Pharmacotherapy for multidrug resistant tuberculosis

Naveen Chhabra, M. L. Aseri, Ramakant Dixit¹, S. Gaur
Departments of Pharmacology and ¹Respiratory Medicine, J. L. N. Medical College, Ajmer, Rajasthan, India

ABSTRACT

The current global concern in the treatment of tuberculosis (TB) is the emergence of resistance to the two most potent drugs namely, isoniazid and rifampicin. Emergence of multidrug resistance tuberculosis (MDR-TB) is now a health problem faced by most of the developing countries as well as developed countries across the globe. MDR-TB is a man-made disease that is caused by improper treatment, inadequate drug supplies, and poor patient supervision. HIV infection and AIDS have been implicated as important cause for this. The review of a published literature suggests that the most powerful predictor of treatment of MDR-TB is a history of treatment of TB. Although the treatment is efficacious, there are also a number of adverse effects caused by drugs used in the treatment of MDR-TB.

Key words: Cycloserine, ethionamide, kanamycin, multidrug resistance tuberculosis, para-aminosalicylic acid

INTRODUCTION

Multidrug resistance tuberculosis (MDR-TB) is defined as resistance to isoniazid and rifampicin, with or without resistance to other anti-TB drugs.¹ The prevalence of MDR-TB is 1–3% in new cases and around 12% in retreatment cases.²,³ MDR-TB differs from drug-resistant tuberculosis (TB), which is a case of TB resistant to one or more anti-TB drugs. Initiation of drug therapy in patients with MDR-TB requires an assessment of history of treatment as well as meticulous laboratory parameters to characterize the susceptibility of the specific strain. Irregular, incomplete, and inadequate treatment is the commonest means of acquiring drug resistant organisms. Poor compliance is also an important factor of acquisition of drug resistance. Anti-TB drugs are classified in Table 1.¹

Table 1: Classification of anti-tuberculosis drugs

| Groups | Drugs |
|--------|-------|
| Group 1: First-line oral anti-tuberculosis agents | Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z) |
| Group 2: Injectable anti-tuberculosis agents | Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Vincomycin (Vi) |
| Group 3: Fluoroquinolones | Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin (Lfx); Moxifloxacin (Mfx); Galithoxacin (Gfx) |
| Group 4: Oral second-line anti-tuberculosis agents | Ethionamide (EtO); Prothionamide (Pto); Cycloserine (Cs); Terizidine (Trd); Para-aminosalicylic acid (PAS); Thioacetazone (Th) |
| Group 5: Agents with unclear role in treatment of drug-resistant tuberculosis | Clofazimine (Cfx); Linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); Thiocetazone (Thz); Imipenem/cilastatin (Ipm/Cln); High dose isoniazid (high dose H); Clarithromycin (Clr) |

Biological and molecular basis of resistance

Tubercular bacilli have spontaneous, predictable rates of chromosomally born mutations that confer resistance to antimicrobial agents. These mutations are unlinked; hence, resistance is usually not associated to an unrelated drug. That the mutations are not under linked is the cardinal
principle underlying chemotherapy of TB. This means that if mutations causing resistance to isoniazid occur in about 1 in $10^5$ replication of bacteria, the probability of spontaneous mutation causing resistance to both isoniazid and rifampicin would be $10^5 \times 10^5 = 10^{10}$.

Acquired resistance is responsible for MDR-TB. In tuberculosis bacilli, resistance is by means of genetic mutations: (a) Codon 531 of the $rpoB$ gene ($rpoB531$) is found to be the most frequent mutation associated with rifampicin resistance. (b) Codon 315 of the $katG$ gene ($katG315$) is found to be the most frequent mutation associated with isoniazid resistance. (c) Six codons: $rpoB531$, $rpoB526$, $rrs513$, $rpsL43$, $embB306$, and $katG315$ are the main locations responsible for MDR-TB.

**Treatment regimens**

Treatment regimens[1] should contain at least four drugs with certain effectiveness. After confirmatory diagnosis of MDR-TB, patients can be treated with either standard MDR regimen or by individually tailored regimen which is based on the drug sensitivity test (DST). Any patient who does not respond to the treatment of Category first or third; any category second patient who remains smear positive at the end of fourth month treatment; contacts of MDR-TB cases will be identified as MDR-TB suspect. These will be tested by culture sensitivity and drug resistance tests. If a patient is confirmed as a non-MDR-TB case; continue Category second or Category first regimen but if MDR-TB is confirmed then Cat. fourth regimen should be started. Revised National Tuberculosis Control Programme (RNTCP) uses Category fourth regimen as the standard regimen for treatment of MDR-TB. Category fourth regimen includes: six drugs—four bactericidal: Ofloxacin (Ofx) or LevoOfloxacin (Lfx); Kanamycin; ethionamide; pyrazinamide and two bacteriostatic drugs: Ethambutol; cycloserine (Cs) during 6–9 months of the intensive phase (IP) and four drugs: ofloxacin (levofloxacin), ethionamide, ethambutol, and cycloserine during the 18 months of the continuation phase (CP). PAS is included in the regimen as a substitute if any drug among ofloxacin (Ofx) or levofloxacin (Lfx); kanamycin; ethionamide; pyrazinamide is not tolerated or any drug among two bacteriostatic drugs is not tolerated.

**Duration of treatment**

The treatment duration is divided into two phases: initial intensive phase (IP for 6 months and the continuation phase (CP) for 18 months. After 6 months of treatment, the patient reviewed and the treatment changed to CP if the fourth month culture result is negative (fourth month culture results are available at the end of the sixth month). If the 4-month culture result remains positive, the treatment is extended by 1 month duration. Extension of IP beyond 1 month will be decided on the results of sputum culture of fifth (available at the end of seventh month) and sixth months. The IP can be extended up to a maximum of 3 months duration based on culture results (i.e. maximum duration of IP is 9 months); after which the patient will be initiated on the CP irrespective of the culture result (either it is +ve or –ve). The duration for CP is 18 months. [1]

**General guidelines to treat MDR-TB**

(a) Use at least four drugs with certain effectiveness. (b) Do not use drugs for which there is a possibility of cross resistance. (c) Use drugs from group 1 to 4 in hierarchical basis of their potency and (d) eliminate drugs that are not safe, i.e. known severe allergy/high risk of severe adverse drug reactions (using two aminoglycosides drugs simultaneously). Preferably the standardized regimen as recommended in the national DOTS-Plus guidelines should be used: [6 or 9 kanamycin, ofloxacin, ethionamide, cycloserine, pyrazinamide, ethambutol/18 ofloxacin, ethionamide, cycloserine, ethambutol]. If the results of second line DST are available, an individualized regimen may be used in such patients after obtaining a detailed history of previous anti-TB treatment [Tables 2-5].

**Role of immunomodulators in MDR-TB**

Immunomodulators available are:
- Levamisole[5]

---

**Table 2: Drugs, their chemical structure and mechanism of action[4,7]**

| Drugs         | Chemical structure                                      | Mechanism of action                                                                 |
|---------------|---------------------------------------------------------|-------------------------------------------------------------------------------------|
| Ofloxacin (Ofx) | Fluoroquinolone (bactericidal)                           | Inhibits bacterial DNA gyrase; inhibits protein synthesis                           |
| Kanamycin     | Aminoglycoside (bactericidal)                            | By binding to 30s subunit; causes misreading of m-RNA and disturbances in initiation of protein synthesis |
| Ethambutol    | A derivative of ethylenediamine, ethambutol, is active only against mycobacteria (bacteriostatic) | Inhibits arabinosyl transferase that mediates the polymerization of arabinose into arabinogalactan within the cell wall |
| Cycloserine   | (4-amino-3-iso-oxazolidinone) Analogue of d-alanine (bacteriostatic) | Inhibits alanin ligase and alanine racemose; inhibits cell wall synthesis |
| Ethionamide   | Introduced in 1956; like isoniazid and pyrazinamide, ethionamide is a derivative of isonicotinic acid. (bactericidal) | Interferes with mycobacterial cell wall synthesis |
| PAS           | Tuberculostatic drug introduced in 1946; structurally related to PABA and sulfonamide | A folate synthesis antagonist |
| Pyrazinamide  | Chemically similar to isoniazid; developed in 1952; weak tuberculocidal | More active intracellular and in acidic medium; inhibits mycobacterial cell wall synthesis by interacting gene encoding fatty acid synthesis |
Table 3: Pharmacokinetic properties of drugs used for treatment of MDR-TB\(^\text{[1,4-7]}\)

| Drug        | Route of administration and absorption | Inhibitory concentration for M. TB | Plasma protein binding, tissue distribution, metabolism and \(T_{1/2}\) | Excretion | Dose |
|-------------|----------------------------------------|-----------------------------------|-------------------------------------------------|------------|------|
| Ofloxacin (Ofx) | Oral; well absorbed; oral absorption is interfered by di/tri valent cations and antacids but not by food | \(<2 \mu g/ml\) | Widely distributed in tissues, average \(T_{1/2} = 3\) to \(10\) h | Largely as unchanged by the renal route | \(BW < 45\) kg = \(600\) mg; \(BW > 45\) kg = \(800\) mg [\(7.5–15\) mg/kg] |
| Kanamycin   | Intravenous; aminoglycosides are very poorly absorbed from whole GIT, almost entire oral dose is excreted in faeces | \(<1 \mu g/ml\) | Concentration-dependant killing; postantibiotic effect +ve; do not enter cells due to polarity | Renal route | \(BW < 45\) kg = \(500\) mg; \(BW > 45\) kg = \(700\) mg [\(15\) mg/kg] |
| Ethionamide | Oral; well absorbed orally but poor GIT tolerance | \(2.5–10 \mu g/ml\) | Widely distributed throughout the body, including the CSF. \(T_{1/2} = 2–3\) h | Renal route | \(BW < 45\) kg to \(500\) mg; \(BW > 45\) kg to \(750\) mg [\(10–20\) mg/kg] |
| Pyrazinamide | Oral; good absorption | \(20 \mu g/ml\) | Converted in pyrazinoic acid (active form of drug) by mycobacterial pyrazaminidase; widely distributed throughout the body, including the CSF. \(T_{1/2} = 8–11\) h | Renal route | \(BW < 45\) kg to \(10\) g; \(BW > 45\) kg to \(12\) g [\(20–30\) mg/kg] |
| PAS         | Oral; completely absorbed from GIT | \(1–5 \mu g/ml\) | Widely distributed in tissues and body fluids except CSF. Metabolizes by acetylation; short half-life (1 h) | 80% of the dose is excreted in urine | \(BW < 45\) kg–\(1250\) mg; \(BW > 45\) kg–\(1500\) mg [\(150–200\) mg/kg] |
| Cycloserine | Well absorbed after oral administration | \(15–20 \mu g/ml\) | Widely distributed throughout body fluids, including the CSF | About 2/3 of dose as unchanged by the renal route | \(BW < 45\) kg to \(500\) mg; \(BW > 45\) kg to \(750\) mg [\(10–20\) mg/kg] |
| Ethambutol  | Oral administration, 75–80% of a dose of ethambutol is absorbed | \(75–80%\) | Widely distributed throughout the body except in the CSF, \(T_{1/2} = 3–4\) h | Renal route | \(BW < 45\) kg to \(800\) mg; \(BW > 45\) kg to \(1000\) mg [\(15–20\) mg/kg] |

Table 4: Formulation and characteristics of anti-tubercular drugs available for MDR-TB\(^{[1,4-7]}\)

| Drugs                  | Formulation | Acceptability | Tolerance | Toxicity |
|------------------------|-------------|---------------|-----------|----------|
| Aminoglycosides        | Vial 0.75 and 1 g, Injection (painful) | Moderate to poor | Medium    |
| Streptomycin; Amikacin |             |               |           |          |
| Kanamycin Capreomycin  |             |               |           |          |
| Ethionamide and prothionamide | Tab; 250 mg | Good | Moderate | Medium    |
| Fluoroquinolones       | Tab; 200 and 400 mg | Good | Good | Low       |
| Ofloxacin              | Tab; 500 mg Granules | Bad (bulk and taste) | Poor | Low       |
| PAS                    | Tab; 250 mg | Good | Moderate | High      |
| Cycloserine            | Tab; 500 mg, 1 g | Good | Moderate | Low       |
| Pyrazinamide           | Tab; 800 mg | Good | Good | Low       |
| Ethambutol             | Tab; 800 mg | Good | Good | Low       |

Table 5: Common adverse reactions encountered to drugs used in MDR-TB treatment\(^{[1,4-7]}\)

| Drugs                  | Common ADRs                                                                 |
|------------------------|-----------------------------------------------------------------------------|
| Cycloserine            | Peripheral neuropathy; CNS depression and psychotic reactions                |
| Pyrazinamide           | Hepatotoxicity (1–5%); nausea; vomiting; drug fever; hyperuricemia; acute gouty arthritis; non-gouty polyarthritis; transient morbilliform rash; dermatitis |
| PAS                    | GIT symptoms; peptic ulceration and hemmorhage; hypersensitivity reactions; skin rashes; hypokalemia; liver dysfunctions; hypothyroidism and goitre on prolonged administration |
| Ethambutol             | Visual disturbances                                                          |
| Ethionamide            | Intense GIT irritation; hypothyroidism with goitre on long duration treatment; liver dysfunctions; peripheral neuropathy; psychiatric symptoms; gynecomastia; menstrual disturbances; impotence; acne; headache |
| Fluoroquinolones       | GIT disturbances, dizziness and convulsions; tendinitis and tendon rupture; arthralgia; rashes; dizziness; hypersensitivity; increase in SGPT and SGOT level, iierum creatine; phototoxicity and photosensitivity (sparfloxacin); cardiotoxicity |
| Kanamycin (aminoglycosides) | Nephrotoxicity; ototoxicity; vertigo; hypocalcemia; hypomagnesemia, hypokalemia; local pain and induration |
**New alternative therapies for MDR TB**

*Some other drugs with initial promising results*

- β-Lactam antibiotics and β-lactamase inhibitors.
- Linezolid (Lzd)
- Phenothiazines:
- Thioridazine, chlorpromazine;
- 3,5-disubstituted thiadiazine thiones.
- Antimalarial agents: Ethyl-5-phenyl-6-oxa-1-aza bicyclohexane-2-carboxylic acid derivative.
- Nitric oxide donors: DETA-NO.
- Plant extracts: the hexane extract from Lantana hispida.
- Snake venom: Small peptide vgf-1 from Naja-astra, a snake isolated from the Yunnan province of China.
- Azoles: Having Cyp-450 inhibiting activity.
- Tubercactinomyicin: Tubercactinomycin resembles viomycin structurally as well as in its mode of action. It acts by inhibiting protein synthesis.
- Riminophenazines: B 746, B 4157, and Clofazimine (Cfz): Cfz is a substituted iminophenazine bright-red dye that inhibits mycobacterial growth and binds preferentially to mycobacterial DNA causing inhibition of transcription.

**Monitoring the MDR-TB**

Close monitoring of MDR-TB patients is essential. Sputum smear and culture should be performed monthly until smear and culture conversion. (*Conversion is defined as two consecutive negative smear and culture taken 30 days apart.) After conversion, the minimum frequency recommended for bacteriological monitoring is monthly for smears and quarterly for cultures. Monitoring of MDR-TB patients by a clinician should be at least monthly until sputum conversion, then every 2–3 months. Each patient’s weight should be monitored monthly. Timely and intensive monitoring and management of adverse effects caused by second-line drugs are essential for MDR-TB treatment.

### Table 6: Some other promising anti-tubercular drugs in various stages of development

| Potential drug | Active or pro-drug | Description | Cellular process inhibited |
|----------------|--------------------|-------------|---------------------------|
| PA-824         | Pro-drug           | Nitroimidazo-oxazine | Mycolic acid synthesis    |
| OPC-67683      | Pro-drug           | Nitroimidazo-oxazine | Mycolic acid synthesis    |
| R027910        | Active             | Diarylquinoline     | ATP synthesis             |
| SQ019          | Active             | Ethylenediamine derivative | Lipid/cell wall synthesis |
| Compound 5     | Pro-drug           | Quinoxaline-oxide derivative | Unidentified |
| Compound 7g    | Unknown            | Quinoxaline-oxide derivative | Unidentified |

### Table 7: Potential regimens for the treatment of patients with MDR-TB and XDR-TB

| Different patterns of resistance to anti-TB drugs | Appropriate therapy | Total duration of treatment, months | Desirable number of active drugs for favorable outcome |
|--------------------------------------------------|---------------------|------------------------------------|------------------------------------------------------|
| INH, RIF                                         | PZA, EMB, FQ, INJ SLD | 18–24                              | 5–6                                                  |
| INH, RIF, EMB                                    | PZA, FQ, INJ SLD     | 18–24                              | 5–6                                                  |
| INH, RIF, PZA                                    | EMB, FQ, INJ SLD     | 24                                  | 5–7                                                  |
| INH, RIF, PZA, EMB                              | FQ, INJ + SLD        | 24                                  | 5–7                                                  |
| INH, RIF, PZA, EMB, FQ                           | INJ + SLD + TLD      | >24                                 | 5–7                                                  |
| INH, RIF, PZA, EMB, INJ                          | FQ + INJ + SLD + TLD | >24                                 | 5–7                                                  |
| INH, RIF, PZA, EMB, FQ, INJ                      | INJ + SLD + TLD      | >24                                 | 5–7                                                  |

INH: Isoniazid; RIF: Rifampicin; PZA: Pyrazinamide; EMB: Ethambutol; SM: Streptomycin; FQ: Fluroquinozine - ciprofloxacin or ofloxacin or levofloxacin or moxifloxacin or gatifloxacin; INJ: Injectable agents such as streptomycin or kanamycin or amikacin or capreomycin or viomycin; SLD: Second-line drugs such as rifabutin, ethionamide, prothionamide, para-aminosalicylic acid, d-cycloserine and thiacetazone; TLD: Third-line drugs such as, CLR: Clarithromycin, AMX-CLA: amoxicillin b-lactam antibiotic with clavulanate β-lactamase inhibitor, CFZ: clofazimine and Lzd: linezolid.; *Capreomycin or viomycin may be used for kanamycin or amikacin or vice versa if no cross-resistance is observed.*
Management of adverse reactions\textsuperscript{1,4-7}

Liver disease
Causative drugs may be Isoniazid, Pyrazinamide and Ethionamide. However because of effectiveness of these drugs (particularly INH and RIF), they should be used even in the presence of existing liver disease. If there is clinical sign/symptoms then evaluate patients; if icterus is present then antitubercular drugs will be withheld; review patients for liver functions tests. If liver functions tests return to normal then treatment will be resumed. Patients should be reviewed at weekly intervals.

Arthralgia
Causative drugs can be: pyrazinamide or quinolones. Management is to initiate therapy with paracetamol or aspirin; if no improvement occurs, then a NSAID will be prescribed and the S. uric acid level should be monitored. If no improvement or worsening of arthralgia then either reduce the doses of offending drugs or withhold temporarily.

Hypersensitivity reactions
Hypersensitivity reactions are usually manageable with antihistaminics; if severe reactions not respond to antihistaminics then offending drug identified by challenge/dechallange tests. If there is generalized erythematous rash associated with fever and or mucous membrane involvement, then withhold all drugs immediately.

GIT disturbances
GIT complaints are common within first few weeks of therapy. Causative drugs can be ethionamide, \textit{para}-amino salicylic acid, PZA, and ethambutol. In the presence of GI symptoms, patient’s serum bilirubin and serum aminotransferases levels (AST, ALT) should be measured. If serum aminotransferase levels are less than three times the upper limits of normal then these are not assumed due to hepatic cause. Advise the patients to take drugs embedded in banana. If vomiting persists then either domperidone or proton pump inhibitor is given 1 h before administration of drugs. Antacids interfere with absorption of fluoroquinolones so should be avoided. If severe vomiting is there, then drugs can be withheld temporarily. Other causes of vomiting as hepatitis/GERD/gastric causes should be ruled out.

Hypothyroidism
PAS and ethionamide alone or both in combination can cause hypothyroidism on prolonged duration. Drug-induced hypothyroidism can occur several months after the beginning of treatment. Drug-induced hypothyroidism may or may not be associated with goitre and can be virtually asymptomatic. Systematic monitoring of patients and their biochemical tests monitoring are mandatory. Hypothyroidism responds to thyroxine. Clinically and biochemical levels returned to normal after administration of thyroxine.

Seizures
Offending drugs can be: cycloserine, pyrazinamide, fluoroquinolones. Seizures that present for the first-time during anti-TB therapy likely to be the result of an adverse effect of one of the anti-TB drugs. Temporary withdrawal of the suspected agent and initiate anticonvulsant therapy (e.g., phenytoin, valproic acid). The dose of pyridoxine is increased to maximum daily dose (200 mg/day). If the suspected agent is essential to the regimen, then reinitiate suspected agent at lower doses. The suspected agent to be discontinued if this can be done without compromising regimen.

Psychotic symptoms
Offending drugs are: Ethionamide/prothionamide, Cycloserine, Isoniazid, and fluoroquinolones. Stop suspected agent for a short-period of time. Some patients will need to continue antipsychotic while psychotic symptoms are brought under control.

Peripheral neuropathy
Offending drugs are: Cycloserine, INH, Streptomycin, Kanamycin, Amikacin, Clarithromycin, Viomycin, and Fluoroquinolones.

Dose of pyridoxine should be increased to maximum daily dose (200 mg per day) and all injectable should be changed to capreomycin. Therapy with tricyclic antidepressants such as amitriptyline and nonsteroidal anti-inflammatory drugs or acetaminophen may help in alleviating the symptoms. Reduce the dose of the suspected agent, if this can be done without compromising the regimen or discontinue the suspected agent if this can be done without the compromising regimen.

Renal toxicity
Offending agents can be: Streptomycin, Kanamycin, Amikacin, Capreomycin, and Viomycin. Special dosing guidelines for adult patients with renal insufficiency and end-stage renal disease are given [Table 8].\textsuperscript{7}

Management of MDR-TB in pregnancy
Pregnancy is not a contraindication for treatment of MDR-TB. Discuss the risk/benefits to the patient. Treatment is started in second/third trimester unless life threatening. Aminoglycosides are avoided until delivery. The main aim is to achieve sputum conversion before delivery. Injectable agents are also avoided, capreomycin is used if it is necessary to administer injectable agent. Avoid Eto because it is teratogenic. Cycloserine: There are limited data on the safety in pregnancy, only indication to use is essential to the regimen, then reinitiate suspected agent at lower doses. The suspected agent to be discontinued if this can be done without compromising regimen.

Breast feeding
Encourage the breast feeding if sputum microscopy is negative. Chemotherapy is the best way to prevent transmission of tubercle bacilli to baby. Most anti-TB drugs are excreted and
Table 8: Recommended doses and frequency for patients with creatinine clearance <30 ml/mn or for patients receiving hemodialysis

| Drug               | Change in frequency | Recommended doses and frequency for patients with creatinine clearance <30 ml/mn or for patients receiving hemodialysis |
|-------------------|---------------------|----------------------------------------------------------------------------------------------------------------|
| Isoniazid         | No change           | 300 mg OD or 900 mg three times per week                                                                   |
| Rifampicin        | No change           | 600 mg OD, or 600 mg three times per week                                                                 |
| Pyrazinamide      | Yes                 | 25–35 mg/kg per dose three times per week                                                                   |
| Ethambutol        | Yes                 | 15–25 mg/kg per dose three times per week (not daily)                                                       |
| Levofloxacin      | Yes                 | 750–1000 mg per dose three times per week (not daily)                                                        |
| Cycloserine       | Yes                 | 250 mg OD or 500 mg/dose three times per week (careful monitoring of evidence of neurotoxicity)              |
| Ethionamide       | No change           | 250–500 mg/dose daily                                                                                      |
| Para-aminosalicylic acid | No change                  | 4 g/dose b.d.                                                                                              |
| Streptomycin      | Yes                 | 12–15 mg/kg per dose 2 or 3 times per week (not daily)                                                       |
| Capreomycin       | Yes                 | 12–15 mg/kg per dose 2 or 3 times per week (not daily)                                                       |
| Kanamycin         | Yes                 | 12–15 mg/kg per dose 2 or 3 times per week (not daily)                                                       |
| Amikacin          | Yes                 | 12–15 mg/kg per dose 2 or 3 times per week (not daily)                                                       |

found in the breast milk. It is recommended to provide infant formula options.

Diabetes mellitus
Diabetes mellitus may potentiate the adverse effects of drugs, renal dysfunction, and peripheral neuropathy. Use of Eto or protonamide may make it more difficult to control insulin levels.

Substance dependence
Encourage the patients of TB for complete abstinence from alcohol or other substances. If the treatment is repeatedly interrupted because of the patient’s dependence, therapy should be suspended until successful completion of treatment. Cycloserine has higher incidence of adverse effects in patients dependent on alcohol or other substances, including a higher incidence of seizures.

HIV/MDR TB/Drug interactions
Nonenteric-coated didanosine contains an aluminum/magnesium-based antacid. When this given along with fluoroquinolones, it results in decreased absorption of fluoroquinolone. It should therefore be given 6 h before or 2 h after fluoroquinolone administration.

CONCLUSION
The current MDR-TB epidemic is the result of ignorance for an important infectious disease, lack of resources for TB control programs, poor case detection, and inadequate/inappropriate therapy. Optimization of treatment regimens along with rapid diagnosis and DST for first- and second-line drugs, greatly improved the clinical outcome. Recent advances in diagnosis of MDR-TB and empirical treatment of patients with several drugs in the initial phase of treatment have further improved the prognosis of MDR-TB. The new anti-TB drugs that are in various stages of development also offer hope that we will not soon run out of treatment options against TB and MDR-TB. This review has summarized the drugs used to treat MDR-TB, common adverse drug reactions occurring during MDR-TB treatment and their management and has highlighted the importance of preventing the development and dissemination of this man-made disease.

REFERENCES
1. RNTCP DOT Plus Guidelines, Jan. 2010. Available from: http://www.tbcindia.org/pdfs/DOTS_Plus_Guidelines_Jan2010.pdf. [Last accessed on 2011 May 30].
2. Paramasivan CS, Venkataraman P. Drug Resistance in tuberculosis in India. Indian J Med Res 2004;120:377-86.
3. Mahadev B, Kumar P. Surveillance of drug resistance to antituberculosis drugs in district of hoogli in West Bengal and Mayurbhanj in Orissa. Indian J Tuberc 2005;52:5-10.
4. Chambers HF, Deck DH. Basic and Clinical Pharmacology. In: Katzung BG, Masters SB, Trever AJ, editors. 11th ed. Noida, UP, India: Tata Macgraw-Hill; 2009.
5. Rang and Dale's Pharmacology. In: Rang HP, Dale MM, Ritter JM, Flower RJ, editors. 6th ed. USA: Churchill Livingstone Elsevier, Elsievier limited; 2007.
6. Bastian I, Colebunders R. Treatment and prevention of multidrug resistant tuberculosis. Drugs 1999;58:633-61.
7. Morbidity and Mortality Weekly Report: Recommendations and reports. American Thoracic Society, CDC. Infect Dis Soc Am 2003;20:11.
8. Edwards D, Kirkpatrick CH. The immunology of mycobacterial disease. Am Rev Respir Dis 1986;134:1062-71.
9. Kaplan G. Recent advances in cytokine therapy in leprosy. J Infect Dis 1993;167:S18-22.
10. Stanford JL, Grange JM, Pozniak A. Is Africa lost? Lancet 1991;338:557-8.
11. Moller DR, Wysocka M, Greenlee BM. Inhibition of IL-12 production by thalidomide. J Immunol 1997;159:5157-61.
12. Brill KJ, Li Q, Larkin R, Canaday DH, Kaplan DR, Boom WH, et al. Human natural killer cells mediate killing of intracellular Mycobacterium tuberculosis H37Rv via granule-independent mechanisms. Infect Immun 2001;69:1755-65.
13. Koh WJ, Kwon OJ, Suh SY, Chung MP, Kim H, Lee NY, et al. 6-Month therapy with aerosolized interferon-gamma for refractory multidrug resistant pulmonary tuberculosis. J Korean Med Sci 2004;19:167-71.
14. Chehnokova OG, Kirkib BS. Use of isofone in combined treatment of patients with actively progressive forms of tuberculosis. Probl Tuberk Bolezn Legk 2003;9:12-4.
15. Ahmad S, Mokaddas F. Recent advances in the diagnosis and treatment of
multidrug-resistant tuberculosis. Respir Med 2009;103:1777-90.
16. Dincer I, Ergin A, Kockagoz T. The vitro efficacy of b-Lactam and
b-Lactamase inhibitors against multidrug resistant clinical strains of
Mycobacterium Tuberculosis. Am J Resp Crit Care Med 2004;169:1103-9.
17. Rodriguez Diaz JC, Ruiz M, Lopez M, Royo G. Synergic activity of
fluoroquinolones and Linezolid against mycobacterium Tuberculosis. Int J
Antimicrob Agents 2003;21:354-6.
18. Ordway D, Vivuetos M, Leandro C, Bettencourt R, Almeida J, Lewis
J, et al. Clinical concentration of thioridazine kill intracellular multidrug
resistant Mycobacterium tuberculosis. Antimicrob Agents Chemother
2003;47:917-22.
19. Kattar D, Tiwary VK, Tripathy RP, Srivastava A, Chaturvedi V, Srivastava
R, et al. Synthesis and antimicrobial activity of 3, 5- disubstituted thiadiazine
thiones. Bioorg Med Chem 2003;11:4369-75.
20. Ninasanont N, Black DS, Chenphen R, Thebtaranonth Y. Synthesis of
ethyl- 5-phenyl-6-oxa-1 azabicyclo [3.1.0] hexane-2-carboxylate derivative
and evaluation of their antimalarial activity. J Med Chem 2003;46:2397-403.
21. Coban AY, Bayramoglu G, Ekinci B, Durupinar B. Antibacterial effect of
NO. Mikrobiyol Bul 2003;37:151-155.
22. Jimenez-Arellanes A, Meckes M, Ramirez R, Torres J, Luna-Herrera J.
Activity against multidrug resistant Mycobacterium tuberculosis in Mexican
plants used to treat respiratory disease. Phytother Res 2003;17:903-8.
23. Xie JP, Yue J, Xiong YL, Wang WY, Yu Q, Wang HH. In vitro activities
of small peptides from snake venom against clinical isolate of drug-resistant
Mycobacterium tuberculosis. Int J Antimicrob Agents 2003;22:172-4.
24. Munro AW, Mclean KJ, Marshall KK, Warman AJ, Lewis J, Ruitel O, et
al. Cytochrome p 450: Novel drug targets in the tuberculosis. Biochem Soc
Trans 2003;31:625-30.
25. Toyohara M, Nagata A, Hayano K, Abe J. Study on the antitubercular
activity of tuberactinomycin, a new antimicrobial drug. Am Rev Respir Dis
1986;100:228-30.
26. Dresser LD, Rybak MJ. The pharmacologic and bacteriologic properties
of oxazolidinones, a new class of synthetic antimicrobials. Pharmacotherapy
1998;18:456-62.

How to cite this article: Chhabra N, Aseri ML, Dixit R, Gaur S. Pharmacotherapy
for multidrug resistant tuberculosis. J Pharmacol Pharmacother 2012;3:98-104.
Source of Support: Nil, Conflict of Interest: None declared.

Announcement

“QUICK RESPONSE CODE” LINK FOR FULL TEXT ARTICLES

The journal issue has a unique new feature for reaching to the journal’s website without typing a single letter. Each article
on its first page has a “Quick Response Code”. Using any mobile or other hand-held device with camera and GPRS/other
internet source, one can reach to the full text of that particular article on the journal’s website. Start a QR-code reading
software (see list of free applications from http://tinyurl.com/y2zh2tc) and point the camera to the QR-code printed in
the journal. It will automatically take you to the HTML full text of that article. One can also use a desktop or laptop with web
camera for similar functionality. See http://tinyurl.com/2bw7fn3 or http://tinyurl.com/3ysr3me for the free applications.