Epidemiologia e trattamento delle micobatteriosi non tubercolari

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IRENE THE ITALIAN REGISTRY OF PULMONARY NON-TUBERCULOUS MYCOBACTERIA

HU HUMANITAS UNIVERSITY

EMBARC The European Bronchiectasis Registry

HUMANITAS RESEARCH HOSPITAL

IRENE THE ITALIAN REGISTRY OF PULMONARY NON-TUBERCULOUS MYCOBACTERIA

Disclosures

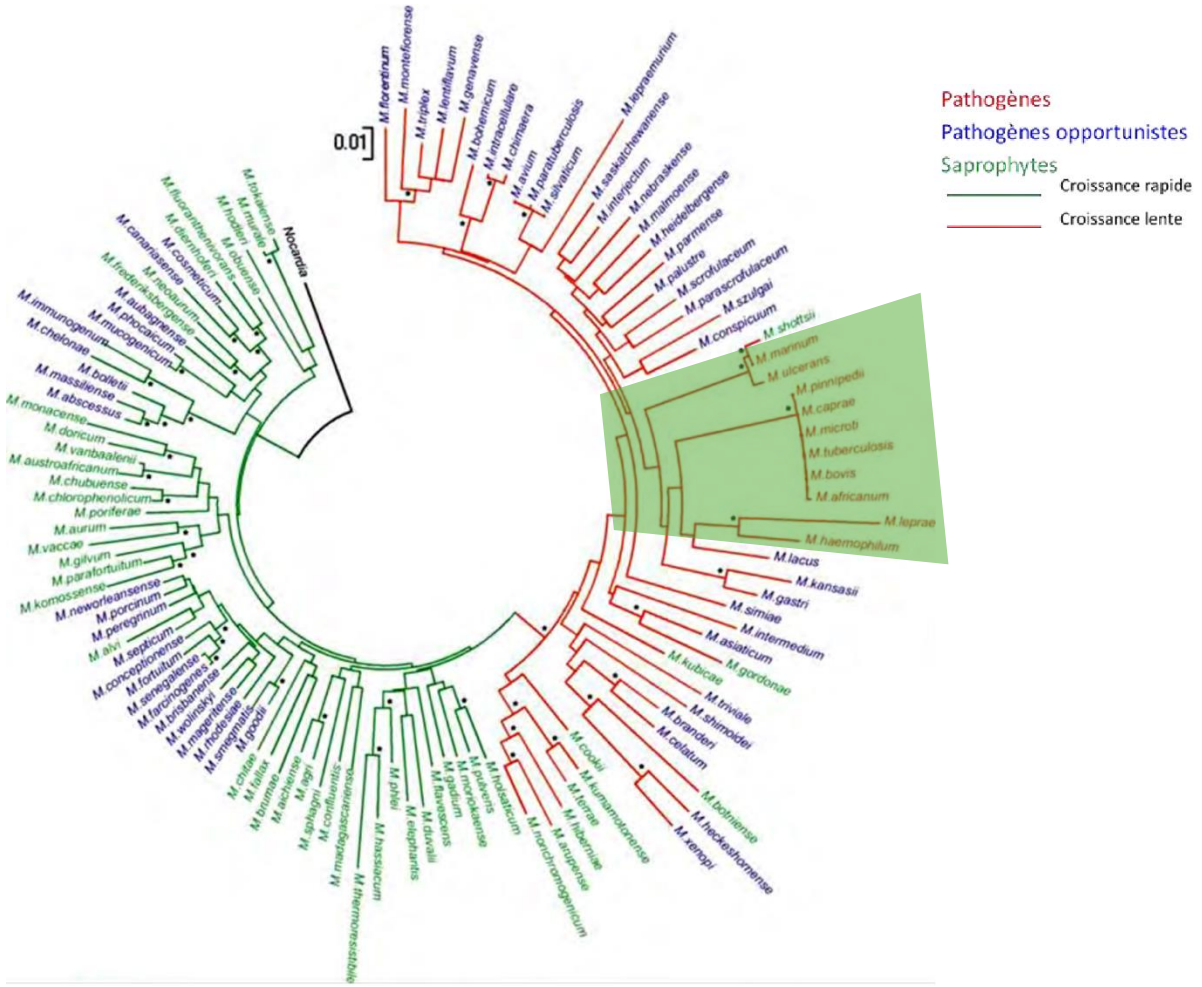
I have no personal or financial conflicts of interest to declare

NTMs do not exist

Over 190 species and subspecies different from:

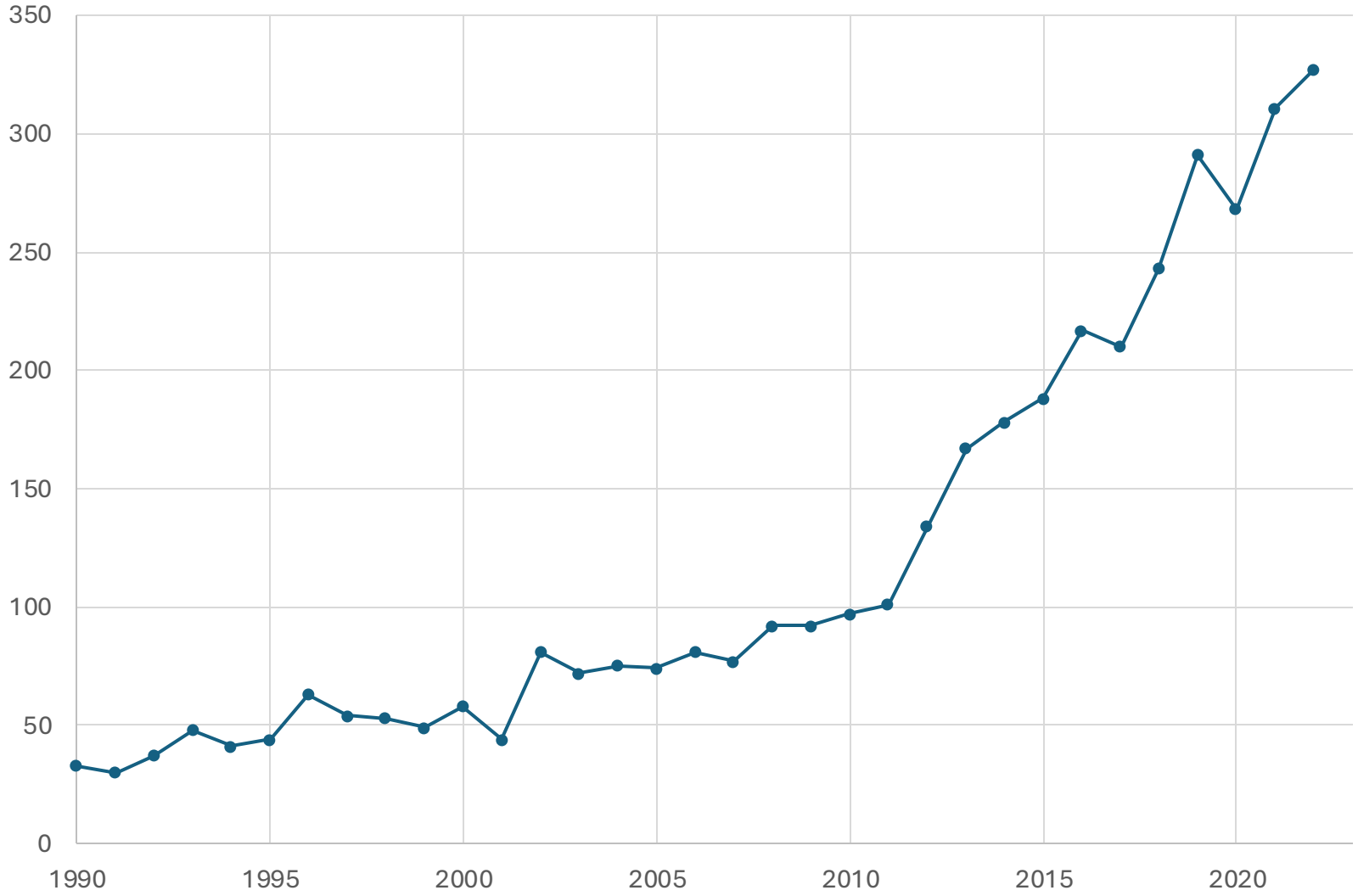
- M. tuberculosis complex
- M. leprae complex
- M. ulcerans

Very heterogeneous group



AUGENSTREICH J. BIOLOGY, 2018.

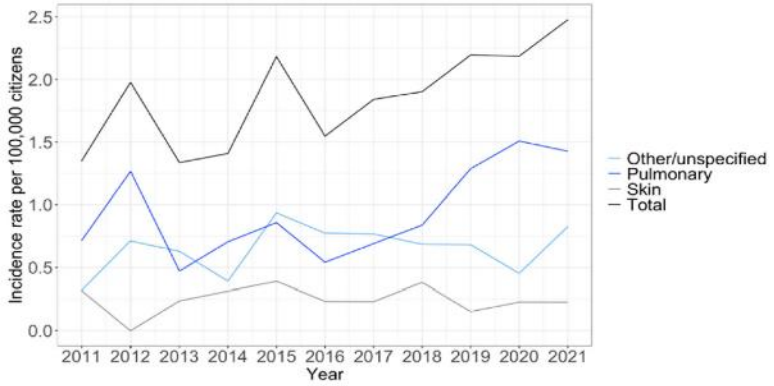
Growing Interest in NTM-Pulmonary Diseases



PUBMED (1990-2022): NON-TUBERCULOUS MYCOBACTERIA & PULMONARY DISEASE

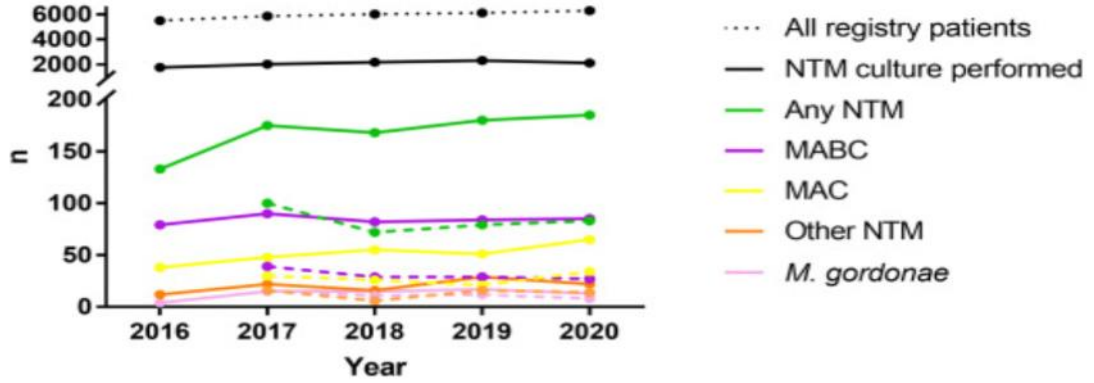
Trends in NTM-Pulmonary Disease

ALL ISOLATES (51% PULM.); DENMARK 2011-2021



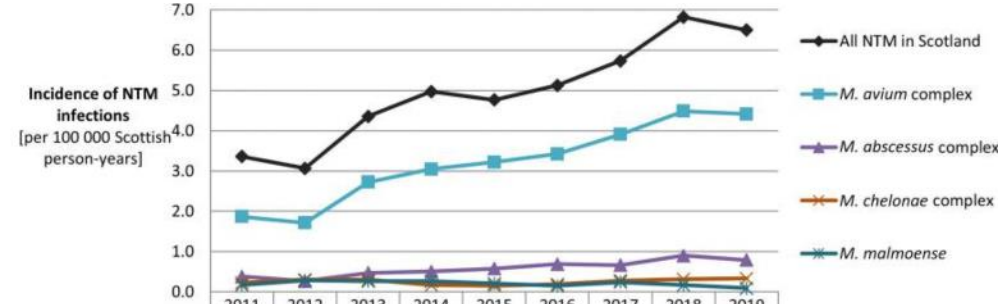
DAHL VN INFECT DIS (LOND). 2023 JUN;55(6):439-443. DOI: 10.1080/23744235.2023.2194411.

CYSTIC FIBROSIS; GERMANY 2016-2020



STEINDOR M INT J INFECT DIS 2023; DOI: 10.1016/j.ijid.2023.01.032

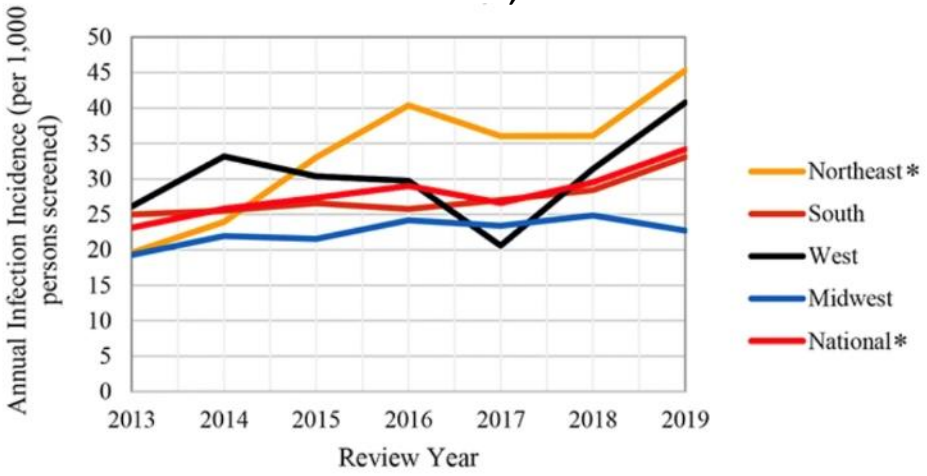
ALL ISOLATES (81% PULM.); SCOTLAND 2011-2019



	2011	2012	2013	2014	2015	2016	2017	2018	2019
All NTM in Scotland	3.4	3.1	4.4	5.0	4.8	5.1	5.7	6.8	6.5
M. avium complex	1.9	1.7	2.7	3.0	3.2	3.4	3.9	4.5	4.4
M. abscessus complex	0.4	0.3	0.5	0.5	0.6	0.7	0.7	0.9	0.8
M. chelonae complex	0.2	0.3	0.3	0.2	0.1	0.2	0.3	0.3	0.3
M. malmoense	0.2	0.3	0.3	0.3	0.2	0.1	0.2	0.2	0.1

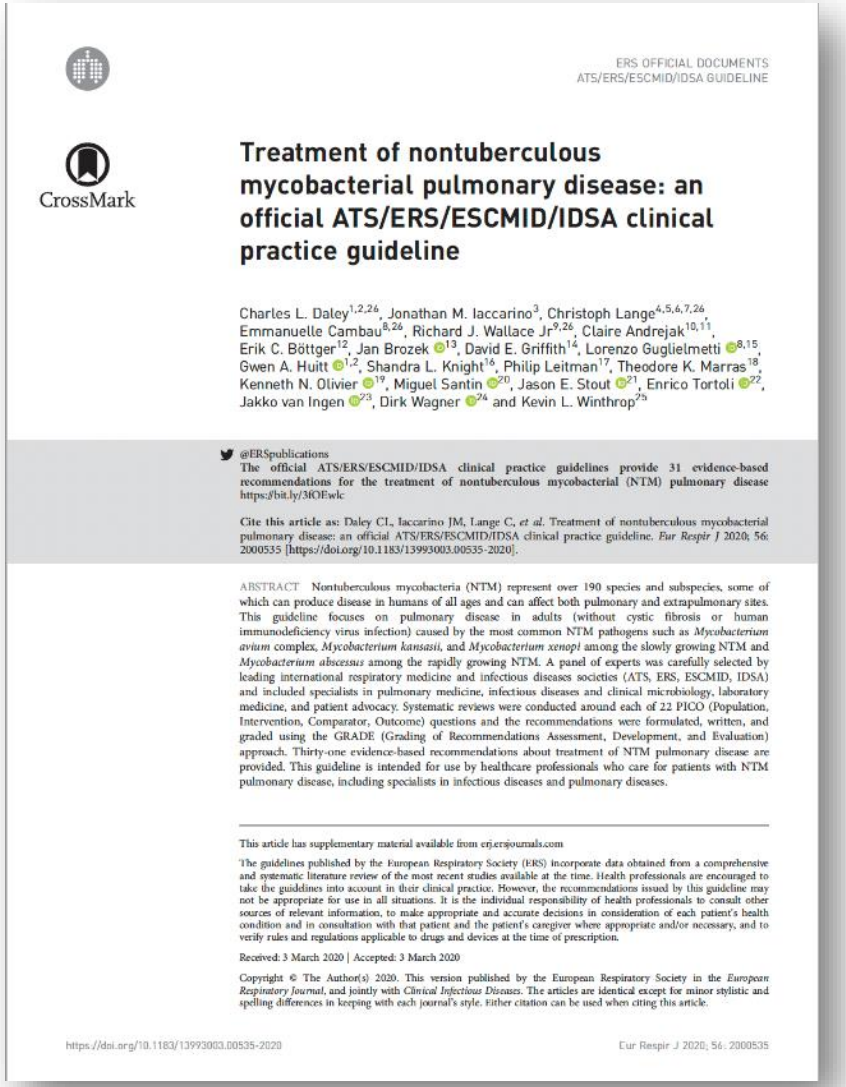
JARCHOW-MAC DONALD A OPEN FORUM INFECT DIS . 2022 DOI: 10.1093/OFID/OFAC665

CYSTIC FIBROSIS; USA 2010-2019



MARSHALL JE BMC INFECT DIS 2023; DOI: 10.1186/s12879-023-08468-6

ATS/ERS/ESCMID/IDSA Guideline



ERS OFFICIAL DOCUMENTS
ATS/ERS/ESCMID/IDSA GUIDELINE

Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline

Charles L. Daley[1,2,26], Jonathan M. Iaccarino[3], Christoph Lange[4,5,6,7,26], Emmanuelle Cambau[8,26], Richard J. Wallace Jr[9,26], 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]

@ERSpublications
The official ATS/ERS/ESCMID/IDSA clinical practice guidelines provide 31 evidence-based recommendations for the treatment of nontuberculous mycobacterial (NTM) pulmonary disease https://bit.ly/3fOEwlc

Cite this article as: Daley CL, Iaccarino JM, Lange C, *et al*. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Eur Respir J* 2020; 56: 2000535 [https://doi.org/10.1183/13993003.00535-2020].

ABSTRACT 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.

This article has supplementary material available from erj.ersjournals.com

The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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EUROPEAN RESPIRATORY *journal*
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

M. avium-complex
M. kansasii
M. xenopi

M. abscessus

DALEY C ET AL. ERJ 2020;56:2000535

Guidelines on Less Common NTM-PD

THE LANCET
Infectious Diseases

Review

Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases

Christoph Lange, Erik C Böttger, Emmanuelle Cambau, David E Griffith, Lorenzo Guglielmetti, Jakko van Ingen, Shandra L Knight, Theodore K Marras, Kenneth N Olivier, Miguel Santin, Jason E Stout, Enrico Tortoli, Dirk Wagner, Kevin Winthrop, Charles L Daley, on behalf of the expert panel group for management recommendations in non-tuberculous mycobacterial pulmonary diseases*

The 2020 clinical practice guideline for the treatment of non-tuberculous mycobacterial pulmonary disease (NTM-PD) by the American Thoracic Society, European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Diseases Society of America; and the 2017 management guideline by the British Thoracic Society covered pulmonary diseases in adults caused by *Mycobacterium avium* complex, *Mycobacterium kansasii*, *Mycobacterium xenopi*, and *Mycobacterium abscessus*. In order to provide evidence-based recommendations for the treatment of less common non-tuberculous mycobacterial (NTM) species in adult patients without cystic fibrosis or HIV infection, our expert panel group performed systematic literature searches to provide management guidance for pulmonary diseases caused by seven additional organisms: *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium genavense*, *Mycobacterium gordonae*, *Mycobacterium malmoense*, *Mycobacterium simiae*, and *Mycobacterium szulgai*. Treatment recommendations were developed by a structured consensus process. The evidence from the scientific literature published in English for treatment recommendations for pulmonary diseases caused by other NTM species was of very low quality, with the exception of *M malmoense*, and based on the evaluation of case reports and case series. For *M malmoense*, results from two randomised controlled trials and three retrospective cohort studies provided a better evidence base for treatment recommendations, although the evidence was still of low quality.

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*Members listed in the appendix
Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany (Prof C Lange MD); German Center for Infection Research (DZIF), Respiratory Medicine & International Health, University of Lübeck, Lübeck, Germany (C Lange); Baylor College of Medicine, Houston, TX, USA (C Lange); Institute of Medical Microbiology, National Reference Center for Mycobacteria, University of Zurich, Zurich, Switzerland (Prof E C Böttger MD); National Reference Center for Mycobacteria and Antimycobacterial Resistance, AP-HP GHU Nord, Mycobacteriology, Inserm, IAME UMR 1137, University of Paris, Paris, France (Prof E Cambau MD); National Jewish Health and University of Colorado Health Sciences (Prof D E Griffith MD, Prof C L Daley MD, L Guglielmetti MD) and Library and Knowledge Services (S L Knight MS), Denver, CO, USA; Sorbonne University, Inserm, Centre for Immunology and Microbial Infections, Paris, France (L Guglielmetti); Radboud Center for Infectious Diseases, Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Netherlands (Prof J van Ingen MD); Department of Medicine, University of Toronto and University Health Network, Toronto, ON, Canada (T K Marras MD); Pulmonary Branch, National Heart, Lung and Blood Institute, Bethesda, MD, USA (K N Olivier MD); Service of Infectious Diseases, Bellvitge University Hospital-IDIBELL, University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

Introduction

The 2020 updated management guideline for patients with non-tuberculous mycobacterial pulmonary diseases (NTM-PD) focuses on population, intervention, comparison, and outcome question-guided management recommendations for pulmonary disease in adults caused by *Mycobacterium avium* complex, *Mycobacterium kansasii*, *Mycobacterium xenopi*, and *Mycobacterium abscessus*.[1,2] However, management options for NTM-PD caused by other clinically relevant non-tuberculous mycobacteria (NTM) covered in the previous management guideline are also needed for the care of affected patients.[3] At present, treatment recommendations for patients with other NTM-PDs are primarily based on expert opinions and often variable. Health-care providers of patients with NTM-PDs should consult with a clinical microbiologist who has expertise in identification and antimycobacterial drug susceptibility testing, and a clinician with expertise in managing NTM disease. However, evidence-based management decisions are needed for patients affected by NTM not covered in the 2017 guideline by the British Thoracic Society (BTS) or the 2020 American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Microbiology and Clinical Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA) guideline.[4]

The panel of members of the 2020 ATS, ERS, ESCMID, and IDSA guideline committee did systematic reviews of the literature, independently of the societies involved in the original task force, to provide management guidance for pulmonary diseases caused by seven additional organisms: *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium genavense*, *Mycobacterium gordonae*, *Mycobacterium malmoense*, *Mycobacterium simiae*, and *Mycobacterium szulgai*.

The following consensus guidance includes recommendations for antibiotics guided by in-vitro susceptibility results. With the exception of *M chelonae* and *M fortuitum*, there are no validated break points defining susceptibility and resistance for any of the antibiotics used for the organisms considered here.[5]

Methods

A search (see appendix pp 4–7) was adapted for execution on the Ovid MEDLINE platform and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, and the Cochrane Central Register of Controlled Trials. Searches were limited to human studies or studies indexed with neither human nor animal and those published in English. A final update was executed on Jan 6, 2020. Teams of two or three independent experts evaluated the search results for eligibility; they supplemented the electronic search by contacting experts and handsearching journals, conference proceedings, reference lists, and regulatory agency websites for relevant articles.

In addition to the systematic reviews, the members of the panel ascertained agreement on management options in a six-step consensus process as previously published.[6,7] The results of the panel experts' votes, either in favour or against the treatment approach, is presented in the appendix (appendix p 1).

General recommendations

The expert panel recommends that health-care providers consult with a clinical microbiologist who has expertise

M. chelonae
M. fortuitum

M, genavense
M. gordonae
M. malmoaense
M. simiae
M. szulgai

LANGE C ET AL. LANCET INFECT DIS 2022; S1473-3099(21)00586-7

The Italian landscape – The IRENE registry

ORIGINAL RESEARCH ARTICLE Open Access

The Italian registry of pulmonary non-tuberculous mycobacteria - IRENE: the study protocol

Inclusion criteria (all should be present):

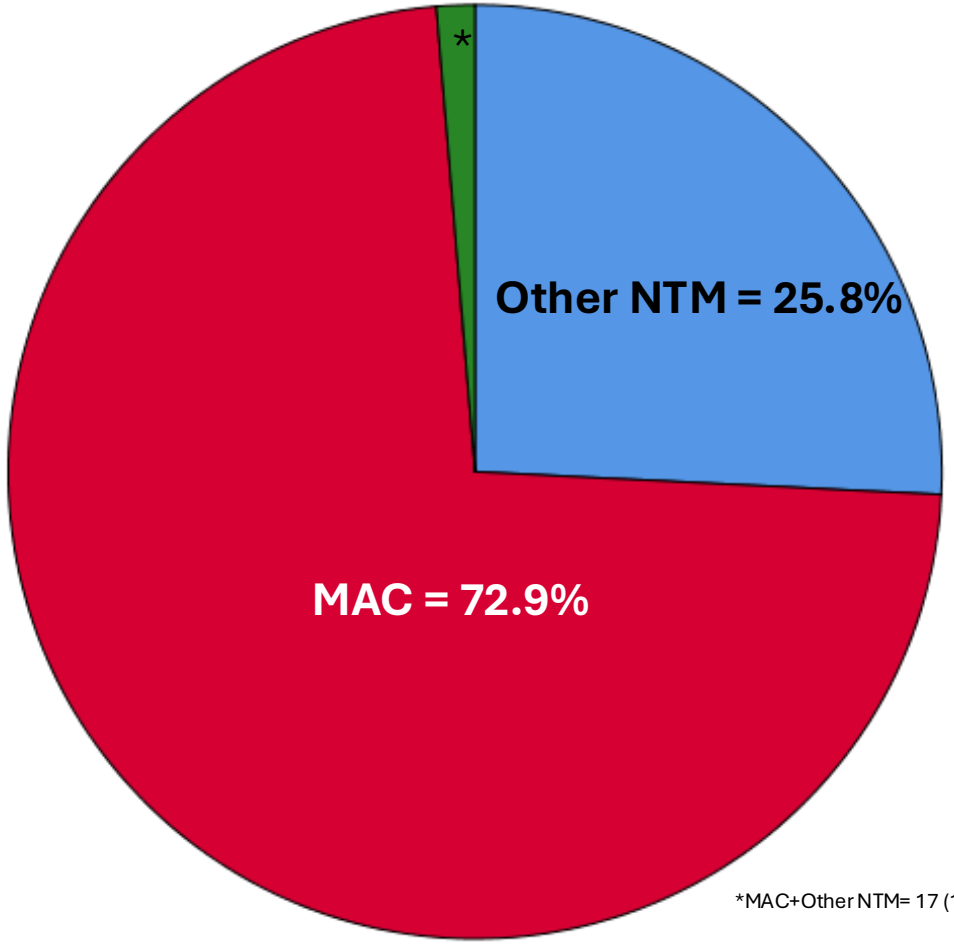
- Age >= 18 years at the time of signing the informed consent
- Any race
- Patients with at least one respiratory (sputum, induced sputum, BAS, BAL, biopsy) isolate of NTM
- At least one isolate from respiratory specimens of NTM in the last year and/or patients who received in the last year or are undergoing treatment for NTM

THE ITALIAN REGISTRY OF PULMONARY NON-TUBERCULOUS MYCOBACTERIA

Periodo: 2017-2023

Centri: 79

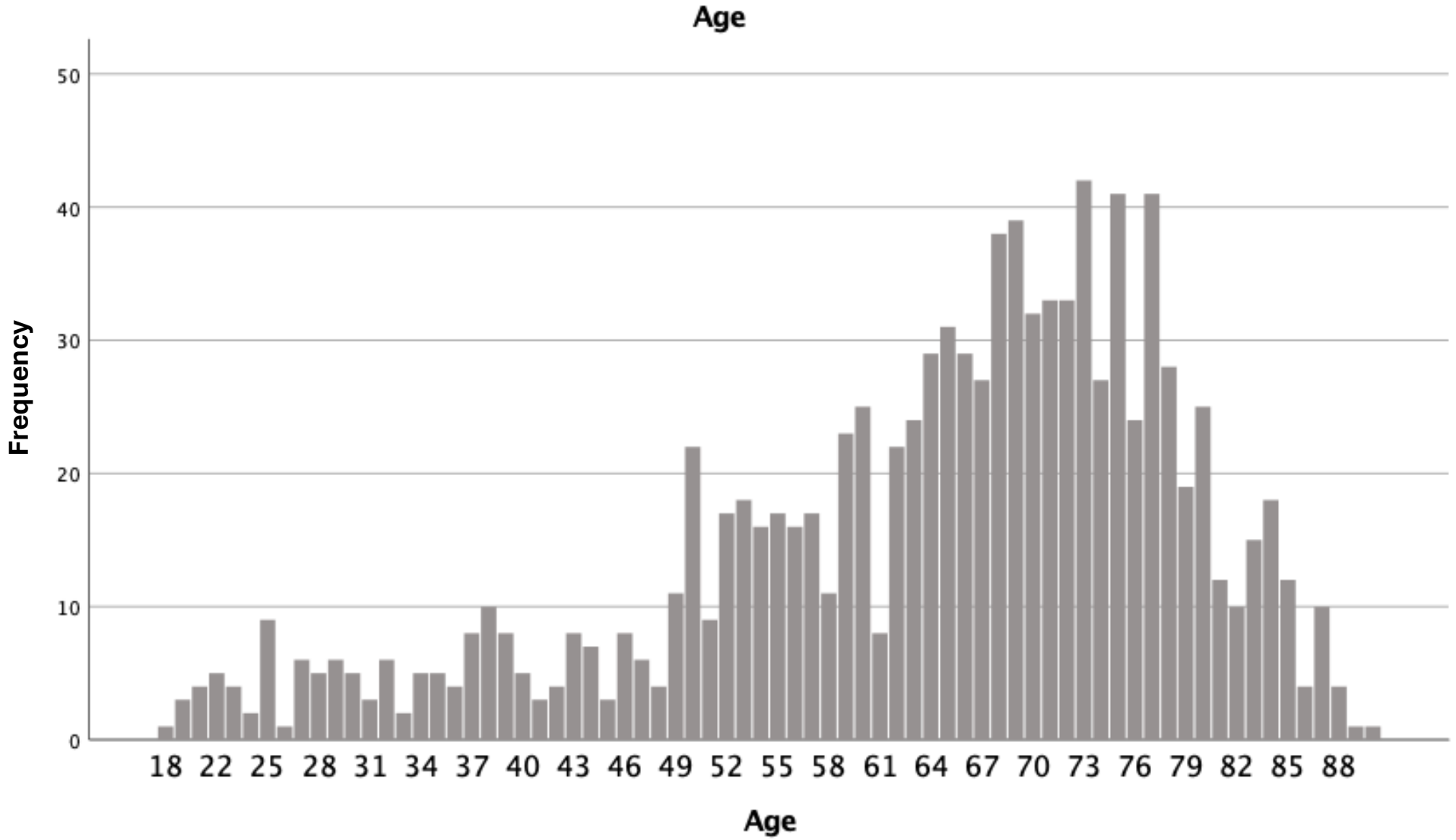
1,288 pazienti



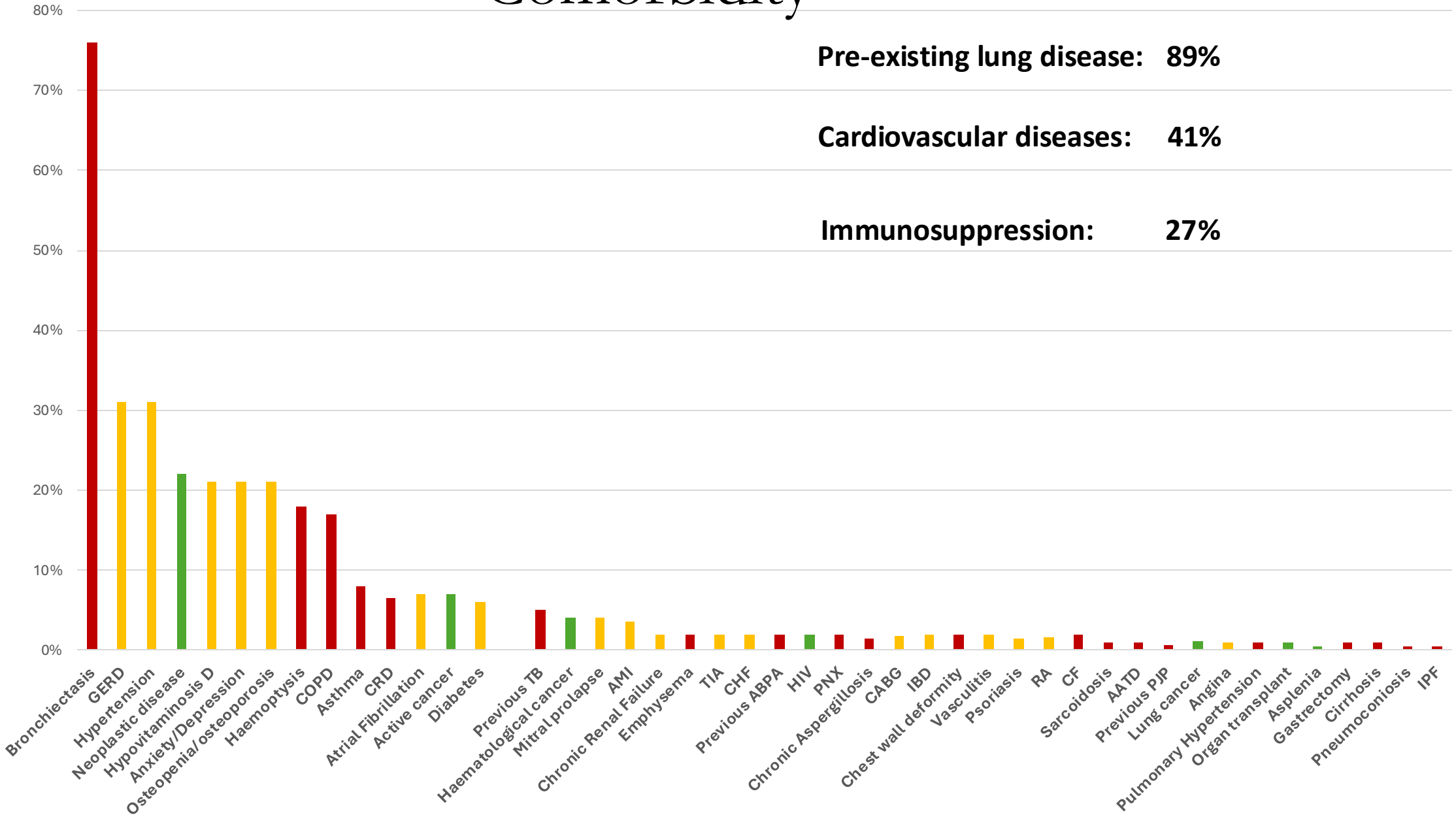
*MAC+Other NTM= 17 (1.3%)

Demographics

Age	67 (55-75)
Female	68%
Caucasian	97%



Comorbidity



Pre-existing lung disease: 89%

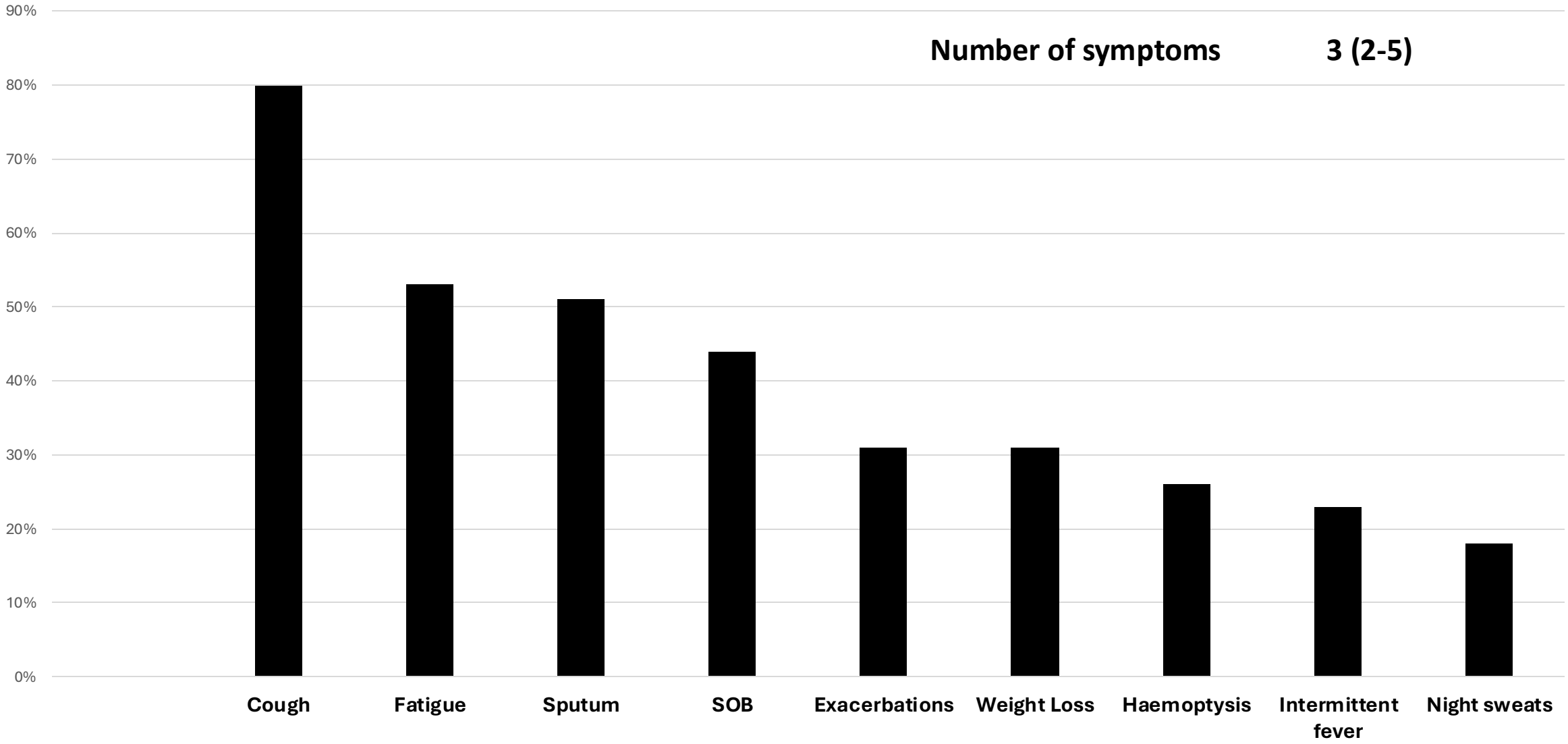
Cardiovascular diseases: 41%

Immunosuppression: 27%

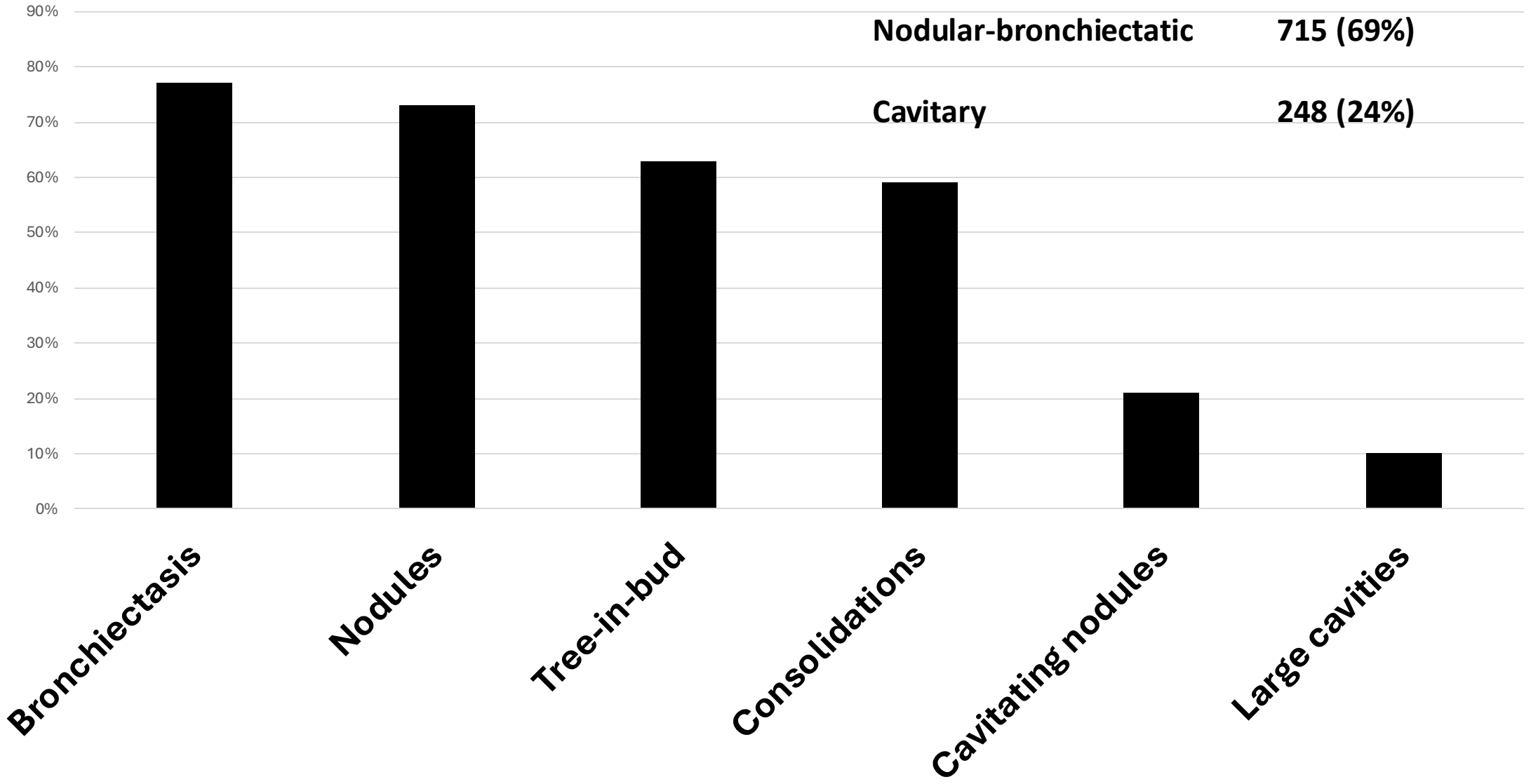
Signs and symptoms

Symptoms presence **83%**

Number of symptoms **3 (2-5)**



Radiology

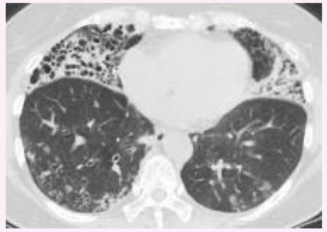

90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Nodular-bronchiectatic 715 (69%)
Cavitary 248 (24%)
Bronchiectasis
Nodules
Tree-in-bud
Consolidations
Cavitating nodules
Large cavities

Diagnosis of NTM-PD

Clinical domain

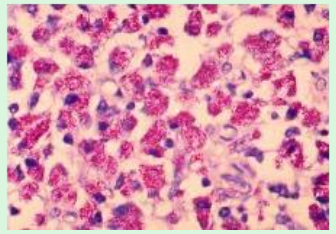
Pulmonary or systemic symptoms

Radiological domain



- Nodular or cavitary opacities on CXR
- Bronchiectasis and tree-in-bud at Chest CT scan

Microbiological domain



- Sputum positive (at least 2 samples)
- BAL/BAS positive
- Biopsy/culture positive

Treatment decision should be individualized

Daley CL. Clinical Infectious Diseases 2020; 71(4):e1-e36

“Watchful waiting” vs. Treatment

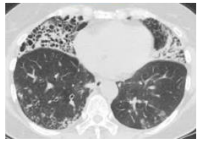
Clinical Domain

Pulmonary or systemic symptoms

\+

Radiological Domain

Nodular or cavitary opacities on CXR or Bronchiectasis and Tree-in-bud at Chest CT



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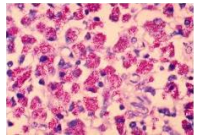
Microbiological Domain

Sputum positive X2
Or
BAS/BAL positive X1
Or
Biopsy + culture



Treatment > Watchful waiting

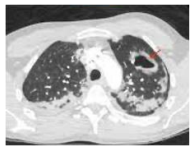
Clinical Domain

Pulmonary or systemic symptoms

\+

Radiological Domain

Nodular or cavitary opacities on CXR or Bronchiectasis and Tree-in-bud at Chest CT



Cavitation

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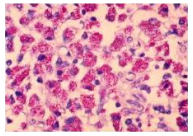
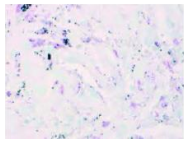
Microbiological Domain

Sputum positive X2
Or
BAS/BAL positive X1
Or
Biopsy + culture





Treatment >>> Watchful waiting

“Watchful waiting” vs. Treatment

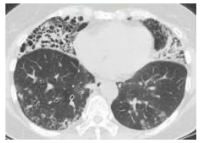
Clinical Domain

Very mild pulmonary or systemic symptoms

+

Radiological Domain

Nodular or cavitary opacities on CXR or Bronchiectasis and Tree-in-bud at Chest CT



+

Microbiological Domain

Sputum positive X2
Or
BAS/BAL positive X1
Or
Biopsy + culture

Watchful waiting > Treatment

1. Pathogenicity of the organism – pro treatment
2. Patient’s symptoms (severe fatigue – pro treatment)
3. Factors associated with poor prognosis (cavitation, low BMI, low albumin, Elevated inflammatory biomarkers) – pro treatment
4. Underlying immunosuppression – pro treatment
5. Risks and benefits of therapy
6. Potentials for recurrence / reinfection
7. Patient’s priorities, wish and ability to receive treatment
8. Goals of therapy

(Take time to discuss this with the patient)

"Watchful Waiting" is not a Passive Process, It is doing SOMETHING!

- Patients with bronchiectasis should be started on airway clearance which can be transformative symptomatically.
- 10%-15% cases have sputum AFB culture conversion (Moon et al, Resp Med; 2019 and Hwang et al ERJ; 2017)
- Airway clearance is likely a necessary element for any successful antibiotic therapy of nodular/bronchiectatic NTM/MAC lung disease
- Management of other detected microrganisms might be appropriate to explore the quote of disease activity related to NTM.
- If not started on antimycobacterial therapy, patients are engaged with a physician who will manage bronchiectasis and evaluate status of NTM/MAC INDEFINITELY.

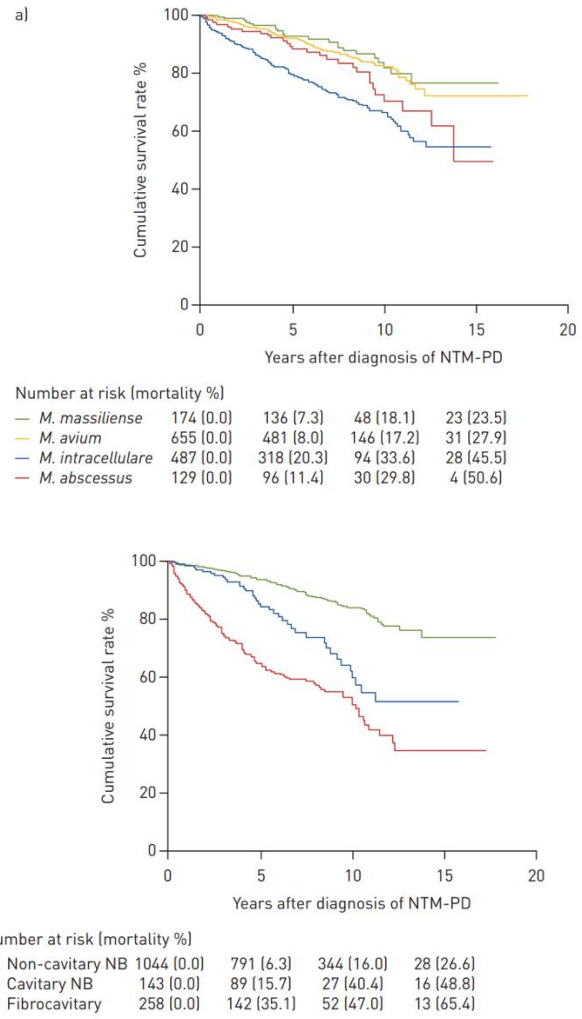
Patients with NTM-PD have high mortality rates

Large cohort study (n = 1,445). Overall mortality rates were:

- 12.4% at 5 years
- 24.0% at 10 years
- 36.4% at 15 years

The following factors were associated with mortality:

- Old age
- Male sex
- Low BMI
- Chronic pulmonary aspergillosis
- Malignancy
- Chronic heart or liver disease
- Elevated ESR



Juhn BW et al. Eur Resp J 2020, 55; 1900798

BACES Score for predicting mortality in NTM-PD

ORIGINAL ARTICLE

BACES Score for Predicting Mortality in Nontuberculous Mycobacterial Pulmonary Disease

Hyung-Jun Kim[1]*, Nakwon Kwak[2,3]*, Hyunsook Hong[4], Noeul Kang[5], Yunjoo Im[5], Byung Woo Jhun[5‡], and Jae-Joon Yim[2,3‡]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Armed Forces Capital Hospital, Seongnam, Republic of Korea; [2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine and [4]Division of Medical Statistics, Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Republic of Korea; [3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; and [5]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

ORCID IDs: 0000-0002-6348-8731 (B.W.J.); 0000-0002-9605-0074 (J.-J.Y.).

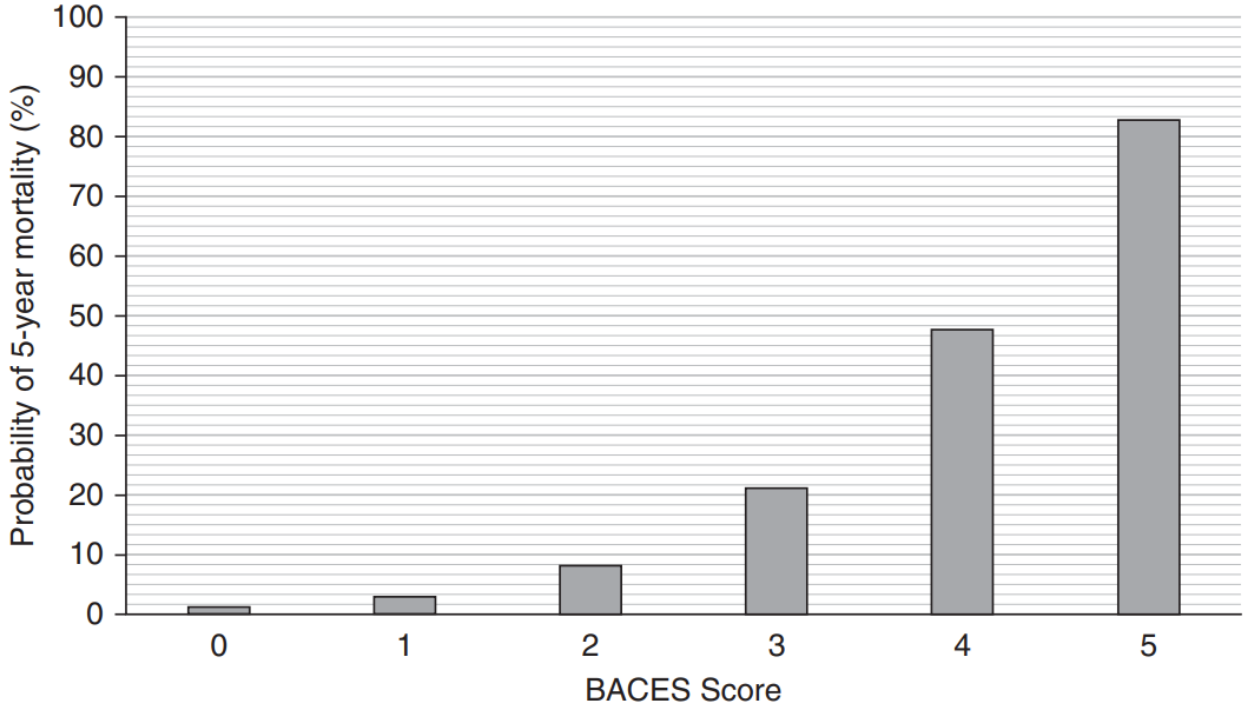
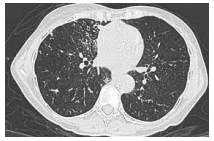


Figure 3. Estimated probability of 5-year mortality in patients with nontuberculous mycobacterial pulmonary disease, according to BACES (body mass index, age, cavity, erythrocyte sedimentation rate, and sex) score.

Kim H-J et al. Am J Respir Crit Care Med 2021, 203; 230

Treatment of MAC-PD

Organism	No. of Drugs	Preferred Drug Regimen[a]	Dosing Frequency
M. avium complex			
Nodular-bronchiectatic 	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly

Treatment should be performed for at least 12 months after culture conversion

Daley CL. Clinical Infectious Diseases 2020; 71(4):e1-e36

NTM-PD diagnosis and treatment

ATS/IDSA/ERS/ESCMID 2020 Pulmonary Disease	**812 (79%)**
ATS/IDSA/ERS/ESCMID 2020 Pulmonary Disease Fibrocavitary	110 (14%)
ATS/IDSA/ERS/ESCMID 2020 Pulmonary Disease Fibrocavitary and Smear Positive	73 (9%)

Intention to treat 82%

Treated 74%

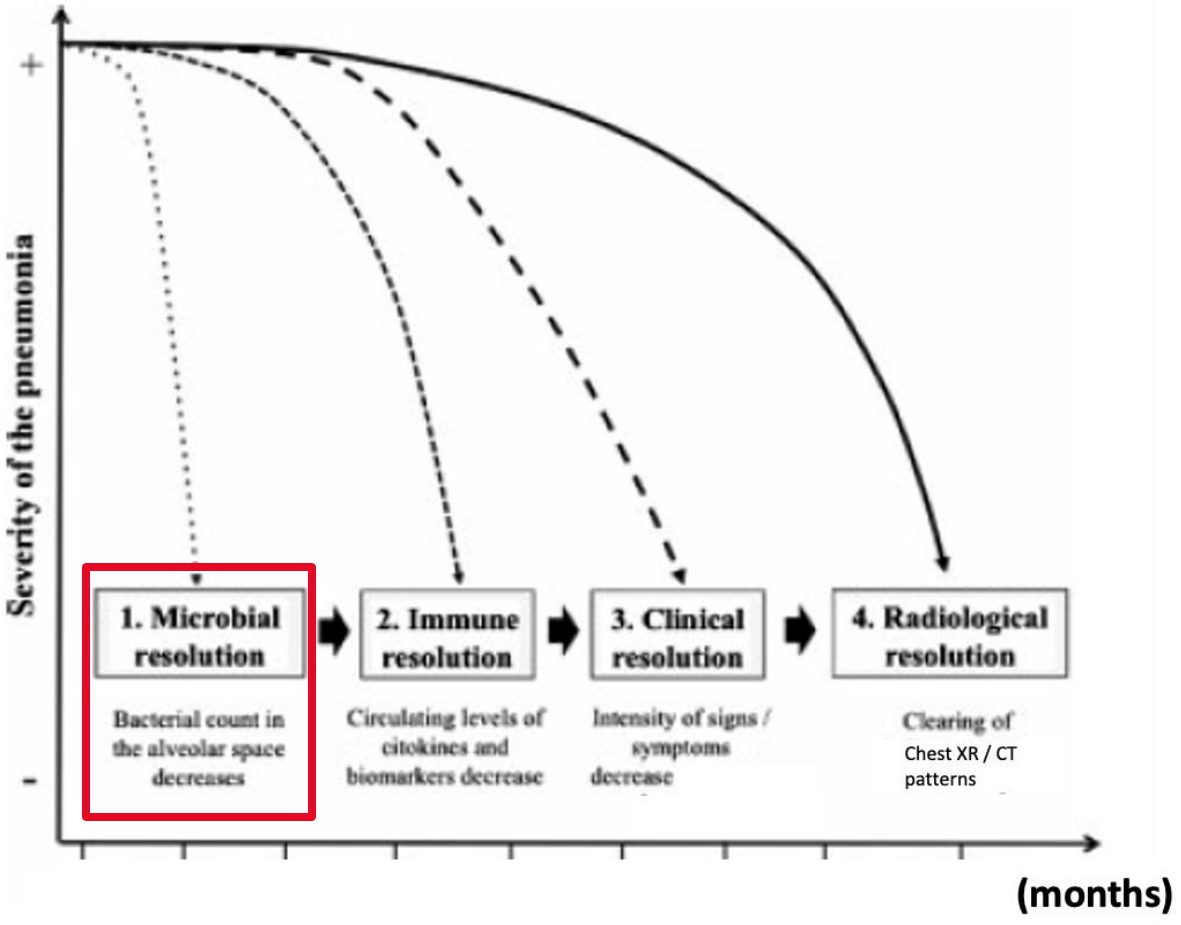
• Risk benefit ratio	73 (7%)
• Patient's preferences	27 (3%)
• Intolerance and Adverse events	3 (0.3%)

NTM-PD treatment

- Timing from NTM-PD Diagnosis and Treatment start: **57 (29-134) days**

- Mean Duration of treatment: **563 days**

What happens after treatment initiation?



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

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- Sputum culture every 1-2 months
- If unable to have spontaneous sputum, induced sputum
- Bronchoscopy in exceptional circumstances

Daley CL. Clinical Infectious Diseases 2020; 71(4):e1-e36

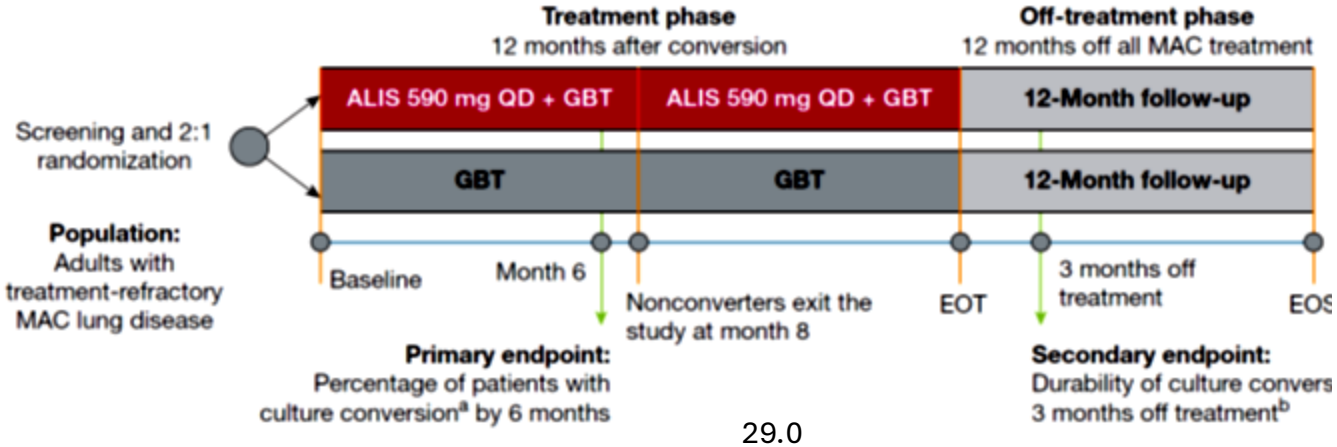
Refractory MAC-PD

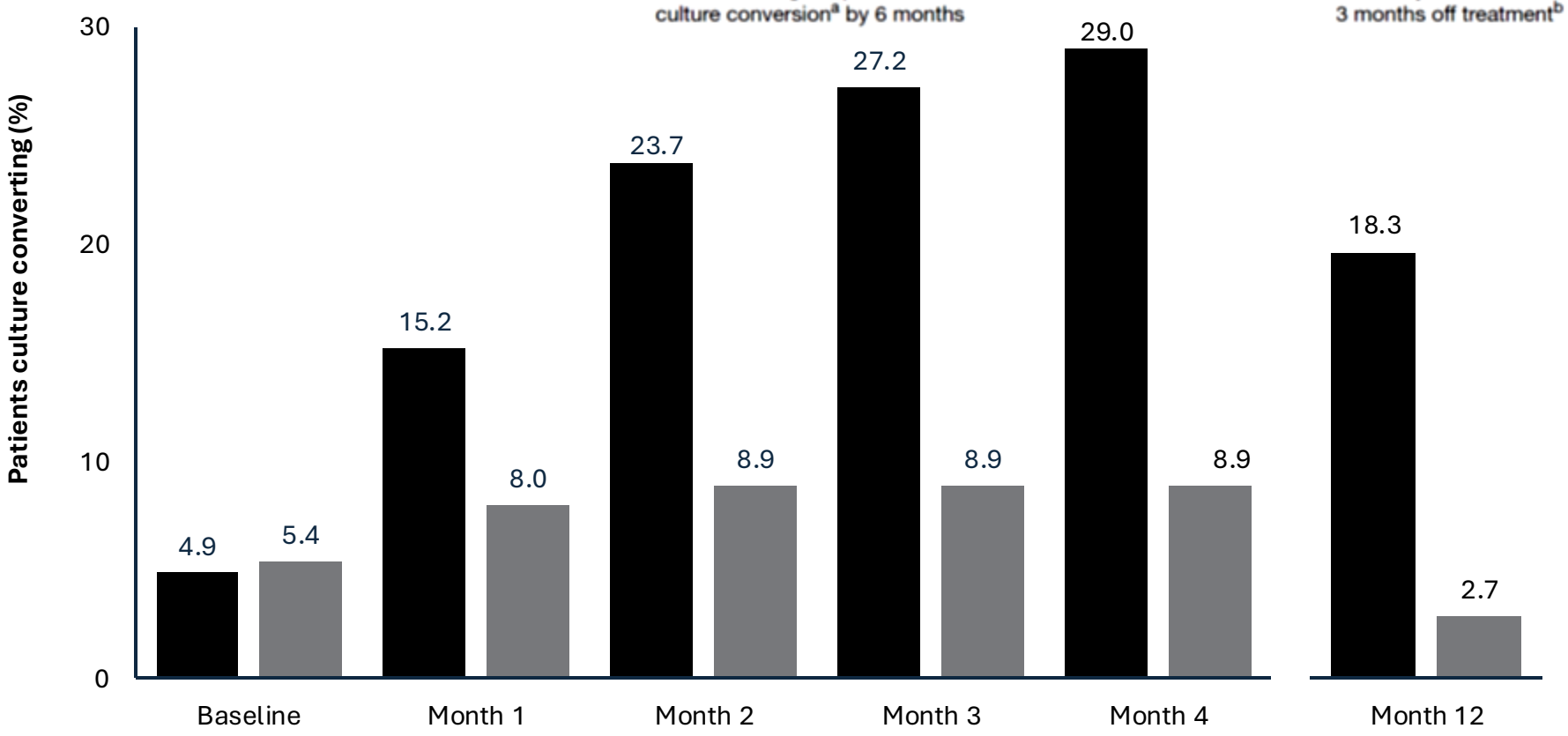
Defined as remaining sputum culture positive after 6 months of guideline-based therapy

Organism	No. of Drugs	Preferred Drug Regimen[a]	Dosing Frequency
M. avium complex			
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
Cavitary	≥3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)[b]	Daily (3 times weekly may be used with aminoglycosides)

Daley CL. Clinical Infectious Diseases 2020; 71(4):e1-e36

The CONVERT study





Griffith D.E. Am J Respir Crit Care Med 2018

Time-to-positivity predicts MAC-PD disease severity and culture conversion

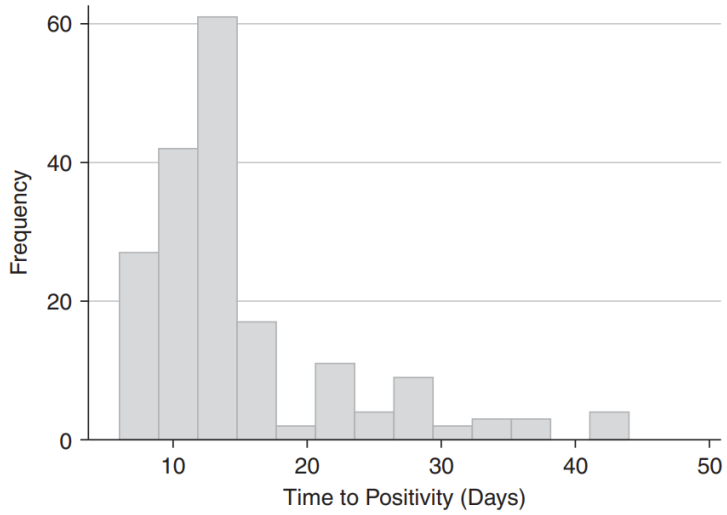


Figure 1. Distribution of index sputum culture time to positivity for *Mycobacterium avium*.

Table 3. Association between time to positivity and markers of disease severity

Variable	Time to Positivity, Median (IQR), d; *n* = Sample Size		*P* Value*
	No	Yes	
Cavity (⩾20 mm)	12 (10–15); *n* = 113	12 (8.5–15); *n* = 12	0.35
Bronchiectasis	13 (10.5–15); *n* = 11	12 (10–15); *n* = 114	0.58
Multifocal bronchiectasis (>2 lobes involved)	12 (10–15); *n* = 56	12 (10–15); *n* = 69	0.90
AFB smear positive	14 (12–21); *n* = 77	10 (7–12); *n* = 48	<0.001
NTM disease	13 (11–15); *n* = 44	12 (9–15); *n* = 81	0.03
Treatment initiated by 3 mo	13 (11–15); *n* = 99	10 (7.5–13); *n* = 26	0.01
Treatment initiated by 6 mo	13 (11–15); *n* = 91	11 (8–15); *n* = 34	0.03

Definition of abbreviations: AFB = acid fast bacilli; IQR = interquartile range; NTM = nontuberculous mycobacteria.
*Wilcoxon rank-sum test/Mann-Whitney *U* test.

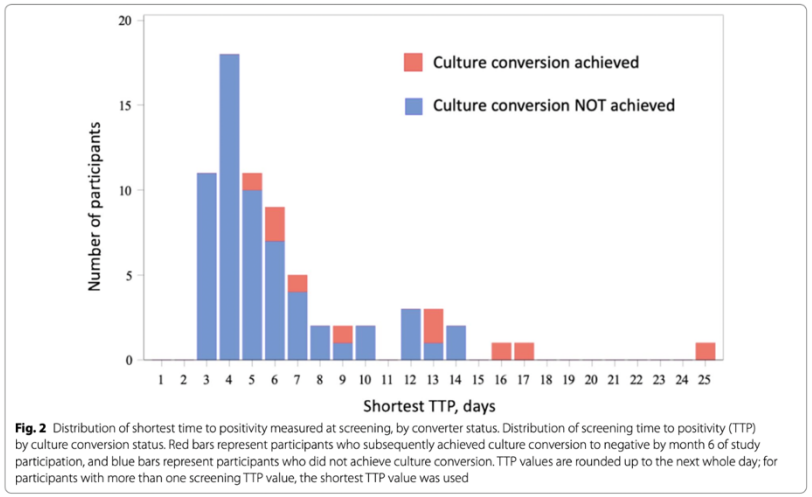


Fig. 2 Distribution of shortest time to positivity measured at screening, by converter status. Distribution of screening time to positivity (TTP) by culture conversion status. Red bars represent participants who subsequently achieved culture conversion to negative by month 6 of study participation, and blue bars represent participants who did not achieve culture conversion. TTP values are rounded up to the next whole day; for participants with more than one screening TTP value, the shortest TTP value was used

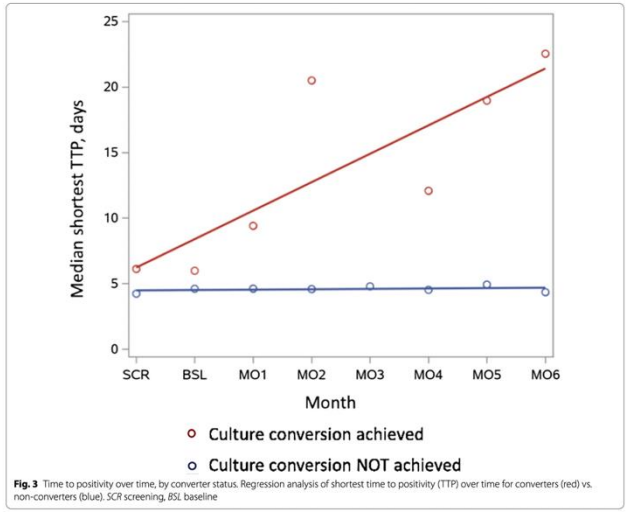


Fig. 3 Time to positivity over time, by converter status. Regression analysis of shortest time to positivity (TTP) over time for converters (red) vs. non-converters (blue). *SCR* screening, *BSL* baseline

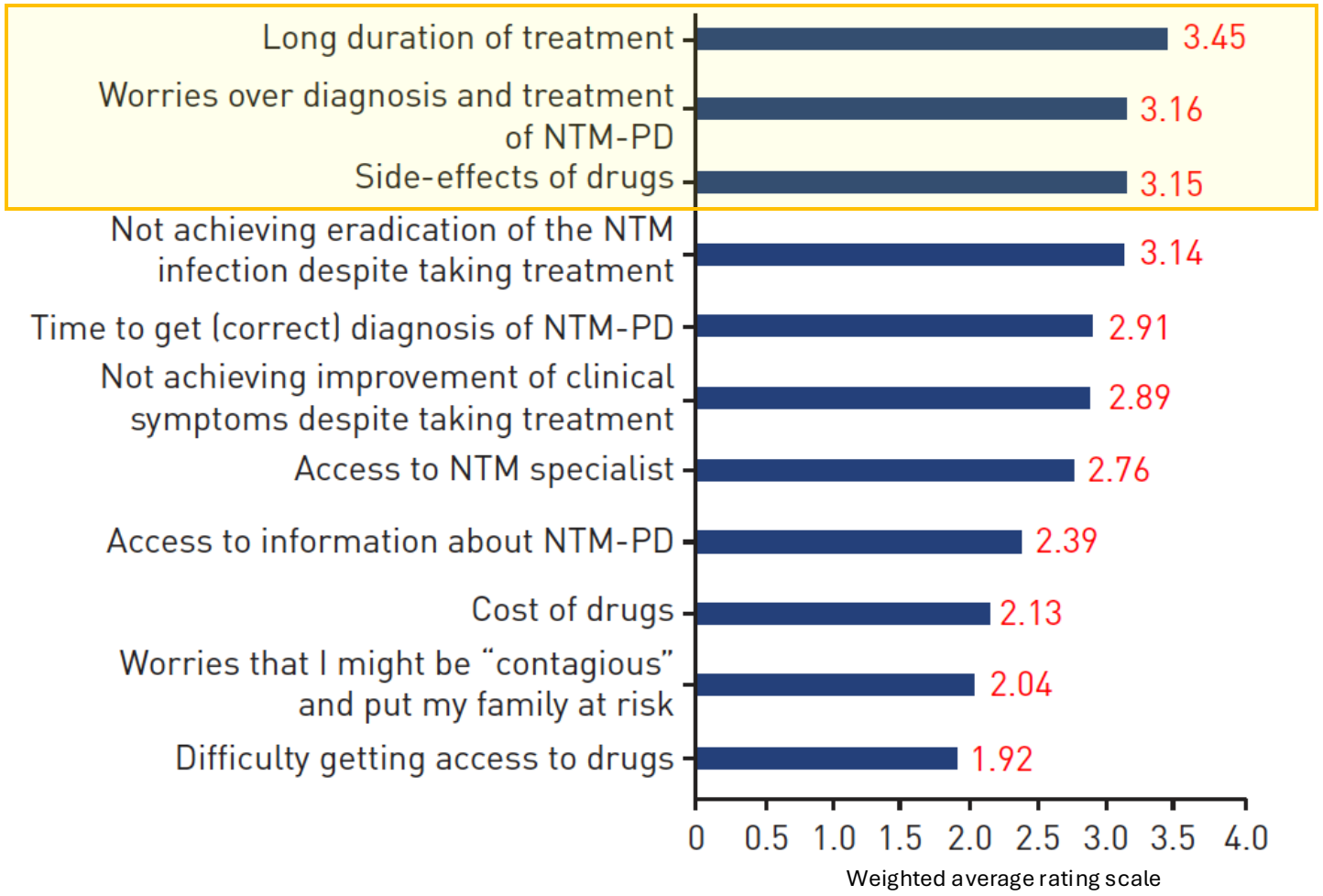
Edwards BD et al. Ann Am Thorac Soc 2022; Mingora CM et al. BMC Infect Dis 2022.

EMBARC
The European Bronchiectasis Registry

ELF

Treatment is a real issue for NTM-PD patients
- The EMBARC-ELF patient survey -

'Which aspects concerning management of NTM-PD posed a challenge for you?'



Shteinberg M, etal. ERJ Open Res 2021;7:00807-2020.

Take-home messages

- MAC is the most prevalent NTM in Italy (and in the world).
- Not all MAC positive samples are MAC-PDs.
- Not all MAC-PDs deserve active anti-mycobacterial treatment.
- If you are starting a treatment, perform a microbiological evaluation after 6 months.

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