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Internal Medicine

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

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Influenza, 2014-2015 — Something Old, Something New

By Stan Deresinski, MD

Dr. Deresinski is Clinical Professor of Medicine, Stanford University.

Dr. Deresinski has served as a one-time consultant for Cubist and Bayer. This article appeared in the February 2014 issue of *Infectious Disease Alert*.

As of early January, influenza activity had reached epidemic proportions in large parts of the United States, with many of those being affected despite prior vaccination.[1] The occurrence of infection in vaccinated individuals is not unexpected since influenza vaccine efficacy is usually only approximately 60%. There is, however, an additional problem during this influenza season because of an unanticipated mismatch between the components of the 2014-2015 vaccine, which are identical to the 2013-2014 vaccine composition, and the dominating circulating virus type. Thus, current trivalent influenza vaccines contain hemagglutinin (HA) derived from an A/California/7/2009 (H1N1)-like virus, an A/Texas/50/2012 (H3N2)-like virus, and a B/Massachusetts/2/2012-like (Yamagata lineage) virus. Quadrivalent influenza vaccines contain these antigens as well as a B/Brisbane/60/2008-like (Victoria lineage) virus.

H3N2 has accounted for greater than 95% of all influenza reported to CDC from U.S. WHO and National Respiratory and Enteric Virus Surveillance System collaborating laboratories during the current influenza season. Unfortunately, most of the circulating H3N2 viruses are antigenically dissimilar to the H3N2 vaccine strain, probably as the result of significant antigenic drift. A similar circumstance occurred during the H3N3-predominant 2007-2008 season in which the virus had also significantly drifted antigenically from the vaccine strain; the vaccine efficacy that year

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was only 43%. Early estimates for the current season indicate that the age-adjusted overall vaccine efficacy (VE) is only approximately 23%.[2] Nonetheless, CDC modeling suggests that a VE of only 10% in older adults could prevent approximately 13,000 influenza-associated hospitalizations in those aged ≥ 65 years in the United States during a moderately severe influenza season such as in 2012–13.

Furthermore, past seasons in which H3N2 was the predominantly identified strain were often characterized by greater severity of disease among children younger than 5 years old and adults older than 65 years old when compared to H1N1- or influenza B-predominant seasons. Thus, CDC has estimated that an average of 28,909 people died from flu during H3N2 seasons from 1976 to 2007, while only 10,648 people died during years in which H3N2 was not predominant. While estimates of influenza-related deaths are incomplete, CDC indicates that the hospitalization rates are higher than in recent years and are similar to those observed during some past seasons in which H3N2 predominated.

Antiviral treatment remains effective, particularly when administered within 48 hours of symptom onset. In situations in which influenza has reached epidemic proportions, treatment can be initiated in outpatients on the basis of a compatible symptom complex and without confirmatory testing. In other circumstances, testing should be performed, but, as the CDC states, "Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza." The recent first-ever CLIA waiver by the FDA of a point-of-care nucleic acid-based influenza diagnostic test (Alere™ i Influenza A&B) may lead to reconsideration of this recommendation.[3] While variable specificity of the test has been reported, all studies appeared to have found a sensitivity in excess of 90% for both influenza A and influenza B virus detection.[4-7]

The current circulating viruses, including the current H3N2 strain, are, with infrequent exception, susceptible to neuraminidase inhibitors, and either oseltamivir or zanamivir can be used to treat most patients in accord with CDC recommendations. Another neuraminidase inhibitor, peramivir, which is administered intravenously in a single (quite expensive) dose was approved by the FDA in December 2014. Its niche would appear to be limited to high-risk inpatients for whom enteral administration of medications is contraindicated because of, e.g., severe ileus or intestinal obstruction. ■

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ABSTRACT & COMMENTARY

Weighing the Harms and Benefits of E-cigarettes

By Seema Gupta, MD, MSPH

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

SYNOPSIS: In a Cochrane review, there is evidence from two trials that nicotine containing e-cigarettes may help smokers to quit long-term compared with non-nicotine type.

SOURCE: McRobbie H, et al. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev* 2014:17;12.

Electronic cigarettes (e-cigarettes) are vaporizing devices designed to look and feel like a traditional cigarette. Often being marketed as tobacco-free nicotine delivery devices, there has been a rapid increase in popularity of these products in recent times. E-cigarettes do not involve tobacco combustion. Instead, liquid stored in a disposable or refillable cartridge or a reservoir, usually comprised of propylene glycol and glycerol, with or without nicotine and flavors, is aerosolized for inhalation. As the e-cigarette aerosol simulates cigarette smoke, the devices are adeptly designed to provide taste and throat sensations similar to smoking a traditional cigarette. E-cigarettes are currently being marketed to current and potential users to replace cigarettes when in smoke-free environments, as well as an aid to quit traditional tobacco smoking. However, the scientific evidence regarding the human health effects of e-cigarettes is limited. So far, studies evaluating whether e-cigarettes are less harmful than traditional cigarettes remain mostly inconclusive, and none of the e-cigarette devices have been approved by FDA as a cessation aid.[1]

In the United States, the 40-year decline in tobacco use has stalled. Since 2005, smoking has remained at about 20-21%, placing more than 46 million people at risk to provide taste and throat sensations similar to smoking a traditional cigarette. E-cigarettes are currently being marketed to current and potential users to replace cigarettes when in smoke-free environment as well as an aid to quit traditional tobacco smoking. However, the scientific evidence regarding the human health effects of e-cigarettes is limited. So far, studies evaluating whether e-cigarettes are less harmful than traditional cigarettes remain mostly inconclusive, and none of the e-cigarette devices have been approved by FDA as a cessation aid.[1] United States, the 40-year decline in tobacco use has stalled. Since 2005, smoking has remained at about 20-21%, placing more than 46 million people at risk for tobacco-related adverse health effects. Therefore, it is vital to evaluate the effectiveness of e-cigarettes in smokers as a cessation aid.

McRobbie and colleagues conducted a Cochrane review to primarily examine the efficacy of e-cigarettes in smokers in achieving long-term abstinence. They also aimed to examine the efficacy of e-cigarettes in reducing traditional cigarette consumption by at least 50% of baseline levels and to assess the occurrence of adverse events associated with their use. Researchers searched for trials published between 2004 and 2014 and found 13 completed studies, including two randomized control trials that compared e-cigarettes with and without nicotine, and had a combined sample size of 662 participants.

These studies were judged to be at low risk of bias, and a meta-analysis was conducted. The pooled results revealed that approximately 9% of smokers who used e-cigarettes that contained nicotine were able to stop smoking for at least 6 months, compared with about 4% of smokers who used nicotine-free e-cigarettes (relative risk [RR], 2.29; 95% confidence interval [CI], 1.05-4.96). Self-reported reduction data from the two studies also demonstrated that of the smokers included in the review who had not quit, 36% of e-cigarette users halved the number of traditional cigarette use, compared with 27% of users who were given the placebos (RR, 1.31; 95% CI, 1.02-1.68). Results were also similar in one study in favor of e-cigarettes when compared with nicotine replacement patch (RR, 1.41; 95% CI, 1.20-1.67). No serious adverse effects related to e-cigarette use were reported from any of the studies.

The study authors conclude that there is evidence from two trials that e-cigarettes help smokers to

stop smoking long-term compared with placebo or non-nicotine e-cigarettes. They also appear to help smokers unable to stop smoking altogether to reduce their cigarette consumption when compared with placebo e-cigarettes and nicotine patches. However, the authors caution about having a low confidence in their findings due to the small number of trials, low event rates, and wide confidence intervals around the estimates.

■ COMMENTARY

The results show beneficial effects of e-cigarettes, but the findings are not without significant limitations. The primary and secondary health impacts of e-cigarettes, for users and the public, cannot be yet fully understood with currently available data. Previous research has identified a number of chemical substances and ultrafine particles in e-cigarette aerosols, cartridges, and refill liquids that are known to be either toxic or carcinogenic or impact respiratory and cardiovascular systems.[2] Additional complicating factors in streamlining research is that there are hundreds of different brands and models of e-cigarettes that vary in the composition of the fluids, and there is neither any uniformity in production nor any regulatory requirement for disclosure. Similarly, much of research methodology in the field also remains to be validated. As a result of these study limitations, critical information and science gaps continue to exist. Significant policy gaps also remain since these products are being produced in various flavors intended to potentially market to the younger population, including children. Survey data reveal that youth are aware of e-cigarettes and use of these products in this population is rapidly increasing.[3] The abuse liability of e-cigarettes as well as health impact from exposure to secondhand and thirdhand smoke remains unknown. There have been reports of unintentional exposures, including ingestion of e-liquids and inhalation of e-cigarette aerosols. For these reasons, it may be prudent for the clinician to avoid making a recommendation in favor of e-cigarettes at this time. A cautious approach may be to wait for the science to develop in order to help guide clinical decision-making with regards to e-cigarettes recommendations. ■

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ABSTRACT & COMMENTARY

Hypoglycemia Increases Cardiovascular Risk in Patients With Type 1 and Type 2 Diabetes

By Jeff Unger, MD

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Dr. Unger does research for Novo Nordisk, Lilly, Sanofi-Aventis, Janssen, GSK, Itarcica, Dance Pharma, Proteus Pharma, and Abbott Diabetes, is a consultant for Novo Nordisk, Janssen, Itarcica, Dance Pharma, Proteus Pharma, and Abbott Diabetes, is on the speaker's bureau for Novo Nordisk, Janssen, and Valeritas, and is a stockholder for Novo Nordisk.

SYNOPSIS: A retrospective analysis of data from the UK Clinical Practice Research Datalink found that hypoglycemia increases the risk of both cardiovascular disease and all-cause mortality in patients with diabetes.

SOURCE: Khunti K, et al. Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: A cohort study. *Diabetes Care* 2015;38:316-322.

This is a retrospective analysis of data from the UK Clinical Practice Research Datalink which includes 265,868 insulin-treated patients age > 30 years diagnosed with diabetes between 2001 and

2007. 3260 were diagnosed with T1DM and 10,422 had T2DM. During a median follow-up of 5 years for type 1 diabetes patients and 4.8 years for those with type 2 diabetes, hypoglycemia was experienced by 573 (18%) and 1463 (14%) of patients, respectively. Compared with patients who did not experience hypoglycemia, the hazard ratio (HR) for CV events among T1DM patients who experienced hypoglycemia was 1.51 (not significant) and 1.61 for those with and without a history of CVD. For T2DM patients, the respective HRs were 1.60 and 1.49. The median time interval between the first hypoglycemia event and the first CV event was 1.5 years for all diabetes patients. Thus, hypoglycemia increases the risk of both CV and all-cause mortality in patients with diabetes.

■ COMMENTARY

The intensive treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was terminated early due to a 22% increased risk of all-cause mortality compared with the standard arm in patients with T2DM. One hypothesis for the increased risk of mortality centers around the role of hypoglycemia as a contributor to incident sudden death in "high-risk" patients. The risk of severe hypoglycemia in ACCORD was associated with higher rather than lower A1C levels in both arms of the study. Hypoglycemia can incite a number of physiologic events, including increased platelet adhesion, increased heart rate, and vasoconstriction. Repeated mild or moderate hypoglycemia can suppress the usual counterregulatory response of catecholamines. A single episode of severe hypoglycemia in a patient who rarely experiences glucose levels < 60 mg/dL is likely to result in a more intensive release of catecholamines, which may trigger malignant arrhythmias in a patient with prolonged Q-T interval. Thus, blunting the catecholamine response may have a protective effect, as well as limit the risk of potentially fatal arrhythmias during a severe hypoglycemic event. This hypothesis is known as "hypoglycemia preconditioning."

Clinically, patients with A1C levels > 8.5 % who have known coexisting cardiovascular disease should be treated to glycemic targets designed to minimize their risk of severe hypoglycemia. Consider prescribing medications that limit inducing hypoglycemia in high-risk patients, such as metformin, DPP-4 inhibitors, GLP-1 receptor agonists, bromocriptine, and SGLT-2 receptor agonists. Basal and prandial insulin analogues are less likely to result in hypoglycemia than human insulin. The use of disposable patch pumps (V-Go pumps) provide an attractive alternative to mixed insulin for patients with T2DM.

Patients with T1DM are not immune to CV death and all cause mortality. Our goal with T1DM patients is to limit the amount of variability experienced by these individuals. One should remember that T1DM is a bihormonal disease state consisting of loss of insulin production by the pancreatic beta-cell, and excessive glucagon production via hypertrophied islet alpha cells. Thus, the off-label use of GLP-1 receptor agonists alone or in combination with an SGLT-2 inhibitor may reduce the postprandial and fasting effects of glucagon excess in patients with T1DM. T1DM patients with hypoglycemia awareness autonomic failure should also be encouraged to use continuous glucose sensors, which will alarm in response to a fall in interstitial glucose levels.

Although long-term exposure to hyperglycemia is a known cause of mortality in patients with diabetes, the immediate risk of acute and severe hypoglycemia cannot be ignored. This study suggests that all patients treated with insulin should be monitored closely for evidence of hypoglycemic events. Clinicians should adjust treatments and glycemic targets for patients at high risk for cardiovascular mortality. ■

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Clinical Briefs

By Louis Kuritzky, MD

Long-term Payoff of Bariatric Surgery

SOURCE: Arterburn DE, et al. *JAMA* 2015;313:62-70.

The benefits of bariatric surgery are gaining new levels of respect as long-term evidence of favorable outcomes — other than cosmetic — continue to accrue. Indeed, in the population of obese diabetics, bariatric surgery is one of the only interventions documented to improve all-cause mortality.

New support for the positive impact of bariatric surgery comes from a retrospec- tive cohort study of patients (n = 2500) who had undergone bariatric surgery in Veteran's Administration (VA) hospitals throughout the United States in the inter- val from 2000-2011. Survival in these patients was compared with a control group matched for age, body mass index (BMI), and type 2 diabetes. The mean pre-surgical BMI in the bariatric surgery group was 47, and mean age was 52 years.

In the follow-up intervals from years 1-5 and, years later, 5-14, there was a distinct advantage favoring bariatric surgery patients, who enjoyed a greater than 50% lower all-cause mortality than matched controls.

Because this study is retrospective, it cannot be regarded as definitive in prov- ing that bariatric surgery reduces mor- tality. Additionally, because these data were collected from VA hospitals, the patient population was disproportion- ately male (74%). Nonetheless, the ac- cumulating evidence consistently points to favorable effects of bariatric surgery upon mortality. ■

Colon Cancer Screening by Stool DNA Testing

SOURCE: *JAMA* 2014;312:2566-2567.

Recent guidelines issued by the American Cancer Society and American Society of Gastroenterology recommend colonoscopy as the preferred screening method for colon cancer, but wisely include the philosophy, "The best colon cancer screening test is the test you can get done!" — reflecting the relative reticence shown by many Americans to undergo colonoscopy. CT colonography compares very favorably colonoscopy, yet many insurers are not willing to pay for it.

Stool DNA testing (trade name Cologuard) is based on the observation that colon cancers consistently shed cells with cancer markers in the stool (example names of such markers include KRAS, NDRG4, BMP3). In the most recent iteration of stool DNA testing kits, an assay for human hemoglobin is also included (eliminating the need for dietary restriction prior to stool testing).

The process is fairly simple: A collection kit is sent to the patient's home, the specimen is mailed back, and if either the colon cancer markers or the human hemoglobin test return positive, the patient needs a follow-up colonic evaluation (e.g., colonoscopy). Some patients (and clinicians) are sufficiently reassured by negative stool DNA testing that they feel comfortable to stop screening at that point. Unfortunately, even though stool DNA testing is very sensitive for colon cancer compared to colonoscopy (sensitivity = 92%), it is much less sensitive for precancerous lesions. Additionally, some false-positives occur with stool DNA testing.

Despite these limitations, stool DNA testing provides a viable way to do colon cancer screening for persons unwilling to undergo other screening methods. Negative stool DNA screening will be sufficiently reassuring to some patients that they will elect not to pursue further more definitive screening. ■

Intracranial Hemorrhage Risk: Are Novel Oral Anticoagulants Better Than Warfarin?

SOURCE: Vespa PM. *JAMA* 2015;312:2562-2563.

Clinicians have commonly overestimated the risk of intracerebral hemorrhage (ICH) during anticoagulant therapy. Indeed, such misapprehensions have sometimes led to failure to employ warfarin (and probably other agents) when indicated for atrial fibrillation. There is little dispute that novel oral anticoagulants (apixiban, dabigatran, rivaroxaban) are simpler to use, since they do not require monitoring and are essentially free of food interactions. Clinical trials with novel oral anticoagulants (NOACs) have consistently documented that NOACs are associated with lesser risk of ICH, which is certainly a good thing … but how much of a good thing?

First, it may come as a surprise that in the modern era, large clinical trials of warfarin treatment in atrial fibrillation demonstrate ICH events consistently below 1% per year. Since the risk of thrombotic stroke in atrial fibrillation — even at a CHADS score of 1 — is approximately 3% per year, the risk:benefit ratio is strongly in favor of anticoagulation.

Atrial fibrillation mega-trials (each > 10,000 patients) have been completed with the three FDA-approved NOACs, each agent demonstrating a reduction in ICH compared to warfarin, with an overall odds ratio of 0.49 — essentially half the risk of ICH with NOACs compared to warfarin. ICH is a devastating consequence of anticoagulation, and although more than 99% of patients treated with warfarin for atrial fibrillation per year will not suffer ICH, the ability to reduce risk for such a dreaded event is an important consideration. ■

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CME QUESTIONS

1. **In the above study by McRobbie et al, which of the following statements is false regarding the effectiveness of e-cigarettes?**

   a. E-cigarettes help smokers to stop smoking long-term compared with placebo.

   b. E-cigarettes help smokers reduce their cigarette consumption when compared with placebo.

   c. E-cigarettes are as effective as nicotine patches to help reduce cigarette consumption.

   d. No serious adverse effects related to e-cigarette use were reported from any of the studies.

2. **In the study by Khunti et al, the median time interval between the first hypoglycemia event and the first cardiovascular event was:**

   a. 2 years.

   b. 1.5 years.

   c. 8 months.

   d. 2.5 years.

2. **Which of the following is correct regarding the 2014-2015 influenza season?**

   a. The predominant virus is H1N1 identical to the 2009 pandemic strain.

   b. The predominant virus is influenza B.

   c. The predominant virus is well-covered by the 2014-2015 vaccine.

   d. The predominant virus is H3N2.

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]

C. difficile

Statins and the Neuromuscular System

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.

Alternating Morphology Every-other-beat

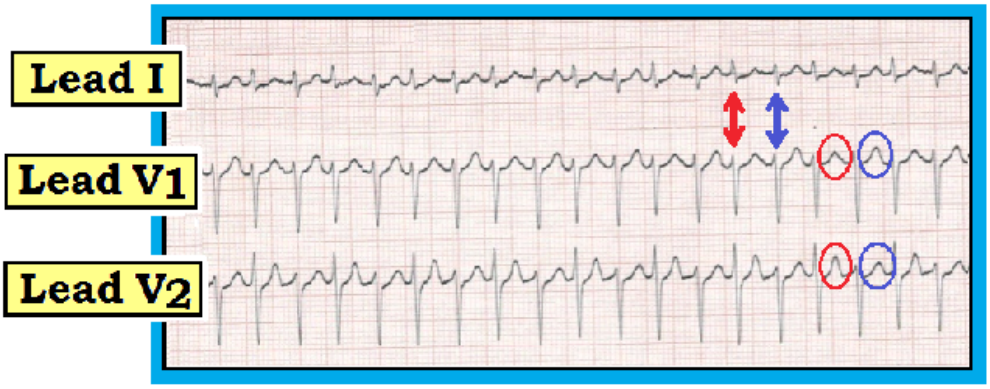

Figure: 3-lead rhythm strip from a patient in a narrow-complex tachycardia.

The simultaneously recorded 3-lead rhythm strip in the Figure was obtained from a patient in a supraventricular (narrow-complex) tachycardia. What is the reason for alternating morphology of the QRS complex (and T wave) with every-other-beat? Does this finding providing useful clinical information?

Interpretation: The underlying rhythm in this simultaneously-recorded 3-lead tracing is a narrow-complex tachycardia. The interesting feature is the variation in morphology with alternate beats. The reason for this variation is electrical alternans. There are actually three components of this rhythm that are changing with alternate beats: 1) QRS morphology, 2) T wave morphology, and 3) the R-R interval.

- Although all QRS complexes are narrow on the 3 leads shown in this tracing — the red and blue double arrows highlight unmistakable variation in QRS amplitude from beat-to-beat (albeit the difference is no more than slight variation in R wave height and S wave depth).
- Red and blue ovals show that there is also subtle-but-real variation in T wave amplitude from beat-to-beat. The consistency of this finding in the absence of baseline artifact indicates that this variation is a real phenomenon.
- Finally, there is slight variation in the R-R interval.

This difference in R-R interval from one beat to the next is so small that it could be easily missed unless measured with calipers. That said, the result is that this is not a "regular" SVT (supraventricular tachycardia) — but rather an irregular SVT rhythm with a repetitive pattern of alternate cycle length variation.

Electrical alternans is a fascinating clinical entity that is frequently misunderstood. Because this ECG finding is so often overlooked, the true incidence of electrical alternans is much higher than is generally appreciated. The term "electrical alternans" encompasses phasic fluctuation in one or more cardiac signals from one beat to the next within the cardiac cycle. This phasic variation may affect complex morphology (of the P wave, QRS complex and/or T wave), as well as interval duration (of the PR interval, QT interval, or R-R interval). Although most commonly associated with pericardial tamponade, there are many other clinical conditions that may produce this phenomenon.

For the SVT rhythm in this case, the presence of electrical alternans is highly suggestive of re-entry as the mechanism of the arrhythmia (not necessarily due to an accessory pathway). Other conditions that have been associated with electrical alternans include acute pulmonary embolus, cerebral hemorrhage, recent cardiac arrest, cardiomyopathy, ventricular dysfunction, pericardial effusion without tamponade, and others. Therefore, recognition of electrical alternans is indication for the clinician to look for an underlying cause. ■

For additional information on alternating morphology, go to http://ecg-interpretation.blogspot.com/2014/02/ecg-interpretation-review-83-psvt-avnrt.html.