Review Article

PROGRAMMATIC MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS: A NEW CHAPTER IN THE STRATEGY OF REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME OF INDIA

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ABSTRACT

Emergence of resistance in Mycobacterium tuberculosis against anti-tubercular drugs particularly multidrug-resistant tuberculosis (MDR-TB) has become a significant public health problem in many of the developing countries including India. Although rate of MDR-TB is relatively low in India but largest number of cases in the country pose a big challenge. As per WHO estimates 99,000 cases of MDR TB emerged in India in 2009, out of which 64,000 had been the cases earlier notified to Revised National Tuberculosis Control Programme (RNTCP). A prevalence of about 3 percent is reported in new cases and 12-17 percent in re-treatment cases in different studies countrywide. Under RNTCP, the programme earlier run as *DOTS plus* has been revised recently and changed to PMDT (*Programmatic Management of Drug Resistant Tuberculosis*) to make it more user friendly and practical, leaving no scope for development of further resistance and prevent transmission of drug resistant bacilli. Specific measures are being taken with in the Revised National Tuberculosis Control Programme of India to address the MDR-TB problem through appropriate management of patients and strategies to prevent the propagation and dissemination of MDR-TB. The programme already implemented successfully in Delhi state, is planned to be followed throughout the country in its three phases A, B and C in each state to provide cover to different categories of MDR-TB cases.

Key words: RNTCP, MDRT-B, XDRT-B, PMDT

Multi-drug Resistant Tuberculosis (MDR-TB)

Drug resistant tuberculosis is encountered in India from the time anti-tubercular drugs were introduced for the treatment of Tuberculosis. Multi-drug regimens were considered more effective with reduced duration of treatment. Multi-drug resistance against first line drugs mainly Rifampicin and Isoniazid leaves a limited choice of treatment with second line drugs with very high death rate of more than 50 percent among MDR-TB cases. Resistance in addition to above if encountered against a fluoroquinolone and any injectable drug used as second line treatment further complicates the situation to transform it to Extensively Drug Resistance Tuberculosis (XDR-TB) carrying an extremely high death rate of above 90 percent. Development of drug resistance in Mycobacterium is caused by genetic mutation making the drug ineffective against mutant bacilli. It is purely a man-made phenomenon resulting due to improper treatment, poor quality drugs and poor adherence to the norms of treatment. Strict implementation of good quality DOTS programme remains first priority for TB control in the country to avert development of any kind of resistance in M. tuberculosis.

Programmatic Management of Drug Resistant Tuberculosis (PMDT)

Programmatic Management of Drug Resistant Tuberculosis (PMDT) strategy deals with the *prevention and control* of MDR-TB through three major components: (i) High quality DOTS implementation (ii) Rational use of anti TB drugs (iii) Strict implementation of infection control measures. Early detection of MDR-TB suspects and their confirmation by rapid culture testing methods and their uninterrupted and complete treatment is to play key role in prevention of the new MDR cases. Following strategies are being implemented under PMDT.

(a) **Good quality DOTS Programme**: The existing Directly Observed Treatment of Short course chemotherapy (DOTS) programme launched in 1993 and expanded in 1997 is supported by five components viz. (i) political commitment (ii) diagnosis by quality microscopy (iii) adequate supply of right drugs (iv) directly observed treatment (v) proper reporting and recording. After confirmation, the case is categorized in any of the two categories I, or II and is given treatment under direct observation by the DOTS provider as per schedule. The treatment is given in two phases i.e. Intensive phase of 2 and 3 months respectively in I and II categories and Continuation Phase of 4 and 5 months respectively.

(b) **Case finding of MDR TB suspects**: Case finding is the initial link in the process of early diagnosis of MDR TB cases and their prompt treatment which is main objective of the programme. Case finding strategy is implemented at three levels. At first level *Criteria A* is implemented in the selected districts where those cases are considered as MDR TB suspects who are either failure of new cases or are the contacts of known MDR TB cases. At second level the selected districts move into *Criteria B* where in addition to criteria A, all those cases that are considered as retreatment cases and smear positive follow up cases are labeled as MDR TB suspects. Third level is *Criteria C* observed in the districts which move up after completing criteria B considering all smear negative cases treated earlier and HIV co-infected cases as MDR TB suspects in addition to criteria B mentioned above.

(c) **Referral of M/XDR TB patients**: On confirmation of a MDR TB suspect, Medical Officer at Peripheral Health Institute (MO PHI) has to make arrangement of sending two sputa samples (one of which is early morning sample and other one is supervised spot sample) in falcon tubes to RNTCP certified culture and drug sensitivity test laboratory (C-DST lab) along with RNTCP request form having all details of the patient. C-DST lab result is to be communicated to the sending agency by fastest means preferably by email or SMS, if the patient is confirmed as a case of MDR TB. If the result is delayed by more than seven days, the patient is placed on RNTCP DOTS treatment till result is awaited.

(d) **Confirmation of the diagnosis** (provision of laboratory services): State level designated laboratory termed Intermediate Reference Laboratory or any other designated RNTCP certified C-DST lab should have following facilities:

(i) Diagnostic culture on solid and/or liquid media.

(ii) Confirmation of resistance to rifampicin by molecular test (Line Probe Assay or any other RNTCP approved technology)

(iii) Confirmation of the species as Mycobacterium tuberculosis or non tubercular Mycobacteria (NTM)

(iv) Testing for susceptibility to at least Isoniazid and Rifampicin by solid or liquid culture.

Molecular (genotype) tests are much faster than phenotype tests as these don't require growth of organism. The turnaround time for C-DST results by solid LJ media is around 84 days, by liquid culture (MGIT) is around 42 days, by LPA Line Probe Assay) is 72 hours and by CB NAAT (Cartridge Based Nucleic Acid Amplification Test) is around two hours.

Diagnosis of MDR TB case is confirmed only when the tests are conducted by RNTCP endorsed testing methods in RNTCP quality assured Culture and DST laboratory. A Tuberculosis patient whose sputum is culture positive for M. tuberculosis and is resistant invitro to Isoniazid and Rifampicin is labeled as MDR TB case. An MDR TB case whose recovered M. tuberculosis is resistant to at least Isoniazid, Rifampicin, a fluoroquinolone (Ofloxacin, Levofloxacin or Moxifloxacin) and a second line injectable antiTB drug (Kanamycin, Amikacin or Capreomycin) is confirmed as a case of XDR TB.

(e) **Treatment of M/XDR-TB cases**: A patient on confirmation as MDR TB or XDR TB case is admitted at DR TB centre (Drug Resistant TB Centre) for pre-treatment evaluation and treatment initiation for a minimum period of 7 days or one month respectively. DR-TB Centres are established and designated by RNTCP at government/private hospitals or medical college hospitals having sufficient place for separate male and female MDR-TB wards and laboratory facilities to deal with M/XDR TB patients. As part of evaluation, a patient undergoes clinical examination, X ray chest, complete hematological and biochemical tests, including thyroid function tests. In case of XDR TB in addition, ECG, serum electrolytes and surgical evaluation of chest is also done. Female patients in reproductive age group need a special counseling on family planning to avoid pregnancy due to toxic side effects of the medicines. Medicines to all patients of M/XDR TB are provided in the boxes which are to be given under supervision of DOTS provider at DOTS centre.

Treatment of MDR TB cases is given in two phases, Initial Phase (IP) of six months is to be treated by Inj Kanamycin, Levofloxacin, Ethionamide, Pyrazinamide, Ethambutol and Cycloserine with the doses adjusted in five weight bands of below 16 kg, 16-25 kg, 26-45 kg, 46-70 kg and above 70 kg. In case of any intolerence Inj Kanamycin is replaced by Inj capreomycin, Levofloxacin by Moxifloxacin and any other oral drug is replaced by Para-aminosalicylic acid (PAS). Continuation phase (CP) of the treatment is started after completion of IP and is continued for a period of 18 months.

Table 1: Adverse reactions caused by second line antiitubercular drugs and their management

Adverse reactions	Drugs	Management by
GI symptoms (diarrhoea, vomiting and abdominal pain	Bulk of drugs, ethionamide, PAS & ethambutol	Domperidone, omeprazole, famotidine, ranitidine
Giddiness	Aminoglycosides, ethionamide, fluoroquinolone & pyrazinamide	Identify the drug, reduce dose or terminate
Ocular toxicity, visual disturbance	Ethambutol	Stop ethambutol, take opinion of ophthalmologist
Ototoxicity, vertigo, (vestibule-auditory disturbances)	Aminoglycosides	Stop the drug, take opinion of specialist
Cutaneous reactions, pruritis	Ethambutol, cycloserine, ethionamide, fluoroquinolone, kanamycin & pyrazinamide	Identify the drug, reduce the dose or terminate it, if reaction is severe
Arthralgia	Pyrazinamide, fluoroquinolones	Paracetamol, ibuprofen, diclofenac sodium
Hypothyroidism	Ethionamide & PAS	Treat with thyroxine
Psychiatric symptoms (anxiety, depression & suicidal tendency)	Cycloserine, fluoroquinolone or ethionamide	Continuation of treatment in consultation with psychiatrist
Nephrotoxicity	Kanamycin, capreomycin	Regular blood urea & serum creatinine monthly in first 3 months then once every three months
CNS symptoms (peripheral neuropathy)	Cycloserine & ethionamide	100 mg of pyridoxine for prevention or 200 mg for tretment
Hepatitis	Pyrazinamide & ethionamide	If icterus is noticed, identify and stop drugs & continue again when LFT is normal

XDR TB cases are treated in Initial Phase for a period of 6-12 months depending upon sputum conversion from positive to negative by seven drugs i.e. Inj. Capreomycin, PAS, Moxifloxacin, high dose of INH, Clofazimine, Linezolid and Amoxyclav. In continuation phase treatment is given for a period of 18 months, consisting of six same medicines except Inj Capreomycin, which

is discontinued. Doses of the medicines are adjusted in two weight bands of below 45 and above 45 kgs of weight. Cases having extensive cavities and damage to the lungs may be considered for surgical excision of lobes.

(f) **Adverse reactions and their management:** Antitubercular drugs are given for a long time and are known to cause variety of adverse reactions that is main cause of break or interruption in the schedule of treatment. Minor reactions are to be dealt with counseling while in cases of severe intolerance drugs are to be replaced by reserve drugs. On appearance of any of the adverse reaction patient is to be admitted preferably at DR-TB centre and decision is taken on reduction of the dose or its termination by replacing it with other suitable drug.

CONCLUSION

Non-resistant Mycobacterium tuberculosis develops into resistant form by mutation due to incomplete or interrupted treatment schedule. The resistant forms of tuberculosis (MDR-TB or XDR-TB) can infect the contacts making new resistant cases. PMDT is a conceptual plan of RNTCP to implement measures throughout the country in phase-wise manner to stop the development of resistance in Mycobacterium and prevent the transmission of resistant form of Tuberculosis. Adherence to the treatment and strict supervision of the programme are the factors to play key role in success of PMDT.

REFERENCES

1. Revised National Tuberculosis Control Programme, Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India, Central TB Division, Director General of Health Services, Ministry of Health & Family Welfare, Nirman Bhavan, New Delhi-110011
2. C N Paramasivan, P Venkataraman, Drug resistance in tuberculosis in India. *Indian J Med Res* 2004: 120; 377-386
3. Laboratory Services in Tuberculosis Control. Part III-culture. WHO/TB/98.258, 1998
4. WHO. Treatment of tuberculosis: guidelines for national programmes. WHO/CDS/TB 2003.313. Geneva: WHO 2003
5. de Jagger P, van Altena R, hearing loss and nephrotoxicity in long term aminoglycoside treatment in patients with tuberculosis. International Journal of tuberculosis & lung diseases 2002; 6: 622-627 cc.