Sepsis Management Update 2014

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Objectives

Discuss 2014 Surviving Sepsis Campaign Guidelines

- Sepsis Screening
- Use of Procalcitonin
- Norepinephrine as first line vasopressor
- Fluid resuscitation

Review recently published ProCESS study

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Crit Care Med 2013; 41:580–637

Revision of the 2008 Surviving Sepsis Campaign (SSC) Guidelines

Six hour “resuscitation” bundle

- Central venous pressure 8 – 12 mm Hg
- Mean arterial pressure (MAP) ≥ 65 mm Hg
- Urine output ≥ 0.5 ml/kg/hr
- Central venous or mixed venous oxygen saturation 70% or 65% respectively
- *In patients with elevated lactate levels target resuscitation to normalize lactate*

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

A Randomized Clinical Trial

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

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

Table 5. Hospital Mortality and Length of Stay

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Care withdrawn, No. (%)	14 (9)	23 (15)		.15

Abbreviations: ICU, intensive care unit; $Scvo_2$, central venous oxygen saturation.
[a] Primary study end point.
[b] Continuous data are compared using an unpaired *t* test; categorical variables, using the χ^2 test.

Surviving Sepsis Campaign Guidelines 2012

Grades of Evidence

Grade 1A

- Glucose protocol (<180)
- Vent weaning SBT protocol
- Sedation protocol
- No renal dose dopamine
- No high-dose steroids
- Low tidal volume for ALI

Grade 1B

- Broad-spectrum antibiotics within 1 hour
- De-escalate antibiotics
- Initial resus with crystalloid
- Avoid hetastarch
- Norepinephrine 1st Line Pressor
- Avoid bicarbonate
- DVT/PUD prophylaxis
- Dobutamine for cardiac dysfunction

Grade 1C

- Avoid paralysis in absence of ARDS
- Early goal-directed therapy
- Cultures before antibiotics
- Early source identification
- Source control within 12 hours
- Consider limiting support
- 30 cc/kg IBW bolus for shock
- Conservative fluids for ARDS
- Avoid phenylephrine
- **Screening for Sepsis**

Dellinger RP, et al. *Crit Care Med.* 2013; 39:165-228

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Dellinger RP, et al. *Crit Care Med.* 2013; 39:165-228

B. Screening for Sepsis and Performance Improvement

1. We recommend routine screening of potentially infected seriously ill patients for severe sepsis to increase the early identification of sepsis and allow implementation of early sepsis therapy (grade 1C).

Rationale: Early intervention is dependent upon the early identification of sepsis

Early initiation of evidence based care has been shown to improve outcomes and decrease sepsis related mortality

Three Step Sepsis Screening Tool
Done Twice Each Day

SICU Bedside Nurse
SIRS score

patient label

10232007

current heart rate _____ time _____
T min _____ time _____
T max _____ time _____
current resp rate _____ time _____
latest WBC count _____ date, time _____

points	0	1	2	3	4
heart rate (bpm)	70 - 109		55 – 69 110 – 139	40 - 54 140 - 179	≤ 39 ≥ 180
T (°C) min		34 – 35.9	32 – 33.9	30 – 31.9	≤ 29.9
T (°C) max	36 – 38.4	38.5 – 38.9		39 – 40.9	≥ 41
T (°F) min		93.1 – 96.6	89.6 – 93.0	86 – 89.5	≤ 85.9
T (°F) max	96.8 – 101.1	101.2 – 102.0		102.1 – 105.6	≥ 105.7
resp rate (br / min)	12 - 24	10 – 11 25 - 34	6 - 9	35 – 49	≤ 5 ≥ 50
latest WBC (kcell / mm^3)	3 – 14.9	15 – 19.9	1 – 2.9 20 – 39.9		< 1 ≥ 40
score (total points)					

If SIRS score ≥ 4, then notify SICU Nurse Practitioner to complete sepsis screening form.

☐ SICU
☐ overflow ☐ MICU ☐ NICU ☐ CCU

Completed by: _____, RN Date / time: _____

Performance improvement review by SICU Medical Director or designee:

☐ sepsis (Phase 1) ☐ severe sepsis (Phase 2) ☐ septic shock (Phase 2)

Start sepsis management protocol ☐ Yes ☐ No

Comments:

_____
_____
_____

Signature: _____, MD Date / time: _____

This form is not a part of the patient's medical record.
Return all completed forms to SICU Nurse Practitioner office.

SICU Nurse Practitioner
Sepsis Screening

1. Vascular access? Yes No

type	dialysis	triple / quad	PICC	port	tunneled	other (IV, art)
date placed						
site						
local finding						
blood culture finding						

Suspicion of: line infection? Yes No

2. Clinical pulmonary infection score (CPIS)

Variable		points
temperature (°C)	time (hhmm)	
36.5 – 38.4		0
38.5 – 38.9		1
> 39.0 or < 36.0		2
blood leukocyte count (# per mm^3)	time (hhmm)	
4,000 – 11,000		0
< 4,000 or > 11,000		1
tracheal secretions	time (hhmm)	
small		0
moderate		1
large		2
purulent (add 1 point if purulent)		+1
oxygenation (PaO_2/FiO_2)	time (hhmm)	
≥ 240 or presence of ARDS		0
< 240 and absence of ARDS		2
chest radiograph	time (hhmm)	
no infiltrate		0
patchy or diffuse infiltrate		1
localized infiltrate		2

score

Intubated / mech vent support? Yes No

date intubated:

pneumonia? Yes No

3. Abdomen

recent abdominal surgery?	Yes	No
abdominal pain?	Yes	No
abdominal distention?	Yes	No
purulent drainage from surgical drains?	Yes	No
intolerance to enteral nutrition?	Yes	No

abdominal infection? Yes No

4. Skin / soft tissue

erythema / drainage from other surgical site?	Yes	No
site		

cellulitis / soft tissue infection? Yes No

5. Urinary tract

urinary catheter?	Yes	No
date placed		
latest urinalysis / urine culture results		

UTI? Yes No

6. Other site

site	

other infection? Yes No

Completed by: _____, NP Date / time: _____

Validation of a Screening Tool for the Early Identification of Sepsis

Laura J. Moore, MD, Stephen L. Jones, MD, Laura A. Kreiner, MD, Bruce McKinley, PhD, Joseph F. Sucher, MD, S. Rob Todd, MD, Krista L. Turner, MD, Alicia Valdivia, RN, and Frederick A. Moore, MD

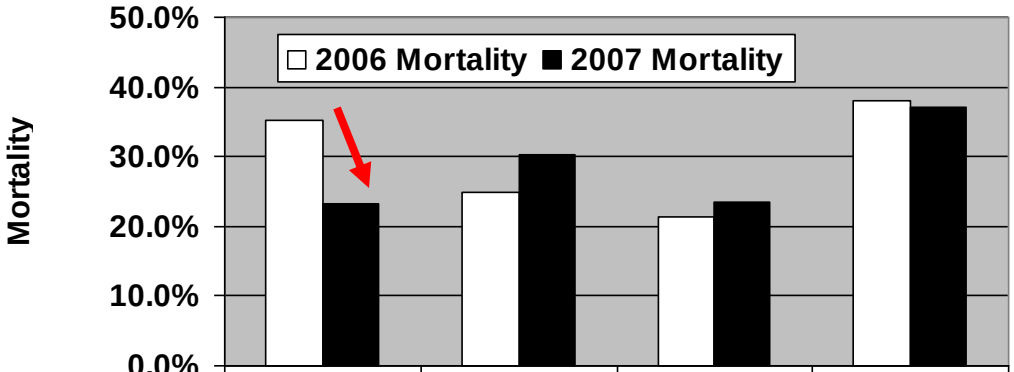
J Trauma. 2009;66:1539–1547.

The Journal of TRAUMA® *Injury, Infection, and Critical Care*

Early Screening and Implementation of Evidence Based Care

TMH Performance Improvement

Mortality for Severe Sepsis/Septic Shock by Unit



	Surg ICU	ER	CV ICU	Med ICU
□ 2006 Mortality	35.1%	25.0%	21.4%	38.0%
■ 2007 Mortality	23.3%	30.3%	23.5%	37.2%

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What is procalcitonin?

- 116-amino acid peptide
- Biomarker that responds to both infection & inflammation
- Can it be used to differentiate sepsis from SIRS?
- Could this be of benefit in sepsis identification?

Should Procalcitonin be Introduced in the Diagnostic Criteria for the Systemic Inflammatory Response Syndrome and Sepsis?

Evangelos J. Giamarellos-Bourboulis, Panagiota Giannopoulou, Paraskevi Grecka, Dionyssios Voros, Konstantinos Mandragos, and Helen Giamarellou

Journal of Critical Care, Vol 19, No 3 (September), 2004: pp 152-157

Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: A systematic review and meta-analysis

Bernard Uzzan, MD; Régis Cohen, MD, PhD; Patrick Nicolas, PharmD, PhD; Michel Cucherat, MD; Gérard-Yves Perret, MD, PhD

Crit Care Med 2006 Vol. 34, No. 7

Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis

Benjamin M P Tang, Guy D Eslick, Jonathan C Craig, Anthony S McLean

Lancet Infect Dis 2007; 7: 210–17

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Procalcitonin does not CLEARLY differentiate between the acute inflammatory pattern of sepsis and other causes of generalized inflammation (such as post-operative inflammation)

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Dellinger RP, et al. *Crit Care Med.* 2013; 39:165-228

Vasopressors

- Target mean arterial pressure of 65 mmHg
- Norepinephrine is now 1st choice
- Vasopressin 0.03 units/minute can be added to norepinephrine
- Vasopressin should not exceed 0.04 units/minute
- Dopamine only in highly selective patients

Why not dopamine?

TABLE 7. Norepinephrine Compared With Dopamine in Severe Sepsis Summary of Evidence

Norepinephrine compared with dopamine in severe sepsis

Patient or population: Patients with severe sepsis
Settings: Intensive care unit
Intervention: Norepinephrine
Comparison: Dopamine
Sources: Analysis performed by Djillali Annane for Surviving Sepsis Campaign using following publications: De Backer D. *N Engl J Med* 2010; 362:779–789; Marik PE. *JAMA* 1994; 272:1354–1357; Mathur RDAC. *Indian J Crit Care Med* 2007; 11:186–191; Martin C. Chest 1993; 103:1826–1831; Patel GP. *Shock* 2010; 33:375–380; Ruokonen E. *Crit Care Med* 1993; 21:1296–1303

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Assumed Risk	Corresponding Risk				
	Dopamine	Norepinephrine				
Short-term mortality	530 per 1000	Study population 482 per 1000 (440 to 524)	RR 0.91 (0.83 to 0.99)	2043 (6 studies)	⊕⊕⊕⊖ moderate[b,c]	
Serious adverse events —Supraventricular arrhythmias	229 per 1000	Study population 82 per 1000 (34 to 195)	RR 0.47 (0.38 to 0.58)	1931 (2 studies)	⊕⊕⊕⊖ moderate[b,c]	
Serious adverse events —Ventricular arrhythmias	39 per 1000	Study population 15 per 1000 (8 to 27)	RR 0.35 (0.19 to 0.66)	1931 (2 studies)	⊕⊕⊕⊖ moderate[b,c]	

[a]The assumed risk is the control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI = confidence interval, RR = risk ratio.

[b]Strong heterogeneity in the results ($I^2 = 85\%$), however this reflects degree of effect, not direction of effect. We have decided not to lower the evidence quality.

[c]Effect results in part from hypovolemic and cardiogenic shock patients in De Backer, *N Engl J Med* 2010. We have lowered the quality of evidence one level for indirectness.

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Dellinger RP, et al. *Crit Care Med.* 2013; 39:165-228

Fluid Resuscitation in Sepsis

- Crystalloids are the first line agent
  - Absence of clear benefit with colloids
  - ALBIOS showed improved survival with albumin in septic shock subgroup
- Recommend 30 cc/kg IBW for shock
- Avoid hydroxyethyl starch solutions

Why not HES?

CRYSTMAS: septic shock patients, no difference in mortality with HES vs. 0.9% NS (31% vs. 25.3%, *p* = 0.37); however the study was underpowered to detect the 6% difference in absolute mortality observed.

6S Trial: septic patients, ***increased mortality rates with 6% HES*** vs Ringer's acetate (51% vs. 43% *p* = 0.03).

CHEST: ICU patients, no 90-d mortality difference with 6% HES vs. 0.9% NS, *n* = 7000 (18% vs. 17%, *p* = 0.26); ***the need for renal replacement therapy was higher in the HES group (7.0% vs. 5.8%; RR 1.21; 95% CI 1.00−1.45; p = 0.04).***

CRISTAL: ICU pts, crystalloid vs. any colloids, Europe, n=2857 pts, no difference in mortality

ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

1818 severe sepsis cases, 100 hospitals

Randomized to albumin or crystalloid

N ENGL J MED 370;15 NEJM.ORG APRIL 10, 2014

Study design

Pts. with severe sepsis or septic shock (6-24 hr)

Positioning of arterial and central venous line
(if not performed earlier)

Randomization

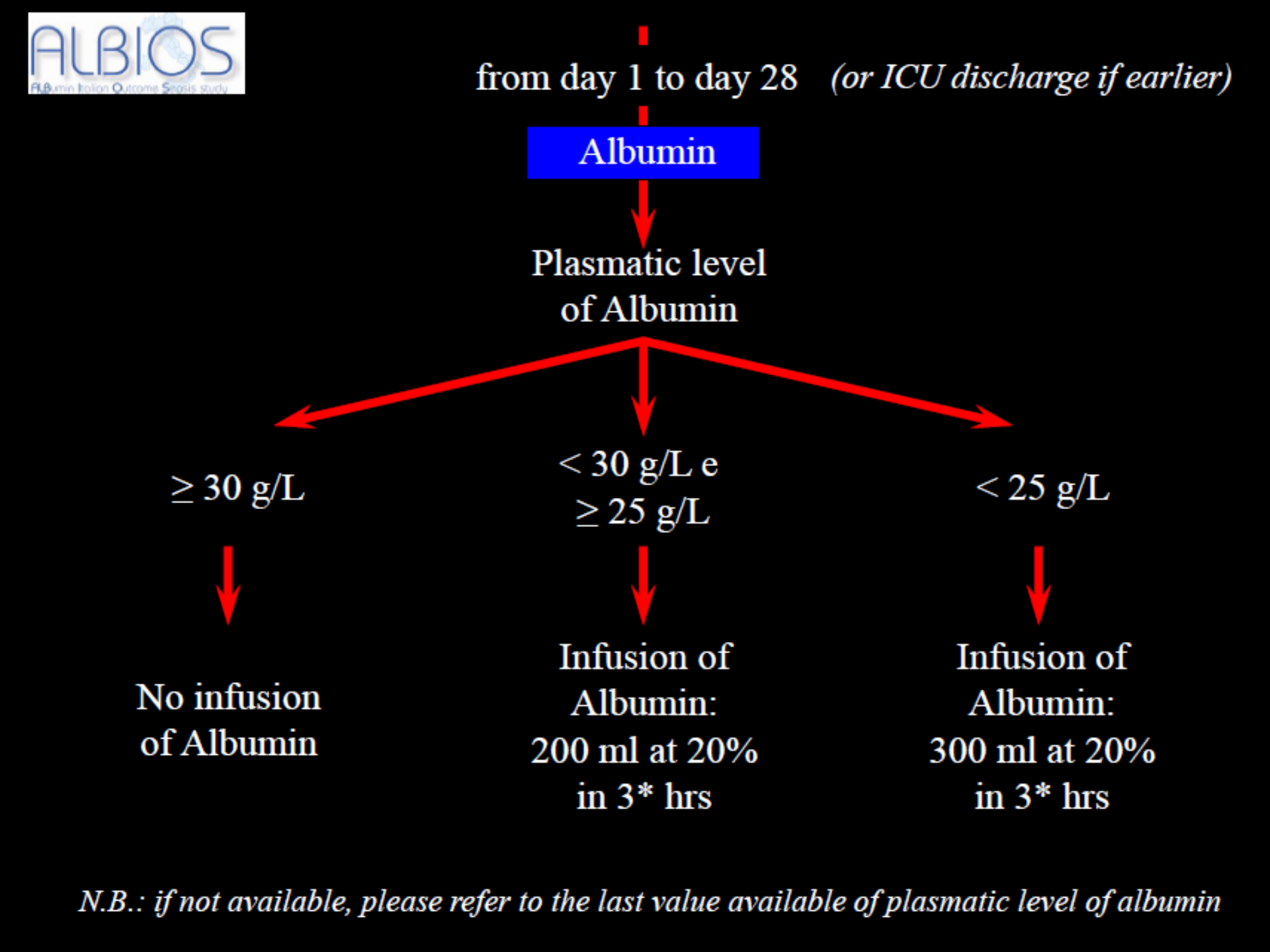
Volume replacement
[Rivers' protocol]

Albumin

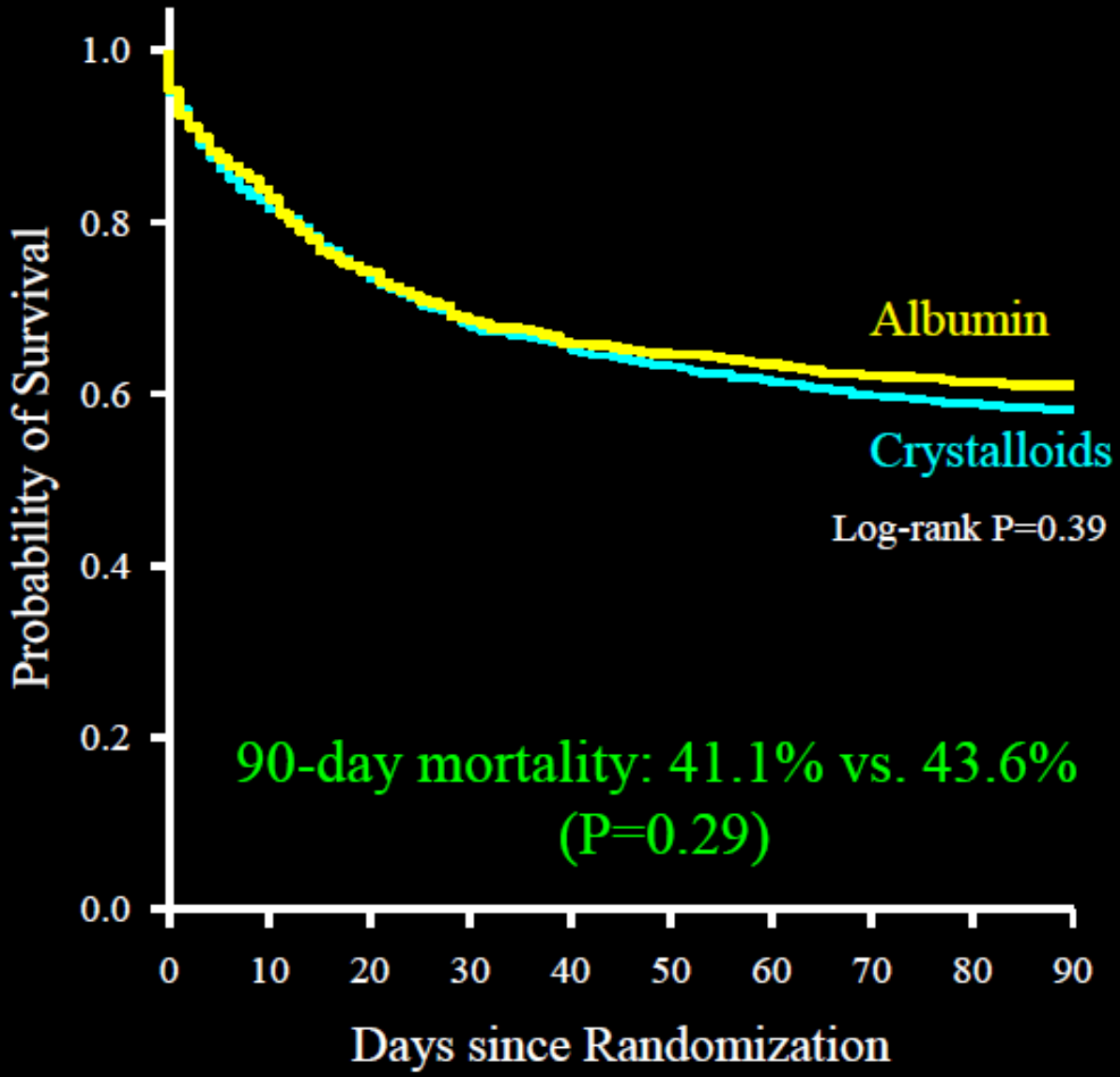
Albumin:
[300 ml at 20% in 3* hrs]
+
crystalloids

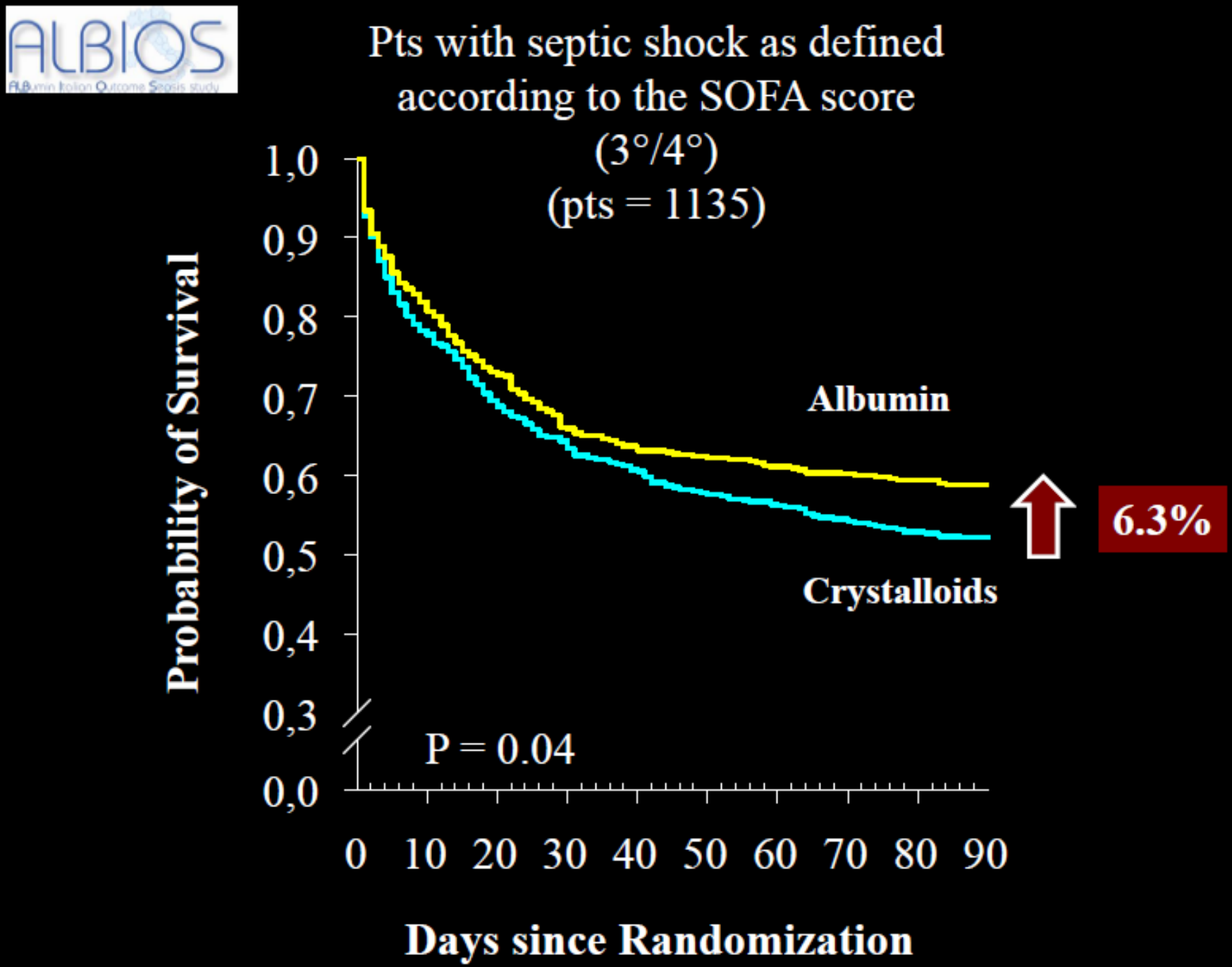
Crystalloids

crystalloids


ALBIOS
ALBumin Italian Outcome Sepsis study
from day 1 to day 28 (or ICU discharge if earlier)
Albumin
Plasmatic level of Albumin
≥ 30 g/L
< 30 g/L e ≥ 25 g/L
< 25 g/L
No infusion of Albumin
Infusion of Albumin: 200 ml at 20% in 3* hrs
Infusion of Albumin: 300 ml at 20% in 3* hrs
N.B.: if not available, please refer to the last value available of plasmatic level of albumin

Overall population
(*1810 pts*)




ALBIOS
ALBumin Italian Outcome Sepsis study
Pts with septic shock as defined according to the SOFA score (3°/4°) (pts = 1135)
Probability of Survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,0
Albumin
Crystalloids
6.3%
P = 0.04
0 10 20 30 40 50 60 70 80 90
Days since Randomization

Conclusions

In patients with sepsis albumin infusion compared to crystalloids alone provided hemodynamic advantages, and more favorable fluid balance without survival benefits.

In patients with septic shock, as recognized at entry, hemodynamic fluid balance advantages were greater than in general population and, in addition, these patients survived significantly more at 90 days.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

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

The ProCESS Investigators*

Study Objectives:

- To determine if early goal directed therapy (EGDT) as described by Rivers et al is generalizable
- To determine which EGDT protocol elements are necessary

Assigned Interventions

Procedure: Early Goal Directed Therapy (EGDT)

Subjects will have a CVC inserted for continuous monitoring of their CVP and Scv02. Early structured treatment will be provided based on subjects' CVP, mean arterial pressure (MAP) and Scv02 measurements.

Procedure: Protocolized Standard Care (PSC)

Routine equipment will be used to monitor subjects' blood pressure and oxygen levels. Early structured treatment is based on the subjects' systolic blood pressure and the study doctors' judgment of fluid status and perfusion status.

Procedure: Usual Care (UC)

Attending physicians will provide routine care to subjects. Study measurements and treatments will be based on the physicians'/sites' standard practices.

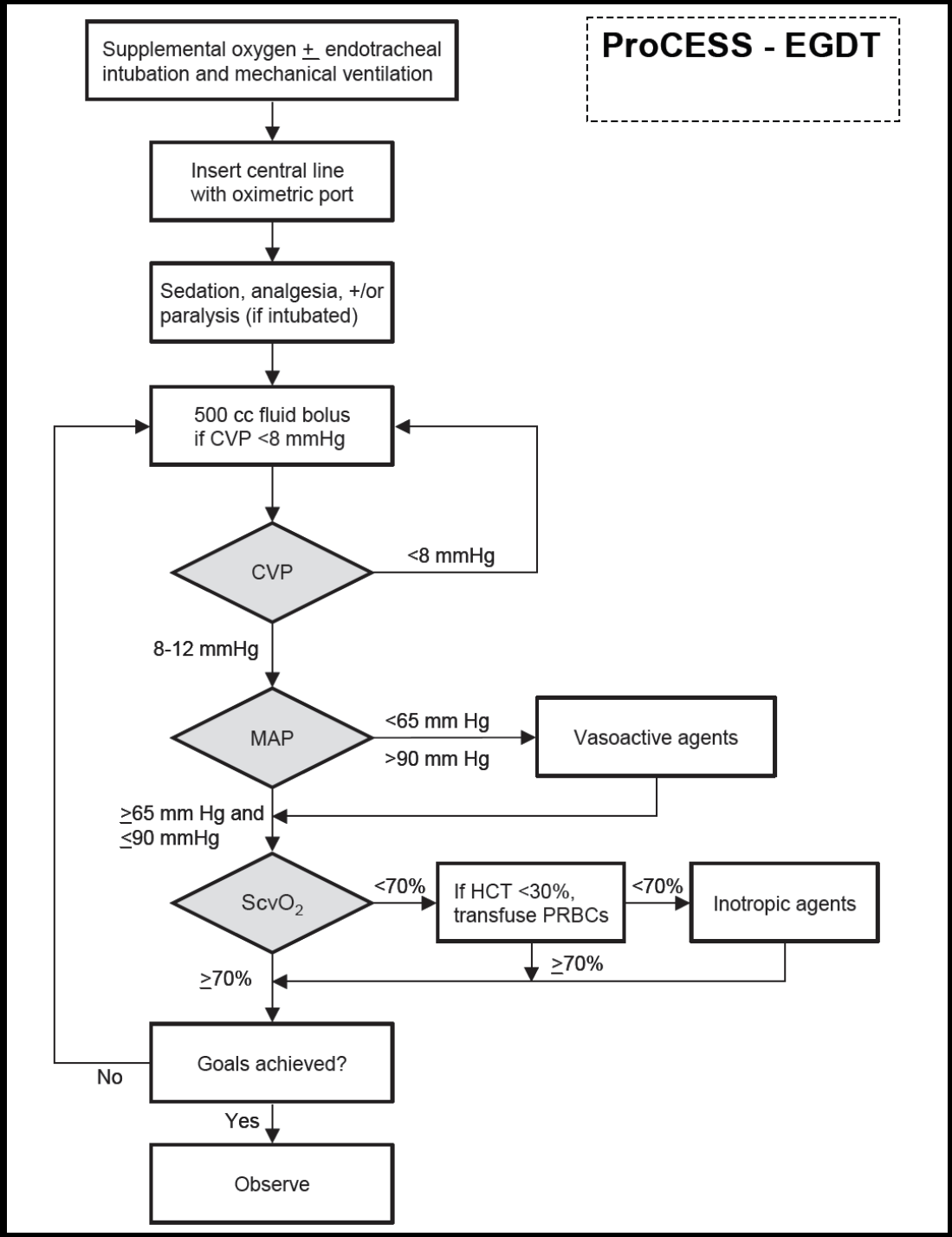
Validation Study
Multicenter Trial
20 sites

ProCESS
Protocolized Care for Early Septic Shock
NIH-sponsored
$8.4 Million

Derek Angus et al.
Univ. of Pittsburgh

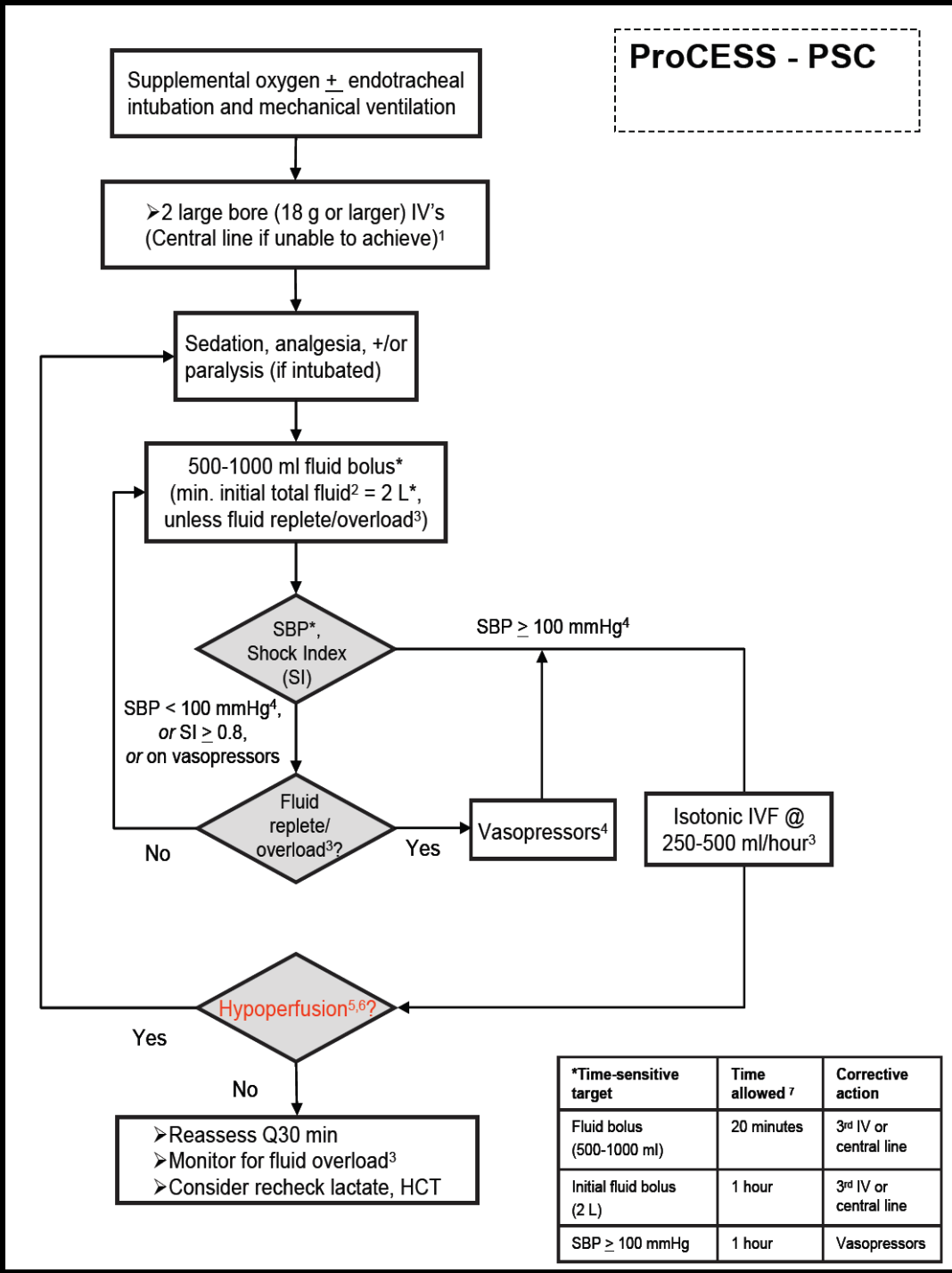
ProCESS EGDT

- Similar to Rivers protocol
- Same goal as Rivers protocol:
- ScvO2 ≥ 70%
- Blood tx to keep Hct > 30%
- No arterial line



Protocolized Standard Care

- No CVP monitoring
- No central venous oximetric catheter
- No ScvO2 goal
- SBP/perfusion monitoring
- Target Hb 7 g/dL
- No arterial line



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

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- N=1341, 31 U.S. Emergency Depts
- **Protocol-based EGDT, n=439**
- **Protocol-based standard therapy,n=446**
- **Usual care, n=456**

ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

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

The ProCESS Investigators*

- Mortality at 60 days:
- **Protocol-based EGDT group (21.0%)**
- **Protocol-based standard-therapy group (18.2%)**
- **Usual-care group (18.9%)**
- Protocol-based therapy vs. usual care
  - RR 1.04; 95% CI, 0.82 to 1.31; P = 0.83
- Protocol-based EGDT vs. protocol-based standard therapy
  - RR 1.15; 95% CI, 0.88 to 1.51; P = 0.31
- No significant differences in 90-day mortality, 1-year mortality, or the need for organ support.

Table 1. Differences in Mortality and Key Clinical Values in the EGDT Study and the ProCESS Study.*

Variable	EGDT Study		ProCESS Study		
	EGDT Group	Control Group	EGDT Group	Protocol-Based Standard-Therapy Group	Usual-Care Group
Predicted mortality on the basis of APACHE II score (%)	40.3	36.9	38.2	37.5	37.9
Actual mortality (%)	30.5	46.5	21.0	18.2	18.9
Lactate (mmol/liter)					
At 0 hr	7.7	6.9	4.8	5.0	4.8
At 6 hr	4.3	4.9	NR	NR	NR
Central venous oxygen saturation (%)					
At 0 hr	48.6	49.2	71.0	NA	NA
At 6 hr	77.3	66.0	NR	NA	NA
Central-catheter rate at 6 hr (%)	100	100	93.6	56.5	57.9

* APACHE denotes Acute Physiology and Chronic Health Evaluation, NA not applicable, and NR not reported.

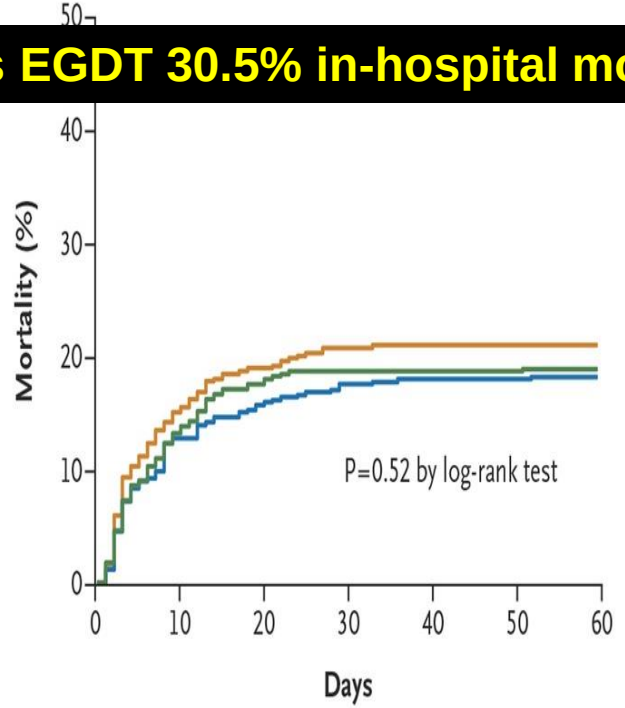
*Average amount of crystalloids given in first 6 hours by group

EGDT 2.8 Liters
PSC 3.3 Liters
UC 2.3 Liters

ProCESS: Cumulative Mortality

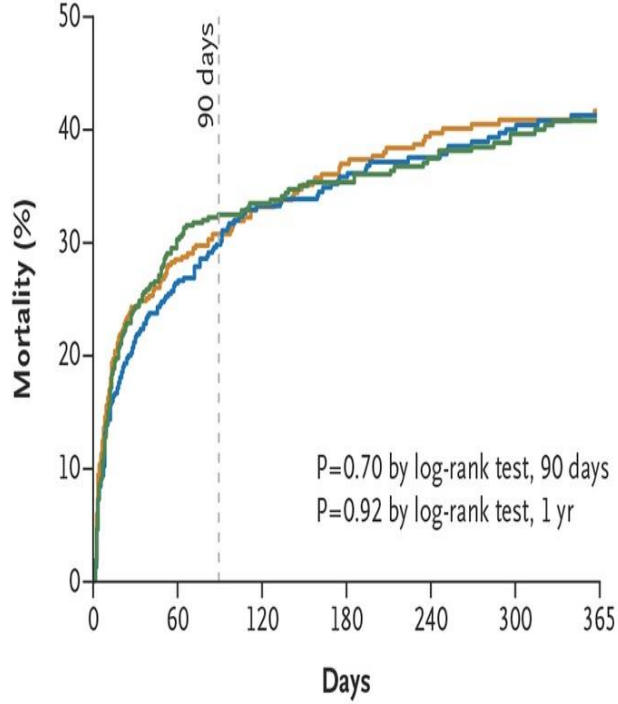
Rivers EGDT 30.5% in-hospital mortality

A Cumulative In-Hospital Mortality to 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



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

Protocol-based EGDT — Protocol-based standard therapy — Usual care

The ProCESS Investigators. N Engl J Med 2014;370:1683-1693

ProCESS Investigator Conclusions

Protocol-based resuscitation of patients diagnosed with septic shock in the ER did not improve outcomes.

ProCESS Investigator Conclusions

Protocol-based resuscitation of patients diagnosed with septic shock in the ER did not improve outcomes.

SHOULD WE ABANDON EGDT???

Important Caveats

- Patients in all groups received an average of > 2 liters of fluid
- >75% of patients received antibiotics prior to randomization into the study
- The 18% mortality rate in the “usual care” groups is much lower than the septic shock mortality rate of 46.5% reported in Rivers original trial
- The majority of patients had central lines inserted

Should we abandon EGDT?

- Early diagnosis and early intervention remain critical
- Two large ongoing trials may clarify
  - ARISE (Australian Resusciation in Sepsis Evaluation RCT)
  - ProMISe (Protocolised Management in Sepsis Trial)

Summary

- Sepsis screening aids in early recognition
- Early, evidence based care is critical
- Procalcitonin is non-specific, not useful
- Norepinephrine is now first line agent
- Fluid bolus 30 cc/kg IBW for septic shock
- ProCESS study has limitations

QUESTIONS?