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

Postoperative Complications in Patients with Obstructive Sleep Apnea

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips serves on the speakers bureaus for Cephalon, Resmed, and Respironics. This article originally appeared in the March 15, 2012, 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 Lilly, Boehringer Ingelheim, Novo Nordisk, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Lilly, Kowa, Novo Nordisk, and Teva. Dr. Roberts reports no financial relationship to this field of study.*

Synopsis: *More than half of patients undergoing non-cardiac surgery and polysomnography had obstructive sleep apnea, which was associated with an increased risk of perioperative complications, including hypoxemia, ICU transfer, and prolonged length of stay.*

Source: Kaw R, et al. Postoperative complications in patients with obstructive sleep apnea. *Chest* 2012;141:436-441.

The cohort for this analysis was assembled from nearly 40,000 patients who underwent preoperative assessment over a 5-year period. The investigators cross-referenced the electronic health record with the sleep laboratory database to identify patients who had noncardiac surgery within 3 years of having a sleep study. Demographic, clinical, diagnostic, and postoperative data were collected from outpatient electronic records, inpatient hospital admission records, and surgical procedure dictation records. Obstructive sleep apnea (OSA) was defined as an apnea plus hypopnea index (AHI) of

Volume 7 • Number 3 • May 2012 • Pages 17-24

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.

more than 5 events per hour of sleep. In patients with more than one procedure, morbidity data and postoperative outcomes were collected for the surgical procedure done closest to the date of the overnight sleep study.

The endpoints for this study were significant postoperative complications, including postoperative hypoxemia, respiratory failure, congestive heart failure, myocardial infarction (MI), atrial fibrillation, delirium, death within 30 days, and hospital length of stay (LOS). Postoperative hypoxemia was defined as oxygen desaturations with a < 90% or > 4% reduction from last recorded value, or by arterial blood gas postoperatively. Postoperative respiratory failure was defined as the need for mechanical ventilation longer than 24 hours, endotracheal reintubation, or tracheostomy. Postoperative congestive heart failure was defined as new pulmonary edema, jugular venous pressure > 10 mmHg, use of diuretic or afterload/preload reducing agents, or physician documentation. Postoperative MI was defined as the appearance of new Q waves > 0.04 sec wide and 1 mV in depth accompanied by elevated levels of troponin T (0.03 ng/mL) and creatine kinase-MB (> 100 IU/L).

A propensity score for the likelihood of sleep apnea for each patient was calculated using logistic regression. The propensity model used in this study included age, sex, race, BMI, use of general anesthesia, American Society of Anesthesiology class, and several comorbidities and their interactions as covariates. The model was statistically quite strong as a predictor of sleep apnea.

The final cohort for the analysis was 471 patients. Of these, 282 (59.8%) had OSA. Patients with OSA were older, (55.9 vs. 46.3 years), predominantly male (44.7% vs. 21.7%), and heavier (BMI 38.3 vs. 33 kg/m^2). They had a higher American Society of Anesthesiologists risk class, and many more medical comorbidities (i.e., COPD, hypertension, diabetes mellitus, coronary artery disease) than patients without OSA. Most of the surgeries were intermediate risk, with abdomino-pelvic and orthopedic procedures dominating. No differences existed between the types of anesthesia used in the two groups, and general anesthesia was more commonly used overall by far (> 80%). After adjustment for the propensity score, the presence of OSA was associated with a higher incidence of overall complications (odds ratio [OR], 6.9; $P = 0.003$), postoperative hypoxemia (OR, 7.9; $P = 0.009$), ICU transfer (OR, 4.43; $P = 0.069$), and longer LOS (OR, 1.65; $P = 0.049$). Severity of OSA measured by the AHI was not associated with postoperative complications. The median LOS was 2 days in the OSA group and 1 day in the control group.

■ Commentary

The two take-home messages from this study are that sleep apnea is very common in perioperative patients and that it is associated with an increased risk of complications, notably increased LOS, ICU transfer, and hypoxemia.

This study is important because it is the largest study to date to determine the prevalence of polysomnographically determined OSA in the general surgical population. Although several previous reports have reported that OSA is a risk factor for increased postoperative morbidity and mortality,[1-4] most have based the diagnosis of OSA on screening questionnaires. A confounder in previous reports has likely been the presence of undiagnosed and unrecognized sleep apnea in the "control group." Because all of the patients in this analysis had sleep studies, those patients who were characterized as not having sleep apnea in this report probably did not. (On the other hand, this cohort was likely "enriched" by sleep apneics, because sleep studies were ordered on the basis of clinical suspicion). A further strength of the current study is that the authors used a propensity score that controlled for factors associated with OSA, including BMI.

Because the prevalence of obesity is increasing in this country, the prevalence of OSA is increasing as well. Between 1990 and 1998, there was a 12-fold increase in the diagnosis of OSA in surgical outpatients.[5] The American Society of Anesthesiologists has published clinical guidelines for the perioperative management of OSA,[2] but these are mostly based on consensus and are not widely used. Further, they are focused on the patients' care while in the facility.

Where to go from here? Awareness is an important first step. Patients who are obese, sleepy, hypertensive, have

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.

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.

witnessed apneas, or big necks are at high risk for sleep apnea. The American Society of Anesthesiologists recommends longer postoperative monitoring in OSA patients after ambulatory surgery and 7 hours of monitoring after the last episode of airway obstruction or hypoxemia while breathing room air in an unstimulated environment prior to discharge from the facility.[2] And our colleagues in anesthesiology will likely make sure that this happens. But what happens after discharge? In a recent study, Liao et al reported a higher AHI and oxygen desaturation index among OSA patients on the third postoperative night compared with preoperatively or on the first postoperative night.[6] This is very likely due to the use of respiratory depressants, especially opioids[7] and/or Rapid-Eye Movement sleep rebound.[6] Options here are to delay discharge, increase at-home monitoring, or reduce respiratory depressant use. None of these choices is particularly attractive, but neither are postoperative complications. ■

r eferences

1. Sharma VK, et al. *Ann Intern Med* 2003;139:707-708.
2. Gross JB, et al. *Anesthesiology* 2006;104:1081-1093.
3. Hwang D, et al. *Chest* 2008; 133:1128-1134.
4. Memtsoudis S, et al. *Anesth Analg* 2011;112:113-121.
5. Namen AM, et al. *Chest* 2002;121:1741-1747.
6. Liao P, et al. *Sleep* 2009;A223:0684.
7. Rosenberg J, et al. *Anaesthesia* 1999;54:323-328.

Myocardial Infarction Symptom Presentation

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

Source: Canto JG, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA* 2012;307:813-822.

Timely recognition and treatment of myocardial infarction (MI) are crucial if we are to achieve optimal outcomes for our patients. Silent ischemia, or the absence of classical symptoms of ischemia, may delay the diagnosis. In patients presenting with MI, delay in diagnosis and treatment may have disastrous outcomes. Accordingly, Canto and colleagues analyzed data from the National Registry of MI (NRMI) to assess the frequency with which men and women were admitted for MI without chest pain and the effect that presenting without chest pain has on mortality.

The investigators studied more than 1.1 million patients (42% women) presenting with MI, both ST elevation MI (STEMI) and non-ST elevation MI (non-STEMI) from 1994-2006. The in-hospital mortality rate was 14.6% for women and 10.3% for men ($P < 0.001$). The proportion of MI patients who presented without chest pain was an alarming 35%. Women presenting with MI were more likely than men to present without chest pain (42% vs. 31%; $P < 0.001$). In addition, advancing age was associated with higher rates of MI without chest pain, but interestingly the gender differences actually became less pronounced with age. Patients presenting without chest pain were more likely to have diabetes, to have delayed presentation, to present with non-STEMI, and to present in Killip class III or IV, whereas those with chest pain were more likely to present with anterior MI and STEMI. Patients without chest pain were less likely to receive aspirin, beta-blockers, antithrombins, antiplatelet agents, or reperfusion therapy. Furthermore, when they did receive the appropriate treatments, those who presented without chest pain experienced significant delays.

After statistical adjustment for clinical characteristics, comorbidities, treatments received, and delays, younger men and women who suffer MI without chest pain were more than twice as likely to die from their MI than those who had chest pain. However, with advancing age this difference was attenuated, and at age ≥ 75 years men were 32% more likely to die and women were 8% more likely to die than their counterparts with chest pain. The authors conclude that in patients hospitalized with MI, women were more likely than men to present without chest pain and had higher mortality than men within the same age group, but sex differences in clinical presentation without chest pain and in mortality were attenuated with increasing age.

■ Commentary

I am struck by the significant rate of MI without chest pain (35%) in this study. Although this was higher in women (42% vs. 31%), the rate of MI without chest pain is still alarmingly high in both sexes and we should have a high index of suspicion for acute MI in patients with atypical presentations. One may intuitively think that non-STEMI were more likely to present without chest pain than STEMI. This is true in the current study, but interestingly more than one-third of all STEMI also presented without chest pain. Delays in treatment were seen in patients without chest pain, and

this could lead to serious outcomes in MI patients. This was demonstrated by the higher mortality in those without chest pain in this study. Interestingly, the difference between genders became less apparent with age, but the total proportion of patients presenting with MI without chest pain increased. The reasons for this remain unknown.

The major limitation of this study is that it is a retrospective analysis of registry data. The participating hospitals may not have collected data equally, and the hospitals participating in the NRMI registry may not serve populations that are truly representative of all regions throughout the United States. However, this is an incredibly large study — involving more than a million patients — which strengthens the conclusions made. We should continue to be vigilant for atypical presentations of MI, particularly in women and older patients. Hopefully, increased awareness of painless MI presentation may hasten diagnosis and avoid treatment delays for our patients. ■

Appropriate Dosage of Vancomycin in End-Stage Renal Disease Patients Requiring Intermittent Hemodialysis

ABSTRACT & COMMENTARY

By Kevin Singh; Sherman Lau, Pharm.D., Jessica C. Song, M.A., Pharm.D.

Jessica C. Song, M.A., Pharm.D, Clinical Supervisor of Pharmacy and Therapeutics, Ambulatory Care, and Mental Health at Santa Clara Valley Medical Center, San Jose, CA, is Associate Editor for Infectious Disease Alert.

Kevin Singh, Sherman Lau and Jessica C. Song report no financial relationships relevant to this field of study.

This article originally appeared in the April 2012 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, FIDSA, and peer reviewed by Timothy Jenkins, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University, and Dr. Jenkins is Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Deresinski does research for the National Institutes of Health, and is an advisory board member and consultant for Merck, and Dr. Jenkins reports no financial relationships relevant to this field of study.*

Infection is the second leading cause of death in hemodialysis patients, with mortality rates ranging from 12-36% in this vulnerable population.[1] Vascular-access related septicemia accounts for approximately 75% of deaths associated with infections, with *Staphylococcus aureus* causing up to 39% of all bacteremias.[1] Moreover, hemodialysis patients have a 100-fold greater risk for experiencing invasive methicillin-resistant *S. aureus* (MRSA) infections than the general population.[1]

At present, the current standard of practice is to use vancomycin, a bactericidal glycopeptide antibiotic for the treatment of hemodialysis patients with catheter-related bloodstream infections caused by MRSA.[1] Vancomycin has a complex pharmacokinetic profile in end-stage renal disease (ESRD) patients requiring intermittent hemodialysis. This agent undergoes three phases of elimination during intermittent hemodialysis: (1) a rapid extraction phase during the intradialytic phase (serum extraction rate of 30-46% with high-flux membranes); (2) administration and redistribution (lasts ~2 hours); and (3) prolonged, linear clearance during the interdialytic interval.[2] Since the half life of vancomycin in anuric patients may range from 100 to 200 hours, a very gradual reduction in concentrations occur during the interdialytic interval (typically 44-68 hours).

A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists recommended a target of a 24-hour area under the concentration curve over the minimal inhibitory concentration (AUC/MIC) of at least 400 in order to achieve clinical success in patients infected by staphylococcal species.[3] However, since multiple vancomycin levels must be drawn from patients in order to calculate AUC/MIC's, a more practical monitoring tool would be to check vancomycin trough levels, given the positive correlation between drug exposure yielded by both parameters. There has been a steady rise in the fraction of *S. aureus* strains with an MIC between 1 and 2 mg/L over the past decade. An estimated 16.2% of *S. aureus* strains in the United States exhibited MICs between 1 and 2 mg/L in 2005.[4] In addition, the emergence of vancomycin-intermediary and vancomycin resistant strains of *S. aureus* has further increased the risk of treatment failure in patients requiring vancomycin therapy.

These changing patterns in epidemiology and susceptibility to vancomycin in *S. aureus* have resulted in substantial changes in the dosing guidelines for this drug, with suggested target trough levels of 15 to 20 mg/L in patients with complicated infections caused by *S. aureus*.[3] To date, underdosing appears to be the main problem in the majority of patients undergoing dialysis.[4] The purpose of this review is to discuss newer clinical prescribing practices regarding vancomycin in patients requiring intermittent hemodialysis.

Vancomycin Dosing

To date, earlier studies of vancomycin dosing in patients undergoing intermittent hemodialysis used inappropriate ther-

apeutic ranges, thereby providing limited guidance for contemporary clinical practice.[5-7] Two investigators studied similar algorithms using a weight-based loading dose of 20 mg/kg (dry body weight), followed by fixed doses of 500 mg (timed with each dialysis session).[5,6] The only difference between the regimens involved the timing of administering vancomycin; one investigator gave the loading and maintenance doses after dialysis,[5] whereas the other investigator had patients receive vancomycin during the final hour of dialysis.[6] Twenty-eight percent of patients who received vancomycin post-dialysis achieved troughs of 15-20 mg/L and 12% of patients achieved similar levels when they received vancomycin during the last hour of dialysis. Pai and associates used a 1000 mg loading dose, with the following maintenance doses: (1) 1000 mg if trough levels fell below 8 mg/L; (2) 500 mg if trough levels ranged from 9 to 15.9 mg/L; and (3) no supplemental dose with trough levels of 16 mg/L and higher. Approximately 20% of patients achieved trough levels of 15.1-20 mg/L.[7]

Taylor et al. recently reported on the outcomes of using their vancomycin dosing protocol in 34 hospitalized hemodialysis patients (weight range, 50-118 kg).[8] Patients received a 20 mg/kg (actual body weight, dose in multiples of 250 mg) loading dose scheduled to end with the dialysis session. Patients received maintenance doses of 1000 mg during the last hour of subsequent dialysis sessions and trough vancomycin concentrations were measured immediately prior to the fourth dialysis session. Thirty-five percent of patients achieved trough vancomycin concentrations between 15 to 20 mg/L and 15% of patients displayed trough concentrations in excess of 25 mg/L. Only 6% of patients had trough concentrations below 10 mg/L.

Vandecasteele and associates proposed the following dosing guidelines for hemodialysis patients requiring vancomcyin therapy: (1) administer a loading dose of 20-25 mg/kg using actual dry body weight (dose not to exceed 4 grams); (2) infuse vancomycin at a rate of 15 mg/minute such that the infusion ends with the dialysis session; (3) check trough concentrations before each dialysis session; (4) aim for a target trough concentration of 15 to 20 mg/L; and (5) maintenance doses should be based on trough levels, interdialytic elapse, residual renal function, and body weight.[1]

Recently, a novel approach for dosing vancomycin in patients undergoing intermittent hemodialysis was highlighted in a report by Vandecasteele et al.[2] A vancomycin dose calculator was developed and assessed for its accuracy in achieving trough concentrations of 15-20 mg/L in 18 patients requiring intermittent hemodialysis. This multivariate model showed that predialysis vancomycin trough concentration, dry body weight, and interdialytic elapse accounted for nearly 95% of the variance observed. Patients received a fixed loading dose infusion of 20 mg/kg timed to end with the dialysis session. The median vancomycin maintenance dose was 8.05 mg/kg (given during subsequent dialysis sessions); approximately 78% of patients achieved trough target concentrations ranging from 15 to 20 mg/L.

r e SISt a n Ce , We IGHt -Ba Se D Do SIn G

Since vancomycin is frequently used in patients undergoing intermittent hemodialysis, healthcare professionals need to monitor trough concentrations of this agent in order to prevent the occurrence of adverse events and sub-therapeutic levels. The emergence of resistance to vancomycin has resulted in a new emphasis on achieving target trough concentrations of 15-20 mg/L in patients with complicated infections caused by *S. aureus*.

Given the poor success rate of achieving trough concentrations of 15-20 mg/L with the use of fixed dosing regimens (1000 mg loading dose, followed by supplemental doses of 500 or 1000 mg), it would be prudent to use weight-based dosing regimens of vancomycin in patients undergoing intermittent hemodialysis. Areas of uncertainty in the dosing of vancomycin in this special population include selection of appropriate doses based on interdialytic elapse and the patients' residual renal function.[2,9] Some experts in the fields of nephrology and infectious disease have proposed using loading doses of 15 mg/kg, 25 mg/kg, and 35 mg/kg, respectively, for 1-day, 2-day, and 3-day interdialytic elapses.[2] Future studies are needed to determine optimal maintenance doses of vancomycin, since patient-specific factors such as weight and the extent of residual renal function may influence dosing.[9] ■

r eferences

1. Vandecasteele SJ, et al. Vancomycin dosing in patients on intermittent hemodialysis. *Semin Dial* 2011; 24: 50-5.
2. Vandecasteele SJ, et al. Implementation of a dose calculator for vancomycin to achieve target trough levels of 15-20 µg/mL in persons undergoing hemodialysis. *Clin Infect Dis* 2011; 53: 124-9.
3. Rybak M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health-Syst Pharm* 2009; 66: 82-98.
4. Vandecasteele SJ, et al. Recent changes in vancomycin use in renal failure. *Kidney Int* 2010; 77: 760-4.
5. Barth RH, et al. Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy. *Kidney Int* 1996; 50: 929-36.
6. Ariano RE, et al. Adequacy of a vancomycin dosing regimen in patients receiving high-flux hemodialysis. *Am J Kidney Dis* 2005; 46: 681-7.
7. Pai AB, et al. Vancomycin dosing in high flux hemodialysis: a limited sampling algorithm. *Am J Health Syst Pharm* 2004; 61: 1812-6.
8. Taylor ME, et al. Practical vancomycin dosing in hemodialysis patients in the era of emerging vancomycin resistance: a single-center experience. *Am J Kidney Dis* 2010; 55: 1163-5.
9. Pallotta KE, et al. Vancomycin use in patients requiring hemodialysis: a literature review. *Semin Dial* 2008; 21: 63-70.

Neuroprognostication in Patients Receiving Therapeutic Hypothermia Following Cardiac Arrest

ABSTRACT & COMMENTARY

By David J. Pierson, MD

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

This article originally appeared in the April 2012 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: *Although current guidelines recommend delaying neuroprognostication during therapeutic hypothermia following resuscitation from cardiac arrest, this review of 55 consecutive patients so managed found that a "poor prognosis" designation was arrived at during the hypothermia period in most of them, including six patients who were eventually discharged with a favorable neurologic outlook.*

Source: Perman SM, et al. Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia. *Crit Care Med* 2012;40:719-724.

Therapeutic hypothermia (TH) has been widely adopted as a management strategy for patients who remain comatose after return of spontaneous circulation following cardiac arrest, as the only therapeutic intervention shown to favorably influence neurologic outcomes. Because sedation and paralysis are used, and because hypothermia itself depresses neurologic function, current guidelines recommend deferring neuroprognostication until the TH period is completed. In this retrospective review of patients managed with post-cardiac arrest TH in the medical and cardiac ICUs of two University of Pennsylvania hospitals, the authors sought to determine when neuroprognostication took place, how it was done, and what the patient outcomes were.

During the 3.5-year period covered by the study, TH was carried out by means of a protocol. Adult patients who had return of spontaneous circulation following cardiopulmonary resuscitation after primary cardiac arrest and whose Glasgow Coma Scale scores were less than 6 were included, so long as they did not have do-not-resuscitate status or another specific contraindication. Hypothermia (32-34° C) was induced using cold intravenous saline and external cooling body wraps, and was maintained for 24 hours once the target temperature was attained. Active rewarming at 0.25-0.50° C/h was then undertaken. Sedating and paralyzing agents were used throughout the TH period, the latter being discontinued once normothermia was reached. For this study, the "intra-TH" period was defined as extending from resuscitation through 15 hours following attainment of normothermia. Patients who survived to discharge were designated according to cerebral performance category as good (full function), moderate cerebral disability (disabled but independent), severe cerebral disability (conscious but disabled and dependent), coma/vegetative state (unconscious), or dead or brain dead.

Of 55 patients who initially met entry criteria and whose charts were reviewed, six were excluded for various a priori reasons, leaving 49 patients (59% male, mean age 56 years). Of these, 28/49 (57%) had documentation of an "intra-TH" poor prognosis in the chart. Documentation occurred prior to achievement of target hypothermia in five patients, during the 24-hour hypothermia period in eight, during rewarming in five, and within the first 15 hours after rewarming in 10. Of the 28 patients assigned a poor prognosis during the TH protocol, 18 (64%) were still receiving sedation and paralytic drugs at the time. Neurology consultation was obtained in 21 of the 28 "poor prognosis" patients, 24 of whom also underwent head computed tomography. Most of the "poor prognosis" designations were assigned by the primary managing team, while the neurology consultant advised waiting until post-TH for prognostication in 43% of instances. Most of the patients assigned an "intra-TH" poor prognosis had a do-not-resuscitate order signed within 48 hours thereafter. Of the 28 patients given an "intra-TH" poor prognosis, 20 (71%) did not survive to discharge, while six (21%) of them were eventually discharged with a cerebral performance score of "good."

■ Commentary

This study found that, in the authors' institution, patients managed with post-arrest TH were often assigned a poor prognosis before completion of the TH regimen, which included sedation and muscle relaxation as part of the protocol. The timing and mechanism of prognostication varied greatly. As the authors point out, further research is clearly needed to determine how best to evaluate the neurological prognosis in patients treated with TH.

In addition to anoxic brain injury, which is the primary target for neurologic assessment following cardiac arrest, sedatives, and paralytics, the effects of hypothermia on their metabolism and clearance, and the hypothermia itself may all contribute to assignment of an inappropriately poor prognosis. The fact that several patients who were discharged in good neurologic condition were initially assigned a poor prognosis prior to completion of the TH protocol emphasizes the importance of not concluding too hastily that the patient has little or no chance of meaningful recovery in the context of TH and its associated interventions. ■

Respiratory Arrest: An Adverse Effect of Polymyxins

ABSTRACT & COMMENTARY

By David J. Pierson, MD

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

This article originally appeared in the April 2012 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: *Two ICU patients experienced respiratory arrest while receiving polymyxin. Given the recent resurgence of use of this antibiotic and its close relative colistin to treat gram-negative infections resistant to newer agents, clinicians should be aware of this infrequent but long-known and potentially fatal adverse effect.*

Source: Wunsch H, et al. Polymyxin use associated with respiratory arrest. *Chest* 2012;141:515-517.

Wunsch and associates describe two patients who suffered respiratory arrest requiring intubation and mechanical ventilation while receiving polymyxin B. The first was a liver-transplant patient with normal renal and respiratory function who developed bacteremia due to *Klebsiella pneumoniae* that was resistant to carbapenem but sensitive to polymyxin B. One hour after the first intravenous dose of polymyxin B was started, the patient was found unresponsive and apneic. After intubation, he had normal sensorium and respiratory mechanics. The second patient had a polymicrobial perinephric abscess following renal transplantation, and developed respiratory distress and acute respiratory acidosis, followed by apnea, shortly after the start of his fourth intravenous infusion of polymyxin B. This patient subsequently reported having been unable to breathe or move his arms at the time of the incident. Re-challenge with a polymyxin B infusion in this patient, considered indicated in the setting of recurrent, resistant infection 2 weeks later, was again followed by respiratory arrest 2 hours after the infusion was begun. Both patients recovered from these episodes promptly and completely after intubation, and the authors were unable to identify other potential causes for the sudden respiratory arrests.

■ Commentary

Polymyxin B and polymyxin E — also known as colistin — are bactericidal polypeptide antibiotics introduced in the late 1940s and formerly widely used in treating gram-negative infections. The drugs have prominent renal and neurological toxicity, however, and with the introduction of gentamycin and other aminoglycosides in the 1960s, their use declined. Over the next 3 decades, the polymyxins were rarely used as other antibiotics effective in treating gram-negative infections became available. However, with the emergence of organisms resistant to newer antimicrobials over the last 10 years, polymyxin B and colistin have seen increasing use, particularly in critically ill patients. In reporting their cases, Wunsch et al also document a steady increase in the use of polymyxin B in their institution since 2000, a 10-fold increase from about one per 1000 hospital admissions to one in 100. The experience at many institutions appears to be similar, particularly referral centers managing immunocompromised patients and individuals with infections due to multidrug-resistant organisms. In addition to intravenous administration, polymyxin B and colistin are increasingly being aerosolized in the treatment of ventilator-associated pneumonia and other serious respiratory infections.

As mentioned, the polymyxins have prominent neurological side effects. These include dizziness, paresthesias, visual disturbances, hearing loss, and neuromuscular blockade, presenting as an acute myasthenia-like syndrome.[1] The latter can cause acute ventilatory failure and respiratory arrest. In what may be the largest reported series of this complication, Lindesmith et al described 11 patients who developed reversible respiratory paralysis after receiving colistin (9 patients) or polymyxin B (2 patients) during the mid-1960s.[2] The drugs had been administered in usual doses, in all but one instance intramuscularly, and respiratory arrest had occurred at widely varying times. Four patients experienced respiratory paralysis 1 to 8 hours after the initial dose, but others had received up to 29 previous doses and the muscle weakness developed at varying periods after a dose. Nearly all of the patients were weaned and extubated within 1-2 days after the event. All 11 of these patients, as well as most of the other reported cases, had underlying renal disease.

This is the first report in decades of neuromuscular blockade from polymyxins causing respiratory arrest. However, the long interval since the last reported cases may well be because of the markedly decreased use of these drugs from the 1970s through the 1990s. With increasing current use of these antibiotics in multiple-drug-resistant infections, however, clinicians should be aware of this potentially life-threatening adverse effect. Whether neuromuscular blockade can also occur with aerosol administration is uncertain but entirely reasonable, particularly in the presence of underlying renal disease. This complication could be difficult to detect in patients already on mechanical ventilation and receiving polymyxin B or colistin for ventilator-associated pneumonia, but it is at least a theoretical cause for inability to wean in such patients. ■

r eferences

1. Falagas ME, Kasiakou SK. Toxicity of polymyxins: A systematic review of the evidence from old and recent studies. *Crit Care* 2006; 10(1):R27.
2. Lindesmith LA, et al. Reversible respiratory paralysis associated with polymyxin therapy. *Ann Intern Med* 1968;68:318-327.

CME / Objectives

Upon completion of this educational activity, participants should be able to:

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems. ■

CME Questions

1. In the study by Kaw and colleagues, patients diagnosed with obstructive sleep apnea (OSA) and undergoing noncardiac surgery were at significantly increased risk for all of the following except:

a. Overall postoperative complications

b. Postoperative hypoxemia

c. Transfer to the ICU

d. Postoperative myocardial infarction

e. Longer length of stay

2. In a recent study by Canto, et al., the following observations were made about patients with myocardial infarction presenting without chest pain:

a. Women were more likely than men to present without chest pain

b. Patients presenting without chest pain were at a higher risk of mortality

c. Patients presenting without chest pain were less likely to receive antiplatelet agents

d. Patients presenting without chest pain were less likely to receive reperfusion therapy

e. All of the above

3. In patients managed with therapeutic hypothermia after cardiac arrest, which of the following is true regarding the ability to prognosticate about neurologic recovery?

a. It is no different from prognostication in patients managed without therapeutic hypothermia.

b. The metabolism and clearance of sedatives and paralytics is unaffected by therapeutic hypothermia.

c. Some patients are inappropriately assigned a poor prognosis before completion of therapeutic hypothermia.

d. The best process to perform neuroprognostication in patients treated with therapeutic hypothermia is currently known.

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. ■