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Critical Care [ALERT]

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

ABSTRACT & COMMENTARY

Electronic Surveillance of Ventilator Settings and Airway Pressures Can Increase the Use of Lung-Protective Ventilation

By David J. Pierson, MD, Editor

SYNOPSIS: This study from a high-volume ICU setting with a fully integrated electronic medical record system evaluated the impact of automated computer-generated notification to tell respiratory therapists and intensivists when ventilated patients with acute lung injury were receiving potentially injurious tidal volumes and airway pressures. Compared to pre-implementation data, use of the notification algorithm was associated with significant reductions in tidal volumes and airway pressures, as well as the number of hours patients were exposed to these risks for ventilator-induced lung injury.

SOURCE: Herasevich V, et al. Limiting ventilator-induced lung injury through individual electronic medical record surveillance. Crit Care Med 2011;39:34-39.

In this study from the Mayo Clinic in Rochester, MN, Herasevich et al tested an electronic algorithm that incorporated patient characteristics and ventilator data and notified clinicians immediately when potentially injurious ventilator settings were being used. Using data from the institution's electronic medical record (EMR), the "sniffer algorithm" for ventilator-induced lung injury (VILI) risk required satisfaction of the following criteria for patients at least 16 years old who underwent invasive mechanical ventilation for > 24 hours in each of three ICUs:

- Presence of acute lung injury (ALI):
  - o PaO_2/FIO_2 < 300 mm Hg, *and*
  - o The words "bilateral" and "infiltrates," or

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Critical Care [ALERT]

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the word "edema," on the radiologist's report of the portable chest radiograph
- Use of potentially injurious ventilator settings:
  - o Plateau pressure > 30 cm H_2O or peak inspiratory pressure (PIP) > 35 cm H_2O, *and*
  - o Set tidal volume > 8 mL/kg predicted body weight (PBW)

At the authors' institution, the EMR acquires all of the above data automatically, within 1 hour of measurement or radiographic exposure. When all the listed criteria were met, a text page was sent to the respiratory therapist assigned to that patient, and also to the critical care fellow on call. The therapist was expected to go to the patient's bedside to assess the validity of the alarm. Subsequent actions, such as discussion of possible ventilator changes among the therapist, fellow, and primary managing physician, were at the discretion of the therapist and fellow receiving the page. Text notification occurred only when the potentially injurious ventilator data thresholds were met for four consecutive 15-minute periods (total 1 hour), and was done only once in any 24-hour period for a maximum of 3 days on any given patient.

The intention was to reduce patient exposure to potentially injurious ventilator settings, as measured by the number of hours that patients continued to have the threshold ventilator-related measurements, as well as to assess clinician responses to the "VILI alert" notification. The electronic surveillance system was already in place prior to the study, so that the authors could compare data on patients ventilated during the preceding 8 months to those collected during the 12 months after the VILI alert system was implemented. In addition, respiratory therapists working in the study ICUs completed a brief on-line satisfaction survey about the system, and incremental costs of implementing the notification system were determined.

Of 9888 potentially eligible patient admissions during the historical control and prospective study periods, 1159 patients were ventilated > 24 hours and 490 cases of ALI were identified using the screening criteria. The study population comprised these 490 patients (42% of the eligible ventilated population), 186 of them from prior to VILI alert implementation and 304 afterwards. Patients in the two groups were well matched by demographics, primary diagnoses, and several measures of illness severity. One hundred eleven text alerts were sent during the study period, of which 65 (in 80 patients) were deemed by the investigators to represent valid VILI risk (positive predictive value of alert, 59%). Of these 65 alerts, all of which included tidal volumes in excess of 8 mL/kg PBW, 12 were from plateau pressures > 30 cm H_2O and 53 were from PIPs > 35 cm H_2O.

The number of alerts generated per day trended downward during the study period, from a mean of 22 in the first month to six in the final month. Mean patient exposure to potentially injurious mechanical ventilation decreased significantly during the study period, from 40.6 ± 74.6 hours to 26.9 ± 77.3 hours ($P < 0.05$). There were no changes in ICU or hospital mortality, or in ICU or hospital length of stay. The 27 respiratory therapists who completed the satisfaction survey and had received VILI alerts were asked whether the system was useful; 48% agreed, 33% were neutral, and 19% disagreed. The authors estimated that running the program took about 10 minutes per day on the part of the trained JAVA programmer who implemented it, with a total cost to the institution of $10,400.

COMMENTARY

This study demonstrates the feasibility and potential effectiveness of fully automated EMR surveillance of mechanically ventilated patients at risk for VILI. As the authors point out, with impending implementation of the Health Information Technology for Economic and Clinical Health Act, as well as current trends toward practice standardization and increased information technology-facilitated

clinical decision support, it very likely offers a preview of the future of ICU care.

That future is not yet here, however, and this study was not perfect. Use of design features such as randomization or at least concurrent rather than historical controls would have been better. Using PIP rather than plateau pressure (which accounted for nearly half of the alerts sent) is problematic, as the former may reflect airway phenomena and other factors unrelated to the risk for VILI, and is not used in most assessments of this or in tailoring lung-protective ventilation (LPV). The system would not distinguish between ALI and cardiogenic pulmonary edema, although, as the authors point out, the use of LPV in the latter condition would not be expected to be harmful.

Comment should also be made about the potential generalizability of the study's findings. It was carried out in a large tertiary referral center, with a fully implemented EMR, that manages large numbers of patients with ALI. The system was thus both easier (and cheaper) to implement and more likely to have an important impact on patient outcomes than might be the case in an institution with fewer ventilated patients or one without the technological means for automated detection of the input variables. On the other hand, the fact that LPV was already widely implemented in the authors' institution at the time of the study suggests that the demonstrated benefits could be even greater at other centers where this is not the case.

The ALI diagnostic criteria used in this study were based on the American-European consensus criteria,[1] which have stood the test of time and are most widely accepted both conceptually and practically for identifying patients with ALI and the acute respiratory distress syndrome (ARDS). However, only two of the four criteria were used, and only a minimalist version of the radiographic component could be extracted into the EMR. Bilateral pulmonary infiltrates compatible with pulmonary edema remain the least precise and most contentious component of the ALI diagnosis. Rubenfeld and associates showed that even an assemblage of recognized ARDS investigators could not agree on which chest X-rays were consistent with a diagnosis of ARDS in the absence of clinical context,[2] so it is hardly surprising that the VILI alerts generated in the present study included numerous false positives.

A page-based system to promote better adherence to LPV as employed in this study is imperfect at best. It is conceptually attractive to imagine closed-loop mechanical ventilation in which LPV could be initiated and maintained automatically using input data similar to those used in this study. This would assure that this life-saving ventilatory strategy was properly and promptly applied to all patients who could benefit from it. However, we are a long way from such a system because of the complexities involved — and not least in the determination of which patients are appropriate.

At present it is hard to imagine a non-human system that could identify and account for all the factors that might influence whether and how LPV should be implemented. Such factors could include hemodynamic instability, acute brain injury, non-pulmonary causes for high airway pressures, other explanations for the oxygenation or radiographic findings, patient preferences and code status affecting the aggressiveness of management, and therapy for coexisting conditions, among many others. In the absence of true closed-loop mechanical ventilation, inclusion in the protocol of the bedside assessment and judgment of an experienced clinician once potential VILI risks have been identified — as incorporated into this study — remains a crucial component of safe and effective mechanical ventilation. ■

[Using PIP rather than plateau pressure (which accounted for nearly half of the alerts sent) is problematic, as the former may reflect airway phenomena and other factors unrelated to the risk for VILI, and is not used in most assessments of this or in tailoring lung protective ventilation.]

References

1. Bernard GR, et al. The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-824.
2. Rubenfeld GD, et al. Interobserver variability in applying a radiographic definition for ARDS. Chest 1999;116:1347-1353.

ABSTRACT & COMMENTARY

Is It Safe to Use Etomidate When Intubating Patients With Sepsis or Septic Shock?

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 demonstrated that single-dose etomidate administration during rapid-sequence intubation was not associated with adverse outcomes in patients with sepsis or septic shock.

SOURCE: Dmello D, et al. Outcomes of etomidate in severe sepsis and septic shock. Chest 2010;138:1327-1332.

Due to its lack of cardiovascular side effects, the short-acting non-barbiturate sedative, etomidate, has been one of the primary agents used to sedate hypotensive patients during rapid-sequence intubation (RSI). While use of this valuable agent is associated with transient, reversible suppression of adrenal function following bolus administration, the effect on patient outcomes resulting from this problem is not clear. Dmello and colleagues sought to examine this question further and determine whether use of etomidate during RSI was associated with increased mortality and other adverse outcomes in a subset of critically ill patients.

To investigate this question, the authors conducted a retrospective cohort study of patients in a multidisciplinary ICU of a single institution. They identified 224 consecutive patients with sepsis or septic shock — defined using consensus criteria developed by the American College of Chest Physicians and Society of Critical Care Medicine — requiring invasive mechanical ventilation within 48 hours of admission. Selected patients were then divided into two groups, those who underwent RSI with etomidate plus a paralytic agent and those who did not undergo RSI and typically received midazolam and fentanyl. The original decision as to whether to use RSI or another technique for intubation was not based on pre-specified criteria and was, instead, at the discretion of the intubating physician. Among data gathered on all patients, they examined whether patients had relative adrenal insufficiency, defined as a random baseline cortisol level < 15 μg/dL or a less than 9 μg/dL response to 250 μg of adrenocorticotropic hormone (ACTH). Treatment protocols following intubation appeared to be at the discretion of the attending physician. Multivariate logistic regression was used to adjust for the effects of age, sex, APACHE II scores, and corticosteroid use, and compare differences in mortality, vasopressor use, ICU length of stay (LOS), and ventilator days between the two groups.

Etomidate was used as part of RSI in 113 patients of the 224 patients included in the study. The average age and APACHE II scores were similar between the two groups of patients. Of those patients who underwent testing, 24% of those in the etomidate group and 22% of those in the non-etomidate group met criteria for relative adrenal insufficiency. Corticosteroids were used in 42% of the etomidate patients and 22% of the non-etomidate patients, although the authors did not comment as to whether there were explicit criteria used to determine who received corticosteroids in this particular ICU. The relative risk of steroid use was 1.34 (95% confidence interval [CI], 1.11-1.61; $P = 0.003$). The relative risk of mortality in the etomidate group was 0.92 (95% CI, 0.74-1.14; $P = 0.51$), while the relative risk of vasopressor use was 1.16 (95% CI, 0.9-1.51; $P = 0.31$). There were no significant differences in ICU-LOS (14 vs 12 days; $P = 0.31$) or ventilator days (11 vs 8 days; $P = 0.13$).

COMMENTARY

Intubation and initiation of invasive mechanical ventilation is an all too common event in the ICU and a significant number of patients must undergo this procedure while in the midst of septic shock. Given how frequently we use etomidate instead of propofol in such situations because of differences in their hemodynamic profiles, it would be important to know whether etomidate's transient effects on the adrenal axis are associated with worse patient outcomes. Were mortality to be increased as a result of adrenal suppression, for example, it would behoove us to consider alternative means for inducing patients during rapid sequence intubation.

Unfortunately, the trial by Dmello and colleagues does not provide a sufficient answer to this question. While the trial did not reveal any significant differences in mortality or vasopressor use, there were significant methodological issues in the study that make it difficult to draw any strong conclusions. Critically ill patients are often so complex that it is difficult to control for enough factors and isolate the effect of a particular intervention on big outcomes, even with a prospective randomized design. Dmello and colleagues used a retrospective design and it does not appear that any specific protocols were used to guide care of the patients. Most decisions were left to the treating physician and not based on pre-specified criteria or guidelines, including the decision whether or not to use rapid-sequence intubation — the key factor separating the two groups in the study. Given these problems, there are likely too many factors that varied in the care of the patients as to make it difficult to attribute the observed outcomes, or lack thereof, to the use of one particular medication at the time of intubation.

Had this trial revealed that mortality was significantly increased with etomidate, we might be in the slightly tricky situation of having to decide whether to change our current practice based on results from a study with methodological problems. With no glaring differences in outcomes, however, it is likely acceptable to continue using etomidate until adequately controlled prospective studies provide further insight into this question. ■

ABSTRACT & COMMENTARY

Can Nebulized Heparin Reduce Ventilator-Induced Lung Injury?

By David J. Pierson, MD, Editor

SYNOPSIS: In this single-center, placebo-controlled clinical trial of 50 patients with acute respiratory failure, nebulized heparin was associated with fewer days of mechanical ventilation, although measures intended to reflect its assumed mechanism of action in reducing microvascular fibrin deposition showed no differences.

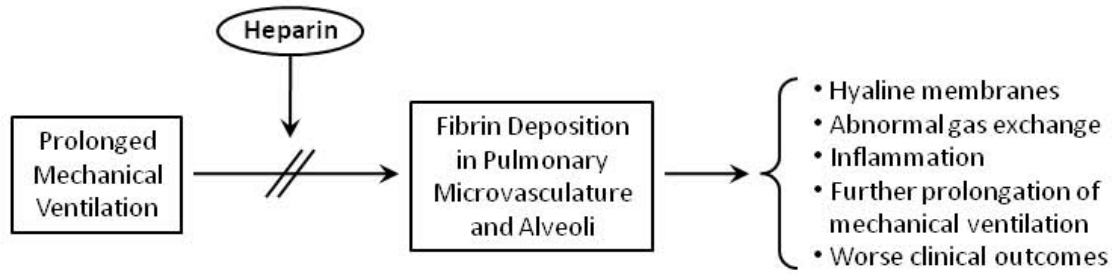
SOURCE: Dixon B, et al. Nebulized heparin is associated with fewer days of mechanical ventilation in critically ill patients: A randomized controlled trial. Critical Care 2010;14:R180..

Laboratory studies and clinical data support the concept that prolonged mechanical ventilation (PMV) can induce or worsen lung injury, via activation of inflammatory mediators and/or microvascular fibrin deposition, processes that may be ameliorated by heparin. This study from a tertiary referral center in Melbourne, Australia, sought to determine whether heparin delivered via aerosol would prevent or reduce ventilator-induced lung injury, as indicated by decreased indices of inflammation in alveolar lavage fluid, improved arterial oxygenation, shortened duration of mechanical ventilation, reduced need for tracheostomy, and decreased ICU and hospital lengths of stay, among adult patients requiring PMV for acute respiratory failure.

For this study PMV was defined as the requirement for invasive ventilatory support for > 48 hours. Patients predicted to require PMV were entered into the study within 24 hours of intubation; exclusion criteria included the use of high-frequency oscillatory ventilation, extracorporeal membrane oxygenation, inhaled nitric oxide, renal replacement therapy, or systemic heparin in therapeutic doses. By means of an Aeroneb Pro® nebulizer, enrolled patients received either heparin (25,000 units in 5 mL saline) or plain saline every 4 or 6 hours depending on body size, for 14 days or until weaned from mechanical ventilation. The primary outcome variable was the PaO_2/FIO_2 ratio, measured once daily at 4:00 am. A variety of inflammatory mediators were measured in bronchoalveolar lavage fluid obtained non-bronchoscopically on study days 1, 2, 4, 8, and 14. Other outcomes measured were ventilator-free days as of 28 days after enrollment among survivors, development of acute lung injury by international consensus criteria following enrollment, tracheostomy, vasopressor- and renal failure-free days, ICU and hospital lengths of stay, and mortality.

The investigators screened 1537 patients admitted to their ICU during the 17 months of the study, of whom 219 met the inclusion criteria and 50 were ultimately enrolled, with 25 patients randomized

Figure. Proposed role of fibrin deposition in the pathogenesis of ventilator-induced lung injury, and potential effect of heparin.



to each study arm. Patients in the heparin and placebo groups were well matched with respect to age, sex, primary diagnosis, severity of illness by APACHE II score (about 20), initial PaO_2/FIO_2 ratio (approximately 170), and presence of acute lung injury on admission (16% in each group). Results showed that the average PaO_2/FIO_2 ratio while ventilated remained the same in both groups. There were no significant differences in any of the eight inflammatory mediators measured, nor in the new acute lung injury or tracheostomy rates, vasopressor- or renal failure-free days, ICU or hospital length of stay, or mortality (18% overall). However, surviving patients who received nebulized heparin had significantly more ventilator-free days as of day 28 than did those who received placebo: 22.6 ± 4.0 vs 18.0 ± 7.1 days (P = 0.02).

COMMENTARY

In the last few years there has been a great deal of interest in mechanical ventilation per se as a contributor to — and even as an initiator of — acute lung injury. Injury has been ascribed to the use of excessive distending volumes and pressures ("barotrauma"), shear stresses involved in the repetitive opening and closing of collapsed lung areas ("atelectrauma"), and the release of injurious mediator substances by mechanical lung distension ("biotrauma"). Prolonged mechanical ventilation has been associated with the deposition of fibrin in the pulmonary microvasculature and alveoli, both in animal models and in patients. This fibrin deposition in turn has been hypothesized to play a role in lung inflammation, hyaline membrane formation, gas exchange abnormalities, and the need for PMV, as well as in clinical outcomes such as mortality and length of stay. These proposed relationships are shown schematically in the Figure *(above)*. By interfering with fibrin deposition, heparin might block or at least attenuate the adverse effects listed on the right side of the figure. The present study is the latest in a series of investigations by these authors in pursuit of this hypothesis.

In this relatively small, single-center clinical trial, the administration of nebulized heparin was associated with more ventilator-free days among surviving patients than was placebo. This is an encouraging finding — although as the authors state it needs to be confirmed by further studies. Heparin is readily available and cheap, but before we all start nebulizing it in our ventilated patients to prevent acute lung injury (an off-label use of the drug), several cautionary points should be made about this study.

Given the rationale for using heparin during PMV, it seems odd that no significant differences were found in any of the other measures reflecting its putative effects as shown in the figure. One would expect that a favorable effect of heparin on ventilator-free days would somehow reflect a reduction in lung injury, facilitating more rapid recovery. There were no differences between the heparin and placebo groups with respect to gas exchange (PaO_2/FIO_2 ratio or $PaCO_2$), peak inspiratory pressure, end-expiratory pressure, delivered tidal volume, or minute ventilation. Nothing is mentioned in the paper about ventilator liberation criteria, other than the use of pressure support for weaning, so in the absence of differences in illness severity, inflammation, or ventilatory status, the reason for the substantial difference in ventilator-free days (mean, 4.6 days) is not apparent. ■

ABSTRACT & COMMENTARY

Can We Use Serum Sodium Levels to Prognosticate in Patients with Pulmonary Embolism?

By Andrew M. Luks, MD

SYNOPSIS: This retrospective analysis of a large number of patients presenting with pulmonary embolism demonstrated that hyponatremia is common in this condition and is an independent predictor of 30-day mortality and hospital readmission.

SOURCE: Scherz N, et al. Prognostic importance of hyponatremia in patients with acute pulmonary embolism. Am J Respir Crit Care Med 2010;182:1178-1183.

Hyponatremia is frequently seen in patients with left ventricular failure and has recently been shown to be associated with right ventricular dysfunction and worse outcomes in patients with pulmonary hypertension.[1] Because right ventricular (RV) dysfunction is associated with poor outcomes in pulmonary embolism (PE), Scherz and colleagues sought to determine if hyponatremia has prognostic significance in this disorder as well.

They conducted a retrospective analysis of data from all patients older than age 18 years discharged from non-governmental acute care hospitals in Pennsylvania over a 2-year period with a diagnosis of PE or a secondary diagnosis of PE and one of several complications or treatments of the disorder including respiratory failure, cardiogenic shock, cardiac arrest, pulmonary hypertension, syncope, thrombolysis, and mechanical ventilation. Severity of illness was quantified using the PE severity index (PESI). They defined hyponatremia as a baseline serum sodium 135 mmol/L or lower and stratified patients into three categories: serum sodium > 135 mmol/L, 130-135 mmol/L, and < 130 mmol/L. Survival analyses and the log-rank test were used to compare the cumulative 30-day mortality and hospital readmission rates by sodium level, while multivariable logistic regression was used to examine the association between serum sodium level and mortality after adjusting for race, insurance, severity of illness, thrombolytic use, and characteristics of the treating hospital.

They evaluated a total of 13,728 patients from 185 hospitals, 2907 of whom (21%) had hyponatremia. Patients with hyponatremia were older, more likely to have comorbid conditions such as heart failure or cancer, more likely to have clinical signs of severe PE such as tachycardia, hypotension, hypoxemia, and altered mental status, and had higher PESI class. Cumulative 30-day mortality was 8.0% for patients with serum sodium > 135 mmol/L, 13.6% with serum sodium 130-135, and 28.5% with serum sodium < 130 mmol/L. In the Kaplan-Meier analysis, survival curves begin to diverge as early as 3-4 days following admission. When compared to those patients with a sodium level > 135 mmol/L, patients with serum sodium 130-135 mmol/L and < 130 mmol/L had adjusted odds ratios for death of 1.53 (95% confidence interval [CI], 1.33-1.76) and 3.26 (95% CI, 2.48-4.29), respectively. Readmission rates were 11.8% in the > 135 mmol/L group, 15.6 in the 130-135 mmol/L group, and 19.3% in the < 130 mmol/L group. All of the above results were statistically significant. Addition of serum sodium to the PESI classification scheme had a statistically significant but modest effect on predicting patient outcomes.

COMMENTARY

To this point, I have never given much thought to serum sodium levels in patients who develop PE. The facts that up to 21% of people present with this common laboratory abnormality following acute PE, and that the abnormality is associated with an increased risk of both readmission and 30-day mortality, argue that perhaps it is time to change that practice. The study by Scherz and colleagues does have some limitations, such as their reliance on ICD-9 codes for the diagnosis of PE rather than radiographic criteria, the exclusion of some younger, healthier patients who did not have serum sodium levels drawn at diagnosis, and the lack of information about right ventricular dysfunction and neurohumoral changes that could be linked causally to the hyponatremia; however, at a minimum, it suggests we should look a little more closely at this data point in our admission laboratory data.

The question that follows then is how can we incorporate this information into our practice. Certainly, the study does not tell us that we should be correcting hyponatremia as a way to improve outcomes as the abnormality is likely just a marker of illness severity and there are no data

indicating that reversing hyponatremia is of any benefit. Instead, the test may do two things. First, it may serve as a reason to admit a patient to a more monitored setting (e.g., ICU rather than a floor bed), keep them in the hospital for extra monitoring rather than quickly discharging them on low molecular weight heparin and warfarin, and arranging closer follow-up upon discharge. Second, it may provide a reason to hold off on more expensive testing, such as echocardiography, to assess the state of RV function. If hyponatremia, like an elevated cardiac troponin or B-type natriuretic peptide, suggests the patient is at high risk for complications following their PE, does the echocardiogram provide any additional information that would change immediate management? Even if you see evidence of RV dysfunction on the echocardiogram, there are no clear data to support the use of thrombolytics or an inferior vena cava filter in that situation, so the study results should not change patient management. Patients who fail to improve or who continue with markedly impaired exertional tolerance might warrant an echocardiogram, but at least up front, the simple, inexpensive, commonly ordered sodium value might save some unnecessary testing and expense.

Until further research clarifies the utility of serum sodium compared to other prognostic tools such as the PESI or cardiac biomarkers, we should likely not rely on the serum sodium value alone to guide management, but the results by Scherz and colleagues strongly suggest we should no longer be ignoring this piece of information. ■

Reference

1. Forfia PR, et al. Hyponatremia predicts right heart failure and poor survival in pulmonary hypertension. Am J Respir Crit Care Med 2008;177:1364-1369.

CME/CNE Questions

32. Which of the following was associated with implementation of an automated system by which clinicians were text paged when their patients' tidal volumes and airway pressures exceeded those recommended for lung-protective ventilation?

a. Decreased duration of exposure to potentially injurious ventilator settings

b. Increased use of settings consistent with lung-protective ventilation

c. Decreased ICU length of stay

d. a and b but not c

33. Based on the results of a retrospective cohort study, which of the following outcomes is associated with the use of etomidate during rapid sequence intubation?

a. Increased mortality

b. Increased vasopressor use

c. Increased use of corticosteroids

d. Decreased ICU length of stay

e. Decreased duration of mechanical ventilation

34. Hyponatremia (sodium < 135 mmol/L) following acute pulmonary embolism is associated with which of the following outcomes?

a. Increased 30-day mortality

b. Increased ICU mortality

c. Increased hospital length of stay

d. Decreased rate of hospital readmission

e. Decreased duration of mechanical ventilation

Answers: 32. d, 33. c, 34. a.

CME/CNE Objectives

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

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

[IN FUTURE ISSUES]

Mechanical ventilation: End of life or loss of independence for elderly?

Hand contamination of anesthesia equipment by clinicians: An infection risk

PHARMACOLOGY WATCH

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

Statin Use in Patients with Abnormal Liver Function

In this issue: Statins and liver function; dosing timing for thyroxine; rivaroxaban for VTE, DVT, and stroke; echinacea and the common cold; and FDA actions.

Statins and liver function

Most physicians are hesitant to use statins in patients with abnormal liver function tests (ALT or AST less than three times the upper limit of normal). A new study suggests that not only are statins safe and effective, they may improve liver abnormalities in patients with fatty liver. In a study recently published in the *Lancet*, 437 patients enrolled in the Greek Atorvastatin and Coronary Heart Disease Evaluation study population were noted to have moderately abnormal liver tests at baseline, which were possibly associated with non-alcoholic fatty liver disease. Of that group, 227 were treated with a statin (atorvastatin) and 210 were not. Patients treated with a statin had substantial improvement in liver tests ($P < 0.0001$), whereas the group not treated with a statin had further increases in liver enzyme concentrations. Cardiovascular events occurred in 10% of atorvastatin-treated patients vs 30% of the non-statin group (60% relative risk reduction; $P > 0.0001$). This was a greater improvement in benefit than seen in patients with normal liver function tests. Fewer than 1% of the participants who received a statin had to discontinue statin treatment because of transaminase concentrations more than three times the upper limit of normal. The authors concluded that "statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in patients with mild to moderately abnormal liver tests that are potentially attributable to nonalcoholic fatty liver disease" (*Lancet* 2010;376:1916-1922). ■

Dosing timing for thyroxine

When is the best time to take thyroxine? Patients are generally told to take it on an empty stomach in the morning and wait at least 30 minutes before eating. A new study suggests that taking thyroxine at bedtime might be a better option. Over 6 months, 105 patients were randomized to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Taking levothyroxine at bedtime lowered thyrotropin levels and increased free thyroxine and total triiodothyronine levels (the primary outcome). Treatment did not change secondary outcomes including quality of life. The authors concluded that taking levothyroxine at bedtime is a good alternative to morning intake (*Arch Intern Med* 2010;170:1996-2003). This would likely benefit patients who find it difficult to wait 30 minutes to eat after taking their thyroxine each morning. ■

Rivaroxaban: an oral, factor Xa inhibitor

Rivaroxaban is an oral, direct factor Xa inhibitor that is approved in several countries for the prevention of venous thromboembolism (VTE) after orthopedic surgery. It is currently being evaluated by the FDA for this indication. Based on the findings of the EINSTEIN study, it appears the drug is also effective for the treatment of acute deep vein thrombosis (DVT). EINSTEIN consists of three randomized trials of rivaroxaban, one for the treatment of acute DVT, one for treatment of acute pulmo-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, Northern California; Assistant Clinical Professor of Medicine, University of California-San Francisco. Dr. Elliott reports no financial relationships to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

nary embolism, and one for continued, long-term treatment in patients who have received treatment for acute DVT or pulmonary emboli. The results of the first and third wings of the study were recently reported in the *New England Journal of Medicine*.

In the DVT treatment arm, 3449 patients with acute DVT were randomized to rivaroxaban (50 mg twice daily for 3 weeks, followed by 20 mg once daily) or subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months. In the continued treatment wing of the study, patients were randomized in a double-blind fashion to rivaroxaban 20 mg once daily or placebo for additional 6 or 12 months after completion of 6-12 months of treatment for VTE. The primary outcome for both studies was recurrent DVT. For the treatment of acute DVT, rivaroxaban was non-inferior to enoxaparin-vitamin K antagonist (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.44-1.04; $P < 0.001$). In the continued treatment study, rivaroxaban had superior efficacy compared to placebo (8 events [1.3%] vs 42 events [7.1%] with placebo; HR 0.18; 95% CI, 0.09-0.39; $P < 0.001$). There were four patients in the rivaroxaban group with non-fatal major bleeding vs none in the placebo group. The EINSTEIN authors concluded that "Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation" (*N Engl J Med* 2010;363:2499-2510).

Rivaroxaban is also being evaluated for the prevention of stroke in patients with nonvalvular atrial fibrillation based on the ROCKET AF study, which was presented at the American Heart Association meetings in November 2010. If approved, it will join the recently approved direct thrombin inhibitor dabigatran (Pradaxa®) for this indication. Both drugs have the advantage over warfarin of not requiring ongoing lab monitoring. ■

Echinacea and the common cold

The National Center for Complementary and Alternative Medicine (NCCAM), a division of NIH, has been in existence for nearly 20 years, much of the time under the intense scrutiny of the mainstream medical community. Despite NCCAM's attempts to verify the effectiveness of alternative healing practices, most if not all rigorously studied modalities have been shown to be ineffective. The benefit of another alternative staple, echinacea, is questioned with the publication of a NCCAM-sponsored study testing the benefit of the herbal remedy for treating the common cold. More than 700 patients in Wisconsin with new-onset common cold were assigned to one of four groups: no pills, placebo pills (blinded), echinacea pills (blinded), or echinacea pills (unblinded). The primary outcome was severity of the cold by self reporting with secondary outcomes of interleukin-8 levels and neutrophil counts from nasal washes. The comparison of the two blinded groups showed a trend toward benefit for the echinacea group (an average decrease in duration of cold of 7-10 hours out of 1 week; $P = 0.089$), but no difference in mean illness duration. There were no differences in the secondary outcomes. The authors concluded that the differences in illness duration and severity were not statistically significant with echinacea compared to placebo (*Ann Intern Med* 2010;153:769-777). ■

FDA Actions

The FDA is removing the breast cancer indication for bevacizumab (Avastin-Genentech). The somewhat unusual move was made after an FDA advisory panel suggested last summer that the drug did not provide a survival benefit for patients with breast cancer and at the same time caused serious side effects. The drug is still approved for treating cancer of the brain, colon, kidney, and lung.

The **FDA advisory panel is recommending approval for the first new diet pill in a decade. Orexigen Therapeutics' Contrave® is a combination of the antidepressant bupropion and the opioid antagonist naltrexone.** The drug was recommended for approval by a vote of 13-7, with some committee members voicing concern about potential side effects of the drug and recommending close post-marketing follow-up and studies to assess the risk of major cardiac events. The recommendation to approve the drug was based on studies that show an average weight loss 4.2% greater than placebo.

The **FDA has approved denosumab for the prevention of skeletal related events (fracture and bone pain) in patients with bone metastases from solid tumors.** The drug, which is given as a once monthly injection, was approved after a 6-month priority review. Denosumab is a monoclonal antibody to RANKL, a protein essential for the formation, function, and survival of osteoclasts. Denosumab in a lower-dose formulation was recently approved for the treatment of osteoporosis under the trade name Prolia™. Amgen Inc. will market the drug for this new indication under the trade name Xgeva™. It is expected to compete strongly with Novartis Pharmaceutical's zoledronic acid (Zometa®), which is approved for the same indication. ■