PNEUMOLOGIA 2018

Milano, 14 – 16 giugno 2018 · Centro Congressi Palazzo delle Stelline

Le micobatteriosi polmonari

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Non-tuberculous mycobacteria (NTM)

NOT assigned to either: [1,2]

- ***Mycobacterium tuberculosis*** **(MTB) complex**
- ***Mycobacterium leprae***

NTM also known as:[2]

- **Environmental mycobacteria**
- **Opportunistic mycobacteria**
- **Atypical mycobacteria**
- **Mycobacteria other than tuberculosis (MOTT)**

NTM

Recognition:

- **Identified soon after MTB, not initially recognized as pathogenic**[2]
- **Suspected as potential cause of human infections in the sanatorium era**[4]
- **1950s: Direct evidence for causation of disease**[4]
- **Opportunistic infections in HIV patients led to wider recognition & investigation**[4]

Characteristics:

- **Environmental mycobacteria**[1,2]
- **Opportunistic pathogens of humans & animals**[3]
- **As of 2015: >172 different species with distinct virulence features**[3]

NTM, non-tuberculous mycobacteria.

1. McShane PJ, Glassroth J. Chest 2015; 148:1517-27; 2. Schönfeld N, et al. Pneumologie 2013; 67:605-33; 3. Faria S, et al. J Pathog 2015; 2015:809014; 4. Orme IM, Ordway DJ. Infect Immun 2014; 82:3516-22.

NTM vs *Mycobacterium tuberculosis*: Key distinctions

NTM	*Mycobacterium tuberculosis*
Environmental bacteria - true/normal inhabitants, not contaminants[1]	Obligate pathogens: require host[1]
Low virulence: not usually pathogenic in the absence of predisposing conditions[2,3]	Pathogenic[3,6]
Human-to-human transmission extremely rare, but some evidence of this in the cystic fibrosis community[4]	Human-to-human transmission[3]
Infection rates increasing, especially in developed countries[5]	Infection rates decreasing, especially in developed countries[5]
Large heterogeneous group of species[6]	*M. tuberculosis* complex contains small group of closely related subspecies[6,7]

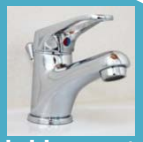
NTM and *Mycobacterium tuberculosis* differ clearly in terms of pathogenicity, infection rates and transmission routes

NTM, non-tuberculous mycobacteria.

1. Primm TP, et al. Clin Microbiol Rev 2004; 17:98-106; 2. Tortoli E. Clin Microbiol Infect 2009; 15:906-10; 3. Tortoli E. FEMS Immunol Med Microbiol 2006; 48:159-78; 4. McShane PJ, Glassroth J. Chest 2015; 148:1517-27 ; 5. Brode SK, et al. Int J Tuberc Lung Dis 2014; 18:1370-7; 6. Van Soolingen D. J Intern Med 2001; 249:1-26. 7. Grange JM. Soc Appl Bacteriol Symp Ser 1996; 25:1S-9S; 7. Cole ST. Microbiology 2002; 148:2919-28.

NTM habitats

Natural waters



Drinking water distribution systems + Biofilm formation

Hot tubs and spas

Acidic, brown-water swamps

Potting soils

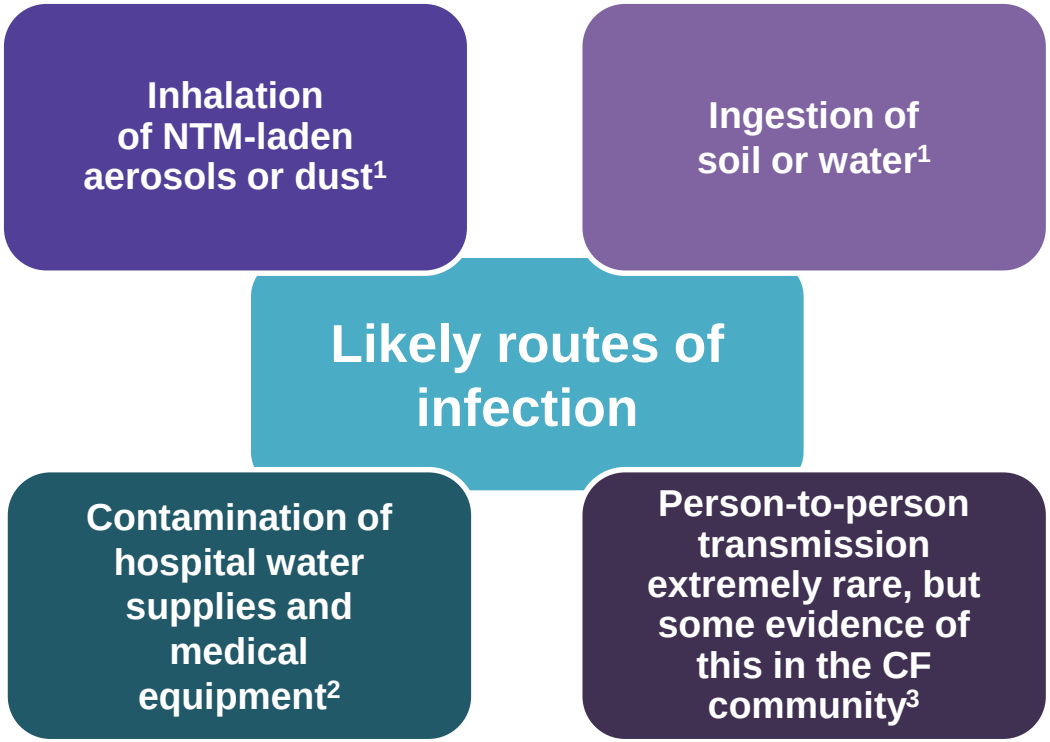
Boreal forest soils and peats

Metal removal fluid systems

NTM habitats are intimately shared with those of humans

NTM, non-tuberculous mycobacteria.
Falkinham JO, 3rd. J Appl Microbiol 2009; 107:356-67; pictures taken from https://pixabay.com/.

Transmission of NTM



Gastroesophageal reflux disease has been indicated as a mediator of NTM pulmonary disease[1]

- **Swallowing of NTM followed by gastric reflux leading to aspiration into the lung**

CF, cystic fibrosis; NTM, non-tuberculous mycobacteria.

1. Falkinham JO, 3rd. J Appl Microbiol 2009; 107:356-67; 2. Johnson MM, Odell JA. J Thorac Dis 2014; 6:210-20;
3. McShane PJ, Glassroth J. Chest 2015; 148:1517-27.

NTM – colonization vs infection

Colonization without infection (i.e. without tissue invasion) may occur

However, colonization has not been proven, and suspected cases may represent indolent or slowly progressive infection

Guideline-based criteria to determine the clinical significance of any NTM identified: Context in which an NTM isolate was obtained has to be considered

NTM, non-tuberculous mycobacteria.
Griffith DE, et al. Am J Respir Crit Care Med 2007; 175:367-416.

NTM disease: 4 main manifestations

Pulmonary disease[1,2]

Predisposing lung conditions[1,3]

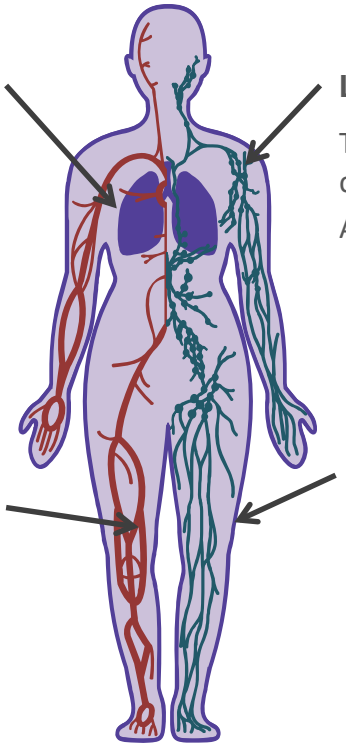
Predisposing genetic factors[4]

Situational (hypersensitivity pneumonitis)[2,3]

The lung is by far the most frequent disease site[1]

Disseminated disease[1,2]

Most commonly seen in association with profound immunosuppression, e.g. HIV infection[2,3]



Lymphatic disease[1,2]

Typically an infantile disease affecting cervical lymph nodes[2]

Also in adults with HIV infection[1]

Skin/soft tissue disease[1,2]

The most common sources include:

- contact with contaminated water or infected fish[2]
- traumas and surgical wounds[2]

Nosocomial infections have been described[3]

Both host factors and organism characteristics influence the susceptibility and manifestations of NTM disease[3]

HIV, human immunodeficiency virus; NTM, non-tuberculous mycobacteria.

1. Griffith DE, et al. Am J Respir Crit Care Med 2007; 175:367-416; 2. Tortoli E. Clin Microbiol Infect 2009; 15:906-10; 3. Johnson MM, Odell JA. J Thorac Dis 2014; 6:210-20; 4. McShane PJ, Glassroth J. Chest 2015; 148:1517-27.

NTM pathogens causing pulmonary disease

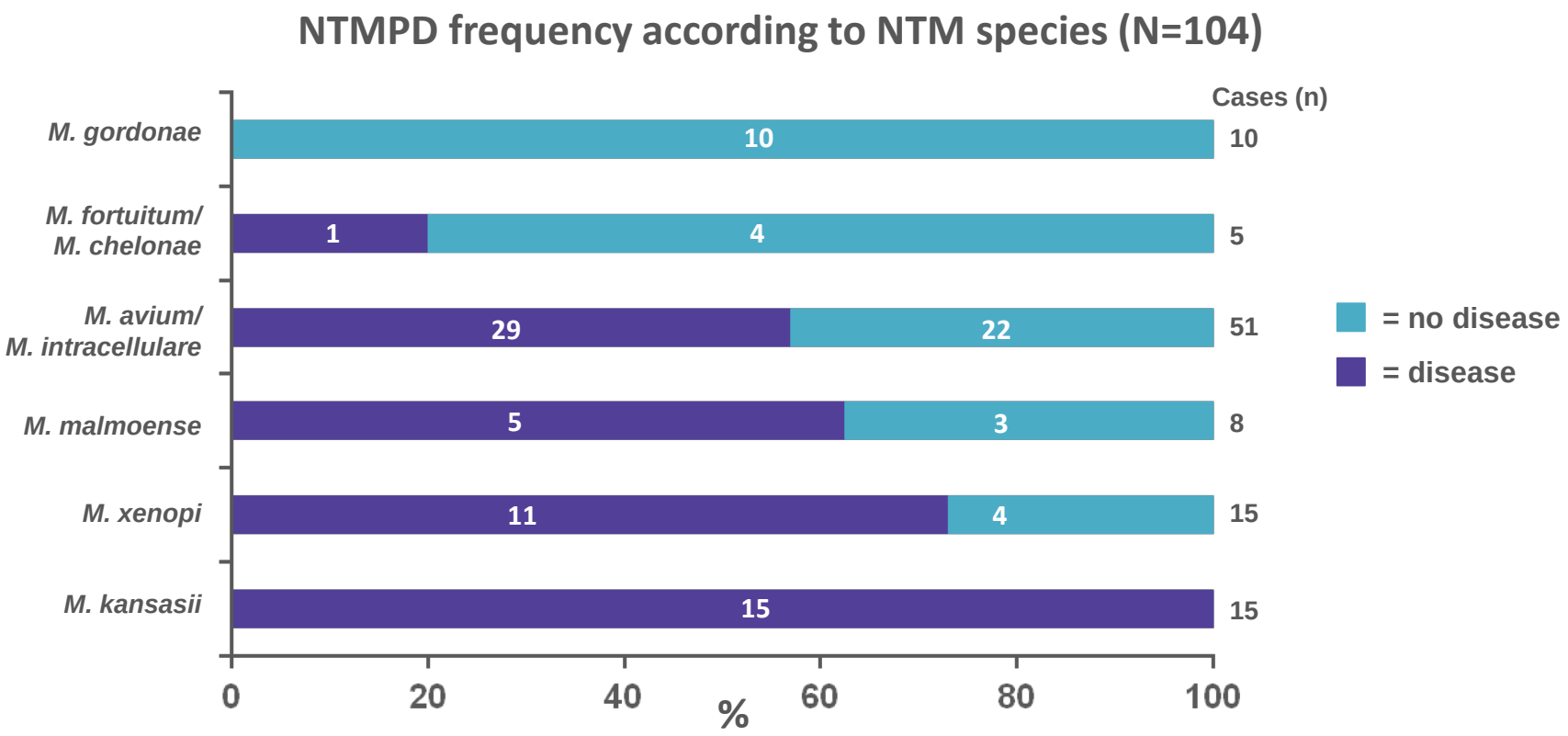
Growth rate classification	Common NTM*[1]	Uncommon NTM*[1]
Slow-growing mycobacteria (SGM)	***Mycobacterium avium* complex (MAC)** ***M. kansasii*** ***M. xenopi*** ***M. malmoense***	***M. asiaticum*** ***M. celatum*** ***M. fortuitum*** ***M. haemophilum*** ***M. scrofulaceum*** ***M. shimoidei*** ***M. simiae*** ***M. szulgai***
Rapid-growing mycobacteria (RGM)	***M. abscessus***	***M. fortuitium*** ***M. chelonae*** ***M. smegmatis***

- **~1/3 of identified species considered clinically significant[2]**
- **Growth rate classification (RGM vs SGM) has clinically important repercussions:[3]**
  - RGM and SGM differ in their antimicrobial susceptibility and treatment regimens; RGM are more likely to be resistant
  - SGM mostly responsible for pulmonary and lymphonodal diseases
  - RGM mostly affect cutis, bones and joints

*In alphabetical order; NTM, non-tuberculous mycobacteria.

1. Griffith DE, et al. Am J Respir Crit Care Med 2007; 175:367-416; 2. Tortoli E. FEMS Immunol Med Microbiol 2006; 48:159-78;
3. Tortoli E. Clin Microbiol Infect 2009; 15:906-10.

Virulence of NTM



NTM species isolated from pulmonary samples vary in virulence: Isolation of *M. kansasii* often correlates with disease

NTMPD, non-tuberculous mycobacterial pulmonary disease.
Adapted from Schönfeld N, et al. Pneumologie 2013; 67:605-33.

Adequate diagnosis and management of NTMPD are challenging

Late diagnosis due to non-specific symptoms and overlapping signs with underlying lung diseases[1]

Therapeutic challenge: Available treatment regimens, adapted from tuberculosis treatment, are complicated and costly undertakings, usually involving 1-2 years of combination antibiotic therapy, with attendant adverse effects, interactions and compliance issues[1,2,3]

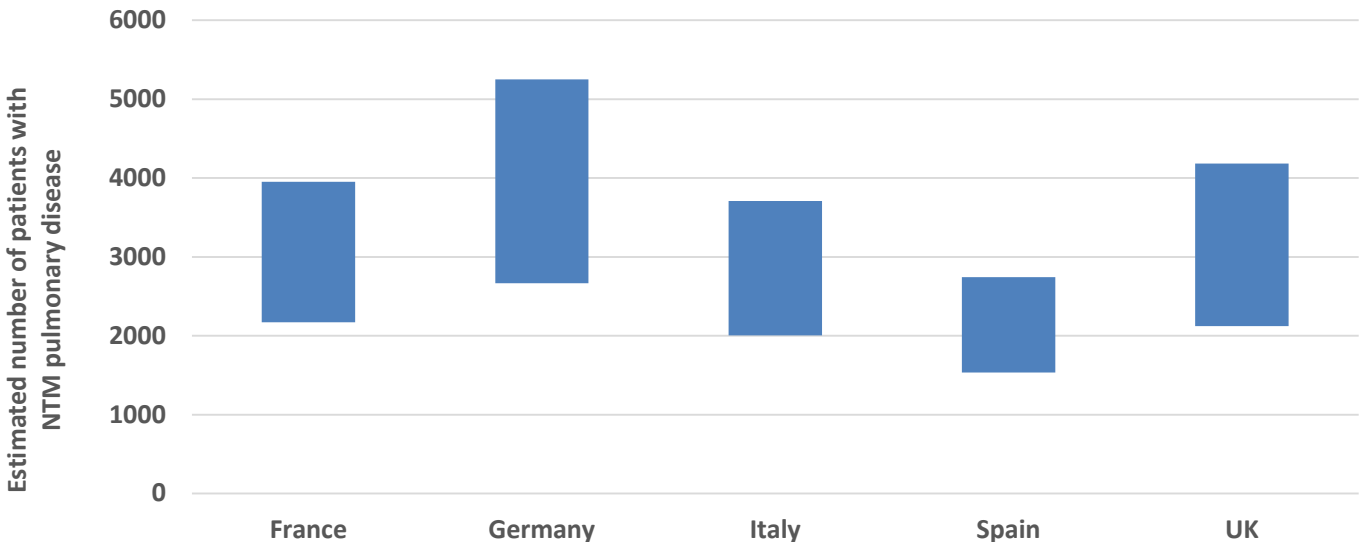
Poor adherence to evidence-based treatment guidelines promotes the development of antibiotic resistance[4]

For **refractory lung disease** only limited data exist on the efficacy of other drugs or interventions[5]

1. Griffith DE, et al. Am J Respir Crit Care Med 2007; 175:367-416; 2. Thomson RM, Yew WW. Respirology 2009; 14:12-26; 3. van Ingen J, et al. Drug Resist Updat 2012; 15:149-61; 4. Adjemian J, et al. Ann Am Thorac Soc 2014; 11:9-16; 5. Griffith DE, Aksamit TR. Curr Opin Infect Dis 2012; 25:218-27.

Prevalence of NTM pulmonary disease

Estimated range of NTM pulmonary disease cases in the EU5[1,2]

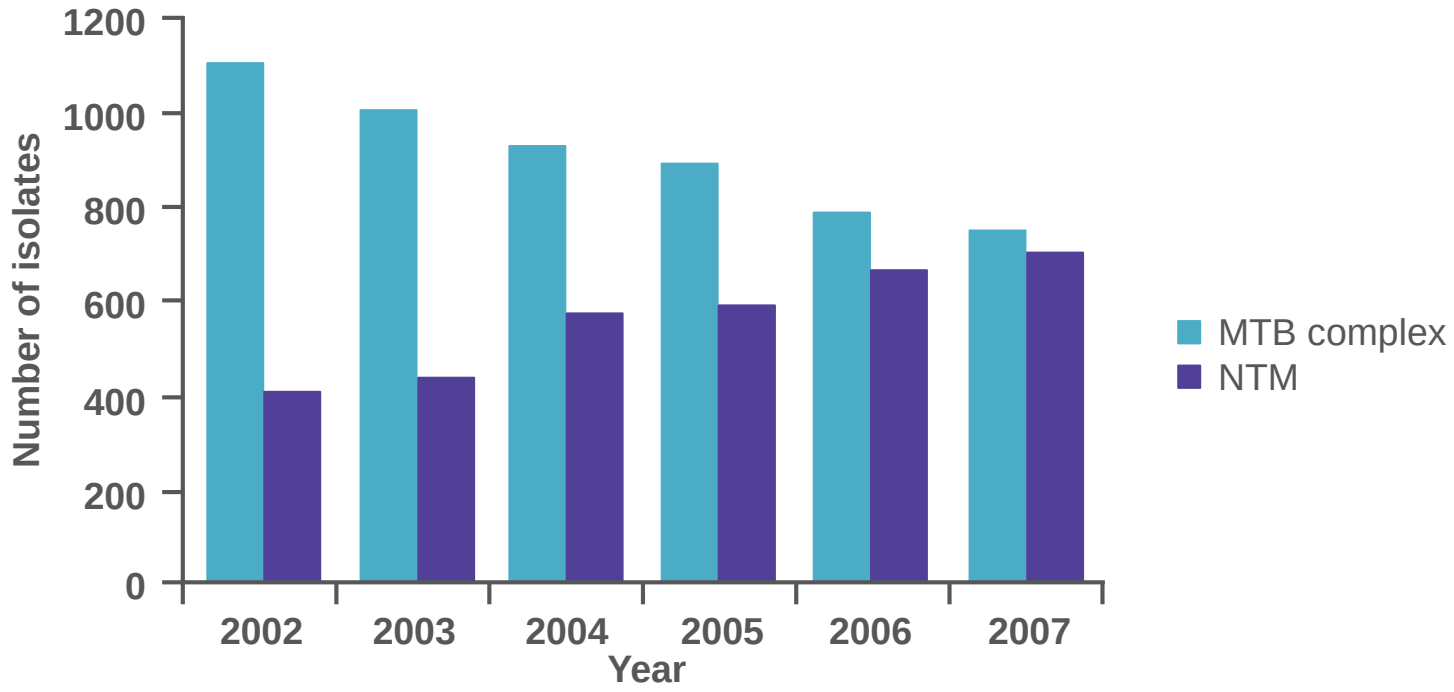


- A limited number of epidemiological data in Europe report the annual prevalence rate of NTM pulmonary disease ranging from 3.3 per 100,000 (based on ICD-10 codes in a German sick fund database for year 2014[1]) to 6.2 cases per 100,000 for EU5 countries (based on expert panel estimate in 2013[2]). This range is substantially below the threshold for orphan diseases as defined by the European Medicines Agency (5 cases per 10,000)[3]
- Across regions, prevalence estimates indicate that NTM lung infection rates (all species) have risen between 1.5 to 6-fold within the span of last 5-30 years[6], overtaking the prevalence of tuberculosis in recent years; prevalence is higher in females than males[7]

1. Wagner D, van Ingen J, Adjemian J, et al. Annual Prevalence and Treatment Estimates for Nontuberculous Mycobacterial Pulmonary Disease in Europe: A NTM-NET Collaborative Study (P1067). Paper presented at: European Respiratory Society International Meeting; September 6-10, 2014; Munich, Germany. 2. Ringshausen F, et al. Prevalence of Nontuberculous Mycobacterial Pulmonary Disease, Germany, 2009–2014. Emerging Infectious Diseases 2016, 22 (6): 1102-1105.3. European Medicines Agency: Public summary of opinion on orphan designation 1 October 2014 EMA/COMP/97247/2014 Rev.1 ; Available at:http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2014/05/WC500166122.pdf Accessed February 25, 2015. 4. Johnson, MM et al. Nontuberculous mycobacterial pulmonary infections, Review Article, 2014; J Thorac Dis. 2014;6(3):210-220. 5. Griffith DE, Aksamit TR. Therapy of refractory nontuberculous mycobacterial lung disease. Curr Opin Infect Dis. 2012;25(2):218-227. 6. Marras TK, Chedore P, Ying AM, Jamieson F. Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario, 1997 2003. Thorax. 2007 Aug;62(8):661-6. 7. https://ntmfacts.com/Susceptibility 8. Hoefsloot, W., et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. Eur Respir J. 2013 42(6): 1604-1613.

Prevalence of NTM vs. MTB infections

Patients with positive cultures for NTM or *Mycobacterium tuberculosis* (MTB) in The Netherlands[1]

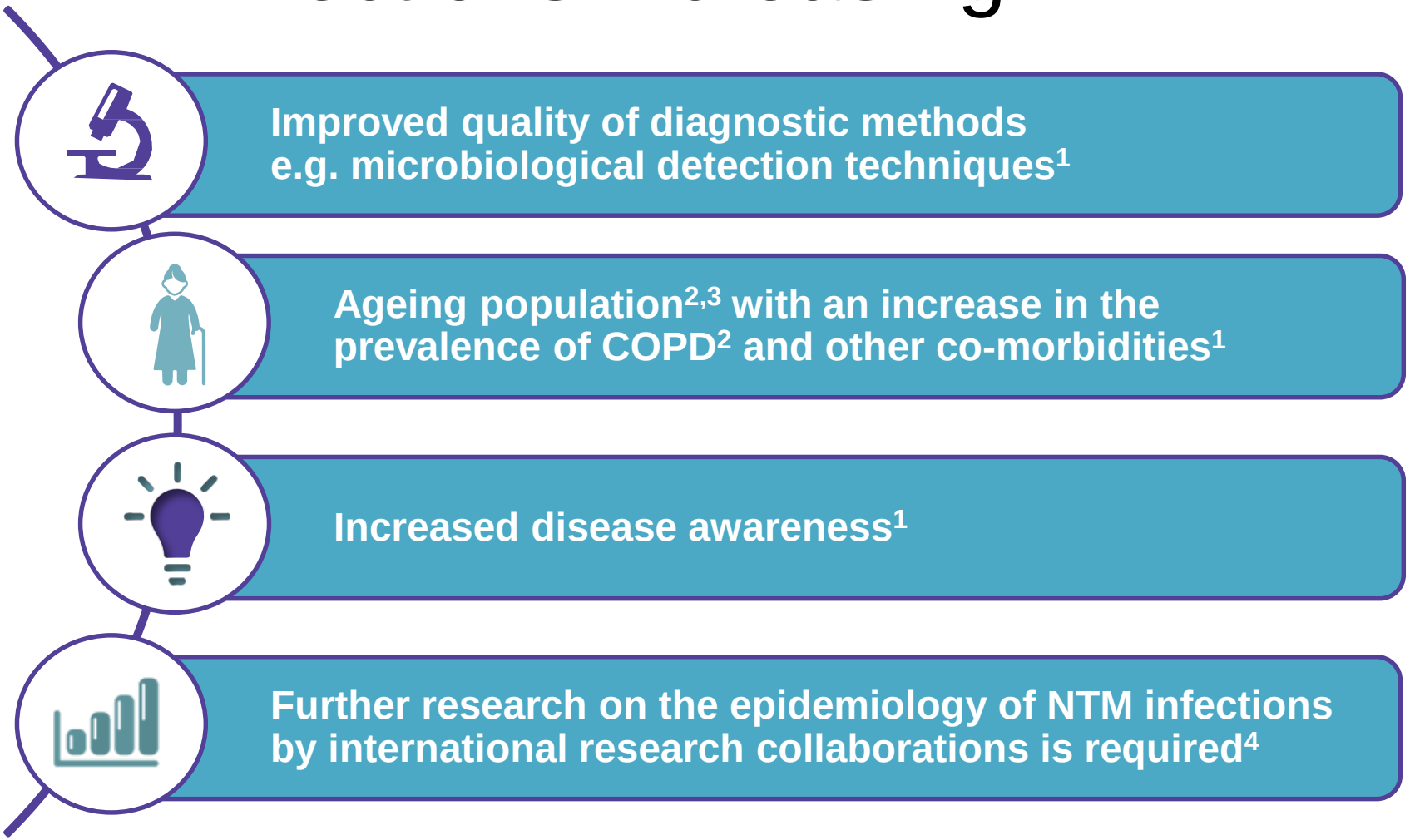


While the incidence of tuberculosis has decreased or stabilized in many industrialized countries the rate of NTM lung infections has increased[1,2]

MTB, *Mycobacterium tuberculosis*; NTM, non-tuberculous mycobacteria.

1. Adapted from Arend SM, et al. Curr Opin Pulm Med 2009; 15:201-8; 2. Marras TK, et al. Thorax 2007; 62:661-6.

Why are the rates of NTM infections increasing?

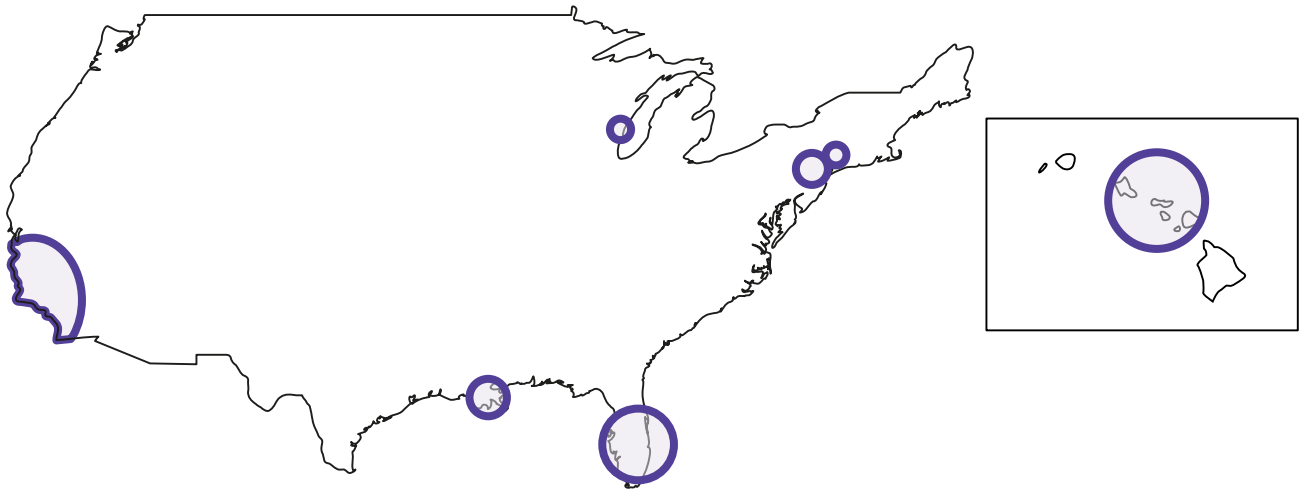


COPD, chronic obstructive pulmonary disease; NTM, non-tuberculous mycobacteria.

1. McShane PJ, Glassroth J. Chest 2015; DOI:10.1378/chest.15-0458; 2. van Ingen J, et al. Int J Tuberc Lung Dis 2010; 14:1176-80;
3. Al-Houqani M, et al. Chest 2012; 141:190-7; 4. Ringshausen FC, et al. BMC Infect Dis 2013; 13: 231.

Environmental risk factors for NTMPD

Areas in the United States with a high risk for a NTMPD infection



Environmental risk factors include:

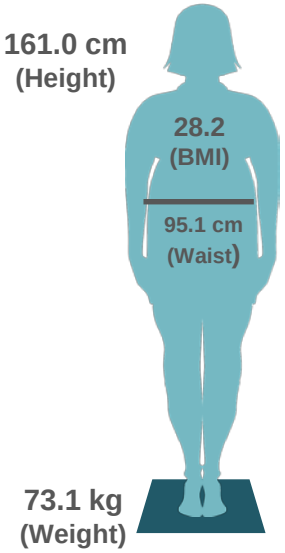
- **Greater population density**
- **Higher education and income**
- **High evapotranspiration and percentages covered by surface water**

NTMPD, non-tuberculous mycobacterial pulmonary disease.
Adapted from Adjemian J, et al. Am J Respir Crit Care Med 2012; 186:553-8.

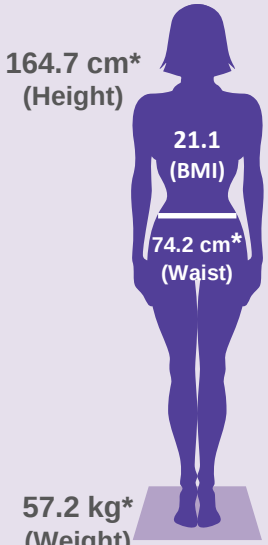
Host risk factors – nodular-bronchiectatic NTM disease

Body morphotype of patients with active NTM infection compared to healthy controls[1]

Matched control subjects*



Female patients (n=60)



- Lean and tall statue[1]
- Low BMI[1,2]
- Skeletal abnormalities[1,2]
  - Scoliosis
  - Pectus excavatum
- Mitral valve collapse[1]
- Among caucasians, women have a higher prevalence than men[3]

There is an association between nodular-bronchiectatic NTMPD and a particular body habitus (e.g., pectus excavatum, scoliosis, mitral valve prolapse) – predominantly in postmenopausal women[1,4]

*NHANES age- and ethnicity-matched female control subjects (2001-2002 data); BMI, Body-Mass-Index; NTMPD, non-tuberculous mycobacterial pulmonary disease.

1. Adapted from Kim RD, et al. Am J Respir Crit Care Med 2008; 178:1066-74; 2. Dirac MA, et al. Am J Respir Crit Care Med 2012; 186:684-91; 3. Adjemian J, et al. Am J Respir Crit Care Med 2012; 185:881-6; 4. Griffith DE, et al. Am J Respir Crit Care Med 2007; 175:367-416.

Host risk factors – fibrocavitary NTM disease

- Males in their late 40s and early 50s[1]

- History of cigarette smoking
- Often, excessive alcohol use[1]

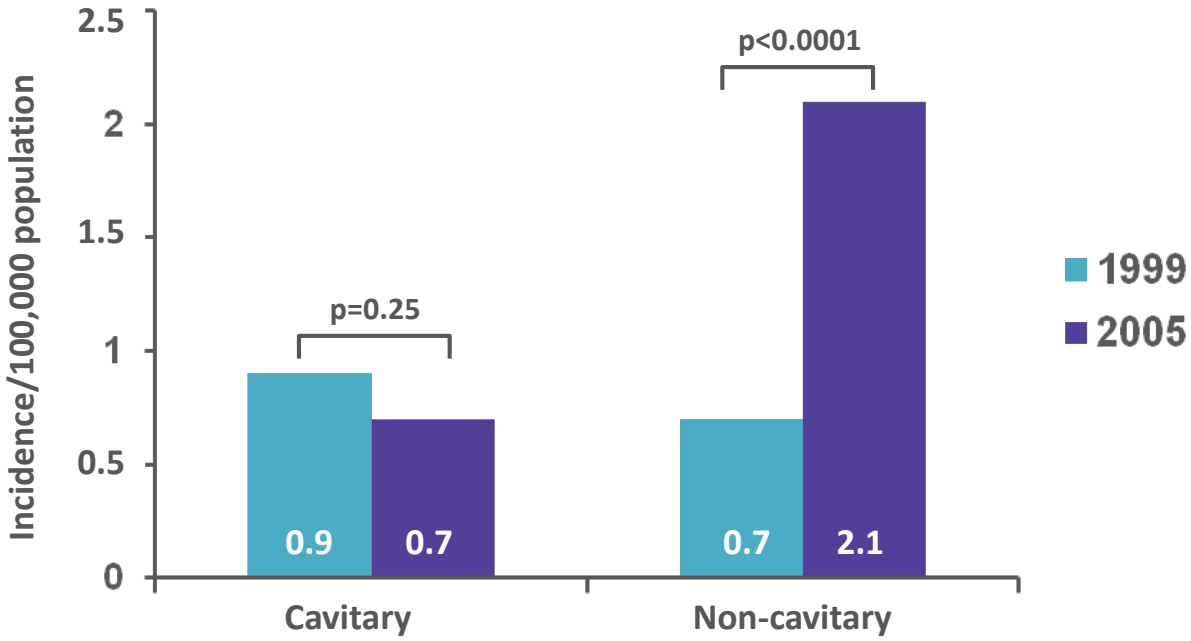
- Structural lung disease e.g. COPD, silicosis or prior tuberculosis[2]

Fibrocavitary NTMPD commonly occurs in older males, often smokers, with a history of underlying lung disease[1,2]

1. Griffith DE, et al. Am J Respir Crit Care Med 2007; 175:367-416; 2. Johnson MM, Odell JA. J Thorac Dis 2014; 6:210-20.

“The pattern of disease has changed over time …

Changes in radiological appearance of NTMPD cases in Queensland, Australia between 1999 and 2005



… from cavitary disease in middle-aged men who smoke to the nodular-bronchiectatic form of disease in older women”

NTMPD, non-tuberculous mycobacterial pulmonary disease.
Adapted from Thomson RM, et al. Emerg Infect Dis 2010; 16:1576-83.

Genetic and iatrogenic factors associated with NTMPD

Genetic predisposition

- **Mutation in CFTR gene[1]**
- **Familial clustering of NTMPD**
  - Majority of cases in non-smoking siblings with high prevalence of scoliosis and CFTR mutations[2]

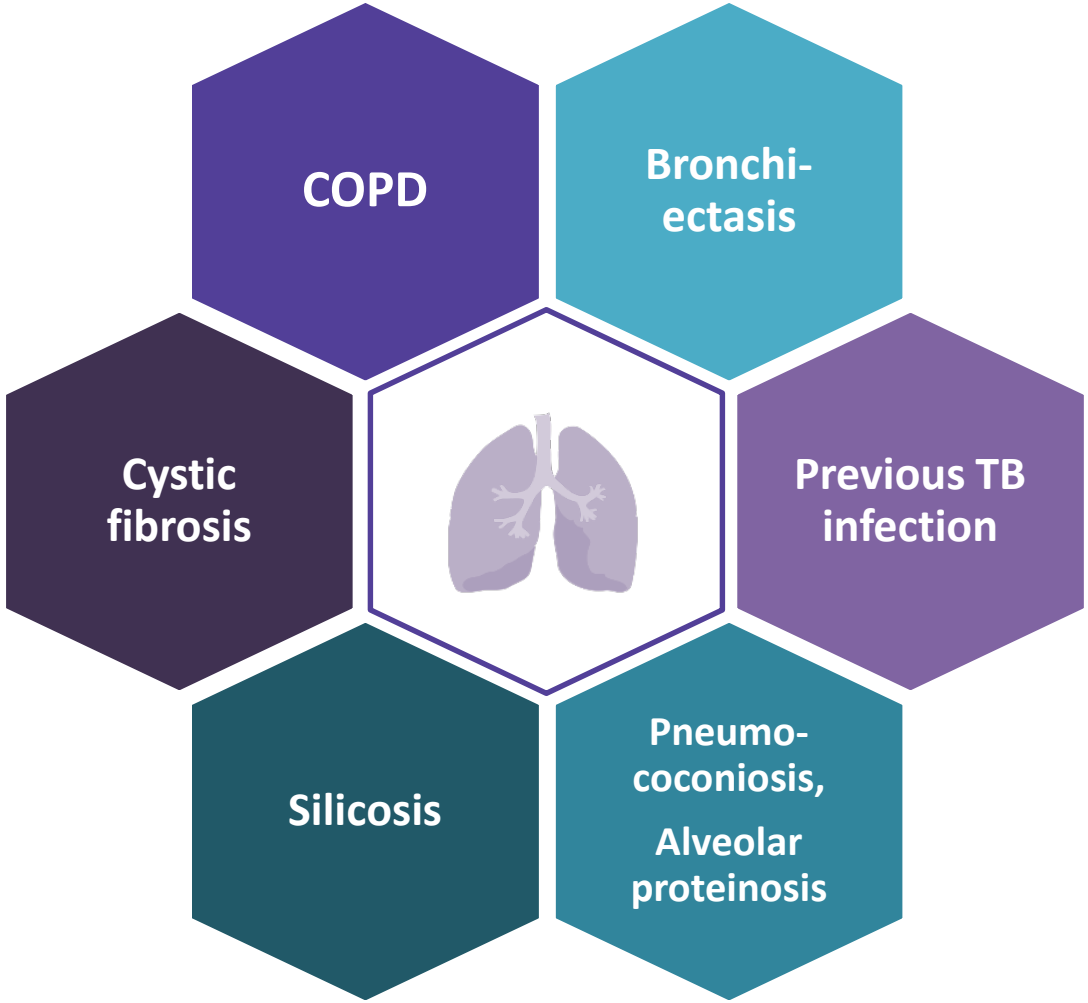
Iatrogenic factors

- **Immunosuppressive treatments associated with NTMPD include:**
  - COPD patients treated with inhaled corticosteroids[3]
  - DMARDs, anti-TNF-α therapy, oral corticosteroids[4,5]
- **Organ transplantation[6,7]**

CFTR, cystic fibrosis conductance regulator; DMARD, disease-modifying antirheumatic drug; NTMPD, non-tuberculous mycobacterial pulmonary disease; TNF, tumor necrosis factor.

1. Kim RD, et al. Am J Respir Crit Care Med 2008; 178:1066-74; 2. Colombo RE, et al. Chest 2010; 137:629-34; 3. Andrejak C, et al. Thorax 2013; 68:256-62; 4. Winthrop KL, et al. Emerg Infect Dis 2009; 15:1556-61; 5. Brode SK, et al. Thorax; 70:677-82; 6. Knoll BM, et al. Transpl Infect Dis 2012; 14:452-60; 7. Daley CL. Curr Opin Organ Transplant 2009; 14:619-24.

Bronchopulmonary factors associated with NTMPD

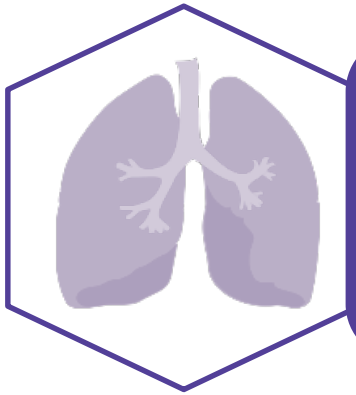


COPD, chronic obstructive pulmonary disease; NMTNPD, non-tuberculous mycobacterial pulmonary disease; TB, tuberculosis.
Sexton P, Harrison AC. Eur Respir J 2008; 31:1322-33.

NTMPD can become a progressive lung disease

NTMPD can become a progressive lung disease[1,2]

If left untreated, MAC lung disease can result in extensive cavitary lung destruction and respiratory failure[2]



Decline in lung function among NTMPD patients (n=68)*[3]

- Mean reduction in FEV_1 was 48 mL/year
- Normal range = 28.4-35.6 mL/year

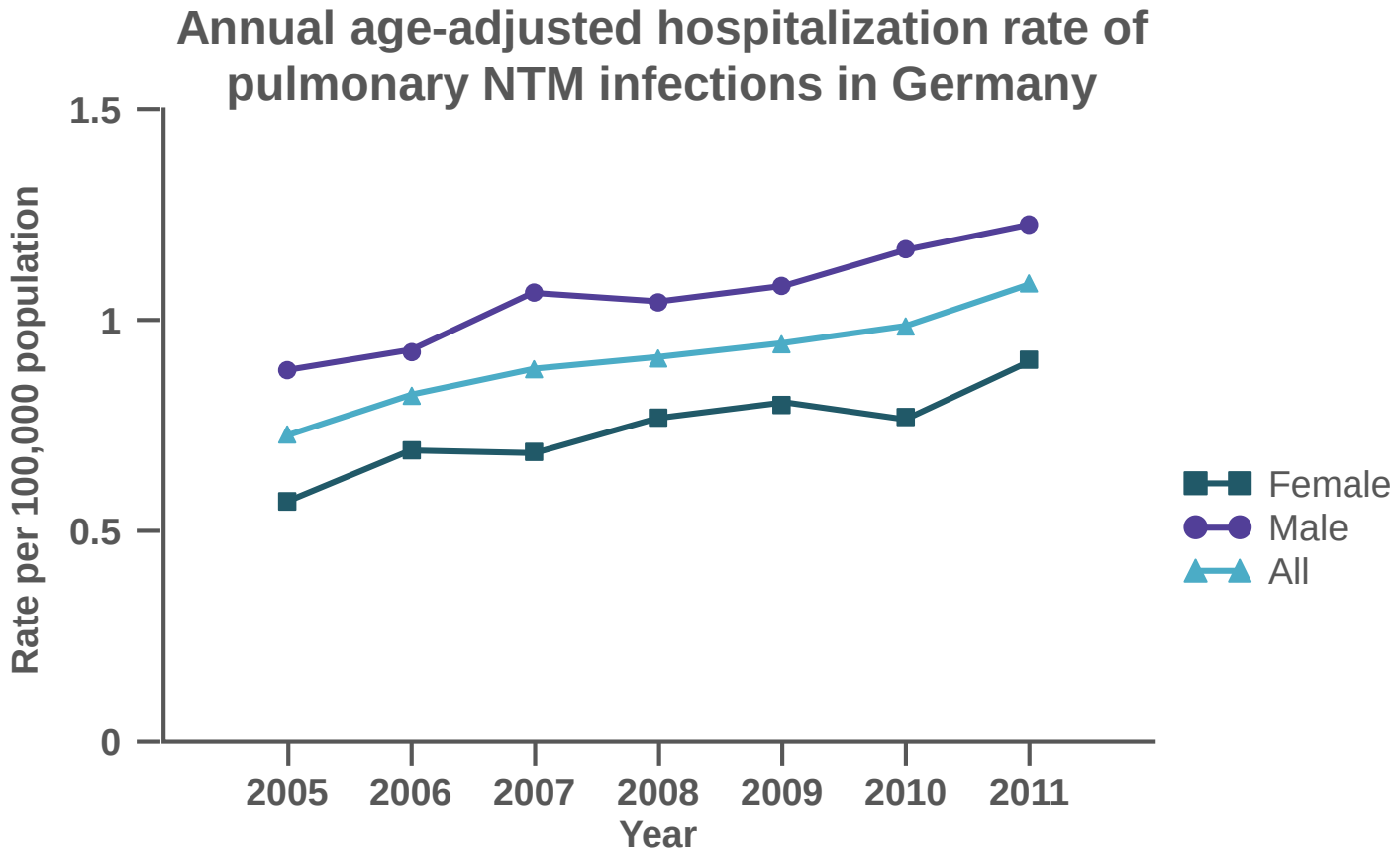
Impaired health-related quality of life in patients with NTMPD is significantly associated with decline in lung function[4]

* Study from Taiwan (01/2000 – 04/2011).

FEV_1, forced expiratory volume in 1 sec; MAC, *Mycobacterium avium* complex; NTMPD, non-tuberculous mycobacterial pulmonary disease.

1. Weiss CH, Glassroth J. Expert Rev Respir Med 2012; 6:597-612; 2. Griffith DE, et al. Am J Respir Crit Care Med 2007; 175:367-416; 3. Lee MR, et al. PLoS One 2013; 8:e58214; 4. Mehta M, Marras TK. Respir Med 2011; 105:1718-25.

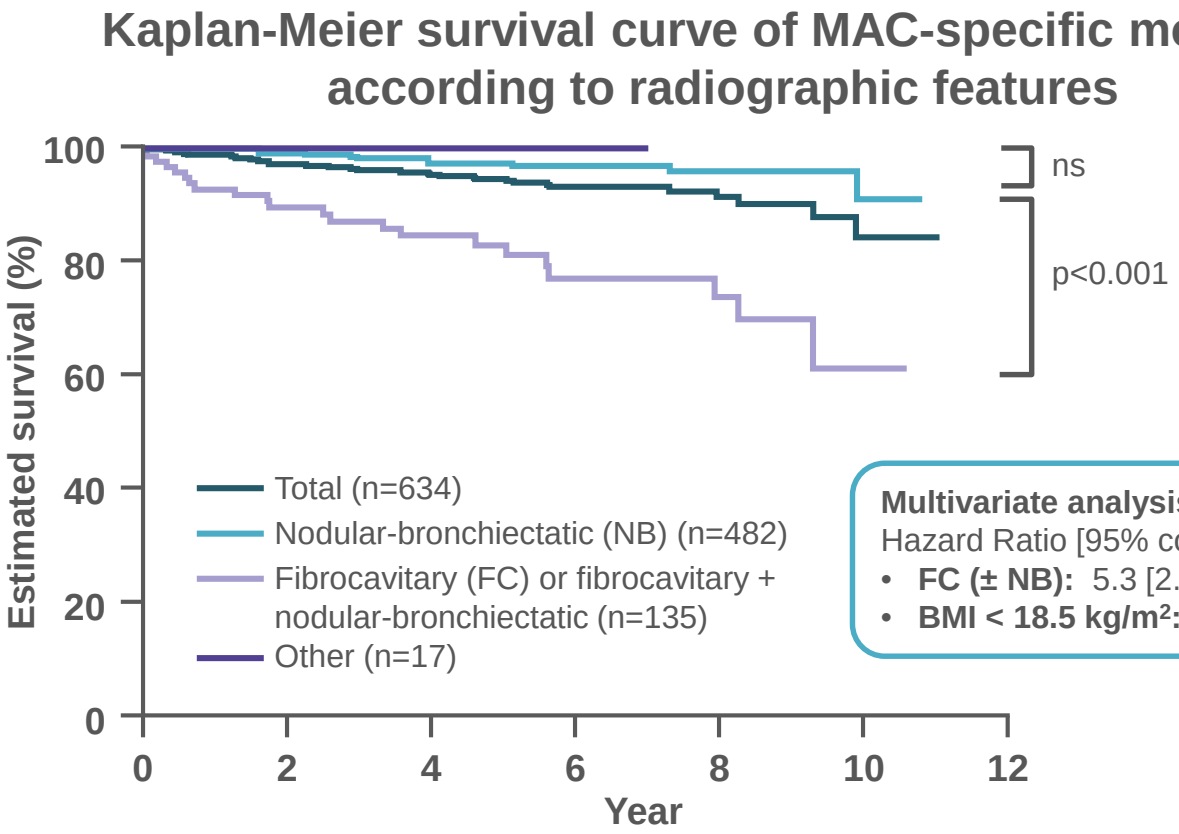
Increasing hospitalization rate for NTMPD



From 2005 to 2011, the annual number of NTM-infection-associated hospitalizations in Germany increased by 4.9% on average ($p<0.00001$)

NTMPD, non-tuberculous mycobacterial disease.
Adapted from Ringshausen FC, et al. BMC Infect Dis 2013; 13:231.

Mortality associated with the different pulmonary NTMPD manifestations caused by MAC



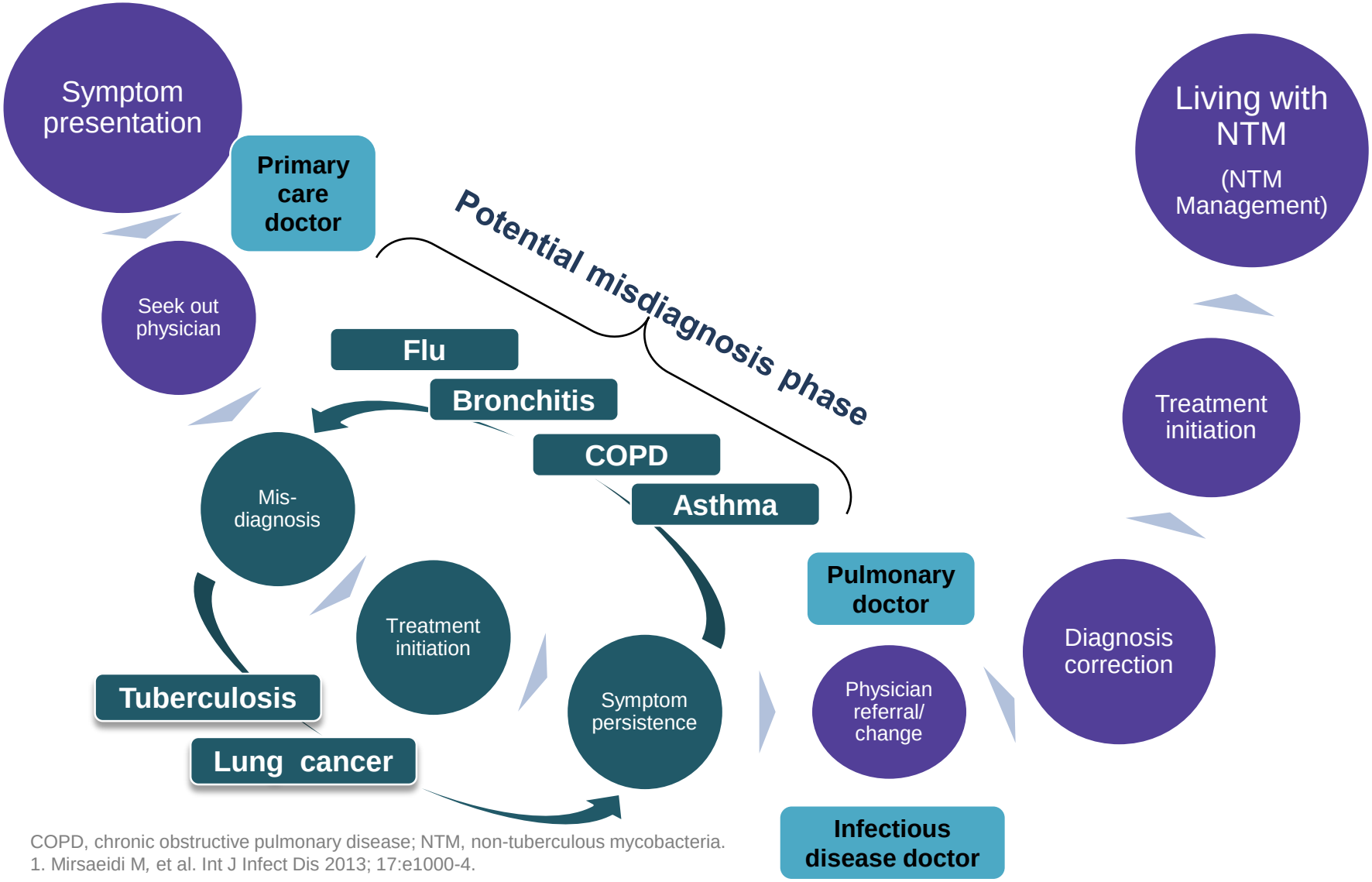
Multivariate analysis of risk factors*
Hazard Ratio [95% confidence interval]
- **FC (± NB):** 5.3 [2.634-10.763], p<0.001
- **BMI < 18.5 kg/m²:** 4.3 [1.655-11.270], p=0.003

Fibrocavitary disease or fibrocavitary + nodular-bronchiectatic disease and low body mass index were associated with greater mortality

*Multivariate Cox proportional hazard model; BMI, body mass index; FC, fibrocavitary; MAC, *Mycobacterium avium* complex; NB, nodular-bronchiectatic; NTMPD, non-tuberculous myocobacterial pulmonary disease; ns, not significant.

Adapted from Hayashi M, et al. Am J Respir Crit Care Med 2012; 185:575-83.

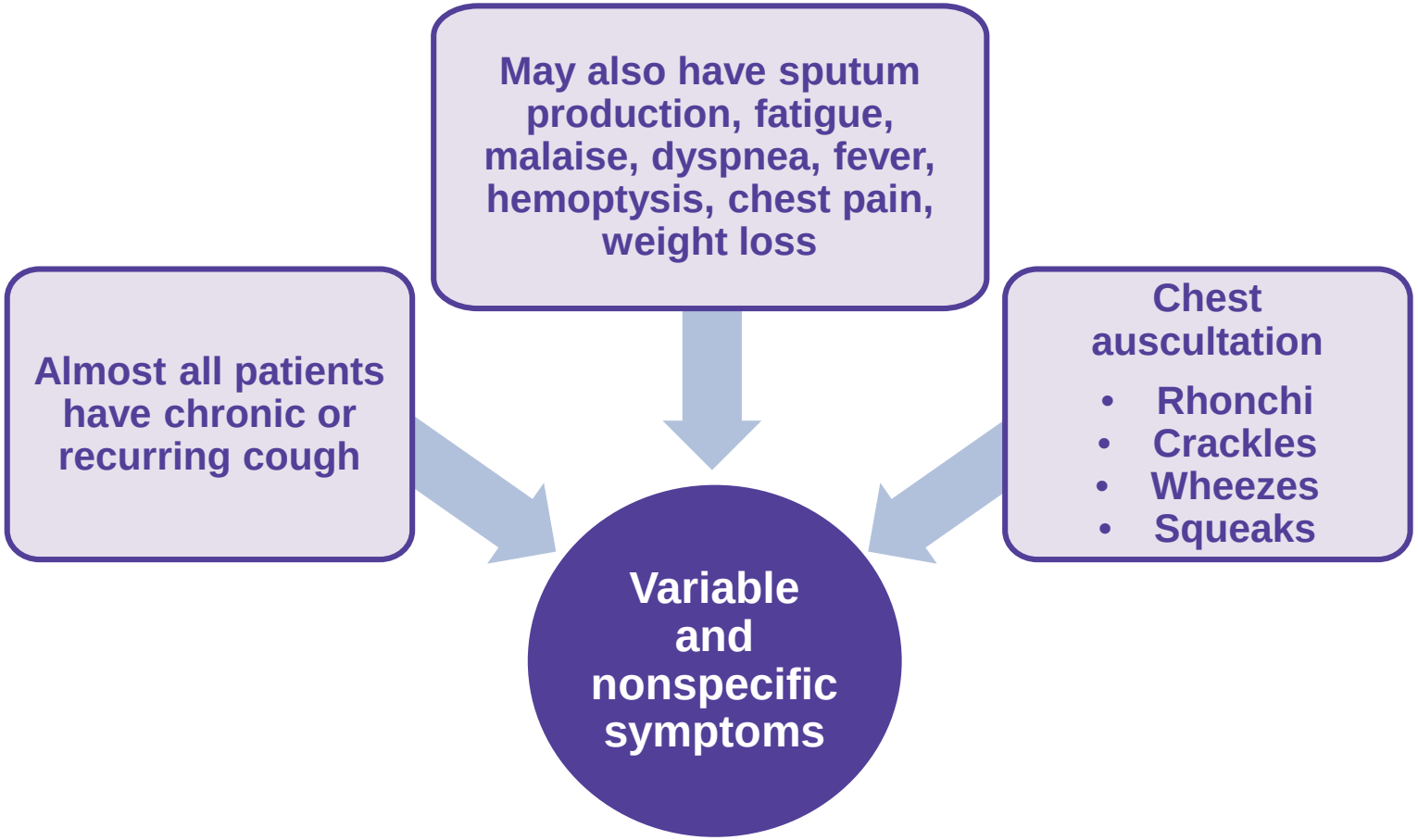
The patient journey is typically long and difficult
Only a few are diagnosed correctly from the outset[1]



COPD, chronic obstructive pulmonary disease; NTM, non-tuberculous mycobacteria.

1. Mirsaeidi M, et al. Int J Infect Dis 2013; 17:e1000-4.

Clinical criteria



Griffith DE, et al. Am J Respir Crit Care Med 2007; 175:367-416.

Microbiologic criteria: Culture of NTM essential for diagnosis

DIAGNOSIS REQUIRES:

Sputum:
Positive NTM culture from ≥3 early morning samples collected on different days

OR

Lung biopsy:
Mycobacterial histopathologic features and positive NTM culture

OR

Bronchial wash/lavage:
Positive NTM culture from ≥1 sample

OR

Combination of samples
Mycobacterial histopathologic features on lung biopsy and ≥1 NTM culture-positive sputum or bronchial wash sample

NTM, non-tuberculous mycobacteria.
Griffith DE, et al. Am J Respir Crit Care Med 2007; 175:367-416.

Radiographic criteria

Radiographic criteria

- Nodular or cavitary opacities on chest radiograph
- **Or** multifocal bronchiectasis with multiple small nodules on HRCT scan
- **And** exclusion of other causes

Fibrocavitary disease

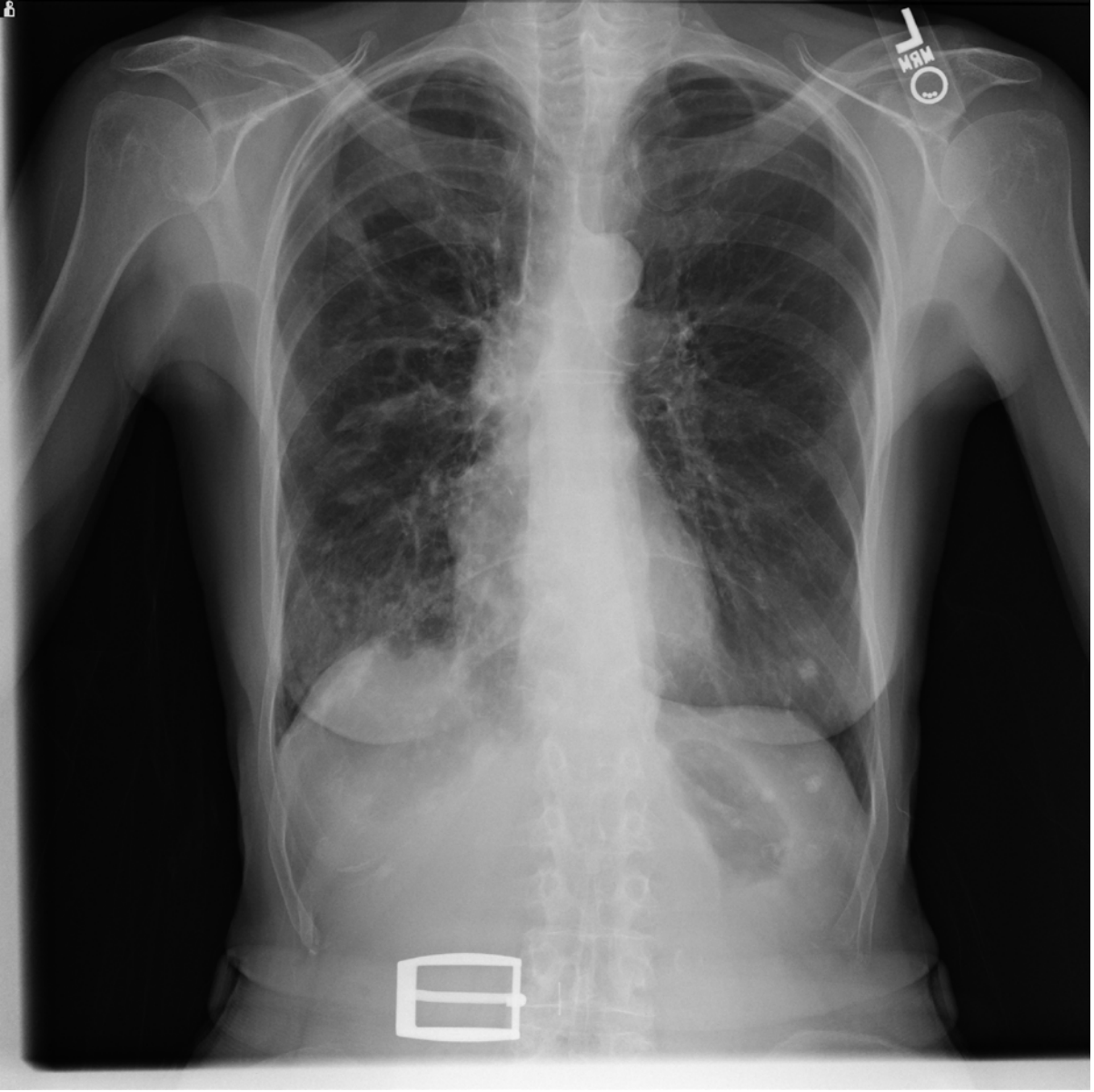
•Can be evaluated using plain chest radiography

Nodular-bronchiectatic disease

- Chest HRCT indicated for evaluation

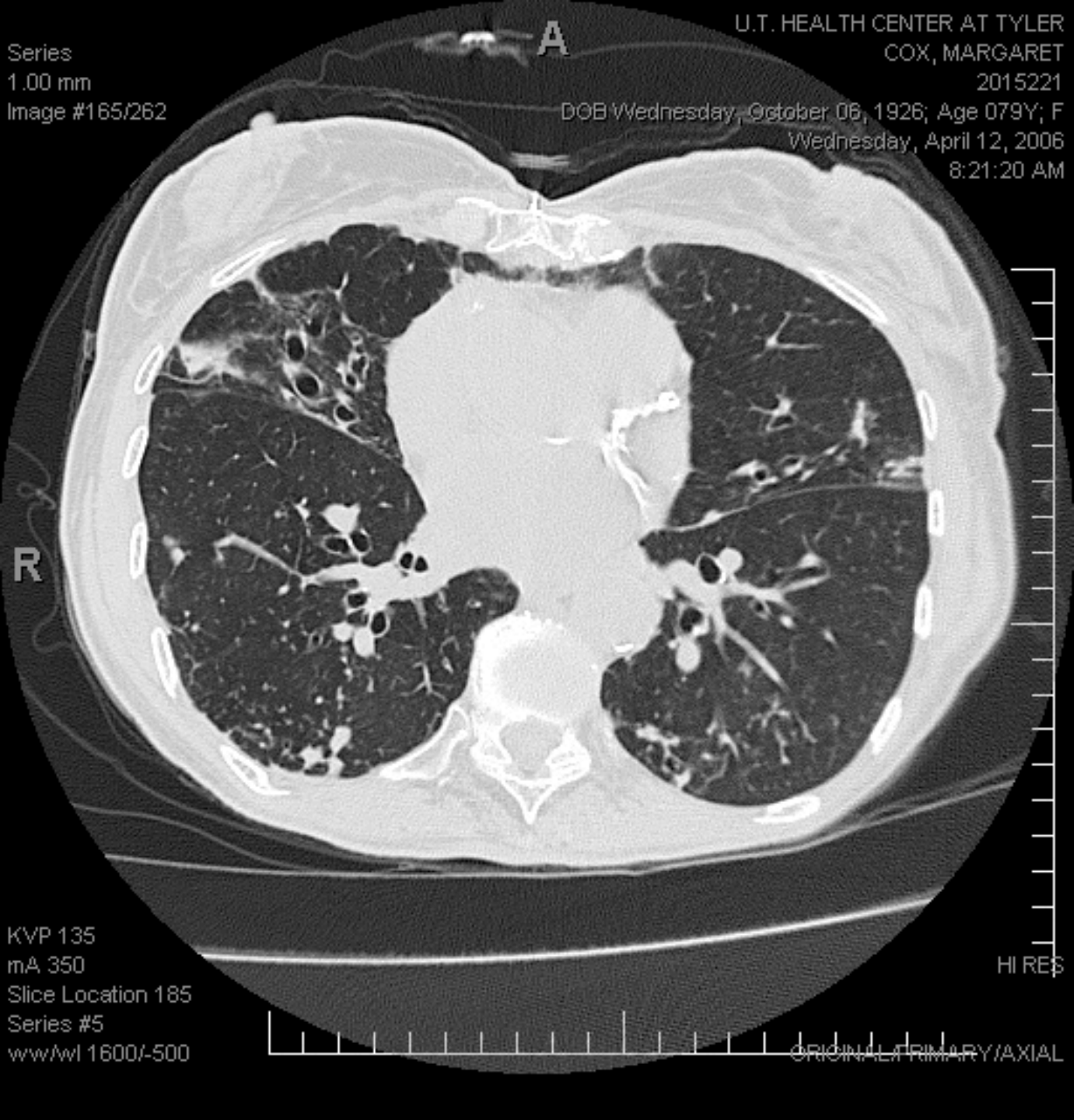
HRCT, high resolution computed tomography.

Griffith DE, et al. Am J Respir Crit Care Med 2007; 175:367-416.

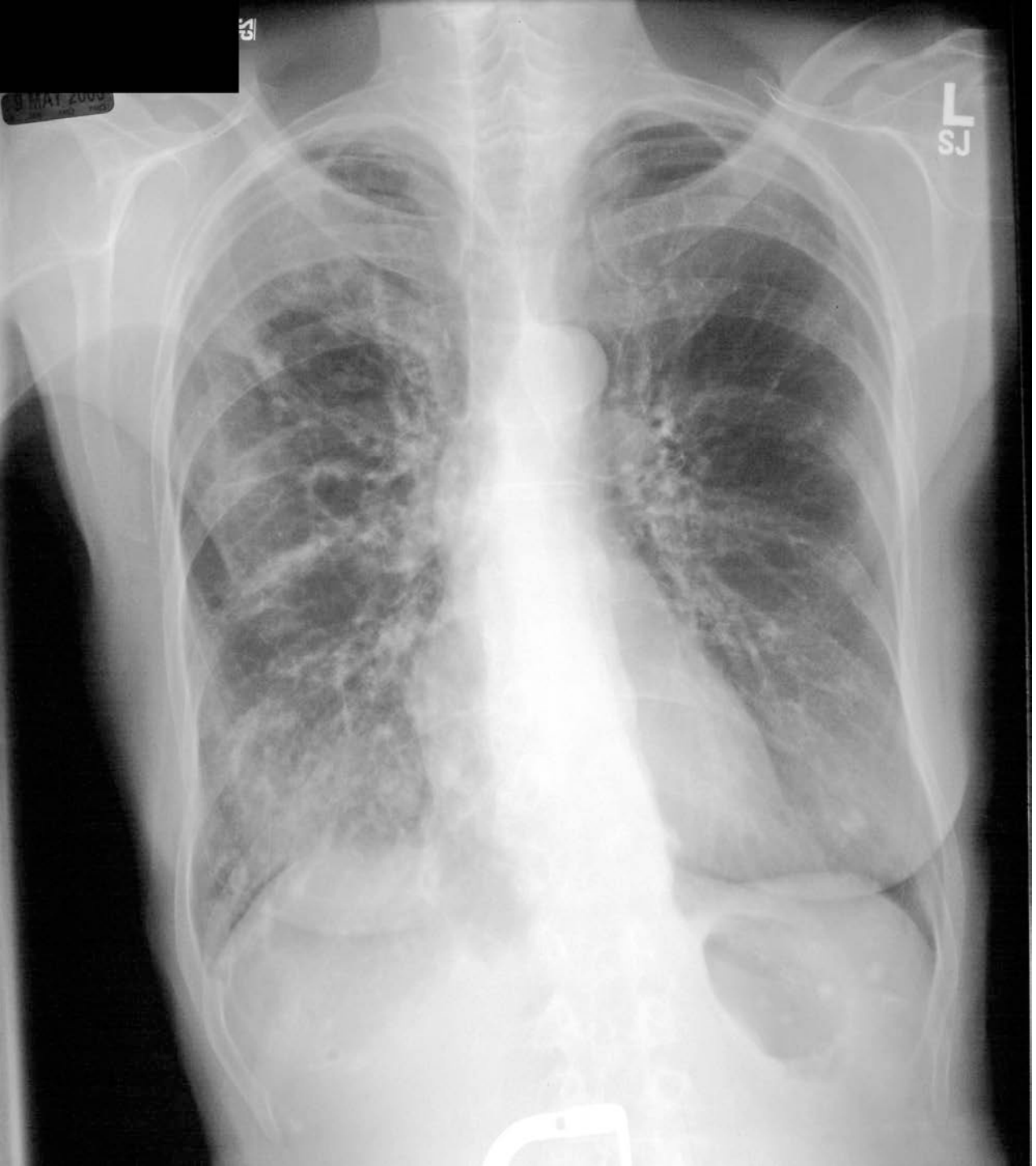


Rx torace: 73 anni, donna, non fumatrice.

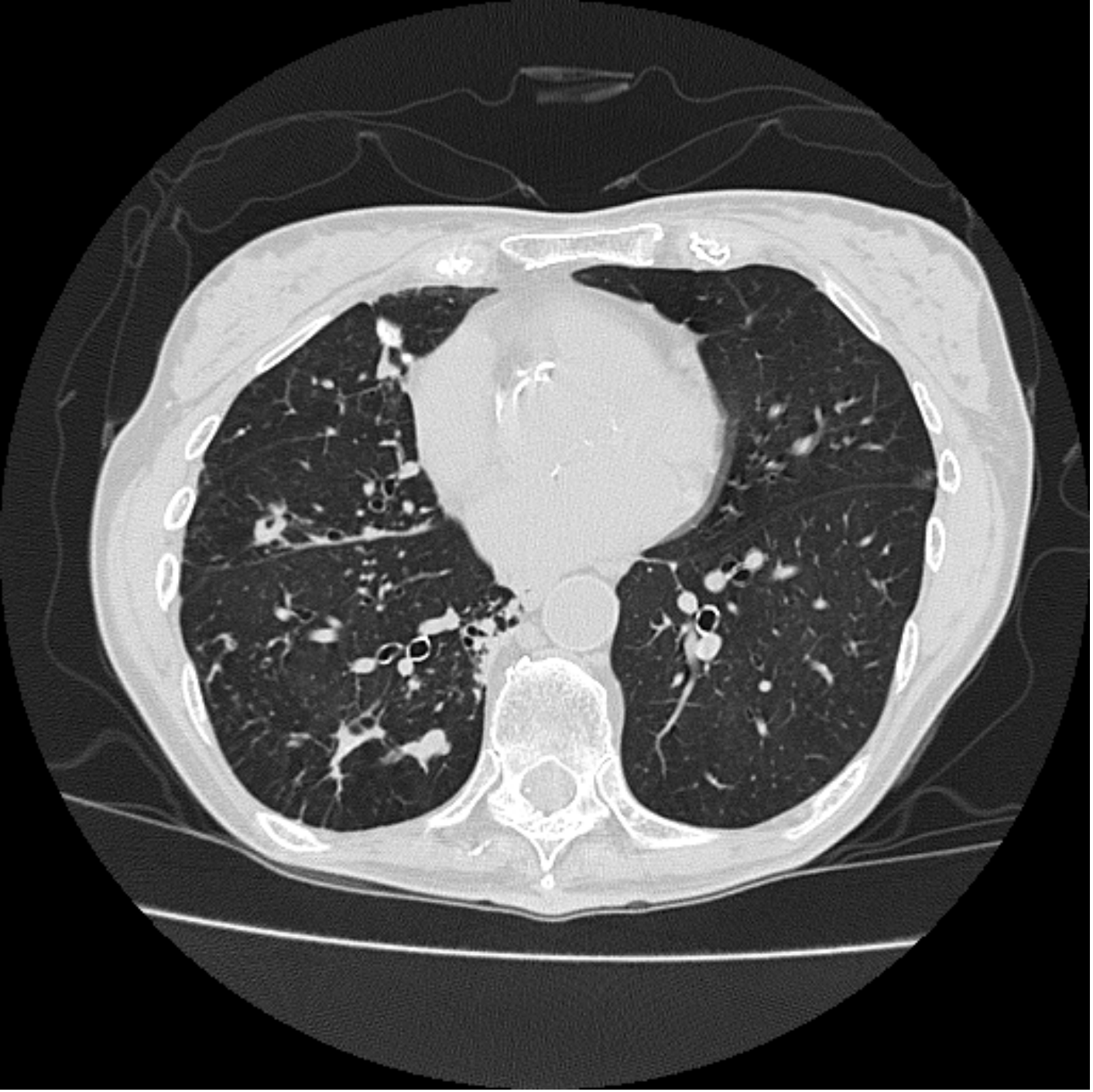
Micobatteriosi polmonare da MAC addensamenti nodulari bilaterali e reticolonodulari



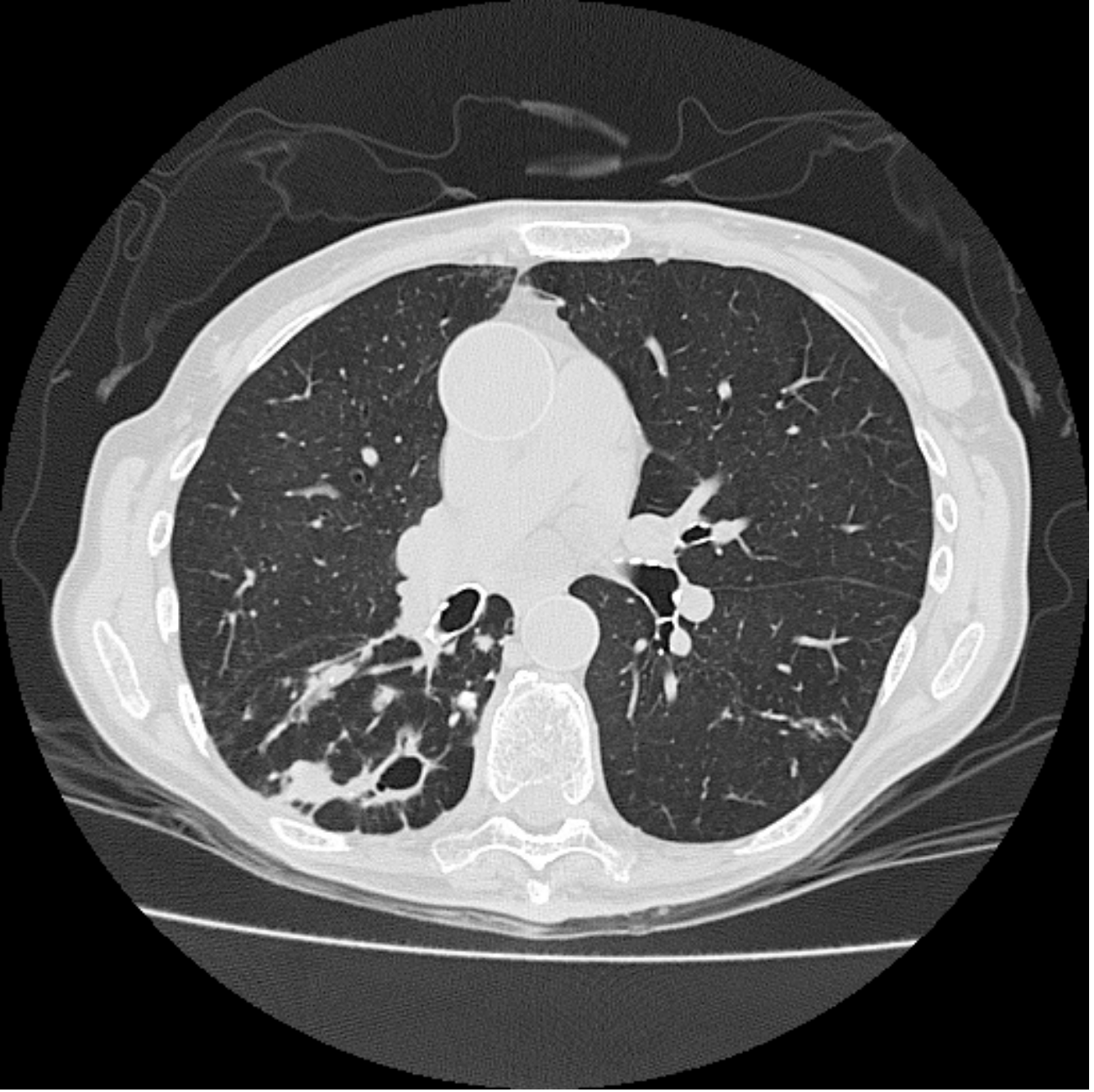
HRCT della stessa pz. che mostra gli addensamenti nodulai bilaterali e le bronchiectasie.



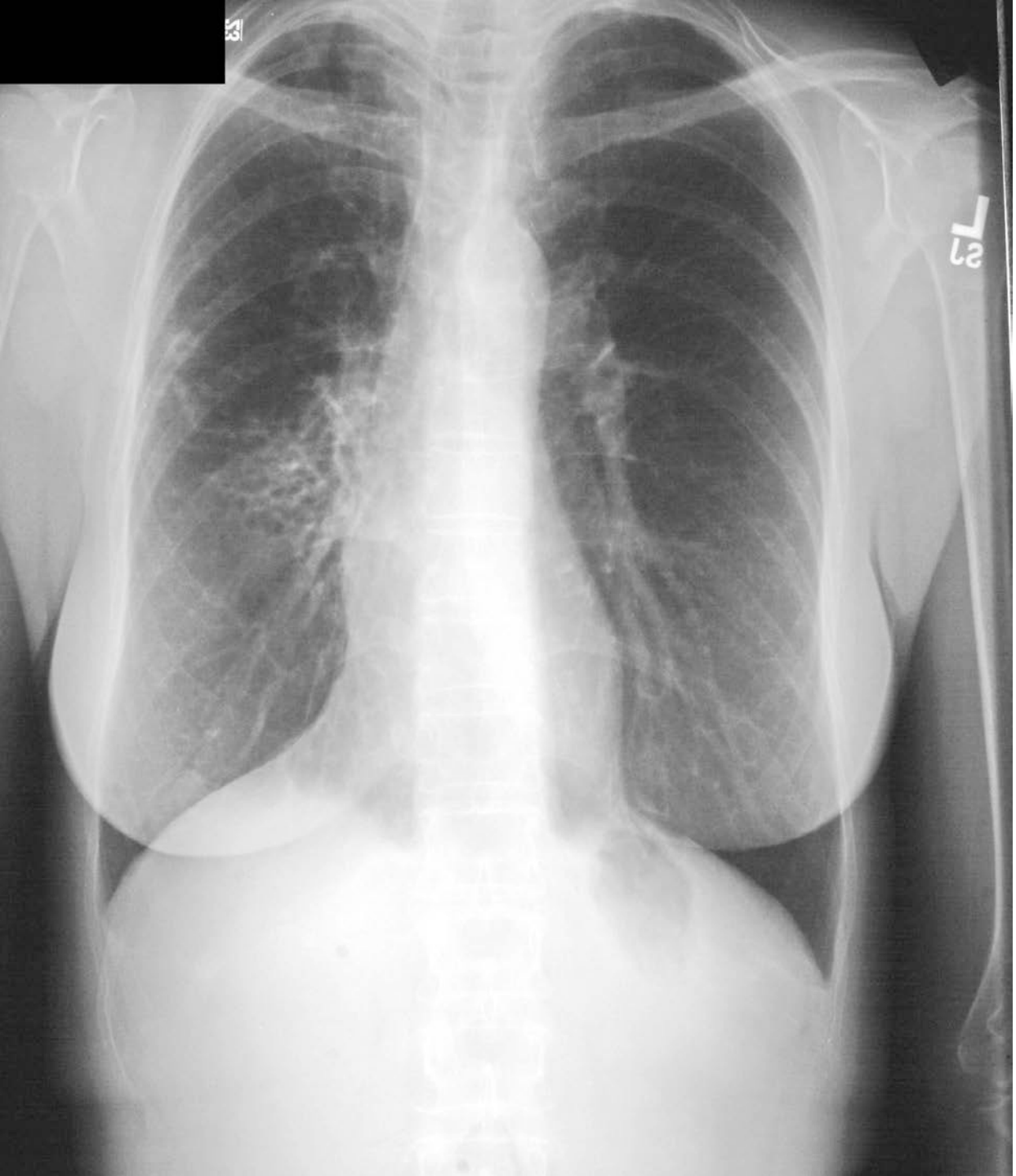
RX torace: 79 anni donna non fumatrice con micobatteriosi polmonare da MAC. Addensamenti nodulari, reticolonodulari ed escavazioni.



HRCT della stessa pz.che mostra i noduli e le bronchiectasie.

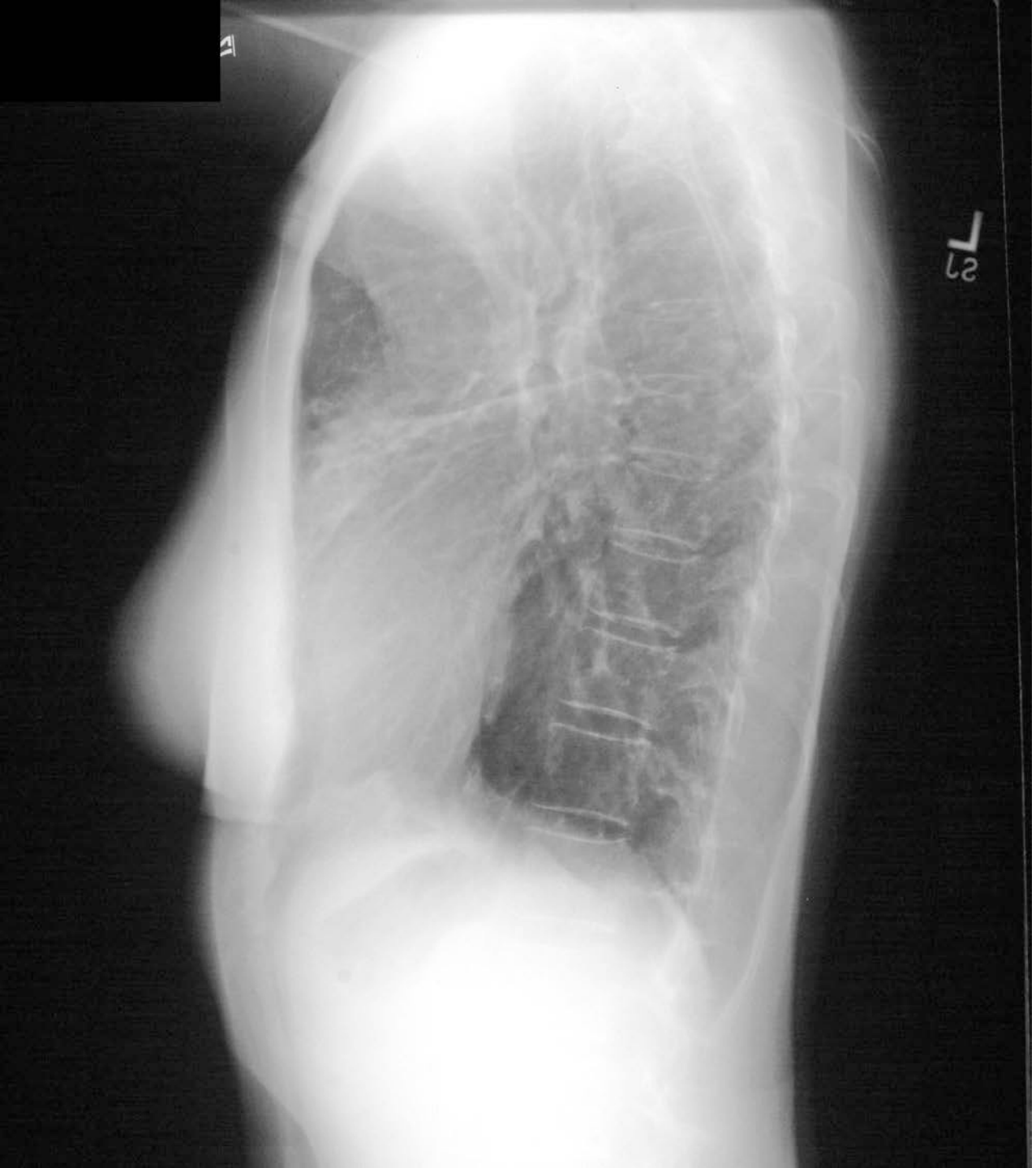


HRCT della stessa pz.che mostra i noduli, le bronchiectasie e le escavazioni.

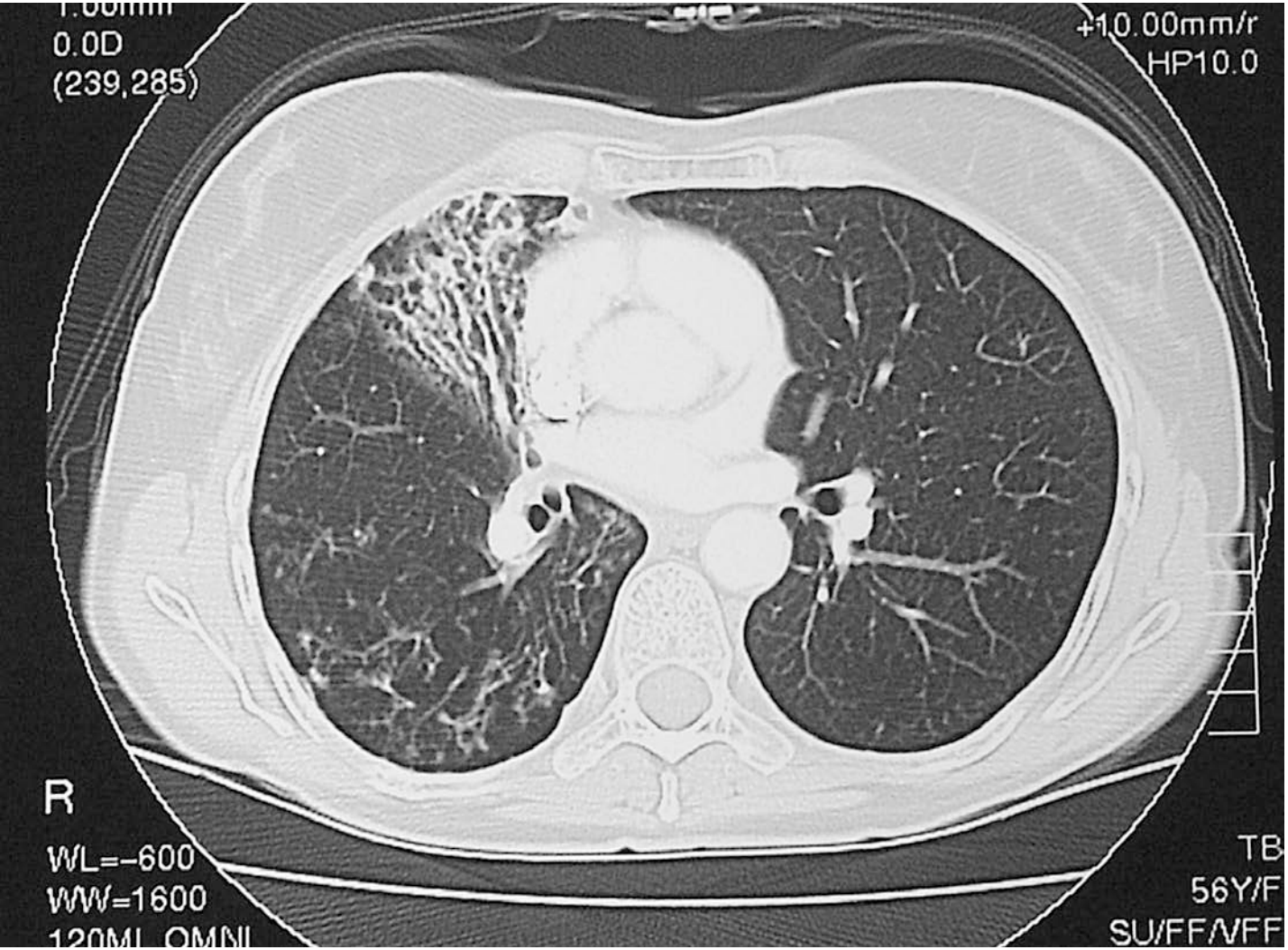


RX torace: donn, 55 anni, non fumatrice.

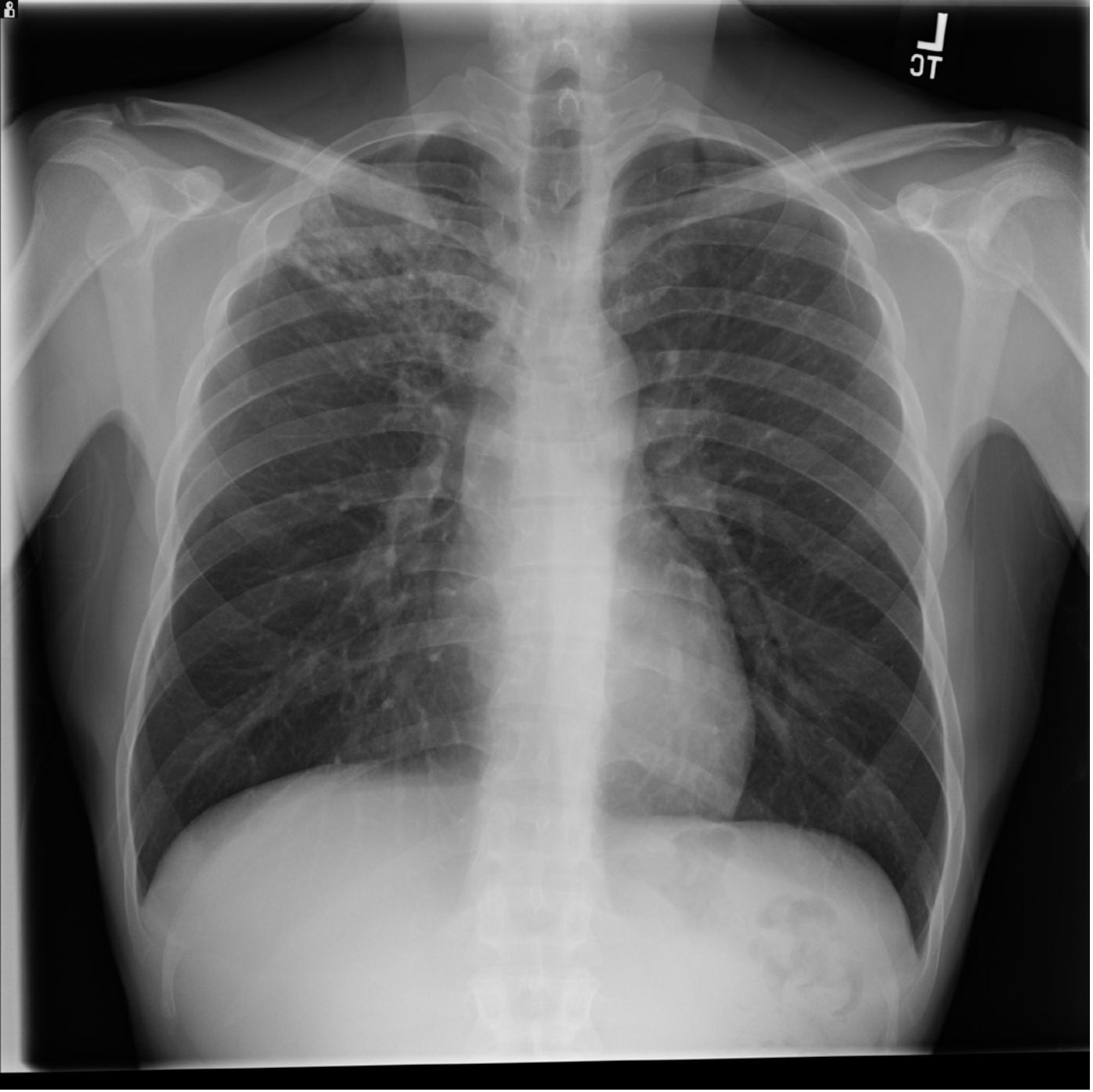
Micobatteriosi polmonare da MAC. Addensamento polmonare escavato del lobo medio.



Stessa pz.
Proiezione laterale.

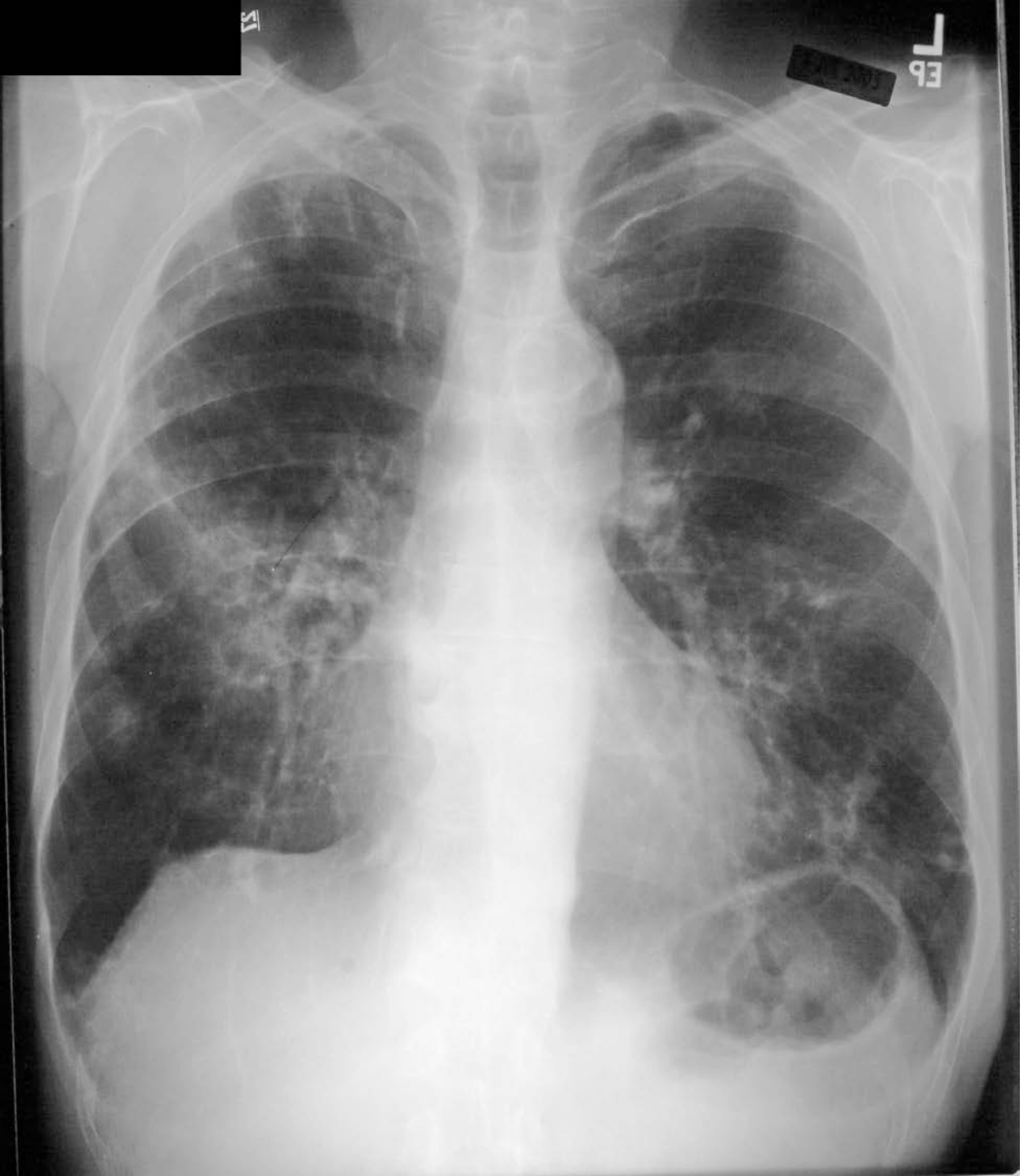


HRCT della stessa pz. Alterazioni bronchiectasiche del lobo medio e nodulazioni del lobo inferiore.



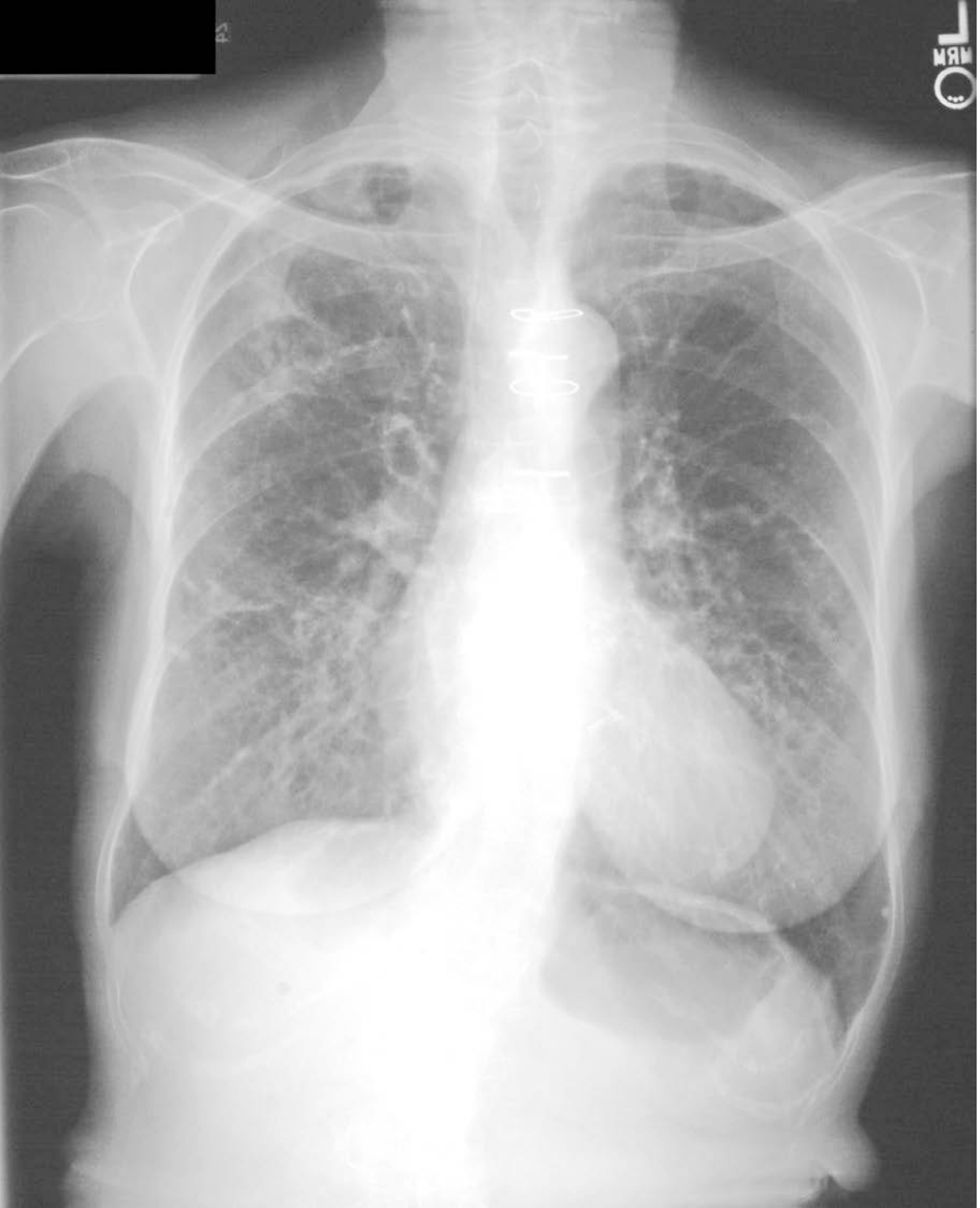
RX torace: 42 anni con malattia da *M. kansasii*.

Addensamenti reticolonodulari bilaterali dei lobi superiori.

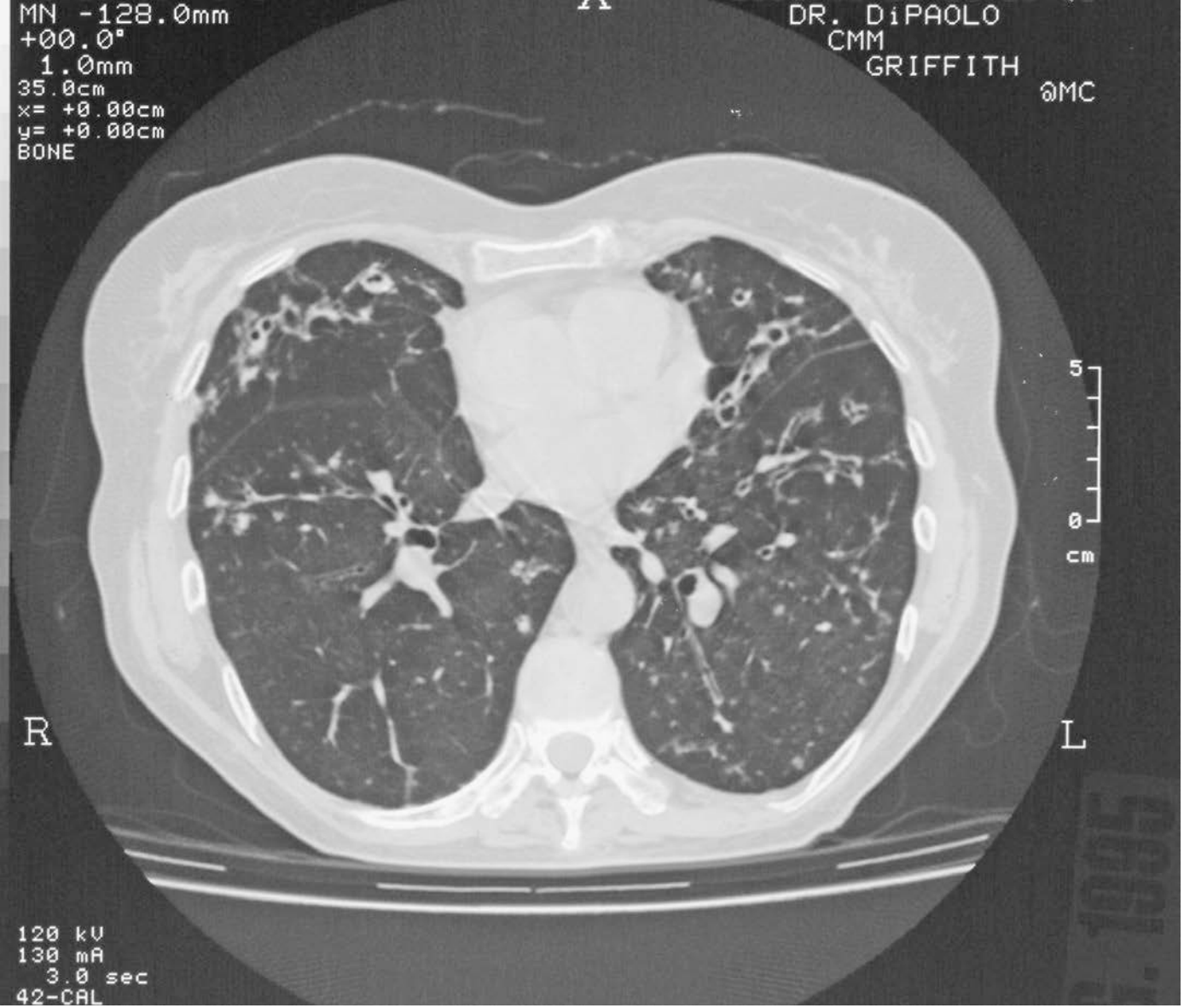


RX torace: Uomo, 77 anni fumatore con micobatteriosi da M. kansasii.

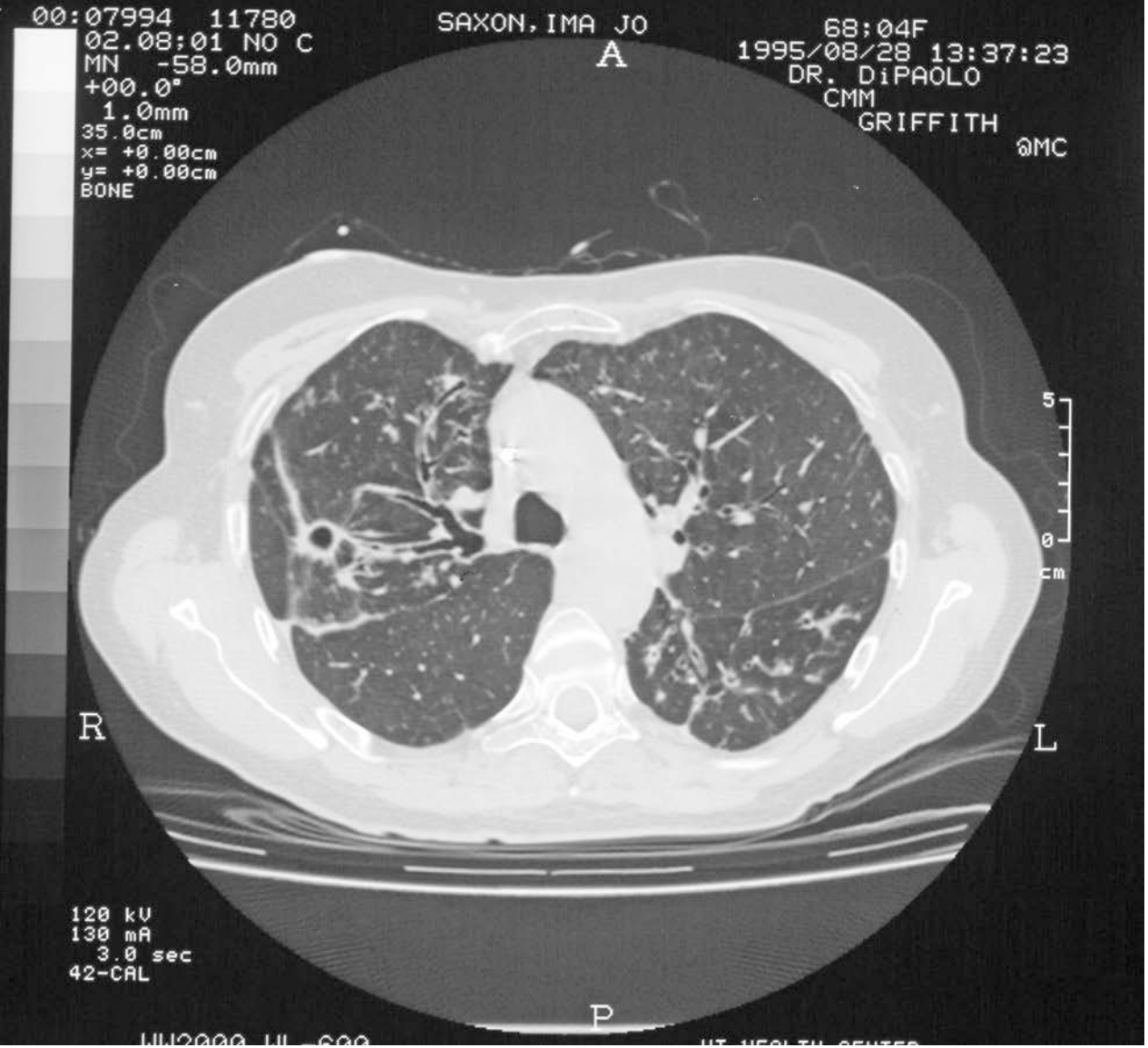
Addensamenti reticolonodularied escavazioni bilaterali



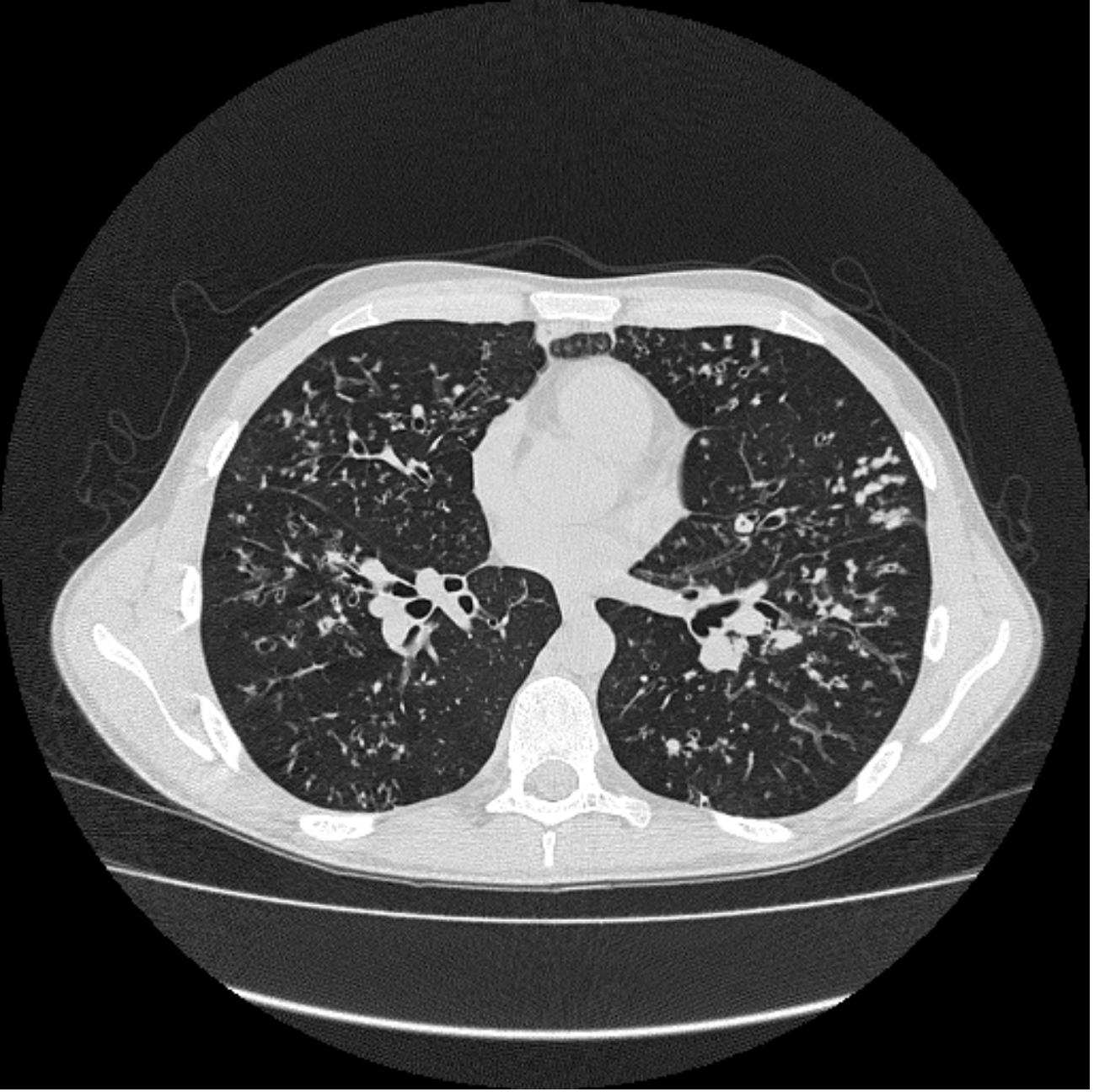
RX torace: 70 anni, femmina, non fumatrice. Micobatteriosi da *M. abscessus* con addensamenti reticolonodulari bilateralied escavazioni.



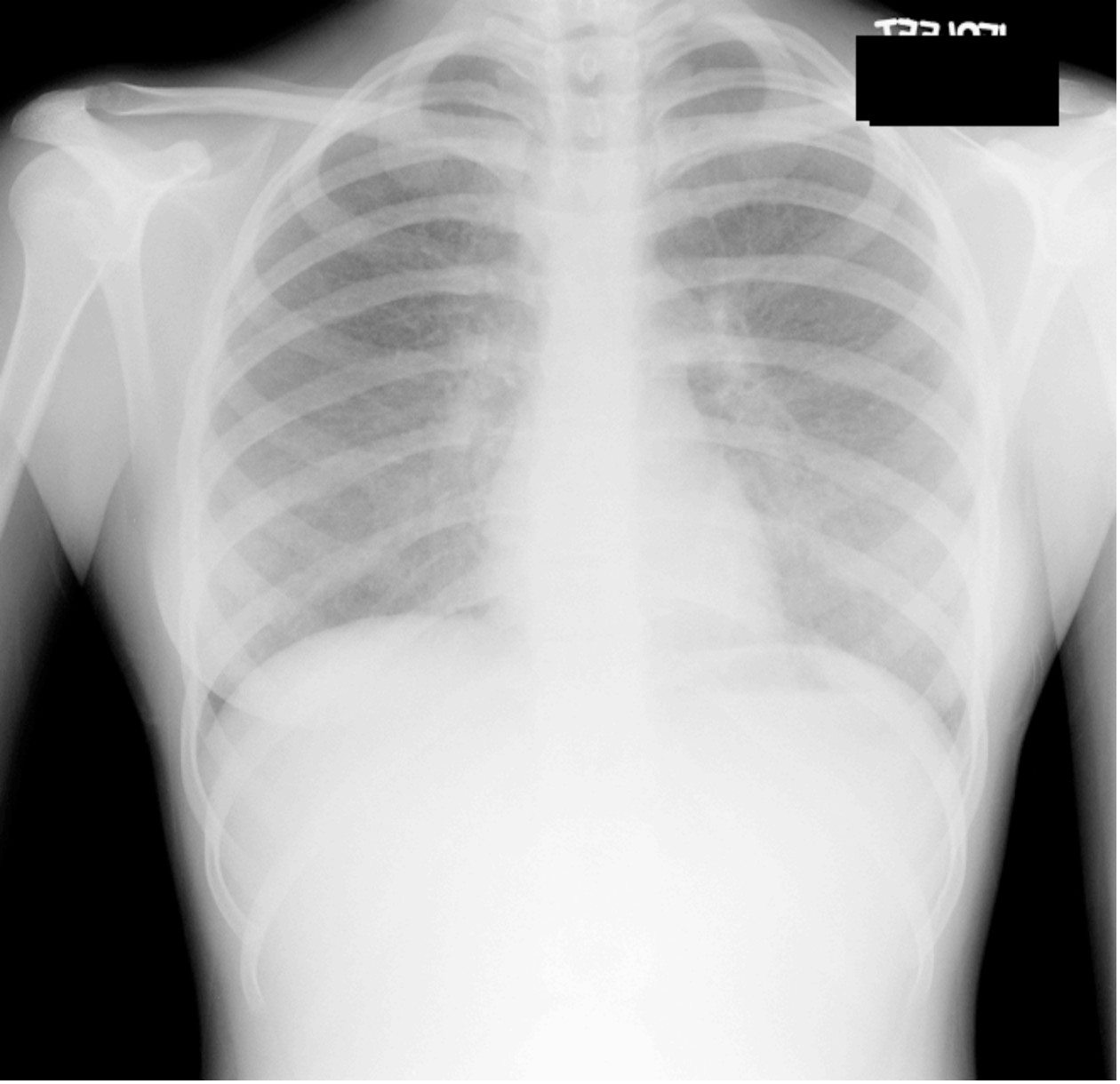
HRCT della stessa pz. noduli e bronchiectasie nei lobi medio, inferiore e nel segmento lingulare.



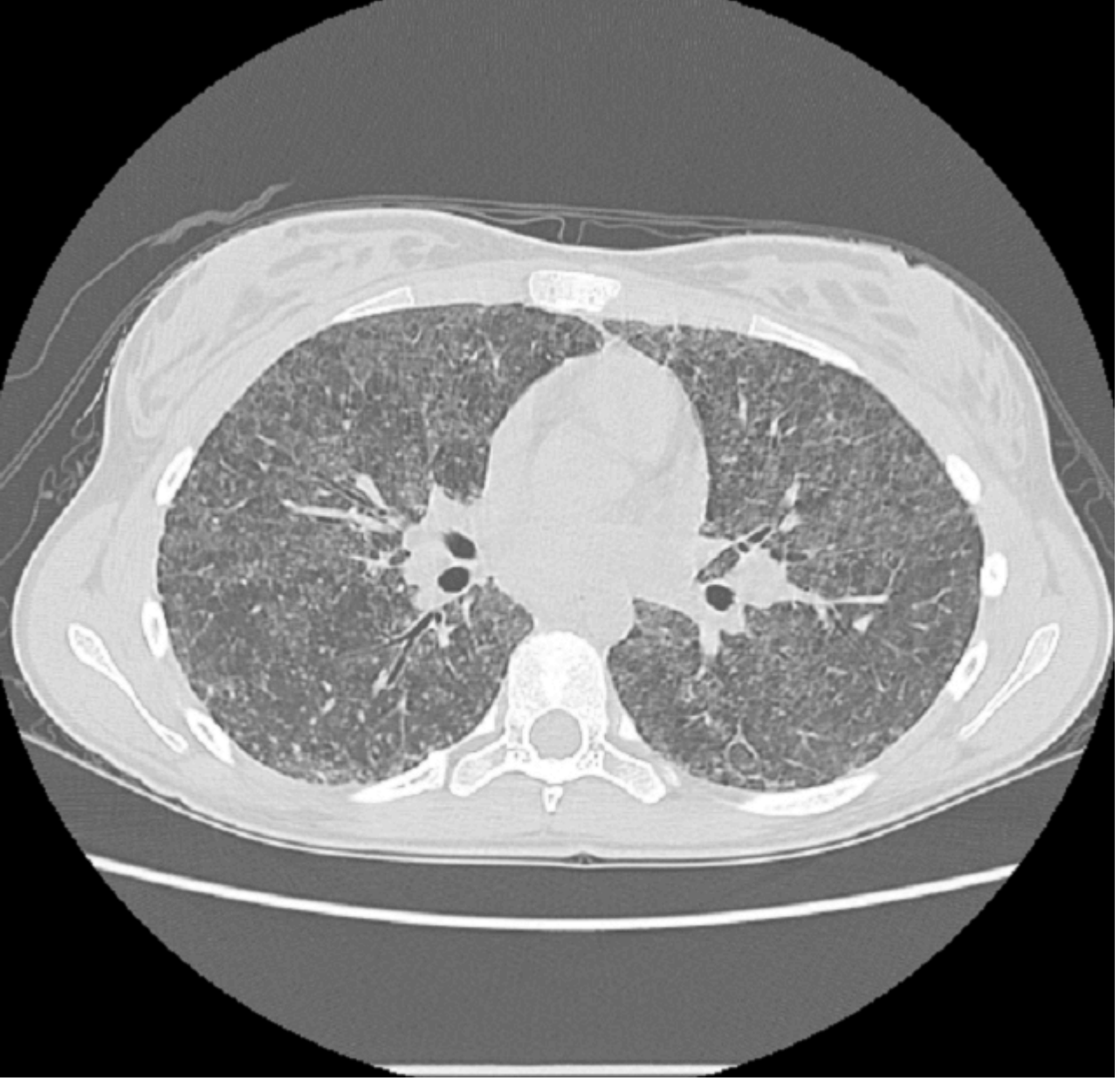
HRCT della stessa pz. che mostra noduli, bronchiectasie e escavazioni



HRCT maschio, 22 anni, non fumatore con fibrosi cistica e micobatteriosi polmonare da *M. abscessus.*
Pz. con infiltrazioni diffuse nodulari e reticolonodulari con aspetto ad “albero in fiore”.



RX torace: 30 anni, mascho, non fumatore, addensamenti reticolari dopo esposizione aereosolizzazione di acqua della vasca idromassaggio.



HRCT stesso pz. con un quadro parenchimale a vetro smerigliato.

Guidance for therapy decisions

Available treatment guidelines:

BTS (2017)

ATS/IDSA (2007)[2]

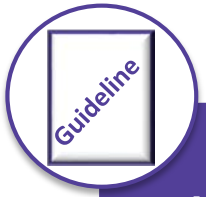
DZK/DGP (2013)[3]

Evidence-based approach to treatment of NTMPD is hampered by a lack of adequately powered randomized clinical trials[4]

ATS, American Thoracic Society; BTS, British Thoracic Society; DGP, Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin; DZK, Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose; IDSA, Infectious Diseases Society of America; NTMPD, non-tuberculous mycobacterial pulmonary disease.

1. BTS. Thorax 2017 .2. Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416; 3. Schönfeld N, et al. Pneumologie 2013; 67:605-33;
4. Johnson MM, Odell AA. J Thorac Dis 2014; 6;210-20.

Antibiotic therapy:
To treat or not to treat – that is the question



Careful implementation of guideline-based diagnostic criteria should prevent unnecessary use of potentially toxic drugs[1]

Semiquantitative criteria (smear microscopy, NTM colony counts) is recommended to determine clinical significance of NTM[1]

?

Radiographic progression may justify treatment even if there is a low bacterial load[2]

Decision to initiate treatment of NTMPD requires individual risk/benefit analysis[1]

NTM, nontuberculous mycobacteria; NTMPD, non-tuberculous mycobacterial pulmonary disease.

1. Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416; 2. Schönfeld N, et al. Pneumologie 2013; 67:605-33.

Clinical and microbiological criteria for diagnosing non-tuberculous mycobacterial lung disease

Clinical (both required)

Pulmonary symptoms, nodular or cavitary opacities on chest radiograph,
or
a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules.
and
Appropriate exclusion of other diagnoses.

Microbiological

Positive culture results from at least two separate expectorated sputum samples. If the results are non-diagnostic, consider repeat sputum AFB smears and cultures.
or
Positive culture result from at least one bronchial wash or lavage.
or
Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or AFB) and positive culture for NTM
or
biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.

BMJ Open Respiratory Research

Macrolides: clarithromycin, azithromycin

Mechanism of action:

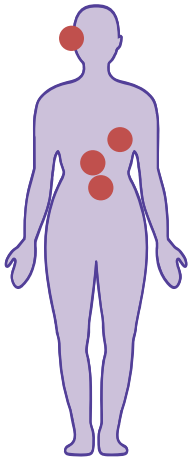
- Inhibition of protein synthesis[1]

Oral regimen for MAC lung disease[2,3]

- Azithromycin: 250–500 mg/day
- Clarithromycin: 2 x 500 mg/day

Major side effects

- GI symptoms (nausea, vomiting, diarrhea, metallic taste)[3]
- Decreased hearing[3]
- Hepatitis[3]
- Risk of QT prolongation and infrequent arrhytmias[4]
  - Fatalities reported[4]
- Clarithromycin inhibits the hepatic metabolism of several agents including rifabutin and some protease inhibitors[3]



GI, gastrointestinal; MAC, *Mycobacterium avium* complex.

1. Barrow WW. Rev Sci Tech 2001; 20:55-70; 2. Schönfeld N, et al. Pneumologie 2013; 67:605-33; 3. Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416; 4. Biaxin prescribing information. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. (accessed 5 Jan 2016).

Ethambutol

Mechanism of action:

- Prevents polymerization of cell wall arabinan[1]

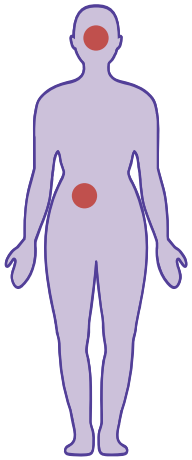
Oral regimen for MAC lung disease[2,3]

- 15 mg/kg/day
- Maximum daily dose: 2,000 mg

Major side effects

- Optic neuritis[3,4]
  - Loss of red/green color discrimination[3]
  - Loss of visual acuity[3]
    - Usually reversible but irreversible blindness has been reported[4]

    → regular ophthalmologic examinations necessary[2]
- Liver toxicity[4]
  - Fatalities reported[4]



MAC, *Mycobacterium avium* complex.

1. Barrow WW. Rev Sci Tech 2001; 20:55-70; 2. Schönfeld N, et al. Pneumologie 2013; 67:605-33; 3. Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416; 4. Myambutol prescribing information. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. (accessed 5 Jan 2016).

Rifamycins

Mechanism of action:

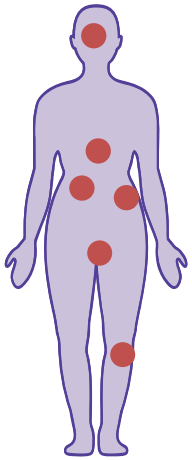
- Inhibit RNA synthesis[1]

Oral regimen for MAC lung disease[2-4]

- Rifampin (rifampicin):
  - 10 mg/kg/day
  - Maximum daily dose: 600 mg
- Rifabutin: 300 mg/day

Major side effects

- Orange discoloration of secretions and urine[5]
- GI disturbances (nausea, vomiting)[5]
- Hypersensitivity (fever, rash)[5]
- Hepatitis[5]
- High drug interaction potential due to CYP450 induction[2]
- 'Flu-like symptoms, thrombocytopenia, renal failure[5]
- Rifabutin only: Polymyalgia, polyarthralgia, leukopenia, granulocytopenia, anterior uveitis (with clarithromycin)[5]



CYP450, cytochrome P450; GI, gastrointestinal; MAC, *Mycobacterium avium* complex.

1. Wehrli W, Staehelin M. Bacteriological Reviews Sept 1971; 290-309; 2. Schönfeld N, et al. Pneumologie 2013; 67:605-33; 3. Rifadin prescribing information. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. (accessed 26 Jan 2016); 4. Mycobutin prescribing information. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. (accessed 25 Jan 2016); 5. Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416.

Aminoglycosides: streptomycin, amikacin

Mechanism of action:

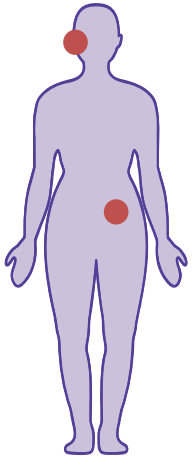
- Inhibit protein synthesis[1]

Regimen for MAC lung disease[2-4]

- Streptomycin[2]: 15 mg/kg/day IV (maximum daily dose, 1,000 mg)
- Amikacin:
  - IV: 15 mg/kg/day[3]

Major side effects

- Dose-dependent vestibular/auditory toxicity[5]
  - Dizziness, vertigo, ataxia, tinnitus, hearing loss[5]
  - May be irreversible[5,6]
- Nephrotoxicity[2,7]



IV, intravenous; MAC, *Mycobacterium avium* complex.

1. Barrow WW. Rev Sci Tech 2001; 20:55-70; 2. Schönfeld N, et al. Pneumologie 2013; 67:605-33; 3. Davis KK, et al. BMC Pulm Med. 2007;7:2; 4. Olivier KN, et al. Annals ATS 2014; 11:30-5; 5. Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416; 6. Streptomycin prescribing information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/064210s009lbl.pdf. (accessed 25 Jan 2016); 7. Smith CR, et al. Johns Hopkins Med J 1978; 142:85-90.

Other drugs used for treatment of NTMPD (1)*

Drug	Dosage	Major side effects	Treatment duration
Imipenem[#1]	*M. abscessus* lung disease: 500 mg 2–4 x daily	GI disturbances, hypersensitivity, seizures, confusion, hepatitis, hematologic abnormalities	2–4 months
Cefoxitin[1]	*M. abscessus* lung disease: ≤12 g/d	Hypersensitivity, hematologic abnormalities	2–4 months
Isoniazid[1]	*M. kansasii* infection: a) Rifampin-susceptible: 5 mg/kg/d (maximum 300 mg/d) b) Rifampin-resistant: 900 mg/d	Hypersensitivity, hepatitis	Until patient culture-negative on therapy for 1 year
Tigecycline[2]	Rifampin-resistant *M. kansasii* infection: 100 mg initial dose followed by 50 mg 2 x daily	Anaphylaxis, liver dysfunction/failure, pancreatitis, increased risk of all-cause mortality	Not specified

*Off-label use for treatment of NTM lung infections; [#]available in fixed combination with cilastatin; GI, gastrointestinal; NTMPD, non-tuberculous mycobacterial pulmonary disease.

1. Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416; 2. Tygacil prescribing information. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. (accessed 7 Jan 2016).

Other drugs used for treatment of NTMPD (2)*

Drug[#]	Major side effects
Fluoroquinolones e.g. moxifloxacin[1]	GI disturbances, CNS symptoms, tendonitis[1]
Sulfonamides[1] e.g. sulfamethoxazole and trimethoprim	GI disturbances, hematologic abnormalities, hypersensitivity[1]
Clofazimine[2†]	Abdominal symptoms, discoloration of body fluids, hair, corneal pigmentation, skin symptoms[2]
Doxycycline[1]	GI disturbances, cutaneous symptoms, CNS symptoms[1]
Linezolid[1]	GI disturbances, hematologic abnormalities, peripheral neuropathy[1]

*Off-label use for treatment of NTM lung infections; [#]no information on dosing and treatment duration available in the treatment guidelines; [†]limited availability.
CNS, central nervous system; GI, gastrointestinal; NTMPD, non-tuberculous mycobacterial pulmonary disease.
1. Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416; 2. Lamprene, International Package Leaflet from 23 June 2005; https://www.lamprene.com/fileadmin/pharmaworld/lamprene/lamprene_packing_insert.pdf (accessed 11 Feb 2016).

Surgical treatment of NTMPD

The more difficult a pathogen is to treat medically, the more surgery should be considered

Expert consultation regarding potential risks and benefits of surgery is important

Surgery should be performed in centers with expertise in both the surgical and medical management of mycobacterial diseases

There are no widely accepted criteria for choosing patients with NTMPD for resectional surgery

NTMPD, non-tuberculous mycobacterial pulmonary disease.
Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416.

Indications for surgical treatment of NTMPD caused by MAC or *M. abscessus*

- ✓ Disease predominantly localized to one lung
- ✓ Able to tolerate resectional surgery (adequate cardiopulmonary reserve)
- ✓ Already received antimicrobial therapy to decrease the mycobacterial burden
- ✓ Shown a poor response to drug therapy
- ✓ Developed macrolide-resistant MAC disease
- ✓ Significant disease-related complications

Surgical resection of limited (focal) disease in a patient with adequate cardiopulmonary reserve to withstand partial or complete lung resection can be successful in combination with multidrug treatment regimens

MAC, *Mycobacterium avium* complex.

Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416.

Goals of therapy: Symptomatic, radiographic, microbiologic

Symptomatic improvement

- Important goal
- May be complicated by progression or exacerbation of underlying pulmonary diseases

Radiographic improvement

- Expected and desirable
- Concomitant lung disease may complicate interpretation
- Potential for improvement may be limited

Microbiologic improvement

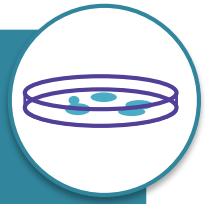
- Primary goal is conversion of sputum cultures to negative

Microbiological goal:
12 months of culture-negative sputum while on therapy

Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416.

NTMPD: Three potential treatment goals

Microbiologic cure
- May be difficult to achieve in:
  - Older, frail patients who cannot tolerate multidrug regimens
  - Patients infected with particular NTM species (e.g., *M. abscessus*)



Microbiologic and clinical improvement
- May require aggressive therapy

Suppressive therapy only
- Less aggressive therapy; requires acceptance of disease as chronic and incurable

Choice of goal depends on the patient and the clinical presentation

NTMPD, non-tuberculous mycobacterial pulmonary disease.
Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416.