Drug-Resistant Tuberculosis

A Tool for TB Nurse Case Management

Drug Resistant TB for Nurses

WHAT: Drug-resistant tuberculosis (DR-TB) is a deadly communicable disease caused by *Mycobacterium tuberculosis* (MTB). DR-TB poses a serious global health threat, impacts individual patients and their families, and imposes tremendous burdens on overextended public health systems. Treatment for DR-TB is associated with more adverse events than treatment for drug-susceptible TB and requires intensive patient-centered case management and support.

HOW: DR-TB can be spread through person-to-person transmission. Drug resistance may develop when TB treatment is inadequate, to include:

- full course of TB treatment not completed;
- incorrect TB treatment (i.e., prescribed regimen, dose or length of time);
- TB drugs not available; or
- drug susceptibility testing not done.

WHO: Drug resistant TB is more common in persons who:

- do not take their TB drugs regularly;
- do not take all of their TB drugs;
- develop TB disease again after previous treatment;
- come from places where DR-TB is common;
- have been exposed to a person that had DR-TB; or
- have poor absorption of TB drugs.

WHERE: About 500,000 new cases of RR/MDR TB are estimated to emerge each year. India, China and the Russian Federation account for one half of the global burden. www.who.int/news-room/fact-sheets/detail/tuberculosis

WHO List of 30 Countries with a High Burden of MDR/RR-TB MDR-TB

Definitions of Drug-Resistance

X identifies resistance

	Centers for Disease Control and Prevention (CDC)						World Health Organization (WHO)			
Drug	**MDR**	**Pre-XDR[3]**		**XDR[3]**			**RR/MDR**	**Pre-XDR**	**XDR[3]**	
Isoniazid (INH)	X	X	X	X	X	X	P or N*	P or N*	P or N*	P or N*
Rifampin (RIF)	X	X	X	X	X	X	X	X	X	X
Fluoroquinolone (FQN)[1]	-	X	-	X	X	X	-	X	X	X
Bedaquiline (BDQ)	-	-	-	X	-	-	-	-	X	P or N*
Linezolid (LZD)	-	-	-	-	X	-	-	-	-	X
2nd line injectable[2]	-	-	X	-	-	X				

P - Positive N - Negative

*By WHO definition, resistance to these drugs can be positive or negative when the patient is being considered for MDR, Pre-XDR, or XDR.

RR-Rifampin resistant MDR-Multidrug resistant XDR - Extensively drug resistant

[1]Levofloxacin or Moxifloxacin

[2]Amikacin, Capreomycin, Kanamycin

[3]Each column indicates one combination of drug resistance that meets the respsective definition of pre-XDR or XDR TB.

Introduction

Early diagnosis of DR-TB and prompt initiation of adequate treatment limits transmission and improves outcomes.

When to "Think DR-TB"

A good medical history is essential to diagnosing DR-TB. Important information includes:

- prior TB treatment;
- worsening clinical and/or radiographic findings while on TB therapy;
- birth, history of residence or frequent travel to a region or country with a high prevalence of DR-TB (or household visitors from these countries);
- exposure to known (or highly suspected) infectious DR-TB; and
- exposure in congregate settings with known drug resistance.

Initial Laboratory Testing for TB

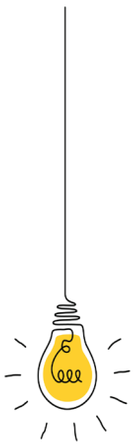
Everyone with possible active pulmonary TB* should have a chest radiograph and:

- sputum specimens (3), collected at least 8 hours apart, examined by Acid Fast Bacilli (AFB) smear microscopy and mycobacterial culture; and
- sputum specimen (1) examined by nucleic acid amplification testing (NAAT), a type of molecular testing.
  - Xpert MTB/RIF assay (a type of NAAT) rapidly identifies *M. tuberculosis* complex **and** mutations in the *rpoB* gene that may confer RIF resistance.

Testing for Drug Resistance

DR-TB is diagnosed by identifying resistance of the MTB isolate through either molecular (genotypic) or culture-based (phenotypic) drug-susceptibility testing.

- Molecular testing using a screening method such as the Xpert MTB/RIF assay **must** be confirmed by DNA sequencing, a more specific method. For more information see: *Issues in Mycobacterium tuberculosis Complex (MTBC) Drug Susceptibility Testing: Rifampin (RIF).* (https://www.aphl.org/aboutAPHL/publications/Documents/ID-2022-MTBC-DST-Rifampin.pdf).



When MDR/RR-TB is Detected

When MDR/RR-TB is detected, standard TB therapy should be discontinued. Unless the patient is extremely ill, providers should wait for molecular results to guide therapy.

- A single drug should not be added.
- If RIF resistance is identified by screening (e.g., Xpert MTB/RIF) and confirmed by molecular testing, culture-based testing **must** be requested for the full spectrum of second-line agents, especially the fluoroquinolones.
- If a specimen identifies resistance in *any* of the preliminary tests, that sample should be sent for DNA sequencing; CDC offers sequencing services for rapid detection of drug resistance, as do other reference laboratories.
  - Molecular detection of drug resistance (MDDR) provides sequencing that detects mutations associated with resistance to RIF, INH, streptomycin, ethambutol (EMB), pyrazinamide (PZA), amikacin (AK) and the fluoroquinolones (FQN).
- Expert consultation should be obtained if drug resistance is suspected or detected.

Discordant Results

- Rifamycins: Molecular testing methods are more sensitive and detect clinically significant low-level resistance which may be missed by culture-based tests (especially liquid tests).
- Moxifloxacin: Culture-based DST often tests for ofloxacin resistance. Isolates resistant to ofloxacin *may* still be susceptible to moxifloxacin; molecular tests can suggest whether moxifloxacin may be useful but a moxifloxacin MIC ≤ 1.0 documents susceptibility.

*Some laboratories may test specimens from patients with extrapulmonary TB.

Diagnosing DR-TB

Treatment Options

Information is rapidly becoming available on new treatment options for patients.

- **A physician with expertise in DR-TB treatment should be involved in the treatment plan for all patients with MDR/RR- and XDR-TB.** Directly observed therapy (DOT) should be used for all patients with MDR/RR- and XDR-TB.
- MDR/RR-TB can be treated using shorter standardized treatment regimens or longer individualized regimens.
  - Shorter oral standardized treatment regimens are preferred for non-pregnant patients aged 15 years or more with pulmonary or non-severe extrapulmonary disease, and no additional contraindications.
  - WHO and CDC note the efficacy of a 6-month bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) regimen and a 6-month bedaquiline, pretomanid, linezolid (BPaL) regimen. (https://www.who.int/publications/i/item/WHO-UCN-TB-2022-2; www.cdc.gov/tb/topic/drtb/bpal/default.htm).
  - WHO indicates that BPaLM may be used programmatically in patients with MDR/RR-TB or pre-XDR-TB, without previous exposure to these medicines. WHO notes that this regimen has sufficient efficacy to be used *without* moxifloxacin (BPaL) in patients with fluoroquinolone resistance or intolerance.
- Standardized 9 to 12-month regimens are currently in use in operational research settings. WHO notes that 9-month, all oral, bedaquiline-containing regimens are preferred over the longer regimens in adults and children without fluoroquinolone resistance and without severe pulmonary or extra-pulmonary TB.
- Longer individualized regimens can be used in all patients; currently, the duration of individualized regimens is 15-18 months for most adults and 12 months in children.
- For all regimens, providers may consider extending treatment based on slow bacteriologic, clinical, or radiographic response.

Treatment Regimens

6-Month Standardized Regimens	
Regimen and Description	**Considerations**

BPaLM regimen
• 6 months of bedaquiline, pretomanid, linezolid (600mg), and moxifloxacin
BPaL regimen
• 6 months of bedaquiline, pretomanid, and linezolid (600 mg)
Treatment Length: Treatment can be extended beyond 26 weeks up to 9 months (39 weeks), based on delayed treatment response within the first 8 weeks (assessed by time of culture conversion and clinical response to treatment) and other underlying clinical factors, or modifications based on adverse events.
Linezolid Dose:
• Data from the ZeNix study suggest that optimal dosing is 600 mg daily.
• WHO recommends attempting to maintain a 600 mg dose throughout treatment, with dose reduction possible due to toxicity or poor tolerability.
• Many experts use therapeutic drug levels to adjust linezolid dose or dosing interval.
• Early evidence suggests fewer adverse effects with trough level <2 mcg/ml. Peak concentration is ≥ 12mcg/ml.
	• BPaLM may be used in patients with MDR/RR-TB who:
	  • are 15 years or older; AND
	  • are not pregnant, AND
	  • have pulmonary or non-severe extrapulmonary TB AND
	  • have not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 month exposure).
	• BPaL may be used in patients who meet these criteria who also have intolerance or resistance to a fluoroquinolone.
	• Experience in extrapulmonary TB is limited.
	• BPAL or BPaLM can be used in people with HIV if compatible with ART regimen.
	(Note: Pretomanid does not have an approved indication for use in pregnant patients.)

Longer Standardized Regimens

The current short course regimen recommended by WHO is 4-6 months of bedaquiline, 6 months of levofloxacin or moxifloxacin, 2 months of linezolid, 6 months of ethambutol, pyrazinamide, isoniazid, clofazimine / 5 months of levofloxacin or moxifloxacin, clofazimine, pyrazinamide, ethambutol. Modifications to regimen composition are being studied globally and are in operational research settings for MDR-TB and fluoroquinolone resistant MDR-TB; delamanid and other newer drugs may be included in these regimens in the future.

Individualized Regimens

Regimen and Description	Considerations
Longer individualized regimens (all oral preferred) • Treatment is initiated with an intensive phase including bedaquiline and at least 3-4 additional drugs for at least 6 months (see table below). • Treatment usually lasts 15-18 months total. • Regimen includes bedaquiline and 2-4 other drugs, which will depend on patient tolerance, response, and drug susceptibility of the isolate.	• Can be used in all patients with MDR/RR-TB (recommended for use in those with severe forms of extrapulmonary/TB meningitis). • Designed based on molecular and culture-based DST results, prior treatment history, potential for cross-resistance or overlapping drug interactions and toxicities, and other key clinical factors. • Careful consideration for safety and potential drug interactions is needed for drug selection in children, pregnant women, and those with HIV.

Key Considerations for Selecting a Regimen

Considerations include pattern of resistance, age, comorbidity, prior TB treatment, site and severity of disease, drug interactions, and patient preference.

In some cases, one type of regimen might be indicated or preferred:

- **Fluoroquinolone resistance:** BPaL may be the preferred option.
- **Resistance to other drugs included in short course regimens:** Longer individual regimens should be used.
- **CNS TB:** BPaL is not approved as limited information is available on CNS penetration for bedaquiline and pretomanid
- **Children < 15 and pregnant patients:** Limited data on BPaLM, BPaL, and other 6-month regimens.

Composition of Individualized Longer Regimens (4-5 drugs total)

Group	Medicine	Comments
Group A	• Levofloxacin or moxifloxacin • Bedaquiline • Linezolid	• Include all three agents, if possible.
Group B	• Clofazamine • Cycloserine/terizidone	• Include one or both; if only two Group A agents can be used, then both Group B agents should be included unless resistance is noted.
Group C[1]	• Delaminid[2] • Pyrazinamide[3] • Ethambutol[3] • Amikacin or Streptomycin[4] • Ethionamide or prothionamide • Imipenem-cilastatin/clavulanate or meropenem/clavulanate • P-Aminosalicylic acid (PAS)	• Add Group C agents IF an adequate regimen of 4-5 drugs cannot be composed with agents from Groups A and B alone (due to resistance or intolerance), • Bactericidal activity and toxicity should be considered in drug selection. ***Good activity and minimal toxicity*** Delamanid, pyrazinamide, imipenem-cilastatin/clavulanate, meropenem/clavulanate) ***Good activity but often significant toxicity and patient discomfort*** Amikacin or streptomycin ***Minimal activity and minimal toxicity*** Ethambutol ***Minimal activity and increased toxicity*** Ethionamide or prothionamide, PAS

1. High-dose INH may be useful, though its utility in most situations is unknown.
2. Data on dosing and safety of bedaquiline are available in children > 6 months of age and for delamanid ≥3 months of age.
3. Ethambutol and pyrazinamide had mixed/marginal performance on outcomes assessed in PS-matched IPDMA; however, some experts may prefer these drugs over injectable agents to build a regimen of at least five effective oral drugs. Use pyrazinamide and ethambutol only when the isolate is documented as susceptible.
4. Because of their toxicity, these drugs should be reserved for when more-effective or less-toxic therapies cannot be assembled to achieve a total of four-five effective drugs. An all-oral regimen is the goal.

Treatment Options for DR-TB II

Characteristics of Commonly-Used Second-Line Drugs for DR-TB

For complete information on these and other drugs for MDR-TB, consult medication package inserts or medication fact sheets in Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd edition available at: https://www.currytbcenter.ucsf.edu/products

Drug	Standard Adult Dosing*	Considerations	Side Effects
Bedaquiline	400 mg once daily for 14 consecutive days; then 200 mg 3 times/wk for 22 wks (may give longer); 26 wks total duration as part of BPaL regimen	CNS penetration unproven; can be safely used with moderate chronic kidney disease (CKD) or moderate liver disease; give with meal to increase bio-availability	QTc prolongation, decreased appetite, nausea, hepatitis, headaches, arthralgias, elevated amylases, vivid dreams
Moxifloxacin	400 mg once daily, PO or IV	Good CNS penetration.	GI upset, dizziness, hypersensitivity, photosensitivity, headaches, arthralgias, tendonitis, tendon rupture (rare), CNS irritability, QTc prolongation, thrush, peripheral neuropathy, elevated liver enzymes (rare hepatotoxicity with moxifloxacin)
Levofloxacin	750-1,000 mg once daily, PO or IV	Good CNS penetration; adjust dose with creatine clearance < 30; avoid caffeine, milk-based products, antacids, or mineral supplements within 2 hrs of medication	
Linezolid	600 mg once daily, PO or IV	Good CNS penetration; trough < 2 µg/ml is associated with lower toxicity	Peripheral and optic neuropathy (reversible with early recognition), anemia, thrombocytopenia, neutropenia, headache, GI upset, rash, serotonin syndrome, lactic acidosis, acute pancreatitis, black hairy tongue
Pretomanid (As part of BPaL or BPaLM regimen)	200 mg once daily for 26 wks	No dose adjustment in patients with mild to moderate renal impairment; use with caution with severe renal impairment; should be taken with food	Hepatotoxicity, myelosuppression, peripheral and optic neuropathy, lactic acidosis, QTc prolongation, pancreatitis *[side effects are for entire BPaL regimen]*
Delamanid	100 mg twice daily for 24 wks (longer is possible)	CNS penetration unknown; can be safely used with moderate CKD or moderate liver disease; should be taken with food	GI upset, dizziness, insomnia, upper abdominal pain, QTc prolongation
Clofazamine	100 mg once daily	Skin darkening and photosensitivity can be limited by early use of sunscreen and lubricants; patients should be advised to minimize sun exposure	Hyperpigmentation, GI complaints, retinopathy, dry skin, ichthyosis, QTc prolongation; note – some patients may become depressed due to skin changes
Cycloserine	250 mg twice daily or 500 mg once daily	Avoid in patients with history of seizures/ psychosis or ETOH abuse; check level before increasing dose >500 mg daily; adjust dose with creatinine clearance < 30; some physicians use pyridoxine 50-100 mg daily	CNS toxicity (psychosis, depression, suicidal ideation, seizures), insomnia, unusual skin reaction
Pyrazinamide	Standard dosing: 25-35 mg/kg once daily	Adjust dose and/or interval with creatinine clearance < 30, avoid with clinical history of gout	Polyarthralgia (non-gouty), asymptomatic hyperuricemia, hepatotoxicity, GI upset, Rare: acute gout, usually in those with pre-existing gout
Amikacin	≤ 59 yrs: initial dosing: 15mg/kg/day (in a single dose IV or IM) 5 days/wk After conversion: 20-25 mg/kg 2-3 days/wk	Avoid these, if at all possible; adjust dose and/or interval with CKD	Ototoxicity - auditory/vestibular (irreversible), renal toxicity, pain at injection site
Streptomycin	>59 yrs: 10 mg/kg (max 750 mg) IV or IM 5 days/wk or 2-3 days/wk after initial period		Ototoxicity - auditory/vestibular (irreversible), renal toxicity, giddiness, perioral numbness, hypersensitivity, pain at injection site
Ethionamide	250 mg 2 times daily or 500 mg once daily	Increase dose gradually; causes hypothyroidism in some patients; Most patients do not tolerate > 500 mg some physicians use pyridoxine 50-100 mg daily; take with food	GI upset, hypothyroidism, metallic taste, hepatitis, headache, hypersensitivity, alopecia, gynecomastia, menstrual irregularity, acne, hypoglycemia, photosensitivity, peripheral neuropathy
Meropenem	1-2 g every 8 hours IV with 125 mg clavulanate {given as amoxicillin-clavulanate) with each dose	Adjust dose with advanced CKD	GI upset, rarely increased liver enzymes

*PO unless otherwise noted. Most 1st and 2nd line TB medications are best taken on an empty stomach or with a small snack; fatty foods should be avoided.

Case management is the cornerstone of successful treatment. Patients on treatment for DR-TB face many challenges, including fear, stigma, and difficult side effects such as nausea and fatigue that may impact their quality of life, capacity to work, and ability to continue activities of daily living.

- Use a patient-centered approach during treatment of DR-TB, listen actively to the patient to identify barriers to treatment, and work collaboratively to identify and select approaches and strategies.
- Help the patient to understand that steps can be taken to minimize side-effects if they occur.
- Remind the patient that treatment will cure the disease and prevent transmission.
- Try to identify and coordinate other support the patient may need.

Evaluation

- Medical history
  - medications
  - co-morbid conditions
- TB history
- Social history/risk factors
- TB symptom screen
- Infectiousness
- TB knowledge assessment

Baseline Assessment

- Laboratory tests (including HIV, TSH, Ca++, K+, and Mg++)
- Weight/BMI
- Pregnancy Test
- Medication Specific:
  - Peripheral neuropathy
  - Visual acuity/Ishihara
  - Mental Health
  - Cardiac/EKG

Patient Education

- What is DR-TB
- TB medications
- Potential side effects and what to report
- Directory Observed Therapy (DOT)
- Monthly toxicity monitoring

Patient Support

- Provide ongoing patient and caregiver education.
- Identify community resources including peer support (e.g., wearetb.com), and mental health services as needed.
- Eliminate adherence barriers.
- Provide incentives and enablers

Ongoing Assessment

Optimized DR-TB regimens lead to better outcomes and shorter treatment duration. Toxicity screening is key to the goal of MDR-TB treatment adherence and completion. When implemented correctly, close monitoring ensures side effects are identified early and responded to promptly, while ensuring the patient remains on the most effective medications possible.

- All patients should have the following monitored at baseline and at least monthly (Additional monitoring is indicated for certain medications; see table on next page.):
  - weight
  - sputum smear and culture
  - CBC, CMP and if appropriate HbA1c, pregnancy test
  - symptoms of TB
  - adherence assessment
- Obtain serum drug levels after initial month of therapy and repeat as indicated.
- Obtain a CXR at 2 months and every 6 months (or at treatment completion).
- See https://www.heartlandntbc.org/wp-content/uploads/2021/12/MDR-TB_Checklist_5.1.20.pdf for a sample MDR-TB Assessment Checklist.

Factors associated with unfavorable outcomes include:

- low BMI/failure to gain weight
- smear positivity/extensive disease
- prior therapy with 1st or 2nd-line drugs
- fluoroquinolone resistance
- extensively drug-resistant TB
- unstable housing
- difficulty with adherence
- substance use disorders

Factors associated with treatment success include:

- good adherence to treatment
- improving nutrition/weight gain
- DOT throughout treatment
- no previous treatment
- good diabetic control
- patient support
- non-smoker

Monthly[1] Toxicity Monitoring by Medication Type

Medication	Assessment							
	Medical Assessment[2]	CBC/CMP	Ca++, K+, Mg++, and/or TSH	EKG	Mental Status Changes	Neuropathy Assessment	Visual Acuity/ Color Vision Assessment	Audiometry[3] /Vestibular Toxicity Assessment
Bedaquiline	Baseline, mo.	Baseline, mo.	Baseline, mo.	Baseline, mo. (preferred)[5]				
Moxifloxacin/ Levofloxacin	Baseline, mo.	Baseline, mo.		As indicated[6]				
Linezolid[4]	Baseline, mo.	Baseline, mo.				Baseline, mo.	Baseline, mo.	
Pretomanid	Baseline, mo.	Baseline, mo.	Baseline, mo.	Baseline, mo. (preferred)[5]				
Delamanid	Baseline, mo.	Baseline, mo.	Baseline, mo.	Baseline, mo. (preferred)[5]				
Clofazimine	Baseline, mo.	Baseline, mo.		As indicated[6]				
Cycloserine	Baseline, mo.	Baseline, mo.			Baseline, mo.			
Pyrazinamide	Baseline, mo.	Baseline, mo.						
Amikacin	Baseline, mo.	Baseline, mo.	Electrolytes only Baseline, mo.					Baseline, mo.
Streptomycin	Baseline, mo.	Baseline, mo.	Electrolytes only Baseline, mo.					Baseline, mo.
Ethionamide	Baseline, mo.	Baseline, mo.	TSH only Baseline, mo.			Baseline, mo.	Baseline, mo.	
Meropenem	Baseline, mo.	Baseline, mo.						

Ca++: Calcium; **K+:** Potassium; **Mg++:** Magnesium; **TSH:** thyroid stimulating hormone

1. Frequency of monitoring may be increased as indicated.
2. Medical assessment including weight, signs and symptoms of TB, indications of drug toxicity, drug-drug interactions; additional assessment as indicated including need for dose adjustment (based on renal function, weight, serum drug level, etc.).
3. 1000 Hz - 8000 Hz
4. Consider drug-drug interactions that might lead to serotonin syndrome.
5. Minimum requirement is baseline and at least weeks 2, 12, and 24.
6. Consider baseline EKG if other cardiac risk factors are present.

Evaluation and Management of Contacts

Contact Investigation: Overall, contact investigation for DR-TB follows the same process used for drug-susceptible TB.

Evaluation: All close contacts of MDR-TB patients should receive a careful evaluation including medical assessment, testing for TB infection, and chest radiograph. Sputum collection X 3 with AFB smear, NAAT (X 1), and culture should be performed as indicated. If culture positive, perform molecular testing and culture-based DST. All contacts > 13 with an unknown HIV status should be screened for HIV.

Treatment for Latent TB Infection with Presumed DR-TB

- The goal of therapy is to prevent progression to TB disease; treatment can only be considered after TB disease is excluded.
- Treatment of TB infection presumed to be caused by an MDR isolate should be based on the susceptibility of the source case.
- Adults and children exposed to MDR-TB should be treated for 6 months with a fluoroquinolone-containing regimen, when the source case is fluoroquinolone susceptible.
- If the source case is resistant to ofloxacin, moxifloxacin may still be effective if the MIC ≤ 1.0 mcg/ml; in this case the moxifloxacin MIC should be documented.
- All contacts, regardless of whether they receive DR-TB preventive therapy, should be educated on signs/ symptoms of TB and encouraged to report them, if they occur.

Isolation

Like all patients with infectious TB, those with DR-TB should be isolated while infectious and appropriate infection control measures used; ***refer to your state/local TB program for guidance regarding the release from isolation for patients with DR-TB.***

- Criteria for considering a patient with DR-TB non-infectious *may* be more stringent than those for drug-susceptible TB.
- Patients **must** be on effective treatment; extended molecular testing or DST results are needed before ending isolation.
- Criteria for ending isolation include smear conversion, two weeks of adequate therapy, significant clinical improvement, and excellent adherence.

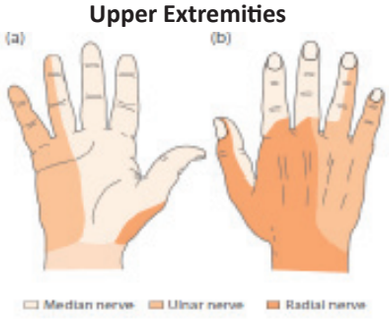
Critical Components of Monthly Nurse Assessment for 2nd-Line Drugs

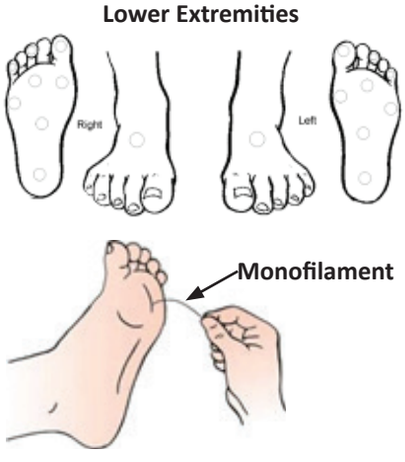
Additional information for selected nurse assessment (see complete toxicity assessment tool)

Peripheral Neuropathy

Peripheral neuropathy may be painful and is often non-reversible. Neuropathy usually manifests initially in the lower extremities, with sensory disturbances, but may also involve the upper extremities. Disturbances are often bilateral. Assess for:

- numbness (using a monofilament or other available tool) or tingling
- burning pain
- temperature sensation
- unsteady gait/balance
- decreased or absent deep tendon reflexes





Vestibular Toxicity

Vestibular damage is often non-reversible. Assess for balance and walking:

- balance (Romberg)/gait/heel-toe walking
- past pointing
- lateral nystagmus

Behavior and Mood

Some TB medications may contribute to depression and in rare cases, suicidal ideation. Depressive symptoms may fluctuate during therapy. Although the risk may be increased in those with a past history of depression, it is not an absolute contraindication to the use of cycloserine. Some patients with depression at baseline improve on cycloserine, as they respond to treatment.

- Use a mental health assessment tool at least monthly.
- Facilitate access to psychological support for patients and family, including antidepressant therapy at usual doses, if needed.
- Review drug-drug interactions with linezolid that may lead to serotonin syndrome.

Hearing

Hearing loss, tinnitus, or fullness in the ears are signs of auditory toxicity which is associated with total cumulative dose of aminoglycosides; however, change can be detected early. Patients with hearing loss at baseline receiving certain medications (e.g., Lasix), or with certain underlying conditions, are at highest risk. Hearing loss is *generally not reversible.*

- Conduct audiometry at baseline and at least monthly to identify hearing loss early.
- Extend screening up to 8000HZ for early diagnosis.

Once hearing loss is detected, a provider will usually stop the aminoglycoside unless there are no other options; continued treatment results in progressive hearing loss.

Vision

Optic neuritis may exhibit as change in color vision or visual acuity. Loss of red-green color distinction may be detected first, however, a decrease in visual acuity is more common. Changes are usually reversible if detected early and medication is discontinued.

- Educate patients to report any vision changes.
- Screen patients using the Ishihara vision test and Snellen eye chart during monthly exams.

If either change is detected, hold linezolid and ethambutol, notify provider, and request referral to an ophthalmologist.


Ishihara Vision Test

Snellen Eye Chart

Sample Evaluation Tools

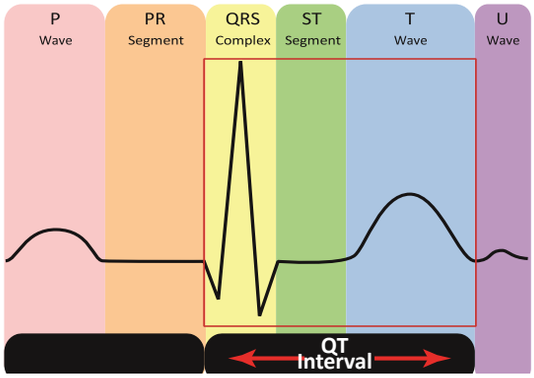
Neuropathy: https://www.heartlandntbc.org/wp-content/uploads/2023/05/Peripheral-Neuropathy-Evaluation-form.pdf
Mental Health: https://www.heartlandntbc.org/wp-content/uploads/2021/12/mental_health_screening_tool.pdf
Hearing /Vision (TB-205): https://www.dshs.texas.gov/tuberculosis-tb/texas-dshs-tb-program-tb-forms-resources

Cardiac Toxicity

QT interval prolongation: Fluoroquinolones, bedaquiline, pretomanid, clofazimine, and delamanid may prolong the QT interval and may predispose patients to arrhythmias, torsade de pointes, and sudden death.

What is the QT Interval?

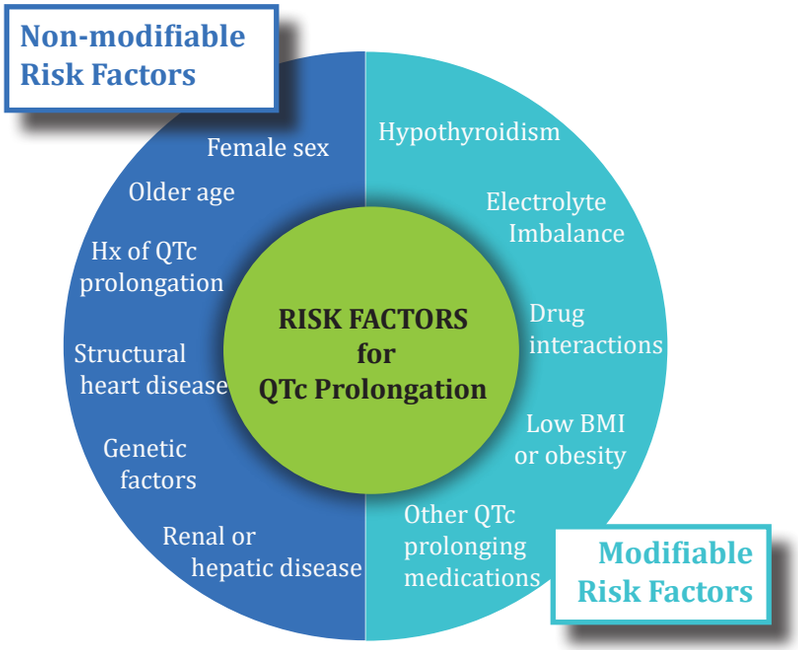
It is the portion of the EKG that begins at the start of the QRS complex and ends at the termination of the T wave. The QT interval is longer in women and those with lower heart rates. The QTc is a correction for extremes in heart rates.



What is the normal QTc Value?

Normal QTc is <450ms in men and <470ms in women. It can vary by up to 75ms in the same individual at different times during the same day. Therefore, it is recommended that EKGs be done at approximately the same time of the day.

Risk Factors for QTc Prolongation



Presence of multiple factors may increase the risk of QT prolongation.

***Note: Many non-TB drugs may cause increased QTc prolongation. See** https://www.tbdiah.org/wp-content/uploads/2020/07/Guidance_on_ECG_monitoring_in_NDR_v2-1.pdf

Assessment and Approach to Prolonged QTc

QTc > 450ms
Asymptomatic

QTc > 470ms

- Draw blood for and correct if abnormal:
  - Electrolytes (Ca++, K+, Mg++)
  - TSH
  - Hgb
- Review other QTc prolonging drugs and stop these if possible
- Perform EKG weekly until normal.

QTc > 500ms
Asymptomatic

- Hospitalize patient, if possible
- Draw blood for and correct if abnormal:
  - Electrolytes (Ca++, K+, Mg++)
  - TSH
  - Hgb (Blood transfusion if needed)
- Stop QTc prolongation drugs sequentially*
- Repeat EKG 24-48 hours
- Refer for cardiology consultation
- Continue to monitor EKG weekly until normal

* Starting with ancillary drugs, then DR-TB drugs with moxifloxacin/levofloxacin (clears rapidly), then pretomanid/clofazimine/delamanid (prolonged clearance), and then bedaquiline (longest half-life)

QTc > 500ms
Symptomatic:
Palpitations, tachycardia, fainting, headache, chest pain, syncope

- Hospitalize patient (intensive or cardiac unit monitoring)
- Draw blood for and correct if abnormal:
  - Electrolytes (Ca++, K+, Mg++)
  - TSH
  - Hgb (Blood transfusion if needed)
- Stop ALL QTc prolongation drugs
- Repeat EKG 24-48 hours
- Refer for cardiology consultation
- Continue to monitor EKG weekly until normal

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