Adverse events associated with Linezolid

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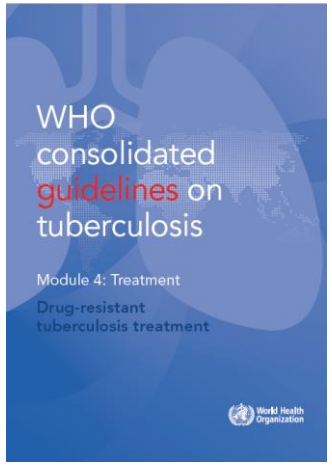
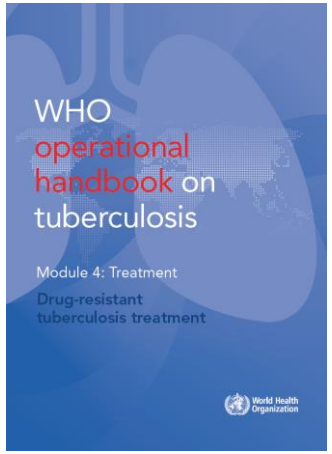
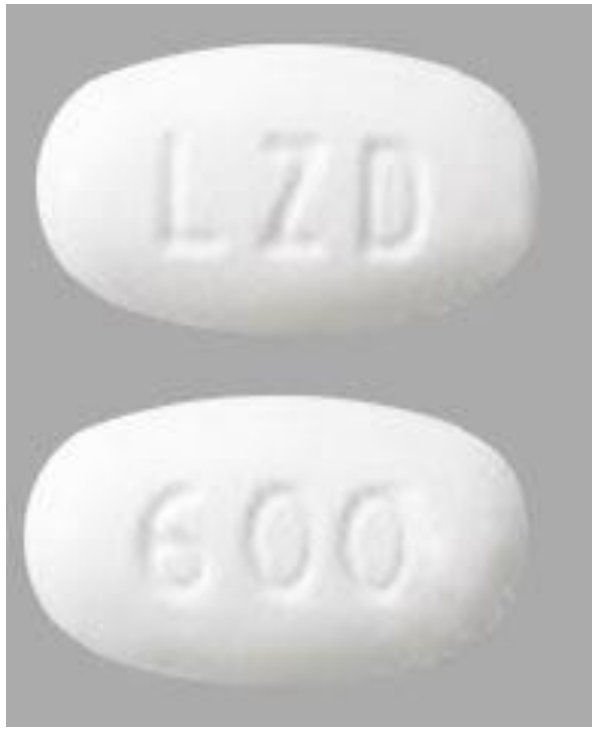
- Joint TB, HIV and Viral Hepatitis Programme, Division of Country Health Programmes

Linezolid







- Group A drug (WHO classification) recommended for the long-term RR/MDR-TB treatment regimens
- Product form - 600 mg tablets
- Administration - once daily throughout the course of treatment
- Most commonly found AE include:
- Peripheral neuropathy
- Optic neuritis
- Myelosuppression

Peripheral neuropathy

- **Peripheral neuropathy** — multiple damage of the peripheral nerves responsible for transmission of impulses from the central nervous system to the muscles, skin and organs, manifested by the peripheral flaccid paralysis, sensitivity disorders, trophic vegetative vascular disorders mainly in the distal parts of the limbs.
- Peripheral neuropathy is a common adverse event observed during DR-TB treatment due to the toxic effect of drugs to the nerves of the peripheral nerve system.
- **It can be caused by the following TB drugs : Lzd, Cs/Trd, H, S, Km, Cm, H, FQ, Pto/Eto, E**
- Peripheral neuropathy is extremely common in patients on linezolid.

Differential diagnosis

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- Injuries, tumors;
- poisoning
- **use of certain drugs;**
- immune disorders, lack of vitamins;
- chronic alcoholism;
- vascular diseases of the lower extremities (obliterating endarteritis), systemic vasculitis, blood disorders (thrombosis);
- disruptions of metabolic processes; endocrine pathology (diabetes mellitus);
- viral and bacterial infections;
- Guillain-Barre syndrome; hereditary neuropathy

Polyneuropathy at the early stages

Reduced sensitivity

Numbness

Neuropathy
at the early stages

Burning sensation

Possible symptoms

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- numbness, lack of response to pain or temperature;
- enhanced touch sensitivity;
- tickling, tingling, burning sensations;
- severe pain, spasms;
- loss of balance; loss of reflexes;
- muscle weakness; significant changes while walking;
- more frequent urination during the day;
- frequent tripping and falling;
- atrophy of damaged muscles.

Clinical management of peripheral neuropathy depending on its severity

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Severity*	Grade 1: mild	Grade 2: moderate to severe	Grade 3: severe	Grade 4: Life threatening
Paresthesia (burning, tingling, etc.)	Mild discomfort: treatment is not required; 1-3 index of subjective severity of sensory neuropathy at either side .	Moderate discomfort; non-narcotic analgesia is required; and / or 4-6 index of subjective severity of sensory neuropathy at either side.	Severe discomfort; or narcotic analgesia is required, leading to improved symptoms; and/or 7-10 subjective severity index of sensory neuropathy at either side.	Disabling; or not manageable by the narcotic analgesia
Action	Discontinuation of Cs/Trd, high doses of H, and Lzd. With alleviation of symptoms, consider re-administration of these medications. Consider re-administration of Lzd at a lower dose (300 mg per day or 600 mg three times a week). If Cs/Trd or high doses of H are not necessary in this regimen, consider discontinuation of these drugs.	Discontinuation of Cs/Trd, high doses of H, and Lzd. If symptoms subside and these medications are necessary in this regimen, consider re-administration of Cs/Trd or high doses of H. Do not re-indicate Lzd. Provide symptomatic treatment as indicated below.	Same as for Grade 2	Same as for Grade 2

Suggested Management Strategy

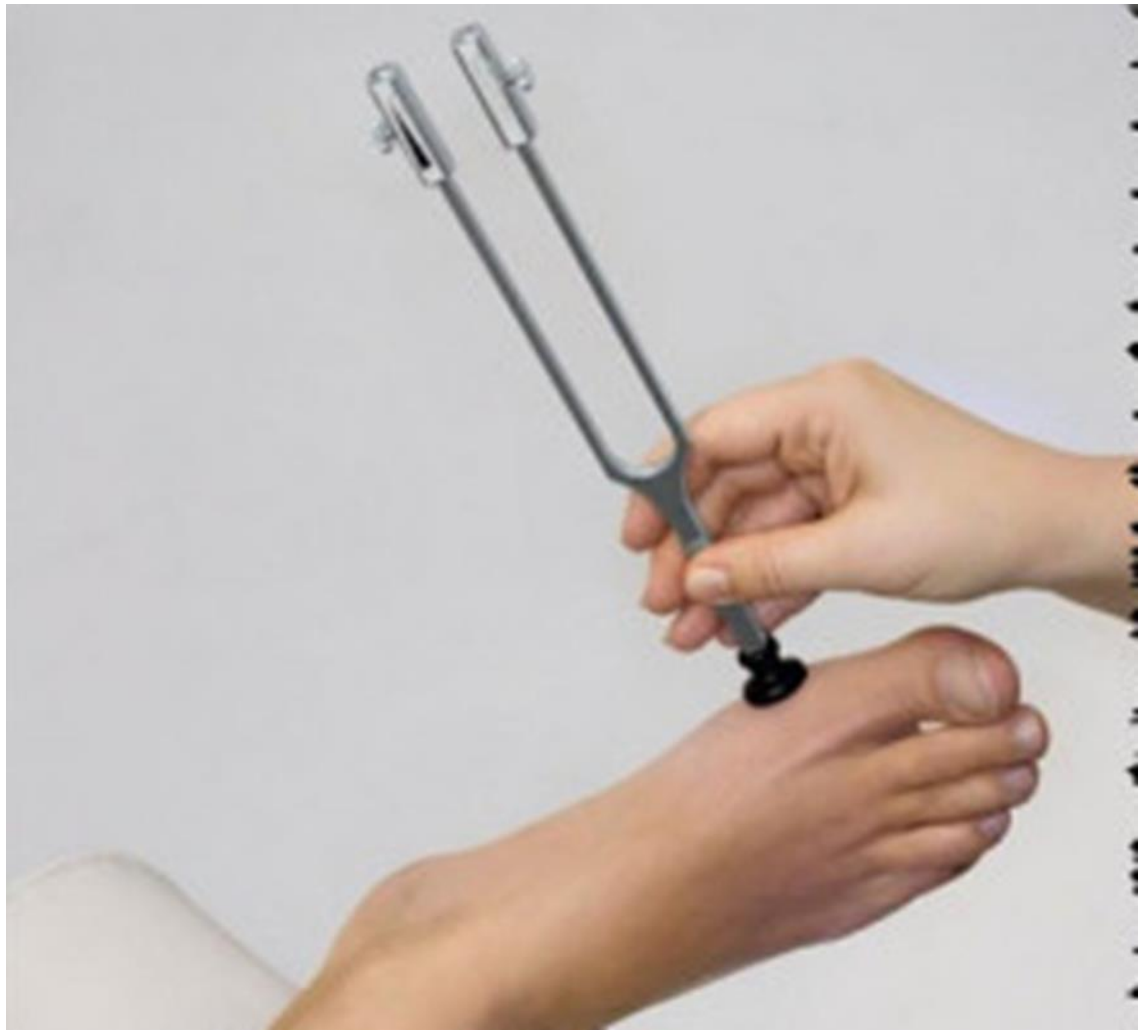
- Many patients, especially with light symptoms, experience relief when the drugs that cause the adverse events are discontinued.
- Linezolid-induced neuropathy is common with its prolonged use, it is often extremely painful and irreversible. Therefore, if symptoms of neuropathy develop (grade 2 or higher), linezolid should be immediately discontinued and never re-started. Consider other anti-TB drugs to add to the treatment regimen.
- In patients with concomitant HIV infection, avoid use of d4T (stavudine) or ddI (didanosine) in combination with cycloserine/terizidone or linezolid due to the increased risk of peripheral neuropathy.

Symptomatic Treatment

- Non-steroid anti-inflammatory drugs or acetaminophen may help to relieve symptoms.
- Tricyclic antidepressants are traditionally used to treat neuropathic pain; however, due to their ability to prolong the QT interval (as well as increase the risk of arrhythmia), they should be avoided when using tall-oral treatment regimens that also extend the QT interval. Besides, simultaneous use of tricyclic antidepressants and linezolid can lead to the development of serotonin syndrome.
- Carbamazepine can effectively relieve pain and other symptoms of peripheral neuropathy. Carbamazepine is a strong inducer of CYP3A4 (Cytochrome P450 3A4) and should not be used simultaneously with bedaquiline or delamanide.

Vibration Test

Rydel-Seiffer Tuning Fork for neurologists 128/64 Hz



Optic Nerve Damage

- Optic nerve damage (optic neuritis)
- TB drugs that might cause it: Lzd, E, Eto/Pto, H, S
- Other possible causes: ddI (didanosine)
- Optic neuritis is an inflammation of the optic nerve, which eventually results in irreversible loss of vision. The first symptom of optic neuritis is usually loss of the ability to distinguish between red and green colours. The best way to test red-green colour vision is Ishihara test. Other symptoms include central scotoma.
- Of all anti-TB drugs, linezolid is by far the most common cause of optic neuritis: up to 18% of patients.
- Diabetic patients are at a higher risk of optic neuritis. Management of such patients should include close monitoring of glucose levels as a preventive measure. Patients with late-stage kidney disease are also at increased risk of optic neuritis.
- Formal assessment of visual acuity in young children can be difficult, and age-appropriate screening tests should be used. Visual acuity can also be assessed by tracking objects, especially when using bright objects or toys. Symptoms of reduced visual acuity in children may include bumping into walls or other objects, tripping, and being unable to grab or find objects.

Suggested Management Strategy

- The drug suspected to have caused the AE (linezolid or ethambutol) should not be re-started.
- Refer the patient to an ophthalmologist for immediate examination and management.
- The condition of a patient with optic neuritis usually improves after the discontinuation of the drug that caused it, if the neuritis is caught at an early stage.
- Consider other anti-TB drugs as an addition to the treatment regimen.

Clinical Management of Patients with Optic Nerve Damage of Various Severity Stages

Severity Stage*	**Stage 1: mild**	**Stage 2: moderately severe**	**Stage 3: severe**	**Stage 4: life-threatening**
Optic Nerve Damage	Asymptomatic; only clinical or diagnostic findings	Reduced visual acuity in the affected eye: 20/40 [6/12] or better	Reduced visual acuity in the affected eye: Worse than 20/40 [6/12], but better than 20/200 [6/60]	Blindness in the affected eye : 20/200 [6/60] or worse
Action	If there is any suspicion of optic neuritis, discontinue Lzd immediately. Do not re-start it.	If there is any suspicion of optic neuritis, discontinue Lzd immediately. Do not re-start it.	If there is any suspicion of optic neuritis, discontinue Lzd immediately. Do not re-start it.	If there is any suspicion of optic neuritis, discontinue Lzd immediately. Do not re-start it.

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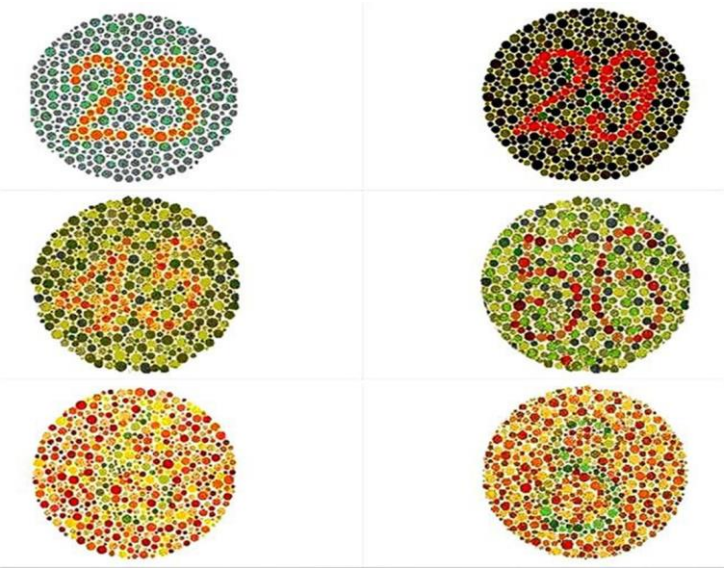

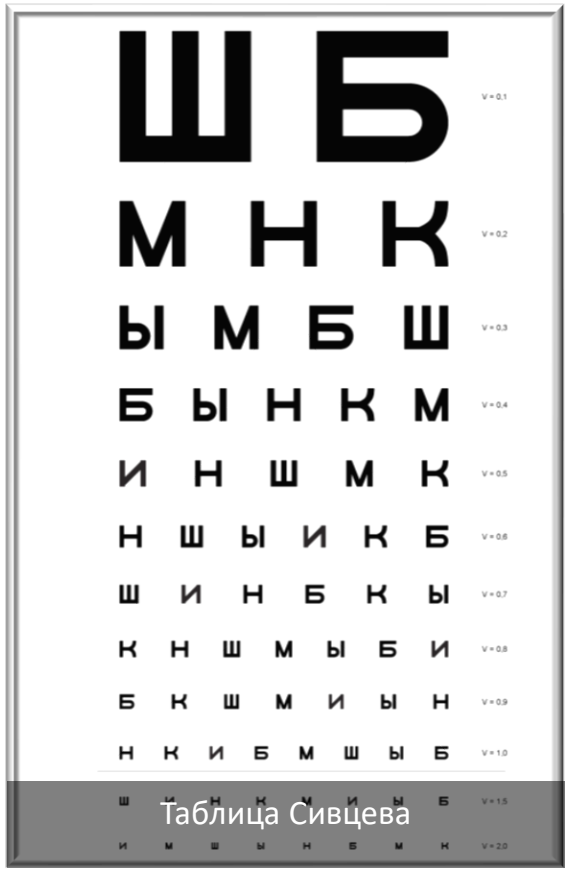

Таблица Сивцева

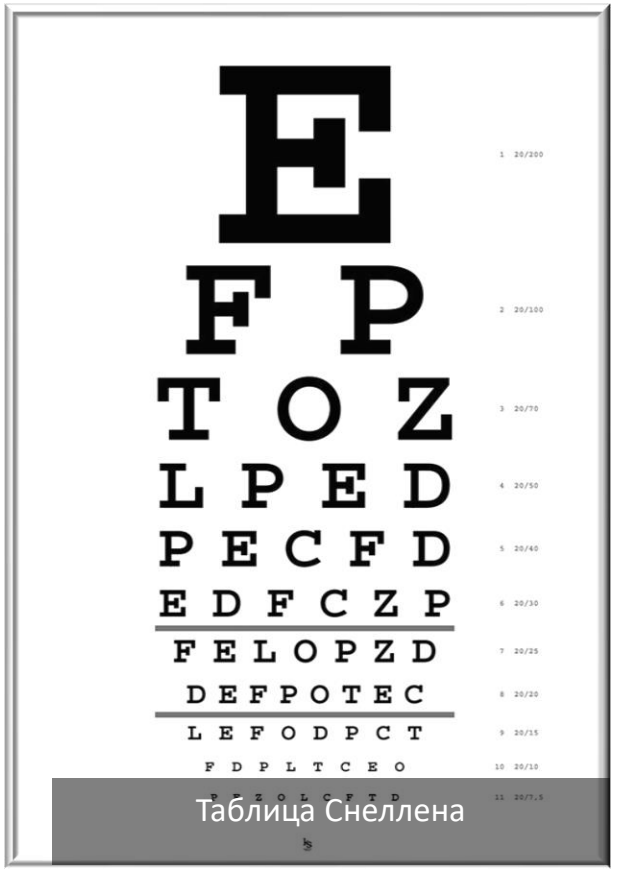

Таблица Снеллена

Ichihara Test

Thank you!

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