

Clinical Case 2

Linezolid: monitoring and management for toxicity

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Agenda & Participant List



**CENTER FOR GLOBAL
HEALTH DELIVERY-DUBAI**
HARVARD MEDICAL SCHOOL

Toxicity associated with linezolid

Adverse effects associate with linezolid:

- **Peripheral neuropathy**
- **Optic nerve disorder (optic neuritis)**
- **Myelosuppression (anemia, thrombocytopenia, or neutropenia)**

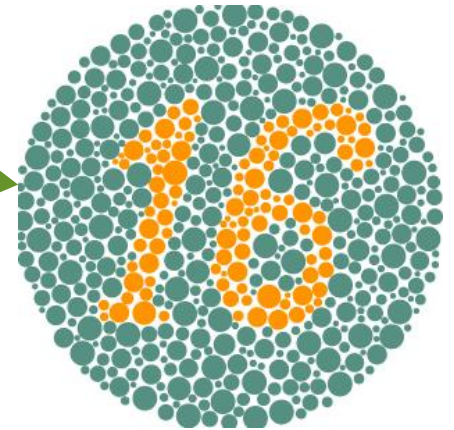
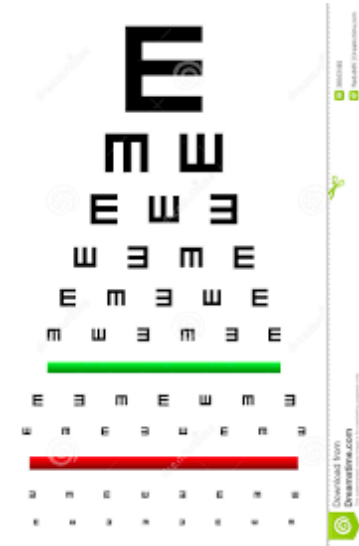
Linezolid is the most toxic drug of the Group A and B drugs.

Any program using linezolid MUST actively monitor for toxicity AND manage any side effects that develop.

What needs to be monitored while on linezolid:

What needs to be monitored while on linezolid:

- **Peripheral neuropathy:**
 - Use **Brief Peripheral Neuropathy Screen (BPNS)** plus decreased vibration sense in the big toes or decreased ankle tendon reflexes.
- **Optic nerve disorder (optic neuritis)**
 - Use **Visual Acuity Test**, usually with the **Snellen Test**
 - Use the **Ishihara Test** – a test for disturbances in color perception
- **Myelosuppression (anemia, thrombocytopenia, or neutropenia)**
 - Check Hgb
 - Check Platelet count
 - Check White Blood Cell (WBC) count



How to screen for peripheral neuropathy

- Skin punch biopsies, nerve conduction studies or other specialized tests are the gold standard but are not necessary for a diagnosis.
- According to the ACTG Brief Peripheral Neuropathy Screen (BPNS), a patient can be diagnosed with peripheral neuropathy if he/she reports typical symptoms (numbness, tingling, burning, pain) **plus** decreased vibration sense in the big toes or decreased ankle tendon reflexes.
- Pain is often described as "burning", "electric", "tingling", and "shooting" in nature. As described, the pain is most often present without associated stimulation, but can be exacerbated by stimuli.
- The Grade of the peripheral neuropathy is based on the subjective symptoms only (the vibratory and reflex tests supplement the clinical picture).
- Peripheral neuropathy can be permanent and extremely debilitating.

(ATCG = AIDS Clinical Trial Group)

How to screen for peripheral neuropathy

ACTG Brief Peripheral Neuropathy Screen (BPNS):

Step 1. Grade Subjective Symptoms

Ask the subject to rate the severity of each symptom on a scale from 01 (mild) to 10 (most severe) for right and left feet and legs. Enter the score for each symptom in the columns marked R (right lower limb) and L (left lower limb).

Normal	Mild ----- Severe									
00	01	02	03	04	05	06	07	08	09	10

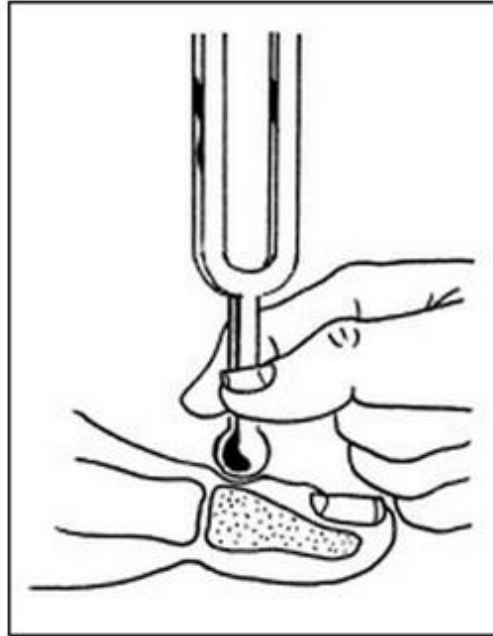
Symptoms	R	L
a. Pain, aching, or burning in feet, legs		
b. "Pins and needles" in feet, legs		
c. Numbness (lack of feeling) in feet, legs		

† Use the single highest severity score above to obtain a subjective sensory neuropathy score.

Subjective Sensory Neuropathy Score	Severity grade
00	0
01 – 03	1
04 – 06	2
07 – 10	3



Peripheral Neuropathy



Vibration perception	Result	Score
Felt > 10 seconds	Normal	0
Felt 6-10 seconds	Mild loss	1
Felt <5 seconds	Moderate loss	2
Not felt	Severe loss	3

Peripheral Neuropathy

Ankle reflexes	Score
Absent	0
Hypoactive	1
Normal deep tendon reflexes	2
Hyperactive	3
Clonus	4

Monthly lab tests and clinical examinations:

[illegible]

Clinical Case :Peripheral neuropathy

A HIV negative patient is in month 2 of the all-oral shorter regimen

Lfx 1g/d)-Bdq (200 three times a week)-Lzd (600mg/d)-Clz(100 mg/day)-Z (1500 mg)

He complains of burning in his feet for three weeks and his skin turning orange-brown in color.

Normal	Mild ----- Severe									
00	01	02	03	04	05	06	07	08	09	10

Symptoms	R	L
a. Pain, aching, or burning in feet, legs	02	03
b. "Pins and needles" in feet, legs	00	01
c. Numbness (lack of feeling) in feet, legs	02	02

Vibratory sensation is > 10 seconds (NORMAL)

Ankle reflexes are normal.

What do you recommend to do in this patient?

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Paresthesia (burning, tingling, etc.)	Mild discomfort; no treatment required; and/or BPNS subjective sensory neuropathy score 1-3 on any side.	Moderate discomfort; non-narcotic analgesia required; and/or BPNS subjective sensory neuropathy score 4-6 on any side.	Severe discomfort; or narcotic analgesia required with symptomatic improvement; and/or BPNS subjective sensory neuropathy score 7-10 on any side.	Incapacitating; or not responsive to narcotic analgesia
Action	<p>Stop Cs/Trd, high-dose H, and Lzd. If symptoms improve, consider restarting these drugs. Consider restarting Lzd at a lower dose (300mg daily or 600 mg thrice weekly).</p> <p>If Cs/Trd or high-dose H are not essential to the regimen, consider suspending these drugs.</p>	<p>Stop Cs/Trd, high-dose H, and Lzd. If symptoms improve, and if the drugs are essential to the regimen, consider restarting Cs/Trd or high-dose H (usually at a lower dose). In most cases, do not reintroduce Lzd.</p> <p>Provide symptomatic relief as described below.</p>	<p>Same as Grade 2.</p> <p>Do not reintroduce Lzd.</p>	<p>Same as Grade 2.</p> <p>Do not reintroduce Lzd.</p>

* Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

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Clinical Case – Peripheral neuropathy

The peripheral neuropathy is most likely secondary to the linezolid (Lzd). Since it is mild, Lzd should be stopped temporarily.

If symptoms improve, consider restarting Lzd at a lower dose (300mg daily or 600 mg thrice weekly).

Clinical Case :Peripheral neuropathy

In this case the Lzd is stopped and patient is asked to return in two weeks

After two weeks the patient reports that symptoms have improved.

Normal	Mild ----- Severe									
00	01	02	03	04	05	06	07	08	09	10
Symptoms									R	L
a. Pain, aching, or burning in feet, legs									01	02
b. "Pins and needles" in feet, legs									00	00
c. Numbness (lack of feeling) in feet, legs									00	00

Vibratory sensation is > 10 seconds (NORMAL)

Ankle reflexes are normal.

Clinical Case :Peripheral neuropathy

The Lzd is restarted at 600 mg three times a week (Monday-Wednesday-Friday).

Clinical Case :Peripheral neuropathy

The patient continues on the regimen

Lfx 1g/d)-Bdq (200 three times a week)-Lzd (600mg/TIW)-Clz(100 mg/day)-Z (1500 mg)

At the month 4 visit he complains of increased burning in his feet for about 3 weeks, much worse than before. The patient smear and culture covered at month 1 and is doing well clinically. **What do you recommend for this patient?**

Normal	Mild ----- Severe									
00	01	02	03	04	05	06	07	08	09	10

Symptoms	R	L
a. Pain, aching, or burning in feet, legs	04	05
b. "Pins and needles" in feet, legs	01	01
c. Numbness (lack of feeling) in feet, legs	02	03

Vibratory sensation is > 10 seconds (NORMAL)

Ankle reflexes are normal.

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Paresthesia (burning, tingling, etc.)	Mild discomfort; no treatment required; and/or BPNS subjective sensory neuropathy score 1-3 on any side.	Moderate discomfort; non-narcotic analgesia required; and/or BPNS subjective sensory neuropathy score 4-6 on any side.	Severe discomfort; or narcotic analgesia required with symptomatic improvement; and/or BPNS subjective sensory neuropathy score 7-10 on any side.	Incapacitating; or not responsive to narcotic analgesia
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Clinical Case – Peripheral neuropathy

The peripheral neuropathy has progressed, it is now moderate (Grade 2).

Since the patient has had 4 months of Lzd and is doing clinically well, it is likely that Lzd is not critical to the regimen. The Lzd should be stopped permanently

(If Lzd is critical to the regimen and Grade 2 neuropathy is present, some clinicians try giving a short holiday from Lzd and then restarting at 300 daily or 600 mg every other day to see if symptoms can be managed. But there is some risk of permanent painful neuropathy).

Clinical Case – Peripheral neuropathy

What TB drugs and HIV drugs can be associated with peripheral neuropathy?

TB and HIV drugs that can cause peripheral neuropathy:

Possible anti-TB drug causes: **Lzd, Cs, H, S, Km, Cm, FQ, Pto/Eto, E**

Possible HIV drugs: **d4T, ddl** .