An intensivist *all* day, keeps the bad outcomes away*

There has been an increasing awareness that organizational factors can influence patient outcomes in the intensive care unit (ICU). For instance, ICU staffing with a trained intensivist is associated with a reduction in ICU length of stay and in-hospital mortality (1, 2). However, access to intensivist care in the ICU varies, with less availability during evening/night, weekend, and holiday hours ("off hours") (3). Because initial management may be crucial to the outcome of critically ill patients (4), lower level staffing during off-hour admissions could be associated with a worse outcome. The relationship of off-hour admissions to patient mortality has been examined in a number of studies of medical, surgical, and critically ill patient populations, with conflicting results (5–10).

In this issue of *Critical Care Medicine*, Dr. Luyt and colleagues (11) examine the role of off-hour admissions to the ICU on inpatient mortality in a large retrospective multicenter cohort study. Using prospectively collected data from 23 ICUs in the Paris metropolitan region, the investigators examined 51,643 consecutive ICU admissions during a 4-yr period, 33,857 (66%) of which were admitted during off hours. Off hours were defined as periods outside of legally mandated day-shift hours in France, divided into night shifts (6:30 PM to 8:29 AM the next day, Monday to Friday), weekends (1:00 PM Saturday to 8:29 AM Monday), and holidays (8:30 AM to 8:29 AM the next morning). During day-shift hours, ICUs were staffed with a median of three board-certified intensivists, one intensivist-in-training, and two residents. In contrast, during off hours, all ICUs were staffed by only one on-site board-certified intensivist or an experienced intensivist-in-training, with an additional medical resident in ten of the participating ICUs.

The primary analysis evaluated the association of off-hour staffing with in-hospital mortality, using a multivariable logistic regression model adjusting for many potential confounders, including age, comorbidity score, simplified acute physiology (SAPS) II score, and type of admission (direct or transfer). Many sensitivity analyses were conducted, including examining different definitions of off hours, using a propensity score methodology, and analyzing the results by SAPS II quartiles, specific diagnoses, and individual hospital.

ICU and in-hospital mortality for the entire cohort were 18% and 22%, respectively. Patients admitted during the day shift were more ill (with a higher mean SAPS II score), had more organ failures, and had a greater need for supportive measures (e.g., mechanical ventilation, hemodialysis) than patients admitted during off hours. Consequently, day-shift vs. off-hour patients had significantly greater ICU and hospital length of stay (8 vs. 7 days and 22 vs. 18 days, respectively) and crude ICU and in-hospital mortality (19% vs. 17% and 25% vs. 21%, respectively).

After adjusting for confounders, in-hospital mortality was not greater for off-hour vs. day-shift admissions (odds ratio, 0.93; 95% confidence interval, 0.87–0.98). The authors' multiple sensitivity analyses consistently yielded similar results.

Initially, the results of this study may seem surprising in that lower ICU staffing during off hours was not associated with higher adjusted mortality for patients admitted during these time periods. These results were unchanged, even for patients in the highest quartile of SAPS II severity of illness score at ICU admission. This result may be due, in part, to the early stabilization of out-of-hospital patients by the physician-led emergency response system in France. Furthermore, because transfers from both the hospital ward and other ICUs were grouped together, imbalances in the type of patient transferred during day-shift vs. off-hour periods, with their differing mortality rates (12–14), may have confounded the results. This limitation was recognized by the authors. Heavier workloads (e.g., teaching activities, family conferences), an increased number of procedures (15), and increased intra-hospital transport for diagnostic and/or therapeutic interventions (16) during the day shift also may have contributed to the lack of mortality difference between the higher staffed day shifts and the lower staffed off-hour periods.

Finally, ICU staffing during off hours may have been sufficient to avoid any negative impact on patient mortality compared with day shifts. The presence of an on-site intensivist (or an experienced intensivist in-training with phone back-up) during off hours likely had an important impact on off-hours care of critically ill patients. This explanation is supported by a recent study that demonstrated a lack of excess mortality in patients admitted during off hours in an ICU with continuous on-site intensivist staffing (17) and another study that demonstrated higher adjusted mortality in an ICU without a dedicated on-site intensivist (or intensivist-in-training) during off hours (18). Existing and projected shortages of intensivists in the United States makes the feasibility of continuous, on-site intensivist staffing difficult, but recommendations for addressing this shortage have been made (19–21). Despite this challenge, the current study may provide additional evidence supporting intensivist staffing and the need to find solutions to intensivist shortages to provide patients the best possible clinical care.

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*See also p. 3.

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Genetics of individualizing patient care*

We try to treat patients as individuals, modifying therapy to suit their specific needs. However, we only partially understand the implications of that statement. Essentially, all patients carry with them a series of propensities to get sick, adapt to environment, and survive that are unique. Perhaps nothing underscores these individual differences than the survival from severe sepsis. Although sepsis affects >750,000 people annually in the United States (1), the linkage between infection, treatment, and mortality is unclear. Not all septic patients progress to multiple organ failure and death, despite presenting with similar degrees of infection and apparent physiologic reserve. Some of these differences in outcome among patients reflect our inadequacies in characterizing the illness severity and therapeutic effectiveness. The interplay of sepsis with host responses is complex, resembling, to our unfocused eye, a diffuse, poorly controlled, and more poorly understood inflammatory response (2). Even the most proximal inflammatory mediator, tumor necrosis factor (TNF), is not detectable in the plasma in all patients with sepsis (3), and treatment with anti-TNF antibodies does not provide protection against mortality (4). Protein C, a modulator of this inflammatory response, has received increased scrutiny since a prospective multiple-center clinical trial of activated protein C improved outcome in septic patients (5). Still, the improved survival was only incremental and its mechanism or mechanisms of action were not defined.

Potentially, genetic differences in individual response could explain some of the variability in outcome. For example, an inherited increased risk for death from certain infections (meningococcemia) exists in identical twins, and there is also increased risk in families with a phenotype of decreased proinflammatory (TNF) or increased anti-inflammatory (interleukin-10) response. The highest risk of death from meningococcemia is carried by families who exhibit both phenotypes (6). These data support a genetic basis for altered survival from sepsis. Importantly, single nucleotide polymorphisms at key loci in the genome have been identified that result in profoundly different survival rates for septic subjects with apparently similar insults (7). The G to A transition at nucleotide position −308 of the TNF gene promoter, the TNF2 allele, correlates with enhanced basal and stimulated TNF production both *in vitro* (8) and *in vivo* (9). This TNF2 allele was more common in patients with septic shock than in healthy volunteers and, in those with septic shock, more common in nonsurvivors (10). Thus, the same single nucleotide polymorphism decreases the risk of dying from meningococcemia but increases the risk of developing septic shock. Presumably, certain phenotypes (e.g., TNF hypersecretion) protect against developing infection while simultaneously conveying an increased risk of death from sepsis should infection occur. Relevant to these points is the study by Drs. Walley and Russell (11) in this issue of *Critical Care Medicine*. They studied the relationship be-

***See also p. 12.**

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tween protein C single nucleotide polymorphisms, the degree of inflammatory response, and outcome from severe sepsis. These workers hypothesized that −1641 A/G and −1654 C/T promoter polymorphisms of the protein C gene are associated with altered outcome in white patients with severe sepsis. They found that patients with the A allele at protein C −1641 had lower survival, more organ dysfunction, and more clinical evidence of systemic inflammation than patients who did not have this −1641 A allele. Furthermore, this genotype displayed a greater proinflammatory interleukin-6 response after cardiopulmonary bypass surgery. In contrast, protein C −1654 was not associated with measurable biological effect. This simple yet elegant description of a new genotypic marker of sepsis was made more relevant by the proven biological efficacy of exogenously delivered activated protein C in severe sepsis (9). Although the authors clearly show a linkage of genotype and phenotype including mortality, organ injury, and inflammation, the linkage between these findings and the therapeutic use of activated protein C is not clear. Thus, this implication of their findings to activated protein C therapy in severe sepsis remains to be elucidated.

As stated by Pinsky (12), "the realization that genetically-determined propensities in responsiveness to immune challenge may be a primary determinant of survival from acute illness blurs our definition of genetic diseases." We are rapidly expanding our knowledge of the determinants of the host response to disease and therapy. As we increase our understanding of these important interactions, we also need to find ways of screening patients before they develop critical illness so that their care can be individualized. Traditionally, disease is defined as an abnormal condition, not an abnormal response to a common occurrence. If subjects are prone to die of otherwise nonlethal insults or will survive more often when others succumb, then our concepts of disease, disease risk, and predicting mortality must change. However, ethical issues will also arise from this knowledge if it is used to limit care or change the cost of healthcare premiums to these same individuals. Clearly, such individualized genetic information is needed and greatly appreciated. Because no one at the present time can change their genetics, knowledge of our genetic propensities will need to be placed in the proper context and this information given to patients with the same sensitivity used now when performing genetic counseling for genetic diseases. Perhaps some day we will all have our genotype measured the way we now have our blood type and blood pressure measured. This information will then be available to the healthcare delivery system so that we may finally manage patients as the individuals they are.

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Noninvasive ventilation for acute respiratory distress syndrome: Breaking down the final frontier?*

Noninvasive ventilation (NIV) has an established role in the management of selected patients with acute respiratory failure (1), particularly those with chronic obstructive pulmonary disease (2), acute cardiogenic pulmonary edema (3), and immunocompromised states (4). However, those with acute respiratory distress syndrome (ARDS) have been much more challenging to support noninvasively, partly because their severely deranged ventilatory mechanics and gas exchange necessitate higher levels of pressure support and positive end-expiratory pressure (5), and partly because they frequently have sepsis or multiple organ system failure that is difficult if not dangerous to manage noninvasively.

Few prior studies have specifically examined the use of NIV to treat ARDS. Rocker et al. (6) reported a cohort of ten patients who received NIV for 12 episodes of ARDS. Intubation rate was 50% and 70% of patients survived, but in the absence of controls, these results are difficult to interpret. In a prospective study on risk factors for NIV failure in patients with acute hypoxemic respiratory failure

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by Antonelli et al. (7), the diagnoses of ARDS or community-acquired pneumonia imparted a 3.75-fold increase in the risk of failure. In the randomized controlled trial of NIV for acute hypoxemic respiratory failure by Ferrer et al. (8), six of seven patients with ARDS failed NIV despite favorable responses to NIV in other subgroups. In a systematic review of NIV for hypoxemic respiratory failure, Keenan et al. (9) concluded that insufficient data supported the use of NIV for ARDS. Thus, delivery of NIV to patients with ARDS has been problematic, associated with a high likelihood of failure and with no convincing evidence that it confers any benefit. A major challenge has been how to select patients with ARDS who have a reasonable chance of succeeding with NIV.

In this issue of *Critical Care Medicine*, Dr. Antonelli and colleagues (10) report the results of a prospective survey of NIV to treat ARDS performed in three intensive care units, two in Italy and one in Spain. Among 479 patients admitted with the diagnosis of ARDS during the 2 yrs of the survey, 332 were intubated initially and 147 (31%) were treated with NIV. Forty-six percent of these eventually failed and were intubated, meaning that 16.7% of the total ARDS cohort was successfully supported with NIV. Not surprisingly, those who avoided intubation had better outcomes than those who failed; ventilator-associated pneumonias in 2% vs. 20%, severe sepsis in 6% vs. 19% and hospital mortality in 19% vs. 54% (all $p < .05$). Predictors of the need for intubation included greater age, higher Simplified Acute Physiology Score (SAPS) II, higher levels of positive end-expiratory pressure, and lower Pao_2/Fio_2 ratios. By multivariate analysis, only SAPS II >34 and Pao_2/Fio_2 ≤175 at 1 hr independently predicted the need for intubation.

These findings are welcome to clinicians because they identify specific thresholds that can be used to select ARDS patients who might be candidates for NIV. The authors suggest using a SAPS II score threshold of 34 to decide whether to initiate NIV; those with a SAPS II score >34 had a 62% chance of failing NIV compared with 32% for SAPS II scores ≤34. Among those started on NIV, a Pao_2/Fio_2 of 175 after the first hour was proposed as a cutoff for deciding whether to continue; those with a value ≤175 had a higher risk of failing (42%) compared with 24% for those with a Pao_2/Fio_2 >175 after the first hour. These suggestions are reasonable, although it could be argued that a trial might still be attempted in selected patients with a SAPS II >34, considering that a majority (51%) avoided intubation if Pao_2/Fio_2 was >175 after an hour. Certainly, patients would have to be good candidates for NIV otherwise and monitored very closely, because mortality was very high (72%) if they subsequently failed.

It should be emphasized that the ARDS patients treated with NIV in the study by Dr. Antonelli and colleagues were highly selected and represented only a minority (31%) of the greater ARDS population. Patients were excluded if they were poor candidates for NIV because they were having a respiratory arrest, were unstable otherwise (e.g., persistent hypotension or myocardial arrhythmias or ischemia), were encephalopathic, or had two or more new organ failures. Also, the centers where the survey was performed were highly experienced in NIV and the results may not be generalizable. Inexperienced centers are advised to gain experience using NIV on more traditional patients before they attempt it for those as challenging as ARDS patients.

Another caveat to consider is that even with the results of the present study, we still have no evidence that establishes the efficacy of NIV to treat ARDS. Observational trials are hypothesis-generating and cannot prove efficacy. In fact, as the authors acknowledge, without a control group to establish what would have happened without the intervention, one cannot even exclude the possibility that NIV was deleterious overall, despite the favorable outcomes in NIV successes.

If NIV is to be used in an ARDS patient, an early improvement in oxygenation is clearly important to justify continuation. Even so, most of the NIV failures in the study by Dr. Antonelli and colleagues occurred between 12 and 48 hrs, and 30% failed after 48 hrs. This emphasizes the need to monitor these patients very closely in an intensive care unit until they have fully stabilized. The occurrence of a respiratory arrest requiring emergency intubation in an NIV patient is a catastrophe that can occur when a needed intubation is delayed. The study by Esteban et al. (11) indicated that such delays increase morbidity and mortality, and this scenario is to be avoided.

ARDS might be considered "the final frontier" of NIV applications in the intensive care unit, Dr. Antonelli and colleagues (10) suggest. Their study brings us closer to practical guidelines for selection of ARDS patients who might try NIV. They must a) be good candidates for NIV—cooperative, medically stable otherwise, able to clear secretions; b) not have multiple organ system failure (ideally with single organ system disease); and c) not have a markedly elevated SAPS II (i.e., ≤34). They should be closely monitored, and if oxygenation doesn't improve sufficiently in the first hour (or two) (i.e., Pao_2/Fio_2 >175 or at least upper hundreds), they should be intubated without undue delay. These suggestions are made with the caveats that the efficacy of NIV for ARDS has not yet been established, nor have any selection guidelines been tested prospectively.

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Inhaled nitric oxide therapy for sepsis: More than just lung*

Nitric oxide (NO) is a potent vasodilator that has an extremely short biological half-life and is rapidly degraded to its main metabolites *in vivo*. It has been included within inhalation mixtures to reduce pulmonary arterial pressures and to decrease ventilation-perfusion mismatching because it was thought to act locally only (1). However, it is increasingly apparent that inhaled NO can have significant peripheral effects (2–4). Corticosteroids were the first antiinflammatory drugs tested in animal and human studies of sepsis and acute respiratory distress syndrome (reviewed in Allary and Annane (5)). At high doses during short courses, they did not induce favorable effects. However, the observation that severe sepsis may be associated with relative adrenal insufficiency or systemic inflammation-induced glucocorticoid receptor resistance prompted renewed interest of a replacement therapy with low doses of corticosteroids during longer periods (5). It has been demonstrated that increased glucocorticoid receptor expression in transgenic mice was correlated with an increased resistance to lipopolysaccharide-induced endotoxic shock (6). It has also been shown that during LPS-induced endotoxemia, inhibition of glucocorticoid receptor binding occurs, thereby reducing effectiveness of endogenous and therapeutic corticoids (7). In this issue of *Critical Care Medicin*e, Dr. Da and colleagues (8) sought to determine whether inhaled NO could stimulate glucocorticoid receptor up-regulation in nonpulmonary tissues, thereby increasing the effectiveness of therapeutic glucocorticoid.

Dr. Da and colleagues (8) used a porcine endotoxin challenge model that revealed that endotoxin infusion down-regulated expression of glucocorticoid receptor in lung, liver, and kidney tissues concomitant with up-regulation of inflammatory markers such as nuclear factor-κB and tumor necrosis factor-α. Simultaneous administration of inhaled NO and glucocorticoid in this porcine sepsis model blunted the inflammatory response not only in lungs but also in systemic organs, which has not been observed with the treatments alone. This experiment presented data that demonstrated that inhaled NO treatment up-regulated expression of glucocorticoid receptors. Because the group that was treated with combined inhaled NO and glucocorticoid presented with reduced histologic damage and arterial blood gases and with improved cardiovascular variables, the data support the conclusion that inhaled NO stimulates up-regulation of glucocorticoid receptors, making steroid therapy more effective in sepsis.

Over the last decade, NO inhalation has proven valuable for treatment of hypoxic pulmonary hypertension in newborns; however, its effectiveness in adult acute respiratory distress syndrome remains uncertain (1). Because NO is rapidly bound to hemoglobin *in vivo*, it was initially suggested that actions of inhaled NO would be limited to the lungs. More recently, clinical and mechanistic reports on the therapeutic use of inhaled NO in a variety of settings have uncovered a surprisingly wide array of changes outside the intended organ (3, 4). The increasingly recognized peripheral effects of inhaled NO are typically dose-dependent and can take place in absence of any change in systemic hemodynamics. Cell-specific effects go well beyond relaxation of vascular smooth muscle and include inhibition of leukocyte adhesion and migration, increases in renal glomerular filtration, and improvement of left ventricular function (3, 9). However, in models of acute lung injury and *Pseudomonas* pneumonia, it has been reported that inhaled NO increased leukocyte recruitment when administered with high F_{IO_2} (10, 11). Thus, effects of inhaled NO on leukocyte recruitment may depend on the co-administered F_{IO_2} concentration and on local redox environment of tissues.

NO is active in every major organ system and possesses different functions, many of which seem to operate independently of guanylate cyclase (12). This pluripotency points to a greater range of NO chemistry than simple diffusion and hemoprotein binding. Red blood cells are now regarded more as deliverers of NO rather than consumers (2). It has been demonstrated that NO reacts not only with heme iron but also with cysteine (Cys)-93 on the β subunit of hemoglobin (13). Whereas reactions with heme iron can inactivate NO, S-nitrosylation of Cys-93 converts hemoglobin into a carrier of NO bioactivity (14). The elevation of S-nitrosothiol proteins, including red blood cell S-nitrosothiol-hemoglobin and hemoglobin[Fe]NO, in sepsis have also been reported (15, 16). Specifically, hemoglobin[Fe]NO accumulates as 5-coordinate α-heme-NO, from which NO release or transfer to the reactivity Cys-β93 residue is impossible. Oxygen dissociation from the 5-coordinate α-heme-NO is, however, favored (the oxygen dissociation curve is shifted rightward) so that oxygen delivery needs may be met without excessive vasodilation (17). Thus, interactions of excess NO with hemoglobin lead to products that divert NO from producing toxicity. Additionally, other intravascular proteins, such as albumin, may be S-nitrosylated by inhaled NO and transport NO bioactivity to distal organs. Stabilization of NO with erythrocytic hemoglobin or other proteins through the

***See also p. 26.**

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reversible S-nitrosylation reaction represents a likely mechanism for these extrapulmonary effects. Therapeutic strategies that exploit this natural mechanism for remote, regulated delivery of NO bioactivity are rational and under active investigation.

By these mechanisms, inhaled NO bioactivity can be transported to systemic organs. However, demonstration of low levels of S-nitrosothiol in lymph draining intestinal extravascular space during inhaled NO therapy suggests that NO bioreactivity may not be able to reach extravascular species (18). Because it is carried to distal organs on proteins such as S-nitroso-hemoglobin and or S-nitroso-albumin, which are too large to transverse even an injured endothelial barrier, these explanations seems logical. Therefore, the systemic effects of inhaled NO probably remain in the vascular space, regulating blood cell–endothelial cell interactions.

Inhaled NO has been reported to modulate apoptosis and exert antimicrobial effects, both of which would attenuate pathophysiology of sepsis (19, 20). S-nitrosylation is one mechanism underlying an anti-apoptotic effect of inhaled NO. Inhaled NO regulates apoptosis of immune cells and also prevents tissue damage by inhibiting parenchymal cell apoptosis in ischemia–reperfusion models (19). Inhibition of caspases, stimulation of anti-apoptotic activity of thioredoxin, and increased expression of heat shock proteins and Bcl-2 are the other anti-apoptotic mechanisms, whereas higher concentrations of NO may cause apoptosis by inhibiting nuclear factor-κB. There are also multiple mechanisms involved in the antibacterial properties of nitrogen oxides, including inhibition of proteins in the bacterial respiratory chain, disruption of iron-sulfur clusters in bacterial proteins leading to the release of free iron that catalyzes toxic oxidative reactions, and inhibition of DNA replication. In addition to bacteriostatic and bacteriocidal effects on pathogens, NO may play a critical role in maintaining pathogen latency (21). The effect of inhaled NO on infections in humans is just beginning to be evaluated (22). The precise effect of inhaled NO on the immune response is likely dependent not only on the concentration of inhaled NO but also on the specific redox environment of the cells. All of these mechanisms may limit organ damage in sepsis. Inhaled NO can also increase endothelial NOS activity in tissues (23). Therefore, these results establish that inhaled NO generates a series of complex interactions during sepsis, meriting further study.

The issues raised by Dr. Da and colleagues (8) are important because they not only illuminate another mediator pathway induced by sepsis but also identified a novel combination therapy. These data should also remind us that sepsis generates extraordinarily complex interactions at the molecular level in systemic tissues that mandate complex therapeutic approaches. In the past, these complex interactions have been explored using specific probes, such as pharmaceutical agonists or antagonists. Although these hypothesis-driven experiments have yielded valuable insights into a limited number of pathways, integrative response of tissues and organs demands approaches that explore these fundamental and complex interactions in a global fashion. Recently, advent of complementary DNA micro-array and proteomic technologies allow for evaluation of global gene up- and down-regulation induced by sepsis so that integrative response to sepsis can be defined and how combination therapies interact can be understood.

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About protocols and guidelines: It's time to work in harmony!*

In this issue of *Critical Care Medicine*, Dr. Bull and colleagues (1) demonstrated that implementation of a mandatory protocol for treating adult patients with diabetic ketoacidosis (DKA) decreased significantly the length of intensive care and hospital stay and the time to correct anion gap and ketone clearance, without increasing the incidence of hypoglycemia. Although many protocols and guidelines for treatment of DKA have already been published (2–4), this is the first article that highlights the benefits of protocol-driven care in the treatment of DKA. DKA is responsible for about 100,000 U.S. hospitalizations per year and uses significant healthcare resources, with an average cost of $13,000 per patient (2). Although a formal health economic analysis was not performed by Dr. Bull and colleagues (1), it is not difficult to estimate that a 30% reduction in the hospital length of stay would result in a cost-saving of around $390 million yearly in the United States alone. The main strength of the study by Dr. Bull and colleagues (1) lies in the explicit link between implementing a detailed protocol and improving process, outcome, and cost of care.

Over the past decades, the clinical information available to physicians has expanded rapidly. Paradoxically, making the best clinical decisions is becoming more difficult. Having too much information can cause as many decision errors as having too little information (5). In present-day medicine, based on continuous quality improvement, information must be relevant to both the process and outcome of care. Guidelines and protocols are therefore becoming increasingly popular to improve quality and cost-effectiveness of care (6, 7).

Despite wide development, dissemination, and implementation, guidelines and protocols have had a limited effect on changing physician behavior. Why? Many physicians think that guidelines and protocols are either too simple or too complicated, promote "cookbook care," lack credible authors or evidence, are biased, decrease flexibility, reduce autonomy, and are not applicable to the practice population. Adherence to guidelines and protocols is therefore often poor. Cabana et al. (8) described a variety of barriers to guideline adherence, such as lack of awareness, lack of familiarity, lack of agreement, lack of self-efficacy, lack of outcome expectancy, the inertia of previous practice, and external barriers. Therefore, strategies to improve guideline and protocol adherence are needed. Rood et al. (9) demonstrated this through using a computerized version of an insulin protocol to target blood glucose in a specific range in the intensive care unit. Medical informatics can bring guidelines, protocols, or even decisions-support tools to the point of care to improve harmonization and quality of care.

However, the best intervention to improve compliance with guidelines and protocols is to ensure that physicians and nurses accept them as the best practice to improve the process and hopefully the outcome of care (5). Leape et al. (10) demonstrated that adherence to guidelines is higher when the recommendations are supported by randomized clinical trials. To ensure quality and credibility of guidelines and protocols, three major criteria should be applied and reported: a description of the development process, a description of the sources of information to retrieve the best evidence, and an explicit linkage of the level of evidence and the strength of recommendation (11).

This is a weakness in the study by Dr. Bull and colleagues (1). Nothing is mentioned about the process of protocol development, dissemination, and implementation (12). Implementation requires strategy. Education, training, decision-support worksheets, computer-assisted choice, and reminders can be important in the sustained use and compliance to the protocol. Passive methods for implementation rarely lead to changes in behavior. Even with strong results of randomized clinical trials, implementation of protocols and adherence to certain protocols can cause a significant struggle (13). An example of this phenomenon in intensive care medicine is the hand hygiene guideline. Despite the overwhelming evidence-based effect, the clarity and simplicity, and despite the massive dissemination, adherence remains poor (14). The 100% compliance with the DKA protocol, as described by Dr. Bull and colleagues (1), is therefore at least striking.

Another weakness lies in the fact that the authors do not describe how DKA was treated in the preprotocol period. If this was quite poor, then the mean reason for the positive effects of the protocol implementation is probably due to educational effects and less to the intrinsic evidence-based value of the protocol itself or to the effect of standardization. Although this does not change the positive results of the study by Dr. Bull and colleagues (1), extrapolation of these results to a center where DKA treatment is already optimal without use of a protocol will be difficult.

Can there be other potential explanations for the remarkable results found by Dr. Bull and colleagues (1)? Is the protocol perfect? No, it is not. Certain aspects in the initial monitoring and evaluation of patients with suspected DKA, such as arterial blood gases and the importance of an electrocardiogram are not mentioned. Continuous electrocardiographic monitoring is recommended in view of hyperkalemia or hypokalemia and conse-

*See also p. 41.

Key Words: diabetic ketoacidosis; guidelines; protocols; decision support; guideline adherence

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quent arrhythmias. A chest radiograph should be obtained if indicated but can be helpful in assessing volume status or to rule out pneumonia, although consolidations may not show on chest radiograph in dehydrated patients (1). Can a protocol be perfect? No! It is not realistic to expect that all possible clinical conditions would be prespecified in a protocol. In this regard, it remains unclear how to interpret the fact that the protocol was mandatory. Does this mean that altering some treatment recommendations with respect to the individual patient and after good clinical judgment were not allowed?

Can the results be explained by the fact that the patients in the postprotocol period were perhaps less sick than in the preprotocol period? This could be possible, although it seems rather unlikely. Moreover, illness severity scores are no predictors for intensive care unit or hospital length of stay in patients with DKA (15).

Despite some weaknesses, in particular in the description of protocol development and implementation strategy, the message delivered by the study by Dr. Bull and colleagues (1) is that successful implementation of guidelines and protocols in daily medical practice can have significant positive effects. It's time to work in harmony!

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Genetic risk factors for acute respiratory distress syndrome: What's the right direction to take?*

Acute lung injury and acute respiratory distress syndrome (ARDS) are the most severe forms of acute respiratory failure, still carrying high mortality and morbidity. The clinical differentiation between the two syndromes is based on the severity of the disease and was defined some years ago by the American-European Consensus Conference (1). Recent epidemiologic data show a crude incidence of 78.9 cases per 100,000 persons-years with an in-hospital mortality of 38.5%. Both incidence and mortality increase greatly with age (2).

For any critical care disease, it is crucial for clinicians to know risk and prognosis factors that permit them to establish early preventive strategies or strong interventional and supportive measures. In fact clinical, physiologic risk and prognostic factors of the most frequent critical care or respiratory diseases are well known, although there are always unexplained cases of fatal resolution. This also applies to acute respiratory failure and ARDS. For example, Hudson and colleagues (3) identified sepsis, multiple transfusions, and multiple traumas as risk factors for ARDS. However, 69 of 271 (25%) patients did not have a defined clinical risk, which is really intriguing. The next step in identifying risk and prognosis was the study of genetic predisposing factors. There are several examples in acute respiratory failure patients, especially in the area of respiratory infections. Waterer and colleagues (4), studying patients with severe community-acquired pneumonia, demonstrated an association with severe respiratory failure and some tumor necrosis factor-α polymorphisms (AA genotype at the LT α + 250 locus). Quasney and colleagues (5) demonstrated that CC and CT genotypes at the SP-B + 1580 site are associated with an increased risk for mechanical ventilation requirement, ARDS, and septic shock in adult patients with community-acquired pneumonia. However, in our opinion, despite the fact that this is probably the right direction to take, these two studies and others in the literature represent only a little piece of the big puzzle,

*See also p. 48.

Key Words: acute lung injury; acute respiratory distress syndrome; acute respiratory failure; *mannose binding lectin-2*; genetics; association studies

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with many other pieces still pending identification (6).

In this issue of *Critical Care Medicine*, Dr. Gong and colleagues (7) are taking a further step in the right direction. Using a nested case control design, they compared 212 Caucasian patients with ARDS to 442 controls genotyped for the functional variants *X*, *D*, *B*, and *C* alleles at position −221 and *codons 52*, *54*, and *57* from the *mannose binding lectin-2 (MBL-2)* gene, which encodes for mannose-binding lectin (MBL), the recognition compound of the lectin pathway of complement activation. The authors found that patients homozygous for the variant at *codon 54B* allele had increased odds of ARDS (odds ratio, 6.7) when compared with heterozygotes and homozygotes for the wild-type allele. In patients with ARDS, the *54BB* genotype was associated with worse organ dysfunction and worse survival. However, what is the clinical significance of this? To answer this question we should make an effort to understand the meaning of this type of genetic studies. The following considerations may help us understand the real meaning of the results presented in this issue (7).

From the point of view of clinicians, the aim of genetic association studies is to obtain information that could help in the clinical management of patients and make specific decisions. This way of thinking has derived from the paradigm of "single gene, single outcome." Only the true genetic diseases alone, with high penetration but very low prevalence, could be regarded this way, but these are the exceptions. However, such approaches have been quite frustrating, and gene candidates have demonstrated no usefulness in clinical management and are plagued by the impression that results are not consistently reproducible (8). In our opinion, some misunderstandings have come about from this approach and some lessons could be learned from *MBL-2* gene variants. *MBL-2* polymorphisms have attracted interest with clinical researchers, since the effect of the restricted number of haplotypes described was demonstrated. The so-called secretor haplotypes (LYPA, LYQA, LXPA, LYQC, LYPB, HYPA and HYPD) can predict 85% of MBL serum levels (9). Since then, MBL deficiency has been related to a wide range of infectious and noninfectious diseases and outcomes (10). Such a haplotype approach instead of a single allele approach is a more physiologic and better answer for common and complex illnesses, rather than more rare single-gene disorders (11). The existence of the linkage disequilibrium between different alleles causes the haplotypes to be considered as a single exposure when studying gene associations. On the other hand, the existence of functional polymorphisms and well-preserved haplotypes like those of *MBL-2* indicates some kind of natural selection, and in most cases this selection follows a model of balancing selection. Under certain conditions, MBL deficiency could act as a protector factor (e.g., diminishing complement activation and limiting tissue damage) or a risk factor for different diseases (e.g., as a risk factor for developing sepsis from a capsular bacteria) (12). These dual effects used to be of low penetration, and their deleterious effect is of importance, depending on their prevalence in the general population, but it is difficult to predict in a single individual, and results could be easily confounded and are very sensitive, depending on laboratory procedures. Besides the intrinsic difficulties of genetic studies associations like population substructuring or keeping the Hardy-Weinberg equilibrium in the control group (13), these observations could explain the frustrating and low reproducibility of genetic association studies. In any case, medical advances that cannot be modulated by natural selection have resulted in new clinical situations that could produce an unexpected rise of such natural deficiencies (e.g., immunosuppressant status due to chemotherapy treatment where innate immunity would take a predominant role). Critically ill patients hospitalized in the intensive care unit, like those with ARDS, could be regarded in that kind of situation. Moreover, clinical genetic association studies like that presented by Dr. Gong and colleagues in this issue may have a relevant role. By taking advantage of genetic diversity, we can get deep insight into the physiopathology of different diseases and clinical outcomes that could set up the basis for basic molecular studies and at the very end detect targets for future drugs to be developed (translational research) (14). Regarding MBL from the clinical approach, the ideal would be to identify clinical situations that could benefit from specific interventions (e.g., administration of recombinant MBL).

Genetic association studies should be encouraged (under the assumption of a proper and sufficiently powerful design and reproducible laboratory procedures), but their approach regarding haplotypes, and even a group of genes, should be regarded much more optimally. Finally, potential limitations of genetic association studies and the biological effect of naturally occurring mutations should be taken into account for a proper interpretation of results.

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Goals for fluid resuscitation: A real challenge*

The development of the pulmonary artery catheter led rapidly to the use of the pulmonary artery occlusion pressure (PAOP) as the gold standard for guiding decisions on fluid management in critically ill children. More recently, the central venous pressure has been recommended as one end point for fluid resuscitation in patients with severe sepsis or septic shock (1). It is well recognized, however, that neither the PAOP nor the central venous pressure accurately predicts ventricular preload or cardiac performance, either in critically ill patients or in normal volunteers (2–7). The explanation for the lack of correlation of pressure measurements with end-diastolic volume or with response to fluid challenge has generally been that ventricular compliance is different in different patient groups. In addition, pressure measurements are affected by afterload, ventilatory pressures, and likely other factors in critically ill patients. Even in normal volunteers, however, the pressure measurements do not correlate well with end-diastolic volume or cardiac performance (7). End-diastolic volume has been reported to be a better indicator of preload in critically ill patients than pressure measurements, but it is not as easily measured (8). The limited usefulness of ventricular filling pressures in predicting optimal preload is likely one factor in the lack of improvement in outcome when a pulmonary artery catheter is used to guide treatment of acute lung injury (9).

In this issue of *Critical Care Medicine*, Dr. Osman and colleagues (10) add further to this ongoing discussion by demonstrating the limited usefulness of right or left ventricular filling pressures in predicting response to fluid challenge. In their retrospective analysis of prospectively collected data on 150 fluid challenges in 96 patients with severe sepsis, they found that neither the central venous pressure nor the PAOP predicted which patients would respond to fluid challenge, defined as an increase in cardiac index of $\geq$15%. Both responders and nonresponders demonstrated an increase in central venous pressure and PAOP. The baseline central venous pressure was not statistically significantly different between responders and nonresponders. The baseline PAOP was statistically, but probably not clinically, significantly lower in responders than in nonresponders (10 ± 4 vs. 11 ± 4 mm Hg, $p < 0.05$). The responders had an increase in stroke volume index and cardiac index, with a decrease in heart rate, whereas the nonresponders had no significant change in any of these variables. It is of interest to note that some patients with quite high filling pressures received fluid challenges, with some responding, reflecting the reality of clinical practice. Another reflection of the "real-world" nature of this study is the finding that most of the patients had been fluid resuscitated, at least partially, before the catheters were placed and pressures measured. These findings reported by Dr. Osman and colleagues (10) are, not surprisingly, consistent with those reported by Ognibene et al. (11) in a similar patient population. Patients with septic shock are dynamic in their clinical status and in their cardiac function as they are resuscitated and as their sepsis syndrome evolves.

Dr. Osman and colleagues (10) argue that cardiac filling pressures should not be used to guide volume therapy, at least after the initial resuscitation, and that targeting a central venous pressure of $\geq$8 mm Hg or a PAOP of $\geq$12 mm Hg will result in some patients receiving more fluid than they need. Their data demonstrating that some patients with a central venous pressure of $>$12 or a PAOP of $>$15 mm Hg responded to fluid challenge suggest that some patients would actually receive less fluid than they need.

How, then, is the clinician to decide when or whether to give more fluid to a critically ill patient? The literature is quite clear that filling pressures are not a reliable measure of ventricular preload. End-diastolic measures are certainly better predictors of cardiac function, but they are not as easy to measure and not universally available. What should be our end point for fluid resuscitation? Using a single parameter is not clinically reliable, as not all end points (cardiac index, heart rate, blood pressure, central venous oxygen saturation, urine output, etc.) will be reached at the same point in time. Does it matter how much fluid we give? The recent report on fluid management strategies in acute lung injury from the ARDS Network trial (12) described no difference in mortality with a liberal vs. restrictive fluid strategy, although the conservative strategy resulted in fewer days of mechanical ventilation and fewer days of intensive care. Despite the limitations of pressure measurements in predicting cardiac performance, the central venous pressure and PAOP were used to classify groups for different fluid management strategies in this trial. At the end of the day, pressure measurements are what we have available to guide our fluid management. Better and more widely available methods for determining cardiac preload and cardiac performance are badly needed to guide the clinician in the management of our critically ill patients, but until then, we are left with pressure measurements and clinical judgment. Our challenge is to find the most effective, and safe, ways to manage our patients and to teach these methods to the next generation of intensivists.

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Implications of staffing ratios and workload limitations on healthcare-associated infections and the quality of patient care*

Occurrence of medical errors has become a major issue of the general public and of healthcare decision makers. In 2001, the U.S. Institute of Medicine estimated the risks of medical error-related deaths in the United States to be 44,000–98,000 deaths per year, letting aside other serious adverse events (1). Healthcare-associated infections are ranked among the top ten causes of death. It is estimated that 1–3% of all deaths in U.S. hospitals are caused by infections (2).

However, epidemiologic research has shown that in hospital settings, prevalence of health care-associated infections is not uniformly distributed. Patients admitted to critical care units such as intensive care units (ICUs) have a higher risk of healthcare-associated infections than those in noncritical care areas (3). Determinants of healthcare-associated infections in ICUs are numerous, yet although some like device-related infections have been extensively studied, other determinants are only partially understood.

It is only recently that the system of patient care as a whole its components have been acknowledged as equally important, although they are likely to become prerequisites for high quality of care. Healthcare workers are central to the system and the complex process of care delivery, but increased demands on their time can conflict with limited resources. As healthcare managers attempt to reduce the increasing costs of the healthcare system by cutting staff numbers, they may in fact be increasing overall costs by increasing complications and decreasing patient safety and satisfaction.

There is growing evidence to suggest that low staffing levels negatively affect patient outcome. In a recently conducted prospective cohort study in a single center, reported in this issue of *Critical Care Medicine*, Dr. Hugonnet and colleagues (4) investigated whether low staffing levels increased the infection risk in critically ill patients. The study cohort encompassed 1,883 patients totaling 10,637 patient-days, of whom 22% developed at least one healthcare-associated infection. The authors then investigated ecologically the association between workload and infection by computing the correlation coefficient between the daily proportion of infected patients and the nurse/patient ratio up to 15 days prior. They observed that the daily proportion of infected patients was correlated with the nurse/patient ratio of 2, 3, and 4 days prior. It was concluded that staffing is a key determinant for healthcare-associated infections in critically ill patients and that a substantial proportion of infections could be avoided if nurse staffing is maintained at adequate levels.

This study is in line with previous literature. Aiken et al. (5) demonstrated that higher nurse/patient ratios were strongly associated with lower mortality rates in dedicated units. Also, patient satisfaction was strongly associated with organizational control of care by bedside nurses. Moore et al. (6) found that the higher the percentage of registered nurses, the more satisfied patients were with nursing care, pain management, education, and overall care. It was also observed that an ICU nurse/patient ratio of $<$1:2 during evening shifts was associated with increased length of stay in the hospital. An ICU nurse/patient ratio of $<$1:2 during a day shift was associated with increased number of patient-days in the ICU (7). However, the more registered nurses per adjusted patient-day were present, the smaller the incidence of urinary tract infections and pneumonia after major surgery (8). Also, increasing patient census and decreasing nursing hours per patient-day were found to be strongly correlated with increased nosocomial infection rates (9). And finally, hospitals with higher registered nurses to patient ratios and higher overall percentage of registered nurses to all nurses had lower than predicted patient mortality rates (10).

However, in most studies measuring infections as outcome, including the most recent work on this issue conducted

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by Dr. Hugonnet and colleagues (4), it is not clear whether the fluctuations in nursing staffing were due to changes in the number of nurses available that day or in the census or complexity of patients in the ICU. This is an important matter because of the association between patient length of stay and infection rate. If the ICU was especially busy at some time because of an atypically large number of long-term, potentially more infectious patients, this would result in a situation with both low nursing staffing and high infection rates. This could be a correlation without causation. In most other studies it is also not clear if the authors attempted to correct for this potential bias by comparing only patients with equal length of stay. Even this would not be a complete correction since the presence of many long-term patients, many infected or colonized, would raise the overall infectivity of the ICU environment as well as worsen the nurse staffing numbers. Hence, one alternative explanation would be that fluctuations in nurse/patient ratios were due to changes in the nurse supply or in the number of patients in the ICU. It is a common experience that very long-term stay patients have more healthcare-associated infections. Potentially, this matter could be partially clarified by providing data for infections in patients who were not long-term ICU occupants—although a unit filled with such patients might be expected to be at a higher risk of transferring pathogenic organisms and, hence, spreading infections.

Identifying a problem does not mean that the solution is easily to achieve. The key point of all these studies is the term "adequate" staffing. However, although Dr. Hugonnet and colleagues (4) have generated substantial evidence that understaffing is a detrimental factor, it would be wrong for readers of the journal to conclude that overstaffing is equally beneficial. There is considerable variation in both the hours of nursing care required and the hours of nursing care delivered from shift to shift in ICUs. How many nurses with different types of skill levels are truly needed from one shift to another? What does it take to reduce or prevent healthcare-associated infections on a surgical ICU? It will be challenging to answer the question what "adequate" staffing is.

Recently, an interesting event occurred in Victoria, Australia. The Australian Nursing Federation successfully won a judgment at the Industrial Relations Commission to implement minimum nurse/patient ratios across all areas of public hospitals, for example, ICU 1:1, neonatal ICU 1:1, and medical and surgical wards 1:4 at daytime, 1:6 at evening, and 1:8 at night.

Nevertheless, it still remains to be clarified precisely how more nurses may lead to fewer infections. Simply thinking that more nurses results in better patient care practice seems ambiguous. An important factor might also be staffs members' knowledge, level of training, and professional experience. One important study on nurse staffing clearly demonstrates that not only nurse workload but also their educational level and professional experience might affect patient mortality (11). One study linked outcomes data for 232,342 patients discharged from 168 nonfederal adult general Pennsylvania hospitals between April 1, 1998, and November 30, 1999, to administrative and survey data providing information on educational composition, staffing, and other characteristics. It was observed that a 10% increase in the proportion of nurses holding a bachelor's degree was associated with a 5% decrease in the likelihood of patients dying within 30 days of admission. The authors concluded that in hospitals with higher proportions of nurses educated at the baccalaureate level or higher, surgical patients experienced lower mortality.

In several studies, increasing skill mix was associated with decreasing length of stay, postoperative complications, pressure ulcer rates, and nosocomial infections. It was shown that more nursing hours and higher skill mix were related to lower rate of pressure ulcers, pneumonia, and urinary tract infections (12), that mortality rates decrease as staffing levels per occupied bed increase for registered nurses (13), and that the higher the nurses' skill mix (up to 87.5% registered nurses) the lower the incidence of adverse occurrences (14).

Hospitals are complex, sociologically rich places that are hard to read and even harder to change (15). At present the literature is insufficient to make a final reasoned judgment about organization of the work environment of nurses. The need to constrain budgets by reducing nursing hours is in conflict with the needs of the hospital's management and in conflict with the needs of patients. Yet, resources necessary for conducting systematic studies of nursing care provided in hospitals and then implementing the practices found to be helpful are scarce, and the cost of primary data collection has limited the number of studies using data aggregated to the individual nursing unit. Further work is needed in the area of nurse interventions. Further work is also needed on the economics of "bottom line" driven executives who see the reduction in staffing costs alone without measuring the true costs of increased morbidity and length of stay and patient satisfaction. If there truly is to be an emphasis on reducing adverse events in hospitals and creating hospital environments that promote health and healing, resources for research related to levels of safe and appropriate nursing numbers and qualification must be found.

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Why does cholecystokinin increase in critically ill patients?*

Cholecystokinin is secreted by I cells in the mucosa of the duodenum and proximal jejunum, when chyme containing fat or protein-rich components enters the duodenum. Historically, cholecystokinin was considered to be a peptide hormone to facilitate digestion and absorption of food. As the word cholecystokinin is coined from Greek *chole* (bile), *cysto* (sac), and *kinin* (to move), it stimulates the bile sac (or gallbladder) to discharge bile, which emulsifies fats and thus helps absorption from the small intestine. It also stimulates secretion of pancreatic lipase, amylase, and trypsin, which catalyze the digestion of fat, protein, and carbohydrate.

Later, cholecystokinin has been found to act not only as a hormone, but also as a neuropeptide. Cholecystokinin and its receptors can be identified in the myenteric plexus of the enteric nervous system and in the central nervous system. One notable central effect of cholecystokinin is that it reduces hunger and reduces food intake (1). Cholecystokinin has also been found to limit the entry of fat-rich chyme to the small intestine by delaying gastric emptying (2). Several studies have shown that physiologic doses of exogenously administered cholecystokinin delay gastric emptying (3) by inhibiting gastric antral motility and increasing the pyloric tone (1) via the vagovagal reflex.

In this issue of *Critical Care Medicine*, Dr. Nguyen and colleagues (4) report abnormally increased plasma cholecystokinin concentrations in critically ill patients. They measured the concentrations in critically ill patients and healthy subjects, during fasting and after intraduodenal infusion of a nutrient, and found that plasma cholecystokinin concentrations during fasting were higher in critically ill patients than in healthy subjects. In addition, intraduodenal feeding increased plasma cholecystokinin concentrations in both groups, but the degree of the increase was greater in critically ill patients. More importantly, among critically ill patients, plasma cholecystokinin concentrations during both fasting and feeding were higher in those who were not tolerant to gastric feeding than in those who were tolerant (4).

So, why does the plasma cholecystokinin concentration increase in critically ill patients? One possibility is due to delayed clearance by impaired kidneys. In fact, the plasma cholecystokinin concentration has been reported to be high in patients with renal failure (5). Dr. Nguyen and colleagues (4), however, have shown that this possibility is not the main cause in critically ill patients because even when patients with renal dysfunction was excluded from data analysis, plasma cholecystokinin concentrations were still higher than in healthy subjects. The increase in the plasma cholecystokinin concentration has also been reported in elderly people (6) and in patients with pancreatitis (7). Elderly people, critically ill patients, and patients with pancreatitis or renal failure tend to be lacking appetite and undernourished. It is possible that the plasma cholecystokinin concentration is increased due to pathologic changes, consequently inhibiting appetite and food intake and delaying gastric emptying. It is also possible that these patients' bodies are actively increasing the plasma cholecystokinin concentration to limit food intake and to minimize energy expenditure and dumping syndrome.

It has long been known that early enteral feeding is beneficial in reducing mortality from sepsis and organ damage in trauma patients and in patients who have undergone operation. It is now becoming clear that enteral feeding may enhance immune function, and this beneficial effect may be mediated by an increased level of cholecystokinin (8–10). For example, in rats with hemorrhagic shock, high-fat enteral feeding inhibited proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6 (8). Injection of cholecystokinin also inhibited proinflammatory cytokines (9), accelerated the transit of chyme in the small intestine, and reduced enteric bacterial overgrowth and translocation (10). Therefore, it is possible that cholecystokinin is actively increased in critically ill patients to suppress proinflammatory cytokines (in expense of delaying gastric emptying).

Cholecystokinin antagonists, such as loxiglumide, accelerate gastric emptying of fat-rich meals in healthy subjects (3) and may be effective in treating patients with pancreatitis by reducing abdominal pain, serum pancreatic amylase, and trypsin concentrations (7). These antagonists may also reduce the gastroesophageal reflux, by reducing the degree of adaptive relaxation of the lower esophageal sphincter (11), and may be effective in treating irritable bowel syndrome. Furthermore, cholecystokinin antagonists could enhance antinociception and reduce opioid tolerance.

It is tempting to conclude that cholecystokinin receptor antagonists are useful in treating delayed gastric emptying in patients who are intolerant to enteral feeding. Nevertheless, caution is required in using cholecystokinin antagonists in critically ill patients because they may abolish the beneficial effects of cholecystokinin on immune function. For example, in rats with hemorrhagic shock, cholecystokinin antagonists impaired fat-induced suppression of proinflammatory cytokines, increased plasma endotoxin level, and resulted in more bacteria translocated to distant organs (8). Other studies have shown that cholecystokinin increases blood flow of the gastric mucosa and protects the gastric mucosa from injury by luminal irritants (12, 13), and thus, these antagonists may abolish cholecystokinin's gastroprotective effects.

***See also p. 82.**

Key Words: cholecystokinin; cholecystokinin antagonists; gastric emptying; enteral feeding; feeding intolerance

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Dr. Nguyen and colleagues (4) measured plasma cholecystokinin concentrations before and during intraduodenal feeding. It is known that there are differences between patients receiving intragastric and those receiving intraduodenal feeding in cholecystokinin release and in gastrointestinal motility (14, 15). Transit of chyme in the small intestine is faster, and the plasma cholecystokinin concentration is higher, during intraduodenal feeding compared with intragastric feeding (15). In addition, during intraduodenal feeding, the fed-state gastrointestinal motility is sustained, whereas during intragastric feeding, the fasting-state motility (phase 3 of the migrating motor complex) may frequently occur (14). Therefore, it is not clear whether the degree of the increase in the plasma cholecystokinin concentration and gut function during intragastric feeding is similar to that during intraduodenal feeding. Nevertheless, the finding by Dr. Nguyen and colleagues (4) is a good start to investigate why plasma cholecystokinin concentration increases in critically ill patients and to seek whether actively lowering it and accelerating gastric emptying, for example by cholecystokinin antagonists, is beneficial to patients with feeding intolerance.

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Resistance in the intensive care unit: Whose problem is it and how can intensivists help?*

The widespread use of potent, broad-spectrum antibiotics has been paralleled by the development of resistance in bacteria, culminating in the prevalence of highly resistant bacteria in some intensive care units (ICUs). This is highlighted by the recent position paper from the Infectious Diseases Society of America, "Bad Bugs, No Drugs" (http://www.idsociety.org/). It is frustrating to note that the Infectious Diseases Society of America itself has taken on this issue, making it a priority, whereas formal organizations representing critical care practitioners have been relatively silent on an issue we grapple with daily. Put simply, critical care physicians are frequent users and abusers of antibiotics, and the ICU often has the worst antibiotic resistance problems in the hospital.

Frustrating all efforts to address issues related to resistance is the fact that the development of new antibiotics targeted at Gram-negative bacteria has essentially come to a halt. No new class of antibiotics developed for Gram-negative sepsis has become available since the 1980s when the carbapenems were released (1). Although newer biopharmaceutical products are in development, it does not seem at all certain that we will be able to engineer ourselves out of the dilemma we face. Although more choices are on the horizon for resistant Gram-positive bacteria, *Staphylococcus aureus* has repeat-

*See also p. 89.

Key Words: antibiotics; infection; intensive care unit; outcome; resistance

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edly shown itself to be able to rapidly adapt to newer agents.

It is in this vein that the study by Dr. Evans and colleagues (2) in this issue of *Critical Care Medicine* has important messages. Although it is a retrospective study, with all the intrinsic biases and problems associated with this approach, it documents some of the excess expense generated in treating resistant organisms. Some of the analyses are difficult to follow, and strangely, there is no comment on attributable mortality from these bacterial infections. Nevertheless it is a significant study that emphasizes the burden of resistant organisms on *our* ICUs and corroborates previous work on the cost of resistant organisms (3).

But whose problem is this resistance? It cannot be, and should not be, solely the responsibility of the Infectious Disease specialists. Unless we take ownership of what goes on in our ICUs, we will never be able to control the conundrum of "bad bugs, no drugs." Although it is easy to point to poor infection control as the culprit that facilitates the spread of resistant pathogens, additional issues are at play that intensivists must acknowledge, such as appropriate use of antibiotics and infection prevention.

Appropriate Antibiotic Use

The intensive care community faces the realistic prospect of untreatable nosocomial infections. It behoves us to use antibiotics appropriately and not abuse the ease of becoming a "just in case" prescriber. In that instance, we are often treating ourselves at the expense of both present and future patients. Antibiotics will kill susceptible bacteria, but within any colony of organisms, resistant bacteria will still grow. Indiscriminate use of anti-infectives propagates the development of resistant organisms. Clinicians must finally comprehend that antimicrobials are the only class of agents used in the ICU for which one physician's practice can affect outcomes in someone else's patient. Specifically, wise antibiotic use translates into employing the correct antibiotic (not necessarily using dual Gram-negative coverage), in the correct dose, for the correct duration, and only in serious, documented infection. Inadequate dosing of any antibiotic, but especially for quinolones, leads to resistance (4). Incorrect dosing of aminoglycosides occurs unless extended interval dosing is used (5). High creatinine clearances in some ICU patients lead to high drug clearances and, hence, potential underdosing of antibiotics (6). Appropriateness now also incorporates the theme of duration in that many of the historical recommendations for treatment duration were based purely on anecdote rather than evidence. For example, it is now evident that in most cases, shorter courses of therapy are acceptable (if not optimal) for such serious infections as ventilator-associated pneumonia (7). Failing to change our practice style to reflect this evidence because "we feel comfortable" with some other duration again ignores the harm we do to our patients when we overuse these agents. Relatedly, "physician comfort" has never been and should never represent an end point in a clinical trial. Therefore, we should abandon this specious argument when articulating why we as a profession often fail to adopt evidence-based results.

Prevention is Better than Cure

Hand washing has traditionally been identified as the most important infection control measure in prevention of the spread of infection. Many have stressed the failure of existing infection control guidelines (8). The poor compliance of existing guidelines illustrates how difficult it is to change people's behavior.

The recent *Draft Guideline for Hand Hygiene in Healthcare Settings* (9), produced by a joint task force of infection control and infectious disease societies and the Centers for Disease Control and Prevention, concluded that alcohol-based hand rubs (waterless) are an acceptable alternative to washing hands with antimicrobial or non-antimicrobial soap. These agents (also known as "hand rub" agents) are effective in decreasing microbial load, can be made more accessible, require less time to use, and are less prone to cause irritant contact dermatitis (10–14).

Are the recently introduced hand rubs going to help to produce better hand hygiene? Maury et al. (11) showed that it takes 60 secs to wash hands vs. 15 secs for the alcohol hand rub and that the number of times alcohol hand rub was used was significantly higher and, hence, infection control compliance was better. Hugonnet et al. (14) demonstrated better compliance with hand rubs, especially when workloads were high (opportunities per hour for hand hygiene), and this was sustained over time. These results mean the busier an ICU is, the less likely the staff are to wash hands and the more likely hand rubs will be used instead. We await level 1 evidence that hand rubs will produce a sustainable improvement in hand hygiene, thereby leading to a decrease in infections. Until such time, or a study to the contrary, we strongly advise widespread usage of these preparations in the ICU.

Beyond hand washing compliance, preventive options exist and have strong evidence supporting their efficacy. Use of the subclavian site for central catheter insertion decreases the risk for catheter-related blood stream infection (15). Similarly, reliance on chlorhexidine for skin preparation substantially improves outcomes (16). For prevention of ventilator-associated pneumonia, simple elevation of the head of the bed decreases the risk for this serious nosocomial infection by nearly 25% (16). We urge readers, however, to walk through their own ICUs and assess what proportion of their ventilated patients are lying flat. Both protocols for sedation and liberation from mechanical ventilation also drive down nosocomial pneumonia rates (16). But rather than adopting these interventions, most hospitals seem to be throwing up their hands and claiming that changing behavior is "too hard." In response, we would refer readers to the insightful comments of the famous rabbinic commentator Hillel, who wrote: "If I am not for myself who will be for me? Yet, if I am for myself only, what am I? And if not now, when?" Indeed, the issue is ownership, and who better able to take ownership of issues related to prevention and resistance than the intensivist at the bedside delivering care to the critically ill.

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B-type natriuretic peptide-guided therapy and prognosis in acutely ill patients with pulmonary disease*

Both N-terminal pro-brain natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) have emerged as critical diagnostic and prognostic tools for treatment of heart failure, especially in the in the emergency room and inpatient settings. The ability of natriuretic peptides to aid clinicians in making accurate diagnoses and optimizing treatment has brought the biomarker much attention and has allowed it to become part of the standard of care for diagnosing and treating heart failure at many institutions around the world.

The correlation of serum natriuretic peptide concentrations with elevated end-diastolic pressure (1, 2) closely parallels dyspnea in heart failure, suggesting that this peptide is uniquely suited for use as a neurohormonal index of progressive heart failure (3). Natriuretic peptide concentrations also parallel New York Heart Association clinical status (4, 5), more than does ANP.

***See also p. 96.**

Key Words: diagnostic tool; heart failure; biomarker

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BNP levels can be elevated in patients with pulmonary disease, but not to the extent that they are in patients with heart failure. In the 1,586 patients presenting to the emergency room with acute dyspnea, admission BNP >100 pg/mL had a sensitivity of 90% and a specificity of 76% for congestive heart failure (CHF) as opposed to other causes of dyspnea, whereas BNP >50 pg/mL had a negative predictive value for CHF of 96% (5). Data from the Breathing Not Properly multinational study found that measurement of BNP levels can expose underlying CHF in patients with bronchospastic diseases such as asthma or chronic obstructive pulmonary disease (6). Of 417 patients studied who had a history of asthma or chronic obstructive pulmonary disease and no history of CHF, 87 (21%) were found to have a final diagnosis of CHF. The mean BNP levels for patients with and without a diagnosis of CHF were found to be 587 and 108 pg/mL, respectively. According to these data, routine BNP testing in patients with a history of asthma or chronic obstructive pulmonary disease may increase the rate of new diagnosis of heart failure by as much as 20%.

A subanalysis of the [B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation] BASEL study looked at the effect of using BNP on the time to treatment in patients with known pulmonary disease. In this randomized trial of patients presenting to the emergency room with dyspnea and a history of established pulmonary disease, clinicians were either aware of or blinded to BNP levels. The findings of the study showed that the group whose BNP levels were disclosed to clinicians received the appropriate treatment sooner (59 mins after presentation) than the group whose BNP levels were withheld (minutes after presentation) (7).

In this issue of *Critical Care Medicine*, Dr. Grasso and colleagues (8) examined the notion that natriuretic peptide levels might help guide treatment of critically ill patients on mechanical ventilation by discovering whether cardiac dysfunction was present during a weaning trial. Presumably, finding and then alleviating a remediable cause of left ventricular dysfunction (such as ischemia) might make the difference in the subsequent outcome of weaning and later discharge from the hospital. Eight of 19 patients (42%) were identified with acute cardiac dysfunction at the end of a weaning trial. Baseline NT-proBNP levels were significantly

higher in these patients than in patients without acute cardiac dysfunction at the end of the weaning trial. The values of NT-proBNP increased significantly during the weaning trial in this group of patients. The fact that the elevation of NT-proBNP had a good diagnostic performance for detecting acute cardiac dysfunction as estimated by receiver operating characteristics curve analysis is further evidence that natriuretic peptides, when used appropriately, may be of value in critically ill patients in the intensive care unit.

A recent study (9) demonstrated that BNP levels in intensive care unit shock might provide powerful information for use in mortality prediction. In this study, the median BNP levels were higher in those who died than those who survived (943 vs. 378 pg/mL, $p < .001$). Also revealed by multivariate analysis was that BNP levels in the highest log-quartile were the strongest predictor of mortality (odds ratio = 4.5). Even though no correlation between a single BNP value and pulmonary artery occlusion pressure in interpatient analysis was demonstrated, it was clear that a BNP <350 pg/mL had a very high negative predictive value (95%) for the diagnosis of cardiogenic shock.

The preceding studies support the study published in 2001 by Kazanegra et al. (10), involving 20 patients with decompensated New York Heart Association class III–IV CHF undergoing tailored therapy, which showed a significant correlation between percent change in occlusion pressure from baseline per hour and the percent change of BNP from baseline per hour. In this study, the authors also showed that the patients who died had higher final BNP levels (1078 pg/mL vs. 701 pg/mL). They concluded that although BNP level will not obviate the need for invasive hemodynamic monitoring, it may be a useful adjunct in tailoring therapy to these patients and may improve the in-hospital management of patients admitted with decompensated CHF.

In a study by Berman et al. (11), BNP levels were obtained in 35 patients with acute respiratory distress syndrome and from 42 patients hospitalized for severe dyspnea with the diagnosis of CHF. The median BNP level in patients with CHF of 773 pg/mL was significantly higher than that of patients with acute respiratory distress syndrome (123 pg/mL, $p < .001$). The area under the receiver operating characteristic curve using BNP to differentiate CHF from acute respiratory distress syndrome was 0.90 ($p < .001$). At a cut point of 360 pg/mL, there was 90% sensitivity, 86% specificity, 89% positive predictive value, and 94% negative predictive value (accuracy, 88%) for acute respiratory distress syndrome vs. CHF. Thus, BNP may be accurate enough to differentiate noncardiogenic from cardiogenic pulmonary edema such that invasive hemodynamic catheter placement may not always be necessary. BNP levels >360 pg/mL suggested that pulmonary edema was of cardiogenic origin.

The merit of these studies is that they show that low BNP levels, tested by a single inexpensive point of care assay, can exclude significant cardiac dysfunction in the intensive care unit setting and may be useful to avoid pulmonary artery catheterization and hence the risks associated with pulmonary artery catheter placement and the necessity of an intensive care unit bed. These studies also show that elevated BNP levels may offer superior prognostic information for the critical care practitioner to help identify patients at highest risk for mortality, such as seen in the study by Dr. Grasso and colleagues (8). Furthermore, Cheng et al. (12) followed the course of 72 patients admitted with decompensated CHF with daily BNP levels and their relationship to 30-day readmission rates or death. Patients who were most likely to have a cardiac event had higher BNP levels at the times of both admission and discharge. Only 16% of patients with a decrease in BNP levels during hospitalization had a subsequent cardiac event, whereas 52% of those with increasing BNP levels during treatment had either readmission or cardiac death. Patients whose discharge BNP levels fell below 430 pg/mL had a reasonable likelihood of not being readmitted within the following 30 days. These data were supported by a recent study by Bettencourt et al. (13), who found that failure of BNP levels to decrease over the hospitalization predicts death/rehospitalization and that discharge levels <250 pg/mL predicted event-free survival.

Although the study by Dr. Grasso and colleagues was performed in only a small cohort of highly selected patients, with the final determination of cardiac or respiratory weaning failure a difficult one, nevertheless, the conclusion that NT-proBNP elevations during the weaning trial might reflect acute cardiac dysfunction needs to be tested in a larger trial. The data add to the potential usefulness of natriuretic peptides in the acute care setting.

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ARDS—Shake, rattle, and roll!*

High-frequency oscillatory ventilation (HFOV) is an unconventional form of mechanical ventilation that may improve oxygenation in patients with the acute respiratory distress syndrome (ARDS) while limiting the lung injury associated with high ventilatory pressures and volumes. HFOV has been used with some success for almost 2 decades in the neonatal population, but there is a more limited although increasing experience in the adult population. In adults, much of the published literature consists of observational studies in which HFOV was used as "rescue" therapy for patients with severe ARDS failing conventional mechanical ventilation (CMV) (1–3). These studies have demonstrated that HFOV, when applied using a lung recruitment strategy, can safely improve oxygenation in this patient population. A prospective randomized trial in 148 adults noted an earlier improvement in Pao_2/Fio_2 ratio in the HFOV group compared with a CMV group, with the benefits not persisting beyond 24 hrs (4). A second randomized controlled trial was stopped prematurely and could not demonstrate any differences in outcomes between the HFOV and CMV groups (5).

The neonatal literature has clearly established the importance of aggressive alveolar recruitment for the successful use of HFOV (6). Whereas the first randomized trial in neonates applied relatively low pressures and demonstrated no benefit (7), several subsequent trials demonstrated an acute oxygenation benefit of HFOV compared with CMV (8–10). These latter trials incorporated an aggressive HFOV recruitment strategy, using recruitment maneuvers and a higher mean airway pressure during HFOV than CMV (8–10). Recruitment can be achieved by an initial sustained inflation recruitment maneuver or alternatively by progressively increasing the mean airway pressure. Ferguson and colleagues (11) evaluated the regular use of recruitment maneuvers in 25 adults with early ARDS. Protocolized application of recruitment maneuvers at HFOV initiation, twice daily and as needed for hypoxemia, resulted in a significant and sustained improvement in oxygenation, which occurred more rapidly than reported in other HFOV studies (1, 2, 4).

Ventilation in the prone position carries a number of potential physiologic benefits, including a recruitment effect (12). Prone positioning has been evaluated in patients with ARDS, with early case series demonstrating significant improvements in oxygenation (13). However, in a large randomized controlled trial in adults with acute lung injury or ARDS, 6 hrs of prone position daily did not reduce mortality compared with conventional treatment, despite physiologic benefits (14). A more recent study, using the prone position for 20 hrs daily, demonstrated a trend toward a survival benefit (15). Another intervention evaluated in the management of ARDS, with a similarly checkered history, is the administration of inhaled nitric oxide (iNO). Although approximately 50% of patients with ARDS respond to iNO with improvements in oxygenation, no survival benefit has been demonstrated (16).

We have previously suggested that combining several such modalities (HFOV, prone, iNO) may provide synergistic oxygenation and lung-protective benefit in the management of patients with ARDS (17). HFOV has been studied in conjunction with iNO (18), recruitment maneuvers (11) and prone positioning (19). We administered iNO to patients receiving HFOV and found that 91% of patients demonstrated a $\geq$20% improvement in Pao_2/Fio_2, a far higher response rate than reported with iNO during CMV (18). In this issue of *Critical Care Medicine*, Dr. Demory and colleagues (20) add support to this concept of combining modalities, demonstrating that HFOV can maintain the beneficial oxygenation effect of prone positioning when patients are returned to the supine position. In contrast, the use of HFOV in supine patients had no effect on oxygenation, and patients treated with CMV had a rapid decline in Pao_2/Fio_2 when turned from prone to supine. We believe that oxygenation was better during prone HFOV than supine HFOV due to the lack of a recruitment strategy during HFOV. This affected the supine HFOV group to a greater extent than the prone HFOV group as the initial prone positioning may have acted as the recruiting maneuver, with HFOV maintaining this lung volume effect. Prone positioning has been shown to result in similar improvements in oxygenation as recruitment maneuvers in patients with ARDS (21).

The current study (20) complements an earlier study by the same group of investigators demonstrating a lack of oxygenation benefit using HFO in the supine position, compared with HFOV in the prone position (19). As in the current study, no preceding recruitment maneuver was used, and the mean airway pressure applied during HFOV was relatively low in comparison to other published studies (1–4). Another possible reason these investigators failed to show improvements in oxygenation with supine HFOV in both of their studies is that the majority of their patients had ARDS of a pulmonary cause. Previous studies evaluating HFOV (22) and recruitment maneuvers (21) suggest that patients with pulmonary ARDS have less recruitable lung tissue than patients with extrapulmonary ARDS.

The strengths of the current report include the randomized design, the rigorous protocol, and the large number of physiologic measurements. We feel that the important conclusions to be drawn are not the

***See also p. 106.**

Key Words: acute respiratory distress syndrome; alveolar recruitment; high-frequency oscillatory ventilation; prone position

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lack of effect of HFOV in the supine position but the importance of initial lung recruitment, which can be achieved through prone positioning. Whether prone positioning provides a benefit over sustained inflation recruitment maneuvers in this situation is unclear; it is, however, a far more difficult and time-consuming intervention. Furthermore, this study supports the concept of a benefit of a synergistic effect of multimodal interventions. Prospective studies would be important to further characterize this effect and identify an optimal approach to "nonconventional" ventilatory support.

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Delirium as destiny: Clinical precision and genetic risk*

In the current issue of *Critical Care Medicine*, Dr. Ely and colleagues (1) describe 53 general medical intensive care unit (ICU) patients whom they evaluated each day with standardized scales to quantify sedation (2) and detect delirium (3). Having documented the presence or absence of delirium, the authors summed all of the days on which the delirium-screening test was positive and considered that number to be the burden of delirium. They correlated this metric with the presence or absence of the APOE4 genotype, a biological marker that has been used to predict the development of Alzheimer's disease (4) and poor outcome following neurotrauma (5). The authors admit that the study is underpowered and cannot draw firm outcome conclusions. They consider, however, that the presence of APOE4 may be linked to more "delirium-positive" days. They also posit that this potential link could lead to "novel therapeutic approaches such as personalized pharmacology for those at greatest risk" (1).

Understanding the biological foundations of disease represents a major aim of scientific medicine, and the authors are commended for exploring the link between an important clinical syndrome, delirium, and a potential biological substrate, the APEO4 genotype. Experienced psychiatrists comment on the propensity

*See also p. 112.

Key Words: APOE4 genotype; genetics; psychiatric disease

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for similar patterns of delirium to recur in patients and their families. The current pilot study (1) suggests that genetic predisposition may be one of the many associations with clinical delirium. Exciting as this prospect may be, several challenges lie ahead for scientists in this area.

Previous work by Dr. Ely and colleagues has been seminal in raising clinician awareness of the presence—-and the consequences—-of delirium in critically ill patients. However, experts in the area disagree on the incidence of delirium. In the current article, Dr. Ely and colleagues (1) report an incidence of 89%; others report an incidence of 11% (6). In addition to determining the presence of delirium, clinicians can quantify its severity with tools specifically developed for that purpose (7). Such evaluations require verbal assessments, which are impractical in the mechanically ventilated patient. The relationship between severity of delirium and its duration has not been explored in ICU populations, nor has any association been reported between either severity or duration of delirium and clinical outcomes.

In particular, the presumption that delirium is one manifestation within a spectrum of brain dysfunction has not been corroborated in critically ill patients. Dr. Ely and colleagues extrapolate from an APOE4 association with outcome in both neurotrauma patients (where prediction of clinical outcomes is, at best, challenging) and Alzheimer's patients to medical ICU patients. This extrapolation relies on the unproven premise that delirium fits into a graded model of "brain failure." Our group has documented that patients with neurologic dysfunction have a lower incidence of delirium than those without (8). This observation suggests that delirium is not one point in an array of many degrees of "brain failure."

Delirium is a syndrome. Its diagnostic criteria are applied to cohorts of patients who are confused and also to those who receive multiple sedative and analgesic medications. The sedative effect of anxiolytic or analgesic medication, and not drug amount, is associated with delirium (8). Also, the criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) for delirium could be satisfied by drug effects or nondrug organic disturbances. These issues confound risk-factor and outcome profiles and may lead to erroneous epidemiologic conclusions. The association of sedative drugs (9) and anesthesia (regardless of drug type or dose) (10) with deleterious outcomes indicates that drug effects should be evaluated as a separate variable in any analysis. The 89% incidence of delirium described in the current article suggests that virtually every medicated patient and every confused patient scored "positive" on the Confusion Assessment Method for the Intensive Care Unit screen. The nature of the association with APOE4, or any other marker, may be different in each group.

Finally, genetic determinism of defined psychiatric diseases is variably, but never entirely, predictive. A genotype that is associated with schizophrenia predicts the disease approximately 50% of the time in homozygous twins (11). A syndrome such as delirium may have multiple associations of variable importance, some of which have only begun to be explored in the complex adult ICU population.

The attribution of genetic association to delirium promises to be ethically challenging. No pharmacologic intervention has convincingly been shown to prevent or effectively treat delirium. If the incidence of delirium really is 89% (1), then almost none of the patients can provide informed consent (an issue not addressed in the present study). Thus, surrogates will be asked to agree to studies to help further "knowledge of pharmacogenomics to tailor clinical care" (1). Patients' families are understandably wary of genetic testing for the purpose of pharmaceutical intervention (12). Genomic predilection may be of interest to the scientist but could expose the patient to discrimination or stigmatization from health insurers or care providers.

Now that we are exploring the biological basis for the delirium syndrome, we must be careful to avoid contaminated samples. We cannot assume that mental disturbances that result from sedatives (and other exogenous compounds) are equivalent to natural (non-drug-induced) forms of delirium. We need to be sure what delirium is. But we are not.

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Selenium in intensive care: Probably not a magic bullet but an important adjuvant therapy*

Being admitted to the intensive care unit for organ failure, critically ill patients are at particularly high risk of developing further organ failures in association with persisting and intense systemic inflammatory response syndrome (SIRS). SIRS is accompanied by high circulating and tissue concentrations of cytokines, increased metabolic rate, and increased production of reactive oxygen species (1). Oxidative damage is widely believed to be harmful, both in the pathogenesis of SIRS and in organ dysfunction. However, despite extensive biochemical evidence of a correlation between the severity of illness and the amount of oxidative stress (e.g., malondialdehyde or F2 isoprostane production), improvement in antioxidant (AOX) status in supplementation trials has only inconsistently led to clinical benefit (2).

In this issue of *Critical Care Medicine*, Dr. Angstwurm and colleagues (3) report the results of a multiple-center prospective, randomized, controlled supplementation trial in patients with severe sepsis: The intervention consisted of an intravenous supplement of 1000 μg of selenium vs. placebo delivered daily for 2 wks after a loading dose. Although there was no significant difference in intention-to-treat mortality rate ($p = .109$), the authors found a significant reduction of 28-day mortality rate in the patients with the highest quartile Acute Physiology and Chronic Health Evaluation III scores from 81.5% (n = 27) to 55.6% (n = 27) and in patients in septic shock with disseminated intravascular coagulation from 66.7% (n = 30) to 40.5% (n = 34). This trial, using a single high-dose antioxidant, supports their 1999 results in a smaller study, in which selenium supplementation, at a much lower dose for 9 days, was associated with significant reductions of acute renal failure and the need for renal replacement therapy and a nonsignificant reduction of mortality (4). In the present study there was no reduction in organ dysfunction, vasopressor therapy, nosocomial pneumonia, or the need for renal replacement therapy. The positive outcome in septic shock and the trends in overall mortality support the hypothesis that improving selenium status and hence reinforcing the endogenous AOX defenses are beneficial in defined conditions.

But there are shortcomings and some concerns to this study. Despite 11 intensive care units taking part, only 249 patients were recruited over 5 yrs. No indication is given of the number of patients recruited per center or how many eligible patients were not recruited. This may mean some preselection of patients. And the numbers present in the most severely ill groups remain small. Furthermore, there is a contradiction between lack of effect on organ failure outcomes but nonetheless an effect on mortality rate. Whereas selenium might specifically affect endothelial function and disseminated intravascular coagulation, it is more difficult to speculate on how mortality rate is improved relative to Acute Physiology and Chronic Health Evaluation III score without affecting organ failure.

SIRS is associated with a redistribution of vitamins and trace elements from the circulating compartment to tissues and organs that are involved in protein synthesis and immune cell production (5), causing a relative deficit in circulating AOXs (6, 7). The latter limit the release of nuclear factor-kB caused by increased reactive oxygen species, and depletion of the circulating compartment's AOXs may be deleterious if prolonged (1). The interpretation of the low plasma levels observed in critically ill patients is complex. Although SIRS redistribution is an important cause, acute losses through biological fluids, dilution due to resuscitation fluids, and insufficient intakes also contribute. In addition, critically ill patients on admission reflect the general population, a large proportion of which have pre-illness low selenium status in Europe and Australasia (8). Low plasma levels may therefore result from prior nutritional deficiency or from illness. The situations where correction of a SIRS-related low plasma selenium, or indeed low plasma zinc, is beneficial need to be established—it is clear that the low plasma iron in SIRS is a protective mechanism and parenteral iron will be harmful (9).

Animal data have shown that preinjury selenium deficiency is associated with increased baseline lipid peroxidation and worsening of oxidative damage after burns that cannot be reversed by supplementation (10). However, the demonstration that selenium deficiency favors the development of virus virulence by DNA mutation, possibly through the reduction of glutathione peroxidase activity (11), suggests that "antioxidation" may be an essential step in defenses against certain infections. A recent meta-analysis investigated whether supplementing critically ill patients with antioxidant micronutrients (trace elements and vitamins) positively influences survival (12). Aggregated trials suggested that overall AOXs were associated with a significant reduction in mortality (risk ratio 0.65, $p = .03$): Only the studies using parenteral AOXs were associated with a significant reduction in mortality (risk ratio 0.56, $p = .02$), whereas those using enteral AOX were not. Selenium-containing supplements appeared to be associated with a reduction in mortality, whereas nonselenium AOXs were not. However, most of the studies performed to that date were small single-center studies. The study of Dr. Angstwurm and colleagues (3) therefore strengthens the conclusions reached in this meta-analysis.

When supplementing, one must bear in mind the possibility of deleterious toxic effects, and AOX may be pro-oxidant under defined conditions. The absence of benefit on kidney function compared

*See also p. 118.

Key Words: mortality; antioxidant; septic shock

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with the prior trial is noteworthy. Selenium toxicity usually relates to chronic intakes in food ingested over many months and years: These data are unlikely to be relevant to acute use of selenium in critically ill patients over 2–3 wks. None of the 11 trials using selenium in the meta-analysis reported deleterious effects of selenium administration, with doses up to 1000 μg per day for 1–3 wks (12), but such effects are difficult to diagnose. In the present study, the plasma selenium values, although significantly increased, remained within upper reference ranges (3). Chronic intakes >450 μg/day are associated with depression of the activity of another important selenoenzyme that is considered a better indicator of safe selenium intakes than the glutathione peroxidase, namely the type I iodothyronine 5' deiodinase (5'DI)—which catalyzes the production of T_3 (13). Without reaching acute toxicity, the 1000-μg doses may nonetheless be excessive. In burn trials, the beneficial clinical effects were reached with lower doses, 300–550 μg/day (14). The optimal acute selenium dose may range somewhere between 500 and 750 μg/day.

The evidence is therefore mounting that selenium is beneficial in some of the most critically ill patients. Although the mechanism of such benefit is likely to be through its antioxidant activities, selenium is present in a large number of proteins not all of which have antioxidant activity, and other modes of action may explain some of the inconsistent effects of AOX supplements; this clearly requires further investigation. Different doses between 500 and 1000 μg per day have to be tested, and larger multiple-center studies need to be performed with high rates of uptake of patients before it can be concluded that high-dose selenium should be routinely used in the most seriously ill patients.

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Nitrogen challenge: Are we any closer to achieving a balance?*

In this issue of *Critical Care Medicine*, Dr. Cheatham and colleagues (1) present the results of their 6-month, prospective, observational cohort study, in which they found a significant loss of proteins in patients with open abdomens compared with those in whom primary fascial closure was achieved. They hypothesized that patients with open abdomens lose large amounts of abdominal fluids containing significant amounts of protein and, hence, are prone to severe protein malnutrition.

Malnutrition in the critically ill is not uncommon and is associated with increased morbidity and mortality (2, 3). It is the metabolic response to critical illness, although an adaptive mechanism to the initial insult, that can lead to organ system dysfunction and, subsequently, to multiple organ failure and death. It is characterized by increased energy expenditure and heat production, fever, accelerated nitrogen excretion and muscle wasting, and glucose intolerance. This metabolic response peaks several days after injury and then wanes after a few weeks, when recovery proceeds.

Therefore, early enteral nutrition has been accepted as the gold standard in the critically ill, as it has demonstrated to improve the nitrogen balance (NB), wound healing, and host immune function; maintain gut integrity; possibly prevent bacterial translocation; and decrease the hypermetabolic response to tissue injury (4).

There is, however, not a single clinical marker to evaluate efficiently the nutritional status of critically ill patients, which makes adequate calorie delivery a

*See also p. 127.

Key Words: malnutrition; nitrogen balance; protein loss; open abdomen; enteral feeding

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difficult task. Many studies have shown the poor correlation between prescribed calorie requirements and the actual calorie delivery (5). Nutrition, in the presence of a functional gut, should be administered by the enteral route whenever possible, but enteral nutrition is not without any problems. Mentec et al. (6) showed that gastric intolerance was associated with an increased risk for pneumonia, longer intensive care stay, and increased risk of death, and Woodcock et al. (7), when comparing enteral nutrition with parenteral nutrition, found the in-hospital mortality in the nonrandomized patients in the enteral nutrition group was significantly higher. The best way to adequately deliver enough calories to the critically ill is still subject of debate.

Dr. Cheatham and colleagues (1) enrolled 56 patients in their study (37 open and 19 closed), with only 25 patients (20 vs. 5 patients) completing the entire 5 days of the protocol. They found the average cumulative calorie intake for the first 5 days was only 45% in the open group vs. 72% in the closed group, which is not surprising because gastric intolerance is not uncommon in the first days of illness, nor are long interruptions of enteral feeding for procedural or surgical intervention, as stated by the authors. Another explanation for this relatively poor result in the open group is the loss of protein via the abdominal compartment. The authors measured the urinary urea nitrogen concentration (UUN) via a 24-hr urine collection for both groups of patients on days 1, 3, and 5 and then calculated the NB (nitrogen intake − (UUN + 4)) on those days. They also measured in the open group the nitrogen concentration of the abdominal fluids. They found a rather constant nitrogen loss of 1.9 ± 1.1 g/L of abdominal fluid loss. The authors then incorporated this loss of protein from the open group in the traditional NB equation and found that, on average, the traditional NB formula underestimates nitrogen loss and overestimates the adequacy of protein administration.

Before commenting on these finding, we could ponder whether the NB is a valid measurement of protein requirement.

The NB is calculated by subtracting nitrogen excretion from nitrogen intake. Nitrogen output includes measurement of urinary losses (urea predominantly), stool losses, integumental losses (skin, hair, and sweat), body fluid losses (ascites, chest drains, and gastrointestinal drainage), and nonprotein nitrogen losses (8). In most studies, only UUN is measured and a constant to account for all other sources of loss not measured: 4 g of nitrogen per day (8) is added. Another formula often used is multiplying the UUN by 1.25 to account for the unmeasured urinary components (the product often defined as total urea nitrogen [TUN]) and to add 2 g for the remaining sources of loss. These variations lead to problems in interpreting the NB.

Konstantinides et al. (9) showed that measuring the UUN is too insensitive for calculating the NB in surgical patients. They measured both TUN and UUN and calculated NB by using UUN as an estimate of TUN (1.25 × UUN) and TUN. In their results, they found a variability ranging between 12% to 112%, or variations of up to 12 g/day if UUN was used. It is therefore clear that the use of the correction factor 1.25 is not consistent in correcting for non–urea nitrogen components. The technology, however, for measuring TUN is often not available in most hospitals, and measuring UUN is much easier. Dr. Cheatham and colleagues (1) are suggesting to revise one of the traditional nitrogen equations into the following formula: nitrogen intake minus (UUN + 4 + 2 × abdominal fluid output in liters). Although in this group of patients the authors have clearly demonstrated that protein requirements were underestimated if not accounted for, it is flawed in that the constant, 4, already accounts for a part (although minimal) of all other sources of nitrogen loss.

Other problems of the NB are the increasing rates of excretion seen with increasing intakes of nitrogen and energy, the variability in how researchers express nitrogen losses, and the effect of the labile nitrogen pool on nitrogen excretion. Therefore, we should be cautious in interpreting the results from NB calculations. If we aim for a positive NB, Twyman et al. (10) showed that in achieving this goal in some of their patients, the daily protein intake required was 2.2 g/kg, subsequently leading to increased blood urea nitrogen and serum glucose levels, the latter being associated with increased morbidity and mortality.

Protein catabolism will continue regardless of intake, and negative balance is unavoidable. Malnutrition in the critically ill should be avoided at all costs for reasons stated previously. Ultimately, an ideal clinical marker of the nutritional status is not available. The reference method is still indirect calorimetry but is expensive, time consuming, not widely available, and not without limits. A rather pragmatic approach for estimating energy requirements (25–30 $kcal \cdot kg^{-1} \cdot day^{-1}$ in men, 20–25 $kcal \cdot kg^{-1} \cdot day^{-1}$ of nonprotein calories and 1.2–1.5 $g \cdot kg^{-1} \cdot day^{-1}$up to 1.8 $g \cdot kg^{-1} \cdot day^{-1}$day of proteins) is easy and still widely accepted.

Dr. Cheatham and colleagues (1) have demonstrated how difficult it is to deliver adequate nutrition to the critically ill and emphasized the need to account for protein loss via the abdominal vacuum dressing in patients with open abdomens. Although reservations remain regarding the accuracy of NB, it may well provide a better estimate of protein loss in this particular group of patients.

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Tracheostomy: May the truth be out there?*

Tracheostomy is a common procedure within intensive care units (ICU), and about 10% of critically ill patients who require mechanical ventilation will have a tracheostomy performed (1). The introduction into clinical practice of percutaneous dilational tracheostomy techniques, combined with the fact that the use of tracheostomy theoretically allows transfer of patients to the ward or to long-term ventilation units (2), may explain the more frequent and earlier use of tracheostomy during the last decades either in trauma or nontrauma patients, as observed by Cox et al. (3) in a recent issue of *Critical Care Medicine*. Despite this common practice of tracheostomy for several decades, only a very few studies have demonstrated a potential benefit of this procedure. Although some authors observed physiologic benefits in terms of respiratory mechanics in selected subgroups of patients (4–6), these results were absent in other studies (7, 8). In fact, most observational cohort studies have observed increased ventilation duration and intensive care length of stay for tracheostomized patients (9).

Although >270 studies were published about tracheostomy performance within the ICU during the last 5 yrs (PubMed database, keywords *tracheostomy* AND *intensive care*), they were mainly dedicated to the technical aspects of the procedure. Major issues remain unanswered, including which patients with acute respiratory failure should have a tracheostomy or when it should be performed.

The placement of tracheostomy is commonly thought to allow a more secure and manageable airway, better communication, earlier and safer enteral feeding, and overall better nursing management of the patient. Tracheostomy was also considered to enhance patients' comfort by removing a major irritant to the patient, that is, the presence of a noxious stimulus in the pharyngeal area (i.e., the orotracheal tube). Until 2005, this topic was only investigated from the physicians' or the nurses' points of view (10). The study by Nieszkowska and colleagues in a recent issue of *Critical Care Medicine* demonstrated that the procedure may improve patients' comfort, while reducing sedation needs (11).

Whereas the current literature mainly analyzed data derived from small randomized groups or selected cohorts of patients, the study in this issue of *Critical Care Medicine* by Dr. Clec'h and colleagues (12) is important as it provides us valuable data about the controversial topic represented by the impact of tracheostomy on outcome. This prospective observational study was conducted using a large French multiple-center database (OUTCOMEREA) that has already been used in several articles (13). The authors aimed to analyze the impact of tracheostomy on mortality, in unselected patients admitted to different French ICUs. To reduce bias, the exposed and control groups were matched using two propensity (to receive a tracheostomy) scores, one derived from a critical care database and the other using variables proposed by experts in a Delphi process (14). More than 160 tracheostomized patients were compared with 572 and 422 control patients. The authors concluded that tracheostomy had no impact on survival in unselected ICU patients and was actually associated with increased risk of post-ICU mortality. The discussion section of their manuscript clearly details the potential confounding factors and methodological biases of their approach. With regard to the impact on post-ICU mortality, the conclusion that it is increased in the presence of tracheostomy has no problems with lack of precision, whereas odds ratios are clearly bounded far away from 1.0 in both models. However, we are not so protected from bias about the impact on final outcome, whereas the propensity scores were derived as probabilities of getting a tracheostomy. The relevant propensity for this question will be the probability of having a tracheostomy still in place upon transfer out of the ICU while free from mechanical ventilation. Although it is plausible that the risk factors for this state are similar to those of getting a tracheostomy in the first place, it is also plausible that different risk factors are involved and that the authors have failed to control for their confounding effects. It may simply be the fact that the patients who are doing poorly in a number of ways (increased severity on admission, numerous adverse events, etc) are precisely those who will still have their tracheostomies kept in place when transferred outside the ICU. It would then not be surprising that they subsequently experience higher mortality.

It would seem rather false to argue that tracheostomy generates various important complications, as compared with data from the 1980s medical literature (15). Several recent studies using percutaneous techniques demonstrated a very few major complications, and one should also question whether they are in fact more frequent than what may be encountered while using "conventional" endotracheal intubation solely (16). However, what is important is not that tracheostomy benefits don't clearly outweigh its risks, but rather the fact that these potential benefits are still not yet clearly identified (just as its real indications)! Moreover, the study by Cox and colleagues (3) also demonstrated that although tracheostomy indications were more frequent, the overall number of dependent patients also increased.

***See also p. 132.**

Key Words: intensive care; outcome; tracheostomy; ventilatory assistance; weaning

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The remaining issue is still identifying which patients will benefit from tracheostomy performance in the ICU. First, one should keep in mind that we must avoid performing early tracheostomy in patients who may have a simple subsequent weaning process. Second, we should not focus on patients who are encountering very difficult weaning (many extubation attempts), as in these cases tracheostomy should be performed because everything else has failed. What is really important and might influence tracheostomy performance in the ICU should be the clinician's ability to identify as early as possible the patients who will encounter difficult or prolonged weaning.

We should never forget that "the ICU is not an isolated environment, and that the impact of our decisions on future care needs, quality of life, and family can be overwhelming" (17). For any patient with a high risk of death, the clinician should have clear communication with the patient (if possible) and family regarding treatment preferences. This conversation is necessary to avoid unwanted and potentially prolonged treatment. When confronted with extended mechanical ventilation and associated care, a significant proportion of patients would accept this care only for an improved prognosis. The major limitation of the already published studies is the lack of a clear identifying marker as to who will need prolonged ventilation (18); thus, tracheostomy may still be discussed individually. The present study provides us some valuable data about the fact that "*the truth* [about tracheostomy] *may be out there . . .*"

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One small step for man . . .*

Each year, more than five million Americans are discharged alive from intensive care following an episode of critical illness (1). With the aging of the population and advances in critical care, this number is expected to grow exponentially over the coming years (2). At this volume, any unwanted lingering consequences of either critical illness or intensive care unit (ICU) interventions will be writ large across the entire public health of a given community.

As greater numbers of patients survive intensive care, it is becoming increasingly evident that quality of life after critical illness is not always optimal, especially in the domain of physical function (3–9). For instance, survivors of the acute respiratory distress syndrome have persistent physical disability as many as 2 yrs after discharge from the ICU (6, 7, 9). Muscle wasting and weakness are commonly reported, and objective measures of physical function, such as the distance walked in 6 mins, are frequently well below population norms. The consequences of these acquired deficits in physical function may be quite profound, leading to disability, social isolation, institutionalization, and significant economic burden for caregivers and society (10).

In medical school, I remember learning the maxim, "For every day down, it takes two to get back up," in reference to the debilitation that many hospitalized patients experience due, in part, to resting in bed. Although other factors, such as illness severity and exposure to corticosteroids, no doubt play a role, prolonged bed rest has well-known adverse physiologic effects, including cardiovascular deconditioning and skeletal muscle atrophy (11). In healthy volunteers, a mere 14 days of bed rest can produce a 1.7% decrease in lean body mass, with a 4.1% decrease in lean thigh mass (12). After 6 wks of bed rest, 25–30% of quadriceps strength is lost (13). Because of the nature of critical illness and the modalities used to manage it, prolonged bed rest seems to be the rule in the ICU. Physical rehabilitation, which has the potential to restore lost function (8), is traditionally not started until after ICU discharge. Given what is known about the effects of bed rest, what if rehabilitation could be started earlier, such as while the patient is still in the ICU, when prevention or at least mitigation of ICU-acquired debilitation might be possible? Would this be feasible and, if so, would it be safe? Would it get patients back on their feet more quickly?

It is precisely these questions that the study by Ms. Bailey and colleagues (14), in this issue of *Critical Care Medicine*, begins to address. Theirs is an innovative study evaluating the feasibility and safety of early physical activity in 103 patients with respiratory failure who required >4 days of mechanical ventilation. Age ranged from 18 to 91 yrs, with a mean (SD) of 62.5 (15.5) years. "Early" was defined as the interval starting with initial physiologic stabilization and ending with ICU discharge. Activity events were sitting on the edge of the bed, sitting in a chair, and ambulating with or without assistance, with the overall goal for each subject to ambulate >100 feet before ICU discharge. Each activity event required the participation of a physical therapist, respiratory therapist, nurse, and critical care technician. The authors attempted to progressively increase a subject's activity level with each subsequent twice-daily physical therapy session. Before initiating an activity, subjects had to meet specific neurologic, circulatory, and respiratory stability criteria. Specifically, subjects had to be awake, not orthostatic or on catecholamine drips, and on relatively low ventilator settings (F_{IO_2} ≤0.6 and positive end-expiratory pressure ≤10 cm H_2O). When needed, a 30-min pre- and postactivity rest period with assist-control ventilation was provided. Careful attention was paid to issues of patient safety, adverse events, and feasibility.

If a picture was ever worth a thousand words, Figure 1, which shows a patient ambulating *while on assist control ventilation*, would have to be it. Remarkably, nearly 70% of survivors were able to ambulate >100 feet before ICU discharge. Since the ability to ambulate is often an important determinant of a patient's ability to return to home, this finding is quite impressive. Participation in activity events was not limited by advanced age, greater numbers of comorbidities, or the presence of an endotracheal tube. The authors were able to provide early activity without hiring additional personnel or increasing staff workload but did so through unit reorganization to make patient activity a priority of care. Adverse events were infrequent, were easily remedied, and did not result in extubation, complications that required additional therapy, extra cost, or longer length of stay.

Nearly all of the subjects were previously admitted to another ICU at the same institution and subsequently transferred to the study ICU. That is not to say that subjects were no longer acutely ill or that this was a long-term acute care setting. Acute Physiology and Chronic Health Evaluation II scores were relatively high on admission to the study ICU, translating to a predicted mortality of ~25%, and mean duration of mechanical ventilation was less than typically seen in a long-term acute care setting. The key observation is that while patients remained critically ill, activity did not start until patients met the established criteria for physiologic stability. This is not a limitation of the study but a word of caution to those who might try to extend these findings to other ICU patients, especially those still within the initial days of their critical illness. The majority of these subjects were medical patients, with smaller proportions being admitted for trauma or surgical diagnoses. As such, it is not clear if this approach would be successful in other critically ill patient

***See also p. 139.**

Key Words: critical illness; respiratory failure; rehabilitation; mobility

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groups. Because there was no control group, the authors were unable to determine whether early activity actually improves either short- or long-term outcomes.

Some of the most important advances in medicine come from challenging existing paradigms and thinking outside the box, something which early activity appears to do. Clearly this is only the beginning and there is much more to be learned. By demonstrating safety and feasibility, the authors have taken an important first step toward conducting a controlled trial of early activity. With this "one small step for man," we may someday see early activity as an integral part of the care of critically ill patients.

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Tools that we use: If you can't measure it, you can't manage it*

Even as critical care medicine focuses on the exciting, futuristic era of genomics and complexity theory, basic, boring, routine physiologic measurements still remain fundamental to the diagnosis and care of critically ill patients. Inaccurate measurements of the simple things, like temperature and blood pressure, can lead to misdiagnoses and poor clinical decision making and result in unintended and undesirable effects on patient care and outcomes. Whether it is a proper size blood pressure cuff, correctly zeroed pressure transducer, correctly placed pulse oximeter strip, or accurate thermometer, an essential part of critical care education and practice is understanding the tools that we rely on, recognizing their flaws and limitations, and being able to troubleshoot them when the results they provide seem inconsistent with our clinical impressions.

The measurement of body temperature, its importance as a cardinal vital sign, and its role in the diagnosis and treatment of disease dates from antiquity (1). In critically ill patients, temperature is routinely and frequently measured, and deviations from normal—either high or low—are concerning. Although measuring body temperature seems simple and straightforward, in reality, very different results are obtained depending on how and where measurements are made. The many techniques available to measure temperature include touching a patient's skin; skin strips; glass and electronic thermometers for measuring oral, rectal, or axillary temperatures; esophageal probes and tympanic membrane wires used during surgery for patients under general anesthesia; infrared ear probes; indwelling Foley catheters containing thermistors to measure bladder urine temperature; and finally, pulmonary artery (PA) flotation catheters that have a thermistor bead at the tip that measures core blood temperature. PA catheter measurements remain the gold standard for temperature measurement in intensive care unit (ICU) patients against which all other methods of measurement are compared (2, 3).

In the current study by Dr. Moran and colleagues (4) reported in this issue of *Critical Care Medicine*, 110 ICU patients had simultaneous temperature measurements made repeatedly at different body sites for 5 days, including both axillae using glass thermometers, both ears using infrared probes set on the devices' "core" temperature setting, PA blood temperatures when a PA catheter was present, and bladder urine temperatures

*See also p. 155.

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when a temperature-measuring Foley catheter was in place. This study differs from previous comparable studies in two important ways. First, the number of prospectively collected measurements was much larger than in any previous ICU temperature measurement study and included multiple, repeated measurements made over time. Second, this large and complex data set provided the authors the opportunity to apply rigorous and sophisticated statistical analysis methodology and to incorporate techniques not previously applied to this type of device-comparison study.

Since 1986, the usual statistical technique used to determine how closely a test device agrees with a gold-standard device has been Bland–Altman (5) measures of agreement. The complexity of this current data set, which includes measurements taken by different observers, unbalanced data, and covariates that might affect the differences between measurement methods, required a more sophisticated analysis. The long, detailed, and dense description of the statistical methods used here—although unfamiliar to many readers of *Critical Care Medicine* and requiring some effort to struggle through—is important, and I believe that intensivists need to become acquainted with these techniques. This article provides a state-of-the-art review of relevant statistical methodology, and it should be used as a reference for further research that compares new measuring devices to gold standards.

One crucial finding of this study that deserves to be emphasized is that, once again, infrared ear probe measurements were inaccurate when compared to PA catheter measurements. Infrared ear thermometers are still widely used in many ICUs due to their ease of use, noninvasiveness, speed, and infection control. However, as noted by these authors, multiple ICU studies have raised concerns regarding lack of agreement between measurements made by these devices and by PA catheters (2, 6–8). Dr. Moran and colleagues (4) diplomatically conclude "that the place of tympanic membrane measurements as accurate reflections of core temperature in the critically ill is not established." After 15 yrs of accumulated evidence, I would be pithier: user, beware.

Does it really matter if a temperature measurement is inaccurate? Does half a degree centigrade in either direction really make a difference in clinical practice? Of course it does! Abnormal temperature is one of the criteria used to determine whether a patient has systemic inflammatory response syndrome/sepsis (9) and is a component of major ICU outcome prediction models, such as the Acute Physiology and Chronic Health Evaluation (10). On a practical level, if a device reads erroneously high, which may only be the difference between 37.9° and 38.4° centigrade, a patient may be mislabeled as having a "fever spike." In ICU patients, a fever spike often leads to an explosion of activity in search of infectious and noninfectious causes, including blood tests, blood and other body fluid cultures, imaging studies that may entail the risk of transport out of the ICU, a potential for invasive drainage of body cavities, and all too often, the initiation or addition of empirical antimicrobials (3, 11)—all avoidable, and all exposing patients to avoidable iatrogenic risk and significant cost.

This study reaffirms that the best non-PA catheter method of measuring temperature in ICU patients remains a temperature-measuring Foley catheter. Although obviously less invasive than a PA catheter, this still requires some invasiveness and the correct catheter and is not cheap. However, I agree with the authors that this seems to be the most consistently accurate method of measuring core body temperature in the critically ill at this time.

An oft-quoted aphorism commonly used in management and quality-improvement circles is that "if you cannot measure it, you cannot manage it." This wisdom applies just as well to the bedside hands-on management of critically ill patients. Consistently accurate and trustworthy measurements—and devices—remain fundamental and essential to providing the highest-quality patient care in the ICU.

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Safety culture: Is the "unit" the right "unit of analysis"?*

All healthcare organizations strive to be "high-reliability organizations," with excellent outcomes and very low rates of failure, despite high intrinsic hazard and high throughput. An essential element of being a high-reliability organization is having a strong "culture of safety" (1–5). Many research groups have been trying to understand and measure what safety culture really means, particularly in the special context of hospital-based care (6–11). In this issue of *Critical Care Medicine*, Dr. Huang and colleagues (12) extend our knowledge about safety culture in the specific high-hazard setting of intensive care units (ICUs), focusing attention primarily on the comparison of different ICUs within a single hospital.

The article by Dr. Huang and colleagues (12) is a continuation of a line of research that measures perceptions of safety culture, or safety climate, as assessed through surveys of individual workers. The survey the authors used started first in aviation with the Cockpit Management Attitudes Questionnaire, and has since been extended into healthcare (13, 14). Perhaps the most important contribution of this article is to establish, for the first time, that safety climate can vary among units of similar type within a given institution. In particular, the authors found that safety climate differed among the four ICUs studied inside the same hospital. Particularly noteworthy (although not fully articulated by the authors) is that one unit's personnel had collective safety climate scores that were distinctly lower than those from other units on five out of the six factors measured.

One interpretation of these data is that there is a poor-performing ICU that needs to be fixed. However, the authors point out that their data do not suggest inter-unit variation in outcomes. On the surface, this unit has good results—it takes care of many elderly patients, conducts significant interventions, but has a lower actual-to-expected mortality rate than the other units. The outcome measures examined are limited to mortality and do not include measures of morbidity that might have been useful in further delineating the relationship between safety climate and outcome. In addition, there may have been patient- and hospital-level variables that were not taken into account, potentially confounding the results. Further, the study may not be sensitive enough to detect a climate-outcome relationship with only a few units sampled (15), and the small size of the study makes it difficult to determine whether the differences found in safety culture between units were due to statistical fluctuations or to true differences.

Another interpretation, equally plausible and consistent with findings from Anita Tucker and Amy Edmonson (16), is that healthcare workers are incredibly resourceful and resilient, working exceptionally hard to achieve good results, even when they encounter major systemic problems in their work units or institutions. Lacking demonstrable proof of poor outcomes, worker efforts to raise patient safety concerns often fail to motivate management intervention, leaving workers to address problems themselves. The workarounds they employ to achieve positive results further hide the need for deeper problem solving and systemic change. Coping with repeated problems without management support for necessary changes can also be incredibly frustrating. Perhaps that frustration manifests itself in lower safety climate scores.

Dr. Huang and colleagues (12) infer from their findings that "safety culture should be assessed at the ICU level, rather than at the hospital level." We agree that one cannot assume that all units in an institution are the same. However, this does not mean that the ICU unit is the "right" level of analysis or that it is sufficient to understand safety climate only at that level. For example, the four units studied all demonstrate seemingly low rates of positive response. Interpreting internal comparisons without external benchmarks could cause a hospital to focus only on its weakest ICU and to miss a potential deficit affecting multiple departments or the hospital as a whole. Rather, as this example suggests, we believe that the authors' finding highlights the need to explore *all* units of analysis in complementary fashion. A single hospital may well have ICUs with different safety climates, but the hospital, composed of many units, still has an aggregate climate that may differ from the aggregate of other hospitals. Further, as the authors point out, within each work unit there may be subcultures, work teams, or individuals that differ. Thus, assessing safety culture at various levels of aggregation, including the aggregated hospital level, is important, both in terms of linking survey data to ethnographic data and in defining the relationship between safety climate and patient safety outcomes.

Dr. Huang and colleagues (12) correctly suggest that it is important not only to assess the mean score for any factor but also the variation across individuals for each factor. High-reliability organization theory indicates that to achieve high reliability, it is important to have a safety culture that is not just strongly positive but that is also highly uniform. In other words, it is not enough for many people to espouse safety principles strongly and enact the appropriate behaviors—nearly *everyone* has to do this nearly *all the time*. Dr. Huang and colleagues (12) use a numerical aggregation system in which, to classify individuals as having given a "positive response" for a specific factor of safety culture, they need to have provided positive answers on nearly all questions comprising that factor. An alternative method used by our own group is to measure the rate of "problematic response" to specific questions and groups of questions (representing factors identified by psychometric analysis) at various levels of aggregations of workers, from single individuals to clusters, by job-type or job-level, and up to entire institutions. However, no one knows the optimum way

***See also p. 165.**

Key Words: safety culture; safety climate; survey research; patient safety

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to assess the strength and uniformity of safety culture from survey data. Continued effort is needed to yield consensus on the most effective way to do so and to present such data to others.

Although measurement differences make data hard to compare directly between studies, the general theme is the same: evidence from different surveys in different places all suggest that there is *not* a highly uniform, positive safety climate of hospital workers. Although many workers answer positively in response to many questions, there is still a substantial rate of answers that is antithetical to the ideal safety culture. Moreover, Dr. Huang and colleagues (12) have shown, as we have, that members of other high-hazard industries (commercial or military pilots) give answers that are much more positive than do healthcare workers when asked nearly identical questions (17, 18).

Another important contribution of this article is the finding that unit directors have different perceptions of the attitudes about patient safety held by their coworkers than those of the workers themselves. The authors found, as we have at the hospital level, that managers' perceptions were significantly more positive than those of front-line personnel (19). If managers and executives do not accurately perceive the hazards at the front lines, they will not be able to address the underlying systems that create these hazards. The persistence of this finding signals a clear need to intervene in ways that help managers to perceive more accurately the risks and faults occurring "at the sharp end" so that they can more effectively work with their subordinates to identify, prioritize, and mitigate patient safety concerns.

Dr. Huang and colleagues (12) also found here, as others have elsewhere (20, 21), that nurses were on the whole less positive about the climate of their work environment than physicians. One might expect the perceptions of physicians and nurses to be associated with different outcomes because of their different expertise and work responsibilities. The more negative outlook of nurses could have a greater negative effect on the safety and quality of patient care because nurses make up the majority of personnel in ICUs. On the other hand, physicians write the orders and wield the most hazardous technologies. Differences in the way doctors and nurses perceive their environment may indicate general communication and coordination difficulties. In addition, understanding the reasons for these differences will be important to develop appropriate interventions. Nurses may be more negative because they spend more time in patient care and therefore observe more problems. It could also be that nurses are treated more poorly by the institutional hierarchy than are their physician counterparts. Nurses' lower relative mean scores regarding working conditions and perceptions of management compared with those regarding teamwork climate and safety climate here suggest that poor treatment may be the larger contributor. Clearly, more research in this area is needed to address this issue.

The authors' finding suggests another, perhaps more important, question—that is, *why* or *how* do units of similar type within the same hospital differ significantly? To answer this question, we need a multifaceted approach: not only do we need more and improved surveys, but we also need studies that can provide more details about the structure and function of the units than can be gleaned from written surveys. Additional research is needed that uses qualitative, field-based methods, including ethnography and action research associated with testing improvement interventions to understand what actually transpires in the work environment that can account for the survey findings we observe. Moreover, what people *say* about their workplace culture may not really describe the culture they and their coworkers actually enact. Only by performing detailed observations of the same units for which there are good survey data can we begin to answer such questions. Further, we need outcome measures that can more sensitively measure the health outcomes of patients, such as the Patient Safety Indicators, recently developed by the Agency for Healthcare Research and Quality (AHRQ) (22). Finally, we need to study several institutions, not just one, to promote the generalizability of the results.

In attempting to assess the role of safety culture in determining patient safety in units, institutions, and in healthcare as a whole, our research methods, units of analysis, and analytic techniques must improve and expand if we are to deepen our understanding sufficiently to answer the questions we seek to address. This study represents a good beginning in examining the patient safety climate within ICU units of a hospital; however, in the end, it raises more questions than it answers. Thus, the work of Dr. Huang and colleagues (12) reminds us that Winston Churchill's famous saying (in 1942 after the second battle of El Alamein) is equally applicable regarding the study of safety culture: "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

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Relation between acute kidney injury and multiple-organ failure: The chicken and the egg question*

Acute kidney injury (AKI) is defined as a rapid decline in glomerular filtration rate (1). The injury of an other organ might lead to kidney injury. Patients with liver failure, for example, might develop the hepatorenal syndrome. High-pressure ventilation, leading to damage of the alveolar membrane, can also induce AKI (2). There is thus no question that AKI can develop as a cause of the damage in other organs.

Inversely, AKI by itself might add to morbidity of intensive care unit patients. Whereas, for a long time, it was accepted that patients with AKI died with, but not of, their failing kidneys, we now understand that the kidney is more than a passive bystander; it is, in contrast, the driving force of a detrimental spiral.

In this issue of *Critical Care Medicine*, Dr. Vieira and colleagues (3) point to an important clinical observation whereby the injured kidneys play an important role in the delayed recovery of lung injury, as judged by the inability for weaning from mechanical ventilation.

***See also p. 184.**

Key Words: acute kidney injury; acute renal failure; sepsis; multiple organ failure; mechanical ventilation

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Is This Retrospective Study Representative?

In the international consensus RIFLE classification (1, 4), patients are categorized as being at R(isk), having ongoing I(njury), or having F(ailure) of their kidneys based on alterations in serum creatinine or urine output, whereas Dr. Vieira and colleagues (3) use a fixed serum creatinine for definition of AKI. Nevertheless, the "control" patients of Dr. Vieira and colleagues (3) are most likely in the R stage of RIFLE, whereas the "AKI patients" were in stage I or F. Indeed, most AKI patients have a 100% increase in serum creatinine level or oliguria, thus complying with stage I or F, whereas controls had a mean increase in serum creatinine of $<50\%$. For the clinical intensivist, it is important to realize that the criterion of a serum creatinine of >1.5 mg%, corresponds with an already important renal insufficiency, and most of the patients in the control group also had some degree of kidney injury. Of note, as in other reports (5), there was an increasing mortality with increasing severity of AKI. Thus, although the RIFLE criteria were not formally applied, it appears that "in spirit," patients were dichotomized in a group of R and a group of I or F patients. The definition of the condition AKI is thus consistent with RIFLE.

Is the Kidney an Innocent Bystander in Multiple Organ Dysfunction?

In the article by Dr. Vieira and colleagues (3), weaning from mechanical ventilation was more difficult in patients with AKI. What are potential explanations for this observation?

It is tempting to state that, inversely, AKI was due to prolonged mechanical ventilation. This seems an unlikely explanation because, at admission to the intensive care unit, AKI patients had a comparable degree of respiratory distress but higher creatinine values, so AKI was already present from the beginning. This fits with the clinical observations of Van Biesen et al. (6), that at the first day of sepsis, and even before creatinine increased, patients who developed AKI later on had a higher F_{IO_2} need and more pulmonary hypertension. Levy et al. (7) demonstrated the subsequent development of new-onset respiratory failure, sepsis, and bleeding in patients who developed AKI after contrast administration. A 20% increase in serum creatinine after cardiac surgery was associated with other organ dysfunction in 79.3% of patients (8). Patients with AKI show marked derangements of oxidative stress and inflammation, correlating with increased mortality (9), indicating that AKI might be a pro-

motor or at least amplifier of systemic inflammatory response.

In a rat model of AKI induced by ischemia reperfusion, Rabb et al. (10) found up-regulation of aquaporin 5 and sodium channels in the lung, leading to pulmonary capillary leak and acute respiratory distress syndrome, and Kelly (11) found increased levels of intercellular adhesion molecule-1 in the heart associated with a decreased cardiac function and cardiac dilation. All these data point to the kidney as being the promotor at a distance of organ dysfunction.

It can also be hypothesized that prolonged weaning in AKI was due to hypervolemia. Indeed, there was no formal evaluation of volume status, and oliguria was a predictor of prolonged weaning, which is compatible with, but not proof of, the volume theory. There is evidence that a liberal fluid administration causes more and prolonged need for mechanical ventilation in intensive care unit patients (12). Remarkably enough, a liberal fluid strategy did not reduce the prevalence of AKI, but in the fluid-restricted patients, there was a higher need for dialysis. Van Biesen et al. (6) found that patients who developed AKI later on had already a higher central venous pressure and F_{IO_2} at the first day, indicating that kidney and lung injury were concomitant processes. In addition, although patients with a spontaneous nonoliguric AKI have a better prognosis than those with oliguria (1), it is also clear that the conversion of oliguric to a nonoliguric state does not improve the outcome of the patient (13). This suggests that the difference in outcome between oliguric and nonoliguric patients is not so much related to differences in volume control but rather that oliguric patients have a different (more severe?) form of AKI. Oliguric AKI is mostly related to sepsis or multiple organ dysfunction syndrome, whereas polyuric AKI is mostly related to toxic causes, which might explain the difference (1). Also, in the study by Dr. Vieira and colleagues (3), it is remarkable that the AKI patients had more sepsis and that presence of sepsis was related to weaning duration in the univariate but not in the multivariate analysis. This points to a substantial collinearity between oliguria and sepsis. Moreover, the relation between AKI and duration of weaning was also present in nonoliguric patients, adding again to the theory that the kidney injury by itself, and not volume status, was the causative factor.

As is admitted by the authors, it might be that prolonged weaning was caused by ventilator-associated pneumonia, which was not evaluated in this study. Even if more ventilator-associated pneumonia was present in the AKI patients, it is of note to realize that decreased leukocyte function is one of the major dysfunctions of the uremic syndrome, once again adding support to the proactive role of the injured kidney in the development and maintenance of multiple organ dysfunction syndrome.

Conclusions

There is increasing evidence that substantial cross-talk between different organs is present after organ injury and that AKI by itself can cause deterioration of other organ functions (6, 10). Recognition that even small changes in glomerular filtration rate may have significant effects on outcomes has prompted the proposal of new definitions of AKI (14, 15).

For the clinician, this implies that all forms of organ damage should be avoided as much as possible and as early as possible: prevention is better than cure. On the other hand, once AKI has developed, a liberal fluid approach will not save the kidney but might lead to longer duration of mechanical ventilation (12).

For prevention of AKI, a high vigilance for AKI is needed, and sequential serum creatinine determinations and close follow-up of urinary output according to RIFLE criteria are needed (15) so that patients can already be detected at earlier stages of AKI. Of note, this demands the knowledge of serum creatinine before admission to the intensive care unit.

From the beginning, and even at mild decreases of glomerular filtration rate, dosage and selection of medications should be adapted and nephrotoxic medications and procedures avoided.

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Are we ready for MEDS in the ED?*

More than any other condition, sepsis dominates modern critical care. At its most severe, when organ failure and shock are present, it presents the twin challenges of providing organ support and of diagnosing and treating the underlying infection. Once a patient reaches the intensive care unit (ICU), the costs of care are substantial and the mortality is high (1). From a societal perspective, although current estimates of the incidence of severe sepsis vary (66 to 200 per 100,000 population) (2, 3), there is no doubt that the associated burden is a major one, on a par with other, better recognized health issues such as cancer and ischemic heart disease (4). It is largely because of this that so much critical care research effort is directed at sepsis, ranging from the laboratory bench to multi–million-dollar, industry-sponsored clinical trials. It is also part of the justification behind the Surviving Sepsis Campaign, which aims to improve the outcomes of patients with severe sepsis through earlier recognition and better process of care, in line with the evidence from recent clinical trials.

However, although this is a familiar landscape to critical care clinicians, the ICU perspective avoids a fundamental truth: the clinically defined syndrome of sepsis merely represents a certain threshold point in the body's response to infection. The moment of infection, when the initial breach of the body's defenses occurs, starting the series of interactions between host genetic and defense factors and infecting organism virulence factors that lead to injury and perhaps ultimately death, has already passed by the time a patient becomes "septic." Moreover, the critical care concept of severe sepsis, reached when signs of end-organ dysfunction begin to appear, represents a point some considerable way into this process, by which time significant tissue damage has already occurred, and the probable mortality is therefore high. For most patients with sepsis, although, the first point of hospital contact is not the ICU, but either the hospital ward or the emergency department (ED), where there are frequently opportunities to intervene and to improve the likely outcome that are unfortunately missed (5, 6).

It is against this background that Dr. Shapiro and colleagues (7), in this issue of *Critical Care Medicine*, provide further detail about the use of the Mortality in Emergency Department Sepsis (MEDS) score, which they first introduced in this journal in 2003 (8). The MEDS score was originally derived mathematically from a large database of ED patients with suspected sepsis, collected predominantly in the year 2000, with the purpose of allowing risk stratification for death to be performed in patients with suspected sepsis while still in the ED. The nine components of the score are readily available basic clinical or laboratory variables, with a degree of weighting then attached to give a final score and risk assessment, and these have now been re-arranged in a PIRO (*P*redisposition, *I*nfection, *R*esponse, *O*rgan dysfunction) format. Interestingly, both lower respiratory tract infection and tachypnea are included as independent risk factors within the score.

The authors advance a number of additional arguments for the value of the MEDS approach. Apart from the obvious one that having information of this type about risk of death in the ED, before patients have deteriorated sufficiently to require ICU admission, is potentially a very valuable way of highlighting the need to act urgently to stabilize and even reverse the disease process while this is still possible, they also make the point that scores developed for the ICU perform less well in the ED. Indeed, there are obvious practical difficulties with scores such as APACHE that require data from the first 24 hrs of ICU admission for proper risk assignment. More importantly, they also suggest that risk stratification and better long-term prognostic information are valuable and influential in decision making among patients, surrogates, and caregivers in the ED context. They suggest that such decisions might include whether to assign novel (and expensive) therapies and how best to use scarce resources. In their original article (8), the authors used 28-day mortality as the end point but, in the current study, have extended this to examine the performance of the MEDS score at 1 yr. The five risk categories that they identify all show considerable increases in mortality for the population over 1 yr as compared with the original 28 days (very low risk, 7% 1 yr mortality; low risk, 20%; moderate risk, 37%; high risk, 64%; and very high risk, 80%), and examination of the Kaplan–Meier curves illustrates that there is substantial probability of further death accrual well beyond the 28-day period, with the curves only flattening after 100 days in the high- and very high–risk groups. This pattern is somewhat different from the available long-term outcome data for patients with severe sepsis, for whom 1-yr mortality rates are more of the order of 40–50% (9, 10). Why should there be such an apparent difference? One possible reason is that only 38% of the patients included in the MEDS derivation database actually had sepsis or severe sepsis, and presumably, not all were admitted to the ICU or selected for continuing active treatment, as would be the case in a sepsis research study database. Indeed, the initial criterion for inclusion in the derivation data set was that a blood culture should be taken either in the ED or within 3 hrs of reaching the hospital floor, so the population is perhaps more accurately described as that in which the physician suspected infection sufficiently to take a blood culture, rather than a true sepsis population. The late death rate also suggests an interaction with other comorbidities, which might perhaps be exclusion criteria in a clinical sepsis study. Another possibility relates to the age of the data used to derive the MEDS score. Although the methodologic approach used for the original development process was robust, and the assessment of the score against 1-yr mortality data has been performed meticulously, all the data used

***See also p. 192.**

Key Words: sepsis; severity of illness; risk stratification; mortality; outcome; prediction; critical care

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for these purposes are >5 yrs old and were collected before the introduction of many of the major recent therapeutic developments in the treatment of severe sepsis, and also before the drive to improve the process of care that underpins the Surviving Sepsis Campaign. As a consequence, it is not possible to know whether the actual numerical outcomes predicted by the different risk bands generated by the score would be valid today.

Whether these weaknesses matter depends ultimately on the use that is made of the score. If its purpose is to be a quick and easy method for ascribing broad categories of risk to patients in the ED, with the aim of ensuring rapid and effective treatment delivery, then this would be worthwhile whatever the precise risk estimates used. Even so, it would be interesting to know whether the MEDS score is any more useful in this respect than the approach of identifying the standard clinical markers for severe sepsis, including the serum lactate (which was not available in the original data set used to generate the MEDS score components), and then initiating effective treatment rapidly, as mandated by the Surviving Sepsis Campaign care bundles. If, however, the MEDS score risk bands are to be used for the more testing task of helping to inform patients and carers in their decision making, then it is extremely important to know that the absolute risk numbers are correct. To tell a patient shortly after arrival in the ED, at a time of great stress, that he or she has an 80% chance of being dead within the year might well color decisions about the value of aggressive treatment. Similarly, to use such information to decide whether to assign a new sepsis therapy, or not to assign it if the patient is in a low-risk band but otherwise fits the treatment criteria, also has major implications. Although there is a great attraction to a score that can be performed so rapidly, there is a requirement to know that the predictions are robust within the population of patients with sepsis who present to the ED today, especially because the score does not have the safety net of including a response to treatment over time. This is further underlined by the repeated finding that most scoring systems do not perform well in terms of predicting individual patient outcome when compared with physician judgment (11).

In reality, for the more ambitious uses of the MEDS score to be robust, more recent data are required, preferably collected in several institutions. This would then allow an understanding of the degree of change that has occurred against the year 2000 benchmark and of any recalibration of the score categories necessary to represent current reality. Nevertheless, the broad categories of risk may still hold true, and it remains extremely important to recognize that a patient is unwell, and to what degree, and to ask the question of whether infection might be the cause. The MEDS score is one way of doing this, and whether it ultimately proves a valuable addition to our approach to treating sepsis will depend on whether enough clinicians are willing to gain sufficient experience in using it to address the uncertainties highlighted above.

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Is the canary still singing?*

Beginning in the 1800s, canaries were commonly carried by coal miners to detect the presence of dangerous and highly lethal gases such as methane and carbon monoxide. Highly sensitive to the presence of these odorless and colorless gases, the canaries would cease singing and fall to the floor of their cage if the levels of these otherwise undetectable gases became excessive. Alerted to the potential for injury and death, the miners would then leave the mine quickly. Without such early warning, the presence of these gases would be known only when either an explosion occurred or the miners succumbed to the lack of oxygen. Today, the expression "canary in a coal mine" is used to refer to an indicator or event which serves as a warning that a potentially detrimental change has taken place and immediate intervention is mandated.

Beginning in the 1990s, elevated intraabdominal pressure (IAP) or "intraabdominal hypertension" (IAH) and the abdominal compartment syndrome (ACS), the development of IAP-induced organ failure, were rediscovered after 150 yrs of obscurity and neglect as significant causes of morbidity and mortality among the critically ill (1–3). As silent as coal mine gases, elevated IAP can easily go unrecognized until irreversible organ failure and even death has occurred. Undetectable by clinical examination alone, serial IAP monitoring has been widely advocated as the "canary in a coal mine" for IAH and ACS (1–5). Such monitoring is essential to diagnosing the presence of IAH, allowing rapid therapeutic interventions to be carried out before significant organ failure or death ensues (1, 3, 6–9).

IAH and ACS differentially affect every organ system of the body based on the severity and chronicity of the elevation in IAP. As a result, the potential effect of IAP on the perfusion and function of each organ system must always be considered during the resuscitation of any critically ill patient. Traditional pressure-based measurements of resuscitation adequacy such as central venous pressure have been demonstrated to be inaccurate and misleading in patients with IAH (10). Although recognizing the potential superiority of regional over global assessments of perfusion adequacy, Cheatham et al. (8) proposed that resuscitation of patients with IAH should be guided by the "abdominal perfusion pressure," calculated as mean arterial pressure minus IAP. Maintenance of this global marker of resuscitation adequacy of >60 mm Hg has been demonstrated by Malbrain et al (9). to be associated with a significantly increased survival from IAH and ACS. Nevertheless, accurate, sensitive, and clinically meaningful markers of regional perfusion adequacy remain the "holy grail" of shock resuscitation. Methods for evaluating the selective perfusion of IAP-sensitive indicator organs, such as gastric tonometry for the stomach and indocyanine green clearance for the liver, have been evaluated and bear further investigation (11). Until these and other as yet undiscovered monitoring technologies are widely available, however, serial IAP monitoring and resuscitation to an abdominal perfusion pressure of >60 mm Hg must continue to be considered the reference standards for treating IAH and ACS (3).

Just as a canary is highly sensitive to dangerous gases, the kidneys are well known to be highly sensitive to the presence of elevated IAP (6). An IAP of only 10 mm Hg (typical of a routine postlaparotomy patient) is associated with significantly reduced renal blood flow, and an IAP of >20 mm Hg is associated with an 11-fold increase in perioperative mortality (6). IAH has been identified as being the fourth–most important cause of renal impairment in critically ill postoperative patients (7). The importance of IAP on renal function has been further demonstrated by Ulyatt (12), who identified that renal perfusion pressure may be quantitated as mean arterial pressure minus *twice* the IAP. Given the marked susceptibility of the kidneys to IAP and the propensity of IAH patients to demonstrate impaired renal function, an accurate assessment of renal insufficiency in the face of early IAH would be of great clinical usefulness.

In this issue of *Critical Care Medicine*, Dr. Kirkpatrick and colleagues (13) present a novel application of renal ultrasound in a porcine model of IAH and ACS. They propose that calculation of the renal resistive index (RI), previously used primarily in the renal transplant patient, may represent a useful, noninvasive, organ-specific assessment of the early effect of IAH and ACS. RI was found to be linearly related to IAP throughout its clinically applicable range (0–60 mm Hg), with an abnormal RI of >0.7 correlating with an IAP of 12–15 mm Hg. This is consistent with the definition of IAH (IAP of ≥12 mm Hg) recently proposed by the World Society of the Abdominal Compartment Syndrome (WSACS) in their consensus guidelines (3). Thus, a noninvasively determined RI of >0.7 may represent a threshold above which more invasive IAP monitoring and abdominal perfusion pressure–based resuscitation may be indicated. Further, RI returned to normal values following resolution of IAH, highlighting its potential as both a diagnostic and resuscitative marker of perfusion adequacy. The authors postulate that there may also be a threshold RI that predicts *irreversible* renal failure and the futility of additional potentially detrimental volume loading. Appropriately, the authors identify that this new application of an existing technology will need to be validated in prospective human trials.

Canaries were utilized in coal mines as recently as 1986, when they were phased out in favor of more modern methods for detecting the presence of dangerous gases. Although serial IAP monitoring is essential to the detection and resuscitation of critically ill patients with IAH, it too will inevitably go the way of the canary, to be replaced by superior, organ-specific indicators of pressure-induced

***See also p. 207.**

Key Words: compartment syndrome; intraabdominal hypertension; intraabdominal pressure; resuscitation; organ failure; renal failure; sonography

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organ dysfunction and failure. This study, along with those to come, represents the beginning of the future for IAH and ACS management. In the interim, however, like the coal miners of old, intensivists must continue to measure IAP in patients at risk for IAH and ACS, constantly vigilant and asking ourselves, "Is the canary still singing?"

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Effect of thoracic epidural anesthesia on right ventricular function and homeometric autoregulation*

Recent large-scale meta-analyses have clearly demonstrated the advantages of thoracic epidural anesthesia (TEA) vs. parenteral opioid analgesia with regard to the effectiveness of postoperative pain control (1, 2). In addition, regional anesthesia, in particular TEA, was shown to be associated with reduced postoperative morbidity and mortality compared with general anesthesia (3–5). The reduced cardiac morbidity and mortality is presumably related to the fact that stress following surgical trauma typically increases adrenergic nervous activity and catecholamine levels, which puts patients with coronary heart disease at increased risk for ischemia and myocardial infarction. Blocking of cardiac sympathetic fibers by TEA may avoid catecholamine-induced vasoconstriction of atherosclerotic coronary arteries and tachycardia-induced plaque rupture (6, 7). In addition, TEA has been reported to have beneficial effects on gastrointestinal and pulmonary function and may have a positive effect on the immunologic and coagulation system (8, 9). The beneficial effects of TEA may be particularly relevant in view of the aging population and the rapidly increasing number of patients with cardiovascular risk factors who are subjected to surgical procedures. However, a potential disadvantage of sympathectomy by TEA might be that it reduces myocardial contractility and deprives the heart of important compensatory reflex mechanisms. A study presented in this issue of *Critical Care Medicine* by Dr. Rex and colleagues (10) investigated the direct effects of TEA on ventricular function. In particular, the authors focused on the functional response of the right ventricle in conditions of increased pulmonary vascular resistance. This topic is clinically highly relevant because right ventricular function is an important determinant of outcome after cardiac surgery, and pulmonary hypertension is a frequent postoperative complication (11–13). Studies have shown that the normal right ventricle responds to increased afterload by enhancing its intrinsic function (contractility) (14, 15). This response, referred to as homeometric autoregulation (16) because ventricular volumes remain unchanged, despite substantially increased systolic pressure, enables the ventricle to maintain stroke volume in face of increased afterload without having to dilate and rely on the Frank–Starling mechanism (heterometric regulation). Homeometric autoregulation was previously demonstrated to exist in both the left and the right ventricle and to be active during both acute and chronic afterload elevations (17, 18). However, the underlying mechanisms are still debated. Proposed mechanisms include the release of endogenous catecholamines (19), substances released from the endocardial endothelium (20), and stimulation of stretch-activated ion channels (21, 22). Dr. Rex and colleagues (10) speculated that the sympathetic nervous system is involved in homeometric autoregulation, and thus, TEA might interfere with this important adaptive mechanism. The authors tested this hypothesis in a series of carefully designed animal studies: pigs were instrumented

*See also p. 222.

Key Words: afterload; contractility; homeometric autoregulation; pulmonary hypertension; right ventricular function; thoracic epidural anesthesia

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with conductance and pressure catheters to assess left and right ventricular function by pressure–volume loops and to measure pulmonary artery pressure. The animals were anesthetized with pentobarbital, sufentanil, and pancuronium and received TEA (bupivacaine) or served as untreated controls. After baseline measurements, pulmonary hypertension was induced by hypoxic ventilation and measurements repeated. The results showed that at baseline, TEA decreased left but not right ventricular contractility, whereas heart rate and cardiac output remained unaffected. Induction of pulmonary hypertension caused an increase in heart rate, cardiac output, and both left and right ventricular contractility in the control animals; however, in the TEA-treated animals, the heart rate response was blunted, cardiac output decreased, and the positive effects on left and right ventricular contractility were abolished. The authors concluded that TEA inhibited the positive inotropic response of the right ventricle to increased afterload, which deteriorated the hemodynamic effects of pulmonary hypertension. The findings support the hypothesis that the sympathetic efferents are involved in homeometric autoregulation and are in line with recent studies regarding the effects of brain death on right ventricular function by Szabo et al (19). Previous studies by de Vroomen et al. (23), however, seemed to favor a local myocardial mechanism. In these studies, no effects on the contralateral left ventricle were found after induction of pulmonary hypertension in a newborn lamb model of respiratory distress syndrome, whereas Dr. Rex and colleagues (10) found a significant increase in left ventricular contractility, as well. However, species differences, a different level of hypoxia, and the immature innervation of the newborn heart may hamper this comparison. Whether the sympathetic nervous system is also involved in homeometric autoregulation of the left ventricle (thus after increased aortic impedance) is unclear. Studies in the isolated (thus denervated) heart indeed tend to show less pronounced homeometric autoregulation than in the intact animal. On the other hand, in the intact animal, afterload dependence of left ventricular systolic function was shown to remain present after surgical denervation (24). Differences between the left and the right ventricle in this respect are certainly conceivable, if only because sympathetic innervation and autonomic balance differ between the two ventricles (25, 26). The differential effects of TEA on the left and the right ventricle for the baseline measurements in the study by Dr. Rex and colleagues (10) further illustrate this.

In summary, the study by Dr. Rex and colleagues (10) is very interesting, not only because it provides valuable new information regarding the hemodynamic effects of TEA, but also because it draws our attention to the mechanism of homeometric autoregulation. This adaptive mechanism is well established in physiologic literature and plays an important role in circulatory homeostasis, particularly for the right ventricle; however, unlike the Frank–Starling mechanism, it is not commonly considered in the clinical arena.

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The pressure is rising*

In this issue of *Critical Care Medicine*, Dr. Souza-Costa and colleagues (1) examine the effects of atorvastatin pretreatment on acute pulmonary embolus (APE)-induced pulmonary hypertension by using an isolated rat lung perfusion model of APE. Recent studies suggested that matrix metalloproteinases (MMPs) may be involved in the development of acute pulmonary hypertension induced by APE (2). Therefore, the present study focused on the possible role of MMPs as well as nitric oxide, another known potent vasodilator, in the pathogenesis of APE-induced pulmonary hypertension (3). In addition, the authors also tested the hypothesis that pretreatment with atorvastatin would improve survival rate attributed to APE by virtue of attenuating APE-induced increases in lung and plasma MMP-2 and MMP-9. The present study suggests for the first time that pretreatment with atorvastatin attenuates APE-induced pulmonary hypertension and increases 24-hr survival rate, possibly by decreasing lung MMP-9 levels induced by APE. Moreover, improved nitric oxide balance by statins further contributed to this reduction in mortality. The implications of this study should be interpreted with caution and within the broader context of the hemodynamic alterations occurring in APE and the ever-growing body of knowledge regarding the pleiotropic effects of statins.

Pulmonary embolism (PE) is a common cardiopulmonary illness with an incidence in the United States that exceeds 1 per 1,000, translating into 150,000 patients per year (4). In the International Cooperative Pulmonary Embolism Registry (ICOPER) of 2,454 consecutive patients from seven countries, 4.2% had massive PE (5). The mortality rate is approximately 15% in the first 3 months after diagnosis (4).

The hemodynamic response to PE depends on the size of the embolus, coexistent cardiopulmonary disease, and neurohumoral effects (4). Acute PE increases pulmonary vascular resistance in a variety of mechanisms. These include hypoxic pulmonary vasoconstriction, physical obstruction of blood flow, and release of humoral factors, such as serotonin, thrombin, and histamine (6, 7). The healthy adult pulmonary circulation is a low-resistance and low-pressure circuit. Thus, an abrupt elevation in arterial pulmonary pressure resulting in an increased right ventricular afterload may lead to hypotension and hemodynamic perturbation that may further progress to clinically overt shock.

Such an increase in right ventricular afterload can cause right ventricular dilation, hypokinesis, tricuspid regurgitation with annular dilation of the tricuspid valve, and ultimately right ventricular failure (7, 8). Right ventricular enlargement may also result in a leftward shift of the interventricular septum, resulting in underfilling of the left ventricle. Consequently, both systemic cardiac output and pressure decrease, potentially compromising coronary perfusion and producing myocardial ischemia, all contributing to left ventricular dysfunction further compromising systemic hemodynamics (7, 8). Increased right ventricular pressure may also compress the right coronary artery, diminish subendocardial perfusion, and limit myocardial oxygen supply (7, 8).

It is, therefore, the entire hemodynamic burden that makes massive PE a life-threatening disease. In fact, the principal criteria for defining PE as massive are arterial hypotension and cardiogenic shock (9). Moreover, early mortality in patients with massive PE is at least 15%, and the extent of hemodynamic compromise is the most powerful predictor of in-hospital death (8, 9). Hence, any intervention with the potential to alleviate this abrupt increase in pulmonary arterial pressure and resistance may be of substantial value.

Statins have a wide variety of properties that are independent of their lipid-lowering ability. These anti-inflammatory, antioxidant, immunomodulatory, antiapoptotic, antiproliferative, antithrombotic, and endothelium-protecting features have been collectively referred to as pleiotropic effects (10, 11).

MMPs are a group of enzymes that degrade the extracellular matrix. Interestingly, they also modulate vascular reactivity and may play an important role in the hemodynamic changes following APE (2). The current findings are further supported by additional data indicating that statins suppress the production of MMP-9 in human abdominal aortic aneurysm wall and reduce MMP-9 secretion by macrophages and vascular smooth muscles (12).

It is well established that statins may profoundly affect nitric oxide availability. This effect has been demonstrated at the molecular, cellular, tissue, and organ level in a wide variety of models (10, 13). Specifically, the current study and several others suggest a potential beneficial effect of increased nitric oxide activity in the context of APE (3). Furthermore, statins have an important effect on guanosine triphosphate cyclohydrolase-1. This enzyme is the rate-limiting step in the synthesis of tetrahydrobiopterin, an essential cofactor for nitric oxide synthase. Statins up-regulate guanosine triphosphate cyclohydrolase-1 expression and thereby increase tetrahydrobiopterin levels in human endothelial cells (14).

Indirect support for the concept that statins may play a role in modulating pulmonary vascular tone comes from research in other forms of pulmonary hypertension, namely primary pulmonary hypertension, hypoxia-induced pulmonary hypertension, and other varieties of secondary pulmonary hypertension. Some of the proposed mechanisms for this effect include inhibition of the isoprenylation of rho and ras family guanosine triphosphatases that influence intimal proliferation as well as statin enhancement of circulating endothelial progenitor cells that may contribute to vascular repair (15). Given the diversity of the pleiotropic effects of statins, it is plausible that their proposed beneficial effect may be related to additional mechanisms that were not explored in the present study.

***See also p. 239.**

Key Words: statins; matrix metalloproteinases; nitric oxide; pulmonary embolus; pulmonary hypertension; mortality

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It should be kept in mind that the present study uses a pretreatment animal model and as such should be viewed as another step setting the stage for clinical trials. There is an important conceptual and practical difference between the prophylactic effect of statins, implied by the current study, and the therapeutic one we typically seek as clinicians. A logical first step would be observational studies to be followed by randomized placebo-controlled clinical trials looking at various physiologic end points such as pulmonary hypertension, hypoxemia, and deadspace ratio. Finally, from the clinician's standpoint, statins will have to stand the ultimate test, that is, the ever-desired short- and long-term survival benefit. The point where statins could be regarded as a part of our arsenal in the management of APE is still quiet distant.

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Including families in quality measurement in critical care*

Over the last several years, it has become increasingly evident to regulatory agencies, hospital administrators, government officials, clinicians, and patients that more attention must be paid to developing reliable measures that reflect the quality of care delivered in intensive care units (ICUs) (1). As concern about patient safety grows, in the face of reluctance to report errors on the part of the healthcare community, there has been more and more discussion about how to objectively evaluate quality in medical care. This is not an easy task. For years, we relied on "outcomes" reporting. Historically, this meant reporting risk-adjusted mortality in addition to some measures of costs and morbidities, such as length of stay, hospital costs, and complications.

More recently, measurement of the processes of care has taken a more prominent role in quality assessment (2). This is founded on the belief that driving process improvement, based on "best practice" models, may be the most effective path to improving outcomes because there are some important advantages of process measures over outcome measures (3–5). Regulatory agencies and quality improvement organizations are establishing programs in which improvement of quality is driven by adherence to process standards, identified through an evidence-based review of the literature (6).

Until recently, end-of-life care in the ICU has not been routinely viewed as a target for quality improvement initiatives. As the search for reliable outcomes measures for end-of-life care continues, there have been recent efforts to identify quality indicators for end-of-life care in the ICU (7, 8). In this issue of *Critical Care Medicine*, Dr. Wall and colleagues (9) provide an important contribution to the field of outcomes measurement by refining a tool that measures family satisfaction with care in the ICU. Building on a previously validated tool, measuring both satisfaction with care and satisfaction with medical decision making, these investigators have further validated several adjustments that should prove extremely helpful for facilitating the measurement of family satisfaction in critical care units. First, the tool is shortened, with fewer items than previously. Second, a scoring method was introduced that should make the results of this tool more appropriate as an outcome measure in research. Finally, with fewer items, the family satisfaction tool will be easier to

***See also p. 271.**

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use on a daily basis in the ICU. This means the tool may be used not only for outcomes research but, on a much more practical level, for assessing and reporting the level of satisfaction that families feel with care delivered in an individual ICU. Family satisfaction surveys have long been viewed as subjective and difficult to interpret. In providing the field with a shortened, validated tool, Dr. Wall and colleagues have provided clinicians with a good opportunity to measure and report, in an objective fashion, the degree to which families are satisfied with what we do in the ICU.

Family satisfaction is one important outcome of critical care, and one that is likely to be very meaningful to critically ill patients as well as their loved ones. However, even more intriguing is the possibility that ongoing measurement of family satisfaction might be used as part of a process to improve care as well. Measuring family satisfaction as one of the elements of quality end-of-life care may allow family satisfaction to be incorporated into a "bundled" approach to quality improvement for end-of-life care. Although this approach is unproven, I believe it will be an important path for future research and quality improvement efforts. For now, as clinicians make plans to monitor the quality of care they provide in the ICU, we can add family satisfaction measurement to the toolbox for quality improvement and outcomes reporting.

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