Antimicrobial Impact on QT Prolongation

Prolonged QTc Interval [1]

>460ms in women, >450ms in men

>500ms is associated with increased risk of Torsades de Pointes (TdP):

~5-7% increased risk for every additional 10ms > 500ms

Which QTc to Use? [1]

- Use a correction formula to calculate the corrected QT (QTc) to adjust for variability

QTcB—Bazett's Formula: $\boldsymbol{QTc = QT/\sqrt{RR}}$

- Potential for overcorrection at high heart rates and undercorrection at low heart rates

QTcF—Fridericia Formula: $\boldsymbol{QTc = QT/\sqrt[3]{RR}}$

- **Shown the best rate correction and significantly improved prediction of 30 day and 1 year mortality**

Risk Factors for QT prolongation[9,10]**:**

- Baseline QT prolongation
- Older age
- Female gender
- Hypothyroidism
- Known long QT mutation in patient or family member
- Coadministration of another QT prolonging drug
- Coadministration of a drug that could inhibit metabolism of the antimicrobial
- Electrolyte disturbances (hypokalemia, hypomagnesemia)
- Heart disease (left ventricular hypertrophy, low ejection fraction, ischemia)
- Other causes of reduced repolarization (hypothermia, extreme bradycardia)

Considerations for obtaining an ECG [9,10]

Patient Population starting QTc Prolonging Antimicrobial	Recommendation
- History of prolonged QTc	- Prior to treatment measure QTcF on ECG - Repeat measurement of QTcF 24 – 48 hours after initiation of antimicrobial, preferably 2 hours after administration - With durations of therapy > 2 weeks, consider repeat ECG with new risk factors or changes in clinical status. May consider monthly monitoring in stable patients with long durations
- No history of prolonged QTc - Risk factors for TdP	- Prior to treatment measure QTcF on ECG - If >460ms in women, >450ms in men repeat measurement of QTcF 24 – 48 hours after initiation of antimicrobial, preferably 2 hours after administration - With durations of therapy > 2 weeks, consider repeat ECG with new risk factors or changes in clinical status
- No history of prolonged QTc - No risk factors for TdP	- ECG monitoring is not necessary unless risk factors emerge

Scenarios where QT interval reported on the ECG may be "falsely increased" by a wide QRS complex:

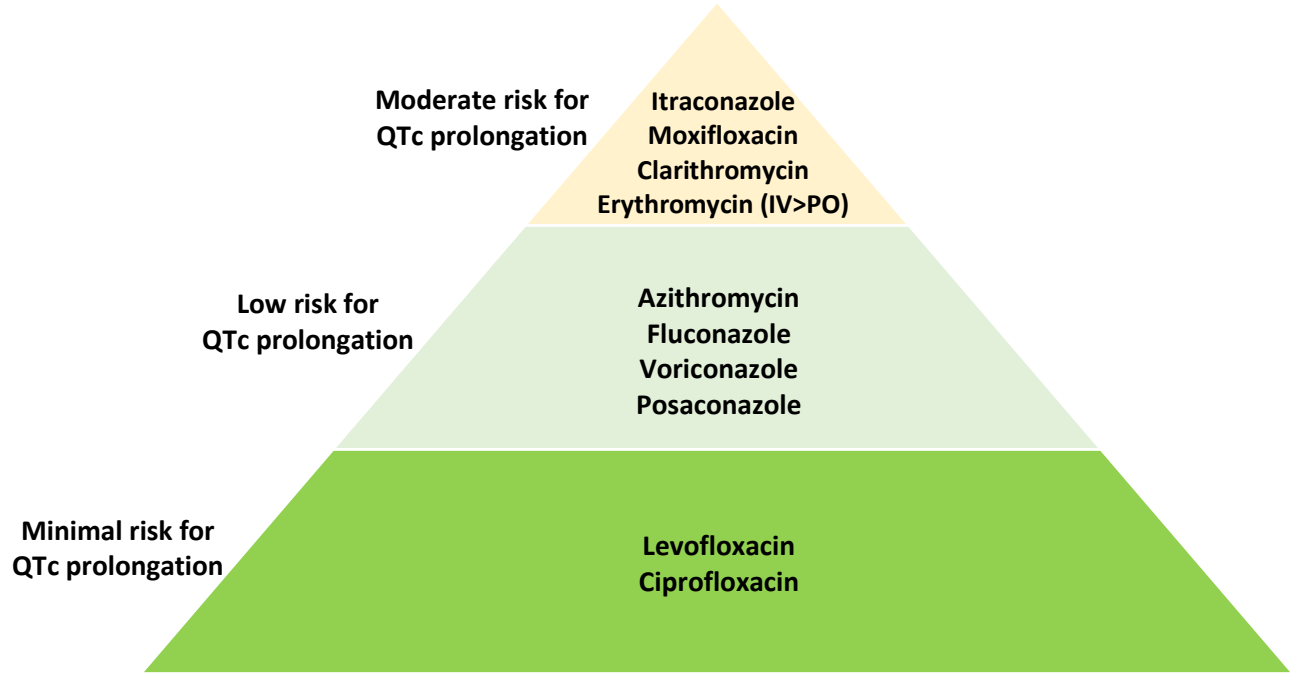
- Ventricular pacing (RV pacing, LV pacing, or Biventricular pacing)
- Left or right bundle branch blocks or interventricular conduction delay
- QRS > 140ms

Antimicrobial Cytochrome P450 impact and average QTc change

Antibiotic Agent	CYP3A4 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP1A2 Inhibitor	Average Impact on QTc
Macrolides					
Erythromycin†	Moderate	---	---	---	**30-50 ms**
Clarithromycin†	Strong	---	---	---	**11-22 ms**
Azithromycin†	---	---	---	---	**10-14 ms**
Fluoroquinolones					
Moxifloxacin	---	---	---	**---**	**10-14 ms** (400mg dose)
Levofloxacin	---	---	---	**---**	**4.73-7.12 ms** (1g and 1.5g dose, respectively)
Ciprofloxacin	Weak	---	---	Moderate	**~3 ms**
Triazoles					
Fluconazole	Moderate	Strong	Strong	---	Less data on the degree of prolongation; Often driven by drug interactions
Voriconazole	Strong	Moderate	Weak	--	**< 10 ms** (800 mg, 1200mg, and 1600mg doses)
Itraconazole†	Strong	---	---	--	Less data on the degree of prolongation; Often driven by drug interactions
Posaconazole†	Strong	---	---	--	**~5 ms**
Isavuconazole†	Moderate	---	---	--	QT **shortening** **13.1ms -24.6** (372 mg and 1116 mg dose, respectively)

***Not inclusive of all potential interactions; †P-glycoprotein inhibitor**

Torsades de pointes (TdP) risk stratification schedules for antimicrobial agents[11]



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