EGDT: live and let die? Dead or alive?

Paolo Groff

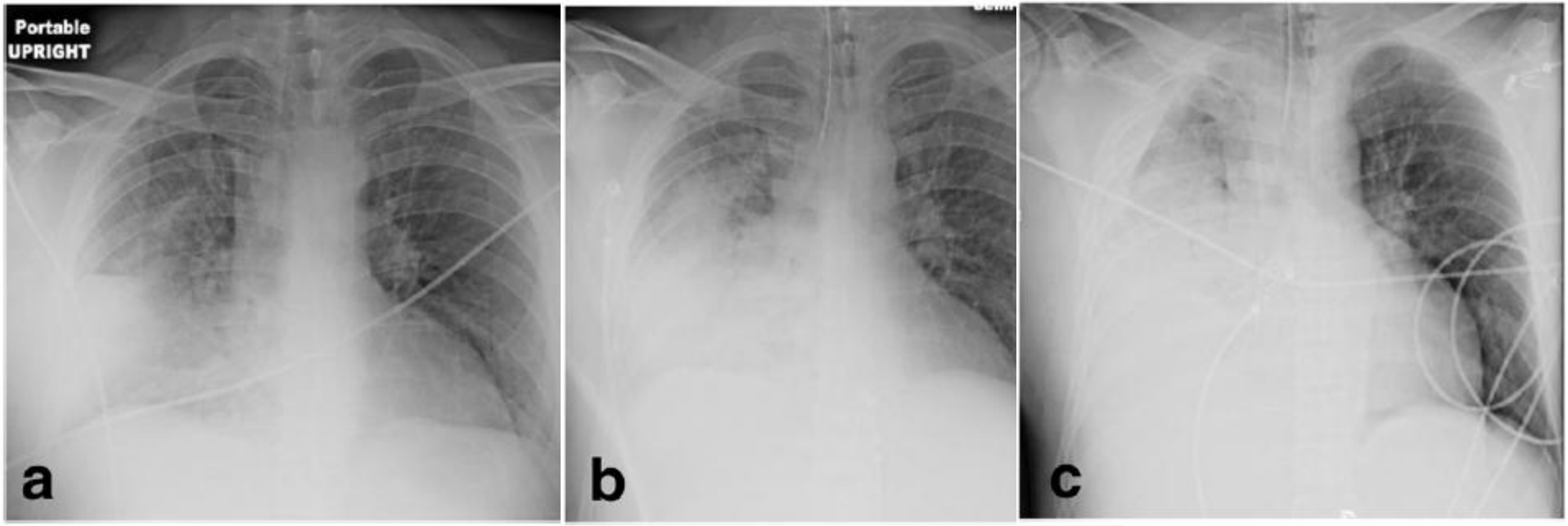
DEA

Ospedale Civile «Madonna del Soccorso»

San Benedetto del Tronto

Caso clinico

- Pz. Di 40 aa, TD. In PS per dispnea ingravescente e febbre.
- Pa 90/55; FR 38/min; FC 120/min; GCS 15/15; TC 39°C; Marezzato.
- pH 7.28; PaO2 45; PaCO2 38; HCO3- 17; Lac 4.1
- Tazobactam-piperacillina, Ciprofloxacina, Fluidi, steroidi, CPAP



Dopo 2 ore di trattamento con CPAP:
pH 7.23; PaO2 60 mmHg; Pa CO2 55; HCO3 -16; Lac 7.2
Intubato e trasferito in RIA

Controllo Rx a 4 ore dall'ingresso e 4 l di fisiologica

Controllo Rx a 12 ore dall'ingresso
E 9 l di fisiologica.
PVC: 10 mmHg
Decesso 6 ore dopo per ipossiemia refrattaria

The New England Journal of Medicine

N Engl J Med, Vol. 345, No. 19 · November 8, 2001

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

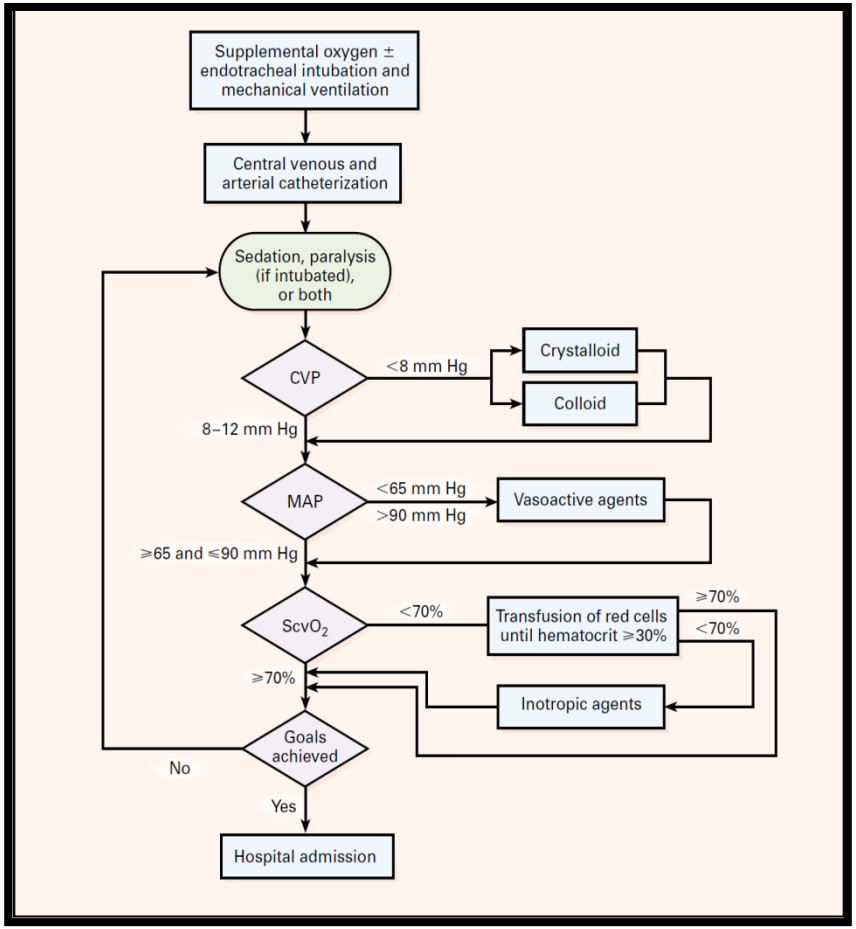


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TABLE 3. KAPLAN–MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.

†Percentages were calculated by the Kaplan–Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

TABLE 4. TREATMENTS ADMINISTERED.*

TREATMENT	HOURS AFTER THE START OF THERAPY		
	0–6	7–72	0–72
Total fluids (ml)			
Standard therapy	3499±2438	10,602±6,216	13,358±7,729
EGDT	4981±2984	8,625±5,162	13,443±6,390
P value	<0.001	0.01	0.73
Red-cell transfusion (%)			
Standard therapy	18.5	32.8	44.5
EGDT	64.1	11.1	68.4
P value	<0.001	<0.001	<0.001
Any vasopressor (%)†			
Standard therapy	30.3	42.9	51.3
EGDT	27.4	29.1	36.8
P value	0.62	0.03	0.02
Inotropic agent (dobutamine) (%)			
Standard therapy	0.8	8.4	9.2
EGDT	13.7	14.5	15.4
P value	<0.001	0.14	0.15
Mechanical ventilation (%)			
Standard therapy	53.8	16.8	70.6
EGDT	53.0	2.6	55.6
P value	0.90	<0.001	0.02
Pulmonary-artery catheterization (%)‡			
Standard therapy	3.4	28.6	31.9
EGDT	0	18.0	18.0
P value	0.12	0.04	0.01

Implementing Early Goal-directed Therapy in the Emergency Setting: The Challenges and Experiences of Translating Research Innovations into Clinical Reality in Academic and Community Settings

Alan E. Jones, MD, Nathan I. Shapiro, MD, MPH, Michael Roshon, MD, PhD

ACADEMIC EMERGENCY MEDICINE 2007; 14:1072–1078

«An important issue that the Surviving Sepsis campaign guidelines did not address is the ability of such a protocol to be translated from the research environment to a clinical care setting in Eds and hospitals with varying resources, staff and training»

«The major challenge is related to technical details regarding the catheter and monitor for ScVO2 monitoring…»

«The task of placing a central line in a timely fashion in a busy ED was known to be a challenge from the beginning…»

«Initially there was high compliance with EGDT protocol, but over time there were more cases missed and protocol violations observed…»

Marik *Annals of Intensive Care* 2014, **4**:21
http://www.annalsofintensivecare.com/content/4/1/21

Annals of Intensive Care
a SpringerOpen Journal

REVIEW Open Access

Iatrogenic salt water drowning and the hazards of a high central venous pressure

Paul E Marik

- Sepsis is primarely a vasoplegic state due to increased production of NO, activation of KATP channels and vasopressin deficiency. This leads to arterial and venodilation, with increased of the unstressed vascular department and decrease of venous retourn. Landry and Oliver, NEJM 2001
- The septic heart respondes poorely to fluid loading, with aFrank-Strling curve depressed downwards and to the right. Ognibene et al, Chest 1988
- Aggressive fluid resuscitation increases fluid extravasation following the increase of hydrostatic microvascular pressure, the shedding of the endothelial glycocalix and the incretion of natriuretic peptides (with ingreased GMP mediated vasodilation and cleavage of membrane bound glycoproteins (Goldenberg and al, Sci Transl Med 2011; Bruegger et al, Am J Physiol Heart Circ Physiol 2005; Berg et al, Acta Anaesthesiol Scand 2002

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Annals of Intensive Care
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REVIEW Open Access

Iatrogenic salt water drowning and the hazards of a high central venous pressure

Paul E Marik

Consequences of volume overload

Pulmonary edema and increased extra-vascular lung water
- Impaired oxygenation
- Altered pulmonary and chest wall mechanics
- Increased work of breathing

Myocardial edema
- Decreased contractility
- Diastolic dysfunction
- Conduction defects

Increased intraabdominal pressure
- Acute kidney injury
- Hepatic dysfunction
- Decreased lung volumes
- Ileus

Gastrointestinal
- Ileus
- Malabsorption
- Bacterial translocation
- Hepatic congestion

Decreased wound healing

Consequences of a high central venous pressure

Decreased venous return and stroke volume
Acute kidney injury
Hepatic congestion
Decreased splanchnic microcirculatory flow

Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy

A Randomized Clinical Trial

Alan E. Jones, MD
Nathan I. Shapiro, MD, MPH
Stephen Trzeciak, MD, MPH
Ryan C. Arnold, MD
Heather A. Claremont, BFA
Jeffrey A. Kline, MD
for the Emergency Medicine Shock Research Network (EMShockNet) Investigators

CARING FOR THE CRITICALLY ILL PATIENT

JAMA, February 24, 2010—Vol 303, No. 8

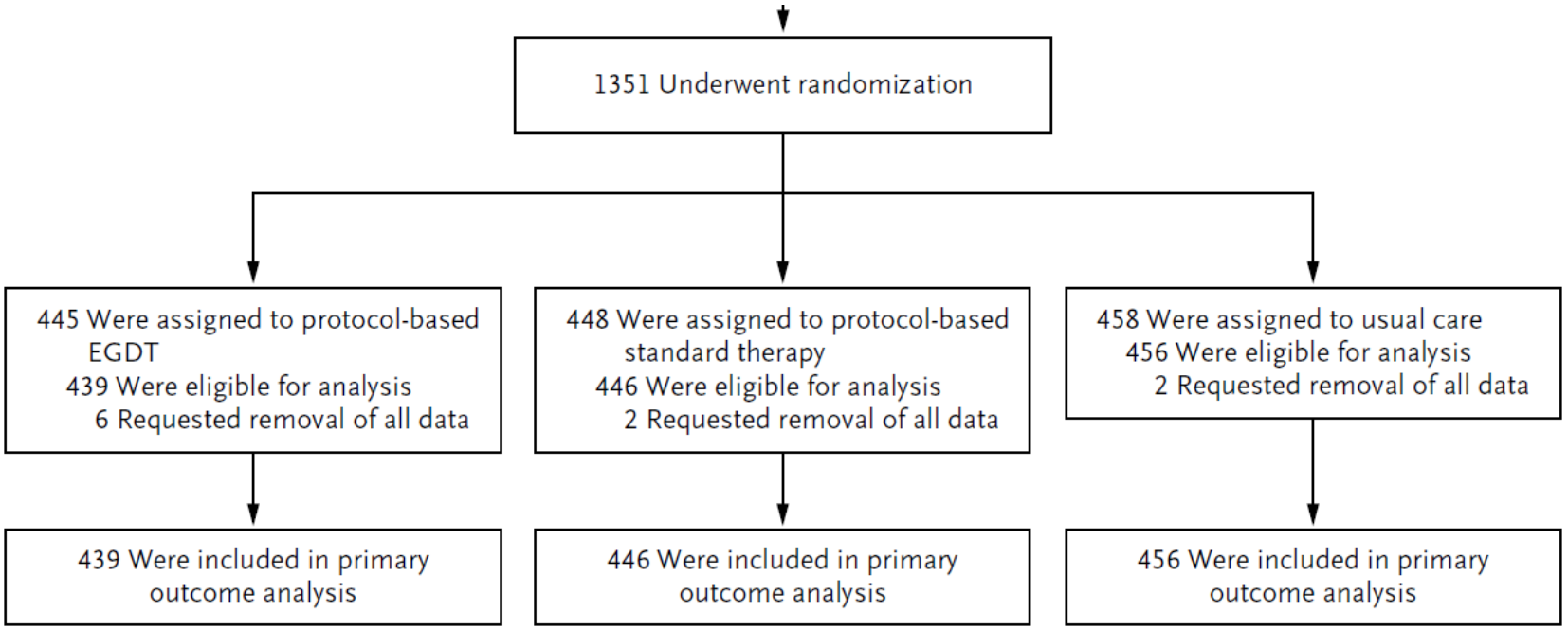
Variable	Lactate Clearance Group (n = 150)	$ScvO_2$ Group (n = 150)	Proportion Difference (95% Confidence Interval)	*P* Value[b]
In-hospital mortality, No. (%)[a]				
Intent to treat	25 (17)	34 (23)	6 (–3 to 15)	
Per protocol	25 (17)	33 (22)	5 (–3 to 14)	
Length of stay, mean (SD), d				
ICU	5.9 (8.46)	5.6 (7.39)		.75
Hospital	11.4 (10.89)	12.1 (11.68)		.60
Hospital complications				
Ventilator-free days, mean (SD)	9.3 (10.31)	9.9 (11.09)		.67
Multiple organ failure, No. (%)	37 (25)	33 (22)		.68
Care withdrawn, No. (%)	14 (9)	23 (15)		.15

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

The ProCESS Investigators*



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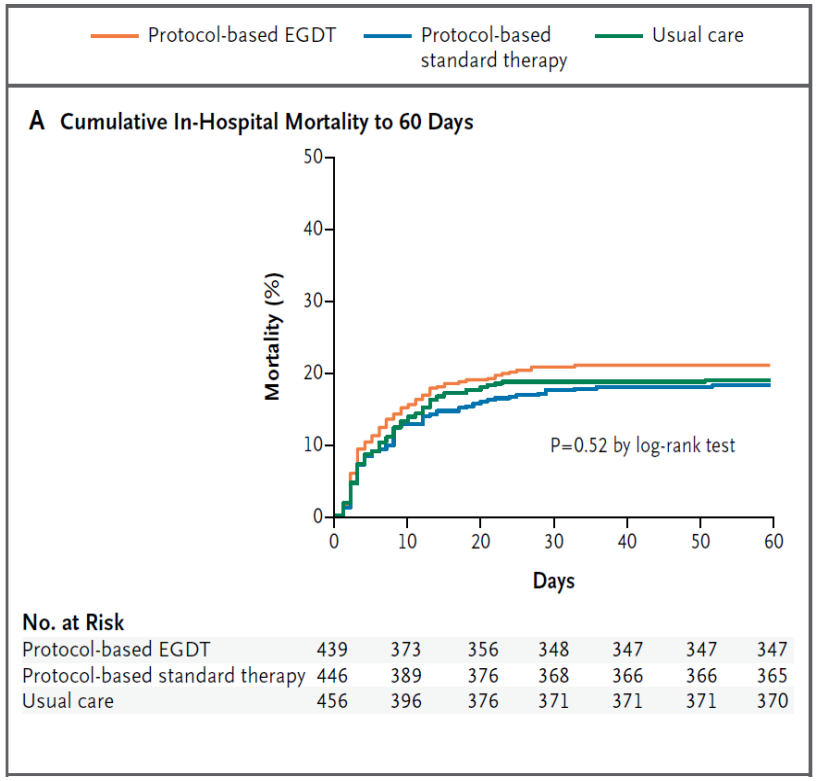
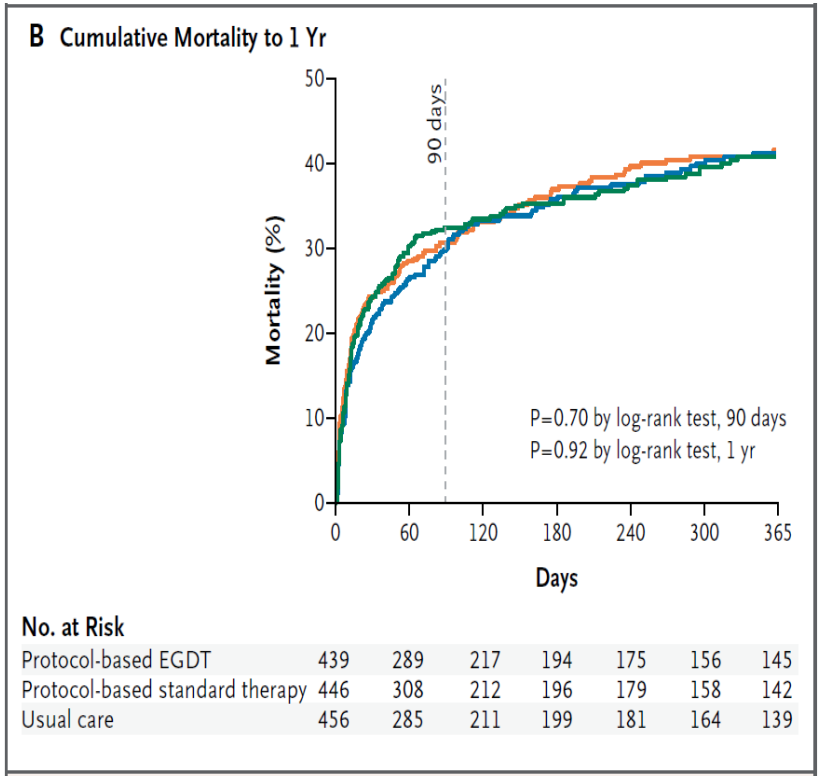
	EGDT	ST	UC
fluidi	++-	+++	+--
Vasopressori	+++	+++	+--
Dobutamina	+++	++-	+--
RBC	+++	+--	+--

Table 2. Outcomes.*

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


Protocol-based EGDT
Protocol-based standard therapy
Usual care
A Cumulative In-Hospital Mortality to 60 Days
Mortality (%)
0
10
20
30
40
50
P=0.52 by log-rank test
0
10
20
30
40
50
60
Days
No. at Risk
Protocol-based EGDT 439 373 356 348 347 347 347
Protocol-based standard therapy 446 389 376 368 366 366 365
Usual care 456 396 376 371 371 371 370


B Cumulative Mortality to 1 Yr
Mortality (%)
0
10
20
30
40
50
90 days
P=0.70 by log-rank test, 90 days
P=0.92 by log-rank test, 1 yr
0
60
120
180
240
300
365
Days
No. at Risk
Protocol-based EGDT 439 289 217 194 175 156 145
Protocol-based standard therapy 446 308 212 196 179 158 142
Usual care 456 285 211 199 181 164 139

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ORIGINAL ARTICLE

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

The ProCESS Investigators*

	Età	APACHE	Comor	Lattati	SvO2
Rivers	67.1	21	Heart, Liver ++	7.7	49.2
ProCESS	60	21	Heart, Liver +-	5	71

Table 1 Contrasting use of fluids and vasopressors (and mortality) in the Early Goal Directed Therapy (EGDT) arms of the Rivers' and ProCESS studies

Study	Fluid 0 to 6 hours (ml)	Fluid 7 to 72 hours (ml)	Fluid 0 to 72 hours (ml)	Vasopressors (%) 0 to 6 hours	60-day mortality (%)
Rivers' EGDT	4,981	8,625	13,443	27.4	44.3
ProCESS EGDT	2,805	4,428	7,220	54.9	21

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.

Original Contribution

Towards a less invasive approach to the early goal-directed treatment of septic shock in the ED☆,☆☆

Daniele Coen, MD *, Francesca Cortellaro, MD, Simone Pasini, MD, Valeria Tombini, MD, Angelica Vaccaro, MD, Lorenzo Montalbetti, MD, Michela Cazzaniga, MD, Daniele Boghi, MD

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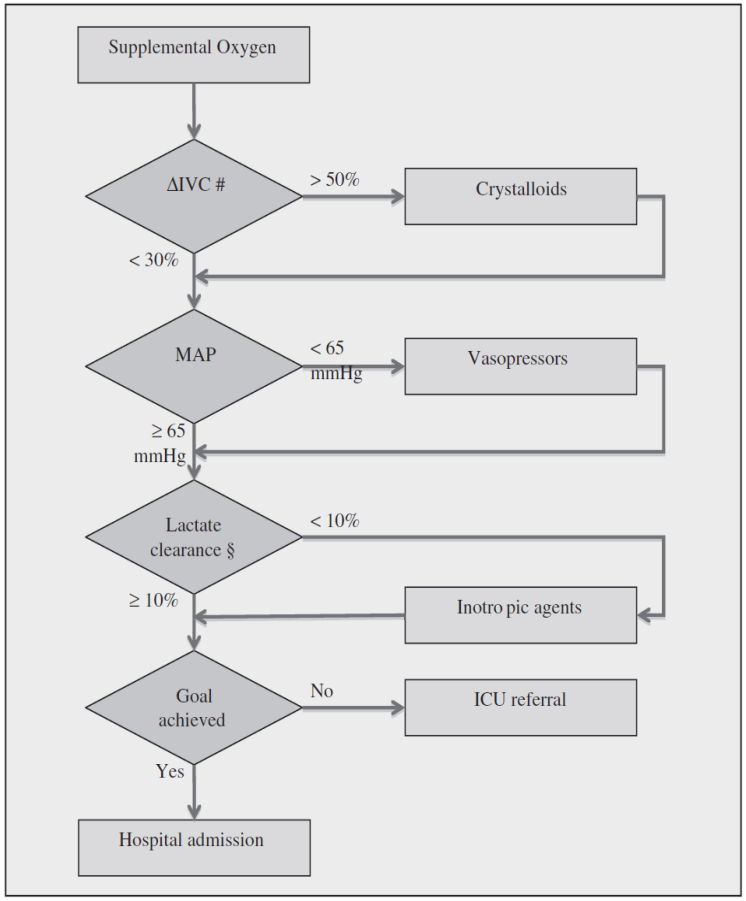
American Journal of Emergency Medicine 32 (2014) 563–568



	Patients (N = 47) [a]
CVC positioned (%)	61.7
Time to CVC (min)	154 [± 111]
Fluids administered (L)	5.2 [± 2.3]
Antibiotic within 1 h (%)	63.8
Antibiotic within 6 h (%)	100
Use of vasopressors (%)	53.1
CVP goal (%)	NA
ΔIVC between 30% and 50% (%) [b]	97.1
MAP >65 mm Hg (%)	89.4
$Scvo_2$ ≥70% (%)	NA
US pattern of lung interstitial syndrome (%)	27.7
Clinical overt pulmonary edema[c]	8.5
Lactate clearance >10% at 2 h (%)[d]	62.1
Lactate clearance >10% at 6 h (%)[d]	70.3
Positive hemocultures[e]	31.8
In-hospital mortality for cryptic shock (%)	23.1
In-hospital mortality for overt shock (%)	44.1
Total mortality at 28 d (%)	34
Total mortality at 60 d (%)	38.3

Conclusioni

- Negli ultimi 15 anni la gestione della sepsi severa/shock settico è notevolmente migliorata grazie all'applicazione del protocollo EGDT, ma anche grazie ad un più precoce trattamento antibiotico e ad una migliore gestione successiva al DEA (controllo glicemia, indicazioni all'emotrasfusione, ventilazione «lung protective»)
- L'efficacia del protocollo EGDT è comprovata da un unico studio randomizzato monocentrico e da studi osservazionali successivi

Conclusioni

- Esistono dei limiti oggettivi all'applicazione su larga scala del protocollo EGDT in tutti i DEA, prevalentemente correlati alla necessità di posizionare un CVC in tutti i pazienti
- Esistono crescenti perplessità relative all'utilizzo di alcuni goal fisiologici (fluid overload, PVC eccessivamente alta)
- Alcuni studi indicano che i vantaggi di un approccio protocol-drived alla fluid resuscitation possono essere conservati utilizzando goal fisiologici meno invasivi, purchè sia data la giusta importanza alla precocità del sospetto clinico e del trattamento empirico


Grazie