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

The ProCESS Investigators*
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patients 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. The protocol prompted placement of a central venous catheter to monitor pressure and ScvO2 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, 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-
Protocol-based Care for Early Septic Shock

12,707 Patients were screened

- 8864 Were ineligible
  - 6841 Did not meet inclusion criteria
  - 2639 Did not have hypoperfusion
  - 2294 Did not have refractory hypotension
  - 120 Could not be assessed for refractory hypotension
  - 993 Did not have suspected infection
  - 621 Did not have ≥2 SIRS criteria
  - 154 Had other reason
  - 2023 Met exclusion criteria
    - 660 Had “Do Not Resuscitate” order
    - 264 Had treating physician who deemed aggressive care unsuitable
    - 194 Required immediate surgery
    - 165 Had active gastrointestinal hemorrhage
    - 162 Had contraindication to central venous catheter
    - 95 Had acute coronary syndrome
    - 71 Had major cardiac arrhythmia
    - 71 Had seizure
    - 69 Had acute pulmonary edema
    - 46 Were participating in another interventional study
    - 42 Had drug overdose
    - 38 Had CD4 count <50/mm³
    - 36 Were transferred from another in-hospital setting
    - 31 Had acute cerebrovascular event
    - 21 Had absolute neutrophil count <500/mm³
    - 18 Had burn or trauma
    - 12 Had contraindication to blood transfusion
    - 8 Had status asthmaticus
    - 20 Had other reason
  - 2492 Were eligible but excluded
    - 1191 Had study logistic issues
    - 631 Had decreased mental capacity and no LAR
    - 569 Declined to participate
    - 101 Had other reason

- 1351 Underwent randomization
  - 445 Were assigned to protocol-based EGDT
    - 439 Were eligible for analysis
      - 6 Requested removal of all data
    - 439 Were included in primary outcome analysis
  - 448 Were assigned to protocol-based standard therapy
    - 446 Were eligible for analysis
      - 2 Requested removal of all data
    - 446 Were included in primary outcome analysis
  - 458 Were assigned to usual care
    - 456 Were eligible for analysis
      - 2 Requested removal of all data
    - 456 Were included in primary outcome analysis

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 ScvO₂ 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>
<thead>
<tr>
<th>Table 1. Characteristics of the Patients at Baseline.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Age — yr†</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
</tr>
<tr>
<td>Residence before admission — no. (%)‡</td>
</tr>
<tr>
<td>Nursing home</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Charlson comorbidity score§</td>
</tr>
<tr>
<td>Source of sepsis — no. (%)</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Intraabdominal infection</td>
</tr>
<tr>
<td>Infection of unknown source</td>
</tr>
<tr>
<td>Skin or soft-tissue infection</td>
</tr>
<tr>
<td>Catheter-related infection</td>
</tr>
<tr>
<td>Central nervous system infection</td>
</tr>
<tr>
<td>Endocarditis</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Determined after review not to have infection</td>
</tr>
<tr>
<td>Positive blood culture — no. (%)</td>
</tr>
<tr>
<td>APACHE II score¶</td>
</tr>
<tr>
<td>Entry criterion — no. (%)</td>
</tr>
<tr>
<td>Refractory hypotension</td>
</tr>
<tr>
<td>Hyperlactatemia‖</td>
</tr>
<tr>
<td>Physiological variables</td>
</tr>
<tr>
<td>Systolic blood pressure — mm Hg</td>
</tr>
<tr>
<td>Serum lactate — mmol/liter**</td>
</tr>
<tr>
<td>Time to randomization — min</td>
</tr>
<tr>
<td>From arrival in the emergency department††</td>
</tr>
<tr>
<td>From meeting entry criteria</td>
</tr>
</tbody>
</table>

* 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 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 \( \text{ScvO}_2 \) 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, \( P = 0.04 \),
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 Appendix).

### Table 2. Outcomes.

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

* 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.
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.; 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 ScvO₂ 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 ScvO₂ 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 ScvO₂ only after the initial fluid bolus had been administered, making a direct comparison problematic.

Nevertheless, 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...
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.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 ScvO2 monitoring.18 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.

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

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