MONITORING & MANAGEMENT OF COMMON ADVERSE EFFECTS OF MDR/XDR-TB TREATMENT

Nausea & Vomiting – Ethionamide, PAS, Bedaquiline, Delamanid

Management:

Counsel patient regarding the high likelihood of this side effect. Awareness of the cause and the probability of the symptoms resolving over time may help the patient to tolerate it

1. **Assess for dehydration and rehydrate if indicated**
2. **Take the medication with a non-fatty meal or before going to bed**
3. **IF STEP 2 IS NOT EFFECTIVE: Initiate anti-emetics 30 min prior to administering MDR-TB drugs**
4. **IF STEP 3 IS NOT EFFECTIVE: Administer ethionamide in two (250 mg mane and 500 mg nocte) or three separate doses – but other drugs should NOT be split**
5. **AS A LAST RESORT: Discontinue use of offending drug and discuss substitution with an expert**

Comments
- Ethionamide most likely agent
- Nausea and vomiting is common in the early weeks of treatment and usually resolves with time on treatment or supportive therapy. Monitor. If no improvement investigate for liver toxicity and other causes of vomiting
- Electrolytes should be monitored and replenished if vomiting is severe
- Reversible upon discontinuation of suspected agent

Diarrhoea – Ethionamide, PAS, Delamanid, Bedaquiline, Linezolid

Management:

Counsel patient regarding the high likelihood of this side effect. Awareness of the cause and the probability of the symptoms resolving over time may help the patient to tolerate it. Advise to maintain adequate fluid intake

1. **Assess for dehydration and rehydrate if indicated – this should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated**
2. **Loperamide, oral, 4 mg immediately, followed by 2 mg after each loose stool. Maximum dose: 16 mg daily (8 tablets)**
3. **AS A LAST RESORT: If severe, persistent and adversely affecting adherence or quality of life, discontinue use of offending drug and discuss substitution with an expert**

Comments
- Reversible upon discontinuation of suspected agent
- Electrolytes should be monitored and replenished if diarrhoea is severe
- Note that *Clostridium difficile*-associated diarrhoea has been reported with use of nearly all antibacterial agents, due to alteration of the normal flora of the colon, thus *C. difficile* should be ruled out if diarrhoea persists

Hearing Loss / Ototoxicity – Streptomycin, Kanamycin, Amikacin, Capreomycin

Monitoring:

Audiometry at baseline, monthly during injectable phase and 3 months after completion of the injectable therapy

Management:

1. **Conduct audiometry and compare with baseline:**
   - **Is there significant hearing loss? i.e. 20 dB or more at one frequency; 10dB in at least 2 adjacent frequencies; or complete loss of response at any frequency?**
   - **Is the hearing loss a new change when compared to the baseline or previous audiograms?**
   - **If abnormal audiometry result, refer to tertiary audiology services if possible for diagnostic testing to determine the type of hearing loss i.e. sensorineural or conductive**
2. **Investigate for other causes of hearing loss (i.e. wax, middle ear infection) and treat appropriately**
3. **If significant sensorineural hearing loss is noted at baseline: Do not initiate an aminoglycoside**
4. **If significant sensorineural hearing loss has occurred after commencing ototoxic treatment: Discontinue suspected drug and change to e.g. bedaquiline, delamanid or linezolid OR refer patient to expert for advice on how to tailor regimen**
5. **If patient reports hearing loss or tinnitus and there are no tertiary audiology services available to confirm sensorineural hearing loss, stop injectable and substitute**

Comments
- Patients with prior exposure to aminoglycosides may have baseline hearing loss
- Patients may develop hearing loss due to other causes while receiving an injectable
- Aminoglycoside-induced sensorineural hearing loss is permanent and generally not reversible; it is also usually bilateral and progressive, affecting the higher frequencies first
- Patients with pre-existing vestibulo-cochlear impairment should be counselled on the risk of further hearing loss
- Informed consent should be obtained before use in any patient
- Concomitant use of furosemide may exacerbate ototoxic effects of these medications

Peripheral Neuropathy – Terizidone, High dose isoniazid, Linezolid

Monitoring:

Symptoms occur most commonly in the lower extremities: Sensory disturbances (e.g. numbness, tingling, burning, pain, loss of temperature sensation), difficulty walking, weakness, and decreased or absent deep tendon reflexes

Management:

1. **Always consider and manage other causes e.g. d4T (switch), HIV (treat)**
2. **Increase pyridoxine dose: Usually 50 mg for each 250 mg of terizidone but may need to be higher (200 mg daily) if on other neurotoxic drugs AND**
3. **Begin exercise regimen, focus on affected regions**
4. **IF STEPS 1 AND 2 ARE NOT EFFECTIVE: Check electrolytes. Consider thiamine if history of alcohol use. Initiate therapy with tricyclic antidepressant drugs (AVOID with bedaquiline). Start with 25 mg/day for one week. If no response, the dose may be increased to 75 mg/day**
5. **IF NONE OF THE ABOVE STEPS ARE EFFECTIVE: Lower dose of linezolid to 300 mg daily**
6. **AS A LAST RESORT: Discontinue suspected drug and discuss substitution with an expert**

Comments
- Patients with co-morbid disease e.g. diabetes, HIV and alcoholism are more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the offending TB drugs
- It may be possible to re-introduce drug at a later stage at a lower dose if peripheral neuropathy resolved, especially if drug is essential in regimen

Arthralgia / Arthritis / Osteo-articular Pain – Pyrazinamide, Fluoroquinolones, Delamanid

Management:

1. **Initiate therapy with non-steroidal anti-inflammatory drugs (if renal function allows it)**
2. **Initiate physiotherapy/exercise where necessary**
3. **IF STEPS 1 AND 2 ARE NOT EFFECTIVE: Lower dose of offending drug, if this will not compromise the regimen, e.g. if using high dose fluoroquinolone. Consider intermittent administration of pyrazinamide**
4. **AS A LAST RESORT: Discontinue offending drug and discuss substitution of delamanid or fluoroquinolone with expert**

Comments
- Symptoms of arthralgia/ arthritis generally diminish over time, even without intervention
- Uric acid levels may be elevated in some patients but are of little therapeutic relevance
- Anti-gout treatment e.g. allopurinol, colchicine does not correct the uric acid levels in these cases

Skin Reactions - Could be several agents

Monitoring and/or Management

Treatment can be continued if rash is mild, but should be stopped for a severe reaction e.g. blistering, mucosal involvement, fever, and refer patient to hospital for re-introduction. Clofazimine often causes skin darkening and dry skin

Comments
- Frequent in patients with HIV infection
- True allergic reactions are uncommon
- Skin darkening and dry skin caused by clofazimine will eventually resolve on completion of treatment or withdrawal of the drug—Reassure the patient

Electrolyte Disturbances — Capreomycin (most frequent), Amikacin, Kanamycin

Monitoring:

Monitor serum potassium and magnesium at baseline and at least monthly during injectable phase or in patients with significant gastrointestinal (GI) losses

Management:

Look for other causes of hypokalaemia e.g. diarrhoea, vomiting, diuretics etc.

1. **Treat associated vomiting or diarrhoea**
2. **Control hyperglycaemia as this causes a rise in insulin, which then pushes potassium into the cells and leads to low serum potassium**
3. **Replenish potassium per mouth or IV e.g. oral Slow-K (2 tabs twice daily) when K^+ < 3.5. Oral potassium supplements are relatively well tolerated (may cause GI effects), are absorbed readily and can be given in fairly high doses safely (therefore more appropriate in outpatient setting). Intravenous supplementation can irritate the veins and is less well tolerated. Smaller doses need to be given, and in an inpatient setting**
4. **Check magnesium levels if potassium levels do not improve as refractory hypokalaemia may be due to low magnesium levels. Occasionally, extracellular magnesium levels on blood monitoring may still appear to be normal even in the presence of intracellular hypomagnesaemia, and so it may be worth supplementing magnesium anyway if there is persistent refractory hypokalaemia which is not responding to potassium supplementation**
   - **If Mg^{2+} < 0.6, supplement with oral Slow Mag (2 to 4 tabs twice daily), or if < 0.4 may consider intra-muscular $MgSO_4$ every 4 to 6 hours. If levels get this low, patient may need admission to inpatient facility to correct electrolyte levels**
5. **REGULAR ECG MONITORING, especially if patient is taking more than one QT-prolonging drug (bedaquiline, delamanid, moxifloxacin, clofazimine)**
6. **Discontinue any other arrhythmogenic drugs e.g. digoxin, amytriptyline, cisapride, and haloperidol. Discontinue other drugs which may cause electrolyte depletion if possible e.g. salbutamol, diuretics (change to potassium sparing diuretics)**
7. **Discontinue aminoglycosides if condition is severe i.e. if patient is symptomatic or has seizures and discuss patient with expert**

Comments
- Commonly associated with GI disturbances
- Reversible once the injectable is suspended
- Although sometimes asymptomatic, may present with fatigue, muscle pain, cramps, pins and needles, lower extremity weakness, behaviour or mood changes, somnolence and confusion
- More severe disturbances can lead to tetany, paralysis and life-threatening cardiac arrhythmias
- Amiloride 5 to 10 mg four times daily or spironolactone 25 mg four times daily may decrease the potassium & magnesium wasting and is useful in refractory cases
- Electrolyte abnormalities may be detected prior to TB treatment, e.g. due to nutritional deficiencies in chronically ill patients. These electrolyte abnormalities should be corrected as far as possible, as they may also increase the risk of QT prolongation posed by drugs such as delamanid, bedaquiline, moxifloxacin and clofazimine

Renal Toxicity – Capreomycin, Kanamycin, Amikacin, Streptomycin

Monitoring:

Monitor renal function at baseline and monthly during injectable phase.

Either use the eGFR supplied by the laboratory or calculate the creatinine clearance. Various formulae can be used.

Management:

Always consider other causes of renal impairment and stop other nephrotoxic drugs if possible

1. **If CrCl or eGFR < 30, stop likely offending agent(s) and consult hospital or Hotline for further advice. If eGFR 30 – 60, reduce doses of renally-cleared drugs and monitor eGFR or creatinine clearance closely (e.g. 1 to 2 times a week). If worsening, may need to withdraw injectable, but if stable on reduced dose, could continue with weekly monitoring**
2. **If injectable is withdrawn, substitute with alternative options such as bedaquiline, delamanid or linezolid. Discuss with TB specialist**
3. **Consider use of capreomycin if patient was on aminoglycoside and if injectable cannot be avoided i.e. if regimen is compromised by too few effective drugs and no others available**

Comments
- History of diabetes or renal disease is not a contraindication to the use of the offending TB drugs, although patients with co-morbidities may be at increased risk for developing renal failure
- Renal impairment may be permanent
- Symptomatic cases may present with any of the following: oliguria, anuria, oedema, shortness of breath or uremic symptoms such as mental status changes
- Avoid other nephrotoxic drugs, e.g. tenofovir

Depression - Terizidone

Management:

1. **Rule out side effects of concomitant medications or drug or alcohol dependence or hypothyroidism**
2. **Refer to psychologist or psychiatrist for assessment and treatment**

Comments
- Importance of personal socioeconomic conditions and confinement to hospital should not be underestimated as contributing factors to depression
- Depression and depressive symptoms may fluctuate during treatment
- History of prior depression is not a contraindication to the use of the offending TB drugs; however, these patients may be at increased risk for developing depression during MDR-TB treatment
- The need to discontinue an anti-TB agent due to refractory depression is extremely rare

Liver Toxicity – Pyrazinamide, Ethionamide, PAS, Isoniazid, Fluoroquinolones, Bedaquiline

Monitoring:

Full LFT at baseline and ALT monthly during intensive phase, thereafter ALT 6 monthly

Management:

1. **If ALT/AST > 5 times the upper limit of normal or more than 3-fold elevated with symptoms, or patient is jaundiced, stop all medicines and consult specialist. If patient is unwell, stop treatment, refer to hospital and re-introduce agents as inpatient**
2. **Rule out other potential causes of hepatitis, such as viral hepatitis, CMV, alcohol use, other medications**
3. **After resolution, monitor liver function every 1-2 months**

Comments
- History of prior hepatitis should be carefully analysed to determine the most likely causative drug(s); these should be avoided in future regimens
- Generally reversible upon discontinuation of offending drug
- Hepatitis is characterized by nausea, vomiting, jaundice, yellow sclera, tea-coloured urine, pale stool and diminished appetite
- Tuberculosis itself may cause hepatitis
- Mild transient raised serum ALT may be observed in the first months of therapy
- Clinically significant hepatitis is almost invariably symptomatic and the diagnosis is confirmed by an elevation in serum transaminases (ALT/AST) or conjugated bilirubin greater than 5 times normal

Need Help?

Contact the TOLL-FREE National HIV & TB Health Care Worker Hotline 0800 212 506 / 021 406 6782

Alternatively send an SMS or "Please Call Me" to 071 840 1572 **www.mic.uct.ac.za**

MEDICINES INFORMATION CENTRE

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Myelosuppression (incl. anaemia, leucopaenia, pancytopaenia, thrombocytopaenia) - Linezolid

Monitoring:

Do monthly FBC for all patients taking linezolid for longer than 2 weeks

Do weekly FBC in patients with:
- **Pre-existing myelosuppression (anaemia, granulocytopaenia or thrombocytopaenia)**
- **Concomitant medications that may decrease haemoglobin levels, depress blood counts or adversely affect platelet count/ function**
- **Chronic infection and who have received previous or are receiving concomitant antibiotic therapy**
- **Severe renal insufficiency**

Management:

1. **Reduce dose or consider transfusion if linezolid is essential in the treatment regimen and myelosuppression develops or pre-existing myelosuppression worsens (Hb <7) or there is significant thrombocytopenia**
2. **Discontinue linezolid if no improvement with transfusion and/or reduced dose. Refer to specialist for alternatives if necessary**
3. **Linezolid may be started later, if anaemia improves**

Comments
- Reversible upon discontinuation
- Avoid concomitant use with other drugs that suppress bone marrow
- The pharmacokinetics of linezolid are not significantly altered in elderly patients aged 65 and over

Seizures – Terizidone, Fluoroquinolones, High dose isoniazid

Management:

1. **Rule out other likely causes e.g. electrolyte disturbances, sub-therapeutic levels of current antiepileptics**
2. **Treat any suspected causes or adjust doses of current antiepileptics**
3. **Refer patient to hospital to initiate anticonvulsant treatment if not a known epileptic. Only valproic acid/lamotrigine can be used in patients on ARVs. Monitor levels, as drug interactions are common**
4. **Increase pyridoxine to 200 mg daily**
5. **May need to stop terizidone in patients on antiepileptics who experience an increase in seizures**

Comments
- Clinical evaluation is generally sufficient unless there is high suspicion of infectious, malignant, vascular or metabolic cause
- Anticonvulsant must be continued until MDR-TB treatment completed or suspected agent discontinued
- History of prior seizure disorder is not a contraindication for the use of the offending TB drugs if the patient's seizures are well-controlled and/ or the patient is receiving anticonvulsant treatment
- Patients with history of prior seizures may be at increased risk of development of seizures during MDR-TB treatment

Psychosis – Terizidone, High dose isoniazid, Fluoroquinolones, Ethionamide

Management:

1. **Manage acute psychosis**
2. **If patient is on high dose isoniazid, increase pyridoxine dose to up to 200mg**
3. **Consult with appropriate expert for assistance and advice about possible drug substitution**

Comments
- Some patients will need to continue antipsychotic treatment throughout MDR-TB treatment
- Prior history of psychiatric disease is not a contraindication to the use of the offending TB drugs, but may increase the likelihood of development of psychotic symptoms
- Psychotic symptoms are generally reversible upon MDR-TB treatment completion or discontinuation of the offending agent

Optic Neuritis / Impaired Vision – Ethambutol, Linezolid

Do eye test at baseline and when indicated

Use Ishihara colour test for retrobulbar neuritis caused by ethambutol, and standard visual acuity tests for optic neuropathy caused by linezolid

Management:

1. **Stop suspected agent. Substitute with alternative option. Discuss with TB specialist**
2. **Refer patient to ophthalmologist**

Comments
- Avoid in patients with impaired vision other than due to near-sightedness, farsightedness or old age (needs reading glasses)
- Usually reverses with cessation of the drug
- Not detectable by fundoscopy, although this may rule out other simple causes of impaired vision, such as cataracts, in elderly, diabetic or HIV-infected DR-TB patients

Arrhythmia/ QTc Prolongation – Bedaquiline, Clofazimine, Delamanid, Fluoroquinolones

Monitoring:

Do baseline ECG and repeat monthly during treatment

When using clofazimine or fluoroquinolones together with bedaquiline or delamanid, monitor QTcF weekly for first month then monthly throughout treatment period

Management:

Initiation:
- **Avoid initiating bedaquiline if QTcF > 450 msec. Could start bedaquiline later, if QTcF < 450 msec**
- **Delamanid may be initiated if QTcF > 450 msec and < 500 msec (provided patient is stable and has no cardiac symptoms)**
- **If prolonged QTcF at baseline, check albumin and electrolytes and correct prior to delamanid/bedaquiline initiation**

On treatment:
- **If QTcF > 450 msec but < 500 msec on at least 2 consecutive ECGs (a few minutes apart) at any time after treatment initiation with bedaquiline or delamanid, continue meds and monitor ECG more closely; no need to withhold either drug unless patient is symptomatic (in which case stop all QT-prolonging drugs and admit for closer ECG monitoring and management)**
- **If QTcF > 500 msec on at least 2 consecutive ECGs (a few minutes apart) while on treatment with delamanid or bedaquiline, withhold all QT-prolonging drugs until QTcF returns to < 500 msec. Refer if patient is symptomatic or if severe electrolyte or albumin deficiency cannot be corrected**

Comments
- Completely reversible upon discontinuation of offending drug
- Avoid other QT-prolonging drugs where possible, otherwise monitor more closely with ECGs
- Many ECG machines default to calculating the corrected QT interval using the Bazett formula (QTcBaz), however most guidelines and recommendations use the Fridericia formula (QTcF) for making treatment decisions. Consider manual calculation of QTcF in cases of prolonged QTc

Hypothyroidism – PAS, Ethionamide

Monitoring:

Do thyroid stimulating hormone (TSH) at baseline and then every 6 months while receiving ethionamide and/or PAS. Monitor monthly for signs/symptoms of hypothyroidism e.g. fatigue, somnolence, cold intolerance, dry skin, coarse hair, constipation, depression and psychosis

Management:

1. **Exclude other causes, including iodine deficiency, medications e.g. lithium, amiodarone, previous radioiodine therapy, pregnancy-associated thyroid dysfunction, and Hashimoto's disease**
2. **Initiate thyroxine if TSH > 10 IU/mL. Start with 50 mcg daily and repeat TSH in one month. If still >10, increase dose by another 50 mcg and repeat again in one month. Continue until TSH levels controlled below 10**

Comments
- Completely reversible upon discontinuation of offending drug
- The use of PAS and ethionamide in combination is more frequently associated with hypothyroidism than their individual use