Multidrug-Resistant Tuberculosis (MDR-TB) is caused by Mycobacterium tuberculosis resistant to both isoniazid and rifampicin with or without resistance to other drugs. MDR-TB is emerging to be a worrisome pandemic of antibiotic resistance world over. Results of resistance surveys from 64 countries, together with data predictive of resistance rates from 72 others suggest that an estimated 273,000 new cases of MDR TB occurred worldwide in 2000 and constituted 3.2 per cent of all new TB cases. Reliable data on the epidemiology of MDR-TB are lacking from India. In India, prevalence of primary MDR-TB in newly diagnosed cases has been observed to be 3.4 per cent or less. Prevalence of MDR-TB among previously treated patients has been observed to be much higher. Isoniazid and rifampicin are keystone drugs in the management of tuberculosis (TB). While resistance to either isoniazid or rifampicin may be managed with other first line drugs, resistance to isoniazid and rifampicin (MDR-TB) demands treatment with second-line drugs which have limited sterilising capacity and are not suitable for short-course treatment. In most of the published studies, previous history of tuberculosis and past history of antituberculosis treatment have been implicated in the causation of MDR-TB suggesting that MDR-TB is largely a man-made tragedy.

Management Strategies

Practical Problems
Good, reliable laboratory facilities for performing mycobacterial culture and drug-susceptibility testing are seldom available in India nations. Therefore, therapeutic decisions are most often made by algorithms or inferences from previous treatment. Guidelines such as those published by the World Health Organization (WHO) are often resorted to choose the treatment regimen. For patients categorised as “treatment failure” the WHO re-treatment regimen consists of three drugs (isoniazid, rifampicin, and ethambutol) for a period of eight months, supplemented by pyrazinamide during the first three months and streptomycin during the first two months. If mycobacterial culture and in vitro sensitivity testing are not routinely performed, it is not possible to establish whether these patients are excreting multidrug-resistant bacilli. If this regimen is administered to treatment failure patients who have actually have MDR-TB, it is evident that the last five months of this regimen amounts to “monotherapy”. Thus, programmatic approach may fail in settings with a high degree of resistance to antituberculosis drugs.
Second-line drugs are very difficult to obtain in small towns and rural areas in India. Reliable pharmacokinetic data regarding bioavailability of most of these formulations is not available either. Moreover, there is no assurance that the most expensive brand names have the best bioavailability profile. Even considering the cheapest brand names available, the cost of drug treatment alone is much beyond the means of the average Indian patient. Therefore, long term compliance is not very good. All these factors constitute significant therapeutic challenges for the clinicians treating MDR-TB in the field setting. Population migration due to poverty to seek better job opportunities, because of natural disasters, political instability and regional conflicts also create mobile populations. These factors make treatment of MDR-TB difficult, as it is difficult for persons who are forced to move for any of a variety of reasons to complete 24 months of treatment.

Drug Treatment of MDR-TB : Evidence From Published Literature

World Scene
In the early reports of outbreaks of MDR-TB in human immunodeficiency virus HIV co-infected patients in hospitals and prisons, the mortality rate was very high ranging form 72 to 89 per cent. In HIV-negative patients, treatment of MDR-TB has been difficult and may only give response rates of the order of 50 per cent with a high mortality rate with persistent positive cultures. However, subsequent studies have documented decreased mortality and improvement in clinical outcome for HIV-positive patients with MDR-TB.

In a recently published study, results of community-based out-patient treatment of MDR-TB were reported form Peru. While the results of susceptibility testing were pending, the patients were treated empirically under direct observation with regimens containing at least five drugs to which their strains were likely to be susceptible. The definitive regimens, determined on the basis of the results of drug susceptibility, contained a minimum of five drugs and lasted for at least 18 months. Of the 66 patients who completed four or more months of therapy, 83 per cent were probably cured (defined as at least 12 months of consecutive negative cultures during therapy); eight per cent died while receiving treatment; and only one patient continued to have positive cultures after six months of treatment. These observations suggest that community-based out-patient treatment of MDR-TB has the potential to yield high cure rates even in resource-poor settings.

Indian Experience
Sparse data are available from published literature regarding the treatment of patients with MDR-TB from India. In a study from New Delhi, additional administration of oral ofloxacin was found to be effective and safe for the treatment of MDR-TB. Reports from Karnataka and Vellore also endorse the usefulness of pefloxacin and ofloxacin in the treatment of MDR-TB. In another prospective uncontrolled study from New Delhi, spar oxacin, in combination with kanamycin and ethionamide was found to be useful in achieving sputum conversion, clinical and radiological improvement in patients with pulmonary tuberculosis who had received adequate antituberculosis treatment with first-line drugs, including supervised category II treatment regimen as per WHO guidelines for five months, and were still sputum smear acid-fast bacilli positive.

Guidelines for The Management of Patients with MDR-TB
When MDR-TB is suspected on the basis of history, or epidemiological information, the patient’s sputum must be subjected to culture and antituberculosis drug-sensitivity testing and the WHO retreatment regimen or the empirical regimens employing “second line” reserve drugs suggested by the American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society (ATS/CDC/IDSA) must be initiated pending sputum culture report. Further therapy is guided by the culture and sensitivity report. These guidelines clearly mention that a single drug should never
be added to a failing regimen. Furthermore, when initiating treatment, at least three previously unused drugs must be employed to which there is in vitro susceptibility.\textsuperscript{10, 25}

When susceptibility testing reports are available, if there is resistance to isoniazid and rifampicin (with or without resistance to streptomycin), during the initial phase, a combination of ethionamide, uroquinolone, another bacteriostatic drug such as ethambutol, pyrazinamide and aminoglycoside (kanamycin, amikacin, or capreomycin) are used for three months or until sputum conversion. During the continuation phase, ethionamide, uroquinolone, another bacteriostatic drug (ethambutol) should be used for at least 18 months after smear conversion.\textsuperscript{10, 25}

If there is resistance to isoniazid, rifampicin and ethambutol (with or without resistance to streptomycin), during the initial phase, a combination of ethionamide, uroquinolone and another bacteriostatic drug such as cycloserine or PAS, pyrazinamide, and aminoglycoside (kanamycin, amikacin, or capreomycin) are used for three months or until sputum conversion. During the continuation phase, ethionamide, o oxacin, another bacteriostatic drug (cycloserine or PAS) should be used for at least 18 months after smear conversion.\textsuperscript{10, 25}

The recently published ATS/CDC/IDSA\textsuperscript{25} guidelines suggest that among the uroquinolones, levo oxacin is most suited for the treatment of MDR-TB given its good safety profile with long-term use. These observations need to be confirmed in prospective studies with a large sample size.

When administering antituberculosis drugs by the parenteral route, proper precautions must be taken. This is particularly relevant in countries like India where, disposable syringes are not always available for giving the injections and the use of improperly sterilized needles would be a health hazard especially in patients with HIV infection and acquired immunodeficiency syndrome (AIDS).

DOTS-plus Strategy

In populations where MDR-TB is endemic, the outcome of the standard short-course chemotherapy regimens remains uncertain. As a consequence, there have been calls for well-functioning DOTS programmes to provide additional services in areas with high rates of MDR-TB. These “DOTS-plus for MDR-TB programmes”\textsuperscript{26, 27} may need to modify all five elements of the DOTS strategy. The suggested modifications include, provision of individualised treatment; provision of laboratory services for on-site culture and antibiotic susceptibility testing; reliable supply expensive second-line agents among others. WHO has established a Working Group on DOTS-Plus for MDR-TB, to develop policy guidelines for the management of MDR-TB to develop protocols for pilot projects intended to assess the feasibility of MDR-TB management under programme conditions. The WHO has also established a unique partnership known as the “Green Light Committee” In an attempt to promote access to and rational use of second-line antituberculosis drugs for the treatment of MDR-TB\textsuperscript{28-30}. If DOTS-plus programmes are established, they may prove beneficial not only for patients with MDR-TB but for all patients with tuberculosis.

Monitoring Response to Treatment

Patients receiving treatment for MDR-TB should be closely followed up. Clinical (e.g., fever, cough, sputum production, weight gain), radiological (e.g., chest radiograph), laboratory (erythrocyte sedimentation rate) and microbiological (e.g., sputum smear and culture) parameters should be frequently reviewed to assess the response to treatment. In addition, considerable attention must be focussed on monitoring the adverse drug reactions which often develop with the second line antituberculosis drugs. Most of the patients who respond to treatment begin to show favourable signs of improvement by about four to six weeks following initiation of treatment. Failure to show positive trend may alert the clinician to resort to alternative measures detailed below.

Newer Antituberculosis Drugs

After the introduction of rifampicin, no worthwhile antituberculosis drug with new mechanism(s)
of action have been developed over the last three decades. Currently available second-line drugs used to treat MDR-TB (Table 1) are four to ten times more likely to fail than standard therapy for drug-susceptible tuberculosis. A series of compounds containing a nitroimidazopyran nucleus (PA-824) that possess antituberculosis activity have attracted attention as potential antituberculosis drugs. It is being hoped that these molecules may offer the practical qualities of a small molecule with the potential for the treatment of tuberculosis.

**Table 1: Second-line Antituberculosis Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dosage</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15 mg/kg (750-1000 mg)</td>
<td>Medium</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>15 mg/kg (750-1000 mg)</td>
<td>Medium</td>
</tr>
<tr>
<td>Amikacin</td>
<td>15 mg/kg (750-1000 mg)</td>
<td>Medium</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15 mg/kg (750-1000 mg)</td>
<td>Medium</td>
</tr>
<tr>
<td>Thioamides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethionamide</td>
<td>10-20 mg/kg (500-750 mg)</td>
<td>Medium</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>10-20 mg/kg (500-750 mg)</td>
<td>Medium</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>20-30 mg/kg (1200-1600 mg)</td>
<td>Low</td>
</tr>
<tr>
<td>Oxacin</td>
<td>7.5-15 mg/kg (600-800 mg)</td>
<td>Low</td>
</tr>
<tr>
<td>Levo oxacin</td>
<td>500-1000 mg</td>
<td>Low</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15-20 mg/kg (1000-1200 mg)</td>
<td>Low</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>10-20 mg/kg (500-750 mg)</td>
<td>High</td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td>10-12 g</td>
<td>Low</td>
</tr>
</tbody>
</table>

Adapted from references 10 and 25.

Surgery

Various surgical procedures ranging from segmental resection to pleuro-pneumonectomy have been performed in patients with MDR-TB with a low mortality (<3%). However, the complication rates are high with bronchopleural fistula (BPF) and empyema being the major complications. Resectional surgery is currently recommended for MDR-TB patients whose prognosis with medical treatment is poor. Indications for surgery in patients with MDR-TB include: (i) persistence of culture-positive MDR-TB despite extended drug retreatment; and/or (ii) extensive patterns of drug resistance that are associated with treatment failure or additional resistance; and/or (iii) local cavitary, necrotic/destructive disease in a lobe or region of the lung that is amenable to resection without producing respiratory insufficiency and/or severe pulmonary hypertension. It should be performed after minimum of three months of intensive chemotherapeutic regimen, achieving sputum-negative status, if possible. The chemotherapeutic regimen needs to continue for prolonged periods after surgery also, probably for well over a year, otherwise recrudescence of the disease with poor survival is a real possibility.

Nutritional Enhancement

When MDR-TB occurs especially in patients with HIV-infection/AIDS, cachexia is profound. Current evidence suggests that tumour necrosis factor-α [TNF-α; molecular weight (mol. wt) 50,000 produced by macrophages] in addition to inducing immunopathological effects such as tissue necrosis and fever, is also thought to induce the catabolic response. Further more, several second-line drugs used to treat MDR-TB result in significant anorexia, nausea, vomiting and diarrhoea interfering with food intake, further compromising the cachetic state. Therefore, nutritional support is a key factor in the care of patients with MDR-TB. Thus, nutritional assessment and regular monitoring of the nutritional state by a nutrition expert should be an essential part of the treatment programme.
Immunotherapy
Several workers have attempted to modify the immune system of patients with tuberculosis to facilitate cure. Agents with potential for immunotherapy are detailed below.

*Mycobacterium vaccae* vaccination
Transiently favourable results were observed when immunoenhancement using vaccination was used to treat drug-resistant tuberculosis patients who failed chemotherapy. However, subsequent reports from randomised controlled trials have not confirmed these observations.

Cytokine Therapy
Recent data suggest that aerosolised interferon-γ (IFN-γ) (500 µg, thrice weekly), may improve disease evolution in subjects affected with MDR-TB. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been used simultaneously with IFN-γ in the successful treatment of a patient with refractory central nervous system MDR-TB. Preliminary data suggest that aerosolised IFN-α (3MU, thrice weekly) may be a promising adjunctive therapy for patients with MDR-TB. Daily low-dose recombinant human interleukin 2 (rhuIL-2) adjunctive immunotherapy has been found to stimulate immune activation and may enhance the antimicrobial response in patients with MDR-TB. Optimal doses and schedules, however, require further studies.

Other Agents
Several agents have evoked interest as potential adjunctive treatment for patients with MDR-TB. Thalidomide and pentoxifylline have been shown to combat the excessive effects from TNF-α. They may be useful in limiting the wasting associated with MDR-TB. Other agents which have occasionally been considered include, levamisole, transfer factor, inhibitors of transforming growth factor-β (TGF-β), interleukin-12 (IL-12), interferon-α (IFN-α) and imiquod an oral agent which stimulates the production of IFN-α. Though there have been anecdotal reports of their usefulness, further studies are required to clarify their role.

Prevention of Nosocomial Transmission of MDR-TB
As MDR-TB poses a significant risk to health care workers, doctors and other patients, the Centers for Disease Control (CDC) in Atlanta have made recommendations to try to prevent such nosocomial transmission. These include: isolation in a single room with negative pressure relative to the outside with six air exchanges per hour, the room to be exhausted to the outside; consideration of ultraviolet lamps or particulate filters to supplement ventilation; use of disposable particulate respirators for persons entering the room and during cough inducing procedures.

Preventive Chemotherapy for Contacts to MDR-TB Cases
For contacts thought to be infected with multidrug-resistant strains of *Mycobacterium tuberculosis*, no satisfactory chemoprophylaxis is available. There is no consensus regarding the choice of the drug(s) and the duration of treatment. The CDC guidelines for the management of persons exposed to multidrug-resistant tuberculosis suggest that patients with risk factors for progression to active disease warrant treatment, although immunocompetent individuals may be observed closely without therapy for at least six months. The two suggested regimens for MDR-TB preventive therapy are: (i) pyrazinamide (25 to 30 mg/kg daily) plus ethambutol (15 to 25 mg/kg daily), or (ii) pyrazinamide (25 to 30 mg/kg daily) plus a quinolone with antituberculosis activity (e.g., levofloxacin or ofloxacin). The recommended duration of therapy is 12 months for those with underlying immunosuppression and at least six months for all others. All patients should be closely followed for at least two years, and a low threshold for referral to a center with experience in managing MDR-TB should be maintained.
Treatment of Latent MDR-TB Infection

Very little is known regarding the usefulness of pyrazinamide and levofloxacin in the treatment of multidrug-resistant latent tuberculosis infection. In a study from Canada, this combination was found to be poorly tolerated regimen as several patients developed severe adverse drug reactions. These issues merit further study.

Prognostic Markers

Park et al reported that extra-pulmonary involvement was a risk factor for shorter survival, while a cavitary lesion on initial chest film and institution of appropriate treatment were positive predictors of survival in patients with MDR-TB. In a recently published study (n=90) from the United Kingdom, median survival time overall was 1379 days and immunocompromised status and increasing age was associated with increasing risk of death. In a study from France, HIV-coinfection, treatment with less than two active drugs, and knowledge regarding the multidrug-resistant status at the time of diagnosis were found to be associated with a poor outcome. In another study from Turkey, older age, history of previous treatment with a larger number of drugs were found to be associated with a poor outcome.

Conclusions

MDR-TB is a therapeutic challenge and is very difficult to treat. It has been shown that DOTS strategy is very effective in not only cutting down the transmission of tuberculosis, but also in preventing the emergence of MDR-TB. In fact, the most effective way to combat MDR-TB is to prevent its occurrence by using the standard antituberculosis treatment regimens employing the DOTS strategy.

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