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Post Tuberculosis Sequelae and Suggestive Intervention Management for Prevention

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***Abstract*: Tuberculosis is major public health problems now a day. First line drugs are mostly used in drug susceptibility tuberculosis, whereas Drug resistance tuberculosis (DR-TB) are treated with combination of both second line drugs & few first line drugs. Due to longer duration using of anti-tubercular drugs having adverse drug reactions (ADRS). Minor adverse effects are quite common & they can be easily managed with symptomatic treatment. However, some adverse reactions of drugs effects like gastrointestinal toxicity, cardiotoxicity, nephro toxicity, central nerve systems toxicity are life threatening. Mostly TB patients having low immunity, malnutrition, Bronchiectasis, Bronchial fibro stenosis, lung cavitation, alternation of parenchyma, scarring of lungs & chronic liver disease are the common post sequelae of TB.**

***Keywords*: Tuberculosis, prevention, sequelae.**

1. Introduction

Mycobacterium tuberculosis is a weekly gram +ve, obligate aerobes which cause tuberculosis a highly infectious disease, which primarily affects the lungs to cause pulmonary TB [1]. India features among the 22-high tuberculosis (TB) burden countries and has accounted for estimated one quarter (26%) of all TB cases [2], [3]. The probability of developing TB is more in individual with medical conditions that weaken immune system such as HIV AIDS, diabetes, organ transplantation, renal disease, malnutrition, alcohol abuses, tumors necrosis factor alpha (TNF -ALFA) antagonists' therapy. It also depends on socioeconomic factors like poor sanitation, air pollution, aging population etc. They're having several drugs resistance to TB (DR - TB). Emergence of drugs resistance TB is still a challenge to TB therapy & effective disease management [4]. The main reason of resistance of MDR/XDR TB is due to Several mechanism like biochemical, molecular & genetically resistance of TB causing bacteria. First line of drugs (FLD) such as isoniazid, rifampicin, pyrazinamide is used aging DR TB [5]. The second line of drugs such as Amikacin, capreomycin, cyclosporine, levofloxacin is used against DR TB. Using of these drugs having many noxious & adverse effects in humans' body that is the main reason of arising the post sequelae symptoms in TB patients [6]. Mechanism involved in DR-TB is mainly due to primary or secondary drug resistance incomplete or suboptimal treatment of mutant of resistant strain which is acquired during treatment of initial sensitive TB is main cause of acquired/secondary drug resistance [7].

2. Post TB Sequelae and its Management Strategies

Due to use of MDR/XDR-TB in a long term, it causes

Table 1
List of antitubercular drugs and their action against disease.

Antitubercular Drugs	Family	Mode of Action	Ref.
First Line of Drugs (FLD)			
Isoni Isoniazid	Hydrazide	Inhibition of mycolic acid synthesis.	[8–10]
pyrazinamide	Amide	Releases of pyrazinoic acid, which causes intake of proton and dysfunction of the ph. balance of mycobacteria, also target the ribosomal protein SI, I.E help in trans translation.	
Ethambutonal	Ethylenediamine	Targeting the polymerization of arabinogalactans & lipoarabinomannans inhibits the mycobacterial RNA synthesis by binding to β subunits of the DNA – dependent polymerase.	
Streptomycin	Aminoglycoside	Inhibits protein synthesis by interact with 30s subunits.	
Second Line of Drugs (SLD)			[11,12]
Kanamycin (1957)	Aminoglycoside	Targets the small subunits 30s ribosome.	
Amikacin	Aminoglycoside	Targets the small subunits 30s ribosome.	[13–15]
Capreomycin	Poly peptide	Targets the small subunits 30s ribosome.	
Cycloserine	Oxazolidinone	Trigger's peptidoglycan synthesis through D- alanine ligase Inhibition.	
Ciprofloxacin	Fluroquinolone	Targets DNA gyrase.	
Ofloxacin	Fluroquinolone	Targets DNA gyrase.	
Levofloxacin	Fluroquinolone	Targets DNA gyrase.	
Ethionamide & prothionamide	Thioamide	Target mycolic acids biosynthesis through the inhibition of INGA.	
Capreomycin	Polypeptide	Targets the small subunit 30s of ribosome.	
Cycloserine	Oxazolidinone	Trigger's peptidoglycan synthesis through D alanine racemase & D alanine ligase inhibition.	

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noxious effect in patient body which develop post TB sequelae in the treatment or after the treatment.

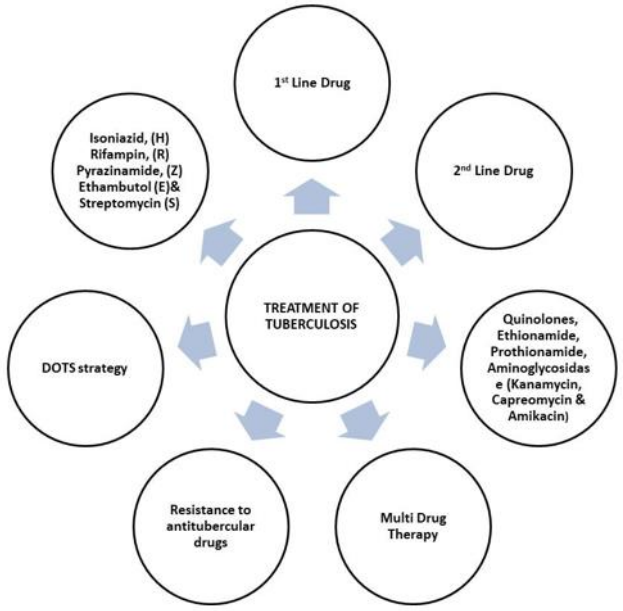

Fig. 1. Graphical representation shows the treatment and drugs used for tuberculosis

3. Adverse Effect First Lines of Drugs of Tuberculosis

A. Pyrazinamide and its Adverse Effect

It inhibits CYP45058 activity and NAD 59 LEVELS are altered in associated with free radical species mediated hepatotoxicity bridging necrosis, lymphocyte infiltration, focal cholestasis, gout and arthralgia, nausea and reduced appétit, Flushing, Photosensitivity is common; drug-induced liver injury Cutaneous hypersensitivity is serious issue [16].

B. Isoniazid and Its Adverse Effect

It metabolizes in liver through two main pathways, in liver acetyl hydrazine is toxic metabolite formed along amidase pathway. isoniazid, the metabolism is very much dependent upon the patient's N-acetyltransferase 2 gene (NAT2) genotype. In patients with a slow acetylator phenotype, there is an accumulation of parent drug and also the potentially toxic metabolite mono-acetyl hydrazine [17], [18]. Slow acetylators develop hepatotoxicity more often than rapid acetylators when receiving normal dose. Peripheral neuropathy, Drug-induced liver injury Cutaneous hypersensitivity, Drug-induced lupus, Seizures and encephalopathy Hemolytic anemia and thrombocytopenia is due to serious effect of isoniazid [19], [20].

C. Rifampicin and its Adverse Effect

It inhibits the major bile salt exposure pump, impending secretion on of conjugated bilirubin at canalicular levels. It also causes heptocellar changes such as centrilobular necrosis, associated with cholestasis, drug-induced vasculitis and hemolytic anemia, Nephrotoxicity, Discoloration of body fluids [21]–[23].

D. Ethambutol and its Adverse Effect

It causes nausea, Arthralgia and elevated uric acid Optic neuritis, drug-induced liver injury (rare), Cutaneous hypersensitivity (rare).

4. Adverse Effects of Second Line of Drugs

A. Adverse Effects of Fluoroquinolones

1) Gastrointestinal adverse effect

Common adverse effects are nausea, anorexia, diarrhea, vomiting and abdominal pain mostly seen in 3-17% adults. Clostridium difficile associated diarrhea also seen in many cases.

2) CNS adverse effects

It seen in 9-11% of adults treated with fluoroquinolones. insomnia, dizziness, headaches, confusion, somnolence, muscle jerks are most common effects whereas delirium, psychosis & seizures is more serious effects. most of fluoroquinolones cause inhibition of GABA or activation of NMDA receptors, sleep disturbances and seizures occur due to ofloxacin, levofloxacin; that related to drugs interaction with NSAIDS, antidepressants, theophylline, and metoclopramide [24]–[26].

3) QT Interval adverse effect

Fluoroquinolones are known to cause prolongation of the QT interval in a dose dependent manner by inhibition of potassium channels coded by HERG gene, effect of fluoroquinolones on QT interval is risk factors for female sex, familial long QT syndrome, heart disease, renal & liver dysfunction, electrolyte abnormalities [27]. Fluoroquinolones induced damage to the curtilage of weight bearing joints also magnesium chelation levofloxacin causes musculoskeletal disorders, fluoroquinolones associated arthropathy has due to receiving ofloxacin & moxifloxacin for treatment of TB [28]–[30].

4) Other rare adverse effects

Stevens- Johnson syndrome & toxic epidermal necrosis & dysglycemia also seen in the 1 % patient due to levofloxacin & of loxacin.

B. Amino glycosidase and it's Adverse Effect

1) Ototoxicity

The injectable antituberculosis medication enters in the cochlear hair cells through a membrane channel .this channel trapped injectable medication in the hair cell, here these are not metabolized .That generating reactive oxygen species by complex with iron (Fe) along with direct interaction between the injectable medications & hair cell mitochondrial rRNA, this results in disruption of mitochondrial integrity which ultimately results in apoptotic cell death that causes 6 genetic mutations in mitochondrial gene encoding 126 rRNA that confers increase risk of cytotoxicity [31]. A patient with cystic fibrosis treated with aminoglycosides showed hearing loss in 7 of 38 (18%) this was associated with drugs concentration [32].

2) Vestibulotoxicity

Vestibular cell located in inner ear & composed of the utricle & saccule which deficit linear movement & semicircular canals which detect rotational movement, is responsible for balance & spatial orientation, the drug's effects the hair cell of vestibular systems [33].

3) Nephrotoxicity

The injectables elicit renal injury primarily by causing renal tubular dysfunction. The injectable enter renal tubular cells after glomerular filtration accumulates there that causes renal tubular cell death via apoptosis or necrosis (unspecified mechanisms). In addition to tubular dysfunction, the injectables have showed to induce altered glomerular filtration & reduced renal blood flow. Tubular dysfunction causes mild wasting of glucose, protein & electrolytes. It seen NEPHROTOXICITY occur in 15 % of adults who receiving twice daily therapy [34], [35].

4) Electrolytes abnormalities

Capreomycin causes high risk of electrolytes abnormalities. It causes the hypokalemia; hypomagnesemia & hypercalcemia are well adverse effects of renal electrolytes specially loss of Mg & K+. The abnormalities also included cumulative dose, low body weight and Choice of injectable. Capreomycin attributed hypokalemia was responsible for one death in cohort of south Africa XRD- TV patients [36]–[38].

C. Ethionamide and Prothionamide Adverse Effects

1) Hypothyroidism

Ethionamide, is structurally similar to methimazole, inhibit organification of iodine & possibly blocks uptake of iodine; a high risk of hypothyroidism was found to be associated with ethionamide/prothionamide & PAS co-treatment and with HIV in a paediatrics cohort. It is a common adverse effect of both ethionamide & prothionamide. In 26 % of the patients, gastrointestinal intolerance was sufficiently serious to switched to suppository form of ethionamide. It causes the diarrhea mostly found in children [39]–[41].

2) Other rare adverse effects

Hepatitis, pellagra like rash, CNS effects, gynecomastia & hypoglycemia also associated with ethionamide or protionamide.

D. Cycloserine & Terizidone

Cycloserin is known to cause CNS adverse effects, reported in 20-30 % of patients it includes dizziness, headache, insomnia, lethargy, slurred speech, anxiety. 6 of 182 children treated for MDR - TB had adverse effects related to Cycloserin use blurred vision, hallucinations, depression [42].

E. Para-Aminosalicyclic Acid (PAS)

1) Hypersensitivity reactions

PAS causes fever, rash also formed exfoliative dermatitis. It mostly seen in adults and children.

2) Hypothyroidism

Due to discontinuation of PAS GOITER was found; hypothyroidism due to blocking of organification of iodine in the thyroid gland. The combinations of PAS & ethionamide were increase the risk of hypothyroidism, mostly children having these symptoms [41].

3) Gastrointestinal intolerance

Vomiting, diarrhea, anorexia, & abdominal discomfort is common adverse effects associated with the use of PAS.

4) Rare adverse effects

Hepatotoxicity and administration of Vitamin K.

F. Linezoid and its Adverse Effects

1) Hematological toxicity

Myelosuppression is observed in pre - clinical evaluations of linezoid. It increases mild anaemia & thrombocytopenia also occurs in treated with linezoid with more than 2 weeks; prolonged treatment of MDR- MDR- TB with linezoid caused anaemia in 38.1 % & thrombocytopenia in 11.8 % [42], [43].

2) Neurotoxicity

Peripheral neuropathy due to linezoid also associated with toxic optic neuropathy, with painless, bilateral central vision loss and gradual loss of colour vision & visual activity. A higher dose of linezoid (600 mg daily) 74.5 % was reported to be associated with statistically increased risk of adverse effects such as anaemia (60 vs 2.5%), leukopenia (17.1 vs 2.0%) activity [44].

3) Other rare adverse effects

Hyperlactatemia & lactic acidosis also reported to be associated with linezoid with discontinuation of the drug reversing effects.

Table 2
Drugs, and their side effects in patients' body

Drugs	Side Effects	Side of Drug Action in Patients Body	Managements	Ref.
Fluroquinolones • Levofloxacin • Moxifloxacin	Gastrointestinal upset, hypersensitivity, dizziness, photosensitivity, headaches, tendonitis, tendon rupture, insomnia, psychosis, seizures, hepatitis, peripheral neuropathy, thrush	Fluroquinolones mostly Causes inhibition of GABA (or) activation of NMDA receptors. 14 Antacids, calcium, zinc, iron & cation decrease in serum level.	Patients can be advised to take the drugs embedded in banana reduce the dose of suspected agent If problem persists, discontinue suspected agent.	[14,15]
Bed aquiline (to be used in children)	QTc prolongation, decreased appetite, nausea, hepatitis, headache, arthralgia.	bed aquiline is metabolized by CYP 3A4, its plasma levels, therapeutic effects and toxicities are prone to modulation by concomitant administration of CYP 3A4 inhibitors and inducers.	Clinical monitoring of symptoms, specific investigations at appropriate intervals, and engagement of the patients and caregivers to report untoward effects of bed aquiline therapy are essential to ensure effective management of adverse.	[45–47]

Linezolid.	Myelosuppression, peripheral and optic neuropathy, lactic acidosis, gastrointestinal upset, serotonin syndrome.	Increases dopamine, norepinephrine. and serotine.	Initiate anticonvulsant therapy (e.g. phenytoin, valproic acid istory of previous seizure. disorder is not a contraindication to the use of agents listed here if a patient's seizures are well-controlled and/or the patient is receiving anticonvulsant therapy	[46]
Clofazimine	Hyperpigmentation, gastrointestinal symptoms, acne flare, retinopathy, ichthyosis, sunburn	It is mostly found in fatty acid as because of lipophilic in nature most predominantly in small intestine, liver, spleen. It is bound to α & β lipo protein in serum.	receptor inhibitor (omeprazole, famotidine, ranitidine) can be initiated other antacids are not to be given since they interfere with absorption of fluoroquinolones. Rarely, severe abdominal distress and acute abdomen have been reported with the use of clofazimine. In such cases, clofazimine should be suspended.	[43]
Cycloserin or Terizidone	Agitation, psychosis, depression, seizures, dizziness, headache, insomnia, slurred	Aggravates CNS side effects of INH and ethionamide/prothionamide11ethionamide/prothionamide	Contraindicated in pts with a history BW > 50 kg: 750 mg OD of epilepsy	[45]
Ethambutol	Nausea, vomiting, abdominal pain, retrobulbar neuritis, hepatotoxicity, eosinophilia, neutropenia, thrombocytopenia, myocarditis, pericarditis, hyperuricemia, hypersensitivity	It is oxidized by an aldehyde dehyderogenases to aldehyde metabolites, followed by coversion to the carboxylic acid 2,2 '-(ethylenediiamino)di –butryic acid. Antacids may decrease absorption, ethionamide may increase adverse of EMB.	The toxicity is reduced by lowering the dose of EMB or reducing the time duration of use of the drug. Baseline screen for visual acuity and colour perception, (repeated monthly); contraindicated in pts with pre-existing lesions of optic nerve; also available for injection.	[44]
Ethionamide or Prothionamide.	Peripheral neuropathy, nausea, vomiting, abdominal pain, hepatitis, hypothyroidism alopecia, hypersensitivity, gynecomastia, hypotension, mental disturbance, photosensitivity, hypoglycaemia	It is structurally similar to methimazole, inhibit organification of iodine & possibly blocks the uptake of iodine. Antacids may decrease absorption. Aggravates risk of neurotoxicity of cycloserine transient increase in INH levels.	Supplement with thyroxine Monitor clinically and undertake estimations of thyroid hormones regularly to adjust thyroxine dose, stop all therapy pending resolution of hepatitis.	[40]
para-aminosalicylic acid.	Gastrointestinal upset, hypothyroidism, hypokalemia, Hypersensitivity, hepatitis, thrombocytopenia, acidosis in patients with renal failure.	May increase drug levels of INH and may aggravate risk of ethionamide hepatotoxicity; decreases digoxin absorption.	Withhold all drugs and treat symptomatically with antihistamines/corticosteroids till the reaction subsides Eliminate other potential causes of hepatitis. Stop suspected agents for short periods of time. Should be taken with acidic food or drink to delay release of granules in patients with enal impairment(crystalluria).	[48]
Pyrazinamide	Lymphocytes infiltration, focal choletasis. bridging necrosis, hepatotoxicity	Lymphocytes infiltration, focal choletasis. bridging necrosis, hepatotoxicity. It inhibits CYP45058 activity & NAD59 levels associated with free radical.	It is managed by using proper dose of pyrazinamide.	[3]
Clarithromycin.	Gastrointestinal discomfort.	Clarithromycin is a substrate and inhibitor of CYP 3A-4. Inhibitors of CYP 3A-4 may increase clarithromycin serum levels while inducers of CYP 3A-4 may decrease the serum levels.	Rash typically appears after the first week of treatment; avoid in the setting of infectious mononucleosis Azithromycin has a better tissue penetration than clarithromycin and is better tolerated but clinical data are lacking on its efficacy in the treatment of tuberculosis	[2]
Thioacetazone	Hypersensitivity; GI intolerance; vertigo; hepatitis	Possible aggravation of aminoglycoside -induced ototoxicity	Should be avoided in HIV+ individuals because of increased risk of Stevens–Johnson Syndrome.	[5]

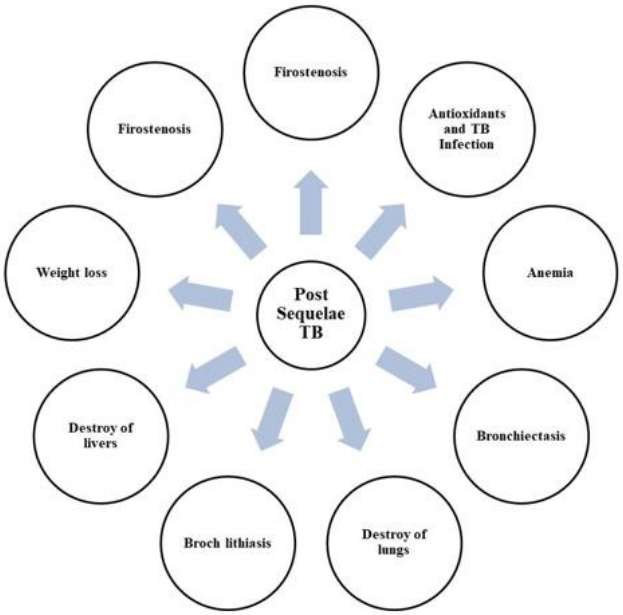

Fig. 2. Post sequelae of TB infection

5. Management of Adverse Drug Resistance

Active TB drug safety monitoring and management (ADSM) has been introduced by WHO to provide active surveillance, for detection of major (or) server ADR'S associated with novel DR-TB regimens [49]. kidney disease, chronic liver diseases, lungs, bronchiectasis are managed by surgery also. When drug-susceptible DST does not match with the patients' clinical progress underlying DR or malabsorption can be responsible, and further investigations like therapeutic drug monitoring (TDM) might be necessary [48], [50].

6. Conclusion

The major challenge faced by patients treated with 2nd line drugs is the toxic nature of these due to long duration of treatment [47]. 6Management of MDR/XDR TB is critical due to 2nd line drugs impact and consequences of the drugs impact in the patients as the results of post TB sequelae also TB infected person suffering in chronic kidney, liver, diseases as well as malnutrition, lung diseases, imbalance of cytochrome c enzyme [49]–[51]. Psychosocial support is an important component of management of Adverse effect. Although the safety tolerability & management of the Adverse effects of both FLD & SLD used in treatment of TB is very important.

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