Can we reduce mortality in sepsis?

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ABSTRACT

Considerable progress has been made over the last 2 decades in diagnosing and treating sepsis. Although the mortality rate is beginning to decline with the development of new therapeutic interventions, it still remains unacceptably high. Five such interventions are discussed in this review article to provide guidance for intensivists on the integration and implementation of new interventions into the intensive care unit. They were shown in randomized, controlled trials to reduce mortality by limiting the tidal volume in acute lung injury or acute respiratory distress syndrome, the early goal directed therapy, the use of recombinant human activated protein C, the use of moderate doses of steroids and the tight control of blood sugar. Each new intervention has a role in the management of sepsis, however they are not mutually exclusive. This article provides guidelines on optimal patient selection and timing for each intervention and provides advice on how to integrate new therapies in intensive care practice so that mortality rates can be reduced.


Se psis is one of the most common cause of death in children and adults.1 Massive investments have been made in developing and evaluating potential therapies and considerable effort has been spent to understand the underlying systemic inflammation and multiple system organ failure that characterize severe sepsis.2 Caring for septic patients creates a financial strain on the health system. Chalfin et al1 analyzed 1,405 patients at a teaching hospital and an estimated mean total charges of $38,304 on survivors and $49,182 on nonsurvivors.3 In 1991, the American College of Chest Physicians/Society of Critical Care Medicine defined sepsis, septic shock, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in a consensus conference with the goal of achieving standardization of terminology.4 Those definitions have been useful from an epidemiological perspective, however an important challenge is to progress from clinical syndromes, as presently defined, to more specific entities delineated by alterations in specific immunologic or biochemical pathways. Such mechanistic definitions will categorize patients in a more homogeneous manner and will help identify patients who could be treated at an early stage of their clinical disease course. By encouraging focused investigation of pathways leading to organ system dysfunction and death, an efficient framework for the development of new therapies that are useful in critically ill patients could be developed.5

Future clinical studies of new therapies must target the following goals: a) To characterize the disease process by identifying which specifically targeted biological mediator is producing organ dysfunction or death. b) To test the efficacy of the drug's ability to modify the actions of the targeted mediator. c) To provide therapies that are more specifically directed at the inciting mechanism as early as possible. Due to the heterogeneous mechanisms that lead to organ system failure, it would not be anticipated that all patients would respond to the same therapy.6 The purpose of this review is to provide relevant information on the 5 interventions that have shown to have a significant positive impact on mortality rates in septic shock. These interventions include: 1. Low tidal volume in acute lung injury/acute respiratory distress syndrome (ALI/ARDS), 2. Early goal directed therapy (EGDT), 3. Activated protein C, 4.

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**Low tidal volume in acute lung injury and acute respiratory distress syndrome.** It has recently been shown that lung damage results from regional over distension of lung units due to high ventilatory volumes and pressures as well from cyclic closing and reopening of alveoli with resultant shear injury, related to allowing areas of the lung to collapse at the end of exhalation.\(^7\) Conventional approaches to mechanical ventilation using tidal volumes of 10-15 ml/kg of body weight, (in normal subjects at rest 7-8 ml/kg), frequently target to achieve normal values for the partial pressure of arterial carbon dioxide and pH. The attainment of normal partial pressure of arterial carbon dioxide and pH is given a higher priority than the protection of the lung from respiratory acidosis and decrease arterial oxygenation and may require changes in the priority of some objectives in the care of these patients.\(^9\) In 1997, Tremblay et al\(^10\) examined the effect of ventilation strategy on the lung inflammatory mediators in the presence and absence of a preexisting inflammatory stimulus in rats. In both stimulated and nonstimulated rats, the presence of inflammatory mediators (TNF-\(\alpha\), IL-\(1\beta\), IL-6, IL-10, macrophage inflammatory protein 2, and IFN-\(\gamma\)) was highest in those rats ventilated with a large tidal volume and zero peak inspiratory pressure. Furthermore, Ranieri et al\(^11\) in 1999, showed that the concentration of inflammatory mediators 36 hours after randomization of the groups in their study was significantly lower in the lung protective strategy group (tidal volume, 7.6+1) than in the control group (tidal volume, 11.1+1.3 ml, \(p<0.0050\)).

To follow on those results, the Acute Respiratory Distress Syndrome Network (ARDSN) conducted a multicenter, prospective randomized study in the United States, including 861 patients recruited from March 1996 through March 1999 from 10 university centers.\(^12\) The trial was conducted to determine whether important clinical outcomes in ALI/ARDS patients would improve with the use of a lower tidal volume during mechanical ventilation. Patients who were intubated and receiving mechanical ventilation were eligible for the study if they had an acute decrease in the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen to 300 or less (indicating the onset of hypoxemia), bilateral pulmonary infiltrates on a chest radiograph showing edema and no clinical evidence of left atrial hypertension or if measured, a pulmonary capillary wedge pressure of 18 mm Hg or less. Patients were excluded if 36 hours had elapsed since they met those 3 criteria. Acute lung injury/ARDS patients were randomly assigned to receive ventilation with either a conventional tidal volume (12 ml/kg of predicted body weight) or a low tidal volume (6 ml/kg). In the group treated with traditional tidal volumes, the initial tidal volume was 12 ml/kg of predicted body weight. This was subsequently reduced stepwise by one ml/kg of predicted body weight if necessary to maintain the airway pressure measured after a 0.5 second pause at the end of inspiration (plateau pressure) at a level of 50 cm of water or less. The minimal tidal volume was 4 ml/kg of predicted body weight. If the plateau pressure dropped below 45 cm of water, the tidal volume was increased in steps of one ml/kg of predicted body weight until the plateau pressure was at least 45 cm of water or the tidal volume was 12 ml/kg of predicted body weight. In the group treated with lower tidal volumes, the tidal volume was reduced to 6 ml/kg of predicted body weight within 4 hours after randomization and was subsequently reduced stepwise by one ml/kg of predicted body weight if necessary to maintain plateau pressure at a level of no more than 30 cm of water. The minimal tidal volume was 4 ml/kg of predicted body weight. If plateau pressure dropped below 25 cm of water, tidal volume was increased in steps of one ml/kg of predicted body weight until the plateau pressure was at least 25 cm of water or the tidal volume was 6 ml/kg of predicted body weight. For patients with severe dyspnea, the tidal volume could be increased to 7-8 ml/kg of predicted body weight if the plateau pressure remained 30 cm of water or less. Plateau pressures of more than 50 cm of water in the group of patients treated with traditional tidal volumes and of more than 30 cm of water in the group of patients treated with lower tidal volumes were allowed if the tidal volume was 4 ml/kg of predicted body weight or if arterial pH was less than 7.15. All other objectives and ventilation procedures, including weaning, were identical in the 2 study groups.

Patients were monitored daily for 28 days for signs of failure of nonpulmonary organs and systems. Blood samples were obtained from 204 of the first 234 patients on day 0 and on day 3 for measurement of plasma interleukin-6 by immunoassay. The trial was stopped after the forth interim analysis for the use of lower tidal volumes, the initial tidal volume was 12 ml/kg of predicted body weight. The mortality rate was 39.8% in the group treated with traditional tidal volumes and 31% in the group treated with lower tidal volumes (\(p=0.007\)). The number of ventilator free days was significantly higher in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes. The median duration of ventilation was 8
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days among patients in both groups who were discharged from the hospital after weaning and 10.5 days among those who died in the group treated with lower tidal volumes and 10 days on the group treated with traditional tidal volumes. The partial pressure of arterial oxygen was similar in the 2 groups at all times, but the positive end expiratory pressure and fraction of inspired oxygen were significantly higher and the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen was significantly lower in the group treated with lower tidal volumes on days one and 3. On day 7, positive end expiratory pressure and the fraction of inspired oxygen were significantly higher in the group treated with traditional tidal volumes. The partial pressure of arterial carbon dioxide was significantly higher on days one, 3 and 7 and arterial pH was significantly lower on days one and 3 in the group treated with lower tidal volumes. Acidosis was corrected by infusions of bicarbonate and by increasing the ventilator rates. The number of days without nonpulmonary organ or system failure was significantly higher in the group treated with lower tidal volumes (p=0.006). The decrease in plasma interleukin-6 was greater in the group treated with lower tidal volumes (p=0.001) and the day 3 plasma interleukin-6 concentrations were also lower in this group (p=0.002). In this large study of patients with acute lung injury and the acute respiratory distress syndrome, mortality was reduced by 22% and the number of ventilator free days was greater in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes. Results of experiments in animal and observational studies in humans showed results consistent with that of the acute respiratory distress syndrome network. These benefits occurred despite the higher requirements for positive end expiratory pressure and fraction of inspired oxygen and the lower ratio of partial pressure of arterial oxygen to fraction of inspired oxygen in the group treated with lower tidal volumes on days one and 3. These results, coupled with the greater reductions in plasma interleukin-6 concentrations, suggest that the group treated with lower tidal volumes had less lung inflammation. Barotrauma occurred with similar frequency in the 2 study groups, a finding consistent with the results of other studies in which the incidence of barotrauma was independent of the airway pressures. The current report is the culmination of a series of mechanistic physiologic studies that have elucidated the key principles to be applied in the treatment of patients with the ARDS. The results confirm that a milder form of mechanical ventilation is therapeutic and associated with fewer side effects in septic shock patients who develop ARDS.

**Early goal directed therapy.** Attempts to replicate the hemodynamic values and patterns of oxygen transport found in survivors of serious illness or injury may improve the outcome of critical illness. Such attempts target the prevention or reversal of tissue hypoxia resulting from the increased demand for oxygen imposed by critical illness and the maldistribution of blood flow regionally and in the microcirculation. Early goal directed therapy represents an attempt to adjust the cardiac preload, afterload and contractility to balance systemic oxygen delivery with oxygen demand. A prospective, randomized, predominantly blinded study was initiated by the EGDT Collaborative Group to examine the results of hemodynamic interventions in the emergency department. Two hundred and sixty three patients from March 1997 through to March 2000 who arrived at an urban Emergency Department with severe sepsis or septic shock were randomly assigned to receive either 6 hours of EGDT or standard therapy (as a control) before admission to the intensive care unit (ICU). Rivers et al examined whether early goal directed therapy before admission to the ICU effectively reduces the incidence of multiorgan dysfunction, mortality and the use of health care resources among patients with severe sepsis or septic shock. After arterial and central venous catheterization, patients in the standard therapy group were treated at the clinicians' discretion according to a protocol for hemodynamic support and were admitted for inpatient care as soon as possible. Patients assigned to EGDT received a central venous catheter capable of measuring central venous oxygen saturation. Patients were treated in the emergency department according to a protocol for early goal directed therapy for at least 6 hours and were transferred to the first available inpatient beds. A 500 ml bolus of crystalloid was given every 30 minutes to achieve a central venous pressure of 8-12 mm Hg. If the mean arterial pressure was less than 65 mm Hg, vasopressor were given to maintain a mean arterial pressure of at least 65 mm Hg. If the mean arterial pressure was greater than 90 mm Hg, vasodilators were given until it was 90 mm Hg or below. If the central venous oxygen saturation was less than 70%, red cells were transfused to achieve a hematocrit of at least 30%. After optimizing the central venous pressure, mean arterial pressure and hematocrit saturation, dobutamine administration was started, if the central venous oxygen was less than 70%. Dobutamine was started at a dose of 2.5 µg/kg of body weight per minute, a dose that was increased by 2.5 µg/kg per minute every 30 minutes until the central venous oxygen saturation was 70% or higher or until a maximal dose of 20 µg/kg per minute was given. Dobutamine was decreased in dose or discontinued if the mean arterial pressure was less than 65 mm Hg or if the heart rate was above 120 beats per minute. Patients in whom hemodynamic optimization could not be achieved received...
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mechanical ventilation and sedatives in an attempt to decrease oxygen consumption.

The results of the study conducted by Rivers et al.38 showed that the patients assigned to standard therapy stayed a significantly shorter time in the Emergency Department than those assigned to EGDT \( p<0.001 \). During the initial 6 hours after the start of therapy, the mean arterial pressure was significantly lower in the group assigned to standard therapy than in the group assigned to EGDT \( p<0.001 \). The goal of 70% or higher for central venous oxygen saturation was met by 60.2% of the patients in the standard therapy group, as compared with 94.9% of those in the early therapy group \( p<0.001 \). The combined hemodynamic goals for central venous pressure, mean arterial pressure and urine were achieved in 86.1% of the standard therapy group, as compared with 99.2% of the early therapy group \( p<0.001 \). During this period, the patients assigned to standard therapy had a significantly lower central venous oxygen saturation \( p<0.001 \) and a greater base deficit \( p=0.006 \) than those assigned to EGDT.

During the period from 7-72 hours after the start of treatment, the patients assigned to standard therapy had a significantly lower central venous oxygen saturation than those assigned to EGDT \( p<0.001 \), as well as a higher lactate concentration \( p=0.02 \), a greater base deficit \( p<0.001 \) and a lower pH \( p<0.001 \). During the same period from 7-72 hours after the start of the treatment, the patients assigned to the standard therapy had a significantly higher heart rate \( p=0.04 \) and a significantly lower mean arterial pressure \( p<0.001 \) than the patients assigned to EGDT, the 2 groups had a similar central venous pressure \( p=0.68 \).

During this period, in hospital mortality rates were significantly higher in the standard therapy group than in the early therapy group \( p=0.009 \), as was the mortality at 28 days \( p=0.01 \) and 60 days \( p=0.03 \). The rate of in hospital death due to sudden cardiovascular collapse was significantly higher in the standard therapy group than in the early therapy group \( p=0.02 \), the rate of death due to multiorgan failure was similar in the 2 groups \( p=0.27 \).

During the period from 7-72 hours, the Acute Physiology, Age and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score (SAPS) II, and Multiple Organ Dysfunction Syndrome (MODS) were significantly higher in the patients assigned to standard therapy than in the patients assigned to EGDT \( p<0.001 \). During the overall period from base line to 72 hours after the start of treatment, there was no significant difference between the 2 groups in the total volume of fluid administered \( p=0.73 \) or the rate of use of inotropic agents \( p=0.15 \), although a greater proportion of the patients assigned to standard therapy than of those assigned to EGDT received vasopressors \( p=0.02 \) and mechanical ventilation \( p=0.02 \) and underwent pulmonary artery catheterization \( p=0.01 \) and a smaller proportion required red cell transfusion \( p<0.001 \). Early goal directed therapy is part of a general supportive measure to restore hemodynamics and prevent organ dysfunction in the emergency department. The systemic inflammatory response syndrome can be self limited or can progress to severe sepsis and septic shock.19 Along this continuum, circulatory abnormalities (intravascular volume depletion, peripheral vasodilatation, myocardial depression, and increased metabolism) lead to an imbalance between systemic oxygen delivery and oxygen demand, resulting in global tissue hypoxia or shock.20 An indicator of serious illness, global tissue hypoxia is a key development preceding multiorgan failure and death.20 The transition to serious illness occurs during the critical "golden hours".21,22 Early hemodynamic assessment on the basis of physical findings, vital signs, central venous pressure and urinary output fails to detect persistent global tissue hypoxia.23,24 A more definitive resuscitation strategy involves goal oriented manipulation of cardiac preload, afterload and contractility to achieve a balance between systemic oxygen delivery and oxygen demand.20 The end points used to confirm the achievement of such a balance (hereafter called resuscitation end points) include normalized values for mixed venous oxygen saturation, arterial lactate concentration, base deficit and Ph.24 Mixed venous oxygen saturation has been shown to be a surrogate for the cardiac index as a target for hemodynamic therapy.29

**Activated protein C.** The inflammatory and procoagulant host responses to infection are closely related. Inflammatory cytokines released in sepsis of and septic shock including tumor necrosis factor $\alpha$, interleukin-1$\beta$ and interleukin-6 are capable of activating coagulation and inhibiting fibrinolysis, whereas the procoagulant thrombin is capable of stimulating multiple inflammatory pathways. The end result may be diffuse endovascular injury, multiorgan dysfunction, and death.27,28 Activated protein C, an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation, is an important modulator of the coagulation and inflammation associated with severe sepsis. Activated protein C is converted from its inactive precursor, protein C, by thrombin coupled to thrombomodulin.29 The conversion of protein C to activated protein C may be impaired during sepsis as a result of the down regulation of thrombomodulin by inflammatory cytokines.30 Reduced levels of protein C are found in the majority of patients with sepsis and are associated with an increased risk of death.31 Previous preclinical and clinical studies showed that the
administration of activated protein C might improve the outcome of severe sepsis. The efficacy of recombinant human activated protein C in reducing mortality in patients with severe sepsis was investigated in a large multicenter, placebo controlled, randomized clinical trial, the protein C Worldwide Wide Evaluation in Severe Sepsis (PROWESS) trial. The study group evaluated whether the administration of recombinant human activated protein C would reduce the rate of death from all causes at 28 days in patients with severe sepsis and have an acceptable safety profile. From July 1998 through to June 2000, eligible patients were enrolled in this randomized, double blind, placebo controlled trial, which was conducted at 164 centers in 11 countries. One thousand six hundred and ninety patients received the study drug or placebo. Twenty eight days after the start of the infusion 30.8% of patients in the placebo group and 24.7% of the patients in the recombinant human activated protein C group had died. This difference in the rate of death from any cause was significant (p=0.005) and was associated with an absolute reduction in the risk of death of 6.1%. The absolute difference in survival between the 2 groups was evident within days after the initiation of the infusion and continued to increase throughout the remainder of the study period. The percentage of patients who had at least one serious adverse event was similar in the 2 groups. The incidence of serious bleeding was higher in the recombinant human activated protein C group than in the placebo group (3.5% versus 2.0%, p=0.06), only in patients who had underlying conditions predisposing them for active bleeding. This difference in the incidence of serious bleeding was observed only during the infusion period, thereafter, the incidence was similar in the 2 groups. There were no other safety concerns associated with treatment with the recombinant human activated protein C on the basis of assessments of organ dysfunction, vital signs, serum chemical data or hematological data. The incidence of thrombotic events was similar in the 2 groups. New infections occurred in 25.5% of the recombinant human activated protein C patients group and 25.1% of the patients in the placebo group (p=0.85). Neutralizing antibodies against activated protein C were not detected in any patient. In this study, the administration of the recombinant human activated protein C reduced the rate of death from any cause at 28 days in patients with a clinical diagnosis of severe sepsis, resulting in a 19.4% reduction in the relative risk of death and an absolute reduction of 6.1%.

The study population was heterogeneous with respect to clinical features but it was homogeneous with respect to the biochemical evidence of systemic inflammation and coagulopathy. Treatment with recombinant human activated protein C decreased inflammation, as indicated by decreases in interleukin-6 levels, a finding consistent with the known anti-inflammatory activity of activated protein C. The anti-inflammatory activity of recombinant human activated protein C may be mediated indirectly through the inhibition of the generation of thrombin, which leads to the decreased activation of platelets, recruitment of neutrophils and degradation of mast cells. Reductions in the relative risk of death were observed regardless of whether the patients had a deficiency of protein C at base line, suggesting that recombinant human activated protein C has pharmacological effects that go beyond simple physiological replacement of activated protein C. This observation further suggests that measurements of protein C are not necessary to identify which patients would benefit from the treatment. The study group concluded that in patients with severe sepsis, an intravenous infusion of drotrecogin alfa activated at a dose of 24 µg/kg per hour for 96 hours was associated with a significant reduction in mortality and an acceptable safety profile.

**Moderate doses corticosteroids.** The value of steroids in septic shock has been debatable. A number of randomized controlled trials failed to show benefits of steroid therapy in improving survival, with an increased incidence of nosocomial infections and subsequent mortality. Relative adrenal insufficiency is common in patients with refractory septic shock. Sepsis seems to be characterized by peripheral tissue resistance to corticosteroids. A phase III randomized, controlled trial was performed in 19 centers in France with 300 patients. Patients were stratified according to their response to the adrenocorticotropic hormone (ACTH) test. There were 229 nonresponder to the corticotropin test (placebo with 115, corticosteroids with 114) and 70 responders to the corticotropin test (placebo with 34, corticosteroids with 36). In nonresponders, there were 73 deaths (63%) in the placebo group and 60 deaths (53%) in the corticosteroid group (p=0.02). Vasopressor therapy was withdrawn within 28 days in 46 patients (40%) in the placebo group and in 65 patients (57%) in the corticosteroid group (p=0.001). There was no significant difference between groups of responders. Adverse events rates were similar in the 2 groups. It was found that a 7 day replacement therapy with hydrocortisone (50 mg intravenous bolus every 6 hours) and fludrocortisone (50 µg tablet once daily) significantly reduced 28 day mortality and duration of vasopressor administration in all patients with septic shock, in particular those with relative adrenal insufficiency. In addition, among the latter, corticosteroid therapy significantly reduced mortality during both ICU and hospital stays and tended to reduce one year mortality. Replacement therapy had no significant effect on the same.
variables in patients who had septic shock without relative adrenal insufficiency. In catecholamine dependent septic shock patients, particularly those with relative adrenal insufficiency, a 7-day treatment with the combination of hydrocortisone and fludrocortisone is safe and associated with a significant reduction in short term and long term mortality. In practice, the authors suggest that all patients with catecholamine dependent septic shock should be given the combination of hydrocortisone and fludrocortisone as soon as a short corticotropin stimulation test is performed. They conclude that in catecholamine dependent, particularly those with relative adrenal insufficiency, a 7-day treatment with the combination of hydrocortisone and fludrocortisone is safe and associated with a significant reduction in short term and long term mortality.

Tight control of blood sugar. Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known. The hypothesis is that hyperglycemia or relative insulin deficiency (or both) during critical illness may directly or indirectly confer a predisposition to complications such as severe infections, polynuropathy, multiorgan failure, and death. A prospective, randomized, controlled trial at one center was carried out to determine whether normalization of blood glucose levels with intensive insulin therapy reduces mortality and morbidity among critically ill patients. All adults, receiving mechanical ventilation admitted to the ICU between February 2000 through to January 2001, were eligible for enrollment in the study after written informed consent had been obtained from the closest family member. Patients were randomly assigned to receive either intensive or conventional insulin therapy. In the intensive treatment group, an insulin infusion was started if the blood glucose level exceeded 110 mg per deciliter and the infusion was adjusted to maintain normoglycemia (80-110 mg/deciliter [4.4-6.1 mmol per liter]). The maximal dose of insulin was arbitrarily set at 50 IU per hour. When the patient was discharged from the ICU, a conventional approach was adopted (maintenance of blood glucose at a level between 180-200 mg/deciliter).

On admission, all patients were fed continuously with intravenous glucose (200-300 g/24 hours). The next day, total parenteral, combined parenteral and enteral or total enteral feeding was instituted according to a standardized schedule, with 20-30 nonprotein kilocalories per kg of body weight per 24 hours and a balanced composition (including 0.13-0.26 g of nitrogen per kg per 24 hours and 20-40% of nonprotein calories in the form of lipids). Total enteral feeding was attempted as early as possible.

A total of 1548 patients were enrolled in the study. In the intensive treatment group, almost all the patients required exogenous insulin and the morning blood glucose level was maintained at a mean value of 103 ± 19 mg/deciliter (5.7 ± 1.1 mmol/liter). In the conventional treatment group, the morning blood glucose level was maintained at a mean value of 153 ± 33 mg/deciliter (8.5 ± 1.8 mmol/liter). Only 39% of the patients treated with the conventional approach received insulin, their mean blood glucose level was 173 ± 33 mg/deciliter as compared with 140 ± 25 mg/deciliter in the patients who did not receive insulin. Hypoglycemia (defined as a blood glucose level of 40 mg per deciliter [2.2 mmol per liter] or less) occurred in 39 patients in the intensive treatment group and in 6 patients in the conventional treatment group. The proportion of patients who required intensive care for more than 5 days was similar in the 2 groups (27% in the intensive treatment group and 31% in the conventional treatment group, p=0.1). The observed reduction in mortality with intensive insulin therapy occurred exclusively in this long term cohort (10.6% mortality in the intensive treatment group versus 20.2% in the conventional treatment group, p=0.005). Intensive insulin treatment reduced episodes of septicemia by 46% (95% confidence interval, 25-67%). Of the episodes of septicemia in the intensive treatment group, 34% were polymicrobial as compared with 23% in the conventional treatment group (p=0.2). The causative pathogens included coagulase negative Staphylococci (accounting for 31.3% of all episodes of septicemia), enterococcus species (14.7%), non fermenting gram negative bacilli (14.7%), inducible Enterobacteriaceae (12.6%), other Enterobacteriaceae (8.4%), and Staphylococcus aureus (7.7%).

Markers of inflammation were less frequently abnormal in the intensive treatment group than in the conventional treatment group (p=0.02). The patients who received intensive insulin therapy were less likely to require prolonged use of antibiotics than were the patients who received conventional treatment, an effect that was largely attributable to the lower rate of bacteremia in the intensive treatment group (75% of patients who had bacteremia received antibiotics for more than 10 days, as compared with 10% of patients who did not have bacteremia, p<0.001). Among patients with bacteremia, those treated with intensive insulin therapy had a lower mortality rate than those treated conventionally (12.5% versus 29.5%), although this difference was not statistically significant. The authors conclude that intensive insulin treatment reduced the number of deaths from multiorgan failure with sepsis, regardless of whether there was a history of diabetes or hyperglycemia.
They also conclude that the use of exogenous insulin to maintain blood glucose at a level no higher than 110 mg/deciliter reduces morbidity and mortality among critically ill patients in the surgical ICU, regardless of whether they had a history of diabetes or not.

In conclusion, the optimal use of existing therapies and the integration of proven new therapies will reduce mortality rates in the ICU. All 5 interventions discussed in this article have provided considerable evidence for their use and promising hope for reducing mortality in patients with sepsis, severe sepsis and septic shock.

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