Introduction

Tuberculosis (TB) has caused morbidity and mortality since centuries to terrorise the mankind as stubborn and die hard disease. The annals of TB are full of the accounts how it extensively swept across large regions of the globe in epidemics and it continues to tease the innovative capabilities of research scientists. In the recent past there has been an upsurge in TB with multi-drug resistance TB (MDR-TB), extensively drug resistant TB (XDR-TB) and now the newer form Totally Drug Resistant TB (TDR-TB) has come up, which is perturbing and warrants focussed attention.

The TDR-TB was first reported in 2009 from Iran when the patients suffering from TB were found resistant to all the first line antitubercular drugs (FLDs) and second line antitubercular drugs (SLDs).[1] The term extremely drug resistance tuberculosis (XXDR-TB) was earlier used in 2007 in Italy, for patients refractory to all FLDs and SLDs.[2-4] In 2012 the print media first time reported about the patients of TDR-TB in India.[5,6] Though XDR and TDR-TB have been reported from many other countries, the reports underrate the true extent of the problem, justifying widespread surveys to find its prevalence.[7,8] The term TDR-TB is not recognised by WHO because absolute correlation of clinical response with drug sensitivity testing (DST) is not established. A patient may show clinical response to an anti-tubercular drug in spite of demonstrating resistance in DST.[9] The WHO expert group in 2012 decided on the possible definitions of TDR-TB and mentioned that the term ‘totally’ may create fear amongst the patients and community and distort the opinion of an average TB patient and the term ‘TDR’ is inadequate to address to this form of TB, so a new definition, apart from the one existing for XDR-TB, is not desirable.[10] Hence WHO...
use of mycobacteriophages as indicators of viability. Greater resistance determined by comparing volatile genotypic molecular methods. Determines ratio between the MIC of test and in 2010, 16 out of the 36 countries with high Rifampicin FLDS including, pyrazinamide, therefore, it is essential to establish measuring the resistance to SLDs is measures ratio of colonies on medicine containing cannot replace conventional tests. Has high specificity and positive predictive value. Nucleic Acid Amplification Test (NAAT) recommends treatment of TDR-TB to be the same as XDR-TB, though it accepts that the newer form being more severe than XDR. We hereby review in brief this super form of TB, known to many as TDR-TB.

Factors contributing to TDR-tuberculosis

Resistant TB is a manmade disaster with negligence on the part of patients, physicians and policy makers. Factors like less use of sputum smear microscopy, excessive dependence on chest radiography, improper combinations of medicines, errors in medicine dosage and duration of treatment, nonor low patient compliance to the treatment has led to the world’s most dreaded totally drug resistant tuberculosis (TDR-TB) which has the potential to create havoc both for the patient and community. The surfing of TDR-TB has challenged the STOP TB strategy, especially in countries with higher prevalence of HIV. Revised National Control TB Programme (RNTCP) and state health authorities are following a wellplanned strategy to face the challenges of drug resistant tuberculosis under supervision of Government of India. These include nationwide directly observed treatment short course (DOTS) coverage, research in monitoring the pattern of drug resistance, rapid detection of drug resistance, and improving methods for prevention and management of drug resistance. The DST, crucial to DOTS plus programme, is being introduced in a phased manner in India.

Role of DST in TDR-tuberculosis

Though culture and drug sensitivity testing (DST) should not blindly be directing the management of TDR-TB, it is important in individualising the drug therapy for TDR-TB patients. The DST should be done in all the patients undergoing retreatment, with chronic TB and those with history of contact with patients with drug resistant TB. In 2010, 16 out of the 36 countries with high burden of tuberculosis did not have single laboratory capable of performing TB culture and DST per five million people. Greater part of the Africa and the Indian subcontinent still remain poorly served in this respect.

Four DST methods viz. absolute concentration method, resistance method, proportion method (with variants), and BACTEC-460 radiometric method have been standardized for FLDS and are used globally for measuring drug resistance [Table 1]. These methods give accurate results when standardized and quality controlled. Most of the DST methods have a turnaround time of several months and empirical regimen should be switched to individual regimen as soon as result is obtained. Newer assays like microscopic observation drug susceptibility assay, line probe assay, bacteriophage assay can be used for rapid detection of drug resistance [Table 1]. Measuring the resistance to SLDs is complicated and lacks standardization for many medicines. The WHO has grouped the SLDs based on their efficacy into five classes [Table 2]. For MDR, XDR and TDR-TB, individualized treatment based on DST reports provides high cure rates provided that the patient adherence is intensively checked. The reliability of DST for SLDs is dependent on the peak serum concentration and minimum inhibitory concentration (MIC) of the anti-tubercular medicines. The SLDs like kanamycin, paraaminosalicylic acid and capreomycin have peak serum concentrations much higher than the MIC, therefore high concentrations can be maintained in the lesions throughout the treatment phase. Some SLDs like cycloserine, ofloxacin, ethionamide have peak serum concentrations closer to MIC values, signifying sub-inhibitory levels during most of the treatment and low reliability of DST for the SLDs. Therefore, it is essential to establish international quality assurance programme for SLD analysis. Other rapid and surrogate methods that can be used are early bactericidal activity (EBA) assay and nucleic acid amplification test (NAAT) for drug resistance which holds immediate promise for scaling up laboratory capabilities [Table 1]. The DST needs recruitment of qualified TB labworkers and DST results need expert interpretation as strains showing susceptibility may not be truly susceptible. Therefore rational use of DST results should exclude resistant SLDs rather than include susceptible SLDs in the treatment regimen. To ensure precision, laboratories with experience and competency in performing FLDS testing should test SLDs.

The RNTCP programme in India has collaborated with Foundation for Innovative New Diagnostics (FIN Diagnostics) in validation and demonstration

<table>
<thead>
<tr>
<th>DST method</th>
<th>Principle</th>
<th>Preferably performed for medicines</th>
<th>Turnaround time</th>
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<tbody>
<tr>
<td>Proportion method (preferred method)</td>
<td>Measures ratio of colonies on medicine containing to the medicine free medium. &gt;1% = resistance.</td>
<td>For most of anti-tubercular medicines except pyrazinamide, fluoroquinolones</td>
<td>28-42 days</td>
</tr>
<tr>
<td>Minimum inhibitory concentration (MIC) or Absolute concentration method</td>
<td>Several concentrations of medicines tested and resistance expressed in terms of MIC.</td>
<td>First line drugs (FLDs) except pyrazinamide, kanamycin, ofloxacin</td>
<td>28-42 days</td>
</tr>
<tr>
<td>Resistance ratio (RR) method</td>
<td>Determines ratio between the MIC of test and reference strain (RR &gt;8 = resistance).</td>
<td>FLDs except pyrazinamide</td>
<td>28-42 days</td>
</tr>
<tr>
<td>BACTEC-460 radiometric method</td>
<td>Resistance determined by comparing volatile radioactive CO2 in control and medicine vial</td>
<td>FLDs, Second line drugs (SLDs), rifabutin</td>
<td>7-10 days</td>
</tr>
<tr>
<td>MODS (Microscopic-observation drug-susceptibility) assay</td>
<td>Characteristic tangles of mycobacterium tuberculosis seen under inverted light microscope Genotypic molecular methods</td>
<td>FLDs</td>
<td>7 days</td>
</tr>
<tr>
<td>Line probe assays</td>
<td></td>
<td>FLDs including, pyrazinamide, ofloxacin, amikacin, capreomycin, Rifampicin</td>
<td>&lt;48 hrs</td>
</tr>
<tr>
<td>Bacteriophage assay</td>
<td>Use of mycobacteriophages as indicators of viability.</td>
<td>FLDs and SLDs, rifabutin, linezolid, capreomycin</td>
<td>48-72 hrs</td>
</tr>
<tr>
<td>Mycobacterial Growth Indicator Tube (MGIT 960 system)</td>
<td>Alternative to BACTEC 460. Is a fluorometric and detects oxygen consumption in the presence / absence of drug</td>
<td>Rifampicin</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Nucleic Acid Amplification Test (NAAT)</td>
<td>Cannot replace conventional tests. Has high specificity and positive predictive value.</td>
<td>Rifampicin</td>
<td>2-4 hrs</td>
</tr>
</tbody>
</table>
studies of the Xpert MTB/RIF assay which is a fully automated Nucleic Acid Amplification Test (NAAT) assay and takes just tworhrs in the diagnosis of Mycobacterium tuberculosis, MDR-TB and HIV with TB. In 2011-12, India was to introduce this WHO-endorsed technology at 18 sites, expected to enable diagnostic service for abouteight million people and improve the quality and accuracy of TB diagnosis for all TB suspects accessing healthcare services through the private or public health sectors. The FIND negotiated preferential pricing structure for the Xpert MTB/RIF assay is expected to favour public sector collaboration with the private health sector for TB diagnostic services. The laboratory expansion plan for India is extensive and provides a model for largescale implementation of culture and DST services in collaboration with the private sector.[27]

New agents and pharmacovigilance in resistant TB

Medicine buyers have to be aware of the fact that efficacy of SLDs is lesser and side effects greater when compared to FLDs. Availability of some of these agents being limited, the cost of remedies is high. Medicine management still remains a major challenge, with 4/24 countries reporting stock outs of SLDs in 2009.[25] Progress could be achieved by facilitating registration and importation of medicines, complyingwithquality assurance standards set by WHO, reinforcingnational medicine management and increasingproduction capacity of the quality assured products. Pharmacovigilance, for resistant TB is recommended because national TB control programmes usually do not measure Adverse Drug Reactions (ADRs) and the contribution of ADRs to mortality is not clear. The widespread recognition by health workers that anti-TB medicines often cause ADRs is inadequate in the published information. There is a dearth of literature about SLDs induced mortality, morbidity and loss in quality of life, particularly in lowresource settings. With the increasing use of extensive regimens for drug-resistant TB, with the added use of ARV therapy in patients with HIV associated TB, and with the advent of new medicines to treat TB, there is strong need for improved pharmacovigilance.[22]

Precautions for prevention of TDR

The currently available treatment of TDR-TB is not consolidated. Precaution in the treatment, prevention of spread of the infected cases and introduction of newer vaccines are some important tools. Any health care provider, public or private, undertaking to deliver the TB services must realize the responsibility to both the individual and the community to fulfil these duties. The Government policies and the curriculum of lab technology needs to ensure that their graduates have the skills to do SLDs-DSTs. Considering the difficulty of providing high quality DST results, centralised, well equipped, wellstaffed and controlled DST services should be preferred over a dense network of low quality DST labs throughout the nation where not only standard DSTs but highly specialised drug susceptibility tests like NAAT are also available so that quality is not compromised.[28]

WHO advises against simply adding a single new medicine to the failing regimens. The compassionate use of experimental medicines outside clinical trials has been addressed by the WHO for TDR tuberculosis.[29]

The XDR and TDR-TB are disasters of human errorscausing failing TB programs, where the remedy for the malady has become a tragic comedy. The TDR-TB threatens the gains made in the past in the treatment of both TB and HIV. Infection control encompasses administrative control to lessen the risks of exposure, infection and disease through policy and practice, environmental controls to reduce concentration of infectious bacilli in the air, in areas where contamination is likely, and personal respiratory protection with N95 masks which filter 95% of the airborne particulates to protect the personnel working in environment with contaminated air. Combination of these strategies can avert TDR-TB even in resource limited settings.[29]

Future demands for TDR management

Future research and development in the fields of surveillance to determine the geographical distribution and extent of TDR-TB, its association with HIV, molecular testing to develop new diagnostic tools for TB diagnosis, drug resistance determination, should be explored to expand the scope of drug resistance surveillance, expansion of MODS to include SLDs needs to be explored. Interaction of SLDs and ARV treatment needs to be studied. Development of new anti-TB medicines and strict implementation of infection control strategies are required to control and prevent the spread of TDR-TB. International standards for TB care must be sincerely adopted and endorsed throughout the world, especially in high burden countries.

Vaccines

Though Bacillus calmittegurine (BCG) reduces the risk of severe paediatric TB, protection offered in adult TB is variable. Newer vaccines are in various phases of clinical trials such as DDA/TDB vaccine, BCG::RD1, rBCG-Hly.[31] Dimethylidioctadecylammonium

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**Table 2: Antitubercular medicine groups based on WHO guidelines for the management of drug resistant tuberculosis, based on the efficacy[22]**

<table>
<thead>
<tr>
<th>Group</th>
<th>Medicines</th>
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<tbody>
<tr>
<td>1</td>
<td>First line oral agents: isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z); rifabutin (RB)</td>
</tr>
<tr>
<td>2</td>
<td>Injectable agents: kanamycin (Km); amikacin (Am); capreomycin (Cm); viomycin (Vm); streptomycin (S)</td>
</tr>
<tr>
<td>3</td>
<td>Fluoroquinolones: moxifloxacin (Mfx); levofloxacin (Lfx); ofloxacin (Ofx)</td>
</tr>
<tr>
<td>4</td>
<td>Oral bacteriostatic second line agents: ethionamide (Eto); prothionamide (Pto); cycloserine (Cs); terizidone (Trd); p-aminosalicylic acid (PAS)</td>
</tr>
<tr>
<td>5</td>
<td>Agents with unclear role in resistant TB: clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high dose isoniazid (high dose H); clarithromycin (Clr)</td>
</tr>
</tbody>
</table>

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*Rifabutin is not in the WHO List of Essential Medicines. It has been added here as it is used routinely in patients on protease inhibitors in many settings, H*High-dose H is defined as 16–20 mg/kg/day.

**Group**

**Medicines**

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2. Injectable agents: kanamycin (Km); amikacin (Am); capreomycin (Cm); viomycin (Vm); streptomycin (S)
3. Fluoroquinolones: moxifloxacin (Mfx); levofloxacin (Lfx); ofloxacin (Ofx)
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(DDA) and trehalosedibehenate (DDA/TTB) liposomes, act as adjuvant and have shown to induce strong humeral responses to the associated antigen without increased reactogenicity and are currently in phase I clinical trials.\textsuperscript{25} rBCG\textsuperscript{ΔureC::Hly} has been equipped with membrane perforating listerolysin (Hly) from listeria monocytogens and provides better protection by increase in CD8+ cell response in aerosol challenge than the conventional BCG vaccine.\textsuperscript{26} BCG::RD1 vaccine has been prepared by reintroduction of RD1 gene locus and is said to provide better protection but also increased virulence.\textsuperscript{24} Mycobacterium vaccae is an inactivated whole cell non TB mycobacterium which has currently completed phase III trial in BCG-vaccinated HIV+ adults.\textsuperscript{29}

Conclusion

As the miniscule microbes continue to score over the so claimed most potent and powerful macrobles of planet earth, the treatment options for TDR-TB continue to remain limited. The patient support, regular follow up, treatment adherence to DST sensitive medicines and palliative support to the patient and families are still cherished but yet missing in the mainstay in management of TDR-TB.

The emergence of TDR-TB indicates the return of powerful TB bacilli with renewed zeal to challenge the researchers to develop new anti-TB medicines and effective vaccines. The health professionals need to realize the need to be more vigilant on the use-misuse of anti-TB medicines and lab workers to attain the skills required in DSTs. It is a reminder to the community at large that prevention still remains better than cure. May the better sense prevail.

References


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