FREQUENCY, TEMPORAL ONSET OF OCCURRENCE AND RISK FACTOR IDENTIFICATION FOR ACQUIRED LONG QT SYNDROME IN A CRITICAL CARE POPULATION

by

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ABSTRACT

**Background:** Acquired long QT syndrome (aLQTS) is a reversible condition characterized by a pathological prolongation of the QT interval that can lead to a polymorphic ventricular tachycardia known as Torsades de Pointe and sudden cardiac death. Identifying the incidence, onset, and risk factors for aLQTS in intensive care init (ICU) populations has not been studied and may help clinicians develop safe monitoring guidelines to identify patients early preventing devastating outcomes.

**Objective:** The objective of this study was to determine the frequency, temporal onset of occurrence, frequency of medications and host risk factors for aLQTS in an ICU.

**Method:** In a retrospective chart review of 88 subjects, hourly electrocardiographic data collected in an ICU were analyzed for baseline, first long, longest, and final corrected QT intervals (QTc) using Bazett’s formula. aLQTS was defined as a QTc interval ≥ 500 milliseconds (ms) or a change in QTc of ≥ 60 ms from baseline. Host risk factors were collected from the physician’s dictated history and physicals and nursing admission databases. Names and timing of each medication administered were collected from the medication record.

**Results:** aLQTS occurred in 52.3% of the ICU sample. All subjects positive for aLQTS (n=46) had a mean onset of 7.4 ± 9.4 hours from ICU admission. Subjects who developed aLQTS after ICU admission (n=32) had a mean onset of
10.6 ± 9.5 hours; 14 were positive on ICU admission. A statistically significant
difference was noted in subjects receiving QT prolonging medications positive for
aLQTS (63.5%, n=33) compared with subjects negative for aLQTS (36.5%,
n=19), ($X^2$[1] = 6.38, $p = .012$). Thirteen subjects (28.3%) developed aLQTS in
the absence of a known QT interval prolonging medication. No host risk factors
were found to have a significant difference between groups positive and negative
for aLQTS.

**Conclusions:** aLQTS was present in approximately one-half of the sample.
Approximately a quarter of the subjects developed aLQTS in the absence of a
known QT prolonging medication, indicating the importance of frequent QTc
monitoring in all patients in ICUs. Larger studies to determine common host risk
factors associated with aLQTS in ICU populations are warranted.
CHAPTER 1
INTRODUCTION AND SIGNIFICANCE

Introduction

The human heart must beat rhythmically on an average of 70 times per minute, 24 hours per day, for approximately 80 years; close to 3 billion contractions without fail to maintain life. There are two types of cells within the heart; cells that coordinate the electrical activity and stimulate the muscle cells that lead to contraction. These beats are coordinated by a network of specialized, autorhythmic cells that are integrated within the contractile myocytes, spreading their action potentials throughout the myocardial cells by way of complex ion channels within the cardiac cell membrane leading to contraction (Calkins, 2007; Schoen, 2005). There are many currents involved in the electrical activity of an action potential known as depolarization and repolarization. Depolarizing currents are due to an inward flux of positive charged ions (sodium and calcium) and repolarization is achieved by a delayed outward flux of positive charged potassium ions out of the cells (Abriel, et al., 2004).

Channelopathies, conditions caused from a malfunction of ion channel subunits or the proteins that regulate them, can affect multiple channels on the cell membrane leading to cardiovascular, neurological, ophthalmic, psychiatric, and other systemic disorders (Riera et al., 2005). Acquired and congenital long QT syndromes (aLQTS and cLQTS, respectively) are the most commonly known
cardiac channelopathies leading to abnormal cardiac electrophysiology, specifically delayed ventricular repolarization. This can be seen as a prolonged QT interval on the surface electrocardiogram (ECG) (Figure 1) (Abriel et al., 2004; Priori, Napolitano, & Schwartz, 2008). The QT interval on the ECG reflects the time at the beginning of ventricular activation and depolarization to the end of ventricular repolarization (Anderson, 2006).

aLQTS is a reversible condition characterized by a pathological prolongation of the QT interval upon exposure to an environmental stressor, most often pharmacologic therapies, that reverts back to normal once the stressor is removed (Kannankeril & Roden, 2007). Other common reversible causes are hypothermia and electrolyte disturbances. aLQTS is far more common than cLQTS (Dumaine & Antzelevitch, 2002; Lankipalli, Zhu, Guo, & Yan, 2005; Saenen & Vrints, 2008).

cLQTSs most often have a persistent prolongation of the QT interval on the ECG at birth (Priori, Napolitano, & Schwartz, 1999). It has recently been implicated in sudden infant death syndrome (Dumaine & Antzelevitch, 2002). Often, diagnosis is made through an incidental find on a routine exam or by clinical manifestations of syncopal episodes or cardiac arrest in healthy young individuals (Crotti, Celano, F., & Schwartz, 2008; Moss & Kass, 2005).
Figure 1

A P-QRS-T complex from a surface electrocardiogram.

The QT interval is measured from the onset of the QRS complex to the end of the T-wave.

Adapted from: www.web-books.com/eLibrary/ON/B0/B7/06MLongQT.html
Both aLQTS and cLQTS predispose individuals to developing ventricular arrhythmias such as Torsades de Pointe (TdP) (Figure 2) and ventricular fibrillation. TdP is a wide complex polymorphic ventricular arrhythmia characterized as a ‘twisting of the pointes’ around the isoelectric line of the ECG. TdP and ventricular fibrillation can lead to a decreased cardiac output, syncope, and sudden cardiac death (Hoffman & Warner, 2006; LaPointe et al., 2006; Wung & Kozik, 2008; Zareba, 2007).

The focus of this dissertation project is on the acquired form of LQTS. With early identification for the development of aLQTS, prevention of adverse events can occur. Acute care and advanced practice nurses play a key role in monitoring patients for the development of aLQTS. Therefore, understanding frequency and causes will help with early identification leading to a reduction of morbidity and mortality in this population.

Significance of the Problem

Estimated annual incidence of sudden cardiac death is one out of 1,000 in western populations, representing approximately 20 percent of all deaths (Abriel et al., 2004; Pueyo, Martinez, & Laguna, 2009; Smith & Cain, 2006). The incidence of all LQTSs is unknown but speculation suggests it is probably more unrecognized than rare and may be as common as the pulmonary channelopathy known as cystic fibrosis (Towbin & Vatta, 2001).
Torsades de Pointe (TdP), polymorphic ventricular tachycardia, associated with acquired long QT syndrome.

The upper and lower strips are continuous rhythm strips. The prolonged QT interval is best seen in the third complex on the upper strip, and the first and third complex of the lower strip. When an early depolarization occurs such as a premature ventricular conduction or as in this example, premature atrial conduction during the vulnerable period of repolarization (explained in detail in chapter 2), TdP can occur as a twisting of points. There are two episodes of TdP at the ends of both upper and lower rhythm strips.
It has been estimated 3,000-4,000 patients die each year from sudden cardiac death caused by LQTS (Chiang, 2004), highlighting the importance of elucidating causes and developing strategies for early identification and prevention.

There are many causes of aLQTS and the most common occurring from QT prolonging medications (Aslam, Aslam, Vasavada, & Khan, 2006; Hoffman & Warner, 2006; Jackman et al., 1988; Justo & Zeltser, 2006; Kunkler, 2002; LaPointe et al., 2006; Roden et al., 1996; Vincent, 2001; Wung & Kozik, 2008). Over the past several decades, new therapeutic medications have been developed for many health conditions and safety with administering these medications is a concern of the Food and Drug Administration and the pharmaceutical industry (Mank-Seymour et al., 2006). The single most common cause of medications being withdrawn from the market is the prolongation of the QT interval and subsequent risk for developing TdP (Gussak, Litwin, Kleinman, Grisanti, & Morganroth, 2004; Roden, 2004).

Prevention of adverse outcomes from aLQTS is challenging because of the multiple classes of medications associated with this condition. Antipsychotics, antidepressants, antibiotics, chemotherapeutic agents and antiarrhythmics are some of the most common classes of offending medications (LaPointe et al., 2006). Approximately 2.8 billion prescriptions were filled in the United States in the year 2000 with an average of ten prescriptions per person (Zareba, 2007). With such a vast array of medications that can cause aLQTS, concurrent use of more than one offending medication is not uncommon and
increases ones risk for an adverse event. It is important for nurses to be aware of the expanding list of potential QT interval prolonging medications (Vincent, 2001; Viskin, 1999). Unfortunately, when surveys were administered to medical practitioners about their knowledge of medication induced aLQTS, 20% indicated they knew very little about it and more than 30% failed to screen current therapies prior to prescribing a QT prolonging medication (Cubeddu, 2003a).

Studies indicate there may be a high incidence of aLQTS and TdP in hospitalized patients, especially those in intensive care units (ICU) due to multiple classes of QT prolonging medications prescribed and an increased incidence of other potential risk factors (Ng et al., 2008). Patients who develop aLQTS very often have at least one other associated risk factor present (Chiang, 2004; Straus et al., 2005). With such a large number of medications known to prolong the QT interval leading to an associated risk of TdP and sudden death, it is clear this potentially fatal, yet preventable syndrome is becoming a public health problem (Kannankeril & Roden, 2007).

Recent monitoring guidelines by the American Heart Association recommend nurses monitor for arrhythmias, ischemia, and QT-interval abnormalities in hospital settings (Drew et al., 2010; Drew et al., 2004). These guidelines address measuring QT intervals for the initiation and on-going monitoring of all new QT prolonging medications. Nurses are responsible for monitoring patients in the ICU setting; therefore, it is important for nurses to
quickly identify patients at risk for developing aLQTS to prevent devastating outcomes.

In 1999, the Joint Commission, an accrediting body for hospitals, convened a Pneumonia Advisory Panel to focus on best practice for pneumonia management (Joint-Commission, 2006). In 2001, the Joint Commission announced a set of measures hospitals would be graded upon to use for Medicare reimbursement scales. In 2004, the Joint Commission added a measure of appropriate antibiotic selection depending on severity of illness and area where patients are admitted within the hospital (ICU or medical floor). Many cases of severe pneumonia are admitted to ICUs requiring concurrent use of two to three classes of antibiotics. These antibiotics can potentially lead to aLQTS, demonstrating the importance of ECG monitoring in the ICU.

Conclusion

aLQTS can lead to devastating arrhythmias and sudden cardiac death. Though the incidence of this syndrome is not fully understood, it may be more common than previously reported. Patients in ICUs are at an increased risk of developing aLQTS due to the administration of multiple offending classes of medications. Recognizing ECG changes such as prolongation of the QT interval becomes an important responsibility for nurses involved in the care of ICU patients. Medication induced aLQTS is reversible when clinicians recognize it early and correct the offending causes. Understanding and recognizing aLQTS has the potential to greatly reduce adverse outcomes in the ICU population.
Research has elucidated mechanisms and predictors underlying aLQTS (Bednar, Harrigan, Anziano, Camm, & Ruskin, 2001; Hubert, Feinleib, McNamara, & Castelli, 1983; Kenigsberg, Khanal, Kowalski, & Krishnan, 2007; Moss et al., 1991; Phang & White, 1943; Xu et al., 2001; Zareba et al., 2003). However, incidence and onset of aLQTS in the ICU setting is not known. There is also a need to elucidate best practice for monitoring patients receiving QT interval prolonging medications. In addition, many clinicians know very little about aLQTS and its associated risks for developing sudden cardiac death. This knowledge may be helpful for nurses to identify patients at risk for developing TdP. With an understanding of the electrophysiology of the QT interval and utilizing stringent monitoring practices, aLQTS and its associated morbidity and mortality can be reduced.

Conceptual Framework and Goals for the Proposed Study

The conceptual framework (Figure 3) guiding this dissertation project was based on a physiological model. The main goal of this study was to determine the frequency of aLQTS in an ICU population. Several classes of medications frequently prescribed to ICU patients are represented by the oval ‘pedals’ in the upper left corner of the diagram. Patients are frequently administered more than one QT prolonging medication as depicted in the center of the overlapping ‘pedals’ where these classes of medications interact. The lower left circle represents the multiple host risk factors associated with aLQTS in each ICU patient, with each ‘pedal’ representing each host risk factor.
Conceptual Framework

This framework depicts a physiological model of an ICU patient at risk for QT interval prolongation. Medications (left upper circle) are the most common cause of aLQTS. Antiarrhythmic, antibiotics and antipsychotics are the most frequently prescribed medications known to cause aLQTS. ICU patients are frequently prescribed more than one medication known to cause aLQTS, depicted as the center of the circle of the overlapping ‘pedals’ increasing their risk for developing aLQTS. aLQTS from medication administration can be unpredictable and the risk increases with the presence of one or more host risk factors. Host risk factors (left lower circle) associated with medication-induced QTc prolongation include hypothermia, hypokalemia, bradycardia, female gender, heart failure, obesity, and myocardial ischemia (each host risk factor is presented by a ‘pedal’).
The center circle of the overlapping ‘pedals’ also depicts overlapping risk factors that may be present in an ICU patient. The two-way arrow between the two large circles shows the interaction between the medications and host risk factors. Together, medications and host risk factors can lead to a prolonged QT interval (one-way arrow).
In addition, the center of the overlapping ‘pedals’ depicts interactions of more than one host risk factor. Medications and host risk factors together can interact (depicted by the double arrow line) and lead to the expression of aLQTS (depicted by the one way arrow).

Because of heart rate variations, the QT interval must be corrected to a heart rate of 60 so that it can be clinically evaluated (to be discussed in chapter 2 in more detail). Expression of aLQTS is defined as a corrected QT interval (QTc) ≥ 500 milliseconds (ms) (Moss et al., 1991) or a change in QTc of ≥ 60 ms (Zareba, 2007) from baseline.

The specific aims of this proposed study are, in an ICU population to describe:

Specific Aim 1: The frequency of aLQTS (corrected QT [QTc] ≥ 500 ms or change from baseline ≥ 60 ms).

Specific Aim 2: The average time period between ICU admission and onset of aLQTS.

Specific Aim 3: Medications that may be associated with aLQTS.

Specific Aim 4: Risk factors (i.e. gender, age, co-morbidities) that may be associated with aLQTS.
CHAPTER 2
LITERATURE REVIEW

Ischemic (reduced blood flow) and structural (a structural or functional abnormality) heart diseases are major causes for the development of ventricular arrhythmias leading to sudden cardiac death. Ischemic disease is an imbalance between the supply and demand of the heart for oxygenated blood. Structural disease is a pathological condition affecting contraction or blood flow through the heart (e.g. myocardial hypertrophy from heart failure or valvular disease such as aortic stenosis) (Schoen, 2005). However, in five to eight percent of cardiac arrest victims, ischemic or structural abnormalities are absent; for many years this was termed idiopathic ventricular fibrillation (Abriel et al., 2004). In the past 10-15 years, molecular biology techniques have demonstrated abnormalities of proteins on the cell membrane, known as channelopathies that control the electrical activity of the heart and cause malignant arrhythmias leading to sudden cardiac death in structurally intact hearts (LaPointe et al., 2006; Yang et al., 2002). Cardiac channelopathies are suspected in 35% of unexplained sudden cardiac death in the young and 9% of sudden infant death syndromes (Tester & Ackerman, 2008). Many types of channelopathies in myocytes can affect the length of the QT-interval on the surface ECG due to action potential alteration.

QT-Interval Measurements

The QT interval length is determined by measuring the beginning of the QRS complex to the end of the T wave on the ECG. It is predominately affected
by the heart rate and can vary from beat to beat (Al-Khatib, LaPointe, Kramer, & Califf, 2003) (Figure 1). The higher the heart rate the shorter the QT interval and vice versa. Therefore, to evaluate and utilize the QT interval clinically or for research purposes, it becomes necessary to correct it for heart rate variations, called the corrected QT (QTc). There are several formulas to correct the QT interval such as Fridericia formula, the Framingham linear regression formula, and the Bazett’s formula (Bazett, 1920; Owens, 2004; Tisdale et al., 2007).

Bazett’s formula (QTc=QT/[RR]^{1/2}) has been criticized for under correcting lower heart rates and over correcting higher heart rates. However, due to its simplicity, the Bazett’s formula is used most often clinically (Karjalainen, Viitasalo, Manttari, & Manninen, 1994; Milne, Ward, Spurrell, & Camm, 1982; Wung & Kozik, 2008). Though validated on cLQTSs, Bazett’s formula may lead to a false-negative or a false-positive result when utilized on medication induced aLQTS patients (Indik, Pearson, Fried, & Woosley, 2006; Malik, 2001).

It has been questioned whether a set equation to correct the QT interval for all patients may be adequate; a formula that is accurate for one individual may be inaccurate when applied to another individual (Malik, 2001). In a recent large study of 14,548 healthy men and women, these three formulas (Friderica, Framingham linear regression, and Bazett’s) were compared. Only minor risk stratification differences were seen while Bazett provided slightly better separation (Dekker, Crow, Hannan, Schouten, & Folsom, 2004). Therefore, these findings support the use of Bazett’s formula in the clinical setting.
There is discrepancy in the literature regarding the normal value of a QTc which varies between 430-450 ms for men and 440-470 ms for women (Al-Khatib et al., 2003; Justo & Zeltser, 2006; Kunkler, 2002). However, there is consensus that any QTc ≥ 500 ms or change from baseline ≥ 60 ms is associated with an increased risk for developing TdP (Moss et al., 1991; Moss et al., 2001; Zareba, 2007). Data from cLQTS studies suggest that the risk of cardiac events increases exponentially as the QTc increases (Moss et al., 2001; Moss et al., 2002; Paulussen et al., 2004). For every 10 ms increases in the QTc, the risk for arrhythmic events increases by five percent. An individual with a QTc of 500 ms has a 34% increased chance of developing arrhythmias than an individual with a QTc of 440 ms (ICH, 2005).

**QT-Interval Physiology**

Complex ion channels within the cardiac cell membrane regulate the flow of ions mediating depolarization and repolarization seen as the QT interval on the surface ECG (Figure 4). Depolarization occurs in a normal cardiac cell by either an external change in voltage or from excitation from an adjacent cell that has already initiated an action potential by movement of current through the gap junctions. Sodium channels change from a closed state to an open state whereby sodium ions rapidly move down a gradient into the interior of the cell. This creates the sodium current ($I_{Na}$) indicated by the rapid upstroke of phase 0 of the action potential.
The QT interval on the surface ECG reflects the action potential duration; the beginning of ventricular activation/depolarization to the end of ventricular repolarization. The action potential reflects the ion channel currents involved that regulate the flow of ions responsible for depolarization and repolarization.

\( I_{Kr} \) – rapid delayed rectifying potassium currents
\( I_{Ks} \) – slow delayed rectifying potassium currents.
\( I_{Na} \) – sodium current

Adapted from: www.web-books.com/eLibrary/ON/B0/B7/06MLongQT.html
Ventricular repolarization occurs predominately from an outward flow of potassium currents by way of two delayed rectifying potassium currents, one rapid (IKr) and one slow (IKs). These currents are the components that commonly operate to achieve repolarization by way of the human Ether-á-go-go-Related Gene (hERG) channel currents, a voltage-gated potassium channel (Kv) (Mitcheson, 2008; Saenen et al., 2007).

Kv channels are protein tetramers with four identical subunits, each comprised of six transmembrane segments (S1-S6). S5 and S6 form the central pore and S1-S4 form the voltage sensors (Lee, Lee, Chen, & MacKinnon, 2005); these regions are hydrophobic amino acids thought to form membrane-spanning domains (Rubart & Zipes, 2008). Specifically, the S4 segment has positively charged amino acids identified to be important for voltage-sensing and converting between the open and closed conformations of the Kv channel (Lee et al., 2005). In the inactivated conformation, the channel cannot open, even if the transmembrane voltage is favorable. S6 helices bundle together at the intracellular end of the pore forming a narrow aperture that restricts the movement of potassium ions (Mitcheson, 2008).

There are many types of Kv channels that act in concert to determine the configuration and duration of the action potential playing a vital role in returning the depolarized cell to its resting state. The hERG channel and its IKr and IKs currents are crucial in normal repolarization of the ventricular myocytes (Mitcheson & Sanguinetti, 1999).
hERG channels contain two aromatic (stronger than expected bonding) drug-binding sites inside its pore allowing a wide range of structurally diverse compounds to interact and alter its biophysical properties (Saenen & Vrints, 2008). Recent structural studies have provided scientists with two distinct features of the hERG channel that may explain why so many drugs bind to and block this particular Kv channel (Sangunetti, 1995; Yang et al., 2002). First, most Kv channels (except hERG) have two proline (amino acid) residues in the S6 segment of their alpha-subunit producing a sharp bend in the four S6 helices that reduces the volume of the channel cavity. Since hERG channels lack the proline amino acid, its inner pore volume is larger and can accommodate larger compounds that can get trapped by closure of the activation gate during repolarization (Mitcheson, 2008). The second feature difference is two aromatic residues (tyrosine and phenylalanine) face the central cavity of the hERG channel allowing a high affinity for Pi-stacking interactions with aromatic moieties (stacking of molecules rendering them structurally strong) found in medications that block this channel (Abriel et al., 2004).

QT-Interval Pathophysiology

In aLQTS, the medication effect on the action potential duration is determined by the balance between the inward and outward currents (Antzelevitch, 2004). In particular, with interference or reduction of the IKr currents, repolarization is prolonged resulting in a net decrease in repolarizing current; L-type calcium channels become abnormally activated leading to an
increased inward current or a reduced outward current (Kannankeril & Roden, 2007). These mechanisms lead to an intracellular surplus of positive ions, delaying ventricular repolarization during phase 3 of the action potential, and seen as a prolongation of the QT interval on the surface ECG (Antzelevitch, 2004; Lankipalli et al., 2005). Furthermore, with L-type calcium channel activation and excess inward flux of calcium currents, a production of early-after depolarizations occur (Figure 5). Early after-depolarizations are oscillations of repolarizing currents during phase 2 or 3 of the action potential. With repetitive early-after depolarizations, ectopic beats or premature ventricular contractions can propagate and lead to TdP (Figure 2) (Al-Khatib et al., 2003; Anderson, 2006; Cubeddu, 2003b; Kannankeril & Roden, 2007; Lankipalli et al., 2005).

In a study utilizing isolated rabbit hearts (Asano, Davidenko, Baxter, Gray, & Jalife, 1997), researchers sought to clarify mechanisms of medication-induced TdP and the role of early-after depolarizations. Bradycardia with complete atrioventricular block was induced by ablation of the atrioventricular node and quinidine sulfate solution was used to produce a prolonged action potential. Results suggested TdP in the isolated rabbit heart preparation resulted from triggered activity from early-after depolarizations.

Prior studies to elucidate the cause of action potential prolongation by erythromycin, a macrolide antibiotic, could not be determined (Daleau, Lessard, Groleau, & Turgeon, 1995; Rupart, Pressler, Pride, & Zipes, 1993).
Figure 5

Early after-depolarizations associated with the QRS complex

A) Late EAD leading to a prolonged QTc from an additional U-wave normally not seen
B) EAD with sufficient amplitude to trigger a premature depolarization

Adapted from: El-Sherif, N. & Turrito, G. (1999). The long QT syndrome and Torsades de Pointe. PACE, 22 (Pt 1); 91-110.
Antzelevitch and colleagues (Antzelevitch, Sun, Zhang, & Yan, 1996) utilized a canine model of myocytes (left ventricular arterially perfused wedges), and an erythromycin preparation. These researchers demonstrated for the first time erythromycin produced significant action potential prolongation through early-after depolarization triggered activity.

Risk Factors Associated with aLQTS

Medications: The most common cause of aLQTS is from pharmacologic therapies (Dumaine & Antzelevitch, 2002; Lankipalli et al., 2005; Saenen & Vrints, 2008). It has been known for decades antiarrhythmic medications can be proarrhythmic. More recently, however, it became apparent other classes of medications also prolong the QT interval (Aerssens & Paulussen, 2005; LaPointe et al., 2006). It has been reported that more than 70 medications on the Swiss market can potentially lead to aLQTS and subsequently sudden cardiac death (Abriel et al., 2004). In a recent United States survey of nearly five million outpatients from health insurance agencies, it was determined the most frequently prescribed medications, known to cause aLQTS, were antibiotics and antipsychotics (Belardinelli, Antzelevitch, & Vos, 2003).

aLQTS from medication administration can be unpredictable in individuals, however, in most cases patients have at least one other identifiable risk factor. Other risk factors have been associated with medication induced QTc prolongation and the subsequent development of TdP. These include hypothermia, hypokalemia, bradycardia, female gender, heart failure, and
myocardial ischemia (Chiang, 2004; Straus et al., 2005). In a population based case-control study from the Integrated Primary Care Information project, a longitudinal observational database of more than 500,000 subjects was developed (Straus et al., 2005). Between January 1, 1995 and September 1, 2003, all deaths were reviewed for cardiovascular symptoms of sudden cardiac death. A subset of 775 sudden cardiac death cases who were exposed to non-cardiac QTc-prolonging medication (list not provided) were then matched with 6,297 similar control subjects. Risk factors studied were cerebrovascular and cardiovascular ischemia (history of myocardial infarction, stroke, or angina pectoris), heart failure, hypertension, diabetes mellitus, arrhythmias, hypercholesterolemia, smoking, and alcohol abuse. The researchers concluded that known potential risk factors alone were associated with an increased risk for sudden cardiac death. Furthermore, concurrent use of a non-cardiac QTc prolonging medication at the time of death was associated with an almost three-fold increased risk of sudden cardiac death.

Ng and colleagues (2008) prospectively evaluated 149 consecutive patients who were prescribed five known QT-prolonging medications (levofloxacin, haloperidol, amiodarone, procainamide, or erythromycin) over a 14-week study in a medical ICU and step-down unit daily until discharge from the unit or until the medication was discontinued. Their goal was to assess the capability, clinical, and economic impact of pharmacists monitoring for drug-induced QTc prolongation. Primary endpoints were QTc > 500 ms or an increase
by ≥ 60 ms over a normal baseline. The incidence of QTc prolongation > 500 ms or with a change ≥ 60 ms over a normal baseline was 58.4%. In another prospective observational study to determine the incidence of QTc prolongation and proarrhythmia in an ICU population, patients were followed for the effect of QTc duration or the incidence of new onset ventricular ectopy when pre-specified QT-prolonging medications were prescribed (full list not provided). Over a three month period, 267 patients with normal baseline QTc intervals (398± 147 ms) were prescribed a QT prolonging medication. The primary endpoint of QTc > 500 ms, QTc increase ≥ 60 ms, and new onset of ventricular ectopy occurred in 38.6%, 29.0%, and 11.0% of the sample, respectively. Of the medications observed in the study, moxifloxacin (48.1%; 52/108 subjects), haloperidol (45.9%; 11/24 subjects), or amiodorone (45.1%; 37/82 subjects) experienced the highest rates of the primary endpoints (Ng et al., 2004)

_Hypothermia:_ Hypothermia has been a known risk factor for cardiac events for many decades (Gould, Gopalaswamy, Kim, & Patel, 1985). Research shows as body temperature decreases, heart rate decreases and QT intervals increase. In a study utilizing anesthetized swine models (Dubin et al., 1999), body temperatures were reduced in eight subjects utilizing anterior and posterior ice blankets. This group was compared to seven normothermic controls. An incremental reduction in body temperature showed a linear increase in the QT interval. This group of researchers concluded that hypothermia significantly
slows ion channel conductance prolonging repolarization, which in turn increases the risk of proarrhythmic activity.

Prolonged QT intervals and the risk of developing TdP may be of concern with the new adjunctive therapy known as induced or therapeutic hypothermia for the post-cardiac arrest patient to minimize neurological sequela. Little has been studied in this population. In a case report (Huang, Tsai, Hsu, & Chen, 2006), a 79 year old woman sustained a cardiac arrest at the triage counter of an emergency room. Cardiopulmonary resuscitation was initiated for ventricular fibrillation. After seven minutes, she had a return of spontaneous circulation and hypothermia was induced to a target body temperature of 32 degrees Celsius. Prior to initiating hypothermia, the woman’s QTc was 549 ms and once cooled, reached a maximum QTc of 686 ms. Rewarming to a target temperature of 37 degrees Celsius at a rate of 0.3 degree Celsius per hour was initiated twelve hours after reaching target body temperature. Her QTc remained prolonged at 686 ms, and 41 hours post initial cardiac resuscitation she developed TdP requiring defibrillation. In ICUs, therapeutic hypothermia is used for post-cardiac arrest patients. More investigation is needed to determine outcomes from hypothermia induced aLQTS.

**Hypokalemia:** Another commonly observed risk factor in aLQTS is hypokalemia. Potassium plays a key role in repolarization of the ventricular cells. Hypokalemia increases the cardiac action potential duration subsequently prolonging the QT interval. This increase in action potential duration associated
with a decrease in extracellular potassium is assumed to be related to faster inactivation of IKr channels responsible for delayed potassium outflow and consequent inhibition of repolarization currents (Hanton, Yvon, Provost, Racaud, & Doubovetzky, 2007; Kannankeril & Roden, 2007).

Increasing the extracellular potassium level has been shown to decrease the potency of IKr blocking medications in vitro normalizing prolonged QT intervals in the presence of quinidine, a known QT prolonging medication. In a double blind study of 12 healthy subjects (3 women and 9 men), each were studied twice (at least five days apart), once on quinidine (300 mg every 5 hours times five doses) and again on a placebo (Choy et al., 1997). Mean baseline serum potassium levels prior to medication administration was 4.1 mEq/dL. After completing all medication doses, a potassium chloride infusion was administered at 0.5 mEq/kg (to a maximum of 40 mEq) over a period of 60 to 70 minutes. ECGs were recorded and venous samples were collected for serum potassium and quinidine levels before and at the end of the potassium infusion. Results showed a marked prolongation of the QT interval associated with quinidine treatment that resolved with the potassium infusion. Repolarization abnormalities were absent with placebo treatment; potassium had no effect in this group. In ICU patient populations, electrolyte abnormalities occur frequently from the use of diuretic medications. Monitoring for prolongation of the QT interval in patients who are at risk for hypokalemia becomes an important responsibility for the nurse to prevent adverse outcomes in the ICU.
**Bradyarrhythmias:** Bradyarrhythmias, in particular complete atrioventricular block has been shown to cause QT prolongation and subsequent TdP (Kurita et al., 1992; Topilski et al., 2007). Volders and colleagues (1999) studied Kv currents and action potential duration from the left and right ventricular midmyocardial cells of 15 adult mongrel dogs that had complete atrioventricular block for nine weeks and compared them with nine dogs in sinus rhythm. In 13 of 15 subjects with complete atrioventricular block, the left ventricular action potential duration was longer in the left than the right ventricle (419 versus 354 ms; p < 0.05) producing an interventricular difference of 65 ms. No difference in left or right action potential durations was seen in the sinus rhythm control group. These results suggest that chronic atrioventricular block was associated with significant reductions of Kv currents in the ventricles, in particular the left ventricle. Also noted in the group with complete atrioventricular block, approximately 15% of the population died suddenly from TdP, often during excitement such as feeding or ambulation.

A case-control study was conducted in 30 human subjects with bradyarrhythmias complicated by TdP and in 113 uncomplicated bradyarrhythmias to define ECG predictors of TdP during acquired bradyarrhythmias (Topilski et al., 2007). Results indicated that neither ventricular rate nor the QRS width predicted the risk of TdP, however, the QTc length correlated with an increased risk of TdP. In yet another case controlled study (Kurita et al., 1992), two groups totaling 14 subjects with complete
atrioventricular block, six with TdP and eight without TdP, were evaluated at two different periods; before (acute period) and after two months post pacemaker implantation (chronic period). ECG findings in the acute period demonstrated the TdP positive group had a significantly longer QTc interval than the TdP negative group. In the chronic period when pacing was initiated at a rate of 70-90 beats per minute (bpm), the TdP positive group no longer showed a significantly longer QTc interval than the TdP negative group. However, when the pacing rate was decreased to 50-60 bpm, the TdP positive group's QTc intervals became significantly longer than the TdP negative group (700 ms versus 529 ms at 50 bpm, and 551 ms versus 503 ms at 60 bpm). This study demonstrated that subjects with TdP in the presence of complete atrioventricular block have a bradycardia-sensitive repolarization abnormality that continues into the chronic period.

Tsuji and colleagues (Tsuji et al., 2002) induced complete atrioventricular block on 34 rabbits leading to a QT interval 120% over their baseline with 71% developing spontaneous TdP. Nine experimental rabbits with atrioventricular block and eight controls in sinus rhythm were studied at 21 days after induction of atrioventricular block. Using a patch-clamp method to study left ventricular myocytes, action potential duration was prolonged and Kv currents were significantly smaller (50%-55%) in the experimental group compared to the control group. This study indicates bradyarrhythmias lead to prominent QT prolongation and high incidence of TdP most likely from a down-regulation of Kv
channel currents though the exact mechanism is still unknown. Atrioventricular block frequently occurs in the ICU. Understanding the association between complete atrioventricular block and a prolonged QT interval can assist the nurse in preventing arrhythmias and the adverse outcomes from its occurrence.

**Female Gender:** Gender differences in the length of the QT interval has been known for more than 90 years (Bazett, 1918). Of the long list of existing risk factors, female gender is consistently observed as having a two to three times occurrence rate of TdP in multiple aLQTS studies (Moss et al., 1991; Zareba et al., 2003), indicating a sex-difference in repolarization and proarrhythmic activity. The length of the QT interval shows no difference between boys and girls in childhood, however, after puberty, the QT interval is consistently longer in women (Kannankeril & Roden, 2007). It has been puzzling to investigators for decades why a gender gap exists in the duration of cardiac repolarization. With the observation that QT intervals shorten after puberty in males but not in females, suggests sex hormones may modulate repolarization. Because the incidence of aLQTS does not decrease after menopause in women, estrogen is not considered to play a role (Lehmann, Hardy, Archibald, Quart, & MacNeil, 1996). However, testosterone has been implicated because studies have shown it increases IKr leading to a shorter QT interval in men (Arya, 2005; Pham, Sosunov, Anyukhovsky, Danilo, & Rosen, 2002; Tanabe, Hata, & Hiraoka, 1999).

In a study of 26 virilized women and 27 castrated men compared to a normal control group of 53 matched subjects, repolarization in the group of
castrated men was slower compared to controls. Virilized women exhibited shorter and faster repolarization compared to controls and castrated men, implicating testosterone as a major contributing factor in shorter QT intervals and possibly explaining the lower risk of TdP in men versus women (Bidoggia et al., 2000).

Pham and colleagues (Pham et al., 2002) tested the hypothesis that female rabbits treated with 5α-dihydrotestosterone for four to five weeks would be protected from developing aLQTS in the presence of dofetilide, a known QT prolonging anti-arrhythmic medication. The experimental group of 32 rabbits was compared to a control group of 29 rabbits, both having equal estrogen levels. The study determined that testosterone given to normal female rabbits shortened baseline action potential duration, decreased the rate-dependence of action potential prolongation, and protected against medication-induced prolongation of the QTc interval.

*Heart failure (HF):* The mortality rate from HF in the United States alone is more than 200,000 lives annually with approximately 50% from sudden unexpected causes presumed to be from ventricular tachyarrhythmias (Hongwei, Lyon, & Akar, 2008). Studies have shown that cells isolated from hypertrophied and failing hearts demonstrate a prolonged action potential duration. As early as 1943, a study suggested a relationship between cardiac mass and QT interval length (Phang & White, 1943). A group of 11 ambulatory subjects, with documented cardiac enlargement without HF, was compared to a second group
of 15 hospitalized subjects with cardiac enlargement and HF. In the HF negative group, a significant relative mean prolongation of the QTc interval (421 ms for six men and 431 ms for five women) was seen compared to normal mean control values (374 ms for men and 388 ms for women). In the HF positive group, an even longer mean QTc interval was observed (430 ms for 12 men and 471 ms for three women). After treatment and recovery from HF, the mean QTc interval in 13 of 15 subjects showed a uniform mean shortening by nine percent. In one additional subject, the QTc did not change, and another had a slight increase in the QTc value. The mean QTc interval for this second group once recovered from HF was 396 ms.

In another study, HF was induced in 13 canines; pacemakers were implanted and set to a rate of 240 bpm for three to four weeks (Kaab et al., 1996). A group of 16 normal control dogs were utilized for comparison. Both groups were euthanized and their cardiac myocyte action potentials were compared. The HF models showed a significantly longer action potential. L-type calcium and sodium currents showed no differences between the two groups. However, potassium currents showed a marked reduction in HF myocytes as compared with controls.

In yet another study by Xu and colleagues (Xu et al., 2001), researchers examined the effect of left ventricular hypertrophy on delayed rectifier potassium currents and their contribution to action potential repolarization in ventricular myocytes. Left ventricular hypertrophy was induced in 26 rabbits and compared
three months later with 24 normal control rabbits. The left ventricular hypertrophy group demonstrated a significantly decreased IKs density and longer action potential duration compared to the control group. Patients with decompensated HF are commonly admitted to the ICU and may be at an increased risk for developing aLQTS.

Myocardial ischemia: Myocardial ischemia is yet another risk factor in the development of TdP. Acute ischemic attacks are associated with an increased risk of sudden cardiac death from arrhythmias and may be associated with a prolongation of the QT interval. A group of 24 subjects with slow coronary blood flow had a statistically significant longer QTc interval when compared with 25 controls with normal coronary blood flow (414 ms versus 388 ms; p < 0.05) (Sezgin et al., 2007). In a case report of two patients following successful emergent angioplasty for acute coronary syndrome, both developed transient QTc prolongation. In both cases, marked QTc prolongation with large inverted T-waves occurred within 24 hours post-angioplasty and remained prolonged for four days. One case developed TdP (Kawabata et al., 2008).

In yet another study, statistically significant QTc interval prolongation was seen in all 74 patients during elective angioplasty which induces coronary ischemia by balloon occlusion (Kenigsberg et al., 2007). ST segment and T-wave changes typically seen in the presence of ischemia (ST-segment depression or elevation; T-wave inversion), occurred in only 7-15% of these patients, indicating QTc duration may be a more sensitive marker for ischemia
than T-wave changes alone. These studies indicate that ischemia increase the risk for QTc prolongation and may be another important risk factor for the development of aLQTS in ICU populations.

**Obesity:** Obesity has been known to be an independent risk factor for cardiac morbidity and mortality for several decades. In the Framingham study of 5,207 patients, a two to seven increased risk of sudden death correlated with baseline weight, coronary heart disease and HF (Bednar et al., 2001; Hubert et al., 1983). Carella and colleagues (1996) found a linear association in QTc interval length with body mass index (BMI). QTc intervals were significantly shorter in those with BMIs below 23 kg/m\(^2\) and progressively and significantly increased as BMI increased. In a study to evaluate a group of 139 adults referred for obesity evaluation, again a relationship was discovered between a higher BMI and longer QTc interval (El-Gamal et al., 1995). Of those whose BMI was greater than 40 kg/m\(^2\), 26% had a QTc greater than 440 ms compared to 4.6% of the general population without heart disease in population based studies (Bednar et al., 2001). In another study of 343 obese individuals without heart disease, hypertension, or diabetes, 23% had a QTc interval greater than 440 ms and 53% had a QTc interval greater than 420 ms (Carella et al., 1996). These studies support that obesity is directly related to QTc interval length and contributes to the risk of sudden cardiac death yet the mechanism is still unknown.
Genetics: It has been proposed that genetics may also be associated with aLQTS. Paulussen and colleagues (2004) examined five known cLQTS genes that encode proteins for the Kv and the sodium voltage-gated channels (potassium channel, voltage-gated, subfamily H, member 2 [KCNH2]; potassium channel, voltage-gated, KQT-like subfamily, member 1 [KCNO1]; sodium channel, voltage-gated, type 5, alpha sub-unit [SCN5A]; potassium channel, voltage-gated, ISK-related subfamily, member 1 [KCNE1]; and potassium channel, voltage-gated, ISK-related subfamily, member 2 [KCNE2]) to determine if a non-penetrant mutation could account for aLQTS. Of 32 subjects who had prolonged QT interval and developed TdP after drug administration, four were found to have missense mutations in one of the genes studied (KCNE1-two cases, KCNE2-one case, and KCNH2-one case) (Paulussen et al., 2004). Yang and colleagues (2002) studied another group of cLQTS related genes (SCN5A, potassium channel, voltage-gated, KQT-like subfamily, member 1 [KvLQT1], and HERG) to determine if individuals who developed medication-associated TdP harbored non-penetrant mutations in these genes. They found a missense mutation in the genes studied in five of the 92 subjects (SCN5A-three cases, KvLQT1-one case, and HERG-one case).

In a study by Petersen and colleagues (2004), using the worm (Caenorhabditis elegans) model, two trafficking proteins generated by the KCNH2 gene were discovered. They then examined the human KCNH2 sequence in subjects with aLQTS and found a point mutation resulting in a
protein substitution in aLQTS subjects (11%) as compared with matched controls (7%), suggesting this gene may have a protective allele for reduced aLQTS susceptibility.

In conclusion, further exploration of both non-genetic and genetic risk factors is needed to help elucidate those at risk for developing aLQTS in the ICU setting. Research has shown patients who develop aLQTS are at risk for TdP and sudden cardiac death. Identifying these patients early with proper cardiac monitoring may reduce the incidence of TdP. ICU patients are at an increased risk for developing aLQTS because the multitude of medications administered and the concomitant host risk factors. Risk factors associated with aLQTS have been studied and identified in the general population (Bazett, 1918; Bednar et al., 2001; Choy et al., 1997; Dubin et al., 1999; Kaab et al., 1996; Kenigsberg et al., 2007; Kurita et al., 1992; Moss et al., 1991; Paulussen et al., 2004; Phang & White, 1943; Sezgin et al., 2007; Topilski et al., 2007; Volders et al., 1999; Zareba et al., 2003); however, risk factors in ICU populations associated with aLQTS have not. Identifying the frequency of aLQTS and associated risk factors in the ICU population is the first step in reducing the incidence of adverse outcomes in this population.

Furthermore, there exists a gap in the literature on best practice for cardiac monitoring for aLQTS in the ICU population. Research, to determine best practice to develop guidelines for ICU populations can assist clinicians in reducing this devastating yet preventable syndrome.
Cardiac Rhythm Monitoring in the Intensive Care Unit

Patients in the ICU setting often require treatment with QT prolonging medications and frequently have risk factors associated with the increased risk for developing aLQTS (Sommargren & Drew, 2007). It has been estimated that approximately one in five ICU patients will develop clinically significant cardiac arrhythmias (Drew et al., 2004; Reinelt, Karth, Geppert, & Heinz, 2001).

Experts from the American Heart Association’s Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young and the International Society of Computerized Electrocardiology, published best practice guidelines for cardiac monitoring in hospitalized patients (Drew et al., 2004). It has been recommended that patients receiving a QT prolonging medication should have a baseline rhythm strip documented in their medical record prior to medication initiation and every eight to 12 hours for 48 to 72 hours after the initiation or an increase in medication dosage (Drew et al., 2010). It is further recommend that drug termination should be considered in any patient who develops a QTc > 500 ms (Sommargren & Drew, 2007). These recommendations are not research based but on expert opinion only. A gap exists in the literature to determine optimal cardiac monitoring of QTc intervals in ICU patients.

Evidence exists that a large number of patients in the ICU setting are at risk for QTc prolongation indicating the importance of ECG assessment. Experts agree QTc monitoring should occur in the ICU setting, however, empirical
evidence to help guide safe and effective monitoring practice in this high risk population is lacking. Understanding the incidence, onset, and associated risk factors for patients with aLQTS in the ICU population can play a crucial role in preventing TdP and sudden cardiac death. With an increased knowledge through research driven guideline development, clinicians can effectively identify aLQTS patients early and reduce its adverse outcomes.

Many medications prolong the QT interval at indeterminate time frames and can vary between patients. For example, a 61-year-old woman with pneumonia was administered intravenous erythromycin, a known QT interval prolonging medication, every eight hours over a 90 minute infusion (Schoenenberger, Haefeli, Weiss, & Ritz, 1990). A marked prolonged QTc interval of 550 ms with extrasystoles and a short run of TdP were noted after the fifth infusion. During the eighth and tenth infusions, QTc intervals were markedly prolonged with TdP. QTc intervals gradually returned to normal over the five to six hours post infusion.

In another case report, an 82-year-old woman was administered intravenous erythromycin every six hours for pneumonia (Katapadi, Kostandy, Katapadi, Hussain, & Schifter, 1997). After receiving the first dose, she started developing premature extrasystoles. Thirty minutes after the second, third and fourth doses, she developed TdP. The QTc interval had progressively prolonged with each dose administered (baseline, 442 ms; first dose, 484 ms; second dose, 650 ms; third dose, 660 ms; and fourth dose, 720 ms). In another case report
involving seven patients with TdP, TdP developed at different times between days two and five after starting amiodorone (Tong, Lau, & Teo, 2001).

These studies indicate that a variation exists not only in medications administered, but also in patients who developed prolonged QT intervals and/or TdP. A gap in the literature exists regarding safe monitoring practices for QT interval prolongation in ICU patients. This indicates a need for best practice cardiac monitoring guidelines in this population.

Conclusion

ICU patients are sicker and potentially at a higher risk for developing aLQTS due to multiple medications received and increased risk factors present. However, identifying the incidence and common risk factors for aLQTS in the ICU population has not been studied. Therefore, determining the incidence, onset, and risk factors of QT interval prolongation in the ICU, may help clinicians identify these patients early and prevent devastating outcomes. Another goal of this study is to determine best practice for QTc monitoring in ICU patients. Results from this study may help clinicians to stratify patients at risk for developing aLQTS and make sound decisions regarding effective cardiac monitoring.
CHAPTER 3

METHODS

This dissertation study was a pilot study to determine frequency, temporal onset, and risk factor identification for aLQTS in an ICU population. A preliminary study which included three analyses was conducted prior to this dissertation study to help determine ICU risk factors, frequency of administration of any QT prolonging medications, and the number of potential subjects admitted to the selected study ICU. This preliminary study helped determine feasibility and potential limitations of the dissertation study. The preliminary study was conducted from July 2008 until May 2009 and was approved by the Catholic Healthcare West (CHW) Internal Review Board (Appendix A).

Preliminary Study

The first analysis was to determine risk factors in subjects who developed aLQTS. A retrospective chart review was completed on subjects who had the Diagnostic Related Group (DRG) code for ventricular tachycardia or long QT syndrome over a six month period. From the list of 100 subjects provided by the hospital coders, 12 met the criteria for aLQTS (QTc ≥ 500 ms). Ages ranged from 51-96 years old, with a mean age of 71 years. Eight of these subjects were men and four were women. Five subjects were admitted to the ICU with an existing prolonged QT interval and seven developed prolongation of their QT interval after ICU admission.
The following co-morbidities were noted in these 12 subjects:
hypertension = 8, diabetes = 3, hyperlipidemia = 3, HF = 4, coronary artery
disease = 3. Three subjects were taking out-patient prescribed psychological
medications (busperone, duloxetine, donepezil, and/or amitriptyline). Two of
these three subjects were on more than one home psychological medication and
had a QTc ≥ 500 ms upon hospital admission. The third subject was on one
antidepressant and had a QTc < 500 ms upon hospital admission. This subject
developed QTc prolongation up to 735 ms once a fluoroquinilone antibiotic was
added. Two additional subjects were on fluroquinolones and three others were
on other types of antibiotics (cephalosporins and doxycycline).

Limitations of this analysis include difficulty in accurately identifying
subjects retrospectively who developed aLQTS in the hospital. Capturing this
population relies on accurate coded diagnoses that come from physician’s
progress notes. Once patients were identified, offending medications may be
discontinued with the QTc interval reverting to normal but the diagnosis not
documented. In addition, patients who developed aLQTS may go unidentified.

A second analysis was conducted to determine what medications were
frequently prescribed to subjects with prolonged QTc intervals ≥500 ms. Monitor
technicians were asked to record subjects over a two month period who
developed QTc measurements ≥ 500 ms and what their prescribed medications
were. Twenty subjects were identified, 10 men and 10 women. The mean age
was 61 years old, with a range from 39 to 86 years. Medications taken by at
least three subjects were as follows: fluroquinolones = 10, beta-blockers = 7, antifungals = 6, cephalosporins = 6, zosyn = 6, vancomycin = 4, clindomycin = 4, amiodorone = 3, and zithromax = 3. Sixteen of the 20 subjects were on at least two of these medications concurrently.

Relying on monitor technicians to collect data on subjects with QTc prolongation and associated medications may result in a lower number of identified subjects who developed aLQTS. Several days would pass with a full data collection log and no additional spaces to record subjects. This indicates the possibility of missed potential aLQTS subjects. Additionally, many technicians admitted to forgetting about the log and to record subjects who developed a QTc interval ≥ 500 ms. The purpose of this analysis was to determine medications that may be associated with QT prolongation in the proposed ICU population; other non-pharmacological risk factors were not collected.

A third analysis was conducted to determine the number of subjects admitted per month to two ICUs (a 20-bed unit and an 11-bed unit for a total of 31 beds) in the proposed research facility. A second aim was to determine the number of QT prolonging medications administered in these ICU subjects. The QT prolonging medications were collected according to the Arizona Center for Education and Research (Arizona) (Table 1). A total of 165 subjects (105 in the 20-bed unit and 60 in the 11-bed unit) were admitted to the ICUs during the month.
Table 1

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<td>Sunitinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telithromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tizanidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vardenafil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**QT-interval prolonging medication list**

Adapted from: www.azcert.org

**Risk:** Drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes.
**Possible Risk:** Drugs that prolong the QT interval and/or in some reports have been associated with Torsades de Pointes but at this time lack substantial evidence for causing Torsades de Pointes.

**Conditional Risk:** Drugs that carry a risk of Torsades de Pointes and/or QT prolongation under certain conditions, such as patients with congenital long QT syndrome, drug overdose or co-administration of interacting drugs.
One-hundred thirteen subjects (68.5%) received at least one QT-prolonging medication (68.5%). The most frequently administered medication was levofloxacin (n=52, 31.5%), an antibiotic used for treating pneumonia. Other frequently prescribed medications were ciprofloxacin (n=23, 13.9%), haldol (n=19, 11.5%), amiodorone (n=18, 10.9%), and fluconazole (n=18, 10.9%). QT intervals were not measured in this preliminary study.

In conclusion, these preliminary analyses suggest that high rates of patients in the ICU are prescribed QT prolonging medications. In addition, there was a high rate of common risk factors amongst subjects associated with aLQTS. Based on the preliminary study, an average of 105 patients was admitted to the 20-bed ICU and at least six suffered from aLQTS monthly. Therefore, it is feasible to recruit 100 subjects for the proposed study.

Design

This was a retrospective descriptive study including 100 consecutive ICU subjects from a population of hospitalized ICU subjects to determine the frequency of aLQTS. The study was conducted in the 20 bed ICU where the preliminary study was conducted. This ICU is in a 300-bed community hospital in Reno, Nevada. The ICU accepts all types of critical care patients including open heart surgery patients. The only population not served by this ICU is trauma patients. One-hundred consecutive subjects admitted to the ICU during October and November of 2009 was included in this retrospective study. Subjects whose QT interval could not be accurately analyzed, such as those with atrial fibrillation,
atrial flutter, bundle branch blocks, or 100 percent paced rhythms were excluded. The average time period for the onset of aLQTS was determined. Medications and risk factors were examined for their associations with the development of aLQTS.

Procedure

This ICU utilizes SpaceLab® cardiac monitors at the bedside of each subject with the ability to continuously monitor two leads and store the rhythm for up to 72 hours in a centralized trending computer database at a nursing station. All subjects admitted to the ICU had their continuous cardiac rhythm monitored and saved on a data saving device. The researcher analyzed hourly QT intervals utilizing the electronic calipers built into the SpaceLab® trending monitor at the nursing station. This analysis required approximately one hour to complete per subject. The monitor then corrected the QT interval using heart rate determined from the preceding R to R interval based on the principal of the Bazett’s formula. QTc intervals were measured hourly from a minimum of a six-second strip for the first three days of ICU admission. These hourly measurements occurred immediately upon admission to the ICU and occurred until ICU discharge or up to 72 hours. Demographic information and medical history were obtained from the medical records retrospectively (details are included in the instrument section).

Analysis of QT intervals: Measurements of the QT interval are subject to variability especially when completed by multiple clinicians where different leads may be used for the measurements (Darpo, Nebout, & Sager, 2006;
Sommargren & Drew, 2007). To insure reliable results, the measurements were conducted exclusively by the researcher. Questions have also been raised whether manual calculations are more accurate than computer generated QT measurements. Drapo and colleagues (2006) analyzed three studies comparing uncorrected QT intervals measured manually with those generated by ECG machines and concluded that manual and automated measurements did not show a statistically significant difference in results.

Abnormal limits for QTc measurements in QT/QTc studies have been recommended (ICH, 2005). These include: absolute QTc prolongation > 450 ms, > 480 ms, or > 500 ms or QTc changes from baseline of >30 ms or >60 ms. Utilizing lower abnormal limits increase the false-positive rate. Since a universal threshold for medication induced aLQTS does not exist, experts agree that a change of QTc from baseline > 30 ms should raise concerns and a change of QTc from baseline > 60 ms should be especially alarming (ICH, 2005; Zareba, 2007). In addition, most cases of drug-induced TdP occur in subjects with QTc intervals > 500 ms (ICH, 2005; Roden, 2004; Zareba, 2007). Therefore, to minimize false positive categorization of aLQTS, a positive aLQTS subject was defined in this study as a change of QTc from baseline ≥ 60 ms or absolute QTc ≥ 500 ms. A negative aLQTS subject was defined as a QTc with no change from baseline < 60 ms or an absolute QTc < 500 ms.

The QT interval was measured from the beginning of the QRS complex to the end of the T wave. There are two methods to identify the end of the T-wave
for manual analysis; threshold method and tangent method. The threshold method (Figure 6) utilizes the point at which the T wave reaches the isoelectric baseline as the end of the T wave and is the most commonly utilized method. The tangent method (Figure 7) is comprised of a tangent drawn from the steepest part of the descending limb of the T wave and the point at which it intercepts the isoelectric baseline and is considered the end of the T wave (Couderc & Zareba, 2005; Panicker et al., 2009).

In a recent study by Panicker and colleagues (2009), both methods were compared amongst eight readers using 100 ECGs for inter-rater and intra-rater reliability. Five consecutive QRS-T complex values for each ECG were averaged. Results indicated that there was no statistically significant difference amongst the two methods; however, the tangent method consistently resulted in a shorter QT interval (9 ms) than the threshold method. SpaceLab® trending monitors utilize the threshold method minimizing false negative results.

Data Management Plan

Data were entered into the 14th edition of SPSS Student Version database (SPSS Inc., Chicago IL.). Each entry was double-checked for accuracy at a later time by the researcher (Duffy & Jacobsen, 2005; Trochim & Donnelly, 2007). Missing variable data, such as weight and BMI, were left blank in the database so that they were excluded from the analysis (Field, 2005).
Threshold method for measuring the end of the T wave

Threshold method of measuring the T wave uses the point where the terminal end of the T wave intersects directly on the isoelectric line.

Tangent method for measuring the end of the T wave

Tangent method for measuring the end of the T wave uses a tangent drawn from the maximal slope of the terminal limb of the T wave to the isoelectric line. The intersection at the isoelectric line is used as the measurement of the end of the T wave. As seen in this example, the T wave appears to be slightly longer before it hits the isoelectric line.
Outliers were identified by locating QTc interval values more than three standard deviations from the mean. No outliers were removed from the final analysis. A p value < 0.05 was considered statistically significant for each analysis. Statistical tests are identified under each aim below.

Specific Aims and Statistical Analysis

**Specific Aim 1**: To describe the frequency of aLQTS (QTc ≥ 500ms or change from baseline ≥ 60ms) in an ICU population

Baseline, first abnormal QTc interval, maximum QTc interval, and final QTc interval measurements were obtained for each subject using the methods described earlier. Baseline QTc interval, obtained on all subjects, was defined as the QTc obtained on ICU admission as hour zero. First long QTc interval was defined as the first QTc interval ≥ 500 ms or ≥ 60 ms from the baseline. Longest QTc interval, obtained on all subjects, was defined as the longest QTc interval obtained during the study monitoring period. Final QTc interval was the last QTc interval obtained at time of discharge from the ICU or at 72 hours (end of the study period).

**Statistical analysis**: Percentage of subjects with positive aLQTS among all subjects was determined. In addition, central tendencies (mean ± two standard deviations [SD], median, mode, and range) were obtained on all subjects’ baseline, first long, longest and final QTc intervals. Mean baseline, first long, longest and final QTc intervals were further compared by gender using t-test to
determine if there was a statistically significant difference between men and women.

**Specific Aim 2:** To describe the average time period between ICU admission and onset of aLQTS in an ICU population

Only subjects who had aLQTS were included in this analysis. The first prolonged QTc interval was used to identify aLQTS. Initial QTc upon ICU admission as well as subsequent hourly QTc intervals were evaluated for aLQTS criteria (≥ 500 ms or ≥ 60 ms from baseline). The final hour QTc was at discharge from the ICU or until the end of the study period at 72 hours. ICU admission time was considered hour zero. If a subject was admitted with a normal baseline QTc interval and developed aLQTS after ICU admission, then the hour of identification was recorded.

**Statistical analysis:** Mean (± two SD) onset for positive aLQTS was determined from time of ICU admission to first QTc interval prolongation by using the hour of the first prolonged QTc interval according to criteria. Two groups were analyzed: all subjects with positive aLQTS including subjects admitted to the ICU with aLQTS; and a second group admitted with a normal baseline QTc interval that developed positive aLQTS after ICU admission. A t-test was used to determine if there was a statistically significant difference for onset of positive aLQTS in all subjects with aLQTS based on gender, ethnicity (white/non-white), and BMI (< 25 kg/m² / ≥ 25 kg/m²).
**Specific Aim 3**: To describe medications that may be associated with aLQTS in an ICU population

Medications included in the study were any QT interval prolonging medication administered by any route (oral or intravenous) in the emergency room, surgical suite, and ICU. Any medication that fell in the one of three risk categories of TdP (drugs with risk; drugs with possible risk; and drugs with conditional risk) from the Arizona Center for Education and Research was included for review (Arizona) (Table 1). Any medication that may have an association with aLQTS but not included on the list by the Arizona Center for Education and Research was investigated further.

**Statistical analysis**: Percentage of subjects who received a QT interval prolonging medication was obtained. Frequency of each medications administered to all subjects was obtained. Chi-square tests were used to test for a significant difference in the number of medications received between groups with positive and negative aLQTS. In addition, the group positive for aLQTS was further analyzed using Chi-square tests to determine if receiving a QT interval prolonging medication increased the risk of developing aLQTS.

**Specific Aim 4**: To describe risk factors (i.e. gender, age, co-morbidities) that may be associated with aLQTS in an ICU population

Demographic information and medical history were obtained from subjects’ medical records to include: age, gender, race/ethnicity, home medications (name, dose, and route), BMI and co-morbidities.
Co-morbidities include hypothermia, hypokalemia, bradycardia with complete atrioventricular block, HF, acute coronary syndrome, hypercholesterolemia, smoking history, and alcohol abuse. Hypothermia was defined as a core body temperature of 34 degrees Celsius or less. Hypokalemia was defined as a potassium level < 3.5 mmol/L. Bradycardia was defined as a heart rate < 50 bpm with the presence of complete atrioventricular block for any duration during the study period. HF was defined as a history or new onset diagnosis in any category as classified by the New York Heart Association (NYHA) (Table 2). Acute coronary syndrome was defined by ECG changes indicative of ischemia (ST segment depression, elevation, or T-wave inversion) with positive troponin-I levels ≥ 0.12 ng/ml.

Hypercholesterolemia was defined as a noted history from the chart review or as a new diagnosis defined as a low-density lipoprotein (LDL) ≥ 100mg/dL or total cholesterol level ≥ 200mg/dL. Positive smoking was defined as currently smoking or subject claimed to have stopped smoking within the prior year. Alcohol or illicit drug abuse was defined as currently abusing alcohol or drugs as noted in the subject’s chart or if the subject experienced alcohol or drug withdrawal during the study period.
Table 2

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Mild)</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).</td>
</tr>
<tr>
<td>Class II (Mild)</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class III (Moderate)</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class IV (Severe)</td>
<td>Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>

New York Heart Association Heart Failure Classifications
*Statistical analysis:* Percentages for the following risk factors were compared between groups positive and negative aLQTS: race, gender, hypothermia, hypokalemia, acute coronary syndrome with positive troponin-I test, positive smoker, alcohol abuse, history of or new onset HF, and hypercholesterolemia.

Risk factors were further analyzed using Chi-square to determine if a statistically significant difference exists between subjects with positive and negative aLQTS. For continuous variables (age and BMI), t-tests were used to determine if a statistically significant difference existed between those with positive and negative aLQTS.

Logistical regression analysis using the backward stepwise method was completed to estimate the probability of positive aLQTS within 72 hours of ICU admission. A total of 15 predictive variables were used in the analysis. These include 10 risk factors (age, gender, BMI, positive smoker, hypercholesterolemia, bradycardia with complete atrioventricular block, hypokalemia, hypothermia, acute coronary syndrome and HF) and five medications (flurane, ondansetron, levofloxacin, azithromycin, and amiodorone).

**Protection of Human Subjects**

Approval from the internal review boards at CHW (the parent company for Saint Mary's Regional Medical Center in Reno) (Appendix B) and the University of Arizona (Appendix C) were obtained prior to the initiation of the research project. A waiver of consent was obtained because this study posed minimal
risks to subjects; no identifying patient information (such as, name or birth date) was obtained from this retrospective chart review. Subjects were assigned a research study number that prevents any future link to any participating subject.
CHAPTER 4

RESULTS

Sample Characteristics

Medical records from a sample of 100 consecutive subjects admitted to the ICU over a five-week period in October and November of 2009 were retrospectively reviewed. Each subject’s medical record was reviewed for medications, demographic information, and potential QT interval prolonging risk factors. QTc measurements were collected using the SpaceLab® monitoring system and reviewed retrospectively. Of the 100 subjects reviewed, 12 were excluded due to rhythms that affected accurate QT interval measurements. These include six with bundle branch block (QRS > 0.11 ms), four with atrial fibrillation or flutter, and two with 100% paced rhythm.

Of the remaining 88 subjects, the mean study period for each was 43.3 ± 24.5 hours. Forty-seven (53.4%) subjects were women and 41 (46.6%) were men with a mean age of 63.5 ± 14.3 years. The majority of subjects were Caucasian (87.5%) (Table 3). The most frequent admitting diagnoses were acute coronary syndromes (21.6%), major surgeries (14.8%), respiratory failure (19.3%), and severe infection with sepsis (11.4%) (Table 4). The majority of subjects were obese (45.5%) or overweight (26.1%) (Table 5). One-fourth of subjects was a positive smoker. Eleven subjects (12.5%) were either dependent on alcohol or illicit drugs.
Table 3

<table>
<thead>
<tr>
<th>Race</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>77</td>
<td>87.5</td>
</tr>
<tr>
<td>African American</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5</td>
<td>5.7</td>
</tr>
<tr>
<td>Native American</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>88</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Frequency of races in the study population
Table 4

<table>
<thead>
<tr>
<th>Admitting diagnosis</th>
<th>Number of subjects</th>
<th>Percent of all subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke &amp; other occlusive vascular disease</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>ACS (chest pain, NSTEMI, and STEMI)</td>
<td>23</td>
<td>26.1</td>
</tr>
<tr>
<td>Respiratory problems (failure, dyspnea)</td>
<td>17</td>
<td>19.3</td>
</tr>
<tr>
<td>Acute alcohol withdrawal</td>
<td>4</td>
<td>4.5</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Severe infection with sepsis</td>
<td>10</td>
<td>11.4</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Surgery (heart, brain, spinal, lung, abdominal)</td>
<td>13</td>
<td>14.8</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Severe abdominal diagnosis</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Subdural hemorrhage</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Cardiac arrest with hypothermia</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Severe hypotension</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>88</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; NSTEMI = non-ST elevation acute myocardial infarction; STEMI = ST elevation acute myocardial infarction

Frequency of admitting diagnosis
<table>
<thead>
<tr>
<th>BMI (kg/m$^2$)</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt; 18.5)</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Normal (18.5-24.9)</td>
<td>20</td>
<td>22.7</td>
</tr>
<tr>
<td>Overweight (25-29.9)</td>
<td>23</td>
<td>26.1</td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>40</td>
<td>45.5</td>
</tr>
<tr>
<td>Unavailable</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Frequency of body mass index by categories
Specific Aim One: To describe the frequency of aLQTS (≥ 500ms or change from baseline ≥ 60ms) in an ICU population

Approximately one-half of the ICU subjects (n=46; 52.3%) were positive for aLQTS during the study period. Forty subjects (45.5%) were positive for aLQTS with a QTc interval ≥ 500 ms upon or after ICU admission was 45.5% (n=40). An additional 6.8% (n=6) had an increase in QTc interval by ≥ 60 ms from the baseline (Table 6).

The mean baseline QTc in all subjects was 454 ± 38 ms with a range of 380-620 ms. The mean longest QTc for all subjects was 498 ± 55 ms with a range of 410-690 ms. The mean final QTc was 446 ± 40 ms with a range of 350-620 ms (Table 7).

In subjects who were positive for aLQTS, the mean baseline QTc was 470 ± 44 ms with a range of 380-690 ms. The mean first prolonged QTc was 511 ± 36 ms, ranging from 410-620 ms. The mean longest QTc was 535 ± 49 ms with a range from 410-690 ms. The final mean QTc was 457 ± 48 ms with a range of 350-620 ms (Table 8).

In subjects who were negative for aLQTS, the mean baseline QTc was 437 ± 18 ms with a range of 390-470 ms. The mean longest QTc was 458 ± 23 ms with a range of 410-490 ms. The mean final QTc was 435 ± 26 ms with a range of 380-480ms (Table 9).
Table 6

<table>
<thead>
<tr>
<th>Positive aLQTS</th>
<th>Criteria</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QTc ≥ 500 ms</td>
<td>40</td>
<td>45.5</td>
</tr>
<tr>
<td></td>
<td>QTc ≥ 60 ms increase from baseline</td>
<td>6</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>46</td>
<td>52.3</td>
</tr>
</tbody>
</table>

Frequency of aLQTS

Table 7

<table>
<thead>
<tr>
<th>QTc in ms</th>
<th>Baseline QTc</th>
<th>First Long QTc</th>
<th>Longest QTc</th>
<th>Final QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>88</td>
<td>46</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Mean</td>
<td>454</td>
<td>511</td>
<td>498</td>
<td>446</td>
</tr>
<tr>
<td>Median</td>
<td>450</td>
<td>510</td>
<td>490</td>
<td>440</td>
</tr>
<tr>
<td>Mode</td>
<td>450</td>
<td>500</td>
<td>480</td>
<td>430</td>
</tr>
<tr>
<td>Range</td>
<td>380-620</td>
<td>410-620</td>
<td>410-690</td>
<td>350-620</td>
</tr>
</tbody>
</table>

Central tendencies of QTc interval measurements for all subjects
Table 8

<table>
<thead>
<tr>
<th>QTc in ms</th>
<th>Baseline QTc</th>
<th>First Long QTc</th>
<th>Longest QTc</th>
<th>Final QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>Mean</td>
<td>470</td>
<td>511</td>
<td>535</td>
<td>457</td>
</tr>
<tr>
<td>Median</td>
<td>465</td>
<td>510</td>
<td>530</td>
<td>450</td>
</tr>
<tr>
<td>Mode</td>
<td>450</td>
<td>500</td>
<td>500</td>
<td>480</td>
</tr>
<tr>
<td>Range</td>
<td>380-690</td>
<td>410-620</td>
<td>410-690</td>
<td>350-620</td>
</tr>
</tbody>
</table>

Central tendencies of QTc interval measurements for subjects with positive aLQTS

Table 9

<table>
<thead>
<tr>
<th>QTc in ms</th>
<th>Baseline QTc</th>
<th>Longest QTc</th>
<th>Final QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>42</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>Mean</td>
<td>437</td>
<td>458</td>
<td>435</td>
</tr>
<tr>
<td>Median</td>
<td>440</td>
<td>460</td>
<td>434</td>
</tr>
<tr>
<td>Mode</td>
<td>450</td>
<td>480</td>
<td>430</td>
</tr>
<tr>
<td>Range</td>
<td>390-470</td>
<td>410-490</td>
<td>380-480</td>
</tr>
</tbody>
</table>

Central tendencies of QTc interval measurements for subjects with negative aLQTS
The baseline, longest, and final QTc durations in all subjects were further compared by gender. The mean baseline QTc in men \((M = 456, \text{SE} = 6.46 \text{ ms})\) was not significantly different than in women \((M = 452, \text{SE} = 5.11 \text{ ms})\), \(t(86) = .493, p = .62\). Of those positive for aLQTS, the mean longest QTc in men \((M = 540, \text{SE} = 9.5 \text{ ms})\) versus women \((M = 531, \text{SE} = 10.8 \text{ ms})\) was not significantly different, \(t(44) = .637, p = .53\). The mean longest QTc for all subjects during the monitoring period between men \((M = 498, \text{SE} = 8.83 \text{ ms})\) and women \((M = 499, \text{SE} = 7.89 \text{ ms})\) did not show a significant difference, \(t[86] = -.098, p = .92\). The mean final QTc in women \((M = 448, \text{SE} = 4.69 \text{ ms})\) versus men \((M = 445, \text{SE} = 7.54 \text{ ms})\) showed no significant difference, \(t(84) = -.4, p = .69\) (Table 10).

**Specific Aim Two: To describe the average time period between ICU admission and onset of aLQTS in an ICU population**

In this study, 46 subjects were positive for aLQTS; 14 were admitted with aLQTS and 32 developed aLQTS after ICU admission. Of the 46 subjects positive for aLQTS including those admitted with a prolonged QT interval, the average onset of QT prolongation was \(7.4 \pm 9.4 \text{ hours}\) (Table 11), with a range of 0-32 hours (Figure 8). Of the 32 subjects who presented to the ICU with a normal baseline QTc and developed aLQTS after ICU admission, the average onset of QT prolongation was \(10.6 \pm 9.5 \text{ hours}\).

Mean QTc intervals were compared between subjects admitted to ICU with aLQTS at baseline with those who developed aLQTS after ICU admission (Table 12).
Table 10

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n/QTc in ms)</th>
<th>Women (n/QTc in ms)</th>
<th>t-test for equality of means</th>
<th>Degrees of Freedom</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline QTc</td>
<td>41/456</td>
<td>47/452</td>
<td>.493</td>
<td>86</td>
<td>.62</td>
</tr>
<tr>
<td>First long</td>
<td>21/540</td>
<td>25/531</td>
<td>.637</td>
<td>44</td>
<td>.53</td>
</tr>
<tr>
<td>Longest QTc</td>
<td>41/498</td>
<td>47/499</td>
<td>-.098</td>
<td>84</td>
<td>.92</td>
</tr>
<tr>
<td>Final QTc</td>
<td>41/445</td>
<td>47/448</td>
<td>-.399</td>
<td>84</td>
<td>.69</td>
</tr>
</tbody>
</table>

Gender differences in QTc interval measurements

Figure 8

Frequency of aLQTS onset by hour
Table 11

<table>
<thead>
<tr>
<th>Criteria</th>
<th>n</th>
<th>Mean</th>
<th>Median</th>
<th>Mode</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>subjects positive for aLQTS including prolonged QTc on ICU admission</td>
<td>46</td>
<td>7.4</td>
<td>2.5</td>
<td>0</td>
<td>0-32</td>
</tr>
<tr>
<td>subjects positive for aLQTS excluding prolonged QTc on ICU admission</td>
<td>32</td>
<td>10.6</td>
<td>8.5</td>
<td>2</td>
<td>1-32</td>
</tr>
</tbody>
</table>

Temporal onset for aLQTS

Table 12

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Positive aLQTS on ICU admission n=14</th>
<th>Positive aLQTS after ICU admission n=32</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline QTc</td>
<td>508</td>
<td>453</td>
<td>.00</td>
</tr>
<tr>
<td>Longest QTc</td>
<td>525</td>
<td>540</td>
<td>.44</td>
</tr>
<tr>
<td>Final QTc</td>
<td>456</td>
<td>458</td>
<td>.90</td>
</tr>
</tbody>
</table>

QTc intervals for positive aLQTS
Subjects positive for aLQTS upon ICU admission had a longer QTc interval ($M = 508, SE = 13.30$ ms) than those who developed aLQTS after ICU admission ($M = 453, SE = 5.11$ ms). This difference was statistically significant, $t(44) = -4.75, p = .00$. The longest QTc interval in subjects admitted positive for aLQTS ($M = 525, SE = 16.84$ ms) compared to subjects who developed aLQTS after ICU admission ($M = 540, SE = 7.49$ ms) showed no significant difference, $t(44) = -.78, p = .44$. The final QTc in subjects admitted with positive for aLQTS ($M = 456, SE = 17.69$ ms) compared with subjects who developed aLQTS after ICU admission ($M = 458, SE = 6.78$ ms) was not significantly different, $t(43) = -.12, p = .90$.

The fourteen subjects admitted positive for aLQTS on ICU admission had the following characteristics: four arrived from the surgical suite, four were admitted with acute coronary syndrome, three were admitted in respiratory failure, two were admitted with severe infections and sepsis, and one was admitted in a hypertensive crisis. Six of the 14 subjects received a known QTc prolonging medication prior to admission to the ICU. Two subjects remained positive for aLQTS on their final QTc intervals. Of these, one subject remained in the ICU but had reached the end of the study period of 72 hours, and the second subject, admitted with hypertensive crisis was discharged to the telemetry unit after 12 hours.

Onset of aLQTS was further compared by gender, race, and BMI (Table 13). Onset for aLQTS in women ($M = 7.80, SE = 1.90$ hours) versus men ($M = 6.9, SE = 2.02$ hours) was not significantly different, $t(44) = -.32, p = .75$. 
Table 13

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>mean hour</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Men/Women)</td>
<td>21/25</td>
<td>6.9/7.8</td>
<td>.75</td>
</tr>
<tr>
<td>Race (White/Non-White)</td>
<td>39/7</td>
<td>7.36/7.57</td>
<td>.96</td>
</tr>
<tr>
<td>BMI (&lt; 25kg/m² / ≥ 25kg/m²)</td>
<td>11/35</td>
<td>5.64/7.94</td>
<td>.48</td>
</tr>
</tbody>
</table>

Gender differences for temporal onset of aLQTS
Non-whites ($M = 7.57$, $SE = 3.50$ hours) versus whites ($M = 7.36$, $SE = 1.50$ hours) were not significantly different in onset of aLQTS, $t(44) = -0.06$, $p = .96$. The onset of aLQTS was not significantly different between BMI categories, $t(44) = -0.72$, $p = .48$. The mean onset of aLQTS was $7.94 \pm 1.70$ hours in subjects who were overweight or obese and $5.64 \pm 2.30$ hours in those with normal weight or underweight.

**Specific Aim Three:** *To describe medications that may be associated with aLQTS in an ICU population*

Fifty-two of the 88 subjects (59.1%) received known QTc prolonging medications. Of these subjects, 33 (63.5%) developed aLQTS and 19 (36.5%) did not. Thirteen subjects underwent elective surgery and eight returned from the operating room with a prolonged QTc interval within two hours. Further investigation of medications received in the operating room was conducted. The analysis discovered that six of the eight surgery subjects (75%) positive for aLQTS received a flurane, a class of anesthetic medications known to prolong the QTc interval. Six frequently used medications were administered prior to QTc prolongation (Table 14) including one anti-emetic, one anti-arrhythmic, three antibiotics, and a commonly used group of anesthetic medications.

The 52 subjects who received a QTc interval prolonging medication were categorized into two groups, those with positive and negative aLQTS (Figure 9). The analysis indicated that those who received QTc prolonging medications were significantly more likely to develop aLQTS ($X^2[1] = 6.38$, $p = .012$).
<table>
<thead>
<tr>
<th>Medication</th>
<th>Frequency</th>
<th>Percent of total subjects</th>
<th>Percent of subjects positive for aLQTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>9</td>
<td>10.2</td>
<td>19.5</td>
</tr>
<tr>
<td>Amiodorone</td>
<td>6</td>
<td>6.8</td>
<td>13.0</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>5</td>
<td>5.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>4</td>
<td>4.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Fluranes (anesthetics)</td>
<td>6</td>
<td>6.8</td>
<td>13.0</td>
</tr>
</tbody>
</table>

Frequency of medication administered prior to QTc interval prolongation
Frequency of QT prolonging medications received by positive and negative aLQTS subjects

<table>
<thead>
<tr>
<th></th>
<th>Number of Pts</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive aLQTS</td>
<td>33</td>
<td>63.5%</td>
</tr>
<tr>
<td>Negative aLQTS</td>
<td>19</td>
<td>36.5%</td>
</tr>
</tbody>
</table>
Further analysis was completed on the 46 subjects' positive for aLQTS (Figure 10). Thirty-three subjects (71.7%) received and 13 (28.3%) did not receive a known QTc prolonging medication, respectively. Utilizing Chi-square a significant difference between the groups who received a QTc prolonging medication compared with the those who did not receive a QT prolonging medication was noted $X^2(1) = 6.38, p = .012$. Although QTc prolongation occurred in the absence of receiving a known prolonging medication, receiving a QTc prolonging medication significantly increases the risk of developing aLQTS.

Specific Aim Four: To describe risk factors (i.e. gender, age, co-morbidities) that may be associated with aLQTS in an ICU population

Subjects positive for aLQTS were compared to those negative for aLQTS in nine categorical variables (Table 15) and two continuous variables (Table 16), including race, gender, hypothermia, hypokalemia, acute coronary syndrome, positive smoking, alcohol abuse, HF, hypercholesterolemia, age and BMI. Among these, no variable showed a statistically significant difference between the two groups.

Three subjects received therapeutic hypothermia post cardiac arrest and all developed prolonged QTc intervals after treatment (550ms-690 ms), however, no difference was seen compared to the group negative for aLQTS ($p=.12$). Among subjects admitted with acute coronary syndrome ($n=23$), more than 50% ($n=13$) were positive for aLQTS.
Figure 10

Frequency of medications administered to positive aLQTS subjects

Table 15

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects positive for aLQTS n (%)</th>
<th>Subjects negative for aLQTS n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race (White/Non-White)</td>
<td>39(84.8%)/7(15.2%)</td>
<td>38(90.5%)/4(9.5%)</td>
<td>.420</td>
</tr>
<tr>
<td>Gender (Men/Women)</td>
<td>21(45.7%)/25(54.3%)</td>
<td>20(47.6%)/22(52.4%)</td>
<td>.85</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>3(6.5%)</td>
<td>0</td>
<td>.09</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>10(21.7%)</td>
<td>4(9.5%)</td>
<td>.12</td>
</tr>
<tr>
<td>ACS with positive troponins</td>
<td>13(28.3%)</td>
<td>10(23.8%)</td>
<td>.64</td>
</tr>
<tr>
<td>Positive Smoker</td>
<td>13(28.3%)</td>
<td>9(21.4%)</td>
<td>.46</td>
</tr>
<tr>
<td>Alcohol Abuse</td>
<td>6(13%)</td>
<td>2(4.8%)</td>
<td>.18</td>
</tr>
<tr>
<td>New onset or history of CHF</td>
<td>7(15.2%)</td>
<td>7(16.7%)</td>
<td>.85</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>21(45.7%)</td>
<td>11(26.2%)</td>
<td>.06</td>
</tr>
</tbody>
</table>

Categorical variable analysis of host risk factors between positive and negative aLQTS subjects
Table 16

<table>
<thead>
<tr>
<th>Variable</th>
<th>Positive aLQTS (mean ± SD)</th>
<th>Negative aLQTS (mean ± SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.05 ± 2.31</td>
<td>65.72 ± 1.99</td>
<td>.13</td>
</tr>
<tr>
<td>BMI</td>
<td>29.16 ± 1.26</td>
<td>30.54 ± 1.40</td>
<td>.47</td>
</tr>
</tbody>
</table>

Continuous variable analysis of host risk factors between positive and negative aLQTS subjects
Presence of acute coronary syndrome showed no statistically significant
difference when compared to the group negative for aLQTS (p=.64). In addition,
14 subjects had HF and 50% (n=7) were positive for aLQTS but showed no
difference from the group with HF and negative for aLQTS (p=.85).

Age of subjects positive for aLQTS ($M = 65.72, SE = 1.99$ years)
compared to those negative for aLQTS ($M = 61.05, SE = 2.31$ years) showed no
statistically significant difference between groups, $t(86) = -1.54, p = .13$.
Additionally, BMI in subjects positive for aLQTS ($M = 30.54, SE = 1.4$ kg/m$^2$)
compared to negative for aLQTS ($M = 29.16, SE = 1.26$ kg/m$^2$) did not reach a
statistically significant difference, $t(84) = -.73, p = .47$.

Logistical regression was used to estimate the probability of aLQTS within
72 hours of ICU admission. Fifteen predictive variables were used in the
analysis. Ten risk factors and co-morbidities examined included age, gender,
BMI, positive smoker, hypercholestoremia, bradycardia with complete
atrioventricular block, hypokalemia, hypothermia, acute coronary syndrome and
HF. Five medications included in the analysis were flurane, ondansetron,
levofloxacin, azithromycin, and amiodorone. Using the backward stepwise
method, among all variables examined, only five medications were found to be
statistically significant predictors for the development of aLQTS: flurane,
ondansetron, levofloxacin, azithromycin, and amiodorone. Other risk factors,
such as age, gender, and co-morbidities, did not show to significantly predict the
development of aLQTS (Table 17).
Table 17

<table>
<thead>
<tr>
<th>Variable</th>
<th>b</th>
<th>SE</th>
<th>Model Log Likelihood</th>
<th>Change in -2 Log Likelihood</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.028</td>
<td>.021</td>
<td>-41.346</td>
<td>1.813</td>
<td>.178</td>
</tr>
<tr>
<td>Gender</td>
<td>.967</td>
<td>.696</td>
<td>-38.331</td>
<td>2.075</td>
<td>.150</td>
</tr>
<tr>
<td>Body mass index</td>
<td>.042</td>
<td>.030</td>
<td>-40.439</td>
<td>2.047</td>
<td>.153</td>
</tr>
<tr>
<td>Positive smoker</td>
<td>-.926</td>
<td>.635</td>
<td>-39.416</td>
<td>2.170</td>
<td>.141</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>-.788</td>
<td>.616</td>
<td>-37.294</td>
<td>1.668</td>
<td>.197</td>
</tr>
<tr>
<td>Bradycardia with complete heart block</td>
<td>18.622</td>
<td>8564.452</td>
<td>-36.460</td>
<td>1.820</td>
<td>.177</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1.271</td>
<td>1.218</td>
<td>-35.550</td>
<td>1.278</td>
<td>.258</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>-15.626</td>
<td>27773.710</td>
<td>-32.476</td>
<td>.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>-.525</td>
<td>.614</td>
<td>-34.911</td>
<td>.732</td>
<td>.392</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>.589</td>
<td>.971</td>
<td>-32.702</td>
<td>.376</td>
<td>.540</td>
</tr>
<tr>
<td>Flurane Anesthetic</td>
<td>-21.141</td>
<td>14774.122</td>
<td>-45.172</td>
<td>7.651</td>
<td>.006</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>-21.155</td>
<td>12148.849</td>
<td>-46.947</td>
<td>11.201</td>
<td>.001</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>-20.426</td>
<td>14615.570</td>
<td>-43.308</td>
<td>3.924</td>
<td>.048</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>-20.684</td>
<td>16629.531</td>
<td>-43.308</td>
<td>3.924</td>
<td>.048</td>
</tr>
<tr>
<td>Amiodorone</td>
<td>-20.701</td>
<td>13694.277</td>
<td>-44.252</td>
<td>5.811</td>
<td>.016</td>
</tr>
</tbody>
</table>

Logistical regression on selected variables for aLQTS
CHAPTER 5
CONCLUSIONS/DISCUSSION

This study showed that the majority of subjects developed aLQTS in the ICU. Subjects who developed aLQTS did so most often in the first day of ICU admission. Several frequently administered medications in ICU appeared to be associated with aLQTS. However, 28.3% subjects who developed aLQTS did not receive a known QT interval prolonging medication indicating the possibility of other unidentified causes. This suggests that other potential risk factors may be associated with this syndrome and could lead to aLQTS in the absence of medications.

Frequency of aLQTS

This is the first study that included consecutive ICU patients to determine an overall frequency of aLQTS in an ICU regardless of medications or risk factors involved. Ng and colleagues (2008, 2004) studied the frequency of aLQTS in a subset of subjects who received a known QTc interval prolonging medication in ICU populations and found the frequency to be 46.6% (Ng et al., 2004) and 58.4% (Ng et al., 2008). Other existing work on frequency of aLQTS has been focused on subjects in non-ICUs (Golzari, Dawson, Speroff, & Thomas, 2007; Molokhia et al., 2008; Ramos-Rios et al., 2010; Seftchick et al., 2009).

In a retrospective chart review of 861 hospitalized subjects in France, Molokhia and associates (2008) estimated that 5-7% of subjects diagnosed with ventricular tachycardia, ventricular fibrillation, or sudden cardiac death were
caused by LQTS (Molokhia et al., 2008). In another study of hospitalized chronic schizophrenic subjects, it was found six-percent developed a prolonged QT interval from antipsychotic polypharmacy (Ramos-Rios et al., 2010). In yet another study to determine the prevalence of prolonged QTc intervals of all subjects admitted to any department in a hospital using admission ECGs, it was found that in a consecutive sample of 258 subjects the prevalence was 3.5% (QTc > 500ms) to 25.2% (QTc > 450ms) (Golzari et al., 2007). Another study was completed to determine the frequency of QTc interval prolongation in an emergency room population. Utilizing a retrospective chart review of 1,558 subjects, those who received an ECG in the emergency room were included in the study. Using criteria for QT prolongation of > 450ms for men and > 460ms for women, 544 subjects (35%) had a prolonged QTc interval and eight percent had QTc intervals >500ms (Seftchick et al., 2009). These studies show a prevalence of aLQTS in non-critical hospitalized populations. ICU patients are critically ill and receive many QT interval prolonging medications yet overall frequency in ICU populations had not been studied.

Results from this study showed 52.3% of ICU subjects develop aLQTS. A prolonged QTc interval was seen more often in subjects receiving a QTc interval prolonging medication compared with those who did not receive a QTc interval prolonging medication. However, nearly 28.3% of those positive for aLQTS did not receive a medication known to cause prolongation of the QTc interval,
indicating the importance of monitoring QTc intervals in all ICU subjects. ICUs should have protocols to analyze and document QTc intervals.

Temporal Onset of Occurrence of aLQTS

In the present study, subjects were frequently admitted with aLQTS (30.4%) or developed it soon after admission (69.6%), on average at 10.6 hours. Subjects admitted to the ICU frequently come from the emergency rooms or operating rooms where multiple medications are administered and QTc interval prolongation occurs (McConachie, Keaveny, Healy, Vohra, & Million, 1989; Michaloudis et al., 1996; Schmeling et al., 1991; Yildirim, Adanir, Atay, Katicioglu, & Savaci, 2004). In this study, six of eight subjects had a large surgery and returned to the ICU from the operating room with aLQTS after receiving a known QTc interval prolonging anesthetic agent. Subjects who were positive for aLQTS at ICU admission (508 ms) showed an average final QTc measurement within normal range (456 ms), indicating the admitting QTc interval was acquired. The results from this study indicate the need to obtain a baseline QTc interval on ICU admission with frequent QTc interval assessments during the ICU stay.

Many factors can play a role in prolongation of the QTc interval at any day and hour during an ICU stay. For instance, patients are frequently admitted for severe infections (e.g. pneumonia) or they can develop a hospital acquired infection any time after admission. This study showed that ten of the 88 subjects (21.7%) were admitted with a severe infection and sepsis and received a known
QTc interval prolonging antibiotic medication (levofloxacin, azithromycin, ciprofloxacin). However, hospital acquired infections were not collected and the onset of aLQTS was studied only in the first 72 hours from ICU admission. Subjects could acquire an infection and receive antibiotics known to aLQTS after the study period of 72 hours from ICU admission.

Current guidelines propose that monitoring the QTc interval should take place in patients before and at a minimum of every eight to twelve hours after receiving a QTc interval prolonging medication (Drew et al., 2010; Drew & Funk, 2006). This study elucidates that these guidelines may not capture all patients in the ICU with positive aLQTS. Further refinement of these guidelines is needed.

Medications and aLQTS

In this study, greater than 78% of subjects with aLQTS received a known QTc interval prolonging medication. Ondansetron, fluranes, amidorone, and fluroquinolones, were four of most frequently used medications associated with prolongation of the QTc interval.

**Ondansetron (Zofran®):** Results from this study showed that ondansetron was the most frequently prescribed medication in subjects with aLQTS. Ondansetron, a medication used for nausea and/or vomiting is frequently used in the hospitalized patient, especially in emergency rooms, post-operatively, and in ICUs. It is a potential QTc interval prolonging medication. Several cases of cardiac dysrhythmias have been reported in the literature after administration of ondansetron (Charbit et al., 2005). In a prospective double-blind study to
determine the effects of ondansetron on the QT interval, sixteen healthy volunteers were randomized to one of four groups to receive either: droperidol (another medication for nausea that has the potential to prolong QT interval), ondansetron, a combination of droperidol and ondansetron, or placebo (Charbit et al., 2008). Results concluded that ondansetron significantly prolonged the QTc interval ($p = 0.014$). In a second single-blind study, 85 subjects with post-operative nausea and vomiting were randomized to receive either droperidol or ondansetron (Charbit et al., 2005). Both antiemetics were associated with a significant longer QTc interval post administration ($p < 0.0001$).

In December 2001, the FDA issued a black-box warning against the use of droperidol as a first choice medication for nausea and vomiting because of the increased risk of QTc interval prolongation and the subsequent incidence of TdP (Habib, 2008). Ondansetron became the first choice medication for the indication of nausea and vomiting. Ondansetron is frequently administered on medical-surgical units and in outpatient clinics where cardiac rhythm monitoring is not used, indicating a risk for unidentified aLQTS and the potential consequence of TdP. These studies along with results from the current study indicate that clinicians should be diligent in monitoring QTc intervals in ICUs when administering ondansetron.

*Anesthetic medications:* In this study, the majority of post-operative subjects (61.5%) returned to the ICU with a prolonged QTc interval. Further analysis showed that six (75%) of those subjects received a flurane agent. It has
been known for several decades that a commonly used class of anesthetic agents known as fluranes, can affect cardiac repolarization leading to aLQTS (McConachie et al., 1989; Michaloudis et al., 1996; Schmeling et al., 1991; Yildirim et al., 2004). Most often reported cases occur in older patients with predisposing risk factors such as electrolyte abnormalities and/or ischemic heart disease (Abe, Takada, & Yoshiya, 1998; Lustik, Eichelberger, Chibber, & Bronsther, 1998). However in one recently reported case, no identifiable risk factors were present in a 35-year old healthy woman. Her pre-operative QTc interval was normal (346ms-388 ms) but she developed a ventricular tachycardic cardiac arrest following QTc prolongation during a simple septoplasty under general anesthesia (Dolenska, 2009).

These studies along with the present study indicate that flurane anesthetic agents are a risk factor for developing aLQTS. The high frequency of aLQTS in the presence of fluranes demonstrates the importance of monitoring QTc intervals in all post-operative ICU patients. Although an ECG is routinely obtained in patients undergoing a surgery, it should be standard practice to document a baseline QTc interval prior to anesthesia induction when possible and monitor QTc interval post-operatively.

Fluoroquinolones: Results from this study showed that fluoroquinolones are associated with developing aLQTS. Fluoroquinolones, specifically levofloxacin (Levaquin®) has become the drug of choice against many respiratory, gastrointestinal, and genitourinary pathogens because of its wide spectrum. Two
medications in this class, grepafloxacin and sparfloxacin have been withdrawn from the market due to adverse cardiac events and deaths (Simko, Csilek, Karaszi, & Lorincz, 2008). Ng and colleagues (2008), found a high frequency (58.4%) of aLQTS in an ICU population attributed to the use of levofloxacin. In another study by Ng and associates (2004), moxifloxacin (another fluoroquinolone) had the highest rate of QTc interval prolongation 48.1% (n=52/108) among all QTc interval prolonging medications (list not reported). Several case reports have identified levofloxacin associated aLQTS (Falagas, Rafailidis, & Rosmarakis, 2007).

In all reported cases of TdP related to fluoroquinolones, at least one concomitant risk factor for TdP was present (Amankwa, Krishnan, & Tisdale, 2004). In the present study, no subjects developed TdP. However, of the six subjects who received a fluoroquinolone and developed aLQTS, all but one (83.3%) had at least one other known risk factor associated with aLQTS. In ten subjects who received a fluoroquinolone and did not develop aLQTS, five (50%) had at least one risk factor for aLQTS. These results indicate the importance of monitoring QTc interval in all patients receiving this class of medications.

**Azithromycin:** Findings from the present study showed a statistically significant association between azithromycin and aLQTS. Macrolide antibiotics such as azithromycin (Zithromax®) are effective for treating upper and lower respiratory tract infections such as pneumonia (Huang, Wu, Hsia, & Chen, 2007). Azithromycin is a semi-synthetic macrolide better tolerated than erythromycin
There have been case reports of QT prolongation when azithromycin is combined with amiodarone or disopyramide (Granowitz, Tabor, & Kirchhoffer, 2000; Samarendra, Kumari, Evan, Sacchi, & Navarro, 2001).

More recently, there have been cases of azithromycin associated aLQTS in the absence of other known QT prolonging medications (Kezerashvili et al., 2007). For example, in a case report, a 90-year-old woman with interstitial pneumonia and respiratory failure (Huang et al., 2007) was started on penicillin (sulbactam) and azithromycin. Four hours after receiving azithromycin, the patient had a pronounced prolonged QT interval leading to a lost consciousness due to TdP. Her electrolytes were within normal limits. Azithromycin was discontinued and her QT interval was normalized the next day. In a second case, a 55-year-old woman with methicillin-resistant staphylococcus aureus sepsis from an implanted pacemaker pocket (Kezerashvili et al., 2007) developed atypical pneumonia on the seventh hospital day. She was started on azithromycin. After her seventh daily dose of azithromycin, she showed two brief episodes of TdP. When prior ECGs were reviewed, it was found that QT prolongation occurred on the day azithromycin was initiated. These findings once again indicate the importance of monitoring QTc intervals in patients receiving azithromycin.

**Amiodarone:** Amiodarone is a Class III antiarrhythmic medication. Its primary mechanism is to prolong repolarization homogeneously in the three
myocardial cells types (epicardial, endocardial, and midmyocardial). This results in QT interval prolongation (Antzelevitch, 2007) but a decreased transmural dispersion of repolarization (Antzelevitch, 2004).

Although amiodarone alone has a low risk of TdP in the presence of QT interval prolongation, concomitant use with other QT interval prolonging medications has shown to increase arrhythmias, mortality, and ICU lengths of stay (Freeman, Dixon, Coopersmith, Zehnbauer, & Buchman, 2008). In the present study, amiodarone was a frequently used medication associated with aLQTS. Nine subjects (10.2%) received amiodarone and six (13.0%) developed aLQTS. Five of these six subjects (83.3%) were administered at least one additional QT interval prolonging medication concomitantly. This indicates that all patients receiving amiodarone should have QTc intervals monitored in the ICU.

A substantial number of medications frequently administered in ICUs have the potential to prolong the QTc interval. The risk increases when two or more such medications are administered concurrently (Curtis et al., 2003; DePonti, Poluzzi, & Montanaro, 2000; Moss, 1999). In the present study, ten subjects (21.7%) received two or more QTc interval prolonging medications in the group positive for aLQTS. Four subjects (9.5%) had more than one QTc interval prolonging medication in the group negative for aLQTS. Logistic regression was used to determine if particular medications may affect the probability of developing aLQTS. Five medications (flurane, ondansetron, levofloxacin,
azithromycin, and amiodorone), significantly predicted the development of aLQTS.

Multiple classes of medications associated with aLQTS are frequently indicated in the ICU (LaPointe et al., 2006; Ng et al., 2008) and those who develop aLQTS frequently have at least one other associated risk factor (Chiang, 2004; Straus et al., 2005). In addition, the lack of knowledge by medical practitioners regarding aLQTS puts patients at risk even further (Cubeddu, 2003a).

Risk Factors and aLQTS

In this study, no statistically significant association between host risk factors and aLQTS was elucidated. Risk factors, such as gender (Arya, 2005; Bazett, 1918; Bidoggia et al., 2000), BMI (Carella et al., 1996; El-Gamal et al., 1995), myocardial ischemia (Kawabata et al., 2008; Sezgin et al., 2007), HF (Phang & White, 1943; Xu et al., 2001), hypothermia (Gould et al., 1985), and hypokalemia (Hanton et al., 2007; Kannankeril & Roden, 2007), have been correlated with prolonged QT intervals in previous studies but not in the present study. Logistic regression was used to determine if particular host risk factors (age, gender, BMI, positive smoker, hypercholesterolemia, bradycardia with atrioventricular block, hypokalemia, hypothermia, acute coronary syndrome and HF) may affect the probability of developing aLQTS. No host risk factors showed to significantly predict the development of aLQTS.
This study was a retrospective descriptive pilot study and a power analysis was not performed. A small sample may have contributed to a lack of power to observe statistical significance between associated risk factors and aLQTS. In larger studies, risk factors have been associated with a higher frequency of aLQTS (Sommargren & Drew, 2007).

Study Limitations

This was a retrospective pilot study and therefore did not allow for control of variables. For instance, recommendations in QT studies for proper lead monitoring is to choose the lead from a 12-lead ECG that has a T-wave with at least 2mm amplitude and a well-defined T-wave end (Drew et al., 2010). Other recommendations include choosing the lead with the longest QT interval from an ECG (Lepeschkin & Surawicz, 1952; Rautaharju, Surawicz, & Gettes, 2009). It was not possible to perform a 12-lead ECG to choose the best lead to measure QT intervals in this retrospective study.

In addition, an important aspect of QT interval measurements is to measure in the same lead over time for consistency (Drew et al., 2010). In the present study, nurses in the ICU change leads periodically depending on what lead is easiest to read with the least amount of artifacts. Subjects may have left the unit for a testing/procedure and returned under the care of a different nurse who may change the monitoring lead that she/he determines best to read. A retrospective analysis showed that 29 subjects (33.0%) had lead changes during the study period. It is possible that baseline, first long QTc, longest QTc, and
final QTc were recorded on one or more different leads in the same subject. The most frequently used lead was lead II (n=65 or 73.9%).

Histories and demographic information were obtained from the medical record. History and physicals dictated by physicians and nursing admission forms by nurses were used to record co-morbidities and reasons for admission. It is unclear if these documents provided comprehensive information as some subjects were admitted in comatose states or very ill, suggesting that information provided by families or friends may be incomplete or inaccurate.

The findings from the present study can only be generalized to subjects admitted to an ICU in the first 72 hours from admission. Subjects requiring additional QT prolonging medications later in their ICU stays were not included. Subjects may receive QT interval prolonging medications later than 72 hours after ICU admission, therefore, the frequency of aLQTS may be higher than reported by the present study.

No subjects developed ventricular arrhythmias in the present study. The staff in the study ICU is educated regarding the risk of arrhythmias in the presence of aLQTS. The study ICU has a protocol to assess QTc intervals every six hours and physicians are notified upon identification of QTc prolongation so that the offending medication can be removed. This study did not collect data on medications removed or changed because of the presence of aLQTS.
Future Studies

This was a small retrospective descriptive study that showed a significant incidence of aLQTS in an ICU population. Monitoring QTc intervals for the entire ICU stay may elucidate an even greater frequency of aLQTS in ICU populations. A power analysis was not completed prior to this study which may have contributed to a lack of association between host risk factors and aLQTS. Future studies with larger sample sizes with sufficient power are needed to determine frequencies of risk factors, such as gender, age, BMI, and co-morbidities associated with aLQTS.

Studies to determine the frequency of aLQTS in telemetry or step-down units are also needed. Patients in these units may be at risk for developing aLQTS because they often are on similar medications administered in the ICU. In addition, patients are frequently transferred to telemetry units from ICUs, surgical suites, or emergency rooms.

Clinical Implications

Hospitalized populations are at the greatest risk for developing aLQTS, yet the incidence and temporal onset of occurrence had not been studied. This was the first study to determine the frequency and temporal onset of aLQTS in an ICU population. This study elucidated that aLQTS was present in approximately half of ICU subjects upon or early after ICU admission. Six frequently administered medications but not host risk factors were found to be statistically significant
predictors for developing aLQTS. In addition, a small group of subjects (28.3%) developed aLQTS in the absence of a known QT interval prolonging medication.

Results from this study elucidates the need to assess QTc intervals on all ICU patients immediately upon admission because nearly one-third of subjects 30.4% (n=14) were admitted with aLQTS. Due to the high frequency of aLQTS after ICU admission, continuous QTc monitoring is also advised. If monitoring equipment is not available to calculate continuous QTc intervals automatically, QTc intervals should be assessed every hour to help identify patients who develop aLQTS early. However, assessing QTc intervals every hour may be difficult in the clinical setting; therefore, further research is needed to determine a feasible and safe assessment interval to capture patients who develop aLQTS early.

Current best practice guidelines recommend monitoring patients receiving a QT prolonging medication prior to initiation of the medication, and every eight to 12 hours for 48 to 72 hours after initiation or an increase in dosage (Drew et al., 2010; Drew & Funk, 2006). These current guidelines for identifying aLQTS may not capture all patients who develop aLQTS in the ICU population. With proper monitoring policies that incorporate a consistent protocol for QTc interval measurements, medication-induced aLQTS may be reversed by early identification and prompt removal of culprit agents. Using consistent equipment, methods, and lead selection should be included in protocol development to
ensure accurate and consistent identification of a prolonging QTc interval (Drew et al., 2010).

Clinicians should identify patients at risk for developing aLQTS early by recognizing frequently used QT prolonging medications in the ICU. These medications can be obtained from the University of Arizona website (http://www.azcert.org).
APPENDIX A

CHW-IRB APPROVAL LETTER FOR PRELIMINARY STUDY
July 29, 2008

Terri Kozik, RN, MS
Saint Mary's Regional Medical Center – Critical Care
235 West Sixth Street
Reno, NV 89503

Re: Incidence of Acquired Long QT Syndrome in a Community Hospital Setting.

Dear Ms. Kozik:

Please be advised that I have reviewed the Request to use Protected Health Information (PHI) for Research Preparation for the above referenced proposed research, and in accordance with CHW IRB #2 Policy and Federal Regulations (45CFR46.110 / 21 CFR50.110), hereby grant expedited approval of this waiver of informed consent. If the purpose, methods or processes of this study change in any way, please contact the IRB to assure that an exempt status is still applicable.

Conduct of this preparation for research must adhere to applicable Federal regulations and the policies of the Institutional Review Board. Assuring participant safety (including confidentiality), and oversight of the research team are included in your responsibilities. The federally registered Catholic Healthcare West Institutional Review Board #2 (#2009) performs its functions in accordance with the Federally Assured No. 00001495.

Please be reminded that any/all solicitations for patient participation must be approved by the IRB prior to publication and any alterations or modifications to the protocol as well as all (including events that have occurred at other sites) adverse effects or reactions must be reported promptly to the Institutional Review board. All correspondence with regulatory agencies, DSMB reports, Investigator Brochures and progress reports should be provided promptly to the IRB as well. Further, any deviations from the protocol must be reported immediately.

Thank you for your continued cooperation and support of the Institutional Review Board. If we can be of any additional assistance, please do not hesitate to contact the IRB Office.

Sincerely,

Craig D Weiner, MD
Chairman
APPENDIX B

CHW-IRB APPROVAL LETTER FOR STUDY
September 11, 2009

Teri Kozik, RN MS CCRN
St. Mary's Regional Medical Center
235 West Sixth Street
Reno, NV 89503

RE: Frequency, Temporal Pattern Of Occurrence And Risk Factor Identification For Acquired Long QT-Syndrome In A Critical Care Population

Dear Ms. Kozik:

Please be advised that I have reviewed the above referenced materials and in accordance with CHW IRB Policy and Federal Regulations (45CFR46.110 / 21 CFR86.110), hereby grant expedited approval of this study with waiver of consent and HIPAA authorization as well as waiver of IRB processing fee.

This project will require annual renewal, which commences on September 11, 2009 and will expire on September 10, 2010. If your project is completed prior to that date, please file a Closure Report to the IRB (the form is on our website at www.cwhrb.com under ‘Forms & documents’).

Conduct of this study must adhere to applicable Federal regulations and the policies of the Institutional Review Board. Assuring participant safety (including confidentiality), and oversight of the research team are included in your responsibilities. The federally registered Catholic Healthcare West Institutional Review Board, Sacramento/Sierra (#2009 & 6573) performs their functions in accordance with the Federallywide Assurance No. 00001489, Catholic Healthcare West.

Please be reminded that any/all solicitations for patient participation must be approved by the IRB prior to publication and any alterations or modifications to the protocol as well as all (including events that have occurred at other sites) adverse effects or reactions must be reported promptly to the Institutional Review board. All correspondence with regulatory agencies, DSMB reports, Investigator's Brochures and progress reports should be provided promptly to the IRB as well. Further, any deviations from the protocol must be reported immediately.

Thank you for your continued cooperation and support of the Institutional Review Board. If we can be of any additional assistance, please do not hesitate to contact the IRB Office.

Sincerely,

Craig D Weiner, MD
Chairman
Institutional Review Board
4001 J Street
Sacramento, CA 95819
916.453.6012 Telephone
916.453.4366 Fax

Catholic Healthcare West
APPENDIX C

UNIVERSITY OF ARIZONA-IRB APPROVAL
LETTER FOR DISSERTATION STUDY
HSPP Correspondence Form

Date: 01/27/10
Investigator: Teri Kozik, PhD Student
Advisor: Shu-Fen Wung, PhD
Project No./Title: 09-1125-01 Frequency, Temporal Pattern of Occurrence and Risk Factor Identification For Acquired Long QT-Syndrome in a Critical Care Population
Current Period of Approval: 01/27/10 – 01/26/11

IRB Committee Information
☐ IRB1 – IRB00000291  ☐ Expedited Review – 01/27/10
FWA Number: FWA00004218

Nature of Submission
☐ New Project

Documents Reviewed Concurrently
☐ Project Review Form (received 12/04/09)  Appr
☐ Questionnaires/Surveys: Data Collection Instruments  Appr

Determination
☐ Approved as submitted effective 01/27/10

Additional Determination(s)
- Expedite Approval (45 CFR 46.110 Category 5): Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
- Waiver of Informed Consent (45 CFR 46.116(d)): the research involves no more than minimal risk to subjects (since this is a retrospective study evaluating medical records); the waiver or alteration will not adversely affect the rights and welfare of the subjects (patient confidentiality will be maintained as data will be de-identified after all data collection is complete); the research could not practically be carried out without the waiver or alteration (this information will be needed to identify medical records for retrieval of information); and whenever appropriate, the subjects will be provided with additional pertinent information after participation (Informed consent will not be used since there is no patient recruitment in this retrospective study).
- Waiver of PHI Authorization (45 CFR 164.512(i)(2)(ii)): the use or disclosure of protected health information involves no more than minimal risk to the individuals (retrospective study evaluating medical records); the alteration or waiver will not adversely affect the privacy rights and the welfare of the individuals (patient confidentiality will be maintained); the research could not practically be conducted without the alteration or waiver (given the retrospective design of the study, it is not feasible to obtain authorization from individual subjects); the research could not practically be conducted without access to and use of the protected health information (this information will be needed to identify medical records for retrieval of information); the privacy risks to individuals whose protected health information is to be used or disclosed are reasonable in relation to the anticipated benefits if any to the individuals, and the importance of the knowledge that may reasonably be expected to result from the research (the study aims to discover a more thorough understanding of the incidence, associated medications, and risk factors in ICU populations for LQTS): there is an adequate plan to protect the identifiers (from improper use and disclosure [data will be coded to link patients discharge information with ECG data and chart information]); there is an adequate plan to destroy the identifiers at the earliest

Reminders: Continuing Review materials should be submitted 30–45 days prior to the expiration date to obtain project re-approval
- Projects may be concluded or withdrawn at any time using the forms available at www.irb.arizona.edu.
- No changes to a project may be made prior to IRB approval except to eliminate apparent immediate hazard to subjects.
- Original signed consent forms must be stored in the designated departmental location determined by the Department Head.

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Form version: 09/23/09
opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law (the case report form and ECG data will be assigned a research number and be removed from any study related paperwork); and there are adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart (only the PI or co-PI will have access to the information which will be stored in a locked private office).

By signing this form, I attest that I do not have a conflict of interest with this project and do not need to recuse myself from review.

Jamie L. Goodwin, PhD
Co-Chair, IRB1 Committee
UA Institutional Review Board

JGG:mm
Cc: Departmental/College Review Committee

Reminders: Continuing Review materials should be submitted 30-45 days prior to the expiration date to obtain project re-approval
- Projects may be concluded or withdrawn at any time using the forms available at www.irb.arizona.edu.
- No changes to a project may be made prior to IRB approval except to eliminate apparent immediate hazard to subjects.
- Original signed consent forms must be stored in the designated departmental location determined by the Department Head.
REFERENCES


El-Sherif, N. & Turrito, G. (1999). The long QT syndrome and Torsades de Pointe. PACE, 22 (Pt 1); 91-110.


