EDITORIAL

The ProCESS Trial — A New Era of Sepsis Management

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The importance of early detection and treatment for reducing the mortality associated with sepsis has been a tenet of medical training since the middle ages, when it was noted that ". . . the physicians say it happens in hectic fever, that in the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure."[1,2] The critical role of the clinician in the early recognition of sepsis continues to this day to be fundamental to our efforts to improve the rate of survival.[3] Identification of the combination of signs and symptoms that make up the systemic inflammatory response syndrome (SIRS)[4] in the context of an infection allows the astute clinician to recognize the malady.

Early recognition of sepsis was incorporated into the trial design, prompts, and protocols of the Protocolized Care for Early Septic Shock (ProCESS) trial, the results of which are now reported in the *Journal*.[5] For all the groups in the trial, the goal was early recognition of sepsis, as specified in the Surviving Sepsis Campaign guidelines,[3] and the design called for early treatment with antimicrobial agents[6] and conservative transfusion thresholds; in addition, the patients received low tidal-volume ventilation and had moderate glycemic control.

Indeed, septic shock was recognized early in a majority of the patients; 76% of the patients received antimicrobial agents by the time they underwent randomization, which occurred a mean of approximately 3 hours after patients' arrival in the emergency department. The rate of intravenous antimicrobial administration 6 hours after randomization was approximately 97%, a finding that suggests that notification that septic shock is present encourages the administration of antibiotics. A study that attributed increased mortality to delays in the administration of appropriate antibiotics[6] suggested that early administration of antibiotics increased survival in all groups of the trial. Indeed, in the ProCESS trial, the early or facilitated recognition of septic shock, administration of intravenous antibiotics, and other best practices were associated with rates of survival that were higher than projected and higher than predicted on the basis of scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II,[7] and a thoughtful design allowed the sample size of the trial to be recalculated to preserve the power of the study to test the primary outcome. One important contribution of the ProCESS trial is the evidence it provides regarding the ongoing role of early recognition of and antibiotic treatment for sepsis in improving survival.

The ProCESS trial also provides transformative insights about the treatments for septic shock that bring generalizable benefits when septic shock is recognized in the first hours after arrival in the emergency department. The use of central hemodynamic and oxygen-saturation monitoring in the protocol-based early goal-directed therapy (EGDT) group did not result in better outcomes than those that were achieved with clinical assessment of the adequacy of circulation. The finding that adjusting therapies to surrogate physiological targets measured with invasive catheters was not required to reduce mortality is consistent with the results of a study that showed that serial measurement of blood lactate levels was noninferior to catheter-derived measurements[8] and of analyses that have not found benefits of the use of pulmonary-artery catheters.[9] State legislation and clinical guidelines, including those endorsed by the National Quality Forum, should be updated to remove the requirement for central hemodynamic moni-

toring and to focus on less costly, lower-risk, and equally effective alternatives.

The association of the implementation of the multifaceted EGDT intervention with significantly lower mortality in an earlier study[10] launched the EGDT era of sepsis management. This milestone study encouraged coordinated efforts[3] to improve the outcomes in patients with this common[11] and life-threatening condition. These efforts translated into the earlier identification of septic shock and into an increased number of patients receiving earlier administration of a larger volume of resuscitation fluid. The ProCESS trial allows refinement of the EGDT approach to fluid administration by defining lower boundaries that are associated with equivalent outcomes and setting limits that are needed to avoid the twin problems of renal failure from too little fluid and pulmonary dysfunction from fluid overload. Another interesting and seemingly paradoxical finding is that patients in whom sepsis was managed without a protocol had an outcome as good as those in patients in whom the sepsis was managed with the use of a protocol. If one assumes that the treatments for septic shock, as well as the timing of the treatments, that would be administered in all emergency departments, regardless of size or available resources, would be equivalent to those used in the no-protocol (usual-care) group of the ProCESS trial (which included strategies for early recognition of sepsis), one could come to the dubious conclusion that protocols and decision prompts do not have a role in the treatment of septic shock. I prefer to think differently. I believe that the prompting, serum lactate screening and assessment of SIRS criteria, and reporting of activities that were parts of the study by Rivers et al. and the ProCESS trial can be applied in clinical practice to ensure early diagnosis and treatment for all patients with septic shock.

The ProCESS trial identifies early recognition of sepsis, early administration of antibiotics, early adequate volume resuscitation, and clinical assessment of the adequacy of circulation as the elements we should focus on to save lives. The publication of the ProCESS trial launches the era of early recognition and treatment in the management of sepsis.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

ABSTRACT

BACKGROUND

In a single-center study published more than a decade ago involving patients presenting to the emergency department with severe sepsis and septic shock, mortality was markedly lower among those who were treated according to a 6-hour protocol of early goal-directed therapy (EGDT), in which intravenous fluids, vasopressors, inotropes, and blood transfusions were adjusted to reach central hemodynamic targets, than among those receiving usual care. We conducted a trial to determine whether these findings were generalizable and whether all aspects of the protocol were necessary.

METHODS

In 31 emergency departments in the United States, we randomly assigned patients with septic shock to one of three groups for 6 hours of resuscitation: protocol-based EGDT; protocol-based standard therapy that did not require the placement of a central venous catheter, administration of inotropes, or blood transfusions; or usual care. The primary end point was 60-day in-hospital mortality. We tested sequentially whether protocol-based care (EGDT and standard-therapy groups combined) was superior to usual care and whether protocol-based EGDT was superior to protocol-based standard therapy. Secondary outcomes included longer-term mortality and the need for organ support.

RESULTS

We enrolled 1341 patients, of whom 439 were randomly assigned to protocol-based EGDT, 446 to protocol-based standard therapy, and 456 to usual care. Resuscitation strategies differed significantly with respect to the monitoring of central venous pressure and oxygen and the use of intravenous fluids, vasopressors, inotropes, and blood transfusions. By 60 days, there were 92 deaths in the protocol-based EGDT group (21.0%), 81 in the protocol-based standard-therapy group (18.2%), and 86 in the usual-care group (18.9%) (relative risk with protocol-based therapy vs. usual care, 1.04; 95% confidence interval [CI], 0.82 to 1.31; P=0.83; relative risk with protocol-based EGDT vs. protocol-based standard therapy, 1.15; 95% CI, 0.88 to 1.51; P=0.31). There were no significant differences in 90-day mortality, 1-year mortality, or the need for organ support.

CONCLUSIONS

In a multicenter trial conducted in the tertiary care setting, protocol-based resuscitation of patients in whom septic shock was diagnosed in the emergency department did not improve outcomes. (Funded by the National Institute of General Medical Sciences; ProCESS ClinicalTrials.gov number, NCT00510835.)

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There are more than 750,000 cases of severe sepsis and septic shock in the United States each year.[1] Most patients who present with sepsis receive initial care in the emergency department, and the short-term mortality is 20% or more.[2,3] In 2001, Rivers et al. reported that among patients with severe sepsis or septic shock in a single urban emergency department, mortality was significantly lower among those who were treated according to a 6-hour protocol of early goal-directed therapy (EGDT) than among those who were given standard therapy (30.5% vs. 46.5%).[4] On the basis of the premise that usual care lacked aggressive, timely assessment and treatment, the protocol for EGDT called for central venous catheterization to monitor central venous pressure and central venous oxygen saturation ($ScvO_2$), which were used to guide the use of intravenous fluids, vasopressors, packed red-cell transfusions, and dobutamine in order to achieve prespecified physiological targets. In the decade since the publication of that article, there have been many changes in the management of sepsis, raising the question of whether all elements of the protocol are still necessary.[5-7]

To address this question, we designed a multicenter trial comparing alternative resuscitation strategies in a broad cohort of patients with septic shock. Specifically, we tested whether protocol-based resuscitation was superior to usual care and whether a protocol with central hemodynamic monitoring to guide the use of fluids, vasopressors, blood transfusions, and dobutamine was superior to a simpler protocol that did not include these elements.

Methods

Study Oversight

We conducted the multicenter, randomized Protocolized Care for Early Septic Shock (ProCESS) trial at 31 hospitals in the United States. The institutional review board at the University of Pittsburgh and at each other participating site approved the registered study protocol, which is available with the full text of this article at NEJM.org. The National Institute of General Medical Sciences funded the study and convened an independent data and safety monitoring board (see the Supplementary Appendix, available at NEJM.org). The $ScvO_2$ monitoring equipment for the study was loaned to the sites by Edwards Lifesciences, but the company had no other role in the study. Study coordinators at each site entered data into a secure Web-based data-collection instrument. The University of Pittsburgh Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center managed all the data and generated blinded and unblinded reports for the data and safety monitoring board. We reported the statistical analysis plan before the data were unblinded.[8] The clinical coordinating team and investigators at the participating sites remained unaware of the study-group outcomes until the data were locked in December 2013. The writing committee vouches for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

Sites and Patients

All the participating sites were academic hospitals with more than 40,000 emergency department visits yearly. To be eligible, the study sites had to use the measurement of serum lactate levels as the method for screening for cryptogenic shock and had to adhere to the Surviving Sepsis Campaign guidelines[9,10] for nonresuscitation aspects of care but could have no routine resuscitation protocols for septic shock and could not routinely use continuous $ScvO_2$ catheters. We recruited patients in the emergency department in whom sepsis was suspected according to the treating physician, who were at least 18 years of age, who met two or more criteria for systemic inflammatory response syndrome[11] (see the Methods section in the Supplementary Appendix), and who had refractory hypotension or a serum lactate level of 4 mmol per liter or higher. We defined refractory hypotension as a systolic blood pressure that either was less than 90 mm Hg or required vasopressor therapy to maintain 90 mm Hg even after an intravenous fluid challenge. We initially required the fluid challenge to be 20 ml or more per kilogram of body weight, administered over the course of 30 minutes, but in April 2010, we simplified the requirement to a challenge of 1000 ml or more administered over the course of 30 minutes. Patients did not have to be in shock on arrival in the emergency department but had to be enrolled in the study in the emergency department within 2 hours after the earliest detection of shock and within 12 hours after arrival. The exclusion criteria are listed in the Methods section in the Supplementary Appendix. All pa-

tients or their legally authorized representatives provided written informed consent. Randomization was performed with the use of a centralized Web-based program in variable block sizes of 3, 6, or 9, with stratification according to site and race.

STUDY INTERVENTIONS

We randomly assigned patients, in a 1:1:1 ratio, to one of three groups: protocol-based EGDT, protocol-based standard therapy, or usual care. The same trained and dedicated physician-led team implemented both the protocol-based EGDT and the protocol-based standard-therapy interventions. The team consisted of at least one available physician who was trained in the protocol-guided resuscitation interventions, a study coordinator who monitored adherence to protocol instructions and provided timed prompts, and a bedside nurse. All study physicians were trained in emergency medicine or critical care medicine and had completed a Web-based certification examination. The protocol-based care began in the emergency department but could be continued elsewhere. Details regarding the training and conduct of the personnel are provided in the Methods section in the Supplementary Appendix. In cases in which a team physician was the bedside provider before enrollment, care was transferred to a nonstudy physician before enrollment.

For patients randomly assigned to protocol-based EGDT, the resuscitation team followed the protocol outlined in Figure S1 in the Supplementary Appendix, which mimics that used by Rivers et al.[4] The protocol prompted placement of a central venous catheter to monitor pressure and $ScvO_2$ and to administer intravenous fluids, vasopressors, dobutamine, or packed red-cell transfusions, as directed. We did not require placement of an arterial catheter for blood-pressure monitoring. The protocol in our study, like the protocol in the study by Rivers et al., specified the amount and timing, but not the type, of resuscitation fluid. Similarly, the protocol in our study specified thresholds for vasopressor use but not the specific choice of vasopressor. The protocol guided only resuscitation, with all other aspects of care, including the choice of antimicrobial agents, given at the discretion of the treating physician.

Protocol-based standard therapy also used a team approach with a set of 6-hour resuscitation instructions, but the components were less aggressive than those used for protocol-based EGDT (Fig. S2 in the Supplementary Appendix). ProCESS investigators designed the protocol-based standard-therapy approach on the basis of a review of the literature, two independent surveys of emergency physician and intensivist practice worldwide,[5,12] and consensus feedback from investigators. Protocol-based standard therapy required adequate peripheral venous access (with placement of a central venous catheter only if peripheral access was insufficient) and administration of fluids and vasoactive agents to reach goals for systolic blood pressure and shock index (the ratio of heart rate to systolic blood pressure) and to address fluid status and hypoperfusion, which were assessed clinically at least once an hour. In contrast to the triggers in the EGDT protocol, protocol-based standard therapy recommended packed red-cell transfusion only if the hemoglobin level was less than 7.5 g per deciliter. The protocol for standard therapy mandated administration of fluids until the team leader decided that the patient's fluids were replete. The standard-therapy protocol, like the EGDT protocol, did not specify the type of fluid or vasopressor and did not specify nonresuscitation aspects of care, which were provided by the treating physician. We assessed adherence to the EGDT and standard-therapy protocols using an algorithm that screened for decision prompts and actions at 2, 4, and 6 hours (Fig. S3 and S4 in the Supplementary Appendix).

For patients in the usual-care group, the bedside providers directed all care, with the study coordinator collecting data but not prompting any actions. Lead investigators at a site could not serve as the bedside treating physician for patients in the usual-care group.

OUTCOME MEASURES

The primary outcome of the study was the rate of in-hospital death from any cause at 60 days. Secondary mortality outcomes included the rate of death from any cause at 90 days and cumulative mortality at 90 days and 1 year. Other outcomes included the duration of acute cardiovascular failure (defined as the duration of the need for vasopressors), acute respiratory failure, and acute renal failure (defined as the duration of mechanical ventilation or dialysis during the acute hospitalization, truncated at 60 days, in patients who

had not had a long-term need for ventilation or dialysis before enrollment); the duration of the stay in the hospital and intensive care unit; and hospital discharge disposition (i.e., discharge to a long-term or other acute care facility, a nursing home, a private home, or other). We collected information on serious adverse events using standard federal guidelines.[13]

STATISTICAL ANALYSIS

We analyzed all data according to the intention-to-treat principle. For the primary outcome, our design tested sequentially whether protocol-based resuscitation (EGDT or standard therapy) was superior to usual care and, if it was, whether protocol-based EGDT was superior to protocol-based standard therapy. We initially calculated that with a sample of 1950 patients, the study would have at least 80% power to detect a reduction in mortality of 6 to 7 percentage points, at an alpha level of 0.05 for both hypotheses, assuming mortality of 30 to 46% with usual care; interim analyses were planned after 650 patients and 1300 patients had been enrolled. The trial did not meet the stopping criteria at the first planned interim analysis (after the enrollment of 650 patients). Before the second interim analysis, we observed that the overall mortality was approximately 20%, which was much lower than anticipated but consistent with the results of a recent study involving similar patients.[14] After consultation with the data and safety monitoring board and the National Institute of General Medical Sciences, and with the group assignments still concealed, we calculated that we would need to enroll a total of 1350 patients to preserve the same power for the same absolute risk reduction.

After spending 0.0005 alpha for the first interim analysis, and after recalculation of the sample size (which removed the requirement for a second interim analysis), the alpha level required for the sequential hypotheses was 0.0494, with no adjustment for multiple testing. We tested for between-group differences in the primary outcome using Fisher's exact test. In the event that protocol-based care (EGDT and standard therapy combined) was not superior to usual care, all other analyses were to be specified as secondary. Because of possible site heterogeneity, we also conducted a secondary analysis using a generalized linear mixed model in which we allowed for a random effect of study site, with treatment group as a covariate; assessed significance with the use of type 3 tests; and used compound symmetry for the covariance structure.

For other end points, we used Fisher's exact test for categorical outcomes and an analysis of variance for continuous outcomes. For survival analyses, we generated Kaplan–Meier estimates, assessed between-group differences using the log-rank test, and expressed the data as cumulative mortality curves. In prespecified subgroup analyses, we used the Breslow–Day test to assess interactions between treatment assignment and subgroups defined according to age, sex, race, source of infection, and enrollment criterion (refractory hypotension or elevated serum lactate level). We also conducted post hoc subgroup analyses according to thirds of values for the Acute Physiology and Chronic Health Evaluation (APACHE) II score, for the baseline serum lactate level, and for the time from detection of shock until randomization, using logistic regression to test for an interaction between treatment assignment and subgroups. Unless otherwise specified, analyses are for tests of differences across the three study groups, with P values of less than 0.05 considered to indicate statistical significance. We used SAS software, version 9.3, for all analyses.

RESULTS

PATIENTS

From March 2008 through May 2013, we enrolled 1351 patients (Fig. 1, and Fig. S5 in the Supplementary Appendix). Ten patients who provided informed consent later requested complete withdrawal from the study, leaving a final cohort of 1341 patients for the analysis: 439 in the protocol-based EGDT group, 446 in the protocol-based standard-therapy group, and 456 in the usual-care group. The three groups were well matched at baseline with respect to demographic and clinical characteristics, as well as the care received before randomization (Table 1, and Tables S1, S2, and S4 in the Supplementary Appendix).

ADHERENCE TO THE PROTOCOL

Adherence to the protocol was high in both protocol-based groups. At 6 hours, incomplete adherence was recorded in 48 of 404 patients in the EGDT group (11.9%) and 19 of 435 patients in the standard-therapy group (4.4%) who could be evaluated (Table S3 in the Supplementary Appendix). In most of the patients who had been ran-

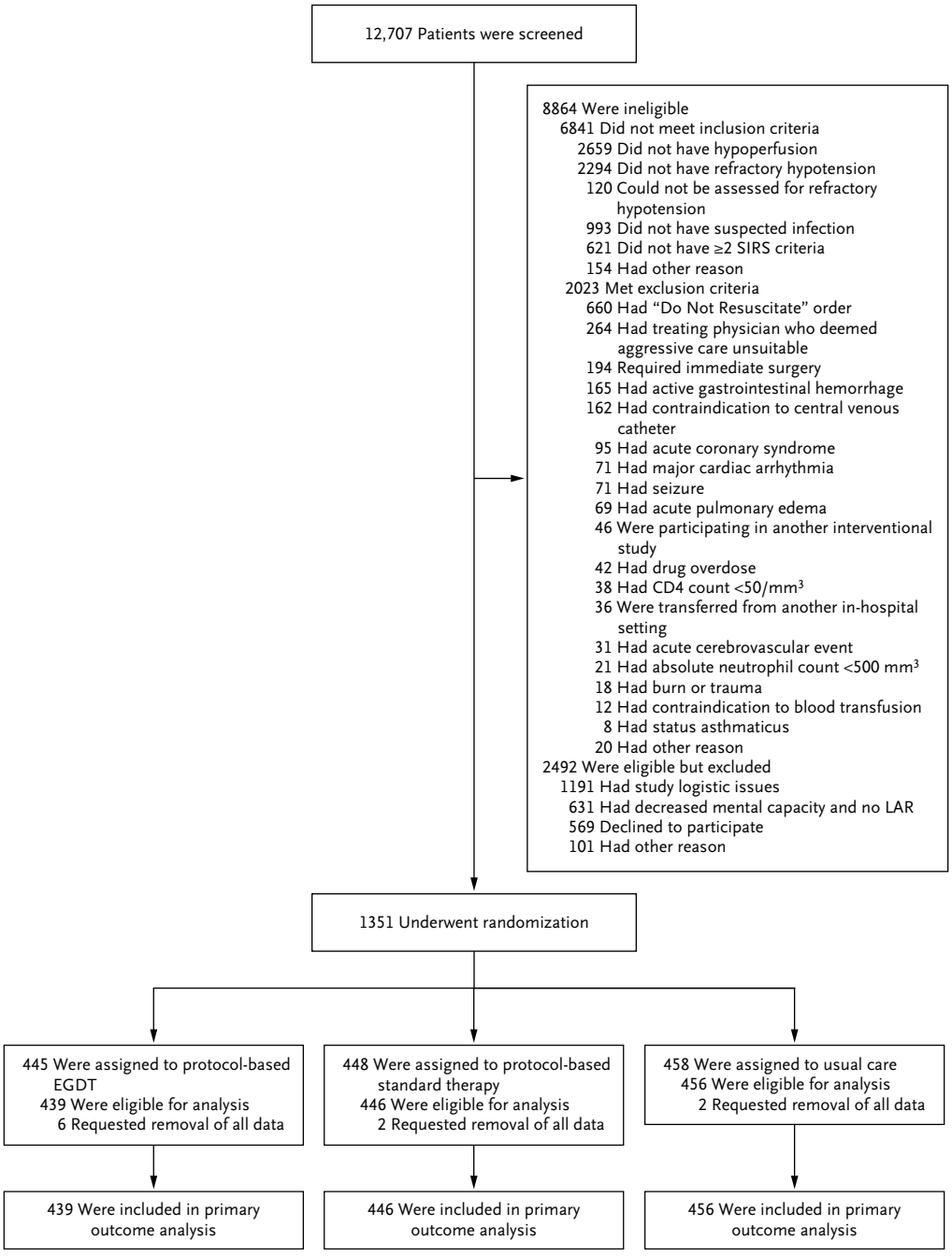

Figure 1. Screening, Randomization, and Follow-up.

EGDT denotes early goal-directed therapy, LAR legally authorized representative, and SIRS systemic inflammatory response syndrome.

domly assigned to EGDT, a central venous catheter for monitoring of $ScvO_2$ was placed promptly (Fig. S6A in the Supplementary Appendix). The reasons for failure to place a central venous catheter, which occurred in 30 of the 439 patients in that group (6.8%), included technical difficulties (10 patients), refusal by the treating clinician (9) or patient (5), the need for emergency surgery (1),

and death (1); no reason was provided in the case of 4 patients). The mean (±SD) $ScvO_2$ after catheterization was 71±13%. Although placement of central venous catheters was not required for patients in the protocol-based standard-therapy group or the usual-care group, central venous catheters were placed in 56.5% of the patients (252 patients) and 57.9% (264 patients) in the two groups, respectively; however, placement occurred later than in the EGDT group (P<0.001)

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Protocol-Based EGDT (N=439)	Protocol-Based Standard Therapy (N=446)	Usual Care (N=456)
Age — yr†	60±16.4	61±16.1	62±16.0
Male sex — no. (%)	232 (52.8)	252 (56.5)	264 (57.9)
Residence before admission — no. (%)‡			
Nursing home	64 (14.6)	72 (16.1)	73 (16.0)
Other	373 (85.0)	373 (83.6)	382 (83.8)
Charlson comorbidity score§	2.6±2.6	2.5±2.6	2.9±2.6
Source of sepsis — no. (%)			
Pneumonia	140 (31.9)	152 (34.1)	151 (33.1)
Urinary tract infection	100 (22.8)	90 (20.2)	94 (20.6)
Intraabdominal infection	69 (15.7)	57 (12.8)	51 (11.2)
Infection of unknown source	57 (13.0)	47 (10.5)	66 (14.5)
Skin or soft-tissue infection	25 (5.7)	33 (7.4)	38 (8.3)
Catheter-related infection	11 (2.5)	16 (3.6)	11 (2.4)
Central nervous system infection	3 (0.7)	3 (0.7)	4 (0.9)
Endocarditis	1 (0.2)	3 (0.7)	3 (0.7)
Other	28 (6.4)	31 (7.0)	26 (5.7)
Determined after review not to have infection	5 (1.1)	14 (3.1)	12 (2.6)
Positive blood culture — no. (%)	139 (31.7)	126 (28.3)	131 (28.7)
APACHE II score¶	20.8±8.1	20.6±7.4	20.7±7.5
Entry criterion — no. (%)			
Refractory hypotension	244 (55.6)	240 (53.8)	243 (53.3)
Hyperlactatemia‖	259 (59.0)	264 (59.2)	277 (60.7)
Physiological variables			
Systolic blood pressure — mm Hg	100.2±28.1	102.1±28.7	99.9±29.5
Serum lactate — mmol/liter**	4.8±3.1	5±3.6	4.9±3.1
Time to randomization — min			
From arrival in the emergency department††	197±116	185±112	181±97
From meeting entry criteria	72±77	66±38	69±45

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics across groups (P values range from 0.10 to 0.96). EGDT denotes early goal-directed therapy.
† Information on age was missing for one patient in the usual-care group.
‡ Information on residence before admission was missing for four patients. The category of nursing home included personal-care homes, skilled or unskilled assisted-living facilities, and extended-care facilities.
§ The Charlson comorbidity index[15] measures the effect of coexisting conditions on mortality, with scores ranging from 0 to 33 and higher scores indicating a greater burden of illness.
¶ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating greater severity of illness.
‖ Hyperlactatemia was defined as a serum lactate level of 4 mmol per liter or higher. The serum lactate level was higher than 2 mmol per liter in 346 patients in the protocol-based EGDT group (78.8%), 340 in the protocol-based standard-therapy group (76.2%), and 359 in the usual-care group (78.7%).
** Data on the baseline serum lactate level were available for 95.5% of the patients overall (1281 of 1341 patients).
†† Not all patients were eligible at the time of arrival in the emergency department.

(Fig. S6B in the Supplementary Appendix) and involved serial monitoring of $ScvO_2$ in only a small proportion of patients (4.0% [18 patients] in the protocol-based standard-therapy group and 3.5% [16 patients] in the usual-care groups, vs. 93.6% [411 patients] in the EGDT group; P<0.001).

RESUSCITATION

During the first 6 hours, the volume of intravenous fluids administered differed significantly among the groups (2.8 liters in the protocol-based EGDT group, 3.3 liters in the protocol-based standard-therapy group, and 2.3 liters in the usual-care group (P<0.001) (Table S4 and Fig. S6C in the Supplementary Appendix). The volume of fluids administered decreased during the 6 hours in all the groups, but patients in the protocol-based standard-therapy group received the greatest volume initially and overall, patients in the usual-care group received the least volume of fluid, and patients in the protocol-based EGDT group received fluid at the most consistent rate (P<0.001 for differences in total volume and P=0.007 for differences over time). Crystalloids were the predominant fluid used in all the groups, administered in 96% of the patients overall. More patients in the two protocol-based groups than in the usual-care group received vasopressors (54.9% in the protocol-based EGDT group and 52.2% in the protocol-based standard-therapy group vs. 44.1% in the usual-care group, P=0.003) (Table S4 and Fig. S6D in the Supplementary Appendix). More patients in the protocol-based EGDT group than in the protocol-based standard-therapy group or the usual-care group received dobutamine and packed red-cell transfusions (dobutamine use, 8.0% vs. 1.1% and 0.9%, respectively; P<0.001; packed red-cell transfusions, 14.4% vs. 8.3% and 7.5%, respectively; P=0.001) (Table S4, and Fig. S6D in the Supplementary Appendix). The use of antibiotics, glucocorticoids, and activated protein C was similar across the three groups (with P values ranging from 0.16 to 0.90) (Table S4 in the Supplementary Appendix).

ANCILLARY CARE

The use of intravenous fluids, vasopressors, dobutamine, and blood transfusions between 6 and 72 hours did not differ significantly among the groups (Table S4 in the Supplementary Appendix). Patients in all three groups had mean values that were consistent with low-tidal-volume ventilation and moderate glycemic control (Table S4 in the Supplementary Appendix). In general, the condition of the patients in all three groups improved over time, with few differences among the groups. By 6 hours, the target mean arterial pressure of 65 mm Hg or higher had been achieved in more patients in each of the protocol-based groups than in the usual-care group (P=0.02), but the mean heart rate did not differ significantly among the groups (P=0.32) (Table S2 in the Supplementary Appendix). Patients in the protocol-based EGDT group had a higher mean international normalized ratio at 6 hours (2.2, vs. 1.7 in the protocol-based standard-therapy group and 1.6 in the usual-care group; P=0.01), whereas patients in the usual-care group had slightly less acidosis at 6 hours and 24 hours (arterial pH, 7.31 in each protocol-based group vs. 7.34 in the usual-care group at 6 hours, and 7.34 in each protocol-based group vs. 7.36 in the usual-care group at 24 hours, P=0.02), but these differences did not persist.

OUTCOMES

By day 60, a total of 92 patients in the protocol-based EGDT group (21.0%), 81 in the protocol-based standard-therapy group (18.2%), and 86 in the usual-care group (18.9%) had died in the hospital (Table 2). The 60-day in-hospital mortality for the combined protocol-based groups (19.5% [173 of 885 patients]) did not differ significantly from that in the usual-care group (relative risk, 1.04; 95% confidence interval [CI], 0.82 to 1.31; P=0.83), nor did mortality differ significantly when the groups were compared separately (with P values ranging from 0.31 to 0.89) (Table 2 and Fig. 2A). There were also no significant differences in 90-day mortality or in the time to death up to 90 days and 1 year (P=0.66 for 90-day mortality and P=0.70 and P=0.92 for cumulative mortality at 90 days and 1 year, respectively) (Table 2 and Fig. 2B). Results were essentially unchanged when adjusted for potential site heterogeneity (odds of 60-day in-hospital death with protocol-based care vs. usual care, 1.08; 95% CI, 0.85 to 1.38; P=0.54).

The incidence of acute renal failure, as indicated by a new need for renal-replacement therapy, was higher in the protocol-based standard-therapy group than in the other two groups (6.0% in the protocol-based standard-therapy group vs. 3.1% in the protocol-based EGDT group and 2.8% in the usual-care group, P=0.04),

Table 2. Outcomes.*

Outcome	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual Care (N=456)	P Value†
Death — no./total no. (%)				
In-hospital death by 60 days: primary outcome	92/439 (21.0)	81/446 (18.2)	86/456 (18.9)	0.83‡
Death by 90 days	129/405 (31.9)	128/415 (30.8)	139/412 (33.7)	0.66
New organ failure in the first week — no./total no. (%)				
Cardiovascular	269/439 (61.3)	284/446 (63.7)	256/456 (56.1)	0.06
Respiratory	165/434 (38.0)	161/441 (36.5)	146/451 (32.4)	0.19
Renal	12/382 (3.1)	24/399 (6.0)	11/397 (2.8)	0.04
Duration of organ support — days§				
Cardiovascular	2.6±1.6	2.4±1.5	2.5±1.6	0.52
Respiratory	6.4±8.4	7.7±10.4	6.9±8.2	0.41
Renal	7.1±10.8	8.5±12	8.8±13.7	0.92
Use of hospital resources				
Admission to intensive care unit — no. (%)	401 (91.3)	381 (85.4)	393 (86.2)	0.01
Stay in intensive care unit among admitted patients — days	5.1±6.3	5.1±7.1	4.7±5.8	0.63
Stay in hospital — days	11.1±10	12.3±12.1	11.3±10.9	0.25
Discharge status at 60 days — no. (%)				
Not discharged	3 (0.7)	8 (1.8)	2 (0.4)	0.82
Discharged to a long-term acute care facility	16 (3.6)	22 (4.9)	22 (4.8)	
Discharge to another acute care hospital	8 (1.8)	2 (0.4)	5 (1.1)	
Discharged to nursing home	71 (16.2)	93 (20.9)	88 (19.3)	
Discharged home	236 (53.8)	227 (50.9)	235 (51.5)	
Other or unknown	13 (3.0)	13 (2.9)	18 (3.9)	
Serious adverse events — no. (%)¶	23 (5.2)	22 (4.9)	37 (8.1)	0.32

* Plus–minus values are means ±SD.
† Unless stated otherwise, P values are for a three-group comparison, with the use of Fisher's exact test for categorical measures and linear models for continuous and normally distributed measures. Skewed outcomes were analyzed with the use of nonparametric alternatives.
‡ The P value for the primary analysis was for a comparison between the two protocol-based groups combined and the usual-care group, with the use of Fisher's exact test. The three-group comparison, with the use of Fisher's exact test, was also nonsignificant (P=0.55), as was each one of the two-way comparisons (with P values ranging from 0.31 to 0.89).
§ Included in the analysis were patients in whom new organ failure developed in the first week after randomization.
¶ A detailed list of serious adverse events is provided in Table S5 in the Supplementary Appendix.

although the duration of therapy did not differ significantly across the groups (Table 2). The rate of admission to the intensive care unit was higher in the protocol-based EGDT group than in the other two groups, although among patients who were admitted, there were no significant between-group differences in the length of stay in the intensive care unit (Table 2). There were no significant differences in the incidence and duration of cardiovascular failure or respiratory failure, nor were there significant differences in the length of stay in the hospital or the discharge disposition (Table 2).

Reports of potentially serious adverse events (excluding death) were rare and did not differ significantly across groups (Table 2, and Table S5 in the Supplementary Appendix). There were no significant interactions between the assigned treatment and any prespecified subgroup with respect to the primary outcome of 60-day in-hospital mortality or with respect to the secondary mortality outcomes (Table S6 in the Supplementary Ap-

pendix). Similarly, in a post hoc analysis, there was no evidence of a treatment effect within ranges of values for the APACHE II score, serum lactate level, or time from meeting the criteria for shock to randomization (Table S7 in the Supplementary Appendix).

DISCUSSION

In our study, adherence to the two experimental protocols was high, and, as expected, protocol-based care, as compared with usual care, resulted in increased use of central venous catheterization, intravenous fluids, vasoactive agents, and blood transfusions. The two protocol-based resuscitation approaches led to a small but transient improvement in blood pressure by the end of the resuscitation period but a higher requirement for intensive care and renal-replacement therapy. There were no significant differences in mortality, either overall or in a number of prespecified and post hoc subgroups.

Our results differ from those of Rivers et al.[4]; however, our study was not a direct replication of that study, and there are probably several factors that contribute to the differences. Although the two trials used similar inclusion criteria, the enrolled populations differed. The study cohorts were similar with respect to many demographic and clinical characteristics, including the severity of illness (Table S8 in the Supplementary Appendix), but the cohort in the study by Rivers et al. was slightly older, had higher rates of preexisting heart and liver disease, and had a higher initial serum lactate level. Although we modified the minimum fluid bolus required to establish the presence of refractory hypotension, the mean volume of the bolus that was administered fell within the range used in the study by Rivers et al. (20 to 30 ml per kilogram). The mean initial $ScvO_2$ reported by Rivers et al. was 49%, which was lower than that in the ProCESS trial. However, early central venous catheterization was considered to be part of usual care in that trial, allowing $ScvO_2$ readings to be made before administration of the initial fluid bolus, the response to which was required to establish refractory hypotension. In contrast, for patients randomly assigned to the protocol-based EGDT group in our study, we measured $ScvO_2$ only after the initial fluid bolus had been administered, making a direct comparison problematic. Nonetheless, the cohort in the study by Rivers et al. may have had, on average, more severe or persistent shock than the patients in our cohort. However, we were unable to show a benefit even when we restricted the analyses to the sickest third of our patients — those with the highest serum lactate levels and those with the highest APACHE II scores.

Both trials used the same EGDT protocol

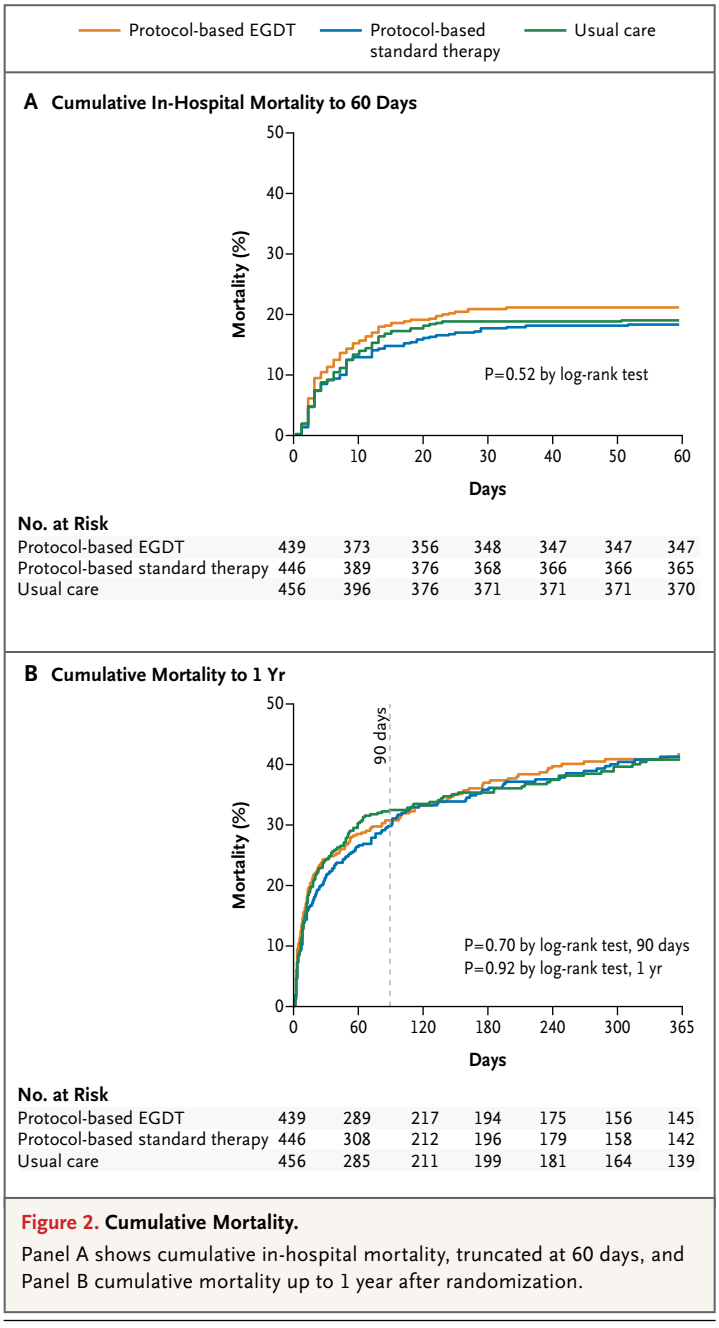

Figure 2. Cumulative Mortality.

Panel A shows cumulative in-hospital mortality, truncated at 60 days, and Panel B cumulative mortality up to 1 year after randomization.

delivered by a trained, dedicated team at each site. Rivers et al. reported nearly perfect adherence but did not provide details regarding the assessment method. Although adherence to the protocol was high in our study, we cannot exclude the possibility that the outcome would have been better if adherence had been perfect. We believe that the rate of adherence in our study parallels the likely performance in any widespread effort targeting the care of patients with septic shock. Furthermore, changes during the past decade in the care of critically ill patients, including the use of lower hemoglobin levels as a threshold for transfusion, the implementation of lung-protection strategies, and the use of tighter control of blood sugar, may have helped lower the overall mortality and may have reduced the marginal benefit of alternative resuscitation strategies.[9,10,16,17]

In 2010, Jones et al. reported the results of a randomized trial involving a patient population similar to ours (Table S8 in the Supplementary Appendix). That trial showed that an EGDT protocol that was based on serial measurement of serum lactate levels was not inferior to an EGDT protocol that used $ScvO_2$ monitoring.[14] In-hospital mortality and the use of intravenous fluids, blood transfusions, and dobutamine were similar to those seen in the ProCESS trial. Other studies showing the benefit of EGDT in adults presenting to the emergency department with septic shock have been observational and open to potential confounding.[18]

There are important limitations to our study. First, although we took many steps to ensure close adherence to the resuscitation protocols, we cannot be sure that elements critical to the success of the protocol in the study by Rivers et al. were not lost during dissemination. Second, we enrolled patients who were recognized to be in septic shock. Our study does not address the extent to which any of these strategies offer advantages in settings where septic shock is not recognized promptly. Third, septic shock occurs in a heterogeneous population, and care before randomization can be variable. Fourth, we had limited power to address whether particular strategies were more effective in specific subgroups. Two ongoing multicenter trials of EGDT, the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial in Australia (ClinicalTrials.gov number, NCT00975793) and the Protocolised Management in Sepsis (ProMISe) trial in the United Kingdom (Current Controlled Trials number, ISRCTN36307479) may offer additional insight.[19,20] Finally, in-hospital mortality among patients requiring life support is strongly influenced by varying practices regarding the withdrawal of care, which could have influenced our findings.

In summary, in our multicenter, randomized trial, in which patients were identified early in the emergency department as having septic shock and received antibiotics and other nonresuscitation aspects of care promptly, we found no significant advantage, with respect to mortality or morbidity, of protocol-based resuscitation over bedside care that was provided according to the treating physician's judgment. We also found no significant benefit of the mandated use of central venous catheterization and central hemodynamic monitoring in all patients.

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Dr. Shapiro reports receiving consulting fees from Thermo Fisher Scientific, fees for serving on a data and safety monitoring board from Cumberland Pharmaceuticals, and grant support from Thermo Fisher Scientific, Rapid Pathogen Screening, Cheetah Medical, and Astute Medical. Dr. Angus reports receiving consulting fees from MedImmune, Ferring Pharmaceuticals, and Roche Diagnostics, lecture fees from Pfizer, fees for serving on a data and safety monitoring board from Eli Lilly, and grant support through his institution from Eisai. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370:1683-93. DOI: 10.1056/NEJMoa1401602

Supplementary Materials for

A Randomized Trial of Protocol-based Care for Early Septic Shock

The ProCESS Investigators

Table of contents

The ProCESS Investigators

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Data Safety and Monitoring Board

Gordon R. Bernard, Vanderbilt University; Donald A. Berry, MD Anderson Cancer Center; Daniel W. Brock, Harvard University; Avital Cnaan, Children's National Medical Center; Norman C. Fost, University of Wisconsin; Roger J. Lewis (chair), Harbor-UCLA Medical Center; Avery B. Nathens, University of Toronto, and; Gordon D. Rubenfeld, University of Toronto.

Supplementary methods

Systemic inflammatory response syndrome criteria

We required patients to have ≥2 of the following 4 criteria: i.) temperature >38° C or <36° C; ii.) heart rate >90 beats per minute; iii.) respiratory rate >20 breaths per minute or PaCO2 <32 mm Hg; and, iv.) white blood cell count >12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms.[1]

Exclusion criteria

We excluded patients who had: a primary diagnosis of acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, major cardiac arrhythmia, active gastrointestinal hemorrhage, seizure, drug overdose, burn or trauma; a requirement for immediate surgery; a known CD4 count <50/mm^2; an advance directive that would restrict protocol implementation; a contraindication to central venous catheterization; a high likelihood of refusing blood transfusion (e.g., Jehovah's Witness); a treating physician who deemed resuscitation to be futile; on-going participation in another interventional study; known pregnancy, or; been transferred from another hospital.

Site team training and conduct

The coordinating center led site training meetings and conducted site visits prior to launch. We used a "train the trainer" approach, where coordinating center investigators trained site principal investigators and coordinators, who then trained any added site study members. We provided training materials via secure website to all sites. The coordinating center provided 24 hour/day telephone access for support and logistical advice, but all clinical judgment and

decision-making rested with the local team. For both protocol arms, the resuscitation teams were in charge of all resuscitation aspects of care, but the treating physician retained control of other care decisions, such as initiation of antibiotics. The resuscitation teams could have other clinical responsibilities but were responsible for ensuring that monitoring evaluations and interventions were executed as per the timed instructions of the protocol. We conducted site visits and held scheduled conference calls to assess conduct and to provide feedback and targeted additional training.

Supplementary Figures

Figure S1. – Protocol for early goal-directed therapy (EGDT).

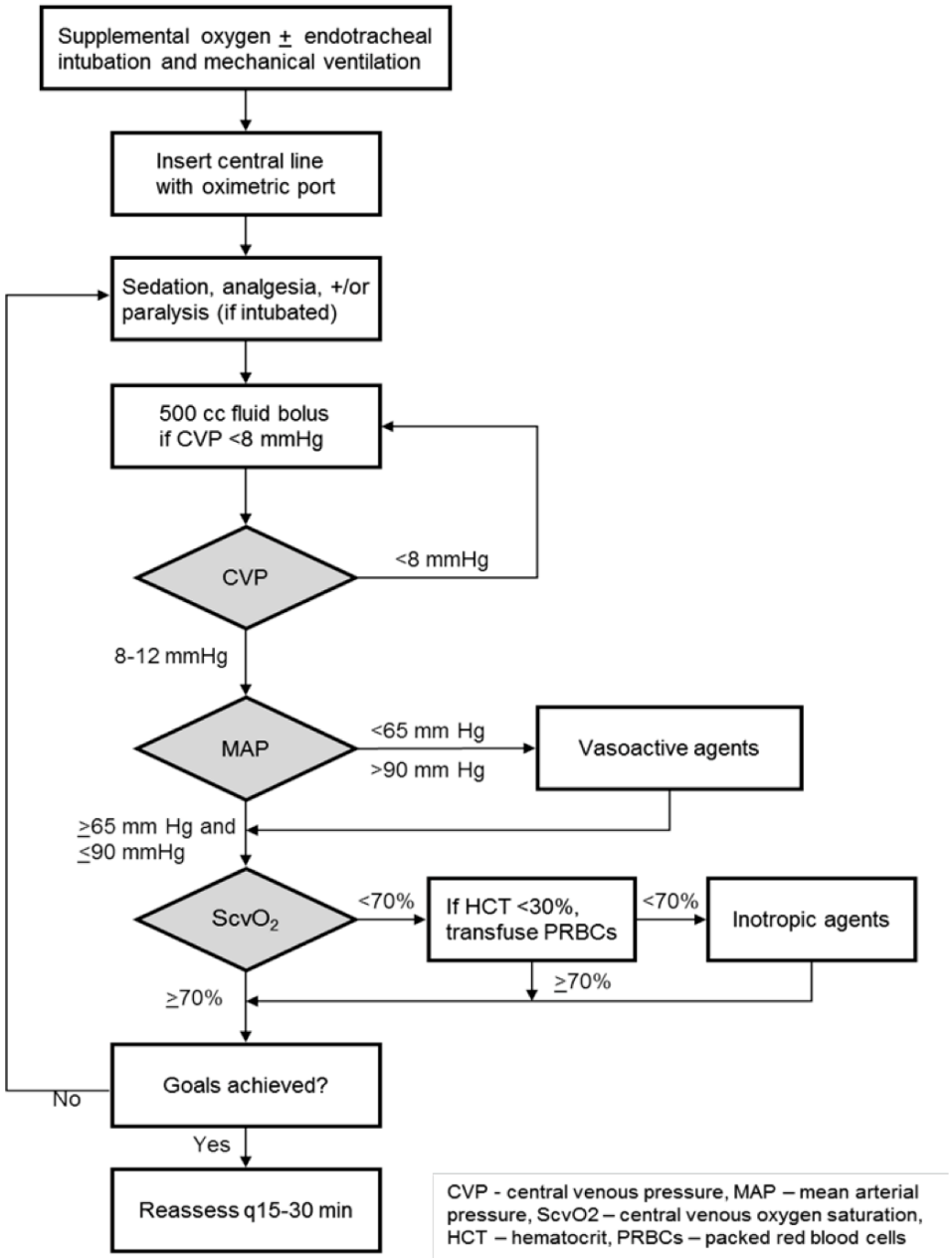
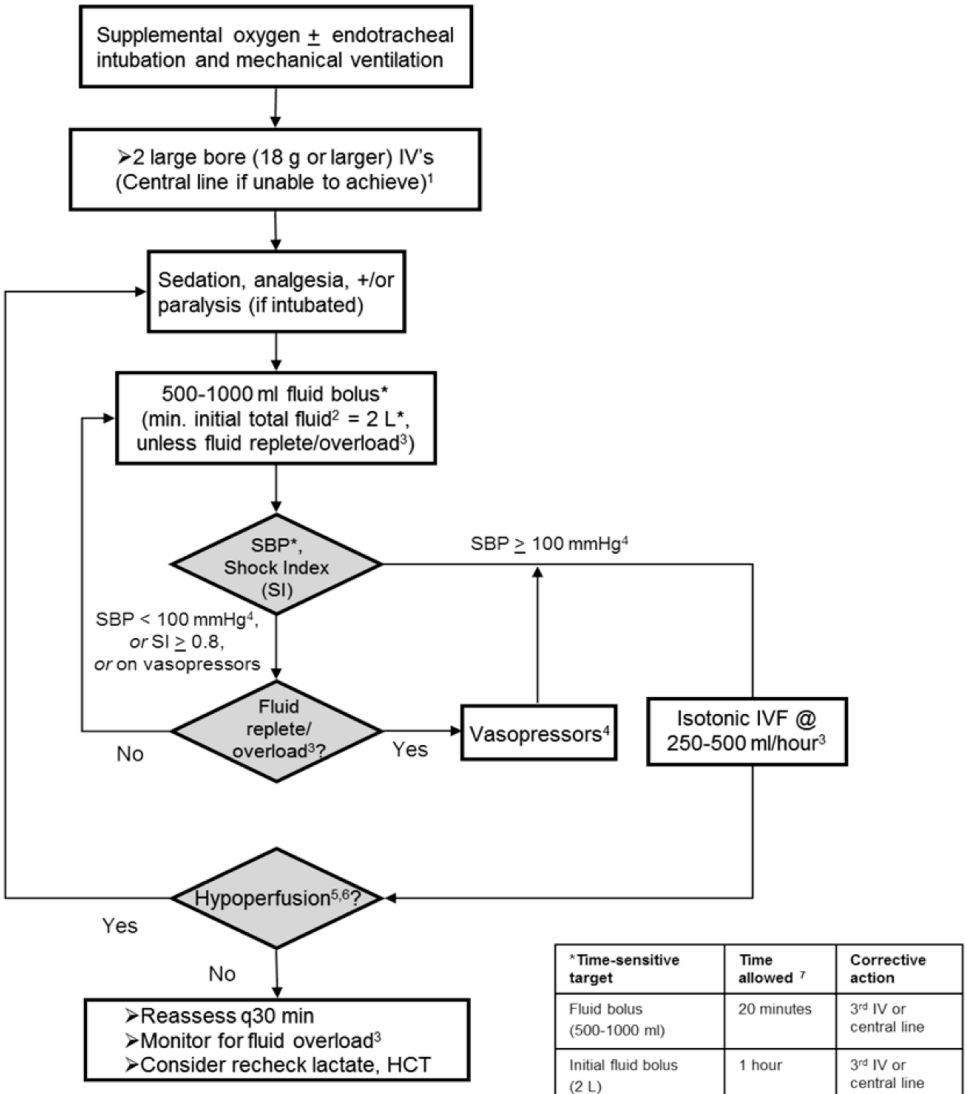


Figure S2. – Protocol for Standard Therapy.

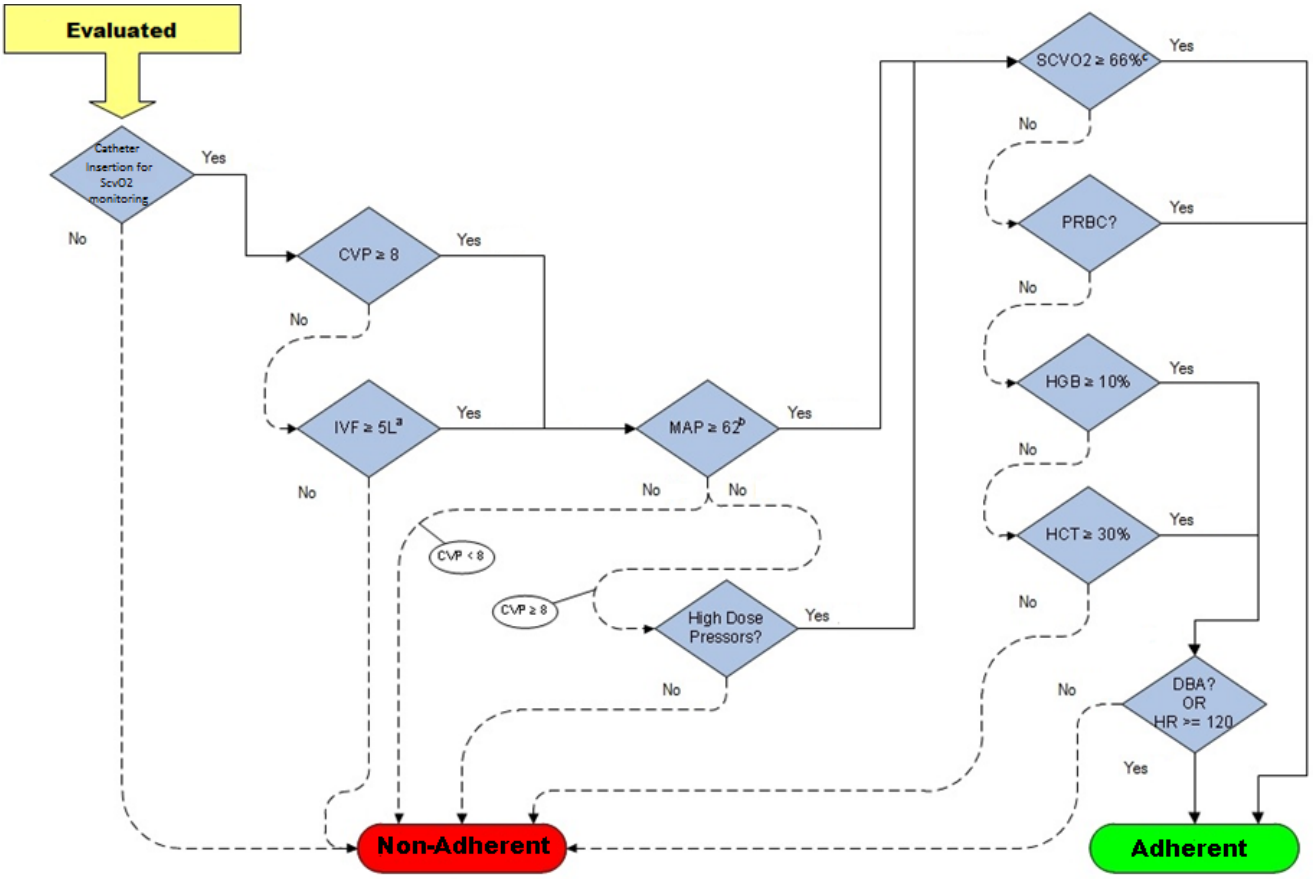


*Time-sensitive target	Time allowed [7]	Corrective action
Fluid bolus (500-1000 ml)	20 minutes	3rd IV or central line
Initial fluid bolus (2 L)	1 hour	3rd IV or central line
SBP ≥ 100 mmHg	1 hour	Vasopressors

IVF – intravenous fluids; HCT – hematocrit; SBP – systolic blood pressure; SI – shock index; CVP – central venous pressure; $ScvO_2$ – central venous oxygen saturation; MAP – mean arterial pressure; PRBC – packed red blood cells.

1. Central line should only be placed and used for venous access. During the 6h intervention, CVP and ScvO2 measurements are discouraged. If time-sensitive fluid targets can be achieved with smaller IVs (e.g., one 18g and one 20g), that is acceptable.
2. Only isotonic fluid should be used (e.g., saline, lactated Ringer's). Colloids are neither encouraged nor excluded.
3. Fluid replete/overload is defined here as a clinical diagnosis by the treating ProCESS Investigator. Signs and symptoms of overload include jugular venous distention, rales, and decreased pulse oximetry readings. Discontinue all IVF (boluses, background rate) once this occurs, until no longer deemed fluid replete/overload.
4. If patient's SBP is within 10% of known baseline SBP, AND patient is not deemed to be clinically hypoperfused, the SBP>100 mmHg target can be deemed fulfilled. Arterial lines allowed if deemed necessary, but not mandatory. Shock index = heart rate / systolic blood pressure.
5. Hypoperfusion is defined here as a clinical diagnosis by the treating ProCESS Investigator. Signs and symptoms include, but are not limited to, MAP < 65 despite SBP > 100, arterial lactate > 4, mottled skin, oliguria, and altered sensorium.
6. Transfuse PRBCs for Hgb < 7.5 g/dL.
7. From time of prompt by protocol (i.e., not from time of physician order, or from when intravenous fluid bag hung).

Figure S3. – EGDT protocol adherence decision nodes at 6 hours.



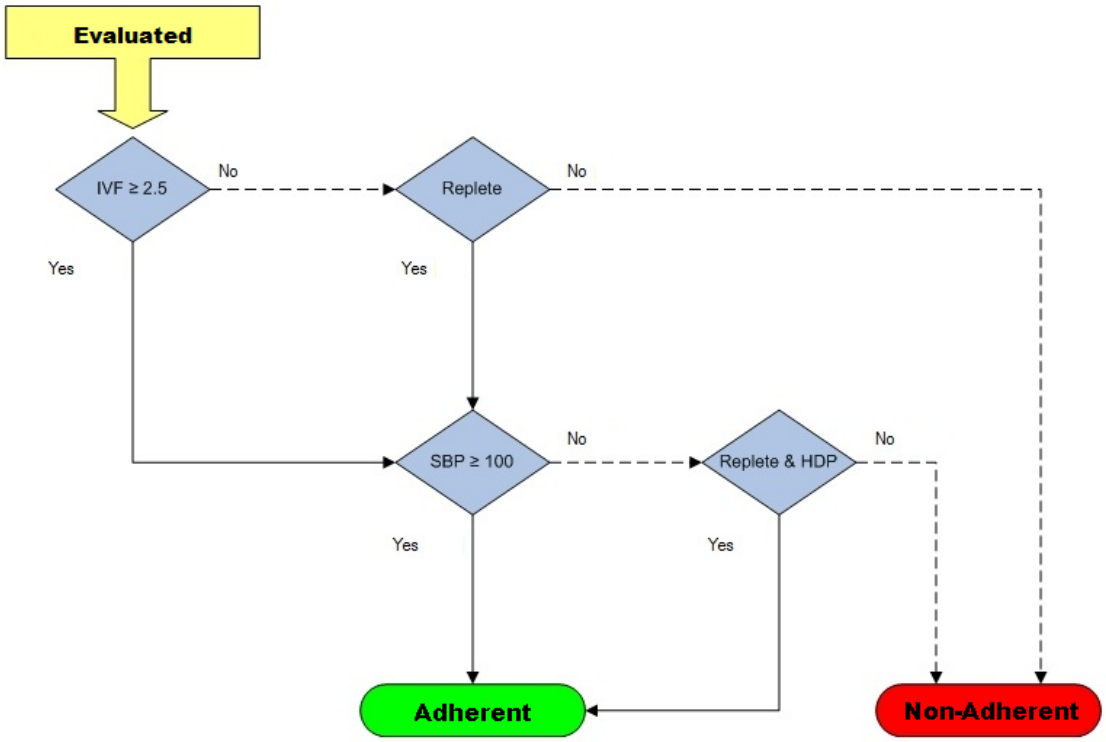
Protocol adherence was assessed by determining adherence to a set of decision nodes prompted by clinical status. Schematics for the decision nodes for EGDT at 6h are presented above. IVF – intravenous fluids; $ScvO_2$ – central venous oxygen saturation; MAP – mean arterial pressure; PRBC – packed red blood cell transfusion; HCT – hematocrit; DBA – dobutamine; HR – heart rate.

[a] IVF $\geq$ 5 or ScVO2 $\geq$ 66%

[b] MAP $\geq$ 62mmHg or (MAP $\geq$ 55mmHg and ScVO2 $\geq$ 66%). We allowed a MAP of 62 to compensate for the variation in the calculation of MAP across different automated blood pressure monitors.

[c] +/- 2% around $ScvO_2$ measurement error deemed as meeting target.

Figure S4. – Standard Therapy protocol adherence decision nodes at 6 hours.



Protocol adherence was assessed by determining adherence to a set of decision nodes prompted by clinical status. Schematics for the decision nodes for PSC at 6h are presented above. IVF – intravenous fluids (volume expressed in liters); SBP – systolic blood pressure (units expressed in mmHg); HDP – high dose pressors.

Figure S5. – Enrollment over time.

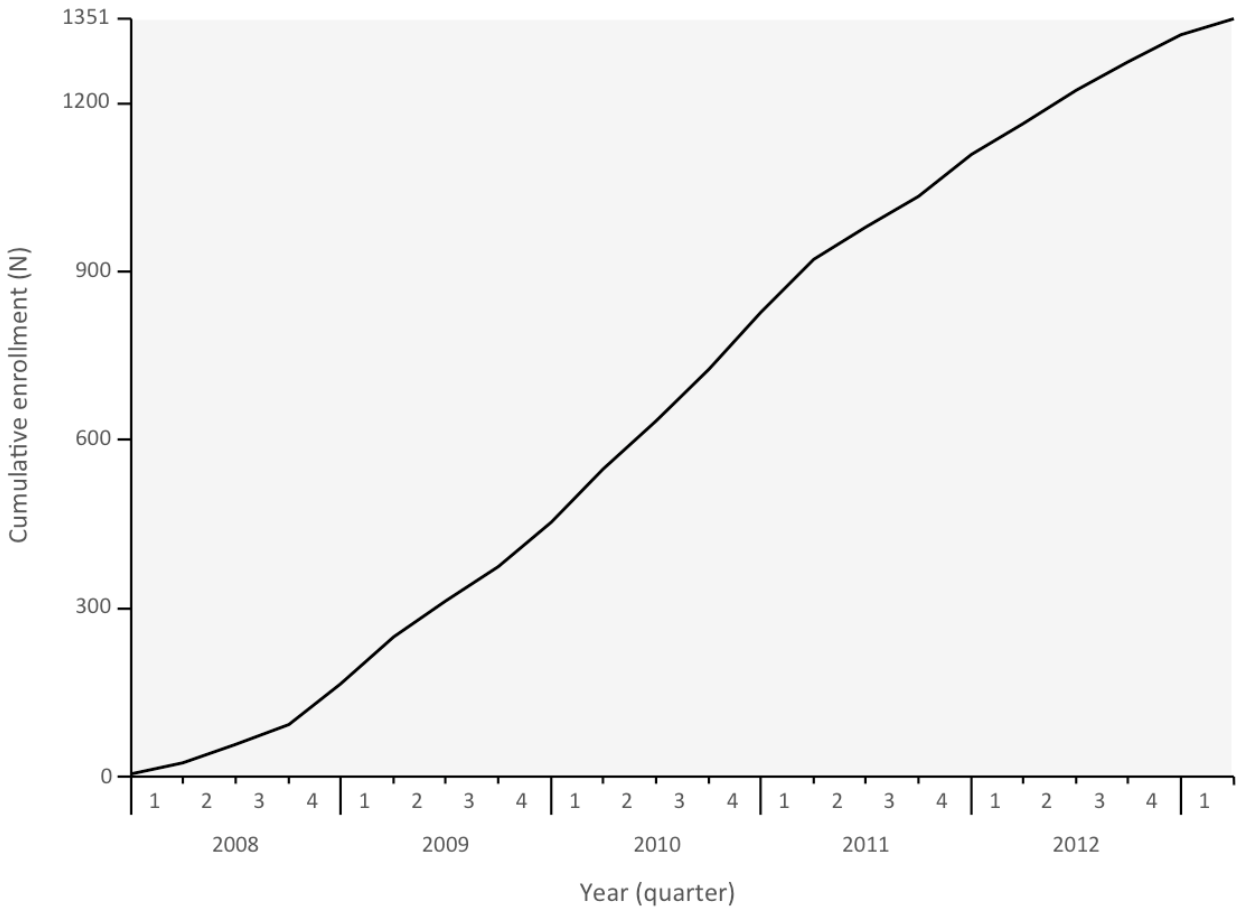
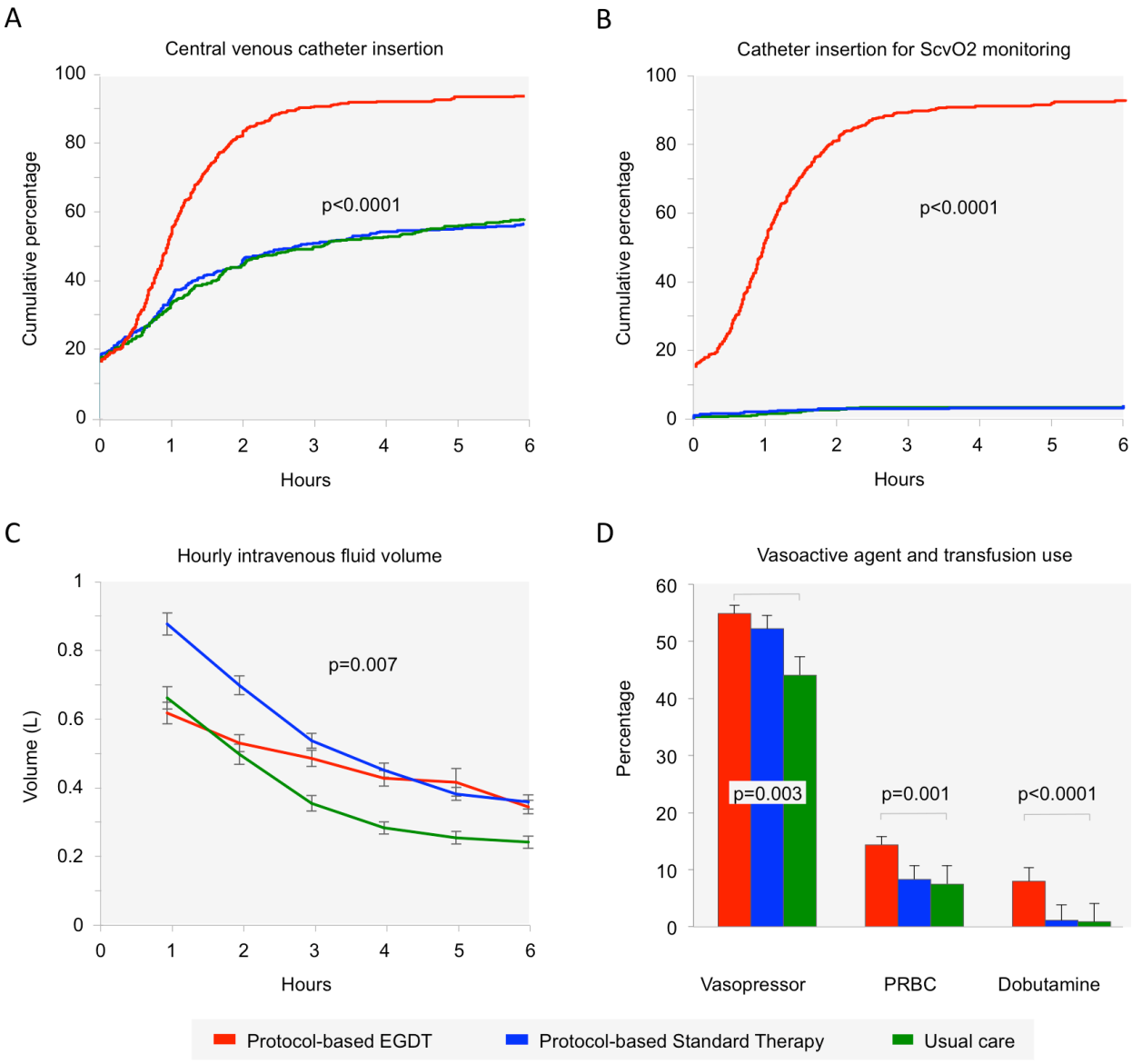


Figure S6. Processes of care during the 6h resuscitation intervention.



Panel A – time (minutes) until a central venous catheter is placed. Panel B – time (minutes) until a central venous catheter for oximetric monitoring is placed. Central venous catheterization defined as use of oximetric catheter or multiple serial $ScvO_2$ measures. Panel C – Intravenous fluid volume by hour (mean $\pm$ SD). Panel D – use of resuscitation interventions. $ScvO_2$ – central venous oxygen saturation; PRBC – packed red blood cell; EGDT – early goal-directed therapy..
P-values represent comparisons across the 3 arms.

Supplementary Tables

Table S1. – Additional sociodemographic characteristics of the patients.[a]

Characteristic	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual care (N=456)
Race[b]			
White	296 (67.4)	308 (69.1)	312 (68.4)
Black or African American	110 (25.1)	111 (24.9)	112 (24.6)
Asian	10 (2.3)	6 (1.3)	10 (2.2)
Other	23 (5.2)	21 (4.7)	22 (4.7)
Ethnicity[c]			
Non-Hispanic	394 (89.7)	396 (88.8)	406 (89.0)
Hispanic	44 (10.0)	50 (11.2)	49 (10.7)
Chronic conditions[d]			
Hypertension	258 (58.8)	260 (58.3)	271 (59.4)
Diabetes mellitus	137 (31.2)	160 (35.9)	161 (35.3)
Chronic respiratory disease	91 (20.7)	96 (21.5)	111 (24.3)
Cancer	72 (16.4)	76 (17.0)	86 (18.9)
Renal impairment	71 (16.2)	59 (13.2)	83 (18.2)
Congestive heart failure	54 (12.3)	51 (11.4)	56 (12.3)
Prior myocardial infarction	43 (9.8)	52 (11.7)	48 (10.5)
Cerebral vascular disease	44 (10.0)	39 (8.7)	43 (9.4)
Peripheral vascular disease	35 (8.0)	34 (7.6)	41 (9.0)
Chronic dementia	26 (5.9)	37 (8.3)	37 (8.1)
Hepatic cirrhosis	33 (7.5)	22 (4.9)	32 (7.0)
Peptic ulcer disease	25 (5.7)	23 (5.2)	24 (5.3)
AIDS and related syndromes	17 (3.9)	9 (2.0)	12 (2.6)

EGDT – early goal-directed therapy.. There were no differences in baseline characteristics across arms.

[a] Values indicated with ± are means ± SD. Values indicated with N (n) are number of patients (%).

[b] Race determined by patient self-report, or by patient's legally authorized representative.

[c] Excludes two subjects with missing ethnicity.

[d] Chronic conditions defined as per Charlson comorbidity index.[3]

Table S2. – Severity of illness, vital signs, and laboratory values from baseline to 72h.

Variable	Baseline	6h	24h	48h	72h
Severity of illness index					
APACHE II					
Protocol-based EGDT	20.8 ± 8.1	-	22.1 ± 8.3	17.2 ± 6.8	16.8 ± 6.6
Protocol-based Standard Therapy	20.6 ± 7.4	-	22 ± 8.8	17.1 ± 6.8	16.9 ± 6.4
Usual care	20.7 ± 7.5	-	21.6 ± 8.3	17.6 ± 6.5	16.7 ± 6.3
p-value	0.90	-	0.61	0.59	0.87
APACHE acute physiology score					
Protocol-based EGDT	15.1 ± 7	-	16.1 ± 7.5	11.6 ± 5.7	11.2 ± 5.7
Protocol-based Standard Therapy	14.8 ± 6.8	-	15.7 ± 7.9	11.3 ± 5.7	11.1 ± 5.3
Usual care	14.6 ± 6.7	-	15.1 ± 7.5	11.4 ± 5.5	10.6 ± 5.2
p-value	0.49	-	0.14	0.74	0.24
Vital signs					
Temperature, °C					
Protocol-based EGDT	37.6 ± 1.4	37 ± 1.1	36.8 ± 1.1	36.7 ± 1.3	36.8 ± 0.8
Protocol-based Standard Therapy	37.6 ± 1.5	36.9 ± 1	37 ± 0.9	36.8 ± 0.8	36.8 ± 0.7
Usual care	37.7 ± 1.4	37 ± 1	36.9 ± 0.9	36.8 ± 0.9	36.7 ± 0.7
p-value	0.68	0.36	0.14	0.30	0.68
Respiratory rate, breaths/min					
Protocol-based EGDT	25.4 ± 7	21.7 ± 6.2	21.8 ± 6.5	21.1 ± 6.1	20.5 ± 5.7
Protocol-based Standard Therapy	25.1 ± 7.1	21.7 ± 6.4	21.3 ± 6.4	20.6 ± 6	20.4 ± 6.1
Usual care	25.3 ± 7.4	21.9 ± 6.6	21.1 ± 6	20.7 ± 5.9	20.4 ± 5.1
p-value	0.81	0.87	0.25	0.53	0.92
Heart rate, beats/min					
Protocol-based EGDT	113.7 ± 22	98.8 ± 19.8	94 ± 18.9	90.8 ± 17.4	89 ± 19.5
Protocol-based Standard Therapy	114.6 ± 22	97.6 ± 18.8	95.1 ± 19.9	91.3 ± 19.5	89.8 ± 17.1
Usual care	114.5 ± 23.1	96.9 ± 19	94.1 ± 18.7	90.2 ± 18.1	87.5 ± 18
p-value	0.82	0.34	0.64	0.70	0.19
Mean blood pressure, mmHg					
Protocol-based EGDT	64.9 ± 16	76.9 ± 12.8	78.9 ± 14.2	84.1 ± 13.9	86.3 ± 14.5
Protocol-based Standard Therapy	66.1 ± 16.6	78.8 ± 15.4	80.2 ± 14.5	84.8 ± 16	86.4 ± 15.2
Usual care	64.7 ± 15.6	76.1 ± 14.4	78.4 ± 14.1	84.2 ± 15	86 ± 16.2
p-value	0.36	0.01[a]	0.15	0.78	0.90
Arterial blood gases					
Arterial pH					
Protocol-based EGDT	7.33 ± 0.12	7.31 ± 0.1	7.34 ± 0.1	7.36 ± 0.1	7.38 ± 0.1
Protocol-based Standard Therapy	7.31 ± 0.13	7.31 ± 0.1	7.34 ± 0.1	7.36 ± 0.1	7.37 ± 0.1
Usual care	7.34 ± 0.13	7.34 ± 0.1	7.36 ± 0.1	7.38 ± 0.1	7.38 ± 0.1
p-value	0.06	0.02	0.02	0.36	0.50
Arterial pCO_2, mmHg					
Protocol-based EGDT	35.7 ± 12.4	35.2 ± 11.3	34.1 ± 9.5	35 ± 9.3	36.5 ± 9.1
Protocol-based Standard Therapy	38.9 ± 16.4	37.9 ± 14.2	35.3 ± 12	36.3 ± 11.7	36.3 ± 9.9
Usual care	36.9 ± 13.8	37 ± 12.5	35.1 ± 10.1	34.5 ± 9.7	35.6 ± 10.4
p-value	0.06	0.12	0.40	0.33	0.80
Arterial pO_2, mmHg					
Protocol-based EGDT	121.8 ± 88.2	120.7 ± 74.6	105.7 ± 53	108.2 ± 51.8	97.3 ± 38.5
Protocol-based Standard Therapy	115.6 ± 92.7	121.6 ± 77.6	110.3 ± 52.8	105.8 ± 43.8	102.6 ± 36.5
Usual care	121.7 ± 103.7	123.1 ± 87.9	112.8 ± 66.3	105.1 ± 39.2	99.6 ± 40.8
p-value	0.06	0.12	0.40	0.33	0.80
Blood chemistry					
Sodium, mmol/L					
Protocol-based EGDT	136.1 ± 6	137.5 ± 5.7	138.3 ± 5.2	138.4 ± 4.8	139 ± 4.9
Protocol-based Standard Therapy	136 ± 6.3	136.9 ± 6.4	138.1 ± 5	138.5 ± 5	141.8 ± 55.3
Usual care	136.5 ± 6.6	136.8 ± 6.9	138.3 ± 5.6	138.8 ± 5.3	139.1 ± 5.5
p-value	0.42	0.50	0.82	0.58	0.47
Potassium, mmol/L					
Protocol-based EGDT	4.3 ± 1	4 ± 0.8	4.1 ± 0.7	3.9 ± 0.6	3.8 ± 0.5
Protocol-based Standard Therapy	4.3 ± 1	4.1 ± 0.9	4 ± 0.7	3.8 ± 0.6	3.8 ± 0.6
Usual care	4.3 ± 0.9	4 ± 0.9	4 ± 0.7	3.9 ± 0.6	3.7 ± 0.6
p-value	0.65	0.56	0.33	0.96	0.57

Table S2 (continued).

Variable	Baseline	6h	24h	48h	72h
Blood chemistry (continued)					
Chloride, mmol/L					
Protocol-based EGDT	100.6 ± 8	107.7 ± 7.3	108.5 ± 6.9	108 ± 6.5	107.5 ± 6.8
Protocol-based Standard Therapy	100.3 ± 7.3	107 ± 7.1	108.1 ± 6.8	108.3 ± 6.2	107.6 ± 6.3
Usual care	100.4 ± 7.7	105.8 ± 8	107.6 ± 7	107.6 ± 6.9	107 ± 7
p-value	0.82	0.05	0.14	0.38	0.48
Blood urea nitrogen, mg/dL					
Protocol-based EGDT	35.1 ± 27.4	34.1 ± 27.6	28.8 ± 21.9	25.4 ± 20	23.4 ± 20.6
Protocol-based Standard Therapy	32.5 ± 22	35.5 ± 42.9	27.3 ± 18.4	24.1 ± 18.4	22.8 ± 18.2
Usual care	35.6 ± 24.4	34.3 ± 23.4	30.8 ± 21.8	27 ± 19.7	25.3 ± 21.1
p-value	0.15	0.90	0.05	0.13	0.27
Creatinine, mg/dL					
Protocol-based EGDT	2.5 ± 2.4	2 ± 1.9	1.8 ± 1.7	1.6 ± 1.7	1.5 ± 1.5
Protocol-based Standard Therapy	2.2 ± 1.9	2.2 ± 1.8	1.8 ± 1.7	1.8 ± 4.9	1.5 ± 1.5
Usual care	2.3 ± 1.9	2 ± 1.6	1.9 ± 1.7	1.6 ± 1.5	1.5 ± 1.5
p-value	0.30	0.43	0.86	0.48	0.88
Glucose, mg/dL					
Protocol-based EGDT	161.2 ± 122.3	149.4 ± 92.1	138.6 ± 63.7	126.2 ± 52.1	123.7 ± 51.3
Protocol-based Standard Therapy	177.4 ± 154.3	162 ± 109.8	138.5 ± 77	127.3 ± 48.9	124.6 ± 50.6
Usual care	164.2 ± 119.4	162.3 ± 98.7	133 ± 63.2	130.1 ± 51.7	129.3 ± 57.8
p-value	0.16	0.34	0.41	0.56	0.36
Hematology					
Hemoglobin, g/dL					
Protocol-based EGDT	11.8 ± 2.6	10 ± 2.1	10.2 ± 1.8	9.8 ± 1.8	9.8 ± 1.7
Protocol-based Standard Therapy	11.8 ± 2.7	9.9 ± 2.3	10 ± 1.9	9.7 ± 1.7	9.8 ± 2.2
Usual care	11.6 ± 2.6	10 ± 2.1	10 ± 1.9	9.8 ± 1.7	9.9 ± 1.8
p-value	0.51	0.74	0.32	0.90	0.84
White blood cells, count/mm^3					
Protocol-based EGDT	15.3 ± 11.6	15 ± 10.3	15.1 ± 10.9	13.2 ± 8.7	12.1 ± 7.8
Protocol-based Standard Therapy	15.6 ± 10.8	15.8 ± 11.1	15.3 ± 11.7	13.1 ± 9.9	11.9 ± 8.4
Usual care	16.8 ± 12	17.8 ± 13.7	16.3 ± 12	14 ± 10.5	12.8 ± 9.2
p-value	0.13	0.11	0.25	0.40	0.34
Platelets, count/mm^3					
Protocol-based EGDT	219.1 ± 126.4	199.7 ± 132.8	175.5 ± 111	159.2 ± 106.4	162.4 ± 112.7
Protocol-based Standard Therapy	231.8 ± 141.7	203.6 ± 134.4	181.9 ± 107.1	162.5 ± 97	163.4 ± 104
Usual care	235.8 ± 143.5	210.4 ± 142.9	187.3 ± 109.5	173 ± 101.9	172.7 ± 101.8
p-value	0.18	0.79	0.30	0.15	0.38
International normalized ratio					
Protocol-based EGDT	1.8 ± 1.9	2.2 ± 2.4	1.9 ± 1	2 ± 1.8	1.7 ± 0.9
Protocol-based Standard Therapy	1.6 ± 0.9	1.7 ± 0.8	1.8 ± 1	1.7 ± 0.9	1.6 ± 0.7
Usual care	1.7 ± 1.2	1.6 ± 0.7	1.7 ± 0.8	1.9 ± 1.2	1.7 ± 1.2
p-value	0.09	0.01	0.18	0.05	0.63

EGDT – early goal-directed therapy; APACHE – acute physiology, age and chronic health evaluation. Data expressed as means ± SD. APACHE II scores calculated using worst values in prior 24h.[4] Mean values for laboratory tests and vital signs expressed where denominator is all subjects with recorded value, using the last value recorded in the time period. P-values are for overall tests across the three arms.

[a] The proportion of patients with a MAP >65mmHg also differed at 6h (83.1% [n=365], 84.1% [n=375], and 77.2% [n=352] for EGDT, PSC, and usual care arms, p=0.02).

Table S3. – Protocol adherence failures.

Protocol adherence failures by hour 6	No. (%)
EGDT protocol	**404 evaluable[a] patients**
Not fully adherent	48 (11.9%)
No $ScvO_2$ monitoring	7 (1.7%)
Failing to administer intravenous fluids despite indications of hypovolemia[b]	12 (3.1%)
Failing to administer high dose pressors[c] for hypotension despite evidence of adequate intravenous fluids	4 (1.0%)
Failing to administer blood transfusion despite low $ScvO_2$ after other measures performed	12 (3.1%)
Failing to administer dobutamine when indicated	13 (3.2%)
Standard therapy protocol	**435 evaluable[a] patients**
Not fully adherent	19 (4.4%)
Failing to administer intravenous fluids despite indications of hypovolemia	1 (0.2%)
Failing to administer high dose pressors[c] for hypotension despite evidence of adequate intravenous fluids	18 (4.1%)

EGDT – early goal-directed therapy.

[a] Reasons for not being evaluated include death, discharge or request for withdrawal of data before 6h.

[b] Inadequate fluids defined as: i.) <5L intravenous fluids despite low central venous pressure with either low ScvO2 or hypotension, or; ii.) ≥5L intravenous fluids but persistent hypotension.

[c] Dopamine >15 mcg/kg/min, epinephrine >0.1 mcg/kg/min, norepinephrine >0.1 mcg/kg/min, neosynephrine >0.4 mcg/kg/min, vasopressin ≥0.4 mcg/kg/min or ≥2 vasopressors.

Table S4. – Resuscitation and processes of care from baseline to 72h.[a]

Intervention	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual care (N=456)	p-value[g]
Pre-randomization				
Intravenous fluids[b] – mL	2254 ± 1472	2226 ± 1363	2083 ± 1405	0.15
Fluids per body weight (mL/kg)	30.5 ± 22.3	29.2 ± 19.1	28 ± 21	
Vasopressor use[c]	84 (19.1)	75 (16.8)	69 (15.1)	0.28
Dobutamine use	0 (0)	0 (0)	0 (0)	
Blood transfusion	5 (1.1)	7 (1.6)	9 (2.0)	0.63
Mechanical ventilation	60 (13.7)	65 (14.6)	63 (13.8)	0.93
Intravenous antibiotics	332 (75.6)	343 (76.9)	347 (76.1)	0.91
Corticosteroids	41 (9.3)	42 (9.4)	38 (8.3)	0.82
Activated protein C	0 (0)	0 (0)	0 (0)	
Randomization to hour 6[d]				
Resuscitation elements				
Central venous catheterization	411 (93.6)	252 (56.5)	264 (57.9)	<0.0001
Central venous oximeter catheterization[e]	409 (93.2)	18 (4.0)	16 (3.5)	<0.0001
Intravenous fluids – mL	2805 ± 1957	3285 ± 1743	2279 ± 1881	<0.0001
Vasopressor use	241 (54.9)	233 (52.2)	201 (44.1)	0.003
Dobutamine use	35 (8)	5 (1.1)	4 (0.9)	<0.0001
Blood transfusion	63 (14.4)	37 (8.3)	34 (7.5)	0.001
Ancillary care				
Mechanical ventilation	116 (26.4)	110 (24.7)	99 (21.7)	0.25
Tidal volume, mL/kg predicted body weight[f]	8.5 ± 2.4	8.1 ± 1.6	8.0 ± 1.8	0.11
Tidal volume, mL/kg body weight	6.7 ± 2.1	6.5 ± 1.9	6.8 ± 2.1	0.32
Intravenous antibiotics	428 (97.5)	433 (97.1)	442 (96.9)	0.90
Corticosteroids	54 (12.3)	48 (10.8)	37 (8.1)	0.16
Activated protein C	1 (0.2)	1 (0.2)	0 (0)	0.55
Processes of care from 6-72 h				
Intravenous fluids – mL	4458 ± 3878	4918 ± 4308	4354 ± 3882	0.08
Vasopressor use	209 (47.6)	208 (46.6)	197 (43.2)	0.38
Dobutamine use	19 (4.3)	9 (2.0)	10 (2.2)	0.08
Blood transfusion	87 (19.8)	93 (20.9)	82 (18.0)	0.54
Mechanical ventilation	148 (33.7)	140 (31.4)	127 (27.9)	0.16
Tidal volume, mL/kg predicted body weight	8.5 ± 2.5	8.6 ± 2.6	8.1 ± 1.8	0.05
Tidal volume, mL/kg body weight	6.7 ± 2.3	6.6 ± 2.4	6.6 ± 2.2	0.81
Processes of care from 0-72 h				
Intravenous fluids – mL	7253 ± 4605	8193 ± 4989	6633 ± 4560	<0.0001
Vasopressor use	265 (60.4)	273 (61.2)	245 (53.7)	0.05
Dobutamine use	41 (9.3)	11 (2.5)	13 (2.9)	<0.0001
Blood transfusion	120 (27.3)	107 (24.0)	102 (22.4)	0.22
Mechanical ventilation	159 (36.2)	152 (34.1)	135 (29.6)	0.10
Tidal volume, mL/kg predicted body weight	8.5 ± 2.5	8.4 ± 2.4	8.1 ± 1.8	0.03
Tidal volume, mL/kg body weight	6.7 ± 2.2	6.6 ± 2.2	6.7 ± 2.2	0.55

EGDT – early goal-directed therapy.

[a] Values indicated with ± are means ± SD. Values indicated with N (n) are number of subjects (%). Denominators are all individuals for whom data are available.

[b] Includes all intravenous crystalloid, colloid and blood product administration.

[c] Vasopressor use defined as dopamine infusion at >5 mcg/kg/min or any infusion of epinephrine, norepinephrine, vasopressin or phenylephrine.

[d] Mechanical ventilation, central venous catheterization, and ancillary care (antibiotics, corticosteroids, and activated protein C) are counted from emergency department arrival to 6h. Resuscitation therapies (intravenous fluids, vasopressor and dobutamine infusions, and blood product administration) are counted from randomization to 6h.

[e] Central venous catheterization defined as use of oximetric catheter or multiple serial $ScvO_2$ measures.

[f] Predicted body weight (PBW) as per http://www.ardsnet.org/system/files/pbwtables_2005-02-02_0.pdf.

[g] P-values are for overall tests across the three arms.

Table S5. – Serious adverse events.

Potential adverse event[a]	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual care (N=456)	p-value[b]
Total events	**23**	**22**	**37**	**0.32**
Allergy/immunology	0	0	0	
Auditory/ear	0	0	0	
Blood/bone marrow	0	0	0	
Cardiac dysfunction	7	5	7	
Coagulation	0	0	0	
Constitutional symptoms	0	0	0	
Dermatology/skin	0	0	0	
Endocrine	0	0	0	
Gastrointestinal	0	0	2	
Growth and development	0	0	0	
Hemorrhage/bleeding	0	0	1	
Hepatobiliary/pancreas	0	2	3	
Infection	1	3	2	
Lymphatics	0	0	0	
Metabolic/laboratory	2	3	3	
Musculoskeletal/soft tissue	0	0	0	
Neurology	2	2	1	
Ocular/visual	0	0	0	
Pain	0	0	1	
Pulmonary/upper respiratory	5	5	10	
Renal/genitourinary	5	1	5	
Secondary malignancy	0	0	0	
Sexual/reproductive function	0	0	0	
Surgery/intra operative injury	0	0	0	
Vascular	1	1	2	

EGDT – early goal-directed therapy; PSC – protocolized standard care.

[a] All reported adverse events were reviewed by the site Principal Investigator and none was deemed related to study intervention.

[b] P-value is for an overall test across the 3 arms.

Table S6. – Pre-hoc subgroup-by-treatment interaction analyses.

Subgroup	p-value for subgroup by treatment allocation interaction[a]		
	Hospital mortality at 60d	Mortality at 90d	One year survival
Age	0.09	0.62	0.69
Race	0.44	0.45	0.93
Sex	0.20	0.44	0.51
Source of infection	0.99	0.66	0.28
Type of shock (hyperlactatemia vs. hypotension)	0.38	0.22	0.10

[a] Interactions tested by Breslow-Day test, assuming significance at $p<0.05$, across all three arms.

Table S7. – Post-hoc subgroup analyses.

Criterion for subgrouping by thirds	All	Comparison across subgroup, p-value	Protocol-based EGDT	Protocol-based Standard Therapy	Usual care	Subgroup by treatment Interaction, p-value	Comparison across arms, p-value
APACHE II							
< 17	36/421 (8.6)	<0.0001	14/136 (10.3)	11/145 (7.6)	11/140 (7.9)	0.79	0.71
17-23	76/490 (15.5)		24/164 (14.6)	26/153 (17.0)	26/173 (15.0)		0.84
> 23	147/430 (34.2)		54/139 (38.8)	44/148 (29.7)	49/143 (34.3)		0.27
Serum lactate[a], mmol/L							
< 3.4	46/430 (10.7)	<0.0001	18/145 (12.4)	19/152 (12.5)	9/133 (6.8)	0.30	0.20
3.4-5.3	78/445 (17.5)		20/145 (13.8)	22/136 (16.2)	36/164 (22.0)		0.16
> 5.3	129/429 (30.0)		52/136 (38.2)	38/145 (26.2)	39/148 (26.4)		0.05
Time to randomization[b], min							
< 47	63/440 (14.3)	0.01	21/140 (15.0)	24/156 (15.4)	18/144 (12.5)	0.41	0.75
47-87	103/454 (22.7)		37/152 (24.3)	33/145 (22.8)	33/157 (21.0)		0.78
> 87	92/440 (20.9)		34/146 (23.3)	24/143 (16.8)	34/151 (22.5)		0.33

Data presented as no. of hospital deaths by day 60/no. of patients (%). Tercile by treatment interaction and treatment effects tested through logistic regression with interaction terms. All analyses tested across the three treatment arms. EGDT – early goal directed therapy; APACHE II – acute physiology, age and chronic health evaluation II score.[4]

[a] Available for 97.2% (1304/1341) of patients.

[b] Available for 99.5% (1334/1341) of patients.

Table S8. – Comparison of study populations across EGDT trials.

Characteristic	Rivers, et al[2]	Jones, et al[5]	ProCESS
No. enrolled	263	300	1341
Age – year	66	61	61[a]
Male sex (%)	51	54	56
Race (%)			
White	-	55	68
Black or African American	-	34	25
Nursing home resident prior to admission (%)	-	19	16[b]
Chronic conditions (%)[c]			
Hypertension	67	-	59
Diabetes mellitus	31	34	34
Congestive heart failure	33	-	12
Hepatic cirrhosis/liver disease	23	-	11
Source of sepsis (%)			
Pneumonia/lower respiratory tract	39	51	33
Urinary tract infection	27	27	21
Intra-abdominal infection	7	20	13
Blood culture positive (%)	35	38	30
APACHE II score	21	-	21
Entry criteria (%)			
Refractory hypotension	-	82	54
Hyperlactatemia	-	39	59
Vital signs			
Temperature (degrees Celsius)	36.3	-	37.6
Respiratory rate	31	-	25.3
Heart rate	116	-	114.3
Systolic blood pressure (mmHg)	108	92	100.7
Mean arterial pressure (mmHg)	75	-	65.2
Serum lactate – mmol/L	7	4	5
Arterial blood gas			
pH	7.32	-	7.33
pCO2 (mm Hg)	31	-	37.1
Blood chemistry			
Blood urea nitrogen (mg/dl)	46.3	-	34.4
Creatinine (mg/dl)	2.6	-	2.3
Hematology			
Hemoglobin (g/dl)	11.5[d]	-	11.7
White blood cell count (x 10^9 cells/ L)	13.9	-	15.9
Platelet count (x 10^9 cells/ L)	213	-	229
International normalized ratio	(prothrombin time 16.2)	-	1.7

EGDT – early goal-directed therapy; APACHE – acute physiology, age, and chronic health evaluation.
Values indicate means unless otherwise stated.
[a] Excludes one subject with missing age
[b] Excludes four subjects with missing domicile prior to admission. Nursing home population includes personal care homes, skilled or unskilled assisted living, or extended care facilities
[c] Chronic conditions defined variably across the trials
[d] Hematocrit is presented in the Rivers et al NEJM 2001 paper. Presented table number is hematocrit divided by 3.

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