



A SYSTEMATIC REVIEW ON TUBERCULOSIS, MULTI-DRUG RESISTANT AND EXTENSIVELY DRUG RESISTANT TUBERCULOSIS

Yatindra Kumar*¹, Punitha Kaviya², Parimalakrishnan S.², Md Mujahid³ and S. P. Singh³

¹Department of Pharmacy, GSVM Medical College, Kanpur, UP, India.

²Department of Pharmacy, Annamalai University, Annamalai Nagar, TN, India.

³Department of Pharmacy, Integral University, Lucknow, UP, India.

⁴Department of Pharmacology, GSVM Medical College, Kanpur, UP, India.

***Corresponding Author: Yatindra Kumar**

Department of Pharmacy, GSVM Medical College, Kanpur, UP, India.

Article Received on 21/12/2017

Article Revised on 10/01/2018

Article Accepted on 31/01/2018

ABSTRACT

Tuberculosis (TB) is a major health issue in low- and middle-income countries like India. India accounts for about 24% of the global TB burden. The burden of communicable diseases such as TB is rising due to multi-drug resistance. Knowledge about how these diseases influence each other is limited. The aim of this review is to critically assess the literature examining the association between 2nd line drugs and drug resistance in TB. In the present study an attempt is taken to address the various problems in tuberculosis, multi-drug resistant and extensively drug resistant tuberculosis patients through systematic review of the literature.

KEYWORDS: Tuberculosis, Multi-drug resistance, Extensively drug resistant tuberculosis, TB Treatment, TB Guidelines.

INTRODUCTION

Tuberculosis (TB) is a communicable disease which spreads through air. This is also known as droplet infection since it gets spread from one person to another through the air. When the person with TB coughs, tubercle bacilli (*Mycobacterium tuberculosis*) are transported in fine droplets from the lungs of the infected person(s) into the air and then it droplet inhaled by healthy person they get infected with TB disease. Due to transmission that tubercle bacilli have when they get spread into the air. The droplets are also extremely small and remain in the air for a long time. Besides the direct transmission from an infected person to an uninfected person, the TB bacilli can also be transmitted by dust. TB bacilli can live for 24 weeks outside the body with the help of sunlight. A rare form of TB also get transmitted through cow's milk and name of the microorganism is *Mycobacterium bovis*, in order to avoid this infection it is always better to drink boiled milk. TB cannot spread to infants from pregnant mother, because it does not cross the placenta except miliary TB. It affects those are having weak immune system, which is major risk factor in causing the infection. Generally it will spread in during waiting hall in a hospital where both the infected and healthy patients whenever they visit the hospital. This can be avoided by separating them and supplying sterile air. [John M-A, 2007].

Mycobacterium tuberculosis (MTB) is a type of bacterium, which cause the disease called tuberculosis (TB). TB is a communicable disease caused by a group of genetically related mycobacteria. They belong to the family Mycobacteriaceae and the order Actinomycetales and are collectively known as the *Mycobacterium tuberculosis complex*. The disease is spread as a result of airborne droplet nuclei dispersed by infected individuals with active TB from their airways through coughing, singing or other activities, and these small particulates can remain suspended in the air for hours. In humans these include the following:

- a) *M. tuberculosis*: The most common causative agent of human mycobacterial infection.
- b) *M. bovis*: Historically an important causative agent of infection transmitted by unpasteurised milk, and currently found in a small percentage in developing countries.
- c) *M. africanum*: Isolated in small groups in West and Central Africa.
- d) Others include *Mycobacterium carnettii* and *Mycobacterium microti* which are also part of the complex but rarely cause infection in humans

Nontuberculous mycobacterium (NTM) is group of mycobacteria which occur naturally, living in water and soil. These include *M. kansasii*, *M. malmoense*, *M. xenophi*, *M. simiae* and *M. avium intracellulare*. They are not directly communicable and the disease is thought

to be acquired from environmental exposure in susceptible individuals who have immunodeficiency or an underlying pulmonary disease with pre-existing cavitation. [Eisenstadt, J and Gerri S. Hall, 1995].

Epidemiology

India is the country with the highest burden of TB and multidrug resistant TB (MDR TB), which accounts for 25% of the global TB burden. As per WHO Global TB Report, 2015, 2.8 million TB occurred in India against 9.6 million cases globally. Nearly 58% and 55% reduction in TB mortality and prevalence rate during 2014 respectively when compared to 1990 and the incidence found to be on declining trend. 0.48 million people died due to TB and 0.13 million MDR TB cases were reported. India is second highest population affected with HIV associated TB in the world. In 2015 around 0.11 million TB cases associated with HIV and among them 37,000 patients were died. Both tuberculosis incidence and mortality rates are decreasing from 2000 to 2015. The incidence of TB has reduced from 2.89 per million per year in 2000 to 2.17 per million per year in 2015 and the mortality due to TB has reduced from 0.56 per million per year in 2000 to 0.36 per million per year in 2015. [Annual Status Report. TB Indian 2017].

Definition and TB Classification System [American Thoracic Society. 2000]

I. TB is classified based on anatomical site of disease into two types as follows.

- a. Pulmonary TB (PTB): TB involving the lung parenchyma or the tracheobronchial tree. This TB includes Miliary TB because there are lesions in the lungs.
- b. Extrapulmonary TB (ETB): TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges

A patient affected by both PTB and ETB should be identified as a case of PTB.

II. TB is classified based on history of previous TB treatment

- a. New patients: Patients never treated for TB nor not taken anti-TB agents for less than 1 month.
- b. Previously treated patients: Patients treated for more than 1 month with anti-TB agents in the past. They are further classified as follows:
 - i. Relapse patients: Patients previously treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB.
 - ii. Treatment after failure patients: Patients treated for TB previously and treatment got failed at the end of course of treatment.
 - iii. Treatment after loss to follow-up patients: Patients treated for TB previously and declared lost to follow-up at the end of course of treatment and previously known as default patients.

- c. Other previously treated patients: Patients treated for TB previously but patients' outcome after the course of treatment is unknown or undocumented.

III. TB is classified based on drug resistance

Classification based on drug resistant to drug susceptibility testing (DST) for *M. tuberculosis*:

- a. Monoresistance: means single drug treated to patients with first-line anti-TB agents.
- b. Polydrug resistance: means more than single drug treated to patients from first-line anti-TB agents (other than isoniazid and rifampicin).
- c. Multidrug resistance: means resistant to isoniazid and rifampicin.
- d. Extensive drug resistance: means resistance to any fluoroquinolone and minimum one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), apart from multidrug resistance.
- e. Rifampicin resistance: resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

The two groups are mutually exclusive. Any patient found to have drug-resistant TB and placed on second-line treatment is removed from the drug-susceptible TB outcome group. Patients with unknown previous TB treatment history do not fit into any of the categories listed above. New and relapse cases of TB are incident TB cases.

Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion. Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.

TB treatment [Payam Nahid and Philip C. Hopewell, 2017; José A. Caminero et al, 2017; J.J. Cherian et al, 2017; Centres for Disease Control and Prevention website].

Treating TB effectively and promptly is important to both protect patients and prevent the spread of TB. People diagnosed with TB and HIV should start TB treatment immediately and then begin antiretroviral treatment within two weeks if they have a low CD4 count (<50 cells/mm³), or within two months if the CD4 count is above 50 cells/mm³. The standard TB treatment regimen is a six-month course of antibiotics, but the duration and drugs used may vary according to a patient's age and type of TB. TB treatment can also be

used to prevent infection with the bacterium from turning into active disease. Treating TB takes longer than other types of bacterial infections because the bacteria that cause TB grow slowly. Even so, pending and future research may help reduce treatment times.

- a. Preventive therapy.
- b. Drug-sensitive TB.
- c. Drug-resistant TB.
- d. Novel drugs.

Preventive therapy

As there is no widely effective vaccine for TB, using TB drugs to treat latent TB infection (LTBI) is one of the best ways to prevent active TB disease. If active disease has been ruled out, the most common treatment for latent TB infection is isoniazid. Isoniazid preventive therapy (IPT) reduces the risk of developing active TB. The standard regimen is 300 mg daily of isoniazid for 6-9 months in adults and adolescents and 5 mg/kg for children; the World Health Organization recommends 36 months or more of treatment for people with HIV, including children.

Clinical trials have shown short courses of preventive therapy — such as using rifampicin alone for four months, or once-weekly isoniazid and rifapentine together for 12 weeks — to be as effective as isoniazid for 6-9 months. These regimens are in use in the U.S. and other low transmission settings. However, it is unclear if these regimens are appropriate for high burden settings, as research has shown that in settings with high rates of TB transmission, the benefits of isoniazid preventive therapy last only as long as the treatment itself. The below table compares various treatment regimens for latent TB infection:

Drugs	Duration	Interval	Minimum Doses
Isoniazid	36 months	Daily	1080
Isoniazid	9 months	Daily	270
Isoniazid	6 months	Daily	180
Isoniazid and rifapentine	3 months	Once weekly	12
Rifampicin	4 months	Daily	120

[Adapted from U.S. Centers for Disease Control and Prevention]

Currently, there is no validated regimen to treat latent infection with drug-resistant strains of TB. The European Center for Disease Prevention and Control (ECDC) recommends finding contacts of people with drug-resistant TB and conducting individual risk assessments that consider the risk for progression to TB disease, the drug-susceptibility pattern of the source case of infection, and the risk for adverse drug events if preventive therapy is initiated. More research is needed both to identify safe and effective treatment options for those infected with drug-resistant TB, and to guide follow up in cases where preventive therapy is not initiated.

Treatment for drug-sensitive TB (DS-TB)

The standard six-month course of treatment consists of two phases: the intensive phase (the first two months) and the continuation phase (the last four months). Treatment may differ for patients with extrapulmonary TB (TB outside of the lungs). During the intensive phase of standard treatment, patients take a daily combination of four medications: isoniazid, rifampicin, pyrazinamide and ethambutol. These four drugs are referred to as first-line drugs, and are off-patent and cheap. In place of rifampicin, rifapentine may be used to allow for intermittent dosing, or rifabutin may be used as it has fewer interactions with HIV medicines and opioid substitution therapy, but these are more expensive than rifampicin and not available in all TB programs. These medicines are used in combination to prevent the bacteria from developing resistance. Within a few weeks of beginning treatment, most patients will start to feel better. If treatment is working, most patients become non-infectious during the intensive phase.

Once the intensive phase is completed, the continuation phase of treatment begins. During this four-month phase, normally only isoniazid and rifampicin (the two most powerful first-line drugs) are taken on a daily basis. If the patient has taken medications regularly and achieves two negative TB tests, his/her TB is considered cured upon completion. Side effects, particularly nausea and abdominal pain, are relatively common. Urine and tears can turn orange, which is harmless but disconcerting if patients are not warned. More severe side effects, such as joint pain, visual impairment, liver damage, and peripheral neuropathy (nerve damage) are less common, but can be serious when they do occur. More information about each first-line drug and its side effects can be found in TAG's activists.

Drugs Used in the Treatment of TB

First-line drugs

Isoniazid (H or INH), rifampicin (R or RIF), ethambutol (E or EMB), pyrazinamide (Z or PZA), rifabutin (RBT) and rifapentine (P or RPT).

Treatment for Drug Resistant TB (DR-TB)

Drug-resistant TB (DR-TB) is TB that has developed mutations that make the four standard first-line drugs ineffective. Drug resistance can arise when medicines are sub-standard, doses are skipped, treatment is interrupted or stopped too soon, or when treatment regimens are inappropriately designed or dosed. Drug-resistant TB can also infect people directly in community or healthcare settings. Drug-resistant TB is lengthier, more expensive and more difficult to treat than drug-sensitive TB. TB that is resistant to at least isoniazid and rifampicin is called multi-drug resistant (MDR) TB. Extensively drug-resistant TB (XDR-TB) is MDR-TB that is also resistant to a second-line injectable drug (amikacin, kanamycin, or capreomycin) and a fluoroquinolone. Pre-XDR-TB is MDR-TB that is resistant to either a second-line injectable or a fluoroquinolone. Treatment for drug-

resistant TB takes longer (up to two years), is less effective (global cure rates are around 50%) and has more side effects.

Second-line drugs

➤ Injectables: kanamycin, amikacin, capreomycin and streptomycin.

- Fluoroquinolones: moxifloxacin, levofloxacin, ofloxacin.
- Oral bacteriostatic: ethionamide, prothionamide, cycloserine, terizidone and p-aminosalicylic acid.
- Agents with unclear efficacy for TB: clofazimine, linezolid, amoxicillin/clavulanate, high dose isoniazid, thioacetazone, imipenem/cilastatin and clarithromycin.

Anti-tuberculosis Agents under Clinical Trials

Drug	Classification	Phase	Sponsor(s)
AZD5847	Oxazolidinone	IIa	AstraZeneca
Bedaquiline	Diarylquinoline	IIb/III	Janssen
Delamanid	Nitroimidazole	III	Otsuka
Pretomanid	Nitroimidazole	III	TB Alliance
SQ109	Ethylenediamine	IIb/III	Sequella/ Infectex
Sutezolid	Oxazolidinone	IIa	Sequella

[Adapted from TAG's 2014 Pipeline Report]

Drug treatment for newly diagnosed tuberculosis

The initial standard treatment includes: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. Once the TB isolate is known to be fully susceptible, ethambutol (or streptomycin, if it is used as a fourth drug) can be discontinued. Following two months of treatment (in the case of sensitive isolates), pyrazinamide must be discontinued. Isoniazid plus rifampin are continued as daily or intermittent therapy for 4 more months. If isolated isoniazid resistance is reported, withdraw isoniazid and resume with rifampin, pyrazinamide, and ethambutol for the entire 6 months. Treatment should be continued if the patient has cavitory disease and the culture sensitivity shows positive even following 2 months of therapy. Directly observed therapy (DOT) is being suggested in all kinds of patients. Patients following DOT, can move on to the above regimens with 2- to 3-times per week dosing followed by an initial 2 weeks of continuous dosing. Patients following twice-weekly dosing must not skip any doses. Daily dose therapy is being recommended for patients who are on Self medications.

Treatment for multi drug resistant tuberculosis

The Treatment pattern for multi drug resistance tuberculosis consists of four drugs with maximum efficacy. With the confirmation of MDR-TB, patients must be treated based on either empirical MDR regimens or based on individualized regimens as per the drug sensitivity testing pattern (DST). Those patients who showed resistance towards category first or third, and towards any drug of the category second showed smear positive at the end of the fourth month treatment, contacts of MDR-TB cases will be identified as MDR-TB suspects. The findings will be based on culture sensitivity patterns and drug sensitivity testing. When multi-TB is confirmed then the patient must be initiated with category 4 regimens. As per Revised National Tuberculosis Control Programme (RNTCP) category 4 regimens are considered to be the Standard regimen therapy for MDR-TB. Fourth category regimen includes

the following six drugs four bactericidal: ofloxacin or Levofloxacin, kanamycin, ethionamide, pyrazinamide and two bacteriostatic drugs: Ethambutol and cycloserine. In the 6 to 9 months of intensive phase (IP) four drugs: ofloxacin or levofloxacin, ethionamide, ethambutol and cycloserine whereas in 18 months continuation phase (CP). PAS is included in the regimen as a replacement for any drugs among ofloxacin or levofloxacin, kanamycin and ethionamide.

Treatment for extensively drug resistant tuberculosis

The recommended therapy for extensive case of resistant tuberculosis includes the combination of four drugs against which the Mycobacterium tuberculosis isolate is likely to be sensitive. Drugs are preferred on the basis of sequential selection process on the basis of safety, efficacy and cost. High dose of isoniazid, pyrazinamide, and ethambutol were found to be adjunct for the treatment of MDR and XDR tuberculosis among the overall first group of oral first line agents. Among the second group fluoroquinolones, the first choice is high-dose levofloxacin. The third group comprises of injectables, which should be used in the following order: capreomycin, kanamycin and amikacin. The fourth group is called the second-line drugs which must be used in the following order: thioamides, cycloserine and aminosalicylic acid. The fifth group includes drugs that are not very effective in terms of safety, efficacy and cost.

TB Guidelines

TB Guidelines were classified into several categories. We have made an attempt to classify guidelines based on the treatment as follows:

- a. Adult treatment guidelines
- b. Paediatric treatment guidelines
- c. Prevention guidelines
- d. Diagnostic guidelines
- e. Surveillance, monitoring and evaluation guidelines
- f. TB/HIV integration guidelines

In this manuscript we have listed few recent treatment guidelines for treating TB and classified based on the level of development is as follows:

Developed Countries

1. Canadian Tuberculosis Standards 2017 – Canada.
2. American Thoracic Society Tuberculosis Guidelines 2016 – USA.
3. European Union Standards for Tuberculosis Care 2013 – Europe.
4. National Tuberculosis Advisory Committee 2017 – Australia.
5. Japanese Clinical Guidelines for Treatment of Pulmonary Tuberculosis – Japan.

Developing Countries

1. Guidelines on Extrapulmonary Tuberculosis for India 2016 – India.
2. National Tuberculosis Management Guidelines 2014 – South Africa.
3. Guidelines for the Clinical Management of Tuberculosis 2007 – Ghana.
4. Botswana Tuberculosis Policy Guidelines 2011 – Botswana.

Under Developed Countries

1. Federal Democratic Republic of Ethiopia Ministry of Health National Comprehensive Tuberculosis 2016 – Ethiopia.
2. National Guidelines for the Management of Tuberculosis 2012 – Bangladesh.
3. Tuberculosis Treatment in Niger 2017 – Niger.
4. Democratic Republic of Congo, Tuberculosis Research & Treatment 2015 – Congo.
5. The National Tuberculosis Program, Mauritania 2015 – Mauritania.

CONCLUSION

The rapid spread in the progression of anti-TB drug resistance in India claims the need for a systematic nationwide surveillance for the reinforcement of the National TB Control Program in establishing treatment programs for revised treatment outcomes. The management of DR-TB is critical and based on laboratory confirmation of TB and a clear understanding of drug resistance aided by drug susceptibility testing (DST) to ensure accurate diagnosis and early intervention of appropriate treatment. Adding to provide valid treatment and reduction in mortality, the prime goal of TB control programs in countries of high TB incidence is to taper the transmission from infectious TB cases. Screening for TB (to diagnose latent TB infection) and prophylactic therapy remains to be the important tools to reduce the risk of progression to TB disease among high risk individuals (close contacts, HIV infected individuals, health care workers, etc.) and be considered in endemic countries to reduce the progression from infection to disease. The growing population (especially in countries like China and India) is likely to inflate the number of TB cases in future.

Smoking rates are huge among men in these countries and in addition with the rising rates of diabetes, the risk of progression to TB disease will also multiply. Interventions such as smoking cessation and early screening for TB can be advocated, but the impact of these interventions in reducing TB risk remains negligible at population level. Malnourishment and sedentary air pollution are the classic risk factors which are found to be bounded with the socioeconomic class of a setting. Rapid urbanization is shown to offset these components to an extent (by decreasing malnutrition rates and increased usage of clean fuels), but increased awareness through IEC (information, education, and communication) activities should be considered. Attempts should also be made to gather the risk factor measurements in conventional surveillance of the TB cases.

REFERENCES

1. American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med.*, 2000; 161: 1376–1395.
2. Annual Status Report. TB Indian 2017 – Revised National Tuberculosis Programme. Central TB Division Directorate General of Health Services, Ministry of Health and Family Welfare, Nirman Bhawan, New Delhi, March 2017.
3. Eisenstadt, J and Gerri S, Hall. Microbiology and classification of mycobacteria. *Clinics in Dermatology*, 1995; 13(3): 197–206.
4. <https://www.cdc.gov/tb/topic/treatment/tbdisease.htm>
5. J.J. Cherian, I. Lobo, A. Sukhlecha, U. Chawan, N.A. Kshirsagar, B.L. Nair, L. Sawardekar, Treatment outcome of extrapulmonary tuberculosis under Revised National Tuberculosis Control Programme, *Indian Journal of Tuberculosis*, 2017; 64(2): 104–108.
6. John M-A, Menezes CN, Chita G, Sanne I, Grobusch MP. High Tuberculosis and HIV Coinfection Rate, Johannesburg. *Emerging Infectious Diseases*, 2007; 13(5): 795 – 796.
7. José A. Caminero, Joan A. Cayla, José-María García-García, Francisco J. García-Pérez, Juan J. Palacios, Juan Ruiz-Manzano, *Diagnosis and Treatment of Drug-Resistant Tuberculosis*, *Archivos de Bronconeumología (English Edition)*, 2017; 53(9): 501–509.
8. Payam Nahid and Philip C. Hopewell, *Tuberculosis Treatment*, In *International Encyclopedia of Public Health*, 2nd Ed, Edited by Stella R. Quah., Academic Press, Oxford, 2017; 267–276.