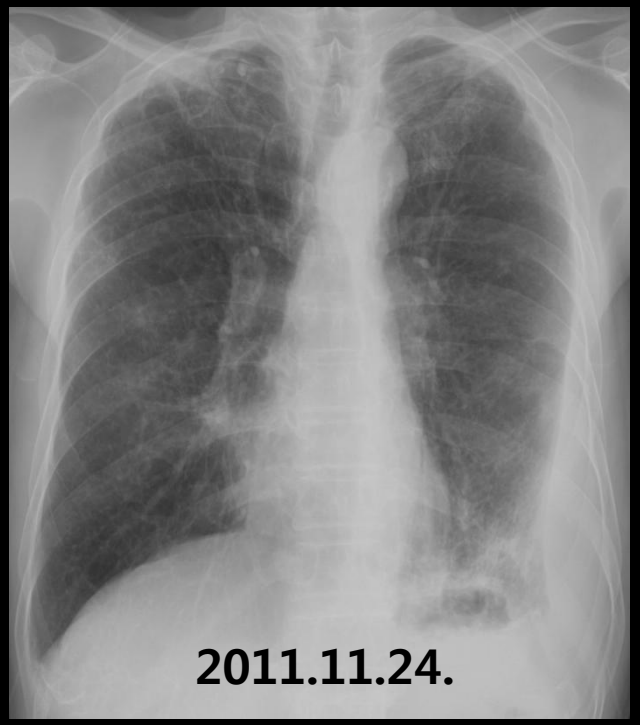
치료를 하지 않더라도 매우 느린 방사선학적 진행

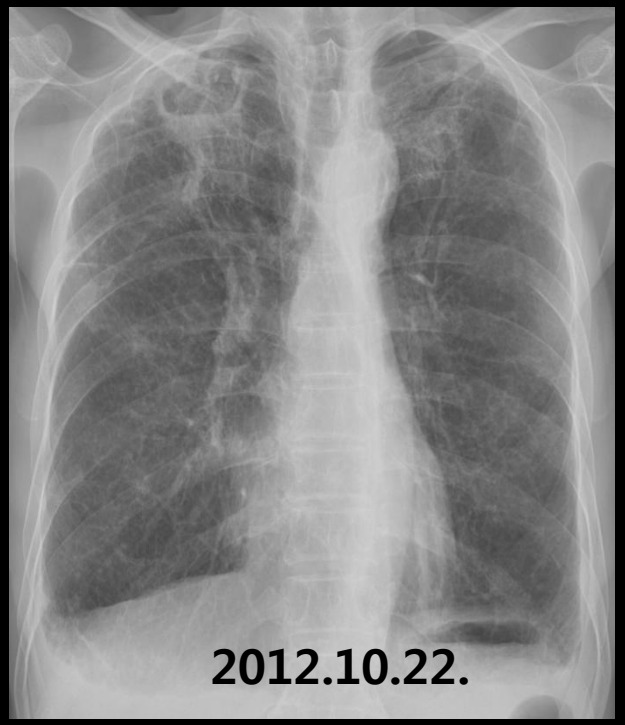


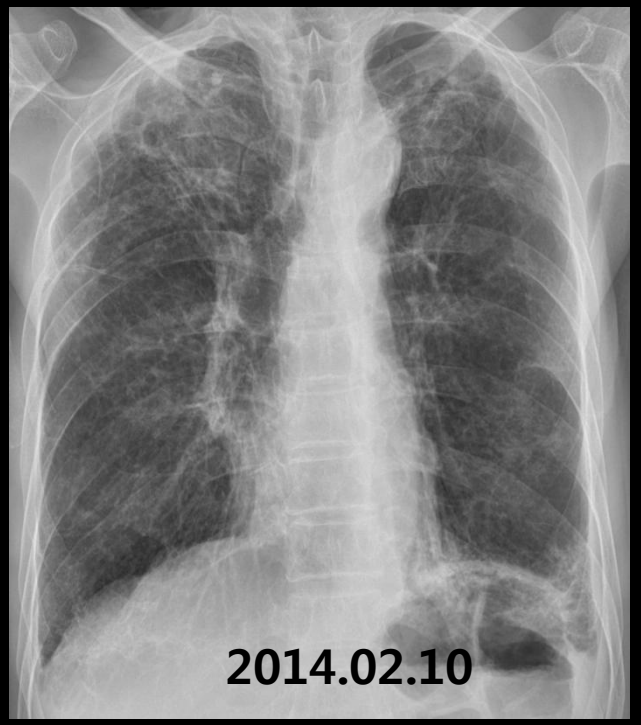
Fibrocavitary form

M/72, chest pain

onset : 1주일







M. intracellulare ▶ MAC 로 2011년 11월부터 치료

중년 이상의 남성, 기저폐질환

(흡연, 음주, COPD, 과거 폐결핵 치료력, 진폐증)

얇은 벽의 공동이 상엽에 존재, 주위 늑막 비후

치료를 하지 않는 경우, 1-2년 내에 진행하여 광범

위한 폐실질의 파괴와 사망 초래

Decision to initiate therapy for MAC

Based on the **potential** **risks** and **benefits** for individual patients.

❖ **Fibrocavitary form** of MAC lung disease

▶ **Immediate** treatment

▶ progressive lung destruction

❖ **Nodular bronchiectatic form** of MAC lung disease

▶ variable disease progression

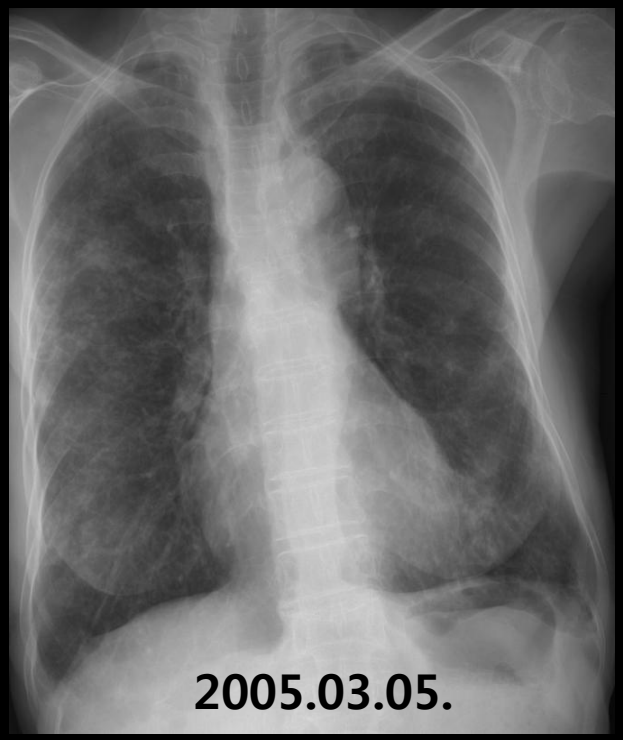
▶ **closely monitor without long-term antibiotic therapy** if there is not progressive or severe disease

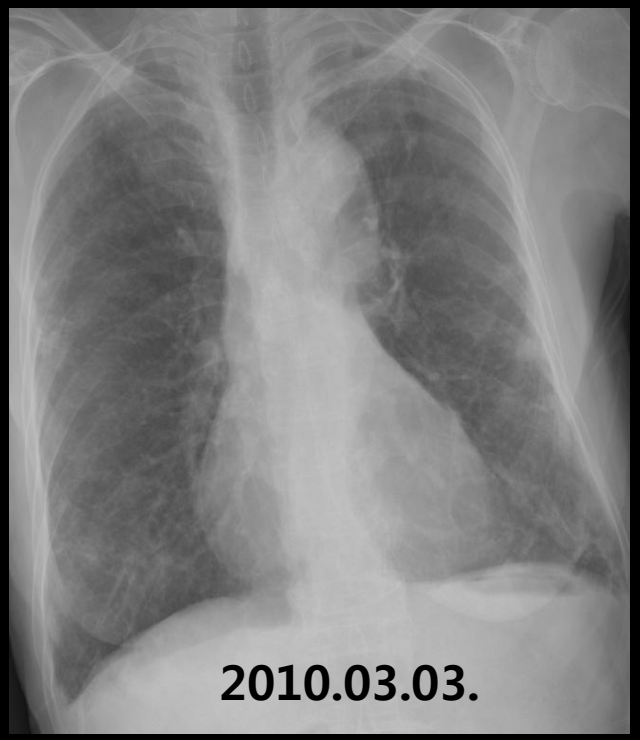
Am J Respir Crit Care Med 2007;175(4):367-416

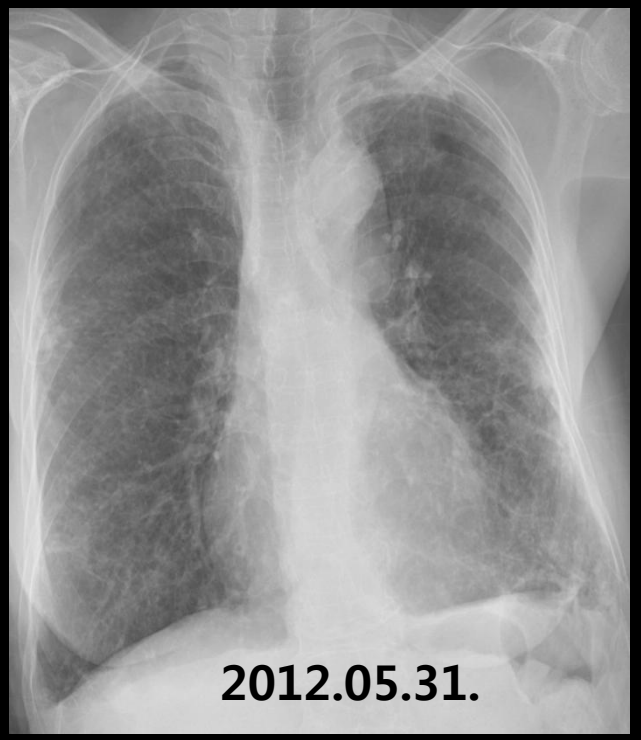
과거로의 여행

F/82, sputum

onset : 5개월







2012년 1월부터 NTM 의심하에 객담 AFB 검사를 시행

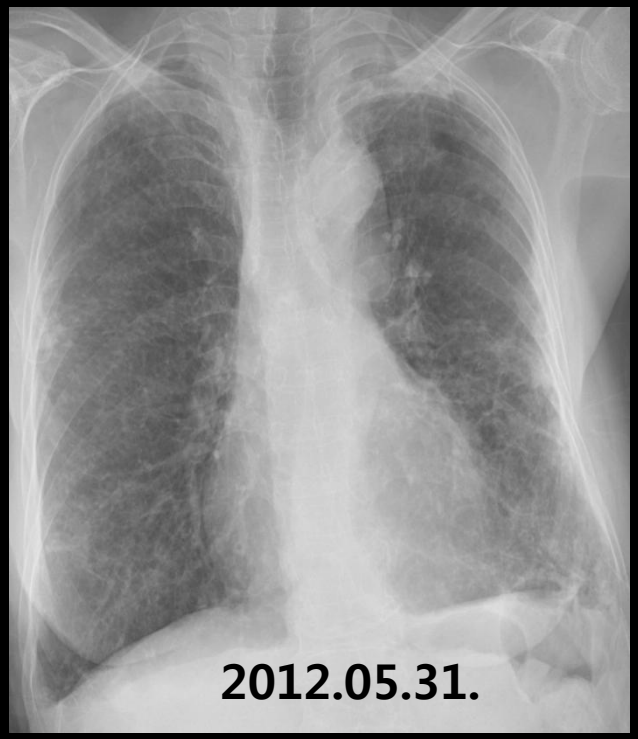
2012. 02. M. intracellulare [sputum]

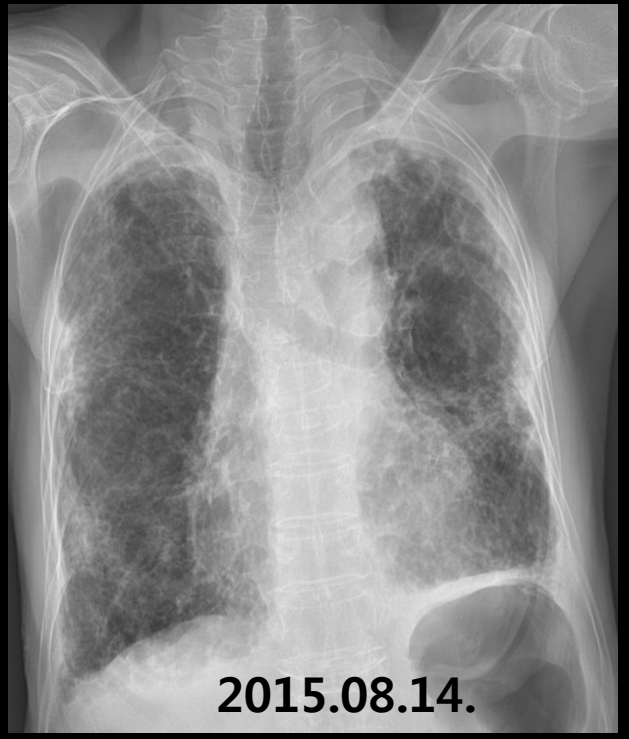
2012. 04. M. scrofulaceum [sputum]

2012. 06. M. kansasii [BAL]

미래로의 여행

F/82, dyspnea





2012년 8월 M. kansasii 에 대해 HRE 시작 -> 시작 5일만에 GI trouble 로 치료거부

2013년 11월 clarithromycin 1,000mg + HRE 시작

-> 객담 검사에서 M. intracellulare 다시 동정되어 INH 중단

Predictor of final progression necessitating initiation of treatment for nodular bronchiectatic MAC lung disease

126 (48%) patients [progressed] vs **139 (52%)** patients [treatment-free]

	Univariate			Multivariate		
	Adj HR	95% CI	*P* Value	Adj HR	95% CI	*P* Value
Age (>60 yr)	1.09	0.76–1.54	0.649		NA	
Male	1.02	0.71–1.47	0.920		NA	
BMI (<18.5 kg/m^2)	1.28	0.84–1.95	0.254		NA	
Mycobacterium intracellulare	1.16	0.81–1.66	0.411		NA	
Sputum AFB smear (+)	1.50	1.06–2.13	**0.024**	1.26	0.87–1.81	0.219
Bronchiectasis (>5)	2.09	1.28–3.42	**0.003**	1.53	0.91–2.56	0.111
Bronchiolitis (>3)	1.83	1.29–2.60	**0.001**	1.45	0.99–2.12	0.053
Cavity (+)	2.16	1.33–3.49	**0.002**	2.06	1.26–3.36	**0.004**
Nodule (+)	1.48	1.04–2.10	**0.030**	1.26	0.87–1.81	0.225
Consolidation (+)	1.66	1.17–2.39	**0.005**	1.55	1.08–2.23	**0.019**
Total CT score (>8)	2.21	1.54–3.17	<**0.001**		NA*	

Ann Am Thorac Soc 2013;10(4):299-306

Assessment of microbiologic responses

❖ **Sputum conversion**

: defined as 3 consecutive negative cultures within 6 months

▶the time of conversion - the date of the first negative culture

❖ **Sputum relapse**

: defined as 2 consecutive positive cultures after sputum conversion

❖ **Favorable microbiologic response**

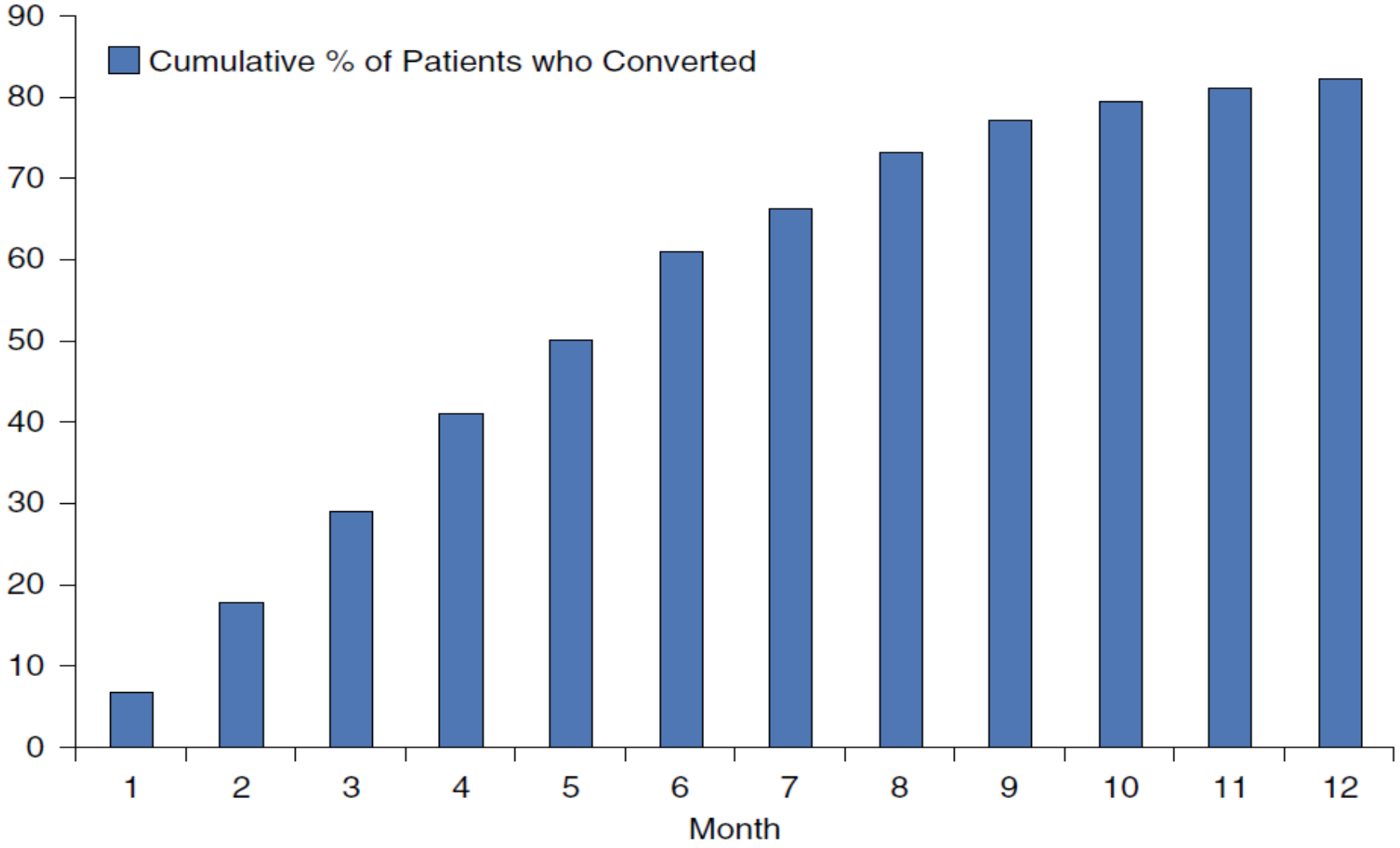
: defined as sputum conversion and maintenance of negative sputum cultures for more than 12 months.

❖ **Unfavorable microbiologic response**

: defined as follows: 1) no sputum conversion, 2) initial sputum conversion with sputum relapse, or 3) death related to MAC lung disease.

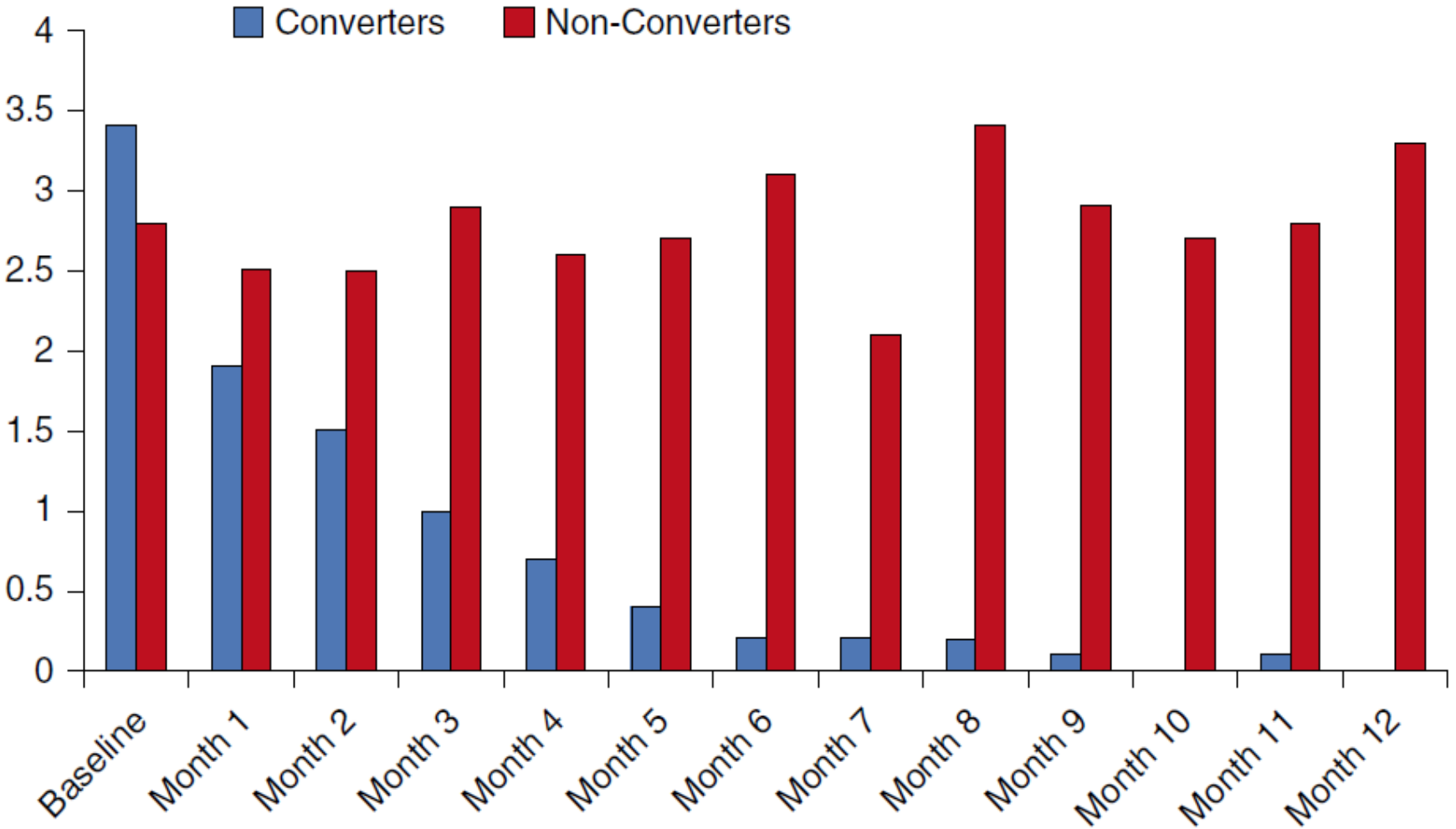
Yonsei Med J 2010;51(6):888-94

Treatment Success using semiquantitative culture analysis for MAC lung disease



Am J Respir Crit Care Med 2015;192(6):754-60

Treatment Success using semiquantitative culture analysis for MAC lung disease



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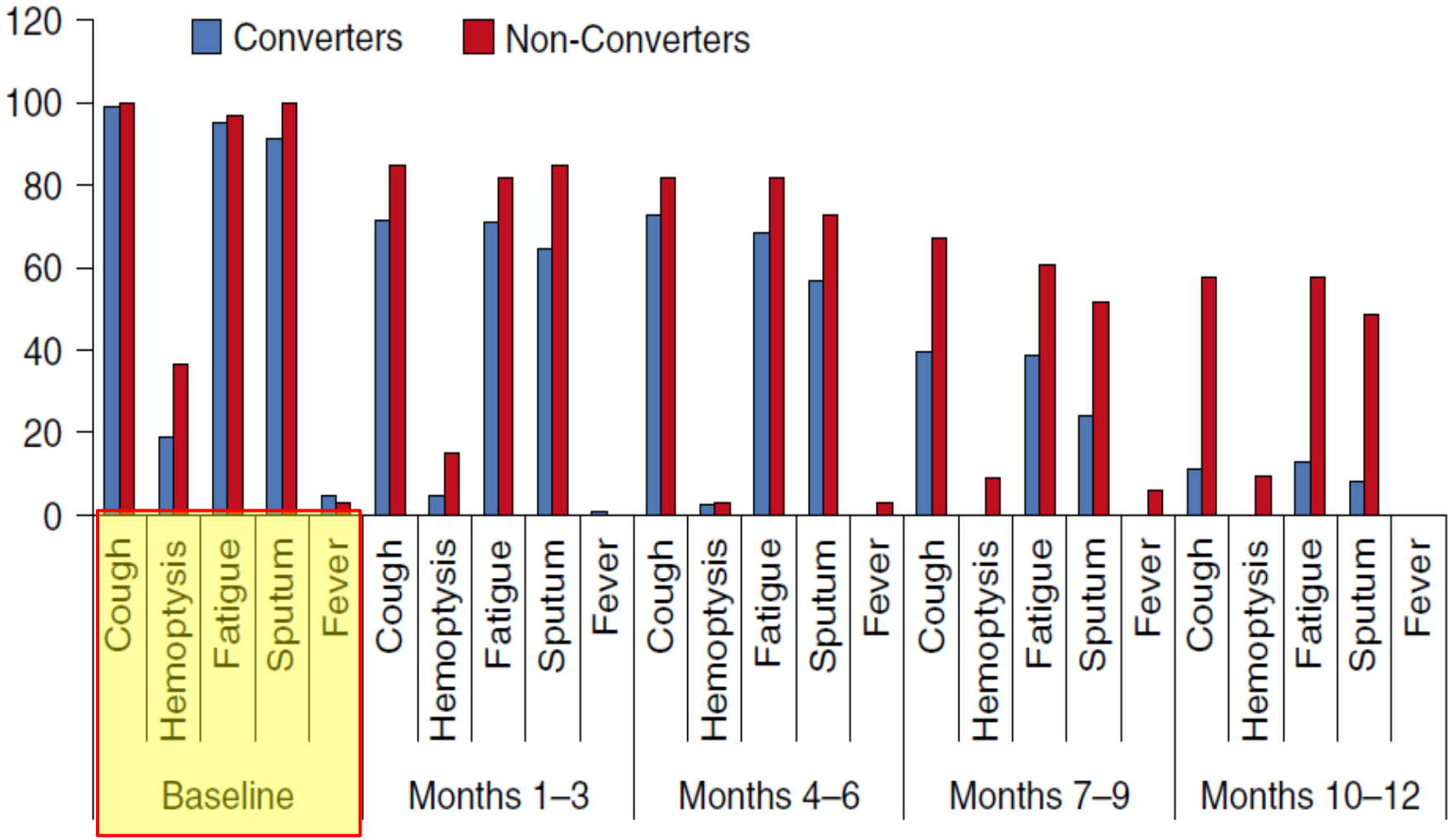
Treatment Success using semiquantitative culture analysis for MAC lung disease



Am J Respir Crit Care Med 2015;192(6):754-60

Treatment Success using semiquantitative culture analysis for MAC lung disease

The change in sputum culture semiquantitative score **from baseline to Month 3** was **highly predictive of subsequent sputum long-term conversion status indicative of treatment success**, as was improvement in cough, and especially early radiographic improvement.

Am J Respir Crit Care Med 2015;192(6):754-60

Predictors for clinical relapse/reinfection in MAC

Clinical Relapse/Reinfection : 25% (48/190)

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	AOR (95% CI)*	*P* Value
Demographics				
Age	1.04 (1.01–1.07)	0.003	1.04 (1.01–1.07)	0.006
Sex (female)	1.77 (0.81–3.84)	0.15	1.75 (0.69–1.79)	0.24
BMI	0.87 (0.80–0.96)	0.005	0.87 (0.78–0.96)	0.008
Ever-smoker	0.48 (0.24–0.97)	0.04	0.49 (0.22–1.10)	0.08
Laboratory evaluation				
Smear positive	1.48 (0.77–2.84)	0.24	1.92 (0.88–4.18)	0.10
Species compared with *Mycobacterium intracellulare*				
M. avium	4.13 (1.18–14.43)	0.03	5.64 (1.51–21.10)	0.01
M. chimaera	4.37 (1.10–17.35)	0.03	4.47 (1.08–18.53)	0.04
Comorbidities†				
COPD	1.99 (0.98–4.05)	0.06	1.78 (0.70–4.51)	0.23
Prior TB	0.94 (0.29–3.11)	0.93		
Malignancy	0.70 (0.34–1.47)	0.35		
Immunosuppressants‡	1.23 (0.56–2.71)	0.60		
Clinical symptoms				
Hemoptysis	2.82 (0.99–8.00)	0.05	1.84 (0.51–6.60)	0.35
Radiographic findings				
Cavitary disease	2.22 (1.07–4.63)	0.03	3.73 (1.38–10.09)	0.01
Bilateral lung disease	2.55 (0.72–8.97)	0.14	1.66 (0.42–6.61)	0.40

Am J Respir Crit Care Med 2015;191(11):1310-7

Predictors of 5-year mortality in MAC disease

- The mortality rate was **33.3%** for untreated chronic MAC patients only vs. **22.2%** for treated MAC patients (P = 0.30).

Table 3 Factors associated with mortality in multivariate analysis

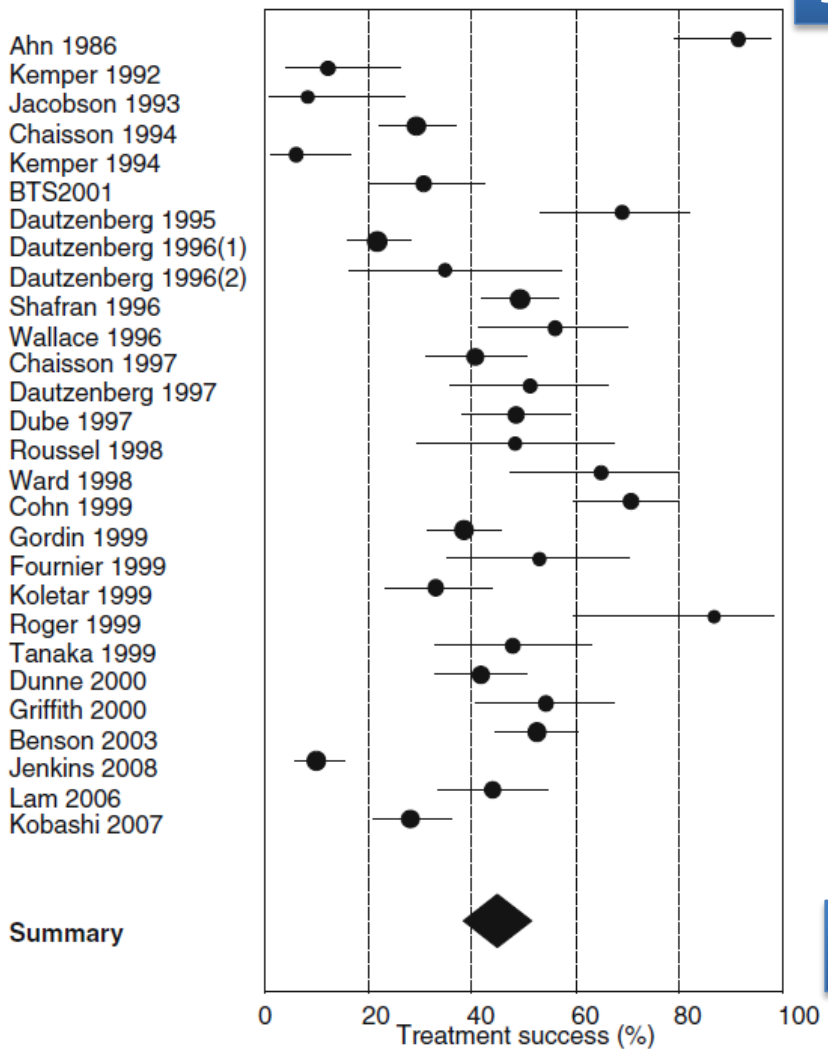
	All MAC patients (n = 78)			Treated MAC patients (n = 54)			Untreated chronic MAC patients* (n = 24)		
Variable	HR	95%CI	*P* value	HR	95%CI	*P* value	HR	95%CI	*P* value
Male sex	1.12	0.70–1.82	0.62						
CCI ⩾1	1.76	1.02–3.23	0.04	1.21	0.65–2.42	0.55	3.08	1.15–14.1	0.02
ILD				7.49	2.29–25.3	0.002			
Malignancy	1.63	0.99–2.61	0.05				3.33	1.40–9.88	0.006
Cavitary lesions	1.82	1.14–2.89	0.01	3.91	1.91–10.2	<0.0001			

*Untreated MAC patients had chronic MAC infection throughout the whole course of follow-up.
MAC = *Mycobacterium avium-intracellulare* complex; HR = hazard ratio; CI = confidence interval; CCI = Charlson comorbidity index; ILD = interstitial lung disease.

- Patients with **cavitary lesions** require **immediate** treatment for sputum culture conversion and to improve their chances of survival.

Int J Tuberc Lung Dis 2012;16(3):408-14

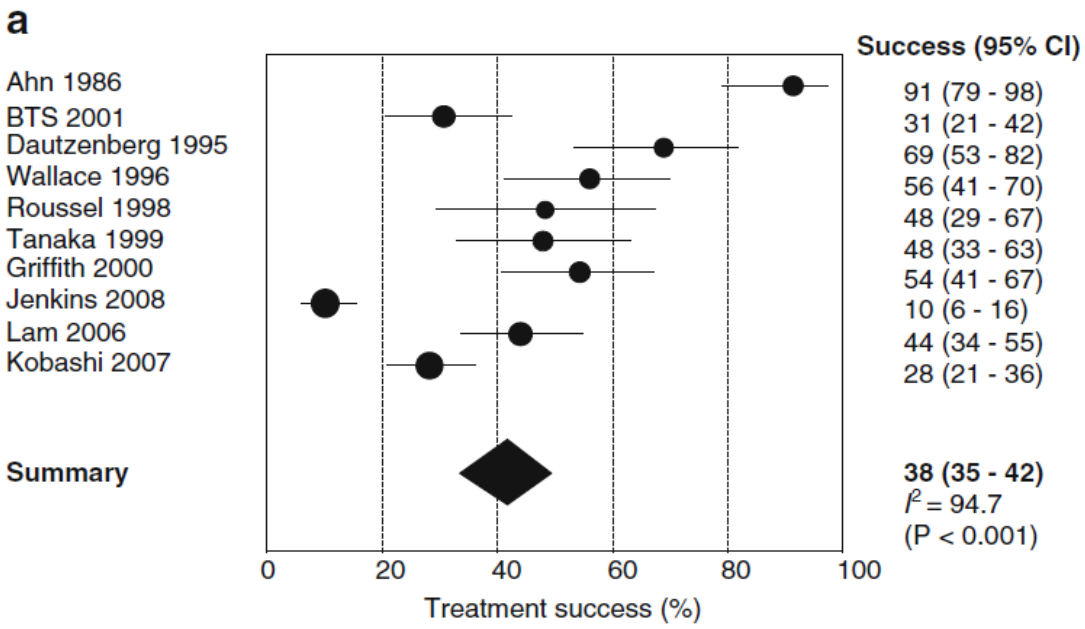
Treatment Outcomes for MAC disease

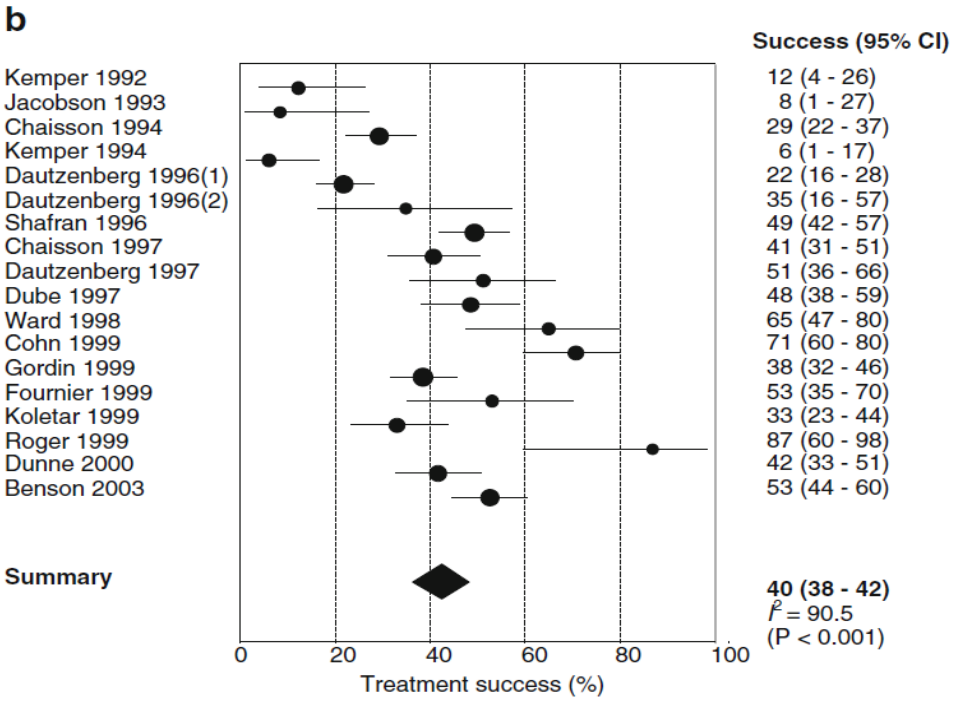


success	failure	relapse	death	default
91 (79 - 98)	9	0	0	0
12 (4 - 26)	44	20	10	15
8 (1 - 27)	63	8	0	21
29 (22 - 37)	28	0	19	24
6 (1 - 17)	50	2	14	28
31 (21 - 42)	15	13	35	19
69 (53 - 82)	16	2	7	7
22 (16 - 28)	30	0	47	1
35 (16 - 57)	65	0	0	0
49 (42 - 57)	17	1	32	2
56 (41 - 70)	6	8	8	22
41 (31 - 51)	17	9	33	0
51 (36 - 66)	11	0	18	20
48 (38 - 59)	26	9	0	16
48 (29 - 67)	28	0	0	24
65 (47 - 80)	8	3	5	19
71 (60 - 80)	4	7	19	0
38 (32 - 46)	61	1	0	0
53 (35 - 70)	24	3	18	3
33 (23 - 44)	60	5	5	0
87 (60 - 98)	13	0	0	0
48 (33 - 63)	20	3	4	15
42 (33 - 51)	25	9	25	0
54 (41 - 67)	15	0	0	31
53 (44 - 60)	40	3	0	5
10 (6 - 16)	9	7	42	39
44 (34 - 55)	20	0	0	36
28 (21 - 36)	21	1	1	18
39%	**27%**	**6%**	**17%**	**12%**

Eur J Clin Microbiol Infect Dis 2014;33(3):347-58

Treatment Success for non-HIV patients ▶

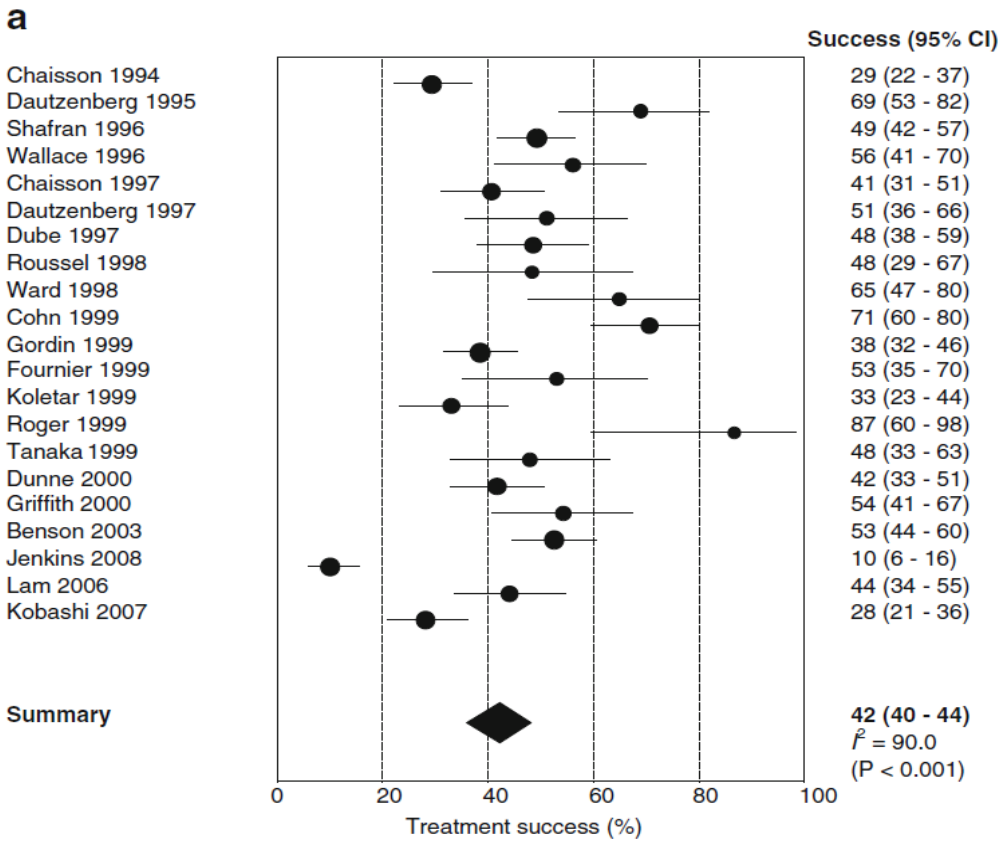


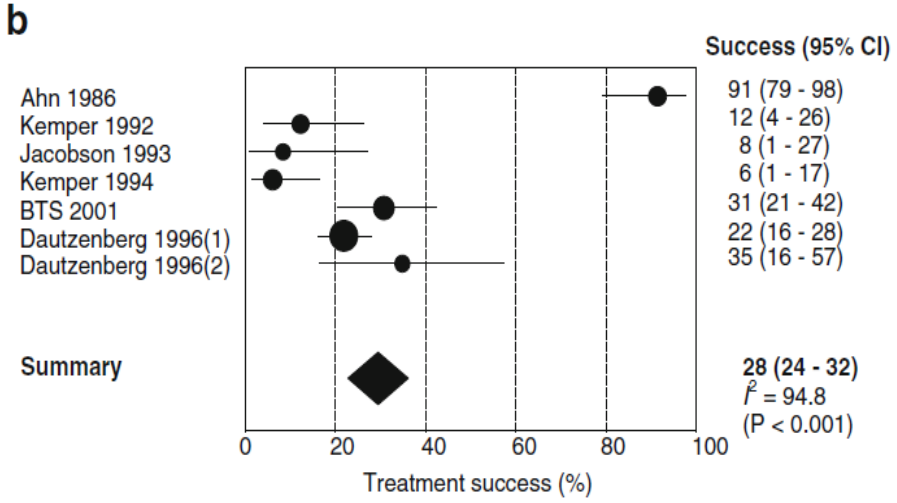


◀ Treatment Success for HIV patients with disseminated MAC disease

Eur J Clin Microbiol Infect Dis 2014;33(3):347-58

Macrolides-containing treatment regimens ▶

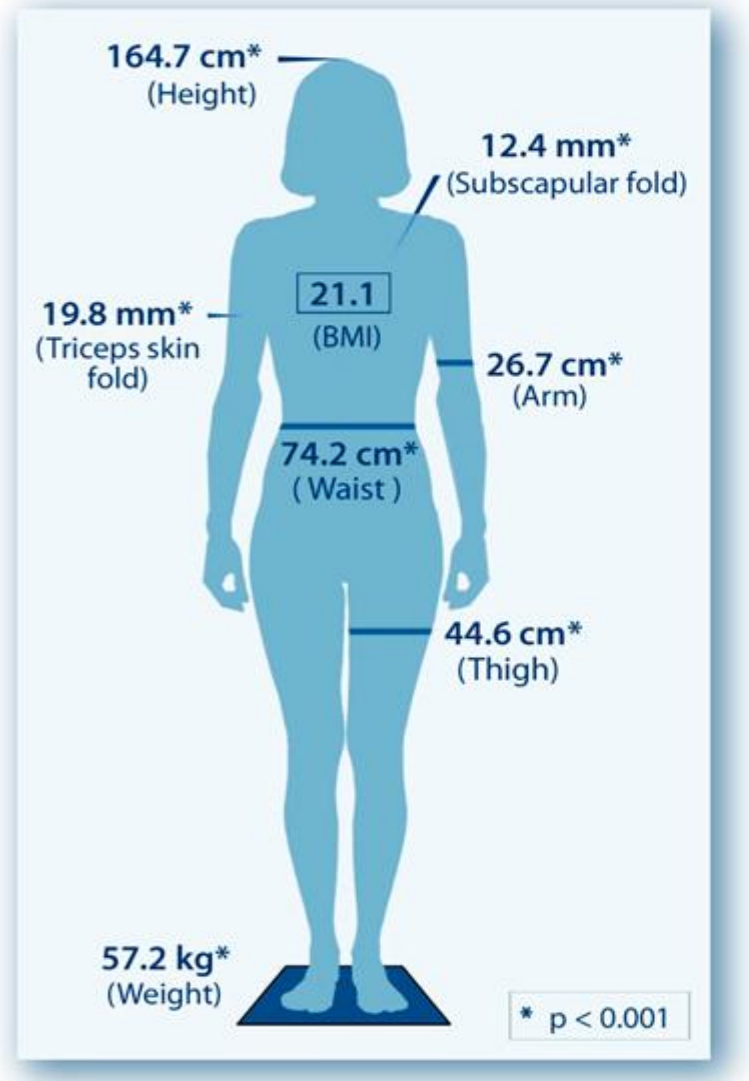


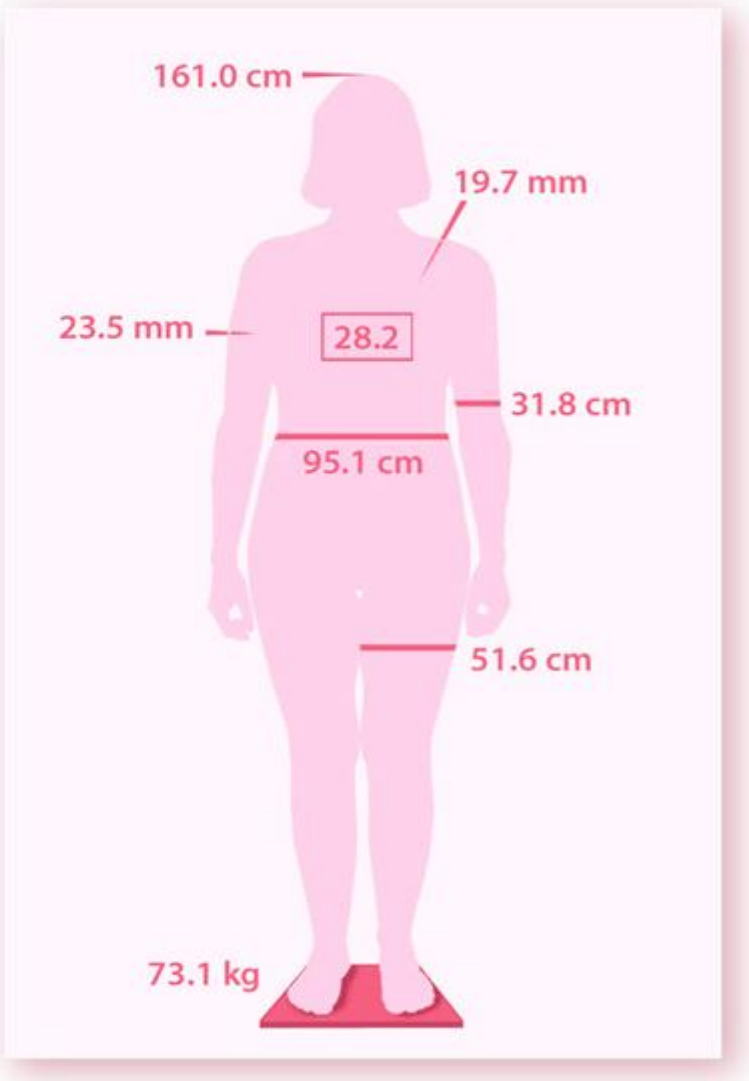


◀ Not macrolides-containing treatment regimens

Eur J Clin Microbiol Infect Dis 2014;33(3):347-58

Schematic depiction of the anthropometrics of the women with pulmonary NTM

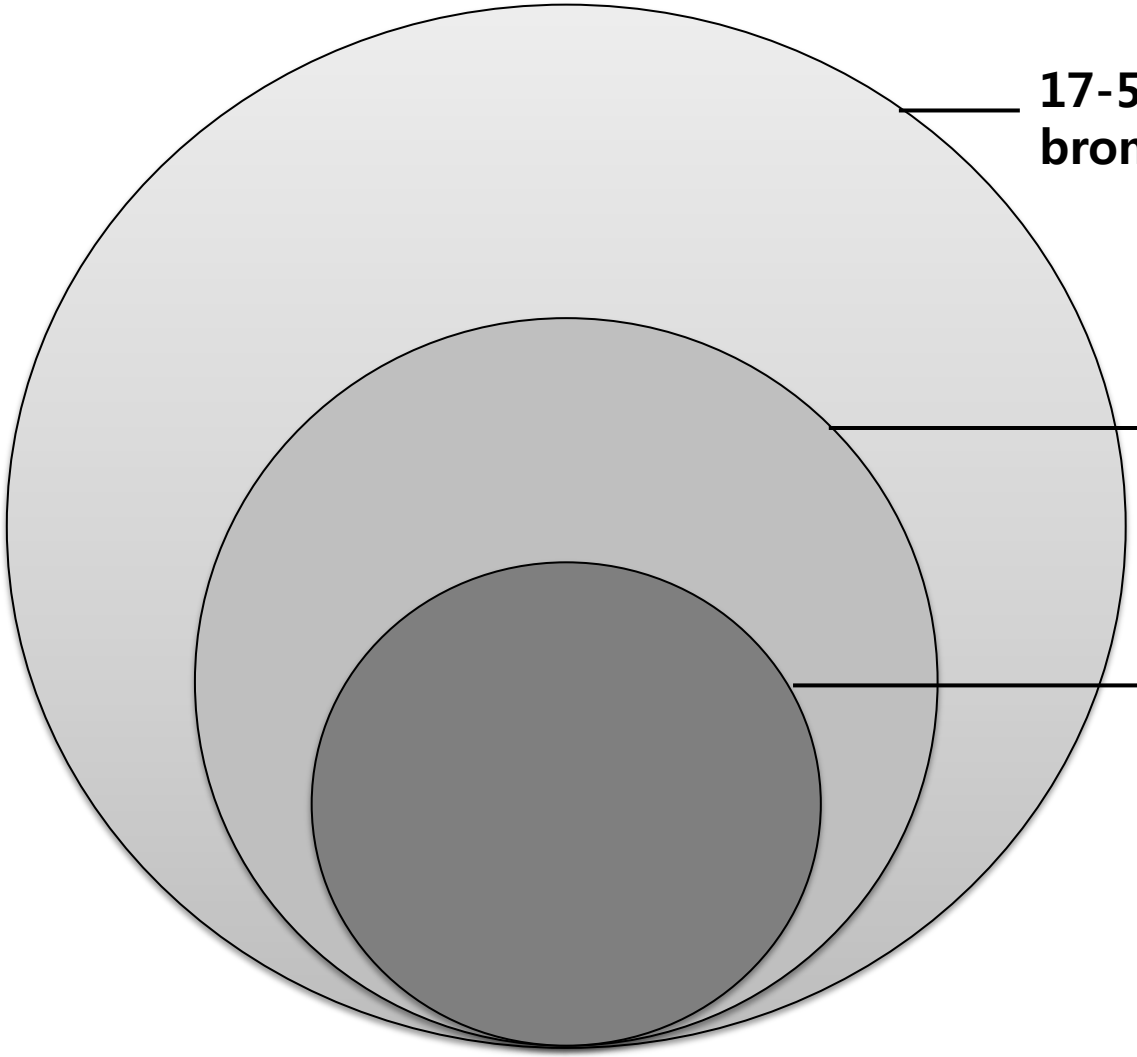




compared with National Health and Nutrition Examination Survey

Am J Respir Crit Care Med 2008;178(10):1066-74

Managing MAC lung disease



17-50 % : treated for nodular bronchiectatic MAC lung disease

50% : Unable to tolerate the initial antibiotic regimen

45 % : clinical relapse or failure of therapy

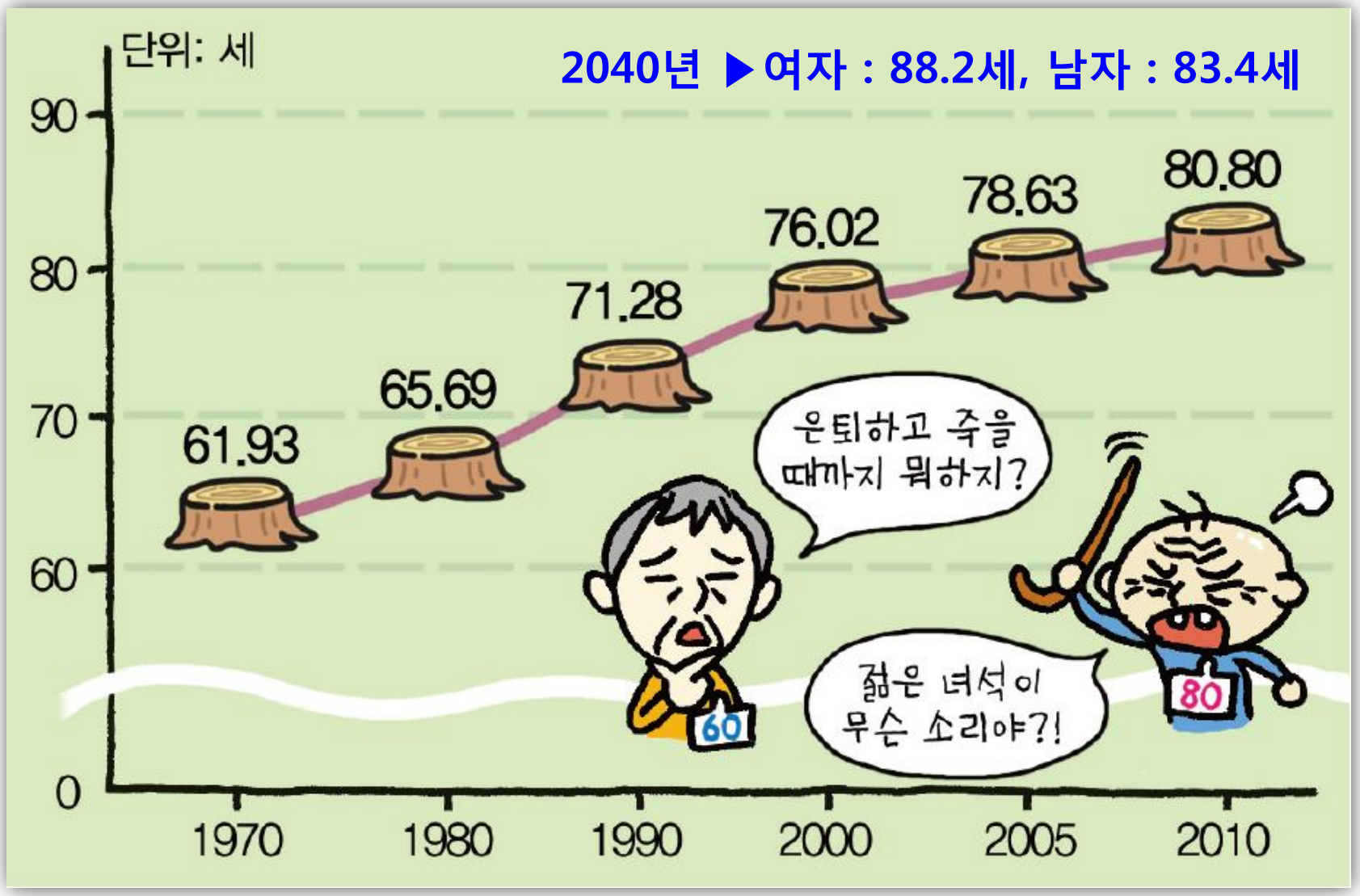
Chest 2012;142(6):1482-8

Summary

❖ Fibrocavitary MAC lung disease 는 즉각적인 치료를 요한다.

	Treatment success ↑	Relapse ↓	Disease progression ↓	Mortality ↓
Old age		X		
Lower BMI		X		
Cavity (+)		X	X	X
Consolidation (+)			X	
Sputum (-) conversion	O			
CCI ≥ 1				X

한국인 평균수명의 변화



통계청

경청해 주셔서 감사합니다