BIBLIOGRAPHIC INFORMATION SYSTEM

Journal Full Title: Journal of Biomedical Research & Environmental Sciences

Journal NLM Abbreviation: J Biomed Res Environ Sci

Journal Website Link: https://www.jelsciences.com

Journal ISSN: 2766-2276

Category: Multidisciplinary

Subject Areas: Medicine Group, Biology Group, General, Environmental Sciences

Topics Summation: 128

Issue Regularity: Monthly

Review Process type: Double Blind

Time to Publication: 7-14 Days

Indexing catalog: Visit here

Publication fee catalog: Visit here

DOI: 10.37871 (CrossRef)

Plagiarism detection software: iThenticate

Managing entity: USA

Language: English

Research work collecting capability: Worldwide

Organized by: SciRes Literature LLC

Manuscript should be submitted in Word Document (.doc or .docx) through

Online Submission

form or can be mailed to support@jelsciences.com

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JOURNAL OF BIOMEDICAL RESEARCH & ENVIRONMENTAL SCIENCES
ISSN: 2766-2276
SUBJECT AREA(S): INFECTIOUS DISEASES | MICROBIOLOGY | BIOMEDICAL SCIENCE | BIOLOGY
DOI: 10.37871

REVIEW ARTICLE

Drug-Resistant Tuberculosis Types and Their Treatment Regimens Using First-Line, Second-Line Injectable, Third-Line, Fluoroquinolones, Aminoglycosides, Cyclic Polypeptides, Novel and Repurposed Anti-Tuberculosis Drugs

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ABSTRACT

Drug-Resistant Tuberculosis (DR-TB) causes high mortality and morbidity rates globally. DR-TB and COVID-19 pandemic are posing a major risk to global public health and economic security, and are jeopardizing efforts in the control, prevention and elimination of TB globally. *Mycobacterium tuberculosis* (MTB) has continued to evolve resistance to anti-TB drugs. Different types of DR-TB have been defined and they include; mono drug-resistant TB, Multi Drug-Resistant TB (MDR-TB), poly drug-resistant TB, pre-Extensively Drug-Resistant TB (pre-XDR TB), Extensively Drug-Resistant TB (XDR-TB), Extremely Drug-Resistant TB (XXDR-TB), and Totally Drug-Resistant TB (TDR-TB). DR-TB is caused by several factors which include: non-adherence, poor compliance, low efficacy anti-TB drugs, delayed diagnosis, interrupted supply, stock-outs, inadequate infection control, HIV co-infection, spontaneous mutations, and chromosomal replication errors. Global TB targets have gone off-track and years of progress reversed due to DR-TB and the COVID-19 pandemic. Treatment failure, death and costs incurred are higher among patients suffering from DR-TB than among those with susceptible TB. For this reason, susceptible TB needs to be diagnosed quickly and treated effectively to prevent its progression to DR-TB. Treatment for susceptible TB requires the use of first-line anti-TB drugs; rifampicin, isoniazid, pyrazinamide, and ethambutol. While DR-TB is treated using the second- and third-line anti-TB drugs. Effective treatment of TB is dependent on: prompt and accurate diagnosis of TB and recognition of drug-resistance; adherence to treatment; robust contact tracing and prophylactic treatment of TB contacts; and screening for TB infection in high-risk groups.

Keywords: Drug-resistant tuberculosis; Multidrug-resistant TB; Extensively drug-resistant TB; First-line anti-TB drugs; Second-line injectable drugs; Third-line anti-TB; Fluoroquinolones; Aminoglycosides; Cyclic polypeptides

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DOI: 10.37871/jbres1542

Submitted: 18 August 2022

Accepted: 28 August 2022

Published: 30 August 2022

BIOLOGY GROUP

INFECTIOUS DISEASES | MICROBIOLOGY | BIOMEDICAL SCIENCE | BIOLOGY

VOLUME: 3 ISSUE: 8 - AUGUST, 2022

How to cite this article: Mumena DK, Kwenda G, Ngugi CW, Nyerere AK. Drug-Resistant Tuberculosis Types and Their Treatment Regimens Using First-Line, Second-Line Injectable, Third-Line, Fluoroquinolones, Aminoglycosides, Cyclic Polypeptides, Novel and Repurposed Anti-Tuberculosis Drugs. J Biomed Res Environ Sci. 2022 Aug 30; 3(8): 988-993. doi: 10.37871/jbres1542, Article ID: JBRES1542, Available at: https://www.jelsciences.com/articles/jbres1542.pdf

Introduction

Tuberculosis (TB) is one of the major global public health concerns causing high mortality rates, it kills one individual every 21 seconds [1,2]. TB is currently the second world's deadliest infectious disease after Coronavirus Disease 2019 (COVID-19), an infectious disease caused by a virus called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [3-5]. TB mortality has severely been impacted by the COVID-19 pandemic and not by HIV/AIDS [5].

Drug-Resistant Tuberculosis (DR-TB) is a serious global public health issue hampering global TB care, prevention, and control [1]. The latest World Health Organization Global TB Report of 2021 showed that in 2020, 132, 222 cases of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) and 25, 681 cases of pre-extensively drug-resistant/extensively drug-resistant tuberculosis (pre-XDR/XDR-TB) were reported globally [5]. While in 2019, 206, 030 MDR/RR-TB and 12, 350 XDR-TB cases were reported globally [6]. In 2018, 186, 772 MDR/RR-TB cases were reported globally [7]. In 2017, 160, 684 MDR/RR-TB cases were reported [8]. In 2016, 153, 119 MDR/RR-TB cases were reported globally [9]. In 2015, 132, 120 MDR/RR-TB cases were reported globally [10]. In 2014, 123, 000 MDR/RR-TB cases were reported globally [11].

DR-TB types include; mono drug-resistant tuberculosis, polydrug-resistant TB, Multidrug-Resistant TB (MDR-TB), pre-Extensively Drug-Resistant TB (pre-XDR-TB), Extensively Drug-Resistant TB (XDR-TB), Extremely Drug-Resistant Tuberculosis (XXDR-TB), and totally drug-resistant TB (TDR-TB) [12]. MDR-TB is resistance to at least Rifampicin (R) and Isoniazid (INH) [1,13]. Pre-XDR TB is resistance to R and INH, plus any one Fluoroquinolone (FLQ) or any one of the second-line injectable drugs [1]. XDR-TB was defined as resistance to R and INH plus any FLQ and any of the second-line injectable drugs [1,13], but has now been re-defined by the World Health Organization as resistance to R and INH, plus any FLQ, and at least one additional group A drug (linezolid or bedaquiline) [14]. TDR-TB is resistance to all first- and second-line anti-TB drugs [15].

DR-TB causes high mortality and morbidity rates globally, and is posing a threat to the elimination of TB [16-18]. The highest mortality and morbidity rates of TB and DR-TB are reported mainly in low-and middle- income countries [19]. Studies on DR-TB development show that among first-line anti-TB drugs INH resistance occur first, followed by R or ethambutol (EMB), then resistance to Pyrazinamide (PZA) and lastly to second-line and third-line anti-TB drugs [19].

DR-TB is caused by several factors which include: poor adherence to TB treatment, poor compliance, poor treatment regimen selection, inadequate drug supply, irregular supply and stock-out of anti-TB drugs, inappropriate TB therapy, delayed diagnosis, delayed drug-susceptibility testing, interruption of treatment, wrong treatment prescriptions, or previous treatment of TB using inadequate or sub-therapeutic or ineffective anti-TB drugs and initiation of ineffective therapy as well as spontaneous chromosomal mutations, and replication errors [1,20-28]. Liang and colleagues in their study found that inappropriate treatment was the most common cause of MDR-TB [29]. Failure to implement effective TB prevention and control measures also facilitates the emergence of the different forms of DR-TB [30-32]. The key factors above including treatment failure, TB relapse, non-compliance to treatment, treatment defaulting, MDR contacts, loss to follow-up cases, and misdiagnosis contribute to the rising cases of DR-TB [33]. Therefore, DR-TB must be managed effectively to reduce mortality, morbidity, and the eventual transmission of *Mycobacterium tuberculosis* (MTB) resistant strains [33].

DR-TB can also be caused by direct infection with resistant MTB strains [34]. DR-TB is mainly caused by mutations and replication errors in target genes [1]. Mutations involve changes in the positions of amino acids [35]. These amino acid changes are point mutations, which include: insertion, deletion, and missense, as well as Single Nucleotide Polymorphisms (SNPs) [19,36]. SNPs and other polymorphisms modify drug targets [37]. Gene mutations in MTB are a major mechanism responsible for causing drug-resistant TB [38]. Another key mechanism for drug resistance is the use of efflux pumps, these biological pumps remove anti-TB drugs out of the mycobacterial cells resulting in resistance to anti-TB drugs [39,40]. Resistance to anti-TB drugs in MTB can also be caused by the beta (β)-lactamase enzymes which inactivates the β-lactam antibiotics [41]. Drug-resistant MTB strains are also able to resist or tolerate the toxic pharmacological effects of anti-TB drugs [42].

The aim of this comprehensive mini-review was to highlight the different types of DR-TB and their treatment regimens using first-line, second-line injectable, third-line, fluoroquinolone, aminoglycoside, cyclic polypeptide, novel, and repurposed anti-TB drugs.

Types of drug-resistant tuberculosis

Mono drug-resistant tuberculosis

Mono drug-resistant TB is defined as a type of TB that is resistant to one first-line anti-TB drug only [3]. Examples of mono drug-resistant TB include: Rifampicin-Resistant TB (RR-TB), and INH resistant TB (INHr-TB). RR-TB is a type of TB that is caused by MTB strains that are resistant to R [43]. INHr-TB is a type of TB that is caused by MTB strains that are resistant to INH [43], it is more common than R resistance, and is a growing public health issue globally because policy and research directions are only focused on R resistance, which is considered as a surrogate marker for MDR-TB [1].

Multi-drug resistant tuberculosis

MDR-TB is a type of drug-resistant TB that is caused by MTB strains that are resistant to both INH and R [44]. R and INH are key first-line anti-TB drugs [22]. The emergence of drug-resistant MTB strains is currently the major drawback to ending the global TB crisis [45,46]. MDR-TB is more complex to manage than Drug-Susceptible TB (DS-TB) [47]. The mortality rate is very high in patients infected with MDR-TB than in those infected with DS-TB [47]. The major set-backs in the fight against drug-resistant TB have been: late diagnosis and treatment of drug-resistant TB using inappropriate regimens [48,49]. It is a challenge for most developing countries globally to quickly diagnose drug-resistant TB and treat these cases empirically until they are declared cured[48,49]. Patients suffering from MDR-TB/RR-TB that are not managed well, spread drug-resistant MTB strains in their communities [46]. Children who live in homes with patients infected with drug-resistant MTB strains are at a very high risk of acquiring these resistant strains [50]. Nosocomial transmission of drug-resistant MTB strains to health care workers as well as to HIV-infected patients has been reported in clinical settings [48].

Pre-extensively drug-resistant tuberculosis

Pre-XDR TB is resistance to INR and R, plus any one FLQ (ofloxacin, levofloxacin, gatifloxacin, or moxifloxacin) or any one of the second-line injectable drugs/SLIDs (capreomycin, kanamycin, or amikacin) [1]. Poor case management of MDR-TB leads to a high prevalence of pre-XDR TB, which can eventually become XDR-TB [1]. Detection of Pre-XDR TB among MDR-TB patients helps to prevent treatment failure of MDR-TB and also enables appropriate steps to be undertaken to prevent progression of Pre-XDR to XDR-TB [1,55,56].

Extensively drug-resistant tuberculosis

XDR-TB was defined as a type of drug-resistant TB that is caused by MTB strains that are resistant to the first-line drugs, INH and R, plus any FLQ, and at least any one of the three SLIDs [51], but has now been re-defined by the World Health Organization as resistance to R and INH plus any FLQ, plus any of the SLIDs (amikacin, capreomycin, or kanamycin), and at least one additional group A drug (linezolid or bedaquiline) [14]. When a patient has both XDR-TB and HIV infection, XDR-TB progresses faster and become more severe than when the patient is infected with XDR-TB only[22].

Totally drug-resistant tuberculosis

TDR-TB is a type of drug-resistant TB that is caused by MTB strains that are resistant to all first- and second-line anti-TB drugs [15]. TDR-TB has been reported in India, Iran, Italy and South-Africa [15,52]. Despite TDR-TB only being reported in these four countries, it may also be present in other countries [53]. However, inadequate molecular diagnostic laboratory facilities, especially in resource limited countries, make it difficult for cases of TDR-TB to be detected[53]. Poorly managed XDR-TB progress to TDR-TB [1].

Classification of anti-tuberculosis drugs

The anti-TB drugs can be classified into five groups (based on their efficacy, safety profiles, drug-class, and experience of use): group [i]. first-line anti-TB drugs (R, INH, PZA, and EMB); group [ii]. Injectable drugs (capreomycin, amikacin, kanamycin, streptomycin); group [iii]. FLQs (moxifloxacin, ofloxacin, levofloxacin); group [iv]. Oral bacteriostatic drugs (cycloserine/terizidone, prothionamide/ethionamide, para-amino salicyclic acid); and group [v]. anti-TB drugs with limited information or unclear efficacy or long-term safety (linezolid, clofazimine, amoxicillin/clavulanate, carbapenems (meropenem and imipenem-cilastatin), high-dose INH, clarithromycin, thioacetazone, delamanid, and bedaquiline) [22,44,54]. Drugs in groups ii, iii, and iv are known as second-line drugs, while those in group v are third-line drugs [54]. Patients suffering from XDR-TB and pre-XDR TB are treated with drug combinations that include those from group v, because they are usually resistant to most of the other remaining anti-TB drugs [54,55].

The Second- and third-line anti-TB drugs are expensive, have severe side effects, and require well trained clinicians to administer, as well as equipped laboratory facilities for Drug-Susceptibility Testing (DST) [56]. These requirements are difficult to achieve in many low- and middle-income countries [56]. Access to second-line DST is poor in many countries, this causes resistant strains MTB to spread successfully unrecognized causing different forms of DR-TB[22].

The drugs pretomanid, bedaquiline, and delamanid were recently approved for use in the management of DR-TB. These drugs have tremendously improved the treatment success rate in patients suffering from MDR/RR-TB [14,57]. Additionally, repurposed drugs, such as clofazimine and linezolid have also improved the treatment of MDR/RR-TB as alternative drugs [14,58]. Treatment for DR-TB requires a drug regimen that contains a minimum of 4 anti-TB drugs to reduce relapse, improve efficacy and prevent further development of resistance.

Treatment of drug-susceptible tuberculosis

MTB can be susceptible or resistant to anti-TB drugs [12]. The treatment of drug-susceptible TB is easier, short, and less expensive, while that for drug-resistant TB is difficult, long and very expensive [43]. The treatment of susceptible TB requires the use of first-line anti-TB drugs namely;

R, INH, PZA, and EMB [59]. Currently drug-susceptible TB is treated for a period of 6 months, and involves two key treatment phases: the first phase is called the "initial phase", it involves treating the TB patient with four first-line anti-TB drugs for 2 months, while the second phase is called the "continuation phase", it involves treating the TB patient with R and INH for an additional period of 4 months [59]. PZA has greatly reduced the duration of treating drug-susceptible TB from a period of 9-12 months to 6 months [60]. The six months treatment is called a "short-course anti-TB therapy" [61]. Drug-susceptible TB is ease to manage than DR-TB [43].

Treatment of drug-resistant tuberculosis

Isoniazid mono-resistant tuberculosis

INHr-TB is becoming common globally, it can be treated using the following drugs: R, EMB, PZA, and levofloxacin for a period of 6 months [43,62]. Levofloxacin is the first choice FLQ used in the treatment of INHr-TB because; it has a good characterized safety profile, and has less known drug interactions [43]. The treatment of INHr-TB can be prolonged beyond six months for patients that have extensive cavitary disease or those who fail to convert to smear-negative or culture- negative after successfully completing treatment [43]. The treatment outcome for INHr-TB patients can sometimes be poor [63], while for others can be successful.

Multidrug-resistant tuberculosis

MDR/RR-TB can be treated for 9-12 months in a standardized shorter treatment regimen, and for 18-20 months in longer treatment regimens. The shorter treatment regimen comprises of all-oral bedaquiline-containing regimen in eligible patients who have not been exposed to second-line anti-TB drugs, and in whom resistance to fluoroquinolones has been excluded[6]. The longer treatment regimen involves the use of three groups of drugs: group A (moxifloxacin/levofloxacin, bedaquiline, linezolid); group B (clofazimine, cycloserine/terizidone); and group C (PZA, amikacin/streptomycin, EMB, imipenem-cilastatin, para-aminosalicylic acid, delamanid, ethionamide/prothionamide, meropenem) [6,43,64]. Meropenem and imipenem-cilastatin are supposed to be administered with clavulanic acid which is available only in formulations combined with amoxicillin (amoxicillin-clavulanic acid). Amoxicillin-clavulanic acid should not be used without imipenem-cilastin or meropeneme [43]. Therefore to treat MDR-TB/RR-TB, the physician needs a combination of five drugs: three drugs from group A and one drug from group B and C above [43]. MDR-TB/RR-TB is a very serious drug-resistant airborne disease [65].

Extensively drug-resistant tuberculosis

XDR-TB can be treated using a regimen comprising of seven effective drugs: two core drugs (linezolid, bedaquiline), one companion drug (clofazimine or cycloserine), one other companion drug (meropenem or ertapenem or imipenem-cilastatin + amoxicillin-clavulanate or delamanid or para-aminosalicyclic acid), and three supporting drugs (one FLQ (levofloxacin or moxifloxacin), one SLID (kanamycin or amikacin or capreomycin) and a high-dose INH) [66]. Using this regimen XDR-TB can be treated for a period of 13-15 months [66]. Patients suffering from Pre-XDR or XDR-TB have fewer treatment options, and their treatment success rates are low globally [56].

Tackling the global drug-resistant tuberculosis crisis

The emergence of MDR-TB and XDR-TB is an obstacle to effective control of TB [67]. DR- TB is a serious public health problem globally [68]. In order to improve TB control, it is important to track the spread of MTB, identify index cases, and detect outbreak cases [69]. Monitoring and proper management of patients infected with drug-resistant MTB strains is key to effective control of drug-resistant TB globally [70]. The five key priority actions to tackle the global drug-resistant TB crisis proposed by the World Health Organization are: provision of high-quality management of drug-susceptible TB; expand the rapid testing and diagnosis of drug-resistant TB cases; provide quick access to effective treatment regimens and proper care of patients infected with drug-resistant TB; practicing of effective infection prevention and control; and increase political will and financing of TB programmes globally [71,72].

Conclusion

Drug-resistant TB is a global public health issue. It is a threat to global TB care, prevention and control. The emergence and successful spreading of resistant MTB strains, reflects a weakness in the management of TB globally. Drug-resistant TB has worsened due to the emergence of the COVID-19 pandemic. When one form of DR-TB is detected early and treated effectively, it will not progress to other deadly forms. Indeed, early detection and effective treatment are key to halt the rising cases of DR-TB globally. Other key factors that can help prevent the emergence and successful transmission of drug-resistant MTB strains include: constant supply of anti-TB drugs, consistent use of directly observed treatment, early drug-susceptibility testing, and implementation of efficient infection prevention and control measures for TB.

Conflict of Interest

The authors declare no conflict of interest with regards to the publication of this review article.

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How to cite this article: Mumena DK, Kwenda G, Ngugi CW, Nyerere AK. Drug-Resistant Tuberculosis Types and Their Treatment Regimens Using First-Line, Second-Line Injectable, Third-Line, Fluoroquinolones, Aminoglycosides, Cyclic Polypeptides, Novel and Repurposed Anti-Tuberculosis Drugs. J Biomed Res Environ Sci. 2022 Aug 30; 3(8): 988-993. doi: 10.37871/jbres1542, Article ID: JBRES1542, Available at: https://www.jelsciences.com/articles/jbres1542.pdf