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Hospital Medicine

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

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ABSTRACT & COMMENTARY

Hospital-Acquired Anemia: What Are the Implications?

By Kenneth P. Steinberg, MD, FACP

Professor, University of Washington School of Medicine, Seattle, WA

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

SYNOPSIS: Hospital-acquired anemia (HAA) is multifactorial in etiology and develops in nearly 75% of hospitalized patients. Moderate and severe HAA are associated with significant increases in hospital mortality, length of stay, and total hospital charges. Whether reducing the frequency and severity of HAA will improve these outcomes remains unknown.

SOURCE: Koch CG, et al. Hospital-acquired anemia: prevalence, outcomes, and healthcare implications. *J Hosp Med* 2013;8:506-512.

SUMMARY

Most hospital-based clinicians are aware that anemia develops in many hospitalized patients. This hospital-acquired anemia (HAA) has many etiologies including phlebotomy, hemodilution from intravenous fluid administration, procedural blood loss, and impaired erythropoiesis from acute illness. Transfusion thresholds in hospitalized patients have decreased over the last decade, but transfusion still carries risk. Given that the magnitude of the problem remains unclear, these investigators set out to study the frequency, severity, and implications of HAA.

This was a retrospective study of 417,301 hospitalizations in adult patients from January 2009 to September 2011 at the Cleveland Clinic Health System. Data were extracted from an administrative database (the University HealthSytem Consortium, or UHC, clinical database) consisting of demographics, baseline comorbidities, and outcomes and combined with hemoglobin data from the hospitals' electronic medical record. Patients were excluded if they had anemia present on admission

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Hospital Medicine
[ALERT]

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or if hemoglobin (Hgb) values were unavailable during the hospitalization. The final dataset consisted of 188,447 hospitalizations. HAA was categorized based on the lowest Hgb value during the hospitalization as no anemia, mild anemia (Hgb > 11 and < 12 g/dL in women, > 11 and < 13 g/dL in men), moderate anemia (Hgb > 9 and ≤ 11 g/dL), and severe anemia (Hgb ≤ 9 g/dL). Outcomes were all-cause in-hospital mortality, total hospital length of stay (LOS), and total hospital charges.

Among patients without anemia at the time of admission, the prevalence of hospital-acquired anemia was an astonishing 74%! Twenty-two percent (22%) developed mild anemia, 30% developed moderate anemia, and 22% developed severe anemia, while 26% did not develop anemia during their hospitalization. As might be expected, patients who developed HAA were older, had more comorbidities, and more commonly had surgical diagnoses than patients who did not develop HAA. Patients with mild HAA did not have higher risk-adjusted mortality than those without HAA, but as the anemia worsened, risk-adjusted hospital mortality increased in a dose-dependent manner compared to patients without HAA: mortality in moderate anemia was 1.51 times higher (95% CI: 1.33-1.71, P<0.001) and in severe anemia was 3.28 times higher (95% CI: 2.90-3.72, P<0.001). HAA was also associated with a significant increase in LOS and hospital charges even when adjusted for all comorbidities. Compared to patients without HAA, patients with severe HAA (Hgb ≤ 9 g/dL) had a mean relative increase in LOS that was nearly double at 1.88 (95% CI: 1.86-1.89, P<0.001) and total hospital charges for severe HAA that were also nearly double at 1.80 (95% CI: 1.79-1.82, P<0.001).

■ COMMENTARY

I believe that this is an important observational study that hopefully will stimulate more work on the prevention of hospital-acquired anemia. These authors identified a very high prevalence of HAA, even higher than I would have anticipated: 52% of patients developed either moderate or severe anemia after hospitalization. Patients who developed severe HAA had over a 3-fold increase in their risk of death even after adjusting for all measured comorbidities. This study suggests that HAA is an independent risk factor for in-hospital death, but causality can be difficult to ascertain in observational studies. Thus, it is not clear that the anemia itself caused the increased mortality. It could be that the anemia was simply a marker of increased risk caused by an unmeasured covariate or other unknown factors. Another concern I have is that the diagnosis of anemia at the time of admission was based on the use of the diagnostic code for Anemia Present on Admission. The accuracy of that code is not clear to me. Thus it is conceivable that this methodology underestimated the number of patients who had some degree of anemia on admission thus over-estimating the prevalence of HAA. Despite those concerns, the strengths of the study include its large size and the widespread acceptance of their particular administrative database for many other studies.

Even if the reported prevalence is an over-estimate, the association of HAA with an increased risk of death and increased LOS and hospital charges are highly significant and important observations. Given the caveats of an observational study, it is conceivable that either the anemia or the treatment thereof is one cause of the adverse outcomes observed in this study. While further studies are warranted, hospitalists are poised to initiate some fairly simple interventions targeting one of the major causes of HAA. By being meticulous in our ordering of laboratory testing, batching laboratory requests, using blood conservation devices in the intensive care units, and in advocating for our hospitals to move to the use of smaller-volume collection tubes (pediatric tubes) we can reduce the amount of blood loss from phlebotomy and laboratory testing. Whether this will translate into improved outcomes has yet to be shown, but this study highlights the importance of hospital-acquired anemia and its prevention. ■

ABSTRACT & COMMENTARY

Digoxin Helps Prevent Admissions in Patients with CHF

By Deborah J. DeWaay, MD, FACP

Assistant Professor, Medical University of South Carolina, Charleston, SC

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

SYNOPSIS: 30-day all-cause hospital admission rates lowered in older patients with chronic systolic heart failure who were started on digoxin when compared to placebo.

SOURCE: Bourge RC, Fleg JL, Fonarow G, et al. Digoxin reduces 30-day all-cause hospital admission in older patients with chronic systolic heart failure. *Am J Med* 2013; 126:701-708.

There is increasing pressure on hospitals to minimize readmission rates, especially in the Medicare population. Since heart failure is a leading cause of hospital admissions, this population of patients is a key group to focus efforts for decreasing these rates. Research done with the Digitalis Investigation Group (DIG) trial has previously shown that the use of digoxin decreased the readmission rate for heart failure. Bourge and his colleagues used the data collected during this trial to investigate the effect of digoxin on older patients with respect to their all-cause hospital admission rate within 30 days of beginning the drug.

These investigators did a secondary analysis of the DIG trial. In this trial, 6800 older patients (average age 72) with chronic heart failure (EF ≤45%) without arrhythmia were randomized to placebo or digoxin. The study was a double-blind and placebo-controlled trial. Most patients were concurrently receiving angiotensin converting enzyme inhibitors and diuretics. The authors did not know how many patients were taking beta-blockers; however, they make the assumption that beta-blocker use was low since it was not yet approved for use in chronic heart failure at the time of data collection. The primary end point of the original study was all-cause mortality. The primary end point of this analysis was all-cause hospitalization within the first 30 days of being started on digoxin. The baseline characteristics for the patients were similar in both groups, except the digoxin group had a lower body mass index compared to the placebo group. The mean age was 72 years. Twenty-five percent of the group was made up of women, and 11% were nonwhite.

The all-cause admission rate was lower in the digoxin group as compared to placebo, 8.1% and 5.4% respectively [HR 0.66, 95% CI (0.51-0.86); P=0.002]. There was no significant change in the hazard ratio when adjustments were made for baseline characteristics. In addition, digoxin significantly reduced all-cause hospitalization at 60 and 90 days after randomization. In the subgroup analysis, the hazard ratios for the digoxin group were significantly lower when compared to placebo for the following groups: age ≤70, male, white, ischemic cardiomyopathy, pre-trial digoxin use, NYHA class III or IV, EF 25-45%, and cardiothoracic ratio >55%.

■ COMMENTARY

This study shows promising effects of using digoxin to minimize hospitalizations in older patients. There are few studies that have shown potential benefit regarding decreasing hospitalizations in chronic systolic heart failure patients. This study also demonstrated that the benefit extended to 90 days. In addition, the sub-group analysis showed that patients with prior digoxin use benefited, so it is conceivable that this benefit would continue once the patient was stabilized on digoxin. The authors acknowledge that this population is very different from a hospitalized group of patients; however, they argue that this finding is significant because it shows a medication with promise to help decrease hospitalizations. This study needs to be repeated using patients with chronic heart failure who are being discharged from the hospital to see if the addition or continuation of digoxin decreases all-cause mortality in that population. The study has several weaknesses. First, the patients studied were primarily white males, and females and nonwhites did not benefit in the subgroup analysis; therefore generalizability to other populations is difficult. Second, the guidelines recommend that patients with chronic heart failure take beta-blockers. This study was performed on patients not on beta-blockers, so it is unclear how beta-blockers would change the effects of digoxin. Beta-blockers and digoxin, although frequently prescribed together, do have a known drug interaction that results in increased bradycardia. Therefore, further studies need to be done to see if the effects of digoxin are changed in a population that is on beta-blockers. Finally, this study did not investigate whether digoxin decreases readmission rates in patients with chronic heart failure and preserved ejection fraction. Despite the constraints regarding generalizability, digoxin is a drug that could possibly be used to decrease hospital readmission rates in older systolic heart failure patients. Further studies need to be performed to see if digoxin should be added to angiotensin converting enzyme inhibitors and beta-blockers as necessary discharge medications. ■

ABSTRACT & COMMENTARY

Same-Day Discharge After PCI

By Andrew J. Boyle, MBBS, PhD

Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

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

This article originally appeared in the September 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: Brayton KM, et al. Same-day discharge after percutaneous coronary intervention. A meta-analysis. *J Am Coll Cardiol* 2013;62:275-285.

Complication rates following percutaneous coronary intervention (PCI) have fallen in recent years. Overnight observation in the hospital after PCI remains the standard of care in the United States. However, because of the low complication rates, there has been a move toward same-day discharge in some countries. In the current environment of cost containment, this approach may represent a way for the health care system to realize substantial cost savings. The Society for Cardiac Angiography and Intervention (SCAI) and the American College of Cardiology (ACC) released a consensus statement in 2009 identifying patients suitable for same-day discharge following PCI, but this has not become part of the ACC/AHA guidelines for PCI. Thus, the use of same-day discharge after PCI remains low in the United States. In this study, Brayton and colleagues update our evidence base by performing a study-level meta-analysis of 37 clinical studies of same-day discharge after PCI.

Their meta-analysis includes 30 studies (enrolling 10,065 patients) that were observational and seven studies (enrolling 2738 patients) that were randomized controlled trials (RCTs). Two-thirds of patients underwent PCI for stable coronary artery disease (CAD). There were some differences between the RCTs and observational study cohorts, in particular the use of transradial PCI was 61% in the randomized trials and 30% in the observational studies. The authors focused mainly on the RCTs to limit selection bias. Their primary efficacy endpoint was the rate of death/myocardial infarction (MI)/target lesion revascularization (TLR) and their primary safety endpoint was the rate of major bleeding/vascular complications. In the RCTs, there was no difference in the incidence of the primary efficacy endpoint of death/MI/TLR (odds ratio [OR] 0.90; P = 0.78), or in the rates of major bleeding/vascular complications (OR 1.69; P = 0.15) between patients randomized to same-day discharge vs overnight observation. In the observational studies, the incidence of death/MI/TLR was 1.0% and bleeding/vascular complications was 0.7% in those discharged on the same day as PCI, confirming low actual event rates in real-world practice. Importantly, the results were largely consistent in studies conducted within the United States vs elsewhere, in studies that included acute coronary syndrome patients and those that did not, and whether radial or femoral arterial access was used.

In patients randomized to same-day discharge, 13% were not actually discharged the same day. When the authors drilled down on the reasons, they found that around half of these were from a trial that randomized patients before PCI instead of after. Deferral of same-day discharge in the other trials was due to access site complications (33%), physician preference (30%), patient preference (17%), recurrent chest pain (11%), noncardiac reasons (4.9%), orthostasis (2.4%), and arrhythmias (1.2%). The authors conclude that in selected patients undergoing largely elective PCI, same-day discharge was associated with a low rate of major complications and appeared to be as safe as routine overnight observation.

■ COMMENTARY

Technical advances in PCI technique have resulted in lower rates of cardiac complications following PCI. In addition, the use of bleeding avoidance strategies, such as radial access, use of smaller guide catheters, and the more widespread use of bivalirudin, have resulted in lower bleeding rates. The rationale for overnight observation of patients after PCI appears to be less compelling in the modern era. However, clinical trial data supporting same-day discharge have been lacking. In particular, there has been concern about the rates of uncommon but serious complications, and most trials to date are underpowered to detect differences in uncommon outcomes. The strength of meta-analyses such as this one is that they have large numbers of patients, allowing detection of less common outcomes. However, there are some important

limitations to this paper. First, this is a study level meta-analysis and individual patient-level data were not available to the authors, which may confound the data. Second, the studies that they reported had varied outcomes over different periods of observation, making standardization difficult. Third, the event rates were not always specified as occurring in the 24 hours after PCI and may have occurred later, but the timing was not reported in some of the original studies. Fourth, each study had its own inclusion and exclusion criteria, making extrapolation to different patient groups difficult. Despite these limitations, this paper shows us that in carefully selected patients, largely elective PCI for stable CAD, same-day discharge after PCI is a reasonable alternative. The observational data presented in concert with the RCT data confirm that the actual event rates are low in real-world settings. The authors go on to offer a protocol for choosing patients for same-day discharge after PCI. Our practice has been that patients having elective PCI for stable, single-vessel CAD are considered for same-day discharge if the procedure is uncomplicated, the patients are at low risk for complications, and there are adequate home supports. However, the patient and lesion characteristics that are optimal for same-day discharge still need to be defined by large prospective, randomized trials. ■

ABSTRACT & COMMENTARY

A Stitch in Time

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorder Center, Samaritan Hospital, Lexington

Dr. Phillips serves on the speakers bureau for PotomaCME.

This article originally appeared in the August 29, 2013, issue of Internal Medicine Alert. *It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Adjunct Clinical Professor, University of North Carolina, Chapel Hill, and Dr. Roberts is Senior Attending Physician, Long Island Jewish Medical Center, NS/LIJ Health Care System, New Hyde Park, NY. Dr. Brunton serves on the advisory board for Abbott, Amarin, Boehringer Ingelheim, Duchesnay, Janssen, Lilly, Novo Nordisk, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Dr. Roberts reports no financial relationship to this field of study.*

SYNOPSIS: In a large, international observational study, patients who had repair of flail mitral valve leaflets within 3 months of diagnosis had better long-term survival and a lower risk of heart failure than those managed with watchful waiting.

SOURCE: Suri RM, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. *JAMA* 2013;310:609-616.

This study is a report from the Mitral Regurgitation International Database (MIDA) registry, which includes 2097 consecutive patients with flail mitral valve regurgitation in six tertiary centers (in France, Italy, Belgium, and the United States). Patients were enrolled in the MIDA registry if they had degenerative mitral regurgitation with a flail leaflet detected by a 2-dimensional transthoracic echocardiography (2D ECHO) diagnosed between 1980 and 2004. To be eligible for this study, they could not have heart failure symptoms, left ventricular ejection fraction < 60%, or left ventricular end-systolic diameter ≥ 40 mm. They also were excluded if they had ischemic mitral regurgitation, significant concomitant aortic valve disease, congenital heart disease, mitral stenosis with previous valve surgery, or a contraindication to surgery due to comorbidity. Each patient's personal cardiologist was responsible for clinical decisions regarding medical management and referral for surgery. Diagnosis of flail leaflet was based on 2D ECHO. "Early surgery" was defined as being performed within 3 months from the ECHO diagnosis. "Initial medical management" was defined as medical management during the first 3 months of follow-up, then either medical or surgical treatment thereafter as deemed appropriate by the patient's physician. The primary endpoint was all-cause mortality, and secondary endpoints were heart failure and new-onset atrial fibrillation.

Of the 2097 patients enrolled in the MIDA registry, 1021 were eligible for this study: 575 of these had medical management and 446 underwent early surgery. The group who had medical management were older (mean 67 vs 62 years), but were less symptomatic, less likely to have pulmonary hypertension, had lower left ventricular end diastolic and systolic diameters, and smaller left atrial diameters. Almost all (93%) of the early surgery patients were able to undergo mitral valve repair (as opposed to replacement). Significantly, during the follow-up period, 339 of 575 patients in the initial medical management group had surgery at a median time of 1.65 years after diagnosis. Of these, only 87% were able to have a valve repair; the others had replacement.

Within 3 months of initial diagnosis, there

were no differences in rates of death or heart failure. However, 30 patients developed new-onset atrial fibrillation, 6.2% after early surgery vs 1.2% during initial medical management ($P < 0.001$), highlighting the predisposition to early atrial fibrillation after surgery.

Ninety-eight percent of patients were followed until death or at least 5 years. Overall, the 10-year survival rate was 76% and the 20-year survival rate was 48%. Survival among the early surgery group was 95% at 5 years, 86% at 10 years, and 63% at 20 years compared to 84% at 5 years, 69% at 10 years, and 41% at 20 years for the initial medical management group ($P < 0.001$, favoring early surgery). This finding did not change much after adjusting for confounders. Mortality rate (per 100 person-years) was lower in patients with early surgery during all periods after diagnosis.

In fact, survival at all points in follow-up was better among the early surgery group regardless of comorbidities, including atrial fibrillation, pulmonary hypertension, or mild symptoms. When analysis was restricted to patients surviving 3 months after diagnosis, long-term survival was again higher after early surgery.

Heart failure developed in 16% at 10 years and 27% at 20 years, but was less frequent after early surgery than after initial medical management at all time points and for all subgroups, even after adjustment for confounders.

Atrial fibrillation occurred in 25% at 10 years and 41% at 20 years. Although there was an increased rate of atrial fibrillation in the postoperative period in the early surgery group, the long-term incidence was not different between cohorts, even after adjusting for confounders and for subgroups.

■ COMMENTARY

The most common cause of primary mitral regurgitation is mitral valve prolapse, which affects about 2% of the overall population.[1] This is a prevalent condition! Mitral valve prolapse results in thickening of the mitral valve leaflets, redundant tissue, and laxity of the chordae tendonae. During ventricular systole, the mitral valve leaflet sags into the left atrium preventing closure of the valve leaflets, which results in regurgitation. Fortunately, in most patients with mitral valve prolapse, regurgitation is mild and the regurgitant volume increases gradually over many years. Because of this, even patients who develop severe regurgitation can be asymptomatic (this adaptive response is not infinite, however, and once the limits of this response are reached, patients develop symptoms and heart failure). Some patients with mitral valve prolapse experience chordal rupture, which allows that untethered leaflet segment to fall into the left atrium in systole. This is termed a flail leaflet. Although mitral valve prolapse is common, flail leaflet is much less so. In this study, Suri and colleagues found an average of only seven patients per year at each tertiary referral center over a 25-year period. In a 5-year, community-based, observational study of more than 800 people with mitral valve prolapse, Avierinos and colleagues observed development of flail leaflet in only 2.4%.[2]

Thus, the current report deals with a very select and specific subset of patients with mitral valve prolapse: those with flail leaflet who did not have classic indications for immediate surgery. This report is relevant to our patients with mitral valve prolapse who are identified when a systolic murmur is heard during a physical examination and/or who have an ECHO for some other reason. This turns out to be a very small subset of those with mitral valve prolapse.

What the current study adds to the literature is the largest, most carefully done prospective observational study of early surgical intervention vs watchful waiting in patients who have mitral regurgitation with a flail leaflet but who do not yet have classic indications for surgical intervention (which are left ventricular dysfunction and significant symptoms). There is controversy in the literature about the appropriateness of early intervention in these patients, which is partly due to the uncertain consequences of uncorrected severe mitral regurgitation.[3] This controversy is reflected in current international consensus statements, in which North American guidelines favor the procedure,[4] but the European guidelines do not.[5] Surgical intervention is risky, and carries both the risk of the procedure and the risk of receiving a mechanical valve (requiring lifelong anticoagulation) or a bioprosthesis (with limited durability and a possible need for repeat future intervention). Compared with valve replacement, mitral valve repair has a much better prognosis, improved survival, excellent long-term durability, and no need for long-term anticoagulation. The difference in repair vs replacement of the valves (93 vs 87% in the early surgery vs initial medical management groups, respectively) is significant in that regard. In addition, it is notable that a majority of those in the watchful waiting group (339 [59%]) underwent subsequent mitral valve surgery anyway, at a median of 1.65 years after the initial diagnosis of a flail leaflet.

Besides having results that seem to favor early surgery, this observational study is notable because it truly is a comparative effectiveness study, as endorsed by the National Heart, Lung, and Blood Institute.[6] Large clinical registries, such as MIDA, are essential in delivering the evidence necessary to evaluate some clinical questions in the absence of or due to the limited feasibility of randomized clinical trials. ■

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ABSTRACT & COMMENTARY

QI Project Reduces Severe Pain and Serious Adverse Events: A Systems Approach to Patient Safety

By Linda L. Chlan, RN, PhD

Dean's Distinguished Professor of Symptom Management Research, The Ohio State University, College of Nursing

Dr. Chlan reports that she receives grant/research support from the National Institutes of Health.

This article originally appeared in the September 2013 issue of Critical Care Alert. *It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle, and Dr. Thompson is Associate Professor of Medicine, University of Washington, Seattle. Drs. Pierson and Thompson report no financial relationships relevant to this field of study.*

SYNOPSIS: A French multidisciplinary team conducted a quality improvement project that was successful in improving pain management and reducing serious adverse events associated with the routine ICU nursing care activities of bathing, massage, linen changes, and repositioning.

SOURCE: de Jong A, et al. Decreasing severe pain and serious adverse events while moving intensive care unit patients: A prospective interventional study (the NURSE-DO project). *Crit Care* 2013;17:R74. [Epub ahead of print.]

Despite the intensity and frequency of pain during common nursing care activities such as turning and repositioning, patients rarely receive premedication prior to these procedures. Pain can induce a stress response in these patients that can lead to serious adverse events (SAE). Documentation of SAEs impacting care quality is poorly understood. To address these care quality gaps, a systems approach by a multidisciplinary French ICU team was used to improve patient safety and quality of care through addressing pain management and adverse events when routine nursing cares were performed. The Plan-Do-Check-Adjust method was used to guide this quality improvement (QI) project. Each phase of the project lasted 1 month, separated by a 4-6 month interstudy phase, for a total project period of 20 months. SAEs were defined as cardiac arrest, new arrhythmia event, and clinically relevant changes in heart rate (tachycardia or bradycardia), blood pressure (hypotension or hypertension), oxygen desaturation, bradypnea, and ventilatory distress.

The QI project began with a questionnaire completed by nurses to assess their knowledge of sedation and analgesia guidelines and any associated challenges with these guidelines. Educational interventions were developed based on these responses, and included posters and face-to-face scheduled classes for all nursing and medical staff. The education consisted of pain assessment (numeric rating scale or behavioral pain scale) prior to any patient movement interventions, analgesic drug therapy, and instituting non-pharmacological interventions such as music in every patient room. Every day between 6 a.m. and 8 a.m., every patient turning was evaluated to measure the impact of the educational intervention on the pain level and physiological indicators of the stress response. Next, a 6-month period of adjusting the medical and nursing care strategies was undertaken. During this time, physicians wrote orders for one or more analgesic medications to be given before the morning nursing care procedures. Following this 6-month period, nursing care activities every day between 6 a.m. and 8 a.m. were evaluated to determine the impact of the care strategies adjustments made previously.

During the evaluation phase of this QI project, pain was assessed by the nurse prior to and during any care movement interventions. SAEs to assess for indicators of the acute stress response to

these movement interventions were measured by physiological parameters. Provision of pharmacological and non-pharmacological therapies was recorded on a flow sheet. Evaluation of the educational interventions revealed that the incidence of severe pain and at least one SAE decreased over the project period, while analgesia administered prior to morning nursing care procedures increased. The incidence of SAEs was observed to decrease except with intubated patients and those with severe pain. This finding highlights the complicated nature of managing mechanically ventilated ICU patients. Unfortunately, the use of music over the project period was not consistently implemented, which may suggest a need for further education and practice implementing this integrative therapy.

■ COMMENTARY

Routine nursing care activities can induce or exacerbate pain, which can lead to a heightened stress response and include any number of adverse events in critically ill patients. Pain is a common experience in critically ill patients for which analgesic medications are frequently administered. However, as the authors point out, moving and other routine nursing care interventions are not perceived by clinicians to be painful. These data suggest otherwise. A number of patients experienced moderate-to-severe pain while receiving necessary routine nursing care such as bathing, turning, or linen changes. Over the course of 20 months, the QI project developed and evaluated demonstrated decreased severe pain and a change in practice to administer analgesic agents early in the day prior to movement-based care activities.

This well-described QI project is the third such project conducted by this multidisciplinary group. This group of clinicians is experienced in doing a quality project and they are well aware of the various pitfalls and challenges associated with implementing changes in practice. This paper by de Jong and colleagues can offer the QI novice a road map for how to conduct such important clinical practice change projects to improve care quality in the ICU. ■

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CME QUESTIONS

1. In the observational study by Koch and colleagues, the development of moderate and severe hospital-acquired anemia was associated with which of the following outcomes?

a. Increased risk of nosocomial pneumonia
b. Decreased risk of venous thromboembolism
c. Increased risk of all-cause, in-hospital mortality
d. Increased risk of myocardial infarction

2. What group of patients were not represented in the study by Bourge et al demonstrating that digoxin decreases 30 day all-cause hospitalization?

a. Patients with chronic heart failure (EF ≤45%)
b. Patients on beta blockers
c. Patients who are 65 and older
d. Patients who are taking angiotensin converting enzyme inhibitors and diuretics

3. In the meta-analysis of same-day discharge after percutaneous coronary intervention (PCI) by Brayton and co-investigators, what group of patients was considered safe to undergo same-day discharge?

a. Patients with decompensated congestive heart failure
b. Patients undergoing emergent PCI
c. Patients undergoing femoral artery catheterization.
d. Patients undergoing elective PCI.

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.

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Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

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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Our Newest Pharmacologic Class for Treatment of Diabetes: SGLT2 Inhibitors

Source: Polidori D, et al. *Diabetes Care* 2013;36:2154-2161.

The role of the kidney in glucose regulation has been underappreciated. Although perhaps counterintuitive, after persistent exposure to elevated glucose levels in the glomerular filtrate presented to the proximal renal tubule, the kidney adapts by reabsorbing *increased* amounts of glucose, thereby *increasing* blood sugar. The sodium glucose cotransporter (SGLT2) receptor is the primary pathway for renal tubular glucose reabsorption; blockade of this receptor results in enhanced urinary glucose excretion. Currently, the only FDA-approved agent for blockade of the SGLT2 receptor is canaglifozin.

In addition to potent SGLT2 receptor blockade, it has been suspected that canaglifozin might affect intestinal absorption of glucose by its modest inhibition of intestinal SGLT1. Polidori et al tested the impact of canagliflozin SGLT1 inhibition by examining the rate of gastrointestinal glucose absorption in healthy volunteers following a 600-kcal mixed-meal tolerance test.

Canagliflozin produced a very modest reduction in glucose absorption over a 6-hour interval (about 6%). The effects were accentuated in the early postprandial intervals, indicating a slowed absorption of glucose that was not attributable to delayed gastric emptying. Blunting of early postprandial glucose absorption should have a favorable effect on postprandial glucose excursions in diabetics.

Although enhanced urinary glucose excretion is the primary mechanism of plasma glucose lowering by SGLT2 inhibitors, modest gastrointestinal SGLT1 inhibition also appears to impact postprandial glucose excursion. ■

Bariatric Surgery vs Intensive Medical Therapy for Diabetes

Source: Kashyap SR, et al. *Diabetes Care* 2013;36:2175-2182.

The benefits of bariatric surgery (BAS) are increasingly recognized for obese patients with type 2 diabetes mellitus (T2DM). Indeed, the mechanisms by which diversionary surgery (e.g., gastric bypass) produces such prompt and dramatic remission in diabetic patients are still being elucidated. Long-term observational data on BAS for persons with severe obesity (body mass index [BMI] > 40) confirm durable weight reduction, improved control of diabetes, and even suggest reduced mortality.

Few trials have directly compared the efficacy of BAS with intensive medical treatment (IMT). Kashyap et al randomized T2DM subjects (n = 60) with moderate obesity (mean BMI = 36) to one of two BAS interventions (gastric sleeve or gastric bypass) or IMT in the Surgical Therapy And Medications Potentially Eradicate Diabetes (STAMPEDE) trial. Currently reported data include outcomes at 24 months.

In essentially every category assessed, BAS patients had superior outcomes to IMT. No BAS-related deaths occurred. At 2 years, degree of A1c control, LDL, HDL, total cholesterol, triglycerides, and CRP were all more improved in the BAS patients than in the IMT patients.

When comparing outcomes in the two BAS groups, even though weight loss was similar between gastric sleeve and bypass surgery, the latter achieved greater improvements in truncal fat reduction, leptin, insulin sensitivity, beta cell function, and incretin responses. BAS is more effective for multiple metabolic markers than IMT over the long term in T2DM patients. ■

Psoriasis and Risk for New Onset Diabetes

Source: Khalid U, et al. *Diabetes Care* 2013;36:2402-2407.

Inflammatory disorders like rheumatoid arthritis (RA) and psoriasis (PSOR) have recently been confirmed to be risk factors for adverse cardiovascular (CV) events, although the precise pathways through which such risk occurs remain controversial. Some have even gone so far as to say that RA should be considered an independent CV risk factor of equal potency to the already registered risk factors like hypertension, history of premature cardiovascular death, etc. Since PSOR and RA share common inflammatory pathways, it's perhaps not surprising that both are associated with CV adversity.

To date, the relationship between PSOR and diabetes mellitus (DM) has been controversial. Since DM is a major contributor to CV events, if PSOR and

DM are related, that would account for some of the increased CV risk.

Khalid et al report on an analysis of the PSOR-DM relationship discerned through a 12-year follow-up of Danish persons ≥ 10 years (n = 4,614,807). They studied the incidence of new-onset DM in PSOR subjects vs controls. A graded linear association between PSOR and new onset DM was found. Compared to the reference population, the incidence of DM in persons with mild PSOR was almost doubled, and in severe PSOR, nearly tripled. ■

Osteoporosis: Are Two Drugs Better Than One?

Source: Tsai JN, et al. *Lancet* 2013;382: 50-56.

Most women today who are receiving pharmacotherapy for treatment of osteoporosis receive oral bisphosphonates (e.g., alendronate, risedronate). Other effective treatments, like teriparatide (TERI) and denosumab (DENO) are usually reserved for more severe cases, in some part because they require parenteral administration.

Even though osteoporosis treatments have shown risk reduction for fracture and improved bone mineral density (BMD), restoration of full bone integrity remains a challenge. As one of the few anabolic tools (as opposed to anticatabolic tools like bisphosphonates), some investigators have tried to augment the favorable activity of TERI by combination with bisphosphonates, but the results have been disappointing. Whether the addition of DENO to TERI might be beneficial was the subject of investigation by Tsai et al. Postmenopausal women with osteoporosis (n = 100) were randomized to DENO, TERI, or both for 6 months. The primary outcome of the study was improvement in BMD.

Combination TERI+DENO appeared to be synergistic, with improvements in BMD greater than either agent alone and arithmetically greater than the anticipated benefit of combined monotherapies. For example, BMD increases at the hip were 4.2% for TERI+DENO, 0.8% for TERI, and 2.1% for DENO. These data support the consideration of TERI+DENO in highest-risk patients, those unable to take other treatments, or patients who fail to respond to other regimens. ■

Long-Term Impact of Weight Management on Blood Pressure

Source: Tyson CC, et al. *J Clin Hypertens* 2013;15:458-464.

The weight loss maintenance (WLM) trial randomized adults (n = 741) with hypertension (HTN) and/or dyslipidemia — but without evidence of cardiovascular disease — to one of several weight loss management programs. Although the initial outcome reports from WLM addressed the relative efficacies of different weight loss strategies over time, this report stratified study participants into those who lost, maintained, or gained weight over the 5-year study period. Tyson et al compared blood pressure effects between the three categories of weight impact, irrespective of which particular method of weight loss had been applied.

At study end, the weight-stable group had gained 0.6 kg, as compared with a 9.1 kg increase in the weight-gain group, and a 7.1 kg decrease in the weight-loss group. The weight-stable and the weight-gain groups were noted to have similar increases in systolic blood pressure (SBP) over 5 years (SBP increase mean 4.2 mmHg), whereas the weight-loss group SBP was not statistically significantly changed.

In contrast to some other trials that report a "legacy effect" (prolonged beneficial impact of early intervention, even after the intervention has ceased), initial weight loss in WLM was not associated with favorable SBP effects if weight was regained. On the other hand, sustained modest weight reduction (< 10% of baseline BMI) had a sustained effect to maintain SBP. Although simply maintaining weight over the long term might appear to be a laudable goal, it is apparently insufficient to favorably affect SBP. ■

The WEAVE Study: Does Special Training in Domestic Violence Improve Outcomes?

Source: Hegarty K, et al. *Lancet* 2013; 382:249-258.

Intimate partner violence (IPV) is a public health problem that knows no boundaries of age, country of residence or origin, economic status, or education. Primary care clinicians, particularly family physicians, are often the first point of clinical contact for victims of IPV, but may lack confidence in their ability to identify and/or address IPV. Hegarty et al report on a trial from Australia in which women who screened positive for concerns about fear of their partner (n = 272) received care from family physicians who were randomized to receive special training in IPV or no intervention. The intervention group physicians participated in the Healthy Relationships Training program, which is intended to provide the ability to respond effectively to women who have experienced IPV and give brief counseling. The primary outcomes of the trial were changes in quality of life (as per the WHO QOL-BREF), safety planning and behavior, and mental health (as per the SF-12) at 1 year.

At 1 year, there was no difference in the primary endpoint between the intervention group and controls. A favorable impact on depression (a secondary endpoint) was seen. However, since the primary endpoint was not achieved, the potential for benefits on depression must remain considered as hypothesis generating. ■

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Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.
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PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

More Side Effects of Fluoroquinolones Coming to Light

In this issue: New side effects of fluoroquinolones; probiotics and antibiotic-related diarrhea; prostate cancer risk and 5-ARIs; and FDA actions.

New study finds dysglycemia risk

Fluoroquinolones, such as levofloxacin, ciprofloxacin, and moxifloxacin, are useful broad-spectrum antibiotics, but they have been associated with tendinopathy, including tendon rupture and QT interval prolongation. Now, two new potential side effects are coming to light. In a new study from Taiwan, more than 78,000 diabetic patients who received fluoroquinolones were monitored for dysglycemia, including hyperglycemia and hypoglycemia. The study looked at users of levofloxacin, ciprofloxacin and moxifloxacin, cephalosporins, and macrolides. The absolute risk of hyperglycemia was 6.9 per 1000 for moxifloxacin and 1.6 for macrolides. The risk for hypoglycemia was 10.0 for moxifloxacin and 3.7 for macrolides. The adjusted odds ratios for hyperglycemia compared to macrolides were: moxifloxacin 2.48 (95% confidence interval [CI], 1.50-4.12), levofloxacin 1.75 (95% CI, 1.12-2.73), and ciprofloxacin 1.87 (95% CI, 1.20-2.93). For hypoglycemia, the adjusted odds ratios were moxifloxacin 2.13 (95% CI, 1.44-3.14), levofloxacin 1.79 (95% CI, 1.33-2.42), and ciprofloxacin 1.46 (95% CI, 1.07-2.00). The risk of hypoglycemia associated with moxifloxacin was even higher if patients were taking insulin. The authors suggest that fluoroquinolones, especially moxifloxacin, are associated with severe dysglycemia in diabetic patients and that clinicians should "prescribe quinolones cautiously" in diabetic patients (*Clin Infect Dis* published online August 14, 2013. DOI: 10.1093cid/cit439). In related news, the FDA is requiring labeling changes for fluoroquinolones regarding the risk of neuropathy. The FDA Drug Safety Communication states that "serious nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken and may be permanent." The warning is for both oral and parenteral forms of the drugs, but not topicals. The FDA recommends that if a patient develops symptoms of peripheral neuropathy associated with a fluoroquinolone, the drug should be stopped immediately and the patient should be switched to a non-fluoroquinolone antibiotic. Further information can be found at the FDA's website at www.fda.gov/Safety/MedWatch. ■

Probiotics and antibiotic-related diarrhea

Probiotics may not prevent antibiotic-associated diarrhea (AAD), including *Clostridium difficile* infections. That was the finding of a randomized, double-blind, placebo-controlled trial in nearly 3000 inpatients aged ≥ 65 years who were exposed to one or more oral or parenteral antibiotics. Patients were randomized to a multistrain preparation of lactobacilli and bifidobacteria or placebo for 21 days. The rate of AAD was 10.8% in the probiotic group and 10.4% in the placebo group ($P = 0.71$). *C. difficile* was uncommon and occurred in 0.8% of the probiotic group and 1.2% of the placebo group ($P = 0.35$). The authors state that "we identified no evidence that a multistrain

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

preparation of lactobacilli and bifidobacteria was effective in the prevention of AAD or CDD." (*Lancet* published online August 8, 2013. doi: 10.1016/S0140-6736(13)61218-0). An accompanying editorial wonders if this study can tip the balance of probiotic evidence, as it was a rigorously performed study vs previous small studies showing a positive effect. But, the current study used only two types of non-pathogenic bacteria (doi: 10.1016/S0140-6736(13)61571-8). Still, the cost effectiveness of routine probiotic use must be questioned based on this study. ■

Prostate cancer risk and 5-ARIs

The debate regarding 5-alpha reductase inhibitors (finasteride [Proscar] and dutasteride [Avodart]) and the risk of prostate cancer continues. Despite good evidence that the drugs reduce the overall risk of prostate cancer, there is also evidence that the drugs may increase the risk of high-grade prostate cancers (Gleason score 7-10). This was a finding of the Prostate Cancer Prevention Trial (PCPT) that was published in 2003. That finding was recently questioned in a study published in the *British Medical Journal* that found no risk of higher-grade prostate cancers (*BMJ* 2013;346:f3406, reported in the August *Pharmacology Watch*). Now, 10 years after the PCPT was originally published as an 8-year study, the 18-year follow-up has been published in the *New England Journal of Medicine*. Of the nearly 19,000 men who underwent randomization in the PCPT, prostate cancer was diagnosed in 10.5% of the finasteride group and 14.9% of the placebo group, a 30% reduction in the rate of prostate cancer (relative risk 0.70; 95% CI, 0.65-0.76; $P < 0.001$). But all of the reduction was in lower-grade prostate cancers. There was a slightly higher rate of high-grade cancer in the finasteride group (3.5% vs 3.0%, $P = 0.05$), but there was no difference in overall mortality. There was also no increase in mortality in men diagnosed with high-grade prostate cancer. The authors conclude that finasteride reduced the risk of prostate cancer by about one-third, and although high-grade cancer was more common in the finasteride group, there was no difference in overall mortality or survival after the diagnosis of prostate cancer (*N Engl J Med* 2013;369:603-610). Dutasteride was also studied in the REDUCE trial and similarly found lower rates of low-grade prostate cancers but increased rates of higher-grade cancers (*N Engl J Med* 2010;362:1192-1202). Some have argued that the higher rate of high-grade cancers is due to higher surveillance and "detection bias," but regardless of the cause, it is reassuring to know that there is no higher risk of mortality, at least in the PCPT. The FDA changed the labeling to both finasteride and dutasteride in 2011 regarding the increased risk of high-grade prostate cancers. ■

FDA actions

The FDA has issued a Drug Safety Communication regarding a case of progressive multifocal leukoencephalopathy (PML) in a patient who was taking fingolimod (Gilenya) for the treatment of multiple sclerosis. This is the first reported case of PML associated with fingolimod in patients who had not previously taken natalizumab (Tysabri). The patient, who lives in Europe, had been on the drug for about 8 months and had previously taken interferon beta-1a, azathioprine, and steroids. Novartis, the manufacturer of fingolimod, indicated it is possible that the patient had PML prior to starting the drug. PML is a rare neurologic disease caused by latent infection with the JC virus. It has been associated with immunosuppressive drugs, including natalizumab.

The FDA has approved a new topical agent to treat facial redness in adults with rosacea. Brimonidine, an alpha-2 agonist, is currently used as an ophthalmic preparation for treating glaucoma. The drug constricts dilated facial blood vessels for up to 12 hours. It is approved in a 0.33% topical gel that is applied once daily. Patients with depression, coronary artery disease, Raynaud's, or other conditions that may be exacerbated by an alpha agonist should use the drug with caution. Brimonidine gel is marketed by Galderma as Mirvaso.

The FDA has approved dolutegravir, a new once-daily HIV integrase inhibitor. It is the third integrase inhibitor on the market after raltegravir and elvitegravir. The drug is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infections in adults and children ≥ 12 years of age weighing at least 40 kg. It may be used in treatment-naïve patients or treatment-experienced patients, including those who have previously taken an integrase inhibitor. Approval was based on four trials in more than 2500 patients that showed efficacy in combination with other antiretrovirals. A fifth trial showed efficacy in HIV-infected children as young as 12 who had not taken an integrase inhibitor. Dolutegravir is marketed by ViiV Healthcare as Tivicay. ■