

Management of Multidrug Resistant Tuberculosis

Zul Dahlan

Department of Internal Medicine, Medical Faculty, Padjadjaran University, Bandung

INTRODUCTION

In the last decade, tuberculosis (TB) has reemerged as one of the leading causes of death (nearly 3 million deaths annually). The estimated 8.8 million new cases every year correspond to 52,000 deaths per week or more than 7,000 each day, which translates into more than 1,000 new cases every hour, every day. These death rates, however, only partially depict the global TB threat; more than 80% of TB patients are in the economically productive age of 15 to 49 years. The emergence of AIDS and decline of socioeconomic standards contribute to the disease's resurgence in industrialized countries. In most developing countries, although the disease has always been endemic, its severity has increased because of the global HIV pandemic and extensive social restructuring due to rapid industrialization and conflicts. A major public health problem worldwide, TB is now a global emergency.

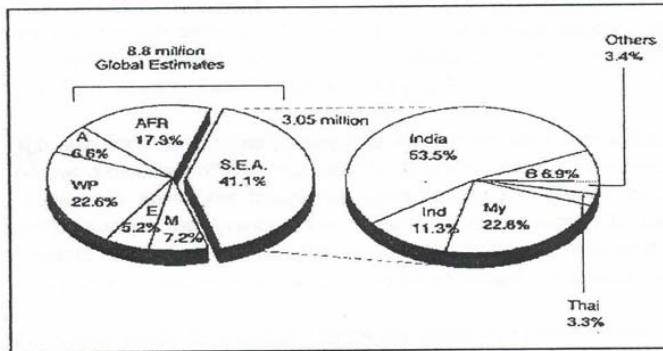


Figure 1. Global incidence of tuberculosis. Of the estimated 8.8 million cases worldwide, more than 40% of the cases are in Southeast Asia; India has approximately 53.3% of those cases. A, Americas; Afr, Africa; WP, Western Pacific; E, Europe; M, Eastern Mediterranean; and SEA, Southeast Asia; Ind, Indonesia; B, Bangladesh; Thai, Thailand; My, Myanmar. *Others include Bhutan, 0.05%; Nepal, 1.2%; Maldives, 0.001%; Sri Lanka, 1%; DPR Korea, 1.2%. (Data from reference 1).

A major cause of drug-resistant TB and treatment failure is patient nonadherence to prescribed treatment. Treatment failure and drug-resistant TB can be life-threatening and pose other serious public health risks because they can lead to prolonged infectiousness and increased transmission of TB in the community.

The World Health Organization (WHO) has for the first time assembled hard evidence that the emergence of drug resistant tuberculosis can be held back by properly controlled treatment programmes⁽²⁾. Directly observed therapy (DOT) has been endorsed by infectious disease experts to contain the international epidemic of tuberculosis and the burgeoning number of drug-resistant cases.

DOT is one method of ensuring adherence; it requires that a health-care provider or other designated person observe while the patient ingests anti-TB medications. DOT should be considered for all patients because of the difficulty in predicting which patients will adhere to a prescribed treatment regimen.

PROBLEM OF DRUG RESISTANCE

Multidrug-resistance tuberculosis (MDRTB) is not a new but "natural phenomenon", an iatrogenic disease arising under the selective pressure of inadequate therapy. Clinically drug resistant is divided into two types, secondary and primary drug resistant tuberculosis (**fig. 1**). Secondary (or acquired) drug-resistant tuberculosis develops when drug resistant tubercle bacilli outgrow susceptible bacilli due to selection and multiplication of resistant mutants by inappropriate therapy. Primary drug-resistant tuberculosis occurs in patients who have never been treated with antituberculosis before, but have become infected with resistant organisms. The term "initial resistance" is used if resistance is observed in the first isolate of a patient who claims never to have had chemotherapy.

The ratio secondary/primary resistance is important since it provides information about the relative contribution of: 1). Inadequate treatment delivery; 2). Transmission to the resistance problem. In some low prevalence countries, drug resistance

¹Presented at 3rd Asia Pacific Conference on Travel Health, 6th National Congress of Tropical Health and Infectious Diseases, Bali, July 21- 23, 2000.

tuberculosis is observed predominantly in immigrants. If this is the case, it is necessary to determine whether drug-resistant tuberculosis as imported, or resulted from poor treatment or transmission after immigration. Control effort should focus on the prevention of inadequate treatment⁽⁴⁾.

The World Health Organization (WHO) has assembled hard evidence that the emergence of drug-resistant tuberculosis can be held back by properly controlled treatment programmes. It warns, however, that the “window of opportunity” to prevent the spread of drug-resistant strains will be missed if urgent action is not taken to persuade more health authorities and doctors to use its recommended treatment strategy, which still reaches only 1 in 5 patients with tuberculosis worldwide. A global report shows a disturbingly high prevalence of drug-resistant strains of *M. tuberculosis* in parts of eastern Europe and Asia.

By contrast, countries that have used the recommended treatment strategy tend to have very low rates of resistance. The report has data from 58 countries and other settings (such as provinces of China) and enough data to detect trends in 28. Its authors warn, however, that the picture is still incomplete. The scale of drug resistance is not fully known in the five countries with the highest incidence of tuberculosis worldwide: India, China, Indonesia, Bangladesh, and Pakistan⁽²⁾

THERAPY

Definition

Diagnosis of drug-resistant tuberculosis is made on the clinical and microbiological data. Therapy is given based on treatment principles, and specific regimens for certain resistance patterns, as proposed by Bureau of TB Control of New York City⁽³⁾. In this protocol, MDRTB refers to a strain of *M. tuberculosis* resistant to at least isoniazid and rifampin.

Treatment of Drug-Resistant Tuberculosis

Unlike protocols for the treatment of tuberculosis susceptible to all first-line anti-tuberculosis medications, it is not possible to develop appropriate, standardized protocols for treatment of known or suspected drug-resistant tuberculosis. Several issues come into play:

- Any treatment recommendation must take into account the drug susceptibility results of an individual isolate;
- Good data are lacking on the efficacy of non-standard regimens; AND
- Side effects to second-line medications, often serious and intolerable, do not allow their use for the recommended period of time in many cases.

Protocols for treatment of MDR-TB should be considered guidelines only. Opinions vary on the best medications to use for an individual patient.

The treatment of drug-resistant tuberculosis serves both an individual (cure), and a public health benefit (breaking the chain of transmission). It seems that treatment outcome of patients with MDR depends to a high degree on the skills of doctors and laboratories. Early diagnosis of tuberculosis, early suspicion of resistance and early appropriate treatment are the most important determinants for improved outcome in MDR tuberculosis (Lambrecht, 1997)⁽⁴⁾.

Multidrug-Resistant TB Treatment Principles⁽³⁾

1. MDRTB should never be treated without expert consultation.
2. An individual must be treated with a regimen of at least two (2), and preferably three (3) anti-tuberculosis medications to which the organism is likely to be susceptible.
3. A single anti-tuberculosis medication should never be added to a regimen that is failing. At least two (2), and preferably three (3) new anti-tuberculosis medications to which the organism is likely to be susceptible, should be added.
4. Treatment for strains of TB resistant to at least isoniazid and rifampin should be given for at least 18 months after culture conversion to negative; and for up to 24 months after culture conversion to negative in some HIV-seropositive individuals or those with cavitary disease.
5. An individual with multidrug-resistant TB should be treated under a program of directly observed therapy (DOT).
6. An individual with multidrug-resistant TB should not be treated with intermittent therapy regimens.
7. For an individual with a positive *M. tb* culture after three (3) months of anti-tuberculosis treatment, at least two (2) treatment decision alternatives are available.
8. If an individual is not acutely ill, or clinically deteriorating, the current or last prior antituberculosis regimen is continued until the new drug susceptibility results are available. This is often referred to as a “holding regimen”.
9. If she/he is acutely ill, or clinically deteriorating, new medications need to be started, based on an assessment of what remaining medications the organism is likely to be susceptible to. The original medications should be continued pending repeat drug susceptibility testing results.
10. If a regimen is not failing, but it is too soon to discontinue any medications (i.e., individual has clinical improvement and *M. tb* cultures have converted from positive to negative) and the individual is having severe-enough side effects from an identifiable medication, precluding its further use, two (2) therapeutic chokes are available, depending upon the duration and success of treatment until the adverse reaction occurred.
11. The medication responsible for the side effect should be omitted and the remainder of the anti-TB treatment regimen continued;
12. Alternatively, a new, previously unused agent for the offending drug should be substituted.
13. If the cause for the adverse reaction (e.g. hepatotoxicity, skin rash) cannot be readily identified, all medications should be discontinued and retested by reintroduction singly into a regimen or trial.
14. Aminoglycosides or capreomycin, when indicated, should be used for the recommended time period of four (4) to six (6) months unless ototoxicity or nephrotoxicity develops. A course of antibiotics which continues six months after culture conversion may be appropriate, if there is extensive disease or slow conversion of sputum cultures. With documented MDRTB, overtreatment is far preferable to undertreatment, which may have dire consequences for the individual and his/her family.

Regiment of anti tuberculosis drug

The goal of treatment is to cure the patient and to prevent

the acquisition of (more) resistance. Decision regarding the choice of regimen in the intensive phase of treatment based on, the results of susceptibility testing, which is rarely available before treatment is implemented. General guidelines to select regimen is then based on Lambregts- Weezenbeek (1997)⁽⁴⁾ :

I. If drug resistance is suspected, but not proven

The choice of the regimen depends on the reason for the suspicion. In these circumstances the following guidelines apply: 1) in a case with a history of previous treatment the initial regimen should contain at least two, but preferably three or four, drugs the patient has not taken before; 2) in a case when the patient is known (or believed) to be infected by a drug-resistant “index case”, the initial phase of treatment should be based on the susceptibility pattern found with the index case; 3) in a case when the patient originates from a region with high levels of drug resistance (mostly INH or streptomycin), an intensive phase with at least four drugs should be started (INH, rifampicin, pyrazinamide, ethambutol). The continuation phase of treatment should not be started until the susceptibility test has proved the strain concerned to be susceptible for both INH and rifampicin; 4) if the suspicion is based on clinical information (persistence of positive smears, poor clinical response, reoccurrence of positive smears after sputum conversion), at least two new drugs must be added. A single drug should never be added to a failing regimen since that may cause acquisition of new drug resistance.

II. General guidelines in cases when the susceptibility pattern is available

a. *INH or INH/streptomycin resistance.* A three drug regimen with rifampicin, pyrazinamide and ethambutol given for 6-9 months is highly effective. Some clinicians prefer continuing isoniazid in the regimen.

b. *Resistance to rifampicin only.* A rational regimen would consist of an initial phase of at least two months (until sputum conversion) with INH, pyrazinamide, ethambutol and streptomycin, followed by a prolonged (the sterilizing effect of rifampicin is lacking) continuation phase with INH and ethambutol.

c. *Mul6dru4g resistance (resistance to at least INH and rifampicin).* Sometimes the most important move a physician can make is to consult a more experienced colleague.

The treatment regimen depends on the susceptibility pattern, the potency of the drugs for which the strain concerned is still sensitive in vitro, and the clinical status of the patient. The optimal duration of such a regimen has yet to be identified. In the literature a duration of 24 months after sputum culture conversion is advised, based on the impression that discontinuation before this time increases the risk of relapse.

Although the treatment of MDR tuberculosis requires an individual analysis for each case, some general guidelines were presented by Iseman (1993)⁽⁵⁾. 1) initiate the therapy in hospital to permit observation of toxicity and intolerance and to allow a change of regimen before strongly aversive conditioning makes the patient psychologically and physically intolerant of antituberculous medication, 2) initiate treatment

with small doses of each drug and increase to the planned dose within 3-10 days; 3) drug dosages and optimal timing of administration should be determined for each patient in order to achieve maximal serum concentrations in the target range with minimal side-effects; 4) absorption of antituberculous drugs should be documented in AIDS patients who are at risk for malabsorption.

In case of MDR tuberculosis the treatment regimen should include at least four, but possibly as many as six or seven drugs, to which the strain concerned is still susceptible. The regimens proposed by Iseman (1993)⁽⁵⁾ are summarized in **table 1**.

The fluoroquinolones (ofloxacin, ciprofloxacin) are preferable to the other second-line drugs with regard to both antimycobacterial activity and safety.

Table 1. Potential regimens for patients with tuberculosis with various patterns of drug resistance⁽⁴⁾

Resistance	Suggested regimen	Duration of therapy months	Comments
Isoniazid, streptomycin, and pyrazinamide	Rifampin Pyrazinamide Ethambutol Amikacin*	6-9	Anticipate 100% response rate and less than 5% relapse rate
Isoniazid and ethambutol (± streptomycin)	Rifampin Pyrazinamide Ofloxacin or ciprofloxacin Amikacin	6-12	Efficacy should be comparable to above region
Isoniazid and rifampin (± streptomycin)	Pyrazinamide Ethambutol Ofloxacin or ciprofloxacin Amikacin*	18-24	Consider surgery
Isoniazid, rifampin, and ethambutol (± streptomycin)	Pyrazinamide Ofloxacin or ciprofloxacin Amikacin*	24 after conversion	Consider surgery
Isoniazid, rifampin, and pyrazinamide (± streptomycin)	Ethambutol Ofloxacin or ciprofloxacin Amikacin Plus 2+	24 after conversion	Consider surgery
Isoniazid, rifampin, pyrazinamide and Ethambutol (± streptomycin)	Ofloxacin or ciprofloxacin Amikacin* Plus 3+	24 after conversion	Surgery, if possible

*; If there is resistance to amikacin, kanamycin and streptomycin, capreomycin is a good alternative. Injectable agents are usually continued for 4-6 months if toxicity does not intervene. All the injectable drugs are given daily (or twice or three weekly) and may be administered intravenously or intramuscularly. †: Potential agents from which to choose : ethionamide, cycloserine, or aminosalicylic acid. Others that are potentially useful but of unproved ability include capreomycin and amoxycyline clavulanate. Clarithromycin, azithromycin, and rifabutin are unlikely to be active.

The MIC of both drugs is low for strains not previously exposed to the drug. However, resistance to fluoroquinolones has been shown to develop if they are used in an inadequate regimen. Fluoroquinolones are well tolerated with little

toxicity despite long-term high dose administration (Iseman, 1993). Of all tuberculous drugs, ethionamide is the most poorly tolerated (severe gastrointestinal distress). Because few patients can tolerate therapeutic doses, its use should be restricted to situations without other alternatives⁽⁵⁾.

Due to high levels of cross-resistance with rifampicin, rifabutin does not play an important role in the treatment of patients with MDR tuberculosis, except in those few patients who have rifabutin-susceptible strains⁽⁵⁾. Pretet and co-workers did report good results with rifabutin-containing regimens in the treatment of MDR, but it is difficult to assess the respective role of rifabutin and companion drugs in cases of successful treatment.

Cycloserine is known for potential central nervous system toxicity⁽⁵⁾. It is advised to monitor serum concentrations (peak concentrations should be 25-35 ug.ml¹). Pyridoxine 50-100 mg.day¹ is often added, although its value has not been proved.

In case of resistance to amikacin, kanamycin cannot be used (cross-resistance), but capreomycin can be used (no cross-resistance with either of these two drugs).

Surgical intervention⁽⁴⁾

Experience with large numbers of patients with MDR tuberculosis indicates that a favourable bacteriological response to chemotherapy usually occurs within 4 months. If sputum conversion does not occur or the patient relapses, the potential benefits of surgery should be as an adjunct to medical treatment. In particular, patients with high levels of resistance to INH, rifampicin and the other first line drugs should be considered for operation, provided their disease is sufficiently localized and they have adequate cardiopulmonary reserve. The goal of surgery is to excise all gross disease.

MANAGEMENT OF CONTACT OF MDR CASES

Therapy Strategy

Person contacted by MDR tuberculosis at the risk of developing active MDR tuberculosis should be advised to take an alternative preventive (AP) regimen, which depending on the susceptibility pattern is advised to use either a quinolone in combination with ethambutol or pyrazinamide, or a combination of ethambutol and pyrazinamide.

Who should be treated with AP-regimens?

Infected contacts with a normal immune status, who have never been infected with tubercle bacilli before, face a 5-10% risk of developing active tuberculosis during their life. Eighty per cent of those who do break down to active disease, do so within 2 years of infection. The risk of break down to active disease is much smaller if the contact case has been infected with tubercle bacilli before (known to have a positive tuberculin skin test or previous disease).

On the other hand, the risk of developing active tuberculosis is much higher in immunocompromised contacts, especially HIV-infected persons, immunodeficiency being the most important determinant of whether a person infected with M. tuberculosis will break down to active disease. Given the unknown effectiveness of these alternative preventive regi-

mens and the high rates of side-effects, the use of these AP regimens should be limited to: 1) infected contacts who are at high risk of developing active MDR tuberculosis; and 2) infected contacts who, after proper information, decide that they prefer preventive treatment. It must be stressed that the likelihood of a recent infection with MDR tubercle bacilli must be assessed according to the diagnostic guidelines, and the presence of active tuberculosis should be ruled out before preventive treatment is started. This advice implies that all contacts of MDR tuberculosis cases should be informed about the relative risk of developing active disease and the increased risk in case of coexistence of HIV infection.

Contacts at high risk of developing active MDR tuberculosis

Immunocompromised persons believed to be recently infected with MDR tubercle bacilli should be advised to take an AP regimen. The choice of this regimen must be based on the last susceptibility pattern found in the index case. Before AP treatment is started, active tuberculosis must be ruled out. Since extrapulmonary tuberculosis is common in HIV-infected persons, these patients should be questioned about nonpulmonary symptoms. Although extrapulmonary tuberculosis cannot be excluded in all cases, the risk must be reduced as much as possible. CDC advises to continue AP-treatment in HIV-infected contacts for 12 months. However, the optimal duration is yet to be clarified. All persons on treatment must be advised to report immediately in case of symptoms and/or side-effects.

Contacts at low (0-10%) risk of developing active MDR tuberculosis

Some contacts, who realize that the chance of remaining healthy is probably >90%, prefer clinical control visits to a 6 month AP regimen of unknown effectiveness, which is often not well tolerated. This policy seems perfectly responsible provided that these contacts are systematically controlled for at least 2 years following infection. At the end of this period their risk is reduced to 0-2%. These patients must be instructed to report in case of (even minor) clinical symptoms. However, some patients cannot endure the presence of, as one patient put it "a time bomb in my body with a 10% risk of exploding".

In those cases an AP regimen can be of great physical and mental support to the patient. Furthermore, the risk of side-effects and poor compliance is probably much smaller in these cases.

Prevention of the occurrence of MDR

In response to the increasing prevalence of drug-resistant TB in the United States, CDC/American Thoracic Society (ATS) has released an update on the previous recommendations for the treatment of tuberculosis (TB) among adults and children⁽¹⁾. The most notable changes. These recommendations include the need for a) in vitro drug susceptibility testing of Mycobacterium tuberculosis isolates from all patients and reporting of these results to the health department, b) initial four-drug regimens for the treatment of TB, and c)

initial directly observed therapy for persons with TB. Adherence to these recommendations will help prevent the occurrence of more cases of drug-resistant TB, reduce the occurrence.

WHO strategy combines case detection through sputum smear microscopy, registration of each patient detected, and standardized multidrug treatment under DOTS. This strategy will detect 70% of TB cases and cure 85% of those newly detected cases. By making sure that patients take their full course of medications, it will prevent MDR-TB from emerging. Dr. Arata Kochi (WHO) announced that more than 100 countries have implemented to some extent the recommended DOT.

The United States implements the DOTS strategy in more than 90% of the total population, but the status of the TB epidemic in this country varies from community to community⁽⁷⁾.

However, only 17% of the world's TB patients are receiving DOTS, in which trained workers and volunteers observe and record patients swallowing the correct dosage of anti-TB medications for the entire 6 or 8 month therapeutic course⁽²⁾.

Decisions regarding the use of expanded or universal DOT should be based on a quantitative evaluation of local treatment completion rates. If the percentage of patients who complete therapy within 12 months is less than 90% or unknown, the use of DOT should be expanded. If greater than or equal to 90% of patients beginning therapy complete a recommended course of therapy within 12 months, the expanded use of DOT may not be necessary. However, even in these circumstances, consideration should be given to extending the use of DOT to increase the treatment completion rate. All patients with TB caused by organisms resistant to either INH or RIF and all patients receiving intermittent therapy should receive DOT.

A program in which DOT is routinely used for all patients had a completion rate of 98%. Although expanding the use of DOT may require additional resources, intermittent, directly observed regimens are cost effective (CDC unpublished data). DOT can be conducted with regimens given once a day, 2 times/week, or 3 times/week.

Post-treatment Evaluation

An individual who was treated for TB resistant to at least isoniazid and rifampin should be evaluated every six (6) months by symptom review and sputum for AFB smear, culture and drug susceptibility testing, and chest x-rays (if pulmonary TB) for two (2) years after completion of treatment.

Other individuals also may be followed at those intervals after treatment completion, including those who:

- were treated for TB resistant to isoniazid alone; or rifampin alone

- are HIV-infected, or otherwise immunocompromised (with any strain of TB, whether susceptible or drug-resistant);
- and
- have completed a full course of anti-tuberculosis treatment.

PROGNOSIS

Multidrug-resistant TB (MDRTB), associated with high death rates of 50% to 80%, spans a relatively short time (4 to 16 weeks) from diagnosis to death⁽¹⁰⁾. Delayed recognition of drug resistance, which results in delayed initiation of effective therapy, is one of the major factors contributing to MDRTB outbreaks, especially in health-care facilities^(11,12). In most countries, MDRTB has increased in incidence and interferes with TB control programs, particularly in developing countries, where prevalence rates are as high as 48%. The high infection and death rates pose an urgent challenge to rapidly detect cases⁽¹⁾.

Multidrug-resistant strains of *Mycobacterium tuberculosis* seriously threaten tuberculosis (TB) control and prevention efforts. Molecular studies of the mechanism of action of antitubercular drugs have elucidated the genetic basis of drug resistance in *M. tuberculosis*. Drug resistance in *M. tuberculosis* is attributed primarily to the accumulation of mutations in the drug target genes; these mutations lead either to an altered target (e.g., RNA polymerase and catalaseperoxidase in rifampicin and isoniazid resistance, respectively) or to a change in titration of the drug (e.g., *InhA* in isoniazid resistance). Development of specific mechanism-based inhibitors and techniques to rapidly detect multidrug resistance will require further studies addressing the drug and drug-target interaction

BIBLIOGRAPHY

1. Ashok Rattan, Awdhesh Kalia, Nishat Ahmad. 1998. Multidrug resistant *Mycobacterium tuberculosis* : molecular perspective. Center for Disease Control Emerging Infectious Diseases, 1998; 4 (2) : 195-207.
2. Brown P. Drug resistant tuberculosis can be controlled, says WHO. *BMJ* 2000; 320 : 821.
3. Bureau of Tuberculosis control, New York City. Section VII : Evaluation and Treatment of Drug-resistant Tuberculosis Policies and Recommendation, 1996.
4. Lambregts-Van Weezenbeek. Drug Resistant Tuberculosis. In *Tuberculosis*, edited by Wilson R. Eur Respir Society, vol. 2, Monograph 4, July 1997 : 298-326.
5. Iseman D. Drug therapy. Treatment of multi-drug-resistance tuberculosis. *N Eng J Med* 1993; 329 : 784-91.
6. CDC Prevention Guidelines. Initial therapy for tuberculosis in the era of multidrug resistance - Recommendation of the Advisory Council for the elimination of tuberculosis. *MMWR* 42 (RR-7); 1993 : 001-8.
7. Mike Bykowski. DOTS may contain tuberculosis epidemic. *International Medical News Group. Pediat News* 1999; 33 (5) : 22.