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Evidence-Based Medicine in the ICU: Important Advances and Limitations

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special report

Evidence-Based Medicine in the ICU*

Important Advances and Limitations

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Evidence-based medicine (EBM) is an important strategy for assessing the vast amounts of published data and applying them appropriately to our patients. However, in intensive care medicine, there is a shortage of "gold standard" randomized controlled trial evidence to support (or not support) therapeutic decisions. In addition, even when well-conducted randomized trials have been performed, we are still left with unanswered questions. In the last 5 years, several clinical trials have yielded positive results with a number of interventions being shown to improve outcomes. Here, we will outline the limitations and advances of EBM in intensive care medicine, by discussing the key findings in the last few years from studies of therapeutic agents for ICU patients. ***(CHEST 2004; 126:592–600)***

Key words: data analysis; randomized controlled trials; sepsis

Abbreviations: ALI = acute lung injury; APACHE = acute physiology and chronic health evaluation; EBM = evidence-based medicine; EGDT = early goal-directed therapy; RCT = randomized controlled trial; $ScvO_2$ = oxygen saturation in the superior vena cava; SDD = selective digestive decontamination; TNF = tumor necrosis factor

Evidence-based medicine (EBM), the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients,"[1] has become a key byword of modern medicine. EBM helps us to practice effectively and efficiently in a medical world where the latest technology is already old hat by the time it arrives in our hospitals and the scientific articles published in this month's leading journals are already dated. EBM is an ongoing process that adapts to the level of evidence available. EBM is not restricted to randomized controlled trials (RCTs) and meta-analyses. Thus, while the RCT provides the "best" evidence for or against performing an intervention or therapy, when no RCTs have been conducted in the field of interest, other forms of evidence can be graded to provide the answers to the question being posed. EBM can thus help in some of the "gray" areas of medicine, where information is incomplete, apparently conflicting, or of poor quality.[2] It can also help to identify those areas of practice that urgently need further higher quality studies and, hence, direct research agendas.[2]

Why So Little RCT-Based Evidence in Intensive Care Medicine?

Michaud et al[3] investigated the proportion of major therapeutic interventions in the internal medical department at their Canadian hospital that were justified by published evidence. They reported that $>60\%$ of the therapeutic clinical decisions were supported by RCT evidence, and in $<7\%$ of decisions was evidence found demonstrating that an alternative therapy was more effective than that selected. However, in intensive care medicine the situation is a little different, with RCT evidence frequently lacking. A few years ago, candidates for

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the board examination in intensive care medicine in Belgium were asked to list which accepted therapeutic interventions had been shown to reduce mortality by RCT in ICU patients.[4] The majority of the 46 examinees were unable to provide an answer. The therapeutic interventions most often cited by the candidates were the open-lung approach in ARDS,[5] early nutritional support, and supranormal oxygen delivery. In 1999, a questionnaire was delivered to the participants of the 19th International Symposium on Intensive Care and Emergency Medicine, which was held in Brussels.[6] Here, the participants were asked to draw up a list of all prospective RCTs evaluating the effects of therapeutic interventions on mortality in adult ICU patients. The survey was self-administered, voluntary, and anonymous. The effective interventions listed included cardiology interventions (*ie*, thrombolytic therapy or therapy with β-blocking agents in patients with acute myocardial infarctions), followed by the administration of N-acetylcysteine in patients experiencing acetaminophen overdoses. Fluid challenge and noninvasive mechanical ventilation also were listed. The possible harmful interventions that were listed included the administration of growth hormones, corticosteroid use in patients with early ARDS, the nitric oxide synthase inhibitor N(G)-monomethyl-L-arginine in patients with severe sepsis, and corticosteroids in patients with severe head trauma. This study confirmed that few ICU interventions have been tested in RCTs and that there were also misconceptions about the RCTs that had been conducted. In particular, many ICU interventions not tested in RCTs are believed to have been tested.

RCT evidence can be lacking for several reasons. First, many treatment strategies are, in fact, lifesaving (*eg*, the use of mechanical ventilation in respiratory failure, the use of blood transfusions in acute hemorrhage, the administration of vasopressor agents in severe shock, and the use of pacemakers in advanced heart block) and could not ethically be put to the RCT test. A second reason is that the ICU population is very heterogeneous, so that it is difficult to show the impact of acute interventions on long-term outcomes. These limitations to RCT design in critically ill patients are relatively difficult to modify. Improving the characterization of critically ill patients may be one way by which study populations can be more effectively grouped, thus reducing the heterogeneity and potential overlap of positive and negative effects. The recent Sepsis Definitions Conference[7] suggested the use of the predisposing factors, infectious insult, immune response, and organ dysfunction system as one means of staging disease development and hence characterizing patients, although this system is in its early stages of development. Genetically based factors and microarray technology are just two of several new technologies that may also provide a means of classifying more homogeneous patient populations.

Actually, the intensive care medicine literature has included more negative trials than positive trials.[8,9] A number of therapeutic strategies have not been shown to be helpful in patients with severe sepsis and septic shock, including high doses of corticosteroids,[10] ibuprofen,[11] anti-tumor necrosis factor (TNF) antibodies,[12,13] TNF receptors,[14] interleukin-1 receptor antagonist,[15] and various platelet-activating factor antagonists.[16,17] Likewise, many studies have been negative in the field of the management of acute lung injury (ALI) or ARDS, including the administration of nitric oxide by inhalation,[18] the administration of surfactant,[19] or the use of different modes of mechanical ventilation. Some interventions have even resulted in worse outcomes, including the use of a TNF receptor in patients with severe sepsis,[20] excessive doses of dobutamine in acutely ill patients,[21] the administration of hemoglobin solutions in trauma patients,[22] and the administration of growth factors.[23] IV fluids, including albumin and RBC transfusions, have been areas of hot debate over the last few years, and even monitoring systems, especially the pulmonary artery catheter, have created controversy. Even some routine practices like mechanical ventilation and sedation may result in worse outcomes. Hence, we end up with a longer list of things to avoid than things to be done!

The Last 5 Years

In the last 5 years, however (finally), we have made some more positive strides in clinical trial results, with a number of interventions having been shown to result in better outcomes.

Noninvasive Mechanical Ventilation

Endotracheal intubation is associated with a number of complications and may unduly prolong the need for mechanical ventilation. A number of studies have emphasized that the use of noninvasive mechanical ventilation could result in lower morbidity rates and even lower mortality rates in patients with COPD.[24,25] The use of noninvasive mechanical ventilation can also significantly reduce the incidence of ventilator-associated pneumonia.[26–28] This technique has found a significant place in modern ICUs, although the benefits in hypoxemic respiratory failure are less well-established.

Important Outstanding Issues: Is noninvasive mechanical ventilation really applied optimally ev-

erywhere? The use of noninvasive mechanical ventilation requires specialized personnel, and limitations in the number of professionals and the degree of expertise may result in less beneficial outcomes. On the other hand, pushing noninvasive mechanical ventilation to its limits may result in catastrophe (*ie*, respiratory arrest), especially in severely hypoxemic patients.

Induced Hypothermia After Cardiac Arrest

Hypothermia can substantially decrease cellular oxygen demand, including that of the neurons, and these observations have led to a number of attempts to induce hypothermia following severe neurologic insults. Although the place of induced moderate hypothermia in patients with severe brain injury has not been clearly established, two studies[29,30] have indicated that hypothermia, when induced as soon as possible after cardiac arrest, may improve neurologic outcomes. Hypothermia in these conditions should be instituted as early as possible and for at least 12 h.

Important Outstanding Issues: To be effective, hypothermia should be instituted as soon as possible, and the techniques used to cool the body may not all have similar efficacy. If timing is such an important issue, hypothermia that is induced in the ambulance with the use of cooling IV catheters and other active measures may yield better outcomes than that induced in the ICU with cooling blankets after an initial period of evaluation that may take several hours.

Prevention of Radiocontrast Agent-Induced Nephropathy

In a recent prospective RCT, Marenzi et al[31] showed in 114 patients with chronic renal failure (creatinine concentration, > 2 mg/dL) that hemofiltration at a rate of 1 L/h in the ICU, initiated 4 to 8 h before a percutaneous coronary intervention, may result in less organ dysfunction than more standard saline solution hydration at a rate of 1 mL/kg/h. The hospital mortality rate was significantly reduced (2% vs 14%, respectively; $p = 0.02$), and even the 1-year mortality rate was lower in the treated patients (10% vs 30%, respectively; $p = 0.01$).

Important Outstanding Issues: The data may need to be reproduced in a larger patient population in a multicenter study before they are widely applied. In addition, an important question is whether we are able to apply this procedure, especially in view of potential limitations in ICU beds and current resource restraints.

Intensive Insulin Therapy in Critically Ill Patients

In a landmark study, Van den Berghe et al[32] randomized $> 1{,}500$ ICU patients to conventional management of hyperglycemia vs intensive management aimed at keeping blood sugar levels within tight limits of 80 to 110 mg/dL. This intensive strategy decreased mortality rates from 8.0 to 4.6% ($p < 0.04$). Moreover, the intensive treatment was associated with significantly fewer patients staying for > 14 days in the ICU, a lower requirement for renal replacement therapy, a lower incidence of hyperbilirubinemia, fewer bloodstream infections, fewer ICU neuropathies, and a reduced need for transfusion.

Important Outstanding Issues: The study included a patient population with moderate disease severity, having a mean APACHE (acute physiology and chronic health evaluation) II score of only 9 and a mortality rate of only 8% in the control group. Moreover, almost two thirds of the patients were admitted to the ICU following cardiac surgery. How this protocol would apply to a population of more severely ill patients or to a medical population can be questioned. In addition, one may argue that these results need to be confirmed in a multicenter study. In particular, one should acknowledge that maintaining blood sugar within tight limits might increase the risks of hypoglycemia. Another important question is whether the beneficial result is due to the tight control of blood sugar or to insulin administration. Further analysis of the results by Van den Berghe et al[33] and those of another recent study by Finney et al[34] suggests that it is more the control of glucose levels than the absolute amounts of exogenous insulin that account for the survival benefit. Although nutritional support should be provided, together with therapy with exogenous insulin, these observations would not specifically support the use of mixtures of glucose, insulin, and potassium. Another issue is cost. Although one may argue that the strategy to maintain normoglycemia is cheap, this may not be the case if serial blood sugar measurements require additional blood sampling, nursing time, and additional glucose analyzers.

Blood Transfusions

A key multicenter Canadian study published by Hebert et al[35] changed our blood transfusion practice. In this prospective RCT involving 25 Canadian centers, patients with a hemoglobin concentration below 9 g/dL were randomized to either a liberal blood transfusion strategy (*ie*, maintaining hemoglobin levels at > 10 g/dL) or a restricted blood transfusion strategy (*ie*, maintaining hemoglobin levels at

> 7 g/dL).[35] The former group received a mean amount of 5.6 U RBCs to raise the hemoglobin concentration from 8.2 to 10.7 g/dL, whereas the latter group received a mean amount of 2.6 U RBCs to raise the mean hemoglobin concentration from 8.2 to 8.5 g/dL. These were critically ill patients with an APACHE II score of about 21. The hospital mortality rate was 28% in the liberal transfusion group but only 22% in the restricted transfusion group, leading to a statistically significant difference ($p = 0.05$). Clearly, the differences in short-term outcome could not be related to different incidences of transfusion-related infections, but they could be due to more subtle alterations in immune function, perhaps resulting in a greater risk of subsequent infections. These results were later confirmed in a large European study including > 3,500 patients, the Anemia and Blood Transfusion in the Critically Ill study.[36] In this study, which was performed in November 1999, transfusions were associated with a worse outcome in a multivariable analysis. Blood transfusions came before hemoglobin concentration in this multivariable analysis, indicating that it is the blood transfusion, rather than the anemia, that is associated with a worse outcome. Moreover, the use of a propensity score to match patients who did or did not receive a blood transfusion indicated significant differences in mortality rates (22.7% vs 17.1%). However, a more recent European study, the Sepsis Occurrence in Acutely Ill Patients study,[37] also including > 3,000 patients and conducted in May 2002, failed to identify a worse outcome in transfused patients. These differences could be due to changes in the risks of blood transfusions and, in particular, to the now widely implemented leukodepletion programs. Indeed, the Canadian experience with universal leukoreduction programs indicated a reduction in mortality rates in patients after cardiac surgery or repair of hip fracture, or in those who required intensive care following a surgical intervention or multiple trauma,[38] as well as a reduction in neonatal morbidity.[39]

Important Outstanding Issues: Are the results of the study by Hebert et al[35] still valid? Perhaps the time has come to repeat this study to find out whether we have pushed the limits as far as is necessary (or too far), in terms of the restriction of blood transfusions.

Development of Drotrecogin Alfa (Activated) in Severe Sepsis/Septic Shock

Several studies have emphasized the complex interplay between coagulation and inflammation in the development of organ failure following sepsis. In one study,[40] the administration of drotrecogin alfa (activated) resulted in significant decreases in mortality rates in patients with severe sepsis and septic shock. The results of this study showed that the safety profile was certainly acceptable. Moreover, the results of a large study of > 2,300 patients, the ENHANCE trial,[41] which were presented at the 2003 American College of Chest Physicians meeting, support the beneficial effects of drotrecogin alfa (activated) on outcome. The mode of action of drotrecogin alfa (activated) has not been entirely elucidated, but it is clearly more than just an anticoagulant effect, especially in view of the negative results from studies with two other natural anticoagulants, antithrombin[42] and tissue factor pathway inhibitor.[43] The results of ongoing studies[44,45] have suggested that its mechanism of action includes antiinflammatory and antiapoptotic protective effects on endothelial cells.

Important Outstanding Issues: The application of these exciting results into clinical practice has been rather slow, certainly in part because of the high costs of this new therapeutic agent. It may also be due to the absence of an immediately visible effect, as no variable can be used to titrate the administration of the drug. Also, the results of therapy with tissue factor pathway inhibitor have been difficult to understand. In the phase III clinical trial including > 1,700 patients,[43] the mortality rates were around 34% in the tifacogin and placebo groups. However, at the time of an interim analysis that included the first 722 patients, the mortality rate was 38.9% in the placebo group but only 29.1% in the tifacogin group ($p = 0.006$). This suggests not only that the study would have been positive if it had been planned to include only the first 722 patients, but also that the treatment was rather harmful in the second half of the study. The reasons for these differences are unclear.

Some people do not prescribe activated protein C because they believe it is too expensive, but is this the correct way to react? We ask for good RCTs and then, when we have them, we do not apply the data. Under such conditions, will the industry continue to develop new strategies?

Other Interventions in Severe Sepsis

Another intervention that led to controversial results is bactericidal permeability-increasing protein. This natural substance that is released by leukocytes can combine with endotoxin to eliminate it. It was, therefore, natural to look for a homogeneous disease state characterized by a massive endotoxin release (*eg*, meningococcemia) to test this agent. In the

largest study involving acutely ill children,[46] 393 patients were randomized to receive either recombinant bactericidal permeability-increasing protein or placebo. This study missed the end point of a significant reduction in mortality rates, but the mortality rate was only 9.9% in the placebo group vs 7.4% in the treated group ($p = 0.48$). In this study, the number of patients with full functional recovery was only 66.3% in the placebo group but was 77.3% in the treated group ($p = 0.02$).

Important Outstanding Issues: This study emphasizes the relatively low mortality rates that were observed in severely ill children, especially when time delays for the patient to reach the ICU and for parents to sign the informed consent form are considered. It also emphasizes the need to investigate the effects of interventions on morbidity and not only on mortality.

Steroids in Septic Shock

The initial studies[47] investigating the effects of massive doses of methylprednisolone (30 mg/kg) in patients with septic shock did not show any benefit. More recent studies have indicated that patients with septic shock may have relative adrenal sufficiency and, therefore, may benefit from moderate doses of hydrocortisone (around 200 mg/d). A French RCT by Annane and coworkers[48] indicated that such a strategy may decrease mortality rates in patients with septic shock.

Important Outstanding Issues: Some have challenged the positive findings of this study as the differences in mortality rate at 28 days failed to reach statistical significance. Also, a big question is whether steroid administration should be guided by adrenocorticotropin stimulation tests, and, if so, which tests?

Vasopressin Administration in Septic Shock

The important concept of relative vasopressin deficiency was introduced by Landry et al[49] in 1997 when they observed that vasopressin levels were remarkably elevated in patients who were in cardiogenic shock but not in those in septic shock. A number of subsequent observations[50,51] have indicated that vasopressin administration could raise BP in septic shock patients and help to decrease the need for norepinephrine therapy. Some studies in animals[52] and in patients[50] also have suggested an improvement in urine output with this therapeutic strategy. Actually, a number of critical care physicians have already adopted this strategy and have used vasopressin in patients with severe septic shock.

Important Outstanding Issues: The vasopressor effects of vasopressin are certainly not surprising, so that reduced requirements for norepinephrine are expected. Vasopressin administration, however, has substantial risks, including pulmonary hypertension and a relative decrease in hepatosplanchnic blood flow. This is precisely why vasopressin was used in the management of bleeding esophageal varices before it was replaced by somatostatin. There is also the risk that vasopressin will be titrated according to BP levels, whereas the concept is more one of hormone replacement with low, fixed doses of this substance. Hence, it would be wise to wait for the results of a multicenter double-blind RCT before administering this hormone routinely in septic shock patients.

Early Goal-Directed Therapy in Severe Sepsis and Septic Shock

How to optimize the treatment of severe sepsis and septic shock has been an important question, especially after the disappointing results of strategies aimed at raising oxygen delivery to supranormal levels.[21] In a single-center RCT, Rivers et al[53] randomized patients with sepsis, arterial hypotension, and/or hyperlactatemia to a standard resuscitation regimen or to so-called *early goal-directed therapy* (EGDT) guided by continuous measurements of oxygen saturation in the superior vena cave ($ScvO_2$) using a modified central venous catheter that was equipped with fiberoptic fibers. In addition to the standard oxygenation, fluid infusion, and vasoactive drug strategies, the authors maintained $ScvO_2$ at least at 70% in the EGDT group using additional fluids, blood transfusions, or dobutamine administration. In the first 6 h following resuscitation, there was no difference in the number of patients receiving vasopressors or mechanical ventilation, but the quantity of IV fluid was significantly greater in the EGDT group. Patients in the intervention group also received blood transfusions and dobutamine more commonly. Interestingly, the total amount of fluid administered during the first 72 h was similar in the two groups of patients, and the number of patients requiring vasopressor therapy, mechanical ventilation, or monitoring with a pulmonary artery catheter was lower in the EGDT group than in the control group.

Important Outstanding Issues: Although the results of this study are most interesting, there are several possible interpretations:

1. One could argue that adequate resuscitation reduced mortality rates, but also that suboptimal management could have resulted in higher mortality rates in the control group. After all,

the standard treatment was possibly suboptimal in this very busy emergency department.
2. Did the early aggressive resuscitation reduce mortality rates, or were they related to the $ScvO_2$ monitoring? In other words, is this particular catheter needed to achieve these better results?
3. One could argue that a pulmonary artery catheter is useless because $ScvO_2$ is a surrogate variable for mixed venous oxygen saturation, or, alternatively, that the pulmonary artery catheter may actually be useful in providing mixed venous oxygen saturation measurements. If the latter is true, even better results may be obtained with pulmonary artery catheterization.
4. One could argue that liberal blood transfusions can reduce mortality (see the controversy about blood transfusions above) or that liberal dobutamine administration can reduce mortality (these results would be opposed to those by Hayes et al[21]).

Whatever our interpretation of the results of this study, the need to rapidly resuscitate the patient with severe sepsis and septic shock is emphasized, leading to the concept of the *septic clock*.

Selective Decontamination of the Digestive Tract

The routine administration of an antibiotic mixture in the form of an oral paste to reduce the risk of nosocomial infections in ICU patients started initially in Groningen, the Netherlands,[54] but it has led to great controversy. Moreover, the topical antibiotic administration must optimally be accompanied by the systemic administration of a broad-spectrum antibiotic like a third-generation cephalosporin. Several meta-analyses have indicated that selective decontamination of the digestive tract (SDD) may be associated with reduced morbidity rates, and even reduced mortality rates, and yet this strategy has not been implemented largely because of the risk of the emergence of resistant organisms. Recently, de Jonge et al[55] published the results of an impressive prospective RCT including 934 patients. In this study, the ICU mortality rate was 23% in the control group but was only 15% in the SDD group ($p = 0.002$). Most interestingly, the incidence of resistant Gram-negative organisms was 26% in the control group but only 16% in the treated group ($p = 0.001$).

Important Outstanding Issues: Should you apply SDD in your ICU? In an accompanying editorial,[56] I raised the issue of the actual rate of antimicrobial resistance in each ICU. Indeed, methicillin-resistant *Staphylococcus aureus* is remarkably rare in Amsterdam, and the rate of vancomycin-resistant enterococcus is also remarkably low. Thus, the results may not immediately apply to other institutions having much greater problems with antimicrobial resistance. In addition, many experts are worried about the long-term emergence of resistant bacteria under increased antibiotic pressure. Such effects may not be apparent in the normal analysis of short-term study results.

ARDS Management

As outlined above, there is little proof that anything can reduce mortality among ARDS patients. Maybe the application of open-lung strategies, as proposed by Amato et al,[5] may improve outcomes, but the optimal setting of positive end-expiratory pressure is still controversial. An important study by the ARDS Network,[57] including 361 patients, showed that ventilating patients with ALI/ARDS with a tidal volume of 6 mL/kg resulted in better outcomes than when a tidal volume of 12 mL/kg was used (mortality rate, 31.0% vs 39.8%, respectively).

Important Outstanding Issues: The study protocol raised a serious dispute over the use of a tidal volume of 12 mL/kg in the control group. Indeed, this tidal volume may be higher than that usually applied in the ICU.[58] It is often claimed that this was a positive step (if not a new strategy) in the management of ALI. The interpretation that I and many others prefer is rather that a tidal volume of 12 mL/kg is worse than a tidal volume of 6 mL/kg. In other words, that using large tidal volumes is harmful. Whether or not a tidal volume of 6 mL/kg should be applied in all patients with ALI is debatable, especially if this requires increased sedation and maybe even a need for a paralytic agents. If the airway pressures are not excessively high, maybe keeping the tidal volume at around 7 or 8 mL/kg may not necessarily be harmful.

Protocol for Sedation

The excessive administration of sedative agents may prolong ICU stays because of progressive awakening and/or an increased incidence of polyneuropathy. In addition, a persistently altered mental status may lead to additional diagnostic testing with, for example, head CT scans to eliminate pathologic intracranial processes. Kress et al[59] showed in a RCT including 128 patients that the daily interruption of sedative infusions could decrease the duration of mechanical ventilation (4.9 vs 7.3 days, respectively; $p = 0.004$) and the duration of ICU stay (6.4 vs 9.9 days, respectively; $p = 0.02$), and could decrease the

use of diagnostic testing (9% vs 27% of patients, respectively; $p = 0.02$) without increasing the rate of complications.

Important Outstanding Issues: Maybe we should implement a protocol to interrupt sedation daily. However, such a strategy, when applied without restrictions, may also carry some of the following risks: neurologic compromise (*eg*, increased oxygen demand for the brain); respiratory alterations (*eg*, discoordination); cardiovascular compromise (*eg*, tachycardia and hypertension); and, of course, possible patient discomfort. It may be just as effective to have an interactive discussion at the bedside systematically raising the question of optimal sedation.

Rounds at the Bedside: The Role of the Intensivist

Studies have consistently indicated that the presence of a properly trained critical care physician can have a significant impact on outcome.[60–62] Pronovost et al[63] also have indicated that rounds at the bedside may result in better outcomes. For effective bedside rounds, a battery of questions should be raised systematically in front of each patient (Table 1).

Important Outstanding Issues: In my opinion, this is one of the few areas of intensive care medicine in which there is no debate![64]

Conclusion

EBM is very important, and the RCT is the indisputable king of evidence, but, as we have seen, RCTs are not always possible to perform. Even when they are available, RCTs do not necessarily provide all the answers and may raise more questions than we started with. Each clinical therapeutic decision must, therefore, be made on the basis of the available evidence, to include RCTs whenever possible, but not to the exclusion of all other forms of evidence. Indeed, a balanced EBM approach relies on the integration of the best research evidence and clinical expertise to treat specific individual patients. Human factors are essential in this process. There is little use in knowing that an intervention is supported by high-grade evidence. It is the application of that knowledge that makes the difference in patient care. And in this application, the importance of good teamwork (*eg*, doctors, nurses, and physiotherapists) cannot be overemphasized.

Table 1—*Questions That Should Be Systematically Raised at the Bedside*

If the patient is mechanically ventilated, can he/she be weaned from mechanical ventilation?
Is pain controlled, is sedation well titrated, and does the patient need restraints?
Is nutrition adequate?
Is the head of the bed elevated?
Is deep venous thrombosis prophylaxis implemented?
Is ulcer prophylaxis implemented?

References

1 Sackett DL, Rosenberg WMC, Gray JAM, et al. Evidence-based medicine: what it is and what it isn't. BMJ 1996; 312:71–72

2 Cook DJ, Sibbald WJ, Vincent JL, et al. Evidence based critical care medicine: what is it and what can it do for us. Crit Care Med 1996; 24:334–337

3 Michaud G, McGowan JL, van der Jagt R, et al. Are therapeutic decisions supported by evidence from health care research? Arch Intern Med 1998; 158:1665–1668

4 Vincent JL. Which therapeutic interventions in critical care medicine have been shown to reduce mortality in prospective, randomized, clinical trials? Crit Care Med 2000; 28:1616–1620

5 Amato MB, Barbas CS, Medeiro DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338:347–354

6 Ferreira F, Vincent JL, Brun-Buisson C, et al. Doctors' perceptions of the effects of interventions tested in prospective, randomised, controlled, clinical trials: results of a survey of ICU physicians. Intensive Care Med 2001; 27:548–554

7 Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31:1250–1256

8 Vincent JL, Sun Q, Dubois MJ. Clinical trials of immunomodulatory therapies in severe sepsis and septic shock. Clin Infect Dis 2002; 34:1084–1093

9 Opal SM, Cross AS. Clinical trials for severe sepsis: past failures, and future hopes. Infect Dis Clin North Am 1999; 13:285–297

10 Bone RC, Fisher CJJ, Clemmer TP, et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987; 317:653–658

11 Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. N Engl J Med 1997; 336:912–918

12 Abraham E, Anzueto A, Gutierrez G, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumor necrosis factor in treatment of septic shock. Lancet 1998; 351:929–933

13 Reinhart K, Menges T, Gardlund B, et al. Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: the RAMSES Study. Crit Care Med 2001; 29:765–769

14 Abraham E, Laterre PF, Garbino J, et al. Lenercept (p55 tumor necrosis factor receptor fusion protein) in severe sepsis and early septic shock: a randomized, double-blind, placebo-controlled, multicenter phase III trial with 1,342 patients. Crit Care Med 2001; 29:503–510

15 Opal SM, Fisher CJ Jr, Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. Crit Care Med 1997; 25:1115–1124

16 Dhainaut JF, Tenaillon A, Hemmer M, et al. Confirmatory

platelet-activating factor receptor antagonist trial in patients with severe gram-negative bacterial sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial; BN 52021 Sepsis Investigator Group. Crit Care Med 1998; 26:1963–1971
17 Suputtamongkol Y, Intaranongpai S, Smith MD, et al. A double-blind placebo-controlled study of an infusion of lexipafant (platelet-activating factor receptor antagonist) in patients with severe sepsis. Antimicrob Agents Chemother 2000; 44:693–696
18 Lundin S, Mang H, Smithies M, et al. Inhalation of nitric oxide in acute lung injury: results of a European multicentre study; the European Study Group of Inhaled Nitric Oxide. Intensive Care Med 1999; 25:911–919
19 Anzueto A, Baughmann RP, Guntupalli KK, et al. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. N Engl J Med 1996; 334:1417–1421
20 Fisher CJ Jr, Agosti JM, Opal SM, et al. Treatment of septic shock with the tumor necrosis factor receptor: Fc fusion protein. N Engl J Med 1996; 334:1697–1702
21 Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994; 330:1717–1722
22 Sloan EP, Koenigsberg M, Gens D, et al. Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock: a randomized controlled efficacy trial. JAMA 1999; 282:1857–1864
23 Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 1999; 341:785–792
24 Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1995; 333:817–822
25 Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet 2000; 355:1931–1935
26 Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med 1998; 339:429–435
27 Nourdine K, Combes P, Carton MJ, et al. Does noninvasive ventilation reduce the ICU nosocomial infection risk?: A prospective clinical survey. Intensive Care Med 1999; 25: 567–573
28 Girou E, Schortgen F, Delclaux C, et al. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. JAMA 2000; 284:2361–2367
29 Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002; 346:557–563
30 Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002; 346:549–556
31 Marenzi G, Marana I, Lauri G, et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N Engl J Med 2003; 349:1333–1340
32 Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patient. N Engl J Med 2001; 345:1359–1367
33 Van den BG, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. Crit Care Med 2003; 31:359–366
34 Finney SJ, Zekveld C, Elia A, et al. Glucose control and mortality in critically ill patients. JAMA 2003; 290:2041–2047
35 Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999; 340:409–417
36 Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. JAMA 2002; 288:1499–1507
37 Vincent JL, Sakr YL, Carlet J et al. Sepsis occurrence in acutely ill patients (SOAP): results of a large European multicenter study [abstract]. Am J Respir Crit Care Med 2003; 167:A837
38 Hebert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. JAMA 2003; 289:1941–1949
39 Fergusson D, Hebert PC, Lee SK, et al. Clinical outcomes following institution of universal leukoreduction of blood transfusions for premature infants. JAMA 2003; 289:1950–1956
40 Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344:699–709
41 Wheeler AP, Doig C, Wright T, et al. Baseline characteristics and survival of adult severe sepsis patients treated with drotrecogin alfa (activated) in a global, single-arm, open-label trial (ENHANCE) [abstract]. Chest 2003; 124 (suppl):91S
42 Warren BL, Eid A, Singer P, et al. Caring for the critically ill patient: high-dose antithrombin III in severe sepsis; a randomized controlled trial. JAMA 2001; 286:1869–1878
43 Abraham E, Reinhart K, Opal S, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. JAMA 2003; 290:238–247
44 Joyce DE, Grinnell BW. Recombinant human activated protein C attenuates the inflammatory response in endothelium and monocytes by modulating nuclear factor-kappaB. Crit Care Med 2002; 30:S288–S293
45 Esmon CT. The protein C pathway. Chest 2003; 124(suppl): 26S–32S
46 Levin M, Quint BA, Goldstein B, et al. Recombinant bactericidal/permeability-increasing protein (rBPIZ1) as adjunctive treatment for children with severe meningococcal sepsis: a randomised trial. Lancet 2000; 356:961–967
47 Bone RC, Fisher CJ, Clemmer TP, et al. The methylprednisolone severe sepsis study group: a controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987; 317:353
48 Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002; 288:862–871
49 Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997; 95:1122–1125
50 Patel BM, Chittock DR, Russell JA, et al. Beneficial effects of short-term vasopressin infusion during severe septic shock. Anesthesiology 2002; 96:576–582
51 Malay MB, Ashton RC Jr, Landry DW, et al. Low-dose vasopressin in the treatment of vasodilatory septic shock. J Trauma 1999; 47:699–703
52 Sun Q, Dimopoulos G, Nguyen DN, et al. Low-dose vasopressin in the treatment of septic shock in sheep. Am J Respir Crit Care Med 2003; 168:481–486
53 Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345:1368–1377
54 Stoutenbeek CP, van Saene HK, Miranda DR, et al. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Med 1984; 10:185–192

55 de Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of the digestive tract on mortality and the acquisition of resistant bacteria in intensive care patients. Lancet 2003; 362:1011–1016
56 Vincent JL. Selective digestive decontamination: for everyone, everywhere? Lancet 2003; 362:1006–1007
57 The ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301–1308
58 Eichacker PQ, Gerstenberger EP, Banks SM, et al. Meta-analysis of acute lung injury and acute respiratory distress syndrome trials testing low tidal volumes. Am J Respir Crit Care Med 2002; 166:1510–1514
59 Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000; 342:1471–1477
60 Pronovost PJ, Angus DC, Dorman T, et al. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. JAMA 2002; 288:2151–2162
61 Higgins TL, McGee WT, Steingrub JS, et al. Early indicators of prolonged intensive care unit stay: impact of illness severity, physician staffing, and pre-intensive care unit length of stay. Crit Care Med 2003; 31:45–51
62 Blunt MC, Burchett KR. Out of hours consultant cover and case-mix-adjusted mortality in intensive care. Lancet 2000; 356:735–736
63 Pronovost PJ, Jenckes MW, Dorman T, et al. Organizational characteristics of intensive care units related to outcomes of abdominal aortic surgery. JAMA 1999; 281:1310–1317
64 Vincent JL. Need for intensivists in intensive-care units. Lancet 2000; 356:695–696

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