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Vol. 41, Issue 9, May 15, 2019
ReliasMedia.com

ABSTRACT & COMMENTARY

Not Just Bulk: Dietary Fiber Crucial to Good Health

By Joseph E. Scherger, MD, MPH

Core Faculty, Eisenhower Health Family Medicine Residency Program, Eisenhower Health Center, La Quinta, CA; Clinical Professor, Keck School of Medicine, University of Southern California, Los Angeles

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

SYNOPSIS: Dietary fiber is crucial to maintaining a healthy gut microbiome. The microbiome helps determine our mental and physical health in ways that continue to be discovered.

SOURCE: O'Grady J, et al. Review article: Dietary fibre in the era of microbiome science. *Aliment Pharmacol Ther* 2019;49:506-515.

Advancing science tells us the microbiome is crucial for human health, both in body and mind. Denis Burkitt, an Irish physician and surgeon (1911-1993), famously said, "If you pass small stools you have to have large hospitals."[1] Until recently, this expression was considered facetious; now, it seems prescient.

Traditionally, dietary fiber has been divided into soluble and insoluble. O'Grady et al reviewed the literature on the interplay of dietary fiber with the human microbiome and resultant metabolic effects. They described three more appropriate biologic effects of fiber: solubility, viscosity, and fermentation. Solubility refers to whether the fiber dissolves in water. Viscosity refers to the consistency of fiber and its effects on digestion, absorption, and satiety. For example, the common fiber supplement psyllium delays the degradation and absorption of nutrients and can reduce total glucose and cholesterol absorption by up to 12%.[2] Fermentation of fiber by the gut microbiota yields short-chain fatty acids that provide energy and exert an immunoregulatory and gut-brain signaling role.[3]

O'Grady et al listed the following dietary fiber subtypes, their sources, and their metabolic effects: cellulose, hemicellulose, lignin, gums, pectin, beta-glucan, inulin, psyllium, oligosaccharides, and resistant starch. All fiber subtypes come from plants.

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

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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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The metabolic effects include increasing stool bulk; stimulating peristalsis; lowering glucose, cholesterol, and triglyceride levels; slowing digestion and absorption; and providing the benefits of fermentation by the microbiota.

Current recommendations from the Academy of Nutrition and Dietetics (formerly known as the American Dietetic Association) call for 14 g of fiber for every 1,000 kcal consumed, or about 25 g for women and 38 g for men daily.[4] Current fiber consumption in the United States is estimated at only 12-18 g/day.[5] Ancestral humans consumed an estimated 100 g of fiber per day.[6] No wonder Burkitt referred to the United States as a "constipated nation."[1]

■ COMMENTARY

The evolutionary biologist Daniel Lieberman considers modern man in an industrialized culture in a state of disevolution.[7] Only recently have we begun to understand the health costs associated with consuming highly processed foods. The good news is that natural plant foods are available to everyone in the United States and elsewhere in supermarkets. Eating an adequate amount of fiber requires education and choices. The gut microbiome plays a major role in determining our mood and physical health. The benefits of a healthy microbiome go far beyond lowering the rate of colon cancer. Primary care physicians should play a leading role in advising patients to eat a diverse number of plants with healthy fiber, also referred to as prebiotics. ■

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ABSTRACT & COMMENTARY

When to Screen for and Treat Asymptomatic Bacteriuria

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: New guideline recommendations indicate that the only unequivocal indications for screening and treatment of asymptomatic bacteriuria are pregnancy and undergoing endoscopic urologic procedures associated with mucosal injury.

SOURCE: Nicolle LE, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2019; March 21. doi: 10.1093/cid/ciy1121. [Epub ahead of print].

The Infectious Diseases Society of America has published its recommendations, which are few in number, regarding the indications for screening and treatment of asymptomatic bacteriuria. Groups to screen and treat are:

- Pregnant patients;
- Patients undergoing endoscopic urologic procedures with associated mucosal trauma; target antimicrobial therapy with

administration of only one to two doses with initiation 30 to 60 minutes prior to the procedure.

Groups for whom screening and treating asymptomatic bacteriuria is *not* recommended include:
- Infants and children;
- Healthy premenopausal and postmenopausal nonpregnant women;
- Functionally impaired older women and men residing in the community or long-term care facilities;
- Diabetic patients;
- Patients who received renal transplants more than one month previously;
- Recipients of non-renal solid organ transplants;
- Patients with impaired voiding resulting from spinal cord injury (considering that symptoms may be atypical, such as due to autonomic dysfunction);
- Patients with short- or long-term bladder catheterization;
- Patients undergoing non-urologic surgery;
- Patients undergoing placement of an artificial urinary sphincter or penile implant or living with such a device; patients undergoing this surgery should receive standard operative antibiotic prophylaxis.

The guideline authors were unable to provide a recommendation for the following because of inadequate evidence:
- Patients with high-risk neutropenia (absolute neutrophil count < 100 cells/mm^3 with anticipated duration ≥ 7 days);
- Patients undergoing removal of a bladder catheter.

Older patients with functional and/or cognitive impairment (with or without a fall) who have known bacteriuria but without local urinary symptoms or systemic signs of infection but with acute mental status change should undergo evaluation for other causes of their symptoms rather than antibiotic administration. For patients who present with sepsis syndrome and no localizing source, broad-spectrum antimicrobial therapy directed at both urinary and non-urinary pathogens is indicated.

■ COMMENTARY

The prevalence of asymptomatic bacteriuria is approximately 1% in school-age girls, almost 5% in sexually active premenopausal women (in whom it is often transient) and in pregnancy, and > 20% in community-dwelling women > 80 years of age. It is rarely present in healthy males, but occurs at elevated frequency in elderly community-dwelling men. In general, antibiotic treatment of asymptomatic bacteriuria is contraindicated because the personal and societal risks of this approach are real and the benefit is nonexistent. The authors of a recent study of 68,265 veterans concluded that "receipt of antimicrobial therapy with activity against asymptomatic bacteria organisms identified in preoperative cultures was not associated with reductions in the risk for postoperative infections, including urinary tract infections and surgical site infections."[1] In a 2018 systematic review and meta-analysis, the authors found no benefit from screening and treatment of asymptomatic bacteriuria in patients undergoing joint arthroplasty.[2]

Prevention of inappropriate screening and treatment of asymptomatic bacteriuria is an important antimicrobial stewardship activity and, frequently, a frustrating one. Adherence to this guideline will be associated with decreased occurrence of adverse reactions to unnecessarily administered antibiotics, the decreased occurrence of *Clostridioides difficile* infection, and reduced selective pressure that leads to antimicrobial resistance. However, altering clinician behavior in this domain often is difficult and frustrating — but increasingly important. ■

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ROUNDS WITH RELIAS

ABSTRACT & COMMENTARY

REM Behavior Disorder, Dementia, and Parkinson's Disease

By Daniel A. Barone, MD, FAASM

Assistant Professor of Neurology, Weill Cornell Medical College, Center for Sleep Medicine

Dr. Barone reports he is on the speakers bureau for Jazz Pharmaceuticals and is a consultant for Molecule Mattress.

SYNOPSIS: In this well-designed prospective cohort study of patients with REM behavior disorder, the investigators reported that 73.5% of patients developed a neurodegenerative disorder after a 12-year follow-up.

SOURCE: Postuma RB, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: A multicentre study. *Brain* 2019;142:744-759.

Idiopathic REM sleep behavior disorder (iRBD) is a well-known early sign of the alpha-synucleinopathies, which include Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). It is characterized by active (sometimes violent) movements during REM sleep and is interpreted as "acting out dreams." As such, the presence of iRBD allows researchers to observe prodromal neurodegenerative states and potentially intervene when neuroprotection becomes available. Postuma et al sought to assess the neurodegenerative disease risk and the predictors of neurodegeneration in a multicenter cohort of patients with iRBD. They included prospective follow-up data from 24 centers of the International RBD Study Group.

In total, 1,280 patients were recruited following a diagnosis of polysomnographically confirmed iRBD without parkinsonism or dementia. The average age was 66.3 ± 8.4 years, and 82.5% of participants were male. Patients underwent motor, cognitive, autonomic, and sensory testing, and were followed prospectively for an average of 4.6 years (range one to 19 years), during which time their risk of dementia and parkinsonism was assessed using a Kaplan-Meier analysis. The authors used Cox proportional hazards analysis to predict phenoconversion and a time-to-event analysis to calculate sample size estimates for disease-modifying trials.

The authors reported a conversion rate from iRBD to a neurodegenerative disorder to be 6.3% per year, with 73.5% converting after 12-year follow-up. Abnormal quantitative motor testing significantly increased the phenoconversion rate (hazard ratio [HR], 3.16), as did objective motor examination (HR, 3.03), olfactory deficit (HR, 2.62), mild cognitive impairment (HR, 1.91-2.37), erectile dysfunction (HR, 2.13), motor symptoms (HR, 2.11), an abnormal DaTscan (HR, 1.98), color vision abnormalities (HR, 1.69), constipation (HR, 1.67), REM atonia loss (HR, 1.54), and age (HR, 1.54). By contrast, the authors did not see significant predictive value of sex, daytime somnolence, insomnia, restless legs syndrome, sleep apnea, urinary dysfunction, orthostatic symptoms, depression, anxiety, or hyperechogenicity on substantia nigra ultrasound. Finally, there was a difference in cognitive variables at baseline between those converting to primary dementia vs. those converting to parkinsonism.

Postuma et al also attempted to determine a sample size estimate for neuroprotective trials. Using phenoconversion as a categorical endpoint, the authors found that sample sizes for a two-year trial with HR = 0.5 ranged from 142 to 366 patients per arm. They pointed out that stratification could decrease sample sizes further. Olfaction and the Movement Disorder Society prodromal criteria appeared to be the two most efficient approaches. It is fortunate that the total sample size for a future neuroprotective trial was discovered to be less than the number of participants who were recruited to this study. Postuma et al confirmed the high phenoconversion rate from iRBD to an alpha-synucleinopathy, and have provided estimates of the potential predictive value of prodromal markers. This information can be used to stratify patients for neuroprotective trials.

■ COMMENTARY

As demonstrated in this large and well-done study, patients with a new diagnosis of iRBD should be examined for existing subtle signs of neurodegenerative disorders. Aside from those studied by Postuma et al, new biomarkers are in development that could further aid risk stratification and perhaps even therapeutic options. For example, Gámez-Valero et al recently reported that glucocerebrosidase gene variants are found in iRBD patients more frequently compared to controls, and this finding is associated with PD and DLB.[1] Similarly, patients with iRBD recently were found to exhibit increased microglial activation in the substantia nigra along with reduced dopaminergic function in the putamen as detected through PET.[2]

Perhaps the most important opportunity for research in the intersection of sleep medicine and neurology is the potential discovery and testing of a neuroprotective strategy to prevent ongoing neurodegeneration in

identified at-risk individuals. The Postuma et al study, along with others, will provide a much better platform for the understanding and treatment for iRBD and for the characterization of its conversion to a more debilitating neurodegenerative disease. To this point, individuals with iRBD are enrolling in the Parkinson's Progression Markers Initiative study,[3] as well as other similar prospective cohorts around the world. ■

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PHARMACOLOGY UPDATE

Romosozumab-aqqg Injection (Evenity)

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.

In April, the FDA approved a first-in-its-class sclerostin inhibitor for the treatment of postmenopausal osteoporosis. Romosozumab is a humanized monoclonal antibody directed at sclerostin, a glycoprotein involved in bone metabolism. Romosozumab is produced using recombinant DNA technology and is distributed as Evenity.

INDICATIONS

Romosozumab is prescribed to treat osteoporosis in postmenopausal women at high risk for fracture.[1] This includes those with a history of osteoporotic fracture or multiple risk factors for fracture or those who have failed or are intolerant to other available osteoporosis therapy.[1]

DOSAGE

The recommended dose is 210 mg (administered as two separate subcutaneous injections, one after the other) once every month for 12 doses.[1] The dose should be administered by a healthcare provider in the abdomen, thigh, or upper arm. Adequate calcium and vitamin D intake during treatment is recommended. Treatment is limited to up to 12 monthly doses as the effect gradually wanes after 12 doses.[2] Romosozumab is available as a prefilled syringe each containing 105 mg/1.17 mL.

POTENTIAL ADVANTAGES

Romosozumab offers a drug with dual actions of increasing bone formation and, to a lesser degree, decreasing bone resorption.[1]

POTENTIAL DISADVANTAGES

Romosozumab may increase the risk of myocardial infarction, stroke, and cardiovascular death.[1] A meta-analysis of major adverse cardiovascular events conducted by the FDA showed a hazard ratio of 1.38 (95% confidence interval, 0.96-1.99; 1.3% vs. 0.9%).[2] Treatment should not be started in patients who had a myocardial infarction or stroke within the preceding year. Osteonecrosis of the jaw and atypical subtrochanteric and diaphyseal femoral fractures have been reported.[1] Hypocalcemia can occur; therefore, correcting hypocalcemia prior to initiating romosozumab and adequately supplementing with calcium and vitamin D are recommended during treatment. Hypersensitivity reactions have been reported. Eighteen percent of subjects developed antibodies to romosozumab; 4.7% of these were neutralizing.[1] Romosozumab targets the canonical Wnt/beta-catenin signaling pathway, which also is involved in hematopoietic and immune cell development.[3] It is unclear whether or how a 12-month treatment with romosozumab affects these pathways.

COMMENTS

Sclerostin inhibits bone formation and enhances bone loss.[4] Inhibition of sclerostin increases bone formation and decreases bone resorption. The efficacy and safety of romosozumab was evaluated in two clinical trials in women with postmenopausal osteoporosis with bone mineral density (BMD) T-score ≤ -2.5 at the total hip or femoral neck.[1,5,6] In Study 1, approximately 18% of subjects had previous vertebral fractures and 22% had previous nonvertebral fractures.[5] Subjects were randomized to romosozumab 210 mg monthly (n = 3,591) or placebo (n = 3,589) for 12 months. In the open-label period, after the treatment period, both groups received subcutaneous denosumab 60 mg every six months for 12 months. Subjects also received supplemental calcium (500 mg to 1,000 mg) and vitamin D (600 IU to 800 IU) daily. The coprimary endpoints were cumulative incidences of new vertebral

fractures at 12 and 24 months. New vertebral fracture rates at month 12 were 0.5% for romosozumab vs. 1.8% for placebo and 0.6% vs. 2.5% at month 24, respectively. These reflect a 73% and 75% relative risk reduction. There were no significant differences in the incidence of nonvertebral fractures. BMD scores were significantly higher compared to placebo at month 12 (difference of 12.7% at lumbar spine, 5.8% at total hip, and 5.2% at femoral neck). After discontinuation of romosozumab, BMD returned to roughly baseline levels within 12 months.[7]

In Study 2, subjects were at a higher risk for fractures (96% with previous vertebral fractures and 38% with nonvertebral fractures).[6] Subjects were randomized to romosozumab (n = 2,046) or alendronate 70 mg every week (n = 2,047) for 12 months. After the double-blind period, all subjects received open-label oral alendronate. The incidence of new vertebral fracture was assessed at month 24. Through month 24, the new vertebral fracture rate was was 4.1% for romosozumab vs. 8% for alendronate (50% relative risk reduction). There was a 19% lower risk of nonvertebral fractures (8.7% vs. 10.6%). Hip fractures were lowered by 38% (2.0% vs. 3.2%). BMD differences at month 12 were 8.7% for lumbar spine, 3.3% for total hip, and 3.2% for femoral neck in favor of romosozumab. Differences were similar at month 24. The authors of a meta-analysis concluded that romosozumab showed a greater reduction of fracture risk and an increase in BMD vs. alendronate and teriparatide.[8] In an open-label, Phase III study, romosozumab was more effective in increasing BMD than teriparatide in postmenopausal women transitioning from an oral bisphosphonate after at least three years of treatment.[9]

CLINICAL IMPLICATIONS

Osteoporosis is a common disorder affecting more than 10 million Americans.[10] In postmenopausal women at high risk for fracture, the Endocrine Society recommends bisphosphonates as initial treatment, with denosumab as an alternative for initial treatment in postmenopausal women at high risk for fractures.[11] Teriparatide and abaloparatide are recommended for those at very high risk for fracture. Romosozumab offers a new treatment option for women with high to very high risk for fractures. Sequential treatment with romosozumab reduced the risk of fracture and produced the greatest BMD increase among currently available treatment at 24 months.[12] Its shortcomings are that treatment is limited to one year and there are potential cardiovascular risks. The FDA requires the drug's manufacturer to conduct postmarketing assessment of cardiovascular safety. The price of romosozumab is $1,825 a month or $21,900 for a full 12-month course. ■

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CME QUESTIONS

1. **Fermentation of dietary fiber by the microbiome results in which of the following?**
   a. Glucose lowering
   b. Cholesterol lowering
   c. Production of small chain fatty acids
   d. Production of omega-3 fatty acids

2. **Based on the new Infectious Diseases Society of America guidelines, which of the following is an indication for screening for and treating asymptomatic bacteriuria?**
   a. Pregnancy
   b. Presence of an indwelling bladder catheter
   c. Diabetes mellitus
   d. Any surgery

3. **REM sleep behavior disorder is characterized by which of the following features?**
   a. Morning sleep paralysis
   b. Active movements during REM sleep
   c. Sleep walking
   d. Obstructive sleep apnea

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]

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Young Acute Myocardial Infarction Patients

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Internal Medicine [ALERT]

ECG Review

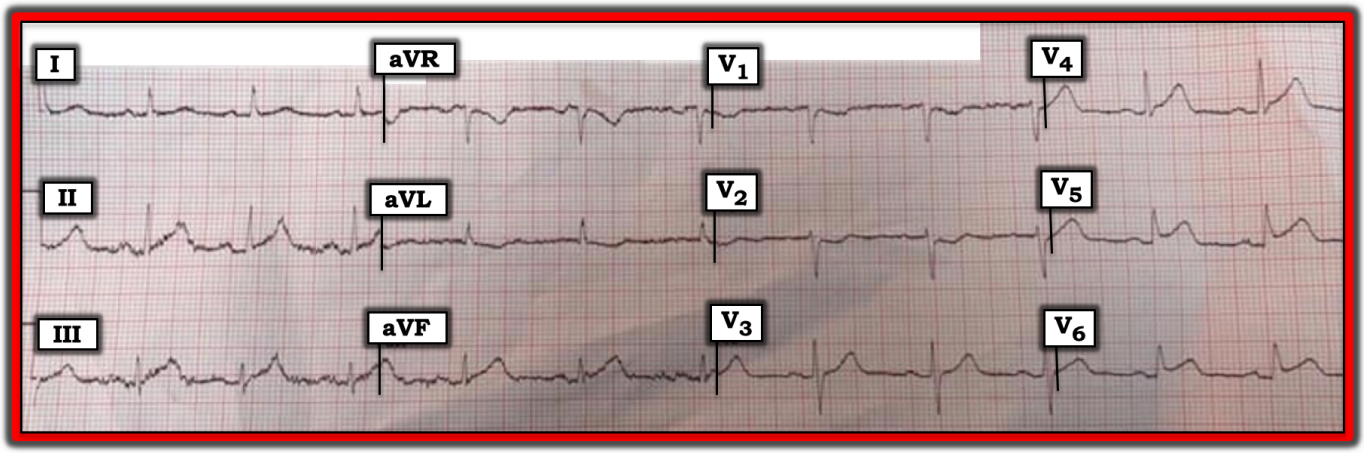
By Ken Grauer, MD

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

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

Can You Predict the Anatomy?

The ECG in the figure below was recorded from an elderly woman with new-onset chest pain. How would one assess this ECG? Is there a "culprit" artery?



Because this ECG was recorded in the ambulance on the way to the hospital, there is significant baseline artifact, which is most notable in the inferior leads. Despite this artifact, it is still possible to interpret this ECG. The rhythm is sinus at a rate between 70 beats/minute and 75 beats/minute. The three intervals (the PR interval, QRS duration, and the QTc) are normal. The frontal plane axis is ~ +40 degrees.

Regarding QRST changes: Q waves are absent; R wave progression in the chest leads is normal, with transition occurring between lead V3 to V4; the lateral chest leads (V4, V5, and V6) manifest 1-2 mm of J-point ST elevation. Although difficult to ascertain because of the artifact, T waves in the three inferior leads (leads II, III, aVF) look larger, wider at their base, and appear to be more peaked than they should be. These are hyperacute T waves. Although subtle, there is some ST-T wave depression in lead aVL and also in leads V1 and V2.

In view of the history of new-onset chest pain in this elderly woman, this ECG strongly suggests acute lateral ST-segment elevation myocardial infarction (STEMI). The ST-T wave depression in leads V1 and V2 makes posterior involvement likely. The hyperacute inferior lead T wave changes suggest inferior wall involvement.

Most acute inferior MIs result from acute occlusion of the right coronary artery (RCA). That said, this patient is much more likely to represent the 10-15% of patients with acute inferior STEMI for whom the "culprit" artery is the left circumflex artery (LCx). This is because the relative amount of ST-segment elevation is higher in the lateral chest leads (V4, V5, and V6) than in the inferior leads. When the RCA is not the dominant vessel, the LCx tends to supply the lateral, posterior, and inferior walls of the left ventricle. This corresponds exactly to the areas of the heart that manifest acute changes in this ECG.

Acute occlusion of the RCA results most commonly in: ST-segment elevation in lead III > lead II; marked reciprocal ST-segment depression in lead aVL that looks like the mirror image of the ST elevation in lead III; ECG evidence that suggests acute RV involvement, such as less ST depression in right-sided lead V1 compared to lead V2 (or even slight ST-segment elevation in lead V1); and not as much ST-segment elevation in lead V6 vs. lead III. None of these features are seen in this case.

Although the relative amount of ST-segment deviation in any given lead in this ECG is modest, it is the composite picture of ST-T wave changes in almost every lead of this ECG that makes the diagnosis of acute LCx occlusion with resultant infero-postero-lateral STEMI in this patient with new-onset chest pain. For optimal treatment, perform cardiac catheterization as soon as possible, with the goal of reperfusion therapy. Repeat ECG within the next half hour should further clarify the clinical picture.

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