# 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?

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

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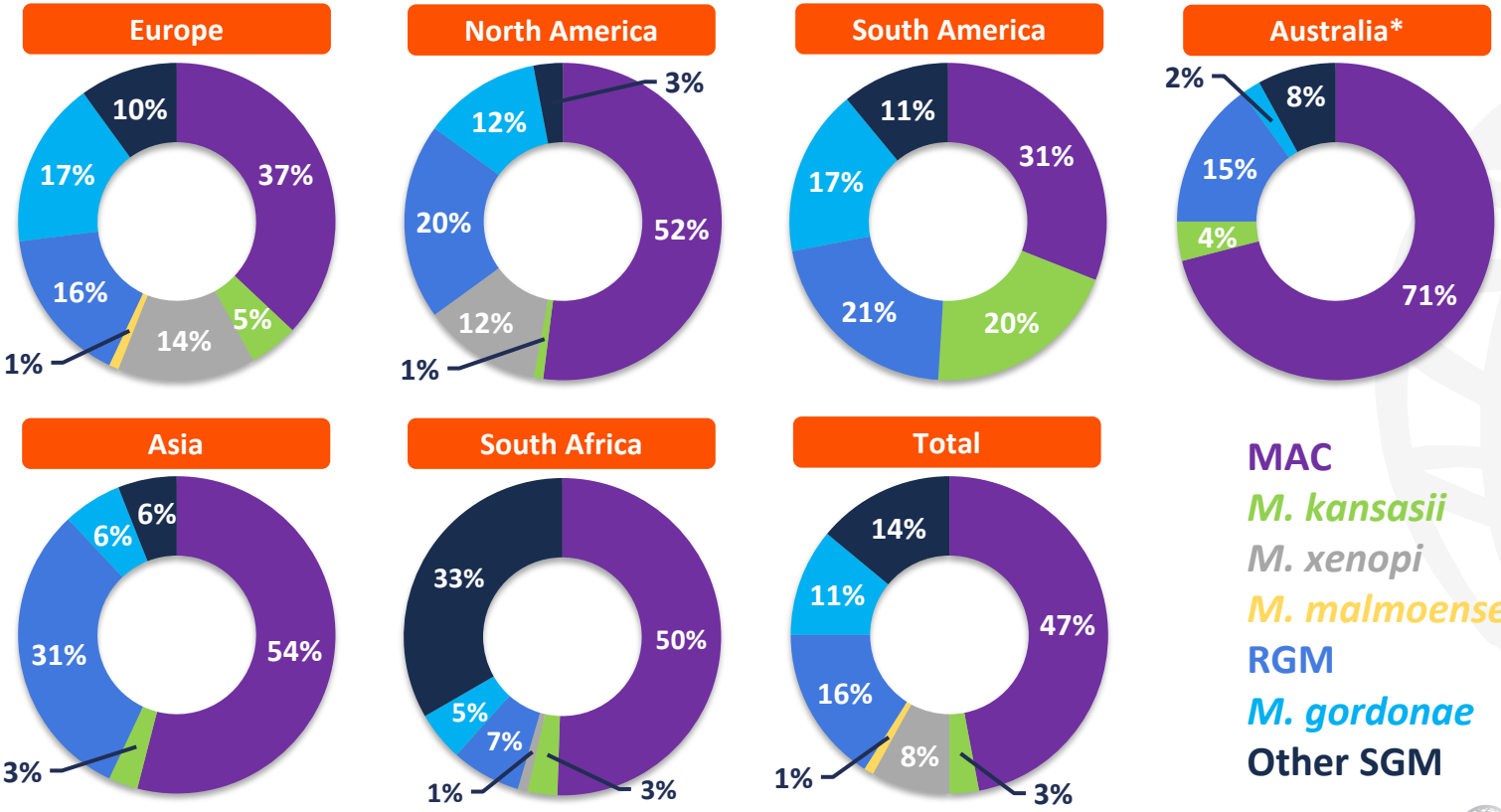
# Global distribution of respiratory NTM isolates




*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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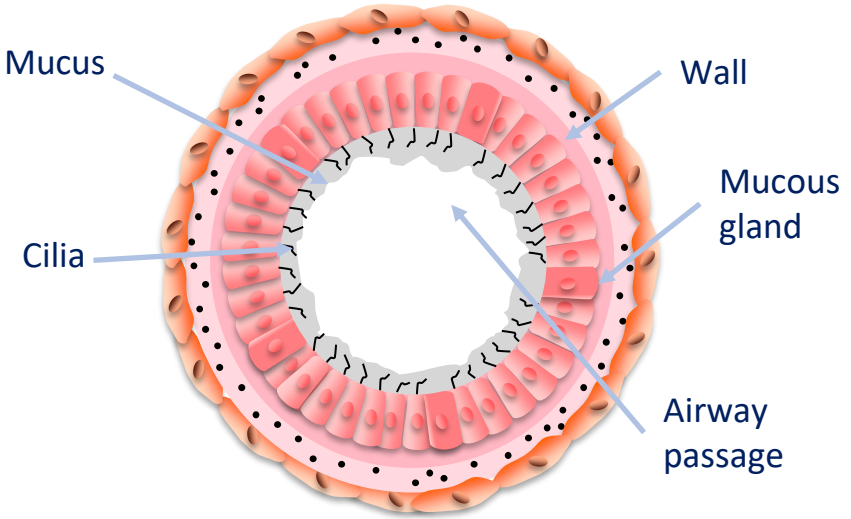
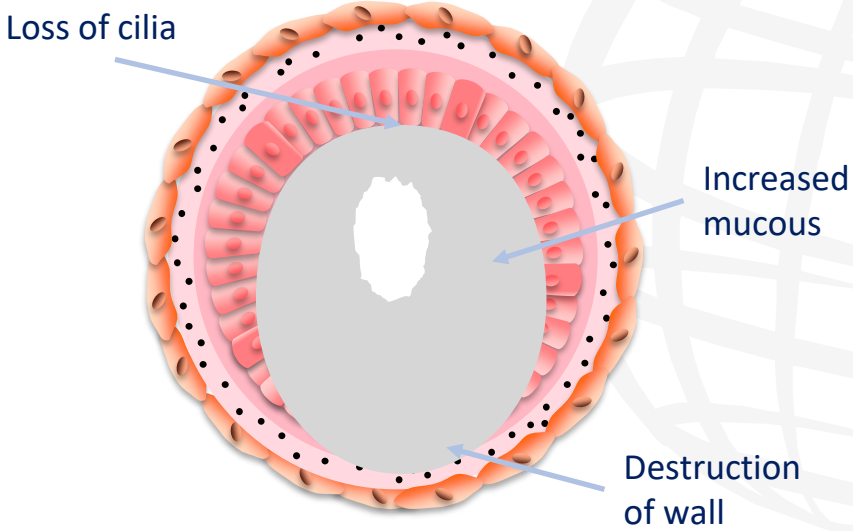
# Bronchiectasis and NTM-LD

**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.

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

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# 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<br>• 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<br>• Consult with testing laboratory to establish their sample requirements, collection technique standards and frequency of collection |
| **Rejection criteria** | • Sputum collection rejection criteria include:<br>  • <3 mL of sputum<br>  • sputum that is predominately saliva<br>  • dry swabs<br>  • samples >7 days from date of collection<br>  • unrefrigerated samples |
| **Confirmation** | • Confirmation of two positive sputum cultures is an important indicator of NTM-LD<br>• Isolation of more than one positive culture of the same species from at least two sputum cultures is recommended<br>• 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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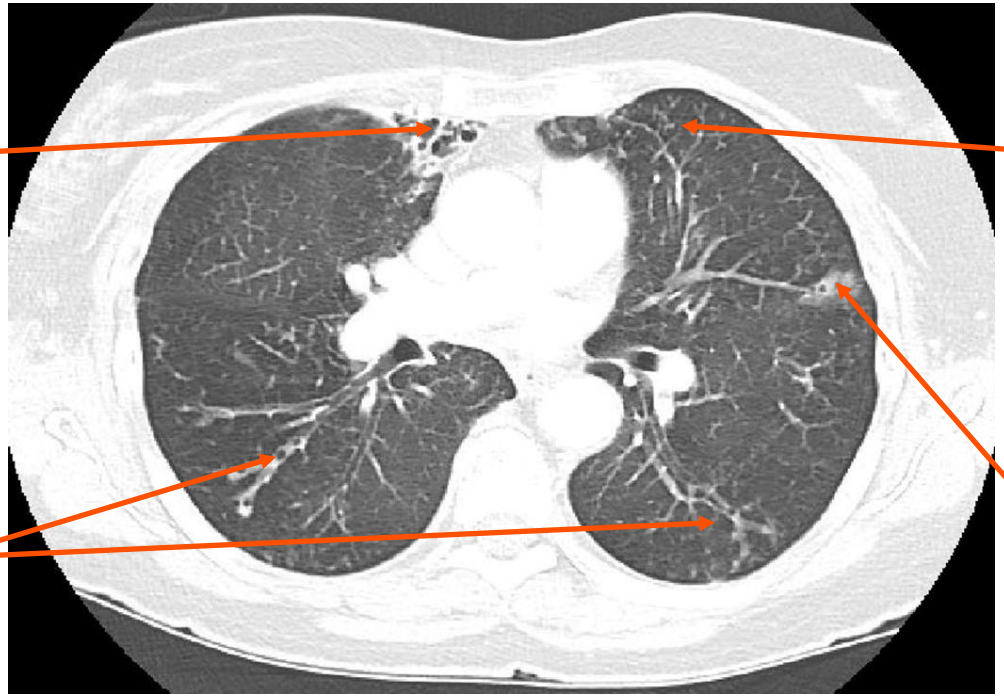
# Bronchiectasis seen in a patient with MAC infection and disease: multiple presentation and multi-focal




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

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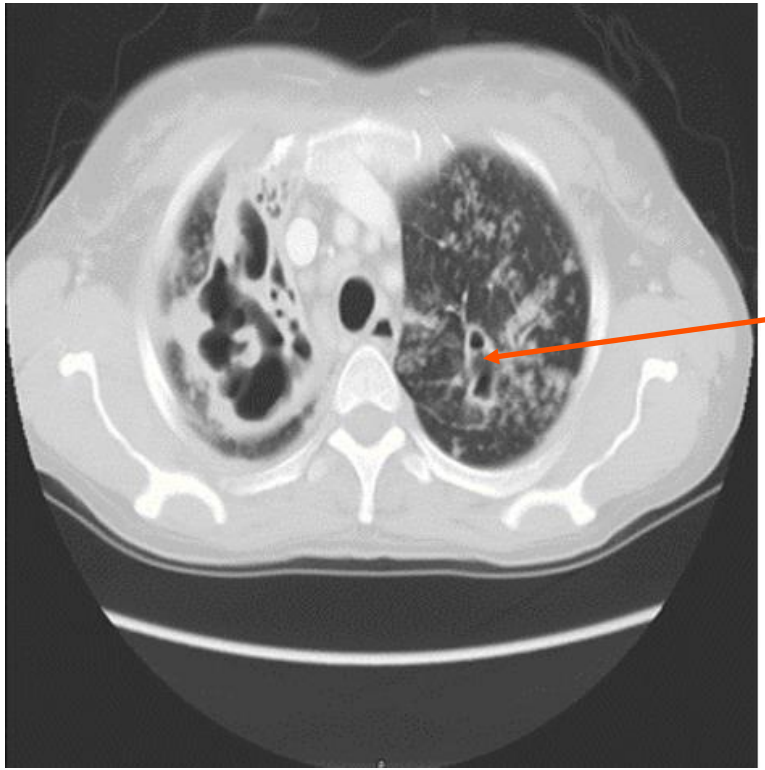
# Cavitary disease seen with MAC disease




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?

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

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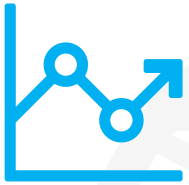
# Clinical factors to consider before initiating antimicrobial therapy

**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.

# Should drug-susceptibility testing be performed before initiating treatment?

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# 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?

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# 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?

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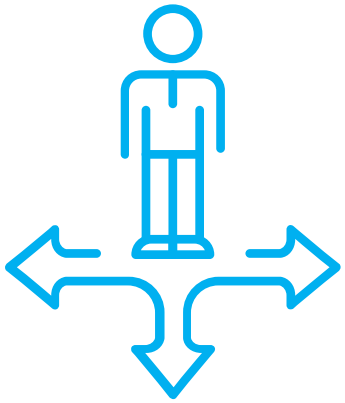
# Recommended treatment regimens for refractory MAC NTM-LD

**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?

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# 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**<br>• Parental: amikacin, imipenem (or cefoxitin) and tigecycline<br>• Oral: azithromycin, clofazimine and linezolid | Daily |
| **Continuation phase**<br>• 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?

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

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# 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?

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# Potential adverse reactions to antimicrobial therapy for NTM-LD

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

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

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

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# 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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