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AHC Media

An Update on Sepsis Clinical Research: Impact on ED Management

Physicians have been searching for the Holy Grail in sepsis treatment for many years. Periodically, emergency physicians are notified that the results of a recent study mandate that we change our practice to be up to date or to satisfy the latest guidelines. The implication is that if you don't change your practice, then you are substandard. Well, I have been around enough to realize that many of these amazing advances do not pan out on subsequent experience. The authors of this issue take us through the ups and downs of several of the landmark sepsis studies in the past 15 years. After reading this, my natural skepticism was reaffirmed; continue to use basic principles and change when the evidence is strong and convincing.

— J. Stephan Stapczynski, MD, Editor

The Trials and Tribulations of EGDT

More than a decade ago, sepsis came to the forefront of research with a publication by Emanuel Rivers et al in 2001 titled "Early Goal Directed Therapy in the Treatment of Severe Sepsis and Septic Shock."[1] Whereas quantitative resuscitation was previously reserved for the treatment of sepsis patients in the intensive care unit, these investigators introduced early goal-directed therapy (EGDT) to the emergency department (ED) treatment of patients with severe sepsis and septic shock. EGDT involved a six-hour resuscitation protocol involving insertion of central line and administration of intravenous fluids, vasopressors, packed red-cell transfusions, and dobutamine infusion according to specific hemodynamic endpoints: CVP 8-12 mmHg, MAP ≥ 65 mmHg, and $ScVO_2$ > 70%.[1] This single center, prospective, randomized study included 263 patients meeting criteria for severe sepsis or septic shock; 130 patients received EGDT in the ED, while 133 control patients received standard care. This study hit the spotlight because it demonstrated that when EGDT was employed for the treatment of severe sepsis and septic shock, patients had a significantly lower in-hospital mortality (30.5%) compared to the in-hospital mortality of patients receiving standard care (46.5%) (P = 0.009).[1] This mortality benefit was also observed long-term, with a 28-day and 60-day mortality rate of 49.2% and 56.9%, respectively, in the standard care arm, compared to 33.3% (P = 0.01) and 44.43% (P = 0.03) in the EGDT arm.[1] As such, this landmark article demonstrated a significant short-term and long-term mortality benefit when early goal-directed therapy was implemented in the ED at the earliest stages of severe sepsis and septic shock.

In 2010, Jones et al published the study titled "Lactate Clearance vs. Central

EXECUTIVE SUMMARY

- Early aggressive supportive care with intravenous fluids and prompt antibiotics is the foundation of sepsis care.
- Consider adding albumin to the resuscitation when large quantities of crystalloid are used.
- Use low-dose hydrocortisone when the patient is refractory to IV fluids and vasopressors.
- Aggressive glucose control is not necessary. Treat with insulin only if the glucose is above 180 mg/dL.

Venous Oxygen Saturation as Goals of Early Sepsis Therapy: A Randomized Clinical Trial."[2] This study was a multicenter, prospective, randomized, nonblinded clinical trial that evaluated the hemodynamic targets of EGDT. Specifically, they evaluated whether lactate clearance, derived from calculating the change in lactate concentration over time, could be an equally effective measure of tissue oxygen delivery and an alternative to central venous oxygen saturation ($ScvO_2$) measurement.[2] Two hundred ninety-four patients meeting criteria for severe sepsis or septic shock were included in data analysis; 147 patients were assigned to the control $ScvO_2$ group, while 147 patients were assigned to the lactate clearance group. After randomization, patients were resuscitated according to the early goal-directed protocol: All patients had central venous catheters placed, received isotonic fluid in boluses to achieve a CVP of 8-12 mmHg, and had vasopressors initiated to maintain a CVP ≥ 65 mmHg.[2] In the control $ScvO_2$ group, as standard protocol, if $ScvO_2$ < 70% packed red blood cells (PRBCs) were transfused to Hct > 30% and dobutamine initiated to achieve an $ScvO_2$ > 70%. In the experimental lactate clearance group, if lactate clearance was not at least 10% after two hours of resuscitation, then PRBCs were transfused to Hct > 30% and dobutamine initiated to achieve a lactate clearance > 10%.

Study results demonstrated no difference in frequency of any treatments administered during the six-hour resuscitation period and throughout the initial 72 hours of hospitalization to maintain high compliance with the target goals (CVP, MAP, and $ScvO_2$, or lactate clearance).[2] Specifically, in the six-hour resuscitation period, patients received 4.5 L crystalloid in the lactate clearance group compared to 4.3 L in the $ScvO_2$ group (P = 0.55); required vasopressors in 72% of patients in lactate clearance group compared to 75% in $ScvO_2$ group (P = 0.60); required PRBC transfusion in 7% of patients in the lactate clearance group compared to 3% in $ScvO_2$ group (P = 0.22); required dobutamine infusion in 3% of patients in the lactate clearance group compared to 5% in $ScvO_2$ group (P = 0.57); required mechanical ventilation in 27% of patients in lactate clearance group compared to 26% in $ScvO_2$ group (P = 0.99); and received parenteral corticosteroids in 12% of patients in lactate clearance group compared to 17% patients in $ScvO_2$ group (P = 0.40).[2] In the intent-to-treat analysis, the in-hospital mortality was 17% in the lactate clearance group (95% CI: 11-24%) compared to 23% (95% CI: 17-30%) in the $ScvO_2$ group, representing a difference in mortality rate of 6% (95% CI: -3-15%).[2] Thus, a goal-directed protocol targeting a lactate clearance of at least 10% produces a similar short-term survival rate as a protocol using $ScvO_2$ monitoring. These study results indicated that measurement of lactate clearance, a quicker and more non-invasive measurement, can be an equally effective alternative to $ScvO_2$ monitoring in goal-directed resuscitation.

In 2014, ProCESS (Protocolized Care for Early Septic Shock) investigators published a prospective multicenter trial titled "A Randomized Trial of Protocol-Based Care for Early Septic Shock."[3] This study sought to determine whether the findings from the original EGDT study by Rivers et al were generalizable and whether all aspects of the protocol were necessary.[3] Thirty-one academic emergency departments across the United States participated in this study. One thousand three hundred forty-one patients meeting criteria for severe sepsis and septic shock were included in data analysis; 439 patients received EGDT according to the original protocol, 456 control patients received standard care, and 446 patients received protocol-based standard therapy. This new treatment arm outlined a protocol of administration of fluid and vasoactive agents to reach goals for systolic blood pressure, shock index, and fluid status, without mandating invasive venous access, aggressive blood transfusion, and inotropic support.

Study results demonstrated that significantly more patients in the two-protocol based groups received a central line (93.2% in EGDT vs. 56.5% in protocol-based therapy vs. 57.9% in standard therapy), vasopressors (54.9% in EGDT vs. 52.2% in protocol-based therapy vs. 44.1% in standard therapy, P = 0.003), dobutamine infusion (8.0% in EGDT vs. 1.1% in protocol-based therapy vs. 0.9% in standard therapy, P < 0.001), and transfusion with PRBCs (14.4% in EGDT vs. 8.3% in protocol-based therapy vs. 7.5% in standard therapy, P = 0.001).[3] However, despite more aggressive therapy in the protocol-based groups, there was no significant difference in 60-day mortality between the treatment groups: 92 deaths (21.0%) in the EGDT group compared to 81 deaths (18.2%) in the protocol-based standard therapy group compared to 86 deaths (18.9%) in the standard care group (P = 0.83).[3] Similarly, there was no significant difference in 90-day mortality between the treatment groups: 129 deaths (31.9%) in the EGDT group compared to 128 deaths (30.8%) in the protocol-based standard therapy group and 139 deaths (33.7%) in the standard care group (P = 0.66).[3] The incidence of acute renal failure and need for new renal–replacement therapy was significantly higher (P = 0.04) in the protocol-based standard therapy group than in the other two groups (6.0% in protocol-based standard therapy vs. 3.1% in EGDT vs. 2.8% in standard care group).[3] However, there were no

significant differences in the incidence and duration of cardiovascular or respiratory failure, hospital length of stay, or discharge disposition. In contrast to the original EGDT study, these study results demonstrated no significant decrease in sepsis morbidity or mortality when patients were treated with a strict protocol-based resuscitation strategy over usual care at the discretion of the treating physician.

Most recently, ARISE (Australasian Resuscitation in Sepsis Evaluation) investigators published the multicenter study titled "Goal-Directed Resuscitation for Patients with Early Septic Shock."[4] Designed to evaluate the effectiveness of EGDT compared to usual care, alongside the ProCESS trial, this study was a prospective, randomized trial conducted at 51 tertiary care and nontertiary care metropolitan and rural hospitals across Australia and New Zealand.[4] This study's design paralleled that of the original EGDT study by Rivers et al. One thousand six hundred patients meeting inclusion criteria for septic shock were included in data analysis; 796 patients were assigned to the EGDT group and received care based on the original EGDT resuscitation algorithm, and 804 control patients received usual care at the discretion of the treating physician. Study results demonstrated that patients in the EGDT group were more likely to receive vasopressor infusion (66.6% vs 57.8%, P < 0.001), red-cell transfusion (13.6% vs 7.0%, P < 0.001), and dobutamine infusion (15.4% vs 2.6%, P < 0.001).[4] However, despite an increased rate of aggressive therapy, there was no significant difference in 28-day mortality (117 deaths [14.8%] in EGDT and 127 deaths [15.9%] in usual care, P = 0.53) or in 90-day mortality (147 deaths [18.6%] in the EGDT group and 150 deaths [18.8%] in the usual care group, P = 0.90) between the two treatment groups.[4] In addition, there were no significant differences in survival time, in-hospital mortality, use and duration of organ support, or length of hospital stay.[4]

Overall, the results of this study were in agreement with those of the ProCESS trial: Adherence to the EGDT algorithm did not offer a survival advantage over usual care for patients presenting to the emergency department with early septic shock.

The Bottom Line: When initially comparing the initial Rivers study with the subsequent studies, one is struck by the apparent decreases in control and treatment mortality rates. In the Rivers study, the control group mortality rate at 30 days was 49%, whereas the usual care group mortality in the PROCESS study was 19% at 60 days, and in the ARISE study it was 16% at 28 days. It raises the question whether Rivers enrolled a more ill group of patients or whether there has been an improvement in usual care of patients with sepsis in the decade after the 2001. The overall impression is that strict adherence to the original early goal-directed therapy strict protocol-based resuscitation strategy introduced by Rivers et al does not confer any morbidity or mortality benefit over standard care. Therefore, care provided at the discretion of the treating physician, with selective administration of intravenous fluids, vasopressors, blood transfusions, inotropes, and other aggressive ICU measures on a per-patient basis can be employed for effective treatment of severe sepsis and septic shock, rather than adherence to a protocolized resuscitation algorithm. Furthermore, targeting resuscitation to lactate clearance should be employed for a less invasive, equally effective alternative to $ScvO_2$ measurement.

Fluid Therapy

In April 2014, the ALBIOS (Albumin Italian Outcome Sepsis) investigators published their findings in a study titled "Albumin Replacement in Patients with Severe Sepsis or Septic Shock."[5] This was a multicenter, open-label, randomized, controlled trial conducted in 100 intensive care units across Italy. The impetus for this trial was the 2004 SAFE (Saline versus Albumin Fluid Evaluation) study, which compared 4% albumin solution with normal saline as fluid replacement in critically ill ICU patients across Australia and New Zealand.[5] The SAFE study demonstrated that use of 4% albumin solution for fluid resuscitation was safe, and had similar mortality outcomes compared to normal saline at 28 days.[5] In following these results, this ALBIOS study was carried out to compare the effects of administration of an albumin solution in resuscitation over crystalloids in the severely septic patient population.[5] One thousand eight hundred eighteen patients met inclusion criteria for severe sepsis and septic shock: 910 patients received 20% albumin and crystalloid solution for 28 days to maintain a serum albumin level ≥ 30 g/L; 908 control patients received crystalloid solution alone for fluid replacement as the control group. Due to loss to follow-up, 895 patients in the albumin group and 900 patients in the crystalloid group were included in data analysis.

Study investigators found a significant difference in hemodynamic parameters in the first seven days: Patients in the albumin group had a significantly higher mean arterial pressure (P = 0.03), lower heart rate (P = 0.002), lower daily net fluid balance (P < 0.0001), and lower cumulative net fluid balance (P = 0.004).[5] However, this did not confer any survival advantage. There was no significant difference in 28-day mortality between study groups: 285 of 895 patients (31.8%) in the albumin group and 288 of 900 patients (32.0%) in the crystalloid group expired (P = 0.94, relative risk, 1.0; 95% CI: 0.87-1.14).[5] Similarly, there was no significant difference in 90-day mortality: 365 of 888 patients (41.1%) in the albumin group and 389 of 893 (43.6%) patients in the crystalloid group died (P = 0.29, relative risk, 0.94; 95% CI: 0.85-1.05).[5] However, in a post-hoc subgroup analysis that included 1121 patients with septic shock and 660 without septic shock, there was a significantly lower mortality at 90 days in the albumin group compared to the crystalloid group (P = 0.03): relative risk with septic shock 0.87, 95% CI 0.77-0.99; relative risk without septic shock 1.13, 95% CI 0.92-1.39.[5] There was no significant difference between the two study groups with respect to the incidence of newly developed organ failure or the median SOFA score.[5] There was, however, a significantly lower cardiovascular SOFA subscore seen in the albumin group compared to the crystalloid group (P = 0.03).[5]

These results indicate that the

addition of albumin to crystalloids during resuscitation of severely septic patients is safe, improves hemodynamics with a larger fluid distribution within the intravascular compartment, but does not confer a survival advantage over crystalloids alone.

The Bottom Line: Crystalloids should be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock, with an initial fluid challenge of 30 mL/kg. Albumin should be considered in fluid resuscitation when patients require significant volume of crystalloid.

The Critical Importance of Early Antibiotics

In 2006, Kumar et al published a study titled "Duration of Hypotension Before Initiation of Effective Antimicrobial Therapy Is the Critical Determinant of Survival in Human Septic Shock."[6] This was a retrospective chart review study conducted across 10 hospitals in Canada and the United States that sought to examine the relationship between delays in initiation of effective antimicrobial therapy and mortality in septic shock.[6] Medical records of 2,731 adult patients with septic shock were included in data analysis. Time of initiation of appropriate antibiotics, time of initial onset of septic shock (first episode of hypotension), and outcome measures were extracted from each medical record and analyzed.

Study results indicated an overall mortality rate of 56.2%.[6] However, there was an impressive 82.7% survival rate for patients who received antibiotics within 30 minutes of initial evidence of hypotension, 77.2% survival rate for patients who received antibiotics within 30-60 minutes of initial evidence of hypotension, and a 79.9% composite survival rate for patients who received antibiotics within the first hour.[6] During the first six hours after the onset of hypotension, each hour of delay in initiation of effective antimicrobial therapy was associated with mean decrease in survival of 7.6% (range 3.6%-9.9%).[6] The in-hospital mortality rate was significantly increased when antibiotics were administered in the second hour compared to the first hour after onset of hypotension (adjusted OR 1.67, 95% CI: 1.120=-2.48).[6] With increasing delays in antibiotic administration, odds ratio of death increased, to a maximum value of 92.54 when antibiotics were delayed more than 36 hours after onset of hypotension (95% CI: 44.92-190.53).[6] The odds ratio between delay in antimicrobial initiation and in-hospital mortality was 1.119 per hour delay in effective antimicrobial therapy (95% CI: 1.103-1.136, P < 0.0001).[6] The time to administration of effective antibiotic therapy was found to be a critical determinant of survival to ICU and hospital discharge. In multivariate analysis with other variables including early fluid resuscitation and vasopressor/inotropic support, time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome (P < 0.0001).[6]

Although limited by the retrospective design of this study, these results suggested that initiation of effective antimicrobial therapy following the onset of hypotension is a critical therapeutic intervention capable of reducing mortality from septic shock. Appropriate antibiotics (i.e., antibiotics to which the pathogen is sensitive) administered within the first hour were associated with increased survival in septic shock patients, and every hour delay in initiation of antibiotic therapy was associated with a 7.6% decrease in survival rate.

A few years later, a study titled "Impact of Time to Antibiotics on Survival in Patients with Severe Sepsis or Septic Shock in Whom Early Goal-directed Therapy Was Initiated in the Emergency Department" by Gaieski et al was released.[7] In this single-center retrospective cohort study, the authors sought to confirm the results published by Kumar et al by evaluating the association between time to antibiotic administration and survival of severe sepsis and septic shock patients.[7] Two hundred sixty-one patients with severe sepsis and septic shock undergoing EGDT therapy were included in data analysis. Data extracted from medical records included triage time, time of qualification of EGDT, time of initial antibiotic administration, and appropriateness of antibiotic selection.

Study results demonstrated a mortality rate of 32.5% for culture-positive patients who received appropriate initial antibiotics in the ED, versus 50.0% for patients who did not receive appropriate initial antibiotics (P = 0.15).[7] There was no significant difference between in-hospital mortality and time from triage to antibiotic administration, or from time of qualification for EGDT to antibiotic administration.[7] There was, however, a significant 13.7% reduction in in-hospital mortality when appropriate antibiotics were administered within one hour (compared to more than one hour) of triage time (P = 0.02, OR 0.30 95% CI: 0.11-0.83).[7] Similarly, there was a significant 13.5% decrease in in-hospital mortality when appropriate antibiotics were administered within one hour (compared to more than one hour) of time from qualification for EGDT (P = 0.03, OR 0.50, 95% CI: 0.27-0.92).[7] In accordance with the results of Kumar et al, this study confirmed that early administration of appropriate antibiotics within one hour results in a significant mortality benefit for patients with severe sepsis and septic shock treated with EGDT.

The Bottom Line: There is retrospective evidence demonstrating a significant mortality benefit with early administration of appropriate antibiotics in patients with severe sepsis and septic shock, with the highest mortality benefit observed when antibiotics are administered within one hour of decompensation. As such, early identification of severe illness, prompt diagnostic studies to identify source of infection, and blood cultures drawn prior to antibiotic administration to ensure correct sensitivities is of critical importance. The goal of therapy is administration of antimicrobials as soon as possible. It is recommended that broad-spectrum antibiotics be administered within one hour of development of severe sepsis or septic shock, with prompt de-escalation to appropriate single-agent therapy based on sensitivities.

The Debate Over Steroids Continues

In 2002, Annane et al published a study titled "Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock."[8] This

was a prospective, placebo-controlled, randomized, double blinded trial performed in 19 intensive care units across France that sought to assess whether a replacement therapy with hydrocortisone and fludrocortisone could improve 28-day survival in patients with septic shock.[8] The impetus for this study was based on previous work demonstrating that severe sepsis may be associated with relative adrenal insufficiency, or systemic inflammation-induced glucocorticoid receptor resistance. Two hundred ninety-nine patients meeting criteria for septic shock were included in data analysis: 151 patients received hydrocortisone 50 mg IV every 6 hours and fludrocortisones 50 µg once a day for 7 days, while 149 patients received placebo as the control group. Patients were further sub-grouped into "responders"and "non-responders" based on response to a corticotropin test; 114 patients in the treatment group and 115 patients in the placebo group were non-responders, i.e., had relative adrenal insufficiency.

Study results demonstrated that non-responders with relative adrenal insufficiency treated with corticosteroids had significantly lower 28-day mortality rates: 73 deaths (63%) in the placebo group versus 60 deaths (53%) in the treatment group (P = 0.04; RR 0.83, 95% CI: 0.66-0.97).[8] One life could be saved for every seven patients treated with corticosteroids (95% CI 4-49).[8] Non-responders in the corticosteroid treatment group also had significantly lower mortality rates by the end of their ICU stay (81 deaths [70%] in the placebo group versus 66 deaths [58%] in the corticosteroid group, P = 0.02; RR 0.82, 95% CI: 0.68-1.00) and by the end of their hospital stay.[8] However, at one-year follow up, there were no significant differences in mortality rates between patients treated with corticosteroids and placebo (88 deaths [77%] in placebo group versus 77 deaths [68%] in the corticosteroid group, P = 0.07; RR 0.88, 95% CI: 0.75-1.04).[8] Non-responders treated with corticosteroids also had a significantly lower median duration of vasopressor therapy: 0 days in the placebo group versus 10 days in the corticosteroid group (P = 0.001, 95% CI: 1.29-2.84).[8] In contrast, in responders with intact adrenal function, there was no significant difference appreciated in 28-day, ICU, hospital, or one-year mortality rates, or in time to vasopressor withdrawal between the treatment group and placebo groups.[8] Of note, there were no significant differences in rates of adverse effects between the placebo and corticosteroid groups. The results of this study suggested that a seven-day course of low-dose hydrocortisone and fludrocortisones significantly reduces mortality in patients with septic shock and relative adrenal insufficiency without increasing adverse effects.

The CORTICUS (Corticosteroid Therapy of Septic Shock) group developed a follow-up study in 2008 to reevaluate the efficacy and safety of low-dose corticosteroid therapy in patients with septic shock.[9] This was a prospective multicenter, randomized, double blind, placebo-controlled study, conducted across several countries in 52 intensive care units. Four hundred ninety-nine patients meeting criteria for septic shock were included in data analysis: 251 patients received therapy with hydrocortisone 50 mg IV every 6 hours for 5 days followed by a 6-day taper, while 248 control patients received placebo. Two hundred thirty-three patients (46.7%) did not demonstrate a response to corticotropin (non-responders), while 254 patients (50.9%) did respond to corticotropin (responders).

Study results demonstrated that among non-responders, there was no significant difference in 28-day mortality between the two groups: 49 in 125 deaths (39.2%) in the hydrocortisone treatment group versus 39 in 108 deaths (36.1%) in the placebo group (P = 0.69).[9,10] Likewise, there was no significant difference in 28-day mortality in responders: 34 in 118 deaths (28.8%) in the hydrocortisone group, versus 39 in 136 deaths (28.7%) in the placebo group.[9,10] Additionally, there was no significant difference in mortality between the two groups at any of the other time points (ICU, hospital, one-year follow-up).[9] In non-responders, there was no significant difference in the proportion of patients who underwent a reversal of shock between the two study groups: 95 of 125 patients (76%) in the hydrocortisone group, and 76 of 108 patients (70.4%) in the placebo group (P = 0.41).[9,10] Similar proportions were also observed in responders. However, the median duration of time until reversal of shock was found to be significantly shorter in all patients receiving hydrocortisone compared to placebo: 3.3 days (95% CI: 2.9-3.9) versus 5.8 days (95% CI: 5.2-6.9) in responders (P < 0.001); 2.8 days (95% CI: 2.1-3.3) versus 5.8 days (95% CI: 5.2-6.9) for non-responders (P = 0.06).[9,10]

Finally, results pointed to an increased incidence of superinfections in patients treated with hydrocortisone compared to placebo (OR 1.37; 95% CI: 1.05-1.79).[9,10] Therefore, in contrast to the results published by Annane et al, this study suggests that the use of low-dose hydrocortisone has no significant effect on mortality in patients with septic shock, regardless of the patient's adrenal responsiveness to corticotropin. Treatment with hydrocortisone was found to shorten the duration of clinical shock; however, this did not confer a mortality benefit and in fact contributed to an increased incidence of superinfections.

The Bottom Line: Although research consistently demonstrates a faster reversal of shock in patients with relative adrenal insufficiency, there is inconsistent evidence regarding whether this confers a mortality benefit and increases the risk of superinfection. The ACTH stimulation test should not be utilized to identify patients who would benefit from corticosteroid use. As a general rule, corticosteroids should not be routinely used for the treatment of septic shock patients in whom fluid resuscitation and vasopressor therapy is able to restore hemodynamic stability. However, in patients with septic shock refractory to both adequate fluid resuscitation and vasopressor administration, low-dose intravenous hydrocortisone could be attempted.

Activated Protein C Stirs Up Controversy

In 2001, the PROWESS (Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) investigators published the study titled "Efficacy and Safety of Recombinant Human Activated Protein

C for Severe Sepsis."[11,12] Activated protein C (APC) is an endogenous protein that modulates the coagulation and inflammation cascade by promoting fibrinolysis and inhibiting thrombosis and inflammation.[11,12] Based on previous research demonstrating reduced levels of APC in septic patients, this study sought to determine whether the administration of drotrecogin alfa activated (DrotAA), the recombinant form of human activated protein C, would reduce 28-day mortality in patients with severe sepsis. This was a phase III prospective, randomized, double-blind, placebo-controlled trial conducted at 164 centers across 11 countries. One thousand six hundred ninety patients meeting criteria for severe sepsis were included in data analysis: 850 patients received a continuous infusion of DrotAA for 96 hours while 840 patients in the placebo group received a continuous 0.9% saline infusion.

Study results demonstrated a significantly lower 28-day mortality in patients treated with DrotAA: 259 of 840 patients (30.8%) in the placebo group expired, while only 210 of 850 patients (24.7%) in the DrotAA group expired (P = 0.005).[11,12] Treatment with DrotAA was found to confer an absolute reduction in risk of death of 6.1%, and a relative reduction in risk of death of 19.4% (95% CI: 6.6-30.5).[11,12] This benefit was observed across all the subgroups analyzed, including the subgroup with normal protein C levels. Furthermore, this absolute difference in survival was appreciated within only days after initiation of protein C infusion, and continued to increase significantly over time.

Although not statistically significant, there was a higher incidence of serious bleeding in the DrotAA group compared to the placebo group (3.5% versus 2.0%, respectively, P = 0.06).[11,12] However, this occurred primarily in patients with an identifiable predisposition to bleeding (GI ulceration, trauma, coagulopathy, low platelet count, etc.), and was observed only during the infusion period.[11,12] There were no other identified complications associated with DrotAA treatment. These results suggested a significant survival benefit when severe sepsis patients were treated with an intravenous infusion of DrotAA for 96 hours: one life saved for every 16 patients treated with DrotAA. On the basis of these results, the Food and Drug Administration approved DrotAA, marketed under the name Xigris, for the treatment of high-risk severely septic patients.

More than a decade later, the PROWESS-SHOCK group published the study titled "Drotrecogin Alfa (Activated) in Adults with Septic Shock."[13] This study was developed as a placebo-controlled trial to confirm the efficacy of DrotAA in reducing mortality in patients with septic shock, as part of the review process for the drug's continued approval.[13] One thousand six hundred ninety-six patients meeting criteria for septic shock with evidence of tissue hypoperfusion were included in data analysis; 852 patients received an intravenous infusion of DrotAA for 96 hours, while 845 patients received 0.9% saline solution as the placebo group.

Study results demonstrated no significant difference in 28-day mortality between the two study groups: 223 of 846 patients (26.4%) expired in the DrotAA group, while 202 of 834 patients (24.2%) expired in the placebo group (P = 0.31, relative risk of death 1.09; 95% CI: 0.92-1.28).[13] Nor was there a significant difference observed in 90-day mortality: 287 of 842 patients (34.1%) expired in the DrotAA group, while 269 of 822 patients (32.7%) expired in the placebo group (P = 0.56, relative risk of death 1.04; 95% CI 0.90-1.19).[13] Time-to-event analysis showed similar results between the two groups.[13] Finally, changes in organ function, assessed through measurement of SOFA score by day 7, did not differ significantly between the two groups.[13]

Monitoring for the safety profile of the drug, there were significantly more non-serious bleeding events in patients treated with DrotAA (72 of 833 patients [8.6%] compared to 40 of 833 patients [4.8%] in the placebo group, P = 0.0002).[13] Although the reported rate of serious bleeding events was higher in patients treated with DrotAA, these rates were not significantly different between the two groups (10 of 833 [1.2%] patients in the DrotAA group compared to 8 of 833 [1.0%] patients in the placebo group; P = 0.81).[13] As such, in direct opposition to the original PROWESS study, the results of the PROWESS-SHOCK study demonstrated no reduction in 28-day or 90-day mortality in septic shock patients treated with DrotAA compared to placebo. As a result, activated drotrecogin alfa (Xigris) was subsequently withdrawn from market.

The Bottom Line: Activated protein C does not confer a mortality benefit and is not recommended in the treatment of severe sepsis and septic shock patients.

Glucose Control

In January 2010, Brunkhorst et al published the results of their VISEP (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) study in the manuscript titled "Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis."[14] The impetus for the VISEP study was the 2001 Van Den Berghe study titled "Intensive Insulin Therapy in Critically Ill Patients."[15] This 2001 prospective controlled trial randomized ICU patients to receive either intensive insulin therapy to maintain blood glucose between 80-110 mg/dL, or conventional insulin therapy to maintain blood glucose between 180-200 mg/dL.

The study found that intensive insulin therapy was associated with a significant reduction in ICU mortality (4.6% mortality with intensive glucose control versus 8.0% mortality with conventional glucose control; P < 0.04) and in-hospital mortality (7.2% mortality with intensive glucose control versus 10.9% mortality with conventional glucose control; P < 0.01).[15] Therefore, as a follow-up to these results, Brunkhorst et al conducted the VISEP study to determine whether intensive insulin therapy also improves outcomes specifically in the septic patient population.[14] This was a multicenter, randomized study conducted across 18 tertiary care hospitals in Germany. Five hundred thirty-seven patients with septic shock were enrolled in the study prior to it being terminated by the data and safety monitoring board due to high rates of hypoglycemia; 247 patients were randomized to the intensive-therapy group and received an

Table. Adjunctive Therapies Under Investigation

Investigational Therapy	Conclusions	Study
The TLR-4 antagonist, TAK 242 (Resatorvid)	TLR-4 antagonist TAK-242 did not suppress cytokine levels in patients with septic shock or respiratory failure, nor did it improve mortality rates in septic shock and respiratory failure patients.[20]	Rice TW, Wheeler AP, Bernard GR, et al. A randomized, double-blind, placebo-controlled trial of TAK-242 for the treatment of severe sepsis. *Crit Care Med* 2010;38:1685.
The human anti-endotoxin monoclonal antibody, HA-1A	Human monoclonal antibody HA-1A was not effective in reducing 14-day mortality rates in patients with gram-negative bacteremia and septic shock.[21]	McCloskey RV, Straube RC, Sanders C, et al. Treatment of septic shock with human monoclonal antibody HA-1A. A randomized, double-blind, placebo-controlled trial. CHESS Trial Study Group. *Ann Intern Med* 1994;121:1.
	Treatment with E5 murine monoclonal antiendotoxin antibody in patients with gram-negative sepsis did not improve short-term survival.[22]	Angus DC, Birmingham MC, Balk RA, et al. E5 murine monoclonal anti-endotoxin antibody in gram-negative sepsis: A randomized controlled trial. E5 Study Investigators. *JAMA* 2000;283:1723.
The human anti-Enterobacteriaceae common antigen (ECA) monoclonal antibody	Treatment with the human monoclonal antibody to Enterobacteriaceae, MAB-T88, did not improve the mortality in patients with presumed Gram-negative sepsis or in those patients with proven enterobacterial common antigen infections.[23]	Albertson TE, Panacek EA, MacArthur RD, et al. Multicenter evaluation of a human monoclonal antibody to Enterobacteriaceae common antigen in patients with Gram-negative sepsis. *Crit Care Med* 2003;31:419.
Granulocyte colony-stimulating factor (filgrastim, G-CSF)	The addition of filgrastim to the antibiotic and supportive care treatment of patients with severe sepsis secondary to pneumonia was safe, but was not effective at reducing mortality rates or complications from this infection.[24]	Root RK, Lodato RF, Patrick W, et al. Multicenter, double-blind, placebo-controlled study of the use of filgrastim in patients hospitalized with pneumonia and severe sepsis. *Crit Care Med* 2003;31:367.
Anti-tumor necrosis factor monoclonal antibody	There was a significant reduction in mortality at 3 days in septic shock patients treated with TNF-alpha MAb. However, there was no significant long-term survival advantage at 28 days following treatment with TNF-alpha MAb among shock patients treated with placebo or TNF-alpha MAb.[25]	Abraham E, Wunderink R, Silverman H, et al. Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome. A randomized, controlled, double-blind, multicenter clinical trial. TNF-alpha MAb Sepsis Study Group. *JAMA* 1995;273:934.
	There was no improvement in survival in septic shock patients treated with monoclonal antibody to human tumour necrosis factor , TNF alpha MAb.[26]	Abraham E, Anzueto A, Gutierrez G, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. NORASEPT II Study Group. *Lancet* 1998;351:929.
Tumor necrosis factor receptor antagonist	Lenercept (p55 tumor necrosis factor receptor fusion protein) had no significant effect on mortality or on the incidence or resolution of organ dysfunction in severe sepsis and septic shock patients.[27]	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.
Interleukin-1 receptor antagonist	A 72-hr continuous intravenous infusion of interleukin-1 receptor antagonist, rhIL-1ra, did not result in a statistically significant reduction in mortality.[28]	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. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med* 1997;25:1115
Antithrombin (formerly known as antithrombin III)	High-dose antithrombin III therapy had no effect on 28-day all-cause mortality in adult patients with severe sepsis and septic. Additionally, high-dose antithrombin III was associated with an increased risk of hemorrhage when administered with heparin.[29]	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.
	Replacement therapy with ATIII reduces mortality in septic shock patients.[30]	Baudo F, Caimi TM, de Cataldo F, et al. Antithrombin III (ATIII) replacement therapy in patients with sepsis and/or postsurgical complications: A controlled double-blind, randomized, multicenter study. *Intensive Care Med* 1998;24:336.
	Treatment with high-dose antithrombin III may increase survival time up to 90 days in patients with severe sepsis and high risk of death. This benefit may be even stronger when concomitant heparin is avoided.[31]	Wiedermann CJ, Hoffmann JN, Juers M, et al. High-dose antithrombin III in the treatment of severe sepsis in patients with a high risk of death: Efficacy and safety. *Crit Care Med* 2006;34:285.
Ibuprofen	In patients with sepsis, treatment with ibuprofen reduces levels of prostacyclin and thromboxane, and decreases fever, tachycardia, oxygen consumption, and lactic acidosis. However, it does not prevent the development of shock or ARDS and it does not improve survival.[32]	Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med* 1997;336:912.

Table. Adjunctive Therapies Under Investigation (continued)

Investigational Therapy	Conclusions	Study
N-acetylcysteine	Early NAC treatment aggravated sepsis-induced organ failure, in particular cardiovascular failure.[33]	Spapen HD, Diltoer MW, Nguyen DN, et al. Effects of N-acetylcysteine on microalbuminuria and organ failure in acute severe sepsis: Results of a pilot study. *Chest* 2005;127:1413.
	NAC can cause cardiovascular depression in septic patients when administered 24 hours after the onset of sepsis. Therefore, clinicians should avoid intravenous N-acetylcysteine use in SIRS and sepsis patients.[34]	Szakmany T, Hauser B, Radermacher P. N-acetylcysteine for sepsis and systemic inflammatory response in adults. *Cochrane Database Syst Rev* 2012;9:CD006616.
Nitric oxide inhibitors	Low doses of a nitric oxide synthase inhibitor, L-NMMA, causes a widespread increase in vascular tone and raises blood pressure in patients with septic shock, with a subsequent fall in cardiac output.[35]	Petros A, Lamb G, Leone A, et al. Effects of a nitric oxide synthase inhibitor in humans with septic shock. *Cardiovasc Res* 1994;28:34.
	The nonselective nitric oxide synthase inhibitor, 546C88, increased mortality in patients with septic shock.[36]	López A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: Effect on survival in patients with septic shock. *Crit Care Med* 2004;32:21.
The bradykinin antagonist, deltibant	The bradykinin antagonist, deltibant (CP-0127) may have some effect on survival in patients with SIRS and gram-negative sepsis.[37]	Fein AM, Bernard GR, Criner GJ, et al. Treatment of severe systemic inflammatory response syndrome and sepsis with a novel bradykinin antagonist, deltibant (CP-0127). Results of a randomized, double-blind, placebo-controlled trial. CP-0127 SIRS and Sepsis Study Group. *JAMA* 1997;277:482.
Growth hormone	In patients with prolonged critical illness, high doses of growth hormone resulted in increased morbidity and mortality.[38]	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.
Intravenous selenium supplementation	The adjuvant treatment of severe sepsis and septic shock patients with high-dose sodium-selenite reduced mortality rates.[39]	Angstwurm MW, Engelmann L, Zimmermann T, et al. Selenium in Intensive Care (SIC): Results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. *Crit Care Med* 2007;35:118.

insulin infusion titrated to a blood glucose between 80-110, while 250 patients were randomized to the conventional-therapy group and received insulin injections titrated to a blood glucose level between 180-200.

Study results demonstrated no significant difference in 28-day mortality (24.7% versus 26.0%, P = 0.74) or 90-day mortality (39.7% versus 35.4%, P = 0.31) between the intensive-therapy group and the conventional-therapy group.[14] In a Cox regression analysis, intensive insulin therapy was not an independent risk factor for survival (hazard ratio 0.95, 95% CI: 0.70-1.28, P = 0.72).[14] There was no significant difference between mean SOFA scores between the two groups (7.8 points in the intensive therapy group versus 7.7 points in the conventional group, P = 0.88), or in rates of acute renal failure, need for renal replacement therapy, use of vasopressors, or number of ventilator days.[14] However, at least one episode of hypoglycemia (BS ≤ 40 mg/dL) occurred in 42 patients (17%) in the intensive therapy group versus 12 patients (4.1%) in the conventional therapy group (P < 0.0001); severe hypoglycemic episodes occurred in 19 patients (7.7%) in the intensive therapy group and 7 patients (2.4%) in the conventional therapy group (P = 0.005); and life-threatening hypoglycemic episodes occurred in 13 patients (5.3%) in the intensive therapy group versus 6 patients (2.1%) in the conventional therapy group (P = 0.05).[14] These study results, in contrast to the findings of the 2001 Van Den Berghe study, demonstrated no mortality or morbidity benefit with intensive insulin therapy for septic shock patients. Instead, intensive insulin therapy was associated with a significantly increased rate of severe hypoglycemic episodes. With no proven mortality benefit and a five- to six-fold increased risk of hypoglycemia, this study concluded that intensive insulin therapy is not recommended for the severely septic patient population.

The Bottom Line: Blood glucose management in severe sepsis patients should target a blood glucose ≤ 180 mg/dL rather than a blood glucose ≤ 110 mg/dL, with insulin therapy initiated with blood glucose readings > 180 mg/dL. When insulin therapy is initiated, close attention to serial glucose levels is required.

Impact on Clinical Practice

For the past decade, the Surviving Sepsis Campaign (SCC) has been the leader in spearheading efforts to reduce the morbidity and mortality associated with sepsis worldwide. Every four years, the SCC publishes International Guidelines for Management of Severe Sepsis and Septic Shock. These guidelines put forth best practice recommendations for the care of severe sepsis and septic shock patients, based on the most current literature and expert opinion.[18] The key recommendations in the most recent 2012 guidelines included:[18]

- Early quantitative resuscitation during the first six hours after recognition;
- Blood cultures before antibiotic therapy;

• Administration of broad-spectrum antibiotics within one hour of recognition of severe sepsis and septic shock;

• Initial fluid resuscitation with crystalloid (minimum 30 mL/kg), and consideration of the addition of albumin, to maintain an adequate mean arterial pressure (MAP);

• Norepinephrine as first choice vasopressor to maintain MAP ≥ 65 mmHg; epinephrine as second-line when an additional agent is needed, or vasopressin as an adjunct to norepinephrine;

• Dobutamine infusion if myocardial dysfunction exists or with ongoing signs of hypoperfusion despite vasopressors.

In October 2012, the National Quality Forum (NQF) endorsed management bundles for the treatment of patients with severe sepsis and septic shock (NQF#0500). These were the first-ever national practice guidelines for the management of sepsis in the United States, and would serve as the benchmark for health care quality measurement by heath care providers, the federal government, and private sector entities. In line with the 2012 SSC recommendations, the NQF endorsed a three-hour management bundle for severe sepsis patients (items 1-3) and a six-hour bundle for septic shock patients (items 1-7):[19]

1. Measure lactate level.
2. Obtain blood cultures prior to administration of antibiotics.
3. Administer broad-spectrum antibiotics.
4. Administer 30 mL/kg crystalloid.
5. Apply vasopressors (for refractory hypotension) to maintain MAP ≥ 65.
6. Measure CVP and central venous oxygen saturation ($ScvO_2$).
7. Re-measure lactate if initial lactate was elevated.

However, in April 2014, the NQF Patient Safety Standing Committee conducted an ad-hoc review of the NQF measure #0500.[19] In light of the evolving literature, they removed item 6 from the above bundle requiring measurement of CVP and $ScvO_2$, but affirmed the importance of the remaining sepsis management bundle elements.[19]

The Bottom Line: Early aggressive supportive care with intravenous fluids and prompt antibiotics is the foundation of sepsis care. Specific recommendations regarding vasopressor therapy, inotropic support, blood transfusions, optimal hemodynamic monitoring, and surrogate markers for determining fluid responsiveness continue to evolve with further research on this topic. We look forward to future studies including the Protocolized Management in Sepsis (ProMISe) trial and the goal-oriented non-invasive sepsis trial (AGONIST), among many others, which are sure to further impact the future of sepsis resuscitation.

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CME Questions

1. Primary physiologic management priorities for early goal-directed therapy focus on which of the following?
   A. urine output, blood pressure, clinical assessment of fluid status
   B. maximizing APACHE scores
   C. CVP and hemoglobin
   D. MAP, CVP, $ScVO_2$
   E. aggressive fluid and ventilatory management
2. Primary outcomes for the ProCESS study indicate which of the following?
   A. a clear advantage for EGDT
   B. a clear advantage for PSC (protocolized standard care)
   C. a clear advantage for control (wild type) care
   D. no clear advantage of any approach
3. In the ARISE study, patients in the EGDT received more vasopressors and blood transfusions. This resulted in which of the following?
   A. a clear mortality benefit for EGDT
   B. a clear mortality benefit for the control group
   C. no clear benefit for either approach
   D. similar rates of survival time, ICU time, hospital stay
   E. C and D
4. Which of the following is true regarding the use of albumin in addition to crystalloid for initial fluid resuscitation in severe sepsis and septic shock?

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CME Objectives

Upon completion of this educational activity, participants should be able to:

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- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

A. It results in a lower SOFA cardiovascular subscore.
B. It provides a significant mortality benefit.
C. It causes dangerous fluctuations in hemodynamics.
D. It does not confer a survival benefit.
E. A and B
F. A and D

5. Which of the following is true regarding early broad-spectrum antibiotics?
A. They should be started within 6 hours.
B. They should be started within 30 minutes.
C. They are not shown to provide a survival benefit.
D. They provide an increasing survival benefit the earlier they are given.
E. They should be targeted for 60 minutes for greatest benefit.
F. A and D
G. D and E

6. Which of the following is correct regarding "stress dose" corticosteroids in sepsis?
A. They should always be given in septic shock.
B. They should only be given after an ACTH test.
C. They have never shown any mortality benefit.
D. They should be reserved for refractory hypotension after fluids.
E. They should be reserved for refractory hypotension after fluids and vasopressors.

7. Which of the following is true about activated protein C?
A. It is safe and effective.
B. It causes severe hypotension.
C. It is associated with bleeding complications, no mortality benefits, and is off the market.
D. It should still be used in initial bundle failures.

8. Which statement is true about inflammatory modulators, cytokines, growth factors, NAC, and ATIII?
A. They have shown significant promise in many phase III trials.
B. They have not had initial animal model successes replicated in humans.
C. They are all clinically available as adjuvant therapies.
D. They have never shown any promise in either animal or human models.

9. A basic initial sepsis bundle does *not* need to include:
A. 30 cc/kg fluid bolus
B. broad-spectrum antibiotics
C. an insulin drip for any glucose > 250 mg/dL
D. early measurement of lactate level
E. blood cultures before antibiotics

10. Which item did the NQF *remove* from its endorsed sepsis bundle in 2014?
A. fluid bolus
B. CVP and $ScVO_2$ measurements for septic shock patients
C. measurement of lactate level
D. vasopressors for refractory MAP < 65
E. blood cultures

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