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A REVIEW ON THE TREATMENT OF TB, MDR TB, XDR TB AND TDR TB

Akash Balwant, Abhijeet Barde, Amitkumar Anandrao Khade

Government College of Pharmacy, Karad, Maharashtra, India

INTRODUCTION

TUBERCULOSIS

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. 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 [1].

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 [2].

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) [3].

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 [4].

TREATMENT

TUBERCULOSIS

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.

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.

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.

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 [5].

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.

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 [6].

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. 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:

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

6. 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 [7].

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. In addition, second-line drugs are extremely expensive compared with the cost of drugs for standard TB treatment [8].

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 [9].

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

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

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

4. 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.

5. 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 [10].

REFERENCE

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