

Multi-Drug Resistant Tuberculosis

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Introduction

Tuberculosis (TB) is a pandemic and half of the cases are in six Asian countries (Bangladesh, China, India, Indonesia, Pakistan and the Philippines). MDR-TB arises due to improper use of anti TB drugs in the drug susceptible TB patients.¹ It is a major health issue, its treatment is more expensive, of a longer duration and gives less than ideal cure rates with higher relapse rates. According to WHO reports, TB is the second largest contributor among infectious diseases to adult mortality. WHO estimates that at least one third of the world population is infected with Mycobacterium Tuberculosis.

HIV/AIDS and TB are closely connected; the term “co-epidemic” or “dual epidemic” is often used to describe their relationship. The incidence of MDR-TB is astonishingly high in HIV/AIDS patients. Patients who are HIV positive have an increased bacterial load due to poor T-cell immunity, higher the bacterial load more the number of drug resistant mutants and there is a problem of drug absorption in these patients due to chronic diarrhoea. Sub-optimal therapy is another reason for development of drug resistance.

Definitions

Primary Drug Resistance : Presence of a drug resistant strain in a person who has never in the past received anti-tuberculosis treatment.

Acquired Drug Resistance: Drug resistance

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in a patient who has received at least one month of prior anti-tuberculosis treatment.

MDR-TB (Multi-drug resistant tuberculosis) : This is defined as tuberculosis bacilli resistant to at least isoniazid and Rifampicin, the most powerful anti-tuberculosis drugs.

XDR-TB (Extensive/extreme drug resistant tuberculosis) : Tuberculosis bacilli are resistant to fluoroquinolones and at least one of the 3 injectable second line drugs (Capreomycin, Kanamycin and Amikacin) in addition to being resistant to isoniazid and rifampicin.²

Pathogenesis of MDR-TB

One of the main reasons for the development of MDR-TB is primary infection with resistant tuberculosis bacilli. Injudicious use of anti tuberculosis treatment is another cause for development of MDR-TB. Two types of patients are more likely to develop resistance, these are patients who attain abnormally low serum levels of anti-tuberculosis drugs and patients who have a weakened immune system example those people who are infected with the human immunodeficiency virus. Since in both a large bacterial load is present the probability that they harbour resistant mutants is greater.

Mutation is the most important cause of development of resistance in tuberculosis bacilli. Higher bacterial loads means more number of drug resistant mutants. In 10^6 bacteria at least one bacteria is found resistant to isoniazid. In 10^7 one mutant bacteria is resistant to streptomycin, one in 10^9 bacilli is resistant to rifampicin, in 10^{14} bacteria one

is mutant to both rifampicin and isoniazid.³ More cavities in the lungs mean a higher bacterial load which means more number of mutants resistant to anti tuberculosis drugs.

Development of resistance can also occur due to numerous patient related causes and doctor related causes. Patient related causes include social factors like alcoholism, drug addiction, poverty and poor understanding of side effects. The doctor related causes include improper drug regimens with improper dosages and poor patient education about the side effects of the medication which often lead to defaulters. Poor drug availability is another factor leading to disrupted treatment and increase in MDR-TB.

Once the treatment of tuberculosis is initiated, the susceptible bacteria decrease which causes a decrease in the bacterial load. But after sometime the mutant bacteria not susceptible to anti tuberculosis drugs start multiplying which causes an increase in the bacterial load. This phenomenon of decrease and then increase in the bacterial load is called the *"Fall and Rise"* phenomenon.

Diagnosis of MDR-TB

A crucial step in the diagnosis and treatment of MDR-TB is the culture sensitivity reports. Laboratories able to report drug sensitivity to anti-tuberculosis drugs are available mostly in the bigger cities highlighting the lack of laboratory facilities in countries most affected by MDR-TB. Since a large Indian population resides in the rural areas and MDR-TB is widespread it is incorrect only to rely on culture sensitivity reports for diagnosis of MDR-TB. Physicians must be trained to diagnose MDR-TB on clinical grounds and on AFB smear, the diagnosis should be supported with culture sensitivity reports whenever possible. When making the diagnosis of MDR-TB on clinical grounds a few important points should be kept

in mind.

"Fall and Rise" phenomenon, a patient who has persistently positive sputum for AFB after 3 months of intensive phase chemotherapy, persistent fever for greater than 1 month in patients with persistent cavities seen radiologically and sputum AFB positive most likely is MDR-TB. History of contact with cases of MDR-TB must be elicited since chances are that the person is primarily infected with resistant bacilli.

Radiology alone should not be used to make a diagnosis of MDR-TB. Pure radiological worsening, fresh shadows on X-ray does not mean that the patient has MDR-TB. New lymph nodes, increased size of previously palpable lymph nodes and development of pleural effusions while the patient is on treatment do not indicate infection with MDR-TB.

Sometimes existing cavities grow atypical mycobacteria which are reported as AFB sputum positive, caution should be exercised while labelling such patients as MDR-TB. A culture is useful in differentiating atypical mycobacteria from mycobacterium tuberculosis.

Radiometric BACTEC 460 TB method. This technique uses carbon 14 labelled palmitic acid in 7H12 medium and is specific for Mycobacterium growth. This detects the presence of mycobacteria based on their metabolism rather than visible growth. Carbon 14 labelled substrate present in the medium is metabolized and 14 labelled carbon-di-oxide is produced and measured by the BACTEC system instrument and reported in terms of Growth Index (GI) values.

Using this method drug susceptibility test can be performed for all anti-TB drugs when sufficient Growth Index (GI) is observed. Mycobacterium can be detected in half the time compared to conventional culture

methods such as the Lowenstein–Jensen medium.⁴ The BACTEC radioactive liquid medium is the fastest way of measuring resistance with results available in less than ten days after isolation of organism.⁵

Treatment of MDR-TB

Drug therapy for MDR-TB has to be formulated carefully for which one has to take a good history which includes previous treatment history which should have details such as which drugs have been taken previously, at what strength, for how long and an assessment about the response achieved in the past to anti-tuberculosis drugs given should be made. Drug interactions and cross resistance must be kept in mind when formulating a chemotherapy regimen.

It is important to discuss with the patients and the relatives the cost and duration of the therapy. Possible adverse effects should be mentioned. The role of surgery (if required) should be explained. Ensuring compliance before starting therapy is an important step towards successful treatment and cure. Drug therapy should be individualized and a single drug should never be added to a failing regimen. It is important to formulate treatment with help of experts since an effective treatment is essential to prevent XRD-TB which has a very high mortality rate. At least 5 to 6 new drugs which have never been taken before should be part of the drug regimen and one of them should be parenteral. It is important to remember that culture sensitivity reports should not be solely relied upon since the intra-laboratory variation is considerable with these. Once the patient is started on formulated anti tuberculosis treatment the culture sensitivity report is awaited which is available in 6 to 8 weeks. Once the report is available the treatment is changed if needed. The change is based on the culture sensitivity report, the

patient's response seen clinically, radiologically and if patient has become sputum negative. Sensitive drugs can be added to the existing successful regime rather than changing it completely.

The duration of treatment is between two years to two and a half years but may even extend to three years. Anti tuberculosis treatment given in the past can affect the formulation of the present anti TB regimen; example Pyrizinamide(PZA) is used in the intensive phase regimen and later on discontinued hence our observation is that PZA can be used in the chemotherapy for MDR-TB. Similarly Ethambutol is bactericidal at higher doses and can be included as one of the second line drugs. These drugs have lesser side effects, are effective and cheaper.

We feel that fluoroquinolones should be avoided as first line drugs to make them useful as effective second line drugs. Resistance to a single fluoroquinolone means reduced sensitivity to all fluoroquinolones. Example patients resistant to Ofloxacin are also resistant to ciprofloxacin, resistance to kanamycin may indicate resistance to streptomycin as well, and if patient is resistant to amikacin then resistance to kanamycin and streptomycin may also exist.

Another drug used is thiacetazone, which can be used in combination with isoniazid.⁶

New Anti-tuberculosis drugs are the need of the hour. There are some promising new drugs at the stage of clinical trials like diarylquinoline TMC207, nitroimidazole PA - 824, diamine SQ -109 to name some.⁷

While being treated the patient response is measured with the help of clinical improvement, radiological improvement, sputum staining and culture reports.

Different second line regimens come with their own set of side effects and these must

be explained to the patient to ensure compliance and to minimize side effects. Initiation should be done with small doses and the planned dose should be reached in 3 to 10 days .

Complications of 2^d line drugs are many and severe, these include:

- 1) Hypothyroidism with ethionamide and PAS.
- 2) Neurotoxicity with linizolide and cycloserine.
- 3) Nephrotoxicity and ototoxicity with aminoglycosides.
- 4) Severe peripheral neuropathy and rashes.
- 5) Tender gynaecomastia with PAS and ethionamide.
- 6) Suicidal tendencies with cycloserine
- 7) Bone marrow suppression with PAS
- 8) Optic neuritis with ethambutol when it is used in high doses.

Just to mention some. Success rate for treatment of MDR-TB is around 70-75% whereas 20% may relapse.

Surgery and MDR-TB

Once upon a time before the onset of chemotherapy era, surgery was considered the line of treatment for tuberculosis. The surgeries included lobectomy, pneumonectomy, plumbage, phrenic nerve paralysis, pneumoperitoneum and thoracoplasty. But after the onset of the chemotherapy era for the treatment of tuberculosis the surgical treatment took a back seat. Today due to the presence of MDR-TB and XDR-TB surgical treatment has made a comeback. Selection of patients and optimizing them pre operatively is essential to the successful outcome of treatment.

- 1) Patient should be on optimal therapy for at least three months before the surgical procedure with an average of 6 to 7

Drugs Used in Treatment of MDR-Tuberculosis

Table 1 : Drugs and dosages of anti tuberculosis medication⁸ used in treatment of MDR-TB

Drugs Used	Usual Adult Daily Dosages
Ciprofloxacin	250 mg b.i.d
Ofloxacin	400 mg b.i.d
Levoflox	750 mg od
Moxiflox	400 mg od
Ethionamide	250 mg b.i.d or t.i.d
Para – aminosalicylic acid	10-12 g/day
Cycloserine	250 mg b.i.d or t.i.d
Roxithromycin	300 mg b.i.d
Azithromycin	500 mg o.d
Clarithromycin	250-500 mg b.i.d
Linizolide	300-600 mg b.i.d
Inj Kanamycin	15 mg/kg
Inj Amikacin	15 mg/kg
Inj Capreomycin	15 mg/kg

sensitive drugs. The chemotherapy is continued post operatively and the duration of chemotherapy remains the same regardless of surgical treatment.

- 2) Since these patients may have treatment failure with medical treatment surgical treatment maybe the only option provided the disease is localized and the patient has an adequate pulmonary reserve. As far as possible patient should be made sputum negative prior to surgery.
- 3) High resolution CT scan should be used to evaluate the presence of persistent thick walled cavities which harbour dormant tuberculosis bacilli, these increase chances of relapse and are an indication for surgery. These are also used to see if the rest of the lung is normal or has minimal disease.
- 4) Prior to surgery, a fibre optic bronchoscopy is warranted to assess the tracheobronchial status; especially stenosis and endobronchial disease which

increases the possibility of developing a bronchopleural fistula.

- 5) During surgery maximum possible diseased lung tissue should be removed.⁹ The surgery options are lobectomy and pneumonectomy though some patients end up undergoing extensive surgeries. Some patients require thoracoplasty which involves removal of rib, so that the thoracic wall collapses obliterates the space remaining after lobectomy or pneumonectomy, these spaces are due to bronchopleural fistulas which are a complication of surgery and responsible for morbidity in these patients. Bronchopleural fistula which happened during a lobectomy can be treated immediately with a thoracoplasty, this is primary thoracoplasty. If thoracoplasty is done after a period of time following a lobectomy to treat bronchopleural fistula it is called secondary thoracoplasty. In patients with bilateral disease it is not possible to do pneumonectomy or lobectomy. Palliative surgery is considered. Patients who are persistently sputum positive or have haemoptysis with cavities undergo thoracoplasty as palliative surgery.
- 6) The anaesthetist should be well trained, experienced and should use a double lumen tube for intubation. Epidural analgesia post operatively is extremely important for pain control and decreases post operative complications. Good ICU backing and a physiotherapist have a crucial role in a successful post-operative outcome.
- 7) Despite disfiguring surgery, in some patients removal of the diseased tissue somehow builds up the patient's confidence and self esteem, due to reassurance that he or she is now disease free and non infectious.

Summary

It has been estimated that only 10% of MDR-TB will be treated in 2008, mainly because the countries with the highest load of MDR-TB are also the ones most lacking in availability of effective diagnostic techniques, finances and supply of medication.¹⁰ Treatment of MDR-TB is expensive and prolonged. The cost of therapy is around five to six thousand per month. Considering additional periodic investigations and duration of treatment; it actually costs a minimum of three to four lakhs. This apart from loss of working hours and mental trauma to patients and their families. Successful treatment of MDR-TB needs physicians who are trained to diagnose MDR-TB clinically and formulate effective treatment regimens supported by culture sensitivity reports whenever possible. Experts need to be involved in the diagnosis and treatment of all suspected cases. Patient education about side effects and importance of adherence to the treatment is a must for successful treatment of MDR-TB.

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