**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**

| Peter J. Kudenchuk, MD | Date Submitted for review: 12/14/09 Revised worksheet |

**Clinical question.**

“In adult patients in polymorphic (wide complex) tachycardia (prehospital and in-hospital) (P), does the use of any drug or combination of drugs (I) compared with not using drugs (or a standard drug regimen) (C) improve outcomes (e.g. reversion rates) (O)?”

Because acute pacing has also been an important component of treatment of some forms of polymorphic ventricular tachycardia (torsade de pointes), it is included in this worksheet for completeness. Thus the clinical question was restated as:

“In adult patients in polymorphic (wide complex) tachycardia (prehospital and in-hospital) (P), does the use of any drug, combination of drugs or acute pacing (I) compared with not using drugs or acute pacing (or a standard drug regimen) (C) improve outcomes (e.g. reversion rates) (O)?”

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Intervention/therapy

**State if this is a proposed new topic or revision of existing worksheet:** Proposed new topic

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

**Search strategy (including electronic databases searched).**

- **MESH:** 
  - #1 “Ventricular tachycardia” (MESH) (8627); 
  - #2 “Cardiopulmonary Resuscitation” (MESH) (6900); 
  - #3 “Antiarrhythmia agents” (MESH) (19211). There was no added value in MESH to search for polymorphic ventricular tachycardia (same yield as ventricular tachycardia), hence MESH-based search was not pursued further.

- **PubMed:** 
  - #1 “Polymorphic ventricular tachycardia and treatment” (616); 
  - #2 “Polymorphic ventricular tachycardia and drug treatment” (282). In addition, searches were conducted under specific types of ventricular tachycardia, including #3 “Catecholaminergic polymorphic ventricular tachycardia and treatment” (22), 
  - #4 “Torsade and ventricular tachycardia and drug treatment” (442), 
  - #5 “Short QT and ventricular tachycardia and drug treatment” (52), 
  - #6 “Brugada syndrome and drug treatment” (160). Based on initial screening of reported therapies for polymorphic ventricular tachycardia, therapy-specific PubMed searches were also conducted, including: 
    - #7 “Polymorphic ventricular tachycardia and pacing” (217), 
    - #8 “Polymorphic ventricular tachycardia and beta blockers” (99), 
    - #9 “Polymorphic ventricular tachycardia and amiodarone” (61), 
    - #10 Polymorphic ventricular tachycardia and magnesium” (44), and 
    - #10 “Polymorphic ventricular tachycardia and isoproterenol” (45).

- **Embase:** “polymorphic ventricular tachycardia and drug treatment” (17).

- **Cochrane:** “polymorphic ventricular tachycardia” –yielded no Cochrane reviews

**Other:** References from published articles gleaned from the searches above were also evaluated, as were references from the previously published 2000 and 2005 Guidelines.

**Summary:** The above searches yielding <650 cases were screened by title; further screened by abstract content and then by actual article content for relevance to the clinical question. Animal studies, pediatric and basic science studies were evaluated for conceptual relevance.
State inclusion and exclusion criteria

Inclusion: Adults with spontaneous occurring polymorphic ventricular tachycardia who received acute pharmacologic or pacing interventions for termination and/or prevention of acute recurrence. Studies inclusive of hemodynamically destabilizing ventricular tachycardia for which morphology was not specified, were also included, although these likely represented a mixture of monomorphic and polymorphic ventricular tachycardias, and were categorized as LOE 5 (extrapolated data).

Importantly, polymorphic ventricular tachycardia is a generic term that characterizes this group of tachycardias by their morphology (see definitions below). Within this broad group, polymorphic arrhythmias are additionally categorized by their presumed mechanism. This distinction is clinically important because it is linked to the propriety and likely success of treatment. Categories of polymorphic ventricular tachycardia included in this evidence review were:

- Long QT (torsade de pointes), familial, acquired and undifferentiated (idiopathic) forms
- Short QT
- Catecholaminergic
- Brugada syndrome
- Ischemia
- Hemodynamically unstable VT of unspecified morphology and mechanism
- Idiopathic normal QT polymorphic VT not specifically attributable to any of the above mechanisms

Exclusion: When little or no adult data were available, pediatric, animal or tissue preparation studies were included, but classified as LOE 5. Rarely a case study was included (and noted as such) in the absence of any other clinical experience, but classified in such instances as LOE 5.

Other limitation: It was presumed that the question under evaluation was directed at polymorphic (wide complex) tachycardia of ventricular origin (polymorphic ventricular tachycardia). Therefore the effect of drug therapy on supraventricular tachycardia presenting in this manner (pre-excited atrial fibrillation) was not considered to be within the domain of the question under evaluation.

Number of articles/sources meeting criteria for further review:

1. Human clinical studies: 31
2. Animal studies: 3
3. Tissue studies: 1
# Summary of evidence

## Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Poor</th>
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<tbody>
<tr>
<td><em><em>Tzivoni (a,fLQTS-Mg) 1988, 392 E</em>; Nademanee (iPMVT-BB) 2000, 742 E</em>;**</td>
<td><em><em>Ohgo (Brugada-iso) 2007, 695 E</em>; Khan (aLQTS-pace) 1981, 1301 E</em>; Keren (aLQTS-iso,pace) 1981, 1167 E*; Keren (aLQTS-pace) 1981, 201 E*; Stern (aLQTS-pace,Mg) 1984, 234 E*; Nguyen (aLQTS-pace) 1986, 340 E*;**</td>
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### Level of evidence

A = Return of spontaneous circulation

B = Survival of event

C = Survival to hospital discharge

D = Intact neurological survival

E = Other endpoint (reversion rate)

** = Other

*italics* = Animal studies

CPVT = catecholaminergic

Gen = general

aLQTS = acquired long QT syndrome

fLQTS = familial LQTS

uLQTS = undifferentiated LQTS

iPMVT = ischemic polymorphic VT

iNQT = idiopathic normal QT polymorphic VT
Evidence Neutral to Clinical question

<table>
<thead>
<tr>
<th>Good</th>
<th>Bhandari (fLQTS-BB) 1985,63 E**</th>
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<tbody>
<tr>
<td>Fair</td>
<td>Tzivoni (iNQT/iPMVT-Mg) 1988,392 E* Nguyen (aLQTS-lido) 1986,340 E* Sumitomo (CPVT-BB,verapamil) 2002,66 E**</td>
</tr>
<tr>
<td>Poor</td>
<td>Varriale (uLQTS;iPMVT-BB,Mg) 2006,283 E**</td>
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</table>

**Level of evidence**

A = Return of spontaneous circulation  
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CPVT = catecholaminergic  
fLQTS = familial/idiopathic LQTS  
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iPMVT = ischemic polymorphic VT  
aLQTS = acquired long QT syndrome  
iQTS = undifferentiated LQTS

Evidence Opposing Clinical Question

<table>
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<tr>
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<th>Shimizu (fLQTS-isoprot) 2000,778 E**</th>
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<tr>
<td>Fair</td>
<td>Keren (aLQTS-isopro) 1981,201 E*; Nguyen (aLQTS-A Rx) 1986,340 E*</td>
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<tr>
<td>Poor</td>
<td>Paul (Brugada-amio) 2006,e489 E* Nagele (Brugada-amio, BB) 2008,56 E*</td>
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Italicics:  
Animal studies  
*reversion rate  
**other
Overview

Treatment approaches to polymorphic wide complex tachycardia (polymorphic ventricular tachycardia (VT)) are generally empiric and with the exception of 3 studies that addressed hemodynamically unstable ventricular tachycardia of unspecified morphology (which likely included some cases of polymorphic VT, but excluded patients with known QT prolongation), have otherwise been based on either small series of patients in uncontrolled studies, case control studies, or compiled case reports. No randomized clinical trials have specifically addressed treatment of polymorphic ventricular tachycardia.

In the literature, polymorphic ventricular tachycardia (PMVT) has more specifically been described within subgroups of patients, categorized by its suspected mechanism, including:

- **Hemodynamically unstable ventricular tachycardia of unspecified morphology and mechanism with structural heart disease**
- **Long QT (torsade de pointes)**
  - Familial, acquired, and undifferentiated (idiopathic) forms
- **Short QT**
- **Normal QT**
- **Catecholaminergic**
- **Brugada syndrome**
- **Ischemic**
- **Idiopathic normal QT polymorphic VT**, defined as PMVT without QT prolongation of undiagnosed etiology, which may or may not be attributable to the above mechanisms.

The approach in developing this worksheet was to provide an evidence review based upon these categories of PMVT. Importantly, treatments may differ or occasionally appear contradictory, depending upon the presumed mechanism for the arrhythmia. In addition, much of this literature has focused on long-term treatment for secondary prevention of PMVT. These studies were included with the presumption that therapies that offer benefit for secondary prevention may perhaps be useful in the acute therapeutic setting as well, but were categorized as LOE 5 because of the extrapolative nature of this presumption.

Definitions

PMVT is defined as a wide complex arrhythmia of ventricular origin with variable, often beat-to-beat changes in QRS configuration, such that there is no uniformity in the appearance of QRS complexes. It is distinguished from monomorphic VT in which all QRS complexes have the same morphologic appearance, and from polymorphic VT in which there are >1 QRS morphologies, but each is monomorphic in its own right (that is, is comprised of 2 or more distinctly different monomorphic VT morphologies). Polymorphic VT is distinguished from ventricular fibrillation (VF) by manifesting some degree of organization, although the continuum between polymorphic VT and VF frequently overlaps. Conceptually, polymorphic VT can be said to lie on the continuum between organized monomorphic VT and VF, as depicted below: Typically, PMVT either self-terminates or deteriorates to pulseless arrest (VF); when ongoing it is rarely hemodynamically stable. Treating PMVT is challenging because although it can be frequently terminated with electrical shock, such success is transient; additional measures (discussed here) are required to prevent its recurrence. ECG abnormalities preceding PMVT can provide a clue as to its potential mechanism and direct therapy. These include QT prolongation, foreshortened QT, bradycardia, ST elevation in the right precordial leads, ECG evidence of acute ischemia. A history can also be revealing, such as of known congenital LQTS, prior precipitation of arrhythmias or syncope by adrenergic stress, or history of antiarrhythmic medication use. Importantly, once distinguished from monomorphic VT, pleomorphic VT or VF, the morphology of the PMVT itself no longer provides a clue as to its likely mechanism. That is, a “torsade-like” twisting configuration of the arrhythmia, whether present or absent, does not reliably distinguish true “torsade de pointes” from polymorphic VT of other etiologies. Nguyen (Circulation 1986) further argued that in circumstances of known or suspected drug-induced PMVT, the QT interval is also of limited value in directing therapy. All such patients (regardless of QT duration) responded to overdrive pacing, whereas administration of class IA antiarrhythmic agents was not beneficial and potentially harmful.

<table>
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<tr>
<th>Monomorphic (organized single morphology) VT</th>
<th>Pleomorphic (&gt;1 monomorphic) VT</th>
<th>Polymorphic (varying morphology) VT</th>
<th>VF (no organization)</th>
</tr>
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</table>

Forms of PMVT, by presumed mechanism, include:

- **Hemodynamically unstable ventricular tachycardia of unspecified morphology and mechanism with structural heart disease**
- **Long QT PMVT**, defined as a polymorphic VT that occurs in context of abnormal QT prolongation (typically >450 msec and often ≥ 500 msec). Long QT PMVT is further characterized as occurring in acquired forms (typically precipitated by antiarrhythmic drug use or hypokalemia, which are typically associated with bradycardia); familial or idiopathic (neither familial nor with an identifiable acquired cause). Treatment of PMVT attributable to LQTS can differ according to whether the disorder is acquired or familial/idiopathic.
- Short QT PMVT, defined as PMVT that occurs in context of an abnormally short QT (typically ≤ 320 msec).
- Normal QT PMVT
  - Catecholaminergic PMVT, defined as an arrhythmia that is typically provoked by stress or exercise and occurs in the absence of QT prolongation or structural heart disease.

- Brugada syndrome, defined as PMVT or VF associated with a distinct ECG pattern consisting of right bundle branch-like conduction and ST elevation in the right precordial leads with evidence of QT prolongation or structural heart disease.
- Ischemic PMVT, defined as a PMVT that is typically provoked by acute myocardial ischemia or infarction and occurs in the absence of QT prolongation.
- Idiopathic normal QT polymorphic VT, defined as PMVT without QT prolongation of undiagnosed etiology, which may or may not be attributable to the above mechanisms.

Discussion

PMVT is a heterogeneous entity, for which there may or may not be clues as to its precise mechanism at the time of acute presentation. This renders its treatment challenging, because treatments vary between the various forms of PMVT, and in some cases may appear contradictory. For example, isoproterenol is recommended for the acquired (bradycardia-associated) form of torsade de pointes, but is felt to be contraindicated in treating its congenital form.

The largest and only randomized controlled clinical trials have been conducted in persons with hemodynamically unstable VT which likely included PMVT but did not specifically characterize VT morphology (LOE 5) (Kowey 1995,3255; Levine 1996,67; Sheinman1995,3264). These studies, which excluded patients with known prolonged QT or suspected drug-induced VT, suggest amiodarone is an effective acute treatment measure based primarily on dose-ranging evidence and comparison against bretylium among patients who failed other pharmacologic therapies. Evidence for the efficacy of therapies aimed specifically at PMVT is weak, generally based on LOE 4-5 evidence and small numbers of studied patients or extrapolations from animal and pediatric studies. For PMVT due to acquired (drug-induced) LQT, overdrive pacing, or pharmacologic acceleration of heart rate with isoproterenol in the setting of bradyarrhythmias have suppressed PMVT (Keren 1981, 1167; Keren 1981,201; Khan 1981,1301; Ngyuen 1986, 340; Stern 1984,234; Yamamoto 1991,261; Yamamoto 1991,1). IV magnesium has also been reported to be useful in PMVT associated with LQT (either congenital or acquired) (LOE 3-5) (Hoshino 2006,112; Bando 1990,69; Stern 1984, 234;TZivoni 1988,392; Yamamoto 1991,261), but notably not for PMVT associated with a normal QT interval (TZivoni 1988,392). Registry data suggests that beta blockers and pacing are effective for secondary prevention or PMVT in patients with congenital LQT, but there are little published data about their use or effectiveness in the acute treatment of PMVT (LOE 5) (Moss 2000,616). There is indirect evidence, based on aggravation of torsade de pointes by isoproterenol in simulated forms of congenital LQT in ventricular muscle tissue preparations that isoproterenol may be contraindicated whereas beta blockers might be beneficial as acute therapy in such patients (LOE 5) (Shimizu 2000,778). Little is known about optimal acute treatment of PMVT associated with Brugada syndrome, but attenuation of ST elevation associated with Brugada and suppression of PMVT has been reported with use of isoproterenol (LOE 4-5) (Maury 2004,130; Miyazaki 1996,1061; Ohgo 2007,695). Catecholaminergic PMVT may be responsive to beta adrenergic blockade, based on the efficacy of such treatment in its secondary prevention (LOE 5), and a single reported (pediatric) experience regarding its acute administration (Derosa 2004,175; Leenhardt 1995,1512; Rosso 2007,1149). Ischemic PMVT may be responsive to beta adrenergic blockade based on a modest uncontrolled clinical experience (LOE 3) (Nademanee 2000,742). Acute treatment of short QT PMVT is not established; quinidine may be useful as a chronic treatment and although available in IV formulation, there are no data for its acute use for this condition (Schimpf 2005,357). A limitation of the numerous trials suggesting efficacy of the interventions described for all these forms of PMVT, is the inability of these studies to necessarily ascribe their “positive,” “neutral,” or “negative” results to the intervention under evaluation or to other concomitant circumstances (such as discontinuation of offending drugs, correction of electrolyte disturbances, or the combined effect of other therapeutic interventions). Specific evidence regarding treatment of each of these forms is summarized below.

Summary

1. Among patients with structural heart disease (ischemic, valvular or cardiomyopathy), in the absence of QT prolongation, or drug-provocation, treatment of hemodynamically unstable VT with IV amiodarone (150 mg/10minutes followed by 1 mg/min x 6 hours followed by 0.5 mg/min) reduced the frequency of recurrent arrhythmias compared to lower doses or bretylium. This evidence rests on three LOE 1 trials of good quality and reasonable size performed in the in-hospital setting, although PMVT was not specifically addressed in these studies (LOE 5) (Kowey 1995,3255; Levine 1996,67; Sheinman1995,3264).

2. PMVT associated with acquired or drug-precipitated LQT may be treated with:
   A. Overdrive pacing (atrial or ventricular) at 90-110 bpm based on a number of LOE 4 studies of small size, and from extrapolation of chronic use of pacing in secondary prevention of PMVT in such patients (LOE 5) (Keren 1981, 1167; Keren 1981,201; Khan 1981,1301; Ngyuen 1986, 340; Stern 1984,234; Yamamoto 1991,261; Yamamoto 1991,1). Generally, however, overdrive pacing is considered preferred treatment if circumstances permit its administration.
   B. IV isoproterenol (2-10 mcg/kg/min) when not contraindicated by the presence of ischemia or hypertension, based on a number of LOE 4 studies of small size (Keren 1981,201; Stern 1984,234), LOE 5 (LOE 4) animal studies (Yamamoto 1991,261; Yamamoto 1991,1), and LOE 5 (LOE 4) isolated ventricular muscle tissue study (Shimizu 2000). Notably, isoproterenol is felt to be contraindicated in congenital or idiopathic LQT based on historical discriptions of the frequent clinical provocation of episodes of PMVT by adrenergic stimulation (stress, startle or
exercise) (Moss 2000,616), and suggestive evidence from a LOE 5 (LOE 4) isolated ventricular muscle study in which it aggravated provocation of torsade in simulated LQT1 and LQT2 models (Shimizu 2000,778).

C. IV magnesium sulfate (25% of 50% solution 2 gms given over 1-2 minutes, followed by a continuous infusion of 2-30 mg/min, with repeat of the bolus as required, based on LOE 3 and LOE 4 clinical studies, and LOE 5 (LOE 4) animal studies (Hoshino 2006,112; Bando 1990,69; Stern 1984, 234; Tzivoni 1988,392; Yamamoto 1991,261).  
D. IV Potassium (0.5 mEq/kg (40 mEq) infused over 60-70 minutes) reversed quinidine-induced QT prolongation in a LOE 2 study of normal subjects and patients with heart failure, but did not address the occurrence or control of actual arrhythmias (Choy 1997,2149).

3. PMVT associated with familial long QT may be treated with:
   A. Overdrive pacing (atrial or ventricular) or beta blockers derived largely from extrapolation from LOE 4 studies of secondary prevention in patients with congenital LQT (LOE 5), and indirect evidence from a LOE 5 (LOE 4) isolated ventricular muscle tissue study, with no published experience regarding the acute use of these therapies (Bhandari 1985,63; Moss 1991,1524; Moss 2000,616; Shimizu 2000,778).  
   B. IV Magnesium sulfate, based on a small LOE 5 (LOE 4) pediatric study of congenital LQT (Hoshino 2006,112).
   C. IV Atropine (0.5 mg IV) based on a small LOE 5 (LOE 4) trial of its use in the prevention of provoked torsade de pointes in patients with congenital LQT (Furushima 1999,714).

4. Catecholaminergic PMVT may be treated with:
   A. Beta blockers based on the frequent precipitation of episodes by adrenergic stress, a LOE 5 (pediatric case report) of successful termination of PMVT with IV propranolol, and LOE 5 (LOE 4) secondary prevention studies using oral beta blockers. Some LOE 5 (LOE 3) secondary prevention studies suggest the combination of a beta blocker and verapamil may be more effective than a beta blocker alone in suppressing PMVT in these patients, but there are no reports of the acute administration of calcium channel blockers for this indication (DeRosa 2004,175; Leenhardt 1995,1512; Rosso 2007,1149; Sumitomo 2003,66; Swan 2005,162).

5. Short QT syndrome (insufficient data for treatment recommendations)
   A. Deployed medications (based on case reports) have included amiodarone, beta blockers and quinidine but not necessarily in the acute care setting (Lu 2006,115; Schimpf 2005,357).

6. Brugada syndrome may be treated with:
   A. IV isoproterenol based on LOE 4 and LOE 5 (LOE 4) evidence of suppression of PMVT and attenuation of ST elevation (Maury 2004,130; Miyazaki 1996,1061; Ohgo 2007,695)
   B. Class IA antiarrhythmic drugs and potentially amiodarone should be avoided based on LOE 5 (LOE 3) and case reports study that extrapolated from the ECG effects of these drugs in patients with Brugada syndrome (Nagale 2008,56; Paul 2006,e489).

7. PMVT associated with acute myocardial ischemia may be treated with:
   A. IV beta blockers based on a modestly sized LOE 3 study of fair quality (Nademanee 2000,742).

Acknowledgements:

Citation List

ANNOTATED REFERENCES NOT CLASSIFIED BY RHYTHM TYPE
(see later reference section for these annotated references classified by rhythm type)


LOE: 4 (n=19 dogs administered quinidine and then induced to torsade (n=10). Magnesium sulfate then administered with evaluation of EP effects, followed by attempts to reinduce torsade (prevented induction in 8/10 dogs); LOE 5 due to extrapolative nature of study Methodological Quality: Fair (no controls) Supportive/Neutral/Opposing: Supportive of magnesium's ability prevent reinduction of torsade, but did not address acute treatment Comment: Extrapolative study because of animal model and that evaluated magnesium's preventive not active therapeutic effect. Magnesium was observed to increase ERP but did nto change QT, resulting in significantly increased ERP/QT.

LOE: 2 (n=15 patients with familial or idiopathic LQTS and 11 controls who underwent EP testing); LOE 5 due to extrapolation from EP lab controlled study
Methodological Quality: Good
Supportive/Neutral/Opposing: Supportive of QT shortening effect from atrial pacing, but was observed both in LQTS and normal subjects; neutral for any effect of IV propranolol on QTc in either patients with LQTS or normals
Comment: Implies a potential QT benefit from atrial pacing in all patients; no effect of beta blocker on QTc.


LOE: 2 (concurrent case control study of n=12 healthy subjects treated with quinidine and n=8 CHF patients, and age-matched normal control subjects, each of whom served as their own control before and after potassium infusion); LOE 5 due to extrapolative nature of study
Methodological Quality: Good
Supportive/Neutral/Opposing: Supportive of potassium infusion as reversing ECG effects of quinidine and CHF (QT prolongation); but did not address arrhythmias
Comment: Extrapolative study demonstrating ability of potassium infusion to reverse ECG effects of quinidine.


LOE: 4 (pediatric case report); LOE 5 based on extrapolation as well as the study representing a single case report
Methodological Quality: Reasonable descriptor but categorized as poor since represents a single case report
Supportive/Neutral/Opposing: Supportive of acute treatment with IV propranolol
Comment: Isolated case report. Included in grid (as a poor study) because of this representing a case report, and because there are no other published data on acute use of beta blockers for this etiology of PMVT


LOE: 4 (n=9 patients with congenital long QT received intracoronary acetylcholine, before and following pretreatment with atropine. Acetylcholine significantly prolonged QT prior to (resulting in torsade in n=4) but not after administration of atropine); LOE 5 due to extrapolative study
Methodological Quality: Good
Supportive/Neutral/Opposing: Supportive of atropine’s potential use in LQTS
Comment: Extrapolative study due to provocation of torsade by acetylcholine and administration of atropine for preventative not therapeutic purposes.


LOE 4 (n=5 patients with congenital LQTS and 5 with acquired LQTS and torsade de pointes treated with a bolus injection of magnesium sulfate (12 mg/kg given over 1-2 min) followed by continuous infusion for 2-7 days. 6/7 responded completely to initial bolus, without recurrence during continuous infusion. One patient received other modes of therapy before magnesium; 6 received only magnesium.); LOE 5 based on pediatric extrapolation
Methodological Quality: Good (6/7 patients only received magnesium)
Supportive/Neutral/Opposing: Supportive of magnesium sulfate for torsade de pointes associated with congenital LQT
Comment: Pediatric study.


LOE: 4 (n=10 patients with torsade due to antiarrhythmic therapy (n=9) or CNS injury (n=1). Isoproterenol was effective in 5/7 patients in whom it was given (felt to be contraindicated in 2 others); ventricular pacing was effective in 4/4 patients in whom it was attempted.
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of isoproterenol and ventricular pacing for acute treatment of acquired torsade.
Comment: Small case series.

LOE: 4 (n=4 patients with torsade associated with quinidine or disopyramide. Isoproterenol was ineffective in 2 and considered hazardous in 2. Ventricular pacing effective suppressed torsade in all 4)
Methodological Quality: Fair
Supportive/Neutral/Opposing: Opposing of isoproterenol’s acute benefit in torsade; supportive of pacing support for treatment of acute torsade
Comment: Mixed outcome study for isoproterenol versus pacing.


LOE: 4 (n=11 patients, 7/11 of whom received acute overdrive ventricular or AV sequential pacing for acquired LTC torsade de pointes that remained unresponsive to withdrawing offending agents and antiarrhythmic medications)
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of temporary overdrive pacing
Comment: Observational study with multiple confounders.


LOE: 1(randomized positive control dose ranging trial); but LOE 5 due to unspecified rhythm morphology
Methodological Quality: Good. Study was blinded with respect to tested drugs, allowed for supplemental doses of blinded study drug during the double-blind period which, if ineffective, could be followed by open label supplemental doses of IV amiodarone or bretylium. Limitation of study was high cross-over rate after 6 hours of treatment.
Supportive/Neutral/Opposing: Neutral in terms of efficacy of the two drugs; supportive with respect to fewer adverse effects with amiodarone as compared with bretylium.
Comment: Multicenter randomized double blind positive controlled comparison of IV amiodarone (at low and moderate dosing regimen) vs bretylium for hypotensive VT or VF refractory to lidocaine and procainamide. Excluded patients with QT > 0.5 seconds. Efficacy defined as ability of study drug to prevent recurrent VT (primary endpoint was events per unit time during the double-blind study period of 48 hrs). Comparable efficacy with respect to arrhythmia event rate during first 48 hrs of therapy seen between 1000mg/24 hr amiodarone group and bretylium group, which was greater than 125 mg/24 hour amiodarone group. Notably during first 0-6 hours of therapy (when largest number of patients were on blinded therapy due to significant drop out rate from bretylium group thereafter) 1000 mg/24 amiodarone tended to be more effective than bretylium in preventing arrhythmia recurrence (p=0.087).


LOE: 4 (n=21 children with catecholaminergic polymorphic VT followed into adulthood, treated with beta blockers); LOE 5 based on extrapolation from a chronic phase preventative study
Methodological Quality: Good (case series, descriptive only). Small study (n=21)
Supportive/Neutral/Opposing: Favors chronic administration of beta blockers for this condition, but does not address acute management
Comment: Extrapolation of chronic to acute care.


LOE: 1 (randomized positive control dose ranging trial); but LOE 5 due to unspecified rhythm morphology
Methodological Quality: Good. Study was blinded with respect to tested dosing regimen, but allowed for open label supplemental drug infusions of known dose, and excluded use of other antiarrhythmic agents.
Supportive/Neutral/Opposing: Supportive of favorable response to treatment; dose response not established.
Comment: Multicenter inpatient study randomly assigned 273 patients with recurrent hypotensive VT or VF (5%) refractory to lidocaine, proainamide and bretylium to low, medium and high doses of IV amiodarone. Number of supplemental doses of IV amiodarone required was significantly greater in the 525 mg (low dose) group than the 2100 mg (high dose) group. Overall, apparent antiarrhythmic response seen in 40% of recipients (primary endpoint). Primary endpoint was proportion of patients who survived with no further episodes of VT and no adverse events requiring drug discontinuation during hours 6-24 of double-blind therapy. Excluded “congenital QT prolongation”.

LOE: Case report
Methodological Quality: Fair
Supportive/Neutral/Opposing: Neutral in providing anecdotal and theoretical basis for some therapies. Insufficient to include in the grid analysis because of its limitation to a case report and review of literature, in which treatment is empiric. Deployed therapies have included the combination of amiodarone plus a beta blocker and quinidine.
Comment: Case report only.


LOE: 4 (n=12 descriptive study); LOE 5 due to extrapolation from po to IV amiodarone
Methodological Quality: Good
Supportive/Neutral/Opposing: Suggests that oral amiodarone is safe in patients who experienced torsade de pointes as a complication of previous antiarrhythmic therapy, in terms of providing long-term rhythm control and freedom from syncope or sudden death.
Comment: Oral amiodarone in patients who had declared a torsade risk to antiarrhythmic therapy. However, amiodarone was not administered during torsade, nor in context of a QT interval perturbed by concurrent antiarrhythmic therapy. Hence, the ability to extrapolate its effects when torsade may be ongoing is not possible.


LOE: Case report
Methodological Quality: Fair; descriptive only
Supportive/Neutral/Opposing: Supportive
Comment: Case report (n=1) of patient with Brugada syndrome in whom VT was suppressed by isoproterenol.


LOE: 3; LOE 5 due to extrapolation of ECG effects of interventions rather than direct termination of arrhythmias.
Methodological Quality: Fair. Testing was selected. A control group (n=3) was present in whom antiarrhythmic drugs had no effect on ST segments
Supportive/Neutral/Opposing: Supportive of isoproterenol
Comment: ST elevation was attenuated by isoproterenol and augmented by class IA antiarrhythmic drugs (procainamide or disopyramide which also increased frequency of PVCs) but not by class IB agents lidocaine or mexiletine) or verapamil in n=4 patients with Brugada syndrome. There was no effect on ST segments by IA drugs in n=3 controls


LOE: 4 (n=30 patients from an International Registry of LQTS who received permanent pacemakers for management of recurrent syncope); LOE 5 due to extrapolative nature of study.
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of permanent pacing resulting in a reduction of recurrent syncopal or cardiac arrest events.
Comment: Extrapolation study that addresses value of pacing in LQTS, but in this instance "prophylactically" not therapeutically. Included in grid since pacing has been a traditional approach to treatment of torsade de pointes.


LOE: 4 (n=869 patients with congenital LQTS treated with beta blockers); LOE 5 due to extrapolation to chronic phase of disease rather than acute treatment of arrhythmias.
Methodological Quality: Good
Supportive/Neutral/Opposing: Supportive of benefit from treatment with long-term beta blockers, but does not address acute interventions. Safety of long-term beta blockers argues for potential benefit in short term use, but this was not addressed by this or other studies
Comment: Benefit from beta blockers in the chronic prophylaxis congenital LQTS may or may not imply benefit from acute use.

LOE: 3 (n=49 patients with recent MI and recurrent VF/VT not all of specified morphology treated in nonrandomized fashion with ACLS-Guided therapies (n=22) versus sympathetic blockade (n=27))
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of value of sympathetic blockade with IV beta blockers on suppression of polymorphic VT refractory to other measures.
Comment: Selected treatment in both patient groups


LOE: 5 (case report)
Methodological Quality: Fair
Supportive/Neutral/Opposing: Opposing use of oral amiodarone and oral beta blockers as potentially aggravating Brugada expression on ECG and VT
Comment: Isolated case report in which amiodarone may have precipitated preexisting silent Brugada ECG pattern and subsequent VT, which may have been further aggravated by addition of metoprolol. When both were discontinued, the arrhythmias resolved as did Brugada ECG pattern.


LOE: 4 (n=45 patients with polymorphic VT, including drug or electrolyte related; excluded patient with familial or idiopathic LQTS)
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of use of drug history rather than LQT interval for predicting response to therapy; supportive of acute pacing therapies (atrial or ventricular at 90-110 bpm) which was effective in virtually all patients in whom it was given regardless of QT interval; opposing class IA antiarrhythmic agents which resulted in recurrence or increased frequency of PMVT; neutral for lidocaine which has inconsistent benefit.
Comment: Provides a number of observations regarding effective and ineffective therapies for PMVT, but uncontrolled with respect to other factors that may have contributed to treatment success (such as withdrawal of offending drugs and/or correction of electrolyte abnormalities).


LOE: 4
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of isoproterenol
Comment: n=67 consecutive patients with Brugada syndrome based on ECG criteria and ≥3 episodes VF electrical (storm) (n=7), documented VF and/or syncope (n=39), or asymptomatic (n=21). Isoproterenol used in 5/7 patients with electrical storm and successfully suppressed VF.


LOE: 5 (case report)
Methodological Quality: Fair
Supportive/Neutral/Opposing: Opposing use of IV amiodarone
Comment: Isolated case report of “unmasking” of Brugada ECG by IV amiodarone, discontinuation of which resulted in ECG resolution.


LOE: 2 (comparison of beta blocker vs beta block plus calcium blocker during exercise stress testing (each subject serving as his/her own control)); LOE 5 based on extrapolation from an acute exercise study
Methodological Quality: Fair (nonrandomized comparison with each patient serving as his/her own control). Small study (n=6)
Supportive/Neutral/Opposing: Favors suppression of VT by combination of beta blockers and calcium channel blocker (verapamil)
Comment: Study included 3 patients in the pediatric age range (8-13 years).

LOE: 4 Review article but compiled 17 patients from previously published case reports, suggesting that antiarrhythmic drugs such as ibutilide, sotalol and flecaainide have been demonstrated to be ineffective in prolongation of the (short) QT interval; only quinidine has been effective in the normalization of the QT interval and rendering arrhythmias noninducible
Methodological Quality: Fair (review of published case reports only)
Supportive/Neutral/Opposing: Suggests a potential benefit of quinidine in chronic treatment, but does address acute treatment issues
Comment: Not included in grid based on descriptive nature of published case reports.


LOE: 1(randomized positive control dose ranging trial); but LOE 5 due to unspecified rhythm morphology
Methodological Quality: Good. Study was blinded with respect to tested dosing regimen, but allowed for open label supplemental drug infusions of known dose, and excluded use of other antiarrhythmic drugs.
Comment: Multicenter inpatient study of 342 patients with recurrent (despite cardioversion) hypotensive VT or VF refractory to lidocaine, procanimide or bretylium were randomized to 3 blinded dosing regimens of IV amiodarone, with supplemental open-label dosing for recurrences. Primary endpoint was VF/VT event rate, defined as number of hypotensive events per hour during the 48 hour double-blind observation period. The event rate decreased with increasing doses of IV amiodarone. Excluded QT $\geq$ 0.55 seconds


LOE: 5 (bench lab study evaluating effect if isoproterenol in models mimicking LQT1, LQT2 and LQT3).
Methodological Quality: Good
Supportive/Neutral/Opposing: Opposing use of isoproterenol in congenital forms of LQT1 and LQT2 based on induction of torsade; and suppression of torsade in LQT3.
Comment: Bench research study using arterially perfused wedge of canine left ventricle and use of a Iks blocker, IKr blocker and augmented INa to create a model of LQT1, LQT2 and LQT3 respectfully. Study raises caution in using isoproterenol in congenital LQTS of LQT1 or LQT2 variety. Also indirectly suggests potential benefit from use of beta blockers in LQT1 and LQT2 but not LQT3.


LOE: 4 (n=16 patients with acquired torsade, treated with a variety of measures including DC shock which was transiently successful in 9/9; lidocaine successful in 0/5, Procanimamide successful in 0/1, Atropine successful in ¼, isoproterenol successful in 7/10, Cardiac pacing successful in 6/6, magnesium sulfate successful in 2/2.
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of isoproterenol, pacing and magnesium
Comment: Small uncontrolled case series.


LOE: 4; LOE 5 based on extrapolation from chronic prevention study and its inclusion of some pediatric patients
Methodological Quality: Fair (case series, descriptive-only study)
Supportive/Neutral/Opposing: Neutral regarding benefit from beta blockers in chronic use (31% of patients were controlled) and calcium channel blocker (verapamil) in 3 of 3 treated patients in long-term follow-up.
Comment: Neutral


LOE: 4; LOE 5 based on extrapolation from an acute exercise study
Methodological Quality: Fair (case series, descriptive-only study)
Supportive/Neutral/Opposing: Favors suppression of ventricular arrhythmias with verapamil in genetically-confirmed RyR2 mutations (congenital ryanodine receptor defect) during exercise testing.
Comment: Does not address acute treatment issues.


LOE: 3 (n=12 with long QT; n=5 without long QT)
Methodological Quality: Fair. Magnesium suppressed PMVT associated with LQT in 12/12. In comparison group of n=5 with chronic ischemic heart disease and polymorphic VT without long QT 0/6 responded to Mg at comparable doses.
Supportive/Neutral/Opposing: Supportive of Mg for PMVT in setting of LQT; opposing for Mg for PMVT without LQT.
Comment: Small study


LOE: 4 (descriptive cohort; n=14 with LQT-associated PMVT; n=10 with normal QT-associated PMVT; n=8 with asymptomatic PMVT)
Methodological Quality: Poor (descriptive only)
Supportive/Neutral/Opposing: Neutral in that unable to determine if use of pharmacologic interventions necessarily had a beneficial or neutral effect (other than if assuming death if the arrhythmia were left untreated).
Comment: Treatment was empiric. In group with normal QT, 7/10 received beta blockers, one of whom died. Of those with LQT, 13/14 received magnesium, 3 of whom died. Data analysis allowed for no real conclusions about treatment efficacy, unless one presumed patients might have died without the treatments provided.


LOE: 4 (n=60 dogs in which n=28 were induced to torsade de pointes after administration of quinidine sulfate. Isoproterenol prevented occurrence of torsade in all 9 dogs in which it was administered, magnesium in 7/9 dogs, and verapamil in 4/10 dogs; LOE 5 due to extrapolative nature of study.
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of isoproterenol and magnesium in preventing reinduction of torsade (less so verapamil).
Comment: Extraprolative study because of assessment of prophylactic but not acute therapeutic efficacy of these interventions in terminating torsade.


LOE: 4 (n=60 dog study without controls in which torsade de pointes was induced in n=34 after administration of quinidine sulfate and then treated with isoproterenol); LOE 5 due to extrapolation from animal study.
Methodological Quality: Fair (no controls)
Supportive/Neutral/Opposing: Supportive of isoproterenol for quinidine induced torsade in animal model.
Comment: Animal model without controls. Isoproterenol was noted to have favorable EP effects in n=9 who underwent electrophysiologic testing (shortening of cycle length, QT, ERP and dispersion of ERP) and prevented occurrence of torsade in all animals.

ANNOTATED REFERENCES CLASSIFIED BY RHYTHM TYPE

Hemodynamically Unstable VT of Unspecified Morphology and Mechanism in patients with structural heart disease and impaired left ventricular function (ischemia, valvular, cardiomyopathy) and without LQTS


LOE: 1(randomized positive control dose ranging trial); but LOE 5 due to unspecified rhythm morphology
Methodological Quality: Good. Study was blinded with respect to tested drugs, allowed for supplemental doses of blinded study drug during the double-blind period which, if ineffective, could be followed by open label supplemental doses of IV amidoarone or betylium. Limitation of study was high cross-over rate after 6 hours of treatment.
Supportive/Neutral/Opposing: Neutral in terms of efficacy of the two drugs; supportive with respect to fewer adverse effects with amiodarone as compared with bretylium.
Comment: Multicenter randomized double blind positive controlled comparison of IV amidoarone (at low and moderate dosing regimen) vs bretylium for hypotensive VT or VF refractory to lidocaine and procainamide. Excluded patients with QT $> 0.5$ seconds. Efficacy defined as ability of study drug to prevent recurrent VT (primary endpoint was events per unit time during the double-blind study period of 48 hrs). Comparable efficacy with respect to arrhythmia event rate during first 48 hrs of therapy seen between 1000mg/24 hr amidoarone group and bretylium group, which was greater than 125 mg/24 hour amidoarone group. Notably during first 0-6 hours of therapy (when largest number of patients were on blinded therapy due to significant drop out rate from bretylium group thereafter) 1000 mg/24 amidoarone tended to be more effective than bretylium in preventing arrhythmia recurrence ($p=0.087$).


LOE: 1 (randomized positive control dose ranging trial); but LOE 5 due to unspecified rhythm morphology
Methodological Quality: Good. Study was blinded with respect to tested dosing regimen, but allowed for open label supplemental drug infusions of known dose, and excluded use of other antiarrhythmic agents.
Supportive/Neutral/Opposing: Supportive of favorable response to treatment; dose response not established.
Comment: Multicenter inpatient study randomized 273 patients with recurrent hypotensive VT or VF (5%) refractory to lidocaine, proinamade and bretylium to low, medium and high doses of IV amiodarone. Number of supplemental doses of IV amiodarone required was significantly greater in the 525 mg (low dose) group than the 2100 mg (high dose) group. Overall, apparent antiarrhythmic response seen in 40% of recipients (primary endpoint). Primary endpoint was proportion of patients who survived with no further episodes of VT and no adverse events requiring drug discontinuation during hours 6-24 of double-blind therapy. Excluded "congential QT prolongation".


LOE: 1 (randomized positive control dose ranging trial); but LOE 5 due to unspecified rhythm morphology
Methodological Quality: Good. Study was blinded with respect to tested dosing regimen, but allowed for open label supplemental drug infusions of known dose, and excluded use of other antiarrhythmic drugs.
Comment: Multicenter inpatient study of 342 patients with recurrent (despite cardioversion) hypotensive VT or VF refractory to lidocaine, procainamide or bretylium were randomized to 3 blinded dosing regimens of IV amiodarone, with supplemental open-label dosing for recurrences. Primary endpoint was VF/VT event rate, defined as number of hypotensive events per hour during the 48 hour double-blind observation period. The event rate decreased with increasing doses of IV amidoarone. Excluded QT $\geq 0.55$ seconds.

**Catecholaminergic Polymorphic Ventricular Tachycardia without QT prolongation (CPVT)**


LOE: 4 (pediatric case report); LOE 5 based on extrapolation as well as the study representing a single case report
Methodological Quality: Reasonable descriptor but categorized as poor since represents a single case report
Supportive/Neutral/Opposing: Supportive of acute treatment with IV propranolol
Comment: Isolated case report. Included in grid (as a poor study) because of this representing a case report, and because there are no other published data on acute use of beta blockers for this etiology of PMVT
Other published studies are directed toward prevention of this form of VT via use principally of beta blockers, in some cases along with verapamil.


LOE: 4 (n=21 children with catecholaminergic polymorphic VT followed into adulthood, treated with beta blockers); LOE 5 based on extrapolation from a chronic phase preventative study
Methodological Quality: Good (case series, descriptive only). Small study (n=21)
Supportive/Neutral/Opposing: Favors chronic administration of beta blockers for this condition, but does not address acute management
Comment: Extrapolation of chronic to acute care.

LOE: 2 (comparison of beta blocker vs beta block plus calcium blocker during exercise stress testing (each subject serving as his/her own control)); LOE 5 based on extrapolation from an acute exercise study
Methodological Quality: Fair (nonrandomized comparison with each patient serving as his/her own control). Small study (n=6)
Supportive/Neutral/Opposing: Favors suppression of VT by combination of beta blockers and calcium channel blocker (verapamil)
Comment: Study included 3 patients in the pediatric age range (8-13 years).


LOE: 4; LOE 5 based on extrapolation from chronic prevention study and its inclusion of some pediatric patients
Methodological Quality: Fair (case series, descriptive-only study)
Supportive/Neutral/Opposing: Neutral regarding benefit from beta blockers in chronic use (31% of patients were controlled) and calcium channel blocker (verapamil) in 3 of 3 treated patients in long-term follow-up.
Comment: Neutral


LOE: 4; LOE 5 based on extrapolation from an acute exercise study
Methodological Quality: Fair (case series, descriptive-only study)
Supportive/Neutral/Opposing: Favors suppression of ventricular arrhythmias with verapamil in genetically-confirmed RyR2 mutations (congenital ryanodine receptor defect) during exercise testing.
Comment: Does not address acute treatment issues.

Ischemic Polymorphic Ventricular Tachycardia without QT prolongation (IPMVT)


LOE: 3 (n=49 patients with recent MI and recurrent VF/VT not all of specified morphology treated in nonrandomized fashion with ACLS-Guided therapies (n=22) versus sympathetic blockade (n=27))
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of value of sympathetic blockade with IV beta blockers on suppression of polymorphic VT refractory to other measures.
Comment: Selected treatment in both patient groups


LOE: 3 (n=12 with long QT; n=5 without long QT)
Methodological Quality: Fair. Magnesium suppressed PMVT associated with LQT in 12/12. In comparison group of n=5 with chronic ischemic heart disease and polymorphic VT without long QT 0/6 responded to Mg at comparable doses.
Supportive/Neutral/Opposing: Supportive of Mg for PMVT in setting of LQT; opposing for Mg for PMVT without LQT.
Comment: Small study

Polymorphic VT with QT prolongation (familial, acquired and undifferentiated (idiopathic) forms of LQTS; torsade de pointes)

Familial

LOE: 2 (n=15 patients with familial or idiopathic LQTS and 11 controls who underwent EP testing); LOE 5 due to extrapolation from EP lab controlled study
Methodological Quality: Good
Supportive/Neutral/Opposing: Supportive of QT shortening effect from atrial pacing, but was observed both in LQTS and normal subjects; neutral for any effect of IV propranolol on QTc in either patients with LQTS or normals
Comment: Implies a potential QT benefit from atrial pacing in all patients; no effect of beta blocker on QTc.


LOE: 4 (n=9 patients with congenital long QT received intracoronary acetylcholine, before and following pretreatment with atropine. Acetylcholine significantly prolonged QT prior to (resulting in torsade in n=4) but not after administration of atropine); LOE 5 due to extrapolative study
Methodological Quality: Good
Supportive/Neutral/Opposing: Supportive of atropine’s potential use in LQTS
Comment: Extrapolative study due to provocation of torsade by acetylcholine and administration of atropine for preventative not therapeutic purposes.


LOE 4 (n=5 patients with congenital LQTS and 5 with acquired LQTS and torsade de pointes treated with a bolus injection of magnesium sulfate (12 mg/kg given over 1-2 min) followed by continuous infusion for 2-7 days. 6/7 responded completely to initial bolus, without recurrence during continuous infusion. One patient received other modes of therapy before magnesium; 6 received only magnesium.); LOE 5 based on pediatric extrapolation
Methodological Quality: Good (6/7 patients only received magnesium)
Supportive/Neutral/Opposing: Supportive of magnesium sulfate for torsade de pointes associated with congenital LQT
Comment: Pediatric study.


LOE: 4 (n=30 patients from an International Registry of LQTS who received permanent pacemakers for management of recurrent syncope); LOE 5 due to extrapolative nature of study.
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of permanent pacing resulting in a reduction of recurrent syncopal or cardiac arrest events.
Comment: Extrapolation study that addresses value of pacing in LQTS, but in this instance “prophylactically” not therapeutically. Included in grid since pacing has been a traditional approach to treatment of torsade de pointes.


LOE: 4 (n=869 patients with congenital LQTS treated with beta blockers); LOE 5 due to extrapolation to chronic phase of disease rather than acute treatment of arrhythmias.
Methodological Quality: Good
Supportive/Neutral/Opposing: Supportive of benefit from treatment with long-term beta blockers, but does not address acute interventions. Safety of long-term beta blockers argues for potential benefit in short term use, but this was not addressed by this or other studies
Comment: Benefit from beta blockers in the chronic prophylaxis congenital LQTS may or may not imply benefit from acute use.


LOE: 5 (bench lab study evaluating effect if isoproterenol in models mimicking LQT1, LQT2 and LQT3).
Methodological Quality: Good
Supportive/Neutral/Opposing: Opposing use of isoproterenol in congenital forms of LQT1 and LQT2 based on induction of torsade; and suppression of torsade in LQT3.
Comment: Bench research study using arterially perfused wedge of canine left ventricle and use of a Iks blocker, IKr blocker and augmented INa to create a model of LQT1, LQT2 and LQT3 respectfully. Study raises caution in using isoproterenol in congenital LQTS of LQT1 or LQT2 variety. Also indirectly suggests potential benefit from use of beta blockers in LQT1 and LQT2 but not LQT3.

Acquired

LOE: 4 (n=19 dogs administered quinidine and then induced to torsade (n=10). Magnesium sulfate then administered with evaluation of EP effects, followed by attempts to reinduce torsade (prevented induction in 8/10 dogs); LOE 5 due to extrapolative nature of study
Methodological Quality: Fair (no controls)
Supportive/Neutral/Opposing: Supportive of magnesium's ability prevent reinduction of torsade, but did not address acute treatment
Comment: Extrapolative study because of animal model and that evaluated magnesium's preventive not active therapeutic effect. Magnesium was observed to increase ERP but did not change QT, resulting in significantly increased ERP/QT.


LOE: 2 (concurrent case control study of n=12 healthy subjects treated with quinidine and n=8 CHF patients, and age-matched normal control subjects, each of whom served as their own control before and after potassium infusion); LOE 5 due to extrapolative nature of study
Methodological Quality: Good
Supportive/Neutral/Opposing: Supportive of potassium infusion as reversing ECG effects of quinidine and CHF (QT prolongation); but did not address arrhythmias
Comment: Extrapolative study demonstrating ability of potassium infusion to reverse ECG effects of quinidine.


LOE 4 (n=5 patients with congenital LQTS and 5 with acquired LQTS and torsade de pointes treated with a bolus injection of magnesium sulfate (12 mg/kg given over 1-2 min) followed by continuous infusion for 2-7 days. 6/7 responded completely to initial bolus, without recurrence during continuous infusion. One patient received other modes of therapy before magnesium; 6 received only magnesium.); LOE 5 based on pediatric extrapolation
Methodological Quality: Good (6/7 patients only received magnesium)
Supportive/Neutral/Opposing: Supportive of magnesium sulfate for torsade de pointes associated with congenital LQT
Comment: Pediatric study.


LOE: 4 (n=10 patients with torsade due to antiarrhythmic therapy (n=9) or CNS injury (n=1). Isoproterenol was effective in 5/7 patients in whom it was given (felt to be contraindicated in 2 others); ventricular pacing was effective in 4/4 patients in whom it was attempted.
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of isoproterenol and ventricular pacing for acute treatment of acquired torsade.
Comment: Small case series.


LOE: 4 (n=4 patients with torsade associated with quinidine or disopyramide. Isoproterenol was ineffective in 2 and considered hazardous in 2. Ventricular pacing effective suppressed torsade in all 4)
Methodological Quality: Fair
Supportive/Neutral/Opposing: Opposing of isoproterenol's acute benefit in torsade; supportive of pacing support for treatment of acute torsade
Comment: Mixed outcome study for isoproterenol versus pacing.


LOE: 4 (n=11 patients, 7/11 of whom received acute overdrive ventricular or AV sequential pacing for acquired LTC torsade de pointes that remained unresponsive to withdrawal of offending agents and antiarrhythmic medications/
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of temporary overdrive pacing
Comment: Observational study with multiple confounders.

LOE: 4 (n=12 descriptive study); LOE 5 due to extrapolation from po to IV amiodarone
Methodological Quality: Good
Supportive/Neutral/Opposing: Suggests that oral amiodarone is safe in patients who experienced torsade de pointes as a complication of previous antiarrhythmic therapy, in terms of providing long-term rhythm control and freedom from syncope or sudden death.
Comment: Oral amiodarone in patients who had declared a torsade risk to antiarrhythmic therapy. However, amiodarone was not administered during torsade, nor in context of a QT interval perturbed by concurrent antiarrhythmic therapy. Hence, the ability to extrapolate its effects when torsade may be ongoing is not possible.


LOE: 4 (n=45 patients with polymorphic VT, including drug or electrolyte related; excluded patient with familial or idiopathic LQTS)
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of use of drug history rather than QT interval for predicting response to therapy; supportive of acute pacing therapies (atrial or ventricular at 90-110 bpm) which was effective in virtually all patients in whom it was given regardless of QT interval; opposing class IA antiarrhythmic agents which resulted in recurrence or increased frequency of PMVT; neutral for lidocaine which has inconsistent benefit.
Comment: Provides a number of observations regarding effective and ineffective therapies for PMVT, but uncontrolled with respect to other factors that may have contributed to treatment success (such as withdrawal of offending drugs and/or correction of electrolyte abnormalities).


LOE: 4 (n=16 patients with acquired torsade, treated with a variety of measures including DC shock which was transiently successful in 9/9; lidocaine successful in 0/5, Procainamide successful in 0/1, Atropine successful in ¼, isoproterenol successful in 7/10, Cardiac pacing successful in 6/6, magnesium sulfate successful in 2/2.
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of isoproterenol, pacing and magnesium
Comment: Small uncontrolled case series.


LOE: 3 (n=12 with acquired long QT; n=5 without long QT)
Methodological Quality: Fair. Magnesium suppressed PMVT associated with LQT in 12/12. In comparison group of n=5 with chronic ischemic heart disease and polymorphic VT without long QT 0/6 responded to Mg at comparable doses.
Supportive/Neutral/Opposing: Supportive of Mg for PMVT in setting of LQT; opposing for Mg for PMVT without LQT.
Comment: Small study


LOE: 4 (n=60 dogs in which n=28 were induced to torsade de pointes after administration of quinidine sulfate. Isoproterenol prevented occurrence of torsade in all 9 dogs in which it was administered, magnesium in 7/9 dogs, and verapamil in 4/10 dogs; LOE 5 due to extraplicative nature of study.
Methodological Quality: Fair
Supportive/Neutral/Opposing: Supportive of isoproterenol and magnesium in preventing reinduction of torsade (less so verapamil).
Comment: Extrapulative study because of assessment of prophylactic but not acute therapeutic efficacy of these interventions in terminating torsade.


LOE: 4 (n=60 dog study without controls in which torsade de pointes was induced in n=34 after administration of quinidine sulfate and then treated with isoproterenol); LOE 5 due to extrapolation from animal study.
Methodological Quality: Fair (no controls)
Supportive/Neutral/Opposing: Supportive of isoproterenol for quinidine induced torsade in animal model.
Comment: Animal model without controls. Isoproterenol was noted to have favorable EP effects in n=9 who underwent electrophysiologic testing (shortening of cycle length, QT, ERP and dispersion of ERP) and prevented occurrence of torsade in all animals.
Undifferentiated


LOE: 4 (descriptive cohort; n=14 with LQT-associated PMVT; n=10 with normal QT-associated PMVT; n=8 with asymptomatic PMVT)
Methodological Quality: Poor (descriptive only)
Supportive/Neutral/Opposing: Neutral in that unable to determine if use of pharmacologic interventions necessarily had a beneficial or neutral effect (other than if assuming death if the arrhythmia were left untreated).
Comment: Treatment was empiric. In group with normal QT, 7/10 received beta blockers, one of whom died. Of those with LQT, 13/14 received magnesium, 3 of whom died. Data analysis allowed for no real conclusions about treatment efficacy, unless one presumed patients might have died without the treatments provided.

Short QT Syndrome (polymorphic VT with short QT) (SQTS)


LOE: Case report
Methodological Quality: Fair
Supportive/Neutral/Opposing: Neutral in providing anecdotal and theoretical basis for some therapies. Insufficient to include in the grid analysis because of its limitation to a case report and review of literature, in which treatment is empiric. Deployed therapies have included the combination of amiodarone plus a beta blocker and quinidine.
Comment: Case report only.


LOE: 4 Review article but compiled 17 patients from previously published case reports, suggesting that antiarrhythmic drugs such as ibutilide, sotalol and flecaainide have been demonstrated to be ineffective in prolongation of the (short) QT interval; only quinidine has been effective in the normalization of the QT interval and rendering arrhythmias noninducible
Methodological Quality: Fair (review of published case reports only)
Supportive/Neutral/Opposing: Suggests a potential benefit of quinidine in chronic treatment, but does address acute treatment issues
Comment: Not included in grid based on descriptive nature of published case reports.

Brugada syndrome


LOE: Case report
Methodological Quality: Fair; descriptive only
Supportive/Neutral/Opposing: Supportive
Comment: Case report (n=1) of patient with Brugada syndrome in whom VT was suppressed by isoproterenol.


LOE: 3; LOE 5 due to extrapolation of ECG effects of interventions rather than direct termination of arrhythmias.
Methodological Quality: Fair. Testing was selected. A control group (n=3) was present in whom antiarrhythmic drugs had no effect on ST segments
Supportive/Neutral/Opposing: Supportive of isoproterenol
Comment: ST elevation was attenuated by isoproterenol and augmented by class IA antiarrhythmic drugs (procainamide or disopyramide which also increased frequency of PVCs) but not by class IB agents lidocaine or mexiletine) or verapamil in n=4 patients with Brugada syndrome. There was no effect on ST segments by IA drugs in n=3 controls


LOE: 5 (case report)
Methodological Quality: Fair  
Supportive/Neutral/Opposing: Opposing use of oral amiodarone and oral beta blockers as potentially aggravating Brugada expression on ECG and VT  
Comment: Isolated case report in which amiodarone may have precipitated preexisting silent Brugada ECG pattern and subsequent VT, which may have been further aggravated by addition of metoprolol. When both were discontinued, the arrhythmias resolved as did Brugada ECG pattern.


LOE: 4  
Methodological Quality: Fair  
Supportive/Neutral/Opposing: Supportive of isoproterenol  
Comment: n=67 consecutive patients with Brugada syndrome based on ECG criteria and ≥3 episodes VF electrical (storm) (n=7), documented VF and/or syncope (n=39), or asymptomatic (n=21). Isoproterenol used in 5/7 patients with electrical storm and successfully suppressed VF.


LOE: 5 (case report)  
Methodological Quality: Fair  
Supportive/Neutral/Opposing: Opposing use of IV amiodarone  
Comment: Isolated case report of “unmasking” of Brugada ECG by IV amiodarone, discontinuation of which resulted in ECG resolution.