Review Article
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A multidimensional approach to the elimination of tuberculosis

Abstract

Significant global efforts have been made in recent years to combat tuberculosis (TB) disease. Despite the fact that social and economic causes of TB have been well known for decades, the range of interventions has, until recently, been mostly restricted to the health domain. *Mycobacterium tuberculosis* that causes tuberculosis, the second-deadliest infectious killer (after COVID-19), which typically damages the lungs. It can spread when TB patients cough or otherwise release bacteria into the air, which can spread the disease. To ensure that significant gaps in outcome-oriented research are recognized and filled, we must promote collaboration among all involved parties in tuberculosis research and control in order to optimise the impact of fundamental research. Consequently, a multisectoral and interdisciplinary strategy is necessary as the global health community works toward the pledges and goals established in two recent high-level political gatherings.

Keywords: tuberculosis, multidimensional approach, multi-drug resistant, diagnosis, treatment

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Abbreviations: TB, Tuberculosis; MDR-TB, Multi-Drug Resistant; XDR-TB, extremely drug-resistant TB; ATT, anti-tuberculosis therapy; AMR, anti-microbial resistance

Introduction

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*. Its rigid and latent persistence in the human body makes its elimination difficult.[1] The world has witnessed another challenge in the form of drug-resistant TB which became a major health concern globally for people and policymakers.[2] The Multi-Drug Resistant TB (MDR-TB) is the state when bacteria resist to a minimum of two first-line drugs rifampicin and isoniazid. While extremely drug-resistant TB (XDR-TB) arises due to resistance of rifampicin, isoniazid, and at least one of the six main classes of second-line drug fluoroquinolone and kanamycin, amikacin, or capreomycin.[2,3] XDR-TB is more prevalent in immuno compromised individuals, particularly those suffering from HIV. It has been observed that no adherence to the proper drug regimen of the anti-tuberculosis drug, unawareness of people affected with TB, and unhygienic conditions increased the chances of drug-resistant TB.[4] Elimination of drug-resistant TB requires early diagnosis, adherence to anti-tuberculosis therapy (ATT), and nutritional support. Epidemiology suggested that the low and middle-income countries badly affected by the MDR and XDR TB. Socio economic condition, political unrest, and unavailability of anti-tuberculosis drug significantly enhance the condition of MDR and XDR TB.[5] Further, delay in diagnosis and low cases detection leads to MDR and XDR TB.[6] In China 74% MDR TB cases have been observed in 2019.[7] Condition in South Africa is more devastating as the country is badly hit by HIV infection. Although the policy makers, social groups and health care providers are putting their effort in this direction but still we have not achieved the satisfactory results. The effort should also include extensive research. The research on TB disease not only requires high expenses and resources but also require good collaboration among health care providers and researchers. The rationale behind such research is to reduce the overall cost of the diagnosis, treatment and rehabilitation. Further, the research on diagnosis and treatment of MDR and XDR TB can reduce the transmission of this disease in the community. It is also imperative that the *Mycobacterium tuberculosis* must be included in anti-microbial resistance (AMR) priority list for further research and development.[8] The review will elaborate the summery of diagnosis and constructive research performed in field of Tuberculosis.

Diagnosis

For diagnosis of any disease it is important that the diagnostic tests should be enough sensitive, specific, cost effective, less invasive and acceptable. The culture based drug susceptibility test has been considered as benchmark test for identification of drug resistant TB in which Lowestein-Jensen medium is used for the incubation of *Mycobacteria* for 3-8 weeks.[9] However, due to its time consuming nature, it is not preferable in low and middle income countries.[10] The molecular diagnosis is considered to be most effective and reliable diagnostic method. Unfortunately XDR TB can't be diagnosed and identified on the basis of a failure of MDR TB treatment regimen.[2] The diagnostic test involved can be seen in Table 1.[12]

Table 1 The diagnostic tests involved

Diagnostic test	Mechanism	Drawback	Reference
Culture sensitivity test	Identification of drug resistant *Mycobacteria*	Time consuming	(Nguyen et al. 2019)[10]
Polymerase chain reaction	Identification of mutant drug resistant bacterial strain	Expensive and required molecular biology lab setup with technically skilled personnel	(Nurwidya et al. 2018)[16]
Xpert MTB/RIF assay	Detects 81-bp fragment of the MTB *rpoB* gene	Expensive and required molecular biology lab setup	(Zeka, Tasbakan, and Cavusoglu 2011)[17]
Geno Type MTBDRsl assays	Detects mutation in *gyr A* gene in *Mycobacteria*	Cannot rule out XDR TB	(Seung et al. 2015)[4]

Table Continued..

Diagnostic test	Mechanism	Drawback	Reference
MeltPro TB assay	Mutation in kanamycin gene can be detected	Expensive and required molecular biology lab setup	(Pang et al. 2016)[3]
Whole genome sequencing	It is employed to look into the genetic markers of the organisms that could affect treatment and infection prognosis.	The first-generation sequencer is relatively slow, however has a high throughput and low cost. The second generation has a lower throughput, higher cost	(Votintseva et al. 2015)[4]

Treatment strategies

The anti TB drug is widely classified into five classes. group one includes first line oral agents, second group includes injectable anti TB drugs, group 3rd Fluoroquinolones, group 4th includes oral bacteriostatic second-line anti-TB drugs, group 5th includes anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents). The antibiotics names of each group are depicted in Table 2. The drug sensitive TB can be cured by Isoniazid, Rifampicin based regimen, but the MDR TB is almost incurable with this regimen.[4] It is imperative to search on effective, safe and shorter drug course for treatment of drug resistant TB.[11] The BPal that is Bedaquiline-pretomanid-Linezolid regimens is endorsed by WHO for drug resistant TB patients.[7] The research suggested that the treatment based on BPaL regimen is cost effective than conventional XRD TB treatment approach.[13]

Table 2 WHO recommended grouping of anti-TB drugs

Group Name	Anti-TB agent	Abbreviation
Group 1. First-line oral agents	Isoniazid	H
	Rifampicin	R
	Ethambutol	E
	Pyrazinamide	Z
	Rifabutin	Rfb
	Rifapentine	Rpt
Group 2. Injectable anti-TB drugs (injectable agents or parental agents)	Streptomycin	S
	Kanamycin	Km
	Amikacin	Am
	Capreomycin	Cm
Group 3. Fluoroquinolones (FQs)	Levofloxacin	Lfx
	Moxifloxacin	Mfx
	Gatifloxacin	Gfx
Group 4. Oral bacteriostatic second-line anti-TB drugs	Ethionamide	Eto
	Prothionamide	Pto
	Cycloserine	Cs
	Terizidone[e]	Trd
	Para-aminosalicylic acid	PAS
	Para-aminosalicylate sodium	PAS-Na
	Bedaquiline	Bdq
	Delamanid	Dlm
Group 5. Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents)	Linezolid	Lzd
	Clofazimine	Cfz
	Amoxicillin/ clavulanate	Amx/Clv
	Imipenem/cilastatin[f]	Ipm/Cln
	Meropenem[f]	Mpm
	High-dose isoniazid	High dose H
	Thioacetazone[g]	T
	Clarithromycing	Clr

Source: WHO recommended grouping of anti-TB drugs - Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis - NCBI Bookshelf (nih.gov)[12]

Future perspective: After the emergence of molecular diagnostic testing, it is possible to take prompt action for TB elimination. However new fast, safe and cost-effective techniques for diagnosis of MDR and XDR TB are still needed. New drug formulation and their prompt clinical trials should be considered in order kill resistant *Mycobacteria*.

Conclusion

The elimination of tuberculosis is indispensable as TB is not only a disease but a social curse. Civil society, medical research council, public health centres and NGO should come forward to eliminate this disease by making policies and effective management plans.[14] Continuous adherence to drug and patient monitoring using algorithm based methodology can give good results in this direction.[12]

Authors contribution

Neha Singh and Khushboo Bhange both equally contributed in conceptualization, review data validation and editing.

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Conflicts of interest

Author(s) declares no conflicts of interest.

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