Multidrug-Resistant Tuberculosis (MDR-TB): Epidemiology, Causes, Pathophysiology, Diagnostic Approaches, Preventive Interventions, and Treatment Challenges/Opportunities – (An Evidence-Based Narrative Literature Review)

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Abstract

Background: MDR-TB (Multidrug-resistant tuberculosis) reportedly proves to be the greatest public health issue on a global scale. The mutation tendency of Mycobacterium tuberculosis substantially elevates its resistance against the recommended pharmacotherapeutic interventions. Limited information on the MDR-TB diagnostic approaches and treatment options is primarily responsible for its extensive progression across resource-limited regions. The frequently reported adverse effects of the standard therapies barricade their long-term use by the MDR-TB patients.

Aim: The presented narrative review attempts to consolidate and strengthen the clinical evidence for improving the MDR-TB diagnosis and treatment decisions in health care settings.

Methods: The author performed an evidence-based analysis of the causative factors, pathophysiology, diagnostic techniques, and treatment options/challenges for MDR-TB through the systematic exploration of databases including Google Scholar, PubMed/Medline, and Cochrane Library. The utilization of these databases was effectively undertaken to explore the peer-reviewed MDR-TB-related articles based on meta-analysis, systematic review, retrospective study, randomized controlled trial, and narrative literature reviews.

Findings: The study findings revealed MDR-TB epidemiology, etiology, diagnostic approaches, preventive measures, pathogenesis, treatment adversities, and therapeutic potential in the context of controlling the prevalence of drug-resistant tuberculosis and related comorbidities.

Conclusion: The study findings advocate the need for improving the overall MDR-TB investigation and treatment process to control the elevated prevalence of MDR-TB among the suspected patients. The study outcomes advocate the requirement of multidisciplinary coordination between clinicians and researchers to effectively improve the medical decision-making quality for enhancing the therapeutic outcomes of MDR-TB patients.

Keywords: MDR-TB, Drug-resistant, tuberculosis, diagnosis, pathophysiology, treatment.

Introduction

Multidrug-resistant tuberculosis (MDR-TB) continues to be the greatest challenge that increasingly elevates the overall health care burden across the globe [24]. MDR-TB reportedly occurs under the impact of increased bacterial resistance against conventional treatment interventions, including rifampicin and isoniazid [14]. Alternatively, MDR-TB patients require second-line therapy in the context of improving their clinical manifestations. *Mycobacterium tuberculosis* is reportedly the most commonly reported pathogen that elevates the prevalence of tuberculosis, particularly in children and adolescents [6]. The significant risk factors of MDR-TB include the inappropriate response to first-line pharmacotherapy, relapse of clinical manifestations, medication non-compliance, *Mycobacterium tuberculosis* re-exposure, epidemic outbreak, and HIV comorbidity [24]. 3% of entire tuberculosis cases are based on multidrug-resistant tuberculosis. The second-line treatment for MDR-TB not only elevates the health care cost but also increases the risk of potential toxicity. Furthermore, limited information on drug susceptibility testing for tuberculosis barricades the appropriate drugs' selection process [29]. This eventually elevates the risk of MDR-TB among predisposed patients. The configuration of person-centered therapeutic approaches is, therefore, highly necessary to minimize the overall recovery time while maximizing the therapeutic outcomes in MDR-TB cases [25]. The global data on MDR-TB

reveals the reported occurrence of 8014 XDR-TB (extensively drug-resistant) cases across 72 nations. The incident cases of tuberculosis majorly include MDR-TB patients who experience substantial predisposition towards XDR-TB. The WHO (World Health Organization) findings reveal the inappropriate treatment pattern among the patients affected with XDR-TB and MDR-TB. For example, 30% of XDR-TB and 54% of MDR-TB patients fail to effectively comply with the desired pharmacotherapy that eventually elevates their risk for comorbidities and mortality [16].

The evidence-based clinical literature does not delineate any globally accepted or standard therapeutic intervention for the complete recovery of MDR-TB patients. The physicians require formulating the treatment regimen following the intensity of relapse, clinical manifestations, and the patient's overall health status. Ethambutol, pyrazinamide, and elevated dosage of isoniazid include the first-line drugs that require oral administration for treating XDR and MDR tuberculosis [2]. The second-line MDR-TB treatment group–(A) drugs include levofloxacin/moxifloxacin (fluoroquinolones), bedaquiline, and linezolid. The elevated dosages of these drugs in many clinical scenarios helps to treat MDR-TB complications. The second-line MDR-TB treatment group–(B) drugs include clofazimine, cycloserine, and terizidone. However, second-line MDR-TB treatment group–(C) drugs include ethambutol, delamanid, pyrazinamide, imipenem-cilastatin, meropenem, amikacin, prothionamide/ethionamide, and p-aminosalicylic acid [14]. World Health Organization (WHO) does not recommend the prioritization of second-line injectable drugs for rifampicin-resistant MDR-TB cases. However, Group–(A) drugs require prioritized oral administration for extended therapy. The clinicians require carefully selecting the appropriate drug combinations based on the MDR-TB patients' clinical manifestations and prognosis in the context of improving the therapeutic outcomes. Furthermore, prospective clinical trials require evaluating comprehensive treatment approaches for minimizing the prevalence and adverse outcomes of MDR-TB. The presented narrative review effectively explores the etiology, causes, pathophysiology, diagnostic approaches, preventive interventions, and treatment modalities for MDR-TB while considering the existing therapeutic challenges. The presented evidence-based findings will not only prove conducive to the configuration of innovative MDR-TB treatment regimen but also improve the clinical decision-making process in the context of minimizing the recovery time and relapse rate of multidrug-resistant patients.
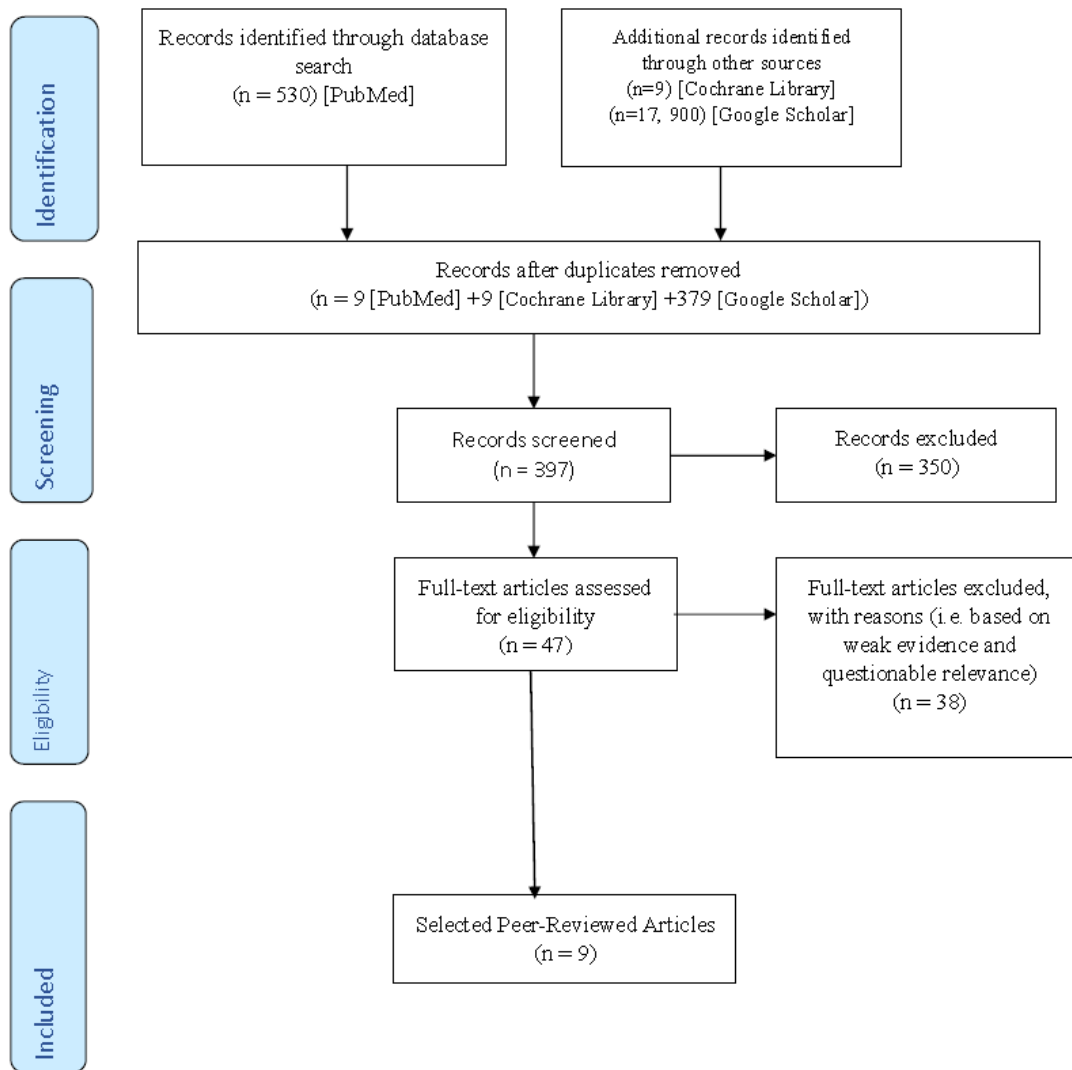
Methods

The narrative review was undertaken through the systematic exploration of evidence-based databases including Google Scholar, PubMed/Medline, and Cochrane Library. The following keyword combinations were effectively utilized through Boolean Operators.

1. "MDR-TB" AND "Causes"
2. "MDR-TB" AND "Pathophysiology"
3. "MDR-TB" AND "Diagnosis/Diagnostic Imaging"
4. "MDR-TB" AND "Prevention"
5. "MDR-TB" AND "Treatment"

The research articles' selection criteria were based on consecutive reviews, retrospective studies, systematic reviews, meta-analysis, randomized controlled trial, and narrative literature reviews. The author selected the research studies between the span of 2010 to 2019. The articles unrelated to MDR-TB and the articles that solely focused on the MDR-TB comorbidities were summarily excluded from the narrative review. The following PRISMA flow diagram effectively elaborates the articles' selection process.

Prisma flow diagram

Results

Literature Summary Table

Author	Study Type	Objective	Methods	Participants	Interventions	Outcomes	Recommendations
Chang and Yew (2013)	Narrative review	The authors effectively recommended preventive and therapeutic approaches for the systematic management of difficult to treat MDR-TB and XDR-TB	The researchers performed a literature review based on MDR-TB/XDR-TB epidemiology, preventive interventions, and comprehensive therapeutic approaches	NA	The researchers evaluated infection control strategies, alternative therapeutic regimen, and adjunctive therapeutic approaches for minimizing the occurrence of MDR-TB/XDR-TB and related clinical complications	- The researchers and clinicians require developing novel therapeutic approaches in the context of improving the clinical management of MDR-TB and XDR-TB cases - The recommended MDR-TB/XDR-TB prevention and treatment approaches require formulation through in-vitro interventions and a combination of pyrazinamide, linezolid, isoniazid (elevated dosage),	- The clinicians require considering various factors including adjunctive surgery, dosing schedules of second-line drugs, and MDR-TB/XDR-TB manifestations in the context of improving the therapeutic outcomes - Drug resistance programs, DOTS (short course approach), and HIV/poverty eradication measures are some of the recommended strategies to elevate the cure rates of the patients affected with MDR-TB and XDR-TB

Author	Study type	Aim	Methods	Sample		Results	Conclusion
Gilpin, Korobitsyn, and Weyer (2016)	Narrative review	The authors evaluated various diagnostic modalities to facilitate early identification of MDR-TB/XDR-TB	The authors explored clinical literature in the context of evaluating the molecular biology applications for MDR-TB assessment	NA	The researchers explored phenotypic/geno typic approaches and three-tiered laboratory network in the context of identifying individualized diagnostic interventions for MDR-TB	and fluoroquinolones - The study outcomes reveal the requirement of following the End TB approach to rapidly identify the MDR-TB patients - The patients affected with TB manifestations must undergo universal drug susceptibility testing in the context of minimizing the risk of MDR-TB treatment delay and associated comorbidities	The thorough optimization of WHO-based diagnostic interventions is highly needed inside the clinical settings in the context of controlling the prevalence of MDR-TB and XDR-TB across the predisposed populations
Girum, Muktar, Lentiro, Wondiye, and Shewangiza w (2018)	Meta-Analysis	The authors attempted to evaluate MDR-TB epidemiology across Ethiopia	The authors performed a systematic literature search based on various databases including African Index Medicus, Cochrane Library, Embase, Global Health Database, and PubMed/Medline The random-effects model was utilized in	The researchers evaluated 7461 subjects affected with MDR-TB/TB through the systematic analysis of	The researchers evaluated MDR-TB prevalence among subjects who exhibited a history of tuberculosis treatment	- The study outcomes revealed an elevated prevalence of MDR-TB among the selected subjects - The study findings revealed multidrug-	Drug susceptibility assessment, timely pharmacotherapy, and adverse effects' prevention include some of the significant strategies to reduce the frequency of MDR-TB cases

Author	Study design	Aim / Method	Sample	Tools / Results	Conclusion
		the context of extracting data related to MDR-TB treatment outcomes, determinants, and prevalence	thirty-four studies		resistant tuberculosis in the context of a serious public health concern that required immediate mitigation - MDR-TB-related co-morbidities including reduced baseline weight, HIV seropositivity, mal-absorption, and treatment adverse effects predominantly elevate the mortality risk of the affected patients
Koch, Cox, and Mizrahi (2018)	Narrative review	The authors performed a systematic assessment of TB pathogenesis in the context of identifying real-time treatment challenges encountered during	NA	- The authors explored evidence-based clinical literature for evaluating drug resistance prone `Mycobacterium tuberculosis` (Mtb) genes and Tb treatment drugs - The researchers developed various evidence-based tools in	The researchers used online tools including PhyResSE, TB Profiler, Poly TB, ReSeqTB, and TBDreamDB for evaluating tuberculosis	The early detection of MDR-TB cases and prompt initiation of appropriate second-line therapy are highly needed for improving the	- Treatment customization for MDR-TB cases is highly needed based on the infecting pathogen's strain type, heterogeneity level, and resistant pattern - Shortened pharmacotherapeutic measures warrant

		the management of MDR-TB	the context of extracting data related to single nucleotide polymorphisms of Mtb genes and other similar mutations		drug resistance pattern	therapeutic outcomes.	implementation for effectively achieving a long-term cure for MDR-TB
Podany and Swindells (2016)	Narrative review	The authors explored novel approaches to reconfigure the standardized TB treatment interventions for preventing the occurrence of TB/MDR-TB/XDR-TB	The authors evaluated evidence-based clinical literature to explore the standardized TB treatment drugs' newly developed/proposed applications in the context of improving the therapeutic outcomes	NA	- The authors explored the TB drug development history between 1921 to 2013 - The authors explored the scope of therapeutic (or TB treatment) modifications based on rifamycins, fluoroquinolones, clofazimine, bedaquiline, delamanid, pretomanid, and oxazolidinones	The study outcomes substantiate the requirement of evaluating the tuberculosis resistance pattern against the newly recommended therapeutic approaches to minimize the risk of MDR-TB treatment failure	The prospective clinical trials require evaluating the proposed MDR-TB therapeutic regimens to effectively control the prevalence/outbreaks of TB/MDR-TB/XDR-TB and related comorbidities/morbidities
Seung, Keshavjee, and Rich (2015)	Narrative Review	The authors evaluated the causative factors, epidemiology, and management approaches for MDR-TB	The authors performed extensive research of clinical literature in the context of acquiring MDR-TB's predisposing factors, therapeutic strategies, and side-	NA	The researchers explored evidence-based clinical literature to evaluate therapeutic modalities, risk	The preliminary causes of MDR-TB include community-based/facility-based transmission, inappropriate	- The administration of community-based programs/robust treatment regimen and early drug resistance identification include some of the significant evidence-based

Author	Type	Objective	Sample	Methodology	Variables	Results	Conclusion
				effects' management interventions	factors, causes, treatment approaches, adverse effects, and epidemiology of MDR-TB/XDR-TB	treatment, drug-resistant pattern amplification based on inadequate pharmacotherapy, and fragile medical systems	strategies warranted to minimize the prevalence of MDR-TB/XDR/TB - Clinicians must overcome the preventable MDR-TB risk factors including, chaotic treatment, short-term pharmacotherapy's amplifier effect, community transmission, and facility-based transmission to effectively improve the management of MDR-TB and XDR-TB cases
Sharma, Sharma, Kadhiravan, and Tharyan (2013)	Systematic review	The comparative assessment of isoniazid versus rifampicin regimens was undertaken in the context of minimizing HIV-negative patients' predisposition towards actively induced tuberculosis	- The selected clinical trials were based on 98% HIV negative children and adults - Sample size: 10717 subjects	- The authors effectively explored various randomized controlled clinical trials and utilized random effects model in the context of pooling the confidence intervals and relative risks for the selected patients - The authors used the GRADE strategy to evaluate the quality of the selected evidence	The authors evaluated clinical practice implications of isoniazid and rifampicin while assessing various attributes, including active tuberculosis, treatment adherence, treatment-limiting adverse episodes, and	- The shorter rifampicin therapy (as compared to isoniazid regimen) does not lead to the elevated active tuberculosis rates - Rifampicin proves effective in improving the tuberculosis treatment accomplishment rate while	The prospective studies require evaluating the frequency of adverse effects and treatment discontinuation rate for assessing the scope of administering a therapeutic combination of isoniazid and rifapentine

					hepatotoxicity (i.e. treatment side-effect)	minimizing the adverse therapeutic outcomes	
Sotgiu, Centis, D'ambrosio, and Migliori (2015)	Narrative review	The authors explored several MDR-TB treatment strategies in the context of evaluating their scope of improvement	The authors evaluated evidence-based articles to effectively explore the rationale and history of tuberculosis management interventions/pharmacotherapy	NA	The authors evaluated various MDR-TB pharmacotherapeutic regimens along with their adverse effects, complications, and therapeutic barriers	- The authors could not find any standard regimen for the satisfactory treatment of MDR-TB - The MDR-TB therapeutic success rate requires substantial improvement while enhancing the affordability and efficacy of MDR-TB treatment drugs in resource-limited facilities	The long-term efficacy of bedaquiline and delamanid warrants prospective investigation in the context of developing robust and comprehensive therapeutic approaches for TB/MDR-TB management in medical facilities
Yang, et al. (2017)	Consecutive review/retrospective study	The authors evaluated the side-effects of MDR-TB medication to facilitate therapeutic modifications warranted to improve the quality	- The researchers explored medical records of the selected subjects for extracting their MDR-TB-related data including clinical outcomes, treatment regimen, adverse effects of the recommended therapy, drug	The researchers included 256 subjects who received MDR-TB therapy inside the selected hospital for a	The researchers recorded the side effects of various MDR-TB medications including isoniazid, rifampicin, ethambutol, pyrazinamide,	The commonly reported side effects of MDR-TB therapy included nephrotoxicity, ototoxicity, dermatological complications, epileptic seizures,	- The reported MDR-TB therapy's side-effects predominantly lead to treatment non-compliance or withdrawal that eventually elevates the risk of morbidity and mortality of the treated patients

of treatment interventions	susceptibility testing outcomes, comorbidities, and demographics for their statistical analysis - The assessment of major and minor side effects of MDR-TB therapy was undertaken through the calculation of their standard deviation and mean interval	tenure of 6 consecutive years	streptomycin, kanamycin, amikacin, prothionamide, para-aminosalicylic acid, cycloserine, levofloxacin, ofloxacin, and moxifloxacin	hypothyroidism, peripheral neuropathy, hepatitis, arthralgia, psychiatric disorder, and gastrointestinal (GI) complications. However, nephrotoxicity and GI disturbance proved to be the least and most commonly reported side effects of MDR-TB therapy	- The clinicians and researchers must undertake prospective studies in the context of formulating comprehensive therapeutic approaches for the successful treatment of MDR-TB patients while minimizing the side effects and other therapeutic complications

Discussion

Significant outcomes

The study findings effectively reveal various pharmacotherapeutic approaches and treatment combinations for the systematic treatment of MDR-TB and XDR-TB. The findings also reveal the absence of any standard approach to minimize the prevalence of MDR-TB and related comorbidities. The timely tracking of the MDR-TB cases and their individualized causes is, therefore, highly necessary for challenging the occurrence of preventable MDR-TB outbreaks.

MDR-TB Epidemiology

The clinicians require thoroughly evaluating the complete epidemiology of MDR-TB for developing robust drug susceptibility interventions to facilitate the individualization of pharmacotherapy based on the reported clinical manifestations [8]. Girum, Muktar, Lentiro, Wondiye, and Shewangizaw (2018) describe HIV-seropositivity, TB medications' side effects, and TB-related comorbidities as the significant predisposing factors related to the increased prevalence of MDR-TB. The research findings reveal a 65-80% therapeutic success rate for MDR-TB patients [8]. This rate does not effectively comply with 75% MDR-TB therapy success requirement stipulated by WHO. The reduced success rate of MDR-TB therapy against the elevated resistance of microbes leads to serious public health concerns across developed or underdeveloped nations of the world. The clinicians require evaluating the baseline weight, HIV seropositivity, mal-absorption, adverse treatment effects, and comorbidities level of the MDR TB patients while recommending their comprehensive treatment approaches. The evidence-based research literature effectively substantiates the MDR-TB epidemiology-related findings of the presented study. The epidemiological findings of 2015 revealed 21% MDR-TB cases with a clinical history of tuberculosis and 3.9% of the preliminary TB patients who reportedly developed MDR-TB and related complications [5]. The literature findings also reveal rifampicin resistance as the greatest cause of MDR-TB among predisposed patients. MDR-TB epidemiology impacts its prevalence and complications in numerous ways. The elevated prevalence of tuberculosis reciprocally increases the medication administration rate among the affected patients. This eventually elevates the risk of bacterial resistance to many folds based on inappropriate drugs combination, treatment non-compliance, and reduced health-related quality of life of the underprivileged patients in resource-limited settings [28]. Furthermore, consistent contact of the tuberculosis survivors with MDR-TB patients substantially elevates their predisposition towards MDR-TB. The absence of ventilation and overcrowding also elevates the prevalence of MDR-TB among high-risk patients. The individuals having known clinical history of TB exhibit an elevated predisposition towards the development of rifampicin resistance that eventually leads to the progression of MDR-Tb and associated comorbidities [10]. Therefore, epidemiology-based findings of the presented study as well as evidence-based clinical literature substantiate the requirement of MDR-TB drugs' susceptibility testing for the predisposed patients to facilitate the timely administration of the appropriate pharmacotherapy [8]. Furthermore, the therapeutic management of MDR-TB must focus on controlling the clinical manifestations while concomitantly minimizing the adverse effects of the selected pharmacotherapy.

Causative Factors of MDR-TB

The narrative review by Seung, Keshavjee, and Rich (2015) describes various causative factors that elevate the prevalence of MDR-TB among predisposed individuals [24]. These causative factors are based on weak clinical approaches, inappropriate medication, drug resistance, community-based transmission, and facility-based infection progression. However, evidence-based research literature also describes various comorbidities that not only elevate the risk of MDR-TB but also decrease the life expectancy of the affected patients. Accordingly, the literature findings reveal HIV as the greatest comorbidity that elevates the risk of MDR-TB to many-fold [4]. The other comorbidities including alcohol abuse, chronic kidney disease, and diabetes mellitus deteriorate the therapeutic outcomes of MDR-TB patients in many clinical scenarios [22]. The clinical literature also reveals 14.1% TB patients affected with single or multiple drug resistance [18]. Furthermore, 7.4% of TB patients tend to develop

severe resistance against isoniazid. The metabolic remodeling of *Mycobacterium tuberculosis* reveals its high tendency for developing antibiotic tolerance, and intrinsic drug resistance [9]. The reduced growth rate, waxy cell wall, and thick structure of *Mycobacterium tuberculosis* are predominantly responsible for its elevated tolerance against various antibiotics. Therefore, the outcomes of the presented study along with the evidence-based findings warrant the thorough investigation of MDR-TB causes to facilitate the customization of the appropriate pharmacotherapy [24]. The early identification of drug resistance through community-based approaches will also improve the therapeutic outcomes and recovery pace of the MDR-TB patients to an unprecedented level.

Pathophysiology/Pathogenesis of MDR-TB

The article by Koch, Cox, and Mizrahi (2018) discusses the pathogenesis of MDR-TB through the utilization of evidence-based tools, including PhyResSE, TB Profiler, Poly TB, ReSeqTB, and TBDreamDB [15]. The findings reveal genetic mutations in *Mycobacterium tuberculosis* as the preliminary cause of MDR-TB development in high-risk patients. The study findings also substantiate the requirement of evaluating *Mycobacterium tuberculosis* resistance pattern, strain type, and heterogeneity level to facilitate the development of shortened pharmacotherapeutic measures for MDR-TB patients. The complex virulence factors of *Mycobacterium tuberculosis* reduce the capacity of alveolar macrophages in the context of ceasing its growth and development in the human host [1]. Furthermore, the ramification of caseous necrosis and development of multinucleated giant cells not only elevates immunosuppression of the host cell lines but also reduces the antibiotic susceptibility of *Mycobacterium tuberculosis*. Eventually, the immunosuppression of the human host along with occupational and socioeconomic risk-factors (i.e. silicosis, malnutrition, and poverty) substantially elevate the level of pathogen's resistance against various antibiotics. Furthermore, the elevated toxicity of MDR-TB/XDR-TB treatment therapies proves to be the greatest barrier against their long-term administration to the MDR-TB/XDR-TB patients [20]. These evidence-based outcomes reveal the requirement of evaluating the pathophysiology and complete treatment history of the MDR-TB patients for effectively improving the overall quality of recommended antituberculosis pharmacotherapies.

Diagnostic approaches

Gilpin, Korobitsyn, and Weyer (2016) emphasize the requirement of following WHO-based diagnostic interventions, including END TB approach and universal drug susceptibility testing to effectively reduce the risk of comorbidities and treatment delay among MDR-TB patients [7]. However, the evidence-based clinical literature also recommends various line probe assays based on GenoType MTBDR and INNO-LiPA Rif. TB kit to effectively facilitate early identification and diagnostic precision of MDR-TB cases. These assays exhibit 100% specificity and 95% sensitivity in the context of tracking a range of MDR-TB/XDR-TB cases [17]. The clinicians recommend the complete investigation of the drug-resistant source and its contact with suspected MDR-TB patients for their early treatment through novel pharmacotherapeutic approaches [23]. The clinicians also require evaluating pediatric patients through clinical examination and standardized diagnostic interventions, since they experience a greater risk for MDR-TB as compared to the adult populations. The clinicians must regularly utilize conventional diagnostic methods and clinically correlate their findings in the context of improving the precision of MDR-TB assessment. Some of the significant diagnostic interventions include radiologic study, AFB culture, nucleic acid amplification testing, line probe assay, and Xpert MTB assay [21]. The findings of the presented study along with the evidence-based outcomes recommend the systematic use of comprehensive diagnostic approaches to reduce the risk of unattended MDR-TB cases in the clinical settings.

Preventive interventions

Podany and Swindells (2016) describe a range of novel treatment strategies and prophylactic approaches to systematically prevent the occurrence of TB, MDR-TB, and XDR-TB outbreaks [19]. For example, they recommend the dosage enhancement of rifampicin beyond the conventional 600mg requirement for improving the therapeutic outcomes for MDR-TB patients. The clinicians must attempt to reduce the recovery time for the MDR-TB patients while configuring elevated-dose combinations of

potential drugs like bedaquiline, delamanid, clofazimine, linezolid, and rifampin [19]. However, researchers require undertaking prospective clinical trials to evaluate the effectiveness of these drug combinations for MDR-TB patients. The evidence-based research literature substantially emphasizes the enhancement of risk assessment approaches to effectively reduce the prevalence of MDR-TB and XDR-TB among predisposed patients. The drug susceptibility studies require radical improvement through clinical trials and observational studies. The researchers also require modifying BCG (Bacillus Calmette-Guerin) vaccine to facilitate its administration to HIV patients for reducing their risk of TB and MDR-TB [11]. Furthermore, the development of molecular genetic approaches, rapid diagnostic strategies, and laboratory information management systems is highly required to effectively improve the quality of TB/MDR-TB/XDR-TB testing in various hospital settings [12]. The clinicians and nurses should initiate various educational services in hospitals/community settings to elevate the tuberculosis knowledge and awareness of the common masses. The outcomes of the presented study and evidence-based clinical literature necessitate the requirement of improving the level of preventive/prophylactic approaches through clinical studies for minimizing the onset and progression of MDR-TB among the high-risk individuals.

Treatment modalities

Chang and Yew (2013) recommend various preventive and therapeutic strategies to reduce the risk/prevalence of MDR-TB [3]. The preventive treatment for the suspected individuals is based on twice-weekly administration of isoniazid and rifampicin for 12 weeks' duration. The focused treatment of HIV patients is highly needed through antiretroviral therapy to reduce their risk of tuberculosis or MDR-TB. The administration of pharmacotherapy to MDR-TB patients reciprocates through clinical correlation of their diagnostic findings and disease manifestations. MDR-TB treatment is based on first-line oral medication, fluoroquinolones, injectable drugs, second-line (oral bacteriostatic) drugs, and other miscellaneous medications. The first-line oral drugs include isoniazid, rifampicin, ethambutol, and pyrazinamide. The orally administered fluoroquinolones include levofloxacin, moxifloxacin, gatifloxacin, and ofloxacin. The injectable drugs for MDR-TB include capreomycin, kanamycin, amikacin, and streptomycin. However, second-line MDR-TB therapy or oral bacteriostatic drugs include ethionamide, prothionamide, para-aminosalicylic acid, cycloserine, and terizidone. However, unconventional MDR-TB drugs include linezolid, amoxicillin-clavulanate, clofazimine, rifabutin, clarithromycin, meropenem-clavulanate, and thioridazine. The clinicians require attempting various combinations of these drugs based on the reported MDR-TB manifestations and therapeutic factors to effectively improve the treatment outcomes. Sharma, Sharma, Kadhiravan, and Tharyan (2013) consider rifampicin therapy as the treatment of choice to improve the MDR-TB treatment success rate [26]. They consider rifampicin as the safest MDR-TB treatment drug based on its minimal side-effects. However, Sotgiu, Centis, D'ambrosio, and Migliori (2015) recommend the need for prospective clinical trials in the context of testing the therapeutic potential of antituberculosis drugs, including bedaquiline and delamanid [27]. Yang, et al (2017) consider the adverse effects of the standard MDR-TB treatment therapies as the greatest barriers against their long-term utilization by the tuberculosis patients [30]. These findings substantiate the modification of existing antituberculosis therapies for improving the treatment outcomes and overall recovery time of MDR-TB patients. WHO guidelines advocate the use of surgical interventions and conventional treatment modification/reclassification to improve the therapeutic outcomes in MDR-TB patients. For example, the guidelines emphasize the administration of at least 5 medicines based on second-line drugs and pyrazinamide for treating the intensive phase of MDR-TB. The shorter drug-resistant TB medication course is based on gatifloxacin (400-800mg), moxifloxacin (400-800 mg), clofazimine (50-100mg), ethambutol (800-1200mg), pyrazinamide (1000-2000mg), prothionamide (300-600mg), and kanamycin (<1g). The outcomes of the presented study and evidence-based findings reveal various therapeutic approaches for MDR-TB management [13]. However, no therapeutic strategy has attained the status of the standardized MDR-TB treatment until date. The researchers, therefore, require undertaking prospective clinical studies while considering MDR-TB's clinical presentation and causative factors in the context of designing comprehensive treatment interventions for tuberculosis prevention and management in the hospital settings.

Conclusion

The presented narrative review proves highly instrumental to the understanding of MDR-TB etiology, causative factors, pathophysiology, diagnostic interventions, preventive approaches, treatment options, and therapeutic barriers. The study outcomes provide substantial clinical evidence to improve the overall decision-making process related to MDR-TB therapy. The MDR-TB relapse and treatment resistance reciprocate with genetic mutations of *Mycobacterium tuberculosis* and inappropriate therapeutic decisions. The physicians, therefore, require thoroughly examining each of the MDR-TB cases or suspected patients for evaluating their therapeutic responses and drug susceptibility pattern. They must utilize evidence-based research literature and correlate the respective outcomes with their patients' clinical manifestations to effectively improve the formulation of robust antituberculosis therapies. Furthermore, shortening of the second-line therapeutic regimen through dosage modifications is also recommended to reduce the risk of MDR-TB relapse and minimize the overall recovery time. The physicians should effectively treat their HIV patients in the context of reducing their predisposition towards MDR-TB and XDR-TB. The enhancement of health-related quality of life of the MDR-TB suspected patients and their poverty eradication are highly warranted to effectively control the elevated prevalence of tuberculosis across the resource-limited regions. The clinicians must stringently follow the WHO-recommended diagnostic approaches to reduce the risk of treatment delays for MDR-TB patients. The clinicians require modifying the presently implemented drug susceptibility testing approaches and monitoring the pharmacotherapeutic adversities to improve the scope of MDR-TB treatment quality. The appropriate determination of causative pathogen and its mutation status through molecular imaging methods is highly needed for the development of targeted MDR-TB management therapies. Furthermore, the clinicians must administer educational sessions at the population level for increasing the awareness of common masses related to MDR-TB risk factors and preventive measures. They must also proactively challenge facility-based and community-based *Mycobacterium tuberculosis* transmissions while regularly monitoring the drug resistance level of MDR-TB patients against the recommended pharmacotherapy. The regular monitoring of the adverse therapeutic outcomes and clinical investigation of the recommended drugs are highly warranted to effectively improve the overall healing process of MDR-TB patients. The findings of the presented study advocate the need for customizing MDR-TB treatment therapy based on a range of diagnostic, therapeutic, clinical, and individual factors. The study outcomes also substantiate the requirement of greater multidisciplinary collaboration between physicians and researchers to facilitate the configuration of robust MDR-TB management interventions across the clinical practice environment.

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