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Multidrug-Resistant Tuberculosis (MDR-TB): An Overview

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Mr. Suraj Narayan Mali

Government College of Pharmacy, Karad (Maharashtra), India-303007.

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ABSTRACT

Tuberculosis (TB) is as old as the mankind. Though the disease was known since ancient times, the organism causing TB was described only a century ago by Robert Koch on March 1882.On the 20th of November 1944, the first successful anti-tubercular chemotherapy was administered using streptomycin. This was followed by the invention of P-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cyclosporine (1955), ethambutol (1962) and rifampicin; 1963. Multidrug-resistant TB (MDR-TB) is caused by an organism that is resistant to at least isoniazid and rifampin, the two most potent TB drugs. These drugs are used to treat all persons with TB disease. 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. Patients with MDR-TB will have to take at least 5 different drugs, including a daily injection for 4 months 5 days a week. Approaches such as DOTS-Plus may have to be employed to effectively control MDR-TB.

INTRODUCTION

Tuberculosis (TB) is as old as the mankind. Though the disease was known since ancient times, the organism causing TB was described only a century ago by Robert Koch on March 1882.Until the middle of the 20th century, there was no definite treatment available for TB. With the availability streptomycin, isoniazid and para-aminosalicylic acid (PAS), in the mid-1940s, predictable, curative treatment for TB became a reality. TB is basically a disease of poverty,with95% of cases and 98% of deaths occurring in developing countries .Of these more than half the cases occur in 5 South East Asian Countries (1).Multidrug-resistant TB (MDR-TB) is defined as a form of TB infection caused by the bacteria that are resistant to treatment with at least two of the most powerful first-line anti-TB drugs, isoniazid (INH) and rifampicin (RMP).Five percent(5%) of all TB cases across the globe in 2013 were estimated to be MDR-TB cases, including 3.5% of newly diagnosed TB cases, and 20.5% of previously treated TB cases (2).MDR-TB as a global epidemiological problem is a relatively recent concern. The WHO guidelines for the treatment of tuberculosis published in 1991 contained only one paragraph concerning chronic patients and did not provide a thorough approach to the problem of multidrug resistance (3).Annually, about 425,000 new MDR-TB cases occur in the world which constitutes about 5% of overall global TB burden. Treatment of MDR-TB takes roughly 20 months; whereas, treatment of drug-susceptible TB takes 6-9 months (4, 2). In general, second-line drugs are less effective, more toxic and much more expensive than the first-line drugs.Under ideal program conditions; MDR-TB cure rates can approach 70% (2). MDR-TB infection may be classified as either primary or acquired. Rates of primary MDR-TB are low in North America and Western Europe: in the US in 2000, the rate of primary MDR-TB was 1% of all cases of TB nationally (2). Resistance to isoniazid is because of mutations at one of two main sites, in either the *kat*G or *inh*A genes. Resistance to rifampicin is nearly always due to point mutations in the *rpoB* gene in the beta subunit of DNA-dependent polymerase. The accurate diagnosis of MDR-TB requires a positive culture of *M. tuberculosis* and drug susceptibility testing (5).

Definition:

Drug-resistant TB is defined as a case of tuberculosis excreting bacilli resistant to one or more anti-TB drugs (6). Multidrug-resistant TB(MDR-TB) is caused by an organism that is resistant to

at least isoniazid and rifampin, the two most potent TB drugs. These drugs are used to treat all persons with TB disease (7, 8, 1).

Epidemiology:

Cases of MDR-TB have been reported in every country surveyed. 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. Because MDR TB is an airborne pathogen, persons with active, pulmonary tuberculosis caused by multidrug-resistant strains can transmit the disease if they are alive and coughing (2).

Global:

The global burden in 2013: Globally, 5%of TB cases were estimated to have had MDR-TB in 2013(3.5% of new and 20.5% of previously treated TB cases). Drug resistance surveillance data show that an estimated 480,000 people developed MDR-TB in 2013 and 210 000 people died. On an average, a 9% of people with MDR-TB have XDR-TB. In 2013, 136 000 of the estimated 300 000 MDR-TB patients who could have been detected were diagnosed and notified (9). As of 2013, 3.7% of new tuberculosis cases have MDR-TB. Levels are much higher in those previously treated for TB –about 20%.WHO estimates that there were about 0.5 million new MDR-TB cases in the world in 2011. About 60% of these cases occurred in Brazil, China, India the Russian Federation and South Africa alone (2). In Moldova, the crumbling health system has led to the rise of MDR-TB (2). In 2013, the Mexico-United States border was noted to be "a very hot region for drug-resistant TB", though the number of cases remained small (2). A study in Los Angeles, California found that only 6% of cases of MDR-TB were clustered. In New York City, a report issued by city health authorities states that fully 80% of all MDR-TB cases could be traced back to prisons and homeless shelters (2).The prevalence of MDR-TB in previously treated cases in Estonia increased from 19% (1994) to 37% (1998) (6,10-13). In Latvia, MDR-TB in new cases continues to be very high. Botswana, Chile, Cuba & Czech Republic, and Uruguay have all showed the very low prevalence of MDR-TB(6, 10, and 11).

India:

The problem of drug resistance was observed in the early studies from India (1, 14, and 15). In India, the prevalence of primary MDR-TB in newly diagnosed cases has been observed to be 3.4% or less. Data meticulously collected at the Tuberculosis Research Centre (TRC), Chennai over the last three decades suggest that rifampicin resistance started appearing in the early 1990s and MDR-TB levels in newly diagnosed patients has been 1% or less (1,16).According to third Global Report of WHO total prevalence of drug resistance among new cases in India (Wardha) is 19.8% and MDR is 0.5%.A study conducted in two districts of south India showed that acquired drug resistance ranged from 69-100% (6,17).

Spread of TB:

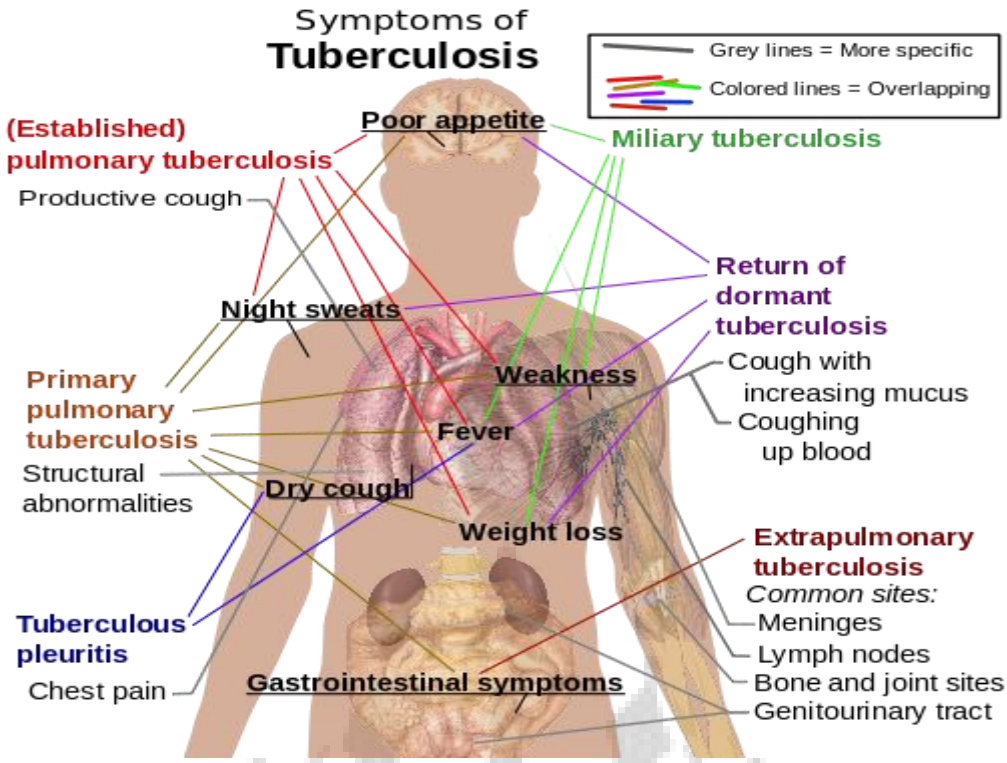
Drug-susceptible TB and Drug-resistant TB are spread the same way. TB bacteria are put into the air when a person with TB disease of the lungs or throat coughs, sneezes, speaks, or sings. These bacteria can float in the air for several hours, depending on the environment. Persons who breathe in the air containing these TB bacteria can become infected.

TB is not spread by:

- ❖ Shaking someone's hand.
- ❖ Sharing food or drink.
- ❖ Touching bed linens or toilet seats.
- ❖ Sharing toothbrushes.
- ❖ Kissing (8).

Symptoms:

The general symptoms of TB disease include a feeling of sickness or weakness, weight loss, fever, and night sweats. The symptoms of TB disease of the lungs may also include coughing, chest pain, and coughing up blood. Symptoms of TB disease in the other parts of the body depends on the area affected (8).



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Types of drug resistance:

Antibiotic resistance in *M. tuberculosis* develops primarily through mutations in chromosomal genes. Drug resistance is of two type: 1) **Primary resistance** and 2) **Acquired resistance**. Primary drug resistance may be defined as drug resistance in patients who has not received any anti-TB treatment in the past. The resistance that develops in a patient who has received prior chemotherapy is defined as acquired drug resistance (6).

Mechanism of *M. tuberculosis* drug resistance:

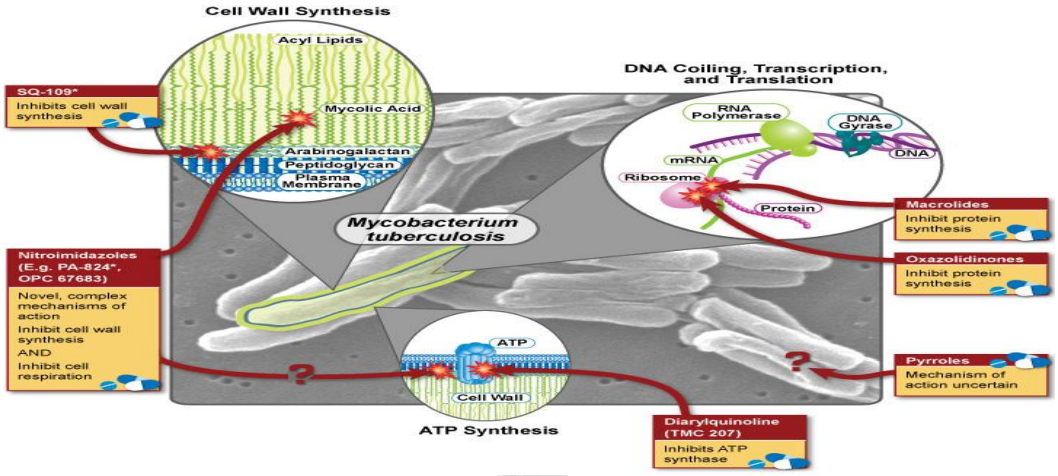
Some of the ways the tubercle bacillus acquires drug resistance are:

I. Cell wall: The cell wall of *M. tuberculosis* consists of complex lipids, and it acts as a permeability barrier from drugs.

II. Drug modifying & inactivating enzymes: The *M. tuberculosis* genome codes for certain enzymes that make it drug resistant. The enzymes usually phosphorylate, acetylate, or adenylate the drug compounds.

III. Drug efflux systems.

IV. Mutations: Spontaneous mutations in the *M. tuberculosis* genome can give rise to proteins that make the bacterium drug resistant, depending on the drug action (2).



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Causes of drug resistance:

✓ Genetic factors

✓ Factors related to previous anti-TB treatment

✓ Lack of laboratory diagnostic facilities (1).

Risk factors for drug resistance (MDR-TB):

Drug resistance is more common in people who:

➢ Do not take their TB medicines regularly

➢ Do not take all of their TB medicines as prescribed by their doctor

➢ Develop TB disease again, after having taken TB medicine in the past

➢ Come from areas of the world where drug-resistant TB is common

➢ Have spent time with someone known to have drug-resistant TB disease (8).

➢ Other factors that may be responsible for increased risk of resistant TB are co-infection with HIV, socio-economically deprived groups in slums, prisons, correctional facilities, day care centers, intravenous drug abusers, anticancer therapy patients, and patients with diabetes mellitus (6).

Diagnosis:

Lowenstein-Jensen (LJ) culture has been used for drug sensitivity testing using (1) absolute concentration method; (2) the resistance ratio method; and (3) the proportions method.These methods require 6-8 wks time (1,18-19). Radiometric methods have been developed for rapid drug-susceptibility testing of *M. tuberculosis*. In the BACTEC-460(Becton-Dickinson) radiometric method, 7H12 medium containing palmitic acid labeled with radioactive carbon is inoculated (1,20-21). The mycobacterium growth indicator tube (MGIT) system (Becton-Dickinson) is a rapid, non-radioactive method for detection and susceptibility testing of *M. tuberculosis* (1,22-23). Luciferase reporter assay is a novel reporter gene assay system for the rapid determination of drug resistance (1,24-26).The Line Probe assay (LIPA; Inno-Genetics NV, Zwijndrecht, Belgium) has been used for rapid detection of rifampicin resistance (1, 27).

Five priority actions to address the global MDR-TB crisis (According to "World Health Organization (WHO)"):

1. Prevent the development of drug resistance through high-quality treatment of drug-susceptible TB.
2. Expand rapid testing and detection of drug-resistant TB cases.
3. Provide immediate access to effective treatment and proper care.
4. Prevent transmission through infection control.
5. Increase political commitment with financing (9).

Treatment of 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 the 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 (7, 28).

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 (2, 7).

DOTS-Plus treatment:

Community-based treatment programs such as DOTS-Plus, an MDR-TB-specializedtreatment using the popular Directly Observed Therapy-Short Course (DOTS) initiative, have shown considerable success in the treatment of MDR-TB in some parts of the world. In these programs have proven to be a good option for proper treatment of MDR-TB in poor, rural areas. A successful example has been in Lima, Peru, where the program has seen cure rates over 80% (2).

Prevention of MDR-TB:

The primary aim in the control of drug resistance and multidrug-resistance TB is to prevent its development in the first place. This can be done by Directly Observed Treatment Short Course

(DOTS), which is the most cost effective way of prevention of MDR-TB. Apart from a strong tuberculosis control program, there is also a need for a continuous and periodic survey of drug resistance (6).There are several ways that drug resistance to TB, and drug resistance in general, can be prevented:

❖ Rapid diagnosis & treatment of TB: One of the greatest risk factors for drug resistant TB is problems in the treatment and diagnosis, especially in the developing countries. If TB is identified and treated soon, drug resistance can be prevented.

❖ Completion of treatment: Previous treatment of TB is an indicator of MDR-TB.If the patient does not complete his/her antibiotic treatment, or if the physician does not prescribe the proper antibiotic regimen, resistance can develop. Also, drugs that are of poor quality or less in quantity, especially in developing countries, contribute to MDR-TB.

❖ Patients with HIV/AIDS should be identified and diagnosed as soon as possible. They lack the immunity to fight the TB infection and are at great risk of developing drug resistance.

❖ Identify contacts that could have contracted TB: i.e. family members, people in close contact, etc.

❖ Research: Much research and funding are needed in the diagnosis, prevention and treatment of TB and MDR-TB (2).

CONCLUSION

By referencing the sources mentioned below and reviewing papers, we come to across to the fact that Multidrug-Resistant Tuberculosis is still increasing at very high rate. Till today, many reviews on tuberculosis drug resistance in M. tuberculosis were published. There are little evidence and much controversy regarding the treatment of MDR-TB. Approaches such as DOTS-Plus may have to be employed to effectively control MDR-TB. Multidrug-Resistant Tuberculosis is a major global concern. We should apply the latest techniques and findings related to MDR-TB in order to decrease the mortality rate. Overall, the emergence of MDR-TB is a reminder that TB control globally needs a massive commitment by scientific, political and financial authorities .If new TB drugs and rapid diagnostics are not developed and implemented shortly, MDR–TB will be an expanding fraction of TB cases.

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