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Focused Clinical Practice Update

The 2023 Canadian Cardiovascular Society Clinical Practice Update on Management of the Patient With a Prolonged QT Interval

Ross A. Davies, MD, (Co-Chair),[a] Virginie Beauséjour Ladouceur, MCDM,[b] Martin S. Green, MD,[a] Jacqueline Joza, MD, MSc,[c] David N. Juurlink, MD, PhD,[d] Andrew D. Krahn, MD,[e] M. Sean McMurtry, MD, PhD,[f] Jason D. Roberts, MD, MAS,[g] Thomas M. Roston, MD, PhD,[e] Shubhayan Sanatani, MD,[h] Christian Steinberg, MD,[i] and Ciorsti MacIntyre, MD, (Co-Chair)[j,k]

[a] *University of Ottawa Heart Institute, Ottawa, Ontario, Canada;* [b] *The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada;* [c] *McGill University Health Centre, Montreal, Quebec, Canada;* [d] *University of Toronto, ICES, Sunnybrook Research Institute, Toronto, Ontario, Canada;* [e] *Center for Cardiovascular Innovation, Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada;* [f] *University of Alberta, Edmonton, Alberta, Canada;* [g] *Population Health Research Institute, McMaster University, Hamilton Health Sciences, Hamilton, Ontario, Canada;* [h] *Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada;* [i] *Institut universitaire de cardiologie et de pneumologie de Québec, Laval University, Québec, Québec, Canada;* [j] *Dalhousie University, Halifax, Nova Scotia, Canada;* [k] *Mayo Clinic, Rochester, Minnesota, USA*

ABSTRACT

A prolonged QT interval on the electrocardiogram is associated with an increased risk of the torsades de pointes form of ventricular arrhythmia resulting in syncope, sudden cardiac arrest or death, or misdiagnosis as a seizure disorder. The cause of QT prolongation can be congenital and inherited as an autosomal dominant variant, or it can be transient and acquired, often because of QT-prolonging drugs or electrolyte abnormalities. Automated measurement of the QT interval can be inaccurate, especially when the baseline electrocardiogram is

RÉSUMÉ

L'allongement de l'intervalle QT à l'électrocardiogramme est associé à un risque accru de torsades de pointes, une forme d'arythmie ventriculaire entraînant la syncope, l'arrêt cardiaque soudain ou un diagnostic erroné de troubles convulsifs. La cause de l'allongement de l'intervalle QT peut être congénitale et héritée par un variant autosomique dominant ou peut être transitive et acquise, souvent en raison de médicaments allongeant l'intervalle QT ou d'anomalies électrolytiques. La mesure automatique de l'intervalle QT peut être

Prolongation of the QT interval is associated with an increased risk of torsades de pointes (TdP) and ventricular fibrillation, which can cause syncope, seizures, and sudden death. The risk of malignant ventricular arrhythmias is largely dependent on the degree of QT interval prolongation. Congenital long QT syndrome (cLQTS) is a cardiac rhythm disorder with predominant autosomal dominant inheritance. Significant QT prolongation can also be acquired (acquired long QT syndrome [aLQTS]) particularly in the setting of electrolyte abnormalities or use of QT-prolonging medications. Individuals with QT interval prolongation unmasked by medication might also harbour a genetic risk. Accurate diagnosis is essential for congenital and acquired long QT syndrome (LQTS) to avoid potentially lethal arrhythmias, and to initiate appropriate treatment strategies such as avoidance of QT-prolonging medications and maintenance of normal electrolytes with or without administration of certain β-adrenergic-blocking drugs.

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Corresponding author: Dr Ross A. Davies, Division of Cardiology, University of Ottawa Heart Institute, 40 Ruskin St, Ottawa, Ontario K1Y 4W7, Canada.

E-mail: radavies@ottawaheart.ca

The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at https://ccs.ca/guidelines-and-position-statement-library/.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of interdisciplinary experts on this topic. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources.

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abnormal, and manual verification is recommended. In this clinical practice update we provide practical tips about measurement of the QT interval, diagnosis, and management of congenital long QT syndrome and acquired prolongation of the QT interval. For congenital long QT syndrome, certain β-adrenergic-blocking drugs are highly effective, and implantable defibrillators are infrequently required. Many commonly prescribed drugs such as antidepressants and antibiotics can prolong the QT interval, and recommendations are provided on their safe use.

inexacte, surtout lorsque l'électrocardiogramme de référence est anormal; une vérification manuelle est donc recommandée. Dans cette mise à jour de pratique clinique, nous proposons des conseils pratiques pour mesurer l'intervalle QT, pour poser un diagnostic de syndrome du QT long congénital ou d'allongement acquis de l'intervalle QT et pour prendre en charge ces affections. Dans le cas du syndrome du QT long congénital, certains médicaments bêta-bloquants adrénergiques sont très efficaces, et les défibrillateurs internes sont rarement nécessaires. De nombreux médicaments couramment prescrits, comme les antidépresseurs et les antibiotiques, peuvent allonger l'intervalle QT; nous émettons donc des recommandations sur leur utilisation sécuritaire.

Method

This Clinical Practice Update is a consensus document that provides practical information for the general clinician. It is not meant to replace existing literature reviews and evidence-based recommendations about LQTS intended for a subspecialist audience, such as those published by the Canadian Cardiovascular Society (CCS)/Canadian Heart Rhythm Society,[1] the American College of Cardiology/American Heart Association/Heart Rhythm Society,[2] and the European Society of Cardiology.[3] This document emphasizes important diagnostic and therapeutic features of managing patients with a prolonged QT interval. It was prepared by a panel composed of cardiologists (general and subspecialty electrophysiologists) and internists with expertise in pharmacology, as well as consultants experienced in education and preparation of guideline documents. Representatives of the CCS (R.A.D., V.B.L., M.S.G., J.J., A.D.K., M.S.M., J.D.R., T.M.R., S.S., C.S., and C.M.), Canadian Heart Rhythm Society (V.B.L., M.S.G., J.J., A.D.K., J.D.R., T.M.R., S.S., C.S., and C.M.), the Canadian Society of Internal Medicine (D.N.J.), and the Canadian Pediatric Cardiology Association (S.S.) formed the primary writing panel. The primary panel wrote the report, followed by review and approval by the CCS Guidelines Committee.

Physiology and Measurement of the QT Interval

What is the QT interval?

The QT interval on the electrocardiogram (ECG) represents the time from the onset of ventricular depolarization to the end of repolarization, thereby reflecting the duration of the ventricular action potential (Fig. 1).[4] At the cellular level, the myocardial action potential is characterized by sequential orchestration of different ion channels. Physiological influences on the QT interval include heart rate, age, sex, circulating catecholamines, and autonomic tone. Variations of the latter are also responsible for the normal diurnal fluctuations of the QT interval.[5]

Measurement of the QT interval

Because automated measurement of the QT interval is universal and easy to use, the question is when manual measurement should be used instead. Computerized measurements of the absolute QT interval and the QT interval corrected for heart rate (QTc) can be inaccurate, especially with baseline artifact, a rapid or irregular rhythm, a widened QRS, or an abnormal ST-T wave configuration.

The American Heart Association Electrocardiography and Arrhythmias Committee Council on Clinical Cardiology, the American College of Cardiology Foundation, and the Heart Rhythm Society made recommendations for the standardization and interpretation of the ECG, including the ST segment, T and U waves, and the QT interval.[6] The QT interval extends from the onset of the QRS complex to the end of the T wave. As explained below in the section on measurement of the QT interval, the QT interval is not actually measured to the end of the T wave but rather to the tangent intersection of the T wave with the baseline. Problems with measuring the QT interval include identifying the onset of the QRS (for example, in preexcitation) and the end of the T wave, selecting the best lead to measure the QT interval, and correcting for differences in rate, QRS duration, sex, and time of day. Current ECG machines use automated digital technology to record all leads simultaneously. The onset of the QRS and the end of the T wave appear different in various ECG leads. Consequently, automatically measured QT intervals are often longer than the QT interval measured in an individual lead. The most common formula to adjust the QT interval for heart rate is Bazett's formula, but this can be inaccurate with increased R-R variability as seen with sinus arrhythmia and atrial fibrillation. In this situation, it is important to use a representative R-R interval rather than the longest QT interval and shortest R-R interval, because this will lead to overestimation of the QTc.

The computer-measured QT interval might be inaccurate when it cannot differentiate the end of the T wave from the start of the TP segment. Also, because the QT interval includes the QRS complex, an adjustment needs to be made when the QRS is widened. The computer does not adjust normal limits for the QT interval on the basis of sex, being longer for young and middle-aged women. Neither automatic nor manual measurements of the QT interval account for diurnal variation or when no QT prolongation is present in a patient with cLQTS (concealed phenotype). The automatically measured QT interval can also vary depending on the ECG device and algorithms used; therefore, serial automated measurements of the QT interval should be performed using the same machine and in a quiet environment with the patient at rest. Consumer products such as smart watches or phones

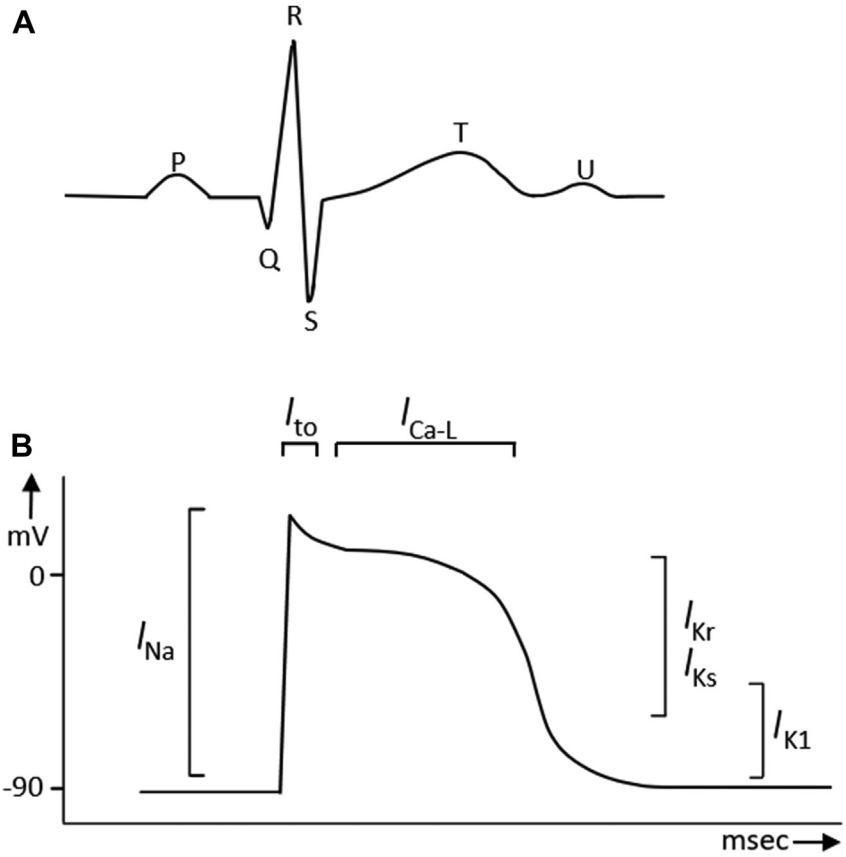

Figure 1. QT interval—relationship of surface electrocardiogram and the myocardial action potential with responsible ion channels.[4] Reproduced from Postema et al.[6] with permission from Bentham Science Publishers, conveyed through Copyright Clearance Centre, Inc.

that record a limited ECG signal are not generally recommended at this time to measure the QTc interval. Although some Holter technology now allows measurement of the QT interval, this also has similar limitations.

Despite the importance of the degree of QT prolongation, there is considerable variability among readers when the QT interval is assessed manually. One accurate manual method is using the maximal slope or tangent technique to define the end of the T wave.[7,8] This measurement of the QT interval begins with the onset of the QRS complex and finishes at the end of the T wave where the tangent of the downslope of the T wave intersects with the baseline (Fig. 2). U waves should not be included in measurement of the QT interval because this falsely prolongs the QT interval, although it might be hard to distinguish the end of the ST segment from the U wave in some situations like cLQTC type 2. However, with the automated ECG, the reader can see the same deflection in all 12 leads at the same time, which helps differentiate a notched T wave from a U wave. The first step in manual measurement of the QTc involves identification of the ECG lead with the longest absolute QT interval, generally lead V_5 or lead II; both leads provide a good reflection of left ventricular activation and typically have larger T waves that are more readily measured. The mean of 3 consecutive absolute QT intervals and the mean of the preceding R-R intervals (both in milliseconds) are entered into Bazett's formula ($QTc = QT/RR^{1/2}$) to calculate the QTc.[4] The accuracy of Bazett's formula is highest for heart rates between 60 and 100 beats per minute (bpm). Limitations of Bazett's formula include undercorrection of QTc at heart rates > 100 bpm and overcorrection at heart rates < 60 bpm. The Fridericia formula ($QTc = QT/RR^{1/3}$) has similar limitations at lower heart rates and increased accuracy at faster heart rates, however, Bazett's formula remains the most used formula in clinical practice. Although there are other formulae for the calculation of QTc such as using a threshold to define the end of the T wave, a discussion of each is beyond the scope of this article. There are free tools available online to calculate the QTc such as the Mayo Clinic QTc calculator (https://www.mayoclinic.org/medical-professionals/cardiovascular-diseases/calculators/corrected-qt-interval-qtc-calculator/itt-20487211) and a variety of smartphone applications such as MDCalc (https://www.mdcalc.com/calc/48/corrected-qt-interval-qtc).

When is the QT interval prolonged?

Normal values for the QTc interval show important sex- and age-dependent differences that should be taken into consideration when discussing QTc prolongation. The normal range for QTc is similar in boys and girls from birth until the onset of adolescence, whereas after puberty, women have longer QTc values than men, attributed to hormonal changes. However, ethnic and racial background are not associated

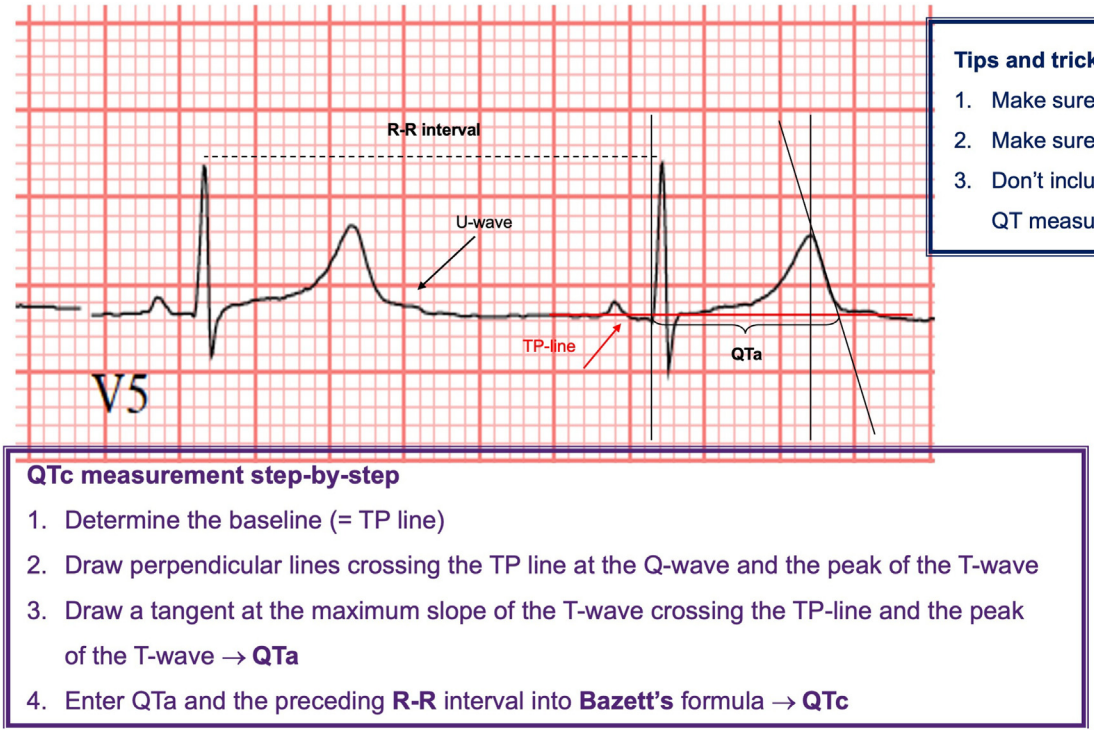

Figure 2. Manual measurement of the QT interval using the tangent method for defining the end of the T wave. QTa refers to the absolute QT interval measured from the electrocardiogram. Bazetts' formula is used to calculate the QT interval corrected for heart rate (QTc).[8] Courtesy of Dr C. Steinberg.

with variation of the QT interval. Normal, borderline, and prolonged QTc intervals for both sexes are summarized in Table 1.[9] Of note, there is overlap between the upper limit of distribution of the QTc in the normal population and the lower limit of distribution in patients with LQTS (Fig. 3).[11] There is no consistent agreement on the normal, borderline, and abnormal limits for the QTc. However, there is a consensus that after puberty a QTc of 450 ms or longer in men or 460 ms or longer in women should be considered borderline prolonged in the absence of major limitations for accurate QTc measurement. The 99th percentile for men is a QTc of 470 msec and for women is 480 msec. QTc values at or greater than these levels should be considered prolonged.[10] It is important to note, however, that QTc prolongation alone is not sufficient evidence for a diagnosis of LQTS. A QTc $\geq$ 500 ms is associated with an increased risk of ventricular arrhythmia. Be sure to look for QT prolongation in the context of unexplained syncope, seizures, and resuscitated cardiac arrest, or a family history of unexplained death (Fig. 4). Note that the QT interval can be prolonged for several days after a cardiac arrest and resuscitation, so serial ECGs are required to avoid overdiagnosis of LQTS. An algorithm for assessment of a prolonged QTc on the ECG is presented in Figure 5.[12]

Although it is important to quantify the duration of the QT interval, the appearance of the T wave itself should also be reviewed, because abnormal T wave morphologies might be observed in patients with cLQTS. For example, patients with type 1 LQTS classically have a broad-based T wave whereas patients with type 2 LQTS are more likely to have a low-voltage, biphasic, notched T wave, and patients with type 3 LQTS might have a late-onset T wave.

Practical tips: Measurement of the QT interval

1. Automated measurement of the absolute QT interval (QTa) and the QT interval corrected for heart rate (QTc) can be inaccurate with an irregular heart rhythm, widened QRS, or an abnormal ST-T wave configuration because the computer has trouble defining the end of the T wave.
2. To measure the QT interval manually, use the maximal slope or tangent method to define the end of the T wave, ideally in leads V_5 or II.
3. Look for QT prolongation in the context of unexplained syncope, seizures, or resuscitated cardiac arrest, or a family history of unexplained sudden death.
4. Measurement of the QT interval immediately after cardiac arrest might be unreliable because of cooling, myocardial, and central nervous system (CNS) injury, so serial ECGs are required to avoid overdiagnosis of LQTS.

Practical tips: Clinical interpretation of the QT interval

1. In the absence of limitations for accurate QTc measurement, a QTc $\geq$ 480 ms is generally considered to be clearly abnormal and QTc $\geq$ 500 ms is associated with an increased risk of ventricular arrhythmia.
2. Clinical correlation is important when interpreting a mildly prolonged QTc with an otherwise normal ECG (Table 1). Consider whether there are associated clinical factors such

as high-risk symptoms, a family history of cLQTS, QT-prolonging medications, or electrolyte abnormalities.
3. If the QTc interval is apparently normal but the history is suggestive of possible cLQTS such as a family history, consider additional testing such as exercise stress testing to detect latent abnormal repolarization. This could represent LQTS with concealed QT prolongation (see the following section on *Diagnosis of Congenital Long QT Syndrome*).
4. In addition to the length of the QTc, consider the appearance of the T wave, because abnormal T wave morphology is associated with cLQTS.

Diagnosis of Congenital Long QT Syndrome

cLQTS is caused by abnormalities in the ion channels responsible for cardiac repolarization, and hence is deemed a channelopathy. There are 3 well recognized autosomal dominant genetic causes, and 14 uncommon genes with less compelling evidence. cLQTS types 1-3 are referred to as LQT1, LQT2, and LQT3 with prevalence of > 50%, 35%-40% and 10%-15%, respectively. These are due to abnormalities of genes *KCNQ1*, *KCNH2*, and *SCN5A* affecting potassium currents I_{Ks} and I_{Kr} (hERG) and the sodium current I_{Na}, respectively.[13] Approximately 15%-20% of patients with clinical cLQTS do not have a recognized variant and are genetically elusive.

Most patients with syncope do not have LQTS. Conversely, not all patients with clinical LQTS will develop symptoms. Even in the absence of symptoms, however, patients with LQTS might benefit from β-blocker therapy and preventative measures such as avoidance of QT-prolonging drugs and maintenance of normal electrolytes (see the section on management of cLQTS). It is important to remember that there are other causes of arrhythmic syncope beyond LQTS. These include other primary electrical disorders such as Brugada syndrome, another familial channelopathy with an abnormal ECG, catecholaminergic polymorphic ventricular tachycardia and idiopathic ventricular fibrillation, as well as arrhythmias arising from ischemic and structural heart disease and cardiomyopathy. Hence, it is important to recognize who and when to investigate for symptoms of concern and when to refer for expert assessment.

When should you worry about undiagnosed cLQTS?

cLQTS can be a cause of unexplained syncope, seizure, cardiac arrest, or sudden death that can be overlooked if a comprehensive approach to diagnosis is not used. The first step in the screening for cLQTS (or any other primary electrical disease) is a detailed history of the index patient, including the circumstances around the event, along with a family history. In patients who present to the emergency room for evaluation of unexplained syncope or a new seizure, it is important to assess the QT interval on the ECG to consider the possibility of cLQTS as the cause of their presentation. It is important to inquire about seemingly unrelated events in the family that could be explained by an arrhythmia, such as unexplained drownings, sudden fatal accidents, and unprovoked seizures, especially if refractory to anticonvulsant drugs. Remember to ask about family history at subsequent visits because new information might arise after speaking with family members. Syncope or presyncope triggered by adrenergic situations in the index patient should be a "red flag" in situations such as exertion or sports, strong emotion, or precipitation by sudden loud noises. Some rare forms of cLQTS might be associated with deafness or muscle weakness.

Table 1. Normal values for the QTc interval[9,10]

	Female (puberty to age 65)	Male (puberty to age 65)
Normal ms	< 460	< 450
Borderline ms	460-479	450-469
Prolonged ms	≥ 480	≥ 470

QTc, QT interval corrected for heart rate.

The second step includes ECG recording with accurate measurement of the QT interval and subsequent correction for heart rate. Further investigations should include exercise treadmill testing (with prolonged ECG recording into the recovery period of 6 minutes in adults and 10 minutes in children), which can unmask abnormal QT prolongation in recovery despite a normal or borderline QTc on the resting ECG.[14] The T wave pattern and the ST segment response to exercise might help identify the genotype. All patients with suspected or confirmed cLQTS should be referred to an inherited arrhythmia or cardiogenetic clinic (in Canada at https://hiro.heartsinrhythm.ca).[15] Information about expert clinics in Canada is available at www.heartsinrhythm.ca and https://www.sads.ca. The latter also links to an international Web site at www.sads.org.

Can individuals with cLQTS have a normal QT interval?

Up to a third of cLQTS patients with a proven pathogenic or likely pathogenic genetic variant will have a normal QT interval on their resting ECG because of circadian fluctuation of the autonomic nervous system and overlap between the upper range of QTc intervals in the otherwise healthy population and those with cLQTS (Fig. 3).[11] Because of the possible "QT-concealment" on the resting ECG, it is important to obtain serial ECG recordings and an exercise treadmill test when investigating suspected cLQTS. Exercise testing can unmask abnormal QT dynamics and is the gold standard for the clinical diagnosis of LQTS. In patients with a family history of LQTS and with an established causative variant, genetic testing is an important part of their diagnostic evaluation.

Exercise ECG testing

The primary diagnostic test in patients with suspected cLQTS is a treadmill exercise test. This includes a "stand-up ECG test" to provoke paradoxical lengthening of the QT interval and marked prolongation of the QTc value.[16] When transitioning from supine to standing before exercise testing, the QT interval will normally lengthen. In cLQTS, the QT prolongation on standing typically persists after heart rate recovery, however, there is no established threshold to declare a test abnormal. Note that the stand-up ECG test has not been shown to be of diagnostic value in children and adolescents. The 4-minute recovery ECG is the most useful ECG on which to focus with treadmill testing and a QTc at 4 minutes in recovery of ≥ 480 ms has been incorporated into the modified Schwartz score diagnostic criteria for cLQTS (discussed below).[9] However, it is insufficient to order a regular treadmill test designed to diagnose coronary artery

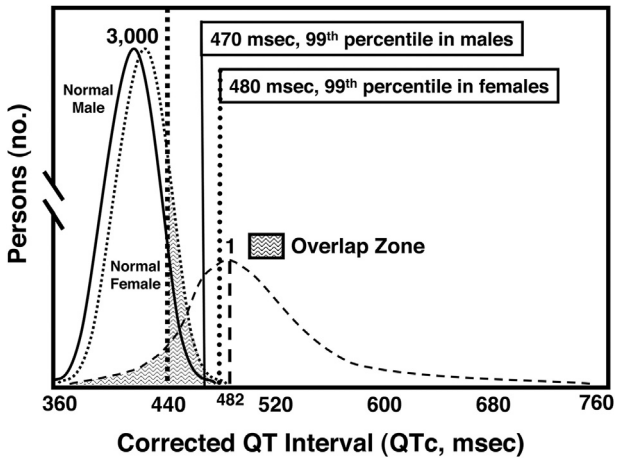

Figure 3. Distribution of QT interval corrected for heart rate (QTc) values among individuals with and without long QT syndrome (LQTS). Shown is the distribution of QTc values derived from healthy post-pubertal males and females. The 99th percentile of 470 ms for males and 480 ms for females is shown. The QTc distribution for LQTS is derived from analysis of the electrocardiograms of all patients with mutation-proven LQTS from the Mayo Clinic's Windland Smith Rice Sudden Death Genomics Laboratory. Here, the average QTc of 482 ms for the LQTS cohort is indicated, along with the maximum QTc (760 ms) and minimum QTc (365 ms) for patients with LQTS. The 440-ms line, often referred to as "borderline QTc," shows the substantial overlap between approximately 10%-15% of humanity and the subset of patients having "concealed" LQTS. Note the break in the *y*-axis, which reflects the fact that the LQTS vs normal distribution curves must consider the 1-in-3000 estimated incidence of LQTS." Reproduced from Taggart et al.[11] with permission from Wolters Kluwer Health, Inc.

disease. The requesting physician must clearly state the indication is "rule out LQTS—look for abnormal QT prolongation especially on the standing and the 4-minute post exercise ECG." If there is doubt about interpretation and suspicion is high, then the test should be performed or reviewed in a cardiac centre, where 12-lead ECGs are performed at 1-minute intervals throughout the test, including early upon standing. During exercise, the QTc interval commonly lengthens in type 1 LQTS and remains prolonged throughout early recovery. Type 2 is characterized by a prolonged QTc value in early exercise and late recovery but might be normal at peak exercise and early recovery (Fig. 6).[14,17] In LQT3, the QT interval usually does not substantially change during exercise, and no specific pattern is established in the other rarer genotypes of cLQTS.

Practical tips: Diagnosis of cLQTS

1. A normal or borderline abnormal QTc interval is common in cLQTS and cannot be used to rule out the condition. This is called "concealed QT prolongation."
2. Patients with cLQTS often have abnormal T wave morphology.
3. Exercise stress testing and especially the 4-minute recovery ECG is the diagnostic test of choice for uncovering QT prolongation in cLQTS. Clearly state that the indication for the test is to "rule out LQTS—look for abnormal QT prolongation especially on the standing and the 4-minute post exercise ECG."

Integrating diagnostic information including genetic testing

A holistic approach to the diagnosis of cLQTS is needed, factoring in the pretest probability of cLQTS, as well as clinical and genetic findings. To account for the many factors to consider, the cLQTS probability or Schwartz score was derived to facilitate diagnosis (Table 2).[3,9] This score assigns points for ECG findings, exercise testing, clinical and family history, and genetic testing when available to generate a low, moderate, or high probability of disease. Genetic testing is useful especially among asymptomatic relatives of a genetically positive proband with cLQTS. However, relying exclusively on genetic data can lead to over- or underdiagnosis, because approximately 15% of cLQTS cases are genetically elusive, and recent data show that the role of rare variants being causal is weak.[8] Finally, after the diagnosis of cLQTS is made in a proband case, cascade family screening with a history, rest and exercise ECG, and genetic testing where appropriate, are recommended for all first-degree relatives.

There is increasing evidence that many genetic variants implicated in monogenic cLQTS over the past 30 years do not cause the syndrome in isolation. In fact, only cLQTS types 1-3 are supported by robust genetic evidence for disease causation.[18] Population-level genomic databases have shown that many apparently healthy individuals with incidentally detected cLQTS variants never develop clinical disease. This means that a "positive" genetic variant does not equate to a clinical diagnosis, especially when the phenotype is absent. However, if a family member of a proband is found to have a proven pathogenic LQTS variant, such as LQTS types 1-3, they should be considered as having cLQTS and should be managed as such, even in the absence of a positive phenotype. Additionally, despite extensive adjudication, some genes and variants remain of "unknown significance" when the genetic findings cannot support or refute the diagnosis. Despite these observations, borderline abnormal phenotypes and genotypes still have practical relevance, such as advising that QT-prolonging drugs be avoided and recommending family-based ECG screening to identify relatives with clearer phenotypes, which further highlights the importance of expert referral. Part of this expert referral includes evaluation by a genetic counsellor before genetic testing. This is an essential component of the care of patients with inherited arrhythmia syndromes including LQTS.

Practical tips: Genetic testing for cLQTS

1. There are 3 autosomal dominant genes with strong evidence for cLQTS (types 1-3) and (presently) 14 uncommon genes with less compelling evidence.
2. Some patients with clinical cLQTS do not have a recognized variant (genetically elusive LQTS).
3. Many patients with cLQTS will never manifest symptoms, but are still advised to avoid QT-prolonging medications.
4. Patients with suspected or confirmed cLQTS should be referred to an inherited arrhythmia or cardiogenetic clinic (in Canada at www.heartsinrhythm.ca or internationally at www.sads.org).
5. When a proband has a causative variant identified, first-degree relatives should be offered genotype-based cascade screening coupled with clinical phenotyping; and with a

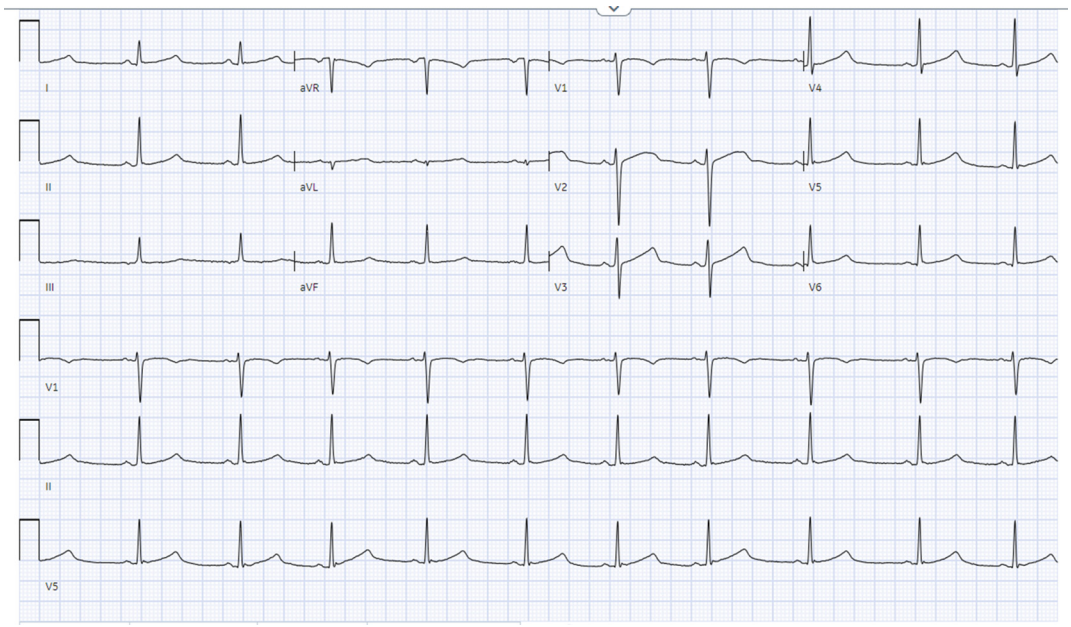

Figure 4. 12-Lead electrocardiogram from a 23-year-old woman with congenital long QT syndrome type 2 due to a familial mutation of the *KCNH2* gene. The QT interval corrected for heart rate is prolonged at 500 ms. Note the characteristic secondary hump on the T wave best seen in lead V_2. Courtesy of Dr M. Green.

genotype-negative proband, first-degree relatives should be offered screening through clinical evaluation with a history, resting ECG, and treadmill testing.

Management of cLQTS

β-Adrenergic blockade

The cornerstone of medical therapy for cLQTS is β-blockade, which dramatically reduces the risk of arrhythmic events.[19] Nonselective β-blockers, such as nadolol and propranolol, confer greater protection relative to β-1 selective agents, particularly atenolol and metoprolol.[20-22] Although nadolol is the β-blocker of choice among individuals considered at intermediate and high risk of events, particularly those with resting QTc values $\geq$ 500 ms and/or previous events, side effects including fatigue may occur, particularly when initiating the medication. Patients considered at lower risk of events may be treated with bisoprolol, which is generally better tolerated, and breakthrough events are rare despite its being β-1 selective.[23] Some patients might be hesitant to take β-blockers because of a concern about depression, but they should be encouraged because this relationship is not supported by a recent meta-analysis.[24] Although the majority of patients in an LQTS clinic tolerate β-blockers which are preferred therapy, some experience side effects. This opens a conversation about alternative therapies for LQTS such as cardiac denervation, mexiletine, pacing, and preventative measures only such as shared decision-making about sports and the importance of avoiding QT-prolonging drugs. It is important to note that the absolute QT interval is minimally altered by β-blockers, especially at heart rates of 60-100 bpm. Introduction at a low dose with gradual uptitration helps to minimize intolerance. Generally dosing of nadolol is 1-1.5 mg/kg with once-daily dosing in adults and once or twice-daily dosing in children, but this is primarily managed by experts in inherited arrhythmia clinics.

Avoidance of QT-prolonging drugs

Although β-blockade provides excellent protection against arrhythmia, avoidance of QT-prolonging medications remains imperative. Among patients receiving β-blockers, the primary reasons for breakthrough events are β-blocker noncompliance and receipt of a QT-prolonging medication (Fig. 7).[25] Avoidance of QT-prolonging drugs can be challenging because of the large number of culprit agents, including many agents used for anxiety and depression. It is also important to recognize that this can be an adverse effect of many medications perceived as innocuous such as macrolide and fluoroquinolone antibiotics. Patients are strongly encouraged to alert their treating physicians and pharmacists to this contraindication. It is important to empower cLQTS patients with the knowledge of how to check medication safety. It is recommended that they become familiar with the online database for QT-prolonging drugs maintained by the Arizona Center for Education and Research on Therapeutic (Web site: www.crediblemeds.org, also available as a smartphone app).

Lifestyle modification including advice about sports

Lifestyle behaviours in cLQTS are also important considerations. Genotype-specific triggers include exercise in general and swimming in particular in LQT1,[26] and sudden loud noises and startles such as alarm clocks in LQT2.[27] Previous

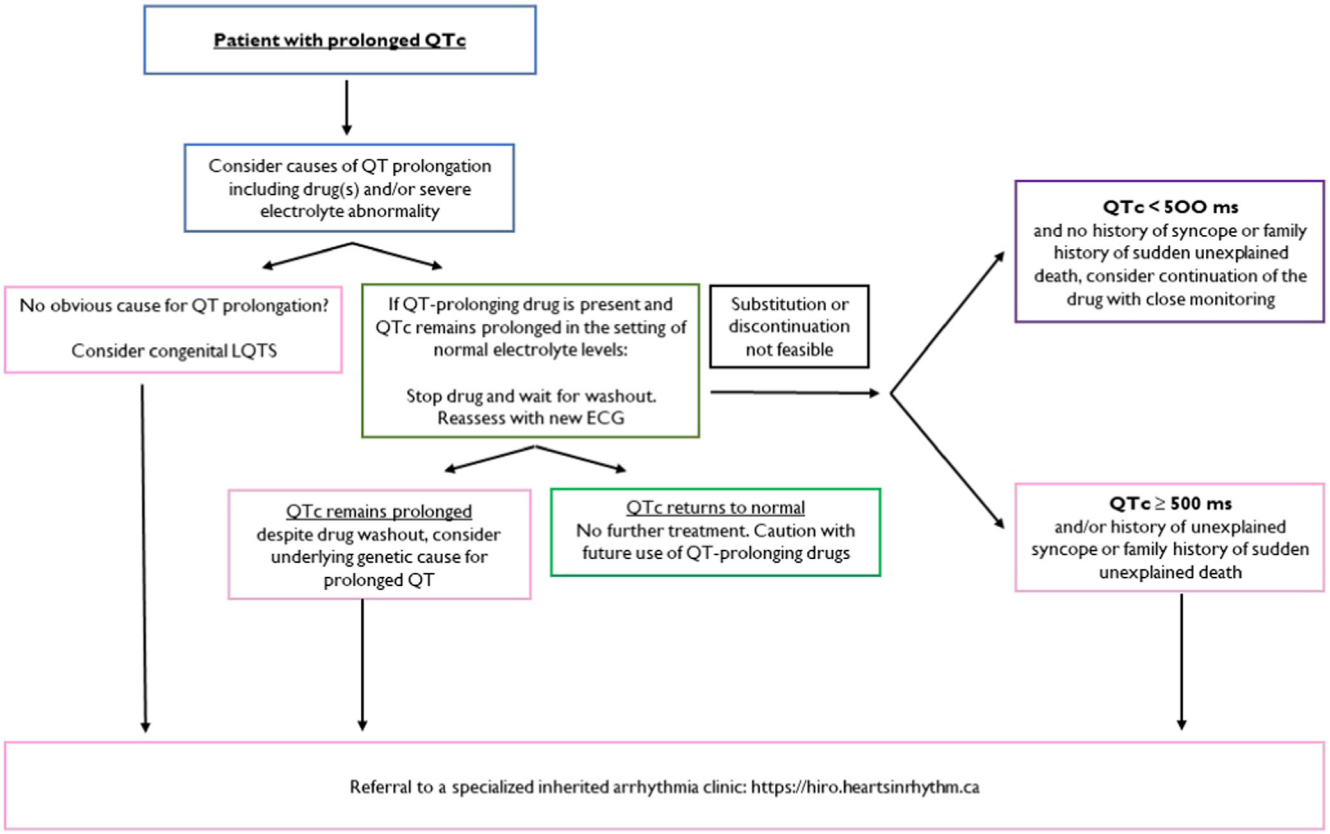

Figure 5. Decision-making algorithm for the patient presenting with a prolonged QT interval corrected for heart rate (QTc). ECG, electrocardiogram; LQTS, long QT syndrome.

guidelines suggested that sports involving more than mild levels of aerobic activities should be avoided.[28] Fortunately, subsequent work has shown that exercise and even competitive sports can be pursued with a low risk of breakthrough events among most optimally managed patients receiving β-blockers.[29-31] For participation in competitive sports, shared decision-making is recommended among patients, families, and their genetic arrhythmia specialist.[32] Although breakthrough events are rare, an automated external defibrillator should be part of an individual's sport safety equipment, the coach should be aware of the patient's condition, and there should be a resuscitation plan in place in the event of cardiac arrest.

A strategy of β-blockade, avoidance of QT-prolonging medication, and appropriate lifestyle modifications provides effective protection from a malignant ventricular arrhythmia in most affected individuals. There is a small percentage of patients who suffer from more severe forms of the condition and might remain at risk, thus necessitating consideration of other treatment modalities, including mexiletine, left cardiac sympathetic denervation, permanent atrial pacing, and implantable cardioverter defibrillator (ICD) therapy.[33-36] ICD implantation carries a significant risk of inappropriate shocks and device-related complications, particularly in young patients with inherited arrhythmia syndromes. As such, ICDs are placed only after careful consideration in this patient population.[37]

Special circumstances including surgery and pregnancy

When planning surgery for a patient with known LQTS, the anesthesiologist needs to ensure that use of β-blockers are continued perioperatively, electrolytes are normalized, and certain agents are avoided (such as the volatile anesthetic agent sevoflurane and the depolarizing neuromuscular junction blocker succinylcholine), which can prolong the QT interval.

In pregnancy, some studies have suggested that β-blocker use might be associated with a small risk of intrauterine growth restriction, however, this risk is considered low and is outweighed by the proarrhythmic risk of forgoing β-blockers when indicated.[38] LQTS patients are advised to continue their β-blocker throughout conception, pregnancy, labour, and the postpartum period, and β-blocker therapy is also considered safe while breastfeeding. The practice of switching β-blockers during pregnancy to metoprolol should be avoided. Nadolol or propranolol are the preferred β-blockers for LQTS, because there are more breakthrough cardiac events with use of metoprolol and atenolol, and their use should be continued throughout pregnancy. Use of any β-blocker at term might cause neonatal β-adrenoceptor blockade, so the neonate should be monitored for bradycardia, hypotension, and hypoglycemia. Vaginal delivery is considered safe, but adequate analgesia should be provided and attempts to minimize the duration of labour should be pursued to avoid protracted and extreme adrenergic surges. Arrhythmic risk has not been shown to increase during

Table 2. Modified congenital LQTS diagnostic score[3,9]

Findings			Points
ECG	QTc	≥ 480 ms	3.5
		460–479 ms	2
		450–459 ms (in males)	1
		≥ 480 ms during 4th minute of recovery from exercise stress test	1
	Torsade de pointes		2
	T wave alternans		1
	Notched T wave in 3 leads		1
	Low heart rate for age		0.5
Clinical history	Syncope	With stress	2
		Without stress	1
Family history	Family member(s) with definite LQTS		1
	Unexplained SCD at age younger than 30 years in first-degree family		0.5
Genetic finding	Pathogenic mutation		3.5

Diagnosis of congenital LQTS with a score > 3.
ECG, electrocardiogram; LQTS, long QT syndrome; QTc, QT interval corrected for heart rate; SCD, sudden cardiac death.
Reproduced from Zeppenfeld et al.[3] with permission from Oxford University Press, based on data from Schwartz and Crotti.[9]

pregnancy; however, an elevated risk has been identified among LQT2 patients during the postpartum period.[39,40] For surgery requiring anaesthetic agents, precautions should be taken to ensure that patients are not exposed to QT-prolonging drugs and that β-blocker doses are not missed during the perioperative period.

Treatment of TdP

A prolonged QT interval increases the risk of a form of polymorphic ventricular tachycardia called TdP. Common causes for TdP include acquired QT prolongation from drugs, but also diarrhea or malnourishment resulting in low potassium and/or magnesium levels, and cLQTS. A typical ECG is shown in Figure 8. Most episodes of TdP in LQTS are self-terminating resulting in syncope or occur as isolated clinical events but occasionally deteriorate to ventricular fibrillation. Fortunately, arrhythmic storm is very rare. In the event of an arrhythmic storm, management consists of β-blockade, cessation of QT-prolonging medications, correction of electrolyte abnormalities, and potentially pursuing supratherapeutic magnesium levels.[41] Amiodarone and procainamide, which are effective for conventional reentry type ventricular tachycardia, should specifically not be used for TdP or arrhythmic storm arising from a prolonged QT interval because they prolong the QT interval further. In the setting of marked bradycardia, particularly with aLQTS, transvenous pacing or isoproterenol may be used, whereas β-blockade can be used with cLQTS for its antiadrenergic effect. Bradycardia and LQTS prolong repolarization and predispose to TdP. TdP is precipitated by premature ventricular contractions that cause post extrasystolic pauses and thus functional bradycardia. β-blockers prevent adrenergic surges that trigger premature ventricular contractions that lead to long/short intervals.

Practical tips: Management of cLQTS

1. The cornerstone of medical therapy is β-blockade, preferably with nadolol or propranolol. Cardiac rhythm devices such as pacemakers and ICDs are rarely required.
2. Tolerance of β-blockade is improved by slow uptitration with the final dosage on the basis of tolerance or blunted exercise heart rate.
3. Avoid QT-prolonging drugs and educate the patient (www.crediblemeds.org, also available as a smartphone app).
4. Most episodes of TdP are due to noncompliance with β-blockade or use of QT-prolonging medications.
5. TdP and arrhythmic storm should be managed with β-blockade, cessation of QT-prolonging drugs, correction of electrolyte abnormalities, increased magnesium, lidocaine, and at times, transvenous pacing. Amiodarone and procainamide are contraindicated because they further prolong the QT interval and promote bradycardia.

Acquired Long QT Syndrome

aLQTS results from an acquired alteration in cardiac ion channels that increase the action potential duration. Most aLQTS cases arise from QT-prolonging drugs[42] that block the I_{kr} ion channel and/or electrolyte abnormalities (Table 3).[43] As a result, nearly all new drugs undergo thorough assessment of their propensity to cause QT prolongation, often in comparison to a positive control such as a single dose of moxifloxacin, an antibiotic that blocks the I_{kr} ion channel.[44] QT prolongation and TdP can also occur through an increase in the late sodium current ($I_{Na\text{-}L}$) which is relevant for drug development and might also further explain apparent differences in the risk of TdP across culprit drugs.[45] Many antidepressants and antipsychotic drugs prolong the cardiac action potential by blocking several cardiac ion channels, causing concern for QT prolongation and risk of TdP.[46]

Electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypocalcemia), severe bradycardia due to sinus bradycardia or atrioventricular block, hypo- and hyperthyroidism, and hypothermia are well established causes of aLQTS or as contributing factors to the risk of drug-induced LQTS. Keep in mind that measurement of the QT interval after cardiac arrest might be inaccurate because of other factors including myocardial and CNS injury. Other less common etiologies of aLQTS include Takotsubo cardiomyopathy[47] and exercise training-induced aLQTS, in which a significant proportion of

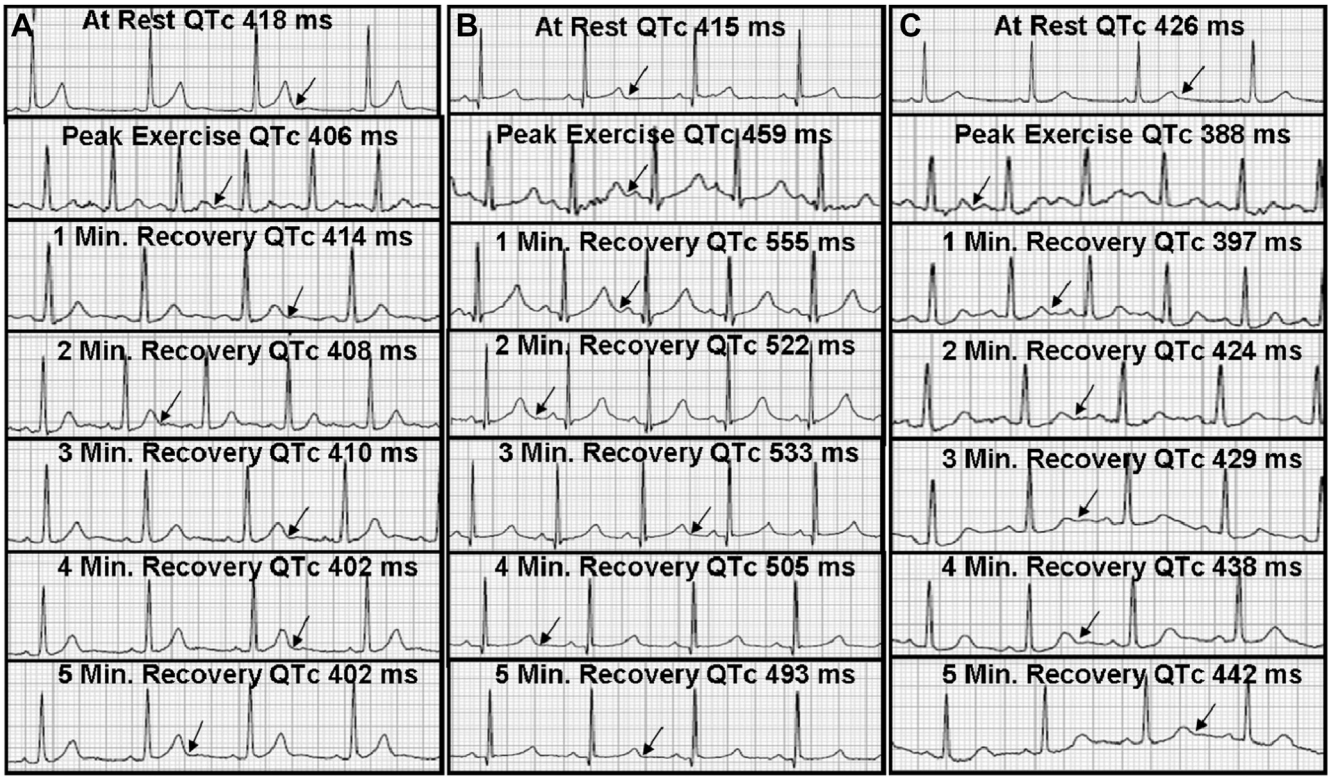

Figure 6. Examples of QTc dynamics during exercise in (**A**) control participants, and (**B**) concealed LQT1 and (**C**) concealed LQT2 patients. Note that in the normal control there is an initial decrease in the QTc at peak exercise with gradual return to baseline with recovery. In the concealed LQT1 patient the QTc lengthens at peak exercise and continues to have QTc lengthening in recovery. In the concealed LQT2 patient, there is an initial decrease in QTc at peak exercise with a continued increase in QTc during recovery beyond baseline. QTc, QT interval corrected for heart rate. Reproduced from Horner et al.[17] with permission from Elsevier.

high-level athletes normalize their ECGs after detraining.[48] Autoimmune and inflammatory conditions have also been reported to prolong the QT interval, at least in part due to the direct inhibition of I_{Kr} by anti-Ro/SSA antibodies.[49]

An increased risk for TdP occurs when the QTc exceeds 500 ms or when a drug increases the QTc by > 60-70 ms, particularly when this increase develops rapidly.[50] Female sex is a well known risk factor for arrhythmias in patients with aLQTS. Patients who develop marked QTc prolongation and TdP typically carry more than 1 risk factor including the presence of underlying cardiac disease, extracardiac diseases, electrolyte imbalances, QT-prolonging drugs, inflammation, and anti-Ro/SSA antibodies. Figure 9 shows QT prolongation in a woman with hypokalemia receiving a QT-prolonging medication.

Although many classes of drugs are associated with aLQTS, there are important within-class differences in risk that warrant mention (Table 4). For example, among the macrolide antibiotics, arrhythmogenicity is highest with erythromycin and lowest with azithromycin.[51] Conversely, among different fluroquinolone antibiotics none are safe. However, there are safe alternatives among antibiotics such as penicillins and cephalosporins. Among the antipsychotic drugs, the risk is highest with ziprasidone, iloperidone, asenapine, amisulpride, and others, whereas it is negligible with aripiprazole, clozapine, and lurasidone. Similarly, among the selective serotonin reuptake inhibitor antidepressants, the risk appears highest with citalopram and escitalopram and negligible with paroxetine and sertraline. However, among CNS medications, stimulants for attention deficit hyperactivity disorder are generally safe. Antiemetics might prolong the QT interval, and low-risk alternatives for susceptible individuals include aprepitant and dexamethasone. Intuitively, the risk of QTc prolongation with a given drug will depend in part on the dose.

It is important to check for complex drug interactions or potential QT prolongation before administration (www.crediblemeds.org, and related smartphone app). Consider an ECG before initiation of a QT-prolonging drug if a severe electrolyte disturbance is present, if already receiving a QT-prolonging drug, or when initiating a high-risk QT-prolonging drug (Table 5). Caution is advised in patients with multiple risk factors for QT prolongation (eg, when combining a diuretic with sotalol, be mindful of the potential for hypokalemia and hypomagnesemia). Many drugs that can prolong the QTc accumulate in the presence of renal disease and require dose reduction to avoid causing TdP. Examples include quinolone antibiotics like ciprofloxacin and antifungal triazoles like fluconazole, as well as many of the antiarrhythmic drugs, such as sotalol.

In most cases of aLQTS, the QT interval normalizes after discontinuation of the offending agent(s) and/or correction of

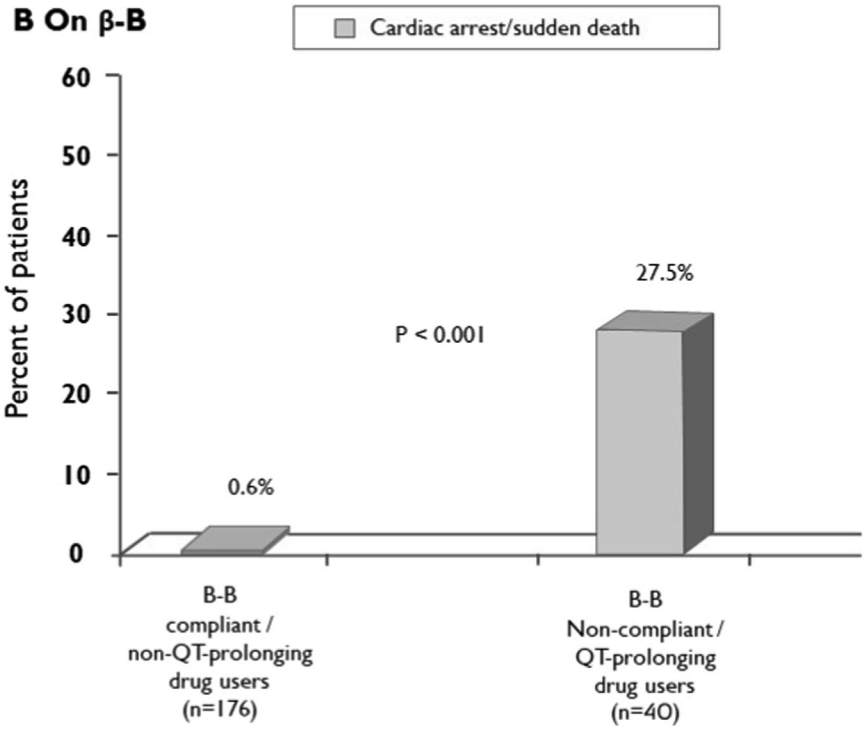

Figure 7. Importance of compliance with β-blockade (B-B) and avoidance of QT-prolonging medications (example from congenital long QT syndrome type 1). Modified from Vincent et al.[25] with permission from Wolters Kluwer Health, Inc.

other contributing factors. When the QT interval does not return to normal, an underlying genetic cause should be considered. Genetic polymorphisms might also increase the risk for development of drug-related arrhythmias. For instance, a polymorphism of the KCNE1 or 2 gene that is present in 1%-2% of the population can be associated with

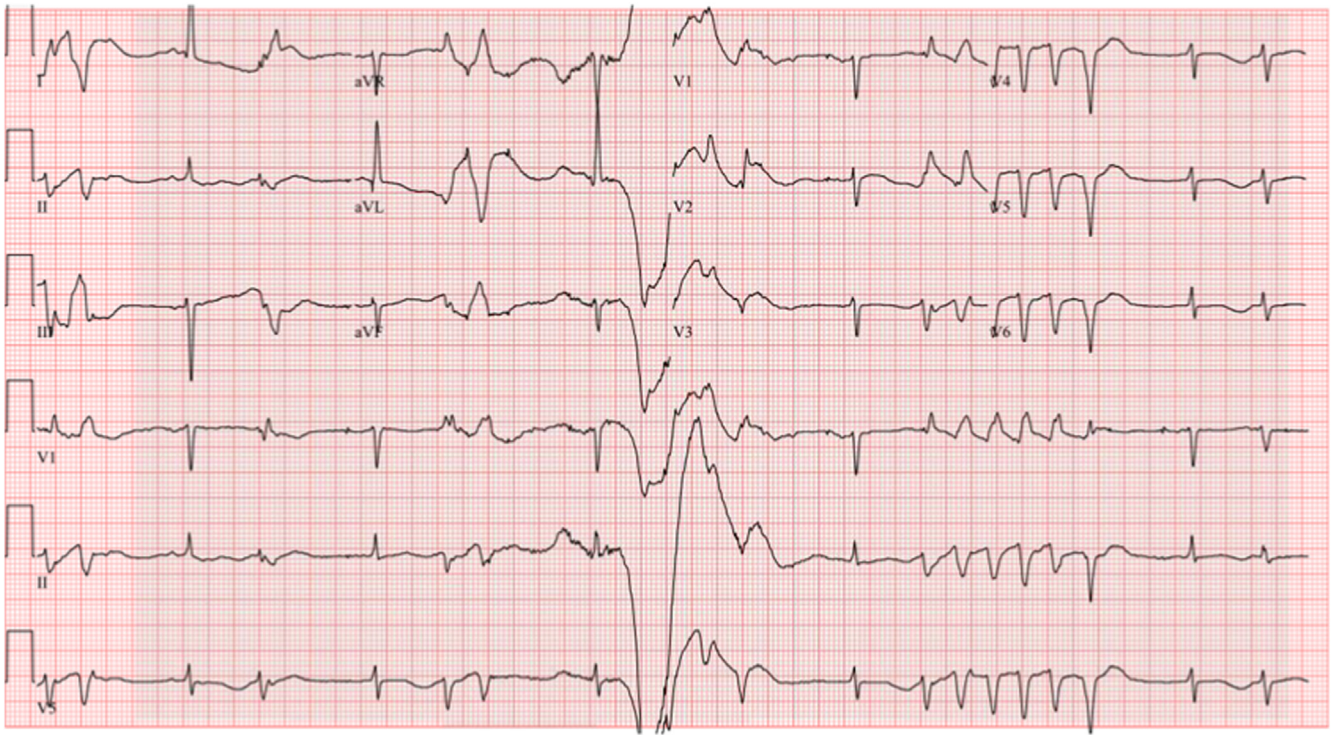

Figure 8. Electrocardiogram showing severe QT prolongation and R on T phenomenon with torsades de pointes arrhythmia. Courtesy of Dr J. Joza.

Table 3. Examples of QT prolonging medications (refer to www.crediblemeds.org for a complete list)

Class of medication	Name of medication
Antibiotics	Erythromycin
	Clarithromycin
	Azithromycin
	Trimethoprim/sulfamethoxazole
	Ciprofloxacin
	Moxifloxacin
Antifungals	Fluconazole
Antiarrhythmics (classes I and III)	Flecainide
	Propafenone
	Mexiletine
	Quinidine
	Amiodarone
	Sotalol
Antipsychotics/antidepressants	Haloperidol
	Olanzapine
	Quetiapine
	Risperidone
	Fluoxetine
	Citalopram
	Escitalopram
	Trazodone
	Venlafaxine
	Desvenlafaxine
	Lithium
	Ziprasidone
	Amisulpride
Antiemetics	Domperidone
	Metoclopramide
	Ondansetron
	Palonosetron
Analgesics	Methadone
	Triptans
Miscellaneous	Chloroquine
	Hydroxychloroquine
	Loperamide (high-dose)

TdP related to administration of QT-prolonging medications such as quinidine or sulfamethoxazole/trimethoprim.[52,53]

When should you order an ECG with a potential QTc-prolonging medication?

Although certain medications such as sotalol and dofetilide require an ECG before initiation, a requirement for doing an ECG is not routine for most medications with QT-prolonging potential. In clinical practice, it is impractical and low-yield to do an ECG on every patient who commences a drug that could possibly prolong the QT interval, so risk stratification and clinical judgement are required, taking into consideration the drug, the dose, and the coexistence of other factors that might influence the risk for QT prolongation. In a low-risk setting, for example, an otherwise healthy person taking or about to start taking a low-risk selective serotonin reuptake inhibitor, like sertraline, and with no other drug- or disease-related reason for QTc prolongation, then routine ECG monitoring is rarely needed. Conversely, if you plan to initiate or increase the dose of a higher-risk QTc-prolonging drug, for example, methadone, especially in a patient with borderline QTc prolongation, then an ECG should be performed after each dose change. In a patient who is already taking a QTc-prolonging drug, and you wish to add another drug that also prolongs the QTc, such as a quinolone antibiotic, it is often preferable to consider an alternate drug that does not affect the QTc, such as an antibiotic like penicillin or cephalosporin if appropriate, rather than just monitoring the ECG. When a patient is taking a QTc-prolonging medication, electrolytes and renal function should be monitored, especially if the patient is taking a diuretic or if there is impaired renal function because of an acute or chronic illness.

Practical tips: Management of aLQTS

1. aLQTS is classically due to QT-prolonging medications or electrolyte disturbances. Common drugs include antidepressants/antipsychotics, antibiotics, and antiarrhythmics. Remember the "anti's"—antibiotics (macrolides and fluoroquinilones), antifungals, antiarrthymics, antipsychotics/ antidepressants, antiemetics, analgesics, (including methadone and triptans), and miscellaneous (including chloroquine). Check for complex drug interactions or potential QT prolongation before administration (www.crediblemeds.org and related smartphone app).
2. There are important intraclass differences among QT-prolonging drugs in the risk of causing an arrhythmia (eg, risk among macrolide antibiotics is highest with erythromycin and lowest with azithromycin), and with selective serotonin reuptake inhibitor antidepressants, risk is highest with citalopram and escitalopram and negligible with paroxetine and sertraline. Conversely, there are safe alternatives among antibiotics such as penicillins and cephalosporins, and among CNS medications; stimulants for attention deficit hyperactivity disorder are generally safe.
3. Increased risk for TdP occurs when the QTc exceeds 500 ms or when a drug increases the QTc by $>$ 60-70 ms, particularly when this increase develops rapidly.
4. Women are at higher risk of aLQTS, along with elderly people and those with underlying structural heart disease.
5. Consider an ECG before initiation of a QT-prolonging drug if an electrolyte disturbance is present, if already receiving a QT-prolonging drug, or when initiating a high-risk QT-prolonging drug.
6. Be cautious in patients with multiple risk factors for QT prolongation (eg, when a diuretic is used with sotalol, be mindful of the potential for hypokalemia and hypomagnesemia).
7. If the QTc does not normalize after removal or correction of the inciting cause, underlying cLQTS should be ruled out.

Pediatric Considerations

Fetal and infant presentation

The first presentation of cLQTS can be in utero. Approximately 50% of fetuses affected by cLQTS will have a lower resting heart rate.[54] Although screening for cLQTS can be initiated prenatally if there is a known pathogenic mutation that segregates with disease in the family, it is much more common to assess the child postnatally. It is important to obtain an ECG after birth when there is a fetal indication or family history of cLQTS.

Although the ECG, especially in the first week of life, can show a transiently prolonged QT interval, even in healthy

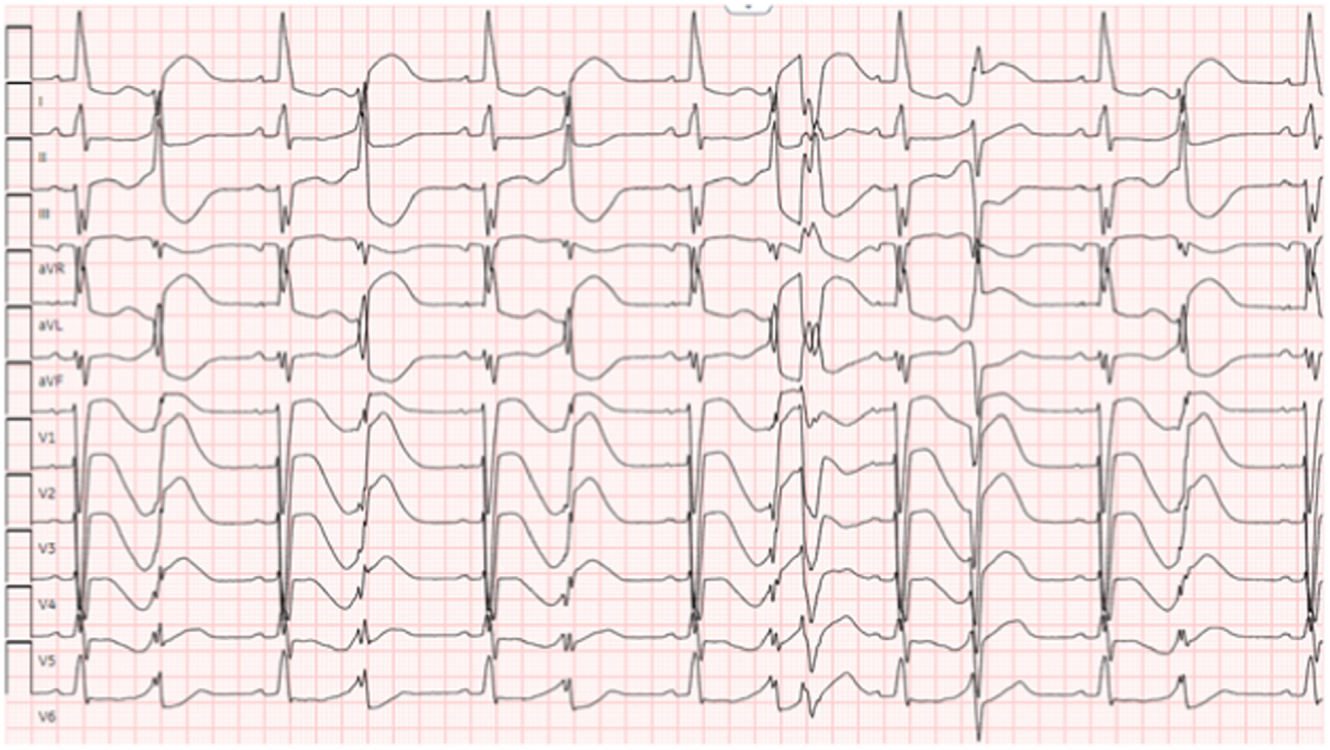

Figure 9. Drug-induced long QT interval corrected for heart rate interval in a 75-year-old woman who presented with a bowel obstruction. The electrocardiogram shows marked prolongation of the QT interval and frequent premature ventricular contractions. Her medications included ondansetron and she had mild hypokalemia. Both factors are known to increase the risk of QT prolongation and therefore torsades de pointes. Courtesy of Dr C. MacIntyre.

newborns, this phenomenon is explained by the inaccuracies of various correction formulae and difficulties with measurement, rather than by true QT interval prolongation.[55] We advise repeating the ECG after 2-3 weeks of age, to overcome these confounders. The decision to initiate treatment with β-blockers in a neonate with indication of cLQTS is on the basis of the absolute QT prolongation and strength of the diagnosis. With a QTc > 500 msec, initiation of a β-blocker is advised while further workup, including screening of the parents, is performed. This is important because sudden infant death syndrome can be an uncommon presentation of cLQTS. Propranolol suspension is administered at a dose of 2-4 mg/kg/d divided 3 times daily in the neonatal period. Confirmatory genetic testing is also recommended, because genotype-specific treatment, prognosis, and follow-up exists for the commonly implicated genes.

Breastfeeding is generally recommended in infants with cLQTS. It is important to review maternal medications to ensure there are no QT-prolonging medications transferred through breast milk. β-blockers can mask the symptoms of neonatal hypoglycemia and cause hypoglycemia. Prolonged fasting can precipitate hypoglycemia and needs to be avoided in infants receiving β-blockers. This is most often a concern during an intercurrent illness.

Table 4. Intraclass differences in risk of QTc prolongation

Drug class	Higher risk	Lower risk	Minimal risk
SSRI antidepressants	Citalopram	Fluoxetine	Sertraline
	Escitalopram	Fluvoxamine	Paroxetine
Antipsychotic drugs	Amisulpride	Haloperidol	Aripiprazole
	Asenapine	Risperidone	Clozapine
	Iloperidone	Quetiapine	Droperidol
	Sertindole	Olanzapine	Lurasidone
	Thioridazine		
	Ziprasidone		
Macrolide antibiotics	Erythromycin	Clarithromycin	Azithromycin
Fluroquinolone antibiotics	Moxifloxacin	Levofloxacin Ciprofloxacin	
5-HT3 antagonist antiemetics	Ondansetron	Granisetron	
		Palonosetron	

5-HT3, 5-hydroxytryptamine 3 receptor antagonist; QTc, QT interval corrected for heart rate; SSRI, selective serotonin reuptake inhibitor.

Table 5. Drug interactions that increase the risk of acquired long QT syndrome and torsades de pointes

Mechanism	Examples
Pharmacodynamic	
Concomitant use of 2 drugs that independently prolong QTc	i) Methadone with ondansetron ii) Sotalol with moxifloxacin iii) Fluoxetine with clarithromycin
Concomitant use of drugs that prolong QTc by different mechanisms	i) Ziprasidone with a thiazide or loop diuretic (ziprasidone prolongs QTc; diuretics might promote K^+ or Mg^{2+} wasting) ii) Itraconazole with cisplatin (itraconazole prolongs QTc; cisplatin might promote Ca^{2+} or K^+ wasting)
Pharmacokinetic	
Concentration of a QTc-prolonging drug increased by another drug	i) Flecainide metabolism (CYP2D6) inhibited by bupropion, paroxetine or terbinafine ii) Pimozide metabolism (CYP3A4) inhibited by verapamil
Mixed	
More than 1 mechanism	i) Quetiapine with itraconazole (both drugs can prolong QTc; itraconazole inhibits quetiapine metabolism via CYP3A4) ii) Sotalol with a proton pump inhibitor (sotalol directly prolongs QTc; PPIs can lead to hypomagnesemia, especially in combination with loop diuretics)

CYP, cytochrome P450; PPI, proton pump inhibitor; QTc, QT interval corrected for heart rate.

Childhood presentation

In children with a parent with clinical cLQTS, in the absence of a confirmed genetic cause, it is important to revisit the possibility of cLQTS as the child matures. A reassessment around school age and another one when the child can complete an exercise test (around 8-10 years of age) are advised. Through childhood, boys with cLQTS type 1 are at higher risk of events than girls, whereas women with cLQTS types 1 and 2 are at higher risk than men in adulthood. Female adolescents have longer QT intervals postpuberty (12-14 years of age).[56] A reevaluation in adolescence is reasonable, because of evolving phenotypes, and the development of confounding symptoms.

When a young patient is first diagnosed with epilepsy in the emergency room or by neurology, and especially when it is refractory to antiseizure medications, it is important to look at the QT interval on the ECG, to make sure there is no significant QTc prolongation suggestive of underlying cLQTS. All pediatric patients with diagnosed or suspected cLQTS should be referred to a specialized pediatric cardiology clinic.

Table 6. Summary of key learning points about managing a patient with a prolonged QT interval

1. **What is the QT interval?**
   The QT interval on the ECG represents ventricular depolarization and repolarization that corresponds to the myocardial action potential from transmembrane flux through ion channels.
2. **How do you measure the QT interval?**
   Using lead II or V_5, the QT measurement begins with the onset of the QRS complex and ends where the tangent of the downslope of the T wave intersects with the baseline. The QT interval is then corrected for heart rate (QTc) using Bazett's or other formulae. The upper normal QTc in men is < 450 ms and in women is < 460 ms and is considered definitely abnormal when ≥ 480 ms. A QTc ≥ 500 ms is associated with an increased risk of torsades de pointes arrhythmia.
3. **What causes a prolonged QT interval?**
   Pathological prolongation of the QTc can be either congenital (cLQTS) or acquired (aLQTS) because of QTc-prolonging medications, abnormal electrolytes, or hypothermia.
4. **What is cLQTS?**
   cLQTS is mostly due to an autosomal dominant mutation (LQTS types 1-3) but can be due to less common variants and sometimes no known variant is identified.
5. **When should you suspect cLQTS?**
   Consider cLQTS with unexplained syncope especially when provoked by exercise, swimming, or a loud noise, seizures, resuscitated sudden death, or a family history of unexplained sudden death.
6. **How do you diagnose cLQTS?**
   There can be overlap between a longer QTc in some normal patients and pathological prolongation. Pathological QTc prolongation especially with abnormal T waves is key to the diagnosis of LQTS, but the QTc can be normal or "concealed" in some patients with cLQTS. This is best identified by exercise testing to identify abnormal prolongation of the QTc on the post exercise electrocardiogram often at 4 minutes. If you need help with diagnosis or management, contact an expert through the Canadian HiRO network (www.heartsinrhythm.ca) or internationally at (www.sads.org).
7. **How do you treat cLQTS?**
   Nadolol in high-risk patients and nadolol or bisoprolol in low-risk patients with avoidance of QT-prolonging medications and maintenance of normal electrolyte levels prevents cardiac events in most patients.
8. **What are QT-prolonging medications?**
   Common "antidrugs" (antibiotic, antifungal, antipsychotic/antidepressant, antiemetic, and analgesic and ancillary such as methadone, triptans, and chloroquine) can prolong the QT interval, but there are important intraclass risks being higher with citalopram than sertraline among selective serotonin reuptake inhibitors and higher for ciprofloxacin and erythromycin than azithromycin and nonexistent for cephalosporins and penicillin among antibiotics. Use the web site www.crediblemeds.org (and the related phone app) to check the risk of a medication causing QT prolongation.

cLQTS, congenital long QT syndrome; LQTS, long QT syndrome; QTc, QT interval corrected for heart rate.

Reflex or vasovagal/vasodepressor syncope has its first peak during the prepubertal rapid growth phase, often leading to multiple follow-up ECGs, even in the absence of a convincing history for pathological arrhythmia. There can be a difference of the QTc interval on the ECG from the emergency department compared with a follow-up ECG.[57] This difference can precipitate a lifelong incorrect diagnosis of cLQTS in a healthy person with reflex syncope. A follow-up ECG, detailed history, and expert consultation are warranted to avoid the false diagnosis of cLQTS.[58] Exercise testing can be difficult to interpret in the pediatric age group. If cLQTS is not easily ruled out despite a nonclassic presentation, like vasovagal syncope or palpitations, it is recommended to generally err on the side of close follow-up before assigning a diagnosis. Genetic testing might be judiciously used by experts in truly ambiguous situations but must be pursued thoughtfully because borderline genetic findings are also common. Most of these borderline situations do not represent cLQTS and do not warrant β-blocker therapy.

Eating disorders are common in adolescents and represent another circumstance in which abnormal repolarization is identified.[59] Electrolyte repletion and refeeding protocols are important in preventing arrhythmias. However, these patients do not typically require β-blockers. Treatment should focus on addressing the underlying eating disorder.

Most pediatric patients, from neonates to adolescents with cLQTS, can be managed similarly to adults with β-blockers and avoidance of QT-prolonging medication. Cardiac rhythm devices are rarely required. Most breakthrough arrhythmic events are due to underdosing or missed doses of β-blockers or prescription of QT-prolonging medication(s). In patients in whom issues with medication compliance are identified, it is important to involve the specialized pediatric cardiology clinic for advice regarding treatment optimization.

The role of exercise restriction is contentious. Healthy active lifestyles are important for normal childhood development, and the evidence for activity restriction in treated cLQTS is lacking. A shared decision-making approach to sports participation is recommended including access to medication, community awareness of cardiopulmonary resuscitation and automated external defibrillator availability, and a safety plan to support activities. However, swimming, which is a specific trigger in cLQTS type 1, should always be under direct supervision.

Practical tips: Management of the pediatric patient

1. Because of faster heart rates, sinus arrhythmia, and age and hormonal factors, measurement of the QT interval is challenging in children and serial ECGs might be needed before a diagnosis can be made.
2. Reflex or vasovagal/vasodepressor syncope is common in the prepubertal rapid growth phase and can lead to serial ECGs and overdiagnosis of cLQTS.
3. Most pediatric patients with cLQTS can be managed with β-blockers and avoidance of QT-prolonging medication. Cardiac rhythm devices are rarely required. Most breakthrough arrhythmic events are due to underdosing or missed doses of β-blockers or prescription of QT-prolonging medication(s).
4. Physical activity and participation in sports can be promoted by safety planning, including access to an automated external defibrillator and supervision, especially around swimming.
5. Genetic testing in children requires expert guidance before testing is initiated, to allow for appropriate informed consent and guidance on response to positive results.

Conclusions

Physicians are frequently faced with patients with borderline or significant QT prolongation. Accurate assessment of the QT interval in conjunction with awareness of the factors and conditions that lead to QT prolongation is important for optimal patient management and for minimizing patient risk. Further, the overlap in patients with cLQTS and otherwise healthy patients makes decisions regarding who warrants additional testing, diagnosis, and treatment a significant challenge. When assessing these patients, it is important to consider the practice tips included in this document (a summary of key learning points is provided in Table 6). Remember that referral to an inherited arrhythmia or a specialized cardiogenetics clinic is strongly encouraged when there is either a suspicion for or a diagnosis of an inherited arrhythmia syndrome.

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