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INSIDE

Noncardiac Surgery in Patients with Coronary Stents

ABSTRACT & COMMENTARY

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

This article originally appeared in the December 2009 issue of Clinical Cardiology Alert. *It was edited by Michael H. Crawford, MD, and peer reviewed by Ethan Weiss, MD. Dr. Crawford is Professor of Medicine, Chief of Cardiology, University of California, San Francisco, and Dr. Weiss is Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Crawford is on the speaker's bureau for Pfizer, and Dr. Weiss reports no financial relationships relevant to this field of study.*

Source: van Kuijk P, et al. Timing of noncardiac surgery after coronary artery stenting with bare metal or drug-eluting stents. *Am J Cardiol*. 2009;104:1229-1234.

PERCUTANEOUS CORONARY INTERVENTION (PCI) WITH BARE-metal stents (BMS) or drug-eluting stents (DES) remains the most common method of coronary revascularization. Dual anti-platelet therapy with aspirin and a thienopyridine dramatically reduces the incidence of coronary stent thrombosis. However, around the time of noncardiac surgery, the risk of stent thrombosis rises. In addition, the bleeding risk also rises in patients who continue dual anti-platelet therapy. Thus, there is considerable uncertainty about the most appropriate time to perform noncardiac surgery in patients who have coronary artery stents, and whether or not to continue dual anti-platelet therapy throughout the perioperative period. Accordingly, van Kuijk et al performed a retrospective analysis of 550 patients who underwent noncardiac surgery at various intervals after PCI and described the incidence of major adverse cardiac events (MACE) in the 30 days following the noncardiac surgery.

From 2000 to 2007, 550 patients at their center underwent PCI and, subsequently, had noncardiac surgery. All patients from 2000-2002 had BMS (n = 174) and all patients from 2002-2007

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had DES (n = 376). Patients with BMS were routinely prescribed aspirin for life and clopidogrel 75 mg daily for at least 30 days. Patients receiving DES were routinely prescribed aspirin for life and clopidogrel 75 mg daily for at least three months (sirolimus) or six months (paclitaxel). Patients with DES had higher cardiac risk profile. They had increased rates of current or former smoking (70% vs. 43%; $p < 0.001$), diabetes (25% vs. 15%; $p = 0.01$), dyslipidemia (57% vs. 47%; $p = 0.02$), were older (63.3 years vs. 61.2 years; $p = 0.04$), had higher incidence of renal failure (11% vs. 4%; $p = 0.01$), and were less likely to be on a calcium channel blocker (26% vs. 48%; $p < 0.001$). In addition, patients receiving DES had longer duration of clopidogrel therapy (six months [1-6 months] vs. two months [1-3 months]; $p < 0.001$) and were more likely to receive statins (61% vs. 52%; $p = 0.05$), likely reflecting the evolution of medical therapy between the years of the procedures. Other baseline clinical demographics were similar between groups.

Patients underwent surgery that was high risk in 22% and 15%, intermediate risk in 49% and 51%, and low risk in 31% and 33% in those receiving DES and BMS, respectively. Perioperative complications were defined as the occurrence of MACE (death, myocardial infarction, stent, thrombosis, or repeat revascularization) within 30 days of the surgery. Intervals between PCI and surgery were arbitrarily divided into < 30 days, < 3 months, and > 3 months for patients receiving BMS, and into < 30 days, 30 days to 3 months, 3 to 6 months, 6 to 12 months and > 12 months for patients receiving DES.

Results: Perioperative MACE occurred more frequently when noncardiac surgery was performed within 30 days of PCI; the incidence declined thereafter. In patients who had received BMS, perioperative MACE occurred in 50% of those undergoing noncardiac surgery within 30 days of PCI, despite all patients receiving dual anti-platelet therapy up until the time of surgery. MACE occurred in 14% undergoing surgery 30 days to 3 months after PCI and in 4% at more than three months after PCI ($p < 0.001$).

In patients who had received DES, perioperative MACE occurred in 35% of those undergoing noncardiac surgery within 30 days of PCI, 13% at 30 days to three months, 15% at 3 to 6 months, 6% at 6 to 12 months, and 9% after 12 months from PCI ($p < 0.001$). After multivariable analysis, noncardiac surgery within 12 months of PCI with DES was associated with an increased risk of perioperative MACE (hazard ratio 2.0, 95% CI 1.1 to 3.5).

In patients who experienced MACE, 45% and 55% had been receiving single and dual anti-platelet therapy, respectively ($p = 0.92$), suggesting that continuing dual anti-platelet therapy perioperatively does not prevent MACE. However, dual anti-platelet therapy was associated with higher rates of severe bleeding than single anti-platelet therapy (21% vs. 4%; $p < 0.001$). Importantly, of all the MACE events that occurred following noncardiac surgery, regardless of the interval since PCI, over 80% were fatal. van Kuijk et al conclude that there is an inverse relation between the interval from PCI to noncardiac surgery and perioperative MACE, and that continuation of dual anti-platelet therapy until surgery did not provide complete protection from MACE.

■ COMMENTARY

There are no prospective, randomized trials to guide the timing of noncardiac surgery in patients who have coronary artery stents. In this retrospective study, van Kuijk et al confirm previous series that the rates of perioperative MACE are high in patients having surgery early after PCI and become lower with time. Importantly, they showed that the risk of perioperative MACE never reaches zero, and that continuation of dual anti-platelet therapy does not abolish this risk. Furthermore, their data highlight the importance of perioperative MACE in this group — the high incidence of death (83% in DES and 91% in BMS) in patients experiencing MACE.

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In deciding the optimal time for noncardiac surgery after PCI, clinicians must make an informed decision about the importance of the surgery vs. the risk of perioperative MACE (which carries a high mortality). Certainly within the first 30 days, the risk of MACE and death are very high, and surgery should be performed only for life-threatening emergencies. Current guidelines suggest that elective surgery should be postponed at least six weeks after BMS and 12 months after DES. These data confirm the importance of waiting. Furthermore, van Kuijk et al have demonstrated that dual anti-platelet therapy does not eliminate the risk of perioperative MACE, but does increase the risk of bleeding. ■

Influenza H1N1 Can Hurt Muscles Bad

ABSTRACT & COMMENTARY

By Joseph F. John, MD

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This article originally appeared in the December 2009 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, and Dr. Price is Assistant Professor, University of Colorado School of Medicine. Dr. Deresinski serves on the speaker's bureau for Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck, and Dr. Price reports no financial relationships relevant to this field of study.*

Source: Ayala E et al. Rhabdomyolysis associated with 2009 influenza H1N1. *JAMA*. 2009;302:1863-1864.

It has been known for decades that influenza viruses have a propensity to affect muscle. Muscle aches from mild to severe occur regularly with the acute attack of the virus. I can remember as a young resident being so sore that I had to be rolled over and back during the first few days of influenza illness.

In the most recent issue of *JAMA*, filled with reports of H1N1 from North America, a short letter to the editor from Stanford University Medical Center highlighted the versatility of 2009 H1N1.

The patient in question is a 28-year-old influenza survivor who had one week of shortness of breath, muscle aches, and fever. Her pulse oximetry on presentation was 80% on room air. Her WBC was only 2800/uL, the LDH was 1875 U/L, and the creatine kinase (CPK) was a massive 27,820 U/L (normal 13-156). There was hemoglobin in the urine and infiltrates on the chest radiograph.

The patient had to be intubated but was able to be treated with oseltamivir and broad-spectrum antibacterials. A bronchoscopic exam revealed very friable hyperemic mucosa. The BAL fluid, when cultured at the California state lab, grew influenza A 2009 H1N1. With intensive critical care, the CPK decreased from 27,820 to 18,000 on day two to 3,000 on day four, and then normalized. She was removed from mechanical ventilation on day 15 and discharged to home at day 18.

■ COMMENTARY

It would be ideal to know how many patients with 2009 H1N1 have major muscle involvement. My clinical impression is that it occurs in < 1% of patients who have seasonal influenza. A 2005 Japanese study of patients with influenza pneumonia placed the value much higher (9.3%), though only 63 patients were studied (*Nihon Kokyuki Gakkai Zashi*. 2005;43:731-735). Yet, for a disease that affects millions of patients per year, even 1% of 1 million is 10,000! When the year of novel influenza ends, perhaps we can get a better idea of the real prevalence.

Whatever the attack rate upon muscle, rhabdomyolysis is a real phenomenon that should fix the attention of providers when they see patients with severe influenza. In the Stanford patient, the CPK returned to normal quickly, but she still needed intubated and critical care in order to survive. The ability to diagnose 2009 H1N1 by viral culture resided in the Public Department of California Health, a testimony to our public health systems that have stepped up to the plate to help document strains of this season's influenza viruses. Culture from fluid obtained by BAL is a caveat of the present case, particularly since the nasopharyngeal sample was negative by PCR.

We await further descriptions of known and unknown complications as we watch the 2009 H1N1 pandemic unravel. Influenza remains a disease that can humble clinicians. Yet to quote a recent poem by the illustrious

physician poet Jack Coulehan, "The grace of humility is a precious gift." ■

Stress Ulcer Prophylaxis: Do No Harm

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, MSc

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Dr. Akhtar reports no financial relationship to this field of study.

This article originally appeared in the December 2009 issue of Critical Care Alert. *It was edited by David J. Pierson, MD and peer reviewed by William Thompson, MD. Dr. Pierson is Professor, Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, and Dr. Thompson is Staff Pulmonologist, VA Medical Center; Associate Professor of Medicine, University of Washington; they report no financial relationships relevant to this field of study.*

Synopsis: *A single-center, retrospective, observational study found that stress ulcer prophylaxis is used in a majority of ICU patients, despite absence of risk factors for stress ulcers.*

Source: Farrell CP, et al. Overuse of stress ulcer prophylaxis in the critical care setting and beyond. *J Crit Care*. 2009 Aug 14; Epub ahead of print.

THIS STUDY'S PRIMARY AIM WAS TO DOCUMENT THE risk factors for stress ulcers and the use of stress ulcer prophylaxis (SUP) in patients upon ICU admission, transfer to the floor, and discharge home. Retrospective chart review was performed for all patients admitted over a four-month period to the mixed medical-surgical ICU of an academic institution. Exclusion criteria were: age < 16 years, admission diagnosis of gastrointestinal (GI) bleeding, new onset gastroesophageal reflux disease or esophagitis, allergy to H_2 antagonists, and withdrawal of care at admission. Data collected included usual demographics, admission diagnoses, and preadmission medications. Risk factors for stress ulcers were categorized as major (mechanical ventilation or coagulopathy) or minor (sepsis, severe hypotension, acute renal or hepatic failure, severe head or spinal cord trauma, history of GI bleeding, severe burn injury, prolonged major surgery, or high-dose corticosteroids). Patients were classified into four groups: presence of a major risk factor, only minor risk factors, no risk factors, or home use of acid-suppressive medications.

The study included 210 patients; 31 others were excluded per the predefined study criteria. Upon admission to the ICU, 87% of patients received SUP. This figure was > 95% for patients with a major risk factor and > 82% for patients with only a minor risk factor. Of the patients with no risk factors for stress ulcers, 68% received SUP. One hundred ninety patients survived to transfer out of the ICU to the ward; of those with no risk factors for stress ulcers, 60% remained on prophylaxis. One hundred eighty-five patients survived to hospital discharge; of those with no risk factors for stress ulcers, 31% were discharged home on prophylaxis. The authors performed some secondary analyses in an attempt to identify potential factors (age, sex, and the previously defined major and minor risk factors for stress ulcers) more likely to be associated with use of SUP; as expected, an association was seen with ventilator-dependent respiratory failure, but little other information could be garnered.

■ COMMENTARY

Use of SUP in the ICU has been part of routine practice for about two decades. Progression of untreated stress ulcers to clinically important GI bleeding clearly worsens ICU morbidity and mortality.[1] The strongest indications for SUP are mechanical ventilation > 48 hours and coagulopathy (platelet count < 50,000/m^3, International Normalized Ratio > 1.5, or partial thromboplastin time > 2 times the upper limit of normal), as reported in Cook et al's large prospective multicenter observational study.[2] A variety of smaller (much less robust) studies suggest increased stress ulcer risk in other ICU populations, including patients with sepsis, hypotension, head or spinal cord trauma, multiple trauma, severe burns, and acute renal or hepatic failure; despite limited data, the recommendation to treat such patients with SUP is included in some expert guidelines.[3] Furthermore, some experts advocate SUP for ICU patients receiving high-dose glucocorticoids (particularly in combination with other risk factors such as aspirin), those with a prior recent history of peptic ulcer disease or GI bleeding, and prolonged ICU stay (one week or longer). Finally, there is essentially no evidence to support use of stress ulcer prophylaxis in non-ICU hospital patients.[4]

In comparing medications available for SUP, H_2 blockers have been shown to be more effective than

sucralfate, and both appear superior to antacids alone; it remains unclear whether proton pump inhibitors are superior or simply equivalent to H_2 blockers. Enteral nutrition may reduce the risk of stress ulceration with clinically important GI bleeding; however, it is unknown whether enteral nutrition alone gives protection equivalent to that offered by acid-suppressive agents.[5]

Farrell et al's report reiterates what has been described previously by other authors. Intensivists are appropriately treating the majority of at-risk patients with SUP; we are also unnecessarily treating a large number (more than two-thirds in this study) of other patients. This excess administration of stress gastritis prophylaxis in the ICU and non-ICU settings is not benign. Patients are placed at risk of common side effects of SUP medications (for example, altered mental status with H_2 antagonists, or diarrhea and other GI upset with proton pump inhibitors), as well as medication interactions and frank allergic reactions. There is evidence to suggest that increased nosocomial pneumonia may be seen with use of certain medications for SUP.[6] In addition, inappropriate medication prescription poses significant economic burdens to hospitals and individuals.[4]

It behooves all of us to do no harm; Farrell et al have reminded us that we must examine our practices and use SUP only for those ICU patients expected to reap benefit. ■

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Both Hyponatremia and Hypernatremia at ICU Admission Predict Poor Outcome

ABSTRACT & COMMENTARY

By David J. Pierson, MD

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

This article originally appeared in the December 2009 issue of Critical Care Alert. *It was peer reviewed by William Thompson, MD.*

Synopsis: *In this study of initial serum sodium values in more than 150,000 adults admitted to ICUs, both hyponatremia (Na < 130 mmol/L) and hypernatremia (Na > 150 mmol/L) were associated with substantially increased ICU and hospital mortality.*

Source: Funk GC, et al. Incidence and prognosis of dysnatremias present on ICU admission. *Intensive Care Med*. 2009 Oct 22; Epub ahead of print.

In this study, using a large database of adult patients admitted to 77 ICUs in Austria from 1998 through 2007, Funk et al examined the association between initial values for serum sodium (either below or above the normal range of 135-145 mmol/L) and the outcomes of ICU and hospital stays. From 176,703 admissions to the ICUs contributing to the database, the authors excluded 8,509 readmissions, 3,292 patients < 18 years of age, and 13,416 patients who lacked a recorded hospital outcome, a valid SAPS II score, or an admission sodium value, but included data on all others. This left 151,486 patients for analysis. Considering the serum sodium value that deviated most from the predicted normal value of 140 mmol/L during the first 24 hours in the ICU, there were 26,782 patients (17.7%) with hyponatremia (Na < 135 mmol/L), 114,170 patients (75.4%) with normonatremia, and 10,534 patients (6.9%) with hypernatremia (Na > 145 mmol/L).

Most patients had initial serum sodium values in the normal range. Hyponatremia was 2.5 times more common than hypernatremia. Most hyponatremic patients (78%) were classified as borderline, with Na = 130-135 mmol/L; while 15% had mild hyponatremia (Na = 125-130 mmol/L) and 7% were severe (Na < 125 mmol/L). Of the patients with initial sodium values that were abnormally high, 73% were borderline (Na = 145-150 mmol/L), 18% were mild (Na = 150-155 mmol/L), and 9% were severe (Na > 155 mmol/L). Statistical evaluation of the seven categories of admission sodium (from severe hyponatremia to severe hypernatremia) revealed a U-shaped curve with respect to hospital mortality. That is, with normonatremia taken as 1.00, odds ratios for death during the hospitalization were 1.32, 1.89, and 1.81 for borderline, mild, and severe hyponatremia, respectively, and 1.48, 2.32, and 3.62 for borderline, mild, and severe hypernatremia, respectively. Hospital mortality was 14.6% for normonatremic patients, 32.9% for mildly and 33.6% for severely hyponatremic patients, and 45.3% and 57.8% for mildly and severely hypernatremic patients, respectively. Using the initial serum sodium value as an indicator, without attempts to account for potential confounders, and compared to a mortality of roughly 15% for normonatremic patients, hospital mortality was about 33% for patients with Na < 130 mmol/L and more than 50% for patients with Na > 150 mmol/L. Multiple regression analysis suggested that hyponatremia and hypernatremia were independent risk factors for mortality.

■ **COMMENTARY**

This is the largest study reported to date that associates initial derangements in serum sodium values with outcomes in critically ill patients. It does not prove that an abnormal sodium level increases mortality in and of itself, but the relationship between sodium levels and mortality persisted with all of the adjustments the authors made for patient demographics and severity of illness. It also does not say anything about the treatment of hyponatremia and hypernatremia, and specifically that optimal correction of these electrolyte abnormalities would improve the results observed here. However, in a large cohort of mixed adult ICU patients with the full spectrum of medical and surgical diagnoses, it confirms previous associations between the presence of substantially abnormal serum sodium values on ICU admission and the likelihood of in-hospital mortality. ■

Do You Come to Work When You're Sick?

ABSTRACT & COMMENTARY

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

This article originally appeared in the December 2009 issue of Critical Care Alert. *It was peer reviewed by William Thompson, MD.*

Synopsis: *Most respondents in this survey of medical students, residents, and staff physicians reported coming to work when they had a respiratory tract infection, with staff physicians most likely to do so.*

Source: Gudgeon P, et al. Do you come to work with a respiratory tract infection? *Occup Environ Med*. 2009;66:424.

This article reports on a questionnaire study administered to medical students, residents in internal medicine and surgery, and staff physicians at the University of Toronto in the summer of 2006. The authors queried the subjects about whether they personally came to work when they had symptoms of a respiratory tract infection, and sought to determine factors that influenced whether they did so.

Gudgeon et al sent their on-line survey to 1202 people, of whom 149/202 medical students (74%), 317/650 residents (49%), and 202/350 staff physicians (58%) responded. Most respondents reported having been ill with symptoms of a respiratory tract infection for 1-2 days or more. Students had, on average, 1.9 more days of illness than residents who, in turn reported 0.9 more illness days than staff physicians, rates that were significantly different. In all three groups, participants reported coming to work when they were sick. Sixty percent of staff physicians indicated that they worked more than 80% of the time when they were sick with a respiratory tract infection; the corresponding proportions of residents and medical students who worked while ill were 51% and 48%, respectively.

Reasons given for staying home from work when ill were similar among the three groups: feeling too sick to work, being concerned about transmitting illness to

others, and having obvious symptoms of a respiratory tract infection. However, reasons offered for coming to work despite the illness varied among the groups. Medical students cited extrinsic factors such as a requirement that they produce a note from a physician to be released from duties, and difficulty obtaining such notes to satisfy university requirements. In contrast, staff physicians most often invoked intrinsic factors such as concern for delivering patient care; this was especially true for surgeons, who cited concerns about having to reschedule procedures.

To explore possible factors influencing the decision to stay home or come to work while ill, the authors asked whether the respondents believed in the legitimacy of a colleague's sick day. Substantially fewer students and residents (45% and 49%, respectively) than staff physicians (79%; $p < 0.001$) agreed that the absence was justified. Residents were also more likely to feel annoyed by the absence of a colleague than were medical students or staff physicians. Surgical residents and staff were more likely to come to work when ill than were their internal medicine colleagues (78% vs. 50%; $p < 0.001$); surgeons also reported a higher threshold for staying home than did the internists, and were less willing to cover a colleague's workload because of illness.

■ COMMENTARY

This concise (one-page) report confirms several previous studies indicating that as many as 80% of physicians come to work when they are ill. The authors use the term "presenteeism" — in contrast to "absenteeism" — to describe this phenomenon. They point out that, like other health care workers, physicians are aware that respiratory tract infections are both easily transmitted and a serious problem, especially in the first few days of illness. They urge health care workers who are ill to either stay home or take deliberate precautions (e.g., mask, frequent hand washing, and avoidance of certain patients) to avoid infecting others. They also suggest system changes to make it easier for medical students to be absent when sick, and the development of coverage mechanisms to accommodate the workload of absent residents.

"Presenteeism" can be as big a problem during epidemic influenza or other rampant respiratory tract infection as staff absenteeism. There is no question that absence from work on the part of physicians and other health care workers causes problems for those who are not sick, but it is also important that staff not risk transmitting illness to both patients and colleagues by coming to work when they are ill. For "presenteeism" to be avoided, individual staff members have to be aware of the need to stay home if they fall ill. The system should not present barriers to staying away from work in such circumstances, and must also make the necessary plans and adjustments to continue functioning when this happens. ■

CME Questions

13. According to the study by van Kuijk et al, which of the following is true in patients undergoing noncardiac surgery after percutaneous coronary intervention (PCI)?

a. Dual antiplatelet therapy prevents perioperative major adverse cardiac events.
b. Regardless of the interval since PCI, 80% of the perioperative major adverse cardiac events were fatal.
c. The highest risk of a perioperative major adverse cardiac event was during the interval of 3-6 months after PCI.
d. The lowest risk of perioperative major adverse cardiac events occurred during the first 30 days after PCI.

14. In the retrospective cohort study by Farrell, et al., which of the following was *true*?

a. The majority of patients admitted to the ICU without risk factors for stress ulcers received stress ulcer prophylaxis.
b. Stress ulcer prophylaxis was appropriately discontinued on nearly all patients upon discharge from the ICU.
c. Stress ulcer prophylaxis is not necessary in the ICU.
d. All of the above

15. In the large database analysis described by Funk et al, exploring the frequency and impact of hyponatremia and hypernatremia on admission to the ICU, which of the following is true?

a. Hypernatremia was more common than hyponatremia.
b. The odds ratio of death was much higher for hyponatremia than for hypernatremia.
c. Multiple regression analysis found that hyponatremia and hypernatremia are independent risk factors for mortality.
d. Neither hyponatremia nor hypernatremia independently affected mortality.

Answers: 13. (b); 14. (a); 15. (c)

CME Objectives

The objectives of *Hospital Medicine Alert* are to:

• review pertinent safety, infection control, and quality improvement practices;

• discuss diagnosis and treatment of acute illness in the hospital setting; and

• review current data on diagnostic and therapeutic modalities for common inpatient problems. ■

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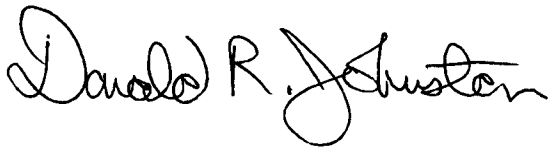

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