An Overview: The Treatment of Tuberculosis

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Abstract: Tuberculosis is an infectious disease which is caused by bacteria. Tuberculosis most commonly affects the lungs, but it can also affect any other organ. The infection doesn’t always result in disease. The human immune defense cells can check and control pathogens, so that progression to disease only occurs in about 10% of adults. However the infection may remain latent and can reactive at any time, also after decades if e.g. the immune system is weakened. If left untreated, tuberculosis is a life-threatening illness. The main burden of tuberculosis is carried by developing countries. The cases of tuberculosis have been declining in Germany for years. But the global increase of tuberculosis affects every region of the world, also developed countries.

In the early 1940s and 1950s, tuberculosis (TB) was the number one cause of death. Patients with TB were admitted to the many sanatoria we had in various parts of the country and were often managed by surgical means. TB chemotherapy became available only in the late 1950s. At this time, TB was already a major cause of morbidity and mortality. Realizing its seriousness, the Malaysian government launched its National TB Control Programme (NTP) in 1961. Multi-drug-resistant tuberculosis (MDR-TB) is defined as tuberculosis that is resistant to at least isoniazid and rifampicin: the two most powerful first-line treatment anti-TB drugs. This type of drug resistance, called acquired drug resistance, occurs in TB because a patient's bacterial population survives for several months during treatment.

Keywords: Drug-resistant, Mycobacterium tuberculosis, Ethambutol.

Introduction

Tuberculosis (TB)

What is TB? Tuberculosis (TB) is a disease caused by bacteria that are spread from person to person through the air. TB usually attacks the lungs, but it can also attack and damage any part of the body, such as the brain, kidneys, or spine. A person with TB can die without treatment. What are the symptoms of TB? The general symptoms of TB disease include feelings of sickness or weakness, weight loss, fever, and night sweats. The symptoms of TB disease of the lungs also include coughing, chest pain, and coughing up blood. Symptoms of TB disease in other parts of the body depend on the area affected.

How is TB spread? TB bacteria are put into the air when a person with TB disease of the lungs or throat coughs, sneezes, or speaks. These germs can stay in the air for several hours, depending on the environment.

Individuals who breathe in the air containing these TB germs can become infected; this is called latent TB infection [1]. People with TB disease are most likely to spread the germs to people they spend time with every day, such as family members or coworkers, since it usually takes prolonged exposure to someone with TB disease for someone to become infected.

Tuberculosis (TB) is a common, and in many cases fatal, infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis. Tuberculosis typically attacks the lungs, but can also affect other parts of the body [2]. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air. Most infections do not have symptoms, known as latent tuberculosis.
About one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those so infected. The classic symptoms of active TB infection are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss [3].

**Latent TB Infection vs. TB Disease**

Tuberculosis is either latent or active.

- **Latent TB** means that you have the TB bacteria in your body, but your body's defenses (immune system) are keeping it from turning into active TB. This means that you don't have any symptoms of TB right now and can't spread the disease to others. If you have latent TB, it can become active TB.

- **Active TB** means that the TB bacteria are growing and causing symptoms. If your lungs are infected with active TB, it is easy to spread the disease to others.

What is latent TB infection? Individuals with latent TB infection do not feel sick, do not have any symptoms, and cannot spread TB bacteria to others [4]. They have TB bacteria in their bodies, but do not have TB disease, which is both symptomatic and infectious. The only sign of latent TB infection is a positive reaction to the tuberculin skin test or TB blood test. However, not everyone infected with TB bacteria becomes sick. Without treatment, about 5 to 10 percent of infected individuals will develop TB disease at some time in their lives. Some individuals have a greater risk of developing TB disease if infected. What is TB disease? In some people, TB bacteria overcome the defenses of the immune system and begin to multiply, resulting in the progression from latent TB infection to TB disease.

Without treatment, the bacteria continue to multiply and destroy the body’s tissue. Some people develop TB disease soon after infection (within the first two years), while others develop TB disease later if their immune system becomes weak, such as individuals with diabetes or those who are also infected with HIV. Individuals with TB disease may spread TB bacteria to others.

Individuals suspected of having TB disease should be referred for a medical evaluation and additional tests. If not treated properly, TB disease can be fatal [5].

**Pathogenesis of Tuberculosis**

Tuberculosis is a highly infectious disease, and is primarily transmitted via inhalation of aerosol droplets expelled by infected hosts. The infectious dose is 1-200 bacilli, but each aerosol droplet can contain 1-400 bacilli, making contact without infection nearly impossible. In addition to its airborne infection, *M. tb* is adept at using the natural defenses of the body for its own advantage.

After infection, the host either develops a primary infection immediately, or no initial infection occurs and the disease remains latent within the body. Upon inhalation, tuberculosis bacteria travel to the lungs and end up in the alveoli, where they are recognized in an immunocompetent host as foreign and are attacked by the body. These macrophages attempt to engulf the bacteria and dissemble them, normally a part of the process of a body defeating disease. However in the case of tuberculosis, it is exactly what the disease wants.

Not all of the bacteria cells will be destroyed no matter how excellent the host's immune system is, and the survivors infect and hijack macrophages feeding on them while increasing the bacteria population. Once macrophages are infected, they either kill the bacteria inside them or the bacteria multiply until they burst the macrophage, leading to further infection and extracellular bacilli (increasing the likelihood of infecting others via aerosol transmission).
The infected areas gradually transform into granuloma, a wall of macrophages intended to contain the infection. This also allows the *M. tb* to continue growing and overwhelm the cells it has infected until they die. Over time the centers of these granulomas necrotize, leading to the mixture of blood and sputum in the lungs tuberculosis is known for.

This is where the disease's progress diverges depending on the individual. For the vast majority of cases, these necrotized lesions heal with some amount of scarring and calcification.

The disease is not gone, and these asymptomatic cases can remain latent for years and even decades [6]. Less than 10% of these latent tuberculosis cases become full blown secondary infections, but those account for nearly 80% of active tuberculosis cases. Almost all transmission occurs from latent tuberculosis reemerging and causing rapid growth of extracellular bacteria (the kind most likely to be transmitted through inhalation of aerosol droplets). Because the disease can lie dormant for so long, seemingly healthy people can easily infect their friends, neighbors, and anyone they have contact with before they can be treated or isolated. While tuberculosis is not unique among diseases for lingering in the body and reemerging (malaria is another notable example), this characteristic does contribute to its prevalence and lethality [7].

**Multi-Drug-Resistant Tuberculosis (MDR-TB)**

Multi-drug-resistant tuberculosis (MDR-TB) is defined as tuberculosis that is resistant to at least isoniazid and rifampicin: the two most powerful first-line treatment anti-TB drugs. This type of drug resistance, called acquired drug resistance, occurs in TB because a patient's bacterial population survives for several months during treatment. MDR-TB is a critical issue to address because it impacts various regions. MDR-TB most commonly develops in the course of TB treatment, and is most commonly due to doctors giving inappropriate treatment, or patients missing doses or failing to complete their treatment [8].

**Extensively Drug-Resistant Tuberculosis (XDR TB)**

Extensively drug-resistant tuberculosis (XDR-TB) is a form of tuberculosis caused by bacteria that are resistant to some of the most effective anti-TB drugs. XDR-TB strains have arisen after the mismanagement of individuals with multidrug-resistant TB (MDR-TB) [9].

**Totally Drug-Resistant Tuberculosis (TDR TB)**

Totally drug-resistant tuberculosis (TDR-TB) is a generic term for tuberculosis strains that are resistant to a wider range of drugs than strains classified as extensively drug-resistant tuberculosis. TDR-TB has resulted from further mutations within the bacterial genome to confer resistance, beyond those seen in XDR- and MDR-TB. Development of resistance is associated with poor management of cases. Drug resistance testing occurs in only 9% of TB cases worldwide. Without testing to determine drug resistance profiles, MDR- or XDR-TB patients may develop resistance to additional drugs [10].

**Treatment**

For initial empiric treatment of TB, start patients on a 4-drug regimen: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. Once the TB isolate is known to be fully susceptible, ethambutol (or streptomycin, if it is used as a fourth drug) can be discontinued. After 2 months of therapy (for a fully susceptible isolate), pyrazinamide can be stopped [11].

Patients with TB who are receiving pyrazinamide should undergo baseline and periodic serum uric acid assessments, and...
patients with TB who are receiving long-term ethambutol therapy should undergo baseline and periodic visual acuity and red-green color perception testing. The latter can be performed with a standard test, such as the Ishihara test for color blindness [12].

After 2 months of therapy (for a fully susceptible isolate), pyrazinamide can be stopped. Isoniazid plus rifampin are continued as daily or intermittent therapy for 4 more months. If isolated isoniazid resistance is documented, discontinue isoniazid and continue treatment with rifampin, pyrazinamide, and ethambutol for the entire 6 months. Therapy must be extended if the patient has cavitary disease and remains culture-positive after 2 months of treatment [13].

Directly observed therapy (DOT) is recommended for all patients. With DOT, patients on the above regimens can be switched to 2- to 3-times per week dosing after an initial 2 weeks of daily dosing. Patients on twice-weekly dosing must not miss any doses. Prescribe daily therapy for patients on self-administered medication [14].

MDR-TB

Patients with MDR TB will have to take at least 5 different drugs, including a daily injection for 4 months 5 days a week. During this time most patients with MDR TB are admitted to hospital so that they can be closely monitored for adherence to treatment and to monitor any side effects [15].

Thereafter patients will need to take at least 3 different drugs for a further 12 – 16 months 5 days a week. Thus, treatment is much longer than for "ordinary TB" [which takes between 6 to 8 months], and can go on for up to 2 years. The length of treatment is to ensure that the disease does not relapse [16].

Usually, multidrug-resistant tuberculosis can be cured with long treatments of second-line drugs, but these are more expensive than first-line drugs and have more adverse effects [17]. The treatment and prognosis of MDR-TB are much more akin to that for cancer than to that for infection. It has a mortality rate of up to 80%, which depends on a number of factors, including:

- How many drugs the organism is resistant to [the fewer the better]?
- How many drugs the patient is given [patients treated with five or more drugs do better]?
- Whether an injectable drug is given or not [it should be given for the first three months at least]?
- The expertise and experience of the physician responsible.
- How co-operative the patient is with treatment [treatment is arduous and long, and requires persistence and determination on the part of the patient]?
- Whether the patient is HIV positive or not [HIV co-infection is associated with an increased mortality]?

The majority of patients suffering from multi-drug-resistant tuberculosis do not receive treatment, as they tend to live in underdeveloped countries or in a state of poverty. Denial of treatment remains a difficult human rights issue, as the high cost of second-line medications often precludes individuals unable to afford therapy [18].

XDR TB

The principles of treatment for MDR-TB and for XDR-TB are the same. Treatment requires extensive chemotherapy for up to two years. Second-line drugs are more toxic than the standard anti-TB regimen and can cause a range of serious side-effects including hepatitis, depression, hallucinations, and deafness. Patients are often hospitalized for long periods, in isolation [19]. In addition, second-line drugs are extremely expensive compared with the cost of drugs for standard TB treatment [20].

TDR TB

Totally Drug–Resistant Tuberculosis (TDR-TB) “for TB strains that showed in-vitro resistance to all first and second line drugs tested [isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide].

TDR-TB patients remained smear and culture positive after 18 months median treatment despite second line drugs. Even changing the treatment to coamoxiclav or
clarithromycin along with high dose of isoniazid led to no improvement [21].

- Double-dose isoniazid: Although their TB strain is resistant to isoniazid, the hope is a higher dose would have some in-vivo efficacy.

- Linezolid: This antibiotic is dreadfully toxic (one in two patients has major side effects that demand withdrawal).

- Clofazimine: This is an anti-leprosy drug that has at least some, albeit weak, anti-TB effect.

- Thioridazine: This is an ancient, cheap, anti-psychotic drug that in some promising lab work by an amazing colleague, Professor Len Amaral, has been shown to have some efficacy in TB.

- Meropenem and clavunate: A paper in *Science* showed these had some effect on TB in mice. They are expensive, and need IV administration, but we are clutching at straws here.

Finally, after completion of full cycle, there is an option of aggressive surgery (if drugs can’t help at least let’s cut out the worst parts). Sadly most patients are too malnourished and have such advanced TB disseminated in both lungs that even this is not an option [22].

References


15. http://sciencespeaksblog.org/2012/01/13


