

## Why is it always about race with you Americans?\*

One of our Canadian hosts uttered these words in jest at a session during the recent American Thoracic Society conference. Although his comments initially made me smile, I have found myself repeatedly reconsidering the implications of his question. I think he is correct. Studying disparities in health outcomes based on factors beyond the patient's control—gender, age, socioeconomic status, race, and ethnicity—is an American tradition.

In this issue of *Critical Care Medicine*, Erickson et al (1) examine the association between race/ethnicity and outcomes for patients enrolled in several of the Acute Respiratory Distress Syndrome Network studies. They find that mortality is significantly higher among African Americans and Hispanics with acute lung injury (ALI) than among white patients. For African American patients, this greater mortality is mediated by higher severity of illness. No such explanation is forthcoming for poorer outcomes among Hispanics. The authors use appropriately complex analytical techniques and they note potential limitations in their analyses and subsequent conclusions. Although many studies have explored disparities in outcomes in other care settings, this study joins a small but growing literature on such differences in critically ill patients (2–6).

The findings of this study are interesting for a number of reasons. For the health services researcher, Erickson's results raise questions about residual confounding and adequate risk adjustment. If the results are valid, the findings imply disparities in care. Differences in access to health care before ALI, in quality of care once ALI is established, and in provider bias might be at work. The authors

use patient demographics and the acute physiology component of the Acute Physiology and Chronic Health Evaluation III score to adjust for differences between subjects. Although this is an accepted method for dealing with nonrandomized data, it has limitations. Their risk adjusting seems to work similarly among all racial groups, but diminishing sample sizes within the groups may result in statistically insignificant differences in risk-adjustment performance but with true clinical importance.

As the authors note, ventilator care in these studies was strictly protocolized. In each clinical trial, randomization would be anticipated to equally distribute the use of cointerventions that could affect outcome. However, this would only be expected between the randomized groups (e.g., 12 mL/kg vs. 6 mL/kg ideal body weight) and would not necessarily result in equality of such unmeasured covariates among racial groups. Another source of potential confounding is the possibility of inaccurate estimates of ideal body weight among the various races. Despite known differences in lung volumes based on race and age, the ideal body weight calculations used by the Acute Respiratory Distress Syndrome Network studies were determined based only on gender and height (7). Considering that non-white groups may have smaller lung volumes than whites of the same gender, height, and age (8), the standardized tidal volumes may have produced higher airway pressures and resultant organ injury for the non-whites.

For the devotees of the “-omics” approach to medical research (e.g., genomics, proteomics, etc.), Erickson's findings argue for studies exploring the biological differences between races and possible pathways involved in ALI severity and death. In the age of “personalized health care,” determination of this variation in pathophysiology may allow for an individualized approach to care. Although some investigators have reported differences among racial groups in biological pathways that could be involved in ALI pathogenesis (9–11), the evolutionary pres-

ures that might lead to such race-based differences in susceptibility to ALI and ALI-related death are not apparent. This lowers the prior probability that any such observed differences are truly meaningful.

A greater threat to the validity of reports of a biological basis for the observed differences in outcomes among various races is the disparity in access to and provision of care. For the translational researcher, it is difficult to detect a true signal due to biological variation among the noise of variation in provided care. Even if the approach to care is standardized once critical illness is established, interpreting observed results would be marred by a lack of understanding of the patient's health and access to health care before the acute disease. From a study design standpoint, exploring differences in biological pathways would best be accomplished by “controlling” all exposures except the variable of interest—as is the case by Erickson et al (1)—race/ethnicity. Although not perfect, a health system that provides equal access to care comes closest to providing such a control. Interestingly, it seems investigators in such systems, such as my Canadian colleague, do not contemplate race as a causative factor in health outcomes to the degree that those of us in the United States do, where obvious differences in the ability to access health care exist. Perhaps this is because Canadian citizens receive similar health care, regardless of skin color or surname, so there is no reason to suspect disparities in outcomes because of these contrived groups.

Considering the perspective of the non-white ALI patient, this study raises difficult and unsettling questions. These might include “Why aren't physicians surprised (or outraged) that African Americans and Hispanics have poorer outcomes?” and “What are physicians doing about it?” One could argue that the studies demonstrating disparities in outcome distract us from these more difficult issues. Do we need additional studies to prove that smoking causes disease or should we dedicate ourselves to eliminat-

\*See also p. 1.

Key Words: race; ethnicity; disparities; acute lung injury; outcome

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ing smoking and developing better treatments for the attendant mortality and morbidity? Similarly, do we need to show that non-white races are at greater risk for poorer health-related outcomes or should we dedicate ourselves to addressing the modifiable risk factors—disparities in health care access and provided care? At this point, does any physician truly believe that the *overall* health of the United States would suffer as a result of equal access to health care? Even if we are not concerned with the care the less privileged receive, our science would certainly be improved if confounding due to differences in patient access to health services was minimized.

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## Intra-aortic balloon counterpulsation in septic shock – really?\*

In severe sepsis and septic shock, every second a moribund patient dies from refractory cardiovascular shock (1). Most intensivists would attribute this cardiovascular shock primarily to a refractory vascular shock and not to myocardial depression, because septic shock typically presents as hyperdynamic, high cardiac output, low systemic vascular resistance state. However, one quarter of adult patients and even more children with fluid refractory septic shock have a hypodynamic cardiovascular profile (2). Furthermore, one would assume the dramatic reduction in afterload seen in septic shock to trigger an even much higher cardiac output than the one seen under normal afterload conditions. With this in mind, it becomes obvious that “septic cardiomyopathy” contributes much more to the shock state as often suggested: 40% of the pa-

tients have a cardiac output corresponding to only 60% to 80% of the expected value, and in further 40% of the patients, cardiac output is even worse (3). Consequently, supporting the heart in septic shock not only by inotropes but also by a mechanical assist device like the intra-aortic balloon counterpulsation (IABC) could be helpful to rapidly overcome the deleterious shock state.

In this issue of *Critical Care Medicine*, Dr. Solomon and colleagues (2) present their study on the effects of cardiovascular support using IABC in a hypodynamic, mechanically ventilated canine sepsis model, triggered by intrabronchial *Staphylococcus aureus* challenge. In animals receiving the highest bacterial dose, IABC improved survival time by 23 hrs, but not survival, and lowered systemic vascular resistance index as well as norepinephrine requirements. On the “dark side” was the increase in blood urea nitrogen and creatinine. The authors conclude that due to their findings in this animal model a randomized controlled trial of IABC therapy may be indicated in carefully selected patients with low cardiac output septic shock and a high risk of death.

This statement looks fine, and the presented data of this excellent animal study

convince me that the implementation of the IABC does something good in dogs with Gram-positive septic shock. As cardiac function is similarly depressed in patients with Gram-positive as well as with Gram-negative septic shock (4), this finding could apply to a broad spectrum of sepsis.

But what can we really expect from the implementation of an IABC in a patient with hypodynamic septic shock? IABC's classic indication is “cardiogenic shock of ischemic etiology.” With the IABC in place in the thoracic aorta, inflation of the balloon in diastole and active deflation in systole induce higher perfusion pressures of the brain and the coronary arteries in diastole and unload the diseased heart by reducing left ventricular afterload in the systole. Of special relevance thereby is the volume shifting of about 40 mL per beat by the IABC, increasing left ventricular ejection fraction and thereby cardiac output in the range of 1L/min. When thinking about implementing IABC technology in other states than cardiogenic shock, then severe pump failure should be the leading factor of the manifest shock state, without the presence of drastic reduction in afterload.

What is the power of the tool “IABC” in the best established indication? Re-

### \*See also p. 7.

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garding the guidelines, IABP implementation in cardiogenic shock complicating myocardial infarction is a class I recommendation, although the evidence indeed is very sparse: The best evidence was gained in patients who had been treated with systemic thrombolysis: in the randomized Thrombolysis and Counterpulsation to Improve Cardiogenic Shock Survival trial (5) no significant benefit of IABC was seen for the total population of 57 patients included, but only for the subgroup in Killip class III/IV (6-month-mortality with and without IABC 39% [n = 18] and 80% [n = 13],  $p = 0.05$ ). For the same patient group treated by percutaneous coronary revascularization, an even higher mortality was found in the Network of Minority Research Investigators registry (6) for the IABC-treated patients (46.5% vs. 42%; odds ratio 1.26,  $p < 0.01$ ).

And what about IABC in septic shock? We have the results of Solomon and colleagues (2) on Gram-positive septic shock in dogs showing some beneficial effects. In newborn lambs infected with group B streptococci, septic shock was improved by IABC as indicated by an increase in cardiac output and a decrease in pulmonary resistance (7). On the other hand, in a porcine model of endotoxemic shock IABC was of no benefit (8). Clinical data are anecdotal and were published more than a quarter of a century ago (9–11), seeing beneficial effects in patients with cold extremities and low cardiac output, but not in those with warm extremities and high cardiac output. Finally, an interesting patient group is the one with cardiogenic shock complicating myocardial infarction, superimposed by sepsis, amounting to 18% of the total population (12). In nearly all of these patients IABC had been implemented, with higher median duration of IABC in place in septic than in nonseptic patients, still with no more complications reported.

Is it time for a randomized controlled trial of IABC therapy in septic patients, as Solomon et al (2) propose? Before answering this crucial question, we should ask what at best we could expect from IABC in such a trial: I should not expect that implementation of IABC per se would reduce mortality in septic shock, this hasn't be shown yet even for the best validated IABC indication. But what we can expect (2) is a lowering of the dosages of potentially detrimental vasopressors and a prolongation of survival time. This

prolongation of survival time we could use to let more causal antiseptic therapy do its best. Knowing that prognosis depends on “early goal directed therapy,” we should start very early in the process, because IABC needs more than 3 and up to 24 hr time to be fully effective (13). And we have to watch carefully renal function under IABC therapy and see whether worsening of renal function may override beneficial IABC effects. Although complications of IABC are rare, their rate could be higher in septic shock owing to coagulation problems due to septic disseminated intravascular coagulation.

The most important consideration before starting a randomized trial will be to exactly define the right patient. In my opinion it will not be enough to define as inclusion criterion “the patient in hypodynamic septic shock” and as exclusion criterion “the patient with hypercirculatory septic shock.” What we need is a quantitative description of the extent of myocardial depression and a quantitative description of the sepsis-induced reduction in afterload, as measured by the systemic vascular resistance (SVR). Only when we correlate cardiac output with the SVR, then we can clearly estimate the “real” extent of cardiac output reduction (3). The “ideal patient” for the IABC is the septic patient with a highly depressed myocardial function and a not severely reduced SVR. We could control the success of IABC by following the cardiac power index/output, which is of prognostic relevance in patients with cardiogenic shock (14).

Is it time to initiate an IABC trial in hypodynamic patients with septic shock? By the way, another intervention being discussed is the use of levosimendan (15). What we have is the very carefully performed experimental work by Solomon et al (2) and others, and additional experimental work will not really advance our decision. Consequently, we should start the claimed clinical trial, accepting that IABC therapy could at best be a bridging intervention to give causal treatment time to work.

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# Recombinant human activated protein C, package labeling, and hemorrhage risks\*

The Food and Drug Administration (FDA) approval of recombinant human activated protein C (rhAPC) for the treatment of severe sepsis was based on the results of the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis Trial (PROWESS) (1). Despite exclusion criteria to eliminate study patients at risk of hemorrhage, bleeding with rhAPC therapy was increased at 28 days (3.5% vs. 2.0%,  $p < 0.06$ ). Members of the FDA advisory panel considering rhAPC were concerned that unless the strict exclusion criteria related to bleeding risk were rigorously applied in clinical use, there would be an even greater incidence of bleeding with this therapy (2). Yet, when rhAPC was approved by the FDA many of the exclusionary criteria related to baseline bleeding risks in the PROWESS trial were labeled as “warnings” in the package insert (3). This labeling allowed physicians to weigh the risks vs. the benefits of administering rhAPC to patients at a high risk for bleeding. However, if these bleeding risks had instead been categorized as “contraindications” such consideration would have been discouraged based on the package labeling.

In this issue of *Critical Care Medicine*, Gentry et al (4) describe the potential consequences of the current package labeling. Seventy-three patients received rhAPC from 2002 to 2005 at two university-based hospitals. Twenty of these 73 patients (27%) met package label criteria for having either a “warning” ( $n = 19$ ) or a “contraindication” ( $n = 1$ ) for use based on bleeding risks. Overall, 9 of the 73 patients (12%) experienced a serious

bleeding event. However, seven of these events occurred in patients identified as having a bleeding risk vs. just two in patients without such a risk. In other words, 7 of the 20 patients with a bleeding risk (35%) had a serious bleeding event when treated with rhAPC. Multivariate analysis also revealed an association between bleeding warnings and increased mortality with rhAPC therapy (odds ratio 5.2,  $p = 0.0098$ ).

The small size of the study by Gentry et al raises concerns regarding a possible sampling error. However, including this report, data are now available from seven studies assessing the incidence of serious bleeding in adult patients receiving

rhAPC based upon package labeling which did not contraindicate its use in patients with baseline bleeding risks (Fig. 1) (4–10). In 6 of these 7 studies, the incidence of serious bleeding was found to be greater than in trials with rigorous exclusion of patients with bleeding risk (1, 11, 12). Bleeding rates were uniformly even higher with package insert labeling guided care in studies done independent of the manufacturer. Lastly, the findings by Gentry et al agree with a relatively similar analysis by Kanji et al (6) in 261 patients showing that the risk of bleeding with rhAPC increased in patients with multiple organ failure and a relative contraindication to rhAPC therapy.

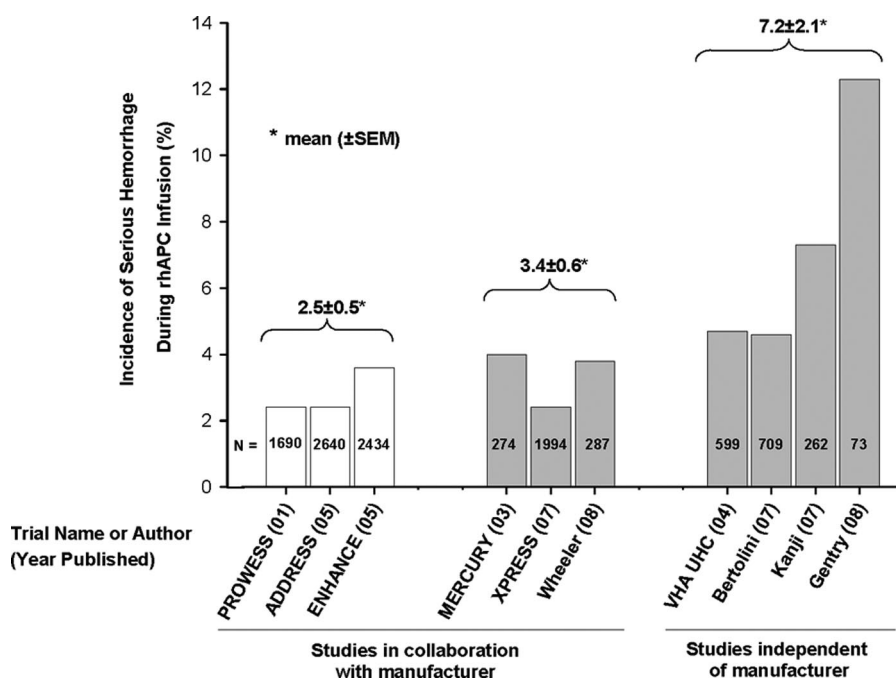


Figure 1. The incidence of hemorrhage in (1) the original Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial of recombinant human activated protein C (rhAPC) and subsequent ones employing similar strict exclusion criteria for all patients with baseline bleeding risks (open bars), or (2) trials or surveys of patients treated with rhAPC based on package labeling that listed some baseline bleeding risks as warnings rather than as contraindications (gray bars) (1, 4–12). \*The mean ( $\pm$ SEM) of incidence of serious hemorrhage during rhAPC infusion for the trials or surveys. N, number of patients; ADDRESS, Administration of Drotrecogin alfa [activated] in early stage Severe Sepsis; ENHANCE, Extended Evaluation of Recombinant Human Activated Protein; MERCURY, Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapy; XPRESS, Xigris (drotrecogin alfa [activated]) and Prophylactic hepaRin in Severe Sepsis; VHA UHC, Voluntary Health Association and University Health System Consortium.

\*See also p. 19.

Key Words: recombinant human activated protein C; prescription drug labeling; bleeding

Dr. Sweeney has a patent pending on a treatment for hemolysis. The remaining authors have not disclosed any potential conflicts of interest.

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The study by Gentry et al is the first to provide data regarding both baseline bleeding risk and Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Patients with APACHE II scores >25 and no bleeding risks had a mortality rate (33%) which was comparable to patients receiving rhAPC in clinical trials that used strict exclusion criteria (Fig. 2). In contrast, patients in the study by Gentry et al with APACHE II scores >25 and bleeding risks had a much higher mortality rate (73%). This finding raises the concern that the beneficial effects of rhAPC observed in PROWESS might be substantially reduced during clinical use if treatment is administered in the presence of baseline bleeding risks. Consistent with this, other observational studies of patients receiving rhAPC based on package labeling have shown higher mortality rates than in PROWESS, even after stratifying for the number of injured organs, another reflection of severity of disease (6, 9).

Precisely how it was determined that exclusionary criteria relating to bleeding risks from the PROWESS trial would be labeled as warnings instead of contraindications is not clear. For example, the presence of an intracranial arterial-venous malformation or aneurysm is cat-

egorized as a warning, whereas an intracranial neoplasm is a contraindication; yet patients recognized to have either condition were excluded from the PROWESS trial and there are no data we know of showing that one condition is a greater risk for bleeding with rhAPC than the other. In this context, Gentry's efforts along with others raise two important questions. First, does the current package labeling ensure a favorable risk-benefit ratio for the clinical use of rhAPC? Second and more generally, do the current guidelines for drafting package labeling require reassessment (13)?

Since its approval in 2001, subsequent randomized controlled trials of rhAPC have shown no benefit and only increased bleeding risks when administered to children (14) and patients with sepsis and a low risk of death (11). Its persistent risk of bleeding in the absence of reproducible efficacy has brought controversy to the role of rhAPC in the treatment of sepsis (15). To clarify this question, another randomized controlled trial is currently underway in septic patients with persistent shock (The PROWESS-SHOCK trial) (16). Until the results from this trial are available for guidance, physicians must still decide which patients should be considered for treat-

ment with rhAPC. In light of the study by Gentry et al and others, one approach for increasing the safety of rhAPC without compromising any potential efficacy is to not administer it to any septic patients with baseline bleeding risks—effectively changing the labeled warnings to contraindications.

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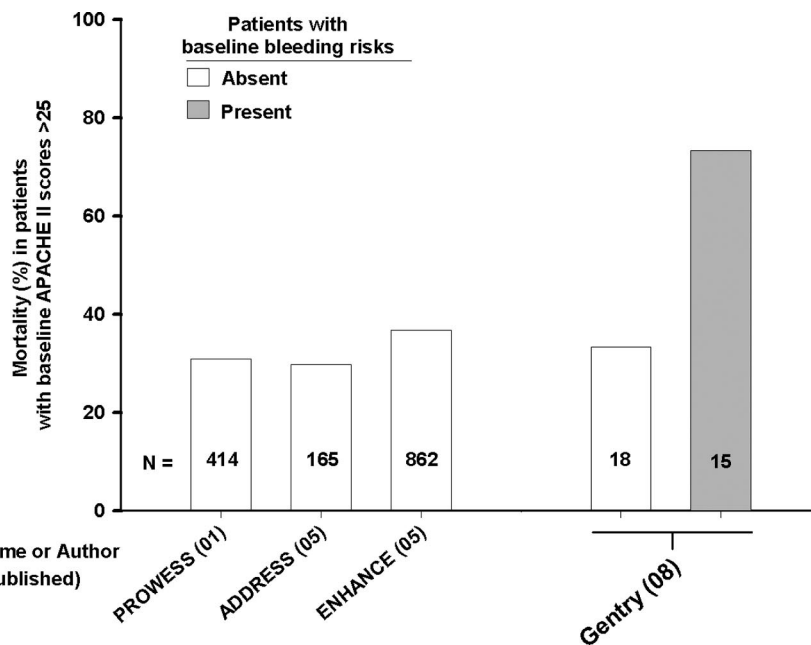


Figure 2. The mortality rate in patients with Acute Physiology and Chronic Health Evaluation (APACHE) II scores >25 treated with recombinant human activated protein C (rhAPC) in (1) three prior clinical trials excluding all patients with baseline bleeding risks (open bars) and in (2) the two subgroups of patients from the study by Gentry et al without (open bars) or with (gray bars) baseline bleeding risks (1, 4, 11, 12). N, number of patients; ADDRESS, Administration of Drotrecogin alfa [activated] in early stage Severe Sepsis; ENHANCE, Extended Evaluation of Recombinant Human Activated Protein; PROWESS, Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis.

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## Do beta-blockers and ACE inhibitors decrease the duration of ventricular fibrillation, or cause spontaneous conversion of ventricular fibrillation?\*

**T**he article entitled “The Potential Mechanisms of Reduced Incidence of Ventricular Fibrillation as the Presenting Rhythm in Sudden Cardiac Arrest” (1) in this issue of *Critical Care Medicine* attempts to offer an explanation of mechanism for this clinical observation.

The experimental model used in this research was to create an infarct by ligation of the left coronary artery of rats after 2 weeks of treatment with propranolol, captopril, or control (no drug). The authors report the major result of their research as the drug treatment groups having “decreased duration of ventricular fibrillation in comparison with controls.” However, the more impressive observation was that all 6 of 6 control rats died with the first episode of ventricular fibrillation (VF). In contrast, all six rats in the propranolol group had a first episode of VF, but spontaneously converted to normal rhythm. Two of eight rats were alive at the end of the experiment at 120 mins, and 6 of 8 reconverted to VF and died in VF or pulseless electrical activity (PEA). Also in contrast to controls, only 2 of 8 captopril pretreated rats had a first episode of VF. Both reconverted to normal

rhythm, with 1 of 8 remaining alive at 120 mins, and 7 of 8 dying after reconvecting to VF or PEA. The total time in VF was approximately 8 mins for controls, 1 min for propranolol pretreated, and 2 mins for captopril pretreated rats. Because the authors sum the data, and do not give individual data about duration of the individual arrhythmias for each rat, it is difficult to interpret the “total time in VF.” It would have been more interesting to know how long the initial episodes of VF lasted in the propranolol and captopril groups before spontaneous conversion, and whether the rats essentially died because of recurrent VF, asystole, or PEA. The implication of reading the article and looking at the tables is that the propranolol and captopril rats had spontaneous conversion of VF, and/or never went into VF and lived longer. However, most of the rats ultimately died in PEA or asystole.

The authors have extrapolated from their data and implied that beta-blocker and angiotensin-converting enzyme (ACE) inhibitor therapy may be converting the first rhythm found in human cardiac arrest victims from VF to PEA or asystole. In the introduction, the authors review the literature (their references 2–7) and, I believe, correctly quote the fact that VF as the presenting rhythm in out-of-hospital cardiac arrest has been declining in the last two decades. They also, I believe, incorrectly imply that asystole and PEA are increasing. Cobb et al (2) reported the first rhythms found by paramedics in responding to cardiac arrests in Seattle in years 1979–1980, 1989–1990, and 1999–2000. The number

of VF arrests declined by nearly 50% from 652 to 410 to 303 in the three time periods. However, the number of PEA arrests (182, 208, 205), and the number of asystolic arrests (238, 248, 231) in the three time periods remained the same. In the “Discussions” section of the article, the authors further quote a population study in Goteborg (3) (not properly referenced in their paper) documenting a modest decrease in VF (from 39% to 32%) and increase in PEA over the same time period of 1980–2000. However, a careful reading of Figure 5 in reference 3 summarizing the Goteborg data shows that PEA rose from 5% to 25% of all arrest from 1981 to 1986, and then remained stable at 20%–25% from 1986 to 2000. Asystole also remained stable at approximately 30% from 1986 to 2000. These are the years most likely to be influenced by the increasing use of ACE and beta-blocker therapy. Thus PEA and asystole may be rising as a percentage of cardiac arrests found by mobile rescue, but mostly because VF arrests are declining. Hopefully, ace inhibitors and beta-blockers are contributing to a reduction of VF, and not conversion of VF to PEA or asystole. The discharge-from-hospital alive rate for resuscitation of out-of-hospital cardiac arrest in Seattle (2) over the past 20 years is stable in the range of 30%, if VF is the initial arrhythmia. The discharge- alive rate if the initial rhythm is PEA or asystole, unfortunately, is also stable at only 4%–5%. Mobile rescue systems with fast response times ( $\leq 5$  minutes), and automated external defibrillators used with 4-minute response times in casinos

**\*See also p. 26.**

Key Words: sudden death; ventricular fibrillation; pulseless electrical activity; asystole; beta blockers; ace inhibitors

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(4) and airports (5) have a higher percentage of VF as the presenting rhythm, and higher save rates. Data from mobile rescue systems with slower response times, in the range of 6–7 minutes, show lower initial rhythm being VF, and higher initial rhythm being PEA or asystole (3, 6). Therefore, in comparing data about initial rhythm, it is important to compare or take note of the response time.

The reasons for the decline of VF as a primary rhythm found in cardiac arrest are multifactorial. Primary prevention of coronary artery disease via control of hypertension and high cholesterol, and reduced smoking, and secondary prevention with numerous drugs and implantable cardioverter defibrillator therapy are contributory. Many studies have shown that beta-blocker (7–9) and ACE inhibitor therapy (10, 11) result in reduced mortality and reduced sudden death risk. The exact mechanism of their benefit is unknown. In this article, the authors present data to suggest that the beta-blockers and ACE inhibitors increase action potential duration and increase fibrillation threshold, and propose this as the possible mechanisms of reduction of time in VF in their study. More interesting, but not talked about in the discussion of this article, is the spontaneous conversion of VF to normal rhythm in 8 of 8 propranolol pretreated infarcted rats, and 2 of 8 captopril pretreated infarcted rats. Spontaneous conversion of VF has been previously attributed to intravenous bretylium therapy given to treat VF arrest, but not (to my knowledge) to ACE

or beta-blocker therapy. Had I been an author of this article, I would have emphasized the observation rather than “reduced time in VF.” Also, in the discussion section, I would have reviewed the literature of drugs causing spontaneous conversion of VF. Beta-blockers have been shown to be antiarrhythmic in man (12). Did any previous studies with beta-blockers or ACE inhibitors in any model show spontaneous conversion of VF? Certainly, spontaneous conversion of VF is relatively rare clinically, but apparently quite common in this animal model.

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## Prevention measures of ventilator-associated pneumonia\*

“These are the things you should have practiced, without neglecting the others.”—Matthew 23:23

**N**osocomial infection is an increasing burden in intensive care units (ICUs), and in the majority of cases they are de-

vice- or intervention-related (1). In particular, ventilator-associated pneumonia (VAP) is the most common complication and is associated with increases in length of stay and mortality (2). These complications are considered to emerge from medical treatment during ICU stay and should be influenced directly by prevention measures (Fig. 1).

To this end, Caruso et al (3) investigated a simple intervention for prevention of VAP in 262 patients in a surgical-medical ICU in an oncology hospital. The reasons for mechanical ventilation in this special popula-

tion at study enrollment were pneumonia (28%), hypoxemic respiratory failure (29.1%), coma (21.8%), shock (10%), neuromuscular disease (1.9%), and others (9.2%). Immunosuppression was diagnosed in 29.9% and was associated with leucopenia in 4.2%. Patients were randomized into two groups and in the intervention group 8 mL of saline was administered endotracheally before suctioning. In patients where VAP was suspected (28.1% of all patients without a significant difference between the two groups), a quantitative bronchoalveolar lavage was performed. A robust cut-

\*See also p. 32.

Key Words: ventilator-associated pneumonia; prevention; endotracheal suctioning; bacterial colonization; mechanical ventilation; intensive care unit

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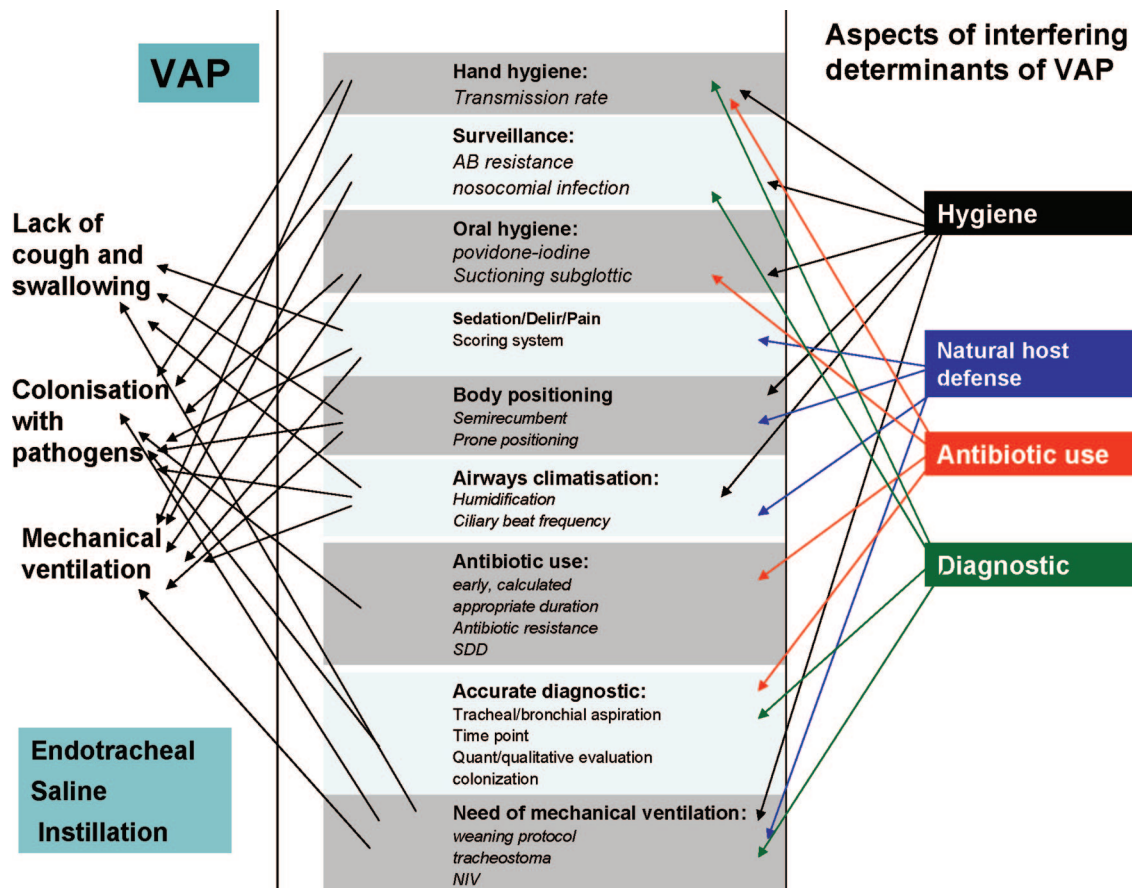


Figure 1. Prevention measures of ventilator-associated pneumonia (VAP). AB, *Acinetobacter baumannii*; SDD, selective decontamination of the digestive tract, NIV, noninvasive mechanical ventilation.

off value for colony forming units/mL  $>10^4$  was used to define a “microbiological proven pneumonia.” In patients in the “saline group,” there were less pneumonias detected. Furthermore, the saline group showed a trend toward less late onset pneumonia due to classic nosocomial pathogens.

This simple intervention—saline instillation before tracheal suctioning—seems to reduce “microbiological proven VAP” in these oncology patients. On face value, this preventative measure seems to be effective and to lend itself easily to a rapid implementation into daily routine. The simplicity of the intervention makes this study very impressive and attractive. It is clear that even successful interventions in clinical studies are difficult to implement in daily routine and that adherence to guidelines is complicated outside of the environment of a clinical study (4–6).

The study does, however, have a number of limitations. The study population was restricted to oncology patients. These patients differ from general ICU populations in terms of incidence of VAP, anti-

biotic pretreatment, immunosuppression, and mortality rate. Therefore, further studies are required in wider patient populations. It should be acknowledged that sophisticated and appropriate statistical analysis, using univariate analysis and a logistic regression analysis, was done in this investigation. Other independent variables with clinical relevance, such as antibiotic treatment in terms of the number of patients receiving antibiotics, immunosuppression, or age, were excluded as significant confounding factors. Caruso et al observed a similar rate of suspicion of VAP in both groups. This unexpected finding might be caused by the relatively weak criteria for suspect in VAP. Only one clinical sign (fever, leukocytosis or leucopenia, or appearance of purulent tracheal secretion) in combination with a new infiltrate was necessary to suspect VAP. It is well established that reliable diagnosis of VAP remains challenging (7). Inappropriate use of antibiotics could in theory have an important influence of the rate of microbiologically proven VAP. Determinants of successful use of antibiotics include early treatment,

adequate duration of antibiotic treatment, consideration of local patterns of antibiotic resistance, and appropriate de-escalation of therapy (8–10). Typical nosocomial pathogens were frequently isolated and the patients trended to late onset pneumonia. As would be expected in a group of critically ill oncology patients, antibiotic was high but did not differ between the two groups. Logistic regression analysis was used to demonstrate that the development of VAP was independent of the number of patients receiving antibiotics.

The saline group and the controls did not differ according to length of stay in ICU or in hospital and did not differ in ICU mortality. The microbiological proven VAP patients stayed longer in ICU and hospital and showed higher ICU mortality rates (66.7% vs. 47.9%), even though the study was not adequately powered to investigate any effects of the intervention on mortality.

Caruso et al hypothesized that the so-called “bacterial biofilm” on the tracheal tube might be reduced through saline instillation and that mobilization of se-

cretions was improved due to coughing on instillation. Efforts to reduce the tracheal tube biofilm is a focus on experimental and clinical research (11). Further studies are necessary to prove that endotracheal instillation of saline does in fact reduce biofilm. Using saline instillation to enhance coughing and secretion mobilization must be carefully considered. This intervention is likely to be very stressful for patients. It should be established whether it is, for instance, absolutely necessary to use a liquid. If it were to transpire that all the benefit of endotracheal saline instillation is accrued through stimulating coughing, then other established means of achieving this should be considered, such as modifying sedation levels and the ability of patients to cooperate (12).

Further Caruso et al speculated that regular saline instillation might lead to less atelectasis and endotracheal tube obstruction. Tube obstruction was, however, rare, and the diagnosis of atelectasis did not differ between the groups. The influence of the intervention on atelectasis and the possible confounding roles of body positioning, effectiveness of humidification, and duration of mechanical ventilation need to be further investigated (13, 14).

Establishing the mechanism by which VAP is reduced by endotracheal saline administration and a verification of these findings in wider populations is necessary before the intervention can be generally recommended. On the other hand, the simplicity of the intervention and the ease with which it could be implemented into daily routine make this study important. Further investigation of how established preventive measures for VAP might in-

fluence the efficacy of this intervention and the effect of the intervention on patient comfort need to be performed before this intervention becomes part of the routing strategies for the prevention of nosocomial infection (15, 16).

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# Sodium bicarbonate for renal protection after heart surgery: Let's wait and see\*

**A**cute kidney injury (AKI) commonly accompanies open heart surgery. Depending on the stringency of its definition, and the type of heart surgery, AKI complicates between 3% and 30% of cases (1). Those patients who develop AKI in this setting are more likely to die, whether in the hospital, (2) within 30 days, (3) or even up to 8 years later (4). Indeed, the 1% of patients who require dialysis for AKI after open heart surgery have a hospital mortality of 60%–70% (5). Even minor changes in the serum creatinine concentration—less than 0.5 mg/dL—within the first 48 hrs of heart surgery are associated with a nearly three-fold increase in 30-day mortality (3).

A multivariable regression analysis suggests that postoperative AKI is independently associated with death (5). A logical extrapolation from this observation is that prevention of AKI in this setting will save lives. Thus, a variety of agents have been investigated for their potential to reduce the incidence of AKI after open heart surgery (1). Several agents have been studied because of the interest they generated in the realm of radiocontrast-associated AKI. For example, Burns et al (6) evaluated *N*-acetylcysteine in patients undergoing open heart surgery, but found no effect on postoperative renal dysfunction. In contrast, a more recent but smaller study found that either *N*-acetylcysteine or fenoldopam, but not the combination, blunted the rise in serum creatinine concentration after cardiac surgery (7).

Sodium bicarbonate has gained repute as a renoprotective agent over the past 20 yrs or so. The theoretical appeal of bicarbonate derives from its effect to inhibit free radical generation, (8) thought to

play a central role in the pathogenesis of AKI (9). Although one early rat study failed to show a protective effect of bicarbonate on ischemia-induced AKI (10), a subsequent study was more encouraging (11). More recently, there have been several positive trials in patients undergoing radiocontrast procedures (12–14). Sodium bicarbonate is inexpensive and has well-recognized side-effects. It is not surprising that it should be considered a promising candidate to prevent AKI in the high-risk, high-stakes setting of open heart surgery.

In this issue of *Critical Care Medicine*, Haase et al (15) report the results of the first randomized, double-blinded, controlled trial of sodium bicarbonate infusion in patients undergoing heart surgery. Compared with those patients who received sodium chloride infusion, fewer patients who got sodium bicarbonate reached the primary renal end point. Furthermore, the postoperative increase in urinary neutrophil gelatinase-associated lipocalin—an early marker of renal dysfunction in some settings (16)—was attenuated in the bicarbonate group.

These observations appear to offer some hope that sodium bicarbonate may protect the kidneys of patients undergoing open heart surgery, and it is tempting—very tempting—to wholeheartedly embrace what appears to be a safe intervention in order to prevent a dire outcome. Nonetheless, it is important to recognize the limitations of this study and to encourage the exercise of restraint in the application of this intervention.

First, this cannot really be considered a study of AKI. The definition of renal dysfunction in this study is extremely liberal. Patients could meet the primary renal end point with total increase in serum creatinine of only 0.3 mg/dL over the first five postoperative days; that is an increase of less than 0.1 mg/dL per day. Using a more stringent definition of AKI (a 50% increase in serum creatinine concentration), the investigators found no difference between groups. Furthermore, there

was no difference between the treatment groups with respect to AKI of any “stage” when a consensus definition of AKI (17) was used. Thus, it would be a mistake to confuse the primary renal outcome in this study with AKI.

Second, the findings in this study can hardly be considered robust when, if only more one patient in the bicarbonate reached the primary renal outcome, the difference between groups would no longer meet the test of statistical significance.

Finally, if the results of this study were to encourage widespread use of sodium bicarbonate in patients after open heart surgery, we might discover some side effects that were not seen in this carefully done trial. The enthusiastic use of sodium bicarbonate outside of a circumscribed protocol might result in more severe systemic alkalization than was seen in this study. Alkalemia in critically ill patients is associated with increased mortality (18). It suppresses ventilation, causing CO<sub>2</sub> retention and relative hypoxemia (19). It acutely increases hemoglobin's oxygen affinity (Bohr effect), which tends to decrease tissue oxygen delivery (20). Alkalemia causes a reduction in ionized calcium concentration, which in turn may lower blood pressure for a variety of reasons (21). So the real-world application of this intervention may play out in ways that will significantly alter the risk:benefit ratio.

The authors are quite careful to emphasize that this is a pilot study, and that a larger trial would be needed to rigorously test the hypothetical benefit of sodium bicarbonate. This is a laudably prudent approach. Cardiothoracic surgeons, intensivists, and nephrologists would do well to “wait and see,” too.

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## \*See also p. 39.

Key Words: acute kidney injury; cardiac surgery; sodium bicarbonate; prevention

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## Is the number of reported critical incidents relevant?\*

First of all, critical incidents are reported and analyzed to spot patient safety problems and to improve patient safety by system changes. This qualitative approach has sharpened our understanding of system problems, which we previously had not been aware of. Soon, a quantitative aspect arose. It has been debated whether the number of reported incidents correlates with quality of care (that is with the true number of incidents and patient outcome) or whether the number reflects the safety culture in a health care institution (1, 2). For both approaches it is

essential to make as many critical incidents as possible known to the intensive care team. The technique of voluntary, anonymous, nonpunitive critical incident reporting was implemented to reach this goal (3). However, whereas a decreasing number of reported incidents indicates improving quality in the former case, a persisting high number of reported incidents is anticipated and regarded as continuing good safety culture in the latter case. In accordance with this latter concept, we even observed increased numbers of critical incident reports after the introduction of a system change, probably because intensive care unit personnel was more aware of the specific problem (4). Conversely, Ligi et al (5) recently presented their results of critical incident reporting in a neonatal unit. They calculated rates of critical incidents per 1000 patient days and they claimed that this prospective method will allow the effect of prevention strategies to be assessed

(5). Others have argued that the number of reported critical incidents cannot be used to track quality of care as there are numerous uncontrollable factors affecting the number of reports in a voluntary reporting system. So, it has been shown that nurses are more likely to report of their own medical errors than doctors (6). Furthermore, regular feedbacks about the reported incidents, evidence of system changes because of reports, anonymity of reporting, and even use of electronic formats for reports (as opposed to paper forms) have all been shown to increase reporting (6, 7). Some of these factors, and therefore the number of reported incidents, may be influenced by the climate or safety culture of the institution (8).

It is to the merit of Snijders et al (9) that they studied the relationship between aspects of safety culture and number of reported critical incidents. This multicenter study, presented in this issue

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### \*See also p. 61.

Key Words: intensive care; newborns; patient safety; incident reporting; outcome

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of *Critical Care Medicine*, was performed concomitantly with the introduction of voluntary, nonpunitive reporting of incidents in eight neonatal intensive care units and one surgical pediatric intensive care unit in the Netherlands. Analyzing the applied method of critical incident monitoring, two particularities must be mentioned because they have been previously shown to influence the number of reports: in the study by Snijders, health care personnel has been encouraged to report nonanonymously (as opposed to anonymous reporting) and patient safety committees provided unit personnel with planned preventive actions related to incidents, obviously without active involvement of the whole intensive care team in the analysis of critical incidents (10).

Applying vigorous statistics, Snijders et al (9) found that the number of self-reported incidents was positively associated with a nonpunitive response to error, and negatively associated with overall perceptions of safety and hospital management support for patient safety. Although the former finding is in line with the assumption that the number of reported incidents equates to the prevailing safety culture, the latter two findings contradict this concept. One would expect high perceptions of safety and excellent management support for patient safety to encourage health care personnel to report on safety issues and therefore positively impact on reporting. However, the results of this study suggest that

some aspects of safety culture (nonpunishment) increase critical incident reporting (“many reports is good”), whereas the decreasing number of reported incidents may correlate with the achievement of certain other safety culture aspects (“many reports is bad”). In the end, as a user of critical incident reporting, I am uncertain whether I should be happy or concerned if a great number of critical incidents is reported.

Snijders et al have made an important contribution to the understanding of critical incident reporting behavior. However, as they acknowledge, further research needs to be done in this field. Important covariates influencing reporting rates have to be considered: profession of reporters, case mix and illness severity, number of admissions, anonymity. Furthermore, one must bear in mind that the monitoring of critical incidents alone does not guarantee improved quality of care. What counts is patient outcome. Therefore, in future research, aspects of safety culture in neonatal and pediatric intensive care should be correlated with outcome measures such as standardized mortality ratio, rate of accidental extubations (per 100 intubation days) or frequency of actual drug errors (per 100 patient days or 100 drug orders) (4).

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## Persistent preoxygenation efforts before tracheal intubation in the intensive care unit are of no use: Who would have guessed?\*

**T**racheal intubation in the intensive care unit (ICU) is associated with significant morbidity and mortality. Although tracheal intubation is probably the third most commonly performed procedure in

the ICU, after arterial and central venous catheterization, there are only about a dozen investigations describing the outcome and/or comparing methods of tracheal intubation in this environment. However, the few investigations that have been published are quite revealing.

Complications from tracheal intubation in the ICU occur in at least 25% of patients and include some combination of need for multiple laryngoscopies, esophageal intubation, aspiration, hypoxemia, hypotension, bradycardia, and cardiac arrest (1–3). Likely resultant problems stemming from these complications,

such as laryngeal injury associated with later failure to protect the airway resulting in associated aspiration pneumonia, myocardial infarction, and neurocognitive impairment have not even been subject to investigation.

A prior investigation by Mort (4) revealed that in 42 consecutive emergency tracheal intubations performed in the ICU over a 15-month period of time, aggressive preoxygenation efforts in expert hands were demonstrated to be at best “marginally effective.” The initial average Pao<sub>2</sub> was 67 mm Hg; after 4 mins of preoxygenation using a manual resusci-

\*See also p. 68.

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tator bag with a tight fitting face mask and 100% oxygen, the  $P_{aO_2}$  increased to an average of only 103.8 mm Hg. Thirty-six percent of patients had less than a 5% rise in their  $P_{aO_2}$ . Patients requiring tracheal intubation primarily for airway protection fared better than those with cardiopulmonary demise, with an increase in  $P_{aO_2}$  from 80.8 to 185.8 mm Hg. Notably, 15 of the 42 patients could not be intubated on first attempt.

In the ICU study reported by Mort et al (5) in this issue of *Critical Care Medicine*, similar aggressive preoxygenation efforts for 4, 6, and 8 mins was compared in 34 ICU patients requiring tracheal intubation over a 7-month period of time. The mean baseline  $P_{aO_2}$  was 61.9 mm Hg. At 4 mins of preoxygenation the  $P_{aO_2}$  averaged 83.8 mm Hg, at 6 mins 88.2 mm Hg, and at 8 mins 92.7 mm Hg. In fact, a quarter of the patients experienced a fall in the  $P_{aO_2}$  from 4 to 8 mins and 50% desaturated during their intubation. Unlike Mort's prior study (4), it seems that no patients requiring simple airway protection were included, which perhaps explains the lower baseline and 4 mins  $P_{aO_2}$  values compared with his previous report. Again difficulty in performing tracheal intubation was encountered with 7 of the 34 patients requiring more than one laryngoscopy.

Failure of the  $P_{aO_2}$  to increase with administration of oxygen is a well-known phenomenon seen with shunt, especially when the shunt fraction exceeds 30% because the increased dissolved oxygen content in the nonshunted blood cannot compensate for the relative lack of bound oxygen content in the shunted blood. I have always found that conceptually it was easy to picture that the shunted blood contained an oxygen "deficit," which is the amount of oxygen it should have contained had it not been shunted; and the nonshunted blood contained an oxygen "surplus," which is the amount of extra oxygen it contained because of exposure to high concentrations of oxygen. The shunted blood's primary deficit is = hemoglobin (g/dL)  $\times$  1.34 (mL  $O_2$ /g hemoglobin)  $\times$  (1 - mixed venous oxygen saturation), whereas the nonshunted blood's exposure to high alveolar concentration of oxygen primarily results in a

relatively miniscule surplus = 0.003 (mL/dL)  $\times$  ( $P_{aO_2} - 100$ ). ICU patients with anemia and hypercatabolism will have a lower than normal (i.e.,  $<0.70$ ) mixed venous oxygen saturation, and the shunt's negative impact on the  $P_{aO_2}$ , thus, is even greater.

Preoxygenation also failed to stem the fall in  $P_{aO_2}$  during tracheal intubation. The main effect of preoxygenation is to replace the nitrogen in the functional residual capacity, which is normally 1500–2000 mL in adults, with 100% oxygen, in order to create a reservoir for the non-shunted blood to draw upon during apnea. In healthy patients undergoing induction of general anesthesia, this technique routinely allows for up to 9 mins of apnea before the  $SpO_2$  falls below 90% (6). In ICU patients, physiologic failure to successfully denitrogenate the functional residual capacity occurs because the closing capacity, the lung volume at which the smallest airways collapse, exceeds the functional residual capacity. Advanced age, smoking history, and morbid obesity, in absence of critical illness, all increase the closing capacity to functional residual capacity ratio. The present study confirms the physiologic prediction that a combination of shunt and denitrogenation failure is particularly detrimental in patients undergoing emergency tracheal intubation in the ICU.

With this clinical and physiologic knowledge, our next step should shift from preoxygenation efforts and instead concentrate on the best method to perform intubation. The use of sedative hypnotics, muscle relaxants, adjuncts such as anticholinergics (e.g., atropine or glycopyrrolate) and equipment choice should all undergo systematic investigation because it thus far seems the safest method, might be the one that promotes the most rapid tracheal intubation.

As an anesthesiologist intensivist it has always struck me as counterintuitive that many, if not most, intensivists try to avoid the use of muscle relaxants when intubating ICU patients. Administration of muscle relaxants to facilitate tracheal intubation in the operating room is standard, even in healthy patients with "easy" airways. In both of Mort's studies (4, 5) etomidate was the hypnotic sedative of

choice, and no muscle relaxant was used. Etomidate administration is associated with myoclonus, does not yield nearly as much muscular relaxation as equipotent doses of propofol, and, without a muscle relaxant, will frequently result in less than adequate laryngoscopy.

Further, most ICUs are not genuinely prepared for intubation difficulty. Operating rooms are almost always equipped with specialized stylets, laryngeal mask airways, fiberoptic scopes, and, more recently, video laryngoscopes, but most ICUs lack this equipment, or have physicians not particularly skilled in their application. Given that as many as 25% of ICU patients prove difficult to tracheally intubate, this is not rational.

The sports metaphor particularly applicable here is that ICUs must raise the level of their game to meet the challenge of the unsecured airway as time on the clock is literally running out.

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# Pressure to perform: Is cardiac output estimation from arterial waveforms good enough for routine use?\*

**I**mproving organ perfusion by managing pressure and flow within the circulation is central to judging the effects of fluid and vasoactive drug administration in critically ill patients. For this reason, blood pressure is measured routinely and usually invasively, via a radial artery catheter, in patients in the intensive care unit. Because invasive blood pressure provides a continuous signal that allows the effect of interventions to be seen immediately, it follows that there is interest in having cardiac output constantly accessible as well. There are several technical options for measuring cardiac output continuously during routine clinical care: most result from the development of the pulmonary artery catheter, use of esophageal Doppler, or devices that derive stroke volume and cardiac output from the arterial pressure waveform—the pressure pulse methods. From a commercial perspective, pressure pulse methods can be divided into those that rely on being “calibrated” based on an independent bolus cardiac output measurement (PiCCO System, Pulsion Medical Systems, Munich, Germany and LiDCO Plus, LiDCO Ltd, Cambridge, UK) and those that are “uncalibrated” (Vigileo FloTrac, Edwards Lifesciences, CA and MostCare PRAM, Vytech SRL, Venice, Italy).

Using arterial waveform analysis to generate beat-to-beat cardiac output is an attractive concept, and indeed, this general approach is now marketed under its own branding—so-called “minimally invasive hemodynamic monitoring.” The devices that are still more popular in Europe than in the United States, are rela-

tively easy to use, and present their information clearly, often with displays that are designed to guide therapy in particular directions. Yet, the concepts behind the different methods for deriving cardiac output from a peripheral blood pressure wave are complex, and the differences in the methodologies are highly technical. Furthermore, the exact algorithms used are commercial secrets not in the public domain, although they are said to use variations of classic physiologic and analytical approaches that have been described in the literature. For institutions and clinicians thinking of investing in and using these methodologies, it is therefore timely to consider just how reliably stroke volume and cardiac output can be derived from the arterial pressure signal.

In this issue of *Critical Care Medicine*, Sun et al (1) have addressed the issue with an article entitled “The cardiac output from blood pressure clinical algorithm trial.” The investigators used their computerized Multi Parameter Intelligent Monitoring of Intensive Care II database to evaluate eight different algorithms to estimate cardiac output from data collected on 120 patients during “routine clinical operations” at Beth Israel Deaconess Medical Center in Boston. Strengths of their approach are as follows:

- Collecting a large database of important physiologic data and using it for multiple purposes (1, 2);
- Evaluating the collected data, using eight different pressure pulse algorithms to estimate cardiac output;
- Providing the database in a publicly and freely available format so that other investigators and commercial vendors have free access to it;
- Stimulating and challenging investigators interested in this important area of patient assessment to improve estimates of cardiac output from arterial blood pressure signals.

Although the authors have provided a “stepping stone” for progression in the

field of near-continuous cardiac output measurement, there are several issues and challenges that have not been resolved, which are listed as follows:

- The quality of the recorded physiologic signals of blood pressure and cardiac output measures must be optimal. Collecting data from routine clinical operations may result in problems, as evidenced by the quality of the blood pressure signals shown in Figure 1 and the derived data shown in Figure 4. Dynamic response of the pressure signals was poor, and the “zeroing” status of the pressure transducer was unknown (3, 4). In addition, only a single thermodilution cardiac output was performed (5).
- It is important to test commercial devices that estimate cardiac output using the arterial pressure waveform. Some have reported that their devices are more accurate than the algorithms tested here (6). The authors stated that the commercial algorithms were “proprietary” and thus not available for them to test. Their statement was surprising because the authors had the “blood pressure signals” available and could have converted them into analog signals and “injected” them into the commercial devices and thus made the comparisons.
- It is important that investigators come to grips with “how good is good enough” as analyses and projections are made (7, 8). Based on the statistics and scatter plots of Figure 3, huge variations in the errors indicate that the cardiac output and other derived parameter estimates were very noisy.
- The authors chose to use methods that “aggregated all the findings” rather than exploring individual situations, such as when patients were in shock or receiving vasodilators. It was unclear if the patient’s medication information was even available to them from their database and from the CareVue computerized charting system (Philips Medical Systems, Andover, MA). If such data had been available, it should have

\*See also p. 72.

Key Words: cardiac output; signal quality; pulse contour; thermodilution; comparison of cardiac output methods

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been added to the MIMIC II database to help answer these questions.

- Furthermore, the authors did not discuss when and how frequently the pulse pressure cardiac output method needed to be “recalibrated.” For example, some commercial device manufacturers recommend recalibration at 8-hr intervals.
- Unfortunately, the authors did not seek to discover the true estimates of cardiac output, but instead merely relied on data coming from routine, but unspecified, data collections protocols at their clinical facility.
- In many situations, the authors seemed to be promoting the MIMIC II database, rather than making the comparisons noted in the title.

The authors raise an unusually rich number of clinical, scientific, and methodologic issues that will be valuable for future discussion. The present study also provides a stimulus to the critical care community to determine whether better data collection and testing methodologies for estimating cardiac output can be achieved from arterial pressure signals. Admittedly, based on the data presented in this article, it would be easy to surmise that available methods were of marginal clinical value at best. Even though the Liljestrand and Zander method from 1928 gave the best estimates, the variation in the cardiac output was still too wide (+1.41 to -1.76 L/min) and gave the correct directional trend for cardiac output for only 78% of the measures. Also, by aggregating the data, Sun et al have not identified particular situations or patient groups where performance might be better or worse, for instance when vasopressors are used, in hypovolemia, in the elderly or

when there is a history of hypertension. As a result, situations where the tested methods might be useful or, even more crucially, be likely to mislead and to be harmful have not been clearly identified. Importantly, of course, this criticism is also true of the commercial systems, which have generally only been tested in small, short-term studies in convenient patient groups (e.g., postoperative cardiac surgery) and with the results also presented in aggregate form, usually compared with pulmonary artery catheter-derived thermodilution cardiac output.

Is it fair to assume that these devices are not yet good enough for clinical use? Clinical users of commercial devices that were not tested here presumably believe that those instruments give reliable information and may well outperform the algorithms tested here—a perspective the manufacturers would certainly endorse. However, the commercial devices may use analytical approaches that are sufficiently different from each other that it would be wrong to assume that they are interchangeable in their performance without confirming data. Indeed, there is still a striking paucity of performance data for these devices considering their increased market penetration and the magnitude of the health care dollar investment being made.

By presenting the shortcomings of the published algorithms for deriving cardiac output continuously from the arterial pressure waveforms, Sun et al have challenged manufacturers of commercial devices to demonstrate how well their systems perform using relevant populations in real-life situations and to do so in a fashion that avoids the pitfalls outlined

above. Clinicians should independently undertake the challenge to carry out and publish results of experiments to establish the performance capabilities of commercially available devices.

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## Going global with sepsis: The need for national registries\*

**S**epsis is a significant public health problem with tremendous economic and societal burden. Not only does sepsis

mortality range from 20% to 80% depending on illness severity (1–5), but survivors of sepsis also experience significant morbidity and reduced quality of life (6, 7). Currently, patients are diagnosed with sepsis according to a consensus definition proposed by the American College of Chest Physicians/Society of Critical Care Medicine, classifying sepsis as a systemic inflammatory syndrome (defined by two or more abnormal clinical findings: temperature, respiratory rate, heart rate, and white

blood cell count) with a concomitant pathologic infection (8). Recent data from the United States show that the incidence of sepsis is increasing, resulting in a growing number of deaths despite an overall decrease in proportionate mortality (i.e., case fatality) (4). In addition, the last several decades have seen an enormous increase in the utilization and cost of intensive care internationally (5, 9). This global expansion of sepsis has made the introduction of critical care registries and large ep-

\*See also p. 81.

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idemiologic studies vital to better understanding disease, improving clinical care, establishing health care policy, and distributing health care resources.

The emergence and growth of these large patient databases has substantially increased our knowledge of sepsis epidemiology in the last two decades, not just within the United States, but worldwide. With this knowledge, we have realized how amazingly similar the global epidemiology of sepsis is. The population-adjusted sepsis incidence rate generally ranges from 50 to 100 sepsis cases per 100,000 persons internationally (2–5, 9–13). Demographically, the average age of patients is also comparable, ranging between 55 and 65 yrs of age with a greater incidence among men (2–5, 9, 14). In this issue of *Critical Care Medicine*, Martin et al (15) corroborate these conclusions in a large, prospective observational study involving 12 Canadian intensive care units, including both community and teaching hospitals, that cared for medical and surgical patients. The authors sought to determine the prevalence and mortality of patients with severe sepsis and variables associated with morbidity and mortality, and thus collected information such as source of admission, diagnosis, illness severity, intensive care unit and hospital length of stay. The authors observed that, in these Canadian intensive care units, severe sepsis occurred in 19.0% of patients with an overall hospital mortality rate of 38.1%—both statistics comparable to previous studies (1, 2, 4, 5).

The results from large epidemiologic sepsis studies, such as the current study, are important for several reasons. First, they illustrate that severe sepsis is a common disorder. Affecting nearly 900,000 people every year in the United States and nearly 20,000,000 people worldwide (4), sepsis is the leading cause of death in non-coronary intensive care units and the 10th leading cause of death overall in the United States (4, 16, 17). However, despite its prevalence, sepsis continues to be disproportionately funded for research compared with other similarly common conditions. The National Institutes of Health estimates that approximately \$49 million will be set aside for sepsis research in 2009 (18), compared with \$380 million for heart disease or even \$400 million for pneumonia/influenza (the eighth leading cause of death in the United States in 2005) (18, 19).

Second, information from large critical care registries will better communicate understanding of disease burden, allowing further characterization of various disease

aspects—i.e., the type of patients affected, frequency of disease, in-hospital and long-term patient outcomes, and the knowledge to institute plans for prevention. This type of information is particularly useful when registries include patients from a wide range of settings (i.e., community and teaching hospitals), with information on sepsis acquisition, infection characteristics, and patient demographics. Interestingly, the authors noted that 64% of severe sepsis cases were nosocomial. This result needs confirmation with further studies, but raises the importance of establishing aggressive preventive measures to reduce infection, such as catheter-related bloodstream infection and ventilator-associated pneumonia. Assembling this tremendous amount of data into a central repository will benefit all physicians and health care workers.

Third, larger epidemiologic studies are critical for determining the design of higher ranking studies, such as randomized controlled trials. In the last decade, there have been significant developments demonstrating the importance of speed and accuracy in diagnosing sepsis and instituting appropriate care. Early goal-directed therapy with expedited fluid management (20), prompt infusion of antibiotics (21, 22), and the institution of a pharmacologic agent to reduce mortality (23) have brought new hope to the management of sepsis. However, as our knowledge about sepsis improves, we are realizing that the sepsis syndrome is a heterogeneous disease, affecting diverse populations in various ways. This heterogeneity may partially explain the disappointing results of randomized clinical trials where strict exclusion criteria tend to limit the study population, and thus also limit generalizability. In the current study, the broad range of prospectively collected information from both teaching and community hospitals makes these data more applicable to a variety of populations, thus overcoming the “population exclusiveness” of randomized clinical trials.

Sepsis remains a major medical concern worldwide, with an increasing incidence globally despite improvements in our knowledge of factors that influence patient risk and outcome. Whether we are discussing regional or international epidemiology studies, of a small or large scale, the compilation of epidemiologic data will allow for disease comparisons and the ability to critically examine disease-specific, patient-specific, and healthcare-specific factors relevant to the disease. By examining this

combination of variables, such as distinct patient populations, varying risk factors and causes, and differences in intensive care unit structure and function, we may reach an even better understanding of the sepsis syndrome as a whole. These factors also, in addition to the remarkably consistent information available from studies to date, highlight the need for large, complete sepsis registries to study factors that affect the health and wellness of populations, allowing us to prioritize public health policies and healthcare resources in one of the most common and deadly conditions worldwide.

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## Lost in translation: Family conferences for families that do not speak English\*

In Fadiman's heartrending *The Spirit Catches You and You Fall Down*, well-meaning physicians try to treat a Hmong child with epilepsy and meet insurmountable cultural and language barriers, resulting in tragedy (1). As the number of non-English speaking people living in the United States grows, similar tragedies may become common.

By law, American hospitals must provide language assistance to patients lacking English proficiency (2). Trained interpreters can improve care and communication (3). Interpreters can also help physicians uncover important background information, allowing them to work more successfully with patients and families.

In the intensive care unit, effective communication is an indispensable feature of family meetings held to make end-of-life decisions. Components of successful meetings include sharing infor-

mation, eliciting wishes, exploring spiritual beliefs, making decisions, and providing emotional support (4–7). The latter is especially important, given that many family members suffer from symptoms of anxiety and depression and may experience subsequent psychiatric sequelae (8, 9).

Unfortunately, many family meetings are suboptimal, even when conducted in English. Conferences are often led by trainees (10). Many clinicians fail to share essential information, listen effectively, or recognize opportunities to provide emotional support (11–13).

Language barriers impose a major obstacle to effective palliative and end-of-life care for patients and families lacking English proficiency. Even when certified translators are employed, much can be lost in translation as reported in a recent study (14). Possible consequences include impaired information transfer, reduced emotional support, less rapport, and, most importantly, a potential failure to achieve meeting goals or make appropriate decisions.

In this issue of *Critical Care Medicine*, Thornton et al (15) compared communication in family conferences requiring interpreters with those who did not. Audiotapes were used to record conferences held to discuss limiting life support and/or to de-

liver bad news. Ten interpreted conferences were compared to 51 held in English. Although conference length was similar, 32% of the time in interpreted conferences was spent translating. Mean duration of clinician and family speech was less during translated meetings—18.4 mins compared with 32.0 mins ( $p = 0.008$ ). This decrease was largely because of reduced clinician speech—10.9 mins compared with 19.6 mins ( $p = 0.001$ ). During interpreted conferences, clinicians provided fewer supportive statements. The authors concluded that families requiring translation may receive less information and emotional support than their English-speaking counterparts.

This is one of the first studies to address an important obstacle to effective end-of-life care for patients and families who do not speak English. Although small, the study is likely to be substantiated by larger investigations in other settings. The authors are known for their outstanding end-of-life research and care (6, 12, 14, 16), and the problems uncovered may well be worse at less sophisticated centers.

It is not immediately obvious why physicians should speak less during translated conferences or why using an interpreter would make it more difficult to provide information and emotional

### \*See also p. 89.

Key Words: limited English proficiency; palliative care; end-of-life decision making; family conferences; death; interpreter; translation

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support. Although the need to translate may intimidate physicians already feeling pressed for time (17), interpreted conferences were actually shorter. Further research will be needed to understand why using interpreters should diminish the quantity and content of physician speech.

The authors acknowledge, as others have recognized, that cultural barriers may impede communication as much as language (1, 15, 16, 18, 19). Although beliefs can vary widely within an ethnic group, certain observations deserve highlighting (1, 3, 16, 18, 19). Some families may view overt directness regarding prognosis as ignorant or cruel. Some may believe that simply talking about death may hasten it. Many families harbor non-Western beliefs regarding the cause of illness or the role God may play in outcomes. Finally, past experiences in other settings, for example being subject to abuse as a refugee, may make it difficult for some families to trust clinicians. Physicians must consider these perspectives as they work with families from non-European-American backgrounds.

Equally important, traditional European-American assumptions about patient autonomy may seem foreign to many families (20). The notion of the patient as an entity independent of the family may strike many as alien, as would attempts to consider what a patient's unique wishes for life support might be (18, 19). Even when patients retain the capacity to make decisions, many families may consider it their duty to spare them from distress and make decisions on their behalf (18). Physicians should be aware of these alternative perspectives when addressing end-of-life options.

There are no entirely satisfactory ways to overcome language and cultural barriers, but recognizing their existence and potential pitfalls is important. When preparing for family conferences, physicians should consider meeting with interpreters beforehand to discuss the likely content (3, 16). Because words and concepts may not translate directly into some lan-

guages, physicians and interpreters should decide whether to attempt strict translation, permit the interpreter some discretion, and/or allow some "cultural brokering" (16). Most importantly, clinicians should make sure the content of family meetings, particularly their own contribution, meets the same standards applied to English speaking families. In this way, we can ensure all patients and families receive outstanding end-of-life care, whatever their background.

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## “Drug dosing in the intensive care unit: The critically ill are a special population too”\*

**H**eparin-induced thrombocytopenia type II (HIT-II) is common in critically ill patients and may be associated with clinical thrombotic complications (HITT). Complete avoidance of heparin exposure is recommended for patients with a current or prior diagnosis of HIT-II (although the latter is a less-proven approach). When HIT-II is diagnosed, anticoagulation with a direct thrombin inhibitor (DTI) until thrombocytopenia has resolved has been shown to decrease the incidence of thrombotic complications (1). Accordingly, the use of a DTI to achieve systemic anticoagulation (partial thromboplastin time [PTT] two- to three-fold above baseline value) is recommended in patients with new HIT-II, even in the absence of clinical thrombosis.

Critically ill patients with acute or chronic renal failure receiving continuous renal replacement therapy (CRRT) commonly receive heparin to maintain circuit patency (2). In the presence of active HIT-II or HITT, systemic anticoagulation with a DTI is recommended, unless there is a contraindication to such therapy, and anticoagulation to maintain CRRT circuit patency is a secondary benefit. In critically ill patients requiring CRRT with a history of HIT-II, but not active thrombocytopenia or thrombosis, avoidance of heparin exposure is still recommended. However, because systemic anticoagulation is not required (in the absence of another indication), there are other options for anticoagulation to maintain circuit patency in addition to DTIs, including regional citrate or avoidance of anticoagulation entirely.

In patients with HIT-II and acute or chronic renal failure receiving CRRT, ar-

gatroban is currently a common choice of DTI if systemic anticoagulation is required. The alternative agents, lepirudin and bivalirudin, are renally eliminated. In contrast, argatroban is hepatically metabolized (25% of regular maintenance dose is recommended in liver disease), and no dosage reduction is recommended in patients with renal failure (3, 4). There is no proven pharmacologic reversal agent for any of the DTIs in clinical use, so appropriate dosing in high-risk patients is crucial. Several publications have documented the expected need to reduce the maintenance dose of argatroban in patients with combined liver dysfunction and renal failure (5, 6). However, it has also become apparent with accumulated clinical experience that many critically ill patients receiving CRRT require lower than recommended maintenance doses of argatroban, even in the absence of clinical or biochemical manifestations of significant liver injury or dysfunction (7, 8). The reason for the impairment of hepatic argatroban clearance in such critically ill patients is unclear and likely multifactorial. Decreased hepatic blood flow, inhibition of drug-metabolizing enzyme function by endogenous substances (uremic toxins, inflammatory mediators) or drug-drug interactions, and occult hepatocellular injury or dysfunction may each play a role (9).

Whatever the cause of impaired argatroban clearance in patients receiving argatroban during CRRT, downward adjustment of maintenance dosing is commonly required, guided by PTT monitoring, even without known severe hepatic dysfunction (2, 7, 8). In this issue of *Critical Care Medicine*, Link and colleagues demonstrated in 30 such patients that the mean maintenance argatroban dose required to achieve a PTT two- to three-fold higher than baseline was always below the recommended dose of 2  $\mu\text{g}/\text{kg}/\text{min}$ . They initiated therapy with a standard bolus followed by a 1  $\mu\text{g}/\text{kg}/\text{min}$  infusion (50% of recommended maintenance dose), and found that the infusion rate was further reduced in the majority of cases ( $n = 22$ ; mean 0.7  $\mu\text{g}/\text{kg}/\text{min}$ ;

range, 0.1–1.5  $\mu\text{g}/\text{kg}/\text{min}$ ) and increased in a small minority ( $n = 5$ ; 1.2–1.5  $\mu\text{g}/\text{kg}/\text{min}$ ). This approach was associated with satisfactory CRRT efficacy (based on azotemia control) and safety (few minor bleeding events). They further demonstrated that decreased serum cholinesterase or albumin levels (markers of hepatic synthetic dysfunction) were predictive of a decreased argatroban maintenance dose requirement, but a normal level did not preclude the presence of decreased argatroban clearance, nor did normal hepatic transaminase levels. The authors also used a technique to assess dynamic hepatic function by infusion of indocyanine green (ICG) with noninvasive detection of plasma disappearance rate (PDR). They found a strong positive correlation between ICG-PDR and argatroban maintenance dose in this population. They found a similarly robust negative correlation between argatroban dose requirement and either of two severity of illness scores, Acute Physiology and Chronic Health Evaluation II or Simplified Acute Physiology Score II. Thus, regression analysis could be used to predict argatroban dose requirement based upon ICG-PDR or severity of illness scores, but they did not perform analyses combining these variables. The use of ICG-PDR to adjust drug dosing in critically ill patients is a somewhat novel and interesting approach, although the authors acknowledge that the value of this approach to predict argatroban dose requirements was not confirmed in a previous publication by Beiderlinden and colleagues (7). Although this small single-center study has several other weaknesses, most acknowledged by the authors, including the lack of argatroban serum concentrations for pharmacokinetic analysis, it highlights the potential to improve therapeutics with low therapeutic index drugs in critically ill patients by using novel tools.

The use of ICG clearance to assess hepatic function is not in widespread routine use, and the potential algorithms for argatroban dosing require prospective, mul-

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### \*See also p. 105.

Key Words: argatroban; continuous renal replacement therapy; heparin-induced thrombocytopenia; thrombin inhibitor; multiple organ failure

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ticenter validation. Meanwhile, the importance of this literature is to highlight the phenomenon of impaired hepatic drug clearance in critically ill patients without apparent significant liver disease or injury. In addition to adjusting drug choice and dose in patients with known renal or liver disease, further adjustment may be required because of altered drug disposition or effect in critically ill patients with synergistic multiple organ dysfunction, through mechanisms that are still incompletely understood. Of course, this phenomenon with respect to argatroban dosing can be addressed now with the use of evolving dosing information (lower initial dose) and the thoughtful use of PTT monitoring (longer half-life and delayed steady state). Accordingly, in addition to labeling and prescribing precautions for some of the usual “special populations” (age, gender, race, renal, or liver impairment), it is increasingly clear that ar-

gatroban dosing should also be adjusted routinely and cautiously in all critically ill patients, particularly those with multiple organ dysfunction, even if liver function appears intact. The critically ill are indeed a “special population.”

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## Is transpulmonary thermodilution cardiac output measurement an advance, or just another technique in search of an application?\*

**P**ulmonary artery catheter (PAC) thermodilution cardiac output (CO) measurement has withstood the test of time as the clinical standard, even while the PAC has fallen out of favor because it has been shown to not improve outcome. The PAC is used by clinicians mostly to measure the CO and wedge pressure, therefore knowledge of the CO alone seems likely to be of little utility, unless something about the PAC in particular is so deleterious, that it overrides any benefit gained by measurement of the CO. Nonetheless, a PubMed search of the phrase “cardiac output” yielded 6718 articles published in English involving human subjects since the year 2000 (1)!

Given intensivists’ general reluctance to abandon CO as a vital sign, the medical equipment industry has sought to provide us with a myriad of methods and their associated devices that continuously display it. Hence we have the NICO, PiCCO, LiDCO, FloTrac/Vigileo, and CardioQ, just to name a few (2).

I have a suspicion, however, that even the medical device manufacturers realize that CO is not an important variable in the critical care arena. Recent elucidation of the effect of positive pressure ventilation on the arterial pulse pressure suggests that quantification of the change in arterial pulse pressure alone is the best way to predict volume responsiveness (3, 4). Therefore, it is less clear why we want to know the CO in the first place. This explains why all of the recently marketed devices purport a slew of other data (e.g., stroke volume variance, extravascular lung water, blood velocity), although many of these measurements are derived from CO determination to begin with.

Transpulmonary CO determination is performed using a cold injectate into the superior vena cava with change in temper-

ature monitored via a proprietary arterial line usually inserted in the femoral or brachial artery, and application of a version of the same Stewart Hamilton equation used in PAC CO determination. This is a key component of the PiCCO monitor (Pulsion Medical Systems, Munich, Germany) that is widely used in Europe and just being introduced in the United States. The basic physiologic premise that the device relies on is that the contour of the arterial pressure waveform can be analyzed and the stroke volume (SV) will equal the integral of the area under the curve divided by the impedance of the aorta ( $Z$ ), or mathematically stated:

$$\frac{SV}{Z} = \int \frac{dP}{dt}$$

The definitive determination of the CO at any point in time will allow calculation of  $Z$  and then only periodic recalibration will be required. Once  $Z$  is determined, assuming that it does not change significantly over time, the SV can be continuously reported based on the integral of the arterial pressure waveform. If the routine ability to definitively determine the CO successfully at

\*See also p. 119.

Key Words: cardiac output; congestive heart failure; intensive care unit; monitoring; transpulmonary; pulmonary artery catheter

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any points in time, or in any large group of patients, is unsuccessful, then the PiCCO monitor would be useless, hence, the importance of the study reported herein by Friesecke et al (5) that specifically addresses whether or not this method of CO determination in patients with severe congestive heart failure equals the CO determined using the PAC.

In the study, PAC and transpulmonary thermodilution CO were compared in 29 hospitalized patients with severe heart failure who had an ejection <35% and were New York Heart Association class III–IV. They used a PAC inserted via a neck vein and a 5 French femoral arterial line with a thermistor tip. Of 339 attempted measurements, 325 yielded adequate data for comparison and revealed a mean CO of 4.4 L/min, with a bias of 0.45 L/min and a percentage error of 27.3%. Like prior studies, the transpulmonary method usually resulted in an overestimation of the CO compared with that obtained by PAC. As the authors note in their introduction, previously reported investigations have demonstrated good agreement in several other patient groups and this study adds heart failure to the list of patient categories that transpulmonary CO in specific, and PiCCO monitoring by inference, might be applicable in.

However, given the rather narrow range of COs obtained, a bias of 0.45 L/min and percentage error of 27.3% might not be so acceptable (see Fig. 2a in Ref. 5). Of note, the inaccurate standard to which new monitors are held is star-

ting and unknown to physicians in general; intensivists are probably just as ignorant in this regard as their peers. To briefly summarize the pertinent statistical literature starting with Bland and Altman (6) and ending with Critchley and Critchley (7), if the PAC CO is only accurate to within  $\pm 15\%$ , and a new monitor under investigation is not expected to be significantly superior, then agreement of  $\pm 30\%$  between the new monitor and the PAC, by statistical fiat, means the new monitor is clinically acceptable!

In sum then, there are some basic facts. Transpulmonary CO can be used in place of PAC thermodilution CO, even in patients with heart failure. The transpulmonary CO is probably  $\pm 30\%$  the actual CO. The transpulmonary CO requires the insertion of a central venous line as well as a relatively large (e.g., 5 French) femoral or brachial arterial line; neither the size nor these sites are the common standards of care, and therefore the claim that it is a “less invasive” method is not entirely accurate. CO determination by any method has not been demonstrated to provide an outcome benefit to critically ill patients. In the only study that investigated outcome using the PiCCO and transpulmonary CO versus PAC, the PiCCO group had a longer duration of mechanical ventilation associated with the administration of more (too much?) fluid (8). So, I do not know why we want to know a patient’s CO, but I am reminded of my favorite Yogi Berra quote, “nobody goes there anymore because it’s too crowded.”

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## A face that matters in distress: Interface selection for acute noninvasive ventilation\*

**N**oninvasive positive pressure ventilation (NPPV) has gained wider application and importance in the management of

both acute and chronic respiratory failure mainly due to the benefits derived from its application. There are several randomized, nonrandomized, and historically controlled trials supporting the use of NPPV in acute respiratory failure (ARef) with hypercapnea and because of chronic obstructive pulmonary disease (COPD) (1). Meta-analysis and systematic reviews in the use of NPPV, has further added value and importance to this mode of treatment (1, 2). The benefits of NPPV in selected patient groups include decreased mortality, decreased need for in-

tubation, reduction in treatment failure, rapid improvement in pH, respiratory rate and  $\text{PaO}_2/\text{FiO}_2$  ratio in the first hour of treatment, reduced infectious complications, and hospital length of stay. Currently, guidelines propose not only the use of NPPV as first line intervention along with usual medical care in all patients with acute exacerbations of COPD, but also recommend NPPV application early in the course of ARef (3, 4).

However, the use of NPPV is not restricted to COPD or hypercapneic ARef.

\*See also p. 124.

Key Words: noninvasive ventilation; acute respiratory failure; interface; hypercapnea; face mask; nasal mask; outcome

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Noninvasive ventilation has shown benefit in the management of AReF associated with immunosuppression, hematologic and solid tumors, and stem cell transplantation where endotracheal intubation has shown worse prognosis (5–8). NPPV has also found its application in weaning from mechanical ventilator, postextubation AReF, pre- and postfiberoptic bronchoscopy and in high-risk group of patients for prevention of extubation failure (9).

The success of NPPV depends on several factors such as patient population, the setting in which the treatment is provided, presence of a well-trained and motivated team, rigorous monitoring, type of ventilator, and, most importantly, the type of interface used. By far the most common reason for NPPV intolerance is interface-related problems. The type of interface preference differs between acute and chronic respiratory failure. A review of studies using NPPV showed that in AReF, NPPV by face mask (63%) is the most commonly used interface followed by nasal mask (31%), nasal pillow, and mouth piece. However, in chronic respiratory failure the common interface used is nasal mask (73%) followed by nasal pillow, facial masks, and mouth pieces (10).

Nasal mask has less discomfort and preserves speech and expectoration of secretions, but the major reason for intolerance of this interface is persistent air leakage through the mouth. Although chin straps have been advocated as a means of reducing mouth leak, there are no convincing data to support its effectiveness (11). Mouth tapes to keep the mouth closed and minimize leakage have been studied in chronic settings (12). However, in practice this would not be acceptable to patients in AReF, who are in significant distress and are predominantly mouth breathers.

Face mask or oronasal mask is commonly used in acute setting with reasonable tolerance (13). The main reason for intolerance of a face mask is related to discomfort such as dry mouth, sore eyes, ear ache, pressure/flow-related issues, claustrophobia, and pressure site ulceration. Air leak is not a major problem with face mask unlike nasal mask. The intolerance to face mask is related to the duration of use and the manner of use—continuous versus intermittent. In clinical practice it is common to manage AReF initially with continuous face mask NPPV (fNPPV) and as the patient improves, intermittent use of fNPPV or nasal NPPV (nNPPV) is considered (13).

In this issue of *Critical Care Medicine*, Girault et al (14) report findings from their prospective randomized controlled trial in patients with hypercapnic AReF because of obstructive, restrictive, or mixed etiology. To date there is only one other randomized controlled trial that compares the use of face mask and nasal mask in hypercapnic AReF in a heterogeneous population of patients with congestive heart failure, sepsis, acute lung injury, asthma, pneumonia, and COPD (15).

In their study, Girault et al (14) compare the initial choice of interface; face mask and nasal mask and its clinical effectiveness and tolerance in patients with hypercapnic AReF. All patients enrolled in the study had hypercapnea, mild respiratory acidosis and NPPV was commenced in the early stage of AReF, a strategy currently recommended by the guidelines on NPPV use. Patients randomized to nNPPV had significant mask failure (75%), occurring within 6 hrs of NPPV therapy, mainly due to buccal air leak (94%), necessitating a change to fNPPV. None in the fNPPV group needed mask change. Patient discomfort secondary to interface was higher in the fNPPV group and the incidence paralleled with the duration of fNPPV use.

In the nNPPV group, no intubation was required among those who did not require a mask change, but in those who needed a change of mask, 18% needed intubation and mechanical ventilation. There were, however, no significant difference in the intubation rate, intensive care unit length of stay, and intensive care unit mortality was noted between the groups. Similar to findings from a previous randomized controlled trial (15), in this study nasal mask rather than face mask was shown to be more effective in reducing  $Paco_2$  and improving pH. There are indeed several limitations to this study. Studies comparing two different interfaces cannot be blinded and it is impossible to eliminate bias. The decision to change masks was based on subjective opinion by the attending physician and not based on objective criteria, and the use of different ventilators to deliver NPPV could cause variations in outcome.

The study by Girault et al (14) adds to the evidence related to the importance of interface selection for NPPV therapy and provides scientific validation to the current clinical practice. In selected group of patients with AReF and with no contraindications, continuous fNPPV should be the first

choice followed by intermittent fNPPV or the use nNPPV. This single center study has shown a success rate of 83% with the use of NPPV for management of AReF. This reiterates the importance of careful patient selection, early application of NPPV, and the appropriate choice of interface for achieving success with NPPV. Unfortunately, this success cannot be immediately translated to the management of hypoxemic AReF, where much of the interest and research currently dwells. Nevertheless, the ultimate goal of a clinician should be to maximize the advantages of NPPV delivered either by face mask or nasal mask and reduce the need for intubation and hospital mortality, even if this benefit is limited to a select patient group.

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## Toll-like receptor pathway signaling is differently regulated in neutrophils and peripheral mononuclear cells of patients with sepsis, severe sepsis, and septic shock\*

**I**mmunomodulation during sepsis could be a potential therapeutic concept. However, this requires a detailed understanding of the time course and pathophysiology of sepsis, which is somehow reflected in the concepts of systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome (1). Today, we are still aiming for biological markers indicating the current immune status of sepsis patients. Equipped with such indicators, a therapeutic immunomodulatory therapy (e.g., directed at monocytes and neutrophils) is feasible (2). The list of potential candidates is long such as phagocytosis activity, hydrogen peroxide production, expression of human leukocyte antigen-DR, CD64, toll-like receptors (TLR), triggering receptor expressed on myeloid cells, and granulocyte-macrophage colony-stimulating factor receptor among others (3–7). In addition to these functional and cell surface related markers, intracellular signaling cascades may also play an important role such as TLR signaling. Extracellular signal-regulated kinase and p38 kinase signaling differ following lipopolysaccharide stimulation in leukocytes from systemic inflammatory response syndrome patients vs. sepsis patients (8). Furthermore, myeloid differentiation 88 short

and single immunoglobulin interleukin-1 receptor-related molecule are up-regulated in monocytes from septic patients (9).

The complexity of the condition “inflammation” suggests that multiple markers in concert with dynamic changes (e.g., time and concentration) need to be identified to discriminate the various states within the pro- (systemic inflammatory response syndrome; sepsis, e.g., caused by bacteria, viruses, fungi and parasites; severe sepsis; septic shock) and compensatory anti-inflammatory response syndrome response.

The administration of lipopolysaccharide to healthy subjects leads to a transient, time-dependent expression of 3714 individual genes in full blood for 24 hrs (10). It has been known for a long time that leukocytes from critical ill patients demonstrate reduced proinflammatory activity (e.g., proinflammatory cytokines) compared with leukocytes from healthy subjects. Controversy still exists regarding the role of the regulation of TLRs as a possible mechanism of this phenomenon (11).

In this issue of *Critical Care Medicine*, Salomao et al (12) have focused on the TLR signaling pathway on the transcriptional level in leukocytes (neutrophils vs. monocytes) from patients with sepsis, severe sepsis, or septic shock. This reflects a reasonable and logical next step, based on the study by Calvano et al (10) which was performed on whole blood leukocytes performed as genome-wide expression analysis on lipopolysaccharide-treated healthy volunteers. Salomao et al have undertaken the effort to translate these

findings into the clinical context further decrypting the findings by Calvano et al by focusing on one central signaling cascade involved in systemic inflammation.

The authors justify their work with the correct assumption that “. . . monocytes and neutrophil function are modulated throughout the *continuum* of sepsis.” However, the work of Salomao et al suffers from two limitations. First, the existence of such a continuum of sepsis is questionable, and second—if it would exist—the authors have not studied this (variable sampling time, allowing up to 72 hrs deviation in the sepsis group). This query is further supported by various animal and human studies indicating fast and significant changes in the expression of genes and proteins being involved in the inflammatory cascade (10). In addition, it is unclear whether the changes seen by Salomao et al in gene expression result in changes in protein levels.

The work of Salomao et al provides evidence that TLR signaling is different in monocytes and neutrophils. Their results indicate that TLR expression in monocytes may not correlate with hyporesponsiveness and that intracellular downstream signals are more likely part of the mechanism involved. Regarding neutrophils, this article is more difficult to interpret in the context of previously described (functional) characteristics of neutrophils from patients with sepsis and septic shock. Studies on neutrophil function or on markers which are thought to reflect their activity resulted in inconsistent findings (5, 13, 14).

The impact of single-nucleotide polymorphisms are increasingly appreciated

### \*See also p. 132.

Key Words: toll-like receptors; sepsis; neutrophils; monocytes; genes

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as players in the pathophysiology of sepsis. TLR4 polymorphism is associated with a higher rate of Gram-negative infections in a surgically critical ill population and is detected in a higher frequency in patients in septic shock compared with a healthy control group. For TLR2, the Arg753Gln polymorphism has been reported to increase the risk of Gram-positive and *Candida* sepsis in critical ill patients (15). Interleukin-1 receptor-associated kinase single-nucleotide polymorphism carriers (~14% in a white population with sepsis) demonstrate a worse outcome when suffering from sepsis than wild-type carriers (16).

High-throughput technologies and multiplexing on pretranscriptional, transcriptional, and posttranscriptional levels allow the detection of large numbers of mediators influencing systemic inflammation. Sepsis research will become more and more challenging in terms of the demand of larger study populations and, hence costs. This warrants more efforts to organize international networks and funding opportunities.

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## Etiologies of troponin elevation in critically ill patients with gastrointestinal bleeding\*

**C**ardiac troponin is the most important serum biomarker for diagnosis and risk stratification of patients who present with symptoms suggestive of acute coronary syndromes. Guidelines on the use and interpretation of troponin have been

created from the disciplines of cardiology (1), emergency medicine (2), and laboratory medicine (3). Despite widespread availability and adoption into routine clinical practice, there are still gaps in the basic science knowledge, and clinical interpretation of results, particularly in patients with nonischemic etiologies. Although not absolutely proven, most clinical investigators believe that release of troponin is an exclusive indicator of myocardial damage. Furthermore, patients with troponin elevations typically have worsening short- and/or long-term outcomes compared with similar patients who have a normal troponin. Therapeutic

measures have not been established in nonischemic injury, because the etiology of troponin release is not known among nonacute coronary syndrome patients. This is particularly true for patients who are critically ill. As the laboratory medicine community continues to improve the analytical sensitivity of troponin assays and lowers the cutoff for myocardial injury, the prevalence of troponin positivity among intensive care unit patients will increase.

In this issue of *Critical Care Medicine*, Vasile et al (4) described a relatively high incidence of cardiac troponin increases in a cohort of critically ill patients who

\*See also p. 140.

Key Words: cardiac troponin; *H. pylori*; catecholamines

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present with acute bleeding. They found an increase in cardiac troponin T that was associated with long-term 1–3-yr mortality (but not short-term, 30-day mortality). This work was unique because it is among the first to subdivide critically ill patients to a specific disease subset. It is also a relevant report because it uses contemporary cutoff concentrations for troponin, i.e., the 99th percentile limits. Many other clinical studies use inappropriately high troponin cutoff concentrations and reducing the true incidence of cardiac injury. Although not directly studied, it is presumed that similar findings will occur with use of cardiac troponin I, the cardiac biomarker that is more widely used. If troponin is to be routinely used to manage intensive care unit patients, more subpopulation studies are warranted. A limitation of this and other studies of this kind, however, is the absence of a therapeutic approach that would minimize long-term risk. Effective management will require knowledge as to the mechanism of cardiac injury.

In peptic ulcer disease and gastrointestinal bleeding, a critical discovery has been elucidating the pathophysiologic role of *Helicobacter pylori*. Perhaps not coincidentally, infectious diseases have also been implicated as a mediator of cardiovascular disease. One debated hypothesis is that chronic presence of *Chlamydia pneumoniae*, *Herpes simplex virus*, *Cytomegalovirus*, and *H. pylori*, produce a systemic inflammatory state that leads to the vulnerability of atherosclerotic plaque within coronary arteries (5). If true, prospective treatment with antibiotics such as azithromycin used to treat these infections should reduce the incidence of coronary artery disease. However, recent studies (6) and a meta-analysis (7) have failed to show a protective effect of antibiotic treatment suggesting that cardiovascular disease is not caused by microorganisms. We can probably conclude that the high incidence of cardiac damage as reflected by increased troponin in patients with gastrointestinal disease is not the result of prolonged exposure to *H. pylori*. Furthermore, in the study by Vasile et al, there was no correlation of troponin increases to short-term

outcomes suggesting more of a role for myocardial toxicity than plaque vulnerability and acute rupture.

An alternate perhaps more plausible mechanism for gastrointestinal bleeding-induced cardiac injury may be related to the role of catecholamine treatment. In a perfused rat heart model, Yunge et al (8) showed that administration of isoproterenol, a synthetic catecholamine resulted in myocardial contraction band necrosis and leakiness of the sarcolemmal membrane. Direct myocardial toxicity was thought to be due to the production of catecholamine oxidation products. In the absence of atherosclerosis or other underlying risk factors, there have been numerous case reports of acute myocardial infarction in patients with high catecholamine concentrations because of the presence of a pheochromocytoma (9, 10). Release of catecholamines has also been implicated in cardiac injury observed in patients with aneurysmal subarachnoid hemorrhage (11), ischemic stroke (12), and noncardiac surgery (13). Given that catecholamines are used in combination with proton pump inhibitors and nonsteroidal anti-inflammatory agents (14), they may be a correlation between the increased incidence of troponin and catecholamine use. If this link can be confirmed, alternate therapeutic approaches for treating gastrointestinal bleeding might be considered, e.g., heater probe therapy. A randomized prospective trial may be difficult to justify or approve. However, if troponin elevations are observed early during catecholamine treatment, considerations could be given to discontinue or reduce catecholamine dosages.

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# A fresh look at the MERIT trial: Do Rapid Response Systems improve outcome?\*

**D**o medical emergency teams (METs) help? Since the mid-1990s, publications described the benefit of MET—physician led, preplanned crisis response teams—in decreasing cardiac arrest or unexpected death rates in hospitals (1–4). These reports were mostly single center before and after trials and led to a debate about their quality (5, 6). Later and despite the data quality, a consensus conference supported the use of rapid response systems (RRS) (7), and the Institute for Healthcare Improvement promoted the intervention. A huge trial was performed to try to answer the question. The study, called *MERIT* (Medical Emergency Response Intervention Trial) randomized hospitals to establish a MET (intervention arm) or continue current care (control arm), and measured the impact on patient outcome. There was no difference in outcome between the trial arms (8), although *MERIT* was unlikely to show a benefit due to underpowering and contamination.

In this issue of *Critical Care Medicine* is a reanalysis of data from *MERIT* (9). It is unusual to re-report data in a *post hoc* analysis because of the obvious scientific concerns. However, this report merits the attention of those curious about the interesting, unexpected, and unexplained finding that both the control and intervention arms had a significant improvement relative to their baseline. Does this mean that there was a Hawthorne effect? On the other hand, perhaps something else was happening.

Chen and colleagues from the *MERIT* study performed the *post hoc* analysis of the *MERIT* database to determine why RRS seem to work in before-and-after tri-

als (indeed among the *MERIT* hospitals themselves), but not between treatment arms in the randomized study (9). The rate of MET interventions is now used as the independent variable instead of the hospital designation as an intervention or control hospital. To compare *MERIT* to a diuretic experiment, the authors' initial report compared urine output among patients who were supposed to take a diuretic and those who were not supposed to, whereas they now compare those who actually took the diuretic and those who did not. Hospitals with a high MET (or MET-like) rate had a significantly lower cardiac arrest rate than the hospitals with a low MET rate.

Chen and colleagues have not answered the question of whether RRS work. But they have done three things of importance. First, they reminded healthcare researchers of an important and sometimes overlooked point in performing and analyzing studies of process and outcome: it is important to determine adherence to each step in the process to begin to determine the impact of the process. This is not new information, but this article shows us the consequences of not addressing the issue. Some have been concerned that a trial of process that randomizes hospitals to control and intervention arms is not feasible because there will inevitably be “contamination” of processes (10). Because no hospital does any process exactly the same way for all patients, the notion of a “pure” intervention or control arm may be wishful thinking. Chen and colleagues offer a methodology to enable others to do future studies of the RRS. If one looks at the rate of use of an intervention as the independent variable (instead of the intervention limb *per se*), such studies are feasible. This study design bundles many processes together, which has the consequence of making it impossible to discern which of the many interventions is responsible for the outcome observed. More focused investigations are required for that.

Second, they have demonstrated that there is a dose-response effect of a RRS-like intervention: the greater the rate of early activation of a team response, the lower the cardiac arrest and unexpected death rate ( $p < 0.01$ ). The study, being retrospective, is observational in nature, but the dose-response relationship adds power to their findings. They have shown that the control hospitals behaved in a way that is similar to intervention hospitals. In essence, they called the cardiac arrest team before an arrest occurring. While not a MET *per se*, they are a MET equivalent used by hospital workers to try to provide better care to deteriorating patients. Still, it is a *post hoc* analysis so one must take care in accepting on face value their analysis.

The third result of this manuscript is that the authors have added another data point to help readers answer the question: “Do METs decrease unexpected in-hospital mortality and cardiac arrest rates?” This may not be important to many who already chosen to implement a RRS at their hospital, but it may help them better justify the costs. For hospitals not convinced by the existing data, it may be the data point that tips the balance toward implementation. For those who remain unconvinced, they have a roadmap for the next and better multicenter trial.

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\*See also p. 148.

Key Words: resuscitation; rapid response system; patient safety; cardiac arrest; critical care

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## Standardized care for nosocomial pneumonia is a valuable tool to improve patient outcomes: How do we get intensivists to listen?\*

**P**neumonia is the most common intensive care unit (ICU)-acquired infection and the number one cause of death from infection in critically ill patients. Current efforts to curtail this serious problem are focused in two directions: improve care through the use of guidelines, with a goal of reducing the mortality of this illness; and alternatively, eliminate the problem of ventilator-associated pneumonia (VAP) altogether through the use of “ventilator bundles,” designed to achieve a “zero VAP rate,” a goal that many claim is possible (1).

Although prevention is a logical and admirable goal, it is unlikely that VAP will ever be eliminated because interventions can only alter modifiable risk factors, and many of the patients in ICUs today have nonmodifiable risks, which make pneumonia unavoidable for some of them. These risks include immune suppressive therapy, comorbid illness, coma, the presence of acute lung injury, malnutrition and renal failure at time of admission, admission after trauma or burns, the use of prior antibiotic therapy, and the need for massive transfusion or major surgery. One concern about the credibility of reports showing a dramatic reduc-

tion in VAP rates with the use of a bundle is the question of whether the frequency of VAP was really reduced, or whether the entity of VAP was simply redefined but the disease, and its consequences, not eliminated. For example, in one recent study, bundle use led to a reduction in VAP rates by nearly 11% overall, and 40% in early-onset pneumonia, but there was no change in the duration of mechanical ventilation, hospital length of stay, or antibiotic treatment duration (2). In addition, when co-variables were considered, there was no significant drop in overall VAP rates. To add credibility to a reported drop in VAP rates, there should be an improvement in the secondary consequences of VAP (such as mortality, antibiotic use, duration of mechanical ventilation), and this has not generally been reported as a benefit of the use of ventilator bundles.

An approach that is more likely to impact the mortality of nosocomial pneumonia (NP) is a focus on improved management through the use of guidelines, which can be implemented into clinical practice by being translated into local protocols for care. Guidelines are evidence-based documents prepared by expert committees and generally endorsed by specialty medical societies, and such guidelines currently exist for NP and community-acquired pneumonia (3, 4). In the ICU, the use of community-acquired pneumonia guidelines has been shown to reduce the duration of mechanical ventilation, while in other settings, the application of guidelines has been able to reduce mortality (5–7). In non-critically ill patients, Dean et al (8) showed that adherence to a guideline for

antibiotic choice was associated with a decreased mortality and thirty-day readmission rate. The same principles have been observed for the application of guidelines to the management of NP. Soo Hoo et al (9) studied the impact of the implementation of the 1996 American Thoracic Society NP guidelines in 61 episodes of severe hospital-acquired pneumonia in a tertiary center, and compared the findings to outcomes before the application of this approach. They observed that implementation of the guidelines resulted in a higher percentage of appropriately treated patients (81% vs. 46%) and a lower mortality at 14 days (8% vs. 43%). Other studies have also found that the use of a locally adapted guideline for VAP could reduce the frequency of inappropriate therapy, and as a result lead to good outcomes, with less total antibiotic use, as measured by duration of therapy (10, 11). More recently, another group of investigators found that a guideline for VAP that focused not only on antibiotic choice but also on diagnostic methods, de-escalating therapy when possible, and shortening duration of therapy, could result in more appropriate antibiotic use and a reduced exposure to antibiotics (12).

In all of these successful applications of guidelines, there were some common features. First the guideline was adapted to local microbiological patterns, a modification that is necessary because each ICU has its own unique bacteriology, and second, there was careful attention to figuring out the best way to implement the recommendations so that they would actually be used by the specific physicians in each setting. It is very clear that each

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### \*See also p. 159.

Key Words: nosocomial pneumonia; guidelines; compliance; appropriate therapy; mortality; patient outcomes

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ICU has its own unique bacteriology and that a local protocol needs to take this information into account (13, 14). One audit study of local microbiological patterns in VAP showed that the addition of a quinolone to a beta-lactam, a recommended option in guidelines, would have had limited bacteriologic benefit for the patients in that hospital, whereas the use of an aminoglycoside would have been more valuable (14). It is however, less certain how to best implement a local protocol in order to optimize physician adherence to the recommendations. In the study by Soo Hoo et al, the local protocol for VAP care was carefully followed, and over 70% of patients had de-escalation on the basis of culture results, a behavior that is much better than the rate of de-escalation in most ICUs that do not have protocols for care (9, 15). In one study of community-acquired pneumonia, adherence to recommendations about timing of the switch from intravenous to oral therapy improved only minimally with the institution of a guideline, yet these recommendations were followed much more carefully when the guideline was combined with prospective intervention and real-time reminders from a local guideline advocate (16). Thus in both community-acquired pneumonia and VAP, guidelines can be valuable, but only if locally adapted and carefully implemented in a fashion that optimizes adherence with the recommendations.

In the current issue of *Critical Care Medicine*, Nachtigall et al (17) evaluated the impact of adherence to a "standard operating procedures (SOP)" in the care of NP, which was applied to patients who were in the ICU for at least 36 hrs. The SOP included using certain diagnostic tests, collecting certain historical data to guide antibiotic choice, and using antibiotics for an appropriate duration. The investigators categorized patient management into those who had a high adherence to the SOP recommendations (>70% compliance) and those with a low adherence to the recommendations (<70% compliance). As in other studies, they related compliance to the protocols with mortality but also looked at other indicators of quality of care and resource utilization, such as length of ICU stay, duration of mechanical ventilation, and duration of therapy. Unlike other studies, adherence was examined daily and not just in the first 24 hrs after diagnosis, and thus adherence was viewed on a con-

tinuum, allowing a refinement from previous investigations. The authors found that the high adherence group had a lower mortality than the low adherence group, although this was not statistically significant. However, the high adherence group did have a significantly shorter duration of therapy, mechanical ventilation, and ICU stay. In addition, duration of therapy and mechanical ventilation was directly related to percent adherence with the protocol and dropped progressively as adherence increased.

One striking observation in this study was the relatively low rate of adherence to the SOP, with only 45 patients falling in the high adherence group and 86 in the low adherence group. The most common cause of low adherence was the use of inappropriate therapy, followed by the application of insufficient diagnostic techniques. Thus, although the authors showed a benefit for having a local protocol they also clearly demonstrated the difficulty with having doctors follow the protocol and the clear difference in outcomes for those who had care according to the protocol compared to those who did not. Thus the challenge is not only to develop the principles for a guideline, but to figure out how to have the guideline widely accepted and implemented. In addition, the findings reiterate that the most effective intervention to improve outcomes in VAP is the use of early and appropriate antibiotic therapy (18, 19).

In our opinion, VAP will not be eliminated by any of the current prevention strategies, although the frequency may be reduced. However, VAP will remain a serious problem, and the most effective way to improve patient outcome is to define the best strategies for management, incorporate them into a locally developed guideline, and then figure out the optimal way to have the guideline actually get used. The findings in the study by Nachtigall et al, along with other data, clearly demonstrate that we have the knowledge base to improve patient outcome. Now, we need the wisdom to figure out how to get our colleagues to routinely apply this information.

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## “We only see what we know”—Johann Wolfgang von Goethe [1749–1832]\*

**B**y their very nature, critical care units are rarified environments, existing at the far end of the medical food chain. Those not directly involved in the practice of critical care medicine might easily conclude that we intensivists are isolated from, and perhaps even oblivious to, the societal and financial storms buffeting healthcare today.

Nothing could be further from the truth. Medical and nursing directors of critical care units are under constant pressure to improve performance and contain costs. These demands will only increase, especially as Congress threatens to cut Medicare payments, a move which will surely be echoed by private insurers. The cost-effective management of critical care units demands that intensivists look beyond the borders of their physical domains and involve themselves in the management of critical illness before it arrives in the intensive care unit. As with any disease, sepsis, the leading cause of intensive care unit mortality, has a far better prognosis when diagnosis and treatment, including early volume resuscitation, are begun before admission to the intensive care unit. The Surviving Sepsis Campaign is an ongoing international collaborative effort to apply a “bundle” of evidence-based guidelines, like early volume resuscitation, to the management of severe sepsis and septic shock (1).

In this issue of *Critical Care Medicine*, Rubulotta et al (2), on behalf of the Surviving Sepsis Campaign, address another piece of the sepsis puzzle, the public’s recognition of sepsis as an important public health issue. Using structured interviews of 6021 individuals in five European countries and the United States, they provide an international perspective on public awareness and perception of sepsis. The results are surprising even to a jaded observer of the public health scene: 88% of interviewees in the United States, France, Italy, Spain, and Great Britain had never heard the term “sepsis”; of those who had, 58% did not recognize that sepsis is a leading cause of death (2). This paper appears to be a sequel to an earlier study by some of these same authors examining physicians’ knowledge and perceptions about sepsis (3). The study found that while most physicians were aware of the severity of the problem posed by sepsis, one in ten physicians, including intensivists, considered sepsis a disease, and only 22% of intensivists and 5% of nonintensivists defined sepsis according to the American College of Chest Physicians/Society of Critical Care Medicine consensus statement (4). Finally, only 17% of the 1058 physicians interviewed agreed on any one definition of sepsis.

One can only speculate how this state of affairs has compromised our collective ability to diagnose and treat sepsis, much less communicate effectively about it. Rubulotta et al also conclude that improving poor public awareness of the sepsis syndrome might well increase philanthropic and governmental funding for sepsis research. They are certainly correct, but this is

just part of the larger issue of health care literacy and its consequences.

The Institute of Medicine defines health literacy as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions” (5). In 2004, the Institute of Medicine issued a report titled “Health Literacy: A Prescription to End Confusion.” They reported that nearly half of all American adults, some 90 million people, have difficulty understanding and using health information and that this leads to higher rates of hospitalization and the use of emergency services, greatly adding to the cost of avoidable health care services (6).

This followed on the heels of the 2003 U.S. Department of Education National Assessment of Adult Literacy survey, which for the first time contained a health literacy component. The report found that 36% of the adult U.S. population had health literacy levels at or below basic levels (7). Indeed, the Agency for Healthcare Research and Quality recently issued an even harsher assessment based on the 2007 National Healthcare Disparities Report: just 12% of American adults had the skills to manage their own healthcare proficiently (8). Finally, the University of Connecticut released a study using the 2006 Medical Expenditure Panel Survey and the National Assessment of Adult Literacy data under the auspices of the National Patient Safety Foundation. This study found that low health literacy was “a major source of economic inefficiency in the U.S. healthcare system.” The economic impact was estimated to be \$106 to \$288 billion annually, enough to insure every one of the more than 47 million Americans who lack health

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**\*See also p. 167.**

Key Words: sepsis; health literacy; healthcare policy; health economics

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insurance coverage. The authors went on to suggest that the future costs of failure to act on present-day low health literacy levels may actually be in the range of \$1.6 trillion to \$3.6 trillion (9).

The study by Rubulotta et al, addressing an often-lethal disease where effective treatment depends as much on recognition as on therapeutic expertise, is both timely and important. Placed in the context of the inexorable rise in healthcare costs, ongoing quality and safety issues, and the growing awareness of the human and economic impact of poor healthcare literacy, the challenge facing critical care is clear: we must step out of our cloistered units and take a leadership role in improving health care literacy. Sepsis is an excellent starting point.

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## May nutrition be hazardous in sepsis?\*

**E**arly nutritional support is advocated by a large number of opinion leaders and in guidelines today. In particular, this applies to the situation following surgery and in the intensive care unit (ICU). So far, the effect of early nutrition on outcome is not evidence-based, and it is not clear whether or not the underlying circulatory status of the patients is a factor of importance (1). Traditionally, a restrictive attitude toward feeding patients on pressor support or on continuous volume substitution is recommended. Still energy is consumed on the level of the basal energy expenditure, even if the patient is in septic shock and on mechanical ventilation. Another part of the discussion concerns the functionality of the gastrointestinal tract in the circulatory compromised patient in the ICU. Can the gut be used? Should it be used preferentially? Studies of splanchnic circulation by invasive techniques indicate that feeding may be started early in mechanically ventilated patients on noradrenaline

(2, 3). Although, in general, this is an area of wild speculations and almost religious beliefs.

When trying to move from prejudices toward evidence-based medicine, practical technical tools are very helpful. The use of ultrasound to monitor splanchnic circulation has been used for decades in the care of solid organ transplant patients (4). In the case of an insufficient circulation in the transplanted organ, reoperation at the earliest possible occasion was a winning strategy. Ultrasound proved to be a very valuable tool for diagnosis of insufficient circulation in the transplanted organ (5). With the use of duplex ultrasound, a semiquantitative estimate of the blood flow in the superior mesenteric artery is possible. This offers an opportunity to evaluate the effects of feeding in critically ill patients without using invasive procedures and without resource-consuming transports to the radiology department.

In a pilot study in this issue of *Critical Care Medicine*, Gatt et al (6) demonstrate the possibilities of this technique. In a number of healthy subjects and ICU patients they clearly show bloodflow changes attributable to feeding. It is well known that feeding increases cardiac output in healthy individuals. In addition, a redistribution of the bloodflow between organs is seen. If this adaptation of the circulation is at hand also in septic pa-

tients in the ICU is not known. Furthermore, the effects on the splanchnic circulation of the inotropic and pressor drugs used on septic patients is a matter of constant controversy (6–8). If the issue is extended to how the pharmaceutical treatment of a compromised circulation interferes with feeding, there are almost no studies available presently. In addition, the possible difference between enterally and parenterally administered nutrition is another question where solid knowledge is lacking in the circulatory compromised patient.

Using animal experiments has obvious limitations. On one hand, the animal models mimicking septic shock usually refer to a specific circulatory alteration, not possible to generalize. On the other hand, there are species specific functions of the gastrointestinal tract (7). Therefore, when a possibility opens up to make semiquantitative measurements of the mesenteric bloodflow bedside in the ICU, a step is taken forward. Gatt et al show results suggesting a difference in the mesenteric circulation in response to enteral vs. parenteral feeding. The relevance of this finding in the absence of simultaneous cardiac output measurements is of a rather speculative nature. Nevertheless, the findings clearly suggest that similar but better controlled studies should be undertaken without delay.

### \*See also p. 171.

Key Words: intensive care unit nutrition; splanchnic bloodflow; ultrasound; bowel ischemia

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The usefulness of the ultrasound technique to evaluate splanchnic circulation when patients are on pharmacologic support is another necessary follow-up, to demonstrate when feeding may be possible to administer. Also, patient groups with intra-abdominal pathology such as hemorrhagic pancreatitis and ascites may present difficulties, which needs to be sorted out. A recent study of probiotics in hemorrhagic pancreatitis demonstrated an increased rate of intestinal ischemia and mortality (9). The full interpretation of these findings may be difficult, the administration of probiotics as well as the postpyloric feeding have been discussed as possible contributors. A noninvasive technique to monitor splanchnic blood flow is particularly useful in future studies when postpyloric feeding is used in nonstabilized, sedated ICU patients on mechanical ventilation.

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## Haloperidol and delirium: Management or treatment?\*

In this issue of *Critical Care Medicine*, Pisani et al (1) report on their study examining the effects of benzodiazepine and opioid administration on the duration of delirium in the intensive care unit (ICU) patient. Duration represents a relatively unexplored variable in the study of delirium, with most research to date focused on occurrence, causation, and treatment. This study demonstrates an association between prolonged course of delirium and use of benzodiazepines or opiates, which is perhaps unsurprising, since both benzodiazepines and opiates have long been identified as likely culprits for iatrogenic deliriogenesis, although as the authors describe, controlled studies investigating this association have yielded inconsistent results.

Another, possibly unexpected, finding is that administration of haloperidol was

also associated with prolonged course of delirium, apparently contradicting well-established clinical wisdom recognizing intravenous haloperidol as a primary intervention for the delirious patient. Indeed, the authors note that “we included haloperidol as a control variable based on the clinical supposition that haloperidol may shorten delirium duration in patients receiving benzodiazepines or opioids.” This supposition underscores a common misconception of the intended role of haloperidol in delirium.

Current understanding of the mechanism of delirium centers on the role of oxidative stress on vulnerable neural structures producing fluctuations in various neurotransmitters (2, 3). This model allows for a “final common pathway” that produces the remarkably consistent core symptoms of delirium (disturbance of consciousness, attention, and cognition developing over a short period of time and fluctuating over the course of the day) despite the broad variation of conditions that may prompt it (4). Neurons particularly vulnerable to oxidative stress include the cholinergic, dopaminergic, histaminergic, noradrenergic, and serotonergic populations (3). Depending on

the neurotransmitter and its route of synthesis, oxidative stress may lead to either increased or decreased availability. The predominant state in delirium is one of hyperdopaminergia and hypocholinergia (3).

Excess dopamine can result in frank hallucinations that are often a cause of agitation in the delirious patient and may also potentiate the excitatory potential of glutamate (5). Since acetylcholine is the primary neurotransmitter of the reticular activating system (which is key to the functions of alertness and attention) hypocholinergia results in the hallmark “clouding of consciousness” and inattention seen in delirium (5). This neurochemical imbalance was the foundation of the initial investigation of haloperidol as an intervention for the delirious patient. Haloperidol and its relatively “clean” blockade of the D2 receptor with very little associated anticholinergic activity seemed an ideal agent since it would serve to correct one major disturbance without exacerbating the other (Edwin H. Cassem, personal communication). Intravenous administration has been shown to minimize extrapyramidal symptoms, the chief adverse effect of haloperidol when given by the oral or

\*See also p. 177.

Key Words: delirium; intensive care unit; haloperidol; antipsychotics; benzodiazepines; opioids

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intramuscular routes (6, 7). After decades of clinical experience, intravenous haloperidol remains the mainstay of delirium management, featuring as the recommended first-line agent in guidelines from the American Psychiatric Association, the Society of Critical Care Medicine, and the American College of Critical Care Medicine (8, 9). More recent laboratory research has revealed that haloperidol, due to its butyrophenone structure, can actually minimize cerebral oxidative stress via sigma-1 antagonism and that dopamine blockade may protect against neuroinjury mediated by glutamate (3, 10, 11).

In the context of this rationale for the use of haloperidol in delirium, it becomes clear that questioning its utility to shorten the course of delirium is something of a misplaced argument. Administration of haloperidol is intended to minimize the effects of neurotransmitter imbalances caused by oxidative stress, it cannot prevent that stress from occurring. Definitive treatment of delirium requires identification and treatment of the underlying cause. Haloperidol can be a temporizing measure, managing the symptoms that might put patient and staff in harm's way, until resolution (either spontaneous or directed) of the somatic cause occurs. It may be hypothesized that the prescription of haloperidol to patients in this study was due to symptoms of a delirium already present (e.g., the 70% of patients who received haloperidol due to agitation), rather than the multitude of indications that may have prompted the administration of opiates or benzodiazepines. Since patients receiving haloperidol likely already had a pronounced delirium, the association with prolonged course seems somewhat less ominous.

The authors note that "the FDA have highlighted serious adverse effects of haloperidol when used off label in an ICU setting," namely prolongation of the corrected QT interval (QTc) with subsequent risk for polymorphic ventricular tachycardia (torsade de pointes). Although it is important to note that since no medication has FDA approval for the management of delirium use of any agent in this regard would be "off label," let us con-

sider other potential candidates. The association of the other clinically available butyrophenone, droperidol, with hypotension has limited its use in the ICU setting. The newer generation of atypical neuroleptics carry more prominent anticholinergic profiles, have lower affinity for the D2 receptor, are associated with greater per-dose prolongation of the QTc, are significantly more costly, and (with the exceptions of olanzapine and ziprasidone) are available only in oral formulation (a route that is typically of little use in the agitated ICU patient) (12). Benzodiazepines also carry prohibitive risks—a study comparing haloperidol, chlorpromazine, and lorazepam for management of delirium in HIV-infected patients resulted in suspension of the lorazepam arm due to significant adverse effects (13). Recent studies on dexmedetomidine have yielded encouraging results, but routine use is limited by massive financial expense for the doses and duration of treatment required in delirium (14).

The authors' calls for further research in the areas of delirium prevention and management are to be commended—the safety and health of our patients and staff alike depend on it. With the manifold limitations inherent in performing exacting research on the clinically delirious ICU patient, much of our current knowledge regarding the management of delirium is based on empirical data and anecdotal experience (albeit empirical data and anecdotal experience spanning >30 yrs of global clinical practice). This knowledge base continues to support intravenous haloperidol as the safest, best understood, and most cost-effective agent for the management of delirium.

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# Can reading a diary improve psychological outcomes in the intensive care unit?\*

**T**he intensive care unit (ICU) can be a stressful place for patients. Critical multisystem illnesses and the diagnostic procedures and therapeutic interventions applied to them can engender worry, uncertainty, fear, and dysphoria. Disorientation, confusion, amnesia, and agitation frequently complicate the course of ICU care. It is not surprising then that intensive care has been associated with delirium, post-traumatic stress disorder (PTSD), other anxiety disorders, and depressive illness, both during and after an ICU stay (1–3). Identification and amelioration of these psychiatric sequelae are desirable.

Previous studies from Sweden and the United Kingdom (UK) have suggested that diaries written by families and caregivers at the bedside—which provide a daily accounting of a patient’s condition and treatment in the ICU—help patients and their families better recall, understand, and cope with the ICU experience after the patient is discharged (4–6). To date, however, no quantitative data have been collected on the effect these diaries may have on the incidence of psychopathology.

In this issue of *Critical Care Medicine*, Knowles and Tarrier (7) report the results of the first randomized controlled trial of the effect of bedside patient diaries on anxiety and depression after ICU care. One month (on average) after discharge from an ICU in the UK, the Hospital Anxiety and Depression Scale was administered to 36 patients. One week later, half of these patients were given the diary that had been written for them during their ICU stay. These patients read the diary with an ICU nurse consultant during a 1-hr verbal feedback session. The other 18 patients were not given their diaries at

this time and did not meet with the nurse. Two weeks later, the Hospital Anxiety and Depression Scale was again administered to all 36 patients. Measures of anxiety and depression had statistically significantly decreased in the experimental, but not in the control, group.

Until now, the benefit of diaries has been solely qualitative; patients (and their families) have reported these journals helped them to accept, understand, and adjust to their severe illness and ICU experience and to recall factual information about their time in the ICU. It has been suggested that accurate memories of ICU care may offer protection from PTSD and other anxiety disorders (8). Diaries may provide one avenue to more accurate recollections and thus less psychological distress. While Knowles and Tarrier did not study the mechanism whereby the diaries produced less anxiety and depression, they have provided the first quantitative evidence of this effect.

The major weakness of this study is that it did not exclude the possibility that patients benefited simply from the verbal feedback session with the nurse rather than the diary *per se*. The authors acknowledge that the “active ingredient” of the diary intervention was not isolated and suggest a methodology for future research to tease apart the differential effects of the diary and the feedback session. Yet another design could include four groups: diary + conversation, diary alone, feedback session alone, neither diary nor feedback session. Previous studies (5, 6) also provided diaries to patients in the context of a meeting and thus have not segregated the effects of each. If it were found that simply discussing the course of ICU care with patients is as effective (or more so) as reading a diary, this would spare the time and effort required to maintain such a journal.

In its characterization of patients as “ICU survivors,” this study aligns itself with a literature that considers ICU care to be “traumatic” and thus liable to spawn PTSD. While certain elements of

ICU care can involve “threatened death or serious injury, or a threat to [one’s] physical integrity” that evokes “intense fear, helplessness, or horror,” to use the words of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (9), we need to be careful not to go too far in considering intensive care a “trauma” in the same sense as motor vehicle accidents, child abuse, rape, terrorist attacks, and other catastrophic events. These latter instances are noxious events not intended to be helpful in any way; in contrast, intensive care is intended to be salutary. When a patient has been discharged from intensive care, is it appropriate then to say that he has “survived” it? In this regard, we may want to find alternative terms for patients who have been treated in ICUs. I suggest “former ICU patients” or “patients post ICU care.”

Of 52 patients approached to participate in this study, 16 (31%) patients declined because they wanted to forget about their ICU experience. Although this refusal to participate may be evidence of avoidance (a core symptom of PTSD), as the authors speculate, alternatively, it may point to these patients’ accurate appraisal of their psychological whereabouts. These patients may have ultimately fared better for not reading their diary. In the Bergbom study (4), 20% of patients and 12.5% of relatives did not find the diary helpful. In the Bäckman and Walther study (5), 33% of participants viewed the diary neutrally. In the Combe study (6), 11% of families refused to keep a diary, 20% of families declined to receive the diary of a deceased patient, and three patients waited >3 months before reading their diaries.

The reasons for these outcomes, refusals, and delays are not known, but they remind us that an individual’s response to stress is unique, and any help the patient may need to adapt more successfully should be tailored and timed according to his needs. The UK National Institute for Health and Clinical Excellence (10), the American Psychiatric Association (11),

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**\*See also p. 184.**

Key Words: diaries; intensive care; anxiety; depression; posttraumatic stress disorder

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and the Australian Centre for Posttraumatic Mental Health (12) all advise against routine psychological debriefing of individuals after a trauma. As the authors of this study indicate, further research is needed on the timing and crafting of psychological assistance (if any) to former ICU patients, and the present data “should not be interpreted as a suggestion that the diaries should replace proper psychiatric and psychological assessment and treatment of ICU patients.”

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# Genetic variability and outcome in the critically ill: Avoiding SNP judgments\*

The past 30 yrs have seen an important increase in the use of intensive care units (ICUs) and in the options available to care for the critically ill. As a result, we have come to recognize two key “branch points” in the natural history of critical illness. The first arises when examining the early response to an insult that results in admission to the ICU (i.e., the syndrome that evolves during the first week). In some patients, an injury, infection or some other insult provokes a normal inflammatory response. This lasts for several days and is followed by an expected recovery. In others, the same constellation of injuries or pathologies may result in an exaggerated response that appears to be “hyper-inflammatory,” the state that, for lack of better terms, we refer to as “systemic inflammatory re-

sponse syndrome (SIRS)” or “sepsis.” The second nexus occurs a bit later. Most patients in whom we stave off immediate and fulminant mortality but who develop SIRS/sepsis can be kept alive for prolonged periods of time. In these long-term survivors there are those who make a dramatic recovery, but also a distressing number who fall victim to a syndrome that for lack of a better term we call “chronic critical illness.” These patients stabilize into a persistent, highly stable but highly abnormal pathophysiologic state. Although data are lacking, it is the impression of many practitioners that recovery from chronic critical illness is unusual. Indeed, it appears that the most common cause of death in this group is the acceptance of the futility of the situation and discontinuation of life support.

Explanations for the divergence at both branch points abound. The theories most commonly advanced to explain the development of SIRS/sepsis involve either 1) an initial injury of such magnitude that the response must be equally robust or 2) a subsequent, frequently occult secondary insult (1). This latter is often referred to as the “two-hit” hypothesis.

Each has been modeled in animals to permit investigation (for example, variability on the sized and number of perforations in the cecal ligation and puncture model or the induction of trauma/burn injury followed by pneumonia/wound infection). In explaining the development of chronic critical illness researchers have advanced 1) the “hibernation” theory where organs that have been insulted “rest” (2, 3) or 2) the “connectivist” theory in which the systems that allow organ systems and even cells to communicate with each other fail (4). However, one theory that can be invoked to explain the changes at each of the branch-points involves genetic variants that result in a different response to the same insult. That is, small, seemingly minor changes in the genes encoding a protein or proteins of importance result in dramatically different responses to the initial insult or to the ability of the organism to restore homeostasis. Single nucleotide polymorphisms, or SNPs, may be responsible for these sorts of changes. If a particular SNP is present at a frequency of at least 1% of a population then it is considered a polymorphism. SNPs may occur in coding or regulatory regions of a gene and several

\*See also p. 192.

Key Words: sepsis; bacteremia; mortality; cytokines; signal transduction

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common ones are associated with disease. For example, the SNP that defines the Factor V Leiden variant occurs in at least 5% of Caucasians and is associated with heritable thrombophilia. Heterozygous carriers have a seven-fold increased risk for recurrent venous thromboembolism but homozygous carriers have an 80-fold increased risk (5). Other common SNPs in several cytochrome P450 genes are responsible for a large portion of the individual variation in response to common drugs (6). For example, the Food and Drug Administration recently re-labeled guidelines for the use of warfarin (<http://www.fda.gov/consumer/updates/warfarin081707.html>). These revisions recommend *CYP2C9* and *VKORC1* genotyping to assess warfarin sensitivity. The *CYP2C9* SNPs produce amino acid substitutions and enzymes with reduced activity for warfarin clearance. The common functional *VKORC1* variant is located in the promoter region of this target of warfarin action. In the absence of exposure to warfarin, the functional consequences of these SNPs are not apparent. Many of the SNPs described in population association studies of inflammatory response genes are positioned in the promoter region of the gene and affect overall gene synthesis levels.

A number of investigators have examined SNPs in attempting to describe the exaggerated response characteristic of SIRS/sepsis. Some investigations have screened large segments of the genome in an attempt to uncover relevant variants. Most have been unable to correlate frequently occurring SNPs with the syndromes. However, genotyping without consideration of the functional context within the clinical presentation, which is often seen in this kind of study, is illogical. Some, however, have been successful (7–16). In this issue of *Critical Care Medicine*, Henckaerts et al (17) examine a series of previous identified SNPs in genes encoding proteins known to be of importance in the innate immune response. These investigators used blood samples from a subset of patients enrolled in a study examining intensive insulin therapy in a Medical ICU in Leuven, Belgium (18). Specific genes were chosen that were known to generate functional abnormalities in: a) gene encoding proteins involved recognition of microbial or inflammatory products called *pathogen associated-molecular patterns* (the membrane bound receptor *TLR2* and *TLR4*, which respond to endotoxin, the soluble receptor mannose-binding lectin and the

intracellular pattern recognition receptor and signaling molecules, *NOD1* and *NOD2*, which respond to peptidoglycan) that are involved in the activation of the nuclear factor (NF)- $\kappa$ B pathway, b) genes encoding intra-cellular (mannose-binding lectin-associated serine protease 2 [*MASP2*]) and extra-cellular (plasminogen activator inhibitor type 1) immune-associated proteases, and c) genes encoding general immune system signaling molecules interleukin (*IL*)-4, *IL*-5, *IL*-6, *IL*-10, tumor necrosis factor (*TNF*)- $\alpha$ , TNF receptor superfamily member 1B (previously *TNFR2*), lymphotoxin alpha (*LTA*, previously *TNFB*) that respond to NF- $\kappa$ B-associated signaling. The results demonstrate that, compared to wild type, patients with at least one *NOD2* variant or carrying the *TLR4* D299G SNP were at higher risk for bacteremia. Those patients carrying both a *TLR4* and a *NOD2* variant were at even higher risk. These patients also were predisposed to earlier acquisition of bacteremia. Although there was no association with hospital mortality in patients carrying only one of these variants, there was increased mortality in patients carrying both. In addition, patients carrying either the D120G or V377A *MASP2* variant had an increased hospital mortality. The presence of a *NOD2* abnormality was associated with impaired monocyte phagocytosis, explaining part of the mortality effect noted when both *NOD2* and *TLR4* variants were present.

These findings are not unique in and of themselves. Wurfel et al (19) recently reported an association between SNPs in the *TLR1* gene and immune responses and outcome in sepsis, and Brenmoehl et al (20) found similar, results regarding *NOD2*. In addition, there are concerns with the statistical methods employed. There are several check points we need to consider when validating genetic association studies (<http://dorakmt.tripod.com/hla/stat.html>). Henckaert et al (17) have provided several instructions in this article. The authors evaluated not only the incidence of blood stream infections, but also the time to that corresponding event using Kaplan-Maier estimates and log-rank test in a separate univariate survival analysis. This intriguing viewpoint was followed by their “2 Step” statistical methods with which they assessed risk of bacteremia and hospital mortality. Colinearity of the intermediate phenotypes was assessed before modeling with a reasonable *p* value cutoff, and the standard

bootstrapping was performed with internal consistency models to eliminate the false effect in multiple testing (in “Step 2”). Furthermore, a permutation test was performed to make sure that these positive results took place by chance. It has been demonstrated that a minimum of  $10^3$  samples are required to evaluate a genetic risk accurately for a polymorphism with a variant frequency of 2% (21). Although the authors introduced a fairly large cohort of 774 ICU patients relative to the variant allele frequencies of the polymorphisms that they analyzed, the patients who developed bacteremia, i.e., a case cohort, were only 8% of the total ICU patients. Even if the levels of bacteremia significantly increased in minor allele carriers of both *NOD2* and *TLR4*, the majority of the patients did not exhibit this phenotype. Furthermore, it is likely that the “bacteremia model” is an “overfit” because there are many variables in a small number of patients with variable outcomes. From time to time, studies where healthy volunteers are included as a control population to build a large control cohort catch our attention. This sort of healthy population should be recognized to have an intermediated character between patients and nonpatients, and the latter nonpatient population should NOT deviate from Hardy-Weinberg Equilibrium. As the authors mentioned, the third limitation of this study is that more ICU patients who develop bacteremia and also match the physiologic characteristics of the noninfected patients are needed to validate this genetic association of susceptibility to bacteremia. In this connection, vulnerability to sepsis and the patients’ outcomes also may be influenced by gender and age (22, 23). Therefore, gender and age-distribution of the patients included in this study could be key pieces of undefined information.

There also is a potential problem with design. The samples analyzed here were derived from a larger investigation into the effects of intensive insulin treatment (18). Because of this, it may be that the observed effect reflects treatment and not genetic variation. The authors analyzed for a treatment effect and did not find one, but the study was not powered to detect this possibility. Similarly, even if both treatment and genetic effects are real, it is possible that one is of greater importance than the other. Indeed, these effects might offset each other—e.g., insulin improves outcome while genetic

variability worsens it, and the effects cancel each other. Again, it is impossible to determine whether this is the case or to construct a human study where this could be investigated. However, genetically manipulated mice might be used to examine the possibility.

Importantly, the observed abnormalities involve signal transduction pathways that modulate gene expression via NF- $\kappa$ B. This transcription factor is directly involved in the expression of genes encoding many cytokines including TNF $\alpha$ , IL-1 $\beta$ , and IL-6. Serum levels of these were obtained on admission and did not appear to be influenced by the presence of functional variants associated with altered outcome. This is important for a number of reasons. We have long contended that serum levels of cytokines are of little biological significance. Although a genetic difference in the kinetics of the cytokine serum level and patient outcome has reported to be influenced by some cytokine-related gene polymorphisms (24), many investigators contend that changes in the local tissue environment, where cytokines exert a paracrine effect, are more likely to determine responses (25, 26). Indeed, studies by one of the authors of this editorial demonstrate that sepsis impairs the function of intracellular pathways that modulate cytokine effects (26, 27). This is especially true for IL-6.

Whether or not vulnerability to bacteremia and poor outcome are influenced by genotype remains a matter of conjecture but the data by the authors provides a firm basis for a calculation and design for definitive study. Gene discovery in humans changed dramatically when it was recognized that variations in human DNA could be assayed directly and used as genetic markers in linkage studies. The International HapMap Project (24) has enabled examination of the genetic background of a particular individual by constructing a haplotype map that includes tagged SNPs. The authors provide the rationale for the selection of their polymorphisms as a supplemental table and make a strong case for examining the selected genes. However, as the authors point out, this study does not encompass the entire genome. Hence, a tag-SNP-based genome-wide association study for sepsis could be performed to find more specific markers that predict which ICU patients might develop sepsis.

Finally, it is intriguing to speculate about the nature of SNPs, immune dys-

regulation and outcome in the critically ill. Although there was no difference in the intention-to-treat cohort in the clinical study from which the samples analyzed by Hanckaerts et al were obtained there was an outcome difference in patients in the ICU for more than three days. This would imply that the majority of deaths occurred as a result of chronic critical illness and not hyper-inflammation, a conclusion that is supported by the SNP associations that result in a failure to respond appropriately to pathogen associated molecular patterns. Our previously mentioned data indicate that cytokine signaling is lost as sepsis progresses and this defect is associated with increased mortality (26, 27). The studies presented by Henckaerts et al lend credence to these findings and suggest that the same may occur in clinical sepsis.

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## A *Gradus ad Parnassum* for adult respiratory distress syndrome— Time for a few more steps\*

**T**he first *Gradus ad Parnassum* was a dictionary of Greek and Latin, and the title, “Steps to Mt. Parnassus,” the home of the Greek Muses, implied that study of the text would lead to mastery of the topic. Such a dictionary, “a Bible and a drum/and five hundred gallons of New England rum” were allegedly the only instruments of instruction necessary when Eleazar Wheelock founded Dartmouth College (1). The title of the dictionary (not the rum) is an apt description of progress defining and treating adult respiratory distress syndrome (ARDS). ARDS was first described in 12 patients with acute respiratory failure (2) who had bilateral infiltrates on their chest radiographs and required mechanical ventilation. They had reduced lung compliance and hypoxemia that could only be corrected by using positive end-expiratory pressure (PEEP). There was no single etiologic cause of their respiratory failure.

There have been two major efforts to define ARDS, and each of the definitions has emphasized the central features of the original cases: acute onset, respiratory failure with hypoxemia, and diffuse

alveolar injury that is not due to elevated left-sided cardiac pressures (3, 4). The etiology of respiratory failure is not relevant to the diagnosis of ARDS in either set of diagnostic criteria. In defining ARDS, there has been a tension between the need for a simple definition that can be applied consistently and the need for a definition sufficiently complex to capture the diversity of patients with ARDS and the range of severity of the syndrome (5). Studies of ARDS using these definitions have resulted in genuine progress understanding and treating ARDS (6–9). Intensivists have much to celebrate—they have gained some mastery treating ARDS, but there have also been problems.

The  $\text{PaO}_2/\text{FiO}_2$  (P/F) ratio is used in definitions of ARDS to establish the presence of abnormal gas exchange and to quantify the severity of lung injury. In the current issue of *Critical Care Medicine*, Allardet-Sevent et al (10) examined the effect of changing the  $\text{FiO}_2$  on the P/F ratio. They studied patients in the ICU ventilated with low tidal volumes and relatively high PEEP levels, and they systematically varied the  $\text{FiO}_2$  at a fixed PEEP level in each patient. The P/F ratio increased significantly in patients as the  $\text{FiO}_2$  was raised above 0.7. Thus, the diagnostic criteria for ARDS and acute lung injury were not stable even in individual patients. The P/F ratio is calculated as if the  $\text{PaO}_2$  and the  $\text{FiO}_2$  were independent variables. The equation is misleading on two counts. First, as the study by Allardet-Sevent et al (10) and a study by Gowda and Klocke (11) show, the  $\text{PaO}_2$  is

not an independent variable. The  $\text{PaO}_2$  varies linearly as a function of the  $\text{FiO}_2$  in the range from 0.4 to 0.6, but alinearly above an  $\text{FiO}_2$  of 0.7. Second, there are additional independent factors determining the P/F ratio: the degree of V/Q mismatch and the level of PEEP (12). When one confronts an equation with three independent variables (V/Q mismatch,  $\text{FiO}_2$ , and PEEP), the logical solution is to fix two of the variables and look at the independent effect of changing the remaining variable. The variable of interest in the P/F ratio is the extent of V/Q mismatch since this serves as a measure of the severity of lung injury, but the remaining variables,  $\text{FiO}_2$  and the level of PEEP, are not fixed when defining ARDS.

There are two additional problems defining ARDS. First, although the description of the x-ray criteria for ARDS is simple, the criteria are hard to apply consistently. There is only modest inter-observer agreement when using chest x-rays to diagnose ARDS (13), unless the interpreters have been trained to interpret the x-ray (14). The second issue is that the etiology of ARDS is not factored into the diagnosis. This implies that the lung has a limited set of pathologic responses to injury, and once injury is present, the fact of the injury is more important than the cause of the injury. Yet, we know that not all ARDS is the same—for example, there are important differences between patients with extrapulmonary and pulmonary causes of ARDS (15). It is remarkable that none of the recent therapeutic advances in treat-

### \*See also p. 202.

Key Words: acute respiratory distress syndrome; acute lung injury; hypoxemia; lung injury; gas exchange; mechanical ventilation

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ing ARDS depends on any specific diagnosis. On the other hand, we are unlikely to identify effective, etiologically specific therapies unless we incorporate the etiology into the classification of ARDS. So the absence of specific therapies may reflect the lack of specificity in our diagnostic criteria.

It is our view that it is time to address these issues and reevaluate (yet again) the diagnostic criteria for ARDS. It is bound to be a fractious process, but it is time to propose some simple rules to define the P/F ratio and interpret the chest radiograph in ARDS. The studies by Allardet-Sevent et al and Gowda and Klocke make it clear that in the  $FiO_2$  range of 0.5–0.7 and  $PaO_2$  range of 50–100 mm Hg, the P/F ratio is stable and representative of the severity of lung disease. Therefore, it seems simplest to set guidelines that restrict the  $FiO_2$  and  $PaO_2$  ranges over which the P/F ratio is measured. We propose that the P/F ratio be measured at the minimum  $FiO_2$  and minimum PEEP that achieve a  $PaO_2$  between 55 and 100 mm Hg. This strategy matches what many intensivists already try to achieve as they manage patients with ARDS; it results in measurements of the P/F ratio over the linear range of the relationship between  $PaO_2$  and  $FiO_2$ ; and it should lead to more consistent P/F ratios across patients. We will leave proposals to improve interpretation of the chest radiograph to wiser heads, but after appropriate instruction, the x-ray criteria for ARDS can be used consistently (14). Finally, we feel that it is time to include

some etiological criterion in the definition of ARDS. This could be as limited as a dichotomous classification based on the presence or absence of sepsis or on the primacy of pulmonary versus extrapulmonary causes of ARDS.

We have an improved understanding of ARDS and growing mastery of the treatment of ARDS. We have made real progress as we take steps to Mt. Parnassus, but we need greater clarity and specificity in the definition of ARDS if we wish to continue this progress.

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## City traffic, acute lung injury, and free enterprise\*

**U**rban myth holds that Boston's Callahan tunnel was the preferred site for collection of nitric oxide (NO) for initial

trials as a selective pulmonary vasodilator in adult respiratory distress syndrome (ARDS). Contemporary studies with NO (1) and carbon monoxide for acute lung injury (ALI) (2) suggest that the earlier investigators had great insight in choice of potent toxins. It is still not clear that NO inhalation markedly effects long-term outcome. Some two decades later, although limited to pulmonary application, the use of extrinsic inhaled agents is still being pursued. As the pages of this and other journals attest, much greater effort is currently being concentrated on endogenous NO. The realization that vascu-

lar endothelial relaxing factor was in fact NO and that NO was in fact involved in many systemic processes (3) provided the opportunity for wider therapeutic application. Currently, this mundane molecule is implicated in physiologic chicanery from hypertension to erectile dysfunction.

Although not yet fully elucidated, intrinsic biochemical production of NO is under intense study . . . *In vivo* NO is produced by nitric oxide synthase (NOS) catalyzing the reaction between oxygen and L-arginine. At least three NOS subgroups; endothelial (eNOS), neuronal

\*See also p. 208.

Key Words: acute respiratory distress syndrome; acute lung injury; nitric oxide; nitric oxide synthase; endothelial nitric oxide synthase; inducible nitric oxide synthase; neuronal nitric oxide synthase; smoke; burn  
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(nNOS), and inducible (iNOS) have been identified. The particular NOS enzyme involved and rate of production has been shown to have protean physiologic consequences. Hyperproduction of NO, for example, by nNOS and iNOS may play a role in neurodegenerative disease, septic shock, postinflammatory tissue damage, rheumatoid arthritis, and ALI. It seems that eNOS synthase produces NO in situations where beneficial effects such as angiogenesis predominate, whereas impaired synthesis can lead to endothelial dysfunction (4). Considerable research has thus been focused on selective inhibitors of NOS by independent researchers (5) and the pharmaceutical industry (6).

In this issue of *Critical Care Medicine*, Enkhbaatar et al (7) present a study on the use of an nNOS inhibitor in ameliorating ALI induced via combined thermal and inhalation injury in an ovine model. The present study reports reduction of vascular leakage, attenuated decrease in plasma oncotic pressure,  $PAO_2/FIO_2$  improvement, and decreased lung water content following 24-hr infusion of the inhibitor. In addition, decreased lung tissue leukocyte concentration, lower 3-nitrotyrosine levels and lower poly(ADP-ribose) polymerase activity were found in the treated group. In fact, although NO produced from the various synthase isoforms is clearly involved as a mediator in lung disease (8), nNOS has not been a favored focus for ALI research. In contrast, iNOS has been investigated (9, 10) and this study closely follows the author's previous study on inhibition of iNOS (11).

Anticipation of a human trial of what seems to be such a beneficial agent raises several questions. Predominant is of course the effect on mortality. Whether selective NO inhibition will improve short-term oxygenation and fail to improve mortality in humans (much as Taylor's study showed for inhaled NO) is as yet unstudied. Are selective inhibitors in fact beneficial or will we see evidence of increased mortality when used in humans such as that occurring with nonselective inhibition? (12) Hopefully not, although the results of the current article indicate that nNOS seems to modulate iNOS. In relation to the current study, are the results applicable to ALI from other than burn injury? Almost certainly yes.

For many years the burn literature has described burn inhalation injury meeting ARDS criteria following combined inha-

lation injury and major tissue injury from thermal, chemical, or electrical agents. It is also clear that those patients with severe inhalation injury alone or major burn alone may develop an ARDS or ALI picture. Based on current knowledge of systemic inflammation this is not unexpected. There has been some confusion with the term inhalation injury itself as it can be taken to indicate inhalation of byproducts of combustion, which have immediate cell level effects, such as carbon monoxide or cyanide. These must be distinguished from products of combustion loosely grouped under "Smoke inhalation," which may take several days to produce ALI. Because of the efficacy of the glottal stop mechanism, it is unusual to have an actual (survivable) thermal injury to the lower respiratory tract itself. However, this can occur in the case of inhalation of superheated gas or steam.

The authors take care to avoid the latter by controlling inhalation temperature of the cotton combustion smoke used to 40°C. They utilize a well-accepted injury model for burns. The use of ignited natural polymers for production of smoke byproducts has been documented in both canine (13) and ovine (14) models. Cotton smoke is further shown to have similar lethality to both wood and synthetics (15). Enkhbaatar et al use carbon monoxide inhalation itself as a marker for efficacy of smoke administration, but it is of necessity treated by application of mechanical ventilation. It should also be noted that authors have used a similar if not identical model and differing treatment modalities for at least three other trials in which ALI occurred, including one involving nNOS and ALI (16). For this study, clinical assessment of the subjects revealed  $PAO_2/FIO_2$  ratios (<300) consistent with milder expression of ARDS, that is, ALI. The study also showed excess production of NO stable metabolites nitrate/nitrites ( $NO_x$ ). This conforms to previous studies of  $NO_x$  in bronchoalveolar lavage samples from patients with ARDS (17). Overall, it appears that the model produces an ALI not unlike that seen with aspiration, toxic gas exposure, pulmonary contusion, fat emboli, pneumonia, multiple trauma, or extended surgery. Although histology was not presented, no report of airway cast formation often seen in combined thermal/inhalation injury was made.

Accepting for the moment that the results of the current study reflect what occurs in ALI of burn/inhalation injury

and may further be more widely applicable, there are several caveats. It has been pointed out that as of yet due to interspecies differences in metabolism there are no methodologies for estimation of NO production rate at an organ-specific level and thus no methods for estimating dose of NOS inhibitors to achieve adequate tissue levels. Neither is there clear evidence that targeting a single molecule will prevent an entire pathophysiologic cascade (18). Nonetheless, the research is well underway. A brief review of the literature reveals several dozen patents and several hundred studies on preproduction NO synthase inhibitors in the last decade. It is obvious that big business acknowledges the potential. Will we all be charged with insider trading if we benefit from stock purchases of the respective companies? Not likely. As the authors acknowledge in the discussion the mechanism by which vascular permeability is reduced is unknown, overall hemodynamics over the short term of the study were not affected by treatment and cytokine-neutrophil pathways seem to have been affected, confirming Hausers caveats (18). The model however seems robust and continued research may lead to a titratable intravenous therapy for ALI/ARDS.

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## Who is the bad guy in acute respiratory distress syndrome? Neuronal nitric oxide synthase, inducible nitric oxide synthase, or both?\*

Smoke inhalation injury is often complicated by pneumonia and represents the major cause of death in fire victims (1). As a matter of fact, more than one million burned patients are annually hospitalized in the United States alone, and more than 20% of this population suffers from the consequences of smoke exposure (2). Although respiratory support, aggressive fluid resuscitation, and early surgical interventions have improved survival of fire victims during the last decade, no specific therapy for the commonly associated smoke inhalation injury has yet been established. Experimental studies enabling a better understanding of the underlying pathophysiology and allowing to establish novel treatment strategies are, therefore, of paramount clinical and socio-economic importance (3).

In this context, previous studies provided evidence that excessive production of nitric oxide (NO) plays a pivotal role in the pathogenesis of acute respiratory distress syndrome (ARDS) (4). NO is synthesized by at least three differ-

ent isoenzymes by electron transfer from nicotinamide adenine dinucleotide phosphate to arginine. Whereas the inducible nitric oxide synthase (iNOS = NOS 2) is typically up-regulated in response to systemic inflammation and oxidative/nitrosative stress, endothelial NOS (eNOS = NOS 3) and neuronal/brain NOS (nNOS/bNOS = NOS 1) are constitutively expressed (5). However, in the presence of cellular distress, such as sepsis or ARDS, nNOS may increase its activity, thereby producing relevant amounts of NO. NO, in turn, may combine with superoxide and form the highly reactive and cytotoxic peroxynitrite (ONOO<sup>-</sup>), leading to tissue damage by nitration of proteins and lipid peroxidation. ONOO<sup>-</sup> may also contribute to single DNA strand breakage with subsequent activation of the adenosine triphosphate-consuming enzyme poly(adenosine diphosphate-ribose) polymerase (PARP). In addition to leading to cell death, PARP has been reported to activate nuclear factor-kappa B and up-regulate iNOS protein expression (5), thereby perpetuating the inflammatory cascade.

Early interruption of the vicious cycle may, therefore, represent a rational approach to limit the degree of injury and to prevent the development of irreversible organ failure. In fact, previous studies have shown that inhibition of either nNOS (6), iNOS (7), or PARP (8) are similarly effective in attenuating the degree

of pulmonary dysfunction in ovine ARDS. Previous work has likewise demonstrated that blockade of nNOS prevents not only ONOO<sup>-</sup> and nitrate/nitrite (NO<sub>x</sub>) formation, but also up-regulation of iNOS mRNA, suggesting that nNOS-generated NO may be the trigger for the cascade of events (9).

When reviewing the current literature on this topic, although limited in extent, one may speculate that a dual approach, including early nNOS and delayed iNOS inhibition, may be a promising option to treat lung injury linked to significant NO production. From our own experience, however, we learned that simultaneous inhibition of nNOS and iNOS may contribute to gastrointestinal malperfusion, thus being detrimental rather than beneficial (9). Given that nNOS is primarily implicated in the early pathophysiologic changes in ARDS (6) and iNOS in the later stage of the disease (7), it is tempting to postulate that selective nNOS inhibition followed by specific iNOS blockade may be a goal-directed therapy.

In the current issue of *Critical Care Medicine*, Lange et al (10) addressed this important subject in a highly sophisticated experimental setting. Using a well established and clinically relevant ovine model of ARDS secondary to smoke inhalation and bronchial administration of live *Pseudomonas aeruginosa* bacteria, the investigators elucidated the effects of the nNOS inhibitor 7-nitroindazole

### \*See also p. 223.

Key Words: acute lung injury; inhalation injury; peroxynitrite

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during the first 12 hrs postinjury and the highly selective iNOS blocker BBS-2 during the second 12 hrs of the experiment on cardiopulmonary functions. The major finding was that this approach reduced the expression of nNOS, iNOS, and PARP and was associated with a reduction in nitrosative stress and less airway obstruction as compared to untreated injured controls. Surprisingly, however, the combination therapy was not superior to previous studies investigating the role of sole nNOS (6) or iNOS inhibition (7) in the same animal model.

Although it is conceivable that nNOS may be the trigger for iNOS activation at an early stage of the disease (9, 11), future studies are needed to address this issue in more detail. In this regard, comparative trials evaluating the effects of selectively blocking nNOS, iNOS, or both enzymes on mortality are needed. In addition, it remains to be determined whether or not the sequel of early nNOS and delayed iNOS inhibition is superior to initial iNOS and subsequent nNOS blockade.

Another interesting finding of the present study (10) is the observation that the combination therapy—most likely by preventing ONOO<sup>-</sup> production—significantly reduced the expression of vascular endothelium growth factor (potent permeability factor) in lung tissue, but failed to attenuate pulmonary edema formation. This, in turn, strongly suggests that other relevant mechanisms beside the NO-PARP pathway are critically involved in the pathogenesis of ovine ARDS.

Although highly specific treatment options may be helpful to identify new pathogenetic mechanisms, there is little expectation that such approach will lead to the discovery of the magic bullet capable of curing ARDS. One may even argue that it is time to investigate the use of treatment bundles, similar to what has been recommended by the Surviving Sepsis Campaign for the management of septic shock (12). Considering the multifaceted pathophysiology of ARDS associated with smoke inhalation injury and bacterial pneumonia, the following characteristic features may be taken into account: a) systemic inflammation with oxidative and nitrosative stress (7, 9, 10, 13, 14); b) capillary leakage with pulmonary fluid flux (13, 15); c) loss of hypoxic pulmonary vasoconstriction and pulmonary shunting (9, 16); and d) increased airway pressures because of

bronchial and bronchiolar obstruction (4, 10, 13, 14, 17). Although NO inhibition undoubtedly plays a crucial role in attenuating all these qualities, it would be interesting to determine the effects of a “cocktail” consisting of nNOS and/or iNOS inhibition plus antioxidants, such as vitamin E (18), selective V1a agonists aiming to reduce the degree of capillary leakage (19), anticoagulants to resolve fibrinogenic cast material in the airway (13–15), and specific antibiotic treatment (14, 20).

Hopefully, the nice and timely study of Lange et al (10) will stimulate researchers to continue working on innovative treatment strategies, aiming to reduce morbidity and mortality of this world-wide clinical problem in the near future. Although the current literature allows the speculation that nNOS is the bad guy instigating iNOS and PARP to do harm, future studies are needed to determine whether or not selective nNOS inhibition has the potential to decrease overall mortality. Given that nNOS blockade improves survival in the experimental setting, clinical pilot studies are warrant.

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# It's all in the gut: Introducing the concept of acute bowel injury and acute intestinal distress syndrome . . .\*

**W**hat this study tells us . . . In this issue of *Critical Care Medicine*, Olofsson et al (1) report the results of a study assessing gastric, intestinal, and renal cortex microcirculation parallel with central hemodynamics and respiratory function during intra-abdominal hypertension (IAH) in a large animal model. On first sight, this looks as a repeat of previously performed pathophysiologic studies in animals on the impact of IAH and abdominal compartment syndrome (ACS) on gut perfusion and cardiopulmonary function (2). Is this really the case? Data were collected prospectively in 26 swine. The authors performed 10 mm Hg stepwise increases of intra-abdominal pressure (IAP) at 10-min intervals up to 50 mm Hg via CO<sub>2</sub> insufflation in 20 animals, whereas six animals without pneumoperitoneum served as controls. The microcirculation was measured via laser Doppler flowmetry at the *mucosal* level for the stomach, colon, and small bowel, at the *seromuscular* level for the colon and small bowel, and also at the level of the renal cortex. The authors observed a progressive drop in microvascular flow at all measurement sites during stepwise increase in IAP. However, when flow was compared relatively with the cardiac output no significant differences could be observed at the mucosal level. Classic effects on cardiac and respiratory function were observed. The authors also found a reasonable correlation between direct IAP and intravesical pressure in 140 paired

measurements, although bias and limits of agreement were unacceptably high. The bottom line is that short-term increases in IAP to extreme levels decreased small bowel mucosal blood flow to a *lesser* extent than the seromuscular blood flow. However, no specific explanation could be given for this observation.

What this study adds... This animal study has a lot of similarities with previously published ones (3). Mucosal blood flow was more preserved during maximal IAP compared with seromuscular flow and this is a new finding (4). This “sparing” of the bowel mucosa suggests the presence of autoregulation/redistribution of microcirculatory (mucosal) blood flow in the small bowel during IAH, which has also been shown during sepsis and ischemia–reperfusion. The authors also successfully incorporated the new consensus definitions and recommendations recently published by the World Society on Abdominal Compartment Syndrome (WSACS, [www.wsacs.org](http://www.wsacs.org)) (5, 6). With regard to the best IAP measurement method it remains unclear whether direct IAP measurement is a good standard with a bias of 5.6 mm Hg (compared with intravesical pressure) and unacceptable high limits of agreement ranging from –4.9 to 16.1 mm Hg (7)! Direct IAP measurement is prone to errors by flow dynamics resulting in rapid increases or decreases in pressure during insufflation. The Verres needle can be blocked leading to over- or underestimation of IAP. For study purposes, it is important that a reproducible IAP measurement is used, and recently fully automated continuous techniques have become available ([www.spiegelberg.de](http://www.spiegelberg.de) or [www.pulsion.com](http://www.pulsion.com)) (8). The article stresses the importance of a good animal model to study the implications of IAH on end-organ function (3). The best model should probably be “pathologic” in which IAH originates from a primary insult, capillary leak, resuscitation, and ischemia-reperfusion.

What this study does not tell us . . . To play the devil’s advocate one could argue

that the questions that the authors tried to answer have already been addressed previously and some may even argue that the article is lacking some “novelty” value and the different effects on mucosal vs. seromuscular blood flow could be related to methodologic issues.

First, preload was not well defined because only central venous pressure was measured and although the pigs had a pulmonary artery flotation catheter no pulmonary artery occlusion pressures were given. The pigs had a low baseline central venous pressure of 5 mm Hg suggesting low preload. It is well known that *volumetric* indices of preload, such as global or right ventricular end diastolic volumes are far more superior than *barometric* ones in the setting of IAH (9, 10). Functional hemodynamics like stroke volume variation or pulse pressure variation give an idea of fluid responsiveness and could have guided further resuscitation of the pigs, but these data as well as pleural pressures to calculate transmural filling pressures were lacking (11).

Second, this descriptive physiologic study was performed in healthy pigs and IAP was increased via pneumoperitoneum. Therefore, it remains questionable whether these results can be extrapolated to the clinical setting. Within this context the terms acute bowel injury and acute intestinal distress syndrome have been recently coined together with acute intestinal permeability syndrome (12). Apart from direct negative impact on cellular organ function, this can also have a deleterious effect through accumulation of extravascular fluids in the tissues. This mechanism of injury is widely recognized and accepted in the lung and kidneys, where it is classified as acute lung injury and acute kidney injury. The same pathologic process occurs in the gut, but this concept is much slower to seep through. However, the role of the gut as the motor of organ dysfunction syndrome cannot be denied and difficulties in assessing gut function should not deter us from recognizing that concept.

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#### \*See also p. 230.

Key Words: abdominal pressure; abdominal compartment; microcirculation; gut perfusion; pathophysiology

Dr. Malbrain is a member of the medical advisory board of Pulsion Medical Systems (Munich, Germany) and has a patient and owns stock in the company; he also has done consulting and received royalties from Holtech Medical. Dr. De laet has not disclosed any potential conflicts of interest.

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Third, it remains unclear how the authors observed a 44% transmission of the IAP increase from 0 to 50 mm Hg to the thoracic compartment (manifested by an increase in end-inspiratory alveolar pressure from 15 to 37 mm Hg), whereas only a 16% transmission to the vascular compartment was observed (increase in central venous pressure from 5 to 13 mm Hg). This is in contradiction to previous studies showing on average an index of transmission of 50% (10, 13).

Fourth, the authors used CO<sub>2</sub> insufflation for creating IAH which may have affected the results. Gases are likely to have systemic effects. Although helium seems quite inert, argon has been observed to influence hemodynamic parameters, and CO<sub>2</sub> can influence CO<sub>2</sub> exchange by resorption (14). Hypercapnia may act on gut vessels by direct vasodilatation and indirect sympathetic stimulation, partly explaining the observations. Therefore, it is unclear to separate the effect of CO<sub>2</sub> and IAP on microcirculatory blood flow.

Fifth, the equilibration time between the different IAP levels was short and the total study lasted only 60 mins. In retrospect, the model would have been more clinically relevant if the sequential levels of IAH had been maintained for 60 mins each rather than 10 mins. The current model therefore is one that mimics “hyperacute” IAH rather than the clinically encountered “acute” or “subacute” IAH.

What future animal studies should look at . . . Having said that and having played the devil’s advocate I rest my case: this study is very interesting and the authors have to be congratulated. It offers a springboard for further refinement of future animal studies. As pointed out by Schachtrupp et al (3) in their article entitled “What is the best animal model for ACS?” the ideal model for studies of ACS has not yet been identified nor presented. The model presented in the study herein has some disadvantages related to the short duration and the effects related to CO<sub>2</sub> absorption. The authors did a good job with the addition of a control group and independent external statistical consulting and they can claim a definite “novelty” value by showing statistically different responses to IAH in the microcirculation of different vascular beds. The most interesting finding being the relative protection of the microcirculation of the mucosa of small bowel and colon.

In analogy to acute lung injury and acute kidney injury, there is certainly a need for basic research into the underlying mechanisms of acute bowel injury.

Ischemia-reperfusion injury research in an animal model in particular seems to show a lot of promise into this pathogenesis. Previous data show that IAH, capillary leak, futile resuscitation, and sepsis go hand-in-hand (15). It is also not unrealistic to suggest that IAH/ACS may impact an even greater number of intensive care unit patients than those affected by sepsis. Future studies should look at the long-term effects (24–48 hrs) of IAH at clinically relevant IAP levels (20–30 mm Hg) on microcirculation. The present study can help others to develop better models and join forces. The fact that alterations in microcirculation were already seen at moderate IAP levels (10–20 mm Hg) raises questions regarding physiologic changes during laparoscopy (where CO<sub>2</sub> seems indeed more appropriate). Future studies should try to integrate these results with global indices of perfusion (lactate, base deficit) and the presence of clinical overt shock. They should also look at the effects of IAH on gastric and small bowel motility as well as gut mucosal barrier function by examining full bowel biopsies.

The results of the present study confirm the importance of IAH/ACS. The WSACS invites interested researchers to join the society and to submit some prospective data for the next world congress (www.wcacs.org) to be held in Dublin, Ireland, June 24–27, 2009. For those who carry the mandate to future IAH/ACS research, the path ahead is clear: using available evidence, we must develop an IAH/ACS therapeutic bundle and apply it in a multiple center, prospective, outcome trial (12). In a separate effort, attempts should be made to better understand the causes and evolution of acute bowel injury and acute intestinal distress syndrome. In our opinion, it is one of the great scientific adventures of the future to link all the data that we have today on organ dysfunction, be it acute lung injury, acute kidney injury, or acute bowel injury, and bring them together in a single broad-based concept, that can explain the different aspects of the systemic inflammatory response syndrome and provide clues for treatment, not only aimed at the organs involved, but at the core of what kills our patients.

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# Can troponin identify those critically ill septic patients who would benefit most from activated protein C treatment?\*

"Imagination is more important than knowledge."—Albert Einstein

Earlier, cardiovascular derangements associated with septic challenges have been ascribed to the inflammatory mediators known as myocardial depressant factors (1), coronary ischemia (2), nitric oxide excessive production (3), interstitial myocarditis (4), increased apoptosis (5), and even subcellular mechanisms involving sodium and calcium homeostasis (6). Despite the growing knowledge of the possible involved mechanisms, our understanding of this serious condition deserves much more imagination to reduce the septic myocardial depression-associated mortality. Nowadays, we are able to identify with more accuracy the septic patients whose myocardium has been compromised by assessing troponin levels (7), a highly sensitive and specific marker of myocardial injury in sepsis. Furthermore, we are able to prognosticate their outcomes and therefore select the best therapeutic approaches (8). But, are we able to reduce their mortality rates? Indeed, John et al (9) in a recent article proposed that activated protein C (APC) treatment of patients with elevated troponin may in fact reduce mortality in a very significant way and attributed this remarkable finding to its direct anti-inflammatory effects.

In this issue of *Critical Care Medicine*, Nacira et al (10) were very auspicious in adding a new piece to this complex puzzle. By means of their experimental study they were able to conclusively demonstrate that APC improved cardiovascular function by decreasing the endotoxin/leukocyte interaction and by modulating the endo-

toxin-induced proinflammatory state. Thus, they hypothesized that APC by decreasing leukocyte activation, reduced leukocyte infiltration both in heart and vessels, thereby decreasing cytokine release and favoring the stabilization of the extracellular matrix. We have previously shown that a real interstitial myocarditis (4) occurs in critically ill septic patients because of emigrated neutrophils into the myocardial tissue. Furthermore, Poon et al (11) demonstrated that inducible nitric oxide synthase seems to be essential for the ability of emigrated neutrophils to cause injury. The ability of the heart to respond to proinflammatory cytokines and pathogen-associated molecular patterns has been reported by several authors. Indeed, various studies suggest that the major input of proinflammatory stimuli and effector molecules such as tumor necrosis factor- $\alpha$ , nitric oxide, and prostaglandins that are present in the heart under infectious or inflammatory conditions are released by infiltrating macrophages and neutrophils (12, 13). The nuclear factor- $\kappa$ B family of transcription plays an essential role in regulating the induction of genes involved in inflammation (14). The transcription of nitric oxide synthase-2 in rodent cells is strictly dependent on nuclear factor- $\kappa$ B activity. It is noteworthy that APC reduced *in situ* the activation of the transcriptional factor NF- $\kappa$ B, thus reducing oxidative and nitrosative stresses in aorta and heart. Of interest, lipopolysaccharide (LPS) receptor (TLR-4)-deficient mice seem to be protected from endotoxin-induced cardiac damage. In fact, cardiac myocytes isolated from LPS-treated mice showed reduced contractility and calcium transients as compared with myocytes from untreated mice. In addition, these LPS-treated mice showed impaired cardiac mitochondrial function. Cardiac myo-

cytes have equivalent amounts of TLR-4 on endothelium, however, only the latter is responsive to LPS (15). Furthermore, signaling pathways downstream of TLR-4 were not activated during direct LPS treatment of myocytes. In conclusion, TLR-4 on leukocytes and not on cardiac myocytes is important for cardiac myocyte impairment during endotoxemia.

Can we speculate from these data that the most severe septic patients have the greatest cell infiltration within the cardiomyocytes, thereby rendering the myocardium less compliant and jeopardizing its contractile properties? Should we stratify these high-risk patients and evaluate their response to APC in a randomized controlled trial? Would this question raise ethical issues? Cost-effectiveness analysis on APC may be considerably different among poorer countries. It is our responsibility to identify those septic patients who might benefit most from APC in a favorable cost-effective analysis.

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\*See also p. 246.

Key Words: troponin; myocardial depression; myocardial injury; activated protein C; TLR-4; leukocytes  
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## Postarrest nitric oxide effect depends on the source\*

Successful resuscitation from cardiac arrest is a multiphase process, which is much more complex than previously understood. The past practice of focusing only on achieving restoration of spontaneous circulation (ROSC) has been unsatisfactory. Although ROSC is an obvious prerequisite for survival, of the 30% of hospital sudden cardiac arrest victims that are initially resuscitated, approximately 80% will die in the hospital, resulting in an overall survival rate of 6.4% nationally (1, 2). Similarly, data from the National Registry of Cardiopulmonary Resuscitation noted that of 14,720 in-hospital arrests, 44% obtained ROSC, but only 17% survived to hospital discharge (3). As such, one important strategy for improving overall cardiac arrest survival is to anticipate the postarrest organ dysfunction, which leads to early death and to intervene to prevent this lethal course. Following ROSC, there is a period of myocardial depression which is particularly harmful to the heart (4, 5). Myocardial dysfunction may be temporary, as in the case of myocardial stunning, or it may proceed to myocyte death. This myocardial depression correlates temporally with the period of

significant postarrest mortality. The underlying mechanisms of postarrest myocardial dysfunction are incompletely understood and have no existing treatment other than empirical beta adrenergic therapy.

The role of nitric oxide (NO) in the postarrest period has been particularly controversial, due in part to the multiple nitric oxide synthase (NOS) isoforms which appear to have opposing effects on the post ischemic heart. For example NOS-2 (iNOS) seems to worsen initial resuscitation from cardiac arrest, whereas NOS-3 (eNOS) and NOS-1 (nNOS) seem to have cardioprotective effects (6). Another confounding factor in delineating the role of NO in the postarrest heart has been the use of non-selective NOS inhibition (e.g., L-NAME) thereby inhibiting to various degrees all NOS isoforms, both protective and detrimental. For example, earlier studies with L-NAME in a swine cardiac arrest model showed improvement in coronary perfusion pressure during CPR as well as improvement in initial ROSC (7). In another study, nonspecific NOS inhibition did not improve initial survival (8).

As such, the article in this issue of *Critical Care Medicine* by Nishida et al (9) is particularly insightful in addressing the role of NOS-3 (eNOS) in the resuscitated heart. They use transgenic models to isolate the effects of NOS-3 in cardiac arrest. This is a robust approach in an *in vivo* mouse cardiac arrest model which supports the recent trend to use transgenic models to understand the role of the various NOS isoforms in the postischemic heart. In recent work using a NOS-2 (iNOS) knockout mouse, postinfarction

dysfunction was significantly improved (10). Of interest in the ever increasing variety of transgenics available, is the report of a mouse model deficient in all three isoforms of NOS (triple n/i/eNOS<sup>(-/-)</sup>) (11). In this model, increased cardiovascular risk is evident and includes spontaneous myocardial infarction (12).

To investigate the postarrest effects in a model with myocardial depression, the authors have developed a mouse model that can be reliably resuscitated after a clinically relevant cardiac arrest period of 9 mins followed by CPR. This model shows early myocardial dysfunction in the postarrest period. To facilitate successful resuscitation in this model, the authors have included mild hypothermia to a core temp of 28°C throughout arrest and resuscitation. Interestingly, they note improved resuscitation rates at this temperature, although this was not the focus on the study.

The strength of this study lies in the demonstration of NOS-3 (eNOS) benefit *in vivo*. The authors have compared their transgenic wild type with a NOS-3 deficient mouse (NOS<sup>(-/-)</sup>) and a NOS-3 deficient mouse with cardiomyocyte restricted overexpression of NOS-3 (NOS3<sup>(-/-)</sup>CTSg). In this analysis, they note worsening of postarrest LV function in the NOS<sup>(-/-)</sup> when compared with the wild type. In the cardiomyocyte restricted overexpression of NOS-3, postarrest LV function re-approximates the wild type phenotype. In seeking to determine the role of NOS-3 in the postarrest period, they note significant effects in noncardiac organs, including

### \*See also p. 256.

Key Words: nitric oxide synthase 3; myocardial stunning; postcardiac arrest; cardiopulmonary resuscitation; nitric oxide

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the brain and liver. A 24-hr neurologic outcome, based on a neurologic score, was worse in the NOS3<sup>-/-</sup> mouse, but equal to the wild type in the NOS<sup>-/-</sup> CTSg. Interestingly, these data suggest that myocyte overexpression of NOS3<sup>-/-</sup> has distant organ effects.

By measuring a number of related parameters, the authors provide some insight on possible NO mediated mechanisms at work in the postarrest period. In NOS-3 deficient animals these include: increased leukocyte recruitment to the liver and heart; increased apoptosis in the heart, liver and brain; caspase-3 activation in the brain hippocampus; and cytokine activation in the heart. Of importance is the reduction in overall survival in the NOS3<sup>-/-</sup> mice. To further identify the role of NOS-3, a fourth group of soluble guanylate cyclase deficient mice (sGC<sup>-/-</sup>) was subjected to the same cardiac arrest protocol. Outcome parameters in this group very closely approximated outcomes in the NOS3<sup>-/-</sup> group in the heart, although there was less of a response in the liver and brain. These data suggest sGC is activated downstream from NOS-3 induced NO production and may function in many of the protective roles mediated by NO in the heart.

These models offer a powerful tool to better define the role of specific NOS and

their downstream effects. Although these transgenic models have been used in other models of cardiac ischemia, their application in cardiac arrest is relatively new but promising.

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## Attenuating the effects of cardiac arrest on hepatic drug metabolism: Just chill out!\*

**S**ignificant physiologic alterations are frequently evident in critically ill patients. These alterations can significantly affect the pharmacokinetics of drugs used in this patient population. Pharmacokinetic changes can be a result of organ dysfunction, most notably the liver and kidneys, but can also be a consequence of the acute phase response, drug interactions, and

therapeutic interventions. Thus, optimal use of drugs in the critically ill patient requires a keen understanding of the potential alterations on the pharmacokinetic processes of absorption, distribution, metabolism, and excretion in this patient subset (1). Critical care practitioners are generally aware of the need for drug dosage adjustments in patients with renal dysfunction with numerous clinical resources available to guide such adjustments. Alterations in hepatic elimination of drugs in the critically ill are less well appreciated despite being a relatively common event.

Hepatic metabolism depends primarily on three physiologic processes: hepatic blood flow, protein binding, and enzyme activity (2). Alterations in one or more of these processes results in varying effects on

hepatic metabolism, depending on the characteristics of the drug (3). For example, the most clinically important group of drugs affected by increases or decreases in hepatic blood flow in critical illness are those that are highly extracted by the liver (extraction ratio >0.7) or have an intermediate extraction ratio (0.3–0.7). Analogously, protein binding effects will be dependent on the extent of protein binding for a particular drug and whether the drug binds to albumin that typically decreases in critically ill patients or  $\alpha_1$ -acid glycoprotein that increases dramatically during the acute phase response. Agents administered in critically ill patients where protein binding alterations may be significant include fentanyl, alfentanil, sufentanil, remifentanyl, diltiazem, nicardipine, verapamil,

\*See also p. 263.

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erythromycin, haloperidol, itraconazole, milrinone, and propofol (4). For drugs that have a relatively low extraction ratio (i.e., <0.3), it is the enzyme activity (i.e., intrinsic metabolism of the hepatocyte) that predominantly affects overall hepatic drug clearance. In general, significant inhibition of cytochrome P-450 (CYP450) isoenzymes (phase I metabolism) have been documented in ischemic and postinjury models as well as in clinical studies (3). This down-regulation is believed to be mediated by proinflammatory cytokines. Effects on hepatic phase II conjugative metabolism (e.g., glucuronidation, sulfation, and acetylation) have also been observed, although the effect is usually less profound than for phase I reactions (3).

Since McKindley et al (3) published a comprehensive review of the literature on hepatic drug clearance in critical illness in 1998, a number of additional investigations have been conducted expanding our knowledge on this topic. One line of research has studied the effects of therapeutic hypothermia on CYP450 metabolism (5–7). These studies have demonstrated decreased hepatic drug metabolism under hypothermic conditions. The article published by Poloyac et al in this issue of *Critical Care Medicine* further extends our understanding of potential pharmacokinetic alterations after cardiac arrest (CA), hypothermic conditions, and rewarming (8). Specifically, the study focuses on the effects of CA on the functional regulation of two major drug regulating cytochrome CYP450 isoenzymes, as well as the attenuation of these effects with moderate hypothermia upon rewarming. Among the drugs that may be affected by down-regulation of hepatic drug metabolism by the CYP450 isoenzymes after CA are amiodarone, calcium channel blockers, fentanyl and midazolam. This is important because these agents may be used to either treat CA or used in critically ill patients who develop CA while receiving intensive care unit care. As detailed in the article, hypothermia (30°C) was induced for 3 hrs with a 1 hr rewarming period after model CA in Sprague-Dawley rats (n = 6 per control group, CA normothermia group, and CA hypothermia group killed at 2 postinjury time points). The effect of moderate hypothermia on the hepatic activity and messenger RNA expression of CYP3A2 and CYP2E1 at 5 and 24 hrs after injury was then measured as well as interleukin-6 (IL-6) concentrations and the effect

of IL-6 on transcriptional regulators. As anticipated, a decrease in both CYP450 isoenzyme activities occurred after CA as well as an approximately ten-fold increase in IL-6. A significant difference and trend toward a decrease in messenger RNA expression for CYP3A2 and CYP2E1, respectively, was also observed. The effects of CA on CYP3A2 and CYP2E1 activity and the increase in IL-6, and their attenuation at 24 hrs under moderate hypothermia conditions followed by rewarming are the principle contributions to the literature emanating from this investigation. Evidence is offered that the observed effects on the CYP450 isoenzymes may be mediated by the effects of IL-6 on enzyme gene transcription. These findings parallel the work of these and other investigators evaluating CA and traumatic brain injury models (5, 9, 10). One of the limitations of this study as pointed out by the authors is that clinical hypothermia for CA is typically performed at temperatures of 32–35°C for 12 to 72 hrs. Thus, it is unclear if the results of this study would have been observed at these higher temperatures. Furthermore, the effects of hypothermia beyond 3 hrs with rewarming were not evaluated. Considering the highly dynamic physiologic conditions observed in critically ill patients after an acute event such as CA and their potential effects on hepatic drug metabolism over time, this latter limitation may be substantial (6, 9, 11, 12).

The blunting of hepatic drug metabolism by moderate hypothermia and normalization upon rewarming is intriguing and could well have significant clinical implications as this therapeutic modality gains momentum for use post-CA and in other conditions resulting in neurologic insults (e.g., traumatic brain injury, stroke, spinal cord injury, etc). In essence, the attenuation of the down-regulation of hepatic drug metabolism after CA would ideally result in the ability to use typical dosing regimens for those agents metabolized by the CYP3A2 and CYP2E1 isoenzymes upon rewarming. In the absence of moderate hypothermia, however, consideration should be given to empirical dosage reductions of these agents to avoid drug misadventures in critically ill patients after CA to account for their diminished hepatic clearance. Animal investigations such as that of Poloyac et al will hopefully stimulate follow-up pharmacokinetic studies in the presence or absence of moderate hypothermia, and upon rewarming to corroborate the findings of this investigation in critically ill patients. Not only

would such investigations have direct clinical implications but would also serve the purpose of increasing the awareness and complexities of hepatic drug clearance alterations after ischemic and traumatic insults in the critically ill patient.

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# Brain tissue oxygen monitoring in traumatic brain injury: Cornerstone of care or another brick in the wall?\*

**P**revention of secondary brain injury by maintaining adequate cerebral perfusion and oxygenation is a cornerstone of the management of severe traumatic brain injury (TBI). Beyond the measurement of intracranial pressure and cerebral perfusion pressure, various methods are used to assess the adequacy of cerebral perfusion including those measuring cerebral blood flow, oxygenation, and metabolic profiles.

There is growing literature on the association between low-brain tissue oxygen (PbtO<sub>2</sub>) and worse outcomes in patients with severe TBI including altered oxygenation and metabolism (1, 2), increased mortality (3, 4), and lower Glasgow Outcome Scale scores (5, 6). The study by Chang et al (7) in this issue of *Critical Care Medicine* examined the relationship between hourly PbtO<sub>2</sub>, measures of intracranial dynamics, and functional outcomes in a sample of severe TBI patients. This study is notable because it extends prior work by using a higher treatment threshold for PbtO<sub>2</sub> and a more sensitive outcome scale in examining the effect of PbtO<sub>2</sub> monitoring and treatment on outcomes in severe TBI.

The Functional Status Examination (8), initially developed for TBI, was used in the present study as the primary measure of functional outcome. The Functional Status Examination has multiple domains that allow for a comparison of functional status to that of preinjury, and with domains such as standard of living and travel/leisure, is truly a health-related quality of life measure. It is interesting to observe in the present report, and in a prior study by Meixensberger et al (9) that more finely tuned outcome

scales may be more sensitive to changes attributable to hypoxic insults. Thus, specific neuropsychological testing or TBI-specific health-related quality of life measures may be of value in future studies.

The identified association between low PbtO<sub>2</sub> and poorer outcome naturally leads to the question of whether oxygen directed therapy to maintain PbtO<sub>2</sub> can be an effective strategy to prevent cerebral hypoxia and secondary brain injury, and whether this translates to improved functional outcome. This raises the need for further understanding of the meaning and clinical significance of PbtO<sub>2</sub>. Brain tissue oxygen monitoring has been thought to reflect oxygen delivery. However, recent work suggests that brain tissue oxygen is not simply a reflection of regional cerebral blood flow but rather reflects the product of cerebral blood flow and cerebral arteriovenous oxygen tension difference (10). Rosenthal et al (10) suggest that PbtO<sub>2</sub> may not directly indicate total oxygen delivery or cerebral oxygen metabolism, but rather reflects diffusion of dissolved plasma oxygen, and low PbtO<sub>2</sub> values indicate low arterial oxygen tension or low cerebral perfusion, situations which are amenable to intervention. Further understanding of the factors determining PbtO<sub>2</sub> in normal and injured brain may lead to targeted strategies to maintain PbtO<sub>2</sub> above a desired threshold.

The level of cerebral ischemia associated with irreversible tissue damage has not been defined for TBI. The 2007 version of the guidelines for management of severe TBI recommendation for treatment threshold of brain tissue oxygen tension is <15 mm Hg with the Licox catheter (11) [level III]. A higher threshold of 20 mm Hg was used in this study, as a level commonly used in practice and to allow exploration of the potential association between hypoxia and functional outcome, beyond the known association of lower thresholds and mortality. Further work to extend these findings is required, as studies to date have varied with

regard to goal parameters, therefore, comparison is somewhat problematic across studies. Questions remaining to be answered include establishment of ischemic thresholds in different injury populations with parameters for treatment to guide further refinement of management guidelines and individual clinician decision making.

The sample in the present study was also relatively young (median age 22). With the growing proportion of older adults experiencing TBI worldwide, it will be critical to understand if there are age-related differences in PbtO<sub>2</sub> following injury given normal cerebral blood flow changes and the high percentage of cerebrovascular comorbidity (12, 13).

However, intracranial pressure were overall low in the sample. An intracranial pressure of 20 cm H<sub>2</sub>O is equivalent to 14.7 mm Hg; this is relatively low and below the threshold at which treatment for intracranial hypertension is generally initiated (level II recommendation >20 mm Hg) (14). Therefore, we would have predicted a lower risk of brain hypoxia at intracranial pressure ≤20 cm H<sub>2</sub>O as seen in this sample. However, PbtO<sub>2</sub> monitoring must be conducted in the context of appropriate clinical assessment by critical care clinicians in order to correlate findings to create a complete and accurate picture to allow management of the TBI patient (15).

Currently, the literature has established that brain tissue oxygen monitoring is of value in both severely injured pediatric and adult TBI patients (16–18). However, monitoring any one parameter in the TBI patient alone is not likely to be adequate and successful use of PbtO<sub>2</sub> monitoring will be in the context of multimodality monitoring, a well trained multidisciplinary health care team, and individualized management strategies. Before brain tissue oxygen monitoring can be widely established as a true cornerstone of care in TBI patients, well-controlled prospective studies need to be conducted to determine

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**\*See also p. 283.**

Key Words: traumatic brain injury; multimodality monitoring; cerebral blood flow; hypoxia

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the independent contribution of brain hypoxia and its management to functional outcomes.

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## Respecting patients' rights at the end of life: Problems with the 2006 Uniform Anatomical Gift Act\*

I believe that most people are inherently well inclined toward their fellow man. That's why when we apply for our driver's license and are asked if we would like to be designated an organ donor, most of us reply that we would be willing. This likely stems from a common feeling that we would want to help our fellow man in case of a catastrophe. However, most of us take it on faith that the organ donation process at the end of our lives will be an ethical, moral, and legal one, and that health care professionals

will respect our rights as patients, even after death. When we undergo an elective surgical procedure, we sign an informed consent form. The clinician carefully goes over the risks and benefits of the procedure, and we make a relatively informed decision after understanding the facts. However, signing an agreement to have "organ donor" printed on our driver's license at the Department of Motor Vehicles would have to be considered an extremely limited form of informed consent. Most people have no idea what kind of unexpected medicines, procedures, and techniques might be performed on our bodies in the event that we suffer a medical catastrophe, even before we are pronounced dead. We trust the medical and legal system to respect our rights as patients, and to perform only appropriate and indicated medical therapies.

In this issue of *Critical Care Medicine*, Iltis et al (1) eloquently explore the ethics

and legality of the 2006 Uniform Anatomical Gift Act (UAGA) and its 2007 amendment (2). The goal of this act is to increase the number of organ donations, a noble goal given that at the time of this writing there are 100,491 patients on the waiting list to receive an organ, and only 9,490 organ donors so far this year through August (3). Under the UAGA revisions, organ procurement organizations have been granted new authority over living patients who have designated a desire (on their driver's license) to become an organ donor after death. Now, life-sustaining interventions may be undertaken on patients before death, under the direction of the organ procurement organizations, to improve the viability of organs or tissues after harvest, unless an advance directive specifically forbids them from doing so.

This is a bold new step in the effort to improve the viability of transplanted organs, but comes at the expense of poten-

### \*See also p. 310.

Key Words: organ donation; brain death; end-of-life care

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tially compromising the ethical and legal standards that govern medicine and U.S. common law. Iltis et al rightfully point out that the UAGA “presumes that a willingness to donate after death implies premortem health care preferences and a willingness to have organ procurement organizations making clinical decisions, such as when to remove a ventilator, on the patient’s behalf while the patient is living.” For patients who have been declared dead by brain criteria, they are legally dead, and the techniques used to preserve their organs with the goal of improved viability after donation may be seemingly more acceptable. But for patients who are to be donors after cardiac death, the administration of medications [e.g., heparin (4)] or the performance of procedures (e.g., central venous catheterization, pulmonary artery catheterization, or determining the time for ventilator removal) before the death of the patient is significantly more problematic. As Iltis et al state, “The 2006 UAGA challenges not only the authority of patients or their surrogates to direct treatment at the end of life, but also the ethical duty of the physician and hospital to care for the individual dying patient.”

The UAGA proposal does not provide adequate avenues for educating patients or their surrogates about the process involved in donation, or in particular what might take place at the time of end-of-life care. It preys on the trust and altruism of the common person who has the good intention of providing the gift of life to others after their death. However, most people do not realize when they sign on to be an organ donor when renewing their driver’s license that their medical care may be sig-

nificantly altered at the end of life, and that a third party may actually dictate to their treating clinicians what medical procedures may or may not be performed (5). Obviously, this creates a conflict of interest for the physician who is caring for the patient dying in the intensive care unit, asking them to focus treatment not on the dying patient, but more in the interest of the potential recipients of that dying patient’s organs. Traditionally, great efforts are made to ensure that the treating clinicians are entirely removed from the process of organ transplantation; otherwise, they might be perceived as having an ulterior motive to terminate one patient’s life prematurely in an effort to procure their organs for another.

The legal precedents for the right to determination of one’s own care at the end of life are well established, even in the setting of incapacitation (6, 7). Furthermore, advanced directives are legal documents that clinicians are expected to follow in the end-of-life care setting (8). The 2006 UAGA asks clinicians to bypass an advance directive if the patient is a designated organ donor on their driver’s license, unless the advance directive specifically stipulates that the organ procurement organization *not* be involved in the care at the end of life. But how many patients are aware of the need for incorporating this kind of language in their advance directives?

The ramifications of this legislation are profound. Before individual states adopt the 2006 UAGA and 2007 revision, they should take into account the principles of informed consent, the clinician’s duty to respect the autonomy of the individual patient he/she is caring for, and

the legality of the process. Patients and health care professionals rely on trust to provide the most modern, advanced, and appropriate care. Instead of denying or ignoring the expressed wishes of the dying patient or their surrogate, we should be involving them in the discussion whenever possible, respecting their autonomy to the very end of their lives.

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## No “canary in the coalmine” for intra-abdominal hypertension\*

**T**he last three decades witnessed our appreciation of the consequences of elevated intra-abdominal pressure (IAP)

(intra-abdominal hypertension [IAH]) in critically ill patients of all types: surgical and medical, traumatic and nontraumatic, adult and pediatric. The progression of this pathologic entity, left unattended, to the full-blown syndrome of multiorgan involvement (collectively called the abdominal compartment syndrome [ACS]) was underscored by numerous studies, both experimental and clinical (1). Recognizing the enormous impact of IAH and ACS on patient outcomes, a World Society on Abdominal Compartment Syndrome was founded in

December 2004 to promote education and research. The international congress proposed a series of consensus definitions for IAH and ACS (2). A monograph on ACS was recently published by members of the executive committee (1).

As emphasized by the consensus opinion, the key to diagnose IAH is to measure IAP by a surrogate, the intravesical pressure (3). Even among clinicians who understand the significance of IAH and ACS, IAP measurement appears to be inconsistent at best. Multiple opinion surveys (4–6) from physicians around the

\*See also p. 316.

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world documented this indifference to IAP measurement among medical intensivists, pediatricians, and even trauma surgeons. It is astonishing that physical examination (inspection and palpation) was cited as their screening method of choice, even though there is literature that it is decidedly misleading with a sensitivity of only 40%–60% and an accuracy of only 60%–77% (7–9).

Are there any other noninvasive substitutes, such as abdominal perimeter (AP), to measure IAP? An important question, because such a parameter would facilitate a wider recognition of elevated IAP. In this issue of *Critical Care Medicine*, Malbrain et al (10), from their prolific clinical laboratories, report on their investigation of this question in 210 paired measurements in critically ill patients. There was a poor but statistically significant correlation between IAP and AP (measured at the “largest point”), but the bias was considerable. The correlation was somewhat better between changes in IAP and AP (the difference between two consecutive measurements). The authors concluded that the AP cannot be used as a clinical estimate for IAP, and that the IAP needs to be measured for the diagnosis of IAH or ACS. To their credit, the authors used Bland and Altman analysis (11) to compare the agreement between the two methods (IAP and AP) and did not rely solely on the use of a correlation coefficient or regression analysis. By plotting the difference between the two measurement techniques vs. their mean, the mean difference or bias can be calculated with 95% confidence interval of the lower and upper limits of agreement of the method under study. As is evident from the report, the confidence intervals are too wide for the AP to be a reliable replacement for IAP.

What about anthropomorphic measurements that have been found useful in the morbidly obese in the estimation of IAP? There are some data to show a good correlation between the sagittal diame-

ter of the abdomen and the IAP (12). Sugerma et al (13, 14) reported that urinary bladder pressure (a reflection of IAP) was greater in the obese than the nonobese, correlated with sagittal abdominal diameter, and was greater in patients with, than those without, morbidity. They also documented, however, that this is true only for central obesity. In their report, the waist to hip circumference (w/h) ratio correlated with urinary bladder pressure only in men, but not women, who often have both peripheral and central obesity. In the absence of a large data set of anthropometric measurements of obese individuals, these parameters (sagittal diameter and w/h ratios) are questionable substitutes for measured IAP.

In summary, Malbrain et al present a simple but important study that reaffirms the inadequacy of alternative methods of estimation of IAP. Reminiscent of the words of Stephen Bergman (under the pseudonym of Samuel Shem) in *The House of God* (15): “if you do not take a temperature, you cannot find a fever,” if you do not measure IAP, you cannot find IAH. Clinicians and intensivists are remiss if they fail to admit there is no “canary in the coalmine” for IAH and ACS.

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# Prevention of bloodstream infections: Basics and beyond\*

**B**lood stream infections are serious, costly hospital-acquired infections. These are the cause of significant morbidity and mortality, as well as an increase in length and cost of hospitalization. Central venous catheters (CVC) are associated with 90% of these hospital-acquired blood stream infections (1). These infections are of major concern in the critical care settings for several reasons: the frequency of CVC use, the susceptibility of the critically ill patients, and the prevalence of high-risk situations, including the presence of pathogenic and multi-drug resistant organisms. CVC-related infections (CVC-RI) have been reported with mortality rates of 4%–20%; a mean 7-day increase in hospital stay and estimated costs of \$3,700–\$29,000 (2). In light of the significance of CVC-RI, prevention is the highest priority. In the United States, this is particularly the case following recent implementation of the Centers for Medicare and Medicaid Services policy eliminating reimbursement for treatment costs resulting from vascular catheter-associated infections (3).

In this issue of *Critical Care Medicine*, Labeau et al (4) report the results of a survey of 3405 European intensive care unit nurses' knowledge of the 2002 Centers for Disease Control and Prevention (CDC) guidelines for preventing CVC-RI (5). The survey comprised ten multiple-choice questions. The authors found a relatively low correct response rate (the mean score was 4.44 on ten questions) and concluded that increased education is required for improving knowledge of CVC-RI prevention guidelines. The authors emphasize that understanding the prevention guidelines is a first step in overcoming barriers to compliance. We agree that knowledge is a key element

of prevention, but there are other required elements to ensure compliance with these guidelines and prevention of CVC-RI.

Of primary importance concerning implementation of guidelines is the clinical relevance of recommendations: do specific recommendations result in better patient outcomes, i.e., less morbidity and mortality? The authors used the CDC guidelines which are evidence-based and for which there was data to substantiate such improvement of outcomes. Of the 84 CDC recommendations related to CVC-RI prevention, 31 are in the IA category. This IA category contains the strategies strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies. The authors chose ten questions as reflective of prevention knowledge. The authors recognized some limitations of the questionnaire, including lack of weighting for the relative importance of prevention strategies. However, of the CDC recommendations, "the basics" are recognized to include hand hygiene and aseptic catheter insertion and maintenance techniques (5–7). We are puzzled by the authors lack of questions concerning these basics, especially the lack of reference to hand hygiene and aseptic technique for insertion and care.

The authors noted ambiguity in the 2002 CDC guidelines relative to disinfectant use and recommended dressing practices. New prevention guidelines are recently published by a consortium of authors affiliated with numerous organizations, including the Infectious Diseases Society of America, Society of Hospital Epidemiologists, Association for Professionals in Infection Control and CDC (8). Publication of these guidelines, using more recent data analysis, should clarify many recommendations. New prevention guidelines could delineate both basic practices and additional approaches required for specific circumstances.

Implementation of guidelines is facilitated by (or hampered by) institutional procedure. For example, nurses may know the value of a 2% aqueous chlorhexidine skin disinfectant. However, im-

plementation of the recommendation may be foiled by an institutional procedure that provides povidone-iodine in the CVC insertion kits. In the quest for guideline compliance, knowledge must be followed by the ability to institute procedural change. An element of procedural change must be a cost/benefit analysis relative to the change. We recognize (as did the authors) the need for addressing cost in prevention strategies. In the United States, the cost/benefit analysis should shift in favor of many prevention strategies. The Centers for Medicare and Medicaid Services "nonpayment" policy will be a great motivator for compliance.

We appreciate the authors' view that nurses have significant responsibility for prevention of CVC-RI. However, the basics of hand hygiene and catheter insertion are the responsibility of all providers, including staff and resident physicians. An emphasis on these basics in physician education programs is essential for adherence to CVC-RI prevention guidelines (and for adherence to all infection prevention strategies). Education of others will play a significant role in implementing prevention guidelines. Educating administrators and supply-chain managers about the essentials of infection prevention will give these persons the knowledge necessary to recognize the importance of procedures, supplies, and purchasing decisions.

We believe that appropriate, consistent, adequate surveillance for CVC-related infections by qualified personnel is essential in evaluating the success of basic prevention strategies. This surveillance data should be reported, as a rate per 1000 CVC days. These rates should be reported to the persons responsible for and capable of establishing and revising procedures. The surveillance findings should be reported and studied in conjunction with mortality and morbidity outcome data, not only at the institutional level but also in comparable regional forums such as the National Healthcare Safety Network (9). The rates should be used as a monitor of compliance and as a guide for the direction of policy and procedure. Analysis of these

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**\*See also p. 320.**

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data will be essential in recognizing the need for additional approaches beyond the basics of infection prevention.

In conclusion, we recognize the importance of the research done by Labeau et al in emphasizing the importance of enhanced knowledge of prevention guidelines through education programs. In addition, we support other key components of infection prevention, including provision of updated guidelines, policy and procedural reinforcement for these guidelines, continued surveillance of infection rates and analysis of morbidity/mortality outcome data, and, of course, further research.

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