**INTRODUCTION**

Atypical mycobacteria are also called nontuberculous mycobacteria (NTM) or mycobacteria other than tuberculosis (MOTT). Nontuberculous mycobacteria are widely distributed in the environment with high isolation rates worldwide. They are divisible into two main groups: (1) the slow grower and (2) the rapid grower, according to their rate of growth on subculture. Most of the slow growers are able to cause human disease, the most common being two members of the *M. avium* complex (MAC), i.e. *M. avium avium* and *M. avium intracellulare*. With rare exceptions, only pathogenic rapid growers are *M. abscessus*, *M. chelonae* and *M. fortuitum*.

**CLASSIFICATION OF NONTUBERCULAR MYCOBACTERIA**

- **Slow growers**
  - Photochromogens
    - *M. kansasii*
    - *M. marinum*
    - *M. simiae*
  - Scotochromogens
    - *M. scrofulaceum*
    - *M. gordonae*
    - *M. avium*
  - Nonchromogens
    - *M. avium intracellulare*
    - *M. xenopi*
    - *M. ulcers*
    - *M. terrae*
    - *M. malmoense*

- **Rapid growers**
  - *M. fortuitum*
  - *M. chelonae*
  - *M. smegmatis*
  - *M. abscessus*

**EPIDEMIOLOGY**

Nontuberculous mycobacteria are ubiquitous in environment. In India, *Mycobacterium tuberculosis* infection has always overshadowed true prevalence of NTM. Although the exact magnitude of NTM is difficult to predict as culture is not a routine part of diagnosing tuberculosis (TB) in India, it varies from 1% to 28%. There is no evidence of animal-to-animal or human-to-human transmission of NTM. Human disease is suspected to be acquired from environmental exposures, although the specific source of infection usually cannot be identified. The most common clinical manifestation of NTM disease is lung disease (94%), but lymphatic (3%), skin/soft tissue and disseminated disease (3%) are also important. The important NTMs are *M. kansasii*, *M. xenopi*, *M. fortuitum-chelonei* complex and MAC. The MAC infections were commonly seen in pre-acquired immunodeficiency syndrome (pre-AIDS) era in patients with chronic obstructive pulmonary disease (COPD), bronchiectasis and occupational lung diseases like silicosis, etc. However, MAC infections are now classically seen in AIDS when CD4 count goes below 50/mm$^3$. *M. genavense* is a new atypical agent seen in AIDS patients.

**PATHOGENESIS**

Three important observations have been made regarding pathogenesis of NTM infections.

1. In patients infected with human immunodeficiency virus (HIV), disseminated NTM infections typically occurred only after the CD4 T lymphocyte number had fallen below 50/µL, suggesting that specific T cell products or activities are required for mycobacterial resistance.

2. In the HIV-uninfected patient group, genetic syndromes of disseminated NTM infection have been associated with specific mutations in different genes, viz.
   - Genes responsible for interferon (IFN)-γ and interleukin (IL)-12 synthesis along with their subunits and receptors ([IFN-γ receptor 1 (IFN-γ R1), IFN-γ receptor 2 (IFN-γ R2), IL-12 receptor b1 subunit (IL-12 β R1), the IL-12 subunit p40 (IL-12 p40)]
   - Genes responsible for synthesis of the signal transducer and activator of transcription 1 (STAT1), and the nuclear factor κ-binding essential modulator (NEMO)

3. There is also an association between bronchiectasis, nodular pulmonary NTM infections and a particular body habitus, predominantly in postmenopausal women (e.g. pectus excavatum, scoliosis, mitral valve prolapse).

**Host Defense and Immune Response**

Mycobacteria are initially phagocytosed by macrophages, which respond with production of IL-12, which in turn, upregulates IFN-γ. IFN-γ activates neutrophils and macrophages to kill intracellular pathogens, including mycobacteria. There is a positive feedback loop between IFN-γ and IL-12, which is critical for the control of mycobacteria, as well as certain other intracellular infections. Disseminated NTM disease is a definite manifestation of immunologic defect, either acquired, such as HIV and iatrogenic factors, or genetic caused by defects in the above IFN-γ/IL-12 pathway genes. However, these genetic factors only predispose to disseminated disease.
**Infectious Diseases**

**Pulmonary Disease**

Lung disease due to NTM occurs commonly in structural lung disease, such as COPD, bronchiectasis, cystic fibrosis (CF), pneumoconiosis, prior TB, pulmonary alveolar proteinosis and esophageal motility disorders. Abnormal CF genotypes and alpha-1-antitrypsin (AAT) phenotypes may predispose some patients to NTM infection. Nontuberculous mycobacteria lung disease also occurs in women without clearly recognized predisposing factors. Bronchiectasis and NTM infection, usually MAC, often coexist, making causality difficult to determine. These patients may carry multiple MAC strains over time, suggesting either polyclonal infection or recurrent infection with distinct strains. It is unclear whether this problem is due to local abnormalities (e.g. bronchiectasis) or due to immune defects. In one study from Japan, 170 patients with MAC lung infection were studied. Of 622 siblings of those patients, 3 had MAC lung disease. The implication is that, the sibling risk for MAC infection is much higher than previously estimated population prevalence.

**Body Morphotype**

Women with nodular NTM pulmonary infections associated with bronchiectasis have similar clinical characteristics and body type, sometimes including scoliosis, pectus excavatum, mitral valve prolapse and joint hypermobility. These phenotypic characteristics may represent markers for specific genotypes that affect both body morphotype and NTM infection susceptibility. Alternatively, the morphotype itself may influence mycobacterial infection susceptibility through poor tracheobronchial secretion drainage or ineffective mucociliary clearance.

**Tumor Necrosis Factor Inhibition**

Interferon-γ and IL-12 control mycobacteria in large part through the upregulation of tumor necrosis factor (TNF)-α, made predominantly by monocytes/macrophages. The critical role of TNF-α in controlling intracellular infections is made clear through the use of TNF-α blocking agents. The potent TNF-α blocking antibodies—infliximab, adalimumab and the soluble receptor etanercept—are effective anti-inflammatory agents and lead to relatively high rates of development of active TB in those who are latently infected. The onset of TB after administration of infliximab ranges from weeks to months. In addition to TB, the TNF-α blocking agents predispose to invasive fungal infections, such as aspergillus, histoplasmosis and coccidioidomycosis. Infections with mycobacteria and fungi are seen with all three agents, but significantly more with infliximab than etanercept. Adalimumab should be regarded as having similar risks. The risk posed by TNF-α blocking agents for predisposing to NTM infections or promoting progression of active NTM infection is unknown. Until more information is available, expert opinion is that patients with active NTM disease should receive TNF-α blocking agents only if they are also receiving adequate therapy for the NTM disease.

**CLINICAL PRESENTATION**

Nontubercular mycobacteria cause four main types of diseases: (1) chronic pulmonary, (2) lymphadenitis, (3) postinoculation and (4) disseminated.

**Chronic Pulmonary Disease**

This is the most common clinical manifestation of NTM. *M. avium complex, M. kansasi* and *M. abscessus*, in the order, are the most frequent NTM pulmonary pathogens. This form of disease usually occurs in patients with predisposing local lung lesions, including industrial lung diseases, old tubercular cavities, COPD, cancer, CF and bronchiectasis, or generalized autoimmune or immunosuppressive disorders. Most patients are middle aged or elderly and men are much more frequently affected than women. The infection is more aggressive in young women with low body mass index.

**Symptoms and Signs**

Virtually all patients have chronic or recurrent cough. Other symptoms variably include sputum production, fatigue, malaise, dyspnea, fever, hemoptysis, chest pain and weight loss. On chest auscultation, finding may include rochii, crackles, and squeaks. Patients with nodular bronchiectatic MAC disease tend to be postmenopausal women, having characteristic morphotype with a thin body habitus with scoliosis, pectus excavatum and mitral valve prolapse.

**Radiology**

A plain chest radiograph is adequate to evaluate fibrocavitary disease. However, high resolution computed tomography (HRCT) chest is now routinely indicated to demonstrate the characteristic abnormality of nodular/bronchiectatic NTM lung disease. Characteristic radiographic findings include:

- Thin-walled cavities with less surrounding parenchymal opacity
- Less brochogenic but more contiguous spread of disease
- More marked involvement of pleura over the involved area of lung.

There are no diagnostically reliable clinical and radiological differences between NTM lung disease and TB, and diagnosis therefore depends on the isolation and identification of causative organism.

**Recommendations**

The minimum evaluation of patients suspected of NTM lung disease should include:

- Chest radiograph, or in absence of cavitations, chest HRCT scan
- Three or more sputum specimen for acid-fast bacilli (AFB) analysis
- Exclusion of other disorders like TB or malignancy

In most cases, a diagnosis can be made without bronchoscope or lung biopsy.

**Clinical and Microbiological Criteria for Diagnosis of NTM Lung Disease (American Thoracic Society)**

Clinical (both required):

1. Pulmonary symptoms, nodular or cavitary opacity in chest radiograph, or a HRCT scan that shows multifocal bronchiectasis with multiple small nodules

2. Appropriate exclusion of other diagnosis

Microbiologic:

1. Positive culture results from at least two separate expectorated samples (A II). If nondiagnostic, consider repeat sputum AFB smear and culture (C III).

2. Positive culture at least one bronchial wash or lavage (C III)

3. Transbronchial or other lung biopsy with mycobacterial histological feature (granulomatous inflammation or AFB) and positive culture for NTM (AI)

4. Patients who suspected of having NTM lung disease but do not meet diagnostic criteria should be followed until firm diagnosis is established or excluded.

5. Making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a decision based on potential risk and benefit of therapy for individual patients.

**Lymphadenitis**

This is principally a disease of young children, occurring most frequently in the second year of life.
The most common form of NTM disease in children is cervical adenitis. Infection of the submandibular, submaxillary, cervical or preauricular lymph nodes in children aged between 1 year and 5 years is the most common presentation of NTM lymphadenitis. In the absence of HIV infection, NTM lymphadenitis rarely affects adults. No risk factors predisposing to cervical lymphadenitis in children have been identified, but children with Bacille Calmette Guérin (BCG) immunization have a reduced risk of MAC cervical adenitis. Currently, approximately 80% of culture-proven cases of NTM lymphadenitis are due to MAC.

Clinical Presentation

The disease occurs insidiously, and is rarely associated with systemic symptoms. The involved lymph nodes are generally unilateral (95%) and not tender. The nodes may enlarge rapidly, and even rupture, with formation of sinus tracts that result in prolonged local drainage. Other nodal groups outside of the head and neck may be involved occasionally including mediastinal nodes. Contrast-enhanced axial CT of NTM lymphadenitis typically shows asymmetric adenopathy with ring-enhancing masses that may involve the fat and skin but with minimal inflammatory stranding of the subcutaneous fat. The most important alternative diagnosis is tuberculous lymphadenitis. With NTM lymphadenitis, there is typically no history of exposure to TB; screening tuberculin purified protein derivative (PPD) skin tests of family members are usually negative and the chest radiograph is normal.

Diagnosis

The utility of fine needle aspiration for obtaining diagnostic material is variable. The presumptive diagnosis of NTM lymphadenitis is based on the histopathologic appearance of the lymph node showing caseating granulomata with or without AFB and, in the majority of cases, a negative tuberculin skin test. Failure of the lymph node culture to yield *M. tuberculosis* provides stronger presumptive evidence for the diagnosis of NTM lymphadenitis. A definite diagnosis of NTM lymphadenitis is made by recovery of the causative organism from lymph node cultures.

Postinoculation Mycobacterioses

**Buruli Ulcer**

This is thought to result from inoculation of causative organism *M. ulcerans* into skin, principally by spiky vegetation. Typically, the initial skin lesion is a single firm painless movable subcutaneous nodule up to 3 cm in diameter. Limbs are the preferred sites, often around joints. The nodule usually ulcerates within 1–3 months. Without treatment, ulcers tend to become inactive and heal by scarring. Disseminated disease may develop from nodules that spread directly and rapidly causing indurated plaques covering even the entire limb. Eyes, breast and genitalia may be damaged or destroyed.

**Swimming Pool/Fish Tank Granuloma**

The causal agent is *M. marinum*. It enters cuts and abrasions acquired during aquatic activities, such as swimming, or tending to topical fish tanks. The cutaneous lesions are usually warty, although pustules and ulcers may develop. Lesions usually heal spontaneously but chemotherapy accelerates healing. There have been occasional reports of tenosynovitis, carpal tunnel syndrome, osteomyelitis and disseminated disease due to *M. marinum*.

Postinjection Abscesses

The most common lesion of postinjection abscesses usually develop due to use of contaminated multidose vaccines or other injected material. Abscesses develop from 1 month to 12 months after injection, tend to be chronic and localized, but multiple abscesses with spreading cellulitis may develop in insulin-dependent diabetics. Localized abscesses usually respond to excision and curettage but chemotherapy may be required for multiple and spreading lesions.

Surgical Inoculation

The most common inoculation occurs during cardiac valve surgery resulting mycobacterial endocarditis with septicemia and osteomyelitis of sternum requiring extensive debridement.

Disseminated Disease

Before HIV became widespread, disseminated disease due to NTM was very rare. Some cases, usually due to MAC or rapid growers, occurred in young people with congenital immunodeficiencies and others, principally due to *M. chelonae*, occurred in renal transplant recipients.

However, the situation changed dramatically after the advent of the HIV pandemic and disseminated NTM disease was reported in 30–50% patients with AIDS. The great majority of such cases (90%) are caused by MAC, usually strains identifiable by DNA homology as *M. avium* rather than *M. avium* intracellulare. Some cases are due to *M. genavense*, a very slow growing species which like *M. avium* avium, has been isolated in diseased birds (Tables 1 and 2).

**Chapter 13 Atypical Mycobacterial Infection**

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Infectious Diseases

Symptoms include fever, night sweats, weight loss, anemia, malaise; these are rather nonspecific and may be caused by other AIDS-related infections. Involvement of intestine may lead to malabsorption or chronic diarrhea. Diagnosis of AIDS-related MAC disease can be made by culture of blood or biopsies of liver, lymph nodes or bone marrow.

TREATMENT

Treatment depends on the site and severity of the infection, the presence of predisposing condition, such as congenital or acquired immunodeficiencies and species of Mycobacterium.

As indicated above, skin lesions may be cured by excision, curettage or drainage. Surgical excision, when technically possible, is used to treat lymphadenitis or localized pulmonary nodules.

BIBLIOGRAPHY


| TABLE 2 | Recommended therapy for M. avium complex lung disease |
|-----------------|---------------------------------|---------------------------------|---------------------------------|
|                | Initial therapy for nodular/bronchiectatic disease | Initial therapy for cavitary disease | Advanced or previously treated disease |
| Macrolides     | Clarithromycin 1 g three times weekly (TIW) Azithromycin 500–600 mg TIW | Clarithromycin 500 mg to 1 g/d Azithromycin 250–300 mg/d | Clarithromycin 500 mg to 1 g/d or azithromycin 250–300 mg/d |
| Ethambutol     | 25 mg/kg TIW            | 15 mg/kg/d                     | 15 mg/kg/d                     |
| Rifamycine     | Rifampin 600 mg TIW     | Rifampin 450–600 mg/d          | Rifabutin 150–300 mg/d or rifampin 450–600 mg/d |
| IV aminoglycoside | None                  | Streptomycin or amikacin       | Streptomycin or amikacin       |