MULTI DRUG RESISTANT TB: A SERIOUS PUBLIC HEALTH ISSUE - ITS RISK FACTORS AND EFFECTIVE CONTROL METHODS

(A Brief Review)

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Abstract: Tuberculosis (TB) and extrapulmonary TB are usually treatable and curable. Occasionally drug-resistant TB occurs when bacteria cannot be treated with TB medications called DR-TB. Based on resistance to antimicrobials TB is classified as rifampicin resistant (RR-TB) and MDR-TB is resistant to rifampicin and isoniazid. Subject to resistance to antibiotics, MDR-TB categorized as pre-extensively drug-resistant TB (preXDR-TB) is a subclass of MDR-TB that may become even more resistant to any fluoroquinolone, the most challenging form of TB to treat, extensively drug-resistant TB (XDR TB), is resistant to rifampicin fluoroquinolone. MDR-TB often emerges in patients who repeatedly have undergone uneven therapies with regular short-period therapies and have worse regimens. TB testing by using quick molecular examinations, propagating methods culture techniques, or sequencing tools to test for drug resistance. Molecular testing of the Xpert® MTB/RIF, Ultra, MTB-XDR, BDMax, Line probe assay (LPA), LAMP, and whole genome sequencing. The management of the DR-TB regimen for all anti-TB medication through orally is more efficient, less toxic, and generally more tolerated and has lately revolutionized the care of DR-TB. These are believed to have better adherence and treatment results. Unfortunately, bedaquiline resistance is increasing, which is concerning given the efforts made to develop and make this novel medication available. WHO recommends that Second-line medications are needed for treatment, instead of earlier regimens lasting 20 months or longer, new oral drug administrations for MDR/RR-TB and pre-XDR-TB treatments which are shortened should be discovered. In the future Linezolid, delamanid, and bedaquiline might obtain an additional important role in MDR-TB therapies in kids and adults, given their 'core drug' profile under exact circumstances.

Index Terms - Sequencing technologies, LAMP, shorter time regimen, long time regimen, WGS.

I. INTRODUCTION

Tuberculosis disease caused by mycobacterium is disseminating via air from person to person. TB normally attack the lungs; however, it has also had an effect on other organs of the body such as spine, kidneys, and brain (EPTB). Usually, TB is treatable and curable; however, People with TB are in risk of dying if they shouldn't receive the right care. Occasionally drug-resistant TB occurs when bacteria are unable to treat with TB medications are called Drug Resistant-TB (DR-TB), Thus, the medication is no longer able to eradicate the TB bacteria. Patients with multidrug-resistant TB (MDR-TB) diseases by a group of Mycobacterium tuberculosis called MTBC, require expensive treatment.

Drug-resistant TB might be further classified into subgroups based on susceptibility to antimicrobials like Rifampicin Resistant (RR-TB) and resistance to rifampicin and isoniazid which is said to be MDR-TB. The therapies for rifampicin-resistant (RR-TB) and Multi-Drug Resistance TB are expensive and has an extremely poor success rate (1, 2, 3). Patients who have repeatedly received uneven therapy with traditional

intensive course and worse medications are ineffective treatments typically acquire MDR-TB; Standard first-line TB medications are practically ineffective for MDR-TB patients (4, 5). Human migration has been intimately connected to the global expansion of MTBC strains (6).

A subclass of MDR-TB resistant to any fluoroquinolone which is said to be pre-XDR-TB (Pre-extensively drug-resistant TB), extensively drug resistant TB (XDR TB) is resistant to rifampicin, and fluoroquinolone, so the treatment needs additional medication with bedaquiline or linezolid. These multi drug resistance pathogens are more harmful to patients and more challenging to treat (7). Around the world, TB and MDR/RR-TB (rifampicin-resistant tuberculosis, RR-TB) cases were identified as 10 million and 206,030 cases respectively in 2019. It is 186,883 cases in 2018, a 10% rise from a previous year.

Rifampicin resistance was detected in 61% of individuals with TB that had been bacteriologically proven in 2019 and 51% in 2017. According to WHO recommendations, TB diagnosis for medication identification of resistance by means of quick molecular assays, propagating techniques, or sequencing methods is necessary (8). Approximately 26.3 million individuals of all ages had TB, diagnosed internationally in 2022, together 649,000 (43%) with MDR/RR-TB (rifampicin-resistant tuberculosis, RR-TB), describing a 10% increase from 483,000 in 2021(9).

Diagnosis of DR TB

Discovery of drug resistance needs verification of TB testing and use of quick molecular tests, culture techniques and sequencing technologies to test for drug resistance. Molecular testing for M. tuberculosis diagnosis and evaluation of mutations in drug-resistant TB increases identification. The Xpert ® MTB/RIF, Ultra, MTB-XDR, BDMax, Line probe assay (LPA), and Loop-mediated isothermal amplification (LAMP) are few molecular techniques that have been developed (10). All of them have many benefits and drawbacks in respect to the rapid outcomes, operator expertise required, Cost, sample type, dependent sensitivity, operator knowledge and detection of resistance mutations should be required (11). Testing for drug susceptibility Primary specimens were cultured in both liquid (BACTEC MGIT 960, Becton Dickinson Diagnostic Systems, Sparks, US) and solid (Löwenstein-Jensen and Stone brink media) media to obtain MTBC isolates.

In accordance with WHO recommendations, phenotypic drug susceptibility testing (DST) was carried out using the MGIT 960 system at critical doses for all medicines other than cycloserine (solid medium) (12). Genotype MTBDR plus and MTBDRsl assays (HAIN life science GmbH, Nehren, Germany) for molecular DST were carried out in accordance with manufacturer guidelines. Amplification and DNA sequencing techniques were used to find mutations in the pyrazinamidase gene, pncA. Using the MGIT 960 technology, phenotypic DST of second-line anti-tubercular medicines was carried out (13).

Due to the time, money, and skill required WGS has thus distant proven prohibitive in the majority of cases. Next-generation sequencing appears to hold promise because it could provide some WGS solutions. An NGS is followed by a specific gene amplification step of the gene segments has been made possible by modern molecular assays. One of these tests is GenoScreen'sDeeplex® Myco-TB, which has a turnaround time of 48 hours and predicts resistance to about 15 anti-TB medications, along with first- and second-line antibiotics, besides the newly recommended bedaquiline, clofazimine, and linezolid. Additionally, the targeted production of multiple gene copies and following sequencing give genetic constituting details on the current species of mycobacterium allow for the identification of other mycobacterial species (14). Recently new tests described additionally include amplification and the steps followed by sequencing selection and rapid accumulation of three locations of the *M. tuberculosis* genome succeeded by nanopore sequencing, with great specificity and sensitivity for rifampicin and isoniazid resistance are the inexpensive and quick improvement of era to their work flow may be mainly applicable in source of partial settings (15). It is now a viable substitute for a variety of anti-TB medications after an analysis compared with selected NGS performed straight from the sputum samples with the help of presently employed techniques for determining drug resistance, including phenotypic testing (16).

Although up to 32,000 kids are thought to build up MDR-TB annually, the best diagnosis and treatment options are not well understood (17). Due to challenges in collecting respiratory samples and the prevalence of paucibacillary (AFB smear and culture negative) illness in children, TB diagnosis in kids is additional challenging comparative to adults (18).

MDR DR TB medications

Second-line medications are needed for treatment, instead of earlier regimens lasting 20 months or longer, Now, MDR/RR-TB and pre-XDR-TB patients can receive treatment for just six months with all-oral regimens. The WHO also advises increased availability to all-oral regimens supported by psychotherapy and keep an eye for side effects (19). Consequently, the formation of MDR-TB still poses a hazard to human health, particularly in some high-burden nations (20). MDR-TB is more complex than sensitive TB because to its worse treatment results, lengthier therapy (about two years), greater therapy costs, and numerous comorbidities (21).

Below table is MDR TB drug categorization for construction of long MDR-TB treatments as following (22).

Drug groups	TB Drugs
Group A	Strongly recommended for extremely effective, strongly advised Ex: levofloxacin and moxifloxacin (Fluoroquinolones), linezolid and bedaquiline
Group B	Restricted and suggested as agents of second option. Ex: clofazimine and cycloserine or terizidone
Group C	If Groups A and B regimen fail to treat then group C drugs are used. Ex: amikacin, ethionamide, p-amino salicylic acid Delamanid, pyrazinamide, imipenem–cilastatin with amoxicillin/clavulanate,

Table 1 WHO combination of recommendations on DR-TB regimen, 2018.

WHO recommended for the below regimens for proper treatment of MDR/RR-TB:

1. Longer regimens (18-20 months) recommended for most patients for personalized treatments in response to therapy.
2. Moderate regimens (15-17 months) recommended for some patients for personalized treatments in response to therapy.
3. Shorter regimens (6-7 months) recommended for some patients for personalized treatments in response to therapy (23).

Regular history-taking, physical examination, chest radiography, specific testing like sonometry, observable tests, electrocardiography, and lab observations are used to keep track of the patient's response to treatment and toxicities (24, 25).

Extensively drug resistant TB treatment

Three novel TB drugs (bedaquiline, delamanid, and pretonamid) introduced almost 50 years after the debut of rifampicin, while other older and repurposed medications gained growing significance to treat MDR-TB, RR-TB and Pre-XDR-TB (26, 27, 28, 29). The management of DR TB regimen for all oral anti-TB medications that are additional efficient and few toxic medications are usually more tolerated has lately revolutionized the care of DR-TB. These are believed to have better adherence and therapy results (30). Unfortunately, bedaquiline resistance is increasing; Researchers need to put efforts to develop novel medication (31).

Future Scenario

For MDR-TB therapy in children and adults might get important role by specific core drug profile, it includes Linezolid, delamanid and bedaquiline. Linezolid, delamanid and bedaquiline might acquire an additional major role in MDR-TB therapy in children and adults specified their 'core drug' profile. Under precise circumstances delamanid and bedaquiline might be review for collective use, though extra RCTs' data is needed. Additional examinations are also essential to set up if great dose of moxifloxacin, and rifabutin, could contribute to the MDR-TB collective weapon to combat (32). Spread of resistant pathogens will back to the age before antibiotics and causing new pandemics. Novel drugs development will require continuing expenditure from funding organizations. Public-Academic-Private as coordinated approach (33).

Summary and conclusion

People with TB and EPTB can definitely come out from the risk with proper care and treatment. MTBC strains develop drug resistance which is said to be Multi Drug Resistance TB (MDR-TB) requires expensive diagnosis and treatment. Muti drug-resistance is classified into rifampicin resistant, pre-XDR-TB and XDR TB. Diagnosis of drug resistance by quick molecular tests such as LPA, LAMP and WGS and sequencing technologies are available. All of them have many benefits and drawbacks. As per WHO

recommendation, the MGIT 960 system Genotype MTBDR plus and MTBDRsl assays are molecular identifications.

Second-line medications are needed for MDR TB treatment. MDR/RR-TB and pre-XDR-TB patients can receive treatment for just six months to 20 months with all-oral regimens. The WHO also advised increased availability of all-oral regimens for DR-TB in 2018 into group A, B and C. Other recommendation on duration of regimen into 3 ways of MDR/RR-TB treatment: 1. longer regimens (18-20 months), 2. Moderate regimens (15-17 months), 3. Shorter regimens (6-7 months).

Control of tuberculosis is a top concern for global health, but the effort to eradicate TB is in threat due to the rise in MDR-TB cases. Relocation and Travel are also increasing the MDR-TB. We are lucky to have new TB-antibiotics were existing and genome sequencing tests are transformed for TB-diagnosis. Confidently, access to common next-generation sequencing of samples from each TB patient will allow us to enhance a thorough observation system in the future.

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