MAYO CLINIC

MAYO CLINIC CENTER FOR TUBERCULOSIS

TB Drug Adverse Reactions

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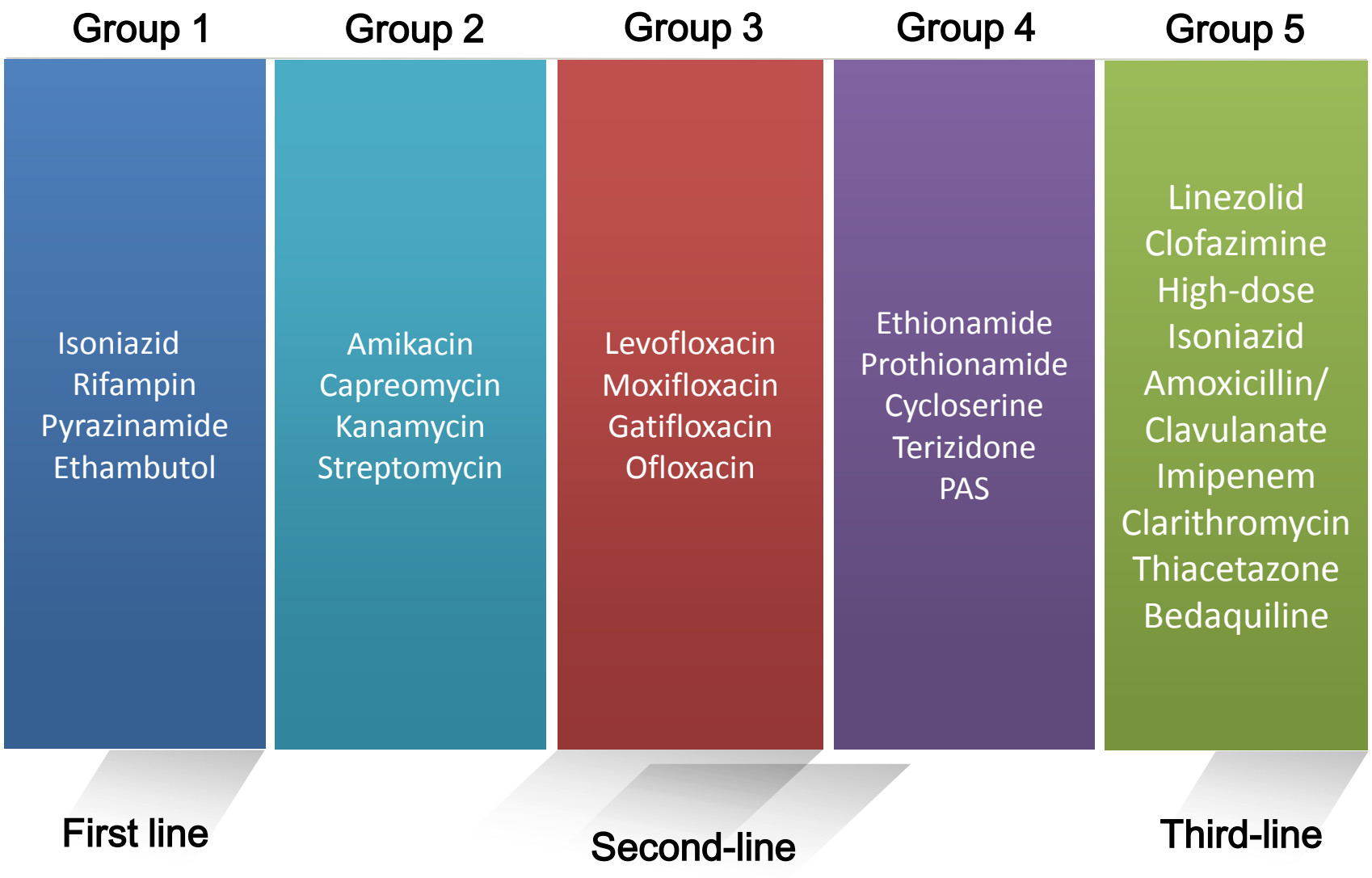
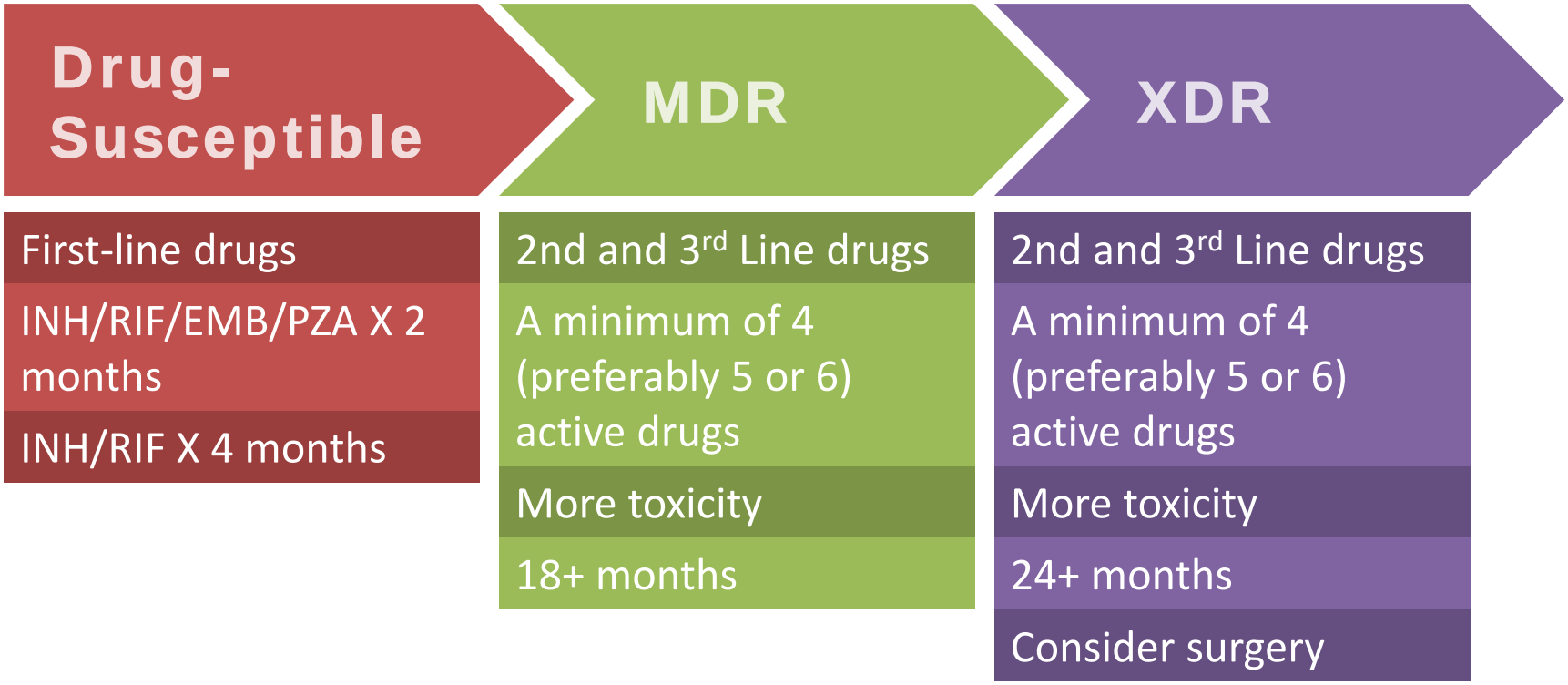
Conflicts/Disclosure

- None.

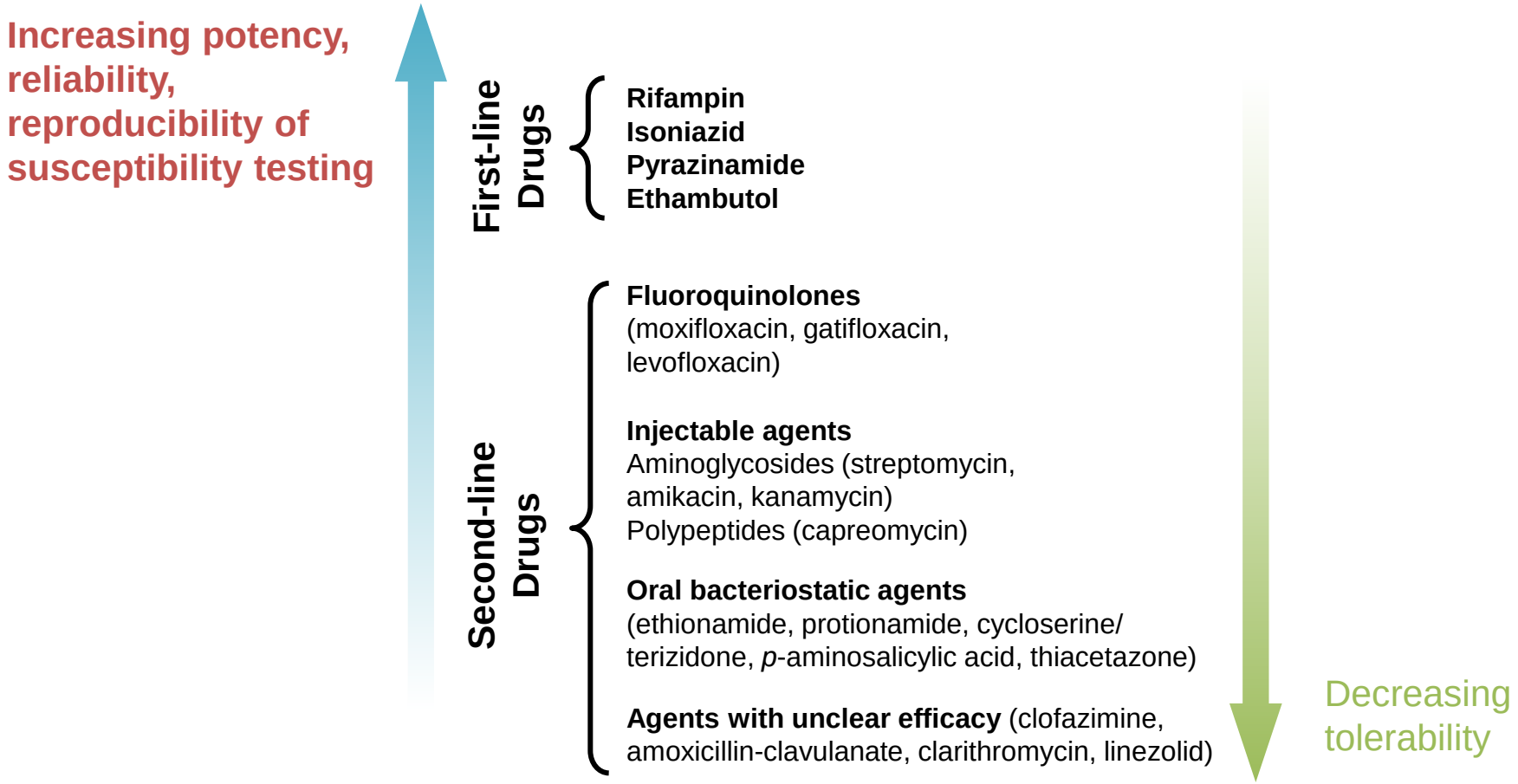
Anti-Tuberculous Drugs



Duration of Tuberculosis Treatment

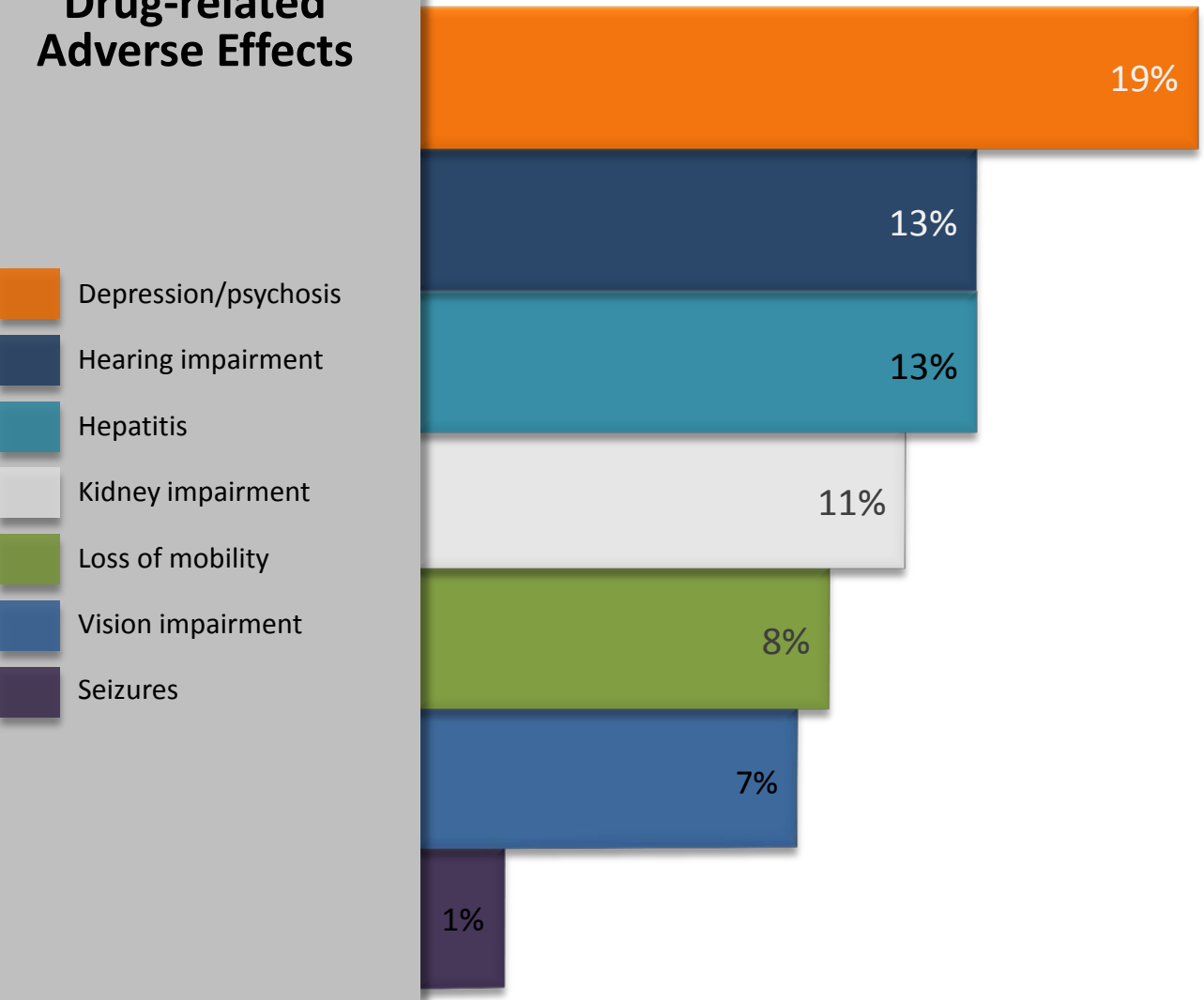


Potency and Tolerability of TB Drugs



Dorman SE, et al. Nat Med. 2007;13:295-298.

DR-TB: Drug-related Adverse Effects



Adverse Events during Treatment of TB

- Very common
  - More than 80% of patients on treatment for DR-TB will have adverse events
- Even mild and common events can affect treatment outcomes
- Some adverse events can be life-threatening
- Some adverse events can cause permanent disability
- Critical drugs may be discarded if not properly addressed
- Timely recognition and management of adverse events important for adherence and completion of treatment

Topics

- Drug-based approach
- Symptoms-based approach

BUT MORE IMPORTANTLY:

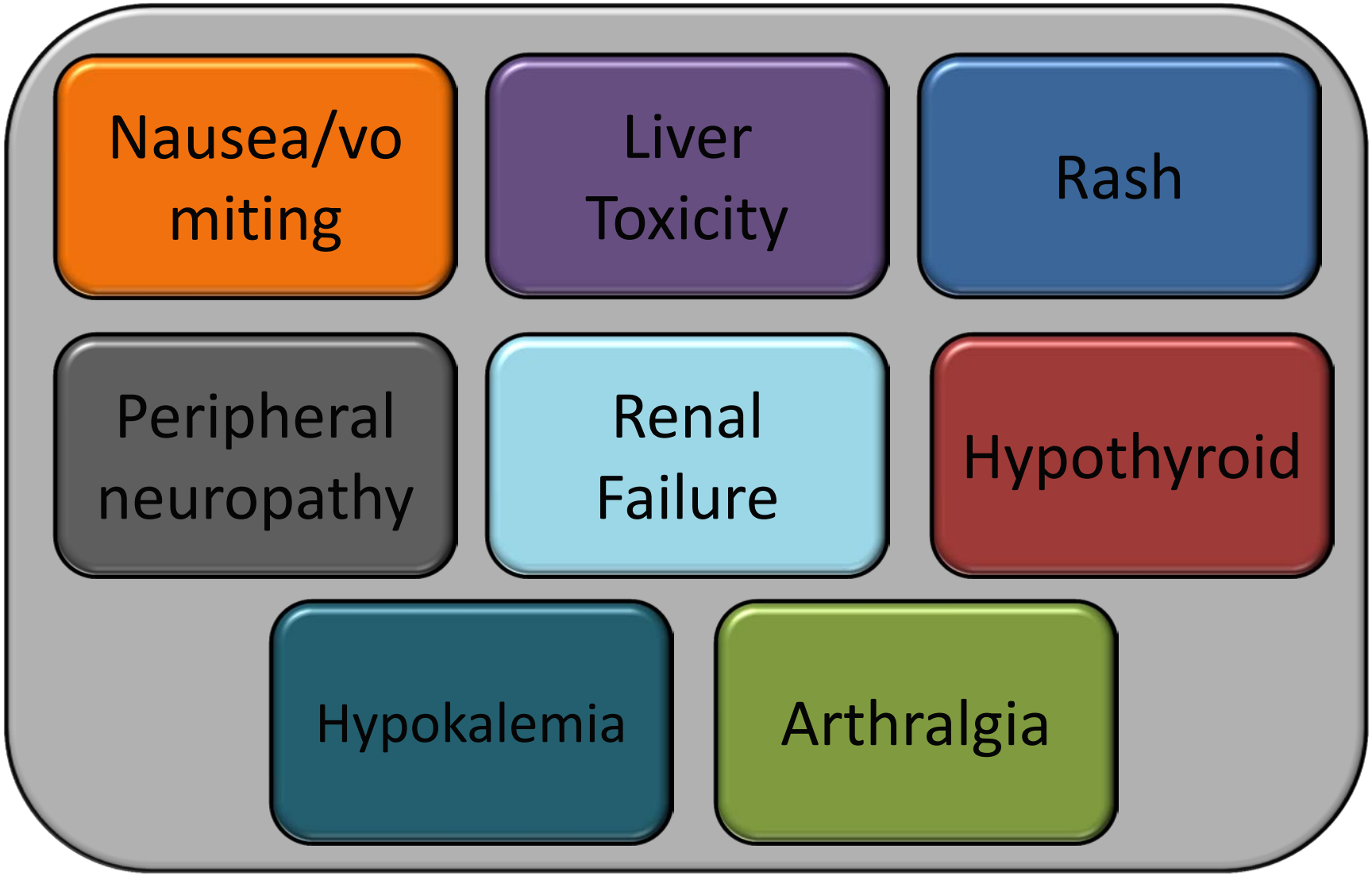
- General approach to managing drug reactions during treatment of tuberculosis

Adverse Effects of First-line Drugs

Drug	Adverse Effect
isoniazid	hepatotoxicity, peripheral neuropathy, CNS effects, lupus-like syndrome, monoamine poisoning
rifampin	flu-like syndrome, hepatotoxicity, anemia, thrombocytopenia, renal failure, drug interactions
pyrazinamide	hepatotoxicity, polyarthralgia, gout
ethambutol	impaired vision, peripheral neuropathy

Adverse Effects of Second-line Drugs

Drug	Adverse Effect
aminoglycoside	ototoxicity, nephrotoxicity,
cycloserine	neuropsychiatric toxicity, peripheral neuropathy
ethionamide	hepatotoxicity, neurotoxicity, hypothyroidism
fluoroquinolone	neurotoxicity, tendinitis, hepatotoxicity
PAS	hepatotoxicity, GI distress, hypothyroidism, coagulopathy



Symptoms-Based Approach

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- Up to 90% early in treatment
- Causes: **Ethionamide, PAS** INH, PZA, FQ, BDQ, preg
- Ensure hydration, fractionate doses, fractionate meals, anti-emetics
- Additional testing: K+, LFTs, pancreatic function
- May need to re-dose medications if vomiting happens within 30 minutes of taking tablets

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1	Liver Toxicity
3	4
5	6
7	8

- More concerning for drug-induced injury when bilirubin and transaminases elevated (Hy's law)
- Viral hepatitis, alcohol, PZA, INH, Rif, any of the TB medications
- Baseline: screen for HBV, HCV
- Screening: symptoms
- Laboratory monitoring if baseline abnormal or with certain conditions

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Rash

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- Up to 10% of patients
- Mild hives to SJS
- Screening: symptoms
- Cause: any drug; consider timing of onset, past episodes
- Mgmt. depends on severity
  - if severe, discontinue therapy and serially reintroduce
- Additional testing: consider infectious causes

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1	2
3	Peripheral neuropathy
5	6
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- Up to 30% of patients
- LZD, INH, CS, Ethionamide
- HIV, DM, alcohol use
- Screening: symptoms, subjective neuropathy scale
- Mgmt.:
  - Decrease LZD; if CS or INH, d/c;
  - Physical therapy; sturdy shoes; SSRIs;
- Management of comorbidity
- B6 for INH, LZD, CS

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Renal Failure

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- Up to 10% during DR-TB Rx
- More common in persons with HIV, DM
- Common causes: injectable, other nephrotoxic drugs (e.g. TDF)
- Screening: monthly on injectables
- Management:
  - Hydration
  - d/c injectable,
  - Manage comorbidity

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Hypothyroid

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- Up to 10% of patients
- More common in HIV infected
- Causes: Ethionamide, PAS
- Screening: symptoms
  - Fatigue, sensitivity to cold, constipation, dry skin, depression
- TSH if on ethionamide, PAS
- Management: Thyroid replacement therapy
- Additional testing: QTc

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1	2
3	4
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Hypokalemia	8

- Up to 15% during DR-TB Rx
- Cause: injectables
- More common with vomiting, diarrhea, alcohol
- Weakness, fatigue, muscle cramps, constipation

Screening: monthly while on injectable, if QTc prolonged

- Mgmt.:
  - Replete K, Mg
  - ensure hydration
- Calcium if QTc prolongation

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Arthralgias

- TB itself can cause arthritis
- Arthralgias are common, usually transient
- Physical exercise may help
- Treatment with nonsteroidal anti-inflammatory drugs may be useful
- If acute swelling, redness, and warmth, aspirate for diagnosis
- PZA may increase uric acid levels
  - Often asymptomatic
  - UA levels don’t match severity
  - If arthritis, usually non-deforming and non-erosive
- Usually do not warrant stopping PZA or other anti-TB drugs

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To panel board main

Interactive Panel List Layout

To panel board main

- Anemia
- Thrombocytopenia
- Leukopenia
- Hearing Loss
- Vision Loss
- Depression
- Psychosis
- Seizures

Anemia

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- Can occur in as many as 25% of patients
- More common in patients with HIV, alcohol use
- Screening: symptoms, HgB monthly if on LZD
- Poor prognostic sign if persists with treatment
- Common causes: TB, LZD, HIV, ART
- Management strategies: iron supplementation, decrease dose of LZD, transfusion if indicated, discontinue other medications

Thrombocytopenia

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- Relatively uncommon (<5%)
- More common in patients with co-morbidities such as HIV, alcohol use
- Screening: symptoms – easy bruising, bleeding
- Common cause: LZD, alcohol
- Mgmt.: lower dose or d/c LZD, monitor for bleeding
- Additional testing: Check WBC, other co-morbidities, alcohol screening

Leukopenia

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- Relatively uncommon (<5%)
- More common in patients with co-morbidities such as HIV, alcohol use
- Screening: Monthly CBC
- Common cause: LZD, alcohol, HIV
- Mgmt.: lower dose or d/c LZD, monitor for infections
- Additional testing: HIV, alcohol screening

Hearing Loss

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- Can occur in as many as 30% of patients
- Major cause of permanent disability
- Screening: symptoms, monthly audiometry while on injectable
- Common cause: injectable agents
- Management strategies: EARLY IDENTIFICATION KEY; discontinue injectable and start BDQ or DLM

Vision Loss

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- Screening: symptoms, visual acuity, color testing
- Common causes: age, cataract, EMB, LZD, Rifabutin
- Management: r/o other causes, d/c or lower dose of EMB and or LZD
- Additional testing: examination of optic nerve

Depression

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- Common, may occur in more than 50% of patients
- Often based on life circumstances; can wax and wane during treatment
- Screening: symptoms
- Common causes: life, CS, INH
- ASSESS FOR HARM TO SELF
- Management: counseling, psychosocial support, group therapy, antidepressants (avoid TCAs on BDQ; avoid SSRIs on LZD); hospitalize if suicidal
- Additional testing: TSH, drug and alcohol screen

Psychosis

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- Can occur in as many as 5% of patients
- Can be severe and life-threatening
- Screening: symptoms
- Common causes: CS, INH, EFV, alcohol withdrawal
- ASSESS FOR HARM TO SELF OR OTHERS
- Management: discontinue CS and replace with new drug (i.e. BDQ, LZD); antipyschotics (avoid haloperidol if on BDQ); hospitalize for safety
- Additional testing: fever, TSH, drug and alcohol screen

Seizures

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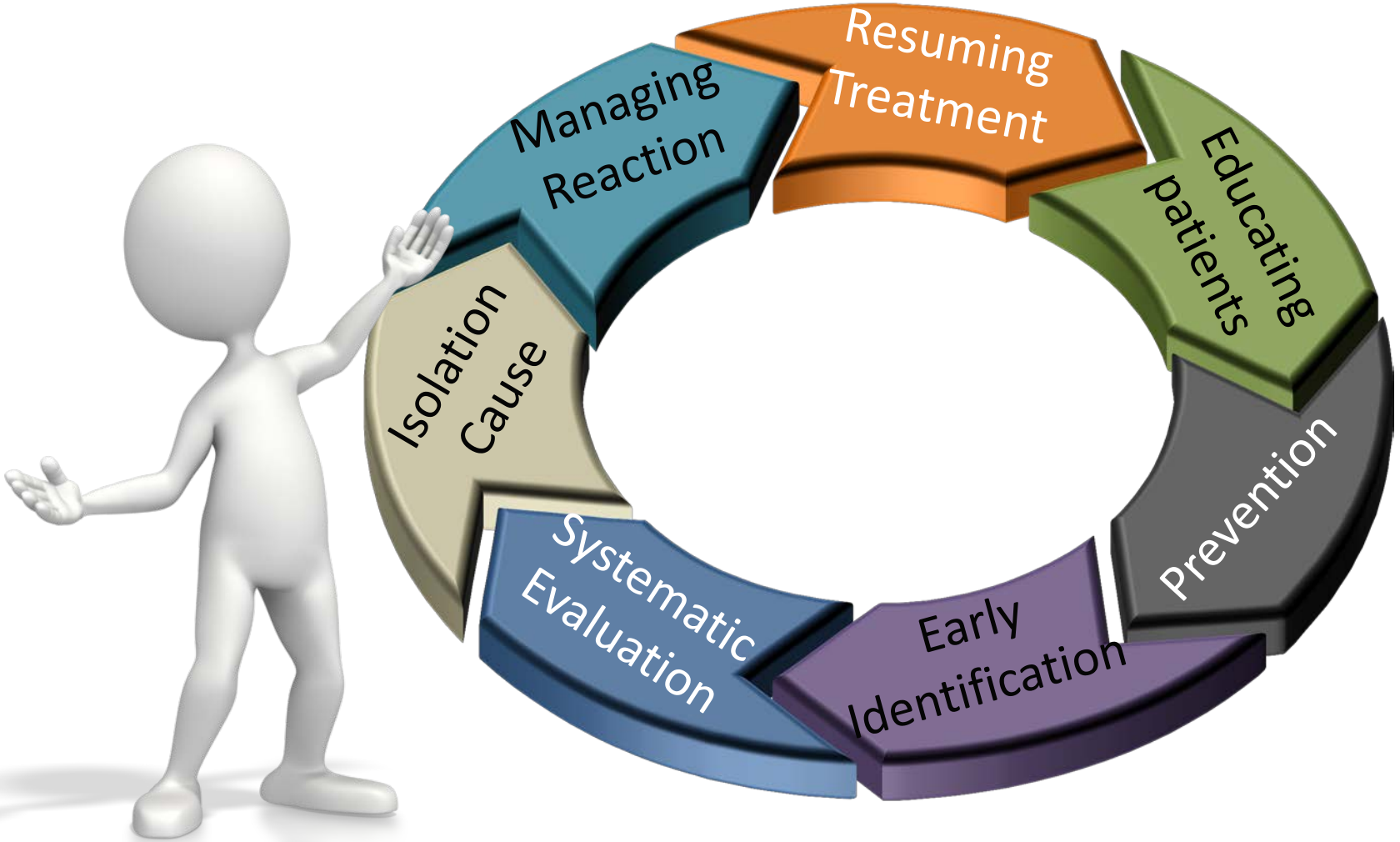
- May occur in up to 10% of patients
- Not felt to be more common if pre-existing condition
- Important to differentiate from syncope
- Screening: symptoms
- Common causes: CS, INH, alcohol withdrawal
- Management: lower dose or discontinue CS or INH, anticonvulsants
- Additional testing: neurologic exam, head CT if focal findings

General Approach



Education

- Importance of treating TB
- Importance of adherence
- Importance of Completion of treatment
- Potential side effects of prescribed treatment
- Simple ways of self managing common side effects
- Communication channel

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Prevention

- Education
- Proper dosing
- Drug interactions
- Comorbidities
  - Liver
  - Kidney
  - CNS

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Early Identification

- DOT
- Clinical visits
- Routine monitoring
- Communication channel for patient complaints/concerns

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Systematic Evaluation

- Drug-based approach
- Symptoms-based approach
- Coordinated
- Thoughtful
- Comprehensive

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Isolation of cause

- May enable single-drug substitution
- Retain key regimen components
- Minimize impact on pill burden and treatment duration

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Managing AE

- Depends on severity
- Simple measures and reassurance may suffice
- Life-threatening will require discontinuation of entire regimen
- May need to check drug levels
- Monitor AE until resolution

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Resumption of Treatment

- The ultimate aim of drug reintroduction is to establish an effective regimen in a safe and speedy fashion.
- Sequential reintroduction may help identify the cause
- Different algorithms exist
- Symptomatic pre/peri treatment may be necessary

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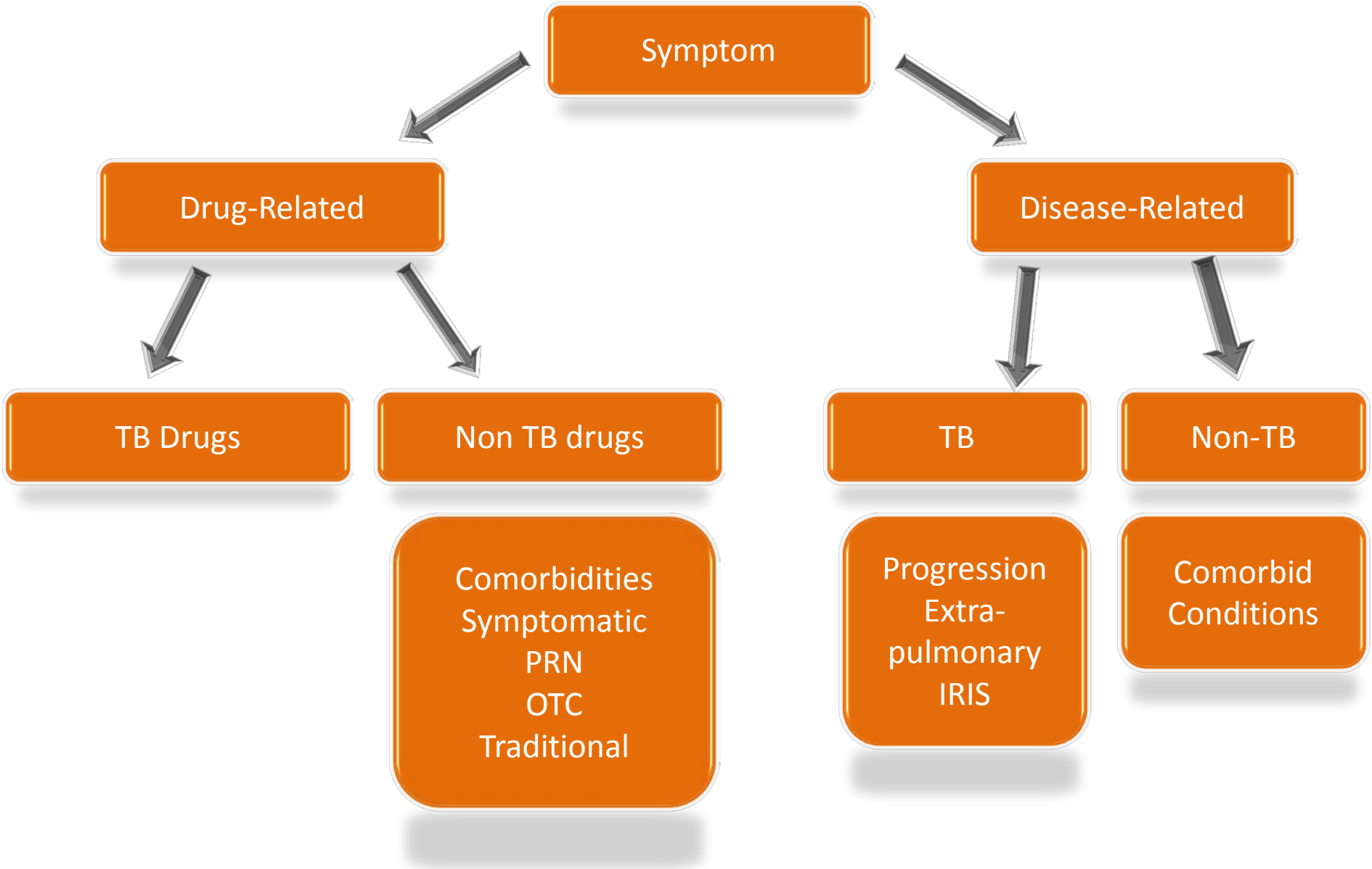
Symptom
Drug-Related
Disease-Related
TB Drugs
Non TB drugs
TB
Non-TB
Comorbidities
Symptomatic
PRN
OTC
Traditional
Progression
Extra-
pulmonary
IRIS
Comorbid
Conditions

Drug Interactions

isoniazid	anti-seizure medication, coumadin
rifampin	Multiple dugs, notably HIV medication, immunomudulators, coumadin
quinolone	drugs causing QT prolongation
pyrazinamide	cyclosporine

ACTG Brief Peripheral Neuropathy Screen (BPNS)

1. Elicit Subjective Symptoms

Ask the subject to rate the severity of each symptom on a scale of 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		

2. Grade Subjective Symptoms

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

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

3. Evaluate Perception of Vibration

Compress the ends of a 128-Hz tuning fork just hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the subject's wrist or hand to be sure that he/she can recognize the vibration or "buzzing" quality of the tuning fork. Again, compress the ends of the tuning fork just hard enough that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the subject to tell you when the "buzzing" stops. Repeat for the other great toe.

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
Unable to or did not assess		8

4. Evaluate Deep Tendon Reflexes

Severity Scales

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory Alteration (includes paresthesia and painful neuropathy) Specify type, if applicable	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures New Onset Seizure ≥ 18 years of age	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)

LFT Monitoring AND CUT-OFFS FOR STOPPING DRUGS

Authority	Monitoring in presence of risk factors (especially liver diseases)	Cut-off levels for DILI and stopping drugs
ATS	Yes	ALT >200 IU/l or, ALT 120 IU/l with symptoms
BTS	Yes	ALT or AST >200 IU/l, rise in bilirubin
ERS, WHO, IUATLD	-	AST > 200 IU/l
HKTBS	Yes	ALT >200 IU/l , bilirubin > 40µmol/l

LFT, liver function test; ALT, alanine transaminase; ALP, alkaline phosphatase; ATS, American Thoracic Society; BTS, British Thoracic Society; ERS; European Respiratory Society; WHO, World Health Organisation; IUATLD, International Union Against Tuberculosis and Lung Disease; HKTBS, Hong Kong Tuberculosis Service

GUIDELINES ON THE MNAGEMENT OF TB-ASSOCIATED DILI

Authority	Stopping TB drugs if clinical or symptomatic hepatitis	When to restart TB drugs	What TB drugs to start	Recommended LFT monitoring on rechallenge	What if DILI recurs
ATS	Yes	ALT < 80	R +/- E full dose After 3-7 days H (full dose) Z only if mild DILI	Check ALT 3-7 days after H rechallenge	Stop last drug added
BTS	Yes	ALT within normal limits	S + E (if unwell or sputum smear positive within two weeks of commencing treatment) H (dose titration, every 2-3 days) R (dose titration, every 2-3 days) Z (dose titration, every 2-3 days)	Daily monitoring of LFT	Stop offending drug, alternative regimen advised by fully trained physician
ERS, WHO, IUATLD	Yes	LFT within normal limits	Start all drugs at full dosage	LFT monitoring (no recommendation on frequency)	Stop all drugs, start S + E and start other drugs one at a time
HKTBS	Yes	-	-	-	-

WHICH RECHALLENGE PROGRAM IS BEST

175 HIV-negative patients randomized to receive one of three rechallenge regimens

Study arm	Regimen
Arm I	H, R, and Z at maximum dosages from day 1
Arm II	R at maximum dosage from day 1, H at maximum dosage from day 8, and Z at maximum dosage from day 15
Arm III	H at dosage of 100 mg/day from day 1, maximum dosage from day 4; R at dosage of 150 mg/day from day 8, maximum dosage from day 11; and Z at dosage of 500 mg/day from day 15, maximum dosage from day 18

NOTE. Maximum dosage was determined according to body weight, as follows: H, 5 mg/kg; R, 10 mg/kg; and Z, 25 mg/kg. H, isoniazid; R, rifampicin; Z, pyrazinamide.

No significant difference in recurrence rate (p=0.69)

Sharma SK et al. Clin Infect Dis 2010;50(6).

Adverse Events during Treatment of TB

- Very common
- Even mild and common events can affect treatment outcomes
- Some adverse events can be life-threatening
- Some adverse events cause permanent disability
- Timely recognition and management of adverse events important for adherence and completion of treatment
- Critical drugs may be discarded if not properly addressed