MULTI DRUG RESISTANT TUBERCULOSIS

Key Words: MDR-TB, RNTCP

The phenomenon of drug resistance was detected very soon after the introduction of Streptomycin for the treatment of tuberculosis in 1947. Today, with the greatly expanded efforts to strengthen tuberculosis prevention and control programmes worldwide, there is growing concern about the currently reported and potential future rates of drug-resistant tuberculosis, and more importantly, the emergence of strains resistant to Isoniazid and Rifampicin, defined as multi-drug resistant TB, or “MDR-TB”. Drug resistance develops either due to infection with a resistant strain, or as a result of inadequate treatment, such as when a patient is exposed to a single drug, or because of selective drug intake, use of inappropriate non-standardized treatment regimens, irregular drug supply, poor drug quality, or rarely, erratic absorption of the medications.

The magnitude of the problem

The emergence of strains of Mycobacterium tuberculosis that are resistant to antimicrobial agents is a world-wide problem. In 1997, the first global report on drug resistance, published by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Diseases (IUATLD) Global Project on Anti-Tuberculosis Drug Resistance Surveillance, contained data from 35 countries1. The 2nd and the 3rd reports, published in 2000 and 2004, provided data from 50 and 63 countries respectively2,3. The latter reported, the median prevalence of resistance to at least one drug among new TB cases as 10.2% (range 0 – 57.1%), with specific drug resistance being 5.9% for Isoniazid and 6.3% for Streptomycin1. According to the said report, the median prevalence of MDR-TB amongst new cases worldwide was estimated to be 1.1% (range 0 – 14.2%). Higher rates of resistance were found amongst previously treated patients, with median prevalence of resistance to at least one drug and MDR-TB being 18.4% and 7.0% respectively3.

In India, drug resistance patterns vary widely across different parts of the country. The data on drug resistance in ‘new’ cases has been variously estimated by different investigators4. The first nationwide survey conducted by Indian Council of Medical Research (ICMR) during the 1960s showed a resistance level of 8.2% to Isoniazid (H) alone, 5.8% to Streptomycin (S) alone, and 6.5% to both the drugs (SH)4. Data published by the Tuberculosis Research Centre (TRC), Chennai have shown a gradual rise in the prevalence of resistance in ‘new’ cases over the past four decades, 3% to 17% for Isoniazid and 3% to 13% for Streptomycin. Drug resistance to Rifampicin emerged during the 1990s and data from the recent studies conducted by TRC and NTI, have reported MDR-TB levels between 0.5% to 3% in new cases and 12% amongst re-treatment cases5,7.

A high prevalence of MDR-TB is mostly due to poor TB case management. Any intervention designed to treat and/or control MDR TB must place the highest priority on correcting such errors in TB management, in the public as well as the private sector, prior to incorporating treatment for MDR-TB cases into the programme.

DOTS and MDR-TB

The WHO recommended strategy Directly Observed Treatment – Short course (DOTS) is the
main weapon in the battle against the global tuberculosis epidemic. DOTS is a systematic strategy with 5 components: sustained political and administrative commitment, access to quality assured diagnosis by sputum-smear microscopy, standardized short-course chemotherapy for all cases of TB under proper case-management conditions, including direct observation of treatment, systems for the maintenance of uninterrupted supply of quality assured drugs, and a recording and reporting system for enabling assessment of treatment outcome. There is abundant evidence that, when all the recommended procedures are in place, chemotherapy under DOTS can achieve cure rates of 90% or more, and prevent the emergence of resistance to first-line drugs.

Evidence from across the world clearly indicates that DOTS programmes have improved the level of treatment success and reduced the transmission of *Mycobacterium tuberculosis*. The Revised National TB Control Programme (RNTCP), based on the internationally recommended DOTS strategy, strongly recommends that Rifampicin-containing regimens are to be used only if given under direct supervision, in order to ensure compliance and to prevent the emergence of drug resistance.

Under the operational conditions, it has been observed that less than 3% of new cases fail to the Category I treatment regimen and 6% fail amongst the retreatment patients treated with the RNTCP Category II regimen. It is being realized that, as DOTS programmes around the world become robust enough to manage the majority of patients who carry drug-sensitive strains, efforts should begin to provide better services for the minority of patients with MDR-TB.

*The Diagnosis and Management of MDR-TB*

The diagnosis of MDR-TB is a laboratory based diagnosis and not a clinical one, and should be made only in those laboratories that have been accredited by a national or WHO/ internationally recognised mycobacteriology reference laboratory, with credible quality assurance systems in place. These laboratories should have the facilities to undertake drug sensitivity testing (DST) to first line drugs (Isoniazid, Rifampicin, Streptomycin and Ethambutol), using standard definitions of resistance. Under RNTCP, it is envisaged to subject patients, who continue to be smear positive at the end of 4 months or later of a Category II retreatment regimen, to culture and DST at such a laboratory. Patients found to have MDR would be provided subsequent standardized RNTCP second line drug regimens.

The DOTS Plus strategy is part of the extended DOTS strategy recommended by the WHO. The RNTCP views the treatment of MDR-TB patients as a “standard of care” issue. Recognizing that the treatment of MDR-TB cases is very complex, the prescribed regimen follows the internationally recommended DOTS Plus guidelines and will be provided from designated RNTCP DOTS Plus sites. These sites will be located in a limited number of highly specialized centres, at least one in each large state, and will have ready access to a state level accredited culture and DST laboratory, the Intermediate Reference laboratory (IRL), under RNTCP. These sites should have sufficient qualified staff available to manage the MDR-TB patients, using standardized second-line drug regimens given under daily DOT, with standardized follow-up protocols. These patients would receive ambulatory DOT, after an initial short period of in-patient care, to stabilize them on the second-line drug regimen. Necessary systems are to be put in place to ensure DOT, uninterrupted second line drug supply and a MIS system for monitoring treatment outcome, adverse drug reactions, etc.

Based on scientific evidence and national, as well as international experience, the Expert Committee on DOTS Plus has recommended the use of a standardized DOTS Plus regimen. The regimen would have 6 drugs in the intensive phase and 4 drugs during the continuation phase. The intensive phase would continue till 3 consecutive smears and cultures are negative, or up to a maximum of 9 months if culture conversion is not obtained. The total duration of treatment would be for 24 months, extendable up to 27
months.

Under RNTCP Phase II, it is planned to first establish a network of RNTCP accredited quality-assured Intermediate Reference Laboratories (IRL), providing culture and DST services for the RNTCP. Concurrently, a network of DOTS Plus sites, as per international guidelines, capable of enrolling and providing care and management for MDR-TB cases would be established. A total of 24 DOTS Plus sites are planned to be established across the country over the next five years, with a view to have in place RNTCP DOTS Plus services that are capable of enrolling for treatment at least 5000 “new” MDR-TB patients every year by 2010. The first DOTS Plus sites will be established in the states of Gujarat and Maharashtra and will be ready to enrol the first patients during 2006.

The cost of MDR-TB treatment at US$ 1600 is prohibitive, compared to less than US$ 10 for RNTCP DOTS treatment. Some of the major challenges in providing cost-effective MDR treatment in the field include: provision of daily DOT over an extended period of 24-27 months; ensuring uninterrupted supply of DOTS Plus drugs; provision of services to manage the anticipated frequent, and sometime severe, adverse drug reactions; managing the contacts of MDR-TB patients; provision of social support to the patients and their families during treatment; and ensuring the establishment of long term sustainable DOTS Plus services under the RNTCP.

MDR-TB reflects the poor primary management of the disease. It is mainly caused by the failure to ensure compliance, rather than the failure of the drugs to cure. The highest priority in fighting MDR-TB therefore must be its prevention. DOTS treatment for TB patients is the most cost effective method of preventing MDR TB and the concerned health personnel, in the public as well as the private sector must adhere meticulously to RNTCP diagnostic and treatment guidelines. However, in the evolving situation of TB control activities in India, the RNTCP appears to be moving gradually towards the provision of accurate and reliable DST facilities and treatment services for MDR-TB patients. The use of the most cost-effective regimens and the provision of support to the patients, to ensure direct observation and completion of treatment, must be provided and sustained as integral to the programme. It needs to be realized that patients with MDR-TB will have, at best, only one chance for cure with second line drugs provided free under the RNTCP.

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REFERENCES

Dr. M.D. Deshmukh was the grand old man working in the field of tuberculosis and chest diseases, a doyen of tuberculosis workers and a multi-splendoured personality. He graduated from the Grant Medical College, Mumbai and was awarded M.R.C.P. from London. He served as an army medical specialist during the Second World War and as a teacher in Wales (U.K.) from 1947 to 1952. On returning to India, he was appointed as Hony. TB Specialist at the Grant Medical College and Sir J.J. Group of Hospitals, Mumbai where he taught for 20 years. During this time, he was examiner and inspector of examinations in tuberculosis in many medical colleges, all over the country. Always interested in research, he had over 100 scientific papers to his credit. He participated and presented papers in many international and national conferences on Tuberculosis. He was a pillar of strength to the Maharashtra State TB Association working as its Honorary Secretary for many years.

His most remarkable work was the pioneering services of anti-TB Shibirs for rural areas. With the extensive experience of Shibirs, he launched an intensive Anti-Tuberculosis drive in the State of Maharashtra where case-finding and BCG Vaccination were done on a mass scale. He organised 13 State TB Conferences and for three conferences he conducted a demonstration Anti-TB Shirib in a rural area along with the conference. He edited a book “Pulmonary Tuberculosis and Some Common Chest Diseases” especially written for the undergraduate and postgraduate students. In the Text Book of Medicine published by the Association of Physicians of India, he contributed the section on ‘Clinical Signs, Diagnosis & Differential Diagnosis of Pulmonary Tuberculosis’.

He was closely associated with the Tuberculosis Association of India for many years and was a member of all its important Committees viz. Central Committee, Executive Committee, Technical Committee, etc. He was Co-Editor of the Indian Journal of Tuberculosis and co-author of the Text Book on Tuberculosis published by the Tuberculosis Association of India. He was Chairman of the Standing Technical Committee in 1964-65 and presided over the 20th All-India TB Conference, at Ahmedabad in 1965. In recognition of his services to the anti-TB movement, the Tuberculosis Association of India awarded him its Gold Medal in 1974.