

LPCH Stanford children's Hospital guidelines for peri-operative management of patients with congenital long QT syndrome:

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What is long QT Syndrome?

Long QT syndrome (LQTS) is a cardiac conduction disorder characterized by a prolonged dispersion of ventricular repolarization. This is manifest by a prolonged QTc interval on surface ECG defined as > 460ms for females and > 450ms for males. This abnormal repolarization results in an increased risk of ventricular arrhythmias such as ventricular tachycardia (VT), torsade de pointes (TdP), or ventricular fibrillation (VF) that can present as syncope, seizures, or sudden cardiac death.

LQTS can be congenital or acquired. Drug induced LQTS is the most common cause of acquired LQTS and will not be discussed here. There are currently 15 known subtypes of congenital LQTS, although this is constantly being updated. LQTS types 1, 2 and 3 account for approximately 90% of the genotype positive patients and LQTS type 1. In general, sympathetic/adrenergic stimulation is thought to be a trigger for ventricular arrhythmias in all LQTS patients, however, there are some activity/environmental triggers thought to be more specific for each of the 3 main types of LQTS. For example, exercise, diving/swimming, and emotional stress are triggers more specific for LQTS type 1. Sudden loud noises, startling, and fear are triggers more specific for LQTS type 2. Lastly, pause dependent ventricular arrhythmias during sleep occurs most often in LQTS type 3.

Treatment of congenital LQTS:

All patients who are gene positive for LQTS or have been clinically diagnosed (but gene negative) with LQTS receive beta blockade as first line therapy. Approximately 25% of patients with clinical LQTS have negative genetic testing as all of the genetic mutations that cause LQTS are not yet known.

While beta blocker therapy is the first line therapy for all patients with LQTS, there is also some evidence to suggest other therapies targeted for specific genotypes. For example, LQTS type 1 is due to a mutation in the KCNQ1 gene. Studies show that beta blockade is extremely effective for reducing the risk of ventricular arrhythmias in LQTS type 1 but less effective in LQTS type 2. LQTS type 2 is due to a mutation in KCNH2 (HERG) channel. LQTS type 3 is due to a gain of function mutation in the SCN5A channel and therefore Mexiletine (a sodium channel blocker) has been used with some benefit.

In patients who have had a sudden cardiac arrest or who have syncope or ventricular arrhythmias despite beta blocker therapy, an Internal Cardioverter Defibrillator (ICD) is placed. Left cardiac sympathetic denervation (LCSD) is recommended for patients in whom an ICD is warranted but refused or contraindicated and/or beta-blockers are either not effective in preventing syncope/arrhythmias, not tolerated, not accepted or contraindicated. Some patients

with LQTS 3 will have an ICD placed for primary prevention because they fall into a higher-risk group.

Aside from anti-arrhythmic therapy, the treatment of congenital LQTS involves lifestyle modifications such as avoiding competitive sports and other known triggers. In addition, patients with LQTS should avoid other drugs that are known to prolong the QT interval.

The CredibleMeds® website reviews all the available evidence has compiled a list of drugs in four categories based on their relative risk of causing TdP in a patient with congenital LQTS. There are over 200 medications on the “Drugs to Avoid (DTA)” list and this list is constantly being updated as new evidence arises. To help physicians interpret evidence for risk of TdP, they have developed the following categories (See Figure 1)

1. **Known risk of TdP:** These drugs prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended. These drugs should only rarely, if ever, be given to patients with congenital LQTS because their risk of TdP is substantial. However, when a safe alternative is not available, and the illness is severe, some physicians with expertise in the treatment of arrhythmias may prescribe these drugs.
2. **Possible Risk of TdP:** These drugs can cause QT prolongation and could theoretically be dangerous in some patients with congenital LQTS. However, there is currently lack of evidence for a risk of TdP when taken as

- recommended and therefore if a drug is medically necessary, it may be prescribed by a medical specialist.
3. **Conditional Risk of TdP:** These drugs are associated with TdP BUT only under certain conditions of their use (e.g. excessive dose, in a patient with conditions such as hypokalemia, or when taken with interacting drugs) OR by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT prolonging drug or by causing an electrolyte disturbance that induces TdP). These drugs can be prescribed safely for most patients with congenital LQTS because each drug's risk is confined to certain conditions. Prescribing physicians should be aware of these conditions before prescribing these medications.
 4. **Congenital LQTS Risk:** These drugs have a theoretical risk of causing arrhythmias in some congenital LQTS patients because they have adrenaline-like effects. However, many of these medications are required for treatment of asthma, ADHD, or nasal congestion. Physicians with expertise in the treatment of arrhythmias may prescribe these medications to carefully selected congenital LQTS patients.

Please refer to the following website for more information:

<https://www.crediblemeds.org>

[Figure 1: Categories of Drugs to Avoid in congenital LQTS](#)

Known Risk

 These drugs should only rarely, if ever, be given to patients with CLQTS because their risk of TdP is substantial. However, when a safe alternative is not available and the illness is severe, some physicians with expertise in the treatment of arrhythmias may prescribe these drugs.

Possible Risk

 These drugs increase QT intervals in some patients and for that reason could theoretically be dangerous in some patients with CLQTS. However, if a drug is medically necessary, it may be prescribed by medical specialists for patients with CLQTS.

Conditional Risk

 These drugs can be prescribed safely for most patients with CLQTS because each drug's risk is confined to certain conditions, e.g. drug overdose, excessive duration of treatment, use with diuretics or drugs that block their elimination, or patients with other risk factors. Patients with CLQTS should be aware of these conditions before taking these medicines.

cLQTS Risk

 These drugs have a theoretical risk of causing arrhythmias in some CLQTS patients because the drugs have adrenaline-like effects. However, many of these medicines are required for treatment of asthma, ADHD or nasal congestion. Physicians with expertise in the treatment of arrhythmias may prescribe these medicines to carefully selected patients with CLQTS.

It is important to remember that some of the categorization may be the result of 1 or 2 case reports or adverse events. The reported events may have had confounding factors such as synergistic use of higher risk medications or times of increased sympathetic stimulation such as emergence from anesthesia. It is prudent to minimize exposure to combinations of drugs with any degree of QT prolong effect, where individual effects on repolarization may be minor and clinically insignificant but the combination may have a deleterious impact.

Anesthesia/Perioperative medications and congenital LQTS:

Measuring QTc prolongation is the traditional method for assessing and quantifying

a drug's impact on electrical repolarization. For example, all volatile agents prolong the QTc interval whereas IV propofol has clinically insignificant effects on the QTc in healthy children (REF). Some experts question whether QTc is a reliable metric for assessing a drug's propensity to induce torsade de pointe as the degree of QTc prolongation may not adequately predict the risk for TdP. An exaggerated transmural dispersion of repolarization (TDR) is thought to be the electrophysiological substrate for torsade de pointe and some experts believe this can be measured on surface ECG as the interval between the peak and end of the T wave (Tp-e). Studies of sevoflurane and propofol in healthy children have demonstrated no increase in Tp-e, which may suggest that neither is torsadogenic. However, since Sevoflurane does markedly prolong the QT interval, the clinical implications of translating results from healthy children to those with LQTS remains unclear. The following is a review of the most commonly used anesthetics and peri-operative medications used.

Volatile anesthetics: All Halogenated volatile agents can prolong the QT interval. Sevoflurane has the most significant effect on QT prolongation and Sevoflurane maintenance has been implicated in a few case reports of ventricular arrhythmias. Sevoflurane has been listed on the crediblemeds.org website as a drug to be avoided in congenital LQTS and is categorized as Known TdP Risk. Isoflurane has been used safely in patients with congenital LQTS and is not listed on the drugs to be avoided on crediblemeds.org.

Ketamine: Has been used safely in the past as a premedication in patients with undiagnosed congenital LQTS. There is a theoretical potential for its sympathomimetic properties to induce TdP but it is NOT currently listed as a drug to be avoided in congenital LQTS on the CredibleMeds® website.

Propofol: Data on QT prolongation is conflicting. Some data shows that Propofol can rapidly reverse QTc prolongation induced by Sevoflurane in healthy patients. However, the CredibleMeds® website has listed Propofol as a drug to be avoided in congenital LQTS and has categorized it as a drug with Known TdP Risk.

Etomidate: Does not affect the rate of ventricular repolarization but a study did show that etomidate prolongs QTc more than propofol in patients undergoing electroconvulsive therapy. It is NOT currently listed as a drug to be avoided in congenital LQTS on the CredibleMeds® website.

Midazolam: Does not modify QTc or the transmural dispersion rate and is considered a safe medication for patients with congenital LQTS. Recommended for pre-operative anxiolysis.

Opioids: Remifentanyl, Alfentanil, Fentanyl and morphine are considered safe in patients with congenital LQTS. Alfentanil has been shown to reverse QT prolongation seen with Suxamethonium during tracheal intubation.

Muscle Relaxation: Suxamethonium should be used with caution since it may prolong QT interval in patients with congenital LQTS or induce a vagal response, which may result in pause dependent TdP. Suxamethonium is NOT currently listed on the CredibleMeds® website. Vecuronium, Atracurium and Cisatracurium do not prolong QTc and can be safely used. Pancuronium should be avoided because of its vagolytic properties and its causal association with VF in a case report, although it is currently NOT listed on the CredibleMeds® website. Rocuronium can also sometimes cause tachycardia and should be avoided if possible, although it is currently NOT listed on the CredibleMeds® website.

Dexmedetomidine: Current evidence for Dexmedetomidine and QT prolongation is limited and conflicting. However, the CredibleMeds® website has listed Dexmedetomidine as a drug to be avoided in congenital LQTS and has categorized it as a drug with Possible risk of TdP.

Anticholinesterase: Administering anticholinergic agents such as atropine and Glycopyrrolate and the resulting tachycardia due to unbalanced sympathetic stimulation may increase the risk for ventricular arrhythmias. However, none of the muscarinic anticholinergic agents or anticholinesterases are listed as drugs to be avoided in congenital LQTS.

Sympathomimetics: Dopamine, Epinephrine, Phenylephrine and Ephedrine are known to cause TdP and are listed on the CredibleMeds® website as drugs to be

avoided in congenital LQTS. They are categorized as Known TdP Risk. Vasopressin is one of the only peripheral vasoconstrictor medications that is considered safe in congenital LQTS and is NOT listed on the CredibleMeds® website.

Anti-emetics: Ondansetron and droperidol are known prolong the QTc and are known to cause TdP. They should definitely be avoided in patients with congenital LQTS. They are listed on the CredibleMeds® website as drugs to be avoided in congenital LQTS and are categorized as Known TdP Risk.

LPCH PERI-OPERATIVE MANAGEMENT GUIDELINES:

There are no published guidelines for optimal peri-operative management of patients with congenital LQTS. As with many pediatric diseases, there remains a lack of a robust evidence to support one particular practice guideline. Current data on the effects of anesthetic and peri-operative medications in patients with congenital LQTS consists of case reports, small case series and retrospective reviews with differing outcomes. Although the true risk of peri-operative arrhythmias is hard to quantify, significant morbidity and mortality has been reported under general anesthesia especially in those with undiagnosed or untreated congenital LQTS. After reviewing the current literature, we have written this document to serve as a guide to peri-operative management of patients with congenital long QT syndrome at Lucile Packard Children's Hospital at Stanford (LPCH).

Pre-operative assessment:

History and physical examination:

In addition to standard pre-operative history and physical exam, any patient with congenital LQTS should be asked specifically about symptom control with current medication regimen (palpitations, dizziness, syncope), compliance with medication and any concerning new symptoms such as fatigue, poor exercise tolerance, nightmares, seizures, pre-syncope or syncope. Any identified new symptoms warrant a pre-operative discussion with the patient's cardiologist or LPCH Electrophysiologist.

Investigations:

1. Look for notes from most recent cardiology clinic visit. If they have not been seen by their primary cardiologist or electrophysiologist within the last year, they should have a clinical evaluation by their primary cardiologist or electrophysiologist before any elective procedure. If they are having an urgent/emergent procedure that should not be delayed, consultation by phone with their primary cardiologist or electrophysiologist is warranted. Their evaluations typically include an ECG, ambulatory heart rhythm monitor, and possibly an exercise stress test depending on their age.
2. Recent ECG (within 3 months of procedure if well controlled)- look for resting HR and QTc interval.
3. Recent electrolytes: K and Mg should be normalized.

Medications:

It is essential to continue anti-arrhythmic drug therapy including on the day of surgery. Patients on B -Blocker therapy may be at increased risk of hypoglycemia and should have blood sugar monitored during the peri-operative period.

Avoid peri-operative physiological and metabolic stressors of myocardial repolarization reserve such as pain, fear, dehydration, hypothermia and electrolyte disturbance.

HIGH Risk Congenital Long QT Patients:

Patients who satisfy ANY of the following criteria:

1. Anyone presenting with new symptoms (syncope, palpitations) that have not yet been adequately evaluated or treated
2. QT interval >500ms
3. Any patient with Long QT and an ICD
4. Timothy syndrome (LQT 8)

A dedicated pediatric cardiac anesthesiologist or an anesthesiologist who has completed advanced training in pediatric cardiac anesthesia should care for patients who have been identified as falling into a high-risk group. A general pediatric anesthesiologist can care for all other congenital Long QT patients.

Induction of anesthesia:

Although IV induction is preferable, the anesthesiologist should consider minimizing pre-operative stress and anxiety.

1. Midazolam premedication is safe and effective.
2. ECG monitoring- recommend trending QTc preoperatively, throughout procedure and post-operative
3. If placement of pre-op IV is thought to be problematic and may cause undue stress to the patient brief periods of sevoflurane induction has been reported in the literature as being safely used without adverse effect **until an IV can be placed.**
4. Both intubation and extubation may trigger ventricular arrhythmias.

Consider topical anesthesia with lidocaine for intubation supplemented with

- an opioid to minimize adrenergic surges. Intravenous B Blocker may also be considered prior to intubation or extubation. It is prudent to avoid high inspiratory pressure peaks and wide inspiratory/expiratory ratios since the Valsalva maneuver may also prolong the QTc.
5. A defibrillator and staff trained in its' use should be readily available during the peri-operative period.

Maintenance of anesthesia:

1. If using a volatile agent, isoflurane is the preferred agent.
2. Opioids may be used safely.
3. Caution with propofol (CredibleMeds® website has listed Propofol as a drug to be avoided in congenital LQTS and has categorized it as a drug with Known TdP Risk) and dexmedetomidine (CredibleMeds® website has listed Dexmedetomidine as a drug to be avoided in congenital LQTS and has categorized it as a drug with Possible risk of TdP).
4. Cis-atracurium or Vecuronium is the preferred NMB agent. Caution with reversal agents. Consider deep extubation if appropriate.
5. Monitor blood sugar.

EMERGENCY MEDICATIONS

Arrhythmias:

1. Esmolol 250-500 mcg/kg IV bolus, 25 mcg/kg/min infusion titrate every 10-15 min up to 250 mcg

2. Magnesium 25-50 mg/kg slow IV bolus
3. Lidocaine 1 mg/kg IV bolus, then 25 mcg/kg/min infusion

Do NOT use amiodarone for arrhythmias in congenital Long QT syndrome as this will further prolong the QT interval.

For Ventricular Fibrillation Arrest – CPR and Defibrillation as soon as possible.

Esmolol, Lidocaine, and Magnesium preferred anti-arrhythmic agents as amiodarone and epinephrine will further prolong QTc and worsen arrhythmias

Hypotension:

1. IV fluid bolus
 2. Vasopressin is safe and the preferred vasoconstrictor medication
- Drugs that are **contraindicated** for routine hypotension - phenylephrine, ephedrine, epinephrine and Dopamine.

Regional anesthesia:

Local anesthetics without epinephrine

Post-operative care:

Post-operative disposition will depend on the patient's condition and the procedure performed. We recommend post-operative hospital admission with telemetric monitoring in an intensive care unit for patients with high risk congenital long QT.