CRITICAL CARE ALERT®

A monthly update of developments in critical care and intensive care medicine

AHC Media LLC Home Page— www.ahcmedia.com

CME for Physicians— www.cmeweb.com; CE for Nurses— www.ceweb.com

AHC Media LLC

INSIDE

Financial Disclosure: *Critical Care Alert*'s editor, David J. Pierson, MD, nurse planner Leslie A. Hoffman, PhD, RN, and peer reviewer William Thompson, MD, report no financial relationships to

Does ECMO Save Lives in Severe ARDS?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In a selected population of younger patients early in the course of severe acute respiratory failure, referral to a specialized center for extracorporeal membrane oxygenation did not improve survival but was associated with better 6-month outcomes when severe disability in patients with complete follow-up was included.*

Source: Peek GJ, et al. Efficacy and economic assessment of conventional ventilator support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. *Lancet* 2009 Sep 15; Epub ahead of print.

PEEK AND COLLEAGUES HAVE RECENTLY PUBLISHED THE LONG-awaited and much-discussed results of the CESAR trial (Conventional ventilatory support vs Extracorporeal membrane oxygenation [ECMO] for Severe Adult Respiratory failure), a British study that has been underway for nearly a decade. The investigators compared venovenous ECMO, in combination with "gentle ventilation" and several other protocol elements, to conventional management in patients with severe acute respiratory failure, primarily looking at mortality and severe disability in survivors but also examining a number of secondary outcomes including cost and quality of life.

The study enrolled patients over a 5-year period from 2001 through 2006, screening patients from hospitals throughout the United Kingdom. Patients meeting entry criteria were randomized to transfer to a single ECMO center (Glenfield Hospital, Leicester) vs continued management at the original hospital, or transfer to a referral center if appropriate. Patients randomized to the conventional management group were managed at the discretion of their physicians, although the use of lung-protective ventilation according to the ARDS Network protocol[1] was encouraged. Entry criteria were age 18-65, "potentially reversible acute respiratory failure," and either a Murray lung injury score[2] *(see Table, page 59)* of 3 or

VOLUME 17 • NUMBER 8 • NOVEMBER 2009 • PAGES 57-64

higher, or refractory respiratory acidosis with an arterial pH < 7.20. Patients were excluded if they had a contraindication to anticoagulation (required for ECMO) or if they had been on mechanical ventilation for more than 7 days with inspiratory pressure > 30 cm H_2O and/or FIO_2 > 0.80.

After arrival at the ECMO center, patients randomized to that treatment group who were hemodynamically stable were managed on pressure-control ventilation with plateau pressure limited to 30 cm H_2O, positive end-expiratory pressure (PEEP) titrated to "optimum saturation," maintenance of hematocrit at 40% or higher, and prone positioning if deemed necessary. If the patient did not respond to this protocol within 12 hours, and required FIO_2 > 0.90 to maintain SaO_2 > 90%, had respiratory or metabolic acidosis with pH < 7.20, or was hemodynamically unstable, cannulation was carried out and ECMO initiated.

A total of 766 potentially eligible patients from 148 centers were evaluated, of whom 180 from 68 centers were enrolled and randomized (90 to ECMO and 90 to conventional management). There were no significant differences between the groups at entry. The patients were young (mean age, 40 years). Respiratory failure was due to pneumonia in 60%, other acute respiratory distress syndrome (ARDS) in 28%, and trauma in 7%. Seventy percent of the patients had 1 or 2 organs failing, while 30% had 3 or more. The median duration of mechanical ventilation prior to study entry was 36 hours, and the median time from study entry to treatment in the ECMO group was 6 hours. Ninety-five percent of all patients qualified by Murray lung injury score (mean PaO_2/FIO_2 76 mm Hg, PEEP 14 cm H_2O, static compliance 27 mL/cm H_2O), with only 5% meeting entry criteria because of acidosis.

Of the 90 patients randomized to transfer to the ECMO center, 5 died prior to or during transport, and 16 improved with the center's conventional management protocol, so that only 68 patients (76%) were put on ECMO. Besides ECMO, other differences in management in the 2 study groups included more use of lung-protective ventilation in the ECMO group (only 70% of the conventional management patients ever received a tidal volume of 8 mL/kg or less vs 93% of the ECMO patients; $P < 0.0001$), and more frequent administration of corticosteroids in the ECMO patients (83% vs 64%; $P = 0.001$). About 80% of the patients in both groups received continuous venovenous hemofiltration. In the ECMO and conventional management groups, there were no differences in the use of prone positioning (36% vs 42%, respectively), high-frequency ventilation (7% vs 14%), or inhaled nitric oxide (10% vs 7%) for severe hypoxemia. Molecular albumin recirculation, a therapy for liver dysfunction, was used in 17% of the ECMO patients but in none of the patients in the conventional management group.

There was a trend toward lower mortality in the ECMO group as compared to the control group (33 vs 44 deaths), although the difference was not statistically significant ($P = 0.07$). When both death and severe disability at 6 months were lumped together, the difference (37% vs 53%) was significantly different ($P = 0.03$) in favor of the patients randomized to be transferred to the ECMO center. A higher proportion of deaths were classified as being due to respiratory failure in the control group (60%) than in the ECMO group (24%). Patients in the ECMO group had longer stays in the ICU (24 vs 13 days) and in the hospital (35 vs 17 days) than patients in the conventional management group, respectively.

With respect to cost and quality of life in survivors, referral to consideration for treatment by ECMO was associated with a gain of 0.03 quality-adjusted life-years (QALYs) at 6-month follow-up. A lifetime model predicted the cost per QALY of ECMO to be $31,112 (95% confidence interval, $12,317-$95,507) in 2005 dollars. Concluding, the authors "recommend transferring of adult patients with severe but potentially

Critical Care Alert, ISSN 1067-9502, is published monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER: Coles McKagen

DIRECTOR OF MARKETING: Schandale Kornegay

SENIOR MANAGING EDITOR: Paula Cousins

GST Registration Number: R128870672.

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

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

Back issues: $40.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issues date.

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail Address: customerservice@ahcmedia.com

Editorial E-Mail Address: paula.cousins@ahcmedia.com

World Wide Web: http://www.ahcmedia.com

Subscription Prices

United States

1 year *with* free AMA Category 1 credits: $319

Add $17.95 for shipping & handling.

(Student/Resident rate: $120)

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 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 25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

AHC Media LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 13.3 nursing contact hours using a 60-minute contact hour.

Provider approved by the California Board of Registered Nursing, Provider # 14749, for 13.3 Contact Hours.

This educational activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of publication.

AHC Media LLC

Questions & Comments

Please call **Paula Cousins,** Senior Managing Editor, at (404) 262-5468.

Table

Murray lung injury score[2]

Total Points from 4 Components:

- **Chest radiograph**
  1 point for each quadrant with infiltrate
- **PaO_2/FIO_2 (mm Hg)**
  ≥ 300 = 0
  299-225 = 1
  224-175 = 2
  174-100 = 3
  < 100 = 4
- **PEEP (cm H_2O)**
  ≤ 5 = 0
  6-8 = 1
  9-11 = 2
  12-14 = 3
  > 15 = 4
- **Static compliance (mL/cm H_2O)**
  ≥ 80 = 0
  79-60 = 1
  59-40 = 2
  39-20 = 3
  < 20 = 4

reversible respiratory failure, whose Murray score exceeds 3.0 or who have a pH of less than 7.20 on optimum conventional management, to a centre with an ECMO-based management protocol to significantly improve survival without severe disability."

■ COMMENTARY

Two previous multicenter randomized controlled trials have evaluated ECMO in the management of severe ARDS. In the 1970s, a study of 90 adult patients with very severe respiratory failure, carried out in 9 medical centers, randomized 42 patients to mechanical ventilation supplemented with partial venoarterial bypass and 48 to conventional mechanical ventilation.[3] Only 4 patients in each group survived. Fifteen years later, a second, smaller trial was carried out, in patients similar to those in the initial study but with all study patients transferred to a single institution for uniform management.[4] This time ventilator management consisted of pressure-controlled inverse ratio ventilation, adjusted by a comprehensive protocol for mechanical ventilation and other interventions, with and without extracorporeal CO_2 removal. Survival in the 21 ECMO patients (33%) was substantially higher than predicted on the basis of other studies, but statistically indistinguishable from that in the 19 non-ECMO patients (42%; $P = 0.8$).

Since the 1970s trial, ECMO has become standard of care for severe neonatal respiratory failure, and has continued to have strong advocates for the management of adults. According to the CESAR investigators, this new, third trial was needed despite the 2 previous studies showing no survival benefit from ECMO, because "neither of these studies has relevance to modern ECMO because the case selection, ventilation strategies, extracorporeal circuit design, and disease management were completely different from modern protocols."

Although it is the largest study conducted so far, the CESAR trial is unlikely to settle the controversy over whether ECMO belongs in the armamentarium for treating severe acute respiratory failure. As pointed out in the accompanying editorial,[5] the new trial's results can be spun in different ways. In their article, the authors present them as positive, emphasizing that the combined outcome of survival and the absence of severe disability was significantly better in the ECMO-referred patients than in those who remained in the community setting for management. They also point out that, according to the statistical methods employed, referral to ECMO is likely to be cost-effective, at least in the British health care system.

The findings can also be presented differently. No significant difference in survival was observed, and it was only when severe disability was added (known to have been present in only 1 of the 180 randomized patients), and the denominator in the conventional management group was adjusted (omitting the 3 patients lost to follow-up), that the primary outcome was significantly better in the ECMO-randomized group. A skeptic might also point out that less than one-quarter of all patients with acute respiratory failure who were referred by their physicians for possible inclusion were accepted into the study; that patients referred for ECMO, whether they received it or not, were managed quite differently than those who remained at their referring institutions, and that these differences might also have contributed to better outcomes.

For example, more ECMO-randomized patients received lung-protective ventilation, the only management approach so far proven to substantially improve outcomes in acute lung injury.[1] Other studies of critically ill patients have also demonstrated that high-volume centers, using more standardized, more guideline-congruent management, have better outcomes; as noted by the authors, some of the CESAR-referring centers manage many fewer cases of ARDS than does the ECMO center. And while referral to the ECMO center was found to be cost-effective for the British health care

system, this might not translate to the American setting, and the analysis did not include the cost involved in setting up and staffing an ECMO program for an institution not presently offering this modality.

What should the clinician make of this study? It clearly does not pertain to the majority of patients with acute respiratory failure, or even to most patients with acute lung injury or ARDS, who can be managed fine with accepted, evidence-based standard care. Nonetheless, there are some patients with acute hypoxemic respiratory failure whose hypoxemia cannot be corrected sufficiently with standard ventilator adjustments — although what "sufficiently" means in this context is highly clinician-specific and open to much debate. In such cases, after correcting any abnormalities in hemoglobin concentration and cardiac function, the options usually considered are: 1) switching to a different ventilator mode, such as from volume assist-control to pressure control or airway pressure-release ventilation; 2) using higher levels of PEEP, with or without pulmonary artery catheter guidance, colloids, and/or vasopressor support; 3) high-frequency oscillatory ventilation; 4) prone positioning; 5) inhaled nitric oxide; 6) an alternative inhaled vasodilator such as prostacyclin; and/or 7) ECMO. The last, ECMO, is not an option for the great majority of intensivists, simply because it is not available locally. Should it be?

I take the following bottom-line messages from this study: 1) We are still not implementing lung-protective ventilation as often or as effectively as we should be; 2) Patients deemed at very high mortality risk on the basis of earlier studies are more likely to survive today than in the past; and 3) Applied routinely in patients with moderately severe hypoxemic respiratory failure, ECMO does not have a dramatic effect on survival. I have never used ECMO, never having worked in a center that did it. Given that limitation, and acknowledging the possibility that ECMO might save some patients who would otherwise die of hypoxemia, it is hard to muster a lot of enthusiasm for setting up ECMO programs in centers that do not now offer it on the basis of the CESAR trial. ■

References

1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-1308.
2. Murray JF, et al. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988;138:720-723.
3. Zapol W, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized *prospective study. JAMA* 1979;242:2193-2196.
4. Morris AH, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care* 1994;149:295-305.
5. Zwischenberger JB, Lynch JE. Will CESAR answer the adult ECMO debate? *Lancet* 2009 Sep 15; Epub ahead of print.

Does the Risk Associated With Hyperglycemia Occur Across All Patient Groups?

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

Pulmonary and Critical Care Medicine, University of Washington, Seattle

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

Synopsis: *This retrospective cohort study reaffirms the link between hyperglycemia and mortality in the ICU, but demonstrates that the risk does not apply equally to all patient groups and, instead, varies based on admission diagnosis.*

Source: Falciglia M, et al. Hyperglycemia-related mortality in critically ill patients varies by admission diagnosis. *Crit Care Med* 2009;37:1-9.

After initial trials showed a mortality benefit from the use of insulin drips and tight glucose control in the ICU,[1] subsequent studies have shown mixed results and, in some cases, increased mortality and episodes of hypoglycemia.[2,3] Falciglia and colleagues sought to determine whether the inconsistency in results across studies might be due to variability in the effects of hyperglycemia across different patient populations.

To answer this question, they conducted a retrospective cohort study using data from 259,040 patients admitted to 173 medical, cardiac, surgical, and mixed ICUs in more than 100 Veterans Health Administration hospitals over a 3-year period from 2002 to 2005. The data used in their analysis were obtained from the VA

Inpatient Evaluation Center, a national VA program that measures risk-adjusted outcomes in VA hospital ICUs and uses that information to guide evidence-based improvements in patient safety and quality of care. As part of this system, customized programs identify patients with ICU stays at each VA hospital and extract relevant data that can be used in subsequent analyses. Mean glucose was calculated for each patient from all values measured on chemistry panels during their ICU stay but did not include values obtained during point-of-care testing for monitoring insulin administration, as these values may be subject to greater measurement error. Patients were then stratified into 5 groups based on their mean glucose levels: 70-110, 111-145, 146-199, 200-300, and > 300 mg/dL. Two-level logistic regression analysis was then used to determine the relationship between hyperglycemia and mortality. In the first level of analysis, age, diagnosis, comorbidity, and laboratory variables were used to calculate a predicted mortality rate while, in the second level of analysis, the predicted mortality risk was combined with the mean glucose value for each patient to determine the association of hyperglycemia with hospital mortality.

The analysis, which included patients who were generally older (66% > 60 years of age) and overwhelmingly male (98%), demonstrated that hyperglycemia was associated with increased mortality regardless of illness severity, the type of ICU, length of time in the ICU, or whether the patient had diabetes. The odds ratio for mortality also increased as mean glucose values increased, varying from 1.31 in patients with mean glucose values of 111-145 mg/dL to 2.85 in patients whose mean values were > 300 mg/dL. The relationship between hyperglycemia and mortality varied based on the patients' admission diagnoses, with a strong relationship between hyperglycemia and mortality in some disorders (e.g., unstable angina, acute myocardial infarction, congestive heart failure, gastrointestinal bleeding, pneumonia, pulmonary embolism, and sepsis) and no relationship in other cases (e.g., COPD, hepatic failure, gastrointestinal malignancy, and patients admitted following surgery for coronary artery bypass grafting, peripheral vascular disease, and hip fracture). Of note, even within the group of disorders for which there was a relationship between hyperglycemia and mortality, the risk still varied between diagnoses.

■ COMMENTARY

There are several interesting aspects of this study. The first is that, as the authors hypothesized, the relationship between hyperglycemia and mortality does, in fact, vary across patient populations. This may help explain why the benefits of insulin drips and tight glucose control, widely adopted in ICUs following a single-center study in a surgical patient population,[1] have not been borne out in subsequent studies looking at broader or different patient populations. This suggests we may need to tailor management of hyperglycemia, and perhaps other problems in the ICU, a bit more and not apply a "one-size-fits-all" approach. Unfortunately, we lack the data at this point to help us adopt a more nuanced approach to the hyperglycemia issue and the likelihood of an adequately powered, prospective trial to help address these issues is low.

The second interesting, and perhaps more distressing, result of this study was that even moderately elevated mean glucose values over the course of an admission (111-145 or 146-149 mg/dL, for example) were associated with an increased risk of mortality across all of the patient populations, a result that puts ICU clinicians in a significant bind. The recent studies examining insulin drips and tight glucose control have largely shown that tight control (80-110 mg/dL) is associated with an increased risk of hypoglycemia and, in a recent, noteworthy trial, an increased risk of mortality.[2] Given this, it would seem reasonable to liberalize protocols a bit and target more moderate levels of control such as 120-150 mg/dL and ensure patients are not markedly hyperglycemic. The study by Falciglia and colleagues, however, suggests that even this modest shift in target glucose levels may be bad for our patients.

How do we resolve this issue? In the long-term, we need additional prospective studies comparing outcomes from insulin protocols targeting several ranges of glucose control. The study above was a retrospective analysis, and only prospective data will help clarify this issue. Until such a trial is completed, we should accept the risks of the mildly elevated levels and avoid overly tight targets. Hypoglycemia is a clear problem with a well-identified cause over which we have control in patients on insulin drips. Mortality is a more amorphous concept and many other factors — which are often difficult to control — may be contributing to this outcome in patients than just hyperglycemia. ■

References

1. Van den Berghe G, et al. Intensive insulin therapy in the critically ill patient. *N Engl J Med* 2001;345: 1359-1367.
2. NICE-SUGAR Study Investigators; et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283-1297.

3. Arabi YM, et al. Intensive versus conventional insulin therapy: A randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med* 2008; 36:3190-3197.

No Method Is Perfect for Detecting Delirium In ICU Patients, but Some Methods Are Better Than Others

ABSTRACT & COMMENTARY

By Richard J. Wall, MD, MPH

Pulmonary Critical Care & Sleep Disorders Medicine, Southlake Clinic, Valley Medical Center, Renton, WA

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

Synopsis: *This study compared two popular tools for assessing delirium in ICU patients (CAM-ICU and ICDSC), and it showed that physicians often underdiagnose delirium in ICU patients.*

Source: van Eijk MM, et al. Comparison of delirium assessment tools in a mixed intensive care unit. *Crit Care Med* 2009;37:1881-1885.

DELIRIUM IS A COMMON AND SERIOUS DISORDER IN ICU patients, with up to 87% incidence in some ICU populations. Studies have shown that delirium is associated with higher costs and complication rates, namely increased ventilator days and longer hospital stays. Several tools are now available that permit ICU clinicians to easily screen for delirium. Two of the most popular tools are the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). Both tools have been validated using the *Diagnostic and Statistical Manual of Mental Health Disorders, 4th edition*.

In the current study, the authors rigorously compared the CAM-ICU and ICDSC against each other in a mixed ICU population. The study was conducted in a 32-bed teaching ICU in the Netherlands, with adult medical, surgical, neurologic, neurosurgery, and cardiothoracic patients. The two tools were also compared against a "gold standard" neuropsychiatric assessment, which was performed by an expert trained in delirium diagnosis.

A total of 126 patients were evaluated (mean age, 62 years; 72% male). As a whole, the study population was moderately ill (mean APACHE, 21). The overall prevalence of delirium was 34% (43/126), with delirious patients older and sicker. Among patients with delirium, the majority (69%) had hypoactive delirium.

Neither tool was especially sensitive for detecting delirium. The CAM-ICU had a sensitivity of 64% and the ICDSC had a sensitivity of 43%. However, the CAM-ICU and ICDSC both had decent specificity for delirium diagnosis (88% and 95%, respectively). Among neurologic patients with another cerebral disorder (e.g., stroke), the CAM-ICU was much more sensitive than was the ICDSC (sensitivity 80% vs 31%, respectively). However, ICDSC specificity was higher in this neurologic subpopulation (93% vs 84%, respectively).

When ICU physicians were asked whether they thought a patient was delirious, their sensitivity for detecting delirium was only 29%. Intensivist attendings and fellows fared slightly better than residents, but their sensitivity was still only 63% (i.e., they missed 37% of delirium cases).

■ COMMENTARY

A few quick questions: Do you routinely measure delirium in your ICU patients? If so, do you know which measurement tool(s) you use? Do you regularly discuss delirium assessment with staff on multidisciplinary rounds?

I imagine many clinicians still answer "no" to these questions. Despite the persistent and energetic efforts of researchers, the saga of delirium testing in ICU patients has been an uphill battle. Dr. Wes Ely, one of the CAM-ICU developers, often tells the story about how his first grant proposal for studying this subject was flatly rejected because the reviewers thought it was an irrelevant topic. Moreover, when he searched the literature for a well-validated delirium instrument that he could use in ventilated patients, he found the following sentence in the Methods section of nearly every delirium study: "Mechanically ventilated patients were excluded."

In less than a decade, the pendulum has swung. Several validated instruments are now available for assessing delirium in mechanically ventilated patients. These instruments are easy to use at the bedside and freely available. A growing body of research has clearly demonstrated the relevance of the topic. Delirium in mechanically ventilated patients is associated with high-

er 6-month mortality, increased length of stay, and higher cost of care.

The ICDSC is an 8-item scoring checklist based on observations made during routine patient care.[1] No patient cooperation is required. Raters complete a checklist based on observations from the previous 24 hours. Items are scored 1 (present) or 0 (absent), for a maximum of 8 points. A score ≥ 4 indicates delirium is present.

The CAM-ICU is another well-validated tool that is easy to administer.[2] Patients must be rousable on the ventilator. It performs well even among patients with dementia, the elderly, and those with high severity of illness. It takes less than 2 minutes to complete and requires minimal training.

Although past studies compared the CAM-ICU and ICDSC against each other, this is the first comparison in a mixed ICU with a large neurologic population. In neurologic patients, the CAM-ICU was clearly more sensitive, a useful finding. However, what I find most startling is the low sensitivity of ICU physicians in detecting delirium. Even ICU attendings and fellows missed 37% of cases. I believe this emphasizes the need for use of a standard screening tool for assessing delirium on a daily basis. We already know that clinician skills for assessing extubation readiness are shoddy — hence, the utility of the daily spontaneous breathing trial. Similarly, clinician skills for assessing delirium are

CME / CNE Questions

27. According to the CESAR trial, as an alternative therapy to conventional mechanical ventilation for patients with severe acute respiratory failure, extracorporeal membrane oxygenation (ECMO):
a. increases survival.
b. shortens ICU stay.
c. shortens hospital stay.
d. All of the above
e. None of the above

28. In the CESAR trial of extracorporeal membrane oxygenation as compared with conventional ventilation for patients with severe acute respiratory failure:
a. ECMO could effectively and safely be implemented in community hospitals.
b. Patient management was the same except for whether they received ECMO.
c. Survival in both patient groups was worse than anticipated.
d. Most patients received corticosteroids.
e. Costs were substantially less in patients randomized to receive ECMO.

29. Which of the following statements about hyperglycemia in the ICU is *correct*?
a. Hyperglycemia is associated with increased risk of mortality regardless of the patient's diagnosis.
b. Hyperglycemia is associated with an increased risk of mortality only when the blood glucose value is above 150 mg/dL.
c. Hyperglycemia is associated with an increased risk of mortality regardless of the severity of illness.
d. The mortality risk of hyperglycemia is affected by the duration of the patient's ICU stay.
e. None of the above

30. In which of the following patient groups is hyperglycemia associated with an increased risk of hospital mortality?
a. Chronic obstructive pulmonary disease
b. Coronary artery bypass graft surgery patients
c. Hepatic failure
d. Sepsis
e. Peripheral vascular disease surgery patients

31. Which of the following is *true* about the Confusion Assessment Method for the ICU (CAM-ICU) tool?
a. It has not been validated against the *Diagnostic and Statistical Manual of Mental Health Disorders, 4th edition*.
b. It cannot be performed on unarousable mechanically ventilated patients.
c. It requires 24 hours to complete.
d. It detected 88% of the cases of delirium in this study.
e. None of the above

32. Which of the following statements is *true* about the study comparing the 2 delirium assessment tools?
a. Most of the patients in the study had agitated delirium.
b. Mechanically ventilated patients were excluded.
c. The ICDSC was more sensitive than the CAM-ICU in detecting delirium.
d. Intensivists (both attendings and fellows) missed 37% of delirium cases.
e. None of the above

Answers: 27. e, 28. d, 29. c, 30. d, 31. b, 32. d.

imperfect. Every ICU should also use a simple tool for screening (and hopefully reducing) delirium. ■

References

1. Bergeron N, et al. Intensive Care Delirium Screening Checklist: Evaluation of a new screening tool. *Intensive Care Med* 2001;27:859-864.
2. Ely EW, et al. Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703-2710.

CME / CNE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

Statement of Financial Ownership

United States Postal Service
Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Critical Care Alert	1 0 6 7 - 9 5 0 2	10/1/09
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta,
Fulton County, GA 30305

Contact Person: Robin Salet
Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*
AHC Media LLC, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*
Publisher *(Name and Complete Mailing Address)*
Robert Mate, President and CEO
AHC Media LLC, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305
Editor *(Name and Complete Mailing Address)*
Paula Cousins, same as above
Managing Editor *(Name and Complete Mailing Address)*
Coles McKagen same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
AHC Media LLC	3525 Piedmont Road, Bldg. 6, Ste 400
	Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Thompson Publishing Group Inc.	805 15th Street, NW, 3rd Floor
	Washington, D.C. 20005

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: Critical Care Alert
14. Issue Date for Circulation Data Below: September 2009

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			466	483
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	317	337
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	15	12
	(4)	Other Classes Mailed Through the USPS	12	9
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			344	358
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	22	24
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			20	20
f. Total Free Distribution *(Sum of 15d and 15e)*			42	44
g. Total Distribution *(Sum of 15c and 15f)*			386	402
h. Copies Not Distributed			80	81
i. Total *(Sum of 15g, and h.*			466	483
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			89%	89%

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2009 issue of this publication. ☐ Publication not required

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: President and CEO — Date: 9/28/09

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*

PHARMACOLOGY WATCH

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

SSRIs and Pregnancy: Increase in Septal Heart Defects

In this issue: Depression and pregnancy, new vaccine recommendations from the CDC, corticosteroids and/or antivirals for Bell's palsy, rasagiline and Parkinson's disease, and FDA Actions.

Use of SSRIs during pregnancy

Depression is common in pregnancy, affecting up to 20% of women, with about 13% taking an antidepressant during pregnancy. A new study from Denmark suggests that use of sertraline (Zoloft®) and citalopram (Celexa®) by mothers during pregnancy is associated with an increased risk of septal heart defects in their children. Researchers utilized the Danish nationwide registry to review nearly 500,000 births from 1996 to 2003. Selective serotonin reuptake inhibitors (SSRIs) in general were not associated with major malformations, but were associated with septal heart defects. Among the individual drugs, sertraline conveyed the highest risk (odds ratio [OR], 3.25; confidence interval [CI], 1.21-8.75), followed by citalopram (OR, 2.52; CI, 1.04-6.10). Use of more than one SSRI was associated with an OR of 4.70 (CI, 1.74-12.7). The absolute prevalence of septal heart defects was 0.5% among unexposed children, 0.9% among children whose mothers received any SSRI, and 2.1% among children whose mother were prescribed more than one SSRI (*BMJ* 2009:339:b3569; Epub ahead of print 23 Sept 2009). Significant in this study was the low overall rate of heart defects and the lack of association of heart defects with paroxetine (Paxil®) or fluoxetine (Prozac®), although the authors consider this a "class effect," and the greatest risk was noted if more than one drug was used during pregnancy. ■

CDC issues new vaccine recommendations

The Centers for Disease Control and Prevention has recently revised several vaccine recommendations:

Quadravalent meningococcal conjugate vaccine. The Advisory Committee on Immunization Practices (ACIP) is recommending revaccination of persons at prolonged increased risk for meningococcal disease. In a statement in the September 25th *Morbidity and Mortality Weekly* Report, ACIP is recommending that persons with increased susceptibility to meningococcal disease, such as those with persistent complement component deficiencies, functional asplenia, prolonged exposure such as those traveling to or living in nations where the disease is epidemic or hyperendemic, should receive a booster with the quadravalent meningococcal conjugate vaccine 5 years after their previous vaccination if they received it at age 7 or older. Children who received the first vaccine between ages 2 and 6 should be revaccinated after 3 years. Those who remain at high risk should continue to be revaccinated every 5 years. The recommended booster vaccine is the MCV4 vaccine (Menactra®).

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Haemophilus influenzae *type b vaccine.* The FDA recently approved Hiberix® for *Haemophilus influenzae* type b (Hib) ending a prolonged shortage of the Hib vaccine. Hiberix is approved as a booster for children ages 15 months to 4 years who have received a primary series of shots. The Centers for Disease Control and Prevention has now issued recommendations that the vaccine can be given as early as age 12 months to facilitate timely booster vaccination. Children who missed a booster because of the recent shortage should receive a booster with any of the Hib vaccines, including Hiberix, at the earliest opportunity.

Hepatitis A vaccine. Hepatitis A vaccine is now recommended for all close household contacts and international adoptees when the children are from intermediate-risk or high-risk areas, with an initial dose being given at least 2 weeks before the child's arrival.

Quadravalent human papilloma virus vaccine. In related news, an FDA advisory panel is recommending that the quadravalent human papilloma virus vaccine (Gardasil®) be approved for males ages 9-26 to prevent genital warts. The vaccine is currently approved only for females in that age group. Meanwhile, the same FDA advisory panel has endorsed the approval of GlaxoSmithKline's Cervarix®, a bivalent HPV vaccine which targets HPV 16 and HPV 18, leading causes of cervical cancer. If approved it would also be recommended in women ages 10-25. The new vaccine protects against 2 of the HPV strains covered by Gardasil, but also contains an adjuvant, which is designed to enhance the immune system's response to these HPV strains. Whether this imparts clinical difference is yet to be seen. The FDA is yet to act on the advisory committee's recommendations. ■

Bell's palsy: Corticosteroids and/or antivirals?

For treatment of Bell's palsy, corticosteroids with or without antivirals have been the subject of much debate. A new meta-analysis suggests that combination therapy may lead to better outcomes. The review included 18 trials with 2786 patients. The outcomes were unsatisfactory facial recovery at 4 months, unsatisfactory short-term recovery, synkinesis and autonomic dysfunction, or adverse effects. Combination therapy with corticosteroids and antivirals resulted in slightly better outcome than steroids alone ($P = 0.05$). Antiviral agents alone did not show a benefit (*JAMA* 2009;302:985-993). At least one source (UpToDate) recommends a typical treatment regimen for Bell's palsy of prednisone 60-80 mg per day along with valacyclovir 1000 mg three times a day for 1 week. ■

Rasagiline and Parkinson's disease

Does rasagiline slow the progression of Parkinson's disease? A recent study suggests lower doses of the drug may be beneficial. In this multinational study, 1176 subjects with untreated Parkinson's disease were randomized to rasagiline 1 mg or 2 mg per day for 72 weeks or placebo for 36 weeks followed by rasagiline for 36 weeks. Disease progression was rated on a standard rating scale. Patients who were started at baseline on rasagiline 1 mg met all endpoints in the primary analysis: a slower rate of worsening between weeks 12 and 36 ($P = 0.01$), less worsening of the score between baseline and week 72 ($P = 0.02$), and non-inferiority between weeks 48 and 72 ($P \leq 0.001$). Interestingly, all 3 endpoints were not met with the higher dose of 2 mg per day. The authors conclude that early treatment with rasagiline at a dose of 1 mg per day provided a possible disease-modifying effect, but suggested the results must be interpreted with caution (*N Engl J Med* 2009;361: 1268-1278). Although the findings of this paper are somewhat confusing, it offers some hope since there is currently no effective therapy to slow or stop disease progression in Parkinson's disease. ■

FDA Actions

The FDA has approved asenapine (Saphris®) for the treatment of schizophrenia and bipolar I disorder in adults. The drug is approved for first-line treatment of both conditions. Schering-Plough provided the agency with safety data in 4500 patients, some of whom were treated for more than 2 years. Like other antipsychotics, asenapine will carry a warning regarding increased mortality in elderly patients with dementia-related psychosis. The drug is expected to be available in the fourth quarter of 2009.

The FDA has lowered the approved age limit for levocetirizine (Xyzal®) to 6 months for children with chronic hives and perennial allergic rhinitis and 2 years for children with seasonal allergic rhinitis. Previously the drug had been approved for children 6 years and older. Levocetirizine is marketed by UCB and Sanofi Aventis. ■