

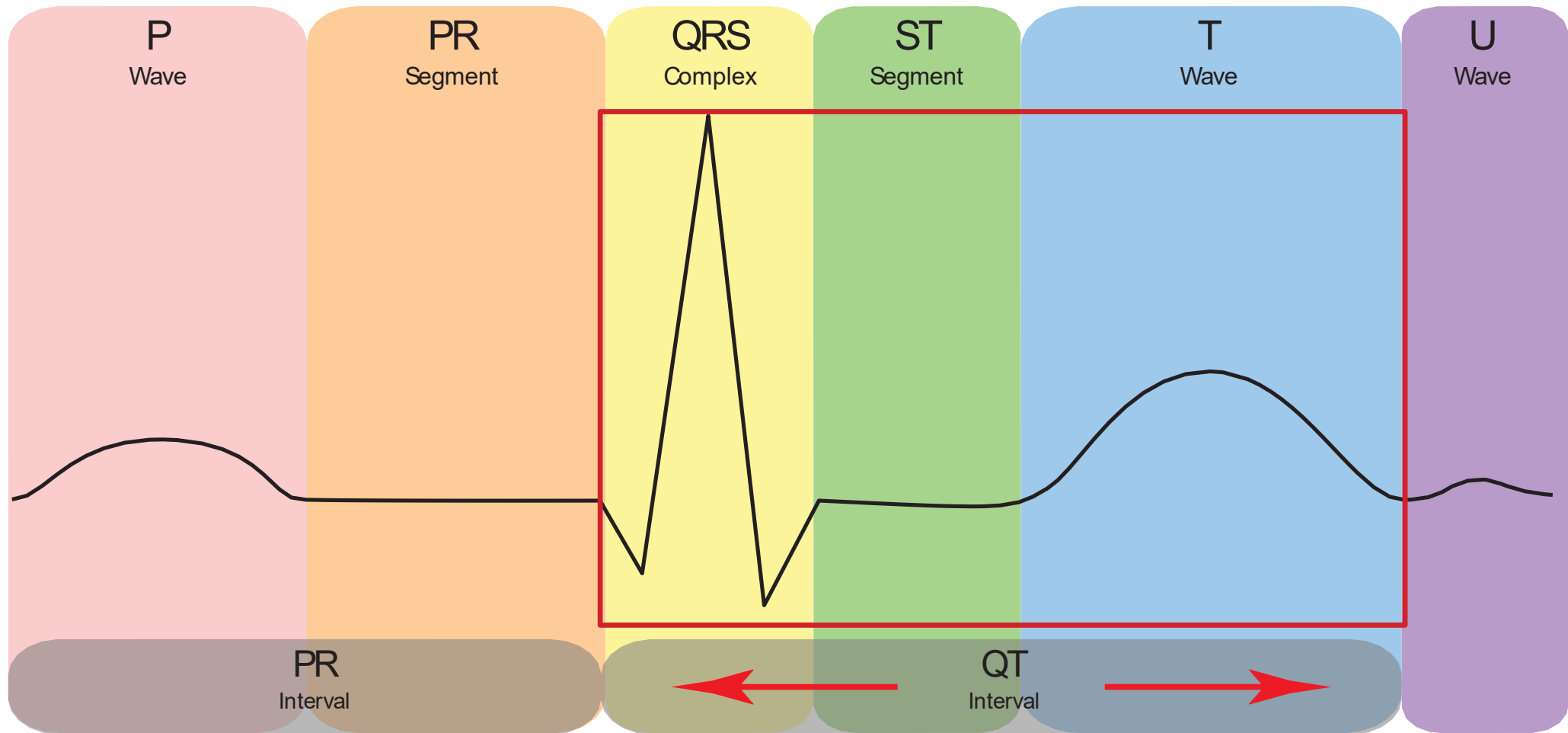
Why Screen With Electrocardiograms?

Otto F.W. Boneta, MD, MPH
DSHS Region 11, TB Physician
10 September 2019

Short Answer:

Drug Induced Long QT
Syndrome (diLQTS)

What is a QT Interval?

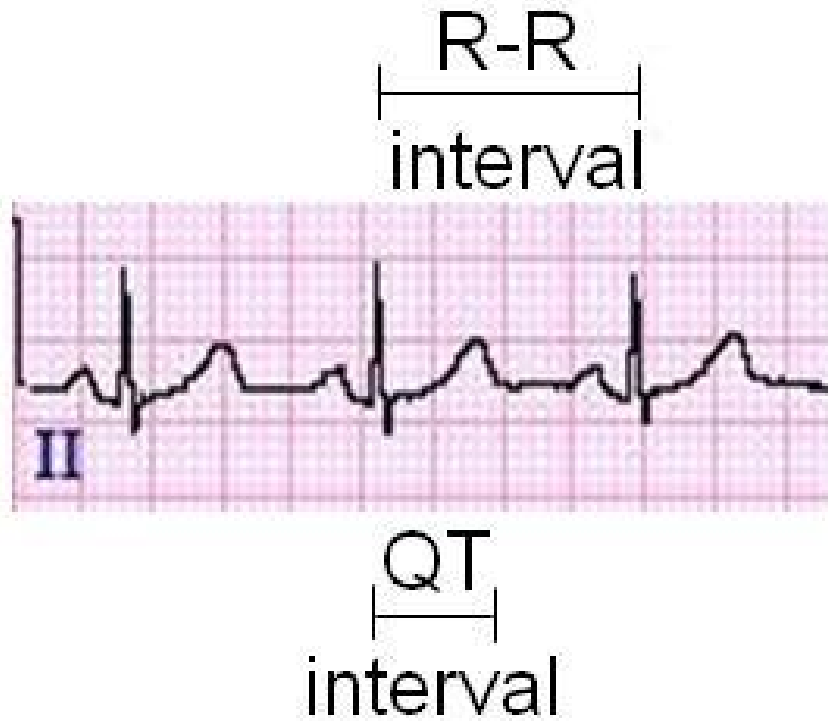


Normal QT / QT_c

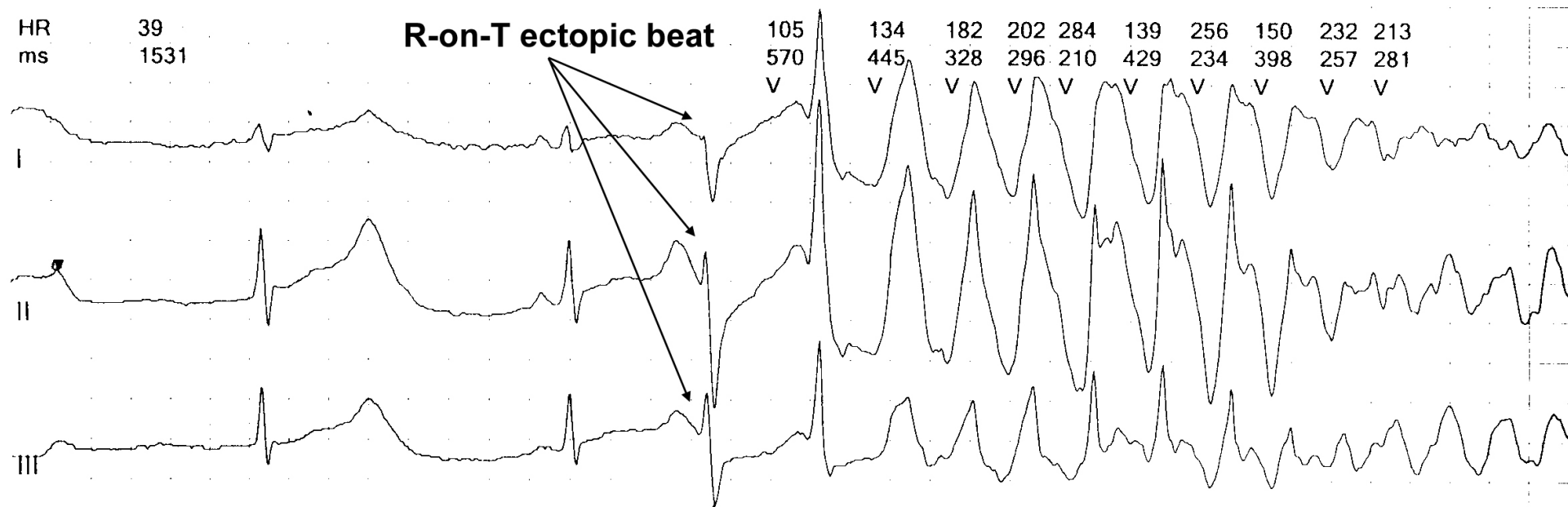
- QT interval affected by heart rate; must be corrected = QT_c
 - Male <450 ms
 - Female <470 ms
- QT_c Prolongation over patient baseline >60 ms is a red flag
- Diurnal variation +/- 75 ms
 - Perform ECG same time of day for best comparison

Why Should I Care About QT Interval?

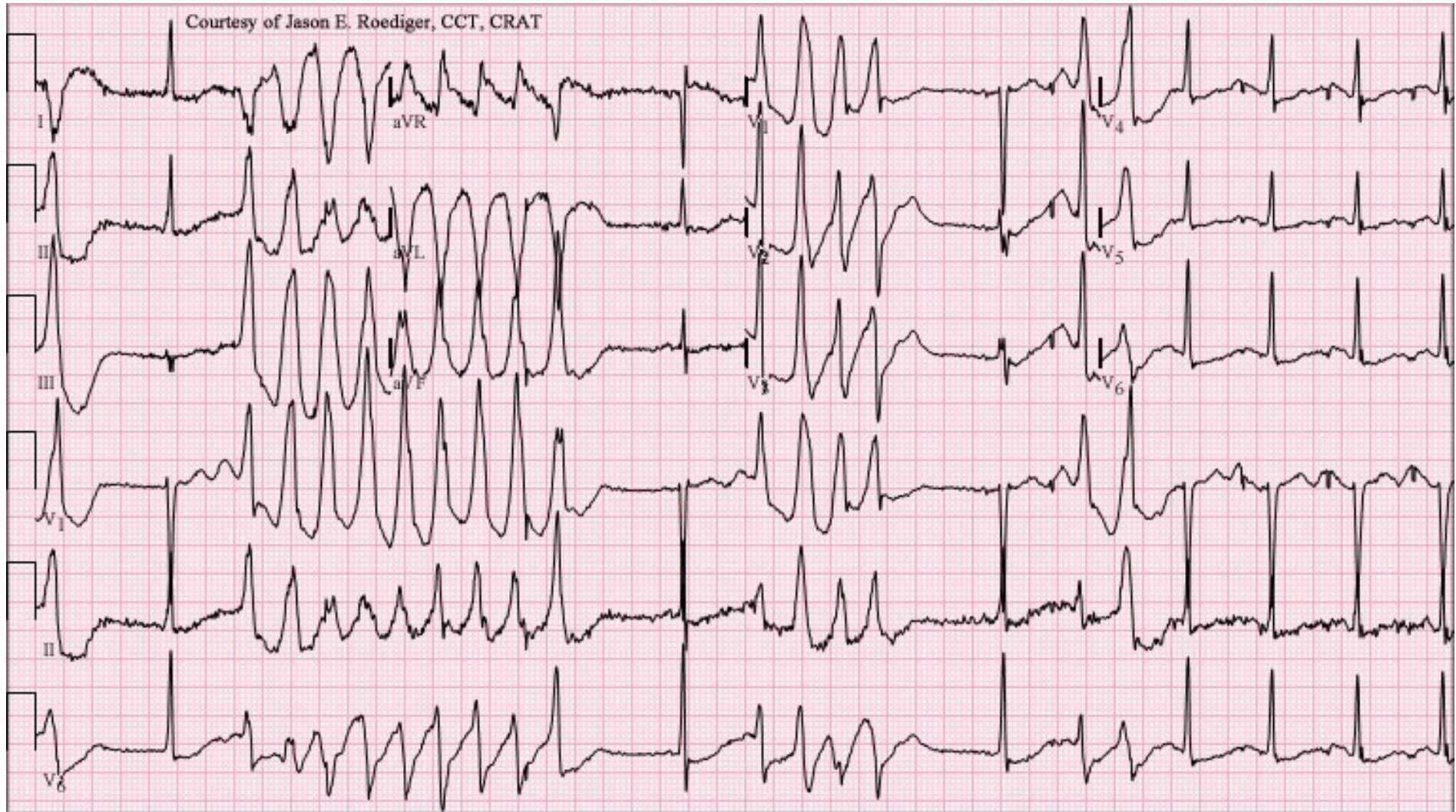
Prolonged QT_c interval = Increased risk of arrhythmia



- Prolonged QT Interval may result in polymorphic V-Tach or Torsades de Pointes (TdP)
- TdP
 - May end spontaneously
 - May end in V-Fib



Torsades de Pointes "twisting of peaks"



THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Predicting the Unpredictable

Drug-Induced QT Prolongation and Torsades de Pointes



Peter J. Schwartz, MD,^a Raymond L. Woosley, MD, PhD^{b,c}

ABSTRACT

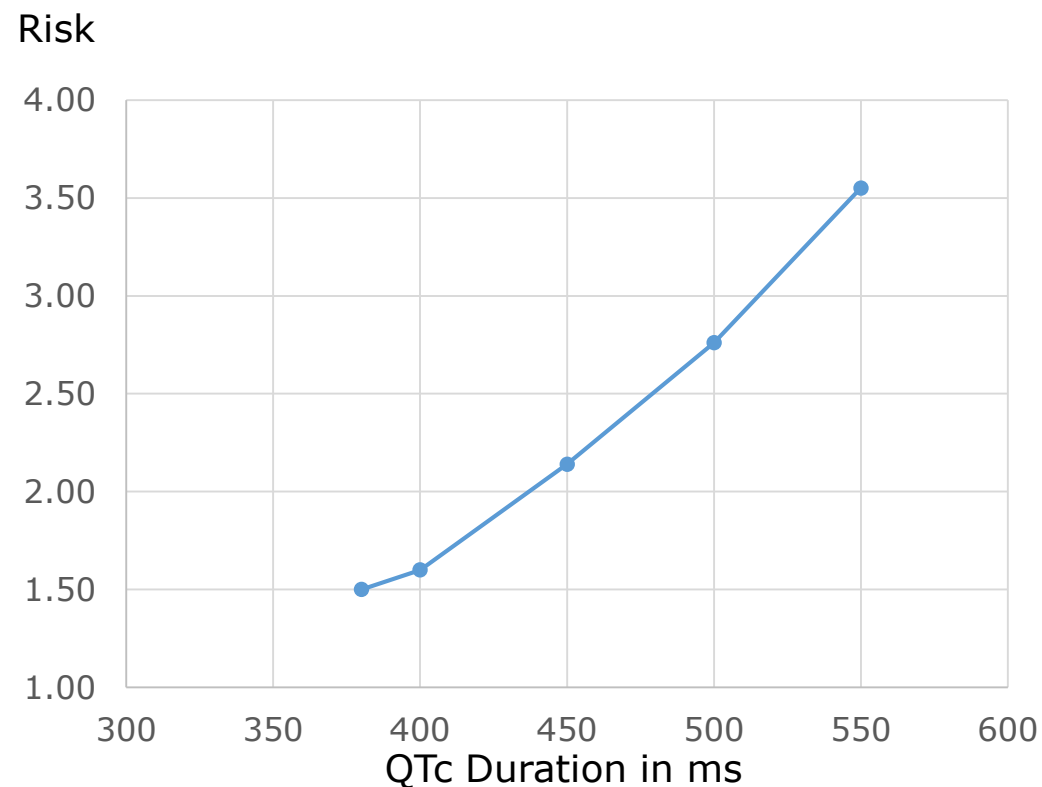
Drug-induced long QT syndrome (diLQTS) and congenital LQTS (cLQTS) share many features, and both syndromes can result in life-threatening torsades de pointes (TdP). Our understanding of their mechanistic and genetic similarities has led to their improved clinical management. However, our inability to prevent diLQTS has resulted in removal of many medicines from the market and from development. Genetic and clinical risk factors for diLQTS and TdP are well known and raise the possibility of TdP prevention. Clinical decision support systems (CDSS) can scan the patient's electronic health records for clinical risk factors predictive of diLQTS and warn when a drug that can cause TdP is prescribed. CDSS have reduced prescriptions of QT-prolonging drugs, but these relatively small changes lack the power to reduce TdP. The growing genetic evidence linking diLQTS to cLQTS suggests that prevention of TdP in the future may require inclusion of both genetic and clinical predictors into CDSS. (J Am Coll Cardiol 2016;67:1639–50) © 2016 by the American College of Cardiology Foundation.

Estimated Risk of TdP

1.052^x Where $x = (QTc - 300) / 10$
(another exponential relationship; not linear)

Example:

- $QTc = 380 \text{ ms}; \text{Risk} = 1.50$
- $QTc = 400 \text{ ms}; \text{Risk} = 1.66$
- $QTc = 450 \text{ ms}; \text{Risk} = 2.14$
- $QTc = 500 \text{ ms}; \text{Risk} = 2.76$
- $QTc = 550 \text{ ms}; \text{Risk} = 3.55$



Risk Factors for TdP

Unmodifiable risk-factors	Potentially modifiable risk-factors (acquired risk-factors)
<ul style="list-style-type: none"> • Female gender • Increasing age • Genetic predisposition <ul style="list-style-type: none"> – Congenital long QT syndrome – Family history of sudden death • History of previous drug-induced QTc prolongation • Structural heart disease/left ventricular dysfunction • Impaired elimination due to renal or hepatic disease 	<ul style="list-style-type: none"> • Electrolyte imbalance <ul style="list-style-type: none"> - Hypokalemia - Severe hypomagnesemia - Hypocalcemia • Hypothyroidism • Structural and functional heart problems <ul style="list-style-type: none"> – Recent conversion from atrial fibrillation (absolute or relative bradycardia) – Ischemic and congestive heart disease – Ischemic cardiomyopathy – Dilated or hypertrophic congestive heart disease – Congestive heart failure • Drug interactions <ul style="list-style-type: none"> – >1 QT-prolonging medicines – Medicines that inhibit the metabolism of another QT-prolonging medicine – Medicines that cause electrolyte abnormalities or renal or hepatic dysfunction • Low BMI: starvation, wasting syndrome or obesity • High drug concentrations due to overdose or rapid IV administration

How to Mitigate Risk of TdP

- Baseline ECG and regular follow-up
- History!!!
 - Medications!
 - Past Medical History
 - Heart failure or arrhythmias
 - Renal or hepatic dysfunction
 - Hypothyroidism
 - Diabetes
 - Family History
 - Sudden Cardiac Death
- Physical Exam / Labs
 - Weight / BMI / nutritional status (both extremes of BMI)
 - Electrolytes
 - Thyroid
- Coordinate with PCM to manage comorbidities and electrolyte imbalances

Medications That May Prolong QT_c

- Challenge TB Guide for QTc Monitoring – Annex 1
- <https://crediblemeds.org/new-drug-list/>

ECG After Completion of TB Therapy

Half-Life of Medicines:

- Mfx: 15-16 hrs
- Lfx: 6-8 hrs; Cfz: 25 days
- Dlm: 38 hrs
- Bdq: 5.5 months

Note: Because of the long half-life of Bdq, if the QTcF is prolonged even if the drug is no longer being given, **continue ECG monitoring until the QTc normalizes**

QTcF ≥ 450 ms (M)/ ≥ 470 ms (F) but ≤ 500 ms confirmed by repeat ECG done ≥ 30 min apart
Note: Calculate QTcF manually following recommended procedure.



Asymptomatic

Signs /Symptoms present: e.g., palpitations, tachycardia, light-headedness, fainting, syncope, chest pain, loss of consciousness



- Check electrolytes (potassium, magnesium and calcium) and manage accordingly. (**Annex 4**).
- Consider replacing QT-prolonging ancillary drugs, e.g., haloperidol, amitriptyline, ondansetron, etc.
- ARTs are usually not stopped or replaced.
- Consider changing Mfx to Lfx, or decreasing Mfx if given high dose.
- **Do weekly ECG.**

Manage as in Algorithm 9a.



QTcF ≥ 450 (M)/ ≥ 470 (F) ms but ≤ 500 ms

- Check TSH and manage accordingly (**Annex 5**)
- Check Hgb and consider blood transfusion, as necessary.
- Continue weekly ECG until normal.

QTcF > 500 ms Manage as in Algorithm 9a.

Annex	Guide
Annex 4a	Potassium replacement therapy
Annex 4b	Magnesium replacement therapy
Annex 4c	Calcium replacement therapy
Annex 5	Severity grading and clinical management of hypothyroidism

Acknowledgment: Jennifer Furin, Alberto Piubello

QTcF >500 ms confirmed by repeat ECG done ≥ 30 min apart
Note: Calculate QTcF manually following the recommended procedure.



Asymptomatic

- Consider hospitalization.
- Check electrolytes (K, Mg, and Ca) and manage accordingly (**Annex 4**).
- **Stop QT-prolonging drugs sequentially starting with ancillary drugs and DR-TB drugs with the shortest half-life Mfx/Lfx, followed by Cfz, Dlm, then Bdq.****
- **Repeat ECG after ≥ 24 hours but < 48 hours.**

Signs/Symptoms present: e.g., palpitations, tachycardia, light-headedness, fainting, syncope, chest pain, loss of consciousness

- **Hospitalize.**
- Check electrolytes (K, Mg and Ca) and manage accordingly (**Annex 4**).
- **Stop ALL QT-prolonging drugs.**
- **Repeat ECG after ≥ 24 hours but < 48 hours.**



QTcF still >500 ms and still asymptomatic

- Check TSH and manage accordingly (**Annex 5**).
- Check Hgb and consider blood transfusion, as necessary.
- Refer to the Case management committee, if needed.
- **Do at least weekly ECG until normal.**

QTcF still >500 ms and signs/symptoms still present

- Check TSH and manage accordingly (**Annex 5**).
- Check Hgb and consider blood transfusion, as necessary.
- Refer to the Case Management Committee, if needed.
- **Do at least weekly ECG until normal.**



QTcF <450 ms (M)/<470 ms (F); patient stable

- **Critical QT-prolonging drugs can be added back.**
- Consider the following adjustments, in consultation with the case management committee:
 - Use Lfx if previously on Mfx, and DST shows susceptibility.
 - Restart Bdq/Dlm, if previously on Bdq/Dlm (while suspending all other QT-prolonging drugs).
 - Suspend Cfz permanently, if not critical.
- **Do weekly ECG and on an ad hoc basis until stable.**

Prolonged QT interval**Possible anti-TB drug causes: Mfx, Cfz, Bdq, Dlm,****Other causes:** Hypokalemia, hypothyroidism, other drugs (e.g., clarithromycin, quinidine, fluconazole, antipsychotics: haloperidol, chlorpromazine, anti-emetics: ondansetron and domperidone, etc.) Refer to <https://www.crediblemeds.org/healthcare-providers/>

Normal Value	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Male (M): <450 Female (F): <470	M: QTcF 450 – 480 ms F: QTcF 470 – 480 ms	QTcF 481 – 500 ms	> 500 ms on at least two separated ECGs (>30 min apart) without signs and symptoms of arrhythmia	> 500 ms and life-threatening consequences (Tdp or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)
Action	<ul style="list-style-type: none"> • Check electrolytes and replete as necessary. • Check TSH and Hgb and manage accordingly. • Monitor ECG more closely; at least weekly until QTcF has returned to < Grade 1. 	<ul style="list-style-type: none"> • Check electrolytes and replete as necessary. • Check TSH and Hgb and manage accordingly. • Monitor ECG more closely; at least weekly until QTcF has returned to grade 1 or less. 	<ul style="list-style-type: none"> • Consider hospitalization and replete electrolytes as necessary. • Stop the QT- prolonging agents sequentially starting with ancillary drugs, DR-TB drugs with the shortest half- life: Mfx/Lfx, then Cfz, Dlm, then Bdq. • Check TSH and Hgb and manage accordingly. • Repeat ECG after 24 hours but <48 hours. 	<ul style="list-style-type: none"> • Hospitalize and replete electrolytes as necessary. • Stop all suspected causative drugs. • Check TSH and Hgb and manage accordingly. • Repeat ECG after 24 hours but <48 hours.

Questions