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QT Interval Prolongation and Second-line Antituberculosis Medicines in Children

An Update and Practical Considerations for Noncardiologists

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Many of the new and repurposed drugs that now form the backbone of rifampicin-resistant tuberculosis (RR-TB) treatment regimens are known to cause QT interval prolongation. In many high-TB burden settings, access to cardiologists with expertise in ECG interpretation is limited. Therefore, clinicians responsible for caring for children with RR-TB must now be knowledgeable about evaluating and managing this adverse effect in children. Here, we provide a concise overview of drug-related QT interval prolongation, the current state of knowledge of QT prolongation of current TB drugs in children, challenges in high-burden settings, and practical guidance for noncardiologist clinicians caring for children with RR-TB.

DRUG-ASSOCIATED QT INTERVAL PROLONGATION OVERVIEW

Drugs with the potential to interact with cardiac cell ion-channels can lead to drug-induced alterations of repolarization, which result in prolongation of the QT interval on electrocardiogram (ECG). The drug-induced polymorphic ventricular tachycardia is a specific type, termed torsade de pointes (TdP), which can lead to sudden death.[1] Unexpected life-threatening adverse outcomes first emerged in the 1990s, which led to regulatory bodies pulling drugs from the market and revising pathways for drug safety approval. Since then, significant work has addressed this problem by focusing on: vetting preclinical drugs for safety; defining specific testing protocols and thresholds for the definition of QT prolongation; and widely available registries to check individual drugs for QT prolongation risk (https://crediblemeds.org). QT-prolonging medications can be safely used with careful predrug screening, close clinical and QT interval monitoring, review of ongoing risk factors and careful attention to drug-drug interactions. Dangerous QT prolongation typically occurs when *combinations* of drugs are used, particularly in individuals with additional risk factors such as cardiac disease, hypokalemia, hypomagnesaemia, or hypocalcemia.[1]

Combination therapy with novel and repurposed drugs that have QT-prolonging properties and the risk of electrolyte imbalances in individuals with TB does pose a risk for prolonged QT. One issue with quantifying risk is that, while TdP and sudden death are always preceded by prolongation of the QT interval, these events are quite rare during safety trials. Marked QT prolongation is used as a surrogate but does not always necessarily lead to the arrhythmia. Available data points to a drug-induced QT prolongation of 500 milliseconds (ms) as an indicator of nontrivial risk of TdP with possible arrhythmic death.[1] Protocols designed for monitoring and modification of treatment regimens usually require 2- to 4-weekly ECGs with thresholds of 460 ms, 480 ms and 500 ms as levels that trigger more close monitoring, holding the culprit drug and stopping all

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QT-prolonging medications. Symptoms of palpitations, dizziness, chest pain and syncope, and a QT interval increase of >60 ms from pretreatment baseline may also trigger closer ECG monitoring. However, these are not in themselves reliable indicators of increased risk of TdP.

QT INTERVAL MEASUREMENT AND INTERPRETATION FOR THE NONCARDIOLOGIST

Guidance and tools for noncardiologists to calculate QT intervals have improved. Attention to obtaining a high-quality tracing by ensuring the child is calm, comfortable and undressed from the waist up, with accurate placement of leads is critical. Automatic reads from the ECG machine are not as accurate as manual reads, so manual measurement and calculation of QTc is advised.[2] Digital tracings allow a "zoomed view" with excellent resolution. The absolute QT interval is measured from the onset of the Q-wave to the termination of the T-wave. Limb lead II or precordial lead 5 (V5) are best for measuring the QT interval; alternative leads may be used when the T-wave termination is poorly visualized.

The normal QT interval is a dynamic parameter that changes physiologically with an individual's heart rate (HR). There are formulae that correct the absolute QT interval for the patient HR of the preceding beat. This "corrected QT interval" (QTc) is reported in units of milliseconds. One beat is the time distance between QRS complexes—frequently referred to as the "R-to-R interval" named for the easily identified peak of 1 R-wave to the next R-wave. The Fridericia correction (QTcF, the QT interval in milliseconds divided by the cubed root of the preceding RR-interval in seconds), and the Bazett correction (QTcB, QT interval divided by the square root of the RR-interval) can be calculated manually with the aid of a calculator or via several online calculators or apps. In practice, both QTcB and QTcF yield similar results when the HR range is within 55–85 beats per minute, and reasonable agreement up to 100 beats per minute. Clinicians should consistently use the same correction algorithm when serially following patients for QT prolongation. Nearly all early phase I/II trials utilize QTcF and detailed physiologic studies have shown that QTcF outperforms QTcB with better agreement to a robust subject-specific reference standard derived QTc. In addition, numerous clinical studies have demonstrated that QTcB overestimates QTc, especially at high HR, and can potentially increase harm by excluding patients from life-saving medications. While QTcF is mostly preferred in older children and adolescents, the issue of HR correction in infants and newborns is an area for further investigation.

CURRENT KNOWLEDGE ON QT INTERVAL PROLONGATION WITH SECOND-LINE ANTITUBERCULOSIS DRUGS IN CHILDREN

Based on World Health Organization (WHO) 2022 updated guidance on treatment of TB in children and adolescents, most second-line TB treatment regimens for people of all ages will include at least one or more QT-prolonging medication, which are discussed below.[3] Overall, the incidence of severe QT prolongation appears to be lower in younger children, perhaps because of a combination of less cardiac comorbidities and exposure to what are typically lower TB drug concentrations.

Fluoroquinolones

Levofloxacin, often considered for RR-TB preventive therapy and currently recommended as a core drug for RR-TB treatment, appears to have a relatively small effect on the QT interval. In contrast, moxifloxacin is often avoided in programmatic RR-TB treatment regimens containing multiple QT-prolonging drugs caused by the higher associated risk of QT prolongation; however, multiple ongoing clinical trials include moxifloxacin in treatment-shortening regimens for children and adults with RR-TB. In a prospective observational study of 70 children receiving treatment for RR-TB disease with levofloxacin-based regimens, 41 children had ECG data available and none had QTcF >450 msec recorded over the 2 hours post-treatment administration.[4] A mean change in QTcF of 4.7 ms was recorded; 5 (13%) children had QTcF change 30–60 ms and 1 had a change >60 ms. Only 1 child received another QT-prolonging drug, clofazimine, and they had a QTcF change of 44 ms.[4] Across 2 observational studies where 85 children received moxifloxacin (mean dose 11 mg/kg/day) within treatment regimens for RR-TB, 5 children had a QTcF ≥450 to <500 ms (4 of 5 were receiving clofazimine), but no child had QTcF >500 ms.[5] As moxifloxacin has a short half-life, the maximum QT effects would be expected within a few days of starting treatment.

Clofazimine

In an early bactericidal activity (EBA) study, clofazimine monotherapy in 15 participants with drug susceptible TB was associated with an increase in QTcB interval of 16–20 ms over 14 days.[6] However, the maximum QT-prolonging effect, with a change in QTcF of up to 28 ms, is predicted to occur at around 6 weeks following initiation of clofazimine monotherapy.[6] Very little is published on the cardiac safety of clofazimine-containing regimens in children with RR-TB. In an observational study of 54 children <16 years old receiving clofazimine-containing treatment for RR-TB, clofazimine concentration was directly associated with QTcF prolongation, but only 6 events of QTcF between 450 ms and 500 ms were recorded.[7]

Bedaquiline

Bedaquiline is now recommended for RR-TB treatment in people of all ages.[3] The maximum change in QTcF associated with bedaquiline is reported to occur after more than 18 weeks of exposure to the drug.[8] In the ongoing pediatric TMC207-C211 phase 2 study, safety data among 30 children in 2 cohorts (15, 5–10 years and 15, 14–17 years of age) receiving WHO-recommended RR-TB regimens including bedaquiline, indicated that 6 (40%) children had QTcF increase of 30–60 ms from baseline but none had QTcF >460 ms over 24 weeks.[9] In an observational pharmacokinetic study of 15 children and adolescents 6–16 years old receiving bedaquiline-containing regimens for RR-TB in routine care, 2 (13%) had mildly prolonged QTcF up to 480 ms but none had QTcF >500 ms.[10] Interim safety data from another ongoing bedaquiline pharmacokinetic study indicate that 3 (27%) of 11 children <6 years of age receiving RR-TB treatment had QTcF increase of 30–60 ms and all received concomitant clofazimine.[3]

Delamanid

The peak QT effect of delamanid among adults with RR-TB is reached at around 8 weeks following drug initiation.[8] Thirty-seven children 0–17 years old were enrolled on Otsuka's NCT01856634 phase I trial where they were exposed to 10 days of delamanid plus OBR, and then progressed into the NCT01859923 phase II trial where they received 6 months of delamanid alongside a longer OBR for RR-TB treatment.[11] Over both studies, no participants had QTcF >480 ms and only 2 children experienced QTcF change >60 ms from baseline.

Bedaquiline and Delamanid Combination

Safety data from a large multicenter, observational study that was part of the endTB project and included patients receiving delamanid and bedaquiline for RR-TB according to WHO guidance and local standards in 16 countries show that the incidence of QT-related adverse events was low. Among

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TABLE 1. Recommendations for QT Interval Monitoring in High-tuberculosis Burden Settings for Children Treated With QT-prolonging TB Drugs

- Regular maintenance of existing machines and consumables and/or introduction of digital machines With remote access to experienced ECG readers.
- ECG operator training to ensure good quality ECG tracings and avoid common artifacts: dense baseline electrical interference, solved by moving ECG leads away from the power cord; baseline wander from either a poorly adherent lead, cord or patient motion; baseline noise from a nearby mobile device or a patient tensing their muscles.
- Clinician awareness of normal QT measurements (<450 ms) and other common factors affecting QT intervals in individuals (diurnal variation, physiologic and emotional state, other drugs, electrolyte or endocrine disturbances)—wherever possible, serial ECG monitoring should be carried out at a similar time of day and when the patient is calm and at rest.
- Readily available guidance (posters, desktop guides) for clinicians not familiar with ECG monitoring for QT prolongation; automatic machine readings may not always report an accurate QTc interval, clinicians can learn to manually calculate QTcF with the correct mathematical formulae, and various apps or electronic resources are available to assist with QTc calculations.
- Ideally, the corrected QT interval (preferably QTcF) should be documented at or near the time of initiation of QT-prolonging drugs, as a baseline measure for future comparison, and ECGs should be repeated monthly for the duration of exposure to the drugs, with consistent use of the same correction algorithm for serial monitoring of QTc; if this is not feasible then ECG monitoring should be prioritized for those at higher risk of QT prolongation (those with comorbidities, electrolyte disturbances and/or exposure to multiple other QT-prolonging drugs).
- More frequent ECG monitoring is advised for children with QTcF >460 ms, and all QT-prolonging drugs should be withheld if QTcF is confirmed as ≥ 500 ms; clinicians should review and correct other potential causes of QT prolongation, especially electrolyte disturbances (low potassium, magnesium, calcium) and use of other concomitant non-TB QT-prolonging medications, before considering reintroduction of QT-prolonging TB drugs when QTcF is <480 ms. Hospital admission for QTcF ≥500 ms is not generally required in otherwise well children, but depends on the feasibility of close cardiac and clinical monitoring in an out-patient setting; hospitalization should be considered in children with prolonged QTcF and severe cardiac symptoms (chest pain, palpitations, dizziness or syncope), electrolyte disturbances and uncontrolled comorbidities (e.g., hyperthyroidism).
- The QT effects of TB drugs are largely additive and regimen composition may have to be reviewed in cases of QTcF ≥500 ms; given the large QT-prolonging effect of clofazimine in particular, it would be prudent to substitute with alternative drugs in these cases.

ECG indicates electrocardiogram; QTcF, corrected QT interval using the Fridericia correction; TB, tuberculosis.

2296 adults and older adolescents receiving both or either of these 2 medications, 63 (2.7%) experienced QTcF >500 ms, or >60 ms increase along with cardiac symptoms; median time to event was 2.5 months (interquartile range 0.9–5.1 months).[12] Two of the 18 reported "sudden deaths" and 2 of the 21 "deaths of undetermined cause" in the entire cohort were patients who had documented QTcF >500 ms, however, additional risk factors possibly contributed to these fatalities.

In the phase 2 DELIBERATE study (ACTG A5343) of 82 adults randomly assigned to receive bedaquiline, delamanid or both for 24 weeks alongside a longer OBR (without clofazimine or moxifloxacin) for RR-TB, there were no reports of QTcF >500 ms over 28 weeks of treatment.[8] QTcF increased over 24 weeks from baseline by a mean of 12.3 ms in the bedaquiline group, 8.6 ms in the delamanid group and 20.7 ms in the combined group, leading the authors to conclude that the QTc prolongation of the 2 drugs combined was not more than additive. Literature on QTc prolongation among children or adolescents receiving both delamanid and bedaquiline is currently limited to a few case reports but do not highlight any unexpected findings.

Pretomanid

Pretomanid is a relatively new anti-TB drug that has not been widely used outside of clinical trials and controlled access programs where it is prescribed within the 3-drug (BPaL; Bedaquiline-Pretomanid-Linezolid) combination for which it was registered. This drug appears to have only a mild QT-prolonging effect which peaks at 1–2 days of exposure.[13] To date, no safety data have been reported for pretomanid-containing treatment regimens for TB in children <18 years.

PRACTICAL CONSIDERATIONS FOR ECG MONITORING IN HIGH-BURDEN SETTINGS

Procurement and distribution of medical equipment and consumables in low- and middle-income countries (LMIC) is challenging, and traditional ECG monitoring requires machines (usually powered by electricity) and a sustainable supply of adult and pediatric leads, paper and toner. Timely access to replacement parts and repair technicians is often not possible, and maintenance problems are common, with estimates that 40%–70% of medical devices in LMIC are inoperable.[14] As a result, access to ECG is often very limited, particularly in African countries. For example, in Mozambique, there are only 40 functioning ECG machines across the country, primarily at district and provincial hospitals, to serve a population of >31 million people living in a land area of 801,590 km^2 (unpublished data, Mozambique National TB Control Program). Even where machines are available, these might not always provide an automatic readout of HR, QT interval and other parameters, and ECG machine operators may not have received instruction on how to modify default settings to choose a specific HR correction algorithm for the QT interval. There are also significant gaps in clinician capacity to interpret ECGs and manually calculate QTc. Decentralized ECG monitoring using portable, battery-powered devices, which produce digital results that can be interpreted via telehealth platforms is a promising solution to overcome these equipment and training barriers.

RECOMMENDATIONS FOR QT INTERVAL MONITORING FOR CHILDREN TREATED WITH QT-PROLONGING TB DRUGS AND CONCLUSION

Table 1 lists key considerations for clinicians in high-TB burden settings for managing children receiving QT-prolonging TB drugs. Additionally, limited capability for ECG monitoring should in most cases not prevent access to effective second-line TB drugs for children with RR-TB as the overall risk of QT prolongation is relatively low, particularly when balanced with the higher risk of poor treatment outcomes if children are denied treatment with these medications.

Monitoring of the QT interval will be a part of RR-TB care for the foreseeable future. With some fundamental knowledge as described here, TB clinicians caring for children are capable of managing this to ensure access for children to safe and effective RR-TB treatment.

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