

A Review of Long QT Syndrome: Everything a Hospitalist Should Know

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ABSTRACT

In this article, we will review various aspects of long QT syndrome (LQTS) necessary for hospitalists who care for children, adolescents, and young adults who have known LQTS and also review presenting features that should make one consider LQTS as a cause of hospitalization. Pediatric hospitalists care for patients who have suffered near-drowning, unexplained motor vehicular accidents, brief resolved unexpected events, sudden infant death syndrome, recurrent miscarriages, syncope, or seizures. These common conditions can be clinical clues in patients harboring 1 of 16 LQTS genetic mutations. LQTS is commonly caused by a channelopathy that can cause sudden cardiac death. Over the years, guidelines on management and recommendations for sports participation have evolved with our understanding of the disease and the burden of arrhythmias manifested in the pediatric age group. This review will include the genetic causes of LQTS, clinical features, and important historical information to obtain when these presentations are encountered. We will review medical and surgical treatments available to patients with LQTS and long-term care recommendations and prognosis for those diagnosed with LQTS.

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Long QT syndrome (LQTS) is more than a prolongation of the QT segment of the electrocardiogram (ECG). As the name “syndrome” implies, a patient should have a prolonged QTc, plus other ECG abnormalities per Schwartz criteria (reviewed later), plus specific clinical and family history. Failure to include these elements in medical decision-making to commonly encountered clinical scenarios frequently seen by pediatric hospitalists can lead to missed opportunities to diagnosis this treatable and potentially fatal disease. The diagnosis typically receives consideration when a screening ECG demonstrates QT segment prolongation or polymorphic ventricular tachycardia known as torsade-de-pointes (TdP). This rhythm can degenerate into ventricular fibrillation and cause sudden cardiac death and present as syncope and/or collapse. LQTS can result from congenital or acquired causes. Congenital causes occur less frequently than acquired and are due to the presence of genetic mutation(s) that affect 1 of the several channels involved with ventricular repolarization. Acquired causes can be secondary to electrolyte abnormalities like hypocalcemia, hypokalemia, hypomagnesemia, drug side effect, or drug–drug interaction. Both causes of LQTS and familiarization of its protean manifestations are important for any hospitalist to understand.

BACKGROUND

Although a less common etiology of LQTS compared with acquired causes, congenital LQTS is most commonly caused by an underlying cardiac channelopathy. LQTS is estimated to affect 1 in 2000 people and is responsible for ~4000 deaths per year in the United States.^{1,2,3} Its clinical manifestations are estimated to be less common (1 in 5000) because most mutation carriers remain asymptomatic.⁴

In 1957, Jervell and Lange-Nielsen⁵ were the first to document this syndrome in Norway in a family with children who were deaf and had QT prolongation, syncope, and death at a young age. This association came to be known as Jervell and Lange-Nielsen syndrome and has an autosomal recessive pattern of inheritance. More commonly, LQTS is inherited in an autosomal dominant pattern and is associated with normal hearing, described as Romano-Ward syndrome in 1964.^{6,7} Although initially described in 1957, much of the research contributing to a better understanding of the disease has occurred only in the past 2 decades. As of 2016, >500 different mutations have been identified in the 16 genes currently known to cause LQTS.^{1,8,9}

Acquired causes of LQTS are far more prevalent than congenital causes of LQTS. Most acquired causes result from adverse

effect of drugs or electrolyte abnormalities, which can interact with the gene related to LQTS2 (*hERG*).^{10,11}

GENETICS

Congenital LQTS results from mutations involving 1 of the many genes coding for ion channels that facilitate the transport of potassium, sodium, and calcium. These ion channels play critical roles in maintaining the heart’s normal rhythm. Despite having at least 16 genetically distinct types of LQTS, at least 75% of the mutations are found in 3 genes: *KCNQ1* (potassium channel), *KCNH2* (potassium channel), and *SCN5A* (sodium channel) causing long QT (LQT) type 1, LQT2, and LQT3, respectively.¹

Often Romano-Ward syndrome is used interchangeably with LQTS, but it is becoming increasingly common to reference the subtype according to the underlying genetic mutation (LQT1 to LQT16). The Jervell and Lange-Nielsen syndrome is caused by mutations in either *KCNQ1*/LQT1 (90%) or *KCNE1*/LQT5 (10%). These genes encode components of the potassium channel, which are critical for function of both inner ear and cardiac conduction.⁹ LQT1 is the most common of the 3 subtypes and has the highest incidence of cardiac events or symptomatic patients at 63%, followed by 46% in LQT2 and 18% in LQT3. However, the likelihood of dying during a

TABLE 1 Distinguishing Features of LQTS For the 3 Most Common Genetic Mutations

Genotype	LQT1	LQT2	LQT3
Genetics	<i>KCNQ1</i>	<i>KCNH2</i>	<i>SCN5A</i>
Frequency, %	35–45	30–35	8–10
Function	Loss	Loss	Gain
Ion current affected	↓ I_{Ks}	↓ I_{Kr}	↑ I_{Na}
Incidence of cardiac events ²² , %	63	46	18
Likelihood of dying during a cardiac event ²² , %	4	4	20
Triggers ²¹	Swimming, exercise, adrenergic stimuli	Loud noises, emotion, peripartum period	Sleep
ECG	Broad-based T wave	Low-amplitude bifid T wave	Long isoelectric ST segment
Response to β -blockade ^{21,33}	+++	++	+
Response to mexilitine ²¹	+	+	++
Exercise restriction	+++	++	Uncertain
Exercise-triggered events ²² , %	68	29	4

+, low likelihood; ++, moderate likelihood; +++, high likelihood.

LQTS event is 5 times more compared with others.¹² (Table 1)

CLINICAL PRESENTATION

Now that we have reviewed the genetics of LQTS, hospitalists need to be made aware of what information to seek when obtaining a family history on patients who they take care of and the conditions that mimic LQTS. LQTS has a variety of clinical manifestations, many of which can find their way to hospitalist services. Patients with LQTS typically present with syncope, fainting spells, brief resolved unexplained events, sudden cardiac death, near-drowning events, aborted cardiac arrest, recurrent syncopal episodes, drop attacks, narcolepsy, or epilepsy.¹³ Although the cardiac events may occur at any age from infancy through middle age, they are most common from the preteen years through the 20s. Of the individuals who do become symptomatic, 50% experience their first cardiac event by the age of 12 years and 90% present by the age of 40 years.¹⁴ Given that patients with LQTS frequently present in the pediatric age range, increasing awareness of its diagnosis is necessary.

Syncope Evaluation

Because LQTS can present to hospitalists as syncope, its evaluation should include a detailed clinical and family history. The history obtained (discussed later) should parse out if the event is due to benign vasovagal syncope or a potentially fatal arrhythmia due to LQTS. Vasovagal syncope is typically associated with a prodrome of tunnel vision, sweating, cold extremities, nausea, and abdominal pain. It is usually associated with abrupt postural changes (laying or sitting to standing). Vasovagal events can result from standing for prolonged periods in hot weather and are exacerbated by hypovolemic states causing dehydration (vomiting and diarrhea). Palpitations usually occur after the onset of dizziness, and if ever related to exercise, vasovagal syncope occurs once the patient begins to cool down and after a period of physical exertion (Table 2). Situational-specific triggers such as pain, cough, laugh, micturition, defecation, and deglutition have also been associated with vasovagal

TABLE 2 Differentiating Characteristics of Presenting Symptoms of LQTS and Vasovagal Syncope

LQTS	Vasovagal Syncope
Sudden onset syncope	Aura first, followed by dizziness or nausea
During exercise	During cooldown after exercise
Swimming, exercise, emotionally, loud noise induced	Typically orthostatic or emotionally induced
May present as convulsive event	May present as convulsive event

syncope. In patients who experience vasovagal syncope, typically an aura occurs before syncope. In contrast, arrhythmia-mediated syncope may have sudden loss of consciousness or occur after a brief prodrome of palpitations.¹⁵ Syncope that occurs during exertion (not during the cooldown phase of exercise) should always be concerning and should alert the hospitalist to consider LQTS as an etiology and thus consider involving a pediatric cardiologist.

Because seizures have been mentioned in the differential, a history of syncope or collapse before a witnessed seizure may indicate the presence of an arrhythmia that causes a hypoxic seizure. It is also estimated that ~25% of autopsy-negative or

unexplained sudden cardiac death in the young, 10% to 15% of sudden infant death syndrome (SIDS), and 9% of miscarried fetuses may be attributable to mutations in either LQTS or catecholaminergic polymorphic ventricular tachycardia susceptibility genes.¹⁶⁻²⁰

Family History

We would like to emphasize to hospitalists the importance of obtaining a family history that covers 3 generations when called to evaluate patients who present with any of the aforementioned presentations. Exploration of family history should seek to determine if any of the following are present: sudden cardiac death or cardiac arrest in young individuals <50 years of age, history of recurrent syncope or

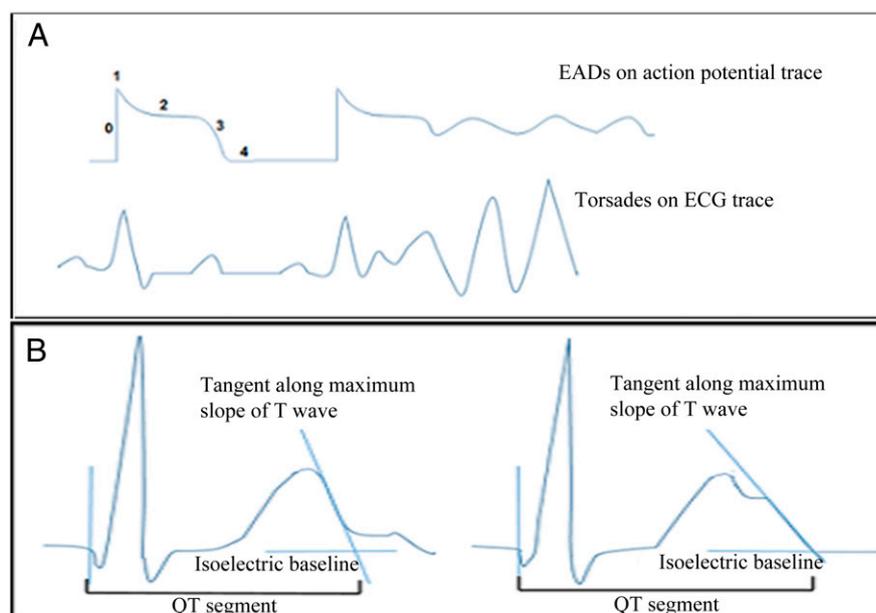


FIGURE 1 A, Demonstrates prolongation of the ventricular action potential with phase 0, phase 1, phase 2, phase 3, and phase 4 of the action potential and a phase 3 depolarization (early afterdepolarization [EAD]) causing Tdp. B, Demonstrates how to measure the end of the T wave on the basis of the T wave tangent.

TABLE 3 The Modified Schwartz Criteria for Determining Probability of LQTS

	1993–2011 LQTS Diagnostic Criteria Points
Electrocardiographic findings	
QTc	
≥ 480 ms	3
460–479 ms	2
450–459 ms (males)	1
QTc fourth minute of recovery from exercise stress test	
≥ 480 ms	1
Tdp	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
Congenital deafness	0.5
Family history	
Family members with definite LQTS	1
Unexplained sudden cardiac death below age 30 among intermediate family members	0.5

In 2011, QTc at fourth minute of recovery from exercise stress was added (ref 26). QTc was calculated by Bazett's formula, in which $QTc = QT/\sqrt{RR}$. Score of 1 or less equals less probability of LQTS. 1.5 to 3 points equals intermediate probability of LQTS. 3.5 points equals high probability.

seizures, narcolepsy, sleep-related deaths, pacemaker or defibrillator implantation in young, congenital deafness, SIDS, unexplained deaths associated with drowning, or motor vehicle accidents.

Genetic Insight From Event

Sometimes the triggers for the syncopal event can provide a clue to the type of genetic defect present. For instance, LQTS can occur in patients who are exposed to an adrenergic stimulus (eg, swimming, diving). This is why patients who carry LQT1 mutations can present as drowning events or with exertional syncope. Patients who carry mutations for LQT2 are at a higher risk for lethal events during arousal and auditory stimulation (loud noises or alarms). Female adolescents with LQT2 have a ninefold increase in risk of experiencing arousal-triggered cardiac events compared with male adolescents in the same age group. This presentation can mimic cataplexy, a finding that is often associated

with narcolepsy. As a result, the peripartum period is a high-risk period for patients who carry LQT2 mutation or with acquired LQTS. Finally, sleep-induced bradycardia appears to be the main trigger in LQT3.²¹

Thus, for any hospitalist who cares for patients with particular LQT types (with the above-noted histories and range of clinical presentations), these arrhythmic triggers should be considered and raise suspicion for the presence of undiagnosed LQTS.

PATHOPHYSIOLOGY OF TORSADES

Mutations in any of the 16 genes mentioned can alter the structure or function of the respective channels affecting the flow of ions. Altered flow of ions, under the right inherited and acquired circumstances (ie, electrolyte derangements or medications), can result in prolonged and heterogeneous cardiac repolarization. In patients with LQTS, the layers of the myocardium repolarize at a different rates, with the midmyocardial cells

having significant prolongation of the action potential duration compared with the epicardial or endocardial cells. The prolongation represents delayed cardiac repolarization and differential repolarization between parts of the ventricles as well as between the epicardium, midmyocardium, and endocardium. This differential repolarization then allows differential signal propagation during phase 3 of the action potential for parts of the heart, while other parts wait to follow suit and allow this depolarization-repolarization difference to continue and propagate as Tdp (Fig 1A). This transmural dispersion of repolarization between the myocardial layers can result in a predisposition of having multiple reentrant circuits that can cause Tdp, which can degenerate to ventricular fibrillation.¹⁰ This phenomenon occurs in LQTS when cardiac action potential duration is prolonged. Action potential prolongation can lead to early afterdepolarizations, in which the preceding action potential triggers a series of abnormal impulses in phase 2 or 3 and may degenerate to Tdp and ventricular fibrillation¹⁰ (Fig 1A). Early after depolarizations are more prone to occur with bradycardia, which is more typical in patients who have sodium channel mutations characteristic of LQTS3.

Finally, R-on-T phenomenon can occur and result in Tdp. This scenario is seen when the R wave of an ectopic beat or premature ventricular contraction falls on the upslope of a T wave of a preceding wave, thus triggering Tdp and ventricular fibrillation.¹¹

DIAGNOSIS

Diagnosing LQTS is challenging because as many as 25% to 33% of patients with genetic LQTS have a concealed QT (normal QT interval).^{22–25} Once the diagnosis of LQTS is considered, published criteria, by Schwartz et al²⁶ in 1993, can be used to help clinicians weigh the likelihood of having LQTS. It later came to be known as the “Schwartz criteria.” In 2011, the Schwartz criteria was updated with the addition of a prolonged QTc >480 ms at 4 minutes of recovery in exercise stress test. (Table 3)²⁷

POINTERS FOR MEASURING QTC

When using a standard 12-lead ECG, a rule of thumb is that a normal QTc is a QT

interval that is less than half of the preceding RR interval. An RR interval is the time elapsed between 2 successive R-waves of the QRS complex. Manual calculation of QTc is important because even with the assistance of ECG software, mistakes can occur in calculations of QTc. A standard 12-lead ECG tracing at a paper speed of 25 mm per second at 10 mm per mV amplitude is generally adequate for accurate measurement of QTc. Bazett's formula $\frac{QT \text{ (seconds)}}{\sqrt{RR \text{ (seconds)}}}$ is widely used to calculate the QTc but may give erroneous results at both slow and fast or irregular heart rates. To calculate QTc, it is best to use QT measurements from leads II, or precordial leads V5 or V6, and it should be determined as a mean value derived from at least 3 to 5 cardiac cycles (heartbeats). Electrophysiologists typically use lead II to determine the QTc because the interval usually consists of a discrete T wave rather than a T and an associated U wave, thus making it easy to measure the QT interval.²⁸ QT is measured from the beginning of the earliest onset of the QRS complex to the end of the T wave, determined by drawing a steep slope (closest to vertical line along the descending side of the T wave). Despite some debate, most pediatric electrophysiologists agree that if U waves >25% of the T wave are present and fused with T waves, they should be included in the QT segment. Often this will be labeled as QTuc because there is no formal guidelines for including prominent U waves in QTc measurements (Fig 1B). However, hospitalists must always be careful to

exclude small U waves, which is the most common mistake when calculating the QTc.²⁹ Individuals who receive 3.5 points using the updated Schwartz criteria should be referred to an electrophysiologist or cardiologist with experience in managing LQTS so that there can be careful consideration to conduct genetic testing.^{30,31}

MANAGEMENT

Medical

β -blockers are the primary treatment of LQTS and are clinically indicated in all individuals with QTc >470 (level of evidence class I). They can also be useful in asymptomatic LQTS with QTc <470 ms (level of evidence class IIa) if there is concern for significant family history of sudden death events or questionable history.³² However, it is important to know that LQT1 and LQT2 mutations are more responsive to β -blockers than LQT3. Longitudinal data have demonstrated that up to 90% of LQT1 and 77% of LQT2 patients treated with β -blockers were free from syncope and cardiac arrest at 5.2 years of follow-up versus 68% of LQT3.³³ Furthermore, not all β -blockers are equally effective. For instance, nadolol, a nonselective β -blocker, is more effective in reducing sudden cardiac death in symptomatic patients compared with propranolol, metoprolol, or atenolol.³⁴ Because pediatric hospitalists treat asthma and diabetes, care should be taken into account given β -blocker therapy as first line for prevention of sudden death. Nadolol is considered first-line therapy even in asthma and diabetes. However, because dose adjustments may be needed, one needs to be

mindful of asthma control and hypoglycemia awareness in patients with asthma and diabetes, respectively. Therefore, involving the necessary specialists in patient care with these conditions would be prudent. Pharmacotherapy in LQT3 can be challenging. β -blockers remain the first-line drug; use of a sodium channel blocker like mexiletine might be considered as adjunctive therapy (level of evidence class IIa).^{32,35} Drugs that are known to cause prolongation of the QT interval should be avoided (Table 4). A comprehensive list can be found on Web sites like crediblemeds.org and torsades.net.^{36,37}

Another important consideration when caring for patients with known LQTS is safe administration of anesthesia when they require procedural and nonprocedural sedation. These interventions should only be performed by an anesthesiologist who has experience and is comfortable caring for patients with LQTS or has dedicated training in cardiac anesthesia because several drugs can prolong the QTc. Telemetry monitoring during and after the procedure in the recovery phase is recommended for at least 5 half-lives of the QT-prolonging medication administered. A repeat 12-lead ECG should be obtained and evaluated before discharge from the hospital.

Tdp Treatment and Prevention

When a patient with congenital or acquired LQTS develops Tdp, the first-line therapy is magnesium sulfate, 25 to 50 mg per kilogram per dose, and cardioversion if unstable or sustained Tdp. If a patient has a prolonged QTc and intermittent ectopy, this is an instance in which isoproterenol or atrial pacing at a faster rate can be helpful to prevent any further Tdp. One also has to know the QTc and mechanism of initiation of the ventricular tachycardia when treating polymorphic ventricular tachycardia as to avoid QTc-prolonging drugs that might otherwise be harmful in this particular situation. Maintaining serum potassium >4.0 mmol per L, magnesium >2.0 mg per dL, and ionized calcium >1.25 mmol per L is often recommended.

SURGICAL

Implantable cardioverter-defibrillators and/or left cardiac sympathetic denervation are

TABLE 4 Common Drugs That Are Known To Cause Prolongation of the QT Interval Should Be Avoided

Drugs and side effect(s)
Antibiotics: macrolides like erythromycin, azithromycin
Anticongestants: albuterol, ephedrine, pseudoephedrine
Antidepressant: citalopram, fluoxetine, sertraline, escitalopram, clomipramine, amitriptyline, nortriptyline
Antiemetic: ondansetron
Antifungals: voriconazole, ketoconazole, fluconazole
Antihistamine: astemizole, terfenadine, diphenhydramine
Appetite suppressants: phentermine, fenfluramine, sibutramine
Central nervous system stimulants: amphetamines, dexamethylphenidate, lisdexamethylphenidate.
Opiate agonist: methadone

A comprehensive list can be found on Web sites like crediblemeds.org and torsades.net.^{36,37}

therapies typically reserved for high-risk patients. High-risk patients have been defined as those patients who have had cardiac events while on β -blocker therapy, history of cardiac arrest, or inability to tolerate β -blockers (ie, severe asthma) (level of evidence class I).³² Regular follow-up is necessary for assessment of β -blocker dose for efficacy and adverse effects, especially during periods of rapid growth, as is often encountered in pediatric patients. Implantable cardioverter-defibrillators are routinely interrogated and monitored for the occurrence of ventricular arrhythmias, inappropriate shocks, or lead complications. For smaller school-aged individuals, availability of an automatic external defibrillator (AED) at home and school along with AED and cardiopulmonary resuscitation training for caretakers and school or team officials is also strongly recommended.

In the past, the diagnosis of LQTS meant restriction from all sports activities. Participation in competitive sports is still a matter of debate among the experts. However, recent evidence has shown that some patients with LQTS can safely participate in certain activities (except swimming in those with LQT1).^{38,39} To assist hospitalists and other physicians in counseling patients and families who deal with LQTS, the American Heart Association and American College of Cardiology issued an updated recommendation on exercise in 2015. This most recent statement "Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 10: The cardiac channelopathies"⁴⁰ has liberalized restrictions recommended in previous statements. It may be reasonable for patients with low-risk LQTS, who have remained asymptomatic for at least 3 months, to participate in competitive sports (except swimming for those with LQT1).^{38,40} Patients should continue to take the following precautions: avoid QT-prolonging drugs, electrolyte derangements, dehydration, hyperthermia, or heat exhaustion. Patients and caregivers should have immediate access to a personal AED, and all school or team officials should be appropriately trained in cardiopulmonary

resuscitation. This is a deviation from earlier recommendations that allowed only class 1A activities (bowling, billiards, curling, cricket, golf, riflery, or yoga). Current recommendations are that patients in which LQTS is suspected or has been diagnosed and remain symptomatic should refrain from sports until evaluated by an electrophysiologist. Thus, at time of discharge from the hospital, for newly diagnosed LQTS patients, it is reasonable to ask them to refrain from any competitive sports until evaluated further by cardiology and/or electrophysiology. Other lifestyle modifications include no swimming or diving in LQT1; modifying loud telephone or cell phone ringtones, alarm clocks, and school or house bells; and encouraging fathers or significant others to be the primary caretaker in peripartum periods for LQT2.

CONCLUSIONS

Our knowledge of LQTS has grown exponentially over the past 2 decades, with an increased understanding of its genetics, clinical course, and management. Because more than half of LQTS patients present at a young age, the initial diagnosis may be made or suspected by the pediatrician or pediatric hospitalist. All hospitalists, pediatric and adult, should remain vigilant for LQTS when caring for patients who experienced near-drowning, unexplained motor vehicular accidents, seizures, syncope or SIDS, or who have a concerning family history because these can be markers for patients harboring an LQTS genetic mutation. Hospitalists should be familiar with commonly used medications and other acquired causes that are associated with prolonging the QTc and know how to treat Tdp. Hospitalists should be aware of historical features that might be clues to the presence of congenital LQTS, indications to involve a cardiologist, pharmacotherapy options, and sports participation guidelines.

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