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Internal Medicine

Evidence-based summaries of the latest research in internal medicine [ALERT]

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ABSTRACT & COMMENTARY

Screening for Prostate Cancer May Offer Survival Benefits

By David Fiore, MD

Professor of Family Medicine, University of Nevada, Reno

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

SYNOPSIS: Using a mathematical model to account for differences in implementation and baseline screening, researchers reassessed mortality data from two major studies and discovered that screening led to a 25-30% reduction of prostate cancer death in both.

SOURCE: Tsodikov A, Gulati R, Heijnsdijk EAM, et al. Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO trials. *Ann Intern Med* 2017 Sep 5. doi: 10.7326/M16-2586. [Epub ahead of print].

The current recommendation from the U.S. Preventive Services Task Force (USPSTF) cautions against screening for prostate cancer in men (Grade D).[1] This recommendation was based largely on results from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial.[2] The authors of this enormous study found no mortality benefit from prostate cancer screening compared to "usual care." The recommendation immediately caused a firestorm of criticism, as did the PLCO trial itself. Partly because of this criticism and partly because of new information, the USPSTF is in the process of releasing an updated recommendation for prostate cancer screening. The draft recommendation proposes a Grade C designation and notes that physicians should discuss the pros and cons of prostate cancer screening with men 55-69 years of age.[3] After age 70 years, the USPSTF continues to recommend against prostate cancer screening.

As noted, critics blasted the PLCO trial, noting there was significant "contamination" of the control group because many subjects in that group received a prostate-specific antigen (PSA) test prior to or during the study period. In fact, in the editorial accompanying the current study, Vickers stated that approximately 50% of patients in the control arm were subjected to PSA testing before enrollment and 90% were subjected to PSA testing during the study period (others cited much lower

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PSA testing rates).[4] These criticisms have continued in the eight years since the original PLCO data were published. In 2012, Gulati et al published a paper using mathematical models to assess the effect of this contamination. They found that the corrected mortality risk in the screened group would be 0.68-0.77, very similar to the results from the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial.[5]

Tsodikov et al tried to correct for the PSA screening contamination in the PLCO trial, and then compared it directly to the ERSPC results. The authors calculated "mean length time" (MLT) for prostate cancer in the two trials, defining MLTs as "the average time by which diagnosis is advanced by screening relative to the date of diagnosis without screening." Tsodikov et al found similar MLTs for the PLCO and ERSPC study groups of about four years. Using these calculations, the authors then concluded that the PLCO study would have revealed a 25-31% reduction in prostate cancer deaths over 11 years compared to an unscreened population, which is similar to the results from the ERSPC trial.

■ COMMENTARY

This interesting study used some advanced math to attempt to compare the prostate cancer mortality of screened vs. unscreened men in both the PLCO and ERSPC trials. Based on concerns about "screening contamination" of the PLCO trial, Tsodikov et al's findings on the PLCO have generated much more interest. Unfortunately, their calculations and assumptions are difficult to parse. It will take time for the medical and public health community to fully vet these results.

However, given the new USPSTF draft recommendations on prostate cancer screening, it seems the pendulum is swinging toward a more nuanced stance on this challenging issue. This is partly in response to the clarification of the harms and benefits of prostate cancer screening, but also a result of better treatment decisions. No longer are men with prostate cancer reflexively receiving aggressive treatment. As the decision on whether to screen men aged 50-69 years has become more nuanced, so, too, has the decision on whether and how to treat these men. It is hard to argue with the draft recommendations of the USPSTF that "clinicians inform men ages 55-69 years about the potential benefits and harms of PSA-based screening for prostate cancer." ■

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ABSTRACT & COMMENTARY

Do Antibiotics Reduce Hormonal Contraceptive Effectiveness?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a Nexplanon trainer for Merck, and has served as a consultant for Bayer and Pharmanest.

SYNOPSIS: Researchers conducted a systematic review of studies that evaluated the effect of concomitant non-rifamycin antibiotic use on hormonal contraceptive effectiveness. Although data are limited, there was no evidence to support the existence of drug interactions.

SOURCE: Simmons KB, Haddad LB, Nanda K, Curtis KM. Drug interactions between non-rifamycin antibiotics and hormonal contraception: A systematic review. *Am J Obstet Gynecol* 2017; July 8. pii: S0002-9378(17)30845-1. doi: 10.1016/j.ajog.2017.07.003 [Epub ahead of print].

This systematic review evaluating drug interactions between non-rifamycin antibiotics and hormonal contraception was conducted by the CDC's Division of Reproductive Health. The review was conducted in support of the most recent update of the U.S. Medical Eligibility Criteria for Contraceptive Use. The review included randomized and non-randomized studies, and all trials contained a control or comparison group. All studies that included women taking any method of hormonal contraception in combination with an oral, intramuscular, or intravenous non-rifamycin antibiotic were included. Clinical outcomes of interest included pregnancy, evidence of ovulation, antibiotic effectiveness, and adverse health effects (breakthrough bleeding, drug side effects). Pharmacokinetic outcomes also were reviewed. The quality of each study was graded with the U.S. Preventive Services Task Force grading system: good (no important limitations, results internally valid), fair (clear limitations but no fatal flaws), or poor (one or more fatal flaws). Meta-analyses could not be conducted because of the heterogeneity of the exposures and outcomes.

Out of 220 possible articles identified, 29 met criteria for inclusion in the review. Four articles were observational studies of pregnancy rates with any antibiotic use. Two of these were case crossover studies, one was a retrospective cohort, and one was a nested case control; the studies were rated as poor to fair in quality. None of these studies, which mostly examined oral contraceptives, showed any effect of antibiotic use on hormonal contraception failure. Next, the authors assessed the 25 trials that evaluated surrogate measures of contraceptive effectiveness (ovulation) and pharmacokinetic outcomes. Penicillins/cephalosporins, tetracyclines, fluoroquinolones, and macrolides were examined when used with oral contraceptives. No differences in ovulation by serum progesterone or ultrasound were observed with ampicillin, doxycycline, temafloxacin, ofloxacin, ciprofloxacin, clarithromycin, roxithromycin, dirithromycin, or metronidazole. Also, there were no significant decreases in any progestin or ethinyl estradiol level caused by antibiotic use in the pharmacokinetic studies. The authors of the pharmacokinetic study evaluated the contraceptive ring and found no interaction with ampicillin or doxycycline.

■ COMMENTARY

There has been persistent concern that concomitant use of antibiotics with hormonal contraception, especially combined oral contraceptives, could impair efficacy and result in pregnancy.[1] Pharmacists and providers often warn patients of this potential. Most of this concern stems from older case reports without controls or patient and provider surveys. Because the typical use failure rate of combined oral contraceptives is 9%,[2] a case report of unplanned pregnancy while taking antibiotics does not necessarily mean the antibiotics caused the contraceptive failure. Although rifampin and rifabutin are known inducers of the hepatic enzymes required for contraceptive steroid metabolism, other antibiotics are not. The authors of this review undertook to survey the known literature and assess the evidence to support the assertion that non-rifamycin antibiotics cause hormonal contraception failures.

This systematic review has several strengths, including strict inclusion criteria and the evaluation of a range of clinical and pharmacokinetic outcomes. However, any systematic review is limited by the studies available. In this case, most of the literature in this area is subject to several limitations and biases. For the observational studies, most did not record pill compliance and were flawed regarding how exposure to antibiotics was measured, as well as tracking pregnancy rates. Furthermore, the pharmacokinetic studies were limited by small sample sizes, weakness in ovulation measurement accuracy, lack of randomization, and lack of control for confounders. Pharmacokinetic studies also are limited, as they represent only a surrogate measure of potential contraceptive failure and not a true clinical pregnancy outcome. In addition, minimum contraceptive efficacy thresholds are not yet established for ethinyl estradiol and progestins.[3] There were no studies evaluating the contraceptive patch, depot medroxyprogesterone acetate, or the etonogestrel implant. Combined oral contraceptive doses studied included only pills containing 30 or 35 mcg of ethinyl estradiol; therefore, lower-dose pills were not evaluated.

Based on this review, the U.S. Medical Eligibility Criteria for Contraceptive Use provided recommendations for contraceptive use with broad-spectrum antibiotics and other types.[4] Although, in general, there is no evidence that broad-spectrum antibiotics interfere with hormonal contraceptive efficacy, there is always the possibility of individual variations in metabolism that could make a patient vulnerable.[5] Therefore, if a patient truly believes she had an unplanned pregnancy due to concomitant antibiotic use with hormonal contraceptives, it is reasonable to advise her to use condoms for backup if she uses antibiotics in the future. Similar to other drug-contraception interactions, it is unlikely that depot medroxyprogesterone acetate or intrauterine devices are affected, and patients who are concerned could switch to these methods. ■

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BRIEF REPORT

What Is the Ideal Target for Blood Pressure Control?

By Matthew E. Fink, MD

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Dr. Fink reports he is a consultant for Procter & Gamble.

SOURCE: Berlowitz DR, Foy CG, Kazis LE, et al. Effects of intensive blood pressure treatment on patient reported outcomes. *N Engl J Med* 2017;377:733-744.

The Systolic Blood Pressure Intervention Trial (SPRINT; *N Engl J Med* 2015;373:2103) showed that among older adults with hypertension and a high risk of cardiovascular disease, blood pressure treatment that targeted a systolic blood pressure of < 120 mmHg (intensive treatment) led to lower rates of cardiovascular events and death than treatment that targeted a systolic blood pressure of < 140 mmHg (standard treatment). This recommendation was controversial, and there was great concern that adoption of the lower blood pressure target into general clinical practice might be limited by concerns regarding its effect on patient-reported outcomes, such as health status, quality of life, and satisfaction with care. In addition, reductions in cerebral blood flow, especially among older patients who have physical and cognitive impairments, might lead to lightheadedness, confusion, and falls with injury. Therefore, researchers organized a study to address quality-of-life outcomes.

Berlowitz et al randomly assigned 9,361 participants with hypertension to a systolic blood pressure target of < 120 mmHg or a target of < 140 mmHg. Patient-reported outcomes included scores on the Physical Component Summary and Mental Component Summary of the Veterans RAND 12-item Health Survey, as well as a patient health questionnaire, which included items for depression, patient-reported satisfaction with care and blood pressure medications, and adherence to blood pressure medication prescriptions. Patients in the intensive treatment arm received an average of one additional antihypertensive medication. Their median systolic blood pressure was 14.8 mmHg lower than the group that received standard care. There were no significant differences in the scores reported by patients regarding quality of life, depression, or patient-reported satisfaction scores. There were no significant differences regarding physical or cognitive function. Satisfaction with blood pressure care and medications was high in both treatment groups, and there were no significant differences in adherence to blood pressure medication prescriptions. The patient-reported outcomes in those who received intensive treatment with a target systolic blood pressure of < 120 mmHg were similar to those who received standard care, supporting the recommendations of SPRINT. ■

PHARMACOLOGY UPDATE

Tisagenlecleucel Suspension (Kymriah)

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

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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 the first cell-based gene therapy for the treatment of acute lymphoblastic leukemia (ALL). This genetically engineered anti-CD19 chimeric antigen receptor (CAR) T-cell therapy is created by reprogramming a patient's own T cells using a lentiviral-vector, resulting in T cells that target leukemia cells that exhibit CD19 on the surface. Tisagenlecleucel is marketed as Kymriah.

INDICATIONS

Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.[1]

DOSAGE

A single-dose unit contains 0.2-5.0 × 10^6 CAR-positive viable T cells per kg of body weight for patients ≤ 50 kg, or 0.1-2.5 × 10^6 CAR-positive T cells for patients > 50 kg.[1] The dose is administered through IV infusion. Premedication with acetaminophen and an H1 antihistamine are recommended. The expanded use of tocilizumab (an anti-interleukin-6 receptor antagonist) has been approved by the FDA to treat CAR T-cell-induced severe or life-threatening cytokine release syndrome (CRS).[2]

POTENTIAL ADVANTAGES

Tisagenlecleucel is the first effective cell-based gene therapy to be approved for ALL. Once administered, it is present in the blood and bone marrow beyond two years.[1] This enhanced persistence may be associated with more durable remission.[3]

POTENTIAL DISADVANTAGES

Serious adverse reactions have been associated with tisagenlecleucel administration, including CRS (79% with 49% grade 3/4), neurological toxicity (e.g., headache, encephalopathy; 65% with 18% grade 3/4), serious infections (59% with 35% grade 3/4), and hypogammaglobulinemia (43%).[1,2] Patients may need to receive immunoglobulin replacement for an indefinite period following treatment.[1] Treated patients may develop secondary malignancies or recurrence of their leukemia.[1] Tisagenlecleucel only targets CD19. It does not target other antigens expressed on B cells, such as CD22 and CD123.[3-5] Patients may relapse with CD19-negative disease. There is a potential for manufacturing failure occurring in up to 9% of cases.

COMMENTS

Tisagenlecleucel is prepared from the patient's peripheral blood mononuclear cells obtained by leukapheresis. A transgene is introduced via a lentivirus vector to express a CD19-directed chimeric antigen receptor and activated with anti-CD3/CD28 antibody-coated beads. CD19 exists on most precursor B-cell ALL tumor cells. The modified T cells feature three components: extracellular antigen-recognition domain, signaling/activation domain (CD3 zeta) to initiate T-cell activation, and a co-stimulatory domain (4-IBB) to enhance the expansion and persistence. The efficacy of tisagenlecleucel was evaluated in a clinical trial of 63 evaluable pediatric and young adults with relapsed or refractory B-cell precursor ALL.[1] The median age was 12 years (range, 3-23 years). Treatment involved lymphodepleting chemotherapy (fludarabine 30 mg/m^2 daily for four days and cyclophosphamide 500 mg/m^2 daily for two days), followed by a single dose of tisagenlecleucel. Efficacy endpoints were complete remission within three months after infusion, the duration of remission, and proportion of subjects with remission and minimal residual disease (MRD) < 0.01% by flow cytometry (MRD-negative). There were two categories of complete remission (CR and CRi). CR was defined as complete remission with < 5% of blast in the bone marrow, no evidence of extramedullary disease, and full recovery of peripheral blood counts without transfusion. CRi was defined as complete remission but with incomplete blood count recovery with or without blood transfusion. With a median follow-up of 4.8 months, 40 subjects achieved CR and 12 achieved CRi. All were MRD-negative. Median onset was 29 days (range 26-31). The median duration of remission has not been reached; therefore, long-term effects (either positive or negative) are unknown.

CLINICAL IMPLICATIONS

ALL is the most common childhood cancer. Approximately 15-20% either do not respond to initial treatment or relapse. Currently, the National Comprehensive Cancer Network lists tisagenlecleucel as a treatment option for relapsed/refractory ALL in those ≤ 25 years of age.[6] For those with Philadelphia chromosome-positive disease, the recommendation is for refractory disease or two or more relapses and failure of two tyrosine kinase inhibitors. For Philadelphia chromosome-negative disease, the recommendation is for refractory disease or after two or more relapses.

The efficacy of tisagenlecleucel is quite robust. For comparison, blinatumomab, a bispecific, T-cell engager that binds to CD19 and CD3 and is approved for both pediatric and adult use, produces CR of 33% in patients < 18 years of age.[7] Tisagenlecleucel is available only through a restricted program under a risk evaluation and mitigation strategy. Hospitals and associated clinics that prescribe/administer this drug must be specially certified and trained to recognize and manage CRS and neurological events.[1] The cost is $475,000 per treatment course. Regulators require researchers to conduct a postmarket observational study involving patients treated with this therapy.[2] ■

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CME QUESTIONS

1. **According the review by Tsodikov et al, based on the results of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial, screening for prostate cancer compared to no screening would:**
   a. not affect prostate cancer deaths.
   b. prevent approximately 25-30% of prostate cancer deaths.
   c. prevent approximately 50-65% of prostate cancer deaths.
   d. would increase overall mortality.

2. **In the systematic review by Simmons et al, articles were graded by which U.S. Preventive Services Task Force system?**
   a. Top-tier, middle-tier, or lower-tier
   b. Level I, II, or III
   c. Good, fair, or poor
   d. Excellent, good, or fair

3. **It is dangerous to lower systolic blood pressure to 120 mmHg when treating hypertension with medications.**
   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]

Irritable Bowel Syndrome, Constipation, and Quality of Life in Women

High Carbohydrate Intake and Mortality

Is a Dabigatran Reversal Agent Effective?

Clinical Briefs

By Louis Kuritzky, MD

Managing Diabetes: First Things First, or Vice Versa

SOURCE: Abdul-Ghani M, DeFronzo RA. Is it time to change the type 2 diabetes treatment paradigm? Yes! GLP-1 RAs should replace metformin in the type 2 diabetes algorithm. *Diabetes Care* 2017;40:1121-1127.

In the absence of contraindications or medication intolerance, metformin has been recommended as the initial treatment choice for patients with type 2 diabetes mellitus (T2DM) for more than a decade. This advice arose from a combination of favorable metformin attributes, including cost, tolerability, safety, and (albeit limited) a relatively favorable cardiovascular profile. But the winds of change are suggesting a potential reconsideration.

Although reduction of microvascular adverse events in T2DM is well-established with "older" antidiabetic agents (e.g., sulfonylureas, metformin, insulin), the authors of this publication argue that our scope of focus for choosing optimum medications should include both efficacy in correcting hyperglycemia as well as the ability of pharmacologic intervention to address the currently recognized basic pathophysiologic defects of T2DM.

Accordingly, glucagon-like peptide-1 (GLP-1) receptor agonists (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide) demonstrate an attractive "better fit." That is, the four cardinal activities of GLP-1 receptor agonists: glucose-dependent insulin secretion, which minimizes the risk of hypoglycemia; glucose-dependent glucagon inhibition, which blocks excess glucagon while maintaining responsiveness of glucagon to hypoglycemia; improved satiety, potentially empowering more effective adherence to healthful dietary restrictions; and delayed gastric emptying, reducing postprandial glucose excursions. These provide complementary activities that address more of the basic pathophysiologic defects of T2DM than most other agents. Finally, members of the class of GLP-1 receptor agonists recently have been shown to reduce cardiovascular events. Together, these attributes suggest GLP-1 receptor agonists might be an appropriate initial treatment for T2DM, supplanting metformin. ■

Considering Routine Preoperative Lab Tests for Elective Surgery

SOURCE: Martin SK, Cifu AS. Routine preoperative laboratory tests for elective surgery. *JAMA* 2017;318:567-568.

Many U.S. clinicians may be unfamiliar with the U.K.'s National Institute for Health and Care Excellence (NICE) agency. Since 1999, NICE has been a world-recognized leader in the development of guidelines for management of disorders such as hypertension, dyslipidemia, and other epidemiologically important topics. Recently, NICE provided recommendations about which laboratory tests (if any) might be considered routinely appropriate preoperatively for elective surgery. The rationale for providing this guidance stems from the observation that, historically, there have been an excessive number of pre-op tests performed that not only provide no benefit for patient outcomes, but actually may cause harm because of unnecessary expense as well as need for follow-up of incidental (usually irrelevant) abnormal findings.

For example, recommendations pertinent to "intermediate surgery" (i.e., inguinal hernia repair, tonsillectomy and adenoidectomy, knee arthroscopy) in essentially healthy individuals are to eliminate preoperative testing entirely. Less healthy individuals, such as those with a severe systemic disease (American Society of Anesthesiologists Grade 3 or Grade 4), should undergo pre-op renal function testing only.

For patients with symptomatic cardiovascular or renal disease, the guidelines call for a complete blood count. Space limitations preclude a comprehensive review of the full contents of this document, which may be accessed readily online.

The authors of the guideline acknowledged a very limited literature from which to draw evidence-based conclusions, and encourage further definitive research on this topic. ■

Measuring Urine Calcium in Nephrolithiasis Patients

SOURCE: Song L, Maalouf NM. 24-hour urine calcium in the evaluation and management of nephrolithiasis. *JAMA* 2017;318:474-475.

Most kidney stones contain calcium, often comprised of calcium oxalate (responsible for up to 80% of cases). Prevention of stone recurrence focuses on dietary interventions, pharmacologic interventions, and hydration. Since stone recurrence is related linearly to the level of calcium in the urine, with no "floor" to this relationship (that is, progressively lower urinary calcium is associated with proportionately lower risk for recurrence), it is valuable to identify the level of urinary calcium excretion in patients with nephrolithiasis and provide interventions to reduce urinary calcium.

Currently, the threshold of urinary calcium defined as "hypercalciuria" is > 300 mg/day in men or > 250 mg/day in women. A more gender-agnostic metric is based on body weight: > 4 mg/kg/day for either gender is considered hypercalciuric. Since studies using so-called "spot urine" measurements have indicated poor correlation with 24-hour specimens, the only accurate way to determine urinary calcium excretion is to perform the 24-hour urine measurement.

High sodium content in the diet increases calcium excretion in the urine, so sodium restriction may be beneficial. Thiazide diuretics reduce urinary calcium excretion and are useful when dietary and hydration steps are insufficient. ■

Internal Medicine [ALERT]

ECG Review

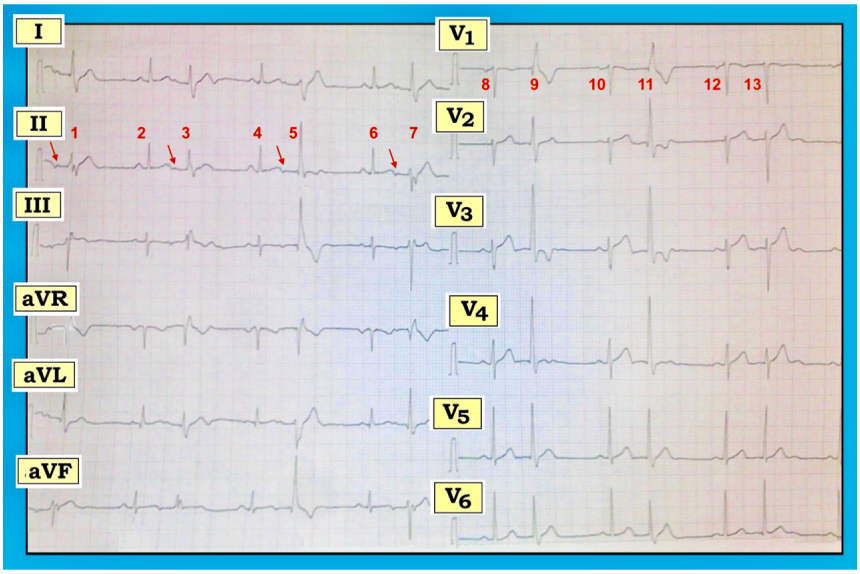
By Ken Grauer, MD

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

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

Aberrant Conduction or Ventricular Bigeminy?

The ECG in the figure below was obtained from an otherwise healthy 20-year-old man when an irregular heartbeat was noted on routine exam. The patient was asymptomatic. How would you interpret this tracing? Are these multifocal (multiform) premature ventricular contractions (PVCs)?



The underlying rhythm is sinus. Virtually every other beat occurs early and looks different, with at least some degree of QRS widening. That said, these wider beats are not PVCs. Instead, the rhythm is atrial bigeminy in that every other beat is a premature atrial contraction (PAC). The reasons why the different-looking beats in this tracing are not PVCs include: Early beats are preceded by premature P waves (red arrows in lead II) and QRS morphology of the early beats is highly characteristic for aberrant conduction.

Aberrant conduction is most likely to take the form of some type of bundle branch block and/or hemiblock pattern. As a result, attention to QRS morphology sometimes may provide invaluable assistance in distinguishing between aberrantly conducted PACs vs. ventricular beats. The interesting feature about this tracing is the changing QRS morphology seen with every other beat. The most common form of aberrant conduction manifests a right bundle branch block (RBBB) pattern. This is because under normal circumstances, the right bundle branch tends to exhibit the longest refractory period, which means that an early-occurring impulse (i.e., a PAC) has the greatest chance to arrive at the AV node at a time when the right bundle branch still is refractory. That said, any form of conduction defect may be seen with aberrant conduction, depending on the relative length of the refractory period for the various conduction fascicles in a given patient. In this case, beats 9 and 11 in lead V1 show typical RBBB aberration. Consistent with this RBBB pattern, beats 9 and 11 demonstrate a wide terminal S wave in simultaneously occurring lateral lead V6. In contrast to beats 9 and 11, there is only minimal aberrant conduction for beat 13.

In the limb leads, the pattern of RBBB aberration is suggested again for alternate beats by the presence of wide terminal S waves in lateral lead I. Additionally, QRS morphology in leads I, II, and III suggests left posterior hemiblock aberration for beat 5, left anterior hemiblock aberration for beat 7, but no hemiblock aberration for beats 1 and 3.

PVCs do not do what we see here. More than the already diagnostic presence of premature P waves preceding each early beat (best seen in the limb leads), changing QRS morphology of every other beat manifesting multiple variations of highly typical conduction defect morphology establishes with 100% certainty that the rhythm is atrial bigeminy with varying forms of aberrant conduction.

For more information about and further discussion of this case, please visit: http://bit.ly/2xdQS11.