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Research Article

CURRENT STRATEGIES IN THE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS

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ABSTRACT

Objective: The objective of the study was to analyze and review the current knowledge about the principles of treatment of multidrug-resistant tuberculosis (MDR-TB), World Health Organization treatment regimen to treat MDR-TB, mechanism of resistance, and risk factors for emergence of resistance, and novel antitubercular drugs (ATDs) available and control measures to improve treatment outcomes of MDR-TB.

Methods: Various articles were reviewed from PubMed and other databases and were analyzed to write the review.

Results: Mycobacterium is a largely curable infectious disease if proper treatment should be followed. The success of the treatment depends on the designing of proper treatment regimen and patient adherence to that medication.

Conclusion: *Mycobacterium tuberculosis* is now the most lethal infectious pathogen. Drug resistance has become a major problem in the treatment of TB. In MDR-TB, the bacteria is resistant to at least isoniazid (INH) and rifampicin (RIF), and in extensively drug-resistant TB the bacteria is resistant to INH, RIF, any fluoroquinolone, and at least one of three injectable second-line drugs for TB such as kanamycin, capreomycin, and amikacin. More recently, a more worrying situation has emerged with the description of *M. tuberculosis* strains that have been found resistant to all antibiotics that were available for testing, a situation labeled as totally drug resistant-TB. Other reasons like poor planning by the authorities and the government may also result in the emergence of resistant strain. Rather than the effective chemotherapy and the moderately protective vaccine, new anti-TB agents, and novel controlled release nanoparticulate system like polymeric nanocarrier systems containing existing ATDs are urgently needed to decrease the global incidence of TB.

Keywords: Mycobacterium, Multidrug-resistant tuberculosis, Extensively drug-resistant tuberculosis, Totally drug-resistant tuberculosis.

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INTRODUCTION

Tuberculosis (TB) is the ninth leading cause of death worldwide that originates from a single microbial agent and ranks above HIV/AIDS. According to the World Health Organization (WHO), 10.4 million TB cases were reported in 2016, of which 1.8 million died with TB, and there were 490,000 multidrug-resistant TB (MDR-TB) cases, of which 600,000 new cases with resistant to rifampicin (RIF), most effective first-line drug and almost half of the cases were in India, China, and the Russian Federation [1]. *Mycobacterium tuberculosis* is the responsible bacteria causing TB. The complete remission of TB will take a minimum of 6 months because the antibiotics work only when the bacteria is in their actively dividing stage and the mycobacterium growth rate is very slow [2]. The biggest problem in the antibiotic treatment is the lack of medication adherence, which will develop the MDR-TB and further lead to extensively MDR. In MDR-TB, the bacteria is resistant, at least to isoniazid (INH) and RIF and in extensively drug-resistant TB (XDR-TB), the bacteria is resistant to INH, RIF, any fluoroquinolone, and a minimum of three injectable second-line drugs for TB such as Kanamycin, Capreomycin, and Amikacin [3].

The existing treatment regimen available to treat MDR/XDR-TB is extremely difficult for social public, medical, and health systems. The person with MDR-TB will receive relapse-free cure after a long time, i.e., after the initiation of treatment, it takes at least 20 months to complete and is undermined by greatest incidence of adverse drug reactions, suboptimal treatment adherence, and more expensive, and less satisfactory outcomes. The treatment of MDR/XDR-TB will be extremely challenging in the absence of a useful vaccine, more effective facilities for culture and sensitivity testing and new therapeutic interventions [4,5]. Improper management of MDRTB may lead to reduced therapeutic outcomes while increasing the risk of extensive drug resistance and it also reflects that the inadequate numbers of second-line drugs are available [6].

The WHO has suggested the basic standard of deciding treatment regimens that comprise one injectable drug and one fluoroquinolone as part of a combination that usually contains four or five agents, including alternative second-line anti-TB agent, if the *M. tuberculosis* strain is found to be resistant to fluoroquinolone. However, the efficacy and safety of these regimens are low, and leads to prolongation of treatment, leaving the necessity for new drugs and combinations against MDR and XDR-TB [7]. Therefore, it is of enormous significance that, for the 1st time in nearly 50 years, two new compounds Bedaquiline and Delamanid have been approved for the management of MDR-TB when a suitable treatment regimen is not otherwise available. In December 2012, Bedaquiline (Beerse, Belgium, Janssen) the first novel drug, received faster approval from the US Food and Drug Administration [8-10]. The second drug, Delamanid (Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan), received sanction from the European Medicines Agency and Japan's Pharmaceuticals Medical Devices Agency in 2014 [11]. Combined with these entirely new drugs, there is rising evidence for the significant role of repurposed medicines, including clofazimine and linezolid, which are showing effectiveness against drug-resistant forms of TB [12].

This review analyzes the risk factors involved in the emergence of MDR TB, mechanism of resistance and newly developed drugs with their antitubercular mechanism and new treatment regimens to resolve the current complications related to the management of MDR/XDR-TB.

Principles of management of MDR-TB

Inappropriate management of MDR-TB can cause worsening of patient outcomes and extensive drug resistance. A few directions can aid rational

therapy: First, treat the entire patient, not laboratory generated numbers, second, go for the highest dose of medications to obtain the desired outcomes with a tolerable level of toxicity, and third, beware of drug-drug interactions that have been studied [13]. The treatment should be observed by an expert center. Second-line drugs having less efficacious than the first-line drugs and are less likely to lead to adverse effects. MDR-TB associated with HIV infection has a high mortality rate [14]. Treatment of MDR-TB depends on medications that are less effective and more harmful than those used in controlling of TB caused by drug-susceptible (DS-TB) or MDR strains. As in susceptible TB forms, MDR-TB also be treated with a combination of drugs to improve the patient complaints and avoid relapses, but unfortunately treatment results for MDR-TB are usually poor. The WHO revised the MDR-TB desired outcome (Table 1) in March 2013. Recently, new treatment guidelines have been published. Unfortunately, existing information regarding the MDR-TB treatment mainly obtained from retrospective cohort analyses, so recommendations contained within in the updated guidelines depend on an evidence of low to very low quality. DS testing (DST) (rapid and/or conventional) is strongly suggested by the WHO in all active TB cases, since individualized treatment regimen may lead to progress of therapeutic outcomes. If the second-line DST results are pending or in context DST is not available, selection of medication should depend on the DST of the strain obtained from the patient or close contacts with MDR-TB, history and frequency of medication use in the patient, and known background drug resistance in the setting. Use of medications to which the strain was reported susceptible exhibited some additional benefit, so regimen should be designed according to culture DST as early as possible [15]. Based on their safety and effectiveness, the WHO suggested five groups of anti-TB drugs. Although currently no data available for supporting the practice of more than four drugs in patients with extensive disease, according to recent data the use of a minimum of six drugs in the intensive phase of infection could be resulted in an improved treatment outcome [16]. It is essential to emphasize the uncertainties about their liability and reproducibility of DST for pyrazinamide (PZA) (and ethambutol [EMB]) as well as the second-line anti-TB drugs other than the parenteral agents and the fluoroquinolones [17].

WHO treatment regimen in the management of MDR-TB

The treatment regimens approved TB medications and their dosage are recommended by the evidence-based WHO guidelines. New TB patients (irrespective of HIV status) should be managed with INH, RIF, PZA, and EMB for the initial 2 months (intensive phase) followed by INH and RIF for the remaining 4 months (continuation phase) [3]. The daily dosage is recommended (although weekly thrice dosing is also beneficial during the continuation phase under directly observed therapy [DOT]) as well as the fixed-dose combinations [18].

The WHO recommended DST (conventional and/or rapid) in all TB cases and particularly for those who having previous medical history. In patients with a medium or low risk of developing MDR-TB retreatment could be started while awaiting DST results. Retreatment could be with an empiric regimen comprising INH, RIF, PZA, EMB, and streptomycin for 2 months, followed by INH, RIF, PZA, and EMB for 1 month, and INH, EMB, and RIF for 5 months [3].

Rational MDR-TB management should comprise a minimum of four active medications: A later-generation fluoroquinolone (Gatifloxacin, levofloxacin, or moxifloxacin) plus an injectable aminoglycoside (amikacin, capreomycin, or kanamycin) plus any first-line medication to which the isolate is susceptible (e.g., PZA) plus the addition of one drug from Group 4 (cycloserine, p-aminosalicylic acid, terizidone, prothionamide, or ethionamide) (Table 2). The drugs in Group 5 can be included when four active drugs belonging to the previous groups are unavailable. In case of parenteral, the minimum length of the intensive phase is 8 months, the continuation phase will take 12–18 months, and the complete remission of mycobacterium approximately took 20 months. As a rule, 18 months are required to be added to the date of the first negative culture to describe the length of treatment. In case of therapeutic failure to attain culture conversion, the underlying reasons (incorrect drug dosage, quality of drug supply, non-adherence factors, malabsorption, and comorbidity) should be identified and possibly, and modified [3].

Mechanism of resistance

More recently, an additional dangerous state has arisen with the description of *M. tuberculosis* strains that have been found resistant to all antibiotics that were existing for the treatment, a situation considered as totally drug resistant-TB [19]. The TB bacteria has natural defenses against some drugs and can acquire drug resistance through genetic mutations. The bacteria does not have the ability to transfer genes for resistance between organisms through plasmids.

Some mechanisms of drug resistance include as follows [20],

Cell wall

The cell wall of *M. tuberculosis* (TB) contains complex lipid molecules which act as a barrier to stop drugs from entering the cell.

Drug modifying and inactivating enzymes

The TB genome codes for enzymes (proteins) that inactivate drug molecules. These enzymes usually phosphorylate, acetylate, or adenylate drug compounds.

Drug efflux systems: The TB cell contains molecular systems that actively pump drug molecules out of the cell. 15% of drug resistance in Gram-negative MDR strains is attributable to efflux-related mechanisms, thereby emphasizing the need for inclusion of efflux-related tests in the diagnostic regimen for MDR clinical bacteria [21].

Mutations

Spontaneous mutations in the TB genome can alter proteins which are the target of drugs, making the bacteria drug resistant.

Table 1: The WHO treatment outcome [4]

Category	Definition
Cured	Treatment successfully finished as suggested by the national policy without any sign of failure, and negative results are obtained, for three or more repeated cultures taken every 30 days, after completing the intensive phase.
Treatment completed	Treatment finished as suggested by the national policy without any sign of failure, but no negative results are obtained, for three or more repeated cultures taken every 30 days, after completing the intensive phase.
Treatment failed	Treatment discontinued or permanent regimen change is necessary for minimum of two anti-TB medications because of the absence of conversion after the end of intensive phase, or bacteriological reversion in the continuation phase after conversion to negative, or data of additional acquired resistance to fluoroquinolones or second-line injectable preparations, or adverse drug reactions.
Death	A patient who dies for any reason during the therapy.
Lost to follow-up	A patient whose treatment was disturbed for two repeated months or more (this category was previously known as "defaulted") and not evaluated a patient whose therapeutic outcome is unavailable (this consists of cases "transferred out" to a different treatment unit and whose therapeutic outcome is unavailable).

WHO: World Health Organization

Table 2: The WHO recommended treatment regimen for MDR-TB [3]

Select an injectable (Group 2)	Kanamycin Amikacin Capreomycin	Select a medication on the basis of DST and treatment history. Usually, streptomycin is not advisable because of the greater incidence of resistance in patients with MDR-TB
Select a higher-generation fluoroquinolone (Group 3)	Levofloxacin Moxifloxacin	Select any later-generation fluoroquinolone. If levofloxacin (or ofloxacin) resistance is already recognized, changes to moxifloxacin avoid concurrent use of moxifloxacin with bedaquiline.
Add Group 4 drugs	Cycloserine Terizidone PAS Ethionamide Prothionamide	Select two or more Group 4 drugs until there are at least four second-line anti-TB drugs likely to be effective. Ethionamide/ prothionamide is considered the most effective drugs in Group 4. Consider the history of treatment, side effect profile and cost DST are not considered reliable for the drugs in this group
Add Group 1 drugs	Pyrazinamide EMB	Pyrazinamide is usually included in most regimens. EMB can be included in the case of full sensitivity. If INH DST is unidentified or awaiting, it can be added to the regimen until DST results become accessible.
Add Group 5 drugs	Bedaquiline Linezolid Clofazimine Amoxicillin/clavulanate Imipenem/cilastatin plus clavulanate Meropenem plus clavulanate high-dose INH, Clarithromycin Thioacetazone	Consider Group 5 drugs if four second-line anti-TB drugs are not likely to be effective from Groups 2 to 4. If drugs are required from this group, it is recommended to include two or more DST is not standardized for the drugs in this group.

WHO: World Health Organization, MDR-TB: Multidrug-resistant tuberculosis, DST: Drug-susceptible testing, INH: Isoniazid, EMB: Ethambutol, PAS: Para-aminosalicylic acid

First-line anti-TB drugs

RIF, mechanism of action of RIF in *M. Tuberculosis* is by binding to the β-subunit of the RNA polymerase, preventing the elongation of messenger RNA. The majority of RIF-resistant clinical isolates of *M. tuberculosis* harbor mutations in the rpoB gene that codes for the β-subunit of the RNA polymerase. As a consequence of this, conformational changes happen that reduce the affinity of drug and leads to the emergence of resistance [22].

INH acts by preventing the synthesis of mycolic acids through the NADH-dependent enoyl-acyl carrier protein (ACP)-reductase, encoded by inhA. Although INH is simple in its structure, resistance to this drug has been related to the mutations in numerous genes, such as katG, inhA, ahpC, kasA and NDH [27].

EMB is bacteriostatic against multiplying bacilli and interfering with the biosynthesis of arabinogalactan in the cell wall. The known mechanism of resistance to EMB has been related to mutations in the gene embB with mutations at position embB306 [28].

Pyrazinamide, mechanism of action comprises alteration of PZA to pyrazinoic acid, which interrupts the bacterial membrane energetics preventing membrane transport. Mutations in the gene pncA remain as the most common reason in PZA resistant strains [29].

Second-line anti-TB drugs

Fluoroquinolones inhibiting the topoisomerase II (DNA gyrase) and topoisomerase IV, two key enzymes for bacterial viability. The major reason for the emergence of fluoroquinolone resistance in *M. tuberculosis* is by chromosomal mutations in the quinolone resistance-determining region of gyrA or gyrB. The most recurrent mutations are happened at position 90 and 94 of gyrA but mutations at position 74, 88, and 91 [30].

Kanamycin, capreomycin, amikacin, and viomycin, these four antibiotics have the similar mechanism of action by preventing the protein synthesis but, while kanamycin and amikacin are aminoglycosides, capreomycin and viomycin are cyclic peptide antibiotics. The most common mutations found in kanamycin-resistant strains are at position 1400 and 1401 of the rrs gene [31].

Ethionamide affects the mycolic acid synthesis by developing an adduct with nicotinamide adenine dinucleotide that inhibits the enoyl-ACP reductase enzyme. Resistance to ethionamide resulted by mutations in etaA/ethA, ethR and also mutations in inhA, which root resistance to both INH and ethionamide [32].

Risk factors for emergence of resistance

Mycobacterium is a largely curable infectious disease if proper treatment should be followed. The success of the treatment depends on the designing of proper treatment regimen and patient adherence to that medication. Drug resistance in *M. tuberculosis* is now known to occur from complex drivers, rather than simply from weak programs and inadequate adherence to treatment. Current evidence proposes that the development of drug resistance can arise despite better than 98% treatment completion. There is increasing evidence that variation in pharmacokinetics (PKs) profiles between individuals (i.e., interindividual variability) is a more likely to cause drug resistance than poor medication adherence. Prior studies have shown that the PK of first-line anti-TB drugs, including INH, PZA, RIF, and EMB show marked interindividual variability. Such variability in PK occurs as a result of demographic characteristics such as gender, age, ethnicity, and body weight, comorbidities, drug interactions, and PK changes occurs due to genetic polymorphisms. As a result of PK variability there could be an insufficient drug exposure at the infection site, facilitating the development of drug resistance [22].

Other noticeable risk factors include close contact to a patient with MDR-TB, migration, and HIV infection. TB contact and previous history of exposure showed more risk for XDR-TB in patients with MDR-TB, although this trend is not statistically significant due to the insufficient number of discontinuation of appropriate therapy, even in the larger studies [4].

Treatment failure or recurrence may be the effect of the use of an inadequate management against MDR/XDR-TB. It is assumed that insufficient quality of anti-TB medications and low exposure may lead to the development of drug resistance in *M. tuberculosis* [33]. HIV is the major risk factor for TB, increasing the risk of disease at least 100 fold.

There are no records stating the minimum period of a preventive therapy or whether it is safe to give medication as monotherapy.

Therefore, until additional data are available, monotherapy may be inadvisable. Adverse drug reactions should be closely monitored and to provide support to ensure adherence throughout the preventive treatment. When preventive therapy is not an option or risks outweigh the benefits, contacts and their clinicians should be educated about the risks of progressing to TB disease. Temporary periodical follow-up can be considered, but easy access to a specialized TB clinic in case symptoms appear to be of higher importance [4].

Novel antitubercular drugs (ATDs)

After 50 years, bedaquiline and delamanid were the two novel anti-TB drugs approved and released in 2012 and 2013.

Bedaquiline, a diarylquinoline compound has potent activity against drug-sensitive and drug-resistant *M. tuberculosis* due to the inhibition of bacterial ATP synthase. Registration was approved based on the outcomes of a Phase IIb clinical trial, while a Phase III trial is still an ongoing process and results are still awaited. In the Stage II of the Phase II registration trial, bedaquiline 400 mg daily was given for the first 2 weeks, followed by 200 mg daily for the remaining 22 weeks. After 24 weeks, subjects continued the MDR-TB optimized background treatment regimen (OBR) consisting of fluoroquinolones (mainly ofloxacin), aminoglycosides (mainly kanamycin), PZA, EMB, ethionamide, and cycloserine/terizidone in various combinations for 96 weeks. Bedaquiline safety concerns, though still uncertain, could be connected to QTc prolongation resulted from the drug and can be detected and yet unsolved higher death rate identified in the group treated with bedaquiline compared to placebo. A new Phase III trials were conducted to obtain the safety and efficacy of bedaquiline when used along with short MDR-TB regimens of 9 and 6 months period. A randomized pilot trial of bedaquiline for 8 weeks evaluated the safety, tolerability, and efficacy of bedaquiline when it is added to a background regimen in newly diagnosed patients with MDR pulmonary TB and they concluded that the bedaquiline based regimen was safe and associated with earlier culture negativity, even though the incidence of adverse events was high and reflects the poor tolerability of the second-line companion agents [34]. Based on the outcomes of these trials, the WHO recommends bedaquiline in adult patients with pulmonary MDR-TB and it is also cost effective.

Delamanid of the nitroimidazole class is the first drug to enter medical practice. The actions initiate, as the drug inhibits the synthesis of a cell-wall component of *M. tuberculosis* [35]. Similarly to bedaquiline, registration was granted subsequently after the results of Phase IIb studies showing better sputum-culture conversion at 2 months, and better final therapeutic outcomes in patients with MDR-TB were published Skripconoka *et al*. [35,36]. Evaluated Delamanid 100 mg and/or 200 mg twice daily in combination with optimized background regimen (OBR) and suggests that treatment with delamanid for 6 months in combination with an OBR can improve outcomes and reduce mortality among patients with both MDR and XDR-TB. As for bedaquiline, QT prolongation is suggested but appears to be of little clinical importance, and the incidence of adverse events is similar to those of patients administering placebo. A Phase III trial on delamanid is still under process: In this trial, the drug is given along with moxifloxacin and HIV-positive patients receiving antiretroviral therapy are included. Two more trials are assessed currently using delamanid for treatment of pediatrics MDR-TB [37].

Control measures to improve therapeutic outcomes of MDR-TB

Infection control procedures are necessary to avoid transmission of *M. tuberculosis*.

Patients must be informed about TB, preventive measures, diagnostic procedures, and treatment modalities in a language that they understand. The persons to be protected are household contacts (e.g., family members), and, in a hospital setting, other patients, healthcare workers, cleaners, administrative staff, etc., and visitors. The finest method to prevent the spread of *M. tuberculosis* is prompt diagnosis and initiation of adequate treatment. Persons with TB should be isolated from other patients and evaluated for TB without waiting in general areas. Hospitalization should comprise airborne isolation precautions for sputum smear-positive TB patients. Infectiousness is significantly reduced once a patient is on suitable regimen and it is probably not essential to keep a patient in hospital until their cultures become negative. In daily practice, strict isolation of a patient is often not possible, such as in a patient with ongoing nicotine addiction. In general, smoking is not allowed in patient rooms and patients with contagious TB, particularly MDR/XDR-TB, should not use common smoking shelters. Any *M. tuberculosis* transmission risk reduction program should contain the issues of administrative and environmental measures and personal respiratory protection. Natural ventilation should be maximized by appropriate architectural design and rational administrative support. Contaminated air exhaust outlets should be located away from windows, air intakes, and engaged areas, or effectively decontaminated by in-duct ultraviolet germicidal irrigation or high-efficiency particulate air filtration [4].

The early identification of resistance is important to control Mycobacterium. Resistance to anti-TB drugs is identified through laboratory tests. Both phenotypic methods that involve culturing *M. tuberculosis* in the presence of anti-TB drugs and genotypic methods that identify specific mutations in the genome of the bacteria associated with resistance against individual drugs can be used.

Management of adverse effects

Drugs used to treat MDR/XDR-TB are often associated with adverse effects. These can occur early or late in treatment. It is very important to identify the development of adverse events and to inform patients about this (Table 3) [4].

Improving individualized approach to drug treatment, therapeutic drug monitoring (TDM): The causes leading to the development of drug resistance in *M. tuberculosis* are well known, and include inadequate treatment (inadequate dose or dosing frequency), non-adherence to the prescribed regimen and PK variability. Dose adjustment is necessary for the patients who are slow responding to the treatment [3]. TDM prevents the development of resistance due to exposure to drug concentration below minimum inhibitory concentrations. TDM is potentially lifesaving as it can defect malabsorption and allow dosage adjustment. TDM is simple because it needs only a small amount of blood volume. Although TDM is still expensive, a gradual decrease in cost is likely to occur in the future as a consequence of an enlarged market [38].

To improve this condition, the TB control strategy recommended by the WHO is the DOT. DOT means that a trained healthcare worker or other designated individual (excluding a family member) provides the prescribed TB drugs and watches the patient swallow every dose. Although DOT is to guarantee the commitment of patients, healthcare professionals and the government to treatment.

Current advances in molecular biology and molecular epidemiology and a better understanding of drug resistance in TB have given a new horizon to its rapid diagnosis. However, the cost-effective techniques and their requirement for sophisticated equipment and skilled personals have excluded their implementation on a routine basis, especially in low-income countries [40].

New drug delivery technology such as the use of novel controlled release nanoparticulate system like polymeric nanocarrier systems containing existing Anti-tubercular drugs (ATDs).. These nanocarriers will help in overcoming the problems associated with the conventional drug delivery system in the treatment of DS and resistant TB. Nanocarrier systems can be used to deliver drugs through the parenteral, oral, nasal, and pulmonary route. Moreover, pulmonary drug delivery of these ATDs loaded nanocarriers helps in depositing site-specific drugs at high concentrations within the diseased lungs, thereby reducing the overall dose of a drug to patients which in turn reduces systemic side effects. Various existing first- and second-line ATDs can be incorporated into nanocarrier systems by using nanotechnological approach [41].

Table 3: Common adverse effects of ATDs used in the MDR-TB [4]

Substance	Common adverse effects	Management
Group I		
EMB	Optic neuropathy	Inform the patient to report decreased vision immediately. Discontinue and refer to an ophthalmologist if vision deteriorates. More likely to occur in patients with renal impairment. For hepatotoxicity, stop the drug; reintroduce in an escalating dose over several days.
Pyrazinamide	Hepatotoxicity, rash, gout	Discontinue drug if hepatotoxicity reoccurs. For reals, manage symptoms; if extensive, stop the drug and consider reintroduction. Discontinue if rash reoccurs. For gout, reduce dose initially and consider starting allopurinol when acute attack has settled.
Group II		
Amikacin	Ototoxicity, nephrotoxicity	Monitor levels of otic and kidney functions monthly. If problems occur, consider reducing dose frequency to 3 times a week. Discontinue if problems persist, but balance risk of cure versus deafness.
Capreomycin	Ototoxicity, nephrotoxicity	Monitor levels, hearing, and renal function monthly. If problems occur, consider reducing dose frequency to 3 times a week. Discontinue if problems persist, but balance risk of cure versus deafness.
Kanamycin	Ototoxicity, nephrotoxicity	Monitor levels, hearing, and renal function monthly. If problems occur, consider reducing dose frequency to 3 times a week. Discontinue if problems persist, but balance risk of cure
Group III		
Levofloxacin	GI disturbances, tendinitis, insomnia	QT interval prolongation may be potentiated with other drugs
Moxifloxacin	GI disturbances, tendinitis, insomnia	QT interval prolongation may be potentiated with other drugs
Group IV		
PAS	Nausea and vomiting, gastritis, hepatotoxicity, hypothyroidism	Rehydrate if necessary. Give anti-emetics 30 min before the medication; several classes of anti-emetic may need to be tried. Twice or 3 times a day divided dose may help. Gastritis can be helped by administering the drug with a small amount of food or giving an antacid or H2 blocker. For hypothyroidism, check TFT.
Prothionamide/ ethionamide	GI disturbances, depression, hepatotoxicity, hypothyroidism	As above depression can be treated with an antidepressant if other causes excluded. Give high-dose pyridoxine, up to 50 mg for every 250 mg of drug. If neuropathy progresses, discontinue drug.
Terizidone/cycloserine	Neurotoxicity, peripheral neuropathy	Discontinue if psychosis develops. Seizures can be managed with anticonvulsants, but the drug may need to be discontinued.
Amoxicillin/clavulanic acid	Hypersensitivity, GI disturbances	Not suitable for patients with penicillin allergy.
Clofazimine	Skin discoloration, GI disturbances	Inform the patient about discoloration of skin and body fluids
Imipenem	Hypersensitivity, neurotoxicity	Monitor blood counts
Meropenem	Hypersensitivity, neurotoxicity	Monitor blood count
Linezolid	Neuropathy, anemia	Monitor blood count; avoid prolonged use, when possible. Stop if peripheral neuropathy or hematological problems occur. Give with pyridoxine.
INH (high-dose)	Peripheral neuropathy, hepatotoxicity	Give with pyridoxine

EMB: Ethambutol, GI: Gastrointestinal, PAS: Para-aminosalicylic acid, TFT: Thyroid function tests, INH: Isoniazid, ATDs: Antitubercular drugs

CONCLUSION

The increased hardship of MDR-TB represents a major threat to TB control. New therapeutic strategies are gradually emerging to reduce reliance on injectable agents, lessen toxicity, and shorten treatment duration. Rather than the effective chemotherapy and the moderately protective vaccine, new anti-TB agents are urgently needed to decrease the global incidence of TB. For the resumption of MDR-TB, an increased understanding regarding the molecular mechanisms of drug action and drug-resistance is needed, and this may provide significant insight into the development of newer compounds. Hence, international cooperation and sustained investment are required to establish the most effective regimens; hence, researchers can expand their access to new drugs without compromising safety and can integrate the novel treatments into coordinated TB control programs alongside comprehensive DST and robust mechanisms for patient support and monitoring.

CONFLICTS OF INTEREST

The authors declare that we do not have any conflicts of interest.

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