Review

Multi-drug resistant tuberculosis: An iatrogenic problem

Surya Kant[1,*], Anand K. Maurya[1], R. A. S. Kushwaha[1], Vijaya L. Nag[2], Rajendra Prasad[1]

[1] *Department of Pulmonary Medicine, C. S. M. Medical University UP, Lucknow, India;*
[2] *Department of Microbiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.*

Summary **The occurrence of resistance to drugs used to treat tuberculosis (TB), and particularly multi-drug resistant TB (MDR-TB) defined as resistance to at least rifampicin and isoniazid, has become a significant public health dilemma in a number of countries and an obstacle to effective global TB control. HIV-associated MDR-TB understanding is vital in providing strategies for treatment of HIV and drug-resistant TB. Better understanding on the basis of drug action and resistance is a key to development of diagnostic strategies, novel drugs, and treatment programs, and to find an approach to study the pathogenicity of drug resistant strains. The effectiveness of strategies such as DOTS-Plus in the management of MDR-TB patients under program conditions should be tested in operational field clinical trials following strictly standardized definitions and nomenclature.**

Keywords: Tuberculosis (TB), multi-drug resistant TB (MDR-TB), anti-tuberculosis drug, DOTS

1. Introduction

Tuberculosis (TB) is the leading cause of death from a curable infectious disease (*1*). On the basis of results of surveys of the prevalence of infection and disease, assessment of the effectiveness of surveillance systems, and death registrations, there were an estimated 8.9 million new cases of tuberculosis in 2004, fewer than half of which were reported to public-health authorities and WHO. About 3.9 million cases were sputum-smear positive which is the most infectious form of the disease (*2-4*).

Drug resistance can be simply defined as the temporary or permanent capacity of organisms and their progeny to remain viable or to multiply in the presence of the concentration of the drug that would normally destroy or inhibit cell growth (*5*). Clinically, drug resistance can be divided into four types (Table 1).

Anti-tuberculosis drug resistance is classified according to the following three definitions (*6*): (*i*) Confirmed mono-resistance: Tuberculosis in patients whose infecting isolates of *M. tuberculosis* are confirmed to be resistant *in vitro* to one first-line anti-tuberculosis drug; (*ii*) Confirmed poly-resistance: Tuberculosis in patients who′s infecting isolates are resistant *in vitro* to more than one first-line anti-tuberculosis drug other than both isoniazid and rifampicin; and (*iii*) Confirmed multi-drug resistant TB (MDR-TB): Tuberculosis in patients whose infecting isolates are resistant *in vitro* to at least isoniazid and rifampicin.

**Address correspondence to:*
Dr. Surya Kant, Department of Pulmonary Medicine, C. S. M. Medical University, Uttar Pradesh Lucknow-226003, India (Erstwhile King George Medical College).
e-mail: dr.kantskt@rediffmail.com

2. Site of drug-resistant tuberculosis disease (pulmonary and extrapulmonary) (*7*)

In general, recommended treatment regimens for drug-resistant forms of TB are similar, irrespective of site. Defining site is important primarily for recording and reporting purposes.

Pulmonary tuberculosis: Tuberculosis involving the lung parenchyma. Tuberculosis intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, therefore constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a pulmonary case.

Extrapulmonary tuberculosis: Tuberculosis of organs other than the lungs, *e.g.* pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. The definition of an extrapulmonary

Table 1. Four types of drug resistance

Type of drug resistance	Definition
Natural drug resistance	When neither the patient with naturally resistant bacilli nor his source of infection has had chemotherapy in the past.
Primary drug resistance	The presence of drug resistance to one or more anti-TB drugs in a TB patient who has received either no or less than one month of prior TB chemotherapy.
Acquired drug resistance	Resistance to one or more anti-TB drug which arises during the course of treatment usably as a result of non adherence to the recommended regimen or faculty prescribing. This is found in a patient who has received at least one month of anti-TB treatment and was referred to as secondary resistance in the past.
Initial drug resistance	Drug resistance in a patient who denies history of previous chemotherapy. In reality it consists of true primary resistance and an undisclosed acquired resistance.

case with several sites affected depends on the site representing the most severe form of disease.

3. Epidemiology of drug resistance (*8-11*)

In India, it is reported that 1-3.4% of new patients have had multi-drug resistant TB (*8*). Studies on acquired resistance have shown rates of resistance to isoniazid ranging from 34.5-67%, for streptomycin around 25% and for rifampicin from 2.8-37.3%.

In western countries, the incidence of MDR-TB has gradually increased (*9*). However, drug resistant TB is not uniformly distributed in the US but more prevalent in large urban areas and coastal or border communities. At Bellevue Hospital Centre which treats approximately 10% of all the TB patients in New York City, combined resistance to isoniazid and rifampicin increased from 2.5% in 1971 to 16% in 1991. The hazards of even brief courses of monotherapy were illustrated in a study by the CDC which found resistance to isoniazid in 25% of isolates from patients who had previously received up to 2 weeks of isoniazid alone. Isoniazid resistance increased to more than 60% among patients receiving 6 months of monotherapy and to more than 80% after 2 years. The main contributing factors to the "epidemic" of MDR-TB in certain cities in the west has been the combination of HIV infection, homelessness, drug addiction and overcrowding leading to rapid spread of the disease.

4. Factors responsible for developing drug resistance

Factors responsible for the development of drug resistance can be clinical, biological or social (Table 2). It is to be noted that one of the most important factors is unreliable treatment regimens prescribed by doctors. These include giving fewer drugs or giving a single drug in a regimen which is failing. This leads to development of resistance to that drug and also other important factors. Out of ignorance and due to lack of proper health education and motivation some patients do not take drugs regularly, and irregular chemotherapy leads to the development of drug resistance.

Table 2. Type of factors associated with drug resistance

Type of factors	Factors associated with drug resistance
1. Clinical factors	Unreliable treatment regimens by doctors • Lesser number of drugs • Inadequate dosage duration Addition of a single drug to a failing regimen Easy availability of drug in private sector Poor drug supply Poor quality of drugs
2. Biological factors	Initial bacillary population Local factors in host favorable for multiplication of bacilli Presence of drug in insufficient concentrations
3. Sociological factors	Irregular intake/inadequate duration Neglect of disease Ignorance Lack of health education

5. Mechanisms of Resistance

Mycobacteria have unique characteristics which endow them with natural resistance to many commonly used antibacterial agents. The hydrophobic cell envelope of *Mycobacteria* poses a barrier to many drugs (*12*). The bacilli also have transporters which flush out the drugs (*13*). Moreover, they can hydrolyze or modify the drug by synthesizing necessary enzymes. This explains why only a few drugs are effective against *M. Tuberculosis* and why they can develop resistance to anti-TB drugs through chromosomal mutations. Resistance to isoniazid can occur due to mutations in the *katG, InhA*, and *kasA* genes, whereas resistance to rifampicin can be affected by mutations in the *rpoB* gene (*15-18*).

6. Multi-drug resistant TB (MDR-TB)

Multi-drug resistant TB is defined as the disease caused by *M. tuberculosis* that is resistant to at least isoniazid and rifampicin with or without resistance to other anti-TB drugs (*19*). Resistance to isoniazid and streptomycin only is probably the most common form of resistance world wide to more than one drug. This

is not strictly multi-drug resistance. Therefore, another separate term is needed to define this combination of resistances. Resistance to streptomycin, isoniazid and another drug or drugs other than rifampicin is probably very uncommon. MDR-TB is naturally a man-made problem, since poor prescriptions, poor case management, lack of coordinated education, and haphazard treatment result in drug resistance. Besides, poor patient compliance (*e.g.* patients' pick-and-choose attitude about medicines from prescribed regimens) is a major hurdle. If treatment failure is observed clinically and the sputum remains positive even after 3-4 months of treatment, then drug resistance should be suspected. Since a culture and susceptibility testing facility is available only in a few places, the exact epidemiological implication of MDR cannot be assessed.

7. Extensive drug resistant-tuberculosis (XDR-TB)

Extensive drug resistant-tuberculosis (XDR-TB) has been reported in all regions of the world (*20*). XDR-TB is defined as resistance to at least rifampicin, isoniazid, a second-line injectable drug (capreomycin, kanamycin or amikacin), and fluoroquinolone (*21*). Control of drug resistant tuberculosis requires a strong health infrastructure to ensure delivery of effective therapy coupled with surveillance and monitoring activities to enable timely intervention to limit transmission and spread of the disease.

8. Magnitude of the MDR-TB problem

The appearance of MDR-TB has followed the pervasive use of rifampicin since the 1970s. The number of incident cases (including new and re-treatment cases) occurring worldwide in 2003 alone was estimated to be 458,000 (95% confidence limits, 321,000-689,000) by The WHO Stop TB (*22*). Widespread cases of MDR-TB could be two or three times higher than the number of incident cases (*23*). Data on drug resistance using standard methodology to establish the global magnitude of resistance to four first-line antituberculosis drugs, such as, isoniazid, rifampicin, ethambutol, and streptomycin, were given by the WHO/IUATLD Global Project on Antituberculosis Drug Resistance Surveillance (*24*,*25*). The standard methodology includes representative sampling of patients with an adequate sample size, standardized data collection distinguishing between new and previously treated patients, and quality-assured laboratory drug sensitivity testing (DST) supported by a network of supranational TB reference laboratories. By 2003, three rounds of the global project had been completed covering 109 countries or regions within large countries (*26*). In spite of these surveillance data, the magnitude of drug resistance is not yet known in many areas of the world with high burdens of TB, such as, most of China, India, Indonesia, Nigeria, and countries of the former Soviet Union. Nevertheless, evidence from half the world's nations confirms that drug resistance is a serious problem worldwide. Many areas of the world face endemic and epidemic MDR-TB, and in some areas the incidence of resistance is alarmingly high as documented by a third global report on antituberculosis drug resistance surveillance. In patients never previously treated, the median prevalence of resistance to any of the first-line drugs, most commonly streptomycin and/or isoniazid, was 10.7% (range 0-57.1%); 20 survey sites exceeded 20%. The median prevalence of MDR-TB was 1.2% (range 0-14.2%); 11 sites exceeded the 6.5% threshold for extreme values, including in the former Soviet Union. In patients previously treated, the median prevalence of any resistance was 23.3% (range 0-82.1%) and of MDR-TB, 7.7% (range 0-58.3%).

Drug resistance was strongly associated with previous treatment. In previously treated patients, the probability of any resistance was over 4-fold higher, and that of MDR-TB over 10-fold higher, than that in untreated patients. The overall prevalence of drug resistance was often related to the number of previously treated cases in the country. Among countries with a high burden of TB, previously treated cases ranged from 4.4% to 26.9% of all patients registered in DOTS programs. In the two largest high-TB burden countries (China and India) re-treatment cases accounted for more than 20% of sputum smear-positive cases (*27*).

9. Extra pulmonary MDR-TB and MDR-TB treatment

Treatment of MDR-TB requires prolonged and expensive chemotherapy using second-line drugs of heightened toxicity. If resistance to the second-line drugs also arises then the disease becomes virtually untreatable. The treatment strategy is the same for patients with pulmonary and extrapulmonary MDR-TB. If the patient has symptoms suggestive of central nervous system involvement and is infected with MDR-TB, the regimen should use drugs that have adequate penetration into the central nervous system (*28*,*29*). Rifampicin, isoniazid, pyrazinamide, protionamide/ethionamide and cycloserine have good penetration; kanamycin, amikacin and capreomycin penetrate effectively only in the presence of meningeal inflammation; *p*-aminosalycilic acid and ethambutol have poor or no penetration.

10. MDR-TB in the era of HIV

An alarming increase in infection due to the human immunodeficiency virus (HIV) has accelerated this situation and it is believed that, as of now, about 3.5

million people in India are infected with HIV (*30*). There is a grave concern in India regarding the increase in HIV-associated TB and the emergence of MDR-TB in both magnitude and severity of the TB epidemic. HIV co-infection is an important challenge for the prevention, diagnosis and treatment of drug-resistant TB, especially in the case of MDR-TB. The local epidemiological prevalence of HIV, MDR-TB, and HIV-associated MDR-TB is important in guiding strategies for treatment of HIV and drug-resistant TB. All Drug Resistance-TB control programs are therefore strongly encouraged to determine the extent of the overlap between the MDR-TB and HIV epidemics (*31*).

11. Diagnosis of MDR-TB in HIV-infected patients

The appearance of MDR-TB in the HIV-infected patient does not differ from that of drug-susceptible TB in the HIV-infected patient (*32*). The diagnosis of TB in HIV-positive people is more difficult and may be confused with other pulmonary or systemic infections. The presentation is more likely to be extrapulmonary or sputum smear-negative than in HIV-uninfected TB patients. This can result in misdiagnosis or delays in diagnosis and, in turn, higher morbidity and mortality. The use of X-ray and/or cultures improves the ability to diagnose TB in HIV patients and is recommended where available. In areas where MDR-TB is known to be a problem in HIV-positive patients, and where resources permit, all HIV patients with TB should be screened for MDR-TB with DST. Rapid diagnostic techniques for MDR-TB should be employed when possible since HIV-infected patients with TB on inadequate antituberculosis treatment, or no treatment, for even short periods of time are at a high risk for death (*33*).

12. Diagnosis/rapid detection of MDR-TB

Multi-drug resistant TB should be suspected in patients if:

• Patient has taken treatment for tuberculosis in the past.

• Isoniazid resistance prevalence in community is more than 4%.

• There is likelihood of patient being exposed to MDR-TB.

• There is poor response to drug treatment as indicated by

a. Prolonged fever or cough,

b. Sputum conversion failure despite four months of standard short course chemotherapy.

Mycobacteria grow slowly and hence drug susceptibility tests take about 10-12 weeks. Rapid testing methods are necessary to detect drug resistance early and institute appropriate drug treatment. Culture sensitivity methods can detect drug resistance in about a week using a phage-based method with luciferase-incorporated phage (*34*,*35*); the BACTEC method is a radiometric technique based on detection of radio labeled CO_2 as a measure of growth index for microorganisms (*36*,*37*); and genotypic techniques involving rapid genotypic analysis of *Mycobacteria* to detect gene mutations causing drug resistance are also available (*38*,*39*).

13. Prevention of multi-drug resistant tuberculosis (*40*,*49*)

There are two main approaches to prevent multi-drug resistance:

(a) Identification and treatment of patients with multi-drug resistant tuberculosis. The aim is to identify their disease and to prevent further transmission.

(b) Identification of persons with tubercular infection and their prophylactic treatment. The aim is to prevent the 5-10% risk of subsequent development of disease.

The accepted guidelines for preventing the transmission of tuberculosis in health care settings with special focus on HIV related issues are:

(a) Patients with active tuberculosis must be identified quickly by using the most sensitive and rapid laboratory methods available.

(b) Confirmed or even suspected infectious tuberculosis patients should be placed immediately in isolation.

(c) Effective antitubercular therapy should he started immediately in diagnosed patients.

(d) Cough inducing procedures (*e.g*. bronchoscopy, sputum induction, administration of aerosol treatment) in confirmed or suspected tuberculosis patients should be carried out in isolated rooms.

(e) Patients and health care workers exposed to multi-drug resistant infectious tuberculosis patients should be evaluated regularly for the presence of infection/disease.

(f) Patterns of drug resistance should be evaluated regularly in the community.

14. Basic principle of chemotherapy in multi-drug resistant tuberculosis (*41-43*,*50*)

1. Treatment should be in a specialized center with standard laboratory facilities.

2. An appropriate regimen for individual patient needs design experience and skill.

3. The regimen should contain at least five drugs including three new drugs, depending upon potency of available drugs and the resistance pattern and previous history of treatment. Any first line oral agent to which the isolate is sensitive should be used. One injectable, one fluroquinolone and as many second-

line bacterostatic agents as needed should be used to make up the five drug regimen in the initial phase of treatment. When five adequate agents are given consider use of additional drugs. Previously used drugs to which bacilli may still be sensitive may be added to the regimen especially if they are powerful.

4. Never add a single drug to a failing regimen.

5. It is effective to combine two potentially ineffective drugs because of cross resistance. Cross resistance has been reported between thioamide and thioacetazone, kanamycin/amikacin with streptomycin (*41,42*). rifampicin with rifapentine, and rifabutin (> 70% strain) among various derivatives of fluoroquinolones. Cross resistance has also been reported between ethionamide and isoniazid, viomycin and kanamycin, viomycin and capreomycin/amikacin are still sensitive to capreomycin.

6. All the drug should be given in a single daily dose preferably, expert PAS is usually given in two divided doses in order to avoid the problem of intolerance. Among thioamides, prothioamide is better tolerated than ethionamide.

7. Intermittent therapy is usually not effective and should be avoided in multi-drug resistance tuberculosis.

8. No drug should be kept in reserve and the most powerful drugs (bactericidal) should be used initially and in maximum combinations to ensure that the first battle is won and won permanently.

9. Therapy should be under direct observation preferably for 3-4 months or until sputum conversion.

10. Surgical treatment should be considered as an adjunct to chemotherapy wherever applicable, as results of chemotherapy are very unpredictable.

11. All measures should be taken to persuade and encourage patients not to stop treatment despite all its discomfort as it is the last treatment that stands between the patient and death.

15. Drugs used in MDR-TB and their toxicities

The second-line drugs used for treatment of multi-drug resistance tuberculosis are given in Table 3 with their dosages in decreasing potency from top to bottom against mycobacterium tuberculosis. It is generally thought that, reserve drugs are frequently associated with very high rates of unacceptable adverse reactions, which need frequent interruption and change of regimen, but in clinical practice it is observed that they are not very toxic. The authors reported that 41%, experienced some side effects but only 21.1% of the patients required stoppage or change of drug in the study of 39% MDR-TB. Thus, it is practically possible to treat the MDR-TB patients with these drugs (*44*). Second-line reserve drugs, their toxicities and management are given in Table 4.

16. Regimen for multi-drug resistant tuberculosis

World Health Organization (WHO) has a recommended regimen (*41*,*42*) without availability of sensitivity results (Table 5) and with availability of sensitivity results (Table 6).

Table 3. Second-line drugs used for treatment of MDR tuberculosis

Drugs	Average daily dosage	Daily dosage (mg)		Type of antimycobacterial activity
		Minimum	Maximum	
Aminoglycoside	15 mg/kg	750	1,000	Bactericidal against activity multiplying organisms
Kanamycin				
Amikacin				
Capreomycin				
Thioamides	10-20 mg/kg	500	750	Bactericidal
Prothionamide				
Ethionamide				
Fluroquinolone				
Ciprofloxacin	15-20 mg/kg	1,000	1,500	Weakly bactericidal
Ofloxacin	7.5-15 mg/kg	600	800	
Sparfloxacin	6-8 mg/kg	400	600	
Levofloxcin		500	750	
Bacteriostatic second-line drugs				Bactericidal
Cycloserine	10-20 mg/kg	500	750	
p-Aminosalycilic acid	200-3,000 mg/kg	10 g	12,000	
Others drugs				
Clofazimine	4-5 mg/kg	100	200	Bacteriostatic
Coamaxyclav		750	2,000	Weakly bactericidal
Clarithromycin	10-15 mg/kg	1,000 mg/kg		Bacterial (pH dependent)
Azithromycin	10 mg/kg	500 mg/kg		
Rifabutin	May be used against some isolates of MDR-TB resistant rifampicin but sensitive to rifabutin.			
Thiacetazone	High rate of site effects in HIV patients.			
High dose Isoniazid	Animal model supports use but conflicting clinical data.			

17. Surgery for MDR-TB (*49*)

Surgery should be considered in patients with persistent culture positive MDR-TB despite effective medical treatment. If the patient has localized disease, reasonable lung function and only two or three (weak) drugs available, surgery should be seriously considered. Resection surgery is done as an adjunct to medical treatment (*45*). Published data has shown that overall cure rate was substantially higher (81-56%) when

Table 4. Toxicities and their management

Drug	Symptoms	Reaction
Kanamycin	Hearing loss	Change to capreomycin Lower the dose of drug Discontinue suspected drug if can be done without compromising regimen
Ethionamide Cycloserine	Psychotic symptoms	Initiate antipsychotic drugs Hold suspected agent for short period (1-4 weeks) lower the dose of drug Discontinue suspected drug if it can be done without compromising regimen
p-Aminosalycilic acid Ethionamide	Nausea and vomiting	Rehydration Initial anti-emetic therapy Lower the dose of drug Discontinue suspected drug if can be done without compromising regimen
Cycolserine	Seizures	Start anticonvulsant therapy Increase pyridoxine to 300 mg/day lower the dose of drug Discontinue suspected drug if can be done without compromising regimen

Table 5. Regimen before (or without) sensitivity results

Initial phase		Continuation phase	
Drugs	Minimum duration in months	Drugs	Minimum duration in months
Aminoglycoside[a]	6	Ethionamide	12-18
Ethionamide	6	Fluroquinolone[b]	12-18
Fluroquinolone[b]	6	Pyrazinamide	12-18
Pyrazinamide	6	Ethambutol +/–	12-18
Ethambutol +/–	6		

[a] Kanamycin, amikacin, or capreomycin. [b] Ciprofloxacin or ofloxancin.

Table 6. Regimen for multi-drug resistant tuberculosis when sensitivity results available

Resistance to	Initial phase		Continuation phase	
	Drugs	Minimum duration in months	Drugs	Duration in months
Isoniazid Rifampicin	Aminoglycoside[a] Ethionamide[b] Fluroquinolone[c] Pyrazinamide Ethambutol +/–	6 6 6 6 6	Ethionamide[b] Fluroquinolone[c] Pyrazinamide Ethambutol +/–	12-18 12-18 12-18 12-18
Isoniazid Rifampicin Streptomycinc[d] Ethambutol	Aminoglycoside[a] Ethionamide[b] Fluroquinolone[c] Cycloserine[e]	6 6 6 6	Ethionamide[b] Fluroquinolone[c] Cycloserine[e]	18 18 18
Resistance to all drugs	Aminoglycoside[a] Fluroquinolone[c] Two of these Ethionamide[b] *p*-Aminosalycilic acid Cycloserine[e]	6 6 6 6 6	Fluroquinolone[c] Two of these Ethionamide[b] *p*-Aminosalycilic acid Cycloserine[e]	18 18 18 18
Susceptibility test to reserve dugs available	Tailor regimen according to Susceptibility pattern[f]			

[a] Kanamycin or amikacin, or capreomycin. [b] If Ethionamide is not available or poorly tolerated (even at a dose of 500 mg/day) use ofloxacin. [c] Ciplofloxacin or ofloxacin. [d] Streptomycin, if still active, if resistant to streptomycin, use kanamycin or capreomycin. [e] *p*-Aminosalycilic acid if cycloserine is not available or too toxic. [f] Individualized regimen is feasible in designated centers of excellence.

Table 7. Relationship of the principles essential DOTS and the DOTS-Plus strategies

DOTS strategy	DOTS-Plus strategy
Political and administrative commitment	Sustained political and administrative commitment
Good-quality diagnosis by sputum microscopy	Accurate, timely diagnosis through quality-assured culture and drug susceptibility Testing
Directly observed treatment	Directly observed treatment
Systematic monitoring and accountability	Standardized recording and reporting system that enable performance monitoring and evaluation of treatment outcome
Uninterrupted supply of good-quality first-line drugs for standardized treatment through outpatient therapy	Uninterrupted supply of quality assured first and second-line drugs; appropriate treatment strategies utilizing second-line drugs under strict supervision

DOTS-Plus is an essential component of the presented National Tuberculosis Control Program to be implemented through program communications.

surgery was more frequently and aggressively applied (*46*). Feasibility and success of surgery appears to be substantially enhanced by nutrient support (*47*).

18. DOTS-Plus

The first WHO endorsed DOTS-Plus programs began in 2000 (*48*). The Green Light Committee (GLC) was established to promote access to high quality second-line drugs for appropriate use in TB control programs. The DOTS Plus strategy is part of the comprehensive DOTS strategy recommended by the WHO. The Revised National Tuberculosis Control Program (RNTCP) views the treatment of MDR-TB patients as a "standard of care" issue. Recognizing that the treatment of MDR-TB cases is very complex, the prescribed regimen follows the internationally recommended DOTS Plus guidelines and is available from designated RNTCP DOTS Plus sites. These sites will be located in a limited number of highly specialized centers, at least one in each large state, and will have ready access to a state level accredited culture and DST laboratory, and the Intermediate Reference laboratory (IRL) under RNTCP. These sites should have sufficient qualified staff available to manage MDR-TB patients, using standardized second-line drug regimens given under daily DOT, with consistent follow-up protocols.

19. Conclusion

The management of MDR-TB is a challenge that should be undertaken by experienced clinicians at centers equipped with reliable laboratory services for mycobacterial cultures and *in vitro* sensitivity testing because it requires prolonged use of costly second-line drugs with a significant potential for toxicity. The judicious use of drugs; supervised standardized treatment; focused clinical, radiological, and bacteriologic follow-up; and surgery at the appropriate juncture are key factors in the successful management of MDR-TB. Genotypic techniques involve rapid genotypic analysis of MDR-TB and newer effective anti-TB drugs are still a distant dream. Innovative approaches such as DOTS-Plus show promise for the management of MDR-TB patients and appear to be a hope for future.

References

1. WHO. The World Health Report 2004: Changing History. World Health Organization, Geneva, Switzerland, 2004.
2. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. JAMA. 1999; 282:677-686.
3. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003; 163:1009-1021.
4. WHO. Global Tuberculosis Control: Surveillance, Planning, Financing. World Health Organization, Geneva, Switzerland, 2006; p. 242
5. Singla R. Management of drug resistance pulmonary Tuberculosis in India. The Cardiothoracic Journal. 1995; 1:312-316.
6. Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2006. 361
7. Francis J. Curry National Tuberculosis Center and California Department of Health Services, 2004: Drug-Resistant Tuberculosis: A Survival Guide for Clinicians.
8. Paramasivan CN, Bhaskaran K, Venkataraman P, Chandrasekaran V, Narayanan PR. Surveillance of drug resistance in tuberculosis in the state of Tamil Nadu. Ind J Tub. 2000; 47:27-33.
9. Trivedi SS, Desai SG. Primary TB drug resistance and acquired Rifampicin resistance in Gujarat, India. Tubercle. 1988; 69:37-42.
10. Jain NK, Chopra KK, Prasad G. Initial and acquired Isoniazid and Rifampicin resistance to *M. tuberculosis* and its implications for treatment. Indian J Tuberc. 1992; 39:121-124.
11. Datta M, Radhamani MP, Salvaraj R, Paramsivan CN, Gopalana BN, Sudeendraa CR, Prabhakar R. Critical assessment of smear positive pulmonary TB patients after chemotherapy under the district TB programme. Tuber Lung Dis. 1993; 74:180-186.
12. Costello HD, Caras GJ, Snider DE Jr. Drug resistance

among previously treated tuberculosis patients, a brief report. Tubercle. 1980; 121:313-316.
13. Blanchard JS. Molecular mechanisms of drug resistance in Mycobacterium tuberculosis. Annu Rev Biochem. 1996; 65:215-239.
14. David HL. Basis for lack of drug susceptibility of atypical Mycobacteria. Rev Infect Dis. 1981; 3:878-884.
15. Cole ST, Brosch R, Parkhill J, *et al*. Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature. 1998; 393:537-544.
16. Telenti A. Genetics of drug resistant tuberculosis. Thorax. 1998; 53:793-797.
17. Ramaswamy S, Musser JM. Molecular genetic basis of antimicrobial agent resistance in Mycobacterium tuberculosis: 1998 update. Tuber Lung Dis. 1998; 79:3-29.
18. Zhang Y, Telenti A. Genetics of drug resistance in Mycobacterium Tuberculosis. In: Molecular genetics of Mycobacteria (Hatfull GF, Jr. Jacobs WR, eds.). Washington American Society for Microbiology, 2000. (in press)
19. Veen J. Drug Resistant tuberculosis: back to sanatoria, surgery and cod-liver oil? Eur Respir J. 1995; 8:1073-1075.
20. Centers for Disease Control and Prevention (CDC). Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugs--worldwide, 2000-2004. MMWR Morb Mortal Wkly Rep. 2006; 55:301-305.
21. Centers for Disease Control and Prevention (CDC). Revised definition of extensively drug-resistant tuberculosis. MMWR Morb Mortal Wkly Rep. 2006; 55:11-76.
22. Zignol M, Hosseini MS, Wright A, Weezenbeek CL, Nunn P, Watt CJ, Williams BG, Dye C. Global incidence of multidrug-resistant tuberculosis. J Infect Dis. 2006; 194:479-485.
23. Blower SM, Chou T. Modeling the emergence of the "hot zones": tuberculosis and the amplification dynamics of drug resistance. Nat Med. 2004; 10:1111-1116.
24. Guidelines for surveillance of drug resistance in tuberculosis. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.320; WHO/CDS/CSR/RMD/2003.3).
25. Anti-tuberculosis drug resistance in the world. Third global report. The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance, 1999-2002. Geneva, World Health Organization, 2004 (WHO/HTM/TB/2004.343).
26. Global tuberculosis control: surveillance, planning, financing. WHO report 2004. Geneva, World Health Organization, 2004 (WHO/HTM/TB/2004.331).
27. Migliori GB, Espinal M, Danilova ID, Punga VV, Grzemska M, Raviglione MC. Frequency of recurrence among MDR-TB cases 'successfully' treated with standardised short-course chemotherapy. Int J Tuberc Lung Dis. 2002; 6:858-864.
28. Holdiness MR. Cerebrospinal fluid pharmacokinetics of the antituberculosis drugs. Clin Pharmacokinet. 1985; 10:532-524.
29. Daley CL. Mycobacterium tuberculosis complex. In: Antimicrobial therapy and vaccines (Yu VL, Merigan TC Jr, Barriere SL, eds.). Philadelphia, Lippincott Williams & Wilkins, 1999; 8:531-536.
30. Joshi PL. HIV/AIDS in India. Ranbaxy Science Foundation Round Table Conference Series. 2000; 6:27-32.
31. Paramasivan CN, Venkataraman P. Drug resistance in tuberculosis in India. Indian J Med Res. 2004; 120:377-386.
32. TB/HIV: a clinical manual. Geneva, WHO, 2003 (WHO/HTM/TB/2004.329).
33. Telenti A, Iseman M. Drug-resistant tuberculosis: what do we do now? Drugs. 2000; 59:171-179.
34. Dickinson JM, Allen BW, Mitchison DA. Slide culture sensitivity tests. Tubercle. 1989; 70:115-121.
35. Jacobs WR Jr, Barletta RG, Udani R, Chan J, Kalkut G, Sosne G, Kieser T, Sarkis GJ, Hatfull GF, Bloom BR. Rapid assessment of drug susceptibilities of Mycobacterium tuberculosis by means of luciferase reporter phages. Science. 1993; 260:819-822.
36. Cooksey RC, Crawford JT, Jacobs WR Jr, Shinnick TM. A rapid method for screening antimicrobial agents for activities against a strain of Mycobacterium tuberculosis expressing firefly luciferase. Antimicrob Agents Chemother. 1993; 37:1348-1352.
37. Good RC, Mastro TD. The modern mycobacteriology laboratory. How it can help the clinician. Clin Chest Med. 1989; 10:315-322.
38. Huebner RE, Good RC, Tokars JI. Current practices in mycobacteriology: results of a survey of state public health laboratories. J Clin Microbiol. 1993; 31:771-775.
39. Telenti A, Imboden P, Marchesi F, Lowrie D, Cole S, Colston MJ, Matter L, Schopfer K, Bodmer T. Detection of rifampicin-resistance mutations in Mycobacterium tuberculosis. Lancet. 1993; 341:647-650.
40. Samaria JK, Matah SC, *et al*. Multidrug Resistant T.B. Postgraduate update, A. Passi Publication.
41. Treatment of tuberculosis: Guidelines for National Programmes. Geneva, WHO, 2003(WHO CDS/TB/2003.313).
42. Crofton J, Chaulet P, Maher D. Guidelines for the management of drug resistant tuberculosis. Geneva, WHO, 1997 (Document WHO /TB/96:210).
43. Mukerjee JS, Rich ML, Socci AR. Programmes and principles in treatment of multidrug resistant tuberculosis. Lancet. 2004; 363:474-81.
44. Prasad R, Verma SK, Sahai S, Kumar S, Jain A. Efficacy and safety of kanamycin, ethionamide, PAS and cycloserin in multidrug resistant pulmonary tuberculosis patients. Indian J Chest Dis Allied Sci. 2006; 48:183-186.
45. Iseman MD. Treatment of multidrug resistant tuberculosis. New Eng J Med. 1993; 329:784-791.
46. Iseman MD, Madsen L, Goble M, Pomerantz M. Surgical intervention in the treatment of pulmonary disease caused by drug resistant mycobacterium tuberculosis. Am Rev Respir Dis. 1990; 141:623-625.
47. Takeda S, Maeda H, Hayakawa M, Sawabata N, Maekura R. Current surgical intervention for multidrug resistant tuberculosis. Ann Thorac Surg. 2005; 79:959-963.
48. DOTS-Plus Guidelines. Revised National Tuberculosis Control Programme March 2006.
49. Prasad R.Management of multi-drug resistant tuberculosis: Practitioner's view point. Indian J Tuberc. 2007; 54:3-11..
50. Arora VK , Arora Raksha (1st. ed.). Practical Approach to Tuberculosis Management. Jaypee Brothers Medical Publishers (P) Ltd. New Delhi, India, 2006.

(Received February 13, 2010; Revised March 27, 2010; Accepted March 29, 2010)