The 2012 Surviving Sepsis Campaign: Management of Severe Sepsis and Septic Shock—An Update on the Guidelines for Initial Therapy

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Abstract With the 2012 Surviving Sepsis Campaign Guidelines, clinicians have access to evidence based guidelines for the treatment of adults with severe sepsis. Some of the important changes include: new recommendations for screening of adults with sepsis for organ dysfunction (grade 1C); lactate normalization as a therapeutic target in early resuscitation (grade 2C); colloids no longer recommended for initial resuscitation (grade 1B); a minimum of 30 mL/kg for initial fluid resuscitation (grade 1C); norepinephrine as the initial vasopressor of choice (dopamine allowed only under specific circumstances) (grade 1B); removal of recombinant human activated protein C for the treatment of severe sepsis (ungraded); removal of permissive hypercapnea as a recommendation (ungraded); and a change of the target blood glucose level to <180 mg/dL (previously 150 mg/dL) (grade 1A). In this article, we review the evidence base for these and other guideline changes for the early treatment of severe sepsis in adults.

Keywords Sepsis · Severe sepsis · Septic shock · Surviving Sepsis Campaign · Guideline · Diagnosis

Introduction

Severe sepsis, defined as sepsis with acute end-organ dysfunction, is a complex, high-risk syndrome that develops from a disproportionate inflammatory response to an infection [1•]. For patients affected, pathogenic virulence factors and the resulting inflammatory response lead to a cascade of organ derangements that can rapidly spiral into multi-organ failure and death. Each year in the United States there are approximately 750,000 cases of severe sepsis, resulting in more than 200,000 deaths [2, 3]. As severe sepsis can result in dysfunction of multiple organ systems, the therapies offered for this syndrome can be complex and diverse. With the publication of the 2012 Surviving Sepsis Campaign Guidelines (SSCG), hospital based clinicians have access to an updated, evidence-based resource for the diagnosis and management of severe sepsis and septic shock [1•]. The enormous quantity of research that has been performed in this field has led to significant changes from the 2008 SSCG [4]. To allow clinicians already familiar with the 2008 SSCG to rapidly update their knowledge base regarding the new guidelines, we sought to summarize the changes for the 2012 SSCG that are important to hospital-based practitioners, and review the evidence supporting the current guidelines.

As with previous iterations of the SSCG, the Grading of Recommendation Assessment, Development and Evaluation (GRADE) system was utilized to assess the quality of evidence (Table 1) [5, 6]. Additionally, the Surviving Sepsis Campaign (SSC) categorizes recommendations as strong or weak, and suggests that the strength of recommendations (1 or 2) should carry more weight in clinical decision making than the level of evidence (A, B, C or D). This recommendation is based on the understanding that many clinical questions would be extraordinarily difficult

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to answer in a randomized controlled trial (i.e., antibiotics vs. placebo), but the strength of observational evidence and consistency of expert opinion in many cases provide adequate support for a strong recommendation.

The SSC has been criticized in the past for its industry ties, and in fact the organization was founded through an unrestricted grant from Eli Lilly, a pharmaceutical company that marketed Xigris (recombinant human activated protein C, or rhAPC) [7]. Since the 2008 guidelines, the SSC has been free of corporate sponsorship, though many of the individual contributors continue to report funding or paid consultation services from Eli Lilly and other corporations. The 2012 SSCG describe a detailed methodology to prevent authors from directly participating in guidelines for which they could have a commercial or academic conflict of interest. Furthermore, with the recent removal of Xigris from the market, the potential motivation for Eli Lilly to significantly influence guideline development has been decreased. With the 2012 SSCG, the Infectious

Disease Society of America has now joined with 27 other pertinent professional organizations to sponsor the guidelines, significantly reducing the potential for conflict of interest influences on the guideline's development.

For this review, we will describe the evidence base for changes relevant to the early care of adults with severe sepsis made since the 2008 SSCG. These therapies include treatment commonly provided in the emergency department, medical wards, and initial therapy commonly performed in the intensive care unit (ICU) setting.

Screening for severe sepsis—diagnosis and performance improvement

The 2012 SSCG include a new emphasis on early screening for severe sepsis, including hospital based performance improvement strategies to monitor screening practices [1•]. Specifically, the 2012 SSCG recommend routine screening of potentially infected seriously ill patients to increase the early identification of severe sepsis (grade 1C) (Table 2). This recommendation is largely based on the results of the SSC monitoring program, which evaluated bundle compliance and patient outcomes for 15,022 patients at 165 geographically disparate clinical sites [8•]. This study demonstrated that SSC bundle compliance, including early diagnosis, was associated with significantly decreased mortality risk from severe sepsis. The SSC bundle also now recommends measuring lactate levels on patients with suspected sepsis within 3 h of identification [1•]. This recommendation is based on numerous studies demonstrating improved outcomes when system wide initiatives are introduced to rapidly, systematically screen for occult tissue hypoperfusion in sepsis [8•, 9–11].

Hospital based performance initiatives have, for the first time, been included in the SSC guidelines with the 2012 revision [ungraded (UG)] (Table 2) [1•]. Though not graded, there is significant evidence linking hospital quality improvement initiatives for severe sepsis with improved outcomes [12–15]. These studies highlight the effect of utilizing multi-disciplinary teams of physicians, nurses, pharmacists, respiratory therapists and dieticians to improve SSC bundle compliance and patient outcomes. These initiatives share common themes, including consistent education, bundle development, and data collection, to allow for continuous feedback and performance improvement. Education and performance feedback are two key areas where hospital wide initiatives have been shown to change physician behavior and improve outcomes [8•, 16].

The 2012 SSCG continue to highlight the need for the early diagnosis of pathogens in suspected severe sepsis, including obtaining blood and appropriate body fluid or tissue cultures prior to starting antibiotics (grade 1C)

Table 1 Grading of evidence for the 2012 Surviving Sepsis Campaign Guidelines for the management of severe sepsis and septic shock

Strength of recommendation^a

1 Strong recommendation

2 Weak recommendation

Factors that may decrease the strength of evidence

- 1 Poor quality of planning and implementation of available RCTs, suggesting high likelihood of bias
- 2 Inconsistency of results, including problems with subgroup analyses
- 3 Indirectness of evidence (differing population, intervention, control, outcomes, comparison)
- 4 Imprecision of results
- 5 High likelihood of reporting bias

Factors that may increase the strength of evidence

- 1 Large magnitude of effect (direct evidence, relative risk >2 with no plausible confounders)
- 2 Very large magnitude of effect with relative risk >5 and no threats to validity (by two levels)
- 3 Dose–response gradient

Methodologic level of evidence

A RCT's

B Downgraded RCTs or upgraded observational studies

C Well-done observational studies with control RCTs

D Downgraded controlled studies or expert opinion based on other evidence

The Grading of Recommendation Assessment, Development and Evaluation (GRADE) system was utilized to guide assessment of the quality of evidence

RCT randomized controlled trial

^a The assignment of a 1-strong or 2-weak recommendation is considered of greater clinical importance than a difference in the level of evidence (A, B, C, D) by the Surviving Sepsis Campaign Guideline Committee

Table 2 Comparison of the 2012 and 2008 Surviving Sepsis Campaign Guidelines—diagnosis, performance improvement, initial resuscitation and fluid therapy [1•, 4]

2008 Surviving Sepsis Campaign Guidelines		2012 Surviving Sepsis Campaign Guidelines	
Intervention	Grade	Intervention	Grade
<i>Diagnosis and performance improvement</i>			
No recommendation	NR	Routine screening of potentially infected, seriously ill patients for severe sepsis to allow earlier implementation of therapy.	1C
No recommendation	NR	Hospital-based performance improvement efforts in severe sepsis	UG
Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration	1C	Significant delay defined as >45 min	1C
No recommendation	NR	2 sets of blood cultures (aerobic and anaerobic bottles) before antimicrobials, 1 percutaneously, 1 via each vascular access device, unless the device placed within 48 h	1C
No recommendation	NR	1,3 beta-D-glucan (2B), Mannan/antimannan antibody (2C) assay if available and invasive candidiasis in differential	2B;2C
Perform imaging studies promptly to confirm and sample any source of infection, if safe to do so	1C	Downgraded	UG
<i>Initial resuscitation and fluid therapy</i>			
If venous oxygen saturation target is not achieved, consider further fluid. Transfuse red blood cells if required to hematocrit of ≥ 30 % and/or start dobutamine infusion, max 20 $\mu\text{g/kg/min}$	2C	In patients with elevated lactate levels target resuscitation to normalize lactate.	2C
Fluid-resuscitate using crystalloids or colloids	1B	Crystalloids as initial choice	1B
No recommendation	NR	Do not use hydroxyethyl starches	1B
No recommendation	NR	Albumin when patients require “substantial” amounts of crystalloids (2C)	2C
Target a CVP of ≥ 8 mm Hg (≥ 12 mm Hg if mechanically ventilated)	1C	Removed	R
Use a fluid challenge technique while associated with a hemodynamic improvement	1D	Based on dynamic or static variables	UG
Give fluid challenges of 1,000 mL of crystalloids or 300–500 mL of colloids over 30 min. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion	1D	Minimum of 30 mL/kg crystalloid (some may be albumin) in patients with septic shock or lactate ≥ 4.0 mmol/L; may need more in some patients	1C
Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement	1D	Fluid challenge until hemodynamic improvement based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables	UG

Includes only guidelines changed between the 2008 and 2012 Surviving Sepsis Campaign Guidelines

UG ungraded, NR no recommendation, R removed

(Table 2) [1•]. Similar to the 2008 SSCG, the updated guidelines recommend that cultures be obtained only if they do not significantly delay initiating antibiotics [4]. For the first time, the precise time-period of a significant delay is defined, with a more than 45-min delay in antibiotic initiation considered too long to wait for obtaining cultures. This time interval was determined from observational studies suggesting that even a 1-h delay in antibiotic initiation for patients with severe sepsis can significantly worsen clinical outcomes [17, 18]. The 2012 guidelines specifically recommend that lumbar puncture (LP) to

obtain cerebrospinal fluid culture should not delay antibiotic initiation if the LP is anticipated to cause more than a 45-min delay in starting antibiotics. The 2012 SSCG continue to encourage drawing cultures from indwelling vascular access devices as well as peripherally, and the need to collect more than 10 mL of fluid with each culture [1•].

The SSC did not find adequate evidence to support the use of biomarkers such as procalcitonin for the diagnosis of severe sepsis or the use of polymerase chain reaction techniques for more rapid identification of pathogens. However, there is a new recommendation to use the

1,3- β -D-glucan assay (grade 2B), and the mannan/anti-mannan assays (grade 2C) to identify invasive candidiasis when this infection is suspected [1•]. These assays provide positive results sooner than traditional fungal cultures, though there is a risk of false-positive assays, and the impact on therapeutic strategies and clinical outcomes has not been fully elucidated [19, 20]. Similar to the 2008 guidelines, the 2012 SSCG recommend prompt performance of imaging studies to confirm potential infectious sources [1•]. However, the evidence grade for this recommendation has been downgraded from a 1C to UG, acknowledging that risks of transport and invasive imaging may exist for critically ill patients, and that there is no high quality evidence to support this guideline.

Initial Resuscitation and Fluid Administration

Along with antimicrobial therapy, early aggressive resuscitative therapy, directed at defined goals, is one of the mainstays of initial sepsis management. Rivers et al., conducted a randomized, controlled study in patients with severe sepsis or septic shock presenting to an emergency department of an urban teaching hospital [21]. The patients were at high risk and had either persistent hypotension after a fluid challenge or serum lactate levels of 4 mmol/L or higher. Two hundred sixty patients were randomized to receive either early goal-directed therapy (EGDT), in a protocol aimed at maximizing the intravascular volume and correcting global tissue hypoxia, or standard therapy in the first 6 h after presentation. The goals in the goal-directed therapy group were:

- Central venous pressure 8–12 mm Hg (achieved with aggressive crystalloid resuscitation)
- Mean arterial blood pressure >65 mm Hg (using vasoactive drugs if necessary)
- Scvo2 above 70 %.

To achieve this third goal, packed red blood cells were infused to reach a target hematocrit of greater than 30 %. For patients with a hematocrit higher than 30 %, but still with an Scvo2 less than 70 %, inotropic agents were added and titrated to the Scvo2 goal of 70 %. In this study, EGDT reduced the in-hospital mortality rate by 16 % (30.5 % in the goal-directed group vs. 46.5 % in the standard therapy group, $P = 0.009$) and also reduced the 28- and 60-day mortality rates by similar proportions [21]. Subsequent studies of a protocol for early recognition and treatment of sepsis have concluded that early aggressive fluid resuscitation decreases the ensuing need for vasopressor support [22]. A resuscitation strategy based on EGDT is thus a

major component of the initial resuscitation bundle recommended by the 2008 Surviving Sepsis Campaign [4].

However, there are multiple areas of debate regarding this resuscitation strategy. Concerns have been raised about the design of the study by Rivers et al., and the mortality rate in the control group, which was higher than one would expect from the patients' Acute Physiology and Chronic Health Evaluation II (APACHE II) scores [23]. In particular, the bundled approach they used precluded the ability to differentiate which interventions were primarily responsible for the outcome benefits. Indeed, there were two major interventions in the EGDT group: a protocol for achieving the goals described and the use of Scvo2 as a goal [21].

Aggressive fluid resuscitation, in general, is considered the most critical element of all the major EGDT interventions, and there is little argument on its value. It continues a prominent role in the 2012 guidelines, recommending (grade 1C) at least 30 mL/kg in patients with shock or lactate ≥ 4 mmol/L (Table 2) [1•]. The main debate centers on the endpoint for determining adequate fluid resuscitation. Central venous pressure (CVP) as a preload marker was central to the EGDT study, but several subsequent studies showed that central venous pressure may not be a valid measure to predict fluid responsiveness [24, 25]. So use of a target CVP has been removed in the new guidelines, replaced with “target resuscitation to normalize lactate” (grade 2C). Use of a fluid challenge technique, based on dynamic (change in pulse pressure, SVI) or static (BP, HR) variables is mentioned, but not graded in terms of recommendation (Table 2).

The choice of colloids or crystalloids for fluid resuscitation is another area of debate. Clinical evidence suggests that albumin is equivalent to normal saline in a heterogeneous ICU population, but subgroup analyses suggest albumin could be superior in patients with septic shock [26, 27]. Studies are ongoing to examine this question (NCT00707122, NCT01337934, and NCT00318942). Currently, the new guidelines recommend crystalloids as the preferred initial fluid (grade 1B), but support the use of albumin when patients require “substantial” amounts of crystalloids (grade 2C). The use of hydroxyethyl starch (HES) in severe sepsis is associated with higher rates of acute renal failure and the need for renal replacement therapy than Ringer's lactate [28]. This is further substantiated by two recent randomized controlled studies, which found that the use of HES for fluid resuscitation in severe sepsis, compared with crystalloids, did not reduce the mortality rate (and even increased it in one study), and was associated with more need for renal replacement therapy [29, 30]. So, there is a 1B recommendation to *avoid* its use in sepsis entirely (Table 2) in the 2012 SSCG.

The use of Scvo2, to monitor adequacy of resuscitation, is another topic of debate, and other, simpler, variables have been evaluated. A 2010 study assessed the non-inferiority of incorporating venous lactate clearance into the EGDT protocol vs Scvo2 [31•]. Both groups had identical goals for central venous pressure and mean arterial pressure but differed in the use of lactate clearance (defined as at least a 10 % decline) or Scvo2 (>70 %) as the goal for improving tissue hypoxia. There were no significant differences between groups in their in-hospital mortality rates (17 % in the lactate clearance group vs 23 % in the Scvo2 group; criteria for non-inferiority met). This suggested that lactate may be an acceptable alternative to Scvo2 as a goal in EGDT. However, a secondary analysis of the data revealed a lack of concordance in achieving lactate clearance and Scvo2 goals, which suggests that these parameters may be measuring distinct physiologic processes [32]. Since the hemodynamic profiles of septic shock patients are complex, some feel it may be prudent to use both of these markers of resuscitation until further studies are completed. However, the 2012 guidelines only support the use of lactate monitoring (grade 2C) (Table 2) [1•].

Given debates over multiple elements of EGDT, a number of prospective randomized trials are under way to evaluate resuscitative interventions. These include the Protocolized Care for Early Septic Shock trial [ProCESS] (NCT00510835), the Australasian Resuscitation in Sepsis Evaluation trial (NCT00975793), and the Protocolised Management of Sepsis (ProMiSe) trial in the United Kingdom (ISRCTN 36307479). These three trials will evaluate, collectively, close to 4,000 patients and will provide additional insights into individual elements, as opposed to the full bundle, of resuscitative interventions in septic shock.

Antimicrobial Therapy and Source Control

The 2012 SSCG persist in advocating antibiotic administration as early as possible, preferably within 1 h, from the recognition of severe sepsis and septic shock (Table 3) [1•]. These guidelines remain unchanged from the 2008 SSCG guidelines, though the evidence supporting rapid antibiotic initiation for severe sepsis (non-septic shock) was upgraded from a grade 1D (downgraded controlled studies or expert opinion) to 1C (well-done observational studies) [4]. This change reflects recent observational studies demonstrating a protective effect for early antibiotic administration. Levy et al. [8•], in the SSC bundle observational compliance study, demonstrated that antibiotic initiation within 1 h of severe sepsis recognition was associated with decreased mortality risk (adjusted OR 0.86, $P < 0.001$). Similarly, a recent systematic review of

observational severe sepsis resuscitation cohort studies found that SSC bundle compliance, and particularly early antibiotic administration, was associated with decreased mortality in severe sepsis [33].

The 2012 SSC guidelines call for administration of antimicrobials with efficacy against all potential pathogens (grade 1B), but a new emphasis has been added to reassess the antimicrobial regimen daily for potential de-escalation (grade 1B) (Table 3). This emphasis has presumably been added to address the issues of antimicrobial resistance, costs and toxicity. The risks of super-infection with *Candida* species, *C. difficile*, or vancomycin resistant *Enterococcus*, have been linked with prolonged antibiotic administration, and early discontinuation or narrowing has been shown to decrease the risk of superinfection with *C. difficile* [34, 35]. The 2012 SSCG advocate using low procalcitonin levels to assist clinicians in the decision to discontinue antibiotics for patients who no longer show clinical signs of infection (grade 2C) [1•]. This fairly low level recommendation was made because observational studies have demonstrated conflicting results regarding the efficacy of this approach [36]. A recent multi-center randomized controlled trial of a procalcitonin-based antibiotic stewardship protocol versus usual care found no significant decrease in antibiotic use for the procalcitonin arm [37]. The preponderance of evidence has shown that a procalcitonin supplemented regimen for antimicrobial stewardship may allow for slightly shorter duration of antimicrobial therapy in sepsis, but the cost effectiveness of this approach has not been validated [38].

Similar to the 2008 SSCG, the 2012 guidelines advise combination antimicrobial therapy for patients at risk of *Pseudomonas* infection (Table 3). New for 2012 is an additional proposal for combination therapy for potential *Acinetobacter* infection, and this guideline has been increased from grade 2D to 2B [1•]. Combination antimicrobial therapy may benefit patients infected by resistant pathogens, but evidence to support this approach has been varied [39]. A 2009 Cochrane Review found no benefit of dual antibiotics relative to monotherapy for gram negative infections in sepsis [40]. However, a more recent meta-analysis showed that when stratified by illness severity, patients at a high short-term mortality risk benefited from combination therapy, while low-risk patients may be harmed with dual therapy [41]. The authors of this review postulate that, in high-risk patients with severe infections, the benefit of early combination therapy may outweigh the potential toxicity of broad-spectrum coverage. One important caveat to these findings is that a significant proportion of research on the utility of combination antibiotic therapy assigned treatment based on culture results. A recent randomized controlled trial of empiric dual versus monotherapy for severe sepsis found no mortality benefit or

Table 3 Comparison of the 2012 and 2008 Surviving Sepsis Campaign Guidelines—antimicrobial therapy and source control [1•, 4]

2008 Surviving Sepsis Campaign Guidelines		2012 Surviving Sepsis Campaign Guidelines	
Intervention	Grade	Intervention	Grade
<i>Antimicrobial therapy</i>			
Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis or septic shock	1D Severe Sepsis; 1B Septic Shock	Change in grade for severe sepsis	1C Severe Sepsis; 1B Septic Shock
Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs	1C	Reassess antimicrobial regimen daily for potential deescalation to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs	1B
No recommendation	NR	Use of procalcitonin or similar biomarkers for antibiotic stewardship	2C
Consider combination therapy in <i>Pseudomonas</i> infections	2D	Consider combination therapy in <i>Pseudomonas</i> and <i>Acinetobacter</i> infections	2B
No recommendation	NR	Specific antibiotic combinations recommended for: respiratory failure and septic shock against <i>Pseudomonas</i> ; for septic shock against <i>Pneumococcus</i>	2B
Consider combination empiric therapy in neutropenic patients	2D	Upgraded	2B
Combination therapy no more than 3–5 days and de-escalation following susceptibilities	2D	Empiric combination therapy should not be used for more than 3–5 days	2B
Duration of therapy typically limited to 7–10 days; longer if response is slow, there are undrainable foci of infection or immunologic deficiencies	1D	Downgraded; added longer course for bacteremia with <i>S. aureus</i>	2C
No recommendation	NR	Initiate antivirals as early as possible if viral origin suspected	2C
Stop antimicrobial therapy if cause is found to be noninfectious	1D	Downgraded	UG
<i>Source identification and control</i>			
A specific anatomic site of infection should be established as rapidly as possible (1C) and within first 6 h of presentation (1D)	1C, 1D	Intervention should be undertaken for source control as rapidly as possible and within first 12 h of presentation	1C
Choose source control measure with maximum efficacy and minimum physiologic upset	1D	Downgraded	UG
Remove intravascular access devices if potentially infected	1C	Downgraded	UG
No recommendation	NR	Consider selective oral decontamination to prevent Ventilator Associated Pneumonia (VAP)	2B
No recommendation	NR	Oral chlorhexidine for mechanically ventilated patients to reduce VAP	2B

Includes only guidelines changed between the 2008 and 2012 Surviving Sepsis Campaign Guidelines

UG ungraded, NR no recommendation, R removed

improvement in organ dysfunction from dual therapy [42]. The 2012 SSCG also advise using local pathogen resistance patterns to guide therapy, and limiting empiric combination antibiotic therapy to 3–5 days (grade 2B) [1•].

The 2012 SSCG include a new recommendation for the initiation of antiviral therapy as soon as possible for patients with severe sepsis possibly caused by certain viral pathogens (grade 2C) (Table 3). Antiviral therapy is specifically recommended for patients with suspected influenza who require hospitalization, those at high-risk of

complications from influenza, and for patients with certain highly pathogenic influenza strains (2009 H1N1, influenza A H3N2, and influenza B). Importantly, the guidelines encourage basing treatment decisions on updated information of the most active viral strains for each influenza epidemic. Finally, the 2012 SSCG continue to recommend discontinuing antimicrobial therapy for patients with severe inflammatory states determined to have a non-infectious etiology. However, while the 2008 SSCG provided a 1D grade for this recommendation, the 2012 SSCG

changed this recommendation to UG, as they recognize that evidence on this topic is limited.

Source control recommendations remain largely unchanged for the 2012 SSCG. The guidelines suggest identifying or excluding a specific anatomic infectious source as soon as possible for patients with severe sepsis [1•]. The recommended timing to obtain source control has been changed from 6-to 12-h and the grade for source-control timing has been changed from a 1D to 1C. This grade change was based on a case-series of children with necrotizing fasciitis, a retrospective cohort of adults with necrotizing soft tissue infections, and an analysis of post-operative abscess formation [43–45]. In the study by Boyer et al. [44], a more than 14-h delay in debridement of necrotizing tissue was associated with a significantly worse outcome. These studies are limited in quality and focused on specific infectious sources, but the SSC felt there was sufficient evidence to support the timing of early source control for all patients with severe sepsis.

The 2012 SSCG support avoiding early debridement for severe pancreatitis, as research has demonstrated better outcomes when surgical intervention is delayed until demarcation of necrotic tissue occurs [46]. The 2012 SSCG also propose prompt removal of potentially infected intravascular access devices, though this recommendation has been downgraded to UG as it is based on expert opinion [47]. Importantly, this recommendation is shared by the Infectious Disease Society of America [48]. Overall the evidence base for early source control in severe sepsis is limited. In spite of the paucity of evidence, the 2012 SSCG advocate early source control whenever possible [1•]. They also acknowledge the potential risks of invasive procedures and transport in critical illness, and advise clinician discretion in determining the timing of definitive source control [1•].

Vasopressors and Inotropes in Sepsis

The 2008 SSCG recommended maintaining mean arterial pressure (MAP) at ≥ 65 mm Hg at (grade 1C) with fluid resuscitation combined with vasoactive medications if unable to support MAP with fluids alone (Table 4) [4]. The 2008 SSCG suggested either norepinephrine or dopamine administered via central catheter as the vasopressor agent of choice (grade 1C). The use of epinephrine, phenylephrine or vasopressin as first line vasopressors was discouraged (grade 2C). Vasopressin 0.03 units/min could be added to norepinephrine with anticipation of an effect “equivalent to norepinephrine alone” (UG). A grade 2B recommendation was given to using epinephrine as the first alternative vasopressor agent in patients with septic shock that was poorly responsive to norepinephrine or dopamine. At the time, it was felt there

was little high-quality data to support one vasopressor over another in the treatment of septic shock. Since these recommendations, several important studies have shed light on this issue and are reflected in the 2012 SSCG [1•].

The 2012 SSCG continues to endorse the importance of maintaining a MAP ≥ 65 mm Hg (grade 1C) (Table 4) [1•]. The use of norepinephrine is now the first line vasopressor if blood pressure is not adequate despite volume support (grade 1B). Epinephrine is suggested in addition to or as a substitute for norepinephrine when another vasopressor is needed to maintain adequate blood pressure (grade 2B). Low-dose vasopressin (0.03 units/min) is not recommended as a first-line vasopressor but can be added to norepinephrine with the intent of reducing norepinephrine dose or raising MAP (UG). The limited role for dopamine is new and is limited to “highly selected patients” with bradycardia and a low risk of tachyarrhythmias (grade 2C). Low-dose dopamine is not recommended for renal protection (grade 1A).

The rationale for these changes is based on new clinical data and an analysis of new data in conjunction with older data. Short-term mortality and serious adverse events, including supraventricular and ventricular arrhythmias, statistically favored norepinephrine over dopamine as the vasopressor of choice in septic shock in a “GRADEpro” analysis of clinical data available [1•]. A pivotal large, multicenter, randomized trial by De Backer et al. [49] treated patients in shock with either dopamine or norepinephrine as the first-line vasopressor. The majority of these patients were in septic shock and, although there was no significant difference in death between treated patients, the use of dopamine was associated with a near doubling of adverse arrhythmia events. A systematic review of randomized clinical trials in septic shock concluded that norepinephrine was superior to dopamine for both hospital and 28-day mortality endpoints [50]. A systematic review and a meta-analysis both evaluated observational and randomized clinical trials comparing dopamine to norepinephrine in the initial treatment of septic shock. Both analyses concluded that dopamine was associated with more arrhythmic events [51•, 52]. Dopamine was associated with greater mortality compared to norepinephrine in the meta-analysis, which combined five observational ($n = 1,360$) and six randomized trials ($n = 1,408$) [51•]. An editorial accompanying the meta-analysis called for physicians to no longer use dopamine as the first vasopressor for septic shock [53].

The lack of strong or even graded recommendations for the use of vasopressin in the treatment of septic shock is the result of very limited high-quality data [54]. A large randomized, multicenter, double-blind trial assigned patients ($n = 778$) with septic shock requiring low-dose norepinephrine to additional vasopressin (0.03 units/min) or

Table 4 Comparison of the 2012 and 2008 Surviving Sepsis Campaign Guidelines—vasopressors and corticosteroids [1•, 4]

2008 Surviving Sepsis Campaign Guidelines		2012 Surviving Sepsis Campaign Guidelines	
Intervention	Grade	Intervention	Grade
<i>Vasopressors</i>			
Norepinephrine (NE) or dopamine centrally administered are the initial vasopressors of choice	1C	NE recommended as first-line vasopressor (upgraded); dopamine removed	1B
No recommendation	NR	Epinephrine (Epi) add to or substituted for NE as needed to maintain adequate BP	2B
Epinephrine, phenylephrine, or vasopressin should not be used as initial vasopressor. Vasopressin may be added to NE with anticipation of an effect equivalent to NE alone.	2C	Vasopressin added to NE to raise MAP or decrease NE	UG
No recommendation	NR	Low dose vasopressin not recommended as single initial vasopressor; higher vasopressin doses only as salvage therapy	UG
No recommendation	NR	Dopamine as alternative vasopressor to NE only in highly selected patients (low risk of tachyarrhythmias, absolute or relative bradycardia)	2C
No recommendation	NR	Phenylephrine not recommended except when NE assoc with serious arrhythmia, CO high with low BP, or salvage	1C
Epi as first alternative agent when BP is poorly responsive to NE or dopamine	2B	Removed	R
In patients requiring vasopressors, insert an arterial catheter as soon as practical	1D	Downgraded	UG
<i>Corticosteroids</i>			
Consider intravenous hydrocortisone (HC) for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors	2C	Added suggested dose of 200 mg/day	2C
HC is preferred to dexamethasone	2B	Removed	R
Fludrocortisone (50 mcg orally once a day) may be included if an alternative to HC is being used that lacks significant mineralocorticoid activity. Fludrocortisone if optional if HC is used	2C	Removed	R
HC dose should be ≤ 300 mg/day	1A	Removed	R
<i>Blood product administration</i>			
Consider rhAPC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II ≥ 25 or multiple organ failure) if there are no contraindications.	2B; 2C if post-operative	Removed	R
Adult patients with severe sepsis and low risk of death (typically, APACHE II ≥ 20 or one organ failure) should not receive rhAPC	1A	Removed	R
Administer platelets prophylactically when counts are $<5,000/\text{mm}^3$; consider platelet transfusion when counts are $5,000\text{--}30,000/\text{mm}^3$ and there is significant bleeding risk; higher platelet counts ($>50,000/\text{mm}^3$) are required for surgery or invasive procedures	2D	Changed to prophylactic transfusion if platelet count <10 K, and <20 K if there is significant risk of bleeding; no change if surgery or procedures required	2D
No recommendation	NR	IVIG not recommended	2B
No recommendation	NR	Selenium not recommended	2C

Includes only guidelines changed between the 2008 and 2012 Surviving Sepsis Campaign Guidelines

rhAPC recombinant human activated protein C, UG ungraded, NR no recommendation, R removed

norepinephrine with variable amounts of open-label norepinephrine added to both groups [55]. There was no significant difference in 28-day mortality between the two groups, although when the prospectively defined less

severe septic shock stratum was evaluated, a lower 28-day mortality was seen in the vasopressin group (26.5 vs. 35.7 %, $P = 0.05$) [55]. In addition, use of vasopressin concurrently with corticosteroid treatment was associated

with reduced 28-day mortality in a retrospective analysis of this data [56]. The use of low-dose dopamine is not recommended in the treatment of the septic patient. Both a randomized, multicenter trial and a meta-analysis have failed to show any clinically significant protection or improvement with low-dose dopamine in critical illness [57, 58].

The 2008 SSCG recommended a trial of inotropic support with dobutamine up to 20 $\mu\text{g/kg/min}$, either alone or added to vasopressors, in the presence of myocardial dysfunction as suggested by elevated cardiac filling pressure and low cardiac output, or in the presence of ongoing tissue hypoperfusion despite adequate intravascular volume and MAP (grade 1C) (Table 4) [4]. Attempting to reach a predetermined supranormal cardiac index was recommended against (grade 1B). The 2012 SSCG continue to endorse these two recommendations (grade 1C and 1B, respectively). The recommendation against targeting predetermined supranormal levels of cardiac index is based on two older trials in critically ill patients and not specifically septic shock patients. These two studies, which aimed at increasing cardiac index to supranormal levels, did not specifically target the first 6 h of resuscitation and failed to improve outcomes [59, 60].

Mechanical Ventilation, Sedation and Neuromuscular Blockers

The 2008 SSCG included ten recommendations regarding mechanical ventilation in the treatment of sepsis-induced acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (Table 5) [4]. These included the use of 6 mL/kg of predicted body weight (PBW) (grade 1B), upper goal of <30 cm H₂O plateau pressures (grade 1C), permissive hypercapnia if needed to minimize plateau pressures and tidal volumes (grade 1C), positive end-expiratory pressure (PEEP) to be set so as to avoid extensive end-expiratory lung collapse (grade 1C), use of prone positioning in patients who are requiring potentially injurious levels of oxygen or plateau pressures if adverse consequences can be avoided (grade 2C), elevation of the head of the bed (grade 1B) to 30°–45° (grade 2C) to limit aspiration, careful consideration of non-invasive mask ventilation (NIV) in patients with mild-moderate ALI/ARDS with a low threshold for airway intubation (grade 2B), regular spontaneous breathing trials with low levels of pressure support, continuous positive airway pressure or a T-piece (grade 1A), avoidance of the routine use of pulmonary artery catheters (PAC) (grade 1A) and use of a conservative fluid strategy for patients with established acute lung injury (grade 1C).

The 2008 SSCG addressed three aspects of sedation, analgesia, and neuromuscular blockade in treating the mechanically ventilated septic shock patient. These included the use of sedation protocols with sedation goals (grade 1B), use of either bolus sedation or continuous infusion targeting predetermined end points using sedation scales with daily interruption/lightening to ensure awakening (grade 1B), and the avoidance of neuromuscular blocking agents (NMBA) if possible with the use of the train-of-four monitor when these medications are indicated (grade 1B) [4].

The 2012 SSCG included 13 recommendations regarding mechanical ventilation in the treatment of sepsis-induced ALI/ARDS. Many of the 2008 SSCG recommendations carry over unchanged, but several old recommendations have been upgraded (Table 5). The Berlin definition of ARDS has been adopted, and there are a number of new recommendations that deserve attention in the 2012 guidelines [61]. Briefly, these include the use of higher rather than lower levels of PEEP in moderate to severe ARDS (grade 2C), use of recruitment maneuvers for refractory hypoxemia (grade 2C), use of prone positioning in experienced facilities for ARDS patients with a partial pressure of arterial oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FIO}_2$) ratio of <100 mm Hg (grade 2B), and in the absence of bronchospasm, beta 2-agonists for the treatment of ARDS should be avoided (grade 1B) [1].

The 2012 SSCG have three recommendations for sedation, analgesia, and NMBA use in mechanically ventilated patients with sepsis, and differ from the 2008 guideline in several respects (Table 5). The 2012 guidelines now recommend that continuous or intermittent sedation should be minimized with continued use of specific titration end-points (grade 1B). The use of NMBA should be avoided in sepsis patients without ARDS and if NMBA are used, either by bolus or continuous infusion, then the patient should be followed with train-of-four monitoring (grade 1C). A short course (<48 h) of NMBA for patients with sepsis-induced ARDS and a $\text{PaO}_2/\text{FIO}_2$ ratio of <150 mm Hg should be considered (grade 2C) [1].

As mentioned above, the overall guidelines for mechanical ventilation in sepsis-related ALI/ARDS have not changed dramatically. Using tidal volumes of about 6 mL/kg of PBW, compared to 12 mL/kg, was upgraded to the highest-level recommendation (grade 1A). The primary data for this recommendation come from the Acute Respiratory Distress Syndrome Network (ARDSnet) study of 861 patients with ALI/ARDS showing a statistically significant reduction in mortality in the lower tidal volume group [62]. An early meta-analysis of low tidal volumes in ALI/ARDS argued that as long as plateau pressures were maintained between 28 and 32 cm H₂O, low tidal volumes should not be standard of care [63]. Two newer meta-

Table 5 Comparison of the 2012 and 2008 Surviving Sepsis Campaign Guidelines—blood product administration, mechanical ventilation, neuromuscular blockade, glucose control and considerations for limitation of support [1•, 4]

2008 Surviving Sepsis Campaign Guidelines		2012 Surviving Sepsis Campaign Guidelines	
Intervention	Grade	Intervention	Grade
<i>Mechanical ventilation and neuromuscular blockade</i>			
Target a tidal volume of 6 mL/kg of predicted body weight in patients with ALI/ARDS	1B	Upgraded	1A
Target an initial upper limit plateau pressure ≤ 30 cm H ₂ O. Consider chest wall compliance when assessing plateau pressure	1C	Upgraded; removed chest wall compliance	1B
Allow PaCO ₂ to increase above normal, if needed, to minimize plateau pressures and tidal volumes	1C	Removed	R
Set PEEP to avoid extensive lung collapse at end-expiration	1C	Upgraded	1B
Consider using the prone position for ARDS patients requiring potentially injurious levels of FIO ₂ or plateau pressure, provided that the facility has experience with proning	2C	Changed to restrict to patients with P/F ≤ 100	2B
No recommendation	NR	Use higher rather than lower PEEP strategies in moderate to severe ARDS (2C)	2C
No recommendation	NR	Attempt recruitment maneuvers for severe refractory hypoxia	2C
No recommendation	NR	Avoid beta2 agonists unless specific indication such as bronchospasm	1B
Do not use a pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS	1A	Removed	R
Avoid neuromuscular blockers if possible. Monitor depth of block with train-of-four when using continuous infusions	1B	Changed to avoid “if possible in the septic patient without ARDS”; downgraded	1C
No recommendation	NR	Short course of NMBA ≤ 48 h for patients with early sepsis-induced ARDS and P/F < 150	2C
<i>Glucose control</i>			
Use intravenous insulin to control hyperglycemia in patients with severe sepsis following stabilization in the ICU	1B	Protocolized approach to blood glucose (BG) management if glucose >180 mg/dL $\times 2$, upgraded	1A
Aim to keep BG <150 mg/dL (8.3 mmol/L) using a validated protocol for insulin dose adjustment	2C	Target BG <180 mg/dL, upgraded	1A
Provide a glucose calorie source and monitor BG values every 1–2 h (4 h when stable) in patients receiving intravenous insulin	1C	Removed	R
Interpret with caution low glucose levels obtained with point of care testing, as these techniques may overestimate arterial blood or plasma glucose values	1B	Downgraded	UG
<i>Consideration for limitation of support</i>			
Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations	1D	Changed to discuss goals/prognosis	1B
No recommendation	NR	Incorporate goals of care into treatment and end of life planning, using palliative care principals where appropriate	1B
No recommendation	NR	Address goals of care as early as feasible, no later than 72 h of ICU admission	2C

Includes only guidelines changed between the 2008 and 2012 Surviving Sepsis Campaign Guidelines

UG ungraded, NR no recommendation, R removed

analyses noted that mortality was significantly improved with lower tidal volumes in ALI/ARDS independent of whether volume or pressure cycled ventilation was used [64, 65], prompting the upgraded recommendation.

A review of plateau pressures used with low tidal volume ventilation in the treatment of patients with ALI suggests that outcomes are better with lower plateau

pressures and that there may be no safe upper limit [66]. A large multicenter, randomized, controlled trial of 767 patients with ALI using tidal volumes of 6 mL/kg of PBW found that a PEEP set to reach a plateau pressure of 28–30 cm H₂O compared to a minimal PEEP (5–9 cm H₂O) did not change mortality but did improve lung function and reduced both duration of mechanical

ventilation and duration of organ dysfunction [67]. In a similar study of 549 patients with ALI/ARDS treated with 6 mL/kg tidal volumes in which patients were randomized to lower or higher PEEP levels (plateau pressure limit of 30 cm of H₂O), no differences in clinical outcomes were demonstrated [68]. A meta-analysis of higher versus lower PEEP in the treatment of ALI/ARDS reported no overall improvement in hospital survival but higher levels of PEEP did show a modest improvement in survival in the subgroup of patients with ARDS [69].

Recruitment maneuvers such as breath-holding sessions at airway pressures of 5–45 cm H₂O have demonstrated variable potential to recruit lung in ARDS patients [70]. A systematic review of forty studies concluded that recruitment maneuvers in ALI significantly improved oxygenation with few serious adverse events [71]. Prone positioning can improve oxygenation in patients with ARDS without deleterious effects on hemodynamics [72, 73]. Several trials have reported no or small mortality improvement with prone positioning [74–78] but a meta-analysis of ten trials found a reduction in mortality in the subgroup of ARDS patients with severe hypoxemia [79]. The meta-analysis cautioned that prone ventilation may be best suited to high-volume centers with experience and equipment to do it safely.

Other approaches to the patient with refractory hypoxemia including high frequency oscillation (HFO) and extracorporeal membrane oxygenation (ECMO) should be considered rescue therapies and only attempted in centers experience in their use. A meta-analysis of HFO in patients with ALI/ARDS suggested it might improve survival and is unlikely to cause harm [80]. Two recent randomized, multicenter HFO trials in patients with moderate to severe ARDS did not reduce mortality [81, 82]. One cohort study and one pseudo-randomized trial have evaluated ECMO in patients with severe hypoxemic respiratory failure with both trials reporting a mortality benefit from the procedure [83, 84]. Further large scale randomized trials will be difficult but are necessary to determine the role of ECMO in the treatment of severe ARDS.

NIV in early ALI patients without other organ failure was given a weak recommendation (grade 2B). The results of trials of NIV in ALI/ARDS patients have been mixed, with some finding reduced incidence of the development of septic shock and improved survival [85], while others have found more variable results and expressed caution about the use of NIV in these often evolving patients [86, 87]. Performing daily spontaneous breathing trials (SBT) in mechanically ventilated patients with ALI/ARDS has been shown to reduce the duration, cost and the number of complications of mechanical ventilation [88]. Even better results were found when daily SBTs were coupled with daily interruption of sedatives [89]. The importance of the grade 1A recommendation [1•] is reflected in the fact that

most ventilator bundles now include SBTs coupled with sedative interruptions.

A meta-analysis of 13 trials with 5,051 patients evaluated the routine use of the PAC in critically ill patients and found no improvement in mortality or days in hospital with its use [90]. The lack of positive outcome data despite more than 20 years of study has resulted in the grade 1A recommendation against the routine use of the PAC in the treatment of septic shock [1•]. Another adjunctive approach is the use of a conservative fluid-management strategy in ALI patients. This recommendation is based primarily on the ARDSnet FACTT trial that showed improved lung function and shortened duration of mechanical ventilation but no difference in mortality or organ failure with a conservative fluid approach [91]. This trial also showed no difference in outcomes with the use of the PAC compared to central venous catheter for fluid management in ALI/ARDS patients.

The final new recommendation regarding mechanical ventilation is to avoid the use of beta-agonists in the absence of evidence of bronchospasm [1•]. Animal models and preliminary human trials suggested that beta-agonists could accelerate the resolution of alveolar edema in ALI [92]. However, two recent trials of aerosolized or intravenous beta-agonists used in patients with ALI/ARDS failed to show clinical improvement, resulting in the recommendation not to use them routinely in ALI/ARDS patients [93, 94].

As noted above, sedation of the critically ill ALI/ARDS patient can be an important variable in the length of mechanical ventilation. The use of continuous intravenous sedation has been associated with prolonged mechanical ventilation [95] and the use of no sedation in critically ill patients is associated with fewer days on mechanical ventilation [96]. Furthermore, the depth of early sedation has been associated with delayed extubation and increased mortality in a multicenter, randomized prospective longitudinal study [97]. In this regard the use of daily interruption of sedation in patients decreases the duration of mechanical ventilation and length of stay (LOS) in the ICU [98]. Similarly, a protocol-directed sedation approach implemented by bedside nurses has been shown to reduce mechanical ventilation, ICU and hospital LOS, and the need for tracheostomy in critically ill patients [99]. Comprehensive clinical practice guidelines recently issued by the American College of Critical Care Medicine address the treatment of pain, agitation and delirium in critically patients and stress the use of light sedation, protocols, daily sedation disruption, and the use of non-benzodiazepine sedatives [100].

The use of a NMBA during the first 48-h of mechanical ventilation in ALI/ARDS patients has been shown to decrease proinflammatory cytokine production and to

reduce mortality and time on the ventilator [101, 102]. Two recent meta-analyses of three randomized, placebo-controlled trials using the NMBA cisatracurium confirmed a reduction in mortality and barotrauma without an increase in critical illness-associated neuromyopathy [103, 104].

The use of a NMBA should not be taken lightly and their use in sepsis patients without ALI/ARDS should be avoided if possible [1•]. The use of train-of-four has been advocated in monitoring patients on NMBA in the ICU [105, 106]. A prospective, randomized controlled trial showed that using peripheral nerve stimulation to assess the degree of blockade and adjust the NMBA dose resulted in lower doses and faster recovery of neuromuscular function and spontaneous ventilation [107].

Other Interventions (Glucose Control, Corticosteroids, Blood Products Administration and Activated Protein C)

The 2008 SSCG made four recommendations regarding blood glucose (BG) control in patients with severe sepsis focused on achieving control with intravenous insulin (grade 1 B), use of a validated insulin protocol to target BG to levels <150 mg/dL, provision of a glucose calorie source with BG monitoring every 1–2 h until BG and insulin infusion rates are stable (grade 1C), and that low glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because of their tendency to overestimate BG (grade 1B) (Table 5) [4].

Seven recommendations focused on the use of corticosteroids in sepsis in the 2008 SSCG (Table 4) [4]. These included the use of hydrocortisone only in septic shock patients unresponsive to fluid resuscitation and vasopressor therapy (grade 2C); that the adrenocorticotrophic hormone (ACTH) stimulation test not be used to identify a subset of septic shock patients who should be treated with hydrocortisone (grade 2B); patients with septic shock should not receive dexamethasone if hydrocortisone is available (grade 2B); oral fludrocortisone should not be given if hydrocortisone is not available and is optional if it is available (grade 2C); patients should be weaned from steroid therapy when vasopressors are no longer needed (grade 2D); doses of corticosteroids >300 mg hydrocortisone daily should be avoided in septic shock (grade 1A), and corticosteroids should not be used in the absence of shock or in the absence of history that would suggest the need for stress doses (grade 1 D) [4].

Blood product administration guidelines from the 2008 SSCG suggested transfusions be limited to hemoglobin counts <7.0 g/dL once tissue hypoperfusion had resolved (grade 1B); that erythropoietin not be used as a specific treatment for anemia associated with severe sepsis (grade

1B); in the absence of active bleeding or planned invasive procedures, fresh frozen plasma (FFP) should not be used to correct laboratory coagulation abnormalities (grade 2D); antithrombin should not be administered to treat severe sepsis; and platelet transfusions should be limited to patients with counts <5,000/mm³ regardless of apparent bleeding, with counts of 5,000–30,000 mm³ when there is a significant risk of bleeding, or when platelets are <50,000/mm³ when surgery or an invasive procedure is planned (Table 4) [4].

The 2008 SSCG downgraded the 2004 SSCG recommendations for the use of recombinant human activated protein C (rhAPC) to a grade 2B for adult patients with sepsis and a high risk of death (APACHE II >25 or multiple organ failure). The 2012 SSCG eliminated the use of rhAPC with its removal from the market [1•].

The 2012 SSCG reduced the glucose control recommendations for patients with severe sepsis to three (Table 5), including a “protocolized” approach to BG levels that includes insulin when two consecutive BG levels are >180 mg/dL and an upper BG target level <180 mg/dL rather than 110 mg/dL as suggested in the 2008 SSCG (grade 1A), that BG levels should be monitored every 1–2 h until insulin infusion rates and BG levels are stable and then every 4 h (grade 1 C), and that point-of-care testing of capillary BG measurements continue to be interpreted with caution (UG) [1•].

The 2012 SSCG recommendations regarding the use of corticosteroids have been reduced to five (Table 4). The recommendations include using 200 mg/day of intravenous hydrocortisone if hemodynamic stability is not obtained with adequate fluid resuscitation and vasopressor therapy (grade 2C). The guidelines are unchanged in recommending against use of the ACTH test to identify septic shock patients who should be treated with hydrocortisone (grade 2B), that steroid therapy should be tapered once vasopressors are no longer needed (grade 2D), and that steroid therapy should not be used in patients with sepsis and no shock (grade 1D). The new guidelines suggest that, if used, hydrocortisone should be given by continuous infusion rather than repetitive bolus injection (grade 2D) [1•].

Updated blood product administration guidelines for patients with no signs of tissue hypoperfusion and no other indication for transfusion recommend transfusion for hemoglobin levels <7.0 g/dL with a target of transfusion to be between 7.0–9.0 g/dL (grade 1B) (Table 4). Guidelines for platelet transfusion were changed and now recommend platelet transfusions prophylactically for counts <10,000/mm³ in the absence of bleeding, <20,000/mm³ if the patient is at significant risk of bleeding, and <50,000/mm³ for active bleeding, surgery or invasive procedures (grade 2D). The 2012 guidelines continue to recommend against the use of erythropoietin for sepsis associated anemia

(grade 1B), against the use of FFP to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D), and against the use of antithrombin (grade 1B) (Table 4) [1•]. The 2012 SSCG offers no recommendation on the use of rhAPC in sepsis because of the drug's removal from the market [1•].

The benefits of tight BG control with insulin infusion were suggested by a large ICU study in which surgical ICU mortality was significantly improved by aiming for BG levels between 80 and 110 mg/dL [108]. A series of trials followed, however, that called the initial trial's findings into question. The same investigators evaluated tight BG control in medical ICU patients showing a significant reduction in morbidity but not mortality [109]. Another large multicenter, randomized, controlled trial of tight BG control in the ICU was stopped early for safety concerns due to increased episodes of hypoglycemia and no clinical benefit [110]. The NICE-SUGAR trial was a large, international, multicenter, randomized trial of 3054 ICU patients assigned either to tight BG control or conventional BG control with a target range of <180 mg/dL. Significant increases in hypoglycemic episodes and mortality were seen in the tight BG control group [111]. A series of systematic reviews and meta-analyses in critically ill patients not limited to sepsis have consistently demonstrated no mortality benefit with tight insulin-based BG control as well as increased episodes of hypoglycemia [112–116]. Several themes to emerge from these studies include the importance of having an insulin-based BG protocol [117], recognition of the variability and potential overestimation of BG determined by point-of-care testing [118–120], and the importance of sending laboratory confirmation of some BG values before making large changes in insulin infusion rates. Recent guidelines for the use of insulin infusions in the management of hyperglycemia in critically ill patients emphasize the need to maintain BG levels below 180 mg/dL and to avoid and detect hypoglycemia [121].

Studies have shown that high-dose steroids do not improve mortality in severe sepsis patients, but a multicenter, randomized, placebo-controlled, double-blind trial of low-dose steroids (intravenous hydrocortisone 50 mg every 6 h and oral fludrocortisone 50 mcg daily) demonstrated a significant reduction in mortality [122]. More than two-thirds of the patients failed to respond to ACTH suggesting relative adrenal suppression. Several small trials of low-dose hydrocortisone (not including fludrocortisone) in sepsis also reported physiologic benefits with some reporting improved mortality [123–125]. A large international double-blind, placebo-controlled, randomized trial of 50 mg of hydrocortisone every 6 h versus placebo (CORTICUS, $n = 499$) found that hydrocortisone did not improve survival in patients with

septic shock [126]. This trial also found no relationship between the serum cortisol response to an ACTH stimulation test and hemodynamic response to low-dose hydrocortisone. Three systematic reviews and meta-analyses since then have concluded that hydrocortisone therapy does not improve mortality but may have a beneficial effect on systemic blood pressure and reduce the need for vasopressor agents [127–129].

A small double-blind crossover study of septic shock patients treated with low-dose hydrocortisone infusion showed improved inflammatory biomarkers and hemodynamic parameters [130]. Hydrocortisone withdrawal on day 6 induced hemodynamic and immunologic rebound effects suggesting that tapering steroids may be important. However, a trial of 130 septic shock patients requiring vasopressor therapy randomized patients to 3 or 7 days of low-dose hydrocortisone therapy and found no mortality difference [131]. Bolus dosing of low-dose hydrocortisone has also been shown to induce significant increases in BG levels compared to constant infusion [132].

No specific studies have investigated the optimal hemoglobin levels in severe sepsis or septic shock patients. A large multicenter, randomized, controlled, clinical trial in critically ill patients determined that a restrictive red-cell transfusion strategy (<7.0 g/dL to maintain hemoglobin between 7.0 and 9.9 g/dL) was superior except in patients with acute myocardial infarction or unstable angina [133]. Similar results were found for critically ill pediatric patients where a threshold for transfusion of 7.0 g/dL decreased transfusion requirements [134]. The use of erythropoietin in critically ill patients has shown a small reduction in transfusion requirements but no other significant clinical outcome differences [135, 136].

Little data exists in severe sepsis patients on the use of other blood products. Nonetheless, several general guidelines exist that encourage conservative use of FFP [137, 138]. Wide variations have been shown in the use of FFP in the ICU and post-transfusion coagulation corrections were small when used [139]. High inappropriate use of FFP has been documented, raising questions about the clinical benefit of FFP in critically ill adults and children [140]. Despite limited data regarding the use of platelets in sepsis patients, general guidelines exist [141]. Thrombocytopenia is very common in critical care and there is wide variation in transfusion thresholds with many transfusions being given without clinically significant hemorrhage [139]. Low-dose prophylactic platelet transfusions appear to be as effective as high-dose platelet transfusions [142]. As guidelines for platelet transfusion draw heavily from clinical experience and literature in chemotherapy-induced thrombocytopenia, more data are required to determine the best use of platelet transfusions in severe sepsis.

Setting Goals of Care

In the 2008 SSCG this section was titled “Consideration for Limitation of Support” [4]. This change likely reflects a new emphasis on a patient-centered approach to care that allows for flexibility based on patient and surrogate decision maker preferences. The 2008 SSCG to “discuss advanced care planning” has also been changed to discuss “goals of care and prognosis”, and the recommendation has been increased from a 1D to 1B (Table 5) [1•, 4]. This change reflects increasing evidence that early establishment of care goals and prognosis are preferred by both patients and family members [143, 144]. Surrogate decision makers also prefer to have the prognosis of patient outcomes disclosed by clinicians, even if the prognosis is uncertain [145]. The 2012 SSCG also encourage the use of palliative care techniques (grade 1B), including family care conferences within 72 h of ICU admission (grade 2C), as evidence has demonstrated improved family satisfaction, decreased stress, shortened ICU length of stay, and facilitated end-of-life decision making [146–148]. In a randomized trial of hospitalized adults, surrogates randomized to advance care planning were 50 % more likely to understand and follow patient’s end-of-life wishes [149]. Proactive palliative care consultation has been shown to decrease length of ICU stay without affecting overall mortality or ICU discharge disposition [148].

Conclusion

In this review, we have highlighted changes to the SSCG for the 2012 edition that are relevant to the early treatment of adults with severe sepsis. Given the significant complexity of care for these high-risk patients, the SSCG provide a useful resource to clinicians for treatment recommendations and should facilitate consistent care across specialties. For this edition, the SSCG has continued to follow a validated approach to guideline development, and has taken important steps to shield its contributors from conflict of interest concerns. As research continues to shed light on areas of uncertainty in the treatment of severe sepsis, additional modifications of the guidelines will be needed. While the SSCG should be considered a resource for best practices in the management of sepsis, clinicians caring for patients with severe sepsis should continue to utilize a patient-centered approach to find the therapeutic strategy that best suits an individual patient and family or surrogate decision maker.

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