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Internal Medicine [ALERT]

Vol. 42, Issue 17, September 15, 2020
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ABSTRACT & COMMENTARY

Diet Modification in Older Women with Fecal Incontinence

By Chiara Ghetti, MD

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

SYNOPSIS: Older women with fecal incontinence manage their symptoms with dietary modification.

SOURCE: Andy UU, Ejike N, Khanijow KD, et al. Diet modifications in older women with fecal incontinence: A qualitative study. *Female Pelvic Med Reconstr Surg* 2020;26:239-243.

This was a qualitative study of older women with symptoms of fecal incontinence (FI). Women were included if they were ≥ age 65 years and reported current bothersome FI symptoms occurring at least monthly over the prior three months. FI symptoms were defined as any uncontrolled loss of liquid or solid fecal material. Subjects also were required to be able to adjust their diets. Women who resided in a care facility, and therefore could not adjust their diet, were excluded. Women with bloody diarrhea, diagnosis of colorectal/anal malignancy, or inflammatory bowel disease also were excluded.

The study authors used qualitative research methods. A trained facilitator following a moderator guide conducted the focus groups. During these sessions, they explored the relationship between diet and symptoms, the tactics women use to manage symptoms, and suggestions regarding dissemination of dietary information. The focus groups were audio-recorded and transcribed verbatim. Under the supervision of a qualitative research scientist, two authors independently coded the transcripts. Coding discrepancies were resolved by consensus. Codes were reviewed and grouped in thematic categories. Focus groups were conducted until no new concepts emerged and thematic saturation occurred.

Twenty-four women were enrolled in the study, and 21 participated in one of three focus groups. Participants

Financial Disclosure: *Internal Medicine Alert's* Physician Editor Stephen Brunton, MD, is a retained consultant for Abbott Diabetes, Acadia, AstraZeneca, and Boehringer Ingelheim; and he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, and Novo Nordisk. Peer Reviewer Gerald Roberts, MD; Editor Jonathan Springston; Editor Jason Schneider; Editorial Group Manager Leslie Coplin; and Accreditations Director Amy M. Johnson, MSN, RN, CPN, report no financial relationships relevant to this field of study.

[INSIDE]

Updated LTBI Guidelines page 131
Secondary Stroke Prevention page 132
Preventing Strokes Pharmacologically page 133
Pharmacology Update: Olinvyk page 134

Internal Medicine
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Internal Medicine Alert (ISSN 0195-315X) is published semimonthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Internal Medicine Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

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were an average of 72 years of age (65-86), 38% were African American, and 62% were white. Subjects reported moderate to severe FI symptoms based on frequency of leakage, with one-quarter reporting daily leakage and more than one-third reporting leakage a couple of times per week. Researchers identified four thematic categories:

- **Discovery of a relationship between FI and diet:** Participants reported an awareness that diet contributed to FI symptoms.
- **Dietary triggers for FI**: Participants reported a range of foods that appeared to trigger FI, including caffeine, dairy (cheese and ice cream), meats, fruits, beans, leafy vegetables, juice, and sauces. Fried food preparation triggered FI symptoms. For some, eating a large volume of food, or even consuming any food at all, triggered fecal urgency and subsequent leakage.
- **Modifications and tactics used**: Participants described several modification tactics, including avoiding food triggers, eating less food, using supplemental fiber, modifying food preparation to avoid frying, giving preference to self-prepared meals, and consuming smaller, more frequent meals.
- **Suggestions for dietary modifications for FI management**: Participants described feelings of shame, which deterred them from seeking care, and thought they would benefit from providers directly addressing FI symptoms and diets with them. Participants preferred balancing modifications with the degree of improvement modifications achieved. Sharing successful techniques was important to the participants, and many thought they would benefit from a support group.

■ COMMENTARY

FI, or accidental bowel leakage, is defined as the accidental loss of liquid and/or solid stool.[1] The prevalence of FI is thought to be 7% to 15% in community-dwelling women and higher in care-seeking women.[2] The risk factors for FI include diarrhea, chronic illness, neurological disorders, and sphincter trauma. Modifiable risk factors include smoking and obesity.[2]

The quality of life burden and emotional effect of FI can be devastating. The economic toll of FI also is quite significant. Despite this, women are reluctant to seek help, with less than one-third of affected women seeking care.[3] A study of primary care providers at Midwestern academic centers revealed that although providers screen for urinary incontinence, most do not screen for FI.[4] The women in the Andy et al study expressed a strong desire for their providers to inquire about FI symptoms and discuss treatment options. An electronic study of 6,000 women revealed terminology used for FI screening was important, with 71% of women preferring "accidental bowel leakage" to "fecal incontinence" or "bowel incontinence."[5]

The American College of Gastroenterology lists numerous treatments for FI, which can result in improvement or resolution of symptoms.[6] These treatments include education, dietary changes, medications, and pelvic floor muscle rehabilitation with biofeedback. Women in the Andy et al study identified many helpful dietary modifications or other techniques; however, the authors did not report whether subjects had received prior counseling from providers. Many of the tactics women reported in this study, including avoiding dietary triggers, align with those recommended by the American College of Gastroenterology.[7]

The efficacy of certain techniques may depend on the etiology of FI. Identifying specifics is critical when evaluating a patient with FI. For example, it is important to assess for frequency and timing of leakage as well as the presence of diarrhea and constipation. The Bristol Stool Form Scale (BSFS) is a helpful, validated tool that categorizes stools into seven types. The types range from type 1 (hard lumps) to type 7 (watery diarrhea).[8] The BSFS chart can aid a provider in initiating a more detailed discussion of bowel function. Liquid stool is more difficult to control; thus, it is essential to identify the presence of diarrhea to discriminate the presence of fecal urgency.

Post-cholecystectomy diarrhea is a frequently forgotten cause of diarrhea and severe fecal urgency. Ultimately, it contributes significantly to FI. Post-cholecystectomy diarrhea may affect more than one-third of patients who undergo cholecystectomy.[9] Merely eating after a period of fasting (even a normal overnight fast) can be extremely problematic to a post-cholecystectomy patient.

Fortunately, some dietary modifications and medical treatment can significantly

affect the post-cholecystectomy diarrhea. In particular, patients benefit from eating smaller regular meals and avoiding long periods of fasting. Patients also benefit from consuming fiber regularly and avoiding greasy foods. Cholestyramine also has been associated with improvements in diarrhea and in diarrhea-related FI. The Andy et al study highlights the need for everyone to inquire and start conversations about FI symptoms with our patients and empowers clinicians to discuss simple lifestyle modifications that may be of great benefit to patients. ■

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BRIEF REPORT

2020 Updated LTBI Treatment Guidelines

By Carol A. Kemper, MD, FACP

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

SOURCE: Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep* 2020;69:1-11.

I explain to patients the risk of progression of their latent tuberculosis infection (LTBI) to active tuberculosis (TB) is about one in 13 people. As one ages, develops diabetes or kidney disease, or needs chemotherapy for any reason, that risk goes up to one in five. This usually grabs the patient's attention. It is especially effective if a clinician tells a patient he or she may be contagious and infect their kids or coworkers. Somehow, if a clinician says the risk is 5% to 10%, it does not sound as bad. Maybe patients do not understand percentages. What they really may not understand is that despite all the modern care, the risk of mortality from active TB in the United States is a surprising 4%, worse than that of COVID-19.

In the United States, 80% of active TB cases are because of progression of untreated LTBI. At least 70% of active TB cases occur in foreign-born persons, many of whom do not want to believe they have been exposed to TB or understand the concept of latent TB. Capturing those individuals and treating them is important for controlling this infection. The last official LTBI treatment guidelines were written in 2000. Since then, a nine-month course of isoniazid (INH) has been considered the standard of care for the treatment of LTBI, and was the comparator regimen for all others. New guidelines, published in February 2020, escaped most physicians' notice, arriving just as COVID-19 cases exploded. A committee formed by the Centers for Disease Control and Prevention (CDC) and the National Tuberculosis Controllers Association reviewed all available publications and treatment data, focusing on 63 publications with meaningful data on LTBI treatment. They systematically graded the outcomes, including the benefits, hepatotoxicity, adverse effects, patient preference, regimen complexity, and cost, as well as the quality of the published data.

The committee recommended three rifamycin-based regimens and two alternate six- or nine-month INH monotherapy regimens for LTBI treatment. They gave priority to shorter-course regimens with similar efficacy, higher rates of completion, and favorable tolerability compared with the former standard nine-month regimen of INH. Benefits and disadvantages presented are relative to this previous standard:

• **Three months of INH and rifapentine**. Strongly recommended for adults and children > 2 years of age, including HIV-positive persons. Benefits: Equivalent

effectiveness, less hepatotoxicity, shorter course, higher rates of completion when administered through directly observed therapy (DOT). Disadvantages: More adverse effects, higher cost, greater regimen complexity and higher pill burden, and lower rates of completion when not conducted through DOT.

• **Four months of rifampin**. Strongly recommended for HIV-negative adults and children of all ages. Benefits: Similar effectiveness, less hepatotoxicity, fewer adverse effects, shorter course. Disadvantages: Numerous drug interactions, difficult to give in HIV infection, medication costs are higher (although offset by shorter course/fewer visits, may be more cost-effective on the whole).[1]

• **Three months of daily INH and rifampin**. Conditionally recommended for adults and children of all ages, including HIV-positive persons when their regimen allows. Benefits: Similar effectiveness, lower risk of hepatotoxicity, and shorter course. Disadvantages: Higher rate of discontinuation for other adverse effects, risk for hepatotoxicity may be greater when both drugs given together, and numerous drug-drug interactions.

• **Six months of INH**. Strongly recommended for HIV-negative adults and children of all ages. Conditionally recommended for HIV-positive adults and children. Benefits: Highly effective, but perhaps not quite as effective as nine or 12 months of INH (controlled data are lacking), inexpensive, shorter than nine months of INH. Disadvantages: Hepatotoxicity, longer treatment duration than the other proposed regimens, lower completion rates.

• **Nine months of INH**. Conditionally recommended for adults and children of all ages, regardless of HIV status. Benefits: Highly effective, inexpensive. Disadvantages: Hepatotoxicity, longer treatment duration, lower completion rates.

These guidelines are for patients with LTBI presumed sensitive to therapy. Recommendations for treatment of exposure to drug-resistant strains of TB were published separately in 2019. However, the risk of INH resistance among those with culture-positive TB with no history of TB who were born in the United States is 5%. Among those who are foreign-born, it is 13%. INH resistance is highest in those born in Vietnam (18%), the Philippines (17%), and India (11%). Approximately 3% of all culture-positive TB cases in Santa Clara County were resistant to rifampin. Perhaps this is another reason to consider a rifamycin-based regimen. ■

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BRIEF REPORT

Cilostazol Appears Effective for Long-Term Secondary Stroke Prevention

By Matthew E. Fink, MD

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

SOURCE: McHutchison C, Blair GW, Appleton JP, et al. Cilostazol for secondary prevention of stroke and cognitive decline: Systematic review and meta-analysis. *Stroke* 2020; July 10. doi: 10.1161/STROKEAHA.120.029454. [Online ahead of print].

Cilostazol is a phosphodiesterase 3 inhibitor widely used in Asia for secondary stroke prevention but approved for use in North America only for symptomatic peripheral vascular disease. In animal studies, it demonstrated weak antiplatelet efficacy, but it stabilizes the endothelium and appears to aid myelin repair. Researchers have theorized cilostazol might be beneficial in preventing the progression of small vessel disease in the brain and, therefore, may produce a secondary effect in preventing vascular dementia. McHutchison et al conducted a systematic review and meta-analysis of randomized, controlled trials of cilostazol to prevent stroke, cognitive decline, or small vessel disease progression in studies published between Jan. 1, 2019, and July 16, 2019. They pooled the data for analysis. They calculated odds ratios (ORs) and 95% confidence intervals (CIs) for recurrent ischemic stroke, hemorrhagic stroke, death, and adverse symptoms. They identified 20 randomized, controlled trials, which included 10,505 patients (18 studies of ischemic stroke and two of cognitive impairment). In a pooled analysis, researchers found that cilostazol

decreased recurrent ischemic stroke (OR, 0.68; $P < 0.0001$), hemorrhagic stroke (OR, 0.43; $P = 0.0001$), deaths (OR, 0.64; $P < 0.0009$), and systemic bleeding (OR, 0.73; $P = 0.04$). However, they noted an increased incidence of headache and palpitations when compared to placebo, aspirin, or clopidogrel.

Cilostazol appeared to be more beneficial when given long term vs. short term (longer than six months) and did not increase the frequency of hemorrhages. The data were insufficient to assess its effects on cognition, imaging, or functional outcomes.

Most studies were performed in Asia-Pacific countries. More trials in Western countries should be initiated to assess the effects of cilostazol treatment on cognitive decline and functional outcomes, as well as on the progression of small vessel disease in the brain. The studies from Asia suggest it is a promising treatment, but it has not been studied sufficiently in clinical trials. ■

BRIEF REPORT

Preventing Recurrent Stroke or Death After Ischemic Stroke, TIAs

By Matthew E. Fink, MD

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

SOURCE: Johnston SC, Amarenco P, Denison H, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med* 2020;383:207-217.

Ticagrelor is a direct-acting antiplatelet agent not dependent on metabolic activation that reversibly binds and inhibits the P2Y receptor on platelets. The Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death (THALES) study was designed to test the hypothesis that 30-day treatment with ticagrelor and aspirin would be superior to aspirin alone in reducing the risk of subsequent stroke or death in patients who experienced a non-cardioembolic ischemic stroke or transient ischemic attack (TIA).

This was a randomized, placebo-controlled, double-blind trial that included patients who had experienced mild to moderate ischemic stroke (National Institutes of Health stroke scale score of 5 or lower) or a TIA who were not undergoing thrombolysis or thrombectomy. Within 24 hours, the patients were assigned to receive a 30-day regimen of either ticagrelor plus aspirin or matching placebo plus aspirin. The primary outcome was a composite of recurrent stroke or death within 30 days. Secondary outcomes were the first subsequent ischemic stroke and the incidence of disability within 30 days. The primary safety outcome was severe bleeding.

A total of 11,016 patients were randomized. The primary outcome event occurred in 5.5% of the ticagrelor-aspirin group and in 6.6% in the aspirin-alone group (hazard ratio [HR], 0.83; $P = 0.02$). Ischemic stroke occurred in 5% of the ticagrelor-aspirin group and 6.3% in the aspirin-alone group (HR, 0.79; $P = 0.004$). Disability did not differ between the two groups. Severe bleeding occurred in 28 patients in the ticagrelor-aspirin group and in seven patients in the aspirin group.

Johnston et al concluded the combination of ticagrelor and aspirin compared to aspirin alone was superior in reducing the risk of stroke or death within 30 days of an acute ischemic stroke or TIA. However, disability did not differ between the groups. Severe bleeding was more common in the ticagrelor group. ■

PHARMACOLOGY UPDATE

Oliceridine Injection (Olinvyk)

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 Food and Drug Administration (FDA) has approved a novel opioid agonist for pain management. Oliceridine is a mu-opioid receptor (MOR) agonist similar to morphine. It is classified as a G-protein-biased ligand, possibly providing analgesic benefit while limiting adverse effects. It is given intravenously in a hospital or other controlled setting. The FDA initially rejected the drug in 2018 over safety concerns. The agency reconsidered and approved it in August 2020. Oliceridine is distributed as Olinvyk.

INDICATIONS

Oliceridine should be prescribed to adults to manage acute pain severe enough to require intravenous opioid analgesic and for whom alternative treatment has not worked.[1]

DOSAGE

The initial recommended dose is 1.5 mg.[1] For patient-controlled analgesia (PCA), the recommended dose is 0.35 mg with a six-minute lock-out. A demand dose of 0.5 mg may be considered. A supplemental dose of 0.75 mg can be given one hour after the initial dose and hourly thereafter, as needed. The cumulative daily dose should not exceed 27 mg. The lowest effective dose and shortest duration should be used and individualized based on pain severity, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse.[1] Oliceridine is available as 1 mg/mL and 2 mg/2 mL single-dose vials and 30 mg/30 mL patient-single-use vials for PCA.

POTENTIAL ADVANTAGES

Oliceridine provides an alternative to opioids for managing moderate to severe pain. It may carry a slightly more favorable risk-benefit ratio because of difference in MOR binding/activation selectivity.[2,3]

POTENTIAL DISADVANTAGES

Oliceridine is available in injectable form only. It shares the same warning as opioids, such as addiction, abuse, misuse, respiratory depression, neonatal opioid withdrawal syndrome, and interaction with benzodiazepine and other central nervous system depressants.[1]

COMMENTS

Biased agonism is the ability of a molecule to activate different signaling pathways when binding to a receptor, in this case MOR.[2,3] Analgesic effects and adverse effects are believed to be caused by activation of different signaling pathways (i.e., G-protein and beta-arrestin-2). Oliceridine shows preferential selectivity for the G-protein pathway in animal models.[2] Conventional opioids are nonselective.

The approval of oliceridine was based on two randomized, placebo- and active-controlled, Phase III studies for moderate to severe pain following orthopedic surgery (bunionectomy; n = 389 in study 1) and plastic surgery (abdominoplasty; n = 401 in study 2).[1,4,5] Most participants were women (85% in study 1 and 100% in study 2). In each study, subjects were randomized to oliceridine (1.5 mg loading followed by a demand dose of 0.1 mg, 0.35 mg, or 0.5 mg), morphine (4 mg loading dose, demand dose 1 mg), or volume-matched placebo. A lockout interval of six minutes was used for all PCA regimens. Clinician-administered supplemental doses of 0.75 mg oliceridine, 2 mg morphine, or volume-matched placebo were permitted. Rescue medication was administered as needed (etodolac 200 mg every six hours).

The primary efficacy endpoint was sum of pain intensity difference (SPID) from baseline at 48 hours (bunionectomy; SPID-48) or 24 hours (abdominoplasty; SPID-24). Responders were defined as: ≥ 30% SPID improvement, no rescue medicine, no early discontinuation, or did not reach protocol-specified dosing limit.

In study 1, FDA-approved dose of oliceridine (0.35 mg and 0.5 mg) and morphine were significantly more effective than placebo. Morphine was numerically (but not statistically) better. Response rates were 62%, 65.8%, and 71%, respectively, and 15.2% for placebo.[4] Results were similar for study 2, with response rates of 76.3%, 70.0%, and 78.3%, respectively, vs. 45.7% for placebo.

Overall, the adverse reaction profiles were similar between oliceridine and morphine. There were some subtle differences. The odds ratio for rescue antiemetic use was significantly smaller with oliceridine vs. morphine in study 1 and numerically smaller in study 2.[4,5] The percentage of patients who required oxygen

supplementation was numerically lower in the oliceridine groups but did not reach statistical significance.[4,5]

In a Phase III, open-label study, 768 subjects (91% completion rate) with moderate to severe acute pain from mainly surgical procedures (orthopedic, colorectal, and gynecological) were evaluated for safety and effectiveness. Thirty-two percent of subjects were ≥ age 65 years, and 46% recorded a body mass index ≥ 30 kg/m^2.[6] Oliceridine appears to be generally well-tolerated and effective. Adverse reactions generally were mild (37%) or moderate (25%), with 2.2% discontinuing early because of adverse events. Nausea was the most common adverse reaction (31%). Changes in pain scores were reported within 30 minutes after the first dose. Discontinuation because of a lack of effectiveness was 4.3%.

CLINICAL IMPLICATIONS

Oliceridine is a novel MOR ligand. Although the preferential selectivity was therapeutically enticing, oliceridine does not appear to translate into any clear clinical advantage relative to improving the therapeutic index or widening the therapeutic window. Oliceridine should be reserved for patients when alternative options are not adequate or not tolerated. Drug Enforcement Agency scheduling is pending. Cost was unavailable at the time of this review. ■

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CME QUESTIONS

1. **Older women with fecal incontinence (FI):**
   a. do not find a relationship between diet and symptoms.
   b. report employing few dietary modifications.
   c. desire that their physician be more proactive in addressing FI symptoms.
   d. do not associate their FI symptoms with specific foods.

2. **Cilostazol is an antiplatelet agent that appears to be at least as effective as aspirin for secondary stroke prevention.**
   a. True
   b. False

3. **After acute ischemic stroke, the combination of ticagrelor and aspirin is more effective and safer for secondary stroke prevention than taking aspirin alone.**
   a. True
   b. False

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

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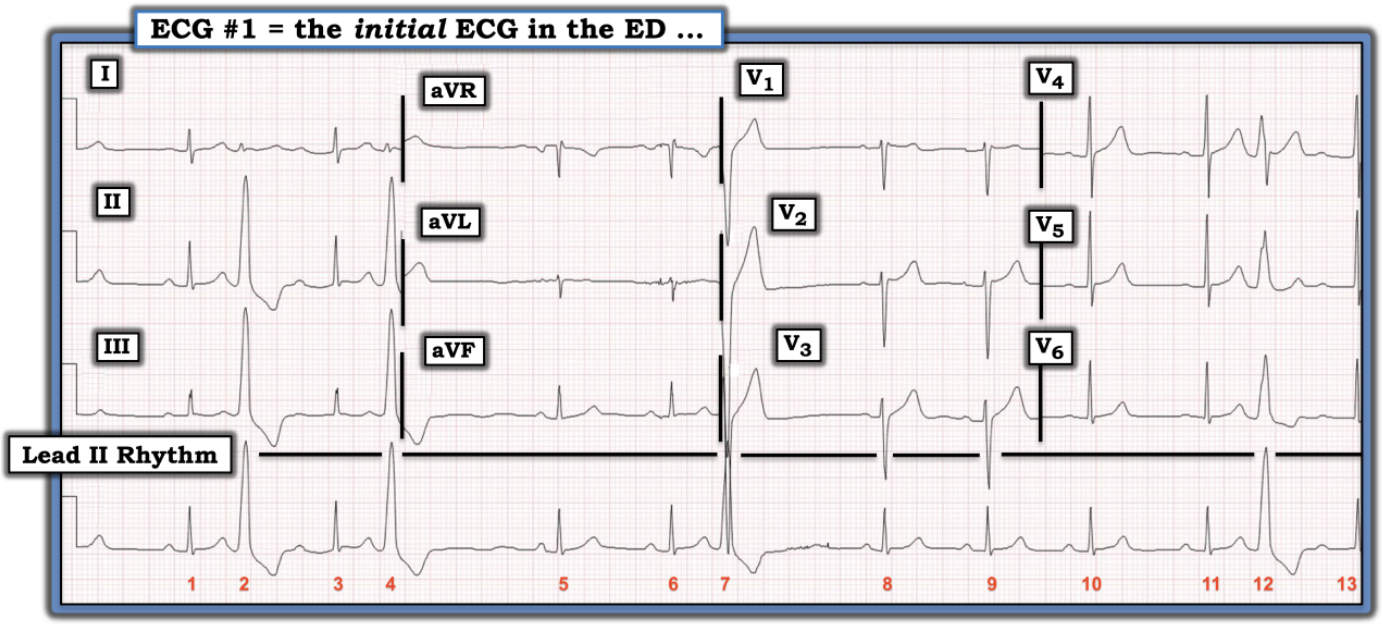
Dr. Grauer reports no financial relationships relevant to this field of study.

What Kind of AV Block?

The ECG in the figure below was obtained from a young adult who presented to the emergency department with dizziness, a near syncopal episode, and chest discomfort. Does this ECG suggest AV block is the cause of his symptoms?



The rhythm in the long lead II at the bottom of the tracing shows an underlying sinus mechanism, with variation in the P-P interval consistent with sinus arrhythmia. There are four premature ventricular contractions (PVCs). The PR interval does not remain constant throughout the tracing. Instead, the PR interval appears to be shorter before beats 5 and 8, and longer before beats 3 and 13. Considering the short pauses following beats 4 and 7, the obvious concern in this patient with near syncope is the rhythm might represent second-degree AV block of the Mobitz I type.

There is no AV block on this tracing. Beats 4 and 7 are PVCs that are followed by a compensatory pause. It is extremely likely that an on-time sinus P wave is hidden within the ST-T wave of beats 4 and 7. Retrograde conduction from these PVCs prevents conduction of these hidden P waves to the ventricles. This results in the brief pause after these PVCs.

Beats 2 and 12 also are PVCs, but they are "interpolated" PVCs, because they are sandwiched between two sinus-conducted beats without a compensatory pause. Because the P waves after these PVCs occur a little bit later in the cardiac cycle, forward conduction to the ventricles is possible, albeit with slight delay. This phenomenon is known as "concealed conduction" since prolongation of the PR interval preceding beats 3 and 13 can be explained only by postulating events not seen on the actual ECG. The point to emphasize is prolongation of the PR interval of the P wave following an interpolated PVC is common, and it is not the result of AV block

Note the PR interval preceding beats 9, 10, and 11 remains the same. This supports our presumption that we are not dealing with Mobitz I second-degree AV block. I suspect the reason for the slightly shorter PR interval preceding beats 5 and 8 is the result of either junctional escape or ectopic atrial escape beats, but not AV block.

Finally, there are no acute ST-T wave changes on this ECG. Therefore, this patient has underlying sinus arrhythmia with frequent uniform PVCs, but no clear evidence for AV block, and no reason forthcoming from this ECG to explain his symptoms of dizziness, near syncope, and chest discomfort.

For more information about and further discussion on this case, please visit: https://bit.ly/30KJIl5.