Abstract

Background: Acquired QT-prolongation in children undergoing treatment for acute lymphoblastic leukemia (ALL) is potentially fatal. To date specific recommendations for ECG monitoring during ALL treatment are lacking. Aim: We aimed to assess the prevalence of QT prolongation and explore possible causes in ALL patients undergoing therapy.

Methods and Results: A retrospective review of the records of all pediatric ALL patients treated between 2018-2021 at the American University of Beirut was conducted. Patients lacking complete ECG records, baseline ECGs, or those with structural or functional heart disease were excluded from the study. QT interval was measured manually, and the longest measurement was chosen. Bazett’s formula was used to correct for heart rate. All medications, the patient was on at the time of the ECG recording were documented. In addition, the level of electrolytes measured within the preceding 24 hrs of the ECG were analyzed. 28 out of 257 ECGs met prolonged QTcB criteria (≥450 ms or ≥60 ms increase from baseline). Using multivariate analysis, age, cyclophosphamide, fluconazole, and voriconazole maintained their significant association with QTcB prolongation. Hypomagnesemia and hypocalcemia showed association with QTc prolongation by bivariate analysis; however, this association could not be confirmed using Multivariate analysis due to the small sample size. The association between ondansetron and trimethoprim/sulfamethoxazole (TMP-SMX) could not be determined as all patients were receiving those two medications. Importantly, life-threatening Ventricular arrhythmias, Torsade de pointes, did not occur in any of our patients. Conclusion: Our study provides insights into factors contributing to QTcB prolongation, including specific medications, chemotherapeutic agents and possibly hypomagnesemia and hypocalcemia. To better understand these associations, larger prospective studies are necessary. In the interim, it is essential to conduct frequent follow-ups with ECGs when using these medications.
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Keywords:
ALL, QT-prolongation, Chemotherapy, ECG

Introduction:
Chemotherapy-induced QT prolongation on ECG is a potentially life-threatening side effect of cancer treatment, particularly in pediatric patients with ALL on therapy. The use of chemotherapy agents, such
as anthracyclines, can cause QT prolongation, which can lead to life-threatening polymorphic ventricular tachycardia (VT) frequently described as torsade de pointes.  

QT prolongation can be readily detected by performing a 12-lead ECG. QT-interval represents the time from ventricular depolarization to complete repolarization and is usually corrected to the patient’s heart rate, thus yielding corrected QT interval (QTc). There are several formulas to calculate the QTc, the most widely used in pediatric patients, is Bazett’s formula (QTc = QT/√RR).

Approximately 66% of FDA-approved chemotherapeutics require cardiovascular monitoring. However, as of now, there remains a dearth of definitive cardiovascular monitoring guidelines or protocols, particularly regarding ECG monitoring, for pediatric ALL patients. Moreover, the benefits of serial (ECG) monitoring to detect QT prolongation in these patients remain unclear.

The National Cancer Institute Common Terminology of Clinical Adverse Events v5.0 classifies QTc prolongation into 4 grades: grade 1 (QTc 450 to 480 ms), grade 2 (QTc 481 to 500 ms), grade 3 (QTc >501 ms; >60 ms change from baseline), and grade 4 (signs/symptoms of serious arrhythmia and TdP). In this study, we define QTc prolongation as QTc[?]450, or an increase by [?] 60 ms from baseline ECG. We will discuss the prevalence of QTc prolongation, and its association with specific chemotherapeutic agents, concomitant medications, and electrolyte imbalances.

**Statistical Analysis:**

Data was entered into a Microsoft Excel sheet, and then transferred to the Statistical Package for Social Sciences (SPSS) version 28 which was used for data cleaning, management, and analysis. Descriptive statistics was carried out using the number and percent for categorical variables, whereas either mean and standard deviation, or median and interquartile range (IQR) were calculated for continuous ones. Bivariate analysis for the association between QTc prolongation and categorical variables was done using the chi-square test, whereas the independent sample t-test was used for the association with continuous variables. Finally, multivariate logistic regression analysis was carried out to identify predictors of QTc prolongation, where statistically significant variables at the bivariate analysis and/or clinically relevant ones were included. Results were reported as odds ratio (OR) and 95% confidence interval (CI). P-value <0.05 was used to indicate statistical significance.

Methods and Results A retrospective review of all pediatric ALL patients, less than 21 years of age, treated in our center from January 2018 to December 2021 was performed. Electronic medical records, at the Cancer Center registry, and the ECG database were reviewed. Patients who lacked complete ECG records, had no baseline ECGs, exhibited structural or functional heart disease on echocardiography, or had ECGs with a QRS duration exceeding 120 msec were excluded from the study. All ECGs were reviewed by the same senior cardiologist who was blinded to the patient’s treatment regimen and to the previous ECGs. QT interval was measured manually using the tangent method in the leads with the clearest T wave, specifically in leads II or V5; and the longest measurement was chosen. Bazett’s formula was used to correct for heart rate, and the resultant corrected QT interval (QTcB) was used in further analysis. All medications, the patient was on at the time of the ECG recording were documented. In addition, the level of electrolytes measured within the preceding 24 hrs of the ECG were analyzed.

We define QTc prolongation in this article as QTc[?]450 ms, or an increase by [?] 60 msec from baseline ECG. A total of 257 ECGs in 112 patients were identified. These ECGs were classified based on various parameters to assess the risk factors associated with QTcB prolongation.

Demographically, the study included 126 ECGs (49%) from male patients and 131 ECGs from female patients. The interquartile range of age was between 1-9 with a mean age of 5 years. Out of the 257 ECGs, 28(11%) fulfilled QTcB prolongation criteria, with intervals ranging between 446-511 msec.

None of our patients developed premature ventricular contractions, runs of ventricular tachycardia or torsade de pointes.
According to the data presented in Table 1, the average age of patients exhibiting QTcB prolongation was $2.89 \pm 4.49$ years, compared to $6.24 \pm 5.39$ years in the non-QTcB prolongation group. The mean body surface area (BSA) was calculated to be $0.88 \pm 0.26$ in the QTcB group as compared to $1.14 \pm 0.49$ m$^2$ in the non-QTcB prolongation group. Statistical analysis revealed significant differences in age ($p=0.002$) and BSA ($p<0.001$) between the two groups, indicating a notable association between young age, smaller BSA, and QTcB interval prolongation. Given that the Bazett Formula for QTc calculation tends to overcorrect the QT interval at fast heart rates, and under correct the QT interval at slow heart rates, it is important to mention that the difference in heart rates in QTcB prolongation group vs no QTc prolongation was not statistically significant.

The associations between chemotherapeutic agents that are part of the ALL-treatment protocol along with adjunct medications used at the time the ECGs were obtained, are shown in Table 2.

When conducting bivariate analysis on the chemotherapy agents included; only cyclophosphamide and daunorubicin displayed significant p-values of <0.01 and 0.05 respectively. All of the adjunct medications mentioned have been significantly associated with QTcB prolongation, as demonstrated in Table 2.

The influence of electrolyte imbalances, values outside the normal range for Calcium, Potassium, Phosphate, and Magnesium on developing QTcB prolongation was also investigated in this study and is reported in Table 3. Positive association was noted between hypomagnesemia and QTcB prolongation, with a p-value of 0.02, and between hypocalcemia and QTcB prolongation, with a p-value of 0.03. Pertinently there were no patients with hypermagnesemia, thus its implications could not be assessed.

Of note, the following are the normal ranges in our institutional lab: Potassium (3.5-5.5 mmol/L), Magnesium (1.6-2.0 mg/dl), Calcium (8-10 mg/dl), and Phosphate (2.8-3.6 mg/dl).

Multiple logistic regression analysis was conducted, and the variables entered in the model were the following: Age, Body Surface Area (BSA), cyclophosphamide, daunorubicin, esmoprazole, fluconazole, levofloxacin, voriconazole, caspofungin, and amphotericin B. The statistically significant variables displayed in Table 4. Although hypomagnesemia and hypocalcemia, as variables showed statistically significant association in the bivariate analysis, they were not included in the multiple logistic regression analysis due to the small sample size that might lead to inflation of the odds ratio.

Significant associations with QTcB prolongation were observed, particularly young age (p-value: 0.007, OR (95% CI): 0.86 (0.78, 0.96)), with a confidence interval that does not cross 1, reinforcing its statistical significance. Cyclophosphamide also demonstrated a noteworthy association (p-value: 0.05 OR (95% CI): 0.27 (0.11, 0.68)) with a confidence interval not crossing 1, such as fluconazole with a p-value of 0.02 OR (95% CI): 0.18 (0.04, 0.81) . Voriconazole also yields a significant p-value of 0.03, however has OR (95% CI): 2.74 (1.11, 6.77), warranting further consideration.

Discussion:

In this study, we define QTc prolongation as QTc $[?]450$ ms, as per the upper limit of normal for children reported by Dickinson$^5$. Although Pearl and colleagues $^6$ reported a cutoff of normal for girls above 14 years as 460 msec, we chose to include all with QTc above 450 msec as a conservative measure. In addition, we define significant QTc prolongation as an increase of $[?]60$ ms from baseline ECG, following the proposal by the National Cancer Institute $^4$. This approach aimed to capture all significant QT changes, particularly in cases where QTc showed considerable prolongation but did not reach the 450 msec cutoff value.

In the existing literature, investigation into the relationship between age, gender, and QTcB prolongation has been undertaken. Notably, studies focusing on familial long QT syndrome since 1978 have reported an unexplained female predominance, despite the absence of germline inheritance patterns $^7$. In this study, age was a significant variable with younger age was found to be associated with QTc prolongation. ECG with prolonged QTc were for patients with mean age of 2.89 +- 4.49 as compared to 6.24 +- 5.39 for patients with normal QTc.
Addressing the correlation between hypomagnesemia and QT prolongation, a recent study observed increased P wave duration, T peak-to-end interval (Tpec), and Tpe/QT ratio in patients with isolated hypomagnesemia. Notably, restoration to normal magnesium levels led to significant improvement, highlighting the critical role of magnesium in cardiac repolarization. However, it is worth noting that since we did not have patients with hypermagnesemia, its effect on QT prolongation could not be determined; taking into consideration a case in the literature by Won Jhang, et al, that described abnormal ECG findings like those of hyperkalemia in a child undergoing dialysis.

Sudden cardiac death (SCD) has garnered substantial attention, with Magnesium emerging as a pivotal intracellular cation influencing Potassium influx, QT duration, and risk factors for ventricular tachycardia/arrhythmias (VT/VF) and SCD. As known, Magnesium administration has become a primary intervention for torsade de Pointes (TdP) thus further signifying the cardio-protective effect of Magnesium.

It is well known that hypocalcemia causes QT prolongation via prolongation of the plateau phase (phase 2) of the cardiac action potential. This causes calcium ion channels to stay open for a prolonged period, allowing a late calcium inflow and the formation of early after-depolarizations that promote re-entry and the development of ventricular arrhythmias. Patients with hypocalcemia might present with ventricular arrhythmias, in particular TdP which may result in loss of cardiac output. None of the patients with prolonged QTc had hyperkalemia, hypercalcemia or hyperphosphatemia.

In reference to Cyclophosphamide and QT prolongation, there is a paucity of literature on this topic. Andreu Porta Sanchez et al, asserted that cyclophosphamide did not exhibit clear arrhythmogenicity. Notably, a modest average increase of 20 msec in QTcB was observed after high-dose cyclophosphamide administration during stem cell transplant in a limited study involving non-Hodgkin’s lymphoma patients. In this study, the significant increase of 60 msec from baseline was used to define prolonged QTcB even if the QTcB interval is less than 450 ms, this yielded a significant association with a p-value of 0.01. In contrast, a study focusing on breast neoplasm patients undergoing chemotherapy regimens including epirubicin, cyclophosphamide, and 5-fluorouracil reported QTc interval prolongation. However, the specific agent responsible for this prolongation was not explicitly identified. Moreover, no data exists on the effects of cyclophosphamide on QTcB prolongation in pediatric ALL patients. Unlike anthracyclines such as daunorubicin, recognized for their cardiotoxic effects, the specific impact of cyclophosphamide on QTcB prolongation remains underexplored, especially within the context of ALL protocols. Interestingly, in our study, doxorubicin did not demonstrate a statistically significant association with QTcB prolongation when compared to daunorubicin and cyclophosphamide.

Some studies have alluded to the dose-related or cumulative effects of anthracyclines and alkylating agents on ejection fraction, particularly referencing cumulative doses of doxorubicin and daunorubicin in comparisons between liposomal and conventional formulations. However, these studies have not extensively delved into the implications on QTc interval. Conversely, alkylating agents like cyclophosphamide have been linked to a direct total-dose cardiotoxic effect on ejection fraction, with a noteworthy absence of information regarding its impact on QTcB prolongation. It is essential to note that the aforementioned studies primarily involved hematopoietic stem cell recipients. These observations underscore the critical need for further investigations to elucidate the nuanced cardiac effects of cyclophosphamide particularly in pediatric populations and within the context of ALL treatment protocols.

In patients planned to receive potential QT-prolonging cancer medications, a complete medical and medication history (including over-the-counter, recreational, and complementary / alternative medicines) should be sought.

As mentioned in the article “Causes and Management of Drug-Induced Long QT syndrome”, it has been shown that not only the gender and electrolyte imbalances act as risk factors for QT prolongation, but the addition of offending drugs act as the main perpetrator, most notably of which are the antiemetics such as ondansetron.
An article published in US Pharmacist entitled Drug-induced QT prolongation further reiterates the risk factors for developing QT prolongation, along with the drugs associated with QT prolongation, however, it is noteworthy to mention that multiple medications are individually known to have QT prolongation as a side effect even if not present in the aforementioned list. A more comprehensive and an exhaustive list of drugs that prolong the QT interval can be obtained from the crediblemeds website at http://crediblemeds.org, and it is updated frequently. These medications include but are not limited to the following, TMP-SMX, ondansetron, esomeprazole, and amphotericin B.

**Implications and Recommendations:**

The study highlights the significance of early detection and intervention for QT prolongation in pediatric leukemia patients. It stresses the need for an effective follow-up plan, especially for patients on high-risk medications like cyclophosphamide and daunorubicin. Despite normal baseline ECG readings, there was a notable development of QT prolongation emphasizing the necessity for frequent cardiac monitoring. Regular follow-up is also crucial for patients with electrolyte imbalances, particularly hypomagnesemia and hypocalcemia. In addition, the study advises diligent monitoring for individually prescribed medications known to prolong the QT interval, such as TMP-SMX, fluconazole, ondansetron, esmoprazole, voriconazole, and amphotericin B. However, it acknowledges limitations such as the small sample size and the retrospective nature of the analysis, which may affect the statistical power and generalizability of the findings.

**Conflict of Interest Statement:**

The authors declare that they have no financial or personal conflicts of interest that could potentially influence the outcomes or interpretations presented in this paper.

The authors express gratitude to Ms. Hoda Hijazi for her expertise and acknowledge Ms. Pamela Moukarzel for her assistance.

**Table 1. Bivariate associations with QTc prolongation.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>No QTc Prolongation (N = 229, 89.10%)</th>
<th>QTc Prolongation (N = 28, 10.90%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Females</td>
<td>118 (51.53%)</td>
<td>13 (46.43%)</td>
<td>0.610</td>
</tr>
<tr>
<td>Age Mean ± SD</td>
<td>6.24 ± 5.39</td>
<td>2.89 ± 4.49</td>
<td>0.002</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5.00 (2.00 - 10.00)</td>
<td>0.00 (0.00 – 6.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BSA Mean ± SD</td>
<td>1.14 ± 0.49</td>
<td>0.88 ± 0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.05 (0.74 - 1.53)</td>
<td>0.74 (0.74 - 1.05)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BSA: body surface area.

**Table 2 Bivariate analysis of chemotherapy agents and adjunct medications on QTc prolongation**

<table>
<thead>
<tr>
<th>Variables</th>
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<th>QTc Prolongation (N = 28, 10.90%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>94 (41.05%)</td>
<td>8 (28.57%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>128 (55.90%)</td>
<td>21 (75.00%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>179 (78.17%)</td>
<td>26 (92.86%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Vincristine</td>
<td>160 (69.87%)</td>
<td>20 (71.43%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>160 (69.87%)</td>
<td>24 (85.71%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>148 (64.63%)</td>
<td>23 (82.14%)</td>
<td>0.07</td>
</tr>
<tr>
<td>6 Mercaptopurine</td>
<td>182 (79.48%)</td>
<td>26 (92.86%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>160 (69.87%)</td>
<td>10 (35.71%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>207 (90.39%)</td>
<td>27 (96.43%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>16 (6.99%)</td>
<td>0 (0.00%)</td>
<td>0.23</td>
</tr>
</tbody>
</table>
Variables | No QTc Prolongation (N = 229, 89.10%) | QTc Prolongation (N = 28, 10.90%) | p-value
--- | --- | --- | ---
Inotuzumab | 9 (3.93%) | 0 (0.00%) | 0.60
Ondansetron | 229 (100.00%) | 28 (100.00%) | -
TMP-SMX | 229 (100.00%) | 28 (100.00%) | -
Esmoprazole | 153 (66.81%) | 13 (46.43%) | 0.03
Fluconazole | 57 (24.89%) | 2 (7.14%) | 0.04
Levofloxacin | 92 (40.17%) | 18 (64.29%) | 0.02
Voriconazole | 75 (32.75%) | 18 (64.29%) | 0.01
Casopfungin | 117 (51.09%) | 20 (71.43%) | 0.04
Amphotericin B | 54 (23.58%) | 13 (46.43%) | 0.01

Table 3: Bivariate analysis of Electrolyte imbalance and QTcB interval

Variables | No QTc Prolongation (N = 229, 89.10%) | QTc Prolongation (N = 28, 10.90%) | p-value
--- | --- | --- | ---
Hypokalemia | 6 (2.60%) | 3 (10.70%) | 0.06
Hypomagnesemia | 3 (1.30%) | 3 (10.70%) | 0.02
Hypocalcemia | 1 (0.40%) | 2 (7.10%) | 0.03
Hypophosphatemia | 5 (2.20%) | 1 (3.60%) | 0.50

Table 4: Multiple logistic regression model predicting QTc prolongation. Variables entered in the model: Age, Body Surface Area, cyclophosphamide, esomoprazole, fluconazole, levofloxacin, voriconazole, caspofungin, amphotericin B, and daunorubicin.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.86 (0.78, 0.96)</td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>0.27 (0.11, 0.68)</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.18 (0.04, 0.81)</td>
<td><strong>0.026</strong></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>2.74 (1.11, 6.77)</td>
<td><strong>0.029</strong></td>
</tr>
</tbody>
</table>

References:


