New guideline-based strategies for improving outcomes in patients with NTM-LD

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Can we reduce time to diagnosis and initiation of treatment?

Dr Juzar Ali

Professor of Medicine
LSU Health Sciences Center
New Orleans, LA, USA

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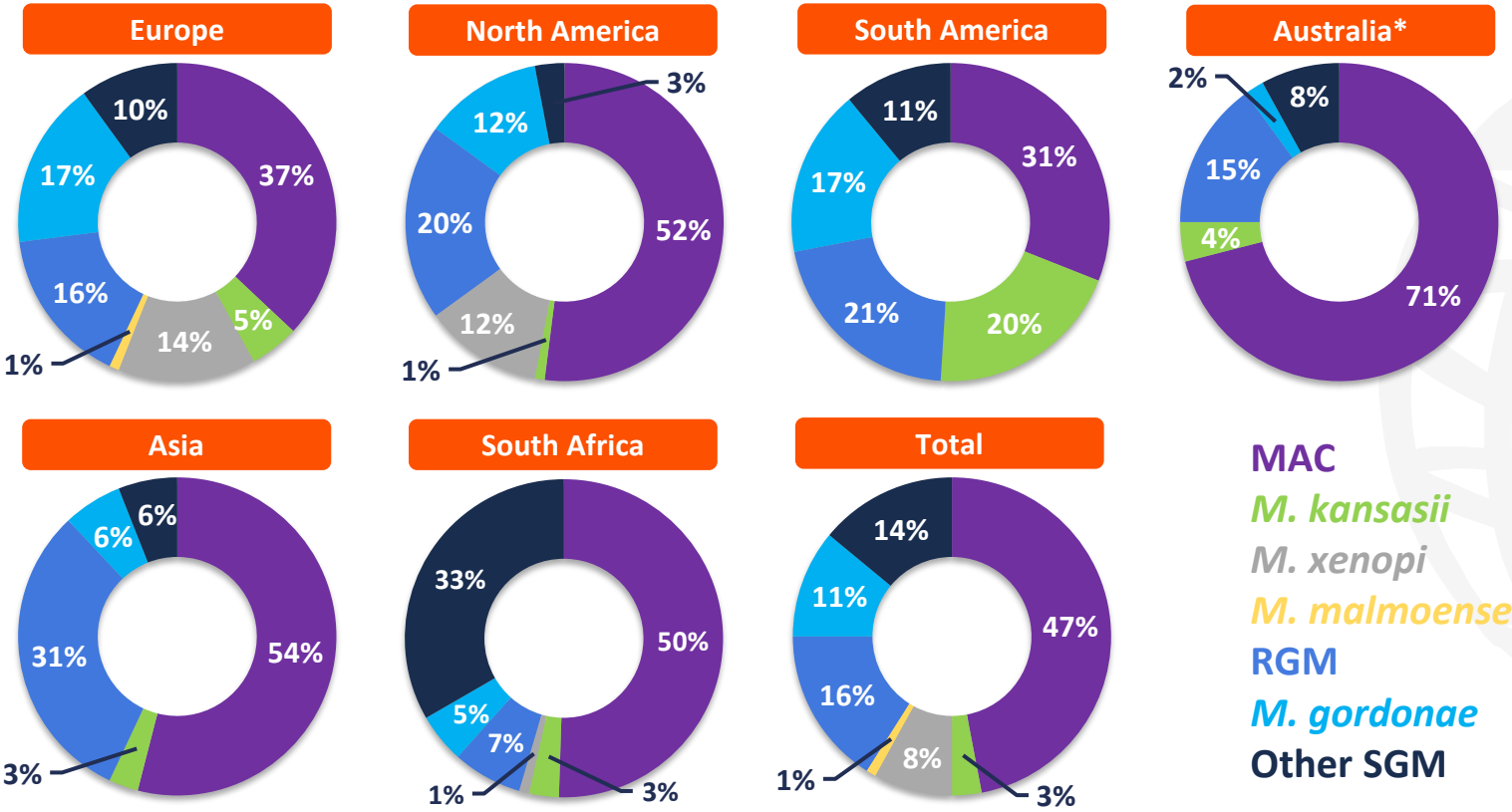
What is the incidence and prevalence of NTM-LD and how does it vary at a geographic and individual level?

Global distribution of respiratory NTM isolates



*Data are specifically for the state of Queensland.

MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacterial; RGM, rapid-growing mycobacteria; SGM, slow-growing mycobacteria.

Hoefsloot W, et al. *Eur Respir J.* 2013;42:1604–13.

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What is the link between bronchiectasis and NTM-LD?

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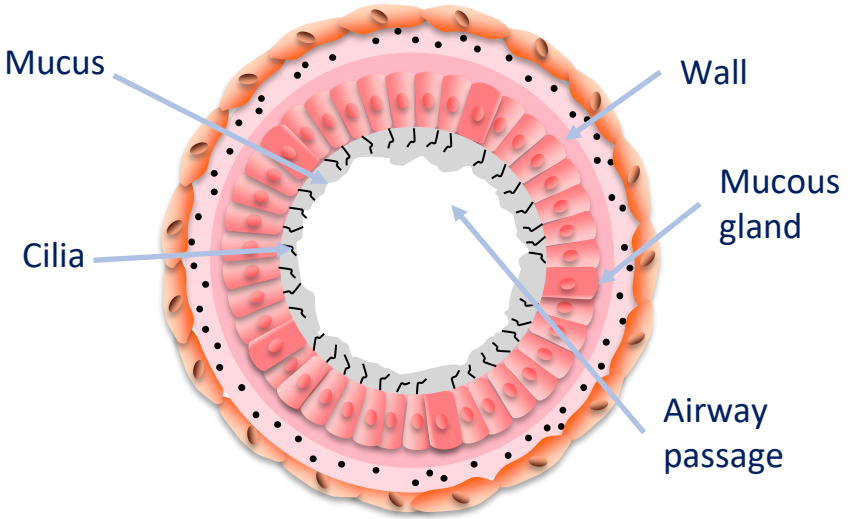
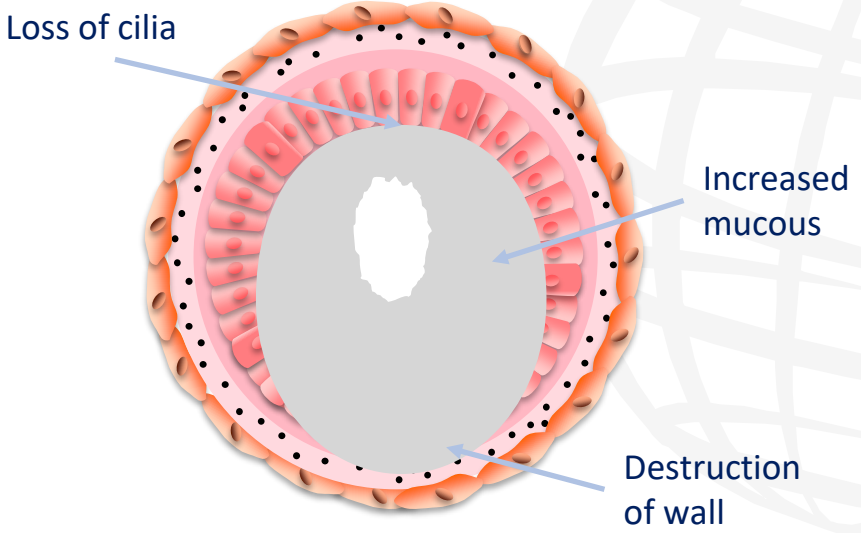
Bronchiectasis and NTM-LD

Bronchiectasis is the primary underlying pathophysiological derangement in patients with NTM-LD, with a cascade of recurrent inflammation and concomitant infection



Structure of healthy bronchus



Structure of a bronchus with bronchiectasis

NTM-LD, nontuberculous mycobacterial lung disease.
Chalmers JD, et al. *Nat Rev Dis Primers.* 2018;4:45.

What are the common pulmonary comorbidities associated with NTM-LD?

Common comorbidities associated with NTM-LD

COPD[1]

- Most frequently observed comorbidity with NTM-LD
- Causes increased disease severity and more exacerbations per year, as well as higher rates of mortality
- Underlying COPD makes treatment of NTM-LD extremely difficult and cure rates are low

Lung cancer[1]

- Incidences of NTM-LD and cancer are increasing, and association between them is recognized but not well characterized
- Given that their clinical and radiologic symptoms can be similar, when treating NTM-LD consideration should be made regarding the concurrence of malignancies

Asthma[2]

- 1.7% of patients with difficult-to-control asthma have NTM-LD as a comorbidity

IPF[1]

- Patients with IPF have significantly higher rates of NTM-LD
- NTM-LD exacerbates IPF
- Treatment for IPF often includes immunosuppressive drugs, steroids and DMARD agents, which can increase the risk for NTM-LD infection and mortality

COPD, chronic obstructive pulmonary disease; DMARD, disease-modifying antirheumatic drug; IPF, idiopathic pulmonary fibrosis; NTM-LD, nontuberculous mycobacterial lung disease.

1. Ali J. *Expert Rev Respir Med*. 2021;15:663–73; 2. Marras TK, et al. *Euro Resp J*. 2016;48:928–31.

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What considerations should clinicians have when performing sputum collection and microbiological assessment?

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Key factors in sputum collection and evaluation

Airway clearance	• **Dual purpose – therapeutic and diagnostic;** may be required before sputum collection • Can comprise of traditional chest physiotherapy or mechanical/pharmacological intervention
Collection	• To ensure the validity of each sputum evaluation, sufficient quality and quantity is required • Consult with testing laboratory to establish their sample requirements, collection technique standards and frequency of collection

Rejection criteria	• Sputum collection rejection criteria include:
	  • <3 mL of sputum
	  • sputum that is predominately saliva
	  • dry swabs
	  • samples >7 days from date of collection
	  • unrefrigerated samples

Confirmation	• Confirmation of two positive sputum cultures is an important indicator of NTM-LD • Isolation of more than one positive culture of the same species from at least two sputum cultures is recommended • The identified NTM species determines the number of required cultures
Follow up	• Sputum should be collected monthly until two or three consecutive cultures are negative for NTM bacteria

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

Ali J. *Expert Rev Respir Med*. 2021;15:663–67.

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What are the benefits of radiological assessment in patients with NTM-LD?

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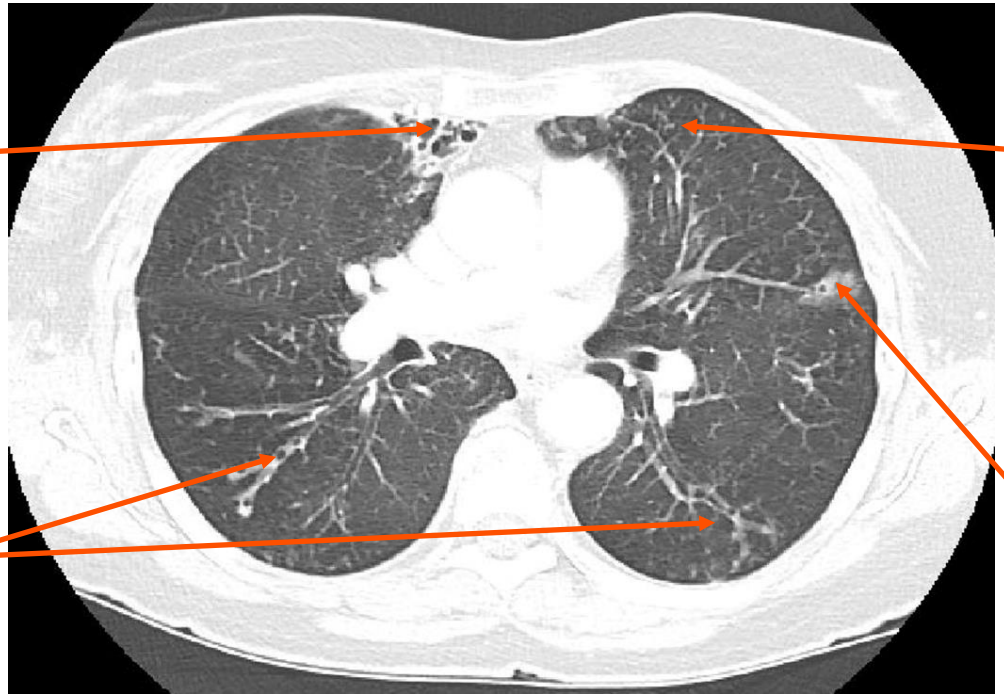
Bronchiectasis seen in a patient with MAC infection and disease: multiple presentation and multi-focal



MAC, *Mycobacterium avium* complex.
Image supplied courtesy of Dr Ali.

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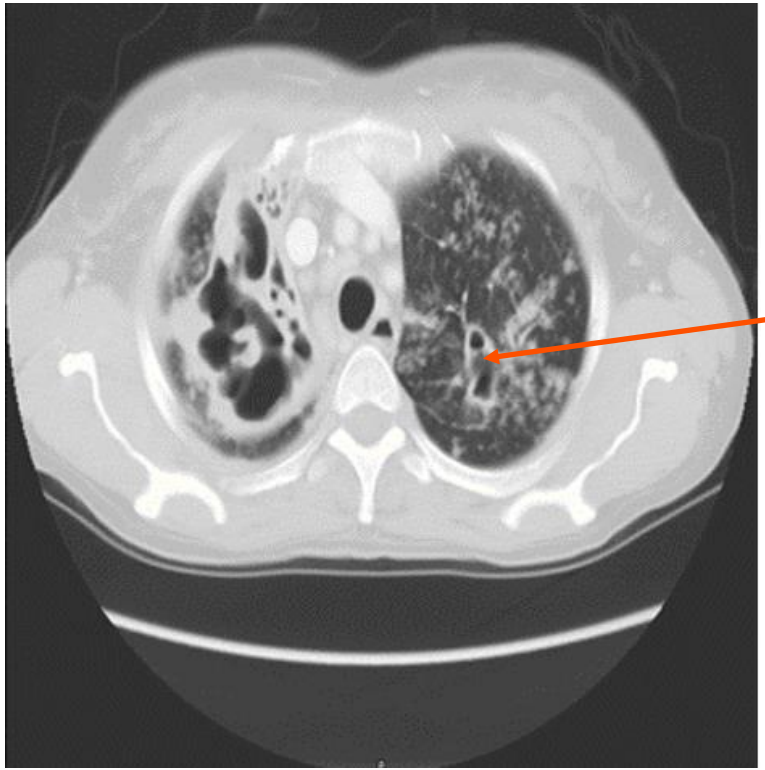
Cavitary disease seen with MAC disease



Bronchiectasis with cavities

MAC. *Mycobacterium avium* complex.
Image supplied courtesy of Dr Ali.

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What do clinicians need to know about new guideline-based treatment options to individualize treatment goals?

Dr Doreen Addrizzo-Harris

Professor of Medicine
NYU Grossman School of Medicine
New York, NY, USA

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Should patients with NTM-LD be treated with antimicrobial therapy or is watchful waiting preferred?

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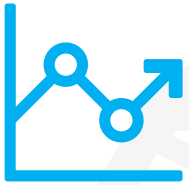
Clinical factors to consider before initiating antimicrobial therapy

Infecting species

- Virulence
- Responsiveness to antimicrobial therapy

Individual patient priorities

- Immune suppression
- Quality of life
- Mild signs and symptoms of disease
- Adverse effects of therapy
- Benefits of antimicrobial therapy
- Potential for recurrence
- Comorbidities



Factors associated with relatively poor prognosis

- Cavitary disease
- Low body mass index
- Low albumin
- Elevated inflammatory markers

The decision to initiate antimicrobial therapy for NTM-LD should be individualized based on a combination of clinical factors

NTM-LD, nontuberculous mycobacterial lung disease.

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

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Should drug-susceptibility testing be performed before initiating treatment?

Drug susceptibility testing for NTM-LD[1]

- CLSI recommendation to perform drug susceptibility testing by **broth microdilution**
- Drug susceptibility testing of primary isolates and relapse/failure isolates should be performed if the NTM isolate is clinically significant

M. kansasii

- Rifampin and clarithromycin are the key drugs to test for potential resistance
- Resistance is defined as a MIC:
  - >2 µg/mL for rifampin
  - ≥32 µg/mL for clarithromycin

M. avium complex

- Clear correlation between baseline macrolide susceptibility of the causative strain and the outcome of treatment with macrolide/ethambutol/rifampin
- Resistance is defined as a MIC:
  - ≥32 µg/mL for clarithromycin[2]
  - ≥64 µg/mL for parenteral amikacin
  - ≥128 µg/mL for amikacin liposome inhalation suspension (ALIS)

M. abscessus

- Evident association for macrolides and amikacin between *in vitro* drug susceptibility and *in vivo* outcome of treatment
- Clofazimine shows *in vitro* activity, acts synergistically with amikacin and macrolides, and prevents the emergence of amikacin-resistant *M. abscessus in vitro*

CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inhibitory concentration; NTM, nontuberculous mycobacteria; NTM-LD, NTM lung disease.

1. Daley CL, et al. *Eur Respir J.* 2020;56:2000535; 2. Nie W, et al. *Biomed Res Int.* 2015;2015:506598.

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What are the treatment options for patients with macrolide-susceptible MAC NTM-LD?

Initial treatment of macrolide-susceptible MAC NTM-LD

A three-drug regimen including a macrolide is recommended over a three-drug regimen without a macrolide

Azithromycin-based treatment regimens in preference to clarithromycin-based regimens are recommended

- In patients with noncavitary nodular/bronchiectatic disease, a macrolide-based regimen three times a week for at least 12 months after culture conversion is recommended
- In patients with cavitary disease, a daily macrolide-based regimen for at least 12 months after culture conversion is recommended

For patients with cavitary or advanced/severe bronchiectatic disease, parenteral amikacin or streptomycin is recommended to be included in the initial treatment regimen

Also recommended for patients with macrolide-resistant MAC pulmonary disease

MAC, *M. avium* complex; NTM-LD, nontuberculous mycobacterial lung disease.
Daley CL, et al. *Eur Respir J.* 2020;56:2000535.

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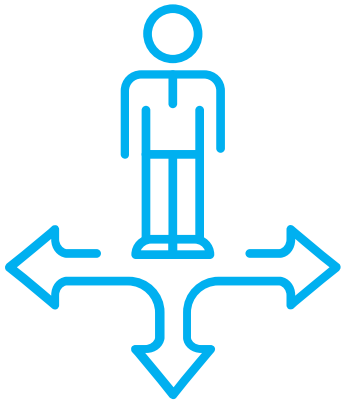
What are the treatment options for MAC NTM-LD for patients who have failed previous therapy?

Recommended treatment regimens for refractory MAC NTM-LD

Refractory disease is defined as remaining sputum culture positive after 6 months of guideline-based therapy



Clinician's choice of:*

- Amikacin liposome inhalation suspension (ALIS)
- Azithromycin
- Rifampin
- Ethambutol
- Amikacin IV†

Daily (three times weekly may be used with aminoglycosides)

Amikacin liposome inhalation suspension (ALIS) has been shown to improve culture conversion when added to guideline-based therapy in treatment-refractory patients with MAC NTM-LD

*Alternative drugs for patients who are intolerant of or whose isolate is resistant to first-line drugs include clofazimine, moxifloxacin, and linezolid. Some experts would consider bedaquiline or tedizolid.

†Consider for cavitary, extensive nodular bronchiectatic disease or macrolide-resistant MAC.

MAC, *M. avium* complex; NTM-LD, nontuberculous mycobacterial lung disease.

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

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What are the treatment options for patients with non-MAC NTM-LD?

Treatment regimens for non-MAC NTM-LD

*M. kansasii**

Rifampin + ethambutol + azithromycin	Daily
Rifampin + ethambutol + azithromycin	Three times weekly
Rifampin + ethambutol + isoniazid	Daily

M. xenopi

Rifampin + ethambutol, and either a macrolide and/or a fluoroquinolone	Daily
Rifampin + ethambutol + amikacin and either a macrolide and/or a fluoroquinolone†	Three times weekly

M. abscessus

Initial phase • Parental: amikacin, imipenem (or cefoxitin) and tigecycline • Oral: azithromycin, clofazimine and linezolid	Daily
Continuation phase • Azithromycin, clofazimine, linezolid and inhaled amikacin	Daily

Choice of how many agents to use is dependent on mutational and inducible resistance status of the strain

*In patients with rifampin-resistant *M. kansasii* or intolerance to one of the first line antibiotics, a fluoroquinolone (e.g. moxifloxacin) can be used as part of a second-line regimen.
†Consider for cavitary, extensive nodular bronchiectatic disease or macrolide-resistant strains.
Daley CL, et al. *Eur Respir J.* 2020 ;56:2000535.

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How can we manage adverse events to improve adherence?

Dr Kevin Winthrop

Professor of Infectious Diseases and Public Health
Oregon Health & Science University
Portland, OR, USA

What do real-word data tell us about adverse events leading to treatment discontinuation?

Real-world studies of treatment outcomes in NTM-LD

US population-based data of discontinuation after 12 months of multi-drug antibiotic therapy for MAC NTM-LD[1]

- Azithromycin + ethambutol + rifamycin: 84.1%
- Clarithromycin + ethambutol + rifamycin: 86.3%
- Macrolide + ethambutol + rifampin: 84.0%
- Macrolide + ethambutol + rifabutin: 90.6%
- Azithromycin + ethambutol + rifampin: 83.3%
- Clarithromcyin + ethambutol + rifabutin: 91.3%

Study at six NTM treatment centres evaluating the tolerability of linezolid in patients with NTM[2]

- Proportion of patients developing linezolid-attributable AEs was similar between:
  - patients using and not using rifampin (33% vs 48%)
  - patients with MAC and *M. abscessus* (37% vs 51%)
- Treatment discontinued in 87% of patients with linezolid-attributable AEs at a median of 20 weeks

Observational, retrospective study of patients with NTM-LD from a regional TB reference centre[3]

- At median follow-up of 31 months:
  - AEs occurred in 37.6% of patients
  - treatment halted in 13.5% of patients
- The main reason for discontinuation of treatment was drug intolerance

AE, adverse event; MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacteria; NTM-LD, NTM lung disease; TB, tuberculosis.

1. Ku J, et al. Presented at: IDWeek 2021, Virtual, On demand, 2021. Abstr 192; 2. Winthrop K, et al. *Eur Respir J.* 2015;45:1177–9; 3. Aliberti S, et al. *Respir Med.* 2020;164:105899.

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What key points should clinicians discuss with patients regarding possible adverse events before initiating therapy?

Potential adverse reactions to antimicrobial therapy for NTM-LD

Macrolides (azithromycin)	• Gastrointestinal • Tinnitus/hearing loss • Hepatotoxicity • Prolonged QTc
Rifampin	• Hepatotoxicity • Cytopenias • Hypersensitivity • Orange discolouration of secretions
Ethambutol	• Ocular toxicity • Neuropathy
Amikacin, streptomycin, tobramycin	• Vestibular toxicity • Ototoxicity • Nephrotoxicity • Electrolyte disturbances
Linezolid	• Peripheral neuropathy • Optic neuritis • Cytopenias
Amikacin liposome inhalation suspension (ALIS)	• Dysphonia • Vestibular toxicity • Ototoxicity • Nephrotoxicity • Cough • Dyspnea
Rifabutin	• Hepatotoxicity • Cytopenias • Uveitis • Hypersensitivity • Orange discolouration of secretions
Isoniazid	• Hepatitis • Peripheral neuropathy
Fluoroquinolone	• Prolonged QTc • Hepatotoxicity • Tendinopathy

QTc, corrected QT interval; NTM-LD, nontuberculous mycobacterial lung disease.

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

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How should clinicians manage adverse events when treating patients with macrolide-susceptible MAC NTM-LD?

Monitoring recommendations for potential adverse reactions to antimicrobial therapy for NTM-LD

Macrolides (azithromycin)	• Audiogram • Liver function tests	**Rifampin**	• Liver function tests • Complete blood count	**Ethambutol**	• Visual acuity and colour discrimination
Amikacin, streptomycin, tobramycin	• Audiograms • BUN, creatine	**Linezolid**	• Visual acuity and colour discrimination • Complete blood count	**Amikacin liposome inhalation suspension (ALIS)**	• Audiograms • BUN, creatine
Rifabutin	• Liver function tests • Complete blood count • Visual acuity	**Isoniazid**	• Liver function tests	**Fluoroquinolone**	• Liver function tests

Clinical monitoring should be performed for all antimicrobial therapies

BUN, blood urea nitrogen; NTM-LD, nontuberculous mycobacterial lung disease.
Daley CL, et al. *Eur Respir J.* 2020;56:2000535.

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How should clinicians manage adverse events when treating patients with treatment-refractory MAC NTM-LD who are receiving treatment with ALIS?

Safety and tolerability of amikacin liposome inhalation suspension (ALIS) during 12-month open-label extension trial

ALIS-naïve cohort	
Grade ≥3 TEAEs	40.0%
TEAE in ≥10% of patients	
Dysphonia	43.3%
Cough	35.6%
Dyspnea	17.8%
Fatigue	14.4%
Hemoptysis	12.2%
Infective exacerbation of bronchiectasis	12.2%
Nausea	10.0%
Diarrhoea	10.0%
Tinnitus	6.7%
TEAE of pulmonary exacerbation*	32.2%
TEAE leading to discontinuation of ALIS	24.4%
TEAE leading to discontinuation of GBT	8.9%
TEAE leading to discontinuation of ALIS and GBT	5.6%

Prior-ALIS cohort	
Grade ≥3 TEAEs	21.9%
TEAE in ≥10% of patients	
Hemoptysis	15.1%
Nasopharyngitis	13.7%
Cough	12.3%
Dyspnea	12.3%
Tinnitus	1.4%
TEAE of pulmonary exacerbation*	30.1%
TEAE leading to discontinuation of ALIS	8.2%
TEAE leading to discontinuation of GBT	5.5%
TEAE leading to discontinuation of ALIS and GBT	1.4%

*Pulmonary exacerbation was defined based on the investigators' best clinical judgment.
GBT, guideline-based therapy; TEAE, treatment-emergent adverse event.
Winthrop KL, et al. *Ann Am Thorac Soc.* 2021;18:1147–57.

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How should clinicians manage adverse events when treating patients with non-MAC NTM-LD?

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Adverse events for common non-MAC treatment regimens

M. abscessus

Treatment	Parenteral multidrug treatment regimen
Adverse events	Tinnitus/hearing loss, hepatotoxicity, gastrointestinal and renal toxicity
Monitoring	Routine toxicity monitoring and baseline and intermittent audiometry testing

M. xenopi

Treatment	Rifampin, ethambutol, and either a macrolide and/or a fluoroquinolone
Adverse events	Ocular toxicity and neuropathy (tendinopathy if using a fluoroquinolone)
Monitoring	Regular monitoring of blood glucose and routine toxicity monitoring test

M. kansasii

Treatment	Rifampin, ethambutol, and either isoniazid or macrolide
Adverse events	Peripheral/optic neuropathy and transient increases in levels from liver function tests
Monitoring	Routine toxicity monitoring tests intermittently throughout treatment and ophthalmic testing

Monitoring frequency for drug-related AEs should be individualized on choice of therapy, age, comorbidities, concurrent drugs and resources

AE, adverse event; MAC, *Mycobacterium avium* complex.

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

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