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

Risk of Cardiac Events After Surgery

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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

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

This article originally appeared in the October 2011 issue of Clinical Cardiology Alert. *It was peer reviewed by Ethan Weiss, MD. Dr. Weiss is Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Weiss is a scientific advisory board member for Bionovo.*

Sources: Gupta PK, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. *Circulation* 2011;124:381-387. Grover FL, Edwards FH. Objective assessment of cardiac risk for non-cardiac surgical patients: An up-to-date simplified approach. *Circulation* 2011;124:376-377.

Perioperative cardiac events are the leading cause of surgical mortality. Thus, there has been considerable interest in predicting which patients are at highest risk. However, current risk prediction schemes have significant limitations. Thus, Gupta and colleagues analyzed the American College of Surgery National Surgery Quality Improvement Program database to determine factors associated with perioperative myocardial infarction (MI) or cardiac arrest, and to develop a risk calculator. Data from 2007 through 2008 were collected from about 200 hospitals in the United States. The 2007 data on more than 200,000 surgeries were used as the derivation set and the 2008 data (also > 200,000 surgeries) were used for validation. Only trauma patients, transplant patients, and those patients younger than 16 years old were excluded. The database included patients with aortic (2.1% of population), cardiac (0.3%), and peripheral arterial surgery (8.3%). Perioperative MI or cardiac arrest was seen in 0.65% of the validation group.

Volume 6 • Number 9 • November 2011 • 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 Von Wedel have no relevant financial relationship related to the material presented in this issue.

Multivariate logistic regression analysis identified five significant predictors of MI or cardiac arrest: type of surgery, functional status, elevated creatinine, American Society of Anesthesiology class, and older age. In the validation set, a risk calculator based on these five factors had an area under the receiver operating curve (AUC) of 0.87, compared to the Revised Cardiac Risk Index (RCRI) of 0.75. In those patients undergoing aortic or noncardiac vascular surgery, the AUC was 0.75 vs the RCRI value of 0.59. The authors concluded that their cardiac risk calculator surpasses the performance of the RCRI and should simplify the informed consent process.

■ COMMENTARY

This paper has elevated the bar on cardiac event risk prediction in patients undergoing surgery of all types, but especially non-cardiovascular surgery. Notably, it uses a computer-based direct logarithmic regression model to determine the risk of MI or cardiac arrest like the STS or Euro-score do for cardiac surgery, rather than a point score system like the RCRI and most older schema (i.e., Goldman, Detzky). You can access the calculator at www.surgicalriskcalculator.com/miorcardiacarrest. The data entry is very simple and involves only five variables. 1. the American Society of Anesthesiology class (1-5): normal healthy patient (1), mild systemic disease, severe systemic disease, severe plus life threatening and moribund (5). 2. functional class as independent or partially or fully dependent (0 or 1); 3. creatinine > 1.5 (0, 1); 4. type of surgery classified as high risk (aortic, brain, hepatobiliary) or moderate (all others); and 5. age as a continuous variable.

One strength of this new schema is that it was derived from > 200,000 patients as compared to > 4000 for the RCRI and it performed better. Also, it includes newer laparoscopic surgeries and it is organ based. In addition, it has better discriminatory power, especially for vascular surgery, as compared to the RCRI.

There are limitations to the surgical risk calculator. The major ones for cardiology consultations are the lack of inclusion of information on stress test results, echocardiogram results, history or evidence of arrhythmias, beta-blocker use, and prior revascularization. These data may significantly alter risk, especially in the patient with known or suspected coronary artery disease. The definition of MI, especially in cardiac surgery patients, is problematic. In this study, they chose three times the upper limit of a normal troponin to exclude demand induced events. This is reasonable, but may be a strength or a weakness depending on your point of view.

I believe this is a significant step forward in this area and believe this new schema should replace the RCRI, especially for most patients undergoing non-cardiovascular surgery. It could be a starting point for evaluating patients undergoing cardiovascular surgery or those with known vascular disease, but other information will need to be considered in these patients before making a final decision on the risk of surgery. Unfortunately this study did not shed any light on the use of preoperative beta-blockers or stress tests, which remain controversial. The editorial by Grover and Edwards emphasizes that risk calculators are only one part of clinical decision making and are definitely not the whole enchilada. They believe this type of objective data will help with patient and family discussions, and consultations with other providers. In conclusion, we now have a better risk predictor tool, but the cardiology consultation has not been replaced by a computer yet. ■

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.

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.

New Oral Anticoagulant for Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD
Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

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

This article originally appeared in the October 2011 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: Granger CB, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-992.

This report is from the ARISTOTLE trial, which was just reported at the recent European Society of Cardiology meeting in Paris. Apixaban is a new direct oral factor Xa inhibitor with a favorable pharmacokinetic profile. This study compared apixaban to adjusted-dose warfarin in patients with nonvalvular atrial fibrillation. The trial had a double-blind, double-dummy trial design. Patients were randomly assigned to treatment with either apixaban or adjusted-dose warfarin. The primary objective was to compare apixaban to warfarin for reducing the risk of ischemic or hemorrhagic stroke or systemic embolism in atrial fibrillation patients. The primary safety outcome was major bleeding.

Patients were eligible for enrollment if they had documented atrial fibrillation and one or more risk factors for stroke. Patients with mitral valve disease, prosthetic heart valves, recent strokes, any need for continuous high-dose antiplatelet therapy, and moderate to severe renal insufficiency were excluded. Patients with a prior history of warfarin therapy were eligible but randomization was stratified according to prior warfarin usage. Apixaban, or matching placebo, was administered with the standard dose being 5 mg twice daily. A lower dose of 2.5 mg twice daily was used in a subset of patients if they had two or more of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or a serum creatinine greater than 1.5 mg/dL. Warfarin was administered and the dose adjusted to achieve a target INR of 2.0 to 3.0. INRs were monitored with the use of a blinded and encrypted point-of-care INR device. An algorithm was provided to guide the adjustment of warfarin or matching placebo dose.

The primary efficacy endpoints were stroke and systemic embolism. Death from any cause and myocardial infarction were key secondary efficacy endpoints. The primary safety endpoint was the occurrence of major bleeding defined as clinically overt bleeding accompanied by a decrease in hemoglobin level of at least 2 g/dL, a requirement for a two-unit packed cell transfusion, or bleeding in a critical site or resulting in death. Efficacy and safety outcomes were adjudicated on the basis of prespecified criteria by a blinded clinical events committee.

Over a 40-month period, 18,201 patients were recruited at 1034 international sites. The groups were well balanced with regard to baseline characteristics with a median age of 70 years, a 65%:35% male:female gender ratio, and a means CHADS2 score of 2.1. Notably, 30% of the patients in both groups had CHADS2 scores ≥ 3. Vitamin K antagonists had previously been used in 57% of the patients and 19% had a history of a prior stroke, TIA, or systemic embolism.

The reduced dose of apixaban (2.5 mg twice daily) or placebo was administered to 428 patients in the apixaban group and 403 patients in the placebo group. Study drug discontinuation was observed in 25.3% of the patients on apixaban vs 27.5% in patients on placebo. Patients on warfarin had an INR in the therapeutic range, a median of 66% of the time.

Stroke or systemic embolism occurred in 212 patients in the apixaban group for an annual rate of 1.27%. In comparison, stroke or systemic embolism occurred in 265 patients in the warfarin group yielding a rate of 1.6% per year. The hazard ratio for the apixaban group was 0.79 with a 95% confidence interval of 0.66 to 0.95. The P value for noninferiority was less than 0.001 and equal to 0.01 for superiority. Hemorrhagic stroke was 49% lower in the apixaban group than in the warfarin group and ischemic or unclassifiable stroke was 8% lower in the apixaban group. The rate of fatal or disabling stroke was 0.5% per year in the apixaban group compared to 0.71% per year in the warfarin group. Among the patients who had ischemic strokes, hemorrhagic transformation was noted in 12 patients on apixaban and 20 patients on warfarin. Fatal strokes were noted in 42 patients in the apixaban group and 67 patients in the warfarin group. All-cause mortality was lower in the apixaban group (3.52% per year) than in the warfarin group (3.94% per year). There was no significant difference in the rate of myocardial infarction between the two groups (0.53% and 0.61%).

Major bleeding occurred at an annual rate of 2.13% in the apixaban group compared to 3.09% in the warfarin group. The rate of intracranial hemorrhage was reduced to 0.33% per year in the apixaban group compared to 0.80% per year in the warfarin group (hazard ratio 0.42; 95% confidence interval, 0.30 to 0.58; $P < 0.0001$). The rate for any bleeding was 25.8% per year in the warfarin group compared to only 18.1% in the apixaban group. Fatal bleeding occurred in 34 patients in the apixaban group compared to 55 patients in the warfarin group.

Subgroup analysis showed consistent beneficial effects of apixaban across all major subgroups. Overall, reported adverse events were equally distributed between the two groups. There were no differences in the frequency of abnormalities in liver function tests or liver related serious adverse events between the two groups.

The authors conclude that in patients with nonvalvular atrial fibrillation, apixaban is superior to warfarin for the prevention of stroke or systemic embolism with less risk for bleeding and a lower overall mortality.

■ COMMENTARY

This is the third large clinical trial showing that a new oral anticoagulant is noninferior or superior to warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. Dabigatran, a direct thrombin inhibitor, was assessed in the RE-LY trial and the result of that trial led to dabigatran's FDA approval last year. Earlier this summer, the ROCKET AF trial compared rivaroxaban, a

factor Xa inhibitor, to warfarin in a similar group of patients. The ARISTOTLE trial reported here again shows that a factor Xa inhibitor compares favorable to warfarin for this indication. I suspect that both rivaroxaban and apixaban will join dabigatran as being approved for this indication within the next year. Several similar agents are also in the clinical development pipeline.

These trials have been enormous, each enrolling more than 18,000 patients. It's unlikely there will be more than one or two such trials for each agent. There are no head-to-head comparisons available or, to my knowledge, planned directly comparing the new agents. Conclusions or claims based on comparisons across different trials are likely to be uncertain. I think we can say that the new agents at the tested doses are at least as effective and safe as adjusted-dose warfarin and certainly they will be easier to prescribe. If the increased cost of the new agents were not a factor, I would likely pick one and use it for initial therapy in most patients with nonvalvular atrial fibrillation. Right now, I don't see evidence that any of the new agents will be clearly superior, but we should watch closely for any later arising problems that may be seen during general usage. ■

Patient Outcomes After Failed Extubation

ABSTRACT & COMMENTARY

By David J. Pierson, MD

Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle

This article originally appeared in the October 2011 issue of Critical Care Alert. *It was peer reviewed by William Thompson, MD. 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: *Failed extubation is more likely to occur in elderly patients with underlying chronic cardiac or pulmonary disease, and patients in whom it occurs have substantially worse clinical outcomes than those who do not require reintubation.*

Source: Thille AW, et al. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med* 2011;Jul 14. [Epub ahead of print]

In this prospective study carried out in a 13-bed French medical ICU, Thille and associates sought to determine the clinical characteristics and outcomes of patients who experienced extubation failure — the requirement for reintubation within 72 hours of either planned or unplanned extubation. Ventilated patients were evaluated daily according to an established protocol, and all patients in the unit were included unless they underwent tracheotomy or had previously been reintubated. In keeping with accepted evidence-based standards, patients were considered for weaning and extubation when their overall medical condition had improved, their vital signs were stable, their gas exchange and support requirements were acceptable, they did not require excessive airway suctioning, and they were capable of initiating respiratory efforts. They then underwent a spontaneous breathing trial, which if successful was followed by extubation. Also included in the study were all patients who extubated themselves, or whose endotracheal tubes became dislodged during routine care. Criteria for reintubation were standardized, and noninvasive ventilation was not routinely used following extubation.

During the 1-year observational period, 340 adult patients were managed with invasive mechanical ventilation. Their mean age was 59 years and 66% were men. Median total durations of mechanical ventilation and ICU stay were 5 and 9 days, respectively; 60% of the patients survived to the weaning period and ICU mortality was 49%. After exclusion of patients who died on the ventilator and those undergoing tracheotomy, planned and unplanned extubations occurred in 168 and 31 patients, respectively. Extubation failure (requirement for reintubation because of respiratory failure, coma, or shock within 72 hours) occurred in 26 (15%) of the planned and in 20 of the unplanned extubations (48% of self-extubations and 100% of accidental extubations). When planned extubation failed, pneumonia occurred commonly (7/26, 27%) and subsequent mortality was high (13/26, 50%).

Patients who met weaning criteria, had successful spontaneous breathing trials, and were electively extubated, but who subsequently failed and had to be reintubated, had the same duration of ventilatory support prior to weaning, diagnoses, and illness severely as their counterparts who did not require reintubation. However, they were older (65 ± 16 vs. 56 ± 17 yr, $P < 0.01$) and were more likely to have underlying chronic cardiac or respiratory disease (65% vs. 39%, $P = 0.02$). Extubation failure occurred in 34% of all patients > 65 years old with chronic cardiac or respiratory disease, compared with only 9% of other patients ($P < 0.01$). Failure of both planned and unplanned extubation was associated with rapid worsening of daily organ dysfunction scores. Mortality was 10 times higher in patients with failed extubation than in those with successful planned extubation.

■ COMMENTARY

In keeping with findings from numerous other studies, the extubation failure rate in this series after patients fulfilled accepted weaning and extubation criteria was 15%. However, the important contributions of the current study are that: 1) the patients who failed planned extubation were not detectably different from those who did not require intubation with respect to illness severity, initial diagnoses, or duration of ventilatory support at the time of the attempt; 2) despite this lack of differences in the evidence-based assessments used

to determine when extubation is appropriate, patients older than age 65 and those with underlying cardiac or respiratory disease were much more likely to fail; and, 3) once they failed, they did very poorly.

Although it is disheartening that the Simplified Acute Physiology II and Sequential Organ Function Assessment scores did not discriminate between successful and unsuccessful extubations, and that using accepted prediction and management practices on patients who were going to fail extubation could not be identified in advance, I find the results useful in at least one important respect. If the results of this study hold up with further investigations and clinical experience, we should consider extubation failure an important event in terms of prognosis when interacting with patients and families — especially when the patient is older than 65 with cardiac and/or respiratory comorbidities. It is encouraging to clinicians and family members alike when a patient passes a spontaneous breathing trial and is initially weaned from ventilatory support after an episode of critical illness. However, when this progress is reversed over the next few days and invasive mechanical ventilation must be resumed, it illustrates the imprecision of our ability to predict how the patient will do, and suggests that the outlook may not be as favorable as we hoped. ■

Candida Chorioretinitis and Endophthalmitis

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center

Dr. Deresinski does research for the National Institutes of Health, and is an advisory board member and consultant for Merck.

This article originally appeared in the October 2011 issue of Infectious Disease Alert. *At that time it was peer reviewed by Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Jenkins reports no financial relationship to this field of study.*

Synopsis: *While 16% of patients with candidemia had possible or probable ocular involvement, only 6 of 370 (1.6%) developed endophthalmitis.*

Sources: Oude Lashof AM, et al. Ocular manifestations of candidemia. *Clin Infect Dis* 2011;53:262-268.

Oude Lashof and colleagues examined the incidence and outcomes of patients with ocular involvement in a randomized, clinical trial comparing treatment of non-neutropenic patients with candidemia with either voriconazole or amphotericin B followed by fluconazole.[1] In that study, no significant differences in overall outcome between treatment arms were detected in the 370 patients who constituted the modified intent-to-treat population and who are the subjects of this substudy. All patients underwent dilated retinal examination at baseline, 7 days, 2 weeks, and 6 weeks after the end of treatment.

Abnormalities thought to be consistent with ocular candidiasis were detected in 60 patients (16%). The ocular lesions were detected at baseline in 49 of the 60 patients (81.7%), while the remaining abnormalities were first seen at follow-up examinations. Twenty had possible, and 40 had probable ocular candidiasis. Among those with probable disease, only 6 had endophthalmitis, with vitritis or "fluffy" lesions extending into the vitreous. One of these patients, with negative retinoscopy at days 1 and 8, and whose central venous catheter was not removed until day 10 of therapy, was first detected after 18 days of treatment. The remaining 36 with probable ocular candidiasis had chorioretinitis defined as deep focal white infiltrates in the retina or hemorrhages, Roth spots, or cotton wool spots with absence of other explanation, such as diabetes mellitus or hypertension, present. If these chorioretinal findings were seen in patients with diabetes, hypertension, or bacteremia, as was true in 20 patients (33.3%), they were classified as possible ocular candidiasis. Designation as proven ocular candidiasis required vitreous sampling, which was not performed in any patient.

Ocular involvement was associated with a somewhat more prolonged duration of candidemia. The median interval from the day of randomization to a first negative blood culture was 4 days (range, 1-18 days) in those with and 3 days (range, 1-26 days) in those without ocular involvement, a difference that was statistically significant ($P = 0.026$). When compared to infection with other species, patients with bloodstream infection with *Candida albicans* were more likely to have ocular involvement, while those infected with *Candida parapsilosis* were less likely to develop this complication.

Of the 6 patients with endophthalmitis, 2 died before repeat retinal examination was performed, 3 had resolution, and 1 (the patient in whom extension of the infection into the vitreous was detected at day 18 of therapy after failure to remove his central venous catheter until day 10) was classified as a therapeutic failure when treatment was discontinued for unknown reasons.

Treatment of probable *Candida* chorioretinitis was successful in 24 of 34 patients (71%), unevaluable in 9, and classified as a failure in 1 patient whose candidemia relapsed with a new retinal lesion after apparently successful initial therapy. No patient with chorioretinitis progressed to endophthalmitis during systemic treatment.

None of the patients received intra-vitreous therapy, so all responses were presumably the result of systemic therapy with the study drugs, whose administration was not apparently prolonged in response to the detection of ocular lesions. The antifungals were administered for a median of 14 days

after the first negative blood culture in both those with and without eye involvement.

■ **COMMENTARY**

The phrase "*Candida* endophthalmitis" often is inappropriately used to describe all forms of endogenous infection of the eye with this fungus. This study illustrates the importance of maintaining the distinction between infection restricted to chorioretinal layers and involvement of the vitreous, for which the term endophthalmitis in this context should be reserved.

The frequency of detection of ocular lesions in patients with candidemia has been reported to be 0%-78%,[2] an absurdly broad range. Nonspecific retinal lesions, such as cotton wool spots and superficial retinal hemorrhages, have been reported to be present in 11%-20% in most recent studies. The picture is further clouded by the fact that such lesions have been reported in 12%-26% of patients with bacteremia in the absence of candidemia. In these reports, however, many patients had confounding illnesses, such as diabetes mellitus.

In this study, as in most others, ocular candidiasis was most often asymptomatic. Thus, at baseline, only 1 patient reported decreased visual acuity, while only the 1 patient in whom endophthalmitis developed during treatment complained of visual loss. This observation is, of course, complicated by the inclusion of critically ill patients in whom visual changes may be underreported.

Ocular lesions were first detected after initial negative examinations in one-fifth of affected patients. Patients whose fungemia persists longer than 3 days after the initiation of therapy may be at increased risk of ocular involvement, as may patients whose infection is caused by *C. albicans*. Infection with *C. parapsilosis* appears to be associated with a lesser risk of eye involvement. The authors recommend that performance of dilated fundoscopy in all patients with candidemia be performed at least 1 week after the initiation of systemic antifungal therapy and that all patients with ocular involvement have follow-up examinations.

It can, however, be asked whether careful and repeated retinal examinations affect outcome. In this study, all patients with chorioretinitis had favorable ocular outcomes. In addition, only 1.6% of patients had endophthalmitis and there was no evidence that its presence necessitated alteration of the planned therapy, with no need for intravitreal therapy or prolongation of systemic administration of antifungals. Similarly, in a study comparing caspofungin to amphotericin B in patients with invasive candidiasis (approximately 80% were candidemic), ocular lesions consistent with *Candida* endophthalmitis (not clearly defined) were detected in 7 of 217 (3.7%) and all resolved after the end of therapy, without added intervention.[3] ■

References

1. Kullberg BJ, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: A randomised non-inferiority trial. *Lancet* 2005;366:1435-1442.
2. Rodríguez-Adrián LJ, et al. Retinal lesions as clues to disseminated bacterial and candidal infections: Frequency, natural history, and etiology. *Medicine (Baltimore)* 2003;82:187-202.
3. Mora-Duarte J, et al; Caspofungin Invasive Candidiasis Study Group. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med* 2002;347:2020-2029.

Secondary Prevention of Postherpetic Neuralgia

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Professor, Department of Introduction to Clinical Medicine, Ross University School of Medicine, Commonwealth of Dominica

Dr. Wilke reports no financial relationship to this field of study.

This article originally appeared in the September 15, 2011, issue of Internal Medicine Alert. *It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Adjunct Clinical Professor, University of North Carolina, Chapel Hill, and Dr. Roberts is Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Brunton serves on the advisory board for Amylin, Boehringer Ingelheim, Novo Nordisk, and Symbiotix; he serves on the speakers bureau of Boehringer Ingelheim, Novo Nordisk, and Teva. Dr. Roberts reports no financial relationship to this field of study.*

Synopsis: *Adding gabapentin to valacyclovir early in the treatment of acute herpes zoster may reduce the incidence of postherpetic neuralgia.*

Source: Lapolla W, et al. Incidence of postherpetic neuralgia after combination treatment with gabapentin and valacyclovir in patients with acute herpes zoster: Open-label study. *Arch Dermatol* 2011;147:901-907.

Postherpetic neuralgia (PHN), pain persisting longer than 3 months after development of a rash, is the most common complication of herpes zoster (HZ). It can be severe, especially in the elderly, with age being the most important factor in predicting its development. The worst cases are very difficult to treat and can sometimes last for months to years. This group of researchers from Texas report on an uncontrolled, open-labeled study performed in a private dermatology clinic that tested the hypothesis that treatment of acute HZ with a combination of gabapentin and valacyclovir would prevent PHN.

Between February 2002 and October 2007, they approached consecutive adults who presented to their office

with acute HZ. Their inclusion criteria included age ≥ 50 years, a clinical diagnosis of uncomplicated HZ presenting within the first 72 hours of vesicles, and an average pain score ≥ 4 on the 10-point Likert scale. Moderate pain was defined as 4-6, and severe pain as 7-10. They had a large number of exclusion criteria including: women who had even the slightest chance of becoming pregnant or were already pregnant or nursing; patients with immune dysfunction or who were receiving immunosuppressive therapy; patients treated with medications directed against the herpesvirus; patients currently receiving gabapentin or a tricyclic antidepressant; patients with liver or renal problems; and patients with ocular involvement of HZ. The investigators recruited 133 subjects, with an average age of 65. Most were white. Two-thirds were female. On presentation, 62% rated the pain ≥ 7. Patients accepted into the study received 1000 mg caplets of valacyclovir, which they took three times a day for 7 days. They were also started on gabapentin 300 mg per day, which was increased weekly to a goal of 3600 mg per day in three divided doses, based on patient tolerance and side effects. At 4 weeks, pain was reassessed. If it was < 4, then gabapentin was stopped. Otherwise, it was continued for another 4 weeks. In either case, discontinuing it was accomplished by tapering it over 1 week. Patients were allowed to continue other pain medication. The subjects had frequent follow-up, at which time pain, sleep disturbance, use of analgesics, and any abnormal sensations were recorded. In addition, quality-of-life questionnaires were collected at each visit.

The endpoint of interest was the presence of pain at 3, 4, and 6 months. Thirty-seven (37) subjects were lost to follow-up; almost half of them reported no pain at their last visit. At 6 months, 9.8% of subjects still reported some pain; 6.8% rated pain > 3. Patients who presented with severe pain were more likely than patients with moderate pain to have pain at the study's end, although this did not achieve statistical significance. There was a trend for patients older than 70 to have persistent pain compared to younger subjects, but again, this was not statistically significant. There was no gender difference. Quality-of-life scores improved for all participants during the course of the study.

■ COMMENTARY

The main weakness of this study is its design. It was neither blinded nor randomized. Secondly, the site of this study was a private dermatology clinic; these patients may differ from those who present to a primary care office.

The reported prevalence of PHN varies wildly, depending on where the study was conducted. For instance, a study in an Icelandic general practice reported a prevalence < 7% in patients older than 60 at 3 months.[1] A meta-analysis of studies that evaluated the efficacy of acyclovir in treating acute HZ estimated a prevalence of 21%.[2] A population-based study from the Mayo Clinic reported 33% in subjects ≥ 79 years of age.[3] The discrepancy probably relates to the methods of patient recruitment to drug trials, the referral of more severely afflicted patients to specialty clinics (as may have occurred in the current study), the rigor of recording data, and how patients are questioned about pain (quantitative vs. qualitative assessment).

The prevention of PHN recalls the phrase, "The best defense is a good offense." Preventing HZ is possible through vaccination.[4] Varicella-zoster vaccine (Zostavax) for the prevention of shingles reduces the incidence of HZ by 51%. Subjects who received the vaccine and went on to develop HZ had a 39% reduction in PHN.[5] Unfortunately, the vaccine has not been widely used for reasons that are both economic and operational; only 2-7% of eligible people have been vaccinated.[6] Merck sells the vaccine to the federal government for about $160, making it the most expensive adult vaccine,[7] but the good news is that Medicare Part D covers it. It needs to be stored in a freezer. In March of this year, the Food and Drug Administration (FDA) lowered the age for the use of Zostavax to 50 years. The vaccine is not 100% effective, and there will always be people who go unvaccinated, so having an effective treatment to prevent PHN would be welcomed.

Currently, valacyclovir and famciclovir are recommended for the treatment of HZ. Twenty years ago, before we had those medications, Whitley and colleagues used acyclovir with prednisone to treat HZ.[8] Although they were able to show quicker healing, earlier resolution of acute pain, and improved quality of life, the resolution of pain at 6 months was not statistically different than placebo. Recommendations for treating PHN include analgesics, gabapentin (starting much later in the disease course than in this study), amitriptyline, carbamazepine, topical lidocaine, topical capsaicin (over-the-counter), and topical triethanolamine salicylate. The FDA recently approved a topical 8% patch formulation of capsaicin (Qutenza) for local treatment of PHN. It is available only by prescription.

Intervention should always balance benefit and harms. Although valacyclovir is FDA-approved for the treatment of HZ and gabapentin for the treatment of PHN, I cannot recommend the early use of both to prevent PHN, based on this study. On the other hand, what harm might befall your patient? Elderly patients are more likely to suffer central nervous system adverse effects (dizziness and drowsiness) from these drugs. If you can reduce that risk, it may be worth a month's trial. ■

References

1. Helgason S, et al. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: Prospective study with long term follow-up. *BMJ* 2000;321:794-796.
2. Wood MJ, et al. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: A meta-analysis of placebo-controlled trials. *Clin Infect Dis* 1996; 22:341-347.
3. Yawn BP, et al. A population-based study of the incidence

and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc* 2007;82: 1341-1349.
4. Chen N, et al. Vaccination for preventing postherpetic neuralgia. *Cochrane Database Syst Rev* 2011 Mar 16;(3):CD007795.
5. Oxman MN, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005;352:2271-2284.
6. Hurley LP, et al. Barriers to the use of herpes zoster vaccine. *Ann Intern Med* 2010;152:555-560.
7. http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm. Accessed August 28, 2011.
8. Whitley RJ, et al. Acyclovir with and without prednisone for the treatment of herpes zoster. A randomized, placebo-controlled trial. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *Ann Intern Med* 1996;125:376-383.

CME Questions

1. Compared to the standard treatment group receiving warfarin, which of the following outcomes were observed in the group randomized to apixaban in the study by Granger and colleagues of over 18,000 patients with atrial fibrillation?

a. Increased major bleeding in the group receiving apixaban.

b. Decreased rate of stroke in the group receiving apixaban.

c. Decreased rate of myocardial infarction in the group receiving apixaban.

d. Increased risk of death in the group receiving apixaban.

2. In the prospective single-center study by Thille and colleagues, patients who failed extubation after passing a spontaneous breathing trial were more likely than patients who did not fail extubation to:

a. Have an increased risk of hospital mortality

b. Have increased rates of nosocomial pneumonia.

c. Be older with more cardiopulmonary co-morbidities.

d. All of the above.

3. According to the study of ocular candidiasis in patients with candidemia by Oude Lashof et al., which of the following observations were made?

a. Patients with candidemia and ocular involvement required longer course of antifungal treatment.

b. Patients with candidal chorioretinitis uniformly also had *Candida* endophthalmitis.

c. Ocular involvement was generally associated with a longer duration of candidemia.

d. Intravitreous antifungal therapy was required in patients with *Candida* endophthalmitis.

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 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. ■