Systemic arterial pressure and fluid responsiveness: not only a swing story

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Distinguishing chemical pneumonitis from bacterial aspiration: Still a clinical determination*

Most pneumonia results from microaspiration of bacteria from a previously colonized oropharynx, but some patients develop infection because of macroaspiration of large volumes of gastric or oropharyngeal secretions. When this occurs, it is clinically recognized as an "aspiration syndrome" and is present in patients who have a source of large-volume aspirate (the stomach, often as a result of recent eating or abnormal motility) in the setting of impaired oropharyngeal reflexes, usually as the result of a reduced level of consciousness or as a consequence of neurologic illness (1). When macroaspiration occurs, it can lead to several types of pulmonary injury, which are difficult to distinguish from one another on clinical grounds, with some needing antibiotic therapy and others not. These include aspiration of gastric acid leading to a chemical pneumonitis or aspiration of bacteria leading to infectious pneumonia. In addition, patients can aspirate food material or foreign bodies, which can obstruct the airway and predispose to distal pneumonia, and they can develop secondary bacterial pneumonia that superinfects a lung that has been injured by gastric acid. As a clinician, it is challenging to decide when to start antibiotic therapy in a patient with an aspiration syndrome, because all of these patients can have lung infiltrates, but antibiotics are only beneficial for pneumonia and not for chemical pneumonitis.

In the current issue of *Critical Care Medicine*, El Solh and colleagues (2), who have done some of the most elegant research in this area, have attempted to determine whether the use of a serum biomarker, procalcitonin (PCT), could be used to separate chemical pneumonitis from bacterial pneumonia in patients with aspiration syndrome. They enrolled 65 consecutive patients with pulmonary aspiration, all of whom were intubated and mechanically ventilated and all having lung infiltrates and measured serum PCT on day 1 and day 3 and collected bronchoalveolar lavage for quantitative cultures within 6 hrs of initial intubation. All patients had aspiration risk factors, including neurodegenerative disease (n = 24), drug overdose (n = 15), cerebrovascular accident (n = 14), or seizure (n = 11). Using a 10^4-colony-forming unit/mL cutoff, 32 patients had bacterial pneumonia, but there was no correlation between the presence of bacterial pneumonia and PCT levels in contrast to studies in other populations of pneumonia patients, in which PCT could separate patients with lung infiltrates as a result of bacterial infection from those with a nonbacterial cause of lung infiltrates (3). Interestingly, in both populations, PCT levels were elevated compared with a control population without pneumonia, suggesting that all patients had a high level of inflammation present. When patients had PCT levels on day 3 that were lower than on day 1, there was a shorter duration of both mechanical ventilation and antibiotic therapy and a lower likelihood of dying than if PCT levels did not fall. The study demonstrated that PCT was not useful, when measured on admission in patients with aspiration syndrome, in predicting whether bacterial pneumonia was present and thus could not be used to guide the decision about whether such a patient with lung infiltrates would benefit from antibiotic therapy.

It is also interesting to consider the bacteriology of aspiration pneumonia in intensive care unit patients that was found in this and in other studies. In a previous study of 95 residents of long-term care facilities who had severe aspiration pneumonia treated with mechanical ventilation, bacteriologic data were collected by performing protected bronchoalveolar lavage within 4 hrs of admission (4). Gram-negative enteric bacilli were present in 49%, *Staphylococcus aureus* was in 12%, whereas only 16% had anaerobes present and when present, they were often with aerobic bacteria and patients usually recovered without receiving specific antianaerobic therapy. In the current study, which did not include only those residing in nursing homes, the bacteriology was slightly different, with *S. aureus* and *Escherichia coli* being the most common organisms identified but with anaerobes present in 10 of 36 bacterial isolates from 32 patients. The findings from these two studies make it very clear that even when infection, and not chemical pneumonitis, is present, routine anaerobic therapy is not needed in most patients with aspiration pneumonia and that this therapy is rarely, if ever, needed in nursing home residents with severe aspiration pneumonia. It is important for intensive care unit doctors to be aware of these findings given the possibility that antianaerobic therapy can lead to the emergence of both *Clostridium difficile* and vancomycin-resistant *Enterococcus*, and thus it is possible to avoid the gratuitous use of these agents in most patients with aspiration syndrome.

The findings in the current study by El Solh and colleagues indicate that the decision to start antibiotic therapy should be a clinical one and not one based on the measurement of biomarkers. In many ways, these findings are not surprising. An older study of 23 patients with closed head injury found that those with aspiration had a higher PCT level than those without aspiration, and that nonsurvivors had higher PCT values than survivors (5). However, in that study, in contrast to the study by El Solh et al, not all patients had aspiration or lung infiltrates, and there was no effort made to separate chemical from bacterial aspiration syndromes. In both of these studies, it seems that when

*See also p. 1251.

Key Words: aspiration; pneumonia; procalcitonin; chemical pneumonitis; bacteriology; anaerobic bacteria

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aspiration is present, probably independent of the presence of bacteria, it is associated with a lung inflammatory response and an increase in PCT that is not specific for the presence of infection. In fact, aspiration of gastric contents can lead to an intense lung inflammatory response. In addition to the inflammatory response to bacteria, the respiratory mucosa may have an inflammatory response to aspirated gastric acid, pepsin, and bile acids, and the resulting inflammation can promote mucus secretion and the influx of neutrophils, which can further amplify the inflammatory response (6). Thus, it is not surprising that aspiration, with or without bacteria, could lead to elevated levels of PCT, an acute-phase reactant. Further complicating the picture is the fact that some patients as a consequence of this chemical injury may have impaired airway defenses and then develop a delayed, secondary bacterial pneumonia. In one study of patients with head trauma, many of whom may have had subclinical aspiration, a high level of PCT on admission was predictive of those who later developed ventilator-associated pneumonia, especially those with severe early-onset ventilator-associated pneumonia (7). However, when ventilator-associated pneumonia did occur in these patients, there was no further rise in PCT, suggesting that PCT was a marker of aspiration-induced inflammation which predisposed to later pneumonia and that persistent elevation of PCT may have been driven by either ongoing inflammation, secondary bacterial infection, or both. Maybe this explains why a fall in PCT in the study by El Solh and colleagues had a good prognosis, because it may have indicated resolving inflammation in the absence of secondary bacterial infection.

How can we use the available information to guide our management of patients with severe aspiration? Clearly, some patients will have early primary bacterial pneumonia and need antibiotic therapy, and in these patients, the selection of therapeutic agents should be guided by the likely etiologic pathogens, which often include enteric Gram-negatives and *S. aureus*, but generally not anaerobes, particularly in those coming from nursing homes. Although it remains difficult to tell whether an infiltrate is secondary to a bacterial infection or chemical-induced inflammation, and whether to start antibiotic therapy, measurement of PCT cannot help us with this decision. However, the available data suggest that possibly serial measurement of PCT could be used to identify a population of patients who have a good prognosis and do not need to continue antibiotic therapy. In fact, a decline in PCT may be the result of resolution of chemical-induced inflammation along with the absence of either a primary or secondary bacterial infection. For now, although we need to rely on clinical judgment to define when to start antibiotics for aspiration, it is possible that in the future we will see more data that show the value of biomarkers to help guide us whether it is safe to stop this therapy.

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Is the time right for 24-hr/7-day coverage?*

At no time in history has the cost of health care been under such scrutiny with an unmatched pressure to deliver quality care at the lowest possible cost. This attention has come from policy makers, regulatory agencies, payers, and consumers and from within health care as well. The intensive care unit (ICU) is a particularly important target for these efforts given that intensive care accounts for nearly 5% of total healthcare costs in the United States and represents as much as 20% of total hospital costs in major medical centers (1, 2). Areas of potential cost savings include appropriate triage of patients, judicious application of expensive therapeutic modalities for those most likely to benefit, and deployment of the most efficient and cost-effective staffing patterns. There has been considerable debate addressing staffing models in ICUs, with recent attention focused on the value added for 24-hr/7-day intensivist in-house staffing models. Intensivist-led or high-intensity critical care service meeting the Leapfrog standard has been associated with improved outcomes in the overwhelming majority of studies published to date (3, 4). Outcomes affected by intensivist-led care include mortality, ICU and hospital lengths of stay, improved house staff education, compliance with established protocols, and use of evidence-based interventions (5–7).

Previously, the addition of overnight intensivist coverage has been demonstrated to improve compliance with recommended processes of care with no effect on mortality (8). Financial modeling of intensivist staffing meeting the Leapfrog standard sup-

*See also p. 1257.

Key Words: critical care; intensive care unit; healthcare costs; cost analysis; economics; outcomes research

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ports an economic advantage using a conservative model in all but the worst case scenarios (9). However, many questions remain concerning the optimal systems for delivery of critical care that include the ICU team's composition with regard to the role of associate practitioners (e.g., physician assistants and nurse practitioners), the effect of ever-changing resident work hours, and the financial implications of various care models.

In this issue of *Critical Care Medicine*, Banerjee and colleagues (10) present the economic implications of deploying 24-hr/7-day intensivist coverage in a large academic medical ICU. The study is a prospectively assessed cohort design comparing one year's admissions before and after institution of mandatory overnight (7 PM to 7 AM) in-house coverage by a trained critical care specialist. The significant findings reported are a 61% decrease in cost estimates for the sickest cohort of patients admitted during overnight hours and a decrease in ICU length of stay from an average of 4.8 to 3.5 days with no effect on ICU or in-hospital mortality. More patients were admitted in the year after the staffing change, with nearly half of these accounted for in the lowest acuity groups. It is not surprising that benefit was realized in the highest acuity patients as severity of illness and complexity of care are where provider expertise would be expected to have the greatest likelihood to make a difference. The authors suggest that the decreased length of stay may be the primary factor in the observed decrease in cost. However, this explanation may not be readily generalized to other ICUs. Recent publications examining the influence of ICU length of stay on cost suggest that it is the first several days of ICU care that are the most costly and fixed costs account for over 80% of total costs (11, 12). Neither of these factors would be expected to change significantly with a simple reduction in length of stay. Cost savings were reported in these studies, but the magnitude was smaller than that reported by Banerjee et al (10). However, it is possible that extending in-house intensivist coverage could positively impact cost in other ways. These include limiting the ordering of unnecessary laboratory testing and imaging studies and preventing adverse events. Additionally, enhanced intensivist coverage may affect the ability to generate revenue, and this was not included in the cost analysis model.

The model includes an estimate of direct medical costs utilizing adjustments based on Medicare Parts A and B. This does not account for costs related to other resources that may be needed to support overnight coverage, including additional work or sleep space, the lack of availability of the night intensivist for unit-related activities, such as formal teaching sessions and meetings that typically take place during regular hours, or its impact on the subsequent day's schedule. The results may also be difficult to generalize given the staffing situation before implementation of overnight on-site coverage and the wide heterogeneity of ICU staffing models in western countries (13). The study unit already employed overnight coverage with in-house residents and a critical care fellow with reported daytime coverage utilizing two intensivists for a unit with a 24-bed capacity and average daily census of 14.4. This staffing may be more robust before the intervention than the current staffing in many ICUs. Furthermore, the study was conducted in a medical ICU, so the results may not be applicable to surgical, mixed, or specialty units. Additionally, a societal perspective on cost would allow an assessment of the long-term economic impact of 24-hr/7-day intensivist coverage.

Demand for ICU resources continues to increase as a result of the aging patient population and the availability and efficacy of therapies for acute and chronic illnesses. However, the demand for trained intensivists clearly outstrips the availability (14). Currently, intensivist-led critical care is employed in a minority of institutions, and around the clock on-site staffing would increase demand even further. Placing more pressure on already limited ICU resources could have the effect of producing and accelerating burnout in already at risk providers. Other staffing options are possible and warrant investigation. Some alternatives to consider include standardizing indications for callback at night or instituting a model of cross coverage. Deployment of a telemedicine system is another possibility. Comprehensive financial analysis and assessment of team satisfaction with alternative models is sorely needed. Despite the limitations, Banerjee and colleagues (10) have made an important contribution to our understanding of economics in the delivery of critical care services, with the current study supporting the financial feasibility and indeed potential advantage of 24-hr/7-day on-site intensivist coverage in a high-acuity academic medical center.

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Glutamine: The struggle for proof?*

We can generally agree that deficits in nutrition will have some impact on the outcome of our patients because when it is extreme, lives are put at risk. However, proving that just one particular component of a nutritional mixture makes a difference to outcome is not easy, especially in a complex process of care such as the critically ill. Therefore, the article by Grau et al (1) is surprisingly encouraging because it adds further weight to the argument that enhancing glutamine provision may have benefits and that our nutritional practices are not yet optimal (2). They study 127 patients predominantly surgical in character recruited from across 12 intensive care units in Spain drawn from a sicker population who required parenteral nutrition (24% of those requiring any artificial feeding). Patients randomized to the glutamine arm completing at least 4 days of feed (per protocol analysis) demonstrated significantly reduced nosocomial pneumonia and urinary tract infections. Glycemic control was improved requiring half the insulin dose.

How is it possible that the addition of this one amino acid to the parenteral nutrition was necessary for this improved outcome? Is it plausible? Why should something as simple as a little extra of one amino acid make this difference? The mistake is to think of glutamine in terms of a "drug" action and to assume that glutamine has a singular pharmacologic action rather than a multilayered metabolic role in a complex system (3). Since the 1970s (4), research has shown that glutamine is one of the most abundant amino acids, freely manufactured in many cell systems, and held free in solution in muscle at a concentration gradient of 32:1 over plasma levels, which transport it in near millimolar concentrations around the circulation. Thus, it has seemed inconceivable that it could become nutritionally essential and was classed traditionally as a nonessential amino acid. However, detailed tracer studies show that it is a major player in many metabolic processes with a very high turnover of approximately 1 g glutamine per kilogram per day (5). This is approximately ten times the normal dietary intake and hence endogenous production is fundamental to maintain an adequate supply. The critically ill patient sustains two pressures on this glutamine supply system; the demand rises (eg, with immune activation and reparative processes) while production is compromised (eg, by immobility and insulin resistance) that leads to a state of conditional essentiality and a functional deficiency ensues. This lack is further compounded when from the 1960s the traditional amino acid solutions for ease of manufacture did not include the less soluble and heat-stable L-glutamine because it was deemed nonessential! Therefore, we should not consider this to be an addition of glutamine but more a restoration of glutamine. Indeed, 20–40 g of glutamine in some patients barely restores plasma levels to normal (6).

The functional impact that replacing glutamine has on outcome is to correct the consequence of low glutamine availability on many cellular systems (synthetic, secretory, protective) where it has been shown that function is compromised within the biologic range observed in our patients (7). It is for this reason that glutamine becomes an essential immune nutrient in the critically ill (8). It is not surprising therefore that a low plasma glutamine has been shown independently related to a worse outcome (9) and why single-site studies of its restoration have indicated an improved survival that is related to duration and dose (10, 11). Overcoming the demands for glutamine with its restoration is therefore integral to recovery. Confirming this in larger multisite studies is a real challenge if the study design does not adequately address the physiological evidence of a progressive deficiency that increases with severity and duration of illness and does not allow for recovery. Designing a study as if glutamine were a simple "drug" in which only dose and delivery matter ignores the consequence of the degree of deficiency and how much is required to keep on correcting the deficiency. The opposite is also true in that less ill patients early on that may not manifest a deficiency do not show any benefit from extra glutamine (12). In the study by Grau, they have rightly selected higher risk patients, attempted to optimally feed their patients, undertake an acceptable degree of glucose control, and delivered a good dose of glutamine. Sadly, as a result of curious licensing restrictions, they could not provide >9 days' supply of glutamine, which may explain why they are unable to show any significant longer-term outcome effect on mortality (intention-to-treat 6-month mortality not significantly improved at 28% vs. 34%). This capping of the duration of feed results in an average of only 5–6 days of glutamine provision, which was only approximately half the average intensive care unit stay. Any potential benefit to the high-risk long stay intensive care unit patients is effectively withdrawn. A 10-day limitation of therapy also occurred in 114 intensive care unit patients in a French multicentered randomized controlled trial that similarly showed a significant reduction in complicated outcomes related to reduced infectious rate and pneumonias (13). This study also showed improved glycemic control. Previous studies had suggested that survival outcome advantages were seen in those fed for at least 5 days and generally >10 days when glutamine was administered for as long as parenteral nutrition required, ie, until they were recovering from gastrointestinal failure (10). A similar weakness in study design and a failure to adequately address the continued glutamine conditional deficiency is seen in a study as yet only presented at conferences, Scottish intensive care glutamine or selenium evaluation trial (SIGNET) (14), which appears to show no outcome benefit. Said to be the largest study to date, it produced a

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Key Words: glutamine; deficiency; parenteral nutrition; infectious outcome; glucose control

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predicable null result by a design that failed to recruit those most at risk, used inadequate dosing, and an even shorter duration of therapy. Glutamine is not a drug and clinical studies need to take this into account. Although low plasma levels have been independently associated with a poor outcome, no study I know of has used this measurement to guide glutamine therapy. That glutamine also improves glycemic control should come as no great surprise to those appreciative of the complexity of glucose metabolism. Glutamine matches alanine as a major gluconeogenic precursor and during stress closely follows lactate as a major carbon shuttle for glucose around the body and provides a noninsulin-dependent mechanism into glucose storage and metabolism and so demand for insulin is less and the insulin resistance reduced. It is important to realize that the benefits are not just one-sided, because normoglycemia results in enhanced protein metabolism and improved endogenous glutamine production (15).

We will see in the coming months or years further large studies attempting to demonstrate whether the addition of glutamine parenterally or enterally is of benefit. If we were designing an amino acid mixture afresh today, there would be no reason pharmaceutically based on what we know physiologically to omit the new soluble glutamine dipeptides from use in the critically ill. We have more clinical evidence for this one amino acid alone than probably all the rest put together! Because this issue is fundamentally about correcting a deficiency that develops with time, any clinical study that treats glutamine as a drug and ignores the deficiency side of the evidence will fall at the first hurdle. Proof is always a struggle and null results from poor studies prove nothing. Clinicians beware the struggle to deliver evidence in nutrition is hard; we only make it worse if we delude ourselves into thinking it is straightforward and simply a matter of size of the study.

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The patient is in cardiac arrest! Let's be snappy: Prepare a bolus of sodium nitroprusside, while I compress the chest. It's not a joke!*

Despite major efforts to improve outcomes from sudden death, average survival rate from cardiac arrest remains dismal and presents a large variation, with a spread between 2% and 50% (1, 2). Among the interventions directed to improve outcome of cardiac arrest, the first is the capability to perform high-quality cardiopulmonary resuscitation (CPR). Accordingly, chest compression potentially reestablishes some cardiac output and organ blood flows, accounting for tissue oxygen delivery and reducing thereby the ischemic injuries to the heart and brain (3).

Over the past decades, a variety of alternatives to conventional CPR have been developed in an effort to enhance perfusion during resuscitation and to improve survival; however, none has consistently been shown to be superior to conventional CPR in routine use (4). Poor outcomes have also raised the question of the optimal pharmacologic approach to augment circulation during CPR. Again, there is no clinical demonstration of survival benefits from administration of a specific vasopressor or combination of vasopressors during CPR, at either standard or higher doses (5–7).

In this issue of *Critical Care Medicine*, Dr. Yannopoulos and colleagues (8) have introduced a new and quite provocative drug intervention to be used during CPR that includes the administration of a potent vasodilator, namely, sodium nitroprusside (SNP). Indeed, this elegant investigation clearly demonstrated that repeated administration of SNP, combined with mechanically enhanced venous return, improved aortic and coronary perfusion pressures and allowed for greater carotid blood flow during CPR, without need for epinephrine. This approach also prevented the development of progressive metabolic acidosis during prolonged CPR, while promoting return of spontaneous circulation and survival. Despite the apparently "nonsense" proposal for an hypotensive drug during cardiac arrest, a valid rationale stands beyond this approach. SNP, by reducing the systemic resistance, would consequently decrease the preload, which in the specific setting was maintained by mechanical interventions, as well as the afterload. The latter effect would allow for increases in cardiac output generated by chest compression and ultimately would provide the possibility to improve tissue perfusion. This is an innovative CPR approach that is finally directed to *really* improving organ perfusion rather than achieving *only potential* benefits expressed by increases in coronary perfusion pressure.

In assessing the perfusion condition during and after resuscitation from cardiac arrest, both investigators and clinicians, in fact, focused on pressure and blood flow through large arterial and venous vessels and cardiac output. Accordingly, it has become apparent that pressures and flows alone may not be predictive of the extent to which microvessels and therefore tissues are perfused (9, 10). More recent investigations, in fact, have shown that there may be dissociation between microcirculatory flow and macrocirculation during CPR, as they are under conditions of septic shock (9–11). Thus, vasopressor drugs, which are given conventionally to reverse arterial hypotension, do not necessarily improve capillary perfusion. On the contrary, they may reduce delivery of oxygen and removal of waste products. Because flow through microvessels provides the ultimate source of tissue perfusion during and following resuscitation from cardiac arrest, interventions directed to maintain the microvascular flow need to be encouraged.

SNP is a potent vasodilator used to treat hypertensive emergencies and heart failure and its primary mechanism of action is the release of nitric oxide (NO). NO reaches microvessels directly and acts as an important vasodilatory factor in these small resistance vessels. Improved splanchnic microcirculation after SNP administration has been demonstrated in a model of septic shock (12). The mechanisms underlying the beneficial effects of SNP during CPR, observed by Dr. Yannopoulos and colleagues (8), therefore are likely to be a consequence of increases in microvascular blood flow and organ perfusion secondary to NO release. However, such explanation may be only extrapolated, due to the lack of direct perfusion measurements. Nevertheless, the good neurologic recovery after a total arrest time of approximately 33 mins is an indirect proof of the hypothesized mechanism. An additional supporting evidence might be reflected by the well-maintained left ventricular compliance throughout the long interval of CPR. During prolonged CPR, in fact, the heart usually presents progressive decreases in left ventricular diastolic and systolic volumes together with increases in left ventricular diastolic pressures (13). Those events, which are indicative of striking decreases in left ventricular compliance and mainly appear after the 7–10 mins of CPR, did not occur with the repeated administration of SNP.

Although the results presented by the active group from Minnesota (8) are very encouraging, caution has to be maintained. A similar approach, based on the addition of nitroglycerin, another NO-releasing agent, to vasopressin or epinephrine had been previously proposed. Indeed, addition of nitroglycerin to common vasopressors improved both myocardial and cerebral perfusions in animals (14); however, no benefits were observed in human patients of cardiac arrest (15). Compared to nitroglycerin, SNP is a more effective arterial vasodilator, and therefore its administration during CPR might be anticipated to be more beneficial in term of tissue perfusion. However, the question pertaining to the potential that SNP, by dilating smaller arterioles and resistance vessels, might decrease blood pressure or diminish the vasopressor effects during CPR has to be better investi-

***See also p. 1269.**

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gated. In fact, it is possible that Dr. Yannopoulos and colleagues have not observed such adverse effects simply because the specific treatment was associated with interventions directed to counterbalance the reduction in preload cuased by sodium nitroprusside, i.e., active compression/decompression, use of inspiratory impedance threshold device, and lower abdominal binding. Preliminary results from Dr. Yannopoulus et al on the use of SNP during standard CPR are encouraging with respect to the safety of this approach; however, a specific assessment of effects of repeated administration of SNP, alone or in association with a vasopressor, throughout standard CPR maneuvers is needed.

In conclusion, notwithstanding the need for further investigations on the safety of SNP during CPR and on its mechanisms of action, the apparently crazy proposal by Dr. Yannopoulos et al to administer a potent vasodilator during CPR has to be applauded and encouraged. Indeed, this "snappy" CPR, by targeting small resistance vessels, has the potential to become an important adjunct to ameliorate organ perfusion during CPR and ultimately improve outcome of CPR.

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Let the treatment fit the disease*

A famous quote in the play *The Mikado* by Gilbert and Sullivan says "let the punishment fit the crime." The concept from this song in Act II is that a treatment should be appropriate, i.e., not too limited and not too severe. In this issue of *Critical Care Medicine*, van den Berg and colleagues (1) show that low-dose glucocorticoid therapy improves survival in murine sepsis, while high-dose steroids do not improve outcome. In this situation, the crime was sepsis and the "punishment" was the treatment. Who would have expected that a musical from the 1800s would provide insights into appropriate therapies for sepsis?

These results should have been predicted based on the literature. Several clinical studies showed that high-dose methylprednisolone did not improve survival (2, 3). The clinical data match the current findings, since high-dose steroids failed to improve survival. The data in the work by van den Berg and colleagues (1) confirm that low-dose steroids provide a benefit even when animals are treated with fluid resuscitation and antibiotics. This extends the significance of their findings, since no one has suggested treatment with only glucocorticoids instead of the standard treatment protocol of treating septic patients with antibiotics and appropriate fluid resuscitation, as highlighted in the Surviving Sepsis Campaign (4).

The current study is also important since it uses the appropriate end points. Measuring biomarkers are currently in fashion for predicting outcome from disease processes, including sepsis (5). The investigators measured circulating levels of several proinflammatory mediators as well as cytokine inhibitors. These were

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Key Words: cytokines; interleukin-6; sepsis; glucocorticoids

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measured 6 hrs after the onset of sepsis, a time when these biomarkers have been documented to correlate with mortality (6, 7). The gold standard for these experimental studies should be outcome, not a reduction in a defined biomarker. Indeed, the treatment protocol that produced the strongest reduction in plasma cytokines had no impact on survival. The work by van den Berg and colleagues (1) raises a cautionary tale, since a clinical study which documented that a treatment that only reduces inflammation cannot be considered to be beneficial if it did not improve survival.

Plasma was collected at the 6-hr time point after the onset of sepsis, a time point selected since it appears to be the earliest time to accurately predict mortality (6). However, the data in the current paper show plasma levels of interleukin-6 that are substantially lower than those found in most previous publications (8–11). It is not clear why the values are substantially lower than virtually all of the previous reports measuring inflammatory biomarkers in septic animals. Additionally, the mechanisms of how the low-dose steroids are effective still remains to be elucidated. The data of van den Berg and colleagues (1) clearly show that it was not due to augmented production of reactive oxygen species.

What lessons can be learned from this study concerning the appropriate treatment for sepsis? First, treatment with high concentrations of glucocorticoids is the equivalent of immunosuppression. While it is abundantly clear that septic animals have augmented inflammation (12), global immunosuppression is not appropriate treatment. Second, it is critical to maintain or enhance innate immunity to appropriately eradicate the infection and improve survival. In this study, treatment with low-dose steroids significantly enhanced the clearance of bacteria. These data are similar to previous work showing that augmenting early innate immunity helps eradicate the pathogen to result in better survival (13). Third, the work by van den Berg and colleagues also demonstrates that timing is important. More specifically, the beneficial effects of low-dose steroids were evident only during the acute phase of the septic response. In this situation, the acute phase was defined as the first 5 days after the onset of sepsis, rather than just the first few hours.

The work by van den Berg and colleagues (1) shows that appropriate treatment blunting the inflammatory response without causing substantial immunosuppression provides the best outcome. This occurred both in the setting of sepsis treated without antibiotics and in the more clinically relevant model of sepsis treated with current standards of care. Additional work remains to be done to discover the mechanisms of these observations. The treatment must fit the disease, just as the punishment must fit the crime.

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Intestinal glucose absorption and glycemic response in the critically ill: The sweet Odyssey continues*

Impaired gastrointestinal motility is associated with intolerance of enteral feeding but is also increasingly recognized as a key determinant of metabolic and inflammatory disorders in critically ill patients (1). In this issue of *Critical Care Medicine*, Deane et al (2) present new and compelling data on gastrointestinal behavior in critical illness. They measured small intestinal glucose absorption and transit time in intensive care unit (ICU) patients and healthy volunteers after administration of a postpyloric feeding bolus. ICU patients had reduced small intestinal glucose absorption, yet they had relatively normal duodenocecal transit times and a more pronounced and longer sustained glycemic response.

Delayed gastric emptying is considered to be a major obstacle for providing early and/or adequate enteral nutrition in ICU patients. Consequently, ICU physicians aim either at improving gastric emptying by administration of prokinetic agents or at bypassing the stomach by using a postpyloric feeding tube. The assumption that this will facilitate or enhance small intestinal nutrient uptake is too much a simplification. A substantial loss of fecal calories has indeed been demonstrated in ICU patients, most of whom receive postpyloric feeding (3). This apparent nutrient malabsorption is linked to accelerated small intestinal transit time and motility disorders, known to occur in enterally fed ICU patients (4). However, the current study as well as previous observations by the same research group (5) does not support a uniform association between disordered gastrointestinal motility and transit time beyond the stomach and jejunal glucose/nutrient absorption. Obviously, the latter is regulated by other factors. Small intestinal chyme flow and mixing (6) as well as alterations in hepatosplanchnic blood flow (7) can significantly mediate nutrient uptake but are not evaluated in this study. The integrity of the enteral contact surface may become significantly compromised during critical illness. However, duodenojejunal villous structure and perfusion, enzyme activity, and glucose transporter system function are difficult to assess in the clinical setting. Also, more subtle mechanisms may impede glucose absorption. For example, iron deficiency is associated with decreased small intestinal glucose absorption in rats (8). This may be relevant to the human situation because iron-deficient erythropoiesis is present in up to 35% of ICU admissions and a substantial number of patients develop an inflammation-related decrease in hemoglobin concentration within the first week of their ICU stay (9).

The authors also observe that the reduction in glucose absorption in the critically ill cohort does not provoke a less pronounced glycemic response. This "glucose intolerance" obviously is not related to the carbohydrate content of the enteral liquid but rather depends on intricate disorders of glucose handling at an extraintestinal level. However, direct exposure of the small intestine to glucose triggers the release of the incretin hormones glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide (10). In healthy humans, incretins exert important biologic effects, including delayed gastric emptying and inhibition of duodenal motility, but they also trigger carbohydrate-dependent insulin release and variably affect glucagon and somatostatin secretion (11). Disorders of this particular homeostatic control mechanism and its implication in critical illness should be further investigated. In this context, the role of prokinetic agents may need re-evaluation. Administration of metoclopramide in healthy volunteers enhances duodenal motor activity but has no effect on glucose absorption. Interestingly, metoclopramide increases glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide secretion but paradoxically lowers plasma insulin secretion (12), which may be of concern in the critically ill.

Our physiological comprehension that reduced glucose absorption normally produces a less pronounced glycemic response is clearly challenged by Deane et al (2), who demonstrate the opposite in ICU patients. To understand this seemingly contradiction, we probably need to explore the new paradigm of chaos and complex nonlinear systems in ICU patients responding to an aggression (13). Indeed, their response matches a complex nonlinear system, which is characterized by an infinite number of possible actions in response to a lone stimulus. An example of such complex nonlinear system is the "butterfly effect," ie, a situation in which a flight of butterflies in China can change the weather in Boston 3 days later. The two events bear no relationship, yet they are the result of the same stimulus. This underscores why homeostasis is not a state of stability *per se* but rather the ability to remain stable while the status is permanently changing. It may explain also why glucose absorption and glucose intolerance can be altered by the same aggression, although they affect glucose metabolism in different and opposite directions. Finally, it is conceivable that glucose malabsorption in ICU patients represents, at least in part, a protective adaptation to defy glucose variability that has been shown to be even more deleterious than hyperglycemia itself (14).

The current findings almost certainly will fuel the ongoing debate on adding parenteral on top of enteral nutrition to meet caloric requirements in ICU patients (15). Deane et al (2) indeed add strong support to the idea that, even when a sufficient volume of enteral feed-

***See also p. 1282.**

Key Words: glucose absorption; hyperglycemia; enteral nutrition; intestinal motility; incretins; critical illness

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ing reaches the jejunum, it remains uncertain whether all these calories are really absorbed. As a consequence, the position of early parenteral nutrition to obtain "qualitative" nutrition goals in critically ill patients, as already recommended by recent guidelines (16), is strengthened.

Some shortcomings of the study deserve attention. The ICU patient group is rather small, heterogeneously composed, and presents highly diverging levels of illness severity. Also, no information is given about the type or extent of resuscitation measures. 3–0 methyl glucose absorption is studied to quantify glucose and, by expansion, nutrient absorption. Although arguably being the best actual marker, 3–0 methyl glucose kinetics await further validation in critically ill subjects, particularly in the presence of important fluctuations in volume distribution during resuscitation and/or renal epuration. Nutrient is delivered as a single postpyloric bolus, which may influence increments in blood glucose concentrations in a different way than the routinely applied continuous infusion. Finally, glucose absorption is evaluated for a relatively short period of time during an evolving illness state. It cannot be excluded that an initially deficient uptake of carbohydrates returns to normal over time as has been shown in postpylorically fed patients after abdominal aortic surgery (6).

In conclusion, Deane et al do expand our understanding of gastrointestinal motility and nutrition handling in the critically ill while at the same time opening exciting perspectives for further research in this area. The debate now continues beyond insulin resistance and hyperglycemia as glucose metabolism itself is deranged in ICU patients.

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Cytochrome *c* oxidase predicts the toll of sepsis*

Sepsis is a spectrum of illness that ranges from minor signs and symptoms to severe organ dysfunction and shock. With an incidence of 3 per 1000 population per year and with mortality ranging between 30 and 50 deaths per 100,000, sepsis ranks in the top 10 causes of death and is a significant financial burden to society (1). Sepsis is a clinical diagnosis; to date the availability of precise tests that could predict the disease course is limited (2). In the current issue of *Critical Care Medicine*, Lorente et al (3) report that, on the basis of their prospective multicenter observational study including 96 patients, cytochrome *c* oxidase (COX) activity and quantity is an independent predictor of survival and could be used as a biomarker of sepsis mortality.

COX is the terminal enzyme of the respiratory chain that drives the transmembrane electrochemical proton gradient to regulate adenosine triphosphate synthesis (4). Genetic defects or functional impairment of COX interrupts oxidative phosphorylation, impairs oxygen utilization, and leads to energy depletion, causing organ dysfunction (4). Previous studies identified that sepsis is associated with impairments of the mitochondrial respiratory cycle owed to interference with COX expression and inhibition of its enzymatic activity (reviewed by Levy and Deutschman [5]).

***See also p. 1289.**

Key Words: Toll-like receptor; Nod-like receptors; nitric oxide; reactive oxygen species; tumor necrosis factor; inflammation; predictive

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The confirmation of COX activity/quantity as a predictive factor for sepsis-associated mortality in humans is one of the merits of the study by Lorente et al (3). This study has also pointed to the feasibility of platelets as primary material for this rapid, easy, and less invasive predictive test, which is likely to gain a place in the toolbox of intensive care unit clinicians. Most importantly, the findings of Lorente et al (3) have the potential to spark further interest in research of sepsis. The pathophysiology of sepsis includes strong and often nonspecific systemic inflammatory response of the host's innate immune system to an often unidentified microbe (1, 2). To date the mechanism of how sepsis disrupts the cellular energy budget is not fully understood. The molecular patterns of microbes and their derivatives, but also endogenous danger signals, are recognized by Toll-like receptor (TLR) and Nod-like receptors, which play key roles in sepsis (6, 7). These receptors trigger a powerful signaling cascade that culminates in production of cytokines (interleukin-1, tumor necrosis factor a, interleukin-6) and biologically active small molecules (nitric oxide, reactive oxygen species) (6–8). Importantly, COX has been linked to reactive nitrogen and oxygen species (5, 9). Furthermore, TLR-triggered inflammatory cytokines, such as tumor necrosis factor a, downregulate mitochondrial function in a reactive oxygen species-dependent manner (10). Thus, the powerful proinflammatory loop that is initially intended for pathogen elimination also acts as a limiting factor in mitochondrial energy production and may lead to failure of the host to win the battle against the pathogen. Several research directions can be envisioned in this area.

From the basic research point of view, it remains to be identified if the energy-limiting COX-mediated mechanisms are unique to sepsis or occur in other types of inflammation, including those associated with autoimmunity, cancer, or metabolic diseases. It is possible that the energy constraint is a protection mechanism linked to antimicrobial defense, similar to the critical role of TLR-dependent limitation of adenosine triphosphate production for estrogen-mediated immunoprotection in Kupffer cells following trauma-hemorrhage (11). If the former hypothesis is true, it remains to be detailed how TLR/Nod-like receptors influence the mitochondria in the general and cellular respiratory chain/COX system in particular. TLRs regulate the balance of mitochondria-dependent cell death and survival and employ mitochondria-linked proteins, such as mitochondrial antiviral signaling protein, in their signaling pathways (6). Answering when, how, and why excessive COX inhibition becomes detrimental and limits the survival during sepsis may be among the top research priorities of this area.

From the translational point of view, the predictive value of the findings from the study of Lorente et al (3) require confirmation at a much larger scale and with a much more diverse patient population. It also remains to be seen if COX reading in platelets is representative of all major organs that could fail during sepsis in humans, including heart, liver, brain, etc. Changes in COX activity associated with normal aging or Alzheimer's disease were found in both platelets and somatic cells (12), suggesting that a platelet-based COX activity test may be representative of somatic cells. However, disparities between respiratory chain activities in platelets vs. somatic cells owed to distinct genetic mutations were also reported (13); thus, the issue of the quality of representation remains. In the study by Lorente et al (3), the predictive value of platelet COX was not limited by the age, gender, comorbidities, site of infection, detection of microbes in the bloodstream, class of involved microorganisms, or employed anti-microbial treatment, as these variables were comparable in survivors and nonsurvivors. On the basis of these findings, it is possible that COX activity is indeed a general indicator of the energy balance; further investigations are needed to prove that COX status truly points to the capacity of the host to cope with the infection. In contrast, COX changes correlated with blood pressure and Sequential Organ Failure Assessment score, reassuring that a platelet-based COX test may be used in addition to other tests in sepsis and may even have the advantage of relatively early prediction.

Finally, the predictive value of COX in sepsis reported by Lorente et al (3) reminds us that mitochondrial resuscitation with exogenous COX was suggested to have therapeutic value for septic heart and to improve survival in mice (14); it remains to be determined if modulation of COX could be useful for managing the clinical course of sepsis in humans. The COX-based therapy is particularly encouraging because it is effective in relatively advanced disease stages in animal models of sepsis (14) while other pathogenesis-based approaches, such as neutralization of proinflammatory cytokines (15) or interference with signaling events or TLR/Nod-like receptors *per se*, are either of limited clinical value or yet to be developed. Ultimately, we are in need of new advances in sepsis; perhaps further investigation will reveal if cellular energy balance has more than just predictive value.

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Bone loss during critical illness: A skeleton in the closet for the intensive care unit survivor?*

"I have no history but the length of my bones."—Robin Skelton

As more patients receive multiple organ support in critical care units, many of whom are elderly and/or have significant comorbidities, attention is turning toward an ever increasing population of intensive care unit (ICU) survivors (1). Critical illness is recognized to result in a "post-ICU syndrome," which can occur whatever the original presenting illness and result in cognitive, neurologic, and physical function impairments, which significantly affect patients' quality of life for many months or years (2). These impairments and disabilities also place a heavy burden on healthcare systems and caregivers (3). In recent years, our knowledge of the prevalence of psychologic and physical problems has improved through cohort studies, and research is beginning to explore the risk factors, mechanisms, and possible treatments that may affect the severity and duration of issues ranging from psychologic conditions such as posttraumatic stress disorder to physical problems such as fatigue and breathlessness. Until now, very little work has specifically investigated the affect of critical illness on the skeleton, having focused mainly on neuromuscular dysfunction.

Osteoporosis is a major public health issue that has been estimated to affect 55% of Americans aged ≥50 yrs, of whom 80% are women (4). It is responsible for millions of fractures annually, mostly involving the lumbar vertebrae, hip, and wrist. The World Health Organization defines osteoporosis as a bone mineral density that is >2.5 SDs below the mean bone mineral density of young adult women (5). The disease can be classified as primary type 1, primary type 2, or secondary. Primary type 1 or postmenopausal osteoporosis is the form most common in women after menopause, whereas primary type 2 osteoporosis occurs after age 75 yrs and is seen in both females and males at a ratio of 2:1. Secondary osteoporosis may arise at any age and affects men and women equally. This form of osteoporosis results from chronic predisposing medical problems or disease or prolonged use of medications such as glucocorticoids.

A significant proportion of patients admitted to ICUs will possess strong risk factors for osteoporosis such as female gender, older age, a positive family history, low body mass index, and white origin. Many will also be smokers, have a history of prior corticosteroid use, chronic inflammatory disease, or reduced mobility (6). Although no studies have formally quantified the prevalence of osteoporosis among patients admitted to critical care units, it is likely that many have this condition. Given the potential for osteoporosis-related fractures to impact on long-term quality of life, together with the availability of potential treatments, it is relevant to understand whether an episode of critical illness increases its severity or rates of disease progression and complications.

In this issue of *Critical Care Medicine*, Orford and colleagues (7) address this issue. They are the first to examine fracture incidence in patients who survive critical illness. The authors estimated fracture incidence for both men and women cared for in a major Australian ICU who required >48 hrs of mechanical ventilation and were able to compare the female cohort with age-matched control subjects from a high-quality prospective population-based osteoporosis study from the same region. Fracture incidence was assessed in the cohort of patients discharged after critical illness by searching electronic radiology reports for a median follow-up time of 3.7 yrs for females and 4 yrs for men. They found that 14% of female and 10% of male survivors who had been ventilated for >48 hrs sustained fractures in the follow-up period. In female survivors, the overall incidence trended to a higher fracture rate over the follow-up period than was present in the population control subjects, but this was not statistically significant (hazard ratio, 1.20; 95% confidence interval, 0.84–1.71; $p = .31$). Interestingly, when older female patients (aged ≥60 yrs) were analyzed as an age-matched subgroup, there was a statistically significant increase in fracture rate suggesting clinically important increases in fracture rates (hazard ratio, 1.65; 95% confidence interval, 1.08–2.52; $p = .02$). Because older women are more likely to have coexisting osteoporosis when they have their critical illness and/or are more prone to developing it, this observation raises the possibility that critical illness itself may accelerate osteoporosis development and increase the chance of fracture.

The study was not prospective such that fracture detection relied on patients having undergone imaging in the radiology departments included in the region. It is possible that fracture underdetection occurred in both critically ill and control populations, and ascertainment bias resulting from imbalance between the groups cannot be excluded. The excess of fractures in the female ICU survivors was attributable largely to vertebral fractures. These comprised a much higher proportion of the fractures in the ICU cohort

***See also p. 1295.**

Key Words: critical care; intensive care; bone and bones; bone resorption; osteoporosis; survivors; quality of life

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Table 1. Potential risk factors for bone loss during critical illness (12)

Risk Factor	Mechanism
Immobility (13, 14)	Increased calcium resorption inhibits parathyroid hormone and 1,25 dihydroxy vitamin D formation
Inflammatory cytokines (12)	Stimulate osteoclast formation and differentiation Stimulate mature osteoclasts Inhibit osteoblast formation
Endocrine dysfunction (12)	Increased cortisol Depressed growth hormone and insulin growth factor-1 Decreased thyroid-stimulating hormone and T4
Vitamin D deficiency (11)	Disturbance in calcium homeostasis
Glucocorticoids (15)	Decrease in osteoblastic activity

(41.7%) than the population control cohort (17.4%) and could also be a form of ascertainment bias perhaps attributable to increased imaging in post-ICU patients, for example, chest radiography for respiratory symptoms. As pointed out by the authors, the retrospective design also makes it difficult to disentangle preexisting risk factors from the effects of critical care, and confounding factors may not have been adequately controlled for. Despite these limitations, the findings raise the possibility that critical illness increases the risk of subsequent osteoporotic fractures.

Bone turnover can be assessed in patients using various biochemical markers (8). These have been broadly categorized as collagenous bone resorption markers, osteoclast regulatory proteins, and bone formation markers. Peptide fragments from the breakdown of mature collagen are the most commonly used measures of bone resorption and include the pyridinolines (pyridoniline and deoxypyridinoline), which can be detected in the serum and the urine (8). Increased bone turnover in critically ill patients, particularly those who require multiple organ support for prolonged periods, has been reported in the literature for well over a decade (9–11). Shapses and colleagues (9) compared bone turnover in a small sample of critically ill patients after gastrointestinal surgery, all of whom were receiving parenteral nutrition, with age-matched healthy volunteers. Excretion of pyridinium crosslinks was increased in the critically ill sample when compared with healthy volunteers and was more pronounced in patients who had a longer ICU stay. Smith et al (10) reported increased bone resorption compared with healthy control subjects in 23 patients with sepsis and trauma measured using pyridinoline/creatinine and deoxypyridinoline/creatinine ratios. The authors found this was particularly pronounced in the subgroup of septic patients who had a tenfold increase in pyridinoline/creatinine ratio and a sixfold increase in deoxypyridinoline/creatinine ratio. Serum markers of osteoblast activity were increased at ICU admission in Van Den Berghe's study of vitamin D in critically ill patients compared with healthy control subjects. This was accompanied by a similar increase in urinary deoxypyridinoline and pyridinoline implying upregulation of both osteoclast and osteoblast activity but with an imbalance in favor of bone resorption (11). These studies all suggest that critical illness is associated with changes to normal bone metabolism, which most likely favor bone breakdown and demineralization.

Although the impact of critical illness on bone mineralization is ill defined, much can be inferred from other settings and the known pathophysiological processes that occur. Factors known to cause bone loss are summarized in Table 1 and have been recently reviewed by Via and colleagues (12). The multiple potential mechanisms whereby critical illness could result in excessive osteoclast activity, bone loss, and demineralization provide a strong biologic plausibility for increased risk of subsequent osteoporosis, especially after prolonged critical illness.

Although the study by Orford and colleagues requires validation in prospective, adequately controlled studies with a low risk of bias, their findings are particularly interesting because potential therapies exist to prevent or minimize the detrimental effects of critical illness on bone metabolism. These include vitamin D and biphosphonate therapy. Biphosphonates in particular are well-established effective treatments for osteoporosis, bone metastases, and other bone diseases. They act by promoting osteoclast apoptosis, thereby reducing bone loss. Some small studies have used both vitamin D and biphosphonates in critically ill patients and demonstrated biochemical evidence of reduced bone resorption (11, 16). The overall excellent safety profile of biphosphonates make them a potentially attractive therapeutic option for the chronically critically ill, although caution is required in patients with renal failure and they have also been associated with fever and atrial fibrillation, both of which could have adverse effects in frail patients.

Orford et al have opened a new avenue of research into the consequences of critical illness. Their data support the need for well-designed prospective cohort studies to confirm whether critical illness increases the risk of subsequent osteoporosis-related fractures together with further well-designed studies to determine the factors that increase bone loss during intensive care. Clinical trials of biphosphonates and/or vitamin D to determine the risk-to-benefit profile of these agents in patients with organ dysfunction are needed. However, the ready availability of these agents raises true hope that intervening in the right patients at the right time during critical illness might result in long-lasting benefits to patients' subsequent quality of life.

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Should we still need to systematically perform catheter culture in the intensive care unit?*

Quantitative catheter culture either using ultrasonication (1) or vortex (2) techniques have proven to be accurate for diagnosing catheter-related bloodstream infections. Indeed, in a recent meta-analysis, the sensitivity of the quantitative culture was 82% and the specificity was 89% for short-term catheters (3).

Contrasting with this result, a further review of available trials showed that only an average of 17% of patients with positive catheter culture had actually catheter-related bloodstream infections (4).

That is why we should question the interest of systematic catheter cultures, having in mind too different objectives: what is the clinical meaning of a positive quantitative catheter culture? Should we accept the Centers for Disease Control and Prevention's definitions of central line-associated bloodstream infections (5), which do not consider catheter culture as an acceptable surrogate of catheter-related bloodstream infections (CRBSI) in intensive care units (ICUs)?

*See also p. 1301.

Key Words: central vein catheter; colonization; treatment

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Clinical Meaning of a Positive Quantitative Catheter Culture

In the monocentric study from Mrozec et al (6), systematic positive catheter culture in the absence of positive blood culture was associated with only 1.3% of subsequent bloodstream infection. This rate of subsequent bloodstream infection was not impacted by antimicrobial treatment. The authors concluded that isolated positive quantitative catheter culture could be considered as a simple colonization without any evidence of catheter-related infections.

The major inclusion criteria differentiating the study of Mrozec et al (6) from the others is that catheter culture was performed systematically, although the ICU has a low rate of catheter colonization. The present study is the only one having used quantitative culture. The specificity of the technique is comparable to the one semiquantitatively (3) and cannot explain this result. Furthermore, it is consistent with the estimated positive predictive value of the technique of 7% when the prevalence of catheter-related bloodstream infection is $<1\%$ (3).

In the Infectious Diseases Society of America guidelines (7), it is clearly mentioned that catheter culture should be performed when a catheter is removed for suspected CRBSI and that catheter culture should not be routinely performed.

However, this recommendation could not be applied in the ICU, because a systemic inflammatory response syndrome is present in $>80\%$ of the patient-days (8). Furthermore, we found in a prospective randomized study involving 3,276 catheters in ICUs (9, 10) that abnormal temperature was present in 1,674 (51%) cases at the time of catheter removal. Furthermore, two of the four systemic inflammatory response syndrome criteria were present in 2,854 (87%) cases. Safdar and coworkers (11) have shown that local signs are not predictive of catheter infections in the ICU.

Finally, the rate of catheter removal without local signs of infections and without systemic inflammatory response syndrome criteria (392 [11%]) became so infrequent in the ICU that a systematic culture is in fact required.

In the present study, the presence or the absence of systemic or local signs of infections has not been systematically collected. However, it should be pointed out that one subsequent bacteremia of two occurred on a patient whose central venous catheter was removed because it was no longer needed, underlying the subjectivity of the infection suspicion criteria. Furthermore, in a previous study exploring the significance of isolated positive culture (12–14), the presence of systemic inflammatory response syndrome criteria or local signs was not predictive of subsequent infections.

Accepting the fact that it is uneasy, in the sickest patients, to define the suspicion of catheter-related infection, the absence of antimicrobial treatment should be questioned. Recent studies that have

Table 1. Summary of recent studies that have explored the significance of isolated catheter cultures

Pathogens Reference, Year	No. of Positive Cases	Reason for CVC Culture	No. (%) of Simultaneous CRBSI	Percent of ICU Patients	No. (%; 95% CI) of Subsequent BSI	Comments
Staphylococcus aureus	99	NA but not systematic; only 38% patients have SIRS criteria	85 (46%) (24 hrs before of after catheter removal)	NA (35% MV patients)	*S. aureus* 14/99 (14.1% [7.3–21])	Semiquantitative culture ≥15 CFU/mL
Ekkelenkamp, 2008 (14)					51% received Abx No Abx: 12/49 patients Abx: 2/50 patients	BCs were not systematically done at catheter removal Significant risk factors for subsequent BSI were corticosteroid use and absence of Abx Neither SIRS nor local signs were predictive factors
S. aureus	77		3 (48 hrs before or after)		*S. aureus* 12/77 (15.6% [7.5–24])	Semiquantitative culture ≥15 CFU/mL
Ruhe, 2006 (13)					77% received Abx No Abx: 7/18 patients Abx: 2/59 patients	BCs was performed in only 57% cases SIRS was not a predictive factor Significant risk factors for subsequent BSI was Charlson index and absence of Abx
S. aureus	74	NA (77% have fever)	NA (72 hrs before and 24 hrs after catheter removal)		*S. aureus* 4/74 (5.4% [0.3–10.6])	Semiquantitative culture ≥15 CFU/mL
Zafar, 2009 (12)					59% received Abx No Abx: 3/30 patients Abx: 1/44 patients	
Candida spp.	58		64 (24 hrs before to 7 days after catheter removal)	91.4% (nonneutropenic)	*Candida* 1/58 (1.7% [0–5.1])	Semiquantitative culture ≥15 CFU/mL
Perez-Para, 2009 (15)					31% received Abx	BC was taken ≥3 days after catheter removal in only one case Absence of antifungals was not a risk factor of poor outcome
All	312	NA	421 (53%) (48 hrs before to 48 hrs after catheter removal)	72%	All 8/312 (2.6% [0.8–4.3])	Semiquantitative culture ≥15 CFU/mL
Park, 2010 (16)					48% received Abx No Abx: 7/161 patients Abx: 1/149 patients *S. aureus* 2/58 (3.5% [0.3–12.4]) *Enterococci* 1/11 (9.1% [0–39.9]) *Pseudomonas aeruginosa* 2/17 (11.8% [2–36]) *Candida* spp. 3/39 (7.7% [1.9–21])	BC was systematically done at catheter removal Considering only the 4 main pathogens, subsequent BSI occurred in 1/68 with Abx and 7/57 with no Abx ($p = .02$)
All	138 (149 pathogens)	Systematic (94.8% cases)	20 (13%) (48 hrs before to 48 hrs after catheter removal)	100%	All 2/149 (1.3% [0–3.2])	Quantitative culture ≥1000 CFU/mL
Mrozec, 2011 (6)					16% received Abx No Abx: 2/121 patients Abx: 0/23 patients[a] *S. aureus*: 0/6 *Enterococcus* sp. 0/13 *P. aeruginosa:* 0/25 *Candida* spp.: 0/2	The rate of true-positive culture was only 159/3007 (5.3%)

CVC, central line catheter; CRBSI, catheter-related bloodstream infection; ICU, intensive control unit; CI, confidence interval; BSI, bloodstream infection; NA, not available; SIRS, sepsis inflammatory response syndrome; MV, mechanical ventilation; Abx, effective antimicrobials started after positive catheter culture; CFU, colony-forming units; BC, blood culture.

[a]Six missing antibiotic susceptibility testings.

explored this topic are summarized in Table 1 (12–16).

The absence of antibiotic treatment should also be discussed according to the recovered micro-organisms. Although the rate of complications (ie, septic shock, severe sepsis, thrombophlebitis) is <20% for the central nervous system, enterococci, and *Enterobacteriaceae* CRBSIs, it reaches 38%, 50%, and 68% for *Staphylococcus aureus*, *Pseudomonas aeruginosa,* and *Candida* spp (17).

Considering the low rate of positive tip culture with *S. aureus* in the present study (6), and the results of five previous studies summarized in Table 1, we still consider that treatment of patients with a *S. aureus*-colonized catheter need to be carefully discussed, especially in patients with previous chronic diseases (13) or corticosteroids therapy (14). Such patients must probably be treated within 24 hrs after removal with short 5- to 7-day therapy in most cases (7). The available data are much fewer and therefore less convincing for the other pathogens. The treatment of patients with isolated positive catheter culture with pathogens other than the central nervous system still requires further prospective trials.

Systematic Catheter Culture Should Take Part of the Definition of CRBSI in ICUs

Systematic catheter culture should also be done in the ICU to accurately identify CRBSIs. It is especially important because the rate of central line-associated bloodstream infections is a main target for improving patient safety and, also, is under the public spotlight. Because financial penalties and punishment are associated to "getting to zero" campaigns (18), it is also key for healthcare workers and hospitals to use reliable and objective surveillance measures. The definition of central line-associated bloodstream infections is only based on one positive blood culture with a pathogen (or two with a common commensal) if the micro-organism is not recovered from any nonblood culture 3 days before and 7 days after blood culture tested positive and, as such, is clearly insufficiently accurate (19). It has been demonstrated that episodes classified as central line-associated bloodstream infections as compared with those classified as secondary bacteremia considerably vary according to experts (20, 21) and to hospitals (19). It will obviously also vary according to the number of blood cultures performed before any new antimicrobial therapy and to the number of nonblood bacterial examinations performed to identify another infectious focus responsible for secondary bloodstream infection.

If performed before a new antimicrobial start, catheter culture, either quantitative or semiquantitative, possesses an excellent negative predictive value, reaching 99% if the prevalence of CRBSI is ≤5% (3). The absence of colonization should be used to rule out the responsibility of a catheter in the presence of bacteremia.

In conclusion, we still consider that systematic catheter culture needs to remain a standard of care in the ICU. The clinical interpretation of a catheter culture positive with pathogens remains an area of further research. A negative culture could accurately help in defining the real rate of catheter infection as a good target for continuous quality improvement programs.

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Dollars and sense in sepsis*

Over the past 2 yrs, the debate about health care has raged across the United States. Initially focusing on the issues of access and cost, nearly all participants in healthcare reform now acknowledge that cost represents the main concern. Costs continue to rise because of a multitude of factors ranging from the expense of new technologies to the aging of the population. These escalating costs drive access by either pricing individuals out of health care or forcing government purchasers to restrict access. Because critical care consumes nearly 0.5% of the national gross domestic product, intensivists must be involved in healthcare reform (1). Historically, physicians have only addressed concerns related to the risk/benefit ratio of an intervention. Now, we are all being asked to consider, either directly or indirectly, the concept of cost relative to benefit. Although the evolution of the concept of "comparative effectiveness" led to consternation about "rationing," the notion of trying to systematically assess the value of an intervention is a crucial part of any effort to rigorously determine how to allocate scarce resources—irrespective of the means for that allocation, whether via a market or a government policy.

Readers should note that cost-effectiveness is a means to an end. It does not represent an end in itself. The results of any specific assessment of a novel therapy's cost-effectiveness are not meant to trump other ethical issues surrounding the determination of whether to adopt or fund a new intervention. Rather, cost-effectiveness analyses (CEAs) are meant to inform the decision-making process (2). In turn, those practicing in the intensive care unit (ICU) must become familiar with the language of CEAs, as we will be asked to either comment on them or alter our care in response to them. CEAs can take many forms. In ICU studies, two general methods are utilized. Cost-minimization analysis represents an effort to determine which pathway or process requires the fewest resources (e.g., which option is cheaper) while maintaining similar overall outcomes (2). True CEA incorporates a more complicated set of variables. CEA aims to evaluate the total costs of an intervention relative to the benefits accrued. Costs are measured in some unit of currency (2). Benefits are often computed in some common denominator that allows one to compare alternate options. For CEA, the appropriate unit for evaluating benefit is the quality-adjusted life year (QALY); one incorporates how many lives are saved along with how long survivors live and the quality of those additional years of life (3). Measurement of QALYs is fraught with complication and nuance. As with all the medical literature, some CEAs are more methodologically rigorous than others. When reviewing a CEA, readers should use the same jaundiced eye and skepticism applied when examining a clinical study.

In this issue of *Critical Care Medicine*, Jones and colleagues (4) present a thought-provoking CEA of an emergency-department-based early goal-directed therapy (EGDT) protocol for patients with severe sepsis. Clinical trial data suggest that EGDT results in improved mortality (5). However, the use of specific catheters to facilitate EGDT can prove costly. More survivors, furthermore, may mean more cost if patients destined to die are saved but in such a state that they consume vast resources. In a prospective sequential study consisting of 285 patients with severe sepsis or septic shock, they found that the use of EGDT was associated with a cost of $5397 per QALY gained (4). They also determined that the probability of cost-effectiveness was 98% at a willingness to pay $50,000 per QALY (4). The $50,000 per QALY threshold, which has come to represent the definition of "cost-effective," is arbitrary, and it remains unclear if and how it should be revised. The authors conclude that EGDT is extremely cost-effective and should therefore be implemented.

The results of this study demonstrate that EGDT is not only feasible but also economically viable. EGDT leads to more survivors and longer life expectancies compared to those not treated with EGDT. EGDT subjects also had longer ICU and hospital lengths of stay. The authors are to be commended for (1) utilizing data from a clinical study to serve as the foundation for their CEA and (2) building specific measures of resource use into their assessment of end points. An important additional strength of their study was the effort to account for all the costs related to the protocol. Their cost calculation includes those related to the initial education and the resources required for the successful execution of their protocol.

Yet, how do we determine costs in medicine? Cost has very little correlation with the "charge" on a hospital bill. Many poorly done CEAs fail to make any effort to grapple with this concern; if the methods do not clearly articulate how charges were adjusted to costs, one should be very cautious of the study's overall findings. Jones et al (4) state that they relied on a hospital work load accounting system that measures costs rather than charges. This methodology, however, remains somewhat opaque. Jones et al also commit an error common in CEAs. They conflate both fixed and variable costs. Fixed costs are those that remain no matter what happens to the patient. Variable costs represent those that can actually be "saved." As one can imagine, most costs related to ICU care are fixed (6). As an example, although a bed day in an ICU may cost several thousand dollars, most of those costs are not recoverable if a patient is not filling the bed (6). Even if the bed is empty, someone has to pay for the hospital overhead, the nurse who is on duty even if there is no patient to treat, and the physician on call.

Hence, CEA essentially represents a series of mathematical models. Despite the issues raised above, the core concern remains the quality of the inputs utilized

***See also p. 1306.**

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for the model. In this respect, the study by Jones and colleagues (4) has multiple limitations. Potential confounding factors may have contributed to the differences the authors observed. The management of severe sepsis and septic shock has significantly evolved. For example, early administration of appropriate antibiotic therapy is a key determinant of survival in severe sepsis (7, 8). Beyond its impact on survival, inappropriate therapy results in longer hospitalizations in severe sepsis (9). One can no longer assume that a septic patient received initially appropriate antibiotic therapy. Unfortunately, Jones et al provide scant information on the approach to antibiotics either before or after the implementation of their EGDT protocol or the actual pathogens isolated. Similarly, Jones and co-workers fail to report information on important aspects of postresuscitation care that may affect both mortality and costs. Although corticosteroid administration in septic shock remains controversial, we lack any description of if and how these were utilized and if their administration differed between the pre- and post-EGDT periods.

In the same vein, it is uncertain if EGDT as it was originally conceived was truly the intervention studied. Since a specific protocol was not in place to guide standardized management of severe sepsis or septic shock other than the resuscitation, it is unclear if physicians truly followed the EGDT approach of Rivers and colleagues (5). Paradoxic to the original EGDT study, Jones et al (4) found an increased length of stay of approximately 2 days in those who received EGDT. This is concerning because biologically one would presume that early aggressive care would decrease the length of stay if it were an effective strategy: patients would get better faster. In fact, this was a key observation of Rivers et al (5). Consequently, there seems to be a biological disconnect as to the utilization of EGDT and recovery in the analysis by Jones et al.

The unblinded, observational nature of the study by Jones and colleagues (4) raises added concerns. This design may have resulted in a Hawthorne-like effect where compliance to early therapy was vigilantly pursued because clinicians knew that performance would be monitored. For the purposes of the CEA, however, several of these biases would favor a conventional rather than the EGDT approach. By attributing a length of stay penalty to EGDT when one might not exist, Jones et al may have overestimated the costs of EGDT. Therefore, EGDT may be more cost-effective then the authors calculate.

Interestingly, the findings of the study by Jones et al (4) are dissimilar to results from earlier reports of emergency-department-based sepsis protocols. A recent economic evaluation of an emergency-department-based sepsis protocol that addressed resuscitation (but without the formal use of EGDT) and antibiotic therapy found that a sepsis protocol not only would be cost-effective but would actually result in a savings of nearly $6000 per severe sepsis admission (10). This benefit was driven by a length of stay and mortality benefit. Possible explanations for the discordance in results between these two studies might reflect differences in cost accounting. This potential underscores the need for those reporting CEAs to be as explicit as possible regarding the determinants of costs.

Despite the limitations in the analysis by Jones et al (4), they confirm that aggressive early resuscitation in severe sepsis is associated with a decrease in mortality. This alone should motivate clinicians to change practice. Certainly, the benefit of aggressive resuscitation coupled with its minimal risk confirms its utility in the setting of severe sepsis. The key next question is the following: how do we ensure that our septic patients receive aggressive resuscitation in the emergency department? This can only be determined through randomized trials that systematically compare various strategies and simultaneously measure markers of resource use along with survival. ICU practitioners can then apply their skills as evidence-based readers of both the clinical and CEA literature to effectively improve outcomes for their patients.

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Trial designs for old problems in a new era*

The randomized controlled trial (RCT) is well established as the investigational "gold standard" in acute medicine. The RCT is particularly suitable for drug development, with well-defined phases of development and a good understanding of placebo (or other) control, superiority or noninferiority design, and sample size and power. Outside pharmaceutical trials, the RCT has been questioned, however, and in intensive care medicine in particular there have been a preponderance of negative trials (1). In a recent opinion piece in this journal, Vincent (2) went as far as suggesting that RCTs should be abandoned in the intensive care unit (ICU), preferring well-conducted observational studies in entire populations to inform ICU practice.

RCTs are problematic when large numbers of patients must be recruited and become particularly difficult when there is a risk of contamination from one subject to another. This contamination can be conceptual, for example, in a "process of care" trial where a protocol or therapeutic approach is being tested such that the treating clinicians may be biased in their approach to subsequent patients after exposure to the intervention protocol (3). Contamination can also be literal, where a procedure designed to reduce infection or affect microbiological colonization can quite literally contaminate the patient in the bed space next door.

In this issue of *Critical Care Medicine*, Jongerden and colleagues (4) use a pragmatic trial solution in their comparison of open and closed endotracheal suctioning. Suctioning is a basic procedure in intensive care that has evolved over 50 yrs from reusable catheters stored in alcohol to disposable open suction catheters to "closed" systems designed to reduce contamination and minimize loss of positive end-expiratory pressure due to disconnection of the ventilator circuit. A comparison of open and closed catheters cannot be blinded, the simple practicalities of such a trial in a busy intensive care make individual patient randomization with individual consent problematic, and bacterial colonization of one patient can at least theoretically affect the patient in the bed next door, confounding such a trial. Instead, Jongerden and colleagues (4) used a crossover cluster design. Four ICUs from two hospitals adopted either open or closed suctioning systems in a random order during a 6-month cluster, before crossing over to the other system in the second 6 months. As a consequence, all patients fitting inclusion criteria could be studied; each suction system was in turn the "standard" system in use in the ICU at that time, so prospective consent by the patients was not required.

Sample size calculation in a cluster RCT can be problematic. If the patient groups are relatively homogeneous, then the study can be powered according to the number of patients, as in a traditional RCT, but if there is significant heterogeneity, then power is instead related to the number of *clusters* (5). This was seen in an important cluster RCT of the introduction of medical emergency teams in hospitals without such a team (6). In a study of 23 heterogeneous hospitals (including university, metropolitan, and rural hospitals), the introduction of an medical emergency team greatly increased emergency team calling but did not affect the incidence of cardiac arrest, unplanned ICU admissions, or unexpected death. The lower than anticipated event rate and higher interhospital variability and intraclass correlation coefficient meant that ultimately the study was underpowered, with only a 20% chance of detecting a difference if in fact there was such a difference to be found. The investigators calculated retrospectively that, to have adequate power to show a 30% difference in composite outcome, they actually needed 100 hospitals in the study (6).

de Smet and colleagues (7), from the same research group as Jongerden, have recently reported an ambitious three-arm crossover cluster RCT of selective decontamination of the digestive tract, selective oral decontamination, or standard care in 13 ICUs in The Netherlands. A cluster RCT design is an ideal way to study a therapy such as selective decontamination of the digestive tract that is actually designed to influence the microbiological ecology of an ICU. The original study plan was problematic, however, failing to take into account analysis of cluster effects or how to address imbalances in baseline characteristics between study groups, with a failure to preclude postrandomization selection bias. To the researchers' credit, these problems were recognized, corrected, and declared openly in the study report in the *New England Journal of Medicine* (7). There are now statements from the Consolidated Standards of Reporting Trials group addressing the appropriate reporting of cluster RCTs (8, 9).

While the design of a good cluster RCT is more difficult and the problems less well understood than those of a traditional individual patient RCT, there are many reasons such a study design needs to be better understood by the critical care trials community and accepted as valid by the general readership. Many of the fundamental questions of intensive care medicine, such as oxygen therapy, basic mechanical ventilation, sedation and delirium management, and nutrition therapy, may be best addressed by large, pragmatic cluster RCTs examining entire ICU populations when individual patient RCTs prove not to be feasible.

Ospina-Tascón et al (1) discussed some of the reasons RCTs in intensive care are so often negative. Another reason is the unrealistically optimistic estimates of effect size that lead to consistently underpowered studies. Aberegg and colleagues (10) examined 38 RCTs of intensive care therapies published in five high-impact journals over 10 yrs. The average predicted absolute effect size was 10.1%, while the average *observed* absolute effect size was 1.4%. Any RCT pow-

*See also p. 1313.

Key Words: randomized controlled trials; cluster randomized controlled trials

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ered to detect an effect size of 10% or more in intensive care is implausibly optimistic and likely to be ultimately underpowered and negative. Part of this relates to the *attributable* mortality of conditions amenable to intervention. While severe sepsis is generally considered to have a mortality of 30% or more (11), much of that is due to underlying chronic medical conditions, and the pure mortality from sepsis is closer to 10% (12). This is very similar to the mortality seen from sepsis in pediatric intensive care (13). To have a 90% power to detect a 1.4% absolute risk reduction from a 10% baseline requires a study with over 18,000 patients. It is impossible to conduct that sort of individual patient RCT for a general, simple intensive care intervention, but using a crossover cluster RCT design recruiting "all comers" is easily and quickly achievable in, for example, 36 ICUs, each recruiting 500 eligible patients in a year.

Just as Jongerden and colleagues (4) used a simple and elegant crossover design to study the simple intervention of closed vs. open suction catheters, this design is equally applicable to much bigger studies of fundamental intensive care interventions. The crossover cluster RCT may well be the clinical trial design of the future.

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Refractory hypoxemia: How to treat it in the real world*

Currently, we have neither a consensus on the definition of refractory hypoxemia nor a consensus on deciding at what point we should use special measures to treat hypoxemia (rescue therapies) (1). Clinicians may be required to use a variety of therapies to mitigate life-threatening hypoxemia: high-frequency ventilation (HFV), extracorporeal membrane oxygenation (ECMO), or prone ventilation. The mortality of acute respiratory distress syndrome (ARDS) has fallen in recent years to around 30% in published clinical trials, but despite the fact that the most profound physiologic derangements in patients with ARDS are related to hypoxemia, only 10% to 15% die of refractory hypoxemia, while most patients with ARDS die of multiorgan failure (2).

However, recently we have known a cohort of patients, often young and previously healthy, infected with a novel H1N1 influenza strain, 2009 pandemic influenza A, which emerged in late March 2009 (3) and quickly spread to all continents, causing 18,000 deaths according to World Health Organization (Geneva, Switzerland) reports. Patients with 2009 H1N1 infection who required admission to intensive care frequently developed ARDS with severe hypoxemia. According to the published data in many countries (4–7), several rescue therapies for severe hypoxemia were used in the subset of patients who developed profound refractory hypoxemia secondary to severe ARDS and did not respond to conventional therapies. We can see differences in these therapies (8). For example, in Canada, HFV is the most frequent therapy in this circumstance (25%), followed by ECMO (4.2%), while the most frequent technique in Spain and South America is prone ventilation (25% and 39% in Argentina). There are no studies clearly demonstrating the superiority of one technique over another, and there are no recommendations on their use in different types of patients.

In this issue of *Critical Care Medicine*, Walkey and Wiener (9) present an interesting secondary analysis of multicentered, randomized, controlled trial data from the National Heart, Lung and Blood Institute ARDS Clinical Trials Network. These studies include 2,632 subjects enrolled between 1996 and 2005. A total of 166 (6.3%) of the subjects received rescue therapy, defined as prone positioning (97 [58%]), inhaled vasodilators (47 [28%]), HFV (12 [7%]), or ECMO (10 [6%]). Use of

***See also p. 1322.**

Key Words: respiratory distress syndrome, adult; prone position; extracorporeal; membrane oxygenation; high-frequency ventilation; mechanical ventilation; refractory hypoxemia

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inhaled vasodilators and HFV increased over time (p values for trend of .04 and .02, respectively). No differences in adjusted outcomes were seen between those who received rescue therapy and those who did not or between rescue modalities.

This study is of great interest despite not being randomized and having no predefined indications for initiating rescue therapies. The pattern of use of rescue therapies is to employ the prone position. Patients were included in the studies until 2005. It is possible that, in 5 yrs, the use of these techniques has changed, especially after the influenza pandemic. Esteban et al (10) described how, in a period of 5 yrs (2004 vs. 1998), ARDS patients were ventilated with significantly lower tidal volumes, a strategy of pressure/volume limitation was applied significantly more often, and positive end-expiratory pressure (PEEP) levels were increased, while they observed a decrease in the use of the prone position (7% vs. 13%).

This pandemic has generated increasing interest in rescue techniques in the management of ARDS, and indeed in recent months, journals have published several studies and meta-analyses (some of them pending publication even years ago), referring to different ventilator and drug management strategies for these patients (11–14).

In the present study, the authors mention that the only strategy clearly shown to reduce mortality for patients with acute lung injury is low tidal volume ventilation. Because adjunctive strategies such as prone positioning, inhaled vasodilators, and HFV have not been shown to improve clinical outcomes with routine use in early acute lung injury/ARDS, it has been suggested that they should be reserved as "rescue therapies" in patients with severe acute lung injury/ARDS.

Interest in the use of these techniques is to significantly improve oxygenation in patients with severe hypoxemia (such improvement in clinical practice is still greater in those patients ventilated without a high level of PEEP), and some of them have shown a tendency to reduce mortality when applied to the more severe patient group (prone or high-frequency oscillation), while others have demonstrated efficacy and good results in an influenza pandemic (ECMO) (7, 15). In the present study, in the group of patients receiving rescue treatment, the mean Pao_2/Fio_2 is 105, while the mean applied PEEP is 11. In comparison, in patients enrolled in the ARDS Network, the PEEP level recommended for that Pao_2/Fio_2 level is much higher (per table preset PEEP in these studies).

There are no studies demonstrating the superiority of one technique over another, and there are no recommendations on their use in different types of patients. Undoubtedly, the technical equipment available in the intensive care unit exerts an influence. For example, HFV requires not only an economic investment, but also specific training of the intensive care unit staff. Prone ventilation has shown improvement in oxygenation in patients with ARDS. In a recent meta-analysis (12) including five randomized, controlled trials, ventilation in prone positioning reduced mortality in patients with the most severe hypoxemia ($Pao_2/Fio_2 < 100$): relative risk 0.84 (95% confidence interval 0.74–0.96, $p = .01$). Therefore, ventilation in the prone position cannot be routinely recommended in patients with ARDS, although in more severe patients the technique can be used. In the context of pandemics such as that commented on above, it may be more practical to use financial resources to procure good conventional mechanical ventilation equipment and train staff in the management of ventilation in the prone position. This strategy can be applied to a larger number of intensive care units with fewer economic opportunities and not necessarily specialized in respiratory care.

In the future, it will be necessary to clarify the role of these strategies and to determine what investments are needed to adequately manage patients with refractory hypoxemia. Probably, at the present time in the real world, the easiest option is the combination of low-volume ventilation, high PEEP, muscle relaxation, and the prone position, but we cannot rule out other treatments such as HFV or ECMO, and probably we need some reference centers with these therapies. In the future, we must determine whether transferring adult patients with severe but potentially reversible respiratory failure to a single center specializing in the management of severe respiratory failure for the consideration of ECMO or HFV would be cost-effective (11).

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Renal protection during liver transplantation: An ounce of prevention is worth a pound of cure*

Acute renal dysfunction is a frequent and ominous complication after orthotopic liver transplantation (OLT), with an incidence ranging between 4% and 94%, depending on the definition criteria used. Its origin is multifactorial, and risk factors include recipient pretransplant status and preexisting renal impairment and perioperative hemodynamic instability, as well as significant intraoperative bleeding and use of blood products (1, 2). More subtle mechanisms, such as the proinflammatory mediators and potent reactive oxygen and nitrogen species released from the reperfused liver graft, may lead to leukocyte and endothelial activation and subsequent injury in remote organs, including the glomerular endothelium (3). In addition, endothelial dysfunction and the imbalance between vasodilatatory (i.e., depleted nitric oxide) and vasoconstrictive (the renin-angiotensin system) factors may further aggravate the renal dysfunction. In the longer term, one should also consider the nephrotoxicity of the calcineurin inhibitors, the mainstay of the current immunosuppression.

Although the routine use of decompression systems and the increasing use of OLT with preservation of the vena cava may have reduced its incidence, various degrees of acute renal dysfunction still occur in up to 78% of the patients undergoing liver transplantation (4). The presence of acute renal impairment has been shown as a prognostic factor for morbidity and mortality before hospital discharge. Patients requiring early renal replacement therapy consumed significantly more healthcare resources (2, 5, 6) and had an increased incidence of chronic kidney disease, another negative prognostic factor (7).

Maintaining the mean arterial pressure above 65 mm Hg is a major objective of intraoperative patient management. This sometimes becomes a real challenge, particularly in the case of standard OLT when the inferior vena cava is interrupted during the anhepatic phase. As fluid restriction and low central venous pressure are desirable, maintaining an acceptable mean arterial pressure would rely mainly on noradrenalin. However, increased use of vasopressors, including noradrenalin, has been demonstrated in itself to increase the incidence of early renal failure and therefore should be used judiciously (1). Other pharmacologic agents (dopamine and dopamine agonists such as fenoldopam) were used to provide intraoperative renoprotection and increase the renal blood flow; however, their use may also result in detrimental increases in portal pressure (8).

In this issue of *Critical Care Medicine*, Dr. Mukhtar and colleagues (9) come to offer a rational solution to many of these challenging problems. In a small but well-designed study, the group explored the impact of terlipressin on the intraoperative hemodynamics as well as its effect on the postoperative renal function in patients undergoing living donor liver transplantation. The authors report improved hemodynamics during OLT as well as superior early renal function in patients receiving terlipressin compared with saline-treated controls. The intervention also achieved a significant reduction in portal pressure in the absence of any evidence of splanchnic hypoperfusion.

Terlipressin, a vasopressin analog with a longer half-life than vasopressin, has come of age, and its beneficial effects on splanchnic flow and renal function in patients with cirrhosis and related complications are well documented (10–13). In summary, the drug has the potential of rapidly reducing the portal pressure and thus the severity of intra-abdominal hemorrhage during surgery. Furthermore, the increased effective arterial blood volume following splanchnic vasoconstriction will increase mean arterial pressure. This will reduce the activity of the renin-angiotensin system and will ultimately result in decreased renal arterial resistance and improved renal blood flow (10).

Besides a relatively low number of subjects, a noteworthy limitation of the study is that it includes only patients without primary renal dysfunction. This is relevant since previous reports indicate that patients with cirrhosis and renal impairment (i.e., hepatorenal syndrome) are the most likely to benefit from the terlipressin therapy while at the same time running the highest risk to develop acute renal dysfunction following OLT (11, 12, 14). One may cynically argue that the heterogeneity introduced by any patients with hepatorenal syndrome may have resulted in less impressive statistics or would have required larger patient groups. In turn, one could reply that a more homogeneous, comparable patient population in the beginning of the study would suggest more convincingly both the putative mechanisms and ultimately the final result.

The short cold ischemia time and subsequent mild ischemia-reperfusion injury may have minimized the potential contribution of the proinflammatory mediators to the renal injury. Longer cold ischemia times and subsequent more advanced ischemia-reperfusion injury could therefore appear as additional damaging elements that should be taken into account. The short observation time could be regarded as another limitation. Nevertheless, the authors were able to better discriminate between the initial renal insult and any additional nephrotoxic effects of the immunosuppressants that may be visible as early as after 1 wk.

The paper of Dr. Mukhtar and colleagues (9) is the first report on the use of terlipressin during OLT. The study represents a logical and timely continuation of other numerous studies performed in the very same patient population that constitutes the main pool of candidates for liver

*See also p. 1329.

Key Words: orthotopic liver transplantation; terlipressin; renal dysfunction; intraoperative hemodynamics.

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transplantation. Hence, the significant renoprotective effects as well as the improved hemodynamics in patients receiving the drug may soon transform terlipressin from a "bridge to transplantation" into a "bridge over transplantation." The feasibility and the favorable safety profile of the approach presented herein herald the potential of terlipressin of becoming attractive for hepatologists, anesthesiologists, and transplant surgeons alike. Future larger clinical trials on more heterogeneous patient populations should identify the optimal dose and timing of administration as well as the most suitable patient groups likely to benefit from this promising strategy.

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Colloids and renal dysfunction: Another brick in the wall of safety concerns*

After Edwin Cohn led efforts to fractionate plasma proteins in blood in the late 1930s and early 1940s for World War II, >35 papers were published before 1950 that described potential uses for the various fractionation products, including albumin. From the 1950s to the 1970s, other investigations elucidated the structure, function, and pharmacokinetic properties of albumin. The increasing use of albumin for questionable indications combined with periodic shortages and cost concerns led to a workshop in 1975 conducted under the auspices of the Division of Blood Diseases and Resources, National Heart and Lung Institute (Bethesda, MD), and the Division of Blood and Blood Products, Bureau of Biologics (Bethesda, MD) (1). The consensus guidelines emanating from the workshop listed four uses of albumin defined as *appropriate*: shock, burns, adult respiratory distress syndrome, and cardiopulmonary bypass. These general uses continue to be listed as major indications in approved labeling for albumin, although the efficacy of albumin for each of them has been the source of ongoing controversy. The 1975 guidelines had other indications described under the headings of *occasional use* or *uses requiring additional data*, but only three indications were considered unjustified: undernutrition, chronic cirrhosis, and chronic nephrosis (2). It is important to note that only one randomized controlled trial (RCT) involving albumin was available when the guidelines were developed and that trial had a number of limitations (3). Many RCTs of albumin were conducted from the late 1970s on, and other colloids, such as the starch products, were developed as potentially cost-effective alternatives. The majority of these RCTs comparing crystalloids and colloids for resuscitation used surrogate markers and frequently did not report pulmonary edema, mortality, or length of stay (4). During the 1990s, meta-analysis was in its honeymoon phase and multiple meta-analyses were conducted to help define appropriate uses of albumin, but the meta-analyses often had conflicting results, and the technique was increasingly being considered hypothesis generating. It was not until the Saline Versus Albumin Fluid Evaluation study that an adequately powered RCT was available to address mortality as an end point, but the lack of difference between albumin and

*See also p. 1335.

Key Words: crystalloids; colloids; sepsis; albumin; acute renal failure; hydroxyethyl starch

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saline for the primary end point leaves clinicians to argue over the interpretation of subset analyses (5).

It is against this backdrop that Bayer et al (6) performed their prospective sequential comparison of colloids and crystalloids in patients with severe sepsis. In this article, published in this issue of *Critical Care Medicine*, they investigate the incidence of acute kidney injury (AKI) and renal replacement therapy in patients who received only crystalloids vs. predominantly hydroxyethyl starch (HES) or gelatin products in previous sequential phases. The results of the before–after study of HES 6% (130/0.4) followed by gelatin 4% were reported in a prior publication; higher cumulative doses of both products were associated with increased renal failure in the *post hoc* analysis (7). The major findings of this study are that crystalloids appear to be as effective as colloids for resuscitation and that a newer (third-generation) starch product and gelatin may increase the risk of AKI and possibly the need for renal replacement therapy. With regard to the starch product, this is in opposition to a number of previous studies that suggested adverse effects, such as AKI and bleeding, were more related to cumulative dose (no relationship to HES dose was found in the current study), increased molecular weight (130 is a medium molecular weight for a HES), and increased degree of starch substitution (0.4 is considered a low degree of substitution), all of which cause accumulation of HES in plasma (8). The results raise concerns of potential class adverse effects of HES products since the findings are consistent with those of Brunkhorst et al (9) in which another HES product (200/0.5) with a medium molecular weight and moderate degree of starch substitution led to increased rates of AKI and need for renal replacement therapy in patients with severe sepsis. Appropriately powered RCTs involving HES 130/0.4 are currently in progress and hopefully will resolve this safety concern.

Another interesting finding of the current study was that hyperoncotic albumin was associated with statistically significant increases in the rates of both AKI and renal replacement therapy in the multiple logistic regression analysis. This was not a study end point, and albumin use was restricted to patients with hypoalbuminemia, but this finding may reinvigorate the debate as to whether hyperoncotic albumin causes renal dysfunction (10, 11). The primary limitation to this study is the single-center, sequential design with multiple *post hoc* adjusted analyses that raises questions concerning validity and generalizability. However, the use of observational designs is only likely to increase given the methodologic difficulties and costs that limit the number of adequately powered RCTs conducted in the intensive care unit setting (12).

Given the ongoing colloid vs. crystalloid debate, what have we learned since the introduction of albumin into clinical use >50 yrs ago? What follows is a list of my top ten items concerning colloids that are *not* worth debating in most clinical situations.

1. Low serum albumin concentrations are associated with worse patient outcomes.
2. Other plasma proteins can take over the functions of albumin as exhibited by patients with analbuminemia who were not diagnosed until later in life (if and when this occurs in patients with more acute hypoalbuminemia is unknown).
3. Exogenous albumin administration will raise serum albumin concentrations (but there is no substantial evidence that it improves patient outcomes).
4. Exogenous albumin and endogenous albumin do not have identical pharmacokinetic and pharmacologic actions.
5. There is no commercially available colloid with properties similar to those of hyperoncotic (i.e., 20% or 25%) albumin, but benefits of the latter product beyond transient changes in surrogate markers have not been demonstrated by high-level evidence.
6. The major adverse effects of albumin have been known for >50 yrs, but the adverse effects of synthetic colloids continue to be elucidated.
7. Clinically important pharmacologic benefits of exogenous colloids (e.g., antioxidant action of albumin) beyond plasma expansion remain to be demonstrated.
8. Exogenous colloids do not increase mortality in the majority of critically ill patients when used for resuscitation (but there is no substantial evidence that they decrease mortality, and they are far more expensive than crystalloids in the United States).
9. Product labeling for colloids is of little guidance in defining appropriate clinical uses.
10. Meta-analyses do not substitute for RCTs or other high-level evidence when defining appropriate uses of colloids.

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Statins and sepsis: A magic bullet or just shooting blanks?*

Despite decades of research and advances in treatment, sepsis, as well as acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), remains a significant source of critical illness and death.

There are 750,000 cases of sepsis annually accounting for almost 2% of all hospital admissions and a hospital mortality rate of approximately 30% (1–3). Sepsis is the tenth leading cause of death in the United States (4, 5), with an estimated annual cost of $16.7 billion (3, 6). ALI/ARDS is also common and associated with significant morbidity and mortality. Rubenfeld et al (7) estimate an annual mortality approaching 40% with a crude incidence of 78.9 and 58.7 cases per 100,000 person years, respectively.

Both sepsis and ALI/ARDS are associated with inflammation. ALI/ARDS is mediated by an intense inflammatory response with associated oxidative injury (8). The most frequent cause of ALI/ARDS is severe sepsis. Sepsis is characterized by endothelial dysfunction, systemic inflammation, immune system dysregulation, and inability to regulate the intense inflammatory response (1, 2, 4, 6, 9, 10). The presence of invading microorganisms and their toxins results in systemic inflammation, production of inflammatory mediators, endothelial dysfunction, and excessive release of proinflammatory cytokines, tumor necrosis factor, C-reactive protein, interleukins, and procoagulants (1, 2, 4, 6, 9, 10). Ultimately, organ dysfunction and death ensue if early and effective treatment is not initiated.

*See also p. 1343.

Key Words: statins; aspirin; sepsis; acute lung injury; acute respiratory distress syndrome; critical care; inflammation; intensive care unit

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Agents with the ability to modify, attenuate, and disrupt this excessive and exaggerated inflammatory phenomenon are of great clinical interest and at the forefront of intense research. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are potent lipid-lowering agents that are used for both primary and secondary prevention of cardiovascular events and produce significant reductions in both morbidity and mortality (11). While lipid lowering itself was initially thought to be responsible for the beneficial effects of statins, more recent findings suggest powerful and diverse pleiotropic effects, including antiinflammatory and immunomodulating properties (10). In addition to lowering cholesterol through competitive antagonism of 3-hydroxy-3-methylglutaryl coenzyme A reductase, which inhibits conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate (11, 12), statins disrupt the synthesis of the isoprenoid derivatives of mevalonate (farnesyl and geranylgeranyl pyrophosphate), which interferes with cellular processes such as proliferation, migration, gene expression, and apoptosis (4, 11, 12). Statins modulate immune response and ameliorate inflammation by blocking immune cell receptors, inhibiting cellular signal transduction, repressing T-cell activation, reducing expression of adhesion molecules and C-reactive protein, and suppressing proinflammatory cytokines (interleukin, interferon, and tumor necrosis factor). Furthermore, statins provide endothelial-stabilizing effects, due to up-regulation of endothelial nitric oxide synthase, increased nitric oxide bioavailability, reduced endothelial adhesion of leukocytes, and antithrombotic effects (1, 2, 4, 6, 8–14). Through these pleiotropic effects, statins can exert powerful and protective effects in bacteremia, sepsis, and various inflammatory states, independent of their lipid-lowering ability (1, 2, 4, 6, 8–14).

These impressive immunomodulatory and antiinflammatory effects appear to improve outcomes in sepsis and ALI/ARDS. Multiple studies have investigated the association between statin use and outcomes in sepsis and ALI/ARDS (1, 2, 4, 6, 7–10, 14–16). In mice, treatment of sepsis with simvastatin was associated with a fourfold improvement in survival time compared with that of untreated mice (17). Human trials further confirm the pleiotropic properties and therapeutic potential of statins. In individuals with chronic renal disease on dialysis, statin use was strongly and independently associated with a reduction in the risk of hospitalization for sepsis (14). Statin use was shown to improve longer term survival (between 31 and 180 days) in postbacteremic patients (4). Furthermore, there was a reduced risk of developing severe sepsis during hospitalization for various bacterial infections (10). A meta-analysis by Janda et al (1) demonstrated a protective effect of statins in patients with sepsis compared to placebo for various infection-related outcomes. Preadmission use of statins in bacteremic patients has been associated with reduced in-hospital mortality (18).

The data are also promising regarding efficacy of statins in reducing negative outcomes in ALI/ARDS. Shyamsundar et al (8) reported that simvastatin exerted antiinflammatory effects in the lungs. Likewise, lovastatin attenuated host defenses, thereby reducing pulmonary inflammation (15). The HARP study (A Randomized Clinical Trial of Hydroxymethylglutaryl–Coenzyme A Reductase Inhibition for Acute Lung Injury) further confirmed that treatment with high-dose simvastatin was safe and effective, producing impressive improvements in pulmonary and nonpulmonary organ dysfunction in ALI (16). The presumed mechanism in these trials was a reduction in inflammatory mediators and immunomodulation secondary to statin use.

Aspirin, a known antiinflammatory agent, has also been investigated for its potential in modulating immune responses, with possible therapeutic indications in the management of sepsis and ALI/ARDS. Salicylic acid, the major *in vivo* metabolite of aspirin, has been shown to reduce virulence of *Staphylococcus aureus* through various antiplatelet and antimicrobial mechanisms (19,

20). These mitigating effects are believed to be secondary to the ability of salicylic acid to interfere with virulence factors, impact intracellular signaling and cytokines, reduce bacterial densities and adhesion (necessary for colonization), and suppress exotoxin (19). Aspirin's effect upon reduction in bacterial densities and improved rates of sterilization in *S. aureus* endocarditis has been shown to be dose dependent (20).

In this issue of *Critical Care Medicine*, H. R. O'Neal, Jr. (21) and coauthors report that prehospital use of statins is associated with reduced rates of severe sepsis and ALI/ARDS but not in-hospital mortality. They conclude that prehospital use of statins may be protective against sepsis and ALI/ARDS and that these effects may be potentiated by prehospital aspirin use. We read with great interest this intriguing study designed to further our understanding of sepsis and ALI/ARDS management.

The investigators performed a cross-sectional analysis of a prospectively collected cohort from the Validating Acute Lung Injury Markers for Diagnosis study of 575 critically ill patients admitted to the medical or surgical intensive care unit. Of these patients, 149 were on statin medication before admission. The main objective was to determine whether prehospital statin use was associated with a lower risk of sepsis, ALI/ARDS, and mortality in critically ill patients. The combined prehospital use of both statins and aspirin was also investigated.

The investigators found that prehospital use of statins was associated with lower rates of having or developing severe sepsis or ALI/ARDS within the first 4 days in the intensive care unit. This study is consistent with a growing pool of data suggesting that statin use may reduce serious inflammatory conditions, such as severe sepsis and ALI/ARDS. Unfortunately, these benefits did not correlate with a reduction of in-hospital mortality in critically ill patients. The investigators speculated that the utility of statins may be in preventing initial inflammatory responses rather than having a therapeutic benefit once organ failure or lung injury occurs. Furthermore, the investigators found that combined use of a statin and aspirin was associated with lower mortality than statin alone in this patient population, suggesting that aspirin use may potentiate the protective effects of statins in severe sepsis and ALI/ARDS. The investigators concluded that prehospital use of statins leads to fewer cases of sepsis and ALI/ARDS and that concomitant aspirin therapy may have additive benefits in preventing these syndromes.

Some study limitations include small sample size, inadequate power for determination of statins' effect on mortality, lack of precision as to actual dose and duration of prehospital statin therapy, lack of continuation of statin in most patients in-hospital, under-representation of non-Caucasian patients, and the potential that statin users may represent patients that are more health conscious and less likely to become septic. Because this study was small, observational, and retrospective, causality cannot be inferred. In addition, there was no accounting for the total number of statin users and nonusers in the geographical area to determine the prevalence of sepsis in these groups. Accordingly, a large, prospective, randomized, controlled trial is required to confirm the ability of statins to prevent and/or treat sepsis and ALI/ARDS and reduce intensive care unit mortality.

Despite these limitations, the study is very intriguing. In addition to the need for a prospective, randomized trial, efforts should be made to evaluate the equivalency of the various, specific statins. Do the pleiotropic effects occur with the same magnitude in all doses and types of statins? Are nonstatin lipid-modifying agents of benefit? Future studies should investigate the utility of other lipid-associated immunomodulatory agents such as peroxisome proliferator-activated receptor-Y agonists (thiazolidenediones), fibrates, and omega-3 fatty acids (fish oils). As always, caution should prevail, and patients should be monitored for unexpected adverse events.

While statins alone are no "magic bullet", their impressive, pleiotropic properties may produce improved outcomes, and they should be considered for inclusion in the armamentarium for management of sepsis and ALI/ARDS.

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Arginine and sepsis: A question of the right balance?*

In this issue of *Critical Care Medicine*, a potentially important advance in the understanding of the complex role of arginine metabolism in sepsis is published (1). Gough and collaborators report a close relationship among the ratio of arginine to dimethylarginines, endogenous competitive inhibitors, and hospital and long-term survival of patients with septic shock. Interestingly, other correlations between the ratio of arginine and its enzymatic byproducts (ornithine and citrulline) and outcome were also searched in the same investigation but were not found.

The story of the arginine pathway in sepsis started some years ago and was characterized by highs and lows. Indeed, sepsis induces changes in arginine metabolism, leading to a complex picture deducted from the findings of clinical trials. After the discovery of the key role of nitric oxide (NO) in the typical cardiovascular alterations of septic shock in the late 1990s, several clinical trials assessed the effects of arginine analogs (monomethylated L-arginine) used to competitively and nonselectively inhibit the NO synthase enzymes. These trials were all negative (2–4) or even associated with an increased mortality rate in the treatment group. These disappointing findings halted clinical research in the field of therapeutic use of competitive analogues and NO synthase inhibitors in septic shock. In parallel, several trials used nutrition formulas enriched with several pharmaconutrients, including arginine. The rationale for the addition of arginine during critical illness was based on the anabolic and immune-enhancing properties of this amino acid. However, the aggregated outcome data collected in septic patients who received supplemental arginine were unfavorably affected (5). Therefore, use of both arginine and its competitive analogs was discouraged during sepsis (6).

These apparently opposite findings from clinical therapeutic trials (detrimental effects associated with supplementation of arginine and with treatment using competitive arginine inhibitors) fueled several areas of experimental and clinical research during the last decade, including hypothesis papers published in this Journal (7). First, the metabolism of arginine and NO during sepsis was further investigated and better understood (1). Plasma levels of arginine are dramatically decreased during sepsis (7). The current understanding of this decrease is based on experiments using stable isotopes in patients with sepsis; increased plasma arginine clearance is not matched with an adequate *de novo* arginine production, itself secondary to reduced citrulline production (8, 9), which leads to reduced NO production in sepsis. Second, arginine was found to play a fundamental role in the innate immune response (10), suggesting that shortage of arginine could thereby be detrimental during infection. Third, sepsis was found associated with increased circulating levels of endogenous competitive arginine antagonists (11–13) as a result of the increased activity of the dimethylarginine–dimethylaminohydrolase enzyme. In particular, plasma asymmetric dimethylarginine concentration was found as a strong and independent risk factor for intensive care unit mortality (14). Fourth, the perioperative use of arginine-supplemented diets was found to decrease postoperative infections and length of stay in a recent meta-analysis (15).

Based on these data, the balance between arginine on the one hand and its endogenous analogs and NO production antagonists on the other hand is suggested to play an important role of modulation of the septic response in relation to the inhibited endogenous NO production (16, 17). In fact, a similar interpretation of the arginine-to-dimethylarginine ratio was suggested to explain the "arginine paradox," ie, improvement of endothelial function (through stimulated NO synthesis) after the addition of arginine, even when circulating arginine concentration is already elevated (18).

The data presented in the article by Gough et al (1) are consistent with the existence of a similar "arginine paradox" in sepsis. Physiologically, the restoration of the arginine-to-dimethylarginine ratio could be desirable to improve several functions disturbed during sepsis, including endothelial and immune function. From a therapeutic viewpoint, future trials of arginine supplementation should consider modulation of the arginine-to-dimethylarginine ratio, presumably leading to normalization of NO production as a therapeutic goal ultimately contributing to improved outcome.

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***See also p. 1351.**

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Therapeutic hypothermia: Is there an unintended surcharge?*

"Every patient you see is a lesson in much more than the malady from which he suffers."—Sir William Osler (1)

Hospital-acquired infections dramatically increase the cost of health care. This is especially true for elderly patients and patients who inhabit critical care units. This is not a revelation. R. Douglas Scott (2), an economist at the Division of Healthcare Quality Promotion, National Center for Preparedness, Detection, and Control of Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, in 2009 extrapolated from prior studies that overall annual direct medical costs of healthcare-associated infections to U.S. hospitals range from $35.7 billion to $45 billion after adjustment to 2007 dollars (using the Consumer Price Index for inpatient hospital services). Even more striking is the estimated impact of prevention through infection control measures. They modeled cost savings as follows: if infection control measures prevented 20% of these infections, then the estimated/extrapolated cost savings ranged from $5.7 billion to $6.8 billion (again using 2007 Consumer Price Index adjustments). At 70% prevention effectiveness, estimated/extrapolated savings increased to $25.0 billion to $31.5 billion.

In 2005, Stone and colleagues (3) aggregated data from multiple studies and estimated the following attributable cost estimates for hospital-acquired infections: $25,546 for a surgical site infection, $36,441 for a bloodstream infection, $9969 for ventilator-associated pneumonia, and $1006 for a catheter-associated urinary tract infection. In 2007, Anderson et al (4) also aggregated multiple studies and arrived at the following figures: $10,443 for a surgical site infection, $23,242 for a bloodstream infection, $25,072 for ventilator-associated pneumonia, and $758 for a catheter-associated urinary tract infection. Both of these studies had methodologic limitations but underscore a significant point regarding the high costs of "nonprevention" and hospital care lapses.

In this issue of *Critical Care Medicine*, Montgardon and colleagues (5) report the frequency of infectious complications in consecutive patients who underwent therapeutic hypothermia postcardiac arrest. In this retrospective study, the authors report that 281 of 421 patients who received therapeutic hypothermia (in the intensive care

*See also p. 1359.

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unit [ICU]) suffered a total of 373 infectious complications. These included 318 diagnoses of pneumonia, 35 bloodstream infections, and 11 catheter-related infections.

In the aggregate, Gram-negative organisms accounted for almost two-thirds of the observed infectious events. Individually, *Staphylococcus aureus* was the most commonly isolated organism. The pulmonary system was the most common site of infection, accounting for 318 of 373 measured infectious events. Most of these lung infections (264 of 318) occurred/developed within the first 48 hrs following ICU admission.

Bloodstream infections were the next most common measured infectious event. Thirty-five patients developed positive blood cultures between 1 and 6 days following ICU admission. Similarly, there were 11 episodes of positive cultures isolated from vascular catheters, eight of which were concomitantly associated with a positive blood culture.

These infectious complications significantly increased duration of mechanical ventilation as well as ICU length of stay. As measured, mortality was not significantly changed in therapeutic hypothermia patients with infectious complications when compared to therapeutic hypothermia patients who did not develop infections. Similarly, favorable neurologic outcomes were achieved in approximately one-third of patients in both the therapeutic hypothermia patient groups that developed infections and those patients who did not.

Why did these patients develop infectious complications? As expected, there is not one answer. The authors of this paper discuss this in detail, providing representative examples from published literature. I would like to further underscore a few likely contributors. First, moderate hypothermia suppresses a variety of immune responses, even in normal hosts. As one example, *in vitro* neutrophil proinflammatory cytokine production, and likely other polymorphonuclear inflammatory responses, is suppressed (6). Second, the risk of aspiration of gastric contents following cardiac arrest is increased but is variably reported with a wide range of values. In 2007, Virkkunen and colleagues (7) reported the frequency of regurgitation and aspiration following out-of-hospital cardiac arrest to be approximately 20% when correlated with radiographic findings (specificity 81%, sensitivity 46%). Third, central venous catheter (CVC) insertion under emergency circumstances is associated with an increased risk of catheter-related and bloodstream infections and especially when these catheters are left in place beyond the immediate resuscitation phase or are subsequently manipulated (e.g., guidewire catheter exchanges) (8).

So, what are the lessons that we should carry forward from this work? How many of these infectious events were specifically preventable? Again, there is not a clear answer. The development of many of these infections is multifactorial (e.g., presence of shock, time to administration of antibiotics, appropriate antibiotic selection, facility compliance with infection control measures, etc.). Recognizing that *S. aureus* was the most frequently isolated organism likely points to the need for better vigilance and protocolization of catheter insertion and maintenance.

As speculation, perhaps therapeutic hypothermia protocols for out-of-hospital cardiac arrest victims should routinely include provisions for early (mandated) removal of CVCs that were placed without full use of a CVC insertion bundle, irrespective of the catheter insertion site, unless there are clear mitigating circumstances. Or should there be a "force function" in the hypothermia protocol so that ICU providers evaluate the ongoing need for a CVC and thus remove the catheter at an earlier time in the care continuum? Daily rounds lists typically include this question (i.e., "Does the patient still require a CVC?"), but compliance and adherence to such guidelines may not be adequate. This sort of approach is not novel; similar questions have been raised by many and for other populations of ICU patients (9).

Given the continued increase in the use of therapeutic hypothermia and its apparent association with increased infectious risk and the major additive costs of these hospital-acquired infections, perhaps this should be further investigated. Would patient risks and costs of an additional invasive procedure (i.e., CVC insertion) offset any potential benefit from catheter removal (i.e., decreased catheter-related infections), or will we discover that some/many patients do not have an ongoing need for a CVC and simply remove some of them sooner?

Catheter-associated infections are not the "whole story" but can be used to drive home a point: infectious complications with therapeutic hypothermia may not worsen overall mortality, but it is our responsibility to seek additional systematic opportunities to further lower the infection risk in this increasing patient population.

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Does it help us to know what questions our patients' families might want to ask?*

In this issue of *Critical Care Medicine,* Peigne et al (1) report the results of an extensive inquiry into important questions asked by relatives of critically ill patients in intensive care units (ICUs). One strength of the article is that the authors used a wide array of sources for generating candidate items as "important questions," including a literature review, surveys of physicians and nurses, recording of actual questions asked by families, and interviews with family members themselves. Using a very structured approach, they then narrowed their results to a list of 21 questions in eight domains by removing duplicates and surveying both physicians and family members about which of the candidate items were most important.

Some of the important questions identified (Table 2 in their article) will seem self-evident to the readers of this journal: "What are the chances that he or she recovers?" or "Is he or she in pain?," whereas others may be surprising: "Can I call to find out how he or she is doing?" or "What is expected of me?" Readers should note that questions which were relevant to medical care only at the end of life were removed from the final list, as the authors' intent was to generate "prompts" relevant to the care of all ICU patients rather than any subpopulation.

So how does the development of such a list of questions add to the literature and how are clinicians to use it? Much of the published literature on communicating with families of critically ill patients consists of expert opinion on how it is best to be done (2, 3). Others have shown that families rank receiving information about their loved ones as one of their most important needs (4, 5) and have attempted to characterize qualities of effective communication (6–8). Efforts to improve communication, either through structured meetings or written materials, have shown benefits in both patient and family member outcomes (9–11). Few if any studies, however, have rigorously addressed the optimal content of such information. Although generating a list of prompt questions cannot completely capture all the important information that families need to receive, it is a great first step.

One possible use of this list of questions would be to inform the development of written materials like brochures that could be given to families of ICU patients on admission describing the typical questions that patients and families may want to ask their physicians. Similar checklists have been found to be useful to oncology patients before meetings with physicians (12), and brochures describing processes of care in the ICU have helped families of critically ill patients understand later clinical information given to them (13). It would of course be worthwhile to study the impact of any informational material developed using the list of questions generated in the current study.

Another possible use of this list of questions is for individual clinicians to keep the various items in mind when talking to families. Many families of critically ill patients are emotionally overwhelmed at the time of their loved one's hospitalization and may not be able to clearly think through what questions they want to ask. It is common for clinicians to suggest that families write down questions that occur to them to prevent forgetting what they wanted to ask the next time they get a chance to talk with the physician. It could move communication one step further if the physician were able to proactively say to a family "Sometimes families whose loved one is in a situation similar to _____'s wonder …" (or "want to know …" or "ask me …"). In addition to showing empathy, such statements may reassure a family that the clinicians at the bedside have helped other patients and their caregivers in similar difficult circumstances.

In the future, it will be interesting to see if families' informational needs change as more ICUs move toward liberal visitation policies and some begin to include families on daily rounds (14). Other areas of further exploration include whether there are questions that would be specific to subpopulations of ICU patients such as in surgical patients, those at the extremes of age, or in patients receiving end-of-life care. It is also possible, as the authors note, that the questions asked would not be the same in cultures with societal values that differ greatly from those in France. Another interesting aspect yet to be addressed is how questions asked of nurses differ from those asked of physicians. One suspects that physicians would learn a great deal about families' concerns and state of mind if they could eavesdrop on the conversations that occur with the healthcare providers that rarely leave the patient's bedside.

Many experienced intensivists probably think that they have a good understanding of what families of their patients want to know. The current study provides a new, data-driven framework to help us all fill in the gaps in those areas where we, and perhaps the families themselves, do not know what it is that they do not know.

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*See also p. 1365.

Key Words: communication; intensive care unit; prognosis; family-centered care; caregiver

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Arterial catheters: "They don't get no respect"*

Peripheral arterial catheters are widely used in critically ill patients for continuous monitoring of the blood pressure and for convenient vascular access to obtain blood for testing. Unfortunately, many clinicians have not recognized the substantial risk of infection that is associated with the use of arterial catheters. In a systematic review of 14 prospective studies that included 4,366 arterial catheters and 21,397 catheter days of observation, Maki et al (1) noted a rate of bloodstream infection of 1.7 per 1,000 arterial catheter days (95% confidence interval, 1.2–2.3). Indeed, this is comparable to the risk of bloodstream infection associated with short-term, nonmedicated central venous catheters (1). Despite this substantial risk, recent national programs to prevent intravascular catheter-associated bloodstream infections in critical care units have largely ignored the role of arterial catheters (2, 3).

Scheduled replacement of central venous catheters via guidewire exchange to prevent infectious complications has been discredited and is strongly discouraged in recently published guidelines (4, 5). Despite several studies indicating that the rate of microbial colonization of arterial catheters is relatively constant over time, and that scheduled replacement of arterial catheters to prevent infectious complications is not likely to be effective (6–9), the issue remains unsettled. Khalifa et al (10) found that catheter colonization was most problematic after day 14 and recommended routine change at 2 wks of catheterization. Lucet et al (11) found that the risk of catheter colonization increased significantly over time after day 7 (in subjects not receiving a chlorhexidine-impregnated dressing) and advocated more study of scheduled replacement.

In this issue of *Critical Care Medicine*, Pirracchio and colleagues (12) add their observations to the body of data concerning scheduled replacement of arterial catheters. In a pre-post, quasiexperimental observational study, the authors compared the rate of arterial catheter colonization and associated bloodstream infection during a 4-yr period when arterial catheters were changed routinely at 5-day intervals (1997–2000) to a 4-yr follow-up period (2001–2004) when arterial catheters were changed as clinically indicated. A total of 1,672 adult surgical intensive care unit patients with arterial catheters were observed, and the authors found that the rate of arterial catheter colonization did not vary between the two time periods (31.32 per 1,000 catheter days [scheduled replacement] vs. 29.79 per 1,000 catheter days [catheter change as clinically indicated], $p = .11$). However, the rate of arterial catheter-related bloodstream infection decreased significantly during the time when arterial catheters were changed only as clinically indicated (3.13 per 1,000 catheter days vs. 1.01 per 1,000 catheter days, $p < .0001$).

This paper is important because it adds support to the clinical practice of changing arterial catheters when clinically indicated and continues to unify the infection prevention practices for vascular catheters (both central venous catheters and arterial catheters). This is also a relatively large study that was conducted over a period of 8 yrs. However, the paper has a number of limitations that must be considered as one places the study in perspective. First, inherent in its design, there is no concurrent control group, and the study is subject to a variety of potential confounding variables. In addition, it is a single-center study examining only adult surgical intensive care unit patients. The site of arterial cannulation was not noted, although several papers indicate an increased risk of infection associated with femoral arterial catheterization (7, 11, 13). As the authors note, the use of chlorhexidine for skin disinfection might have resulted in a decreased risk of infection compared to the alcoholic povidone-iodine that was in routine use during the study. Also, the transducer administration sets were replaced only when the arterial catheter was replaced, which is not consistent with current guidelines (5). Interestingly, the authors noted a significant decrease in bloodstream infection associated with less frequent

*See also p. 1372.

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changing of arterial catheters, but the rate of catheter colonization was unchanged. This runs counter to our understanding of the pathogenesis of vascular catheter-related infection, in which colonization is a necessary prerequisite for infection. As the rate of colonization in this study (approximately 30 per 1,000 catheter days) is anywhere from two to four times higher than in other studies (6, 7, 9–11), one wonders whether this discrepancy between colonization and bloodstream infection is artifactual and due to the sampling process.

In conclusion, although the role for scheduled catheter replacement for prevention of infection may still be debated and would be settled only by well-designed, adequately powered, prospective, randomized trials in appropriately matched patient populations (adult and pediatric, surgical and medical, site of cannulation, etc.), the resources required for such studies are probably in excess of what is available and may be better spent elsewhere. Instead, I would argue that the pathogenesis of central venous catheter infection and arterial catheter infection is similar and that similar preventive measures should be employed. Arterial catheters should be afforded the respect they deserve, and they should be inserted by trained individuals using strict aseptic precautions (chlorhexidine skin antisepsis and sterile barrier precautions). Arterial catheters should be cared for very carefully (aseptic technique for accessing the catheter, use of chlorhexidine for site disinfection with dressing changes) and removed as soon as they are not needed. By following these recommendations, as a previous editorialist for this journal recently noted (14), the question of the need for routine catheter replacement would most likely become irrelevant.

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"Don't get no respect" is borrowed from the American comedian Rodney Dangerfield (1921–2004).

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Time to fire the sim educators? Not quite yet*

Simulation-based training is expanding rapidly. Curricula are being migrated from conventional teaching models to simulation, and areas that were not previously taught are being added to curricula. Foremost among the latter are nontechnical skills, which include domains such as situational awareness, team leadership, role allocation, and crisis management. Until now these skills have been acquired by intensivists through osmosis, through modeling, through trial and error, or in some cases not at all.

Simulation has created a means of teaching and practicing these skills, which are separate from the book knowledge that has classically been seen as the basis for effective practice as an intensivist. Crisis resource management originated in aviation safety but its role in medicine is increasing in parallel with technologic advances that have made mannequin patient simulators and simulated critical care environments widely available.

Simulation-based training is expensive in comparison to traditional teaching methods. Sophisticated patient simulators are expensive to purchase, and many educators see this as the barrier prohibiting adoption of a simulation program. However, the upfront purchase costs of equipment are far outweighed by the staff costs associated with the delivery of simulation training. Typically scenarios are run with a

*See also p. 1377.

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high instructor-to-learner ratio using specialty-specific content experts (eg, intensivists) to facilitate a postscenario debrief.

Although there has been a dramatic expansion in access to simulation equipment, there has been a lag in funding staff time to provide training with that equipment and an even more pronounced lag in research to determine the best allocation of the substantial resources involved.

In this issue of *Critical Care Medicine*, Boet et al (1) make some progress toward determining optimal resource allocation for nontechnical skills training using simulation. They provided anesthesiology residents with an introductory session on nontechnical skills and then assessed their performance in a pretest scenario. After a learning intervention, the participants' posttest performance was assessed by blinded raters. The intervention consisted of either a standard debrief or the opportunity to watch a video of their scenario and reflect on their performance with the assistance of the Anesthesia Non-Technical Skills (ANTS) scale.

Importantly, learners in both groups improved their performance. This supports previous studies that have shown that nontechnical skills can be learned (2, 3), resulting in objective (and sustained [2]) improvement in performance. However, there was no difference in improvement between the debriefing group and the self-reflection group.

This study has innovatively used the ANTS scale as an independent teaching device. The ANTS scale (4) is a validated tool to measure markers of nontechnical performance in an anesthesia context. Its development is the result of collaboration between industrial psychologists and anesthetists. Its closest analog in intensive care is the Ottawa Global Rating Scale (5, 6), a useful tool that has yet to undergo the same degree of validation.

The ANTS scale was designed for assessment and as a common language for training, teaching, and debriefing. Another powerful role is as a research tool to compare different modes of nontechnical skills teaching. Armed with this tool, objective comparisons can be made between different teaching strategies to determine those that are most educationally effective and also those that are most cost-effective.

The same research group has previously used the ANTS scale to demonstrate that there is no benefit in participating in a simulated scenario without some kind of feedback (3). This concurs with studies of procedural simulation that found limited benefit from interacting with the simulator in the absence of any postsimulation feedback (7, 8).

Boet et al have used a novel form of feedback that consists solely of the learner reflecting on their own performance using the scenario video and the ANTS scale. When performed by a motivated learner, introspection can identify and target that learner's personal deficiencies. Reflection is a valuable technique that is gaining acceptance as a means for professional learning. Indeed, some credentialing organizations are allowing structured reflection as a means for accumulating continuing professional development points (9). Targeted reflection may provide more value for the individual than a blunderbuss of information not directed at the learner's own deficits.

This study raises the possibility of reflective learning using the ANTS tool outside of simulation. After a real clinical crisis event, one could use the ANTS system as a scaffold to reflect on one's own practice and guide a "self-debrief." Admittedly, this would be limited by the lack of a video recording to provide objective feedback. Video was likely to be a major driver for learning in the study by Boet et al. Whether reflecting on the ANTS scale (without video feedback) would be of benefit remains unanswered. In simulated scenarios, it has been shown that instructor-facilitated debriefing using video did not confer additional benefit over an instructor debrief without video (3).

The study by Boet et al suggests an enticing model for delivering simulation training. Providing nontechnical skills training without an expert facilitator would generate a significant cost saving. However, there are limitations in the applicability of the results of this study. Specifically, the participants in this study were the sole learners in each scenario while the rest of the scenario participants were confederate actors. Outside of anesthesiology, scenarios are often more complex involving multiple physician participants. Also, the scenarios were short and algorithm-driven, different from complex scenarios that would be more typical of intensive care practice.

Additionally, it is difficult to see how self-reflection could be applied to a team of interdisciplinary learners; having more than one participant present in a debrief mandates a competent facilitator to manage the group dynamic.

In summary, this study opens an exciting avenue for nontechnical skills training that may reduce the cost burden associated with simulation. It also highlights the value of the ANTS scale, first as a potential teaching tool in its own right and second for research that can help identify strategies that achieve the most educational benefit for the teaching dollar.

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Do we really have other tools for respiratory failure besides mechanical ventilation?*

Mechanical ventilation has been the mainstay of treatment for respiratory failure. Modern-day mechanical ventilation has evolved from the days of the polio epidemic (1). As intensivists we have appreciated its benefits and risks through many years of experience and research. In striving to "do no harm," we have adopted methods to ventilate patients that subject them to less lung injury as we treat their respiratory failure. For example, we have discovered the use of noninvasive positive pressure ventilation in respiratory failure. In addition, newer drugs and technologies are helping our unlucky patients to accommodate to the ventilator while they recover.

Nonetheless, in the past decade, we have come to appreciate the impact of ventilator-induced lung injury. Ventilator-induced lung injury is a result of barotrauma, volutrauma, atelectrauma, and biotrauma (2). A result of this recognition led to the pioneering Acute Respiratory Distress Syndrome Network study, which suggested that tidal volumes of 6 mL/kg and plateau pressures of <30 cm H_2O reduced this type of intrinsic injury to the lung (3). While it is true that techniques of sedation interruption and better patient/ventilator synchrony are now being used, how can we be sure that patients are not harmed *despite* lower tidal volume ventilation as suggested by the Acute Respiratory Distress Syndrome Network study? Could there be a better way to support lung failure altogether?

Investigators have addressed this dilemma in the past. This year's Society of Critical Care Medicine lifetime achievement award winner, Professor Luciano Gattinoni, and colleagues (4) demonstrated that we could use extracorporeal membrane oxygenation to permit the lungs to "rest" in patients with severe acute respiratory distress syndrome. The mortality rate in that series was 51%, which was acceptable as a form of rescue therapy. However, Professor Gattinoni also showed the untoward effects of extracorporeal support, including blood loss. More recently, a form of pumpless arteriovenous lung support (iLA Novalung GmbH, Hechingen, Germany) was used for critically hypoxic/hypercapnic patients (5). The requisite arterial access carries with it the risk of limb ischemia, which has ultimately been the limiting factor in these studies.

In this issue of *Critical Care Medicine*, Batchinsky et al (6) demonstrate that extracorporeal removal of carbon dioxide can decrease the required minute ventilation in a swine model while maintaining normocarbia. The authors studied anesthetized subjects over a 72-hr period of mechanical ventilation combined with extracorporeal carbon dioxide removal. They were able to maintain a "normal" blood gas in their uninjured model. They differentiate venovenous carbon dioxide removal from other modes of extracorporeal support. Extracorporeal membrane oxygenation is the more labor intensive one that requires higher blood flows. Arteriovenous carbon dioxide removal requires less blood flow to achieve similar results, but it also requires that the patient's heart is functioning adequately. In Batchinsky's experiment, a new motor-driven extracorporeal venovenous carbon dioxide removal device (Hemolung, ALung Technologies, Pittsburgh, PA) was able to eliminate CO_2 at even lower blood flows that were more comparable to those of conventional dialysis. This aspect of their preliminary study makes their work appealing. CO_2 removal via the Hemolung was demonstrated to reduce the minute ventilation by half while maintaining normocarbia.

While the Hemolung device is more portable and user-friendly, the management of the extracorporeal membrane oxygenation circuit is a resource-intensive process that requires, among other things, a team of specialists, limiting its availability to only a handful of quaternary care centers. Extracorporeal membrane oxygenation uses a higher blood flow (4–5 L/min) across its circuit to deliver oxygen and remove carbon dioxide. In contrast, the Hemolung only requires 450 mL/min to achieve the same results. The goal of the present work is to achieve maximal CO_2 elimination with less blood flow through the circuit. This concept could be used as an adjunct to limit the duration of mechanical ventilation. Along the same vein, Terragni et al (7) looked at the reduction of tidal volume to below ARDSNet levels to limit volutrauma. In this way, the multitude of challenges that clinicians face can be adequately overcome.

In using the Hemolung device, a possible concern is that the infectious risk of an invasive cannula and the need for heparinization to run through the extracorporeal circuit must be weighed against the risks of conventional mechanical ventilation and more sophisticated modalities of lung support such as high-frequency oscillatory ventilation and airway pressure release ventilation. The authors argue that any risks associated with the use of the Hemolung device are comparable to risks associated with conventional renal replacement therapies. Heparinization was monitored by activated clotting times, which were in the same range as for conventional dialysis, and plasma-free hemoglobin was not affected during venovenous carbon dioxide removal (8).

The current experiment is a good foundation to help demonstrate that a more portable extracorporeal gas exchanger could be useful as an adjunct to mechanical ventilation in the treatment of respiratory failure and acute respira-

***See also p. 1382.**

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tory distress syndrome while minimizing some complications. Future iterations may include more dead space ventilation to make the experiment clinically relevant to the orally intubated patient. It could also be used in conjunction with noninvasive positive pressure ventilation in those patients who otherwise might need tracheal intubation. The authors have intimated that further studies would more closely simulate the current intensive care unit experience and compare it prospectively to cutting-edge modalities such as high-frequency oscillatory ventilation and airway pressure release ventilation.

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Conflicting roles of FcγRIIa H131R polymorphism in pneumonia*

Invasive pneumococcal disease, defined as infection of otherwise sterile sites such as bacteremia and meningitis, is a leading cause of morbidity and mortality worldwide. Invasive pneumococcal disease accounts for >43,000 cases and 5000 deaths annually in the United States alone (1). Among adults, *Streptococcus pneumoniae* is the leading cause of pneumonia, both in the outpatient and inpatient setting, and often leads to bacteremia, severe sepsis, and death (2). Pneumococcus often resides in the nasopharynx without adverse sequelae. Why some individuals develop pneumonia or invasive pneumococcal disease has been the focus of several studies. Both pathogen and host-related factors leading to pneumococcal pneumonia and invasive pneumococcal disease have been identified (3). The polysaccharide capsule appears to play an important role in evading phagocytosis, an important host defense mechanism. Binding of complement and specific immunoglobulin (IgG_2) to the capsule allows for efficient phagocytosis. The Fcγ receptor, particularly the FcγRIIa or CD32a receptor on the immune cells, plays an important role in immunophagocytosis (4). A single nucleotide polymorphism within the gene encoding this receptor leads to a histidine (H) to arginine (R) substitution at amino acid position 131 (FcγRIIa [H/R]) within the ligand binding site, resulting in lower affinity for IgG and impaired phagocytosis.

Understanding the effect of the FcγRIIa (H/R) polymorphism on susceptibility to infections has generated considerable interest. Several studies examined the role of this polymorphism in susceptibility to infections with encapsulated organisms, including pneumococcal and meningococcal disease. Early studies suggested that the arginine allele was associated with a higher risk of invasive pneumococcal disease (5–7). However, the small sample size (<100 cases of pneumococcal disease enrolled in these studies) was an important limitation and some studies suggested no association (8).

In this issue of *Critical Care Medicine*, Solé-Violán et al (9) present results of a multicenter observational cohort study in 1262 patients with community-acquired pneumonia (CAP). In a subset of patients with pneumococcal pneumonia (n = 319), they examine the role of the FcγRIIa (H/R) polymorphism on susceptibility to pneumococcal disease and risk of bacteremia, severe sepsis, and mortality. A case–control design was used to determine the association with susceptibility and an inception cohort approach to determine the association with outcomes of pneumococcal CAP. This study has several strengths. To date, it is one of the largest cohorts of pneumonia, particularly pneumococcal pneumonia, to examine the role of this genotype. Rigorous assessment was conducted to determine the microbiological etiology, and pneumococcal disease was identified in 319 (41.5%) cases. The authors used appropriate statistical methods, using a conservative approach (Bonferroni correction) to adjust for multiple comparisons performed on additional polymorphisms analyzed in the present study and those assessed previously in this cohort. They also adjusted for known risk factors associated with invasive pneumococcal disease, including age and chronic diseases.

In contrast to prior studies that showed either no association or a higher risk of invasive pneumococcal disease for subjects homozygous for arginine genotype, this study showed a twofold higher risk of bacteremic pneumococcal disease for subjects homozygous for the histidine genotype. Several potential explanations for these conflicting results are possible.

*See also p. 1388.

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First, spurious associations are common in gene-association studies as a result of a large number of comparisons and these results may represent type 1 error (false-positive results). Second, the polymorphism may be in linkage disequilibrium with another polymorphism associated with invasive pneumococcal disease. The authors did examine potentially functional polymorphisms in other FcγR genes in tight linkage disequilibrium in the vicinity of the FcγRIIa gene in Hapmap. However, linkage disequilibrium could be with genes located at some distance from the FcγRIIa gene on the same chromosome, such as C-reactive protein, interleukin-10, and serum amyloid A or even located on other chromosomes (epistasis). Third, the discrepant results may be the result of age differences because most of the positive studies were from children. None of the studies controlled for polysaccharide vaccine status. Because children generate significantly higher IgG_2 levels than adults, this may be a partial explanation for discrepant results by age as well.

However, it is plausible that these results are true. Genotypes in FcγRIIa receptors play a variable role in susceptibility to different infections. For example, studies have shown that subjects with the ancestral histidine allele are associated with a higher risk of severe malaria (10). Individuals with the arginine polymorphism may be protected from mounting a host response in areas where malaria may be endemic. The malaria data combined with the results from Solé-Violán et al may indicate that two of the most powerful selection forces in ancient African populations—malaria and severe pneumonia—favored survival in humans with the arginine mutation.

The real issue in the discrepancies between earlier studies of the FcγRIIa polymorphism and pneumococcal pneumonia may be the result of different phenotypes. Invasive pneumococcal disease, which includes not only bacteremia, but also meningitis and empyema, was used as a phenotype in some studies. The pathogenesis of these different phenotypes may not be the same and therefore the association with functional polymorphisms may vary. Solé-Violán et al demonstrated a significant association only with bacteremia, not susceptibility for CAP, susceptibility to pneumococcal CAP, organ failure, or mortality. Therefore, bacteremia represents a distinct phenotype within pneumococcal CAP resulting from an inability to localize the infection to the lung. An intriguing possibility is that the critical issue with the FcγRIIa polymorphism association with bacteremia is its affinity for C-reactive protein rather than IgG_2. With its opsonizing properties, C-reactive protein binding to the FcγRIIa R allele may be more important in the initial innate immune response to clear bacteremia. Another important aspect of localization in pneumococcal pneumonia is activation of coagulation within the alveolar space. C-reactive protein has recently been shown to increase tissue factor activation (11), a critical step in the host response to pneumonia (3). Recent studies have suggested that a higher pneumococcal genomic load in the circulation may be associated with increased risk of severe sepsis (12) and it would be easy to hypothesize that the FcγRIIa H allele would be one cause of a higher bacterial load. No association with mortality or multiorgan system failure in the study of Solé-Violán et al suggests this polymorphism alone is not sufficient to increase mortality or organ failure. The discrepancy between bacteremia and these end points has long been known.

It is likely that the adverse associations between pneumococcal CAP and both of the FcγRIIa alleles are real. The lower affinity for IgG_2 with the R allele may increase susceptibility to pneumococcal and *Haemophilus pneumoniae* pneumonia, particularly in children. Vaccination to increase the IgG_2 levels may be the logical strategy to protect these patients. Conversely, the lower affinity of the H allele for C-reactive protein may be more important for opsonization and coagulation activation, leading to bacteremia in older adults. The almost equal FcγRIIa (H/R) allelic frequencies in nearly every population studied supports this concept of balanced risk.

This very well-done study by Solé-Violán and collaborators demonstrates that, even in this era of genomewide association studies, candidate gene studies still play an important role in understanding genetic determinants and pathogenic mechanisms underlying infectious diseases. The results of this study reinforce the need to develop collaborations to pool large cohort studies akin to the approach used in several recent genomewide association studies (13). Careful phenotyping, including by etiologic agent, is particularly important to assess genetic factors related to specific infections rather than clinical syndromes. An etiologic agent is identified in fewer than half of CAP cases, and therefore, even a single large cohort of >1000 subjects such as that of Solé-Violán et al may have inadequate power. For example, *H. influenzae* CAP may also be influenced by the FcγRIIa (H/R) polymorphism, but only 19 cases were available for analysis in this study. Several cohorts with similar diagnostic methods and patient characterization will have to be combined to examine genetic markers associated with specific etiologic agents and to replicate important findings.

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Systemic arterial pressure and fluid responsiveness: Not only a swing story*

The obvious is that which is never seen until someone expresses it simply.—Kahlil Gibran (1883–1931)

When, a century ago, Erlanger and Hooker (1) published their paper and proposed pulse pressure (PP, i.e., the difference between systolic arterial pressure [SAP] and diastolic arterial pressure) as an estimate of stroke volume (SV), they could not have anticipated that this finding was to become part of the basis of measurement of cardiac output (CO) in critically ill patients (1, 2). Indeed, SAP and PP occur as a consequence of the periodic nature of heart ejection and arterial system features. Basically, the larger the SV output, the greater the amount of blood that must be contained in the arterial tree and therefore, the greater the pressure rise and fall during systole and diastole, thus causing a higher PP (2). In its conventional two-element form (with respect to the character of ejection), the Windkessel model represents the circulation in terms of parallel peripheral resistance and capacitance components (3). The capacitance, explicitly the arterial compliance (C = change in pressure related to change in volume), is predominantly determined by the aorta (3) and estimated from the simpler approach of C = SV/PP (4, 5). It is apparent from the present approximation that elevation of PP can be secondary to a rise in SV or a fall in C.

In this issue of *Critical Care Medicine*, Monnet and colleagues (6) present a well-designed study on the effects of volume expansion and norepinephrine (NE) on invasive systemic arterial pressure in ICU patients. The authors found that PP and SAP could be used for detecting the fluid-induced change in CO, in spite of a lack of sensitivity (6). The predictive strength of a fluid-induced increase in PP of >17% to detect a significant fluid-induced increase in CO was moderate (area under the receiver-operator characteristic curve 0.78) with in multivariate analysis; changes in PP significantly related to change in SV and to age (6). Indeed, with aging, the aorta and elastic arteries stiffen, which decreases C and increases SAP and PP for a given SV (5). On the other hand, the changes in systemic arterial pressure components were unable to detect the change in CO induced by NE (6).

In regards to applied physiology, the elegant design used to compare the influence of two different mechanisms (able to increase CO) on SAP and PP has the merit to provide two substantial clinical implications. First, the arterial pressure monitoring is not sufficient for assessing hemodynamic effects of NE in shocked patients. Second, changes in PP (and SAP) following volume expansion are specific markers of fluid-induced change in CO, even in spontaneously breathing patients. A more fundamental point when considering the current study relevance to clinical practice is whether it is reasonable to continue to use arterial pressure monitoring without assessing CO measurements in shocked patients. In my opinion, the major contribution of this work is that they demonstrate that pressure is not equivalent to flow. Indeed, the present study sustains the international conference recommendations by providing physiologic relevance to support CO monitoring of shocked patients needing NE infusion (7). This present work also adds to our current understanding a further point, which is that we should keep in mind that the low sensitivity of fluid-induced changes in PP to detect a fluid-induced increase in CO is particularly true in young patients, where the correlation between changes in PP and changes in SV following fluid therapy was found to be logically weak (6).

However, regarding discussion of data, some points remain incompletely resolved in the study by Monnet and colleagues (6). First, the authors believe that it was the physiologic issues of arterial C and pulse wave amplification phenomenon that produced the weak correlation between the fluid-induced changes in PP and SAP and fluid-induced changes in CO (6). It is interesting to see that they emphasize the role of pulse wave reflection throughout the arterial tree (8) to explain the weak sensitivity of SAP and PP to predict fluid responsiveness (low fraction of real responders correctly identified), and not the more apparent decrease in peripheral vascular resistance and small vessel tone that could follow volume expansion (9). Indeed, there is no reason that after increasing arterial tone, NE should change the mechanical properties of the arterial system (Fig. 1, from *E* to *E′*), making PP unable to track trends in

***See also p. 1394.**

Key Words: shock; hemodynamic monitoring; fluid responsiveness; arterial pressure; aortic elastance

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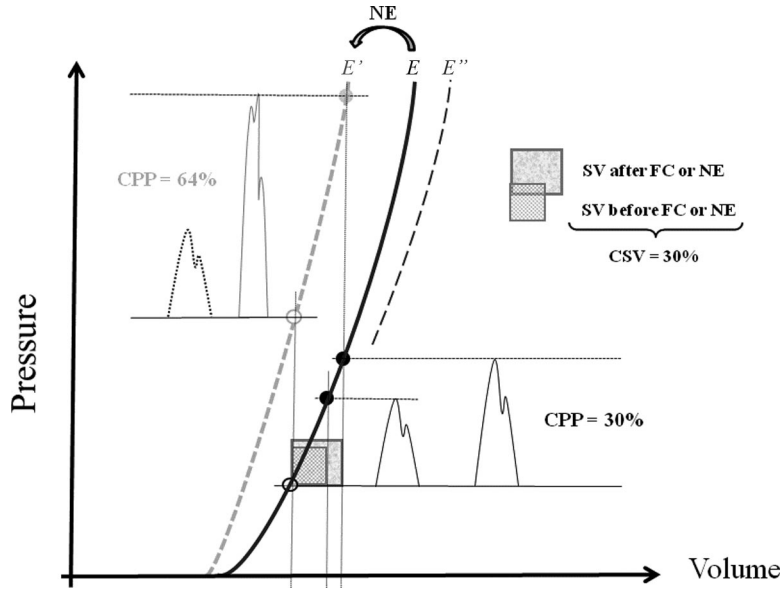

Figure 1. "Volume-pressure curve" mathematical conception of the systemic arterial system showing how a same stroke volume (*SV*) change (30%) after fluid challenge (*FC*) (curve *E*) or norepinephrine (*NE*) infusion (curve *E′*) could produce two different values of changes in pulse pressure (*CPP*). After NE infusion, the curvilinear aortic elastance curve shifted from *E* to *E′*. To simplify, we displayed a model where volume pressure relationship did not change after volume expansion (No shift from *E* to *E″*).

CO, as proposed by the authors. Without that, the inverse phenomenon occurs in case of decrease in arterial tone (Fig. 1, from *E* to *E″*) (3). From my point of view, volume expansion can induce shear stress, decreasing arterial tone (9) with a relative increase in C, particularly in the septic population studied (Fig. 1). Indeed, it is evident that a decline in arterial tone decreases the arterial tree pressures at each volume (5, 10). These observations are consistent with a previous report demonstrating that a decrease in arterial tone increases aortic C (11).

The second point is related to the complex effects of NE on PP. Indeed, from the data in Table 3 in the paper by Monnet and colleagues (6), it appears that global end-diastolic volume increased significantly after NE infusion. The present finding is related to the ability of NE to increase cardiac preload via enhancement of venous tone (recruitment of unstressed blood volume) and cardiac contractility, as already demonstrated by the same team (12). On the basis of these considerations, it is more likely that the increase in PP following NE infusion is related to both changes in C, pulse wave reflection and also preload.

In summary, these findings provide striking evidence on the relative importance of systemic arterial pressure in shocked critically ill patients. The key messages from this work are that clinicians can be reasonably confident that a patient is fluid responsive when PP increases >17% following volume expansion. Furthermore, in cases of NE therapy, particularly at moderate and high doses, CO monitoring is mandatory. The authors are to be congratulated on a study that allows the clinician to remove any ambiguity regarding the role of arterial pressure assessment. Indeed, regarding the usefulness of arterial pressure monitoring, the swing is only part of the solution.

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Hypercapnia in acute illness: Sometimes good, sometimes not*

Generations have been taught that one of the major functions of the lungs is to rid the body of CO_2, a waste gas. While obviously correct, this conveys the idea that CO_2 is at best useless or at worst toxic. For decades, clinicians have realized that mechanical ventilation, although life-saving, can cause lung injury, which can in turn increase mortality. Hickling et al (1) coined the term "permissive hypercapnia," extending to the adult setting what Wung et al (2) had reported in neonates: that less vigorous ventilation, while associated with hypercapnia was, more importantly, also associated with better outcome. The same principle had been described in status asthmaticus (3).

In such scenarios, permissive hypercapnia was considered to represent a sparing of the lungs from the physical and inflammatory damage caused by overly aggressive ventilation (i.e., ventilator-associated lung injury), a concept that is largely accepted. However, the idea that the elevated CO_2 might play a part in improving outcome was subsequently proposed. "Therapeutic hypercapnia," the deliberate induction of hypercapnic acidosis to protect against organ injury, was suggested as a hypothesis (4) a decade after permissive hypercapnia was described in acute respiratory distress syndrome (1). This hypothesis was followed by a large body of laboratory research directed to identifying the settings in which hypercapnia might help (5). An understanding of the underlying mechanisms of hypercapnia's effects in critical illness is essential if we are to translate its therapeutic potential while minimizing risk.

Most mechanistic studies have focused on nuclear factor kappa B, a central transcription factor implicated in multiple acute inflammatory states, and have supported hypercapnia's ability to modulate the activity of this pathway. However, studies at the molecular level have shown that inhibition of nuclear factor kappa B by hypercapnia can have paradoxical effects: it can ameliorate sepsis-induced endothelial injury (6) and it can inhibit healing following shear-induced epithelial injury (7). Additional studies have provided evidence of benefit through inhibition of xanthine oxidase, the Axl tyrosine kinase receptor, and cyclooxygenase-2. In contrast, hypercapnia can reduce lung fluid clearance, potentially by modifying adenosine monophosphate-dependent protein kinase and sodium-potassium adenosine triphosphatase (8).

Thus, approaching a mechanistic understanding of hypercapnia in lung injury is complicated. Even the basic question of whether buffering the hypercapnia is beneficial or harmful is unclear, with some studies demonstrating that buffering obliterates hypercapnic protection (9) and others showing that it improves cell repair (10). Molecular approaches, required to elucidate mechanisms, are most readily applied in cell culture models, but such models make it difficult to replicate the complexity of the *in vivo* or even *ex vivo* models, where interactions between different cell types and a variety of physiologic responses contribute to both the injury and the protection. Underlying all of this remains the fact that while many injurious pathways have been characterized (in a variety of models), the molecular mechanisms of sepsis-associated lung injury are not fully understood, making it difficult to select candidate mechanisms for hypercapnic protection. For example, even if hypercapnic repression of nuclear factor kappa B activity became clearly delineated, this pathway still retains the potential to exert both beneficial and adverse effects, reducing inflammatory injury but possibly abrogating the ability to fight infection.

The paradox of the same therapy causing benefit and harm in different settings is not new and is starkly illustrated in two important laboratory studies of hypercapnia in pneumonia. In experimental *Escherichia coli* pneumonia studied over 6 hrs, hypercapnia attenuated disease progression and preserved lung function (11). In the same model studied over 2 days, the outcomes were very different (12); hypercapnia worsened the pneumonia and was associated with greater impairment of lung function and worse injury. This mechanism appears to be the hypercapnic inhibition of neutrophil function. This lessens the inflammatory burden on the lung in the early stages but later permits increased bacterial proliferation, which ultimately worsens the pneumonia. Thus, in this field, paradoxes abound with different effects in different models, and in different physiologic systems within individual models.

In this issue of *Critical Care Medicine*, Norozian and colleagues (13) provide important additional insights. In a model of experimental sepsis induced by systemic endotoxin in spontaneously breathing rats, exposure to inhaled CO_2 resulted in a higher ratio of proinflammatory vs. anti-inflammatory cytokines in the lung, but the opposite was observed in the spleen. Reviewing the literature of the last decade, we can see that this pattern of "paradoxical" effects is not unexpected; however, the explanation is uncertain. We wonder if the differential effects observed here may be explained by the spontaneous ventilation. Sepsis induces hyperventilation—it is one of the systemic inflammatory response syndrome criteria— and exposure to hypercapnia is a powerful additional ventilatory stimulant. While hypercapnia-induced hyperventilation does not cause lung injury, hyperventilation caused by other respiratory stimulants certainly can, as demonstrated in sheep over 20 yrs ago (14). Thus, it is possible that hypercapnia had an overall anti-inflammatory effect, as observed in the spleen, but that the inflammatory milieu induced by intense hyperventilation pushed the balance toward a net proinflammatory effect in the lung.

For the clinician or the clinical trials designer, these paradoxical effects are worrisome but expected. Syndromes in

*See also p. 1400.

Key Words: hypercapnia; lung function; hyperventilation; inflammation

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the intensive care unit are often not diseases with identifiable lesions (15) but are poorly understood processes sometimes labeled with usable but simplistic acronyms that can sell short the underlying biological complexity. The paradoxical effects observed by Norozian et al (13) fall right in line with what we have come to expect in studies of critical illness—the answers are not simple, but valuable studies like this contribute to a slowly evolving understanding that will eventually help patients in the future.

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Blockade of interleukin-6 in murine sepsis revisited: Is there an indication for a new therapy in human patients?*

Sepsis can be defined as a widespread inflammatory response of the whole body to an infection (1). Sepsis remains the leading cause of death among critically ill patients with infection. In the United States, more people die from sepsis than coronary artery disease, stroke, or cancer (2, 3). Currently, there are approximately 750,000 cases of severe sepsis per year. However, the incidence of sepsis is expected to increase in the near future. According to recent estimates, we may see as many as one million additional cases of sepsis per year by 2020. Mortality of sepsis ranges from 20% to 50% depending on the severity of the disease (2–5). The most serious consequences of sepsis include septic shock, acute respiratory distress syndrome, and multiple organ failure/dysfunction syndrome. These developments significantly raise the death toll in patients with sepsis (1, 3, 5). Overall lack of an effective treatment constitutes the major factor contributing to high mortality in sepsis (1).

Systemic inflammatory response syndrome is a hallmark of sepsis. Systemic inflammatory response syndrome is characterized by an excessive proinflammatory response of the host. Proinflammatory cytokines are most likely the primary mediators of the septic response. Many of these cytokines have been implicated in the pathogenesis of sepsis, including tumor necrosis factor, interleukin (IL)-1, and IL-6. Although IL-6 has both pro- and anti-inflammatory properties, the association between high levels of this cytokine and mortality has been observed in patients with severe sepsis (6).

IL-6 is a multifunctional cytokine involved in directing immune responses and regulating of hematopoiesis, inflammation, and oncogenesis. Its many biologic activities are at the root of pathogenic properties of this cytokine. Furthermore, IL-6 displays its pleiotropic activities by interacting with two different proteins: a specific receptor (IL-6R) and gp130, the common signal transducer of cytokines related to IL-6 (7).

In this issue of *Critical Care Medicine* Barkhausen et al (8) used a standardized cecal ligation and puncture model of sepsis to study the effects of blockade of IL-6 signaling. The authors used a neutralizing anti-IL-6 antibody to completely inhibit IL-6 signaling or a sgp130Fc fusion protein to block only IL-6 transsignaling.

*See also p. 1407.

Key Words: sepsis; therapy; inflammation; cytokines; IL-6

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They observed that treatment with the sgp130Fc fusion protein but not with the anti-IL-6 antibody extended the life of septic animals. Vyas et al (9) reported similar finding regarding anti-IL-6 antibody in mice subjected to cecal ligation and puncture. In contrast, Riedemann et al (10) found the anti-IL-6 antibody protective in a similar animal model. These studies used comparable amounts of the antibody from the same source but different strains of mice. Finally, another study (11) showed lack of the protective effect of the sgp130Fc fusion protein in a model of hemorrhagic shock and sepsis (caused by cecal ligation and puncture). This is a more severe model with lower survival than that of Barkhausen et al (8).

So what are implications of these findings for the therapy for human sepsis? Barkhausen et al (8) correctly pointed out that IL-6 is not always a bad guy in sepsis. On the other hand, gp130 is not specific for IL-6. Although blockage of IL-6 proved beneficial for patients with other inflammatory/autoimmune diseases (7), many more studies are needed to establish whether this is true for septic patients.

One should also consider an overwhelming failure of many anti-inflammatory therapies in patients with sepsis. Clinical trials with antitumor necrosis factor strategies and recombinant IL-1 receptor antagonist were not successful in improving the outcome of patients with sepsis. Two groundbreaking studies demonstrated that neutralization of tumor necrosis factor prevented death of animals with sepsis (mice injected with a lethal dose of lipopolysaccharide or baboons infused with high quantities of viable *Escherichia coli*). Later these observations were confirmed by many other investigators. Furthermore, elimination of IL-1 was shown to have a similar protective effect in animals exposed to lethal doses of lipopolysaccharide or living bacteria. These experimental studies led to the design of the probably most infamous clinical trials in patients with severe sepsis. It is common knowledge the trials did not yield the desired outcomes making the scientific, medical, and pharmaceutical communities wary of pursuing other anti-inflammatory strategies in patients with sepsis (12, 13).

Among therapies that have shown some success in patients with sepsis are early goal-directed therapy, activated protein C, adrenal corticosteroids, and intravenous immunoglobulins. Obviously the search for better therapeutic targets continues, and the latest include apoptotic pathways (1, 2).

Does all that mean that IL-6 is out of the loop? Not necessarily. A study by Eichacker et al (12, 14) suggests that the efficacy of anti-inflammatory therapy in sepsis may depend on the individual patient's severity of illness. Certain therapeutic strategies may be only beneficial in patients with more severe disease whose risk of dying is high. In such cases, therapies aimed at reducing excessive host response make more sense. In fact, in several clinical trials (a human monoclonal antibody [HA-1A] directed against endotoxin, the p55 tumor necrosis factor receptor fusion protein, recombinant IL-1 receptor antagonist, and the Monoclonal Anti-TNF: A Randomized Clinical Sepsis [MONARCS] study [afelimomab; antitumor necrosis factor antibody]), reduction in mortality in patients with sepsis was proportional to the severity of illness (12).

In summary, at the present time, one cannot completely discount the possibility that targeting gp130 may yet find its place among successful therapies for septic patients. For now more studies are needed to understand the differences between various mouse strains and to define beneficial and harmful activities of IL-6 in sepsis. Finally, because gp130 is not specific for IL-6, other possible mechanisms of protection than downregulating IL-6 signaling should be considered. All in all, it seems that the question of whether blocking of IL-6 in sepsis would be worthwhile remains to be answered but at the same time at least deserves to be addressed.

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Human serum albumin as a resuscitation fluid: Less SAFE than presumed?*

Since the first Cochrane meta-analysis suggested that fluids containing albumin may increase the absolute risk of death when compared with crystalloids (1), the use of albumin as a resuscitation fluid has been controversially discussed (2, 3). More recently, other authors suggested that albumin might at least be "indicated in some highly selected populations of critically ill patients" (4). In fact, albumin administration improved organ function in hypoalbuminemic patients (serum albumin ≤ 30 g·L^{-1}) (5) and was associated with a decreased risk of death in severe sepsis (6). In addition, in combination with terlipressin, it is frequently used for the management of the hepatorenal syndrome in patients with cirrhosis (7). Finally, it is also well established that, beyond its oncotic pressure-related effects on the intravascular volume, albumin has marked anti-inflammatory and -oxidative properties (8), which were nicely demonstrated both in experimental animals (9) and in patients with acute lung injury (10). Nevertheless, the overall result of the Saline versus Albumin Fluid Evaluation (SAFE) study was that albumin did not show any outcome benefit as a resuscitation fluid when compared with saline (11).

In their elegant rodent study, which represents the logic extension of a previous work (12), Kremer et al (13) now add an interesting piece to this yet unsolved albumin puzzle. In a well-established model of murine endotoxemia, they compared the effects of infusing equal volumes of human serum albumin (HSA) 4% and 20% with those of a three times higher amount of saline. The authors have the merit of using a posttreatment design with fluid administered 4 and 12 hrs after the endotoxin challenge. In addition to the analysis of various mediators of the inflammatory response as well as parameters of oxidative and nitrosative stress, the flow-mediated vasomotricity was determined as a marker of endothelial vasodilation. Endotoxin alone was associated with the expected marked activation of the inducible isoform of the nitric oxide synthase and the nuclear transcription factor κB, whereas the constitutive, endothelial nitric oxide synthase was significantly depressed. Consequently, both the formation of nitric oxide and the superoxide radical were significantly enhanced, which in turn resulted in a marked depression of the acetylcholine-induced mesenteric arterial dilation. In good agreement with their previous work (12), the authors found that administration of HSA 4% significantly attenuated both the endotoxin-induced systemic hyperinflammation as well as the enhanced oxidative and nitrosative stress and thereby blunted the otherwise pronounced metabolic acidosis. These findings coincided with a significantly enhanced expression of heme oxygenase-1, a stress protein involved in the protection against oxidative stress, and the nuclear respiratory factor-2, a protein governing mitochondrial biogenesis. Finally, HSA 4% normalized the endothelial flow dilation *in vitro*. In contrast to these therapeutically promising properties, HSA 20% exerted just the opposite effects; not only did it fail to attenuate the endotoxin-induced hyperinflammation, but, in particular, HSA 20% significantly reduced the expression of heme oxygenase-1. This finding coincided with a comparable severity of metabolic acidosis like in the endotoxic mice that received no volume resuscitation at all. This latter observation deserves particular attention; clearly, the Cl^- levels did not show any intergroup difference despite a three times lower Cl^- load in the HSA 4%- and HSA 20%-treated mice than in the saline-treated animals, but the twice higher albumin concentrations most likely contributed to this metabolic acidosis resulting from a decreased strong ion difference. Nevertheless, albeit the authors did not show any data on cellular energy metabolism (eg, tissue lactate, pyruvate, ketone body ratio), it is tempting to speculate that the more severe metabolic acidosis may have also been caused by mitochondrial dysfunction resulting from the enhanced formation of reactive oxygen and nitrogen species. In this context, another intriguing question must be raised: Why did the HSA 20%-treated mice present with the most severe renal dysfunction and ultimately die as early as the saline-treated animals and those that did not receive any fluid resuscitation? Unfortunately, no hemodynamic data are available so that it remains open whether fluid overload resulting from the increased oncotic pressure contributed to the early death in this group.

How can we explain the authors' striking findings? The study by Kremer et al (13) can be referred to as a further example of the equivocal role of oxidative stress and antioxidant treatment, respectively, in the critically ill and thereby nicely highlights the "radical paradox" (14); after oxidative damage has started, any (nonenzymatic) antioxidant can become a pro-oxidant by reducing transition-metal ions into their lower oxidation states, and, consequently, the more powerful a compound is as a reducing molecule, the more (oxidative) damage it may cause. Other authors provided examples of this paradox for *N*-acetylcysteine; in rodent endotoxin-induced acute lung injury, mortality was either reduced or increased depending on the dose administered (15), and albeit being the antidote for acetaminophen poisoning, prolonged treatment even increased organ damage (16). Finally, selenocompounds also showed either beneficial or deleterious effects depending on the specific molecule used, the dose, concentration, and the way of administration (17, 18). Clearly, based on

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its chemical properties, HSA may also exert both anti- and pro-oxidant effects (8), and Kremer et al now provide elegant proof that the "radical paradox" may also limit the use of albumin.

What do we learn from these data? Early this year an updated meta-analysis in this journal showed that "the use of albumin-containing solutions for the resuscitation of patients with sepsis was associated with lower mortality compared with other fluid resuscitation regimens" (19). The authors concluded that "until the results of ongoing randomized controlled trials are known, clinicians should consider the use of albumin-containing solutions" under these conditions. The study by Kremer et al now demonstrates that, most likely depending on the dosing and timing, in some patients, HSA may not only lack therapeutic efficacy, but may even be harmful. Unfortunately, until now, intensive care physicians are lacking the appropriate techniques to discriminate between the patients who will profit from its use and those ones in whom deleterious effects are likely to occur.

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Therapeutic hypothermia after cardiac arrest: It's about time*

Sudden cardiac arrest represents a major public health burden. Even if cardiopulmonary resuscitation is successful in achieving return of spontaneous circulation (ROSC), the effects of cardiac arrest are often devastating. A major contributor to death or disability in these patients is cerebral anoxia. More than half of patients successfully resuscitated from cardiac arrest die in the hospital, but those who survive commonly face permanent and crippling brain injury. The advent of therapeutic hypothermia (TH), the first proven therapy to attenuate the effects of anoxic brain injury after cardiac arrest, has offered promise for a condition once thought to be untreatable. However, important questions remain regarding the optimal use of TH, and some of the most pressing questions are centered on the *timing* of the intervention. For example, how soon must TH initiation occur after ROSC to be effective? How long should it be continued to maximize potential benefit?

In this issue of *Critical Care Medicine*, Che and co-workers (1) report the results of a laboratory investigation that represents a valuable step in the process of answering these questions. Using a rat asphyxial cardiac arrest model, the authors tested the hypothesis that the efficacy of post-cardiac arrest TH is dependent on the timing of the onset of therapy and the duration of therapy. The authors randomized the animals (n = 268) to normothermia vs. TH initiated 0, 1, 4, or 8 hrs after ROSC with a TH duration of either 24 or 48 hrs. They found a significantly higher 7-day survival compared to normothermic controls when TH was initiated 0, 1, or 4 hrs after ROSC but not 8 hrs after ROSC. They also found a significantly higher proportion of survival with good neurologic function compared to normothermic controls when TH was initiated 0, 1, or 4 hrs after ROSC but not 8 hrs after ROSC. Although these outcome measures (7-day survival and survival with good neurologic function) were not found to be significantly different in the analysis of TH duration, the authors found that surviving hippocampal cornu ammonis 1 pyramidal neuron counts were significantly higher in the group treated with 48 hrs of TH compared to 24 hrs of TH.

This is an important study. We interpret these results to confirm the hypothesis that sooner is indeed better for TH after resuscitation from cardiac arrest. The available clinical data at the present time are less clear. A recent randomized trial among patients who were resuscitated from out-of-hospital cardiac arrest compared TH induction by paramedics in the field to TH induction after arrival in the Emergency Department and found no difference in the proportion of favorable outcome (2). In addition, some observational data in human subjects resuscitated from cardiac arrest have not shown a significant association between early achievement of target temperature and improved outcome (3). However, these clinical reports should be interpreted with some caution. In the randomized trial of prehospital vs. Emergency Department-based TH, both groups had identical mean body temperatures after 1 hr, suggesting that the earlier attempts at TH induction in the field may have been insufficient. In observational studies, the association between time to target temperature and outcome can potentially be confounded by a number of factors, including a patient's intrinsic body temperature before TH initiation; e.g., moribund patients with exceptionally poor prognoses are often intrinsically hypothermic after ROSC and thus can be expected to have a shorter time to target temperature. Therefore, it is reasonable to postulate that optimal timing of TH induction is challenging (or perhaps impossible) to test with nonexperimental study designs. Although the present study from Che et al (1) is a laboratory investigation, we believe that this represents the best and most rigorous data to date on the topic of timing of TH induction, and it lends support to the concept that TH should be initiated as quickly as feasible in post-cardiac arrest patients.

The findings from Che et al (1) regarding optimal duration of TH (24 vs. 48 hrs) are especially intriguing and hypothesis generating. Although no significant difference was found in the outcome measures of 7-day survival or survival with good neurologic function between the different durations of therapy, the higher surviving hippocampal cornu ammonis 1 pyramidal neuron counts with longer duration of TH support the concept that longer may also be better. The limitations of an animal model do not permit identification of many more subtle but important manifestations of brain injury that survivors of cardiac arrest commonly experience, such as cognitive deficits and neuropsychiatric effects. Accordingly, we believe that the findings from Che et al (1) provide ample scientific rationale to test the hypothesis that longer duration of TH is beneficial in human subjects resuscitated from cardiac arrest. We believe that this type of clinical trial should be considered high priority for the resuscitation science community so that the optimal strategy for TH can be better defined, and perhaps this could further improve the chance of a favorable outcome from this devastating condition.

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***See also p. 1423.**

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The n-3 polyunsaturated fatty acids: Another option in the management of persistent pulmonary hypertension of the newborn?*

Persistent pulmonary hypertension of the newborn (PPHN) affects primarily term or near-term infants and has significant morbidity and mortality risks. Under normal circumstances, at birth, pulmonary vascular resistances decrease abruptly and pulmonary blood flow increases. In PPHN, because of various reasons this does not occur. Conditions associated with PPHN include meconium aspiration syndrome, pulmonary hypoplasia associated with congenital diaphragmatic hernia, pneumonia or sepsis in term infants, and respiratory distress syndrome in near-term infants. In some cases there is no apparent underlying lung disease, and the term "primary PPHN" is used (1).

PPHN usually leads to respiratory failure—hypoxemia and respiratory acidosis determined by pulmonary vasoconstriction, followed by heart failure, multiorgan dysfunction, and, in some cases, death. In recent years, in developed countries, mortality rates have declined to approximately 10% (1).

The currently accepted and investigative therapeutic options for PPHN include mechanical ventilation, correction of acidosis, inhaled nitric oxide, sildenafil, and milrinone (for cases that do not respond to inhaled nitric oxide) (2, 3). Extracorporeal membrane oxygenation has been used as a rescue option, but its use is diminishing after the introduction of high-frequency oscillatory ventilation and inhaled nitric oxide. Inhaled prostaglandin I_2, recombinant human superoxide dismutase, and the blockade of endotelin A receptors have been used on an experimental basis (4–6).

In the study published in this issue of *Critical Care Medicine*, Dr. Houeijeh and colleagues (7) suggest that an intravenous lipid formulation containing predominantly n-3 polyunsaturated fatty acids (n-3 PUFA) is effective in lowering pulmonary vascular resistance; it increased pulmonary blood flow, with a longer-lasting effect on the constricted pulmonary vasculature of the fetal lamb, apparently without significant side effects.

Diets rich in n-3 PUFA have long been proven by epidemiologic studies to lower cardiovascular risks and have especially reduced mortality after a myocardial infarction, but few studies have shown primary prevention yet (in Inuit, Chinese, and Japanese, but also in Western populations) (8).

The n-3 PUFA cause endothelial relaxation and promote arterial compliance, decrease systemic vascular resistances and, thus, blood pressure, reduce plasma triaylglycerol, and have anti-thrombotic, anti-arrhythmic, and anti-inflammatory effects, thus lowering the risk of myocardial infarction, atherosclerosis, and cardiovascular-related mortality.

The n-3 PUFA have a regulatory impact on different processes of inflammatory and immune cell activation in diseases such as experimental transplantation and lung injury, rheumatoid arthritis, and inflammatory bowel disease, and in surgical and trauma patients. Eicosapentaenoic acid and docosahexaenoic acid (DHA) are the precursors of recently identified potent anti-inflammatory lipids (resolvins and protectins). The resolvins regulate polymorphonuclear leukocyte infiltration and interleukin-12 production, block transendothelial migration, and thus lead to resolution of inflammatory responses (9).

Mice that are able to endogenously produce n-3 PUFA from n-6 PUFA showed decreased inflammatory responses in experimental and human studies of acute lung injury, without dietary or parenteral nutritional intervention (10).

Critically ill patients have increased levels of free fatty acids (secondary to inflammatory processes, immunologic responses, and responses to vasoactive drugs and inotropes). In addition, many such adult patients have "western style" diets, with an increased intake of saturated fats and n-6 PUFA, with a ratio of n-6 PUFA to n-3 PUFA being 15:1. When administered enteral or parenteral nutrition in the intensive care unit, they receive predominantly n-6 PUFA lipid formulations, which are currently the most widely available.

Makrides et al (11) have shown that maternal supplementation with DHA during the latter half of pregnancy was associated with significantly lower rates of preterm birth, birth weight <2500 g, and admission to the neonatal intensive care unit.

DHA is important for normal development and function of the prenatal and postnatal central nervous system. Clinical studies with DHA and eicosapentaenoic acid demonstrated benefits in treating attention deficit hyperactivity disorder, autism, dyspraxia, dyslexia, and aggression (12).

Prasertsom et al (13) showed that infusing a lipid formulation in prematurely born infants with respiratory distress syndrome actually increased pulmonary resistance, causing concern over the use of such products in a population that has been shown to need early parenteral nutrition. That was probably attributable to

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the fact that they used a predominantly n-6 PUFA lipid formulation (13). Omegaven, a predominantly n-3 PUFA lipid formulation, was used with good results in infants with short bowel syndrome with parenteral nutrition-associated colestasis (14, 15).

Several experimental studies have addressed the issue of n-3 PUFA effects on pulmonary vasculature and its use in pulmonary hypertension. Rats ingesting a fish oil diet were shown to have increased levels of eicosapentaenoic acid and DHA in their lungs. Rats fed fish (and corn) oil diets also had lower media thickness in large and medium arteries than did rats fed regular diets (16).

In a model of isolated rat lung, exposure to a fish oil diet did not alter acute intrinsic pulmonary vascular reactivity, despite pronounced changes in lung phospholipid fatty acid profile, possibly because of the lack of influences from cardiac output, autonomic nervous system, and the rheologic properties of the blood (17).

Possible mechanisms by which n-3 PUFA exert their effects include decreases in production of thromboxane A_2, prostaglandin E_2 metabolites, leukotriene B_4, interleukin-1, interleukin-6, tumor necrosis factor-α, and platelet-derived growth factor, as well as a reduction of platelet aggregation by increased production of prostaglandin I_3. They also increase concentrations of thromboxane A_3, prostaglandin I_2, and leukotriene B_5. Currently, similar studies performed with newborns—either animals or humans—do not seem to exist.

No significant side effects were described for n-3 PUFA; however, until now no large and long-term studies have been conducted with lipid formulations containing predominantly n-3 PUFA. The study by Houeijeh et al (7) provides a new approach to the management of PPHN. Its design has allowed the authors to show convincingly that a predominantly n-3 PUFA-containing lipid formulation lowers pulmonary vascular resistances and increases pulmonary blood flow in lamb fetuses. The response is not impaired by nitric oxide synthase inhibition, but it is affected by K^+ channel blockers and inhibitors of cytochrome P450 epoxygenase (enzyme involved in the metabolism of eicosapentaenoic acid and DHA) (7).

Several issues need to be discussed with respect to the design of the study before one can assume that an effective new treatment option for PPHN will be soon available. The study was conducted on fetuses, rather than newborns; furthermore, they were preterm whereas most newborns with PPHN are term or near term. Fetal Pa_{O_2} is much lower than that of a newborn (20–25 mm Hg). Fetal pulmonary circulation becomes more responsive to the vasodilator effect of oxygen with advancing gestational age. Even exposed to intrauterine hyperoxia (Pa_{O_2} up to 400 mm Hg in the mother), the response of the fetus does not exceed 40 mm Hg. Houeijeh et al (7) do not mention the level of O_2 to which the ewes were exposed during the experiment, but all lambs had physiologic Pa_{O_2} throughout the experiment, irrespective of the type of PUFA they received.

Houeijeh et al (7) do not mention the n-3 PUFA status of ewes included in the study. Al et al (18) have shown that maternal status of n-3 PUFA is decreasing during the second half of pregnancy, which in turn affects the n-3 PUFA status of the newborn. Preterm infants have lower n-3 PUFA levels in comparison to term newborns (19). Furthermore, the 24-hr fasting may have influenced the n-3 PUFA status of the ewes. One cannot be sure that the changes seen in the pulmonary artery pressure and pulmonary blood flow were solely attributable to exogenous n-3 PUFA. It remains to be seen if a similar experiment conducted with newborn animals with induced PPHN would yield the same results.

Given the disadvantages of the predominantly n-6 PUFA-containing lipid formulations currently used in parenteral (and enteral) nutrition in newborns and the numerous, at least theoretical, benefits of the n-3 PUFA-containing ones, it would make sense to start using the latter solutions in this age group. Nevertheless, many of the anti-inflammatory and immunomodulatory effects have not yet been proven to translate into clinical benefits in adults (20). The few clinical trials conducted in newborns to date should temper, at least for the time being, the enthusiasm created by the numerous potentially beneficial effects of n-3 PUFA. Presently, one cannot extrapolate the results of studies conducted with fetuses because their pulmonary vasculature response to n-3 PUFA may not be identical to that of newborns. Similar studies need to be conducted with newborn animals with PPHN and then replicated in clinical trials before we can hope to add n-3 PUFA to the therapeutic arsenal of PPHN.

Nevertheless, a switch to predominantly n-3 PUFA lipid solutions could prove beneficial for patients (newborns, infants, and adults) with a variety of illnesses, including PPHN, as shown in the study by Houeijeh et al (7). The optimal quantity and type of n-3 PUFA and the optimal ratio to their n-6 counterparts remain to be established in the future.

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From xenon to argon: A more clinically accessible neuroprotectant?*

Ischemic injury to the nervous system in the form of stroke, trauma, or anoxia is a major cause of death and disability. The search for effective therapies has led to some success: Thrombolytic therapy is currently the cornerstone of acute stroke treatment. Hypothermia is seeing wide adoption for treatment of cerebral anoxia post-cardiac arrest. Still, outcomes in various forms of brain injury remain overall poor, and clinical application remains limited.

The search thus continues for additional therapeutic strategies that can provide neuroprotection to the injured central nervous system and improve patient outcomes. The ideal neuroprotective agent would be effective, easy to administer, safe, and cheap.

Such an agent could find wide clinical applications in stroke, traumatic brain injury, spinal cord injury, and anoxia. A broad range of agents have shown efficacy in experimental studies but failed in clinical trials. These failures have led to the Stroke Therapy Academic Industry Roundtable, a general set of guidelines for rigorous preclinical testing of potential candidate drugs (1).

One such category of neuroprotective agents are the noble gases. Noble gases are a group of monatomic colorless, odorless agents, with very low chemical reactivity, and include helium, neon, argon, krypton, xenon, and radon. These gases can interact with amino acids and thus have biological effects (2).

Xenon is the most widely studied agent and is a known anesthetic. It has also been shown to be a neuroprotectant (possibly through *N*-methyl-D-aspartate receptor antagonism) in multiple and varied experimental scenarios (3).

The anesthetic properties of xenon, as well as its cost and the cost of its necessarily closed delivery system, have limited the translation of these experimental successes into clinical trials. Despite the extent of the experimental data, no phase II or III clinical trials have been conducted (4).

Unlike xenon, argon is ubiquitous (more common than carbon dioxide in the earth atmosphere), cheap, and available via extraction from liquefied air. Under normobaric conditions, it has no anesthetic or hemodynamic properties. Recently, *in vitro* studies of neuronal injury have shown that argon, like xenon (but not the noble gases helium, neon, and krypton), has neuroprotective properties (2, 5).

In this issue of *Critical Care Medicine*, Ryang et al (6) report on their experiment testing the effectiveness of argon in improving neurologic outcomes in a rat transient middle cerebral artery occlusion stroke model. This is a widely used model mimicking the human disease. Indeed, animals treated with a 50% argon mix, delivered via an open face mask, had smaller infarcts and better functional outcomes. As the first study showing *in vivo* effectiveness of argon as a neuroprotectant, it is of considerable interest as it opens the door for further confirmation of preclinical utility. Further investigation of dose, confirmation of longer term efficacy, benefit in other stroke models, testing in a broader range of animals, including aged animals and animals with comorbid conditions, will be necessary.

The ease of delivery, low expense, and likely limited side effects will likely lead to rapid clinical investigation if the preclinical data are there. Patients and clinicians eagerly await any advance in the field of neuroprotection, and maybe for argon, noblesse oblige.

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***See also p. 1448.**

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"C" is for sepsis?*

Vitamin C (L-ascorbic acid) was first identified in the late 1920s and has been advocated for the treatment of many diseases, some with justification and others without. Vitamin C is synthesized by most mammals except humans, other primates and a few other notable exceptions, such as guinea pigs, necessitating dependence on dietary sources. Ascorbic acid is an antioxidant; it donates electrons to form dehydrate-L-ascorbic acid (DHA), which is then reduced back to ascorbic acid by other antioxidants, most notably glutathione. It is necessary for the action of several metabolic enzymes, including those responsible for the synthesis of collagen, which is why absence of vitamin C in the diet causes scurvy, a disorder of collagen formation.

Sepsis is the main cause of death in the intensive care unit in the developed world. It is essentially a dysregulated inflammatory response with massive release of cytokines and microvascular dysfunction, leading to tissue hypoxia, mitochondrial dysfunction, and adenosine triphosphate depletion (1). Very low levels of protective antioxidants, including vitamin C, have been consistently reported in patients with sepsis due to increased consumption and losses, redistribution, and decreased dietary intake and associated with oxidative damage, mitochondrial dysfunction, and increased morbidity and mortality (2–4). Vitamin C is equally bioavailable as either DHA or L-ascorbic acid, and cells can take up ascorbic acid through Na^+-dependent ascorbate cotransporters. However, intracellular ascorbic acid levels can also be increased by uptake of DHA via the facilitative glucose transporters. Once inside the cell, DHA is immediately converted to ascorbic acid by reduced nicotinamide adenine dinucleotide phosphate-dependent thioredoxin reductase or glutathione-dependent DHA reductase. Inflammatory cytokines, including tumor necrosis factor α and interleukin-1β, inhibit uptake of ascorbic acid via the Na^+-dependent ascorbate cotransporters, and poor control of glucose, resulting in acute hyperglycemia, which is common in sepsis, can reduce DHA uptake through competition for transport by glucose.

In this issue of *Critical Care Medicine*, Dr. Fisher and colleagues (5) administered L-ascorbic acid or DHA to mice that had been given lipopolysaccharide to cause an inflammatory response and lung injury. It was found that both forms of vitamin C reduced the lethality of the lipopolysaccharide treatment and reduced inflammation and microvascular thrombosis in the lungs. Vitamin C has additional benefits over and above antioxidant effects, including maintenance of the microvascular circulation through endothelial barrier cell function and restoration of nitric oxide activity (6–8). The study by Fisher et al (5) is comprehensive and certainly adds to what is known about the effect of vitamin C in sepsis-induced lung injury. The data are convincing and are very transparently presented, and the numbers of mice in each experimental group are small. However, these animals received no analgesia and no fluid resuscitation. Such an experimental approach is not clinically relevant.

Fisher and colleagues (5) suggest that vitamin C may be a useful adjunct to treatment of patients with sepsis, but haven't we been here before? It was reported well over a decade ago that vitamin C and other antioxidants decline rapidly in critically ill patients (2–4) and that animal models of sepsis suggested a benefit of vitamin C and antioxidant supplementation in general (9–11). Several recent reviews have advocated specific targeting of mitochondria for antioxidant protection in sepsis (12–14). Numerous small-scale clinical studies have been undertaken, but despite numerous reviews and commentaries highlighting the need (7, 11, 15, 16), large clinical trials have not been forthcoming. A meta-analysis published 5 yrs ago reported that antioxidant therapy, including vitamin C, may be associated with reduced mortality in critically ill patients but qualified this by stating that the number of trials included was small and the inferences were weak and again called for large-scale clinical trials (17).

So, it seems we are still asking, "Is C for sepsis?"

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Dilate, dilute, constrict, or else in treating hemorrhage?*

The effective treatment of hemorrhage typically focuses on reestablishing central blood pressure to ensure tissue perfusion. Adequate tissue perfusion is achieved through normalization of the functional capillary density, a parameter that directly reflects the local (capillary) blood pressure (1). The functional capillary density is directly correlated with the capillary pressure, which in turn is a function of the central blood pressure. In principle, increasing the central blood pressure should result in an increase in the functional capillary density; however, when the increase in central blood pressure is generated by inducing vasoconstriction, transmission of the enhanced central blood pressure to the peripheral vasculature can be restricted. Conversely, strategies to decrease resistance and thereby enhance the transmission of central pressure to the capillary bed is often thwarted due to the drop in central pressure associated with the excessive vasodilation. In this seeming conundrum, manipulating the blood viscosity can be used as an additional parameter to balance competing processes.

Viscosity is maximal in the central circulation and decreases in the peripheral circulation as hematocrit progressively decreases in the microcirculation. Blood viscosity is a direct function of hematocrit. Blood viscosity is a factor in hemorrhagic shock since autotransfusion and a portion of resuscitation involve fluid therapy that dilutes the red blood cell mass. Manipulation of hematocrit and plasma viscosity has been shown to be effective in pressurizing capillaries and restoring the functional capillary density (2).

In this issue of *Critical Care Medicine*, the results of Salazar Vazquez et al (3) further illustrate the point that the combined manipulation of the central blood pressure and viscosity via the use of so-called hemoglobin-based oxygen carriers (HBOCs) can be used to restore the blood volume, oxygen-carrying capacity, and blood pressure. The use of HBOCs as blood substitutes has been limited and contentious in part due to side effects such as hypertension (4). The present study indicates that it is possible to harness the overlooked potential of vasoactive HBOCs. The earlier study of Cabrales et al (5) in moderate hemodilution (18% hematocrit) provides the first indication that vasoactive hemoglobin solutions used as hemodiluent provide improved microvascular conditions over a conventional colloidal plasma expander (6% dextran, 70 kDa). This effect was directly attributable to the increased central blood pressure (104 ± 8 vs. 89 ± 7 mm Hg) at the lowest dosage of plasma hemoglobin (1.2 ± 0.2 g/dL) and reversed for the higher dosages.

The use of vasopressors in the treatment of hemorrhagic shock is an accepted practice, although its benefit is debated. Its use is probably justified in conditions in which blood pressure cannot be maintained by any other means. However, if we accept the idea that the ultimate goal of resuscitation is to ensure capillary flow, it is apparent that vasoconstriction is not a means for achieving this objective unless there is a concomitant decrease in the impediment to the transmission of central pressure to the periphery. In other words, the vasoconstriction strategy will work if the increased central pressure "leaks through" to the periphery. This combination of effects could be attainable if, under conditions of increased central blood pressure due to vasoconstriction, the blood viscosity were significantly lowered in the peripheral vessels. This combination is shown by Salazar Vasquez et al (3) to be operative when there is hemodilution due to the use of nonviscogenic vasoactive HBOCs.

These considerations are not necessarily an endorsement of routine clinical application of infused acellular hemoglobins. Several HBOCs have been associated with forms of oxidative damage and nitric oxide depletion (6). The take-home message from this study is that the hypertensive effect *per se* can have a therapeutic value if properly titrated and separated from other toxicities specific to hemoglobin solutions. Furthermore, Salazar Vazquez et al (3) point out that in general the management of the oxygen-carrying capacity, fluid volume, and blood pressure may be best accomplished by directly manipulating independent variables. This combinatorial approach, however, can require multiple assessments, decisions, and interventions, an option that may not always be practical or available. The present work suggests that the use of a single intervention that encompasses this combinatorial approach may be possible through nonviscogenic vasoactive (nontoxic) HBOCs. It remains to be seen how

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Key Words: hemoglobin-based oxygen carrier; hemorrhagic shock; viscosity

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this approach compares to those based on directly manipulating bioactive nitric oxide levels through the use of either HBOCs that are capable of nitrite-based reactions that can compensate for depleted nitric oxide levels or nitric oxide/S-nitrosothiols-generating materials.

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New uses for my old friend*

In this issue of *Critical Care Medicine*, Liu et al (1) have taken the first steps to identify a new potentially effective treatment for elevated intracranial pressure (ICP) in the setting of bacterial meningitis. Bacterial meningitis has an unusually high incidence in China, where patients present with a higher degree of severity at a later stage (2). The development of a therapy with increased efficacy that could potentially be applied in the later stages of disease in patients with worse severity has important implications for the treatment of bacterial meningitis in China and other countries as well (3, 4). In recent years, two key strategies to reduce morbidity and mortality in the setting of bacterial meningitis have been proposed. They are the control of the inflammatory cascade with steroids and the reduction of ICP through the control of cerebral edema in the setting of bacterial meningitis (3–5). In their article, Liu et al demonstrate that adjunctive 3% hypertonic saline treatment has a significant positive effect on the physiology of bacterial meningitis in their rabbit bacterial meningitis model. Its application significantly elevated the mean arterial pressure, reduced the ICP, improved the cerebral perfusion pressure, and reduced cerebral edema while attenuating brain damage. It did so with superior efficacy as compared to 20% mannitol. In addition, it had noted secondary biological effects, such as inhibition of brain aquaporin 4 expression and decreased inflammation and neutrophil count, suggesting a reduction in inflammation in these patients. The use of hypertonic saline infusion as a treatment for elevated ICP in the setting of bacterial meningitis is the introduction of an old friend to a new task.

Hypertonic saline has been used clinically as an osmotic agent to reduce cerebral edema and increase cerebral perfusion pressure since the late 1990s. It was first reported as an effective osmotic agent during the turn of the century when it was noted to significantly reduce the brain volume of animals when applied intravenously (6). In the past decade, the pharmacologic properties of hypertonic saline have been studied in rodents (7, 8). In rodent models it has been noted to decrease leukocyte activity and to be an agent that decreases cerebral edema and cerebral water content (7–9). In the late 1990s, a number of clinical observations led to its widespread clinical application for ICP control. In many institutions, it supplanted mannitol as the agent of choice for reduction of ICP in brain injury of all types. These clinical observations included reports by Quereshi and Suarez and their colleagues (10, 11) that hypertonic saline was effective in reducing elevated ICP in all forms of brain injury. Others noted the efficacy of hypertonic saline in the reduction of ICP in patients with traumatic brain injury and ischemic stroke (12, 13).

Since the expansion of its clinical use in the 1990s, more recent animal studies have noted a number of physiologic properties demonstrating the increased efficacy of hypertonic saline in comparison to mannitol. These include an increased reduction in brain water and cerebral edema with longer efficacy and increased reduction of end organ water, including the lungs (7, 8, 14). This is achieved without apparent effects on the permeability of the blood brain barrier (9). While this animal research has addressed these physiologic effects, no work has been done on more basic molecular systems affecting specific diseases or injuries.

This recent study is the first time that hypertonic saline has been implicated as being truly beneficial for the treatment of any disease in a basic animal model. Its clinical efficacy has not yet been tested in humans with bacterial meningitis, and this study paves the way for potential future human trials (1). Using this animal model, they have demonstrated previously unanticipated biological effects of therapy, such as inhibition of leukocyte activity and a reduction in the molecular biological activity of the aquaporin 4 associated with cerebral edema (15). It represents a new application for the use of hypertonic saline therapy and sets a new standard for hypertonic saline research.

As this story unfolds, we can begin to study the effects of hypertonic saline in other diseases, such as stroke and traumatic brain injury, with an eye on concurrent effects on inflammation and aquaporins. In the meantime, we may consider the use of this agent in human trials on bacterial meningitis in countries such as

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Key Words: hypertonic saline, inflammation, bacterial meningitis, aquaporin 4

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China where this disease has a high enough incidence for such a study to be practical.

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Mind over matter!*

With an overall incidence of three to ten per 100,000 person-year, infectious endocarditis (IE) is an uncommon condition yet one that often exhibits devastating consequences. The widespread application of echocardiography, especially transesophageal echocardiography, has greatly aided in confirmation of a clinical suspicion of IE. This has implications for the critical care physician; now it has become increasingly an "inhouse" investigation for both diagnostic and monitoring purposes. This takes on added importance because the changing epidemiology of the disease has ramifications. Once associated with young adults with previously identified valve pathology, usually resulting from rheumatic fever, now the patients are mostly much older. In developed countries, newer predisposing factors have emerged. These include valve prostheses, degenerative valve sclerosis, and intravenous drug use. Often IE develops as a result of what is defined as health care-associated IE, either nosocomial or increasingly nonnosocomial from home-based nursing or intravenous services, hemodialysis, intravenous chemotherapy, or a nonhospital healthcare facility (1). One epidemiology study of hospital admissions for IE over a 6-yr period found an annual overall incidence of 4.7 per 100,000, peaking at 25.2 per 100,000 for males aged 80–84 yrs and 14.5 per 100,000 for females aged 80–84 yrs (2). Health care-associated IE occurred in 30% with a significantly higher mortality and adjusted hazard ratio for all-cause mortality of 1.62.

The classic microbiologic pattern of streptococcal infections on rheumatic valve disease still predominates in developing countries, whereas in developed countries, a different pattern now presents (3, 4). This changing epidemiology impinges on the type of complications resulting from the underlying IE, namely that of an increased incidence of embolism associated with *Staphylococcus aureus* endocarditis. Systemic embolism occurs in 22–50% of all patients with IE and is frequently associated with dramatic consequences (5). Although any vascular bed can be affected, the central nervous system accounts for 65% of embolic events with 90% of these in the middle cerebral artery territory (6).

It can be assumed that patients with IE admitted to the intensive care unit (ICU) represent the more seriously affected cohort, deepening the challenges of managing an uncommon, potentially devastating condition, which continues to evolve in regard to microbiologic flora and patient population. Therefore, the descriptive multicenter study from France examining the importance of IE in the critically ill population, with particular focus on neurologic outcome, published in this issue of *Critical Care Medicine* is a welcome addition to the literature (7). In this 19-month study involving 33 ICUs and recruiting 225 patients with definite IE, the functional outcomes of those patients with neurologic complications

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Key Words: infectious endocarditis; echocardiography; neurological complications

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were determined using the modified Rankin Scale score. The cohort included those admitted to the ICU with a diagnosis of IE, or alternatively those who developed IE while in the ICU. It does not include patients admitted postoperatively after valve surgery for IE. Of the 198 with left-sided IE, one or more neurologic complications were experienced by 108 (55%) of the patients. The complications included ischemic stroke, cerebral hemorrhage, meningitis/meningeal reaction, brain abscess, and mycotic aneurysm. The factors associated with neurologic complications in this study—*S. aureus,* mitral valve IE, and nonneurologic embolic events—are consistent with larger epidemiologic studies undertaken on patients with IE in developed countries.

The outcome should dismay the treating physician with only 29% of patients with neurologic complications achieving a reasonable outcome with a modified Rankin Scale score of <3 (walking without assistance) at 3 months. Of the remainder, 62% died and 9% were left with severe disability. Can we do better?

Would earlier diagnosis assist? The overall risk of embolism in IE is 20–50% of patients with new events dropping dramatically to 6–12% after start of antibiotic therapy (8). Certain characteristics known to predispose to embolism may be identified earlier with regular echocardiographic monitoring. These include the presence of large vegetations (>10−15 mm in size), mitral valve disease, multivalvular involvement, and increasing vegetation size while receiving antibiotics (9). For example, a 15-mm mobile mitral valve vegetation with underlying *S. aureus* may create a different urgency to a 4-mm vegetation on the aortic valve with blood cultures positive for *Enterococcus* (10). Half the patients in the French study underwent surgery regardless of the presence of pre-existing neurologic complications. This led to a better outcome compared with those who were not operated on who experienced a mortality rate of 88%.

Would a more aggressive surgical approach improve the outcome? The positive place of surgery when cardiac failure exists, especially when undertaken early, was clearly established >20 yrs ago (11). A recent North American study of 19,543 operations for IE between 2002 and 2008 identified an operative mortality of 8.2% at 30 days with a complication rate of 53% (12). The risk factors identified leading to a higher mortality rate are those commonly found in the ICU.

Because the patients identified in the French study included those admitted to an ICU with a focus on cerebral complications, the role of surgery in this specific subgroup needs close examination. Derex and colleagues (13) in reviewing the impact of stroke on therapeutic decisionmaking in cases of IE highlight the absence of large prospective trials to assist in decisionmaking, particularly in regard to surgery. Stroke is the main cause of death after cardiac failure with a death rate as high as 58%. There is concern about coronary bypass surgery in such patients and the role of anticoagulation. Current practice is to delay surgery in the event of a large cerebral infarction or hemorrhage to prevent neurologic deterioration.

An important message from this informative study, considering many of the patients presented with cerebral damage on admission, is to consider more aggressive monitoring of disease progression and a more aggressive surgical approach. Of those patients with a well-validated indication for surgery, 58 (37%) did not receive it. Despite concerns regarding surgery, there are few other therapeutic options available. Where increased risk of further embolism exists, surgery should be considered early in all patients. In the absence of hard supportive evidence, a multidisciplinary approach is recommended to assess the likely benefit of early surgery in this group of patients in whom two-thirds experience a poor neurologic outcome or die.

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Choosing brain over lungs: Who wins?*

In a secondary analysis of a prospective, observational, multicenter trial, Pelosi and colleagues (1) examined 4,968 consecutive patients to compare differences between critically ill patients with and without brain injury. Neurologic patients included in the analysis were defined as having either a stroke (hemorrhagic or ischemic) or traumatic brain injury. Specifically, only patients with a Glasgow Coma Score ≤13 during the first 48 hrs of intensive care unit admission and with the neurologic insult being the primary cause for necessitating mechanical ventilation were included. There was no significant difference in ventilation strategy, adherence to lung protective ventilation, and timing to tracheostomies between both groups. The subgroup of neurologic patients with hemorrhagic stroke had an increased intensive care unit mortality with all neurologic patients having a longer duration of mechanical ventilation, fewer extracranial organ dysfunctions, and a higher overall rate of tracheostomies.

Given the current limited data on the optimal ventilatory management of neurocritical care patients, this study was able to highlight some interesting points, albeit with some important considerations. The first consideration is the choice of including only neurologic patients with Glasgow Coma Score ≤13 within the first 48 hrs, which seems arbitrary and may have eliminated patients with mild traumatic brain injury and good-grade neurovascular patients in a specific timeframe who would likely have experienced good outcomes. Second, neurologic patients, who had a longer duration of mechanical ventilation, paradoxically experienced fewer adverse rates (eg, barotrauma, acute respiratory distress syndrome), especially given the large proportion of patients who received higher tidal volumes as well as low levels of positive end-expiratory pressure (≤5 cmH_2O), both of which could increase the incidence of ventilator-induced lung injury. One also needs to consider the effect of withdrawal of life-sustaining therapies on the reported increase in mortality among patients with hemorrhagic stroke; unfortunately, no data were collected on this confounder in the original study. Finally, this study is a *post hoc* analysis of a large prospective trial and was not designed, or powered, to compare neurologic patients with other medical–surgical intensive care unit patients. Nevertheless, this study has raised some important questions, which may inform future research in neurocritical patients and move this field forward.

First, should the ventilation strategy used in neurocritical patients be different from other critically ill patients, particularly those with acute respiratory distress syndrome? Concerns regarding the negative effects of hypercapnia and high intrathoracic pressures on intracranial pressures have led clinicians to "choose the brain over the lungs" in dealing with neurocritical patients with concomitant acute respiratory distress syndrome. Indeed, there are limited data on the use of lung protective ventilation (ie, lower tidal volumes, permissive hypercapnia, higher levels of positive end-expiratory pressure) in neurocritical patients as a result of concerns for secondary brain injury (2–5). A large, randomized controlled trial would be better suited to answer this question. Perhaps the issue of timing is most critical with early management and prevention of worsening brain injury taking precedence over other organ dysfunction but then shifting to optimizing extracranial organ dysfunction later on. The optimal point at which the focus in a neurocritically injured patient with multiorgan involvement should change from preventing secondary neurologic injury to preventing morbidity and mortality from extracranial organ dysfunction remains unclear.

Second, what effect does prognostication, an area of research that is increasingly being investigated (6, 7), have on short- and long-term outcomes in neurocritical patients? The authors conclude that patients with hemorrhagic stroke have a higher rate of intensive care unit mortality (48% compared with 37%, 29%, and 30% for ischemic stroke, traumatic brain injury, and nonneurologic patients, respectively; $p < .001$), yet how much of this is related to physician withdrawal of life-sustaining therapies? Unfortunately, data on withdrawal of life-sustaining therapies were not collected in this study. Furthermore, what information are clinicians and family members scrutinizing in making these decisions? A prospective study evaluating physiological, laboratory, imaging, and serum biomarkers that may help to predict both the best neurologic outcome and mortality in neurocritical patients would be helpful to inform the end-of-life decisionmaking process. Furthermore, the underlying cause of death has not been investigated in detail among neurocritical patients. Is the cause of death the underlying brain injury and its sequelae or the extracranial organ dysfunction? For instance, patients with acute respiratory distress syndrome and hypoxemic respiratory failure typically die of sepsis and multiorgan failure and not hypoxemia per se (8). Understanding the cause of death in neurocritical patients could help answer the question of whether we truly should be choosing "the brain over the lungs" and other affected organs in these patients.

Third, although the incidence of tracheostomies was found to be increased in neurologic patients, the timing of these procedures was similar among the nonneurologically injured patients despite having worse Glasgow Coma Scores and longer duration of weaning. The optimal timing for tracheostomy in neurocritical patients, who may have delayed awakening and meeting traditional thresholds for extubation, is an important issue to be answered by future studies (9). Early tracheostomies in neurocritical patients may minimize adverse events and improve outcome as has been suggested by previous studies (9–11).

Finally, what role should subspecialized neurocritical care units play in the man-

*See also p. 1482.

Key Words: critical care; intensive care units; neurosciences; neurocritical care; mechanical ventilation; outcome

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agement of critically ill neurologic patients? Like trauma patients, one might hypothesize that the management of complex neurocritical patients with multiorgan dysfunction would be improved in units with subspecialty consultants and expertise, resulting in improved patient outcomes (12). Pelosi and colleagues discuss their preliminary data supportive of this hypothesis, consistent with previous studies (13–15). Examining the differences in specific protocols and processes of care (eg, "neuroprotective" ventilation strategy, multimodal neuromonitoring, early tracheostomy) between these units and general medical–surgical intensive care units would help elucidate the mechanism by which there is a difference in outcomes. Answers to these questions would help to clarify whether choosing "the brain over the lungs" is a reasonable strategy or using an aggressive approach to the management of multiorgan dysfunction in neurocritical patients, tailored for "neuroprotection" (eg, lowest tidal volumes that allow for normocapnia, highest level of positive end-expiratory pressure without affecting intracranial pressure), is warranted right from the start.

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Kidney injury in kids following bypass surgery: More to know*

One of the most vexing problems following congenital heart surgery is the occurrence of acute kidney injury (AKI) (1). Identifying indicators for AKI would be of major benefit in designing therapies to prevent injury or provide early treatment that may limit progression to renal failure (2). An initial step in this process has been to standardize definitions of AKI in pediatric patients. More than 30 published definitions of AKI exist in the literature. Nevertheless, the two most widely accepted classification schemes for AKI are the risk, injury, failure, loss, and end-stage kidney injury and Acute Kidney Injury Network (AKIN) scoring systems (3–5). The risk, injury, failure, loss, and end-stage scheme uses the change in glomerular filtration rate/serum creatinine or urine output to categorize renal function into stages based on the percent change from baseline or the degree of oliguria. A modified definition has been developed for use in pediatrics. The AKIN score also uses the degree of oliguria and percent change from baseline for serum creatinine but adds an absolute increase in serum creatinine (by 0.3 mg/dL) to the criteria whereby patients would qualify for stage I AKI. Furthermore, the decline in kidney function must occur over 48 hrs.

In this issue of *Critical Care Medicine*, Li et al (6) reported the results of a multicenter evaluation of the incidence of AKI in children following congenital heart disease repair. The article is limited to patients >30 days old and does not include patients in the highest Risk Adjustment for Congenital Heart Surgery congenital heart disease categories. Overall, 42% of patients developed AKI within the first 3 days after surgery. Factors associated with an increased risk of AKI were age, weight, body surface area, preoperative creatinine, higher Risk Adjustment for Congenital Heart Surgery category, and duration of cardiopulmonary bypass. Furthermore, the development of AKI led to longer durations of mechanical ventilation and longer hospital stays.

The study is purported to be a multicentered evaluation of AKI in postoperative

*See also p. 1493.

Key Words: renal failure; children; cardiopulmonary bypass

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cardiac patients using the newly defined criteria as a basis from which other pediatric studies can be compared. If only it were true. First, the use of "multicentered" seems a bit of a stretch, as the majority of patients (70%) came from one center, with only 8% being contributed by one of the three sites. Furthermore, since one of the main purposes of the article was to describe the incidence of AKI using "standard" AKIN definitions, it would have been optimal if the authors had actually used the complete consensus criteria, that is, change in serum creatinine or urine output. In the current study, AKI was defined as a rise in serum creatinine of 50% or more from baseline within the first 7 days after surgery. The AKIN score, however, stratifies AKI into three stages whereby the first stage is an increase in creatinine to 150–200% of baseline or an absolute increase of >0.3 mg/dL. The AKIN criteria also require the decline in renal function to occur within 48 hrs as opposed to 7 days as suggested in this article. If one applies the risk, injury, failure, loss, and end-stage criteria, "injury" is defined as a doubling of the baseline serum creatinine or decrease in urine output (<0.5 mL/kg/hr) for 12 hrs, which is also inconsistent with the definitions used in a recent report (7). These variances could have substantial impact on the validity of the identified risk factors for AKI described in this article.

The authors also used an intraoperative hypotension score that is not easily comparable to other measures. Perhaps something like the inotrope score, which has been used in other postoperative cardiac reports, or an overall organ failure score may have been a more appropriate measure (8, 9). Finally, there was no discussion regarding the timing of administration of nephrotoxic agents in relation to the occurrence of kidney injury. The lack of inclusion of infants <30 days old, no patients in high-level Risk Adjustment for Congenital Heart Surgery categories, and no mention of whether corticosteroids were used in the priming of the cardiopulmonary bypass circuit are also factors that were not part of this report but would be interesting to know more about in the future.

This article gives some ongoing information regarding the incidence of kidney injury in postoperative cardiac patients. It also reveals how much more work there is to be done to refine standardized language describing injury and further evaluate causative factors and potential preventive measures.

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Traumatic shock resuscitation with a 1:1 plasma to packed red blood cell ratio: Is it to please ourselves or the injured?*

Exsanguination after trauma is the leading cause of preventable death in our society (1). Further to this, some recent prospective epidemiologic studies showed that the relative incidence of uncontrolled bleeding related deaths is increasing compared to that of head injury related deaths on the basis of studies during the past 30 yrs (2).

Considering the significance of traumatic shock, it is surprising that the shock resuscitation strategy has hardly changed between the Vietnam War era and the early 2000s (3). The mechanistic categorization of shock into classes I–IV and the idea of "responders," "transient responders," and "nonresponders" based on crystalloid boluses drove trauma resuscitation for decades without the rationale behind them being questioned.

Although the basic principles of hemorrhagic shock resuscitation are straightforward (hemorrhage control, replacement of volume, clotting factors, and oxygen carrying capacity), understanding the underlying complexity of the shocked patient's physiology is still far from clear. The human brain needs to rationalize and simplify processes that are beyond its comprehension.

The 2 L of lactated Ringer's solution bolus was a simplistic empirical approach to evaluate blood pressure/heart rate response and develop surgical management strategies. Obviously it did not account

*See also p. 1507.

Key Words: trauma; shock; resuscitation; transfusion; hemostasis

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for the time of injury or patient factors and ignored the fact that blood pressure is a poor surrogate marker of shock. Further to this, the rapid elevation of blood pressure, the dilution of clotting factors, hypothermia, and potential rebleeding are all consequences of this approach. Like with any good research (4), the logical idea behind crystalloid resuscitation can be translated falsely to clinical practice and cause harm. In crystalloid-based overresuscitation, in an edematosus patient with dysfunctional organs, impending acute lung injury, abdominal compartment syndrome, and multiple-organ failure result. Aiming for the best, being more aggressive (supranormal resuscitation), we have unintentionally done more harm by creating avoidable complications with preload-driven resuscitation of major trauma patients (5).

The re-recognition of the importance of hemostasis and the recall of the fading positive memories of fresh whole blood created the concept of a 1:1 fresh frozen plasma (FFP) to packed red blood cell (PRBC) ratio for traumatic shock resuscitation. This strategy is an attractive one, makes sense, is relatively easy to follow with the implementation of a massive transfusion protocol, and eliminates the need for many laboratory tests and consults. This concept has rapidly spread without level I scientific evidence. Most of the available evidence to support a 1:1 ratio is based on trauma registry based retrospective studies with historical controls.

Rajasekhar et al (6) performed an elegant systematic review on the potential survival benefit of the low or high FFP to PRBC transfusion ratio, which is presented in this issue of *Critical Care Medicine*. Their methodology is robust, and the topic is very relevant to our current era of practice with institutions adopting the 1:1 strategy across the world. On the basis of this systematic review, the current paradigm shift of our practice is based on 11 observational (three prospective, seven retrospective, and one case-control) and no randomized studies. The lack of randomized studies does not mean that these are poor-quality studies. According to the Newcastle Ottawa Scale, they score between seven and nine on the scale of nine. The high scores of these studies imply that we have close to the highest level of achievable evidence from observational studies. Observational studies show association between treatment and outcomes rather than causation.

The authors conclude that most studies support the survival benefit of higher FFP/PRBC ratios, but they caution us about the extreme heterogeneity and potential bias of these studies. They discuss in detail the survival bias, which is only infrequently addressed by these studies. Interestingly, only three studies reported the use of institutional massive transfusion protocol; it is unclear what ratios these patients received before reaching the most frequently used >10 units of PRBC/24 hrs inclusion criteria.

The potential problem with any studies using historical controls is that between the two groups many potential changes in the management could have occurred. I believe the most significant one is the restricted use of crystalloids. Crystalloid resuscitation fluids are proinflammatory by themselves (7), and their excessive usage is an independent predictor of some lethal postinjury complications. Hemostatic resuscitation is associated with a decreased amount of crystalloid use and increased ratio of transfused FFP to PRBC. Most reports tend to praise the effect of improved ratios of FFP of PRBC without acknowledging the significance of using less crystalloids.

The current review rightly concludes there is insufficient evidence to support the use of a fixed 1:1 ratio of FFP to PRBC in massively transfused patients and recommends randomized controlled trials to evaluate the safety and efficacy of 1:1 transfusion protocols be performed.

Many of the readers would get to this conclusion; I believe a systematic review in this field could discuss the potential hurdles of the future randomized controlled trials on this topic. Although there is a lack of evidence showing causation, in many institutions the 1:1 resuscitation strategy is already the standard of care regulated by strict protocols. It might be difficult to convince institutional review boards to step back and use "inferior" resuscitation strategies and potentially harm patients. Further to this, what is the best ratio to compare 1:1 with, especially in the context that we are not sure that 1:1 is the optimal one? Consistently controlling for fixed ratios during the early phases of the demanding trauma resuscitation is a major methodical challenge. A randomized controlled trial of this magnitude would probably only be feasible in the best performing trauma centers, where the avoidable trauma mortality is already very low. This could easily lead to futility of an expensive trial as we have learned from recent experience (8).

Dr. Rajasekhar and colleagues (6) performed an important summary of the current evidence highlighting the need for higher level studies. This paper is probably a turning point in the literature from where journal editors will not be keen to consider further observational studies with historical controls. It is time to show that fixed FFP/PRBC ratios during trauma resuscitation do benefit our patients and not just serve as a simplified recipe for the solution of a "bloody" complex problem.

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Benefits of statins in the critically ill: Promising but not proven*

In recent years there has been growing interest in the pleiotropic effects of statins and their potential role in sepsis and acute lung injury (ALI). Statins inhibit the enzyme hydroxymethylglutaryl coenzyme A reductase, which is the rate-limiting step in the conversion of hydroxymethylglutaryl coenzyme A to mevalonate. All statins work in a similar manner to inhibit mevalonate production and thus to reduce cholesterol. Inhibition of mevalonate also inhibits the production of proteins that act as intracellular lipid attachments to convert proteins to a more lipophilic state to facilitate interaction with cellular membranes. This process, known as prenylation, is required for function of the small guanosine triphosphate binding proteins, which have crucial roles in a variety of cellular effects, including production of proinflammatory cytokines and regulation of endothelial cell permeability. These processes are important in the pathogenesis of sepsis and ALI (1).

In this issue of *Critical Care Medicine*, Brealey et al (2) highlight that the reduction in mevalonate also results in a fall in ubiquinone levels, which may have implications for the use of statins in the critically ill. Ubiquinone is necessary for electron transfer within the mitochondrial respiratory chain and possesses antioxidant effects and cell signaling properties (2). Mitochondrial dysfunction may contribute to multiorgan failure in sepsis (3). Theoretically, the reduction in ubiquinone levels may offset the beneficial effect that statins might have in sepsis and ALI. So what is the balance of evidence on the potential role of statins in the critically ill?

In patients with sepsis, most observational studies suggest that statins are associated with better outcomes (4). Similarly, most observational studies have suggested a beneficial effect of statins in patients with pneumonia (5). In a prospective observational study in patients with ALI, there was a trend to lower mortality in patients receiving statins during their intensive care unit stay (6). It is not clear if the better outcomes observed in these studies in the patients who received statins were due to the statins themselves as opposed to statins representing a surrogate marker for improved access to healthcare. Simvastatin modulates pathogenic mechanisms important in the development of lung injury and sepsis. In a double-blind, placebo-controlled study in a model of ALI induced by inhaled lipopolysaccharide in healthy human volunteers, participants were randomized to simvastatin or placebo orally for 4 days before lipopolysaccharide inhalation. Pretreatment with simvastatin reduced pulmonary and systemic inflammation (7). These findings are supported by a randomized placebo-controlled study that found 80 mg of simvastatin for 4 days reduced systemic cytokine responses induced by intravenous lipopolysaccharide in healthy subjects (8). In addition, a study in patients with acute bacterial infection found that simvastatin, commenced before the development of sepsis-induced organ dysfunction, also reduced the levels of systemic inflammatory cytokines (9). Finally, in a recent randomized placebo-controlled study (a randomized controlled trial of Hydroxymethylglutaryl-CoA reductase Inhibition for Acute Lung Injury [the HARP STUDY]), 60 patients with ALI received 80 mg of simvastatin or placebo. This study demonstrated a significant reduction in nonpulmonary organ dysfunction with reduced Sequential Organ Failure Assessment scores at 14 days. Pulmonary dysfunction improved, although this failed to reach statistical significance (10). On the basis of the available data, several large multicentered trials are now planned or ongoing investigating the effects of statins in sepsis and ALI. The HARP-2 (Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in acute lung injury to reduce pulmonary dysfunction, International Standardized Randomised Controlled Trial Number 88244364) and SAILS trials (Statins for Acutely Injured Lungs from Sepsis, ClinicalTrials.gov identifier NCT00979121) are ongoing and aim to examine the effect of statins in ALI.

Brealey et al (2) highlight low ubiquinone levels as a potential mechanism by which statins may not be effective in the critically ill. In a prospective study of 236 patients with cardiac failure, low plasma ubiquinone levels were an independent predictor of mortality. However, this study did not demonstrate that statin use increased mortality (11). In a subset of 1,191 patients with cardiac failure taken from the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial, there was no association between either ubiquinone levels or rosuvastatin and mortality (12). The significance of ubiquinone levels in an intensive care unit setting has yet to be elucidated. Low plasma ubiquinone levels may not be mirrored by falls in muscle and mitochondrial ubiquinone. Sepsis itself may result in a fall in plasma ubiquinone levels, and statins may reduce ubiquinone levels due to a reduction in low- and high-density lipoprotein levels, which act as ubiquinone carriers (2).

To date there are no human data regarding ubiquinone levels or the use of ubiquinone replacement in sepsis or ALI. Ubiquinone deficiency has also been implicated in myopathy and rhabdomyolysis due to statins (2). Whether ubiquinone is important in the critically ill treated with statins where courses of statins will be short (typically 14–28 days) and patients are closely monitored remains uncertain. Data from prospective trials in the critically ill show low levels of adverse effects with no reported excess adverse effects in the statin groups, although patient numbers are small (13–15). Another consider-

***See also p. 1514.**

Key Words: statins; sepsis; acute lung injury; critical care; ubiquinone; mitochondria

Dr. McAuley received consultancy fees and served on advisory boards for GlaxoSmithKline (Middlesex, UK) and has received lecture fees from AstraZeneca (London, UK) for educational meetings. He has also received grant support for a study examining simvastatin in ALI (MRC London, UK). Dr. O'Kane's spouse has received consultancy fees and served on advisory boards for GlaxoSmithKline (Middlesex, UK) and has received lecture fees from AstraZeneca (London, UK) for educational meetings, although Dr. O'Kane has no other personal financial relationship with GlaxoSmithKline or AstraZeneca. Dr. Kane has also received grant support for a study examining simvastatin in ALI (MRC London, UK). Dr. McGuigan has not disclosed any potential conflicts of interest.

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ation on the potential effects of statin therapy relates to changes in lipid metabolism in critically ill patients. There is a reduction in total cholesterol. The mechanism for this remains unclear, but it is possible that hydroxymethylglutaryl coenzyme A reductase is already maximally downregulated, which may attenuate any benefit of additional inhibition by statins.

There is strong evidence that statins may be a potentially beneficial pharmacologic treatment in the critically ill. Although the data to date are reassuring, there are still limited safety data on the use of statins in the critically ill. The excellent review by Brealey et al (2) is an important reminder about the potential for adverse effects of statins, including those mediated through decreased ubiquinone levels. It also highlights the need for large clinical trials powered for important clinical outcomes in patients with sepsis and ALI to answer the question of whether statins improve outcomes and are safe in the critically ill.

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Toxic epidermal necrolysis and Stevens-Johnson syndrome: Things we should know!*

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe skin reactions characterized by low incidence and high mortality. According to the literature, these disorders affect between 1 and 6 people per million annually and are associated with mortality rates of 1–5% in SJS and of 10–35% in TEN (1). The prognosis depends on how early the disorders are diagnosed and how sufficiently they are treated. In this issue of *Critical Care Medicine*, Gerull and colleagues (2) summarize definitions, causes, the clinical course, and therapy of TEN and SJS. We think that this profound review may help to detect and to treat patients suffering from TEN and SJS.

The authors state that SJS and TEN are clinically very similar except for their distribution. One commonly accepted classification defines <10% of body surface area affected as SJS and >30% of body surface area affected as TEN; involvement of 15% to 30% of body surface area is considered SJS-TEN overlap (1, 2). It is widely accepted that drugs, especially sulfa drugs, antiepileptics, and antibiotics, are the most common causes (1–5). Other factors that are associated with a higher incidence of TEN/SJS are infectious diseases, such as human immunodeficiency virus and hepatitis, but also noninfectious conditions, including radiotherapy, lupus erythematosus, and others (1–3). According to the literature presented in this review, the diagnosis is usually obvious by the appearance of the

*See also p. 1521.

Key Words: Stevens-Johnson syndrome; toxic epidermal necrolysis; skin diseases; drug toxicity.

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initial lesions and the clinical symptoms. Histologic examination of sloughed skin shows necrotic epithelium, a distinguishing feature.

Gerull and coworkers (2) state that in spite of more profound knowledge, the exact mechanism remains unknown.

Within 1 to 3 wks after the start of the offending drug, patients develop a prodrome of malaise, fever, headache, cough, and conjunctivitis. Macules, often in a "target" configuration, then appear suddenly, usually on the face, neck, and upper trunk. These simultaneously appear elsewhere on the body, coalesce into large flaccid bullae, and slough over a period of 1 to 3 days. Nails and eyebrows may be lost along with epithelium.

In severe cases of TEN, large sheets of epithelium slide off the entire body at pressure points (Nikolsky sign), exposing weepy, painful, and erythematous skin. Painful oral crusts and erosions, keratoconjunctivitis, and genital problems accompany skin sloughing in up to 90% of cases. Bronchial epithelium may also slough, causing cough, dyspnea, pneumonia, pulmonary edema, and hypoxemia. Glomerulonephritis and hepatitis may develop (1–5).

Based on the recent literature, the authors state that the treatment is most successful when SJS-TEN is recognized early and treated in an inpatient setting. We think that severe TEN is similar to extensive burns; patients are acutely ill, may be unable to eat or open their eyes, and suffer from massive fluid and electrolyte losses. They are at high risk of infection, multiorgan failure, and death. With early and sufficient therapy, survival rates approach 90%. Therefore, we think that burn units may be indicated for the treatment of severe cases. This is according to other recent publications (5) as well as the review by Gerull et al (2).

Based on the literature (1–5), treatment is mainly based on the following factors: drugs should be stopped immediately, patients should be isolated to minimize exposure to infection, and skin care includes infection prevention and prompt treatment of secondary bacterial infection. Gerull et al (2) state that based on the available literature, the use of special drugs to treat STS-TEN remains controversial; not only does the use of high-dose systemic corticosteroids remain controversial, but plasmapheresis and early high-dose intravenous immune globulin also render conflicting results.

Finally, there is high evidence that the appropriate management of extensive skin wounds and the nutritional and critical care support afforded by treatment in burn units have contributed significantly to the increasing survival of patients suffering from these kinds of potentially lethal illnesses.

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'Reversible brain death'—Is it true, confounded, or 'not proven'?*

"The time has been that when the brains were out the man would die and there an end. But now they rise again."—Macbeth. Act III, Scene IV

In 1902, a study by Harvey Cushing (1) reported apnea developing during attempted drainage of an intracranial abscess and persisting during artificial ventilation for 23 hrs before death. In describing another case of brainstem compression, he presaged modern concepts of brain death—"… the vasomotor mechanism gave way, respiration ceased in conjunction with the fall in blood pressure, and, as in the majority of these conditions, the heart continued to beat for some time *after death had actually ensued*." Brain death—"la mort du système nerveux" ("death of the nervous system")—was first described in detail in France in 1959 in a study by Wertheimer (2) and later the same year in a study by Mollaret and Goulon (3) that used the term "le coma depassé" ("a state beyond coma").

Equating *brain death* with *death*, which Joseph Murray (4) had suggested to the Harvard Committee (5) in 1967 (rejected at that time), began to be accepted after the views of the Medical Royal Colleges of the United Kingdom (6) in 1979 ("It is the conclusion of the Conference that the identification of brain death means that the patient is dead …"), and the President's Commission (7) in 1981 "… death depended on either irreversible cessation of circulatory and respiratory functions or irreversible cessation of all functions of the entire brain."

Although there are no worldwide consensus criteria for the determination of brain death (8), variation between various international codes of practice is attributable not to differences in the examination of brainstem reflexes (nor in the importance of the exclusion of potential confounders), but in the requirements for the

***See also p. 1538.**

Key Words: brain death; cardiac arrest; induced hypothermia; organ donation; anoxic-ischemic encephalopathy

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determination of apnea, the number of examinations and examining physicians, and the place of "confirmatory" tests (9).

The American Academy of Neurology 1995 practice parameter (10) is not incongruent with codes of practice from many other jurisdictions and probably represents a fair and reasonable summary of international views. A recent evidence-based review of this document (11) included this robust statement: "In adults, recovery of neurologic function has not been reported after the clinical diagnosis of brain death has been established using the criteria given in the 1995 AAN practice parameter."

A subsequent report of two cases of "apparently reversible brain death" (12) has been seen as confounded (13). The report in this issue of *Critical Care Medicine* by Webb and Samuels (14) should cause every intensivist to pause for thought. The findings in this case suggest that either there was confounding of the clinical examination (perhaps by residual medication) or that there was some long-duration but nevertheless reversible "hibernation" of brain stem neurons—perhaps peculiar to the specific circumstances of the hypoxic–ischemic insult and induced hypothermia.

Induced hypothermia in this case was only mild, less than that used in the two seminal trials (15, 16), and not present at the time of clinical examination for brain death. To what extent induced hypothermia modifies the prognostic value of subsequent clinical examination is still unclear (17–19) with some recent reports suggesting that, after hypothermia and rewarming, poor motor response at 72 hrs might not have such a dire prognosis as previously thought. Because of the time course of recovery in brainstem function after resuscitation from cardiac arrest, some (but not the American Academy of Neurology) guidelines recommend delaying clinical examination for brain death until 24 hrs after resuscitation (20). Whether such an interval should be lengthened when induced hypothermia has been used during the first 24 hrs (even if the patient is now normothermic) has not been addressed in any clinical guidelines. In this case, however, the first clinical examination for brain death did not occur until 72 hrs after return of spontaneous circulation, approximately 16 hrs after return to normothermia.

Against the possibility of residual drug effect is the apparently reliable documentation of a temporary return of brainstem function (reactive pupils, cough, gag, and spontaneous respiration). This was documented once, at 56 hrs after return of spontaneous circulation, 6 hrs after fentanyl (and propofol) infusions were stopped. The next clinical examination, 16 hrs later, was apparently consistent with brain death. If sedation alone was to account for this finding, there would surely have to have been some increase in drug effect between 56 and 72 hrs after return of spontaneous circulation. The authors provided data on the amount of sedation, noting that the patient ("recorded weight 135 kg") received "2 μg/kg/hr of fentanyl for 20 hrs and 4 μg/kg/hr for 16 hrs (total of104 μg/kg)" between 14 and 50 hrs after return of spontaneous circulation. The total dose of fentanyl was thus approximately 14 mg. There was biochemical evidence of both renal and hepatic dysfunction at this time. The metabolism of fentanyl is poorly described in concomitant hypothermia, hepatic impairment, and renal impairment. The duration of fentanyl effect after prolonged infusions is greatly prolonged by renal dysfunction (21). Hepatic metabolism of fentanyl is reduced by hypothermia (22), probably by reduced hepatic blood flow. It is usually stated that the dominant metabolites of fentanyl are at most very weakly active (less than morphine) at opioid receptors (23). The possibility of "rebound" in plasma levels of fentanyl after rewarming from hypothermia has been suggested in an experimental model (24). Unfortunately, there were reportedly no stored blood samples available from this case, which might have retrospectively permitted toxicologic examination.

Finally, for completeness and without prejudice, it should be noted that a single dose of pancuronium (as an example of a neuromuscular blocker with markedly prolonged clearance in renal dysfunction) given (inadvertently) at some time between 56 and 72 hrs after return of spontaneous circulation, could have confounded this report. The authors report that no neuromuscular blockers were given and that neuromuscular transmission was therefore not tested. This practice accords with the American Academy of Neurology and other guidelines (20), which only recommend such testing "when NMBs have been administered." In light of (albeit infrequent) wrong-drug administration errors (25), or rarely even deliberate administration, perhaps such testing should always be carried out before clinical examination for brain death.

Whether this case truly represents "reversibility of brain death" or is another example of a situation in which clinical examination has been confounded remains, I believe, "unproven." How then should this report affect clinical practice? It further emphasizes the importance of meticulous attention to methodologic conformance with accepted guidelines (and documentation) and it highlights ways in which clinical examination might conceivably be confounded. It raises the issue of whether the intactness of neuromuscular transmission should be established on every occasion, not just when neuromuscular blockers are known to have been administered. Finally, it should encourage intensivists to submit all cases of apparently anomalous findings to peer review and worldwide collegial scrutiny, for the common good.

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