Congenital Long-QT Syndromes
Who’s at Risk for Sudden Cardiac Death?

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The congenital long-QT syndromes (LQTS) were initially described approximately 50 years ago. The principal events are syncope, seizures, and ventricular tachycardia, characteristically torsade de pointes. Most often, this arrhythmia is self-terminating, producing a syncopal episode; however, LQTS is responsible for a significant proportion of sudden cardiac deaths (SCDs) in young people without structural heart disease, estimated to have an incidence of approximately 1 in 2500 and causing thousands of deaths annually. Characteristic ECG signs of LQTS include QT-interval prolongation and T-wave abnormalities. The heart rate–corrected QT interval (QTc) can range from 370 to >700 ms, clearly overlapping that of normal individuals, and a single ECG may not manifest the stereotypical features. Some patients have a normal or borderline QTc at rest but prolongation with exertion or β-adrenergic stimulation. Provocative testing with exercise or catecholamine infusion may improve the sensitivity of LQTS clinical detection. The inciting triggers are somewhat mutation-specific. Patients with potassium channel mutations typically have episodes during physical or emotional stress, whereas those with sodium channel defects have more events with bradycardia and during sleep. Symptoms, including syncope or SCD, can manifest anytime from the neonatal period to adulthood. Because risk stratification is still being refined, it is often recommended that most LQTS patients be treated with β-adrenergic blocking medications, but a diagnostic challenge is deciding who needs more specific or aggressive therapies. Interventions for LQTS include implantation of a permanent pacemaker or implantable cardioverter defibrillator (ICD), as well as consideration of left cardiac sympathetic denervation. If interventional therapy is warranted, what procedures are right for which patients, and when is the optimal time to intervene? The competing risks of the disease versus potential complications from the procedures or devices often increase the complexity of the clinical decision-making rationale.

Over the past few decades, the International Long-QT Syndrome Registry has been enormously successful in prospectively enrolling many LQTS families from multiple countries. From this effort, several important findings have been reported, including the impact of age, gender, and genotype on outcomes in this large collection of LQTS patients. The International LQTS Registry has attempted to hone risk stratification by dividing its patient cohort into discrete age groups and has recently reported findings for adolescent and young adult patients. In the current issue of Circulation, Goldenberg and colleagues from the International LQTS Registry now separately report the findings from the youngest age cohort (children <13 years old) and the oldest age cohort (adults >40 years old).

LQTS Risk Stratification in Children
In the present report about LQTS in children, the authors have reviewed data submitted from contributing centers on >3000 children who were enrolled before their teenage years, focusing predominantly on fatal or near-fatal events. They identified clinical risk factors of marked QTc prolongation (>500 ms) in boys and syncope in both boys and girls to be significant predictors of aborted cardiac arrest or SCD during childhood. The syncope association with risk was time-dependent, because more recent syncope portended a higher hazard ratio than a remote history of syncope. Girls accounted for 63% of the children in the registry, and they had a slightly but statistically significant longer baseline QTc. Despite this, boys had a markedly higher rate of events (5% for boys, 1% for girls). These clinical risk factors persisted even when analyzed separately by genotype. Interestingly, a family history of SCD did not portend a higher likelihood of events during childhood, regardless of genotype.

Congenital deafness was also associated with serious adverse events, but segregated with syncope, and was therefore not found to be an independent risk factor. The total rate of serious events was quite low. Somewhat surprisingly, although the vast majority of the patients in the registry were already diagnosed with LQTS, and β-blockers have been shown to be safe and effective, only 21% of the children were being treated with a β-blocker, including some who had discontinued medication therapy. Treatment with a β-blocker reduced the risk of aborted cardiac arrest or SCD by approximately half in this pediatric cohort. A very small number of children received other antiarrhythmic medications, <2% received a pacemaker, 1% received an ICD, and 1% underwent left cardiac sympathetic denervation.

These findings are consistent with other series evaluating children with LQTS. Most studies of pediatric and young adult patients with LQTS show a higher risk of serious events, including SCD, with longer QTc values, history of syncope, or aborted SCD. The use of cardiac rhythm man-
agement devices, particularly ICDs, has grown substantially, even among younger and smaller patients with LQTS.\textsuperscript{26,27} Although it would seem logical that a positive family history of SCD is a surrogate for a malignant mutation, this has not been borne out as a higher independent risk factor for SCD in the present or in previous studies of children with LQTS.

The present report from Goldenberg and colleagues confirms a low mortality rate, with only 53 events (not all fatal) during nearly 12 years of follow-up in 3015 children with LQTS, which yields an annual serious event rate of 0.15%. One wonders whether this number could be reduced even further if more of the children in the registry were adequately treated with \(\beta\)-adrenergic blocking medications. When this event rate is countered against the potential complications related to ICD implantation and lead failure in children,\textsuperscript{28–29} the short- and long-term risks of interventional device therapy in low-risk LQTS children might outweigh the perceived benefits, which emphasizes the importance of the present report and highlights the continued need for improved risk stratification. Although the ICD clearly has life-saving value, it is not for everyone, and the majority of patients with LQTS can be treated effectively with \(\beta\)-blocker monotherapy.

### LQTS in Adults After Age 40

In the companion report, Goldenberg and colleagues present their findings from the International LQTS Registry from adults >40 years of age.\textsuperscript{22} This likely completes the registry’s series of age-related publications, along with the prior reports describing adolescents and young adults with LQTS. In the present report, the authors attempt to assess whether adults with LQTS who have lived to 40 years have a continued risk for serious cardiac events, including SCD. They assessed data from 2759 subjects 41 to 75 years old, stratified by QTc, for serious cardiac events, including SCD. They assessed data in the children, recent syncope was a predictor of serious events, with some similarities in risk stratification to prior studies reported for younger adults, including QTc, gender, and genotype.\textsuperscript{12,30–33}

#### Summary

These 2 clinical series highlight the importance of long-term surveillance and data collection. The identification of risk factors to improve stratification of patients with more precision is crucial, because not all patients with LQTS will clearly benefit from invasive treatments. It is clear from the present series and others that the majority of patients can be managed safely and effectively with medical therapies and trigger avoidance. The selection of the high-risk patient who may benefit from interventional therapies such as left cardiac sympathetic denervation or cardiac rhythm management devices must be balanced carefully with the risk of arrhythmic sudden death. Congenital LQTS is clearly not 1 homogeneous syndrome but rather related syndromes with clinical, genetic, and phenotypic heterogeneity. The International LQTS Registry has proved invaluable for the rich data set that continues to provide interesting findings to help manage patients of all ages with LQTS.

#### Disclosures

Dr Berul has received research support from Medtronic and Boston Scientific. He is a consultant for Medtronic, Johnson & Johnson, and Novartis Pharmaceuticals.

#### References


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