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Hospital Medicine

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

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ABSTRACT & COMMENTARY

Penicillin to Prevent Recurrent Cellulitis?

By Jennifer A. Best, MD, FACP, FHM

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

SYNOPSIS: Following an index episode of recurrent cellulitis, penicillin decreased the rate of recurrent leg cellulitis during a 12-month prophylactic period as compared with placebo, but this effect was not observed to be sustained.

SOURCE: Thomas KS, Crook, AM, Nunn AJ, Foster KA, Mason JM, et al. Penicillin to prevent recurrent leg cellulitis. *New Engl J Med* 2013;368:1695-703.

Cellulitis, or infection of the skin and soft tissue, is a common admission diagnosis in hospitalized patients. Acute episodes of cellulitis are managed with courses of intravenous and/or oral antibiotics to treat the most common causative bacterial species, *Staphylococcus* and *Streptococcus*. However, as many patients have underlying conditions predisposing to recurrence, such as vascular disease, immunosuppression or skin disruption, it would be beneficial if effective prophylactic therapy were available. Though consensus guidelines recommend prophylaxis for recurrent cellulitis, few high-quality trials are available to support this recommendation. Thomas and colleagues investigated the efficacy of prophylactic low-dose penicillin for the prevention of recurrent leg cellulitis in the PATCH 1 (Prophylactic Antibiotics for Treatment of Cellulitis at Home) trial.

In this randomized, double-blind, placebo controlled trial, 274 patients with recurrent leg cellulitis were identified during hospitalization or through advertising in the United Kingdom and Ireland. All subjects were recruited within 24 weeks of their most recent

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[ALERT]

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recurrence. Recurrent cellulitis was defined as 2 episodes within the past 3 years. Study inclusion required substantiation of the diagnosis by dermatologist exam or record review plus patient interview for the following: warmth, tenderness, acute pain, unilateral erythema (or bilateral erythema, if symptoms temporally corresponded with the most erythematous leg) or unilateral edema. All patients with an uncertain diagnosis were excluded, as were patients using antibiotics for cellulitis prophylaxis within 6 months of recruitment, those with penicillin allergy, and those with precedent leg ulcer, surgery or trauma.

Study patients were randomized to receive penicillin 250 mg twice daily for 12 months or placebo following acute treatment for an index episode of cellulitis. Patients maintained pill counts and an adverse event and health care utilization log and received phone calls from study coordinators every 3 months during prophylaxis (0-12 months) and every 6 months during follow up (to 36 months).

The primary study outcome was time from randomization to next recurrence of leg cellulitis. Notable secondary outcomes included comparisons between the prophylaxis and follow-up phase (total recurrences and development of new edema or ulcers), adverse events (including drug reactions), healthcare utilization and cost effectiveness utilizing national reference costs and the effects of known cellulitis risk factors. Data were analyzed based on intention to treat.

The penicillin and placebo groups were similar at baseline. All patients were followed for at last 18 months. 78% of study patients reported at least 75% compliance with medications; compliance in each group was comparable. During prophylaxis, the primary outcome — median time to recurrence — was longer in the penicillin group (626 days) as compared with placebo (532 days) and the rate of recurrence was significantly lower with penicillin (22% v. 37% for placebo; HR 0.55; $p < 0.01$). The number needed to treat to prevent 1 case of recurrent leg cellulitis was 5. However, during the follow-up period, there were no significant differences between the two groups in the following secondary outcomes — rate of recurrence and repeat episodes, development of edema or ulceration, adverse events, healthcare utilization or cost. Predictors of prophylaxis failure included high BMI (≥33), ≥3 episodes of cellulitis and edema.

In summary, these data confirm the high rate of recurrent leg cellulitis among patients with previous episodes — among all study participants, 53% experienced at least one recurrence during the study period. Though prophylactic low-dose penicillin was effective over 1 year in increasing the time to recurrence and overall recurrence rate, this effect was not sustained to 3 years.

This study does build on a previous study of an ineffective 6-month prophylactic period, but does not clarify whether a prophylactic period longer than 12 months would extend this effect. In addition, this study does not evaluate penicillin's effect on prophylaxis for cellulitis at other sites or whether other non-penicillin agents might be more effective.

Finally, given that some patient groups were less likely to benefit from penicillin, it is likely that one prophylactic approach may not fit all. Further research to clarify these questions will be required before prophylactic penicillin therapy is offered to eligible hospitalized patients with acute episodes of recurrent cellulitis. ■

ABSTRACT & COMMENTARY

In-Hospital Cardiac Arrest Outcomes

By John P. DiMarco, MD, PhD

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Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

This article originally appeared in the May 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: Chan PS, et al, for the American Heart Association Get with the Guidelines-Resuscitation investigators. Long-term outcomes in elderly survivors of in-hospital cardiac arrest. *N Engl J Med 2013*;368:1019-1026.

The Get with the Guidelines-Resuscitation registry is a large, prospective registry of in-hospital cardiac arrests that analyzes data to promote quality improvement. In this paper, Chan and colleagues report the long-term outcomes in Medicare-age patients who suffered an in-hospital cardiac arrest and survived to discharge. The study cohort was drawn from 523 acute care hospitals that submitted data to the Get with the Guidelines-Resuscitation registry between 2000 and 2008. Data were collected on 10,316 Medicare age eligible patients. Of these, approximately 70% could be linked to Medicare claims data for the survival analysis. For patients with cardiac arrests during multiple hospitalizations, only the first event was included. The outcomes of interest were survival and freedom from readmission during the first year after discharge. Multivariable logistic-regression models were used to examine predictors of 1-year survival. The models included patient clinical characteristics, diagnoses, post-arrest neurological status, characteristics of the arrest, and clinical and administrative aspects of the arrest.

There were 6972 survivors of in-hospital cardiac arrests in the cohort. Ventricular fibrillation and pulseless electrical activity were the most common cardiac arrest rhythms. Heart failure, myocardial infarction, and renal insufficiency were present in 25% of patients. At hospital discharge, 48% of the patients had mild or no neurologic disability, with 34% having moderate, and 17% either had severe neurologic disability or were in a vegetative state. At discharge, 55% of the patients were transferred to an inpatient skilled nursing or rehabilitation facility, 40% were discharged home, and 5% went to a hospice. Life table analysis showed that the overall rate of survival was 82% at 30 days, 72% at 3 months, 59% at 1 year, and 50% at 2 years. Survival probability decreased with increasing age. Other factors associated with survival were white race, female gender, ventricular fibrillation as the presenting rhythm, and milder post-arrest neurologic disability. Hospital readmission was also common. Sixty-five percent of the patients were readmitted within 1 year after discharge and 76% had been readmitted by 2 years.

The authors conclude that the Get with the Guidelines-Resuscitation Registry provides important data about the outcomes of in-hospital cardiac arrest. If patients survive to discharge, a significant proportion will survive long-term, but repeat hospitalizations will be common.

■ COMMENTARY

It has been estimated that in-hospital cardiac arrest occurs with a frequency of about 6.6 per 1000 hospitalized adult patients, with about 50% in intensive care units and 50% in other settings. Since patients with in-hospital cardiac arrest are often already seriously ill, survival to hospital discharge is low, with most studies showing rates of less than 20-25%. However, as shown here, if patients do make it to discharge without severe neurologic damage, long-term survival is possible. This makes improvements in hospital programs to prevent and treat in-hospital cardiac arrest critically important.

The American Heart Association has recently published a position paper on strategies

to improve survival after in-hospital cardiac arrest.[1] This comprehensive document should be required reading for all cardiologists who provide in-hospital care. ■

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1. Morrison LJ, et al. Strategies for improving survival after in-hospital cardiac arrest in the United States: 2013 consensus recommendations: A consensus statement from the American Heart Association. *Circulation* 2013; 127:1538-1563.

ABSTRACT & COMMENTARY

Is Your Smart Phone Spreading Infection in the ICU?

By David J. Pierson, MD

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

This article originally appeared in the May 2013 issue of Critical Care Alert. *It was peer reviewed by William Thompson, MD. Dr. Thompson is Associate Professor of Medicine, University of Washington, Seattle. He reports no financial relationships relevant to this field of study.*

SYNOPSIS: Bacteria were present on the cell phones of all hospital clinicians studied, with potentially pathogenic microorganisms isolated from 29% of them. Contamination with pathogens was found more commonly with smart phones than with non-smart phones, and by multivariable analysis no other factor was associated with this difference.

SOURCE: Lee YJ, et al. Contamination rates between smart cell phones and non-smart cell phones of healthcare workers. *J Hosp Med* 2013;8: 144-147.

Lee and colleagues administered questionnaires and performed bacterial cultures on the cellular phones of 203 clinicians (39% physicians, 52% nurses, 9% medical assistants) working in three university-affiliated teaching hospitals in Seoul. The questionnaire included data on participant demographics (age, gender, occupation) as well as behavior regarding cell phone use (type of cell phone, frequency and reasons for use, and cleaning of cell phones). The investigators touched the anterior and posterior surfaces of the phones onto blood agar plates and classified the recovered bacteria according to pathologic potential. Among probable pathogenic microorganisms, representative drug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus*, and imipenem-resistant *Acinetobacter baumannii* were categorized as drug-resistant pathogens. The participants' mean age was 29 years and 79% were women. A total of 115 (57%) were smart phone users and 88 (43%) used non-smart phones. The smart phone users were slightly younger (28 vs 29 years, $P = 0.03$), but this was the only significant difference between the groups. Only a minority of all cell phone users reported taking special measures to clean them.

All 203 cell phones had positive cultures: 4% had a single organism recovered, 19% had two organisms, and 76% had three or more. The most commonly cultured microorganism was coagulase-negative *staphylococci*, isolated from 96% of the phones. Gram-positive bacilli and *Micrococcus* species were also frequently recovered. Probable pathogenic bacteria were isolated from 58 cell phones (29%). *S. aureus* was the most common of these, and it was MRSA in 8 of the 50 instances. *Acinetobacter baumannii* was recovered from five phones. Probable pathogens were isolated more often from smart phones (35% vs 20% of non-smart phones, $P = 0.03$). The total colony count of probable pathogens from smart phones was also higher (average, 5.5 vs 5.0 from non-smart phones, $P = 0.01$). Among all the factors examined for possible association with phone contamination, only the phone's being a smart phone was found to be a risk factor for contamination by bacteria with pathogenic potential (adjusted odds ratio [OR] 4.02; 95% confidence interval [CI], 1.43-11.31; $P = 0.01$). Using the cell phone more than 10 times during working hours appeared to be associated with pathogen contamination; however, this correla-

tion failed to reach statistical significance (OR, 2.9; 95% CI, 0.9-9.3; P = 0.07).

■ COMMENTARY

This study found that health care workers' smart phones were more frequently contaminated with potentially pathogenic bacteria than non-smart phones. The authors postulate two reasons for this — that smart phones have larger surfaces that are more often touched by the user's fingers, and that they may be used more times during the day, since clinicians can use them for more work-related tasks than non-smart phones.

Other studies have documented frequent bacterial contamination of the cell phones of health care workers — along with their stethoscopes and various parts of their attire — as well as of the bed rails, monitors, bedside curtains, computer keypads, and other features of the patient's immediate environment. Direct linkage between such contamination and specific cases of hospital-acquired infection has generally been lacking, although it is hard to ignore the possibility of this or measures aimed at avoiding it. Cell phones are now carried by virtually all health care workers. Today, more and more of these are smart phones, which are increasingly being integrated into clinical and administrative aspects of critical care. How concerned we should be about their contamination with potential pathogens is not entirely certain, but we should be aware of the fact that such organisms are present not only on our hands but also on the things we carry around with us in the ICU. ■

ABSTRACT & COMMENTARY

Not Everything That Can Be Counted Counts!

By Rahul Gupta, MD, MPH, FACP

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

This article originally appeared in the April 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, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Kowa, Novo Nordisk, and Teva. Dr. Roberts reports no financial relationship to this field of study.*

SYNOPSIS: As a federal program rolls out to award providers with incentives for achieving meaningful use in electronic health records, wide measure-by-measure variation can jeopardize the validity of electronic reporting.

SOURCE: Kern LM, et al. Accuracy of electronically reported "meaningful use" clinical quality measures: A cross-sectional study. *Ann Intern Med* 2013;158:77-83..

The Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 was signed into law as part of the "stimulus package" representing the largest U.S. initiative to date that is designed to encourage widespread use of electronic health records (EHRs).[1] Being progressively adopted by hospitals and clinicians, EHR systems have the potential to transform the health care system from a mostly paper-based industry to one that uses information technology to create, store, maintain, and exchange health records. EHRs have been widely touted to improve the quality of patient care as well as provide cost savings by increasing practice efficiencies, improving care coordination, improving accuracy of diagnosis and health outcomes, and increasing patient participation in their care.[2] With the goal of promoting the use of EHRs across the nation, the term "meaningful use" is often used for a set of standards defined by the Centers for Medicare & Medicaid Services (CMS) Incentive Programs that govern the use of EHRs and allow eligible providers and hospitals to earn incentive payments by meeting specific criteria. To achieve meaningful use, eligible

providers and hospitals must adopt certified EHR technology and use it to achieve specific objectives. These objectives are further divided into three stages, the first being focused on data capture and sharing. Coming soon will be stage two with objectives and measures centered on advanced clinical processes, followed by stage three scheduled for 2016 with focus on improved outcomes. While the EHR Incentive Program offers up to $27 billion in incentives for meaningful use that began in 2011, those who do not achieve it would be facing financial penalties by 2015.[3] As providers would be required to submit "clinical quality measures" from their EHRs, it is critical that we ensure the EHR reporting is the valid reflection of the delivered care.

In the current study, Kern et al attempt to test the accuracy of electronic reporting in a community-based setting for 12 quality measures, 11 of which are included in Stage 1 of Meaningful Use Clinical Quality Measures. In this cross-sectional study conducted at a federally qualified health center with a commercially available EHR system, 150 patient records were randomly sampled using 2008 data for each quality measure, resulting in 1154 unique patients. Nearly two-thirds were women, the mean age of patients was 55 years, and patients had a median of four visits in 2008. Electronic reporting of these measures was then compared with manual review of records to determine accuracy of reporting. The researchers found that sensitivity and specificity varied significantly based on the specific type of quality measure. For instance, sensitivity ranged from 46% (for appropriate asthma medication) to 98% (for having HbA1C test done in diabetics). Specificity ranged from 62% (for LDL cholesterol control in diabetics) to 97% (for pneumococcal vaccination). Similarly, positive and negative predictive values as well as positive and negative likelihood ratios also varied by measure. When absolute rates of recommended care were evaluated, only three measures with statistically significant electronic reporting-manual review differences were found. These included the underestimation in electronic reporting of rates of appropriate asthma medication (absolute difference, -39%) and pneumococcal vaccination (absolute difference, -21%), as well as overestimation in rate of LDL cholesterol control in diabetics (absolute difference, 20%) compared with manual review.

■ COMMENTARY

Consistent with previous work in the field, research by Kern et al finds that there is wide measure-by-measure variation in accuracy of electronic reporting of clinical quality measures when compared with manual patient chart review. While there are several thoughtful reasons for these variations, such as not all the information from patient charts (e.g., free-text notes or scanned documents) makes it to electronic reporting, it is disappointing to observe that as a system we have not yet been able to resolve these "technical incongruities," especially when our patients' lives are at risk. As this study focuses on the effect of data source on performance measure validity, if a measure cannot be reliably collected, it cannot be valid. As evident by the above study, considerable issues continue to exist with data accuracy and completeness for medication and problem lists, which are the building blocks for reportable measures. It is evident that for a meaningful EHR system to exist, several "meaningful" steps have to be accomplished. These include a clear and concise documentation of the care delivered that can be accurately captured and then automatically transmitted without losing data in the process. Once such a system is established, creating a set of clinical quality measures to be considered for meaningful use is straightforward. Perhaps we have the cart in front of the horse at this time. However, it is not too late to retool our way of systems thinking and begin to reconfigure EHR systems that recognize and extract clinical information from patient charts rather than force the care provider to fill in structured fields that can alter the workflow. The purpose of EHRs should be to improve practice efficiency and patient care coordination, resulting in improved outcomes that do not force clinicians to alter their clinical workflow to suit the reporting needs of the EHRs. It's a work in progress, albeit slow. ■

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Ampicillin plus Ceftriaxone for Enterococcal Endocarditis

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow is a consultant for Siemens Diagnostic.

This article originally appeared in the May 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: A nonrandomized, observational, comparative multicenter cohort study was conducted at 17 European medical centers. Patients treated with ampicillin+ceftriaxone (AC) were generally more ill at baseline than patients treated with ampicillin+gentamicin (AG). Despite this there was no difference in mortality or treatment failure between the groups. Interruption of treatment due to adverse events was more frequent in the AG-treated patients, mainly due to new-onset renal failure.

SOURCE: Fernandez-Hidalgo N, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating Enterococcus faecalis infective endocarditis. *Clin Infect Dis* 2013; 56: 1261-8.

This large multicenter observational study reports on the results of treatment of patients with *Enterococcus faecalis* infective endocarditis (IE) with either AC (n=159) or AG (n=87). Primary outcome measures were death during treatment or at 3 month follow up, treatment failure, relapse, and adverse events requiring treatment withdrawal. A larger proportion of AC-treated patients had previous chronic kidney disease (CKD) than AG treated patients (33% vs. 16%) and cancer (18% vs. 7%). There were no differences in mortality on treatment between the groups (22% vs. 21%) or at 3 months after treatment (8% vs. 7%), treatment failure (1% vs. 2%) or in relapses (3% vs. 4%). However, treatment interruption due to adverse events was much more frequent in AG-treated patients than in patients receiving AC (25% vs. 1%). This was almost entirely due to new onset renal failure (>= 25% increase in serum creatinine above baseline; 23% vs. 0%).

■ COMMENTARY

IE due to *Enterococcus* remains one of the most challenging infections encountered by ID specialists. The organism itself (in contrast to most streptococci and staphylococci) is inhibited but not efficiently killed by cell wall-active antibiotics, rendering these agents essentially bacteriostatic against enterococci. It was shown by Bob Moellering in the 1960's that aminoglycosides (which are not active by themselves at achievable serum concentrations vs. streptococci) result in synergistic bacterial killing when combined with cell wall-active agents. Since bacteria trapped in the dense fibrin-platelet matrix of the vegetation are protected from phagocytosis by neutrophils, the mainstay of therapy of IE due to enterococci has been penicillin, ampicillin or vancomycin in combination with an aminoglycoside, administered for 4-6 weeks. While cure rates are high with these regimens, the nephrotoxicity and ototoxicity of these aminoglycoside-containing regimens is considerable.

Recently some data have suggested that as little as 2 weeks of combination therapy followed by 2-4 weeks of single agent therapy with a cell wall active agent result in high cure rates. However, the toxicity of just 2 weeks of aminoglycoside treatment is significant. In addition, aminoglycosides only are effective in synergy with cell wall-active agents if the isolate of *enterococcus* does not display high-level resistance to that particular aminoglycoside. In vitro data suggest that certain B-lactam agents (including ceftriaxone) in combination with penicillin or ampicillin result in enhanced killing vs. enterococci. A small case series of patients with IE due to high-level aminoglycoside-resistant *enterococcus* suggested that ampicillin plus ceftriaxone provides effective therapy in vivo as well.[1] This large non-ran-

domized trial suggests that ampicillin plus ceftriaxone is as effective as traditional aminoglycoside-containing regimens with significantly less toxicity for all cases of *E. faecalis* IE. Clearly prospective randomized trials are in order. ■

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1. Gavalda J, et al. Brief communication: treatment of Enterococcus faecalis endocarditis with ampicillin plus ceftriaxone. *Ann Int Med* 2007; 146: 574-9.

CME INSTRUCTIONS

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

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

CME QUESTIONS

1. According to the study by Chan and colleagues, elderly patients who survive to hospital discharge after an in-hospital cardiac arrest have a 2-year survival rate of:
a. 82%
b. 72%
c. 50%
d. 10%

2. In the study by Fernandez-Hidalgo, et al., comparing treatment of enterococcal endocarditis with ampicillin-ceftriaxone to ampicillin-gentamicin, which of the following outcomes was observed:
a. Ampicillin-ceftriaxone was superior to ampicillin-gentamicin in efficacy and safety.
b. The two drug regimens were equivalent in efficacy and safety.
c. The two drug regimens were equivalent in efficacy but the ampicillin-gentamicin group had more renal failure.
d. Ampicillin-gentamicin was superior to ampicillin-ceftriaxone in efficacy with equivalent toxicity.

3. Lee and colleagues demonstrated that cell phones in the ICU are contaminated with potentially pathogenic bacteria. Which of the following characteristics was associated with a phone being contaminated:
a. Lack of hand-washing
b. The cell phone being a smart phone
c. The user not wearing gloves
d. The number of people who shared the cell phone

4. In the PATCH 1 trial, the effect of low-dose prophylactic penicillin was lessened in patients with the following risk factors:
A. BMI less than 33
B. Edema
C. Antibiotic use in the previous 6 months.
D. None of the above

CME OBJECTIVES

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

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

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.*

Do Perioperative Beta-Blockers Reduce Mortality?

In this issue: Beta-blockers and noncardiac surgery; prenatal medication exposure and risk of autism; reasons for statin discontinuations; and FDA actions.

Perioperative beta-blockers

The use of perioperative beta-blockers has been debated for decades. Now, a large study from the U.S. Department of Veterans Affairs (VA) suggests that the drugs may be of benefit in selected patients. In a retrospective cohort analysis, exposure to beta-blockers on the day of or the day following noncardiac surgery was evaluated among a population-based sample of nearly 137,000 patients from 104 VA medical centers. The main outcome was all-cause 30-day mortality and cardiac morbidity. Overall, 55,138 patients (40%) were exposed to beta-blockers, although the rate was nearly 68% in those undergoing vascular surgery. Exposure increased with increased cardiac risk factors. Death occurred in just over 1% of patients and cardiac morbidity occurred in just under 1%. Overall, exposure to beta-blockers was associated with a lower mortality (relative risk [RR] 0.73%; 95% confidence interval [CI], 0.65-0.83; $P < 0.001$; number needed to treat [NNT], 241). The effect was greater in patients with higher cardiac risk factors, which include high-risk surgery, cerebrovascular disease, ischemic heart disease, heart failure, diabetes, and renal insufficiency. When stratified by the revised Cardiac Risk Index variables, patients with two or more cardiac risk factors had a RR of 0.63 (95% CI, 0.50-0.80; $P < 0.001$; NNT, 105), with three risk factors the RR was 0.54 (95% CI, 0.39-0.73; $P < 0.001$; NNT, 41), and with four or more risk factors the RR was 0.40 (95%CI, 0.25-0.73; $P < 0.001$; NNT, 18). This effect was limited to patients undergoing nonvascular surgery. Beta-blocker exposure also significantly reduced the rate of nonfatal Q-wave infarction or cardiac arrest by 37%. The authors conclude that in patients undergoing noncardiac, nonvascular surgery, perioperative beta-blockers significantly reduced 30-day all-cause mortality in patients with two or more cardiac risk factors and support the use of the drugs in these patients. They also suggest a multicenter randomized trial to assess the benefit in patients with low-to-intermediate risk. The authors were unable to find a benefit in stroke risk or in patients undergoing vascular surgery. They were also unable to determine if various beta-blockers (such as metoprolol vs atenolol) were of benefit or if the benefit was from various dosing regimens. (*JAMA* 2013; 309:1704-1713). ■

Medication use and pregnancy

Two studies suggest that certain medications used during pregnancy may increase the risk of autism in offspring. In the first, which looked at antidepressants in pregnancy, researchers from Sweden reviewed the records of 4429 children with autism spectrum disorder (ASD) as well as 43,000 age- and sex-matched controls. A history of maternal, but not paternal, depression was associated with an increased risk of ASD and the association was confined to women reporting anti-

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.

depressant use during pregnancy (adjusted odds ratio 3.34; 95% CI, 1.50-7.47; $P = 0.003$). This association was irrespective of whether serotonin reuptake inhibitors or non-selective monoamine reuptake inhibitors (tricyclic antidepressants) were used. The association was confined to autism without intellectual disability. Still, the use of antidepressants accounted for only 0.6% of cases of ASD during the study, so the drugs were "unlikely to have contributed significantly towards the dramatic increased prevalence of autism spectrum disorders" (*BMJ* 2013;346:f2059). In the other study, researchers from Denmark reviewed the records of children exposed in utero to valproate (used to treat seizures and other neuropsychological disorders in mothers). Of more than 655,000 children born between 1996 and 2006, 5437 identified with ASD, including 2067 with childhood autism. The overall risk of autism in all children was 1.53%, but of the 508 children exposed to valproate, the absolute risk was 4.42% (95% CI, 2.59-7.46%) for ASD and 2.50% (95%CI, 1.30-4.81%) for childhood autism (adjusted hazard ratio, 5.2). The risk was similar regardless of the indication for use of valproate in the mother. These findings suggest that maternal use of valproate significantly increases the risk for ASD and childhood autism in offspring. The authors suggest that a risk-benefit analysis should be considered for women on valproate in their childbearing years (*JAMA* 2013;309:1696-1703). ■

Discontinuation of statins

Most patients who stop statins due to side effects will tolerate the drugs if rechallenged, according to the findings of a new study. In a retrospective cohort study using data from two Boston hospitals, researchers reviewed the records of nearly 108,000 patients on statins and found statin-related events such as muscle pain documented in 18,778 (17.4%). Of those patients, 11,124 stopped the drugs at least temporarily and 6579 were restarted within the subsequent 12 months. The vast majority of patients restarted on a statin tolerated the drug (92.2%), although about half were eventually switched to a different statin. The authors conclude that statin-related side effects are common and often lead to discontinuation; however, most patients who are rechallenged can tolerate statins long-term. They suggest that "statin-related events may have other causes, are tolerable, or may be specific to individual statins rather than the entire drug class" (*Ann Intern Med* 2013;158:526-534). ■

FDA actions

The FDA has updated labeling of the new tamper-proof oxycodone (OxyContin), while at the same time denying approval of generic forms of the original formulation of oxycodone. The new labeling indicates that the product "has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)." The agency's refusal to approve generic forms of the original formulation was based on the increased risk of abuse inherent in the non-tamper proof form leading to the risk of serious adverse events including overdose and death. Because of this, the agency has determined that the benefits of the original OxyContin and its generics no longer outweigh its risks and it has been withdrawn from sales. The new tamper-proof formulation is more difficult to crush, break, or dissolve. If tampered with, it forms a viscous hydrogel that cannot be easily injected or snorted. Oral abuse is still possible.

The FDA has approved a fixed combination of doxylamine succinate and pyridoxine for the treatment of nausea and vomiting due to pregnancy. This is a reintroduction of a product widely used between 1956 and 1983. Then marketed as Bendectin, the product was voluntarily withdrawn by the manufacturer due to lawsuits related to birth defects, although evidence of risk was not supported by scientific evidence. The reapproval was based on a study of 261 women experiencing nausea and vomiting due to pregnancy in which the drug was more effective than placebo in relieving symptoms. Since the 1980s, observational studies have shown that doxylamine and pyridoxine do not pose an increased risk of harm to the fetus. The recommended starting dose is two tablets taken at bedtime on an empty stomach. The combination is marketed by Duchesnay Inc. as Diclegis.

The FDA has approved prothrombin complex concentrate for the rapid reversal of anticoagulation by warfarin and other vitamin K antagonists. Plasma is the only other option for this use currently available, and prothrombin complex can be given at significantly lower volume than plasma. The product is made from pooled plasma of healthy donors that is processed to minimize the risk of viral and other diseases. The approval was based on a study of 216 patients who were anticoagulated and had major bleeding. Plasma complex concentrate was found to be similar to plasma in its ability to stop major bleeding. Plasma complex concentrate is marketed by CSL Behring as Kcentra. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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Risks and Benefits of an Extended 10-year Tamoxifen Regimen for Breast Cancer

Source: Davies C, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of estrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805-816.

The prevailing 5-year tamoxifen regimen for breast cancer has been shown to reduce breast cancer mortality by as much as one-third over a 15-year interval; a comparison with a shorter regimen (1-2 year) found the longer duration to be superior. Would even longer tamoxifen administration (i.e., > 5 years) provide even greater risk reduction of breast cancer and its consequences, and if so, would longer regimens induce greater toxicity to other non-targeted tissues (e.g., induction of endometrial cancer)?

The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial randomized women with estrogen receptor-positive breast cancer (B-CA) to either 5 years (n = 3418) or 10 years (n = 3428) of tamoxifen. Follow-up continued for 5 years after conclusion of the 10-year tamoxifen course. The estrogen-receptor positive B-CA group actually represents only about half of all of the women enrolled in ATLAS; the estrogen-receptor negative population of ATLAS demonstrated no risk reduction through longer tamoxifen administration.

Numerous outcomes favored 10-year tamoxifen over 5 years and were statistically significant: B-CA recurrence (617 vs 711 cases), B-CA mortality (639 vs 722 deaths), and ischemic heart disease death or hospitalization (127 vs 163 cases). On the negative side of the equation, all-cause mortality was not impacted by the longer tamoxifen regimen, and there was a significant increase in pulmonary embolism (41 vs 21 cases) as well as endometrial cancers (116 cases vs 63 cases).

These results were apparently sufficiently impressive enough to make the cover story in the *Lancet*. Your reviewer, however, takes pause at the fact that — similar to the situation with results for prostate cancer screening, which has recently been diminished by convincing evidence that screening may reduce prostate cancer mortality but not total mortality — a 10-year tamoxifen regimen reduces B-CA mortality but not total mortality, and has not-insubstantial adverse effects as well as costs. ■

Is There More Pro than Con in Probiotics in Critically Ill Adults?

Source: Barraud D, et al. Impact of the administration of probiotics on mortality in critically ill adult patients. *Chest* 2013; 143:646-655.

The technical definition of probiotic offered by the World Health Organization and the Food and Agriculture Organization sounds promising enough: "viable microorganisms that, when ingested in a sufficient amount, can be beneficial for health." Unfortunately, the existing literature on the benefits of probiotics is not quite so convincing.

Barraud et al performed a meta-analysis of randomized, controlled trials published between 1950-2012 in which probiotics were used in the intensive care unit (ICU) setting, ultimately netting 13 clinical trials, all published after 2002 (n = 1439). The probiotic used in each of these trials was in the *Lactobacillus* family, and although some trials used only one *Lactobacillus* strain, several trials used mixed strains of *Lactobacilli*. Endpoints included ICU mortality, hospital mortality, ICU infections, incidence of diarrhea, and duration of mechanical ventilation.

Of the above-mentioned endpoints, a statistically significant favorable odds ratio was seen only for the incidence of ICU-acquired pneumonia, even though the overall larger category of ICU-acquired infections was not statistically significantly improved. Although the failure to achieve significance to numerous endpoints is disconcerting, the authors point out that since probiotic administration is generally safe, the favorable impact on ICU-acquired pneumonia (a reduction of approximately 40%) might prompt consideration for use in patients known to be particularly at risk for this consequence. ■

Are OSA Outcomes Better in the Hands of Sleep Specialists than Primary Care Clinicians?

Source: Chai-Coetzer CL, et al. Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: A randomized trial. *JAMA* 2013;309:997-1004.

The recognition of obstructive sleep apnea (OSA) as a health burden of compelling epidemiologic presence with significant impact on both quality of life

and cardiovascular health has been recognized by health care providers of essentially all disciplines. Increasingly, sophisticated sleep laboratory monitoring devices allow ever more detailed (and usually more costly) understanding of sleep dysregulation. At the same time, awareness of the frequency and consequences of OSA among diverse disciplines of medicine has resulted in a sufficiently burgeoning population of individuals who merit screening that sleep labs are often unable to keep pace with the increasing demand.

A proliferation of simpler, home-based tools for the identification and potential management of OSA that can be used by sleep specialists and primary care clinicians alike has prompted the question of whether outcomes for OSA patients attended by sleep specialists (who are usually not primary care clinicians), typically with complex sleep analysis tools (which are most commonly employed in a specific sleep laboratory), are superior to outcomes for patients attended by primary care clinicians with less sophisticated home-based tools.

The authors report on a randomized, controlled, non-inferiority trial of patients with OSA identified and treated either in a university sleep laboratory by sleep specialists or by community primary care practices. The primary outcome was improvement in the Epworth Sleepiness Scale, a commonly used and validated scoring system for monitoring sleepiness associated with OSA.

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At the end of the 6-month trial, scores on the Epworth Sleepiness Scales were identical in both groups, and outcomes in the primary care group were determined to be non-inferior to sleep specialist care. Hopefully, primary care clinicians will become more involved in the identification and management of OSA, since equally salutary outcomes are seen in their hands as in the hands of sleep specialists. ■

Inhaled Steroids Increase Risk of TB in COPD Patients

Source: Kim J, et al. Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. *Chest* 2013; 143:1018-1024.

Reactivation of tuberculosis (TB) is an ongoing concern among patients who receive immunosuppressive agents such as TNF-alpha agents for rheumatoid arthritis. Similarly, long-term use of systemic steroids (i.e., ≥ 30 days) in amounts as small as 7.5 mg/day of prednisone increases the risk of TB. Inhaled corticosteroids (ICS) have been associated with systemic effects such as growth retardation (in asthma), reduced bone mineral density, and increased risk of pneumonia (in chronic obstructive pulmonary disease [COPD]). Whether ICS might also be associated with risk for development or reactivation of TB has not been fully clarified.

Kim et al performed a retrospective analysis of COPD patients (n = 620) in a university hospital in South Korea (where the background prevalence of TB is substantially greater than many other nations) to compare the rate of TB activation in persons who had received ICS with controls. To eliminate the confounding factor of systemic steroid use, COPD patients who had received ≥ 7.5 mg for 1 month or more were excluded from the analysis.

There was a substantially greater and statistically significant risk for development of active TB among COPD patients who had been treated with ICS (hazard ratio = 9). In patients whose baseline chest x-ray showed evidence of prior (but quiescent) TB, the hazard ratio for activation of TB was 25!

Although the prevalence of TB is much greater in Korea than in the United States, these data suggest greater vigilance for TB activation in patients chronically using ICS, especially if their x-rays indicate evidence of prior TB. ■

The ASH Position Paper on Orthostatic Hypotension

Source: Shibao C, et al. ASH position paper: Evaluation and treatment of orthostatic hypotension. *J Clin Hypertens* 2013;15:147-153.

Standing from a seated or supine position is normally associated with minimal, if any, blood pressure (BP) change, thanks to homeostatic mechanisms that alter splanchnic and peripheral blood compartments by selective intravascular redistribution and vascular tone. When BP change upon standing exceeds 20/10 mmHg, a diagnosis of orthostatic hypotension (OH) is established. Although tilt-table testing is often suggested for formal diagnosis, simple office measurement of BP 1-3 minutes after standing suffices.

Although sometimes OH produces minor distracting symptoms of dizziness that may be diminished by standing slowly, leg crossing, maintenance of good fluid balance, etc., it can also be a cause of falls, with anticipatable subsequent catastrophes such as hip fracture. Additionally, OH epidemiological data have noted an association between OH and stroke.

A variety of commonly used medications can precipitate or exacerbate OH, including alpha blockers, diuretics, vasodilators, dopamine agonists, and tricyclic antidepressants, modulation of which may OH improve symptoms. Pharmacologic treatments for OH include fludrocortisone (to increase intravascular volume), midodrine (a short-acting vasopressor agent), and other sympathomimetic agents.

OH is also seen in several primary neurologic disorders such as Parkinson's disease, multiple system atrophy, and Lewy body dementia.

Clinicians should suspect OH particularly in patients who report dizziness, unexplained falls, or syncope, although even symptoms such as blurred vision or neck/shoulder pain ("coat hanger" distribution pain) may reflect OH. Fortunately, a variety of lifestyle and pharmacologic treatments can be helpful. ■