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A REVIEW ON TUBERCULOSIS: PREVENTION AND DIAGNOSIS

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ABSTRACT

Tuberculosis is a leading killer of young adults worldwide and the global scourge of multi-drug resistant tuberculosis is reaching epidemic proportions. It is endemic in most developing countries and resurgent in developed and developing countries with high rates of human immunodeficiency virus infection. This article reviews the current situation in terms of drug delivery approaches for tuberculosis chemotherapy. A number of novel implant-, microparticulate-, and various other carrier-based drug delivery systems incorporating the principal anti-tuberculosis agents have been fabricated that either target the site of tuberculosis infection or reduce the dosing frequency with the aim of improving patient outcomes. These developments in drug delivery represent attractive options with significant merit, however, there is a requisite to manufacture an oral system, which directly addresses issues of unacceptable rifampicin bioavailability in fixed-dose combinations. This is fostered by the need to deliver medications to patients more efficiently and with fewer side effects, especially in developing countries. The fabrication of a polymeric once-daily oral multiparticulate fixed-dose combination of the principal anti-tuberculosis drugs, which attains segregated delivery of rifampicin and isoniazid for improved rifampicin bioavailability, could be a step in the right direction in addressing issues of treatment failure due to patient non-compliance.

KEYWORDS: Tuberculosis, Antibiotics, Resistance.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by bacteria whose scientific name is Mycobacterium tuberculosis. It was first isolated in 1882 by a German physician named Robert Koch who received the Nobel Prize for this discovery. TB most commonly affects the lungs but also can involve almost any organ of the body. Many years ago, this disease was referred to as "consumption" because without effective treatment, these patients often would waste away. Today, of course, tuberculosis usually can be treated successfully with antibiotics.

There is also a group of organisms referred to as atypical tuberculosis. These involve other types of bacteria that are in the *Mycobacterium* family. Often, these organisms do not cause disease and are referred to as "colonizers" because they simply live alongside other bacteria in our bodies without causing damage. At times, these bacteria can cause an infection that is sometimes clinically like typical tuberculosis. When these atypical mycobacteria cause infection, they are often very difficult to cure. Often, drug therapy for these organisms must be administered for one and a half to two years and requires multiple medications. One third of the world's population is thought to have been infected with M. tuberculosis, and new infections occur at a rate of about one per second. In 2007 there were an estimated 13.7 million chronic active cases, and in 2010 there were 8.8 million new cases, and 1.5 million deaths, mostly in developing countries. The absolute number of tuberculosis cases has been decreasing since 2006 and new cases since 2002. In addition, more people in the developing world contract tuberculosis because their immune systems are more likely to be compromised due to higher rates of AIDS. The distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5–10% of the U.S. population test positive.

Signs and Symptoms

Main symptoms of variants and stages of tuberculosis with many symptoms overlapping with other variants, while others are more (but not entirely) specific for certain variants Multiple variants may be present simultaneously. Only about 5-10% of those without HIV, infected with tuberculosis develop active disease during their lifetime. In contrast 30% of those co-infected with HIV develop active disease. Tuberculosis may infect any part of the body but most commonly occurs in the lungs (known as pulmonary tuberculosis). Extra pulmonary TB is when tuberculosis occurs outside of the lungs and may co-exist with pulmonary TB. General symptoms such as: fever, chills, night sweats, appetite loss, weight loss, fatigue, and finger clubbing may also occur.

Diagnosis

Mycobacterium tuberculosis (stained red) in sputum

Diagnosing tuberculosis based on signs and symptoms is difficult. A definitive diagnosis is made by identifying the causative organism (*Mycobacterium tuberculosis*) in a clinical sample (for example, sputum or pus). When this is not possible, a probable—although sometimes inconclusive—diagnosis may be made using imaging (X-rays or scans), a tuberculin skin test (Mantoux test), or a, Interferon Gamma Release Assay (IGRA).

Figure 1: Mycobacterium tuberculosis (stained red) in sputum.

Mantoux tuberculin skin test

Mantoux tuberculin skin tests are often used for routine screening of high risk individuals. Currently, latent infection is diagnosed in a non-immunized person by a tuberculin skin test, which yields a delayed hypersensitivity type response to an extract made from *M. tuberculosis* Those immunized for TB or with past-cleared infection will respond with delayed hypersensitivity parallel to those currently in a state of infection, so the test must be used with caution, particularly with regard to persons from countries where TB immunization is common.

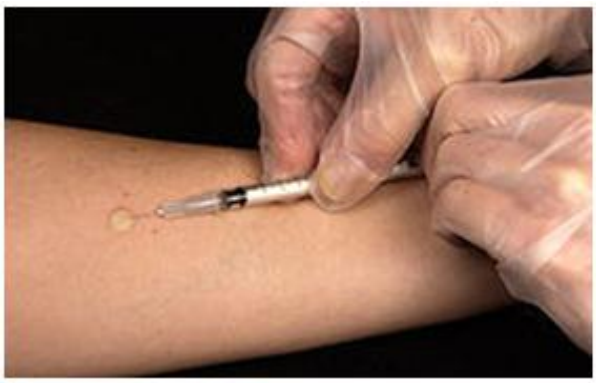

Figure 2: Mantoux tuberculin skin test.

Prevention

Tuberculosis prevention and control efforts primarily rely on the vaccination of infants and the detection and appropriate treatment of active cases. The World Health Organization has achieved some success with improved treatment success and a small decrease in case numbers.

Vaccines

The only currently available vaccine as of 2011 is Bacillus Calmette-Guérin (BCG) which while effective against disseminated disease in childhood, confers inconsistent protection against pulmonary disease. It is the most widely used vaccine worldwide with more than 90% of children vaccinated However the immunity that it induces, decreases after about ten years.

Public Health

The World Health Organization (WHO) declared TB a global health emergency in 1993 and in 2006 the Stop TB Partnership developed a Global Plan to Stop Tuberculosis that aims to save 14 million lives between its launch and 2015. A number of targets that they have set are not likely to be achieved by 2015 due to the increase in HIV associated tuberculosis and multi-drug resistant tuberculosis.

Causative Agent of Tuberculosis: The Mycobacterium tuberculosis complex includes strains of five species—M. tuberculosis, M. canettii, M. africanum, M. microti, and M. bovis and two subspecies—M. caprae and M. pinnipedii. The main cause of TB is Mycobacterium tuberculosis, a small, aerobic, nonmotile bacillus. The high lipid content of this pathogen accounts for many of its unique clinical characteristics. It divides every 16 to 20 hours, which is an extremely slow rate compared with other bacteria, which usually divide in less than an hour. Mycobacteria have an outer membrane lipid bilayer. In contrast M. bovis, the etiologic agent of bovine tuberculosis, causes only 5%–10% of human tuberculosis cases with a pathobiology indistinguishable from the one caused by M. tuberculosis and a wider host spectrum. The impact of M. bovis in human health declined sharply after the advent of pasteurization but there are records of new cases among immunocompromised individuals as well as reactivation cases amongst elderly individuals.

Risk Factors Associated With Tuberculosis: A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; 13% of all people with TB are infected by the virus. This is a particular problem in sub-Saharan Africa, where rates of HIV are high5. Of people without HIV who are infected with tuberculosis, about 5–10% develop active disease during their lifetimes, in contrast, 30% of those coinfected with HIV develop the active disease Tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the principal diseases of poverty. Those at high risk thus include: people who inject illicit drugs, inhabitants and employees of locales where vulnerable people gather (e.g. prisons and homeless shelters), medically underprivileged and resource-poor communities, high-risk ethnic minorities, children in close contact with high-risk category patients, and health-care providers serving these patients. Chronic

lung disease is another significant risk factor. Silicosis increases the risk about 30-fold. Those who smoke cigarettes have nearly twice the risk of TB compared to nonsmokers.

Pathogenicty of Tuberculosis: About 90% of those infected with M. tuberculosis have asymptomatic, latent TB infections (sometimes called LTBI), with only a 10% lifetime chance that the latent infection will progress to overt, active tuberculosis disease. In those with HIV, the risk of developing active TB increases to nearly 10% a year. If effective treatment is not given; the death rate for active TB cases is up to 66%. The source of infection is usually an open case of pulmonary tuberculosis. Tuberculosis is an airborne disease, since the infectious bacilli are inhaled as droplets from the atmosphere. In the lung, the bacteria are phagocytosed by the alveolar macrophages. Dried bacilli in dust are much less infectious. Spread occurs most often among household or other close or prolonged contacts of open cases; whose sputum may have over 10,000 bacilli per ml. infection also occurs infrequently by ingestion, for example, through infected milk, and rarely by inoculation. The majority of inhaled bacilli are arrested by the natural defences of the upper respiratory tract. Bacilli reaching the lungs are ingested by the alveolar macrophages. The interaction of mycobacteria components with macrophage receptors, such as Toll-like receptors (TLRs) results in the production of chemokines and cytokines. The dendritic cells that engulf bacteria then mature and migrate to the lymph nodes 4, 11, 12. Once there, CD4 and CD8 T cells are primed against mycobacterial antigens. Primed T cells expand and migrate back to the focus of infection in the lungs, probably in response tomediators produced by infected cells. This phenomenon of cell migration towards the infection focus culminates in the formation of a granuloma, the hallmark of TB.

The essential pathology in tuberculosis is the production in infected tissues of a characteristic lesion, the tubercle. This is an avascular granuloma composed of a central zone containing giant cells with or without cessation, and a peripheral zone of lymphocytes and fibroblasts. Tuberculosis lesions are primarily of two types: exudative and productive. The exudative type is an acute inflammatory reaction with accumulation of dema fluid, polymorphonuclear leucocytes, and later of lymphocytes and mononuclear cells. This is typically seen when the bacilli are many and virulent and the host response is more in the nature of DTH than of protective immunity.

Clinical Diagnosis of Tuberculosis: Clinical diagnosis of tuberculosis may be established by demonstrating the bacillus in the lesion by microscopy, isolating it in culture or by transmitting the infection to experimental animals. Demonstration of hypersensitivity to tuberculoprotein may be useful in some cases. Molecular diagnostic methods have also been introduced. The diagnosis of tuberculosis is divided into the following stages of infection which are: Active Tuberculosis Diagnosing active tuberculosis based merely on signs and symptoms is difficult, as is diagnosing the disease in those who are immunosuppressed. Sputum microscopy and culture in liquid medium with subsequent drug-susceptibility testing are currently recommended as standard methods for diagnosing active tuberculosis. The use of solid culture medium is more cost-effective in resource poor countries. Interferon-gamma release assays and tuberculin skin tests have no role in the diagnosis of active disease. The polymerase chain reaction (PCR) can be used to detect Mycobacterium tuberculosis DNA in sputum and other specimens. Nucleic acid amplification tests and adenosine deaminase testing may allow rapid diagnosis of TB. These tests, however, are not routinely recommended, as they rarely alter how a person is treated. Blood tests to detect antibodies are not specific or sensitive, so they are not recommended.

A new molecular diagnostic test called Xpert MTB/RIF assay detects M. tuberculosis complex within 2 hours, with an assay sensitivity that is much higher than that of smear microscopy. In HIV infected patients, the test has a rate of case detection that is increased by 45%, as compared with smear microscopy. Serological tests are not useful in diagnosis, though antibodies to many bacillary antigens have been demonstrated in the sera of patients. Detection of antibody to Mycobacterial lipo-arabinomannan has been reported to be of some value. Latent Tuberculosis Screening and treatment for latent M. tuberculosis infection are indicated for groups in which the prevalence of latent infection is high (e.g., foreign born persons from regions in which tuberculosis is endemic), those in whom the risk of reactivated disease is high (e.g., patients with HIV infection or diabetes and patients receiving immunosuppressive therapy), and those with both factors (e.g., recent contacts of patients with tuberculosis). The Mantoux tuberculin skin test is often used to screen people at high risk for TB. A positive tuberculin test indicates hypersensitivity to tuberculoprotein denoting infection with tubercle bacillus or BCG immunization, with or without clinical disease. The test becomes positive 4-6 weeks after infection or immunization. Tuberculin allergy wanes gradually and disappears after 4-5 years in the absence of subsequent contact with the bacillus. False negative test may be seen in certain situations like military tuberculosis, convalescence from some viral infection like measles, lyphoreticular malignancy, severe malnutrition, immunosuppressive therapy or impaired cell mediated immunity. False negative results may also be due to inactive PPD preparations and improper injection technique. Repeated tuberculin testing will not cause a positive reaction in a noninfected person, but may enhance the intensity of response in reactive individuals. This booster effect is useful in persons showing a negative or equivocal test due to waning allergy, in whom retesting after a week may induce a positive response (two step testing). Retesting is to be done at a site different from the earlier one. Tuberculin

testing may be used as an aid in diagnosing active infection in infants and young children, to measure prevalence of infection in an area, to select susceptible or as an indication of successful vaccination. Tuberculin testing of cattle has been of great value in the control of bovine tuberculosis.

Treatment of Tuberculosis: It has been established that sanatorium regimens, bed rest, fresh air and rich food, as well as operative interventions, such as artificial pnumothorax and thoracoplasty are not essential for cure if domiciliary treatment with effective antituberculous drug is given in optimal dose and duration. The following treatments strategies can be used for the proper cure of tuberculosis disease. 1. Antituberculous Drugs Antituberculous drugs are of two types, bactericidal and bacteristatic. Of the bacterialcidal drugs, rifampicin (R) and pyrazinamide (Z) are called sterilizing drugs because they are able to effectively kill the bacilli in the lesions. Of the other bactericidal drugs, isoniazid (H) is effective only against replicating bacilli and streptomycin (S) only against extracellular bacilli and so are not by themselves able to sterilize the lesions. The bactericidal drugs, along with the bacteristatic drug ethambutol (E), constitute the first line drugs in antituberculous therapy. The old practice of daily administration of drugs for two years or so has been replaced by short course regimens of 6-7 months, which are effective and convenient. A typical example of such a schedule for a new smear positive case is a combination of four drugs i.e, isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) given three times a week during an initial intensive phase of two months, followed by 4-5 months of continuing phase with only two drugs isoniazid and rifampicin (HR) three times a week. 2. Chemotherapy Chemotherapy has revolutionized the management of tuberculosis. The major problem in chemotherapy is drug resistance, which in tubercle bacilli is due to mutation, with an approximate rate of once in 108 cell divisions.

3. Multidrug Resistant Tuberculosis (MDR-TB) Drug resistance may be primary (pretreatment initial), when the patient is infected with a strain of tuber bacilli which is already resistant or acquired (Secondary post treatment). A very serious consequence of unchecked drug resistance has been the emergence and spread of multidrug resistant tuberculosis (MDRTB). The term multidrug resistance means only resistance to two or more drugs, in the context of tuberculosis, it specifically refers to resistance to rifampicin and isoniazid, with or without resistance to one or more other drugs. This is because rifampicin (R) and isonazid (H) form the sheet anchor of shortterm chemotherapy and any strain resistant to both these drugs is unlikely to respond to treatment. MDR-TB is a global problem, menacing the poor and the rich nations alike. It may be primary or acquired. Its presence in those with concomitant HIV infection makes it more dangerous. When the first line drugs become ineffective, second line drugs have to be tried. Large numbers of old and new drugs are being used such as quinolones, aminoglycosides, macroslides, para amino salicyclic acid, thiacetozone, cycloserine, capreomycin and others. They are unsatisfactory, being much less effective, costlier, and more toxic and requiring prolonged treatment schedules. It is in this context that the directly observed therapy under supervision (DOTS) becomes important. This strategy can prevent deterioration of the resistance problem by ensuring the patient's compliance. Restoration of cellular immune capacity by transfer factor had been shown many years ago, to help recovery in immunodeficient patients. Prevention of Tuberculosis (TB) prevention consists of two main parts. The first part of TB prevention is to stop the transmission of TB from one adult to another. This is done through firstly, identifying people with active TB, and then curing them through the provision of drug treatment. With proper TB treatment someone with active TB disease will very quickly not be infectious and so can no longer spread the disease to others. The second main part of TB prevention is to prevent people with latent TB from developing active, and infectious, TB disease. Anything which increases the number of infectious people, such as the presence of TB and HIV infection together, or which increases the number of people infected by each infectious person, such as ineffective treatment because of drug resistant TB, reduces the overall effect of the main BCG vaccine The TB vaccine called Bacillus Calmette-Guerin (BCG) was first developed in the 1920s. It is one of the most widely used of all current vaccines, and it reaches more than 80% of all new born children and infants in countries where it is part of the national childhood immunization programme2 . However, it is also one of the most variable vaccines in routine use. The BCG vaccine has been shown to provide children with excellent protection against the disseminated forms of TB; however protection against pulmonary TB in adults is variable. Since most transmission originates from adult cases of pulmonary TB, the BCG vaccine is generally used to protect children, rather than to interrupt transmission amongst adults. The BCG vaccine will often result in the person vaccinated having a positive result to a TB skin test.

CONCLUSION

Tuberculosis remains a major cause of death worldwide. The rise and spread of drug resistance and synergistic interaction with the HIV epidemic are posing difficult challenges and threatening global efforts at tuberculosis control. Despite the intensive work on the Mycobacteria field and the use of cutting-edge technology, such as EM techniques and genome-wide screenings for Mycobacteria and host, many questions remain unanswered. This can be explained by the Mycobacterium complexity and its ability to adapt to the host environment. New molecular diagnostics have made earlier and improved diagnosis of active disease possible.

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