ORIGINAL ARTICLE

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators*

ABSTRACT

BACKGROUND

After a single-center trial and observational studies suggesting that early, goal-directed therapy (EGDT) reduced mortality from septic shock, three multicenter trials (ProCESS, ARISE, and ProMISe) showed no benefit. This meta-analysis of individual patient data from the three recent trials was designed prospectively to improve statistical power and explore heterogeneity of treatment effect of EGDT.

METHODS

We harmonized entry criteria, intervention protocols, outcomes, resource-use measures, and data collection across the trials and specified all analyses before unblinding. After completion of the trials, we pooled data, excluding the protocol-based standard-therapy group from the ProCESS trial, and resolved residual differences. The primary outcome was 90-day mortality. Secondary outcomes included 1-year survival, organ support, and hospitalization costs. We tested for treatment-by-subgroup interactions for 16 patient characteristics and 6 care-delivery characteristics.

RESULTS

We studied 3723 patients at 138 hospitals in seven countries. Mortality at 90 days was similar for EGDT (462 of 1852 patients [24.9%]) and usual care (475 of 1871 patients [25.4%]); the adjusted odds ratio was 0.97 (95% confidence interval, 0.82 to 1.14; P=0.68). EGDT was associated with greater mean (±SD) use of intensive care (5.3±7.1 vs. 4.9±7.0 days, P=0.04) and cardiovascular support (1.9±3.7 vs. 1.6±2.9 days, P=0.01) than was usual care; other outcomes did not differ significantly, although average costs were higher with EGDT. Subgroup analyses showed no benefit from EGDT for patients with worse shock (higher serum lactate level, combined hypotension and hyperlactatemia, or higher predicted risk of death) or for hospitals with a lower propensity to use vasopressors or fluids during usual resuscitation.

CONCLUSIONS

In this meta-analysis of individual patient data, EGDT did not result in better outcomes than usual care and was associated with higher hospitalization costs across a broad range of patient and hospital characteristics. (Funded by the National Institute of General Medical Sciences and others; PRISM ClinicalTrials.gov number, NCT02030158.)

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*The Protocolized Resuscitation in Sepsis Meta-Analysis (PRISM) study is a collaboration of the Protocolized Care for Early Septic Shock (ProCESS) Investigators, based in the United States; the Australasian Resuscitation in Sepsis Evaluation (ARISE) Investigators, based in Australia and New Zealand; the Protocolised Management in Sepsis (ProMISe) Investigators, based in the United Kingdom; and the International Forum for Acute Care Trialists. A complete list of the investigator groups is provided in the Supplementary Appendix, available at NEJM.org.

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In 2001, Rivers and colleagues reported on a 263-patient, single-center, randomized, controlled trial of early, goal-directed therapy (EGDT) versus usual care in patients presenting with septic shock to an urban emergency department in the United States.[1] EGDT is a 6-hour resuscitation protocol for the administration of intravenous fluids, vasopressors, inotropes, and red-cell transfusion to achieve prespecified targets for arterial blood pressure, central venous pressure, central venous oxygen saturation, and hemoglobin level. EGDT reduced hospital mortality from 46.5% to 30.5%,[1] prompting many institutions worldwide to adopt EGDT.[2] Three subsequent, government-funded, multicenter, randomized, controlled trials from the United States (Protocolized Care for Early Septic Shock [ProCESS]),[3] Australasia (Australasian Resuscitation in Sepsis Evaluation [ARISE]),[4] and the United Kingdom (Protocolised Management in Sepsis [ProMISe])[5] failed to show lower mortality with EGDT than with usual care.

A meta-analysis combining the average results of the trials also indicated no overall benefit from EGDT.[6] There is considerable heterogeneity, however, in patients in whom septic shock develops and in usual care across hospitals; consequently, important treatment effects in patient subgroups or particular settings may have been missed.[7]

A prospective meta-analysis of individual patient data would provide greater statistical power to identify subgroup effects. The ProCESS, ARISE, and ProMISe investigators therefore planned this prospective meta-analysis of individual patient data (called the Protocolized Resuscitation in Sepsis Meta-Analysis [PRISM] study) before enrollment of the first patient into the first trial and harmonized entry criteria, intervention protocols, outcomes, major resource-use measures, and data collection across the three trials.[8] The goals of the current study were to use pooled data from the three trials to determine the effect of EGDT versus usual care on 90-day mortality and secondary clinical and economic outcomes and to compare the effects of EGDT across prespecified patient and care-delivery subgroups.

Methods

Study Design

All three trials evaluated the EGDT protocol, as described in the article by Rivers et al.[1] Core aspects of best care, including early recognition of sepsis and prompt delivery of intravenous fluids and antimicrobial agents, were promoted in the EGDT groups and the usual-care groups and reinforced through trial eligibility criteria.

We published the statistical analysis plan and a priori hypotheses for the current study before unblinding of any results from the three trials (ClinicalTrials.gov number, NCT02030158); the protocol is also available with the full text of this article at NEJM.org. Each trial supplied individual patient data after publication[3-5] and after the trial-level meta-analysis.[6] Before pooling data, we compared trial protocols, case-report forms, and data dictionaries to identify any recoding needed. We then provided a detailed data-set specification to each trial team to prepare the data file for pooling. After receipt of the data, we checked for missing or duplicate values and for consistency and plausibility, resolving data queries through direct consultation with each trial team before analysis. We did not reassess risk of bias because that had been performed for the trial-level meta-analysis.[6]

The final data-set specification is shown in Table S1 in the Supplementary Appendix, available at NEJM.org. The primary outcome measure was all-cause mortality at 90 days. Secondary outcome measures were in-hospital and 28-day mortality; duration of survival to 1 year; duration of stay in the emergency department, intensive care unit, and hospital; receipt and duration of invasive mechanical ventilation, vasopressors, and renal-replacement therapy; and costs and cost-effectiveness at 90 days.

Prespecified subgroups according to baseline patient characteristics were age, sex, severe coexisting conditions (liver, respiratory, cardiovascular, and renal conditions and immunocompromised state, all defined according to Acute Physiology and Chronic Health Evaluation [APACHE] II criteria), site of infection, and severity of illness. Severity of illness was operationalized in eight ways, according to eligibility criteria met (refractory hypotension, hyperlactatemia, or both), serum lactate level, illness-severity score (APACHE II Acute Physiology Score [range, 0 to 60, with higher scores indicating greater severity of illness] and APACHE II score [range, 0 to 71, with higher scores indicating greater severity of illness]), organ dysfunction (Sequential Organ Failure Assessment score), treatment (invasive mechanical ventilation [yes or no] and vasopres-

sors [yes or no]), and risk of death (derived from a customized model; see the Supplementary Appendix). Prespecified subgroups according to care-delivery characteristics were time from emergency department presentation to randomization, time of randomization (weekday or weekend and day or night), time from emergency department presentation to first administration of intravenous antimicrobial agents (available for the ProCESS and ARISE trials), and underlying intensity of care (derived from propensity models for the use of vasopressors or fluids during usual care; see the Supplementary Appendix).

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STATISTICAL ANALYSIS

The individual trials each had 80 to 90% power to detect an absolute difference in mortality of 6.5 to 8.0 percentage points between the EGDT group and the usual-care group, under the assumption of a baseline mortality of 24 to 40%, depending on the trial. Because this was a prospective meta-analysis of individual patient data, the sample-size calculation was undertaken before the results of the individual trials were available. On the basis of a control event rate of 25 to 35%, a statistical power of 80%, and a two-sided P value of 0.05 (with no allowance for heterogeneity of treatment effect or clustering of outcomes across trials), this study could detect an absolute between-group difference in 90-day mortality of 4 to 5 percentage points and an interaction effect (odds ratio) of approximately 1.5 or 1.6 for a subgroup representing one half or one quarter of the total sample, respectively.

We conducted all analyses on an intention-to-treat basis. We used one-stage, hierarchical regression modeling (patients nested in sites nested in trials), with site as a random effect and trial as a fixed effect. We determined heterogeneity among trials by fitting a fixed interaction between treatment and trial. We analyzed binomial outcomes using hierarchical logistic regression, reported as odds ratios and 95% confidence intervals; survival time (censored at 1 year) using hierarchical (shared frailty) Cox proportional-hazards regression, reported as hazard ratios and 95% confidence intervals; and continuous outcomes using hierarchical linear regression, reported as differences in means and 95% confidence intervals. We presented survival to 1 year using a Kaplan–Meier survival curve.

We performed a secondary analysis of the primary outcome using the same hierarchical regression structure with adjustment for prespecified baseline covariates of age, sex, last systolic blood pressure before randomization (<90 or ≥90 mm Hg), APACHE II score, and invasive mechanical ventilation at randomization (yes or no). Analyses of binomial secondary outcomes were adjusted for the same covariates. To determine heterogeneity between prespecified subgroups, we added fixed interaction terms between treatment and subgroup to the adjusted model for the primary outcome. To ascertain whether any variation in treatment effect across subgroups was consistent among the trials, we fitted three-way fixed interactions among trial, treatment, and subgroup. We analyzed continuous subgroup variables by dividing the cohort into thirds.

Our cost-effectiveness analysis compared the outcomes and costs, from the health-services perspective, up to 90 days after randomization. We used the combined mortality but reported cost and cost-effectiveness estimates separately for each trial because the interpretation of pooled cost-effectiveness estimates is unclear when drawn from health care systems with different cost structures.[9] The resource use for each patient was combined with trial-specific unit costs to report the incremental costs of EGDT versus usual care. We calculated quality-adjusted life-years (QALYs) up to 90 days by combining survival time with quality-of-life scores from the EuroQol questionnaire (EQ-5D-5L) administered at 90 days in the ProMISe trial, using the area-under-the-curve approach.[10] We estimated incremental costs and QALYs of EGDT versus usual care with a seemingly unrelated regression model,[11] with trial as a fixed effect for costs. We report results for each trial overall and for the same prespecified subgroups as for the clinical outcomes. We report incremental net monetary benefits by valuing QALYs at recommended thresholds for a QALY gain and performed sensitivity analyses to test the robustness of our results to alternative assumptions (see the Supplementary Appendix).

All analyses were performed with the use of SAS software, version 9.4 (SAS Institute), or Stata software, version 11.2 (StataCorp), and a two-

Table 1. Patient and Care-Delivery Characteristics at Baseline.*

Characteristic	EGDT (N=1857)	Usual Care (N=1880)
Patient characteristics		
Age — yr†		
Median	65	65
IQR	53–75	53–76
Male sex — no. (%)	1065 (57.4)	1104 (58.7)
≥1 Severe coexisting condition — no./total no. (%)‡	546/1854 (29.4)	526/1880 (28.0)
Site of infection — no. (%)		
Lungs	657 (35.4)	620 (33.0)
Abdomen	172 (9.3)	163 (8.7)
Blood	172 (9.3)	172 (9.1)
Central nervous system	28 (1.5)	19 (1.0)
Soft tissue	154 (8.3)	153 (8.1)
Urinary tract	356 (19.2)	371 (19.7)
Other	113 (6.1)	149 (7.9)
Unknown	196 (10.6)	218 (11.6)
Determined ultimately to have no infection	9 (0.5)	15 (0.8)
Entry criterion met — no./total no. (%)		
Refractory hypotension only	821/1854 (44.3)	833/1880 (44.3)
Hyperlactatemia only	717/1854 (38.7)	732/1880 (38.9)
Both refractory hypotension and hyperlactatemia	316/1854 (17.0)	315/1880 (16.8)
Last values before randomization		
Systolic blood pressure — mm Hg		
Median	94	94
IQR	83–112	82–111
Mean arterial pressure — mm Hg		
Median	67	67
IQR	59–78	59–78
Serum lactate — mmol/liter		
Median	4.3	4.2
IQR	2.5–5.9	2.4–5.9
APACHE II Acute Physiology Score — median (IQR)§	11 (7–15)	11 (7–15)
APACHE II score — median (IQR)¶	16 (12–21)	16 (12–21)
SOFA score — median (IQR)‖	4 (2–6)	4 (2–6)
Customized risk of death — median (IQR)	0.21 (0.11–0.37)	0.22 (0.11–0.36)
Care-delivery characteristics		
Time from ED presentation to inclusion criteria met — min		
Median	85	81
IQR	40–150	36–145
Time from ED presentation to randomization — min		
Median	162	159
IQR	119–223	115–221
Receiving antimicrobial agents at randomization — no./total no. (%)	1726/1856 (93.0)	1742/1880 (92.7)

Table 1. (Continued.)

Characteristic	EGDT (N=1857)	Usual Care (N=1880)
Time from ED presentation to first IV antimicrobial agents — min**		
Median	75	72
IQR	42–120	42–119
IV fluids administered before hospital presentation until randomization — no./total no. (%)	1801/1846 (97.6)	1818/1871 (97.2)
Volume administered — ml		
Median	2000	2000
IQR	1250–3000	1200–3000
Volume administered per kilogram of body weight — ml		
Median	27.5	27.7
IQR	16.5–42.3	16.2–41.7

* Data are from the Protocolized Care for Early Septic Shock (ProCESS) trial, the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial, and the Protocolised Management in Sepsis (ProMISe) trial. The numbers of patients with data available for analysis were as follows: age, 1857 in the group that received early, goal-directed therapy (EGDT) and 1879 in the group that received usual care; systolic blood pressure, 1809 and 1824; mean arterial pressure, 1318 and 1352; serum lactate, 1626 and 1645; customized risk of death, 1849 and 1878; time from emergency department (ED) presentation to inclusion criterion met, 1853 and 1878; time from ED presentation to first intravenous (IV) antimicrobial agents, 1091 and 1095; volume of IV fluids administered, 1846 and 1871; and volume of IV fluids administered per kilogram of body weight, 1723 and 1687. For details on data harmonization, see Table S1 in the Supplementary Appendix. IQR denotes interquartile range.

† Age was estimated for 7 patients in the ProMISe trial.

‡ Severe coexisting conditions were defined according to Acute Physiology and Chronic Health Evaluation [APACHE] II criteria.

§ APACHE II Acute Physiology Scores range from 0 to 60, with higher scores indicating greater severity of illness.

¶ APACHE II scores range from 0 to 71, with higher scores indicating greater severity of illness.

‖ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure. Baseline urine output was not used in the calculation of the renal SOFA score in the ARISE and ProMISe trials.

** Shown are data for patients who received IV antimicrobial agents before randomization in the ProCESS and ARISE trials. All patients in the ProMISe trial received IV antimicrobial agents before randomization (time not recorded).

sided alpha level of 0.05. Complete-case analysis was used for clinical outcomes because data were missing for less than 0.5% for all outcomes; multiple imputation was used for missing quality-of-life scores. We did not adjust for multiple comparisons; with 22 planned subgroup analyses, 1 or 2 significant interaction tests ($P<0.05$) would be expected on the basis of chance alone.[12]

RESULTS

STUDY PATIENTS

From March 2008 through July 2014, the three trials enrolled 4211 patients at 138 hospitals in the United States (ProCESS); Australia, New Zealand, Finland, Hong Kong, and the Republic of Ireland (ARISE); and England (ProMISe). The 448 patients randomly assigned to receive protocol-based standard therapy in the ProCESS trial were excluded from the current study, resulting in 3763 patients randomly assigned to either usual care (1892 patients) or EGDT (1871 patients). After the exclusion of patients who withdrew consent, underwent randomization in error, or were lost to follow-up at 90 days, 3723 patients (98.9%) were included in the primary analysis and 3511 (93.3%) were followed up to 1 year (Fig. S1 in the Supplementary Appendix). Patient and care-delivery characteristics were well balanced at baseline (Table 1, and Tables S2 and S3 in the Supplementary Appendix).

PRIMARY OUTCOME

Mortality at 90 days did not differ significantly between the two groups. Death occurred in 462 of 1852 patients (24.9%) in the EGDT group and in 475 of 1871 (25.4%) in the usual-care group (Table 2). The adjusted odds ratio was 0.97 (95% confidence interval [CI], 0.82 to 1.14; $P=0.68$).

Table 2. Outcomes.*

Outcome	EGDT (N=1857)	Usual Care (N=1880)	Incremental Effect (95% CI)	P Value	
				Overall Comparison	Comparison among Trials
Primary outcome: death at 90 days — no./total no. (%)	462/1852 (24.9)	475/1871 (25.4)	0.97 (0.82 to 1.14)†‡	0.68	0.73
Secondary outcomes: mortality					
Death at hospital discharge — no./total no. (%)§	370/1857 (19.9)	365/1878 (19.4)	1.02 (0.85 to 1.21)†	0.86	0.42
Death at 28 days — no./total no. (%)	375/1854 (20.2)	385/1873 (20.6)	0.96 (0.81 to 1.15)†	0.68	0.57
Secondary outcomes: duration of stay from randomization					
In ED — hr					
Median	1	1			
IQR	0 to 3	0 to 3			
Mean	2.1±3.3	2.2±3.0	−0.1 (−0.3 to 0.1)¶	0.19	<0.001‖
In ICU					
Admitted to ICU — no. (%)	1684 (90.7)	1532 (81.5)			
First stay — days					
Median among patients admitted	3	4			
IQR	2 to 6	2 to 6			
Mean overall	4.9±6.6	4.5±6.4	0.5 (0.1 to 0.9)¶	0.02	0.76
Total stay, including readmissions — days					
Median among patients admitted	4	4			
IQR	2 to 7	2 to 7			
Mean overall	5.3±7.1	4.9±7.0	0.5 (0.0 to 0.9)¶	0.04	0.78
In hospital — days§					
Median	9	9			
IQR	5 to 17	5 to 17			
Mean	14.8±17.5	14.9±26.2	−0.1 (−1.5 to 1.4)¶	0.92	0.39
Secondary outcomes: receipt and duration of organ support in ICU					
Respiratory support: invasive mechanical ventilation in ICU					
Receipt — no./total no. (%)	565/1852 (30.5)	544/1874 (29.0)	1.05 (0.89 to 1.24)†	0.57	0.04**
Duration — days					
Median among patients receiving support	4	4			
IQR	2 to 8	2 to 8			
Mean overall	2.1±5.5	1.9±5.2	0.2 (−0.2 to 0.5)¶	0.36	0.58

Cardiovascular support: vasopressors or inotropes in ICU					
Receipt — no./total no. (%)	1040/1854 (56.1)	923/1873 (49.3)	1.42 (1.23 to 1.64)†	<0.001	0.40
Duration — days					
Median among patients receiving support	2	2			
IQR	1 to 4	1 to 4			
Mean overall	1.9±3.7	1.6±2.9	0.3 (0.1 to 0.5)¶	0.01	0.52
Renal support: renal-replacement therapy in ICU					
Receipt — no./total no. (%)	204/1852 (11.0)	198/1874 (10.6)	1.02 (0.81 to 1.28)†	0.88	0.91
Duration — days					
Median among patients receiving support	3	4			
IQR	2 to 7	2 to 7			
Mean overall	0.7±3.3	0.6±2.4	0.0 (–0.1 to 0.2)¶	0.68	0.99
Cost-effectiveness analysis††					
Total costs up to 90 days — $					
ProCESS	32,178±30,181	30,930±30,150	1276 (–1799 to 4352)¶	0.42	
ARISE	25,014±25,737	22,973±22,822	2042 (–264 to 4352)¶	0.08	
ProMISe	14,112±15,120	12,906±16,017	1183 (–1418 to 3783)¶	0.37	
EQ-5D-5L score among survivors at 90 days‡‡	0.623±0.313	0.625±0.309	–0.002 (–0.039 to 0.000)¶	0.91	
QALYs among all patients to 90 days	0.058±0.048	0.058±0.048	0.000 (–0.004 to 0.004)¶	0.96	
Incremental net benefit at 90 days — $§§					
ProCESS			–1266 (–4373 to 1841)	0.43	
ARISE			–2032 (–4378 to 314)	0.09	
ProMISe			–1172 (–3813 to 1469)	0.39	

* Plus–minus values are means ±SD. For details on data harmonization, see Table S1 in the Supplementary Appendix. CI denotes confidence interval, ICU intensive care unit, and QALY quality-adjusted life-year.

† Shown is the adjusted odds ratio, with adjustment for age, sex, last systolic blood pressure before randomization (<90 or ≥90 mm Hg), APACHE II score, and receipt of invasive mechanical ventilation (yes or no).

‡ The unadjusted odds ratio for the primary outcome was 0.98 (95% CI, 0.84 to 1.14; P=0.78).

§ Data were censored at 60 days after randomization in the ProCESS trial.

¶ Shown is the difference in means.

‖ The incremental effect (difference in means) according to trial was as follows: ProCESS, 0.3 (95% CI, –0.1 to 0.7); ARISE, –0.6 (95% CI, –0.9 to –0.3); and ProMISe, 0.2 (95% CI, 0.0 to 0.4).

** The incremental effect (adjusted odds ratio) according to trial was as follows: ProCESS, 1.51 (95% CI, 1.12 to 2.04); ARISE, 0.98 (95% CI, 0.78 to 1.23); and ProMISe, 0.98 (95% CI, 0.76 to 1.26).

†† Missing data were multiply imputed.

‡‡ Quality of life was assessed with the use of the EuroQol questionnaire (EQ-5D-5L; a score of 0 indicates death and 1 perfect quality of life), which was administered to eligible patients in the ProMISe trial at 90 days after randomization. For all patients in the ProCESS and ARISE trials and those in the ProMISe trial who did not complete an EQ-5D-5L questionnaire, we used all available covariate information to estimate each patient's quality-of-life score with multiple imputation.

§§ The incremental net benefit was calculated by multiplying the QALY gain (or loss) by $100,000 and subtracting from this the incremental cost.

There was no interaction with respect to treatment effect among the trials.

SECONDARY OUTCOMES

Duration of stay in the intensive care unit (first admission and total days) and receipt of cardiovascular support (both percentage of patients and duration) were greater in the EGDT group than the usual-care group (Table 2). No other secondary outcomes differed significantly. Duration of stay in the emergency department was shorter in the EGDT group than in the usual-care group in the ARISE trial but not in the ProCESS or ProMISe trials. There was no significant difference in the duration of survival to 1 year between the two groups (hazard ratio, 0.98; 95% CI, 0.86 to 1.11; P=0.75) (Fig. 1).

SUBGROUP ANALYSES

Of the 16 a priori patient characteristics evaluated in subgroup analyses (Fig. 2), only 2 had significant interactions. In particular, there was no evidence of benefit associated with EGDT in the subgroups with the most severe septic shock, including those with a serum lactate level of 4.1 mmol per liter or more (1796 of 3258 patients [55.1%]; mean, 6.7 mmol per liter), those who presented with both hypotension and hyperlactatemia (628 of 3720 patients [16.9%]; mean systolic blood pressure, 89 mm Hg; mean serum lactate level, 6.7 mmol per liter), those in the upper third of APACHE II scores (1217 of 3723 patients [32.7%]; mean score, 24.6), and those in the upper third of predicted risk of death (1227 of 3715 patients [33.0%]; 90-day mortality, 46.2%). EGDT was associated with higher mortality among patients with severe chronic liver disease (117 of 3720 patients [3.1%]) than among those without such disease and lower mortality among those with severe chronic respiratory disease (370 of 3720 patients [9.9%]) than among those without such disease.

Among the six a priori care-delivery characteristics evaluated, we found no treatment-by-subgroup interactions (Fig. 3). In particular, analyses of treatment effects according to differences in usual care showed no interaction and no evidence of benefit at sites providing less aggressive resuscitation, despite considerable variation among sites in the propensity to adminis-

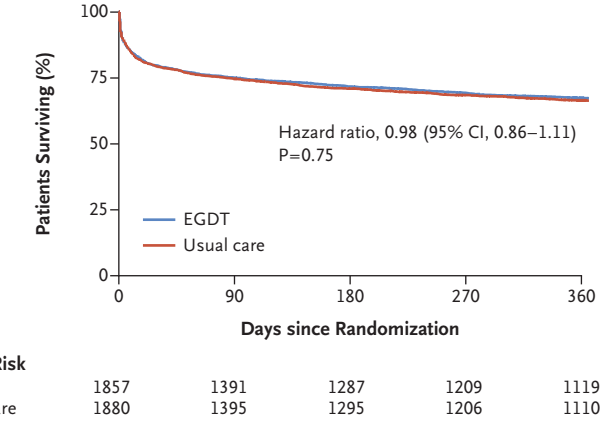


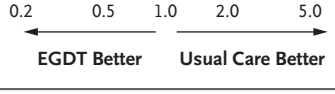
Figure 1. Patient Survival over a Period of 1 Year.

There was no significant difference in the duration of survival to 1 year between the group that received early, goal-directed therapy (EGDT) and the group that received usual care. Data with respect to survival were censored at the actual date that the patient was last known to be alive or at 365 days. CI denotes confidence interval.

Figure 2 (facing page). 90-Day Mortality According to Patient Subgroup.

For details on data harmonization, see Table S1 in the Supplementary Appendix. Odds ratios were adjusted for age, sex, last systolic blood pressure before randomization (<90 or ≥90 mm Hg), Acute Physiology and Chronic Health Evaluation (APACHE) II score (range, 0 to 71, with higher scores indicating greater severity of illness), and receipt of invasive mechanical ventilation (yes or no). The size of the square corresponds to the number of patients in each subgroup. Age was estimated for seven patients in the Protocolised Management in Sepsis (ProMISe) trial. The odds ratios according to trial for immunocompromised state versus no immunocompromised state were as follows: Protocolized Care for Early Septic Shock (ProCESS), 1.26 (95% CI, 0.72 to 2.20) versus 0.82 (95% CI, 0.58 to 1.17); Australasian Resuscitation in Sepsis Evaluation (ARISE), 1.23 (95% CI, 0.60 to 2.50) versus 0.96 (95% CI, 0.73 to 1.26); and ProMISe, 0.66 (95% CI, 0.33 to 1.29) versus 1.08 (95% CI, 0.83 to 1.40). For site of infection, patients with other or unknown site include those with an infection in the central nervous system and those who were determined ultimately to have no infection. Three patients did not meet the eligibility criteria for refractory hypotension or hyperlactatemia. APACHE II Acute Physiology Scores range from 0 to 60, with higher scores indicating greater severity of illness. Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure.

Subgroup	EGDT	Usual Care	Odds Ratio (95% CI)	P Value: Overall Comparison	P Value: Comparison among Trials
	no. of deaths/total no. of patients (%)				
Overall	462/1852 (24.9)	475/1871 (25.4)	0.97 (0.82–1.14)	0.68	0.73
Age				0.69	0.85
<57 yr	111/611 (18.2)	112/655 (17.1)	1.09 (0.81–1.46)		
57–71 yr	145/619 (23.4)	139/575 (24.2)	0.96 (0.73–1.25)		
≥72 yr	206/622 (33.1)	224/641 (34.9)	0.92 (0.73–1.17)		
Sex				0.71	0.98
Female	192/790 (24.3)	195/772 (25.3)	0.95 (0.75–1.20)		
Male	270/1062 (25.4)	280/1099 (25.5)	1.01 (0.83–1.23)		
Severe coexisting condition					
Liver				0.01	0.12
No	427/1790 (23.9)	455/1813 (25.1)	0.94 (0.80–1.09)		
Yes	34/59 (57.6)	20/58 (34.5)	2.51 (1.12–5.63)		
Respiratory				0.01	0.18
No	415/1658 (25.0)	409/1692 (24.2)	1.05 (0.90–1.23)		
Yes	46/191 (24.1)	66/179 (36.9)	0.54 (0.34–0.85)		
Cardiovascular				0.84	0.89
No	442/1800 (24.6)	456/1824 (25.0)	0.98 (0.84–1.14)		
Yes	19/49 (38.8)	19/47 (40.4)	0.92 (0.40–2.15)		
Renal				0.36	0.69
No	446/1787 (25.0)	454/1808 (25.1)	0.99 (0.85–1.16)		
Yes	15/62 (24.2)	21/63 (33.3)	0.67 (0.29–1.53)		
Immunocompromised state				0.92	0.01
No	357/1568 (22.8)	375/1609 (23.3)	0.97 (0.82–1.14)		
Yes	104/281 (37.0)	100/262 (38.2)	1.02 (0.70–1.46)		
Site of infection				0.39	0.35
Lungs	171/656 (26.1)	172/618 (27.8)	0.93 (0.72–1.19)		
Abdomen	49/172 (28.5)	43/163 (26.4)	1.08 (0.66–1.77)		
Blood	59/171 (34.5)	60/172 (34.9)	0.98 (0.62–1.53)		
Soft tissue	24/154 (15.6)	16/152 (10.5)	1.58 (0.79–3.16)		
Urinary tract	61/354 (17.2)	79/369 (21.4)	0.74 (0.51–1.08)		
Other or unknown	98/345 (28.4)	105/397 (26.4)	1.10 (0.79–1.52)		
Severity of illness					
Eligibility criterion met				0.09	0.53
Refractory hypotension	121/819 (14.8)	146/831 (17.6)	0.81 (0.62–1.06)		
Hyperlactatemia	213/715 (29.8)	221/727 (30.4)	0.98 (0.78–1.22)		
Both	128/315 (40.6)	108/313 (34.5)	1.32 (0.94–1.83)		
Last lactate level before randomization				0.26	0.21
<2.1 mmol/liter	44/313 (14.1)	52/342 (15.2)	0.92 (0.59–1.43)		
2.1–4.0 mmol/liter	64/397 (16.1)	83/410 (20.2)	0.76 (0.53–1.09)		
≥4.1 mmol/liter	319/912 (35.0)	297/884 (33.6)	1.07 (0.88–1.30)		
APACHE II Acute Physiology Score				0.95	0.65
<9	96/677 (14.2)	96/643 (14.9)	0.97 (0.71–1.32)		
9–13	134/572 (23.4)	135/598 (22.6)	1.03 (0.78–1.35)		
≥14	232/603 (38.5)	244/630 (38.7)	0.98 (0.77–1.23)		
APACHE II score				0.24	0.82
<14	74/666 (11.1)	58/650 (8.9)	1.30 (0.90–1.88)		
14–19	137/576 (23.8)	158/614 (25.7)	0.89 (0.69–1.17)		
≥20	251/610 (41.1)	259/607 (42.7)	0.94 (0.75–1.18)		
SOFA score				0.34	0.47
<3	69/527 (13.1)	75/503 (14.9)	0.85 (0.60–1.22)		
3 or 4	127/547 (23.2)	118/579 (20.4)	1.17 (0.88–1.56)		
≥5	266/778 (34.2)	282/789 (35.7)	0.94 (0.76–1.16)		
Customized risk of death				0.65	0.97
<14%	46/617 (7.5)	55/634 (8.7)	0.85 (0.57–1.29)		
≥14% and <30%	135/609 (22.2)	133/628 (21.2)	1.06 (0.80–1.39)		
≥30%	280/619 (45.2)	287/608 (47.2)	0.93 (0.74–1.17)		
Invasive mechanical ventilation				0.55	0.62
No	386/1670 (23.1)	401/1708 (23.5)	0.98 (0.83–1.15)		
Yes	76/182 (41.8)	74/163 (45.4)	0.87 (0.55–1.37)		
Vasopressor infusion				0.17	0.21
No	360/1559 (23.1)	393/1592 (24.7)	0.92 (0.78–1.09)		
Yes	101/291 (34.7)	82/277 (29.6)	1.23 (0.85–1.77)		



Subgroup	EGDT	Usual Care	Odds Ratio (95% CI)	P Value: Overall Comparison	P Value: Comparison among Trials
	no. of deaths/total no. of patients (%)				
Overall	462/1852 (24.9)	475/1871 (25.4)	0.97 (0.82–1.14)	0.68	0.73
Time to randomization				0.83	0.06
<132 min	174/593 (29.3)	190/657 (28.9)	1.00 (0.78–1.28)		
132–197 min	161/636 (25.3)	162/598 (27.1)	0.93 (0.71–1.20)		
≥198 min	127/623 (20.4)	123/616 (20.0)	1.04 (0.78–1.39)		
Randomization					
Day of week				0.28	0.90
Weekday: Mon.–Fri.	408/1621 (25.2)	423/1617 (26.2)	0.95 (0.81–1.11)		
Weekend: Sat.–Sun.	54/231 (23.4)	52/254 (20.5)	1.20 (0.77–1.85)		
Time of day				0.62	0.99
Day: 8:00 a.m. to 7:59 p.m.	400/1564 (25.6)	411/1566 (26.2)	0.96 (0.82–1.13)		
Night: 8:00 p.m. to 7:59 a.m.	62/288 (21.5)	64/305 (21.0)	1.06 (0.71–1.58)		
Time from ED presentation to first IV antimicrobial agents				0.74	0.26
<51 min	89/369 (24.1)	94/370 (25.4)	0.92 (0.66–1.29)		
51–99 min	68/356 (19.1)	69/360 (19.2)	0.97 (0.66–1.42)		
≥100 min	87/363 (24.0)	83/363 (22.9)	1.13 (0.79–1.62)		
Intensity of underlying care					
Standardized vasopressor use				0.60	0.42
1: lowest use	141/551 (25.6)	140/554 (25.3)	1.02 (0.77–1.33)		
2: intermediate use	167/746 (22.4)	187/751 (24.9)	0.87 (0.68–1.11)		
3: highest use	139/512 (27.1)	143/534 (26.8)	1.03 (0.78–1.36)		
Standardized fluid-volume use				0.45	0.11
1: lowest use	143/610 (23.4)	137/620 (22.1)	1.09 (0.83–1.44)		
2: intermediate use	179/700 (25.6)	205/721 (28.4)	0.86 (0.68–1.10)		
3: highest use	122/485 (25.2)	126/483 (26.1)	0.95 (0.71–1.27)		

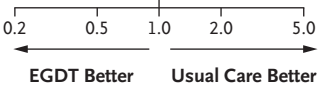


Figure 3. 90-Day Mortality According to Care-Delivery Subgroup.

For details on data harmonization, see Table S1 in the Supplementary Appendix. Odds ratio were adjusted for age, sex, last systolic blood pressure before randomization (<90 or ≥90 mm Hg), APACHE II score, and receipt of invasive mechanical ventilation (yes or no). The size of the square corresponds to the number of patients in each subgroup. Data for time from emergency department (ED) presentation to first intravenous (IV) antimicrobial agents are only for patients who received IV antimicrobial agents before randomization in the ProCESS and ARISE trials; all patients in the ProMISe trial received antimicrobial agents before randomization (time not recorded). Results for intensity of underlying care were reported for 115 (83%) of the 138 participating sites with at least three patients who received usual care.

ter vasopressors (mean propensity according to third, 23.2%, 44.2%, and 65.3%) or intravenous fluids (mean volume according to third, 1.3, 2.0, and 3.4 liters) in the usual-care group.

In the total of 22 analyses, there were 2 significant interaction tests. This finding is consistent with the 1 or 2 such tests that would be expected by chance alone.

COSTS AND COST-EFFECTIVENESS

In each of the three trials, the average cost up to 90 days was higher with EGDT than with usual care (Table 2, and Fig. S2 and Table S13 in the Supplementary Appendix). Average quality-of-life scores and QALYs were similar in the two groups; thus, for each trial, the average incremental net monetary benefit for EGDT versus usual care was negative, and the probability that EGDT is cost-effective was less than 0.25 across all realistic willingness-to-pay thresholds (Fig. S3 in the Supplementary Appendix). The sensitivity analysis showed that these base case results were robust to alternative assumptions (Fig. S4 in the Supplementary Appendix). Although the estimated incremental net benefit of EGDT was positive for a few of the prespecified subgroups, these results had wide 95% confidence intervals that included zero (Table S14 in the Supplementary Appendix).

DISCUSSION

The results of our prospective meta-analysis of individual patient data provide a more granular

and robust insight than the results of the individual trials and of our trial-level meta-analysis into the overall effectiveness of EGDT versus usual care in patients presenting to the emergency department with septic shock. We found no evidence that EGDT resulted in lower mortality than usual care, a finding that is consistent with the results of our trial-level meta-analysis.[6] We also found that, although the three trials occurred in geographically distinct health care systems, there was no evidence of any trial-specific effect.

Concerns exist that the divergent findings between the trial by Rivers et al.[1] and the three large, multicenter, randomized, controlled trials are because the patients included in the trial by Rivers et al. were sicker.[13] We found no evidence of treatment benefit with EGDT in patients with greater severity of illness, despite using several approaches to identify subgroups of very sick patients that were considerably larger than the entire population in the trial by Rivers et al. For example, the cohort in the upper third of predicted risk of death, which was more than four times as large as the entire population in the trial by Rivers et al., had similar mortality in the EGDT group and the usual-care group (approximately 45%); mortality was also similar to that in the control group in the trial by Rivers et al. We do not believe, therefore, that differences in severity explain the differences in findings. There were treatment interactions between EGDT and the presence of either severe preexisting respiratory or liver disease, but these effects were inconsistent and probably spurious, given the small number of patients with these coexisting conditions and the large number of subgroup analyses.

Another important concern raised about the recent trials was that usual care may have been superior to that reported in positive studies, explaining the failure to show a benefit with EGDT. Our subgroup analyses explored whether the effect of EGDT depended on the usual resuscitation practice in an emergency department; despite wide variation in practice, even in those emergency departments with the least aggressive practice, there was no evidence of benefit. As noted previously, all three trials are more recent than the trial by Rivers et al., and early recognition of sepsis and prompt delivery of intravenous fluids and antimicrobial agents were promoted in all treatment groups. It remains possible that general advances in the provision of care for sepsis and septic shock, to the benefit of all patients, explain part or all of the difference in findings between the trial by Rivers et al. and the more recent trials.

Unlike the results of observational studies,[14,15] which were proposed as evidence supporting the ongoing use of EGDT,[2,13] this prospectively defined analysis of individual patient data relies exclusively on random assignment, avoiding biases related to confounding by indication, regression to the mean, or secular trends in sepsis-related mortality.[16,17] This collaboration among trial groups also shows that key methodologic aspects of independently conducted research can be harmonized in advance, facilitating the generation of a richer evidence base to guide clinicians dealing with complex conditions such as septic shock. The return on investment for the patient, investigator, and funding agency is enhanced by our model of early collaboration among research groups, aligning key measurements and using a prespecified plan to perform a prospective meta-analysis of individual patient data to answer questions beyond the scope of each individual trial.

Nonetheless, there are important limitations to this analysis. Although the overall sample size is large, some clinically important subgroups are small, which limits statistical power. The analysis is also limited by the underlying internal and external validity of the three trials. None were blinded, which may introduce bias. Patients were enrolled in both academic and nonacademic metropolitan and rural hospitals across several regions of the world. However, the control groups may not be representative of usual care in all settings, especially those in low-income and middle-income countries.

Although our analysis confirms that EGDT as a packaged protocol of care is not superior to usual care, there are still unresolved questions regarding the most effective fluid and vasopressor regimens, the role of hemodynamic monitoring, and appropriate targets in the resuscitation of patients with sepsis and septic shock. Even though a policy that mandates routine measurement of central venous pressure and central venous oxygen saturation in all patients with sepsis did not improve outcomes, clinical judgment should always be applied because, in specific circumstances, there may be a role for these

measurements. The future of sepsis therapy may yet lie with protocols that permit a more individualized approach that is based on a greater understanding of the complex interplay among host genetics, individual pathophysiological features, and the infective agent.[18-20]

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Dr. Angus reports receiving consulting fees from Ferring Pharmaceuticals; Dr. Reade, receiving fees for presenting trial results to an industry group by Pfizer; and Dr. Singer, receiving grant support, fees for serving on an advisory board, and a royalty to fund research from Deltex Medical, grant support from Mologic and the Defense Science and Technology Laboratory, and fees for serving on an advisory board from Merck Sharp & Dohme and Bristol-Myers Squibb. 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.

APPENDIX

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