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Multidrug-resistant tuberculosis

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Multidrug-resistant tuberculosis (MDR-TB) caused by *Mycobacterium tuberculosis* resistant to both isoniazid and rifampicin with or without resistance to other drugs is among the most worrisome elements of the pandemic of antibiotic resistance. Globally, about three per cent of all newly diagnosed patients have MDR-TB. The proportion is higher in patients who have previously received antituberculosis treatment reflecting the failure of programmes designed to ensure complete cure of patients with tuberculosis. While host genetic factors may probably contribute, incomplete and inadequate treatment is the most important factor leading to the development of MDR-TB. The definitive diagnosis of MDR-TB is difficult in resource poor low income countries because of non-availability of reliable laboratory facilities. Efficiently run tuberculosis control programmes based on directly observed treatment, short-course (DOTS) policy is essential for preventing the emergence of MDR-TB. Management of MDR-TB is a challenge which should be undertaken by experienced clinicians at centres equipped with reliable laboratory service for mycobacterial culture and *in vitro* sensitivity testing as it requires prolonged use of expensive second-line drugs with a significant potential for toxicity. Judicious use of drugs, supervised individualised treatment, focussed clinical, radiological and bacteriological follow up, use of surgery at the appropriate juncture are key factors in the successful management of these patients. In certain areas, currently available programme approach may not be adequate and innovative approaches such as DOTS-plus may have to be employed to effectively control MDR-TB.

Key words Diagnosis - epidemiology - multidrug-resistant tuberculosis (MDR-TB) - predictors for development - prognostic factors- treatment

Tuberculosis (TB) is as old as the mankind[1-3]. TB is the most common cause of death due to a single infectious agent worldwide in adults[4]. In 1993, the World Health Organization (WHO) took an unprecedented step and declared TB to be a global emergency[4-6]. According to the recent estimates, one-third of the human population (about 1.86 billion people) was infected with *Mycobacterium tuberculosis* worldwide in 1997[7] . TB is principally a disease of poverty, with 95 per cent of cases and 98 per cent of deaths occurring in developing countries. Of these, more than half the cases occur in five South-East Asian countries[7]. In 1997, nearly 1.87 million people died of TB and the global case fatality rate was 23 per cent. This figure exceeded 50 per cent in some of the African countries where human immunodeficiency virus (HIV) is highly prevalent[7]. It is estimated that between 2002 and 2020, approximately 1000 million people will be newly infected, over 150 million people will get sick, and 36 million will die of TB if proper control measures are not instituted[4].

Though the disease was known since ancient times, the organism causing TB was described only a century ago by Robert Koch on 24th March 1882[3]. Until middle of the 20th century, there was no definitive treatment available for TB. With the availability streptomycin, isoniazid and para-aminosalicylic acid (PAS), in the mid 1940s, predictable, curative treatment for TB became a reality[2]. The introduction of rifampicin, pyrazinamide and ethambutol in the subsequent years ushered in the era of short-course treatment. Further, the fully supervised sanatorium based treatment of the earlier days also gave way to the totally unsupervised domiciliary treatment. Soon, it was felt that TB could be easily contained and possibly eradicated. The advent of HIV infection, the acquired immunodeficiency syndrome (AIDS) pandemic in the 1980s[1,8,9], struck a blow to this optimism and there has been a global resurgence of TB. Strains of *M. tuberculosis* resistant to both isoniazid and rifampicin with or without resistance to other drugs have been termed multidrug-resistant strains. Multidrug-resistant tuberculosis (MDR-TB) is among the most worrisome elements of the pandemic of antibiotic resistance because TB patients that fail treatment have a high risk of death[10-14].

RATIONALE FOR STRICT DEFINITION

Isoniazid, the most powerful mycobactericidal drug available, ensures early sputum conversion and helps in decreasing the transmission of TB. Rifampicin, by its mycobactericidal and sterilising activities is crucial for preventing relapses. Thus, isoniazid and rifampicin are keystone drugs in the management of TB. While resistance to either isoniazid or rifampicin may be managed with other first-line drugs, resistance to both isoniazid and rifampicin (MDR-TB) demands treatment with second-line drugs. These drugs have limited sterilising capacity and are not suitable for short-course treatment. Thus, patients with MDR-TB require prolonged treatment with drugs that are less effective and more toxic. Therefore, it is necessary to distinguish MDR-TB from mere drug-resistant tuberculosis by performing mycobacterial culture and sensitivity testing because the therapeutic implications are different.

It is possible to strictly define a given isolate of *M.tuberculosis* as multidrug-resistant only after performing mycobacterial culture and *in vitro* sensitivity testing. Under programme conditions, these facilities are usually not available and patients are labelled as "treatment failure", "re-treatment failure" and "chronic cases" as per the guidelines issued by the WHO[15]. It is likely that several of these patients may be excreting multidrug-resistant organisms. Keeping these facts in mind, the term MDR-TB has been used in this review in the strict sense of the definition referring to isolates resistant to both isoniazid and rifampicin with or without resistance to other drugs.

TERMINOLOGY OF DRUG RESISTANCE

Primary resistance is that which has not resulted from the treatment of the patient with the drug concerned. It includes resistance in wild strains which have never come into contact with the drug (natural resistance) and the resistance occurring as a result of exposure of the strain to the drug but in another patient. Initial resistance is the resistance in patients who give a history of never having received chemotherapy in the past. It includes primary resistance and resistance to previous treatment concealed by the patient or of which the patient was unaware[16,17].

The term "acquired resistance" has often been used with the implication that resistance has developed due to exposure of the strain to antituberculosis drugs and the consequent selecting out of resistant mutant bacilli. However, some of the drug-resistant isolates in previously treated patients may actually represent primary resistance among patients who remain uncured[18,19]. In the strict sense, the term "acquired resistance" can be used to refer to strains proven to have drug resistance in a reliable laboratory which were subsequently isolated from a patient in whom initial susceptibility testing was done to document the presence of a drug susceptible strain earlier[18,19]. If initial drug susceptibility testing has not been done, the term "resistance among previously treated patients" would be a more appropriate term than "acquired drug resistance" [18,19]. Susceptible strains are those that have

not been exposed to the main antituberculosis drugs and respond to these drugs in a uniform manner. Resistant strains differ from the sensitive strains in their capacity to grow in the presence of higher concentration of a drug. Wild strains are those that have never been exposed to antituberculosis drugs. Naturally resistant strains are wild strains resistant to a drug without having been in contact with it. It is species specific and has been used as a taxonomic marker[16,17].

EPIDEMIOLOGY

World

Though studies published from the developing world suggested that drug resistance was a potential problem[20,21], it was the emergence of MDR-TB in USA in the 1990s which attracted the attention[22,23]. The global extent of the problem of drug-resistant tuberculosis is evident in the report by the WHO-International Union Against Tuberculosis and Lung Disease (IUATLD) Global Project on Anti-tuberculosis Drug Resistance Surveillance between 1994 and 1997 which described the prevalence of resistance to four first-line antituberculosis drugs in 35 countries[24]. In this study[24], resistance to antituberculosis drugs was found in all 35 countries surveyed suggesting that it is a global problem. The prevalence of acquired resistance to any drug ranged from 5.3 per cent in New Zealand to 100 per cent in Ivanovo Oblast, Russian Federation, with a median value of 36 per cent. Resistance to all four drugs among previously treated patients was reported in a median of 4.4 per cent of the cases (range 0-17%). The median prevalence of acquired MDR-TB was 13 per cent, with a range of 0 per cent (Kenya) to 54.4 per cent (Latvia). There are several "hot spots" around the world where MDR-TB prevalence is high and could threaten control programmes[24]. These include Estonia, Latvia and two Russian oblasts (territories) in Europe; Argentina and the Dominican Republic in the Americas; and Côte d'Ivoire in Africa.

This survey did not include temporal changes in the prevalence of resistance. Further, in some countries with high burden of TB, such as China, India, and Russia, surveys were conducted only in one administrative unit if, any and this was not representative of the national scenario. Therefore WHO-IUATLD survey[24] was extended to define this problem further[25]. Between 1996 and 1999, patients in 58 geographic sites were surveyed[25]. For newly diagnosed patients, the frequency of resistance to at least one antituberculosis drug ranged from 1.7 per cent in Uruguay to 36.9 per cent in Estonia (median, 10.7%). The median prevalence of MDR-TB among new cases of tuberculosis was only 1.0 per cent, but the prevalence was much higher in Estonia (14.1%), Henan Province in China (10.8%), Latvia (9%), the Russian oblasts of Ivanovo (9%) and Tomsk (6.5%), Iran (5%), and Zhejiang Province in China (4.5%). A significant decrease in multidrug resistance was observed in France and the United States. In Estonia, the prevalence in all cases increased from 11.7 per cent in 1994 to 18.1 per cent in 1998[25]. 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[26].

India

Reliable data on the epidemiology of MDR-TB are lacking from India[1]. Though the problem of drug resistance was observed in the early studies from India[20,21], resistance to both isoniazid and rifampicin has been a recent phenomenon. It is felt that the phenomenon of MDR-TB is on the rise and is bound to reach much more menacing proportions[27-44].

In India, prevalence of primary MDR-TB in newly diagnosed cases has been observed to be 3.4 per cent or less (Table I). Data meticulously collected at the Tuberculosis Research Centre (TRC), Chennai over the last three decades suggest that rifampicin resistance started appearing in the early 1990s and MDR-TB levels in newly diagnosed patients has been one per cent or less[36].

Prevalence of MDR-TB among previously treated patients has been observed to be higher. In a study conducted at a referral tuberculosis hospital in Amargadh, Gujarat[28], multidrug resistance in previously treated cases was observed to increase

Table I. Prevalence of multidrug resistant *M. tuberculosis* isolates among new cases in India

Place	Study period	No. of isolates tested	Resistance to isoniazid and rifampicin with or without resistance to other drugs (%)
Gujarat[28]	1983-86	570	0
North Arcot district[29]	1985-89	2779	1.6
Pondicherry region[29]	1985-91	2127	0.7
Bangalore[30]	1980s	436	1.1
Bangalore[31]	1985-86	588	1.4
Kolar[31]	1987-89	292	3.4
Jaipur[33]	1988-91	1009	0.8
Tamil Nadu state[35]	1997	384	3.4
Composite North Arcot district*[43]	1999	282	2.8
Composite Raichur district†[43]	1999	278	2.5

*North Arcot district in Tamil Nadu state has now been split into two smaller districts. Composite North Arcot district refers to these two smaller districts Vellore and Tiruvannamalai

† Raichur district in Karnataka has now been split into two smaller districts. Composite Raichur district refers to these two smaller districts Raichur and Koppal

Superscript numerals indicate reference nos.

from 25.2 per cent in 1983 (n=305) to 33.8 per cent in 1986 (n=260). In the North Arcot district, between 1988-89, six per cent of the 3357 patients initiated on antituberculosis treatment were found to have MDR-TB[29]. More recently, in a study from Gujarat [44], the patterns of drug resistance were studied among previously treated tuberculosis patients who remained symptomatic or smear-positive despite receiving antituberculosis drugs under the DOTS programme for a minimum period of five months. Of the 1472 patients studied, 804 (54.6%) were treatment failure cases and 668 (45.4%) were relapse cases; 822 patients (373 failure and 449 relapse) were culture-positive. Of these 822 patients, 482 (58.6%, 261 failure and 221 relapse) were resistant to one or more drugs. Resistance to rifampicin and isoniazid with or without resistance to other drugs was seen in 289 of the 822 patients (35.2%). However, caution has to be exercised in interpreting the prevalence figures published in studies with a small sample size because of inherent methodological concerns.

The global epidemic of HIV infection/AIDS

Neville *et al*[45] described the emergence of drug-resistant TB as the third epidemic. It is generally accepted that patients with HIV infection/AIDS are at a greater risk of developing TB[8,18,22,23,46]. In persons with HIV infection/AIDS, factors such as increased vulnerability, increased opportunity to acquire TB (due to over crowding, exposure to patients with MDR-TB, increased hospital visits), and malabsorption of antituberculosis drugs resulting in suboptimal therapeutic blood levels inspite of strict adherence to treatment regimen have all been postulated as the possible causes for increased risk of acquiring MDR-TB. Data from published literature also support this view[18,22,23,47,48].

BIOLOGIC AND MOLECULAR BASIS OF DRUG RESISTANCE

Spontaneous chromosomally borne mutations occurring in *M. tuberculosis* at a predictable rate is

Table II. Antituberculosis drugs and the gene(s) involved in their resistance

Drug	Gene(s) involved in drug resistance
Isoniazid	Enoyl acp reductase *(inhA)*
	Catalase-peroxidase *(katG)*
	Alkyl hydroperoxide reductase *(ahpC)*
	Oxidative stress regulator *(oxyR)*
Rifampicin	RNA polymerase subunit B *(rpoB)*
Pyrazinamide	Pyrazinamidase *(pncA)*
Streptomycin	Ribosomal protein subunit 12 *(rpsL)*
	16s ribosomal RNA *(rrs)*
	Aminoglycoside phosphotransferase gene (*strA)*
Ethambutol	Arabinosyl transferase (*emb A,B* and *C*)
Fluoroquinolones	DNA gyrase *(gyr A* and *B)*

thought to confer resistance to antituberculosis drugs[49-53]. A characteristic feature of these mutations is that they are unlinked. Thus, resistance to a drug is usually not associated with resistance to an unrelated drug. A tuberculosis cavity usually contains 10^7 to 10^9 bacilli. If mutations causing resistance to isoniazid occur in about 1 in 10^6 replications of bacteria, and the mutations causing resistance to rifampicin occur in about 1 in10^8 replications, the probability of spontaneous mutations causing resistance to both isoniazid and rifampicin would be 10^6 x 10^8 = 1 in 10^{14}. Given that this number of bacilli cannot be found even in patients with extensive cavitatory pulmonary tuberculosis, the chance of spontaneous dual resistance to rifampicin and isoniazid developing is practically remote[49-53]. Thus, the fact that mutations are unlinked forms the scientific basis of antituberculosis chemotherapy. The primary mechanism of multiple drug resistance in tuberculosis is due to perturbations in the individual drug target genes[51,52]. Table II lists the molecular mechanisms of drug resistance as they are understood today[49-53].

Scanty information is available regarding the molecular basis of drug resistance in India. In studies published from India[54,55], in addition to the previously reported mutations, several novel mutations were also observed in the *rpoB* (rifampicin), *katG* and the ribosomal binding site of *inhA* (isoniazid), *gyrA* and *gyrB* (ofloxacin), and *rpsL* and rrs (streptomycin). Mani *et al*[56] analysed the mutations in 44 drug-resistant and six drug-sensitive *M. tuberculosis* clinical isolates from various parts of India in the 81-bp rifampicin resistance-determining region (RRDR) of the *rpoB* gene by DNA sequencing. Fifty three mutations of 18 different kinds, 17 point mutations and one deletion, were observed in 43 of 44 resistant isolates. Three novel mutations and three new alleles within the RRDR, along with two novel mutations outside the RRDR, were reported by these workers[56]. These observations suggest that while certain mutations are widely present, pointing to the magnitude of the polymorphisms at these loci, others are not common, suggesting diversity in the multidrug-resistant *M. tuberculosis* strains prevalent in this region. Further, it was observed that rifampicin resistance was found to be an important marker for checking multi-drug resistance in clinical isolates of *M. tuberculosis*[54].

DIAGNOSIS OF MDR-TB

Conventional methods

Traditionally, Lowenstein-Jensen (LJ) culture has been used for drug sensitivity testing using (*i*) absolute concentration method; (*ii*) the resistance ratio method; and (*iii*) the proportions method[16,17]. With the conventional methods, 6-8 wk time is required before sensitivity results are known.

In absolute concentration method, the minimal inhibitory concentration (MIC) of the drug is

determined by inoculating the control media and drug containing media with a carefully controlled inoculum of *M. tuberculosis*. Media containing several sequential two-fold dilutions of each drug are used. Resistance is indicated by the lowest concentration of the drug which will inhibit growth (defined as 20 colonies or more at the end of four weeks)[16,17]. In resistance ratio method, MIC of the isolate is expressed as a multiple of the MIC of a standard susceptible strain, determined concurrently, in order to avoid intra- and inter-laboratory variations. These two methods require stringent control of the inoculum size and hence are not optimal for direct sensitivity testing from concentrated clinical specimens. In the proportions method, the ratio of the number of colonies growing on drug containing medium to the number of colonies growing on drug free medium indicates the proportion of drug resistant bacilli present in the bacterial population. Below a certain proportion called critical proportion, a strain is classified as susceptible, and above that as resistant[16,17].

Modern methods

Radiometric methods have been developed for rapid drug-susceptibility testing of *M. tuberculosis*[57-59]. In the BACTEC-460 (Becton-Dickinson) radiometric method, 7H12 medium containing palmitic acid labelled with radioactive carbon (^{14}C-palmitic acid) is inoculated. As the mycobacteria metabolise these fatty acids, radioactive carbon dioxide ($^{14}CO_{2)}$ is released which is measured as a marker of bacterial growth. The proportions method has been modified by incorporating the BACTEC technique in place of the conventional Lowenstein-Jensen culture. With this modification, sensitivity results will be available within 10 days[57,58].

The mycobacteria growth indicator tube (MGIT) system (Becton-Dickinson) is a rapid, non-radioactive method for detection and susceptibility testing of *M. tuberculosis*[59,60]. The MGIT system relies on an oxygen-sensitive fluorescent compound contained in a silicone plug at the bottom of the tube which contains the medium to detect mycobacterial growth. The medium is inoculated with a sample containing mycobacteria and with subsequent growth mycobacteria utilise the oxygen and the compound fluoresces. The fluorescence thus produced is detected by using a ultraviolet transilluminator. Studies carried out both with cultures and direct clinical samples showed comparable results with the BACTEC and the proportions method[60].

Restriction fragment length polymorphism (RFLP) patterns used to categorise isolates of *M. tuberculosis* and to compare them, has facilitated the elucidation of molecular epidemiology of TB[61]. In this technique, DNA is extracted from the cultured bacilli. A restriction endonuclease such as PvuII cleaves the element at base pair 461. Subsequent steps involve separation of DNA fragments by electrophoresis on an agarose gel, transfer of the DNA to a membrane (Southern blotting), followed by hybridisation and detection with a labelled DNA probe. The DNA from each mycobacterial isolate is depicted as a series of bands on an X-ray film to create the fingerprint. A banding pattern reflecting the number and position of copies of IS*6110* (a 1361 base pair insertion sequence) within the chromosomes is obtained and this depends on the number of insertion sequences and the distance between them. As the DNA fingerprints of *M. tuberculosis* have been observed not to change during the development of drug resistance, RFLP analysis has also been used to track the spread of drug-resistant strains[61]. Recently, Goulding *et al*[62] determined the value of fluorescent amplified-fragment length polymorphism (FAFLP) analysis for genetic analysis of *M. tuberculosis* and suggested that FAFLP can be used in conjunction with IS*6110* RFLP typing to further understand the molecular epidemiology of *M. tuberculosis*.

Ligase chain reaction (LCR) involves the use of an enzyme DNA ligase which functions to link two strands of DNA together to continue as a double strand. This can occur only when the ends are complementary and match exactly, and this method facilitates the detection of a mismatch of even one nucleotide[63-65]. Luciferase reporter assay is a novel reporter gene assay system for the rapid determination of drug resistance[66-68]. It is based on the gene coding for luciferase, an enzyme identified as the light producing system of fireflies. In the

presence of adenosine triphosphate (ATP), it interacts with luciferin and emits light. The luciferase gene is placed into a mycobacteriophage. Once this mycobacteriophage attaches to *M.tuberculosis*, the phage DNA is injected into it and the viral genes are expressed. If *M. tuberculosis* is infected with luciferase reporter phage and these organisms are placed in contact with antituberculosis drugs, susceptibility can be tested by correlating the generation of light with conventional methods of testing. This technique has the potential to identify most strains within 48 h[66-68].

FASTPlaqueTB-RIF, a rapid bacteriophage-based test, to identify rifampicin susceptibility in clinical strains of *M.tuberculosis* after growth in the BACTEC-460 semi-automated liquid culture system has also shown potential to rapidly aid in the diagnosis of MDR-TB[69,70].

Polymerase chain reaction (PCR) based sequencing has often been employed to understand the genetic mechanisms of drug resistance in mycobacteria[71]. This technique allows for detection of both previously recognised and unrecognised mutations. The PCR-based methods are not readily applicable for routine identification of drug resistance mutations because several sequencing reactions need to be performed for each isolate. However, for targets such as *rpoB*, where mutations associated with rifampicin resistance are concentrated in a very short segment of the gene, PCR-based sequencing is a useful technique[71].

The Line Probe assay (LiPA; Inno-Genetics NV, Zwijndrecht, Belgium) has been used for rapid detection of rifampicin resistance[71]. LiPA technique is based on the reverse hybridisation method, and consists of PCR amplification of a segment of the *rpoB* gene followed by denaturation and hybridisation of the biotinylated PCR amplicons to capture probes bound to a nitrocellulose strip and detection of the bound amplicons producing a colour reaction. The interpretation of the banding pattern on the strip allows the identification of *M. tuberculosis* complex and detection of *rpoB* mutations. DNA microarray technology used for mycobacterial species identification has also been used for rapid detection of mutations that are associated with resistance to antituberculosis drugs[72,73]. However, most of the modern diagnostic methods are confined to research laboratories and are several years away from being available for use in the field setting.

Role of multidrug transporters

Multidrug transporters comprise four families of transmembrane efflux proteins that actively pump out a broad range of structurally unrelated compounds from the interior of the cell, using either proton motive force or ATP supplied energy[74]. These proteins are expressed by all organisms ranging from prokaryotes to higher eukaryotes, including human cells. They mediate both intrinsic and acquired resistance to various drugs of a multitude of organisms such as *Pseudomonas* sp., *Candida* sp., *Plasmodium* sp. and cancer cells[74]. P-glycoprotein is a human analogue of these multidrug transporters and is expressed on immune effector cells[75]. It has been observed that infection of experimental cell lines by *M. tuberculosis* results in increased expression of P-glycoprotein and decreased accumulation of isoniazid inside the cells[76]. Apart from the up regulation of host cell P-glycoprotein, *M. tuberculosis per se* expresses at least three multidrug transporter proteins Tap, Lfr *A* and Mmr[77-79]. The potential contribution of these multidrug transporter proteins in the causation of MDR-TB merits further evaluation. These transmembrane efflux proteins also appear to be novel targets for drug therapy in future.

POTENTIAL CAUSES OF DRUG RESISTANCE

Various factors have been implicated in the causation of MDR-TB[80]. These are discussed below:

Genetic factors

Though there is some evidence to postulate host genetic predisposition as the basis for the development of MDR-TB, it has not been conclusive[81-84]. In a recent study from India[83], patients with HLA-DRB1*13 and -DRB1*14 were found to have two-fold increased risk of developing MDR-TB. Park *et al*[84] found that susceptibility to MDR-TB in Korean patients was strongly associated with HLA-

DRB1*08032-DQB1*0601 haplotypes. The exact role of these factors is not known. It is likely that these loci or the alleles linked with them play a permissive role in conferring increasing susceptibility to the development of MDR-TB.

Factors related to previous antituberculosis treatment

Incomplete and inadequate treatment: Review of published literature strongly suggests that the most powerful predictor of the presence of MDR-TB is a history of treatment of tuberculosis. TB patients in India get treated with DOTS regimens not only through the Revised National Tuberculosis Control Programme (RNTCP), but also receive treatment from private medical practitioners. Irregular, incomplete, inadequate treatment is the commonest mean of acquiring drug resistant organisms.

Mahmoudi and Iseman[85] observed that among the 35 patients with MDR-TB patients, errors in management decisions occurred in 28 patients, at an average of 3.93 errors per patient[85]. The most common errors were the addition of a single drug to a failing regimen, failure to identify preexisting or acquired drug resistance, initiation of an inadequate primary regimen, failure to identify and address noncompliance and inappropriate isoniazid preventive therapy. Moreover, the group in which management errors occurred had more extensive acquired drug resistance compared to the group where there were no errors [85].

Use of single drug to treat TB is another common predisposing cause in the Indian setting. This could have occurred because of ignorance, use of penicillin/ streptomycin combinations; use of rifampicin for other diseases, and economic constraints. Furthermore, there is a problem of using unreliable combinations with an appreciable failure rate such as thiacetazone/isoniazid as initial treatment. Another common error in prescription practice is the "addition syndrome". If another drug is added to the existing regimen when the patient appears to deteriorate clinically and if resistance had developed to the drugs in use, adding another drug effectively amounts to monotherapy with the drug. There is also a risk of use of unreliable drugs with poor bioavailability (*e.g.*, rifampicin, isoniazid, pyrazinamide combinations). Use of antituberculosis drugs by unqualified persons or alternative medicine practitioners in bizarre regimens for inadequate periods is an important problem in our country. Free availability of antituberculosis drugs over the counter may contribute to this.

Inadequate treatment compliance: The change- over from fully supervised sanatorium treatment to unsupervised domiciliary treatment has affected compliance significantly. Poor compliance with treatment is also an important factor in the development of acquired drug resistance. In a study conducted in south India[37], it was observed that only 43 per cent of the patients receiving short-course treatment (n=2306) and 35 per cent of those receiving standard chemotherapy (n=1051) completed 80 per cent or more of their treatment[37].

Noncompliance with prescribed treatment is often underestimated by the physician and is difficult to predict. The drug defaulter, just like placebo reactor is not a consistent or readily identified person[86]. In the west, demographic factors such as age, sex, marital status, education level and socio-economic status have not been found to correlate with the degree of compliance. On the other hand, certain factors such as psychiatric illness, alcoholism, drug addiction and homelessness do predict noncompliance[86,87]. This may not be entirely true in the Indian context and the relevance of these factors in the Indian scenario merits further study.

Considering the changing epidemiological scenario DOTS is presently being advocated by the WHO to be the only effective way to control tuberculosis[4,88,89]. However, DOTS has not been adopted universally and the control programmes in several parts of the world are chaotic[80].

Santha *et al*[90] studied the risk factors associated with default, failure and death among TB patients treated in a newly implemented DOTS programme in south India. In this study, 676 patients were registered during the one year study period. In multivariate analysis, higher default rates were

associated with irregular treatment [adjusted odds ratio (AOR) 4.3; 95 per cent confidence intervals [(95% CI) 2.5-7.4], male sex (AOR 3.4; 95%CI 1.5-8.2), history of previous treatment (AOR 2.8; 95% CI 1.6-4.9), alcoholism (AOR 2.2; 95%CI 1.3-3.6), and diagnosis by community survey (AOR 2.1; 95%CI 1.2-3.6). Patients with MDR-TB were more likely to fail treatment (33 vs. 3%; $P<0.001$). More than half of the patients receiving category II treatment who remained sputum-positive after three or four months of treatment had MDR-TB, and a large proportion of these patients failed treatment. Higher death rates were independently associated with weight less than 35 kg (AOR 3.8; 95% CI 1.9-7.8) and history of previous treatment (AOR 3.3; 95% CI 1.5-7.0)[90].

Johnson *et al*[91], in a study of 109 culture-positive pulmonary tuberculosis patients found a high incidence of drug resistance in previous treatment defaulters while only four of the 27 new incident cases had MDR-TB. The various reasons for default included travel to different places, symptom relief, adverse drug reactions and inability to afford treatment[91].

Lack of laboratory diagnostic facilities

Good, reliable laboratory support is seldom available in developing nations. Unfortunately, these are the areas where MDR-TB is a major health hazard. When facilities for culture and sensitivity testing are not available, therapeutic decisions are most often made by algorithms or inferences from previous treatment. Guidelines such as those published by the WHO are often resorted to choose the treatment regimen[15].

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[15]. 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 WHO re-treatment regimen is administered to treatment failure patients who actually have MDR-TB (resistance to rifampicin and isoniazid with or without resistance to other antituberculosis drugs), it is evident that during the last five months the patient will be receiving isoniazid, rifampicin and ethambutol only and this would amount to "monotherapy" with ethambutol. Thus, "programmatic approach" to the management of "treatment failure" patients may fail in some settings as is evident from the following reports[92,93]. The programme of tuberculosis control using first-line therapy and DOTS was assessed in 467 patients with sputum-positive tuberculosis in a prison setting in Baku, Azerbaijan[92]. Drug resistance data on admission were available for 131 patients and 55 per cent of patients had strains of *M. tuberculosis* resistant to two or more drugs. Mortality during treatment was 11 per cent, and 13 per cent of patients defaulted. Overall, treatment was successful in 54 per cent of patients, and in 71 per cent of those completing treatment. One hundred and four patients completed a full treatment regimen and remained sputum-positive. Resistance to two or more drugs, a positive sputum result at the end of initial treatment, cavitary disease, and poor compliance were independently associated with treatment failure. The authors concluded that the effectiveness of a DOTS programme with first-line therapy fell short of the 85 per cent target set by WHO. First-line therapy may not be sufficient in settings with a high degree of resistance to antibiotics[92].

Similar observations were made in another study with results of treatment with first-line drugs for patients enrolled in the WHO and the IUATLD's global project on drug-resistance surveillance[93]. Patients with tuberculosis in the Dominican Republic, Hong Kong Special Administrative Region (People's Republic of China), Italy, Ivanovo Oblast (Russian Federation), the Republic of Korea, and Peru were studied in this retrospective cohort study. Of the 6402 culture-positive cases evaluated, 5526 (86%) were new cases and 876 (14%) were re-treatment cases. A total of 1148 (20.8%) new and 390 (44.5%) re-treatment cases were drug resistant, including 184 and 169 cases of MDR-TB, respectively. Of the new cases, 4585 (83%) were treated successfully, 138 (2%) died, and 151 (3%) experienced short-course chemotherapy failure. Overall, treatment failure and mortality were higher among new MDR-TB cases

than among new susceptible cases. Even in settings using 100 per cent direct observation, cases with multidrug resistance had a significantly higher failure rate than those who were susceptible [10 vs 0.7%; relative risk (RR), 16.9; 95% CI, 6.6-42.7; $P<.001$]. The data suggest that standard short-course chemotherapy, based on first-line drugs, is an inadequate treatment for some patients with drug-resistant TB[93]. Although the DOTS strategy is the basis of good TB control, the strategy should be modified in some settings to identify drug-resistant cases sooner, and to make use of second-line drugs in appropriate treatment regimens[94-98].

PREDICTORS FOR THE DEVELOPMENT OF MDR-TB

Certain factors have been documented to be associated with the development of MDR-TB. In an analysis to identify determinants of drug-resistant TB, population-based representative data on new and previously treated patients with TB collected within an international drug resistance surveillance network were studied[99]. Of the 9,615 patients, 85.5 per cent were new cases and 14.5 per cent were previously treated cases. Compared with new cases, patients who received treatment in the past were more likely to have resistance to antituberculosis drugs. An approximately linear increase was observed in the likelihood of having MDR-TB as the total time of prior antituberculosis treatment measured in months increased. Multivariate analysis revealed that prior antituberculosis treatment but not HIV positivity, was associated with MDR-TB[99]. In a study from Saudi Arabia[100], previous history of antituberculosis treatment and young age were found to be risk factors associated with the development of MDR-TB. In a study from New Delhi[83], the presence of past history of tuberculosis, poor compliance to treatment, low socioeconomic status and body mass index (BMI, kg/m^2) $\leq$18 kg/m^2 were independent contributors to the risk of developing MDR-TB. 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[83,99-103].

MANAGEMENT

In the early reports of outbreaks of MDR-TB in HIV co-infected patients in hospitals and prisons, the mortality rate was very high ranging form 72 to 89 per cent[104-108]. However, subsequent studies have documented decreased mortality and improvement in clinical outcome for HIV-seropositive patients with MDR-TB who were started on at least two drugs with *in vitro* susceptibility against the MDR-TB isolate[96,109,110]. Even in HIV seronegative 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[95-97,111,112].

In resource-poor nations, the treatment of MDR-TB has been considered to be very expensive and available only at referral centres. In a recently published study[113], 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 the 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, 55 (83%) were probably cured (defined as at least 12 months of consecutive negative cultures during therapy). Five of these 66 patients (8%) died while receiving treatment. Only one patient continued to have positive cultures after six months of treatment. Low haematocrit [hazard ratio (HR) 4.09; 95% CI, 1.35 to 12.36] and a low BMI (kg/m^2) (HR, 3.23; 95% CI, 0.90 to 11.53) were found to be the predictors of the time to treatment failure or death. 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[113].

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[10].

In an uncontrolled study from Manipal, Karnataka[114], pefloxacin, with its low cost and high safety profile was considered to be a useful companion drug in selected cases. A prospective uncontrolled study from New Delhi[115] reported that sparfloxacin, in combination with kanamycin (for the initial 3 to 4 months) and ethionamide treatment was useful in achieving sputum conversion, clinical and radiological improvement in nine 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 positive. In a study from Vellore, Tamil Nadu[116], combination therapy containing ofloxacin was useful in achieving sputum conversion in 26 of 49 (53%) patients and culture conversion occurred in 16 of 26 (61.5%) patients. Clinical and radiological response was noted in 31 (56%) and 13 (32.5%) out of 40 patients respectively.

Prognostic markers

Park *et al*[96] 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 from the United Kingdom[112], overall median survival time was 1379 days (95% CI 1336 to 2515). Median survival time was 858 days (95% CI 530 to 2515) in immunocompromised individuals and 1554 (95% CI 1336 to 2066) days in immunocompetent persons. Median survival in patients treated with three drugs to which the bacterium was susceptible on *in vitro* testing was 2066 days (95% CI 1336 to 2515), whereas, in those not so treated survival was 599 days (95% CI 190 to 969). Immunocompromised status, failure to culture the bacterium in 30 days or to apply appropriate treatment with three drugs to which the organism is susceptible, and age were significant factors in mortality. An immunocompromised patient was nearly nine times more likely to die, while application of appropriate treatment reduced the risk. Increasing age was associated with increasing risk of death (risk ratio 2.079; 95% CI 1.269 to 3.402) suggesting that, for every 10 yr increase in age the risk almost doubled[112]. In a study from France[117], in patients with MDR-TB, 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 study from Turkey[118], older age and history of previous treatment with a larger number of drugs were found to be associated with a poor outcome.

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 re-treatment regimen[15] or the empirical regimens employing second-line reserve drugs (Tables III and IV) suggested by the American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society of America (ATS/CDC/IDSA)[119] 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[15,119].

When susceptibility testing reports are available and there is resistance to isoniazid and rifampicin (with or without resistance to streptomycin) during the initial phase, a combination of ethionamide, fluoroquinolone, 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, fluoroquinolone, another bacteriostatic drug (ethambutol) should be used for at least 18 months after smear conversion[15,119](Table IV). If there is resistance to isoniazid, rifampicin and ethambutol (with or without resistance to streptomycin) during the initial phase, a combination of ethionamide, fluoroquinolone and another bacteriostatic drug such as cycloserine or PAS, pyrazinamide, and aminoglycoside (kanamycin, amikacin, or capreomycin) are used for three months

Table III. Daily dosage and toxicity status of second-line antituberculosis drugs

Drug	Daily dosage dose (range)	Toxicity
Aminoglycosides		
Streptomycin	15 mg/kg (750-1000 mg)	Medium
Kanamycin	15 mg/kg (750-1000 mg)	Medium
Amikacin	15 mg/kg (750-1000 mg)	Medium
Capreomycin	15 mg/kg (750-1000 mg)	Medium
Thioamides		
Ethionamide	10-20 mg/kg (500-750 mg)	Medium
Prothionamide	10-20 mg/kg (500-750 mg)	Medium
Pyrazinamide	20-30 mg/kg (1200-1600 mg)	Low
Ofloxacin	7.5-15 mg/kg (600- 800 mg)	Low
Levofloxacin	500-1000 mg	Low
Ethambutol	15-20 mg/kg (1000-1200 mg)	Low
Cycloserine	10-20 mg/kg (500-750 mg)	High
Para-aminosalicylic acid	10-12 g	Low

Source: Refs. 15, 119

or until sputum conversion. During the continuation phase, ethionamide, ofloxacin, another bacteriostatic drug (cycloserine or PAS) should be used for at least 18 months after smear conversion[15,119].

The recently published ATS/CDC/IDSA[119] guidelines suggest that among the fluoroquinolones, levofloxacin 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 AIDS.

Second-line drugs are very difficult to obtain in small towns and rural areas in India. Therefore, reliable supply of drugs is a difficult problem. Moreover, there is a wide variation in the price range between different pharmaceutical brands. Reliable pharmacokinetic data regarding bioavailability of most of these formulations are not available and 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, natural disasters, wars, political instability and regional conflicts also create mobile populations. These factors make treatment of MDR-TB difficult[120,121].

DOTS-plus strategy

DOTS is a key ingredient in the tuberculosis control strategy. In populations where MDR-TB is endemic, the outcome of the standard short-course regimen remains uncertain. Unacceptable failure rates have been reported and resistance to additional agents may be induced[80]. 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"[80,94,121] may need to modify all five elements of the DOTS strategy: (*i*) the treatment may need to be individualized rather than standardised; (*ii*) laboratory services may need to provide facilities for on-site culture and antibiotic susceptibility testing; (*iii*) reliable supplies of a wide range of

Table IV. Suggested treatment for patients with MDR-TB

Resistance pattern	Initial phase		Continuation phase	
	Drugs	Minimum duration (months)	Drugs	Minimum duration (months)
Resistance to isoniazid and rifampicin with or without resistance to streptomycin	Aminoglycoside Ofloxacin or levofloxacin Pyrazinamide Ethambutol Ethionamide	3	Ofloxacin or levofloxacin Ethambutol Ethionamide	18-24
Resistance to isoniazid, rifampicin and ethmbutol with or without resistance to streptomycin	Aminoglycoside Ofloxacin or levofloxacin Pyrazinamide Ethionamide Cycloserine	3	Ofloxacin or levofloxacin, Ethionamide Cycloserine	18-24

During the ontinuation phase antituberculosis drugs are administered for a period of at least 18 months after sputum conversion
Source: Refs. 15,119

expensive second-line agents; (*iv*) operational studies would be required to determine the indications; and (*v*) financial and technical support from international organizations and Western governments would be needed in addition to that obtained from local governments. WHO has established a Working Group on DOTS-Plus for MDR-TB, to develop policy guidelines for the management of MDR-TB and 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 (GLC) in an attempt to promote access to and rational use of second-line antituberculosis drugs for the treatment of MDR-TB[123-125]. 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. A detailed description of these adverse drug reactions is beyond the scope of this review. Majority 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 other measures outlined below.

Newer antituberculosis drugs

Currently available second-line drugs used to treat MDR-TB (Table III) are four to ten times more likely to fail than standard therapy for drug-susceptible tuberculosis[94-98]. After the introduction of rifampicin, no worthwhile antituberculosis drug with new mechanism(s) of action has been developed in over thirty years. Moreover, no new drugs that might be

effective in treatment of MDR-TB are currently undergoing clinical trials. It appears that effective new drugs for tuberculosis are at least a decade away[98]. Recently, a series of compounds containing a nitroimidazopyran nucleus that possess antituberculosis activity have been described[122]. After activation by a mechanism dependent on *M. tuberculosis* F420 cofactor, nitroimidazopyrans inhibited the synthesis of protein and cell wall lipid. In contrast to current antituberculosis drugs, nitroimidazopyrans exhibited bactericidal activity against both replicating and static bacilli. Lead compound PA-824 showed potent bactericidal activity against multidrug-resistant *M. tuberculosis* and promising oral activity in animal infection models. It is being hoped that these nitroimidazopyrans offer the practical qualities of a small molecule with the potential for the treatment of tuberculosis[122].

Surgery

Various surgical procedures performed for patients with MDR-TB have ranged from segmental resection to pleuro-pneumonectomy[126-130]. Based on the experience reported in the literature about surgery for MDR-TB, it can be concluded that the operation can be performed with a low mortality (<3%). However, the complication rates are high with bronchopleural fistula (BPF) and empyema being the major complications. Sputum positivity at the time of surgery, previous chest irradiation, prior pulmonary resection and extensive lung destruction with polymicrobial parenchymal contamination are the major factors affecting morbidity and mortality. Over 90 per cent of the patients achieve sputum-negative status post-operatively. Although operation related mortality is less than three per cent, deaths due to all causes occur in about 14 per cent patients. Even this compares favourably with over 22 per cent mortality due to TB in a similar group of patients treated medically[126]. More liberal use of muscle flaps to reinforce the bronchial stump and fill the residual space has helped significantly in reducing the rates of BPF, air leaks and residual space problems. These must be used in patients with positive sputum, when residual post-lobectomy space is anticipated, when BPF already exists pre-operatively or when extensive polymicrobial contamination is present.

Thus, 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 was 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 operative risks are acceptable and the long-term survival is much improved than that with continued medical treatment alone. However, for this to be achieved, 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

Tuberculosis is a wasting disease. The degree of cachexia is most profound when MDR-TB occurs in patients with HIV-infection/AIDS[131]. While the mechanisms involved in weight loss are not well known, current evidence points to tumour necrosis factor-α (TNF-α) to be the cytokine responsible for this phenomenon. TNF-α, in addition to inducing immunopathological effects such as tissue necrosis and fever, is also thought to induce the catabolic response[132]. Further, several second-line drugs used to treat MDR-TB such as PAS, fluoroquinolones cause significant anorexia, nausea, vomiting and diarrhoea interfering with food intake, further compromising the cachectic state. Therefore, nutritional support is a key factor in the care of patients with MDR-TB, especially those undergoing major lung surgery. Though definitive evidence is not yet available, it is generally believed that malnourished patients are at a greater risk of developing post-operative complications[126].

Nutritional assessment and regular monitoring of the nutritional state by a dietician are essential for

the successful management of MDR-TB patients and should be an essential part of such programmes. When the routine measures are not able to improve the nutritional status and induce weight gain, nasogastric feeding may be employed to supplement the diet. When the patients are very sick and have severe nutritional deficit, feeding gastrostomy/ jejunostomy may have to be performed.

Immunotherapy

Ever since the early attempts by Robert Koch, several workers have attempted to modify the immune system of patients with tuberculosis to facilitate cure[133,134]. The measure employed in the earlier days included heliotherapy, dietary supplementation including milk and cod-liver oil. It is likely that these interventions acted through 1,25 $(OH)_2$ D_3, which is now recognised to have significant effects on T-lymphocyte and macrophage function. Agents with potential for immunotherapy are detailed below.

Mycobacterium vaccae vaccination: Transiently favourable results were observed when immunoenhancement using *M. vaccae* vaccination was used to treat drug-resistant tuberculosis patients who failed chemotherapy[133,134]. It was postulated that *M.vaccae* redirected the host's cellular response from a Th-2 dominant to a Th-1 dominant pathway leading to less tissue destruction and more effective inhibition of mycobacterial replication[133]. However, subsequent reports from randomised controlled trials have not confirmed these observations[135].

Cytokine therapy: With further understanding of the molecular pathogenetic mechanisms of tuberculosis, several attempts have been made to try cytokines in the treatment of MDR-TB. Recent data, however, suggest that interferon-γ (IFN-γ) and interferon-α (IFN-α) may improve disease evolution in subjects affected with pulmonary tuberculosis caused by multidrug-resistant (IFN-γ) and sensitive (IFN-α) strains. The mechanisms involved are not known, even though it has been reported that IFN-gamma-secreting CD4+ Th cells may possess antituberculosis effects. In addition, IFN-a can induce IFN-γ secretion by CD4+ Th cells, and both types of IFN may stimulate macrophage activities[133].

Aerosolised IFN-γ (500 μg, thrice weekly) has been found to produce transient, but clinically encouraging responses in patients with MDR-TB in an open-label trial[136]. The observed benefits included unsustained sputum smear conversion to negative, delayed growth of cultures and shrinkage of cavities. 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[137].

Giosue *et al*[138], studied the usefulness of aerosolised IFN-α in the treatment of MDR-TB. In this study, seven patients who were non-responders to a second-line antituberculosis treatment after six months of directly observed treatment were given aerosolised IFN-α (3 MU, three times a week) for two months as adjunctive therapy. A transient decrease in the colony number per culture was observed. Preliminary data suggest that aerosolized IFN-α may be a promising adjunctive therapy for patients with MDR-TB. Optimal doses and schedules, however, require further studies.

Interleukin-2 (IL-2) has been used in the treatment of lepromatous leprosy and is believed to act by enhancing IFN-γ production. By the same analogy, IL-2 may be useful in the treatment of MDR-TB. Johnson *et al*[139] reported the usefulness of low-dose recombinant human interleukin 2 (rhuIL-2) adjunctive immunotherapy in MDR-TB patients. In this study MDR-TB patients on best available antituberculosis chemotherapy also received rhuIL-2 for 30 consecutive days (daily therapy), or for five days followed by a nine-day rest, for three cycles (pulse therapy). Placebo control patients received diluent. The cumulative total dose of rhuIL-2 given to each patient in either rhuIL-2 treatment group was the same. Patient immunologic, microbiologic, and radiologic responses were compared. The three treatment schedules induced different results. Immuneactivation was documented in patients receiving daily rhuIL-2 therapy. Numbers of CD25+ and CD56+ cells in the peripheral blood were increased in these patients, but not in patients receiving pulse rhuIL-2 or placebo. In addition, 62 per cent patients receiving daily rhuIL-2 demonstrated reduced or cleared sputum bacterial load while only 28 per cent pulse rhuIL-2 treated and 25 per cent controls showed bacillary clearance. Chest radiographs of 58 per cent patients

receiving daily rhuIL-2 indicated significant improvement over six weeks. Only 22 per cent pulse rhuIL-2-treated patients and 42 per cent placebo controls showed radiologic improvement. The authors concluded that daily low dose rhuIL-2 adjunctive treatment stimulates immuneactivation and may enhance the antimicrobial response in MDR-TB.

Other Agents

Several agents have evoked interest as potential adjunctive treatment for patients with MDR-TB. Though very little information is available regarding their clinical usefulness, they are described here considering their therapeutic potential. Thalidomide[48,140] and pentoxifylline[141,142] have been shown to combat the excessive effects from TNF-α. These may be useful in limiting the wasting associated with MDR-TB. Other agents which have occasionally been considered include, levamisole[143,144], transfer factor[145], inhibitors of transforming growth factor-β (TGF-β)[146], interleukin-12 (IL-12)[133], interferon-α (IFN-α) and imiquimod an oral agent which stimulates the production of IFN-α[147]. 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 CDC in Atlanta have made recommendations to try to prevent such nosocomial transmission[148]. 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 and treatment of latent multidrug-resistant tuberculosis infection

For contacts thought to be infected with *M. tuberculosis* resistant to both isoniazid and rifampicin, no satisfactory chemoprophylaxis is available. There is no consensus regarding the choice of the drug(s) and the duration of treatment. The CDC has put forth guidelines for the management of persons exposed to multidrug-resistant tuberculosis[149]. The guidelines recommended that the likelihood that (*i*) the contact is newly infected; (*ii*) the infecting strain is multidrug-resistant; and (*iii*) the contact will develop active tuberculosis should be considered. The CDC recommendations[149] also stress the importance of obtaining drug susceptibility results from the isolate of the presumed source case and the use of more than one drug, since the efficacy with drugs other than isoniazid has not been demonstrated in large trials. 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[149]: (*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 centre with experience in managing MDR-TB should be maintained.

It has been observed that prophylaxis with pyrazinamide and levofloxacin in solid organ transplant recipients possibly exposed to MDR-TB was associated with limited tolerability due to the high frequency of adverse events[150]. 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[151], this combination was found to be poorly tolerated regimen as several patients developed severe adverse drug reactions. These issues merit further studies.

In conclusion, treatment of MDR-TB is a challenge which should be undertaken by experienced clinicians at centres equipped with reliable laboratory service for mycobacterial culture and *in vitro* sensitivity testing. Judicious use of second-line drugs,

supervised individualised treatment, focussed clinical, radiological and bacteriological follow-up, judicious use of surgery at the appropriate juncture are key factors in the successful management of these patients. In certain areas, currently available programme approach may not be adequate and innovative approaches such as DOTS-plus may have to be employed to effectively control MDR-TB.

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