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Recent Trends in Treatment of Multidrug Resistant-Tuberculosis-A Review

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Abstract

Drug resistance is reduction in effectiveness of an anti-microbial agents used in inhibiting the microorganisms or curing a disease. *Mycobacterium tuberculosis* is responsible for causing tuberculosis can acquire multiple drug resistance by not responding to Isoniazid and Rifampicin the two most powerful anti-TB agents. The complications of drug resistance in TB elevates due to some of the risk factors like inadequate treatment compliance, non-compliance of the patients to the treatment.

Proper diagnosis of the disease and switching to modified drug therapy may improve the treatment outcome. The drug treatment involves usage of combination of drugs Isoniazid, Rifampicin, Ethambutol along with other anti-microbial agents, and nutritional therapy, immunotherapy. In this review we discussed about the occurrence, treatment of multi drug resistance tuberculosis along with drugs under trials and nutritional requirements.

Keywords: Multi drug resistant tuberculosis; *Mycobacterium tuberculosis*; Non-compliance; Nutritional therapy; Immunotherapy

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium species* (*M. tuberculosis* in humans and *M. bovis* in cattle). The mortality rate is high for tuberculosis next to AIDS. Researches showed that approximately about more than one billion deaths occurred due to tuberculosis around the world till now. TB is progressive and spreads through the respiratory tract as a nasal delivery.

The development of the disease from initial infection to active primary tuberculosis occurs within 1-3 years. The development of resistance is multi-faceted and is influenced by some of the factors like socio-economic, pathological and environmental conditions [1,2].

Epidemiology

In India, the incidence of multi drug resistant tuberculosis is 3.4% (or) less. Of these, Rifampicin resistance accounts for about 1% or less [3].

Multidrug-resistant tuberculosis (MDR-TB)

It is a condition in which mycobacterium tuberculi develops resistance to Isoniazid and Rifampicin, the two most effective first line anti-TB medicines. Patients with Multi Drug-Resistant Tuberculosis (MDR-TB) require treatment with second-line treatment regimens, which are more complex than those used to treat patients without drug-resistant TB [4].

Extensively Drug-Resistant TB (XDR-TB) is a condition in which *Mycobacterium tuberculi* responds only to few second-line anti-TB medicines [5].

Drug resistance

Drug resistance is reduction in effectiveness of a medication such as an antimicrobial in killing a microbe or condition.

Natural resistance

Some microbes have always been resistant to certain anti-microbial agent. They are devoid of the metabolic process or the target site which is affected by the particular drug. Eg: Gram negative bacilli are normally unaffected by Penicillin G and *M. tuberculosis* is insensitive to tetracyclines

Acquired resistance

It is the development of resistance by an organism (which was sensitive before) due to the use of an AMA over a period of time.

Pathogenesis

Most bacilli of mycobacterium undergo frequent mutations and thus exhibit resistance to drugs, thus requiring usage of multiple drug regimens. The mutation rates for different drugs are as included in Table 1.

Drug	Average Mutation Rate
Isoniazid	2.56×10^{-8}
Rifampicin	2.25×10^{-10}
Ethambutol	1×10^{-7}
Streptomycin	2.95×10^{-8}
Pyrazinamide	1×10^{-3}

Table 1: Mutation rates of selected drugs.

In the treatment using a first line drug, the number of TB bacilli is decreased due to the action of drug in killing the organisms. Even though, some of the organisms survive and become drug resistant mutants.

The multiplication of these mutants gradually leads to production of sufficient number of bacilli enough for reappearance of symptoms. This is termed "the fall and rise phenomenon". Resistance is produced automatically for every anti tubercular drug each at one time gradually. The main aim of modern therapy for tuberculosis is to control the multiplication of the resistant mutants.

This can be achieved by using multiple drug regimens (not less than three anti-tubercular drugs) which can control the resistant mutants to 10-18 times. Wild type bacilli are more resistant and survive while others which show resistance to only single drug will be destroyed [5-8].

Multidrug transporters

Multidrug transporters contain trans-membrane efflux proteins that actively pump out a broad range of compounds from the interior of the cell, using either proton motive force or ATP supplied energy. They are responsible for acquiring resistance of a multitude of organisms to various drugs.

P-glycoprotein is a human analogue of these multidrug transporters and is expressed on immune effector cells. Infection by *M. tuberculosis* results in increased expression of P-glycoprotein and decreased accumulation of Isoniazid and Rifampicin inside the cells [9-11].

Occurrence of resistance to anti-tuberculosis treatment

Incomplete and inadequate treatment

It mainly occurs with usage of monotherapy (with single drug). This may also be due to ignorance, use of penicillin/streptomycin combinations, use of rifampicin for other diseases, and economic constraints.

Inadequate treatment compliance

Poor compliance due to improper knowledge and care is also responsible for development of the resistance. Demographic factors and socio-economic status do not show effect on degree of compliance while psychological factors can effect compliance [12,13].

Relation between dose and drug resistance

A drug shows its action at different doses in different individuals. This is because a drug does not show same concentration versus time profile in all subjects.

It indicates that low plasma drug concentrations can lead to emergence of drug resistance. The response of the pathogen to a particular drug is related to concentration– time profile.

For *M. tuberculosis*, during the initial phase of treatment, the shape of the concentration– time curve is U shaped (Figure 1) indicating that drug exhibited its action. As the time passed, the curve changed to inverted U shape (Figure 2), indicating the development of resistance of *M. tuberculi* to drug [14].
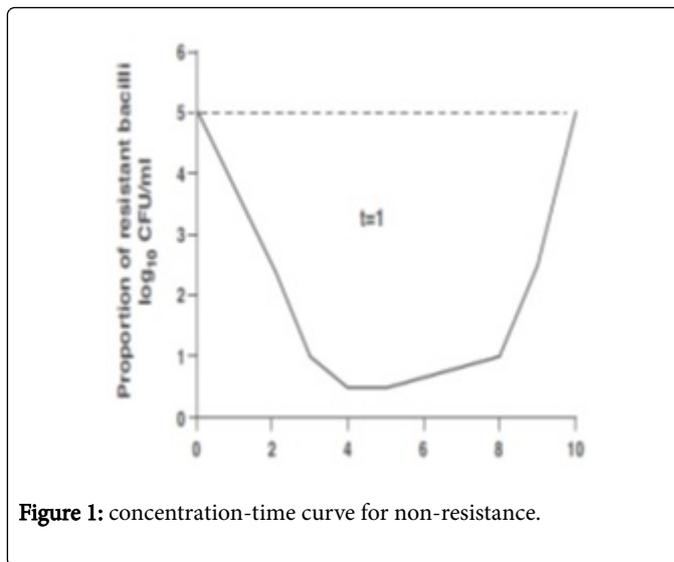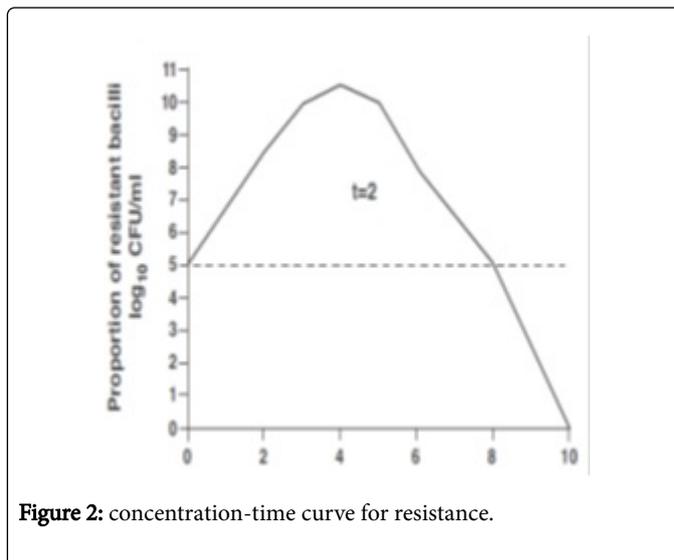

Figure 1: concentration-time curve for non-resistance.

Figure 2: concentration-time curve for resistance.

Diagnosis

When multi drug resistant tuberculosis is suspected, it is confirmed by sending the patient's sputum to anti tubercular drug sensitivity testing. The diagnosis of drug-resistant TB is made by performing Drug-Susceptibility Testing (DST) to the strain of TB obtained from the patient [15].

Diagnostic Methods

Patients with drug-resistant TB are divided into three major categories. They are:

1. Those who are in contact with drug-resistant TB.
2. Those who are previously treated.
3. Those with interrupted therapy [16,17].

Conventional methods

Mostly, Lowenstein-Jensen (LJ) culture is used for drug sensitivity testing.

The different conventional diagnostic methods are:

1. Absolute concentration method
2. The resistance ratio method
3. The proportions method

Absolute concentration method

In this method, the culture media and drug containing media is inoculated with a carefully controlled inoculum of *M. tuberculosis*. Minimum Inhibitory Concentration (MIC) of the drug is determined. Lower concentration of the drug inhibiting the growth indicates lesser resistance.

The resistance ratio method

This method uses minimum inhibitory concentration of a standard susceptible strain as standard to avoid variations.

The proportions method

It is the method of choice for evaluating the drug resistance. This method correlates the number of colonies increasing in size on drug hold medium to the drug free medium. It designates the segment of drug resistant bacilli available in bacterial population.

Modern methods

Radiometric methods are being used now-a-days in order to diagnosing tuberculosis. One of such methods is BACTEC-460 (Becton- Dickinson) method. In this, a medium containing palmitic acid labeled with radioactive carbon is inoculated with mycobacteria which slowly metabolize the palmitic acid. Due to this, radioactive carbon dioxide is released which is an indicator of bacterial growth [18-20]. The other most commonly used method is RFLP (Restriction Fragment Length Polymorphism) method. In this, fragment patterns are used to categorize the isolates of the organisms and compare them with each other [21]. The Mycobacterium Growth Indicator Tube (MGIT) system is another method which is used for detection and susceptibility testing. This system utilizes an oxygen-sensitive fluorescent compound in a silicone plug placed at the bottom of tube containing the medium and is used to detect mycobacterial growth [22,23].

Objectives of Anti-TB Treatment

1. Rapid decline of bacterial count which decreases morbidity and mortality and to cease transmission.
2. Prevent the out broke of drug resistant variant strains, and
3. Prevent the worsening of condition.

Prevention of Resistance

1. Isoniazid which is the most potent prophylactic drug is used predominantly in the first week followed by rifampicin to prevent resistance.
2. To avoid drug resistant variants, use multiple drugs which shows evidence on efficacy.
3. Treatment is advised for adequately long period, with examining of attachment to treatment, to eradicate the remaining surviving organisms that are accountable for the worsening of condition.

4. Almost all the successful mode of averting drug resistance is to adhere to the authoritative recommendations for treatment and make sure that all doses taken correctly.

Re-treatment

For patients classified as therapy failure the WHO recommends the re-treatment regimen with in a span of eight months. The regimen is made up of three drugs (isoniazid, rifampicin, and Ethambutol). In addition to this, pyrazinamide is specified all over the first three months and streptomycin all over the first two months. Uncertainty mycobacterial culture and *in vitro* sensitivity testing are not regularly conducted. Because, it is not feasible to institute whether these cases are evacuating the multidrug-resistant bacilli. Supplemental management of oral ofloxacin was established to be potent and secure for the treatment of MDR-TB. Pefloxacin having high safety profile and is inexpensive so it was scrutinized to be an efficacious associate drug in selected cases. Sparfloxacin is assimilated with kanamycin specified during the first three to four months. And finally ethionamide management was helpful in attaining sputum conversion, clinical and radiological development. Other prophylactic agents like carbapenems exhibit optimistic effect and supportable in incorporation with clavulanate for management of MDR-TB (Table 2) [24].

Resistance pattern	Alternative treatment options	Duration of therapy (months)
INH	RIF, PZA, EMB (FQ)	6-9
RIF	INH, PZA, EMB, STR or INH, PZA, EMB, FQ (STR)	9
INH, RIF, PZA	FQ, INJ, second-line therapy	24
PZA	INH, RIF, EMB	9
EMB: Ethambutol; FQ: Fluoroquinolone; INH: isoniazid; INJ: Injectable Agent (Capreomycin, Kanamycin, Amikacin); PZA: Pyrazinamide; RIF: Rifampin; STR: Streptomycin.		

Table 2: Possible drug administrations for patients with tuberculosis with diverse standards of drug resistance.

Newer anti-tuberculosis drugs

TB medication has been persistent for a period of ten years and frequently composed of acquiring ten pills per day to a greater extent for a least possible of six months. In case of MDR-TB, twenty pills per day for 18-24 months. At present accessible second-line drugs used to treat MDR-TB are four to ten times more acceptable to fail than standard remedy for drug non resistant tuberculosis. This prolonged regimen is not only more expensive than first-line antibiotics, but also appears with severe toxic side effects and psychological stresses. In sequence to oppose MDR and XDRTB and the generally expand of antibiotic unaffected TB strains, the requirement of newer anti-TB drugs is upcoming. In 2012 and 2013, two new anti-tubercular drugs were approved. They are Bedaquiline and Delamanid. Bedaquiline (diarylquinoline derivative) acts by inhibiting bacterial ATP synthetase and possess potent activity against drug resistant and drug sensitive *M. tuberculosis*. Delamanid (nitro imidazole derivative) acts by inhibiting synthesis of cell wall components. In the last few months, a sequence of compounds hold a nitroimidazopyran nucleus that own anti tubercular activity have been discovered and are under trials [25].

Drugs under Trials

TMC207

It is a novel diarylquinoline and is also known as R207910. It acts by exhibiting its effect *in vitro* as an antibacterial agent against oxidative-reproduction, drug-susceptible, MDR *M. tuberculosis*, antibiotic-sensitive *M. tuberculosis*. It particularly prevents the mycobacterial ATP-synthase, consequently decreasing bacterial energy output in the form of ATP molecules [25,26].

PA-824

It is a nitro-imidazoles derivative (nitroimidazo-oxazine). PA-824 is a prodrug which needs stimulation by bacterial de-hydrogenase and nitro-reductase to obstruct mycolic acid (important constituent in cell layer of mycolata taxon responsible for pathogenicity) synthesis. Moxifloxacin and pyrazinamide are indicated as antibacterial agents exhibiting their activity against tuberculosis in mice [27,28].

OPC-67683

It is a dihydroimidazo-oxazole. It possesses potent antibacterial activity against antibiotic susceptible and MDR *M. tuberculosis* both in *in vitro* and *in vivo* conditions. It acts by inhibiting mycolic acid output in the cell wall [29].

Though the finding of latest anti-TB drugs with less resistance are in progress under trials, their invention and expansion is quiet complex and expensive ($800 million to $1 billion)

Recommendations for therapy of patients with MDR-TB

When susceptibility experiment investigations are accessible and there is an opposition to isoniazid and rifampicin but with or without resistance to streptomycin. In the beginning period, an association of ethionamide, fluoroquinolone, and other bacteriostatic drugs such as ethambutol, pyrazinamide and aminoglycoside like kanamycin, amikacin, or capreomycin are administered for three months up to the time of sputum transformation.

In continuation phase, ethionamide, fluoroquinolone, and other bacteriostatic drug such as ethambutol can be used for not less than 18 months following stain transformation.

On condition that there is resistance to rifampicin and ethambutol but with or without resistance to streptomycin throughout the starting period and an association of ethionamide, fluoroquinolone and other bacteriostatic drugs such as cycloserine, pyrazinamide, and aminoglycosides like kanamycin, amikacin, or capreomycin are used for three months.

TB-DOTs (Directly Observed Treatment, Short Course)

DOTS programs have been developed to control the unacceptable failure rates and to combat the resistance of drug resistant mutants against anti-tubercular drugs.

The main five elements of DOTS strategy are:

1. The therapy may require being categorized rather than standardized;
2. Laboratory facilities may be required to supply resources for on-site culture and antibiotic susceptibility testing;

3. Authentic supplies are an extensive area of expensive second-line drugs;
4. To regulate the manifestations needed some operational studies and
5. Economic and scientific support from international organizations and Western governments must be required moreover procured from local governments [30-32].

Preventive measures

1. Isolation of the effected patient to a separate room and changing the air inside about six times for every hour.
2. Room should be ventilated using ultraviolet lamps or HEPA filters to supplement ventilation;
3. Use of disposable masks for persons entering the room to avoid spreading.

Immunotherapy in MDR-TB

As *M. tuberculae* is pathogen, immune system improvement can play a major role in combating the organisms. This can be achieved in a number of ways:

1. Vaccination: Vaccination for tuberculosis stimulates the host's immune system and protects the individual by enhancing the eradication of mycobacterial population. BCG vaccine (Bacillus Calmette Guerin): It is the most commonly used TB vaccine though other vaccines are also available which are under use and trials. It is highly affordable and safe when compared to other vaccines. The BCG vaccine is usually administered at birth and at an early age of 4-6 weeks to provide protection against all kinds of tuberculosis. However, babies with HIV/AIDS should not be vaccinated. BCG vaccine is not generally given to adults as the results are variable.
2. Cytokine therapy: It includes administration of interferon-γ (IFN-γ, 500 μ thrice weekly) and interferon-α (IFN-α, 3MU thrice weekly). These interferons help in activating the macrophages which inhibit multiplication of mycobacterial population.
3. Miscellaneous: The miscellaneous agents mainly used include Thalidomide and pentoxifylline Other agents include levamisole, transfer factor, Transforming Growth Factor (TGF) inhibitors, and agents involved in IFN-α generation [33].

Surgery

Surgery accounts for lower death rate with less than 3.5% though respiratory complications may persist.

The important factors responsible for death rate are severe chest irradiation, pulmonary abscission, extreme pulmonary damage, any other microbial infections and sputum positivity.

Conditions for performing surgery:

1. Presence of MDR-TB irrespective of prolonged treatment; and/or
2. Substantial standards of drug resistance that are related with treatment collapse or auxiliary resistance.
3. Internal cavitary, necrotic illness in a lobe of the lung was modified during abscission without developing respiratory insufficiency and extreme pulmonary hypertension [34-37].

Nutritional support

Nutritional support plays a key role in treating MDR-TB patients. The first line and second line anti-tubercular drugs are highly efficacious and can cause abdominal pain, headache, nausea, dizziness and diarrhea interrupting with food absorption. This ultimately results in decreased body weight and weakness. Dietary supplementation in such patients must include milk and cod liver oil (Table 3) [38-40].

Types of nutrients	Examples
High calorie foods	Banana, whole wheat bread, coconut milk, avocados, chia seeds, walnuts, pine nuts, blueberries.
High protein foods	Eggs- 6 g per 1 large egg, Milk-8 g per 1 cup, whey protein-24 g per scoop, chicken breast-24 g per oz, canned legumes-20 g per 1 cup, peanuts-6 g per 2 oz, cashews-6 g per 2 oz, almonds-6 g per 2 oz, green peas-7 g per 1 cup, Wheat germ-6 g per 1 oz, ground nuts-38 g per 1 cup.
Vitamins	Vitamin C rich juices like Orange juice, a powerful antioxidant that can help the body to fight against tuberculosis bacillus. Carrot, tomato, gooseberry, and pine apple juices. Vitamin A rich foods like Orange, mango, papaya, sweet pumpkin, carrots.
Minerals	Zinc rich foods like pumpkin seeds, dark chocolate, sesame seeds, watermelon seeds, wheat germ, chickpeas, squash seeds. Selenium rich foods like Brazil nuts, fortified eggs, flax, spinach, beef liver, sardines. Iron rich foods like red meat, sea food, beans, apricots, raisins.

Table 3: Nutritional chart for TB

Conclusion

Not only regarding tuberculosis, but also in relation to other microbial and infectious diseases, resistance towards antibiotics results in treatment failures, progression of disease and infections.

So, treatment should be directed towards using drugs which either suppress the resistance of organisms towards antibiotics or improve the efficacy of other anti-TB drugs. Resistance repression is explained as one medication intercept the resistance to another, but not one drug intercept the resistance to itself. By taking appropriate measures and strictly following the therapy, the MDR-TB might be suppressed to a greater area.

Acknowledgement

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