Best Practice Advances in Front-Line Management to Optimize Clinical Outcomes in

NONTUBERCULOUS MYCOBACTERIAL (NTM) LUNG DISEASE

Focus on Prompt Intervention, Individualized Treatment Goals, Patient-Reported Outcomes, Symptom Improvement, Regimen Adherence, and Guidelines-Based Antimicrobial Therapy

1

This CME-certified simulcast symposium is jointly provided by the UMASS Chan Medical School and CMEducation Resources.

Commercial Support: Supported by an educational grant from Insmed

2

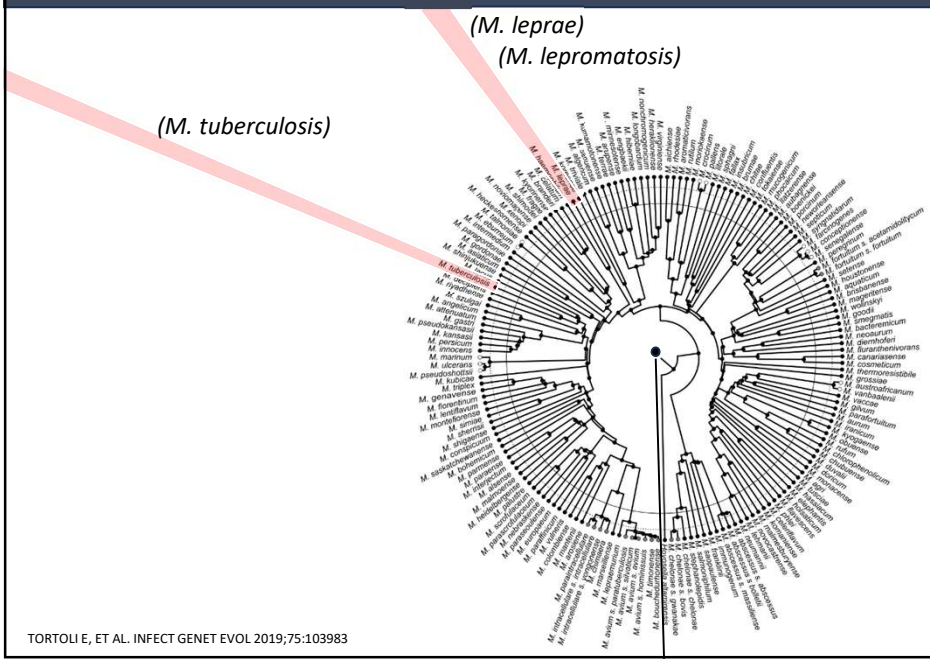
The Mandate for Individualized Care in Persons with NTM Lung Disease and Limited Options

Risk and Severity-Directed Patient Management

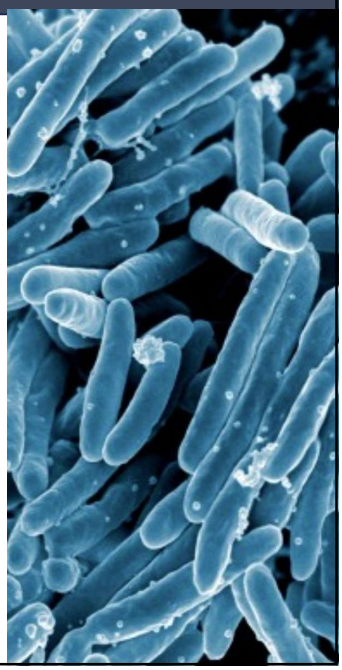
Professor Christoph Lange, MD – Program Chair
Medical Director
Research Center Borstel
Borstel, Germany

3

What are NTMs?

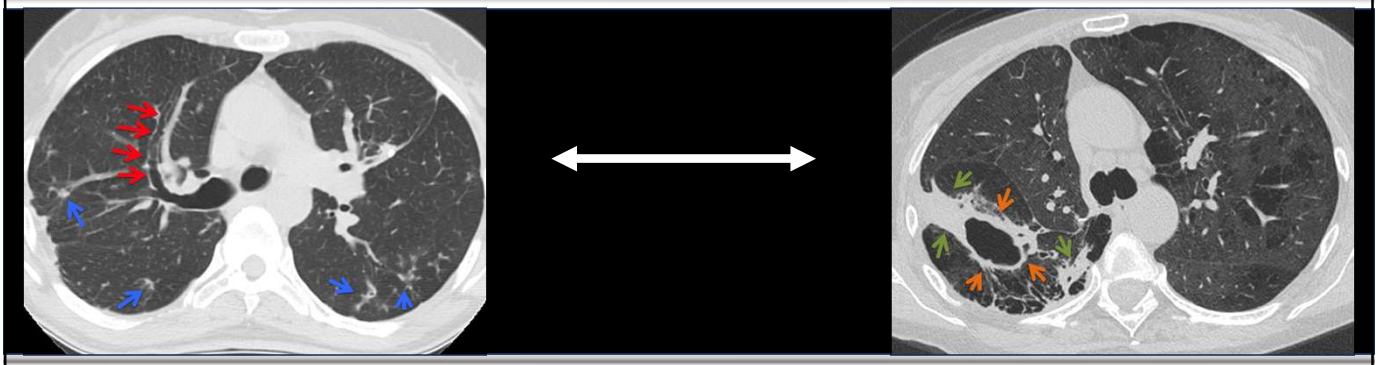


TORTOLI E, ET AL. INFECT GENET EVOL 2019;75:103983



4

What are NTM-Pulmonary Diseases?

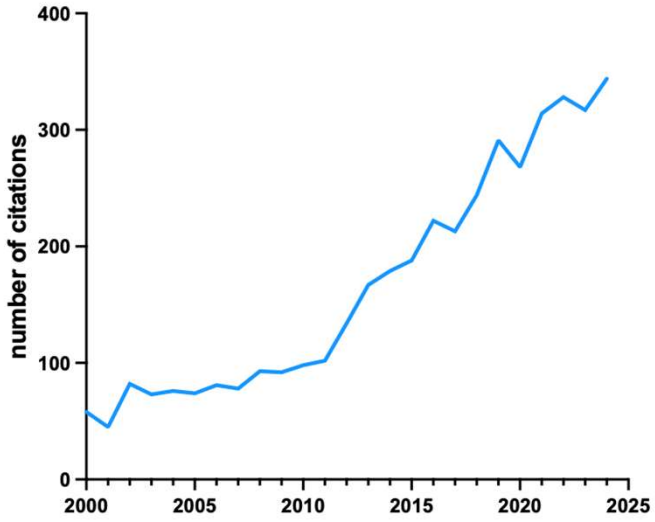


NODULAR-BRONCHIECTATIC

FIBRO-CAVITARY

5

Growing Interest in NTM-Pulmonary Diseases

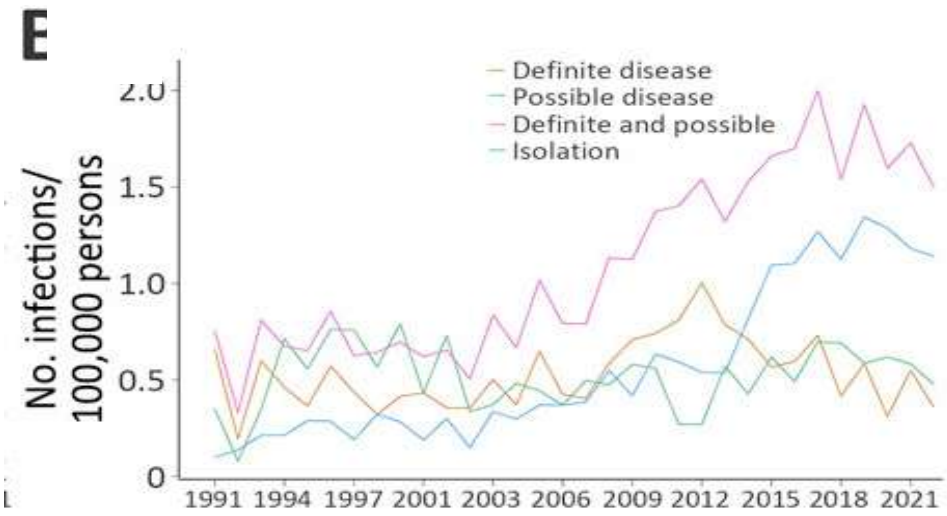


PUBMED (2000-2024): NON-TUBERCULOUS MYCOBACTERIA & PULMONARY DISEASE

6

Increasing Incidence of NTM-PD ?

Example Denmark



EMERG INFECT DIS . 2024 SEP;30(9):1755-1762.

7

Risk factors for NTM-PDs

Risk

- Pulmonary Diseases
  - **Bronchiectasis**
  - **Past pulmonary TB**
  - COPD
  - Pneumoconiosis
  - Silicosis
  - Cystic fibrosis
- Inhalative corticosteroids
- Advanced age
- Diabetes mellitus
- Alkohol use disorder
- Cigarette smoking
- Warm climate
- Living in coastal areas

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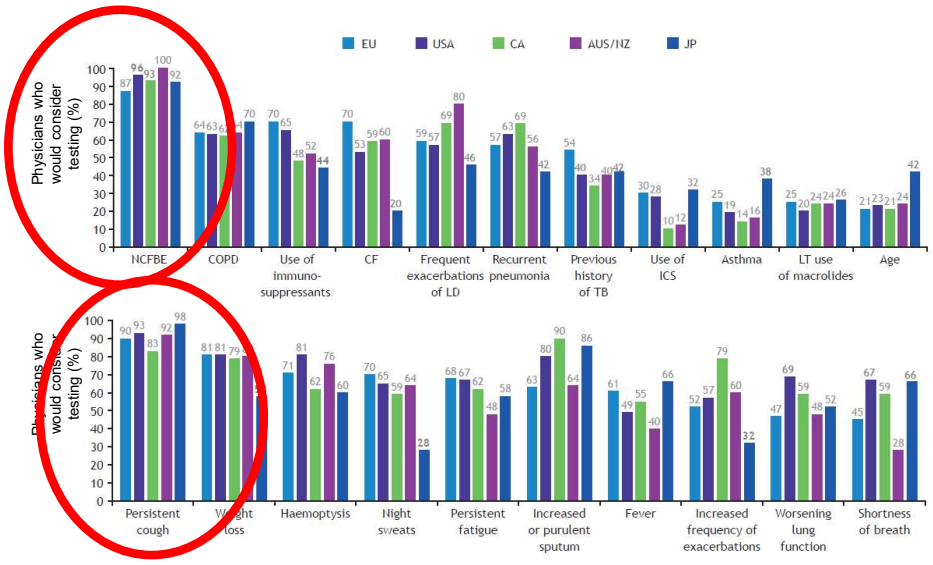
Who Should be Screened For NTM-PD?

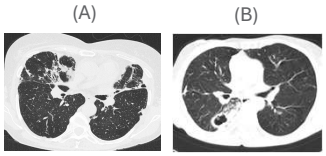


LOEBINGER M.R., ET AL. ERJOPEN RES. 2024, DOI: 10.1183/23120541.00737-2022

9

When is Infection a Disease?

+



+

Clinical

Respiratory symptoms
and
Exclusion of another disease

Imaging

Nodular (A) or cavitary(B) abnormalities on chest X ray
or
Multifocal bronchiectasis, multiple small noduli in HRCT

Microbiology

Positive culture ≥ 2 sputum samples
or
≥1 BAL/bronchial washing
or
1 histology + 1 culture from biopsy or sputum of the same species

DALEY C ET AL. ERJ 2020;56:2000535

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When is Infection a Disease?

	CRITERIUM	FAVOURS DISEASE
1	GROWTH	ACID-FAST BACTERIA VISIBLE
2	ISOLATION	REPEATED ISOLATION OF THE SAME SPECIES
3	SOURCE	ISOLATION FROM A STERILE SOURCE
4	SPECIES	PATHOGENIC SPECIES (E.G. M. KANSASII)
5	HOST FACTORS	IMMUNODEFICIENCY

WOLINSKY E: REV INFECT DIS 1981; 3: 1025–1027

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ATS/ERS/ESCMID/IDSA Guideline


Clinical Infectious Diseases

IDSA FEATURES

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

CrossMark

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

DALEY C ET AL. ERJ 2020;56:2000535

M. avium-complex, M. kansasii, M. xenopi, M. abscessus

- MAC: Azithromycin, ethambutol + rifampicin
- *M. xenopi:* Azithromycin, ethambutol + rifampicin or FQ
- *M. kansasii:* Rifampicin, isoniazid + ethambutol
- *M. abscessus:* DST! Combination of oral und i.v. therapy

12

Guidelines on Less Common NTM-PD

M. chelonae, M. fortuitum, M, genavense, M. gordonae, M. malmoense, M. simiae, M. szulgai

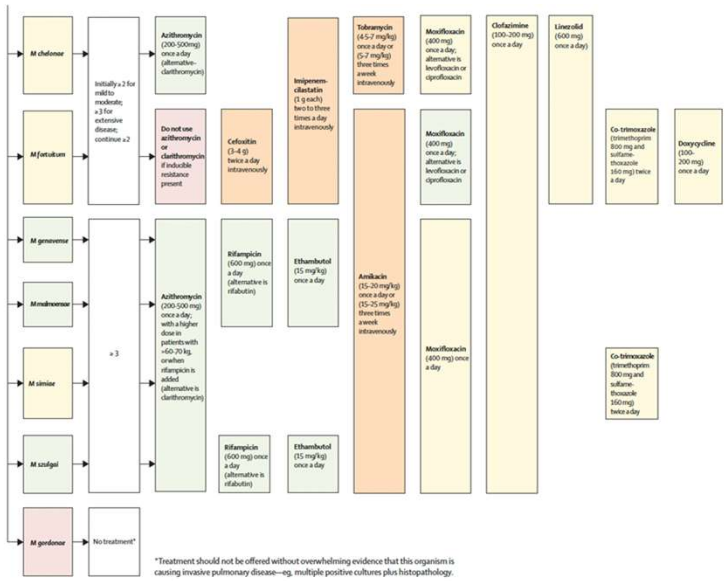
Review

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

Introduction

Methods

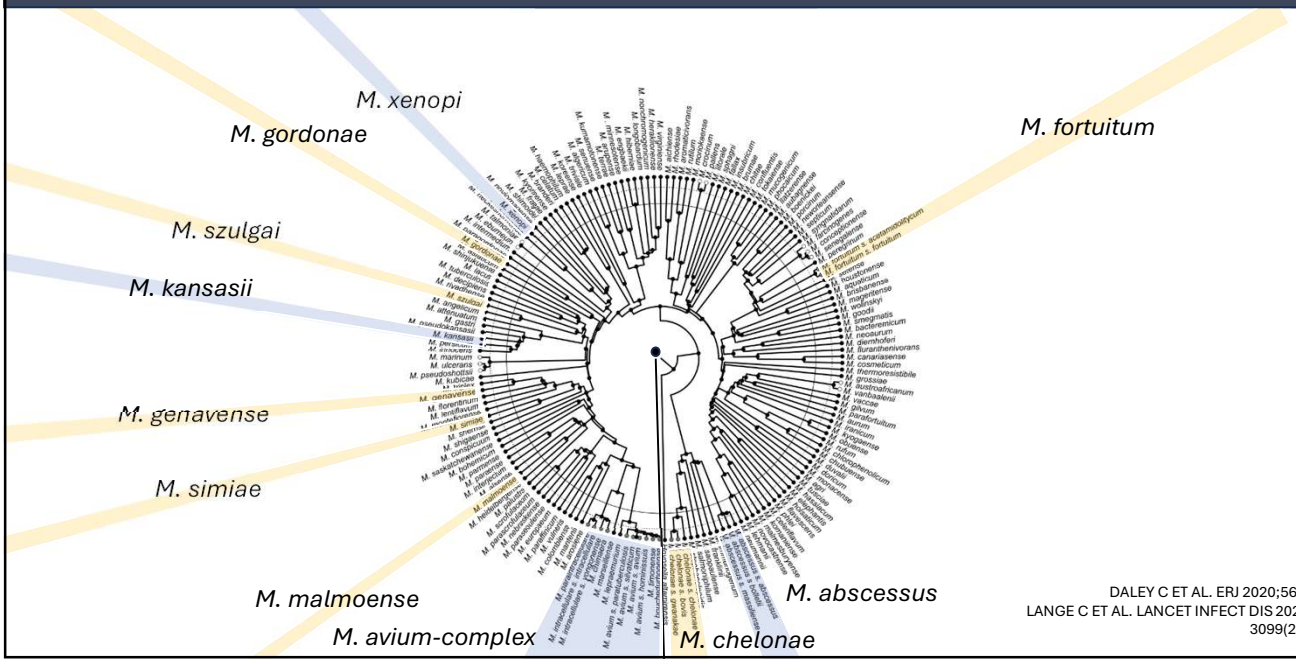
General recommendations



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

13

Evidence-Based NTM-PD Management



DALEY C ET AL. ERJ 2020;56:2000535;
LANGE C ET AL. LANCET INFECT DIS 2022; S1473-3099(21)00586-7

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Distinguished Expert Faculty

Professor Stefano Aliberti

Professor Stefano Aliberti MD PhD
Professor in Respiratory Medicine
Humanitas University, Milan, Italy
Chief, Respiratory UNIT
IRCCS Humanitas Research Hospital, Milan, Italy
Chair, Italian Registry on Non-Tuberculous Mycobacteria (IRENE)

12:55 – 13:10 hrs
Antimicrobial Decision-Making in MAC Lung Disease

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Distinguished Expert Faculty

Professor David E. Griffith

Professor David E. Griffith MD PhD
Professor of Medicine
National Jewish Health
Denver, Colorado, USA

13:10 – 13:25 hrs
Translating Results of New MAC Lung-Focused Trials

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Distinguished Expert Faculty

Professor Christoph Lange

Professor Christoph Lange, MD PhD
Medical Director
Research Center Borstel - Leibniz Lung Center, Germany
Professor of Respiratory Medicine and International Health
University of Lübeck, Germany

13:25 – 13:45
Applying New Trial-Based Evidence, Guidelines, and Individualized Approaches to Real World Management for MAC Lung Disease

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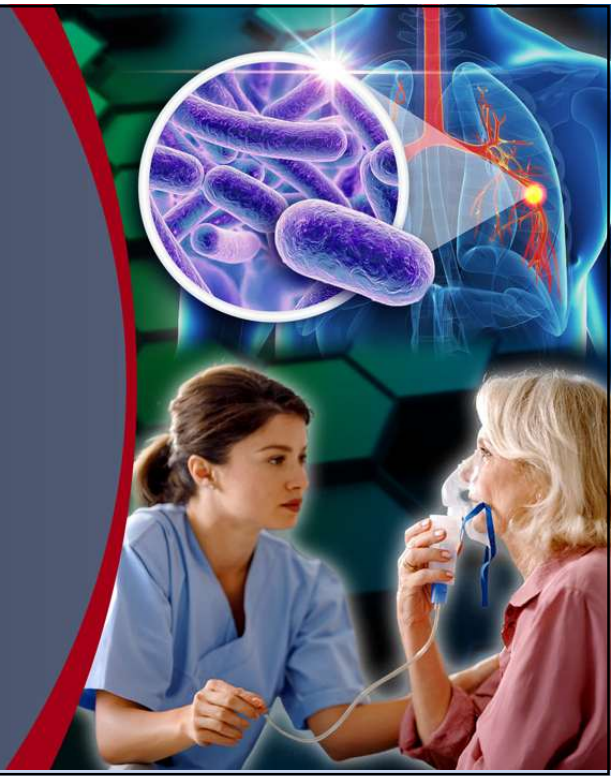
Antimicrobial Decision-Making in MAC Lung Disease

Optimizing Treatment Outcomes and Microbial Conversion



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Humanitas University, Milan, Italy
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Chair, Italian Registry of Pulmonary Non-Tuberculous Mycobacteria (IRENE)

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Clinical Case

19

Clinical Case

- Female, 80 years
- Retired philosophy teacher
- Former smoker, 36 p/y (quit)

20

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Comorbidities:
- GERD/hiatal hernia
- Cerebrovascular disease
- **Glaucoma → bilateral full blindness**
- **Mild hearing loss induced by 2 weeks of azithromycin (1 tablet three times per week), subsequently discontinued**
- **Epilepsy on valproate**

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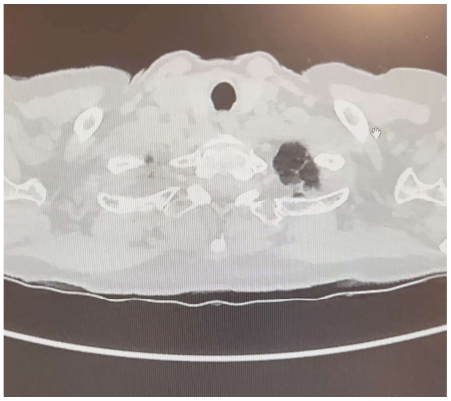
Two Chest CT (March 2024; September 2025):
- Bilateral cylindrical bronchiectasis; varicoid pattern in RML; mucus plugging; diffuse tree-in-bud; **progressive changes**



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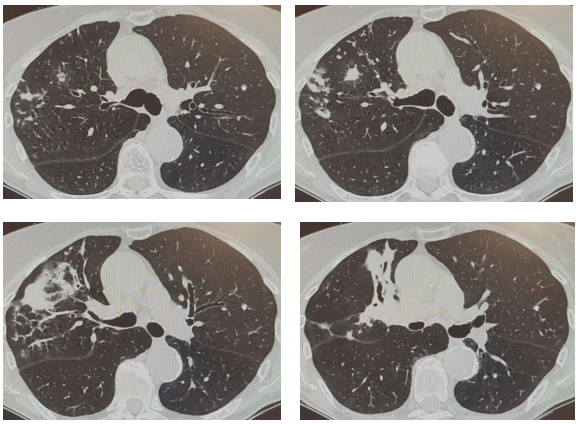
- Bilateral cylindrical bronchiectasis; varicoid pattern in RML; mucus plugging; diffuse tree-in-bud; progressive changes

Pulmonary function (September 2025):
- **FEV_1 65% predicted (post-BD)**



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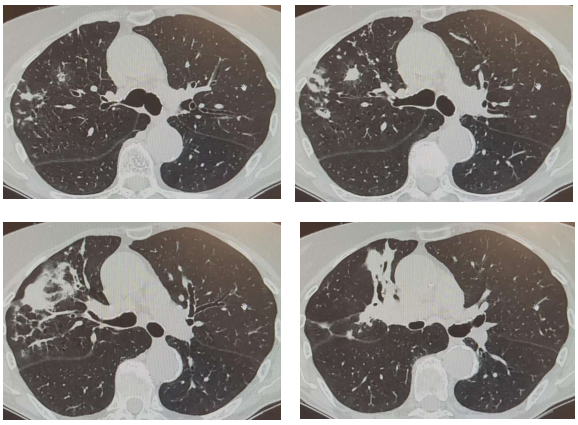
Clinical Case

Symptoms:
- Chronic cough for many years, attributed to GERD

- Daily cough with an impact on QoL
- Marked asthenia
- ~7 kg weight loss in 1 year (BMI 17.0)
- Nocturnal cough worse supine
- Mild haemoptysis (2025)

Exacerbations:
- 4 in 2025, none hospitalized, treated with antibiotics (ciprofloxacin, amoxicillin-clavulanate, tetracyclines) with only transient benefit

Immune profile:
- Relative T- and B-lymphocyte reduction; IgG subclasses normal



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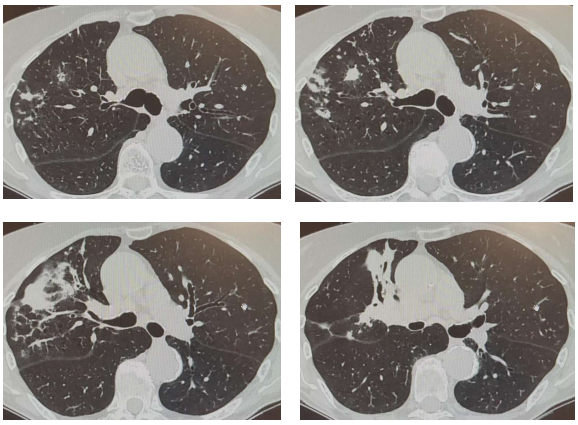
Clinical Case

BAL (June 2025):

- *Mycobacterium avium*
  - Smear Positive
  - Time To Culture Positivity ~1 week
  - Macrolide susceptible
  - Amikacin MIC 32
- *Aspergillus spp.*
  - Rare colonies
  - Galactomannan 1.2 (positive)
  - PCR DNA detected



- **What is driving the disease?**
- **Would you initiate treatment?**
- **If so, what would you target?**

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Initial Evaluation for Antimicrobial Decision-Making

Host factors	Disease severity	Disease progression	Clinical relevance
Age Increasing risk of intolerance and adverse events **Comorbidities** **Drug intolerances** Consider dose reduction or thrice-weekly regimens Consider interactions with other drugs, *e.g.* azoles **Patient wishes** **Aim of treatment** Aiming for cure or disease control?	**Radiological** Fibrocavitary disease **Clinical** Weight loss, fever, haemoptysis, respiratory failure Biochemical markers **Microbiological** Smear positivity	**Radiological** Development of cavitation or fibrosis, increasing nodules or tree-in-bud changes **Clinical** Worsening symptoms, development of new symptoms, weight loss **Microbiological** Development of new or increasing smear positivity	**NTM species** Some species more pathogenic than others **Immunosuppression** Primary immunodeficiency HIV infection Immunosuppresive therapy Anti-TNF-α therapy Corticosteroids **Lung transplantation** Need for *M. abscessus* eradication

Recommendation

In patients who meet the diagnostic criteria for NTM pulmonary disease, 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).

Daley CL. Eur Respir J 2020 ;56:2000535; Cowman S. Eur Respir J 2019; 54: 1900250

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The Microbiological Domain

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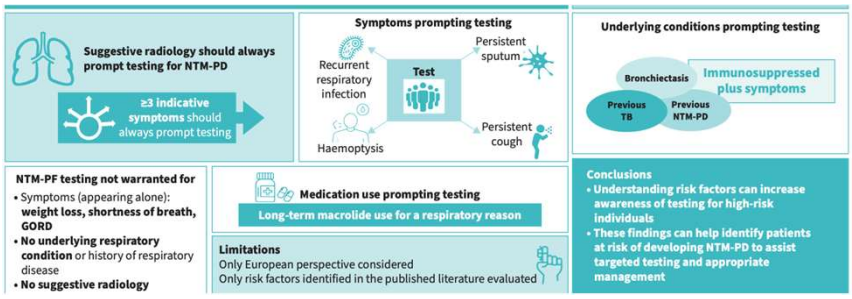
The Microbiological Domain

Systematic microbiological testing

Daily talk with the Lab

- Species (and subspecies) identification*
- Appropriate and reliable DST
- (Ideally) Genotyping of the same species isolates if recurrent

Identifying those to be tested



*12 MAC: M. avium, M. intracellulare, M. chimaera, M. colombiense, M. arosiense, M. vulneris, M. bouchedurhonense, M. timonense, M. marseillense, M. yongonense, M. paraintracellulare and M. lepraemurium (van Ingen et al., Int J Syst Evol Microbiol 2018;68:3666)

**12 European experts used a three-round modified Delphi process to identify clinical symptoms and comorbidities that increase a person's risk for NTM-PD indicate the need for testing (Loebinger MR. ERJ Open Res 2024; 10: 00791-2023)

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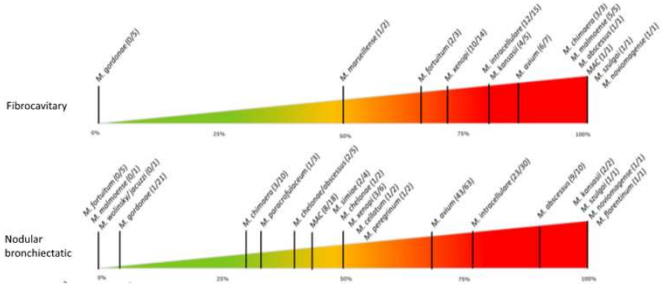
The Microbiological Domain

Species



Vande Weygaerde. BMC Infectious Diseases 2019;19:1061

Macrolide resistance

	culture conversion
Macrolide-susceptible	
• non-cavitary	60-80%
• cavitary	50-80%
Macrolide-resistant	
• no surgery, no IV aminoglycoside	5%
• surgery plus IV aminoglycoside	15%
• surgery plus aminoglycoside for ≥ 6 months	80%

Kwak N. Clin Infect Dis 65: 1077; Griffith AJRCCM 2006; Jeong AJRCCM 2015; Wallace Chest 2014; Koh ERJ 2017, Moon AAC 2016

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The Microbiological Domain

Smear Positivity as a risk factor for DISEASE PROGRESSION

	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

Hwang JA. Eur Respir J. 2017 Mar 8;49(3):1600537

Non-cavitary nodular bronchiectatic MAC-PD

Risk factors	Multivariate analysis	
	Adjusted OR (95% CI)	*P* value
Age ≤60 years	1.630 (1.036–2.564)	0.035
BMI ≤18.5 (kg/m^2)	0.515 (0.310–0.855)	0.010
COPD	0.827 (0.410–1.669)	0.596
Cough	1.458 (0.923–2.303)	0.106
Any systemic symptom[a]	2.917 (1.606–5.299)	< 0.001
Positive AFB smear	2.041 (1.214–3.432)	0.007
Mycobacterium intracellulare isolates	1.584 (0.998–2.514)	0.051
No. of involved lobes ≥4	1.652 (1.021–2.674)	0.041

Kwon BS. Respir Med. 2019 Apr;150:45-50

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The Microbiological Domain

Smear Positivity as an indication for treatment

Variable	Smear (-) (N=77)	Smear (+) (N=48)	*P* Value[a]
Cavity (□20μ μ)	6 (7.8)	6 (12.5)	0.52
Bronchiectasis	69 (89.6)	45 (93.8)	0.53
Multifocal Bronchiectasis (>2 λοβεσινπολπεδ)	41 (53.2)	28 (58.3)	0.71
NTM Disease	40 (51.9)	41 (85.4)	**<0.001**
Τρεαμι εντ Ινπατιον βψ 3 Μοντησ	10 (13.0)	16 (33.3)	**0.01**
Τρεαμι εντ Ινπατιον βψ 6 Μοντησ	13 (16.9)	21 (43.8)	**0.002**

Edwards BD. Ann Am Thorac Soc 2022; 19: 925

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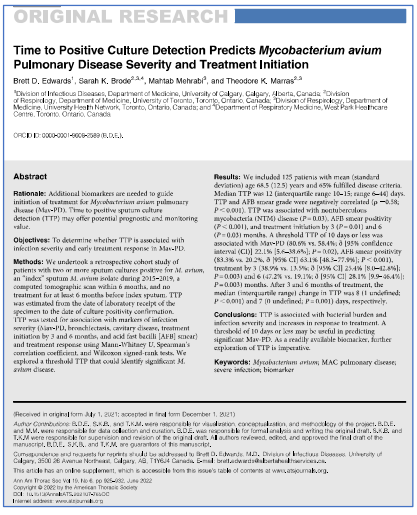
The Microbiological Domain

Time to Culture Positivity



ORIGINAL RESEARCH

Time to Positive Culture Detection Predicts *Mycobacterium avium* Pulmonary Disease Severity and Treatment Initiation

Brett D. Edwards[1], Sarah K. Brode[2,3,4], Mahlab Mehrabi[2], and Theodore K. Marras[2,3]

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ORCID ID: 0000-0001-9009-5989 (B.D.E.).

Abstract

Rationale: Additional biomarkers are needed to guide initiation of treatment for *Mycobacterium avium* pulmonary disease (Mav-PD). Time to positive sputum culture detection (TTP) may offer potential prognostic and monitoring value.

Objectives: To determine whether TTP is associated with infection severity and early treatment response in Mav-PD.

Methods: We undertook a retrospective cohort study of patients with two or more sputum cultures positive for *M. avium*, an "index" sputum *M. avium* isolate during 2015–2019, a computed tomographic scan within 6 months, and no treatment for at least 6 months before index sputum. TTP was estimated from the date of laboratory receipt of the specimen to the date of culture positivity confirmation. TTP was tested for association with markers of infection severity (Mav-PD, bronchiectasis, cavitary disease, treatment initiation by 3 and 6 months, and acid-fast bacilli [AFB] smear) and treatment response using Mann–Whitney U, Spearman's correlation coefficient, and Wilcoxon signed-rank tests. We explored a threshold TTP that could identify significant *M. avium* disease.

Results: We included 125 patients with mean (standard deviation) age 64.5 (12.5) years and 65% fulfilled disease criteria. Median TTP was 12 (interquartile range: 10–15; range: 6–42) days. TTP and AFB smear grade were negatively correlated ($\rho = -0.38$, $P < 0.001$). TTP was associated with nontuberculous mycobacteria (NTM) disease ($P = 0.03$), AFB smear positivity ($P < 0.01$), and treatment initiation by 3 ($P = 0.01$) and 6 ($P = 0.03$) months. A threshold TTP of 10 days or less was associated with Mav-PD (80.6% vs. 56.4%; δ [95% confidence interval (CI)] 22.1% [5.6–36.6%]; $P = 0.02$), AFB smear positivity (83.3% vs. 20.2%; δ [95% CI] 63.1% [48.5–77.9%]; $P < 0.001$), treatment by 3 (38.9% vs. 13.5%; δ [95% CI] 25.4% [8.0–42.8%]; $P = 0.003$) and 6 (47.2% vs. 19.1%; δ [95% CI] 28.1% [10.9–46.4%]; $P = 0.003$) months. After 3 and 6 months of treatment, the median (interquartile range) change in TTP was 8 (1 undefined; $P < 0.001$) and 7 (0 undefined; $P = 0.001$) days, respectively.

Conclusions: TTP is associated with bacterial burden and infection severity and increases in response to treatment. A threshold of 10 days or less may be useful in predicting significant Mav-PD. As a readily available biomarker, further exploration of TTP is imperative.

Keywords: *Mycobacterium avium*; MAC pulmonary disease; severe infection; biomarker

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Author Contributions: B.D.E., S.K.B., and T.K.M. were responsible for visualization, conceptualization, and methodology of the project. B.D.E., and M.M. were responsible for data collection and curation. B.D.E. was responsible for formal analysis and writing the original draft. S.K.B. and T.K.M were responsible for supervision and revision of the original draft. All authors reviewed, edited, and approved the final draft of the manuscript. B.D.E., S.K.B., and T.K.M. are guarantors of this manuscript.

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

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Internet address: www.atsjournals.org

BMC Infectious Diseases

RESEARCH Open Access

Time-to-positivity of *Mycobacterium avium* complex in broth culture associates with culture conversion

Christina M. Mingora[1], Bryan A. Garcia[2], Kevin C. Mange[3], Dayton W. Yuen[3], Monika Ciesielska[3], Jakko van Ingen[4], Patrick A. Flume[5] and Susan E. Dorman[1,3*]

Abstract

Background: Mycobacterial time to positivity (TTP) in liquid culture media has predictive value for longer term outcomes in pulmonary tuberculosis, but has not been thoroughly studied in nontuberculous mycobacterial pulmonary disease. This study sought to evaluate for association between TTP and sputum culture conversion to negative in pulmonary disease caused by Mycobacterium avium complex (MAC).

Methods: Data from the CONVERT trial (NCT02344004) that evaluated efficacy of guideline-based therapy with or without amikacin liposome inhalation suspension in adults with refractory MAC-PD (Mycobacterium avium complex pulmonary disease) were analyzed. We evaluated TTP measures for sputum obtained prior to study treatment initiation and at monthly visits, assessing reproducibility of measures as well as association of TTP with culture conversion on treatment.

Results: Data from 71 participants with at least one screening visit TTP value were analyzed. For participants who provided more than one sputum sample at a given visit, there was moderate between-sample reliability, with median intraclass correlation coefficient 0.62 (IQR 0.50, 0.70). Median TTP at screening was longer in those participants who subsequently achieved vs. did not achieve culture conversion (10.5 [IQR 9.0] days vs. 4.3 [IQR 2.8] days, $p = 0.0003$). Individuals with culture conversion by study treatment month 6 were more likely to have a screening TTP > 5 days compared to those who did not achieve culture conversion (OR 15.4, 95% CI 1.9, 716.7, $p = 0.0037$) and had increasing TTPs over time.

Conclusions: TTP prior to and on treatment is associated with microbiological treatment response in patients with MAC-PD.

Keywords: Non-tuberculous mycobacteria, Mycobacterium avium complex, Biomarker

Background

The prevalence of non-tuberculous mycobacterial pulmonary disease (NTM-PD) is increasing, and species from the *Mycobacterium avium* complex (MAC) are the most common etiology [1–3]. Current guidelines for treatment of MAC pulmonary disease (MAC-PD) recommend a prolonged course of combination antimicrobial therapy [4]. Despite treatment, outcomes remain sub-optimal and conversion of sputum cultures to negative, considered a surrogate for pathogen eradication, is not universally achieved; a meta-analysis reported a sputum culture conversion rate of 60% and a recent expanded systematic review reported a culture conversion rate of 56.3% [5–7].

[Chest Infections Research Letters] CHEST

Mycobacterium Growth Indicator Tube Time-To-Positivity Can Serve As an Early Biomarker of Treatment Response in *Mycobacterium avium* Complex Pulmonary Disease

To the Editor:

The recommended treatment regimen for *Mycobacterium avium* complex pulmonary disease (MAC-PD) consists of three drugs: rifampicin, ethambutol, and azithromycin. IV amikacin can be added in the initial 2 to 3 months for patients with severe or recurrent disease.[1] With the recommended treatment regimens, 63% of treated patients attain culture conversion[2]; the median time-to-culture-conversion amounted to 4 (range, 1 to 12) months in a previous study.[3] Because culture conversion requires multiple negative cultures that need to be incubated for 8 weeks, it takes up to 8 months to demonstrate culture conversion.[3] Hence, there is a clear need for a biomarker to predict earlier on whether conversion will be reached or whether a change in treatment regimen is necessary to achieve it.

The use of (semi)quantitative culture analysis has been suggested as a relative rapid biomarker of treatment response.[4,5] Yet the methods applied in the two existing studies, colony-forming unit counts and a semiquantitative scale, are labor-intensive and not available in routine laboratories. Clinical trials of TB treatment have shown clear correlations between *M TB* colony-forming unit counts and the time-to-positivity (TTP) of the widely used Mycobacterium Growth Indicator Tube (MGIT) automated broth culture system[6]; this correlation was also observed in a smaller study in MAC-PD.[7]

Here, we study the use of TTP in the MGIT automated broth culture system as a biomarker for treatment response in MAC-PD.

Methods

Using current criteria, we performed a retrospective chart and laboratory database review of adult patients who received a diagnosis of macrolide-susceptible MAC-PD[1] who received treatment for at least 8 months at Radboud University Medical Center (Nijmegen, the Netherlands) from 2013 to 2019. Patients were excluded if no sputum culture result was available in baseline (treatment start date ± 1 week), after 8 months (± 2 weeks) of antibiotic treatment, if less than three sputum cultures were performed or if no TTP data were available during the first 6 months of treatment. When multiple cultures with TTP data were available from the same timepoint during treatment, the average was used.

Demographic data, disease manifestations (bronchiectasis, cavitary disease), treatment regimen and culture status after 8 months of treatment and (if available) at the end of treatment were recorded from the electronic medical file and laboratory information system. We applied the NonTuberculous Mycobacteria – Network European Trials group (NTM-NET) outcome definitions for nontuberculous mycobacterial pulmonary disease (NTM-PD)[1]: for culture conversion, a more lenient definition was used: two consecutive negative cultures, collected at least 4 weeks apart. Conversion date was defined as the date of the first negative culture.[1]

Sputum samples were decontaminated with the N-acetyl-L-cysteine-sodium hydroxide method and concentrated by centrifugation before incubation in MGIT automated liquid culture and of Lowenstein-Jensen solid medium. MGIT liquid cultures were incubated for 42 days. Isolated mycobacteria were identified in MAC with the use of the line(LiPA) Mycobacteria v2 (Innogenetics) line probe assay, which includes species-specific probes for *M avium*, *M intracellulare*, and *M chimaera*.[8] Multimicrobial TTP data of MGIT liquid culture were recovered from the laboratory information system and recoded to days to reflect differences in time between sputum expectoration and laboratory processing. For negative MGIT cultures, a TTP of 43 days was recorded. Statistical comparisons between groups were made using χ^2 and Fisher's exact tests (two-sided otherwise, with the use of SPSS software (version 25; IBM).

Results

converters and nonconverters (7.68 ± 4.64 vs 4.87 ± 2.20 days; $P = .03$) overall and in the 60 patients who were treated with three-drug regimens (ie, excluding those with most severe manifestations 7.98 ± 5.07 vs 4.82 ± 2.36 days; $P = .047$). A baseline TTP of >7 days was associated with

370 Research Letters [2017 CHEST FEBRUARY 2018]

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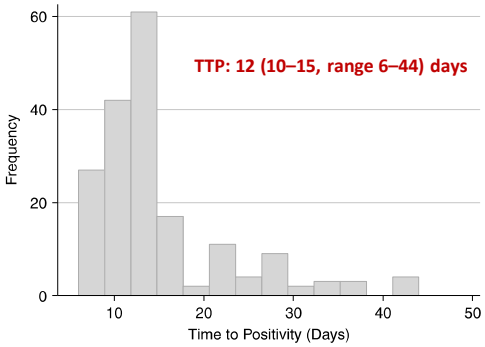
The Microbiological Domain

- Retrospective cohort study
- 125 pts
- Toronto Western Hospital NTM clinic
- 2015-2019

Time to Culture Positivity`



TTP associated with:

- NTM disease (P=0.03)
- AFB smear positivity (P<0.001)
- Treatment initiation within 3 months (P=0.01) and 6 months (P=0.03)

	≤10 Days (*n* = 36)	>10 Days (*n* = 89)	*P* Value*
Disease presence	29 (80.6)	52 (58.4)	0.02
AFB smear positive	30 (83)	18 (20)	<0.001
Treatment initiation at 3 mo	14 (38.9)	12 (13.5)	0.003
Treatment initiation at 6 mo	17 (47.2)	17 (19.1)	0.003

Edwards BD. Ann Am Thorac Soc 2022; 19: 925

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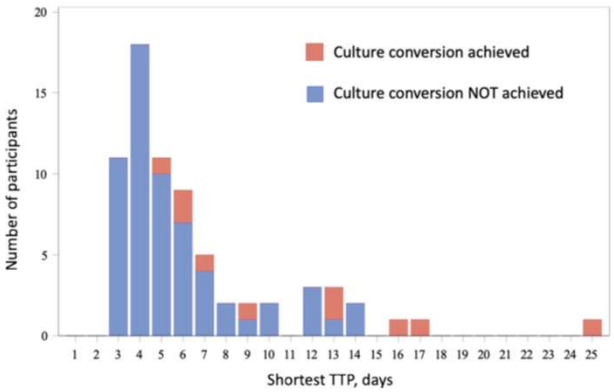
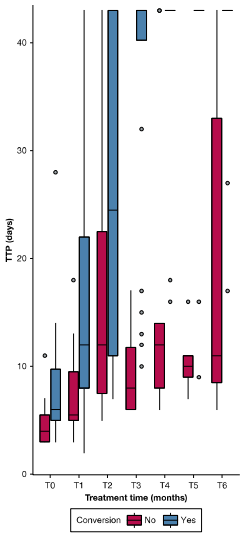
The Microbiological Domain

- CONVERT data
- 71 pts
- Broth culture + TTP Radboudumc Center Lab

Time to Culture Positivity



The median TTP at screening was longer in those participants who achieved culture conversion compared to those who did not: 10.5 (IQR 9.4) days vs. 4.2 (IQR 2.8) days, p = 0.0002 (shortest measured screening TTP) and 10.9 (IQR 7.0) days vs. 6.3 (IQR 4.3) days, p = 0.0013 (longest measured TTP)



Mingora CM. BMC Infect Dis 2022;22: 246

Danho R. CHEST 2022; 161: 370

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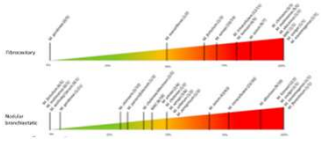
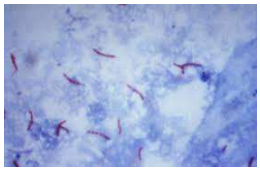
The Microbiological Domain - Longitudinally

Species



- Culture Negativity
- Appearance of new NTM
- Other bacteria / fungi

Smear



- Negativity
- Increase
- Decrease

Resistances

	culture conversion
Macrolide-susceptible	
• non-cavitary	60-80%
• cavitary	50-80%
Macrolide-resistant	
• no surgery, no IV aminoglycoside	5%
• surgery plus IV aminoglycoside	15%
• surgery plus aminoglycoside for ≥ 6 months	80%

- Occurrence of resistance

Time to Positivity

- Not applicable
- Increase
- Decrease

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The Radiological Domain

Host factors	Disease severity	Disease progression	Clinical relevance
Age Increasing risk of intolerance and adverse events **Comorbidities** **Drug intolerances** Consider dose reduction or thrice-weekly regimens Consider interactions with other drugs, *e.g.* azoles **Patient wishes** **Aim of treatment** Aiming for cure or disease control?	**Radiological** Fibrocavitary disease **Clinical** Weight loss, fever, haemoptysis, respiratory failure Biochemical markers **Microbiological** Smear positivity	**Radiological** Development of cavitation or fibrosis, increasing nodules or tree-in-bud changes **Clinical** Worsening symptoms, development of new symptoms, weight loss **Microbiological** Development of new or increasing smear positivity	**NTM species** Some species more pathogenic than others **Immunosuppression** Primary immunodeficiency HIV infection Immunosuppresive therapy Anti-TNF-α therapy Corticosteroids **Lung transplantation** Need for *M. abscessus* eradication

Recommendation

In patients who meet the diagnostic criteria for NTM pulmonary disease, 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).

Daley CL. Eur Respir J 2020 ;56:2000535; Cowman S. Eur Respir J 2019; 54: 1900250

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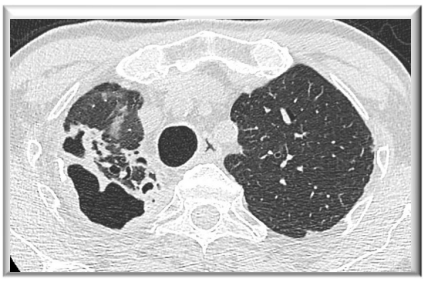
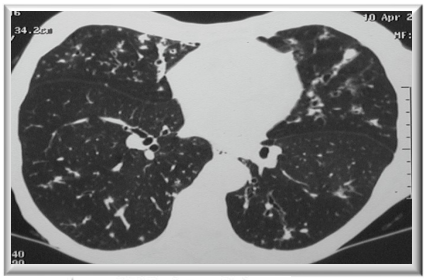
The Radiological Domain





Predictors of MAC-PD Progression	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age years	0.99 (0.98–1.00)	0.07	0.99 (0.98–1.00)	0.04
Male	0.98 (0.77–1.24)	0.85		
BMI kg·m^{-2}	0.89 (0.86–0.93)	<0.001	0.93 (0.88–0.97)	0.002
Smoker	0.89 (0.70–1.13)	0.34		
Presence of comorbidity	0.91 (0.71–1.16)	0.45		
Presence of systemic symptom*	1.56 (1.19–2.05)	0.001	1.49 (1.10–2.03)	0.01
sputum AFB positive	2.30 (1.80–2.94)	<0.001	1.81 (1.35–2.43)	<0.001
Causative organism		0.001		0.36
M avium	1		1	
M intracellulare	1.51 (1.19–1.93)		0.87 (0.64–1.18)	
Fibrocavitary pattern	2.70 (2.10–3.46)	<0.001	2.10 (1.52–2.91)	<0.001
Number of Involved lobes	1.38 (1.26–1.52)	<0.001	1.18 (1.05–1.32)	0.005

* systemic symptoms included fever, fatigue or weight loss at the time of diagnosis.

Hwang JA. Eur Respir J 2007; 49: 1600537

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Radiological Predictive Features

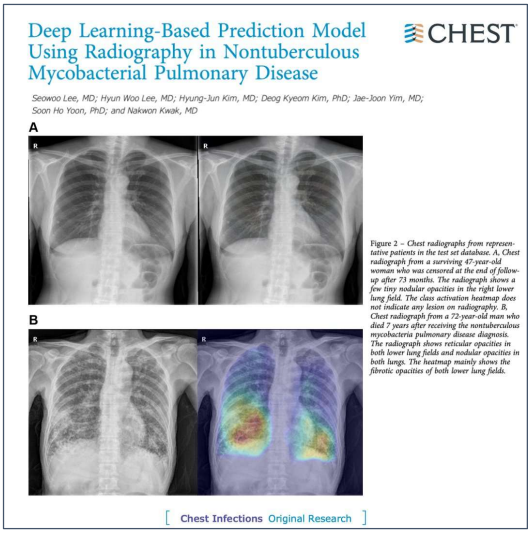
The Song Score (MAC-PD)

CT Finding (Maximum No. of Points)	Score			
	0	1	2	3
Bronchiectasis (12 points)				
Severity	Absent	Mild (bronchus diameter > adjacent vessel diameter)	Moderate (bronchus diameter = 2–3× vessel diameter)	Severe (bronchus diameter > 3× vessel diameter)
Extent	Absent	1–5 segments	6–9 segments	> 9 segments
Bronchial wall thickening	Absent	Mild (wall thickness = adjacent vessel diameter)	Moderate (vessel diameter < wall thickness < 2× vessel diameter)	Severe (wall thickness ≥ 2× vessel diameter)
Mucus plugging	Absent	1–5 segments	6–9 segments	> 9 segments
Bronchiolitis (6 points)				
Severity	Absent	Mild (identifiable; peripheral lung < 2 cm from pleura)	Moderate (definite; involvement > 2 cm from pleura)	Severe (extensive; extending to central lung)
Extent	Absent	1–5 segments	6–9 segments	> 9 segments
Cavity (6 points)				
Severity	Absent	Mild (diameter < 3 cm)	Moderate (3 cm < diameter < 5 cm)	Severe (diameter ≥ 5 cm)
Extent	Absent	1–3 in number	4–5 in number	> 5 in number
Nodules (10–30 mm in diameter) (3 points)	Absent	1–5 segments	6–9 segments	> 9 segments
Consolidation, lobular, segmental, or peribronchial (3 points)	Absent	< 3 segments	3–5 segments	> 5 segments
Bullae (3 points)	Absent	Unilateral (< 4 in number)	Bilateral (< 4 in number)	Bilateral (> 4 in number)
Emphysema (3 points)	Absent	1–5 segments	> 5 segments	NA
Mosaic perfusion (3 points)	Absent	1–5 segments	> 5 segments	NA
Lobar volume decrease (3 points)	Absent	1 lobe	2 lobes	≥ 3 lobes
Total CT score (add subtotals)[a]				

Note—Scoring system is a modified version of the scoring system used to evaluate cystic fibrosis [9, 10]. NA = not applicable.
[a]Maximum possible score = 42 points.

- The total CT score showed a significant correlation with the RV/TLC ratio, FEV1, FVC

Song J. Am J Roentgenol 2008; 191: 1070



Deep Learning-Based Prediction Model Using Radiography in Nontuberculous Mycobacterial Pulmonary Disease

CHEST

Seowoo Lee, MD; Hyun Woo Lee, MD; Hyung-Jun Kim, MD; Deog Kyeom Kim, PhD; Jae-Joon Yim, MD; Soon Ho Yoon, PhD; and Nakwon Kwak, MD

A

B

Figure 2 – Chest radiographs from representative patients in the test set database. A, Chest radiograph from a surviving 47-year-old woman who was censored at the end of follow-up after 73 months. The radiograph shows a few tiny nodular opacities in the right lower lung field. The class activation heatmap does not indicate any lesion on radiography. B, Chest radiograph from a 72-year-old man who died 7 years after receiving the nontuberculous mycobacteria pulmonary disease diagnosis. The radiograph shows reticular opacities in both lower lung fields and nodular opacities in both lungs. The heatmap mainly shows the fibrotic opacities of both lower lung fields.

[Chest Infections Original Research]

Lee S. Chest 2022; 162: 995

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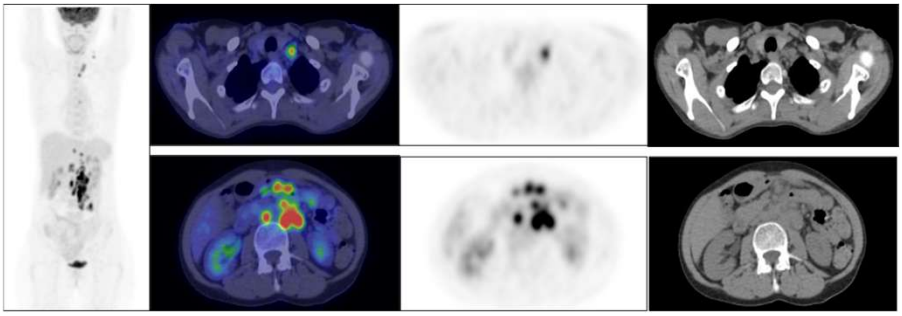
Radiological Predictive Features

PET-CT



- Case series
- Turin, Italy
- 20 pts
- Mainly "accidental"

"Ideally, FDG-PET and SUVMax measurement should possibly be part of the baseline assessment for patients newly diagnosed with NTM-LD "

Stroffolini G, et al. J Infect 2023

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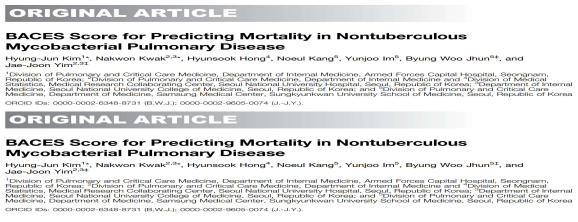
The BACES Score to Predict Mortality in NTM



ORIGINAL ARTICLE

BACES Score for Predicting Mortality in Nontuberculous Mycobacterial Pulmonary Disease

Hyung-Jun Kim[1*], Nakwon Kwak[2,3*], Hyunsook Hong[4], Neeul Kang[5], Yunjoo Im[5], Byung Woo Jhun[2†], 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 [3]Division of Medical Statistics, Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Republic of Korea; [4]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.).

ORIGINAL ARTICLE

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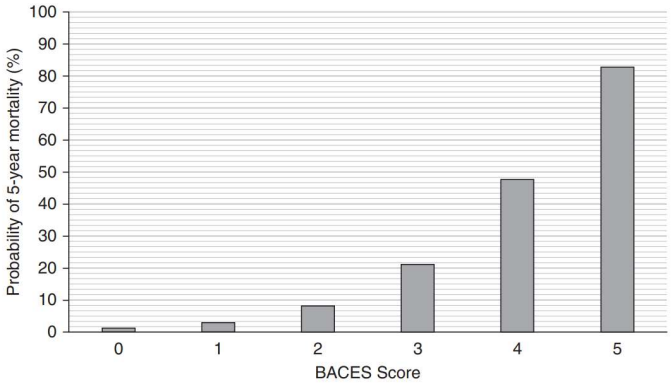
[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Armed Forces Capital Hospital, Seongnam, Republic of Korea; [2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine and [3]Division of Medical Statistics, Medical Research Collaborating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

- BACES: Body mass index, age, **<u>cavity</u>**, erythrocyte sedimentation rate and sex



- Estimated 5-year risk of mortality was 1.2% with score 0 and 82.9% with score 5

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

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Conclusions

- Smear and Time-To-Positivity to be added in the microbiological report and to be interpreted also longitudinally
- AI and PET-CT to support the radiological evaluation
- Multidisciplinary approach to manage comorbidities
- A large consensus on SoPs to be conducted after treatment initiation (as well as during watchful waiting) is needed
- This should lead to a general agreement on outcomes definitions in real life

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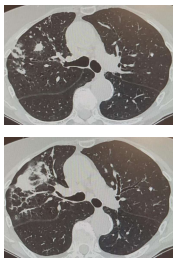
Clinical Case - Key Issues and Open Questions

- Female, 80 years
- Retired philosophy teacher
- Former smoker, 36 p/y (quit)

Comorbidities:
- GERD/hiatal hernia
- Cerebrovascular disease
- Glaucoma → bilateral full blindness
- Mild hearing loss induced by 2 weeks of azithromycin (1 tablet three times per week), subsequently discontinued
- Epilepsy on valproate

Two Chest CT (March 2024; September 2025):
- Bilateral cylindrical bronchiectasis; varicoid pattern in RML; mucus plugging; diffuse tree-in-bud; progressive changes

Pulmonary function (September 2025):
- FEV_1 65% predicted (post-BD)



Symptoms:
- Chronic cough for many years, attributed to GERD
- Daily cough with an impact on QoL
- Marked asthenia
- ~7 kg weight loss in 1 year (BMI 17.0)
- Nocturnal cough worse supine
- Mild haemoptysis (2025)

Exacerbations:
- 4 in 2025, none hospitalized, treated with antibiotics (ciprofloxacin, amoxicillin-clavulanate, tetracyclines) with only transient benefit

Immune profile:
- Relative T- and B-lymphocyte reduction; IgG subclasses normal

BAL (June 2025):

Mycobacterium avium
- Smear Positive
- Time To Culture Positivity ~1 week
- Macrolide susceptible
- Amikacin MIC 32

Aspergillus spp.
- Rare colonies
- Galactomannan 1.2 (positive)
- PCR DNA detected

MAC Lung Disease — Treat Now or Defer?

Arguments to TREAT now
- Symptom burden (chronic cough, **asthenia**, **weight loss**, functional decline) and **radiologic progression**.
- BAL AFB+ with short TTP supports active disease

Arguments to DEFER / monitor
- Major **tolerability barriers**: prior **macrolide-associated hearing loss**; **blindness** precludes monitoring for ethambutol optic toxicity
- Polypharmacy (valproate, statin, etc.)

If TREATING MAC
- Consider **macrolide-sparing** combinations (e.g., clofazimine-based backbones), acknowledging evidence limitations
- **Adjunctive inhaled amikacin** or LAI if LTO with **ototoxicity/nephrotoxicity** monitoring plan

If DEFERRING MAC therapy
- **Tight surveillance**

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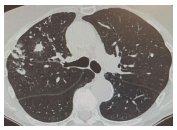

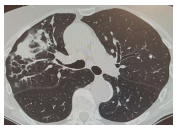

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Aspergillus spp.
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- PCR DNA detected

Aspergillus — Treat Now or Not?

Microbiological clarification first
- Complete Aspergillus work-up: total IgE; specific IgE and **IgG to *A. fumigatus* and Aspergillus spp** (ABPA unlikely)

Arguments to TREAT
- GM/PCR positivity in BAL + symptoms and progressive CT could reflect **fungal airway disease/early CPA**

Arguments to DEFER
- **Rare colonies** on culture; single BAL positivity; potential **hepatotoxicity** and **drug–drug interactions** (valproate)

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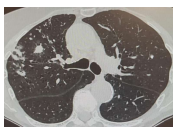

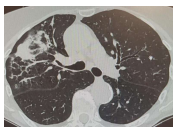

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- ~7 kg weight loss in 1 year (BMI 17.0)
- Nocturnal cough worse supine
- Mild haemoptysis (2025)

Exacerbations:
- 4 in 2025, none hospitalized, treated with antibiotics (ciprofloxacin, amoxicillin-clavulanate, tetracyclines) with only transient benefit

Immune profile:
- Relative T- and B-lymphocyte reduction; IgG subclasses normal

BAL (June 2025):

Mycobacterium avium
- Smear Positive
- Time To Culture Positivity ~1 week
- Macrolide susceptible
- Amikacin MIC 32

Aspergillus spp.
- Rare colonies
- Galactomannan 1.2 (positive)
- PCR DNA detected

Non-microbiological Interventions That Impact Outcomes

- **Airway clearance**: reinforce ACBT; consider **nasal irrigation**
- **Nutrition/rehab**: BMI 17.0 → nutritional support; graded physical reconditioning for fatigue
- **Vaccinations**: **PCV20** and **Hib** (as appropriate) at clinical stability

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Antimicrobial Decision-Making in MAC Lung Disease

Optimizing Treatment Outcomes and Microbial Conversion Based on Time to Culture Positivity (TTP), Systematic Microbiological Testing, and Radiologic/Bronchiectasis Severity Scores

THANK YOU

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Translating Results of New MAC Lung-Focused Trials Evaluating Quality-of-Life Improvements, TTP, and Microbial Conversion Metrics to Optimize Antimicrobial Drug Selection

David E. Griffith, MD
Professor of Medicine
National Jewish Health
Denver, CO

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Topics for Today's Talk

- Rapid diagnosis of MAC lung disease
- Recommended treatment regimens for MAC lung disease
- Treatment of refractory MAC lung disease
- U.S. and European Guidelines for prescribing ALIS
- The ARISE study: ALIS as first line MAC therapy
  - PRO results
  - Microbiologic results
- Anti-inflammatory treatment of bronchiectasis

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Time to Culture Positivity (TTP) Predicts Who Will Need Therapy

- Retrospective cohort study of 125 patients with 2 or more positive sputum cultures for *M. avium (*Edwards B, et al. An Amer Thorac Soc. 2022;6:925)

  Conclusions: TTP is associated with bacterial burden and infection severity and increases in response to treatment. A threshold of 10 days or less may be useful in predicting significant MAV-PD.

- Data from the ALIS CONVERT trial. 71 participants with at least one screening visit TTP value.

  Conclusions: TTP prior to and on treatment is associated with microbiological treatment response in patients with MAC-PD. (Mingora CM, et al.BMC Infect Dis. 2022;22(1):246.)

48

Serum Cell-Free DNA-based Detection of MAC Infection

Li L et al. Am J Respir Crit Care Med. 2024;209:1246-1254.

- The CRISPR MAC assay detected MAC cfDNA in MAC PD with 97.6% (91.6-99.7%) sensitivity and 97.6% (91.5-99.7%) specificity overall.
- Serum MAC cfDNA concentrations markedly decreased after MAC-directed treatment initiation in patients with MAC PD who demonstrated MAC culture conversion.
- This study provides preliminary evidence for the utility of a serum-based CRISPR MAC assay to rapidly detect MAC infection and monitor the response to treatment.

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Recommended Treatment Regimens for MAC Pulmonary Disease

	No. of Drugs	Preferred Regimen[a]	Dosing Frequency
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
Cavitary	≥ 3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)[b]	Daily (IV aminoglycoside may be used 3 times weekly)
Refractory[c]	≥ 4	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin liposome inhalation suspension or IV (streptomycin)[b]	Daily (IV aminoglycoside may be used 3 times weekly)

a. Alternative drugs could include clofazimine, moxifloxacin, linezolid (tedizolid), bedaquiline
b. Consider for cavitary, extensive nodular bronchiectatic or macrolide resistant disease
c. Sputum culture positive after 6 months of guideline-based therapy

Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

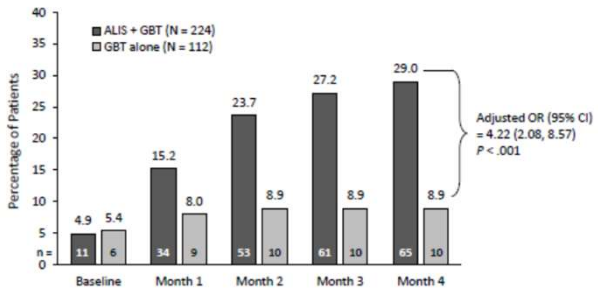
50

Treatment Refractory MAC Pulmonary Disease
Inhaled Amikacin

Guideline recommendation

In patients with MAC pulmonary disease who have failed therapy after at least six months of guideline-based therapy, we recommend addition of amikacin liposome inhalation suspension (ALIS) to the treatment regimen rather than a standard oral regimen, only (Strong recommendation, moderate certainty in estimates of effect).

CONVERT Study – Randomized, controlled study of ALIS in treatment refractory MAC pulmonary disease



Proportion of Patients With Negative Sputum Cultures for MAC

Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

Griffith D, et al. AJRCCM 2018;198:1559-1569

51

Sustainability and Durability of Culture Conversion

In patients who achieved culture conversion by month 6 in CONVERT:

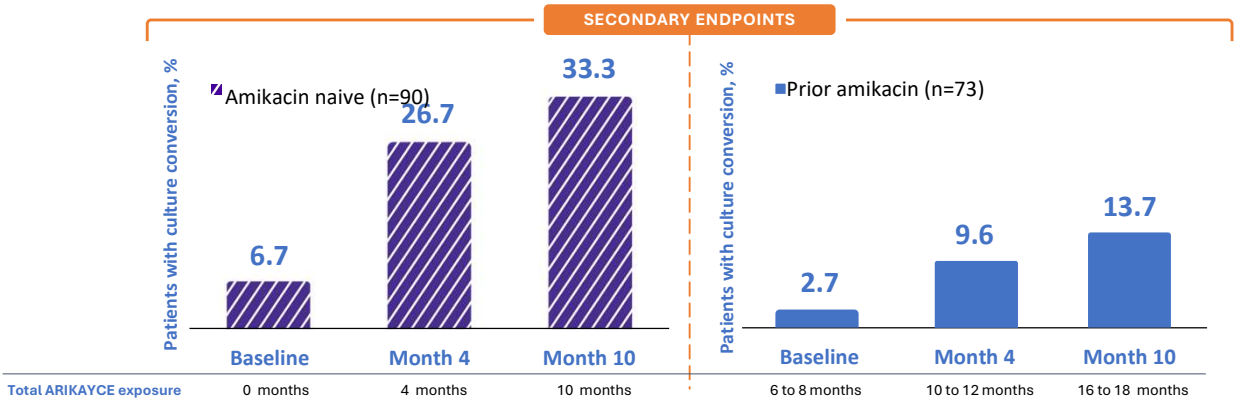
- Was conversion **sustained** (negative results for 12 mos on treatment)
- Was conversion **durable** (negative results for 3 mos and 12 mos after treatment)

		% Remaining Culture Negative		
Condition	Time of Measurement	ALIS +GBT	GBT	P-value
Sustained	12 months on therapy	63.1%	30.0%	0.064
Durable	3 months after therapy	55.4%	0%	0.0017
	12 months after therapy	46.2%	0%	< 0.0001

Griffith D, et al. *Chest* 2021;160:831-842

52

Culture Conversion Was Achieved With Extended Use of Amikacin Beyond 6 Months in INS-312



The secondary endpoint of change from baseline in 6MWT distance did not demonstrate clinical benefit by Month 6 or Month 12 in both the amikacin-naive and prior-amikacin treatment arms.

6MWT, 6-minute walk test.

Winthrop KL et al. *Ann Am Thorac Soc*. 2021;18(7):1147-1157. doi:10.1513/AnnalsATS.202008-925OC

53

Amikacin Liposomal Inhalation Suspension (ALIS) for Treatment ***Refractory*** MAC Lung Disease (2020 NTM Guidelines)

- ALIS recommendation in 2020 Guidelines made on the basis of two large randomized prospective trials
- The only "strong recommendation" for MAC therapy
- The only FDA approved therapeutic agent for MAC
- Not recommended (or FDA approved) for initial MAC therapy
- The most significant change in NTM therapy recommendations between the 2007 and 2020 guidelines.
- Parenteral amikacin recommended as part of initial therapy for cavitary or "severe" nodular/bronchiectatic disease (no change)

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FDA Approval for ALIS in Refractory MAC Lung Disease
What is wrong with this picture?

- I can think of NO other mycobacterial disease where you wait for your best drug (macrolide) to fail before adding your second best drug (ALIS). It is a recipe for acquired mutational resistance to both drugs.
- The optimal use of ALIS is including it in the initial MAC treatment regimen.

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ALIS in Europe and in the U.S.

The US Food and Drug Administration (FDA)

- In patients with MAC pulmonary disease who have failed therapy after at least six months of guideline-based therapy, we recommend addition of amikacin liposome inhalation suspension (ALIS) to the treatment regimen rather than a standard oral regimen, only. (strong recommendation, moderate certainty in estimates of effect).

The European Medicines Agency (EMA)

- The EMA recommended ALIS for use in the European Union in 2020 to treat non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium Complex (MAC) in adults with limited treatment options.

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A Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Multicenter Study to Validate Patient-Reported Outcome Instruments in Adult Subjects with Newly Diagnosed Nontuberculous Mycobacterial Lung Infection Caused by Mycobacterium Avium Complex:

The ARISE Study

Data from an investigational study
ALIS is not yet approved in this patient population

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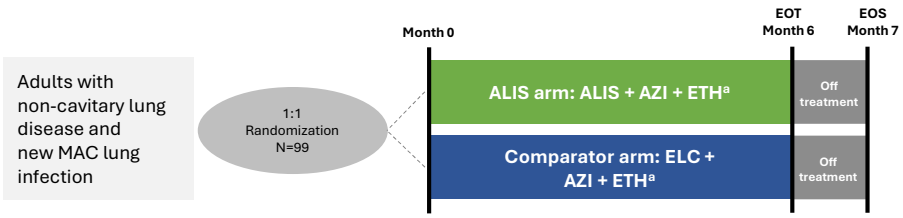
INS-415 ARISE Study Design



[a]ALIS 590 mg QD or placebo (ELC) QD plus AZI 250 mg QD and ETH 15 mg/kg QD PO

- **Primary Objective:** PRO validation for use in patients with MAC lung disease
- **Secondary Objectives:** Safety & microbiological/culture conversion
  - Symptom improvement and microbiological outcomes are assessed 1 month after completion of study treatment to remove potential confounding by known respiratory side effects of inhaled agents
- **Exploratory Objectives:** Between-group differences for PRO Scores and for culture conversion endpoints

ALIS: amikacin liposome inhalation suspension; AZI: azithromycin; ELC: empty liposome control; EOS: end of study; EOT: end of treatment; ETH: ethambutol; MAC: *Mycobacterium avium* complex; PO: orally; PRO: patient-reported outcomes; QD: once daily

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Correlation Between Culture Conversion and QOL-B Respiratory Domain Score Changes in ALIS Arm

	ALIS Arm[a] (N=48)		
	Culture converted by month 6	**Not culture converted by month 6**	**Difference**
Change in QOL-B RD score (Baseline to month 7)	+15.74	+3.53	**+12.21**
(95% confidence interval)	(+11.45, +20.03)	(-5.34, +12.41)	(+2.33, +22.08)
p-value			**0.0167**
	Culture converted by month 7	**Not culture converted by month 7**	**Difference**
Change in QOL-B RD score (Baseline to month 7)	+14.89	+4.50	**+10.39**
(95% confidence interval)	(+10.47, +19.31)	(-4.40, +13.40)	(+0.42, +20.37)
p-value			**0.0416**

ANCOVA model includes change from baseline as the response variable and baseline QOL-B RD score, and culture conversion status as independent variables using observed data

[a]ALIS arm, ALIS + AZI + ETH
ALIS: amikacin liposome inhalation suspension; AZI: azithromycin; ETH: ethambutol; LS: least-squares; QOL-B RD: Quality of Life-Bronchiectasis Respiratory Domain

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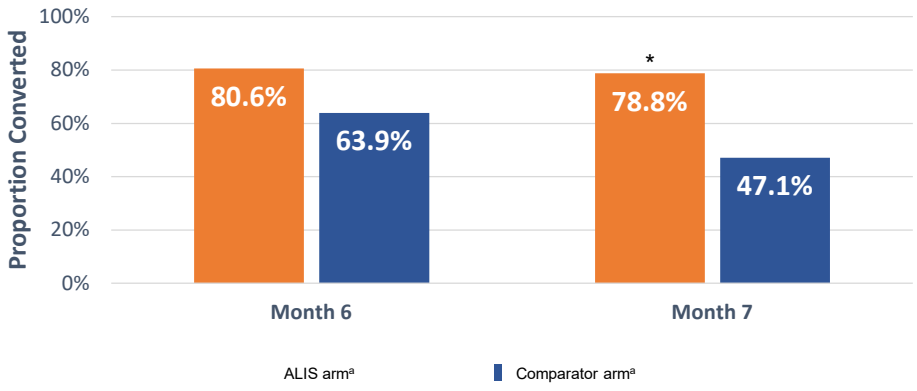
Culture Conversion by Month 6 and by Month 7

Prespecified analysis with imputation



Proportions estimated by standardized logistic regression with treatment group and history of MAC lung infection as factors in the model with multiple imputation for missing data

*p-value = 0.0010, "Nominally statistically significant" because no hierarchical testing or adjustment for multiplicity was conducted

[a]ALIS arm, ALIS + AZI + ETH; Comparator arm, ELC + AZI + ETH
ALIS: amikacin liposome inhalation suspension; AZI: azithromycin; ELC: empty liposome control; ETH: ethambutol; MAC: *Mycobacterium avium* complex

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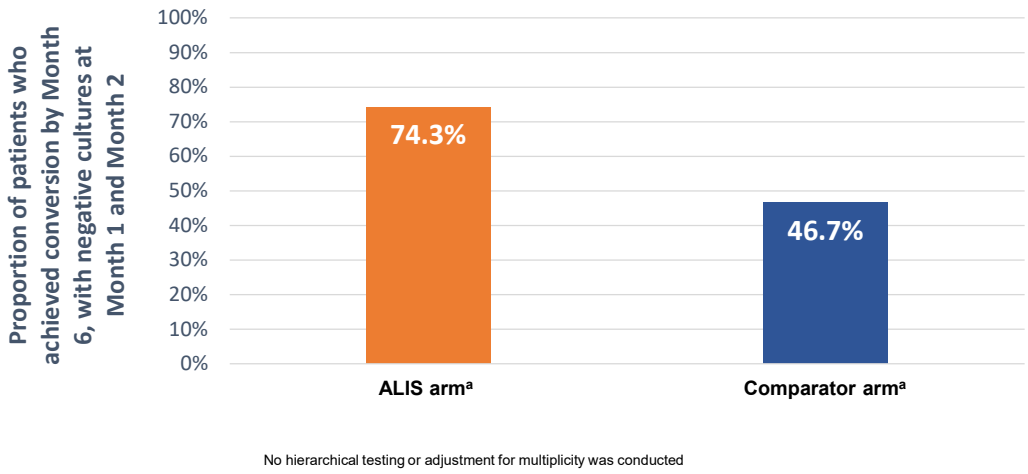
Conversion by Month 6, Conversion by Month 2, the First Possible Time to Measure Conversion, as Defined in the Study



No hierarchical testing or adjustment for multiplicity was conducted

[a]ALIS arm, ALIS + AZI + ETH; Comparator arm, ELC + AZI + ETH
ALIS: amikacin liposome inhalation suspension; AZI: azithromycin; ELC: empty liposome control; ETH: ethambutol

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Summary

- ARISE study aimed to establish that QOL-B RD is reliable to measure respiratory symptoms in patients with MAC lung disease (tool is not validated until determined as such by the FDA)
- Secondary objectives included assessment of culture conversion and change in patient reported outcomes
  - Higher culture conversion achieved in the ALIS arm vs the comparator arm at month 7 with nominal statistical significance (*P*=0.0010).
  - Culture conversion achieved earlier in the ALIS arm vs the comparator arm
  - Greater improvement in QOL-B RD score within the ALIS arm vs the comparator arm approaching clinical significance
  - Greater improvement in QOL-B RD observed in ALIS converters compared to ALIS non-converters
  - Within each study arm, there was an improvement of PROMIS Fatigue score but no statistical difference observed between arms

ALIS arm, ALIS + AZI + ETH; Comparator arm, ELC + AZI + ETH
ALIS: amikacin liposome inhalation suspension; ELC: empty liposome control; PROMIS Fatigue SF 7a: Patient-Reported Outcome Measurement Information System Fatigue-Short Form 7a; FDA: U.S. Food and Drug Administration; QOL-B RD: Quality of Life - Bronchiectasis Respiratory Domain

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Summary

- No new safety events observed in the ALIS arm and in general safety was as expected with ALIS/ELC administration on a macrolide and ethambutol background regimen
- A 15-month confirmatory study (12 months on-treatment, 3 months off-treatment) is ongoing (ENCORE; NCT04677569)

ALIS arm, ALIS + AZI + ETH; Comparator arm, ELC + AZI + ETH
ALIS: amikacin liposome inhalation suspension; ELC: empty liposome control; PROMIS Fatigue SF 7a: Patient-Reported Outcome Measurement Information System Fatigue-Short Form 7a; FDA: U.S. Food and Drug Administration; QOL-B RD: Quality of Life - Bronchiectasis Respiratory Domain

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FDA Approval for Brensocatib in NCFBE

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE

Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

Authors: James D. Chalmers, M.B., Ch.B., Ph.D., Pierre-Régis Burgel, M.D., Ph.D., Charles L. Daley, M.D., Anthony De Soyza, M.B., Ch.B., Ph.D., Charles S. Haworth, M.B., Ch.B., M.D., David Mauger, Ph.D., Michael R. Loebinger, M.D., Ph.D., +11, for the ASPEN Investigators* Au

Published April 23, 2025 | N Engl J Med 202

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FDA Approves BRINSUPRITM (Brensocatib) As The First And Only Treatment For Non-Cystic Fibrosis Bronchiectasis, A Serious, Chronic Lung Disease

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Brensocatib in NCFBE: ASPEN Study Design and Baseline Characteristics

Global phase III ASPEN trial assessed rate of bronchiectasis exacerbations in people receiving brensocatib (10 mg and 25 mg) compared with placebo at 359 clinical sites in 35 countries from Dec 2020-March 2023

Adults aged 18-85 yr with bronchiectasis confirmed by radiologic evidence and having experienced ≥2 exacerbations in prior 12 mo
(N = 1682)

- **Brensocatib** 10 mg PO QD (n = 583)
- **Brensocatib** 25 mg PO QD (n = 575)
- Placebo (n = 563)

- Demographics: mean age 61.3 yr; 64.7% female
- Disease severity: ~70% moderate to severe Bronchiectasis Severity Index
- Exacerbations: 29.3% had ≥3 exacerbations in past yr
- *P. aeruginosa:* present in 35.7% of patients
- Regional BSI scores: highest in Australia/New Zealand (8.3), lowest in Latin America (5.9)
- Cause of disease: idiopathic in 58.4%
- *P. aeruginosa*–positive vs negative patients:
  - Worse lung function
  - Higher long-term macrolide use (21.5% vs 14.0%)
  - More inhaled corticosteroid use (63.5% vs 53.9%)
- Antibiotic use: notable regional differences in long-term antibiotic use for bronchiectasis with *P. aeruginosa*

Primary end point: Annualized rate of pulmonary exacerbations over a 52-wk period

Chalmers. ERJ Open Res. 2024;10:00151. Chalmers. NEJM. 2025;392:15692

65

ASPEN Trial Subgroup Analysis: Results

Purpose: evaluate the efficacy of brensocatib, a selective DPP1 inhibitor, in reducing pulmonary exacerbations in bronchiectasis

Primary outcome: significant reduction in annualized exacerbation rates vs placebo:

- 10 mg: ↓ 21% (RR: 0.789; *P* = .0019)
- 25 mg: ↓ 19% (RR: 0.806; *P* = .0046)

Subgroup consistency: treatment benefits observed across:

- *P. aeruginosa* status
- Prior exacerbation history
- Geographic regions (notably strong effect in Japan)

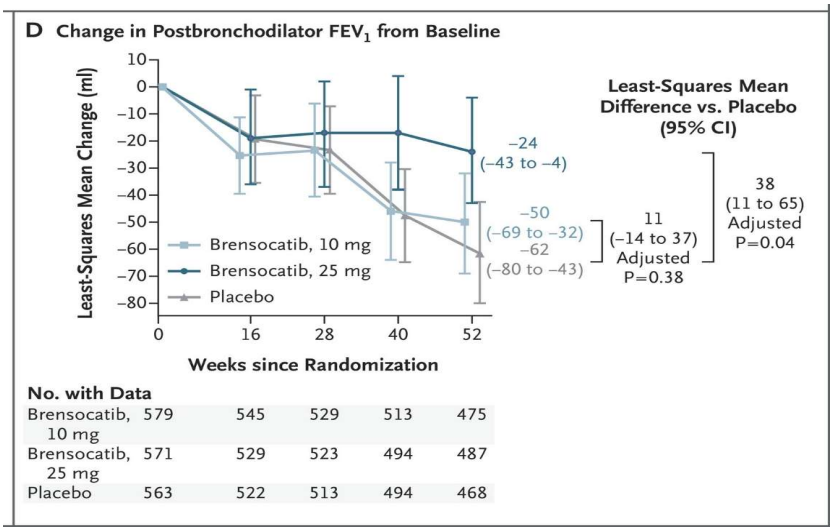
Safety: AE incidence similar across groups; COVID-19, cough, headache, nasopharyngitis most common

Conclusion: Brensocatib consistently reduced exacerbations across nearly all subgroups, highlighting its potential as the first targeted treatment for bronchiectasis

Metersky. CHEST. 2024;166:A6554.

66

ASPEN Trial Pulmonary Function Results



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Brensocatib ASPEN trial

Chalmers. ERJ Open Res. 2024;10:00151. Chalmers. NEJM. 2025;392:15692

- A total of 1721 patients received brensocatib or placebo.
- Annualized rate of pulmonary exacerbations was **1.02 in the 10-mg brensocatib group, 1.04 in the 25-mg brensocatib group, and 1.29 in the placebo group**.
- The hazard ratio for the time to the first exacerbation was 0.81, with the 10-mg dose and with the 25-mg dose.
- In each brensocatib group, **48.5% of patients remained exacerbation-free at week 52**, as compared with 40.3% in the placebo
- At week 52, **FEV_1 had declined by 50 ml with the 10-mg dose, 24 ml with the 25-mg dose, and 62 ml with placebo**
- The incidence of adverse events was similar across groups, except for a higher incidence of hyperkeratosis with brensocatib.

CONCLUSIONS

Among patients with bronchiectasis, once-daily treatment with brensocatib (10 mg or 25 mg) led to a **lower annualized rate of pulmonary exacerbations than placebo**, and the decline in FEV_1 was less with the 25-mg dose of brensocatib than with placebo

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Impact of Time Between Diagnosis and Treatment for NTM Pulmonary Disease on Culture Conversion and All-Cause Mortality

- 712 patients who received antibiotics for 6 or more months after diagnosis of NTM-PD
- Median waiting period without antibiotics among all patients was 4.8 months
- After treatment initiation 479 (67%) patients achieved culture conversion with 6 months.
- **No association between the waiting period and 6-month culture conversion or death**

Im Y et al. Chest 2022, 161; 1192

69

Impact of Time Between Diagnosis and Treatment for NTM Pulmonary Disease on Culture Conversion and All-Cause Mortality

- 6-month culture conversion demonstrated a significant negative correlation with death
- In the subgroup treated for more than 12 months, 12-month culture conversion was also associated with reduced death
- **This study suggests that for patients who are treatment refractory at 6 months that an intervention resulting in sputum culture conversion could reduce NTM disease mortality. ALIS significantly improves sputum culture conversion for treatment refractory patients.**
- **Preliminary data also suggests that ALIS improves sputum culture conversion if given with initial therapy.**

Im Y et al. Chest 2022, 161; 1192

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Applying New Trial-Based Evidence, Guidelines, and Individualized Approaches to Real World Management for MAC Lung Disease

Real-World Case Studies Optimize Antimicrobial Treatment Plans and Regimen Adherence

Professor Christoph Lange, MD – Program Chair
Medical Director
Research Center Borstel
Borstel, Germany

71

A New Patient in the OPD

59 year old woman

Background	• January, 2021 • Non-smoker
Medical history	• Chronic cough • Night seats • Weight loss (?)

72

A New Patient in the OPD

59 year old woman

Background	• January, 2021 • Non-smoker
Medical history	• Chronic cough • Night seats • Weight loss (?) • **Fatigue**

73

A New Patient in the OPD

59 year old woman

Background	• January, 2021 • Non-smoker
Medical history	• Chronic cough • Night seats • Weight loss (?) • **Fatigue**
Examination	• 59 kg, 174 cm • BP 135/80, HR 76, Sat 98%, RR 12 • Pectum excavatum • Normal breath sounds • Mid systolic click

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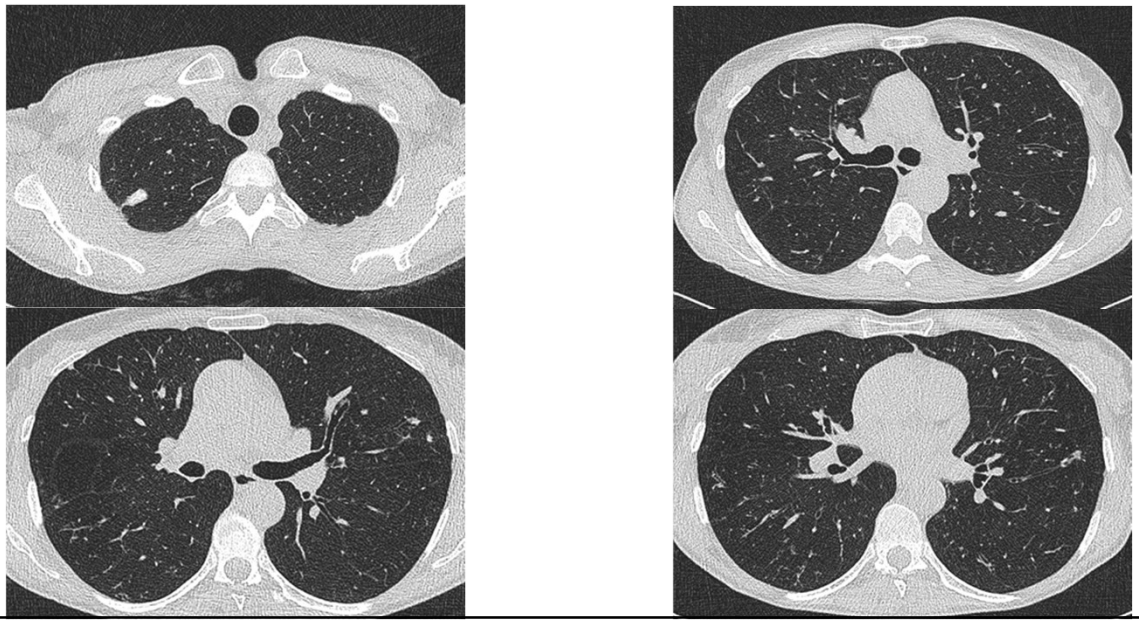
CT-Thorax – January, 2021



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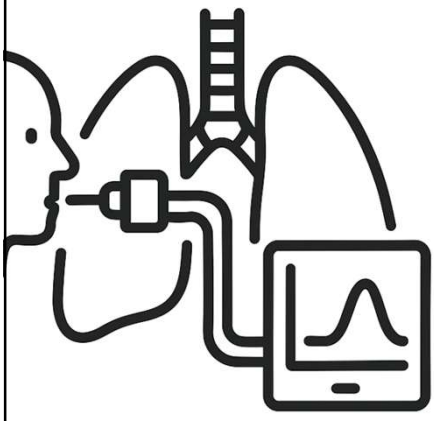
Lung Function Testing - January, 2021



FVC	3.16	100%
FEV_1	2.14	79%
FEV_1/FVC	68%	

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Microbiology

- No AFBs on sputum microscopy
- *1 x M. intracellulare*
- S: macrolides, amikacin
- Time to culture positivity: 10d4h

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When is Infection a Disease?

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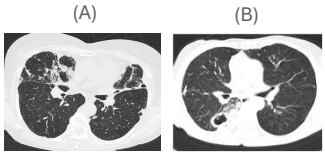

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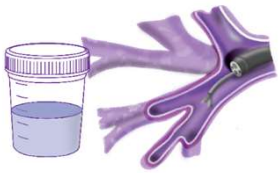

Clinical	Imaging	Microbiology
Respiratory symptoms **and** Exclusion of another disease	Nodular (A) or cavitary(B) abnormalities on chest X ray **or** Multifocal bronchiectasis, multiple small noduli in HRCT	Positive culture ≥ 2 sputum samples **or** ≥1 BAL/bronchial washing **or** 1 histology + 1 culture from biopsy or sputum of the same species

DALEY C ET AL. ERJ 2020;56:2000535

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When is Infection a Disease?

	Criterium	Favours disease
1	Growth	Acid-fast bacteria visible
2	Isolation	Repeated isolation of the same species
3	Source	Isolation from a sterile source
4	Species	Pathogenic species (e.G. *M. Kansasii*)
5	Host factors	Immunodeficiency

WOLINSKY E: REV INFECT DIS 1981; 3: 1025–1027

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Decision

No treatment necessary

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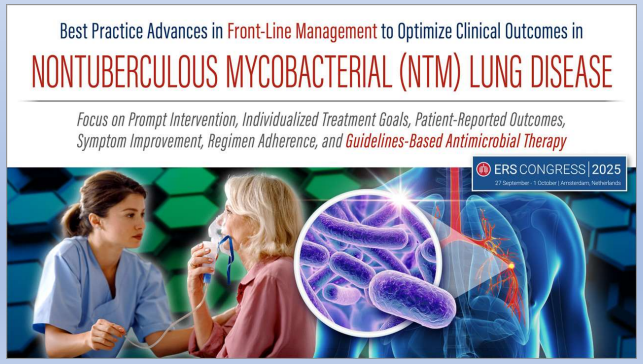
Monitoring

How should physicians monitor patients off treatment?



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Monitoring: The NTM-PD Diary

Research Center Borstel
Leibniz Lung Center

Clinical diary for patients with non-tuberculous mycobacteria pulmonary diseases (NTM-PD)

Name: Date of birth: Mycobacterium_____ Month: Year:

Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Comments
Temperature* (°C)																	
Weight (kg)																	
Night sweats (y/n)																	
Cough (1 - 24)**																	
Sputum amount (1 - 4)**																	
Sputum color***																	
Hemoptysis (y/n)																	
Fatigue****(1-10)																	

Date	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Comments
Temperature* (°C)																
Weight (kg)																
Night sweats (y/n)																
Cough (1 - 24)**																
Sputum amount (1 - 4)**																
Sputum color***																
Hemoptysis (y/n)																
Fatigue**** (1-10)																

*Temperature: always use the same method (rectal, axillary, in-ear or oral, note in „comments")
** Cough frequency: Any cough within 60 min. counts as 1x. Max score = 24 (at least one cough each hour of the day)
** Sputum amount: 1= (almost) none, 2= little 3= much, 4= very much
*** Sputum color: transparent (t); white (w); yellow (y); green (g); brown (b); no sputum: leave blank
****Fatigue: on a scale from 0 (very fit) to 10 (absolute exhausted)

Sputum microscopy
☐ pos. grade: ☐ neg.

Sputum culture
☐ pos. T2C+: ☐ neg.

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Monitoring: The NTM-PD Diary

Clinical diary for patients with non-tuberculous mycobacteria pulmonary diseases (NTM-PD)

Name: Date of birth: Mycobacterium Month: 2 / 2021 Year:

Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Comments
Temperature* (°C)																	
Weight (kg)																	
Night sweats (y/n)																	
Cough (1 - 24)**																	
Sputum amount (1 - 4)**																	
Sputum color***																	
Hemoptysis (y/n)																	
Fatigue****(1-10)																	

Date	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Comments
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Sputum color***																
Hemoptysis (y/n)																
Fatigue**** (1-10)																

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Bouncing back…September, 2024

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September, 2024

- Increasing fatigue

- Chronic cough
- Night sweats
- Weight loss

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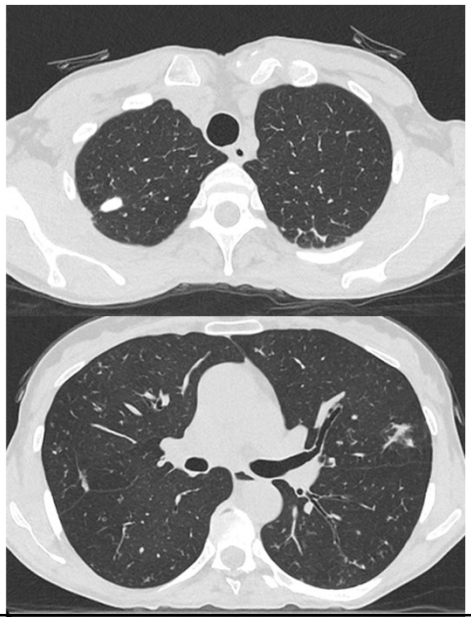
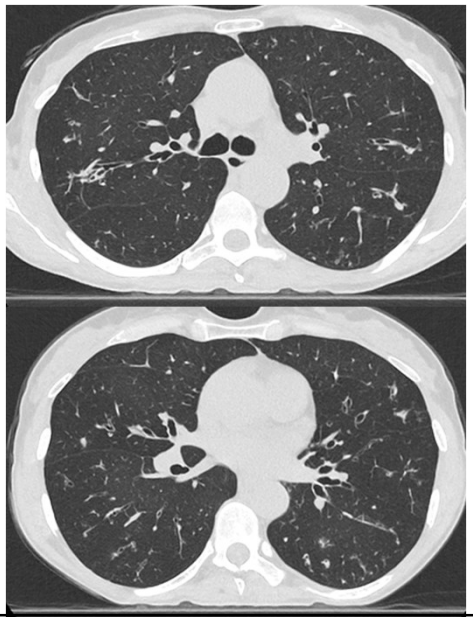
CT-Thorax - September, 2024





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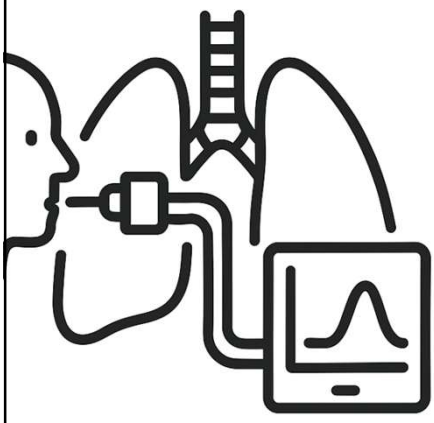
Lung Function Testing – September, 2024



FVC	2.84	82%	- 18%
FEV_1	1.71	62%	- 17%
FEV_1/FVC	60%		- 8%

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Microbiology – September, 2024

- + AFBs on sputum microscopy
- 3 x *M. intracellulare*
- S: macrolides, amikacin
- time to culture positivity 5d 23h

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Monitoring: The NTM-PD Diary

Clinical diary for patients with non-tuberculous mycobacteria pulmonary diseases (NTM-PD)

Name: Date of birth: Mycobacterium _____ Month: 10/2024 Year:

Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Comments
Temperature* (°C)	37.6	37.8	37.6	37.6	37.6	37.6	.6	.6	37.7	37.6	37.6	37.6	37.6	37.6			
Weight (kg)	55.2	55.2	55	55	54.6	54.6	54.5	54.5	54.4	54.2	54.2	54.2	54.1	54.2			
Night sweats (y/n)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y			
Cough (1 - 24)**	8	8	9	9	10	10	10	9	10	10	10	10	10	10			
Sputum amount (1 - 4)**	3	3	4	4	4	4	4	4	4	3	4	4	3	3			
Sputum color***																	
Hemoptysis (y/n)																	
Fatigue****(1-10)	8	10	10	10	10	10	10	10	10	10	10	10	10	10			

Date	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Comments
Temperature* (°C)																
Weight (kg)																
Night sweats (y/n)																
Cough (1 - 24)**																
Sputum amount (1 - 4)**																
Sputum color***																
Hemoptysis (y/n)																
Fatigue**** (1-10)																

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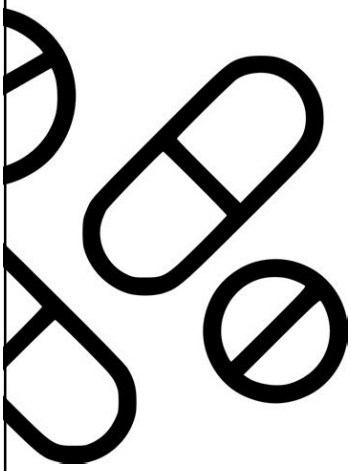
Treatment of MAC-PD



- Macrolide based therapy
- Azithromycin is better than clarithromycin
- At least 3 active substances
- Makrolide, ethambutol + x (x=rifampicin or clofazimine)
- Severe disease: cavities, ++(+) nodular-bronchiectatic or makrolid-r: amikacin/streptomycin
- Consider amikacin liposomal inhaled suspension when otions are limited
- Less severe nodulare-bronchiectatic disease: therapy 3 x/week
- Duration: 12 months beyond the time of culture conversion

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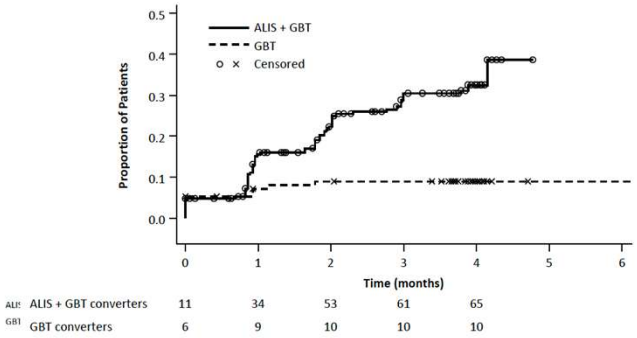
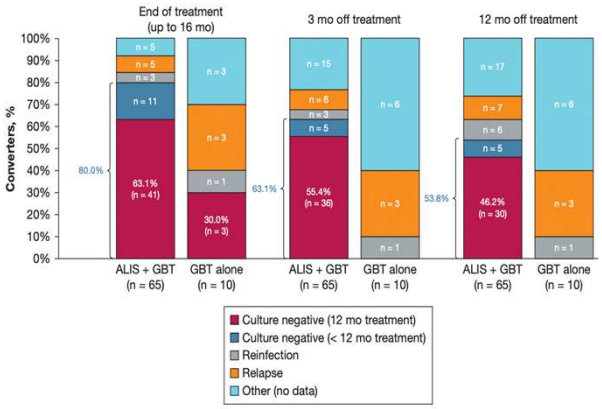
Improving Outcome (ALIS – CONVERT Study)

SIGNIFICANT INCREASE IN CULTURE CONVERSION



54% SUSTAINABLE SUCCESS



GRIFFITH D.E. AM J RESPIR CRIT CARE MED. 2018 DEC 15;198(12):1559-1569; GRIFFITH D.E. CHEST 2021;160(3):831-842

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ALIS vs IV Amikacin

Fold difference in penetration

	ALIS vs i.v. amikacin
Macrophages	274.2
Airways	69.5
Lung tissue	42.7
Plasma	0.2

i.v., intravenous

ZHANG J, ET AL. FRONT MICROBIOL 2018;9:915

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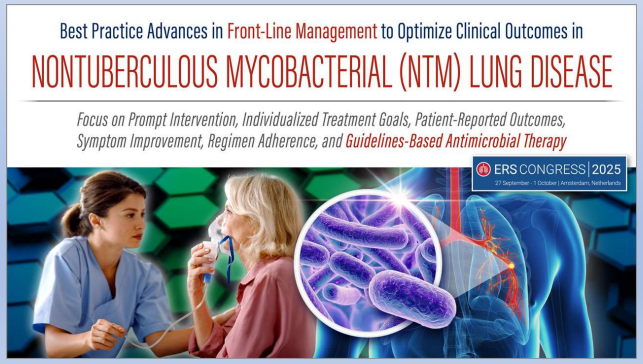
Considerations Before Treatment Initiation

What Should Physicians Consider Before Treatment For NTM-Pulmonary Disease Is Initiated?



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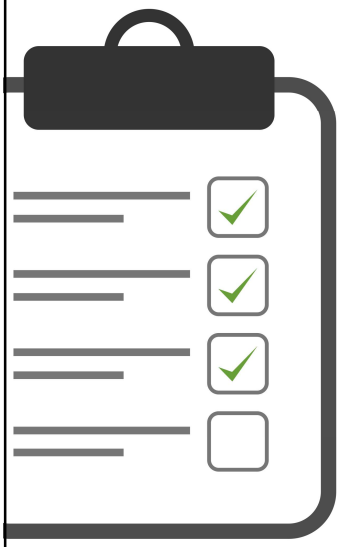
Checklist Before Treatment is Initiated



- Physician‘s decision to initiate treatment
- Patient‘s decision to initiate treatment
- All caretakers informed
- Counselling on adverse events and treatment monitoring schedule
- Counselling on cigartette smoking discontinuation (if applicable)
- Baseline BMI
- Counselling on nutrition
- Baseline imaging studies
- Surgical options have been considered
- Studies on treatable immunodeficiencies have been performed
- Adjunctive therapy options have been considered
- (MAC-DST)
- Baseline time-to-culture positivity*

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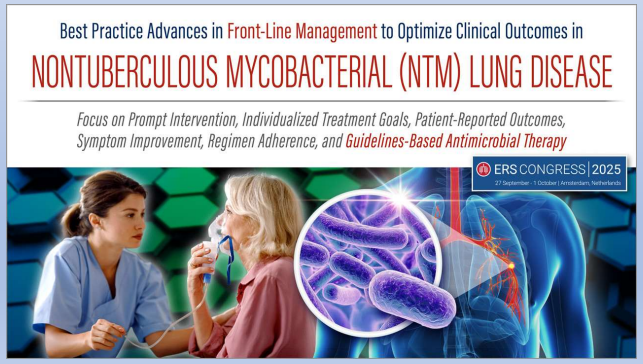
Obstacles

What obstacles must be expected in the course of therapy?



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Obstacles to Be Expected

- Adverse events
- Drug-drug-interactions
- Non-adherence
- Insufficient drug levels
- Non culture conversion
- Paradoxical reactions

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Monitoring: The NTM-PD Diary

Clinical diary for patients with non-tuberculous mycobacteria pulmonary diseases (NTM-PD)

Name: Date of birth: Mycobacterium Month: 10/2024 Year:

Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Comments
Temperature* (°C)	37.6	37.8	37.6	37.6	37.6	37.6	37.6	37.6	37.7	37.4	37.6	37.6	37.6	37.6	38.3	37.5	
Weight (kg)	55.2	55.2	55	55	54.6	54.6	54.5	54.4	54.4	54.2	54.2	54.2	54.1	54.2	54.2	54.2	
Night sweats (y/n)	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	
Cough (1 - 24)**	8	8	9	9	10	10	10	9	10	10	10	10	10	10	10	10	treatment initiation
Sputum amount (1 - 4)**	3	3	4	4	4	4	4	4	4	3	4	4	3	3	3	3	
Sputum color***																	
Hemoptysis (y/n)																	
Fatigue****(1-10)	8	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	

Date	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Comments
Temperature* (°C)	36.7	36.5	36.4	36	36.2	35.9	35.6	35.5	36	36.3	36.1	36.5	36.6	36.6	36.6	
Weight (kg)	53.2	53.4	53.4	53.4	53.5	53.5	53.8	54	54	54	54.2	54.2	54.2	54.3	54.3	
Night sweats (y/n)	y	n	y	n	n	n	n	y	n	n	y	n	n	n	n	
Cough (1 - 24)**	10	9	9	8	8	7	7	7	6	5	5	4	4	4	4	
Sputum amount (1 - 4)**																
Sputum color***																
Hemoptysis (y/n)																
Fatigue**** (1-10)	9	8	8	8	7	7	7	6	6	5	5	4	4	4	4	

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Monitoring: The NTM-PD Diary

Clinical diary for patients with non-tuberculous mycobacteria pulmonary diseases (NTM-PD)

Name: Date of birth: Mycobacterium Month: 11/2024 Year:

Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Comments
Temperature* (°C)	35.5	35.6	35.6	35.5	35.4	35.4	35.5	35.5	35.6	35.6	35.6	35.6	35.6	35.6	35.5	35.5	
Weight (kg)	54.4	54.4	54.4	54.4	54.4	54.5	54.6	55	–	–	55.2	55.2	55.2	55.3	55.2	55.3	
Night sweats (y/n)	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	
Cough (1 - 24)**	4	3	4	3	2	3	3	2	2	1	1	2	1	0	1	0	
Sputum amount (1 - 4)**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Sputum color***																	
Hemoptysis (y/n)																	
Fatigue****(1-10)	4	3	3	3	4	4	3	2	2	3	3	3	2	3	2	2	

Date	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Comments
Temperature* (°C)	35.5	35.5	35.5	35.4	35.5	35.5	35.5	35.5	35.6	35.5	35.6	35.6	35.5	35.6	35.5	
Weight (kg)	55	55.2	55.3	55.3	55.4	55.4	55.3	55.4	55.4	55.5	55.5	55.5	55.6	55.5	55.5	
Night sweats (y/n)	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	
Cough (1 - 24)**	0	0	1	1	0	0	0	0	0	0	0	0	1	0	0	
Sputum amount (1 - 4)**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Sputum color***																
Hemoptysis (y/n)																
Fatigue**** (1-10)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	

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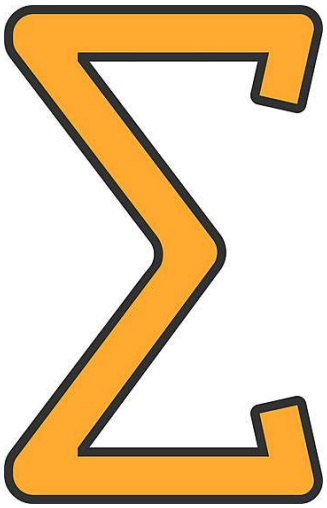
Summary: Optimizing Outcomes in MAC-PD



- Screen for MAC-PD in patients with risk factors
- Balance the decision about treatment carefully
- Use a checklist before initiating treatment
- Provide adequate treatment. The first hit is the best.
- “Limited Options“—Consider antimicrobial intensification as first step
- Monitor treatment
- Expect obstacles and mitigate side effects

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