

MULTI DRUG RESISTANT TUBERCULOSIS (MDR-TB) – TUBERCULOSIS RESISTANT TO POWERFUL FIRST LINE ANTI TB DRUGS: A REVIEW

Raghvendra^{1*}, Satyanand Tyagi², Pramod Yadav², Sunanda Saxena², Rajesh A. Dodia³, Tanvi D. Patel⁴

¹ Department of Pharmaceutics, Aligarh College of Pharmacy, Aligarh (dt), U.P, India-202001.

² K.N.G.D Modi Institute of Pharmaceutical Education & Research, Modinagar, Ghaziabad (dt), U.P, India-201204.

³ Department of Pharmaceutics, Shree Laxminarayanev college of pharmacy, Bharuch (dt), Gujarat, India-392 015.

⁴ Department of Pharmacognosy, Babaria Institute of Pharmacy, Vadodara (dt), Gujrat, India-391 240.

*Email: raghvendra_mpharm@rediffmail.com

ABSTRACT

Multi-drug resistant tuberculosis is defined as resistance to isoniazid and rifampicin whether there is resistance to other drugs or not. In practice resistance to isoniazid and streptomycin only is probably the commonest form of resistance worldwide to more than one drug. This is not strictly multi-drug resistance. Perhaps another separate term is needed to define this combination of resistances. 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. This article presents a brief review of Multi-drug resistant tuberculosis with an emphasis on its various aspects associated i.e. introduction, epidemiology as well as treatment; the article reveals the different approaches in the management of Multi-drug resistant tuberculosis as well as various probable causes of drug resistance.

Keywords: Tuberculosis, drug resistance, isoniazid, rifampicin, epidemiology, multidrug-resistant tuberculosis.

INTRODUCTON

Tuberculosis or TB is a common and often deadly infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis* in humans. Tuberculosis usually attacks the lungs but can also affect other parts of the body. It is spread through the air, when people who have the disease cough, sneeze, or spit. Most infections in humans result in an asymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease, which, if left untreated, kills more than 50% of its victims. The classic symptoms are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. Infection of other organs causes a wide range of symptoms. Tuberculosis (TB) is as old as the mankind. TB is the most common cause of death due to a single infectious agent worldwide in adults. According to the recent estimates, one third of the human population (about 1.86 billion people) was infected with *Mycobacterium tuberculosis* worldwide in 1997. 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. In 1997, nearly 1.87 million people died of TB and the global case fatality rate¹⁻⁵.

Before the discovery of specific antibiotics for the treatment of tuberculosis, there was no cure. Mortality of those with pulmonary disease (disease of the lungs) was about 50%. The introduction of anti-tuberculosis drugs in the 1950s and the development of the various drug regimens meant that by the 1980s there was a 98% chance of cure. However, treatment had to be continued

with good quality drugs for as long six months to ensure cure. The difficulties in ensuring this occurs, especially in resource poor countries, has resulted in an increasing incidence of tubercle bacteria resistant to the most effective drugs; so called multi-drug resistant tuberculosis. Multi-drug-resistant tuberculosis (MDR-TB) is defined as TB that is resistant at least to isoniazid (INH) and rifampicin (RMP), the two most powerful first-line anti-TB drugs. Isolates that are multiply-resistant to any other combination of anti-TB drugs but not to INH and RMP are not classed as MDR-TB.

MDR-TB develops during treatment of fully-sensitive TB when the course of antibiotics is interrupted and the levels of drug in the body are insufficient to kill 100% of bacteria. This can happen for a number of reasons: Patients may feel better and halt their antibiotic course, drug supplies may run out or become scarce, or patients may forget to take their medication from time to time. MDR-TB is spread from person to person as readily as drug-sensitive TB and in the same manner.

Epidemiology

MDR-TB most commonly develops in the course of TB treatment⁶, and is most commonly due to doctors giving inappropriate treatment, or patients missing doses or failing to complete their treatment. MDR-TB strains are often less fit and less transmissible, and outbreaks occur more readily in people with weakened immune systems⁷⁻⁹ (e.g., patients with HIV).

Outbreaks among non immune compromised healthy people do occur, but are less common. A 1997 survey of 35 countries found rates above 2% in about a third of the



countries surveyed. The highest rates were in the former USSR, the Baltic States, Argentina, India, and China, and were associated with poor or failing national tuberculosis control programmes.

It has been known for many years that INH-resistant TB is less virulent in guinea pigs, and the epidemiological evidence is that MDR strains of TB do not dominate naturally. A study in Los Angeles found that only 6% of cases of MDR-TB were clustered. Likewise, the appearance of high rates of MDR-TB in New York City in the early 1990s was associated with the explosion of AIDS in that area¹⁰.

Treatment of MDR-TB

The treatment of multi-drug resistant tuberculosis is specialised, complex and expensive and should only be undertaken at recognised centres with experience of managing such patients. Usually, multidrug-resistant tuberculosis can be cured with long treatments of second-line drugs, but these are more expensive than first-line drugs and have more adverse effects. The treatment and prognosis of MDR-TB are much more akin to that for cancer than to that for infection. It has a mortality rate of up to 80%, which depends on a number of factors, including

- ❖ How many drugs the organism is resistant to (the fewer the better)
- ❖ How many drugs the patient is given (patients treated with five or more drugs do better)
- ❖ Whether an injectable drug is given or not (it should be given for the first three months at least)
- ❖ The expertise and experience of the physician responsible
- ❖ How co-operative the patient is with treatment (treatment is arduous and long, and requires persistence and determination on the part of the patient)
- ❖ Whether the patient is HIV positive or not (HIV co-infection is associated with an increased mortality).

The majority of patients suffering from multi-drug-resistant tuberculosis do not receive treatment, as they tend to live in underdeveloped countries or in a state of poverty. Denial of treatment remains a difficult human rights issue, as the high cost of second-line medications often precludes individuals unable to afford therapy. In general, treatment courses are measured in months to years; MDR-TB may require surgery, and death rates remain high despite optimal treatment. However, good outcomes for the patient are still possible¹¹. The treatment of MDR-TB must be undertaken by a physician experienced in the treatment of MDR-TB. Mortality and morbidity in patients treated in non-specialist centers are significantly inferior to those of patients treated in specialist centers.

In addition to the obvious risks (i.e., known exposure to a patient with MDR-TB), risk factors for MDR-TB include HIV infection, previous incarceration, failed TB treatment, failure to respond to standard TB treatment, and relapse following standard TB treatment. Treatment of MDR-TB must be done on the basis of sensitivity testing. It is impossible to treat such patients without this information. If treating a patient with suspected MDR-TB, the patient should be started on SHREZ (Streptomycin + Isonicotinyl Hydrazine + Rifampicin + Ethambutol + Pyrazinamide) + MXF + Cycloserine pending the result of laboratory sensitivity testing. There is evidence that previous therapy with a drug for more than a month was associated with diminished efficacy of that drug regardless of *in vitro* tests indicating susceptibility¹², so, detailed knowledge of the treatment history of that patient is essential.

A gene probe for *rpoB* is available in some countries, which serves as a useful marker for MDR-TB, because isolated RMP resistance is rare (except when patients have a history of being treated with rifampicin alone). If the results of a gene probe (*rpoB*) are known to be positive, then it is reasonable to omit RMP and to use SHEZ+MXF+cycloserine. The reason for maintaining the patient on INH is that INH is so potent in treating TB that it is foolish to omit it until there is microbiological proof that it is ineffective (even though isoniazid resistance so commonly occurs with rifampicin resistance).

When sensitivities are known and the isolate is confirmed as resistant to both INH and RMP, five drugs should be chosen in the following order (based on known sensitivities):

- ❖ an aminoglycoside (e.g., amikacin, kanamycin) or polypeptide antibiotic (e.g., capreomycin)
- ❖ PZA
- ❖ EMB
- ❖ a fluoroquinolone: e.g., moxifloxacin (ciprofloxacin should no longer be used);
- ❖ rifabutin
- ❖ cycloserine
- ❖ a thioamide: prothionamide or ethionamide
- ❖ PAS
- ❖ a macrolide: e.g., clarithromycin
- ❖ linezolid
- ❖ high-dose INH (if low-level resistance)
- ❖ interferon- γ
- ❖ thioridazine
- ❖ Ampicillin

Drugs are placed nearer the top of the list because they are more effective and less toxic; drugs are placed nearer



the bottom of the list because they are less effective or more toxic, or more difficult to obtain. In general, resistance to one drug within a class means resistance to all drugs within that class, but a notable exception is rifabutin: Rifampicin-resistance does not always mean rifabutin-resistance, and the laboratory should be asked to test for it.

It is possible only to use one drug within each drug class if it is difficult finding five drugs to treat then the clinician can request that high-level INH-resistance be looked for. If the strain has only low-level INH-resistance (resistance at 1.0 mg/l INH, but sensitive at 0.2 mg/l INH), then high dose INH can be used as part of the regimen. When counting drugs, PZA and interferon count as zero; that is to say, when adding PZA to a four-drug regimen, another drug must be chosen to make five. It is not possible to use more than one injectable (STM, capreomycin or amikacin), because the toxic effect of these drugs is additive: If possible, the amino glycoside should be given daily for a minimum of three months (and perhaps thrice weekly thereafter). Ciprofloxacin should not be used in the treatment of tuberculosis if other fluoroquinolones are available¹³.

There is no intermittent regimen validated for use in MDR-TB, but clinical experience is that giving injectable drugs for five days a week (because there is no-one available to give the drug at weekends) does not seem to result in inferior results. Directly observed therapy helps to improve outcomes in MDR-TB and should be considered an integral part of the treatment of MDR-TB¹⁴. Response to treatment must be obtained by repeated sputum cultures (monthly if possible). Treatment for MDR-TB must be given for a minimum of 18 months and cannot be stopped until the patient has been culture-negative for a minimum of nine months. It is not unusual for patients with MDR-TB to be on treatment for two years or more.

Patients with MDR-TB should be isolated in negative-pressure rooms, if possible. Patients with MDR-TB should not be accommodated on the same ward as immunosuppressed patients (HIV-infected patients, or patients on immunosuppressive drugs). Careful monitoring of compliance with treatment is crucial to the management of MDR-TB (and some physicians insist on hospitalisation if only for this reason). Some physicians will insist that these patients remain isolated until their sputum is smear-negative, or even culture-negative (which may take many months, or even years). Keeping these patients in hospital for weeks (or months) on end may be a practical or physical impossibility, and the final decision depends on the clinical judgement of the physician treating that patient. The attending physician should make full use of therapeutic drug monitoring (in particular, of the amino glycosides) both to monitor compliance and to avoid toxic effects.

Some supplements may be useful as adjuncts in the treatment of tuberculosis, but, for the purposes of

counting drugs for MDR-TB, they count as zero (if four drugs are already in the regimen, it may be beneficial to add arginine or vitamin D or both, but another drug will be needed to make five).

- ❖ arginine¹⁵ (peanuts are a good source)
- ❖ Vitamin D¹⁶

The drugs listed below have been used in desperation, and it is uncertain as to whether they are effective at all. They are used when it is not possible to find five drugs from the list above.

- ❖ imipenem¹⁷
- ❖ co-amoxiclav^{18,19}
- ❖ clofazimine^{20,21,22}
- ❖ prochlorperazine²³
- ❖ metronidazole²⁴

The following drugs are experimental compounds that are not commercially available, but may be obtained from the manufacturer as part of a clinical trial or on a compassionate basis. Their efficacy and safety are unknown:

- ❖ PA-824²⁵ (manufactured by Pathogenesis Corporation, Seattle, Washington)
- ❖ R207910²⁶ (Under development by Johnson & Johnson)

In cases of extremely resistant disease, surgery to remove infection portions of the lung is, in general, the final option. The center with the largest experience in this is the National Jewish Medical and Research Center in Denver, Colorado. In 17 years of experience, they have performed 180 operations; of these, 98 were lobectomies and 82 were pneumonectomies. There is a 3.3% operative mortality, with an additional 6.8% dying following the operation; 12% experienced significant morbidity (in particular, extreme breathlessness). Of 91 patients who were culture-positive before surgery, only 4 were culture-positive after surgery. Community-based treatment programs such as DOTS-Plus, a MDR-TB-specialized treatment using the popular DOTS (directly observed treatment, short-course) initiative, have shown considerable success in the treatment of MDR-TB. These programs have proven to be a good option for proper treatment of MDR-TB in poor, rural areas. A successful example has been in Lima, Peru, where the program has seen cure rates of over 80%²⁷.

Potential Causes of Drug Resistance

1. 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 conclusive²⁸⁻³⁰. 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.

2. Incomplete and inadequate treatment

Review of published literature strongly suggests that the most powerful predictor of the presence of MDR-TB is 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 Iseman³¹ 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. The most common errors were the addition of a single drug to a failing regimen, failure to identify pre-existing or acquired drug resistance, initiation of an inadequate primary regimen, failure to identify and address non-compliance 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.

3. 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 regimen³². 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 months¹⁵. 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.

Acknowledgement

The authors are thankful to the Management of the Aligarh College of Pharmacy for providing facilities to utilize the library and internet in the college.

REFERENCES

1. Grange JM, Zumla A, The global emergency of tuberculosis: what is the cause? , J R Soc Health, 122, 2002, 78-81.
2. Raviglione MC, Snider DE Jr, Kochi A, Global epidemiology of tuberculosis: morbidity and mortality of a worldwide epidemic, JAMA, 273, 1995, 220-226.
3. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC, Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring project, JAMA, 282, 1999, 677-686.
4. Bloom BR, Murray CJL, Tuberculosis: Commentary on a reemerging killer, Science, 257, 1992, 1055-1064.
5. <http://www.cdc.gov/tb/publications/factsheets/drtb/mdrtb>.
6. Iseman MD, "Treatment of multidrug-resistant tuberculosis", N Engl J Med, 329 (11), 1993, 784-791.
7. Edlin BR, Tokars JI, Grieco MH, et al, "An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome", N Engl J Med, 326, 1992, 1514-1521.
8. Pitchenik AE, Burr J, Laufer M, et al, "Outbreaks of drug-resistant tuberculosis at AIDS centre", Lancet, 336, 1987, 440-441.
9. Fischl MA, Uttamchandani RB, Daikos GL, et al, "An outbreak of tuberculosis caused by multiple-drug resistant tubercle bacilli among patients with HIV infection", Ann Intern Med, 117, 1992, 177-183.
10. Frieden TR, Sterling T, Pablos-Mendez A, et al, "The emergence of drug-resistant tuberculosis in New York City", N Engl J Med, 328 (8), 1993, 521-556.
11. Mitnick C et al, "Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru", N Engl J Med, 348 (2), 2003, 119-128.
12. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, "Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin", N Engl J Med, 328, 1993, 527-532.
13. Ziganshina LE, Vigel AA, Squire SB, "Fluoroquinolones for treating tuberculosis", Cochrane Database Sys Rev, 2005, (3), CD004795.
14. Leimane V, et al, "Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study", Lancet, 365 (9456), 2005, 318-26.
15. Schön T, Elias D, Moges F, et al. "Arginine as an adjuvant to chemotherapy improves clinical outcome in active tuberculosis", Eur Respir J, 21 (3), 2003, 483-488.



16. Rockett KA, Brookes R, Udalova I, et al, "1,25-Dihydroxyvitamin D3 induces nitric oxide synthase and suppresses growth of Mycobacterium tuberculosis in a human macrophage-like cell line", *Infect Immunity*, 66 (11), 1998, 5314–5321.
17. Chambers HF, Turner J, Schechter GF, Kawamura M, Hopewell PC, "Imipenem for treatment of tuberculosis in mice and humans", *Antimicrob Agents Chemother*, 49 (7), 2005: 2816–2821.
18. Chambers HF, Kocagoz T, Sipit T, Turner J, Hopewell PC, "Activity of amoxicillin/clavulanate in patients with tuberculosis", *Clin Infect Dis*, 26 (4), 1998, 874–877.
19. Donald PR, Sirgel FA, Venter A, et al, "Early bactericidal activity of amoxicillin in combination with clavulanic acid in patients with sputum smear-positive pulmonary tuberculosis", *Scand J Infect Dis*, 33 (6), 2001, 466–469.
20. Jagannath C, Reddy MV, Kailasam S, O'Sullivan JF, Gangadharam PR, "Chemotherapeutic activity of clofazimine and its analogues against Mycobacterium tuberculosis. In vitro, intracellular, and in vivo studies", *Am J Respir Crit Care Med*, 151 (4), 1995, 1083–1086.
21. Adams LM, Sinha I, Franzblau SG, et al, "Effective treatment of acute and chronic murine tuberculosis with liposome-encapsulated clofazimine", *Antimicrob Agents Chemother*, 43(7), 1999, 1638–1643.
22. Janulonis E, Sofer C, Song HY, Wallis RS, "Lack of activity of orally administered clofazimine against intracellular Mycobacterium tuberculosis in whole-blood culture", *Antimicrob Agents Chemother*, 48 (8), 2004, 3133–3135.
23. Shubin H, Sherson J, Pennes E, Glaskin A, Sokmensuer A, "Prochlorperazine (compazine) as an aid in the treatment of pulmonary tuberculosis", *Antibiotic Med Clin Ther*, 5 (5), 1958, 305–309.
24. Wayne LG, Sramek HA, "Metronidazole is bactericidal to dormant cells of Mycobacterium tuberculosis", *Antimicrob Agents Chemother*, 38 (9), 1994, 2054–2058.
25. Stover CK, Warrener P, VanDevanter DR, et al, "A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis", *Nature*, 405 (6789), 2000, 962–996.
26. Andries K, Verhasselt P, Guillemont J, et al, "A diarylquinoline drug active on the ATP-synthase of Mycobacterium tuberculosis", *Science*, 307 (5707), 2005, 223–227.
27. Shin S, Furin J, Bayona J, Mate K, et al, "Community-based treatment of multidrug-resistant tuberculosis in Lima, Peru: 7 years of experience", *Social Science & Medicine*, 59, 2004, 1529-1539.
28. Weyer K, Kleeberg HH, "Primary and acquired drug resistance in adult black patients with tuberculosis in South Africa: results of a continuous national drug resistance surveillance programme involvement", *Tuberc Lung Dis*, 73, 1992, 106-112.
29. Carpenter JL, Obnibene AJ, Gorby EW, Neimes RE, Koch JR, Perkins WL, "Antituberculosis drug resistance in south Texas", *Am Rev Respir Dis*, 128, 1983, 1055-1058.
30. Sharma SK, Turaga KK, Balamurugan A, Saha PK, Pandey RM, Jain NK, et al, "Clinical and genetic risk factors for the development of multidrug-resistant tuberculosis in non-HIV infected at a tertiary care center in India: a case-control study", *Infect Genet Evol*, 3, 2003, 183-188.
31. Mahmoudi A, Iseman MD, "Pitfalls in the care of patients with tuberculosis. Common errors and their association with the acquisition of drug resistance", *JAMA*, 270, 1993, 65-68.

