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INSIDE

Successful Decrease in Therapy Duration for Community-Acquired Pneumonia

ABSTRACT & COMMENTARY

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

This article originally appeared in the December 2012 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, FIDSA, and peer reviewed by Timothy Jenkins, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University, 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 this single-center, prospective study, median duration of antibiotics for community-acquired pneumonia (CAP) decreased from 10 to 7 days with an antibiotic stewardship program that included education and prospective feedback to the managing team.*

Source: Avdic E, et al. Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. *Clin Infect Dis* 2012;54:1581-1587.

One of the unintended consequences of the Centers for Medicare & Medicaid Services (CMS) performance measures for CAP was that clinicians often started antibiotics too quickly in patients without infection. Subsequently, the requirement that antibiotics be initiated within 6 hours of patient presentation was

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retired as of Jan. 1, 2012. Another concern has been that antibiotics are continued longer than necessary. The Infectious Diseases Society of America/American Thoracic Society guidelines on CAP note that available data on short-course treatment (i.e. 5 to 7 days) do not suggest any difference in outcome compared to longer courses.[1] Overuse of antibiotics can lead to deleterious effects, including drug toxicities and *Clostridium difficile* infection (CDI).

Avdic and colleagues sought to determine if certain outcomes in CAP (decreasing duration of treatment, increasing use of microbiology to narrow therapy, and decreasing duplicate therapy within 24 hours, such as receiving two doses of a respiratory fluoroquinolone) could be improved. They conducted a single-center, prospective, pre- and post-intervention study that included all adult patients admitted to an inpatient medical service between two distinct time periods, January 1st to March 31st 2008 and February 1st to May 10, 2010. Those excluded were (1) residents of extended care facilities; (2) patients diagnosed with cystic fibrosis; (3) patients admitted to the oncology service; and (4) patients admitted for pneumonia in the preceding 30 days. After the initial observation period in 2008, a three-part intervention to improve management of CAP was undertaken. It consisted of a survey of the medical staff to assess their knowledge regarding management of CAP; an educational lecture presented to the staff that included survey results and evidence-based information about duration of therapy; and a prospective review of the management of patients with CAP by the antibiotic stewardship pharmacy specialists with oral feedback regarding suggested changes. The primary outcome measured was duration of antibiotic therapy. Secondary outcomes were percentage of cases where microbiology data was used to narrow therapy and percentage of patients receiving duplicate therapy.

Sixty-two patients were included in the pre-intervention period, and sixty-five in the intervention period. Patient characteristics were similar during both time frames, although there were more patients with alcohol abuse in the pre-intervention period. The median pneumonia score index (PSI) was 82 in both periods. Forty-eight stewardship interventions were made in 34 patients during the intervention period, and 69% of them were accepted by the managing team. In 2008, 21 patients (34%) had a causative organism identified, compared to 9 (14%) in 2010. This led to a change in therapy based on susceptibility testing in 3 of 16 cases (19%) in 2008 and 4 of 6 cases (67%) in 2010. Patients in the intervention group were more likely to be discharged home without antibiotics compared to the pre-intervention group (26% vs. 14%, respectively). More patients were discharged home with a respiratory quinolone in 2008 (63%) than in 2010 (35%). Furthermore, fewer patients in the intervention period received duplicate therapy within 24 hours in the intervention group (90% in 2008 vs. 55% in 2010). The median duration of therapy was decreased in the intervention group from 10 to 7 days ($P < .001$), and the most frequent duration was 8 to 10 days in the pre-intervention period and 6 to 7 days in the intervention period. There was a similar length of stay between both groups (4 days in 2008 and 5 days in 2010). Of note, the 30-day readmission rate was higher in the pre-intervention period (9 [14%] in 2008 vs. 5 [8%] in 2010). Finally, 3 patients in the pre-intervention and 1 in the intervention group developed CDI.

■ COMMENTARY

Previous research has shown that decreasing the length of antibiotic therapy can slow development of resistance in respiratory pathogens.[2] In the present study, sputum cultures were rarely collected in the emergency department, and most patients received at least one dose of an antibiotic before one was obtained. This was unfortunate since negative or nondiagnostic sputum cultures often led to unnecessarily broad spectrum antibiotic therapy for longer than was clinically needed. The narrowing of antibiotics in patients with positive culture results increased by 47% in the intervention group. This finding along with shortening antibiotic duration has the potential to both decrease the emergence of resistance and minimize antibiotic adverse events.

The study was limited in several ways. First, it was conducted at a single center and had a small number of patients. Second, patients might not have taken the antibiotics they were prescribed at discharge, which could have impacted the 30-day readmission rate. Third, the intervention period occurred shortly after the H1N1 influenza pandemic, which could have affected the rates of admission

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Questions & Comments
Please call Russ Underwood, Executive Editor, at (404) 262-5521 or e-mail at russ.underwood@ahcmedia.com.

for CAP, severity of illness, type of bacterial pathogens, and the practice behaviors of the physicians. Finally, the institution had an experienced antibiotic stewardship program so the results might not be generalizable to other institutions. Although the authors comment on the rates of CDI in the pre- and intervention periods, the small number of patients (3 and 1, respectively) do not allow for the assumption of causality.

In conclusion, this study demonstrates that it is possible for antibiotic stewardship interventions to make a notable impact on the treatment of CAP. Future guidelines on CAP should continue to emphasize shorter treatment courses to minimize the ongoing threat of antibiotic resistance.

References

1. Mandell LA, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44(Suppl 2):S27-72.
2. Albrich WC, et al. Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Emerg Infect Dis* 2004;10:514-517. ■

The Positive Impact of Antimicrobial Stewardship Programs in Pediatrics

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

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

This article originally appeared in the December 2012 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, FIDSA, and peer reviewed by Timothy Jenkins, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University, 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.*

Sources: Newland JG, et al. Impact of a prospective-audit-with-feedback antimicrobial stewardship program at a children's hospital. *J Pediatr Infect Dis Soc* 2012;1:179-186.

Stach LM, et al. Clinicians' attitudes towards an antimicrobial stewardship program at a children's hospital. *J Pediatr Infect Dis Soc* 2012;1:190-197.

In the first report (Newland et al), a quasi-experimental study with a control group (also known as a nonrandomized, postintervention design) was performed from 2004–2010 to determine the impact of an antimicrobial stewardship program (ASP) implemented in March 2008 in a tertiary care children's hospital that was based on prospective-audit-with-feedback. The control group included 25 children's hospitals.

A 5-step process was followed to develop the ASP. The team included an infectious disease physician, clinical pharmacist, and data analyst that worked closely with infection control, information systems, and the clinical microbiology laboratory. The clinical pharmacist documented use of broad-spectrum antimicrobials using an electronic health record system. Recommendations were communicated to the clinician caring for the child, with infectious diseases consultation for complex issues.

The team reviewed 10,460 antibiotics prescribed to 8,765 patients over the 30 months following the intervention in March 2008. The most common antibiotics reviewed included ceftriaxone, cefotaxime, ceftazidime, and vancomycin. A total of 2,378 recommendations were made in 1,703 (19%) patients, with the most common recommendation being to stop antibiotics (41%). Agreement with the recommendations occurred initially in 80% of cases, with overall compliance determined to be 92%, which did not change over time. In the intervention group, there was a strong temporal relationship between the ASP and a decline in the use of all antibiotics of 7% (P=0.045) in days of therapy per 1000 patient-days, and 8% (P=0.045) in length of therapy per 1000 patient-days. There were no increases seen in mortality or readmission rates during the study period.

In the second report (Stach et al), an electronic survey was administered to clinicians two years after the implementation to assess their attitudes toward the ASP. There were 205 of 365 participants (56%) that responded. Of these, 80% (160 of 199) had never worked with an ASP before the intervention. Respondents agreed that the ASP decreased the improper use of antibiotics (162 of 194, 84%), improved the quality of care of hospitalized children (159 of 194, 82%), and provided knowledge and education about appropriate antibiotic use (177 of 194, 91%). Adverse interpretations included a perceived loss of autonomy (22 of 194, 11%), perceived interference with clinical decision-making (12 of 194, 6%), and feeling threatened (9 of 194, 5%).

A majority of respondents (116 of 189, 61%) did not have a preference on whether the infectious disease physician or clinical pharmacist should communicate with the clinicians. However, many clinicians preferred communication from the infectious disease physician (44 of 189, 23%) or both the physician and pharmacist (29 of 189, 15%). Many clinicians (76 of 189, 40%) appreciated

face-to-face interaction for communication rather than a page. Among attending physicians, most (71 of 96, 74%) felt that it was acceptable to be informed of recommendations through residents or nurse practitioners.

■ **COMMENTARY**

This study documents that a prospective ASP can successfully decrease the use of broad-spectrum antibiotics in a tertiary care children's hospital. The magnitude of decrease was comparable to that observed among adult institutions.

The clinician's compliance with recommendations using this type of ASP was very high, providing insight to the potential benefit of using a prospective-audit-with-feedback over other strategies such as requiring preauthorization. There were substantial positive feelings among clinicians with this approach, with the vast majority believing that the ASP improved the quality of care for hospitalized children. Also, the clinicians reported minimal negative impact, such as a sense of interference with clinical decision-making and threatened autonomy.

This report illustrates that the five steps to successfully implement a prospective-audit-with-feedback antibiotic stewardship program are:

(1) developing the ASP team;

(2) determining the stewardship strategies and antimicrobials to monitor;

(3) establishing a method of identifying patients;

(4) designing an evaluation of the program;

(5) implementing the program. ■

NSAIDS Post Myocardial Infarction

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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This article originally appeared in the December 2012 issue of Clinical Cardiology Alert. *It was 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: Olsen AM, et al. Long term cardiovascular risk of non-steroidal anti-inflammatory drug use according to time passed after first-time myocardial infarction: A nationwide cohort study. *Circulation* 2012;126:1955-1963.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) early after myocardial infarction (MI) has been shown to increase the risk of death or recurrent MI, but little is known about the long-term risks. Thus, this group from Denmark evaluated their national database and identified more than 99,000 patients who survived 30 days after discharge following their first MI. Of these patients, 44% filled at least one prescription for NSAIDs during a 5-year follow-up period between 1997 and 2009 when the study ended. All NSAIDs were only available by prescription, except ibuprofen. Ibuprofen was available from late 2001 on, but only in 200 mg doses with a maximum of 100 tablets. The primary outcomes were all-cause mortality and cardiac death or readmission for MI. The use of any NSAIDs was associated with an increased risk of death (HR 1.59, 95% CI, 1.49-1.69) after 1 year and HR 1.63 (CI, 1.52-1.74) after 5 years. Cardiac death or MI was also increased (HR 1.30, CI, 1.22-1.39) after 1 year and HR 1.41 (CI 1.28-1.53) after 5 years. Diclofenac exhibited the highest increase in mortality (HRs 2.07-2.73 over first 5 years). The authors concluded that the use of NSAIDs was associated with an increased risk of coronary events for more than 5 years after the first MI.

■ **COMMENTARY**

This population-wide observational study strongly suggests that all NSAIDs should be avoided after MI because there is a persistent increase in coronary events even after 5 years. Although naproxen exhibited the least increase in events, it has a higher likelihood of causing gastrointestinal (GI) bleeding than celecoxib, and bleeding in post-MI patients is not safe. Of course, this study does not establish causation, but there are potential mechanisms that would make the assumption of causation biologically plausible.

This is one of several cardiovascular studies to come from epidemiologists in Denmark who are mining their national databases. Such studies have the strength of large numbers, but suffer from a lack of comprehensive clinical factors that can produce unmeasured confounders. However, they believe this is unlikely because their sensitivity analysis suggests that if such a factor was present in the population at a frequency of 20%, it would have to raise the risk of mortality by about four-fold to influence the results. In fact, they repeated their analysis after excluding patients with rheumatoid arthritis and it did not change the results.

It is highly unlikely that there will ever be a randomized, controlled trial on this issue. So at this point, all NSAIDs should be avoided if possible post MI. If they do need to be used, naproxen may be the best choice unless the patient is at high risk of GI bleeding. Also, the adverse

effects of NSAIDs have been shown to be dose related, so the lowest dose for the shortest time should be used. Since most NSAIDs in the United States are available over the counter, physicians must instruct their post-MI patients about this issue. ■

Psychological Distress Decreased When Families Completed Daily ICU Diary

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, RN, PhD

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Leslie A. Hoffman reports no financial relationships relevant to this field of study. This article originally appeared in the December 2012 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: *Family members who received a diary written during their family member's ICU admission had lower levels of symptoms related to post-traumatic stress disorder.*

Source: Jones C, et al. Intensive care diaries and relatives' symptoms of posttraumatic stress disorder after critical illness: A pilot study. *Am J Crit Care* 2012;21:172-176.

Family members of patients recovering from critical illness may experience psychological problems, including anxiety, depression, and post-traumatic stress disorder (PTSD). Jones and colleagues reasoned that provision of an ICU diary, written in everyday language by ICU staff, would be beneficial to family members by providing an explanation of daily events and opportunity for expression of feelings and contribution to the plan of care. Subjects were family members of patients who were admitted to the ICU for > 72 hours and mechanically ventilated for > 24 hours. The recruitment sites were two general adult ICUs in England and Sweden. The median ICU stay for patients enrolled in the study was 14 days (range, 4-50 days).

Each patient had a diary written for them by staff while they were in the ICU and family members contributed if they wished. At discharge from the ICU, patients and family members were randomized into two groups: one received the diary as soon as they wished but within 2 months of discharge (n = 15), and the second group at 3 months after discharge (n = 15). There were no significant differences between groups in age, length of ICU stay, hours of mechanical ventilation, or APACHE II scores. Family members completed a standardized questionnaire designed to detect PTSD symptoms 1 and 3 months following ICU discharge. At 3 months, scores reflecting PTSD symptoms were significantly lower (P = 0.03) in the group that received the diary within 2 months of discharge, indicating fewer PTSD symptoms.

■ COMMENTARY

This study, conducted in two European ICUs, provides interesting information regarding potential benefits of a simple intervention that may decrease psychological distress following ICU admission. The authors relate that ICU diaries are in "wide use" in Scandinavia and the United Kingdom, but the benefits of this practice have rarely been evaluated. Findings of their study are similar to those reported by a French group[1] from a study enrolling a similar-sized sample (n = 49) followed over a longer period. In the French study, scores reflecting PTSD symptoms were decreased at 12 months, but not at 3 months.

Both studies had a number of limitations: sample size was small and reported benefits did not occur until months after ICU discharge, raising the potential that intervening events were responsible for the change. Nevertheless, provision of the diary was not reported to cause any ill effects and patients and family members had the option of not reading its content. The structure of the French diary was similar to an information booklet; it included an organizational chart of the ICU with staff photos and a photo of an empty ICU bed with explanations of equipment and monitoring systems. Photos of a mechanical ventilator and other equipment were added if used. The first entry was contributed by the ICU physician who summarized the patient's medical history and condition. ICU staff contributed to the following pages by writing a daily narrative in everyday language that provided a status update. Family members contributed as they wished. At discharge, an ICU staff member wrote a conclusion expressing wishes for a good recovery. This intervention merits consideration as a means to reduce patient distress: it is simple to implement, has potential benefit, and has no apparent untoward effects. ■

Reference

1. Garrouste-Orgeas M, et al. Impact of an intensive care unit diary on psychological distress in patients and relatives. *Crit Care Med* 2012;40:2033-2040.

Cancer May Be a Risk Factor for Ischemic Stroke

STROKE ALERT

By Matthew E. Fink, MD

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Matthew Fink, MD, is a retained consultant for MAQUET.

This article originally appeared in the December 2012 issue of Neurology Alert. *It was peer reviewed by M. Flint Beal, MD. Dr. Beal is Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center. Dr. Beal reports no financial relationships relevant to this field of study.*

Source: Schwarzbach CJ, et al. Stroke and cancer. The importance of cancer-associated hypercoagulation as a possible stroke etiology. *Stroke* 2012;43:3029-3034 .

A history of cancer in a patient with ischemic stroke often raises additional concerns for the clinician, including assessment of cancer activity, as well as possible thrombophilias. The use of thrombolytic agents is also controversial in patients with active cancers. These investigators in Mannheim, Germany, attempted to assess the role of cancer-associated hypercoagulability as a risk factor for stroke by comparing a group of 140 patients with active cancer (solid tumors, excluding hematological malignancies and brain tumors) and ischemic stroke to a group of age- and sex-matched controls who had ischemic stroke without any cancer history. They collected data prospectively, including laboratory data, MRI, etiology and risk factors for stroke, types of cancer, deep vein thrombosis or pulmonary embolism, and D-dimer levels.

One hundred forty stroke/cancer patients were compared to 140 stroke controls. In the cancer patients with stroke, an unidentified cause for stroke ($P < 0.001$) and infarction in multiple vascular territories ($P < 0.001$) were more frequent, and D-dimer levels were significantly higher ($P < 0.05$) in patients with stroke and cancer. In the noncancer stroke patients, conventional risk factors, such as hypertension ($P < 0.05$) and hyperlipidemia ($P < 0.01$), were more common. Deep vein thrombosis and pulmonary embolism were more frequent ($P < 0.01$) and D-dimer levels were higher ($P < 0.01$) in cancer-associated stroke compared to controls. Lung and pancreatic cancer were significantly overrepresented and manifested higher D-dimer levels compared to patients with stroke and other types of cancer.

This study supports the concept that there is a hypercoagulable state associated with solid tumor cancers, especially in those who have an elevated D-dimer level, and that cancer may be a risk factor for ischemic stroke. The role of antithrombotic therapies in this group of patients is unknown and needs further investigation. ■

Serious Cardiac Arrhythmias May Occur During First 72 Hours After Stroke

STROKE ALERT

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Matthew Fink, MD, is a retained consultant for MAQUET.

This article originally appeared in the December 2012 issue of Neurology Alert. *It was peer reviewed by M. Flint Beal, MD. Dr. Beal is Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center. Dr. Beal reports no financial relationships relevant to this field of study.*

Source: Kallmunzer B, et al. Serious cardiac arrhythmias after stroke: Incidence, time course, and predictors — a systematic, prospective analysis. *Stroke* 2012;43:2892-2897.

Investigators of the stroke arrhythmia monitoring Database in Erlangen, Germany, performed continuous telemetric cardiac rhythm monitoring on 501 acute stroke patients admitted to their stroke unit. Arrhythmias were systematically detected and categorized in a prospective fashion, and time of onset and predisposing factors were noted.

Significant cardiac arrhythmias occurred in 25.1% of all patients during the 72 hours of monitoring, with the highest risk period being the first 24 hours after admission. Serious tachyarrhythmias (ventricular or supraventricular arrhythmias > 130 beats per minute) were more frequent then bradyarrhythmias. All arrhythmias were independently associated with higher patient age and higher NIH Stroke Scale scores (more severe stroke). The risk of serious cardiac arrhythmias declines during the first 72 hours after stroke and is at highest risk during the first 24 hours. Patients with more severe strokes and advanced age are at highest risk, and continuous cardiac monitoring is strongly advised during the initial 3 days of hospitalization. ■

Can We Predict Long-Term Cognitive Impairment in Survivors of Critical Illness?

ABSTRACT & COMMENTARY

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

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Synopsis: *In survivors of critical illness with documented cognitive impairment at discharge, commonly used cognitive screening tests do not predict which of these patients will experience long-term cognitive impairment.*

Source: Woon FL, et al. Predicting cognitive sequelae in survivors of critical illness with cognitive screening tests. *Am J Respir Crit Care Med* 2012; 186:333-340.

As more patients are surviving critical illness, there is documentation of serious cognitive, physical, and psychiatric consequences arising from lengthy ICU stays in these patients. Numerous studies have demonstrated new cognitive impairments in ICU survivors, yet there is no evidence available as to which patients are likely to experience long-term cognitive impairments after hospital discharge. The study by Woon and colleagues was conducted to address this knowledge gap. The researchers wanted to determine if commonly used cognitive screening tests administered at hospital discharge could be used to predict cognitive impairments, termed cognitive sequelae, 6 months later.

The baseline cognitive screening tests were the Mini-Mental State Examination (MMSE), which is the "gold standard" for cognitive status screening, and the Mini-Cog used to detect cognitive impairments; both were administered at hospital discharge. A battery of cognitive tests was administered 6 months after discharge from the hospital, including the Wide Range Achievement Test-3 Reading subtest (WRAT-3) and the Wechsler Abbreviated Scale of Intelligence (WASI). A number of neuropsychological tests were also administered 6 months after discharge to look for the presence of cognitive sequelae, including attention, upper extremity motor speed, language, memory-delayed recall, long-delay recall, mental processing speed, and executive function. Detailed information on this extensive battery of cognitive and neuropsychological tests can be found in the article by Woon et al.

Patients receiving mechanical ventilation for > 48 hours who were 18-85 years of age were recruited from the Shock Trauma ICU and Respiratory ICU at LDS Hospital and Intermountain Medical Center in Salt Lake City, Utah, from August 2007, through December 2008. Of the 319 patients who initially met the study inclusion criteria, only 70 (50% male) participated in the cognitive assessments at hospital discharge. Of these 70 participants evaluated at hospital discharge, 10 died between discharge and the 6-month follow-up period, three declined to participate, and four were lost to follow-up contact. A final sample of 53 participants completed the 6-month follow-up, with an average age of 54 years, mean hospital length of stay of 25 days, mean ICU length of stay of 13.3 days, and mean duration of mechanical ventilation of 8.8 days.

At hospital discharge, 39% of the participants were impaired on both the MMSE and the Mini-Cog; 64% were impaired on the MMSE only with 45% impaired only on the Mini-Cog. Perhaps not surprisingly, only 28% of the patients had normal scores on both cognitive screening tests. At 6 months post-hospital discharge, controlling for pre-ICU cognitive function, education, depression, and days of mechanical ventilation, the MMSE and Mini-Cog scores were not found to predict cognitive sequelae in this sample. However, a number of the measured cognitive sequelae were found in these ICU survivors at the 6-month follow-up including, most prominently, impaired memory (38%), executive dysfunction (36%), and slow upper extremity motor speed (26%). Of note, the researchers did not assess for the presence of delirium at any time in this study.

■ COMMENTARY

The primary aim of the study by Woon and colleagues was to determine if the MMSE and the Mini-Cog could predict cognitive sequelae in survivors of prolonged critical illness. While the findings addressing the primary aim were not found to be statistically significant, the most clinically significant finding from this article is the marked cognitive sequelae in this sample of ICU survivors. Of note, this sample of study participants was relatively young (54 years of age) with impairments in memory and executive function 6 months after hospital discharge. These findings have important implications for quality-of-life outcomes in survivors of prolonged critical illness and their ability to return to work.

The small sample of only 53 participants out of an initial group of more than 300 patients limits the generalizability of these findings to ICU survivors in general. However, the marked cognitive impairments in these patients should give pause to all ICU clinicians when discussing post-ICU outcomes with patients and their family members. Surviving a prolonged critical illness may come with significant cognitive, physical, and psychiatric consequences that can directly impact quality of life. ■

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. ■

CME Questions

1. In the population-based observational study by Olsen and colleagues, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) after a first myocardial infarction was associated with what outcomes:

a. An increased risk of death after 1 year but not after 5 years.

b. An increased risk of MI after 1 year but not after 5 years.

c. An increased risk of MI and death for at least 5 years after the first MI.

d. A lower risk of MI but increased risk of death at 1 and 5 years.

2. Antimicrobial stewardship programs are associated with:

a. A decrease in the use of broad-spectrum antibiotics

b. A decrease in the duration of antibiotic treatment

c. No increase in mortality or readmission rates

d. All of the above

3. In the study by Jones et al. of critically ill patients, family diaries written during the ICU stay led to:

a. An increased risk of post-traumatic stress disorder in patients

b. A decreased risk of post-traumatic stress disorder in patients

c. An increased risk of insomnia at 3months after ICU discharge

d. No significantly change in any measurable outcomes

CME Instructions

1. Read and study the activity, using the provided references for further research.

2. Log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.*

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

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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.*

Zolpidem and Risk of Falls in Hospitalized Patients

In this issue: Zolpidem and risk of falls; AVR and anticoagulation; statins in cancer patients; and FDA actions.

Zolpidem and risk of falls

Zolpidem (Ambien) increases the risk of falls in inpatients, according to a new study from the Mayo Clinic. The records of hospitalized patients who were not in the intensive care unit were reviewed in this retrospective cohort study. The rate of falls was compared in those who were administered zolpidem vs those for whom it was prescribed but not administered. After controlling for age, gender, insomnia, delirium, dose of zolpidem, Charlson comorbidity index, Hendrich's fall risk score, length of stay, visual impairment, gait abnormality, dementia/cognitive impairment, and concomitantly administered meds, the rate of falls was four times higher in those administered zolpidem (n = 4962) vs those who were prescribed but did not receive zolpidem (adjusted odds ratio 4.37, 95% confidence interval [CI], 3.34-5.76; $P < 0.001$). The authors conclude that zolpidem was a strong, independent, and potentially modifiable risk factor for inpatient falls. The authors suggest that changing order sets so that zolpidem use is not encouraged could potentially reduce fall rates in hospitalized patients. They also suggest that there is limited evidence to recommend other hypnotic agents as safer alternatives (*J Hosp Med* published online Nov. 19, 2012. doi: 10.1002/jhm.1985). ■

Anticoagulation and AVR

Bioprosthetic valves are preferred to mechanical valves for aortic valve replacement (AVR) in the elderly because of lack of need for anticoagulation in the long-term, but short-term anticoagulation is required. The duration of anticoagulation after valve replacement has been unclear. Now, a new study from Denmark suggests 6 months is optimal. Using the Danish National Patient Registry, more than 4000 patients who had a bioprosthetic AVR between 1997 and 2009 were identified. Rates of stroke, thromboembolic events, cardiovascular death, and bleeding were assessed along with warfarin treatment duration. Rates of events per 100 person-years in patients not treated vs those treated with warfarin for 3 months were 7 vs 2.7 for stroke, 13 vs 4 for thromboembolic events, 11.7 vs 5.4 for bleeding, and 32 vs 3.8 for cardiovascular death. The rate of cardiovascular death was 6.5 vs 2.0, favoring warfarin from 90 days to 179 days. The authors conclude that stopping warfarin within 6 months of bioprosthetic AVR surgery was associated with increased cardiovascular death. These findings challenge the current guidelines that recommend 3 months of antithrombotic treatment after AVR surgery suggesting that "patients will gain from an additional 3 months of warfarin treatment in terms of reduced cardiovascular death without risking significant increase in bleeding events" (*JAMA* 2012;308:2118-2125). An accompanying editorial states that this study provides important information to help clinicians understand the benefits and risks of warfarin use after bioprosthetic aortic valve implantation, but it

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.

does not address the issue of adjunctive aspirin or the role of new novel oral anticoagulants (*JAMA* 2012;308:2147-2148). ■

Statins in patients with cancer

Patients taking a statin when diagnosed with cancer have a better prognosis than patients who are not taking statins, according to a new study. This study also used the Danish Registry in which all patients with a cancer diagnosis between 1995 and 2007 were evaluated. Roughly 19,000 patients were on a statin prior to diagnosis and 277,000 were not. Those taking statins were 15% less likely to die of any cause and 15% less likely to die of cancer (hazard ratio 0.85, 95% CI, 0.82-0.87 for cancer). The benefit was present regardless of statin dose or cancer type. The authors suggest that this is biologically plausible since cholesterol is needed for cell proliferation. They suggest "a need for trials of statins in patients with cancer" (*N Engl J Med* 2012;367:1792-1802). Previous studies have suggested reduced cancer mortality with statins in patients with prostate cancer and reduced recurrence rates in breast cancer patients. ■

FDA actions

The FDA has concluded a safety review of dabigatran (Pradaxa) and found that the drug is not associated with more serious bleeding events than warfarin. The review was done using insurance claims and data from the FDA's Sentinel Initiative. According to the FDA, the bleeding rates are consistent with the observations from large clinical trials, including RE-LY, which showed that bleeding rates in patients newly started on dabigatran were similar to rates associated with new use of warfarin. Therefore, the FDA has not changed its recommendation regarding dabigatran (FDA Drug Safety Communication, Nov. 2, 2012). The next day, *The New York Times* published an article reporting that dabigatran has been associated with more than 500 deaths in the United States since it was introduced. It also detailed several tragic cases of bleeding deaths associated with the drug. The article indicts the FDA stating "… the approval process was not sufficiently rigorous because it allowed a potentially dangerous drug to be sold without an option for reversing its effects." The article also mentions more than 100 lawsuits that have been filed in federal courts "…and thousands more are expected" (*The New York Times* Nov. 3, 2012:B1).

The FDA has expanded the approval of rivaroxaban (Xarelto) to include treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), both for acute treatment and prevention of recurrence. The drug is already approved for prevention of DVT and PE after knee and hip replacement surgery and for prevention of stroke in patients with non-valvular atrial fibrillation. It is the first oral drug approved to treat DVT and PE since warfarin was approved 60 years ago; but unlike warfarin, rivaroxaban can be used as monotherapy from diagnosis until treatment is discontinued. Approval was based on three studies of nearly 9500 patients with DVT or PE randomized to rivaroxaban, enoxaparin/vitamin K antagonist, or placebo. Rivaroxaban was equivalent to enoxaparin/vitamin K antagonist and superior to placebo for preventing recurrent DVT or PE.

The FDA has approved a new egg-free flu vaccine for adults. The vaccine is manufactured using cultured mammalian cells instead of fertilized chicken eggs. The manufacturer claims that the cell culture technology enables a rapid response to public health needs, such as a pandemic, since cell culture technology allows vaccines to be manufactured within weeks as opposed to traditional flu vaccines that depend on a large number of fertilized chicken eggs to grow the virus. Cell culture technology is used for several other vaccines including polio, rubella, and hepatitis A vaccines. Approval was based on a randomized, controlled clinical study of 7700 adults ages 18-49. The new vaccine was 83.8% effective in preventing influenza when compared to placebo. Injection site reactions are the most common side effects. The new vaccine is marketed as Flucelvax by Novartis.

The FDA has approved the first Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Tofacitinib, dosed orally twice a day, is approved for RA patients who have failed methotrexate. The drug will compete with the parenteral RA drugs adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade). Tofacitinib carries a boxed warning regarding the increased risk of opportunistic infections, tuberculosis, cancers, and lymphoma; increases in cholesterol and liver enzymes; and decreases in blood counts. Approval was based on seven clinical trials in which the drug showed improvements in clinical response and physical function compared to placebo in patients with moderate-to-severe RA. Tofacitinib will be marketed by Pfizer as Xeljanz. The cost is projected to be just over $2000 per month, similar to other non-methotrexate biologic treatment options. ■

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By Louis Kuritzky, MD

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Gabapentin for Chronic Cough

Source: Ryan NM, et al. Gabapentin for refractory chronic cough: A randomised, double-blind, placebo-controlled trial. *Lancet* 2012;380:1583-1589.

CHRONIC UNDIFFERENTIATED COUGH — that is, cough without any readily visible explanation such as upper respiratory infection, lower respiratory infection, pulmonary lesion, heart failure, etc. — usually turns out to be one of three entities: post-nasal drip, asthma, or acid reflux. Indeed, empirically trying meds for such maladies usually resolves the cough. Nonetheless, despite exhaustive investigation, some patients remain with cough of undetermined etiology, at which point the treatment is problematic.

It has been suggested that chronic cough might reflect a central neural sensitization process that has some pathologic similarities to neuropathic pain. Since gabapentin works well for neuropathic pain, could it also have a positive effect on chronic cough?

Ryan et al studied a population of patients with chronic cough (n = 62) in whom secondary causes (e.g., infection, reflux, asthma) had been eliminated. Study subjects were randomized to gabapentin (up to 1800 mg/d) or placebo for 10 weeks.

At the end of the trial, gabapentin improved cough-related quality of life more than placebo and was well tolerated. Considering that in neuropathic pain trials the dose of gabapentin has been up to twice as high (3600 mg/d), it is reassuring to note that moderate gabapentin doses provide clinically relevant cough improvements. In an era of closer scrutiny applied to use of opioids, another alternative for chronic undifferentiated cough is welcome. ■

Can Statins Reduce Cancer-Related Mortality?

Source: Nielsen SF, et al. Statin use and reduced cancer-related mortality. *N Engl J Med* 2012;367:1792-1802.

IT IS GENERALLY BELIEVED THAT THE PRIMARY mechanism of statin-related cardiovascular (CV) risk reduction is achieved through reductions in LDL. That statins might have other pleiotropic actions, such as plaque stabilization, is the subject of much controversy. Recently, recognition of the impact of statins on new-onset diabetes (a relative 9% greater risk than non-statin users) has given reason for pause. For secondary prevention, the risk-benefit ratio is prominently positive for statin therapy, but much less convincing for primary prevention. A similar picture is emerging in reference to aspirin in CV prophylaxis.

Reminiscent of the aspirin story (i.e., even though primary prevention with aspirin has never been shown to reduce mortality, the favorable effects on CV events — when combined with recently recognized cancer risk reduction — sweetens the deal), we are presented now with the suggestion that statins also reduce cancer-related mortality.

Nielsen et al report on a large dataset of Danish patients who had a diagnosis of cancer (n = 295,925) over the 1995-2007 interval. A comparison was made between statin never users (n = 277,204) and statin users (n = 18,721) with respect to overall and cancer-related mortality.

Statin users had a 15% relative risk reduction for cancer-related death when compared to non-users. Thirteen different cancer types were specified, each of which demonstrated similar benefit. The authors suggest that the cholesterol synthesis-limiting effects of statins may disrupt cancer cell membrane stability and cellular processes, leading to the beneficial observed effects. ■

Are All of Those Multivitamin Dollars Well Spent?

Source: Sesso HD, et al. Multivitamins in the prevention of cardiovascular disease in men: The Physicians' Health Study II randomized controlled trial. *JAMA* 2012; 308:1751-1760.

AMERICANS HAVE BEEN DEPICTED AS AN overly pill-happy lot, much more motivated to take a statin than incorporate dietary change for cholesterol, or take a sulfonylurea rather than exercise and lose weight to improve their diabetes, etc. For a while, the idea of multivitamins seemed like a no-lose proposition; after all, few of us were keeping track of the amounts of essential nutrients we ingest, so multivitamins appeared to provide, at worst, an innocent and inexpensive nutrient insurance policy.

In an era in which essential nutrient deficiency is a stark rarity, the use of vitamin and nutrient supplements is increasingly called into question.

The Physicians' Health Study II is a controlled trial of adult (age > 50 years) male U.S. physicians (n = 14,641) randomized to a daily multivitamin or placebo.

Over a follow-up period of (median) 11.2 years, there was no discernible difference between placebo and a daily multivitamin on CV events, stroke, or mortality.

A parallel "sister study" from the Physicians' Health Study reported a week later in *JAMA* had slightly more encouraging news: Within the same population as mentioned above, the risk of total cancer was reduced by 8% in multivitamin users. Although the risk reduction for cancer was small, and the *P* value only marginally significant, for clinicians who would advocate for multivitamins in the face of failed CV data, the cancer outcomes are modestly more sanguine. ■

Relapsing Lyme Disease: Fact or Fiction?

Source: Nadelman RB, et al. Differentiation of reinfection from relapse in recurrent Lyme disease. *N Engl J Med* 2012;367:1883-1890.

A CHARACTERISTIC DERMATOLOGIC MANIfestation of the acute phase of Lyme disease (LYME) is erythema migrans. With appropriate antibacterial treatment of LYME, the etiologic bacterium *Borrelia burgdorferi* is typically eradicated, and further disease progression is prevented. Untreated LYME can induce repetitive episodes of erythema migrans, as can LYME treated with antibiotics to which *B. burgdorferi* is not susceptible. In an individual patient, it may be difficult to differentiate disease relapse from new infection with a different strain of *B. burgdorferi*.

Genotyping of *B. burgdorferi* surface proteins allows determination of specific bacterial subtypes. Nadelman et al performed such analysis on patients (n = 17) who had experienced two episodes of erythema migrans. Each of the patients had received appropriate antibacterial treatment.

The second episode of erythema migrans was not caused by the same strain of *B. burgdorferi* in any of the patients, indicating that in each circumstance the patient had suffered reinfection rather than relapse. Whereas clinicians may have suspected relapse in patients with repeated episodes of LYME, it appears that reinfection with a new strain is more likely to be responsible. ■

Hypertension and Gout

Source: McAdams-DeMarco MA, et al. Hypertension and the risk of incident gout in a population-based study: The atherosclerosis risk in communities cohort. *J Clin Hypertens* 2012;14:675-679.

GOUT AND HYPERTENSION ARE OFTEN SEEN together. Indeed, there has been a substantial degree of discussion about the potential for elevated levels of uric acid to cause hypertension. The "storyline" remains incomplete, however, because of the observational nature of the data, confounders like thiazide diuretics (which of course elevate uric acid in treated hypertensives), and renal insufficiency, which is common in hypertension and is also associated with elevated uric acid. If uric acid is ultimately proven to increase the incidence of hypertension, it will still remain to be determined whether lowering urate can reduce hypertension safely and effectively.

The Atherosclerosis Risk in Communities study (ARIC) study population provides a dataset for evaluating the association between gout and hypertension. Adults (n = 15,792) from four different metropolitan areas were followed for approximately 10 years.

There was a strong relationship between gout and hypertension. Participants with hypertension were almost two to three times as likely to develop gout, even after adjustment for confounders. For instance, when results were evaluated only among persons not taking thiazide diuretics, a positive association between hypertension and gout was still found. The authors posit that the relationship between hypertension and gout is mediated through blood pressure-induced renal damage that leads to increased levels of uric acid. ■

Zoledronic Acid Treatment of Osteoporosis in Men

Source: Boonen S, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. *N Engl J Med* 2012;367:1714-1723.

WHEN HEARING THE WORD OSTEOPOROsis, most clinicians think "pink," as if the disorder only affected women. To the contrary, 30% of hip fractures occur in men, and the post hip-fracture mortality in men is higher than women. Although the dataset about preferred treatments is less robust for men than women, trials of oral bisphosphonates have been shown to provide meaningful fracture risk reduction for men and women.

Zoledronic acid (ZOL) is a parenterally administered bisphosphonate that has been previously demonstrated to provide significant reduction in osteoporotic fractures in women. For treatment of osteoporosis, ZOL is administered as a single intravenous dose, repeated in 1 year.

Boonen et al performed a placebo-controlled randomized trial in osteoporotic men (n = 1199). As in most osteoporosis trials, calcium (1000-1500 mg/d) and vitamin D (800-1200 IU/d) supplements were administered in both the treatment and placebo arms of the study. The primary outcome variable of the study was new vertebral fractures.

At the end of the 2-year study, men who had received ZOL enjoyed a 67% relative risk reduction in new vertebral fractures (1.6% vs 4.9%), as well as improved bone mineral density. There were no serious drug-related adverse events. Risk for osteoporotic vertebral fracture in men is promptly and effectively reduced by zoledronic acid. ■

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