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Management of Congenital Long QT Syndrome: Commentary from the Experts

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Supplemental Material:

Supplemental Tables I-IV

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Abstract

While published guidelines are useful in the care of patients with long QT syndrome (LQTS), it can be difficult to decide how to apply the guidelines to individual patients, particularly those with intermediate risk. We explored the diversity of opinion among 24 clinicians with expertise in LQTS. Experts from various regions and institutions were presented with 4 challenging clinical scenarios and asked to provide commentary emphasizing why they would make their treatment recommendations. All 24 authors were asked to vote on case-specific questions so as to demonstrate the degree of consensus or divergence of opinion. Of 24 authors, 23 voted and one abstained. Details of voting results with commentary are presented. There was consensus on several key points, particularly on the importance of the diagnostic evaluation and of beta-blocker use. There was diversity of opinion about the appropriate use of other therapeutic measures in intermediate-risk individuals. Significant gaps in knowledge were identified.

Keywords

long QT syndrome; beta-blocker; genetic testing; implantable cardioverter-defibrillator; left cardiac sympathetic denervation; Sudden Cardiac Death; Genetics

Introduction

Patients with long QT syndrome (LQTS) encompass a broad spectrum of ages and risk categories. While there is usually consensus about how to treat the lowest and highest risk patients, it can be difficult to decide how to apply the guidelines to individual patients with intermediate risk. This document explores the diversity of opinions among experts, from various regions and institutions, in nuanced management decisions that may not be addressed by consensus documents.

Four clinical scenarios are presented to several experts in the field, who provide a commentary emphasizing why they make their treatment recommendations and what influences their management. These discussions emphasize differing points of view as well as points of agreement (summarized in tables 1 and 2). Second, all authors are asked to vote on case-specific questions, so as to demonstrate the degree of consensus or lack thereof. After each case, a separate group of experts summarizes the key points and suggests what gaps in our knowledge should inform further investigation (summarized in table 3). Of 24

authors, 23 voted and one abstained. The voting questions and results are compiled in Figures 1–4 (full voting summary is provided in Supplemental data).

Case 1 [Experts: Etheridge (section leader), Ackerman, Schwartz, Shimizu]

A 12-year-old boy presents with family history of LQTS; the proband is LQTS genotype negative. The child has moderate QT prolongation (QTc 480 ms) and no syncope. He is an avid athlete. Would you start a beta-blocker, which one and how much? How would you counsel regarding safe sports participation? What kind of follow up and testing should he have?

Response

It is critical to be certain that a robust assessment of the proband has been undertaken and that the diagnosis is certain¹. Detailed information concerning the proband and family members should be elicited, including any symptoms suggesting arrhythmic syncope, unexplained drowning, or sudden death at a young age.

Intense physical training can markedly prolong the QT interval and a period of 3–4 months of deconditioning (complete training cessation) may result in normalization of repolarization in genotype-negative subjects with a negative family and personal history². In a study of 2000 elite athletes, the QTc was prolonged in 7 (0.4%)³, yet a QTc < 500 ms without symptoms or familial disease was unlikely to represent LQTS. Isolated QT prolongation in an athlete may represent the effect of delayed repolarization as a result of increased left ventricular mass or other effects of athleticism on remodeling of the heart's electrical system.⁴

One should consider repeating genetic testing in the proband if the original was conducted in a research lab particularly because more modern and sophisticated testing capabilities can increase the yield of testing⁵. A genetic confirmation would be important as LQTS genotype and mutation location allow for risk stratification, impact therapy and improve prognostic capabilities^{6, 7}.

Evaluation should also include exercise testing. The QT during and after exercise may better characterize the phenotype in this gene-negative patient. Analysis of postural and exercise changes in the QT/RR relationship, can point to a phenotype possibly consistent with LQT1, LQT2 or LQT3^{8–10}.

An echocardiogram at least once in the life of this child is indicated to assess for secondary causes of QTc prolongation such as left ventricular hypertrophy, subclinical myopathy or congenital heart defect⁴.

A 12-lead Holter can identify dynamic changes in the QT interval and assess for unsuspected arrhythmias. In LQT3 patients, bradycardia or sinus pauses can increase risk; knowledge of the QT at these times is important⁷. Cardiac events in LQTS are strongly associated with triggers linked to inappropriate QT adaptation to changes in heart rate.

Treatment

If, after thorough evaluation, the patient is believed to have LQTS, even if indeed genotype-negative LQTS, beta-blocker therapy is indicated unless there is a compelling reason against it (e.g. significant asthma). LQTS experts have long known that beta-blocker therapy reduces risk and events in LQTS¹¹ including LQT3¹². Not all beta-blockers are equal and nadolol and propranolol are superior to metoprolol¹³, and atenolol should be avoided¹⁴. When initiating a beta-blocker in an asymptomatic patient, starting with a small dose and increasing gradually in combination with good hydration can improve tolerance. The goal beta-blocker dose is 2–3 mg/kg/day of long-acting propranolol or divided three times a day in the short acting preparation, or 1–1.5 mg/kg/day of nadolol.

If a beta-blocker use is not possible a left cardiac sympathetic denervation (LCSD) can be considered as it has been found to be protective in high-risk patients with LQTS¹⁵. The child should undergo a yearly or twice a year evaluation with ECGs, exercise tests and possibly repeat Holter monitoring. There is lack of agreement about how often to repeat a Holter monitor. In patients incapable of performing an exercise test, annual Holter monitoring can be used to assess therapy efficacy and adherence. A Holter can be helpful if there are new symptoms. In LQT3 where events occur with rest or sleep, a Holter every 1–2 years can be used to assess for asymptomatic events. The patient should avoid medications that lengthen repolarization (www.crediblemeds.org) if possible.

Sports participation

The experts differ in their recommendations for sports participation. Some would allow full sports participation in this asymptomatic patient if compliant with therapy¹⁶, while others would limit the patient to mild-moderate exercise if this patient proves to have a LQT1 phenotype. Several experts would restrict competitive swimming and diving and voice concern about solitary exercise in a remote location. All feel that if sports are undertaken this should be under the guidance of a LQTS expert and the patient, family, and (if applicable) coach should agree about the participation. An automatic external defibrillator (AED) should be available during practices and games and the coach should know AED location and use. The patient should avoid increasing core body temperature as this can lengthen the QT¹⁷ and there should be a focus on excellent hydration.

Case 1 Summary: Aziz and Shoemaker

The patient presented in Case 1 is a genotype negative 12-year-old boy with no LQTS-related symptoms. The first “controversy” identified in the group relates to the veracity of the diagnosis of LQTS. The potential of left ventricular hypertrophy and its influence on prolonging repolarization should be appreciated in an athlete. Additionally, a thorough family history, exploration of additional phenotype (exercise stress testing, Holter monitoring, echocardiogram) and repeat genetic testing through commercial analysis are all reasonable means of clarifying the diagnosis of LQTS in this patient.

Once confirmed, experts reviewing the case shared consensus on treatment which would ultimately include beta-blockade (preferably nadolol or propranolol) and avoidance of

medications that prolong the QTc. Sports participation was debated though the availability of an AED during sports was supported by all expert members.

Among the voting panel, near consensus existed for repeating genetic testing and treatment with a beta-blocker (Figure 1 and supplemental table I). Over 70% of voters would not escalate to LCSD or implantable cardioverter defibrillator (ICD) if the patient could not tolerate beta-blocker therapy. Sports participation was highly controversial, and responses were dependent on the assumption that beta-blocker therapy was tolerated. Most voters said shared-decision making was crucial with a nuanced discussion of the specific activity, its risks, and strategies for safe participation (e.g. bystanders, AEDs).

Gaps in knowledge here include management recommendations for genotype negative LQTS, sports participation/restriction, and a greater understanding of the clinical significance and management of patients with exercise-training induced QT prolongation.

Case 2 [Experts: Cerrone (section leader), Roberts, Sy, Viskin]

A 60-year-old active man struggling with depression is noted to have QT prolongation on an ECG following initiation of QT prolonging anti-depressant medications. His QTc is 570 ms and his resting heart rate 50 bpm. Genetic testing shows a disease-causing pathogenic variant in *KCNQ1*. He has a remote history of exertional syncope. His psychiatrist indicates multiple different anti-depressant medications have been tried unsuccessfully and insists that the current regimen be continued. Would you start a beta-blocker? Would you consider device implantation?

Response

A QTc > 550 ms occurs infrequently in LQT1, even among patients on QT-prolonging medications. Hence, it is important to first confirm that the QTc measurement is accurate; inclusion of the U-wave can lead to spuriously long values. It would also be useful to review any ECGs that preceded the initiation of QT-prolonging medications. Assuming the QTc value is accurate, it is probably his most important risk factor^{18, 19}.

The 5-year risk of life-threatening arrhythmias in untreated LQT1 with QTc > 560 ms is estimated in the range of 5%, albeit not adjusted for age¹⁸. The history of exertional syncope is concerning, although the risk is time-dependent, being more significant for a recent event (<2 years ago) than if it was remote (>10 years ago)²⁰. It would be important to clarify the nature of the presentation, timing and whether additional stressors were present.

Older LQTS patients are not well represented in registries, have a lower relative risk of sudden death due to LQTS compared to younger patients, and a higher risk of mortality from non-LQTS conditions; still, there remains an attenuated but still substantial risk of sudden death in patients > 40 years with LQTS and a prolonged QTc²¹. However, it is important to highlight that the presumed new onset prolongation of his QTc to > 550 ms secondary to medication has altered his arrhythmic substrate.

The presence of a pathogenic/likely pathogenic *KCNQ1* variant identifies this patient as at lower risk compared to other genetic forms, once treatment is started. Genetic testing should

be reviewed for the presence of common to intermediate prevalence QT predisposing variants, such as KCNE1-p.D85N, that are not always included in standard reports²². Cascade screening in family members is vitally important, and this patient's benign life-course may not be the same as other affected family members.

His entire medication regimen and an electrolyte panel should be scrutinized for other reversible factors. It is imperative to highlight to both the patient and the psychiatrist that the anti-depressant has likely resulted in a problematic increase in his arrhythmic risk and, if at all possible, should be stopped or, at the very least, the doses reduced. Although the majority of antidepressants and antipsychotic drugs have been linked to QT prolongation, there are some agents that seem to have less or no effect on QT interval and the potential of switching to a safer agent should be discussed with the psychiatrist. The patient should meticulously avoid any other medications that prolong the QT interval (<https://www.crediblemeds.org>). One should also inform him about the effects of specific foodstuff (like grapefruit) on the QT interval and their potential proarrhythmic effects²³.

Would you start a beta-blocker?

All panelists agree that beta-blocker is indicated in this case, because it is extremely effective in preventing arrhythmic events in patients with LQT1, and the benefits are likely maintained in older patients^{11, 18, 24}. Nadolol is the first choice, starting with a low dose and then up-titrating to 1 mg/kg which should be reasonably well tolerated even considering the presence of resting bradycardia. The 'maximal tolerated dose' should be based on its impact on his quality of life rather than his absolute heart rate. Depression should not be viewed as a contraindication to beta-blocker therapy. Indeed, recent large-scale data that analyzed the risk of psychiatric adverse events linked to beta-blocker use suggest that depression does not occur more frequently in beta-blocker users compared to placebo²⁵. Additionally, another study from the Danish population-based registry investigating the relation between hypertension and depression showed that beta-blocker therapy was associated with decreased rate of depression²⁶. In case of severe side effects or poor compliance, one could try different beta-blockers and also inform him of the existence of LCSD as an alternative option.

Would you consider device implantation?

Three experts advised against device implantation despite the marked QT prolongation. Although a QTc >500 ms has been associated with increased risk of life-threatening arrhythmias in LQTS, beta-blockers are particularly effective for LQT1, to the point that even patients who present with cardiac arrest in the absence of therapy may be safely treated only with beta-blockers²⁴, as long as they are compliant with the medication and avoid QT-prolonging drugs. The patient's age, beta-blocker-naïve status and remote nature of previous syncope are mitigating factors^{27, 28}. An ICD would be indicated if the patient experiences recurrent syncope on beta-blocker²⁷. The option of long-term monitoring with an implantable loop recorder (ILR) which could provide information of HR response to beta-blockers and adjudicate the underlying rhythm with symptoms, could be discussed if short-term monitoring is unrevealing.

One expert would consider an ICD, since there are limited data available for LQT1 patients with QTc values > 550 ms^{11, 18, 24, 29}. Furthermore, among LQT1 patients who suffer breakthrough events despite beta-blockade, QT-prolonging medications are a known contributing factor²⁴. Assuming his QTc values remained > 550 ms and his anti-depressant regimen could not be adjusted (which should only be considered acceptable in exceptional circumstances), one could offer invasive therapy and discuss both an LCSD and a dual chamber ICD, the latter of which would additionally allow for intentional atrial pacing for rate stabilization.

Case 2 Summary (Cutler and Roden)

This case raises several key questions: how does age at LQTS diagnosis impact sudden death risk? Does the magnitude of QT prolongation (>550 ms here) increase sudden death risk independent of age? How can we manage patients who have comorbid conditions or drug therapies that may also prolong QT?

The panelists observe that although the risk of sudden death in LQTS decreases with age, particularly in men, the severe QT prolongation (>550 ms) in this case was worrisome and the consensus was that at a minimum this patient should be treated with a non-selective beta-blocker. More advanced therapies would be considered if there is breakthrough syncope/ventricular arrhythmia on beta-blocker therapy. The need for any QT prolonging medications should be carefully evaluated and these should only be continued if alternatives are unavailable and the indication is compelling. There is a role for shared decision making in evaluating these risks and benefits.

Figure 2 shows the distribution of expert opinion from the entire expert panel regarding management decisions relevant to Case 2. There was overall agreement that this patient should be started on non-selective beta-blocker therapy at the initial patient visit. If a non-selective beta-blocker is not tolerated, 50% of experts would consider a selective beta-blocker vs 36% who would escalate management (e.g. to ICD or LCSD). Finally, there was again divergence of opinion regarding escalation of therapy if QT interval remained prolonged after initiation of beta-blocker therapy. Supplemental Table II provides a summary of expert comments relevant to Case 2.

In conclusion, Case 2 highlights important knowledge gaps related to age-dependent sudden death risk, the modulating impact of the extent of QT prolongation, and the dilemma that arises when patients with LQTS need QT-prolonging drugs for other serious conditions.

Case 3 [Experts: Wilde (section leader), Lubitz, Krahn, Priori]

A 29-year-old woman is found to have LQT2 with QTc 500 ms on family screening. She has not had syncope. She is 10 weeks pregnant with her first child. She has mild chronic asthma for which she uses a rescue inhaler 1–2 times monthly. What testing and treatment would you offer at this time? Would you start a beta-blocker? Would you recommend LCSD? Would you recommend ICD?

Response

Evaluation

Risk stratification in LQTS is a sensitive issue and it is obviously important to avoid serious arrhythmias potentially leading to sudden cardiac death. In particular the QTc interval and the symptom status are of relevance. Family history, not provided for this case, seems unimportant. A recent study including over 1700 LQTS patients (551 with LQT2) aimed to create an evidence-based risk classification scheme to personalize the quantification of risk¹⁸. With the characteristics given (i.e. QTc of 500 ms, asymptomatic) her 5-year risk of a lethal arrhythmic event *off therapy* would be 4.5% (95% CI: 1.5–7.4). Pregnancy is not a high risk period for the mother, unlike the post-partum period that *is* high risk, especially for LQT2 women³⁰.

Beta-blocker therapy and considerations for pregnancy

There is no doubt that beta-blocker therapy reduces her risk significantly, and that should be the first line of therapy to be initiated. Nadolol or propranolol, both non-selective beta-blockers, are the preferable beta-blockers^{13, 18}. However, with her mild chronic asthma, nonselective beta-blockers might lead to unacceptable side effects. The experts diverge on treatment options: some favor starting with low-dose non-selective beta-blocker and advancing the dose as tolerated. Others would start with metoprolol which, similar to propranolol, has not been shown to be detrimental during pregnancy³¹, and which can be dosed to a higher level. In addition, asthma may worsen during the pregnancy, usually in the 3rd trimester. If worsening occurs within 4–6 weeks on a non-selective beta-blocker, switching to the beta-1 selective beta-blockers metoprolol or bisoprolol would be appropriate. Atenolol should not be used in LQTS and early reports suggested the possibility of atenolol-associated intrauterine growth retardation.³¹

Further investigation ideally includes ambulatory cardiac rhythm monitoring, and on a discretionary basis an exercise test, to identifying any high-risk subclinical arrhythmias (non-sustained polymorphic ventricular tachycardia) and assess peak heart rate.

Potassium and magnesium levels should be measured and optimized if needed. Beta-blockers should be started as soon as possible, after the above investigations or immediately after a baseline ECG with evident QTc prolongation, and additional therapy is not needed at this point in time. A repeat exercise test to demonstrate reduction in peak heart rate is recommended, with potential titration of beta-blocker in the third trimester as the volume of distribution in the mother increases. In the months after birth, the risk for LQT2 women is increased, so that is an important period for strict medication adherence and symptom surveillance. In addition, beta-blockers are expressed in breast milk, so education and awareness of the effects and the very small risk of infant hypoglycemia is important in counselling and managing both mother and baby. QT-prolonging drugs should be avoided at any time during her further life (www.crediblemeds.org and related smartphone app).

Genetic counseling and evaluation of the baby

The patient should be informed that her child will have a 50% chance of inheriting the same LQT2 mutation. There is a small chance that he or she will develop a phenotype in utero or shortly after birth, which can be monitored with standard fetal assessment³². Maternal blood for circulating fetal cells can be tested to determine the gene status of the fetus, but this is typically deferred to the post-partum period. An umbilical cord blood sample could be stored in order to obtain the genotype of the child.

The risk for arrhythmias with hemodynamic compromise at labor and delivery for the mother is estimated to be at a moderate level, mandating additional surveillance including involvement of a pregnancy heart team with expertise in inherited arrhythmia syndromes with careful heart rhythm monitoring and some experts additionally prefer an intravenous line.

Case 3 Summary (Kaufman and Perez)

This case is challenging because the patient has high-risk features; LQT2 in a woman soon to enter the risky post-partum period, with QTc 500 ms but asymptomatic. The situation is further confounded by her diagnosis of asthma requiring intermittent use of a rescue inhaler. The published guidelines^{27, 33} recommend beta-blocker therapy if tolerated, with intensification of therapy to LSCD or ICD in “high-risk” patients when beta-blocker is poorly tolerated. The clinician is left to determine how high the risk is in an individual patient, and when the benefits of aggressive treatment outweigh the risks.

The primary commentators agreed on treating with non-selective beta-blocker, but if her asthma worsened, they would consider switching to either metoprolol or bisoprolol. Most would start treatment after baseline ambulatory monitoring and exercise testing, if these were timely. The commentators recommended special surveillance during delivery, did not mandate Caesarian section, and discussed the need for fetal monitoring and genetic counseling.

Among the voting panel, all recommended beta-blocker therapy, with 15 waiting until timely completion of appropriate baseline investigations and with 7 favoring medication initiation immediately after the 12-lead ECG. None of the experts recommended consideration of LSCD or ICD (Figure 3 and Supplemental Table III). While most (19) experts agreed on vaginal birth with close monitoring, 2 favored Caesarian section and one commented that plans for future pregnancies could be factored in. It is notable that data from multiple LQTS registries have not pointed to a high risk for the mother at the time of delivery.

Case 3 highlights the complexity of managing LQTS in pregnancy. Gaps in knowledge include evidence for birth plan procedures and beta-blocker tolerability in pregnant persons.

Case 4: [Experts: Towbin (section leader), Behr, Schulze-Bahr, Zareba]

A 24-year-old male suffered a non-exertional near syncopal spell at age 15 years. His past medical history was notable only for intermittent asthma. His ECG at that time showed QTc 490 ms and he was diagnosed with LQTS. A disease-causing variant was identified in *KCNH2* (i.e., LQT2). An electrophysiologist implanted a single chamber ICD but failed to

start beta-blocker. The patient has never had syncope, repeat near syncope, nor appropriate shocks from his device. He is seeing you for the first time and requests ICD removal. His QTc today is 485 ms and he still has not taken a beta-blocker. What other data would you request? Would you start a beta-blocker? Would you consider device extraction?

Response

General considerations

This patient's history has several important features including a single non-exertional *near* syncopal event at the age of 15 years but no history of any cardiovascular-related illness before or in the 9 years since the "event". He has never had actual syncope or repeat near syncope and he has not had any appropriate shocks, even though he has not received beta-blocker therapy.

The experts agreed that this LQT2 patient with near syncope at the age of 15 years should have been treated with beta-blockers and there was no indication for an ICD. With only intermittent asthma, beta-blockers should be tried with caution as clinical practice indicates that such patients usually tolerate beta-blockers, which could be administered at a lower dose if needed. Furthermore, use of beta-blockers decreases the risk of cardiac events that could be augmented by beta-2 agonists^{34, 35}. There is a significant difference between the risks of cardiac events between LQT2 males and females after the age of 15 years with females showing over 3-fold higher risk of cardiac events and 2.5-fold higher risk of cardiac arrest or sudden cardiac death than males^{6, 36, 37}. Incremental risk in adult LQT2 males over the lifespan is very low especially with QTc below 500 ms³⁷.

Additional Data

Additional data would help the experts to evaluate this case, including what the specific pathogenic variant in *KCNH2* is and where it is located, as some variants and regions (pore region) of the channel are associated with more severe disease and worse outcomes³⁶.

In addition, they would like to know what the T-wave morphology looked like at rest as notching or flattened T-waves are associated with more aggressive forms of LQTS^{10, 38–40}, and further, how the T-wave responds to exercise (normalization is a good prognostic indicator)¹⁰.

Complete phenotyping information would be useful, including resting and exercise-associated QTc and the QTc change, and whether there are PVCs.

Finally, they would want to know the family history as well as the working and living environment to determine if there are potential triggers for arrhythmia initiation, like loud noise. They wish to know the severity of the asthma, whether brittle or not, and if this has resolved as he has become older. They would inquire about a family history with cascade screening (if not done before), although family history is of less significance than patient's personal history of cardiac events⁴¹.

Beta-blocker

The panel of experts agreed that they would initiate beta-blocker therapy while he still has a functional ICD⁴². Recognizing that he has a history of asthma, they would follow him closely for respiratory symptoms. He should take the beta-blocker just before going to bed (as late as possible to avoid the potential of arousal in the AM after awakening and avoiding a triggered arrhythmia). They would use nadolol first or bisoprolol as second line (especially if the asthma is still active)^{13, 43, 44}. Long-acting metoprolol twice daily could be a possible second-line therapy although limitations of metoprolol are acknowledged^{13, 44}. If none of these are tolerated, mexiletine would be a potential therapy⁴⁵. Efficacy would be assessed by limitation of maximal heart rate with exercise, and QTc shortening at rest or during exercise. In addition, excessive bradycardia, defined by age⁴⁶, would result in discontinuation of the beta-blocker.

Device Extraction Considerations

The panel agreed to consider device extraction if the medical therapy demonstrated efficacy and no untoward side effects developed. They would strongly recommend avoidance of QT prolonging medications/beta-mimetics. In fact, the patient did not appear to meet ICD implant criteria initially⁴⁷. Near syncope with QTc < 550 ms, but especially < 500 ms, is not an indication for an ICD, especially without beta-blocker therapy. Syncope on beta-blocker therapy could qualify this patient even with his QTc of 485 ms.

If medical therapy was not tolerated or was not efficacious but the patient still wanted the ICD extracted following careful counselling about the risks of extraction, then this would be his choice and some experts found this acceptable.

One expert suggested possible LCSD with suitable counseling, particularly if there were other markers suggestive of risk as described above, e.g. pore-localizing variant, late-coupled ventricular ectopic complexes during exercise ECG testing, or follow-up QTc measurements exceeded 500 ms and/or syncope. However, the other 3 experts did not perceive an indication for LCSD⁴⁸.

Case 4 Summary (Chung and Eckhardt)

Controversial issues in this case include: 1) whether a patient without LQTS-associated symptoms, with asthma and LQT2 should be started on a beta-blocker, if so which one; 2) if the ICD was or remains indicated, and 3) whether the ICD should be extracted.

Experts reviewing the case agreed that beta-blockers should be started (with some variance in the type and timing) and that he does not have clear indications for ICD implantation by today's guidelines and consensus statements. A male age 15–40 years with QTc <500 ms and no prior syncope is a lower risk patient particularly because he was beta-blocker naïve at implant. Case reviewers also thought that information on the specific mutation and phenotyping might be useful, including T wave morphology, response to exercise, and family history.

Within the entire expert panel participating in the voting questions, almost all agreed that a non-selective beta-blocker was preferred, one would give bisoprolol and one would not give

the beta-blocker (Figure 4 and Supplemental Table IV). If he could not take a beta-blocker, the group diverged in opinion on use of mexiletine and in offering LCSD. Device extraction responses were nuanced in both the reviewing panel and voting panel and largely qualified with additional comments, highlighting the role of shared decision making and balancing risks of extraction.

Gaps in knowledge here include the lack of randomized trials of beta-blockers, mexiletine, prophylactic LCSD, and ICDs in LQTS with reliance on retrospective observational studies. Likewise risks of retained unnecessary hardware vs. extraction in young patients is unclear.

Conclusions

Expert consensus statements provide guidelines for treatment of patients with LQTS. However, the clinician must apply these guidelines with care and good judgement to avoid over- or under-treating patients. The initial evaluation is critical for establishing a diagnosis and assessing individual risk. Once the diagnosis (and more than trivial risk) has been established with confidence, most patients will benefit from beta-blocker therapy, with careful selection of particular beta-blocker and dose. Although it is important to counsel against use of QT-prolonging medications, it is not infrequent for LQTS patients to have other serious illness with indication for use of QT-prolonging agents; in such patients, therapy must be individualized to optimize outcomes. Invasive therapies such as LCSD or ICD implantation are indicated in the rare patient with substantial risk despite beta-blocker therapy and/or with significant contraindication to its use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures:

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Non-standard abbreviations and acronyms:

LQTS	long QT syndrome
LCSD	left cardiac sympathetic denervation
AED	automatic external defibrillator
ICD	implantable cardioverter defibrillator

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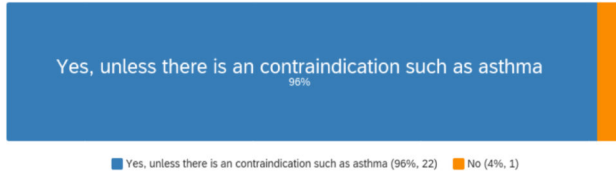
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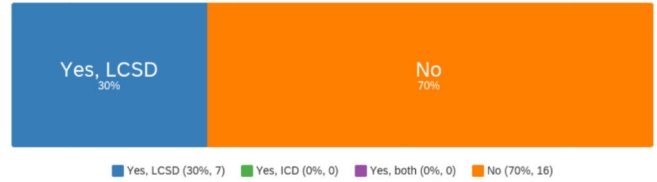
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CASE 1 SURVEY RESULTS

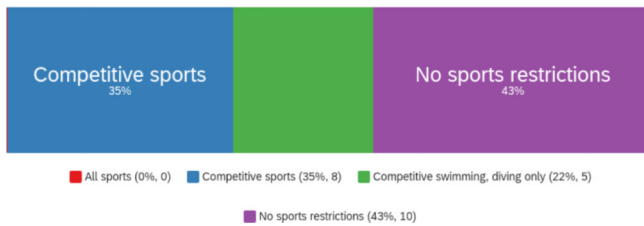
Q1 - Case 1, this patient, assuming that after a period of deconditioning and additional testing you are convinced he has LQTS should be treated with a beta blocker?



Q2 - Case 1, this patient, assuming that after a period of deconditioning and additional testing you are convinced he has LQTS, should be treated with more advanced therapy if he cannot take a beta blocker?



Q3 - Case 1, this patient, assuming that after a period of deconditioning and additional testing you are convinced he has LQTS, should be restricted from:



Q4 - Case1: Considering this patient, assuming that after a period of deconditioning and additional testing you are convinced he has LQTS, there should be repeat commercial genetic testing on the proband or the patient if it has been > 10 years since the proband was tested or testing was done in a research lab.

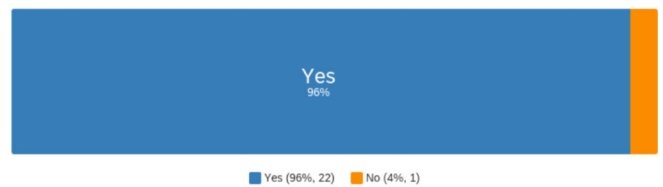
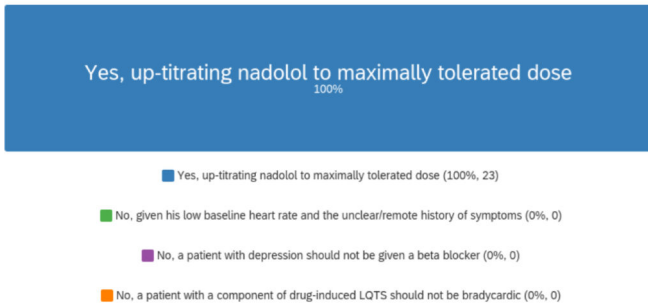


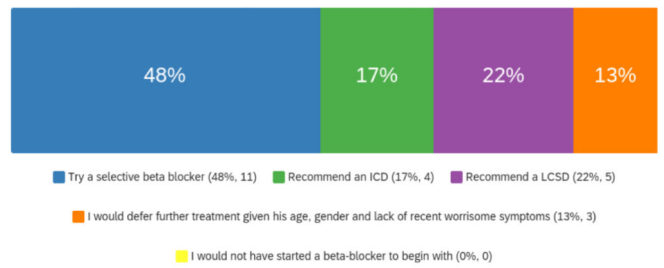
Figure 1: Survey results are presented for questions pertaining to case 1.

CASE 2 SURVEY RESULTS

Q8 - Case 2: Would you start him on a betablocker at the time of the first visit?



Q9 - Case 2: If the patient does not tolerate either Nadolol or Propranolol, what would you do next?



Q10 - Case 2: Nadolol is introduced and tolerated. His QTc and resting heart rate remain 570msec and 50bpm, respectively. Do you believe more invasive intervention is indicated?

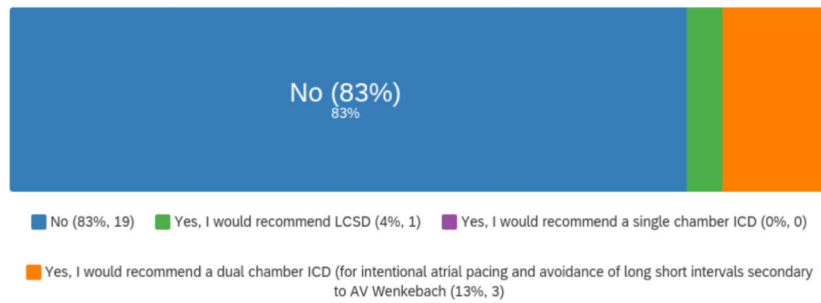
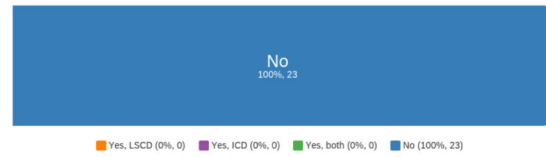
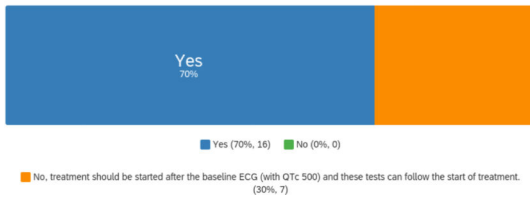


Figure 2: Survey results are presented for questions pertaining to case 2.

CASE 3 SURVEY RESULTS

Q12 - Case 3, this patient should be treated with a beta blocker immediately after timely appropriate investigations (ambulatory cardiac rhythm monitoring monitoring, exercise test).

Q13 - Case 3, this patient should be treated with scaled-up therapy (LCSD, ICD)



Q14 - Case 3, this patient, assuming there are no obstetrical indications for Caesarian section, should have special care during delivery.

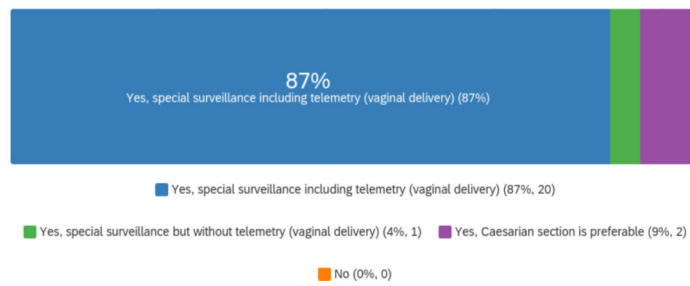
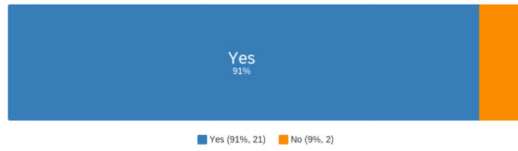


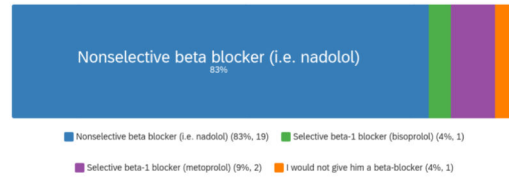
Figure 3: Survey results are presented for questions pertaining to case 3.

CASE 4 SURVEY RESULTS

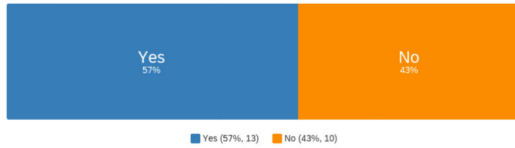
Q16 - In this Case 4 (questionably symptomatic LQT2 male with asthma and QTc 485ms), would you insist on starting a beta blocker?



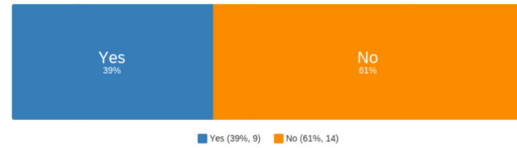
Q17 - Case 4: What kind of beta-blocker would you give?



Q18 - Case 4: If he cannot take beta blocker, would you offer him mexiletine?



Q19 - If he cannot take beta blocker or mexiltine, would you offer him LCSD?



Q20 - Would you consider device extraction?

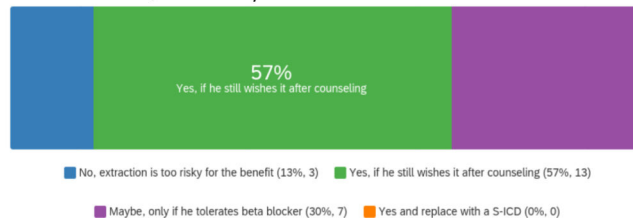


Figure 4: Survey results are presented for questions pertaining to case 4.

Table 1:

Points of Agreement

A robust evaluation is crucial to avoid misdiagnosis and inappropriate treatment.
The QT interval must be measured accurately, excluding the U-wave.
Isolated long QT < 500 ms in an athlete may resolve with deconditioning.
Previous genetic testing conducted in a research laboratory should be repeated.
Baseline tests should include exercise ECG, echocardiogram (once), and Holter monitor.
A child with LQTS should have serial evaluations every 6–12 months.
A child with LQTS should receive nadolol 1–1.5 mg/kg or long-acting propranolol 2–3 mg/kg unless there is a contraindication.
Pregnant LQTS patients should be treated with beta-blockers regardless of symptoms
Post-partum period for LQT2 is a particularly vulnerable time for arrhythmic events and treatment with surveillance should be emphasized
ICDs implantation for primary prevention without a beta-blocker trial is rarely indicated, and evaluation of clinical indications of previously implanted devices should be thoroughly reconsidered

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Table 2:

Points of Controversy

LCSD should be considered if beta-blocker use is not possible in a person with moderate-risk LQTS.
An ICD could be avoided in a patient with LQTS type 1 and QTc > 550 ms unless symptoms occur on beta-blocker.
A selective beta-blocker could be used if a non-selective beta-blocker was not tolerated in a patient with high-risk LQTS.

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Table 3:

Gaps in Knowledge

What restrictions should be placed on sports participation?
What is the best beta-blocker initiation strategy in LQTS?
Is prophylactic LCSD appropriate instead of beta-blocker in low- to medium-risk patients?
What are the long-term risks of retained unnecessary hardware versus extraction in young patients?
What is the role of pacing in LQTS types 2 and 3?
What is the role of subcutaneous ICD in LQTS who will then not have the benefit of atrial pacing?
What is the best strategy for treating depression in LQTS?
What is the best strategy for treating LQTS in patients with asthma?

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