Review Article

Adverse Drug Reactions in Drug-Resistant Tuberculosis Management: A Clinical Approach

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ABSTRACT

Tuberculosis is a contagious disease caused by *Mycobacterium tuberculosis*, leading to increased mortality and morbidity. Although many new diagnostic tests and treatments have emerged for TB, there is still a big question as to why it is not ending. The disease roots easily due to many confounding factors such as patient noncompliance, development of ADR during treatment and the evolution of drug resistance, etc. The drugs used in treatment have a higher proportion of side effects; hence, the incidence of ADR also escalates due to polypharmacy, extended duration of treatment and the dose used. For identification and prevention, close monitoring should be done. ATT induced adverse effects are a leading cause of death and the reason for prolonged treatment, thus, this may result in noncompliance and treatment failure. The aim was to address the clinical approach of ADR caused by the anti-tubercular drug. The most common ADR reported were gastritis, hepatitis, hypersensitivity reactions and the major causative agent is pyrazinamide. Majority of patients required treatment modification due to ADRs. Sometimes the ADR developed is unnotified and can lead to a serious reaction. If the ADR is properly monitored and reported, it may minimize morbidity and better therapeutic outcomes can be achieved. More than 20% of patients developing negative outcomes due to ADR and about 15-18% of patient's therapy were stopped due to ADR. Proper identification, reporting, management, or prevention can increase compliance and positive outcomes of therapy.

Key words: Tuberculosis, Drug-resistant Tuberculosis, ADR Management, Tuberculosis drugs, Tuberculosis treatment.

INTRODUCTION

Tuberculosis (TB) is brought about by a bacterium called *Mycobacterium tuberculosis* and these microbes normally affect the lungs along with other parts of the body, for example, the kidney, lymph nodes, spine, cervix, etc. Not every person has any symptoms, therefore, two TB-related conditions exist: dormant latent TB infection (LTBI) and TB illness.[1] If TB is not managed properly it can be fatal and becomes a challenge for clinicians and health care workers due to its high rate of incidence and variability. One of the most shocking things is drug-resistant (DR) TB, which is defined as resistance to at least isoniazid (H) or rifampicin (R)**.**[2] There, are mono, Multi and extensive drug-resistant (XDR) TB. From a microbiological point of view, resistance is caused by a genetic change that makes medication inadequate against the bacilli. The treatment of DR-TB is challenging because of the duration and adverse effects of drugs used for treatment. These can lead to a high rate of mortality and morbidity and can be prevented by following proper guidelines. DR-TB management is under Programmatic management of drug-resistant tuberculosis (PMDT). The proper management of ADR can be effective in reducing the rate of mortality and morbidity and thereby increases the positive treatment outcome.

The occurrence of ADR events may lead to discontinuation or interruption of therapy before completion of the course, which can lead to preventable morbidity, further resistance, failure of treatment, reduction in quality of life, etc. In TB, the duration of course, dose and number of tablets are

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high; therefore, it is very important to monitor adverse events routinely or periodically. Not only serious one but also some minor ones are to be identified, report and should take further steps to curb the reaction. Many patients apart from TB will be exhibiting different comorbidities, especially HIV/AIDS, kidney disease, liver disease and hearing problems, etc which further requires a managemental procedure as they may develop a variety of reactions.[3]

The severity and complexity of ADR depend upon administration (dose, frequency, duration) and individual characteristics of the patient (Genetics, Nutrition).[4,5] The probability of ADR occurrence is high in patients who have been previously treated or exposed to anti-TB medicine. This will lead to losing confidence in the program and generation of unwanted fake news leading to mission failure to end communicable disease TB. Not only these, but it will also lead to an increase in spread among the community. Making it difficult to calculate the efficacy and safety or the benefit of the program with the ADR having a prominent place. In 2012 WHO introduced the pharmacovigilance program in tuberculosis care, following which India joined hands with the pharmacovigilance program to minimize and record the ADR during the treatment.

DR-TB is fatal or deadly but can be treated and cured using drugs, which may be harmful to patients in many ways. Thus, this review mainly focuses on how the patient's quality of life or safety can be increased along with the epidemiology of ADR.

ADVERSE REACTIONS TO DRUG RESISTANT TUBERCULOSIS TREATMENT

Every patient who is enrolled in DR-TB management has at least one ADR during treatment, which was unnotified or unreported as many of them have minor ADR or some ADRs in low frequency were ignored. Thus, the experience and knowledge of ADR are required to identify ADR and provide proper care to the patient. Rabahi *et al.* 2017 said the most frequent ADR in the DS-TB regimen is urine color change, gastric problems, Skin reactions, jaundice and joint pain. These are only with four drugs H, R, Pyrazinamide (Z) and Ethambutol (E).[6] Zhang *et al.* 2017 observed that arthralgia, gastrointestinal disorders, hypothyroidism (9%) were the most frequent or predominant ADR in DR-TB treatment.[7] From different studies, the most common or relevant ADR of DR-TB therapy are alopecia, amylase and/or lipase elevation, anaphylaxis, arthralgia AST and/or ALT elevations cardiac muscle abnormalities like myalgia, cardiac rhythm disturbances, depression, diarrhea, dysglycaemia and hyperglycemia, hyperuricemia, electrolyte disturbances (hypokalaemia, hypomagnesemia), flatulence, gastritis and abdominal pain, giddiness, gynecomastia, hematological abnormalities, headache, hearing loss, hepatitis, hypothyroidism, lactic acidosis, metallic taste, nausea and vomiting, nephrotoxicity, optic neuritis, peripheral neuropathy, psychotic symptoms, QT prolongation, rash, seizures, suicidal ideation, superficial fungal infection and thrush, tendonitis and tendon rupture, vestibular toxicity (tinnitus and dizziness) etc[8-10] (Table 1).

As per the guidelines, several lab parameters should be checked during the therapy and that too at a particular interval to rule out safety. The ADR details and occurrence rate should be informed to the patient before the treatment to avoid further confusion or complexity. The basic management is based on the severity of ADR, if it is minor or mild drug therapy, the treatment can be continued with the help of a supportive drug if needed. Another option is the reduction of dose in some cases because almost all ADRs are dose-dependent or stop the drug and substitute with another drug. Mental support has a high impact on the management of ADR, hence may adopt various tools like patient counselling, education of family members, family support, health care support, etc. to make patient mentally stable.

All ADR should be properly identified, managed, reported and should perform causality assessment as directed by the pharmacovigilance program for TB care, which was initiated by WHO in 2012.[11]

The stopping of drugs due to adverse drug reactions were reported in above 20% of the patients hence, it becomes necessary to discuss how each ADR can be managed and what drugs can cause the particular ADR.[12]

ALOPECIA

Alopecia is very common with presence in a high number of patients, due to its long duration of treatment. Usually, drug-induced alopecia is a diffusing non-scaring type and many of the patients are not aware or are not able to identify alopecia where the hair loss is very low.[13,14] The main causative agent is isoniazid, Eto (Ethionamide), Pto(Prothionamide), where the loss of hair is temporarily seen during the introduction of therapy and the loss of hair will not progress during treatment. Sometimes rather than loss of hair, it is been observed that there is hair thinning. In all circumstances of alopecia, the patient should be encouraged to tolerate the reaction for a better outcome. There were no reported cases regarding the significant cosmetic change. The drugs usually will inhibit cell division or lead to the death of hair matrix cells, which

Table 1: Major adverse drug reactions and causative agents.

ADR	Causative agent
Alopecia	Isoniazid, Ethionamide, Prothionamide
Arthralgia	Pyrazinamide, Fluoroquinolones, Bedaquiline, Ethambutol
Depression	Cycloserine, Fluoroquinolones, Isoniazid, Ethionamide, Prothionamide
Diarrhea/ Flatulence	Para amino salicylic acid, Ethionamide, Prothionamide, Fluoroquinolones, Amoxicillin/ Clavulanic acid, Clarithromycin
Dysglycaemia and hyperglycemia	Ethionamide, Prothionamide, Gatifloxacin, Isoniazid, Rifampicin
Electrolyte imbalance	Capreomycin, Kanamycin, Amikacin, Streptomycin
Gastritis and Abdominal pain	Ethionamide, Prothionamide, Para amino salicylic acid, Clofazimine, Fluoroquinolones, Isoniazid, Ethambutol, Pyrazinamide
Giddiness	Kanamycin, Amikacin, Capreomycin, Ethionamide, Fluoroquinolones, Pyrazinamide
Gynaecomastia	Ethionamide, Prothionamide, Isoniazid
Hematological Abnormalities	All drugs (Linezolid, Rifampicin)
Headache	Bedaquiline, Cycloserine
Hearing loss	Streptomycin, Kanamycin, Amikacin, Capreomycin
Hepatitis	Pyrazinamide, Isoniazid, Rifampicin, Prothionamide, Ethionamide, Para amino salicylic acid, Fluoroquinolones, Bedaquiline
Hypothyroidism	Ethionamide, Prothionamide, Para amino salicylic acid
Lactic acidosis	Linezolid
Metallic taste	Ethionamide, Prothionamide, Fluoroquinolones, Ethambutol
Nausea and Vomiting	Ethionamide, Prothionamide, Para amino salicylic acid, Pyrazinamide, Ethambutol, Bedaquiline, Clofazimine, Linezolid, Amoxicillin/Clavulanic acid
Nephrotoxicity	Streptomycin, Kanamycin, Amikacin, Capreomycin, Rifampicin
Optic neuritis	Ethambutol, Linezolid, Ethionamide, Prothionamide, Clofazimine, Isoniazid, Streptomycin
Peripheral neuropathy	Cycloserine, Linezolid, Isoniazid, Streptomycin, Kanamycin, Am, Capreomycin, Fluoroquinolones, Prothionamide, Ethionamide, Ethambutol
Psychotic symptoms	Cycloserine, Isoniazid, Fluoroquinolones, Ethambutol
QT prolongation	Bedaquiline, Dlm, Fluoroquinolones, Clofazimine, Clarithromycin
Rash, allergic reaction, anaphylaxis	All drugs
Seizures	Cycloserine, Isoniazid, Fluoroquinolones
Suicidal ideation	Isoniazid, Ethionamide, Prothionamide
Superficial fungal infection and thrush	Fluoroquinolones
Tendonitis and Tendon rupture	Fluoroquinolones
Vestibular toxicity	Kanamycin, Amikacin, Capreomycin, Cycloserine, Fluoroquinolones, Isoniazid, Ethionamide, Linezolid

*Only included main causative agents under each ADR.

in turn leads to the tapering of the hair shaft and will push the hair follicles into an early resting phase.[15] The condition gets resolved, when drugs are stopped or may start supportive therapy in severe cases, which include scalp cryotherapy, minoxidil, spironolactone, finasteride and special care for hair and scalp etc. to make the patient overcome the inferiority of hair lose.[16]

ARTHRALGIA

Arthralgia is frequently observed in patients on anti-tubercular treatment especially with pyrazinamide, ethambutol, fluoroquinolone and bedaquiline. The incidence of joint pain is higher when fluoroquinolones or pyrazinamide-fluoroquinolone combination is administered when compared to pyrazinamide alone.[17] The symptoms of arthralgia like joint pain generally diminish over time even without even adopting any intervention.

Pyrazinoic acid, one of the major metabolites of PZA (pyrazinamide), inhibits the renal tubular secretion of uric acid and increase the tubular reabsorption of uric acid.[18] Whereas ethambutol reduces the renal clearance of uric acid.[19] The resulting hyperuricemia can lead to arthralgia and very rarely can develop into arthritis. Serum uric acid level may be elevated in patients on pyrazinamide but there is little clinical relevance to support the addition of anti-hyperuricemia therapy.

A total of 2% of cases are reported with arthralgia, so initiate the therapy with non-steroidal anti-inflammatory drugs (indomethacin 50mg twice daily or ibuprofen 400-800 mg three times daily). Paracetamol (500-1000mg 2-3 times daily) is also effective when given together with an anti-inflammatory drug. If the symptoms do not resolve, lower the dose, or discontinue the suspected agent without compromising the regimen.[20]

DEPRESSION

Cycloserine (Cs), Fluoroquinolones (FQs) and Eto/Pto can induce symptoms of depression which may fluctuate. History of previous depression may increase the likelihood of developing depression during treatment but is not a contraindication factor in the use of any of the anti-TB agents. If significant depression is present at the start of treatment, avoid the therapy with Cs.[21] Any underlying emotional/socio-economic issues must be assessed and evaluated along with the valuation of coexisting substance abuse.

Cycloserine induced depression may be due to the binding and modulation of N-methyl-D- Aspartate receptors (NMDAR) at the NMDAR-associated glycine site.[22] Isoniazid interferes with several metabolic processes essential for the normal functioning of the neuron.[23]

The incidence of depression was found to be 13.3% requiring psychological support for the patient and family, if needed introduce anti-depressant therapy (amitriptyline, fluoxetine) when depression is more significant. Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) should be given together and avoid patients with linezolid (Lzd) because of the risk of development of serotonin syndrome. Pyridoxine should be administered to patients receiving cycloserine (for every 250mg of Cs 50 mg of pyridoxine). Consider lowering the dose of the suspected agent (reducing the dose of Cs and Eto to 500 mg daily) or discontinuing the suspected anti-TB drug without compromising the regimen.[24]

DIARRHEA AND/ OR FLATULENCE

The offending agents that cause diarrhea are Para aminosalicylic acid (PAS), fluoroquinolones, Eto/Pto, Amx/Clv, Cl. PAS often causes diarrhea within the start of therapy and inform the patients that it usually resolves over time and motivate them to tolerate some degree of loose stools and flatulence. Diarrhea along with flatulence and cramping can cause significant difficulty for patients but very rarely the drugs may be discontinued.[8-10]

Drug-induced diarrhea results from a drug that either increase the active secretion of ions and pulling fluid into the lumen or decrease the absorption of water and electrolytes in the lumen. Serum electrolytes especially the potassium and patient's dehydration status should be monitored at all times.[25]

The incidence of the case is around 50%. For uncomplicated diarrhea (no melena and fever), loperamide per oral (PO) (4mg by mouth followed by 2 mg after each loose stool to a maximum of 10 mg/day) may be used intermittently. Adequate fluid intake should be maintained to prevent dehydration. In case of severe diarrhea (melena, severe abdominal pain, or fever), consider other causes such as acute bacterial enteritis, lactose intolerance, or pseudo-membranous colitis related to broad-spectrum antibiotics such as Levofloxacin, moxifloxacin, etc. It is also recommended not to use loperamide in severe diarrhea.[26]

DYSGLYCAEMIA

Antitubercular treatment (ATT) can initiate hypoglycemia or hyperglycemia in a patient. In some cases, even after stopping the therapy hypoglycemia continues. The drugs reportedly produced 2% of early hyperglycemia cases due to increased intestinal absorption and glucose impaired tolerance as the major reason behind this reaction. Diabetes is also quoted as a risk factor for tuberculosis and many drugs interact with anti-diabetic drugs leading to variation in glycaemic control.[27,28]

The rifampicin, isoniazid, Gatifloxacin, Eto, Pto will cause the hyperglycaemic condition. The condition can continue even after the treatment ceases. If the dysglycaemia level crosses the limit the drugs should be replaced with suitable other drugs, preferably the choice should be PAS. Diabetes or dysglycaemia should treat accordingly because glucose control is important in the treatment of TB as both the diseases are interrelated.

ELECTROLYTE IMBALANCE

Drugs like aminoglycosides, streptomycin (S) and other drugs can induce Hyponatremia, Hyperkalaemia, hypokalaemia, hypochloraemia, hyperammonaemia, hypomagnesemia, hypocalcemia considered to be the major electrolyte disturbances that occur in TB treatment.[29] As per the report, 11.4% of patient have electrolyte disturbances and 25% of cases remains unreported. Among aminoglycosides, the Capreomycin (Cm) is the most common drug that induces this imbalance, but not restricted to, as other drugs can also cause the imbalance. A better choice is to switch Cm to another aminoglycoside. The imbalances are reversible

when treatment is stopped but sometimes may need supportive therapy. The electrolyte imbalance may also be caused due to other ADRs like vomiting and diarrhea, hence treated accordingly.

At all times monitor serum potassium, magnesium, calcium, sodium frequently in patients with DR-TB treatment. In severe cases of disturbances, the patient may need hospitalization (K< 2.0mEq/L). If there are any signs or symptoms for dehydration given oral or IV fluids immediately to normalize the fluid level. In the case of marked muscle weakness, cardiac arrhythmias, or severe hypokalaemia, IV replacement of potassium will be urgently needed. In the case of hypokalaemia supplement potassium and provide empirically magnesium therapy (magnesium gluconate, 1000 mg BD), because if hypomagnesemia is not managed then syndrome of resistance to the correction of potassium occurs (recurrence of hypokalaemia). ECG should monitor in a patient with severe disturbances and withdraw drugs which bring in QT-prolongation. As we mentioned it's reversible upon discontinuation but it will take weeks or months to normalize the situation. Therefore, treatment or supplements should continue until the course of treatment or suspected drug completes and the normalization of all electrolytes takes place.[8-10]

A precautionary measure to be adopted at all times and regular monthly electrolytes monitoring should be performed, in case if imbalance has occurred, according to the severity daily or weekly measurement is recommended. Mild changes are usually asymptomatic. Oral potassium, magnesium, or calcium should be administered either two hours before or four to six hours after fluoroquinolone dose, as they can interfere with fluoroquinolone absorption. Amiloride 5 to 10 mg OD or spironolactone 25 mg OD per oral will reduce potassium and magnesium wasting due to TB drugs and will be in use in refractory patients. Encourage patients to include potassium-rich foods like grapefruit juice, tomatoes, oranges, etc. in their diet. The doses of a replacement should be calculated based on individual needs following the guidelines of WHO (Table 2).[9]

GASTRITIS AND ABDOMINAL PAIN

Abdominal pain is often associated with serious side effects such as pancreatitis, lactic acidosis and hepatitis. To confirm the cause, appropriate laboratory tests have to be performed and suspend the suspicious agents such as PAS, Eto, Pto, Cfz, FQs, H, E and Z. Gastritis is often characterized by burning sensation or discomfort, sour taste in the mouth followed by abdominal pain. If hematemesis and melena are present it indicates the threat of bleeding gastric ulcers.[30]

For gastritis, initiate medical therapy with H-2 blockers (ranitidine 150 mg twice daily) or PPIs (omeprazole 20

Table 2: Dosing of replacement therapy.[9]

Electrolyte[^]	Level	Dosing	Frequency of monitoring
Potassium	4.0 or more	None	Monthly
	3.6–4.0	None	Monthly
	3.3–3.5	40 mEq orally daily	Monthly
	2.9–3.2	60–80 mEq orally daily	Weekly
	2.7–2.8	60 mEq orally three times a day	One to two days
	2.4–2.6	80 mEq orally every eight hours	Daily
	<2.4	10 mEq/hr IV and 80 mEq orally every six to eight hours	One hour after infusion, every six hours with IV replacement
Magnesium	2.0 or more	None	Monthly
	1.5–1.9	1000 mg–1200 mg/day	Monthly
	1.0–1.4	2000 mg/day	One to seven days
	<1.0	3000 mg–6000 mg/day	Daily
Calcium (Total nonionized Ca value adjusted for low albumin)	>8.5 mg/dl	None	
	7.5–8.4	500 mg three times a day	Monthly
	7.0–7.4	1000 mg three times a day	One to two weeks
	<7.0	Consider intravenous and taper to 1000 mg three times a day	One to four days

[^]Potassium: The normal preparation of a potassium chloride infusion is 40 mEq in 200 ml of normal saline. Do not exceed an infusion rate of 20 mEq/hr (100 ml/hr). Magnesium: Quantities greater than 2000 mg are usually given by IV or intramuscular (IM). The normal preparation is magnesium sulfate 2 g in 100 ml or 4 g in 250 ml of 5% dextrose or normal saline. Do not exceed an infusion rate of 150 mg/min (2 g in 100 ml administered over one to two hours, 4 g in 250 ml administered over two to four hours). Calcium: Normal calcium is 8.5–10.3 mg/dl (2.12–2.57 mmol/l). To adjust for low albumin in nonionized values of calcium, use this formula: Corrected calcium = 0.8 × (4.0 – measured albumin) + reported calcium. If ionized calcium is being tested, it does not need to be adjusted for low albumin and normal value is 4.5–5.6 mg/dl (1.11–1.30 mmol/l).

mg once daily). In case of severe abdominal pain, stop the suspected agent for a short period (1-7 days) and avoid the use of antacids simultaneously with FQs as they interfere with the absorption of FQs.[31] Severe abdominal distress has been reported with Cfz, but the reports are rare and if it occurs, Cfz may be suspended.

GIDDINESS

The suspected agents that cause giddiness are aminoglycosides, Eto, FQs and/or Z. Initially, the patient has to be counselled, when he/she complains of giddiness, over sleepiness, or poor concentration. In severe cases, the offending drug should be identified by administering the drugs one at a time and observe the response. If the offending agent is identified, adjust its dose, or terminate the drug if required. [8-10]

GYNAECOMASTIA

Drug-induced gynecomastia varies from 20 to 25%, but the antitubercular therapy (ATT) occasionally only is been incriminated for the occurrence of this reaction. Mainly Eto and Pto cause these reactions, but several case reports are there confirming that isoniazid can also be a causative agent for gynecomastia.[32] As we know, as per the demographic profile that the number of patients is high in the male community and this reaction can be troublesome for them. In some cases, the galactorrhoea was reported, so it is recommended that in the case of tuberculosis, encourage the patients to tolerate the adverse effect until their therapy completes. Usually when the treatment has stopped the size of the breast, gets resolved to normal. In some very rare cases to rectify the issue surgery may be required. The basic mechanism behind this effect is not understood yet. Some of the proposed or identified mechanisms are inhibition of testosterone synthesis or action, enhancement of testicular production of estrogens and direct action of estrogens or like substances leading to gynaecomastia.[33]

HEMATOLOGICAL ABNORMALITIES

Includes abnormalities like anemias, leukopenia, neutropenia, Lymphopenia, thrombocytopenia, red cell aplasia, coagulation abnormalities and eosinophilia which may be diagnosed based on the hematological profile like haemoglobin, differential count, international normalised ratio, mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), packed cell volume (PCV), haemoglobin distribution rate (HDW), platelets, red blood cells and white blood cells etc. All the anti-Tb drugs will cause abnormalities mainly Lzd and R. In PTB patients without HIV the prevalence of these abnormalities is 46% and with HIV it raises to 60%.[34] Then we can imagine the rate of the same in DR-TB treatment, where a high dose and various variety of drugs are employed for treating the condition. In these abnormalities, anemia is the predominant one, along with DC variation. The differential identification of the condition is one the most important thing i.e. whether it's due to drugs or any other non-drug related one.

The main mechanism indued is directly by the drug or its metabolite involved in immune reaction.[35] The Lzd will mainly cause the myelosuppression (suppression of RBC, WBC and Platelet) that occurred by the production of antiplatelet antibodies.[36] In such a condition, the Lzd should be stopped and manage the setback by adding blood transfusion if required into the therapy. In such a patient it is recommended not to reintroduce the Lzd, but if the Lzd is of utmost importance or where it can't be excluded, then after resolving myelosuppression reintroduce the drug in a low dose (300mg). In the case of anemia, supplements may help to resolve the condition and if the situation is severe blood transfusion must be provided. Thrombocytopenia purpura is common with rifampicin, intermittent use has caused triggering of the body's immune mechanism to attack the own cells.[37] In this situation, the drug should stop immediately and should never be reintroduced along with treatment for shock, renal failure and thrombocytopenia should be implemented. All other conditions should be symptomatically managed and if the reaction is severe the drug should stop and never reintroduce again.

HEADACHE

During the initial months of DR-TB therapy, headaches are common and can present as migraine or cluster headache. The offending agents that cause headaches are Bdq and Cs and are usually self-limited.[38]

Cyclosporine reduces the cerebral blood flow by its effect on thromboxane A2 release and production of prostacyclin 9 or by its sympathetically mediated contractile effects on vascular smooth muscle to induce headaches.[39,40]

Rule out other serious causes of headaches including meningitis and other infections of CNS by reviewing a head CT scan and CSF analysis. To minimize headache, start with a low dose of Cs (250-500mg) and gradually increase the dose over 1-2 weeks to achieve the target level. Pyridoxine helps to prevent neurotoxicity in patients receiving Cs, also can initiate the management by deploying analgesics like ibuprofen or paracetamol.[40] For refractory headache, low dose tricyclic antidepressants can be used and practice good hydration.

HEARING LOSS

Hearing loss is dependent on the duration of treatment and dose of the drug. The occurrence of toxicity is by functional impairment or cellular degeneration of tissues in the inner ear. Many factors will increase the risk of the same e.g. age, dehydration and elimination inhibition by other drugs, etc. so, should consider the factors before starting with other therapy. If the treatment is continued the condition can get worsen and it can become permanent with loss of hearing leading to deafness. In cases, even if the drugs are stopped, then also the chances of progression and worsening of the condition might occur.[41] About 63% of patients who were on aminoglycosides showed the symptom of toxicity and >4% with other drugs (S).[42] Symptoms are similar to vestibular toxicity, which includes tinnitus, the ringing of ears, balance loss, deafness and orientation issues, etc.[43]

If there are any signs of hearing loss, then record an audiogram and compare it with an initial one. If any relevant change is observed then, the dose of an aminoglycoside may be varied to 2-3 times a week. Can change the therapy to Cm, if other aminoglycosides were used. After adjustment of the dose, if the hearing loss progress, stop the drug and substitute with other (Oral group 4 or Bdq/Dlm) drugs. If no substitution is available then the suspected agent can be used based on the patient's interest and only the progression may be prevented. All the patients must be evaluated for hearing tests before treatment because there will be the availability of baseline for hearing loss which can be used to compare for loss of hearing in drug-exposed patients and in particular to the elderly (High risk). This small step of appropriate monitoring of the patients will help in the future, to prevent hearing loss. In the case of mild to moderate hearing loss, hearing aids can be used if it benefits the patients. As a final option cochlear transplant can be done to relieve the patient. It is also been observed that the concomitant use of loop diuretics in renal insufficient patients can further aggravate and trigger hearing loss.[44]

HEPATITIS

Hepatitis is more frequent among patients receiving anti-tubercular treatment especially with Z, H, R, PAS, FQ, Pto/Eto and Bdq. The severity can vary from minor nonspecific changes in hepatic structure to fulminant hepatic failure, cirrhosis and liver cancer.[45] Most of the hepatotoxic reactions are dose-related and some are caused by drug hypersensitivity. The symptoms of hepatitis include nausea, vomiting, jaundice, tea-coloured urine, scleral icterus, decreased appetite and pale stool. The principal risk factors for anti-TB drug-induced hepatotoxicity include high alcohol intake, older aged, pre-existing liver disease, infections e.g., hepatitis A, B, C, D, E; cytomegalovirus, Epstein- Barr virus, yellow fever, rubella and HIV. Anti-TB drug-induced Hepatotoxicity may occur within weeks to several months.[46]

The polymorphism of N-acetyltransferase 2(NAT2) genes and glutathione-S-transferase (GST) are the major risk factors for ATT-induced hepatitis. The hepatic NAT and GST are involved in the metabolism of anti-tubercular drugs. Isoniazid is cleared mainly by the acetylation by NAT2 and the acetyl-isoniazid gets metabolized to mono-acetyl hydrazine (MAH) and finally gets transformed to nontoxic diacetyl hydrazine. The reactive metabolites of MAH are toxic to tissues through free radical generation. Rifampicin inhibits the major bile salt exporter pump and causes conjugated hyperbilirubinemia.[47]

There must be a routine screening of liver function while on therapy, especially during the first months of therapy there may be a mild transient elevation of transaminases and it usually remains asymptomatic. The diagnosis of hepatitis is confirmed by a significant elevation in serum transaminases and is usually symptomatic.

The incidence of ATT induced hepatotoxicity is reported between at a rate of 2 to 28%. If liver enzymes are greater than five times the upper limit of normal, stop all anti-TB drugs. If still, the liver enzymes continue to increase, an unrelated cause must be suspected. If the liver enzymes revert to normal and symptoms gets resolved, then restart the anti-TB drugs with the agents least likely to cause hepatotoxic (Cm or aminoglycoside, FQ and Cs).[48] Then for one week, the remaining hepatotoxic agents (PAS, R, H, Z, Eto/Pto) can be continued one at a time while checking the liver enzymes at the end of each week. In this manner, the offending agent can be identified.

HYPOTHYROIDISM

One of the known adverse effects related to anti-TB drugs is hypothyroidism. The offending drugs that cause hypothyroidism are ethionamide /protionamide and PAS. The most common symptoms associated with hypothyroidism are fatigue, somnolence, cold intolerance, voice change, dry skin, coarse hair and constipation as well as occasional depression and psychosis. In rare cases, hypothyroidism may lead to the development of cardiac disease and pericardial effusion.[49]

By inhibiting thyroid hormone synthesis through a mechanism of iodine organification inhibition, they cause

hypothyroidism.[50] Hypothyroidism can be ruled out by examining whether there is any thyroid enlargement or if there is a delayed deep tendon reflexes and diagnosis can be confirmed by evaluating the serum level of TSH (>10 IU/ml).

The incidence is around 23% and it is treatable and reversible upon discontinuation of the offending agent. When a combination of Eto/Pto with PAS is used, hypothyroidism can be common than when each drug individually is used. In most cases of treatment-induced hypothyroidism, the patient only requires replacement by means of hormone therapy without discontinuing the treatment. Initiate the hormone replacement therapy with levothyroxine 75-100 mcg daily for young adults, 50 mcg daily for older ones and in patients with significant cardiovascular disease start with 25mcg daily. TSH has to be monitored every 1-2 months and increase the dose by 12.5-25 mcg until TSH normalizes below 5 IU/ml. After treatment completion thyroid dysfunction resolves and hormone replacement can be discontinued.[10]

LACTIC ACIDOSIS

Lactic acidosis is a major ADR that can develop during the course of treatment. Many studies conducted inside and outside India states that lactic acidosis is one of the reasons for death during treatment. The drug linezolid is a major causative agent for this type of ADR. But, in some reports, the culprit drug is isoniazid, particularly when given in high dose and it rarely causes a similar condition in low dose.[51] The chance of occurrence of lactic acidosis is reported only in cases, where the drugs are been used for/ during a prolonged period of time (≥28 days).[52]

In the case of Lzd, cross-reaction with mammalian cellular process occurs which disrupts mitochondrial protein synthesis involved in the electron transport chain. But in the case of isoniazid, inhibition of metabolism of lactate (lactate to pyruvate) is occurring.[53] The incidence rate of reaction is >6.8% and can lead to death if not managed properly.[54] The diagnosis of the same can be done using a blood test for lactic acid. The management should be according to the individual patient by the following protocol. Bicarbonate should be given if the PH is less than 7.0. and the drug linezolid or suspected drug should be stopped if lactic acidosis occurs.

METALLIC TASTE

Many of the drugs used in the treatment are having a metallic taste especially Eto, Pto, FQs but in some other studies the drug E is also a major causative agent. Can't predict an exact rate of incidence rate and the patients should be encouraged by the providers to tolerate the metallic taste or properly managing the diet by including and excluding some ingredients until the treatment is completed. Also, can be advised to take sugar-free mints/ chew gum or chew ice for masking the metallic taste.[55] The reason for the metallic taste is a change in chemosensory receptors which is due to alterations in the biochemical targets, transduction pathways, enzymes and transporters by the offending medications.[56] The normal taste sensation or exact sensing of taste returns to normal when the treatment discontinues.

NAUSEA AND VOMITING

Nausea and vomiting are frequent during the early weeks of therapy especially with Eto/Pto, PAS, Z, Cfz, Lzd, Amx/Clv and Bdq. The drugs can induce nausea and vomiting through stimulation and activation of the chemoreceptor trigger zone. If vomiting is severe check for the creatinine and electrolyte level to ascertain electrolyte imbalance.[57]

The mainstay of ATT induced nausea and vomiting is anti-emetics (Domperidone) which is administered 30 min before the drug administration. A course of histamine H2-antagonists (ranitidine) or proton pump inhibitors (omeprazole) can also provide relief. In patients with significant vomiting (especially if diarrhea is present), hydration status should be assessed and give intravenous fluids if necessary. For refractory vomiting, temporarily discontinue or reduce the dose of the suspected agent. To rule out which medicine causes nausea and vomiting, give a trial stoppage of medicine for 2-3 days and then reintroduce by gradually increasing the dose. If the offending drug is Eto, it is better to administer with milk or after milk or at bedtime to avoid nausea. If severe vomiting is present, withhold the drugs temporarily and rule out other causes of vomiting like hepatitis. If hematemesis is present, the Hb level should be monitored and treated for bleeding ulcers.

For all patient's the nausea and vomiting should be treated by a three-phase approach:

First phase: Adjust the medication without lowering the overall dose.

- Administer Eto/Pto at night.
- Administer PAS two hours after other anti-TB drugs.
- If PAS is given once daily, administered in 2 divided doses.

Second phase: Administer anti-emetics

- Initiate with metoclopramide 10 mg 30 min before anti-TB drugs (maximum 15 mg twice daily). If neurological problems are present, do not use metoclopramide.
- If the symptoms do not resolve, add Ondansetron or promethazine with metoclopramide.
- Ondansetron: 8 mg twice daily 30 min before anti-TB drugs. It prolongs the QT interval and avoids in patients taking medicines that increase the QT interval (Bdq or Dlm).
- If Ondansetron is not available, promethazine 25mg 30 min before anti-TB drugs are given (maximum 50 mg 3 times daily).

Third phase: temporarily stop the drug or reduce the dose

- Consider reducing the dose of the suspected drug and if necessary, suspend the drug completely until the symptoms resolve.

If the patient is anxious about nausea caused by medications called anticipatory nausea, consider adding a short-acting benzodiazepine (diazepam 5mg) 30 min before the intake of anti-TB drugs. Once nausea resolves, stop diazepam and do not give diazepam for more than 2 weeks because it may cause tolerance.[8-10]

NEPHROTOXICITY

Many drugs are found be nephrotoxic in one or other mechanism which includes altered intraglomerular hemodynamics, tubular cell toxicity, crystal nephropathy, inflammation, rhabdomyolysis, thrombotic microangiopathy, etc.[58] Major causative agents are S, aminoglycosides, R, H and E which are associated with this type of reaction. The nephrotoxicity can be diagnosed by measuring the serum creatinine level. In being it is usually asymptomatic; therefore, it becomes very important to constantly monitor the creatinine level during the course of treatment.

Co-morbidities (History of diabetes, renal disease) are not a contraindication to use these agents but these comorbidities may increase the risk for the occurrence of renal failure. Caution must be there in such a situation. The impairment may be permanent.

Before the initiation of therapy, every patient should be evaluated for renal function. If the patient is a case of renal failure or needs dose adjustment then all TB medicines should be adjusted accordingly to the creatinine clearance and renal dosage adjustment guidelines. As per guidelines of WHO the blood urea and serum creatinine test should be done every month, up to 3 months after treatment initiation and every 3 months thereafter that until treatment completes to help monitor and identify unknown toxicity.

If any of the above-mentioned symptoms/signs emerge, the drug should withhold with frequent monitoring of creatinine and electrolyte until normal. The management should be done based on Nephrologist opinion. An exact evaluation should be done in order to confirm whether it is due to drug or not, because of contributing factors inducing similar effect like diabetes, NSAIDs and other medicines, dehydration, CHF, urinary obstruction, UTI and prostate hypertrophy thereby to make a conclusive decision on discontinuation of the drug.[59] If the renal function stabilizes or improves, resume the drug or switching to another drug belonging to the same category (Cm can be used if any other drug of the same class is previously been used) with the change in dosing (3 times weekly). Substitution is another way out and only restart the drug if it is unavoidable in the regimen along with close monitoring. If again the levels are rising with 2-3 times weekly then suspend the drugs and adjust according to creatinine clearance. The Risk of toxicity can be reduced by promoting fluids, avoiding other nephrotoxic drugs and other correctable risk factors.[60]

OPTIC NEURITIS

The occurrence of optic neuritis or vision problem is rare. The reaction is a toxic type that can damage the entire vision. The sign is a loss of red-green colour distinction due to mitochondrial dysfunction, disruption of blood flow to the optic nerve and other unknown mechanism involved in it. Manly decreased vision in center field (bilateral/unilateral), swelling of the optic nerve, visual field defects were major symptoms. The occurrence is slow and painless thus may be unnoticed initially.[61,62]

E, Lzd, Eto, Pto, Cfz, H, S can cause optic neuritis. If a reaction occurs the drugs should be stopped permanently, especially E and Lzd because they are having a high risk of causing the reaction. The patient should be thoroughly evaluated by an ophthalmologist and the distinction problem will be rectified once the drugs have been stopped. If the patient is diabetic, control the glycaemic level because it can affect or trigger a similar reaction. Studies conducted in India, recorded that only 0.6 to 3% of susceptible cases.[63-65] But Garg *et al.* has reported a loss of visual acuity in 9.4% of patient's eyes, visual field defects in 6.3%, optic disc abnormalities in 4.7% and colour vision abnormalities in 12.3%.[66]

PERIPHERAL NEUROPATHY

Peripheral neuropathy refers to the damage of nerves that carries messages to and from the brain and spinal cord to the rest of the body or vice versa. This occurs with numerous anti-tubercular drugs but is most common with Cs, Lzd, H and rarely with Eto/Pto, FQs, aminoglycosides, Cfz, Bdq and E. Linezolid can induce peripheral neuropathy after prolonged use which is extremely painful and usually non-reversible.[67]

They tend to present with loss of vibration and proprioception and usually localized to the feet and/or the hands which is described as a classic "stocking and glove" distribution. Development of sensory symptoms (e.g., numbness, tingling, burning, pain, loss of temperature sensation, difficulty in walking, weakness and decreased or absent tendon reflexes) precedes the development of any muscular or proprioceptive symptoms, but sometimes the patient may complain of tripping or losing their balance.

The action of anti-TB drugs against *Mycobacterium tuberculosis* leads to the depletion of pyridoxine which is toxic to the nerve. Isoniazid form a complex with hydrazine, which thereby gets excreted in the urine, results in a relative deficiency of biologically active pyridoxine. Due to the disruption of mitochondrial function in neurons, LZD causes peripheral neuropathy and the diagnosis is based on clinical assessment.

In specialized TB centres, the objective quantitative assessment such as electromyography (EMG), nerve conduction studies (NCS), quantitative sensory test (QST) may be available at high cost only or may not be readily accessible, so diagnosis is based on clinical assessment. For the diagnosis of peripheral neuropathy in patients with TB, one of the scales known as Subjective Peripheral Neuropathy Score may also be used, to assess the condition of the patient. Where the patients are asked about a set of symptoms and asked to rate them on a scale of 1-10 if present, based on the score the severity of PN may be determined by calculating the overall score.[10]

In the general population, the incidence is around 1.1% but, in the elderly, it is 6% and in order to prevent the occurrence of peripheral neuropathy, all patients should receive pyridoxine daily. The usual dose of pyridoxine for prophylaxis in all patients receiving Cs and Lzd is 50mg daily (for every 250 mg of Cs) and 10 mg in patients receiving H who are at risk of peripheral neuropathy. Pyridoxine is only effective when given alone rather than as part of vitamin B complex therapy. For treatment, pyridoxine 100-200 mg daily is given until the symptoms resolve. The most common offending agent is Lzd and about 60-70% of patients on Lzd with 600 mg/day dose may develop PN and pyridoxine does not help in preventing Lzd induced PN. Thus, should consider stopping H, if at all used and if possible, switch the aminoglycoside to Cm. Without compromising the regimen, reduce the dose of Cs. Consider other contributing causes such as diabetes or malnutrition and consider physical therapy which may be of benefit to the patient.[9]

Initiate medical therapy with NSAIDs and Paracetamol. If the symptoms do not resolve, start with amitriptyline 25 mg at bedtime for one week, then 50mg HS in the next week and increase up to a maximum of 150 mg/day. SSRIs and antidepressant drugs of TCIs are not recommended. Carbamazepine can also be used in severe cases starting with 200 mg once daily for one week, then 200mg BD for one week and then 200 mg three times a day. The medication may be discontinued only if an alternative drug is available and the regimen is not compromised.[68]

PSYCHOTIC SYMPTOMS

Drugs such as isoniazid, cycloserine, ethambutol and fluoroquinolones can cause psychosis. Ethambutol induced psychosis is rare. The symptoms are visual or auditory hallucinations, delusions, paranoia and bizarre thoughts. For early detection, caregivers should be familiar with these symptoms.

The possible mechanism for cycloserine induced psychosis is the modulation of N-methyl-D-aspartate receptor (NMDAR) antagonists and partial agonism by the drug at NMDAR associated glycine site.[69] Isoniazid causes vitamin B6 deficiency which leads to disturbance of normal tryptophan metabolism. It also inhibits the activity of pyridoxal-5-phosphate which leads to the depletion of GABA and other synaptic transmitters resulting in psychotic symptoms.[23] The exact mechanism of ethambutol induced psychosis is currently unknown.

The incidence of psychosis is about 12% and the previous history of psychiatric disease is not a contraindication to the use of the above agents, but its use may increase the likelihood of developing psychotic symptoms during treatment. Psychosis occurs most commonly with Cycloserine and if the patient shows suicidal ideation, keep the patient under 24-hr surveillance, discontinue Cs and initiate antidepressant therapy. Reduce the dose of Eto/Pto to 500mg daily until the patient is stable. If no improvement occurs after holding Cs, hold H and or

Eto/Pto. For acute psychosis, stop Cycloserine for a short period (1-4 weeks) and once the symptom resolves, Cs may be resumed usually at a lower dose. Some patients may require other agents, who are not able to tolerate the re-initiation of Cs. Initiate antipsychotic therapy with haloperidol, if moderate to severe symptoms persist. Some patients will need to continue antipsychotic therapy throughout the treatment period if Cs is continued. In such patients, antipsychotic therapy may be tapered slowly and discontinued upon completion of anti-TB therapy. Always check the creatinine level of the patient on Cs and a decrease in renal function can result in toxic levels of Cs, which can cause psychosis. Pyridoxine should be administered to a maximum daily dose of 200 mg to prevent neurological manifestations.

QT PROLONGATION

The mechanism of QT prolongation is blockage of the inward potassium rectifier channel.[70] The incidence or prevalence rate of drug-induced QT prolongation is not known but more than 3% of non-cardiac patients developed QT prolongation as per one of the studies. Bdq, Dlm, FQs, Clarithromycin, Cfz and some supportive drugs like Ondansetron are the major causative agents. This will cause QT prolongation and lead to torsade de pointes, arrhythmias and sudden death. If QTc value is found to be >500ms, stop all suspecting drugs and confirm the QT prolongation by ECG. Maintain serum electrolytes to the normal range in elevated condition. Ensure that no other drugs have a QT-prolonging effect which is given as supportive therapy, if yes stop it and analyse the condition of renal and hepatic function. Should adjust the dose of FQs if any impairment occurs. Among FQs, Mfx and Gfx cause the greatest risk and others have less risk. Before treatment, the ECG should be monitored and if any QT prolongation drugs are giving for the first 4 weeks, the ECG should be monitored on monthly basis. Many psychotic, prokinetics, 5-HT3 receptor antagonists, antifungals, etc. will cause and trigger the reaction therefore try to avoid the combination of these drugs. Grade 1 and 2 are asymptomatic which do not need any treatment and can continue the drug with caution. Grade 3 and 4 are recurrent, persistent and arrhythmic which need hospitalization. Every ECG elevation should be double-checked. Also, rule out other causes of reaction and treat them accordingly.

RASH, ALLERGIC REACTION AND ANAPHYLAXIS

Hypersensitivity reactions can occur with any of the anti-tubercular drugs. The most common agents that can cause allergic reactions are isoniazid (H), rifampicin (R) and pyrazinamide (Z). The incidence rate of reaction is 4 – 6%. Hypersensitivity reactions are often characterized by an allergic reaction like pruritus, flu-like syndrome, angioedema, urticaria, shock and shortness of breath.

The mechanism underlying is antibody-mediated immune reactions or type B reaction, which is dose-dependent and can occur at any time during treatment. The allergic reaction associated with INH and R is due to its metabolites (monoacetyl hydrazine and desacetyl rifampicin).[71]

The incidence of these reactions is 61.5% and is usually managed by deploying antihistamines. In mild cases, it may be managed symptomatically. But in serious allergic reactions, firstly rule out any other potential causes not related to drugs. If there is no obvious cause, all therapies will be stopped and an antihistamine is given up to 3-4 times daily. Once the reaction resolves, the remaining drugs will be reintroduced as a "challenge" one at a time to check which drug causes the ADR and permanently may suspend the causative agent.[72] If the rash is more severe, start with $1/10^{th}$ of the original dose and slowly increase the dose. The most likely culprit is to be added last in the challenge and if the agent is not essential, there is no need of re-introducing the drug as a challenge. The order of reintroduction is H, R, Z, Eto, FQ, Cs, E, PAS and Cm. In case of anaphylactic reactions, manage with standard emergency protocols including the use of epinephrine. In case of severe generalized rash, a parenteral corticosteroid (dexamethasone IM or IV 2-4mg 4 times daily) may be administered. Flushing reaction to R or Z is usually mild and resolves with time. Minor dermatological reactions are managed with hydrocortisone cream for localized rash, prednisone in a low dose of 10-20 mg/day for several weeks may also be given. Clofazimine can cause dry skin and in this case, moisturizing lotion is recommended. Avoid tyramine containing foods (cheese, red wine) that can precipitate hot flushes, itching. Any drug which results in Steve-Johnson syndrome should never be reintroduced, not even as a challenge. The challenging dose of TB drugs is mentioned in Table 3.

If any dose, which was used as a test and cause any reaction, then discontinue the drug if it is not essential to the regimen. Can continue by desensitization in case of essential drugs and these should take place under health care setting to obtain fast response towards any reactions.

SEIZURES

The offending agents associated with seizure are Cs, H, FQs while other causes are epilepsy, meningitis, encephalitis, alcohol withdrawal, hypoglycemia, malignancy. During

Table 3: Dose of Rechallenging.[10]

Drug	Day 1	Day 2	Day 3
H	50 mg	Full dose	
R	75 mg	300 mg	
Z	250 mg	1000 mg	
Eto/Pto	125 mg	250 mg	
FQ	50 mg	200-250 mg	Full dose
Cs	125 mg	250 mg	
E	100 mg	500 mg	
PAS	1 g	4 g	
Cm, Am, Km	125 mg	500 mg	

ATT induced seizure, the patient may fall, make jerking movements, choke, or vomit.

INH metabolites inhibit pyridoxine phosphokinase (convert pyridoxine to pyridoxal 5 phosphate) and result in decreased pyridoxal-5-phosphate levels and decreased GABA synthesis, which is the major inhibitory neurotransmitter in CNS as well as increased glutamate levels (a primary excitatory neurotransmitter). The functional depletion of pyridoxine can cause seizures.[73] Check the serum electrolyte levels (sodium, potassium, magnesium, chloride and bicarbonate).

If the patient has experienced the seizure for the first time, hold the suspected agents and initiate anticonvulsant therapy (carbamazepine, phenytoin or valproic acid are most commonly used) and are generally continued until DR-TB treatment is completed. When the seizure has resolved, reintroduce the above agents one at a time. Cs can be restarted only if it is essential to the regimen. If it is reinitiated, start with a lower dose. However, if an alternative is available, do not start Cs. Drug-drug interaction between anti-seizure drugs and anti-TB drugs (especially H and R) can result in sub-therapeutic levels of anti-seizure drugs. History of previous seizure disorder is not an absolute contraindication to the use of suspected agents but they should be controlled with anti-epileptics before starting TB treatment. Check the creatinine level in patients taking Cs. A decrease in renal function results in toxic levels of Cs, which can cause seizures. Pyridoxine has to be administered to a maximum daily dose of 200 mg to prevent neurological manifestations.

SUPERFICIAL FUNGAL INFECTION AND THRUSH

Antibiotics used to treat TB especially FQs will kill all bacteria harmful and beneficial which will lead to yeast infections or other fungal infections.[74] The prevalence is increasing nowadays and it is probably mostly seen, in aged people and those with HIV or immune comprised individuals.[75]

The infection can develop in vaginal, penile, skinfold, mouth areas, throat. Itching, irritation, redness, burning sensation are major symptoms of the reaction.[76] Proper identification and treatment involving topical antifungals or a short course of oral antifungals can be employed as management therapy.

TENDONITIS AND TENDON RUPTURE

Tendonitis is not common, but still, 2% of the patients have this problem. But the tendon rupture is rare and the tendon rate is high in elderly, diabetic patients and those who are doing new physical activities. FQs are the major cause of tendinitis and tendon rupture. When significant inflammation of tendons or sheaths occur, it can be managed by giving NSAIDs, especially ibuprofen 400 mg four times daily or Naproxen and in some cases, the stoppage of drugs can be considered.[77] The tendonitis will resolve once the drug is stopped.[78]

If the treatment is not possible (Failure, Resistance, other reasons) without the particular agents then the dose should be reduced and if possible, the joint must be strictly under rest. The patient should be informed of the same and later provide Symptomatic treatment.

VESTIBULAR TOXICITY

The exact mechanism of toxicity is unknown but the drugs can damage the inner ear especially the vestibular area. The vestibular toxicity includes tinnitus and dizziness.

More than 33% of patients have reported with vestibular toxicity by aminoglycosides and >5% by other drugs.[79] Those who had previous exposure to the same drugs have a high risk of toxicity and the elderly population are more prone to vestibular toxicity. The suspected drugs are S, aminoglycosides, Cs, FQs, H Eto, Pto, Lzd. The early symptoms that can help to identify the toxicity are fullness in the ear and intermittent ringing. If these symptoms are reported then change the dosing interval of the drugs especially injectables to 2-3 times a week. Cm is suggestible over other aminoglycosides if they have previous exposure. Also, evaluate whether the condition is progressing or not, with comparison to the effects, if not resolved. Even after dose adjustment, if the condition is progressing then stop the drug to get rid of symptoms and to prevent permanent damage. Every time the injectables will be suspected first, other drugs should be withdrawn, if injectables are not the reason for toxicity and after observation of the improvement in symptoms the drugs may be added back one by one to find out the culprit drug, which has triggered the toxicity. Meclizine,

Table 4: Basic management of ADR.

ADR	Management
Alopecia	Encourage to tolerate; Resolved when treatment stopped; if needed supportive therapy- scalp cryotherapy, drugs, scalp care
Arthralgia	Lower the dose or discontinue the suspected agent
Depression	Psychological support and antidepressant therapy
Diarrhea/ Flatulence	Encourage fluid intake; withhold the therapy
Dysglycaemia and hyperglycemia	Replace the drug; treat the condition accordingly
Electrolyte imbalance	Withhold; supportive therapy
Gastritis and Abdominal pain	Withheld
Giddiness	Identify the offending agent and lower the dose or discontinue.
Gynaecomastia	Encourage to tolerate; Resolved when treatment stopped.
Haematological Abnormalities	Stop drug in severe cases; No reintroduction; Supportive therapy
Headache	Encourage good hydration
Hearing loss	Withheld/adjust/stop accordingly; substitution; hearing aid, surgery
Hepatitis	Stop the drugs
Hypothyroidism	Hormone replacement therapy
Lactic acidosis	Stop the drug; According to lactic acidosis protocol and individual patient provide therapy. Bicarbonate administration
Metallic taste	Encourage to tolerate; Resolved when treatment stopped.
Nausea and Vomiting	Encourage fluid intake; withheld
Nephrotoxicity	Withheld/adjust/stop accordingly; substitution
Optic neuritis	Stop the drug; Resolved when drug stops; ophthalmologist consultation
Peripheral neuropathy	Correct the vitamin deficiencies
Psychotic symptoms	Stop the suspected drug for a short period
QT prolongation	Maintain electrolytes; If QTc > 500ms stop the drug; Hospitalisation
Rash, allergic reaction, anaphylaxis	Rechallenge and dechallenge the drugs to identify the offending agent.
Seizures	Withheld
Suicidal ideation	Discontinue Cs
Superficial fungal infection and thrush	Continue with supportive therapy
Tendonitis and Tendon rupture	Stop/ Reduce dose; supportive therapy; joint rest
Vestibular toxicity	Withheld/adjust/stop accordingly

Table 5: Some of the Recommended Drugs for the ADR Management.

ADR	Suggested Drugs for Management
Alopecia	Minoxidil, Spironolactone, Finasteride
Arthralgia	NSAIDs, Codeine
Depression	SSRI (Sertraline, fluoxetine), amitriptyline
Diarrhea/ Flatulence	Loperamide, Racecadotril
Electrolyte imbalance	Electrolyte supplement- oral/IV/ diet- Amiloride, spironolactone
Gastritis and Abdominal pain	H-2 blockers, PPIs, Avoid antacids
Hematological Abnormalities	Supplements
Headache	Ibuprofen or paracetamol
Hepatitis	Supportive therapy
Hypothyroidism	Levothyroxine
Insomnia	Hypnotics
Nausea and Vomiting	Fluid intake, Domperidone, omeprazole, Ondansetron, metoclopramide, prochlorperazine, promethazine
Peripheral neuropathy	Pyridoxine(neurological prophylaxis); amitriptyline
Psychotic symptoms	Antipsychotic therapy
Rash, allergic reaction, anaphylaxis, itching, hypersensitivity	Anti-histamines, hydrocortisone cream, calamine lotions, corticosteroids
Seizures	Anticonvulsants
Severe Anxiety	Lorazepam, Diazepam, Clonazepam
Suicidal ideation	Psychiatric counselling
Superficial fungal infection and thrush	Topical/oral- Fluconazole, Clotrimazole lozenges, nystatin suspension, itraconazole liquid
Tendonitis and Tendon rupture	NSAIDs (Ibuprofen, naproxen)
Vestibular toxicity	Meclizine, dimenhydrinate, prochlorperazine, promethazine

dimenhydrinate, prochlorperazine, promethazine can be opted as the treatment. Every week or frequently the patient should be asked about unsteadiness, tinnitus and dizziness to rule out toxicity.[59,80]

OTHERS

There are so many other ADR due to DR-TB treatment like hyperthyroidism, myalgia, pancreatitis, etc. In every case, the frequent monitoring and evaluation should be done to find out the efficacy and safety of drugs. This will help in assessing the incidence, causality, identifying the drugs and finally leading to prevention. According to

the induced ADR, treatment should be managed properly. In some cases, the drug should be withdrawn or stopped and in some cases the drugs may be continued. In TB, the ADR plays a major role in compliance and treatment outcomes. Many treatments failed due to ADR and thus require proper education and imparting of knowledge in patients regarding ADR in TB, this will definitely help the further spread and prevention of disease. Both patients and treatment providers should be aware of this fundamental pattern of treatment to further reduce the scenario of TB.[15,81]

Summary of management and drugs that can be used for some ADRs are mentioned in Table 4 and 5. Even if there are so many management policies, all ADR should be managed based on individual patient's characters (age, comorbidities, gender, other medications, etc.)

CONCLUSION

TB treatment will cause a variety of ADR and sometimes it can be fatal if it is not properly managed. Some of the ADRs are minor and can be managed without the discontinuation of treatment. But some may be severe and in that case either modification or discontinuation of treatment is required. The major culprit of severe irreversible ADR that occurred in DR-TB is pyrazinamide and kanamycin. The ADR will reduce both the compliance and the success rate of treatment. Regular monitoring of patients allows the identification and proper management of adverse reactions. The management is based on individual ADR, can treat symptomatically, withhold the drug or withdraw the drugs.

ABBREVIATIONS

H: Isoniazid; **E:** Ethambutol; **Z:** Pyrazinamide; **R:** Rifampicin; **S:** Streptomycin; **Km:** Kanamycin; **Am:** Amikacin; **Cm:** Capreomycin; **FQs:** Fluoroquinolones; **Bdq:** Bedaquiline; **Dlm:** Delamanid; **Lzd:** Linezolid; **Cs:** Cycloserine; **Cfz:** Clofazimine; **PAS:** Para amino salicylic acid; **Eto:** Ethionamide; **Pto:** Prothionamide; **TB:** Tuberculosis; **LTBI:** Latent TB infection; **DR:** Drug-resistant; **XDR:** Extensive drug-resistant; **ADR:** Adverse drug reaction; **MDR:** Multidrug resistant tuberculosis; **NMDAR:** N-methyl-D-Aspartate receptors; **PMDT:** Programmatic management of drug-resistant tuberculosis; **ATT:** Antituberculous therapy; **Gfx:** Gatifloxacin; **OD:** Once daily; **BD:** Twice daily; **PO:** Per oral; **PN:** Peripheral neuropathy; **Amx/Clv:** Amoxicillin/Clavulanic acid; **Amk:** Amikacin; **HS:** At bed time; **Cl:** Clarithromycin; **SSRIs:** Selective serotonin reuptake inhibitors.

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