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A Team Based Approach for Improving

NTM-LD Diagnosis & Management

KEY TAKEAWAYS

Learning Objectives

- Describe key steps in NTM-LD diagnosis and how to reduce time to patient identification
- Incorporate practice guidelines, the latest evidence, and a multidisciplinary approach into management strategies for NTM-LD patients
- Assess how individualized treatment plans may help to further address complex cases of NTM-LD

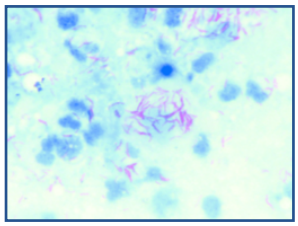
Common Mycobacterial Species Causing Disease

- Mycobacterium Tuberculosis Complex
  - *M. Tuberculosis*
  - *M. Bovis*
  - *M. africanum*
- Mycobacterium leprae
- Rapidly growing nontuberculous mycobacteria
  - *M. fortuitum complex*
  - *M. chelonae*
  - *M. abscessus**
  - *M. smegmatis*
  - *M. mucogenicum*
- Slow growing nontuberculous mycobacteria
  - *M. kansasii**
  - *M. marinum*
  - *M. gordonae*
  - *M. scrofulaceum*
  - *M. xenopi**
  - *M. avium complex (MAC)**
    - *M. avium*
    - *M. intracellulare*
    - *M. chimaera*
    - (others)

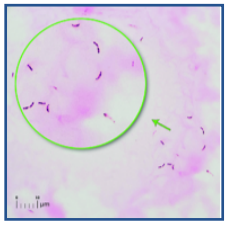
* Nontuberculous mycobacterial species that most commonly cause lung disease

Laboratory Diagnosis of Mycobacteria

- Acid Fast Smear is done by either Ziehl-Neelsen or Kinyoun
- AFB Culture:
  - Solid medium: Lowenstein-Jensen and agar Middlebrook 7H10 or 7H11
  - Liquid medium: Mycobacteria growth indicator tube (MGIT)
  - Can take 4-6 weeks to grow
  - To identify mycobacteria, conventional biochemistry tests are used
- Early identification utilizes DNA probes
  - *M. tuberculosis* complex culture identification test—Rapid DNA Probe
  - *MAC* Culture Identification Test—Rapid DNA Probe



Ziehl-Neelsen[1]



Kinyoun[2]

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KEY TAKEAWAYS

Decreasing Time to Diagnosis[3]

- "Time is tissue"
  - Time to diagnosis of NTM-LD can be as long as 3-5 years
  - Diagnostic delays often lead to destruction of lung tissue
- Clinical presentation is often nonspecific
  - Need to have a high index of suspicion
  - Consider NTM in patients who present with persistent cough and nonspecific symptoms, especially if present for more than 6 weeks
- Sputum samples
  - Multiple samples should be obtained/tested (ideally ≥ 3)
  - Send specifically for AFB Smear and Culture

2020 NTM Diagnostic Guidelines Essentially Unchanged[4]

Disease Criteria (unchanged from 2007 guidelines)	
Clinical	Pulmonary/systemic symptoms
Radiology	CXR-nodules, cavities, or CT-bronchiectasis with multiple small nodules
Micro	With ≥ 2 sputa → 2 positive cultures, or With 1 BAL/wash → 1 positive bronchial wash, or With biopsy → positive biopsy culture, or 1 positive culture and biopsy evidence of disease

Symptoms + Imaging findings + Microbiology = Disease…

…deciding to initiate antimicrobial therapy for NTM-PD should be individualized based on clinical factors, the infecting species, and individual patient priorities. Decision should include a discussion with the patient that outlines the potential side effects of antimicrobial therapy, the uncertainties surrounding the benefits of antimicrobial therapy, and the potential for recurrence including reinfection.

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Risk Factors Associated With Progression of NTM-PD[5]

Host/demographic	Laboratory
• Male sex • Younger age • Presence of comorbidities • Low body mass index	• Elevated inflammatory indices (ESR, CRP) • Anemia • Hypoalbuminemia
Radiographic	**Microbial**
• Fibrocavitary disease • Extent of disease	• Bacterial load • Species

Drug Susceptibility Testing for Pulmonary MAC

Interpretation is unclear for most drugs, except...

Macrolides:

- Resistance (clarithromycin MIC ≥ 32 mcg/mL) → poor response/outcomes

Amikacin (IV)

- Susceptible MIC ≤ 16 mcg/mL
- Intermediate MIC 32 mcg/mL
- Resistant MIC ≥ 64 mcg/mL

Amikacin Liposomal Inhalation

- Susceptible MIC ≤ 64 mcg/mL
- Resistant MIC ≥ 128 mcg/mL

- Resistance associated with treatment failure despite amikacin administration
- RCT of inhaled amikacin → no patients with isolate MIC > 64 converted sputum

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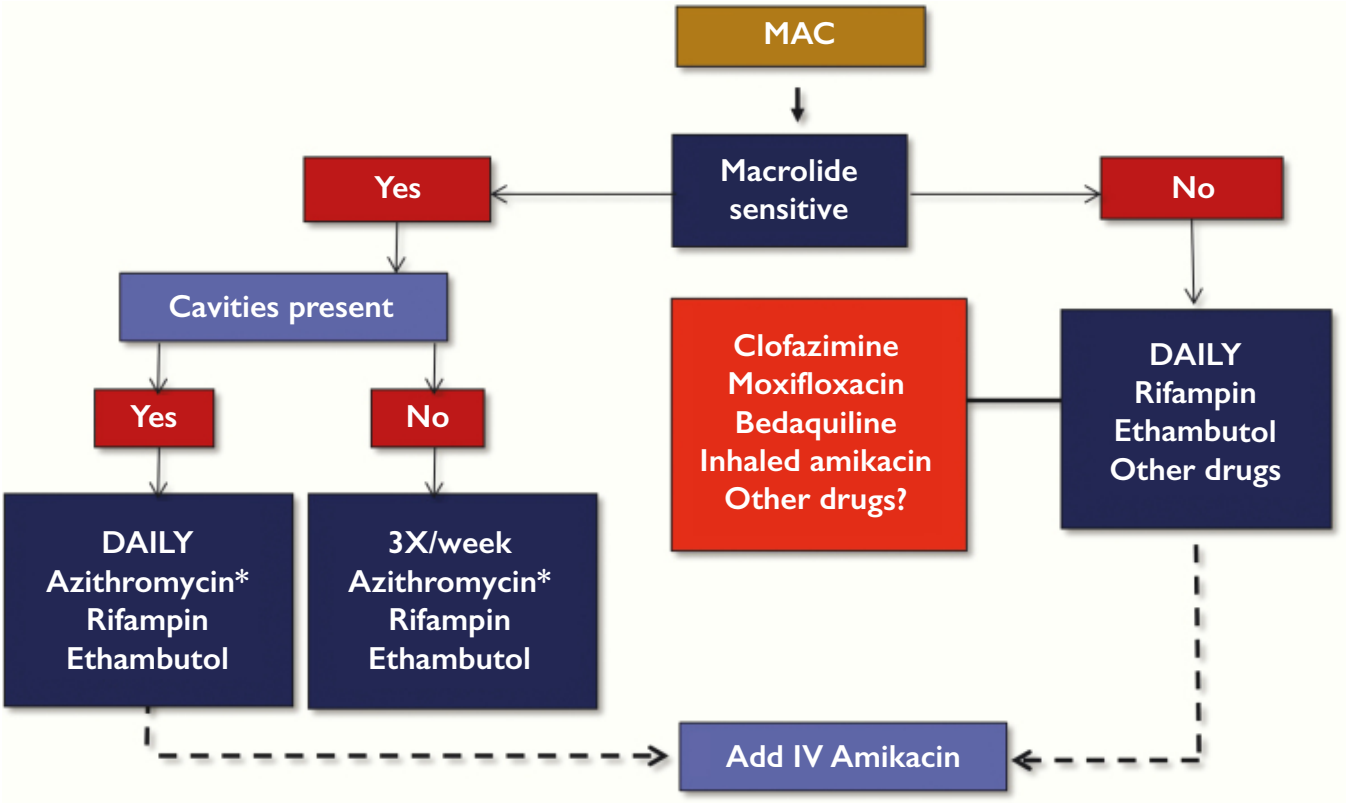
K E Y T A K E A W A Y S

MAC-PD Treatment Algorithm[5]



*Clarithromycin is an alternative

Duration: 12 mos culture negatvity

Adding ALIS Increases Culture Conversion–CONVERT Study

- Amikacin-susceptible MAC-PD and positive sputum despite ≥ 6 month guidelines-based therapy (GBT) randomized (2:1) to ALIS+GBT or GBT alone
- Primary endpoint: culture conversion (3 consecutive monthly sets, 2-3 specimens each) by month 6
- N = 224 ALIS + GBT vs 112 GBT alone, mean age 65, bronchiectasis in 63% and COPD in 14%
- Conversion: 65/224 (29.0%) with ALIS + GBT vs 10/112 (8.9%) with GBT alone (4.2 (2.1-8.6), $p < 0.001$)
- Respiratory adverse events (dysphonia, cough, and dyspnea) in 87% of ALIS + GBT and 50% of GBT participants
- Adding ALIS to GBT in treatment-refractory MAC-PD achieved significantly greater culture conversion by month 6 than GBT alone

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KEY TAKEAWAYS

Monitoring for Side Effects[8]

- Patients are best managed via multidisciplinary team given the frequency of adverse reactions
  - ~20-37% of patients with pulmonary MAC discontinue therapy
- Common side effects requiring monitoring

Side Effect	Clarithro-mycin	Azithro-mycin	Rifampin	Clofazimine	Rifabutin	Etham-butol	Amino-glycosides*	Macro-lides	Fluoro-quinolones
Gastrointestinal intolerance	✓	✓	✓	✓					
Abnormal liver function tests	✓	✓	✓						
Low white blood cell count			✓		✓				
Impaired visual acuity or color vision						✓			
Decreased auditory function		✓					✓		
Vestibular toxicity							✓		
Decreased renal function							✓		
Peripheral neuropathy				✓		✓	✓		
Prolonged QTc				✓				✓	✓

Treatment Considerations in Cavitary Disease

- Take cavitary disease seriously
- Treatment outcomes are worse in cavitary disease; use of injectable aminoglycosides can increase culture conversion. Daily oral therapy is recommended over three times weekly.
- IV Amikacin (or Streptomycin) is given daily-3 times per week for 8-16 weeks in addition to oral medications
- Use with caution for patients with renal disease. Some experts consider use of inhaled liposomal amikacin in these cases.

Resources/References

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