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ABSTRACT & COMMENTARY

Substance Abuse and Myocardial Infarction

By Michael H. Crawford, MD

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Dr. Crawford reports no financial relationships relevant to this field of study.

SYNOPSIS: Among patients ≤ 50 years of age with first myocardial infarctions, use of cocaine or marijuana increased the likelihood of an ST-segment elevation myocardial infarction and the subsequent risk of all-cause and cardiovascular mortality.

SOURCES: DeFilippis EM, Singh A, Divakaran S, et al. Cocaine and marijuana use among young adults with myocardial infection. *J Am Coll Cardiol* 2018;71:2540-2551.

Lee JD, Schatz D, Hochman J. Cannabis and heart disease: Forward into the great unknown? *J Am Coll Cardiol* 2018;71:2552-2554.

As more states legalize recreational marijuana, its use is on the rise, yet we know little about its health effects. Cocaine is well recognized as a risk factor for myocardial infarction (MI).

DeFilippis et al studied the prevalence of substance abuse among patients ≤ 50 years of age with their first MI and its relation to outcomes. Investigators used chart review or toxicology screen on MI admission to determine if patients used cocaine or marijuana prior to MI. Patients who used both substances were put in the cocaine group for subanalyses. Opioid use was discovered but was not analyzed because there were insufficient data to distinguish prescription use from nonprescription use. Methamphetamine and other substances also were detected but constituted too few cases for analysis. The primary outcomes of interest were all-cause and cardiovascular mortality. Among 2,097 young MI patients, 11% used cocaine or marijuana, one-third of whom used both substances. ST-segment elevation myocardial infarctions (STEMIs) were more common in the substance abuse patients (65% vs. 52%; $P < 0.001$). Diabetes and hyperlipidemia were less common in substance abuse patients (15% vs. 20%; $P = 0.05$; and 46% vs. 61%; $P < 0.001$, respectively). Tobacco use was more common in substance abuse patients (70% vs. 49%; $P < 0.001$). Substance abuse was associated with a higher cardiovascular mortality (hazard ratio [HR], 2.22; 95% confidence interval [CI], 1.27-3.70; $P = 0.005$) and all-cause mortality (HR, 1.99; 95% CI, 1.35-2.97; $P = 0.001$) after adjustment for baseline covariates

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over a mean follow-up of 11 years. The authors concluded these findings support the current guidelines, which recommend screening young adults with their first MI for substance use and counseling users about the importance of abstinence to prevent future events.

■ COMMENTARY

This analysis exhibits that despite a generally lower incidence of traditional risk factors, substance users had a higher incidence of STEMIs than nonusers. This generates the hypothesis that substance abuse is a risk factor for early MI. Also, MIs in the substance abuse group were more likely to be discovered because of out-of-hospital cardiac arrest, which was driven by the marijuana users. Cocaine has been recognized as a trigger for acute MI, probably because cocaine use increases heart rate, blood pressure, and coronary vasoconstriction. However, we know comparatively little about the effects of marijuana. Marijuana can be similar to tobacco smoking in that one inhales burning vegetable matter in both instances. Still, other effects probably could be attributed to chemicals in marijuana, which would be more relevant to vaporized cannabis oil and edibles. There is evidence that tetrahydrocannabinol increases plasma catecholamines, impairs vascular endothelial function, and decreases myocardial contractility. Thus, marijuana may not be the benign recreational drug that it is touted to be. The major limitation to the DeFilippis et al study was the potential effects of multiple confounders. The investigators adjusted the HR calculations for other known risk factors and showed about a two-fold increase in all-cause and cardiovascular mortality. However, cocaine and marijuana users also could smoke tobacco, drink alcohol, or take opioids. Also, substance users may be more likely to participate in other risky behaviors and have a higher prevalence of hepatitis C, HIV, and depression. These factors could affect mortality post-MI and were not assessed in this study. Also, the prevalence of substance abuse in the risk population (age < 50 years) could not be ascertained. Thus, the relative risk of substance abuse causing an MI is unknown. What is clear is that substance abuse patients are at higher risk for adverse events post-MI. When one encounters a patient with an MI who uses substances, it would be reasonable to counsel him or her that quitting would be in their best interest. ■

ABSTRACT & COMMENTARY

Canagliflozin Reduces Risk of Heart Failure Hospitalizations for Diabetic Patients

By Van Selby, MD

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Dr. Selby reports no financial relationships relevant to this field of study.

SYNOPSIS: In type 2 diabetes mellitus patients with a higher risk of cardiovascular disease, canagliflozin lowered the risk of cardiovascular death or heart failure hospitalization. Patients with pre-existing heart failure may experience even greater benefit.

SOURCE: Rådholm K, Figtree G, Perkovic V, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: Results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018; Mar 11. pii: CIRCULATIONAHA.118.034222. doi: 10.1161/CIRCULATIONAHA.118.034222. [Epub ahead of print].

There is growing evidence of an association between sodium-glucose cotransporter 2 (SGLT2) inhibitors and improved cardiovascular outcomes in diabetic patients. These benefits may be even more pronounced for patients with pre-existing cardiovascular conditions such as heart failure (HF) in whom the

risk of adverse cardiovascular events is particularly high. However, few investigators have compared the relationship between SGLT2 inhibitors and cardiovascular events in patients with pre-existing HF vs. those without HF.

The authors of the Canagliflozin Cardiovascular Assessment Study (CANVAS) randomized 10,142 patients with type 2 diabetes mellitus (T2DM) to the SGLT2 inhibitor canagliflozin to placebo. During a mean follow-up of 188 weeks, canagliflozin was associated with a reduced risk of HF hospitalization. In this secondary analysis, Rådholm et al evaluated the association between canagliflozin and the combined outcome of cardiovascular death or hospitalized HF. Also, they compared the effects of canagliflozin in the 14.4% of patients with pre-existing HF to those without HF.

In the overall population, canagliflozin was associated with a reduced risk of cardiovascular death or hospitalized HF (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.67-0.91). The observed benefit was even greater among patients with a history of HF (HR, 0.61; 95% CI, 0.46-0.8; $P = 0.021$ for the comparison to those without HF). Canagliflozin is associated with increased risks of amputation, fracture, and volume depletion. However, this risk was not higher in patients with HF compared to those without. The authors concluded that among patients with T2DM and elevated risk of cardiovascular disease, canagliflozin reduces the risk of cardiovascular death or HF hospitalization. Further, the benefits may be greatest in patients with baseline HF.

■ COMMENTARY

T2DM and HF coexist frequently. No previous class of glucose-lowering therapy has been shown to reduce the risk of HF hospitalization in this population. The EMPA-REG OUTCOME trial was the first to show a reduction in HF hospitalization with an SGLT2 inhibitor (empagliflozin). The magnitude of the observed benefit was surprising to many observers, but data from CANVAS and a recent large retrospective study have added support for the HF-related benefits of SGLT2 inhibitors. Using data from a large, rigorous, international, clinical trial, Rådholm et al have shown that canagliflozin substantially lowers the risk of a meaningful outcome (cardiovascular death or hospitalized HF). Furthermore, patients with pre-existing HF may derive even greater benefit. The observed HR of 0.61 among patients with pre-existing HF is comparable to long-standing, guideline-recommended therapies for chronic HF. SGLT2 inhibitors produce many cardiovascular effects. The exact mechanism by which they improve outcomes is not understood fully. In CANVAS, the benefits of canagliflozin were observed early, suggesting a hemodynamic or volume-related effect. SGLT2 inhibitors induce natriuresis and osmotic diuresis, lower blood pressure, and reduce arterial stiffness. Longer-term, SGLT2 inhibitors produce anti-atherosclerotic effects and affect cardiac metabolism favorably.

It is important to note that adverse events were no more frequent in HF patients compared to the general population. With everything considered, the growing evidence supporting HF-related benefits of SGLT2 inhibitors makes this a compelling therapy to offer patients with HF and diabetes. There was no left ventricular ejection fraction criteria for defining the HF population within CANVAS. Therefore, it is reasonable to consider SGLT2 inhibitors in patients with HF and preserved ejection fraction (in whom diabetes is common and few effective therapies exist) in addition to those with systolic HF.

The story of SGLT2 inhibitors for reducing cardiovascular outcomes still is in its early stages. The Rådholm et al study was a secondary analysis; therefore, it must be interpreted with caution. With only 14% of the total study population in the HF group, we cannot draw firm conclusions regarding the increased benefit among HF patients. There are multiple ongoing trials that will help us understand the mechanism by which these agents exert their benefit and to identify the patients who will benefit most. There are even trials underway evaluating the benefit of SGLT2 inhibitors in patients with HF but not diabetes. For now, these agents should be strongly considered in diabetic patients with HF (or other cardiovascular disease). Cardiovascular practitioners who are not comfortable prescribing drugs for treatment of diabetes can suggest these agents to their patients' primary care providers or endocrinologists, highlighting the cardiovascular benefits. ■

ABSTRACT & COMMENTARY

Clinicians Prescribe Antibiotics for Excessive Duration in Patients With a Diagnosis of Acute Sinusitis

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Clinicians inappropriately prescribe antibiotics most often to patients with a diagnosis of acute sinusitis for durations much longer than recommended.

SOURCE: King LM, Sanchez GV, Bartoces M, et al. Antibiotic therapy duration in US adults with sinusitis. *JAMA Intern Med* 2018;178: 992-994.

Antibiotic therapy often is prescribed when it is unnecessary (and, therefore, by definition, more likely to be harmful than beneficial). Even when antibiotic therapy is appropriate, it often is administered for durations well beyond the time when its benefit has passed and only negative consequences remain, such as adverse reactions and continued unnecessary risk of selection of antibiotic resistance.

King et al have determined more precisely the actual practice of front-line clinicians regarding their prescribed duration of antibiotic therapy for patients with a diagnosis of acute sinusitis. The researchers examined the new antibiotic prescriptions for adults in association with a diagnosis of acute sinusitis in the 2016 National Disease and Therapeutic Index. They identified 3,696,976 visits meeting their criteria and found that the median duration of prescribed therapy was 10 days. Approximately two-thirds of antibiotics were prescribed for 10 days or longer.

Although azithromycin is administered most often for five days, its unusual pharmacokinetics with very slow elimination from tissues generally is considered to result in approximately 10 days of antibiotic exposure. A reanalysis of the data with removal of azithromycin from consideration found that, for the remaining prescribed antibiotics (80% of the total), an astounding 91.5% of prescriptions were for 10 days or longer. Furthermore, only 7.6% were for seven days, and 0.5% were for five days.

■ COMMENTARY

The most recent Infectious Diseases Society of America guideline (2012) recommends that for patients with a diagnosis of uncomplicated acute sinusitis who meet certain criteria (basically, severe or worsening illness or at least 10 days of symptoms), the duration of treatment should be five to seven days. Furthermore, the guideline recommends that macrolides, such as azithromycin, not be used for empiric therapy because of the high rate of resistance among pneumococci.

This study included prescriptions from a broad range of physician practitioners, including family practice, general practice, internal medicine, pediatrics, and emergency medicine. It documents what we already know: Physicians of all types often prescribe antibiotics for durations well in excess of the duration for which maximum benefit is achieved.

Implementing antimicrobial stewardship principles in the settings in which these therapies are prescribed is a critical element of the work ahead. ■

ABSTRACT & COMMENTARY

Initial Management of Patients With Medication-overuse Headache

By Louise M. Klebanoff, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Klebanoff reports no financial relationships relevant to this field of study.

SYNOPSIS: As part of a randomized treatment trial for medication-overuse headache, a simple protocol that provided early advice on stopping excessive medications was effective in one-third of patients, even before any prophylactic medications were started.

SOURCE: Corbelli I, Sarchielli P, Eusebi P, et al; SAMOHA Study Group. Early management of patients with medication-overuse headache: Results from a multicenter clinical study. *Eur J Neurol* 2018;25:1027-1033.

Medication-overuse headache (MOH) is a chronic headache disorder resulting from frequent intake of pain medication, including analgesics, nonsteroidal anti-inflammatory drugs, triptans, opioids, and ergotamine. The estimated prevalence of MOH in the Western world is 1-2%, with a peak incidence of 5% in women 40-50 years of age. Patients with MOH score lower on quality-of-life assessment scales compared to patients with chronic headaches without MOH, episodic headache, and healthy controls. Despite the frequency of the condition and the high burden of disability it causes, there is no established consensus on the standard of care. Withdrawal of the abused medication is advised, but recommendations regarding the methods of detoxification and administration of prophylactic medications are inconsistent. In addition, the prognosis remains poor, with approximately 30% of patients relapsing within one year of withdrawal of medication.

Patients with MOH can be divided into two subtypes, simple (Type I) and complex (Type II). Type II patients present with significantly more comorbidities, including psychopathology (mood, anxiety, or substance addiction disorders), a long duration of MOH (> 1 year), a history of relapse following withdrawal, and daily use of multiple doses of symptom medication. Corbelli et al reported on patients enrolled in the multicenter, placebo-controlled Sodium vAlproate in the Treatment of Medication Overuse HeadAche (SAMOHA) study. At the initial visit, patients were given simple advice regarding MOH. Patients were advised to stop the abused medication. After initial assessment, each patient completed a four-week observation period followed by a six-day inpatient detoxification phase during which the abused drugs were discontinued. Then, patients continued on a 12-week, double-blind treatment period during which they received valproate 800 mg/day or placebo. After the four-week observational period, patients were reassessed to see if they still met International Headache Society revised criteria for MOH, at which point they were randomized to the treatment arm of the study. Researchers screened 130 patients at nine participating centers. Most patients (80%) were women; the mean age was 42 years; and the headaches were chronic for an average of 4.6 years, with an average of 24 days of headache per month. The most commonly abused medications were acetaminophen, acetylsalicylic acid, or other nonsteroidal anti-inflammatory drugs.

After the initial observation period, 88 patients still met inclusion criteria and continued the study; 34 patients no longer met inclusion criteria. The patients whose headaches improved so that they no longer met inclusion criteria were significantly younger and had a significantly shorter history of chronicity compared to those who continued to meet inclusion criteria. Since a significant proportion of patients with MOH improved after receiving simple advice, it is important to counsel patients regarding MOH early in their clinical care. Additionally, when conducting studies regarding the management of MOH, it is important to include an observation period of following simple advice to ensure that the patients studied have persistent MOH.

■ COMMENTARY

This research suggests that simple advice given at an early clinical assessment can be helpful in the management of MOH, especially in younger patients with fewer years of chronic headache. Further, when conducting research on this patient population, an observation period is needed to exclude patients who rapidly improve following simple advice. The patients with persistent MOH who failed to improve following simple advice have more psychological comorbidities, experience a longer duration of chronic headache, and remain more challenging to treat. The management of this patient population, including recommendations regarding type of detoxification and institution of prophylactic medications, needs further study. Perhaps the results of the completed SAMOHA study will provide additional treatment recommendations. ■

PHARMACOLOGY UPDATE

Tafenoquine Tablets (Krintafel)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a single-dose treatment for radical cure (prevention of relapse) of *Plasmodium vivax* malaria. It is the first new treatment for *P. vivax* in more than 60 years. Tafenoquine, which is chemically similar to primaquine, received priority review as well as orphan and breakthrough therapy designations. It is marketed as Krintafel.

INDICATIONS

Tafenoquine is indicated for the radical cure of *P. vivax* malaria in patients ≥ 16 years of age who have received appropriate antimalarial therapy for acute *P. vivax* infection.[1]

DOSAGE

The recommended measurement is a single dose of 300 mg (2 × 150 mg). It is coadministered on the first or second day of the appropriate antimalarial therapy (e.g., chloroquine) for acute *P. vivax* malaria.

POTENTIAL ADVANTAGES

Tafenoquine is the first single-dose radical cure for *P. vivax* because of its long elimination half-life (approximately 15 days). Tafenoquine showed similar recurrence-free efficacy to primaquine for 14 days.[2]

POTENTIAL DISADVANTAGES

There is risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[1] G6PD testing must be performed before prescribing. Tafenoquine is contraindicated in patients with G6PD deficiency or unknown G6PD status. Use in pregnancy is not recommended, as the G6PD status of the fetus is unknown. Infant G6PD status should be determined before breastfeeding. The long elimination half-life of tafenoquine would be problematic if given inadvertently to a patient with G6PD deficiency. Other adverse reactions include methemoglobinemia, psychiatric effects, and hypersensitivity reactions.

COMMENTS

The efficacy of tafenoquine was established in a double-blind trial that included 522 adult subjects who were positive for *P. vivax*.[1,2] Subjects were randomized to tafenoquine (2 × 150 mg on either day 1 or 2; n = 260), active control (primaquine 15 mg once daily on days 2-15; n = 129), or placebo (n = 133). All subjects received chloroquine 600 mg on days 1 and 2 and 300 mg on day 3. The primary efficacy endpoint was freedom from recurrence at six months. This was defined as initial clearance of *P. vivax*, took no antimalarial drugs, and were confirmed parasite-free at the six-month assessment. Recurrence-free efficacy rates at six months were 60% for tafenoquine, 64% for primaquine, and 26% for placebo.

CLINICAL IMPLICATIONS

According to the World Health Organization's latest *World Malaria Report*, there were 216 million cases of malaria in 2016.[3] The two species that pose the greatest threat are *Plasmodium falciparum* and *P. vivax*, with the former prevalent in Africa and the latter dominant in Asia, Latin America, and in some parts of Africa.[3] The life cycle of the malaria parasite involves the mosquito and human hosts.[4] During a blood meal, sporozoites of *P. vivax* are inoculated into the human host. These infect the liver cells, mature, and reenter the bloodstream, infecting healthy erythrocytes. For *P. vivax*, a dormant stage (hypnozoites) persists in the liver and is the source of relapse. Tafenoquine is active against the liver stage, including hypnozoites, as well as other stages in the life cycle in humans.[1]

The limitation of tafenoquine is the risk of hemolytic anemia in G6PD-deficient individuals. The estimated G6PD deficiency prevalence is 7-15%.[5] In areas where the frequency of G6PD deficiency allele is > 10%, an estimated 15% of males and 25% of females will be unable to receive tafenoquine.[5] In these patients, the World Health Organization recommends primaquine at 0.75 mg base/kg body weight once a week for eight weeks with close medical supervision.[6] The cost for tafenoquine was not available at the time of this review. ■

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CME QUESTIONS

1. **Acute myocardial patients who use cocaine and marijuana have a higher incidence of:**
   a. all-cause mortality.
   b. cardiovascular mortality.
   c. ST-segment elevation myocardial infarction.
   d. All of the above

2. **A secondary analysis of a recent trial of canagliflozin vs. placebo in diabetics showed reduced rates of:**
   a. cardiovascular death and hospitalization for heart failure.
   b. amputation.
   c. fractures.
   d. volume depletion.

3. **Patients with simple medication-overuse headaches should:**
   a. receive medications for headache prophylaxis.
   b. be admitted for inpatient detoxification.
   c. continue analgesics as needed.
   d. learn about medication-overuse headache and be advised to stop the abused medication.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Dual Antiplatelet Therapy for Acute Ischemic Stroke and TIA

Use of Amyloid PET Imaging for Diagnosis of Dementia

Vitamin C for Postoperative Atrial Fibrillation Risk

Internal Medicine [ALERT]

ECG Review

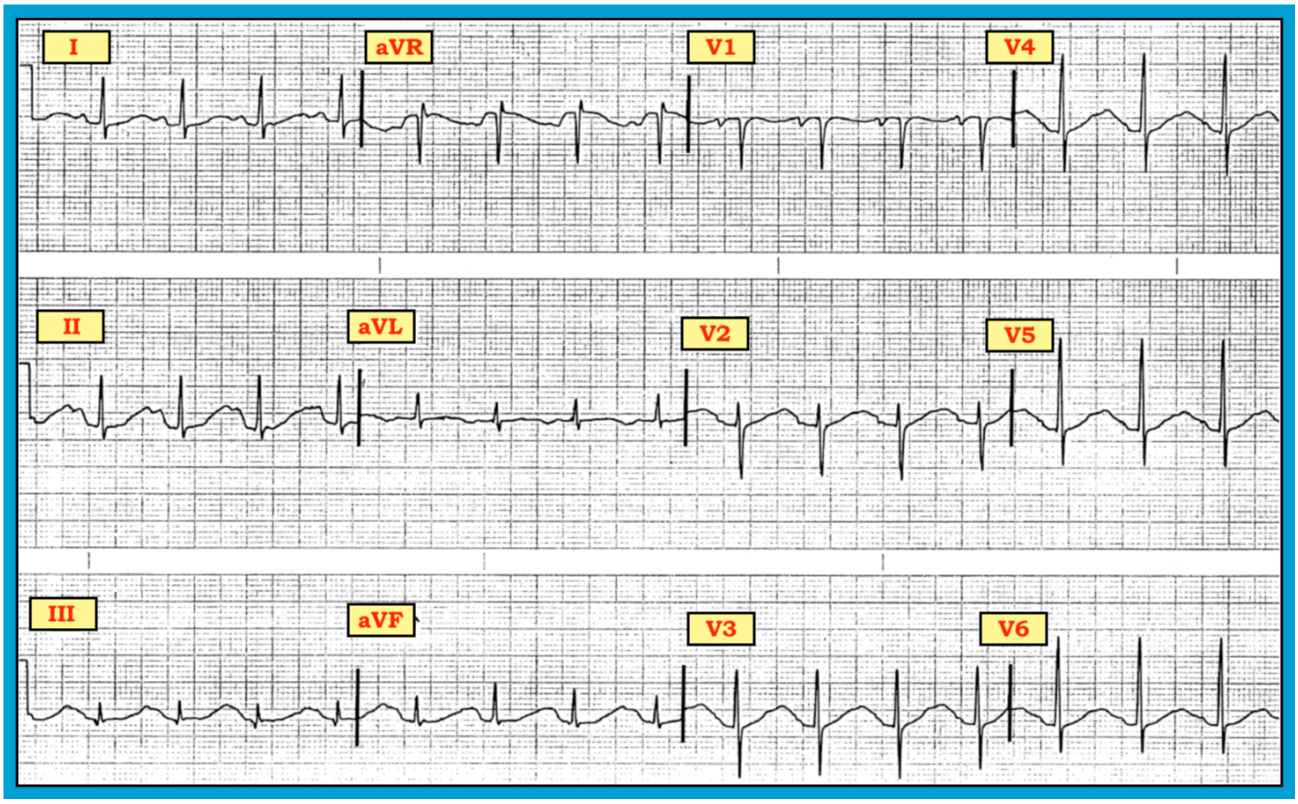
By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

Dr. Grauer reports no financial relationships relevant to this field of study.

What is the Key ECG Finding?

A 59-year-old woman presented to a medical facility in an unresponsive state. Staff presumed the patient had sepsis. The patient underwent an ECG that medical staff read as "normal." How might one interpret the ECG in the figure below? Which clinical entities could contribute to the irregular findings?



Although P waves are not easily observable in lead II, they are clearly visible with a constant PR interval in leads I and V1. Thus, the underlying rhythm is sinus tachycardia at a rate of ~100/minute. Regarding intervals, the PR interval is normal, and the QRS complex is narrow. However, the QT interval is extremely long. Regarding the rest of the systematic interpretation, the mean QRS axis is normal (about + 40 degrees). There is no chamber enlargement, and one can observe nonspecific ST-T wave abnormalities in several leads (without significant ST elevation or depression).

The principal finding is the very long QT interval, although it is difficult to determine if the suggestion of slight notching toward the end of the T wave in several leads is due to partial fusion with the P wave or fusion with a large U wave. Regardless, the QT interval for this tracing is markedly prolonged. Therefore, the key ECG finding is the long QT. Recognition of a significantly prolonged QT interval should prompt consideration of three causes: drugs, "Lytes" (i.e., electrolyte disorders, specifically Ca++, low serum K+, or Mg++), and central nervous system (CNS) calamities (including bleeding, tumor, seizure, stroke, trauma, or coma).

Of note, while ischemia/infarction and conduction defects also may produce QT lengthening, these conditions usually will be obvious from the ECG. When the principal ECG abnormality is a long QT interval, think "Drugs-Lytes-CNS" as the likely cause(s). Then, correlate clinically.

Because she was unresponsive and staff presumed sepsis, the patient's altered mental status might account for the prolonged QT visible on her ECG. Additional clinical information is needed on this patient to determine if drug effect, electrolyte disturbance, *and/or* additional CNS insult also might contribute to the ECG abnormalities.

For more information about and further discussion on this case, please visit: https://bit.ly/2MdyrUU.