

Treatment of Sepsis in the Surgical Intensive Care Unit

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ABSTRACT: Since the Surviving Sepsis Campaign Guidelines (SSG) were published in 2004, critical care physicians can readily access the evidence and current recommendations regarding management of patients with severe sepsis and septic shock. However, several issues including a potential conflict of interest in developing the guidelines were disclosed. There have also been dramatic changes in the management of sepsis, supported by high levels of evidence. SSG 2008 was developed to update the evidence using a new grading system. We reviewed select topics, routinely addressed by intensivists in the surgical intensive care unit, that have changed between SSG 2004 and SSG 2008: namely, glucose control, and administration of steroids, recombinant human activated protein C (rhAPC) and total parenteral nutrition.

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based on the quality of research and the impact of a particular therapy. EBM-derived treatment protocols have been shown to improve patient outcomes [4]. The development of these treatment protocols and guidelines is seen as a means to assure quality patient care and, as a result, is increasingly supported by the insurance industry and government as the standard of health care delivery. The complexity of the literature on sepsis and the potential impact that this disease has on health care spending spurred the call for guidelines for the management of sepsis. This was the impetus for the development of the Surviving Sepsis Campaign.

In 2004 the SSC published the first international guidelines for treatment of severe sepsis and septic shock to provide clinicians the best recommendations for improving outcome in septic patients. The recommendations were compiled by 11 organizations, including the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, over the course of 2 years. The recommendations represent the second phase of a three-phase process to create a consensus statement, to standardize care, and to improve worldwide survival of sepsis. The initial phase was started in 2002 in Barcelona; the third phase represents ongoing use of guidelines to evaluate the impact of the guidelines on outcomes. The EBM recommendations were derived from a modified Delphi methodology [5] and were published as guidelines in the journals *Critical Care Medicine* and *Intensive Care Medicine* in 2004 [6,7]. Key recommendations included early goal-directed therapies, appropriate diagnostic maneuvers, antibiotic therapies, and resuscitation measures. Additional recommendations regarding treatment of acute lung

injury/acute respiratory distress syndrome, blood glucose control, and prophylactic measures were included. These guidelines

were disseminated on an internet website (www.survivingsepsis.org), using a distinctive logo, pocket guide and newsletter as a marketing strategy.

The recommendations of the SSC, however, were criticized by some. While there were no industry representatives on the SSC committee or industry input into the development of the publicized recommendations, there was a perceived conflict of

For Editorial see page 689

Severe sepsis and septic shock are increasingly leading to morbidity and mortality among surgical patients. Of approximately 750,000 annual cases of sepsis, about 160,000 occur in surgical patients at a cost of \$17 billion. These patients have a mortality rate of 30–40% despite adequate therapy [1]. Compared to medical patients, patients with sepsis from a surgical source have a 7 day longer hospital length of stay and are more costly [2]. A significant body of literature and numerous clinical studies have arisen as a result of millions being affected by organ dysfunction secondary to infection (severe sepsis) and refractory hypoperfusion induced by infection (septic shock). The product of this has been conflicting recommendations and confusion over best practice. Evidence-based medicine has emerged in the last decade as a means to assure best practice [3]. EBM evaluates the literature and develops treatment protocols

It has been clearly demonstrated that an increasing number of patients in the surgical ICU develop severe sepsis and septic shock

interest. The meeting expenses and staff support for the SSC were provided by an unrestricted industry educational grant. Eichacker and co-authors in a 2005 article [8] charged that Eli Lilly had undue influence on guideline development. Ninety percent of the grant came from Eli Lilly, the manufacturer of recombinant human activated protein C. Of interest, rhAPC was recommended by the U.S. Food and Drug Authority for the treatment of sepsis only in the sickest of the sick. This resulted in a poor market performance and in the eyes of some detractors was apparently the impetus for Eli Lilly's support of SSC. Additionally, the Infectious Disease Society declined to endorse SSC due to a suboptimal grading system and concerns over industrial support. These issues were addressed in the 2008 SSC update. Specifically, a revised grading system was used, additional organizations were added to the committee, and industrial support was not accepted.

The 2008 SSC guidelines were developed based on the GRADE system of rating the quality of evidence and an independent determination of strength of recommendations [9] [Table 1]. The updated and revised SSG were published in 2008 in the same journals as in 2004 [10,11]. As in 2004, key areas of intervention addressed in 2008 included early goal-directed therapies, antibiotic usage, source control, resuscitation fluids and vasopressors, indications for steroid use, ventilator strategies in lung injury, blood glucose control, sedation schemes, deep venous thrombosis, and gastrointestinal bleeding prophylaxis.

As the SSG 2008 is beyond the extent of this review, we will focus on four areas addressed by the SSG that underwent revision between the versions based on new data. These are blood glucose control, indications for steroid administration, appropriate utilization of rhAPC, and total parenteral nutrition. The current recommendations for these four areas have

The recommendations in SSG 2008 were drastically revised from SSG 2004, based on newly emerged data

undergone significant evolution in the last few years and warrant a more detailed examination.

BLOOD GLUCOSE CONTROL

Blood glucose control has emerged as a major component in sepsis prevention and management. In the past, insulin drips were considered for diabetic patients only and the fear of hypoglycemia led clinicians to routinely accept glucose levels of 200 mg/dl. With the recognition that diabetics had universally worse outcomes and hyperglycemia impaired wound healing even in non-diabetics, the import of glucose control was appreciated [12]. In fact, studies looking at non-diabetic cardiac patients and non-diabetic stroke patients revealed worse outcomes with hyperglycemia [13,14]. A prospective randomized controlled

study of intubated patients in a surgical intensive care unit examined a tight glucose control regimen (80–110 mg/dl) against a liberal glucose

control protocol (180–200 mg/dl) [15]. The results of this study demonstrated that a TGC regimen decreased ICU mortality from 8% to 4.6% and from 20% to 10% in those with less than 5 days length of stay. Strict glycemic control decreased hospital mortality by one-third. Morbidity from bloodstream infections, acute renal failure and polyneuropathies was also significantly decreased with TGC. The study by Van den Berghe et al. [15] resulted in a flurry of publications regarding glucose control in the ICU and in septic patients. TGC entered evidence-based medicine as part of ventilator-associated pneumonia and the SSC guidelines. Additional multivariate regression analysis of the Van den Berghe data indicated that glucose level and insulin dose were related to decreased mortality and that maintaining glucose levels of 110–150 mg/dl resulted in a higher mortality than did 80–110 mg/dl [16]. In SSG 2004, maintaining appropriate glucose levels with continuous insulin infusion was recom-

rhAPC = recombinant human activated protein C

TGC = tight glucose control

Table 1. Grading system in Surviving Sepsis Campaign Guideline 2008*

Grade of recommendation/description	Supporting evidence
1A Strong recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies
1B Strong recommendation, moderate quality evidence	RCTs with important limitations or exceptionally strong evidence from observational studies
1C Strong recommendation, low or very low quality evidence	Observational studies or case series
2A Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies
2B Weak recommendation, moderate quality evidence	RCTs with important limitations or exceptionally strong evidence from observational studies
2C Weak recommendation, low or very low quality evidence	Observational studies or case series

*Ref 7.

RCTs = randomized controlled trials

mended. Despite the existing data, the target glucose level was set to maintain glucose levels under 150 mg/dl (8.3 mmol/L) (Grade D). In addition to the fear of hypoglycemic complications during TGC, detractors noted that this single-center study was not powered adequately to examine each increment of glucose control and may limit its ability to be extrapolated to other patients besides cardiac surgical patients who are intubated. Furthermore, another single-center prospective observational study by Finney and colleagues [17] demonstrated that a target glucose level < 145 mg/dl (8.0 mmol/L) would be beneficial in reducing mortality in critically ill patients.

To clarify these issues, several studies attempted to replicate the impact of TGC in other patient populations. Although a similarly protocolized prospective randomized study of 1200 (17% diabetic) medical ICU patients yielded improved ICU and hospital length of stay, ventilator days, and incidence of acute kidney injury, it failed to show improved hospital mortality with TGC [18]. However, subgroup analysis did reveal improved mortality rates with TGC in patients who stayed in the ICU for more than 3 days. The data are less clear in injured patients. Scalea and co-researchers [19] explored the influence of TGC in over 2000 trauma populations. In their observational study, implementation of TGC significantly improved overall infection rate, ICU and hospital stay, and mortality rate. In another study employing TGC, Sperry and collaborators [20] found that patients who sustained blunt trauma with shock revealed a 24 hour glucose maximum of > 180 mg/dl and had an 80% increase in mortality if the 24 hour glucose maximum exceeded 180 mg/dl. Interestingly, in this work the elevated mortality rate was not associated with a higher rate of infection or multiple organ failure, suggesting that hyperglycemia served as a marker of poor outcome in this population without concomitant infection. The results of these studies suggest that in trauma patients rationally implemented TGC may be warranted.

TGC, while adopted in ICU care, carries a risk of hypoglycemia, as revealed by two randomized control studies [21,22]. The Glucontrol study [21] was a large-scale multi-institutional trial in Europe that compared blood glucose targets of 80–110 mg/dl to 140–160 mg/dl in a mixed SICU/MICU group of patients. This study examined all glucose levels, not only the 8 a.m. level as in previous studies by Van den Berghe et al. [15,18]. The study was powered to show a 4% reduction in mortality as a primary outcome. However, it was stopped early after accruing 1101 patients of the projected 3500 because of concerns of hypoglycemia and related complications in the TGC group. The study found a hypoglycemia rate of 8.6% in the TGC group and 2.4% in the control group (target level 140–160 mg/dl). Mortality was 17% in the TGC group and

32.6% in the hypoglycemic cohort. In the control group, mortality was 15.2% and 50% in the hypoglycemic cohort. Another multi-institutional trial focusing on a severe sepsis population, the VISEP trial [22], was also stopped early due to a high incidence (17%) of hypoglycemia in the TGC group. A large multi-country, multicenter randomized control trial (NICE-SUGAR trial) recruited mixed ICU populations to compare the mortality between two glycemic control groups (80–110 mg/dl and 140–80 mg/dl) [23]. Their primary outcome, 90 day mortality, was significantly higher in the TGC group (27.5% vs. 24.9%). The incidence of hypoglycemia was lower than in prior trials but still higher than in the control group.

Based on these recent data, SSG 2008 recommendations upgraded the use of intravenous insulin to control hyperglycemia in patients with severe sepsis following stabilization in the ICU (Grade 1B recommendation). The aim of intravenous insulin should be to keep blood glucose lower than 150, using a validated protocol for insulin dose adjustment (Grade 2C recommendation). Many regulatory bodies have embraced

a tight glucose target (80–110 mg/dl) as the standard. As noted in SSG 2008, careful attention must be paid to prevent and detect severe hypoglycemia. While

there are strong data to support this in cardiac surgery patients and patients in the ICU with length of stay more than 3 days, broader adoption necessitates simplified protocols and minimizing of hypoglycemic episodes.

The debate on the management of sepsis in the surgical ICU is still ongoing

STEROID ADMINISTRATION

High dose steroids were routinely employed in septic shock patients until Bone and co-workers [24] debunked this practice in 1991. On the other hand, Bollaert et al. [25] showed that low dose steroid (hydrocortisone 300 mg/day) administration significantly improved the shock reversal rate (68% vs. 21%, $P = 0.007$) and 28 day mortality was lower in those given steroids (32% vs. 63%, $P = 0.09$). Steroid use in sepsis had a renaissance encouraged by a 2002 study by Annane and colleagues [26]. This multicenter randomized clinical trial examined use of the glucocorticoid hydrocortisone plus the mineralocorticoid fludrocortisone in septic patients who did not respond to fluid replacement and required use of vasopressors. In this population, corticosteroids provided a survival advantage (hazard ratio 0.67) and afforded an earlier wean from vasopressors (hazard ratio 1.91). There was no difference in the incidence of adverse events. SSC 2004 recommended the use of low dose intravenous corticosteroids for septic patients who require vasopressors after fluid resuscitation.

Since the publication of the 2004 guidelines, additional data regarding steroid use have emerged. Significantly different results were found in another multicenter trial from Europe (CORTICUS) [27]. This study examined 28 day mortality, length of stay, and complications in septic patients who were

unresponsive to fluid resuscitation requiring vasopressors. The majority of patients were surgical (65%) and had septic shock with documented infection; 47% were non-responders to an ACTH stimulation test. Patients in the steroid arm received 50 mg of intravenous hydrocortisone every 6 hours for 5 days that was then tapered. Fludrocortisone was not administered in this study. There was no difference in 28 day mortality regardless of response to an ACTH stimulation test (39.2% vs. 36.2%, $P = 0.69$ in ACTH-unresponsive patients and 28.8% vs. 28.7%, $P = 1.00$ in ACTH-responsive patients). While earlier reversal of shock was identified in the hydrocortisone group, infectious complications were more common in this group.

In light of these two conflicting studies the SSC recommendations give relatively tempered guidelines. Intravenous hydrocortisone should be considered only in septic shock patients who are only poorly responsive to fluid resuscitation and vasopressor therapies (Grade 2C recommendation). Additionally, given the fact that there was no difference in response to steroids between responder and non-responder in the ACTH stimulation test, this test should not be used to select the septic shock patients to be given steroids (Grade 2B recommendation). This represents a much less enthusiastic endorsement for the use of this therapy between versions of the SSG.

ADMINISTRATION OF RHAPC

In spite of the millions of dollars spent and the dozens of clinical trials on sepsis until recombinant human activated protein C was studied, no agent was found to improve survival. PROWESS [28] was a multicenter randomized double-blinded randomized trial that demonstrated improved survival in the rhAPC group. A 6.1% reduction in absolute total mortality and a relative risk reduction of 19.4% were conferred by rhAPC infusion in patients with severe sepsis and septic shock. The PROWESS study was stopped early; however, procedural questions persisted. Most notably, the survival benefit was noted only in post hoc analysis in patients with higher APACHE II scores (Acute Physiology and Chronic Health Evaluation II) and increasing organ dysfunction, which led the FDA to approve rhAPC therapy only in patients with dysfunction in more than one organ and APACHE score ≥ 25 . Despite concerns about the understated results of the PROWESS trial [29], SSG 2004 highly recommended rhAPC for patients at high risk of death (APACHE II ≥ 25 , sepsis-induced multiple organ failure, septic shock, or sepsis-induced acute respiratory distress syndrome) (Grade B).

A study designed to broaden the application of rhAPC to less severe patients was the ADDRESS trial [30]. Severe sepsis patients with a low risk of death (APACHE II score < 25 or single organ failure) were included in this trial. ADDRESS was stopped early due to a lack of efficacy. While there was no significant difference in 28 day mortality (18.5% in the rhAPC

Table 2. Contraindications of recombinant human activated protein C

Active internal bleeding
Intracranial, intraspinal surgery or severe head injury within 2 months
Hemorrhagic stroke within 4 months
Patient with an epidural catheter
History of intracranial neoplasm, known mass lesion or brain herniation
Trauma patient with high risk of bleeding
Known allergy to recombinant human activated protein C

group vs. 17.0% in the placebo group, $P = 0.34$) and in-hospital mortality (20.6% vs. 20.5%, $P = 0.98$), serious bleeding complications were significantly higher in the rhAPC group (3.9% vs. 2.2%, $P = 0.02$). Thus, SSG 2008 significantly weakened its recommendations of the use of activated protein C. Several contraindications exist for rhAPC [Table 2]. Most of the contraindications concern the risk of bleeding. This bleeding risk approached clinical significance in the PROWESS trial and was realized in the ADDRESS trial. Registry studies indicate that the risk of bleeding may actually be higher than reported in the clinical trials. Therefore, while rhAPC is the first pharmacological treatment for sepsis, its indications are limited to a relatively narrow patient population. The SSC recommendations are for rhAPC therapy in patients with high risk of death with severe sepsis and no contraindications related to bleeding risk (Grade 2B recommendation; 2C if within 30 days postoperative). SSC does not recommend rhAPC for adult patients with severe sepsis and low risk of death (Grade 1A recommendation). In summary, rhAPC is an expensive therapy that is indicated in extremely septic patients and carries a high risk of bleeding complications especially in post-surgical patients.

ADMINISTRATION OF TOTAL PARENTERAL NUTRITION

Nutritional support is one of the pillars of surgical care; without it, wound healing is compromised and the risk of infection dramatically increases. University of Pennsylvania researchers developed total parenteral nutrition as a means of supporting patients who cannot sustain enteral nutrition [31]. Clearly, patients sustained on total parenteral nutrition do better than those subjected to starvation. However, total parenteral nutrition is inferior compared to enteral nutrition. A number of studies reported that patients receiving total parenteral nutrition had significantly poorer outcomes compared to patients given enteral nutrition in an ICU setting [32-34]. Furthermore, in a recent meta-analysis [35] that predates the use of TGC, there was no increase in mortality with total parenteral nutrition, but an 8% increase in all infections, a 3.5% increase in catheter-related bloodstream infections, and a 1.2 day increase in length of stay.

SSG 2004 recommended a continuous supply of glucose substrate once insulin infusion is started to maintain glucose

levels. While the glucose source can be either enteral or parenteral, it was suggested to maximize the benefits of enteral and minimize the risk of parenteral nutrition. However, most studies in the aforementioned meta-analysis predate the implementation of TGC, which might abate the risk of parenteral nutrition. Our group addressed this question in a prospective cohort study of ICU admissions who were assigned total parenteral nutrition if enteral nutrition was not tolerated by day 3 [36]. TGC was utilized in all. Despite a lower mean glucose level in the total parenteral compared to the total enteral nutrition patients, the former increased the risk of infectious complications. A multiple logistic regression model demonstrated a nearly fivefold increased risk of catheter-related bloodstream infections. Sena and colleagues [37] evaluated the outcome of 567 severe blunt injury patients who received enteral versus parenteral nutrition. Seventy-five percent achieved enteral nutrition with 17% receiving early parenteral nutrition. In the parenteral cohort there was a 2.1 relative risk of infection while the combination of enteral and parenteral nutrition significantly increased the mortality relative risk by 2.3. Although SSG 2008 recommends that all patients receiving intravenous insulin in the ICU receive a glucose calorie source, there is a lack of consensus about the optimal route of feeding. Since enteral nutrition is often contraindicated or intolerable for the patients in the surgical ICU, recent ESPEN guidelines recommend the initiation of parenteral nutrition within 24 to 48 hours for clinically ill patients who are not expected to be on normal nutrition within 3 days of admission [38]. However, clinicians must weigh the risk of total parenteral nutrition when thinking about nutritional support in critically ill patients who cannot tolerate the enteral route.

SUMMARY

Based on the criticism of undue industry influence in the creation of the initial document and new clinical trials with divergent results, the SSG were recently revised substantially. We have focused on changes in the use of tight glucose control, and on administration of steroids, activated protein C and total parenteral nutrition in the septic patient. Uniformly, recommendations in these areas have been softened due to new findings. While tight glucose control may decrease mortality, there is significant concern about the risk of hypoglycemia in the septic patient population and, consequently, the recommended target glucose levels have been altered. The data in support of steroids are even less clear and suggest that cortisol stimulation testing may be unnecessary. Additionally, the role of mineralocorticoids in the improved survival of septic patients is currently unknown due to the different use of this drug across the two major studies. Additionally, only the most critical patients may benefit from rhAPC and will be exposed to significant bleeding risk with that therapy. Finally,

total parenteral nutrition carries inherent risks and should be considered only in patients with long-term inability to receive enteral nutrition. The literature in the field of sepsis management is dynamic and warrants the attention and consideration of a dedicated practitioner to provide the best, most contemporary therapies for the surgical patient.

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