Management of patients with NTM-LD: Improving adherence for optimal outcomes

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Approaches to reduce time to diagnosis and initiation of guideline-based treatment

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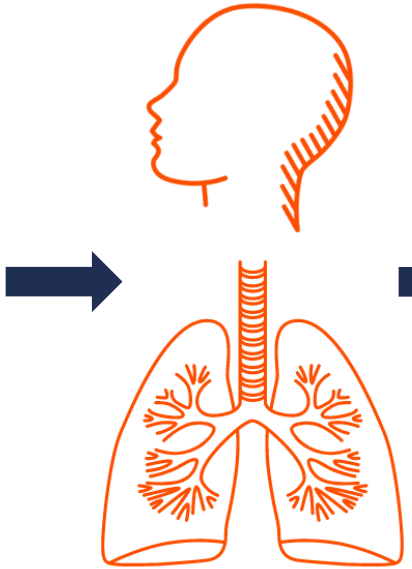
Clinical presentation of NTM-LD

What is NTM-LD?

NTM-LD is the most common clinical manifestation of NTM infection and can lead to chronic, debilitating disease. Up to **85%** of NTM-LD cases are caused by **MAC.**[1]

Risk factors

- **Environmental**[2,3] (water, soil, dust)
- **Host**[2,3] (structural lung diseases, e.g. bronchiectasis, COPD)
- **Genetic**[3] (e.g. AATD, CF, PCD)
- **Immunologic**[2] (e.g. HIV, immunosuppressant exposure, including biologics and corticosteroids)
- **Host-susceptible phenotype**[4] (e.g. tall slender body habitus, pectus excavatum)



Symptoms[1,3]

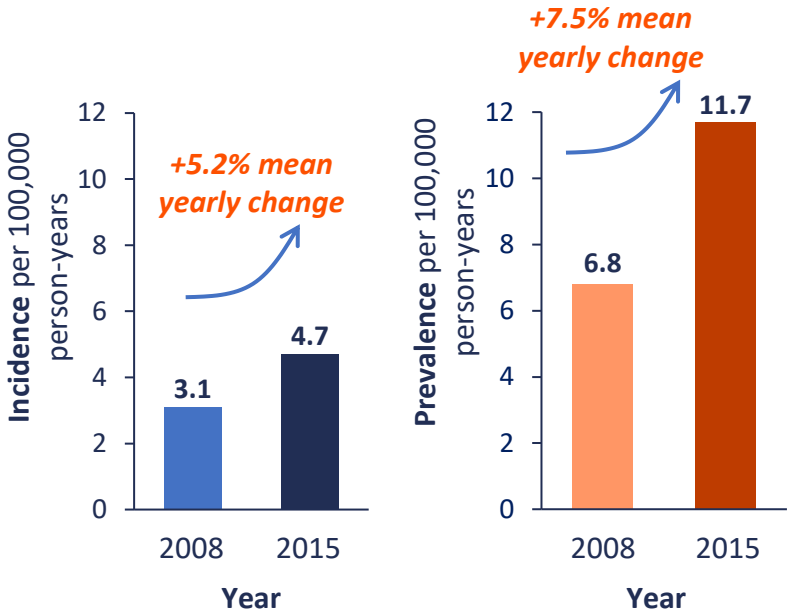
- Cough
- Dyspnoea
- Excessive mucus production
- Fatigue
- Fever
- Haemoptysis
- Night sweats
- Weight loss

AATD, alpha-1-antitrypsin deficiency; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacteria; NTM-LD, NTM-lung disease; PCD, primary ciliary dyskinesia.

1. van Ingen J, et al. *Expert Rev Respir Med*. 2021;15:1387–401; 2. Feng J-Y, et al. *J Formos Med Assoc*. 2020;119(Suppl. 1):S23-31; 3. Pathak K, et al. *Int J Gen Med*. 2022;15:7619–29; 4. Sexton P, Harrison AC. *Eur Respir J*. 2008;31:1322–33.

Challenges associated with NTM-LD

1 Increasing prevalence and incidence in the USA[1]



2 Diagnostic challenges[2]

Diagnosis is challenging due **to non-specific symptoms** and **overlapping features** with other lung diseases, e.g. bronchiectasis and COPD

It can take up to **20 months** from initial clinical presentation to diagnosis

3 Burden of disease[3]

Delays in diagnosis may lead to:

- Worsening symptoms
- Decrease in social and physical functioning
- Decline in mental health
- Inappropriate management of the disease

COPD, chronic obstructive pulmonary disease; NTM-LD, nontuberculous mycobacterial lung disease.

1. Winthrop KL, et al. *Ann Am Thorac Soc*. 2020;17:178–85; 2. Ali J. *Expert Rev Respir Med*. 2021;15:663–73; 3. van Ingen J, et al. *Expert Rev Respir Med*. 2021;15:1387–401.

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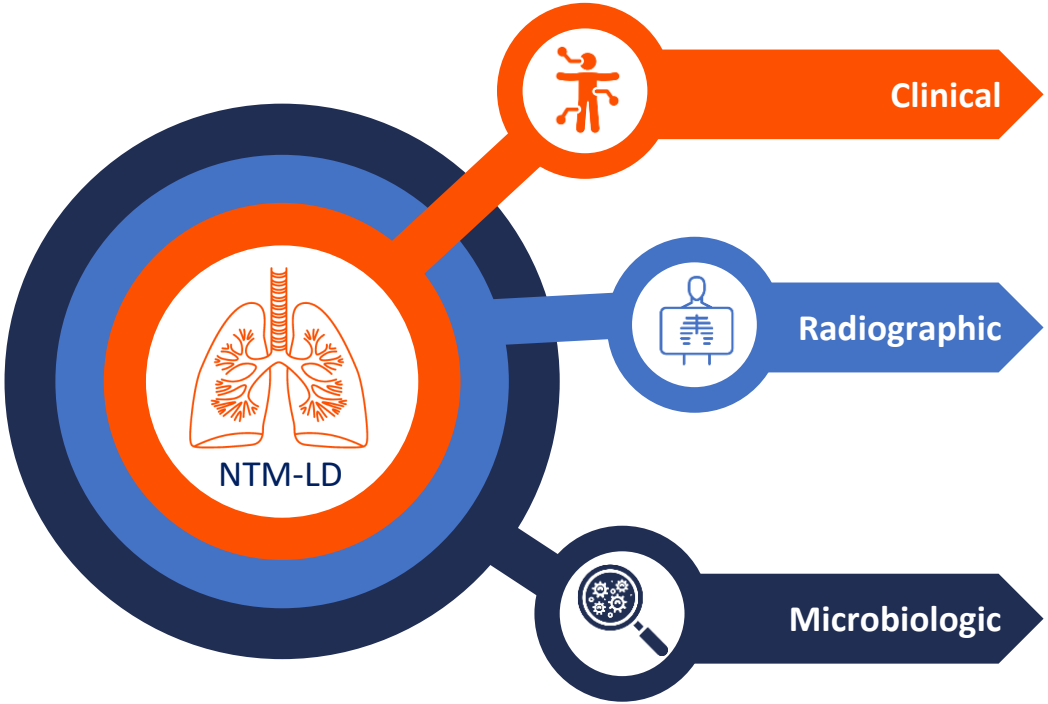
Diagnostic criteria for NTM-LD



- Pulmonary or systemic symptoms
- Exclusion of other diagnoses

- Nodular or cavitary opacities on chest radiograph, or bronchiectasis with multiple small nodules on chest HRCT scan

- Positive culture results from ≥2 separate expectorated sputum samples
  OR
- Positive culture result from ≥1 bronchial wash or lavage **OR**
- Transbronchial/lung biopsy with mycobacterial histologic features and positive NTM culture from biopsy or ≥1 sputum/bronchial wash

HRCT, high-resolution computed tomography; NTM, nontuberculous mycobacteria; NTM-LD, NTM-lung disease.

Daley CL, et al. *Eur Respir J*. 2020;56:2000535.

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The setting of individualized treatment goals in collaboration with patients

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Recommended treatment regimens for macrolide-susceptible MAC NTM-LD

Disease type	Drug regimen	Dosing frequency
Nodular-bronchiectatic	**Three-drug macrolide-based regimen:** Azithromycin, in preference to clarithromycin Rifamycin (rifampin or rifabutin) Ethambutol	**TIW or QD** (based on severity) **for ≥12 months** after culture conversion
Cavitary	**Three-drug macrolide-based regimen** **+/- amikacin IV* (streptomycin)**	**QD for ≥12 months** after culture conversion **TIW for aminoglycosides**
Refractory†	**Three-drug macrolide-based regimen** **+ ALIS‡ OR amikacin IV* (streptomycin)**	**QD** **TIW for aminoglycosides**

*Consider for cavitary, extensive nodular-bronchiectatic disease or macrolide-resistant MAC in the initial treatment regimen; †Defined as remaining sputum culture-positive after 6 months of guideline-based therapy; ‡ALIS has been shown to improve culture conversion when added to guideline-based therapy in treatment-refractory patients with MAC pulmonary disease.
ALIS, amikacin liposome inhalation suspension; IV, intravenous; MAC, *Mycobacterium avium* complex; NTM-LD, nontuberculous mycobacterial lung disease; QD, once daily; TIW, three times a week.

Daley CL, et al. *Eur Respir J*. 2020;56:2000535.

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Alternative treatments for MAC NTM-LD

Drug (off-label use)	Dose and frequency	Monitoring
Clofazimine*[1,2]	100–200 mg QD	Clinical monitoring; liver function; ECG (QTc)
Bedaquiline†[3]	Weeks 1–2: 400 mg QD Weeks 3–24: 200 mg TIW	Clinical monitoring; liver function; ECG (QTc)
Linezolid[1,4]	600 mg QD	Clinical monitoring; visual acuity/colour discrimination; CBC
Tedizolid[5]	200 mg QD	Clinical monitoring; CBC
Inhaled amikacin parenteral formulation (when ALIS not available)[1]	250–500 mg QD	Renal, auditory and vestibular toxicity

*An investigational new drug application is required for clofazimine in the USA; †Approved for multidrug-resistant tuberculosis.
ALIS, amikacin liposome inhalation suspension; CBC, complete blood count; ECG, electrocardiogram; MAC, *Mycobacterium avium* complex; NTM-LD, nontuberculous mycobacterial lung disease; TIW, three times a week; QD, once daily; QTc, corrected QT interval.

1. Daley CL, et al. *Eur Respir J*. 2020;56:2000535; 2. FDA. Clofazimine PI. Available at: https://bit.ly/3WGdHWD (accessed 8 November 2022); 3. FDA. Bedaquiline PI. Available at: https://bit.ly/3UlgVwV (accessed 8 November 2022); 4. FDA. Linezolid PI. Available at: https://bit.ly/3SIiEuL (accessed 8 November 2022); 5. FDA. Tedizolid PI. Available at: https://bit.ly/3DO52Zh (accessed 8 November 2022).

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Improving efficacy and decreasing drug-related toxicity

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Key adverse reactions to antimicrobial therapy for NTM-LD

Drug	Adverse reactions
ALIS	• Cough • Dysphonia • Dyspnoea • Nephrotoxicity • Ototoxicity • Vestibular toxicity
Amikacin, streptomycin, tobramycin	• Electrolyte disturbance • Nephrotoxicity • Ototoxicity • Vestibular toxicity
Ethambutol	• Neuropathy • Ocular toxicity
Macrolides (azithromycin and clarithromycin)	• Gastrointestinal • Hepatotoxicity • Prolonged QTc • Tinnitus/hearing loss
Rifamycin (rifampin or rifabutin)	• Cytopenia • Hepatotoxicity • Hypersensitivity • Orange discolouration of secretions

Clinical monitoring*

*Monitoring frequency should be individualized based on treatment regimen, age, comorbidities, concurrent drugs, overlapping drug toxicities and resources.
ALIS, amikacin liposome inhalation suspension; NTM-LD, nontuberculous mycobacterial lung disease; QTc, corrected QT interval.
Daley CL, et al. *Eur Respir J.* 2020;56:2000535.

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Real-world treatment outcomes in NTM-LD (USA)

Clinical outcomes in patients undergoing macrolide/azalide therapy for nodular/bronchiectatic MAC-LD

Retrospective single-centre review of patients (N=180) completing >12 months of macrolide/azalide multidrug therapy

- Sputum conversion to negative in **86%** of patients
- Treatment success* in **84%** of patients
- **No patients** developed treatment resistance

Treatment regimen modification occurred more frequently with daily vs intermittent therapy **(80% vs 1%; p=0.0001)**

9% of treatment episodes discontinued prior to 12 months of planned treatment due to medication intolerance; **1%** due to macrolide/azalide intolerance

*Sputum conversion without true microbiologic relapse with the original infecting MAC genotype.
MAC-LD, *Mycobacterium avium* complex lung disease; NTM-LD, nontuberculous mycobacterial lung disease.
Wallace RJ, et al. *Chest*. 2014;146:276–82.

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Real-world treatment outcomes in NTM-LD (Europe)

Clinical outcomes in patients undergoing multidrug antibiotic therapy for NTM-LD at a TB reference centre[1]

Observational, retrospective study of patients (N=170) at a median follow-up of 31 months

- Side effects occurred in **37.6%** of patients
- Treatment failure* in **4.1%** of patients
- Treatment discontinued in **13.5%** of patients

Median time to treatment discontinuation due to side effects was **234 days** after treatment initiation

The main reason for discontinuation of treatment was **drug intolerance**

*Defined as re-emergence of multiple positive cultures or persistence of positive cultures with the causative species from respiratory samples after ≥12 months of antimycobacterial treatment, while still on treatment.[2]

NTM-LD, nontuberculous mycobacterial lung disease; TB, tuberculosis.

1. Aliberti S, et al. *Respir Med*. 2020;164:105899; 2. van Ingen J, et al. *Eur Respir J*. 2018;51:1800170.