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JOURNAL CLUB

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ARTICLE

"Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases". Lange C, et al. *Lancet Infect Dis* 2022;22(7):e178-e190 e12. DOI: 10.1016/S1473-3099(21)00586-7. PMID: 35090639

CLINICAL QUESTION

The 2020 revised guideline for the management of pulmonary NTM disease addressed the most common species to cause pulmonary disease. However, other NTM can also produce pulmonary disease although much less commonly. How should you manage these less common causes of NTM pulmonary disease?

SUMMARY

Background:

Nontuberculous mycobacteria (NTM) represent approximately 200 species and subspecies and pulmonary disease caused by NTM is increasing in many areas of the world, including the United States. The 2020 multi-society [American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Microbiology and Clinical Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA)] NTM guideline updated management strategies for patients with NTM pulmonary diseases (NTM-PD) and focused on population, intervention, comparison, and outcome (PICO) question-guided management recommendations for pulmonary disease in adults caused by *Mycobacterium avium* complex, *Mycobacterium kansasii*, *Mycobacterium xenopi*, and *Mycobacterium abscessus.*[1,2] However, management options for NTM-PD caused by other clinically relevant NTM covered in the previous 2007 management guideline are also needed for the care of affected patients.[3]

Methods and Results:

The panel members of the 2020 ATS, ERS, ESCMID, and IDSA guideline committee performed systematic reviews of the literature, independently of the societies involved in the original task force, to provide management guidance for pulmonary diseases caused by seven additional organisms: *Mycobacterium chelonae, Mycobacterium fortuitum, Mycobacterium genavense, Mycobacterium gordonae, Mycobacterium malmoense, Mycobacterium simiae,* and *Mycobacterium szulgai.* A search was adapted for execution on the Ovid MEDLINE platform and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, and the Cochrane Central Register of Controlled Trials. Searches were limited to human studies or studies indexed with neither human nor animal and those published in English. Teams of two or three independent experts evaluated the search results for eligibility; they supplemented the electronic search by contacting experts and handsearching journals, conference proceedings, reference lists, and regulatory agency websites for relevant articles. In addition to the systematic reviews, the members of the panel ascertained agreement on management options in a six-step consensus process as previously published.[6-8] Most of the evidence reviewed were case series and case reports which are often biased toward successful outcomes.

Rapidly growing NTM

M. chelonae is an unusual cause of pulmonary disease. A systematic literature review by two independent experts identified 18 case reports and case series describing 57 patients with *M. chelonae* pulmonary disease.

Treatment for *M. chelonae* pulmonary disease initially includes at least two drugs for mild to moderate disease or three drugs in more severe disease that the organism shows in-vitro susceptibility to. Treatment

often includes one or two intravenous drugs (imipenem-cilastatin and/or aminoglycoside) to be continued for an initial period, usually for 4–16 weeks, to achieve control of disease; tobramycin is the preferred aminoglycoside. At least two oral drugs, one of which should be a macrolide that has demonstrated in-vitro susceptibility; favored antibiotics include azithromycin or clarithromycin, a fluoroquinolone (e.g., moxifloxacin), clofazimine, or linezolid, based on in-vitro drug susceptibility test results. Treatment should be continued for 12 months post-conversion to culture negative.

M. fortuitum is a relatively common respiratory isolate but uncommon cause of lung disease**.** A systematic literature review by two independent experts identified 45 case reports and case series describing 150 patients with *M. fortuitum* pulmonary disease. Among the RGM, *M. fortuitum* is susceptible *in vitro* to greater number of drugs.

Treatment for *M. fortuitum* pulmonary disease should include at least two drugs for mild-to-moderate disease or three drugs in more severe disease that the organism shows in-vitro susceptibility. Treatment often includes one or two intravenous drugs to be continued for an initial period, usually for 4–16 weeks, to achieve control of disease; amikacin is the preferred aminoglycoside. Other favored intravenous drugs are imipenem-cilastatin or cefoxitin. At least two oral drugs that have demonstrated in-vitro susceptibility should be continued. Favored oral antibiotics include fluoroquinolones (e.g., moxifloxacin or levofloxacin), trimethoprim-sulfamethoxazole, linezolid, clofazimine, or doxycycline. Treatment should be continued for 12 months post-conversion to culture negative.

Slowly Growing NTM

M. genavense is a rare cause of NTM-PD. The organism is fastidious and does not grow on solid media. A systematic literature review by two independent experts identified only five case reports and case series describing six patients with *M. genavense* pulmonary disease.

Treatment for *M. genavense* pulmonary disease includes at least three drugs that the organism shows in-vitro susceptibility. The panel suggests the following treatment regimen: azithromycin, rifampicin, and ethambutol. In case of intolerance or drug resistance to macrolides, rifamycins, or ethambutol, the following drugs can be used instead: moxifloxacin, amikacin intravenously, or clofazimine. Treatment should be continued for 12 months post-conversion to culture negative.

M gordonae is typically a non-pathogenic NTM. A systematic literature review by two independent experts identified only nine case reports and case series describing 13 non-immunosuppressed adults with *M. gordonae* pulmonary disease. Even when current diagnostic criteria are met, treatment is seldom necessary.

In the rare situation when treatment is necessary, a combination of a macrolide, rifampicin, and ethambutol is suggested. Treatment should be continued for 12 months post-conversion to culture negative.

M. malmoense is one of the more common causes of NTM-PD in northern Europe and can produce progressive disease. A systematic literature review by two independent experts found two randomized controlled trials and three retrospective cohort studies. In addition, two systematic reviews were identified that addressed treatment outcomes or treatment recommendations for *M. malmoense* pulmonary disease.

Treatment for *M. malmoense* pulmonary disease generally includes at least three drugs: azithromycin or clarithromycin, rifampicin, and ethambutol. Additional drugs may include moxifloxacin or clofazimine. Based on the utility of amikacin for most NTM species (except *M. chelonae*), favorable in-vitro drug

susceptibility profiles, and expert opinion, the addition of parenteral amikacin can be considered in severe cases, such as cavitary disease. Treatment should be continued for 12 months post-conversion to culture negative.

M. simiae is isolated in certain regions that tend to be hot and dry. Even after isolation from a respiratory specimen *M. simiae* is seldom disease producing. However, given its high in vitro resistance pattern, when disease occurs it is very difficult to treat.

Treatment for *M. simiae* pulmonary disease generally includes at least three drugs: azithromycin or clarithromycin, moxifloxacin, trimethoprim-sulfamethoxazole, amikacin intravenously, or clofazimine. Surgical resection of affected lobes should be evaluated as an adjunctive treatment option. Treatment should be continued for 12 months post-conversion to culture negative.

M. szulgai is an unusual cause of NTM-PD but can produce progressive disease**.** A systematic literature review conducted by two independent experts identified 25 retrospective case reports and case series, including a total of 44 patients with *M. szulgai* pulmonary disease.

Treatment for *M. szulgai* pulmonary disease should include at least three drugs that the organism shows in-vitro susceptibility for. A combination of rifampicin, azithromycin or clarithromycin, and ethambutol should be considered. Clofazimine can be substituted for the macrolides, rifamycins, or ethambutol if there is intolerance or drug resistance to one of the latter three. Intravenous amikacin is an alternative in case of intolerance or resistance to the recommended orally available drugs. There is no evidence to recommend surgery as part of the treatment for *M szulgai* pulmonary disease. Treatment should be continued for 12 months.

GROUP OPINION

Treatment of other less common NTM pulmonary diseases is based primarily on small cases series and expert opinion. Of the rapid growers reviewed, treatment of *M. fortuitum* is associated with the highest treatment success. Among slow growers, *M. malmoense* and *M. szulgai* have the greatest likelihood of treatment success. For *M. malmoense* there are two randomized controlled trials that demonstrated good treatment outcomes with the recommended regimen. We treat most of the less common NTM with a "MAC" regimen that includes a macrolide, rifamycin and ethambutol with amikacin in cavitary disease. However, *M. simiae* has high in vitro resistance to these agents and often requires additional antimicrobials and consideration for surgical resection. We find *M. szulgai* to be more virulent than the other NTM reviewed, but treatment response and outcomes are usually better.

Reference:
Lange C, Böttger EC, Cambau E, Griffith DE, Guglielmetti L, van Ingen J, Knight SL, Marras TK, Olivier KN, Santin M, Stout JE, Tortoli E, Wagner D, Winthrop K, Daley CL; expert panel group for management recommendations in non-tuberculous mycobacterial pulmonary diseases. Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases. Lancet Infect Dis. 2022 Jul;22(7):e178-e190. doi: 10.1016/S1473-3099(21)00586-7. Epub 2022 Jan 25. PMID: 35090639.