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ABSTRACT & COMMENTARY

Can Antibiotics Lead to Colon Cancer?

By Joseph E. Scherger, MD, MPH

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SYNOPSIS: Swedish researchers saw an association between frequent antibiotic use and proximal colorectal cancer.

SOURCE: Lu SSM, Mohammed Z, Häggström C, et al. Antibiotic use and subsequent risk of colon cancer: A Swedish nationwide population-based study. *J Natl Cancer Inst* 2021; Sep 1:djab125. doi: 10.1093/jnci/djab125. [Online ahead of print].

A nationwide, population-based study in Sweden was conducted with a matched, case-controlled design. Data were collected from national registers where information was gathered from 2005 to 2016. The authors studied 40,545 cases of colorectal cancer with 202,720 controls, noting frequent antibiotic use was associated with a higher risk of proximal colon cancer (odds ratio, 1.17; 95% confidence interval, 1.05-1.31). The most common offending antibiotics were quinolones and sulfonamides with or without trimethoprim. There was an inverse association with rectal cancer in women. Other investigators have found a relationship between antibiotic use and colorectal cancer.[1,2] The composition and function of the gut microbiome are believed to play a role in colorectal cancer development.[3,4] Antibiotics disrupt the gut microbiome and may result in dysbiosis, hindering the anti-inflammatory effects of some bacteria and producing more pathogenic bacteria.

■ COMMENTARY

Clinicians have come to better understand the risks of antibiotics and the importance of the gut microbiome. The rise in colorectal cancer cases among younger adults has led to calls to start screening patients at a younger age. Consider why this is happening. Dietary factors certainly play a role, especially consuming processed carbohydrates and meat. The potential role of antibiotics in causing colorectal cancer is poorly recognized. Association is not causation, but this study and other investigations raise concern. Anytime clinicians use antibiotics, especially repeatedly, consider the risk-benefit ratio and realize these drugs can cause harm. Diverticulitis is one example of a common inflammatory condition that may not require antibiotics in uncomplicated cases.[5,6] ■

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ABSTRACT & COMMENTARY

Clostridioides difficile Infection: Guideline Update

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: Fidaxomicin is preferred over vancomycin for initial and recurrent cases. Bezlotoxumab is recommended in many cases of recurrent infection and initial infection in patients at high risk of recurrence.

SOURCE: Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults. *Clin Infect Dis* 2021;73:e1029-e1044.

Johnson et al have provided a focused update of the 2017 Infectious Diseases Society of America — Society for Healthcare Epidemiology of America clinical practice guidelines for *Clostridioides difficile* infection (CDI).[1] The update is limited to three new recommendations, one each dealing with the treatment of initial and recurrent infection, and one dealing with prevention of further recurrences. All are considered conditional; the first two are based on low certainty evidence and the third is based on very low certainty evidence.

For initial episodes of CDI, fidaxomicin therapy is recommended, rather than a standard course of vancomycin. For recurrent episodes of CDI, likewise fidaxomicin therapy is recommended, rather than a standard course of vancomycin. For patients with a recurrence in the previous six months, bezlotoxumab administration is recommended together with standard of care therapy.

■ COMMENTARY

The optimal management of CDI is an ever-evolving process. Among the knottier issues is that of diagnosis of the disease in the absence of a gold standard — and this is not addressed in the update. Nonetheless, this document provides useful guidance regarding the relative benefit of fidaxomicin over vancomycin therapy in initial and recurrent episodes of infection, as well as the use of bezlotoxumab in recurrent disease. No change in the previous recommendation for fecal microbiota transplantation (FMT) has been made, and the "opinion of the panel" is patients who have experienced a third recurrence despite appropriate therapy may be offered FMT. However, the panel noted that since 2017, there have been two FDA alerts about the treatment modality: two related to transmission of antibiotic-resistant *Escherichia coli* and one raising issues regarding COVID-19.

The recommendation regarding the preference of fidaxomicin over vancomycin likely could have been made at the time of the 2017 guideline, but the major impediment undoubtedly was the remarkable cost differential between the two therapies. The high cost of fidaxomicin persists and is addressed in the current document. For this reason, the current recommendation acknowledges the implementation of the fidaxomicin recommendation "depends upon available resources" and includes a statement indicating vancomycin remains an acceptable alternative. High-dose enteral vancomycin continues to be recommended for cases of fulminant CDI.

The panel noted that for those patients with a first recurrence of CDI, a tapered regimen and a pulsed regimen of vancomycin are acceptable alternatives to fidaxomicin. For

patients with multiple recurrences, acceptable options for fidaxomicin are tapered and pulsed vancomycin, followed by rifaximin or FMT.

In addition to the use of bezlotoxumab in those with recurrent CDI as indicated earlier, its use may be considered during initial episodes in individuals with risks for recurrence, such as severe CDI on presentation, age > 65 years, or the presence of immunocompromise. The monoclonal should be administered during receipt of standard of care. However, the benefit of both fidaxomicin and bezlotoxumab relates to their ability to prevent recurrent CDI. The evidence is next to nonexistent regarding whether the combination is superior in this regard to the use of either agent alone — an important consideration given the potential financial toxicity of each. ■

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ABSTRACT & COMMENTARY

Proton-Pump Inhibitors and Community-Associated *Clostridioides difficile* Infection

By Richard R. Watkins, MD, MS, FACP, FIDSA, FISAC

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SYNOPSIS: A nationwide cohort study of adults in Denmark found that proton-pump inhibitor (PPI) use was associated with a moderately increased risk of community-associated *Clostridioides difficile* infection, and the risk remained elevated up to one year after PPI treatment had ended.

SOURCE: Inghammar M, Svanström H, Voldstedlund M, et al. Proton-pump inhibitor use and the risk of community-associated *Clostridium difficile* infection. *Clin Infect Dis* 2021;72:e1084-e1089.

The authors of several observational studies over the last 15 years have reported an association between *Clostridioides difficile* infection (CDI) and proton-pump inhibitor (PPI) use. However, many studies have been criticized for their observational design and lack of sufficient adjustment for confounding variables. One way to adjust for confounders is a relatively new type of study design called the self-controlled case-series (SCCS), which compares periods of exposure and non-exposure within individuals, thereby controlling for all confounders that remain constant over the observation window. Inghammar et al conducted a large nationwide study to determine the risk of community-associated CDI (CA-CDI) in adults prescribed PPIs using an SCCS design.

The study included Danish adults age 20 years and older in a nationwide database diagnosed with CA-CDI between February 2010 and December 2013. A case of CA-CDI was defined based on guidelines from the Infectious Diseases Society of America as a first positive test for *C. difficile* based on culture, molecular assay, or toxin test among individuals who reported symptoms in an outpatient setting or two or fewer days after hospitalization, who produced no other positive CDI tests within the preceding eight weeks, and had not been hospitalized in the preceding 12 weeks. PPI exposure was defined based on four periods: new use, defined as a PPI prescription among individuals without PPI use in the prior 365 days; current use, defined as ongoing treatment with one tablet per day of a PPI from the first day of treatment until treatment cessation; intermediate use, defined as the period zero to six months (0-179 days) after treatment cessation; and past use, defined as six to 12 months (180-364 days) after treatment cessation.

There were 3,583 cases of CA-CDI in 3,338 individuals during the study period. The median age was 65 years (interquartile range, 44 to 80 years), and 38% were male. CA-CDI occurred in 964 individuals who currently were using PPIs, 324 cases occurred after intermediate use, 123 occurred after past use, and 2,172 occurred during periods without PPI use. The adjusted incident rate ratio (IRR) was 2.03 (95% CI, 1.74-2.36), comparing PPI use with nonuse. The increased risk continued to be elevated in later periods: 1.54 (95% CI, 1.31-1.80) for zero to six months and 1.24 (95% CI, 1.00-1.53) for six to 12 months after current use.

After comparing the incidence of CA-CDI during current use of PPIs with periods of nonuse, the unadjusted IRR was found to be 2.78 (95% CI, 2.40-3.22). Adjusting for hospitalization, antibiotic use, and corticosteroid use resulted in an adjusted IRR of 2.03 (95% CI, 1.74-2.36). The increased risk was lower but still elevated in later periods (adjusted IRR, 1.54 [95% CI, 1.31-1.80] for zero to six months and adjusted IRR,

1.24 [1.00-1.53] for six to 12 months after current use of PPIs). Estimates for the association between current use of PPIs and CA-CDI were similar regarding sex and age.

■ COMMENTARY

Most previous studies of the association between PPIs and CDI were conducted with hospitalized patients. These individuals tend to be older, sicker, and have more antibiotic exposures than patients who develop CDI in community settings. Therefore, the analysis by Inghammar et al is interesting because it focused on this latter, less studied group. The key finding was the use of PPIs was associated with approximately two times the risk for acquiring CA-CDI. The risk was lower after PPI treatment stopped, but it remained significantly higher up to 12 months afterward.

Clinicians should realize there is mounting evidence suggesting an association between PPI use and CDI. They should carefully assess the potential benefits of PPI use compared to the risk of CA-CDI, especially in patients with a history of CDI. In such cases, perhaps an alternative agent would be a better choice, or the PPI could be used but for a limited time. The mechanism by which PPI use increases the risk for CDI has not yet been fully elucidated. It is believed PPIs suppress the capacity of the normal microbiome in limiting the proliferation of *C. difficile*. Further experimental evidence is needed to test this hypothesis.

Despite the robust study design, a few limitations are worth mentioning. First, some PPIs can be purchased over the counter in Denmark, which could have led to misclassification of drug exposure. Second, although the SCCS design enables patients to be used as their own controls, which minimizes the effect of time-fixed confounders, residual confounding remains theoretically possible since there was no randomization here. Finally, the results of the study might not be generalizable to other populations in different geographic areas.

Definitive proof that PPIs cause CDI likely will require a randomized clinical trial. Considering the relatively low incidence of CDI in the community, this would require many individuals to be enrolled. Until then, clinicians must be aware of the risks associated with PPIs and prescribe them with the best available evidence in mind. ■

ABSTRACT & COMMENTARY

Iron Therapy for Acute Heart Failure

By Michael H. Crawford, MD

Professor of Medicine, Lucy Stern Chair in Cardiology, University of California, San Francisco

SYNOPSIS: Giving intravenous ferric carboxymaltose to stabilized post-acute heart failure patients with iron deficiency improved quality of life vs. placebo-treated patients within four weeks, which persisted during subsequent therapy for up to 24 weeks.

SOURCE: Jankowska EA, Kirwan BA, Kosiborod M, et al. The effect of intravenous ferric carboxymaltose on health-related quality of life in iron-deficient patients with acute heart failure: The results of the AFFIRM-AHF study. *Eur Heart J* 2021;42:3011-3020.

AFFIRM-AHF showed that for patients who were hospitalized with acute heart failure caused by reduced left ventricular ejection fraction (HFrEF) and iron deficiency (ID), treatment with intravenous (IV) ferric carboxymaltose (FCM) was safe and reduced the risk of HF rehospitalizations, but did not reduce cardiovascular death.[1] One of the prespecified secondary outcomes was health quality of life (QOL), which is the subject of the Jankowska et al report.

ID was defined as a serum ferritin lower than 100 ng/mL, or 100 ng/mL to 299 ng/mL if the transferrin saturation was less than 20%. IV FCM was administered just before discharge from a hospitalization for acute HFrEF and at six weeks after discharge, then at 12 and 24 weeks (if necessary). Health QOL was assessed before randomization in the hospital and repeated at weeks 2, 4, 6, 12, 24, 36, and 52. Health QOL was determined by the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12), from which the overall summary score (OSS) and the clinical summary score (CSS) were derived for up to 52 weeks. The 1,108 patients included in the intention to treat analysis were a mean age of 71 years, recorded a mean EF of 33%, and 55% were men. Completion of the KCCQ-12 was 96% at week 2 and 73% at week 52. Most of this decline was because of mortality. KCCQ-12 scores ranged from 0-100, where 100 is the best QOL. The baseline OSS for the FCM group was 38 and 37 for the placebo group; the corresponding CSS were 41 and 40, respectively.

After week 4 post-discharge, FCM patients exhibited significantly greater improvements in OSS and CSS vs. placebo patients. The adjusted mean difference at week 4 was 2.9 (95% CI, 0.5-5.3; $P = 0.018$) for

OSS and 2.8 (95% CI, 0.3-5.3; $P = 0.029$) for CSS. At 24 weeks, the mean difference was 3.0 for OSS (95% CI, 0.3-5.6; $P = 0.028$) and 2.9 for CSS (95% CI, 0.2-5.6; $P = 0.035$). At 52 weeks, the effect had attenuated but still favored FCM patients (OSS mean difference = 1.44; CSS = 0.63). Sensitivity analyses that incorporated mortality and the effect of COVID-19 on QOL showed similar results to the main analysis. The authors concluded that in patients hospitalized for acute HFrEF with ID and treated with IV FCM, clinically meaningful improvements in health QOL were observed as early as four weeks after discharge and lasted up to 24 weeks.

■ COMMENTARY

The AFFIRM-AHF study led to fewer hospitalizations, but showed no effect on mortality. Staying out of the hospital could mean one feels better, but a formal analysis of QOL is preferable. Thus, this analysis of the QOL data in AFFIRM-AHF is of interest. Jankowska et al showed treatment with IV FCM started in the hospital just before discharge and continued intermittently if ID persisted for 24 weeks improved QOL by about three points on the KCCQ-12 score vs. placebo. With a score range of 0-100, a three-point advantage over placebo seems modest at best. However, as the authors argued, this is a relevant change, which correlates with subjective well-being. This is like the changes observed for other pharmacological agents, such as the gliflozins and sacubitril/valsartan, and interventions, such as exercise training. To put this in perspective, the change in KCCQ-12 scores seen with cardiac resynchronization therapy is about 10 points in "good responders" to this device therapy where overall responses are heterogeneous. The KCCQ-12 focuses on symptom frequency, physical and social limitations, and QOL impairments. The KCCQ-23 features better psychometric properties but takes more time to complete, which reduces compliance. Also, the 12-question version correlates well with the 23-question version. The attenuation in effect after 24 weeks is not entirely surprising considering no further FCM was given after 24 weeks by protocol.

ID is associated with a poor prognosis in HFrEF, regardless of the presence of anemia. It is largely underdiagnosed and undertreated. One reason is the diagnosis of ID in HF is problematic. Ferritin levels are affected by inflammatory stress, renal dysfunction, malnutrition, and the catabolic state seen in severe HF. Also, volume shifts during the treatment of HF may increase or decrease ferritin levels. Interestingly, after the treatment of acute HF, ferritin levels tend to rise for six weeks without any therapy, perhaps because of lower plasma volume. Thus, to see changes in QOL at six weeks in the FCM group is remarkable.

Treating frank anemia in HF is known to improve outcomes, especially if the hemoglobin is < 8 g/dL. Why would iron therapy improve outcomes in the absence of frank anemia? Presumably because iron is a key component of muscle energetics. Based on the Jankowska et al study, after hemodynamic stabilization of acute HFrEF, if ID is identified, give FCM before discharge and reassess at six weeks and every three to four months after, with further administration of FCM as indicated. ■

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PHARMACOLOGY UPDATE

Dihydroergotamine Nasal Spray (Trudhesa)

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.

The FDA has approved a new intranasal formulation of dihydroergotamine mesylate (INP104) for the acute treatment of migraine headaches. This formulation uses a proprietary precision olfactory delivery (POD) technology developed by Impel NeuroPharma. Dihydroergotamine mesylate (DHE) has been available as a nasal spray (Migranal) since 1997. INP104 is distributed as Trudhesa.

INDICATIONS

DHE nasal spray can be prescribed to treat migraine in adults with or without aura.[1]

DOSAGE

The recommended dose is 1.45 mg (0.725 mg into each nostril).[1] The dose may be repeated, if needed, a minimum of one hour after the first dose. Do not use more than two doses within a 24-hour period or three

doses within seven days. INP104 is available as four single-dose units (each containing 4 mg of DHE) and one nasal spray device.

POTENTIAL ADVANTAGES

POD delivers DHE to the upper nasal cavity and may prevent or reduce drug dripping out of the nose or into the nasopharynx, thereby improving systemic availability.[2] INP104 showed comparable bioavailability with intravenous DHE and shorter time to reach peak plasma levels and four times higher plasma levels than Migranal.[2]

POTENTIAL DISADVANTAGES

INP104 shares the same contraindications and warning as other DHE formulations (e.g., peripheral ischemia following coadministration with strong CYP3A4 inhibitors, patients with cardiovascular risk factors).

COMMENTS

The efficacy of INP104 is based on the relative bioavailability compared to DHE nasal spray (Migranal) in healthy subjects. INP104 was evaluated in a Phase III, open-label study of subjects with mainly moderate to severe headache pain who self-administered INP104 with self-recognized migraine attacks.[3] INP104 used for 24 weeks (up to 52 weeks) showed acceptable safety and tolerability. Nasal endoscopic examination did not show clinically significant changes in nasal mucosa or olfactory function abnormalities. About two-thirds of subjects self-reported pain relief at two hours after their first dose and close to half experienced pain relief at one hour. For those who were pain free, recurrence was 7.1% and 14.3% at 24 hours and 48 hours, respectively.

CLINICAL IMPLICATIONS

Migraine headache is a common disorder characterized by recurrent attacks.[4] It is more prevalent in women than men (18% to 26% vs. 6% to 9%). When possible, preventive therapy should be considered to reduce the number, severity, and duration of attacks.

For acute treatment, acetaminophen and nonsteroidal anti-inflammatory drugs are considered first-line solutions for mild to moderate attacks. Triptans are considered first-line treatment for moderate to severe attacks and best taken early in an attack. Patients may respond to certain triptans, not others, and some do not respond.

DHE has less receptor specificity than triptans but slower dissociation from the receptors and is considered second-line therapy for moderate to severe migraine attacks. It can be given early or late during an attack. INP104 provides an improved formulation with a better delivery device, enhancing bioavailability. The cost for INP104 is $850 for four units. Migranal is $3,427 for eight units; a generic version is $440 for eight units. ■

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CME QUESTIONS

1. **Investigators found proton-pump inhibitor (PPI) use was associated with a moderately higher risk of community-associated *Clostridioides difficile* infection. How long did the risk remain elevated after PPI treatment ended?**
   a. 36 months
   b. 12 months
   c. 18 months
   d. 24 months

2. **For patients with systolic heart failure and iron deficiency, treatment with ferric carboxymaltose resulted in significant improvements in quality of life by:**
   a. two weeks.
   b. four weeks.
   c. 12 weeks.
   d. 24 weeks.

3. **What antibiotics were implicated as a potential cause of colorectal cancer?**
   a. Penicillins
   b. Cephalosporins
   c. Quinolones
   d. Macrolides

4. **In updated guidelines, vancomycin is preferred over fidaxomicin for initial and recurrent cases of *Clostridioides difficile* infection in adults.**
   a. True
   b. False

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]

Localized Slow Wave Sleep in the Awake but Inattentive Brain

Why Exercise Alone Does Not Result in Fat Loss

Internal Medicine [ALERT]

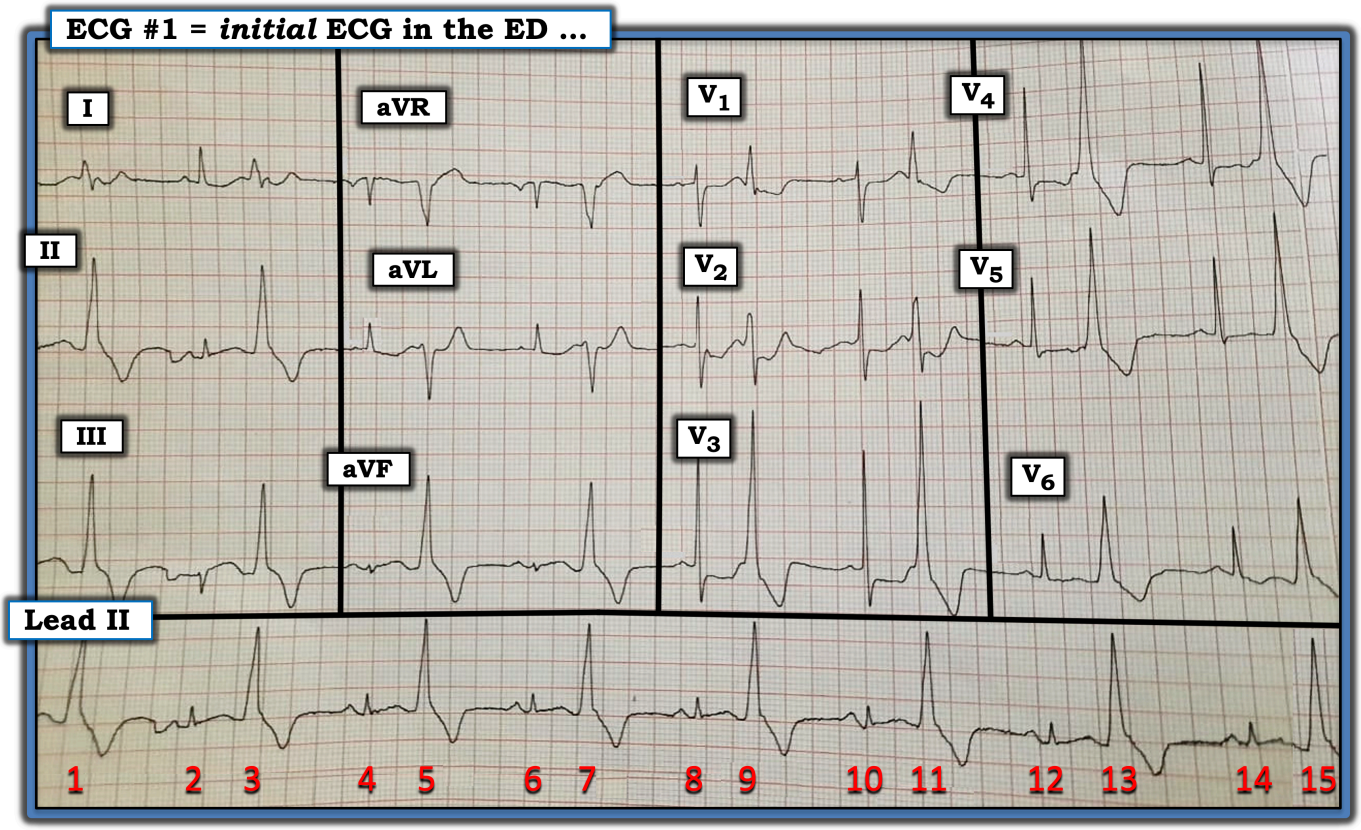
ECG Review

By Ken Grauer, MD

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

In Addition to the Rhythm

The ECG in the figure below was obtained from a middle-aged woman who presented with a febrile illness and shortness of breath. She reported no chest pain. In addition to the rhythm, what else is going on?



The obvious finding in this 12-lead ECG and long lead II rhythm strip is ventricular bigeminy as every other beat is a premature ventricular contraction (PVC). Especially because of the large size of the PVCs, our attention is easily diverted from an even more important finding on this tracing.

Each even numbered beat on this ECG is sinus-conducted. Focusing attention on the ST-segment and T waves for each sinus-conducted beat, note the ST-segment is coved with a straight "take-off" in each inferior lead. There is subtle-but-definite ST elevation in lead III and a lesser degree of ST elevation for the tiny QRS complex in lead aVF. There is reciprocal ST depression in both high-lateral leads (leads I and aVL). There is early transition, with abrupt development of a predominant R wave already by lead V2. The ST-segment is abnormally straightened in each of the six chest leads. Each chest lead manifests some degree of ST depression, which is maximal for sinus-conducted beats 8 and 10 in lead V3.

The rhythm in the figure is ventricular bigeminy. Despite the lack of chest pain, the ECG in the figure suggests this patient has experienced a recent (if not acute) inferior-posterior myocardial infarction. It is estimated that at least one-quarter of all myocardial infarctions are "silent" (i.e., occur in the absence of chest pain). This case provides an example of this that might not have been noticed had it not been for the abnormal cardiac rhythm.

For more information about and further discussion of this case, please visit: https://bit.ly/3cDHmKk.