QT-Prolonging Antibiotics: More Than You Wanted to Know

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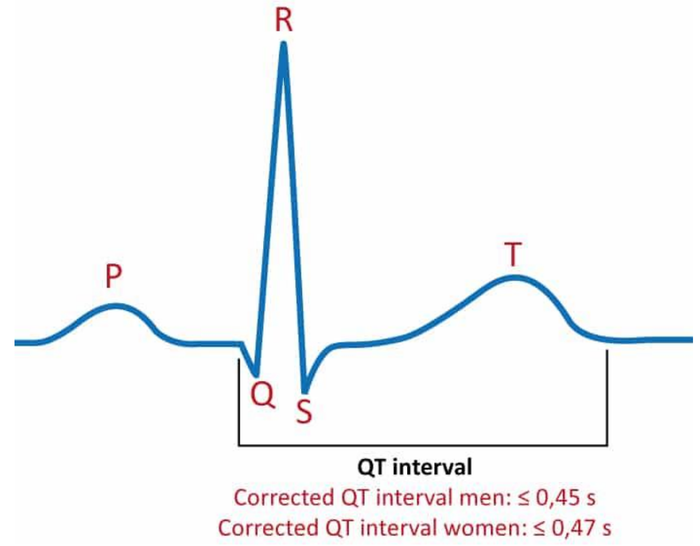
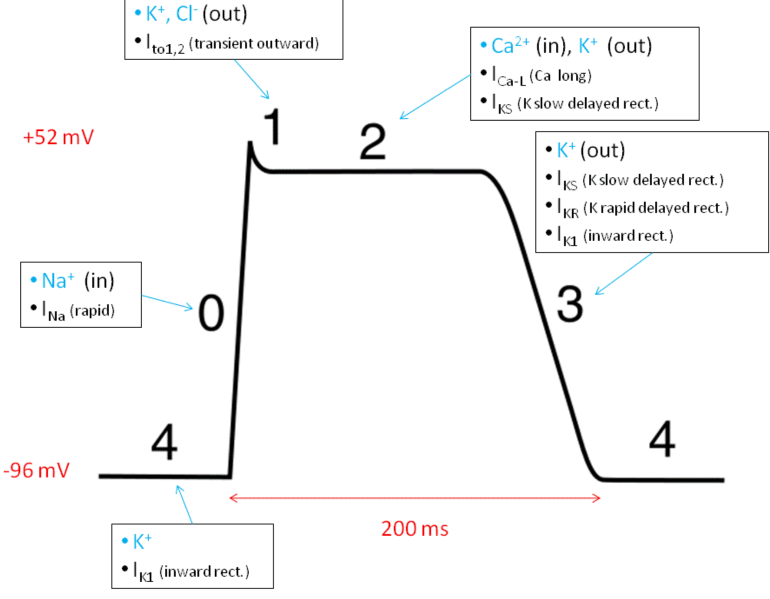
What is the QT Interval?

- Interval between the beginning of the QRS complex and end of the T-wave





https://ecgwaves.com/wp-content/uploads/2016/09/lqts1.jpg

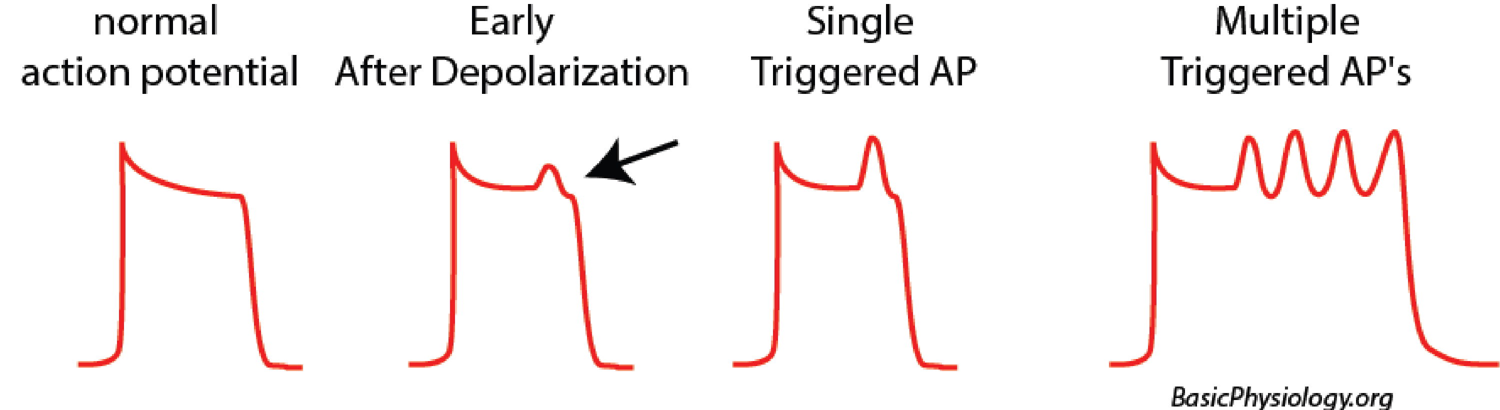
“Normal” QT Interval

- QT intervals are similar for males and females before puberty
- At puberty, QT shortens in males, then slowly lengthens over time
- Difference is minimal in elderly people
- Adult males: <460 ms = “normal”, ≥470 ms = “prolonged”
- Adult females: <470 ms = “normal”, ≥480 ms = ”prolonged”
- QT is affected by electrolytes, hormones, circadian rhythm
- QT fluctuates quite a bit (mean lengthening of 13 ms during sleep)

Lazzerini PE, et al. JACC Clin Electrophysiol. 2025;11(11):2376-2393. doi:10.1016/j.jacep.2025.07.009

QT Prolongation and Torsades

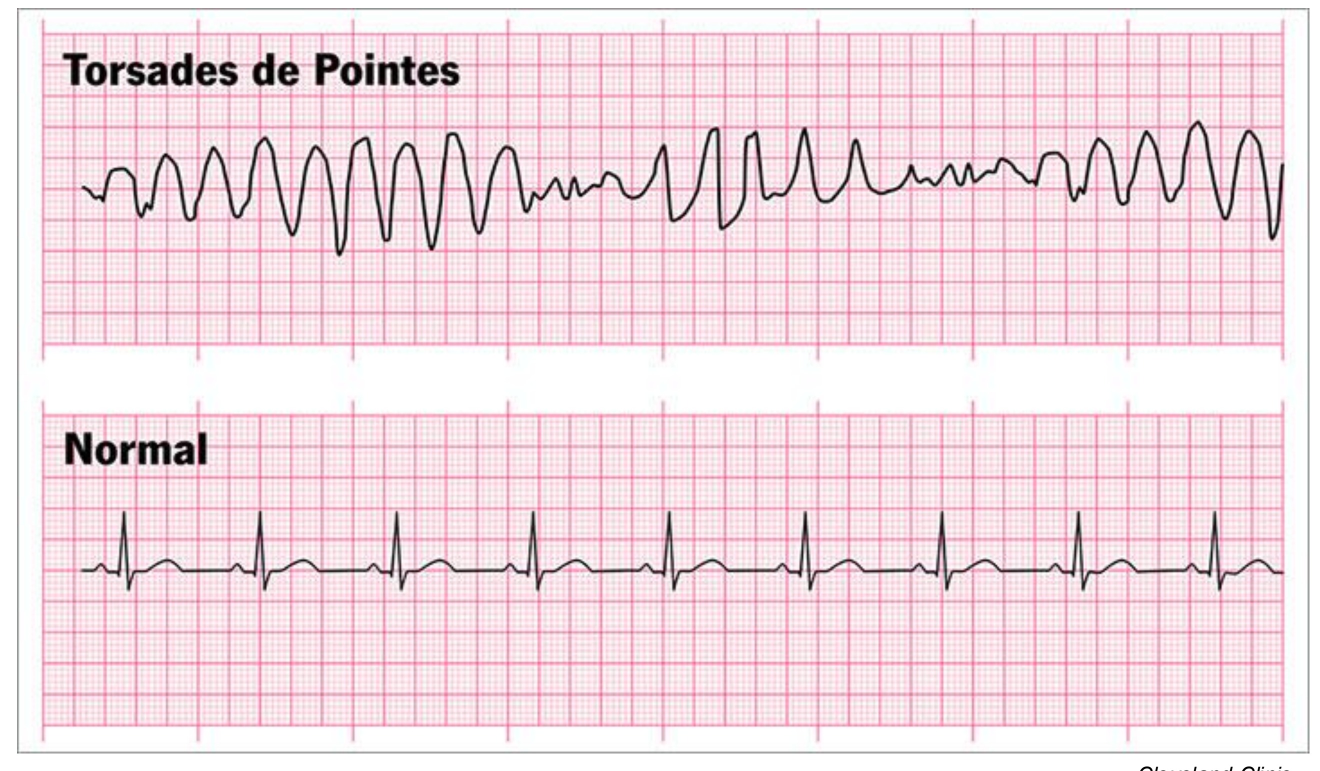
- Abnormally prolonged repolarization can lead to EAD's due to reactivation of calcium channels



Issa ZF. Ventricular arrhythmias in inherited channelopathies. In: Clinical Arrhythmology and Electrophysiology: A Companion to Braunwald's Heart Disease. 4th ed. Elsevier; 2024.

QT Prolongation and Torsades

- EAD’s can trigger TdP



Cleveland Clinic

Measuring the QT Interval

- Repolarization rate changes with heartrate
- Most commonly used formula to “correct” the measured QT for heartrate is Bazett’s Formula (1920’s, based on himself and his students)
- Bazett’s underestimates QT at low HR (<60) and overestimates at high HR (>90)

$$QT_c = \frac{QT}{\sqrt{RR}}$$

Measuring the QT Interval

- Automated QTc measurement tends to be 30-40 ms longer than manual[1]
- Measure manually if ECG is messy or abnormal
- ECG machine has most trouble with abnormal T-wave morphology
- Use “tangent method” to identify the end of the T-wave
- Use lead with the clearest T-wave morphology (often II or V5)
- Use an alternate correction (i.e. Friderica) for HR <60 or >90

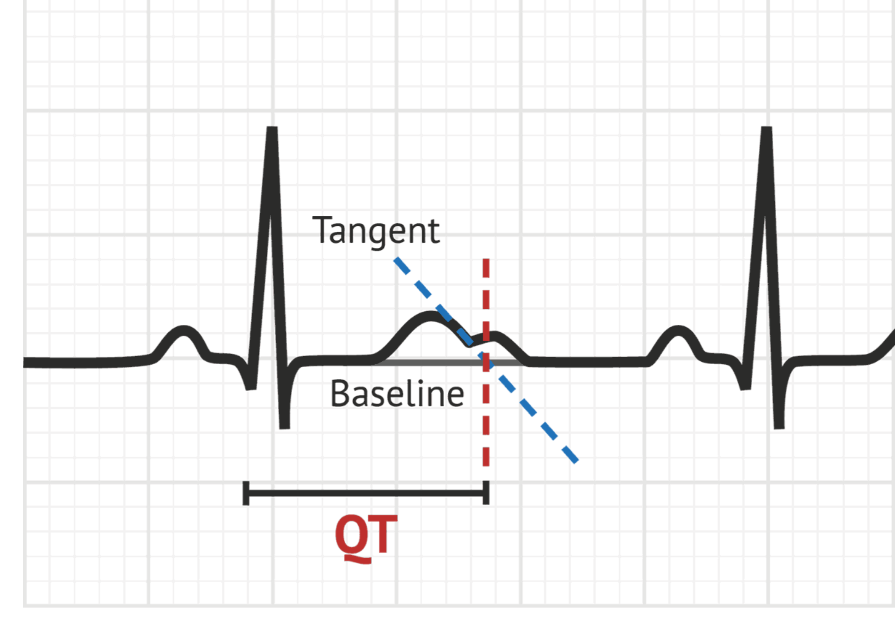


Image from LITFL

1.Schläpfer J, et al. J Am Coll Cardiol. 2017;70(9):1183-1192. doi:10.1016/j.jacc.2017.07.723

Widened QRS

- The JT interval is really what we're interested in
- If QRS>120 ms, QT will be artificially prolonged
- Correction methods:

→Bogossian Formula:

QT_{adj}=QT – 1/2QRS

→Use JT interval (correct for rate): >400 ms = increased risk

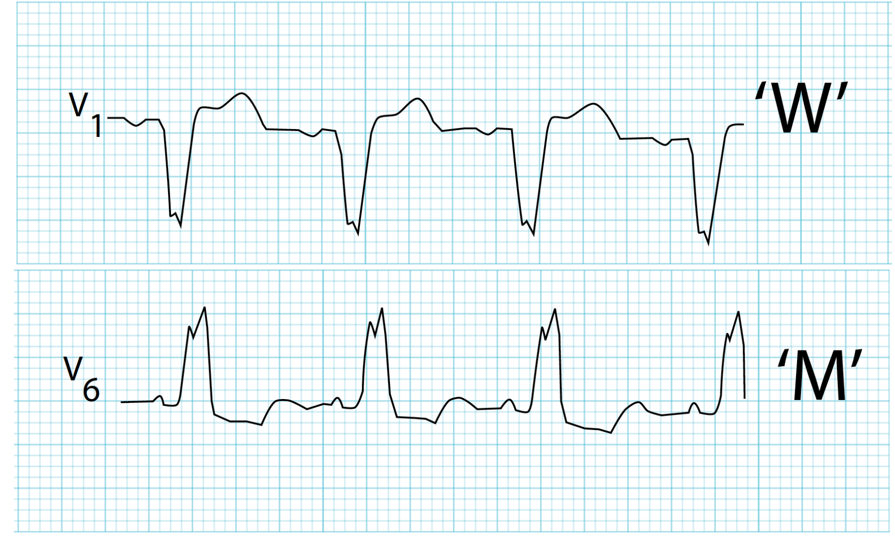


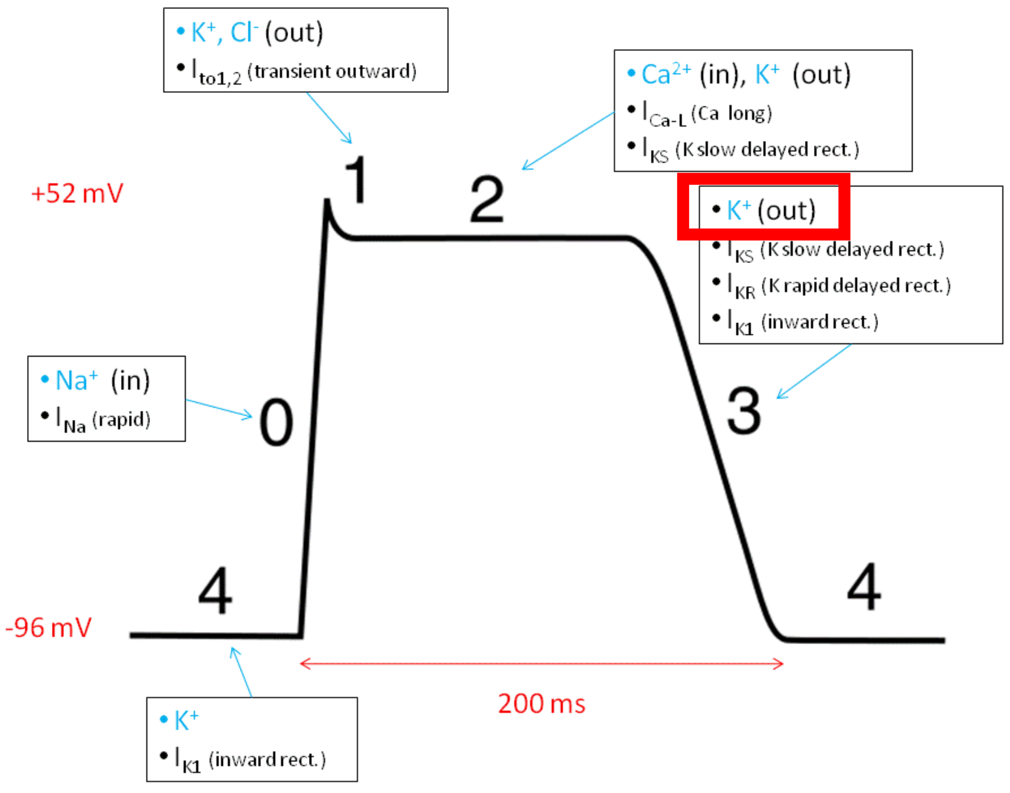
Image from LITFL

Risk factors for Acquired Long-QT/TdP

- **Ischemia**
- **Cardiomyopathies**
- Medications
- **Electrolyte abnormalities (low K, Mg, or Ca)**
- **Bradycardia**
- **Female**
- **Congenital LQTS**
- Hypothyroidism
- Hypothermia

Drug-Induced QT-Prolongation

- Mechanism: Inhibition of the hERG potassium channel (*KCNH2 gene)*



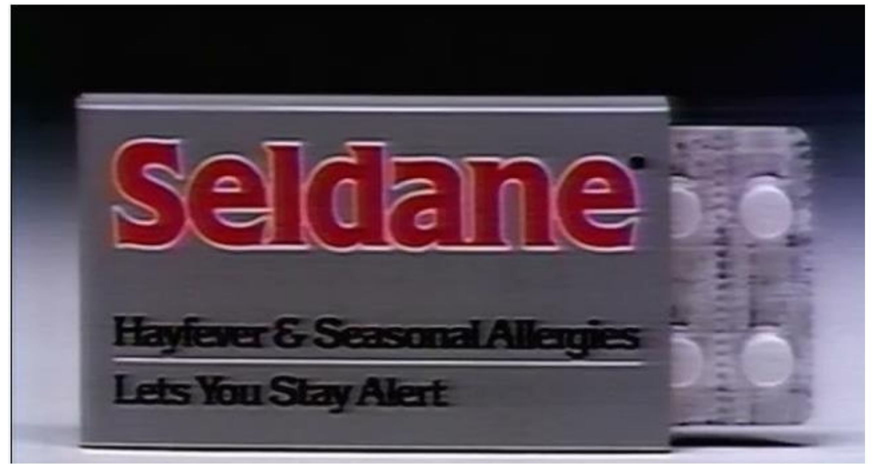
TdP Due to Medications

- TdP initially observed in patients with cardiomyopathy
- 1964: “quinidine syncope” found to be due to TdP[1]
- TdP due to medications is real and rare[2]
- Drugs have been withdrawn due to risk of TdP
- Risk of QT prolongation ≠ risk of TdP
- Risk of QT prolongation ≠ risk of SCD or other arrhythmias

1. Zeltser D, et al. Medicine. 2003;82(4):282.
2. Tisdale JE, et al. Circulation. 2020;142(15):e214-e233. doi:10.1161/CIR.0000000000000905

How it Started: The Terfenadine Story

- Introduced in 1985 as the first non-sedating antihistamine



How it Started: The Terfenadine Story

N
OH
OH
CYP3A4
N
OH
OH
OH
O

Terfenadine

Terfenadine carboxylate

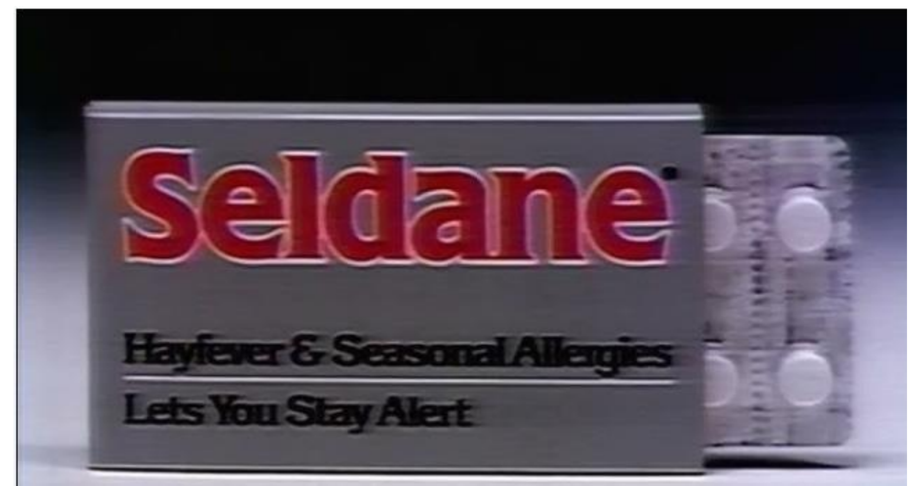
Wikipedia Images

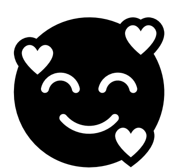
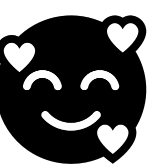
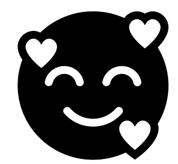
Oops…

- 1990 case report of a healthy woman who developed TdP on terfenadine + ketoconazole[1]
- 1993 paper demonstrated terfenadine inhibits hERG but its active metabolite does *not*[2]
- Terfenadine dangerous when combined with CYP3A4 inhibitor
- Withdrawn from the market in 1997 after 125 deaths from arrhythmia

1. *Monahan BP, et al. JAMA. 1990;264(21):2788-2790.*
2. *Woosley RL, et al. JAMA. 1993;269(12):1532-1536.*

Hooray



Thanks, Dr. Woosley!

Credible Meds

- Catalogues drugs and assigns a category:

Known Risk of TdP

Possible Risk of TdP

Conditional Risk of TdP

Regulation of QT-prolonging Drugs: The TQT

- “Thorough QT” (TQT) study that drugs must undergo for FDA/EMA approval
- Positive control = moxifloxacin (predictable 10-15 ms prolongation)
- If a drug prolongs the mean QTc ≥ 5 ms (10 ms with upper CI)- will have a warning and much closer monitoring in subsequent phases
- This is less than typical QT variability in healthy people, so very sensitive cutoff
- Industry moving to “concentration-QT modeling” during phase I

Roden DM. J Physiol. 2016;594(9):2459-2468.
FDA

Antimicrobials

- Azithromycin ❌
- Moxifloxacin ❌
- Levofloxacin ❌
- Ciprofloxacin ❌
- Fluconazole ❌
- Voriconazole *
- Posaconazole *

Credible Meds

But what is the actual risk?

- Answer: very hard to know but seems to be low
- QTc is an imprecise marker of risk of SCD[1]
- Incidence: reports to regulatory bodies and drug companies
- Issues with underreporting (inadequate investigation of sudden deaths)
- Issues with overreporting (premature or inaccurate attribution of blame to a particular drug)

1. Bednar MM, et al. Progress in Cardiovascular Diseases. 2001;43(5, Supplement):1-45.

But what is the actual risk?

Circulation

Drug-Induced Arrhythmias

A Scientific Statement From the American Heart Association

*Incidence per 1 million person-years

Antibiotic	Azithromycin	0.97‖
	Ciprofloxacin	…
	Clarithromycin	…
	Erythromycin	0.4
	Levofloxacin	0.2
	Moxifloxacin	…
	Roxithromycin	…
Antifungal	Fluconazole	…
	Pentamidine	Up to 21

Tisdale JE, et al. Circulation. 2020;142(15):e214-e233.

So what is the actual risk?

- Azithromycin at normal doses prolonged QTc on average 5-10 ms[1]
- **Azithromycin causes increased risk of cardiovascular death and all-cause mortality compared to amoxicillin[2]**
- Levofloxacin increased QTc 3.5-5 ms on average after 1 supratherapeutic dose[3]
- Levofloxacin increased risk of ventricular arrhythmia (OR 1.44) and cardiovascular death (1.77) compared to amox-clav[4]
- Ciprofloxacin at normal doses didn't change the QTc in 88 patients[5]
- 16 cases of TdP due to triazoles between 1997 and 2023. Fluconazole 63%, voriconazole 37%[6]

1. FDA Prescribing Information for Azithromycin
2. Ray WA, et al. New England Journal of Medicine. 2012.
3. Noel GJ, et al. Clinical Pharmacology & Therapeutics. 2003;73(4):292-303
4. Chou HW, et al. Clinical Infectious Diseases. 2015
5. Liu W, et al. Journal of Antimicrobial Chemotherapy. 2026
6. Kitaya S, et al. Microorganisms. 2024

The Bottom Line

Genetics
→LQTS-1–LQTS-7
→Unknown ion channel mutations

Underlying cardiac disease
→ Ischemia
→ CHF
→ Bradycardia
→ Atrial fibrillation

Electrolyte derangements
→Hypokalemia
→Hypomagnesemia
→Hypocalcemia

Organ impairment
→Renal insufficiency
→Severe hepatic disease

I_{Kr}-blocking comedications or CYP3A4 inhibitors
→ www.torsades.org

Prescritption of QT-prolonging drug (antimicrobials listed)
→ Macrolides/ketolides
→ Quinolones
→ Azoles
→ Pentamidine
→ TMP-SMZ

Torsades de Pointes

Owens RC, et al. Clin Infect Dis 2005;41

So what do we know?

- TdP from antimicrobials seems to be very rare
- Almost always in the setting of **multiple risk factors**[1]
- Most significant RF include

  →Baseline QT prolongation (could be subclinical LQTS)

  →Female

  →Age >65

  →Bradycardia

  →Cardiomyopathy

  →Electrolyte derangements (low K, low Mg)

1. Zeltser D, et al. Medicine. 2003;82(4):282.

Using QT-prolonging Antimicrobials

- TdP in a low-risk patient from an antimicrobial alone is **extremely** unlikely and routine monitoring is not generally warranted
- Baseline 12-lead ECG prior to starting a QT-prolonging antimicrobial is reasonable for certain patients (i.e. elderly woman with CHF on Lasix)
- Reasonable to stop (or not start) an antimicrobial if QTc >500 ms (pay attention to the QRS!) or >60 ms increase from baseline
- Ciprofloxacin risk is probably negligible
- Levofloxacin and Azole risk: real but still quite low
- Azithromycin causes very little QT prolongation but could it be causing other arrhythmias?

Monitoring in High-Risk Patients

- ACC/AHA:

→Any **outpatient** at risk: Baseline ECG + repeat "every 3-6 months depending on risk factors"

→For high-risk **inpatients**, ECG should be repeated 8-12 h after first dose

→Monitor renal function and electrolytes for patients at risk (i.e. on diuretics)

Tisdale JE, et al. Circulation. 2020;142(15):e214-e233.

Questions?