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

HOSPITAL MEDICINE ALERT

AHC Media LLC Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

Delayed Transfer to the ICU Increases LOS and Mortality

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, PhD, RN

Department of Acute/Tertiary Care, School of Nursing, University of Pittsburgh

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

This article originally appeared in the November 2007 issue of Critical Care Alert. It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor, Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, and Dr. Thompson is Staff Pulmonologist, VA Medical Center; Associate Professor of Medicine, University of Washington. Drs. Pierson and Thompson report no financial relationships relevant to this field of study.

Synopsis: *Critically ill emergency department patients with a ³ 6 hour delay in ICU transfer had an increased hospital length of stay and higher ICU and hospital mortality.*

Source: Chalfin DB, et al. Impact of delayed transfer of critically ill patients from the emergency department to the intensive care unit. *Crit Care Med.* 2007;35:1477-1483.

THIS STUDY EXAMINED OUTCOMES IN 50,322 PATIENTS ADMITTED to the emergency department and later transferred to the ICU during the period from 2000-2003. Study data were obtained from Project IMPACT, a voluntary database that includes a nationwide sample of 120 adult ICUs in 90 hospitals. Patients admitted from the emergency department to the ICU were divided into two groups: those remaining in the emergency department ≥ 6 hours (delayed) and those remaining < 6 hours (non-delayed).

Patients whose admission to the ICU was delayed (n = 1,036) or non-delayed (n = 49,286) were similar in age, gender, and do-not-resuscitate status, as well as APACHE II score (P = NS). Among hospital survivors, the median hospital length of stay was 7.0 days (delayed) vs 6.0 days (non-delayed) (P < .001). ICU mortality was 10.7% (delayed) vs 8.4% (non delayed) (P <.01). In-hospital mortality was 17.4% (delayed) vs 12.9% (non-delayed) (P <.001). A diagnosis of sepsis was more common in the delayed group (P <.001), whereas multiple trauma (P <.01), coronary artery disease (P <.001) and respiratory diagnostic categories (P <.01) were more common in the non-delayed group. When examined using logistic regression, delayed admission, advancing age, higher APACHE II score, male gender, and

Financial Disclosure

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, has no relevant financial relationship related to the material presented in this issue.

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, selected and reviewed the articles contained within this issue on November 10, 2007.

a diagnosis of either trauma, intracerebral hemorrhage, or neurologic disease were associated with lower hospital survival (odds ratio for delayed admission, 0.79; 95% confidence interval, 0.561-0.895).

COMMENTARY

Today our emergency care system faces an epidemic of crowded emergency departments, patients experiencing long waits to be seen and admitted, and ambulance diversions. Hospitals are faced with the difficulty of simultaneously meeting the needs of patients who require urgent and lifesaving care and providing non-urgent care for the uninsured who use the emergency department as a safety net. The Institute of Medicine reports that 40% of hospitals experience crowding on a daily basis in their emergency department.[1] More than one-third report using diversion (closure to ambulance traffic) within the past year as a consequence of a lack of critical care beds.

In this study, critically ill patients whose admission to the ICU was delayed had a longer hospital stay and an increase in ICU and hospital mortality. As might be expected, there was considerable overlap in the APACHE II diagnostic categories between delayed and non-delayed patients. Among delayed patients, those with sepsis were significantly more likely to be delayed. In patients with septic shock, mortality can be significantly reduced if goal-directed therapy is instituted as soon as the diagnosis is made. Categories of patients diagnosed with other "time-sensitive" conditions, such as coronary artery disease or trauma, did not experience delays, suggesting that the time-sensitive nature of sepsis management may not be fully appreciated.

A second concern relates to the availability of critical care beds as a cause of the delay. Boarding of critically ill patients in the emergency department while waiting for an available bed is a common occurrence. Noting this, the Institute of Medicine recently identified emergency department boarding as a major public health concern,[1] a conclusion supported by study findings.

There were several limitations to this study. It used retrospective data and, therefore, could not identify the cause of the observed delays. The database did not include information about institutional characteristics, physician or nurse staffing or other variables, such as board certification or eligibility, or the availability of specialists, which might have influenced outcomes. Further studies are necessary to identify the specific factors that led to a prolonged emergency department stay and ways to modify them. ■

Reference

1. The future of emergency care in the United States health system: Institute of Medicine, 2006. Available at: http://www.iom.edu.

Hospital Medicine Alert, ISSN 1931-9037, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
MANAGING EDITOR: Leslie Hamlin.
MARKETING PRODUCT MANAGER: Shawn DeMario.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Hospital Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

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.

Subscriber Information

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

Subscription Prices

United States
1 year with Free *AMA PRA Category 1 Credits™*: $249
Add $12.95 for shipping & handling.
(Student/Resident rate: $125).

Multiple Copies
Discounts are available for group subscriptions. For pricing information, please call Tria Kreutzer at (404) 262-5482.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

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

AHC Media LLC designates this educational activity for a maximum of *20 AMA PRA Category 1 Credits™*. Physicians should only claim 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.

AHC Media LLC

Questions & Comments

Please call **Leslie Hamlin**, Managing Editor, at (404) 262-5416 or e-mail at leslie.hamlin@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Predicting Respiratory Failure in Guillain-Barré Syndrome

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Medical College of Cornell University, NewYork-Presbyterian Hospital

Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

This article originally appeared in the November 2007 issue of Neurology Alert. It was edited by Matthew Fink, MD, and peer reviewed by M. Flint Beal, MD. Dr. Fink is Vice Chairman, Professor of Critical Care Neurology, NewYork-Presbyterian Hospital, and Dr. Beal is Professor and Chairman, Department of Neurology, Cornell University Medical College. Drs. Fink and Beal report no financial relationship relevant to this field of study.

Synopsis: *Phrenic nerve conduction studies may be a promising method to anticipate respiratory failure in patients with GBS.*

Source: Ito H, et al. Phrenic nerve conduction in the early stage of Guillain-Barre syndrome might predict the respiratory failure. *Acta Neurol Scand* 2007; 116:255-258.

PREDICTING RESPIRATORY FAILURE EARLY DURING THE course of Guillain-Barré syndrome (GBS) by a

simple, accurate method would decrease morbidity and mortality. Blood gas measurements, forced vital capacity, negative inspiratory force, and clinical acumen are notoriously insensitive. Phrenic nerve conduction studies may prove helpful. Nerve conduction studies were performed on 15 patients admitted between 1999 and 2006 to the Kansai Medical University Department of Neurology (Osaka, Japan) with clinical and cerebrospinal fluid findings characteristic of GBS. None had received immunomodulating therapy, including intravenous immunoglobulin or plasma exchange, and none were ventilated or receiving oxygen. Phrenic nerve stimulation was performed percutaneously, posterior to the sternocleidomastoid muscle, at the upper level of the thyroid cartilage, with diaphragmatic recording on the anterior axillary line at the 8th intercostal space. Distal latency and peak-to-peak amplitude of both phrenic nerves were summed. Statistical analysis was performed using the Mann-Whitney non-parametric rank sum test, with $P < 0.05$ considered significant.

Three patients with summed phrenic nerve latency > 30 ms required ventilatory assistance; one by mechanical means and two with oxygenation. Bilateral diaphragmatic peak-to-peak amplitude was < 0.3 mV in these patients. None of the patients with summed latency < 30 ms required respiratory assistance, and all but one of these had a summed amplitude > 0.3 mV. Respiratory embarrassment was not found to correlate with the presence of bulbar palsy, anti-ganglioside antibodies, or the results of conventional peripheral nerve conduction studies, including the tibial, peroneal, median, or ulnar nerves. Vital capacity less than 80% was seen in only one patient with summed latency > 30 ms. Respiratory failure in GBS may be predicted by the presence of increased summed latency or motor amplitude of bilateral phrenic nerves. Larger studies are warranted to confirm this notion.

COMMENTARY

Among 154 patients with GBS seen between 1998 and 2006, the demyelinating, rather than the axonal, form of GBS was more predictive of the need for mechanical ventilation ($P = 0.0003$). Vital capacity greater than 81%, and an amplitude drop of less than 45.5% in distal to proximal peroneal nerve motor evoked response, was associated with less than a 2.5% likelihood of requiring ventilation.[1] Clinical and electrophysiological parameters can be useful predictors of respiratory failure in GBS. None is fail safe, but thorough investigation of such patients should forestall the unexpected. ■

Reference

1. Durand MC, et al. Clinical and electrophysiological predictors of respiratory failure in Guillain-Barre syndrome: A prospective study. *Lancet Neurol* 2006; 5:1021-1028.

Statin Withdrawal in Acute Stroke: Adverse Outcomes?

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD

Associate Professor, Department of Neurology, Weill-Cornell Medical College, Attending Neurologist, NewYork-Presbyterian Hospital

Dr. Segal is on the speaker's bureau for Boehringer-Ingelheim.

This article originally appeared in the October 2007 issue of Neurology Alert. It was edited by Matthew Fink, MD, and peer reviewed by M. Flint Beal, MD.

Synopsis: *Withdrawal of statin therapy in acute ischemic stroke may lead to increases in death and disability.*

Sources: Colivicchi F, et al. Statin treatment withdrawal in ischemic stroke: A controlled randomized study. *Neurology.* 2007;69:904-910.

STATIN THERAPY HAS A WELL-RECOGNIZED ROLE IN the primary and secondary prevention of stroke. Statins may also have a neuroprotective effect in the setting of acute stroke. This has been well documented in animal models, and high-dose acute statin therapy is currently under investigation in human subjects. Pretreatment with statins is also likely to have benefit. Discontinuation of statins in the acute setting may precipitate vascular dysfunction and exacerbate ischemic events, including both stroke and myocardial infarction.

In a single-center study in Spain, Blanco and colleagues studied 215 patients with acute ischemic stroke, 89 of whom were previously taking statin medications. These patients were randomly assigned to have statin therapy withheld for 3 days (statin withdrawal group) or to be treated with 20 mg atorvastatin either orally or via nasogastric tube (statin treated group). All patients were treated with statins starting on day 4, including the 126 remaining patients who had not previously been treated with statin therapy (reference group).

At 3 months, 60% of patients in the statin withdrawal group met the primary outcome variable of death or dependence, compared with 39% in the statin treated group. The adjusted odds ratio favoring a poor outcome

among statin withdrawal patients was 2.39, increasing to 4.66 (1.46 - 14.91) after adjustment for age and stroke severity. Early neurological deterioration, defined as an increase of ≥ 4 points on the NIHSS, was observed in 65% of statin withdrawal patients, compared with 21% of statin treated patients. Infarct volume was also greater in the statin withdrawal group, with a mean increase of 37 mL, compared with treated patients. In post-hoc analyses, statin withdrawal patients also fared more poorly than patients in the reference group with regard to all end points — death and dependency, early neurological deterioration, and infarct volume.

In a related study, Colivicchi and colleagues studied 631 patients with an ischemic stroke and followed them for one year to assess their adherence to statin therapy. Among 409 patients who received atorvastatin therapy, 163 discontinued this medication, and among 222 patients who received simvastatin, 83 had stopped taking it at one year. Among the 631 patients, 116 (18%) died during one-year follow up. After adjusting for confounding variables, including stroke severity, discontinuation of statin was an independent predictor of mortality, with a hazard ratio of 2.78. This effect was more pronounced with early discontinuation, leveling off in the 9-12 month interval. Discontinuation of anti-platelet therapy was also an independent predictor of death, though with a less profound effect (hazard ratio of 1.81).

Statin therapy was discontinued due to side effects (most commonly dyspepsia) in a minority of patients (29%), and was unexplained in the remaining 71%. Patients who discontinued statins were older and more commonly female. Statins were more likely to be continued among patients who were diabetic or who had a history of previous stroke.

COMMENTARY

As Blanco indicates, animal, as well as human data strongly suggest that withdrawal of statin therapy in an acute stroke patient may impair vascular function and trigger a dangerous inflammatory and prothrombotic state. This raises a major red flag in our treatment of acutely hospitalized stroke patients. Patients on previous statin therapy who have the medication discontinued face a 4.7-fold increase in their risk of death or dependency due to their stroke. This effect is even more pronounced among patients not previously receiving statin medications.

These data raise important practical implications regarding the "nuts and bolts" of emergency room and immediate hospital care for acute stroke patients. Patients with severe strokes who cannot take oral medications due to dysphagia, must receive these via nasogastric tube. Such patients are commonly made NPO, with feeding and oral medication administration delayed until their swallow status can be clarified. These issues are particularly germane to patients receiving thrombolysis. Among patients receiving intravenous tPA, our protocol mandates placement of a Foley catheter prior to thrombolysis since such an invasive procedure cannot be performed once tPA has been administered. The same would likely apply to a nasogastric tube.

The data of Colivicchi and colleagues are more difficult to understand. Discontinuation of statin therapy was highly associated with post-stroke mortality, but it is not clear if this was a cause, or more likely, merely an effect of practice patterns among patients with more devastating strokes. It is testament to the inconclusive nature of this study that the justification for cessation of statin therapy was unexplained in over 70% of patients. In addition, while over 80% of the deaths were attributed to cardiovascular causes, data such as these, gleaned from death certificates, is unlikely to reflect the true etiology of their demise. Notably, recurrent stroke was not documented as the cause of death among any of the patients from whom statins were withdrawn. ■

ECG Diagnosis of Acute Myocardial Infarction

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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

Dr. Crawford is on the speaker's bureau for Pfizer.

This article originally appeared in the November 2007 issue of Clinical Cardiology Alert. It was peer reviewed by Rakesh Mishra, MD, FACC. Dr. Mishra is Assistant Professor of Medicine, Weill Medical College, Cornell University; Assistant Attending Physician, NewYork-Presbyterian Hospital.

Synopsis: *In patients admitted to hospital with possible AMI, the consideration of both ST-segment elevation and depression in the standard 12 lead-ECG recording significantly increases the sensitivity for the detection of AMI with only a slight decrease in the specificity.*

Source: Martin TN, et al. ST-segment deviation analysis of the admission 12-lead electrocardiogram as an aid to early diagnosis of acute myocardial infarction with a cardiac magnetic resonance imaging gold standard. *J Am Coll Cardiol.* 2007;50:1021-1028.

ALTHOUGH ECG IS THE STANDARD INITIAL SCREENing test for acute coronary syndromes, its value

for the diagnosis of acute myocardial infarction (MI) is difficult to determine because of the vagaries of serum biomarkers. Contrast-enhanced magnetic resonance imaging (MRI) is a unique gold standard for the early detection of acute MI, and may be useful for determining the diagnostic accuracy of the ECG. Thus, this study from Glasgow, United Kingdom, is of interest.

Martin and colleagues enrolled 116 patients seen at one hospital with new-onset chest pain and interpretable ECGs. MI was confirmed in 58 by the presence of delayed hyperenhancement on MRI done a mean of 50 hours after onset of symptoms. The ECG diagnosis of acute ST segment elevation MI (STEMI) followed the usual criteria, but they also included a STEMI-equivalent category with ≥ 1 mm ST depression in ≥ 2 contiguous leads, or one lead that is anatomically contiguous to one lead with ST elevation. Current ECG STEMI criteria detected 50% of acute MIs, with a specificity of 97%. Adding the STEMI-equivalent criteria increased sensitivity to 84% and minimally reduced specificity (93%). Including troponin resulted in 10 false positive MI diagnoses: 6 by troponin elevation alone; 2 by ECG criteria alone; and 2 by both. Two of the 4 falsely positive by ECG met new STEMI-equivalent criteria. Hannan et al concluded that considering ECG ST segment depression, as well as elevation, significantly increases the sensitivity for acute MI diagnosis without a major impact on specificity.

COMMENTARY

ECG remains the mainstay of the early triage of chest pain patients because of its wide spread availability, low cost, and ability to identify myocardial ischemia or infarction. Imaging may be more accurate, but is not widely available. Serum biomarkers are very sensitive, but may be normal early in the course of acute MI. However, this study showed that the detection of STEMI, where triage to reperfusion strategies is most critical, using standard ECG criteria, was only 50%. This increased to 84% without significant changes in specificity when ST segment depression in 2 anatomically-contiguous leads, or in one lead anatomically contiguous to a lead with ST elevation, was considered. For example, ST segment elevation in lead aVL and ST depression in lead III (negative ST in lead III reflects ST elevation in a nonexistent lead near aVL). Two contiguous leads with ST depression (eg, V1 and V2) would reflect ST elevation in 2 nonexistent leads opposite them on the posterior lateral wall. This makes sense from an ECG point of view, and proved reliable in this study. Acceptance of this modification of the ECG criteria for STEMI would increase the number of patients with chest pain triaged to reperfusion, with a specificity rate in the 90% range.

Of course there are some caveats. This study showed that about one quarter of patients presented challenges in ECG interpretation, and were excluded. The challenging conditions included evidence of prior MI, left ventricular hypertrophy, rapid atrial fibrillation, WPW, bundle branch block, right ventricular hypertrophy, and extensive artifacts. The prevalence of infarction was high in this study (50%), which resulted in positive predictive values in the 90% range. If a lower MI prevalence was considered — say 20%, the positive predictive value would fall into the 75-85% range, but this requires further investigation. Contrast-enhanced MRI cannot distinguish the age of an MI, but in this study, all the MRI-diagnosed MIs had elevations and declines in serum biomarkers consistent with acute MI. Also, MRI currently has a spacial resolution of about one cubic centimeter, so smaller MIs would not be detected. Perhaps some MRI-negative, biomarker-positive patients have such small MIs. Hannan et al referred to these as "necrosettes." Presumably, such small MIs would be low-risk events, and reperfusion may not greatly influence prognosis. They may even represent "supply/demand imbalance" events rather than thrombotic occlusions. In this study, all MRI positive patients had a troponin I > 4.4 ng/mL. The average troponin I in those with a negative MRI was 1.4 ng/mL.

ECG mavens have long recognized that ST depression in I, aVL, or V1-4 may represent left main coronary artery thrombosis, so the concept that significant ST depression may represent an acute thrombotic condition, best treated with reperfusion, is not new. This study shows that it could help detect more STEMI than current ECG criteria without unacceptable increases in false positives. It seems worth keeping in mind when triaging chest pain patients. ■

New Drug for Atrial Arrhythmias

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant. This article originally appeared in the November 2007 issue of Clinical Cardiology Alert. It was edited by Michael Crawford, MD, and peer reviewed by Rakesh Mishra, MD.

Synopsis: *Dronedarone was significantly more effective than placebo in maintaining sinus rhythm and in reducing the ventricular rate during recurrence of arrhythmia.*

Source: Singh BN, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med.* 2007;357:987-999.

THIS PAPER GIVES THE RESULTS OF 2 TRIALS THAT evaluated the effects of dronedarone, a new antiarrhythmic agent, on the recurrence of atrial fibrillation or atrial flutter. The 2 studies reported were identical placebo-controlled, double-blind, parallel-group trials, with one conducted in Europe and the other in non-European countries. The data from the 2 studies were quite similar, and in this report, only the combined data will be discussed.

Patients qualified for the studies if they were at least 21-years-old and had had at least one episode of atrial fibrillation within the preceding 3 months. Patients could be cardioverted after screening, but had to be in sinus rhythm for at least one hour before randomization. Use of class I or class III antiarrhythmic agents was not permitted. Other criteria for exclusion included class III or class IV heart failure, significant sinus bradycardia, or a PR interval of greater than 0.28 seconds. Patients with a serum creatinine level of ≥ to 1.7 mg/dL were also excluded. Most patients had previously received treatment with one or more antiarrhythmic drugs, including amiodarone in 30%. Patients were randomly assigned in a 2:1 ratio to receive either 400 mg of oral dronedarone twice daily or matching placebo. Patients were followed with periodic transtelephonic electrocardiograms both on a regular schedule and whenever they had symptoms. They were also seen frequently for electrocardiograms and blood tests. The primary end point of the trial was time from randomization to the first documented recurrence of atrial fibrillation. For the purpose of the study, a recurrence was defined as an episode lasting for at least 10 minutes, confirmed by electrocardiography or transtelephonic monitoring.

The combined trials enrolled 820 patients who received dronedarone and 409 in the placebo group. The mean age was 63 years, and 69% were male. A history of hypertension was present in 50% of the placebo patients and in 60% of the dronedarone patients. Other structural heart disease was present in approximately 40% of the patients in both groups. The mean left ventricular ejection fraction was 58% in groups. Only a small percentage of patients had a history of congestive heart failure. Most patients had failed one or more antiarrhythmic drugs.

For the 2 trials combined, the median times to a documented recurrence of atrial fibrillation were 116 days in the dronedarone group and 53 days in the placebo group. The cumulative recurrence rate at 12 months was 64.1% in the dronedarone group and 75.2% in the placebo group (hazard ratio 0.75; *P* less than 0.001). If recurrences in the first 5 days of treatment were excluded, the hazard ratio decreased slightly to 0.72 (*P* less than 0.001). As anticipated from its pharmacologic profile, dronedarone decreased heart rate by 6.8%, prolonged the QT interval by 23.4 m/sec, and prolonged the QTc interval by 9.0 m/sec. There was no change in QRS duration. Among patients with documented recurrences, dronedarone slowed the ventricular rate from 117 ± 30 bpm in the placebo group to 103 ± 26 bpm. Hospitalization or death was seen in 30.9% of the placebo group vs 22.8% of the dronedarone group, with a hazard ratio 0.73 ($P = 0.01$). Dronedarone was well tolerated. There was no significant increase in the incidence of any of the following adverse reactions: cough, dyspnea, bradycardia, heart failure or shock, neurologic or gastrointestinal disorders, or hepatic enzyme elevations. More patients in the placebo group than the dronedarone group developed hyperthyroidism. There was no significant difference in the incidence of hypothyroidism. Serum creatinine became elevated in 2.4% of dronedarone group vs 0.2% in the placebo group ($P = 0.004$).

Singh and colleagues conclude that dronedarone is an effective antiarrhythmic drug that reduces the recurrence of atrial fibrillation with a favorable side-effect profile.

COMMENTARY

Dronedarone is an antiarrhythmic drug that is structurally similar to amiodarone and has a similar electrophysiologic profile due to effects on multiple cardiac ion channels. However, the dronedarone molecule does not contain iodine, a factor which has been linked to the thyroid and pulmonary adverse reactions observed during amiodarone therapy. In this trial, dronedarone had a modest favorable effect on the recurrence of atrial fibrillation. However, most patients in the trial had previously failed one or more antiarrhythmic drugs, and the 25% to 30% reduction in atrial fibrillation recurrence is, therefore, likely to be clinically

important. It is also significant that dronedarone was quite well-tolerated. The adverse events profiles between the placebo and dronedarone groups did not differ. The trial, however, did not include patients with advanced (class III or class IV) heart failure. Patients with advanced heart failure had been previously evaluated in an earlier trial (ANDROMEDA) during which there had been a suggestion of increased mortality. Subsequent reexamination of that trial's results suggested that heart failure management had been influenced by the effect of dronedarone to raise serum creatinine, and this perhaps explained the increase in mortality in the dronedarone group. However, the effects of dronedarone on serum creatinine are not due to changes in glomerular infiltration rate, but rather to tubular secretion of creatinine, and alterations in the dosage of angiotensin converting enzyme inhibitors was probably not appropriate. Additional studies with dronedarone in older and higher-risk patient groups are now underway. If they support the safety of the drug in these later groups, dronedarone should prove an important addition to our antiarrhythmic armamentarium. ■

Micafungin for Invasive Candidiasis

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

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

Dr. Deresinski serves on the speaker's bureau for Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. This article originally appeared in the November 2007 issue of Infectious Disease Alert. It was peer reviewed by Connie Price, MD. Dr. Price is Assistant Professor, University of Colorado School of Medicine. She reports no financial relationship relevant to this field of study.

Synopsis: *Micafungin at doses of both 100 mg and 150 mg daily was non-inferior to caspofungin in the treatment of invasive candidiasis and there was no significant difference in outcomes when the two doses of micafungin were compared.*

Source: Pappas PG, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis*. 2007;45:883-893.

Patients with invasive candidiasis were randomized to blinded treatment with either caspofungin (70 mg on day one, followed by 50 mg daily), or one of 2 doses of micafungin (100 mg or 150 mg daily). Approximately 85% of the 595 randomized patients had candidemia. Patients in each treatment arm received a median of 14 days of therapy, including 4-7.5 days of oral fluconazole in 15.1%-21.9% in each arm, as allowed by protocol. Almost three-fourths of infections were due to *Candida albicans*, followed in frequency by *C. tropicalis* (16.6%), *C. glabrata* (16.4%), and *C. parapsilosis* (15.9%). Neutropenia was present at baseline in 8.4% of patients.

The size of the population randomized was chosen in order to have a > 90% power to determine non-inferiority of micafungin at a lower bound of the difference between treatment arms of -15%. Treatment success, defined as investigator-determined clinical and mycological success at the end of blinded intravenous therapy in the modified intent-to-treat population, was the primary efficacy end point, and was achieved in 76.4%, 71.4%, and 72.3% of patients assigned micafungin 100 mg, micafungin 150 mg, and caspofungin, respectively. Both micafungin regimens were noninferior to treatment with caspofungin. This remained true at subsequent evaluations, with the last occurring 6 weeks after the end of all antifungal therapy. There was no significant difference between treatment arms in the treatment of infections due to *C. albicans* or the non-albicans species. The median time to blood culture negativity was 2 days in the micafungin 100 mg group, as well as in the caspofungin group; it was 3 days in the group given micafungin 150 mg.

Approximately one-fourth of patients in each group did not have their intravenous catheters removed, a feature associated with poorer overall response, regardless of assigned treatment. Thus, treatment success was achieved in 77.9% of 384 patients whose IV catheter was removed or replaced, while only 63.2% of 144 patients whose catheter remained in place were successfully treated (P = .001). The overall mortality was 29.6%, and did not differ significantly among the treatment groups.

■ COMMENTARY

This is the latest in the past several years in a series of randomized, therapeutic trials evaluating newer antifungal agents in the treatment of invasive candidiasis, and the first to compare 2 echinocandins. Previously, caspofungin therapy was comparable to the use of amphotericin B deoxycholate in a primary analysis and superior in a clinically evaluable population.[1] Anidulafungin was found to be superior to fluconazole,[2] while voriconazole was non-inferior to

amphotericin B deoxycholate,[3] and micafungin was non-inferior to liposomal amphotericin B.[4] Thus, we have a variety of trials that provide us with data to assist us in deciding on optimal anti-candidal therapy, but strangely, the answer remains somewhat muddy. It seems to me that it would be generally preferred to use an agent other than an amphotericin B preparation, given the complexities of administration and toxicity of these products. Fluconazole is active against most, but not all Candida isolates, so that it probably should not be used as empiric therapy in patients with severe, potentially life-threatening infections. Voriconazole is active against some fluconazole-resistant Candida. The echinocandins seem to be emerging as the preferred initial empiric therapy of many clinicians, but the choice among the 3 available echinocandins is more difficult and is not made easier by the study reviewed here.

Some comparisons indicated a non-significant trend toward superior outcomes in patients receiving 100 mg of micafungin daily compared to those receiving a higher dose. If correct, this finding would be consistent with a paradoxical effect, in which higher concentrations are less effective at inhibiting growth of the microorganism than are some lower doses.

Another interesting observation was that only 11 of 595 (1.8%) had chorioretinits at baseline, a figure much lower than has been reported in the past with candidemia, but consistent with the results in some other clinical trials. This suggests that earlier observational studies, which reported an incidence as high as 30%, were either grossly inaccurate or the patients had suffered from prolonged candidemia before it was recognized and treated. ■

References

1. Mora-Duarte J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med*. 2002;347:2020-2029.
2. Reboli AC, et al. Anidulafungin versus fluconazole for the treatment of invasive candidiasis. *N Engl J Med*. 2007;356:2472-2482.
3. 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.
4. Kuse ER, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidiasis: A phase III randomised double-blind trial. *Lancet*. 2007; 369:1519-1527.

CME Questions

7. In the study by Chalfin et al, which information was included in the database?
a. institutional characteristics
b. physician or nurse staffing
c. availability of specialists
d. All of the above

8. Among GBS patients, which was more predictive of the need for mechanical ventilation?
a. the axonal form
b. the demyelinating form
c. Neither A nor B
d. Both A and B

9. Which of the following strongly suggests that withdrawal of statin therapy in an acute stroke patient may impair vascular function?
a. animal data
b. human data
c. Both A and B
d. Neither A nor B

Answers: 7. (d); 8. (b); 9. (c)

CME Objectives

The objectives of *Hospital Medicine Alert* are to:

• review pertinent safety, infection control, and quality improvement practices;

• discuss diagnosis and treatment of acute illness in the hospital setting; and

• review current data on diagnostic and therapeutic modalities for common inpatient problems. ■

CME Instructions

Physicians participate in this CME program by reading the issue, using the references for research, and studying the questions. Participants should select what they believe to be the correct answers, then refer to the answer key to test their knowledge. To clarify confusion on any questions answered incorrectly, consult the source material. ■