Antimicrobial-Associated QT Interval Prolongation: Pointes of Interest

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Until recently, cardiac toxicity manifesting in the form of arrhythmias related to QT interval prolongation was uncommonly appreciated within the antimicrobial class of drugs, but it was well described among antiarrhythmic agents. Antimicrobials that are associated with QT prolongation include the macrolides/ketolides, certain fluoroquinolones and antimalarials, pentamidine, and theazole antifungals. Although, in most cases, mild delays in ventricular repolarization caused by these drugs are clinically unnoticeable, they may serve to amplify the risk for torsades de pointes (TdP) when prescribed in the setting of other risk factors. Conditions or variables that influence proarrhythmic risk include sex, age, electrolyte derangements, structural heart disease, pharmacokinetic/pharmacodynamic interactions, and genetic predisposition. It is important that clinicians be knowledgable about drugs with QT liability, as well as the risk factors that increase the probability of TdP. Additionally, because TdP remains a difficult-to-measure adverse event, we must rely upon multiple data sources to determine the risk versus the benefit for newly approved drugs.

Cardiac toxicity can occur as an unintended consequence of drug therapy and is considered to be an increasingly important, but rare, medication-related adverse event. In the United States alone, between 300,000 and 400,000 people die annually of sudden cardiac death [1]. Torsades de pointes (TdP), a potentially fatal polymorphic ventricular tachyarrhythmia (figure 1), often occurs in association with a prolonged QT interval or a heart-rate–corrected QT interval (QTc), and it may present as sudden death, syncope (originally described as “quinidine syncope” in the 1920s), dizziness, palpitations, seizures, ventricular tachycardia, or not at all (asymptomatic) if the duration of TdP is relatively short and terminates spontaneously.

It has been cited that the optimal source for determining medication-related adverse events is reliant upon several factors [2]. Unfortunately, for rarely occurring, medication-related adverse events, such as TdP, there is no single study that will reliably determine risk; clinical trials involving anti-infectives are simply not powered to detect TdP and may not even include patients who are at high risk for TdP. Because preclinically, studies to determine a drug’s proclivity to prolong the QT interval have traditionally lacked uniform methods or a uniform model, and because these studies may or may not have been conducted prior to a drug’s approval, there are abundant and sometimes discrepant cardiac risk data for some drugs and little or no cardiac risk data for others. Improvements to ensure a more standardized approach to cardiac risk assessment were introduced in 2005. The International Conference on Harmonization (ICH) topic E14 [3] (clinical strategies) and ICH topic S7B [4] (nonclinical strategies) address what constitutes a thorough evaluation of a drug’s impact on the QT/QTc interval for sponsors seeking approval for new drugs. Although viewed as an advancement in determining cardiac risk for drugs with QT liability, some controversy still exists [5]. Because more compounds with QT liability may be identified earlier in development, it is important not to dismiss all of them, because their benefits (e.g., their activity against drug-resistant pathogens) may outweigh their risks. Once a drug is approved, spontaneous adverse event reporting databases, such as the Food and Drug Administration’s (FDA’s) Adverse Event Reporting System (AERS), remain useful for identifying signals or trends that may not be detected in clinical trials.

Herein, we review the mechanisms and risks for TdP and provide an overview of the antimicrobial agents marketed in North America that are associated with QT interval prolono-
Importantly, because ICH standardization documents for cardiac risk assessment were published in November 2005, robust comparative data for most antimicrobials do not exist. As such, it remains difficult to infer risks within and among antimicrobial classes.

THE QT INTERVAL

The standard surface electrocardiogram (ECG) represents a temporal and spatial summation of individual action potentials across the entire heart (figure 2). The QRS complex corresponds to the depolarization phase of the action potential. The width of the QRS complex roughly correlates with the time required for the wave of depolarization to travel through the ventricular myocytes and to activate the left and right ventricles. The QT interval encompasses both the depolarization phase and the repolarization phase of the action potential. In the absence of intermittent intraventricular conduction delays (e.g., intermittent or variable bundle branch block), changes in the QT interval reflect changes in cardiac repolarization.

A variety of distinct ion channels and transporters exist in the heart that are responsible for maintaining normal cardiac conduction. The human ether-à-go-go–related gene (hERG) encodes the rapid component of the delayed rectifier potassium current (I_{Kr}), which regulates the outward flow of potassium from the myocyte. I_{Kr} is the predominant current responsible for repolarization of the myocytes of the ventricles. Impaired functioning of I_{Kr} results in the accumulation of intracellular potassium ions, which, in turn, delays ventricular repolarization and is ultimately quantified by measurement of the QT interval. The QT interval is also modulated by an individual’s heart rate, autonomic tone, sex, and age [6]. The QT interval is dynamic, with a large variability that exists from beat-to-beat, diurnally, and from day-to-day [7–9]. Other factors that influence the width of the QT interval include concomitant interacting drugs, electrolyte concentrations, and myocardial ischemia [10, 11]. Thus, using the QT interval as a surrogate marker to predict a rarely occurring event like TdP is a complicated practice.

Methods to correct for some of the variability inherent in QT interval—chiefly, heart rate—do exist. Several correction formulas are used, including the Bazett and Fridericia formulas [12, 13]. Limitations exist with each formula, however, and experts have agreed that an optimal approach to correcting for heart rate remains to be validated [14–16]. For clinical risk assessment, ICH E14 recommends rate correction by the Bazett and Fridericia formulas and encourages the analysis of a concurrent positive control group to support the use of a rate correction method that examines individual subject correction [3].

QTc as a surrogate marker. The QT interval can be captured in several ways, including through continuous 12-lead ECG (Holter) recordings over a defined period of time or as single measurements timed at the expected peak concentration after a single dose or at a steady state. ICH E14 is not specific about the method of ECG measurement to be used, but continuous or Holter monitoring appears to be favored by many experts [3]. In Phase I studies involving healthy volunteers, a range of exposures can be explored and a robust ECG recording database is of great importance. This is particularly critical if there is potential for great variability in a drug’s pharmacokinetics.

A drug’s effect on the QTc interval, expressed as mean changes, was also addressed by ICH E14, but some controversy exists. Regulatory concern was defined as a mean effect on the QTc value of 5 ms, as evidenced by the upper limit of the 95% CI of 10 ms [3, 5]. Although these numbers represent regulatory concern, because of the wide intraindividual and interindividual variation surrounding the mean QTc, debate remains regarding the significance of such absolute numbers. ICH E14 recommends categorical analyses of outlier values for risk assessment. These include the number of patients with an overall QTc interval >500 ms occurring during treatment and analyses performed at lower thresholds so as to avoid false-negative results (e.g., >30-ms and >60-ms QTc increases from baseline) [3].

The evaluation of drugs that result in small changes in the QTc interval remains challenging. One reason is that the risk of TdP varies, even among individuals with equivalent degrees of QT prolongation, suggesting that some patients are more susceptible to the effects of these small changes than are others [17, 18]. From a clinical perspective, when using antimicrobials that have QT liability, issues related to the host, the drug, and the need for therapy must be considered.

Individual host susceptibility. QT prolongation has traditionally been separated into 2 general categories: (1) inherited
long QT syndrome (LQTS), and (2) acquired LQTS (most commonly drug associated). Although seemingly distinct, a genetic predisposition (a clinical or subclinical inherited forms of LQTS) may underlie many “acquired” forms of TdP [19–21]. Most cases of drug-induced TdP appear to occur in the so-called “susceptible” population. The term “reduced repolarization reserve” was introduced to describe a repolarization adaptation to a variety of insults [16, 22]. This concept suggests that an accumulation of multiple risk factors predisposes an individual to TdP. In the normal ventricle, there exists virtually no potential for TdP to develop; this is principally because of the repolarizing currents—in particular the IKr and the slow component of the delayed rectifier potassium current—in maintaining a large repolarization reserve that encourages electrical stability. Some notable amplifiers that contribute to the probability of TdP include inherited LQTS, bradycardia, congestive heart failure (down-regulated IKr), hypokalemia, hypomagnesemia, older age, female sex, and, of course, the use of drugs that delay repolarization (in particular, the administration of potent IKr blockers, such as the class Ia/III antiarrhythmics). When multiple risk factors accumulate (figure 3) [23], repolarization reserve becomes exhausted, which results in electrical instability within the ventricle and increased risk of TdP.

An analysis of patients receiving QT-prolonging antimicrobials demonstrated that multiple risk factors for TdP were evident in most cases. Of 69 cases of TdP, patients had, on average, at least 2 risk factors, including female sex (64.5%), heart disease (52.6%), hypokalemia (30.6%), drug interactions (31.5%), excessive drug dose (8.7%), and LQTS (15.9%) [24].

**DRUG-RELATED FACTORS**

“QT liability” associated with most antimicrobials is primarily caused by an intrinsic capacity to interfere with the functioning of IKr [6, 25]. Because the magnitude of the effect on the QT interval appears to be concentration dependent, variables that interfere with the pharmacokinetics of a drug may further increase the risk of TdP.

Drugs that are substrates and/or inhibitors of cytochrome P450 (CYP) enzymes are associated with “metabolic liability.” As a result of increased exposure to an IKr-blocking agent, risk of TdP may increase [26, 27]. CYP3A4, the most important enzyme in human drug metabolism, is responsible for the biotransformation of nearly 60% of all oxidized drugs and is frequently associated with serious drug interactions [27]. Although CYP3A4 is polymorphically expressed, the allelic variants of CYP3A4 appear to be much less likely to have functional phenotypic implications than are the variant alleles of CYP2C9 and CYP2C19, which demonstrate clinically significant genetic polymorphism manifesting most commonly as the poor-metabolizer (PM) phenotype [26–30]. The PM phenotype often results in dramatically reduced clearance of drug substrates and a corresponding increase in drug exposure. Therefore, the use of CYP substrates that intrinsically prolong the QT interval in patients who express the PM phenotype may
lead to unacceptably high risk for TdP. Increased drug exposure may also occur in the context of kidney disease, because it leads to decreases in glomerular filtration [31] as well as in CYP activity [32].

**STRENGTHS AND LIMITATIONS OF POSTMARKETING PHARMACOVIGILANCE STUDIES**

Because rarely occurring adverse events may not be identified during drug development, postmarketing studies are necessary. Advantages to postmarketing studies include the following: (1) evaluation of a drug under more “real-world” conditions, (2) robust sample sizes, (3) inclusion of broader age and weight extremes, and (4) identification of trends/signals related to rare or unexpected harms. Shortcomings to these studies include a number of biases: (1) they are retrospective and fail to account for potentially important contributory confounding variables, (2) report forms are often incomplete, (3) multiple reports of the same adverse drug reaction may exist in the database, (4) adverse drug reactions can be miscoded, and (5) adverse drug reactions are often underreported (particularly for older drugs) [33]. Conversely, newer agents are more likely to be scrutinized because of enhanced prescriber and media attention (the Weber effect) [6].

Highlighting some of these limitations, an AERS review of antimicrobial-associated TdP noted that actual ECG data to support the diagnosis of TdP were available for only 24%–36% of patients [34]. Additionally, 11% of the reports were also missing vital demographic information, such as age and sex, and nearly 40% of the cases originally identified in the database had to be excluded. Thus, causality and incidence cannot be determined, but, importantly, signals and trends can be identified.

**MACROLIDES, AZALIDES, AND KETOLIDES**

This group of antimicrobials, with the exception of the azalides, is associated with dual-risk mechanisms (e.g., metabolic liability and intrinsic Ik channel antagonism) [35, 36]. Variation exists within the macrolide family of compounds in terms of both Ik inhibitory potency and CYP3A4 inhibition potential (table 1). The moderate-to-poor absorption of the macrolides/azalides/ketolides may contribute to the observed difference in TdP incidence between intravenous and oral formulations of the same drugs. In 1 case series of erythromycin-associated TdP, 16 of 23 patients received intravenous, high-dose (3–4 g/day) erythromycin, and 3 of 23 received oral erythromycin (1.5–2 g/day) [37–39]. Marked differences in exposure were noted between the 2 dosages and routes, with typical peak erythromycin concentrations of 30 μg/mL (900 mg intravenously) versus 2–4 μg/mL (500 mg orally), respectively [40]. Nonclinical models support erythromycin’s concentration-dependent effect on action potential duration over a range of drug concentrations [41].

Other major contributing factors to macrolide/ketolide-associated TdP risks include the coadministration of CYP3A4 inhibitors (resulting in increased drug exposure) [42–44]. This was highlighted by a retrospective evaluation of an outpatient Medicaid population that reported that patients who were re-
Table 1. Intrinsic delayed rectifier potassium current (I_Kr) inhibitory potency, metabolic liability, and renal dosing considerations.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>CYP substrate</th>
<th>CYP inhibition</th>
<th>Renal dosing adjustment required</th>
<th>hERG inhibition (IC_{50}) μmol/L</th>
<th>hERG references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potent hERG-blocking non-antimicrobials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dofetilide</td>
<td>3A4</td>
<td>No</td>
<td>Yes</td>
<td>&lt;1.0</td>
<td>[92]</td>
</tr>
<tr>
<td>Sotalol</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>&lt;1.0</td>
<td>[92]</td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>3A4</td>
<td>3A4</td>
<td>Yes</td>
<td>32.9, 45.7</td>
<td>[35, 36]</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>3A4</td>
<td>3A4</td>
<td>Dose adjustment for end stage renal disease</td>
<td>38.9, 72.2</td>
<td>[35, 36]</td>
</tr>
<tr>
<td>Desmethyl erythromycin (a metabolite of erythromycin)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>147.1</td>
<td>...</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>3A4</td>
<td>3A4</td>
<td>For CLCR &lt;30 mL/min, the dose has not been established</td>
<td>42.5</td>
<td>[52]</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>No</td>
<td>1A2</td>
<td>Yes</td>
<td>966</td>
<td>[58]</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>130, 329</td>
<td>[58, 59]</td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>260</td>
<td>[59]</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>No</td>
<td>1A2</td>
<td>No</td>
<td>93</td>
<td>[59]</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>430, 827, 915</td>
<td>[58–60]</td>
</tr>
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<td>Moxifloxacin</td>
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<td>No</td>
<td>No</td>
<td>65, 129, 354</td>
<td>[58–60]</td>
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<td>Sparfloxacin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>18–37</td>
<td>[58, 59]</td>
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<td>Imidazoles/triazoles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>2C9, 2C19, 3A4</td>
<td>2C9, 2C19, 3A4</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>2C9, 2C19, 3A4</td>
<td>2C9, 2C19, 3A4</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Ketoconazole</td>
<td>2C9, 2C19, 3A4</td>
<td>3A4</td>
<td>No</td>
<td>49</td>
<td>[78]</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>2C9, 2C19, 3A4</td>
<td>2C9, 2C19, 3A4</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2.5</td>
<td>[91]</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>0.04</td>
<td>[91]</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2.6</td>
<td>[91]</td>
</tr>
</tbody>
</table>

NOTE. CLCR, creatinine clearance; hERG, human ether-a-go-go-related gene; IC_{50}, inhibitory concentration 50%; NA, not available.

* It is important to understand that the values represented in this column were often obtained noncomparatively by different testing methods under dissimilar testing conditions and because of this, a direct comparison of values cannot be made to state that one drug is more likely to cause TdP than another. In addition, they reflect IC_{50} values, and it is well known that drugs capable of blocking 10–20% of I_{Kr} function (IC_{10} or IC_{20} values) at clinically achievable free drug concentrations can be associated with TdP (e.g., dofetalide, terfenadine, cisapride, and risperidone).

b No longer marketed in United States.

Receiving erythromycin were twice as likely to experience sudden death due to cardiac causes than were control subjects (i.e., recipients of amoxicillin and/or CYP3A4 inhibitors) [45]. When CYP3A4 inhibitors and erythromycin were concurrently prescribed, patients experienced a 5-fold greater risk of cardiac sudden death.

The concurrent administration of clarithromycin and cisapride provides further evidence of the importance of metabolic liability. When administered individually, the mean effect on the width of the QTc interval was an increase of 6 ms; however, concurrent administration resulted in a 25-ms mean prolongation of the QTc interval [46]. Many reported TdP cases involving clarithromycin have been in patients concurrently receiving contraindicated drugs [47–51]. Similarly, ketoconazole and telithromycin administered alone resulted in a mean increase in the QTc interval of 6.4 ms and 3.3 ms, respectively [52]. However, when administered concurrently, telithromycin exposures significantly increased (95% increase in area under the curve from 0–24 h), resulting in a mean increase in the QTc interval of 10.49 ms (P = .004) [52]. Other comparative studies have also demonstrated telithromycin’s ability to prolong the QT interval [53].

Azithromycin is distinguishable from the macrolides/keto- lides, despite case reports of cardiac toxicity [54, 55]. Azithromycin minimally inhibits CYP3A4, which results in the lack of an appreciable interaction with CYP3A4 substrates; thus, azithromycin appears to be the safest macrolide derivative from a cardiac toxicity perspective [56].
The FDA evaluated the postmarketing reports of TdP cases for macrolides as well as for several fluoroquinolones in the AERS database [34, 57]. Macrolides accounted for the majority of reported cases of TdP (77%). Multiple risk factors often existed, including concurrent administration of a QT-prolonging or contraindicated drug, advanced age, cardiac disease, organ dysfunction, and electrolyte derangements.

**FLUOROQUINOLONES**

QT interval prolongation is a class effect among the fluoroquinolones; however, similar to that for the macrolides, azalides, and ketolides, there appears to be some intraclass variability. Several studies have reported the effects of the fluoroquinolones on the Ikᵣ current (table 1) [58–60]. In contrast to the macrolides and ketolides, the fluoroquinolones as a class lack metabolic liability (table 1) [23]. Ciprofloxacin’s inhibition of CYP1A2 is relatively inconsequential, given the fact that it is uncommon for drugs with QT liability to be metabolized by this isoform [61, 62]. Also, unlike the macrolides, the route of administration of fluoroquinolones is unlikely to contribute to TdP risk because exposure is similar, regardless of the route of administration.

Moxifloxacin has undergone the most rigorous preclinical and clinical QTc risk assessment of any marketed antimicrobial to date [5]. Across various cardiac risk assessment studies (hERG, telemetered dogs, the rabbit ventricular wedge, and clinical studies), moxifloxacin has demonstrated small, but consistent, effects on cardiac end points [63]. Proarrhythmic exposures of moxifloxacin are not observed following clinically prescribed doses, corresponding with comparatively low postmarketing reports of TdP [69].

A review of the AERS database revealed that 24% of cases of fluoroquinolone-associated TdP occurred in the context of coadministration with another QT interval–prolonging drug, underlying cardiac disease (62%), renal impairment (7%), hypokalemia or hypomagnesemia (17%), and female sex (67%); the mean age of patients was 72 ± 15 years [57]. A more recent AERS analysis from the period 1997–2003 revealed reports of TdP associated with ciprofloxacin use (n = 2), moxifloxacin use (n = 18), gatifloxacin use (n = 33), and levofloxacin use (n = 47) [64]. Other case series support the multifactorial nature of fluoroquinolone-associated TdP [65, 66].

A double-blind, randomized study with a primary end point of cardiac safety compared levofloxacin with moxifloxacin in elderly hospitalized patients with community-acquired pneumonia [67]. Holter monitors recorded continuous ECGs in patients for the first 72 h of therapy. Mean changes (± SD) in the QTc interval at day 3 were −2.5 ± 22.9 ms and 6.4 ± 23.2 ms for levofloxacin and moxifloxacin, respectively. No differences between agents, however, were noted in cardiac adverse events determined either by the investigator or by Holter monitor findings. One outlier value (QTc increase >60 ms) existed for each drug, and 1 case of TdP was documented in a patient receiving levofloxacin. No differences in cardiac adverse events were observed in a relatively high-risk population of hospitalized elderly patients.

A large, placebo-controlled clinical trial studying the effects of gatifloxacin on atherosclerotic plaques observed in 2000 patients receiving 10 days of gatifloxacin per month for ~1.6 years [68]. In this relatively high-risk group of patients, no cases of TdP were observed, and there were 9 and 11 cases of sudden death that occurred during the study in the gatifloxacin and placebo arms, respectively [69].

Despite apparent differences between moxifloxacin and levofloxacin in hERG studies (table 1), hERG data alone cannot be used to distinguish clinical risk between agents. Integrating data derived from hERG studies, clinical trials, and postmarketing evaluations, the overall risk for TdP among the currently marketed fluoroquinolones appears to be similar between moxifloxacin and levofloxacin [57, 59, 60, 63, 64, 66, 67, 70–73]. Gatifloxacin’s risk appeared to be similar to that of moxifloxacin and levofloxacin [57, 59, 63, 64, 68, 70, 71], whereas the current risk associated with gemifloxacin remains difficult to ascertain because of limited use in more-severely ill populations. Ciprofloxacin remains the safest drug in this class, as indicated by very few reported TdP cases and its high hERG IC₅₀ values.

**IMIDAZOLE AND TRIAZOLE ANTFUNGALS**

Ketoconazole, itraconazole, fluconazole, and voriconazole have been shown to prolong the QT interval and to be associated with TdP, with the majority of reports of TdP stemming from drug interactions and involving ketoconazole and itraconazole [74–88]. Akin to the macrolides, the azoles are “dual-risk” agents. Limited hERG data are published for azoles, and show mild inhibitory effects for the class [88]. The metabolic liability potential of the azoles is presented in table 1. Voriconazole is characterized by nonlinear pharmacokinetics, so an increase in dose from 200 mg to 300 mg has been shown to yield a 2.5-fold increase in exposure [88]. In addition, allelic polymorphisms of CYP2C19 have demonstrated the greatest impact on voriconazole clearance, resulting in either poor or extensive metabolism of this drug and leading some to suggest the need for therapeutic drug monitoring [89]. No postmarketing database evaluations characterizingazole-associated TdP have been published.

**MISCELLANEOUS ANTIMICROBIALS**

Pentamidine has been associated with a number of TdP reports, as reviewed elsewhere [6]. Its risk does not stem from direct Ikᵣ inhibition; rather, chronic pentamidine administration reduces membrane expression of Ikᵣ [90]. For antimalarials, hal-
Haloftantrine offers the greatest torsadogenic risk in the current antimalarial armamentarium, whereas mefloquine appears to be among the safest (despite chloroquine having a similar hERG affinity)[91]. One caveat exists: halofantrine must not be given simultaneously with or subsequent to mefloquine, because of the increased risk of sudden death.

**SUMMARY**

The number of risk factors for QT interval prolongation—both host- and drug-related—are numerous. Unlike the class Ia/III antiarrhythmics (e.g., sotalol, dofetilide, and quinidine), whose risk for TdP is >1% when used at clinically prescribed doses, TdP that is associated with currently marketed antimicrobials that carry QT liability (except for halofantrine) is rare. An imbalance of literature exists for newer drugs compared with older ones, primarily because of recent advances in study methodologies and recent regulatory scrutiny making comparisons between antimicrobials exceedingly difficult. It appears that the antimicrobials discussed herein serve as amplifying agents for the development of a proarrythmic state, albeit to different degrees. Patients with diagnosed LQTS or those receiving Class Ia or III antiarrhythmics are at greatest risk. Careful evaluation of risks-versus-therapeutic benefits in selecting an antimicrobial with QT liability is warranted. Attention to drug interactions, dosing adjustment in the context of organ dysfunction, and familiarity with FDA product labeling will decrease the probability of cardiac toxicity.

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**References**