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# Congenital long QT syndrome: Considerations for primary care physicians

## ABSTRACT

Congenital long QT syndrome is an inherited disorder of cardiac repolarization that predisposes to syncope and to sudden death from polymorphic ventricular tachycardia. The disorder should be suspected when the electrocardiogram shows characteristic QT abnormalities, or when there is a family history of long QT syndrome or of an event that raises suspicion of long QT syndrome, such as sudden death, syncope, or ill-defined "seizure" disorder. We can now classify some types of congenital long QT syndrome according to their genetic mutations and their triggers, such as exercise, rest, or startle.

## KEY POINTS

Because of the heterogeneity of the syndrome, genotyping is often useful in making therapeutic decisions, such as avoiding alarm clocks in bedrooms in patients with long QT genetic type 2, or restricting physical activity (particularly swimming) in patients with genetic type 1.

When patients on beta-blocker therapy experience further syncopal episodes or aborted cardiac arrest and are considered at high risk, implantation of a cardioverter-defibrillator is appropriate.

In a select few patients, left cervical-thoracic sympathetic denervation may be appropriate.

*Dr. Daubert has disclosed that he has received consulting fees from Medtronic and CryoCor corporations and has ownership interest in Boston Scientific..

CONGENITAL LONG QT SYNDROME is one of a group of abnormalities of cardiac repolarization that can cause syncope and sudden death in apparently healthy people. It was once considered very rare, but current estimates of its prevalence range from 1 in 2,500 people to 1 in 7,000,[1,2] and its prevalence is expected to increase with heightened awareness and screening.

Our understanding of the genetic basis of long QT syndrome is increasing, giving us the ability to classify different types of the disease. For instance, one type is triggered by exercise, especially swimming. Another is associated with sleep or inactivity, and electrocardiographic abnormalities lessen with an increased heart rate. Yet another type can be triggered by a startle, something as simple as an alarm clock going off.

Given the increasing recognition of long QT syndrome and its risks, primary care providers are likely to find themselves encountering challenging management decisions. In this review, we seek to provide a practical overview to aid in clinical decision-making. Our focus is on congenital forms of long QT syndrome rather than on those that are acquired, eg, by the use of certain drugs. Of note, although there is no cure for this condition, appropriate therapy can dramatically reduce the risk of sudden death.[3–5]

## 10 GENOTYPES OF LONG QT IDENTIFIED

First described in 1957 by Jervell and Lange-Nielsen,[6] congenital long QT syndrome became an area of intensive research, and 25

years ago an international registry of patients and their families was established.[7] Initially, research was limited to clinical factors such as symptoms and electrocardiographic features, but advances in molecular genetics have accelerated our understanding of this disease.[7,8]

Although the homozygous form of QT prolongation, Jervell and Lange-Nielsen syndrome,[6] was recognized first because of its greater clinical severity, most affected patients have a heterozygous mutation pattern, termed the Romano-Ward syndrome.[9,10]

To date, 10 distinct genetic types of long QT syndrome have been identified, designated LQT1 through LQT10. Each is associated with an abnormality in a specific ion channel (or subunit of an ion channel) that regulates the cardiac action potential.

Even though genetic testing is becoming more accessible, a specific mutation cannot be identified in 30% or more of people with clinically confirmed long QT syndrome.[11] Most patients successfully genotyped have LQT1, LQT2, or LQT3; of these, 45% to 50% have LQT1, 40% to 45% have LQT2, and 5% to 15% have LQT3.[11–13] Given the overwhelming prevalence of LQT1, LQT2, and LQT3 and, hence, the relative robustness of the data on them, we will limit the rest of our discussion to these three types.

**Many patients with LQT1 have cardiac events while swimming**

## QT INTERVAL ELECTROPHYSIOLOGY: PROLONGATION, ARRHYTHMOGENESIS

With each heartbeat, cardiac cells go through a cycle of electrical depolarization and repolarization, as sodium, potassium, and calcium ions move across the cell membrane via specific channels. In the ventricles, the cycle (FIGURE 1) consists of five phases:

- **Phase 0:** The cell swiftly depolarizes as sodium rapidly moves into the cell via the INa channel. This depolarization leads to the stimulus for the cell to contract.
- **Phase 1:** The cell rapidly partially repolarizes as potassium leaves the cell via the Ito channel.
- **Phase 2:** Repolarization reaches a plateau, with sodium continuing to enter the cell via INa channels (although the current is much slower than in phase 0) along with calcium via L-type ICa channels, somewhat balanced by outward movement of potassium (the rapid-acting current, or IKr, and later the slow-acting current, or IKs). During this phase the cell is still relatively refractory, ie, it cannot fire again.
- **Phase 3:** The cell repolarizes further, as the outward currents (IKr, IKs, and the inward-rectifier, or IK1) increase.
- **Phase 4:** The cell is completely repolarized and ready to go through the cycle again.

Phases 0 through 3 are of longer duration in long QT syndrome, and this longer duration is seen as prolongation of the QT interval on the electrocardiogram.

Complicating the picture, different anatomic areas of the heart have different numbers and types of ion channels, and the resulting electrical heterogeneity is important in understanding the arrhythmogenic mechanisms in long QT syndrome. The ventricle itself comprises three layers: the epicardium, the mid-myocardium ("M-cell" layer), and the endocardium. Each of these layers repolarizes at a different rate, a phenomenon referred to as "transmural dispersion of refractoriness." The M-cell layer has a stronger late INa current and weaker IKs current than the epicardium and endocardium. A consequence of this difference has been noted during bradycardia, when the large contribution of late INa fosters relatively greater prolongation of the M-cell action potential, which increases transmural dispersion of refractoriness and the potential for reentrant arrhythmias.[14]

### LQT1: Events occur during exercise

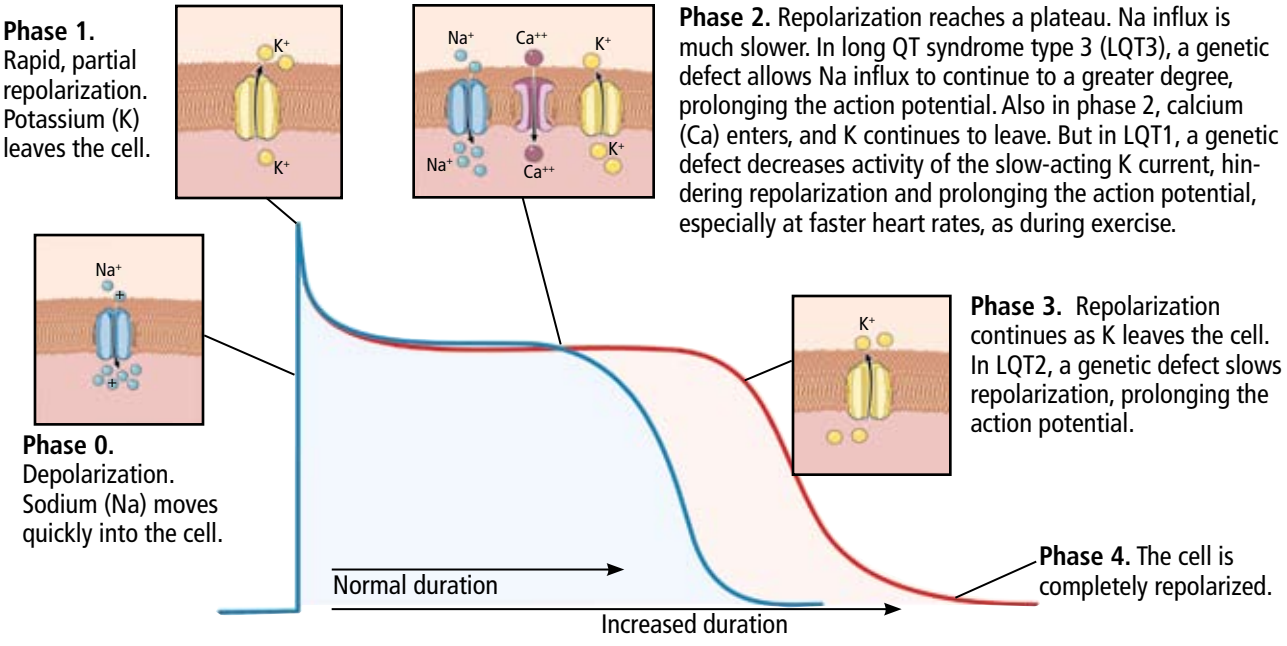
People with LQT1, the most common variant of long QT syndrome, are more likely to have a cardiac event during exercise than patients with LQT2 or LQT3. In particular, and for as yet unexplained reasons, many patients with LQT1 have cardiac events while swimming.[15] These observations suggest a potential role for beta-blocker therapy in these patients to reduce the maximal heart rate and blunt the effects of adrenaline. The benefits of beta-blockers have been confirmed experimentally and clinically.[3,16,17]

LQT1 is associated with a mutation in the KvLQT1 gene (also known as KCNQ1), which codes for a protein (alpha subunit) that co-assembles with another protein (minK, or

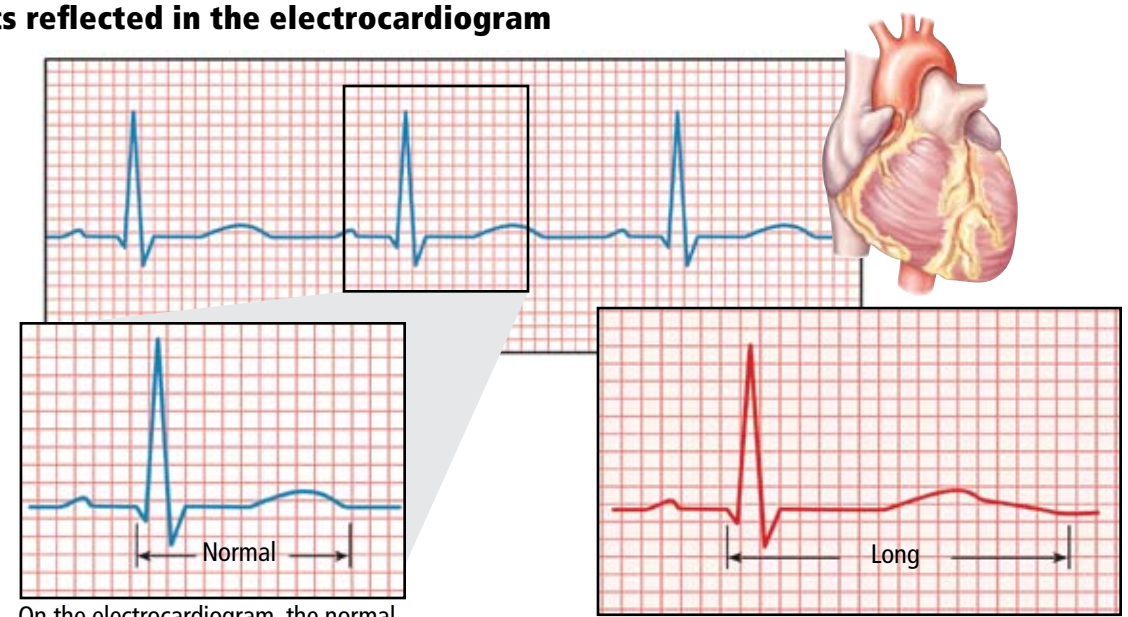
# How defective genes prolong the QT interval

**Several gene mutations can cause an increase in the duration of the cardiac action potential, especially phases 2 and 3, leading to long QT syndrome.**

## Effects on the action potential duration




## Effects reflected in the electrocardiogram




On the electrocardiogram, the normal QT interval is 350-440 ms.

The prolonged action potential appears electrocardiographically as a long QT interval. If the corrected QT interval (QTc) is 440-460 ms (borderline long) or > 470 ms (prolonged), then long QT syndrome should be suspected.

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**FIGURE 1**

beta subunit) to form the slow component of the delayed rectifier potassium channel IKs. (Interestingly, LQT5 also results from a mutation in minK, therefore explaining some of the clinical similarities between LQT1 and LQT5.)

Under normal circumstances, IKs activity is up-regulated by beta-adrenergic stimulation.[14] This, combined with its slow inactivation, leads to a greater number of channels remaining active during rapid heart rates, resulting in a commensurate abbreviation of the action potential duration. In the case of LQT1, however, a decrease in the activity of IKs hinders the normal truncation of the action potential duration, resulting in prolonged repolarization times. Not unexpectedly, this effect is more marked at higher heart rates.

Furthermore, and perhaps more importantly, the addition of beta-adrenergic input to an IKs-deficient system markedly increases the gradient of repolarization across the ventricular myocardium, thereby setting the stage for reentry.[14]

This heart rate dependency of transmural dispersion of refractoriness manifests clinically when one examines the factors that predispose patients to arrhythmic events in the various genetic types of long QT syndrome.

**Genotype, history of syncope, and QTc: key factors in clinical decision-making**

### LQT2: Events triggered by startle or auditory stimuli

Although patients with LQT2 are less likely than patients with LQT1 to have episodes during exertion, they are more likely to have arrhythmic events triggered by auditory stimuli or sudden startle.[18]

LQT2 is caused by a loss of the rapid component of the delayed rectifying potassium current IKr. The IKr channel, like the IKs channel, is heteromeric, with two subunits labelled HERG and MiRP1. In LQT2 the HERG subunit is affected, resulting in a loss of function and, hence, less repolarizing current. This leads to prolongation of the action potential. Similar effects are seen in LQT6, in which a mutation in the MiRP1 subunit reduces IKr. Under normal conditions, the IKr current activates slightly earlier than IKs. It should also be noted that unlike IKs, the IKr current is not influenced by adrenergic tone.

### LQT3: Events occur during sleep or inactivity

Patients with LQT3, unlike those with LQT1, are prone to syncope or cardiac arrest during inactive periods or sleep. In fact, their electrocardiographic abnormalities actually become less marked with increased heart rate due to increased adrenergic tone, a clinical feature that may be useful in discerning this particular genotype.[19]

LQT3 is caused by a mutation in SCN5A, the gene encoding the sodium channel INa. This mutation results in an increase in sodium influx into the cell during phase 2 and phase 3 and, hence, prolongation of the action potential duration. (A loss-of-function mutation—ie, the opposite change—in this protein is believed to be responsible for the Brugada syndrome.)

Beta-blockade has not been shown to confer the same protection in LQT3 as in LQT1 and LQT2, but it has also not been shown to increase events. There is some evidence to support pacemaker therapy to avoid bradycardia as a means of decreasing the event rate in this population.[20] There is also evidence to suggest a benefit from drugs such as flecainide (Tambocor) or mexiletine (Mexitil), which inhibit the late sodium current, but these trials are ongoing and therapy with these agents cannot be recommended at this time.[21]

## CONSIDER THE DIAGNOSIS IF THE QTc IS ABOVE 440 MS

When long QT syndrome is suspected, the diagnosis[22] starts with the surface electrocardiogram. The QT interval runs from the onset of the QRS complex to the end of the T wave, with normal values being from 350 to 440 ms. The U-wave should be excluded from the measurement if distinct from the T wave; on the other hand, complex, multiphasic T waves or T-U complexes should be included.[23,24]

The QT interval is adjusted for heart rate. This corrected QT interval (QTc) equals the QT interval (in seconds) divided by the square root of the RR interval (in seconds). If the QTc is greater than 470 ms (ie, prolonged) or 440–460 ms (borderline), then long QT syndrome must be considered. After puberty, females have a QTc about 10 ms longer on average than males.

However, structural heart disease such as significant hypertrophy,[25] ischemia,[26] infarction,[27] or heart failure[28] and other factors may also affect repolarization, and if any of these is present, the prolonged QTc may not represent congenital long QT syndrome. Drug-induced or other acquired causes of a long QT interval (such as hypokalemia) should also be excluded.[29]

### Is the prolonged QT interval 'high normal' or pathogenic?

As with many other variables in medicine, the QTc has a Gaussian distribution. Hence, some people who seem normal, ie, they have no identifiable gene mutation or symptoms, may have a QTc of 460 to 470 ms.[11] This overlap of "high normal" QTc and true long QT syndrome presents a key diagnostic challenge, ie, how to identify patients truly at risk without incorrectly labeling and restricting normal patients.[30–32]

Given the relatively low prevalence of long QT syndrome in the general population (≤ 1 in 2,500), an asymptomatic patient with a borderline QTc (eg, 450 ms), normal T-wave morphology, and no family history of long QT syndrome or sudden death is much more likely not to have the syndrome. Conversely, a QTc that is "normal" does not mean the patient does not harbor a long QT mutation, especially when a family member has been definitively diagnosed.[31]

Compounding the problem of diagnosis, clinicians and some cardiac specialists often either measure the QTc incorrectly or disagree on how to measure it in actual tracings to diagnose or exclude long QT syndrome.[33]

### Analyzing T wave morphology

After analysis of the QT interval, attention is directed to the T wave morphology. Abnormalities such as low amplitude, inversion, or notches support the diagnosis of long QT syndrome and are helpful if the QTc is borderline-long.[34] Moss et al[35] showed that characteristic patterns of the ST segment and T wave yield clues to the genotype in patients with long QT syndrome. In their study of patients of known genotype, they provided one of the earliest indications of genotype-specific patterns in this syndrome.[35] In addition, if possible, one should look for dynamic changes in the QTc with exercise, as this too can provide insight not only to the diagnosis, but also to the particular genotype. In the absence of exercise electrocardiography, provocative testing with infusion of epinephrine (with ready availability of external defibrillation) has also proven informative.[19,33,36]

**TABLE 1**

**Diagnosis of long QT syndrome in the absence of genetic testing**

| FEATURES | POINTS[a] |
|---|---|
| **Electrocardiography**[b] | |
| Corrected QT interval (QTc) > 480 ms | 3 |
| QTc 460–470 ms | 2 |
| QTc 450 ms (males) | 1 |
| Torsades de pointes | 2 |
| T wave alternans | 1 |
| Notched T wave (three leads) | 1 |
| Low heart rate (for age) | 0.5 |
| **Clinical history**[c] | |
| Syncope with exertion or emotion | 2 |
| Syncope (other) | 1 |
| **Family history**[c] | |
| Family history of definite long QT syndrome | 1 |
| Family history of unexplained sudden death before age 30 of first-degree relative[b] | 0.5 |

[a] 4 = very high probability, 2–3 = intermediate probability, 1 = low probability

[b] QTc prolongation in the absence of drugs known to affect QTc

[c] Syncope, family history items can only include one entry in category

FROM SCHWARTZ PJ, MOSS AJ, VINCENT GM, CRAMPTOM RS. DIAGNOSTIC CRITERIA FOR THE LONG QT SYNDROME. AN UPDATE. CIRCULATION 1993; 88:782–784. REPRINTED WITH PERMISSION.

### What is the clinical picture and family history?

Naturally, the above information needs to be analyzed in the context of the larger clinical picture (TABLE 1). Specifically, is there a history of syncope or ill-defined seizure disorder? Convulsive syncope due to polymorphic ventricular tachycardia from QT prolongation is sometimes misinterpreted as a seizure. Are family members similarly affected, or is there a history of sudden death in the family?

### What are event triggers?

When symptoms or events are identified, it is often illuminating to discern the circumstanc-

es surrounding the events, with attention to possible triggers. Clearly, when events are associated with swimming or loud noises or startling situations, the clinical likelihood of long QT syndrome increases dramatically. In the absence of a positive genotype, the diagnosis is often measured in probabilities (TABLE 1). If a patient has been genotyped as positive, then he or she is called "genotypically affected"; the phenotype depends on whether the QTc is prolonged, but beta-blockade is advisable in genotype-positive patients regardless.

### Could it be another repolarization abnormality?

Finally, one needs to be vigilant for other repolarization abnormalities, such as those seen in the Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, or even short QT syndrome, as well as normal variants. While the diagnosis of these disorders is beyond the scope of this review, they are seen in a similar demographic group and have similar symptoms. Short QT syndrome is due to a gain of function of one of the potassium channels, the opposite of what is seen in long QT syndrome. Also, whereas LQT3 is caused by a gain of function of the sodium channel (SCN5A), the opposite functional change in the sodium channel (ie, a loss of function) produces Brugada syndrome (or conduction system disease).

**In one study, QTc > 500 ms was the most powerful predictor of events**

## STRATIFYING THE RISK OF AN EVENT

Once the diagnosis has been made, the next objective is to determine the patient's risk of a serious arrhythmic event, information that helps in choosing one therapeutic alternative over another.

Several studies have analyzed the differing clinical courses of the three main phenotypes. In 1998, Zareba and colleagues[37] published an analysis of cardiac events among 541 genotyped patients from the international long QT registry. Included were 112 patients with LQT1, 72 with LQT2, and 62 with LQT3. The authors evaluated several factors, including the likelihood of having an event (syncope, cardiac arrest, or sudden death) before age 40, the influence of gender and QTc on the event rate, and the lethality of events. Although the likelihood of an event was significantly higher with LQT1 and LQT2, the death rate from the events was essentially the same across all three groups, reflecting the higher likelihood of fatal events in those with LQT3. Furthermore, within each genotype, the longer the QTc, the greater the event rate.[37] These findings underscore the heterogeneity of long QT syndrome and the need to consider factors such as genotype (when available) and QTc when making clinical decisions.

In 2003, Priori et al[38] revisited the issue of risk stratification, this time looking at 647 patients drawn from 196 families genotyped with long QT syndrome and followed for a mean of 28 years.[38] They evaluated the influence of QTc, genotype, and gender on the risk of a first long-QT-related event occurring before age 40. Without therapy, by age 40, 13% of patients had died suddenly or had had a cardiac arrest, thus defining the "natural history" of the disease. A QTc longer than 500 ms was the single most powerful predictor of events. Also, in those with LQT2, females fared worse than their male counterparts, while the opposite was true in the cohort with LQT3, and no sex bias was observed in the cohort with LQT1.[38] Unlike the situation in the study of Zareba et al, events in patients with LQT3 were not more likely to be lethal.

### 'Silent carriers'

Another finding of the study[38] was that the cohort with LQT1 had a 36% prevalence of a "silent carrier" state, ie, having a mutation but a normal QTc. Although the risk of events was lower in silent carriers, it was not zero. This underscores the importance of genetic screening of family members of symptomatic individuals, even if the family members have normal electrocardiograms.

### A risk stratification scheme

Priori et al[38] proposed a risk stratification scheme to aid in clinical decision-making, emphasizing the high risk of events, including death, associated with a QTc greater than 500 ms in LQT1 or LQT2, as well as in males with LQT3. TABLE 2 incorporates data from these and other studies into a novel risk-stratification scheme.[3,37–40]

In a recent study in 812 adults ages 18 to

40 who had long QT syndrome mutations,[41] predictors of life-threatening events including aborted cardiac arrest or death due to QT prolongation included female sex (males had many fewer events after age 18), a QTc interval exceeding 500 ms, and recent syncopal events. Adults with LQT2 had more events when syncope was included. Beta-blockers reduced the rate of aborted cardiac arrest or death by 60%.

## THERAPEUTIC CONSIDERATIONS

### Beta-blocker therapy

In 2000, Shimizu and Antzelevitch[17] studied the effects of beta-adrenergic agonists and antagonists in an experimental model of LQT1, LQT2, and LQT3. The transmural dispersion of refractoriness was indeed increased by beta-agonists in LQT1 and LQT2, whereas it was actually reduced in LQT3. This finding was not entirely unexpected, based on the underlying defect in each subtype; it was also in keeping with the clinical observation of the increased event rate with activity or emotional triggers in LQT1 and LQT2, as opposed to the predisposition for events at rest in LQT3.

A retrospective analysis of the international registry[3] found that beta-blockers reduced the overall rate of cardiac events by 68% in probands and 42% in affected family members. Unfortunately, patients who had an event before they started beta-blocker therapy still faced a 32% chance of another event over the next 5 years while on therapy (including a 5% risk of cardiac arrest); in patients who had a history of aborted cardiac arrest, the rate of recurrent arrest on therapy was 14% over the same period. Furthermore, only patients with LQT1 or LQT2 benefitted from beta-blockers.

A subsequent analysis that included only adults showed a 60% reduction in the event rate with beta-blockade.[41] The influence of the type and the dose of beta-blocker on prognosis has not been conclusively proven, but experience is greatest with propranolol (Inderal) and nadolol (Corgard).

### Implantable cardioverter-defibrillators

Given the incomplete effectiveness of beta-blockers in preventing sudden death in long QT syndrome, implanting a cardioverter-defibrillator may be appropriate in some patients.[42]

In 2003, Zareba et al[40] published a retrospective analysis of cardioverter-defibrillator implantation in 125 patients with long QT syndrome who had an aborted cardiac arrest while taking a beta-blocker. These patients were compared with a group of patients with long QT syndrome who also experienced aborted cardiac arrest while on beta-blockers but who did not receive a cardioverter-defibrillator. In 3 years, 2% of those with cardioverter-defibrillators died, compared with 9% in the medically treated group.

Additional studies have corroborated the effectiveness of implantable cardioverter-defibrillators, including in children.[43,44]

**An analysis of the international registry showed a 60% reduction in event rate in adults on beta-blockers**

### Sympathetic denervation

Given the early observations of events during times of increased adrenergic tone, removal of sympathetic input to the heart via left cervical-thoracic sympathetic denervation (ganglionectomy) has been used as a means of preventing events in patients with long QT syndrome.[45] However, this therapy is not widely available and is used mainly in young children, in patients with Jervell and Lange-Nielsen syndrome, and in patients who re-

**TABLE 2**

**Risk stratification in long QT syndrome**

**Highest risk**
Prior cardiac arrest
Syncope with exertion/emotion on beta-blockade
Recent syncope and QTc > 500 ms (on or off beta-blockade)
Jervell and Lange-Nielsen syndrome

**High risk**
Asymptomatic, LQT2 or LQT3 and QTc > 500 ms
LQT2 and female sex
LQT2 and pore region mutation

**Intermediate risk**
Prior syncope (other than above)
Asymptomatic, LQT1 and QTc > 500 ms on beta-blocker therapy
Other groups or combinations

**Lower risk**
Asymptomatic, QTc < 500 ms
LQT1, age > 30 (no recent syncope), on beta-blocker therapy

ceive frequent implantable cardioverter-defibrillator shocks who are taking beta-blockers.

### Flecainide, mexiletine, oral potassium

As mentioned above, flecainide and mexiletine, which inhibit the late sodium current, have been suggested as beneficial, but these trials are ongoing, and therapy with these agents is not recommended at this time.[21]

Potassium supplementation, either directly or via spironolactone (Aldactone), is also being studied, especially for LQT1 and LQT2.

## PREGNANCY AND LONG QT SYNDROME

As we have shown, the molecular heterogeneity of long QT syndrome can make it both a diagnostic and a therapeutic challenge under the best of circumstances, and this is even more so in pregnancy.

Relatively little has been published about the natural history of long QT syndrome in pregnancy. One retrospective study[22] included 422 women from the international registry who had had at least one pregnancy: 111 probands and 311 first-degree relatives. The first-degree relatives were further classified as "affected," "borderline," or "unaffected" on the basis of their QTc. The primary end point was the occurrence of long-QT-related death, aborted cardiac arrest, or syncope.

**The cause of the clustering of events postpartum is not known**

Events were markedly more frequent in the 40 weeks after delivery than during the 40 weeks of pregnancy or the 40 weeks immediately preceding pregnancy. Other notable findings were that beta-blockers dramatically reduced the event rate and that events were rare in first-degree relatives classified as borderline or unaffected.

The exact cause of the clustering of events in the postpartum period is unknown. While it is tempting to invoke the relative bradycardia of the postpartum period or perhaps the hormonal influence on the sympathetic drive, this remains speculative. Other recent data confirm that the postpartum period is a time of high risk, suggest that women with LQT2 are at higher risk than those with LQT1, and substantiate that beta-blocker therapy is indicated and safe during pregnancy.[46–48]

## DRUGS TO AVOID

The list of drugs that prolong the QT interval is already quite long and seems to grow daily. Generally, drugs that block the rapid component of the delayed rectifier potassium channel (IKr) are the offenders; this is, essentially, an iatrogenic form of LQT2. Examples include macrolide antibiotics (eg, erythromycin), phenothiazine antipsychotics (including some antiemetics), and class III antiarrhythmics. Also to be avoided are sympathomimetics.

While the propensity of erythromycin or droperidol (Inapsine) to prolong the QT interval is well known, lesser-known offenders such as methadone (Dolophine) are often involved in clinically significant arrhythmic events.[49] Often, a second drug delaying the metabolism or excretion of another drug is responsible.

Keeping abreast of all the drugs that prolong the QT interval can be challenging, but fortunately, several excellent resources are available, including two user-friendly databases, **www.torsades.org** and **www.long-qt-syndrome.com**. In addition, for use at the point of care, most PDA or pocket drug databases provide similar information. As a general rule, the agents listed in these sources are safe for use in the general population but greatly increase the risk of arrhythmia in patients with long QT syndrome.

When choosing an agent and weighing its arrhythmic risk, one should be mindful of its therapeutic window, its metabolism and excretion pathways, and its interactions. A narrow therapeutic window poses a potential problem in and of itself: when a drug with a narrow therapeutic window also has only one means of metabolism or elimination, the risk of adverse events is considerably magnified. Drug-drug interactions are especially relevant with antiarrhythmic agents; in such cases it is advisable to consult with a cardiologist or electrophysiologist.

## EMOTIONAL AND PSYCHOLOGICAL ASPECTS AND RESOURCES

The diagnosis of long QT syndrome nearly always has a large emotional and psychologic impact on the patient and family and entails the need the need for emotional adjustment,

**TABLE 3**

**Recommendations for genetic testing in long QT syndrome**

| TEST | RECOMMENDATION |
|---|---|
| **Comprehensive genetic testing for long QT syndrome** | |
| Proband with definite long QT syndrome | Definitely indicated |
| Proband with probable long QT syndrome | Probably indicated |
| Family member with previously identified familial mutation | Not indicated (See below) |
| **Targeted genetic testing for previously identified familial mutation** | |
| Family member with borderline-long corrected QT interval (QTc) | Definitely indicated |
| Family member with QTc > 480 ms | Possibly indicated |
| Family member with QTc < 430 ms | Probably indicated |

perhaps requiring counseling. The patient's or family's fear of sudden death on learning of the diagnosis is obvious. If the diagnosis in the family was made after a family member died, the other members may have guilt about their survival and about not having pushed health care providers for a diagnosis earlier. Parents can feel emotional trauma and guilt about transmitting the mutation to a child.

A recommendation to quit a sport, which may have been one of the patient's favorite activities or a source of identity, is often one of the hardest adjustments patients and families face. Patients and their physicians can find information and support from the Cardiac Arrhythmias Research and Education Foundation (**www.longqt.org**) and the Sudden Arrhythmia Death Syndromes Foundation (**www.sads.org**).

## GENERAL TIPS

Congenital long QT syndrome should be suspected when the electrocardiogram shows the characteristic QT abnormalities or when there is a history of syncope or ill-defined "seizures" in the patient or in the patient's family.

Because of the heterogeneity of the syndrome, genotyping is often useful in making therapeutic decisions. (See TABLE 3 for recommendations on who should undergo genetic testing.) Examples are the avoidance of alarm clocks in bedrooms of patients with LQT2 and the restriction of physical activity (particularly swimming) in those with LQT1.

As a general rule, beta-blockers are advised for probands and affected family members. When patients on beta-blocker therapy experience further syncope or aborted cardiac arrest, implantation of a cardioverter-defibrillator is appropriate. These devices carry concerns, such as infection or fracture of the leads and the lifelong need for generator changes; therefore, they should be reserved only for those patients at high risk. In a selected few, left cervical-thoracic sympathetic denervation may be appropriate as well.

## REFERENCES


1. **Vincent MG**. Long QT syndrome. Cardiol Clin 2000; 18:309–325.
2. **Quaglini S, Rognoni C, Spazzolini C, Priori SG, Mannarino S, Schwartz PJ**. Cost-effectiveness of neonatal ECG screening for the long QT syndrome. Eur Heart J 2006; 27:1824–1832.
3. **Moss AJ, Zareba W, Hall WJ, et al**. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. Circulation 2000; 101:616–623.
4. **Schwartz P, Periti M, Malliani A**. The long Q-T syndrome. Am Heart J 1975; 89:378–390.
5. **Priori SG, Napolitano C, Schwartz PJ, et al**. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA 2004; 292:1341–1344.
6. **Jervell A, Lange-Neilsen F**. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J 1957; 54:59–68.
7. **Moss AJ, Schwartz PJ**. 25th anniversary of the International Long QT Syndrome Registry: an ongoing quest to uncover the secrets of long QT syndrome. Circulation 2005; 111:1199–1201.
8. **Roden DM, Viswanathan PC**. Genetics of acquired long QT syndrome. J Clin Invest 2005; 115:2025–2032.
9. **Romano C, Gemme G, Pongiglione R**. Aritmie cardiache rare in età pediatrica. Clin Pediatr 1963; 45:656–683.
10. **Ward O**. A new familial cardiac syndrome in children. J Ir Med Assoc 1964; 54:103–106.
11. **Napolitano C, Priori SG, Schwartz PJ, et al**. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. JAMA 2005; 294:2975–2980.
12. **Zareba W**. Genotype-specific ECG patterns in the long QT syndrome. J Electrocardiol 2006; 39:S101–S106.

13. **Modell SM, Lehmann MH**. The long QT syndrome family of cardiac ion channelopathies: A HuGE review. Genet Med 2006; 8:143–155.
14. **Antzelevitch C, Shimizu W**. Cellular mechanisms underlying the long QT syndrome. Curr Opin Cardiol 2002; 17:43–51.
15. **Schwartz PJ, Priori SG, Spazzolini C, et al**. Genotype-phenotype correlations in the long QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001; 103:89–95.
16. **Zygmunt AC**. Intracellular calcium activates chloride current in canine ventricular myocytes. Am J Physiol 1994; 267:1984–1995.
17. **Shimizu W, Antzelevitch C**. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2, and LQT3 models of the long QT syndrome. J Am Coll Cardiol 2000; 35:778–786.
18. **Wilde AAM, Jongbloed RJE, Doevendans PA, et al**. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQT2) from KVLQT1-related patients (LQT1). J Am Coll Cardiol 1999; 33:327–332.
19. **Shimizu W, Noda T, Takaki H, et al**. Diagnostic value of epinephrine test for genotyping LQT1, LQT2, and LQT3 forms of congenital long QT syndrome. Heart Rhythm 2004; 3:276–283.
20. **Van den Berg MP, Wilde AA, Viersma TJW, et al**. Possible bradycardiac mode of death and successful pacemaker treatment in a large family with features of long QT syndrome type 3 and Brugada syndrome. J Cardiovasc Electrophysiol 2001; 12:630–636.
21. **Moss AJ, Windle JR, Hall WJ, et al**. Safety and efficacy of flecainide in subjects with long QT-3 syndrome (delta-KPQ mutation): a randomized, double-blind, placebo-controlled clinical trial. Ann Noninvasive Electrocardiol 2005; 10(suppl 4):59–66.
22. **Rashba EJ, Zareba W, Moss AJ, et al**. Influence of pregnancy on the risk for cardiac events in patients with long QT syndrome. Circulation 1998; 97:451–456.
23. **Goldenberg I, Moss AJ, Zareba W**. QT interval: how to measure it and what is "normal." J Cardiovasc Electrophysiol 2006; 17:333–336.
24. **Moss AJ**. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. Am J Cardiol 1993; 72:23B–25B.
25. **Jouven X, Hagege A, Charron P, et al**. Relation between QT duration and maximal wall thickness in familial hypertrophic cardiomyopathy. Heart 2002; 88:153–157.
26. **Kenigsberg DN, Khanal S, Kowalski M, Krishnan SC**. Prolongation of the QTc interval is seen uniformly during early transmural ischemia. J Am Coll Cardiol 2007; 49:1299–1305.
27. **Halkin A, Roth A, Lurie I, Fish R, Belhassen B, Viskin S**. Pause-dependent torsade de pointes following acute myocardial infarction: a variant of the acquired long QT syndrome. J Am Coll Cardiol 2001; 38:1168–1174.
28. **Tomaselli GF, Zipes DP**. What causes sudden death in heart failure? Circ Res 2004; 95:754–763.
29. **Roden DM, Viswanathan PC**. Genetics of acquired long QT syndrome. J Clin Invest 2005; 115:2025–2032.
30. **Taggart NW, Haglund CM, Tester DJ, Ackerman MJ**. Diagnostic miscues in congenital long-QT syndrome. Circulation 2007; 115:2613–2620.
31. **Vetter VL**. Clues or miscues? How to make the right interpretation and correctly diagnose long-QT syndrome. Circulation 2007; 115:2595–2598.
32. **Mason JW, Hancock EW, Gettes LS**. Recommendations for the standardization and interpretation of the electrocardiogram: part II: electrocardiography diagnostic statement list: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: Endorsed by the International Society for Computerized Electrocardiology. Circulation 2007; 115:1325–1332.
33. **Viskin S**. Drug challenge with epinephrine or isoproterenol for diagnosing a long QT syndrome: should we try this at home? J Cardiovasc Electrophysiol 2005; 16:285–287.
34. **Schwartz PJ**. The long QT syndrome. In: Kulbertus HE, Wellens HJJ, editors. Sudden Death. The Hague: Martinus Nijhoff, 1980:358–378.
35. **Moss AJ, Zareba W, Benhorin J, et al**. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation 1995; 92:2929–2934.
36. **Vyas H, Hejlik J, Ackerman MJ**. Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. Circulation 2006; 113:1385–1392.
37. **Zareba W, Moss AJ, Schwartz PJ, et al**. Influence of the genotype on the clinical course of the long QT syndrome. N Engl J Med 1998; 339:960–965.
38. **Priori SG, Schwartz PJ, Napolitano C, et al**. Risk stratification in the long QT syndrome. N Engl J Med 2003; 348:1866–1874.
39. **Schwartz PJ, Moss AJ, Vincent GM, Crampton RS**. Diagnostic criteria for the long QT syndrome. An update. Circulation 1993; 88:782–784.
40. **Zareba W, Moss AJ, Daubert JP, et al**. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. J Cardiovasc Electrophysiol 2003; 14:337–341.
41. **Sauer AJ, Moss AJ, McNitt S, et al**. Long QT syndrome in adults. J Am Coll Cardiol 2007; 49:329–337.
42. **Daubert JP, Zareba W, Rosero SZ, Budzikowski A, Robinson JL, Moss AJ**. Role of implantable cardioverter defibrillator therapy in patients with long QT syndrome. Am Heart J 2007; 153:53–58.
43. **Groh WJ, Silka MJ, Oliver RP, Halperin BD, McAnulty JH, Kron J**. Use of implantable cardioverter-defibrillators in the congenital long QT syndrome. Am J Cardiol 1996; 78:703–706.
44. **Silka MJ, Kron J, Dunnigan A, Dick M, 2nd**. Sudden cardiac death and the use of implantable cardioverter-defibrillators in pediatric patients. The Pediatric Electrophysiology Society. Circulation 1993; 87:800–807.
45. **Moss A, McDonald J**. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. N Engl J Med 1971; 285:903–904.
46. **Heradien MJ, Goosen A, Crotti L, et al**. Does pregnancy increase cardiac risk for LQT1 patients with the KCNQ1-A341V mutation? J Am Coll Cardiol 2006; 48:1410–1415.
47. **Khositseth A, Tester DJ, Will ML, Bell CM, Ackerman MJ**. Identification of a common genetic substrate underlying postpartum cardiac events in congenital long QT syndrome. Heart Rhythm 2004; 1:60–64.
48. **Seth R, Moss AJ, McNitt S, et al**. Long QT syndrome and pregnancy. J Am Coll Cardiol 2007; 49:1092–1098.
49. **Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS**. Torsade de pointes associated with very-high-dose methadone. Ann Intern Med 2002; 137:501–504.


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