REVIEW ARTICLE

# Evidence-Based Management of Critically Ill Patients: Analysis and Implementation

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A number of important clinical trials focusing on critically ill patients have been completed in the last few years. These trials have been among the first critical care clinical trials to demonstrate mortality reduction in the critically ill. As in any adaptation of evidence-based medicine, it is essential to closely examine the trials and to determine whether the demonstrated benefits can be translated to the individual patient. In addition to the primary outcome, usually survival benefit, it is also important to examine cost-effectiveness. All of the trials examined in this review were able to demonstrate mortality reduction. Most focused on patients with severe sepsis, because this population has been associated with both frequent mortality and increased hospital costs. Some of the interventions, such as small tidal volume mechanical ventilation in patients with acute lung injury or the administration of low-dose corticosteroids for patients with septic shock, are cost-effective and relatively simple to implement. Others, such as use of activated protein C in patients with severe sepsis or "tight" glycemic control in patients with hyperglycemia, require either significant pharmaceutical expenditure or, possibly, additional health care personnel. Nevertheless, the trials discussed represent significant advances in the field of critical care medicine and should at least be considered for implementation in all intensive care units.

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A number of large clinical trials over the past 3 yr have provided an evidence base for optimizing the care of patients with critical illness. This review examines five randomized, prospective clinical trials published since 2000 that have changed the management of critically ill patients, especially those with severe sepsis (1–5). These five trials were chosen on the basis of their success in reducing mortality in critically ill patients. Although the standard of care cannot be established by a single trial, the results of these trials are robust enough to support at least consideration of practice change in the intensive care unit (ICU). As in any adaptation of evidence-based medicine to individual treatment decisions, careful consideration should be given to patient differences that may affect therapeutic efficacy. The purpose of this review is to critically examine these trials, highlight their strengths and weaknesses and, most importantly, focus on potential implementation problems.

## Identification of Patients with Severe Sepsis

Because of the prevalence, severity, and cost of severe sepsis, most studies discussed in this review enrolled patients with severe sepsis. Severe sepsis is the physiologic response to overwhelming infection. The prevalence of this disorder has been shown to be as high as 3 cases per 1000 in the United States (US), with enormous economic consequences, including expenditures of nearly $17 billion annually (5). To study patients with sepsis and identify appropriate patients for treatment, standard definitions need to be used. In 1992, the American College of Chest Physicians and the Society of Critical Care Medicine published the results of a consensus conference that established definitions of sepsis (Table 1) (6). The importance of these definitions includes the fact that they establish the importance of the systemic inflammatory response syndrome in identifying the presence of severe sepsis. Most clinical trials in patients with severe sepsis have enrolled such patients as defined by the consensus conference. These patients are thought to be ill enough

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**Table 1.** American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Definitions for Sepsis, Adapted from Reference 2

| Definition | Criteria |
|---|---|
| Infection | Inflammatory response to microorganisms or invasion of normally sterile tissues |
| SIRS (systemic inflammatory response syndrome) | Clinical response to infection manifested by ≥2 of the following:<br>Temperature ≥38°C or ≤36°C<br>HR ≥90 bpm<br>Respirations ≥20 breaths/min<br>WBC count ≥12,000/μL or ≤4,000/μL or >10% immature neutrophils |
| Sepsis | Confirmed or suspected infection plus ≥2 SIRS criteria |
| Severe sepsis | Sepsis and ≥1 organ dysfunction |
| Septic shock | Sepsis plus hypotension (<90 mm Hg) despite fluid resuscitation |

HR = heart rate; WBC = white blood cell.

to have life-threatening sepsis, but not so ill as to be refractory to intervention. Whereas it is relatively simple to identify patients in shock, a patient with small urine output and tachypnea without hypotension also meets criteria for severe sepsis. Limitations of the consensus definitions include subjective assessments and lack of specific fluid resuscitation recommendations. A more recent consensus conference recommended adoption of the PIRO model to more effectively identify and track patients with sepsis (7). PIRO represents 1) the predisposition of patients to respond in differing ways to infection, including genetic predisposition and preexisting disease; 2) infection, recognizing that different infections may lead to different responses in different patients; 3) response, which recognizes that physiologic responses may vary, as may serum levels of inflammatory markers; and 4) organ dysfunction, recognizing the interactions between failing organs (Table 2). Now that there are effective clinical interventions for severe sepsis, awareness of this syndrome needs to be increased.

**Table 2.** PIRO[a] Model of Sepsis Syndrome

| Signs and symptoms of sepsis |
|---|
| Chills |
| Unexplained altered mental status |
| Tachycardia |
| Immature neutrophils |
| Decreased urine output |
| Poor capillary refill |
| Petechiae |
| Tachypnea |
| Decreased platelets |
| Altered WBC count |
| Decreased skin perfusion |
| Skin mottling |
| Hypoglycemia |

[a] PIRO indicates predisposition, infection, response, and organ dysfunction. Predisposition refers to genetic predisposition or contribution from coexisting illness. Infection represents different responses to different organisms in diverse patients. Response describes the inflammatory markers made by a variety of cells, which may allow early identification of the deleterious response to infection. Organ dysfunction identifies the interaction of diverse organs in leading to multiple organ dysfunction (7).
WBC = white blood cell.

## Pathophysiology of Sepsis Syndrome

Sepsis syndrome represents the systemic response to overwhelming infection. Substantial preclinical and clinical experimental work has identified the interaction between bacterial antigens and circulating leukocytes as the event that starts the inflammatory cascade leading to sepsis (8,9). This interaction is governed by the innate immune response, consisting of both cellular elements (monocytes, neutrophils, and macrophages) and soluble proteins (cytokines, complement, and acute phase proteins). Macrophages may be the first line of defense, because they migrate to the site of infection and play a regulatory role in the initial response (10). Activated leukocytes release cytokines, particularly tumor necrosis factor (TNF) and interleukins-1 and -6. These cytokines in turn recruit additional leukocytes and activate transcription of genes for proinflammatory proteins. More recently, it has been recognized that sepsis and the resulting multiple organ dysfunction syndrome (MODS) result, at least partially, from abnormalities in the coagulation pathway. The same cytokines described above cause activation of the extrinsic coagulation pathway via tissue factor and also act to inhibit fibrinolysis by stimulating the release of thrombin-activatable fibrinolysis inhibitor and plasminogen activator inhibitor-1. Counterregulatory molecules, such as activated protein C (APC) and antithrombin III (ATIII), are depleted (11). The result of this systemic activation of the coagulation pathway is diffuse endothelial damage in multiple organs, leading to MODS and death. Nearly all patients with sepsis demonstrate at least one abnormality in the coagulation system (12). Until recently, no interventions in these pathways had been shown to decrease mortality in sepsis, and one, aimed at neutralizing TNF by using soluble TNF receptor, was halted because of increased mortality in the treatment group (13). The reasons why cytokine blockade and nonspecific antiinflammatory therapies such as large-dose corticosteroids have been unsuccessful in sepsis syndrome are complex. Although

these interventions are effective in animal models, results have not been reproducible in human clinical trials. It is likely that cytokines such as TNF and interleukin-1, although harmful at large concentrations, also serve an important physiologic role in host defense, and complete neutralization leads to increased mortality due to secondary infections.

## Endocrine Dysfunction in Critical Illness

Recently, clinical trials have focused on endocrine abnormalities in critically ill patients. Two areas in particular, "functional" adrenal insufficiency and "tight" glycemic control with insulin infusion, have led to large, prospective, randomized trials. Debate has long raged regarding steroid therapy for patients with septic shock. Critically ill patients, particularly those with septic shock, tend to have peripheral steroid resistance (14,15). In addition, steroids can reverse shock, but this increase in arterial blood pressure was not associated with improved survival (16). Whereas early trials demonstrated no benefit or harm from large-dose steroid treatment early in sepsis (17,18), smaller doses of steroids were not systematically examined. Annane et al. (19) identified that patients with septic shock frequently had relative adrenal insufficiency and that their response to corticotropin predicted survival. They pursued these findings with a randomized, placebo-controlled, prospective trial (2) of small-dose corticosteroids (hydrocortisone 50 mg/d for 7 days) in patients with severe sepsis. Patients were stratified according to their response to cosyntropin stimulation testing, with patients unable to increase cortisol levels by $>9$ $\mu$g/dL classified as adrenally insufficient. Approximately two thirds of the 300 patients enrolled showed adrenal insufficiency, and in those patients corticosteroid therapy resulted in a reduction in mortality rate from 63% to 53% ($P = 0.023$). In the patients with normal adrenal responsiveness who received corticosteroids, there was no survival benefit, nor was there an unadjusted mortality benefit for the combined groups.

How, then, should we treat critically ill patients with shock? Given the above data, treatment of all patients with small-dose corticosteroids is unreasonable. A more practical approach may be to perform adrenal responsiveness testing, give an initial dose of hydrocortisone, and then determine whether to continue corticosteroid therapy on the basis of the results of that testing. This recommendation has not been tested prospectively.

Critically ill patients are frequently hyperglycemic. The metabolic response to critical illness includes stimulation of the hypothalamic-pituitary-adrenal axis, resulting in increased growth hormone and prolactin levels. Growth hormone levels are high early in the course of critical illness and then typically become quite low. Takala et al. (20) demonstrated that growth hormone administered to patients with prolonged critical illness resulted in increased mortality when compared with placebo. Cortisol levels are usually increased, and these endocrine changes result in hyperglycemia. Catecholamines, both endogenous and exogenous, also contribute to the hyperglycemia of critical illness. Whereas previous practice was to treat only marked hyperglycemia (e.g., $>$200 mg/dL), more recent evidence suggests that control should be much more rigorous. van den Berghe et al. (4) performed a prospective, randomized trial of intensive insulin therapy in critically ill patients, most of whom had undergone cardiac surgery. The intervention group received an insulin infusion to maintain serum glucose concentration between 80 and 100 mg/dL, whereas the control group blood glucose was maintained between 180 and 200 mg/dL. ICU mortality was decreased in the treatment group from 8% to 4.6% ($P < 0.04$). In addition to mortality reduction, the patients with insulin infusion had fewer infections, decreased transfusion requirements, and a shorter duration of mechanical ventilation. The mechanism for this outcome is unclear. Possibilities include both the avoidance of hyperglycemia and a therapeutic effect of insulin.

Can the results of this study be extrapolated to other critically ill patients? Unlike patients in the other studies discussed, the patients in this study did not require a diagnosis of sepsis to be enrolled. It is possible that because of a longer length of stay, these patients may have obtained even greater benefit. This hypothesis, however, must be tested prospectively.

A recently published prospective observational study examined the effects of glucose control in 523 patients admitted to a single surgical ICU (21). In this trial, the primary determinant of a bad outcome was hyperglycemia rather than hypoinsulinemia. That is, less mortality was associated with glycemic control rather than with a protective effect of insulin administration. Indeed, increased insulin dosing was associated with increased mortality across all ranges of glycemia. These data suggest that keeping blood glucose less than 140 mg/dL may provide a survival benefit similar to that with the "tighter" range of 80–110 mg/dL used by van den Berghe et al. (4).

Synthesis of these two studies is difficult. There is agreement that hyperglycemia is associated with increased mortality, but it remains unclear whether this is a function of insulin resistance or whether control of hyperglycemia with large doses of insulin is harmful. Implementation of strict glucose control protocols is difficult. For example, implementation of a similar protocol in our 24-bed medical/surgical ICU required extensive nurse and physician training. Episodes of hypoglycemia need to be monitored and additional glucose measuring equipment needs to be purchased.

Should all patients treated with the protocol have arterial lines in place? Multiple finger sticks in patients with ischemic digits can be painful and may lead to potential complications. Finally, a workflow analysis revealed that for a nurse to care for 2 patients on the protocol would require nearly 2 h of a 12-h nursing shift. Where does this additional time come from?

## Mechanical Ventilatory Support

Most patients with sepsis syndrome have a component of respiratory failure that frequently leads to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) and the need for mechanical ventilation. Patients who develop ALI or ARDS as a consequence of sepsis syndrome have higher mortality than patients who develop ALI or ARDS from other clinical conditions (22). In addition to appropriate antibiotic therapy, the manner in which these patients are mechanically ventilated significantly affects outcome. In a large, multicenter, prospective trial of traditional (12 mL/kg ideal body weight (IBW)) versus low (6 mL/kg IBW) tidal volume in patients with ALI, the patients ventilated with small tidal volume had a 31% mortality, whereas in patients treated with larger tidal volume, mortality was 39.8% ($P < 0.007$) (1). These patients had both improved respiratory function and decreased MODS. The mechanism whereby this lung-protective ventilation strategy decreased mortality is not entirely clear, but it is thought to be due to decreased pulmonary cytokine release into the systemic circulation. Ventilation of injured lungs with large tidal volumes leads to cytokine release into the alveolar and intravascular space and potentiates lung injury (23). Large tidal volume ventilation has also been demonstrated in an animal model to increase translocation of bacteria across the lung and into the circulation, worsening septic physiology (24,25). Recently, the ARDSnet trial has been criticized; it has been suggested that tidal volume in the control arm was too large, causing harm (26). This criticism has been carefully rebutted (27), and at this time, small tidal volume ventilation represents the standard of care for patients with ALI.

## Early Goal-Directed Resuscitation

The standard of care for critically ill patients remains largely supportive. Early identification of these patients, however, may decrease mortality by rapid intervention. Resuscitation of patients in shock is essential. Whereas there is little evidence that the type of resuscitation fluid is important (colloid versus crystalloid) (28), there is evidence that early optimization of hemodynamic status can have a significant mortality benefit. In a randomized, prospective trial of patients with septic shock, Rivers et al. (29) demonstrated that early, goal-directed resuscitation guided by central venous oxygen saturation decreased in-hospital mortality from 46.5% in the standard treatment group to 30.5% in the early goal-directed therapy group ($P < 0.009$). These patients were treated by protocol in the emergency department for 6 h before admission to the ICU.

Although the Rivers et al. (29) study has generated significant enthusiasm because of its mortality benefit, additional analysis is required before broad implementation. Although it was not a trial of supranormal oxygen delivery, the treatment group did receive additional inotropic therapy. Interestingly, the Rivers et al. study is in agreement with those by Boyd et al. (30) and Wilson et al. (31), which studied surgical patients prospectively, in contrast to those of Hayes et al. and Gattinoni et al., both of which studied primarily medical patients in whom severe sepsis was well established (32,33). The Hayes et al. and Gattinoni et al. studies found harm and no effect, respectively, in medical patients treated with supranormal oxygen delivery.

How, then, do we interpret the findings of the Rivers et al. (29) study? The most important difference between this study and those that preceded it may well be the early, rapid intervention (in the emergency department). Other factors may include the short duration of therapy (only 6 h) and the strict protocol used, which included transfusion to a hematocrit of 30% and increased the use of dobutamine in the treatment group.

If early goal-directed therapy is to be implemented, there are a number of important considerations: 1) therapy should be initiated as early as possible, ideally in the emergency department; 2) this therapy requires the use of a central venous oxygen saturation catheter and monitoring device, the cost of which is significantly more than a traditional central venous or pulmonary artery catheter; 3) patients with low central venous oxygen saturation are transfused to a hematocrit of 30%, a controversial practice (34); and 4) patients with acute coronary syndromes should be excluded. Given these caveats, it is likely that early, protocol-driven resuscitation is superior to delayed resuscitation. Whether the use of central venous oximetry is applicable in other populations, particularly those with longer-standing septic physiology, remains untested. Implementation of early goal-directed therapy will require close collaboration with the emergency department, because these patients need rapid treatment either in the emergency department or immediately upon arrival in the ICU. If the primary benefit of this therapy is that intervention was earlier and given the, at best, mixed results of later intervention with goal-directed therapy, it may well be important to use this therapy only if it can be achieved early.

**Table 3.** Summary of Evidence-Based Management of Critically Ill Patients

| Intervention | Control mortality (*n*) | Intervention mortality (*n*) | *P* value | NNT |
|---|---|---|---|---|
| Goal-directed resuscitation (28)[a] | 46.5% (133) | 30.5% (130) | 0.009 | 7 |
| Small-dose corticosteroids (2)[b] | 63% (115)[c] | 53% (114)[c] | 0.02 | 10 |
| Lung-protective ventilation strategy (1)[a] | 39.8% (429) | 31% (432) | 0.007 | 12 |
| Tight glycemic control (4)[a] | 10.9% (783) | 7.2% (765) | 0.01 | 28 |
| Activated protein C treatment (3)[b] | 30.8% (840) | 24.7% (850) | 0.005 | 17 |

NNT = number of patients needed to treat to achieve survival benefit.
[a] In-hospital mortality.
[b] Twenty-eight-day mortality.
[c] Subset of patients with evidence of relative adrenal insufficiency.

Early goal-directed therapy may have no benefit or may even be harmful if it is used later in the course of severe sepsis.

## Manipulation of the Coagulation Pathway: APC

Since the pathophysiology of sepsis and MODS has been demonstrated to include activation of the coagulation pathway, several investigations have focused on trying to decrease morbidity and mortality by manipulation of this process. For example, it has been recognized that children with meningococcemia develop severe coagulation abnormalities characterized by disseminated intravascular coagulation and diffuse thrombosis (35). The thrombosis may cause limb loss and contributes to MODS. These patients with meningococcemia have low levels of APC, a vitamin K-dependent clotting factor that has multiple effects. Protein C, when bound to the thrombomodulin/thrombin complex, is cleaved to form APC. Protein C is a critical protein that functions to regulate excessive thrombosis in the microcirculation. APC blocks factors Va and VIIIa, inhibiting thrombin generation and, therefore, excessive coagulation (36). In addition, APC inhibits plasminogen activator inhibitor-1 and thrombin-activatable fibrinolysis inhibitor, naturally occurring inhibitors of fibrinolysis. This function allows clearance of abnormal endothelial fibrin, which likely contributes to continuing inflammation and cytokine release. Finally, APC decreases the expression of endothelial cell adhesion molecules that, when expressed, bind and activate circulating neutrophils. Other important proteins that regulate excessive coagulation and that have been tested as therapeutic targets in sepsis include ATIII and tissue factor pathway inhibitor (TFPI).

Recognition of the regulatory effects of APC led to the development of recombinant APC. This compound was tested in a randomized, prospective, double-blinded, placebo-controlled trial in patients with severe sepsis (PROWESS; Protein C Worldwide Efficacy Trial in Severe Sepsis) (3). The trial was halted after enrollment of 1690 patients because of efficacy in the treatment group. The patients treated with APC had a mortality of 24.7%, whereas those given placebo had a mortality of 30.8% ($P = 0.005$). The treated patients also had an increased risk of significant bleeding (3.5% versus 2.0%). This bleeding was the most important adverse effect identified in the trial. PROWESS was the first successful therapeutic trial for patients with severe sepsis. Interestingly, whereas APC was effective, ATIII and TFPI, both of which were highly successful in phase II trials and which act in a manner similar to APC, were unsuccessful when tried in a similar patient population with severe sepsis (37,38). Why APC was successful may relate to its pleiotropic effects. In particular, APC has profibrinolytic activity, whereas ATIII and TFPI do not; they primarily act as anticoagulants.

Has treatment with APC become the standard of care? It is difficult to determine this standard on the basis of a single clinical trial. The trial was large and multicentered, and although APC treatment provided significant survival benefit, it remains controversial (39,40). Criticism of the PROWESS trial includes the patient selection criteria and the bleeding risk. The major risk from APC is bleeding. With open-label use of APC after completion of the PROWESS trial, 2.5% of patients had intracranial hemorrhage (39). Bleeding risk was especially increased in patients with platelet counts $<30{,}000/\mu L$ or with an international normalized ratio more than 3.0. In a retrospective analysis, it appears that all of the benefit of APC was in the sickest 50% of patients when determined by Acute Physiology and Chronic Health Evaluation (APACHE II) scoring. On this basis, the US Food and Drug Administration has mandated a randomized, placebo-controlled trial enrolling patients with less illness severity to determine efficacy in this patient population.

There is no doubt that this therapy is expensive, costing approximately $7000 per course. In a separate economic analysis, Manns et al. (41) predicted that the cost of therapy would be $28,000 per quality year of life saved and that in the 50% of patients enrolled with APACHE II scores <25 (the median APACHE II

score), the cost would be more than $500,000. This issue and others remain to be solved by subsequent trials with APC. Until then, APC is the only specific pharmacotherapy to demonstrate efficacy in severe sepsis.

When to treat patients with APC is now a clinical decision that must be made by intensivists. A practical approach is to first optimize patient care according to the best evidence-based practices discussed previously. Patients who have been appropriately resuscitated, are considered at risk of death, and do not have an excessive risk of bleeding should be treated with APC, because the evidence supporting this practice is robust.

## Summary

The management of patients with severe sepsis has changed profoundly in the last 3 yr. Whereas these patients were previously treated with supportive care, we now have multiple, evidence-based practices that have been demonstrated to decrease mortality. Table 3 summarizes the major trials discussed and the strength of the evidence supporting their implementation. These practices should be considered for adoption in all modern ICUs. With the increasing incidence of this devastating disease, additional therapies are desperately needed to decrease the substantial morbidity and mortality from sepsis syndrome.

With the promise offered by these therapies comes the sobering reality of implementation. More than just cost, these therapies can have significant complications (hypoglycemia with insulin infusion or bleeding with recombinant human APC) that are potentially devastating. Other implementation barriers include the demands on limited resources (physicians and nurses). All the trials described used rigid protocols with strict inclusion and exclusion criteria. The difficulty for the clinician lies in deciding whether an individual patient, who may or may not meet all the study criteria, will benefit from these therapies. Perhaps this is one of the key underpinnings of another evidence-based practice: the use of trained intensivists to decrease mortality in critically ill patients (42).

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