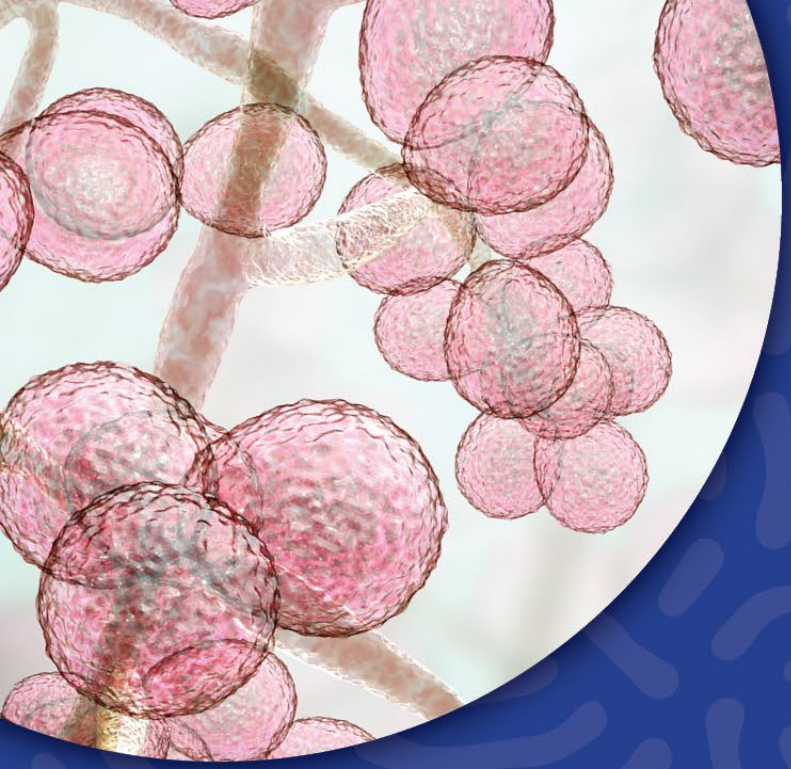

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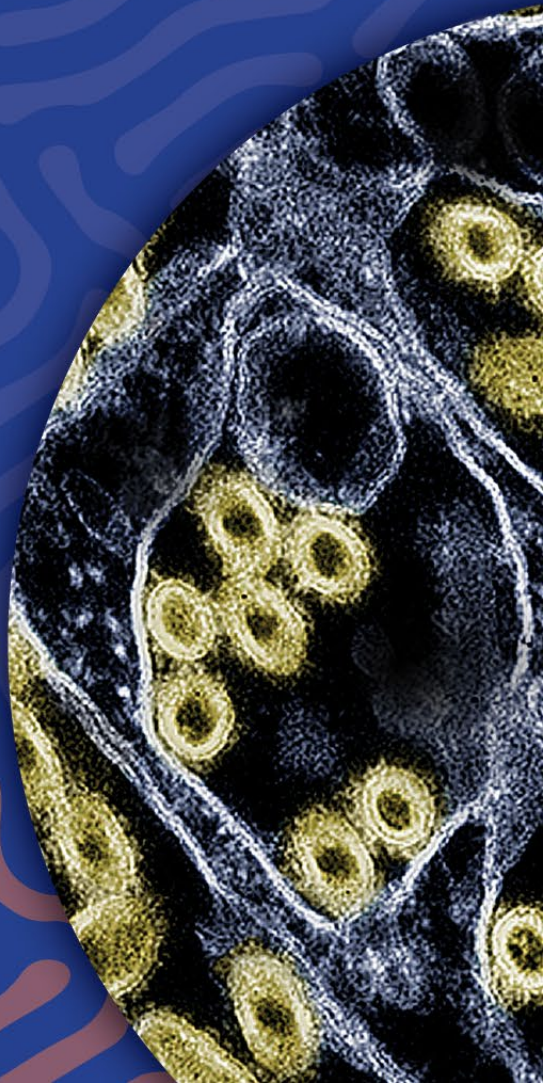

Epidemiology of NTM Pulmonary Disease: Understanding the Healthcare Provider Perspective

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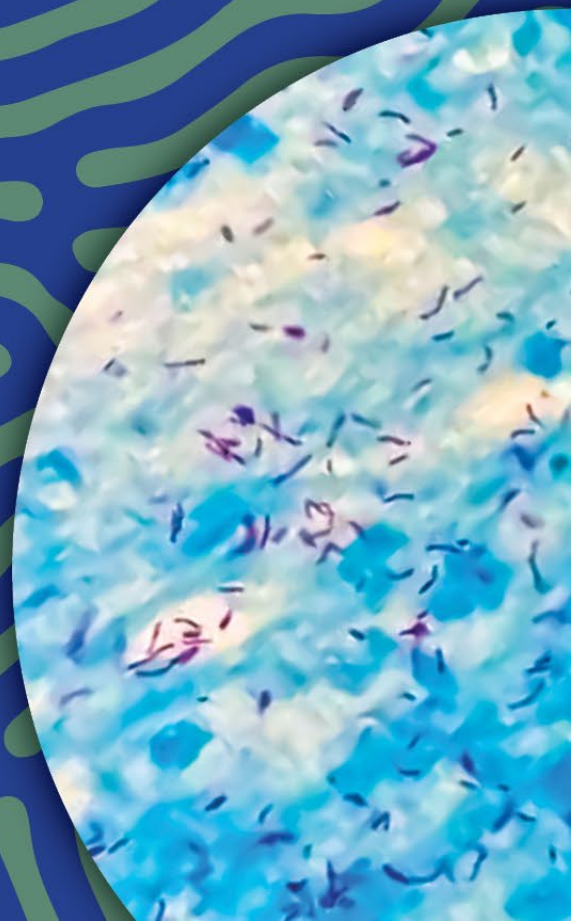
Disclosures

Funding from the Cystic Fibrosis Foundation



Objectives

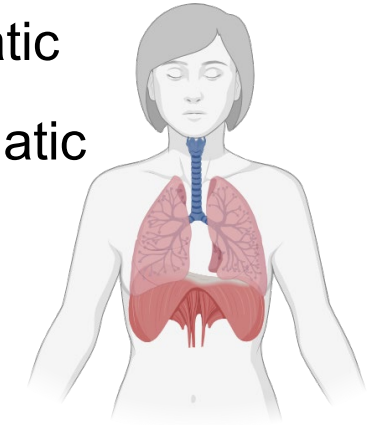
- Name risk factors for NTM pulmonary disease
- Recall epidemiology of human NTM pulmonary disease
- Discuss guidelines for clinical laboratory recommendations
- Recognize utility of preserving NTM isolates

Introduction:
Nontuberculous mycobacteria (NTM)

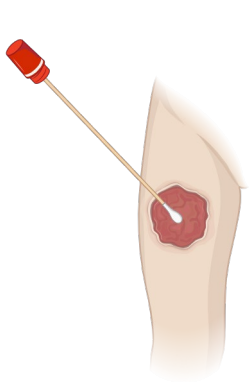
- NTM represent over 190 species and subspecies
  - Exceptions *Mycobacterium tuberculosis* complex, *Mycobacterium leprae* complex, and *Mycobacterium ulcerans*
- Most common human NTM infections
  - Slow growing
    - *Mycobacterium avium* complex (MAC) including *M. avium*, *M. intracellulare*, and *M. chimaera*
    - *Mycobacterium kansasii*
    - *Mycobacterium xenopi*
  - Rapidly growing
    - *Mycobacterium abscessus* complex

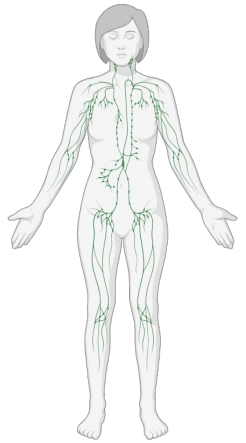
Introduction: NTM infections

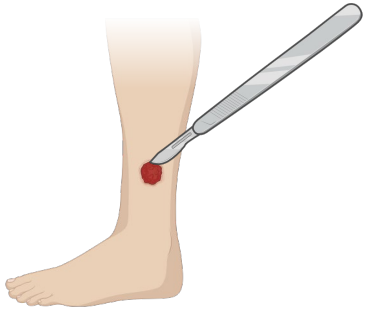
- Pulmonary
  - Symptomatic
  - Asymptomatic



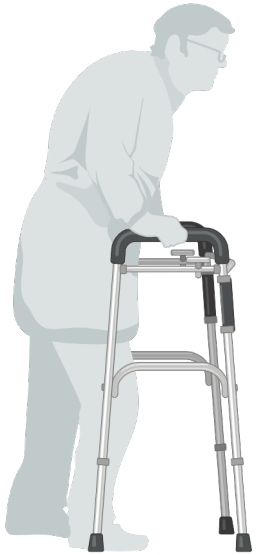
- Extrapulmonary







- Infections occur in all age groups



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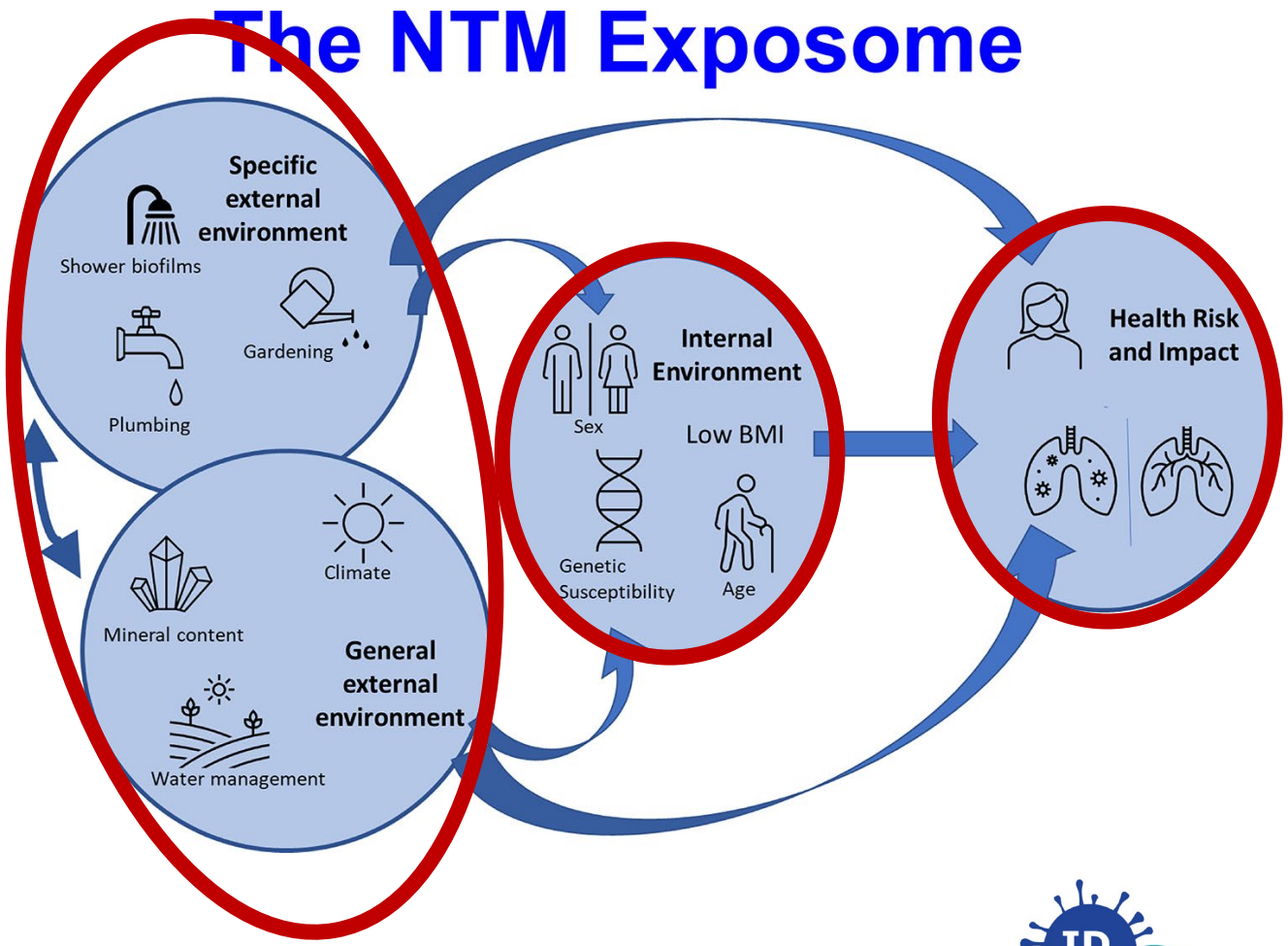
NTM infection: Risk factors

- A complex interplay between a susceptible host and environmental risk factors
- Cumulative contacts to a variety of exposures will increase risk of infection and disease



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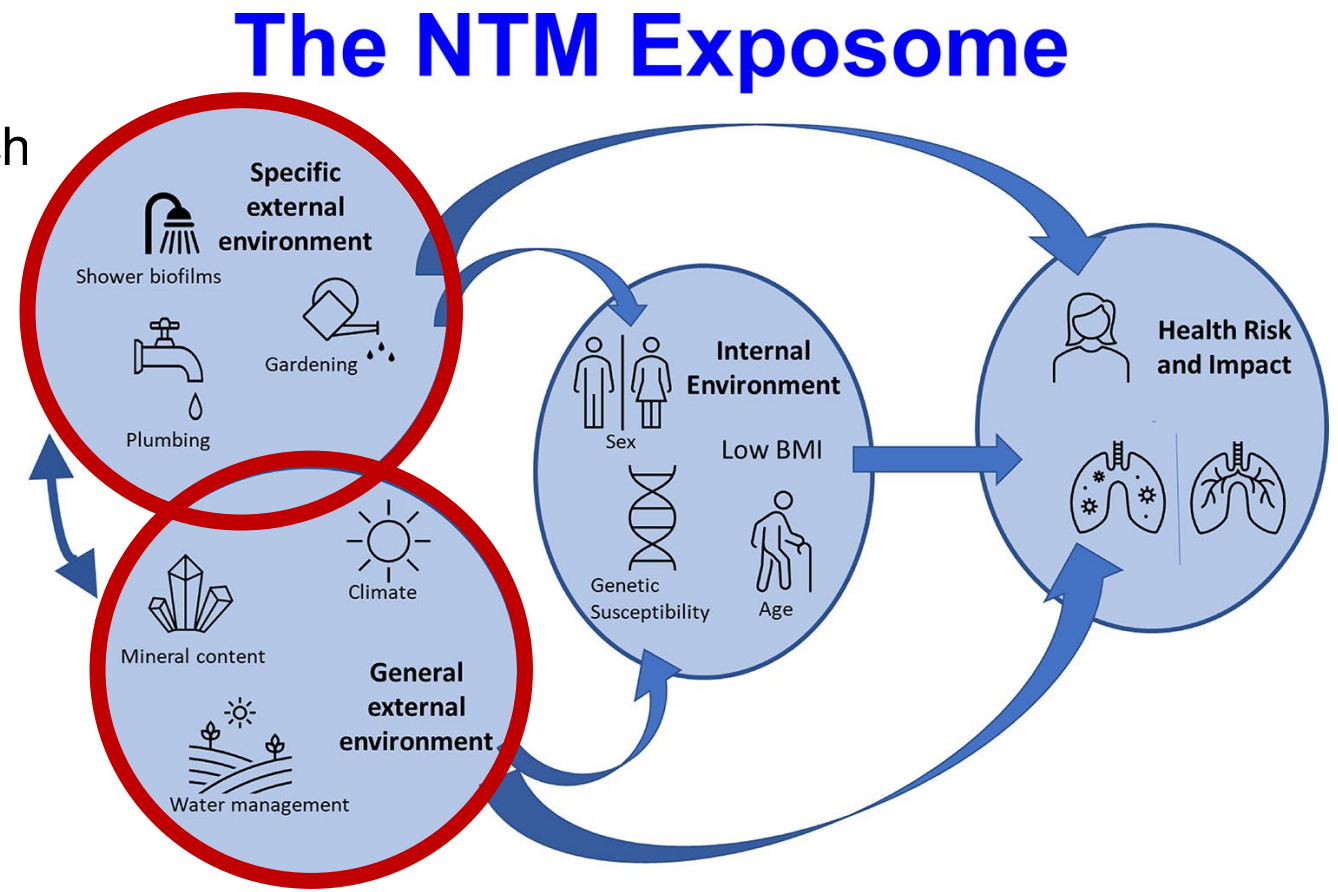
Prevots DR et al. Global Epidemiology of Nontuberculous Mycobacterial Pulmonary Disease: A Review. Clin Chest Med. 2023

Risk factors for NTM infection: The Environment

- Specific exposures
  - Exposures estimated from studies which associate individual behaviors or household factors with human NTM pulmonary isolation or disease
- General exposures
  - Exposures not unique to a single individual but rather affect the broader population
  - Exposures beyond the control of an individual



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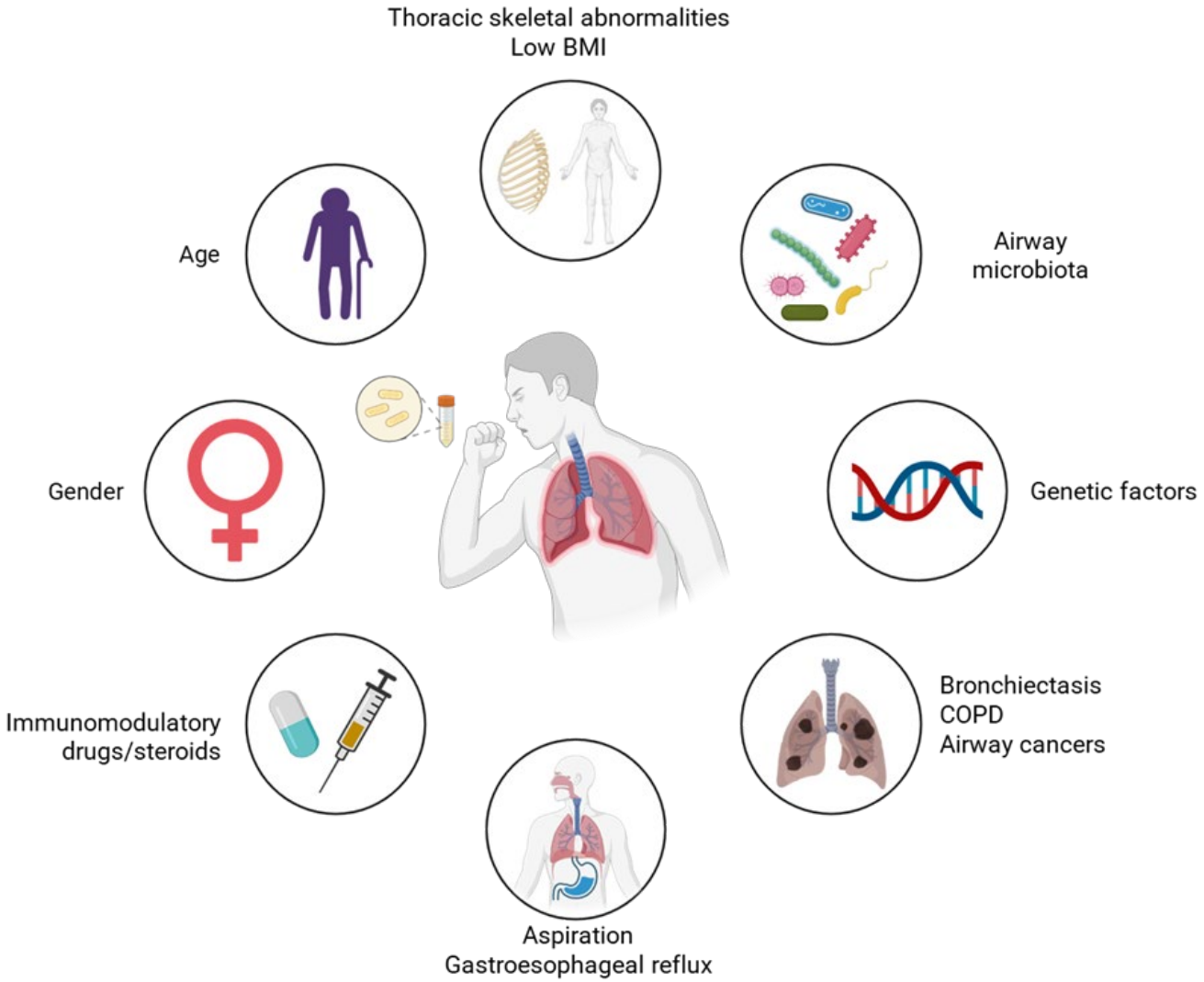
Prevots DR et al. Global Epidemiology of Nontuberculous Mycobacterial Pulmonary Disease: A Review. Clin Chest Med. 2023

Risk factors for NTM infection: The Host



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Prevots DR et al. Global Epidemiology of Nontuberculous Mycobacterial Pulmonary Disease: A Review. Clin Chest Med. 2023
Caverly LJ et al. Cystic fibrosis airway microbiota associated with outcomes of nontuberculous mycobacterial infection. ERJ Open Res. 2021

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NTM pulmonary isolation is increasing over the last decade

- Systematic review and meta-analysis conducted for global culture-based microbiologic data
- Included
  - Studies with culture-based data for at least 3 years
  - At least 200 samples
  - Data from 47 publications
  - Over 18 countries
- Findings
  - 82% reported increasing NTM isolation#
  - 66.7% reported increasing NTM disease^

#ATS microbiologic criteria, ^radiographic and clinical criteria

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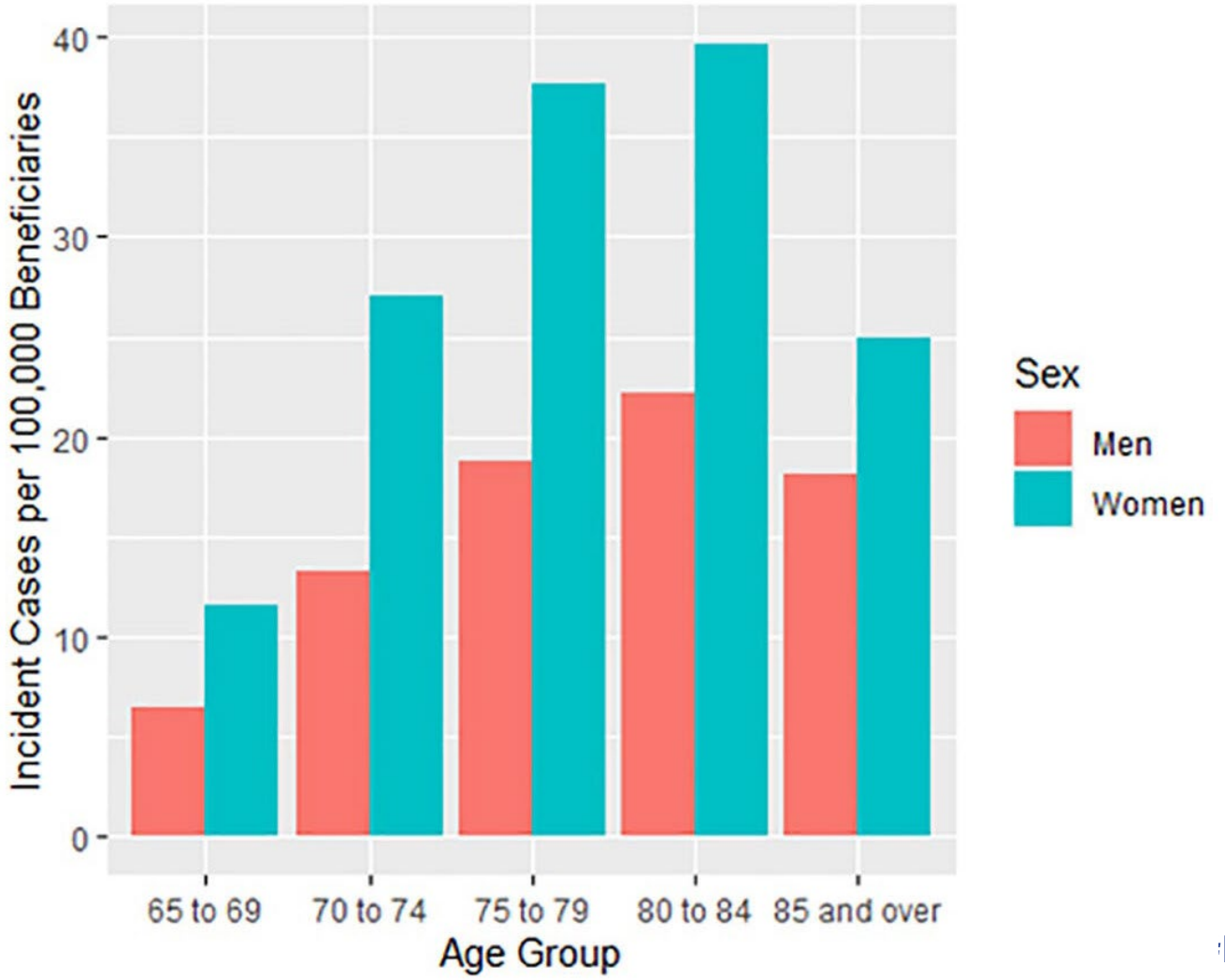
APHL ID LAB CON 2025

Prevots, DR et. al. Global Epidemiology of Nontuberculous Mycobacterial Pulmonary Disease: A Review. Clin Chest Med. 2023

Average annual incidence of NTM pulmonary disease 2010-2019 in US Medicare beneficiaries >64 years



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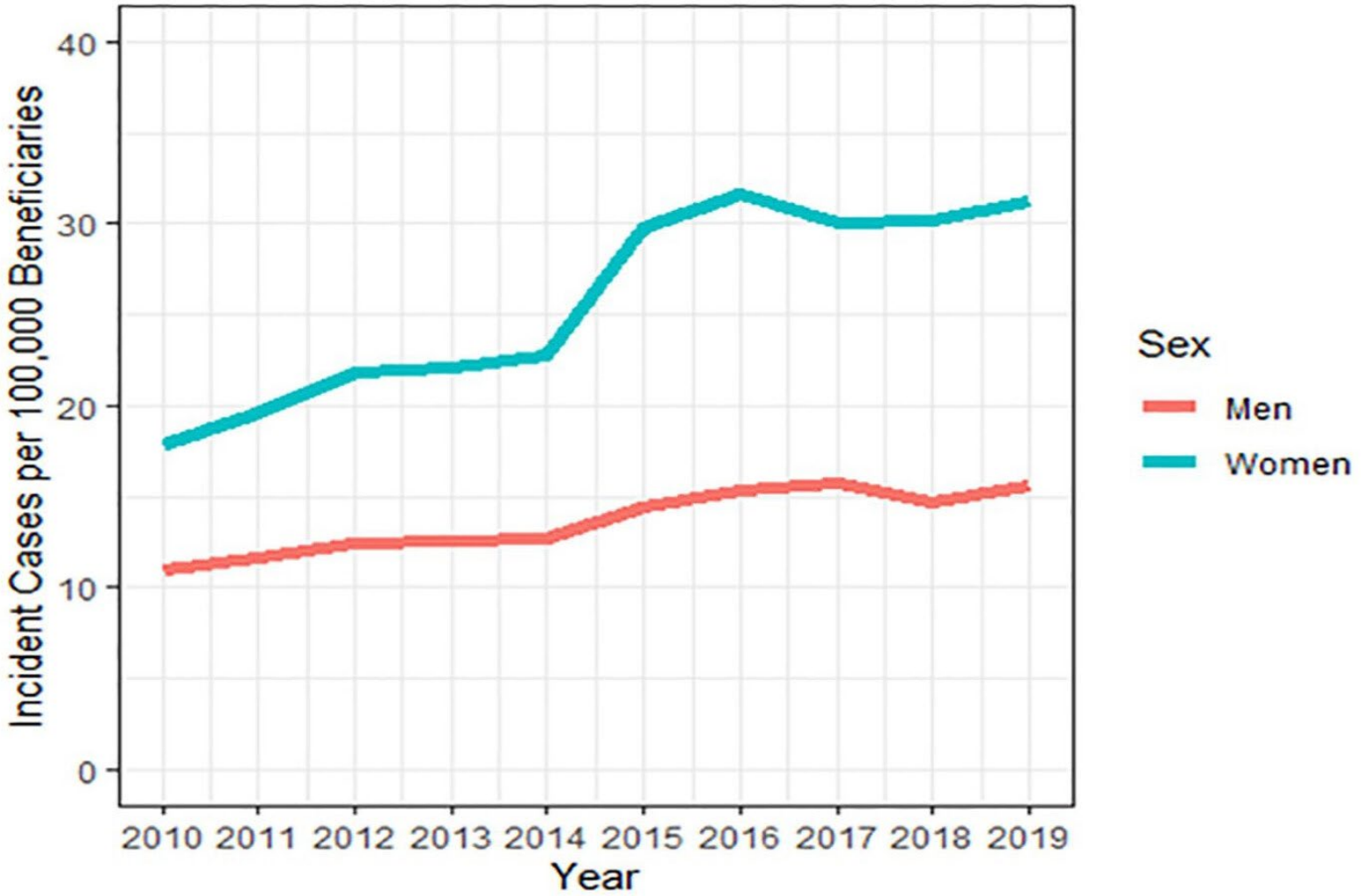
Gross, JE et al. Pulmonary nontuberculous mycobacterial infections among women with cystic fibrosis and non-cystic fibrosis bronchiectasis. Ther Adv Respir Dis. 2025

Annual incidence of NTM pulmonary disease by sex 2010-2019 in US Medicare beneficiaries >64 years



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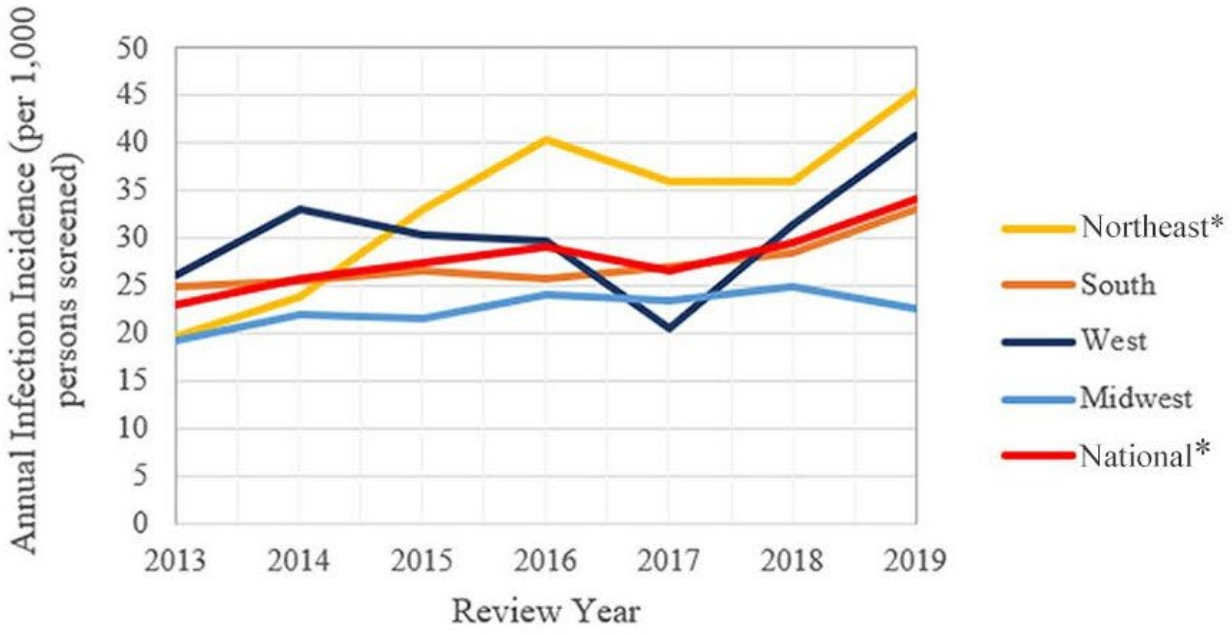
Gross, JE et al. Pulmonary nontuberculous mycobacterial infections among women with cystic fibrosis and non-cystic fibrosis bronchiectasis. Ther Adv Respir Dis. 2025

Annual incidence of NTM pulmonary disease by species 2013-2019 in US Medicare beneficiaries >64 years

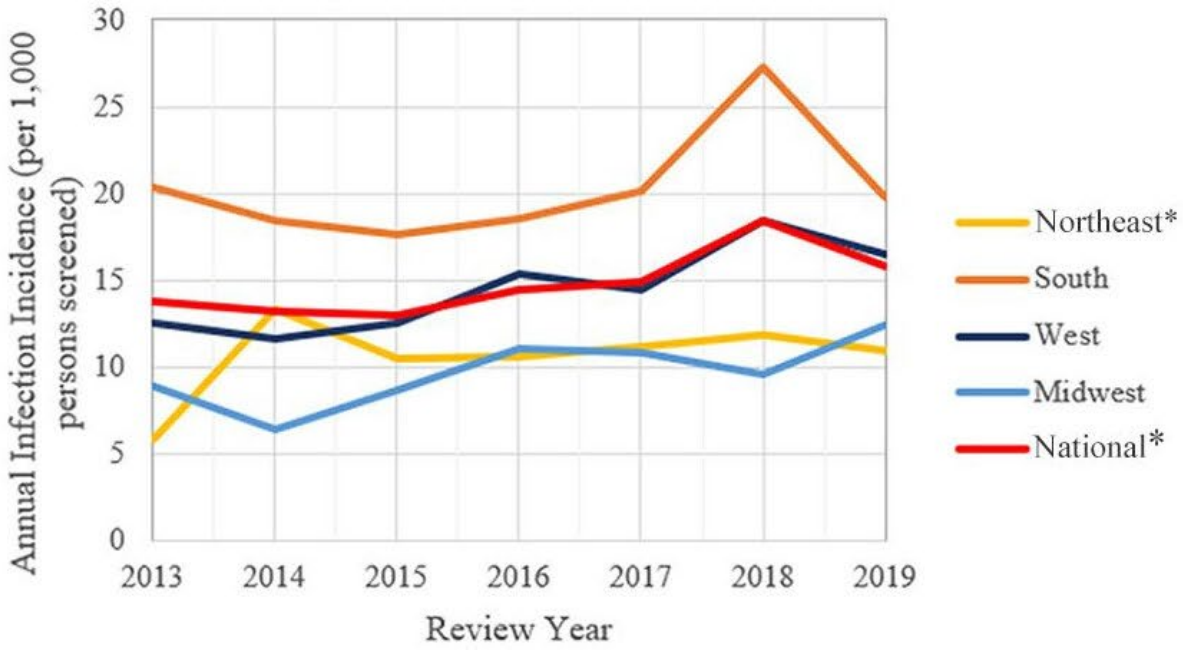
(a)

MAC



(b)

M. abscessus



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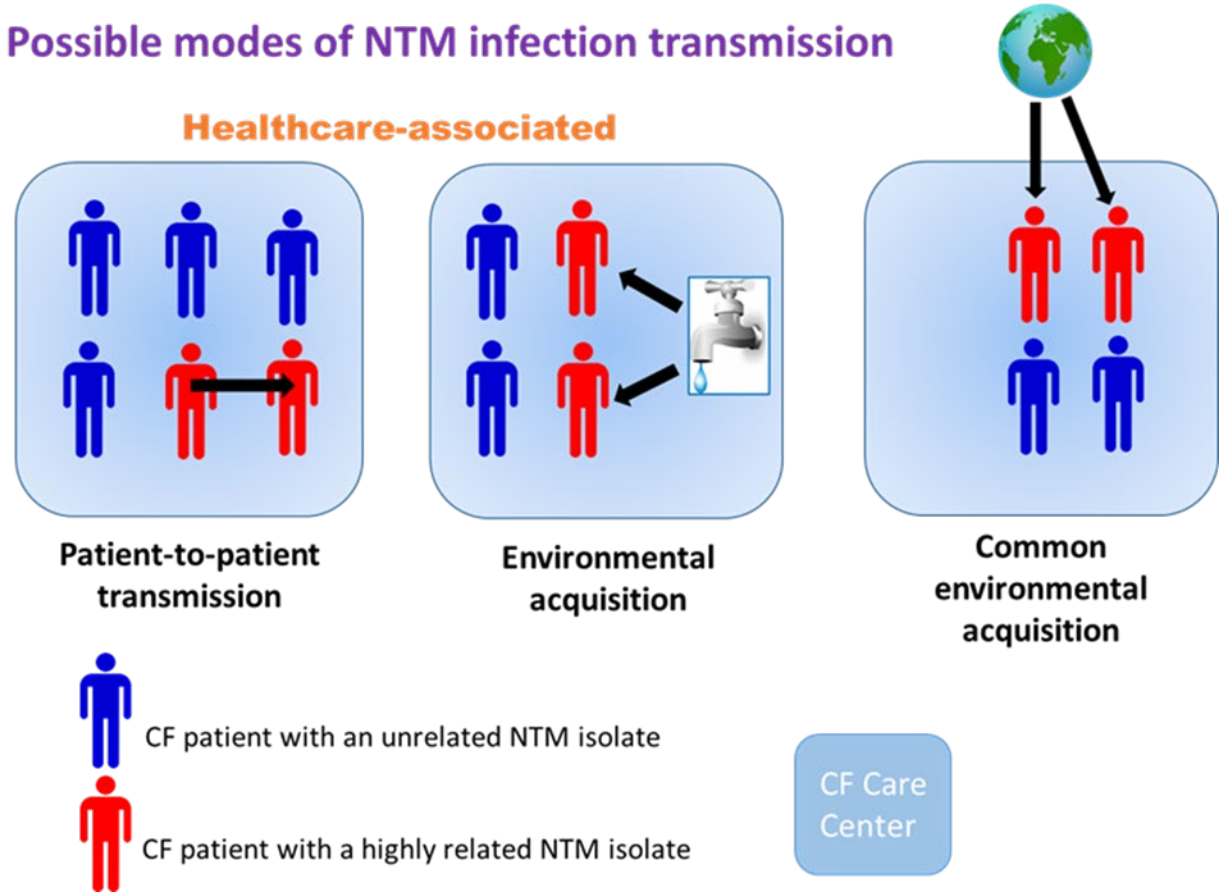
Gross, JE et al. Pulmonary nontuberculous mycobacterial infections among women with cystic fibrosis and non-cystic fibrosis bronchiectasis. Ther Adv Respir Dis. 2025

Acquisition of NTM

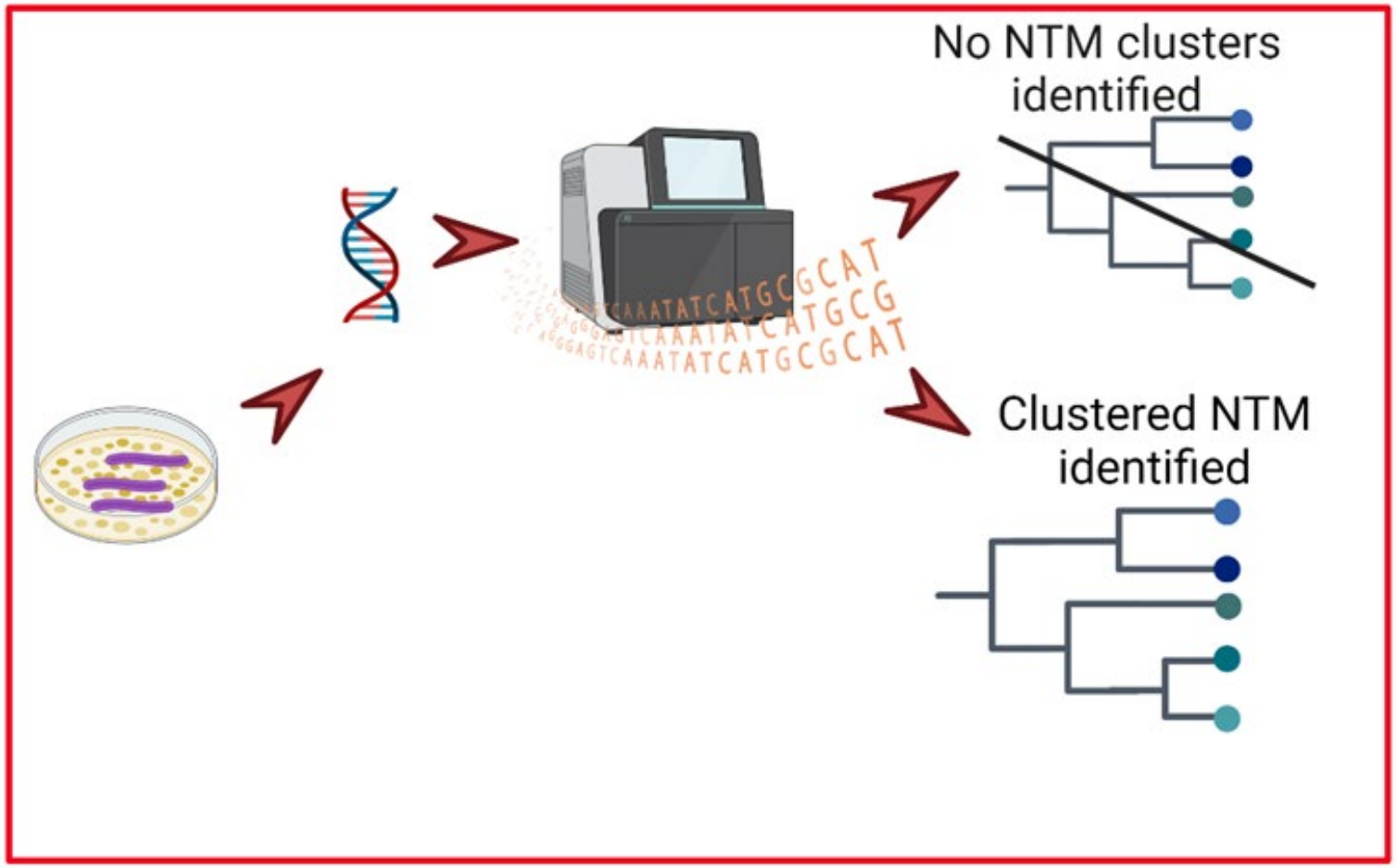
- Usually acquired from the environment
- Person-to-person transmission of NTM has been described



Gross JE, et al. *AJRCCM*. 2022

NTM outbreak investigations

- Whole genome sequencing can identify clustered infections
- Availability of isolates is crucial to outbreak investigations



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Approach to Diagnosis and Treatment

Practice Guideline > Eur Respir J. 2020 Jul 7;56(1):2000535. doi: 10.1183/13993003.00535-2020. Print 2020 Jul.

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

Charles L Daley [1 2 3], Jonathan M Iaccarino [4], Christoph Lange [5 6 7 8 3], Emmanuelle Cambau [9 3], Richard J Wallace Jr [10 3], Claire Andrejak [11 12], Erik C Böttger [13], Jan Brozek [14], David E Griffith [15], Lorenzo Guglielmetti [9 16], Gwen A Huitt [1 2], Shandra L Knight [17], Philip Leitman [18], Theodore K Marras [19], Kenneth N Olivier [20], Miguel Santin [21], Jason E Stout [22], Enrico Tortoli [23], Jakko van Ingen [24], Dirk Wagner [25], Kevin L Winthrop [26]

Practice Guideline > Thorax. 2016 Jan;71 Suppl 1(Suppl 1):i1-22. doi: 10.1136/thoraxjnl-2015-207360.

US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis

R Andres Floto [1], Kenneth N Olivier [2], Lisa Saiman [3], Charles L Daley [4], Jean-Louis Herrmann [5], Jerry A Nick [6], Peadar G Noone [7], Diana Bilton [8], Paul Corris [9], Ronald L Gibson [10], Sarah E Hempstead [11], Karsten Koetz [12], Kathryn A Sabadosa [11], Isabelle Sermet-Gaudelus [13], Alan R Smyth [14], Jakko van Ingen [15], Richard J Wallace [16], Kevin L Winthrop [17], Bruce C Marshall [18], Charles S Haworth [19]; US Cystic Fibrosis Foundation and European Cystic Fibrosis Society

Affiliations + expand

PMID: 26666259 PMCID: PMC4717371 DOI: 10.1136/thoraxjnl-2015-207360

Diagnosis

Clinical and microbiologic criteria for diagnosis of nontuberculous mycobacterial pulmonary disease[#]

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

Source: Official ATS/IDSA statement [4]. AFB: acid-fast bacilli; NTM: nontuberculous mycobacteria. [#]: expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination. Patients who are suspected of having NTM pulmonary disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded. Making the diagnosis of NTM pulmonary disease does not *per se*, necessitate the institution of therapy, which is a decision based on the potential risks and benefits of therapy for individual patients. [¶]: when 2 positive cultures are obtained, the isolates should be the same NTM species (or subspecies in the case of *M. abscessus*) in order to meet disease criteria.

Griffith, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007

The clinical lab:
Critical role in diagnosis of NTM disease

- Sample processing and culture
  - Preferred decontamination with 0.25% N-acetyl-L-cysteine and 1% NaOH (NALC-NaOH)
  - Culture on both liquid and solid media
    - ↑ sensitivity of culture by 15%
    - Löwenstein-Jensen medium is most sensitive
    - Clinical and Laboratory Standards Institute (CLSI) currently recommends use of 7H10 and 7H11 solid media
      - Temperatures of 36±1°C for slow growers and 28±2°C for rapid growers
  - Patients with a high suspicion of NTM pulmonary disease with negative cultures
    - Review decontamination procedures
    - Consider use of supplemented media and molecular detection
    - Use a *Mycobacterium* genus specific assay used in conjunction with nucleic acid sequencing, to distinguish *M. tuberculosis* complex from NTM

The clinical lab: Species identification

- Essential to the clinician
- Molecular identification preferred
    - Probe-based assays
        - Easier to perform but lack discriminatory power
        - Can lead to misidentification and oversimplification of NTM phylogeny and epidemiology
    - Gene sequencing
        - Higher discrimination up to the subspecies level
        - Target genes
            - 16S rRNA gene sequencing
                - limited discriminatory power, particularly for the *M. abscessus-M. chelonae* group
            - *hsp65* and *rpoB* genes and 16S–23S internal transcribed spacer (ITS)

The clinical lab: Species identification continued

- Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry
  - Not all species and subspecies can be differentiated with this approach
  - When applied to newly positive liquid cultures, only 50% of isolates can be immediately identified
  - Subculture on solid media until the occurrence of visual growth is needed to obtain good MALDI-TOF results

The clinical lab: Species identification continued

- All clinically relevant isolates of NTM should be identified by molecular methods
- Isolates from patients who are being treated for NTM pulmonary disease should be frozen and saved
  - Key to distinguish reinfection from relapse

The clinical lab: Drug susceptibility testing

- MAC infections
- Improved outcomes with macrolide-ethambutol-rifampicin regimen
    - Acquired macrolide resistance due to point mutations in the *23S rRNA* (*rrl*) gene
    - Acquired amikacin resistance due to resistance conferring mutations in the *16S rRNA* (*rrs*) gene
        - Breakpoint MICs lead to cessation of therapy
            - ≥64 μg·mL−1 for parenteral amikacin
            - ≥128 μg·mL−1 for amikacin liposome inhalation suspension
    - Tentative breakpoints exist for linezolid and moxifloxacin

The clinical lab: Drug susceptibility testing

- *M. abscessus*
  - Parenteral drugs
    - Amikacin, imipenem, cefoxitin, and tigecycline
  - Oral drugs
    - Macrolides, oxazolidinones (linezolid) and clofazimine
  - Clofazimine
    - Acts synergistically with amikacin and macrolides
    - Prevents the emergence of amikacin-resistant *M. abscessus in vitro*

The clinical lab: *M. abscessus* subspecies differences

- Ssp. *abscessus* and *bolletii*
  - *erm*(41) results in inducible macrolide resistance
    - May be measured *in vitro* by prolonged (i.e. up to 14 days) incubation of microdilution trays
    - Or investigated by molecular detection and characterization of the erm(41) gene.
- *M. abscessus* subsp *massiliense*, the *erm*(41) gene is nonfunctional
    - Renders strains macrolide susceptible
- All *M. abscessus* subspecies can develop constitutive macrolide resistance owing to 23S RNA (*rrl*) gene mutations
  - Susceptibility testing panels for *M. abscessus* should include
    - Amikacin, cefoxitin, imipenem, clarithromycin, linezolid, doxycycline, tigecycline, ciprofloxacin, and moxifloxacin

Research Gaps

- Globally changing trends in NTM species
- Increased need for more species-specific analyses to improve our understanding of NTM epidemiology
- Improved understanding of risk factors for NTM disease
  - Host
  - Environment

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Summary

- NTM pulmonary isolation and lung disease are increasing globally
  - Most cases occur among persons aged >50 years
  - Isolate-based analysis across countries/regions reveal distinct trends in NTM species
  - MAC is predominant in most regions
- Making NTM pulmonary disease a reportable condition could improve surveillance and our understanding of specific risk factors

The NTM clinician's wish list

- Molecular identification of all clinically relevant NTM
  - Including follow-up isolates of patients undergoing NTM pulmonary disease treatment
- Microbiological identification to the species/subspecies level
  - Accurate diagnosis
  - Treatment
  - Prognostication
  - Outbreak surveillance
- Preservation of NTM isolates
  - Essential to distinguish reinfection from relapse when recurrence occurs
  - Critical for outbreak investigation

Thank you!

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