CRITICAL CARE ALERT®

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

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INSIDE

Leapfrog and Critical Care: Evidence and Reality in the ICU

ABSTRACT & COMMENTARY

Synopsis: *Leapfrog Group's standards for critical care are not grounded sufficiently in evidence to mandate their stringent and universal implementation. Rather, most of the guidelines are grounded in common sense and rational extrapolation of the data. As such, they are a reasonable starting point for debate by physicians and policymakers about optimal methods of achieving intensivist-guided care of critically ill patients.*

Source: Manthous CA. *Am J Med*. 2004;116:188-193.

THE LEAPFROG GROUP FOR PATIENT SAFETY (WWW.LEAPFROGgroup.org) made some specific suggestions for improvement of hospital care. The Leapfrog Group was established by the Business Roundtable, which consists of the chief executive officers of several large corporations that purchase health insurance for more than 34 million health care consumers. They consider 3 practices to have tremendous potential for saving lives by reducing preventable mistakes in hospitals: computerized physician order entry; evidence-based hospital referral; and ICU physician staffing.

In this article, Manthous outlines the Leapfrog standards for critical care, which are available on the Web at www.leapfroggroup.org/FactSheets/ICU-FactSheet.pdf, and critically examines the evidence used to justify them.

The following are the primary recommendations for improvement of critical care as published in this article:

1. Intensive care units should be staffed by board-certified intensivists, to coordinate and manage the care of patients;
2. Intensivists should staff ICUs for a minimum of 8 hours per day, 7 days per week;
3. Intensivists should respond to more than 95% of calls for assistance within 5 minutes;
4. Either the intensivist—a "fundamentals of critical care" certified physician—or an appropriately certified "physician extender" should arrive at the bedside within 5 minutes in 95% of cases.

Certification of intensivists is achieved by completion of an

accredited fellowship program sanctioned by the Boards of Internal Medicine, Surgery, Pediatrics, and Anesthesiology. Care "extenders" are physicians or allied health care personnel who provide critical care during hours when the intensivist is not available on site. (Certification to become an "extender" is achieved by attending to a 2-day course sponsored by the Society of Critical Care Medicine.)

In addition to maintaining the previous guidelines, the medical advisory panel of the Leapfrog Group suggested the following additional measures in 2003:

1. Expanding Leapfrog standards to pediatric critical care;
2. Loosening the criteria for qualifications of "intensivists" in order to "grandfather" practitioners who graduated before 1987;
3. Limiting care by each intensivist to one ICU at any given time;

Manthous asserts that many of the Leapfrog Group's standards for critical care are not grounded sufficiently in evidence to mandate their stringent and universal implementation. On the other hand, no published studies have demonstrated harm associated with intensivist care and, according to Manthous, these guidelines make common sense, and if sufficient manpower were available, they could serve as the starting point to formulate realistic goals. Added to that, he raises several important questions regarding the optimal model of ICU practice and the role of the emerging hospitalist movement in addressing the critical care manpower shortfall.

COMMENT BY FRANCISCO BAIGORRI, MD, PhD

My comment about the Manthous article is logically conditioned by my experience as an intensivist who has been working for more than 20 years in closed ICUs, in public university hospitals. This experience makes me hypercritical about this organizational structure. In my opinion, one of the main drawbacks of this system is that it can easily induce a fragmentation of the care process. It is quite obvious that critically ill patients should be treated by adequately qualified professionals. However, although they are absolutely not opposing concepts, I am not sure whether compliance with Leapfrog guidelines may complicate the development of critical care as a service to a particular patient population and the necessary multi-disciplinary approach that it requires.

There is an increasingly complex population of hospitalized patients on a continuum of severity of illness with critically ill patients. I feel strongly that critical care requires services that extend beyond the physical boundaries of intensive care to avoid what Shoemaker said: ". . .intensive care units give too much too late to too few.[1]" The evidence about the benefit of hemodynamic optimization in the early presentation of disease, such as in the emergency department,[2] supports an organization that focuses on the level of care that individual patients need rather than on beds and buildings.

Nowadays advances in networking may help us to redefine the physical and organizational boundaries of the critical care unit. No longer a self-contained entity interacting as needed with other hospital departments, tomorrow's critical care units are likely to regularly draw on resources—both human and technological—located outside the unit's physical space.[3] In April 1999, the UK Department of Health (www.dh.gov.uk) established a review of adult critical care services, and invited an expert group to develop a framework for the future organization and delivery of critical care. This group developed the concept of comprehensive critical care as a new approach based on severity of illness. The characteristics of such a service should ensure:

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VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

ASSISTANT MANAGING EDITOR: Robert Kimball.

SENIOR COPY EDITOR: Christie Messina Petrone.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

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Editorial E-Mail Address: robert.kimball@thomson.com

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1. Integration—A hospital-wide approach with services which extend beyond the physical boundaries of intensive care and high dependency units, making optimum use of available resources including beds
2. Networks—A service that is provided across NHS Trusts, working to common standards and protocols, taking responsibility for all the critically ill in all specialties within a geographical area
3. Workforce development—A planned approach to workforce development including the recruitment, training and retention of medical and nursing staff, and balancing the skill mix so that professional staff are able to delegate less skilled and non-clinical tasks
4. A data collecting culture promoting an evidence base—A service underpinned by reliable information that will ensure the delivery of effective clinical care, demonstrated through comparative audit.

These characteristics together with Leapfrog guidelines are certainly a reasonable starting point for debate by physicians and policymakers about optimal methods of achieving intensivist-guided care of critically ill patients. ■

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Predicting Outcome in Pulmonary Embolism Using CT Angiography

ABSTRACT & COMMENTARY

Synopsis: *No CT variables predicted severe in-hospital morbidity and mortality (death from pulmonary embolism, death from any cause, or cardiac arrest) in patients with PE. However, ventricular septal bowing and increased RV/LV diameter ratio were both strongly predictive of less severe morbidity, namely, subsequent ICU admission, and oligemia was associated with subsequent intubation and vasopressor use.*

Source: Araoz PA, et al. *J Thorac Imaging*. 2003;18(4):207-216.

THE RADIOLOGY GROUP AT THE UNIVERSITY OF California, San Francisco, attempted to determine whether variables measured on the basis of CT angiography would predict in-hospital morbidity and mortality in patients with pulmonary embolism. Between January 1998 and January 2001, CT scans from 173 patients that were positive for pulmonary emboli were reviewed from 2 hospitals using (initially) single detector and (later) multidetector scanners. The scans were reviewed for the following potential indicators of adverse outcome: leftward ventricular septal bowing; increased right ventricle to left ventricle diameter ratio; clot burden, increased pulmonary artery to aorta diameter ratio; and oligemia. Outcome measurements included death from pulmonary embolism, death from any cause, cardiac arrest, and milder outcomes such as intubation, the use of vasopressors, or admission to the intensive care unit.

Ventricular septal bowing and increased RV/LV diameter ratio both predicted ICU admission, and oligemia was associated with subsequent intubation and vasopressor use. However, no CT variable predicted in-hospital morbidity and mortality in patients with pulmonary emboli. There were several limitations to the study, including the use of single detector scanners early on, a potential bias in patient selection due to the 2 hospitals' lack of use of CT in 1997 for PE, a relatively small sample size, and technical limitations of CT angiography for evaluating right ventricular dysfunction.

COMMENT BY JAMES E. McFEELY, MD

In the last several years, the use of CT angiography has greatly increased as a diagnostic test for proximal pulmonary emboli. The reasons for the increase are various and include the increased availability of multidetector helical scanners with improved sensitivity for clot, the ease of obtaining CT studies, and the associated difficulty in obtaining nuclear medicine studies, particularly during off-hours. CT technology for finding pulmonary emboli is rapidly improving. It is possible that, in the future, electrocardiographically gated helical multiplaner CT pulmonary angiography may be more useful for finding wall motion abnormalities.

As stated Araoz and colleagues, the surface echocardiogram remains the test of choice to evaluate right ventricular dysfunction in patients with acute pulmonary emboli. It is also probably a better choice if you are attempting to predict the in-hospital morbidity and mortality that may result from this phenomenon. ■

Noninvasive Ventilation in Hypoxemic Respiratory Failure

ABSTRACT & COMMENTARY

Synopsis: *The use of noninvasive positive pressure ventilation (NPPV) is effective to reduce intubation and mortality in patients with acute hypoxemic respiratory failure.*

Source: Ferrer J, et al. *Am J Respir Crit Care Med*. 2003;168:1438-1444.

NONINVASIVE POSITIVE-PRESSURE VENTILATION (NPPV) was assessed in 105 patients with severe acute hypoxemic respiratory failure. Patients had a PaO_2 ≤ 60 mm Hg or SpO_2 ≤ 90% while breathing oxygen at a maximal concentration of 50% without hypercapnia. They were randomized to receive NPPV or high-concentration oxygen therapy without positive pressure. The primary outcome variable was intubation rate. Both groups had similar characteristics.

Compared with oxygen therapy, NPPV decreased the need for intubation (25% vs 52%; P = .01), decreased the incidence of septic shock (12% vs 31%; P = .028), decreased intensive care unit mortality (18% vs 39%; P = .028), and increased the cumulative 90-day survival (P = .025). Both arterial hypoxemia and tachypnea improved more as a function of time in the NPPV group (P = .029 for each). Multivariate analyses showed that NPPV was independently associated with decreased risks of intubation (odds ratio, 0.20; P = .003) and 90-day mortality (odds ratio, 0.39; P = .017). The use of NPPV prevented intubation, reduced the incidence of septic shock, and improved survival in these patients compared with high-concentration oxygen therapy.

COMMENT BY DEAN HESS, PhD, RRT

There is as much high-level evidence for the use of NPPV as for any therapy used in critical care. More than 20 randomized controlled trials have investigated this therapy in the past 10 years. The strongest evidence for use of NPPV is for patients with COPD exacerbation, this having been subjected to several recently published meta-analyses.[1-3] In such patients, NPPV decreases need for intubation and mortality. There is also accumulating evidence that NPPV decreases the risk of nosocomial pneumonia.

The evidence supporting the use of NPPV in patients with acute hypoxemic respiratory failure is generally considered weaker than that for COPD exacerbation. That said, previous randomized studies have reported benefit for patients with respiratory failure following solid organ transplant,[4] immunocompromised patients,[5] patients developing respiratory failure following lung resection surgery,[6] and those with multiple etiologies of hypoxemia.[7]

The present study provides additional evidence for the use of NPPV in patients with acute hypoxemic respiratory failure. The causes of respiratory failure in this study were varied and included pneumonia, cardiogenic pulmonary edema, thoracic trauma, acute respiratory distress syndrome (ARDS), acute severe asthma, postoperative respiratory failure, and interstitial pneumonitis. The results of this study indicate that the use of NPPV in patients with acute hypoxemic respiratory failure decreased the need for intubation, the incidence of septic shock, and the levels of tachypnea and arterial hypoxemia, and also improved ICU and 90-day survival compared with patients receiving high-concentration oxygen therapy.

It is important to note that patients were ventilated using the BiPAP Vision ventilator (Respironics Inc) Murrysville, Pa), and that an oronasal mask was used as the first choice. Unlike other ventilators designed specifically to provide NPPV, the Vision ventilator is able to deliver high oxygen concentrations. Moreover, an oronasal mask decreases leak and thus allows application of higher expiratory pressure levels. Although the conclusion is speculative, prior anecdotal experience of poor patient response to NPPV in this patient population may have been due to the use of equipment that was unable to provide sufficient oxygen and expiratory pressure levels.

Evidence is accumulating that NPPV should be considered in patients presenting with acute hypoxemic respiratory failure. NPPV should be considered in patients in whom the cause of hypoxemic respiratory failure is likely to be resolved quickly (that is, over several days). NPPV may be less successful in patients with severe hypoxemia related to ARDS, in whom the course of mechanical ventilation can be expected to be more prolonged. Such patients may be better served by invasive ventilatory support and application of the ARDSnet management strategy. However, this has not been subjected to high-level study.

NPPV decreases the intubation rate, but does not eliminate the need for intubation. In this study, as in previous studies, the intubation rate in patients receiving NPPV was 25%—significantly less than that for those randomized to conventional therapy, but still substantial.

Sometimes clinicians believe that NPPV is not effective because some patients require intubation despite the best efforts to apply it. As demonstrated in this study, 1 in 4 patients who receive NPPV eventually need to be intubated in spite of the clinicians' best efforts to avoid intubation. Nonetheless, the intubation rate is lower with NPPV than with conventional therapy. Moreover, the use of NPPV not only reduces the intubation rate, but it also affords a survival benefit for patients.

Clinician efforts to use NPPV to avoid intubation improve patient-important outcomes. Accumulating evidence suggests that this applies not only to patients with COPD exacerbations, but also to those with acute hypoxemic respiratory failure. ■

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Special Feature

Critical Care Management of the Jehovah's Witness Patient

By Grant E. O'Keefe, MD

Few clinical situations place intensive care practitioners in a more uncomfortable position than does treating patients of the Jehovah's Witness faith. The faith-based refusal of autogenous or allogenic blood transfusions conflicts with the typical life-saving intent implicit in the critical care environment. However, it is our obligation to have a basic level of understanding of the set of beliefs that leads to the choice to refuse this specific set of life-saving therapies, while accepting other aspects of modern medical care. In this article, I will review 4 areas in which critical care practitioners must be knowledgeable in order to care for these challenging patients. In addition to being based upon the published literature, I will make limited general reference to my own experiences in caring for Jehovah's Witness patients and their families. The 4 areas are: 1) religious basis for not accepting blood transfusions; 2) ethical responsibilities for critical care providers; 3) effect of profound anemia on outcomes and; 4) treatment options.

Religious Basis for Not Accepting Blood Transfusions

Jehovah's Witnesses view life as God's gift that is represented by blood. They believe the Bible's command that Christians must "abstain from blood" (New Testament; Acts 15:28,29). According to the Jehovah's Witness faith:

> "Blood is sacred in God's eyes and the soul, or life, is in the blood. Jehovah requires that we abstain from blood. This means that we must not take into our bodies in any way at all other people's blood or even our own blood that has been stored. True Christians will not accept a blood transfusion. They will accept other kinds of medical treatment, such as transfusion of non-blood products. They want to live, but they will not try to save their life by breaking God's laws." (Taken from: http://www.watchtower.org/library/rq/index.htm?article=article_12.htm)

Additional biblical passages are considered by Jehovah's Witnesses to forbid the use of blood, which, while clearly not stated in medical terms, are viewed as ruling out transfusion of whole blood, packed red blood cells, and plasma, as well as white blood cell and platelet administration. The results of accepting these therapies are of great personal and spiritual consequence to those of the Jehovah's Witness faith—the denial of eternal salvation.

Thus, Jehovah's Witnesses will not accept treatments that involve the removal and storage of blood or blood products, including autotransfusion of stored blood or techniques of intra-operative hemodilution involving temporary blood storage. However, many will accept the transfusion of albumin and other blood components (coagulation factors, immune globulins, etc). Furthermore, it is felt that the Bible does not comment directly on organ transplantation nor do they infer that these biblical passages refer to organs or non-blood tissue. Therefore, receipt of organs and non-blood tissues is not prohibited, and is left to be decided by the individual.

Ethical Responsibilities for Critical Care Providers

There are many discussions of the ethical decision-making specifically relating to the treatment of Jehovah's Witnesses or their children. Those included in the list of references provide an excellent discussion of

these issues in more detail than presented here. While this is not meant to be a general discussion of biomedical ethics, it is important to consider how the issue of the right to refuse a blood transfusion for religious reasons is evaluated. One of the most widely used frameworks is that of the "4 principles", which include: 1) respect for persons or autonomy; 2) beneficence or maximizing benefits; 3) nonmaleficence or avoiding harm; and 4) justice or fairness in the distribution of risk and benefit.

The principle of respect for persons states that we must respect a competent individual's decision-making autonomy, even if it may (or will) lead to their death. It could be argued that, in the case of refusal of a life-saving blood transfusion, the principle of respect for persons conflicts with the principle of beneficence. However, we must examine this conflict from the patient's perspective, and when doing so it is evident that the harm of receiving a transfusion (denial of eternal salvation) is greater than the harm of refusal (end of mortal life), essentially placing these principles in congruence.[1] Other approaches determining how to resolve this dilemma exist and essentially arrive at a similar conclusion although through different methods, for other reasons and often with considerable criticism of the "4 principles" approach.[2]

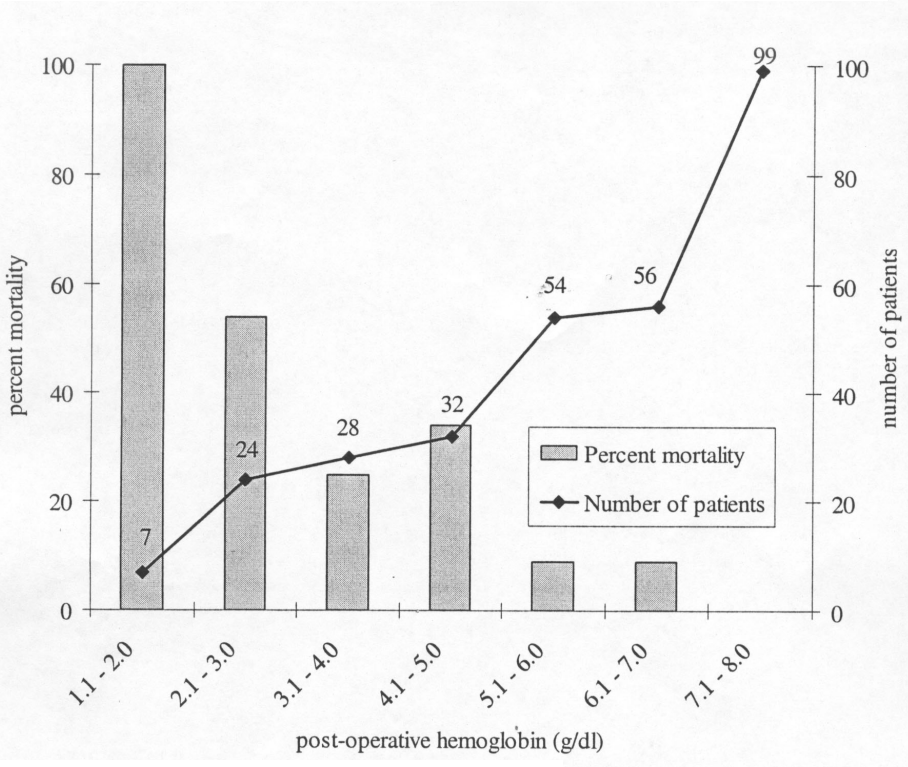
In contrast to the situation of competent adults deciding for themselves, the balance of both ethical and legal opinion regarding children and individuals not considered competent favors overriding a parent or guardian's authority and using blood transfusions when medically necessary. In a 1944 ruling (*Prince v Massachusetts*) the United States Supreme Count determined that a Jehovah's Witness parent could not neglect her child's education in order to sell magazines. This ruling indicated that the right of religious freedom is limited insofar as it leads to child abuse, neglect or failure to respect the rights of children. Failing to provide life saving blood transfusions legitimately falls within this intent of this ruling. It is thus considered appropriate when necessary to save a child's life, to override parental or guardian decisions regarding the use of blood and blood products.

Effect of Profound Anemia on Medical Outcomes

Although the results of recent studies in critically ill patients support minimizing the use of red blood cell transfusions and that it is safe (and perhaps appropriate) to permit mild-to-moderate anemia (hemoglobin ~ 7 g/dL), the safety of lower hemoglobin concentrations is uncertain.[3] Observational studies of patients refusing blood transfusions give us some information in this regard. In a combined series of 300 surgical patients with post-operative hemoglobin values of 8 g/dL or less, the risk of death and major morbidity was related to hemoglobin concentration.[4] Patients in this series had undergone a range of emergency and elective surgical procedures, mostly under general anesthesia. Overall postoperative mortality was 16%. As shown in the Figure, the case-fatality rate was 100% for the most profoundly anemic patients (Hemoglobin 2 g/dL or less), although there were only 4 patients in this group.

Figure

Mortality According to Postoperative Hemoglobin Concentration



Adapted from: Carson J, et al. Transfusion. 2002;42:812-818.

The case-fatality rate remained quite high for patients with a minimum postoperative hemoglobin value of 5 g/dL or less. The presence of preexisting cardiovascular disease had a marked effect on mortality in those with hemoglobin concentrations in the middle of this overall range (3.1-6.0 g/dL), increasing mortality almost 4-fold from 11% to 41%.

These data refer specifically to postoperative patients, and may not precisely reflect the effect of profound anemia on outcome in a more general critically ill group of patients. There is little information regarding profound anemia in the ICU, but it is clear that hemoglobin levels below 8.0 g/dL are associated with an increased mortality.[5] While it is difficult to completely separate the effects of anemia from those of blood transfusions on ICU outcomes, since they are so highly correlated, there is some evidence suggesting independent effects of anemia.[6] Thus, taken together, existing data allow us to provide families and patients with an estimate of how hemoglobin levels of less than 7-8 g/dL will influence outcome.

Treatment Options

Minimizing iatrogenic blood loss and considering therapeutic options that (while seemingly more invasive) more reliably control bleeding are appropriate and obvious considerations. Point-of-care systems exist for blood chemistry analysis that do not require that blood be removed from the patient. Whether these systems warrant the extra expense as compared to simply drawing smaller volumes of blood and limiting testing is uncertain. It may be helpful to have direct discussions with the Director of Laboratory Medicine to determine the minimum volumes of blood needed for various analyses.

It is also important to establish early in the course of the illness what is and is not acceptable to the patient. As indicated above, individuals may accept certain treatments, such as intra-operative blood salvage with immediate transfusion, whereas others may not. For many, the critical factor in accepting auto-transfusion is whether the system is closed, with the circuit and patient remaining in continuity. By ensuring this principle of keeping the blood in continuity with the patient, acute normovolemic hemodilution is often acceptable to a Jehovah's Witness. This issue is particularly relevant in emergent and elective surgical procedures associated with large blood loss. It is thus important to discuss these specific issues with patients and their families early and often.

Often, these issues are introduced by the patient or by family members. It is my experience that Jehovah's Witnesses are knowledgeable of their options and often have a contact person affiliated with a "bloodless medicine program," particularly if they live in a moderate- to large sized metropolitan area. Information about these programs is available through the Internet, although the quality and accuracy of the information likely varies widely. It is important for us as critical care clinicians to expect and accept a request by family members for us to discuss and consult with a representative of such a program. It is my experience that such consultations can be helpful, indicating to the patient and family that we will consider all options, and that the individuals involved in these programs are knowledgeable and not overbearing.

The management of bleeding patients (as in gastrointestinal hemorrhage, blunt abdominal trauma, etc) requires experienced surgical decision-making-particularly in this era of newer, nonoperative approaches for treating hemorrhage. In many circumstances, operative treatment (eg, splenectomy for trauma or surgical ligation of a bleeding duodenal ulcer) is the most "conservative" and appropriate option, that should be considered earlier then may otherwise be the case. In other circumstances, an earlier and more aggressive approach to the use of newer nonsurgical approaches (eg, transcathether angioembolization, vascular stent graft placement, etc) may seem warranted. However, there is a near absence of information, even in the form of case reports and case series, addressing the safety of such newer approaches in patients in whom our options for blood product use are limited. Therefore, any decisions to use these newer options for bleeding control or management of vascular emergencies must include input from all clinical services potentially involved in managing the problem at hand (eg, surgery, interventional radiology, gastroenterology, etc).

In all cases, attempts to maximize erythropoiesis are warranted and should be started early. Iron supplementation with oral ferrous sulfate (325 mg by mouth 3 times daily, providing a total of 195 mg of elemental iron) is often recommended, but gastrointestinal absorption is questionable in severely ill patients, particularly those with ongoing evidence of shock or those with an ileus.[7] Therefore, it is reasonable to consider parenteral iron supplementation. Our approach has been to use iron sucrose (100 mg intravenously once daily for a maximum of 10 days). The risk of anaphylaxis appears to be less with iron sucrose or iron gluconate than with iron dextran. Whether parenteral iron provides greater availability, higher hemoglobin concentrations, and better outcomes is completely unknown.

Recombinant human erythropoietin has been evaluated in clinical trials involving a wide range of dis-

eases associated with anemia including critical illness. The drug has been shown to increase hemoglobin concentrations and to reduce the need for red blood cell transfusions in anemic critically ill patients.[7,8] Although it is not our standard practice to use erythropoietin in our general population of critically ill patients, we will use it early in Jehovah's Witness patients. The recommended dose is 40,000 U weekly for anemic critically ill patients. For critically ill Jehovah's Witness patients, other authors have suggested more aggressive strategies involving more frequent (up to daily) and somewhat higher (600 U/kg body weight) doses. Our approach has been to use 40,000 U daily for 3 days and then return to a once-weekly schedule. After administration, reticulocytosis often begins within 5 days and peaks around 8 days. Increases in hemoglobin concentrations are generally not seen until 8-12 days after administration.[9]

Hemoglobin substitutes represent an emerging therapy that seems ideally suited for critically ill and anemic Jehovah's Witness patients. Cothren and colleagues reported on a seriously injured patient whom they treated with recombinant erythropoietin and Polyheme, an stroma-free polymerized and pyridoxalated hemoglobin solution (Northfield Laboratory, Ill).[10] However, it will be some time before this and other artificial hemoglobin products are approved and/or available for general use. Furthermore, while this particular substitute appears safe, the cumulative benefits in improving outcomes in addition to other aspects of care are suggestive but not established.[11,12] ■

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CME / CE Questions

1. **As far as the Leapfrog standards for critical care are concerned, which of the following recommendations are included?**
   a. Intensivists should respond to more than 95% of calls for assistance within 5 minutes.
   b. The intensivist, a "fundamentals of critical care" certified physician, or "physician extender" should arrive at the bedside within 5 minutes in 95% of cases.
   c. Intensive care units should be staffed by board-certified intensivists, to coordinate and manage care of patients.
   d. All of the above
   e. (a) and (b) but not (c)

2. **As far as the evidence for each of the Leapfrog guidelines is concerned, which of the following assertions are true?**
   a. These guidelines are based on strong scientific evidence.
   b. These guidelines are based on weak or no scientific evidence.
   c. Harm has been shown to be associated with intensivist care.
   d. (a) and (c)
   e. (b) and (c)

3. **Which of the following CT angiographic parameters predicts in-hospital mortality in patients with pulmonary emboli?**
   a. Leftward ventricular bowing
   b. Clot burden
   c. Increased RV/LV diameter ratio
   d. Oligemia
   e. None of the above

4. **Which of the following was associated with need for intubation in patients with pulmonary emboli?**
   a. Leftward ventricular bowing
   b. Clot burden
   c. Increased RV/LV diameter ratio
   d. Oligemia
   e. None of the above

Answers: 1 (d); 2 (b); 3 (e); 4 (d)

CME / CE 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.

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Risk of Adenocarcinoma in Barrett's Esophagus

Source: Murray L, et al.*BMJ(USA)*. 2003;3:534-535

ALTHOUGH SURVEILLANCE OF BARrett's esophagus (BES) for early detection of esophageal adenocarcinoma (E-CA) has become routine, the cost efficacy of this intervention is only scantily described.

Population data from Northern Ireland include all incident cancers. Murray and colleagues identified all subjects who had undergone esophageal biopsies with a diagnosis of BES between 1993 and 1999 and followed them up until 2000 identifying the number of subjects who were ultimately diagnosed with E-CA. Subjects who were diagnosed with E-CA within 6 months of the initial biopsy were not included in the data analysis.

Of 15,670 esophageal biopsies, almost 3000 met criteria for BES. In a follow-up period of 3.7 years (range, 1-8 years) 29 E-CA cases were identified. The mean yearly rate for E-CA was 0.26%, and 2.5 times higher in men than women. Risk was greatest in men older than 70 with specialized intestinal metaplasia found at esophageal biopsy, in whom the annual incidence was > 1%. Murray et al comment that when E-CA annual risk is 1%, surveillance may be cost-effective but that based upon these data, restricting surveillance to only the "high-risk" population would miss two-thirds of the incident cases of cancer. Our knowledge about the optimum schedule for BES surveillance remains incomplete. ■

Long-Term Effect of Doxazosin, Finasteride, and Combination for BPH

Source: McConnell JD, et al. *N Engl J Med*. 2003;349:2387-2398.

BENIGN PROSTATIC HYPERPLASIA (BPH) is commonly treated with alpha blockers such as doxazosin (DOX), alpha reductase inhibitors such as finasteride (FIN), or both. Long-term trials of DOX and FIN in combination have not been previously available to allow clinicians to compare the effect of alpha blockers, alpha reductase inhibitors, or both upon BPH symptoms. In addition to the value of symptom control, long-term treatments that reduce the need for surgical intervention are desired by clinicians and patients alike. Previous trials of alpha reductase inhibitors alone have indicated success in reducing the need for surgical intervention and the frequency of acute urinary retention.

Approximately 3000 men with symptomatic BPH who had not previously undergone surgical intervention, and whose PSA was < 10, were randomized to placebo, DOX, FIN, or DOX + FIN. The primary outcome was the first occurrence of a meaningful increase in the AUA symptom score (4 points or greater on a scale of 30).

Compared to placebo, both FIN and DOX had a statistically significant effect on the AUA symptom score (34-39% risk reduction). For this same end point, the benefit of combination therapy (DOX + FIN) was significantly greater than either agent alone. The risk of required surgical intervention or acute urinary retention was significantly reduced by FIN and DOX + FIN, but not DOX alone. Clinicians now have multiple logical options for long-term treatment of BPH. ■

Once Daily Valacyclovir to Reduce Herpes Transmission

Source: Corey L, et al. *N Engl J Med*. 2004;350(1):11-20.

AMONG GENITAL HERPES VIRUS (HSV-2) discordant couples, couples in whom one partner is HSV-2 infected and the other has not been, several strategies have been used to reduce likelihood of transmission to the uninfected partner. None of the strategies, save abstinence, can provide perfect assurance that HSV-2 transmission will not occur.

Asymptomatic persons shed HSV-2 and place their sexual partners at risk of transmission even during asymptomatic periods. It has been reported that subclinical viral shedding is the primary source of HSV-2 transmission. Antiviral treatment can reduce both the amount of time subclinical viral shedding occurs and the intensity with which virus is shed.

HSV-2 discordant monogamous couples (n = 743) were randomized to 500 mg valacyclovir QD (VAL) vs placebo for 8 months.

Only 4 of 743 susceptible partners on VAL developed symptomatic infection during the study period, compared with 16 placebo recipients (hazard ratio = 0.25). Similarly, seroconversion was found in 14 of 743 VAL-treated susceptibles, vs 27 of 741

on placebo. Placebo-treated patients excreted HSV-2 on 10.8% of days, compared with 2.9% of days with VAL treatment.

Once-daily VAL can reduce, but not eliminate, HSV-2 transmission. ■

Use of B-Type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea

Source: Mueller C, et al. *N Eng J Med*. 2004;350:647-654.

The etiology of acute dyspnea (DSP) can be diverse, and it is often especially difficult to separate pulmonary from cardiac causes. Recently, brain natriuretic peptide (BNP)—so called because of its original identification in porcine brain—has become recognized as a valuable diagnostic tool because it promptly rises in response to pathologic cardiac ventricular wall stress (eg, heart failure), and its levels are proportional to the degree of cardiac dysfunction. BNP is not affected by pulmonary conditions such as COPD, unless COPD has been of sufficient severity to result in right ventricular failure.

Whether standard clinical evaluation or BNP-based diagnosis provides more effective management for acute DSP was studied in this trial (n = 452) Primary end points were time to discharge and cost, both of which would be presumed to be adversely affected by inaccurate initial diagnosis.

Evaluation for all patients in the emergency department included an initial history and physical, EKG, oximetry, blood chemistry, chest X-ray and (for half of the group) point-of-contact BNP testing (15 minute on-site results). A BNP level > 100 pg/mL was considered sufficiently elevated to be consistent with heart failure.

Use of BNP testing provided an advantage for time-to-discharge from the ED (63 minutes vs 90 minutes), need for hospitalization (75% vs 85%), time to hospital discharge (8 days vs 11 days), and intensive care costs ($874 vs $1516)

Use of BNP testing, in concert with traditional diagnostic tools, shortens the time to initiation of specific and appropriate treatment, and hospitalizations. Overall, use of the BNP test reduced total treatment cost by more than 25%. ■

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Association Between C-reactive Protein and Age-related Macular Degeneration

Source: Seddon JM, et al. *JAMA*. 2004;291:704-710.

Age-related macular degeneration (AMD) is an important cause of loss of visual acuity, and because there are few effective treatments, enhanced prevention is paramount. The association between some cardiovascular risk factors (eg, smoking, dyslipidemia, obesity) and AMD has not gone unnoticed. Since C-reactive protein (CRP) has been associated with cardiovascular risk, it has become an item of interest whether CRP is similarly associated with AMD.

Study subjects (n = 4757) comprised persons with mild (n = 1063), intermediate (n = 1621), and advanced (n = 956) AMD, and controls (n = 1117). Subjects were followed every 6 months with tests of visual acuity and fundoscopy.

CRP levels were particularly discordant in persons with advanced AMD compared to those with no AMD. Even after statistical adjustment for age, sex, smoking, and obesity, CRP levels maintained a relationship with AMD. Persons in the 90th percentile for CRP had almost a 2-fold increased odds ratio for AMD. Seddon and colleagues suggest that CRP elevation is an independent risk factor for AMD. Since this is the first evidence to implicate inflammation (as manifest by CRP) etiologically in AMD, it remains to be shown whether modulation of CRP might have favorable effects on this end point. ■

VZV Reactivation in Astronauts

By Carol Kemper, MD, FACP

Source: Mehta SM, et al. *J Med Virol*. 2004;72:174-179.

Stress is a known trigger for reactivation of herpes viruses. Just the physical and psychological trauma of swapping alpha-male mice between 2 mouse colonies and the resultant battle for new alpha-male-dom has been shown to trigger reactivation of HSV in about half the mice. Herpes zoster can also reactivate after stress, including the stress of surgery.

After a 47-year-old healthy astronaut developed herpes zoster 2 days before a space flight, Mehta and associates decided to examine whether the stress of space flight can result in the reactivation of VZV. A total of 312 saliva samples, obtained from 8 astronauts before, during, and after space flight were examined by PCR. Amazingly, 61 of 200 (30%) specimens obtained during and after space flight were positive, compared with 1 of 112 (< 1%) obtained in a 234-265 day period before flying. No VZV was detected in 88 samples from 10 control subjects, who did not fly. Seven of 8 astronauts had at least 1 positive specimen during flight (2-12 days), while all 8 had anywhere from 1-8 positive specimens within 15 days of returning to earth. ■

Dr Kemper is Clinical Associate Professor of Medicine, Stanford University, Palo Alto, Calif.

PHARMACOLOGY WATCH

Estrogen Found to Not Affect Heart Disease, Breast Cancer

The NIH has halted the estrogen-alone wing of the Women's Health Initiative (WHI) a year before its scheduled end. The 11,000 postmenopausal women who have had a hysterectomy and were enrolled in the estrogen-alone trial recently received a letter informing them of the preliminary results of the study and asking them to stop their study medication. After nearly 7 years of follow-up it appears that estrogen alone does not affect the rates of heart disease or breast cancer (either positively or negatively), both key findings of the estrogen/progesterone wing of the study, which was halted in July 2002. The researchers did find, however, that estrogen alone led to a slightly higher incidence of stroke (8 per 10,000), similar to the rate found in the estrogen/progesterone wing. Estrogen alone was also found, however, to decrease the risk of hip fracture. The NIH statement also says that older women (65 and older) showed a trend toward increase risk of probable dementia or mild cognitive impairment with estrogen-alone treatment. All of the women in the study were taking Wyeth & Co.'s conjugated estrogen product, Premarin. The full results of the trial will be published in a major peer-reviewed journal in the next 2 months. The NIH statement concurs with the guidance from the FDA, which states that hormone use should be limited to treatment of moderate-to-severe menopausal symptoms, vulvovaginal atrophy, and prevention of osteoporosis (as a second-line drug). The NIH statement is available on its web site at www.nih.gov/news.

Antibiotics Associated With Cancer Risk

Is antibiotics use associated with an increased risk of breast cancer in women? The question, which was first raised decades ago, has been the subject of much debate, but now a new study suggests that the answer may be yes. Researchers looked at data from more than 10,000 female members of the Group Health Cooperative in Washington state and identified 2266 women with invasive breast cancer and 7953 randomly selected controls without breast cancer. The variable evaluated was cumulative days of antibiotic use over the study period from January 1993 to June 2001. Increasing cumulative days of antibiotic use was associated with increased risk of breast cancer. The categories were 0 days, 1-50, 51-100, 101-500, 501-1000, and > 1001 days. The odds ratios (95% CI) for breast cancer were, respectively, 1.00 (reference), 1.45 (1.24-1.69), 1.53 (1.28-1.83), 1.68 (1.42-2.00), 2.14 (1.60-2.88), and 2.07 (1.48-2.89) ($P < .001$ for trend). Increased risk was seen in all antibiotic classes, including women taking tetracycline or macrolides for treatment of acne or rosacea. After adjusting for age, length of enrollment, and use of postmenopausal hormones, the death rate from breast cancer also increased with cumulative days of antibiotic use. The authors conclude that use of antibiotics was associated with an increased risk of incidence of breast cancer and death from breast cancer; however, it cannot be determined

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. Telephone: (404) 262-5413. E-mail: christie.petrone@thomson.com. 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.

from the study whether antibiotic use is causally related or whether the indication for use of antibiotics was the primary factor (*JAMA*. 2004; 291:827-835). The link between antibiotics for breast cancer is plausible since antibiotics affect intestinal microflora, thus affecting phytochemical metabolism in the gut. Phytochemicals are thought to play an inhibitory role in the carcinogenesis pathway. Antibiotics also affect immune and inflammatory responses, which may lead to mammary carcinogenesis. An accompanying editorial reviews the possible mechanisms of the antibiotic/breast cancer connection and suggests that this study provides more questions and answers but that further research is needed. In the mean time, antibiotic use in women should be scrutinized, especially when other treatment options are available (*JAMA*. 2004;291:880-881).

Topiramate Effective Against Migraine

Topiramate is an effective agent for migraine prevention, according to a new double-blind study of 483 migraine patients. The drug, which is approved for prevention of seizures, was used in maximal doses of 50, 100, or 200 mg for 18 weeks in patients aged 12-65, who had at least a 6-month history of migraine and averaged 3-12 migraines per month. Mean monthly migraine frequency decreased significantly in the 100-mg ($P = .008$) and 200-mg ($P \leq .001$) doses, and the benefit was seen within the first month of therapy. Migraine days and use of rescue medication were also significantly reduced in the 100-mg and 200-mg groups. Adverse events included paresthesia, fatigue, and nausea (*JAMA*. 2004;291:965-973). Johnson & Johnson has already received conditional approval from the FDA for topiramate for the indication of migraine prevention pending additional safety information.

Statin Therapy For Heart Failure

Statin therapy has been found to be beneficial for a number of chronic illnesses; now add 2 more to the list. Statins have been found to benefit patients with advanced ischemic and non-ischemic heart failure. Researchers from UCLA reviewed the records of 551 patients with systolic heart failure with ejection fractions of 40% or less. After risk adjustment, statin use was associated with improved survival without the necessity of urgent transplantation in both non-ischemic and ischemic heart failure patients (91% vs 72% [$P < .001$] and 81% vs 63% [$P < .001$], at 1-year follow-up, respectively) (*J Am Coll Cardiol*. 2004;43:642-648). A new, large, randomized trial shows statins may also reduce the risk of stroke. As part of the Heart Protection Study in the United Kingdom, 3280 adults with cerebrovascular disease and an additional 17,256 patients with other occlusive arterial disease or diabetes were randomized to simvastatin 40 mg per day or placebo. Over the 5-year treatment period, there was a significant 25% proportional reduction in the rate of first stroke (4.3% simvastatin vs 5.7% placebo; $P < .0001$). The entire benefit was found in reduction in ischemic stroke. There was no difference found in the rate of hemorrhagic stroke, either increase or decrease. Simvastatin also reduced the number of TIAs ($P = .02$) and requirement for carotid endarterectomy or angioplasty ($P = .0003$). Among patients with pre-existing cerebrovascular disease, there is no apparent reduction in the stroke rate, but there was a highly significant 20% reduction in the rate of any vascular event ($P = .001$). Interestingly, benefit was seen in all levels of LDL, even in patients with LDL levels less than 116 mg/dL. The authors conclude that statin therapy reduces the risk of ischemic stroke by one-quarter to one-third in these at-risk patients (*Lancet*. 2004;363:757-767).

FDA Actions

The consumer watchdog group Public Citizen is calling for the FDA to ban AstraZeneca's new statin, rosuvastatin (Crestor), because of the risk of myositis and rhabdomyolysis. The drug, which was introduced to the American market in September, has been associated with 7 cases of rhabdomyolysis, 9 cases of renal failure, and 1 death. Myositis is a class affect of statins, especially the high-potency statins like Crestor. AstraZeneca states that the drug has been used in more than 1 million patients and that its benefits outweigh the risks. The FDA banned Bayer's cerivastatin (Baycol) in 2001 because of more than 100 deaths associated with the drug due to rhabdomyolysis.

Drug Approved to Target Angiogenesis

The FDA has approved the first monoclonal antibody that targets tumor angiogenesis. Genentech's bevacizumab (Avastin) is approved for the treatment of metastatic colorectal cancer. The drug works by binding vascular endothelia growth factor, thus inhibiting the formation of new blood vessels in tumors. In clinical trials the drug was found to extend survival time in patients with metastatic colorectal cancer by several months. ■