Management of Selected Adverse Events

QTc prolongation

QTc prolongation is being increasingly mentioned as an adverse event. This is due in part to a focus on QTc by regulators and researchers. It is important to know that QTc prolongation in and of itself is NOT an adverse event. Rather, the focus on QTc prolongation is important because it is a RISK FACTOR for developing Torsades de Pointes (TdP), a fatal cardiac arrhythmia. There are several medicines that prolong the QTc interval, but many of them are not associated with TdP or any clinical cardiac events. It should be noted that the QTc prolongation with bedaquiline (BDQ) and delamanid (DLM) was not associated with any clinical cardiac complications.

In addition to medications, other risk factors for TdP include gender, advanced age, low heart rate, electrolyte abnormalities, congestive heart failure, and a genetic predisposition to developing arrhythmias. Programs, providers, and patients must weigh the risks of QTc prolongation and possible cardiac events with the risk of undertreated drug-resistant tuberculosis (DR-TB) and the risks associated with other second-line drugs (SLD).

Patients with QTc prolongation often have vague symptoms or no symptoms. They may present with palpitations or a rapid heart rate, dizziness, or syncope. Any patient with these symptoms should undergo a QTc evaluation and if prolongation is present, hospitalization should be considered. In addition, routine QTc monitoring should be done monthly.

Calculation of the QTc interval

The QT interval is measured in milliseconds (msec) and is defined as the period of time from the beginning of the Q wave until completion of the T wave. Because the QT interval depends on the heart rate, the timing must be corrected (hence QTc). There are several formulas for doing so, each of which has its own limitations. The most commonly used correction formula is the Fridericia formula.

There are electrocardiogram (ECG) machines that can automatically correct the QTc interval and provide a reading. However, these machines tend to overcall the duration and, therefore, the interval should be calculated manually if QTc prolongation is noted. There are multiple websites that can correct the QT interval if the RR interval (i.e., heart rate) and the QT intervals are entered (http://lifeinthefastlane.com/ecg-library/basics/qt_interval/). If such resources cannot be accessed, the interval can be calculated manually by taking the measured QT interval and dividing it by the cube root of the calculated RR interval (QT interval/$\sqrt[3]{}$RR interval). A prolonged QTc interval is generally considered to be greater than (>) 450 msec (although in women, a normal QTc interval can be as high as 470 msec). Handheld devices may also be

considered to screen for QTc prolongation, with those who have QTc prolongation being referred for a full 12-lead ECG.

Clinical Management

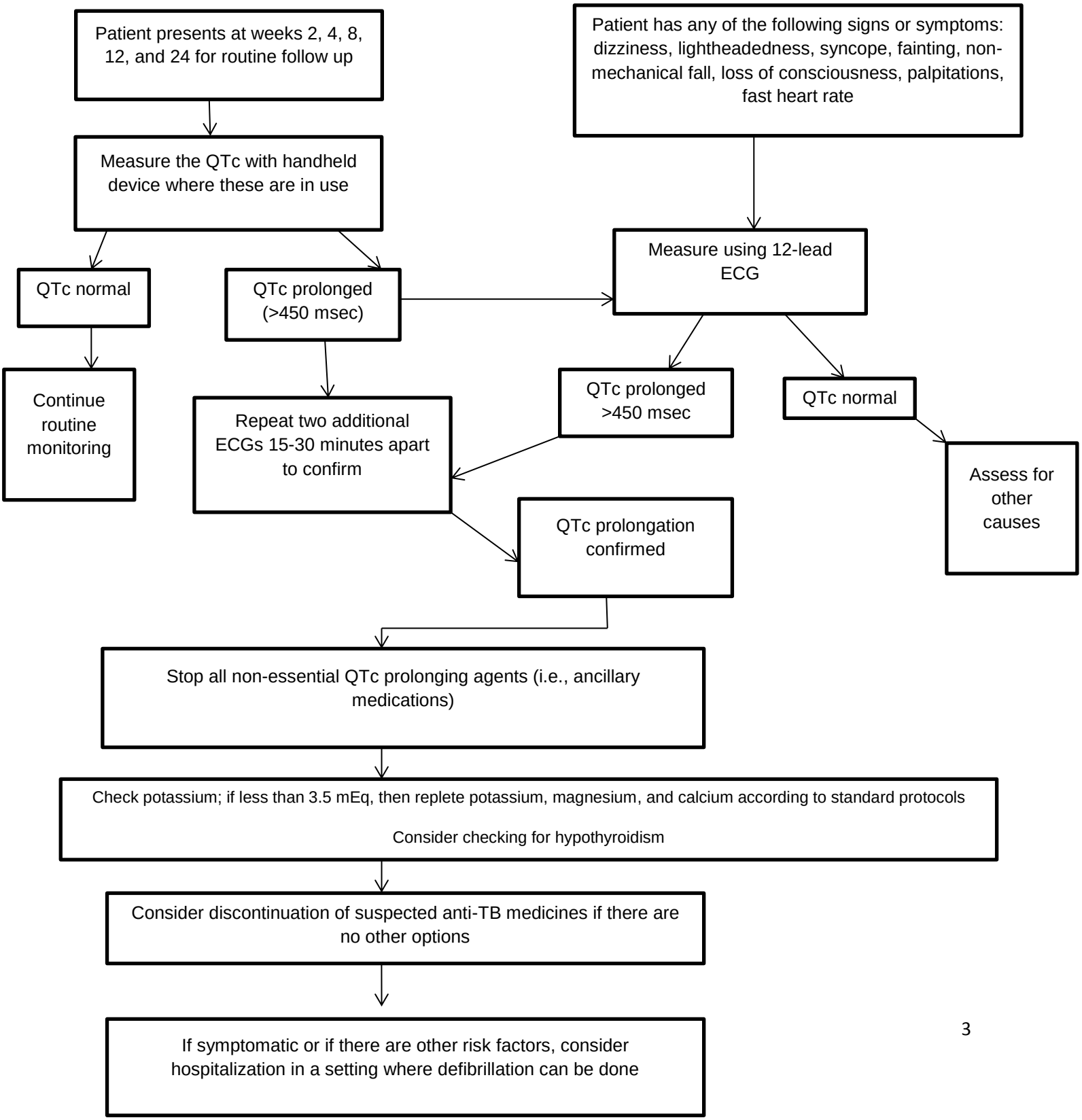
The clinical management of QTc prolongation must take many factors into account. Chief among them is that QTc prolongation is only one risk factor for developing TdP. Moreover, no confirmed clinical cardiac complications have been reported with BDQ, DLM, or clofazimine (CFZ) in clinical trials or in expanded access studies reported to date. Thus, the decision to stop the use of a potentially life-saving medicine in the context of QTc prolongation must be weighed against the risk of other adverse events and that of untreated or undertreated DR-TB. The algorithm given below presents possible management options when there is QTc prolongation noted. In general, the following points should be considered when QTc prolongation is seen:

- If the QTc prolongation was detected using a handheld device, a full 12-lead ECG should be done.
- Repeat the ECG two additional times within 15-30 minutes of one another to confirm the QTc prolongation. Consider discussing the case with a cardiologist, either in the local setting or through an international consultation.
- Assess for symptoms, including dizziness/syncope, palpitations, chest pain, fainting, falling down, fast heart rate. If symptoms are present, take urgent action.
- Discontinue all unnecessary QTc prolonging medicines (i.e., ancillary medications).
- Check and replete electrolytes (i.e., potassium, magnesium, calcium).
- Consider assessment for hypothyroidism as this has been associated with the development of TdP.
- If there are no other options, discontinue BDQ, DLM, or CFZ, keeping in mind the long half-life of BDQ and CFZ.
- If symptomatic, consider admission to a facility where defibrillation is available.

If medications are discontinued, doses are changed, or a patient is hospitalized due to the development of QTc prolongation, these changes should be recorded and reported as part of active pharmacovigilance.

Algorithm for QTc Assessment and Management

Medicines known to prolong the QTc interval include BDQ, DLM, CFZ, moxifloxacin, levofloxacin, and clarithromycin.



Anemia

Patients with anemia can often present with vague symptoms, but chief among them are fatigue, dyspnea, and pallor. On examination, these individuals may have pale conjunctiva and a rapid heart rate. Patients on linezolid (LZD) should have a complete blood count (CBC) checked monthly to monitor for anemia.

Patients with DR-TB often have multiple comorbidities and reasons to develop anemia, including HIV and other opportunistic infections (OI). When a medication is suspected, LZD and zidovudine (AZT) are the most likely culprits. LZD and AZT should be avoided in persons with a hemoglobin of less than 8 g/dL, unless there are no other alternatives. Patients with baseline anemia may need iron therapy prior to starting LZD. However, many patients have anemia of chronic disease and will improve when on adequate therapy. In persons with baseline anemia (i.e., hemoglobin of < 8 gm/dL) the use of BOTH AZT and LZD should be avoided.

If a person develops a hemoglobin of < 8 gm/dL while on therapy, antiretroviral therapy (ART) should be changed if the person is on AZT. Other causes of anemia should be assessed, and if no other causes are found, then LZD should be discontinued until the hemoglobin is above 8 gm/dL again. At this point, LZD could be restarted at a lower dose (i.e., 300 mg/day).

If the patient develops a hemoglobin of <8 gm/dL with symptoms of respiratory insufficiency, then transfusion should be considered. If erythropoietin is available, this should also be considered. Otherwise, transfusions should be considered for patients with a hemoglobin of 7 gm/dL or less, depending on access to and the safety of the blood supply.

If medications are discontinued, doses changed, or a patient is hospitalized or transfused due to the development of anemia, these changes should be recorded and reported as part of active pharmacovigilance.

Thrombocytopenia

Patients with thrombocytopenia can present with a variety of complaints, including nose bleeds, bleeding gums, easy bruising, and rashes. On examination, these patients often have petechiae. Patients with DR-TB often have multiple comorbidities, including HIV and other OIs. When a medication is suspected, the likely cause of thrombocytopenia is LZD. Patients on LZD should have a CBC checked monthly to assess for thrombocytopenia.

Patients who have a platelet count of 50,000 mm3 should have their LZD withheld while investigating other causes. If no other cause can be identified, then LZD should only be restarted at a lower dose (i.e., 300 mg/day) once the platelet count has normalized. In patients with a

platelet count of <10,000 mm3 or in whom severe bleeding is occurring, platelet transfusion should be considered.

If medications are discontinued, doses changed, or a patient is hospitalized or transfused due to the development of thrombocytopenia, these changes should be recorded and reported as part of active pharmacovigilance.

Optic neuritis

Patients with optic neuritis can present with a number of symptoms, including decreased visual acuity and changes in the way they perceive colors. However, they often have no complaints at all and, therefore, routine visual acuity monitoring should be done. If a change from baseline is noted, formal red/green color testing should be done as well as a funduscopic exam of the optic nerve. Ethambutol can also cause optic neuritis. If the patient is on ethambutol, this medicine should be stopped when the patient has visual complaints along with changes in color perception and/or evidence of edema of the optic nerve. LZD should be lowered to a dose of 300 mg and if problems persist, LZD should be discontinued.

If medications are discontinued or doses changed due to the development of optic neuritis, these changes should be recorded and reported as part of active pharmacovigilance.

Nausea/Vomiting/Abdominal Pain

These gastrointestinal symptoms are common in patients being treated for DR-TB. Excellent management protocols are available in other field guides. Medications commonly associated with nausea and vomiting include ethionamide and para-aminosalycilic acid (PAS). In patients on BDQ and/or CFZ, additional factors should be considered. If the abdominal pain is severe or the nausea and vomiting protracted, then pancreatitis should be ruled out. Lipase should be evaluated, and if present, potential causes of it should be considered, including ART (i.e., stavudine [D4T]), HIV, or alcohol use). If no other underlying cause can be identified, BDQ should be discontinued. If the patient does not have pancreatitis, then acute abdomen should be considered, with CFZ being the most likely agent. Both of these medicines accumulate in the adipose tissue and, therefore, even with discontinuation, adverse events may take time to resolve.

Patients on new medications and CFZ who have nausea, vomiting, or diarrhea should have their potassium checked frequently because they are at risk of developing hypokalemia and fatal arrhythmias in the context of BDQ, DLM or CFZ use.

If medications are discontinued, doses changed, or a patient is hospitalized due to the development of nausea, vomiting, or abdominal pain, these changes should be recorded and reported as part of active pharmacovigilance.

Malnutrition

Patients with DR-TB and malnutrition are at high risk for poor outcomes. Therefore, aggressive nutritional support for all DR-TB patients is recommended as part of routine care. Patients on DLM are at higher risk for medicine-related adverse events if they are malnourished, especially if their serum albumin is below 2.8 gm/dL. In patients with albumin levels near this value, aggressive protein and calorie supplementation are recommended.

If medications are discontinued, doses changed, or a patient is hospitalized due to the development of malnutrition, these changes should be recorded and reported as part of active pharmacovigilance.

Neuropathy

Patients with neuropathy often present with burning, tingling, or numbing pain in their feet and hands. Neuropathy can become so severe that it limits mobility and greatly decreases the quality of life. Patients with DR-TB are at high risk for developing peripheral neuropathy for a variety of reasons, including TB, HIV, alcohol use, or other medications.

Excellent protocols for the management of peripheral neuropathy are included in other field guides. Patients on LZD are at high risk of developing neuropathy. In a patient with signs and symptoms of neuropathy, the LZD dose should be lowered to 300 mg/day while other causes are being investigated. This should be done early in therapy as there is some potential for the neuropathy to be reversible if detected early.

If medications are discontinued, doses changed, or a patient is hospitalized due to the development of neuropathy, these changes should be recorded and reported as part of active pharmacovigilance. A brief screening tool for neuropathy is provided below.

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

With the subject seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the subject's ankle to 90 degrees. Using a reflex hammer, the examiner then strikes the Achilles tendon. The tendon reflex is felt by the examiner's hand as a plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon is struck. Use reinforcement by having the subject clench his/her fist before classifying the reflex as absent.

Ankle reflexes	*Score*
Absent	0
Hypoactive	1
Normal deep tendon reflexes	2
Hyperactive	3
Clonus	4
Unable to or did not assess	8