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The Surviving Sepsis Campaign's Revised Sepsis Bundles

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Abstract

The Surviving Sepsis Campaign (SSC) sepsis care bundles have recently been revised. The original 6-h resuscitation bundle which included rapid antibiotic administration and hemodynamic support with early goal-directed therapy (EGDT) has been divided into two bundles; one including antibiotic and fluid support to be completed within 3 h, and the other including vasopressor support and measures of central venous pressure and oxygen saturation to be completed within 6 h. The original 24-h management bundle targeting glucose control, administration of corticosteroids and recombinant human activated protein C (rhAPC), and limitation of plateau airway pressures during mechanical ventilation is no longer recommended. Past and recent reports by the SSC and others have suggested that compliance with the original bundles was low and their impact unclear. Examination of the revised bundles in the context of issues and questions arising with the original ones suggest that while compliance with new 3-h bundle will be high, compliance with the 6-h bundle will continue to be low.

Keywords

Sepsis; Septic shock; Bundles; Bundled care; Treatment; Surviving Sepsis Campaign

Introduction

The Surviving Sepsis Campaign (SSC) has entered its second decade and its primary goal continues to be the worldwide reduction of sepsis-related mortality through the promotion of efficacious programs of care [1]. To this end, during its first decade the SSC developed guidelines for the care of sepsis, which have now been revised twice [2, 3, 4•]. Based on the original guidelines, two sets of sepsis care bundles were developed: an acute resuscitation bundle and a management bundle to be completed within 6 h and 24 h of patient presentation, respectively (Table 1) [5]. These bundles have been the focus of a performance

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improvement program the SSC has promoted for the care of septic patients over the past 8 years [6•]. However, with the most recent revision of the SSC guidelines, new sepsis bundles have been formulated that include components of the original 6-h bundle divided into two bundles to be completed within 3 h and 6 h (termed the 3-h and 6-h bundles); the original 24-h management bundle has been discontinued (Table 1) [4••].

In the US alone, nearly a quarter of the 750,000 people who suffer from sepsis die annually, and the goal of the SSC to reduce this mortality rate is an important one [7]. The most recent SSC guidelines represent the work of 65 participants from 30 professional societies and more than 25 such societies have helped sponsor them [1]. However, from the beginning, several of the components taken from the first set of guidelines and included in the original bundles raised concerns among clinicians [8–11]. Furthermore, while the SSC's performance improvement program has subsequently enrolled more than 30,000 patients, bundle compliance as a whole has appeared low, and bundle impact unclear [6•, 12•, 13••]. Here we consider the potential impact of the newly revised SSC bundles in the context of experience with the original ones.

Formulation of and Concerns with the Original SSC Bundles of Care

At the time the SSC was initiated, care bundles had been proposed to promote rapid adoption of proven therapies, benchmark performance, and improve patient outcomes [14]. A bundle was perceived as a small, straightforward set of evidence-based practices (i.e. components) that when performed collectively, have proven benefit, greater than the sum of its individual components [15•]. The Institute of Healthcare Improvement (IHI) and Joint Commission on the Accreditation of Hospitals (JCAHO) embraced the bundle concept while also stipulating that bundle components should be scientifically proven and/or well accepted and noncontroversial [15•, 16, 17].

The original SSC bundles comprised components based on recommendations from the first SSC guidelines (Table 1) [2]. However, several of the included components were not yet scientifically proven and/or well accepted, noncontroversial practices (Table 1) [8, 11, 13••, 18, 19]. For the 6-h bundle, while the benefit of rapid and appropriate antibiotic administration, and fluid and vasopressor support were widely accepted for sepsis, targeting a central venous pressure (CVP) of 8 to 12 mmHg and obtaining central venous oxygen saturation (ScvO₂) measurements and targeting a level of 70 % with packed red blood cells (PRBC) and dobutamine were controversial [11, 13••]. This quantitative resuscitation strategy termed early goal-directed therapy (EGDT), was based on the results of a single trial [20]. Although this trial showed a substantial decrease in mortality rate in treated patients compared to controls (46.5 % vs. 30.5 %), its findings were questioned [8, 11, 18, 21]. The trial was a single-center study which enrolled 263 patients who appeared to have unique characteristics compared to other septic populations: they had significantly higher comorbidities and lower ScvO₂; there was also an uncharacteristically high control mortality rate [11]. Treated patients, but not control patients, were cared for in a specialized emergency department unit staffed with additional personnel [22]. Initial fluid resuscitation within the first 6 h, titrated to similar targets and intended to be equal in the study groups, was lower in controls ($p < 0.001$). Dobutamine titrated to target ScvO₂ was only used in 19 patients (1 control and 18 treated patients) within the first 6 h. It was also later reported that the trial analysis excluded some randomized patients [21].

Independent of the trial originally testing EGDT, concerns were raised that CVP and ScvO₂ are poor measures of intra-vascular volume and the adequacy of tissue oxygenation, respectively, and previous studies employing dobutamine to improve oxygen delivery in

septic patients had demonstrated harm [8, 10, 11, 23, 24]. Even as the SSC promoted the SSC bundles, other trials testing EGDT were planned or were underway [13•, 17, 19]

Three of the four components in the 24-h management bundle were also questioned. Glucose control and its stipulated ranges were based on a single-center study in postoperative cardiac patients who did not have sepsis when enrolled [25]. The safety and usefulness of glucose control in potentially sedated and unstable septic patients were unclear, and trials examining this therapy were planned. Stress dose corticosteroids had shown benefit in a subgroup analysis of one large trial, and when examined in a meta-analysis of this and several small studies [2, 26, 27]. However, the SSC had itself judged the evidence supporting corticosteroids as intermediate only, since convincing overall benefit had not been demonstrated in large randomized controlled trials (RCTs) [2]. Such studies were anticipated. Finally, application of recombinant human activated protein C (rhAPC) was controversial [9]. The Food and Drug Administration (FDA), while approving rhAPC, had restricted it to high-risk patients and required the manufacturer to perform confirmatory studies.

Thus, while interest in EGDT, glucose control, corticosteroids and rhAPC justified their consideration in the sepsis guidelines, they were not yet unequivocally proven, well-accepted, or noncontroversial, and their inclusion in bundles was premature. Ongoing questions at the time about these therapies raised the possibility that overall compliance with the original SSC bundles might be low.

Application and Impact of the Original SSC Bundles of Care

While the 6-h and 24-h sepsis bundles themselves have never been tested in prospective, RCTs, there are many studies by investigators both associated with and independent of the SSC of their application and impact. Two of the largest studies were by the SSC itself, one published in 2010 and one more recently in 2012 [6•, 12•].

Data Collected by the SSC

The SSC not only formulated the sepsis bundles but also promoted their use with a performance improvement program to which hospitals could subscribe [7]. This program included educational materials as well as tools for tracking and storing patient characteristics, compliance with bundle components and outcomes. These data were entered into databases at individual hospitals for review by local caregivers, and could also be submitted to a centralized SSC database maintained at offices of the Society of Critical Care Medicine (SCCM).

The SSC first reported on findings from this central database in 2010 [6•]. Data from 15,022 patients with severe sepsis and septic shock from 165 hospitals in North and South America and Europe collected between January 2005 and March 2008 were presented. Analysis was limited to data from the first 2 years of collection from hospitals reporting on 20 or more subjects over a minimum of 3 months. Data from sequential quarterly periods were examined to determine whether bundle use (i.e. compliance) and outcomes had changed over the study period. Lack of compliance with a component could be related either to failure to administer treatment itself or to achieve a treatment's goal.

The second report in 2012 examined data from 25,375 patients at 186 hospitals in the United States and Europe, including some patients from the earlier report, collected between January 2005 and January 2010 [12•]. Analyzed data were limited to the first 4 years of collection from hospitals. This second study's objective was to compare care and outcomes in patients with severe sepsis and septic shock in the US versus Europe. For both reports,

patients' sex, age, comorbidities and formal severity of illness scores were not available due to restrictions in data collection.

In the 2010 report, the SSC noted that over the 2-year study period compliance rates for administering all applicable components together had increased significantly for both the 6-h and 24-h bundles but remained at 36 % or less (from 10.9 to 31.3 % for the 6-h bundle, $p<0.0001$; and from 8.4 to 36.1 % for the 24-h bundle, $p=0.008$). Some individual components were associated with higher compliance than the bundles overall (Table 2). Comparison of the data from the first and last quarter from each hospital, including those enrolled for less than eight quarters, also showed increased compliance overtime, though to a lesser degree (10.9 to 21.5 % and 8.4 to 25.5 % for the 6-h and 24-h bundles, respectively; $p<0.0001$ for both; Table 2). Compliance was reported to increase the longer individual hospitals enrolled patients, although only 34 hospitals contributed data over the entire study period.

In the 2012 report, compliance with both the 6-h and 24-h bundles remained less than 30 % whether examined overall or in the US and Europe separately (Table 2) [12•]. These data are difficult to interpret, however, because changes in compliance over the study period were not provided. On the one hand low compliance rates in this report may reflect patients enrolled early in the SSC. On the other hand, the 2012 report included 10,000 more patients than the one from 2010, many presumably enrolled after the bundle program had been widely promoted. Also, data were collected for up to 4 years from hospitals, and as in the 2010 study, longer hospital participation should have been associated with greater increases in compliance.

Based on the 2010 report, unadjusted hospital mortality decreased from 37 % to 30.8 % ($p=0.001$) over the study period (2005 to 2008). After adjustment for available baseline characteristics, bundle components reported to be associated with lower mortality rates included obtaining blood cultures, timely administration of antibiotics, achieving blood glucose control and target plateau pressures ($p<0.0001$ for all), and, in patients with shock, administration of rhAPC ($p=0.02$). While the 2012 report noted that mortality in patients in Europe was significantly higher than in the US (41.1 % vs. 28.3 %, $p<0.0001$; Table 2), changes in mortality rates over time were not provided.

The SSC concluded in the 2010 report that the campaign had influenced the care of septic patients, and that this was accompanied by reduced mortality [4•, 6•]. As noted in the report, however, whether these two observations were related is unknown due to confounding variables, including an inability to account for patient comorbidities and severity of illness and the potential influence of changes in care independent of the bundles. An editorial accompanying the SSC 2010 report noted that absence of a control group and lack of quality control during data entry further weakened the conclusions [13•]. Significant differences in mortality rates comparing patients from the US and Europe in the recent 2012 report also raises the possibility that variation in the geographic distribution of enrolled patients over time may have influenced mortality rate trends noted in the 2010 report. Furthermore, mortality from sepsis in Australia and New Zealand where the SSC bundles were not instituted was reported to have decreased significantly from 2002 to 2005 [28]. Thus, based on data from the two SSC reports, while compliance with the bundles was noted to increase significantly from 2005 to 2008, this increase was small at best and of unknown relevance with respect to survival.

Other Studies Showing Compliance with Sepsis Bundles and Outcomes

The supplement to the 2012 SSC guidelines cites a series of studies supporting the efficacy of early quantitative resuscitation in reducing sepsis-related mortality [4•]. These studies

enrolled patients both before and after the SSC bundles were formally proposed in 2004. Some of these studies were observational and lacked defined control groups with which to compare the effects of bundle use, or included nonseptic patients. However, 20 of the cited studies did compare the outcome and care of septic patients before and after sepsis bundles were instituted, and provide a possible basis for comparison (Table 3). The studies included in Table 3 were those cited in the SSC guidelines to support the application of the bundles. This is therefore a potentially biased selection of studies. Any attempt to systematically assess the reported effects of sepsis bundle implementation on outcome in sepsis patients or an examination of how individual bundle components might correlate with outcome would require a full review of the literature and rigorous meta-analysis which were beyond the scope of the present project. The primary point of Table 3 is to demonstrate that even in studies the SSC has relied upon to support the use of the sepsis bundles, the compliance with several of the components, most importantly use of CVP and ScvO₂, as well as use of the complete bundles, has been highly variable and, in many cases, very low. Some of these studies assessed components from both the 6-h and the 24-h sepsis bundles, and others only from the former.

Notably, while significant reductions in mortality rates with bundle use were reported in ten of the cited studies, compliance with individual components varied across studies (range 2 to 100 %). Moreover, overall compliance with complete bundles (the 6-h and/or the 24-h bundles, or a defined “custom bundle”) was also variable (range 0 to 68 %) and was 44 % in five of the nine studies with data for both the bundle and control groups. Thus, to what degree improvements in survival could be attributed to compliance with bundles in these studies, as opposed to other factors, is unknown. Importantly, increased awareness of sepsis, the institution of educational programs, use of therapies independent of the bundles, and the absence of concurrent controls may have influenced the reported differences in survival.

Two RCTs supporting 6-h bundle components were also cited in this supplement. One, the original trial testing EGDT, has been described above [20]. The other was a relatively small study in 224 septic ICU patients comparing conventional treatment to a modified resuscitation strategy that targeted CVP, mean arterial pressure (MAP) and urine output, but not ScvO₂ or lactate [29]. If goals were not met in the intervention arm, a pulmonary artery (PA) catheter was placed for measurement of cardiac output. Although a significant improvement in survival was reported in the intervention arm, the findings are difficult to interpret. No data comparing baseline hemodynamic parameters or how they changed with therapy in each group were provided; nor were there data regarding the adequacy and timeliness of antibiotics.

Considering the Revised SSC Sepsis Bundles in the Context of the Original Bundles

As it enters its second decade, the SSC is encouraging healthcare workers to renew their commitment to reducing mortality from sepsis, including their adoption and institution of the revised sepsis bundles [1]. However, comparison of the original and revised bundles highlights key weaknesses and potential lessons learned with the former, and suggests why compliance may or may not improve with the latter.

The SSC no longer recommends the 24-h management bundle including targeted blood glucose control, corticosteroid and rhAPC administration in suitable patients, and limitation of airway pressures during mechanical ventilation [4••]. As noted previously, at the time the SSC formulated this bundle, three of these practices were of unclear benefit for many septic patients. In retrospect, questions regarding these treatments were well grounded. A series of RCTs over the past decade have failed to demonstrate the widespread usefulness of any of

these three treatments for sepsis [4••]. Thus, as suggested by others, inclusion of components not yet clearly proven for sepsis and undergoing continued investigation may have been a major reason for the low compliance rate noted with the 24-h bundle [13••]. In contrast, as both the 2010 and 2012 SSC reports show, limiting airway pressures during mechanical ventilation, a well-accepted practice, was associated with relatively high compliance rates both before and after institution of this bundle [6•, 12•].

The new SSC sepsis bundles are composed of elements of the original 6-h resuscitation bundle, now allocated to two bundles: a 3-h bundle directed at rapidly evaluating septic patients and administering antibiotics and, in hypotensive patients, fluids; and a new 6-h bundle advocating vasopressors to maintain MAP $\geq$ 65 mmHg in patients unresponsive to fluids, followed by CVP and ScvO₂ measurement if hypotension persists. While the bundles stipulate measurement of these latter hemodynamic parameters (via invasive procedures), the SSC states that, “For performance improvement quality indicators, resuscitation target thresholds are not considered. However, recommended targets (CVP $\geq$ 8 mmHg and ScvO₂ $\geq$ 70 %) are included with the bundles for reference purposes”. The 6-h bundle also recommends re-measurement and normalization of lactate.

Based on how the original 6-h bundle has been reformatted it is possible that compliance will be relatively high with the new 3-h bundle, but low with the new 6-h one. With respect to the 3-h bundle, the two treatments it includes (i.e. rapid administration of antibiotics and fluid resuscitation in patients with hypotension) fulfill IHI and JCAHO criteria; they are well accepted and noncontroversial [15•]. Compliance with antibiotic administration was relatively high in both reports from the SSC, and in the first one appeared associated with reported increases in survival [6•, 12•]. In a prior meta-analysis of eight studies (one randomized and seven before and after studies) examining the institution of the SSC 6-h and 24-h bundles in more than 1,200 patients, we found that the only component consistently and significantly increased with the bundles was timely and appropriate antibiotic administration [17]. Many other studies have documented the importance of timely antibiotics for severe infection and sepsis [4••]. The need for early fluid support is also widely accepted for patients presenting with sepsis and hypotension, although there is no consensus about hemodynamic targets to which these should be titrated [11, 13••, 30]. Administration of fluids and vasopressors achieved relatively high compliance in both SSC studies [6•, 12•]. The volume of initial fluid recommended in the new bundle does differ from the original ones (30 vs. 20 ml/kg, respectively) and the basis for this is unclear. The 3-h bundle also stipulates that blood cultures and a lactate level should be obtained. While it is widely believed that obtaining blood cultures before antibiotics is important for directing therapy in septic patients, the impact of measuring lactate is less clear [11, 31–33]. Nevertheless, widespread recognition of the need to promptly identify and treat septic patients with antibiotics and, when necessary, fluids, may ensure relatively high compliance with this new 3-h bundle.

In contrast, the new 6-h bundle includes components derived from EGDT that continue to be debated. Compliance with CVP and ScvO₂ targets in the SSC reports was low, whether this was related to failure to measure these parameters or to achieve stated targets. The benefits of inserting a central venous catheter to measure and target CVP and ScvO₂ (8 mmHg and 70 %, respectively) are still unproven for the management of sepsis [11, 18, 34]. In several surveys, physicians and nurses have indicated that questions about the soundness of or the resources required to institute EGDT were important reasons for low compliance with the original 6-h resuscitation bundle [35–37].

The revised 2012 SSC guideline recommendations cite a randomized trial from China as new evidence corroborating the effectiveness of EGDT incorporating CVP and ScvO₂

targets [38]. Although an English abstract appears online, the full text of the paper is only available in Chinese. Based on a translation of the entire paper, this was a multicenter, prospective, RCT carried out at eight hospitals in China enrolling 314 patients with severe sepsis and septic shock between January 2005 and January 2008. The study compared regimens of treatment termed conventional (151 patients) or EGDT (163 patients). While the online abstract suggests that this EGDT was similar to the original study testing it, the translated paper describes something quite different. Conventional treatment included fluid resuscitation within 1 h with a volume of crystalloid and colloid solution (2:1) equal to 3 % of the patient's weight. Within 6 h, conventional treatment included achieving a CVP of 8 to 12 mmHg, systolic blood pressure (SBP) 90 mmHg, MAP 65 mmHg and urine output 0.5 ml/kg/h, all with either fluids, blood or cardiac drugs at the physician's discretion. EGDT included conventional treatment as well as achieving ScvO₂ 70 % within the first 6 h. If targets were not met, PRBC were to be transfused for hematocrit <30 %. However, if targets were still not met, very different from EGDT described in the SSC guidelines, in this study patients were to have a PA catheter placed to determine PA occlusion pressure (PAOP). For PAOP 18 mmHg, "cardiac drugs" were to be given; if <18 mmHg, additional fluids were to be given. Whether PA catheter cardiac outputs were obtained is not described, nor is it stated how this invasive intervention was controlled for in the conventional treatment patients. The paper reports that compared to conventional treatment, EGDT (as described) was associated with a significant reduction in mortality (43.5 vs. 24.8 %, $p=0.001$). However, the paper does not provide necessary data to support this conclusion, including: comparisons between study groups of baseline comorbidities, measures of targeted parameters before and after treatment, quantities of therapy administered, time to and appropriateness of antibiotics, and the rates of adequate surgical source control.

The revised 6-h bundle also stipulates remeasurement of lactate if the initial value was elevated (i.e. following measurement in the 3-h bundle), with the goal of then normalizing lactate levels. The guidelines state that lactate normalization may be used either as an alternative target, or in combination with ScvO₂, for guiding resuscitation of patients with severe sepsis-induced tissue hypoperfusion. Two studies are cited to support this recommendation [39, 40]. One study compared hospital mortality in 300 septic patients, randomized to resuscitation guided by either ScvO₂ or serial lactate levels (aiming for a clearance rate of 10 % in the first 6 h) [39]. The investigators sought to show that resuscitation based on changes in lactate was not inferior to guidance with ScvO₂. While there was no significant difference in mortality between the two groups, only 10 % of randomized patients (30 patients) actually received therapy (dobutamine or PRBC transfusion) based on lactate or ScvO₂ levels; thus, the study lacked sufficient power to address the question asked.

The other study compared the effects on mortality in 348 critically ill patients of resuscitation guided by serial lactate levels with the goal of reducing lactate levels by 20 % per 2 h during the first 8 h of ICU stay versus standard care by clinicians blinded to serial lactate levels [40]. Only 38 % of patients had sepsis. Unadjusted hospital mortality was not significantly different between the two groups (either all patients or septic patients only), nor was there a significant difference in changes in serial lactate levels for up to 72 h following admission. Although after adjusting for predefined risk factors, mortality in the lactate group was decreased, this group also received treatments not typically described in EGDT protocols (e.g. vasodilators such as nitroglycerine or ketanserin; and analgesics, sedatives and cooling strategies to decrease oxygen demand). The recommendation targeting normalization of lactate in septic patients and the data supporting it were graded 2C in the 2012 guidelines (i. e. weak recommendation and low quality of data) [4••]. It is therefore unclear why this recommendation was included as a component in a sepsis bundle.

At the present time, questions persist as to whether and how several of the resuscitative measures and goals included in the newly revised SSC 6-h bundle benefit septic patients. At least three large multicenter studies in various stages of completion are addressing the efficacy of EGDT and its components [17]. Until the results of such trials are available, the inclusion of unproven and controversial interventions and targets in the revised 6-h bundle may result in low compliance. In fact, based on the unproven benefit of these components, the American College of Chest Physicians along with several other groups have called upon the National Quality Forum (NQF) not to adopt them in a proposed NQF performance improvement plan [34].

Conclusion

Efforts by the SSC to increase awareness of sepsis among healthcare workers and to expedite and improve the identification and treatment of this lethal condition are laudable. However, if bundles are to be employed in these efforts, all included components must be proven and/or well accepted and noncontroversial, not only to meet criteria of the IHI and JCAHO, but more importantly to ensure benefit for patients, and to engender high rates of compliance among healthcare workers. At this time, given that components in the revised SSC 6-h sepsis bundle are of unproven benefit to patients with sepsis and continue to undergo investigation, they are unsuitable for inclusion in care bundles and as measures of performance.

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Table 1
Original and revised Surviving Sepsis Campaign (SSC) sepsis bundles

Original SSC bundles based on the 2004 sepsis guidelines [5]	Revised SSC bundles based on the 2012 sepsis guidelines [4•]
<p>6 h Resuscitation Bundle (to be completed within 6 h)</p> <ul style="list-style-type: none"> • Measure serum lactate concentration • Obtain blood cultures prior to antibiotic administration • Administer broad spectrum antibiotic within 3 h of emergency department (ED) admission and within 1 h of non-ED admission • In the event of hypotension and/or serum lactate > 4 mmol/L: <ul style="list-style-type: none"> - Deliver an initial minimum of 20 mL/kg of crystalloid or equivalent - Administer vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mmHg • In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L: <ul style="list-style-type: none"> - Achieve a central venous pressure (CVP) of 8 mmHg - Achieve a central venous oxygen saturation (ScvO₂) 70 % or mixed venous oxygen saturation (SvO₂) 65 % 	<p>3 h Bundle (to be completed within 3 h)</p> <ul style="list-style-type: none"> • Measure lactate level • Obtain blood cultures prior to administration of antibiotics • Administer broad spectrum antibiotics • Administer 30 mL/kg crystalloid for hypotension or lactate > 4 mmol/L <p>6 h Bundle (to be completed within 6 h)</p> <ul style="list-style-type: none"> • Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) > 65 mmHg • In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate > 4 mmol/L (36 mg/dL): <ul style="list-style-type: none"> - Measure central venous pressure (CVP)* - Measure central venous oxygen saturation (ScvO₂)* • Re-measure lactate if initial lactate was elevated*
<p>24 h Management Bundle (to be completed within 24 h)</p> <ul style="list-style-type: none"> • Administer low-dose steroids for septic shock in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for low-dose steroids based on the standardized protocol. • Administer human activated protein C (rhAPC) in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for rhAPC. • Maintain glucose control 70, but 150 mg/dL • Maintain a median inspiratory plateau pressure (IPP) < 30 cmH₂O for mechanically ventilated patients. 	<p>*Targets for quantitative resuscitation included in the guidelines are CVP of 8 mmHg, ScvO₂ of 70 %, and normalization of lactate.</p> <p>24 h Management Bundle no longer recommended</p>

Table 2
Summary of compliance rates with (i.e. percentage of patients receiving) all applicable individual components from the 6-h and 24-h bundles as well as with the complete bundles (i.e. all applicable components administered) as reported by the SSC in 2010 and 2012 [6, 12]

	2010 SSC study in North and South America and Europe			2012 SSC study in North America and Europe		
	Initial quarter (n=2,791)	Middle quarters (n=10,909)	Final quarter (n=509)	USA (n=18,766)	Europe (n=6,609)	Combined (n=25,375)
Initial care bundle (first 6 h)						
Lactate measured	61	72.5	78.7	70.1	71.9	70.6
Blood cultures before antibiotics	64.5	76.3	78.3	83.7	64.7	78.8
Antibiotics ^a	60.4	67	67.9	70.8	63.9	69
Fluids and vasopressors	59.8	71.1	77	70	72.6	70.7
CVP >8 mmHg	26.3	33.9	38	25.7	45.2	30.8
ScvO ₂ >70 %	13.3	21.7	24.3	17.1	25.8	19.4
Complete 6-h bundle	10.9	21.1	21.5 ^b	21.6	18.4	20.8
Management bundle (first 24 h)						
Steroids policy	58.3	66.8	73.9	59.6	71	62.6
Administration of rhAPC policy	47.4	49.9	53.5	39.8	64.2	46.2
Glucose control	51.4	55.4	56.8	53.5	56.8	54.4
Plateau pressure control	80.8	82.6	83.8	84.7	85.1	84.8
Complete 24-h bundle	18.4	23.3	25.5 ^b	19.8	28.2	22

n number of patients reported on, CVP central venous pressure, ScvO₂ central venous oxygen saturation, rhAPC recombinant human activated protein C

^a From the time of presentation, broad-spectrum antibiotics were to be administered within 3 h for an emergency department admission and within 1 h for a non-emergency department intensive care unit admission

^b Compliance rates for all resuscitative and management measures at the end of the 2-year study period (rather than at the final quarter for each hospital) were 31.3 % and 36.1 %, respectively. Compliance was reported to increase the longer a hospital participated in the SSC [6]

Table 3
Studies investigating mortality and bundle compliance before and after implementation of the original 6-h, or 6-h and 24-h, sepsis bundles, and cited in the 2012 SSC Guidelines Supplement as supportive of administering early quantitative resuscitation for sepsis [4••]

Study	Study period	Group	No. of patients	Compliance with (% of patients receiving) 6-h bundle components					Compliance with (% of patients receiving) 24-h bundle components												
				Hospital or 30-day mortality	Lactate measured	Bid ex before antibiotics	Timely or time to antibiotics ^a	Fluids ³	Vasopressors	CVP	8 mmHg	ScvO ₂	70 %	Complete 6-h bundle	Steroids	rhAPC	Glucose control	MV limited by PPL	Complete 24-h bundle	Custom bundle ^b	
																					%
Studies utilizing both 6-h and 24-h bundle components																					
Kortgen et al.	2002–2003	Control	30	53 %	<0.05	–	100 %	2.8 l	100 %	–	–	–	–	–	43 %	0 %	60 %	–	–	–	
		Bundle	30	27 %	–	47 %	100 %	2.5 l	100 %	–	83 %	–	–	100 %	23 %	100 %	–	–	–		
Shapiro et al.	2000–2004	Control	51	29 %	0.3	–	94 %	2.9 l	45 %	–	–	–	–	24 %	0 %	–	–	–	–		
		Bundle	79	20 %	–	–	99 %	4.1 l	80 %	–	–	–	–	29 %	4 %	–	–	–	–		
Nguyen et al.	2003–2005	Control	253	39 %	<0.01	–	87 %	2.8 l	44 %	36 %	23 %	–	–	59 %	14 %	–	–	–	0 %		
		Bundle	77	21 %	–	100 %	100 %	2.8 l	51 %	100 %	100 %	–	–	78 %	6 %	–	–	–	51 %		
De Miguel-Yanes et al.	2005	Control	53	23 %	0.62	12 %	6h	–	–	–	–	–	–	–	–	–	–	–	0 %		
		Bundle	50	18 %	–	46 %	3.8 h	–	–	–	–	–	–	–	–	–	–	–	26 %		
Lefrant et al.	2006	Control	230	40 %	0.02	59 %	46 %	1 l	–	29 %	3 %	–	3 %	57 %	0 %	53 %	–	–	1 %		
		Bundle	215	27 %	–	75 %	56 %	1.5 l	–	48 %	27 %	11 %	71 %	9 %	54 %	–	–	–	4 %		
Ferrer et al.	2005–2006	Control	854	44 %	0.04	39 %	67 %	41 % ^c	–	21 %	6 %	5 %	45 %	44 %	45 %	86 %	11 %	–	–		
		Bundle	1465	40 %	–	50 %	69 %	47 % ^c	–	27 %	11 %	10 %	55 %	52 %	50 %	83 %	16 %	–	–		
El-Solh et al.	2001–2007	Control	87	57 %	–	45 %	91 %	2.5 l	–	–	–	–	16 %	2 %	–	–	–	–	–		
		Bundle	87	54 %	–	93 %	95 %	4.0 l	–	–	–	–	95 %	13 %	–	–	–	–	–		
Caste llanos-Ortega et al.	2004–2008	Control	96	57 %	0.001	16 %	49 %	59 %	–	71 %	55 %	1 %	12 %	4 %	51 %	80 %	0 %	–	–		
		Bundle	384	38 %	–	75 %	57 %	84 %	–	75 %	56 %	11 %	24 %	4 %	57 %	82 %	1 %	–	–		
Shiramizo et al.	2005–2009	Control	100	54 %	–	72 %	58 %	1.7 l	96 % ^c	60 %	50 %	6 %	76 %	40 %	48 %	82 %	15 %	–	–		
		Bundle	464	16 %	–	82 %	62 %	2.4 l	80 % ^c	65 %	56 %	14 %	100 %	97 %	46 %	94 %	44 %	–	–		
Studies utilizing only resuscitation bundle components																					
Trzeciak et al.	2003–2005	Control	16	44 %	0.09	–	3b	3.5 l	44 %	–	–	–	–	31 %	14 %	–	–	–	–	–	
		Bundle	22	18 %	–	–	2.5 h	5.7 l	59 %	100 %	90 %	90 %	36 %	33 %	–	–	–	–	–	–	
Micek et al.	2004–2005	Control	60	48 %	0.14	17 %	60 %	2.8 l	100 %	5 %	–	–	50 %	12 %	–	–	–	–	–	–	
		Bundle	60	35 %	–	78 %	87 %	3.8 l	72 %	48 %	45 %	22 %	3 %	–	–	–	–	–	–	–	

Study	Study period	Group	No. of patients	Compliance with (% of patients receiving) 6-h bundle components					Compliance with (% of patients receiving) 24-h bundle components											
				Hospital or 30-day mortality	Lactate measured	Bid ex before antibiotics	Timely or time to antibiotics ^a	Fluids ³	Vasopressors	CVP	8 mmHg	ScvO ₂	70 %	Complete 6-h bundle	Steroids	rhAPC	Glucose control	MV limited by PPL	Complete 24-h bundle	Custom bundle ^b
Focht et al. ^d	2004–2006	Control	79	27 %	0.21	–	–	–	3.4 h	3.3 l	34 %	–	–	–	6 %	4 %	–	–	–	
		Bundle	302	19 %	–	–	2.2 h	4.7 l	67 %	–	–	–	–	–	40 %	2 %	–	–	–	
Zubrow et al.	2003–2007	Control	?	62 %	<0.0001	–	–	–	–	–	–	–	–	29 %	–	–	–	–	–	
		Bundle	?	31 %	–	–	–	–	–	–	–	–	–	68 %	–	–	–	–	–	
Gumani et al.	2006–2008	Control	64	61 %	0.004	–	–	–	56 %	31 %	–	–	–	–	–	–	–	–	–	
		Bundle	54	33 %	–	–	85 %	72 %	–	–	–	–	–	–	–	–	–	–	–	
Crowe et al.	2004–2008	Control	205	27 %	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
		Bundle	216	33 %	–	94 %	98 %	99 %	85 %	–	–	–	–	–	69 %	–	–	–	–	
Nguyen et al.	2008–2009	Control	128	–	–	77 %	79 %	77 %	100 %	77 %	–	43 %	18 %	13 %	–	–	–	–	10 %	
		Bundle	428	–	–	91 %	100 %	96 %	–	69 %	–	–	64 %	55 %	–	–	–	–	44 %	
MacRedmond et al.	2003–?	Control	37	51 %	0.02	92 %	–	–	2.66 h	–	–	–	–	–	–	–	–	–	14 %	
		Bundle	37	27 %	–	100 %	92 %	–	–	–	–	–	–	–	–	–	–	–	62 %	
Cannon et al.	2003–2009	Control	1554	43 %	<0.001	58 %	–	–	2.87 h	2.5 l	48 %	–	–	–	–	–	–	–	–	
		Bundle	4801	29 %	–	54 %	–	–	1.66 h	2.7 l	44 %	–	–	68 %	–	–	–	–	–	

CVP central venous pressure, ScvCo2 central venous oxygen saturation, rhAPC recombinant human activated protein C, MV mechanical ventilation, PPL plateau pressure, Bid ex blood cultures

^aSome study reports give the actual time to administration of antibiotics or amount of fluids given rather than the percentage of patients who received these therapies within a specified time period

^bSome investigators tracked “complete bundle compliance” with a customized bundle, which included components from the 6-h and 24-h bundles

^cPercentage represents combined compliance for fluids and vasopressors

^dThis study included subjects analyzed in two other studies by the same investigators (references 10 and 16 in the 2012 SSC supplement), which are therefore not included in this table