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

HOSPITAL MEDICINE ALERT

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

Omeprazole and Clopidogrel — Is There a Clinically Meaningful Interaction?

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 January 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 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 is on the speaker for Astra-Zeneca, and Dr. Weiss reports no financial relationships relevant to this field of study.*

Source: Bhatt, DL et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010:363:1909-1917.

GASTROINTESTINAL (GI) BLEEDING IS A MAJOR COMPLICATION OF dual anti-platelet therapy (DAPT) with aspirin and clopidogrel. Omeprazole reduces the risk of GI bleeding in this setting. However, studies of platelet function have suggested that omeprazole also may reduce the efficacy of clopidogrel-mediated platelet inhibition. Whether this translates into an increase in ischemic events is controversial. Clinical-trial data are conflicting, with some studies showing increased cardiovascular events in patients on DAPT who also take omeprazole, compared to those who do not take omeprazole, but other studies are failing to show any association. However, to date, these studies have all been retrospective. Bhatt and colleagues report the first prospective, randomized, placebo-controlled trial to address this issue.

The study aimed to enroll approximately 5,000 patients with coronary artery disease who were prescribed DAPT with aspirin and clopidogrel but, due to withdrawal of sponsor funding, the trial stopped early. Only 3,873 patients were randomized to receive either omeprazole 20 mg daily vs. placebo, and the trial

VOLUME 5 • NUMBER 12 • FEBRUARY 2011 • PAGES 89-96

NOW AVAILABLE ONLINE
www.ahcmedia.com

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.

had both a GI primary endpoint and a cardiovascular primary endpoint. The GI primary endpoint was a combination of upper GI bleeding and reduction in hemoglobin of at least 2g/dL (or decrease of hematocrit by 10%), presumed to be due to upper GI bleeding, gastric or duodenal ulcer, gastric or duodenal erosions, obstruction, or perforation. The primary cardiovascular endpoint was a composite of cardiovascular death, myocardial infarction, coronary revascularization, or ischemic stroke. Inclusion criteria were patients over 21 years of age with coronary artery disease who were receiving aspirin and clopidogrel after presenting with either acute coronary syndrome or placement of a coronary stent. Exclusion criteria included prolonged hospitalization, the need for either shorter- or longer-term proton pump inhibitor (PPI) therapy, use of H2 blockers, misoprostol or sucralfate, pre-existing erosive esophagitis, varices or previous gastric surgery, oral anticoagulation, recent fibrinolytic, or prior clopidogrel use for > 21 days.

Results: Baseline characteristics were well-matched in the placebo and omeprazole groups, with mean age 69 years, two-thirds male, approximately 50% positive for *Helicobacter pylori*, and 9% using NSAIDS. The omeprazole group had a significantly lower rate of the primary GI endpoint (1.1% vs. 2.9%; $p < 0.001$); this included lower rates of GI bleeding. Importantly, the presence or absence of *H. pylori* and the use of NSAIDs made no difference to this outcome. All the components of the composite GI primary outcome were numerically higher in the placebo group. There was no difference between the placebo and omeprazole in the cardiovascular primary endpoint (54 events vs. 55 events; $p = 0.98$). This was consistent across all subgroups and all components of the composite endpoint. The rate of serious adverse events also did not differ between groups (10.1% vs. 9.4% in omeprazole and placebo groups, respectively; $p = 0.48$). The only difference in adverse events was a higher rate of diarrhea with omeprazole (3.0% vs. 1.8%; $p = 0.01$). The authors conclude that among patients receiving aspirin and clopidogrel, prophylactic use of a PPI reduced the rate of upper GI bleeding. There was no apparent cardiovascular interaction between clopidogrel and omeprazole, but they add that their results do not rule out a clinically meaningful difference in cardiovascular events due to the use of a PPI.

■ COMMENTARY

There has been much discussion about the risks of GI bleeding with DAPT and the potential interactions between clopidogrel and PPIs. Platelet-function studies have suggested that PPIs interfere with the anti-platelet effect of clopidogrel. However, the clinical-event rates from post-hoc analyses of clinical trials have been conflicting about whether there is a clinically relevant interaction between these drugs. This prospective trial reassures us that omeprazole does indeed reduce GI bleeding in patients on DAPT. Furthermore, it does not suggest a clinically meaningful interaction between these two drugs, in terms of cardiovascular events. However, the authors point out that the observed event rate was lower than expected, and this reduces the power of the study. Thus, they do not consider this definitive proof of a lack of interaction. This sentiment is echoed by the upcoming ACCF/AHA/ACG 2010 Expert Consensus Document on the Concomitant Use of PPIs and Thienopyridines (in press). This document highlights the lack of evidence of a clinical outcome from such a proposed interaction, but also acknowledges the biological plausibility that such an interaction may exist, particularly in some subgroups, such as poor metabolizers of clopidogrel. They recommend individualizing the risks of GI bleeding vs. ischemic events in every patient before deciding on the use of PPIs, rather than prescribing them to everyone. In those patients taking aspirin and clopidogrel who are at high risk for GI bleeding, it is reasonable to prescribe PPIs.

It is important to note that there may be important differences between PPIs in terms of their effects on cytochrome p-450 and, therefore, they may have different effects on clopidogrel metabolism. The results of the current study may not be generalizable to all PPIs. Conversely, there may be differences between clopidogrel and the newer P2Y12 inhibitors, such as prasugrel, and

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.

MANAGING EDITOR: Leslie Hamlin.
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 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 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 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.

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.

the current results may not necessarily apply to these new agents. Decisions regarding anti-platelet and PPI agents will need to be individualized for each patient. ■

Study Supports More Appropriate Blood Pressure Levels for Post-ACS Patients

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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

Dr. Crawford is a speaker for Astra-Zeneca.

This article originally appeared in the January 2011 issue of Clinical Cardiology Alert. *It was peer reviewed by Ethan Weiss, MD.*

Source: Bangalore S, et al. What is the optimal blood pressure in patients after acute coronary syndromes? Relationship of blood pressure and cardiovascular events in the pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction (PROVE IT-TIMI) 22 trial. *Circulation*. 2010;122:2142-2151.

The relationship between blood pressure and cardiovascular events remains controversial, especially in patients with coronary artery disease who may need increased pressures to have adequate myocardial perfusion. Thus, Bangalore and colleagues analyzed data from the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial to determine the relationship of blood pressure to cardiovascular outcomes in patients with acute coronary syndromes (ACS). Blood pressure was managed at the discretion of the patient's physician. For this analysis, average blood pressure was calculated using all post-baseline values until the end of the study or an event occurred. The main drug intervention results of the trial have previously been reported for the 4,162 patients with ACS. All patients were divided into blood pressure groups in increments of 10mm/Hg. The primary cardiovascular event outcome was reached in 24% of the patients. The relationship between blood pressure and these events exhibited a J- or U-shaped curve, with increased events at low or high systolic blood pressure. This relationship held in the raw data after adjustment for differences in baseline characteristics of the patient. Cardiovascular events were lowest, at a blood pressure of 136/85 mm Hg. The curve was flat between pressures of 110 to 130 mm Hg systolic and 70 to 90 mm Hg diastolic. These findings were similar in the drug-treatment groups vs. the entire cohort. Examination of individual cardiovascular events showed that there were too few strokes (< 1%) to derive a meaningful relationship to blood pressure. Separating the data by systolic and diastolic blood pressure did not change the results. So a low diastolic pressure was no worse than a low systolic pressure for cardiac ischemic endpoints. The authors concluded that too low a blood pressure, especially < 110/70 mm Hg may be dangerous in post-ACS patients.

■ COMMENTARY

This study further supports the growing data that lower is not always better in blood-pressure control. That there is a J- or U-shaped curve with blood pressure and mortality is obvious; the only argument is where the nadir is. The conventional wisdom is that in high-risk individuals for cardiovascular (CV) events such as diabetics, the level should be at the lower end of the normal range, or < 120/80 mm Hg. However, the data to support this recommendation is sparse, and the recent ACCORD trial showed that there was no difference in CV events in type-II diabetes patients treated to a target systolic blood pressure of < 140 vs. < 120 mm Hg.

Several studies have shown similar results in more general high-risk populations. The Hypertension Optimal Treatment study showed a nadir for CV events at about 145/85 mm Hg. The Framingham post-myocardial infarction study showed similar results, as did the International Verapamil Trandolapril study and ON TARGET. Also, a recent Cochrane meta-analysis showed no difference in CV events with blood pressures of < 135/85 vs. 140-160/90-100 mm Hg. Thus, it seems we can return to the old standard of < 140/90 mm Hg, and not worry too much if we cannot quite get a patient below that level without adverse drug effects.

Of course, this was an observational study that did not control medication use or set targets for blood pressure. There were major differences in the clinical characteristics of the different blood-pressure groups. They attempted to correct for the obviously important differences such as age, but it is impossible to control for every factor, and there is always the possibility of unmeasured comorbidities influencing the results. Also, a relationship between blood pressure and events does not prove causation. In addition, there were more patients with blood pressures < 110mm Hg (about 1,500) than with blood pressures > 140 (about 600), and very few with pressures > 160 (63). So, the study was biased toward finding problems with low blood pressures. Finally, the results are only applicable to ACS patients with tight lipid control, since this was the population studied.

The mechanism of this observed relationship, if it is causal, cannot be elucidated from this study. However, analyses showed that it was not explained by pulse pressure. In fact, the ratio of myocardial infarction to stroke tended to increase at low diastolic pressures. This suggests that stroke is independent of pulse pressures. The likely reason myocardial infarcts increased is the lowered coronary perfusion pressure anticipated with a low diastolic-driving pressure in the coronary arteries, rather than the widened pulse pressure. Post-ACS patients would be expected to be especially vulnerable to reduced coronary dividing pressure. The nadir for diastolic pressure and CV events was 80-90 mm Hg in this study and >130 mm Hg for systolic blood pressure. Thus, in post-ACS patients, blood pressures nearer the 140/90 normal upper limit may be the most appropriate. ■

Early Aggressive Therapy to Reduce Serum Lactate Levels Improves Outcomes in Critically Ill Patients

ABSTRACT & COMMENTARY

By David J. Pierson, MD

Professor, Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle

Dr. Pierson reports no financial relationships relevant to this field of study. This article originally appeared in the January 2011 issue of Critical Care Alert. *It was peer reviewed by William Thompson, MD. Dr. Thompson is Associate Professor of Medicine, University of Washington. Dr. Thompson reports no financial relationships relevant to this field of study.*

Synopsis: *In a multicenter study, critically ill patients with initial hyperlactatemia had improved outcomes (including shorter ICU stays and lower adjusted mortality) compared to control patients when they were managed for the first 8 hours with a resuscitation protocol targeted at reducing the lactate level by at least 20% every 2 hours.*

Source: Jansen TC, et al; LACTATE study group. Early lactate-guided therapy in intensive care unit patients: A multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med*. 2010;182:752-761.

Carried out in four ICUs in the Netherlands, this study evaluated the effects of a serum lactate-guided resuscitation protocol during initial management of critically ill patients with elevated lactate levels, as compared to standard management not guided by serial lactate measurements. Adult patients with admission lactate levels of 3.0 mEq/L or greater were enrolled during a 2-year period. Patients with conditions that might either generate more lactate (such as grand mal seizures) or affect its clearance (such as severe liver disease) were excluded. Patients were randomized on admission to the ICU, and were managed either according to the protocol or without serum lactate guidance for the initial 8 hours; thereafter, their management was according to the judgment of their treating intensivists.

Patients in the control group had management targeted at a mean arterial pressure > 60 mm Hg, heart rate < 100/min, central venous pressure 8-12 mm Hg (12-15 mm Hg in ventilated patients), urine output at least 0.5 mL/kg/hr, hemoglobin at least 7 g/dL, and arterial oxygen saturation at least 92%. In this group, central venous oxygen saturation ($ScvO_2$) monitoring was allowed at the discretion of the managing intensivist, but lactate levels were not made available during the 8-hour intervention period. In the intervention (lactate-guided) group, the above management goals were the same, with the addition of a targeted reduction in serum lactate of at least 20% every 2 hours until the level was 2.0 mEq/L or less, and the goal of achieving and maintaining a $ScvO_2$ value of at least 70%. Arterial blood was preferentially used for lactate measurement, but the use of venous or capillary blood also was allowed; measurement was by means of a hand-held point-of-care device (Accutrend®, Roche Diagnostics; Mannheim, Germany), which was provided for the study by the manufacturer.

There were 177 patients in the control group and 171 patients in the lactate-targeted group. Their ages, demographics, admission diagnoses, APACHE II scores (mean ~23), and sequential organ failure assessment (SOFA) scores (mean ~9) were comparable. Most of the patients were admitted to the ICU within 6 hours of hospital admission, and median time from ICU admission to randomization was less than 1 hour. The lactate group received more fluids and vasodilators, although there were no differences between the groups with respect to the patients' lactate levels themselves. Hospital mortality in the control group was 43.5% as compared to 33.9% in the lactate group, a nonsignificant difference (P = 0.067). However, when adjusted for predefined risk factors, mortality was lower in the lactate group (hazard ratio, 0.61; 95% confidence interval, 0.43-0.87; P = 0.006). SOFA scores were lower between 9 and 72 hours after starting the study in the lactate patients; they also had fewer hours of vasopressor therapy, shorter periods of mechanical ventilation, and shorter ICU stays. The authors conclude that lactate-guided initial fluid

and hemodynamic management among critically ill patients with initial hyperlactatemia is beneficial.

■ COMMENTARY

In this multicenter, open-label randomized controlled study, the use of a serum lactate-guided resuscitation protocol during the initial 8 hours in the ICU, aimed at reducing lactate levels by at least 20% every 2 hours until they were 2 mEq/L or less, reduced ICU length of stay and also — after adjustment for various factors — both ICU and hospital mortality. Although the mechanism is unclear, blood lactate levels correlate inversely with prognosis in critically ill patients, irrespective of the type of critical illness or the presence of either shock or organ failure. Attention has thus naturally focused on the possible effects on patient outcomes of measures to reduce serum lactate, particularly in the early hours of treatment for critical illness. Current evidence indicates that mortality relates to the primary disease process generating the increased serum lactate (primarily through tissue hypoxia) rather than the lactate molecule itself, and reducing lactate levels by infusing dichloroacetate does not reduce mortality.

Although the setting was somewhat different and only about 40% of the patients had severe sepsis or septic shock, this study supports the findings of the widely heralded, single-center, emergency department study of Rivers et al in patients with sepsis,[1] which has been used as the basis for broad application of early goal-directed therapy in critically ill patients. The findings of Jansen et al will likely be used to support wider use of lactate monitoring in the ICU, in addition to the use of $ScvO_2$ monitoring and the hemodynamic and other components of early goal-directed therapy for severe sepsis and septic shock.

If past critical care experience is any guide, these things also may begin to be used in clinical settings different from those in which the results were obtained. Based on its findings, the current study supports a lactate-guided strategy of fluid and hemodynamic management in critically ill patients starting immediately on presentation to the ICU and continuing for the next 8 hours. Whether additional benefit might accrue from the use of this strategy beyond 8 hours, or if it is initiated later in the course of the patient's illness, is unknown and must await the results of additional studies.

Reference

1. Rivers E, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368-1377.

Managing Influenza in Patients with Hematologic Malignancies

SPECIAL FEATURE

By Jerome Yates, MD

Hematology/Immunology Unit,
National Institute on Aging, NIH

Dr. Yates reports no financial relationships relevant to this field of study. This article originally appeared in the January 2011 issue of Clinical Oncology Alert. *It was edited by William B. Ershler, MD, and peer reviewed by V.R. Veerapalli, MD. Dr. Ershler is Director, Institute for Advanced Studies in Aging, Washington, DC; Member, INOVA Fairfax Cancer Center, Fairfax, VA, and Dr. Veerapalli is Staff Clinician, INOVA Fairfax Cancer Center, Fairfax, VA. Drs. Ershler and Veerapalli report no financial relationships relevant to this field of study.*

A 74-YEAR RETIRED VETERINARIAN PRESENTS TO THE EMERgency department (ED) with shortness of breath. He was recently diagnosed with diffuse large-cell lymphoma with prominent abdominal lymphadenopathy and positive bone marrow and has been treated with two cycles of R-CHOP. He has tolerated the chemotherapy well, without nausea, vomiting, or significant cytopenia after either cycle. The third cycle was scheduled to begin in five days. Shortness of breath developed progressively over the prior two days and has been associated with cough, low-grade fever, headache, and increasing fatigue. He lives with his wife, who is well. His past medical history is significant for hypertension and hyperlipidemia, both controlled with medication. He does not currently smoke, although he has a 40 pack/year history, having quit approximately 10 years ago. He drinks moderately (1-2 cocktails/evening).

In the ED, physical examination revealed a mildly dyspneic man. Blood pressure was 128/78, pulse was 94 and regular, and respiratory rate was 18/min. O_2 saturation was 90% on room air. There were rales at the right base, heard posteriorly. The abdomen did not reveal palpable mass, tenderness, or organomegaly. The extremities were free of edema, and there was no clubbing or cyanosis. Oxygen was administered at 2L/min by nasal prong, and the O_2 saturation rose to 96%. A chest X-ray revealed haziness in the right middle lobe, consistent with an interstitial pneumonia. Complete blood count revealed a white count of 11.3K/cu mm, with 88% neutrophils, hemoglobin was 10.4 g/dL, and the platelet count was 140K/cu mm. Blood and urine cultures were obtained. A nasopharyngeal swab was positive for influenza (and this was later confirmed to be seasonal H1N1 influenza). The patient was admitted to the hospital for treatment.

CASE DISCUSSION

As with influenza occurring in healthy adults, its occurrence in patients with malignancy typically is heralded by upper respiratory symptoms, headache, and fever. However, these systemic symptoms, including fever, myalgia, and fatigue, may be reduced, or completely absent, in patients who are immunologically compromised. For example, among hematopoietic cell transplant (HCT) recipients, in whom this has been studied prospectively,[1] most patients were afebrile and lacked systemic symptoms. It is possible that the cytokine response associated with acute influenza infection may be decreased in these patients, either because of their disease or the treatment thereof. Furthermore, the symptomatic phase typically lasts for 1 to 2 weeks in immunocompromised patients, although viral shedding may be prolonged beyond that.[2]

INFLUENZA PNEUMONIA

For most immunologically competent adults who are diagnosed with influenza, the symptoms, though often dramatic, are usually self-limited. However, when influenza progresses to a lower respiratory infection, the outcome can be devastating for both immune-competent and immune-deficient patients. The progression from upper- to lower-tract disease occurs after a median of one week in patients with hematologic malignancies,[2] presenting clinically and radiographically as viral pneumonia. One significant risk factor for progression to lower-tract disease is profound lymphopenia.[2,3] The impacts of corticosteroids and/or rituximab on influenza severity and outcome are conflicting, with no randomized trials assessing these effects. It is possible that steroids prolong viral shedding, but this might be balanced by a reduction in the inflammatory cytokine response. The effect of corticosteroids and immunomodulating drugs on the progression of influenza infection is an important but under-studied clinical-research domain. There have been very few studies that have evaluated the outcome of influenza disease relative to the underlying immunosuppression or pre-existing conditions, although a recent meta-analysis found an average case-fatality rate of 17%, with a range of 0% to 33% among HCT recipients infected with seasonal influenza.[4]

MANAGEMENT

Certainly, influenza pneumonia may be complicated by bacterial or fungal co-infection, and this would seem more likely in immunologically compromised patients. In such patients, diagnostic vigilance must be high and the threshold for the addition of antibiotic and/or antifungal medicine low.

There are treatments for influenza of proven, albeit modest benefit. Once again, these agents have not been adequately studied in randomized trials specifically in patients undergoing chemotherapy or other forms of cancer treatment. Antiviral susceptibilities of circulating influenza strains must be continually evaluated. Due to documented resistance to M2 inhibitors exhibited by 2009 H1N1 strains, amantadine and rimantidine probably should still not be used as single agents to treat or prevent influenza A. There are two 2 neuraminidase inhibitors (zanamivir and oseltamivir) that are currently approved for the treatment of influenza. These compounds are licensed for inhaled (zanamivir) and oral (oseltamivir) use, with intravenous agents now available only under special circumstances (i.e., under Emergency Use Authorization through the U.S. Centers for Disease Control and Prevention).

Redelman-Sidi and colleagues[5] provided some insight on the effects of optimal management of influenza during the recent H1N1 pandemic (2009). Among 45 influenza-confirmed cancer patients treated at Memorial Sloan Kettering Cancer Center, progression to lower respiratory tract disease occurred in 27%. In that cohort, 37% of patients were hospitalized for an average of 7 days (range, 3-15 days), and one person required admission to the intensive-care unit care without mechanical ventilation. Almost all patients were treated with oseltamivir. This is in contrast to a number of other reports in which, even with optimal therapy, death rates in patients with lower respiratory influenza among cancer patients were high.[6]

Although there is little evidence derived from sufficiently powered, randomized clinical trials, it is prudent to be aggressive in the management of immune-compromised patients with proven influenza pneumonia. Treatment should be initiated promptly, and should probably continue to the point of clinical resolution and beyond if there is still shedding of the virus.[7]

CASE STUDY

With all of this in mind, I would concur with hospitalization for the patient described above. His symptoms are of reasonably short duration, but as mentioned above, in patients receiving chemotherapy, steroids, and rituximab, the infection might be of longer duration than would have been predicted based upon the appearance of his symptoms. That stated, I would suggest a pulmonary-medicine consultation for bronchoscopy and lavage (to rule out concurrent bacterial or fungal infection). I would probably start the patient on oseltamivir and then consult with an infectious-disease specialist to determine whether a higher dose of this drug, combina-

tion antiviral drugs, or procurement of an intravenous agent (such as peramivir) would provide a better chance for successful outcome. High-level supportive care is likely to be essential. And, of course, the third cycle of R-CHOP will need to be delayed until there is complete resolution of infection. ■

References

1. Peck AJ, et al. Respiratory virus infection among hematopoietic cell transplant recipients: Evidence for asymptomatic parainfluenza virus infection. *Blood*. 2007;110:1681-1688.

2. Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: Risk factors, mortality, and the effect of antiviral therapy. *Clin Infect Dis*. 2004;39:1300-1306.

3. Chemaly RF, et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: A retrospective study at a major cancer center. *Medicine (Baltimore)*. 2006;85:278-287.

4. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: A review of infection frequency, morbidity, mortality, and vaccine responses. *Lancet Infect Dis*. 2009;9:493-504.

5. Redelman-Sidi G, et al. 2009 H1N1 influenza infection in cancer patients and hematopoietic stem cell transplant recipients. *J Infect*. 2010;60:257-263.

6. Hajjar LA, Mauad T, Galas FR, et al. Severe novel influenza A (H1N1) infection in cancer patients. *Ann Oncol*. 2010;21:2333-2341.

7. Casper C, Englund J, Boeckh M. How I treat influenza in patients with hematologic malignancies. *Blood*. 2010;115:1331-1342.

Cognition after Sepsis

ABSTRACT & COMMENTARY

By Joseph Safdieh, MD

Assistant Professor of Neurology,
Weill Medical College, Cornell University

Dr. Safdieh reports no financial relationships relevant to the field of study.

This article originally appeared in the December 2010 issue of Neurology Alert. *It was edited by Matthew E. Fink, MD, and peer reviewed by Alan Z. Segal, MD. Dr. Fink is Interim Chair and Neurologist in Chief, Department of Neurology and Neuroscience, Weill Cornell Medical College, New York Presbyterian Hospital, and Dr. Segal is Associate Professor of Clinical Neurology, Specialty Area. Drs. Fink and Beal report no financial relationships relevant to this field of study.*

Synopsis: *Episodes of severe sepsis in older adults is associated with worsening cognition and functional status.*

Source: Iwashyna TJ, et al. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010; 304:1787-94.

IT HAS BEEN SUSPECTED, BASED ON OBSERVATIONS AND SMALL case series, that after surviving an episode of severe sepsis, some patients develop a new, but not previously well defined, decline in their levels of cognitive and physical functions. In this large study, the investigators set out to answer whether there indeed is a worsening of cognitive function and functional ability after an episode of severe sepsis. The study data were derived from a large, prospectively collected database of U.S. residents from 1998-2006 called the Health and Retirement study; 9,223 subjects had baseline cognitive and functional assessment. Based on review of Medicare claims, 516 survived a hospitalization for severe sepsis and 4,517 survived hospitalization for another reason. All of the subjects had follow-up cognitive and functional assessments.

The investigators demonstrated that the prevalence of moderate to severe cognitive impairment increased by an absolute risk of 10.6% (OR, 3.34) in patients who survived hospitalization for sepsis. Without an episode of sepsis, hospital survivors had a 6.1% rate of moderate to severe cognitive impairment after discharge, which increased to 16.7% if there was an episode of severe sepsis. Non-sepsis-related hospitalizations were not associated with cognitive decline. Sepsis-related hospitalizations also significantly worsened functional ability, causing an average of 1.57 new functional limitations in activities of daily living in subjects who were previously at a normal functional baseline.

■ COMMENTARY

Neurologists and other physicians often notice that when older patients are discharged from the hospital after a critical illness, they are "not the same as before." This study rigorously confirms this observation. Not only do patients hospitalized for severe sepsis develop cognitive deterioration, but they also decline in multiple functional abilities. This study demonstrates these clinical observations by using a reliable, prospective database.

What is the actual impact of sepsis on patients and their families? The study demonstrates that severe sepsis causes a functional loss of an average of 1.57 components of activities of daily living, post-hospitalization. Lost functions include walking, dressing, bathing, eating, getting into and out of bed, toileting, preparing a hot meal, grocery shopping, making phone calls, taking medications, and managing money. Each of these 11 items is critically important for independent function, and the loss of 1-2 of them after hospitalization can be devastating for a patient and increases the cost of care and the burden on caregivers. A significant question raised, but not answered in this study is "What is the mechanism of the development of cognitive impairment and functional disability in severe sepsis?" Many factors may play a role, including generalized inflammation and injury from cytokines, metabolic dysfunction, hypotension, cerebral hypoperfusion, coagulation disorders and cerebral infarction, among others. Clearly, this study has identified a common and serious problem. The next step is to develop better therapies for patients with sepsis and to evaluate cognitive and functional outcomes, not just survival. ■

CME Questions

16. In the study by Bhatt, et al, what was the observed interaction between clopidogrel and omeprazole in patients with coronary artery disease?

a. Omeprazole reduced the effect of clopidogrel and led to more cardiovascular events.

b. Omeprazole reduced the risk of upper GI bleeding and did not increase the risk of cardiovascular events or other serious adverse effects of clopidogrel.

c. Clopidogrel reduced the effect of omeprazole leading to an increased risk of upper GI bleeding.

d. Omeprazole increased the risk of serious adverse effects in patients on clopidogrel compared to placebo.

17. According to the study by Bangalore and colleagues on patients with an acute coronary syndrome, cardiovascular events were lowest with blood pressures:

a. below 110/70, if tolerated.

b. above 150/90.

c. between 110/70 and 120/80.

d. between 130/80 and 140/90.

18. Based on the recent report by Jansen, et al, patients managed with an aggressive protocol to reduce serum lactate levels experienced which of the following outcomes?

a. No change in hospital mortality

b. Increased risk of pulmonary edema

c. Reduced risk-adjusted hospital mortality

d. Increased risk of acute kidney injury

Answers: 16. (b); 17. (d); 18. (c)

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. ■