EVIDENCE-BASED INFORMATION FOR HOSPITALISTS, INTENSIVISTS, AND ACUTE CARE CLINICIANS

HOSPITAL MEDICINE ALERT

AHC Media Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

New phlebovirus associated with severe febrile illness in Missouri
page 67

In patients with lacunar strokes, addition of clopidogrel to aspirin does not reduce risk of recurrent stroke
page 68

IABP for MI with cardiogenic shock?
page 69

Stroke risk with warfarin interruption
page 70

Tele-ICU: Is it worth it?
page 71

Is Doxycycline Protective Against the Development of *C. difficile* infection?

ABSTRACT & COMMENTARY

By Richard R. Watkins, MD, MS, FACP

Division of Infectious Diseases, Akron General Medical Center, Akron, OH; Associate Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH

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

This article originally appeared in the October 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: *A historical cohort study from San Francisco General Hospital evaluated patients ≥18 years old that were hospitalized and received at least one dose of ceftriaxone. In a multivariable analysis, for every day a patient also received doxycycline the rate of* Clostridium difficile *infection was 27% lower than for those who did not receive doxycycline (hazard ratio, 0.73%; 95% confidence interval, 0.56-0.96).*

Source: Doernberg SB, et al. Does doxycycline protect against development of *Clostridium difficile* infection? *Clin Infect Dis* 2012;55:615-620.

Clostridium difficile infection (CDI) is a major complication associated with antibiotic usage, and its incidence continues to increase. Management of CDI remains challenging despite new therapies and many patients suffer from recurrences. Interventions to limit acquisition of the disease are therefore urgently needed. Not all antibiotics predispose to CDI equally, and there is some clinical evidence that certain

Volume 7 • Number 9 • November 2012 • Pages 65-72

NOW AVAILABLE ONLINE
WWW.AHCMEDIA.COM

Financial Disclosure:

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, executive editor Russ Underwood, and associate managing editor Jill Drachenberg have no relevant financial relationship related to the material presented in this issue.

antibiotics may be associated with a lower risk or even prevent it. Investigators sought to determine if doxycycline could avert CDI among patients who received ceftriaxone, a high-risk antibiotic. They performed a historical cohort study between June 1, 2005, and Dec. 31, 2010, that included hospitalized patients ≥ 18 years of age who received at least one dose of ceftriaxone. Patients were excluded who were diagnosed with CDI in the 30 days prior to admission through 2 days after admission, or if diagnosed with CDI before they received ceftriaxone. The main outcome of interest was the onset of CDI within 30 days of initiation of ceftriaxone. The cohort consisted of 2,734 hospitalizations, with 2,305 different patients.

The results of the study were that 39% of patients (1,066) received doxycycline during their hospitalization, and 5 developed CDI for an incidence rate of 1.67 per 10,000 patient-days. Of the patients who did not receive doxycycline, 38 developed CDI, an incidence rate of 8.11 per 10,000 patient days. Unadjusted analysis found white race to be associated with a 2.67-fold higher hazard of CDI compared with nonwhite race (95% confidence interval, 1.46-4.89; P = 0.001). There was a trend toward a protective effect with male gender (P = 0.06). On bivariate analysis, for every day of additional antibiotic receipt besides ceftriaxone, the hazard for acquiring CDI increased by 4%. For every day of doxycycline receipt the unadjusted hazard was 0.67-fold lower for developing CDI compared to patients not receiving doxycycline.

On multivariable analysis, for each additional day that a patient received doxycycline the rate of CDI was 27% lower compared to a patient not receiving it when adjusted for age, gender, race, comorbidities, duration of hospitalization, pneumonia diagnosis, surgical admission, and duration of ceftriaxone and other antibiotics. When a patient received a 5 day course of doxycycline the hazard for developing CDI was 0.21 fold that of a patient not receiving it when adjusted for other factors in the model (95% confidence interval, 0.05-0.82). The hazard ratio for developing CDI in a patient who received a 5 day course of doxycycline and ceftriaxone compared to a macrolide and ceftriaxone was 0.15 (95% confidence interval, 0.03-0.77), and was 0.13 compared to a 5 day course of a fluoroquinolones and ceftriaxone (95% confidence interval, 0.03-0.62). The strongest predictor of developing CDI was time spent in the hospital and the hazard for each day was 15.1 fold higher than for an outpatient.

The study had several limitations. First, all patients in the cohort were given ceftriaxone which would have increased their baseline risk for CDI. This made it difficult for the investigators to determine the increased risk of CDI specifically due to the duration of ceftriaxone. Second, trauma patients could have caused confounding of the results as they were commonly male and nonwhite, two groups shown in the study to have lower incidence of CDI. Third, measurement bias may have occurred since hospitalized patients who develop diarrhea are more likely to be tested for CDI than those who have been discharged. Fourth, antibiotics received before hospitalization were not recorded and could underestimate the subsequent risk for developing CDI. Finally, the authors did not identify the strain(s) of *C. difficile* present during the study.

■ COMMENTARY

Doxycycline plus a β-lactam antibiotic is an alternative recommendation for the treatment of patients hospitalized for community-acquired pneumonia (CAP) in the current IDSA/ATS guidelines.[1] The majority of patients with CAP admitted to the general floor at my hospital (which is similar in size to the authors') receive either levofloxacin or ceftriaxone plus azithromycin, while those admitted to the ICU receive levofloxacin or azithromycin plus ceftriaxone. The recent report on the cardiovascular risks associated with macrolides makes doxycycline look appealing.[2] It will be interesting to see if doxycycline usage in clinical practice increases in light of this study, especially for CAP. Furthermore, if doxycycline decreases the risk of developing CDI there would be even more reason to use it over macrolides and possibly quinolones, the latter of which carry a high risk for CDI.

The mechanism behind the possible protective effect of doxycycline is unknown. Several theories have been proposed, including its in vitro activity against anaerobic bacteria (including *C. difficile*), attenuating *C. difficile* toxin production, and the fact that doxycycline is mostly absorbed in the upper gastrointestinal tract which would spare the normal flora in the colon.[3,4] Tigecycline, a derivative of minocycline, has been used successfully in refractory cases of CDI.[5]

In the present study, patients who received doxycycline had

Hospital Medicine Alert, ISSN 1931-9037, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305. Website: www.ahcmedia.com.

EXECUTIVE EDITOR: Russ Underwood.
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to *Hospital Medicine Alert,* P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

AHC Media

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: russ.underwood@ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $249
Add $17.95 for shipping & handling.
(Student/Resident rate: $125)

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of *20 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for hospitalists, intensivists, and acute care clinicians. It is in effect for 36 months from the date of the publication..

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

shorter courses of antibiotics overall, which would intuitively decrease their risk for CDI. It was not randomized, which could predispose to confounding and uncertainty as to whether the observed association was due to the treatment or the type of patient to whom the treatment was administered. For instance, the cohort patients who received doxycycline were more likely to have had pneumonia on admission, less likely to have been admitted to a surgery service, had higher Charlson comorbidity indices, and received shorter courses of additional antibiotics. Moreover, the authors did not determine whether patients in the cohort had an episode of CDI more than 30 days prior to hospitalization, as this may have led to increased risk. The incidence of CDI in this study was lower compared to prior studies. This might have been due to the enzyme immunoassay testing method used, which has poor sensitivity. Whether it impacted the results is uncertain.

The incidence of CDI shows no sign of abating, and current infection control practices and antimicrobials are unlikely to curtail the epidemic. Novel and innovative solutions are required and will likely be the key to controlling the disease. Despite its limitations, this study has an important finding: Hospitalized patients treated with ceftriaxone who also received doxycycline had a lower risk for developing CDI. Indeed, it could lead to adjustment of the paradigm for treating CAP by making doxycycline plus ceftriaxone first-line therapy. However, additional studies that verify the favorable association between CDI and doxycycline should be performed before changes to the current guidelines can be recommended. ■

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. Ray WA, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881-1890.
3. Noren T, et al. In vitro susceptibility to 17 antimicrobials of clinical Clostridium Difficile isolates collected in 1993-2007 in Sweden. *Clin Microbiol Infec* 2010; 16:1104-1110.
4. Joshi N, et al. Doxycycline revisited. *Arch Intern Med* 1997;157:1421-1428.
5. Venugopal AA, et al. Current state of Clostridium difficile treatment options. *Clin Infect Dis* 2012;55 Suppl 2:S71-76.

New phlebovirus associated with severe febrile illness in Missouri

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Chairman, Department of Medicine, Santa Clara Valley, Medical Center; Clinical Professor, Stanford University School of Medicine

Dr. Winslow is a consultant for Siemens Diagnostic.

This article originally appeared in the October 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: *Two men presented to a hospital in northwestern Missouri in June 2009 with fever, fatigue, diarrhea, thrombocytopenia and leukopenia. Both had a history of frequent recent tick bites. A novel phlebovirus was isolated in cell culture from patient blood. Electron microscopy revealed virus particles consistent with Bunyaviridae. Sequencing identified the viruses as novel members of the phlebovirus genus.*

Source: McMullan LK, et al. A new phlebovirus associated with severe febrile illness in Missouri. *New Eng Jrl Med* 2012;367:834-41.

Two men (one age 57 with no prior significant illnesses and one age 67 with type 2 diabetes) from northwestern Missouri presented separately to a hospital with illnesses characterized by fever, fatigue, diarrhea, thrombocytopenia and leukopenia. Hepatic transaminase levels subsequently became elevated in both patients, peaking between 8 and 10 days. Both reported frequent tick bites with most recent tick exposure 5-7 days prior to onset of illness. The patients were initially suspected of having ehrlichiosis and were given doxycycline pending diagnostic studies. Both patients eventually recovered from their illnesses but had symptoms of fatigue for as long as 2 years following their acute illnesses.

Blood samples sent to CDC were negative by PCR for Ehrlichia and rickettsiae of the spotted fever group. Subsequent serologic studies were negative for antibodies to spotted fever group rickettsiae and typhus. Leukocytes collected from the patients on day 2 of hospitalization were inoculated into DH82 cells and showed cytopathic effect, which was transferable to fresh DH82 cells. Electron microscopy revealed enveloped particles averaging 86 nm in diameter, typical of a virus in the Bunyaviridae family. RNA isolated from infected cell cultures was sequenced using next-generation sequencing and was found to be similar to phleboviruses in the Bunyaviridae family. Sequences from the two patients were similar, but not identical, suggesting that the two patients were infected independently. Phylogenetic analysis showed clustering of these two new viruses with other tickborne viruses most closely related to severe fever with thrombocytopenia syndrome virus (SFTSV). Viral RNA of the novel virus was also detected in bone marrow from the second patient. Both patients demonstrated IgG antibody to the novel virus by ELISA more than 2

years following their acute illnesses.

■ **COMMENTARY**

One of the main reasons I decided to become an infectious diseases specialist when I was doing my Medicine residency during the 1970s was because I really enjoyed the challenge of trying to figure out what was wrong with very sick (usually febrile) patients. It was also during my internship that I cared for a patient with severe multi-lobar pneumonia who had recently attended a convention of the American Legion at the Bellevue-Stratford hotel in Philadelphia (about 2 years later the CDC finally identified the etiologic agent *Legionella pneumophila*). The next year I cared for a 14-year-old girl who developed a faint sunburn-like rash, fever, and multisystem organ failure shortly after beginning to use a newly marketed super-absorbent tampon (vaginal culture did grow *Staphylococcus aureus*, and a few months later other cases of menstrual TSS were identified in the U.S.). At the end of my fellowship training, Mike Gottlieb in Los Angeles described the first cases of Pneumocystis pneumonia in young gay men and we knew we were dealing with another new infectious disease (AIDS). During my career, the identification of new syndromes and newly recognized etiologic agents of disease has continued with great regularity (Hantavirus pulmonary syndrome, SARS, pandemic H1N1 and many others come to mind).

This is an interesting case report which while not completely fulfilling Koch's postulates, almost certainly represents a newly recognized tick-borne viral infection in North America. Many of the clinical and laboratory manifestations of this illness are similar to the also recently described SFTS bunyavirus illness seen in China.[1] Although the two patients described in the case report had severe illness, the spectrum of disease and extent of subclinical infection associated with this newly recognized phlebovirus is unknown. Also, while it is most likely that the common tick, *Amblyomma americanum*, is the vector for this virus, limited sampling of ticks in Missouri did not reveal the virus.

Coincidentally, Toscana virus (another phlebovirus originally isolated in 1971 in Tuscany) was recently shown to be responsible for 15% of cases of aseptic meningitis between July and October in northern Italy.[2] Since this latter virus has been recognized previously as a common cause of aseptic meningitis in the Mediterranean basin, its recognition recently in northern Italy may be a reflection of changing ecology related to global climate change. ■

References

1. Yu X-J, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. *New Eng Jrl Med 2011;364:1523-32.*
2. Vocale C, et al. Toscana virus infections in northern Italy: Laboratory and clinical evaluation. *Vector-borne and Zoonotic Diseases* 2012;12:526-9.

In Patients with Lacunar Strokes, Addition of Clopidogrel to Aspirin Does Not Reduce Risk of Recurrent Stroke

STROKE ALERT

By Matthew E. Fink, MD

Professor and Chairman, Weill Cornell Medical College and Neurologist-in-Chief, New York Presbyterian Hospital

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

This article originally appeared in the October 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: The SPS3 Trial Investigators. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med* 2012;367:817-825.

Small subcortical brain infarcts, known as lacunar strokes, account for about 25% of all ischemic strokes. They are believed, in most cases, to be caused by disease of small penetrating arteries, i.e., lenticulostriate branches of the middle cerebral arteries, and are the most common cause of "silent" brain infarcts and vascular dementia. Lacunar infarcts were included in studies of intravenous thrombolysis, and they are treated with r-tPA within the appropriate time window. However, secondary prevention of lacunar strokes with antiplatelet therapies has not been specifically studied using MRI as a sensitive method to detect new infarcts.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial compared two randomized interventions, clopidogrel 75 mg with aspirin 325 mg vs aspirin 325 mg alone in patients who had a lacunar stroke (≤ 2 cm) within 180 days of enrollment. There were 3020 patients enrolled, with a mean age of 63 years, and 63% were men. After a mean follow-up of 3.4 years, the risk of recurrent stroke was not significantly reduced with dual antiplatelet therapy, compared to aspirin alone (2.5% per year vs 2.7% per year). The risk of major hemorrhage was almost doubled with dual antiplatelet therapy vs aspirin alone (2.1% per year vs 1.1% per year; hazard ratio [HR], 1.97). All-cause mortality was increased in the dual antiplatelet therapy group (hazard ratio, 1.52; 95% confidence interval, 1.14-2.04; $P = 0.004$), but this increase in mortality was NOT accounted for by fatal hemorrhages. In patients with lacunar stroke, the addition of clopidogrel to aspirin did not reduce the risk of recurrent ischemic stroke, but did increase the risk of serious bleeding and death. ■

IABP for MI with Cardiogenic Shock?

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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

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

This article originally appeared in the October 2012 issue of Clinical Cardiology Alert. *It was edited by Michael H. Crawford, MD, and peer reviewed by Ethan Weiss, MD. Dr. Crawford is Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco, and Dr. Weiss is Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Crawford reports no financial relationships relevant to this field of study, and Dr. Weiss is a scientific advisory board member for Bionovo.*

Source: Thiele H, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012; Aug 26. [Epub ahead of print.]

Patients who present with acute myocardial infarction (MI) complicated by cardiogenic shock represent a group at high risk for early mortality. Current guidelines recommend the use of intra-aortic balloon pump (IABP) for these patients, but there are few randomized, controlled trial data to support this. Thiele and colleagues studied the effects of IABP in 600 patients presenting with MI and cardiogenic shock. Patients were eligible for the study if they presented with acute MI (with or without ST elevation) and cardiogenic shock, defined as a systolic blood pressure (BP) lower than 90 mmHg for ≥ 30 minutes, or the requirement for catecholamine infusion to maintain BP > 90 mmHg, plus signs of pulmonary congestion and end-organ hypoperfusion (altered mental status, oliguria, cold clammy skin, or elevated serum lactate). Exclusion criteria included age ≥ 90 years, resuscitation from cardiac arrest for > 30 minutes, severe peripheral arterial disease precluding IABP, aortic regurgitation ≥ grade II, shock for > 12 hours, mechanical cause for shock (e.g., ruptured papillary muscle), or life expectancy < 6 months. Patients were randomized to receive IABP (n = 301) vs no IABP (n = 299) in an open-label fashion. All patients were expected to undergo early revascularization. The IABP could be inserted before or after percutaneous coronary intervention (PCI) and the mode of revascularizaton was left to the discretion of the operator. The primary endpoint was 30-day, all-cause mortality.

The baseline characteristics were similar between groups. The median age was 70 years; two-thirds were male and one-third were diabetic. The median systolic BP was 89 mmHg at study entry. There was no difference between groups in the primary endpoint of death at 30 days (39.7% in the IABP group vs 41.3% in the control group; $P = 0.69$). The authors performed intention-to-treat and per-protocol analyses of the primary outcome, as well as a multivariable analysis, and there were no differences between groups by any of these methods. There was no difference in mortality when the IABP was placed before or after PCI. Subgroup analysis revealed no difference in mortality between the IABP group and the control group when stratified by gender, diabetic status, STEMI vs non-STEMI, anterior MI vs non-anterior MI, BP above or below 80 mmHg, or first vs subsequent MI. When stratified by age, those younger than 50 years appeared to have a mortality benefit with IABP (19.4% in IABP group vs 44.1% in control group), but there was no difference in the 50-75 years group or the > 75 years group and the *P*-value for interaction with age did not reach statistical significance.

There were no differences in the rates of in-hospital stroke, recurrent MI, stent thrombosis, bleeding, sepsis, or peripheral arterial complications requiring intervention. There were no differences in the secondary endpoints of serum creatinine, C-reactive protein, and lactate levels. The authors conclude that the use of IABP did not significantly reduce 30-day mortality in patients with cardiogenic shock, complicating acute MI in those who undergo early revascularization.

■ COMMENTARY

This is a resoundingly negative study. Not only was the primary endpoint of all-cause mortality negative, the secondary endpoints were also all negative. Importantly, there were no differences whether the patient was experiencing a STEMI or non-STEMI. There was some suggestion that young patients may benefit from IABP, but this did not reach statistical significance. This study calls into question the routine use of IABP in patients with cardiogenic shock complicating MI. Should we abandon IABP completely in this setting? Or are there some patients who may still benefit from IABP in cardiogenic shock complicating MI? I think there are still some patients who may benefit from *selective* use of IABP in this setting. First, there may be benefit for IABP in patients with impaired coronary flow after PCI, as IABP counterpulsation augments coronary perfusion. Second, the use of IABP may allow lower doses of inotropes/pressors. In some patients, such as those with arrhythmias caused by inotropes, there may be a benefit to ceasing the inotropes and IABP may be the only way this is possible. In this paper, we are not told about adequacy of coronary flow after PCI or about arrhythmias.

Some limitations of the study should be acknowledged. First, we are not told of the effect of IABP on other meaningful endpoints, such as heart failure and ejection fraction. If there is improvement in these parameters, there may be an indication for using IABP despite a lack of mortality benefit. Second, subjects were not blinded to which group they were in; however, the clinical events committee was blinded to the treatment group of each subject. Third, we are not told details of PCI, in particular, how many patients underwent culprit-only vs multivessel stenting. This is important as it may affect overall mortality.

This study reaffirms that the mortality associated with cardiogenic shock complicating acute MI remains very high,

despite early revascularization and modern intensive medical therapy. There is a need for better treatment in this group of patients. Perhaps newer percutaneously placed left ventricular assist devices may take over from IABP in the treatment of cardiogenic shock, but this remains to be tested in adequately powered clinical trials. ■

Stroke Risk with Warfarin Interruption

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco

This article originally appeared in the October 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.*

Sources: Raunso J, et al. Increased short-term risk of thromboembolism or death after interruption of warfarin treatment in patients with atrial fibrillation. *Eur Heart J* 2012;33:1886-1892. Hohnloser S, et al. The hazards of interrupting anticoagulation therapy in atrial fibrillation. *Eur Heart J* 2012; 33:1864-1866.

The risk of interrupting prophylactic warfarin for stroke prevention in atrial fibrillation (AF) patients is unclear. Thus, these investigators from Denmark evaluated their national health registry and found 102,591 patients > age 30 with a first-time hospitalization for AF between 1997 and 2008. Valvular AF patients were excluded. Follow-up was started 7 days after hospitalization to ensure achievement of steady-state warfarin dosing. Warfarin therapy was subsequently determined by their national pharmacy database and warfarin usage was estimated based on the supply of medications dispensed. The primary outcome was the combined endpoint of all-cause mortality or hospitalization for thromboembolism. The mean follow-up was 3.5 years. During warfarin therapy, the primary endpoint occurred in 6.9/100 patient-years. At least one treatment interruption occurred in 72% of the patients and these patients had lower CHADS2 scores compared to the no interruption group (1.34 vs 1.56, $P < 0.001$). The median duration of interrupted therapy was 36 days. Among the 16,738 primary events, 49% occurred during the treatment interruption, for a rate of 14.2/100 patient-years. More events occurred during the first 90 days of interruption (31.6/100 patient-years) and leveled off after 180 days. The hazard ratio for treatment interruption was 2.9 (95% CI 2.8-3.0). Also, the hazard ratio was similar if death was excluded as an endpoint. The authors concluded that interruption of warfarin therapy in non-valvular AF patients increased the short-term risk of death or thromboembolism, especially during the first 90 days of treatment interruption.

■ COMMENTARY

Because of their national health systems, many European countries have very large patient databases that dwarf those at some of our single hospital systems or even multicenter trial databases. Although limited by their retrospective observational nature and the unique structure of national databases, their sheer size makes these analyses important. This study from Denmark has two interesting findings. First, the incidence of warfarin therapy interruption in AF patients is high, about three-quarters of patients, and the median length is relatively long, 36 days. Randomized AF therapy trials have noted interruptions at a frequency of 15-30%. Clearly, real-world experience is very different from trials. Second, the risk of thromboembolism or death rises three-fold in the first 90 days of interrupted therapy, then tapers off. Thus, real world patients on warfarin stroke prophylaxis for AF are often at considerable risk because of therapy interruptions.

Interestingly, there were no subgroup differences in the incidence of the primary event whether stratified by age, sex, duration of therapy, or CHADS2 score. Also, excluding death as an endpoint did not appreciably alter the results, suggesting that the important events were thromboembolism. This raises the question of the etiology of the increase in events. One possibility is that warfarin is preventing strokes and after its withdrawal the stroke rate returns to its natural state (the so-called catch-up phenomenon). Another is that there is a warfarin withdrawal phenomenon that actually increases the rate of thromboembolism over what it would naturally be. Although there are some experimental data showing that coagulation factors transiently rise above normal levels after warfarin withdrawal, there are no clinical mechanistic data to support this theory. Finally, it is possible that whatever occasioned the interruption in therapy was the cause of the event, such as surgery (confounder). Unfortunately, this study is not able to sort out these potential mechanisms.

Other studies have shown that warfarin can be interrupted for clinical reasons such as surgery or due to patient decisions unrelated to their health conditions. This study does not specify the reasons and we have no clinical data such as INR values. Also, we do not know if the interruptions were transient or the patients stopped therapy. Although the median duration of interruption was 36 days, the 75th percentile was 207 days. Specific guidelines exist for medical issues such as high INR values, episodes of major bleeding, and surgery, which should minimize the risks of thromboembolism, so one could conclude that the majority of the interruptions that lead to events were in the patient decision category. If so, it behooves us to empha-

size the importance of continuous therapy to our patients. Perhaps the use of the newer oral anticoagulants, which do not require INR-based management, will improve patient compliance. ■

Tele-ICU: Is It Worth It?

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, MSc
St. Luke's Idaho Pulmonary Associates, Boise

Dr. Akhtar reports no financial relationships relevant to this field of study.
This article originally appeared in the October 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: *Based on their review of prior published studies of telemedicine ICUs and the initiation of a telemedicine ICU in a Veterans Health Administration hospital system, the authors find that costs of implementation are substantial and the sum impact on hospital expenses and profits remains unclear.*

Source: Kumar G, et al. The costs of critical care telemedicine programs: A systematic review and analysis. *Chest* 2012; Jul 10. [Epub ahead of print.]

Kumar et al set out to describe the cost of ICU telemedicine programs (tele-ICU). They had two objectives: to systematically review the existing literature reporting costs of tele-ICU programs and to provide cost figures for tele-ICU implementation in a Veterans Health Administration (VHA) hospital network.

The literature review spanned about 11 years (Jan. 1, 1990 to July 1, 2011); 5 years (2006-2010) of research abstracts from relevant national organizations were included. The authors defined tele-ICU as "any form of technology that used telemedicine to facilitate communication between remotely located intensivists and distant providers or patients in an ICU." Included studies had to involve tele-ICU implementation and present relevant cost data. The studies were graded on quality using published criteria. At least two authors independently abstracted data using a predefined data extraction tool. The authors had access to detailed cost data for tele-ICU implementation in a seven-hospital VHA network (8 ICUs and 74 ICU beds); they applied validated depreciation methods to projected costs for the first year of operation (the system did not become active until August 2011). In order to compare the VHA data to the figures reported in the literature, costs were classified as tele-ICU program costs (technology, staffing, and real estate; presented as costs per ICU bed) or hospital variable costs (resources used in patient care).

Of 852 studies, eight (comprising 29 ICUs) met inclusion criteria; they were of lower methodological quality and varied considerably in type of technologies, setting, duration of monitoring per 24 hours, and costs entailed and reported. Overall estimated cost for a tele-ICU program for 1 year (implementation, site operation, and staffing) ranged from $50,000-$100,000 per ICU bed. Only six studies addressed hospital variable costs and sum impact on hospital expenses; those with authors having ties to the tele-ICU vendor reported cost savings (up to $3000 per patient) and profits (up to $4000 per patient). The remainder found no savings and possible increased costs. VHA network data revealed overall 1-year costs of $70,000-$87,000 per ICU bed; the authors note that due to prior existence of an electronic health record and other integrated structures at the VHA, costs of implementation may be lower than they would be in other hospital networks.

■ COMMENTARY

Telemedicine (defined by the American Telemedicine Association as "use of medical information exchanged from one site to another via electronic communications to improve patients' health status") has been in existence in some form for several decades. These technologies are funded by health care systems themselves, rather than by third-party payors. Tele-ICU appears to be an attractive approach to improving access to (and potentially quality of) care in this era of shortage of specialists and rising population of older and sicker patients. There also seems to be potential for cost savings by increasing efficiency and quality of care, reducing adverse outcomes and length of stays, and even decreasing overall staffing costs. Robust data supporting these hypotheses, though, are lacking.

Kumar et al's work is a valuable first step in trying to better understand the cost-effectiveness of tele-ICU. Their report is limited by the quality and variability of previously published data (particularly the lack of detailed financial data for implementation or ultimate outcomes) and the fact that the VHA data presented are primarily projected, not actual, costs. However, the costs of implementation that these authors report are the most accurate and detailed numbers published to date and they provide a good framework for further study. In order to understand the true potential benefits of tele-ICU, we need additional detailed reports of costs of initiation and ongoing operation of tele-ICU in parallel with clinical outcomes data and their sum impact on health care expenses. It will also be important to try to elucidate the effect on patient, family, and staff experiences. Should every hospital set up a tele-ICU? Is tele-ICU cost effective only for health care systems of certain size or volume? Are benefits of tele-ICU significant for those facilities that already have on-site intensivists? Will ICU care be out-sourced and thus impact health care provider employ-

ment or reimbursement? Could tele-ICU depersonalize patient and family experiences?

Interest in tele-ICUs has grown rapidly and more and more U.S. health care systems (per Kumar et al, at least 40 thus far) are implementing them. As the authors note, the long-term viability of these systems remains unclear; this considerable initial enthusiasm is unlikely to last unless a positive clinical and financial impact is demonstrated. Is tele-ICU worth it? Stay tuned for the answer. ■

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 historical cohort study of patients who were hospitalized and received ceftriaxone, published by Doernberg and colleagues, those who received doxycycline instead of azithromycin or a fluoroquinolone had:**

a. A higher rate of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

b. A longer hospital length of stay.

c. A lower risk of developing *Clostridium difficile* infection.

d. Lower mortality.

2. **The randomized controlled trial by Thiele, et al., of an intra-aortic balloon pump (IABP) in patients with an acute myocardial infarction and cardiogenic shock expected to undergo revascularization demonstrated which of the following outcomes?**

a. The use of an IABP did not reduce 30-day mortality.

b. The use of an IABP increased the risk of in-hospital stroke.

c. The use of an IABP increased the risk of acute kidney injury.

d. All of the above.

3. **In the randomized controlled trial of dual-antiplatelet therapy versus aspirin alone in patients with a lacunar stroke, the addition of clopidogrel to aspirin was associated with all of the following outcomes except:**

a. An increased risk of serious bleeding

b. An increased risk of mortality

c. A significantly decreased risk of recurrent ischemic stroke

d. No significant effect on the risk of recurrent ischemic stroke

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.*

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

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.

5. Once the evaluation is received, a credit letter will be sent to you. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

VOLUME 17, NUMBER 11 PAGES 21-22 NOVEMBER 2012

Secondary Prevention of Lacunar Stroke

Source: SPS3 Investigators. *N Engl J Med* 2012;367:817-825.

LACUNAR STROKES (L-CVA) ARE SMALL subcortical brain infarctions that may comprise as many as 25% of ischemic strokes. Aspirin (ASA) monotherapy is already established as appropriate treatment for secondary prevention of ischemic stroke, as is clopidogrel (CLOP) monotherapy. In the CAPRIE trial, CLOP provided a *marginal* advantage over ASA for major adverse cardiovascular events (absolute risk reduction = 0.5%) in the overall study population, leading some to advocate clopidogrel routinely over ASA. It is often underrecognized that in the CAPRIE trial, study subjects who enrolled specifically because of previous stroke did *not* experience any statistically significant stroke reduction with CLOP compared to ASA; the outcomes were the same.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial is the first published trial to compare the efficacy of ASA monotherapy vs ASA + CLOP in reference to L-CVA. The study population included more than 30% Hispanics, concordant with the observation that L-CVA is more common in Hispanics.

At the conclusion of the trial (3.4 years mean), ASA + CLOP was *not* more effective than ASA alone in preventing L-CVA. Among the study population (n = 3020 adults with prior L-CVA), most new strokes were L-CVA (71%).

Unfortunately, as has been seen in other studies of combined ASA + CLOP, bleeding risk was significantly increased compared to ASA alone, as was all-cause mortality. Two prior trials in vasculopathic populations (MATCH, CHARISMA) have arrived at similar conclusions: For persons with stable non-acute vascular disease, ASA + CLOP is not more beneficial than ASA alone, but incurs greater bleeding risk. ■

Quality-of-life Effects of PSA Screening

Source: Heijnsdijk EA, et al. *N Engl J Med* 2012;367:595-605.

THE EUROPEAN RANDOMIZED STUDY OF Screening for Prostate Cancer (ERSPC) is a clinical trial in which adult men (n = 162,243) were randomized to prostate-specific antigen (PSA) screening or no screening. While this trial did find a statistically significant reduction in prostate cancer deaths, overall mortality was not affected, supporting the current recommendations by the United States Preventive Services Task Force (USPSTF) that PSA screening be abandoned. Although the USPSTF decision was based on the "hard" data about mortality, there is likely also substantial quality-of-life (QOL) burden engendered from PSA screening, since many — indeed, the vast majority of — men diagnosed with prostate cancer through PSA screening will die with, not from, their prostate cancer. Additionally, adverse effects of intervention for (the mostly) early prostate cancer detected through screening are not uncommon, and include erectile dysfunction and incontinence. Finally, even in men who elect not to have a surgical intervention in response to prostate cancer detected as a result of PSA screening, it would take little imagination to envision substantial ongoing concerns/anxieties referable to that diagnosis.

Heijnsdijk et al report that per 1000 men screened by PSA, nine fewer prostate-cancer related deaths would occur and 73 life-years would be gained. After adjustment for overdiagnosis and overtreatment of prostate cancer subsequent to PSA screening, these benefits were reduced by almost one-fourth. In an era when PSA screening is no longer supported because of an insufficiently favorable risk:benefit ratio, recognition of the negative QOL impact of PSA screening may help clinicians (and their patients) better come to terms with the now well-recognized limitations of PSA screening. ■

PSA Elevations After Prostate Cancer Radiotherapy

Source: Crook JM, et al. *N Engl J Med* 2012;367:895-903.

SINCE PROSTATE CANCER (PCA) IS OFTEN ANdrogen-dependent, PCA recurrences after radiotherapy are often treated with androgen deprivation by means of regimens consisting of continuous luteinizing hormone-releasing hormone agonists (LHRHa) combined with antiandrogens. Unfortunately, such treatment is associated with hot flashes, decreased libido, urinary symptoms, and fatigue. Might intermittent androgen deprivation be equally effective, but less problematic as far as adverse effects?

Crook et al randomized patients who had undergone radiation treatment for PCA but had a post-treatment PSA > 3.0 ng/dL to continuous or intermittent androgen deprivation.

For overall mortality, intermittent androgen deprivation was non-inferior to continuous treatment. The time to development of castration-resistant disease (the stage at which androgen deprivation no longer represses disease progression) was significantly longer for intermittent treatment. Similarly, the adverse effects of hot flashes, libido, and urinary symptoms were all significantly fewer in the intermittent treatment group. In addition to necessitating a substantially reduced amount of medication (and of course, expense), intermittent androgen deprivation regimens are non-inferior for overall mortality, and are associated with superior quality of life. ■

Attenuated CV Benefits of Clopidogrel in Diabetes

Source: Andersson C, et al. *JAMA* 2012; 308:882-889.

There is no controversy over whether antiplatelet therapy (e.g., aspirin, clopidogrel, prasugrel) reduces cardiovascular (CV) events when used for secondary prevention (i.e., post-acute coronary syndrome, post-myocardial infarction [MI], post-stroke). It is equally apparent that risk reduction through antiplatelet therapy is not equal among all risk groups. For instance, although aspirin (ASA) consistently shows CV risk reduction in mixed populations post-MI, two clinical trials of ASA comprised solely of diabetics failed to show benefit. Diabetics are known to have greater platelet reactivity, and their platelets are relatively resistant to antiplatelet effects as measured by medication-induced platelet aggregation inhibition testing.

Comparative benefits of clopidogrel in diabetics vs non-diabetics have not been described well enough. To assess whether diabetics fare as well with clopidogrel post-MI as non-diabetics, Andersson et al reviewed data from the Danish nationwide administrative registries of patients discharged from the hospital post-MI (n = 58,851), of which 12% had diabetes.

One-year follow-up compared outcomes among all persons treated with clopidogrel. Although all groups did have CV risk reduction from clopidogrel treatment, there was a significant difference between diabetics and non-diabetics, favoring non-diabetics. For instance, the hazard ratio (HR) for all-cause mortality was more than twice as favorable for non-diabetics (HR = 0.75, a 25% reduction) than diabetics (HR = 0.89, an 11% reduction).

The obstacle of clopidogrel-resistant platelets can be overcome by dose intensification (i.e., more clopidogrel), combination therapy (i.e., clopidogrel + ASA), or consideration of another P2y12 agent (i.e., prasugrel). Unfortunately, however, each of these methods has been associated with an increased risk for bleeding. Optimization of antiplatelet therapy in diabetics remains somewhat elusive. ■

Is A1c Always the Best Game in Town to Monitor Type 2 Diabetes?

Source: Wright LAC, Hirsch IB. *Diabetes Spectrum* 2012;25:141-148.

Even as time-honored a metric as A1c has limitations. There are, for instance, situations in which A1c can markedly mis-estimate actual sustained glucose concentrations. Since A1c measurement requires hemoglobin to be exposed to excess glucose for the entire life of a red cell (90-120 days), anything that shortens red cell life (e.g., thalassemia, Hgb C, HbS, hemolysis) will *underestimate* actual sustained glucose levels (since red cells don't live long enough to become fully glycosylated). Hemoglobin F, which is persistent in a small percentage of adults, glycosylates so rapidly that even very modest elevations of glucose can induce marked elevations of A1c (A1c 12%-17% or greater), grossly *overestimating* sustained glucose levels.

Fructosamine is a composite measure of relatively short-lived serum proteins that have become converted into irreversible ketoamines, of which glycated albumin is the primary component (approximately 90%). Since this process occurs over a few weeks, red cell life span — shortened or not — has no impact. Similarly, however, the measurement of fructosamine only provides an observation window of the sustained glucose levels in the preceding 2-3 weeks. Any condition that alters serum protein turnover (eg, thyroid dysfunction, hypopoproteinemia, nephrotic syndrome) can invalidate fructosamine measurement.

Glycated albumin, the primary protein constituent of fructosamine, has been compared with A1c and fructosamine in patients with advanced chronic kidney disease, and found to be the most accurate marker in this population, although it is subject to the same perturbations as fructosamine mentioned above.

One other serum marker not used commonly in the United States, but widely used in Japan, is 1,5 anhydroglucitol (1,5-AG), which reflects sustained glucose over a 2-14 day period. Normally, 1,5-AG is reabsorbed by renal tubules; when plasma and urine glucose are high, they compete with 1,5-AG for reabsorption, resulting in loss of 1,5-AG in the urine, with a corresponding diminution in plasma 1,5-AG. This metric has been found to be particularly useful in measurement of postprandial glucose excesses.

For the time being, A1c will remain the metric of choice for most patients. When A1c and individual glucose measurements are discordant, consideration of another metric is appropriate. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.
This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.

AHC Media