Latest Diagnostic and Treatment Strategies for the Congenital Long QT Syndromes

Michael J. Ackerman, MD, PhD

Windland Smith Rice Cardiovascular Genomics Research Professor
Professor of Medicine, Pediatrics, and Pharmacology
Director, Long QT Syndrome Clinic and the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory
President, Sudden Arrhythmia Death Syndromes (SADS) Foundation
Learning Objectives to Disclose:
• To **RECOGNIZE** the “faces” (phenotypes) of the congenital long QT syndromes (LQTS)
• To **CRITIQUE** the various diagnostic modalities used in the evaluation of LQTS and **UNDERSTAND** their limitations
• To **ASSESS** the currently available treatment options for the various LQT syndromes and **EVALUATE** their efficacy

Conflicts of Interest to Disclose:
• Consultant – Boston Scientific, Gilead Sciences, Medtronic, St. Jude Medical, and Transgenomic/FAMILION
• Royalties – Transgenomic/FAMILION
Congenital Long QT Syndrome

- Normal QT interval
- Prolonged QT

1. Syncope
2. Seizures
3. Sudden death

Torsades de pointes
Congenital Long QT Syndrome

- Normal QT interval
- Prolonged QT
- Torsades de pointes

1. Syncope
2. Seizures
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- 1957 – first clinical description – JLNS
- 1960s – Romano-Ward syndrome
- 1983 – “Schwartz/Moss score”
- 1991 – first LQTS chromosome locus
- March 10, 1995 – birth of cardiac channelopathies

Torsades de pointes
Congenital Long QT Syndrome
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1957 – first clinical description – JLNS
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1983 – “Schwartz/Moss score”
1991 – first LQTS chromosome locus
March 10, 1995 – birth of cardiac channelopathies

1995 - 2004 - research LQTS testing
August 2004 - clinical LQTS genetic test
April 2008 - +ve BCBS TEC summary
August 2011 - HRS/EHRA Guidelines
Congenital Long QT Syndrome

August 2011
HRS/EHRA Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

Ackerman, Priori, et al. *Heart Rhythm* 8:1308-1339, 2011

May 2013
HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes

Long QT Syndrome

Expert Consensus Recommendations on Diagnosis

1. **LQTS is diagnosed:**
   a) In the presence of an LQTS risk score $\geq 3.5$ in the absence of a secondary cause for QT prolongation, \textit{and/or}
   b) In the presence of an unequivocally pathogenic mutation in one of the LQTS genes, \textit{or}
   c) In the presence of a QTc $\geq 500$ ms in repeated 12-lead ECG and in the absence of a secondary cause for QT prolongation.

2. **LQTS can be diagnosed** in the presence of a QTc between 480-499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.
LQTS Diagnostic Criteria (1993-2011)  
- aka “The Schwartz Score” -

**Electrocardiographic Findings**

<table>
<thead>
<tr>
<th>Points</th>
<th>Electrocardiographic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>A   QTc &gt; 480 ms</td>
</tr>
<tr>
<td>2</td>
<td>460-479 ms</td>
</tr>
<tr>
<td>1</td>
<td>450-459 ms (in males)</td>
</tr>
<tr>
<td>1</td>
<td>B   QTc 4th minute of recovery from stress test &gt; 480 ms</td>
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<td>C   Torsade de pointes</td>
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<tr>
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<td>D   T wave alternans</td>
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<td>F   Low heart rate for age (&lt; 2nd percentile)</td>
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**Clinical History**

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<thead>
<tr>
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<tbody>
<tr>
<td>2</td>
<td>A   Syncope</td>
</tr>
<tr>
<td></td>
<td>With stress</td>
</tr>
<tr>
<td></td>
<td>Without stress</td>
</tr>
<tr>
<td>1/2</td>
<td>B   Congenital deafness</td>
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**Family History**

<table>
<thead>
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<tr>
<td>1</td>
<td>A   Family members with definite LQTS</td>
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LQTS Diagnostic Criteria (1993-2011)  
- aka “The Schwartz Score” -

### Points

#### Clinical History

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<tr>
<th>A</th>
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<tbody>
<tr>
<td>A</td>
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| B   | Congenital deafness | 1/2 |

#### Family History

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#### The Story is King!

- \( \leq 1 \): Low Probability of LQTS
- 1.5 to 3: Intermediate Probability of LQTS
- \( \geq 3.5 \): High Probability of LQTS
Congenital Long QT Syndrome

Normal QT interval

Prolonged QT

1. Syncope
2. Seizures
3. Sudden death

Starting Point of LQTS Evaluation
- The Story -
“Don’t Blow Off a Blackout”

SNAP TO! FAINTING CAN SPELL TROUBLE.

Glamour March 2000
“Don’t Blow Off a Blackout”

EXERTIONAL/AUDITORY/
POSTPARTUM
SYNCOPE/SEIZURES
ARE MALIGNANT
UNTIL
PROVEN
OTHERWISE!!
Be a Detective

WHO?
WHAT?
WHEN?
WHERE?
WHY?
~ 40% of the patients that came to Mayo Clinic with the diagnosis of LQTS left without it!

Taggart … Ackerman. *Circulation* 115:2613-2620, 2007

Vanilla Faint + Borderline QT ≠ Possible LQTS

QT Inflation Secondary to U Wave Inclusion
Congenital Long QT Syndrome

- Normal QT interval
- Prolonged QT

1. Syncope
2. Seizures
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Starting Point of LQTS Testing
- The 12-Lead ECG -

Torsades de pointes
**Electrocardiographic Findings**

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The ECG and LQTS

QTc = 760 ms

QTc = 362 ms
Inaccurate electrocardiographic interpretation of long QT: The majority of physicians cannot recognize a long QT when they see one.

Sami Viskin, MD,† Uri Rosovski, MD,‡ Andrew J. Sands, MPhil, MB, BCh,‡

QTc calculated **INCORRECTLY** by
- < 5% of LQTS experts
- > ONE-THIRD of heart rhythm specialists
- > THREE-FOURTHS of cardiologists
The ECG and LQTS

“Teach-the-Tangent” or “Avoid-the-Tail”
The ECG and LQTS

LQT Genotype by ECG?

1. LQT1
2. LQT2
3. LQT3
4. LQT9
5. Don’t

QTc = 475
Measuring the QT Interval – 5 Pearls

1. Use lead II and/or V5! Stay away from V2 and V3!

2. If your QT interval matches the computer’s QT interval, you have verified the computer’s QTc!

3. If the QT interval is less than ½ the RR interval, the QTc will be < 460 ms!

4. If sinus arrhythmia or AF present, do NOT take the maximum QT interval and the minimum RR interval! That will grossly inflate the QTc. Take the average!

5. Remember that the patient’s QTc reality will be UNDERESTIMATED at low heart rates (< 50 bpm) and OVERESTIMATED at high heart rates (> 100 bpm)!
Measuring the QT Interval

BONUS PEARL – Wide QRS QTc Adjustment
In wide QRS scenarios, easiest to just make a “wide QRS adjustment”. QTc(adjusted) = QTc – [QRS – 100].

A. Confirm the computer’s QTc - 560 ms for example
B. Note the QRS because of the paced rhythm, BBB, etc. – 220 ms for example, then
C. QTc(adjusted) = 560 – [220 – 100] = 560 – 120 = 440!
I Think a QTc > ___ is Too Long

1. 420 ms
2. 440 ms
3. 460 ms
4. 480 ms
5. 500 ms
Persons (no.)

QTc (ms)

Normals

LQTS

"BORDERLINE"

482 ± 57 ms

360 ms

800 ms

340 360 380 400 420 440 460 480 500 520 540 560 580 600 620

QTc (ms)
Increased Risk
- HR > 2.5 (boys 1-12 yrs)
- HR > 2 (10 – 20 yrs)
- HR > 4 (18 – 40 yrs)

"Prolonged QTc"

QTc > 450 – males
QTc > 460 – females

AHA/ACCF/HRS Recommendations

< 1% PPV for LQTS
- Frequency: 1 in 4000
- PPV: > 50%
- Direct EP referral
Persons (no.)

QTc (ms)

Males

Females

Normals

> 480 ms in women

LQTS
Persons (no.)

Males

Females

Normals

QTc (ms)

Norms

LQTS

1

2500

> 470 ms in men

340 360 380 400 420 440 460 480 500 520 540 560 580 600 620
- Frequency: 0.2 – 1% (1 in 100 to 1 in 500)
- PPV: 4 – 25%
- HR ≥ 50; QRS ≤ 120 ms
- HR < 50, repeat test
- If QRS ≥ 120 ms, then
  \[ QTc(qrs) = QTc - [QRS - 100] \]
The ECG and LQTS

ECG Diagnosis
1. Normal
2. Abnormal

$QTc = 415$
The ECG and LQTS

Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.

Ackerman, Priori, et al. *Heart Rhythm* 8:1308-1339, 2011

QTc = 415
Congenital Long QT Syndrome

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Latest Diagnostic Strategies
- Genetic Testing -

Torsades de pointes
# Latest Diagnostic and Treatment Strategies for the Long QT Syndromes – Genetic Testing

<table>
<thead>
<tr>
<th>Disease</th>
<th>Diagnostic</th>
<th>Prognostic</th>
<th>Therapeutic</th>
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<tbody>
<tr>
<td>LQTS</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>CPVT</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>BrS</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CCD</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SQTS</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AF</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HCM</td>
<td>++++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>ARVC</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>DCM</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LVNC</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RCM</td>
<td>+</td>
<td>+</td>
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Ackerman, Priori, et al. *Heart Rhythm* 8:1308-1339, 2011
1. Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient’s clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype.
2. Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions which might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e. otherwise idiopathic) on serial 12-lead ECGs defined as QTc > 480 ms (prepuberty) or > 500 ms (adults).

Ackerman, Priori, et al. *Heart Rhythm* 8:1308-1339, 2011
3. Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing **may be considered** for any **asymptomatic** patient with otherwise idiopathic QTc values > 460 ms (prepuberty) or > 480 ms (adults) on **serial** 12-lead ECGs.

4. Mutation-specific genetic testing **is recommended** for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.
~75% of LQTS patients have a mutation in one of these three genes
KCNQ1 (LQT1)

SCN5A (LQT3)

KCNH2 (LQT2)

KCNE1 (LQT5)

KCNE2 (LQT6)

< 1%

30-35%

5-10%

25-30%

Khositseth and Ackerman. Cardiac Repolarization – Chapter 20, 2003
Gene-Suggestive ECG Patterns

KCNQ1 (LQT1)

SCN5A (LQT3)

KCNH2 (LQT2)

Khositseth and Ackerman. *Cardiac Repolarization* – Chapter 20, 2003
Gene-Specific Triggers

KCNQ1 (LQT1)
SCN5A (LQT3)
KCNH2 (LQT2)

Gene Specific Responses to Beta Blocker Therapy

KCNQ1 (LQT1)

SCN5A (LQT3)

KCNH2 (LQT2)

Khositseth and Ackerman. *Cardiac Repolarization* – Chapter 20, 2003
Is the “X” that marks the spot truly THE disease-causing mutation?
Genetic Testing’s Achilles’ Heel

- “Maybe” Test Result

“Possible Deleterious”
“Variant of Uncertain Significance (VUS)”

“Genetic Purgatory is a Real Place and its Scary!”

MAYO CLINIC
Congenital Long QT Syndrome

Normal QT interval

Prolonged QT

1. Syncope
2. Seizures
3. Sudden death

Latest Treatment Strategies

Torsades de pointes
Congenital Long QT Syndrome

Normal QT interval

Prolonged QT

Torsades

www.qtdrugs.org

www.crediblemeds.org
Congenital Long QT Syndrome

- Normal QT interval
- Prolonged QT
- Torsades de pointes

1. Syncope
2. Seizures
3. Sudden death
Treatment Options for LQTS

LQTS ≠ LCSD

Beta-Blocker Therapy

©2002 Mayo Clinic
Treatment Options for LQTS

?? No Active Therapy Necessary If
- Asymptomatic male
- > 40 years old
- QTc < 460 ms
- Haploinsufficient, LQT1-causing C-terminal missense mutation

# Treatment Options for LQTS

<table>
<thead>
<tr>
<th>Beta-Blocker Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadolol – 1-1.5 mg/kg/day or 50 mg/m(^2)/day – QD or BID</td>
</tr>
<tr>
<td>Propranolol – 3-4 mg/kg/day (BID, LA, TID for the liquid)</td>
</tr>
</tbody>
</table>

### Caution w/ Using Atenolol and Metoprolol!
- Chatrath, Bell, Ackerman. *Pediatr Cardiol* 25:459-465, 2004
- Chockalingam …Wilde. *JACC* 2012

### Propranolol and/or Mexiletine/Ranolazine (LQT3)
Indications for ICD Therapy

Secondary Prevention

• Aborted cardiac arrest
• Rx intolerance or breakthrough

©2002 Mayo Clinic
Indications for ICD Therapy

Primary Prevention

• QTc > 550 ms and not LQT1
• LQT2 women, QTc > 500 ms, +/- Sx
• Infants with 2:1 AV block?
• JLNS (LQTS w/ deafness)?
• +ve FHx of SCD (=1, >1, >2)?
• LQT3?
Indications for ICD Therapy

Primary Prevention

• QTc > 550 ms and not LQT1
• LQT2 women, QTc > 500 ms, +/- Sx
• Infants with 2:1 AV block?
• JLNS (LQTS w/ deafness)?

Treatment Options for LQTS

Beta-Blocker Therapy

ICD

LCSD

©2002 Mayo Clinic
• 1916 - First left stellectomy for angina (Jonnesco)
• 1961 - First bilateral sympathectomy for VT (Estes and Izlar)
• 1968 - First LCSD for VT (Zipes et al.)
• 1970 - First LCSD for LQTS (Moss and McDonald)
• 2003 - First reported videoscopic LCSD for LQTS (Li et al.)
• 2009 - Largest series of videoscopic LCSD (Mayo Clinic)
• Denervation of lower half of the left stellate ganglion (T1) and the sympathetic chain from T2 through T4
LCSD has a potent anti-fibrillatory effect in LQTS

Schwartz et al. Circulation 2004

LCSD’s anti-fibrillatory effects caused by:

- “Norepinephrine ablation”
- Improved repolarization as evidenced by a decrease in QTc in ~30%
Left Cardiac Sympathetic Denervation

Videoscopic Denervation Therapy at Mayo

- N = 152 LCSDs from November 2005 to present
- Average age: $19 \pm 17$ years
  (4 weeks of age to 85 years)
- LQTS (89, LQT1 in 37, LQT2 in 20, LQT3 in 8);
  CPVT (19); Cardiomyopathy (9); IVF (9)
- LQTS: QTc = 497 ± 67 ms
Indications for Videoscopic Left Cardiac Sympathetic Denervation Surgery

- History of appropriate VF-terminating ICD shocks
- Rx intolerance or breakthroughs
- Young (< 12 years) where Rx not deemed “protective enough” but ICD-related morbidity seems excessive – “Bridge to ICD” -

Collura, Johnson, Moir, Ackerman. *Heart Rhythm* June 2009
2. Genetic tests are PROBABILISTIC tests! “X” does NOT always mark the spot!

3. Most do not need and should not receive an ICD!

4. Remember denervation therapy and its anti-fibrillatory effect. Don’t just let the ICD keep firing!

Take Home Points
1. Remember to “be a detective”, “avoid the tails” (exclude the U waves), and take careful stock of the patient with a QTc ≥ 500 ms!
Dr. Scholl Foundation, CJ Foundation for SIDS
Hannah Wernke Memorial Foundation
Sheikh Zayed Saif Mohammed Al Nahyan Fund
National Institutes of Health
“To heal the sick and advance the science”
Dr. Charles W. Mayo