

## PREVENTION OF MULTI DRUG RESISTANT, EXTENSIVELY DRUG RESISTANT AND TOTAL DRUG RESISTANT TUBERCULOSIS

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### INTRODUCTION

Tuberculosis occurs world wide and remains an important cause of morbidity and mortality in many countries. In 2013 there were an estimated 9 million new cases of tuberculosis and an estimated 11 million prevalent cases causing death to 1.5 million people globally. There were an estimated 2.2 million (26% of the total cases) new cases in India and 0.28 million people died in our country due to tuberculosis in 2013. It is a cause for concern as India stands first in terms of absolute number of cases, closely followed by China (1). It is a real paradox because pathogenesis, transmission, prevention, diagnosis and specific therapy are all well known for tuberculosis.

Ideally good chemotherapy should achieve 100% sputum conversion provided correct regimens are prescribed and taken. There will be hardly any relapse if duration of treatment has been sufficient and there will be no emergence of drug resistance. Every treatment failure should be regarded as a failure by the doctor. He has either prescribed a bad or unreliable regimen or he has failed to ensure that the patient takes the regimen as prescribed (2-4). Drug resistant tuberculosis has been reported since the early days of introduction of anti TB chemotherapy, but multidrug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) and more recently total drug resistant tuberculosis (TDR-TB) has been an area of growing concern, and is posing threat to global efforts of tuberculosis control. Prevalence of Drug Resistant TB mirrors the functional state and efficacy of tuberculosis control programmes and realistic attitude of the community towards implementation of such programmes (5). Poor TB control generates MDR-TB and the misuse of 2<sup>nd</sup> line drugs generates XDR-TB and TDR-TB. Drug resistance in our country is due to inadequate tuberculosis control services, less well trained doctors in modern chemotherapy, wide spread inadequate treatment by private practitioner of various systems of medicine and quacks and inadequate management of already drug resistant tuberculosis (6-10). Drug resistant tuberculosis is one of the important reasons of morbidity and mortality in tuberculosis

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The Global Tuberculosis Report 2014 estimated that 3.5% of newly diagnosed and 20.5% of previously treated Tuberculosis cases had MDR-TB. It has been estimated that 480,000 MDR TB cases emerged and 210,000 death occurred due to MDR –TB in 2013 globally. In India estimates showed that the prevalence of MDR-TB among new and previously treated patients was 2.2% and 15% respectively. It is estimated that 99,000 cases of MDR-TB emerge every year of which 62,000 were among notified cases of TB in 2013. XDR-TB has been reported in all regions of the world and it has become a serious emerging threat to global public health especially in countries with a high prevalence of Human Immunodeficiency Virus (HIV). 9% of MDR-TB cases were found to have XDR-TB. To date, a cumulative total of 100 countries have confirmed at least one case of XDR-TB (1). Although isolated reports, both published and unpublished, indicate the existence of XDR-TB in India, it is not possible as yet to estimate its magnitude and distribution from the available data. According to the data reported on XDR-TB from India, it varied from 1.5% to 11% of MDR-TB cases (11-14). XDR-TB has raised the possibility that the current drug susceptible TB will be replaced with a form of TB with severely restricted treatment options. This would halt the progress made in recent years to control TB globally. Thus it is evident that, MDR-TB, XDR-TB and TDR-TB is a man made problem and its emergence can be prevented. Management of MDR-TB and XDR-TB is more difficult, complicated, challenging and more costlier and so the saying "Prevention is better than cure" holds strength here. The present write up gives an

overview of general principles for treatment of Tuberculosis for the prevention of MDR-TB, XDR-TB and TDR-TB.

### **GENERAL PRINCIPLES FOR THE PREVENTION OF MDR, XDR AND TDR-TB**

General principles for treatment of Tuberculosis for the prevention of MDR, XDR and TDR-TB are as follows

1. No single drug therapy for treatment of tuberculosis as drug resistance usually follows and is permanent. Never add a single drug to a failing regimen. If he is getting worse, his bacilli may be resistant to all drugs being used. Adding one drug is the same as giving one drug alone. The patient will soon develop resistance to the new drug also (15).

2. All the drugs should be administered in single dose preferably, as serum peak concentration of drug has greater and more prolonged inhibitory effect on tubercle bacilli compared to minimum inhibitory concentration (MIC) in the serum following administration of the same dose in divided doses (16-17).

3. Use only standard, time tested drug regimens recommended by various national and international agencies.

4. Use drugs in adequate doses and for adequate duration.

5. Never use unreliable chemotherapy even for a short time.

6. Always prescribe good quality medicines if you are prescribing fixed dose combinations, make sure that they are of good quality as supported by frequent bioavailability test (18-20).

7. Be kind and sympathetic to the patient. He is much more likely to come back and complete his treatment if he has confidence in you and believes that you are his well-wisher.

8. Follow up the patient regularly, motivate and make sure that patient takes full recommended course of treatment for adequate duration. If possible make sure that some one sees the patient taking every dose (directly observed therapy).

9. Always assess adverse effects due to medications and address them quickly and adequately (21-22).

10. Use rifampicin only in tuberculosis or leprosy. Avoid misuse of rifampicin as it is one of the most potent

anti tuberculosis drugs available at present. Development of resistance to rifampicin will lead to multi drug resistant tuberculosis (MDR-TB).

11. Relapse after good and adequate treatment is rare. If relapse has occurred after good and adequate treatment or after too short duration of regular treatment, such cases can be treated with previously used drug regimens. Five drug (2SHREZ / 1HRZE / 5HRE) regimen would be much effective and safe (15).

12. In the group of previously treated patients with one or several courses of chemotherapy and who remain sputum positive (by smear and/or culture) three sub populations can be observed. (a) Patients existing bacilli still sensitive to all drugs. (b) Patients existing bacilli resistant to atleast isoniazid but sensitive to rifampicin.

(c) Patients bacilli resistant to atleast, isoniazid and rifampicin. The respective proportion of the three subpopulations varies according to chemotherapy applied in the community and number of courses of chemotherapy and type of regimens received by the patients. In the patients who have failed after the first course of chemotherapy, the proportion of patients existing bacilli sensitive to all drugs is usually higher than the proportion of two other subpopulations. For such patients WHO retreatment regimens of five drugs (2SHRZE/1HRZE/5HRE) under direct supervision can cure majority of patients having either sensitive bacilli or bacilli resistant to isoniazid and/or streptomycin but still sensitive to rifampicin (15-23).

13. In patients who have failed after several courses of previous treatment perhaps with bad or unreliable drug regimens or after two or more courses of chemotherapy under National Tuberculosis Control Programme (last being the fully supervised standard WHO retreatment regimen of five drugs), the proportion of patients with MDR-TB can be as much as 50-70%. Treatment of such patients requires expertise as planning of treatment is very complex and a mistake at this stage can be fatal (23-25).

14. Early suspicion, diagnosis and appropriate treatment of MDR-TB is essential to prevent morbidity, mortality and transmission of MDR-TB. MDR-TB *suspect* refers to any patient who fails a new treatment regimen (Cat I) or any Cat II patient who remains smear positive at the end of the fourth month of treatment or later (26-27). Ideally every such patient should be subjected to culture and Drug Sensitivity Testing (DST) for Mycobacterium Tuberculosis from a quality accredited laboratory before starting a retreatment regimen. Subsequently when the culture and DST report confirms MDR-TB, an appropriate treatment regimen containing

at least 4 new drugs, the patient has not taken previously or to which the bacilli is considered to be sensitive are given. There are 5 groups of Anti Tuberculosis drugs. Include drugs from group 1 to 5 in hierarchical order. Use any first line oral agent such as Pyrazinamide, Ethambutol, Rifabutin (Group-1) to which isolate is sensitive, use one injectable- Kanamycin, Capreomycin, Amikacin (Group-2), one fluoroquinolone- Levofloxacin, Moxifloxacin, Ofloxacin (Group-3) and add as many second line bacteriostatic agents- Ethionamide, Prothionamide, Cycloserine, Terizidone and Para-aminosalicylic acid (Group-4) to make up at least 4 effective drugs. Group-5 drug such as Bedaquiline, Delamanid, Clofazimine, Linezolid, Amoxicillin / Clavulanate, Thiacezalone, Imipenem / Cilastatin, High-dose Isoniazid and Clarithromycin are not recommended for routine use except where an adequate regimen is impossible with Group (1-4). Do not use ciprofloxacin as antitubercular drug. In standardized treatment, Drug Resistance Surveillance (DRS) data from representative patient populations are used to base regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen. This type of treatment regimen is followed in resource poor, low income nations like India. The Govt of India has thereby introduced the CAT IV as standardized treatment for MDR-TB patients which consists of 6-9 months of intensive phase comprising of Kanamycin, Levofloxacin, Ethionamide, Cycloserine, Pyrazinamide, Ethambutol followed by 18 months of continuation phase comprising of Levofloxacin, Ethionamide, Cycloserine and Ethambutol. Para-amino salicylic acid is included in the regimen as a substitute drug if any bactericidal drug (Kanamycin, Levofloxacin, Ethionamide and Pyrazinamide) or two bacteriostatic drugs (Ethambutol and Cycloserine) are not tolerated. All care providers must use proper and appropriate regimens in MDR and XDR-TB patients.

15. Treatment of XDR-TB is more difficult and expensive. Less powerful second line and group five drugs are required for treatment. Hierarchical system of drug groups usage applies in XDR-TB also. At least 5 drugs with proven susceptibility or which are most likely to be effective should be used. Use any Group 1 agents that may be effective. Use an injectable agent to which the strain is susceptible and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents, it is recommended to use one the patient has never used before. (strain may be resistant to injectable in vitro, though not necessarily in vivo). Use a later-generation fluoroquinolone such as moxifloxacin. Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective. Use two or more agents from Group 5. Consider high-dose isoniazid treatment if low-level resistance is documented. Consider adjuvant surgery if

there is localized disease. Under programmatic management of drug resistance tuberculosis (PMDT), government of India has a standardized treatment for the management of XDR-TB patients. Prospectively named "CAT V", the regimen is expected to consist of 7 drugs, with 2 reserve/substitute drugs. All drugs are to be given on a daily basis under supervision of a DOT provider. The Category V regimen would be of (24-30) months duration, with 6-12 months Intensive Phase (IP) and 18 months Continuation Phase (CP). The Intensive Phase will consist of Capreomycin, PAS, Moxifloxacin, High dose-INH (600-900mg), Clofazimine, Linezolid and Amoxicillin / Clavulanate while the Continuation phase will consist of PAS, Moxifloxacin, High dose-INH (600-900mg), Clofazimine, Linezolid, and Amoxicillin/ Clavulanate. Reserve/Substitute drugs would be Clarithromycin and Thiacezalone. The change from IP to CP will be done only after achievement of culture conversion i.e. 2 consecutive negative cultures taken at least one month apart. In case of delay in culture conversion, the IP will be extended from 6 months up to a maximum of 12 months.

16. Avoid widespread misuse of second line anti-tuberculosis drugs (SLD's) like ethionamide / prothionamide, cycloserine, PAS, kanamycin / capreomycin, fluoroquinolones (levofloxacin, ofloxacin, moxifloxacin), clofazimine, macrolides etc. in suspected resistant cases if you are not well trained to manage such cases as these are the only drugs available at present which have some hope of cure. Inappropriately using these valuable drugs might convert a MDR-TB case into extensively drug resistant tuberculosis (XDR-TB) and total drug resistant tuberculosis (TDR-TB). A preliminary study by the author among sixty MDR suspect patients showed 88.8% of MDR and 72.2% MDR suspect cases had taken SLD's for more than one month. The most commonly used SLD was fluoroquinolones (63.36%), ethionamide (47.72%) and kanamycin (40.9%) (28).

17. Some Physicians feel keeping certain drugs in reserve but this is a serious error. It is a prescription for losing one battle after another. Physicians treating such patient should note that the most powerful drugs available should be used initially and in maximum combination so as to ensure that the first battle is won and won permanently.

18. Treatment of Tuberculosis benefits both the community and the patient. Thus any public/private health care provider undertaking to treat a patient with TB is assuming an important public health responsibility that includes not only prescribing an appropriate regimen but also ensuring adherence to the

treatment until treatment is completed. Therefore the responsibility for successful treatment of TB is placed primarily on the provider or program initiating therapy, *rather than on the patient* (29-32). All measures should be taken to ensure adherence by persuading and encouraging such patients and their family members not to stop treatment despite all its discomfort as it is the last that stands between the patient and death (24-25).

19. Delay in recognition of MDR-TB, prolonged periods of infectiousness, crowded wards, and mixing TB and HIV patients all contribute to nosocomial transmission. However, in view of its seriousness, every programme or physician attempting to treat MDR-TB should also undertake a systematic review of current practices and ensure that everything possible is done to prevent transmission among patients and to staff by implementation of adequate infection control precautions (33).

20. Extrapulmonary Drug resistant tuberculosis is treated with the same strategy and duration as pulmonary Drug-resistant tuberculosis. If the patient has symptoms suggestive of central nervous system involvement and is infected with Drug-resistant Tuberculosis, the regimen should use drugs that have adequate penetration into the central nervous system (34). Rifampicin, isoniazid, pyrazinamide, prothionamide / ethionamide and cycloserine have good penetration into the cerebrospinal fluid (CSF); Kanamycin, amikacin and capreomycin do so only in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration. The fluoroquinolones have variable CSF penetration, with better penetration seen in the later generations.

### CONCLUSION

Emergence of multi-drug resistant tuberculosis (MDR-TB), extensively drug resistant tuberculosis (XDR-TB) and total drug resistant tuberculosis (TDR-TB) is a man-made problem and is always due to medical error. If our tuberculosis control programme is effectively implemented, all doctors can prescribe reliable regimens using reliable drugs and if they can ensure (by directly observed treatment and education of the patient and his family) that it is taken as prescribed, virtually all patients should be cured without any relapse and no drug resistance should occur. Laboratory services for early diagnosis and adequate and proper treatment of MDR-TB and XDR-TB must be strengthened. It must be emphasized that optimal treatment of MDR-TB alone will not curb the epidemic. Efforts must be focused on the effective use of first line drugs in every new patient so as to prevent the ultimate emergence of MDR-TB. The proper use

of second-line drugs in every patient of MDR-TB must be ensured to cure existing MDR TB, to reduce transmission of MDR-TB and to prevent XDR-TB and TDR-TB.

### CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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