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Internal Medicine

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ABSTRACT & COMMENTARY

Does Triple Inhaled Therapy for COPD Decrease Exacerbations Compared to Dual Therapy?

By Tim Drake, PharmD, MBA, BCPS

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

SYNOPSIS: A single dose of inhaled triple therapy improved exacerbations compared to dual therapy in COPD patients.

SOURCE: Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018;378:1671-1680.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for treatment of COPD include inhaled, long-acting beta-agonists (LABA), inhaled, long-acting muscarinic agents (LAMA), inhaled corticosteroids (ICS), and short-acting beta- or muscarinic inhalers (SABA, SAMA).[1] Historically, there have been combination inhalers such as LAMA/LABA or ICS/LABA.[2] The GOLD guidelines call for a stepped approach to treating COPD, starting with LABA or LAMA therapy and progressing to combination therapy. Eventually, if the patient exhibits severe symptoms or multiple exacerbations, clinicians will add an ICS to current therapy, which will necessitate double or triple therapy.[1]

Despite the recommendations, the use of ICS in COPD has remained controversial because of the reduced role of inflammation in COPD.

Lipson et al conducted the InforMing the PAthway of COPD Treatment (IMPACT) trial to compare the efficacy and risks of triple inhaled therapy vs. dual inhaled therapy for high-risk COPD patients. This was a Phase III, randomized, double-blind, parallel-group, intent-to-treat, multicenter study of a triple combination of fluticasone furoate 100 mcg (ICS), umeclidinium 62.5 mcg (LAMA), and vilanterol 25 mcg (LABA) in a single inhaler. This single inhaler combination was compared to the dual combination of fluticasone furoate 100 mcg

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and vilanterol 25 mcg in one inhaler and the dual combination of umeclidinium 62.5 mcg and vilanterol 25 mcg in a single device for 52 weeks. During this time, Lipson et al observed the differences in rates of COPD exacerbations. Secondary outcomes included change in FEV_1 readings, change in the St. George's Respiratory Questionnaire score, time to first exacerbation, time to death from any cause, and all outcomes stratified by an eosinophil count of at least 150 cells per microliter at baseline. The authors recruited patients who were ≥ 40 years of age, presented with COPD symptoms, and demonstrated an FEV_1 reading of < 50% of predicted with a history of at least one moderate or severe exacerbation in the previous year, or an FEV_1 reading between 50% and 80% and at least two moderate exacerbations or one severe exacerbation in the previous year.

A total of 4,151 patients received triple therapy, 4,134 patients received the ICS/LABA combination, and 2,070 patients received the LAMA/LABA combination. Baseline characteristics were similar across the three groups. On entry, 38% of patients already were on triple therapy with a separate ICS, LAMA, and LABA, 29% were on an ICS with LABA, and 8% were using a LAMA/LABA product. The triple therapy group showed a rate of 0.91 severe or moderate exacerbations per year compared with 1.07 in the ICS/LABA group and 1.21 in the LAMA/LABA group. This resulted in an odds ratio of 0.85 (95% confidence interval [CI], 0.80-0.90) for the triple therapy compared to an odds ratio of 0.75 (95% CI, 0.70-0.81) for ICS/LABA. For secondary outcomes, there was an improvement in FEV_1 and the patient questionnaire for the triple therapy group compared to both of the dual-therapy groups. Mortality was lower with the groups that included an ICS. Overall, there was not a significant difference in adverse events. The exception was for pneumonia, which occurred in 8% of patients on triple therapy compared to 7% on ICS/LABA and 6% on LABA/LAMA. This resulted in a hazard ratio of 1.53 (95% CI, 1.22-1.92) in the triple therapy group compared to the LABA/LAMA combination. The authors concluded that triple therapy resulted in fewer moderate-to-severe exacerbations, improved quality of life, and better lung function compared to dual therapy.

■ COMMENTARY

The treatment of COPD is problematic because of the progressive nature of the disease and the fact that no medication or combination of medications has been shown to alter the progression of the disease. Medicare is responsible for most costs associated with the treatment of COPD.[3] Additionally, most inhalers used to treat COPD are brand name only and relatively expensive. This leads to a high cost burden for Medicare Part D members who are likely to enter the "gap" in coverage if only prescribed one inhaler for COPD per month. Out-of-pocket estimates for two-inhaler therapy is around $1,500 per year and triple-inhaler is almost $3,000 per year.[4]

The new triple combination of fluticasone furoate, umeclidinium, and vilanterol combines multiple therapy regimens into one inhaler. Although this inhaler is more expensive than dual inhalers, it is less expensive than using a dual inhaler with another single-entity inhaler. This product also may help with patient compliance with the one-puff, once-daily dosing.

This study also proved that it is more efficacious than dual therapy in more advanced COPD patients. The number needed to treat to prevent one moderate-to-severe exacerbation was 3.33 for the triple therapy group compared to the LAMA/LABA and 6.25 for triple therapy compared to the ICS/LABA group. The number needed to harm for pneumonia was 34 for the triple therapy compared to the LAMA/LABA therapy. Considering the cost of a hospitalization for a COPD exacerbation, the use of the triple therapy product in advanced stages of COPD appears to be safe and cost effective. ■

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ABSTRACT & COMMENTARY

Invasive Procedures and the Risk of Infective Endocarditis

By Jeffrey Zimmet, MD, PhD

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

SYNOPSIS: This large study suggests that several invasive, nondental medical procedures may be triggers for subsequent infective endocarditis, reopening the debate regarding prevention and management.

SOURCE: Janszky I, Gémes K, Ahnve S, et al. Invasive procedures associated with the development of infective endocarditis. *J Am Coll Cardiol* 2018;71:2744-2752.

Infective endocarditis (IE) is a condition that occurs in relatively low absolute numbers, but confers a very high risk for morbidity and mortality. U.S. guidelines for the prevention of IE have focused on bacteremia following dental procedures, with less coverage devoted to gastrointestinal (GI) and genitourinary (GU) tract procedures. It seems likely that the 2007 American Heart Association IE guideline update, along with its European counterpart, was well-received by dentists, because it removed the recommendation for prophylactic antibiotics prior to dental work for all but the highest-risk patients (those with a prosthetic heart valve, with a prior history of IE, for certain patients with complex congenital heart disease, and for cardiac transplant recipients with valvulopathy). Likewise, this update removed the recommendation for the use of antibiotic prophylaxis for procedures involving the GI and GU tracts. Other invasive procedures, including so-called "clean" invasive procedures such as coronary angiography, received no mention.

Much of the change in guidelines was based on the lack of convincing evidence for the efficacy of prophylactic antibiotics for prevention of IE. Clinicians often assume that the risk for endocarditis with medical procedures is negligible as well, but data addressing this point are missing from the debate.

To address this shortfall, Janszky et al analyzed all cases of endocarditis in Sweden over a 14-year period following the 1997 adoption of a standardized classification system for coding of medical procedures. To avoid confounding, the authors used a case-crossover design in which each patient served as his or her own control. For each case, the occurrence of medical procedures in the 12-week period preceding the endocarditis diagnosis was compared with the 12-week period one year earlier.

Over the course of the study period, 7,013 cases of IE in adult patients were identified. Researchers found multiple invasive procedures were associated with an increased risk of endocarditis. Among outpatient procedures, this included not only GI and GU procedures such as colonoscopy (relative risk [RR], 2.89; 95% confidence interval [CI], 1.35-6.17) and cystoscopy (RR, 1.59; 95% CI, 0.98-2.58), but also coronary angiography (RR, 4.75; 95% CI, 1.61-13.96), bone marrow puncture (RR, 4.33), and bronchoscopy (RR, 5.0), as well as transfusion and hemodialysis. The same procedures performed on an inpatient basis appeared to have similar or stronger associations with subsequent endocarditis, with the RR for bronchoscopy, for example, rising to 16. Coronary artery bypass grafting had an especially strong association (RR, 13.8), as well as a conglomeration of other major and minor cardiovascular therapeutic procedures, including aortic surgery and pacemaker insertion (RR, 9.75). Phacoemulsification, a common procedure that would not be expected to lead to transient bacteremia, was not associated with elevated risk. The study included no information about antibiotic prophylaxis, and the authors did not have access to microbiological data on the pathogens involved in endocarditis.

The authors concluded that multiple invasive medical procedures appear to contribute to the subsequent development of IE. They argued for a potential reconsideration of prophylactic antibiotics for certain high-risk patients and procedures.

However, more strongly, the authors contended that this knowledge supports a renewed focus on aseptic technique in procedures, and that increased awareness of the risk following certain procedures could lead to earlier diagnosis and improved outcomes.

■ COMMENTARY

This is the largest study to date linking invasive procedures to an increased risk of endocarditis. The completeness and high reported accuracy of the Swedish National Patient Register add to the strength of the study, and the case-crossover design represents an improvement over traditional case-control studies.

A range of invasive procedures, including but by no means limited to dental procedures, could lead to a transient bacteremia, which is a necessary condition for the formation of an infective vegetation. Transient bacteremia always will be a frequent outcome of certain procedures; cystoscopy and colonoscopy come to mind. However, for others, varying levels of sterile technique can lead to different results. For example, in cardiac catheterization, there is significant variability in sterile technique from institution to institution, with variable use of hats and masks. It is rare that the cath lab is considered a completely sterile environment exactly like the OR. Because of the variable time delay between transient bacteremia and development of clinically evident IE, the inciting procedure may well not be identified as causative on a case-by-case basis. There is room for improved aseptic technique in this procedure, as in others identified in the study, including bone marrow biopsy and basic vascular access for hemodialysis.

The stratified analysis suggested that the risk of invasive inpatient procedures was higher in the latter half of the study period than in the earlier period. Whether this is at all attributable to the newer guidelines restricting prophylactic antibiotics surely will add to the debate. Based on their analysis, the authors estimated that 476 high-risk patients would need to receive prophylactic antibiotics to prevent one case of IE, assuming that prophylaxis was 100% effective. This number was considerably lower for certain high-risk procedures (83 for bronchoscopy, for example). This will add information for future guidelines and, if confirmed, could result in altered prophylaxis recommendations for certain patients and procedures. However, it is more likely that the overall approach will be less about antibiotic prophylaxis and more about improving sterility, where possible, while developing system-based approaches to the management of procedure-related bacteremia. ■

BRIEF REPORT

Worse Than Snake Oil

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

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

SOURCE: Bottichio L, Webb LM, Leos G, et al. Notes from the field: *Salmonella oranienburg* infection linked to consumption of rattlesnake pills — Kansas and Texas, 2017. *MMWR Morb Mortal Wkly Rep* 2018;67:502-503.

Of all *Salmonella* serotypes, *Salmonella oranienburg* is an unusual cause of clinical illness. Occasional infections and small outbreaks have occurred worldwide, and a recent 2016 CDC posting attributed a small outbreak of *S. oranienburg* in three states involving eight individuals to shell eggs from Missouri. National *Salmonella* surveillance data, last published for 2016, indicate that 1.5% of 32,271 clinical *Salmonella* isolates reported from humans were due to *S. oranienburg*. Parallel 2016 data from the National Veterinary Services Laboratory described 5,258 clinical isolates from animals, including reptiles, with none ascribed to *S. oranienburg*.

A bottle of rattlesnake pills seized by the Texas Department of State Health Services during an investigation of *Salmonella* infection yielded *S. oranienburg*. The isolate was forwarded to PulseNet, the national molecular subtyping network, which identified multiple similar isolates by pulsed-field gel electrophoresis (PFGE). These cases included a man in Kansas with a recent *S. oranienburg* infection. During his initial interview, which included various questions about vitamins and supplements, the individual did not report taking rattlesnake pills. On a subsequent interview, he admitted to purchasing such pills in Mexico and took five capsules in the week before getting sick.

Rattlesnake "pills" are basically dehydrated, ground up rattlesnake meat stuffed into gel caps. These may be sold locally in health food stores and are available online. The FDA has not reviewed nor approved this item. A quick search found an advertisement for a bottle of 150 "capsulas vibora de cascabel" for acne for only $24, promising that snake pills "clean out your system and gets rid of built up toxins." Other ads target individuals with cancer and HIV, and soap products made from rattlesnake are purported to be useful for rashes and psoriasis. In December 2017, the CDC issued a health alert warning that rattlesnake meat or pills may be a source for *Salmonella* infection. In addition to *S. oranienburg*, rattlesnake pills and meat have resulted in infection from *S. enterica spp. arizonae*. ■

ABSTRACT & COMMENTARY

Sepsis-related Neurologic Dysfunction Strongly Associated With Long-term Mortality

By Betty Tran, MD, MSc

Assistant Professor of Medicine, Pulmonary and Critical Care Medicine, Rush University Medical Center, Chicago

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

SYNOPSIS: In this multicenter, retrospective study, acute neurologic dysfunction was the organ dysfunction most strongly associated with short- and long-term mortality in patients surviving a sepsis hospitalization.

SOURCE: Schuler A, Wulf DA, Lu Y, et al. The impact of acute organ dysfunction on long-term survival in sepsis. *Crit Care Med* 2018;46:843-849.

Based on the most recent Sepsis-3 definitions, sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Organ dysfunction is measured by an increase in the Sequential Organ Failure Assessment (SOFA) score; even a modest increase in SOFA score is associated with in-hospital mortality in excess of 10%.[1] However, given the heterogeneity in sepsis presentations, it is not clear if different organ dysfunction is associated with different outcomes. In this retrospective study of randomly selected patients admitted for sepsis through the ED at 21 Kaiser Permanente Northern California hospitals, Schuler et al aimed to study the effect of each of six different types of acute, sepsis-related organ failure (hepatic, renal, coagulation, neurologic, cardiac, respiratory) on long-term mortality. Acute organ dysfunction was quantified using the SOFA score, with modification for selected organ systems to include other clinically relevant data and recorded as a maximum at 48 hours and over the course of hospitalization. Outcomes included hospital mortality and post-sepsis mortality only in patients who were discharged alive. Care was taken to adjust for concomitant organ dysfunction in patients who could be experiencing multiple organ dysfunction. Several sensitivity analyses were performed, including a propensity score model to adjust for presepsis/hospital risk factors that could predispose patients to specific organ dysfunctions.

Overall, 30,163 septic patients were evaluated, with a median follow-up time for survivors of 797 days (interquartile range, 384-1,219 days). Overall hospital mortality was 9.4%, one-year mortality was 31.7%, two-year mortality was 44.0%, and three-year mortality was 59.7%. The most prevalent organ dysfunction was cardiac (62.4%), with the least common liver (16.5%). The organ dysfunctions most strongly associated with hospital mortality were neurologic (odds ratio [OR], 1.86; $P < 0.001$), respiratory (OR, 1.43; $P < 0.001$), and cardiac (OR, 1.31; $P < 0.001$).

Acute neurologic dysfunction was the organ dysfunction most strongly associated with increased long-term mortality (for each 1-point increase in SOFA subscore, OR, 1.18; 95% CI, 1.15-1.20; $P < 0.001$). This finding remained consistent in all sensitivity analyses, including adjustment for other concomitant organ dysfunction, as well as propensity score models accounting for presepsis conditions that influenced acute organ dysfunction more than any other condition.

■ COMMENTARY

This study adds to the growing body of research focused on long-term patient outcomes and sequelae after a hospitalization for sepsis. We know that acute neurologic dysfunction occurs commonly in septic patients,[2] and that it is associated with adverse outcomes;[3] hence its incorporation into the quick SOFA score aimed to identify patients at increased risk for poor outcomes due to infection. Although these findings will need to be validated in other studies, Schuler et al suggested that acute sepsis-related neurologic dysfunction is the organ dysfunction that most strongly correlates to short- and long-term mortality.

Strengths of this study included long-term follow-up for a large cohort, detailed adjustment for confounding factors (such as illness severity and concomitant other organ dysfunction), and a sensitivity analyses. The sensitivity analysis included a robust propensity score model that accounted for more than 3,000 diagnosis codes. These codes identified presepsis clinical conditions with clinical face validity that carried the highest likelihood of development of acute organ dysfunction, which allows for one to isolate the effect of sepsis hospitalization rather than chronic organ dysfunction. Whether this is a true causative relationship is unclear based on the retrospective nature of this study. However, this finding may carry implications for sepsis-related in-hospital and discharge prognoses to inform patients' families/surrogates, as well

as provide insight for future investigations into the mechanisms by which sepsis affects long-term survival. ■

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PHARMACOLOGY UPDATE

Plazomicin Injection (Zemdri)

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

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

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

The FDA has approved a new semi-synthetic aminoglycoside for the treatment of complicated urinary tract infections (cUTI). Plazomicin received priority review and orphan status designation. It is marketed as Zemdri.

INDICATIONS

Plazomicin is indicated for the treatment of adults ≥ 18 years of age with cUTI, including pyelonephritis caused by susceptible microorganism(s) *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae*.[1]

DOSAGE

The recommended dose is 15 mg/kg every 24 hours, administered intravenously over 30 minutes for four to seven days in patients with creatinine clearance ≥ 60 mL/min.[1] For patients with creatinine clearance > 30 mL/min (but < 60 mL/min), the dose is 10 mg/kg every 24 hours. For those with creatinine clearance < 30 mL/min, the dose is 10 mg/kg every 48 hours. Therapeutic drug monitoring is recommended in patients with renal impairment to ensure that the plasma trough level is below 3 mcg/mL. Plazomicin is available as 500 mg single-dose vials.

POTENTIAL ADVANTAGES

Plazomicin has shown in vitro bactericidal activity against aminoglycoside and beta-lactam-resistant, multidrug-resistant *Enterobacteriaceae* isolates.[2,3] It retains activity against many strains that produce aminoglycoside-modifying enzymes, making it more active compared to traditional aminoglycosides.[4]

POTENTIAL DISADVANTAGES

Plazomicin shares the same basic boxed warnings as other aminoglycosides, namely nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal toxicity.[1] Microorganisms that produce metallo-beta-lactamases may be resistant to plazomicin.[1] The manufacturer hoped to receive FDA approval for blood stream infections; however, the agency declined approval, citing inadequate evidence of efficacy.[5]

COMMENTS

The approval of plazomicin was based mainly on a randomized, double-blind, noninferiority, active-controlled trial in subjects with cUTI (including 42% with pyelonephritis).[1,7] Subjects were randomized to plazomicin (15 mg/kg once daily) or meropenem (1 g intravenously every eight hours). Switching to an oral antibacterial was allowed after a minimum of four days or a maximum of seven days of intravenous therapy. The total duration of treatment was seven to 10 days. Efficacy was assessed based on a microbiological-modified intent-to-treat (mMITT) analysis that included subjects who received the study medication and exhibited at least one baseline uropathogen. Those with organisms resistant to study drugs were excluded. The mMITT population included 191 subjects in the plazomicin group and 197 subjects in the meropenem group. Efficacy endpoints were composite cure at day 5 and composite cure at the test-of-cure (TOC) visit at day 17 (± 2). Composite cure was defined as resolution or improvement of clinical cUTI symptoms and microbiological eradication (uropathogens reduced to < 10^4 colony-forming units). Cure rates were 88% for plazomicin compared to 91.4% for meropenem on day 5, and 81.7% vs. 70.1% for day 17. Both met the criteria for noninferiority, with a significantly higher cure rate at TOC. Microbiological eradication also favored plazomicin at TOC (89.5% vs. 74.6%).

CLINICAL IMPLICATIONS

According to the CDC, untreatable and hard-to-treat infections from multiple drug-resistant, carbapenem-resistant *Enterobacteriaceae* (CRE) bacteria are on the rise among patients in medical facilities.[6] The mortality rate is nearly 50% for hospital patients who contract bloodstream infections from CRE bacteria.[6] Plazomicin joins the new beta-lactamase inhibitor combinations

(meropenem-vaborbactam and ceftazidime-avibactam) against CREs for cUTIs. Plazomicin provides another option. Its use should be determined by patients' clinical features and bacteria susceptibility.[8] The FDA informed the manufacturer that there was insufficient evidence to approve the drug for the treatment of bloodstream infection, which may limit its utility.[9] ■

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CME QUESTIONS

1. Which statement is true concerning the use of inhaled corticosteroid (ICS) use in patients with COPD?
a. ICS is indicated as a first-line treatment for COPD.
b. ICS is indicated for multiple exacerbations.
c. ICS is indicated for COPD only if given with a long-acting beta-agonist.
d. ICS is not indicated for COPD, only for asthma.

2. Which of the following procedures carries a high risk of subsequent infective endocarditis?
a. Bronchoscopy
b. Colonoscopy
c. Cystoscopy
d. All of the above

3. In the study by Schuler et al, which organ dysfunction was most strongly associated with hospital mortality in patients hospitalized for sepsis?
a. Renal
b. Cardiac
c. Respiratory
d. Neurologic

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.

Internal Medicine [ALERT]

ECG Review

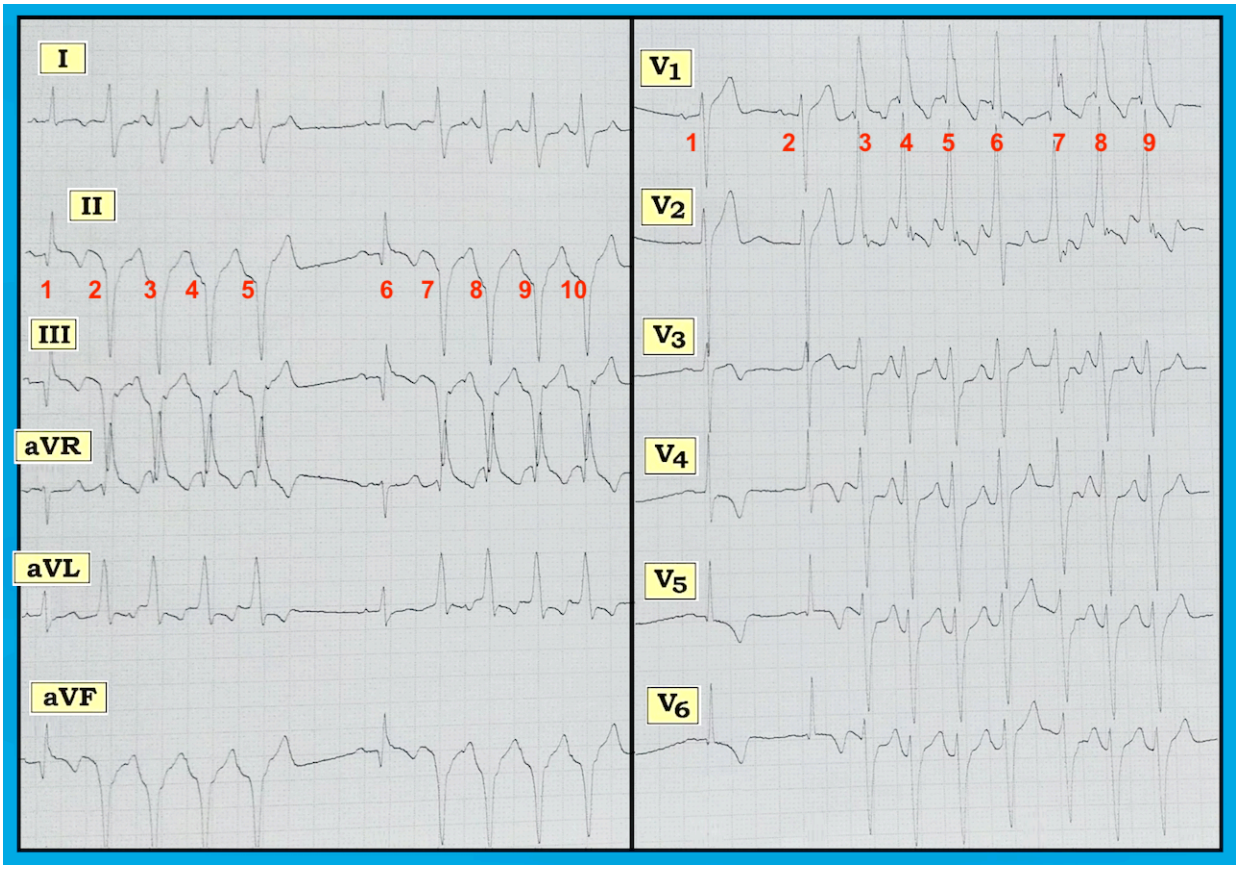
By Ken Grauer, MD

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

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

Runs of VT, or Aberrant Conduction?

A 47-year-old man presented with a history of intermittent dizziness over the previous two days. He was hemodynamically stable at the time the ECG in the figure below was obtained. How would you interpret the rhythm? Is there any clue to a possible etiology for this patient's arrhythmia?



The underlying rhythm is sinus, as determined by the presence of upright P waves with a fixed and normal PR interval before beats 1 and 6 in lead II. Two consecutive sinus beats occur at the beginning of lead V1, which tells us that the underlying sinus rate is ~70/minute. Sinus beats are interrupted on three occasions by runs of a wide tachycardia. These runs are regular for the most part, although some irregularity can be seen in lead V1. Do these runs of wide beats constitute aberrant conduction of a supraventricular rhythm or ventricular tachycardia (VT)?

Although VT usually is a fairly regular rhythm, this is not always the case. The slight irregularity for the run of wide beats in lead V1 is not inconsistent with VT. QRS morphology of the wide beats in leads I, V1, and V6 resembles a pattern consistent with right bundle branch block aberration. That said, QRS morphology of the wide beats in each of the inferior leads reveals an all-negative complex. This constitutes extreme axis deviation, and is highly suggestive of VT. This is because there is almost always at least some positive deflection in the inferior leads when the rhythm is supraventricular.

An additional finding in support of VT: The etiology of the runs of wide beats is inherent in assessment of the sinus-conducted beats. Thus, beats 1 and 6 in the inferior leads show Q waves, ST segment coving with some ST elevation, and T wave inversion. In the chest leads, sinus-conducted beats 1 and 2 show ST segment coving with fairly deep, symmetric T wave inversion in leads V3-V6. These ECG findings strongly suggest acute or recent infarction with ischemia, which is a common precipitating substrate for runs of non-sustained VT.

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