

NONTUBERCULOUS MYCOBACTERIA

Introduction to Mycobacteria

The genus *Mycobacterium* causes more suffering and death throughout the world than all other bacteria combined. The most notorious and widely recognized Mycobacteria are *M. tuberculosis*, the bacillus that causes the pulmonary and extrapulmonary diseases known as tuberculosis, and *M. leprae*, the organism that causes the cutaneous and neural disorder known as leprosy.

Slender and raylike bacilli, mycobacteria share a distinctive staining property, a result of their lipid-rich cell walls. Once stained, mycobacteria resist decolorization when exposed to acidified organic solvents and, therefore, are



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informally designated acid-fast. This characteristic is perhaps the best known property of the genus. The design of these unique cell walls also allows the hydrophobic organisms to float on the surface of aqueous media. Mycobacteria are obligate aerobes but, of the more than 60 species that have been well-defined, only *M. tuberculosis* is an obligate pathogen.

Nontuberculous Mycobacteria (NTM)

Mycobacterial species, other than *M. tuberculosis* and *M. leprae*, may be referred to as nontuberculous mycobacteria (NTM), although controversy exists over this designation. In the past, they variously have been referred to as atypical, anonymous, environmental or unclassified. MOTT, the acronym for Mycobacteria Other Than Tuberculosis, may also be used to describe these microbes.

NTM are a heterogenous group of bacilli that are generally found in the environment (water and soil). Unlike the organisms that cause tuberculosis and leprosy, NTM are thought to be contracted from environmental sources and not from infected humans. Most are saprophytic, but some NTM are pathogens which may cause severe disease or even death.

NTM differ from the classic tubercle bacilli in several aspects. NTM have a wider temperature range for growth, including temperatures not found in the human body, and their growth rates tend to be more variable than *M. tuberculosis*. Unlike tuberculosis, which is inherently drug susceptible, wild strains of NTM have varying patterns of natural drug resistance, typically manifesting resistance to isoniazid and pyrazinamide with varying susceptibility to rifampin, ethambutol and streptomycin. This heterogenous resistance makes therapy far less predictable than with disease caused by *M. tuberculosis*.

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Infections from NTM

Lung infections from NTM range in severity from rapidly progressive, destructive pneumonic disease to indolent disorders, with minimal physical manifestations evident in the short term. While these infections frequently are associated with pre-existing disease or trauma, it is important to emphasize these individuals do not have apparent defects of immunity. Rather they have mechanical or other functional disturbances of the airways and lungs, which promote susceptibility to the infections. The underlying lung disorders coupled with the organisms' heterogeneous resistance to drugs complicates treatment protocols greatly; this makes a standard approach to treatment problematic.

On the Rise

Although it is unclear why, human infections due to NTM appear to be increasing at a significant rate across the United States. These increases, which occurred before the appearance of AIDS, are not due to the impact of human immunodeficiency virus infection. Interestingly, this overall increase includes a growing number of individuals who do not have clear predisposing lung disorders or factors. In addition, a disproportionate number of cases seem to occur among women, and more cases than in the past are involving young people. At National Jewish Medical and Research Center, we employ early diagnosis and aggressive medical treatment as the bulwarks of our program to control the infection and assure life expectancy and quality of life.

This upsurge may indicate a change in the ecosystem and the distribution of mycobacteria in our water supply. In fact, tentative evidence supports Legionnaire's disease as a model to study the spread of NTM. As is thought to be

the case with NTM, legionella bacteria are not spread from person-to-person but are generally inhaled from a water source.

Mycobacterium avium Complex (MAC)

Mycobacterium avium complex is the most common cause of infections due to NTM. It is responsible for progressive and, if untreated, usually fatal disease, especially in immunocompromised patients.

At National Jewish, we have recognized an association between physical features, especially among young women, and vulnerability to pulmonary MAC disease. We have observed among MAC patients thoracic skeletal anomalies, including pectus excavatum and scoliosis, as well as an unexpectedly high prevalence of mitral valve prolapse.

Many MAC patients, however, do have underlying lung disease or other predisposing factors. These would include cigarette-induced chronic bronchitis and emphysema, a history of tuberculosis with resultant scarring and bronchiectasis, inorganic dust exposure, and fibrotic disorders, including idiopathic fibrosing alveolitis and those associated with rheumatoid arthritis or ankylosing spondylitis.

These disorders may predispose to MAC by interfering with the clearance of mucus. When there is excessive mucus production, abnormally thick or tenacious secretions, or anatomic distortions that impede mucus clearance, mycobacteria can thrive and invade. Thus, cystic fibrosis appears to be an increasing factor in NTM lung disease as these individuals, due to impaired care, live ever longer lives.

Diagnosis of active or invasive disease is more difficult than *M. tuberculosis*, since MAC, prevalent in the environment, may be recovered from a nonsterile space and may not necessarily

reflect disease or vice versa. This distinction is critical, since incorrectly withholding treatment may expose a patient to progressive lung disease or even death. Conversely, prescribing medication to a patient without disease is costly and places them at risk for detrimental or toxic effects.

Diagnosis of active MAC disease is based on clinical signs and symptoms (malaise, fever, chills, night sweats, cough, sputum production, hemoptysis, pleuritic and nonpleuritic chest pain, dyspnea, weight loss, fever), sputum bacteriology and chest x-ray.

Early in the disease, symptoms may be minimal and the recovery of microbes difficult. With patients who are not producing sputum, bronchoscopy is typically done. A biopsy of the lung may also be performed to aid in the diagnosis.

Although the chest films of MAC patients reflect a wide spectrum of abnormalities, many appear to indicate classic tuberculosis: unilateral or bilateral upper lobe, apical posterior, fibronodular, partially consolidated, cavitory shadowing. There is a subset of MAC patients, more often female, who show mainly lower lobe, nodular subpleural shadowing, typically bilateral.

Because of the many variables involved, there have been no randomized clinical trials to determine which therapies or combination of therapies are most effective in treating pulmonary MAC disease. Indeed, therapy is difficult and controversial for three main reasons: MAC strains are very drug resistant; there exists a high probability of intolerance to or toxicity of one or more drugs; and the extent or type of disease varies greatly.

Susceptibility testing to determine the choice of drugs for MAC disease is problematic. Although the 1997 American Thoracic Society guidelines do not advocate this testing, a study

at National Jewish found a statistically significant association between susceptibility *in vitro* and response to therapy. MAC have a strong natural resistance to antimycobacterial drugs, making multidrug regimens necessary. Drugs including isoniazid, rifampin, ethambutol and streptomycin may be used to treat newly diagnosed pulmonary MAC disease. Also, multiple studies have shown the new macrolide, clarithromycin, to be active in susceptibility testing against MAC isolates. Because of the toxicity of the drugs, patients must be carefully monitored. Complete blood counts, liver function studies, visual acuity testing and audiograms should be administered regularly to check for hepatitis, bone marrow suppression, ototoxicity and optic neuritis.

For some patients, including those with localized, lobar disease and those with total destruction of one lung, surgical resection may be considered, although morbidity and mortality are high.

Mycobacterium kansasii

M. kansasii is the second most common cause of NTM pulmonary disease. Recovered most often from water, *M. kansasii* are thought to be transmitted by this source. One survey revealed *M. kansasii* clustering in larger cities, initiating theories of person-to-person transmission or transmission from some other unique urban source.

Predisposing factors include chronic obstructive pulmonary disease, smoking-induced chronic bronchitis and chronic inorganic dust exposure; these conditions were associated with more than half the cases in several reports. In all these series, the majority of cases were male.

Some *M. kansasii* patients are asymptomatic (detected on routine chest x-ray) while others

present various combinations of sparsely productive chronic cough, low-grade fever, malaise and nonpleuritic chest pain. Chest films may show cavities with thin walls and upper zone disease with less fibronodular and confluent shadowing than is typical of both *M. tuberculosis* and MAC. Pleural effusions are uncommon. In addition, *M. kansasii* can produce both nodular and diffuse cutaneous extrapulmonary disease.

Barring toxicity or acquired drug resistance, drug therapy for *M. kansasii* disease is relatively straightforward. A standard daily regimen of isoniazid, rifampin and ethambutol for eighteen months cures ninety-five percent of the pulmonary *M. kansasii* cases. Resectional surgery may be considered for patients with localized disease who experience toxic effects or extensive drug resistance.

Rapidly Growing Mycobacteria (RGM)

Rapidly growing mycobacteria (RGM), specifically *M. abscessus*, *M. chelonae* and *M. fortuitum*, are being reported more frequently in the United States. Their numbers are small but they are associated with considerable morbidity. There is also a high incidence of iatrogenic infections with RGM. While the means of transmission is not certain, they may be introduced by aspiration of esophagogastric contents since some patients have underlying esophageal disease which predispose them to aspiration.

Common on chest films of RGM patients is diffuse, irregular, patchy nodular shadowing without frank cavitation. Rarely, however, do patients show obvious symptoms of illness. While standard antimycobacterial drugs have relatively no activity against RGM, parenterally administered compounds and other drugs are potentially active against these species.

Patients are usually begun on treatment when they develop a relentless cough that interferes with normal activities such as sleeping. They are then admitted to a hospital for intravenous drug therapy for approximately eight hours. After careful monitoring, patients may be instructed in self-administration of the drugs or assisted by a home healthcare professional. There is no standard duration of treatment but most often antibiotics are given for three to six months after the sputum cultures have become negative.

Ongoing Studies at National Jewish Medical and Research Center

National Jewish Medical and Research Center is the nation's leading center with a treatment program for refractory drug-resistant tuberculosis and NTM infections. National Jewish continues to examine the role of specific medications in treating pulmonary disease due to NTM. A sophisticated laboratory, operated with a grant from the National Institutes of Health, is devoted to research on potential new drugs for treating NTM infections. *In vitro* susceptibility testing and pharmacokinetic monitoring are performed to optimize drug levels in patients and give the best possible care. Also, National Jewish is performing a retrospective analysis to determine the outcomes of such testing, i.e. whether drug toxicity is reduced.

In collaboration with the Centers for Disease Control, National Jewish has developed a national registry for patients with NTM infections. A doctor or healthcare provider can register a patient by calling 1-800-5511-NTM (1-800-551-1686).

Reference

Iseman MD. Nontuberculous mycobacterial infections, Chapter 167. In: Infectious Diseases, Gorbach SL, Bartlett JG, Blacklow NR (eds). WB Saunders Company, Philadelphia, pp 1513-1528, 1998.

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For Referrals of NTM patients: 1-800-5511-NTM

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