MANAGEMENT OF ADVERSE EFFECTS OF DR-TB TREATMENT

NEED HELP?
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Myelosuppression (incl. anaemia, leucopaenia, pancytopaenia, thrombocytopaenia) - Linezolid, Rifabutin

Monitoring:
Do FBC + diff at baseline, week 2, 4 and then monthly while on linezolid. If on rifabutin, do monthly. 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
- Severe renal insufficiency

Management:
Anaemia (Hb < 8) on short-course DR-TB treatment:
1. **If Hb < 8 at baseline:** initiate medical work up and treat underlying conditions. Only consider initiating linezolid while Hb <8 g/dL if patient is under close monitoring in hospital with option for transfusion. If close monitoring and/or hospitalisation is not possible, avoid linezolid and start a longer regimen. If linezolid is started in hospital and Hb does not improve and stabilise above 8 g/dL, switch to a longer individualised regimen in which linezolid is replaced by Group C agents including delamanid
2. **If Hb < 8 during short-course treatment, after Hb > 8 at baseline:** investigate for other causes and, depending on the duration of linezolid and the severity of the drop in Hb, either: hospitalise with close monitoring for linezolid reintroduction, switch to longer regimen with substitution of linezolid, or continue the shorter regimen without linezolid (discuss with PCAC/NCAC or experienced clinician for last option)

Anaemia (Hb < 8) on long-course DR-TB treatment (baseline or after having received linezolid):
If patient admitted: start or continue/re-challenge linezolid under close clinical monitoring, review FBC and differential for assessment of aetiology of anaemia, and appropriate management or discontinuation of linezolid in cases of worsening anaemia (preferably under supervision of a clinician experienced in DR-TB)
Alternative option: avoid linezolid and continue longer regimen without linezolid. Substitute with delamanid or other Group C medicines. Hospitalisation not required if patient is clinically stable and not symptomatic of anaemia. Assess aetiology of anaemia as outpatient. Hb might improve with DR-TB treatment
Thrombocytopaenia (platelets < 50 x 10^9/L) or neutropaenia (< 0.75 x 10^9/L):
1. Stop linezolid until thrombocytopaenia or leucopaenia/neutropaenia resolves
2. Initiate medical work up, and treat underlying conditions
3. Consider substituting linezolid if withheld for > 2 weeks
4. If patient is also on rifabutin, discuss with a TB expert

Comments:
- Reversible upon discontinuation
- Avoid concomitant use with other medicines that suppress bone marrow
- The pharmacokinetics of linezolid are not significantly altered in elderly patients aged 65 and over
- Linezolid and co-trimoxazole can be used concomitantly
- Neutropaenia is one of the primary reasons for discontinuation of rifabutin

Liver Toxicity – Pyrazinamide, Ethionamide, Isoniazid, Bedaquiline, Clofazimine, Delamanid, PAS, Fluoroquinolones, Rifabutin

Monitoring:
ALT at baseline. Repeat if patient presents with nausea and vomiting, right upper quadrant pain and tender liver, visible jaundice, clinically unwell or any evidence of liver injury
Management:
1. Stop all medicines if ALT > 5 times the upper limit of normal (ULN) or if > 3 times the ULN and patient has symptoms of drug-induced liver injury
2. Rule out other potential causes of hepatitis, such as viral hepatitis, CMV, alcohol use and other medicines
3. Wait for liver function to return to normal or at least < 3 times ULN before considering re-challenge
4. RR-TB medicines should be reintroduced sequentially, every 5 to 7 days, with monitoring of liver function before introducing the next medicine
5. The least hepatotoxic medicines should be added first: linezolid, delamanid and fluoroquinolone (levofloxacin preferred) can be given all together to provide a backbone regimen
6. Then introduce potentially hepatotoxic medicines (clofazimine, bedaquiline, ethionamide, isoniazid) one by one every 5 to 7 days while monitoring liver function tests to identify the causative medicine
7. Pyrazinamide should not be reintroduced
8. After resolution of DILI, monitor liver function every 1-2 months

Comments:
- History of prior hepatitis should be carefully analysed to determine the most likely causative medicine(s); these should be avoided in future regimens
- Generally reversible upon discontinuation of offending medicine
- 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

QTc Prolongation – Bedaquiline, Clofazimine, Moxifloxacin, Delamanid

Monitoring:
Do baseline ECG. Repeat at weeks 2 and 4, and then monthly while on bedaquiline. Repeat 3 monthly after stopping bedaquiline
Management:
Assess if patient is taking other QT interval prolonging medicines
At initiation:
- Delay initiation of bedaquiline if QTcF > 450 ms. Can start bedaquiline later, if QTcF < 450 ms
- Delamanid may be initiated if QTcF > 450 ms and < 500 ms (provided patient is stable and has no cardiac symptoms)
- If prolonged QTcF at baseline, check albumin and electrolytes, stop QT-prolonging medicines, treat abnormal TSH and correct prior to delamanid/ bedaquiline initiation

On treatment:
***QTcF > 450 ms and with symptoms* consistent with a possible cardiac arrhythmia (syncope, fainting, chest pain, palpitations, dizziness or loss of consciousness):** hospitalise patient. Do medical assessment, withhold all medicines that may prolong QT until cause of symptoms has been assessed
QTcF > 450 ms < 470 ms with no symptoms: continue routine monitoring
QTcF > 470 ms but < 500 ms with no symptoms: repeat ECG at rest on the same day. If still prolonged but asymptomatic, repeat ECG weekly until patient is stable; check TSH, check and correct electrolytes; review history of administration of other (non-TB) medications that may prolong QT
QTcF > 500 ms with no symptoms: repeat ECG at rest; check and correct electrolytes, check TSH, assess for other causes and withhold all QT-prolonging medicines (including the TB medicines moxifloxacin, delamanid, clofazimine and bedaquiline). Discuss patient with experienced RR-TB clinicians and/or a cardiologist. These medicines may be re-challenged sequentially once QTcF improves to < 500 ms - monitor ECG closely during re-challenge

Comments:
- Completely reversible upon discontinuation of offending medicine
- Avoid other QT-prolonging medicines 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
- Levofloxacin is preferred to moxifloxacin as it has a smaller risk for QT prolongation
- Delamanid causes small increases in QT interval

Nausea & Vomiting – Ethionamide, PAS, Bedaquiline, Delamanid, Clofazimine

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 DR-TB medicines
4. **IF STEP 3 IS NOT EFFECTIVE:** Consider separating the dosing of ethionamide and PAS from the other medicines by administering in the evening. Consider reducing the dose of ethionamide and building up to full dose over 2 weeks
5. **AS A LAST RESORT:** Discontinue use of offending drug and discuss substitution with an expert

Comments:
- Ethionamide most likely agent
- Nausea and vomiting are 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, pancreatitis, or increased intracranial pressure
- Electrolytes should be monitored and replenished if vomiting is severe
- Reversible upon discontinuation of suspected agent

Depression – Terizidone, High dose isoniazid

Management:
1. Rule out side effects of concomitant medications, drug or alcohol dependence and/or hypothyroidism
2. Refer to psychologist for counselling or psychiatrist for assessment (assess for suicidal/homicidal ideation) and treat with antidepressants if needed
3. Avoid use of tricyclic antidepressants as these can prolong QT interval
4. Consider substitution of terizidone or high-dose isoniazid

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 medicines. These patients may, however, be at increased risk for developing depression during DR-TB treatment
- The need to discontinue an anti-TB medicine due to refractory depression is extremely rare

Psychosis – Terizidone, High dose isoniazid, Fluoroquinolones

Management:
1. Manage acute psychosis
2. Refer for psychiatric support, assess for suicidal/homicidal ideation
3. Consider substitution of offending medicine

Comments:
- Some patients will need to continue antipsychotic treatment throughout DR-TB treatment
- Prior history of psychiatric disease is not a contraindication to the use of the offending TB medicines, but may increase the likelihood of development of psychotic symptoms
- Psychotic symptoms are generally reversible upon DR-TB treatment completion or discontinuation of the offending agent
- Haloperidol and risperidone can both cause QT prolongation, so increase frequency of ECG monitoring in patients receiving these medications

Seizures – Terizidone, Fluoroquinolones, High dose isoniazid, Carbapenems

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 for head CT and to initiate anticonvulsant treatment if not a known epileptic. Check for drug interactions in patients on ARVs. Monitor levels, as drug interactions are common
4. Consider substitution of terizidone or high-dose isoniazid

Comments:
- Anticonvulsant must be continued until DR-TB treatment completed or suspected agent discontinued
- History of prior seizure disorder is not a contraindication for the use of the offending TB medicines if the patient's seizures are well-controlled and/ or the patient is receiving anticonvulsant treatment
- Patients with a history of prior seizures may be at increased risk of development of seizures during DR-TB treatment

Skin Reactions - Could be several agents

Monitoring and/or Management:
Treatment can be continued if rash is mild. Stop treatment if rash is severe e.g. blistering, mucosal involvement and fever. Refer patient to hospital for re-introduction. Patients with a severe rash should be discussed with NCAC or other RR-TB experts. Clofazimine often causes skin darkening and dry skin

Comments:
- Counsel patients regarding the possibility of skin darkening and dry skin caused by clofazimine and that it will eventually resolve. Give emollient creams and monitor for skin and soft tissue infection if patient is scratching
- Skin reactions frequently occur in patients with HIV infection
- True allergic reactions are uncommon

Hearing Loss / Ototoxicity – Amikacin

Monitoring:
Baseline and at month 3 in all patients. If on an aminoglycoside (e.g. amikacin), do audiometry monthly while on injectable, and 3 and 6 months after completion of the injectable therapy
Management:
Conduct audiometry and compare with baseline: If any hearing symptoms or if hearing loss > 30dB at multiple frequencies, stop injectable. Consider substituting with an alternative drug such as delamanid

Comments:
- Aminoglycosides (e.g. amikacin) should only be given as part of salvage or rescue therapy
- If significant sensorineural hearing loss is noted at baseline: Do not initiate an aminoglycoside
- Patients with prior exposure to aminoglycosides may have baseline hearing loss
- Injectable agents should not be used if hearing loss cannot be formally monitored by audiometry
- 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 vestibulocochlear 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

Diarrhoea – PAS, Ethionamide, 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 4 mg, oral 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

Hypothyroidism – Ethionamide, PAS

Monitoring:
Do thyroid stimulating hormone (TSH) at baseline and then every 3 months if on ethionamide and/or PAS, or as required if QTcF is prolonged. 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. Consider thyroxine supplementation if clinical hypothyroidism or raised TSH and decreased FT4
3. If raised TSH and normal FT4 repeat both in 1 month
4. Initiate thyroxine if TSH > 10 IU/mL. Start with 50 mcg daily and repeat TSH in one month. Monitor TSH every month and increase the dose by 25 mcg until TSH normalises (TSH < 5 mIU/L)

Comments:
- Thyroid dysfunction resolves upon discontinuation of the causative medicine, but thyroxine replacement must continue for at least 2 to 3 months after completed RR-TB treatment
- The combined use of PAS and ethionamide is more frequently associated with hypothyroidism than when used as individual medicines

ARV = antiretroviral; CT = computerised tomography; DR-TB = drug-resistant tuberculosis; ECG = electrocardiogram; FBC + diff = full blood count and differential; FT4= free thyroid hormone; Hb = haemoglobin; HIV = human immunodeficiency virus; NCAC = National Clinical Advisory Committee; PCAC= Provincial Clinical Advisory Committee; QTcF = corrected QT interval using Fridericia's formula; RR-TB = rifampicin-resistance tuberculosis; TB = tuberculosis; TSH = thyroid stimulating hormone; ULN = upper limit of normal

Peripheral Neuropathy – Linezolid, High dose isoniazid, Terizidone

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. In addition to asking about symptoms, all patients should be examined for signs of peripheral neuropathy at each clinic visit. This includes testing of peripheral reflexes (i.e. ankles, wrists, knees) and sensory testing with a monofilament
All patients on terizidone and isoniazid should receive pyridoxine to prevent peripheral neuropathy. Use doses of 50 mg/day for adults, 25 mg/day for children aged 5-12 years, and 12.5 mg/day for children less than 5 years old
Management:
1. Always consider and manage other causes e.g. HIV (treat)
2. Note that pyridoxine doses of > 100 mg may cause or worsen peripheral neuropathy and should be avoided. Pyridoxine does not prevent linezolid-induced neuropathy
3. Begin exercise regimen, focus on affected regions
4. **IF STEPS 1 AND 3 ARE NOT EFFECTIVE:** Check electrolytes. Consider thiamine if history of alcohol use. Consider therapy with pregabalin or gabapentin to treat pain. Avoid use of tricyclic antidepressants as these can prolong the QT interval
5. If clinically evident that the neuropathy interferes with patient's daily activities, stop terizidone, isoniazid and/or linezolid and substitute with another effective agent (such as delamanid)

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 medicines
- Linezolid induced neuropathy occurs mostly with long-term use (> 2 months) and does not respond to pyridoxine
- Neuropathy can be challenging to monitor in young children, thus a shorter course of linezolid could be considered in young children

Arthralgia / Arthritis / Osteo-articular pain – Pyrazinamide, Fluoroquinolones, Bedaquiline

Management:
1. Initiate therapy with non-steroidal anti-inflammatory medicines (if renal function allows it)
2. Initiate physical therapy, massage, topical therapy where necessary
3. **IF STEPS 1 AND 2 ARE NOT EFFECTIVE:** Consider substitution or withdrawal of pyrazinamide
4. If still no improvement discuss substitution or withdrawal of fluoroquinolone or bedaquiline 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
- Fluoroquinolones can rarely cause Achilles' tendon rupture

Optic Neuritis / Impaired Vision – Ethambutol, Linezolid, Rifabutin

Monitoring:
Rifabutin: Monitor at baseline and monthly for visual disturbances, painful inflamed eye(s) and photophobia
Linezolid/Ethambutol: Regular testing (baseline and monthly) of visual acuity with Snellen chart or age appropriate measure, including papillary responses and "fixate and follow" response in children < 2 years of age and symbol charts in children aged 3 to 5 years
Management:
1. Withhold ethambutol and/or linezolid and/or rifabutin and refer patient to ophthalmologist for further evaluation and management. Do not reintroduce without discussing with NCAC (or another RR-TB expert) and preferably with ophthalmologist
2. If the patient has RR-TB with extensive disease or further resistance, and optic toxicity due to linezolid is ruled out by an ophthalmologist, reintroduction of linezolid may be considered with careful monitoring

Comments:
- Avoid in patients with impaired vision other than due to near-sightedness, farsightedness or old age (needs reading glasses)
- Usually reverses on discontinuation of the medicine
- 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

Electrolyte Disturbances — Amikacin

Monitoring:
Monitor serum potassium and magnesium at baseline. Repeat monthly if on injectable agent, otherwise repeat as required if vomiting or diarrhoea or if QTcF prolonged, or if patient is clinically unwell through treatment
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. If potassium is low (< 3.5mEq/L), replace with oral potassium. Oral potassium supplements are relatively well tolerated (may cause GI effects), are readily absorbed and can be given in fairly high doses safely (therefore more appropriate in outpatient setting). If potassium < 2.5 mEq/L, hospitalise patient and replace with intravenous potassium. Intravenous supplementation can irritate the veins and is less well tolerated, smaller doses need to be given
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
5. If magnesium < 0.6 mmol/L, supplement with oral magnesium, or if < 0.4 mmol/L may consider intra-muscular magnesium sulphate every 4 to 6 hours. If levels get this low, patient may need admission to inpatient facility to correct electrolyte levels
6. MONITOR ECG REGULARLY, especially if patient is taking more than one QT-prolonging drug (bedaquiline, delamanid, moxifloxacin, clofazimine)
7. Discontinue any other arrhythmogenic medicines e.g. digoxin, amitriptyline and haloperidol. Discontinue other medicines which may cause electrolyte depletion if possible, e.g. salbutamol, diuretics (change to potassium sparing diuretics)
8. Discontinue aminoglycosides if condition is severe i.e. if patient is symptomatic or has seizures. 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
- 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 medicines such as delamanid, bedaquiline, moxifloxacin and clofazimine

Renal Toxicity – Amikacin

Monitoring:
Baseline creatinine. Repeat monthly if on injectable agent. If baseline creatinine was abnormal, or if patient is clinically unwell through treatment repeat as required
Management:
Always consider other causes of renal impairment and stop other nephrotoxic medicines if possible
If creatinine rises > 1.3 times the upper limit of normal (ULN) or potassium is elevated, stop injectable and substitute with alternative medicine

Comments:
- History of diabetes or renal disease is not a contraindication to the use of the offending TB medicines, 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 medicines, e.g. tenofovir

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