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Hospital Medicine

Evidence-Based Information for Hospitalists Intensivists, and Acute Care Physicians [ALERT]

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ABSTRACT & COMMENTARY

Is Written Sign-Out Sufficient for Attending Hospitalists?

By Kenneth P. Steinberg, MD, FACP
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Dr. Steinberg reports no financial relationships in this field of study.

SYNOPSIS: Effective hand-offs and sign-outs are core competencies for hospitalists. This study suggests that attending hospitalists frequently use written sign-outs to address overnight inquiries but that the sign-outs are not reliably useful. Written-only sign-outs may not be sufficient for safe overnight care.

SOURCE: Fogerty RL, et al. Effectiveness of Written Hospitalist Sign-outs in Answering Overnight Inquiries. *J Hosp Med* 2013;8:609-614.

■ SUMMARY

Hospital medicine is a rapidly growing specialty, and hospitalists can significantly impact the quality of care for hospitalized patients. One unique challenge of the hospitalist model is the shift-based care requiring transfers, or hand-offs, of care at shift change. Cross-coverage can be a high-risk aspect of care, and poor sign-outs can negatively impact cross-coverage, thus threatening patient safety. The Society of Hospital Medicine recognizes hand-offs and sign-outs as core competencies for hospitalists, but little is known about the quality of sign-out between hospitalists. For this reason, Fogerty and colleagues at Yale-New Haven Hospital attempted to assess how well hospitalist sign-outs prepared the night team for overnight events.

The study took place on the non-teaching Hospitalist Service at a large, urban, academic medical center (Yale-New Haven Hospital). A written sign-out built into the electronic health record is the major mechanism for shift-to-shift information transfer at that hospital. Verbal

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Hospital Medicine
[ALERT]

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sign-out is reported to rarely occur on that service. The study took place on 6 non-consecutive days over a 6-week period of time. For every inquiry about a patient's care received by the night hospitalist, that hospitalist recorded who originated the inquiry, the clinical significance, the sufficiency of written sign-out, which information was used other than the written sign-out, and whether the inquiry was about an event that had been anticipated by the daytime team. Informed consent was obtained from all participating hospitalists. A composite quality score for the written sign-out was used. The score gave 1 point for each of the following elements: diagnosis or presenting symptoms, general hospital course, current clinical condition, and whether the sign-out had been updated within the last 24 hours. The composite score could range from 0 – 4. The primary outcome measure was the quality and utility of the written-only sign-out as defined via a subjective assessment of sufficiency by the covering physician. Specifically, the question was whether the written sign-out was adequate to answer the query without seeking additional information.

The night hospitalists recorded 124 inquiries during the study. Most (82%) were from nursing staff. None of the written sign-outs had a composite score of 0 or 1; 4% had a composite score of 2; 46% had a composite score of 3; and 50% had a composite score of 4. Seventy-two percent (72%) of the written sign-outs included neither anticipatory guidance nor tasks (a to-do list). Overall, the sign-out was considered sufficient to respond in only 30% of the inquiries, while 77% of the inquiries were considered to be clinically important by the hospitalist. Sign-out was considered to be sufficient to answer the majority of the order reconciliation inquiries but was less effective at helping to answer inquiries about clinical change, medications, and plan of care.

■ COMMENTARY

Most studies on the quality of hand-offs and sign-out have focused on trainees (residents and students). This study demonstrates that attending hospitalists also rely on sign-out, despite their higher level of training, as the written sign-out was used to help respond to three-quarters of the overnight inquiries. However, the written sign-out was felt to be sufficient to answer less than one-third of the inquiries in which it was referenced. Most notable, perhaps, was the suggestion that sign-outs were more likely to be effective if they included more anticipatory guidance for possible events.

Quite honestly, this is not a particularly strong study. It is a single-center study with a small sample size over a short period of time. The composite quality score is not well validated, making its use suspect, and patient outcomes were not evaluated. However, it is one of the first to look at the quality of attending-level hospitalist sign-out. Due to the structure of the service at Yale-New Haven Hospital, the study is also able to focus primarily on the sufficiency of written sign-out. The investigators made the observation that written-only sign-out was insufficient to deal with the majority of the cross-coverage inquiries. Most experts recommend that there be both written and verbal components to handoff communication, and this study appears to support the contention that written-only handoffs are insufficient. Perhaps, as noted by the authors, the written sign-outs could be improved by including more anticipatory guidance (e.g., "if... then..." statements). Anecdotally, I am a believer in the value of a supplemental verbal sign-out. Nonetheless, I agree with the authors' conclusion that more work is necessary to better understand the benefit of improving written sign-out as well as the additional impact of verbal sign-out on overnight patient safety. ■

ABSTRACT & COMMENTARY

Is Cardioversion After Acute Atrial Fibrillation Safe Without Anticoagulation?

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Dr. Gerstenfeld does research for Biosense Webster, Medtronic, and Rhythmia Medical.

This article originally appeared in the November 2013 issue of Clinical Cardiology Alert. *It was edited by Michael H. Crawford, MD, Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco, and peer reviewed by Ethan Weiss, MD, Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Crawford reports no financial relationships relevant to this field of study, and Dr. Weiss is a scientific advisory board member for Bionovo.*

Source: Airaksinen KE, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: The FinCV (Finnish CardioVersion) Study. *J Am Coll Cardiol* 2013;62:1187-1192.

In clinical practice, patients with atrial fibrillation (AF) duration < 48 hours often undergo cardioversion without systemic anticoagulation. The Finnish CardioVersion (FinCV) study reviewed the comprehensive database from three Finnish hospitals to identify all patients undergoing cardioversion with AF onset < 48 hours prior without prior systemic anticoagulation. All AF episodes were confirmed by 12-lead ECG. The primary endpoint was thromboembolic event within 30 days after cardioversion. There were 5116 cardioversions performed in 2481 patients who all had AF onset < 48 hours and no prior anticoagulation. There were 38 definite embolic events (0.7%, 95%CI, 0.5-1.0%) in the 30 days after cardioversion, 31 strokes, four transient ischemic attacks, two pulmonary embolisms, and one systemic embolism. In addition, 11 patients died within 30 days, including two from fatal strokes. Independent predictors of embolic events included age (odds ratio [OR], 1.05; 95% CI, 1.02-1.08); female sex (OR, 2.1; 95% CI, 1.1-4.0), heart failure (OR, 2.9; 95% CI 1.1-7.3), and diabetes (OR, 2.3; 95% CI, 1.1-4.9). The highest risk of thromboembolism (9.8%) was identified in patients with heart failure and diabetes, whereas those without heart failure and < 60 years of age had the lowest risk (0.2%). None of the patients with failed cardioversions had embolic events. The authors concluded that the risk of thromboembolic complications post-cardioversion of AF of < 48 hours' duration is high in certain categories of patients when anticoagulation is not used.

■ COMMENTARY

It has often been taught that patients with AF < 48 hours' duration can undergo cardioversion without transesophageal (TEE) echocardiogram or prior anticoagulation, while in patients with prior AF lasting > 48 hours, either 3 weeks of therapeutic anticoagulation or a TEE is needed. One of the challenges of this approach is uncertainty regarding the prior duration of AF. Unless a patient is hospitalized or has an implanted pacemaker, symptoms from AF can be unreliable. Nevertheless, there are some patients who can tell the minute their AF initiates, and then call to undergo cardioversion. It is well described that immediately after cardioversion, there is "stunning" of the left atrium, and that left atrial appendage velocities actually decrease as spontaneous thrombus can form immediately. This occurs whether cardioversion is electrical, chemical, or spontaneous. However, the duration of stunning is related to the prior duration of AF, so those with brief prior AF duration may recover left atrial function quickly. It is for this reason that some have performed cardioversion of low-risk patients on aspirin if they present within 48 hours. This study points out that although the overall stroke risk in this patient group with AF < 48 hours is low (1%), it is higher in those with stroke risk factors (~10%). Fortunately, the same risk factors that predict stroke in AF patients, namely age, diabetes, and congestive heart failure, were predictive of recurrent stroke in this study. Therefore, it seems prudent that in patients with any CHADS2 stroke risk factors, anticoagulation should be initiated and continued for 30 days

after cardioversion, even if the AF duration is < 48 hours. This is much easier to do with the newer oral anticoagulants. The need for continued anticoagulation can be reassessed after 30 days, depending on the patients' rhythm. If the duration of AF prior to presentation is at all unclear, then either 3 weeks of oral anticoagulation or a TEE should be performed prior to cardioversion. Importantly, if a TEE is being performed, one should achieve therapeutic anticoagulation before cardioversion in these patients. This can be achieved by giving the first oral dose of a novel anticoagulant 2 hours prior to cardioversion. For those with truly lone AF and clear recent onset AF, the risk of stroke with cardioversion is low (< 0.2%). I still tend to start a novel anticoagulant prior to and for at least 48 hours after cardioversion in these patients, given the possible deleterious effect of left atrial stunning and low risk of bleeding with short-term anticoagulant use. ■

ABSTRACT & COMMENTARY

Dabigatran Not Safe For Prosthetic Heart Valves

By Andrew J. Boyle, MBBS, PhD

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

This article originally appeared in the November 2013 issue of Clinical Cardiology Alert. *It was edited by Michael H. Crawford, MD, Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco, and peer reviewed by Ethan Weiss, MD, Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Crawford reports no financial relationships relevant to this field of study, and Dr. Weiss is a scientific advisory board member for Bionovo.*

Source: Eikelboom JW, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;369:1206-1214.

Dabigatran is a novel anticoagulant that has been shown to be at least as good as warfarin at preventing thromboembolism in atrial fibrillation (AF). It is an oral direct thrombin inhibitor that requires no blood tests to monitor its effectiveness. Thus, it has distinct advantages over warfarin. Patients with mechanical heart valves require lifelong anticoagulation with warfarin. If dabigatran proved to be equivalent to warfarin, it would be an attractive alternative for patients with mechanical valves. Eikelboom and colleagues performed a randomized, controlled clinical trial of dabigatran vs warfarin in patients with mechanical heart valves. They separated their study sample into two cohorts: cohort A, who were randomized within the first week after mitral or aortic valve replacement surgery, and cohort B, who were randomized at least 3 months after surgery. These cohorts were randomized 2:1 to receive dabigatran or warfarin. Interestingly, the dose of dabigatran was higher than used in the AF trials. Initial dosing began at 150 mg, 220 mg, or 300 mg twice daily, depending on renal function, and then the dose was escalated to maintain a serum trough level of over 50 ng/ml. Warfarin was dosed to an INR of 2.0-3.0, or 2.5-3.5 depending on thromboembolic risk.

The data safety monitoring board terminated the trial early because the dabigatran group had an excess of both thromboembolic and bleeding events. Two hundred and fifty-two patients were enrolled. The mechanical valve locations were aortic in 68%, mitral in 28%, and both in 4%. Ischemic stroke occurred in 5% of the dabigatran group and none in the warfarin group. Thrombosis of the mechanical valve without symptoms was detectable in 5% of the dabigatran group and none of the warfarin group. The composite endpoint of stroke, transient ischemic attack, systemic embolism, myocardial infarction (MI), or death occurred in 9% of the dabigatran group and 5% of the warfarin group (hazard ratio [HR], 1.94; 95% confidence interval [CI], 0.64-5.86; $P = 0.24$). Major bleeding occurred in 4% of the dabigatran group and 2% of the warfarin group. It is noteworthy that all major bleeding was pericardial and all occurred in cohort A (early after surgery). Bleeding of any type occurred in 27%

vs 12% of the dabigatran and warfarin groups, respectively (HR, 2.45; 95% CI, 1.23-4.86; *P* = 0.01). The authors conclude that the use of dabigatran in patients with mechanical heart valves was associated with increased rates of both thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk.

■ COMMENTARY

The results of this study are a blow to those on lifelong warfarin for mechanical heart valves. The ease of use of dabigatran compared to warfarin is a major step forward for many patients. But this is exactly the reason we do clinical trials. One cannot extrapolate that effectiveness in one disease state or indication for a drug will necessarily mean that it will be effective in another.

The reason for the failure of dabigatran in both thromboembolic and bleeding endpoints deserves some discussion. The achievement of adequate serum trough levels was less in the early group (cohort A) and this group had higher thrombo-embolic complications. However, they also had higher major bleeding rates, suggesting that it is it not purely a dosing problem. Dabigatran is successful in AF, where thrombosis occurs in the left atrial appendage under conditions of low flow due to stasis and endothelial dysfunction. But in patients undergoing valve surgery, there are large amounts of tissue factor released due to the trauma of surgery, and exposure to the sewing ring and prosthetic valve leaflets can activate the contact pathway of thrombosis. Warfarin acts at multiple sites in the coagulation cascade, including the tissue factor and contact pathways (factors VII and IX), as well as inhibiting the final common pathway, including thrombin. In contrast, dabigatran only inhibits thrombin. The authors suggest that the activation of multiple pathways may lead to an overwhelming amount of thrombin that dabigatran at these doses cannot inhibit. Warfarin's less specific mechanism of action may be the reason it is more effective in patients with mechanical heart valves.

It should be noted that this was a phase 2 study designed to assess the serum trough levels of dabigatran. It was not designed to test efficacy of the drug. However, the data safety monitoring board terminated the study due to the excess number of endpoints in the dabigatran group. It is technically underpowered to accurately determine the magnitude of event rates, but the direction of both thromboembolic and bleeding event rates were clearly against dabigatran. For now, this means that the novel anticoagulants must not be used in lieu of warfarin for mechanical heart valves. ■

ABSTRACT & COMMENTARY

C. diff Transmission: It's Complicated

Surprisingly, most CDI cases are not transmitted by symptomatic patients

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports no financial relationships in this field of study.

This article originally appeared in the November 2013 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, FIDSA, and peer reviewed by Timothy Jenkins, MD. Dr. Deresinki is Clinical Professor of Medicine, Stanford University, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, and Dr. Jenkins is Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Deresinski does research for the National Institutes of Health, and is an advisory board member and consultant for Merck, and Dr. Jenkins reports no financial relationships relevant to this field of study.*

Source: Eyre DW, et al. Diverse Sources of *C. difficile* Infection Identified on Whole-Genome Sequencing. *N Eng J Med* 2013;369:1195-1205.

The prevailing theory of *Clostridium difficile* transmission is that most cases occur after recent exposure to symptomatic patients in health care settings. Infected patients are known to shed large numbers of *C. difficile* spores and current infection control recommendations focus on preventing spore transmission from the environment

through contact precautions and decontamination of surfaces and equipment. However, the rate of *C. difficile* infection (CDI) continues to increase, bringing into question the effectiveness of these methods.

A new study by Eyre and colleagues provides evidence that the widely accepted paradigm of horizontal *C. difficile* transmission may not be valid. Over a period of 3.6 years the investigators performed whole genome sequencing on more than 1,200 clinical isolates of *C. difficile* from the Oxford University Hospitals. Any two cases were considered to be linked if they met two conditions: no more than two single-nucleotide variants (SNVs), and the patients had direct or indirect contact while one was symptomatic, or contact occurred within a 12-week incubation period.

The analysis determined only 35% of the isolates were genetically linked to a prior case, while 45% had more than 10 SNVs and therefore were not related. Patients with genetically linked isolates tended to be older than those with genetically distinct isolates (median age 81 years vs. 76 years, respectively; $P < 0.001$). Moreover, 38% of the linked cases had ward contact with the previous genetically related case while 9% shared the same time in the hospital but were never on the same ward. Interestingly, no hospital-based contact could be established for 46% of the patients, implying diverse sources of acquisition. For instance, some of the patients were in the same medical practice (10%) or lived in the same postal-code district (11%) as previous cases, but no pairs of patients with 2 or fewer SNVs attended the same outpatient clinic on the same day. Among the 45% of cases that represented transmission from sources other than symptomatic cases, it is reasonable to conclude their CDI was acquired from either asymptomatic individuals or some other environmental reservoir i.e., food, animals, or surfaces.

There are a few limitations to the study that require mention. First, the toxin testing used by Eyre and colleagues has been largely supplanted by more sensitive assays (e.g. polymerase chain reaction or nucleic acid tests) which probably led to an underestimation of *C. difficile* incidence in the local regions. Second, the institutions that participated in the study housed patients in four-bed bays, an arrangement that is unusual in the U.S. Since the majority of patients in U.S. hospitals are in private rooms that afford less opportunity for patient-to-patient contact, the rate of *C. difficile* transmission is likely to be different between the two countries. Third, the study was conducted during a period when infection control precautions to limit the spread of *C. difficile* were widely practiced, which likely reduced the impact of symptomatic patients. Finally, it is possible that *C. difficile* has other still-unidentified reservoirs in the environment or hospitals that are important for transmission. In the study, the authors did not perform whole genome sequencing on any strains from extended-care facilities, which are known to be sources for outbreaks of *C. difficile*.

■ COMMENTARY

This study is significant because it provides evidence that in a majority of cases, CDI is not transmitted by symptomatic patients. Instead, asymptomatic individuals or other sources are likely to be the main perpetrators. This finding compels us to re-examine infection control protocols whose goal is to limit the transmission of multidrug resistant pathogens like *C. difficile*. This is not to say we should abandon basic control methods since the infrequent transmission from symptomatic patients in the study hospitals may attest to their effectiveness. Rather, future studies that elucidate novel routes of transmission can identify currently unknown sources of CDI. For example, should all patients who are admitted to the hospital be screened for *C. difficile?* If so, what should happen to asymptomatic carriers, especially since isolation in general is unpopular with patients, their families, and health care workers?

Another take away point from this study is that perhaps more emphasis should be placed on minimizing disruptions to the gut microbiome and its restoration (i.e. through probiotics) should be a priority. Although physicians and the public already have more than enough reasons to limit the use of unnecessary antibiotics, the threat of acquiring CDI is a valid concern and should be taken into consideration whenever these agents are prescribed. As Eyre and colleagues note, the rate of fluoroquinolone and cephalosporin usage in the UK fell between 2006 and 2009, and during this period active restriction of these agents in one Scottish hospital resulted in a relative reduction of 77% in the

incidence of CDI. Thus, reducing the susceptibility of patients to CDI may be more effective than lowering transmission rates. Finally, this study demonstrated the usefulness of whole genome sequencing in determining the transmission of one major disease and this method holds great promise for uncovering the mechanisms of transmission for other serious pathogens. ■

ABSTRACT & COMMENTARY

ID Consultants Lower Mortality and Cost of Hospital Stay

By Carol A. Kemper, MD, FACP

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This article originally appeared in the November 2013 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, FIDSA, and peer reviewed by Timothy Jenkins, MD. Dr. Deresinki is Clinical Professor of Medicine, Stanford University, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, and Dr. Jenkins is Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Deresinski does research for the National Institutes of Health, and is an advisory board member and consultant for Merck, and Dr. Jenkins reports no financial relationships relevant to this field of study.*

Source: Schmitt S, et al. Infectious disease specialty intervention is associated with decreased mortality and lower healthcare costs. *Clin Infect Dis,* 2013 Sep 25 [Epub ahead of print].

The most heavily curb-sided specialty may also be one of the more valuable, especially in an era of cost-consciousness, and focus on quality markers such as shorter stays and fewer 30-day readmissions. The impact of ID consultation on important markers, such as length of ICU stay, length of hospital stay, mortality, and frequency of 30-day readmission was assessed for patients admitted to an acute care hospital (ACH) with at least one of 11 specific infections between January 2008 and November 2009. These common infections were selected based on the ability to query fee-for-service Medicare claims based on DRG code (bacteremia, *C. difficile* infection, central line-associated bloodstream infection, bacterial endocarditis, HIV, meningitis, osteomyelitis, prosthetic joint infections, septic arthritis, septic shock, and vascular device infections).

A total of 101,991 ACH stays with ID consultation and 170,366 without ID involvement (59.8%) were examined. Patients with ID consultation generally had more than one infection, and were more likely to be male, they were younger, more likely to be admitted to ICU, and were more likely admitted to a teaching hospital compared to those without ID intervention. From this cohort, the authors selected a matched sample of ACH hospitalizations that involved ID intervention (61,680) and that did not involve ID intervention (65,102). Prior to adjusting for any risk factors, patients with ID intervention generally appeared more ill, had longer lengths of hospital stay, more days in ICU, but a lower index stay mortality.

After adjustment for risk factors, cases with ID involvement had statistically significantly lower rates of index stay (odds ratio, .89), lower rates of 30-day mortality (OR, .86), and lower rates of 30-day readmissions (OR, .96). In addition, stays with ID involvement within the first 2 days of hospitalization were associated with a significantly lower 30-day mortality (OR, .87) and readmission rate (OR, 0.92). Furthermore, those cases were associated with a 3.8% reduction in overall hospital stay, 5.1% fewer ICU days, and significantly lower cost of hospital charges, Medicare payments to ACH, and Medicare payments to all providers. These differences were small (on the order of 2.9% to 6.2%) but highly statistically significant.

In a multivariate analysis using case controls, involvement of an ID specialist in the care of patients admitted to ACH resulted in improved outcomes and a lower cost of care, especially when the ID consultant was involved early in the hospitalization. ■

CME Instructions

To earn credit for this activity, please follow these instructions:

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4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Questions

1. According to the study by Schmitt et al., ID consultation for one of 11 specific infections led to the following beneficial outcome(s):

a. Decreased 30-day mortality

b. Lower 30-day readmission rates

c. Significantly decreased hospital charges

d. All of the above

2. In the retrospective study of a comprehensive database in Finland by Airaksinen, et al., patients undergoing cardioversion for atrial fibrillation of less than 48 hours duration without anticoagulation or a transesophageal echocardiogram had:

a. No increased risk of stroke.

b. A small (< 1%) risk of stroke even in the presence of CHADS2 stroke risk factors.

c. A high risk (approximately 10%) of thromboembolism in the presence of CHADS2 stroke risk factors.

d. An increased risk of stroke if cardioversion failed to restore normal sinus rhythm.

3. The study by Fogerty and colleagues looked at the sufficiency of sign-out by hospital medicine attendings on a non-teaching service. What characteristics did they observe?

a. Written sign-out was rarely supplemented with verbal sign-out.

b. The written sign-out was judged to be sufficient to answer less than one-third of the overnight inquiries.

c. Almost three-quarters of written sign-outs neither included anticipatory guidance nor tasks.

d. All of the above.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and;
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems.

[IN FUTURE ISSUES]

More original commentary by and for hospitalists

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By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Goldilocks Unable to Find Amount of Antioxidants That's Just Right

Source: Bjelakovic G, et al. *JAMA* 2013; 310:1178-1179.

The observation that excess oxidative stress is associated with diverse pathologic consequence has been consistently coupled with the obvious next intellectual step: antioxidants *should* be beneficial to prevent these consequences. Unfortunately, no Goldiloks has stepped forward to inform us which antioxidant is too much, which is too little, and which is just right. Or maybe the antioxidant hypothesis is just a fairy tale, after all?

This is not the first time that observational hypotheses have disappointed. In two clinical trials of antioxidant supplementation in persons at risk for lung cancer (combined n > 45,000), the first trial found an *increase* in lung cancer and mortality, and the follow-up trial was discontinued almost 2 years early because of similar outcomes.

This most recent Cochrane systematic review included 78 trials (n = 296,707) performed in both primary and secondary prevention modes. The "bottom line" is worth quoting: "Antioxidant supplements are not associated with lower all-cause mortality. Beta carotene, vitamin E, and higher doses of vitamin A may be associated with *higher* all-cause mortality." Some naysayers would suggest that we have not yet fulfilled the Goldilocks systematic approach: Maybe we used too little, maybe we used too much, or maybe we used the wrong formation, and have not yet found the approach that's "just right." For now, the science does not support a role for antioxidants in primary or secondary prevention. ■

Antipsychotics Are Associated with Increased VTE Risk

Source: Wu CS, et al. *J Clin Psychiatry* 2013;74:918-924.

Antipsychotics have suffered a beleaguered course of late: literature showing little efficacy advantage of newer vs older agents, concerns about increased mortality associated with their use, etc. A recent report suggests that antipsychotic treatment is also associated with a clinically meaningful increase in risk for venous thromboembolism (VTE), comprised of deep vein thrombosis plus pulmonary embolism.

Wu et al performed a case-control study of enrollees in the National Health Insurance Research Database of Taiwan to compare cases of confirmed VTE (n = 2162) with age-matched controls without VTE (n = 12,966). Initial analysis looked simply at the relative risk of antipsychotic use in persons with VTE vs controls. Second-step analysis adjusted for confounders.

Overall, the adjusted odds ratio for VTE in current antipsychotic users was 1.52 (i.e., current users were 52% more likely to experience VTE than controls); the odds ratio was substantially worse (3.26: a more than 3-fold increase in risk) for new users. These concerning results were attained even after correction for confounding factors such as utilization of thrombogenic medications (e.g., oral contraceptives) and medical comorbidities associated with increased VTE risk (e.g., congestive heart failure). Analysis of different classes of antipsychotics did not find any particular distinction among them. The mechanism by which antipsychotics might increase VTE risk is uncertain, although the authors posit that antipsychotic-induced sedation could lead to less physical activity with subsequent venous stasis. In any case, these data suggest vigilance for VTE in persons prescribed antipsychotics, especially in the early months of use. ■

Physician Visits for Itching

Source: Shive M, et al. *J Am Acad Dermatol* 2013;69:550-556.

If results from the National Ambulatory Medical Care Survey conducted by the CDC are correct, pruritus as a presenting complaint in ambulatory care may merit more of our attention. In a retrospective review of data from 1999-2009, there were approximately 7 million office visits per year in which pruritus (or itching) was indicated as a presenting symptom. In comparison, there were almost 18 million visits per year for low back pain. Since itch may or may not have been specifically indicated when syndromes such as a drug allergic reaction occur, the authors suggest that these numbers likely *underestimate* the true prevalence of pruritus.

The consequences of pruritus may range from minor nuisance to intolerable. Indeed, patients taking opioid analgesia frequently mention pruritus as a treatment-limiting adverse effect. Fortunately, clinicians have a diversity of agents to treat pruritus, including multiple generations of antihistamines as well as steroids (topical and systemic). Finally, it has been

recognized for more than 2 decades that doxepin — traditionally used as an antidepressant — has antihistaminic potency as much as 50 times greater than the most potent "traditional" antihistamines such as hydroxyzine. Because of this antihistaminic potency, doxepin is often used in refractory urticaria, when other antihistamines have failed, even though sedation is common at typical therapeutic doses. ■

Consequences of Non-Adherence in Treated Hypertensives

Source: Cummings DM, et al. *J Am Soc Hypertens* 2013;7:363-369.

The relationship between elevated blood pressure (BP) and stroke is linear and continuous. An abundance of clinical trial data indicate that treatment of hypertension (HTN) by means of numerous diverse classes of antihypertensives lowers stroke risk by ≥ 40%. Clinical trials, however, are not "real life." The Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study is examining a large population (n = 30,239) of southeastern men and women with HTN. Their assessment of the relationship between self-reported degree of antihypertensive medication adherence and serious outcomes (stroke/TIA) from a subset population (n = 15,071) is quite sobering.

During a 5-year window of observation, study participants were grouped into four categories of adherence using the Morisky scale, which translates into general groupings of high, good, moderate, and low adherence. Perhaps not surprisingly, mean systolic BP in the high adherence group was substantially better than the low adherence group (131 mmHg vs 138 mmHg). Incidence of stroke or TIA was 8% higher in the lowest adherence group compared to the highest. Good BP control has meaningful payoff; every decrement of adherence less than that is costly. ■

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Long-Term Risk-Reduction Benefits of Sigmoidoscopy and Colonoscopy

Source: Nishihara R, et al. *N Engl J Med* 2013;369:1095-1105.

Participants from two large observational studies provide an opportunity to evaluate the risk reduction accrued from either colonoscopy (COL) or sigmoidoscopy (SIG). The Nurses' Health Study (n = 121,700 female nurses) and the Health Professionals Follow-up Study (n = 51,529 male health professionals) have more than 20 years' prospective follow-up of their participants. During this interval, there were 1185 cases of colon cancer and 474 deaths from colon cancer.

Skeptics have long held fast to the tenet that SIG had an advantage over COL: proven risk reduction for colon cancer mortality for the former. Although the intuitive additional advantage of examining the entire colon with COL seemed a no-brainer, purists argued that whether COL was truly better than SIG was not yet proven, and that since COL was associated with greater risks (perforation, adverse effects from sedation, etc.), there was reasonable basis to continue with SIG as a preferred method. In accord with this philosophy, noting the many missed opportunities for colon cancer screening and prevention, advocacy groups rallied around the call-to-action, "The best colon cancer screening test is whichever one you can get done!"

These data may change that perspective, since the risk reduction for colon cancer death was almost twice as great for COL as SIG (hazard ratios, 0.59 vs 0.32). The "no-brainer" part of the equation was also resoundingly confirmed: COL reduced mortality from proximal colon cancer by more than half compared to no risk reduction through SIG. ■

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Warfarin Outperforms Dabigatran in Patients with Mechanical Heart Valves

Source: Eikelboom JW, et al. *N Engl J Med* 2013;369:1206-1214.

The atrial fibrillation (AF) headlines have been filled with celebration over the efficacy of factor Xa inhibitors (e.g., rivaroxaban, apixaban) and direct thrombin inhibitors (e.g., dabigatran) for prevention of thrombotic events. Since warfarin — though highly effective, exhaustively studied, and time-tested — also has distinct clinical burdens (e.g., need for monitoring, food interactions, drug interactions), agents that were at least as efficacious for thrombotic risk reduction — with fewer of these same clinical burdens — were welcomed.

Success in AF, however, does not necessarily translate into other pathologies. Eikelboom et al studied patients with recent mitral or aortic mechanical valve replacement (n = 252). Subjects were randomized to dabigatran or warfarin. About one-fourth of these patients also had AF.

The trial had to be discontinued early because of untoward events in the dabigatran group: stroke occurred in 5% of the dabigatran group vs none in the warfarin group, and major bleeding was twice as common on dabigatran (4% vs 2%). Although earlier trials in animals were encouraging, these data indicate that warfarin is safer and better tolerated in patients with recent surgery for prosthetic mechanical heart valves. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Reglan Safe in Pregnant Women for Nausea and Vomiting

In this issue: Reglan safe in pregnancy; battle brewing over naming of biosimilar drugs; and FDA actions.

Reglan safe in pregnancy

Use of the anti-nausea medication metoclopramide (Reglan) in pregnancy is not associated with an increased risk of major congenital malformations, spontaneous abortion, or stillbirth. These were the findings of large, register-based cohort study from Denmark. The safety of metoclopramide in pregnancy has been of concern because it is increasingly used to treat pregnant women with nausea and vomiting. Metoclopramide-exposed pregnant women were matched with unexposed women in a 1:4 ratio, with more than 40,000 exposed women in the cohort, of whom more than 28,000 received the drug in the first trimester. The drug was not associated with major malformations or any of more than 20 individual malformations. There was no increase in spontaneous abortion, stillbirth, preterm birth, low birth weight, or fetal growth restriction (*JAMA* 2013; 310:1601-1611). ■

Battle over naming of biosimilar drugs

A battle is shaping up between biotech companies and the Generic Pharmaceutical Association (GPhA) over the naming of biosimilar drugs. Biosimilars, or "follow-on biologics," are products whose active ingredient is an approved version of a previously approved biopharmaceutical. Since biologics are generally manufactured in a complex process that may include molecular clones and proprietary cell lines, it is virtually impossible for the manufacturers of a biosimilar to match the process step-by-step. This results in small differences between the innovator product and the follow-on product (hence the name "biosimilar"). With billions of dollars of revenue at stake, biotech companies, such as Genentech and Amgen, have been lobbying federal and state legislators to tighten the rules regarding use of biosimilars. There has also been concern that the FDA might prohibit biosimilar manufacturers from using the same generic name as the original drug, a move that biotech companies would endorse and the GPhA would strongly oppose. A bipartisan group of senators recently entered the fray by penning a letter to the FDA urging the agency to allow biosimilars to share the name of the innovator product. Led by Republican John McCain and Democrats John Rockefeller and Tom Harkin, six senators urged the FDA to follow the intent of the Biologic Price Competition and Innovation Act, suggesting that if biosimilars were not allowed to share the same name it would undermine "the safety and accessibility of affordable biosimilars." The FDA had been in support of allowing biosimilars to share generic names, but the sudden removal of a page from the FDA website that contained a 2006 statement supporting same-name biosimilars prompted the concern of the senators. ■

FDA Actions

The FDA is recommending that hydrocodone-containing pain medications (Vicodin, Norco,

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Lortab, and others) be upgraded from schedule III to schedule II. The move would put significant restrictions on the drugs, including requiring a physician signature for each prescription, no refills, and no phone or fax prescriptions. Hydrocodone would join other powerful opioids including oxycodone, morphine, fentanyl, and methadone in the more restricted schedule II category. The FDA is reacting to the epidemic of prescription drug abuse and addiction that has decimated some communities in this country and has led to the overdose by tens of thousands, including teenagers and young adults. Prescription drug overdoses now outnumber illegal drug overdoses 3:1. The Drug Enforcement Agency has been pushing for stronger controls on hydrocodone for years, but physician and pharmacy organizations have successfully argued that the change unfairly impacts legitimate patients and would increase physician and pharmacy workloads. Hydrocodone/acetaminophen combination drugs were the most frequently prescribed medications in the United States last year. The change is likely to take effect by mid-2014.

Meanwhile, the FDA has approved an extended-release hydrocodone product for the management of severe pain requiring daily, around-the-clock treatment. The drug is an extended-release formulation of hydrocodone that is dosed twice a day. It is available in six strengths — 10, 15, 20, 30, 40, and 50 mg capsules. Because of concerns of addiction and abuse, and the greater risk of overdose and death associated with extended-release and long-acting formulations, hydrocodone extended-release should be reserved for patients in whom alternative treatment options are ineffective, not tolerated, or one otherwise provides inadequate pain management. The approval of hydrocodone extended-release was controversial given that the drug is not packaged as a tamper-proof capsule, theoretically allowing it to be crushed, chewed, or even injected. Experience with abuse of extended-release oxycodone (OxyContin) prompted the FDA to require Purdue Pharmaceuticals to reformulate the drug into a tamper-proof capsule in 2010. Some in the FDA felt this new formulation of hydrocodone should be similarly packaged, but the drug was approved without such restrictions. Hydrocodone extended-release will be schedule II, and marketed by Zogenix Inc. as Zohydro.

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The FDA has approved two new drugs to treat pulmonary arterial hypertension (PAH). Macitentan is a dual endothelin-receptor antagonist, while riociguat is a first in class soluble guanylate cyclase stimulator. Macitentan is a once-daily pill that is approved to treat PAH. Its safety and efficacy was established in a 2-year, randomized, placebo-controlled trial of 742 patients. Patients in the active treatment group had delayed progression of the disease and improved symptoms. Macitentan is manufactured by Actelion Pharmaceuticals and will be marketed as Opsumit. Riociguat is also an oral agent given three times a day. It is approved for PAH and also for chronic thromboembolic pulmonary hypertension (CTEPH), the first drug to be approved for this latter indication. Safety and efficacy for PAH was shown in a trial of 443 patients in which treated patients had improved 6-minute walk times after 12 weeks. It was shown to be effective for CTEPH in a study of 261 patients in which treated patients had improved walk times at 16 weeks. Riociguat is marketed as Adempas by Bayer HealthCare.

An FDA advisory group has recommended approval of simeprevir and sofosbuvir, two long-awaited agents to treat hepatitis C virus (HCV). Both are oral drugs and have higher cure rates compared with currently available agents. Simeprevir is a protease inhibitor, similar to currently available agents such as telaprevir and boceprevir, while sofosbuvir is a new type of hepatitis c antiviral called a nucleotide analogue (or "nuke"). Sofosbuvir has been highly anticipated as clinical trials suggest that it results in sustained virological responses as high as 90%, and may eventually be part of an all-oral regimen for HCV along with ribavirin. The FDA is expected to approve both drugs by mid-December. Simeprevir will be marketed by Johnson & Johnson while sofosbuvir will be marketed by Gilead Sciences. ■