Natural History and Burden of Refractory *Mycobacterium avium* complex Pulmonary Disease

Beyond Boundaries : Global Perspectives on TB and NTM-PD Management

6th KATRD TB/NTM International Symposium
Korean Academy of Tuberculosis and Respiratory Diseases
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PULMONARY &
CRITICAL CARE MEDICINE

Natural History and Burden of Refractory *Mycobacterium avium* complex Pulmonary Disease

DISCLOSURE

Director: Bronchiectasis and NTM Association, Education, Awareness and Advocacy
Past-chair: U.S. Bronchiectasis Research Registry
Research clinical study activity (no personal funding or research support):

- *All funding directly made to the Mayo Foundation for Medical Research and Education*
- U.S. Bronchiectasis Research Registry
- Insmed, inhaled liposomal amikacin, brensocatib
- BI, BI1291583
- Verona, ensifentrine
- Zambon, inhaled colistin
- AztraZeneca, benralizumab
- Armata, AP-PA02 phage
- Spero, SPR720
- Electromed, HillRom, RespiTech

Consultant:

- Boehringer Ingelheim

WORLD BRONCHIECTASIS DAY JULY 1ST

Bronchiectasis & NTM ASSOCIATION

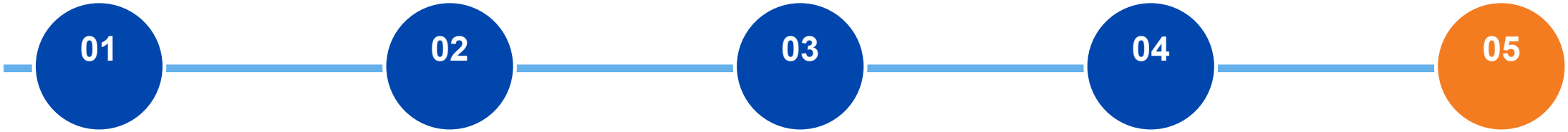
MAYO CLINIC

Three messages should shape practice

1. **Refractory MACPD is a trajectory with burden before and after the 6-month milestone**
2. **Symptoms, exacerbations, hospitalizations, and HCRU remain substantial**
3. **Risk can be reduced through correct initial therapy, early reassessment, and individualized goals**

Aksamit et al. Respir Med. 2025;246:108220; Moreira-Sousa et al. Eur Respir J. 2026;67:2500400.

A five-part clinical story



Why refractory MACPD matters

Natural history and burden

Healthcare utilization

Risk and prevention

Assessment and treatment

Primary sources: Respir Med. 2025; Pulm Ther. 2026; Eur Respir J. 2026.

Why refractory MACPD matters

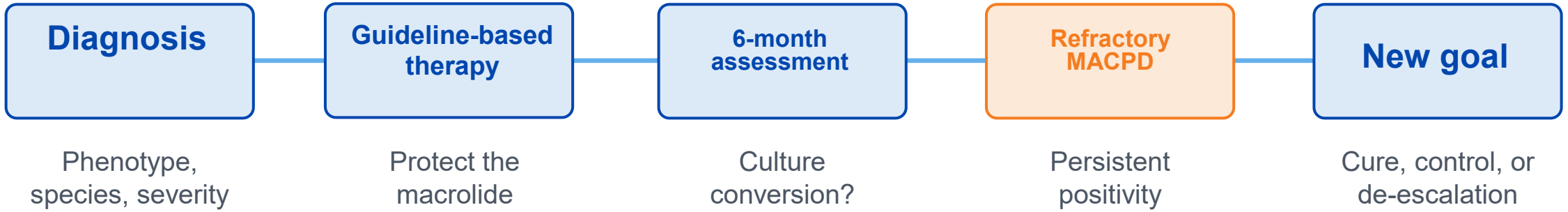
01

The refractory label is a late marker in a long, burdensome disease course.

Daley et al. Clin Infect Dis. 2020;71:e1-e36; Aksamit et al. Respir Med. 2025;246:108220.

MACPD is a trajectory, not a binary state

Treatment goal — **Sustained culture conversion, symptom improvement, functional preservation, and acceptable treatment burden**



The decision at month 6 is a reassessment point - not an automatic mandate to intensify.

Daley et al. Clin Infect Dis. 2020;71:e1-e36; Moreira-Sousa et al. Eur Respir J. 2026;67:2500400.

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Treatment failure begins with an objective milestone

No culture conversion after 6 months of appropriate guideline-based therapy

1

Microbiology

Required anchor

Persistent positive cultures

2

Clinical course

Context, not mandatory

Symptoms, weight, function, quality of life

3

Radiology

Context, not mandatory

Progression, cavities, new disease burden

Moreira-Sousa et al. Eur Respir J. 2026;67:2500400; Daley et al. Clin Infect Dis. 2020;71:e1-e36.

The burden starts before the refractory label

Before treatment	Treatment visit	Pre-refractory visit	Refractory visit
Symptoms and structural lung disease	Exacerbations 54% Hospitalizations 19%	Exacerbations 46% Hospitalizations 13%	Exacerbations 39% Hospitalizations 13%



Clinical implication

Waiting for the label can miss a prolonged window of morbidity, treatment optimization, and supportive care.

Aksamit et al. Respir Med. 2025;246:108220.

Prevention starts with the first prescription

Correct regimen

Macrolide + ethambutol + third active companion drug

Baseline

Correct intensity

Daily therapy for cavitary or advanced disease; consider IV aminoglycoside

Months 1-3

Correct monitoring

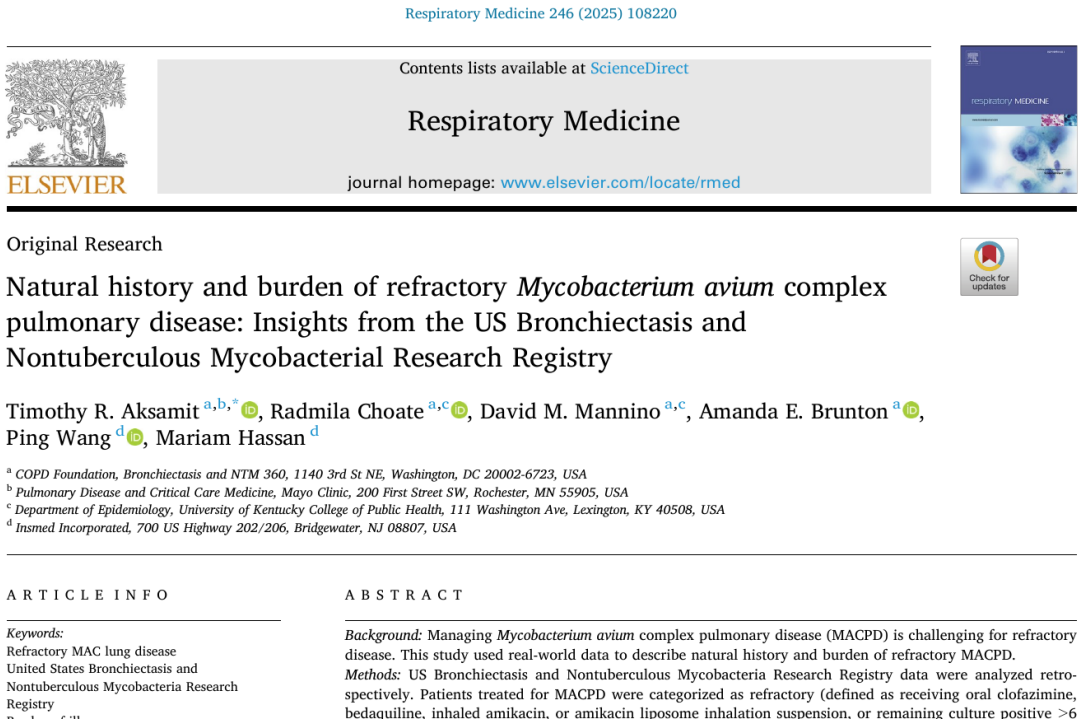
Monthly cultures, toxicity surveillance, adherence and interaction checks

Month 6

Daley et al. Clin Infect Dis. 2020;71:e1-e36; Morimoto and Daley. Ann Am Thorac Soc. 2025;22:651-659.

Respiratory Medicine 2025

02



Respiratory Medicine 246 (2025) 108220

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Original Research

Natural history and burden of refractory *Mycobacterium avium* complex pulmonary disease: Insights from the US Bronchiectasis and Nontuberculous Mycobacterial Research Registry

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ARTICLE INFO

Keywords:
Refractory MAC lung disease
United States Bronchiectasis and Nontuberculous Mycobacteria Research Registry

ABSTRACT

Background: Managing *Mycobacterium avium* complex pulmonary disease (MACPD) is challenging for refractory disease. This study used real-world data to describe natural history and burden of refractory MACPD.
Methods: US Bronchiectasis and Nontuberculous Mycobacteria Research Registry data were analyzed retrospectively. Patients treated for MACPD were categorized as refractory (defined as receiving oral clofazimine, bedaquiline, inhaled amikacin, or amikacin liposome inhalation suspension, or remaining culture positive >6

What the US Bronchiectasis and NTM Research Registry reveals about natural history and burden.

Aksamit et al. Respir Med. 2025;246:108220.

BRONCHIECTASIS DAY JULY 1ST

Bronchiectasis & NTM ASSOCIATION

MAYO CLINIC

The study asked two clinically practical questions

1. **How do refractory and nonrefractory patients differ at the treatment visit?**

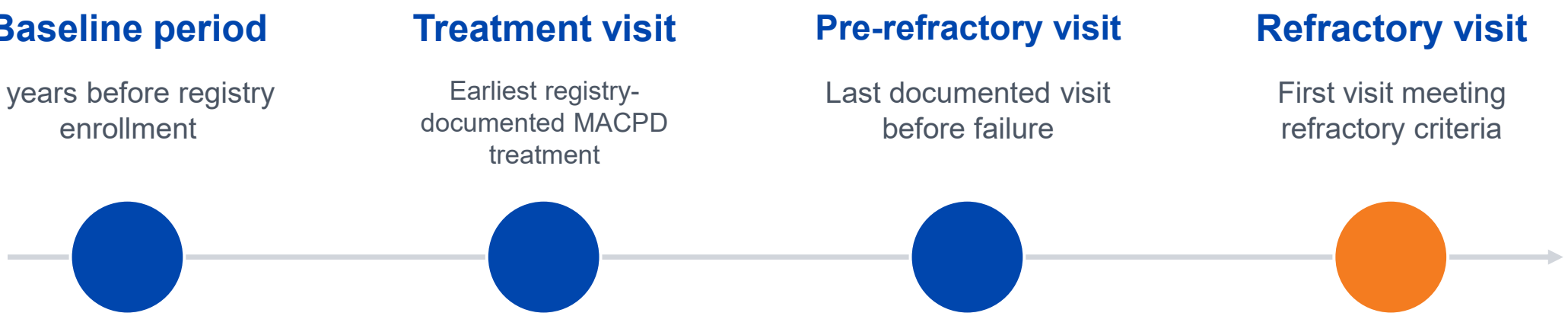
2. **What happens immediately before and when incident refractory disease is identified?**

US Bronchiectasis and NTM Research Registry

Academic specialty centers | standardized clinical, microbiologic, imaging, symptom, treatment, exacerbation and hospitalization data

Aksamit et al. Respir Med. 2025;246:108220.

The refractory definition combined microbiology and treatment patterns

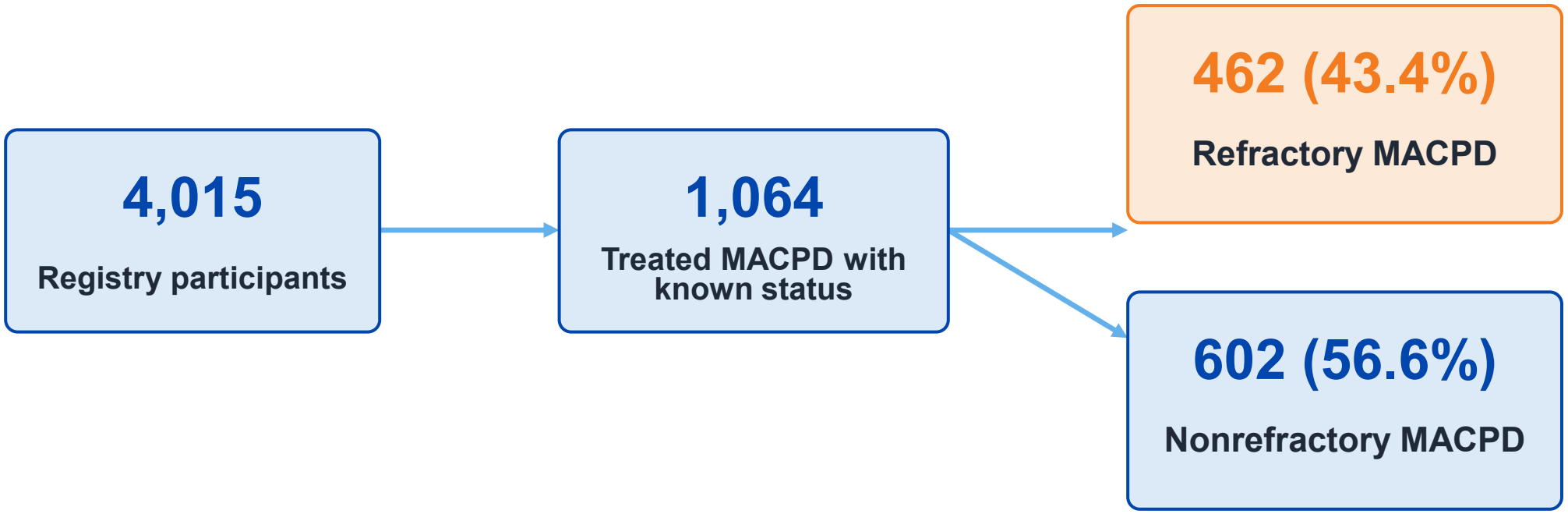


Refractory = positive cultures for >=6 months during treatment OR use of clofazimine, bedaquiline, inhaled amikacin, or ALIS

Aksamit et al. Respir Med. 2025;246:108220.

Natural History and Burden of Refractory *Mycobacterium avium* complex Pulmonary Disease

Nearly half of treated patients met the study definition of refractory MACPD



Within the refractory cohort

265 prevalent at enrollment

197 incident refractory cases

The 43.4% estimate reflects the registry population and the study definition - not a population incidence rate.

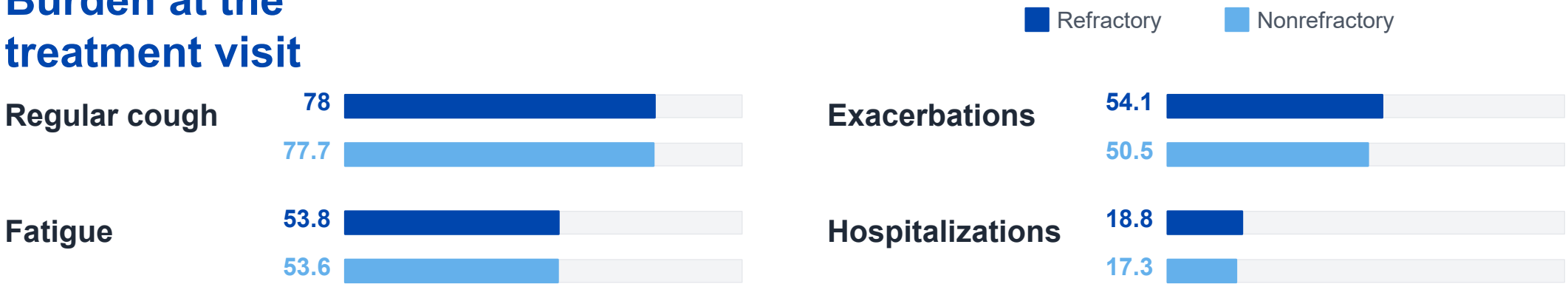
Aksamit et al. Respir Med. 2025;246:108220.

Natural History and Burden of Refractory *Mycobacterium avium* complex Pulmonary Disease

The registry cohort was older, predominantly female, and structurally complex

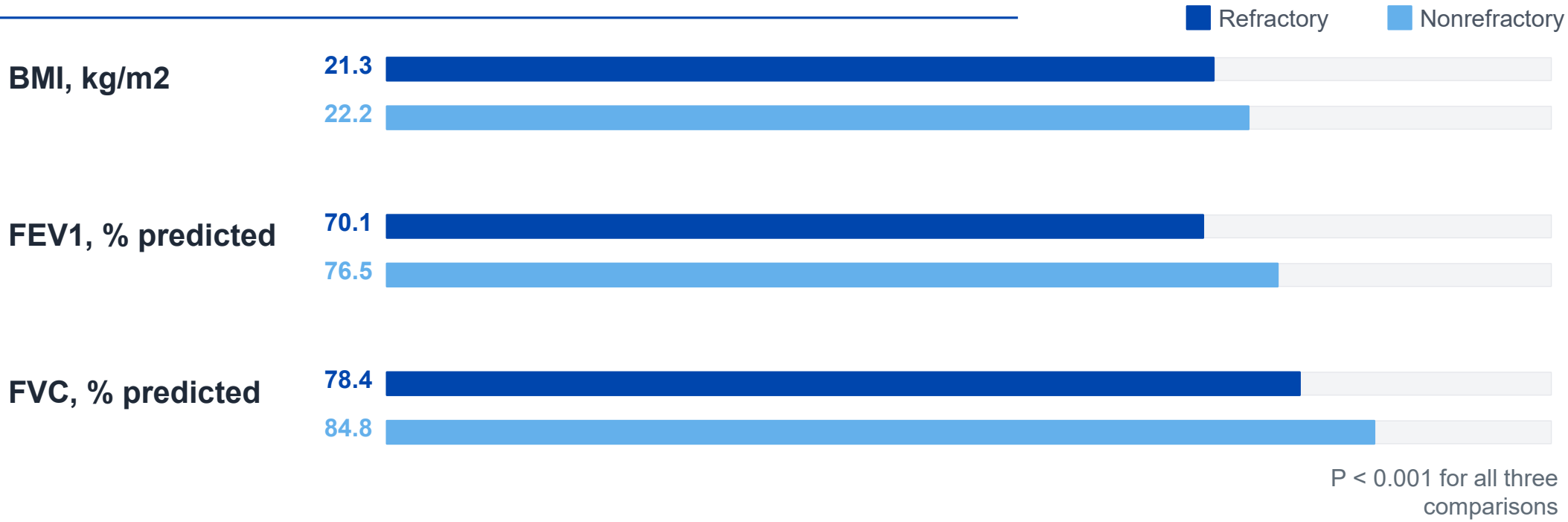
66.8 y	81.8%	92.5%	43.0%
Mean age	Female	Bronchiectasis	AFB smear-positive

Burden at the treatment visit



Aksamit et al. Respir Med. 2025;246:108220.

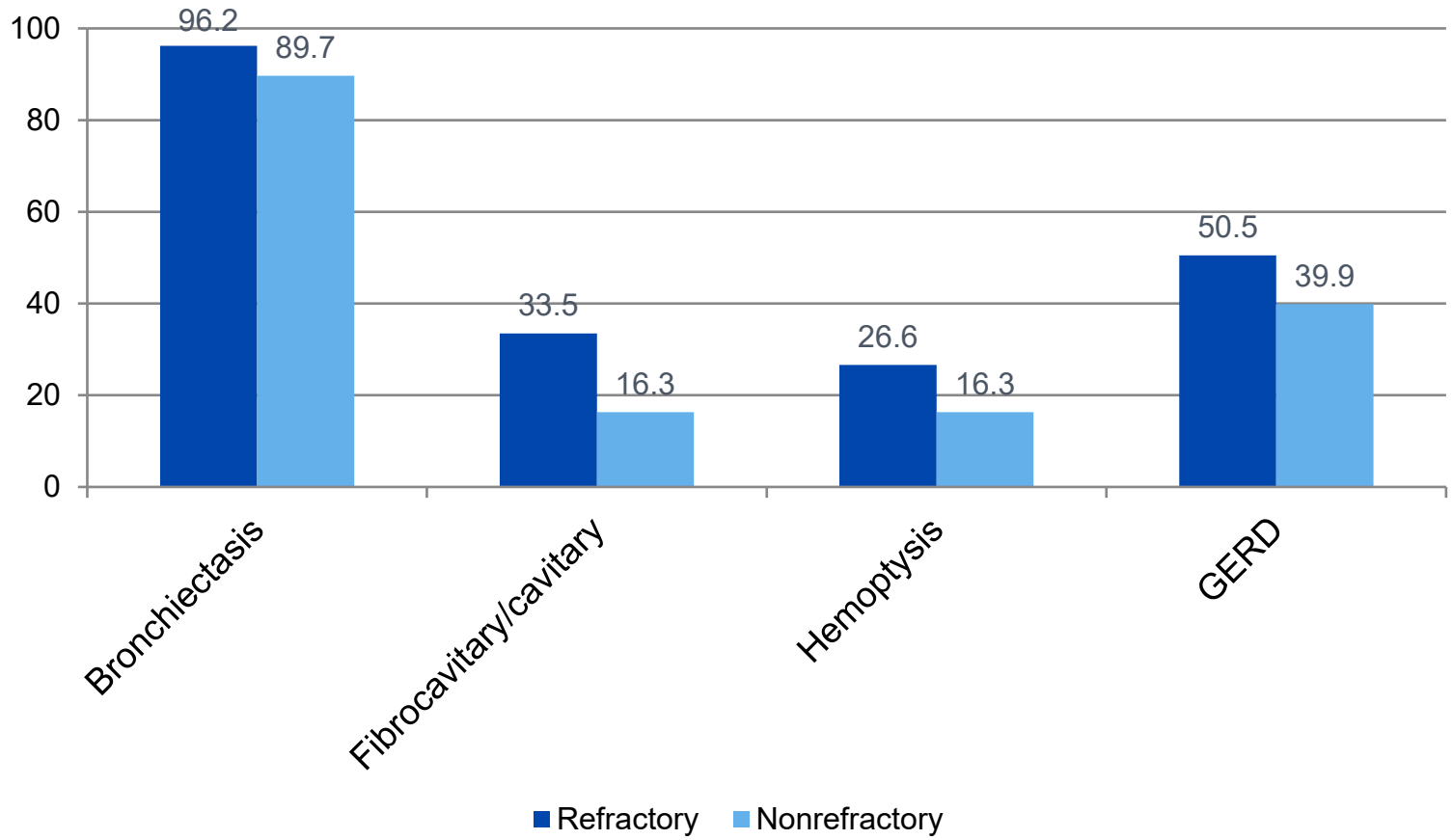
Lower BMI and lung function marked the refractory cohort



Association, not prediction: these differences identify vulnerability but do not prove who will become refractory.

Aksamit et al. Respir Med. 2025;246:108220.

Cavitary phenotype was the clearest differentiator



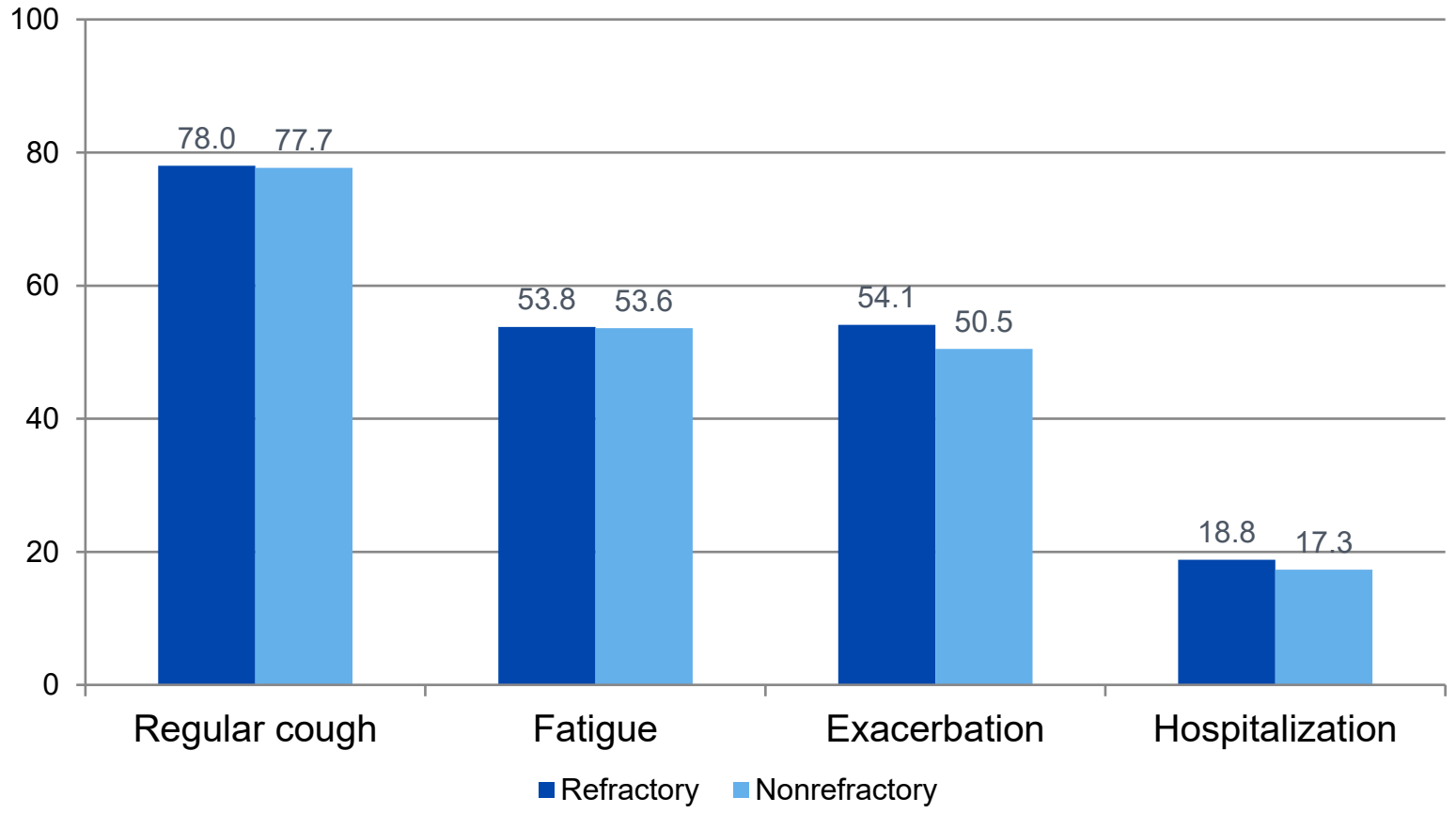
2.1x

higher prevalence of fibrocavitary/cavitary disease

Cavitation should trigger higher initial treatment intensity and closer monitoring.

Aksamit et al. Respir Med. 2025;246:108220.

Symptoms and HCRU were high regardless of refractory status



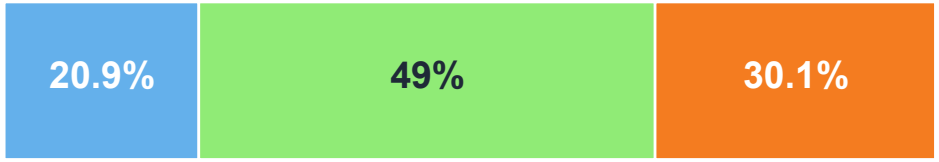
What this means

- Culture status alone underestimates burden
- Bronchiectasis care is essential in both groups
- Hospitalizations are not confined to refractory disease

Aksamit et al. Respir Med. 2025;246:108220.

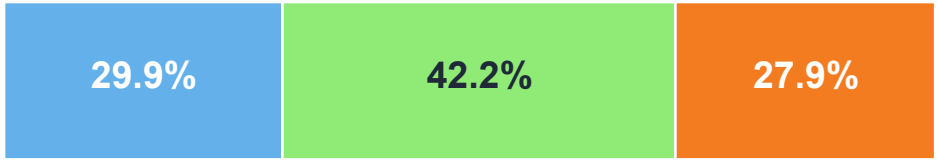
Baseline bronchiectasis severity was already moderate

Refractory



Mean mBSI 7.3

Nonrefractory



Mean mBSI 6.7

Mild Moderate Severe

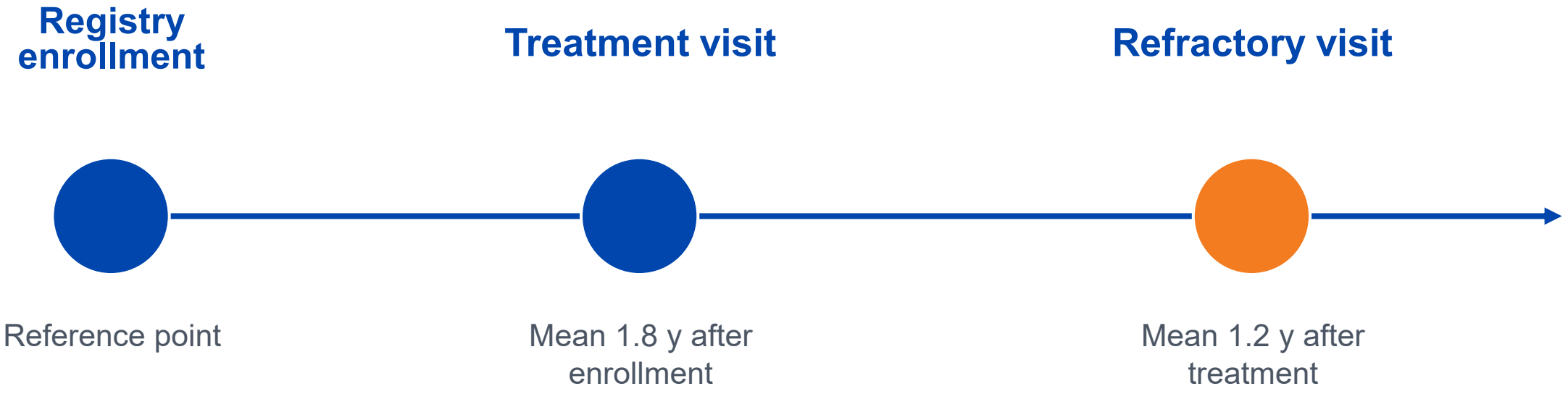
P = 0.042 for mean score

Both groups had mean scores in the moderate range; the refractory group shifted toward moderate/severe categories.

Aksamit et al. Respir Med. 2025;246:108220.

Natural History and Burden of Refractory *Mycobacterium avium* complex Pulmonary Disease

Incident refractory disease was recognized about a year after treatment



197 incident refractory cases

Annual visit windows mean the exact onset of failure may have occurred earlier.

Aksamit et al. Respir Med. 2025;246:108220.

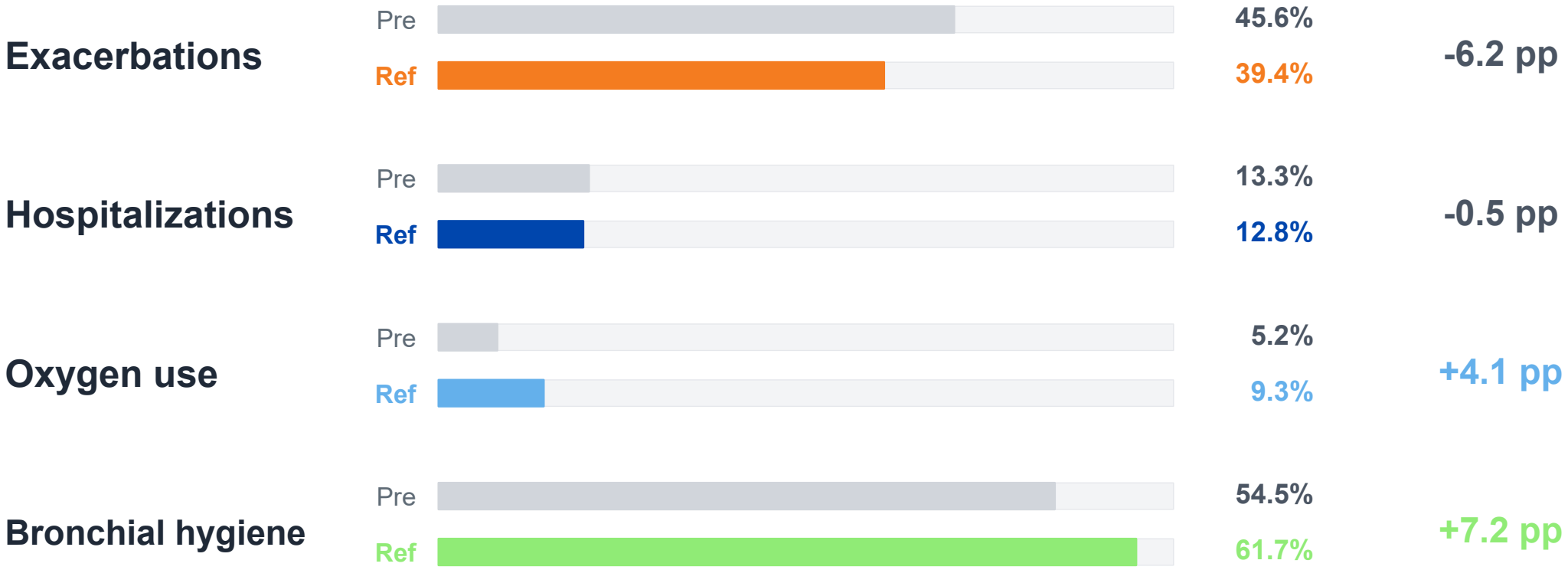
Symptoms persisted as patients crossed into refractory disease

	Pre-refractory visit		Refractory visit	Change
Cough	72.7%	→	76.1%	+3.4 pp
Dyspnea	48.2%	→	50.4%	+2.2 pp
Fatigue	53.4%	→	54.9%	+1.5 pp

The change was small; the symptom burden was already established before refractory disease was recognized.

Aksamit et al. Respir Med. 2025;246:108220.

Exacerbations and hospitalizations remained common



Clinical burden remained high; supportive-care use increased across the transition.

Aksamit et al. Respir Med. 2025;246:108220.

Before failure, only mean BMI separated incident cases

Signal detected

Mean BMI

21.4 vs 22.2 kg/m2

P = 0.038

Underweight prevalence was not different

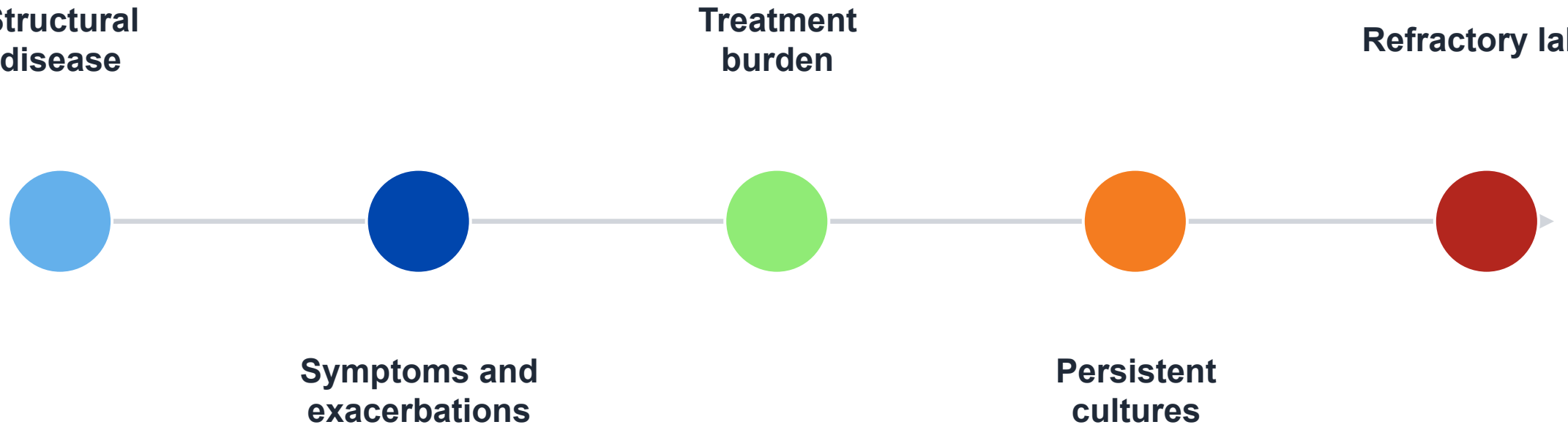
No clear signal

- Cough, dyspnea, fatigue
- FEV1 and FVC
- Exacerbations
- Hospitalizations

A single clinical feature cannot reliably identify future refractory disease.

Aksamit et al. Respir Med. 2025;246:108220.

The refractory label arrives after the burden is established



Clinical response

Treat the whole trajectory: optimize antimicrobial therapy, bronchiectasis care, nutrition, function, and patient goals before month 6.

Aksamit et al. Respir Med. 2025;246:108220.

The study is clinically rich - and deliberately descriptive

Strengths

- Large treated MACPD cohort
- Clinical, microbiologic, imaging and HCRU detail
- Incident cohort with adjacent visits
- Real-world specialty-center practice

Limitations

- Retrospective registry analysis
- Annual visit windows and missing data
- Surrogate refractory definition
- Referral-center selection and no causal inference

Best use: burden characterization and hypothesis generation - not a prediction model or treatment-effect estimate.

Aksamit et al. Respir Med. 2025;246:108220.

Four actions follow from the registry data

1	**Screen early**	Low BMI, lower lung function and cavitation identify vulnerability
2	**Monitor all**	Symptoms do not distinguish who will become refractory
3	**Act at month 6**	Persistent cultures require a structured reassessment
4	**Treat burden**	Exacerbations, hospitalization and quality of life require parallel care

The goal is earlier recognition without labeling every symptomatic patient as refractory.

Aksamit et al. Respir Med. 2025;246:108220; Moreira-Sousa et al. Eur Respir J. 2026;67:2500400.

Healthcare resource utilization

03

Pulm Ther (2026) 12:221–235
https://doi.org/10.1007/s41030-025-00324-z

ORIGINAL RESEARCH

Healthcare Resource Utilization in Refractory MACLD: Comparison of an Amikacin Liposome Inhalation Suspension (ALIS) Cohort with a Non-ALIS Cohort

Timothy R. Aksamit · Catherine Waweru · Emily Welch · Elsie Divinagracia · Ping Wang · Leona Markson

Received: August 12, 2025 / Accepted: October 1, 2025 / Published online: November 14, 2025
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ABSTRACT

Introduction: Add-on treatment with amikacin liposome inhalation suspension (ALIS) to a antibiotic for refractory MACLD. Hospitalizations (all-cause, respiratory-related, nontuberculous mycobacteria (NTM)-related) and emergency room (ER) visits at 0–6-month and 7–12-month

Refractory disease affects patients and health systems - and utilization may change after add-on therapy.

Aksamit et al. Pulm Ther. 2026;12:221-235.

The claims study compared two real-world add-on strategies

ALIS cohort

N = 116

Initiated ALIS

Baseline: 6 months before index
Follow-up: 0-6 and 7-12 months

Non-ALIS cohort

N = 63

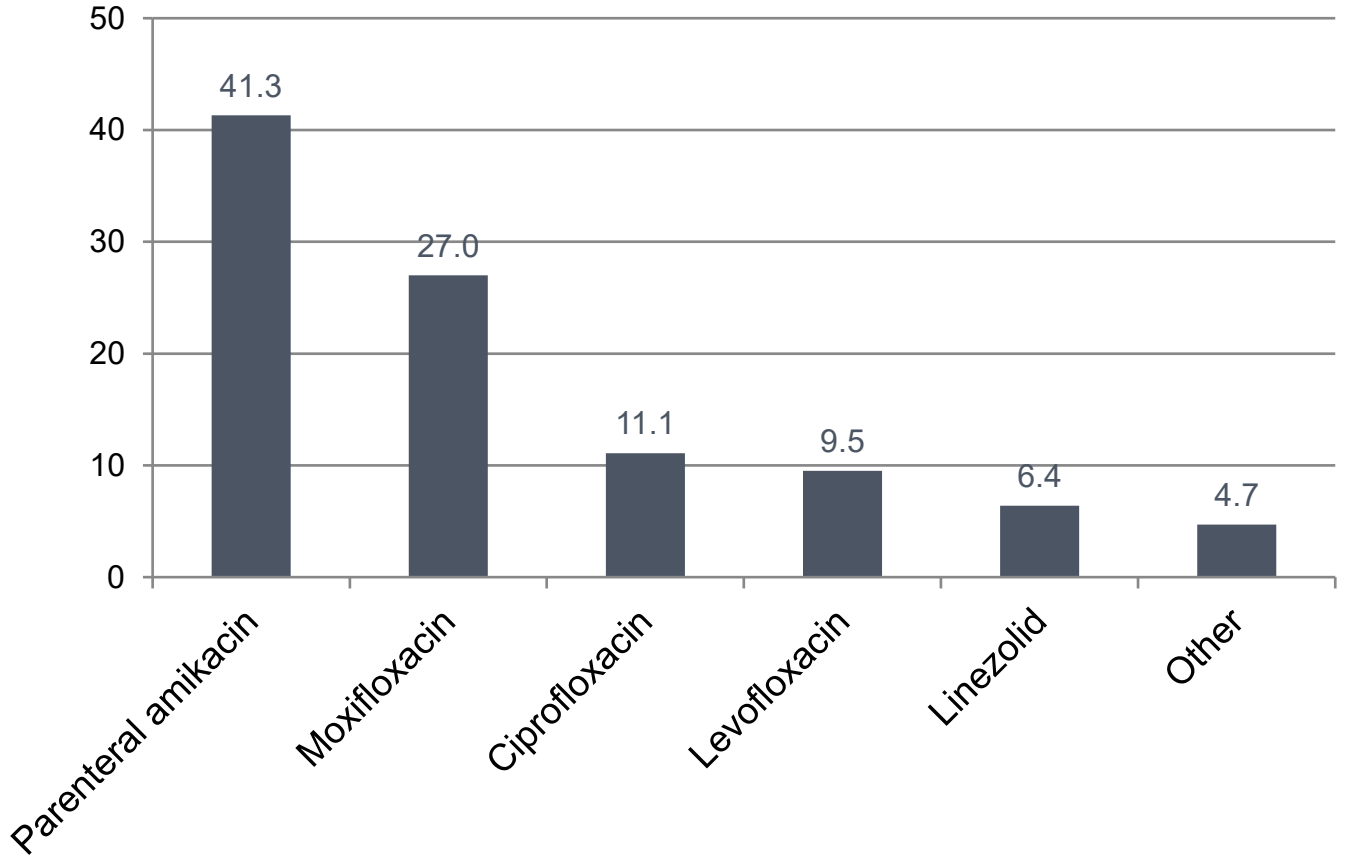
Initiated other add-on antibiotic

Baseline: 6 months before index
Follow-up: 0-6 and 7-12 months

Outcomes: all-cause, respiratory-related and NTM-related hospitalization; ER visits; length of stay

Aksamit et al. Pulm Ther. 2026;12:221-235.

The non-ALIS comparator was clinically heterogeneous



Important asymmetries

- Historical controls: 67% indexed before 2019
- Baseline pulmonary burden numerically higher in ALIS cohort
- Drug exposure and concomitant regimen incompletely captured
- Clofazimine not captured

Interpret as comparative real-world evidence, not randomized efficacy.

Aksamit et al. Pulm Ther. 2026;12:221-235.

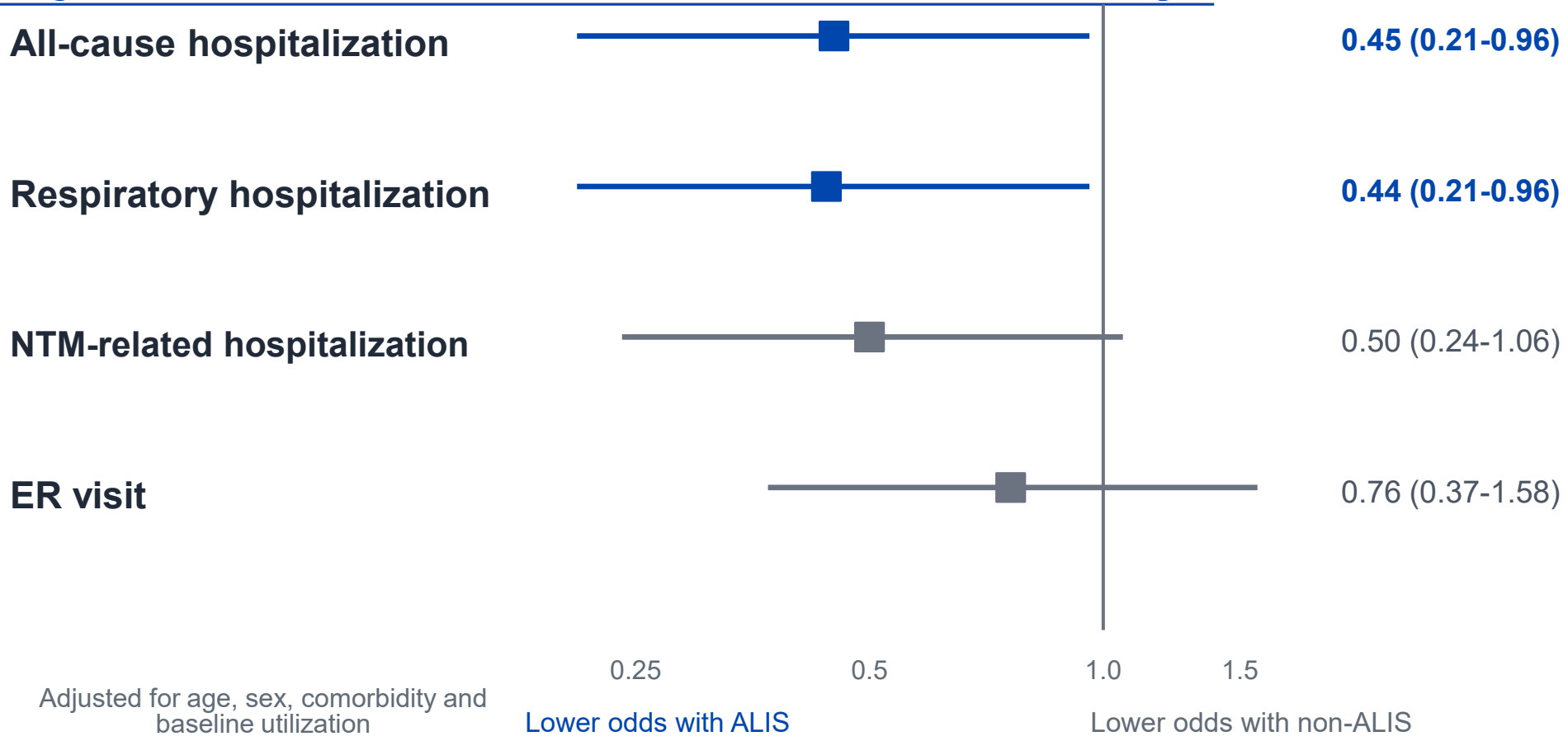
Hospitalization burden fell 7-12 months after ALIS initiation

	ALIS cohort Baseline → 7-12 months	Non-ALIS cohort Baseline → 7-12 months
All-cause	22.4% → 12.1% -10.3 pp	22.2% → 23.8% +1.6 pp
Respiratory-related	20.7% → 8.6% -12.1 pp	20.6% → 17.5% -3.1 pp
NTM-related	19.8% → 9.5% -10.3 pp	17.5% → 14.3% -3.2 pp

P < 0.05 versus baseline for all three ALIS comparisons at 7-12 months; no significant follow-up change in the non-ALIS cohort.

Aksamit et al. Pulm Ther. 2026;12:221-235.

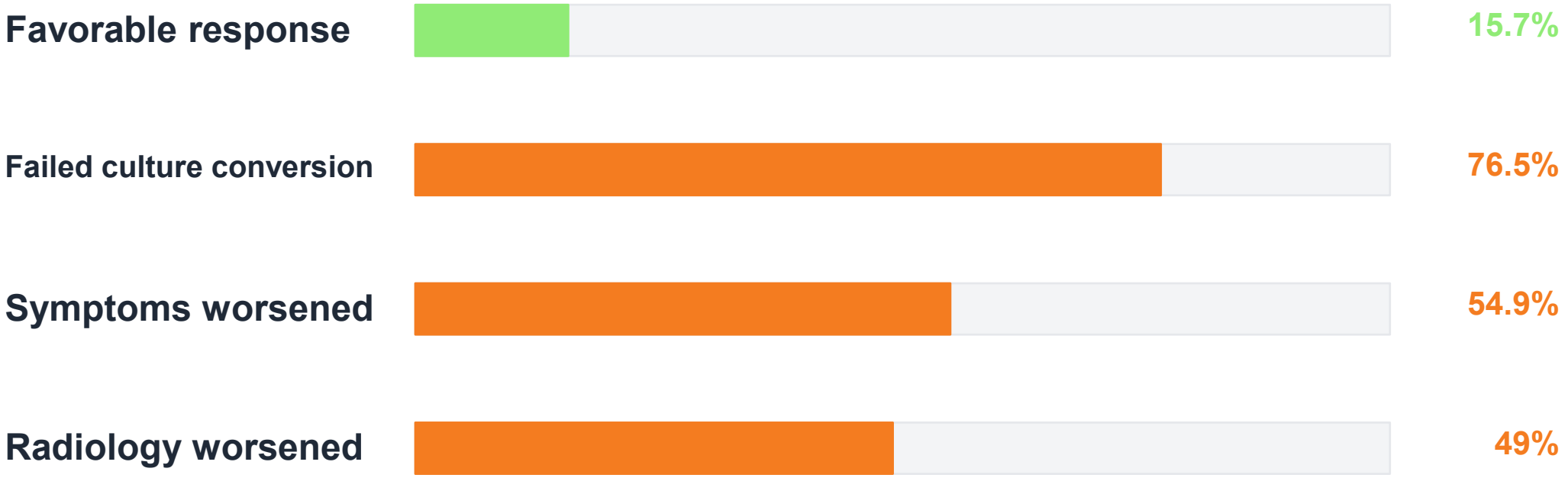
Adjusted odds favored ALIS - but causality remains uncertain



Aksamit et al. Pulm Ther. 2026;12:221-235.

Historical empiric salvage regimens delivered poor outcomes

51 patients | 82.4% fibrocavitary disease | pre-ALIS era



Adding poorly supported drugs to a failing regimen is not a substitute for reassessment, susceptibility data, and a coherent multidrug plan.

Jo et al. J Infect Chemother. 2014;20:602-606.

The evidence base is broad in questions and thin in certainty



- 24 nonrandomized studies; 17 retrospective cohorts
- Heterogeneous species, definitions, regimens and outcomes
- No meta-analysis feasible
- Supportive-care evidence especially limited

Clinical consequence

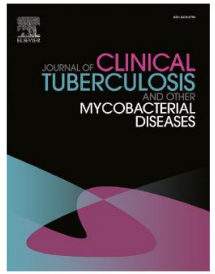
Management must combine the best available evidence with specialist expertise, patient goals, and explicit uncertainty.

Moreira-Sousa et al. Pulmonology. 2026;32(1):2632467.

Why refractory disease develops

04

Journal Pre-proof



Macrolide-resistant Mycobacterium avium complex pulmonary disease: A narrative review

Yoonis Cumar, Lina Davies Forsman, Thomas Schön, Christian Wejse, Victor Naestholt Dahl

PII: S2405-5794(26)00067-7

DOI: https://doi.org/10.1016/j.jctube.2026.100645

Reference: JCTUBE 100645

To appear in:

Please cite this article as: Y. Cumar, L.D. Forsman, T. Schön, et al., Macrolide-resistant Mycobacterium avium complex pulmonary disease: A narrative review, (2026), https://doi.org/10.1016/j.jctube.2026.100645

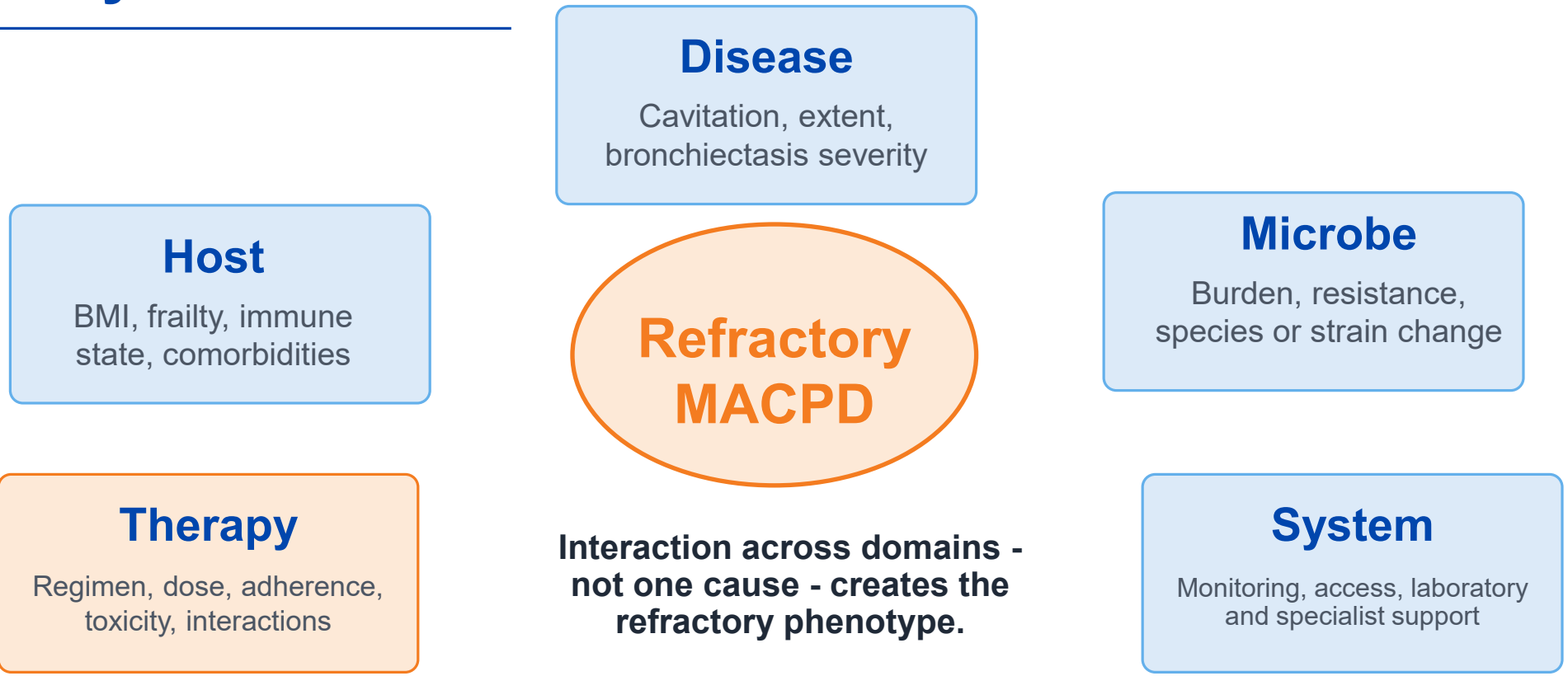
This is a PDF of an article that has undergone enhancements after acceptance, such as

Risk reflects the interaction of host, disease, organism, treatment, and care delivery.

Section 4

Cumar et al. J Clin Tuberc Other Mycobact Dis. 2026;100645; Aksamit et al. Respir Med. 2025;246:108220.

Refractory MACPD is multifactorial



Some factors are risk markers; others are modifiable contributors.

Aksamit et al. Respir Med. 2025;246:108220; Moreira-Sousa et al. Eur Respir J. 2026;67:2500400.

Host reserve and disease phenotype shape risk

Host reserve

- Low BMI or weight loss
- Reduced lung function
- Frailty and limited performance status
- Immunosuppression and comorbidity

Disease phenotype

- Cavitary or fibrocavitary disease
- Advanced or severe bronchiectasis
- High radiographic burden
- AFB smear positivity or high bacterial burden

These features justify closer monitoring and, for severe/cavitary disease, higher initial treatment intensity.

Aksamit et al. Respir Med. 2025;246:108220; Morimoto and Daley. Ann Am Thorac Soc. 2025;22:651-659.

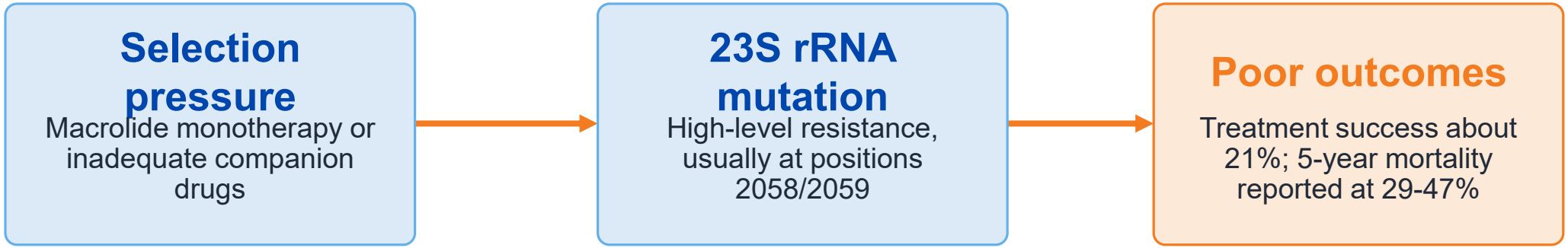
Microbiology can signal persistence, resistance, or a different disease

1	**Persistent positivity**	Failure to convert by 6 months
2	**High burden**	Smear positivity or short time to culture positivity
3	**Acquired resistance**	Repeat macrolide and amikacin susceptibility after failure
4	**Organism change**	Reinfection, strain shift, or another NTM species
5	**Competing pathogens**	Pseudomonas, Aspergillus, and other infections

A positive culture does not always mean the same organism, the same susceptibility pattern, or the same driver of symptoms.

Moreira-Sousa et al. Eur Respir J. 2026;67:2500400; Cumar et al. 2026; doi:10.1016/j.jctube.2026.100645.

Macrolide resistance is often preventable - and difficult to rescue



Avoidable pathways

- Long-term macrolide before excluding NTM disease
- Omission or interruption of ethambutol
- Adding a macrolide to an inadequately active regimen

Protection strategy

- Use a guideline-based multidrug regimen
- Maintain ethambutol when feasible
- Confirm adherence and drug exposure

Cumar et al. J Clin Tuberc Other Mycobact Dis. 2026;100645; Daley et al. Clin Infect Dis. 2020;71:e1-e36.

Many contributors to failure are modifiable

Regimen

- Too few active drugs
- Wrong frequency for phenotype
- Single-drug addition to failure

Exposure

- Nonadherence or intolerance
- Malabsorption
- Drug-drug interactions or underdosing

Care delivery

- Infrequent cultures
- Delayed AST or expert input
- Untreated bronchiectasis and comorbidity

Before labeling biology as refractory, verify that the patient actually received, absorbed, and tolerated an appropriate multidrug regimen.

Moreira-Sousa et al. Eur Respir J. 2026;67:2500400; Morimoto and Daley. Ann Am Thorac Soc. 2025;22:651-659.

A six-step checklist can reduce avoidable refractory disease

1. **Confirm** — Species, phenotype, severity, macrolide and amikacin susceptibility
2. **Protect** — Macrolide with ethambutol and an appropriate third active drug
3. **Match** — Daily vs intermittent therapy and initial aminoglycoside to disease severity
4. **Support** — Airway clearance, nutrition, comorbidity and coinfection management
5. **Monitor** — Monthly cultures, toxicity, adherence, interactions, weight and function
6. **Escalate** — Expert reassessment if cultures remain positive at 6 months

Prevention is not certainty - it is disciplined reduction of avoidable risk.

Daley et al. Clin Infect Dis. 2020;71:e1-e36; Morimoto and Daley. Ann Am Thorac Soc. 2025;22:651-659.

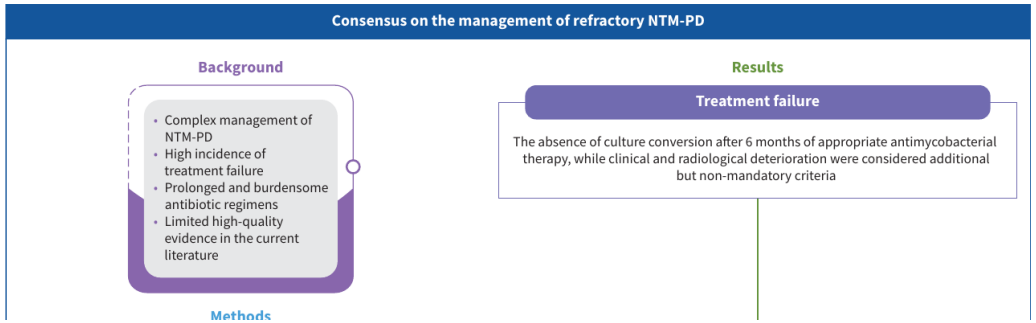
Assessment and treatment

05

EUROPEAN RESPIRATORY JOURNAL
TASK FORCE REPORT
D. MOREIRA-SOUSA ET AL.

Consensus on the management of refractory nontuberculous mycobacterial pulmonary disease

Diana Moreira-Sousa, Beatriz Martins, Ana Aguiar, Marina Pinheiro, Onno Akkerman, Timothy R. Aksamit, Stefano Aliberti, Claire Andrejak, Charles L. Daley, Jakko van Ingen, Christoph Lange, Marc Lipman, Michael R. Loebinger, Mateja Jankovic Makek, Kozo Morimoto, Rachel M. Thomson, Dirk Wagner, Kevin L. Winthrop, Jae-Joon Yim and Raquel Duarte



Confirm true failure, define the goal, and build a patient-tailored plan.

Moreira-Sousa et al. Eur Respir J. 2026;67:2500400.

Confirm true treatment 'failure' before changing therapy

1 Reconfirm microbiology
Monthly cultures, smear, species, time to positivity

2 Repeat susceptibility
Macrolide and amikacin; emerging resistance

3 Audit the regimen
Drugs, dose, frequency, duration and companion activity

4 Check exposure
Adherence, intolerance, absorption and interactions

5 Re-image
CT progression, cavity evolution, localized disease

6 Exclude alternatives
Pseudomonas, Aspergillus, aspiration and other causes

7 Reassess the patient
Symptoms, weight, function, quality of life, comorbidities, preferences and goals

Do not add one drug to a failing regimen - ???

Moreira-Sousa et al. Eur Respir J. 2026;67:2500400; Daley et al. Clin Infect Dis. 2020;71:e1-e36.

Choose the treatment goal before choosing the next drug

INTENSIFY

- Curative intent remains realistic
- Progressive clinical/radiologic disease
- Patient accepts treatment burden
- Localized disease or surgical option

DE-ESCALATE

- Low probability of cure
- Treatment toxicity exceeds benefit
- Stable disease with symptom-focused goals
- Patient prioritizes quality of life

Shared decision-making + specialist consultation

Moreira-Sousa et al. Eur Respir J. 2026;67:2500400.

Natural History and Burden of Refractory *Mycobacterium avium* complex Pulmonary Disease

Intensification should be coherent, susceptibility-informed, and multidisciplinary

1	**Optimize the backbone**	Macrolide if susceptible + ethambutol + active companion; correct dose/frequency
2	**Add ALIS**	Recommended for persistent culture positivity after >=6 months of guideline-based therapy
3	**Use systemic aminoglycoside selectively**	Cavitary, advanced/severe, or macrolide-resistant disease; monitor toxicity
4	**Consider surgery**	Localized disease, adequate reserve, expert center, optimized perioperative regimen
5	**Consider expert-selected alternatives or trials**	Clofazimine and other agents based on susceptibility, prior exposure, safety, and evidence

Evidence strength is uneven: ALIS has randomized trial support; most other salvage options rely on observational data and expert consensus.

Daley et al. Clin Infect Dis. 2020;71:e1-e36; Moreira-Sousa et al. Eur Respir J. 2026;67:2500400.

Supportive care is active treatment - not a fallback

Always optimize

- Airway clearance and respiratory rehabilitation
- Nutrition, exercise, oxygen when needed
- Bronchiectasis coinfections and comorbidities
- GERD, aspiration, immune state and psychosocial support

When curative therapy is not feasible

- Simplify the regimen while protecting against resistance
- Use intermittent courses for symptom control in selected patients
- Stop antibiotics when burden exceeds likely benefit
- Revisit the plan if disease worsens or new options emerge

Document the goal: cure, disease control, symptom relief, or treatment cessation.

Moreira-Sousa et al. Eur Respir J. 2026;67:2500400; Morimoto and Daley. Ann Am Thorac Soc. 2025;22:651-659.

Natural History and Burden of Refractory *Mycobacterium avium* complex Pulmonary Disease

Recognize earlier. Reassess systematically. Personalize the goal.

Burden

Symptoms, exacerbations, hospitalizations and resource use are substantial before and after refractory status.

Risk

Low BMI, reduced reserve and cavitary disease identify vulnerability; regimen quality and macrolide protection are modifiable.

Action

At 6 months, confirm true failure and choose intensification or de-escalation through shared decision-making.

Aksamit et al. Respir Med. 2025;246:108220; Aksamit et al. Pulm Ther. 2026;12:221-235; Moreira-Sousa et al. Eur Respir J. 2026;67:2500400.

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WORLD BRONCHIECTASIS DAY
JULY 1ST

Bronchiectasis & NTM ASSOCIATION

MAYO CLINIC