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REVIEW PAPER

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Multi Drug Resistant Tuberculosis

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ABSTRACT

Introduction. Tuberculosis is one of the oldest infections known to mankind. Of all infectious diseases, tuberculosis causes the most fatalities of any infection. The incidence of tuberculosis on the rise due to the increased prevalence of HIV infection. The incidence of drug resistance strains of mycobacterium is also on the rise. When the mycobacterium is resistant to both INH and rifampicin it is called multi drug resistant tuberculosis. There is a primary and an acquired type of drug resistance. Multidrug resistant tuberculosis is a not only a problem for the patient but also for society at large. The treatment of multidrug resistant tuberculosis requires an entirely different approach.

Aim. In this review, we are going to describe the etiopathogenesis, diagnosis, investigations and treatment of multi drug resistant tuberculosis.

Material and methods. Analysis of the current literature.

Results. Genetic factors, previous treatment, and other factors predisposes the onset of drug resistance. By early detection and prevention of spread of drug resistant strains we can prevent the spread of resistant strains.

Conclusion. Drug resistance in tuberculosis is a very complex and dangerous problem. We have to prevent the development and spread of MDRTB. Good quality drugs should be used and made available to all sections of the population. Enhancing the National tuberculosis programs is the best way to attain an effective way to control this menace.

Keywords. BACTEC, MDRTB, multi drug resistant tuberculosis, *Mycobacterium,* tuberculosis

Introduction

Tuberculosis is believed to be as old as mankind's documented history. It is associated with poverty, malnourishment and poor hygiene and hence is more common in developing countries.[1] The incidence is gradually increasing all over the world. There is resurgence of tuberculosis associated with emergence of HIV infection worldwide. One third of cases are found to live in South East Asian countries.[2] It is the single largest cause of death due to infection. The incidence varies in different parts of the world from 10 per 100,000 (North America), 100 to 300 per 100,000 (Asia and Western Russia) and more than 300 per 100,000 people in central and Southern Africa.[3]

Tuberculosis is caused by *Mycobacterium tuberculosis*. There are two strains of *Mycobacterium tubercu-*

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losis, human and bovine type. Most human infection is caused by the human type. Bovine type produces gastrointestinal infection especially in persons consuming unpasteurized milk. Initially mycobacterium was thought to be a bacteria living in the soil which caused tuberculosis like disease in animals. After man started domesticating cows the disease got transmitted to man. However, sometime later this theory was disproved by studying the genome of bovine and human species.[4] It was thought that migration of man to different regions helped in the spread to various parts of the world. Indo-Europeans spread TB to Asia and Europe.[5] Robert Koch was first responsible for identifying tubercle bacilli. According to Rene Dubos, environmental factors also play major role in the causation of TB.[6]

Pathogenesis and clinical features

Tuberculosis usually occurs as an aerosol spread. Sometimes it can occur following drinking unpasteurized milk, but is very rare nowadays. Hence, the most common form of TB is pulmonary. Extra pulmonary TB usually occurs as a result of spread from the pulmonary site. According to Walleran, there are four stages in the pathogenesis of TB. During the first 2 to 8 weeks following inoculation the bacilli enters into the lymphatic circulation and reaches the regional lymph node – Gohn complex. In the next stage, there is hematogenous dissemination of the bacilli to different parts of lung and other parts of body. In this stage, fatal disease like meningitis or disseminated tuberculosis can occur and can last for about 3 months. During next 2 years there can be pleurisy. It may be due to hematogenous spread or spillover of bacteria into pleural space. In the fourth and last stage, the disease regresses in most cases.[4,7] In non-HIV infected patients about 3-5 % develop extra pulmonary disease within a year. 3-5% of patients will have a deactivation of the disease later. This stage lasts for about three years. In HIV infected patients, more than 50% will have either a reactivation or get new infection. In either case, the lung is the most common site and disease is severe and progressive as compared to non HIV positive patients.[8]

Common clinical symptoms of tuberculosis are loss of weight, loss of appetite, malaise, etc. In pulmonary TB there will be cough, chest pain and hemoptysis. Back pain, spinal deformities and neurological deficits can occur in Potts disease whereas severe muscle wasting with painful limitation of movements and ankyloses occur in osteo-articular TB. Meningitis is common in neurological involvement. Diarrhea, anemia, weight loss in gastrointestinal variety and matted lymph node enlargement in lymph node involvement.[9]

When the infecting mycobacterium is resistant to both INH and rifampicin it is called multi drug resistant tuberculosis (MDRTB or MDR/RR-TB). Now we will go into the details about the commonly used anti-tuberculous drugs both first and second line and their characteristic features. After that we will discuss about the drug resistance, the mechanisms, investigations, prevention and WHO consolidated guidelines for drug resistant tuberculosis (2018).

Anti-tuberculous Drugs

INH is one of the most common bactericidal drugs used in the treatment and prevention of TB. Food interferes with its absorption. It is metabolized in the liver. It acts by inhibiting cell-wall synthesis. Rifampicin is another bactericidal drug. It inhibits DNA-dependent RNA polymerase enzyme. It is also metabolized in liver. According to concentration, pyrazinamide can be either bactericidal or bacteriostatic. It can be used for the treatment of MDRTB.[10] Ethambutol resistance can occur when administered to previously given patients. This can be prevented by administering along with a second line drug. Ethambutol inhibits production of various metabolites in the bacilli. Because of ototoxicity and nephrotoxicity, streptomycin is rarely used for the treatment. It is used for short periods along with other drugs when other less toxic drugs are less effective.[11] Levofloxacin is one of the common oral drugs given in MDRTB. It is a safe fluoroquinolone, acts by inhibiting bacterial topoisomerase 4 and DNA gyrase enzymes which are essential for DNA replication, repair and recombination. In MDRTB where the organism is sensitive to fluoroquinolone and other first line drugs cannot be used moxifloxacin is an option. It also acts by inhibiting bacterial DNA gyrase.[12] Rifapentine was an agent used along with INH in DOTS regimen twice weekly in the intensive phase and once weekly in the continuation phase. When used along with other sensitive drugs ethionamide can be used to treat any form of active TB. Ethionamide is a bactericidal or bacteriostatic second line drug according to its concentration. Amikacin and cycloserine are other second line drugs which can be used in MDRTB. Capreomycin is a second line drug which is effective when first line drugs are ineffective or cannot be used because of toxicity. Rifabutin is particularly effective second line drug especially in people with HIV on treatment where rifampicin is contraindicated. Para-aminosalicilic acid can prevent the onset of resistance to INH and streptomycin. When used along with other drugs it is effective in MDRTB. Clofazimineis very rarely used for treating MDRTB.[13,14] Budaquiline is a diarilquinoline which acts by inhibiting mycobacterium adenosine 5-diphosphate synthetase by breaking the pathway for energy generation. It is reserved drug for treating MDRTB when other treatment regimens are ineffective for MDRTB of lung.[15]

In a tuberculosis granuloma, there will be rapidly dividing bacilli and non-rapidly dividing bacilli. The central

caseous area is relatively hypoxic and having low metabolic activity. Here the non-rapidly dividing bacilli become non-dividing. They are called persisters or dormant bacilli. They cannot be killed by usual drugs or body's immune mechanism. They get reactivated once immune system is weak. Prolonged treatment is necessary to eradicate the non-rapidly multiplying or dormant bacilli. Both these types are resistant to bactericidal drugs. But prolonged treatment with second line drugs is showings some promising results. INH is the most potent drug for Sputum conversion and preventing transmission. Rifampicin helps to sterilize the colony by preventing relapse.[16,17]

Drug resistance in tuberculosis

According to WHO, in 2016 there was a 4.1% increase in new occurrences of resistant tuberculosis and about 19% of the existing patients develop resistance to one or more drugs. There are 123 countries from which at least a case of extensive drug resistance is reported (XDRTB). XDRTB means resistance to at least four core anti tuberculosis drugs. It can involve MDRTB. 88% of MDRTB casea are seen in middle or high income countries. Out of these, 60% occur in China, India, Brazil, Russia and Africa. In some eastern European countries, more than one third of cases of tuberculosis is MDRTB. In 2012 more than 90% of notified cases of MDRTB are from 30 countries. There is an increased incidence of MDRTB due to increased incidence of HIV infection.[18]

A combined resistance to both INH and Rifampicin is called multi drug resistant tuberculosis (MDRTB). It can be associated with resistance to other drugs also. To establish the diagnosis of MDRTB the organism must be cultured to get a sensitivity test in-vitro. Most of the MDRTB patients are labelled as treatment failures, re-treatment failures and chronic cases. The problem of MDRTB is not only for the patient themselves but to the entire society due to spread of resistant bacilli in the community.[19]

Primary resistance is the resistance of the bacilli in a patient who has never been exposed to that drug. It can be resistance seen in wild strain or when the bacilli become resistant due to exposure to that drug in another patient earlier. Initial resistance include primary resistance, and the patient can conceal exposure to drugs and developed resistance often unknowingly. Acquired resistance is the resistance developing due to exposure to a particular drug. It is very difficult to establish this diagnosis because it may be bacilli which developed primary resistance in another patient. To diagnose acquired resistance we have to culture and verify the sensitivity of the drug before and after developing resistance which is not possible always. So drug resistance among previously treated patients will be a better term rather than acquired resistance. Resistant strains can grow in a high concentration of antibiotics.[20,21]

Chromosomal mutations occurring in *Mycobacterium tuberculosis* is the reason for drug resistance. They occur at a predictable rate. Resistance to one drug doesn't cause resistance to an unrelated drug because these mutations are unlinked. The number of bacilli in a tuberculosis lesion is about 10 million to 100 million and the chance of developing spontaneous resistance to both INH and Rifampicin is due to spontaneous mutation is very remote. Hence scientists now believe that perturbation in the individual drug target genes is responsible for primary resistance to multiple drugs in tuberculosis. It is said that if there is resistance to Rifampicin there is probability of resistance to other drugs also.[22]

Drug

- Isoniazid
- Rifampicin
- Pyrazinamide
- Streptomycin
- Ethambutol
- Fluoroquinolones
- Enoylacpreductase (inhA)
- Catalase-peroxidase (katG)
- Alkyl hydroperoxidereductase (ahpC)
- Oxidative stress regulator (oxyR)
- RNA polymerase subunit B (rpoB)
- Pyrazinamidase (pncA)
- Ribosomal protein subunit 12 (rpsL)
- 16s ribosomal RNA (rrs)
- Aminoglycoside phosphotransferase gene (strA)
- Arabinosyltransferase (emb A,B and C)
- DNA gyrase (gyr A and B)

Diagnosis of MDRTB

The conventional methods involve culturing the bacilli in Lowenstien-Jensen medium (LJ medium). But the disadvantage is that it takes 6 to 8 weeks for obtaining sensitivity results. There are three conventional methods (1) absolute concentration method (2) the resistance ratio method and (3) the proportions method. In absolute concentration method the minimum inhibitory concentration (MIC) is determined by inoculating the control media and drug containing media with controlled inoculated of Mycobacterium tuberculosis. Mediums containing Sequential two fold dilution of each drug is used. In resistance ratio method the chance of intra and inter observer error is less. Here the MIC of the testing sample is expressed as the multiple of the MIC of the standard strain tested simultaneously. In proportion method there is no need to strictly control the size of inoculums. In this method, the number of colonies grown in the medium with and without drug is compared. There is a critical proportion of number of colonies expected to form from which the proportion of drug resistance bacilli is determined.[23,24]

Other advanced methods

It has been shown that liquid based medium can detect paucibacillary tuberculosis in a shorter time. BACTEC-460 is a liquid based medium, radiometric method. 7H12 medium containing palmic acid labelled with radioactive carbon is used. The amount of carbon dioxide produced due to metabolism of the bacilli is quantified. In this method, the results will be available within two weeks.

The BACTEC – MGIT (Mycobacterium growth indicating tube) is the most common liquid based medium for detection of bacilli from tissue other than blood, urine, and bone marrow culture. The IGT contains Middlebrook medium 7H9 broth supplemented with antibiotics and other enrichment materials. The inoculated tube is incubated at 36 degrees and continuously monitored by BACTEC 960 or manually for 42 days. Mycobacterial growth is detected by fluorescent indicator embedded in silicone at the bottom of the tube. Studies have shown that there are comparable results with both proportion method and BACTEC.[25]

Restriction fragment length polymorphism (RFLP) is a technique used for genome mapping. Here the DNA fragment is divided into pieces by restriction enzymes and divided fragments are separated according to their length using gel electrophoresis. This technique is used to categorize and compare the DNA sequence of *M. tuberculosis*. It is found that DNA fingerprinting of M. Tuberculosis is not changed during development of drug resistance. Hence, RFLP can be used to track the drug resistant bacilli in the community. Recently Fluorescent amplified fragment length polymorphism (FAFLP) is also used for genomic mapping of *M. tuberculosis*.[26]

Luciferase reporter mycobacterophage: Here a suitable mycobacterophage is identified which can infect *M. tuberculosis*. Using genetic engineering techniques, luciferin is taken up by mycobacterophage. Later the cultured sputum sample is infected with phage. If viable bacteria are present, light is produced in presence of luciferin. If there is absence of diminishing light on treating with a particular drug it is indicative of resistance. This technique is a rapid and affordable method of detecting tuberculosis and MDRTB which give results in 2 days.[27] In many parts of the world, rifampicin resistance is considered as a good predictor of MDRTB. FAST plaque TB-RIF is a bacteriophage based test for detecting susceptibility to rifampicin.

Polymerase chain reaction (PCR) is used to identify the genetic basis for drug resistance. PCR can detect recognized mutations and new mutations. PCR is not routinely used for detection of drug resistance, but target mutations of rpo - B are useful for detecting rifampicin resistance and used commonly. Line probe assay is based on a reverse hybridization method. It is also useful for detecting rifampicin resistance. It consists of PCR amplification of rpo-B gene.[28]

Predisposing factors for MDRTB

Genetic factors

It is shown that there is an increase in IL-2 levels and decrease in IL 4 and IL10 in patients with MDRTB. It has been shown that interleukin gene polymorphism is associated with drug resistance in tuberculosis. There is an increased predisposition for MDRTB in patients with HLA DRB*13, HLA DRB*14 in the Indian population and HLA DRBI*08032and HLA DQB1*0601 in the Korean population. The mechanism of resistance is mainly due to a barrier mechanism where there is decreased permeability or efflux of drug and enzymatic degradation.[29,30]

Previous treatment with anti-tuberculosis drugs

Previous treatment failures can relapse after successful treatment, discontinuation of treatment, inadequate treatment, treatment with single drug or addition of drug to a failing regimen. It is very difficult to treat patients with recurrence and treatments remain infective for long time. There is a four-fold association of previous incomplete treatment with MDRTB. Incomplete treatment means discontinuation of treatment during any phase of treatment. The main reason for discontinuing treatment are feeling of well-being after sometime, they feel that the treatment is doing no good to them and when a smear-positive case become smear-negative. Patients with supervised treatment regimen showed less resistance. There is increased risk of toxicity to treatment of MDRTB if they were treated with second line drugs during their previous treatment. According to WHO the prevalence of MDRTB is 22% (newly detected cases) and 60% in previously treated patients. Inadequate compliance to treatment due to any reason can leads to drug resistance. If a person is infected with a strain resistant to a medicine is given additional medicines along with resistant drug chance that the organism developing resistance to other drugs also. Poor quality drugs and inadequate supply of drugs can cause acquired resistance.[31]

Lack of resources for diagnosis and treatment

Tuberculosis is a disease of the past in most developed countries. Most of the burden of tuberculosis is in the countries with poor resources. Out of 9.4 million new cases of tuberculosis in 2008, 60% of cases were in Asia and 33% in Africa. One of the major causes for tuberculosis in poor / developing countries is poverty. It can lead to malnutrition, over-crowding and lack of access to free or accessible treatment. In developing countries lack of laboratory facilities for the diagnosis and lack of medical experts for the treatment of such patients make the problem of MDRTB even worse. Even though chemotherapeutic agents are available, second line drugs are costlier and need to be taken for a lon-

ger time making such treatment inaccessible for most people. More than that empirical treatment with second line drugs without definitely diagnosing drug resistance and lack of compliance can lead to increased prevalence of MDRTB in developing countries.[31]

HIV infection

There is an increased incidence of tuberculosis with HIV infection. The major cause of death in HIV infected patients is tuberculosis. There is an increase incidence of tuberculosis due to prevalence of HIV infection and also an increase in MDRTB. But there is no conclusive evidence to suggest that HIV infection is a cause for MDRTB. There is higher mortality for MDRTB treatment in adults even though the success rate of treatment for MDRTB is same irrespective of HIV infection status.[30,31]

Prevention of MDRTB

The first step to prevent spread of MDRTB is early detection and treatment of drug sensitive tuberculosis and making sure that they adhere to proper treatment regimen. Screening of at risk patients like immunocompromised patients and close contacts of tuberculosis patients should be done for early diagnosis. The causes for non-adherence to treatment must be analyzed and rectified. Social and financial support should be provided at times.

In areas where drug resistance is prevalent, early and prompt detection and proper treatment is essential to curtail the spread of MDRTB. In many low and middle income countries, the absolute number of MDRTB cases is more than the retreatment cases. Unfortunately, there is no routine test for detection of MDRTB in all cases; it is done only in retreatment cases. So a large number of MDRTB cases remain undetected. Hence screening for resistance must be done for new cases also though it is not practical in developing countries.[32]

General health levels and work level conditions needs to be improved. Make the general population well aware of the means of spread and problems of MDRTB. We have to take measures to prevent poverty, overcrowding, malnutrition especially in homeless shelters, refugee camps, nursing homes and boarding schools.

We have to improve the quality of health care. It should be available to everyone and should ensure that high quality medicines are available and accessible. Many countries have regulations which control the availability of first line drugs only through the national tuberculosis program (NTP). It has been found that many first and Second line drugs distributed through the private sector is of inferior quality. Over the counter sale of tuberculosis drugs should be banned. Make tuberculosis a notifiable disease. Government should make diagnosis and treatment of tuberculosis free of cost. There must be social protection schemes for the patients. These can help the patient to adhere to treatment.[33]

Treatment of MDRTB

For the purposes of treatment, drug resistant tuberculosis is divided into rifampicin resistant TB (RRTB) and INH and rifampicin resistance (MDRTB) and MDRTB associated with resistance to other drugs also. The common drugs used for treatment of resistant tuberculosis are classified as follows:

Group A (Fluoroquinolones)

Gatifloxacin, levofloxacin and moxifloxacin are the fluoroquinolone which are very effective in the treatment of RRTB and MDRTB. They should be included in the treatment of resistant tuberculosis unless contraindicated. The use of ciprofloxacin and ofloxacin as second line drugs is no longer recommended. High doses of group A drugs have shown benefits in RRTB and MDRTB with a high safety profile. It can prolong QT intervals so used cautiously with drugs like budaquiline, clofazimine anddelamind which are having the same effect.[34]

Group B (Injectable second line drugs)

Aminoglycosides like amikacin, capriomycin, and kanamycin are commonly included in the long term treatment regimen for RRTB and MDRTB. Due to potential side effects it is not recommended in children unless there is resistance to fluoroquinolones. Unless contraindicated, it should be included in the treatment. Streptomycin is not used as a second line injectable drug routinely. Only when other three drugs cannot be used and if streptomycin is sensitive, it is included in the treatment. We have to monitor the development of ototoxicity and nephrotoxicity when these drugs are used.

Group C (Other core second line drugs)

Ethionamide/prothionamide ,cycloserine or terizidon, linazolid and clofazimine are used in this order of preference. Prothionamide can replace ethionamideandterizidon for clofazimine. The main use of these core drugs is to increase the number of effective drugs in the intensive phase to four. If pyrazinamide cannot be included then other agent is added. Gastrointestinal side effects can occur with ethionamide and prothionamide. When used in combination with PAS can produce reversible hypothyroidism. Cycloserine causes neuropsychiatric side effects. Lactic acidosis, thrombocytopenia, andanemia can occur with linizolid.

Group D

These are agents which are not included in the core group of drugs. These drugs are added to core group of drugs unless there is resistance, no interaction with other drugs or pill burden. They are sub classified as follows.

D1 group

This group includes pyrazinamide, ethambutol and high dose INH. Pyrazinamide resistance is seen associated with RRTB and hence avoided when rifampicin resistance is present. Otherwise pyrazinamide is shown to produce success when added to any regimen. High dose of INH is found to be effective in RRTB. In short course regimens for MDRTB, high dose INH are an integral part of treatment. High dose INH is also effective in children even in HIV positive cases. Due to ocular toxicity, the use of ethambutol must be weighed against other factors.

D2 group

These include two newer drugs. WHO recommends their limited use. Unless a large series of RCTs available, their wide spread use of them is not common. The drugs available are delamind in children and adolescents and budaquiline in adults.

D3 group

These include para-aminosalicylic acid (PAS), imipenam – cilastatin, merepenamclavulanate , amoxicillin clavulanate and thioacetazone. PAS is found to produce poor success in the treatment hence its use is not recommended routinely. Imipenam and amoxicillin are having same adverse effects but they should be always used together with clavulanate. Until 1990, thioacetazone was used as a first line drug but stopped using because of severe skin reactions especially in HIV positive individuals. Hence its use is contraindicated in HIV positive individuals.

The WHO consolidated the guidelines on drug resistant tuberculosis in 2018, by dividing the second line drugs into three main groups.

Group A: Fluoroquinalones (Levofloxacin and Moxifloxacin), bedaquiline and linezolid. These drugs are highly effective and recommended to include in all regimens unless contraindicated.

Group B: Clofazimine and cycloserine or terizidone are conditionally recommended as agents of second choice.

Group C: This includes all other drugs that can be used when a regimen cannot be composed with Group A and Group B agents. These drugs are ranked by the relative balance of benefit to harm usually expected of each. They include kanamycin and capriomycin (not recommended for use in MDRTB regimen), gatifloxacin and high dose isoniazid, thioacetazone (not recommended). Clavulanicacid is used only as companion agent along with carbapenems.

Longer MDR-TB regimen drug composition

To start with a four drug regimen, all three group A agents and at least one group B agent should be included in MDR/RR -TB. At least three agents are included after bedaquiline is stopped. If only one or two agents are included from group A, both group B agents are to be included. If agents from group A and B cannot be included group C agents are added to complete it.

Kanamycin and capriomycin are not included in longer MDR/RR-TB regimen where as we can include levofloxacin and moxifloxacin. There is a strong recommendation for inclusion of bedaquilinein patients older than 18 years. Linezolid should be included in longer regimen. In the case of drugs like clofazimine, cycloserine, ethambutol,pyrazinamide, imipenam-cilastatin, morepenam and amikacin, there is conditional recommendation with very low certainty in the estimates of effects. There is conditional recommendation against the use of ethionamide or prothionamide, para amino salicylic acid in long term regimen. Clavulanic acid should not be included in the treatment of MDR/RR-TB longer regimen. Delamind may be included in long term regimen in children above 3 years

The total duration of a longer regimen treatment is 18 months and can be modified according to patient's response to treatment. At least 15 to 17 months of treatment after culture conversation is recommended for most patients and can be modified according to response to therapy. In longer regimen that contain amikacin or streptomycin an intensive phase of 6 to 7 months is suggested for most patients.

Short term regimen

In MDR/RR –TB patients who have not been treated for more than one month with second line medications used in short term regimen or in patients in whom resistance to fluoroquinolone or second line injectable agents has been excluded, a shorter MDRTB regimen of 9 to 12 months may be used instead of longer regimen.

The monitoring of patients with long term regimen is done using sputum culture instead of sputum smear microscopy to assess the response to treatment. This has to be repeated every month.

For patients with combined HIV and MDRTB, the antiretroviral treatment need to be started as early as possible, say, within 8 weeks of starting second line treatment for MDRTB.

Lobectomy or wedge resection of lung may be used along with recommended MDRTB regimen in indicated patients.

Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment.

Tuberculosis produces weight loss and cachexia. The exact mechanism is not known. Since tuberculosis affects malnourished and immunocompromised patients. It is more common for MDRTB to occur in such patients. It is said that tumor necrosis factor alpha by its catabolic ac-

tivity can also lead to cachexia. So it is essential to screen the nutritional status of the patients regularly throughout the treatment. Also necessary actions should be taken to improve the nutritional status of the patients.[34,35]

Several other treatments like immunotherapy using *M. vaccae*, using interferons and IL-2 are there for the treatment of MDRTB. But further research is needed before they can be used for treatment.

Conclusion

Drug resistance in tuberculosis is a very complex and dangerous problem. We have to prevent the development and spread of MDRTB. Good quality drugs to be used and made available to all sections of population. Enhancing the National tuberculosis programs is the best way to attain an effective way to control this menace.

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