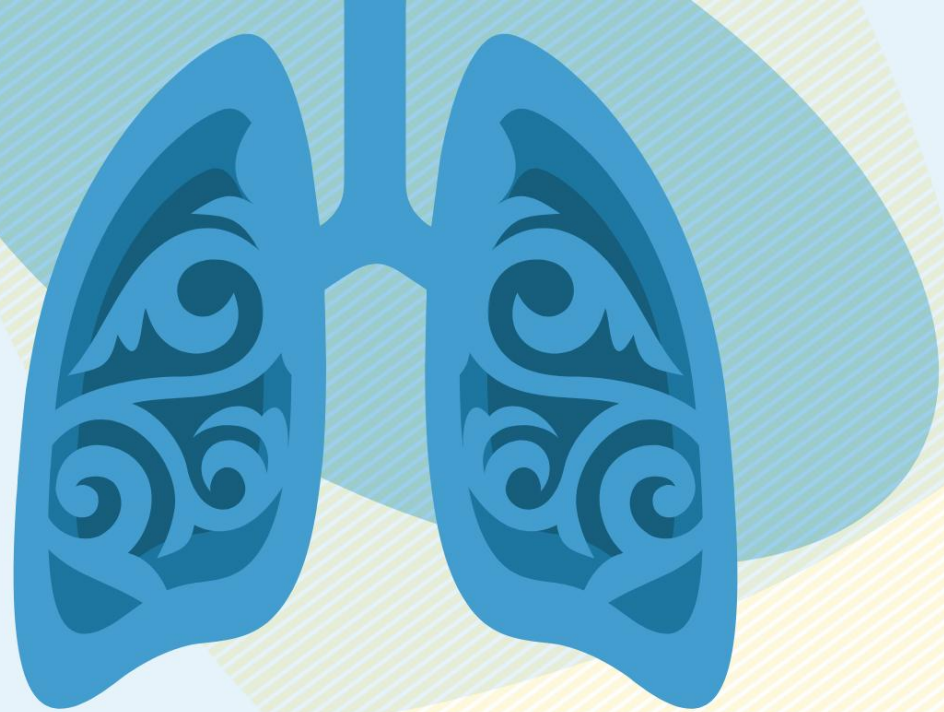
Management of adverse events in MDR/RR-TB treatment



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REGIONAL WORKSHOP ON ACCELERATED IMPLEMENTATION OF WHO GUIDELINES
ON TB PREVENTION, DIAGNOSIS, AND DRUG-RESISTANT TB (DR-TB) TREATMENT

Topics to be covered

- Rate of adverse events with BPaL M, BDLLfxC, modified 9-month regimens and 9-month in clinical trials
- Management of adverse events of special interest
  - Myelosuppression
  - Peripheral neuropathy
  - Optic neuropathy
  - Hepatoxicity
  - Cardiotoxicity

Rate of adverse events on clinical trials

Trial	Grade3- 4	Adverse event related to drug
Zenix[a]	24-31%	17%
PRACTECAL (BPaLM)[b]	23%	
BEAT Tuberculosis	37%	25%
End TB[c]	55-61%	6-18%

[a] Conradie, Bagdasaryan et al. 2022
[b] Nyang'wa, Berry et al. 2024
[c] Guglielmetti, Khan et al. 2025

Adverse events of special interest

Myelosuppression

- Anemia
- Neutropenia
- Thrombocytopenia

Peripheral neuropathy

Optic neuropathy

Hepatotoxicity

Cardiac toxicity

Myelosuppression

May affect all the cell lines but tends to cause anemia

Tends to occur in the first 8 weeks.

Anaemia is common co-morbidity with TB

- Undernutrition
- Anemia of chronic disorder
- HIV co-infection
- Blood loss due to hemoptysis

Detection and management of anemia (1)

Management of anemia when starting treatment

Baseline full blood count/Hb

- If HB is above 8g/dl start L containing regimen and repeat in 2 weeks
- If Hb is below 8g/dl
  - Consider admission
  - Consider transfusion
  - If starting treatment, repeat in 1 week
  - Warn patient about symptoms of anemia and how to get help

There is no place for starting the regimen without linezolid

Detection and management of anemia (2)

Management of anemia during treatment

Repeat full blood count/Hb at 2 weeks and then every month while on linezolid

- If HB is above 8g/dl continue at full dose (600mg)
- If Hb is below 8g/dl
  - Consider admission
  - Consider transfusion
  - Assess for symptoms of anemia
  - Interruption of linezolid and repeat FBC in a week or less
  - Reintroduced linezolid at 600mg or 300mg
  - Warn patient about symptoms of anemia and how to get help
  - Keep dose interruptions to the minimum

Detection and management of neutropenia and thrombocytopenia

Full blood count at initiation, 2 weeks and then every month while on linezolid

- If absolute neutrophil counts is less that 0.75 10^6/l or platelet counts is less that 100 10^9/L, repeat in a week or less
  - If persistent, consider interruption of linezolid Interruption of linezolid and repeat FBC in a week or less
- Reintroduce linezolid at full dose
- Keep dose interruptions to the minimum

Detection and management of peripheral neuropathy

Requires clinician and patient awareness

Other common causes of peripheral neuropathy

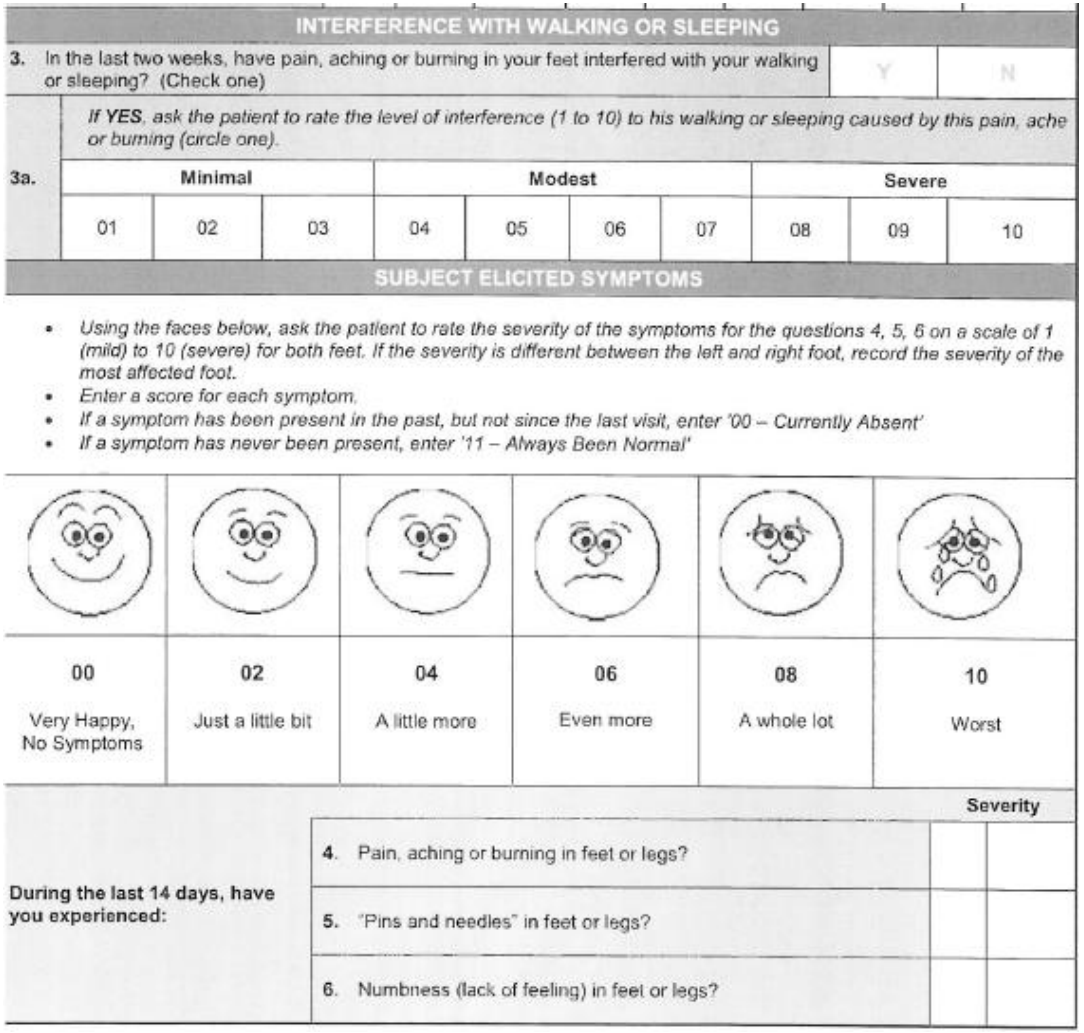
- Diabetes
- HIV infection
- Alcohol
- Other medications e.g., INH

Tends to occur later in treatment (from 16 weeks)

Check at every visit if there is pain, pins and needles, loss of sensation or paresthesia

Detection and management of peripheral neuropathy

- Difficult to grade severity
- Ask patient about interruptions of daily life esp. sleep



INTERFERENCE WITH WALKING OR SLEEPING

3.	In the last two weeks, have pain, aching or burning in your feet interfered with your walking or sleeping? (Check one)	Y	N

If YES, ask the patient to rate the level of interference (1 to 10) to his walking or sleeping caused by this pain, ache or burning (circle one).

3a.	Minimal			Modest				Severe		
	01	02	03	04	05	06	07	08	09	10

SUBJECT ELICITED SYMPTOMS

- *Using the faces below, ask the patient to rate the severity of the symptoms for the questions 4, 5, 6 on a scale of 1 (mild) to 10 (severe) for both feet. If the severity is different between the left and right foot, record the severity of the most affected foot.*
- *Enter a score for each symptom.*
- *If a symptom has been present in the past, but not since the last visit, enter '00 – Currently Absent'*
- *If a symptom has never been present, enter '11 – Always Been Normal'*

00	02	04	06	08	10
Very Happy, No Symptoms	Just a little bit	A little more	Even more	A whole lot	Worst

During the last 14 days, have you experienced:		Severity	
	4. Pain, aching or burning in feet or legs?		
	5. "Pins and needles" in feet or legs?		
	6. Numbness (lack of feeling) in feet or legs?		

Detection and management of peripheral neuropathy

- If occurs early in treatment prior to clinical and microbiological response

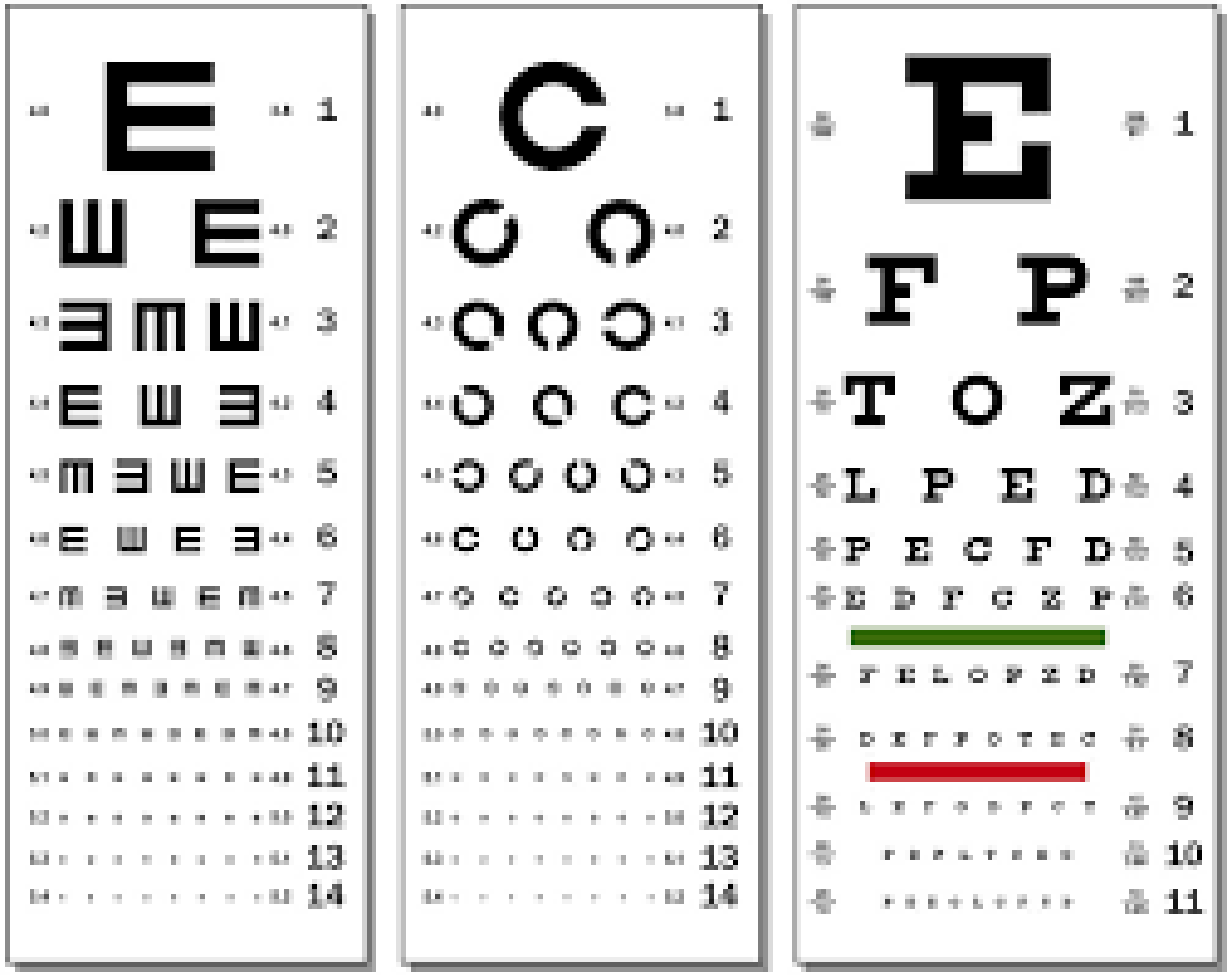
Interrupt	• Interrupt linezolid only
Monitor	• Monitor for resolution of symptoms
Re-introduce	• When symptoms are manageable at a lower dose
Permanently discontinue if recurs	

- If occurs later in treatment after to clinical and microbiological response

Interrupt	• Interrupt linezolid only
Monitor	• Monitor for resolution of symptoms
Consider	• Consider permanent discontinuation of 16 weeks of treatment have been completed

Detection and management of optic neuritis

- Done at initiation and at every visit while of linezolid
- If there is a two-line drop, consider optic neuritis.
- If possible, fundoscopy or ophthalmology referral
- Interrupt linezolid until diagnosis is excluded.



Hepatotoxicity

Competing risks for Hepatotoxicity

- Alcohol
- Viral Hepatitis
- Other toxins

Drug Causes

- PZA
- INH
  - BDQ, Mpm, Amx/Clv, Eto/Pto, Cfz, Trd/Cs, PAS

Often asymptomatic

Monitoring liver function

Monthly transaminase measures (ALT/AST)

Grade 2 >3.0–5.0 × ULN (upper limit of normal)

- Continue the treatment regimen; follow patients until resolution (return to baseline) or stabilization of AST/ALT levels

Grade 3 >5.0–20.0 × ULN

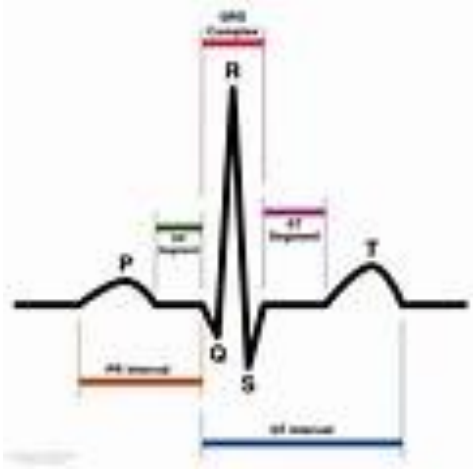
- Grade 3 Stop all drugs, including anti-TB drugs
- Exclude other causes
- repeat LFTs weekly

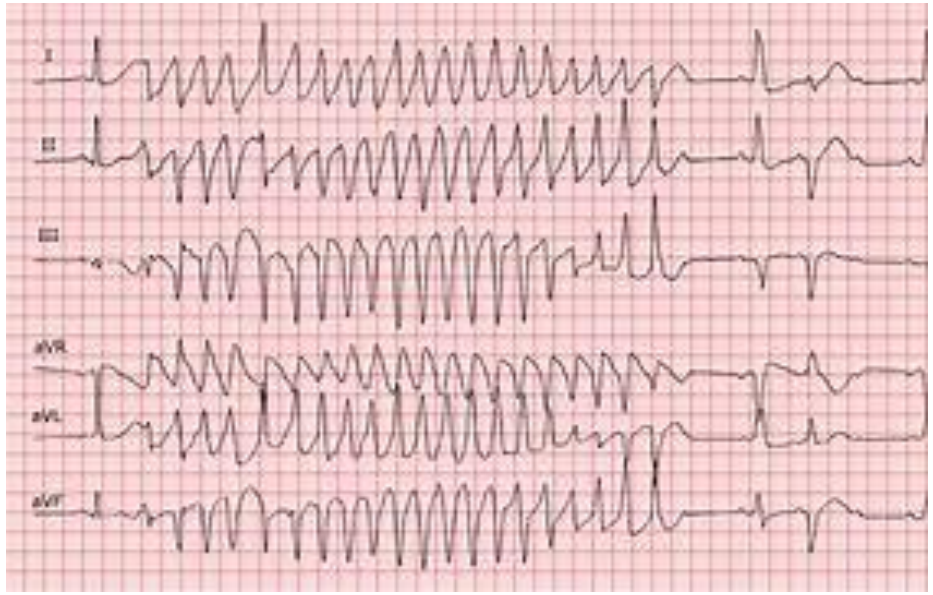
Grade 4

- Stop all drugs, including anti-TB drugs
- Exclude other causes
- repeat LFTs weekly
- treatment may be reintroduced WITHOUT PZA after toxicity is resolved

Cardiotoxicity

- Prolongation of the QT interval
- If QTc F is above 500ms, predisposes to Torsades de Points
- Causative agents: BDQ, clofazimine, moxifloxacin, delaminid.





Adverse events to bedaquiline

Prolongation of the QT interval

- If QTcF above 500
  - Check for reversible courses, e.g. electrolytes, hypothyroidism
  - Exclude other QT prolonging drugs
  - If persistent, stop BDQ and moxifloxacin

Cardiotoxicity

BDQ, Moxi, Clofazimine, DLM

>500 ms without signs or symptoms of serious arrhythmia

- Repeat ECG after allowing the patient to rest for at least 10 min
- Hospitalize if possible and replete electrolytes as necessary
- If QTcF remains >500 ms, stop the regimen and repeat ECG within 2–5 days
- Ensure that the patient is not taking any other QT-prolonging drugs
- Exclude hypothyroidism

>500 ms with signs or symptoms of serious arrhythmia

- TdP or polymorphic ventricular tachycardia, or symptoms of serious arrhythmia
- The whole regimen needs to be stopped
- hospitalize and replete electrolytes as necessary
- Ensure that the patient is not taking any other QT-prolonging drugs
- Exclude hypothyroidism

In conclusion

6-9 months of treatment for RR-TB is a breakthrough

The Adverse Events are predictable and can be managed mostly at a primary care level.

Safety in pregnancy and children has not yet been established for all drugs

THANK YOU!

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