Texila International Journal of Clinical Research
Volume 6, Issue 1, Aug 2019

The Emerging Global Challenge of Multidrug-Resistant Tuberculosis (MDR-TB) Therapy (An Expert Opinion)

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Abstract

MDR-TB (Multidrug-Resistant Tuberculosis) reportedly proves to be the greatest health care burden responsible for a substantial deterioration of health-related quality of life of underprivileged people across the globe. MDR-TB. The late diagnosis of MDR-TB, absence of standardized therapy, and treatment delays are some of the significant factors that substantially elevate comorbidity and mortality risk of the affected patients. HIV positive MDR-TB patients experience a drastic reduction in their life expectancy and wellness outcomes. The WHO guidelines recommend various treatment regimens for the systematic treatment of MDR-TB. Category-4 therapy proves to be the standard treatment option for MDR-TB patients. However, the clinicians still require closely monitoring the clinical history of their MDR-TB patients/suspects in the context of including the most appropriate drugs in category-4 therapy. The elevated side-effects of MDR-TB therapies lead to treatment non-compliance and discontinuation of category-4 intervention. This eventually increases the frequency of MDR-TB-related comorbidities and mortality on a global scale. The clinicians and researchers require revisiting the already approved MDR-TB treatment regimens in the context of modifying the drugs' combinations and/or dosages for decreasing the length of overall therapy while minimizing the risk of side effects. The researchers require undertaking prospective clinical trials to evaluate the therapeutic targets of unapproved MDR-TB treatment drugs in the context of optimizing the treatment combinations. Furthermore, the enhancement of drug susceptibility techniques and the thorough clinical examination of each MDR-TB case are highly required to effectively improve the overall quality of the selected antituberculosis therapy.

Keywords: *MDR-TB, Drug-resistant, Tuberculosis, Pharmacotherapy, Adverse-Effects, Recommendations.*

Introduction

MDR-TB (Multidrug-Resistant Tuberculosis) impacts more than 3% of children affected by tuberculosis manifestations (Jenkins & Yuen, 2018) [9]. Approximately, 22% of MDR-TB children experience high predisposition for comorbidities and mortality. Similarly, adults and elderly MDR-TB patients experience mortality risk based on their comorbidities, ineffective medications, and nosocomial infections (Chingonzoh et al., 2018) [3]. The 2014 data for tuberculosis reportedly reveals 9.6 million TB cases across the globe (Qadeer et al., 2016) [24]. Approximately, 1.3 million people across the globe experience morbidity based on their TB and/or MDR-TB manifestations (Asgedom, Teweldemedhin, & Gebreyesus, 2018) [1]. The MDR-TB treatment is based on multiple drugs that require administration for an extended duration in the context of improving the clinical outcomes (Paul, 2018) [14]. The progression of MDR-TB occurs in reciprocation with the elevated drug resistance of *Mycobacterium tuberculosis*. The patients co-infected with HIV experience an elevated risk of MDR-TB and XDR-TB as compared to the healthy population. The standardized MDR-TB treatment therapies are based on fluoroquinolones, second-line injectable drugs, core second-line medicines, and other miscellaneous agents. The fluoroquinolones include levofloxacin, moxifloxacin, and gatifloxacin. The second line injectables are based on amikacin, kanamycin, and capreomycin. The second line core drugs include prothionamide, ethionamide, linezolid, and clofazimine. However, the additional MDR-TB treatment drugs include D1-pyrazinamide, ethambutol, isoniazid (elevated dose), D2-bedaquiline, delamanidD3-PAS, imipenem-cilastatin, meropenem, amoxicillin-clavulanate, and thioacetazone (Mukherjee, Lodha, & Kabra, 2017) [13].

DOI: 10.21522/TIJCR.2014.06.01.Art006
ISSN: 2520-3096

The presently approved MDR-TB treatment medicines exhibit the potential to challenge the progression of *Mycobacterium tuberculosis* in the human host; however, the associated side-effects and toxicity prove to be the major therapeutic barriers that reduce the scope of their optimization in various health care settings. The WHO (World Health Organization) report on global tuberculosis (TB) prevalence reveals a substantial progression of TB across South Africa, Bangladesh, Nigeria, Pakistan, Philippines, Indonesia, China, and India. Furthermore, adults experience a greater predisposition towards TB development as compared to children inside the reported regions. 90% of adult TB cases across the developing nations include 9% HIV patients and 64% males (WHO, 2018) [37]. The World Health Organization provides basic guidelines to effectively minimize the prevalence and clinical complications of MDR-TB across the high-risk regions (WHO, 2018a) [38]. These guidelines advocate the requirement of treating the preliminary stage of tuberculosis through the appropriate pharmacotherapy. The guidelines also emphasize the need for improving the use of diagnostic approaches to facilitate the timely tracking of tuberculosis in suspected patients. Furthermore, the guidelines advocate the need for standardizing the infection control policies across the clinical settings to reduce the risk of MDR-TB and related comorbidities. The guidelines also support the requirement of using second-line therapy through the appropriate clinical correlation in the context of enhancing the recovery phase of MDR-TB patients. The presented expert opinion accordingly discusses the available therapeutic options for MDR-TB prophylaxis, treatment, and prevention while delineating the therapeutic constraints based on treatment side-effects and/or non-compliance issues. The critical analysis of category-4 MDR-TB therapy in the presented paper is based on improving the overall treatment outcomes and supporting the need for prospective research studies to facilitate the radical elimination of tuberculosis across the globe.

Methods

The author explored evidence-based (peer-reviewed) articles, databanks, and credible websites in the context of evaluating MDR-TB treatment options, category-4 therapy implications, therapeutic considerations, side-effects, therapeutic advantages, medical recommendations and/or therapeutic challenges. The selected articles were based on the year range of 2002-2019. The articles that discussed solely the action of category-4 therapy on other comorbidities (i.e. excluding MDR-TB) were summarily excluded from the expert analysis.

Results

The evidence-based expert opinion reflects the following outcomes regarding MDR-TB therapy, MDR-TB treatment considerations, treatment side-effects/complications, risk factors, and medical recommendations.

MDR-TB Therapy Challenges				
MDR-TB Therapy Options	MDR-TB Treatment Considerations	Side-Effects of MDR-TB Treatment	Therapeutic Benefits of MDR-TB Treatment	Medical Recommendations/Therapeutic challenges
1. The standard category-4 therapy is based on pyrazinamide, kanamycin, levofloxacin, ethionamide, cycloserine, and para-aminosalicylic acid 2. The individualized category-4 therapy varies from one patient to another based on the reported medical history and clinical manifestations 3. Category-4 therapy must include a minimum of 5 medications, including oral and injectable drugs 4. The physicians need to thoroughly monitor the adverse effects of category-4 therapy during its initial phase of administration 5. The maintenance therapy for MDR-TB is majorly based on the combination of oral medications	1. The patients with an elevated risk of MDR-TB require category-4 therapy for improving their clinical manifestations 2. HIV patients require category-4 therapy administration at an early stage of their MDR-TB 3. The medium-risk patients require an appropriate HIV and therapeutic monitoring prior to the initiation of their category-4 therapy 4. The patients undertaking category1/2 therapies require regular monitoring of their TB manifestations to assess the requirement of category-4 therapy 5. The drug susceptibility testing outcomes play a decisive role in formulating the appropriate drug dosages for MDR-TB treatment 6. The patient must not exhibit pregnancy, liver complications, jaundice, chronic disease, renal complications, cardiovascular manifestations and prior	1. The side-effects of pyrazinamide include acute skin irritation, fever, malaise, dysuria, vomiting, nausea, anorexia, and arthralgias 2. Sensorineural hearing loss predominantly impacts the diabetic patients who continue receiving Kanamycin for an extended duration 3. The preliminary side-effects of levofloxacin for MDR-TB patients include fever, skin rash, eosinophilia, and seizures 4. Ethambutol predominantly causes allergic reactions and hepatotoxicity in	1. Pyrazynoic acid of pyrazinamide impacts the therapeutic targets, including coenzyme-A/pantothenate, trans-translation, and energy production 2. Pyrazinamide effectively reduces the overall length of MDR-TB recovery in the treated patients 3. Kanamycin effectively deteriorates the protein synthesis mechanism of *Mycobacterium tuberculosis* that resultantly leads to the improvement in MDR-TB manifestations 4. Levofloxacin destabilizes topoisomerase II activity of *Mycobacterium tuberculosis* that eventually disrupts its multiplication across the host cell lines. 5. Ethambutol exhibits the capacity to disrupt the	1. The researchers must conduct experimental studies regarding the implications of chemoprophylaxis across the regions affected with an elevated prevalence of multidrug-resistant tuberculosis 2. Genotyping proves to be a promising approach to improve the precision of drug susceptibility testing for tuberculosis 3. Diabetes screening of the MDR-TB patients is essentially needed to evaluate their risk of kanamycin-based hearing loss 4. The dosage optimization and hepatic monitoring are highly required not only to reduce the risk of anaphylaxis or hepatic trauma but also to minimize the scope of *Mycobacterium tuberculosis* resistance against category-4 therapy 5. The therapeutic incapacity of ethambutol in the latent phase of MDR-TB warrants prospective investigation through clinical trials

DOI: 10.21522/TIJCR.2014.06.01.Art006
ISSN: 2520-3096

	history of 2nd line antituberculosis drugs 7. The category-4 therapy for the MDR-TB patients requires administration for a minimum of six months' duration and until the acquisition of negative sputum culture outcome 8. The maintenance phase of category-4 therapy is based on a tenure of 12-18 months 9. The follow-up interventions require administration for two years' tenure 10. The early tracking of MDR-TB and its manifestations is highly warranted to minimize the risk of treatment failure	the tuberculosis patients 5. The prolonged administration of ethionamide elevates the risk of hepatotoxicity, gall bladder dysfunction, and jaundice 6. The side-effects of cycloserine include peripheral neuritis, anemia, tremor, behavioral complications, wakefulness, coma, sleep disturbance, depression, somnolence, vomiting, nausea, gastrointestinal disturbance, and ataxia 7. The prolonged administration of para-aminosalicylic acid to MDR-TB patients leads to hypersensitivity reactions; however, the drug	cell wall integrity of tuberculosis pathogen; however, its candidature for category-4 therapy is not yet justified in evidence-based clinical literature 6. Ethionamide challenges *Mycobacterium tuberculosis* multiplication through the irreversible disruption of its cell wall via mycolic acid inhibition 7. Cycloserine effectively induces peptidoglycan dysfunction across the bacterial cell wall 8. Cycloserine effectively cross BBB (blood-brain barrier) and experiences 70-90% absorption across the gastrointestinal mucosa 9. Para-aminosalicylic acid disrupts the folic acid production of *Mycobacterium tuberculosis* that eventually leads to its irreversible inactivation	6. The close therapeutic monitoring of ethambutol is highly warranted to evaluate its cost-benefit ratio versus the risk of adverse effects 7. The regular monitoring of the MDR-TB patients' hepatic function is highly needed to reduce their predisposition for hepatic injury during ethionamide therapy 8. The assessment of ethionamide's minimum inhibitory concentration in the context of its standardized dosage and evaluation of its cross-resistance based on ethR/ethA genes' mutations are substantially required for improving the therapeutic outcomes 9. The dosage optimization and drug susceptibility testing measures are highly warranted in the context of cycloserine administration for effectively improving the therapeutic outcomes in MDR-TB patients 10. Dihydrofolate reductase mutation in *Mycobacterium tuberculosis* leads to its cross-resistance against dihydrofolate synthase inhibition activity of para-aminosalicylic acid

		is contraindicated for the patients affected with severe hepatic impairment and end-stage renal disease		

DOI: 10.21522/TIJCR.2014.06.01.Art006
ISSN: 2520-3096

Discussion

MDR-TB treatment approaches

The presented study evaluates a range of comprehensive treatment approaches for MDR-TB patients/suspects based on their risk level, clinical history, and other independent factors in the context of improving the prognostic outcomes. This subsection is based on credible clinical literature findings related to MDR-TB assessment and management. The WHO conventions for MDR-TB management advocate the use of standardized or individualized therapy in the context of improving the clinical outcomes. The standardized MDR-TB treatment approaches are based on the drug resistance surveillance data obtained from various treatment groups that receive similar therapeutic interventions. The standardized treatment approaches not only help in curing MDR-TB patients but also assist in preventing the development of *Mycobacterium tuberculosis* in the suspected individuals (WHO, 2014) [36]. Contrarily, the individualized therapeutic regimens warrant customization following the MDR-TB patient's clinical history, physical examination outcomes, and drug susceptibility findings. The site of MDR-TB plays a pivotal role in determining the appropriate standardized or customized therapy for the affected patients.

The physician requires evaluating the laboratory outcomes and patient type in the context of taking an evidence-based decision regarding the category of MDR-TB treatment. For example, the physician should administer category-1 treatment to the patients with smear-negative findings, smear-positive findings (for new cases), and extrapulmonary MDR-TB status (WHO, 2009) [35]. However, category-2 is based on smear-positive findings, past clinical history of tuberculosis, and relapse of TB manifestations. The physician requires administering category-4 treatment to MDR-Tb patients who fail to completely recover after receiving the initial pharmacotherapy. The category – 1 treatment during its intensive phase reciprocates with the drugs' combination including rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E). The dosage of these drugs varies following the weight of tuberculosis patients. For example, the patients with weight 19 kg or less should receive rifampicin, isoniazid, pyrazinamide, and ethambutol combination in dosages of 10-25mg per kilogram per day. However, the patients within the weight range of 20-35kg require consuming 2-tables of RHZE regimen. Similarly, the patients with a weight range of 36-50kg and greater than 50kg need to receive 3 and 4 tables of RHZE regimen following the standard TB management conventions. The maintenance phase of tuberculosis is based on the administration of isoniazid and rifampicin in dosages ranging from 2-4 tablets for the patients with a weight range of 20-50kg. However, the tuberculosis patients with less than 20kg weight require consuming 10mg of rifampicin-isoniazid combination per kg per day (Rabahi, Junior, Ferreira, Tannus-Silva, & Conde, 2017) [25].

The physicians require carefully monitoring the tuberculosis patients' symptoms during the course of category-1 therapy. The successful accomplishment of the initial antituberculosis therapy and complete elimination of *Mycobacterium tuberculosis* from the host's body is highly necessary for minimizing the risk of MDR-TB and related comorbidities. Furthermore, the physicians require administering DOT (Directly Observed Therapy) for effectively treating tuberculosis relapse cases or following the initial treatment failure (Azhar, 2012) [2]. The selection and administration of the appropriate DOT therapy are based on the frequency of bacterial multiplication in tuberculosis patients. For example, the physicians require administering isoniazid, rifampicin, and streptomycin to the tuberculosis patients affected with rapidly disseminating extracellular pathogen. The bactericidal action of the selected drugs' combination in such a scenario leads to the gradual disintegration of the extracellular pathogen. However, treatment non-compliance or inappropriate dosage substantially elevate the risk of treatment failure and MDR-TB development. Similarly, the tuberculosis relapse cases manifested with slow intracellular dissemination of *Mycobacterium tuberculosis* or other TB pathogen warrant the administration of rifampicin, isoniazid, and pyrazinamide combination for effectively achieving the everlasting cure. This therapeutic combination completely sterilizes the invading pathogen and leads to its elimination from the host body. Contrarily, the administration of inappropriate dosage or therapeutic non-adherence facilitates the late growth of the causative pathogen that eventually induces tuberculosis relapse or MDR-TB development in the human host.

The clinicians should recommend genotyping in the context of evaluating or ruling out the risk of TB relapse or reinfection in the suspected patients and accordingly administer category-2 therapy based on the bacterial pathology (Millet et al., 2013) [12]. The category-4 treatment for MDR-TB is based on a combination of kanamycin, ofloxacin, ethionamide, cycloserine, pyrazinamide, and ethambutol for a duration of 6-9 months. However, the maintenance phase of the same therapy is based on the administration of ofloxacin, ethionamide, cycloserine, and ethambutol for 18 months' duration. The standardized DOTS (Directly Observed Treatment Short Course Therapy) is based on the coadministration of kanamycin (500-750mg), ofloxacin (600-800mg), ethionamide (500-750mg), ethambutol (800-1000mg), pyrazinamide (1250-1500mg), cycloserine (500-750mg), and Na PAS (para-aminosalicylic acid) (10-12mg) (Grover & Takkar, 2008) [7]. The general conventions for category-4 therapy configuration are based on the inclusion of 5 or more drugs, first-line medications, injectables, quinolones, and drug resistance information (WHO, 2009) [35]. The selection of first-line drugs should effectively follow the drug susceptibility test outcomes. This indicates that the tuberculosis pathogen must exhibit susceptibility for the selected first-line medicine. The inclusion of the injectable drug in category-4 regimen follows the requirement of the long-term therapy. The inclusion of quinolone follows the requirement of selecting moxifloxacin, levofloxacin, or ofloxacin based on the patients' symptoms. The analysis of the patient's therapeutic history and drug resistance details is highly required for the systematic selection of the appropriate category-4 drugs (WHO, 2009) [35]. The other types of standardized category-4 therapies for adult MDR-TB patients are based on the following combinations.

Drugs' Combination-1	Drugs' Combination-2	Drugs' Combination-3 for the Patients Undergoing Antiretroviral Therapy	Drugs Combination-4 for the Patients Undergoing Antiretroviral Therapy
1750mg/3.5 tabs of pyrazinamide	150mg/6 tablets of pyridoxine	Combivir (zidovudine+Lamivudine) – 1 tablet	Combivir (zidovudine+Lamivudine) – 1 tablet
4g/1 sachet of para-aminosalicylic acid	4g/1 sachet of para-aminosalicylic acid	960mg/1 tablet of cotrimoxazole	Efavirenz – 1 tablet
250mg/1 capsule of cycloserine	500mg/2 capsules of cycloserine		
250mg/1 tablet of ethionamide	500mg/2 capsules of cylcoserine		
500mg/2 tablets of levofloxacin	500mg/2 tablets of ethionamide		
1000mg/1 injection of kanamycin			

The assessment of the patients' MDR-TB risk level is highly necessary to systematically evaluate their drug resistance predisposition. The migrant workers/health workers with newly diagnosed tuberculosis and the patients treated after their TB recurrence experience a moderate predisposition for MDR-TB. The newly diagnosed patients with moderate MDR-TB risk require undergoing sputum culture followed by drug susceptibility testing. The patients affected with TB relapse also require similar diagnostic intervention followed by category-2 therapy. The clinicians require tracking high-risk patients in the context of individualizing their category-4 treatment based on the reported clinical history and disease manifestations. The patients who experience close contact with the MDR-TB patients require undergoing their sputum culture assessment followed by the drug susceptibility testing of the respective contact person. The category-4 therapy initiation for the MDR-TB patients, suspects, or household contact persons at an early stage is highly required to minimize their risk of comorbidities and mortality. The TB patients who exhibit an HIV positive status or develop worsening clinical symptoms during the administration of category-1 treatment also prove to be the candidates for category-4 therapy. Furthermore, the patients who exhibit a smear-positive outcome during the 20th week of their category-1 or category-2 therapy also require category-4 regimen for controlling their clinical manifestations. The patients with a known history of 2nd line therapy also need to undergo drug

DOI: 10.21522/TIJCR.2014.06.01.Art006
ISSN: 2520-3096

susceptibility testing and sputum culture tests prior to the selection of the appropriate category-4 therapy.

Therapeutic Benefits of MDR-TB Drugs

Pyrazinamide is a category-4 drug antituberculosis drug that plays a pivotal role in reducing the overall length of tuberculosis therapy. Its direct action on the non-replicating persisters makes it a preferable treatment option for MDR-TB patients. Pyrazinamide acts on numerous therapeutic targets including coenzyme-A/pantothenate, trans-translation, and energy production (Zhang, Shi, Zhang, & Mitchison, 2013) [40]. Pyrazinamidase of pncA gene facilitates the production of therapeutically active pyrazinoic acid from pyrazinamide prodrug. *Mycobacterium tuberculosis* mutants including MT3240, MT3246, MT2968, MT1199, MT1372, MT2345, and MT1058 exhibit energy metabolism defects that eventually elevate their susceptibility against pyrazinamide. The clinicians, therefore, require screening these mutants and selectively defining therapeutic targets based on their occurrence in the tuberculosis pathogen. The targeted therapy in such scenarios should effectively deteriorate the functionality of the selected mutants in the context of improving the TB prognosis. Pyrazinamide therapy proves effective for the human hosts invaded by slowly dividing intracellular TB bacilli. Pyrazinamide requires a slightly acidic pH for its therapeutic action. The pncA assay for genotypic susceptibility assessment is associated with 85% diagnostic accuracy (Pholwat et al., 2014) [15]. The clinicians require using high-resolution melt assessment to effectively evaluate pyrazinamide resistance mutations in the pncA gene of *Mycobacterium tuberculosis.*

Kanamycin of category-4 therapy is based on dibekacin, tobramycin, kanamycin-B, and kanamycin-A (Salian et al., 2012) [28]. Kanamycin effectively deteriorates ribosomal decoding-A location through protein synthesis disruption of the tuberculosis pathogen. The glucopyranosyl moiety of kanamycin contains variable hydroxy and amino group locations. The H-O5 and 6′-OH bonding pattern at position 2’ of kanamycin are primarily responsible for its therapeutic activity. The aminoglycoside antibiotic ‘Kanamycin’ integrates with 30S ribosomal subunit of *Mycobacterium tuberculosis* and disrupts t-RNA reading mechanism. This eventually misleads the protein configuration of TB pathogen in the human host. The drug susceptibility testing is essentially required before the inclusion of kanamycin in MDR-TB therapy.

Levofloxacin is a drug of choice for treating the tuberculosis patients affected with resistance against rifampicin, ethambutol, and isoniazid (Richeldi et al., 2002) [27]. The administration of levofloxacin to MDR-TB patients is based on the approved dosage range of 250-750mg. The inclusion of levofloxacin in category-4 TB therapy effectively reduces the overall treatment span and recovery phase. The CSF (cerebrospinal fluid) penetration power of levofloxacin also makes it the drug of choice for treating tuberculosis meningitis. Levofloxacin actively destabilizes bacterial topoisomerase II/DNA gyrase of *Mycobacterium tuberculosis* after diffusing through its cell wall structure (Tunitskaya, Khomutov, Kochetkov, Kotovskaya, & Charushin, 2011) [32]. This substantially impairs DNA repair, RNA transcription, and DNA replication processes of *Mycobacterium tuberculosis* that eventually leads to the cessation of its overall cell growth.

The bacteriostatic action of ethambutol is responsible for disrupting the cell wall consistency of *Mycobacterium tuberculosis* (Ghiraldi-Lopes et al., 2019) [6]. Ethambutol deactivates the cell wall polysaccharide ‘arabinogalactan’ through the inhibition of arabinosyl transferases that eventually disrupts bacterial multiplication in the human host. The prolonged administration of ethambutol not only challenges the replication of tubercle bacilli but also reduces the RNA synthesis of *Mycobacterium tuberculosis.* The entire strains of Mycobacterium kansasii and *Mycobacterium tuberculosis* exhibit an elevated susceptibility against ethambutol.

The nicotinamide derivative ‘ethionamide’ ceases the mycolic acid synthesis across the cell wall of *Mycobacterium tuberculosis* that eventually leads to its lysis and cell wall disruption (PubChem_NCBI, 2019d) [21]. The researchers continue to evaluate the bactericidal or bacteriostatic potential of ethionamide. The consistent monotherapy of ethionamide gradually facilitates its resistance in *Mycobacterium tuberculosis*. Ethionamide resistance of *Mycobacterium tuberculosis* generally attributes to the spontaneous mutations in ethR and ethA genes (Varma-Basil & Prasad, 2015) [34]. The clinicians require determining the risk of ethionamide resistance in MDR-TB patients following the prolonged administration of category-4 therapy.

The D-Alanine amino acid analog 'Cycloserine' is a broad-spectrum antibiotic that potentially retards the synthesis of bacterial cell wall through the induction of peptidoglycan dysfunction (PubChem_NCBI, 2019e) [22]. Cycloserine competitively inhibits the secretion and enzymatic activities of D-alanine ligase and L-alanine racemase that eventually ceases bacterial multiplication. Cycloserine experiences 70-90% gastrointestinal absorption and overcomes the blood-brain barrier in MDR-TB patients (PubChem_NCBI, 2019e) [22]. The 10-12 hours half-life of cycloserine substantiates its dosage optimization for the MDR-TB patients. Cycloserine also does not encounter any cross-resistance following its concomitant administration with category-4 tuberculostatic drugs.

Para-aminosalicylic acid effectively competes with para-aminobenzoic acid in the context of disrupting the folate synthesis mechanism of *Mycobacterium tuberculosis* (PubChem_NCBI, 2019f) [23]. The bacteriostatic activity of Para-aminosalicylic acid results in cell death and growth retardation of *Mycobacterium tuberculosis* in an irreversible manner.

Therapeutic challenges of MDR-TB drugs

The sustainable mutations in Rps A (drug target) and pnc A genes lead to the resistance of TB pathogen against pyrazinamide (Zhang, Shi, Zhang, & Mitchison, 2013) [40]. The pyrazinamide resistant strains of TB pathogens also exhibit panD mutations. The presently reported pyrazinamide susceptibility studies usually reveal incorrect resistance outcomes. However, pnc A gene sequencing appears to be a cost-effective and feasible measure to improve the precision of pyrazinamide susceptibility testing. The mechanism of TB microbe's slow division is not yet known to the clinicians. The therapeutic effects of pyrazinamide on *Mycobacterium tuberculosis* correlate with its action on the bacterial division pattern (Pubchem_NCBI, 2019). The clinicians, therefore, require evaluating the causative mechanism of TB pathogen's slow division for the development of new therapeutic targets while improving the molecular configuration of pyrazinamide. The evidence-based research literature reveals a range of transport mechanisms and enzyme targets, including pyrazinamidase defect that facilitates the development of pyrazinamide resistance in MDR-TB patients (Stehr, Elamin, & Singh, 2015) [30]. The high-resolution melt assessment technique for pyrazinamide resistance evaluation is associated with elevated cost and 15% risk of failure (Pholwat et al., 2014). The greatest diagnostic challenge is, therefore, based on the use of this technique in resource-intensive clinical settings or resource-limited regions.

Retrospective studies reveal the high-risk of the sustained dysfunction of microangiopathic inner-ear processes, kidney complications, and sensorineural hearing loss in kanamycin treated diabetic patients (Heysell et al., 2018) [8]. These outcomes warrant diabetes screening of the MDR-TB patients in the context of taking an evidence-based decision regarding the inclusion or exclusion of kanamycin in category-4 therapy. Diabetes screening not only elevates the overall therapeutic cost but also leads to a substantial delay in selecting the appropriate MDR-TB management therapy. Kanamycin resistance does not develop in more than 5% of the patients who receive category-4 therapy for their MDR-TB treatment (Kumari, Banerjee, & Anupurba, 2018) [10]. However, the severity of its side-effects leads to therapeutic non-compliance in treated patients.

The researchers continue to debate in relation to the dosage criteria of levofloxacin for MDR-TB patients. The 6-8 hours half-life of levofloxacin correlates with the requirement of multiple dosages to effectively minimize the risk of drug-resistant TB mutant activation (PubChem_NCBI, 2019b) [19]. The once-daily dosage of levofloxacin, therefore, might not provide a survival advantage to all of the MDR-TB patients. Levofloxacin administration elevates the risk of AST/ALT elevation and cholestatic hepatitis in MDR-TB patients. Some of the MDR-TB patients spontaneously develop jaundice or exhibit hepatocellular injury within 7-21 days of levofloxacin administration. The prolonged administration of levofloxacin elevates the risk of vanishing bile duct syndrome, cholestasis, extended jaundice, and acute liver failure. The levofloxacin anaphylaxis leads to hepatic trauma, toxic epidermal necrolysis, and Stevens-Johnson Syndrome (PubChem_NCBI, 2019b) [19]. These findings substantiate the requirement of the liver, kidney, and immune system monitoring of MDR-TB patients to minimize the frequency of their clinical complications during category-4 therapy administration. The MDR-TB patients/suspects must also undergo allergy testing to identify their levofloxacin susceptibility pattern and risk of clinical complications.

DOI: 10.21522/TIJCR.2014.06.01.Art006
ISSN: 2520-3096

The half-life of ethambutol is based on 3-4 hours in patients not affected by renal function complications (PubChem_NCBI, 2019c) [20]. However, kidney dysfunction extends the half-life of ethambutol from 4 hours to 8 hours. The dosage optimization for the enhancement of therapeutic effects proves to be the biggest therapeutic challenge for clinicians. Furthermore, ethambutol does not appear highly effective for MDR-TB patients with a clinical history of meningitis due to its selective CSF penetration capacity. Furthermore, ethambutol impacts the function of susceptible *Mycobacterium tuberculosis* strains during their active multiplication phase. This reveals the incapacity of ethambutol to treat the latent phase of MDR-TB (PubChem_NCBI, 2019c) [20]. The drug probably fails to treat the early stage of MDR-TB in suspected patients. These outcomes reveal the questionable utilization of ethambutol for MDR-TB prevention in the absence of a definitive diagnostic affirmation. The elevated risk of hepatotoxicity barricades the selection of ethambutol in category-4 drugs; however, prospective clinical studies are highly warranted to closely monitor the concomitant therapeutic effects of ethambutol-pyrazinamide therapy for MDR-TB patients.

The unavailability of a robust ethionamide susceptibility testing intervention challenges the proactive assessment of MDR-TB prognosis and therapeutic outcomes (Varma-Basil & Prasad, 2015) [34]. The clinicians require evaluating the ethionamide resistant strains of *Mycobacterium tuberculosis* for minimizing the risk of category-4 treatment failure in MDR-TB patients. The assessment of ethionamide's relationship with its minimum inhibitory concentration and standard dose is also required to facilitate its dosage optimization in the context of reducing the overall duration of category-4 therapy.

The coadministration of cycloserine with isoniazid is not recommended based on the high-risk of central nervous system toxicity (PubChem_NCBI, 2019e) [22]. The MDR-TB patients affected with alcohol abuse also experience high-risk of seizures following the administration of cycloserine. Approximately, 9.1% of MDR-TB patients experience adverse drug reactions following the administration of cycloserine. The scientific community continues to struggle and debate on the dosage optimization of cycloserine for MDR-TB patients. This is because cycloserine's dosage of 10 mg/kg in many clinical scenarios fails to induce the desired minimum inhibitory serum concentration in the treated patients (Li et al., 2019) [11]. The drug susceptibility testing and dosage adjustment of cycloserine prove to be the greatest diagnostic/therapeutic challenges encountered by clinicians and researchers until date.

MDR-TB patients develop resistance against para-aminosalicylic acid through dihydrofolate reductase mutation or dihydropteroate synthase inhibition that eventually reduces the antimetabolite production in the human host (Zheng et al., 2013) [41]. The cross-resistance to dihydrofolate synthase inhibitors develops under the impact of riboflavin biosynthesis protein overexpression by para-aminosalicylic acid-resistant clinical isolates. The researchers, therefore, require conducting prospective studies to evaluate the pathophysiological pathways of para-aminosalicylic acid resistance in MDR-TB patients that substantially elevates the risk of their category-4 therapy failure. The co-administration of para-aminosalicylic acid with other antituberculosis drugs effectively improves the therapeutic outcomes; however, its single administration is not supported by evidence-based clinical literature.

Side-Effects of MDR-TB drugs

Pyrazinamide is associated with acute skin irritation, fever, malaise, dysuria, vomiting, nausea, anorexia, and arthralgias. The clinicians require administering a test dose of pyrazinamide before including this drug in the therapeutic regimen for MDR-TB treatment. The therapeutic non-compliance of category-4 therapy in many scenarios is based on the reported side-effects of pyrazinamide (Pubchem_NCBI, 2019) [17].

Kanamycin is associated with irreversible autotoxicity and vestibular toxicity (PubChem_NCBI, 2019a) [18]. The long-term administration of kanamycin to MDR-TB patients elevates the risk of gait defect, dizziness, vomiting, nausea, and vertigo. The rare sensitivity reactions associated with kanamycin administration include Stevens-Johnson syndrome, angioedema, erythema multiforme, toxic epidermal necrolysis, and exfoliative dermatitis.

The evidence-based research literature reveals an elevated risk of seizure following the administration of levofloxacin to the MDR-TB patients affected with meningitis (Pranger, Werf,

Kosterink, & Alffenaar, 2019) [16]. The commonly reported immunoallergic manifestations associated with levofloxacin administration include eosinophilia, skin rash, and fever. The researchers, therefore, require conducting prospective studies in the context of performing pharmacodynamic/pharmacokinetic analysis of levofloxacin to effectively evaluate the dosage requirement and exposure level of levofloxacin for TBM (tuberculosis meningitis) and MDR-TB patients. The levofloxacin dosage optimization could probably reduce the frequency of its side-effects in treated patients.

Ethambutol is associated with the minimal risk of hepatic trauma. Ethambutol induced allergic reactions are based on erythema multiforme, Stevens-Johnson Syndrome, and skin rashes (PubChem_NCBI, 2019c) [20]. The prolonged administration of ethambutol elevates the risk of liver disease and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome accompanied by an increase in serum aminotransferase. The acute impact of ethambutol in MDR-TB patients leads to the development of eosinophilia, focal pneumoconiosis, pulmonary fibrosis, convulsions, dermatitis, cholestasis, and jaundice.

The prolonged administration of ethionamide to MDR-TB patients elevates their risk for hypothyroidism and gastrointestinal complications (Thee, Garcia-Prats, Donald, Hesseling, & Schaaf, 2016) [31]. Ethionamide therapy does not induce life-threatening complications in most of the clinical scenarios. Ethionamide therapy substantially elevates the MDR-TB patients' predisposition towards gall bladder disease, liver injury, and jaundice. The regular monitoring of liver function is, therefore, necessarily required to minimize the risk of hepatotoxicity during the prolonged administration of category-4 therapy.

The long-term administration of cycloserine is associated with the episodes of tremor, behavioral complications, wakefulness, coma, sleep disturbance, depression, somnolence, vomiting, nausea, gastrointestinal disturbance, and ataxia (PubChem_NCBI, 2019e) [22]. Cycloserine administration also elevates the risk of pyridoxine's renal elimination that eventually leads to the development of peripheral neuritis or anemia. The prolonged administration of cycloserine to MDR-TB patients leads to mental confusion, drowsiness, conjunctivitis, and visual disturbances.

The side-effects of para-aminosalicylic acid are based on hypersensitivity reactions including jaundice, hepatitis, thrombocytopenia, agranulocytosis, leukopenia, eosinophilia, joint pain, exfoliative dermatitis, vasculitis, fever, and pruritis (Drugs.com, 2019) [5]. The administration of para-aminosalicylic acid is contraindicated in MDR-TB patients affected with severe hepatic impairment and end-stage renal disease. This is because these patients fail to tolerate the drug that eventually leads to treatment failure. The researchers, therefore, require exploring alternative drugs' combinations to overcome the pitfalls/challenges encountered during the administration of category-4 therapy to MDR-TB patients.

Conclusion and future recommendations

The WHO guidelines recommend multiple MDR-TB treatment regimens including fluoroquinolones, 2nd line injectables, other core 2nd line drugs, and miscellaneous medicines. Each of the recommended MDR-TB treatment drugs exhibits an elevated potential to minimize the dissemination of *Mycobacterium tuberculosis* in the human host. Clinicians and researchers recommend various comprehensive combinations of these approved drugs in the surge of providing a complete cure to MDR-TB patients. However, several side effects and therapeutic challenges barricade the formulation of standard MDR-TB therapy. The absence of an appropriate drug susceptibility testing measure, treatment cost, and therapeutic contraindications substantially elevate the risk of medication non-compliance and treatment failure in MDR-TB patients. The severe adverse effects including nephrotoxicity, ototoxicity, dermatological complications, epileptic seizures, hypothyroidism, peripheral neuropathy, hepatitis, arthralgia, psychiatric disorder, and gastrointestinal disturbances lead to the discontinuation of antituberculosis therapy among MDR-TB patients (Yang et al., 2017) [39]. The category-4 therapy despite its proven effectiveness against MDR-TB encounters various shortcomings that barricade its standardization for the entire MDR-TB patients.

Evidence-based clinical literature supports the requirement of conducting prospective experimental studies or randomized controlled trials for evaluating the effectiveness of unapproved drug candidates for MDR-TB treatment. Some of these unapproved MDR-TB treatment drugs include co-trimoxazole

DOI: 10.21522/TIJCR.2014.06.01.Art006
ISSN: 2520-3096

(including trimethoprim/sulfamethoxazole), bedaquiline (elevated dosage), linezolid (elevated dosage), and ciprofloxacin (Van et al., 2013) [33] (ClinicalTrials.Gov, 2019) [4] (Shim & Jo, 2013) [29]. Furthermore, the clinicians and researchers must study new therapeutic combinations of the approved MDR-TB management drugs in the context of enhancing the therapeutic outcomes while concomitantly shortening the length of therapy and minimizing the intensity/frequency of side-effects (Rendon et al., 2016) [26]. However, the short-term MDR-TB treatment improvement measures are based on the development of the appropriate drug susceptibility interventions to effectively individualize the therapeutic approaches for reducing the overall treatment tenure. Furthermore, the clinicians must actively evaluate MDR-TB suspects through their physical examination and review of systems while investigating their sources of infection to identify the type of TB causing pathogen for its focussed treatment. The clinical correlation of the MDR-TB patients' manifestations is highly needed to effectively improve their prognostic outcomes. The clinicians and researchers must also develop focussed, holistic, and person-centered therapies for the systematic treatment of preliminary TB infections to reduce the risk of MDR-TB outbreaks on a global scale.

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