Acute pancreatitis is a common disease with relatively high morbidity and mortality rates. Although the clinical course for most patients with acute pancreatitis is mild, severe acute pancreatitis continues to be a clinical challenge. Potentially lethal attacks are due to the systemic inflammatory response syndrome leading to multiple organ failure. At present, there is no treatment for severe acute pancreatitis, other than supportive critical care (1).

The events that regulate the severity of acute pancreatitis have not been completely defined. It is generally believed that the earliest events occur within acinar cells and result in acinar cell injury. Subsequent to acinar cell injury, recruitment of inflammatory cells and production of inflammatory mediators also occurs and influence the degree of severity (2). The release of potent reactive oxygen and nitrogen species by activated inflammatory cells greatly influences the degree of recovery and, eventually, may lead to cell death by necrosis and apoptosis. The role of oxidative stress in acute pancreatitis has been evidenced directly by pancreatic glutathione depletion and increased lipid peroxidation (3). As highly reactive species, free radicals and oxidants induce oxidation of sulfhydryl groups and thiethers, as well as nitration and hydroxylation of aromatic compounds, thus influencing the structure and function of many enzymes, macromolecules, lipids, and nucleic acids (3). Current evidence suggests that these reactive species not only damage cellular structures but also provoke cellular responses through activation of signal transduction pathways, including the nuclear factor (NF)-κB. Activation of this transcription factor induces a coordinate expression of genes of several inflammatory mediators, including cytokines and adhesion molecules (4, 5). Under these molecular events, cellular injury is further aggravated by the fact that the overproduction of oxidants overwhelms the endogenous antioxidant capacity. Thus, it appears that antioxidant therapy could alleviate the effects of oxidative stress and emerge as an additional therapeutic modality of acute pancreatitis.

In this issue of Critical Care Medicine Dr. Yang and colleagues (6) evaluate the effect of ethyl pyruvate on the local inflammatory response and distant organ injury in a murine model of necrotizing pancreatitis. The authors adopted a novel model of pancreatitis, which was achieved by subjecting the animals to a choline-deficient diet and injection of cerulein and Escherichia coli lipopolysaccharide. This experimental procedure was chosen because it induced pancreatic injury associated with distant organ damage and mortality, thus very closely resembling the clinical conditions of human severe pancreatitis. The authors show that administration of a Ringer’s solution supplemented with ethyl pyruvate instead of Ringer’s lactate alone reduces liver and lung injury, reduces gut mucosal permeability and bacterial translocation to mesenteric lymph nodes, and ameliorates survival. These therapeutic effects of ethyl pyruvate are associated with reduced DNA binding of NF-κB in the pancreas, which well correlates with reduced tissue gene expression of proinflammatory cytokines.

It has been well established that, in addition to supplying energy, pyruvate (CH3COCOO−), a key intermediate in the oxidative or anaerobic metabolism of glucose, is also able to detoxify harmful oxidants. Pyruvate’s antioxidant properties stem in part from its α-keto carboxylate structure, which enables it to directly, nonenzymatically neutralize peroxides and peroxynitrite (7). Therefore, these antioxidant capabilities could potentially protect the pancreas from the ravages of reactive oxygen and nitrogen intermediates. However, the usefulness of pyruvate as a therapeutic agent is greatly limited by its high instability in solution. In an effort to take advantage of the ability of the antioxidant properties of such a compound, the authors have developed a novel resuscitation fluid, which consists of a simple derivative of pyruvic acid, ethyl pyruvate, dissolved in a calcium-containing balanced salt solution, Ringer’s ethyl pyruvate solution (6, 8–11). This solution appears to possess remarkable anti-inflammatory properties, as the authors have previously shown that treatment with Ringer’s ethyl pyruvate solution can improve outcome in a variety of animal models of critical illness, such as hemorrhagic shock, sepsis and ischemia, and reperfusion injury (8).

However, the anti-inflammatory properties of ethyl pyruvate appear to be different from the parent compound pyruvate. For example, although pyruvate has been shown to possess protective effects, the formulation adopted by the authors is much more efficacious and durable than sodium pyruvate in a murine model of endotoxic shock (11).

This ethyl pyruvate solution also possesses a unique mechanistic property, which differs from other antioxidants previously tested in pancreatitis. Despite augmenting total glutathione concentrations, ethyl pyruvate causes a further depletion of this important thiol. Although it is unclear to what extent glutathione depletion contributed to the beneficial effects of ethyl pyruvate in pancreatitis, Dr. Yang and colleagues propose that availability of glutathione disulfide may inhibit NF-κB activation and production of proinflammatory mediators (6, 12). This intriguing mechanism of protection remains to be examined. As the most abundant intracellular thiol, reduced glutathione plays a critical role as an intracellular redox buffer and may determine the balance of transcription for proinflammatory and antioxidant mediators through inhibition of several transcription factors (13). Thus, one would expect that depletion of glutathione would switch the cellular environment to a proinflammatory state. However, several experimental studies prove that this is not always the

*See also p. 1453.

Key Words: oxidative metabolism; glutathione; pancreatitis; nuclear factor-κB

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case. It has been previously reported that systemic administration of the glutathione-depleting agent diethylmaleate prevents up-regulation of adhesion molecules in various inflammatory models, thus suggesting that this agent may offer benefit in systemic inflammatory response (14, 15). Similar findings in murine hepatocytes suggest that extramitochondrial glutathione depletion alters the thiol-disulfide redox state, leading to inhibition of NF-κB transactivation of survival genes, which contribute to the sensitization to tumor necrosis factor-induced apoptosis (16). High glutathione disulfide concentrations inhibit the DNA binding activity of NF-κB in T cells (17). In consideration of this dual role and inconsistent effects of glutathione redox changes on gene transcription, it is interesting to note that controlled clinical studies have not provided clear data about the therapeutic efficacy of glutathione precursor supplementation in pancreatitis (18).

It is clear that a better understanding of the precise mechanisms of action of ethyl pyruvate will provide insightful information, including the role played on oxidative stress, and will certainly improve our therapeutic approach to pancreatitis and other serious inflammatory conditions.

Nevertheless, ethyl pyruvate again proved itself to be a very efficacious, relatively safe, and very simple supplement to Ringer’s solution. Further controlled clinical trials are needed to determine exactly whether supplements of ethyl pyruvate should be added to resuscitation fluids. Ideally, resuscitation fluids should be able to enhance oxygen delivery, ensure microcirculatory organ perfusion, and neutralize the reactive toxic molecules and inflammatory mediators released during tissue injury. The promising experimental results of this study in acute pancreatitis (6) suggest that supplementation of resuscitation fluids with ethyl pyruvate may be a real possibility.

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Delay of neutrophil apoptosis can exacerbate inflammation in sepsis patients: Cellular mechanisms*

C irculating neutrophils are activated in sepsis in response to systemic signals generated by microbial products and/or mediators released from tissue macrophages responding to pathogenic signals. Once activated, these neutrophils migrate across the endothelium and through the interstitium to the site of injury, and there they release reactive oxygen species, and pro- teases to eliminate microbes/pathogens. A number of studies have supported the concept that, in their activated state, neutrophils also release the lytic products along the migratory route, thereby injuring the host’s bystander endothelial and parenchymal cells as well as damaging the extracellular matrix (1). The latter actions of neutrophils can understandable exacerbate both tissue injury and inflammation in sepsis. Previous studies also have indicated that under inflammatory conditions, the life span of neutrophils, which in their resting state is constitutively determined by spontaneous

See also p. 1460.

Key Words: neutrophils; sepsis; microbial products; tissue macrophages; tissue injury; inflammation
apoptosis (2), is prolonged through a significant delay in apoptosis (3). Additionally, recent studies have shown that such delay in apoptosis leading to a decrease in uptake of apoptotic neutrophils by tissue macrophages causes a decrease in the release of anti-inflammatory mediators by the macrophages and thereby a delay in the resolution of inflammation (4). Thus, a delay in the resolution of inflammation accompanying the delay in neutrophil apoptosis can exacerbate host tissue damage in the injured/ill hosts. Hence, investigations leading to elucidation of cellular mechanisms of sepsis-related modulations in neutrophil apoptosis can provide insights into disturbances in the resolution of inflammation in critically ill sepsis patients. In this issue of Critical Care Medicine, Dr. Taneja and colleagues (5) report studies describing some details of mechanisms of apoptosis of circulating neutrophils isolated from sepsis patients.

Several previous studies have suggested that apoptotic rate is suppressed along with an enhancement of reactive oxygen species/protease release functions when neutrophils from healthy individuals/animals are cultured and stimulated with neutrophil-activating agents such as chemoattractants (e.g., N-formyl-methionyl-leucyl-phenylalanine), chemokines (e.g., interleukin-8), lipopolysaccharide (LPS), granulocyte colony stimulating factor, and granulocyte-macrophage colony stimulating factor or with cellular Ca2+ mobilizing agonists or are exposed to hypoxia/reoxygenation conditions simulating ischemia-reperfusion injury (1, 6–8). These agents/agonists/conditions of tissue oxygen deprivation could well be the very factors that can, individually or in some combination, suppress apoptosis and heighten the other functions in neutrophils isolated from trauma/sepsis patients or animals subjected to such injury conditions. A notable finding in the report by Dr. Taneja and colleagues (5) is a marked difference in effect, ex vivo, of LPS compared with that of sepsis syndrome in critically ill patients both on the magnitude as well as mechanism of suppression of neutrophil apoptosis. The dose of LPS employed ex vivo would appear to be compatible to what might cause the systemic inflammatory response syndrome (9). The apoptotic rate observed in sepsis patients was less than one fifth of that observed after exposing healthy persons’ blood neutrophils to LPS; the decrease in apoptosis seemed to correlate with a down-regulation of caspase-3 messenger RNA and activity. Because caspase-3 is the final common distal “executioner” enzyme in the pathway to apoptosis, its down-regulation in the neutrophils of both sepsis patients and healthy persons exposed to LPS was not altogether unexpected.

The effect of both LPS direct stimulation ex vivo and sepsis seemed to be up-regulation of nuclear factor (NF)-κB activation, which is a known antiapoptotic factor in neutrophils (2, 3), but with a discernible difference in the contribution of NF-κB in antiapoptosis with blockade of NF-κB in the LPS vs. sepsis groups. Thus, although the effect of LPS might be primarily through NF-κB activation, sepsis may delay apoptosis via both NF-κB-dependent and independent mechanisms. More pertinent, in LPS-exposed neutrophils, transcriptional expression of caspase-1 (interleukin-converting enzyme) was up-regulated leading to a presumable augmentation of synthesis and activation of interleukin-1β and a subsequent autocrine action of interleukin-1β inhibiting apoptosis (5). On the other hand, there was decrease in interleukin-converting enzyme transcripts and unaltered interleukin-converting enzyme activity in neutrophils from sepsis patients compared with those from healthy individuals. Although not alluded to by Dr. Taneja and colleagues, their mechanistic analysis may be taken to support a view that neutrophil apoptotic suppression in sepsis syndrome is to a large extent independent of effects of LPS. However, it is not possible to definitively include or exclude the role of any of the inflammatory factors, including LPS or the ones mentioned previously, from comparisons of observed ex vivo effects of these factors with those of sepsis syndrome in patients or animal models of injury. This contention is supported by recent studies showing interactions between neutrophils and monocytes/macrophages playing a role in neutrophil responses (10, 11).

Like monocytes and macrophages, neutrophils themselves possess the ability to detect and respond to microbes and their products via their own toll-like receptors (TLRs)/CD14. Recent studies point to an essential cooperative involvement of monocytes/macrophages in the generation of the various neutrophil responses to microbial signals, including modulations in their life span (11, 12). There is evidence now that unless highly purified neutrophils, obtained by the use of a negative selection technique, are employed in experimental studies, the results of neutrophil studies reflect also the cooperative effects of contaminating monocytes in the isolated neutrophil preparation (11, 12) and that gradient-based separation of neutrophil, as was done in the study by Dr. Taneja and colleagues and in most previous studies, invariably results in a low-level neutrophil contamination with monocytes. Moreover, with particular reference to studies of the ex vivo effect of commercially obtained LPS preparations on neutrophils, there would be the expected interaction not only between LPS and neutrophil TLR4 receptor system but also between the contaminant lipopeptide, present in commercial LPS preparations, and neutrophil TLR2 system, as well as possible interactions with monocyte TLR4/TLR2 receptors (12).

LPS alone, as a purified preparation without lipopeptide, has been shown to exert an antiapoptotic effect on purified neutrophils, without monocytes, during early periods of culture (4 hrs) but not at 22 hrs in culture (12, 13). Crude LPS, acting on neutrophils prepared by using gradient-based techniques, likely stimulates both neutrophils and monocytes through the TLR4 as well as TLR2 receptors; thus both the effect of LPS and the interactive effect of monocytes on neutrophil apoptosis are exerted through the TLR4/TLR2 receptor system. The effect of the neutrophil survival factor granulocyte-macrophage colony stimulating factor produced by activated neutrophils/monocytes is known to involve TLR2 rather than TLR4 on neutrophils (14). Although TLR4 and TLR2 receptors have been considered to be respectively activated in a somewhat selective manner by Gram-negative bacterial product LPS and Gram-positive bacterial products peptidoglycan and lipoteichoic acid, the aforementioned findings indicate that both of these receptor systems are involved when LPS alone acts on neutrophils in the presence of monocytes. Of the two receptors, neutrophil TLR2 may be more abundant than TLR4, but TLR4 has been considered to exert a more profound influence in the modulation of apoptosis (12). TLR4 receptor modulations are thus likely to be potentially more relevant for therapeutic modulation of neutrophil functions and survival (11).

The relatively more pronounced inhibition of apoptosis in neutrophils harvested from sepsis patients is likely a re-
sult of complex interactions with monocytes/macrophages through both TLR4 and TLR2 pattern recognition receptor molecules. We can also speculate that sepsis syndrome-related neutrophil apoptosis delay might also be related to nonbacterial pathogenic signals such as cellular Ca\(^{2+}\) overload, tissue hypoxia, and/or ischemia-reperfusion injury in regional gastrointestinal/pulmonary vascular beds. The latter events in the gastrointestinal and pulmonary beds may prime neutrophils as well as alter their apoptotic behavior. Recent studies from our own laboratory have shown that apoptotic delay in circulating neutrophils can occur in a rat model of burn injury which does not involve an overt bacterial invasion of the host (15).

Dr. Taneja and colleagues provide another important insight into the mechanisms contributing to sepsis-caused modulation of neutrophil apoptosis. They report on finding stability of potential difference across the mitochondrial inner membrane, retention of intramitochondrial cytochrome c, and an inhibition of caspase-9 in sepsis patient neutrophils (15). Dissipation of the mitochondrial membrane potential and loss of intramitochondrial cytochrome c, reflective of an opening of the mitochondrial permeability transition pore, are requisites for the onset of spontaneous neutrophil apoptosis through the so-called “intrinsic” mitochondrial pathway of apoptosis culminating in the activation of caspase-9, which in turn is responsible for the activation of the final “executioner” enzyme, caspase-3 (3, 15). Caspase-3 can alternatively be activated by caspase-8, which is activated as an event downstream to the “extrinsic” death receptor pathway of apoptosis triggered by Fas and/or tumor necrosis factor receptor (3). Previous studies have shown that although Fas/tumor necrosis factor receptor pathways triggered by certain proinflammatory cytokines and growth factors can affect apoptosis in healthy human blood neutrophils, they are not the main mechanism of spontaneous neutrophil apoptosis (3). A lesser role of inhibition of Fas receptor-mediated apoptosis with a preponderance of inhibition of the mitochondrial pathway in the sepsis-related delay of apoptosis, indicated in the observations of Dr. Taneja and colleagues (5), is in keeping with the relative roles of the death receptor and mitochondrial pathways in spontaneous apoptosis in resting neutrophils. An overall net activation vs. deactivation of the mitochondrial pathway, respectively, in resting and stimulated neutrophils would seem to depend on differential expressions and activities of pro- and antiapoptotic proteins of the Bcl 2 gene family; a relative abundance of the pro-apoptotic proteins over the antiapoptotic ones may be characteristic of a shorter half-life of neutrophils in healthy hosts and vice versa in activated neutrophils in the injured hosts. The findings of a phenomenon of “silencing” of neutrophils’ mitochondrial apoptotic pathway with the onset of uncontrolled inflammatory condition in critically ill/injured hosts underscores the importance of potential shifts in ratios of expressions/activities of pro- and antiapoptotic members of Bcl 2 family proteins.

Dr. Taneja and coworkers (5) did not find a difference in the delay of neutrophil apoptosis in surviving vs. dying sepsis patients. Although in their study, as is true of a majority of human studies, the presence of a positive correlation may be identifiable between an adverse pathophysiologic variable and patient survivability, absence of such a correlation may simply imply that patient mortality might be dependent on additional pathologic variables. Assessments of impact of delayed neutrophil apoptosis on host mortality may be more feasible in studies in animal models of sepsis, which allow for a better control of factors related to host’s genetic, nutritional, and environmental variabilities.

Overall, the studies of Dr. Taneja and colleagues provide important insights into cellular mechanisms of possible causes of failure of resolution of inflammation in developing sepsis. Such information was hitherto not available and has the potential to lead to the development of novel anti-inflammatory therapeutic strategies.

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β₂-agonists for treatment of pulmonary edema: Ready for clinical studies?*

Pulmonary edema is a common cause for hypoxemic respiratory failure. Once edema has accumulated, irrespective of its etiology, the alveolar fluid needs to be reabsorbed for the epithelium to heal. However, there are no clear guidelines as to how edema clearance out of alveolar spaces can be accelerated. There is significant evidence from animal models, including the article by Dr. McAuley and colleagues (1) in this issue of Critical Care Medicine, where β-agonists have been shown to accelerate edema clearance in normal and injured lungs (2–4). β-agonists via activation of β₂-adrenergic receptors (β₂ARs) regulate key proteins of alveolar epithelial active Na⁺ transport such as the amiloride-sensitive epithelial Na⁺ channels (ENaC), cystic fibrosis transmembrane conductance regulator, and Na,K-adenosine triphosphatase (ATPase) in animal models as well as in human lung tissue.

Stimulation of β₂AR up-regulates alveolar epithelial active Na⁺ transport by increasing the activity of ENaC and Na,K-ATPase and protein abundance at the plasma membrane. Whereas β₂AR-mediated short-term regulation of Na⁺ pumps occurs within minutes via highly regulated recruitment from intracellular compartment through phosphorylation of intermediary proteins and RhoA-kinase (5, 6), long-term regulation is carried out via translation of α₁-subunit of Na,K-ATPase and ENaC subunits through protein kinase A-induced phosphorylation of cyclic adenosine monophosphate (cAMP)-responsive elements and posttranscriptional regulation (via mitogen-activated protein kinase/extracellular signal-regulated kinase and rapamycin sensitive pathways) (7). Similar to ENaC and Na,K-ATPase, data from airway epithelial cells convincingly indicate that β₂AR signaling increases Cl⁻ flux through cystic fibrosis transmembrane conductance regulator (8, 9).

Dr. McAuley and colleagues (1) confirmed that clinically relevant concentrations of β₂-agonists in the alveolar epithelial lining fluid-edema (10) increased alveolar fluid clearance (AFC) and decreased pulmonary edema in a model of acute lung injury (ALI). They also showed that salmeterol was the most effective β₂-agonist in resolution of pulmonary edema in an acid-induced ALI model similar to their previous report in hydrostatic pulmonary edema (11). Although salmeterol was more potent than albuterol, the maximal rate of cAMP-dependent AFC was similar with both medications.

The difference between the current study and previous investigations that evaluated the effects of similar concentrations of β₂-agonists on AFC was the determination of maximal cAMP-dependent AFC in rat lungs. There is a large body of evidence showing that β₂-agonists at similar doses increase AFC in normal lungs and in models of ALI such as hypoxia (2) and ventilator-induced lung injury (3). In view of the previous reports and the data that cAMP is the second messenger for β₂AR, it is reassuring that stimulation of β₂AR achieved maximal cAMP-dependent AFC. These findings support previous work showing that inhaled β₂-agonists can achieve alveolar concentrations to cause maximal stimulation of fluid clearance, and they suggest clinical relevance to the management of patients with pulmonary edema. Most patients with pulmonary edema due to ALI have impaired ability to clear excess of alveolar epithelial fluid, and those who have higher rates of clearance (a minority of these patients) have better outcomes (12).

Some aspects of this report need further elucidation. For example, it is surprising that β-agonists selectively improved endothelial but not epithelial permeability. Also, the response to the β₂-agonists was delayed, which is somewhat different from the effects of β₂-agonists on alveolar epithelial cells, which occur within minutes. Previously published effects of β-agonists in other models of lung injury such as acute heart failure (high left atrial pressure), hyperoxia, and ventilator-induced lung injury models suggested that improvement in clearance occurs rather quickly within 1 hr (2, 3, 13). However, most of the previous reports showing beneficial effects of β₂AR in models of lung injury have been limited to animal models with mild to moderate ALI. This raises the question of whether in more severe models of injury or clinical situations such as acute respiratory distress syndrome, the epithelium is critically injured and even denuded interfering with and offsetting the beneficial effects of β-agonists on the alveolar epithelium. As such, it is unclear whether β₂AR-dependent mechanisms of up-regulation of active Na⁺ transport would be preserved during severe lung injury. Theoretically, another limitation of β₂-agonist therapy is the receptor desensitization. Sustained, high-dose albuterol infusion diminishes adenylyl cyclase (formation of cAMP) and protein kinase A activity in the alveolar epithelium (14).

The study by Dr. McAuley and colleagues (1) is an important step in the right direction leading us to propose a clinically testable hypothesis of whether β₂-agonist treatment by enhancing permeability and the clearance of pulmonary edema improves survival of patients with hypoxemic respiratory failure. These findings are encouraging, and we believe that time is right to design clinical studies and evaluate the therapeutic potential of β₂-agonists in patients with pulmonary edema.

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*See also p. 1470.

Key Words: adrenergic receptor; albuterol; isoproterenol; salmeterol; acute respiratory distress syndrome; acute lung injury; alveolar epithelium

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When will it be clear?*

The search for a relationship between performance based on volume of experience and outcomes is at the forefront of our thinking in judging quality of care. Drs. Marcin and Ramano’s study (1), in this issue of Critical Care Medicine, attempts to evaluate the relationship between a hospital’s volume and changes in hospital volume over time as predictors of mortality rate and readmission rates for trauma patients in the state of California. These authors suggest that for younger patients, there is no relationship between volume and mortality rate. For elderly patients, higher annual volume is associated with lower mortality rate. Furthermore, the authors suggest that higher than average monthly trauma volumes within one hospital are associated with an increased likelihood of readmission. This suggests that a high volume overextends existing resources beyond their capacity (1).

Several studies have suggested a relationship between trauma center volume and outcomes (2–6). Nathens et al. (2) found an association of improved mortality rate in trauma centers admitting >650 patients with an Injury Severity Score >15. With the assumption that typical trauma admissions are approximately 4 or 5 to 1 times the number of patients with Injury Severity Score ≥15, this suggests that overall trauma hospital volume of 2,500–3,000 patients is necessary to achieve this volume performance relationship. Part of the reason the present study may have not been able to show this association is that there are only about two hospitals in California that would achieve these volumes. The statistical analysis of the present study may not have been able to detect a significant mortality rate relationship with volume because of this problem.

Other studies suggesting a relationship between volume and outcome in seriously injured patients have been less compelling (3–6).

For other surgical diseases, there does seem to be a more compelling argument (7, 8). For diseases such as carotid endarterectomy or coronary artery bypass, mortality rate does seem to depend on the number of patients undergoing these procedures in an individual hospital. The ability to create discrete differences in outcome using trauma patients is not as easy because most of the less severely injured patients will not show differences in mortality based on volume. It is critical for studies to focus on the patients with the highest likelihood of mortality if a volume performance relationship is to be demonstrated.

Perhaps a greater issue with regard to trauma patients is the fact that to achieve concentration of large numbers of severely injured patients in individual trauma centers, a better acceptance of regionalization of trauma needs to be developed. This is essential so that excessive numbers of trauma centers in individual geographic areas do not dilute this experience below a critical volume threshold. This type of study is important as we develop regionalization of trauma and other diseases associated with high mortality rate. We need to make public health policy and regionalization decisions with the best interest of patients at heart, and as more of this type of data are available, these decisions will become easier.

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On speaking less and listening more during end-of-life family conferences*

In this issue of Critical Care Medicine, Dr. McDonagh and colleagues (1) report their findings on family-provider communication about end-of-life care from 51 audiorecorded family conferences drawn from four intensive care units in the Seattle area. Specifically, the authors hypothesized that increased proportion of family speech during family conferences would be associated with greater family satisfaction. The topic of inquiry is important and timely given the centrality of good communication and positive family-provider relations to end-of-life care and indications that there is considerable room for improvement (2–5). The family conference provides a novel, valuable setting for data collection given the growing emphasis on incorporating patient and family perspectives into efforts to improve the quality of dying and death in the United States (6–8).

Family experience and satisfaction with hospitalization often rest with the quality of family-staff communication, relationships, and the extent to which families and staff members are engaged in partnership (9–11). If bad news is communicated poorly, it can result in confusion, long-lasting distress, and resentment; if done well, it can promote understanding, acceptance, and adjustment (12). As the authors emphasize, there is little doubt that good communication is vitally important and worthy of our concern. Indeed, families rate the communication skills of clinicians as having equal or greater importance than their clinical skills (13, 14). Families remember the words and manner of clinicians long after they have forgotten the medications, procedures, and details of treatment. Unfortunately, strained and limited family-staff communication is often cited by family members as problematic and in need of improvement. Half of all families of intensive care patients have reported experiencing inadequate communication with physicians (2). Similarly, in a study examining what is wrong with end-of-life care, 44% of families suggested improvements emphasizing communication and access to providers (4). In a recent review of pediatric palliative care, Stильlon and Papadatou (15) concluded that communication among patients, families, and clinicians needs to be radically improved.

This and previous work of McDonagh and colleagues (1, 16) is distinguished by a dedication to systematic empirical study of end-of-life communication to better understand and guide clinicians regarding how to improve communication with families in the context of a specific setting, the family conference. The family conference at the end of life is arguably one of the pivotal events of hospitalization and one that naturally lends itself to communicative interchange between families and providers. At its best, the conference can bring family members and providers together to exchange information, consider and weigh the clinical options, share in the emotional burden of care, and set the course for continued treatment, palliation, or withdrawal of life-sustaining therapy. At other times, the conference can be a dreaded, tension-filled event for families and providers alike. Communication challenges can arise within families or between families and providers when there are differences of opinion and strong feelings about continuing aggressive treatment, redirecting to palliative care, or withdrawing life support (17). Conflict and communication difficulties can develop and flare within families when there are complex issues of culpability, shame, guilt, and blame associated with the patient’s illness. There is little wonder that providers could benefit from empirically derived guidelines, given the admittedly high stakes and demands for communicative competence that characterize family conferences.

Access to families and recruitment for the study comprised a necessarily step-wise and delicate process that resulted in the audiotaping of just under half of all eligible conferences. The researchers were denied access to several eligible families based on requests by the treating physicians and nurses. Of course, most at issue here are concerns about selection bias and generalizability of findings. It was not possible for the researchers to determine whether those families to whom they were denied access or who refused participation differed in any way from those families who ultimately par-

*See also p. 1484.

Key Words: family-provider communication; end of life; intensive care unit; family conferences; family satisfaction; quality of dying

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ences, talking 71% of the time compared verbally dominated the family confer-

menced and included ratings of the physi-

logistic and methodological challenges.

Results demonstrated support that in-

decisions, and how well the family
understanding of health care choices and

for end-of-life discussions to follow a review of

is important to them now (23–25). The inclusion

which, ultimately, encouraged patients to

raters spent nearly twice as much time and

in health care conversations by listening

and impersonal health care system, may

greater sense of family needs being met,

who had more time to talk reported not

who spoke 75% of the time compared

are understood by fellow clinical-re-

nullify the notion of their own anxiety or wish to

proportion of family speech in

with family members (29%). The findings

early in the conversation, what they

In general, clinicians

verbally dominated the family confer-

and worry (20, 21). Indeed, the prevailing

In summary, this study of family-

communicative ability and listen-

change meaning relative to survival and

medical residents who spoke 75% of the
time during do-not-resuscitate discus-
sions (18). The range of physician talking

(33–97%) was quite remarkable, how-

and listening, better understanding of the

it affects what it all means relative to survival

and need to know, the basis, both of

More over, the expert clinicians excelled in the

use of a patient-centered, partnership-

between families and providers, invite family

results show promise and are fertile areas

experience inadequate communication with

patients, families and providers.

The role and impact of psycho-

providers may decrease family anxiety

and worry (20, 21). Indeed, the prevailing

mode of end-of-life discussions that fo-

fuses on organ systems and individual

treatments, in which providers do most

of the talking, may be too specific to

facilitate decision making or to meet the

family’s psychosocial needs in the face

of death (6). It is not uncommon for

end-of-life discussions to follow a review of

systems approach or to present informa-

tion on a need-to-know basis, both of

which can leave the family wondering

what it all means relative to survival and

quality of life (22). It should be acknowl-

dged that these modes of communica-

tion empower and showcase providers

rather than patients and families. To

equalize this power and agenda-setting

differential, several models of end-of-life

communication emphasize the impor-
	ance and necessity of asking the family,

early in the conversation, what they

know, what they want to know, and what

is important to them now (23–25). The

include of such questions can help to

build collaborative relationships between

families and providers, invite family per-

spectives and input, and promote dia-

logue between people rather than mono-

logue. Beyond guidelines and curricula

for end-of-life discussions, there is grow-

ing recognition and emphasis on provider

relational skills, self-awareness, and

expression of humanity during conversa-

tions with families (25–28). Indeed, ac-

cessing and showing one’s humanness in

health care conversations by listening

more, inviting reflection, and acknowl-

dging emotions may be the “other be-

haviors” that the authors allude to that

may accompany less physician talking, and

helps families to feel heard.

In summary, this study of family-

provider communication during end-of-

life family conferences offers compelling
data on the importance of providing fam-

ily members with opportunities to talk, to

be listened to, and to be heard. Families

who had more time to talk reported not

only greater satisfaction with the confer-

ence, including better impressions with

the physician’s communication ability

and listening, better understanding of

the health care choices and decisions,

and greater sense of family needs being met,

but also less conflict. The take-home

message for providers is to speak less and
to listen more in family conferences. Too

often, providers can open with long

monologues, overwhelm families with

facts, or verbally dominate conferences,

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Acute brain injury: If hypothermia is good, then is hyperthermia bad?*

*See also p. 1489.

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Much has been written about the “details” of critical care medicine and their potential impact on patient outcome and well-being. As examples, plasma glucose management, airway pressure, detection of adrenal insufficiency, presence of intensivists in the intensive care unit (ICU), deliberate hypothermia postcardiac arrest, and the use of activated protein C in sepsis are all discussed as details that can affect outcome (2–7).

Although acknowledging the importance of this work, it remains our incum-
of hyperthermia to almost all patients with neurologic injury who would be found in a neurologic ICU.

The detrimental consequences of hyperthermia on cerebral ischemia have been well documented in both animal models and clinical practice. In rodent models of global and focal cerebral ischemia, elevated brain temperature increased both the rate of maturation and extent of cerebral infarction. This appears to occur with even small and/or delayed increases in temperature (11–13).

The exact mechanism by which hyperthermia may increase neuronal death and worsen overall outcome is speculative. Several lines of evidence point to a role for increased neuronal excitotoxicity. In animal models, hyperthermia increases neurotransmitter release, accelerates free radical production, increases extracellular glutamate concentrations (an excitotoxin), and potentiates the sensitivity of neurons to excitotoxic injury (11).

Presumptive evidence for increased excitotoxicity during hyperthermia is corroborated by a) an observed increase in cellular depolarization in the ischemic penumbra surrounding damaged neuronal tissue; b) observed increases in neural intracellular acidosis; and c) measured inhibition of enzymatic protein kinases responsible for synaptic transmission and cytoskeletal function (14–16). Additionally, worsened cerebral edema in hyperthermia may be mediated by an increase in neuronal proteases (17).

Whatever the exact mechanism, temperature regulation in neurologic injury appears to be important. The majority of clinical studies have suggested that hyperthermia worsens functional neurologic outcome whereas mild hypothermia is neuroprotective. Two randomized clinical trials have supported the use of mild hypothermia after cardiac arrest with suspected global anoxia (7, 18). Interestingly, the failure of a recent neuroprotective agent in ischemic stroke has been potentially attributed to an increase in temperature observed in the treatment group (19).

What has not been established is whether the maintenance of euthermia in patients with neurologic injury is in itself neuroprotective. Traditional methods to control for fever have largely been ineffective in the neurologic patient population (20). Dr. Diringer and colleagues (21) have previously reported on the feasibility of using intravascular devices to maintain euthermia in a neurologic population. Other extracranial devices are currently being tested.

The groundwork has now been laid for a trial comparing aggressive maintenance of euthermia with traditional methods in a neurologic patient population. For decades, neurologic textbooks advocated for the aggressive treatment of fever (22). Perhaps now we soon may be able to prove them right.

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Think globally and act regionally: How do we use the computed tomography scan assessment of lung inflation in acute respiratory distress syndrome?*

In their seminal article, Webb and Tierney (1) illustrated how inflation pressures of 40 cm H₂O can cause pulmonary edema in normal rat lungs. Dreyfuss et al. (2) later demonstrated the physiologic correlate that normal rats ventilated with high inflation pressures rapidly developed pulmonary microvascular injury with alveolar flooding of edema with high protein content. These same authors went on to prove that this mechanical ventilator-associated acute lung injury was due to high tidal volume rather than high inflation pressure (3).

Early reports of computed tomography (CT) of the lungs of patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) revealed the distribution of infiltrates to be markedly heterogeneous with areas of the lung being radiographically normal (4, 5). It was the revelation from CT scans that led to the understanding that patients with ALI/ARDS were at risk of developing further acute lung injury from the primary means of supportive care. However, the same studies that related overinflation to acute lung injury in rats also showed a protective effect of positive end-expiratory pressure (PEEP) (1, 3). Consequently, a lung-protective strategy employing a higher than normal level of PEEP and reduced tidal volume to avoid cyclic overinflation and derecruitment of alveoli in patients with ARDS was shown to reduce 28-day mortality rate and improve the rate of weaning from mechanical ventilation (6). Subsequently, a large, multiple-center, randomized controlled trial sponsored by the National Institutes of Health was stopped after enrollment of 861 patients due to a 22% relative reduction in mortality rate with tidal volumes of 6 mL/kg compared with 12 mL/kg predicted body weight, definitively proving the benefit of ventilating patients with ALI/ARDS with low tidal volumes.

In this issue of Critical Care Medicine, Dr. Nieszkowska and colleagues (7) report a reanalysis of CT data demonstrating regional differences in recruitment and overinflation at zero end-expiratory pressure and after application of PEEP 15 cm H₂O in patients with ALI with and without chronic obstructive pulmonary disease. The current report builds on a large body of work by this group using CT analysis to evaluate regional distribution of lung inflation in ALI/ARDS (8–12). They have previously shown that the loss of lung volume disproportional affects the lower lobes with reduction of volume along the cephalocaudal axis and is correlated with PEEP-induced recruitment in the cephalad and nondependent regions of the lungs in the supine patient (8). Interstitial edema or alveolar edema rather than atelectasis predominates in ARDS with collapse of alveoli occurring in the supine position due to mechanical compression by the diaphragm and heart (10). The association between air and tissue heterogeneity, PEEP-induced overdistension, and the presence of a lower inflection point on the lung pressure-volume curve provided a physiologic correlation to CT findings (9). Although recruitment as detected by CT has been traditionally quantified byGattinoni et al. (13) as the reduction in nonaerated tissue with the application of PEEP, this group has adopted the approach of calculating the volume of gas penetrating both poorly aerated and nonaerated lung regions after pressure is applied (11). Using these methods of analysis, Dr. Nieszkowska and colleagues (7) have correlated the degree of PEEP-induced overinflation based on the heterogeneity of the loss of aeration and presence of chronic obstructive pulmonary disease (7, 12).

As a result, Rouby et al. (12, 14) advocated the use of the radiographic morphologic pattern to guide the application of PEEP, using higher levels of PEEP only in the minority of patients who show a diffuse loss of aeration. The recommendation by Dr. Nieszkowska and colleagues (7) to supplement moderate levels of PEEP in the patients with focal loss of aeration with nitric oxide, intravenous almitrine, and prone positioning is logical. Certainly the concern for overinflation in ventilator management in ALI/ARDS is beyond dispute. These authors acknowledge the limitations of their analysis, particularly density averaging based on the size of the voxel and the contribution of paralytics to diaphragmatic displacement.

However, there is also limitations inherent in extrapolating physiologic data to clinical practice. For example, the ARDS Network performed a subsequent ventilation trial which, in addition to using low tidal volume, randomized patients with ALI/ARDS to a high PEEP/low FiO₂ strategy or a low PEEP/high FiO₂ strategy. This trial was stopped after 550 patients for lack of efficacy (15). In addition, although prone positioning has been shown in some patients with ALI/ARDS to improve oxygenation, a randomized controlled trial failed to show improved survival (16).

The data from CT studies of the lung in patients with ALI/ARDS are useful in understanding not only the complexity of the disease but also the impact of an intervention as routine in the intensive care unit as the application of PEEP. One can hypothesize why high levels of PEEP may be a better management strategy for patients with a diffuse morphologic pattern of nonaeration, and a moderate level of PEEP combined with prone positioning, nitric oxide, or intravenous almitrine.
may be better for patients with a lobar morphologic pattern. However, like most innovations in medicine, the evidence for improved outcomes and recommendations to alter clinical practice can best be derived from randomized controlled trials.

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Affordable health care for all Canadians?*

The article by Dr. Needham and colleagues (1) in this issue of Critical Care Medicine demonstrates clearly that use of mechanical ventilation has increased in Ontario over the 1992–2000 period by 9% and paralleled the increase in aging of the Canadian population in this province. Because of a decline in general hospital bed capacity, the proportion of hospital inpatient days devoted to patients receiving this intervention increased by 69%. The incidence of mechanical ventilation in Ontario at the end of the time period was shown to be approximately the same as that in the United States.

These findings will be surprising to those familiar with comparisons of health care in the United States and Canada. Canada is generally seen as the more cost-constrained system, with lower costs in part due to reduced use of high-technology and capital intensive interventions (2, 3). For ICU care in particular, it has been shown that Canada has relatively fewer intensive care unit (ICU) beds, lower ICU costs, and a lower tendency to use the ICU for particular patient groups (4, 5). Mechanical ventilation appears to be an exceptio to this trend.

The time period covered by this study was one of considerable budget fluctuations in Ontario. From 1992 through 1996, Ontario public expenditures on health decreased annually but experienced large increases after 1998 (6). Inpatient bed days decreased by 26% as reported in the article by Dr. Needham and colleagues (1). Given the egalitarian emphasis of Canadian health policy relative to the United States (7) and the cost-constrained environment, one might expect that expensive technologies would be constrained relative to those in the United States. However, mechanical ventilation has not followed this pattern. It is expensive, used for a relatively small group of people, and frequently used near the end of life. The hospital mortality rate reported in this study was about 30%, and at the end of the time period studied 46% of patients with ventilation were over age 70. Yet the number of inpatient days for mechanically ventilated patients as a proportion of total adult inpatient bed days increased by 30%. Given the overall restrictiveness of healthcare budgets, this would seem to imply that hospital care for nonventilated patients was reduced more than it would have been otherwise. One wonders about the specific opportunity costs of such a strategy, that is, what hospital services and types of patients were characterized by decreasing proportions of hospital days.

Yet, despite the seemingly generous allocations given to ventilation, an increase in mortality rate of ventilated patients over time was a major finding.

*See also p. 1504.

Key Words: mechanical ventilation; intensive care unit utilization; intensive care unit; Charlson index; Canadian healthcare system

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of the study and was contrary to the authors’ working hypothesis. A possible explanation of this was a changing patient mix including increased severity of illness. The authors attempted to take this into account by using information on age, diagnosis, and comorbidity. In particular, they used the Charlson index, which relies on coded comorbidities, to help explain severity trends in ventilated patients (8). However, there is reason to believe that secondary diagnosis coding in administrative data in Ontario increased quite dramatically during this period (9). Some of the measured increase in comorbidity might have been due to changes in coding practices. This issue should be addressed before drawing any conclusions about disease severity. The Charlson index would be considered limited compared with the validated general ICU severity scoring systems, but these are not available in administrative databases.

Another possible explanation for the increase in mortality rate, of course, is that the mortality rate increase reflects issues related to patient safety or quality of care. Patients on mechanical ventilation require complex coordinated care regarding sedation, setting the tidal volume, weaning, and minimizing so-called “self-extubation” (10–13). For these quality and safety concerns, the Leapfrog Group has promulgated a clear vision of the credentials and time commitment of the intensivist.

Hospital ICU care should be managed by physicians certified (or eligible for certification) in critical care medicine who are present during daytime hours; who provide care exclusively in the ICU; and who, at other times, can return ICU pages promptly and rely on a certified “effector” to implement telephonic orders (14). The latest version of the Society of Critical Care Medicine’s mission statement emphasizes the role of the “integrated ICU team of dedicated experts directed by trained and present physicians” (personal communication, Society of Critical Care Medicine).

The authors note that this increase in mortality rate should be the subject of further investigation, and we agree.

The article by Dr. Needham and colleagues (1) highlights important policy issues that will only become more prominent as the population ages and public expectations for health care continue to increase. The resource use for mechanical ventilation and its increase over time is striking. Indeed, since the article omits cardiac surgery patients, a patient group for which mechanical ventilation is important, it underestimates the total amount of resource use devoted to this technology. We agree with the authors that knowledge of these trends is important for healthcare resource planning. However, we suggest that it is important that the policy and planning response to trends for technologies such as mechanical ventilation not be itself a mechanical extrapolation of increasing utilization into increased resource commitment but rather a careful weighing of the alternatives and opportunity costs in the context of overall healthcare needs. Otherwise, affordable health care will not be available for Canadian patients who are not on life support.

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Sepsis: Let's go back to the infectious process*

Should we liken pneumococcal meningitis to postoperative coagulase-negative staphylococcal meningitis? Do pneumococcal meningitis and pneumococcal pneumonia raise the same problems? Of course not.

However, in most studies of sepsis, the exact cause of infection is not clearly reported. Usually, even in the most recent and largest studies (1–7), the sites of infection are listed but the microorganisms are either not given at all (2) or not described in detail (1, 3, 5, 6). As a result, the reader cannot determine the rate of a specific common infectious disease, such as pneumococcal pneumonia. On the contrary, the number and the severity of organ dysfunctions are reported and sometimes used for subgroup analyses (3, 8). However, prompt and appropriate management within the first hours of the infectious process may markedly decrease the severity of infection-related organ dysfunctions and the associated mortality rate (9, 10).

The variability in the causes of sepsis probably explains the considerable variation in mortality rates associated with severe sepsis in the placebo arms of randomized trials or in epidemiologic studies (11–13). For example, in the study by Alberti et al. (12) based on the European sepsis database, the outcome of critically ill infected patients depended not only on the severity of acute organ dysfunction or shock but also on characteristics of the infectious process such as nosocomial origin; aerobic Gram-negative bacillus, enterobacteria, or Staphylococcus aureus as the causative organism; and gastrointestinal or unknown portal of entry.

In an attempt to better describe the infectious process, Dr. Cohen and coworkers (14) conducted a study reported in this issue of Critical Care Medicine in which they graded infections based on the median crude mortality rate (from \( \leq 5\% \) for grade I to \( \geq 30\% \) for grade IV) reported in previous studies of patients with infections that were similar in terms of site and causative microorganism. The data were categorized according to the number of published articles and of study patients (from >100 patients and more than five studies for category A to anecdotal case-reports for category E). Dr. Cohen and coworkers recommend that their Grading System for Site and Severity of Infection (GSSSI) be used to compare the type and severity of infections in clinical trials of patients with sepsis. Their approach is clearly meritorious.

However, whether the crude mortality rate can serve as a surrogate for the severity of infection is debatable, especially in intensive care unit patients, who are exposed to many causes of death. Even in studies dealing with very common infections such as S. aureus bacteraemia, the crude mortality rate varied widely across studies, from \(<4\%\) to \(>80\%\) (15). This variability can be ascribed to many causes, including patient-related factors such as susceptibility to infection, chronic underlying diseases, and intensity of the host response; infection-related factors such as virulence of the microorganism (16), site of the infection (presence of endocarditis or line infection in our subsequent example), and resistance to available antimicrobials (15); and treatment-related factors such as promptness and appropriateness of the initial antimicrobial (17) and symptomatic (10) treatment.

Another very important source of variability that is not taken into account, as acknowledged by Dr. Cohen and coworkers (14), is related to the possible confusion generated by pooling community- and hospital-acquired infections. For example, coagulase-negative staphylococcal bloodstream infections have the same grade as pneumococcal bloodstream infections (grade III: mortality 18% and 20%). However, the infection-related mortality rate is close to zero in the former but is substantial in the latter. If the GSSSI were used to characterize infections in a randomized trial, and if chance led to a higher rate of staphylococcal bloodstream infections in one arm and to a higher rate of pneumococcal bloodstream infections in the other arm, the grades would be similar but the expected mortality rates very different, so that the results would be misleading.

Finally, although all available reports were taken into account, the number of studies and patients was very small for some infections. For example, the grades of coagulase-negative S. aureus pneumonia and enterococcal pneumonia were based on only two and four patients, respectively. These small numbers cast doubt on the validity of the grade estimates.

Nevertheless, as suggested by the authors, the GSSSI could be improved over time by using additional data. For this purpose, and to improve our interpretation of the results of future randomized studies of sepsis, the exact causes of infection (microorganisms, infection sites, and community- or hospital-acquired infection) and the promptness and appropriateness of antibiotic treatment should be reported, at least in online supplements.

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How will we respond to chronic critical illness?*

Dr. Nelson and colleagues (1) have conducted a valuable study of chronic critical illness, and the hard-hitting news is not good. Study patients had a median hospital stay of 50 days. Ninety percent of the patients were symptomatic with an average of 8.6 symptoms each; 44% experienced pain at the highest levels of distress. After enduring this arduous process, only half were liberated from the ventilator, more than half died by 3 months after discharge, and only 4% went home. The study was carefully designed to get opinions from respondents while they were in the midst of their intensive care unit (ICU) experience, and data collection instruments were meticulously selected to reflect the experiences of chronically critically ill (CCI) patients.

For the reader who is not knowledgeable about chronic critical illness, these data need to be put in context. CCI patients tend to be those requiring intensive care for weeks to months. Although researchers and administrators do not use a uniform definition, some investigators, like the authors of this study, have used the performance of tracheostomy for continued mechanical ventilation as an indicator of CCI. This definition, which is associated with Diagnosis Related Group 483, allows for study of such patients in administrative databases making large epidemiologic studies possible (2). It should be acknowledged that other studies of chronically ventilated patients do not yield quite such unfortunate results (2). This is likely a reflection of the variability in defining CCI patients. Studies to stratify CCI patients and improve outcome prediction will be valuable (3). It should also be pointed out that not all chronically ventilated patients fare as poorly as the CCI population (4).

Given these caveats, how should clinicians respond to marked symptoms and poor outcomes of CCI patients? Efforts to mitigate symptoms should take precedence. Clinicians should be cognizant of how often these patients experience hunger, thirst, and should make it a habit to ask about and attend to these symptoms. Protocols to improve quality of care ought to standardize such efforts. Expertise about communicating with mechanically ventilated patients should always be part of respiratory care. Relief of dyspnea and pain should be handled sensitively and be balanced with efforts to wean from mechanical ventilation.

But aside from the need to relieve symptoms, clinicians will need to wrestle with extraordinarily tough life-sustaining treatment decisions. Given the marginally beneficial outcomes, should tracheostomy be performed or not? How long a therapeutic trial should patients undergo? Certainly intensivists are used to such decisions. Will the strategies used in acute illness apply for CCI? In caring for an acutely ill patient, the adept critical care specialist tries as much as possible to assess the likely outcomes of different treatment options and respect the patient’s treatment preferences in establishing a plan of care. It is quite likely that these practices, when combined with the skills of palliative medicine and rehabilitation medicine, will apply to CCI.

But perhaps it is time to go beyond the lessons we have learned in caring for acute critical illness at the bedside, to develop better strategies for prioritizing critical care. We know that patients who face life-threatening illness often wish to have life-sustaining treatment, even in the face of variable quality of life and poor

Drotrecogin alfa (activated) in the treatment of severe sepsis patients with multiple-organ dysfunction: Data from the PROWESS trial. Intensive Care Med 2003; 29:894–903


*See also p. 1527.

Key Words: chronically ill; critical illness; health priority; mechanical ventilation; Medicare; patient preference; resource allocation

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orities to services regarding the benefits of ICU patients. The median hospital charge was $120,000. The overall cost in the United States for CCI patients was thought to be in the range of $22 billion of the $64 billion spent on all ICU patients in 1994 (2).

In circumstances such as these, society faces competing concerns about respect for patient autonomy and the need to allocate limited resources effectively and fairly. How then might we proceed? We need to engage the lay public in these issues earlier in the allocation process and in a manner that makes the public aware of the competing options. Rather than exclusively asking patients whether they want life-sustaining care at the time of critical illness, we need to involve the public in consideration of the opportunity costs of offering expensive potentially ineffective care (5, 6). The public is capable of facing coverage decisions if we pose them as trade-offs. When we have asked elderly Medicare enrollees to set priorities to services regarding the benefits that will be insured through the Medicare program, such as critical care and long-term care, they are up to the task (7). It may be useful to begin to have them consider more fine-grained decisions such as the costs and benefits posed by CCI. One might object that research has taught us that asking these questions of individuals prospectively when respondents are relatively well will yield different responses than when they are in the midst of critical illness. But it is possible to improve the capacity of individuals to prioritize prudently (8, 9). One might also object that prognostic uncertainty makes the outcomes of decisions uncertain. But making decisions on the basis of probabilistic information is ultimately inescapable. The earlier we engage the public in such discussions, the more skilled they will be at dealing with the issues, the fairer the process can be, and the more willing they will be to accept the priorities that are set. Some may suggest that this approach is too callous. It is not intended to be. When we take into account the other compelling needs of the chronically ill that we might attend to, such as rehabilitation and long-term care, or the competing claims of other segments of the population that we are remiss in caring for, sorting out how to apportion healthcare resources seems warranted.

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The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score: Useful tool or paralysis by analysis?*

Necrotizing soft tissue infections (NSTIs, known commonly as necrotizing fasciitis, Fournier gangrene, and a host of other appellations) are rare and dangerous—a threat to life and limb. Even with state-of-the-art care, the mortality rate is still approximately 25%. The danger derives from the fulminant pro-

*See also p. 1535.

Key Words: necrotizing soft tissue infection; necrotizing fasciitis; diagnostic testing; debridement; C-reactive protein; propensity scoring

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are incited by inoculation related to tissue injury. The clinical diagnosis of NSTI is made easier when rapidly progressive erythema and edema are present. Skin necrosis and epidermolysis are unusual in cellulitis but are late manifestations of NSTI. Lymphangitis and lymphadenitis are unusual in NSTI. Crepitus is a very sensitive indicator of NSTI but is nonspecific, as it is also a late manifestation. As the infection progresses, tenderness may be present beyond the margin of erythema, cutaneous anesthesia and necrosis develop, and the patient usually manifests sepsis or severe sepsis (e.g., fever, tachycardia, tachypnea, leukocytosis, and organ dysfunction if severe). However, to achieve optimal outcomes, cases of NSTI need to be identified and treated before such obvious advanced disease develops.

Variability in presentation may also be related to the causative organism. Most cases (type I NSTI, ~80%) are polymicrobial infections (e.g., staphylococci, enteric Gram-negative bacilli, anaerobes) where the bacteria act synergistically to create extensive tissue destruction and rapid progression. About 20% of cases of NSTI (type II) are caused by a single organism (usually Streptococcus pyogenes, but other Streptococcus species or Clostridium species can be causative). Indolent infections may be caused by organisms such as viridans streptococci, whereas clostridial myonecrosis may produce marked systemic toxicity but no overtly skin changes whatsoever.

Every patient will have screening laboratory tests performed; some studies (4, 5) have suggested that patients with an elevated white blood cell count (>14,000/μL), hyponatremia (<135 mEq/dL), and a modestly elevated blood urea nitrogen concentration (>15 mg/dL) are more likely to have an NSTI rather than cellulitis. A prediction model based only on white blood cell count and serum sodium concentration showed a negative predictive value of 99% (5), which is excellent for a screening test. Such tests perhaps have their greatest potential role to assist clinicians who see NSTI only rarely with the accurate diagnosis of early or equivocal cases.

In this issue of Critical Care Medicine, Dr. Wong and colleagues describe a new diagnostic tool for the diagnosis of NSTI, the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) Score (6). Six readily available laboratory tests (white blood cell count, and concentrations of C-reactive protein, hemoglobin, sodium, glucose, and creatinine) were analyzed in a statistically valid manner to develop a weighted 13-point scale that should be easy to calculate at the bedside. Patients who score ≤5 points are unlikely to have an NSTI (but not guaranteed, the negative predictive value being about 96%), whereas those who score ≥8 points are more likely to have an NSTI (positive predictive value 93%). The statistical validation of the model is robust, with areas under the receiver-operating characteristic curve of 0.97–0.98 and a Hosmer-Lemeshow goodness-of-fit chi-square p value of .91 (the higher, the better).

That said, there are numerous problems. The diagnosis of NSTI is inherently suspect, because histologic confirmation was not obtained for all cases. The data sets were about 15% incomplete for both the developmental and validation cohorts with respect to C-reactive protein concentrations, whereas the final model is weighted heavily by the concentration of C-reactive protein (four points for >150 mg/L, with no other variable being weighted more than two points). It is not stated whether the validation cohort was prospective (prospective independent validation will be crucial for widespread adoption of the model). Most important, it is not demonstrated whether implementation yields earlier diagnosis and improved outcomes. Moreover, neither the authors’ contention that serial calculations that show an increasing score despite antibiotic therapy are a clue to NSTI, nor their contention that therapeutic interventions correct the measured perturbations and therefore decrease the accuracy of the score during hospitalization, is supported by the data presented and certainly not proved.

The biggest problem is that the practitioner still has to do something intelligent with the information. To the extent that calculation of the LRINEC score means that high-risk cases are identified by practitioners sooner than otherwise, and a rational management plan is the result, then this tool is a real advance. An NSTI is a true surgical emergency; suspicion of NSTI, in the opinion of many authorities including myself, should prompt exploration of the affected area in the operating room without delay. To the extent that identification of a high-risk patient by the LRINEC score leads to additional diagnostic testing (e.g., computed tomography, magnetic resonance imaging, biopsy with frozen section), the process becomes “paralysis by analysis,” and life and limb are placed in peril by the delay engendered. I regret that the authors provided the algorithm found in Figure 3 of their article and did not just stick to their score and its validation. The algorithm is speculative, and the reader is advised to discount it or disregard it entirely. The “finger test” is a figment of the imagination. Seriously ill patients are cumbersome to manage in the magnetic resonance imaging suite owing to the requirement that devices (e.g., pumps, ventilators) must be constructed of nonferrous metals. High-risk patients suspected of having an NSTI belong in the operating room, period (and not via the hyperbaric oxygen chamber either, by the way).

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Predicting mortality from sepsis: Is protein C a true crystal ball?

Numerous advances have been made in recent years in understanding the pathogenesis of sepsis; nonetheless, the incidence of this disease and the often fatal septic shock associated with it both continue to increase. Although recent advances in the management of sepsis have improved patient care, the morbidity and mortality that result from sepsis still remain high (1, 2).

Typically, sepsis results from an acute infection that presents with procoagulant and pro- and anti-inflammatory components (3). These septic responses are associated with the release of both pro- and anti-inflammatory cytokines and subsequently with the activation of leucocytes as well as the complement and coagulation cascades (4). The development of multiple organ failure characteristic of this disease is thought to result from activation of the coagulation cascade and the subsequent development of disseminated intravascular coagulation, which severely compromises organ blood flow, leading to organ failure and death (5–7). Nitric oxide is another endogenous vascular factor associated with cardiovascular dysfunction in sepsis that mediates both vascular collapse and myocardial depression (8, 9), thereby exacerbating the effects of disseminated intravascular coagulation on organ blood flow and failure.

Protein C (PrC) is an important part of the clotting cascade, which, when activated by interaction with thrombin/thrombomodulin, exerts antithrombotic, profibrinolytic, and anti-inflammatory activities (10). Interestingly, activation of PrC may be impaired in sepsis by inflammatory cytokines (11), and concentrations of PrC are reduced in septic patients; this reduction is associated with poor clinical outcome (12–14). Furthermore, recent studies with recombinant human activated PrC revealed that administration to severely septic patients reduced mortality rates significantly (15). These findings, part of the Worldwide Evaluation in Severe Sepsis study group (PROWESS), suggest that reductions in PrC concentrations may, in fact, play a central role in the development of disseminated intravascular coagulation and organ failure in sepsis.

In this issue of Critical Care Medicine, Dr. Heuer and colleagues (16) have investigated the regulation of PrC in the cecal ligation and puncture (CLP) model in the rat, a widely accepted clinically relevant animal model of sepsis. The goals of this study were to evaluate PrC concentrations in this model and determine whether they are related to outcome and also to identify other possible inflammatory and immune factors that might also predict mortality. To that end, some 62 different biomarkers were assayed in each blood sample.

Dr. Heuer and colleagues (16) suggest that in the CLP rat model of sepsis, an inflammatory hypercoagulable state exists, which is characterized by severely reduced PrC concentrations. Compared with surviving rats, those that died early in the CLP protocol exhibited significant changes in 30 variables indicative of coagulopathy, inflammation, and muscle damage, including lower plasma concentrations of PrC and higher plasma concentrations of D dimer, cytokines/chemokines, and myoglobin. Twenty of the variables exhibited a moderate to strong correlation with the time of death (r > .70), suggesting that PrC as well as plasma D dimer and the chemokines macrophage inflammatory protein-2 and KC are biomarkers predictive of mortality in septic rats. The particular strength of this study lies in its ability to correlate various biomarkers with the time of death following sepsis, suggesting a predictive value for these markers in determining outcome and mortality in this rat model of sepsis. The apparently strong correlation between depressions in plasma PrC and early death is of particular value, since it links PrC, a key player associated with the coagulopathy, disseminated intravascular coagulation, and multiple organ failure of sepsis, with the time of death in this CLP model.

Despite these important new findings in the CLP model of sepsis, this study does have several weaknesses that limit its applicability to understanding the mechanisms underlying the development and mortality of sepsis. Foremost is that a role for PrC in the development and mortality of sepsis has already been established in humans, including a predictive correlation (12–14) and experimental treatments with recombinant activated human PrC that are reported to reduce mortality (15). Thus, it is now more important to understand how and why PrC concentrations are depressed during the development of sepsis. Therefore, the present studies would have been strengthened considerably by a more hypothesis-driven experimental approach, which could investigate the mechanisms underlying the significant reductions in plasma PrC concentrations, as well as the effects of exogenous PrC administration on mortality in the CLP model of sepsis. Furthermore, the nonselective “shotgun” approach to merely characterizing changes in numerous biomarkers without a clearly defined rationale adds little to our understanding of the CLP model or sepsis in general. Thus, a more hypothesis-driven approach would better enhance our understanding of the role of PrC (and other valid biomarkers) in the development and mortality of sepsis.

Historically, the ability of physicians to successfully identify those patients at the highest risk of a poor outcome from sepsis has been extremely variable, probably due to the heterogeneity of numerous patient variables such as age, body weight, gender, degree of infection, immune function, and underlying secondary disease. The ability to predict outcome from sepsis could be of great value in determining the most appropriate clinical therapies. To that end, the present work by Dr. Heuer and colleagues (16) adds to this eventual clinical goal by identifying an important clinical marker, PrC, that can be used to predict mortality in a

*See also p. 1570.

Key Words: cecal ligation; chemokines; cytokines; mortality assessment; protein C; sepsis

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widely accepted, clinically relevant animal model of sepsis, the CLP rat model. Effective use of this model in future studies may then lead to the use of PrC or other biomarkers as a true “crystal ball” to predict the outcome of sepsis in the human population.

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Perfusing the brain after traumatic brain injury: What clinical index should we follow?*

Traumatic brain injury (TBI) results in a significant and prolonged reduction in cerebral blood flow that can lead to critical oligemia and additional brain injury. Indeed, in the early hours after TBI, ischemia can occur in up to 30% of patients with TBI (1–3) and in a greater percentage of those patients with fatal TBI (4). The primary goal of intensive care is to ensure that this does not occur, and hence clinicians require a treatment monitoring end point that has validity in determining whether the amount of blood and oxygen getting to the brain is adequate. Moreover, this end point should be easy to use. Cerebral perfusion pressure (CPP), defined as the difference between mean arterial pressure and intracranial pressure, has been the main bedside monitoring endpoint to determine whether the brain of a comatose patient is being optimally perfused. CPP is typically defined as a global number as is considered to be equally distributed within the intracranial vault. Under normal conditions, with mean arterial pressure of 80–100 mm Hg and intracranial pressure of 5–10 mm Hg, CPP can be expected to be 70–85 mm Hg. Under conventional limits of intact autoregulation, cerebral blood flow (CBF) remains normal as CPP varies between 60–140 mm Hg. Thus, CPP >60–70 has been considered to be adequate. In most recent studies and in the current TBI guidelines, CPP thresholds have been in this range.

The problem with using CPP as the monitoring end point is that after traumatic brain injury, autoregulation can be disturbed and hence the relationship between CPP and CBF can be altered and unpredictable. The concept of normal pressure autoregulation is that with increasing blood pressure, the brain’s muscular arterioles undergo progressive vasocnstriction and thus diminish the amount of blood passage into the distal vascular bed. Conversely, there is compensatory vasodilation with reductions in blood pressure. In contrast, impaired autoregulation is characterized by a complete or incomplete ability of the brain muscular arterioles to perform compensatory vasocnstriction or vasodilation with increases or decreases in blood pressure, respectively. This phenomenon has been well documented in human TBI (5–7). The state of autoregulation can be assessed using transcranial Doppler ultrasound (TCD). Recently, TCD has been used to determine the degree to which autoregulation is intact over time in the intensive care unit (8–12). These investigators have documented that a) autoregulation is frequently but not universally impaired after TBI; b) impairment of au

*See also p. 1579.
Key Words: brain trauma; head injury; cerebral perfusion pressure; cerebral blood flow; intracranial pressure; coma; jugular venous oximetry; microdialysis

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Cerebral blood flow (CBF) is a critical variable in the assessment of cerebral perfusion and autoregulation. In the following, we will discuss some recent studies that have investigated the role of CBF in trauma patients and suggest that CBF can be used to indirectly indicate the expected change in CBF. Unfortunately, this is somewhat misleading, since a formal test of autoregulation, a direct comparison of CBF at different CPP values, was not done in this study.

The study by Dr. Wintermark and colleagues (13) makes an important point, namely that one cannot determine what the CBF is by measuring CPP alone. Moreover, autoregulation may be impaired. New methods such as TCD and CT-perfusion are able to non-invasively determine CBF directly and therefore when combined with CPP are better able to indicate whether we are delivering enough blood flow compared with CPP measures alone. In addition, since CBF is heterogeneous after TBI, the regulation of cerebral blood flow and metabolism during the acute phase of head injury, and its significance for therapy. Eur J Neurol Sci 1978; 39:213


Wintermark M, Chiolero R, van Melle G, et

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Access to critical care: Medical rationing of a public right or privilege?*

In this issue of Critical Care Medicine, Dr. Sinuff and colleagues (1) present a meta-analysis of published observational studies in an attempt to elucidate the impact of rationing intensive care unit (ICU) beds. Their key conclusions are that patients refused ICU admission had significantly increased risk of mortality; that the most important factors for denial of admission were increased age, severity of illness, and medical diagnosis; and that ICU bed resources were more constrained when patients were sicker. The study raises important policy issues: a) access to scarce, complex, and expensive medical care; b) the conflicting duties to treat and to ration; c) incentives affecting ICU admissions; and d) the implications of variability in the critical triage process.

Rationing inevitably occurs when the demand for an essential good or service exceeds its supply. In the United States, health care is not a substantive constitutional due process right, but it can reasonably be argued that health care has evolved from a “privilege” into a “right” as a consequence of public expectation. However, in actuality, health care rationing is widespread in the United States (2, 3). Physicians may not have legal duties toward people whom they have not accepted as patients (4, 5); however, medical ethics may impose a higher standard. On the other hand, hospitals have many layers of responsibility to render appropriate levels of medical care (6, 7).

Rationing must also ask, How much health care is one entitled to? Unlimited resources are not financially feasible, but rationing becomes increasingly controversial when decisions involve life and death. On the other hand, should physicians have a duty to ration resources as gatekeepers in order to provide the “greatest good for the greatest number”? Critical care consumes a disproportionate share of health care costs. From 1997 to 2001, in-hospital care costs increased by $83.6 billion. Although health care accounted for 14% of the U.S. 2001 gross domestic product, or $1.4 trillion, ICU care accounted for $142 billion, or 1% of the 2001 gross domestic product. ICUs account for 20% of U.S. hospital costs but represent only 5% of hospital beds. Additionally, an estimated 4.4 million patients are admitted to U.S. ICUs each year (8). Simply stated, costs limit access to health care. However, the physician’s fiduciary duty to act in the best interests of his or her patient is fundamentally inconsistent with pressures to restrict resource expenditures to individuals; individualized rationing creates a conflict of interest (9). Thus, physicians’ rationing efforts must be directed through policy development. Established procedural criteria must form the basis for “triage.” During triage, the physician makes value judgments on the basis of a myriad of complex criteria; the result is a relatively subjective quantitative analysis wherein relative weights are assigned to variables and scored by some algorithm. The AMA Council on Ethical and Judicial Affairs (10) lists factors that may be used in triage; however, there is no truly standardized list or algorithm. Optimally, these decisions should be made by experienced intensivists to minimize the possibility of error, although “error” connotes a review process which seldom occurs. Subjectivity makes possible the discrimination against vulnerable population segments such as the aged or extremely ill (11). Also, subtle economic incentives (12) encourage selection of less complex patients during triage since these patients are likely to favorably skew performance measures for the unit, the practitioners, and the institution (survival rates, functional outcome measures, scorecards, length of stay, and cost of care); such “outcome” data are monitored by consumers and underwriters. Studies have concluded that political power, medical provincialism, and income maximization may influence allocation decisions more than medical need (13). Triage decision makers often attempt to meet the minimal expectations of stakeholders perceived as “important” and at “times of resource shortage...search for that stakeholder for whom a lower level of performance would be least objectionable or for that stakeholder who has the least power to object” (14). Indeed, do-not-resuscitate orders obtained under the situational duress of rationing may be unjustified. The conclusion is that the future

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*See also p. 1588.

Key Words: access; conflicts of interest; critical care; duty of care; health policy; intensive care; intermediate care; outcome; outreach; rationing; resource allocation; step-down unit; triage

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basis for triage decisions must become systematic, homogeneously applied, evidence-based, defensible, and transparent.

Finally, if the severity of illness within an ICU fluctuates widely with demand, there is “slack” within that system. Critical patients either are denied admission to the ICU or are discharged prematurely during times of high demand; it is also likely that patients who do not meet ICU admission criteria are inappropriately admitted to ICUs during periods of lower demand, or both. Patients who are not admitted nonetheless require appropriate care. Hospitals lacking post-ICU discharge support resources will hold patients (e.g., the chronically ventilated, or those patients who although clinically improved cannot be safely discharged to floors); these patients consume ICU resources, increase health care costs, and bar access to others. Also, it is also obvious that patients denied ICU access even temporarily will become a greater resource burden with time. Since the longer a patient remains in shock, the more likely it is that he or she will develop irreversible organ damage, delay of ICU care increases the likelihood of long-term morbidity, with corresponding individual and societal costs (15). Conversely, the use of ICUs to care for noncritically ill patients is a societal cost: Payers reimburse for unnecessary ICU utilization, which is required to maintain ICU staffing and hospital support operations during times of low acuity or census.

Effective solutions require urgent re-assessment of the efficiency and efficacy of ICU utilization, since the demand for ICU resources will inevitably increase paralleling the demographics of aging Americans (16) and the increased prevalence of chronic diseases. There must be a paradigm shift in which hospital resources are reorganized and the ICU becomes a fluid concept rather than one defined by four walls. The impact of triage is thus lessened and critically ill patients of varying severity can be cared for at levels corresponding to their medical needs. Hospital providers at all levels must be capable of delivering effective pre-ICU and post-ICU care—through cross-training, critical care “outreach,” or ICU co-management. Monitoring technology must be extended to improve safety through early detection of adverse events. Finally, the availability of step-down, intermediate care, and weaning units must be increased to facilitate rapid discharge and minimize lower acuity admissions. Hospitals may also need to access the monitoring capabilities of the emergency room or recovery room during times of acute inpatient decompensation; such alternate venues may lessen the individual impact of rationing, but the patients and bed usage must be managed by intensivists. Finally, uniform severity of illness scoring systems and evidence-based criteria must form the basis for justification of ICU admission, discharge, and resource allocation decisions. James E. Szalados, MD, MBA, MHA, FCCM
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