Published in final edited form as:

Crit Care Med. 2010 February ; 38(2): 668–678. doi:10.1097/CCM.0b013e3181cb0ddf.

Bundled care for septic shock: An analysis of clinical trials*

Amisha V. Barochia, MBBS, Xizhong Cui, MD, PhD, David Vitberg, MD, Anthony F. Suffredini, MD, Naomi P. O'Grady, MD, Steven M. Banks, PhD[†], Peter Minneci, MD, Steven J. Kern, BS, Robert L. Danner, MD, Charles Natanson, MD, and Peter Q. Eichacker, MD
Critical Care Medicine Department (AVB, DV, XC, AFS, NPO, SJK, RLD, CN, PQE), Clinical Center, National Institutes of Health, Bethesda, MD; and the Department of Surgery (PM), The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA.

Abstract

Context—Sepsis bundles have been developed to improve patient outcomes by combining component therapies. Valid bundles require effective components with additive benefits. Proponents encourage evaluation of bundles, both as a whole and based on the performance of each component.

Objective—Assess the association between outcome and the utilization of component therapies in studies of sepsis bundles.

Data Source—Database searches (January 1980 to July 2008) of PubMed, Embase, and the Cochrane Library, using the terms sepsis, bundles, guidelines, and early goal directed therapy.

Data Extraction—Inclusion required comparison of septic adults who received bundled care vs. nonprotocolized care. Survival and use rates for individual interventions were abstracted.

Main Results—Eight unblinded trials, one randomized and seven with historical controls, were identified. Sepsis bundles were associated with a consistent ($I^2 = 0\%$, $p = .87$) and significant increase in survival (odds ratio, 1.91; 95% confidence interval, 1.49–2.45; $p < .0001$). For all studies reporting such data, there were consistent ($I^2 = 0\%$, $p = .64$) decreases in time to antibiotics, and increases in the appropriateness of antibiotics ($p < .0002$ for both). In contrast, significant heterogeneity was seen across trials for all other treatments (antibiotic use within a specified time period; administration of fluids, vasopressors, inotropes, and packed red blood cells titrated to hemodynamic goals; corticosteroids and human recombinant activated protein C use) (all $I^2 \geq 67\%$, $p < .002$). Except for antibiotics, sepsis bundle components are still being investigated for efficacy in randomized controlled trials.

Conclusion—Bundle use was associated with consistent and significant improvement in survival and antibiotic use. Use of other bundle components changed heterogeneously across studies, making their impact on survival uncertain. However, this analysis should be interpreted cautiously as these studies were unblinded, and only one was randomized.

Keywords

sepsis; septic shock; bundles; bundled care; treatment

*See also p. 733.

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[†]Deceased.

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, barochiaav@mail.nih.gov

Care bundles or protocols that combine several medical practices have been proposed as tools to promote rapid adoption of proven therapies, benchmark performance, and improve patient outcomes (1). Reports that several practices instituted together could reduce the prevalence of catheter-related infection or mortality in mechanically ventilated patients supported this approach (2, 3). Care bundles have also been proposed based on the holistic principle that the whole is greater than the sum of its parts (4). Based on this therapeutic approach, the Institute for Healthcare Improvement and the Centers for Medicare and Medicaid Services recently proposed instituting “all or none” performance measures (5, 6). Hospital performance, and possibly re-imbursement in the future, may be based on the frequency with which all elements of a care bundle were administered together (7, 8).

The Joint Commission and Institute for Healthcare Improvement have recommended that components of a bundle should individually have proven benefit and wide acceptance, and together have even greater benefit (1, 9, 10). Importantly, bundle proponents encourage determination that individual components add to aggregate beneficial effects on outcome (6). However, there is currently no consensus on methods and standards for the development and testing of valid care bundles.

Although promising, care bundles pose challenges. Several care bundles posted on the Internet have not undergone rigorous peer review (11, 12). Some bundles addressing the same problem—sepsis—differ in content and compliance rates (13). Many bundles lack strong evidence for the efficacy of one or more of their individual components (14). Importantly, adoption of all bundle elements as a single intervention limits the ability to test the interdependent and independent efficacy of individual components (15). Therefore, the introduction of care bundles may mandate changes in standard care without the ability to fully monitor the impact of component parts. Resolving these issues has become critical as care bundles have evolved from preventing complications (e.g., catheter-related infections) to treating life-threatening conditions (e.g., sepsis).

As bundle development and application lack clear standards but are increasing in frequency, we examined this approach for the treatment of sepsis. We performed a meta-analysis of clinical trials, testing the impact of sepsis bundles compared with nonprotocolized care. Component therapies of interest were adopted from two widely instituted sepsis bundles, i.e., a 6-hr acute bundle and a 24-hr management bundle (Table 1) that were based on guidelines originally developed by the Surviving Sepsis Campaign and available at the time of these clinical trials (12, 16). Our goals were to examine the effect of bundle institution on survival and the application of individual bundle components.

METHODS

Literature Search

We conducted an English language search of PubMed, Embase, and Cochrane databases from January 1980 to July 2008 to find human trials of sepsis care bundles in adults (≥ 18 yrs old), using these search terms: sepsis, septic shock, treatment, guidelines, protocols, early goal directed therapy, and bundles. The studies that were included had to enroll only septic patients, use a central venous oxygen saturation (ScvO₂) measure to guide therapy, have a control (historical or concurrent), and record mortality rates. The included studies also had to quantify usage of at least five of the nine following therapies, whether or not they were explicitly part of the sepsis bundle that was instituted: antibiotics; fluids; vasopressors; inotropic agents; packed red blood cell (PRBC) transfusions; corticosteroids; recombinant human activated protein C (rhAPC); insulin; or mechanical ventilatory tidal volumes. Criteria for sepsis or septic shock in patients receiving bundled care had to be consistent

with the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference definitions (17).

Two investigators independently reviewed included studies by using a standardized data collection form. A third author resolved any discrepancies. Survival and frequency of use of out-lined therapies were the outcomes of interest and tabulated across studies. Other abstracted data included : 1) study design; 2) dates of enrollment; 3) study setting; 4) imbalances in study groups at baseline, including risk assessment scores; 5) presence of educational or other aids during bundle institution; 6) criteria defining septic shock; 7) treatments monitored, whether part of a bundle or not; 8) time over which treatment was assessed; 9) whether targeted hemodynamic goals were measured and analyzed; and 10) criteria employed to define the appropriateness of antibiotic use.

Statistical Analysis

All estimation of treatment effect and tests of inference were performed with the R package metabin. We assessed the heterogeneity of the treatment effects of bundled care on clinical outcomes and treatment strategies of interest, using the Breslow-Day test and an associated I^2 statistic (18, 19). As previously described, an I^2 statistic with a value of 0% indicates no observed heterogeneity, and increasing values reflect increasing heterogeneity; a value of >25% denotes at least low-to-moderate heterogeneity (20). We used the Mantel-Haenszel test to estimate the overall odds ratio (OR) and 95% confidence intervals (CI) of survival and of receiving the therapies of interest using a random-effects model (21). The differences in the duration before antibiotic administration (in hrs) and volumes of crystalloid given (in mL) between bundled care and control patients were estimated, using the weighted mean and its associated 95% CI. Conventional forest plots were prepared for survival and for individual bundle elements analyzed. When significant heterogeneity was present for an outcome, a jackknife sensitivity analysis was performed by sequentially removing each study to detect individual studies responsible for the heterogeneity. For outcomes in which removal of a single trial resulted in a complete resolution of heterogeneity, the overall estimate after removal of the outlier is presented.

RESULTS

Overview of Included Studies

Eight of 981 published articles found in our literature search met the inclusion criteria (22–29) (Fig. 1). One study employed an unblinded prospective, randomized design (Table 2); the rest compared the effects of bundled care with a previously treated control group (i.e., before and after study designs). Subjects were identified prospectively (i.e., first controls, followed later by bundle patients) in two trials and by retrospective chart review in five studies. Besides historical controls, one trial also included as controls nonrandomized contemporaneous patients who did not complete all components of the bundle. In all but one study (24), patients were initially treated in the Emergency Department, but all eight included data from subsequent patient care in the intensive care unit. Four trials reported some baseline study group imbalances (23–25, 27); however, severity of illness scores were reported to be similar between control and bundle patients in all eight studies. The Acute Physiology and Chronic Health Evaluation II score employed in seven trials to assess severity of illness varied from as low as 20 ± 7 and 21 ± 10 in control and bundle patients in one study to as high as 40 ± 16 and 42 ± 18 in another study. Six trials reported using educational programs for medical workers, as well as aids, including sepsis carts and tool kits, specialized sepsis nursing flow sheets, and dedicated lines of communication to infectious disease experts or surgical services at protocol initiation (22, 25–29). For all protocol patients, sepsis and septic shock were defined by the American College of Chest

Physicians consensus criteria (17); however, criteria for enrollment varied across studies (Table 3). No study provided data regarding the duration of illness before the time when criteria for septic shock or for inclusion in the study were reached.

Antibiotic treatment was tabulated from studies using three criteria: 1) number of patients receiving antibiotics within a specified time period (i.e., 3 hrs, 4 hrs, or 6 hrs from presentation); 2) actual mean time from presentation to antibiotic administration; or 3) number of patients receiving appropriate antibiotics based on culture results (30) (Table 4). Crystalloid usage was reported as total volume in milliliters given within a specified time period. Vasopressor, inotrope, PRBC, low-dose corticosteroid, and rhAPC usage was reported as the number of patients receiving treatment (Table 5). Although all eight studies included early goal directed therapy in a bundle, only four provided baseline patient data regarding those parameters (e.g., central venous pressure, mean arterial pressure [MAP], ScvO₂) that served as triggers for interventions (22, 25, 27, 28). Furthermore, for only one trial were the base-line data complete, and this study alone of the eight reported data showing how targeted parameters changed with treatment (22). Three studies reported on the use of intensive insulin therapy, and no study reported tidal volumes or airway pressures during mechanical ventilation (Table 4).

Survival

Across the eight studies, the effect of bundled care on survival was consistent (test for heterogeneity: $I^2 = 0\%$, $p = .97$) (Fig. 2). Overall, there was a statistically significant increase in the odds of surviving with bundled care compared with controls (OR, 1.91; 95% CI, 1.49 – 2.45; $p < .0001$).

Components of Care Consistently Increased With Bundled Care Across Studies

Across the four studies reporting such data, the difference in time to antibiotic administration (in hrs) between bundle and control patients was consistent ($I^2 = 0\%$, $p = .89$). Time to antibiotics (hours from time of admission) significantly decreased (weighted mean difference, -0.58 hrs [-0.85 to -0.33]; $p < .0001$) with bundled care. There was also across five studies a consistent ($I^2 = 0\%$, $p = .76$) (Table 5 and Fig. 3) and significant increase in the odds of receiving appropriate antibiotics with bundled care compared with controls (OR, 3.06; 95% CI, 1.69–5.53; $p = .0002$).

Components of Care Not Consistently Increased With Bundled Care Across Studies

Across studies reporting these data, significant heterogeneity existed in the effect of bundled care on changes in the use of the following seven interventions: antibiotics within a specified time period ($I^2 = 77\%$, $p = .002$); crystalloids ($I^2 = 89\%$, $p < .0001$); vasopressors ($I^2 = 84\%$, $p < .0001$); inotropes ($I^2 = 67\%$, $p = .01$); PRBC ($I^2 = 73\%$, $p = .001$); corticosteroids ($I^2 = 87\%$, $p < .0001$); and rhAPC ($I^2 = 88\%$, $p < .0001$) (Tables 5 and 6; Figs. 3, 4, and 5). With the exception of timely antibiotics, these bundle components were more likely to have a low quality evidence base and to have received a weak recommendation in updated guidelines (Table 7) (31). Importantly, these less well-accepted interventions are all undergoing additional testing in randomized controlled trials (Table 8).

Nonetheless, bundle components demonstrating heterogeneity were further analyzed to determine whether any one study accounted for most of the observed variability. Removal of any one study failed to significantly reduce heterogeneity in the use of fluids, vasopressors, corticosteroid or rhAPC (I^2 remained 74% to 91%, with $p = .002$ to $p < .0001$). However, a single study was identified as the source of heterogeneity for both antibiotic administration within a specified interval ($I^2 = 0\%$, $p = .40$ after removal) and PRBC transfusion ($I^2 = 0\%$, $p = .51$ after removal) (22). Likewise, removal of another study resolved heterogeneity in

inotrope usage ($I^2 = 0\%$, $p = .57$) (27). Bundled care compared with controls significantly increased the odds of receiving antibiotics within a specified period (OR, 3.89; 95% CI, 1.98–7.64; $p < .0001$) and the use of inotropes (OR, 6.89; 95% CI, 2.33–20.38; $p = .001$) among the remaining studies. Although PRBC transfusion occurred more frequently with bundled care, this intervention did not reach statistical significance (OR, 1.45; 95% CI, 0.94–2.26; $p = .095$).

DISCUSSION

Sepsis care bundles were associated with consistent and significant increases in survival across eight studies. Two of three measures of antibiotic use were also consistently and significantly improved across the studies reporting such data. In contrast, there was significant heterogeneity in the effect of bundled care on the use of all remaining bundle components analyzed. Insulin therapy and lung protective strategies were insufficiently reported and, therefore, not analyzed.

Numerous studies over the past 20 yrs have demonstrated improved outcomes in life-threatening infections with early administration of appropriate antibiotics, and multiple clinical guidelines emphasize such care (31–57). In a recent, large, retrospective study in septic patients with hypotension ($n = 2731$), every hour of delay in appropriate antibiotic administration was associated with a significant increase in mortality (32). Based on such evidence supporting the critical need for early appropriate antibiotics in treating serious infections, the Surviving Sepsis Campaign gave this treatment a strong rating (Grade 1B) in their updated 2008 guidelines (31). Importantly, use of early appropriate antibiotics for sepsis meets the stated requirement of the Joint Commission and Institute for Healthcare Improvement that bundle components be proven and well-accepted interventions (1, 9).

Resuscitation fluid volumes and the percentage of patients receiving vasopressors were not consistently altered by bundled care. This heterogeneity was not related to any individual study. Although bundles in each of these studies targeted a central venous pressure goal of 8 mm Hg to 12 mm Hg for fluid administration and an MAP of 65 mm Hg for vasopressors, levels outside of this range were likely employed clinically in some patients and may have contributed to heterogeneity. Notably, only one trial provided data regarding the levels of central venous pressure and MAP actually reached with bundled treatment and these exceeded the stipulated goals in many patients (22).

Hemodynamic support with fluids and vasopressors is as important as antibiotics in reducing mortality from septic shock (58). Nonetheless, differences in physician practice and among patient populations could lead to heterogeneity in application of these interventions. There is considerable variation in the ranges of central venous pressure and MAP which physicians believe should be targeted in septic patients (59). Furthermore, a central venous pressure goal of 8 mm Hg to 12 mm Hg may be too low in some septic patients or unnecessarily high in others (60–62). Many experts recommend fluid titration based on the response to carefully monitored boluses, rather than using arbitrary targets (63). Although the Surviving Sepsis Campaign guidelines provide a strong recommendation for these target numbers (Grade 1C), they also stipulate the importance of individualizing care (31). A single center trial that used the same central venous pressure and MAP targets in both study arms to titrate crystalloids and vasopressors is cited as the primary evidence to support these targets (22). As such, these targets were not tested and their use is questioned (64–68). Importantly, the effectiveness of these targets is now being reevaluated in large, multicentered randomized controlled trials (69) (Tables 7 and 8). Although rapid fluid and vasopressor resuscitation is indispensable for sepsis, optimal goals for such therapy may differ in patients based on underlying medical conditions, and their use should be individualized (67).

Administration of PRBC and inotropes to obtain an ScvO₂ of 70% was also not consistently altered with bundles over the eight studies. Although PRBC use became consistent after removal of one trial (22), it was not significantly different with bundled care. In contrast, removal of another trial (27) did consistently increase inotrope use significantly. Of note, however, the efficacy of administering PRBC and inotropes to achieve an ScvO₂ of 70% in patients with sepsis is unclear. How often this goal was reached with bundled care in seven of the eight trials analyzed is not reported. The 2008 Surviving Sepsis Campaign guidelines give such treatment during the early resuscitation of septic shock a weak recommendation (Grade 2C). Inotropic support and PRBC transfusions targeted to ScvO₂ are being further tested in ongoing randomized controlled trials to determine their efficacy in sepsis (69) (Tables 7 and 8). Accordingly, at present, these interventions do not meet Joint Commission and Institute for Healthcare Improvement criteria for inclusion in a bundle (1, 9).

Bundled care did not uniformly change low-dose corticosteroid and rhAPC use across trials and this may also relate to variations in practice or patient populations (70–76). However, as questions persist regarding the risks and benefits of these therapies for sepsis, either when administered individually or together, they continue to undergo investigation (77–79) (Tables 7 and 8). The Surviving Sepsis Campaign guidelines gave these therapies a weak recommendation for use in patients with severe sepsis and septic shock (Grade 2C for steroids, and 2B/2C for rhAPC). Although these agents may benefit some septic patients, until such subgroups are clear, their inclusion in care bundles is inappropriate.

Consistent use of earlier and appropriate antibiotics with care bundles could plausibly have contributed to the consistent increases in survival noted across these studies. However, other factors may have also contributed, independent of component therapies. Importantly, six of the trials described education or treatment aids to improve bundle utilization (22, 25–28). Consequently, unmeasured effects (e.g., earlier recognition of patients requiring surgical intervention or more readily available nonbundled therapies, such as respiratory support) may have changed outcomes. A large, multicentered, sepsis trial in Spain tested the effects of an intense educational program on bundle treatment goals and outcome first early (immediately after education) and then later (1 yr after education). Although attainment of treatment goals increased early but not later, survival was improved throughout (80).

Limitations of this meta-analysis include lack of methodologic rigor in the studies analyzed (lack of blinding, before-after study designs, retrospectively identified historical controls, potential selection bias, duration of sepsis, completeness of data collection, use of unadjusted data), which may confound their findings. Variation in factors, such as participating healthcare workers and patients studied, as well as the natural trend for general care to improve over time in hospitals, may have favored better outcomes with bundled care (81, 82). Also, consistency per se as used in our analysis may not be a strong indicator of cause and effect. Finally, this analysis included both nonrandomized and randomized studies.

Lung protective mechanical ventilation and strict glucose control with intravenous insulin have been included in some sepsis bundles (12). However, these therapies were either not assessed or insufficient data were available to determine their application in the analyzed studies. Primary evidence to support intravenous insulin control of glucose in septic patients came from a single trial, which reported that intensive insulin therapy improved survival in cardiac surgery patients. Subsequent controlled trials in critically ill patients, including those with sepsis, have not reproduced this benefit, and have suggested such therapy increases the frequency of hypoglycemia and may worsen outcome (83–85). This experience with

intensive insulin therapy demonstrates the risks of incorporating therapies into bundles before sufficient evidence supports such practice.

Although bundle use to ensure timely delivery of therapies with recognized benefit may be important in the Emergency Department and intensive care unit, institution of current sepsis bundles may force physicians to provide unproven or even harmful care. As administered and studied to date, only antibiotics meet the stated criteria of proof for bundle inclusion (1, 9). Furthermore, despite acknowledgment that the performance of care bundles should be assessed both as a whole and based on the contribution of individual components, methodology for such assessment has not been developed. At this time, reliance on nonrandomized designs and the absence of detailed results regarding application of bundle components and ancillary changes in management severely limit our ability to interpret clinical trials of bundled care.

Acknowledgments

This study was supported, in part, by The Intramural Research Program of the National Institutes of Health and the NIH Clinical Center, Bethesda, MD.

Dr. Banks, senior mathematical statistician, Critical Care Medicine Department, National Institutes of Health, died unexpectedly during the final stages of writing this manuscript. Dr. Banks dedicated his life's work to advancing science; his colleagues mourn his loss.

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Figure 1.
Study selection.

Figure 2. Effect of bundled care on the odds ratio of survival (95% confidence interval [CI]) for the seven studies analyzed and overall.

Figure 3. Effect of bundled care on antibiotic therapy including: *A*, antibiotics within a prespecified time period; *B*, mean time to antibiotics; and *C*, percentage of patients receiving appropriate antibiotics. *CI*, confidence interval.

Figure 4. Effect of bundled care on therapies based on set central venous pressure, mean arterial blood pressure, and central venous oxygen saturation goals including: *A*, total crystalloid use; and *B–D*, the percentage of patients receiving vasopressors, inotropes, and packed red blood cells (*PRBC*), respectively. *CI*, confidence interval.

Figure 5. Effect of bundled care on the percentage of patients administered (A) corticosteroids and (B) recombinant human activated protein C. *CI*, confidence interval.

Table 1

Components in two sepsis bundles formulated by the Surviving Sepsis Campaign (12, 16)

Bundle Title	Components
Acute sepsis bundle (To be completed within 6 hrs of admission)	Obtain microbiology samples and lactate measure Administer appropriate antibiotics Administer early goal directed therapy including: <ul style="list-style-type: none"> - Fluids to achieve a central venous pressure of 8 to 12 mm Hg - Vasopressors to achieve a mean arterial blood pressure > 65 mm Hg - Maintain central venous oxygen saturation >70% with packed red blood cells or inotrope therapy
Sepsis management bundle (To be completed within 24 hrs of admission)	Administer low-dose corticosteroids based on hospital policy Administer recombinant human activated protein C based on hospital policy Maintain glycemic control (120–150 mg/dL) Maintain plateau airway pressures 30 cm H ₂ O in mechanically ventilated patients

Table 2

Study designs

Study (reference)	Rivers et al (22)	Trzeciak et al (23)	Kortgen et al (24)	Shapiro et al (25)	Micek et al (26)	Nguyen et al (27)	Jones et al (28)	El Solh et al (29)
Year published	2001	2006	2006	2006	2006	2007	2007	2008
Study design ^a	Prospective, randomized	Before-after ^b	Before-after ^b	Before-after ^b	Before-after	Before-after ^{b,c}	Before-after	Before-after ^b
Data collection								
Controls	3/97–3/00	1/03–1/04	1/02–8/02	2/00–2/01	12/04–11–05	10/03–9/05	8/04–9/05	3/01–4/04
Bundled care	3/97–3/00	1/04–1/05	8/02–12/03	11/03–11/04		4/04–9/05	11/05–10/06	5/04–2/07
Setting	ED	ED/ICU	ICU	ED/ICU	ED/ICU	ED/ICU	ED	ED/ICU
Aids to facilitate protocol care ^d	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Study group imbalance in baseline criteria	No	Yes	Yes	Yes	No	Yes	NA ^e	No
APACHE II scores ^e								
Control	20.4 ± 7.4	25 ± 10	31 (26/35)	25 ± 10	22 ± 7	30 ± 11	NA	40 ± 16
Bundled care	21.4 ± 6.9	23 ± 11	35 (30/37)	24 ± 10	23 ± 10	29 ± 11	NA	42 ± 18

NA, not available; ICU, intensive care unit; ED, emergency department

^a All trials were unblinded;^b employed subjects defined retrospectively by chart review;^c also included nonrandomized contemporary controls;^d specialized education of health workers, dedicated areas of care, sepsis medication carts, tool kits, flow, sheets, order sets, dedicated lines of communication to sepsis experts, quality improvement programs or department head communications to increase compliance;^e Acute Physiology and Chronic health Evaluation (APACHE) II scores are reported as mean ± SD, except in the Kortgen study, which reported median (25th/75th percentile) values.

Table 3

Study inclusion criteria

Rivers et al (22)	Trzeciak et al (23)	Kortgen et al (24)	Shapiro et al (25)	Mirek et al (26)	Nguyen et al (27)	Jones et al (28)	El Solh et al (29)
2 SIRS criteria ^a	Suspected or confirmed sepsis ^a	Patients with septic shock ^a	Suspected infection with 2 SIRS criteria ^a	Suspected infection with 2 SIRS criteria ^a	Suspected infection with 2 SIRS criteria ^a	Suspected infection with 2 SIRS criteria ^a	Sepsis ^a
AND	AND		AND	AND	AND	AND	AND
SBP 90 mm Hg after 20–30 mL/kg fluid challenge	SBP <90 mm Hg after 1500 mL fluid challenge		SBP <90 mm Hg after 20–30 mL/kg fluid challenge	Vasodilatory shock with MAP 65 mm Hg requiring fluids and vasopressors	SBP <90 mm Hg or MAP <65 mm Hg	SBP 90 mm Hg after 20 mL/kg fluid challenge	SBP <90 mm Hg after adequate fluid challenge
OR			OR		OR	OR	OR
Lactate 4			Lactate >4		Lactate 4	Lactate 4 and need for ICU admission	Decrease in SBP by >40 mm Hg from baseline

SIRS, systemic inflammatory response syndrome; SBP, systolic blood pressure; MAP, mean arterial pressure; ICU, intensive care unit.

^aAs defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (17).

Table 4

Bundled care treatments and mortality end points

	Rivers et al (22)	Trzeciak et al (23)	Kortgen et al (24)	Shapiro et al (25)	Micek et al (26)	Nguyen et al (27)	Jones et al (28)	El Solh et al (29)
Initial treatment time Analyzed	0–6 Hrs	Time in ED	0–6 Hrs	0–6 Hrs	Time in ED	Time in ED	0–6 Hrs	0–6 Hrs
Protocol treatments								
Antibiotics	No	No	Yes	Yes	Yes	Yes	Yes	Yes
EGDT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Corticosteroids	No	No	Yes	Yes	Yes	Yes	No	Yes
rhAPC	No	No	Yes	Yes	Yes	No	No	Yes
Low tidal volume	No	No	Yes ^a	Yes ^a	No	No	No	No
Intensive insulin	No	No	Yes ^b	Yes ^b	No	No	No	Yes ^b
Nonprotocol treatments reported								
Antibiotics	Yes	Yes	—	—	—	—	—	—
Corticosteroids	No	Yes	—	—	—	—	Yes	—
rhAPC	No	Yes	—	—	—	Yes	Yes	—
Low tidal volume	No	No	—	—	No	No	No	Yes ^a
DVT prophylaxis	No	Yes	No	No	No	No	No	Yes ^c
Mortality end point	In hospital	In hospital	28 day	28 day	28 day	In hospital	In hospital	28 day
EGDT parameters reported at baseline	MAP, CVP, Hct, ScvO ₂ , Lactate	NA	NA	Hct, ScvO ₂ , Lactate	NA	CVP, Hb, ScvO ₂ , Lactate	CVP, ScvO ₂ , Lactate ^d	NA
EGDT parameters reported after treatment	MAP, CVP, Hct, ScvO ₂ , Lactate	NA	NA	NA	NA	NA	NA	NA

ED, emergency department; EGDT, early goal-directed therapy; rhAPC, recombinant human activated protein C; DVT, deep venous thrombosis; MAP, mean arterial pressure; CVP, central venous pressure; Hct, hematocrit; ScvO₂, central venous oxygen saturation; NA, not available; —, treatment was included in the protocol.

^aPatients were reported as being ventilated with lung protective ventilation, but actual mean tidal volumes were not reported;

^bdata not provided regarding adequacy of glucose control, or mean blood glucose values in control and treatment groups;

^call patients were reported as receiving DVT prophylaxis, but no details regarding dose or duration of medication used was provided;

^dScvO₂ and CVP data not available for controls.

Table 5

Bundled care antibiotic therapy

Study (reference)	Rivers et al (22)	Trzeciak et al (23)	Kortgen et al (24)	Shapiro et al (25)	Micek et al (26)	Nguyen et al (27)	Jones et al (28)	El Solh et al (29)
Antibiotics received by (time period ^b)	<6 hrs	—	<6 hrs	<6 hrs	<3 hrs	<4 hrs	—	<4 hrs
Controls, %	92.4	NA	100	94.1	60	87.4	NA	91
Bundled care, %	86.3	NA	100	98.7	86.7	100	NA	95
Mean $\pm$ SD time, hr to antibiotics								
Controls	NA	3.0 $\pm$ 2.7	NA	2.7 $\pm$ 2.0	NA	1.5 $\pm$ 1.8	2.4 $\pm$ 2.0	NA
Bundled care	NA	2.5 $\pm$ 1.7	NA	2.0 $\pm$ 1.4	NA	1.0 $\pm$ 1.2	1.7 $\pm$ 1.2	NA
Appropriate antibiotics received ^a								
Controls, %	94.3	NA	77.8 ^b	88.2	71.7	NA	NA	84
Bundled care, %	96.7	NA	85.7 ^b	97.5	86.7	NA	NA	97
Definition of appropriate antibiotics provided ^c	No	No	No	Yes	Yes	No	No	Yes

NA, not available.

^a Percentages are reported as published in original studies unless otherwise specified;^b percentages are calculated based on positive culture data;^c appropriate antibiotic use was defined as the use of an antibiotic to which subsequently cultured pathogens were sensitive, based on microbiological culture data (30).

Table 6

Bundled care: Other therapies

	Rivers et al (22)	Trzeciak et al (23)	Kortgen et al (24)	Shapiro et al (25)	Micek et al (26)	Nguyen et al (27)	Jones et al (28)	El Solh et al (29)
Fluids ^a								
Controls	3499 ± 2438	3509 ± 2312	2750 (1750/3750)	2871 ± 1773	2825 ± 1624	2807 ± 2091	2540 ± 2400	2490 ± 1020
Bundled care	4981 ± 2984	5685 ± 3021	2450 (1625/3870)	4107 ± 2590	3789 ± 1730	2755 ± 1477	4660 ± 1800	3960 ± 1990
Vasopressors ^b								
Controls, %	30.3	43.8	NA	45.1	100	43.9	34.2	NA
Bundled care, %	27.4	59.1	NA	79.7	71.7	50.6	68.8	NA
Inotropes ^b								
Controls, %	0.8	0	0	1.9	NA	26.5	1.3	NA
Bundled care, %	13.7	9.1	20	7.6	NA	23.4	2.6	NA
PRBC ^b								
Controls, %	18.5	0	16.7	5.8	6.7	12.6	1.3	13.0
Bundled care, %	64.1	13.6	16.7	10.1	20	14.3	5.2	14.0
Corticosteroids ^c								
Controls, %	NA	31.3	43.3	23.5	50	16.2	6.3	16.0
Bundled care, %	NA	36.4	100	29.1	21.7	29.9	40.3	95.0
rhAPC ^c								
Controls, %	NA	14.3	0	0	11.7	1.6	3.8	2.0
Bundled care, %	NA	33.3	23.3	3.8	3.3	29.9	3.9	13.0

NA, not available; PRBC, packed red blood cells; rhAPC, recombinant human activated protein C.

^aMean ± SD volume in mL of fluids administered during the initial period analyzed, except Kortgen et al who reported median (25th/75th percentile) values;^b% of patients receiving these therapies during initial period analyzed;^c% of patients receiving these therapies during similarly monitored periods.

Table 7

Summary for the therapies analyzed including the association between bundle use and their administration, the strength of recommendation and quality of evidence supporting their use in septic shock based on the GRADE system,^a and whether randomized controlled trials (RCT) are under way or planned to determine the effectiveness of these therapies in septic shock

Therapy	Consistent Association Between Bundle Use and Administration of Therapy	SSC 2008 Guidelines Grade		On-going or Planned RCT ^b
		Recommendation	Quality of Evidence	
Antibiotics				
Rapid antibiotics	Yes	Strong	Moderate	None
Appropriate antibiotics	Yes	Strong	Moderate	None
Fluids for CVP 8–12 mm Hg	No	Strong	Low	ProCESS, ARISE, ProMISE
Vasopressors for MAP 65 mm Hg	No	Strong	Low	ProCESS, ARISE, ProMISE
Inotropes for ScvO ₂ 70%	No	Weak	Low	ProCESS, ARISE, ProMISE
PRBC for ScvO ₂ 70%	No	Weak	Low	ProCESS, ARISE, ProMISE
Corticosteroids	No	Weak	Low	HYPRESS, APROCCHS
rhAPC	No	Weak	Moderate	PROWESS-SHOCK, APROCHHS

CVP, central venous pressure; MAP, mean arterial pressure; PRBC, packed red blood cells; rhAPC, recombinant human activated protein C.

^aThe GRADE system as employed in the SSC guidelines (31);

^b see Table 8 for details regarding these trials.

Table 8

Summary of ongoing or planned randomized controlled trials testing the effectiveness of early goal directed therapy (EGDT), low-dose corticosteroids, or recombinant human activated protein C (rhAPC) in septic shock

Trial Name	Design	Inclusion Criteria	Study Groups	Completion Date
Protocolized Care for Early Septic Shock (ProCESS) ^a NCT00510835	Multicentered, randomized, open-label, active control, parallel assignment safety/efficacy study	Infection, sepsis, refractory shock, hypotension	EGDT vs. Protocolized standard care vs. standard care	January 2010
Australian Resuscitation Sepsis Evaluation (ARISE) ^b	Multicentered, randomized controlled study	Early severe sepsis	NA	NA
Protocolized Management of Sepsis, UK Based (ProMISE) ^b	Multicentered, randomized controlled study	Early severe sepsis	NA	NA
Hydrocortisone for Prevention of Septic Shock (HYPRESS) ^a NCT00670254	Multicentered, randomized, double-blind, placebo-controlled parallel assignment safety/efficacy study	Infection, sepsis, vasopressor dependent shock	Hydrocortisone vs. placebo	May 2011
Efficacy and Safety of rhAPC in Adults with Septic Shock (PROWESS-SHOCK) ^a NCT00604214	Multicentered, randomized, double-blind, active controlled, placebo-controlled parallel assignment safety/efficacy study	Infection, SIRS, vasopressor dependent shock	rhAPC vs. placebo	NA
rhAPC and Corticosteroids for Human Septic Shock (APROCCHS) ^a NCT00625209	Multicentered, randomized, doubleblind, placebo-controlled parallel assignment safety/efficacy study	Infection, vasopressor dependent shock	P-HC/FC + P-rhAPC vs. HC/FC + P-rhAPC vs. P-HC/FC + rhAPC vs. HC/FC + rhAPC	December 2010

NA, not available; SIRS, systemic inflammatory response syndrome; P, placebo; HC, hydrocortisone; HC/FC, hydrocortisone and fludrocortisone.

^a Ongoing;

^b planned.