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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 this field of study.

Early Goal-directed Therapy for Sepsis

ABSTRACT & COMMENTARY

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

Synopsis: *One-year mortality post-severe sepsis and septic shock was significantly reduced after implementation of an early goal-directed therapy protocol for sepsis in a large urban emergency department.*

Source: Puskarich MA, et al. One year mortality of patients treated with an emergency department based early goal directed therapy protocol for severe sepsis and septic shock: A before and after study. *Crit Care* 2009;13:R167; Epub ahead of print.

EARLY GOAL-DIRECTED THERAPY (EGDT) HAS BEEN SHOWN TO reduce hospital mortality from severe sepsis and septic shock. Puskarich et al hypothesized that long-term outcome would also be improved. They performed a prospective observational study of 1-year outcome of patients presenting to the emergency department (ED) with severe sepsis or septic shock in the year before ("pre") and the 2 years after ("post") implementation of an EGDT protocol. Their protocol was derived from that of Rivers et al[1] with minor differences; a lactate level was not required and the resuscitation was transferred to ICU physicians as soon as an ICU bed became available (rather than after 6 hours).

Eligible subjects were > 17 years old, met usual criteria for sepsis, and had persistent hypotension after fluid resuscitation (20 mL/kg isotonic fluid bolus) or lactate ≥ 4.0 mM with anticipated need for ICU stay. The pre-implementation phase was 13 months and patient resuscitation and care were as per the discretion of the emergency medicine physician. The post-implementation phase was 24 months. The authors gathered data on usual demographics, severity of illness, ICU and hospital lengths of stay, and use of specific sepsis therapies such as activated protein C. At ≥ 15 months

after enrollment, searches of a large regional medical record database and social security death index were performed; if the patient's status was still unknown after these searches, the patient was assumed to be alive.

The study enrolled 293 patients; 8 were eliminated post-hoc as they died within 6 hours of enrollment, leaving 79 subjects in the pre-implementation and 206 subjects in the post-implementation group. The 2 groups were well-matched, except for more end-stage renal disease in the pre-implementation group and slightly greater severity of illness and lower initial blood pressures in the post-implementation group. More subjects in the post-implementation group received corticosteroids for sepsis. In terms of outcomes, post-implementation patients had longer ICU lengths of stay and trended toward longer hospital stays, received more intravenous fluids and vasopressors, and were more likely to be intubated. One-year mortality was significantly less at 37% in the post-implementation group compared to 49% in the pre-implementation group, which translates to an estimated number needed to treat of 8.

■ COMMENTARY

In 2001, Rivers et al published a landmark study of the early management of patients with severe sepsis or septic shock.[1] They randomized 263 patients presenting to their ED with severe sepsis or septic shock to standard therapy or 6 hours of a fairly simple but aggressive protocol targeting a specific central venous pressure, mean arterial pressure, and central venous oxygen saturation. They found that their early goal-directed therapy reduced organ dysfunction and severity of illness; most significantly, hospital mortality was 30.5% in the treatment group, compared to 46.5% in the control group.

This intervention is now recommended as standard of care for sepsis.[2] Implementation, however, has lagged.[3]

The study by Puskarich et al is an interesting addition to the literature. The overall hospital mortality from severe sepsis and septic shock in this study is less than that observed by Rivers et al (27% in the pre-implementation group and 17% in the post-implementation group), although the relative reduction with EGDT is similar and this adds support to the efficacy of that intervention. The etiology of the difference is unknown but changes in overall ED and hospital care over time (timing and appropriateness of initial antibiotics, for instance) and differences in patient populations may be important contributing factors.

The authors' hypothesis that EGDT may improve long-term outcomes is intriguing, but it is difficult to associate intervention in the first few hours of a medically complicated septic patient's care with outcome at 1 year. A very robust analysis would be needed to truly support this association. The authors use multivariate regression models (it is unclear whether their variables were defined a priori) to attempt to adjust for some factors that could account for long-term mortality differences. However, the non-contemporaneous (and thus unmatched and non-randomized) small patient populations in this study and the very limited information about patient characteristics, their care, and course beyond the initial few hours of hospitalization are significant limiting factors. Thus, I believe the question of whether EGDT directly impacts long-term outcomes such as 1-year mortality remains unanswered.

Perhaps most importantly, this study serves as an excellent example of the feasibility of implementing EGDT protocols in any ED and will, hopefully, lead hospitals without such protocols in place to reconsider EGDT. ■

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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.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

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To Prone or not to Prone … That Is the Question

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

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

Synopsis: *This multicenter, unblinded, randomized trial demonstrated that prone positioning was not associated with a mortality benefit in patients with ARDS, including subgroups with moderate and severe hypoxemia.*

Source: Taccone P, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2009; 302:1977-1984.

Prone positioning has been advocated as a management strategy for patients with acute respiratory distress syndrome (ARDS), but despite evidence of improved oxygenation with the technique, numerous studies have yet to establish a mortality benefit from the practice. Post-hoc analysis of data from an earlier trial did suggest, however, that a mortality benefit might be present in patients with the most severe hypoxemia.[1] Taccone and colleagues sought to test this finding in a prospective manner by applying prone positioning to ARDS patients with moderate and severe hypoxemia and evaluating whether the practice led to improvement in survival for these patients.

To test their hypothesis, the authors conducted a multicenter, unblinded, randomized controlled trial in 23 centers in two countries. Eligible patients included those 17 years and older, receiving mechanical ventilation and meeting accepted diagnostic criteria for ARDS. Patients were excluded from the study if more than 72 hours had elapsed since the diagnosis of ARDS, or if they had a history of solid organ or bone marrow transplantation or had any condition precluding prone positioning (e.g., intracranial hypertension, spine or pelvic fractures). Included patients were randomly assigned to the control (supine positioning) or intervention (prone positioning using a Rotoprone rotational bed for > 20 hours per day until resolution of acute respiratory failure or the end of the 28-day study period) group, and were stratified into two groups based on the severity of their hypoxemia at the time of enrollment: moderate hypoxemia (PaO_2/F_IO_2 ratio, 100-200 mm Hg) and severe hypoxemia (PaO_2/F_IO_2 ratio < 100 mm Hg). Patients in both groups were ventilated using a standard protocol requiring tidal volume ≤ 8 mL/kg, plateau pressure ≤ 30 cm H_2O, and standardized adjustments in positive end-expiratory pressure (PEEP) and F_IO_2 to maintain PaO_2 at 70-90 mm Hg. All other therapeutic decisions (e.g., antibiotics, sedation) were at the discretion of the treating physician. The primary outcome measure was 28-day mortality, while secondary outcome measures included mortality at ICU discharge and 6 months, Sequential Organ Failure Assessment (SOFA) scores at 28 days, and ventilator-free days during the 28-day study period.

A total of 342 patients were included in the final analysis (168 prone, 174 supine). Of these patients, 192 were classified as having "moderate" hypoxemia (94 prone, 98 supine) while the remaining 150 had severe hypoxemia (74 prone, 76 supine). Patients in the intervention group were prone a mean of 8.4 ± 6.3 sessions lasting on average 18 ± 4 hours per day. Twenty percent of patients in the prone group missed at least one proning session due to factors such as hemodynamic instability, facial edema, or malfunction of continuous renal replacement therapy. Twenty patients in the supine group (11.5%) received prone positioning as a rescue procedure. Across the entire study population, the PaO_2/F_IO_2 ratio was higher in the prone group compared to the supine group. Mortality at 28 days was the same in the prone and supine groups (31% vs 32.8%) and there were also no statistically significant differences in mortality between patients with moderate (prone, 25.5% vs supine, 22.5%) or severe hypoxemia (prone, 37.8% vs supine, 46.1%).

There were no differences in secondary outcomes between the prone and supine groups across the entire study population or within the predefined subgroups. The complication rate was significantly higher in the prone group (95% with at least one complication compared to 76% in the supine group) with the prone

patients having a higher incidence of need for increased sedation or paralysis (80% vs 56%), airway obstruction (51% vs 34%), vomiting (29% vs 13%), loss of venous access (16% vs 4%), hypotension or need for pressors (72% vs 55%), and endotracheal tube displacement (11% vs 5%).

■ COMMENTARY

This paper is yet another entry in a line of studies that shows the same pattern of results with regard to the effect of prone positioning in patients with ARDS — improvements in oxygenation that do not translate to improvements in important patient outcomes. By looking specifically at patients with severe hypoxemia (PaO_2/F_IO_2 < 100 mm Hg), the study by Taccone and colleagues was supposed to address an important limitation of previous studies — their inclusion of patients with a wide range of abnormalities in oxygenation — that was purported by proning proponents to be masking a survival benefit that would otherwise be seen in the more severely ill patients. As we see now, however, even within the most severely ill ARDS patients, proning has no impact on survival.

In addition to the persistent inability to demonstrate a mortality benefit, there are other data in this paper that should give pause to those considering the utility of this technique. In particular, even though they used a specialty proning bed rather than manual proning techniques, there was a high complication rate in the prone patients, with more than 94% of them experiencing at least one complication such as endotracheal tube dislodgement, loss of venous access, airway obstruction, hypotension, and need for increased sedation and paralysis. This surprisingly high complication rate forces one to step back and wonder whether the use of proning not only doesn't provide benefit to our patients, but may also put them at risk for more harm.

Will the results of this study change practice and decrease the use of this expensive modality? That is probably unlikely to happen. Like a lot of the therapies used in the management of patients with critical hypoxemia, including inhaled vasodilators, extracorporeal membrane oxygenation (ECMO), and alternative modes of mechanical ventilation, this therapy has its proponents and those whose assessment of its utility is affected by anecdotal experiences of patient improvement. It is hard to look at the single patient at the bedside who is experiencing severe, life-threatening hypoxemia and not use a technique that "worked" in a previous patient. At some point, however, the preponderance of the evidence has to win out and we need to step back and consider whether this therapy is really safe and beneficial. ■

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Expedited ICU Admission from the ED Decreases Mechanical Ventilation Days and ICU Stay

ABSTRACT & COMMENTARY

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

Synopsis: *Expedited admission (< 2 hours) of critically ill patients who require intubation and mechanical ventilation from the emergency department to the ICU improves patient outcomes.*

Source: Cline SD, et al. Expedited admission of patients decreases duration of mechanical ventilation and shortens ICU stay. *Am J Emerg Med* 2009;27: 843-846.

Prior studies have demonstrated that delayed transfer of critically ill patients from the emergency department (ED) to the ICU (> 6 hours) prolongs ICU and hospital stay. The purpose of this retrospective study was to determine whether this difference persists when ED wait time is reduced to < 2 hours. Subjects were 78 patients age 55.3 ± 13.1 years (range, 26-75 years) with respiratory failure of sufficient severity to require intubation and mechanical ventilation prior to transfer from the ED to the ICU. Patients directly admitted to the ICU from outside hospitals or patients for whom care was withdrawn in < 24 hours were excluded.

Two patient groups were identified. The expedited group (n = 12) remained in the ED < 120 minutes prior to ICU transfer and the non-expedited group (n = 66) waited > 120 minutes. Mean wait time for the entire group was 250 ± 148 minutes. No significant between-group differences were found for age, sex, chronic health conditions, or the condition that precipitated need

for mechanical ventilation (that is, primarily exacerbation of COPD, heart failure, neurologic disorders, substance abuse, or pneumonia). APACHE II scores were similar between the expedited and non-expedited patients (21.4 ± 9.5 vs 20.4 ± 8.5; $P = 0.8998$) as were SAPS II scores (47.3 ± 12.8 vs 45.0 ± 14.8; $P = 0.3632$). However, mean duration of mechanical ventilation was shorter for the expedited vs the non-expedited group (28.4 ± 33.4 vs 67.9 ± 99.2 hours; $P = 0.0431$). Length of ICU stay was also shorter (2.4 ± 2.2 vs 4.9 ± 5.2 days; $P = 0.0209$). The length of hospital stay also tended to be shorter (6.8 ± 7.4 vs 8.9 ± 7.8 days; $P = 0.0609$). No significant between-group differences were found for ICU survival or survival to discharge.

■ COMMENTARY

Multiple factors influence the wait time for an open bed, including ICU bed availability, hospital admission policies, ED staffing, and wait times for diagnostic procedures. Findings of this study suggest that such delays can increase time on mechanical ventilation and days in the ICU, factors that substantially increase costs. The time interval examined in this study (< 2 hours) was considerably shorter than that examined in a prior study (< 6 hours) by Chalfin et al,[1] which reported essentially the same findings in a larger sample of patients admitted from the ED to the ICU. In contrast to the Chalfin study, which examined outcomes in all patients admitted to the ICU from the ED, the present study only enrolled patients who required intubation and mechanical ventilation prior to ICU transfer. Mean elapsed time in the ED before transfer to the ICU was slightly more than 4 hours, shorter than the interval examined by Chalfin et al.[1]

What can be done to remedy this situation? The first step is to recognize the value of rapid movement through the system. Because of its busy nature, crowding, and practice characteristics, e.g., the need to simultaneously manage the care of patients with varying acuity, ED clinicians may not be able to provide the close monitoring that critically ill patients receive in the ICU or have the best resources to provide this care. Transfer entails a handoff, which inevitably results in the need to review the current management plan, assess patient response, and determine what changes, if any, might be needed, additional factors that might impact patient outcomes. Patients who may be beginning to stabilize in the ED must be transported to another setting and routines begun again. Findings of this study suggest that systems of care that promote rapid transfer from the ED to the ICU are likely to result in better outcomes and lower costs. The results also suggest that relatively minor differences in time spent in the ED (< 2 hours) can produce significant differences in outcomes. ■

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Special Feature

Families in the ICU: What Intensivists Should Know

By Richard J. Wall, MD, MPH

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

EVERY INTENSIVIST RECOGNIZES THAT FAMILIES PLAY A prominent role in ICU decision making. These roles vary considerably between families (and often drastically between members of the same family). The reasons for this variability include family factors such as relationship to the patient, ethnicity, cultural background, age, education, and level of trust with providers. Patient factors also impact family decision making such as severity of illness, patient preferences, and the level of prognostic certainty. To complicate matters, many patient factors are not static. Moreover, clinicians bring their own personal biases and variable levels of training with handling families into these interactions. Not surprisingly, ICU clinicians describe this as one of the most challenging aspects of their job.

In the current essay, I will discuss key areas of research on families in the ICU. I will briefly present a rationale for why you should even care about this topic. The remainder of the essay will be devoted to examining what is known about ICU family satisfaction, the concept of shared decision making, and ways to improve physician-family communication.

Why Focus on Families in the ICU?

Focusing on ICU families is important from a quality standpoint. A key component of quality care is patient-centeredness. Because families play a key role in ICU decision making, delivering patient-centered care requires delivery of family-centered care. Indeed, most

critically ill patients prefer that their families be relied upon for decision making, even if the family's wishes and the patient's advance directives disagree.[1]

Focusing on ICU families improves patient care. Family-focused interventions can resolve decisional conflicts, increase the likelihood that families come to a definitive treatment decision, reduce ICU length of stay, and decrease the use of non-beneficial treatments.[2-4]

Focusing on ICU families is important because these individuals have unique needs. These needs can be classified into five domains: support, comfort, proximity, information, and assurance.[5] A variety of studies have demonstrated that nearly all of these needs are actionable and under the direct control of ICU clinicians. Studies also suggest that ICU families need our help because they are at risk. Many family members experience post-traumatic stress or depressive symptoms when their loved one is in the ICU,[6] and this may impact their decision-making ability. In addition, ICU families are at risk for conflict between themselves and with providers. From a practical standpoint, delivering family-centered care is a smart business strategy because lawsuits are less likely when families experience open, honest communication.[7]

Family Satisfaction

Recent studies have focused on measuring and understanding family satisfaction. In a multicenter Canadian study, provider-family communication had more influence on overall family satisfaction scores than patient-related aspects of care.[8] Similarly, another multicenter French study found that the key predictors of family satisfaction were information exchange and communication with providers.[9] This desire for information exchange is a recurring theme among ICU families regardless of whether the patient lives or dies.[10]

Several tools are available for measuring family satisfaction in the ICU. The best known and original tool is the Critical Care Family Needs Inventory (CCFNI).[5] This 45-item instrument has been rigorously validated for more than 20 years and translated into numerous languages. A shorter 14-item version was released in 1998.[11] The CCFNI is easy to administer and score. Each item is rated from 1 to 4. However, the CCFNI lacks many items on decision making, a shortcoming that prompted development of newer tools.

The Family Satisfaction in the ICU survey (FS-ICU) is a 24-item questionnaire designed to measure family satisfaction with ICU care.[12] The first 14 items measure satisfaction with overall care, whereas the last 10 items measure satisfaction with decision making. Researchers have used the FS-ICU in several studies. Recently, the FS-ICU was used by the American College of Chest Physicians in a multicenter intervention study.[13] The instrument has been translated into several languages and is available on-line.[12]

A final tool is the 20-item Critical Care Family Satisfaction Survey.[14] The various items are rated on a 5-point Likert scale, and distributed among 5 subscales. The instrument has been translated into a few languages, but research experience is still limited.

Family Decision Making in the ICU

Acknowledging that ICU clinician-family communication is often inadequate, Curtis and White recently published a guideline for conducting evidence-based family conferences.[15] A portion of this excellent paper is dedicated to the concepts of decision making in the ICU.

Intensivists often view their role in ICU decision making in one of three ways: 1) parentalism (doctor makes treatment decisions with little input from family); 2) informed choice (doctor provides information but withholds opinions and allows family to bear the burden of decision making); or 3) shared decision making (both physician and family express their opinions and jointly reach a decision).

Curtis and White propose a stepwise approach for improving family decision making in the ICU. Shared decision making is the default starting point. First, the physician should determine the patient's prognosis, and if possible, the certainty of that prognosis. Second, the physician should inquire as to the family's desired decision-making role, given the prognostic information. Third, the physician should adapt his/her communication approach to the family's desired role. Finally, this cycle should be repeated as new clinical information becomes available and prognosis changes.

In the beginning of an ICU stay, a shared decision-making model may be most appropriate. However, as the prognosis becomes poorer and the certainty about this prognosis becomes higher, physicians might want to shoulder more of the decision-making burden, thereby allowing the family to cede responsibility for these uncomfortable decisions. This is sometimes referred to as "informed assent." Of course, this will largely depend on the family's desired role, hence step 2 above.

When meeting with family members, use the principle of "substituted judgment," i.e., what would the patient say if he/she were present. In general, families are often unable to state their role preference unless they first understand the prognostic certainty. Realize that family members may shift their preferences, at which point the physician must reevaluate and shift his/her own role.

Table

Strategies for improving the quality of ICU family conferences

- Hold conference within 72 hours of admission
- Identify a private place for family conference
- Ensure consistent information from team members
- Increase proportion of time spent listening to family
- Decrease proportion of time spent talking to family
- Make empathic statements
- Acknowledge difficulty of having a loved one in the ICU
- Acknowledge difficulty of surrogate decision making
- Recognize commonly missed opportunities
- Explore the patient's values and preferences
- Explain the concept of surrogate decision making to family
- Assure non-abandonment of both patient and family
- Assure that the patient will not suffer
- Explicitly support decisions made by the family

Adapted from: Curtis JR, White DB. Practical guidance for evidence-based ICU family conferences. *Chest* 2008;134:835-843.

In my opinion, what makes this paradigm helpful is that it explicitly reminds us that the purpose of a family conference is not to coerce the family into agreeing with what the medical team thinks is best. Rather, the purpose of a conference is to share clinical information and elicit the family's preferred role for decision making. Physicians must view themselves as a dynamic variable, constantly reassessing the situation and adapting their communication style to fit the family's desired decision-making role.

Improving Family Conferences

Observational studies have uncovered useful strategies for improving the quality of ICU family conferences *(see Table, above)*. Several of these strategies have been combined into a 5-letter mnemonic (VALUE) for improving clinician-family communication: value, acknowledge, listen, understand, elicit *(see Figure, above)*. A few are worth highlighting. McDonagh et al showed that family members were more satisfied with physician communication if the physician talked less (and listened more) during the conference.[16] Curiously, the total conference duration did not correlate with family satisfaction. Stapleton et al examined physician statements during family conferences, and found three types of statements were associated with higher family satisfaction: 1) assure that the patient will not be abandoned; 2) assure that the patient will not suffer; and 3) support the family's decisions.[17]

Figure

VALUE mnemonic for improving clinician-family communication in the ICU[17]

V … **V**alue family statements
A … **A**cknowledge family emotions
L … **L**isten to family
U … **U**nderstand the patient as a person
E … **E**licit question from the family

The VALUE mnemonic was recently used in a randomized trial aimed at improving clinician-family communication for patients dying in the ICU.[18] By simply using the VALUE mnemonic and handing out a bereavement pamphlet during family conferences, physicians were able to dramatically reduce family member psychological stress. At 3 months after ICU stay, the prevalence of anxiety and depression symptoms were dramatically lower in the intervention group (anxiety: 45% vs 67%; $P = 0.02$; depression: 29% vs 56%; $P = 0.003$). The intervention group also had less post-traumatic stress symptoms (45% vs 69%; $P = 0.01$). Although the authors could not determine how much of the effect was due to the pamphlet vs the mnemonic, the results were nonetheless impressive.

Summary

Family members are an integral part of today's ICU, and most want to share in decision making for their loved one. These family members have unique needs and are under incredible psychological stress. The quality of physician-family communication directly impacts family satisfaction with ICU care, and several instruments are now available for easily measuring ICU family satisfaction. A growing body of research has shed light on various ways that physicians can improve ICU family conferences. A recent randomized trial suggests that performing evidenced-based family conferences can improve long-term psychological outcomes in family members who have a loved one in the ICU. ■

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CME / CNE Questions

37. Rivers et al's early goal-directed therapy protocol for severe sepsis and shock:
a. required all patients to be intubated at presentation.
b. reduced organ dysfunction but did not alter mortality.
c. targeted specific central venous pressure, mean arterial pressure, and central venous oxygen saturation parameters.
d. focused on care after admission to the intensive care unit.
e. targeted reduction in median time to antibiotic administration.

38. Which of the following statements is *true* concerning the use of prone positioning in patients with ARDS and severe hypoxemia (PaO_2/F_1O_2 ratio < 100 mm Hg)?
a. Mortality at 28 days is improved compared to patients ventilated in the supine position.
b. Mortality at 6 months is improved compared to patients ventilated in the supine position.
c. The incidence of complications is higher than in patients ventilated in the supine position.
d. The number of ventilator-free days is increased relative to patients ventilated in the supine position.

39. If critically ill patients who required intubation and mechanical ventilation remained in the ED for > 2 hours prior to transfer to the ICU:
a. ICU stay increased significantly.
b. mortality decreased significantly.
c. survival to discharge decreased significantly.
d. no differences were seen in time on mechanical ventilation.

40. When preparing for an ICU family conference, what is the recommended first step?
a. Assess patient's preferences for end-of-life care.
b. Assess the patient's overall prognosis and certainty of the prognosis.
c. Determine if the family wants an informed choice decision-making model.
d. Establish a consistent communication style that does not vary.

Answers: 37. c, 38. c, 39. a, 40. b.

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.

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*.

Niacin Beats Ezetimibe Head to Head

In this issue: *Statin and niacin increase HDL-C, omeprazole reduces effectiveness of clopidogrel, darbepoetin increases risk of stroke, statins decrease risk of gallstone disease, FDA Actions.*

Statin plus niacin or ezetimibe?

Raising HDL-cholesterol (HDL-C) with niacin plus a statin is superior to lowering LDL-cholesterol (LDL-C) with ezetimibe plus statin in reversing atherosclerosis according to the widely reported ARBITER trial published on-line in the *New England Journal of Medicine* in November and simultaneously reported at the American Heart Association meeting in Orlando, FL. The trial enrolled more than 200 patients with coronary heart disease or a coronary heart disease equivalent who were receiving long-term statin therapy with an LDL-C < 100 mg/dL along with an HDL-C < 50 mg/dL for men or 55 mg/dL for women. The patients were randomly assigned to receive extended-release niacin (target is 2000 mg/day) or ezetimibe (10 mg/day). The primary endpoint was the difference in change from baseline in mean and maximal carotid intima-media thickness after 14 months. The trial was terminated early in July of 2009. Both drugs were effective in their roles — the mean HDL-C in the niacin group increased by 18.4% over the 14-month study period ($P < 0.001$) and the mean LDL-C level in the ezetimibe group decreased by 19.2% ($P < 0.001$). Niacin significantly reduced LDL-C and triglycerides as well, while ezetimibe lead to a reduction in HDL-C and triglycerides. Niacin was superior to ezetimibe in reducing the primary endpoint, leading to a reduction of both mean ($P = 0.001$) and maximal carotid intima-media thickness ($P \leq 0.001$ for all comparisons). Paradoxically, greater reductions in LDL-C seen with ezetimibe were significantly associated with increases in the carotid intima-media thickness. The incidence of major cardiovascular events was also lower in the niacin group than in the ezetimibe group (1% vs 5%; $P = 0.04$ by the chi square test) (published on-line at: www.nejm.org; Nov. 15, 2009).

The study has received enormous attention not only because of the primary endpoint, but also because of the significant reduction in major adverse cardiac events in the niacin group, even though the numbers were quite small. At least one editorialist laments the early termination of the study and feels that it is impossible to make recommendations regarding the "adjuvant agent of choice" based on the small numbers (The HALTS Trial — Halting Atherosclerosis or Halted Too Early; published on-line at: www.nejm.org; Nov. 15, 2009). Still, this study provides enough evidence to consider adding niacin to a statin in patients who are at risk of or have low HDL-C. It also deals another blow to ezetimibe (Zetia®) and its partner drug ezetimibe/simvastatin (Vytorin®).

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Omeprazole's effect on clopidogrel

The FDA has issued a warning regarding the combination of clopidogrel (Plavix®) with omeprazole (Prilosec®) citing new data that suggest that the combination reduces clopidogrel's effectiveness by about half. Studies reported in 2009 suggested that omeprazole may block clopidogrel's conversion to its active metabolite via CYP2C19, an enzyme that is inhibited by omeprazole. New studies requested by the FDA from the manufacturers confirm a significant interaction between the two drugs, which can significantly hinder clopidogrel's ability to prevent platelet aggregation in patients at risk for heart disease. Omeprazole and clopidogrel are commonly prescribed together to prevent GI bleeding. At this time it is unclear whether this interaction extends to other proton pump inhibitors, although physicians are encouraged to avoid a combination of clopidogrel with esomeprazole (Nexium®, cimetidine (Tagamet®), and other drugs known to inhibit CYP2C19. The FDA is recommending that patients who need GI protection in conjunction with clopidogrel may safely use ranitidine (Zantac®), famotidine (Pepcid®), nizatidine (Axid®), or oral antacids.

Darbepoetin and risk of stroke

Darbepoetin alfa (Aranesp®) is commonly used in patients with chronic kidney disease and diabetes for the treatment of anemia. A new study suggests that the drug may be associated with increased risk of stroke in this patient population. More than 4000 patients with diabetes, chronic kidney disease, and anemia were randomly assigned to darbepoetin alfa to achieve a hemoglobin level of 13 g/dL or placebo with rescue darbepoetin alfa if hemoglobin levels dropped < 9 g/dL. The primary endpoints were the composite outcomes of death or cardiovascular event, and death or end-stage renal disease. After a follow up of 2.5 years, darbepoetin alfa was ineffective at preventing either primary outcome, and, more importantly, the rate of fatal or nonfatal stroke occurred almost twice as often in the treatment group (101 patients assigned to darbepoetin alfa vs 53 patients assigned to placebo; HR, 1.92; 95% confidence interval, 1.38-2.68; $P < 0.001$). The authors conclude that the use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who are not undergoing dialysis did not reduce the outcome of death, cardiovascular events, or renal events, but was associated with increased risk of stroke. For many "this risk will outweigh the potential benefits" of the drug (*N Engl J Med* 2009;361:2019-2032). Erythropoiesis-stimulating agents have come under fire in the treatment of cancer-associated anemia, and now in renal patients as well. As pointed out in an accompanying editorial, the risks and benefits of these agents must be weighed, namely an increased risk of stroke vs a perceived improvement in quality of life (*N Engl J Med* 2009; 361:2089-2090).

Statins and gallstone disease

Statins have been shown to reduce the risk of cardiovascular disease and death from all causes. Now another potential benefit is being reported: Statins may reduce gallstone disease. Utilizing a large patient database from the United Kingdom, researchers looked at the risk of developing gallstones followed by cholecystectomy in relation to exposure to lipid-lowering agents. The longer patients took statins, the lower the risk for gallstone disease, with patients who had filled 20 or more prescriptions noticing 36% reduction in risk (AOR, 0.64; 95% confidence interval, 0.59-0.70). The authors conclude that long-term use of statins is associated with a decrease risk of gallstones followed by cholecystectomy (*JAMA* 2009;302:2001-2007).

FDA Actions

The FDA has approved a new topical treatment for the treatment of post-herpetic neuralgia (PHN). The capsaicin 8% patch must be applied to the skin by a health care professional since placement may be quite painful, requiring the use of a local topical anesthetic. The patch is applied for one hour during which patients must be monitored, including observation for increases in blood pressure. The patches may be cut to conform to the area of pain and up to 4 patches may be used. The one-hour application is reported to provide up to 12 weeks of reduced pain from PHN. The capsaicin 8% patch will be manufactured by Lohmann Therapie-Systems and distributed by NeurogesX as Qutenza™.

The FDA has approved romidepsin for the treatment of cutaneous T-cell lymphoma in patients who received at least one prior systemic therapy. The drug is a histone deacetylase inhibitor, the first of a new class of antineoplastics. Romidepsin will be marketed as Istodax® by Gloucester Pharmaceuticals. ■

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