CONTROL OF MULTI DRUG RESISTANT TUBERCULOSIS: PRINCIPLES AND PRACTICES

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INTRODUCTION

Multidrug Resistant Tuberculosis (MDR-TB) is defined as disease due to M. Tuberculosis that is resistant to Isoniazid (H) and Rifampicin (R) with or without resistance to other drugs. MDR-TB has been an area of growing concern to human health world wide and posing a threat to the control of tuberculosis. Current estimates report the prevalence of primary and acquired MDR TB in India is 2.2% and 15 % respectively. It is estimated that 99,000 MDR-TB cases emerge every year in India, representing 20% of the global burden. Out of 99,000 cases 62, 000 were among notified cases of tuberculosis in India in 2013 (1).

An MDR-TB Suspect is defined as a TB patient who fails a new (Category I) treatment regimen and any retreatment (Category II) patient who is sputum smear positive at the end of the fourth month of treatment or later (2,3). Diagnosis of MDR TB is based on clinical, radiological and bacteriological evidences. Clinical evidence comprises of the symptoms and signs suggestive of TB and past history of anti -tubercular therapy. History of prior treatment with antitubercular drugs is most important. The main predictor of resistance to a particular drug is the demonstration of its prior use in monotherapy for more than one month. To obtain evidence of possible inadvertent or direct monotherapy, it is essential to be meticulous in obtaining the history of anti-tuberculosis treatment in all patients suspected of MDR-TB.There should be a detailed evaluation into the drugs used, the drug dosages if previous drug prescriptions are available, whether the drugs were fixed dose combinations or separate drugs, their reliability in terms of WHO approved bioavailability, whether the patients were compliant to these drugs, supervised or unsupervised treatment and any drug intolerance that included partial or complete drug defaulting. Any real masked monotherapy previously received by the patient can be identified with reasonably good accuracy and one can accurately predict resistance to specific drugs and prevent their inclusion in the retreatment plan (4,5). The other important aspects of history include contacts with known case of resistant tuberculosis and patient's place of residence which may have a high prevalence of drug resistance. Though radiological worsening is not a very reliable indicator for predicting drug resistance, it serves to compliment the clinical and bacteriological evidence of the patient. Change in size of cavities and increase in size of existing lesions and appearance of new lesions are signs of disease progression and activity. The presence of multiple or giant cavities and destroyed lung increases the probability of drug resistance.

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The bacteriological evidences serve as the gold standard in the detection of MDR-TB. This is based on sputum smear microscopy and culture of M. tuberculosis and drug susceptibility testing (DST). Sputum smear microscopy, after starting standard chemotherapy can show a positive, negative or suboptimal response. While positive response is characterized by sputum conversion at 2/3 months of chemotherapy, a negative response could mean persistent smear positivity at the end of 3 months of adequate chemotherapy and a suboptimal response by an initial fall in the sputum grade followed by a gradual rise - the so called 'fall & rise' phenomenon while the patient is on anti-tubercular therapy. The last two patterns increase the probability of drug resistant tuberculosis. Diagnosis is confirmed by DST from reliable and reputed laboratories under constant quality control. However, one has to keep in mind the limitation of highly specific DST because the technique

is complex, difficult to perform accurately even when skilled personnel are available and laboratory facilities are of high standard (6). Further one should realize that laboratories vary in reliability, errors do occur in labs, different DST reports are obtained from the same patient from different labs. There is often lack of standardization, coordination and cross checking by national and international reference laboratories in our country. Susceptibility testing for isoniazid, rifampicin, fluoroquinolones and the injectables agents is very reliable. For other agents it is less reliable and basing individualized treatments on DST for these agents should be avoided. The Effectiveness or ineffectiveness of a drug cannot be predicted by DST with 100% certainty (7).Furthermore, the DST to second line drugs (SLD'S) is very variable . Keeping above facts in mind it is pertinent that DST should not be accepted uncritically.

MOLECULAR TECHNIQUE

Molecular techniques have been used for identification of resistance associated mutation. WHO with stop TB partnership endorsed line probe Assays in low resource countries in 2008. Which can do rapid screening of patients with MDR-TB risk within 2 days (8). The Xpert MTB RIF assay endorsed by WHO in 2010 enables simultaneous detection of Mycobacterium Tuberculosis and Rifampicin resistance (reliable proxy for MDR TB) directly from sputum and other extra pulmonary specimen except blood in less than 2 hours (9). The assay is robust enough to be performed outside of conventional laboratories at district and sub district level of health system but requires uninterrupted power supply. It provides accurate results and can allow rapid initiation of MDR TB treatment pending results from conventional culture and DST (10,11).

TREATMENT

For treatment of MDR-TB, standardised, empirical and individualized approaches have been laid down(12-14). Individualized treatment based on individual DST and prior treatment history is costly and needs skilled professionals, standardized treatment is simple, less costly and same treatment is given to all patients. Designing an individualized appropriate regimen need skill and treatment of MDR-TB is very difficult in the hands of many physicians with restricted knowledge who dare to treat these patients and create worsening problems. Therefore individualized treatment need specialized physicians experienced in dealing with such cases since this treatment represent the patient's last chance of a cure. Regimen should contain atleast four drugs that are highly likely to be susceptible based on drug susceptibility test from accredited, reliable laboratories, potency of the available drugs and/or previous intake of anti-tuberculous drugs. Design treatment regimens with a consistent approach based on the hierachy of the five groups of anti-tuberculosis drugs. Use any first line oral agent (Ethambutol, Pyrazinamide, Rifabutin) to which isolate is sensitive, use an injectables (Kenamycin, Amikacin, Capreomycin) and one fluoroquinolones (Ofloxacin, Levofloxacin, , Moxifloxacin) and add as many second line bacteriostatic agents (ethionamide/ Prothionamide Cycloserine/ Terizidone, p-aminosalicylic acid) to make atleast four effective drugs. Group five drugs (Bidaquiline,Delamanid, Clofazimine, Linezolid, Amoxycalv, Thioacetazone, Imipenem/Cilastatin, High dose Isoniazid, Calrithromycin) are not recommended for routine use except where as an adequate regimen is impossible with group (1-4). Do not use ciprofloxacin as an anti-tubercular agent. Injectables agent should be continued at least for 6-9 months. It is important that a single drug should never be added to a failing regimen and it is ineffective to combine two drugs of the same group or to add a drug potentially ineffective because of cross resistance. No drug should be kept in reserve and the most powerful drugs should be used initially and in maximum combination so as to ensure that first battle is won and won permanently. All patients initiated on treatment and their family members should be intensively counseled prior to treatment initiation and during all follow up visits. To reduce the risk of development of resistance to second line anti tuberculous drugs and promote optimal treatment outcomes, all efforts should be made to administer treatment under direct observation (DOT) over the entire course of treatment. If DOT is not possible, attempts to ensure treatment adherence should be made by checking empty blister packs during follow up visits every month (15,16). All measures should be taken to persuade and encourage patients not to stop treatment despite all its discomforts as it is the last resort that stands between life and death. Surgical treatment should be considered as an adjunct to chemotherapy whenever applicable and when results of chemotherapy are very unpredictable.

CURRENT PROPOSAL & CONCLUSION

Current proposal of programmatic management of drug resistant tuberculosis(PMDT) (2,3,13,14) by WHO highlights the comprehensive management strategy to control MDR TB. Treatment of MDR TB is difficult, complicated, much costlier, challenging and needs experience and skills. MDR TB is a man made problem and its emergence can be prevented by prompt diagnosis and effective treatment of all TB case. Effective use of first line anti-tuberculosis drugs in every new patients of tuberculosis to prevent the multi-drug resistant strains and proper use of second line drugs to treat patients with MDR TB are the top

priorities for the proper control of MDR TB. Sound infection control measures to avoid further transmission of MDR TB and research towards development of new diagnostics, drugs and vaccines should be promoted to control MDR-TB.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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