

MAIN ANTI-TUBERCULOSIS DRUGS ADR SYMPTOMS AND THEIR MANAGEMENT

1. E-learning objectives

This module aims to:

Increase student's knowledge on ADRs symptoms that are commonly associated to each of the main anti-TB drugs;

Spread the knowledge about their management.

ADR	SUSPECTED AGENT	SOME SUGGESTIONS ABOUT MANAGEMENT (it is a physician duty)
2. How to deal with Nausea and vomiting	Ehionamide, protionamide, pyrazinamide, Kanamycin, Amoxicillin/Clavulanic Acid, imipenem/cilastatin, Clofazimine, Delamanid, levofloxacin, moxifloxacin, linezolid, PAS,	<ol style="list-style-type: none">1. Assess for dehydration; and rehydrate if indicated.2. If mild symptoms and no signs of dehydration,<ul style="list-style-type: none">o Encourage patients to increase fluid intake (water, juice, tea).o Encourage patient to continue treatment– Start antiemetic therapy Metoclopramide (Caution when taking QT prolonging Drugs)– Promethazine– If vomiting is severe and nonresponsive to above measures, chlorpromazine3. If there is dehydration or persistence of symptoms,<ul style="list-style-type: none">• Initiate rehydration accordingly• Refer patient to the treatment initiating center if nausea and vomiting persist despite adjustments to the dosing schedule.
3. How to deal with Gastritis	PAS, Ehionamide, protionamide	<ol style="list-style-type: none">1. Give antiTB drugs with small food, avoid caffeine, cigarettes and assess for signs of severity2. If mild symptoms give H2- blockers, proton-pump inhibitors.3. Decrease the dose of the offending drug if symptoms are not controlled by PPI.4. If severe initiate rehydration and refer to the treatment initiating center.
4. How to deal	Kanamycin, Amikacin,	<ol style="list-style-type: none">1. Confirm that this is not due to ear wax or other conductive problems.

with Hearing loss	Capreomycin	<ol style="list-style-type: none"> 2. Check whether patient has history of hearing loss previously 3. Document hearing loss objectively (preferably using audiometry) and compare with baseline audiometry if available. 4. If ototoxicity is confirmed consider shifting regimen. regimen is not compromised. 5. Refer, if it is new event or worsening of complaint. 6. Hearing loss is generally not reversible <p>Note: Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of these drugs.</p>
5. How to deal with Peripheral Neuropathy	isoniazid, linezolid, levofloxacin,	<ol style="list-style-type: none"> 1. Increase pyridoxine 2. Initiate therapy with tricyclic antidepressants such as amitriptyline. Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. <p>Note: Neuropathy may be irreversible; some patients may experience improvement when offending agents are suspended</p> <p>Patients with co-morbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here.</p>
6. How to deal with Seizure	isoniazid, levofloxacin, moxifloxacin, linezolid. Imipenem/cilastatin	<ol style="list-style-type: none"> 1. Suspend suspected agent 2. Initiate anticonvulsant therapy (e.g. Phenytoin, Valproic Acid). 3. Increase pyridoxine 4. Refer after controlling seizure <p>Note: Patients with history of previous seizures may be at increased risk for development of seizures during therapy with these drugs.</p> <p>History of previous seizure disorder is not a contraindication</p>
7. How to deal with Hepatotoxicity	pyrazinamide, isoniazid, Rifampin, PAS, Ethambutol, Ethionamide, prothionamide, Moxifloxacin, Levofloxacin, linezolid, bedaquiline	<ol style="list-style-type: none"> 1. Stop all therapy pending resolution of hepatitis. 2. Reintroduce Anti Tb drugs starting from list of less hepatotoxic drugs once it resolves. <p>Pyrazinamide is considered the most hepatotoxic drug and can be taken out of the regimen</p> <p>Note: in such patients HBV, HCV should be screened</p>
8. How to deal	Rifampin, Amikacin,	<ol style="list-style-type: none"> 1. Monitor Serum electrolyte for disturbance as it may coexist with raised serum creatinine

with Nephrotoxicity (body swelling, decreasing urine, new onset or worsening hypertension)	kanamycin, streptomycin, capreomycin	elevation. 2. Calculate GFR and determine degree/ severity of kidney Injury. 3. Do not reintroduce injectable or decrease frequency since as alternate novel drugs are available. Note: Be careful. Renal impairment may be permanent
9. How to deal with Depression	Clofazimine, cyloserine, levofloxacin,	1. Improve socioeconomic conditions. 2. Group or individual counseling. 3. Initiate antidepressant therapy. 4. Refer if severe depression Note: Socioeconomic conditions and chronic illness should not be underestimated as contributing
10. How to deal with Arthralgia	Bedaquiline, delamanid, pyrazinamide	1. Initiate therapy with nonsteroidal anti-inflammatory drugs. 2. Consider decreasing the dose of suspected drug if not compromising the regimen.
11. How to deal with QT prolongation	Levofloxacin, moxifloxacin, bedaquiline, clofazimine, delamanid	1. Monitor more closely; at least weekly ECG until QTcF has returned to less than grade. Replete electrolytes as necessary. 2. If severe: Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.

12 Key-points

Different anti-TB drugs can give different types of toxicity, including gastrointestinal toxicity, ototoxicity, hepatotoxicity, nephrotoxicity, cardiotoxicity and neurotoxicity;

In order to correctly manage anti-TB drugs ADR symptoms, after ruling out other possible causes, the physician may decide to stop the treatment, to adjust drug dosages, to initiate a different treatment or just to monitor the patient more closely.

13 References

1. Bibliography National Programmatic management of Drug resistant TB in Ethiopia Participant's manual_May 2019
2. IBM_Micromedex_ Web_ Application Access

14 Intermediate Questionnaire

According to what you read about adverse drug reactions (ADRs) management, what should a physician do first if a patient has nausea and vomiting after taking an anti-TB drug?

- a. **assessing for dehydration and rehydrating the patient if indicated**
- b. initiating therapy with tricyclic antidepressants
- c. initiating therapy with nonsteroidal anti-inflammatory drugs
- d. confirming that this is not due to ear wax or other conductive problems

Teaching:

“(Some suggestions about the management [of nausea and vomiting]): assess for dehydration and rehydrate the patient if indicated.”.

Arthralgia is an ADR caused by:

- a. delamanid and cycloserine
- b. **delamanid and bedaquiline**
- c. bedaquiline and isoniazid
- d. cycloserine and isoniazid

Teaching:

“(ADR) Arthralgia: (associated anti-TB drugs) delamanid, bedaquiline and pyrazinamide.”.