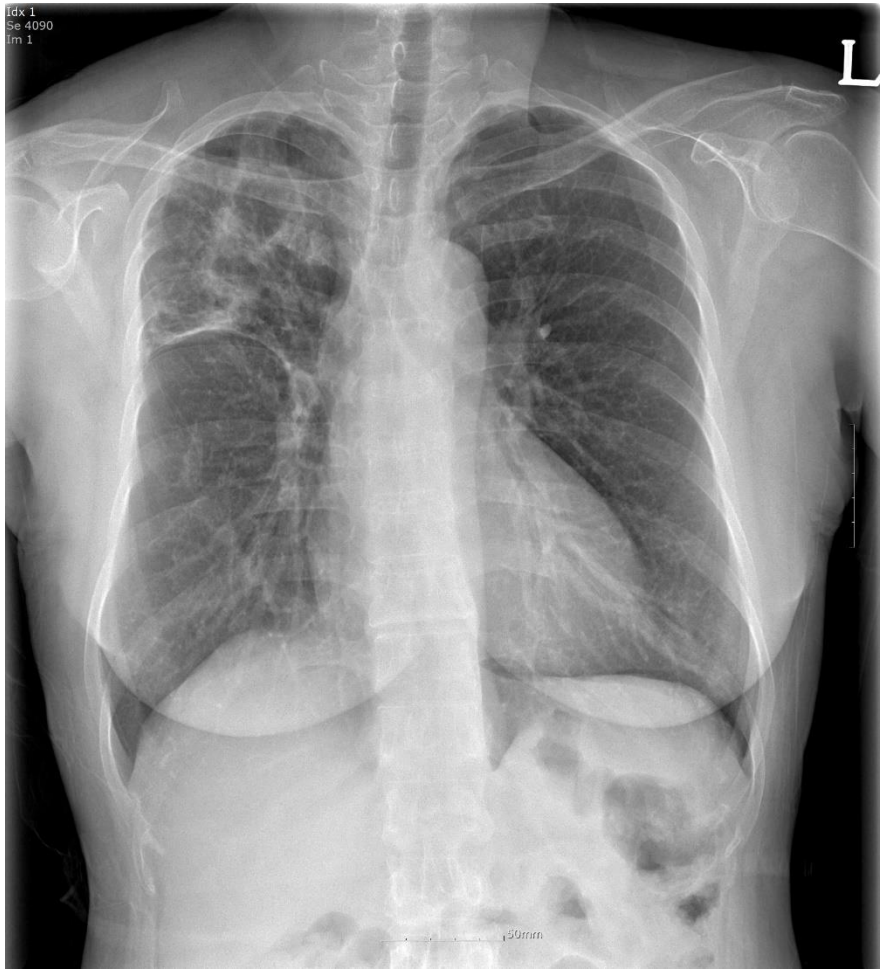
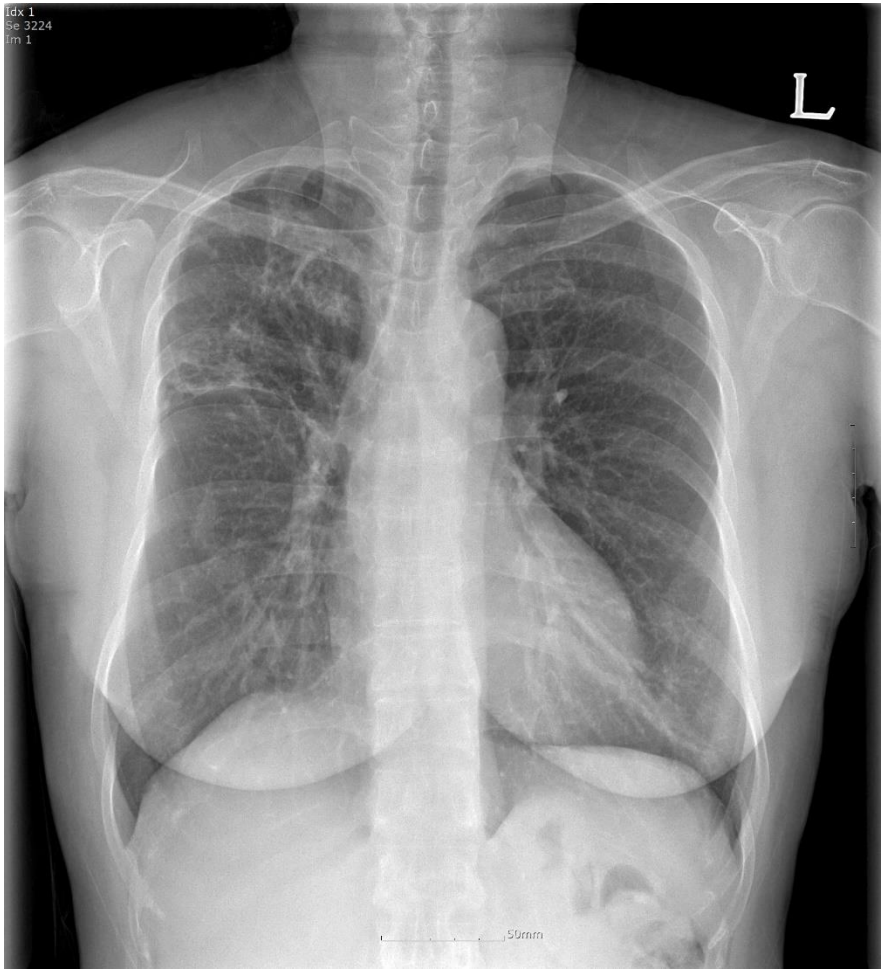
NTM 치료의 시작과 끝

Dong-A University Medical Center

동아대학교 병원
호흡기내과 강보형

60세 여자, 결핵 치료 중 NTM 배양되어 의뢰





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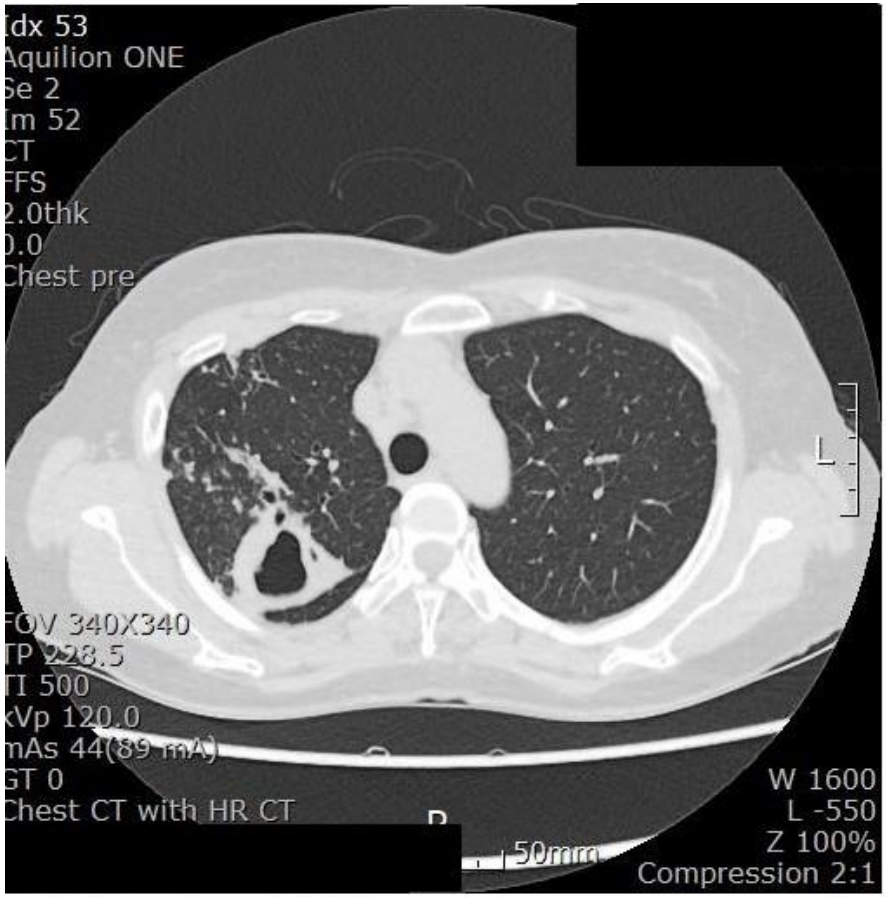


CT 상 active pul.TB/ 객담 도말 양성

결핵치료 중 배양에서 **NTM** 확인

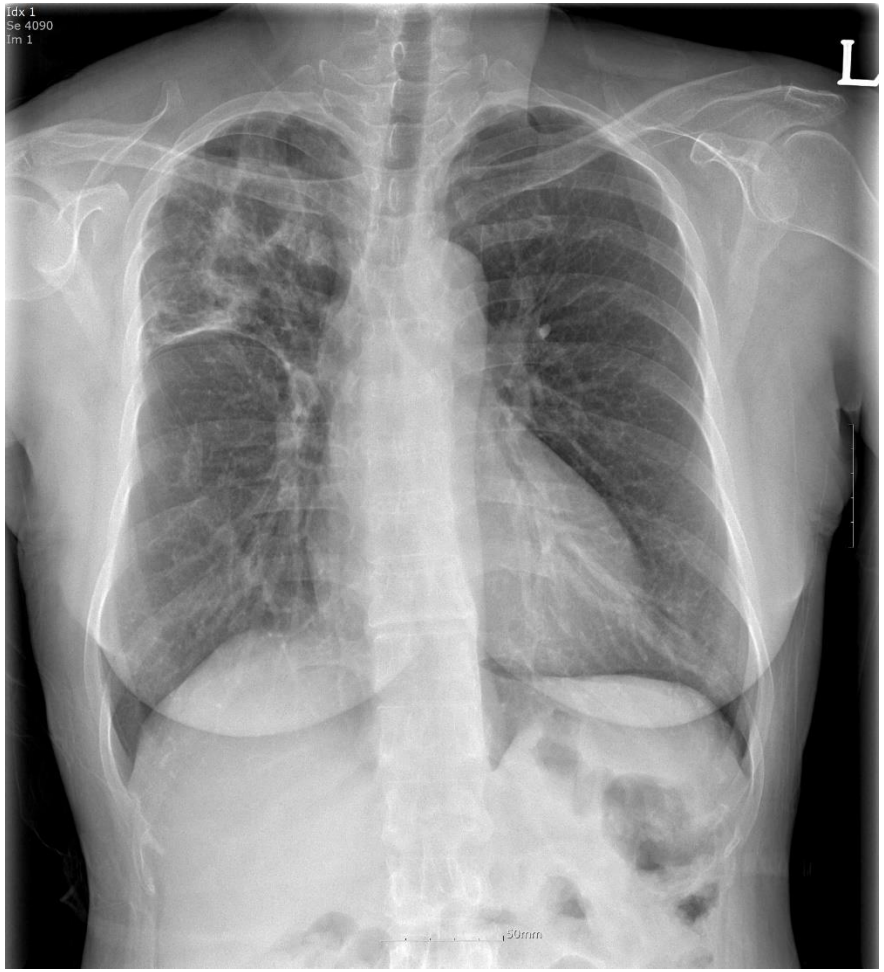
NTM ID: M. intracellulare

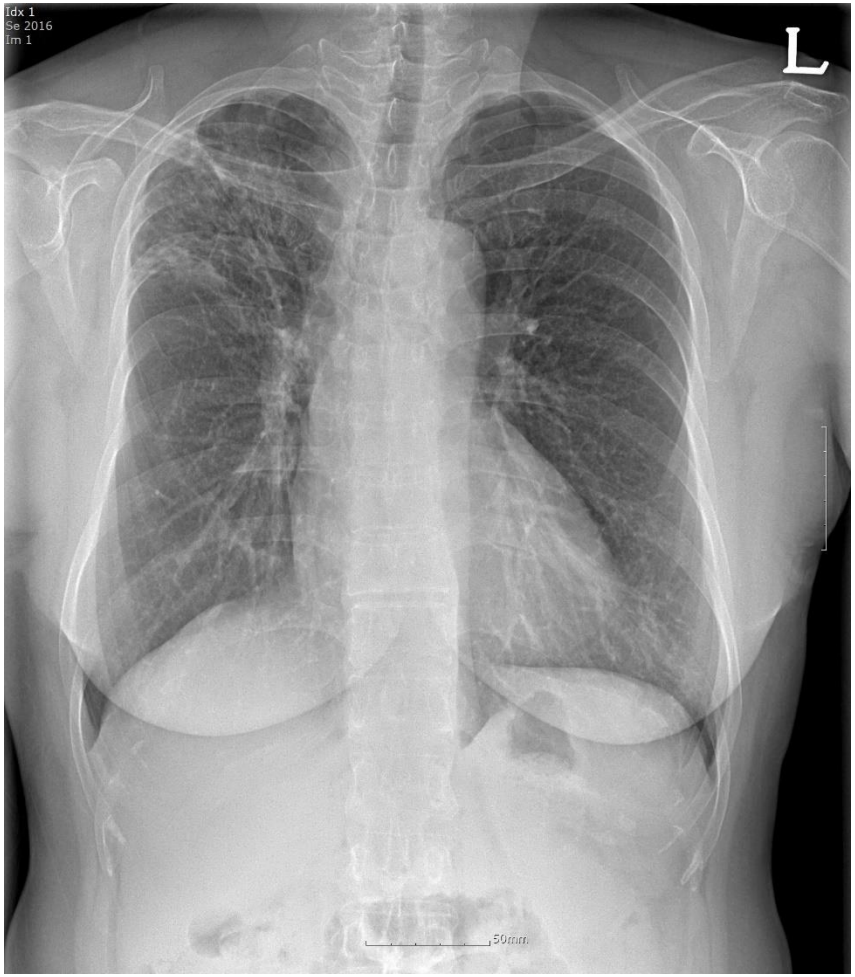
DST: calri/moxi/LZD s/s/s

NTM PD 로 진단변경

Clarithromycin, rifampin, ethambutol

60세 여자, 결핵 치료 중 NTM 배양되어 의뢰





균 음전 12개월, 총 17개월 치료

NTM PD 의 치료의 시작과 끝

임상적, 영상학적으로 **NTM PD** 의심이 되고
객담배양검사에서 **2**회 이상 양성이거나
기관지내시경 검사 검체 에서 **1**회 이상 양성 일때

환자의 연령, 동반질환, 증상
영상의학적 소견 및 질병의 진행
원인균과 배균량에 따라 치료를 시작

최소 균 음전 후 **12**개월

Real world?

Adverse events/ Drug resistance

Drugs	Adverse Reactions
Macrolides	GI trouble Tinnitus/hearing loss Hepatotoxicity Prolonged QTc
Ethambutol	Ocular toxicity Neuropathy
Rifampicin	Hepatotoxicity Cytopenias Hypersensitivity
Amikacin	Vestibular toxicity Ototoxicity Nephrotoxicity Electrolyte disturbances
Cefoxitin	Cytopenias Hypersensitivity
Moxifloxacin	Prolonged QT Hepatotoxicity Tendinopathy

Drugs	Adverse Reactions
Linezolid	Peripheral neuropathy Optic neuritis Cytopenias
Clofazimine	Tanning of skin Hepatotoxicity Prolonged QT
Tigecycline	Nausea/vomiting Hepatitis/pancreatitis
Imipenem	Rashes Cytopenias Nephrotoxicity

Clin Infect Dis 2020;71(4):e1-e36

발간등록번호 11-1352159-000765-14
ISBN 978-89-6838-818-7

KOREAN GUIDELINES FOR TUBERCULOSIS
(4th EDITION)

결핵 진료지침

(4판)

2020

부록

1. 비결핵 항산균 폐질환

1. 서론

비결핵 항산균(nontuberculous mycobacteria; NTM)은 결핵균과 나병균을 제외한 항산균을 말한다. NTM은 현재까지 150여 종이 넘는 균종이 알려져 있으며 계속 새로운 균종이 밝혀지고 있다. NTM으로 인한 질환은 (1) 폐질환, (2) 림프절염, (3) 피부, 연조직, 골감염증, (4) 파종성 질환(disseminated disease) 등 4가지 특징적인 임상 증후군으로 분류된다. 이 중 폐질환은 NTM으로 인한 질환의 90% 이상을 차지하는 가장 흔한 형태이며, 국내에서도 최근 임상 검체에서 NTM이 분리되는 빈도와 NTM 폐질환으로 진단, 치료 받는 환자들이 증가하고 있다.

2. 역학

대부분의 NTM은 자연수와 토양 등 자연환경에 널리 분포하고 있으며, 병원성이 낮은 균이다. 사람과 사람 사이에서의 전염은 일반적으로 없으며, 따라서 NTM에 감염된 환자를 격리할 필요는 없다. NTM 폐질환은 주위환경에 존재하는 균이 공기를 통해 호흡기에 감염되어 발생하며, 소아에서 주로 발생하는 NTM 림프절염과 후천면역결핍증후군 환자에서 발생하는 파종성 질환은 경구를 통한 오염된 물의 섭취가 질병 발생에 중요한 것으로 여겨지고 있다.

NTM 폐질환을 일으키는 원인균의 분포는 국가에 따라 그리고 국가 내에서도 지역에 따라 다양하다. 국내에서는 1981년 *Mycobacterium avium* complex 폐질환 증례가 처음으로 보고된 이후 1990년대 다양한 원인균에 의한 NTM 폐질환 증례가 보고되었다. NTM 폐질환의 국내 역학자료는 2000년 이후 많이 발표되었는데 현재까지 국내 연구결과를 종합하면 우리나라에서도 NTM 폐질환의 원인균으로 가장 흔한 균은 *M. avium* complex이다. 두 번째로 흔한 균은 *M. abscessus* complex이다. *M. kansasii* 폐질환은 국내에서 환자 수가 조금씩 증가하고 있지만 아직까지는 상대적으로 드물게 발생하고 있다.

2007

American Thoracic Society Documents

An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases

David E. Griffith, Timothy Aksamit, Barbara A. Brown-Elliott, Antonino Catanzaro, Charles Daley, Fred Gordin, Steven M. Holland, Robert Horsburgh, Gwen Huitt, Michael F. Iademarco, Michael Iseman, Kenneth Olivier, Stephen Ruoss, C. Fordham von Reyn, Richard J. Wallace, Jr., and Kevin Winthrop, on behalf of the ATS Mycobacterial Diseases Subcommittee

This Official Statement of the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) was adopted by the ATS Board Of Directors, September 2006, and by the IDSA Board of Directors, January 2007

CONTENTS

SUMMARY

Diagnostic Criteria of Nontuberculous Mycobacterial Lung Disease

The minimum evaluation of a patient suspected of nontuberculous mycobacterial (NTM) lung disease should include the following: (*1*) chest radiograph or, in the absence of cavitation, chest high-resolution computed tomography (HRCT) scan; (*2*) three or more sputum specimens for acid-fast bacilli (AFB) analysis; and (*3*) exclusion of other disorders, such as tuberculosis (TB). Clinical, radiographic, and microbiologic criteria are equally important and all must be met to make a diagnosis of NTM lung disease. The following criteria apply to symptomatic patients with radiographic opacities, nodular or cavitary, or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules. These criteria fit best with *Mycobacterium avium* complex (MAC), *M. kansasii*, and *M. abscessus*. There is not enough known about most other NTM to be certain that these diagnostic criteria are universally applicable for all NTM respiratory pathogens.

This document has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 175. pp 367–416, 2007
DOI: 10.1164/rccm.200604-571ST
Internet address: www.atsjournals.org

2020

Clinical Infectious Diseases

IDSA FEATURES

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

Charles L. Daley,[1,2,a] Jonathan M. Iaccarino, Jr.[3] Christoph Lange,[4,5,6,7,a] Emmanuelle Cambau,[8,a] Richard J. Wallace,[9,a] Claire Andrejak,[10,11] Erik C. Böttger,[12] Jan Brozek,[13] David E. Griffith,[14] Lorenzo Guglielmetti,[8,15] Gwen A. Huitt,[1,2] Shandra L. Knight,[16] Philip Leitman,[17] Theodore K. Marras,[18] Kenneth N. Olivier,[19] Miguel Santin,[20] Jason E. Stout,[21] Enrico Tortoli,[22] Jakko van Ingen,[23] Dirk Wagner,[24] and Kevin L. Winthrop[25]

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Nontuberculous mycobacteria (NTM) represent over 190 species and subspecies, some of which can produce disease in humans of all ages and can affect both pulmonary and extrapulmonary sites. This guideline focuses on pulmonary disease in adults (without cystic fibrosis or human immunodeficiency virus infection) caused by the most common NTM pathogens such as *Mycobacterium avium* complex, *Mycobacterium kansasii*, and *Mycobacterium xenopi* among the slowly growing NTM and *Mycobacterium abscessus* among the rapidly growing NTM. A panel of experts was carefully selected by leading international respiratory medicine and infectious diseases societies (ATS, ERS, ESCMID, IDSA) and included specialists in pulmonary medicine, infectious diseases and clinical microbiology, laboratory medicine, and patient advocacy. Systematic reviews were conducted around each of 22 PICO (Population, Intervention, Comparator, Outcome) questions and the recommendations were formulated, written, and graded using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. Thirty-one evidence-based recommendations about treatment of NTM pulmonary disease are provided. This guideline is intended for use by healthcare professionals who care for patients with NTM pulmonary disease, including specialists in infectious diseases and pulmonary diseases.

Keywords. nontuberculous; *Mycobacterium avium* complex; *Mycobacterium kansasii*; *Mycobacterium abscessus*; *Mycobacterium xenopi*.

EXECUTIVE SUMMARY

The American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA) jointly sponsored the development of this Guideline to update the treatment recommendations for nontuberculous mycobacterial (NTM) pulmonary disease in adults. NTM represent over 190 species and subspecies (http://www.bacterio.net/mycobacterium.html), many of which can produce disease in humans of all ages and can affect both pulmonary and extrapulmonary sites. Attempting to cover such a broad array of species and disease in a guideline using current guideline development methods is impossible. Therefore, this guideline focuses on pulmonary disease in adults (without cystic fibrosis or human immunodeficiency virus [HIV] infection) caused by the most common NTM pathogens comprising *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium xenopi* among the slowly growing

Received 17 February 2020; editorial decision 18 February 2020; accepted 5 March 2020; published online July 6, 2020.

[a]C. L. D., C. L., E. C., R. J. W. are cochairs of this guideline committee.

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Clinical Infectious Diseases® 2020;XX(XX):1–36

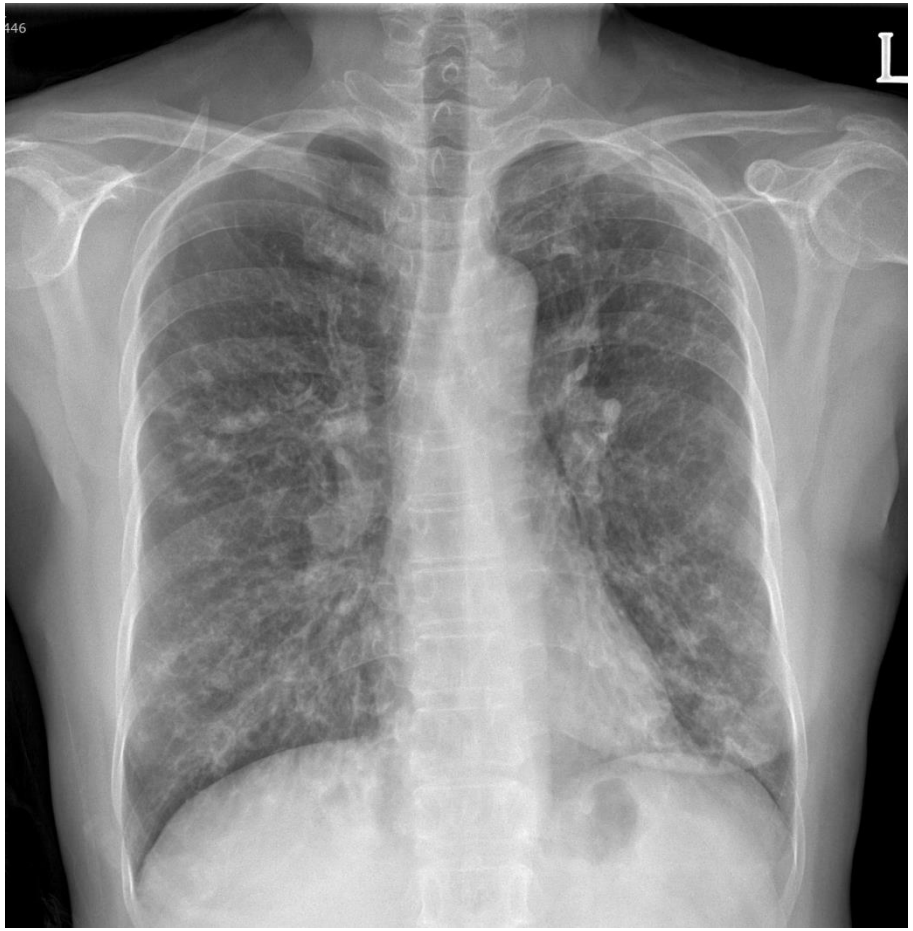
This is a joint publication between Clinical Infectious Diseases and the *European Respiratory Journal*. The articles are identical except for minor stylistic and spelling differences in keeping with each journal's style. Either citation can be used when citing this article.
DOI: 10.1093/cid/ciaa241

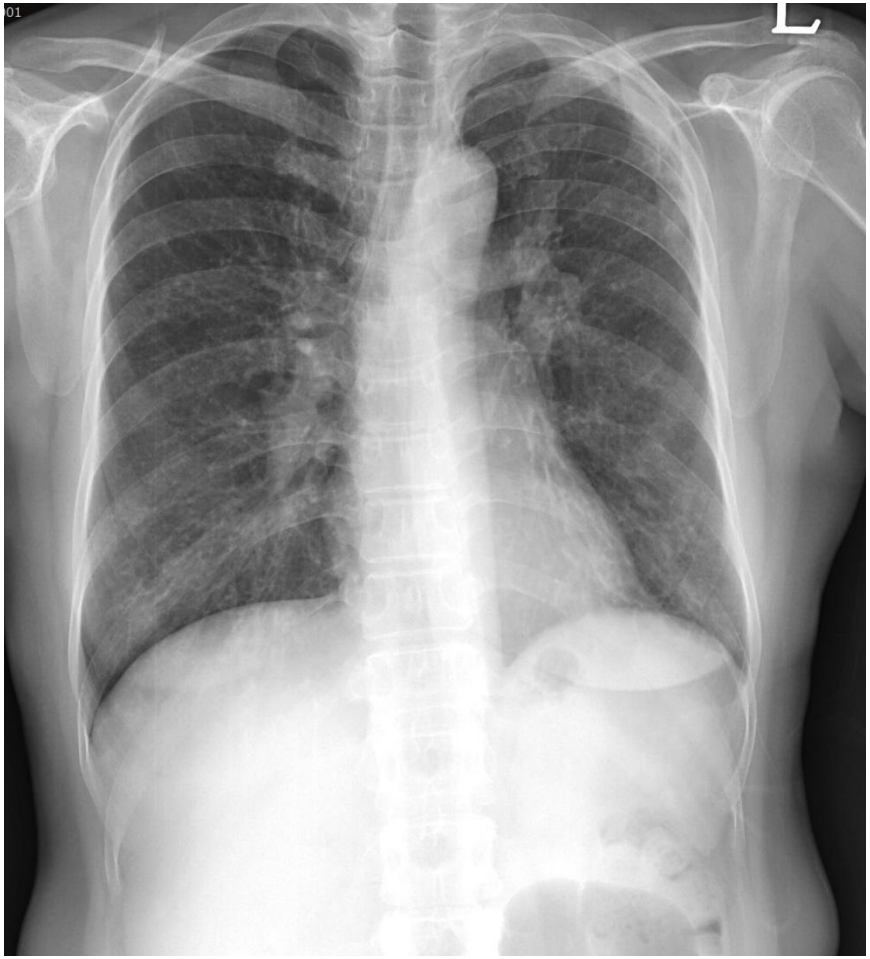
Contents

- **NTM clinical practice guideline** (ATS/ERS/ESCMID/IDSA)
  - **diagnostic criteria**
  - **timing of treatment**
  - **treatment regimen/ duration**

- **Cases**

66세 여자, 사진상 NTM 악화 의심되어 치료 위해 의뢰





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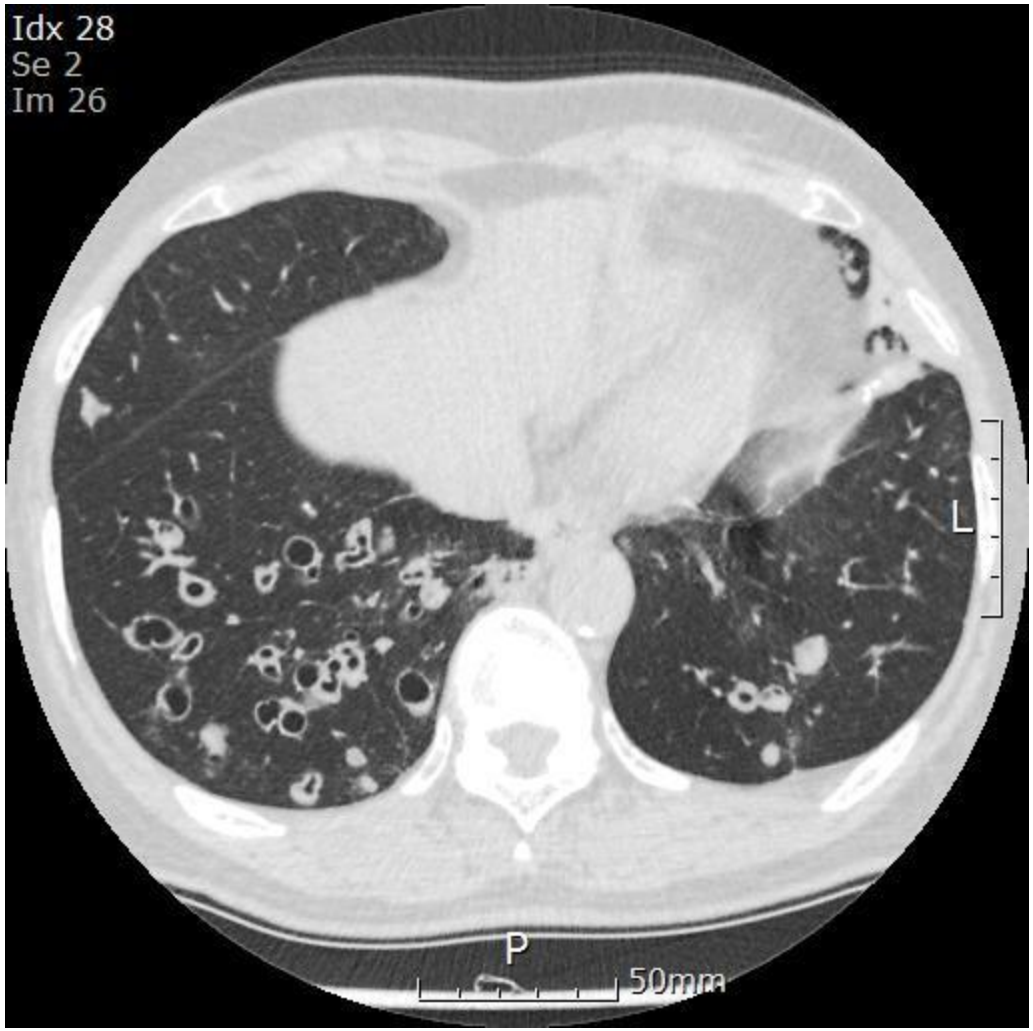

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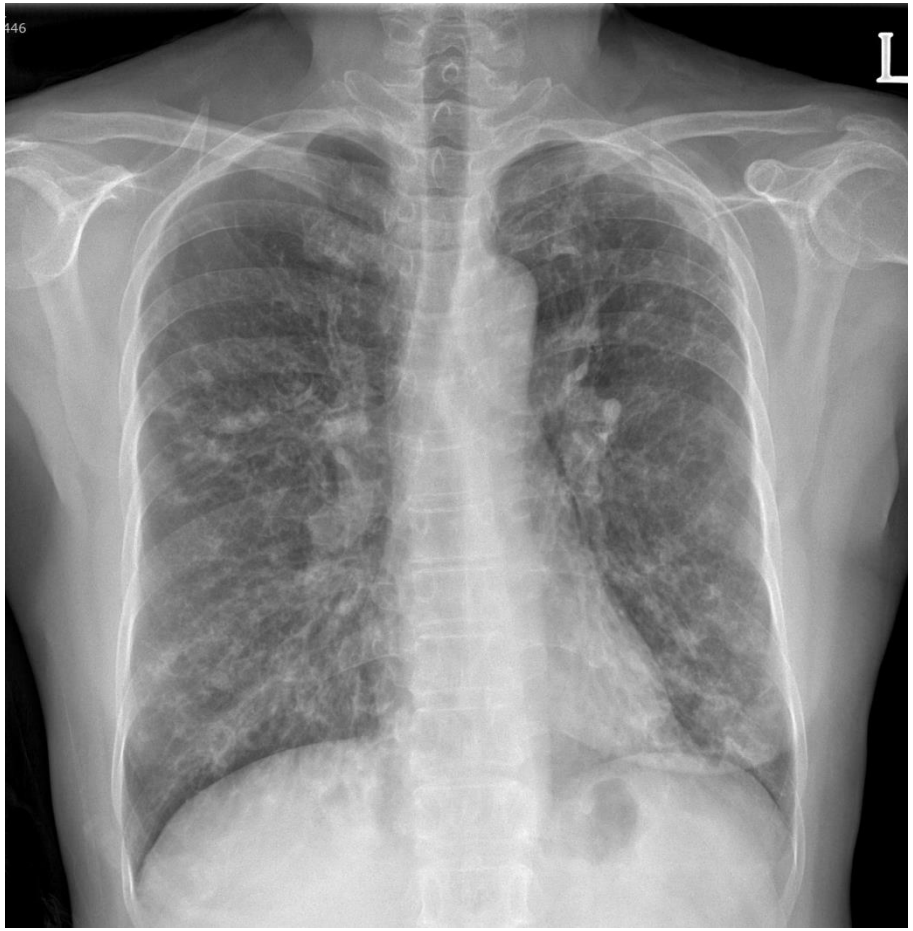
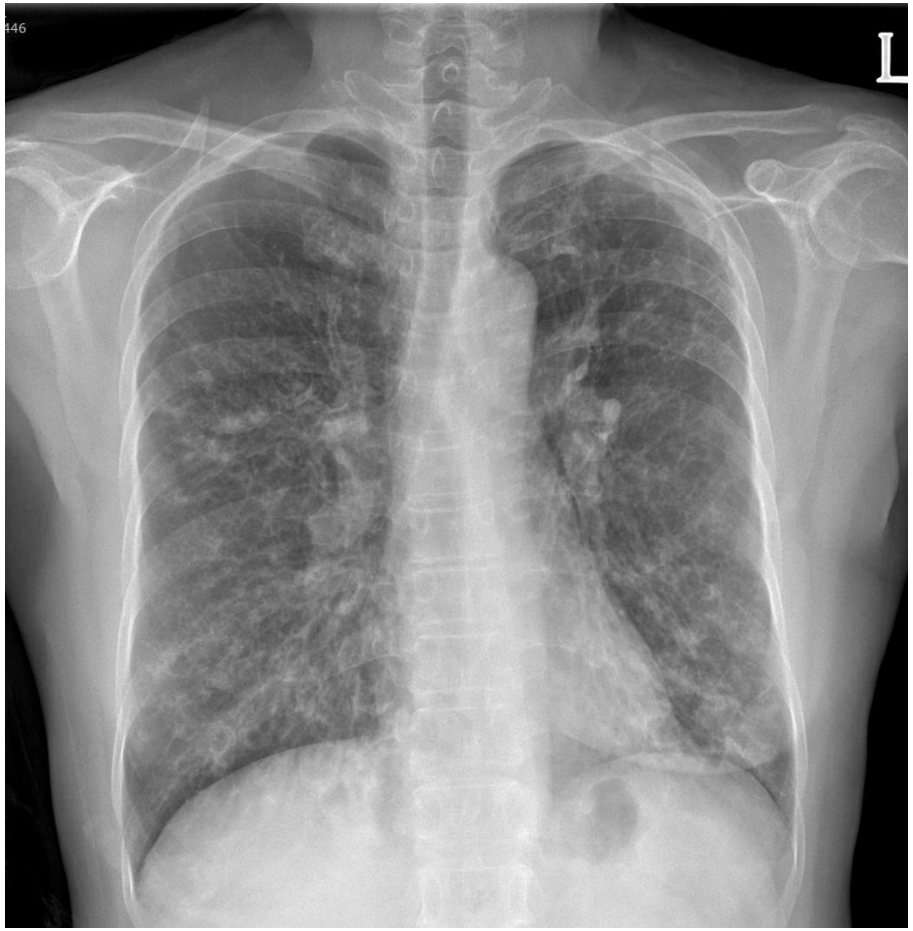


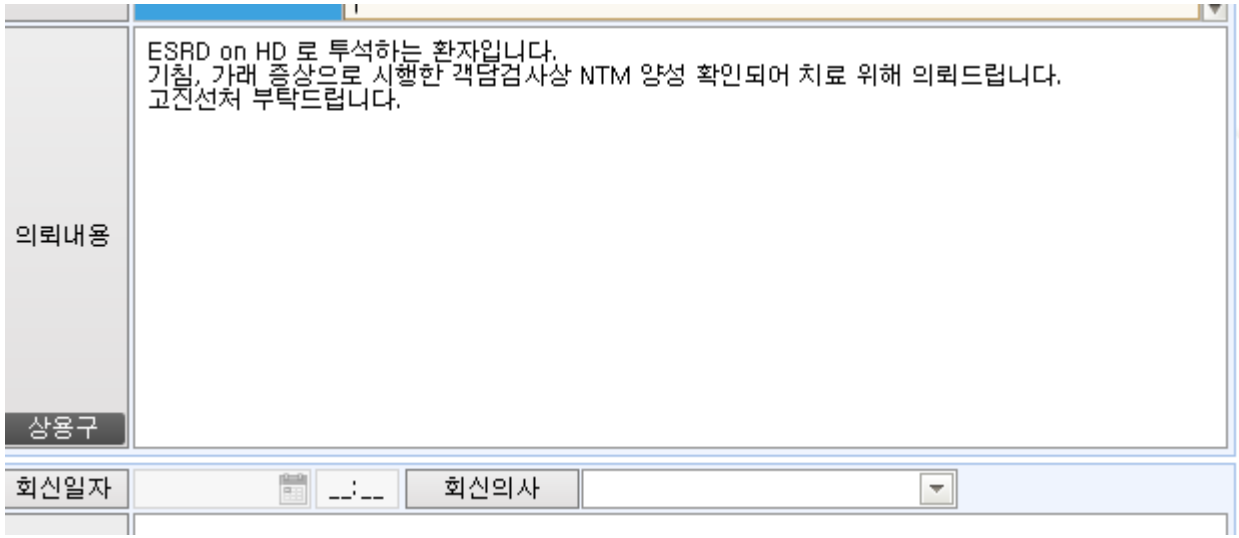
CT reading:

Slightly increased extent of superimposed infection with underlying cystic and tubular bronchiectasis in both lungs. r/i NTM progression

66세 여자, NTM 치료로 의뢰



1) **Close follow up**
2) **NTM** 치료
3) 객담검사 반복
4) 기관지내시경 시행


의뢰내용
ESRD on HD 로 투석하는 환자입니다.
기침, 가래 증상으로 시행한 객담검사상 NTM 양성 확인되어 치료 위해 의뢰드립니다.
고진선처 부탁드립니다.
상용구
회신일자
__:__
회신의사

Diagnostic criteria for NTM pulmonary disease

Clinical	Pulmonary or Systemic Symptoms	
Radiologic	Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules	Both Required
and	Appropriate exclusion of other diagnoses	
Microbiologic[b]	1. Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures **or** 2. Positive culture results from at least one bronchial wash or lavage **or** 3. Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM	

Clinical symptoms

cough, sputum, chest pain, shortness of breath

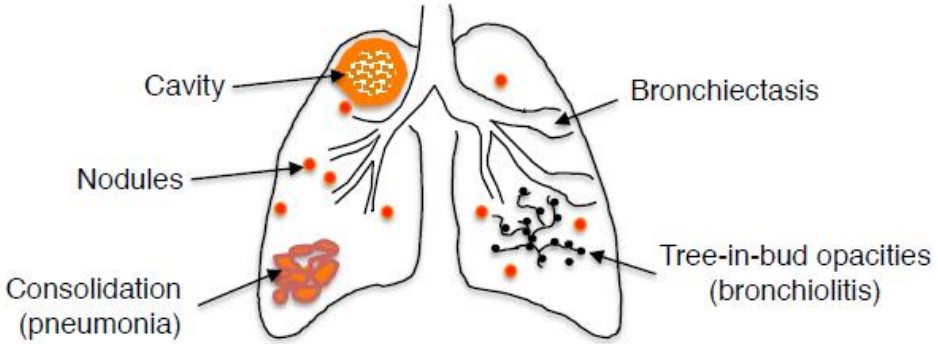
fever, fatigue, night sweats

Clin Infect Dis 2020;71(4):e1-e36

CT findings

Bronchiectasis with multiple small nodules

Nodules, consolidation, tree-in-bud opacities, and/or cavities



Microbiological findings

≥2 NTM positive sputum cultures

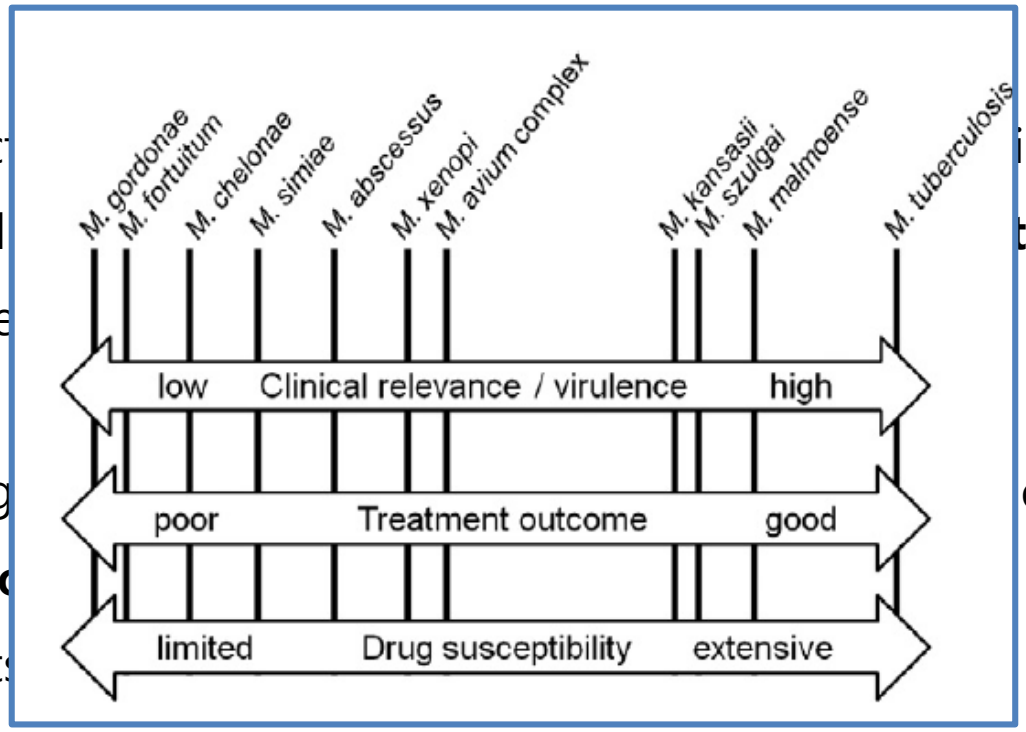
one positive bronchoscopy culture

lung biopsy c/w NTM lung pathology and a positive NTM culture (biopsy/sputum)

- **Expert consultation** should be obtained when NTM are recovered that are either infrequently encountered or that **usually represent contamination.**

- Suspect … iagnostic criteria **should** … **tablished** or exclude…

- Making … **ecessitate the initiatio**… potential risks and benefits…



Clinical significance of positive sputum culture

Diagnosis of Disease Caused by Mycobacterium avium Complex*

- **299 patients, new cavitary or infiltrative lesion**

  Single isolation (114 patients) – 2 % NTM LD

  Two isolations (29 patients) – 90 % NTM LD

  Three isolations (40 patients) – 98 % NTM LD

  four or more (116 patients) – 100% NTM LD

Chest 1991;99:667-69

Factors associated with subsequent nontuberculous mycobacterial lung disease in patients with a single sputum isolate on initial examination

TABLE 1. Clinical characteristics of patients with a single isolation of NTM (n = 202)

Characteristic	Total (n = 202)	MAC (n = 70)	*M. che-abs* (n = 40)	*M. kansasii* (n = 21)	*M. fortuitum* (n = 71)
Age	70 [13–99]	71 [32–93]	70 [48–89]	71 [45–99]	68 [13–93]
Male	120 (59%)	47 (67.1%)	21 (53%)	16 (76%)	36 (51%)
Number of sputum samples within 1 year	7.8 ± 3.5	8 ± 3.54	7.8 ± 3.8	7.4 ± 3.2	7.6 ± 3.3
Microbiology follow-up period, months	12.0	14.9	12.7	14.2	8.1
Clinical follow-up period, months	26.2	28.8	26.9	24.8	23.7
Presence of subsequent positive culture	44 (22%)	19 (27%)	8 (20%)	5 (24%)	12 (17%)
Diagnosed as NTM pulmonary disease	8 (4%)	6 (9%)	1 (3%)	1 (5%)	0
Age	57 [48–70]	57 [49–64]	48	70	NA
Male	5 (63%)	4 (67%)	0	1 (100%)	NA
Months to 2nd positive cultures	2 [1–11]	1.5 [1–11]	2	6	NA
Months to diagnosis of NTM-LD (from single isolate of NTM)	4.5 [1–23]	2.5 [1–23]	7	6	NA
Microbiology follow-up months	22.5 [1–39]	17.5 [1–31]	39	16	NA
Clinical follow-up months	36 [12–60]	36 [12–60]	39	19	NA
Underlying disease					
Old pulmonary tuberculosis	35 (17%)	15 (21%)	5 (13%)	5 (24%)	10 (14%)
Chronic obstructive pulmonary disease	35 (17%)	16 (23%)	4 (10%)	5 (24%)	10 (14%)
Malignancy	62 (31%)	24 (34%)	11 (28%)	5 (24%)	22 (31%)
Diabetes	36 (18%)	12 (17%)	9 (23%)	2 (10%)	13 (18%)
CKD (serum creatinine >2 mg/dL)	17 (8%)	7 (10%)	5 (13%)	0	5 (7%)
Radiographic findings					
Bronchiectasis	70 (35%)	28 (40%)	10 (25%)	10 (48%)	22 (31%)
Cavitary	6 (8%)	1 (1%)	1 (2%)	2 (10%)	2 (3%)
Nodules	10 (14%)	2 (3%)	1 (3%)	3 (14%)	4 (6%)
Consolidation	35 (17%)	11 (16%)	13 (33%)	3 (14%)	8 (11%)
Radiographic score ≤2	127 (63%)	40 (57%)	24 (60%)	12 (57%)	51 (72%)

Clin Microbiol Infect 2015'21:250.e1-7

Factors associated with subsequent nontuberculous mycobacterial lung disease in patients with a single sputum isolate on initial examination

TABLE 2. Factors associated with subsequent **NTM** lung disease in bronchiectatic patients ($n = 48$) and subsequent culture positivity for **NTM** in all patients ($n = 202$) with a single isolate of *Mycobacterium avium* complex, *M. chelonae-abscessus*, or *M. kansasii* ($n = 48$), by multivariate logistic regression analysis

Outcome	Variables	Percent(s) of patients developing outcome	p	OR (95% CI)
Subsequent NTM lung disease	Age: ≤65 vs. >65 years	32% vs. 4%	0.006	32.13 (2.72–379.33)
	Malignancy: Present vs. Absent	30% vs. 13%	0.048	14.35 (1.02–201.13)
	Initial radiographic score: >2 vs. ≤2	20% vs. 14%	0.027	20.06 (1.40–286.25)
Subsequent culture-positivity for NTM	Age: ≤65 vs. >65 years	33% vs. 15%	0.002	3.29 (1.56–6.92)
	Bronchiectasis: Present vs. Absent	40% vs. 12%	<0.001	5.46 (2.59–11.49)

NTM, nontuberculous mycobacteria.

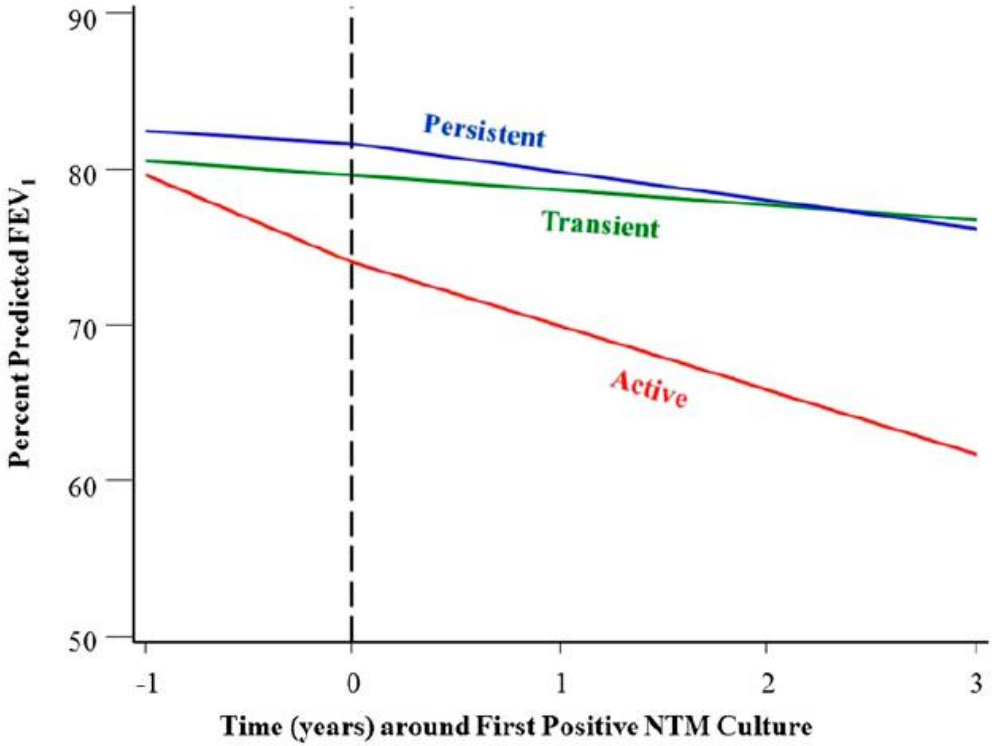
8/202 patients (4%) developed NTM-LD on follow-up

Bronchiectasis was a strong predictor

"*M. fortuitum*" and "no bronchiectasis", predictor of non-development of NTM -LD

Clin Microbiol Infect 2015'21:250.e1-7

Clinical Significance of a First Positive Nontuberculous Mycobacteria Culture in Cystic Fibrosis



96 patients

Transient: 22 patients, 23%

Persistent: 37 patients, 38.5%

Active: 37 patients, 38.5%

Ann Am Thorac Soc 2014;11(1): 36-44

Clinical significance of a single isolation of pathogenic nontuberculous mycobacteria from sputum specimens ☆

Table 1
Sputum cultures and patients diagnosed with NTM lung disease.

Organisms	Patients with initial single sputum culture	Subsequent sputum examinations during follow-up (median, IQR)	Patients diagnosed with NTM lung disease (%)
M. avium complex	120	3 (2–8)	16 (13)
M. avium	67	3 (2–8)	9 (13)
M. intracellulare	53	3 (2–8)	7 (13)
M. abscessus	62	5 (2–12)	10 (16)
M. kansasii	8	3 (1–7)	0 (0)
Total	190	3 (2–8)	26 (14)

Table 2
Characteristics of 26 patients who were diagnosed with NTM lung disease.

Characteristics	No. (%) or median (IQR)
Age, years	63 (55–66)
Gender, female	14 (54)
Body mass index, kg/m^2	20 (18–23)
Ex- or current smoker	8 (31)
Underlying diseases	
Bronchiectasis	15 (58)
Previous pulmonary tuberculosis	6 (23)
Lung cancer	1 (4)
Idiopathic pulmonary fibrosis	1 (4)
Chronic pulmonary aspergillosis	1 (4)
Chronic pulmonary obstructive disease	2 (8)
Solid malignancy other than lung cancer	3 (12)
Chest CT findings	
Bronchiectasis	26 (100)
Bronchiolitis	20 (77)
Nodules	2 (8)
Consolidation	3 (12)
Cavity (or cavities)	2 (8)
Duration from first sputum culture to second sputum culture, months	30 (15–46)

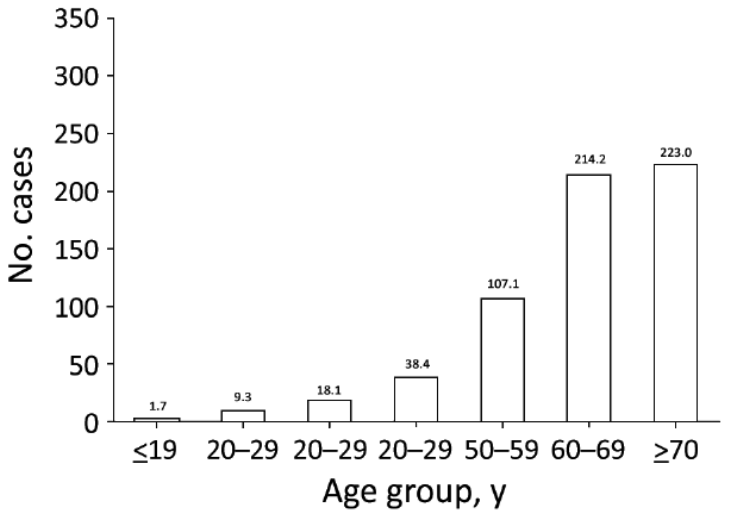
A single sputum culture positive for pathogenic NTM could be an early sing of true NTM lung disease

Diagn Microbiol Infect Dis 2013;75:225-6.

Timing for treatment: risks and benefits

- Making the diagnosis of NTM PD **dose not per se, necessitate the initiation of therapy**, which is decision based on the potential risks and benefits of therapy for individual patients

Drugs	Adverse Reactions
Macrolides	GI trouble Tinnitus/hearing loss Hepatotoxicity Prolonged QTc
Ethambutol	Ocular toxicity Neuropathy
Rifampicin	Hepatotoxicity Cytopenias Hypersensitivity
Amikacin	Vestibular toxicity Ototoxicity Nephrotoxicity
Cefoxitin	Cytopenias Hypersensitivity
Moxifloxacin	Prolonged QT Hepatotoxicity Tendinopathy



Clin Infect Dis 2020;71(4):e1-e36

Risk factors for poor prognosis/ NTM PD progression

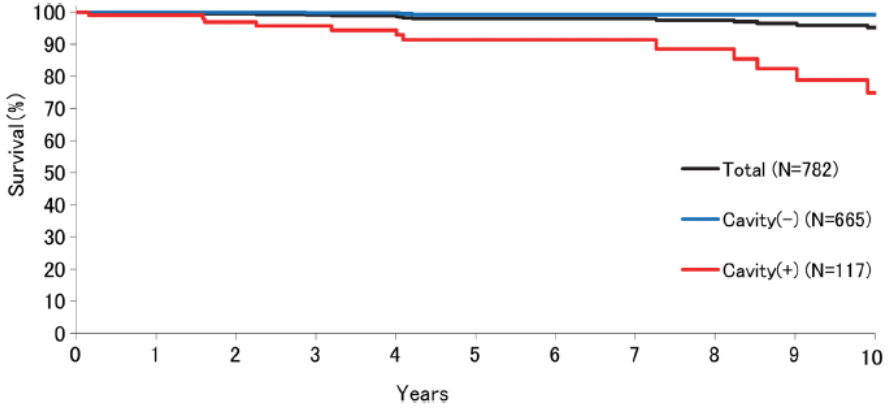
- 782 HIV-negative patients with NB MAC-LD
- Median follow-up period was 4.3 years

Table 3 The risk of all-cause mortality, MAC-LD progression mortality and radiographic deterioration in multivariate Cox regression models

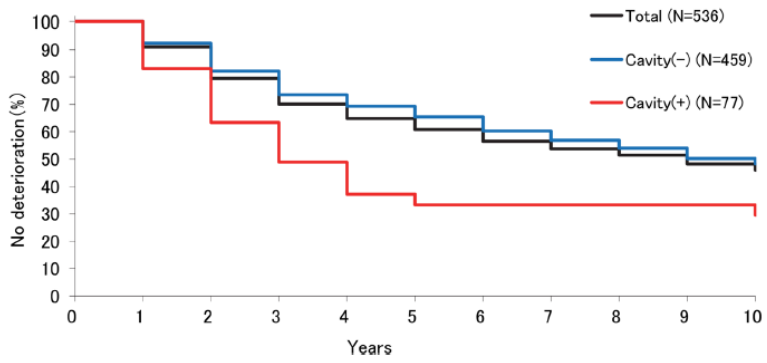
Variable	Multivariate Cox regression Final model		
	Adjusted HR	95% CI	p Value
All-cause mortality (n=782)			
Male (vs female)	1.958	1.357 to 2.823	<0.001
Age ≥70 years (vs <70 years)	4.232	2.746 to 6.523	<0.001
Body mass index <18.5 kg/m^2 (vs ≥18.5 kg/m^2)	1.725	1.093 to 2.723	0.019
Some bloody sputum (vs none)	0.542	0.542 to 0.927	0.025
ESR ≥40 mm/h (vs <40 mm/h)	1.849	1.140 to 2.999	0.013
Alb <3.5 g/dL (vs ≥3.5 g/dL)	3.159	1.708 to 5.844	<0.001
MAC-LD progression mortality (n=782)			
Age ≥70 years (vs <70 years)	3.369	1.257 to 9.027	0.016
Some cavity (vs none)	11.911	4.512 to 31.4444	<0.001
2–4 drugs in first-line treatment (vs 0 or 1)	4.135	1.671 to 10.235	0.002
Radiographic progression (n=536)			
Underlying IPF (vs none)	2.191	1.325 to 3.624	0.002
Haemoglobin <11.3 g/dL (vs ≥11.3 g/dL)	1.852	1.265 to 2.713	0.002
CRP ≥1.0 mg/dL (vs <1.0 mg/dL)	1.520	1.081 to 2.136	0.016
Some cavity (vs none)	1.651	1.181 to 2.307	0.003

BMJ open 2015;5:e0080058

- 782 HIV-negative patients with NB MAC-LD
- Median follow-up period was 4.3 years



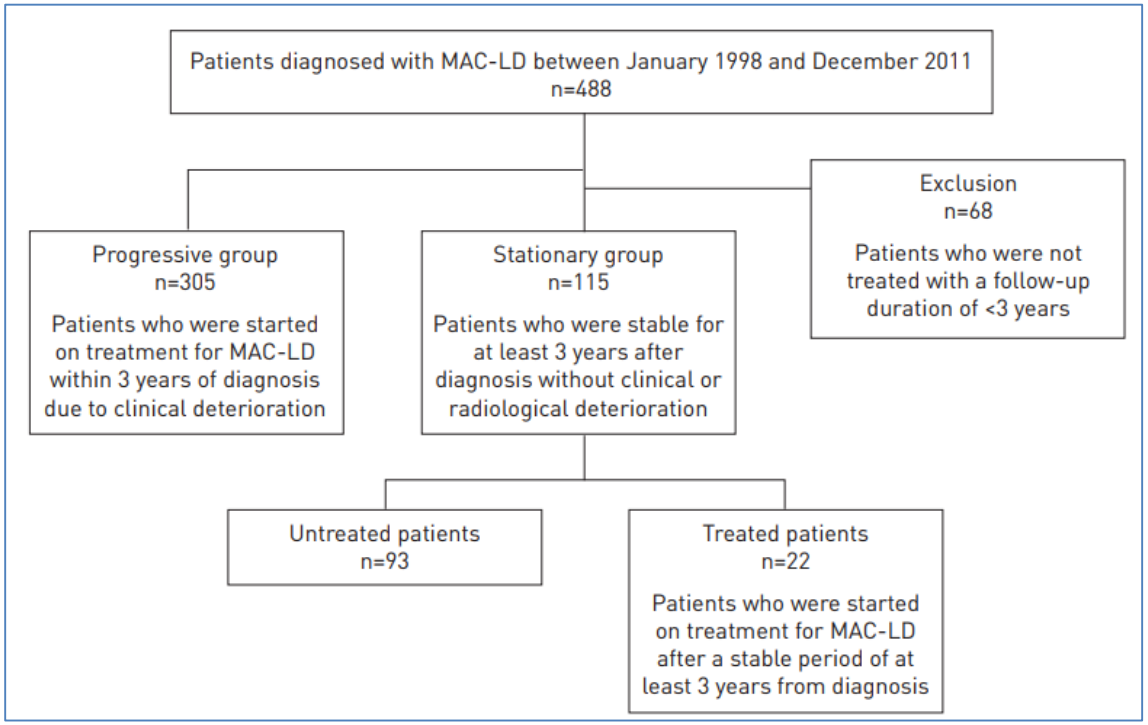
5-year, 10-year mortality 2%, 4.8%
with cavity 8.5%, 25.1%
without cavity 0.8%, 0.8%



5-year, 10-year radiographic deterioration rates 39.1%, 54%
with cavity 66.7%, 70.4%
without cavity 34.6%, 51.7%

BMJ open 2015;5:e0080058

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



420 patients

Progressive 305 px. (72.6%)

Stationary 115 px. (27.4%)

treated 22 px. (19.1%)

negative conversion 45 px. (51.6%)

Eur Respir J 2017;49:1600537

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age years	0.990 (0.980–1.001)	0.072	0.987 (0.975–0.999)	0.040
Male	0.976 (0.767–1.243)	0.846		
BMI kg·m^{-2}	0.890 (0.856–0.925)	<0.001	0.926 (0.882–0.973)	0.002
Smoker	0.887 (0.695–1.133)	0.337		
Past history of pulmonary TB	1.269 (0.991–1.624)	0.059	0.987 (0.746–1.306)	0.928
Presence of comorbidity[¶]	0.911 (0.714–1.162)	0.452		
Presence of systemic symptom[+]	1.560 (1.191–2.045)	0.001	1.490 (1.095–2.028)	0.011
Positive sputum AFB smear	2.298 (1.795–2.941)	<0.001	1.811 (1.350–2.428)	<0.001
Causative organism		0.001		0.364
Mycobacterium avium	1		1	
Mycobacterium intracellulare	1.512 (1.186–1.928)		0.869 (0.642–1.177)	
Radiological type: fibrocavitary	2.695 (2.099–3.460)	<0.001	2.102 (1.519–2.908)	<0.001
Involved lobes	1.384 (1.260–1.519)	<0.001	1.178 (1.050–1.322)	0.005
FVC % pred	0.991 (0.984–1.998)	0.011	1.001 (0.994–1.009)	0.712

Predictors of disease progression

- systemic symptoms
- positive AFB smear
- radiological type
- older age/ higher BMI – less likely

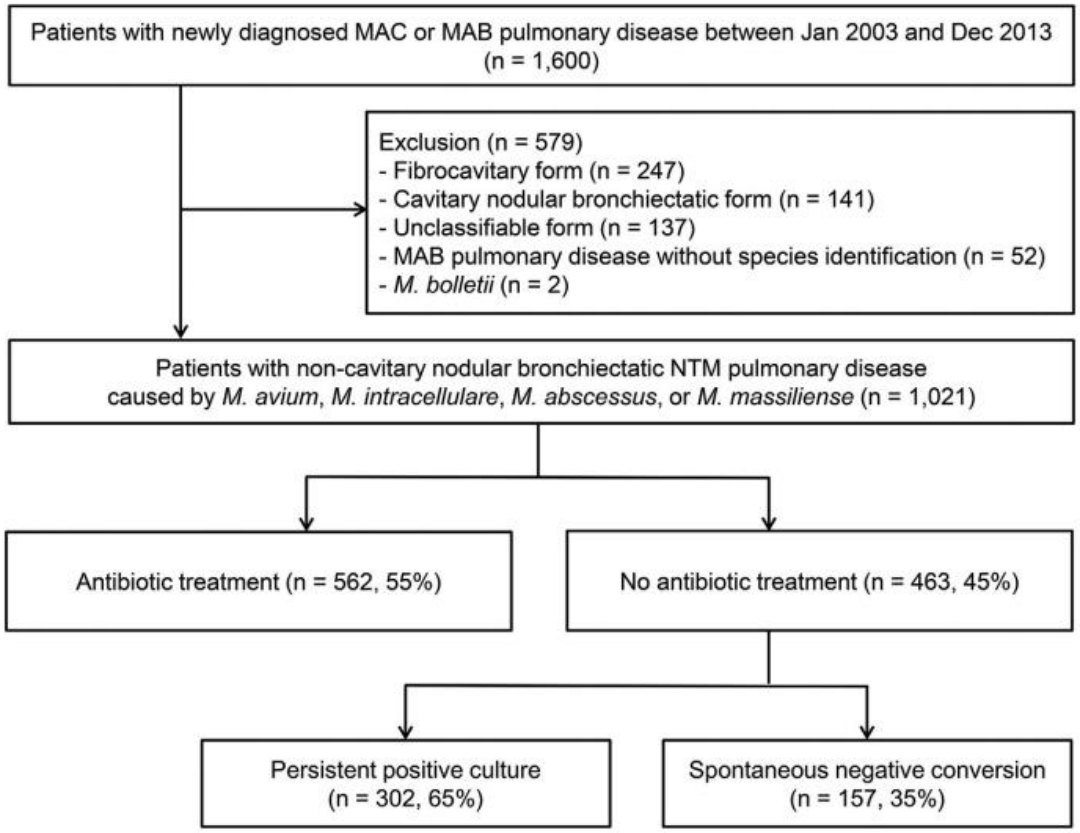
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age years	0.969 (0.945–0.994)	0.015	0.973 (0.948–0.999)	0.043
Male	1.087 (0.612–1.929)	0.776	0.885 (0.484–1.621)	0.693
BMI kg·m^{-2}	1.108 (1.018–1.205)	0.017	1.101 (1.007–1.205)	0.035
Nonsmoker	0.961 (0.542–1.704)	0.892		
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

Predictors of spontaneous sputum conversion

- younger Age
- higher BMI
- anti-TB medication
- positive smear – less likely

Eur Respir J 2017;49:1600537

Long-term natural history of non-cavitary nodular bronchiectatic nontuberculous mycobacterial pulmonary disease



1021 patients

Progressive 562 px. (55%)

Stationary 463 px. (45%)

negative conversion 157 px. (35%)

Respiratory med 2019;151:1-7

Table 2
Factors associated with antibiotic treatment initiation after diagnosis.

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Female	1.17 (0.97–1.40)	0.096	0.97 (0.74–1.27)	0.836
Younger age, yr[a]	1.01 (0.99–1.01)	0.470	1.01 (1.01–1.02)	0.025
Lower BMI, kg/m^2[b]	1.05 (1.02–1.09)	< 0.001	1.04 (1.01–1.08)	0.028
Non-smoker	1.27 (1.02–1.59)	0.036	1.17 (0.85–1.62)	0.335
Etiology				
MAC	Reference	0.969	Reference	0.110
MAB	0.99 (0.81–1.23)		0.83 (0.66–1.04)	
Underlying disease				
Previous history of TB	1.30 (1.09–1.54)	0.003	1.23 (1.01–1.50)	0.039
COPD	1.12 (0.91–1.38)	0.296	0.93 (0.72–1.21)	0.601
Malignancy	0.76 (0.57–1.03)	0.075	1.05 (0.74–1.48)	0.792
Diabetes mellitus	1.14 (0.84–1.55)	0.407	1.34 (0.94–1.92)	0.105
Symptom				
Cough	1.89 (1.55–2.31)	< 0.001	1.36 (1.05–1.75)	0.019
Sputum production	1.95 (1.59–2.40)	< 0.001	1.47 (1.13–1.91)	0.004
Hemoptysis	1.25 (1.04–1.50)	0.019	1.12 (0.91–1.37)	0.286
Sputum smear positivity	1.20 (1.02–1.42)	0.031	1.19 (0.99–1.43)	0.067
No. of involved lobes on HRCT	1.30 (1.22–1.38)	< 0.001	1.22 (1.14–1.31)	< 0.001
FEV_1% predicted	0.99 (0.98–0.99)	0.001	1.00 (0.99–1.01)	0.690
CRP, mg/dL	1.00 (0.98–1.03)	0.799	1.00 (0.97–1.03)	0.962

Predictors of disease progression

younger age, lower BMI, previous history of TB

cough, sputum

No. of involved lobes on HRCT

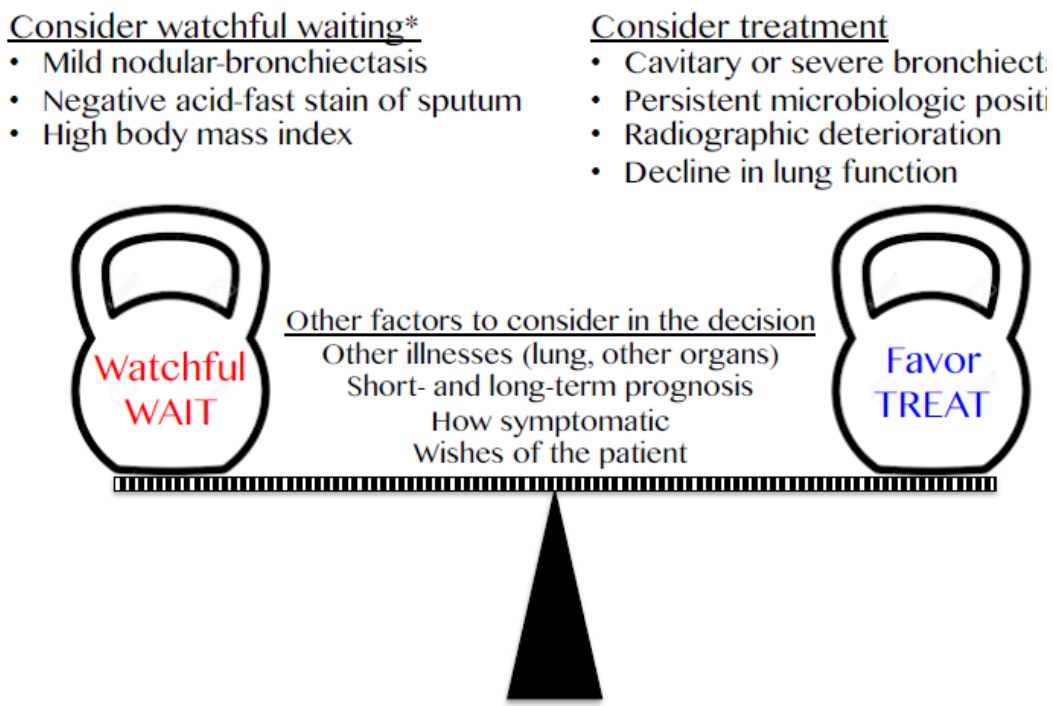
Respiratory med 2019;151:1-7

Table 4
Factors associated with spontaneous culture conversion without antibiotic treatment.

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Female	1.04 (0.75–1.45)	0.803	0.91 (0.53–1.56)	0.741
Younger age, yr[a]	1.01 (1.00–1.02)	0.143	1.00 (0.98–1.02)	0.687
Lower BMI, kg/m^2[b]	0.99 (0.94–1.05)	0.798	0.98 (0.93–1.04)	0.558
Non-smoker	1.01 (0.70–1.47)	0.949	1.01 (0.57–1.79)	0.977
Etiology				
MAC	Reference	0.548	Reference	0.288
MAB	1.12 (0.77–1.64)		1.29 (0.81–2.04)	
Underlying disease				
Previous history of TB	0.91 (0.63–1.30)	0.599	0.76 (0.49–1.17)	0.212
COPD	0.81 (0.52–1.27)	0.361	0.66 (0.36–1.19)	0.166
Malignancy	1.02 (0.63–1.66)	0.927	0.91 (0.50–1.68)	0.770
Diabetes mellitus	1.15 (0.62–2.12)	0.662	1.25 (0.56–2.81)	0.583
Symptom				
Cough	0.98 (0.71–1.35)	0.889	0.86 (0.54–1.36)	0.510
Sputum production	1.15 (0.83–1.60)	0.407	1.21 (0.76–1.94)	0.428
Hemoptysis	0.73 (0.48–1.11)	0.143	0.71 (0.43–1.17)	0.175
Sputum smear positivity	0.84 (0.60–1.17)	0.302	0.80 (0.53–1.19)	0.268
No. of involved lobes on HRCT	0.98 (0.88–1.09)	0.764	0.92 (0.81–1.05)	0.233
Pulmonary function test, FEV_1% predicted	0.99 (0.98–1.01)	0.282	0.99 (0.97–1.00)	0.103
CRP, mg/dL	1.00 (0.97–1.03)	0.885	1.00 (0.97–1.04)	0.809

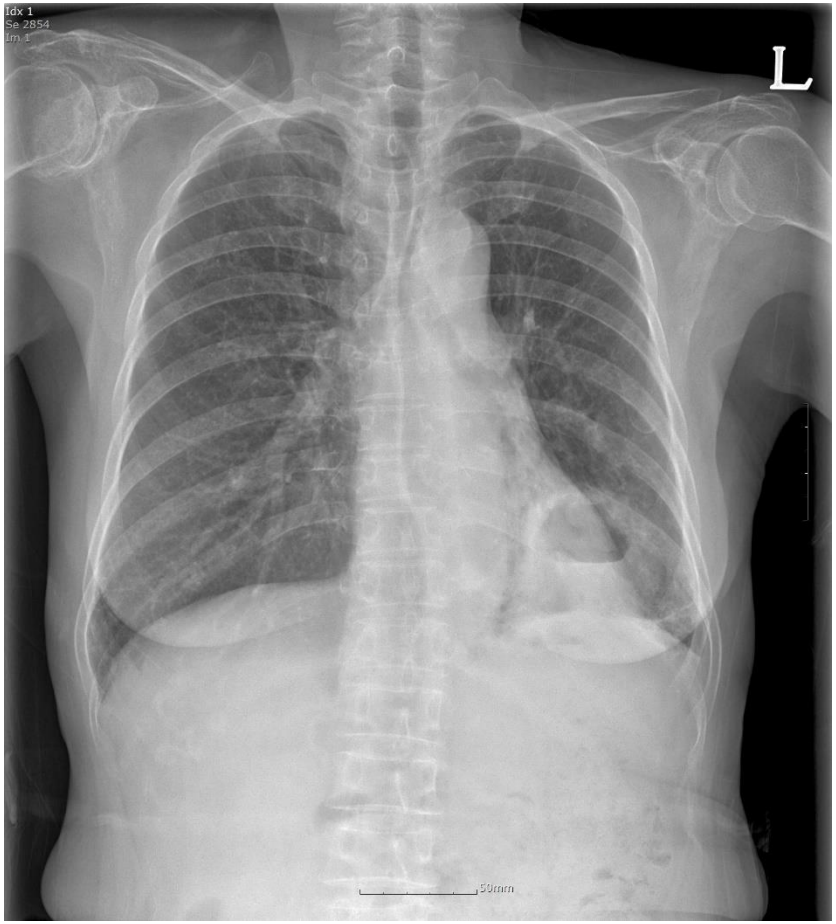
Respiratory med 2019;151:1-7

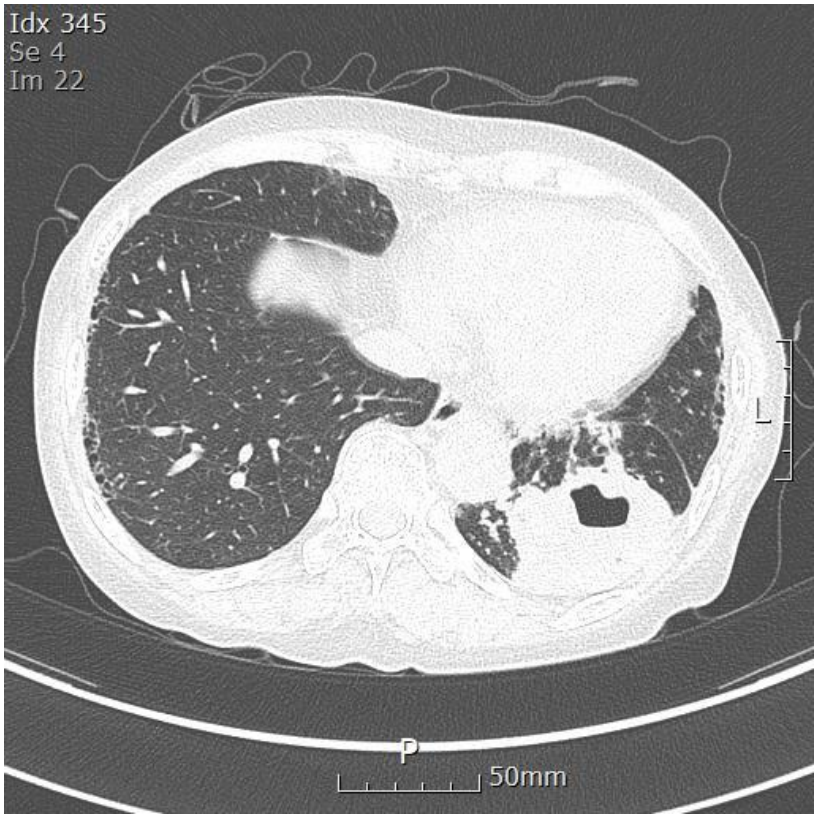
1. In patients who meet the diagnostic criteria for NTM pulmonary disease (Table 2), we suggest initiation of treatment rather than watchful waiting, especially in the context of positive acid-fast bacilli sputum smears and/or cavitary lung disease (conditional recommendation, very low certainty in estimates of effect).



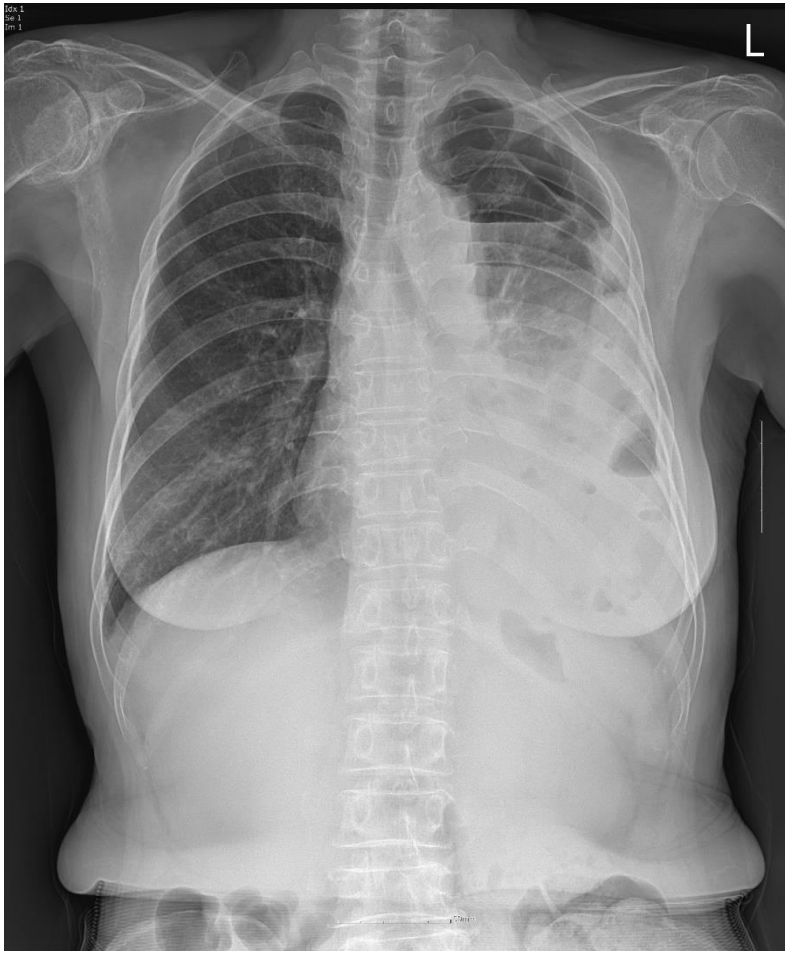
https;//www.ntminfo.org/wp-content/uploads/2019/06/NTMsupplementalGuide.pdf

65세 여자, SLE 로 f/u 중 cavitary lung lesion 으로 의뢰





65세 여자, SLE 로 f/u 중 cavitary lung lesion 으로 의뢰



Sputum AFB 2+

PCR: NTM, culture: NTM

Pleural fluid AFB –/ culture NTM

NTM ID: M. intracellulare

DST: calri/moxi/LZD S/I/I

Clarithromycin, rifampin, ethambutol

Treatment regimens for MAC

MAC	No.	Preferred regimen	Dosing frequency
Noular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin Ethambutol	3 times weekly
Cavitary	≥ 3	Azithromycin (clarithromycin) Rifampicin Ethambutol Amikacin IV (streptomycin)	Daily (3 times weekly may be used with AGs)
Refractory	≥ 4	Azithromycin (clarithromycin) Rifampicin Ethambutol Amikacin IV or inhalation	Daily (3 times weekly may be used with AGs)

Azithromycin daily 250-500mg/ **thrice 500mg**
Ethambutol daily 15mg/kg thrice 25mg/kg
Amikacin 10-15mg/kg thrice 15-25mg/kg, at least 2-3 months

Clin Infect Dis 2020;71(4):e1-e36

Discontinuation rates attributed to adverse events and treatment outcomes between clarithromycin and azithromycin in *Mycobacterium avium* complex lung disease: A propensity score analysis

Table 2
Comparison of discontinuation rates attributed to adverse events between clarithromycin and azithromycin.

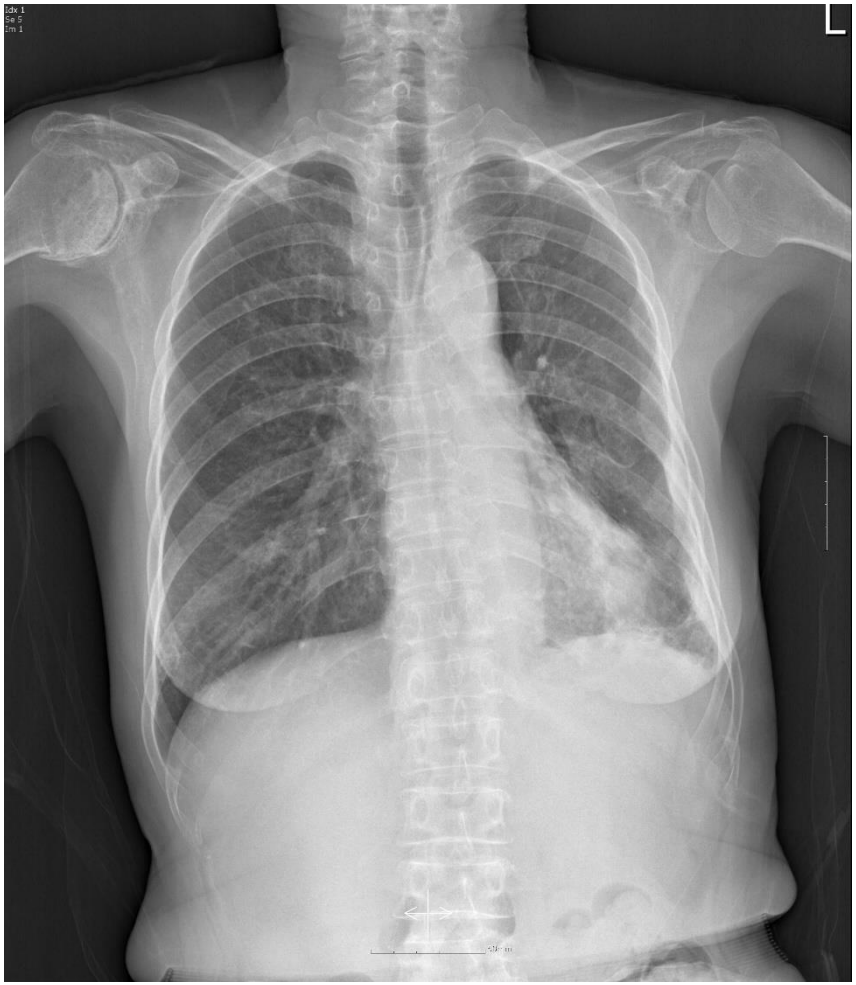
Analysis	CLR-containing regimen ($n = 466$)	AZM-containing regimen ($n = 94$)	*P* value
Unadjusted analysis			
Discontinuation of initial CLR or AZM attributed to adverse events	113 (24.2%)	9 (9.6%)	0.002
Not resuming treatment after discontinuation	57	8	
Attempt treatment by switching drug	56*	1†	
Inverse probability of treatment weighting			
Discontinuation of initial CLR or AZM attributed to adverse events	115 (24.6%)	9 (9.6%)	0.001
Not resuming treatment after discontinuation	58	8	
Attempt treatment by switching drug	57	1	

Table 5
Analysis of azithromycin treatment success rate compared with clarithromycin treatment success rate.

	Treatment Success	*P* value
Crude OR (95% CI)	1.104 (0.535–2.278)	0.788
Adjusted OR (95% CI)*	1.032 (0.488–2.180)	0.935
Adjusted OR by IPTW (95% CI)	0.863 (0.447–1.749)	0.670

J Glob Antimicrob Resist 2020;22:106-112

65세 여자, SLE 로 f/u 중 cavitary lung lesion 으로 의뢰



Whole body Skin rash d/t EMB

음전 1년 후 SLE flare up (RFP....)

Next ?

Ethambutol is the best companion drug for preventing macrolide resistance

- **237 patients with MAC-PD**

  standard regimen 122

  macrolide and ethambutol 58

  macrolide and rifampicin 32

  macrolide only 25

Macrolide	237 (100.0%)
Duration, months	18.6 (16.3–24.3)
Ethambutol	224 (94.5%)
Maintenance (≥6 months)	180 (80.4%)
Duration, for patients with maintenance, months	18.0 (12.1–22.0)
Duration, for patients without maintenance, months	1.2 (0.0–3.2)
Rifampicin	179 (75.9%)
Maintenance (≥6 months)	154 (86.0%)
Duration, for patients with maintenance, months	18.7 (16.7–24.3)
Duration, for patients without maintenance, months	0.0 (0.0–0.5)

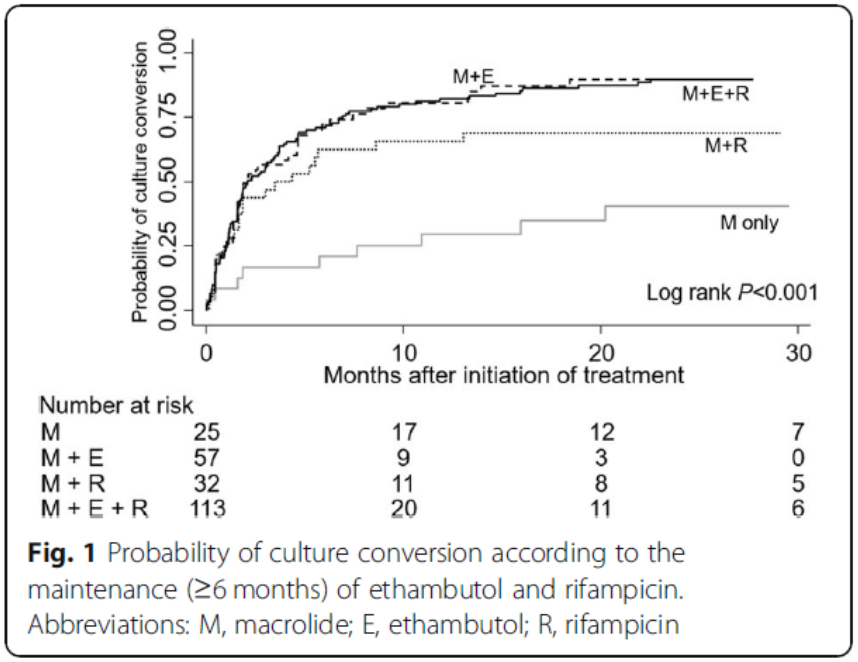


Fig. 1 Probability of culture conversion according to the maintenance (≥6 months) of ethambutol and rifampicin. Abbreviations: M, macrolide; E, ethambutol; R, rifampicin

BMC pulmonary medicine 2019;19:212

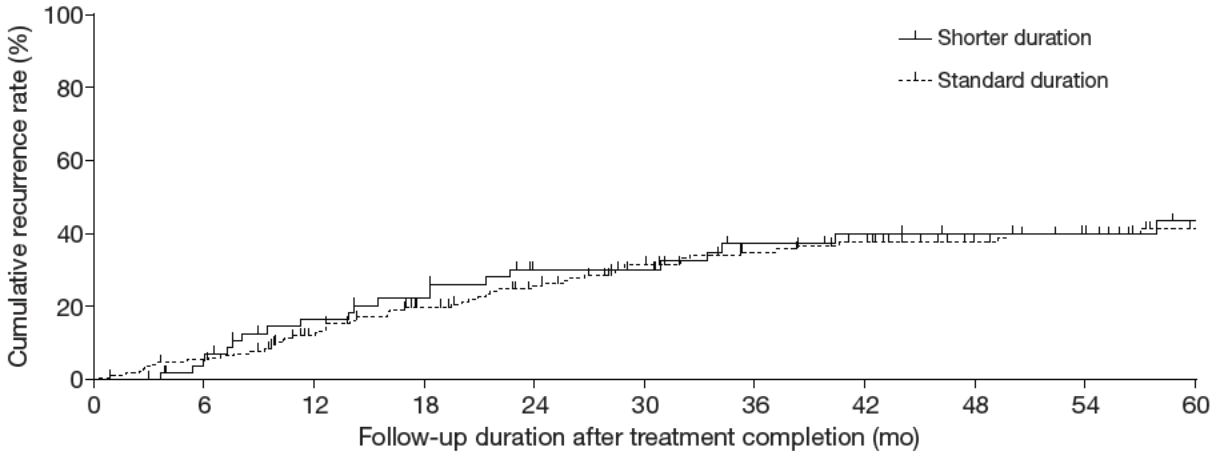
Treatment Outcomes after Discontinuation of Ethambutol due to Adverse Events in *Mycobacterium avium* Complex Lung Disease

Characteristics	Unadjusted subjects			Matched subjects		
	Standard regimen (n = 315)	EMB discontinuation (n = 47)	*P* value	Standard regimen (n = 164)	EMB discontinuation[a] (n = 44)	SMD
Age, yr	59.9 ± 10.5					
Age ≥ 60 yr	164 (52.1)					
Gender, women	201 (63.8)					
Body mass index, kg/m^2	20.7 ± 2.5					
Current or past smoker	84 (26.7)					
Previous history of TB treatment	131 (41.6)					
Comorbidities						
Malignancy	58 (18.4)					
COPD	43 (13.6)					
Diabetes mellitus	28 (8.9)					
Etiology						
Mycobacterium avium	160 (50.8)					
Mycobacterium intracellulare	155 (49.2)					
Type of disease			0.002			0.080
Noncavitary NB	223 (70.8)	21 (44.7)		84 (51.2)	21 (47.7)	
Cavitary NB	54 (17.1)	16 (34.0)		43 (26.2)	13 (29.6)	
Fibrocavitary	38 (12.1)	10 (21.3)		37 (22.6)	10 (22.7)	
Positive AFB smear	125 (39.7)	27 (57.5)	0.032	87 (53.1)	24 (54.6)	0.030
Use of injectable aminoglycoside	150 (47.6)	30 (63.8)	0.055	85 (51.8)	28 (63.6)	0.241
Treatment failure[d]	52 (16.5)	15 (31.9)	0.020	30 (18.3)	13 (29.6)	-

A total of 38.3% (18/47) patients were treated with only macrolide and rifampin after discontinuation of EMB, without the addition of other drugs. The treatment outcome of these patients was comparable to that of those who completed the standard regimen, despite the discontinuation of the second most important drug, EMB. The reason for this unexpectedly similar outcome is unclear, but may be due to a relatively longer treatment duration of EMB before discontinuation in the patients treated only with macrolide and rifampin (9.6 ± 5.2 months, 52.4% of the total treatment duration) compared with the other patients who discontinued EMB (5.9 ± 4.3 months, 35.7% of the total treatment duration, P = 0.029

J Korean Med Sci 2020;35(9):e59

Outcome of shorter treatment duration in non-cavitary nodular bronchiectatic *Mycobacterium avium* complex lung disease



No. at risk											
Shorter duration	59	54	45	41	33	32	26	24	22	20	16
Standard duration	169	159	138	118	103	88	77	70	56	51	43

J Thorac Dis 2020;12(3):338-348

Treatment regimen for M. kansasii

- Isoniazid/Rifampicin/Ethambutol daily
- Macrolides/Rifampicin/Ethambutol daily or TIW
- Rifampicin-resistance Isoniazid/Ethambutol/Fluoroquinolones
- Could be treated for a fixed duration of 12 months

Clin Infect Dis 2020;71(4):e1-e36

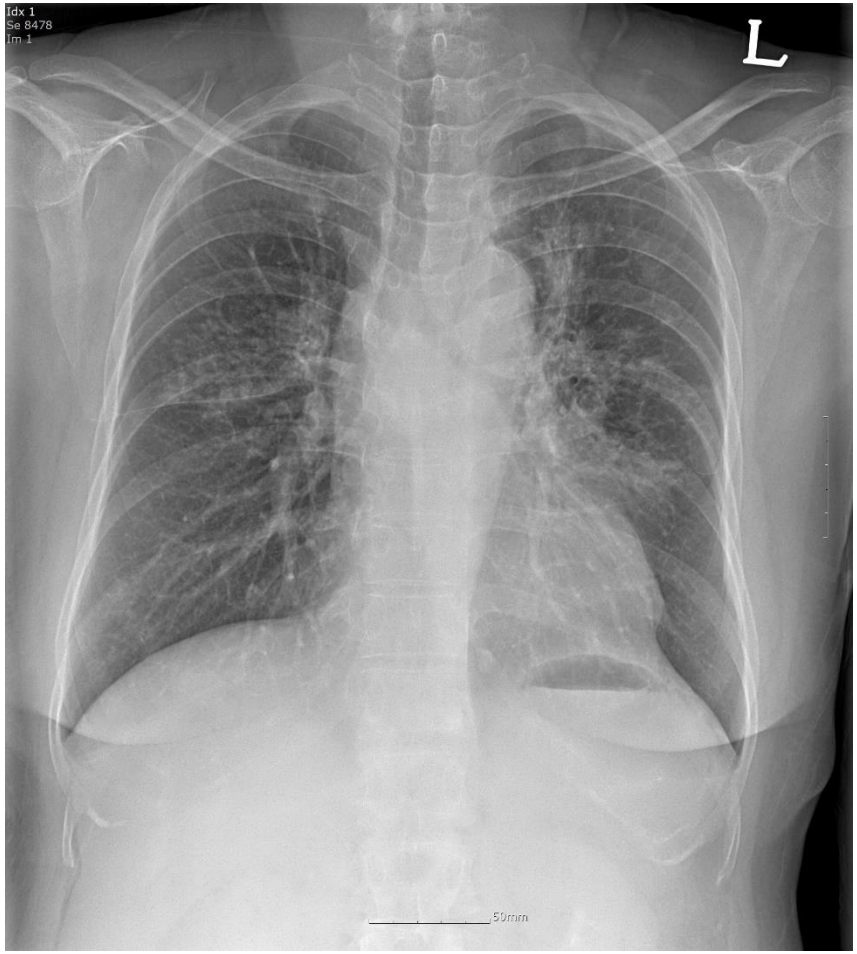
Treatment with a macrolide-containing regimen for *Mycobacterium kansasii* pulmonary disease

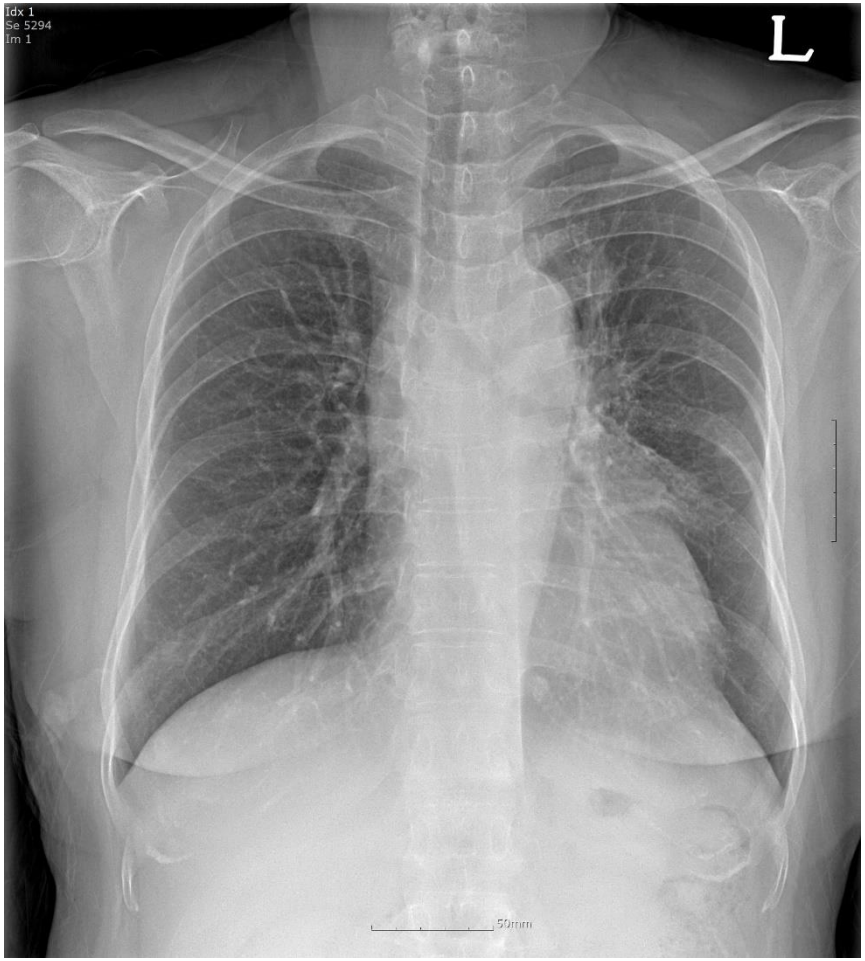
- **24 INH group, 25 azithromycin group**

	Total (n = 49, 100%)	Isoniazid group (n = 24, 49%)	Macrolide group (n = 25, 51%)	*P* value
Favorable outcome	41 (84)	19 (79)	22 (88)	0.46
Unfavorable outcome	8 (16)	5 (21)	3 (12)	
Follow-up loss during treatment	5	3	2	
Discontinuation of therapy due to drug adverse reactions	2	2	0	
Transfer out during treatment	1	0	1	
Symptomatic response at 12 months				0.62
Improved	28 (56)	12 (50)	16 (64)	
Unchanged	13 (26)	7 (29)	6 (24)	
Worsened	0 (0)	0 (0)	0 (0)	
Unavailable[a]	8 (16)	5 (21)	3 (12)	
Radiologic response on HRCT at 12 months				0.15
Improved	36 (74)	16 (67)	20 (80)	
Unchanged	5 (10)	3 (12)	2 (8)	
Worsened	0 (0)	0 (0)	0 (0)	
Unavailable[a]	8 (16)	5 (21)	3 (12)	
Total treatment duration, months[b]	17.6 (14.6–18.5)	17.9 (14.5–18.5)	15.4 (14.7–18.5)	0.71
Time to culture conversion, months[b]	1.5 (0.9–3.0)	2.0 (0.9–3.3)	1.2 (1.0–2.9)	0.84
Total follow-up duration after treatment completion, months[b]	13.5 (4.5–33.9)	16.9 (3.7–40.5)	10.7 (4.5–32.3)	0.36

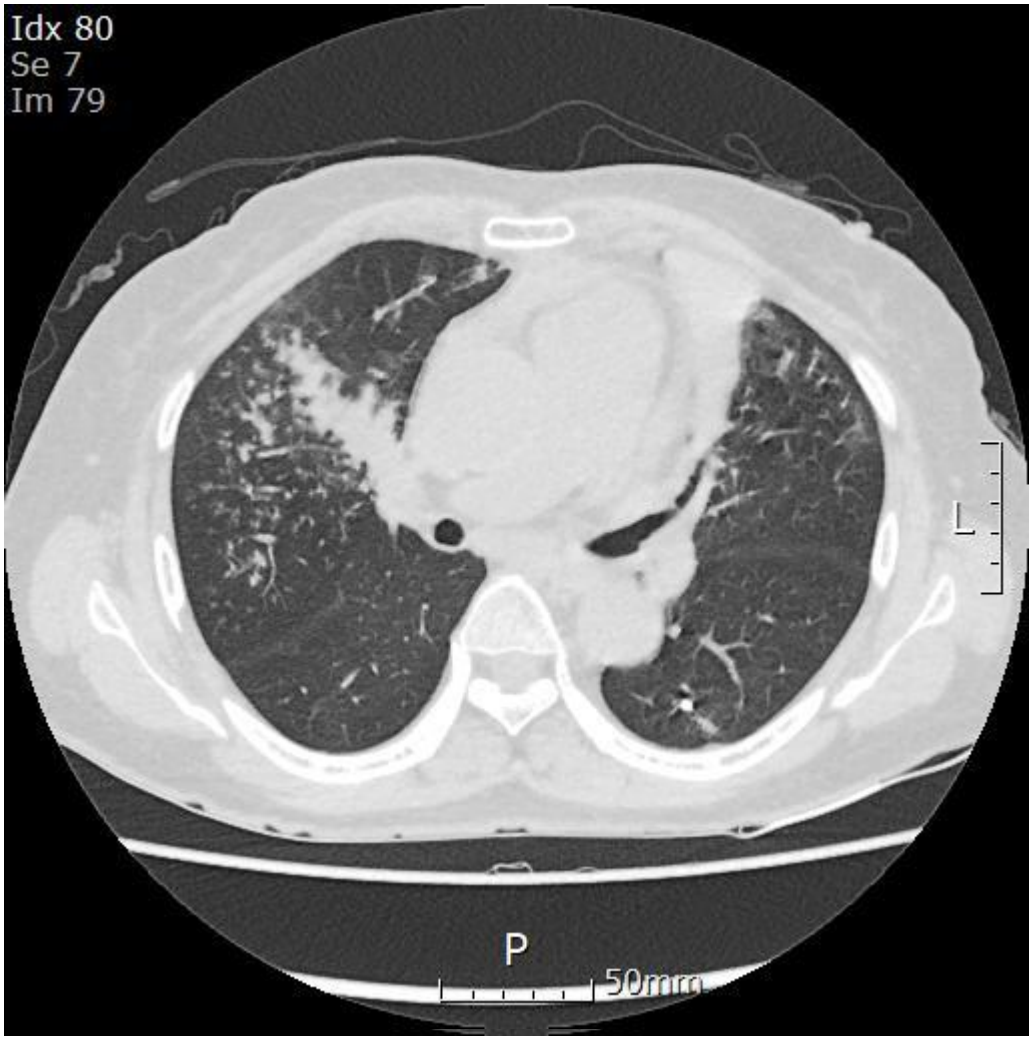
Respiratory medicine 2019;148:37-42

58세 여자, SCLC 로 f/u 중 결핵 의심되어 의뢰





58세 여자, SCLC 로 f/u 중 결핵 의심되어 의뢰



Sputum AFB smear: negative

AFB culture: NTM * 3회

NTM ID: M. abscessus

AN	Amikacin	S	8
FOX	Cefoxitin	I	32
CFX	Ciprofloxac	R	16
CIR	Clarithromyc	IR	<=0.5,8
DX	Doxycycline	R	>32
IMI	Imipenem	S	4
MXF	(MXF) Moxif	R	4
RFP	(RFP) Rifamp		>16
SXT	Trimethoprir	R	8/152
TOB	Tobramycin		16
EMB	(EMB) Ethamt		32
LNZ	(LNZ) Linezc	S	8

Treatment regimens for M. abscessus

Macrolide Susceptibility Pattern				
Mutational[a]	Inducible[b]	No. of Drugs[c]	Preferred Drugs	Frequency of Dosing
Susceptible	Susceptible	Initial phase ≥ 3	*Parenteral (choose 1–2)* Amikacin Imipenem (or Cefoxitin) Tigecycline *Oral (choose 2)* Azithromycin (clarithromycin)[d] Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides)
		Continuation phase ≥ 2	*Oral/inhaled (choose 2–3)* Azithromycin (clarithromycin)[d] Clofazimine Linezolid	
Susceptible	Resistant	Initial phase ≥ 4	*Parenteral (choose 2–3)* Amikacin Imipenem (or Cefoxitin) Tigecycline *Oral (choose 2–3)* Azithromycin (clarithromycin)[e] Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides)
		Continuation phase ≥ 2	*Oral/inhaled (choose 2–3)* Azithromycin (clarithromycin)[e] Clofazimine Linezolid Inhaled amikacin	

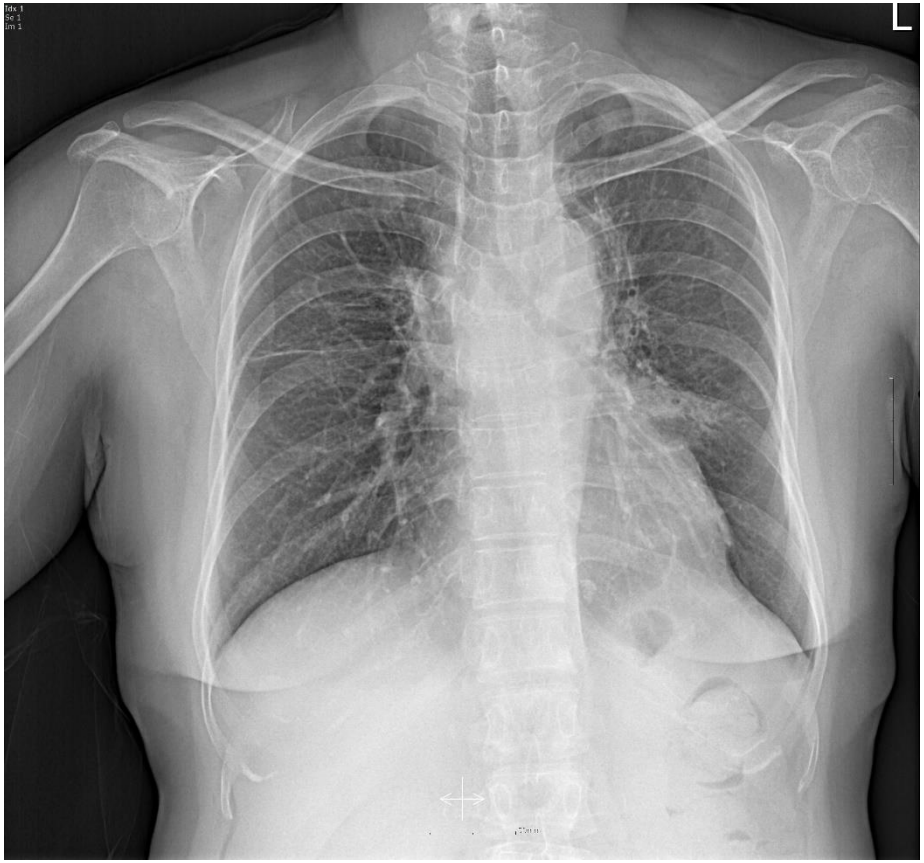
IV amikacin 10-15mg/kg

IV high-dose cefoxitin (12g/d)

IV imipenem 500mg bid-qid

Clarithromycin/ azithromycin

58세 여자, SCLC 로 f/u 중 결핵 의심되어 의뢰



Day #16

Azithromycin, cefoxitin, amikacin

Dizziness, headache, fever, edema

Next ?

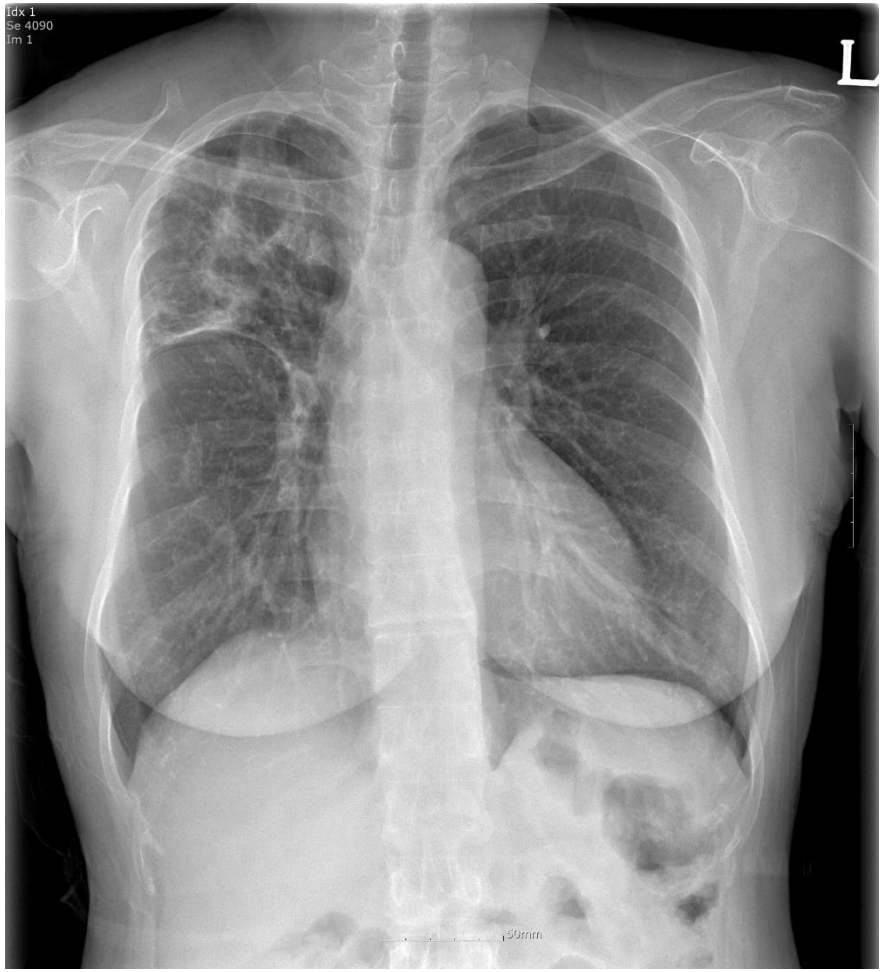
Treatment of *M. abscessus* Pulmonary Disease—Summary

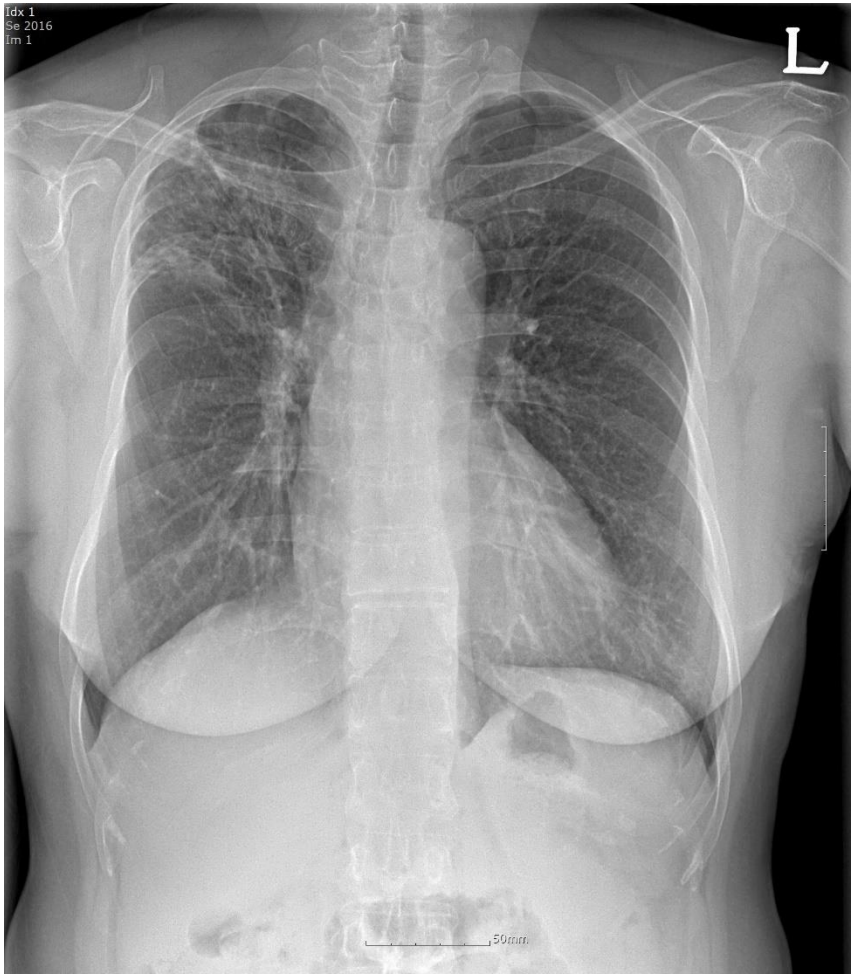
The optimal drugs, regimens, and duration of therapy are not known. Patients with *M. abscessus* pulmonary disease caused by strains *without* inducible (typically *M. massiliense*) or mutational macrolide resistance should be treated with a macrolide-containing multidrug regimen that includes at least 3 active drugs (guided by in vitro susceptibility) in the initial phase of treatment (the phase including intravenous agents) (Tables 3 and 5). In patients with *M. abscessus* pulmonary di-

Without inducible : macrolide-containing regimen at least 3 active drugs

With resistance: macrolide-containing regimen at least 4 active drugs

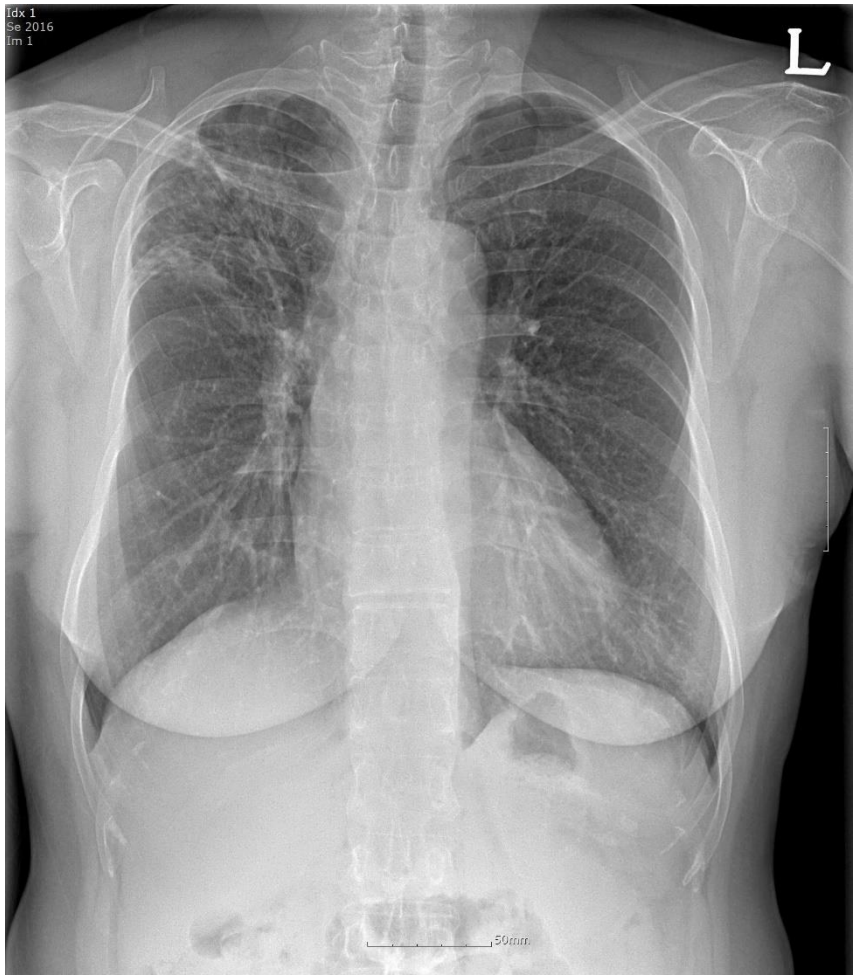
60세 여자, 결핵 치료 중 NTM 배양되어 의뢰

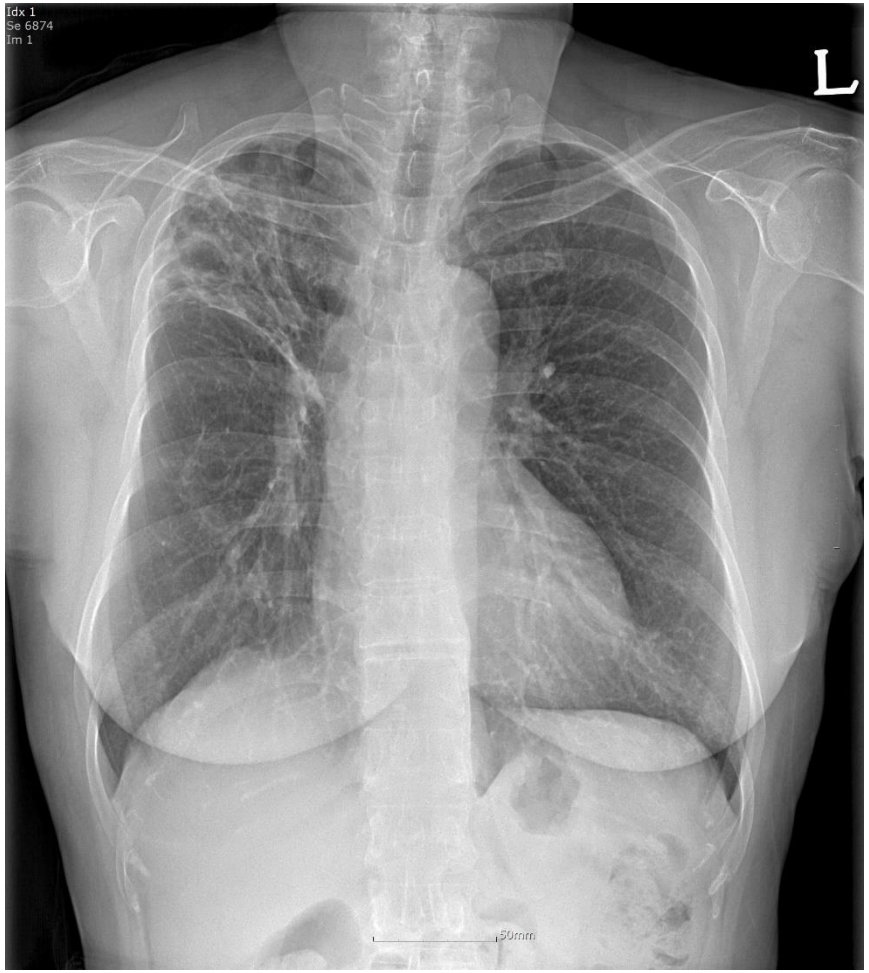




균 음전 12개월, 총 17개월 치료

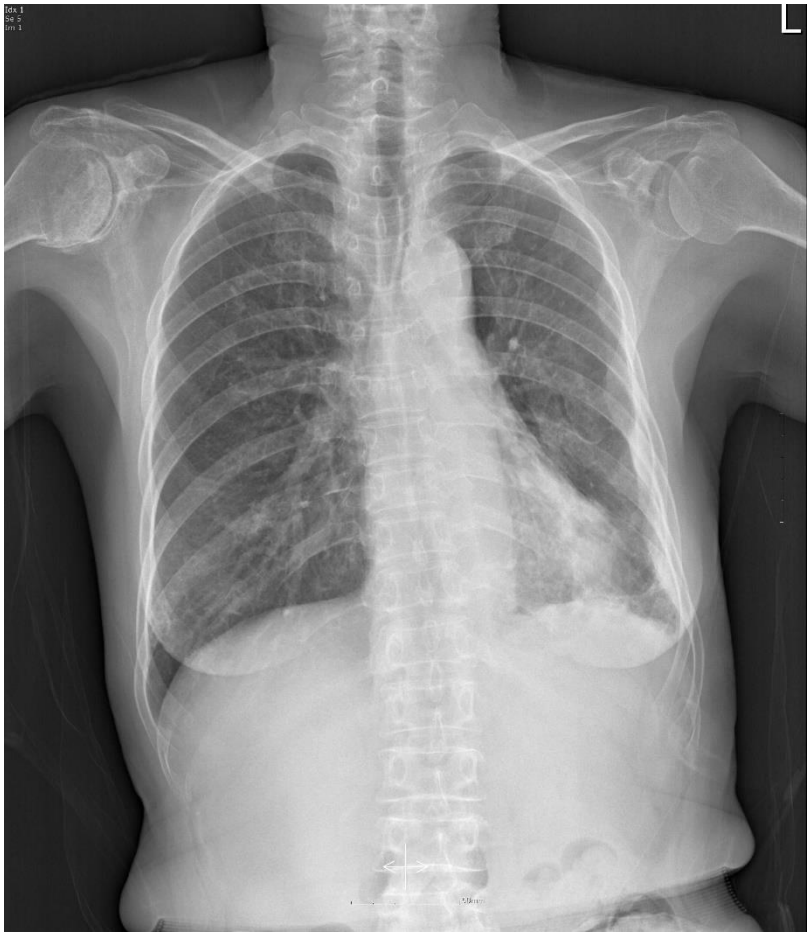
60세 여자, 결핵 치료 중 NTM 배양되어 의뢰





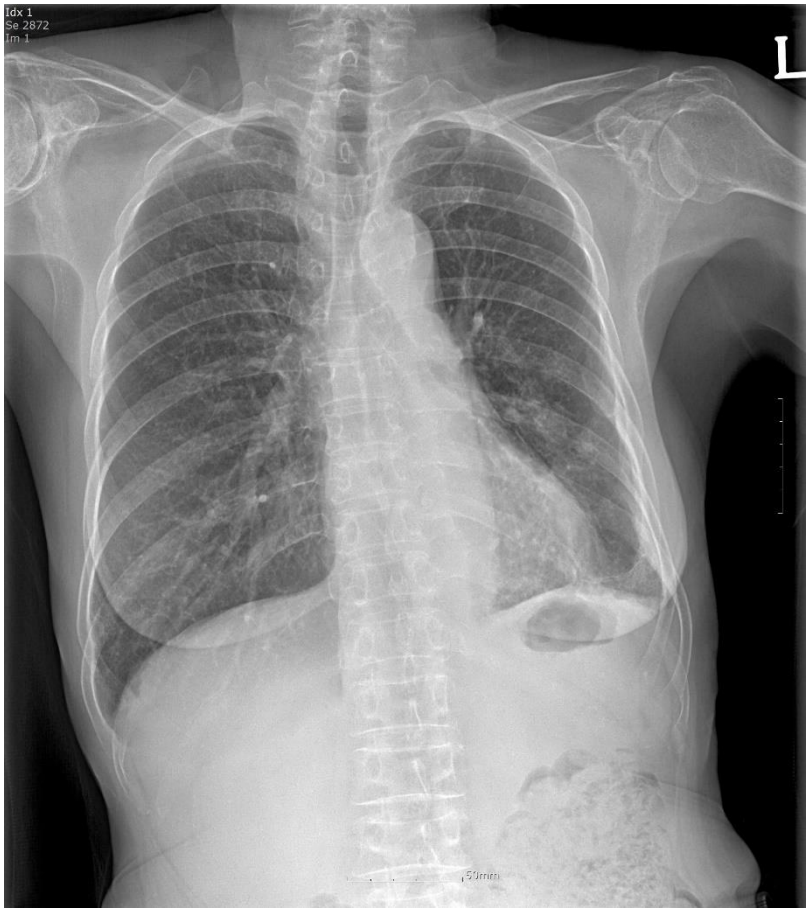
치료 종료 후 2년 경과, 균 양전

65세 여자, SLE 로 f/u 중 cavitary lung lesion 으로 의뢰



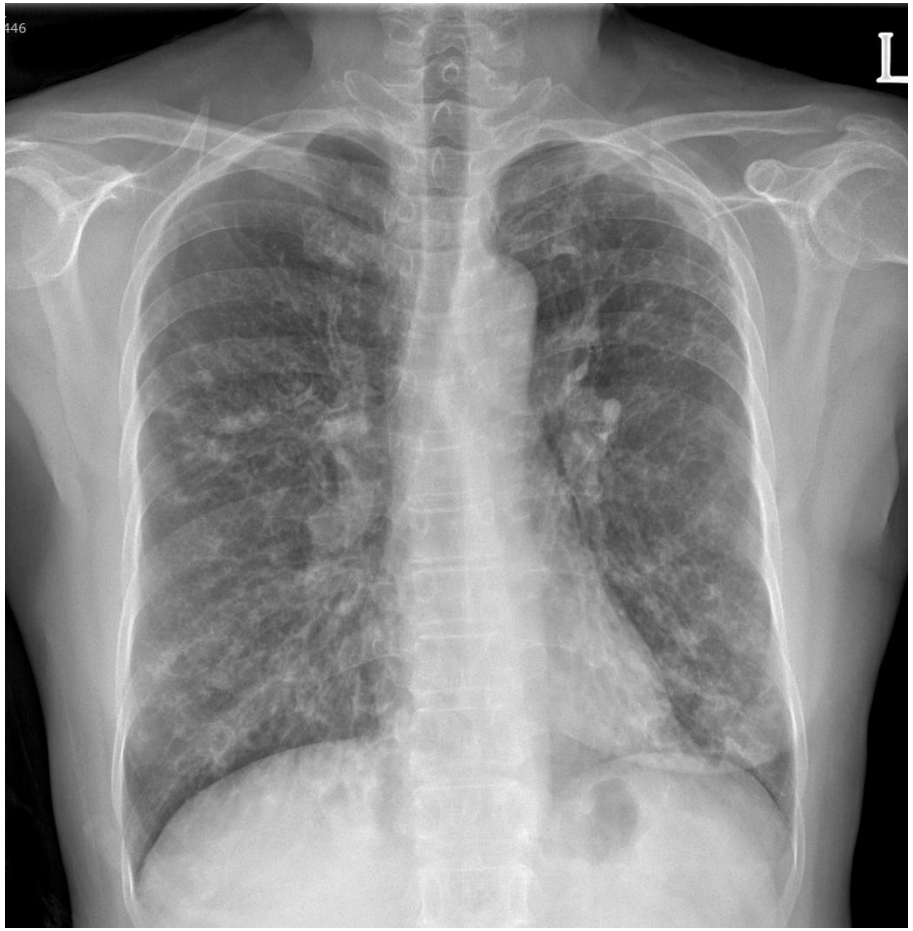
치료 3개월부터 **RFP, Azi**

균 음전 **1년** 후 **SLE flare up** 으로 종료



치료 종료 **3년 6개월** 후 **CXR**

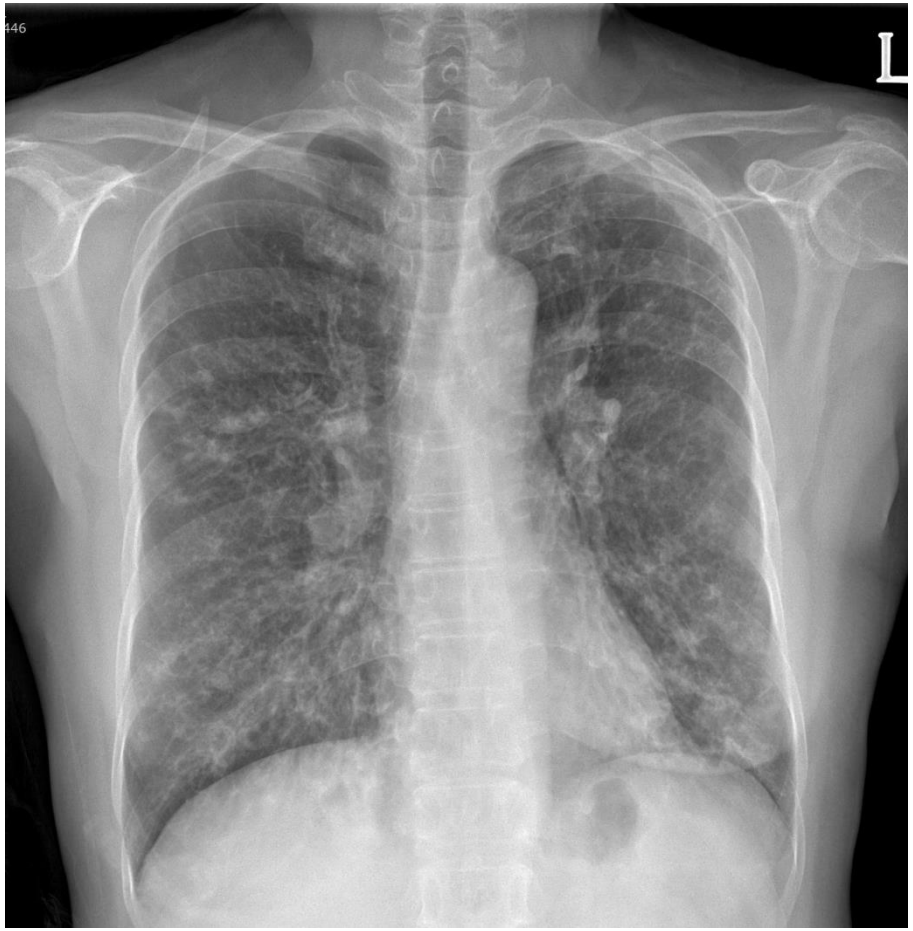
66세 여자, NTM 치료로 의뢰



CT reading:

Slightly increased extent of superimposed infection with underlying cystic and tubular bronchiectasis in both lungs. r/i NTM progression

66세 여자, NTM 치료로 의뢰



CT reading: r/i NTM

BFS 시행 후 바로 NTM 치료 시작

AFB smear/culture: negative

TB & NTM PCR: negative

Sputum: P. aeruginosa

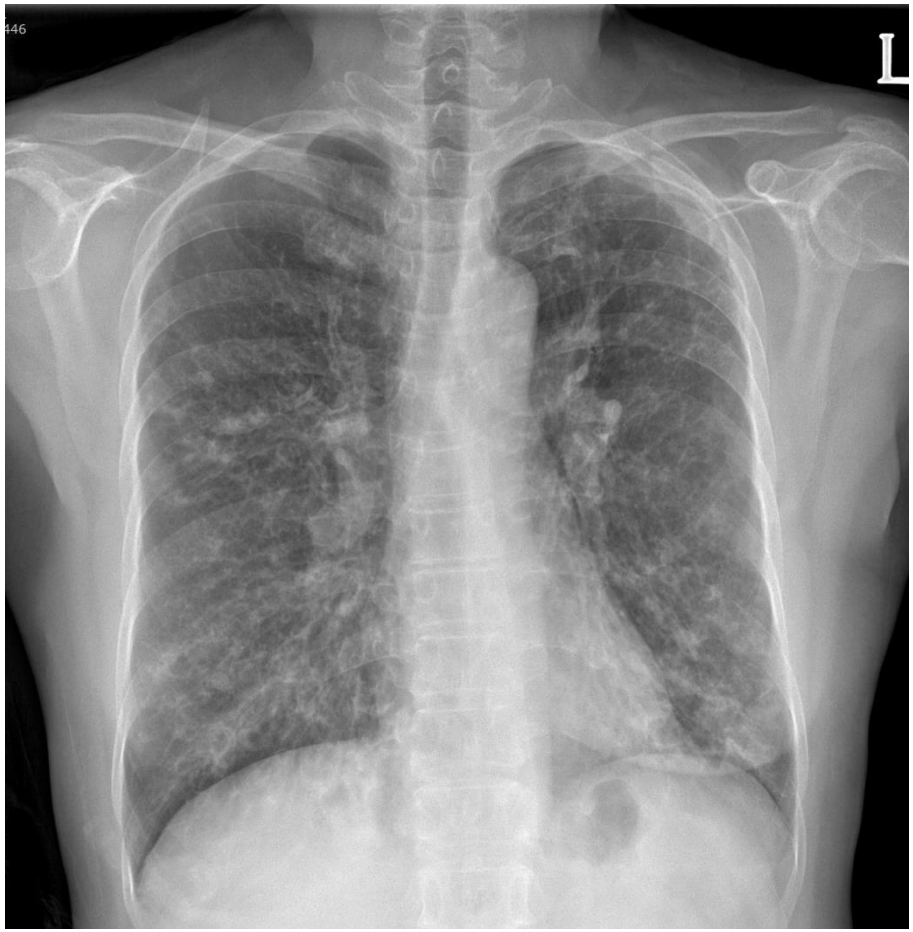
PFT: FEV1/FVC 59 FEV1 41 FVC 55

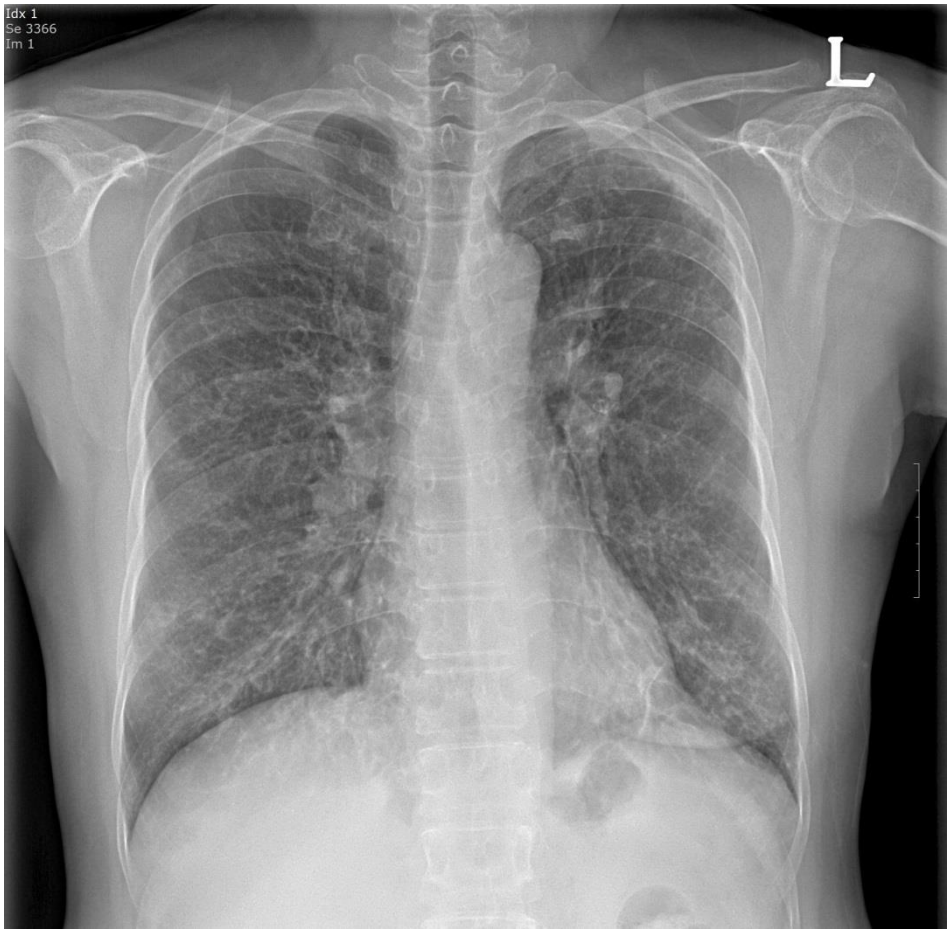
NTM 치료 중단

Ciprofloxacin 750 mg bid

LAMA 시작

66세 여자, NTM 치료로 의뢰

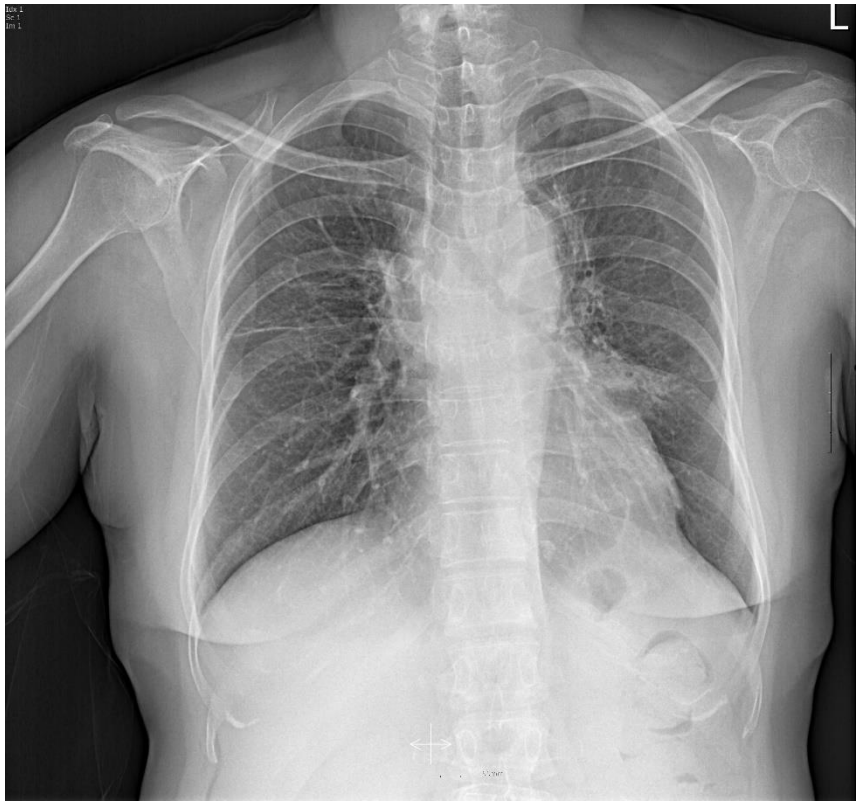




FEV1 40% -> 60% 호전

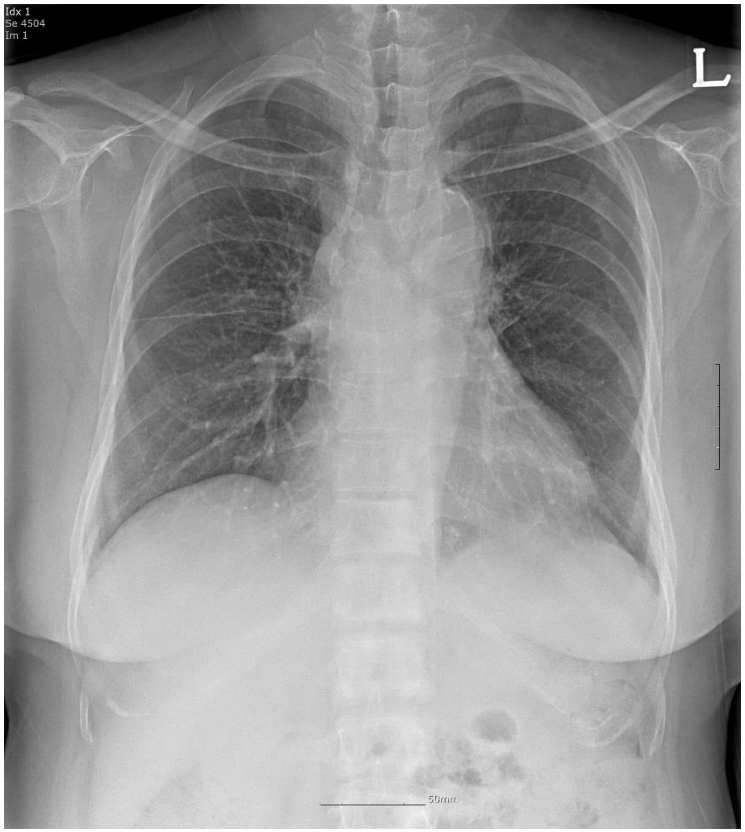
기침, 가래, 호흡 호전

58세 여자, SCLC 로 f/u 중 결핵 의심되어 의뢰



주사치료 **4주/ azi, moxi** 만 유지

균 음전 **1년** 후 종료



치료 종료 **6개월** 후 **CXR**

NTM LD 의 치료의 시작과 끝

- **NTM PD**는 임상적, 영상 의학적 및 미생물학적 기준을 만족해야 한다.
- 기준에 만족하지 않을 때도 정확한 진단 또는 배제가 될 때까지 주의가 필요하다.
- 진단기준이 치료의 기준은 아니다.
- 치료의 시작과 끝은 정답은 없다. **Individualized approach** 가 필요하다.

경청해 주셔서 감사합니다.

Dong-A University Medical Center