Clarithromycin, QTc interval prolongation and *torsades de pointes*: the need to study case reports

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Abstract:

Background: The manufacturers of clarithromycin sought a drug similar in efficacy to erythromycin but with a superior side-effect profile. They generally achieved this outcome, but postmarketing findings identified a series of reports linking clarithromycin to QTc interval prolongation and *torsades de pointes* (TdP) ultimately leading to a Black Box Warning. We sought to clarify risk factors associated with TdP among case reports of patients receiving clarithromycin linked to QTc interval prolongation and TdP.

Methods and results: In a detailed literature search, we found 15 women, five men, and one boy meeting our search criteria. Among the 17 adults with reported clarithromycin dose and concurrent QTc interval measurement, we found no statistically significant relationship between clarithromycin dose and QTc interval duration. This did not change for the adults who developed TdP. Among adults, major risk factors were female sex (15), old age (11) and heart disease (17). A total of eight adult subjects had all three major risk factors and 14 of the 20 adults had at least two major risk factors. All adult subjects had at least two risk factors besides clarithromycin. A total of four of the 20 adults received cisapride and three received disopyramide. Three adults were considered to suffer from some aspect of the congenital long QT syndrome.

Conclusions: We believe that the risk factor description for this drug should be refined to emphasize the major risk factors of (1) female sex, (2) old age and (3) heart disease.

Keywords: Clarithromycin, drug-induced QTc interval prolongation, risk factors, *torsades de pointes*

Introduction

Clarithromycin is the most widely used macrolide antibiotic in the United Kingdom and is strongly recommended for patients with severe community-acquired pneumonia [Schembri *et al.* 2013]. The drug's use among patients with chronic obstructive pulmonary disease or community-acquired pneumonia is associated with increased cardiovascular events over the course of a year among patients requiring hospitalization with acute coronary syndrome, decompensated heart failure, serious arrhythmias, or sudden cardiac death (SCD) [Schembri *et al.* 2013]. Because increased cardiovascular risk persisted over the next year after clarithromycin was discontinued [Schembri *et al.* 2013], the immediate effect of the drug did not explain the above findings even though

clarithromycin has a proarrhythmia effect linked in some fashion to QTc interval prolongation and *torsades de pointes* (TdP) [Bril *et al.* 2010].

Bril and colleagues, in a study of antimicrobial agents linked to QTc interval prolongation, outlined risk factors using a flowchart [Bril *et al.* 2010]. Drug-related risk factors were separated into administration, pharmacokinetic interactions and pharmacodynamic interactions. Host-related risk factors included modifiable ones (internal environmental disturbances, heart disease, central nervous system and dysautonomy) and those that cannot be modified (older age, female sex, structural heart disease, long QT syndrome and ion channel polymorphisms). Based on our experience with a case report

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format [Vieweg *et al.* 2012, 2013a, 2013b; Kogut *et al.* 2013], we seek to organize risk factors to better help clinicians manage patients requiring treatment with clarithromycin.

Background

In the 1970s, the Japanese drug company Taisho Pharmaceutical developed the macrolide antibiotic clarithromycin aiming to improve on erythromycin's spectrum of activities, frequency of administration and tolerability [Zuckerman, 2004]. A branded version was introduced into the Japanese market in 1991 and the US market later in the same year. Less than 6 years after its introduction, clarithromycin was linked to erythromycin's adverse electrophysiological properties including drug-induced TdP [Kundu *et al.* 1997; Paar *et al.* 1997; Sekkarie, 1997]. This linkage is exacerbated by the common coprescription of QTc interval prolonging drugs in the outpatient setting [Curtis *et al.* 2003] and the coprescription of drugs blocking CYP3A4 [Sagir *et al.* 2003]. Clarithromycin went generic in Europe in 2004 and in the US in mid-2005.

Clarithromycin pharmacology

Pharmacokinetics and pharmacodynamics

The pharmacokinetics of clarithromycin are similar to those of erythromycin [McConnell and Amsden, 1999]. Clarithromycin is rapidly absorbed from the gastrointestinal tract. Clarithromycin has the greatest bioavailability of any of the macrolides [McConnell and Amsden, 1999]. Clarithromycin pharmacokinetics are basically linear and the steady-state concentration of this metabolite is reached within 3–4 days [Abbott Laboratories, 2013].

The postantibiotic effect of clarithromycin varies according to the pathogen [McConnell and Amsden, 1999]. However, the *in vivo* significance of this *in vitro* observation has not been determined. Clarithromycin penetrates infected tissue sites extensively. Efficacy is based on maintaining a drug concentration above the minimum inhibitory concentration and clarithromycin is dosed with a frequency to meet this requirement.

Clarithromycin as a hERG channel inhibitor

A common feature of drugs associated with acquired long QT syndrome and TdP is their ability to produce pharmacological inhibition of the activity of the hERG (*human Ether-a-go-go Related Gene*) potassium ion channel and its

native cardiac equivalent, the rapid delayed rectifier K^+ current, I_{Kr} [Finlayson *et al.* 2004; Hancox *et al.* 2008]. Macrolide antibiotics including clarithromycin have been reported to inhibit the hERG channel current (I_{hERG}) [Abbott *et al.* 1999; Volberg *et al.* 2002; Stanat *et al.* 2003; Duncan *et al.* 2006]. For example, using hERG channel expression in mammalian (HEK 293) cells, Volberg and colleagues demonstrated I_{hERG} inhibition by six macrolide drugs of which clarithromycin was the most potent (half maximal inhibitory concentration, IC_{50} , of $32.9 \mu M$), whilst erythromycin exhibited intermediate potency (IC_{50} of $72.2 \mu M$) and oleandomycin was the least potent (IC_{50} of $339.6 \mu M$) [Volberg *et al.* 2002]. However, in a separate study using a similar hERG expression system, in a direct comparison erythromycin was reported to be more potent than clarithromycin (IC_{50} values of 38.9 and $45.7 \mu M$, respectively). In that study both drugs were also reported to inhibit I_{hERG} when this was elicited with an action potential shaped waveform [Stanat *et al.* 2003], consistent with an ability to reduce the contribution of I_{hERG}/I_{Kr} to action potential repolarization and, hence, the QT interval. Clarithromycin has been shown to prolong action potential duration (APD) in rabbit cardiac tissues in a concentration-dependent fashion (over concentrations ranging between 3 and $100 \mu M$) and to reduce native I_{Kr} amplitude [Gluais *et al.* 2003]. For a given drug concentration, APD prolongation was found to be greater for Purkinje fibers than for ventricular myocytes [Gluais *et al.* 2003], presumably because the comparatively impoverished repolarization reserve of Purkinje fibers makes them particularly sensitive to hERG/ I_{Kr} blocking drugs [Gintant, 2008; Hancox *et al.* 2008]. In experiments on intact perfused rabbit hearts, high concentrations of clarithromycin prolonged both monophasic action potential and QT interval duration [Milberg *et al.* 2002]. In the presence of simulated hypokalemia, clarithromycin could produce cellular arrhythmogenic events [early afterdepolarizations (EADs)] and TdP [Milberg *et al.* 2002]. Thus, the preclinical literature demonstrates that at some concentrations clarithromycin can inhibit I_{hERG}/I_{Kr} , prolong action potential repolarization and, under appropriate conditions, predispose towards arrhythmia.

An intriguing aspect of clarithromycin's ability to inhibit hERG channels is the potential for this action of the drug to vary between individuals.

In 1999, Abbott and colleagues discovered an accessory protein, MiRP1 (also referred to as KCNE2), that can co-assemble with hERG, modifying I_{hERG} properties and drug sensitivity [Abbott *et al.* 1999]. A MiRP1 mutation, Q9E-hMiRP1, which was identified in a patient treated who survived clarithromycin-induced TdP and ventricular fibrillation, was found *in vitro* to increase markedly hERG's sensitivity to inhibition by clarithromycin [Abbott *et al.* 1999].

Analysis of static and dynamic complex variables

Multiple regression analysis evaluates the effects of more than one independent variable on a dependent variable. However, the assumption is that neither variable changes in the course of analysis. Risk factors associated with drug-induced QTc interval prolongation and TdP may change dynamically and the risk factors themselves may be approximations of more specific factors [Vieweg *et al.* 2012, 2013a, 2013b; Kogut *et al.* 2013].

Elements of nonlinear phenomena include chaos, fractals, cellular automata, genetic algorithms and fuzzy logic. They have been brought together by Willi-Hans Steeb in the 5th edition of his book *The Nonlinear Workbook* [Steeb, 2011]. Components likely best describe the interaction of drug-linked QTc interval prolongation and attendant risk factors to produce TdP [Vieweg *et al.* 2012, 2013a, 2013b; Kogut *et al.* 2013].

Methods

We conducted a systematic review of case reports published up to and including 17 April 2013. Initially, we entered the following MeSH terms: 'clarithromycin and QTc prolongation' (13) and 'clarithromycin and torsade' (10) into Medline. We searched CredibleMeds (<http://www.azcert.org/>) for case reports of clarithromycin, QTc interval prolongation and *torsades de pointes* (19). This search was initiated via AZCERT: ("Clarithromycin"[MeSH] AND ("Long QT Syndrome"[MeSH] OR "Torsades de Pointes"[MeSH])) OR (((torsade[ti] OR torsadogenic[ti] OR torsades[ti] OR torsadogenesis[ti] OR torsadogenic[ti] OR torsadogenicity[ti] OR qt[ti]) AND clarithromycin[ti])). We searched EMBASE (0) and Cochrane (0) only for case reports. Only human studies were included. We also reviewed reports from our files and reference lists yielding a total of 21 cases as shown

in Table 1. (A more detailed case narrative appears in the appendix.) Titles and abstracts were independently reviewed by two investigators (WVRV and AB). Disagreement was resolved by consensus.

Results

We found 15 women, five men and one boy (Table 1). Among the 17 adults with reported clarithromycin dose and concurrent QTc interval measurement, we found no statistically significant relationship between clarithromycin dose and QTc interval duration (Pearson's $r = -0.086$, $p = 0.744$; Kendall's τ_B $r = -0.185$, $p = 0.359$; Spearman's rho $\rho = -0.223$, $p = 0.390$). These findings did not change for the adults who developed TdP (Pearson's $r = -0.093$, $p = 0.785$; Kendall's τ_B $r = -0.159$, $p = 0.541$; Spearman's rho $\rho = -0.161$, $p = 0.636$). Among adults, major risk factors were female sex (15), old age (11) and heart disease (17). A total of eight adult subjects had all three major risk factors and 14 of the 20 adults had at least two major risk factors. All adult subjects had at least two risk factors besides clarithromycin. A total of four of the 20 adults received cisapride and three received disopyramide. Three adults were considered to suffer from some aspect of the congenital long QT syndrome.

Discussion

In healthy volunteers, the administration of clarithromycin did not lengthen the QTc interval [Van Haarst *et al.* 1998]. However, plasma clarithromycin levels were not reported in this study. In our study, there was neither parametric nor nonparametric statistical association between drug dose and QTc interval measurement.

The finding of congenital long QT syndrome in three (ages 29, 76 and 79 years) of our 21 patients (14.3%) is quite surprising because the prevalence in the general population is approximately 1:2000 [Schwartz *et al.* 2009]. Our finding argues strongly for inquiry into a family history of cardiac arrhythmia, presyncope, syncope and SCD before administering clarithromycin.

Cisapride and disopyramide

Among our 20 adult patients (Table 1), four received cisapride (Cases 4, 5, 6 and 10) and all four had at least two major risk factors (female sex, old age and heart disease). That is, clinicians may have to take into consideration

Table 1. Risk factors for QTc interval prolongation and torsades de pointes (TdP) by case reports among patients receiving clarithromycin (CAM).

Case/arrhythmia	QTc [ms]	CAM daily dose	Female sex	Elderly	Heart disease	Hypo-K ⁺	Hypo-Mg ⁺⁺	Bradycardia	CYP3A4 blockers	QTc prolonging drugs	Additional risk factors
1 [Lai <i>et al.</i> 1996] 70-year-old woman No arrhythmia documented	641	500	Yes	Yes	Yes	No	No	No	No	Sotalol	Acute medical illness, chronic medical illness
2 [Kundu <i>et al.</i> 1997] 27-year-old woman Ventricular tachycardia	468	500	Yes	No	No	No	No	No	No	No	Acute medical illness
3 [Paar <i>et al.</i> 1997] 74-year-old woman Ventricular fibrillation	625	500	Yes	Yes	Yes	Yes	No	No	Disopyramide	Disopyramide	Acute medical illness, chronic medical illness
4 [Sekkari, 1997] 52-year-old woman TdP	630	1000	Yes	No	Yes	No	No	No	Cisapride	Cisapride	Acute medical illness, chronic medical illness
5 [Sekkari, 1997] 83-year-old man TdP	Unknown	1000	No	Yes	Yes	No	No	No	Cisapride	Cisapride	Acute medical illness, chronic medical illness
6 [Gray, 1998] 53-year-old woman TdP	456	1000	Yes	No	Yes	No	No	No	Cisapride, fluoxetine	Cisapride, fluoxetine	Acute medical illness, chronic medical illness
7 [Lee <i>et al.</i> 1998] 40-year-old man TdP	670	1000	No	No	Yes	No	No	No	No	No	Acute medical illness, chronic medical illness, impaired liver function
8 [Lee <i>et al.</i> 1998]	775	1000	Yes	No	Yes	No	No	No	No	No	Acute medical illness, (continued)

Table 1. Continued.

Case/arrhythmia	QTc (ms)	CAM daily dose	Female sex	Elderly	Heart disease	Hypo-K ⁺	Hypo-Mg ⁺⁺	Bradycardia	CYP3A4 blockers	QTc prolonging drugs	Additional risk factors
25-year-old woman TdP											chronic medical illness
9 [Hayashi <i>et al.</i> 1999] 76-year-old woman TdP	710	400	Yes	Yes	Yes	Yes	No	No	Disopyramide	Disopyramide	Acute medical illness
10 [Piquette, 1999] 77-year-old woman TdP	640	1000	Yes	Yes	Yes	Yes	No	No	Cisapride	Cisapride	Acute medical illness, chronic medical illness
11 [Kamochi <i>et al.</i> 1999] 78-year-old woman TdP	654	400	Yes	Yes	Yes	Yes	No	No	No	No	Acute medical illness
12 [Kamochi <i>et al.</i> 1999] 62-year-old man TdP	600	400	No	No	No	No	No	No	No	No	Acute medical illness, chronic liver disease
13 [Abbott <i>et al.</i> 1999] 76-year-old woman TdP	540	1000	Yes	Yes	Yes	Yes	No	No	No	Erythromycin	Mutation to MiRP1 protein, acute medical illness, chronic medical illness
14 [Choudhury <i>et al.</i> 1999] 76-year-old woman TdP	640	500	Yes	Yes	Yes	No	No	No	Disopyramide	Disopyramide	Acute medical illness, chronic medical illness, mild renal failure
15 [Wasmer <i>et al.</i> 1999]	680	Unknown	Yes	No	Yes	No	No	No	No	No	Congenital long QT syndrome, (continued)

Table 1. Continued.

Case/arrhythmia	QTc (ms)	CAM daily dose	Female sex	Elderly	Heart disease	Hypo-K ⁺	Hypo-Mg ⁺⁺	Bradycardia	CYP3A4 blockers	QTc prolonging drugs	Additional risk factors
29-year-old woman TdP											acute medical illness
16 [Vallejo Camazon <i>et al.</i> 2002] 30-year-old man Monomorphic ventricular tachycardia	580	1000	No	No	Yes	No	No	Yes	Cotrimoxazole	Cotrimoxazole, methadone	Acute medical illness, chronic medical illness, chronic liver disease
17 [Diaz Garcia <i>et al.</i> 2005] 80-year-old man None	560	1000	No	Yes	Yes	No	No	No	No	No	Acute medical illness, chronic medical illness
18 [Hensey and Keane, 2008] 79-year-old woman TdP	542	500	Yes	Yes	Yes	No	No	No	No	Amiodarone	Acute medical illness, chronic medical illness, suspected congenital long QT syndrome
19 [Buchanan Keller and Lemberg, 2008] 50-year-old woman TdP	620	Unknown	Yes	No	No	Yes	No	No	No	Fluoxetine	Acute medical illness
20 [Alesso <i>et al.</i> 2009] 71-year-old woman Sustained ventricular tachycardia	570	1000	Yes	Yes	Yes	No	No	Yes	Ciprofloxacin	Amiodarone, Ciprofloxacin	Acute medical illness,
21 [Cetin <i>et al.</i> 2012] 6-year-old boy TdP	600	Unknown	No	No	No	No	No	No	No	No	Acute medical illness

other risk factors even when clarithromycin and cisapride are co-administered. Three of our patients (Cases 3, 9 and 14, ages 74, 76 and 76 years, respectively) received disopyramide and all three were elderly and had heart disease. Again, clinicians may have to look beyond the co-administration of clarithromycin and disopyramide to more completely explain drug-related QTc interval prolongation and TdP. These observations highlight the point that these drugs when combined with clarithromycin act synergistically to increase QTc interval duration and increase the risk of subsequent TdP, but may not be the only risk factors in operation.

Risk factors discussed in the literature

In 2001, Bednar and colleagues identified 16 risk factors for QTc interval prolongation and TdP [Bednar *et al.* 2001]. In 2003, Witchel and coworkers described high-risk patients [Witchel *et al.* 2003]. In 2003, Viskin and colleagues identified 12 risk factors [Viskin *et al.* 2003]. In a study of 249 patients, Zeltser and coworkers made the point most patients at increased risk for QTc interval prolongation and TdP have readily identifiable risk factors [Zeltser *et al.* 2003]. The majority of their 249 patients had at least one risk factor that could be easily identified and 71% had ≥ 2 easily identifiable risk factors for QTc interval prolongation and TdP. In addition, most women (female sex being the most common identifiable risk factor) had additional risk factors.

Multiple-hit hypothesis

Owens and Ambrose in their study of TdP associated with fluoroquinolones describe the 'multiple-hit hypothesis' in which several factors influence TdP development [Owens and Ambrose, 2002]. Many prescribed drugs including antibiotics and antipsychotics unfavorably affect I_{Kr} kinetics. However, this impact in-and-of itself rarely explains substantial QTc interval prolongation and resultant TdP [Zareba and Lin, 2003]. Combining the list of risk factors produced by several authors produces the following items [Zareba and Lin, 2003; Sauer and Newton-Cheh, 2012]: (1) prolonged QTc interval, (2) female sex, (3) advanced age, (4) bradycardia, (5) hypokalemia, (6) hypomagnesemia, (7) structural heart disease, (8) cardiac arrhythmias, (9) drug combinations including ion channel blockers and CYP450 inhibitors, (10) reduced repolarization reserve and (11) genetic polymorphisms of gene coding cardiac ion channels or enzymes in liver metabolizing drugs.

Pathogenic theories include (1) triangulation (short-term variability of action potentials preceding TdP [Michael *et al.* 2007]), (2) reverse-use dependence (action potential prolongation at slower heart rates [Hondeghe and Snyders, 1990]), (3) short-term viability (instability [Sauer *et al.* 2012]), (4) repolarization dispersion [Sauer and Newton-Cheh, 2012]—these four known together as TRIaD [Sauer and Newton-Cheh, 2012]—and (5) EADs [Sauer and Newton-Cheh, 2012].

We need to use all available information about risk factors for QTc interval prolongation and TdP

As pointed out by Owens and Ambrose [Owens and Ambrose, 2002], information from spontaneous reporting rates (case reports) is not synonymous with incidence rates (all cases occurring over a specific interval such as a year). However, we believe that if regulatory agencies more vigorously emphasize (perhaps through a reward system) the need for pharmaceutical companies and clinicians to report all major drug-related adverse cardiac events, spontaneous reporting rates for drug-related QTc interval prolongation and TdP would better approximate incidence rates. If more information unfolds supporting the hypothesis that drug safety related to QTc interval prolongation and TdP more depends on clinical assessment (such as case reports) than preclinical studies such as hERG analysis, clinicians may have better guidance when prescribing drugs and more drugs may reach the level of phase II and phase III studies ultimately providing a better selection of possible treatments for patients with serious illnesses.

However desirable it may be to have (1) baseline EKGs, (2) serum concentrations of nonclarithromycin drugs and (3) genetic information identifying subjects with the congenital long QT syndrome, the clinician is left to decide on the merits and demerits of clarithromycin administration based on the presence or absence of more readily available risk factors for QTc interval prolongation and TdP. We propose that sufficient information based on case report analysis exists to presently identify the triad of (1) female sex, (2) old age and (3) heart disease as major risk factors for QTc interval prolongation and TdP among patients about to receive clarithromycin. We believe that the FDA and manufacturer of clarithromycin should provide this

information in the clarithromycin Black Box Warning. The closer the patient comes to having all three major risk factors, the more likely clarithromycin administration will link to QTc interval prolongation and TdP.

Limitations

The topic discussed in this manuscript is not new [Raschi *et al.* 2013], but we believe merits discussion from a clinical point of view. Owing to the low incidence of TdP, QTc interval prolongation is used as a surrogate marker of drug-induced TdP risk [Shah, 2005]. Large cohort or population studies and ‘thorough QT’ investigations on healthy volunteers can index the likelihood and extent of QTc interval prolongation with individual drugs, but nonetheless usually provide information on a surrogate marker for TdP rather than TdP itself. By contrast, case reports provide direct clinical information in the setting of TdP occurrence. Consequently, case reports provide valuable insight into risk factors concomitant with drug administration. However, the low incidence of TdP means that the numbers of case reports with individual drugs tend to be limited, as is the case here for clarithromycin, and results from our 21 case reports (20 adults and one child) must only be extrapolated to larger groups with great caution. Another potential limitation with case reports is selection bias as fatalities may not always be reported. Thus, both large sample/population data and case report information need to be considered together when attempting to gain an overall picture of TdP risk of particular drugs.

Conclusion

The FDA has taken the position that current information identifies clarithromycin as an at-risk drug for QTc interval prolongation and TdP. In addition to clarithromycin administration, risk factors include (1) uncorrected hypokalemia or hypomagnesemia, (2) clinically significant bradycardia, (3) patients receiving Class IA or Class III antiarrhythmic drugs and (4) elderly patients. On the basis of case report analysis, elderly female patients with heart disease may be particularly at risk.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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Appendix: Detailed narrative of case reports linked to clarithromycin-induced/associated QTc interval prolongation and/or TdP

Case	Narrative
1 [Lai <i>et al.</i> 1996]	<p>70-year-old woman was admitted to evaluate syncope after collapsing at home while watching TV. Past medical history included coronary heart disease requiring angioplasty twice (1 year and 3 years before this presentation), paroxysmal atrial fibrillation, obstructive hypertrophic cardiomyopathy and rheumatoid arthritis. Cardiac problems were well controlled before the onset of syncope. Medications included sublingual nitroglycerin, sotalol, prednisone, hydroxychloroquine and methotrexate. Four days before admission, she presented to the emergency department (ED) complaining of cough, low-grade fever and a left lung infiltrate. EKG then showed normal sinus rhythm and QT/QTc interval of 440/498 ms without evidence of ischemia. She received clarithromycin 250 mg BID for presumed respiratory infection.</p> <p>On current admission, EKG showed sinus bradycardia (50 beats/minute) and QT/QTc interval of 696/641 msec without evidence of ischemia. Serum potassium was normal. Neither atrial fibrillation nor TdP occurred. Clarithromycin and sotalol were stopped. Over the next 5 days, QTc interval returned to normal and she was discharged to home.</p> <p>QTc 641 ms; clarithromycin dose 500 mg TdP not documented. Risk factors were female sex, old age, heart disease, acute medical illness, chronic medical illness, sotalol and clarithromycin.</p>
2 [Kundu <i>et al.</i> 1997]	<p>27-year-old woman presented to the ED with a 3-day history of irregular pulse and intermittent palpitations. She was a medical resident and may have been more alert and concerned about bodily changes. She denied chest pain, dyspnea, diaphoresis, weakness, nausea, vomiting or diarrhea. She gave a history of several weeks of clear rhinorrhea for which she had taken terfenadine 60 mg and phenylpropanolamine 60 mg each BID for 1 week. She believed she suffered from sinusitis. Previously, she had used terfenadine for allergies with no adverse effects. After stopping terfenadine and</p> <p>(continued)</p>

Continued.

Case	Narrative
	<p>phenylpropanolamine for 4 days to avoid drug interactions, she started clarithromycin 250 mg BID. Palpitations started after the 6th dose of clarithromycin. Medical history was free of cardiac, pulmonary, endocrine or psychiatric disease. Review of systems was otherwise negative and she denied taking drugs, ethanol, tobacco, caffeine or other medications except for oral contraceptives. In the ED, her pulse was irregular and telemetry showed many premature ventricular contractions (PVCs) and runs of nonsustained ventricular tachycardia (VT). During these arrhythmias, blood pressure and arterial oxygen saturation remained normal. EKG showed normal sinus rhythm and a QTc interval of 468 ms. Chemistries were normal and terfenadine was not detected in the serum. She was admitted and clarithromycin stopped. Over the next 4 hours, PVCs and brief runs of VT resolved. The next day, echocardiography was normal and QTc interval was 420 ms. She remained asymptomatic over the next year even when taking phenylpropanolamine.</p> <p>QTc 468 ms; clarithromycin dose 500 mg VT did not occur. Risk factors were female sex, acute medical illness and clarithromycin.</p>
3 [Paar <i>et al.</i> 1997]	<p>74-year-old woman admitted for evaluation of <i>Helicobacter pylori</i>-related chronic duodenal ulcer. Past medical history included 7-year disopyramide (200 mg BID) treatment for tachycardia-bradycardia syndrome with QTc interval never >440 ms. Admission EKG showed sinus rhythm, right bundle branch block (RBBB), and normal QTc interval. Treatment for <i>H. pylori</i> was started with omeprazole (20 mg BID), clarithromycin (250 mg BID) and metronidazole (400 mg BID). Renal function was normal. After an uneventful hospital course, she collapsed 6 days after admission and ventricular fibrillation (VF) was documented. After resuscitation, QTc interval was prolonged (625 ms) with no U-wave present. Hypokalemia was present (3.0 mmol/l) presumably related to epinephrine administration during resuscitation. Disopyramide level was at the upper therapeutic level (4.6 µg/ml) with markedly prolonged half-life (40 hours). Disopyramide was stopped and hypokalemia corrected. However, QTc interval prolongation persisted until hospital day 9 and then returned to normal. Two days later she was discharged from the ICU and 20 days later from the hospital.</p> <p>QTc 625 ms; clarithromycin dose 500 mg VF did occur. Risk factors were female sex, old age, heart disease, acute medical illness, chronic medical illness, hypokalemia, disopyramide (both directly and as a CYP3A4 blocker) and clarithromycin (both directly and as a CYP3A4 blocker).</p>
4 [Sekkarie, 1997]	<p>Case 1: 52-year-old woman with diabetes mellitus, end-stage renal disease, coronary artery disease requiring bypass grafting, diabetic gastroparesis and chronic obstructive lung disease presented with acute bronchitis. Clarithromycin 500 mg BID was started. Other medications included transdermal nitroglycerin, iron, erythropoietin, calcitriol, calcium acetate, ipratropium inhaler and cisapride 10 mg TID. Hemodialysis was uneventful and she returned home at noon. Six hours later, she took cisapride just before supper. Shortly after finishing eating, she lost consciousness for a minute recovering spontaneously. EMS found her awake and in sinus rhythm. On hospital arrival, TdP was noted and she again lost consciousness. Cardioversion restored sinus rhythm and consciousness. EKG showed sinus rhythm, severe T-wave inversion anteriorly and QTc interval prolongation (630 ms). Lidocaine was then administered and she was transferred to the ICU. Cisapride and clarithromycin were stopped. Cardiac enzymes were normal, serum potassium was 3.6 mmol/l, and other chemistries were unremarkable. No further cardiac arrhythmias occurred and lidocaine infusion was</p> <p style="text-align: right;">(continued)</p>

Continued.

Case	Narrative
5 [Sekkarie, 1997]	<p>stopped. Within 36 hours, anterior T-wave inversion returned to normal. QTc interval slowly returned to normal (440–480 ms). Cardiac catheterization demonstrated patent bypass grafting with good filling. Left ventricular ejection fraction was 40%. She was discharged with no further cardiac problems on follow up. Manufacturer analysis showed that at 15 hours, the last dose of cisapride produced a serum level of 91.6 ng/ml with an elimination half-life of about 24 hours. Following hospital discharge, persistent vomiting returned refractory to noncisapride drugs. Cisapride was again given at 10 mg TID. A week later morning cisapride level, 15 hours after her 6 PM dose, was 14.6 ng/ml. She continued to do well taking 5 mg BID.</p> <p>QTc 630 ms; clarithromycin dose 1000 mg TdP did occur. Risk factors were female sex, heart disease, acute medical illness, chronic medical illness, cisapride (directly and as a CYP3A4 blocker) and clarithromycin (directly and as a CYP3A4 blocker).</p>
6 [Gray, 1998]	<p>Case 2: 83-year-old man with chronic renal failure (ischemic nephropathy) and attendant anemia, coronary artery disease requiring bypass grafting, ischemic cardiomyopathy, sick sinus syndrome requiring pacemaker placement, diffuse atherosclerotic vascular disease, peptic ulcer disease, and gastroesophageal reflux disease presented to his gastroenterologist complaining of a foreign body in his esophagus while eating. Medications included erythropoietin, furosemide, alprazolam, amlodipine, ranitidine, iron, temazepam, aspirin, nitroglycerin, methocarbamol and cisapride 10 mg QID. Esophagogastroduodenoscopy showed impacted food and diffuse gastritis. <i>H. pylori</i> infection was diagnosed and he was given clarithromycin 500 mg BID. One week later, he presented to the ED with weakness, vomiting and episodes of falling and unconsciousness. He was admitted for cardiac monitoring. Physical examination revealed a cachectic and chronically ill man who appeared dehydrated. Chemistries included serum creatinine 4.8 mg/dl, serum potassium 4.3 mmol/l and serum magnesium 2.2 mg/dl. Cardiac monitoring showed nonsustainable episodes of TdP. An earlier EKG showed a paced rhythm of 70 BPM. Cisapride and clarithromycin were stopped. He received 1 g magnesium sulfate IV. Pacing was increased to 100 BPM. He gradually improved and serum creatinine decreased to 2.7 mg/dl. He recovered and was discharged.</p> <p>QTc unknown; clarithromycin dose 1000 mg TdP did occur. Risk factors were old age, heart disease, acute medical illness, chronic medical illness, cisapride (directly and as a CYP3A4 blocker) and clarithromycin (directly and as a CYP3A4 blocker).</p>
	<p>53-year-old woman presenting to the ED following two separate automobile accidents. She could not recall events just before each accident and 'may have blacked out twice'. She denied headaches, visual changes, chest pain, dyspnea, sweating or nausea but acknowledged possible light-headedness. She denied experiencing loss of bladder or bowel control before the accidents. She did recall awakening when observers tried to remove her from her car after the second accident. The duration of unconsciousness was unknown. She denied confusion after regaining consciousness. Her husband stated that her car was sideswiped in mid-afternoon. Later, she struck a parked car and was transported to the ED. In the ED, a lower-lip laceration was repaired. Otherwise, her physical findings were unremarkable. Recently, she had been hospitalized for pneumonia with findings on echocardiogram of mild concentric left ventricular hypertrophy and trace mitral regurgitation. A thallium study was normal and gastrointestinal work-up revealed hiatal hernia and ulcers. Treatment for pneumonia included clarithromycin 500 mg</p> <p>(continued)</p>

Continued.

Case	Narrative
7 [Lee <i>et al.</i> 1998]	<p>BID. She also took cisapride 20 mg QID. Additional medications included a clonidine patch, fluoxetine 20 mg daily, omeprazole 20 mg daily and prochlorperazine suppositories for nausea. Serum potassium and magnesium levels were normal. Admission EKG showed a QTc interval of 456 ms. Two days later it was 396 ms. Extensive cardiac and neurologic workup of syncope was normal. Her physicians concluded that she had experienced multiple episodes of TdP-induced syncope.</p> <p>QTc 456 ms; clarithromycin dose 1000 mg TdP assumed but not documented. Risk factors included female sex, heart disease, fluoxetine, acute medical illness, chronic medical illness, cisapride (both directly and as a CYP3A4 blocker) and clarithromycin.</p>
8 [Lee <i>et al.</i> 1998]	<p>Case 1. 40-year-old male IV drug addict with bronchiectasis and core pulmonale was hospitalized with fulminant bronchopneumonia. Chemistries showed impaired liver function with absent serologic markers for viral hepatitis. EKG showed normal sinus rhythm (80 BPM), right axis deviation, right ventricular strain and normal QTc interval (430 ms). Echocardiography showed dilated pulmonary artery and severe tricuspid regurgitation. He did not respond to IV penicillin and gentamicin and treatment was switched to IV ceftazidime and vancomycin and oral clarithromycin (500 mg BID). A week later, recurrent TdP appeared with degeneration into ventricular fibrillation requiring countershock and cardiopulmonary resuscitation. QTc interval was prolonged (670 ms). Serum electrolytes were normal. Overdrive ventricular pacing controlled the ventricular arrhythmia. Clarithromycin was stopped. A week later, the QTc interval was normal. He remained well over the next year.</p> <p>QTc 670 ms; clarithromycin dose 1000 mg TdP did occur. Risk factors included heart disease, acute medical illness, chronic medical illness, impaired liver function and clarithromycin.</p>
9 [Hayashi <i>et al.</i> 1999]	<p>Case 2. 25-year-old woman with Goodpasture syndrome, end-stage renal failure on hemodialysis and chronic hepatitis was admitted for bronchopneumonia. Serum electrolytes and liver enzymes were normal. Renal function tests consistent with renal failure. EKG showed sinus tachycardia (114 BPM) and normal QTc interval (420 ms). Echocardiography showed mild left ventricular dilatation with a 40% ejection fraction. Treatment included IV ceftazidime, amikacin and oral clarithromycin (500 mg BID). One week later, she developed recurrent TdP with seizures and hypotension. QTc interval was prolonged (775 ms). After stopping clarithromycin, QTc interval returned to normal. No further episodes of TdP occurred and she remained free of cardiac arrhythmias at 9-month follow up.</p> <p>QTc 775 ms; clarithromycin dose 1000 mg TdP did occur. Risk factors included female sex, heart disease, acute medical illness, chronic medical illness and clarithromycin.</p>
9 [Hayashi <i>et al.</i> 1999]	<p>76-year-old woman referred for presyncope. She had taken disopyramide 100 mg TID (QTc interval prolongation 510 ms before admission) to treat supraventricular arrhythmias since her myocardial infarction 5 years earlier. Additional medications included nitrates and diltiazem 30 mg TID. Five days before presentation, she started taking clarithromycin 200 mg BID for upper respiratory infection. Initial EKG showed QTc interval prolongation (710 ms) and old inferior myocardial infarction and admission potassium was 2.8 mmol/l and remaining chemistries were normal including cardiac enzymes. Following admission, several episodes of self-terminating TdP occurred. On admission, plasma disopyramide level was 3.2 µg/ml (therapeutic range 1–2 µg/ml). All medications were stopped and hypokalemia was corrected. 14 hours after admission, serum</p> <p>(continued)</p>

Continued.

Case	Narrative
10 [Piquette, 1999]	<p>potassium was 4.3 mmol/l and no further episodes of TdP occurred. However, QTc interval prolongation (670 ms) persisted. By hospital day 10, QTc interval was 450 ms.</p> <p>QTc 710 ms; clarithromycin dose 400 mg TdP did occur. Risk factors were female sex, elderly, heart disease, disopyramide (both directly and as a CYP3A4 blocker), hypokalemia, acute medical illness and clarithromycin (both directly and as a CYP3A4 blocker).</p> <p>77-year-old woman presented to ED with 2-week history of dyspnea, cough producing green sputum and sudden worsening of shortness of breath. Physical examination and chest X-ray was consistent with worsening heart failure and probable left lower pneumonia for which she was admitted. Past medical history included heart failure, chronic obstructive pulmonary disease, rheumatic fever as a child, mitral valve replacement, atrioventricular ablation and ventricular pacemaker for atrial fibrillation. Pre-admission medications included furosemide 80 mg BID, hydrochloride 25 mg daily, potassium chloride 16 mEq BID, captopril 50 mg TID, warfarin, cisapride 10 mg TID, oxazepam 15 mg QHS and budesonide, albuterol, salmeterol and ipratropium bromide inhalers. Potassium chloride was reduced to 16 mEq daily, captopril reduced to 25 mg TID, cisapride inadvertently increased to 20 mg TID and the other medications continued as recorded above. Trimethoprim/sulfamethoxazole 10 mg Q8H IV and clarithromycin 500 mg BID were started for pneumonia. Admission QTc interval was prolonged (520 ms). One month before, this value was normal (440 ms) at a paced rate of 70 BPM. She remained relatively stable over the next 48 hours and then was found to be unresponsive. She was intubated and transferred to the ICU where serum potassium was 4.1 mmol/l, serum magnesium was 1.94 mEq/l and serum creatinine was 1.37 mg/dl. Antibiotics and captopril were stopped. Medications included ipratropium 2 ml with albuterol 1 mg Q2H, albuterol 1 ml/h PRN and methylprednisolone 120 mg IV, followed by 100 mg BID. Shortly after arriving in the ICU, cardiac monitoring showed polymorphic ventricular tachycardia (180 BPM). Repeat serum potassium was 3.3 mmol/l and QTc interval was prolonged (640 ms) at a paced ventricular rate of 70 BPM. Multiple episodes of ventricular tachycardia continued during the night for which she eventually received a lidocaine infusion. Magnesium was given for recurrent TdP. On several occasion, electrical cardioversion was required. Lidocaine was stopped. The next morning, the consulting pharmacist hypothesized that the concomitant administration of cisapride and clarithromycin may have induced TdP. Both drugs were stopped. Additional magnesium was given, the serum potassium level kept above 4.5 mmol/l, and the pacing rate was increased to 80 BPM. She was subsequently discharged from the hospital and there was no recurrence of the cardiac arrhythmias over the next 32 months.</p> <p>QTc 640 ms; clarithromycin dose 1000 mg TdP did occur. Risk factors were female sex, elderly, heart disease, hypokalemia, acute medical illness, chronic medical illness, cisapride (both directly and as a CYP3A4 blocker) and clarithromycin.</p>
11 [Kamochi <i>et al.</i> 1999]	<p>Case 1. 78-year-old woman hospitalized because of a syncopal episode. Medications included digoxin, nilvadipine, pravastatin and lofazeprate. One day before, because of a respiratory infection, she was started on clarithromycin (400 mg daily) and chlorpheniramine (12 mg daily). On admission, she was mildly anemic. Other chemistries were normal except for mild hypokalemia (3.3 mmol/l). Admission EKG showed marked QT interval prolongation (520 msec) at a heart rate of 95 BPM (calculated QTc interval 654 ms—Bazett), right bundle branch block (RBBB) and atrial fibrillation. She was transferred to</p> <p>(continued)</p>

Continued.

Case	Narrative
12 [Kamochi <i>et al.</i> 1999]	<p>the ICU for cardiac monitoring. One hour later, she lost consciousness coincident with developing TdP. A temporary pacemaker was inserted (rate 80 BPM) and magnesium sulfate infused for 4 days. Echocardiography showed an enlarged left atrium with normal left ventricle and ejection fraction. Chest X-ray showed cardiac enlargement. At the time of hospital discharge 10 days later, the QTc interval was normal.</p> <p>QTc 654 ms; clarithromycin dose 400 mg TdP did occur. Risk factors were female sex, elderly, heart disease, acute medical illness, hypokalemia and clarithromycin.</p>
13 [Abbott <i>et al.</i> 1999]	<p>Case 2. 62-year-old man with idiopathic interstitial pneumonia and chronic hepatitis C was treated with theophylline, cloperastine (cough suppressant), clarithromycin 400 mg daily and zopiclone (hypnotic). Soon thereafter, he was rushed to the hospital because of seizures and cyanosis. Cardiac monitoring showed nonsustained episodes of TdP. EKG showed normal sinus rhythm (69 BPM), QT interval prolongation of 560 ms (calculated QTc interval 600 ms—Bazett). Chemistries include electrolytes were normal except for mildly elevated liver enzymes. Clarithromycin was stopped. He received 2 g of magnesium sulfate IV and a temporary pacemaker was placed. Chest X-ray was consistent with interstitial pneumonia and cardiac size was normal. Echocardiography was normal. He was discharged with no further cardiac arrhythmia. 40 days later, QT interval was 480 ms at a heart rate of 56 BPM (calculated QTc 464 ms).</p> <p>QTc 600 ms; clarithromycin dose 400 mg TdP did occur. Risk factors were acute medical illness, chronic liver disease and clarithromycin.</p>
14 [Choudhury <i>et al.</i> 1999]	<p>76-year-old woman with history of hypertension, type 2 diabetes mellitus and stroke was admitted to the hospital with pneumonia. Baseline EKG showed a normal QTc interval (460 ms). Echocardiography showed concentric left ventricular hypertrophy with mild-to-moderate diffuse hypokinesia without ventricular dilatation. She received 7 doses of IV erythromycin 500 mg Q6H and then was switched to oral clarithromycin 500 mg Q12H. After the 2nd dose of clarithromycin, she developed TdP and then ventricular fibrillation requiring defibrillation (QTc interval 540 ms). She was hypokalemic (2.8 mmol/l). Mutation to MiRP1 protein was found.</p> <p>QTc 540 ms; clarithromycin dose 1000 mg TdP did occur. Risk factors were female sex, elderly, heart disease, mutation to MiRP1 protein, acute medical illness, chronic medical illness, hypokalemia, erythromycin and clarithromycin.</p>
	<p>76-year-old woman with history of myocardial infarction, coronary artery bypass grafting, left ventricular dysfunction and symptomatic PVCs suppressed with disopyramide (150 mg BID for previous 19 years) was hospitalized because of chronic bronchitis, dehydration and hypotension. Five days before admission, she started clarithromycin 250 mg BID administered by a local community clinic for bronchitis. Other medications included digoxin 0.25 mg daily (level 1.7 mg/dl), theophylline 200 mg BID, losartan 50 mg BID, furosemide 40 mg daily, aspirin and bronchodilators.</p> <p>The initial EKG showed sinus rhythm, left bundle branch block and prolonged QTc interval (498 ms) that had lengthened since the previous QTc interval (477 ms). All medications were stopped except for theophylline and inhalers. Electrolytes were normal and cardiac enzymes were negative. Several hours after admission, she developed two self-terminating episodes of TdP linked to syncope. At this time, disopyramide level was in the upper normal range (4.1 mg/ml—normal range 2–5 mg/ml). Electrolytes at this time remained normal and cardiac enzymes remained negative. Serum creatinine concentration was 1.8 mg/dl consistent with mild renal impairment.</p> <p>(continued)</p>

Continued.

Case	Narrative
15[Wasmer <i>et al.</i> 1999]	<p>QTc interval had further lengthened (640 ms). Coronary arteriography showed a depressed left ventricular ejection fraction (20%) unchanged since 1993. Two of three grafts remained patent. 48-hour Holter monitoring showed a 5-beat run of asymptomatic monomorphic ventricular tachycardia at a slow rate. Electrophysiologic studies could not induce ventricular tachyarrhythmia. She was discharged receiving no further antiarrhythmic treatment.</p> <p>QTc 640 ms; clarithromycin dose 500 mg TdP did occur. Risk factors were female sex, elderly, heart disease, acute medical illness, chronic medical illness, mild renal failure, disopyramide (both directly and as a CYP3A4 blocker) and clarithromycin.</p>
16 [Vallejo Camazon <i>et al.</i> 2002]	<p>29-year-woman with recurrent syncope, QTc interval prolongation (680 ms) and documented TdP was diagnosed as having long QT syndrome. She was treated with clarithromycin shortly before the first syncopal episode. No prior EKGs existed. Owing to persisting QTc interval prolongation more than 6 months after stopping clarithromycin and QTc interval prolongation in her uncle, she was diagnosed with congenital long QT-syndrome. She started a beta-blocker and remained free of symptoms.</p> <p>QTc 680 ms; clarithromycin dose unknown TdP did occur. Risk factors were female sex, congenital long QT syndrome, acute medical illness and clarithromycin.</p>
17 [Diaz Garcia <i>et al.</i> 2005]	<p>30-year-old man positive for hepatitis C and HIV and enrolled in a methadone detoxification program was admitted for treatment following 10 days of cough, mucopurulent sputum, pleuritic pain, fever and dyspnea. At that time, he had a viral load of 90,000 copies/ml and CD4+lymphocyte index of 36. Chest X-ray showed an alveolar pattern in both bases consistent with bilateral pneumonia. Laboratory testing showed arterial desaturation, anemia, elevated serum creatinine (2.4 mg/dl), hyponatremia (129 mmol/l) and potassium of 5.0 mmol/l. EKG showed sinus tachycardia (100 beats/minute) and normal QTc interval (350 msec). Initial treatment included infusion of two packed red cells and correction of hyponatremia. IV antibiotics included cefepime (2g Q8H), clarithromycin (500mg Q12H), and cotrimoxazole (trimethoprim 240 mg + sulfamethoxazole 1200 mg Q6H). 48 hours later, EKG showed bradycardia (35 BPM), QTc interval prolongation (580 ms) and ventricular bigeminy. 24 hours later, he developed a self-limited episode of monomorphic ventricular tachycardia (150 BPM) in a RBBB configuration (QRS 160 ms). Clarithromycin and cotrimoxazole were stopped and IV cefepime continued. Cardiac enzymes were normal. Echocardiography showed a slightly dilated left ventricular and depressed ejection fraction (23%). Immediately thereafter, no new episodes of ventricular tachycardia occurred. 4 days later, the QTc interval was normal (360 ms).</p> <p>QTc 580 ms; clarithromycin dose 1000 mg Monomorphic ventricular tachycardia did occur. Risk factors were heart disease, acute medical illness, chronic medical illness, bradycardia, methadone, cotrimoxazole (both directly and as a CYP3A4 blocker), chronic liver disease and clarithromycin.</p>
	<p>80-year-old man presented to the ED with 3 days history of cough and productive sputum. Medical history included coronary artery disease and chronic obstructive pulmonary disease controlled. At admission, white blood cell count was elevated (18,600) and serum creatinine, electrolytes and cardiac enzymes were normal. Initial EKG showed sinus tachycardia and ST segment depression in the lateral leads. Chest X-ray was inconclusive for pneumonia. He was treated with oral clarithromycin 500 mg BID. After 48 hours, EKG showed QTc interval prolongation (560 ms) and T-wave inversion in the anterior</p> <p>(continued)</p>

Continued.

Case	Narrative
18 [Hensey and Keane, 2008]	<p>leads. He remained asymptomatic. An echocardiogram showed no wall motion abnormalities. Clarithromycin was stopped and amoxicillin + clavulanic acid started. One week later, the EKG was normal. QTc 560 ms; clarithromycin dose 1000 mg TdP did not occur. Risk factors were elderly, heart disease, acute medical illness, chronic medical illness and clarithromycin.</p>
19 [Buchanan Keller and Lemberg, 2008]	<p>79-year-old woman presented to the ED with her first syncopal episode. Past medical history included appropriately treated hypertension, hypothyroidism and chronic obstructive pulmonary disease. Neurological history and examination was unremarkable. Penicillin allergy was noted. Admission EKG showed atrial fibrillation that reverted to sinus rhythm with first-degree AV block and QTc interval prolongation (496 ms). A diagnosis of community-acquired pneumonia was made based on dyspnea and productive cough. Clarithromycin (250 mg BID) and ceftriaxone were started. Within 24 hours of starting antibiotic treatment, she developed brief runs of paroxysmal ventricular tachycardia/TdP (QTc interval 542 ms) and amiodarone infusion was started. Amiodarone was stopped following evidence of complete heart block interspersed with paroxysmal ventricular tachycardia. Unremarkable studies ensued including serum electrolytes, coronary arteriography and echocardiography (small pericardial effusion). Overdrive pacing at 90 BPM was commenced with a temporary pacing wire. However, the wire dislodged with failure to capture at 6 mV. She was transferred to a tertiary care center. Clarithromycin was stopped. A permanent DDDR pacemaker was placed. A beta-blocker was started. At the time of discharge QTc interval was prolonged (500 ms). QTc 542 ms; clarithromycin dose 500 mg TdP did occur. Risk factors were female sex, elderly, heart disease, suspected congenital long QT syndrome, acute medical illness, chronic medical illness, amiodarone and clarithromycin.</p>
20 [Alesso <i>et al.</i> 2009]	<p>50-year-old woman with history of hypertension and depression admitted for cardiac monitoring following two episodes of syncope during preceding 2 days. Chest X-ray was normal. Serum potassium was 3.3 mmol/l. She had been treated with clarithromycin for an upper respiratory tract infection. Other medications included HCTZ, fluoxetine and potassium supplement. TdP recurred deteriorating to ventricular fibrillation requiring defibrillation. Posterior fascicular block was noted on the EKG and the QTc interval was 620 ms. QTc 620 ms; clarithromycin dose unknown TdP did occur. Risk factors were female sex, hypokalemia, acute medical illness, fluoxetine and clarithromycin.</p>
	<p>71-year-old woman was hospitalized with acute respiratory failure and rapid atrial fibrillation. She was allergic to penicillin, smoked and had previously undergone a hysterectomy. On the first day, she received amiodarone as a 300 mg bolus followed by a 900 mg/day infusion slowing the ventricular rate to less than 100 BPM and then converting to sinus rhythm with negative T waves. On day 2, she received clarithromycin 1 g/day and ciprofloxacin 1 g/day for community-acquired pneumonia. On day 3, rapid atrial fibrillation recurred and hemodynamics worsened prompting mechanical ventilation. EKG on day 4 showed sinus or nodal rhythm (58 BPM) and QT interval prolongation. Sustained ventricular tachycardia developed and was treated with amiodarone infusion. Ciprofloxacin and clarithromycin were stopped and ceftriaxone started. On day 5, she had probable nodal rhythm with bradycardia and a QT interval of 640 ms. Amiodarone dose was decreased and she developed rapid atrial fibrillation. On day 6, she had sinus or atrial rhythm, bradycardia, (continued)</p>

Continued.

Case	Narrative
21 [Cetin <i>et al.</i> 2012]	<p>and QT/QTc interval prolongation (630/570 ms). QTc 570 ms; clarithromycin dose 1000 mg daily Sustained ventricular tachycardia did occur. Risk factors were female sex, elderly, heart disease, bradycardia, acute medical illness, ciprofloxacin (CYP3A4 inhibitor and directly linked to TdP), amiodarone and clarithromycin (potent CYP3A4 inhibitor and directly linked to TdP).</p> <p>6-year-old boy had started clarithromycin treatment 6 days earlier for atypical pneumonia presented to the pediatric cardiology clinic for evaluation of a heart murmur. 12 hours before presenting to the clinic, he had a syncopal episode. There was no family history of syncope or SCD. Vital signs were normal. A 2/6 systolic murmur was noted in the mesocardiac area. Chemistries were normal. EKG showed normal sinus rhythm (88 BPM) and QTc interval prolongation (600 ms). Echocardiography was normal. 24-hour Holter monitoring only showed QTc interval prolongation. Audiometrics were normal. One week after stopping clarithromycin, QTc interval was normal. Treating clinicians excluded congenital long QT syndrome. QTc 600 ms; clarithromycin dose unknown TdP assumed but not documented. Risk factors included acute medical illness and clarithromycin.</p>