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ABSTRACT & COMMENTARY

Overnight Vital Signs – Are They Always Beneficial?

By Jennifer A. Best, MD, FACP

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

SYNOPSIS: Low MEWS score may be beneficial in identifying a subset of hospitalized patients unlikely to benefit from nocturnal vital sign monitoring.

SOURCE: Yoder JC, Yuen TC, Churpek MM, Arora VM, Edelson DP. A prospective study of nighttime vital sign monitoring frequency and risk of clinical deterioration. *JAMA Intern Med.* Published online July 1, 2013

The practice of checking vital signs at regular intervals in hospitalized patients throughout the day and night (i.e. q4 hours) is long standing, yet has never been prospective evaluated in regards to its utility. Though new derangements in temperature, blood pressure, respiratory rate or pulse may herald the development of a new or worsening condition, routine interruptions in a patient's clinical care or sleep routine may increase fatigue and decrease patient satisfaction. This practice is also labor intensive, which may decrease staff satisfaction and detract from other clinical duties.

Increasingly, scoring systems such as the Modified Early Warning System (MEWS) Score have been used to identify a subset of hospitalized patient at higher risk of clinical deterioration. The MEWS score is a composite of five variables: temperature (in degrees C), systolic blood pressure, pulse, respiratory rate and level of consciousness, as determined by the acronym AVPU (whether the patient is Alert, uses his Voice, responds to Pain or is Unresponsive). Each of these variables is assigned a point score of 0-3, based on its percent derangement from baseline or absolute value. A MEWS score of 5 or more has been shown to be linked with higher mortality and risk of ICU admission.[1] Until now, it has been unknown whether the MEWS score may also identify a subset of patients unlikely to benefit from frequent monitoring of vital signs, notably overnight, where the potential for sleep interruption is greatest.

In a research letter published online in the July 1,

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Hospital Medicine
[ALERT]

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2013 issue of *JAMA Internal Medicine*, Dr. Jordan Yoder and hospital medicine colleagues at the University of Chicago describe a prospective, cohort study in which the risks of adverse events and sleep disruption for hospitalized patients were stratified by an evening MEWS score, documented prior to 11:00 pm. Vital sign data were extracted from the electronic health record. Tracked adverse events included ICU transfers and cardiac arrests within 24 hours of MEWS score documentation. Disruptions and adverse event rates were then compared across all MEWS categories.

By study's end, 54,096 patients (reflecting 182,828 patient-days) had been included. The study population was predominately female (57%) with a median age of 56 years and a median MEWS score of 2. A total of 1699 adverse events occurred. As MEWS score increased, the adverse event rate also increased (ranging from 5 events per 1000 patient-days for scores of ≤1 to 157 events per 1000 patient-days for scores of ≥7; P=0.003). All patients, regardless of MEWS score, were found to have had frequent vital signs checks, with a median of 2 vital sign checks nightly, accounting for at least 1 sleep disruption for the vast majority of nights (99%). In addition, 45% of these sleep disruptions affected patients with MEWS scores of ≤1 — the population shown to have the lowest adverse event rates.

These investigators conclude that in this study population, routine vital sign collection was common and did not appear to be linked to clinical risk, as patients with the lowest MEWS scores had vitals checked as frequently as those with higher scores. A low evening MEWS score was found to be associated with a low risk of cardiac arrest and ICU admission, suggesting that some evening disruptions might be eliminated without harm to these patients. Such elimination may reduce sleep deprivation, which has been linked to readmissions.[2] Furthermore this may allow for shifts in resource allocation toward more acutely ill hospitalized patients, allowing for earlier recognition of decline and rapid intervention.

Though this is a single site study utilizing only one clinical index of risk and does not investigate the risks and benefits of specific intervals of vital sign monitoring (i.e. q4H, q6H, q8H), these results suggest that routine monitoring of overnight vital signs for all patients may not be beneficial. These data suggest that further determination of the effects of more targeted vital sign monitoring on a general hospital population from the standpoint of safety, sleep deprivation and patient satisfaction may be worthwhile. ■

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ABSTRACT & COMMENTARY

Macrolide Antibiotics May Increase the Risk of Statin Toxicity

By Deborah DeWaay, MD, FACP
Assistant Professor, Medical University of South Carolina
Dr. DeWaay reports no financial relationships in this field of study

SYNOPSIS: The toxicity of statins was increased in older adults who were coprescribed the CYP3A4 inhibitors clarithromycin or erythromycin.

SOURCE: Patel A, Shariff S, Bailey D, et al. Statin Toxicity From Macrolide Antibiotic Coprescription. *Annals of Internal Medicine* 2013;158(12):869-876

Statins are used world-wide to treat hyperlipidemia. Three of the most common statins used are atorvastatin, simvastatin and lovastatin. Cytochrome P450 isoenzyme 3A4 (CYP3A4) metabolizes these 3 medications. The U.S. Food and Drug Administration cautioned providers that there is a potential for increased statin toxicity when these statins are combined with other medications that inhibit CYP3A4. Clarithromycin and erythromycin are macrolide antibiotics that inhibit CYP3A4 and have been shown to increase statin levels when patients take both medications. Patel and colleagues investigated the risk of statin toxicity in adults 65 years and older who were coprescribed clarithromycin or erythromycin while taking a statin.

This population-based, retrospective cohort study identified 721,277 patients 65 years and older who had a continuous prescription for a statin metabolized by CYP3A4 (atorvastatin, lovastatin or simvastatin) and who were also prescribed a macrolide antibiotic (clarithromycin, erythromycin or azithromycin). The data were collected from 4 databases: the Ontario Drug Benefit database, the Canadian Institute for Health Information database, the Ontario Health Insurance Plan database and the Registered Persons Database of Ontario. These databases contain records on all prescriptions dispensed to patients 65 years and older, all hospitalizations, inpatient and outpatient services health claims and demographics. These databases have been used successfully for research in the past.

This cohort was divided into 2 groups, those who received a prescription for clarithromycin or erythromycin (CYP3A4 inhibitors) and those that received azithromycin (does not inhibit CYP3A4). Although the reason for the antibiotic prescription was not recorded, the authors assumed that the reasons would be similar since there are similar indications for these antibiotics. The following patients were excluded: those who received more than one antibiotic prescription at once, those with inconsistent statin use before the coprescription was made, those who were within their 1st year of drug coverage eligibility, recent hospital discharge prior to starting the antibiotic, those on other CYP3A4 inhibitors (such as protease inhibitors) and ESRD patients. The patients were followed for 30 days after their initial date of the antibiotic prescription. The primary endpoint was rhabdomyolysis requiring hospitalization. Secondary endpoints were hospitalization for acute kidney injury or hyperkalemia, and all-cause mortality.

The baseline characteristics for the two groups were similar. The group with continuous statin use who took clarithromycin or erythromycin was more likely to be hospitalized for rhabdomyolysis (RR, 2.17 [95% CI, 1.04 to 4.53]) or acute kidney injury (RR, 1.78 [CI, 1.49-2.14]) and had a higher risk for all-cause mortality (RR, 1.56 [CI, 1.36 to 1.80]) than the group who took azithromycin. There was no significant difference in the risk for hospitalization for hyperkalemia. The number needed to harm for those patients taking a statin with clarithromycin and erythromycin for rhabdomyolysis was 5870, for acute kidney injury it was 499 and for all-cause mortality it was 399. The absolute risk increase for rhabdomyolysis for those patients taking clarithromycin or erythromycin was 0.02 (95% CI 0.01 to 0.03). In addition, this group had an absolute risk increase of 0.2 (95% CI 0.14 to 0.26) and 0.25 (95% CI 0.17 to 0.33) for hospitalization for acute kidney injury and all-cause mortality respectively.

■ COMMENTARY

Although the absolute risk for rhabdomyolysis and acute kidney injury was low but statistically significant, the prevalence of statin use with macrolide antibiotics is so high this study warrants attention. There are several limitations to this study. First, each individual drug could not be assessed separately despite the large sample size. Second, the associations seen cannot be deemed causal since this is an observational study. Third, it depends on correct coding and the accuracy of the databases. However, the use of diagnosis codes can be an insensitive measure of hospitalizations for acute kidney injury, hyperkalemia and rhabdomyolysis. Therefore, the number of adverse events may actually be higher than presented in this study. Any hospitalization in an older adult can cause significant morbidity in and of itself and therefore it is logical to avoid these drug interactions if possible. When caring for an older hospitalized patient who is stable on their statin therapy, it is reasonable to consider using azithromycin instead of clarithromycin or erythromycin when selecting a macrolide antibiotic, either for intravenous or oral use. In addition, these drug interactions should be put on the differential diagnosis list in patients who present to the hospital with acute kidney injury or rhabdomyolysis and have a recent history of exposure to the drugs analyzed in this study. ■

ABSTRACT & COMMENTARY

Chest Pain and Dyspnea? Taking Steroids? Think PE.

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips serves on the speakers bureau for PotomaCME.

This article originally appeared in the July 15, 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: Corticosteroid use is associated with an increased risk of symptomatic pulmonary embolism. The greatest risk is in the first 30 days of use and increases with increasing steroid dose.

SOURCE: Stuijver DJ, et al. Use of oral glucocorticoids and the risk of pulmonary embolism: A population-based case-control study. *Chest* 2013;143:1337-1342.

The purpose of this study was to quantify the risk of symptomatic pulmonary embolism (PE) in patients taking corticosteroids. To address this question, the authors used a large database containing demographic details and complete medication histories of more than 2 million people in The Netherlands. Because virtually all patients in The Netherlands are registered with a single pharmacy, records for prescription drug use are essentially complete. This report is the result of a population-based, case-control study of this database. For purposes of this analysis, cases were defined as adult patients with a first hospital admission for PE between 1998 and 2008. Diagnosis of PE was objectively confirmed in more than 95% of these cases. Each case had up to four age- and sex-matched controls from the same database of patients who had not been hospitalized for PE.

For each patient, the investigators identified all prescriptions for oral (systemic) glucocorticoids, including cortisone, hydrocortisone, prednisone, prednisolone, triamcinolone, methylprednisone, dexamethasone, and betamethasone. Patients were classified as never users, current users, or former users on the basis of the timing of the prescription and the PE event. For current users, duration of current glucocorticoid use was categorized as recent use (PE diagnosed in the first 30 days of steroid use), intermediate use (PE diagnosed between 31 and 365 days of steroid use), and long-term use (more than a year of steroid use at the time of PE). The authors also calculated cumulative steroid dose at the time of PE. Daily dose equivalents of prednisolone 10 mg were as follows: cortisone 37.5 mg, hydrocortisone 30 mg, prednisone 10 mg, triamcinolone 7.5 mg, dexamethasone 1.5 mg, and betamethasone 1.5 mg. The analysis controlled for other risk factors for PE (trauma and fractures, malignancy, pregnancy, cardiovascular disease, diabetes, and surgery) and for medications that could reduce the risk of PE (vitamin K antagonists, heparins, and antiplatelet agents [i.e., aspirin, clopidogrel bisulfate, and dipyridamole]).

The analysis included 4495 patients who had PE and 16,802 controls. Overall, the mean age was 60 years, and women comprised 57% of both groups. Current use of glucocorticoids was more frequent among those patients who had PE (13.1%) than controls (2.5%). After adjustment for confounders, the risk estimate (odds ratio [OR]) for PE among corticosteroid users was 4.4 (95% confidence interval [CI], 3.8-5.0). Former users had a much lower increased risk of PE (cases, 8.4%; control subjects, 6.7%) with an adjusted OR of 1.2 (95% CI, 1.1-1.3).

Among those currently using corticosteroids, the risk of PE was highest within the first 30 days of glucocorticoid use (adjusted OR, 5.9; 95% CI, 2.3-7.9) and gradually decreased with longer duration of use. The adjusted OR was 1.9 (95% CI, 1.3-2.9) for long-term use (> 1 year). The association between glucocorticoids and PE varied depending on the dose of glucocorticoids used. A clear dose-response relationship was observed, with low-dose glucocorticoids carrying a two-fold increased risk of PE (adjusted OR, 1.8; 95% CI, 1.3-2.4) up to a 10-fold increased risk for the highest daily dose of glucocorticoids (adjusted OR, 9.6; 95% CI, 4.3-20.5). Almost always, the risk of PE was highest within the first 30 days of glucocorticoid use, irrespective of the dose.

■ COMMENTARY

Glucocorticoids have become one of the most widely prescribed medications, and are currently used by about 1% of the adult population.[1] Despite their undeniable benefits, corticosteroids are accompanied by numerous side effects, including increased cardiovascular morbidity and mortality.[2,3] Endogenous glucocorticoid excess among patients with Cushing syndrome has been associated with an increased incidence of venous thromboembolism (VTE) both during active disease and after surgery.[4] But the effect of exogenous glucocorticoids on VTE risk is less clear. For one thing, it is difficult to separate any potential effect of corticosteroids on VTE risk from the risk resulting from the indication for which they are given. However, several in vitro studies have revealed that exogenous glucocorticoids enhance both synthesis and secretion of von Willebrand factor and plasminogen activator inhibitor-1, suggesting a direct activation of coagulation and inhibition of fibrinolysis.[5-7]

This large, population-based, case-control study has demonstrated that use of oral glucocorticoids was associated with a four-fold increased risk of PE both in a time- and dose-dependent fashion. The greatest risk was within the first 30 days of glucocorticoid use and for the highest daily dose. However, even among low-dose glucocorticoid users, patients were at the highest risk of PE within the first month after treatment onset compared with long-term users.

The authors acknowledge the fact that glucocorticoids are frequently prescribed in conditions that are inflammatory (and therefore thrombogenic), such as chronic obstructive pulmonary disease, arthritides, and cancer, which makes it very difficult to parse the precise role in the increased risk of PE in those who take steroids. At the very least, however, the current study should heighten our index of suspicion for PE in patients who are taking corticosteroids, especially early in the course and at high doses. ■

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ABSTRACT & COMMENTARY

Preventing ICU Infections: An Effective Application of An Old Public Health Strategy

By Michael Young, MD

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

This article originally appeared in the July 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: Despite better compliance with hand hygiene and screening, use of isolation, and other techniques, ICUs remain notorious breeding grounds for hospital-acquired infections. A universal decolonization strategy reduces the total number of ICU bloodborne infections.

SOURCE: Huang SS, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med* 2013;368:2255-2265.

INTRODUCTION

In the 1840s, the Hungarian physician Ignaz Semmelweis demonstrated that maternal mortality was reduced by 90% when physicians washed their hands with a chlorinated solution prior to doing pelvic exams on women in labor. The physician community at that time was harshly skeptical of Semmelweis's observations and recommendations. Women of the time were aware that something was lethal about having babies in the hospital. Some women in the 1840s preferred having their babies literally in the street vs the high-mortality obstetrical wards in teaching hospitals. A century and a half later, hand hygiene is widely accepted as a technique to reduce transmission of infections among hospitalized patients. Uniform compliance with recommended hygiene practices remains disappointing.

About 100 years after Semmelweis's discovery that hand hygiene really matters, ICUs came into existence. It made sense to clinicians to cluster the sickest

patients in one area of the hospital to more conveniently apply new technologies such as mechanical ventilation, central venous lines, and the rapidly evolving skill sets of clinicians who focused on managing critically ill patients. Unfortunately, those life-preserving technologies and the ICU population of patients and their clinicians became reservoirs of methicillin-resistant *Staphylococcus aureus* (MRSA) as early as the 1960s. By 2005, it was estimated that hospitals see more than 18,000 deaths/year from MRSA — more deaths than those reported from AIDS and breast cancer combined. The ICU was no small contributor to the rising death toll from MRSA infections.

In the past two decades, a number of strategies have come into use to prevent the spread of MRSA and other infectious agents in the ICU. The effectiveness of some of these strategies, such as screening patients for MRSA, isolation, contact precautions, and decolonization, has been uncertain. The study by Huang and colleagues provides clinicians, nurses, and infection control specialists much needed guidance.

ABSTRACT

The authors conducted the study in 43 Hospital Corporation of America hospitals, including 74 ICUs. A 12-month baseline period was followed by an 18-month intervention period in which participating hospitals were randomized, using a stratified technique, to one of three infection control groups. In group 1, > 90% of ICU patients received screening and isolation if their nasal swab was positive for MRSA. Contact precautions were used among patients who screened positive for MRSA. In group 2 ("targeted decolonization"), MRSA screening and isolation occurred as in group 1. MRSA-positive patients underwent a 5-day decolonization process. In group 3 ("universal decolonization"), patients were not screened on admission to the ICU. All ICU patients in group 3 received twice-daily intra-nasal mupirocin for 4 days, plus daily baths with chlorhexidine-soaked cloths during the patients' entire ICU stay.

Adherence to the infection control interventions in each of the three groups was encouraged by monthly educational teleconferences and use of on-site hospital personnel. Infections/pathogens were defined using Centers for Disease Control and Prevention (CDC) criteria. Compliance rates of 85% were cited.

There were nearly 100,000 patients enrolled in each of the three groups and the groups had largely similar baseline demographic characteristics. MRSA-positive isolates and the risk of developing a bloodborne pathogen were significantly reduced by universal decolonization. With universal decolonization, the number needed to treat to prevent one bloodstream infection was 54 ICU patients. The rate of bloodborne infections from MRSA was not reduced by either targeted or universal precautions.

■ COMMENTARY

Limitations of the study include lack of an explicit and detailed protocol for each of the three groups. In addition, it remains uncertain if routine use of chlorhexidine and mupirocin will lead to resistance. Severity of illness on ICU admission was not reported. Most of the hospitals included in the study were community hospitals, so it remains unknown if similar results will be seen in large teaching hospitals. It is also unclear why a decrease in MRSA colonization rates, the primary outcome, was not associated with a decrease in MRSA bacteremia.

Study strengths are considerable. Implementing universal decolonization was undertaken with existing personnel without apparent increased costs. The sample size was substantial. Randomization ensured similar baseline characteristics. The size of the reduction in MRSA colonization and positive blood cultures was both statistically and clinically significant. Finally, use of universal decolonization techniques in ICUs is becoming a more common practice.

Should this study change standard infection control measures in our ICUs? I believe that the answer to this question is an emphatic yes. As this study demonstrates, isolation and contact precautions lack effectiveness at preventing infection, and they also reduce clinician bedside presence. Arguably, it is intensivist bedside presence that is at least partly responsible for the improved patient outcomes seen with the intensivist "high intensity" model. In addition, from the use of "bundles" in the ICU over the past 10 years, such as those used for ventilator-associated pneumonia, central line infection reduction, and early resuscitation for sepsis, we have learned that ICU outcomes dramatically improve when a practice becomes universal and applied to all rather than applied selectively or simply at physician discretion.

Will many or all ICUs make the change to universal decolonization soon? This seems less certain, but my forecast is largely positive for the following reasons. We recognize that changes in hospital infection control practices involve complicated organizational and cultural shifts. However, physicians and hospitals change practice patterns over a period of months rather than over years if certain forces align, including: a convincing level of medical evidence; minimal cost to implementing the intervention; the intervention makes "life" easier for the clinicians; and authoritative groups such as the Society of Critical Care Medicine, the American Thoracic Society, and the CDC endorse the change in practice. Finally, the "stick" used by regulatory bodies such as the Centers for Medicare & Medicaid Services can provide powerful incentives to accelerate change in practice.

In summary, this is the time for us to develop a new infection control bundle in the ICU that includes universal decolonization. If Semmelweis were alive today, he would surely agree with this approach. On the other hand, he might be distraught to learn that in 2013 we are still struggling to achieve better compliance with hand hygiene. ■

ABSTRACT & COMMENTARY

Early use of Daptomycin Compared to Vancomycin for MRSA Bacteremia

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 July 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.*

SYNOPSIS: In a matched, retrospective cohort study, early use of daptomycin compared to vancomycin in MRSA bacteremia with vancomycin MICs > 1 µg/mL resulted in improved clinical outcomes, including less clinical failure at 30 days, lower mortality and less persistent bacteremia.

SOURCE: Murray KP, et al. Early Use of Daptomycin Versus Vancomycin for Methicillin-Resistant *Staphylococcus aureus* Bacteremia with Vancomycin Minimum Inhibitory Concentration > 1 mg/L: A Matched Cohort Study. *Clin Infect Dis* 2013; 56:1562-1569

Methicillin-resistant *Staphylococcus aureus* bacteremia (MRSAB) is a frequently-encountered infection that can lead to a number of serious complications, such as infective endocarditis, septic arthritis, and vertebral osteomyelitis. This has led to the increased use of vancomycin, followed by a corresponding increase in MRSA strains with vancomycin minimum inhibitory concentrations (MICs) > 1 µg/mL. Data suggest MRSA isolates with higher vancomycin MICs are associated with worse clinical outcomes, although current clinical guidelines from the Infectious Diseases Society of America do not recommend the early use of alternative therapy.[1] A recent case-control study showed a mortality benefit in patients switched to daptomycin after failing vancomycin.[2] Murray and colleagues sought to compare clinical outcomes in patients with MRSAB and vancomycin MICs > 1 µg/mL who were switched to daptomycin within 72 hours after starting vancomycin therapy.

The investigators conducted a retrospective, matched cohort study on patients with MRSAB treated with vancomycin or daptomycin at four hospitals within the Detroit Medical Center between January 2005 and March 2012. Starting in February 2008, one of the centers implemented a treatment guideline that required the use of daptomycin if the vancomycin MIC was between 1/µg/mL and 2 µg/mL. Included patients were adults with an MRSA bloodstream isolate with an initial vancomycin MIC > 1 µg/mL who received vancomycin or daptomycin for at least 72 hours. Exclusion criteria were if pneumonia or an intravenous catheter was the source of bacteremia, dialysis for acute or chronic renal failure, or if an alternative MRSA therapy was used for ≥ 72 hours prior to starting daptomycin or vancomycin.

Among 1863 consecutive cases of MRSAB with a vancomycin MIC > 1µg/mL, 85 daptomycin-treated patients were matched to 85 vancomycin-treated patients. There was no significant difference in median length of ICU stay (7 days in the daptomycin group vs. 5 days in the vancomycin group; P = .824). The median duration of vancomycin therapy prior to daptomycin was 1.7 days and the median daptomycin dose was 8.4 mg/kg. In the crude analysis, treatment with daptomycin was associated with significantly less clinical failure at 30 days than vancomycin (20.0% vs. 48.2%; P < .001). In multivariate logistic regression analysis, vancomycin was associated with significantly higher risk of clinical failure at 30 days (adjusted odds ratio, 4.5). Furthermore, patients in the daptomycin group had lower mortality compared to those who received vancomycin (3.5% vs 12.9%; P = .047), less persistent bacteremia (18.8% vs. 42.4%; P = .001), and shorter duration of bacteremia (3 days vs. 5 days; P = .003). Length of stay and duration of therapy was not significantly different between the two groups. Average hospital charges were higher in the daptomycin group ($95,244 vs. $86,504; P = .643). In the vancomycin group, 25.9% of patients experienced nephrotoxicity, with the median vancomycin trough 18.1 µg/mL. However, many of them were also receiving an aminoglycoside. One patient in the daptomycin group had a significant elevation in serum CPK concentration but it was not associated with any symptoms and promptly returned to normal after the daptomycin was switched to vancomycin.

■ COMMENTARY

The results of this study strongly suggest a benefit

from using daptomycin instead of vancomycin early in the course of MRSAB when the vancomycin MIC is > 1µg/mL. However, a few words of caution are necessary. First, the average dosage of daptomycin (8.4 mg/kg per day) was higher than is often used in clinical practice, although this did not result in increased toxicities. One interpretation of this finding is perhaps the FDA-approved dose of 6 mg/kg per day is too low for some MRSABs. Second, this was a retrospective study and the results may have been influenced by missed cases, selection bias and/or other unknown variables. Third, patients with intravenous catheter-associated MRSABs (one of the most common clinical etiologies for the condition) were excluded from the study. As noted in an accompanying editorial, patients with renal failure were excluded and there is some evidence that daptomycin is less effective in this population.[3] Another concern about the early switch to daptomycin is cost. Changing from vancomycin to daptomycin increased medication charges by an average of $11,000 per patient. Likewise, hospital charges were also higher in the daptomycin group (approximately $9,000 more per patient) despite the improved clinical parameters.

How do the results of this study affect clinical practice? Ideally a multicenter, prospective study that includes a broad range of patients and conditions (i.e., central-line related bacteremias, dialysis patients) should be conducted to give clinicians better insight into which patients would most benefit from an early switch to daptomycin. However, until such a study is performed it is unlikely that current practice guidelines will be modified. Nonetheless, there seems to be little downside (except cost) and increasing data based on this study and others that early daptomycin is beneficial for many patients with MRSAB. Additional pharmacoeconomic analyses that take into account the impact of daptomycin vs. other agents on length of stay and readmission rates would also be welcome.

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CME QUESTIONS

1. A Modified Early Warning System (MEWS) Score is derived from all EXCEPT which of the following variables

a. Pulse rate
b. Level of consciousness
c. Diastolic blood pressure
d. Respiratory rate
e. Temperature

2. Which of the following antibiotics inhibit the cytochrome P450 isoenzyme 3A4?

a. Clarithromycin
b. Azithromycin
c. Erythromycin.
d. Amoxacillin
e. A and C

3. According to the study by Stuijer and colleagues, which of the following statements about the risk of pulmonary embolism in patients taking glucocorticoids is true:

a. Use of glucocorticoids decreased the risk of pulmonary embolism.
b. The risk of pulmonary embolism was highest during the first 30 days of glucocorticoid use.
c. The risk of pulmonary embolism was not dose-dependent.
d. Former users of glucocorticoids were not at increased risk for pulmonary embolism.

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.

Clinical Briefs in Primary Care™

The essential monthly primary care update

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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Continuing Warfarin for Pacemaker/ICD Implantation is Safer Than Bridging

Source: Birnie DH, et al. *N Engl J Med* 2013;368:2084-2093.

The decision process to determine the optimal scheduling of antithrombotic therapy in the perioperative period is complex. The most recent AT9 CHEST guidelines suggest discontinuation of warfarin 5 days prior to pacemaker/implantable cardioverter-defibrillator (PCM-ICD) implantation, complemented with heparin bridging. This method is somewhat unwieldy, expensive, and has not been confirmed by a large, randomized trial as optimizing risk reduction. During transition from warfarin to heparin, an interval of increased risk for thromboembolism occurs in some, and the use of heparin has also been shown to frequently be associated with device-pocket hematoma.

In the Bridge or Continue Coumadin for Device Surgery Randomized Controlled trial, 681 PCM-ICD patients were randomized to continued warfarin or heparin bridging. Patient selection criteria also included high baseline annual thromboembolism risk (≥ 5%). The primary outcome of the trial was incidence of significant device-pocket hematoma (DPH), which can result in prolongation of hospitalization, need to stop anticoagulation, or additional surgery.

There was a dramatic difference in risk for the DPH primary endpoint between subjects continued on warfarin uninterrupted (3.5%) and subjects randomized to heparin bridging (16%). Risk reduction through continuation of warfarin was not associated with any increased incidence of major surgical adversities compared with bridging. Continuation of warfarin, uninterrupted, was associated with more than 80% reduction in risk of DPH compared to bridging, while not compromising other measures of safety. ■

Bariatric Surgery Impact on Cholesterol Metabolism

Source: Benetti A, et al. *Diabetes Care* 2013;36:1443-1447.

Bariatric surgery techniques are often described as restrictive (e.g., gastric banding) or diversionary (e.g., biliointestinal bypass). While diversionary surgery (DIV) is associated with greater weight loss and more rapid metabolic changes than restrictive surgery (RES), the greater simplicity and reversibility of the latter are pertinent in selecting which intervention is preferred.

Although the impact of bariatric surgery on diabetes has been much publicized, the impact of bariatric surgery on cholesterol is less well recognized. To date, most of the favorable impact on cholesterol has been attributed to weight loss. Over the long term, DIV is associated with greater weight loss than RES. However, since DIV and RES are associated with similar overall weight loss during the first postoperative 6 months, one could compare cholesterol metabolism of the two types of surgery independent of weight loss.

Benetti et al compared cholesterol metabolism in DIV with RES (n = 20). They found that with DIV, reduced cholesterol absorption produced a decrease in LDL and non-HDL, associated with enhanced catabolic LDL receptor activity in the liver.

Because metabolic changes in both groups in reference to glucose, insulin, insulin resistance, and weight loss were similar, the authors suggest that these favorable cholesterol metabolic changes are induced specifically with DIV, and because weight loss over the specified interval was essentially equivalent, the changes in lipids are not fully explained by weight loss. ■

The Do-it-Yourself Diabetes Diagnosis Kit

Source: Bethel MA, et al. *Diabetes Care* 2013;36:1483-1488.

In the last decade, the threshold for diagnosis of diabetes has expanded to lower levels of fasting glucose, inclusion of reference laboratory A1c, and refinement of the definitions of prediabetes. Use of the oral glucose tolerance test (OGTT) appears to be less and less necessary, considering the relative convenience of other diagnostic tests. Could a self-administered OGTT change the balance and be a positive addition to the diagnostic portfolio?

Bethel et al report on a self-administered OGTT home use kit (SmartGRA) used by 30 diabetic and non-diabetic subjects. The kit includes instructions to guide the user through the process of timed capillary glucose measurement as well as a wireless data recorder for glucose levels, the results of which are *not* visible to the user (glucose measurements are wirelessly transmitted to the clinic for evaluation).

Was self OGTT accurate? In a word,

yes. Comparison of OGTT reports generated by SmartGRA vs office-based testing found comparable reproducibility of results. Although the results of home OGTT tended to overestimate glucose levels compared to the reference laboratory, this emerged as a problem with device calibration, which should be able to be remediated. Overall, subjects found the device easy to use.

As a proof-of-concept trial, these results lend credence to the idea that OGTT — generally conceded to be sufficiently unwieldy so that other diagnostic tests are preferred — might merit reconsideration if a well-calibrated, similarly patient-friendly device comes to market. ■

Low Creatinine Excretion Associated with Mortality in Type 2 Diabetes

Source: Sinkeler SJ, et al. *Diabetes Care* 2013;36:1489-1494.

Creatinine excretion (CER), as measured by the 24-hour urinary excretion of creatinine, has recently been noted to be associated with increased mortality, both in persons with underlying renal disease and the general population. CER reflects overall lean muscle mass, so that declines in CER may simply reflect deconditioning, loss of muscle mass, cachexia, malnutrition, etc., each of which may have a negative impact on mortality.

Sinkeler et al report on data accrued from two previously completed trials of angiotensin receptor blockers in diabetic nephropathy: Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan trial and the Irbesartan Diabetic Nephropathy trial. Twenty-four hour urinary CER was measured at baseline for the majority (n = 2360) of participants. Since mortality data from both trials are available, the relationship between CER and mortality can be evaluated.

Across the population studied, each halving decrement of CER was associated with a doubling of mortality risk. Since the primary association of CER is with muscle mass, the authors pose the interesting question of whether efforts expended to improve muscle mass, such as enhanced exercise and nutrition, might favorably effect mortality in this population. ■

Diabetes and Cognitive Function

Source: Spauwen PJJ, et al. *Diabetes Care* 2013;36:1554-1561.

The relationship between vascular disease and type 2 diabetes is consistent: Risk for microvascular events (retinopathy, neuropathy, and nephropathy) and macrovascular events (stroke and MI) is increased compared to non-diabetics. Additionally, when diabetics suffer macrovascular events, the consequences are typically more severe than similar events in non-diabetics.

The etiology of cognitive impairment is often multifactorial, including vascular insufficiency. Diabetics have a higher prevalence of cognitive impairment than non-diabetics, but the rate of cognitive decline in diabetics has not been studied.

The Maastricht Aging Study is comprised of 10,396 adults residing in the province of Limburg, the Netherlands. A sample from this population (n = 1290) underwent extensive neuropsychological testing at baseline, 6 years, and 12 years. At baseline, approximately 5% of the population had type 2 diabetes, with an incidence of an additional 5% over subsequent 6-year intervals.

When compared with controls, diabetics had a significant rate of cognitive decline over 6 and 12 years. Even when adjusted for variables that are more commonly comorbid in diabetics (hypertension, dyslipidemia, obesity), the acceleration in cognitive decline was greater in diabetics. As might be intuitive, diabetics with baseline cognitive impairment progressed at a more rapid rate than those without. Whether any specific intervention among diabetics (e.g., better control of glucose, lipids, blood pressure) might ameliorate the exaggerated rate of cognitive decline remains to be determined. ■

Benefits of Screening for Lung Cancer with Low-Dose CT

Source: The National Lung Screening Trial Research Team. *N Engl J Med* 2013;368:1980-1991.

Lung cancer (LCA) is responsible for more deaths than any other cancer worldwide. The burgeoning growth of smoking in developing countries suggests that this dismaying fact is unlikely to diminish in the foreseeable future. Clinical trials of screening for LCA through chest x-ray (CXR) did not show improved outcomes, likely because of its relatively poor discriminative ability in early disease.

The National Lung Screening Trial enrolled smokers and ex-smokers with at least a 30 pack-year history. Participants were randomized to an annual low-dose CT × 3 (n = 26,714) or standard chest x-ray (n = 26,035).

A positive radiographic finding on at least screening was seen in three times as many CT screenees as chest x-ray (27.3% vs 9.2%). LCA was diagnosed in 1.1% of the CT group vs 0.7% in the CXR group.

Screening for LCA was found to reduce LCA-related mortality by 20% and all-cause mortality by 7%.

Most of the abnormalities detected by low-dose CT screening were benign, so that the positive-predictive value for a positive CT was only 3.8% (i.e., about 4% of study subjects with any positive suspicious finding on CT turned out to have LCA). Reassuringly, repeatedly negative low-dose CT had a negative predictive value of 99.9% (i.e., essentially no one who had negative sequential CT screening was diagnosed with LCA during the screening and follow-up period). ■

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PHARMACOLOGY WATCH

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

Prostate Medications and Cancer Risks — New Evidence

In this issue: Risk of high-grade prostate cancers; clopidogrel and stroke risk; antibiotics and statins; and FDA actions.

Prostate cancer risk and 5-ARIs

The 5-alpha reductase inhibitors (5-ARI) finasteride (Proscar) and dutasteride (Avodart) are used to treat lower urinary tract symptoms in men. They are known to reduce prostate-specific antigen (PSA) levels and there was hope that they may also reduce the incidence of prostate cancer. But in two large trials, PCPT (finasteride) and REDUCE (dustasteride), despite a nearly 25% reduction in the overall rate of prostate cancer, the risk for high-grade prostate cancers was increased (Gleason score 8-10). Debate has raged for the last several years about the significance of these findings and whether the increase was real or spurious due to detection bias. A new study from Sweden attempts to clarify this issue. Using the National Prostate Cancer Register along with prescription data, nearly 27,000 cases of prostate cancer were identified along with some 134,000 matched controls. More than 7800 men were exposed to a 5-ARI, including 1500 with prostate cancer and 6300 controls. As noted in previous studies, the risk of prostate cancer decreased with increasing duration of use of a 5-ARI. With 3 years of treatment, the risk of prostate cancer was 28% lower in the treatment group (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.59-0.89; $P < 0.001$ for trend). The reduction was seen primarily for Gleason score 2-6 and score 7 tumors ($P < 0.001$ for trend for both). However, as opposed to previous studies, the risk for higher grade tumors was not significantly increased, although the risk was not decreased either. By 3 years, the OR was 1.23 (95% CI, 0.90-1.68; $P = 0.46$ for trend), but did not reach statistical significance. The ORs for shorter exposures were 0.96 for 0-1 year exposure, 1.07 for 1-2 years, and 0.96 for 2-3 years. The authors conclude that men treated with a 5-ARI for lower urinary tract symptoms had a lower risk of prostate cancer with Gleason scores 2-7 and no evidence of increased risk of Gleason score 8-10 of cancers up to 4 years of treatment (*BMJ* 2013;346:f3406). The FDA issued a safety warning in 2011 regarding finasteride and dutasteride and the risk of high-grade prostate cancers and it is unlikely that this study alone will reverse that, but it is reassuring for the millions of men who take these drugs for lower urinary tract symptoms. ■

Clopidogrel could reduce stroke risk

Adding clopidogrel to aspirin in patients with minor stroke or a transient ischemic attack (TIA) may help reduce the risk of stroke within the next 90 days, according to a new study from China. In a randomized, double-blind, placebo-controlled trial, nearly 5200 patients were seen within 24 hours after onset of minor ischemic stroke or high-risk TIA and randomized to a combination of clopidogrel with aspirin or aspirin alone. The combination group was given clopidogrel at an initial dose of 300 mg followed by 75 mg per day for 90 days along with aspirin 75 mg per day for the first 21 days, while the aspirin alone group got placebo plus aspirin 75 mg for 90 days. The primary outcome was stroke (isch-

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emic or hemorrhagic) during 90 days of follow-up in an intention-to-treat analysis. Stroke occurred in 8.2% of the clopidogrel-aspirin group as compared to 11.7% in the aspirin alone group (hazard ratio 0.68; 95% CI, 0.57-0.81; $P < 0.001$). Moderate or severe hemorrhage occurred in seven patients in the clopidogrel-aspirin group and eight in the aspirin alone group. The rate of hemorrhagic stroke was the same (0.3%) in both groups. The authors conclude that among patients with TIA or minor stroke who are seen within the first 24 hours of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the next 90 days. The combination does not increase the risk of hemorrhagic stroke or hemorrhage (*N Engl J Med* published online June 26, 2013). An accompanying editorial states that this trial "proves the concept that dual platelet therapy can be more effective than single platelet therapy in preventing early recurrent stroke in patients with acute symptomatic atherothrombosis...," and also shows that dual platelet therapy can be given without excess harm in patients with acute focal brain ischemia. There is slight concern that the results may not apply to non-Chinese patients with different forms of underlying arterial disease (*N Engl J Med* published online June 26, 2013). ■

Antibiotic coprescription and statins

Use caution if you prescribe clarithromycin or erythromycin to patients on statins. Both drugs (but not azithromycin) inhibit cytochrome P450 isoenzyme 3A4, which can increase blood concentrations of statins, especially atorvastatin, simvastatin, and lovastatin. Researchers from Canada looked at the records of continuous statin users who were prescribed clarithromycin (n = 72,591) or erythromycin (n = 3267) with azithromycin use as a comparator (n = 68,478). The risk of hospitalization for rhabdomyolysis within 30 days was the main outcome. Although the absolute risk was low, concomitant use of clarithromycin/erythromycin with atorvastatin, simvastatin, or lovastatin was associated with a higher rate of hospitalization with rhabdomyolysis, especially in those with acute kidney injury. There was also an increase in all-cause mortality when the drugs were combined (absolute risk for rhabdomyolysis 0.02%, with acute kidney disease 1.26%, all-cause mortality 0.25%, relative risks 2.17, 1.78, and 1.56, respectively). These data suggest that coprescription of clarithromycin or erythromycin with a statin that is metabolized by CYP3A4 (atorvastatin, simvastatin, and lovastatin) increases the risk of statin toxicity (*Ann Intern Med* 2013;158:869-876). ■

FDA actions

The FDA has approved paroxetine for the treatment of hot flashes (vasomotor symptoms) associated with menopause. Paroxetine is a selective serotonin reuptake inhibitor (SSRI) and has the same active ingredient in the antidepressant Paxil. It is the first non-hormone based drug approved for this indication. The safety and efficacy of the drug was established in two randomized, double-blind, placebo-controlled trials of 1175 postmenopausal women with moderate-to-severe hot flashes that showed paroxetine was more effective in relieving symptoms than placebo. This new form of paroxetine contains 7.5 mg of the drug and is dosed once daily at bedtime. Paroxetine for depression and other psychiatric indications is dosed at 10-40 mg. All forms of paroxetine carry a boxed warning about increased risk of suicide. There is also concern about reduced effectiveness of tamoxifen if both medications are taken together. Paroxetine 7.5 mg for hot flashes is marketed by Noven Therapeutics as Brisdelle.

The FDA has approved a new formulation of selegiline — a once-daily, orally dissolving tablet — for the treatment of Parkinson's disease (PD) in patients who are losing responsiveness to levodopa/carbidopa. Most PD patients start treatment with levodopa/carbidopa, but for many, the effectiveness wanes with increasing "off" periods during which time symptoms worsen. In clinical trials, the new combination of selegiline reduced "off" periods by an average of 2.2 hours per day compared to 0.6 hours for placebo. The dissolvable tablet uses a new system that delivers more drug at a lower dose. The drug company claims this results in fewer side effects. Selegiline, a monoamine oxidase (MAO) inhibitor, has been available as a generic and also as the branded drugs Eldepryl and Zelapar. Like other MAO inhibitors, it can cause severe, even fatal, reactions if given in combination with certain other drugs including meperidine, tramadol, SSRIs, TCA antidepressants, and the over-the-counter medication dextromethorphan. The new orally dissolving selegiline is marketed by Valeant Pharmaceuticals as Zelapar.

The FDA has approved the TNF blocker golimumab for the treatment of ulcerative colitis. The drug was previously approved to treat rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The approval for ulcerative colitis was based on two studies of more than 800 patients, one group had failed other treatments and the other group were responders who were evaluated for maintenance. In both groups, golimumab was superior to placebo. Golimumab is marketed by Janssen Biotech as Simponi. ■