

## Mycobacterial infection

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### INTRODUCTION

Tuberculosis and leprosy are two well known mankind diseases that are caused by members of the genus *Mycobacterium*. When originally named in 1896, this genus contained the leprosy bacillus (*Mycobacterium leprae*) observed by Armour Hansen in 1874 and the tubercle bacillus (*Mycobacterium tuberculosis*) observed and cultured by Robert Koch in 1882. As time went by, other bacilli similar to those of Koch's tubercle bacilli were isolated from various sources mostly from various animals.

One of the common properties shared by these organisms is the characteristic staining reaction. They have the ability to resist decolorization in the presence of a weak mineral acid after being stained with an arylmethane dye (acid-fastness). Presently, the genus is defined more precisely on the basis of its antigenic structure and cell wall chemistry, particularly by the length of the carbon chains in long chain fatty-acids, termed mycolic acids.

From the purely clinical point of view, mycobacteria are divisible into 3 groups (Grange and Collins, 1983). These are:

- (1) the obligate pathogens *M. tuberculosis* and *M. leprae*,
- (2) species that normally live freely in the environment but also cause 'opportunistic' infections in man. This group have been referred to by many names such as 'anonymous, atypical, non-tuberculous and mycobacteria other than tubercle (MOTT), and
- (3) species that never, or with extreme rarity, cause disease, such as *M. paratuberculosis* and *M. lepramurium*.

### TUBERCULOSIS

This is by far the most common mycobacterial disease. After decades of decline, tuberculosis is back and from a global perspective, tuberculosis remains the leading cause of death by infectious disease. In developing nations between 0.1 - 0.3 percent of the population become infected each year. It is estimated that every year, between 50 - 100 million people are infected by the tubercle bacillus and of these, 10 - 15 million develop overt disease and 3 million die.

The disease usually starts in the lungs and can spread to other body organs. Other sites in which the disease often occurs include lymph nodes, bone, kidneys, reproductive system, intestine, skin and central nervous system. The disease is transmitted through air-borne droplets, usually by inhalation of bacteria coughed up by infected persons. Not all patients with tuberculosis are infectious. For transmission to occur, there must be a communication between the active lesions and the outside world.

The first symptoms of tuberculosis include fever, cough, weight loss, night sweats and malaise. Sputum direct smear or sputum culture are used to confirm the diagnosis. Some patients may need other methods of investigations such as serological tests or histopathological analysis to help confirm the diagnosis. Management of confirmed cases include strict supervision of taking 3-4 types of medication for at least 6 months, health education, contact investigation and follow up programme. First line drugs used for treatment are isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin. Second line drugs include cycloserine, kanamycin, capreomycin, amikacin and p-aminosalicylic acid.

The classic pattern for tuberculosis is markedly modified in patients suffering from AIDS. The HIV, the causative agent of AIDS has a profound effect on T-4 helper cells which regulate immune function against tuberculosis. The clinical manifestations of tuberculosis in AIDS more closely resemble primary disease in children than the usual adult-type disease. Some modifications are needed in the management of these patients especially on the duration of treatment and the need for antimicrobial susceptibility tests.

### LEPROSY

*Mycobacterium leprae*, unlike other mycobacteria that cause disease in man, is not isolated in the laboratory as it has never been convincingly cultured *in vitro*. Nevertheless, it is possible to obtain a limited growth of the bacillus in mouse footpads. Leprosy is, after tuberculosis, the most prevalent mycobacterial infection. WHO estimated presently about 8-10 million sufferers of the disease throughout the world. It is principally a disease of skin and superficial nerves but it also

affects the nose from which numerous bacilli are shed.

Leprosy occurs in several forms due to the so called 'spectrum' of immune responses (Ridley and Jopling, 1966). Tuberculoid leprosy pictures a high degree of immunological activity with the formation of tuberculosis-like granuloma. At the other end of the 'spectrum' when the relevant immune responses are suppressed, lepromatous leprosy will occur when the lesions are teeming with bacilli. Between these two, there is a wide range of intermediate forms i.e. borderline tuberculoid, mid-borderline and borderline lepromatous.

The diagnosis is by direct smear examination of 'slit skin smears' stained by the Ziehl-Neelsen method. The slit skin smear examination is repeated at intervals during treatment and gives an indication of the efficacy of chemotherapy. For nasal involvement, the nasal discharges are examined for bacilli using the same method of staining. The nasal mucosa can be scraped and examined after staining. When no bacilli are detectable, and when the diagnosis remains in doubt, a biopsy of a representative lesion is indicated. The examination of skin biopsies requires considerable experience, for which purpose, an elliptical piece of skin 12 by 3 mm, including the full thickness of the dermis is needed.

Treatment is by long duration multiple drugs therapy using dapsone, clofazamine and rifampicin.

**OTHER MYCOBACTERIOSES**

Other mycobacterial infections of man are, in relation to tuberculosis and leprosy, uncommon. Non-tuberculous mycobacteria are of low pathogenicity. Person to person spread seems not occur. Investigators postulated that the transmission is due to inhalation of organisms in aerosols originated from stagnant estuary waters, giving rise to human exposure, colonization, infection and sensitization, and sometimes overt disease. The commonest organism is *M. avium complex (MAC)*, commonly cultured from ground waters, dust and soil.

HIV patients are particularly susceptible to non-tuberculous mycobacterial infection. The reasons are not very clear. The literature suggests that monocyte-macrophage phagocytosis of MAC may be usually "permissive" for growth of these organisms inside the cells or it could be due to inadequate stimulation of macrophages by T cells, natural killer cell defects, or other as yet undiscovered host defense defects in these patients.

Four main types of 'atypical' mycobacterial infection occur. First, lymphadenopathy, usually cervical and usually caused by *M. avium-intracellulare* and *M. scrofulaceum*, in young children aged between one and five years. Unless it is associated with HIV infection, this disease is self limiting. Second, progressive lung disease occurs, usually in elderly men with underlying lung damage. This type may respond to standard anti-tuberculosis therapy, though in *vitro* testing

**TABLE 1: Non-tuberculous mycobacteria that can be isolated from human material**

| <u>Group</u>   | <u>Potential pathogens</u>   | <u>Non/rare pathogens</u>   |
|--|--|---|
| Photochromogens<br>(Slow growing-old<br>Runyon group I)      | <i>M. kansasii</i><br><i>M. marinum</i><br><i>M. simiae</i><br><i>M. asiaticum</i> |   |
| Scotochromogens<br>(Slow growing-old<br>Runyon group II)     | <i>M. scrofulaceum</i><br><i>M. szulgae</i><br><i>M. xenopi</i>                    | <i>M. gordonae</i><br><i>M. flavescens</i>                                  |
| Nonphotochromogens<br>(Slow growing-old<br>Runyon group III) | <i>M. avium</i><br><i>M. intracellulare</i><br><i>M. ulcerans</i>                  | <i>M. terrae complex</i><br><i>M. gastrae</i><br><i>M. nonchromogenicum</i> |
| Rapid growers<br>(Old Runyon group IV)                       | <i>M. fortuitum</i><br><i>M. chelonae</i>  | <i>M. smegmatis</i><br><i>M. phlei</i><br>Other species                     |

of the organism may show resistance. The most common species have again been MAC and *M. kansasii*. Other pathogens occasionally causing pulmonary disease are *M. xenopi*, *M. fortuitum*, *M. chelonae*, *M. szulgai*, *M. terrae*, *M. malmoense* and *M. asiaticum*. The clinical picture and roentgenographic picture in pulmonary infection due to MAC and *M. kansasii* are difficult to distinguish from that due to *M. tuberculosis*. Third, widespread disease involving multiple organs. This commonly occurs in immunosuppressed individuals such as the patient with AIDS, certain neoplasia, transplant recipients or patients suffering from hairy cell leukaemia. Such infections are commonly fatal. Fourth, infections resulting from the implantation of mycobacteria into tissues as the result of injections, accidental trauma and surgery. The most common species causing this infection are *M. chelonae* and *M. fortuitum*.

Distinct syndromes of skin infection can be caused by two non-tuberculous species, *M. marinum* and *M. ulcerans*. Lesions caused by *M. marinum* are usually solitary, slowly evolving, nodular, verrucous skin lesions commonly on the elbows, knees, dorsum of the feet and hands. Lesions of *M. ulcerans* are erythematous nodules with central cyanosis and undermining, appearing on distal parts of extremities.

The most direct approach to the diagnosis of non-tuberculosis mycobacterial disease is to demonstrate several positive cultures from the specimen obtained. Nucleic acid probes commercially available can help with the rapid diagnosis of MAC and differentiation from *M. tuberculosis*. The polymerase chain reaction (PCR) technique is also a useful tool as its sensitivity and specificity are very high.