ORIGINAL RESEARCH PAPER

Medicine

NONTUBERCULOUS MYCOBACTERIAL INFECTIONS

KEY WORDS:

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Nontuberculous mycobacteria (NTMB) are environmental organisms capable of causing chronic disease in humans.[1]

NTMB diseases are seen worldwide. Most industrialized nations report an incidence rate of 1 to 2 cases per 100,000 persons.[2]

Nontuberculous mycobacteria (NTM) are mycobacterial species other than those belonging to the *Mycobacterium tuberculosis* complex (*M. tuberculosis, M. bovis, M. africanum, M. microti, and M. canetti*) and M. leprae. They are free living organisms in the environment and to date 151 NTM species have been identified. NTM are free living environmental micro-organisms that have been isolated from tap water, soil, domestic and wild animals and food products.

NTM are classified as either slow growing (>7 days) or rapid growing (<7 days) based on laboratory culture. Overall, the most common NTM entity causing clinical disease is *M. avium complex* .

The prevalence of NTM-related lung disease appears to be increasing.[3]

NTM can cause four clinical syndromes in humans.

- **Pulmonary disease**, caused primarily by M. avium complex (MAC) and M. kansasii. Others implicated in Lung disease includes M. abscessus, M. fortuitum, M. xenopi, M. malmoense, M. szulgai, and M. simiae.
- **Superficial lymphadenitis**, caused by MAC, M. scrofulaceum, and, in northern Europe, M. malmoense and M. haemophilum
- **Disseminated disease**, caused by MAC and less commonly by the rapidly growing mycobacteria [RGM], eg, M. abscessus, M. fortuitum, and M. chelonae
- **Skin and soft tissue infection** usually as a consequence of direct inoculation, caused primarily by M. marinum and M. ulcerans

NTMB can present as a hypersensitivity-like pulmonary syndrome, commonly known as hot tub lung.[4] This is likely to be a manifestation of both parenchymal inflammation and active infection. Mycobacteria are resistant to disinfectants and growth is enhanced by hot, humid environments, especially standing water sources such as hot tubs or other undrained indoor sources.

PULMONARY DISEASE

Clinical:

- Chronic or recurring cough
- Other symptoms:
- Sputum production
- Fatigue and malaise
- Dyspnea,
- Fever
- Hemoptysis
- Chest pain
- Weight loss

DIAGNOSIS

A diagnosis of NTM pulmonary disease should be established in a combination of clinical, radiological, bacteriological, and histological criteria [5].

Radiology:

(A) Chest Xray

1. Primarily fibrocavitary

Characteristics:

(1) Thinwalled cavities with less surrounding parenchymal opacity
(2) Less bronchogenic but more contiguous spread of disease
(3) More marked involvement of pleura

2. Nodules and Bronchiectasis

(B) HRCT Chest :

90% of patients with mid and lower lung field noncavitary disease with M. avium complex have associated multifocal bronchiectasis, with many patients having clusters of small (5 mm) nodules in associated areas of the lung.

Microbiology :

Isolation of NTMB in culture is essential for the diagnosis of NTMB lung disease. In cases of pulmonary disease (the most common site of infection), bronchial cultures should be obtained.[6]

a) Positive culture results from at least two separate sputum samples Or
b) Positive culture result from at least one bronchial wash or lavage, Or
c) Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or acid-fast bacilli [AFB]) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.

LYMPHADENOPATHY

NTM granulomatous lymphadenopathy is most commonly seen in children aged 6 months to 5 years. A typical presentation is one of a persistent, unilateral cervical lymph node that may be fluctuant with overlying skin inflammation**.** Mostly caused by by MAC and M. scrofulaceum.

Disseminated Infection

NTM infections may disseminate in hosts with impaired immunity. Disseminated disease in severely immunocompromised patients (most commonly caused by MAC and less commonly by the rapidly growing mycobacteria [RGM], eg, M. abscessus, M. fortuitum, and M. chelonae). Disseminated MAC was common in AIDS patients prior to the introduction of combination antiretroviral therapy in 1994. Since then, the rate of disseminated MAC in AIDS patients has decreased dramatically. Disseminated NTM disease in non-HIV patients is uncommon but has been reported in patients who have had solid organ or bone marrow transplantation, chronic corticosteroid usage with or without other immunosuppressive agents

Skin and soft tissue

NTM infections usually occur after trauma, surgery or other procedures.Bone and joint infections are usually acquired by direct inoculation from an environmental source or a contiguous infection. Hands and wrists are the most frequently reported sites of NTM tenosynovitis. A long list of NTM have been reported to cause skin and/or soft-tissue infection, but the most common organisms are M. marinum, M ulcerans, M. fortuitum, M. abscessus and M. chelonae.

Pre-treatment checklist For NTM
All Three diagnostic criteria fulfilled?
☐ Clinical symptoms Yes / No
☐ Radiology Yes / No
☐ Microbiology Yes / No

Baseline weight :
Bloods:
☐ FBE:
☐ LFT:
☐ UEC:
☐ BGL/HbA1c:
☐ Uric acid
☐ HIV
☐ Hepatitis screen

Visual assessment (Ethambutol treatment)
☐ Ishihara test :
☐ Acuity : R:6/
L:6/

ECG (Macrolide/fluoroquinolone: QTc)

Vestibular-acoustic assessment (Amikacin/Streptomycin treatment)

☐ Audiometry

Contraception discussion (women)
Review drug interactions:
Clarithromycin susceptibility (MAC):
Clinical photography (skin lesion):

Pulmonary NTM disease care plan

Every visit - monthly	**Every 3 months**	**6 and 18months**
NTM disease symptoms	Chest Xray	ChestXray
Drug side effects	NTM symptoms	

Compliance
Weight
Vision: Acuity & Ishihara
Sputum (smear & culture)
Bloods: FBE, LFT
(Amikacin/streptomycin):
Urea and Electrolytes,
Audiometry

ORGANISM	DRUG	*DURATION*
M. avium complex (MAC) lung disease (macrolide susceptible)	Daily Clarithromycin OR azithromycin Ethambutol RIFAMPICIN Rifabutin (RBT) ± Ainoglycosides (streptomycin [SM] or Amikacin) Clofazimine and fluoroquinolones may be useful	*12 months Culture negative*
MAC lymphadenitis	Daily or thrice weekly clarithromycin/Azithromycin **RMP+/- EHAMBUTOL**	*3-9 months*
M. kansasii lung disease	Daily RMP, EMB, INH Consider clarithromycin Azithromycin Moxifloxacin/Aminoglycoside	*12 months after Culture Negative*
M. fortuitum (LUNGdisease **Skin)**	**A**zithromycin or clarithromycin and RMP or EMB ± doxycycline, amikacin, imipenem, FQN, sulfonamides, cefoxitin	*12 months after culture negative*
M. marinum skin/soft tissue	Clarithromycin, EMB +/- RMP	*3-6 months Longer if deeper structures affected*
Disseminated MAC	*Clarithromycin 500 mg orally daily plus lifelong or control of HIV EMB 15 mg/kg orally daily CD4 to >100 x 106 /L for at +/- RBT 300 mg orally daily*	*6 months 12 months after culture Negative*

MAC:
Mild to moderate:
Nodular/Bronchiectatic disease
Three times weekly Treatment

Clarithromycin 500 mg orally, 12-hourly, thrice weekly OR
Azithromycin 500 mg orally, thrice weekly

PLUS
Ethambutol 25 mg/kg orally, thrice weekly

PLUS
Rifampicin 600 mg (adult less than 50 kg: 450 mg) ; 50 kg or more: 10 mg/kg up to 600 mg) orally, thrice weekly

Severe Nodular/Bronchiectatic disease
OR
Fibrocavitatory disease

Daily Treatment
Clarithromycin
500 mg (adult less than 50 kg or more than 70 years: 250 mg) , 12-hourly
OR
Azithromycin 250 mg orally, daily

PLUS
Ethambutol (adult) 15 mg/kg orally, daily

PLUS EITHER
Rifampicin 600 mg (adult less than 50 kg: 450 mg : 50 kg or more: 10 mg/kg up to 600 mg) orally,daily
OR
Rifabutin 300 mg orally, daily

Additional therapeutic options
For patients with severe disease or with poor response include addition of an aminoglycoside. Amikacin or streptomycin : 25 mg/kg IM 3 times weekly

Adjuvant interferon gamma
Surgical resection : localised disease or a solitary nodule

Drug Side Effects:

Azithromycin/Clarithromycin :
Gastrointestinal disturbance (nausea, vomiting, diarrhea)
Decreased hearing
Hepatitis

Ethambutol
Optic neuritis (loss of red/green color discrimination, loss of visual acuity)

Rifampin, Rifabutin
Orange discoloration of secretions and urine
Staining of soft contact lenses
Gastrointestinal disturbance (nausea, vomiting)
Hypersensitivity (fever, rash)
Hepatitis
"Flu-like" syndrome
Thrombocytopenia
Renal failure

Streptomycin /Amikacin, /Tobramycin
Vestibular/auditory toxicity (dizziness, vertigo, ataxia, tinnitus, hearing loss) Renal toxicity

Duration of therapy — Treatment should be continued until sputum cultures are consecutively negative for at least one year.

Therefore, the typical duration of treatment is 18 to 24 months, but it can be longer for some individuals.

Treatment failure may be related to treatment noncompliance or intolerance, anatomic defects (cavitation or bronchiectasis), or drug resistance (especially to macrolides). Relapses and reinfections are also common and may not be related to drug susceptibility Macrolide resistance occurs and typically results from macrolide monotherapy or the concomitant use of quinolones.[10] Regimens that do not include ethambutol are also associated with the development of drug resistance. Unfortunately, in cases of macrolide resistance, mortality occurs within 1 year in approximately one third of patients and, nearly half of patients will die within 2 years. In these cases, a prolonged course of medical therapy that includes parenteral agents in association with surgical resection can improve outcomes.

Intravenous amikacin or streptomycin for 2 to 3 months should be considered in severe or refractory cases.

Surgical resection has been shown to improve outcomes in some patients with NTMB infection and should be considered as an adjuvant or alternative to medical therapy.[11] Although there are no established criteria, surgery is best indicated for patients experiencing a poor response to medical therapy or who are treatment failures.

Patients with anti-IFN-γ autoantibodies (a rare underlying disease for NTM) have impaired IFN-γ signaling which may lead to severe disseminated infections with intracellular pathogens including primarily NTM [11]. Rituximab has no role in the treatment of NTM disease except this rare condition.

REFERENCE

1. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367-416.
2. Falkinham JO 3rd. Nontuberculous mycobacteria in the environment. Clin Chest Med. 2002;23:529-551.
3. Holt W, Abraham K, Dufour R, McDermott K, Tarr A. Nontuberculous mycobacteria lung infections: pre-index comorbidity and utilization patterns at a large US health plan. Program and abstracts of ID Week 2015; October 7-11, 2015; San Diego, California. Abstract 574.
4. Khoor A, Leslie K, Tazelaar H, Helmers R, Colby T. Diffuse pulmonary disease caused by nontuberculous mycobacteria in immunocompetent people (hot tub lung). Am J Clin Pathol. 2001;115:755-762.
5. S. M. Arend, D. Van Soolingen, and T. H. Ottenhoff, "Diagnosis and treatment of lung infection with nontuberculous mycobacteria," Current Opinion in Pulmonary Medicine, vol. 15, no. 3, pp. 201–208, 2009.
6. Sugihara E, Hirota N, Niizeki T, et al. Usefulness of bronchial lavage for the diagnosis of pulmonary disease caused by Mycobacterium avium-intracellulare complex (MC) infection. J Infect Chemother. 2003;9:328-332.
7. Wallace RJ Jr, Zhang Y, Brown-Elliott BA, et al. Repeat positive cultures in Mycobacterium intracellulare lung disease after macrolide therapy represent new infections in patients with nodular bronchiectasis. J Infect Dis. 2002;186:266-273
8. B. Kampmann, C. Hemingway, A. Stephens et al., "Acquired predisposition to mycobacterial disease due to autoantibodies to IFN- ," The Journal of Clinical Investigation, vol. 115, no. 9, pp. 2480–2488, 2005