

Lac-time?*

Adequate resuscitation during the initial phase of severe sepsis therapy is critical. Even in the absence of arterial hypotension, global tissue hypoxia can lead to endothelial injury and activation of proinflammatory and coagulation pathways. Endothelial injury is thought to be a pivotal element in the development of multiple-organ dysfunction syndrome in sepsis (1, 2). Although the resuscitation phase of therapy is typically only a small fraction of the total length of stay in the hospital, the therapy provided during this time period has a major impact on long-term outcome variables including mortality (3). Serial lactate measurements can provide important information about the effectiveness of the resuscitative efforts.

The utility of a serum lactate measurement as an indicator of anaerobic tissue metabolism in the acute phase of sepsis therapy is a matter of debate (4). Serum lactate will be elevated in the presence of anaerobic metabolism and may identify patients who are on the supply-dependent part of the curve in the oxygen consumption/oxygen delivery relationship. However, lactate has several limitations in the identification of tissue hypoxia. Lactate can be elevated in the absence of anaerobic metabolism by a number of other mechanisms including pyruvate dehydrogenase enzyme dysfunction, an epinephrine-driven increase of $\text{Na}^+\text{-K}^+$ -adenosine triphosphatase activity, or impaired clearance of lactate secondary to hepatic dysfunction (5). Despite the fact that a high lactate concentration in sepsis may not necessarily indicate tissue hypoxia, several studies have reported that elevated lactate identifies sepsis patients with an increased risk of death compared with patients without lactate elevation (6,

7). Regardless of etiology of a high lactate concentration in sepsis patients, a decrease during acute resuscitation is likely good.

In this issue of *Critical Care Medicine*, Dr. Nguyen and colleagues (8) report the results of a prospective observational study of lactate clearance during resuscitation of emergency department (ED) patients with severe sepsis and septic shock. The authors hypothesized that effective lactate clearance during sepsis resuscitation would be associated with decreased mortality rate. One hundred and eleven ED patients with severe sepsis or septic shock (sepsis plus hypotension and/or lactate >4 mmol/L) were enrolled. Univariate comparisons were made between survivors and nonsurvivors, and variables reaching statistical significance were included in a multivariate logistic regression analysis to identify independent predictors of in-hospital mortality. The authors found that survivors had a higher lactate clearance than nonsurvivors, and lactate clearance had a significant inverse relationship with mortality in multivariate logistic regression analysis. A cutoff for "high" lactate clearance vs. "low" lactate clearance was prospectively defined as the value for lactate clearance (measured in percent decrease over the 6-hr resuscitation) that yielded the maximum sum for sensitivity plus specificity for in-hospital mortality. Patients above this cutoff (high lactate clearance) were found to have decreased in-hospital mortality compared with patients below the cutoff (low lactate clearance).

The findings of this study are not completely new. Effectiveness of lactate clearance during resuscitation of patients with sepsis (9) has been shown to be predictive of mortality, with rapid lactate clearance conferring a survival advantage. The term "lac-time" as introduced by Bakker et al. (9) refers to the duration of time that a patient spends with lactate above a prospectively defined value thought to represent a threshold above which anaerobic

metabolism was likely occurring. Although lactate clearance and lac-time have previously been identified as important in the intensive care unit, Dr. Nguyen and (8) colleagues have taken this principle and studied it for the first time in the ED setting, during the earliest hours of disease presentation.

The authors also performed a randomized controlled trial of early goal-directed therapy (EGDT) for severe sepsis and septic shock in the ED (3). In that study, the patients in the EGDT group had the first 6 hrs of resuscitative efforts in the ED guided by central venous oximetry measurements in addition to central venous pressure and mean arterial pressure (MAP). The EGDT group in that study demonstrated a 16% absolute risk reduction for 28-day mortality compared with the control patients, in whom only central venous pressure, MAP, and urine output were targeted. Although the subjects of this lactate clearance study did not have central venous oximetry targeted as an end point of resuscitation, all patients received central venous catheterization, arterial catheterization, and titration of therapy in the ED to achieve prospectively defined values for central venous pressure, MAP, and urine output. Given the findings observed in this current study of lactate clearance, coupled with the magnitude of the mortality benefit from the authors' previous landmark study of ED-based EGDT, it would seem that the effectiveness (or lack of effectiveness) of initial resuscitation in sepsis could potentially be a major confounding factor in clinical trials of novel antisepsis therapies. In the future, perhaps the manner of initial resuscitation should be controlled for in prospective severe sepsis investigations.

It is also notable that 29% of the patients in the low lactate clearance group did not have hypotension, and the mortality rate in that group was 55.6%, a higher mortality rate than in the patients who had septic shock with a high lactate clearance. The difference in mortality

*See also p. 1637.

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rate between patients with high vs. low lactate clearance would not have reached statistical significance if the nonhypotensive severe sepsis patients were excluded from the analysis. These findings speak to the fact that conventional physiologic variables such as systolic blood pressure (i.e., macrocirculatory variables) are insensitive for determining which patients are in need of aggressive resuscitation (3), and the findings provide additional evidence that "cryptic shock" (occult global tissue hypoxia in the absence of arterial hypotension) (10) is a real and clinically important entity. Previously, this state was commonly referred to as "compensated shock," where a surge of endogenous catecholamines was able to maintain MAP while occult hypoperfusion was taking place in the tissues. Altered tissue perfusion in normotensive patients with severe sepsis is likely explained by heterogeneity of microcirculatory blood flow (11).

This prospective observational study contributes to the body of evidence that adequacy of resuscitation (as defined by lactate clearance) in the initial phase of sepsis therapy can be associated with long-term clinical outcome including 60-day mortality rate. However, although lactate and lactate clearance are important markers that are relatively easy to measure in clinical practice, there are no data to support the substitution of lactate clearance in place of other end points of resuscitation that were associated with an outcome benefit with EGDT. A markedly elevated lactate is an important marker of hypoperfusion that likely indicates the need for additional resuscitative efforts. But what interventions? In the absence of invasive hemodynamic measurements, lactate alone is limited in that it will not identify whether the patient needs more intravascular volume expansion,

more vasopressor agent, or more inotropic support. The same could be said for other indicators of hypoperfusion such as high base deficit or even low urine output. A protocol using end points of resuscitation derived from invasive monitoring, on the other hand, can help pinpoint where the problem is and guide therapy accordingly. Currently, consensus recommendations (12) for the resuscitation of severe sepsis patients in the pre-intensive care unit phase of therapy are based on data from the authors' original EGDT study and include targets of central venous pressure, MAP, and mixed venous oxygen saturation/central venous oximetry. These recommendations from the Surviving Sepsis Campaign (12) were endorsed by 11 professional societies including the American College of Emergency Physicians; however, most hospitals in the United States do not yet use invasive monitoring for patients with severe sepsis or septic shock in the ED setting. Therefore, it would be tempting for institutions without an EGDT program to look at the results of this observational study as a justification for performing an "aggressive" resuscitation in the ED without invasive monitoring, following lactate clearance instead. At this point, however, lactate clearance as a target or end point in sepsis resuscitation has not been studied prospectively in a randomized controlled fashion. There is likely general agreement that lactate measurement as a screening tool for cryptic shock is useful. However, whether it would be of benefit to incorporate lactate clearance as an additional element of an EGDT resuscitation protocol is unclear and worthy of further investigation.

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Evolution of B-type natriuretic peptide in evaluation of intensive care unit shock*

Congestive heart failure (CHF) is a major and increasing cause of death and disability in United States. Its prevalence is attributable to the drastic increase in cardiovascular risk factors such as obesity and diabetes and improved survival rate after acute myocardial infarction (and subsequent development of CHF). CHF has a prevalence of 4.9 million and an incidence of 550,000 cases per year. The extremely high readmission rates for CHF patients account for significant resource use (1–4).

Until recently, owing to the subjectivity of methods used to distinguish heart failure from pulmonary conditions, determining the cause of dyspnea has been difficult especially in the urgent care setting. In 2002, the Breathing Not Properly as well as other studies demonstrated that B-type natriuretic peptide (BNP) not only significantly increases diagnostic accuracy (Fig. 1) (5–7) but also correlates with long-term morbidity and mortality in patients with chronic heart failure presenting to the emergency department (8).

Since elevations of BNP are related to presence and severity of CHF, it is no surprise that it is a powerful marker for prognosis and risk stratification in the setting of heart failure. In a recent study of 78 patients referred to a heart failure clinic, BNP showed a significant correlation to the heart failure survival score (9). In addition, changes in plasma BNP concentrations were significantly related to changes in limitations of physical activities and were a powerful predictor of functional status deterioration. Hence, BNP concentrations may be able to accurately objectify New York Heart Association classification (6). Harrison et al. (8)

followed 325 patients for 6 months after an index visit to the emergency department for dyspnea. Higher BNP concentrations were associated with a progressively worse prognosis. The relative risk of 6-month CHF admission or death in patients with BNP concentrations >230 pg/mL was 24 times the risk of concentrations less than this. Cheng et al. (10) followed the course of 72 patients admitted with decompensated CHF with daily BNP concentrations and their relationship to 30-day readmission rates or death. Patients who were most likely to have a cardiac event had higher BNP concentrations both at the time of admission and at discharge. Only 16% of patients with a decrease in BNP concentrations during hospitalization had a subsequent cardiac event, whereas 52% of those with increasing BNP concentrations during treatment had either readmission or cardiac death. Patients whose discharge BNP concentrations 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. (11), who found that failure of BNP concentrations to decrease over the hospitalization period predicted death/rehospitalization and that discharge concentrations <250 pg/mL predicted event-free survival. In another study by Berger et al. (12), 452 high-risk cardiovascular patients with ejection fraction <35% were followed for 3 yrs. In this study, BNP with a cut-point of 130 pg/mL was the only independent predictor of sudden cardiac death in a multivariate analysis with standard variables like ejection fraction, New York Heart Association class, or antiarrhythmic medication. Recently, Wang et al. (13), the investigators from the Framingham Offspring Study, showed that the utility of BNP concentrations >20 pg/mL were associated with an increase by >60% in the long-term (5 yrs) risk of death even in asymptomatic middle-aged persons (Fig. 2).

In another important article, published in this issue of *Critical Care Medicine*, Dr. Tung and colleagues (14) demonstrate that BNP concentrations in intensive care unit shock might provide powerful information for use in mortality prediction. Median BNP concentrations were higher in those who died than those who survived (943 pg/mL vs. 378 pg/mL, $p < .001$). Also, using multivariate analysis, they showed that BNP concentration in the highest log-quartile was the strongest predictor of mortality (odds ratio = 4.50). Even though they showed no correlation between a single BNP value and pulmonary artery occlusion pressure in inter-patient analysis (which could be explained by variation of individual patients, age, gender, ethnicity, baseline and dry BNP concentration, and to some extent by renal function), it is clear that a BNP <350 pg/mL had a very high negative predictive value (95%) for the diagnosis of cardiogenic shock. This study support the study published in 2001 by Kazanagra et al. (15), 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 (Fig. 3). In this study, the authors also showed that the patients who died had higher final BNP concentrations (1078 ± 123 pg/mL vs. 701 ± 107 pg/mL). The authors concluded that although BNP concentrations will not obviate the need for invasive hemodynamic monitoring, these concentrations may be a useful adjunct in tailoring therapy to these patients and may improve the in-hospital management of patients admitted with decompensated CHF. Even though Dr. Tung and colleagues (14) could not differentiate cardiogenic from noncardiogenic shock using BNP, BNP concentrations have been a useful surrogate of occlusion

*See also p. 1643.

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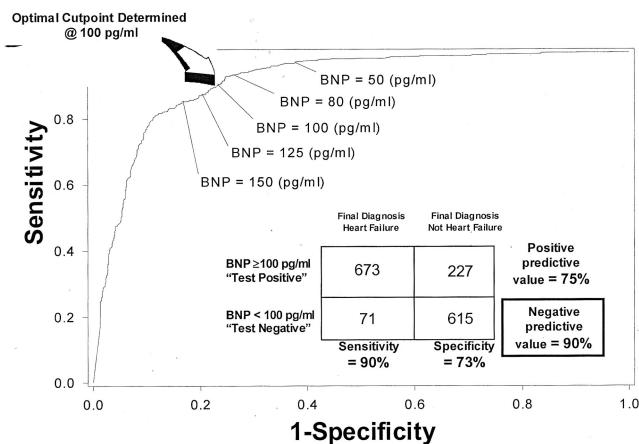


Figure 1. Sensitivity vs. specificity for heart failure by B-type natriuretic peptide concentrations. Data from the Breathing Not Properly Multinational Study; adapted with permission (6).

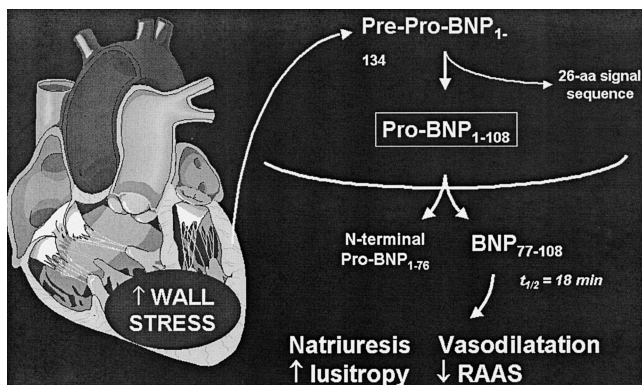


Figure 2. Shows the secretion of B-type natriuretic peptide (BNP; 132 amino acids) in response to wall stress and then its sequential breakdown to a 76-amino acid N-terminal fragment and a 32-amino acid active hormone.

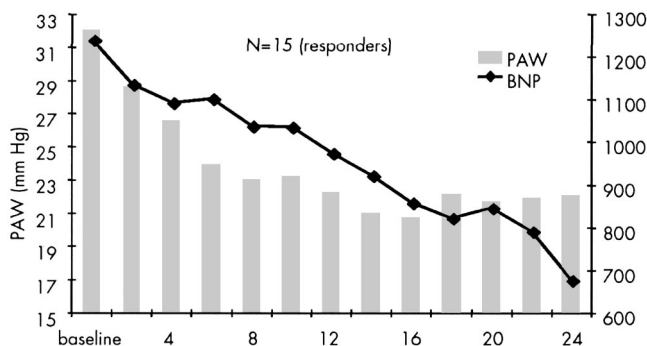


Figure 3. The correlation of treatment induced change in pulmonary artery occlusion pressure (PAW) with change in B-type natriuretic peptide (BNP) from baseline. Adapted with permission (15).

pressure and are useful in differentiating heart failure from lung disease, and BNP may be useful not only in excluding cardiogenic shock but also in differentiating cardiogenic from noncardiogenic pulmonary edema. In a study by Berman et al. (16), BNP concentrations were obtained in 35 patients with acute respiratory distress syndrome

(ARDS) and from 42 patients hospitalized for severe dyspnea with a diagnosis of CHF. The median BNP concentration in patients with CHF of 773 pg/mL was significantly higher than patients with ARDS (123 pg/mL, $p < .001$, Fig. 4). The area under the receiver operator characteristic curve using BNP to differentiate CHF from ARDS was 0.90

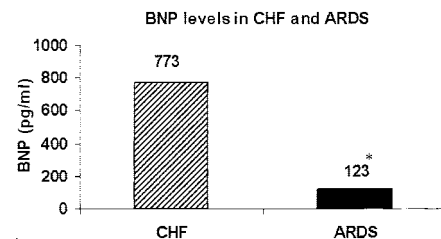


Figure 4. B-type natriuretic peptide (BNP) concentrations in coronary heart failure (CHF) and acute respiratory distress (ARDS) syndrome patients. Adapted with permission (16). * $p < .001$.

(0.83–0.98, $p < .001$). At a cut-point of 360 pg/mL, there was 90% sensitivity, 86% specificity, 89% positive predictive value, and a 94% negative predictive value (accuracy = 88%) for ARDS 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. Hence, BNP concentrations >360 pg/mL suggest CHF as the diagnosis of pulmonary edema.

There are very few limitations of the study by Dr. Tung and colleagues (14), including small sample size and single point BNP testing, but the utility of multiple BNP testing in monitoring the hemodynamic state of patients has been already addressed by Kazanagra et al. (15). The merit of this study is in that it shows that low BNP concentrations, tested by a single inexpensive point of care assay, can exclude cardiogenic shock (a high pulmonary artery occlusion pressure or low cardiac index) in the intensive care unit and may be useful to avoid pulmonary artery catheterization and the risks associated with pulmonary artery placement as well as the necessity of an intensive care unit bed. Also, elevated BNP concentrations may offer superior prognostic information to the critical care practitioner to help identify patients at highest risk for mortality.

BNP is the first biomarker to prove its value in a) screening for left ventricular dysfunction; b) assessing prognosis while monitoring patients; c) tailoring management and titrating therapy (17); d) providing objectivity in assessing discharge and admission criteria; e) predicting and decreasing adverse cardiac events and readmissions in heart failure patients (18); and f) characterization and prognostication of intensive care unit patients in shock.

To conclude, this rapid, inexpensive, point-of-care test, which is simple to administer in a variety of clinical settings, can enable care providers to facilitate and optimize care of heart failure patients. As with everything there are limitations to BNP testing, as it is not a standalone test; however, when used judiciously, it could be a powerful tool in the hands of clinicians. Emerging clinical data will help further refine biomarker-guided therapeutic and monitoring strategies involving BNP.

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Nurse-assessed tool for evaluating death in the intensive care unit*

Over the last few decades, intensive care unit (ICU) care has evolved from a technical endeavor to a holistic approach that combines state-of-the-art life support and a strong focus on communication and empathy within the patient-family-staff triad (1–3). This second component, known as patient- and family-centered care, has been investigated in epidemiologic (4–12) and interventional

studies (13–15), which have identified areas for improvement (16). Although patient- and family-centered care is initiated at ICU admission when the patient's outcome is still uncertain, specific needs of dying patients and their relatives have been identified (17–19), and considerable effort has been directed at providing patients and their families with a “good death” (20–23).

In 2002, Curtis et al. (24) provided clinicians with an easy-to-use instrument aimed at improving the care of dying patients. Using the perceptions of family members interviewed after the death of their relatives in the ICU, these authors developed a reliable and valid tool for assessing the dying experience (24). Their 31-item Quality of Dying and Death

(QODD) questionnaire assesses symptoms, patient preferences, and satisfaction with care. Curtis and coworkers showed that symptom assessment and treatment, continuity of care, and good communication within the patient-family-staff triad were associated with a better quality of death. In this issue of *Critical Care Medicine*, the same group turned the spotlight onto nurses as a valuable source of information about the quality of dying in the ICU (25). Instead of asking physicians or family members how they perceived death in the ICU, Dr. Hodde and colleagues (25) asked nurses. The authors based this approach on data showing that nurses are both more critical about end-of-life care than physicians and less likely to be distressed by after-

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death questionnaire completion than family members. To collect ICU nurses' perceptions in a reliable manner, Dr. Hodde and colleagues developed a shortened version of their QODD, which they obtained by deleting the items that were not relevant to the ICU or could not be readily assessed by nurses. This 14-item tool proved feasible for nurses' assessments of death in the ICU: The response rate was 72%, and most of the items were completed in most of the questionnaires. In addition, the evaluation of factors associated with better quality of dying, as assessed by the nurses, produced useful information. Not dying alone, not having CPR within the last 8 hrs before death, and being a neurologic or neurosurgical patient were independently associated with better quality of dying, as assessed by the nurses. The association between better quality of dying and not dying alone, whether the person present was a family member or an ICU staff member, strongly suggests that a prepared death was more likely to be a good death. Absence of CPR within the last 8 hrs is consistent with do-not-resuscitate orders, again suggesting that these deaths were prepared.

The focus placed by Dr. Hodde and colleagues (25) on ICU nurses' perceptions is welcome. The authors have actively promoted communication within the ICU team to ensure that every nurse is aware of the details of each patient (26). This approach empowers the nursing staff, and it is in this setting that the single-center study was conducted. Whether the results can be generalized to other ICUs where communication among ICU staff members is less satisfactory deserves consideration.

A number of studies have indicated that nurses have a high level of awareness and knowledge about end-of-life issues. Nevertheless, divergences have been reported in the opinions and perceptions of ICU nurses regarding the areas of information (7, 27, 28), decision making (29, 30), or satisfaction with the end of life (31–34). Moreover, studies have suggested that nurses may underestimate the usefulness of intensive care (35) and that the length of nursing experience may negatively affect the nurse's ability to assess family members' needs (36). Therefore, although the current study establishes the feasibility of using the 14-item QODD to collect nurses' perceptions about dying in the ICU, studies comparing assessments by various categories of

health care professionals, and also by family members, would be useful.

The study by Dr. Hodde and colleagues (25) carries an important message for everyday practice in the ICU. A simple tool is available for asking nurses how they perceive the quality of dying in their ICU. Use of this tool would be expected both to improve communication within the ICU team by making other health care professionals aware of nurses' perceptions and to identify areas where further efforts are needed to provide dying ICU patients with a good death.

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The survival benefit of intensive care*

In this issue of *Critical Care Medicine*, Dr. Simchen and colleagues (1) have given us information that is long overdue on the survival benefit to be gained from intensive care. In a study of critically ill patients in Israel, the authors screened the entire patient population in five hospitals on selected days to identify study subjects. Among those meeting the criteria for critical illness, 27% were admitted to the intensive care unit (ICU), 24% were admitted to other specialized care units, and 49% were admitted to regular wards. This was an observational study of the impact of ICU care made possible by the shortage of ICU beds. The decision to admit patients to the ICU was left in the hands of their physicians. Adjusting for age and severity of illness, the authors found that admission to the ICU was associated with a greater likelihood of survival for the first 3 days after the onset of critical illness. Thereafter, the survival curves were parallel for patients receiving care in and out of the ICU setting.

Needless to say, the study results will not be considered as definitive as they would be were this a randomized controlled trial (RCT). But in an era in which the provision of critical care, when avail-

able, is the standard of care, such an RCT would be severely criticized from an ethical standpoint. This is so despite the fact that we have never had definitive studies of the benefits of providing ICU care (2). We have relied largely on historically controlled studies (3). This conundrum of a standard of care that is insufficiently understood but impossible to study thoroughly is typical of the difficulty of diffusion of technology and its canonization as the standard of care before it has been fully evaluated. Under these circumstances, the study by Dr. Simchen and colleagues is an appropriately designed and very valuable test of the impact of intensive care admission.

The findings are consistent with those found by Lundberg and colleagues (4), who found that patients with positive blood cultures who were managed in the ICU were more likely to survive than culture-positive patients who were managed on the hospital ward. The findings also complement other data indicating that early resuscitation is important to improve survival from shock (5).

Certainly we should recognize the limits of any inferences we can make from this study. Critical care includes a myriad of interventions that may vary from one institution to another and from country to country. The alternatives to ICU care also vary among institutions and countries. In this study of Israeli hospitals, for instance, ventilatory support is available on non-ICU wards, which may not be the case at other hospitals. Hence, the outcome of comparisons like this one, if performed elsewhere, might not be the same. It would be extremely useful to

see how results of similarly designed observational studies conducted in other countries would compare.

It remains to be determined what exactly it is in the delivery of critical care that confers a survival benefit. Critical care is a complex mixture of multidisciplinary and highly trained staff, coordinated organization of care, and multifaceted monitoring and intervention. We have much research ahead to identify the crucial components that make a difference. Evidence indicates that merely offering more interventions is not necessarily better (6, 7).

But even in the absence of understanding the mechanism or the essential factors that determine the impact of critical care on survival, the study findings can be valuable to critical care practitioners. We often engage in discussion with patients and families about alternative therapeutic approaches without sufficient information about the impact of various therapeutic options on the outcome. How can we knowledgeably consider whether to offer intensive care to a debilitated chronically ill or terminally ill patient who is experiencing a superimposed acute illness, in the absence of understanding what difference it will make?

Information like that provided here can be helpful to policymakers as well. Institutions that are deciding whether to allocate resources to create more ICU beds and health systems that are considering the utility of providing critical care services will find this kind of information valuable. For health systems in developing countries that are financially pressed

*See also p. 1654.

Key Words: survival benefit; intensive care; bed shortage; survival curves

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to deliver necessary care, this kind of information is particularly worthwhile.

The authors suggest that since only the first 3 days make a difference in survival, it may be possible to discharge critically ill patients earlier than is currently the norm in order to admit other critically ill patients for whom there might otherwise not be available space. Such a suggestion must be taken as speculative and would need further study. It should be noted that the ethics of such a study would entail risks to patients. Cutting back or limiting services to patients in the face of cost constraints is an activity fraught with possible safety risks to patients. Although an observational study such as the one conducted by Dr. Simchen and colleagues (1) did not include interventions that warranted institutional review board review, studies that involve comparisons of standard care with new strategies for cost containment need to be conducted with the appropriate ethical scrutiny (8). Serious consideration must be given to the amount of notification that must be provided (8).

As we study strategies to deliver intensive care most cost effectively, other issues arise as well. It will be important to consider what outcome measures are relevant to measure. Survival is useful as a definitive measure, but other measures should be considered. Along with examining the impact of alternative care strategies on hospital mortality, we should observe other outcomes like functional status. Studies that look at long-term

outcomes past the point of hospital discharge may yield differences we would not notice were we to look only at survival to hospital discharge (9).

To put this study in context, we should note that there are other strategies for making the most of critical care skills, such as taking those skills outside the ICU. Studies in the literature indicate the value of ICU-type teams managing high-risk patients on the hospital ward (5, 10, 11) and the provision of ICU-type care in the emergency department (12). Another venerable midway strategy involves the creation of intermediate care units (13).

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Extracorporeal endotoxin adsorption in septic patients—Does it work?*

In this issue of *Critical Care Medicine*, Dr. Reinhart and colleagues (1) present the results of a phase II trial on an extracorporeal endotoxin adsorber in suspected Gram-negative septic patients. Endotoxin is an

important factor in the pathogenesis of Gram-negative sepsis. Therefore, several anti-endotoxin-directed approaches have been tested in clinical trials to reduce sepsis morbidity and mortality rates. Application of neither E5 nor HA-1A as a monoclonal approach has been shown to be effective (2, 3). So far, it could not be shown that polyvalent immunoglobulins directed against endotoxin effectively reduce mortality rate in septic patients (4). Based on promising results in animal studies, hemofiltration and plasmapheresis techniques have been used to reduce endotoxin concentrations. Again, clinical

trials have not yet demonstrated a reduction of mortality rate by these regimens (5). The idea behind the trial by Dr. Reinhart and colleagues (1) is sophisticated: The adsorber concept aims to reduce both endotoxin and proinflammatory cytokines such as tumor necrosis factor (TNF)- α (6). This innovative approach tries to balance the disadvantages of the broad and unspecific extracorporeal methods of removing endotoxin and cytokines by plasmapheresis or hemofiltration, on the one hand, and the highly specific anti-endotoxin and anti-cytokine strategies. Unfortunately, we have to ask

*See also p. 1662.

Key Words: sepsis; endotoxin; cytokines; clinical trial; extracorporeal adsorber

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ourselves why this trial is again one of the "negative" ones.

In recent large-scale trials, studies have shown that Gram-positive septicemia is at least as frequent as Gram-negative (7, 8). Not surprising, in the current trial not more than one third of the patients were affected by Gram-negative bacteria only. Although inclusion criteria aimed to include patients with Gram-negative infection, in 11.9% of the patients Gram-positive and in 17.9% a mixture of organisms were detected; in 43.3% of the cases, no causative organism could be identified. The small portion of Gram-negative sepsis may have led to lack of power of the trial even though there was no proven treatment effect in the subgroup of patients with Gram-negative infections. The low efficacy rate in the interim analysis may have also been caused by the low rate of Gram-negative infections.

The most important question is whether the trial was appropriately designed to evaluate the endotoxin adsorber technique. The technique used has previously been shown to effectively reduce endotoxin concentrations (6). However, in the current trial, the endotoxin concentrations were not significantly different in the adsorber and the nonadsorber group. Although this might be due to underdetection of endotoxin by the test used (9), it is possible that the applied hemodialysis was ineffective in reducing endotoxin concentrations. As discussed by the authors, intermittent endotoxemia may have led to comparable clinical results in both groups. This thesis is supported by the fact that TNF- α was not effectively removed from plasma and TNF- α concentrations were comparable in both groups. In contrast, anti-TNF-antibody treatment in patients with sepsis syndrome results in long-lasting reduction of TNF concentrations (10). It remains unclear whether extended, longer lasting adsorber treatment would have resulted in lower endotoxin and TNF- α concentrations—and improved pathophysiology.

In recent years we have become aware of the importance of drug-drug interactions in intensive care patients. Based on previous, unpublished trials, the authors report that the adsorber system used interacts with a variety of drugs such as heparin and insulin. Although no dramatic effects have been clinically de-

tected, one has to keep in mind the very difficult appraisal of adverse events in highly complex clinical situations on ICU. In addition, the beneficial immunomodulatory effects of heparin and insulin therapy may have been disturbed without being noticed by the investigators.

Beyond these physiologic aspects, there are methodologic issues that might help explain the failure of the trial. Although in the first part of the trial, the biggest and statistically "significant" reduction in Acute Physiology and Chronic Health Evaluation II scores was detected in patients with peritonitis, this finding could not be verified in the final analysis of the trial. Statistically speaking, the authors were right to modify the inclusion criteria after interim analysis. However, statistical significance must go hand in hand with clinical and pathophysiologic conclusiveness. Peritonitis is a complex syndrome of a variety of underlying diseases that needs specific treatment (11, 12). From the pathophysiologic point of view, it is therefore questionable whether patients with peritonitis are the most likely patient group to profit from anti-endotoxin therapy. However, it has to be stressed that the innovative approach of adaptive statistical design of trials may reduce the number of patients needed to be included in trials, if this approach is adequately used.

In addition to failure to show effectiveness, the trial failed to show that the adsorber technique reduced endotoxin load. Nevertheless, the approach of immunomodulatory therapy in sepsis by nonspecific methods of influencing the entire inflammatory response without suppressing it is still promising. We therefore agree with the authors that further investigation is warranted. Before commencement of a second mid-sized trial, we need to know more about the adsorber therapy (possibly modified by longer treatment periods), whether it can effectively reduce concentrations of endotoxin and (proinflammatory) cytokines, and how it interacts with drugs, hormones, and the immune system.

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Acute renal failure and diuretics: Propensity, equipoise, and the need for a clinical trial*

Development of acute renal failure has important consequences for patients, physicians, health care purchasers, and society. Even a modest deterioration of renal function increases mortality rate (1), and there is little doubt that severe dysfunction requiring renal replacement therapy is an important determinant of outcome in patients admitted to intensive care (2). Adverse outcomes occur as a direct consequence of uremia and indirectly from iatrogenic events related to its management. Prolonged hospital stay, increased medical and surgical procedures, other hospital costs, follow-up, and lifelong renal support or transplantation (3) are some of the unwelcome consequences.

Given this enormous burden of morbidity and mortality, investigators have explored a variety of approaches to prevent or ameliorate the course of acute renal failure. These have included use of mannitol, loop diuretics, dopamine and its analogs, natriuretic peptides, calcium channel blockers, and acetylcysteine (4–6).

Currently, use of loop diuretics remains one of the most frequently used strategies for this purpose. These drugs have theoretical potential to improve outcomes by decreasing renal tubular ischemia through reduced tubular oxygen consumption, improving fluid status through induction of diuresis, and eliminating or delaying the need for renal replacement therapies. Paradoxically, the potential to worsen outcomes through volume depletion or by delaying treatment of other manifestations of uremia such as immune dysfunction is also present, nosocomial infections being a particular problem for such patients. Outcome data to support the use of loop diuretics remain sparse, and the ade-

quacy and relevance of animal models are questioned (5). In many of the available studies, there has been no benefit in terms of important patient-centered outcomes, and in some outcomes have proved unfavorable (5–7).

The report of Mehta et al. (8) for the PICARD Study Group amplified fears that such diuretic strategies may actually be detrimental to critically ill patients. They reported the results of a retrospective observational study of 552 patients that employed propensity scoring methodology (9, 10) to match patients receiving diuretic and those who did not. The authors found an odds ratio of 1.8 for death or nonrecovery of renal function of those receiving diuretics, which approximates to a relative risk of 1.25 for those outcomes (11). Although acknowledging the limitations of observational studies, the PICARD Group concluded that, “it is highly unlikely that diuretics afford patients any material benefit.” They also recommended that in the absence of contrary data, “the widespread use of diuretics in critically ill patients with acute renal failure should be discouraged.”

However, in this issue of *Critical Care Medicine*, Dr. Uchino and coworkers (12) report less striking findings from a similar but prospective observational study of 1,743 patients for the BEST Kidney Group of the effects of diuretics on mortality rate and clinical outcomes. As well as being prospective and larger, this study has improved methodological rigor by the use of three methods of data modeling. In particular, one of their criticisms of the PICARD study was that the propensity model used did not take account of the potential serious problem of colinearity, a problem that was formally addressed by the BEST Group. It is noteworthy, however, that this problem did not lead to divergent results in the BEST study. All three propensity models, including the model used to deal with colinearity, yielded almost identical, small, but statistically insignificant increases in mortality rate for patients receiving di-

uretics. The odds ratio for death was approximately 1.2 for all models, and results from simple data analysis were also similar with an odds ratio for death of 1.25. Other crude outcomes such as intensive care unit and hospital length of stay, intensive care unit mortality rate, and hospital discharge without renal replacement therapy all favored the group that did not receive diuretics. In contrast to the PICARD Study Group, the BEST authors have concluded that use of diuretics in critically ill patients with acute renal failure is not associated with higher mortality rate. They further opine that there is full equipoise for a randomized clinical trial and suggest that it is desirable and feasible, which will require evaluation of almost 5,000 patients.

In support of the need for a clinical trial is the fact that diuretics are commonly used in the management of impending or established acute renal failure. Also, the consequences of acute renal failure are great. However, the argument of the BEST authors that there is full equipoise is weaker. Both their study and that of the PICARD group, amounting to >2,000 patients in total, document overall detriment to patients, not benefit. Demonstrable clinically important benefits from available randomized controlled trials are conspicuous by their absence, and some also suggest harm (6). It might alternatively be concluded that the biological basis for renal salvage by use of loop diuretics is weak and that supportive evidence from clinical trials or well-conducted observational studies is weaker still.

It is fashionable to call for randomized controlled clinical trials to answer questions of therapeutic effectiveness. However, there are situations when reliance on observational data might be preferred (13). Propensity scoring is a powerful tool that has improved the utility of observational data and been useful in scrutinizing critical care practices (9). Thus, despite the important consequences of acute renal failure, the

*See also p. 1669.

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apparent lack of demonstrable benefits in human studies should mitigate caution against premature and overenthusiastic calls for a randomized controlled trial.

Before such a trial is considered, further groundwork would be helpful. Re-evaluation of results from the PICARD Study Group to indicate whether potential problems identified by the BEST group are important would be useful as would an up-to-date systematic review of available studies. Only if such analyses provide reasonable hope that patients with acute renal failure could benefit from loop diuretics should a clinical trial be undertaken. It is possible that we already have sufficiently robust evidence to eschew the use of loop diuretics in patients with acute renal failure in locations where renal replacement therapies are readily available. The balance of risks to our research subjects and patients vs. our desire to

reduce medical uncertainty must always be carefully considered (14).

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Unidentified acids in severe malaria: Lessons for critical care*

The anion gap, a time-honored calculation examined in nearly every intensive care unit (ICU) patient every day, continues to be an active area of interest and investigation for ICU physicians. Many questions are relevant to contemporary ICU practice: Is the traditional calculation of the anion gap the best method to assess the presence of metabolic acidosis? What constitutes the unmeasured acids contributing to an elevated anion gap seen in many ICU patients? How good is the anion gap as a prognostic factor? The article by Dr. Dondorp and colleagues (1) in this issue of *Critical Care Medicine* bears on each of these issues.

Historically, the anion gap was calculated as the plasma sodium concentration minus the sum of the plasma chloride and bicarbonate concentrations. With the ubiquitous measurement of plasma elec-

trolyte panels and albumin and lactate concentrations, the anion gap calculation can be made more exact by taking into consideration loss of unmeasured anions (hypoalbuminemia), gain of anions (hyperlactatemia), and increased cations (increased potassium, calcium, magnesium, lithium). An even more precise approach (the Stewart method), albeit one that requires a programmable calculator, is based on the principles of electrical neutrality and conservation of mass (2, 3). This approach allows quantification of the contributions of lactate, dilution, albumin, and phosphates to acid-base balance and better delineation of the contributions of the “missing” acid load to pH.

It has been estimated that >3,000 people die of malaria worldwide each year, with falciparum malaria remaining a major cause of childhood mortality in the tropics (4). In this issue, Dr. Dondorp and colleagues (1) report findings from a prospective study of 268 consecutive adult patients hospitalized in an intensive care unit in Vietnam with severe falciparum malaria (1). Using the Stewart approach, Dr. Dondorp and colleagues found that nonlactate unmeasured

plasma anions are quantitatively the greatest contributor to the metabolic acidosis of severe malaria. This analysis provides the clearest documentation to date of the presence and magnitude of unexplained anions in systemic illness. Left unknown, however, is whether these observations apply outside the field of malariology.

It has long been recognized that substantial portions of the anion gap in metabolic acidosis remain unexplained (5, 6), and the studies by Dr. Dondorp and colleagues (1) do not directly address the nature of the unexplained missing ions. Dr. Dondorp and colleagues did find, however, that shock, renal failure, and liver dysfunction were all significant predictors of the strong ion gap and therefore likely play a role in the accumulation of these unmeasured anions. Furthermore, the authors have carefully shown that acute renal failure only partly explains the presence of these extra anions. A recent study by Mizock et al. (5) revealed that pyroglutamic acid as well as ketones and anion accumulation from kidney failure does not explain the increased strong ion gap

*See also p. 1683.

Key Words: acidosis; anion gap; strong ion gap; prognosis; acid-base balance; malaria

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in critically ill patients (5). Other possible candidates include pyruvate and hepatic derived compounds during states of sepsis and severe liver disease; however, none of these agents have been consistently found or well studied in the ICU setting (2, 7).

Metabolic acidosis, especially as characterized by base excess and elevated serum lactate, is well recognized to be a harbinger of poor prognosis in critically ill patients (8). Several studies have reached conflicting conclusions regarding the predictive value of unmeasured anions toward patient mortality in the setting of metabolic acidosis and severe illness (9–11). These contradictory results are likely explained by differences in study populations, illness, treatment (especially resuscitation fluids), and methodology. In particular, many of these studies were limited by small patient samples and retrospective study designs. The most recent and complete investigation of unmeasured anions in critically ill patients was performed by Rocktaeschel et al. (12). They found that unmeasured anions, regardless of the method used to calculate them, were not accurate predictors of hospital mortality (12). Although this study was retrospective, it employed sound methodology and included the largest and broadest adult ICU population.

In the patient population studied by Dr. Dondorp and colleagues, the strong ion gap was a significant independent prognostic factor for hospital mortality. However, although achieving statistical

significance, neither the odds ratio (1.10) nor the area under the receiver operating characteristic curve (0.73) for strong ion gap toward mortality was exceptionally impressive. In this group of severely ill patients with malaria, none of the receiver operating characteristic curves characterizing the association between mortality and other acidosis factors (lactate, classic anion gap, standard base deficit) were particularly robust, as all of these values were <0.80 . These findings are not entirely inconsistent with a prior report, and disagreements are likely to be related to the different patient populations and disease processes under study (12).

In summary, Dr. Dondorp and colleagues (1) demonstrate that as yet unidentified anions are the major contributing factor to the metabolic acidosis complicating severe malaria. Clearly, the origin and nature of these constituents may have prognostic and pathophysiologic implications, and continued efforts should be directed toward unraveling their identity.

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Early tracheostomy—Has its time arrived?*

Questions surrounding early tracheostomy are so common that definitive answers are needed. Is the current practice of placing tracheostomies in patients on mechanical ventilation after 10–14 days correct? Initial evidence from >2 decades ago placed a

caution on early tracheostomy (1–2). However, recently only one paper has not supported the use of early tracheostomy, and this study had author-noted methodological limitations (3). Recent studies consistently favor the use of early tracheostomy in terms of improved clinical outcomes (4–7). However, several questions regarding tracheostomy remain unanswered. For example, what is early tracheostomy? Is it performed on day 2, day 7, or day 10 of mechanical ventilation? Does tracheostomy have a better impact on certain patient populations, for example, trauma vs. complex medical patients?

It is not even clear if the decision to perform a tracheostomy is simply a timing issue. Some authors have reported that factors other than absolute time a patient has an endotracheal tube in place may be associated with benefits of early tracheostomy (8–9). For example, should a tracheostomy be considered in a patient who does not show improvement on chest radiograph and has $>50\%$ of lung field involvement with alveolar infiltrates? Are certain types of patients, such as trauma patients rather than complex medical patients, more likely to benefit?

*See also p. 1689.

Key words: tracheostomy; timing of tracheostomy; mechanical ventilation; complications; airway

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Despite these questions, there appears to be accumulating evidence in favor of early tracheostomy. Benefits regarding safety and efficacy have been reported in favor of early tracheostomy. Factors such as fewer days on mechanical ventilation, less incidence of ventilator-associated pneumonia, and reduced mortality rates have been cited (4–7). Less well studied but just as important are the issues of safety and comfort. The placement of the tracheostomy allows for a more secure and manageable airway, better communication, earlier and safer enteral feeding, and overall better nursing management of the patient (10–12). Tracheostomy also removes a major irritant to the patient, that is, the presence of a noxious stimulus in the oropharyngeal area. This may be a major factor in the need for sedation in the mechanically ventilated patient.

Sure to provide more discussion in favor of early tracheostomy is the article in this issue of *Critical Care Medicine* by Dr. Rumbak and colleagues (13). These authors provide some remarkable findings in support of early tracheostomy (defined as placement of percutaneous tracheostomy by day 2). They also clearly address safety concerns cited against the use of tracheostomy. Some of the key findings address safety (less oral and pharyngeal damage, fewer accidental extubations) and efficacy (a remarkable reduction in mortality [30 vs. 70%], reduced incidence of pneumonia, less time on the ventilator, and a reduced ICU length of stay). The authors clearly demonstrate the safety of percutaneous tracheostomy and a lack of complications when performed by qualified clinicians. The study was strengthened by standard weaning and sedation practices.

Is this study able to put to rest the controversy over timing of tracheostomy? Unfortunately, the answer is no. Although this is an important study and one that will help support the early placement of tracheostomies, there are limitations to the study. One major limitation is the lack of a clear identifying marker as to who will need prolonged ventilation. The authors state that any patients expected to be on the ventilator >14 days were randomized to early tracheostomy. This is too subjective an assessment. How

long a patient is going to require mechanical ventilation is exceedingly difficult to predict. The other limitation is the use of an Acute Physiology and Chronic Health Evaluation score of >25. This limits the generalization of this study to patients with a high risk of death. There may be a population that does not have this high severity of illness score but would still benefit from tracheostomy.

Related to the high Acute Physiology and Chronic Health Evaluation score is the concept of addressing end-of-life issues before tracheostomy (or any procedure) is considered. 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 (14). This conversation is necessary to avoid unwanted and potentially prolonged treatment.

Subsequently, further studies are needed looking for markers for early tracheostomy. In the absence of these markers, a study that examines the impact of tracheostomy on mechanically ventilated patients who are not off the ventilator and show no signs of weaning by day 2 or 3 might be helpful.

Despite these limitations of the literature, evidence is suggesting that early tracheostomies are safe and effective. The current article by Dr. Rumbak and colleagues (13) is a powerful incentive to consider early tracheostomy in any patient with a high severity of illness who is not likely to wean quickly. The authors also provide evidence that the earlier the tracheostomy is performed, the better. The current standard of day 10–14 for tracheostomies has little to support its practice. The reason clinicians are hesitant about switching to early tracheostomy is concern over accepting a practice that is not grounded in sound research. However, the evidence seems to favor early rather than late tracheostomy. A real concern in terms of the current standard of delayed tracheostomy may be the committing of the classic type I error—accepting a practice that is incorrect.

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Sonographic assessment of the hypotensive patient: Is this Jones a winner?*

Vital signs are called vital for a reason: instability in any one signifies an increased risk of mortality (1). Management of emergency department (ED) patients with unstable vital signs has two major goals: the first is to stabilize the patient, and the second is to identify life-threatening conditions in a timely fashion. The approach to the unstable patient follows a predictable algorithm: assess and stabilize the airway, next the breathing, and finally circulation. Assessment and securing of an unstable airway is usually straightforward. Likewise, derangements in breathing are often initially amenable to the application of supplemental oxygen and/or positive-pressure ventilation. Correction of inadequate circulation, as determined by the presence of hypotension, is less amenable to an algorithmic approach. If one takes a simplistic view of the causes of hypotension, they can be categorized as volume depletion, depressed cardiac function, or reduced systemic vascular resistance. The management of each of these broad categories of hypotension is not only distinct, but also potentially harmful if the wrong cause is being treated. For example, administration of vasopressor therapy to the patient with hypovolemia can potentially worsen end-organ perfusion. The patient with a cardiovascular cause of hypotension can be sent into cardiogenic shock through aggressive volume resuscitation. Finally, a number of causes of hypotension require timely interventions, such as surgery for a leaking abdominal aortic aneurysm (AAA) and demand early, definitive, and accurate diagnoses.

In many cases, the cause of hypotension is readily identified through patient history and physical examination. The patient with a known history of dilated cardiomyopathy presenting with evidence of

pulmonary congestion and hypotension is relatively straightforward to manage. Likewise, the nursing home patient with fever, "dirty" urine, and hypotension is rarely a clinical enigma. For many patients who present with transient or sustained hemodynamic instability, the origin is not readily apparent, even after the initial assessment. Adjunctive and readily available tools to assist the physician in narrowing the differential diagnosis, such as the electrocardiogram and chest radiograph, can provide clues to a diagnosis but are rarely definitive. Accurate assessment of the hemodynamic status and diagnoses are usually dependent on advanced imaging studies and/or hemodynamic monitoring, which require transport of an unstable patient out of the department or admission to an intensive care unit. Final diagnoses are often made hours after the initial presentation, with potentially harmful delays in the initiation of appropriate therapies.

The concept of using ultrasound to rapidly identify potentially life-threatening conditions is not new and has been the rationale behind the now-routine use of ultrasound by ED physicians for a wide range of clinical applications. Early descriptions of the role of ultrasound in the ED emphasized the focused or limited examination, which was to answer a specific clinical question, such as, "Is there an AAA, or is there free fluid within the peritoneal cavity?" After more than a decade of clinical use, its role has evolved to not only answer discrete clinical questions, but also to focus the clinical workup of patients who present with vague and poorly defined complaints, such as abdominal pain and hemodynamic instability. For the unstable patient, ultrasound can rapidly focus the diagnostic workup toward conditions that cause either cardiac failure or volume depletion or require surgical intervention, such as a ruptured AAA or hemodynamically significant pericardial effusion. The FAST (focused abdominal sonography in trauma) examination for the

trauma patient was first described in the early 1970s and is the best studied and clinically validated use of ultrasound in the acute care setting (2–4). Performed simultaneously with the primary survey, it rapidly identifies free fluid (presumably blood) within the pericardium, pleural recesses, and peritoneal cavity. It can be repeated in response to changes in clinical stability and has virtually replaced diagnostic peritoneal lavage in the trauma setting. In this issue of *Critical Care Medicine*, Dr. Jones and colleagues (5) describe a similar use of ultrasound for the atraumatic hypotensive patient—a comprehensive sweep of the heart, abdomen, and inferior vena cava (IVC) to assess cardiac function and volume status and to exclude the presence of pericardial tamponade, free intraperitoneal fluid, and AAA (5). The goals of both uses of ultrasound are similar: to rapidly identify life-threatening processes and to focus the diagnostic workup.

Bedside ultrasound provides both structural and functional information about the heart and pericardium. Cardiac causes of hypotension, such as profound myocardial dysfunction or pericardial tamponade, are readily identified. Studies have shown that ED physicians are able to accurately describe left ventricular function as poor/severely depressed, moderate/depressed, or normal (6–9). Physician estimates are most accurate at extremes of cardiac function, e.g., severely depressed or normal, which also have the greatest potential clinical value in this setting (8). Identification of markedly depressed left ventricular function in an unstable patient will shift the resuscitation efforts toward conditions that affect cardiac contractility, such as ischemia and toxidromes. Conversely, demonstration of normal or hyperdynamic cardiac function will allow the clinician to focus the workup toward non-cardiac causes of hypotension.

Identification of a pericardial effusion is relatively straight forward, appearing as an anechoic area surrounding the

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heart. Pericardial effusions are common in patients with a wide variety of clinical conditions, and a recent study (7) found effusions in nearly one third of ED patients presenting with unexplained hypotension or dyspnea. Tamponade physiology is characterized by increasing pressures within the pericardial sac that impair diastolic filling and can be readily appreciated on ultrasound as diastolic collapse of the right atrium and ventricle (10).

Assessment of volume status with sonography relies on the relationship between right atrial pressure and IVC distention and compliance. As central venous pressures rise, the diameter of the IVC will increase and the vein will become "plethoric." In normal individuals, the caliber of the IVC will vary with respirations and predictably collapse when the patient forcibly inhales or "sniffs." As right atrial pressures rise, the IVC will become distended and vary less with respiration. Attempts to directly correlate IVC dimensions with right atrial pressures have had variable results. A study by Mintz et al. (11) found that a right atrial pressure of ≥ 10 mm Hg correlated with an end-diastolic diameter of ≥ 10 mm/m². Others have looked at the degree of respiratory variation in IVC diameter. One study found that when IVC diameter varied $< 50\%$, right atrial pressures were likely to be ≥ 10 mm Hg, and for IVC variations $\geq 50\%$, right atrial pressures were ≤ 10 mm Hg (12, 13). Variations in inspiratory "effort" can affect measurements in a single monitoring period and may remain a limiting factor in defining quantitative parameters. Additional factors that may affect the feasibility of using sonography to assess central pressures are positive-pressure ventilation and underlying obstructive pulmonary disease.

Ultrasound is the study of choice to identify AAA. Its role is simply to demonstrate the presence or absence of an aneurysm. Sonographic measurements of the aorta have been shown to correlate well with measurements obtained on computed tomographic scanning. The presence of an AAA in the setting of hypotension is virtually diagnostic of a leaking AAA and mandates immediate surgical exploration (14, 15).

Previous studies relevant to this application of ultrasound have focused on the ability of ED physicians to obtain and interpret images of single-organ pathology. A comprehensive scanning protocol

to assess the unstable atraumatic patient has been previously described (16, 17). These protocols screen for fluid within the pericardial and peritoneal cavities and the presence of an AAA, assess cardiac function, and were described in the context of case reports. One study describes three scenarios in which a sonographic screening examination identified life-threatening conditions that included a large AAA in a patient with syncope, a 40-yr-old with shortness of breath whose ultrasound showed a large pericardial effusion, and a 45-yr-old with flank pain who had free intraperitoneal fluid from a ruptured spleen (17). In contrast, the second study described the case of a patient with hypotension and normal ultrasound protocol, which focused the diagnostic workup of the treating physician in an appropriate manner (16). Both studies demonstrate the potential value of such protocols, the first being to demonstrate sonographic pathology and the second to rapidly "rule-out" these same conditions.

The next question is whether such protocols, when used prospectively in an undifferentiated population of hypotensive patients, improve patient outcomes? The study to answer that question is a prospective, randomized trial with a control group that did not receive ultrasound. That study does not exist. It appears that despite the paucity of data, the use of ultrasound for assessing the critically ill patient has become a standard of care in many institutions, and having such a control group may actually compromise care.

This article by Jones et al. (5) is the first to prospectively assess the clinical impact of incorporating ultrasound into the assessment of the hypotensive patient. They describe a protocol (which I will refer to here as the "Jones protocol") that included all the windows previously described in the earlier protocols, in addition to an assessment of IVC caliber and right ventricular function. They used the physician's working diagnosis as their outcome measure and showed that physicians were more likely to have the correct final diagnosis in their differential when their patients were evaluated with the Jones protocol. The reader must make a leap of faith to assume that having an accurate working diagnosis translates into better patient care, one I think is not too far a stretch.

In contrast to the earlier case reports, few patients in this study had sonographic examinations that were diagnos-

tic, e.g., demonstrating the presence of an AAA, free intraperitoneal fluid, or pericardial tamponade. For the majority of patients, the role of ultrasound was primarily to eliminate certain diagnoses. There was also considerable overlap in sonographic findings among the final diagnoses. For example, in patients with distributive/infectious causes of hypotension, IVC collapse $> 50\%$ was the most frequently observed finding, which is expected; but severe left ventricular dysfunction (14%) and free intraperitoneal fluid (13%) were also found. It is widely appreciated that sepsis can impair cardiac contractility, and the clinical relevance of myocardial dysfunction demonstrated on bedside ultrasound in the septic patient deserves further study. Left ventricular dysfunction and right ventricular dilation were not surprisingly the most commonly observed findings in patients with cardiovascular causes of hypotension, but nearly 54% of these patients also had a pericardial effusion. Yet, no patient had pericardial tamponade as a final diagnosis.

The sonographic findings in the vast majority of patients in this study cannot be neatly categorized by diagnosis, which is not surprising given the complexity of our patients, particularly the unstable ones. It is widely appreciated that "classic" presentations of critical illnesses are uncommon, and acute illness is often superimposed on myriad chronic conditions and pathologies. The beauty of the bedside sonographic study is that it can be performed simultaneously with resuscitation efforts and is interpreted in the context of other clinical data. The benefits are sometimes difficult to quantify without looking directly at outcomes in a large randomized trial. Real benefits include confirmation of the physician's clinical impression, support of gross assessments of volume status and cardiac function, and exclusion of a few discrete clinical entities.

The challenge is to objectify those subtle findings to determine reliability and reproducibility. For example, are there sonographic markers of IVC dimension and collapse that correlate with central venous pressures? Can they be used to monitor response to therapy? We also need to describe the spectrum of sonographic findings that can be seen in discrete clinical entities, such as sepsis and their clinical relevance. What is the meaning of profound left ventricular dysfunction in the patient with sepsis who

also has a collapsed IVC? This study by Jones et al. (5) is an important first step in showing that ultrasound lends some clarity to the murky waters of the undifferentiated hypotensive patient and raises many more questions.

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Medication vehicle injury—Using the proper restraint?*

When does the solvent used as a vehicle for medications with limited solubility become significant in the care of a critically ill patient? The report by Dr. Arroliga and colleagues (1) in this issue of *Critical Care Medicine* illustrates the challenges posed by delivery of propylene glycol (PG) infused as a consequence of high doses of lorazepam. When the Sedation and Analgesia Guidelines were published, there were only case reports of propylene glycol toxicity with lorazepam therapy, suggesting adverse effects with doses >18 mg/hr (2). Although the current report fails to illustrate the potential magnitude or clinical significance of propylene glycol toxicity, it reminds us that no sedative agent is

completely without risk in the high doses and long durations frequently used in the critically ill.

Dr. Arroliga and colleagues (1) report on patients receiving lorazepam at doses >10 mg/hr. The high-dose lorazepam infusion rate was correlated with elevated single-serum PG concentrations after 48 hrs. Elevated PG concentrations were seen in six of nine patients studied. Importantly, osmolar gap was a strong predictor of propylene glycol concentration. The patients had osmolar gap values >20 and PG concentrations of 94–350 mg/dL.

A similar report focused on patients receiving only doses of ≥ 1 mg/kg/day of lorazepam and described a relationship between osmolar gap and PG concentration (3). Although lower doses were studied and lower PG concentrations observed, there was a similar relationship between PG concentration and osmolar gap. Yahwak et al. (3) suggested using osmolar gap as a surrogate for PG concentration monitoring, with a goal to avoid an osmolar gap ≥ 10 because of

concerns with potential PG concentrations above 18 mg/dL. However, the clinical consequences of an elevated osmolar gap were not described.

What is missing from these reports is a correlation between a broad range of PG concentrations and a clinical risk of toxicity. Individual case reports suggest that serum creatinine elevations, acute renal failure, or anion gap metabolic acidosis may result from lorazepam infusions, but actual serum PG concentrations are infrequently reported (1, 2). Case reports fail to elucidate the role of PG toxicity when critically ill patients are at risk for these symptoms from a variety of insults.

Typical clinical laboratories are unlikely to have the capacity for PG measurement in a timely fashion. The use of an osmolar gap appears to be a reasonable surrogate for the prediction of PG concentration (4); however, the optimal breakpoint to identify clinical toxicity risk remains to be identified.

Propylene glycol kinetics have been studied in volunteers, and an elimina-

*See also p. 1709.

Key Words: sedation; lorazepam; propylene glycol; osmolar gap; toxicity; adults

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tion half-life of 2.3 ± 0.7 hrs was reported following a 4-hr infusion (5). The elimination rate in critically ill patients has not been described. Propylene glycol is oxidized by alcohol dehydrogenase to lactate, subsequently to pyruvate, and acetate and is also cleared renally unchanged or as a glucuronide conjugate. The alcohol dehydrogenase enzyme system is complex and heavily influenced by genetic traits, enzyme induction or suppression, and nutritional effects.

Clinically, patients receiving lorazepam should receive the lowest possible dose to meet the sedation assessment tool goal. The likelihood of PG accumulation appears to increase with lorazepam dose. The use of opioids for analgesia may reduce lorazepam requirements. However, patients with a history of alcohol or sedative use may be difficult to sedate. The dose of intravenous lorazepam may be reduced with concurrent oral lorazepam administration as tablets (the oral liquid also contains propylene glycol). Combination sedation using a benzodiazepine and propofol may reduce the dosing requirements of both agents (6). Alternative sedatives including midazolam, propofol, or dexmedetomidine also have potential risks in high doses, including metabolite accumulation and propofol

infusion syndrome (2, 7, 8). Practitioners must be knowledgeable of the risks associated with high-dose sedative infusions.

The PG content of concurrent medications should also be considered. Etomidate, diazepam, esmolol, nitroglycerin, pentobarbital, phenytoin, phenobarbital, and trimethoprim/sulfamethoxazole are delivered in various concentrations of PG.

Thus, it appears that clinicians need to have a heightened awareness of the potential for PG accumulation with lorazepam infusion and show restraint when titrating these agents to clinical effect. Specific guidelines for dosing and minimization of adverse effects remain to be identified, although a loading regimen followed by the lowest effective maintenance dose is recommended (2). A prospective clinical trial needs to be performed to elucidate the clinical significance of elevated PG concentrations during lorazepam therapy.

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Procalcitonin mode of action: New pieces in a complex puzzle*

An early and reliable diagnosis of sepsis, generally characterized as the excessive activation of an innate host response to infection, is crucial in the clinical setting. Five North American and European intensive care societies have, therefore, recently reviewed the strengths and weaknesses of current sepsis definitions, highlighting the

need to develop better methods for identifying appropriate patient populations not only for sepsis trials, but also for routine bedside use (1)

PCT, the prohormone of calcitonin, was first described as a 116-amino acid protein with a molecular mass of about 14 kDa. The introduction of a sensitive sandwich-type luminescence-based immunoassay detection system allowed extensive clinical studies evaluating the concentration of PCT in different clinical scenarios (2-4). An ideal sepsis marker should allow an early diagnosis, should help to differentiate infectious from noninfectious causes of systemic inflammation, and should inform about the course and prognosis of the condition. It was shown that PCT covers

some of these features, e.g., it is more helpful than C-reactive protein and proinflammatory cytokines in discriminating between viral and bacterial infections and between infectious and noninfectious causes of acute respiratory distress syndrome (3-6). Its use significantly improved the sensitivity and specificity of a diagnosis of clinical sepsis (5). Most recently, it was demonstrated that PCT-guided antimicrobial treatment reduces the use of antibiotics, without jeopardizing clinical outcome in patients with suspected respiratory tract infections (7).

Despite its potential clinical usefulness, surprisingly little is known about the biological properties of PCT and its source of origin. Research tools such as

*See also p. 1715.

Key Words: sepsis; procalcitonin; calcitonin gene-related peptide; biological markers; diagnosis

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pure native or recombinant PCT for *in vitro* studies and well-characterized antibodies for Western blot analysis are missing (8). So far it is known that PCT is encoded by the *Calc-I* gene (11p15.4) and is represented by six highly conserved exons. The transcript encoding exons 1–4 yields a protein composed of 141 amino acids. The secreted form of this protein, called PCT, has a length of 116 amino acids and a predicted mass of about 12.8 kDa. The signal peptide of this preform directs secretion of PCT via the secretory pathway. Evidence is accumulating that human blood mononuclear cells express PCT; its expression and release is induced by treatment with lipopolysaccharide and other sepsis-related cytokines (9).

It was shown that PCT acts as a modulator of the inflammatory/immunologic host reaction (10). In this issue of *Critical Care Medicine*, Dr. Linscheid and colleagues (11) examine the expression of PCT and calcitonin gene-related peptide in different human cell models. The authors investigated gene expression of two CALC-I transcripts and correlated these results with data obtained by highly sensitive antibody-linked assays. Dr. Linscheid and colleagues conclude that a transient PCT expression in peripheral blood mononuclear cells follows mechanical cell activation, such as cell adherence. In contrast to others (9), they found no PCT expression after lipopolysaccharide and interleukin-1 stimulation, which may be due to considerable unspecific cell activation after mechanical stress. The main finding of this investigation is that parenchymal cells are likely to constitute a major source of sepsis-related PCT secretion, which may reach more than 1000-fold levels above normal.

The special merit of this publication is that for the first time, a reliable multimodal model is presented that may explain the dramatically raised PCT serum levels induced by the transition

from infection to sepsis. According to the authors' hypothesis, infectious and inflammatory stimuli can lead to an initial priming of monocytes with transient PCT expression and secretion, followed by monocyte recruitment to the site of infection. This transient PCT secretion is primarily limited locally and may explain the only moderately elevated serum levels in localized infections. The major source of elevated PCT serum levels in severe sepsis and septic shock seems to originate from a different source, namely parenchymal cells (i.e., adipocytes).

Given the potentially harmful effects of PCT, which have been demonstrated in neutralization studies with improved outcome in animal sepsis models using PCT antibodies (12), a closely regulated, biphasic behavior of PCT secretion seems biologically reasonable. As the clinical usefulness of PCT is becoming more evident, it is encouraging that our understanding of the complexity of PCT regulation and its biological role is growing as well.

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Multiple converging mechanisms for postburn intestinal barrier dysfunction*

Severe burn injury can frequently produce multiple organ failures, including gastrointestinal tract dysfunction. In particular, the gastrointestinal tract response to burn is highlighted by altered epithelial cell turnover, absorptive capacity, and intestinal permeability to macromolecules and bacteria. Transient mesenteric hypoperfusion has been generally attributed as the primary cause for diverse gastrointestinal tract pathology associated with severe burn. They range from commonly encountered ileus to infrequent but often lethal diffuse necrotizing enterocolitis (1). In addition to the primary gastrointestinal tract pathology, gut can be the source for systemic release of vast numbers of proinflammatory mediators that contribute to other organ system dysfunction. The concept of postburn intestinal barrier dysfunction with resultant bacterial translocation has been the focus on the potential cause for sepsis and multiple organ failures, including acute respiratory distress syndrome, in severely burned patients (2–6). Despite extensive basic and clinical research, the exact cellular mechanism involved in this process remains largely unknown.

In this issue of *Critical Care Medicine*, Dr. Al-Ghoul and colleagues (7) examined multiple potential mechanisms that contribute to the postburn intestinal barrier dysfunction. Recently, the investigators found that a causal relationship exists between postburn hyperactivation of neutrophils and increased intestinal permeability leading to bacterial translocation (8–10). Others have shown that thermal injury produces significant changes in intestinal cell proliferation and migration (11, 12). Based on these recent reports, the au-

thors set out to determine whether epithelial cell renewal, E-cadherin expression, and neutrophil extravasation contribute as converging mechanistic factors in the burn-induced increases in intestinal permeability. They used a well-established rodent scald burn model, which produces 30% total body surface area scald burns, and evaluated potential multiple mechanisms in the ileal segments for burn-induced bacterial translocation at 3 days postburn.

To examine the epithelial cell proliferation and migration, a single intraperitoneal injection of BrdU was administered at various time points before sacrificing sham and burned rats. They were able to demonstrate that burn injury causes significant delay in ileal crypt cell proliferation as well as migration as assessed by BrdU immunopositive cell counts. They also showed a decrease in the expression of E-cadherin along with an increase in enterocyte apoptosis by immunohistochemical analysis. Because these findings are descriptive in nature, they lack data showing a cause and effect relationship. Nonetheless, both qualitative and quantitative interpretations of these results do suggest that impaired junctional integrity and enterocyte apoptosis along with impaired intestinal epithelial cell turnover rate contribute to postburn intestinal barrier dysfunction.

Next, they performed immunohistochemical staining for granulocyte, elastase and double labeling for von Willebrand factor and granulocytes to colocalize endothelial cells with respect to neutrophils on postburn day 1. They determined that burned rats had increased intestinal lamina propria neutrophil infiltration and extravasation along with elastase immunopositive cells to speculate that increased neutrophil-derived elastase activity lead to E-cadherin degradation and subsequent intestinal barrier breakdown. Myeloperoxidase activity was also significantly increased in ileal samples from burned

rats on postburn day 3. The increased rate of bacterial translocation (*Enterococcus faecalis*) to mesenteric lymph nodes, liver, spleen, and blood from burned rats was significant when compared with sham rats (ranging from 50% to 100%). However, as the authors observed, an increase in ileal permeability with bacterial translocation has also been demonstrated in other models that do not involve neutrophil-derived elastase activity. Endotoxins have been shown to induce increases in intestinal mucosa barrier permeability through xanthine oxidase activation in complement-deficient and macrophage-hyporesponsive mice (13) and regulate enterocyte turnover by Toll-like receptors by endogenous tumor necrosis factor- α (14).

So, is the neutrophil extravasation, impaired epithelial renewal, and junctional E-cadherin primarily responsible for intestinal barrier dysfunction postburn? Burn injury has a profound effect on intestinal epithelial homeostasis, where it produces increases in both apoptosis and proliferation (15). This complex and dynamic regulatory mechanism of intestinal epithelial cell turnover, which is very susceptible to external stimuli, such as severe burns, is not fully understood. Furthermore, the potential role of vast proinflammatory mediators, specifically various cytokines, released during immediate postburn period (<24 hrs) and their effects on systemic inflammatory response should not be underestimated in better elucidating the cellular mechanisms involved in postburn intestinal barrier dysfunction.

The authors should be congratulated for this article with excellent illustrations of immunohistochemical analyses. They admirably propose a theory of converging multiple mechanisms for postburn intestinal barrier dysfunction in which increases in trans- and para-cellular intestinal permeability occur as a result of impaired enterocyte renewal and decreased junctional E-cadherin levels sub-

*See also p. 1730.

Key Words: burn; intestinal barrier dysfunction; neutrophil influx; E-cadherin

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sequent to increased neutrophil influx and extravasation within the villus lamina propria.

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Programmed neuronal death in sepsis: Caught in a crossfire or a planned sacrifice?*

In this issue of *Critical Care Medicine*, Dr. Messaris and colleagues (1) provide further insight into the complexity of sepsis and its associated neurologic morbidity. Septic encephalopathy has been described as a clinical syndrome, but it was usually assumed that, like most metabolic encephalopathies, the neuronal dysfunction was reversible (2, 3). Dr. Messaris and colleagues found brain damage in a rat model of sepsis: The hippocampus, cerebellar Purkinje cells, and choroid plexus cells underwent apoptosis (programmed cell death) compared with nonseptic control rats. Apoptotic neuronal death has been found in humans dying of sepsis but in a different distribution, namely the autonomic nuclei of the brain (4). Despite species differences, the brain is one of the organs affected in sepsis and the

insult is not always reversible. A common pathogenic mechanism may involve the production of cytokines, with induction of inducible nitric oxide and resultant compromise of the microcirculation (5).

There are some alternative possible explanations for neuronal death other than cytokine-related apoptosis. The regions of neuronal death, the hippocampus and cerebellar Purkinje cells, are territories vulnerable to ischemic damage. Could this have been the mechanism for their death, due to either systemic or regional (microcirculatory) hypoperfusion? Although the authors attempted to maintain adequate circulating blood volume, systemic circulation could have been compromised.

The authors' finding of an advantage for survival with increased cytochrome-c activation (one of the markers of a pathway of apoptosis) seems counterintuitive, but this may again reflect the complexity of sepsis, in which the net effect of survival or death reflects a balance between the antimicrobial effects of the immune response vs. the deleterious systemic effects of proinflammatory cytokines and,

in the brain, the balance of proapoptotic and antiapoptotic mechanisms (6). The authors propose that apoptosis may confer an advantage by preventing an inflammatory reaction in the brain, but this is highly speculative and perhaps unrealistically teleological. Apoptosis is almost always an adverse outcome of sepsis in various organs (7–9).

The study by Dr. Messaris and colleagues (1) should serve as an incentive to explore cellular (including neural) protection without compromising the defensive response to infection.

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*See also p. 1764.

Key Words: sepsis; apoptosis; neuronal death; septic encephalopathy

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Fluid overload in multiple organ dysfunction syndrome: A prediction of survival

In this issue of *Critical Care Medicine*, the article by Foland et al. (1), which identifies fluid overload as a predictor of survival at the commencement of continuous renal replacement therapy (CRRT), reinforces emerging literature. CRRT has become a standard of care for patients with multiorgan dysfunction syndrome and acute renal failure in the intensive care unit (ICU) setting (2). Whereas CRRT has been used for almost two decades in both the pediatric and adult populations, predictors of survival at the commencement of CRRT have been an ongoing research (3, 4).

In the last few years, the use of goal-directed therapy as a way to avoid fluid excess for multiple organ dysfunction syndrome has proven to be effective for the improvement of survival. In separate works by Rivers et al. (5) and Brandstrup et al. (6) in septic and surgical populations, fluid restriction as opposed to fluid excess appears to improve ICU survival. Furthermore, in the PICARD study group, data show that the avoidance of CRRT and the use of diuretic therapy diminishes survival (7). Thus, data have emerged that goal-directed therapy to avoid volume excess but also avoidance of

diuretics and, instead, initiation of CRRT affect survival.

From a solute clearance perspective in 2000, Ronco et al. (8) identified that increasing dosing of dialysis improves survival. Furthermore, they identified in their prospective work that the blood urea nitrogen (BUN) at the onset of CRRT initiation can predict outcome in that septic patients with a lower BUN had a greater survival rate than those with higher BUN at the initiation of CRRT.

These works by Foland et al. (1) take a cumulative experience of goal-directed therapy, as well as historical data, on early initiation and have identified and reinforced other data that fluid overload at the initiation of CRRT will predict survival. Data go back as early as 1994 by Lane et al. (9), who identified in the bone marrow transplant population that those patients with volume excess >10% at the initiation of hemodialysis had a poorer survival rate compared with those who had <10% volume excess. More recent data by Goldstein et al. (10) of 21 children who had multiple organ dysfunction syndrome identified that in patients in an ICU who were undergoing CRRT, the fluid overload at the initiation of CRRT was predictive of outcome. Followup on that data in 2004 by Michael et al. (11) identified the same in the bone marrow transplant population. These data do not appear to be pediatric specific. In an abstract by Mehta et al., presented at the meeting of the American Society of Nephrology in 2003, he demonstrated that fluid overload at the time of CRRT initiation can predict outcome, reinforcing the previous pediatric specific data (12).

Foland et al. (1) present data of CRRT in 113 pediatric patients in a convective (CVVH) modality. This population was

the typical cross-section of pediatric patients in the ICU with multiple organ dysfunction syndrome and inborn error of metabolism, as well as patients with primary renal failure. This work expands over 5 yrs duration and transitions from older historical machinery to more recent state-of-the-art machinery. There was no difference in outcome in the historical vs. the more recent state-of-the-art machinery era. During this same time, a similar hemofiltration membrane from two different sources was used; therefore, there was no ability for membrane comparison.

In this retrospective analysis, it was shown that early initiation of CRRT as identified by less fluid accumulation appears to affect outcome. Essentially, what that identified, in this large series of patients, was that the PRISM III score at initiation of ICU admission was not predictive, yet the PRISM III score at the initiation of CRRT was predictive of outcome. Furthermore, the survival fluid overload that was measured from 7 days before until the time of the initiation of CRRT was 9.3% volume excess in the survivors vs. the nonsurvivors with 15%.

The strength of this article is its large numbers and that it was done in a center with controlled and consistent care. Furthermore, the strength of this program is that they have a staff directed toward CRRT that also deals with all extracorporeal therapies, allowing for a truly invested group in extracorporeal therapy, including extracorporeal membrane oxygenation and CRRT. The weakness of this article is that it is retrospective and that the data are from a single center. I think this weakness is minimized by the fact that this is the largest series that reinforces the pediatric data by Lane et al. (9),

*See also p. 1771.

Key Words: fluid overload; continuous venovenous hemofiltration; continuous renal replacement therapy; outcome; multiorgan dysfunction syndrome; PRISM III
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Goldstein et al. (10), and Michael et al. (11) and the adult data by Mehta et al (12).

The pendulum has swung with the concept of goal-directed therapy of low fluid resuscitation, early use of vasopressors, and early initiation of CRRT as factors that appear to predict improvement and survival in the ICU. This work by Foland et al. (1) is an accomplishment for the pediatric population, yet this is not a pediatric-specific article. Data from this article are equally applicable to the adult population, as seen by the work of Mehta et al (12).

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Recombinant tissue plasminogen activator in children with meningococcal purpura fulminans—Role uncertain*

Early aggressive resuscitation is vital in children who present with, or who develop, severe meningococcal disease. Among the difficulties in the management of severe meningococcal disease is recognition of early meningococcal disease. On presentation to hospital, as many as 20% of children have no rash or lack the characteristic (petechiae or purpur) rash of meningococcal disease (2). The rash may develop later. Furthermore, children may present outside routine hours and so may be managed by less experienced staff. Increasing information supports the notion that septic patients who are resuscitated promptly with high volumes of fluid will have a better outcome than children resuscitated more slowly or with lower volumes of fluid (3, 4). In a randomized controlled trial com-

paring early aggressive resuscitation in accident and emergency with routine management, those resuscitated more promptly had lower mortality rates (5).

The standardized approach to the ill child advocated by Advanced Pediatric Life Support and Pediatric Advanced Life Support allows the earlier identification of severe disease and improves management in the "golden hour" when such interventions are likely to be most effective. Severely ill children are then transferred to a pediatric intensive care for further management. With this approach, a reduction in mortality rate of children with severe meningococcal disease has been demonstrated (6, 7). The reduction in mortality rate in intensive care has occurred in the absence of any specific evidence-based interventions. Of the novel therapies trialled in meningococcal disease, none has produced a statistically significant reduction in mortality rate or been introduced into routine clinical practice (8)

Some children remain desperately ill despite aggressive treatment. In these children, novel treatments have been

used, often in desperation. The importance of endothelial dysfunction has become increasingly clear in sepsis and has been confirmed by the effect of activated protein C in reducing mortality rate in severely ill adults with sepsis, although it was associated with an increase in the rate of severe bleeding (9). A disturbance of coagulation is present in most children presenting with meningococcal disease and is worse in the more severely ill children. Expression of thrombomodulin and endothelial cell protein C receptor is reduced in the dermal vasculature of children with severe meningococcal sepsis, which may contribute to the impairment in protein C activation seen in such patients (10). More recently, the results of a phase II study of protein C concentrate in 40 children with severe meningococcal sepsis suggest that treatment with protein C concentrate is safe in children with purpura fulminans (11).

Plasminogen activator concentrations are depressed in meningococcal disease. As well as this, polymorphisms of the plasminogen activator gene are related to disease severity in meningococcal disease.

*See also p. 1777.

Key Words: aggressive resuscitation; meningococcal disease; high-volume fluid

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In this issue of *Critical Care Medicine*, Dr. Zenz and colleagues (12) report the effect of tissue plasminogen activator (tPA) in children with severe meningococcal disease. Of 62 children treated in 24 different hospitals with tPA for poor perfusion or severe ischemia, or sometimes both, 29 children died. Five of the 62 children had intracerebral hemorrhages, of whom three died. This mortality rate is not unusual in a severely ill group of children with meningococcal disease, and although an intracranial hemorrhage rate of 5 of 62 seems high, in the absence of a comparison group, no reliable conclusions may be drawn. How should these findings affect our clinical practice?

The authors are to be commended for pulling together a case series from 24 different hospitals in eight different countries, and they rightly argue for more randomized controlled trials, which will serve best to answer these questions. However, within their series there is a limited amount of clinical information about the children. This is disappointing. Treatment with other agents that may disturb perfusion (e.g., norepinephrine) or ameliorate it (e.g., prostacyclin) is not listed. Treatment with inotropes is not described, nor is the presence of renal failure. The paucity of information renders the series difficult to interpret. The median Pediatric Risk of Mortality (PRISM) predicted mortality rate of 57 of the children was 0.683, which is higher than the sum of the mortality rate of the tPA-treated children (29 of 62, 47%). However, in recent series, the PRISM-predicted standardized mortality rates of children with severe meningococcal disease have been consistently <1, and this rate was less than one half in the latest series (6). As only the median PRISM-predicted mortality is given (and only for a proportion), the standardized mortality rate cannot be calculated.

A randomized controlled trial will be difficult to run for many reasons: The infrequency of the patients will require a multiple-center study, but even so, recruitment in each center will be slow. There will be difficulties with informed consent. The indication for treatment will need to be clearly outlined (limb salvage or generally poor perfusion). It is likely to be difficult to standardize treatment across the many different centers, especially in the most ill children, who will be suitable for tPA treatment. These reasons do not preclude a randomized controlled trial but are the very reasons why we

should attempt to derive the maximum information that we can from uncontrolled use of tPA, both to inform the design of a proposed randomized controlled trial and to inform practice in the absence of a trial. For this purpose, more clinical information about the children is needed. To gather information about rare events from different units across different countries is difficult. As well as this, in recent years greater emphasis on the protection of privacy and respect for autonomy has constrained information gathering, so threatening epidemiologic research and publication of case series. Requirement for consent for a clinical database produces important selection biases (13).

So, in answer to our previous question, the place of tPA is no clearer now than in previous communications on the use of tPA (14–16). The question of whether it reduces mortality rate or increases the rate of intracranial hemorrhage will be answered conclusively only by a randomized trial. To the plea of an earlier editorial regarding the use of tPA—that a randomized controlled trial should be performed (17)—we should add the plea for more complete clinical information in high-quality case series. The important message remains that the mainstay of the management of meningococcal disease remains the early identification and immediate appropriate resuscitation and management of children, some of whom are desperately ill, others of whom are reasonably well.

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