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. DOI: 10.1056/NEJMoa1401602

Supplementary Materials for

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

The ProCESS Investigators

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The ProCESS Investigators

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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).

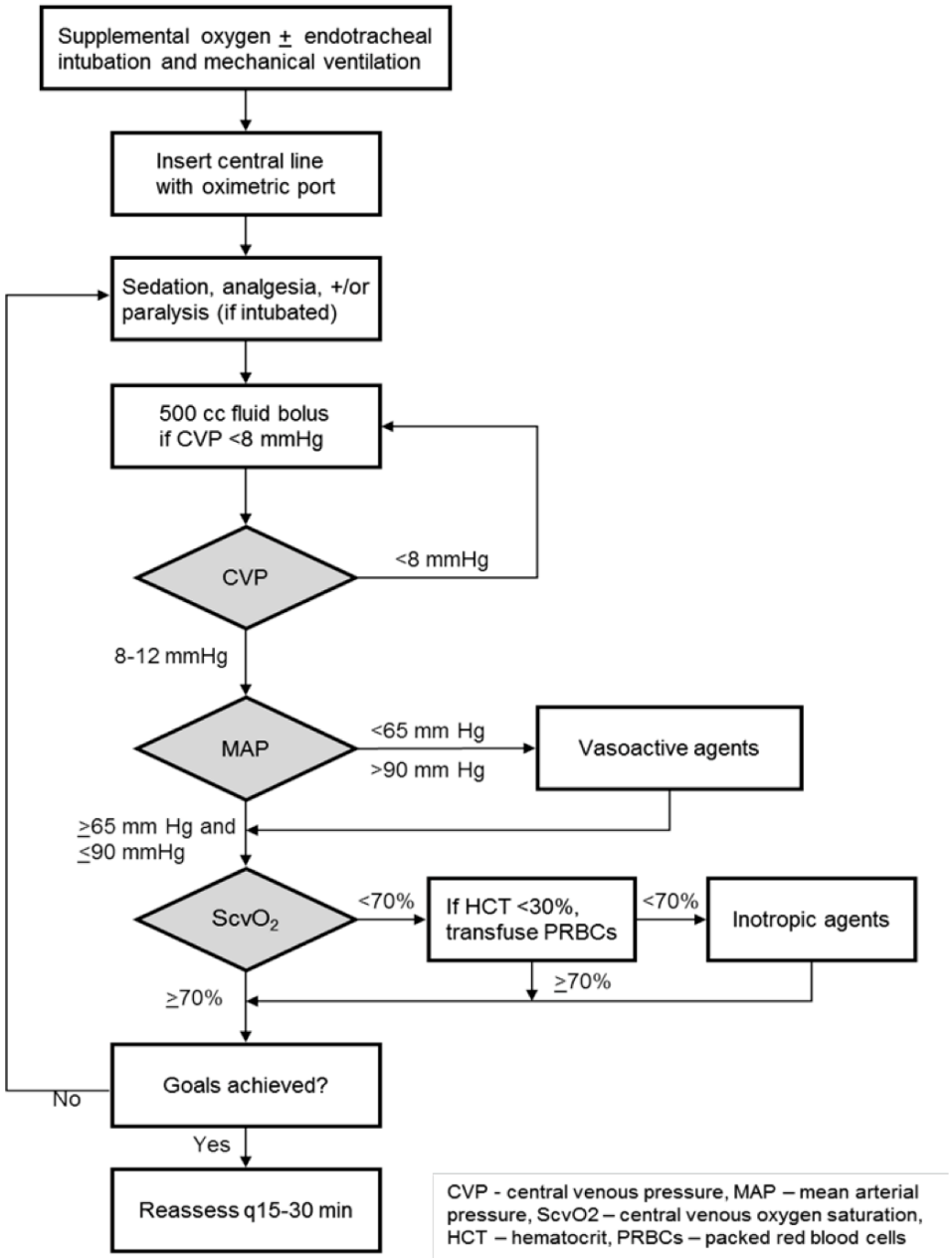
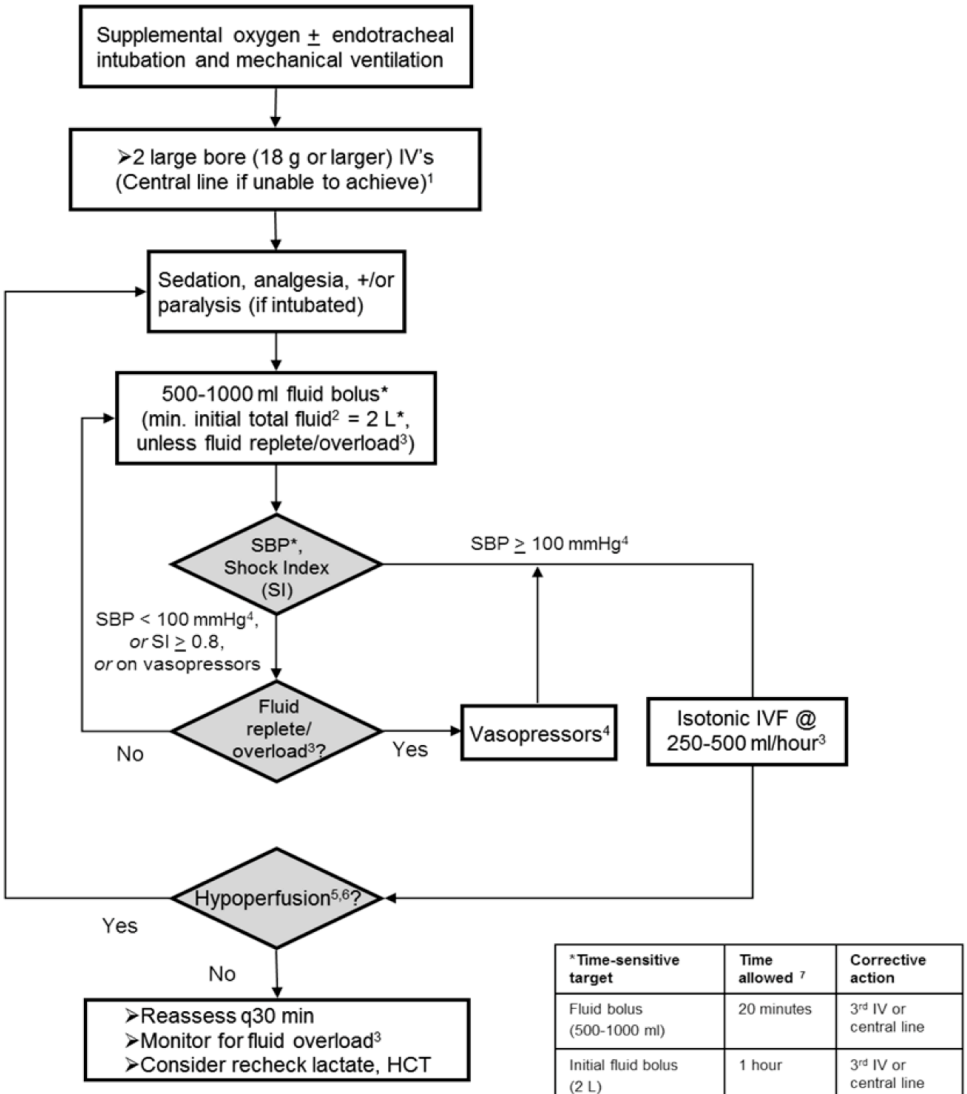


Figure S2. – Protocol for Standard Therapy.

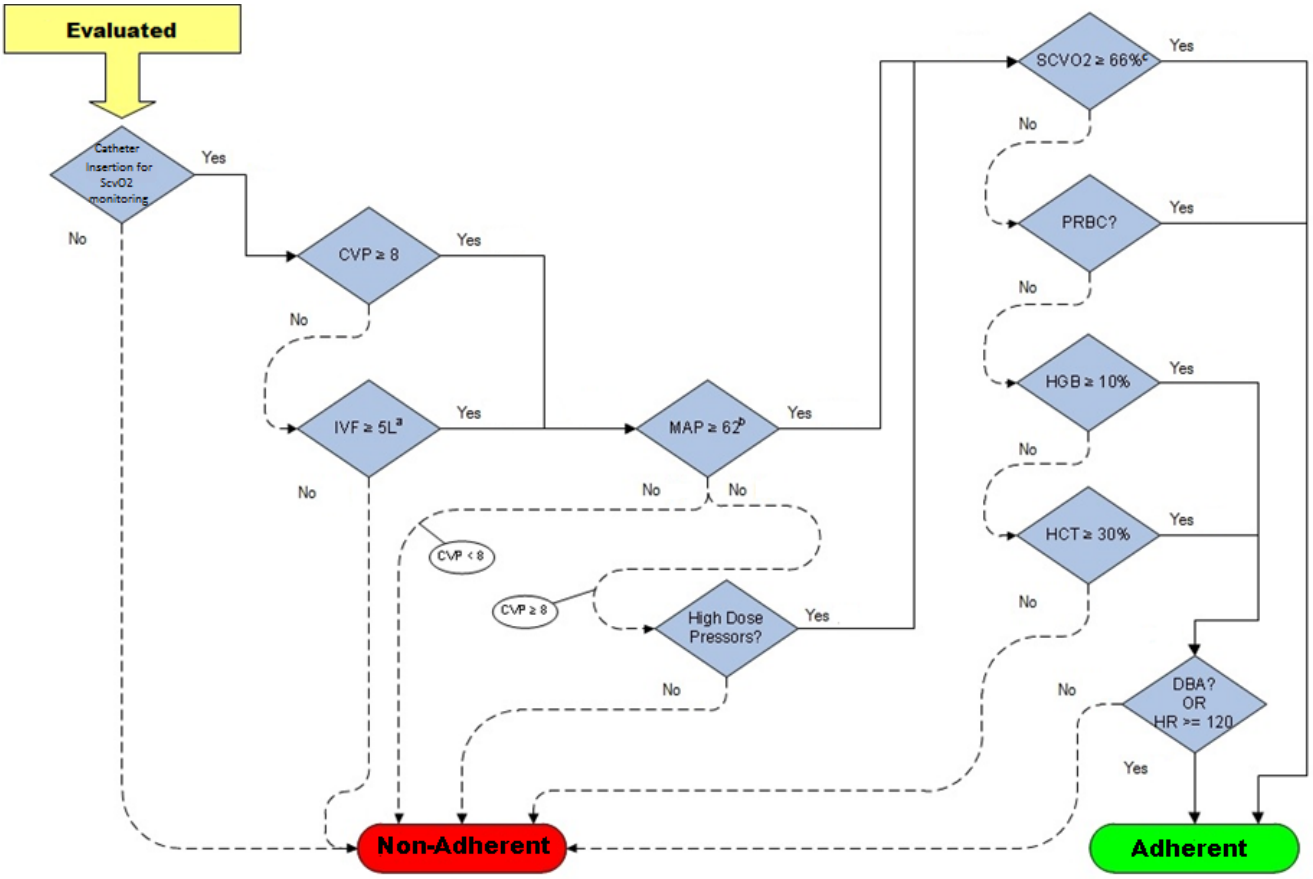


*Time-sensitive target	Time allowed [7]	Corrective action
Fluid bolus (500-1000 ml)	20 minutes	3rd IV or central line
Initial fluid bolus (2 L)	1 hour	3rd IV or central line
SBP ≥ 100 mmHg	1 hour	Vasopressors

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.



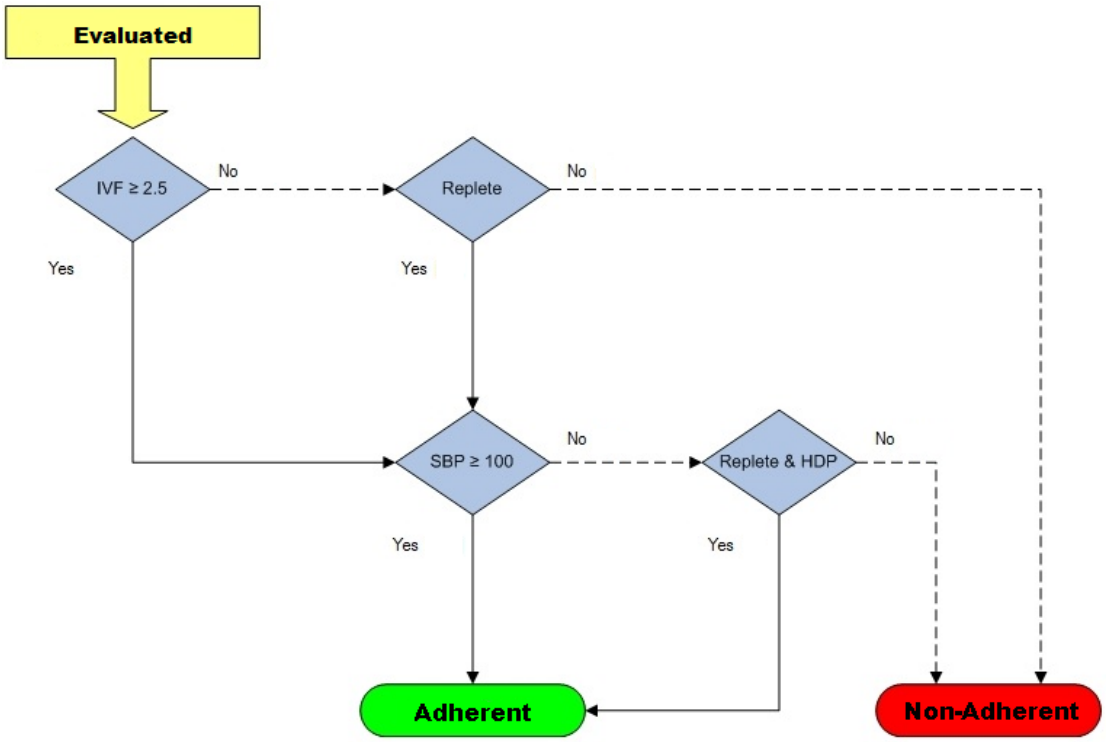
Protocol adherence was assessed by determining adherence to a set of decision nodes prompted by clinical status. Schematics for the decision nodes for EGDT at 6h are presented above. IVF – intravenous fluids; $ScvO_2$ – central venous oxygen saturation; MAP – mean arterial pressure; PRBC – packed red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

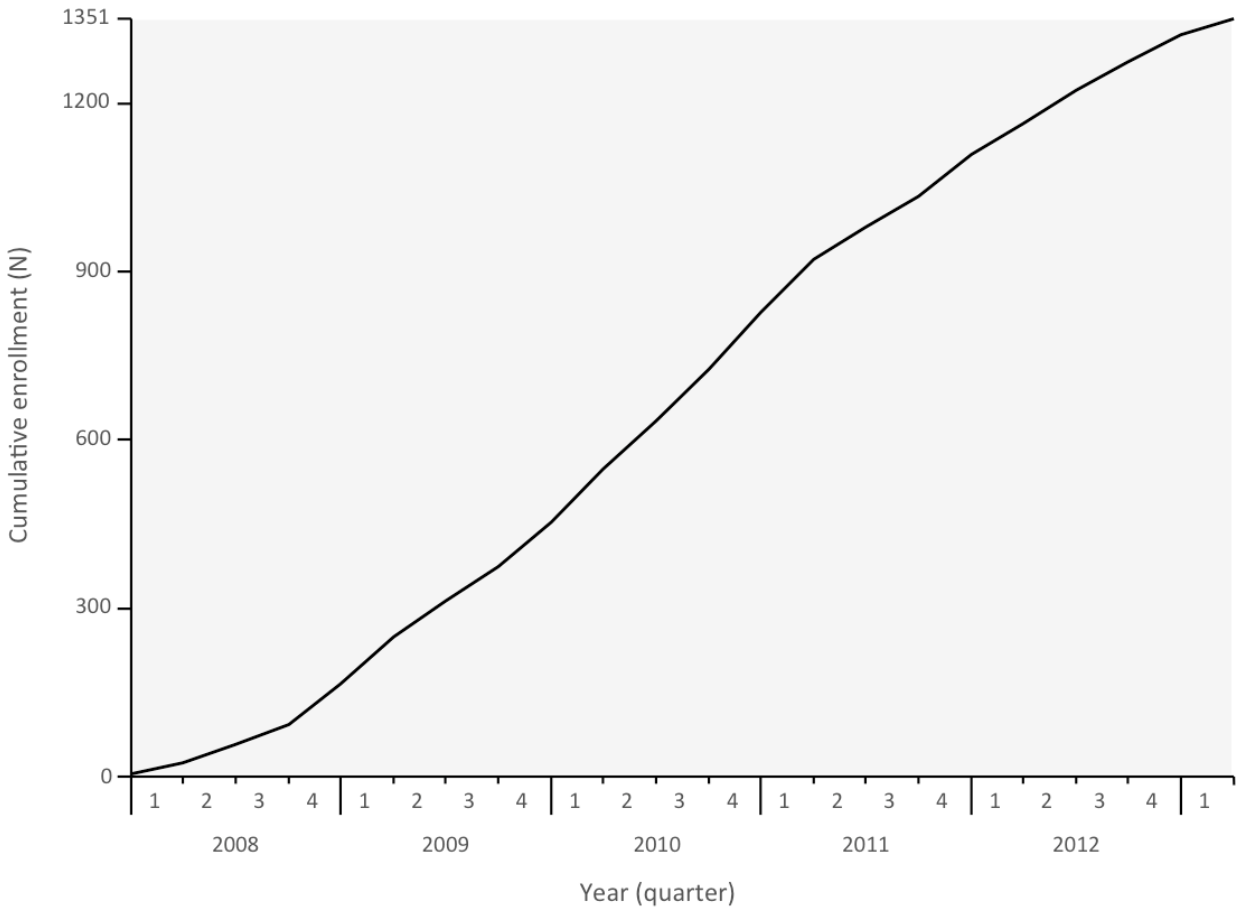
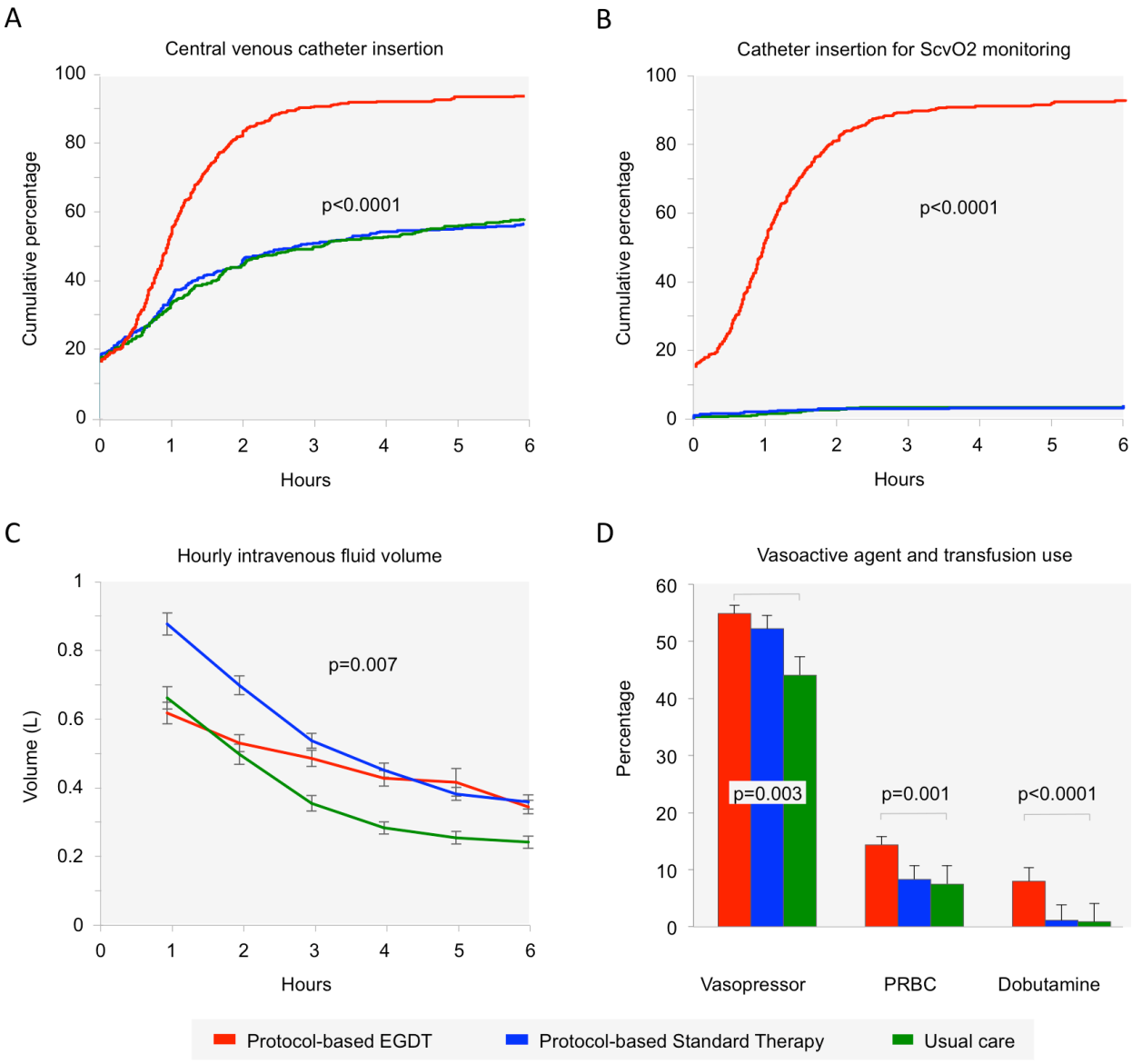


Figure S6. Processes of care during the 6h resuscitation intervention.



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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