

# *Shock settico e sepsi: diagnosi e gestione terapeutica*

C.A. Volta

U.O. Anestesia e Rianimazione Universitaria

# Intanto bisogna capire di cosa parliamo!

Clinical Review & Education

Special Communication | **CARING FOR THE CRITICALLY ILL PATIENT**

## The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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EDITORIAL

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## New Definitions for Sepsis and Septic Shock Continuing Evolution but With Much Still to Be Done

Edward Abraham, MD



# Old definitions

- Sepsis : infection + SIRS
- Severe sepsis : sepsis + sepsis -induced organ dysfunction or tissue hypoperfusion
- Septic shock : sepsis -induced hypotension persisting despite adequate fluid resusciation

# Sepsis

According to the new definitions, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection clinically characterized by an acute change of 2 points or greater in the SOFA score



Table 1. Variables for Candidate Sepsis Criteria Among Encounters With Suspected Infection

Systemic Inflammatory Response Syndrome (SIRS) Criteria (Range, 0-4 Criteria)	Sequential [Sepsis-related] Organ Failure Assessment (SOFA) (Range, 0-24 Points)	Logistic Organ Dysfunction System (LODS) (Range, 0-22 Points) <sup>a</sup>	Quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) (Range, 0-3 Points)
Respiratory rate, breaths per minute	Pao <sub>2</sub> /Fio <sub>2</sub> ratio	Pao <sub>2</sub> /Fio <sub>2</sub> ratio	Respiratory rate, breaths per minute
White blood cell count, 10 <sup>9</sup> /L	Glasgow Coma Scale score	Glasgow Coma Scale score	Glasgow Coma Scale score
Bands, %	Mean arterial pressure, mm Hg	Systolic blood pressure, mm Hg	Systolic blood pressure, mm Hg
Heart rate, beats per minute	Administration of vasopressors with type/dose/rate of infusion	Heart rate, beats per minute	
Temperature, °C	Serum creatinine, mg/dL, or urine output, mL/d	Serum creatinine, mg/dL	
Arterial carbon dioxide tension, mm Hg	Bilirubin, mg/dL	Bilirubin, mg/dL	
	Platelet count, 10 <sup>9</sup> /L	Platelet count, 10 <sup>9</sup> /L	
		White blood cell count, 10 <sup>9</sup> /L	
		Urine output, L/d	
		Serum urea, mmol/L	
		Prothrombin time, % of standard	

Abbreviation: Fio<sub>2</sub>, fraction of inspired oxygen.

<sup>a</sup> Measurement units for LODS variables per original description by Le Gall et al.<sup>9</sup>



## Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Assessment  
For  
for SChristoph  
André Sch  
Clifford S.

**MAIN OUTCOMES AND MEASURES** For construct validity, pairwise agreement was assessed. For predictive validity, the discrimination for outcomes (primary: in-hospital mortality; secondary: in-hospital mortality or intensive care unit [ICU] length of stay  $\geq 3$  days) more common in sepsis than uncomplicated infection was determined. Results were expressed as the fold change in outcome over deciles of baseline risk of death and area under the receiver operating characteristic curve (AUROC).

D. Rea, MD, MPH;  
FRCP;

**IMPORTANCE** The Third International Consensus Definitions Task Force defined sepsis as "life-threatening organ dysfunction due to a dysregulated host response to infection." The performance of clinical criteria for this sepsis definition is unknown.

**OBJECTIVE** To evaluate the validity of clinical criteria to identify patients with suspected infection who are at risk of sepsis.

**DESIGN, SETTINGS, AND POPULATION** Among 1.3 million electronic health record encounters from January 1, 2010, to December 31, 2012, at 12 hospitals in southwestern Pennsylvania, we identified those with suspected infection in whom to compare criteria. Confirmatory analyses were performed in 4 data sets of 706 399 out-of-hospital and hospital encounters at 165 US and non-US hospitals ranging from January 1, 2008, until December 31, 2013.

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# Results

Among **ICU encounters** in the validation cohort (n=7932 with suspected infection, of whom 16% died), the predictive validity for in-hospital mortality **was lower for SIRS** (AUROC 0,64) and **qSOFA** (AUROC 0,66) vs **SOFA** (AUROC 0,74) or **LODS** (AUROC 0,75)

# Results

Among **non-ICU** encounters in the validation cohort (n=66.522 with suspected infection, of whom 3% died), **qSOFA** had predictive validity (AUROC 0,81) that **was greater than** SOFA (AUROC 0,79) and SIRS (AUROC 0,76)



# qSOFA

Hypotension  
Systolic BP  
<100 mmHg

Altered  
Mental  
Status

Tachypnea  
RR >22/Min

Score of ≥2 Criteria Suggests a Greater Risk of a Poor Outcome

Modified Early Warning Score							
Vital sign	3	2	1	0	1	2	3
Systolic blood pressure (mmHg)	< 70	71-80	81-100	101-199		≥ 200	
Heart rate (bpm)		< 40	41-50	51-100	101-110	111-129	≥ 130
Respiratory rate (bpm)		< 9		9-14	15-20	21-29	≥ 30
Temperature (C)		< 35		35-38.4		≥ 38.5	
AVPU				Alert	React to Voice	React to Pain	Unresponsive
Glasgow Coma Scale				14-15	10-13	4-9	3

MEVS > 5

Subbe CP, Duller B, Bellomo R. Effect of an automated notification system for deteriorating ward patients on clinical outcomes. Crit Care. 2017;21:52.

# Septic shock

Defined as a subset of sepsis in which circulatory, cellular, and metabolic abnormalities are associated with greater risk of mortality than sepsis alone

# Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit

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in-hospital mortality was highest for NEWS (area under the curve [AUC], 0.77; 95% confidence interval [CI], 0.76–0.79), followed by MEWS (AUC, 0.73; 95% CI, 0.71–0.74), qSOFA (AUC, 0.69; 95% CI, 0.67–0.70), and SIRS (AUC, 0.65; 95% CI, 0.63–0.66) ( $P < 0.01$

**Conclusions:** Commonly used early warning scores are more accurate than the qSOFA score for predicting death and ICU transfer in non-ICU patients. These results suggest that the qSOFA score should not replace general early warning scores when risk-stratifying patients with suspected infection.



# Septic shock – clinical criteria

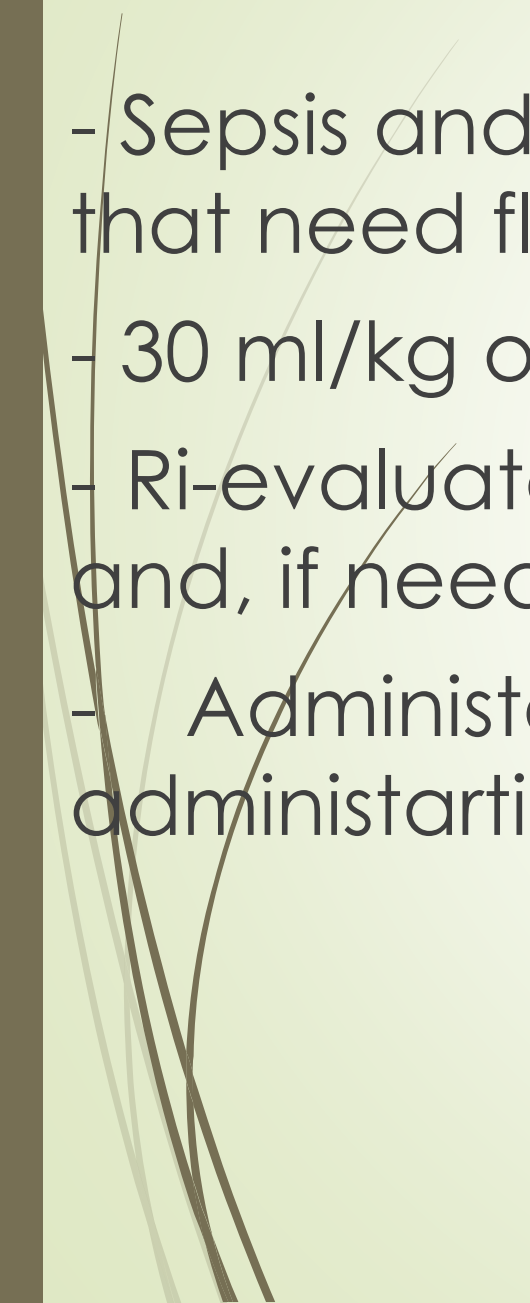
- Sepsis with fluid-unresponsive hypotension
- Need for vasopressors to maintain mean arterial pressure  $> 65$  mmHg
- Serum lactate level  $> 2$  mmol/L



*What to do in patients with  
septic shock?*

# Fluids therapy



- Sepsis and septic shock: medical emergencies that need fluids ASAP!
  - 30 ml/kg of crystalloids in the first 3 hours
  - Re-evaluate frequently haemodynamics variables and, if needed, give more fluids!
  - Administer albumin in case of elevated administration of crystalloids. (weak evidence)
- 

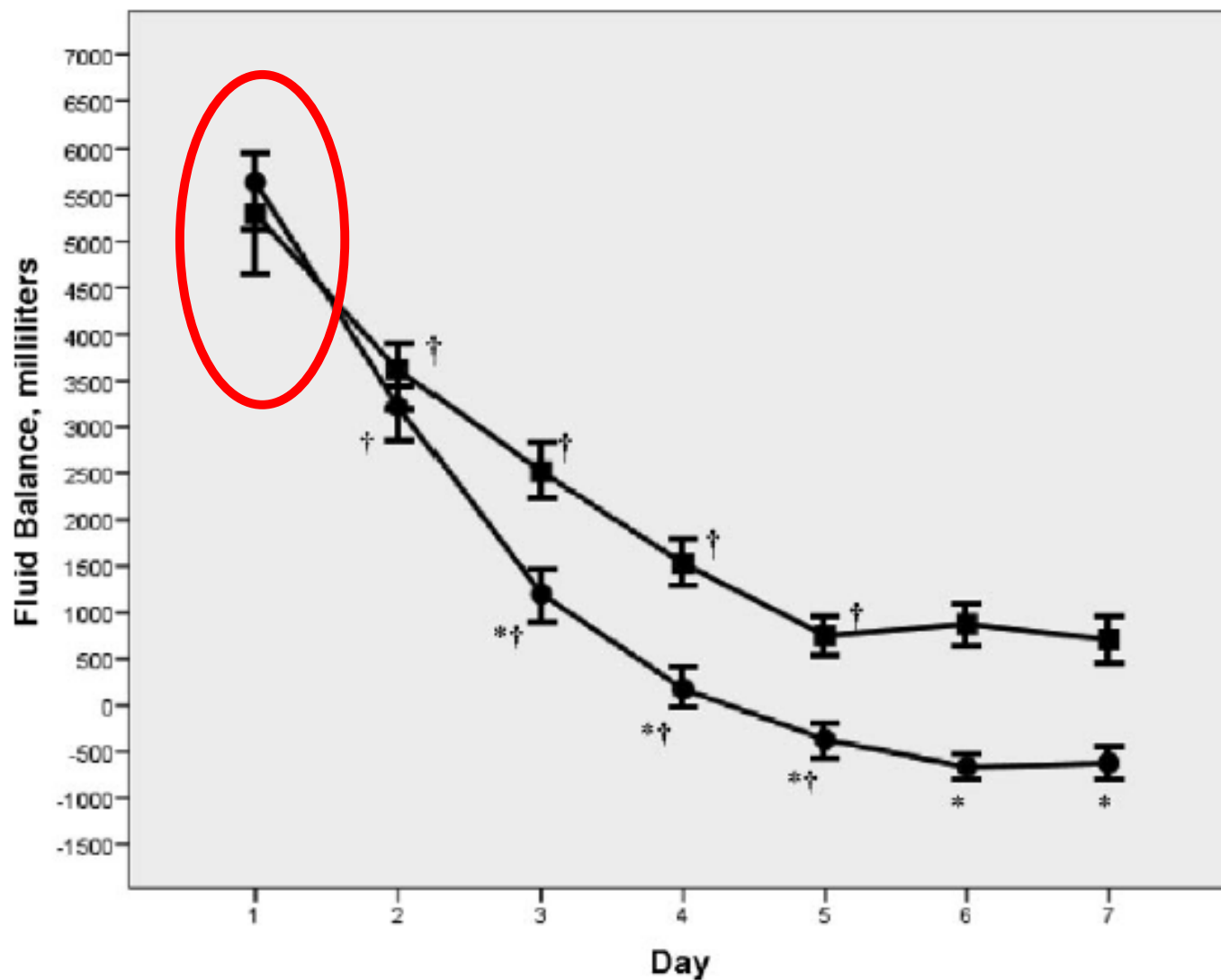


FIGURE 1. Mean ( $\pm$  SE) daily fluid balance (in milliliters) for days 1 through 7 following the onset of septic shock. Nonsurvivors are depicted by squares, and survivors by circles. \* =  $p < 0.05$  pairwise compared between survivors and nonsurvivors (ANOVA for repeated measures); † =  $p < 0.05$  compared with the previous time point (ANOVA for repeated measures).



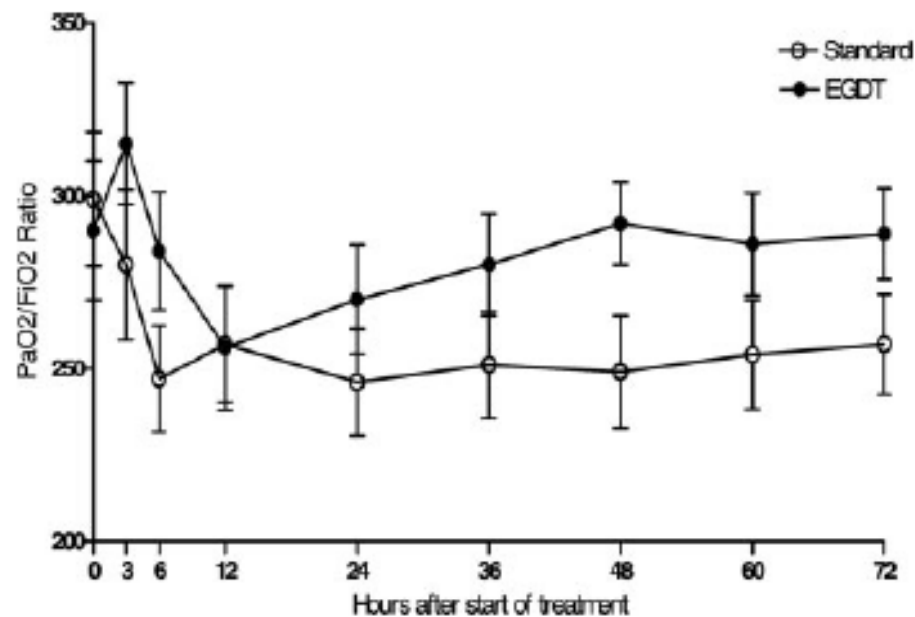


FIGURE 4. Comparing the PaO<sub>2</sub>/fraction of inspired oxygen (FIO<sub>2</sub>) ratios between the EGDT and standard-care groups. Despite more volume resuscitation in the EGDT group during initial 6 h, there was no net difference in PaO<sub>2</sub>/FIO<sub>2</sub> ratio ( $p = 0.34$ ).

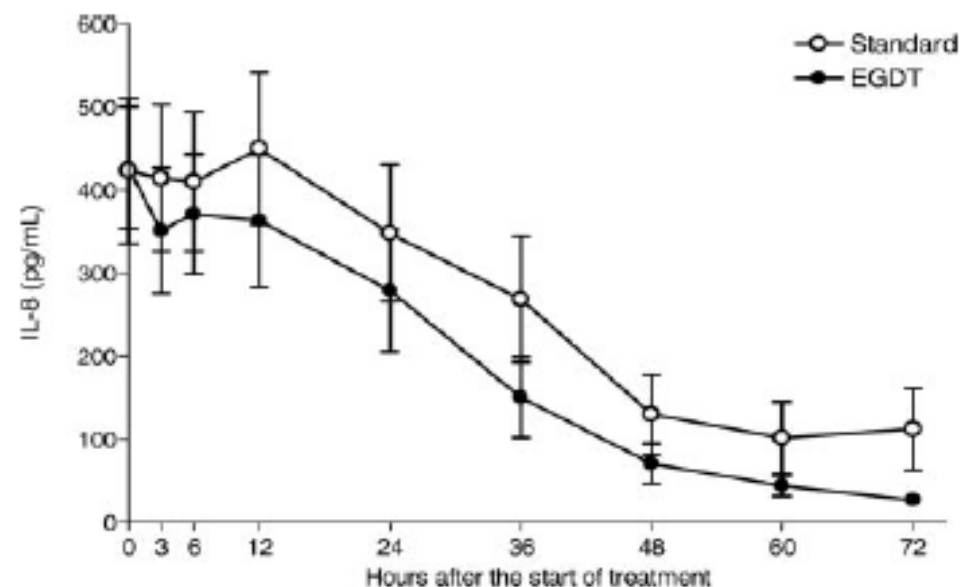


FIGURE 5. The effect of EGDT on inflammation. EGDT effects on inflammation (IL-8) associated with ALI. EGDT patients had a corresponding lower level of IL-8 and a decreased rate of mechanical ventilation in the subsequent 7 to 72 h time period ( $p = 0.045$ ).

(CHEST 2006; 130:1579–1595)

# Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis\*

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**Design:** A retrospective cohort study of patients admitted with sepsis, not undergoing any surgical procedures, and treated in an ICU by hospital day 2. We used propensity score matching to control for confounding and compared the following outcomes after resuscitation with balanced versus with no-balanced fluids: in-hospital mortality, acute renal failure with and without dialysis, and hospital and ICU lengths of stay. We also estimated the dose-response relationship between receipt of increasing proportions of balanced fluids and in-hospital mortality.

**Conclusions:** Among critically ill adults with sepsis, resuscitation with balanced fluids was associated with a lower risk of in-hospital mortality. If confirmed in randomized trials, this finding could have significant public health implications, as crystalloid resuscitation is nearly universal in sepsis.

ORIGINAL ARTICLE

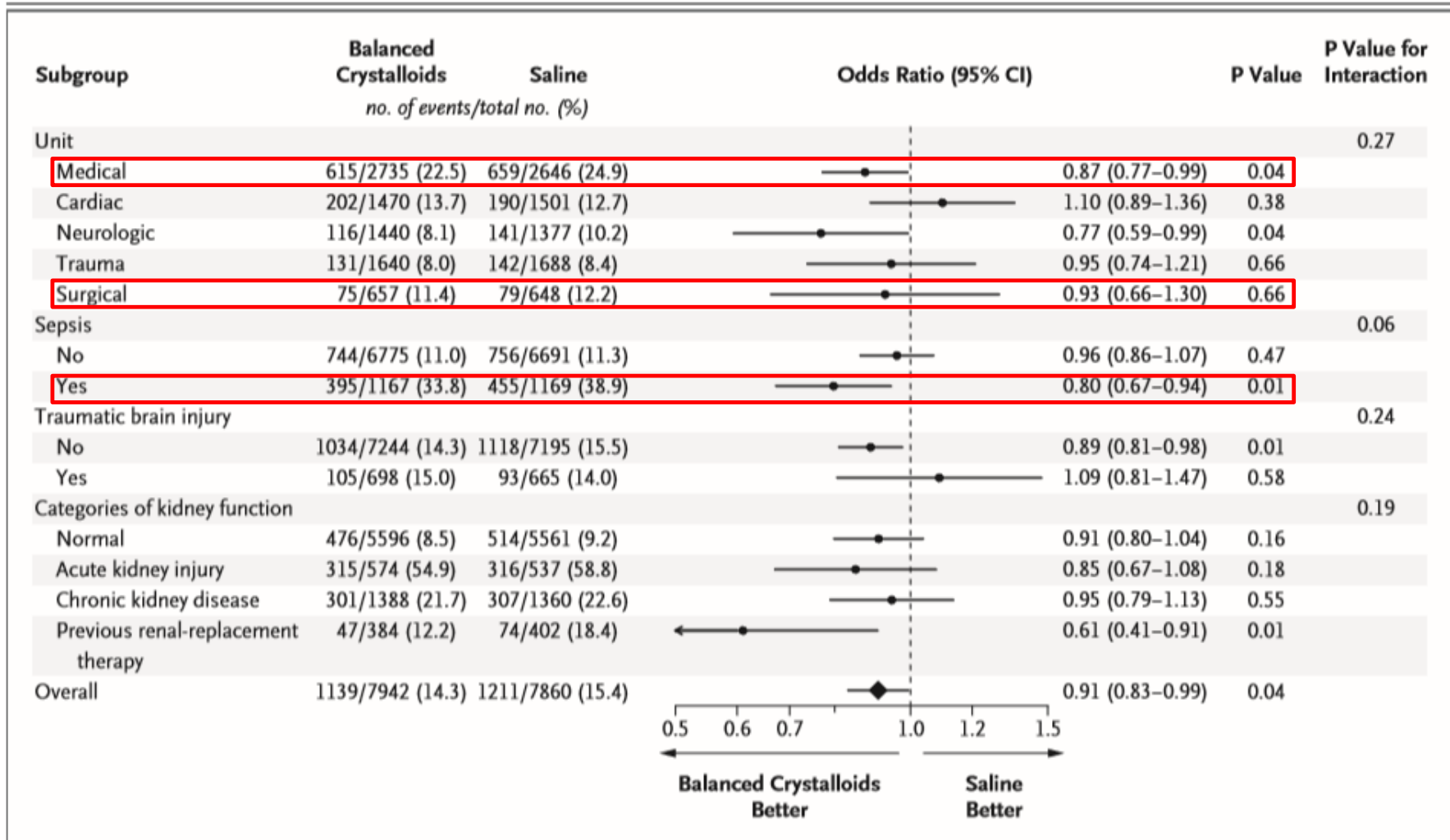
## Balanced Crystalloids versus Saline in Critically Ill Adults

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### CONCLUSIONS

Among critically ill adults, the use of balanced crystalloids for intravenous fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction than the use of saline. (Funded by the Vanderbilt Institute for Clinical and Translational Research and others; SMART-MED and SMART-SURG ClinicalTrials.gov numbers, NCT02444988 and NCT02547779.)



**Figure 3.** Subgroup Analysis of Rates for the Composite Outcome of Death, New Receipt of Renal-Replacement Therapy, or Persistent Renal Dysfunction.



# Fluids therapy

**Do not use HES in presence of septic shock.**

**Do not use gelatins**

**Use crystalloids**

HESs are colloids for which there are safety concerns in patients with sepsis. A meta-analysis of nine trials (3456 patients) comparing 6% HES 130/0.38–0.45 solutions to crystalloids or albumin in patients with sepsis showed no difference in all-cause mortality (RR 1.04; 95% CI 0.89–1.22) [250]. However, when low risk of bias trials were analyzed separately, HES use resulted in higher risk of death compared to other fluids (RR 1.11; 95% CI 1.01–1.22; high-quality evidence), which translates to 34 more deaths per 1000 patients. Furthermore, HES use led to a higher risk of RRT (RR 1.36; 95% CI 1.08–1.72; high-quality evidence) [250]. A subsequent network meta-analysis focused on acute resuscitation of patients with sepsis or septic shock and found that HES resulted in higher risk of death (10 RCTs; OR 1.13; CrI, 0.99–1.30; high-quality evidence) and need for RRT (7 RCTs; OR 1.39; CrI, 1.17–1.66; high-quality evidence) compared to crystalloids. When comparing albumin to HES, albumin resulted in lower risk of death (OR 0.73; CrI, 0.56–0.93; moderate-quality evidence) and a trend toward less need for RRT (OR 0.74; CrI, 0.53–1.04; low-quality evidence) [237]. Overall, the undesirable con-



Evaluate cardiac function.

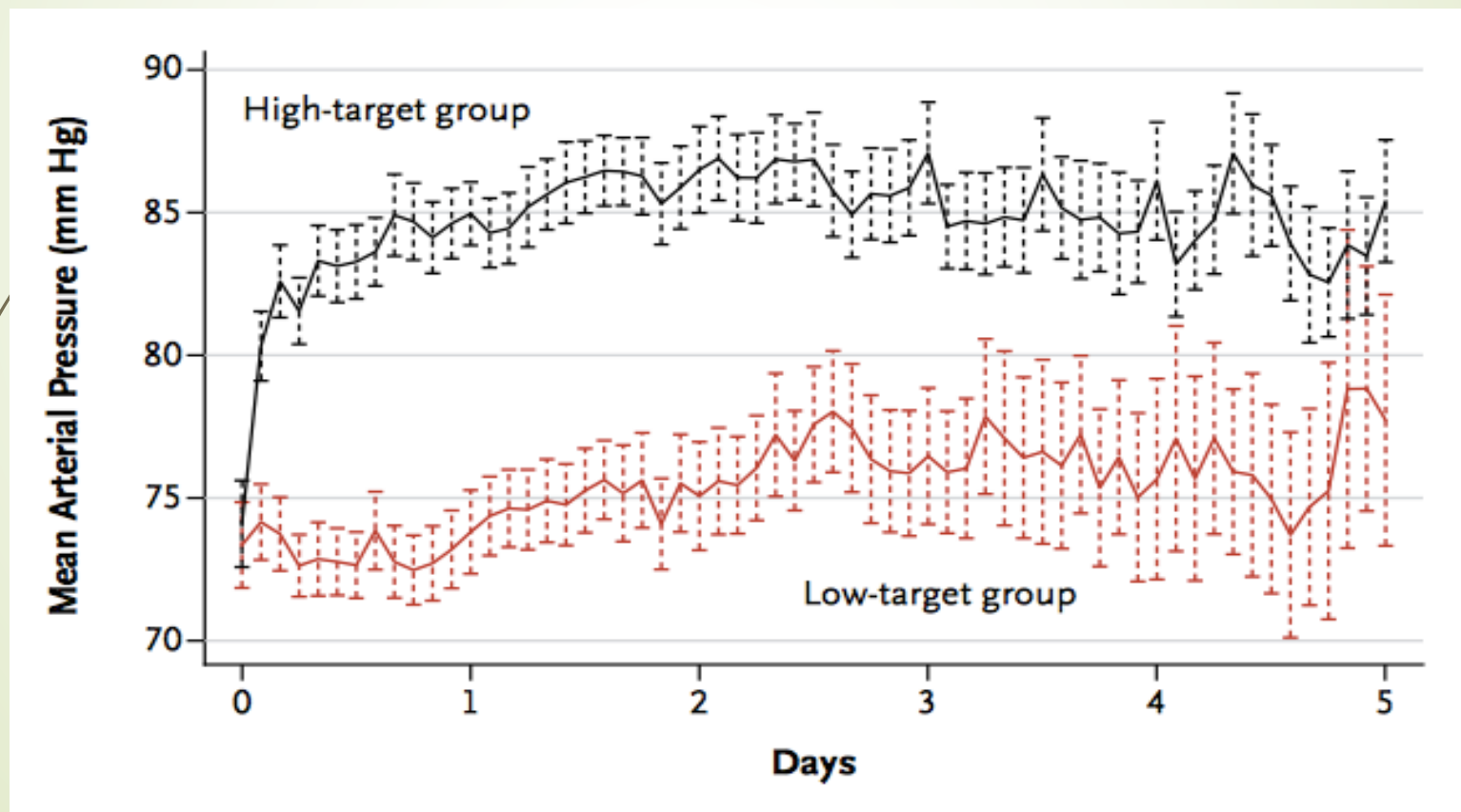
Evaluate dynamic variables (stroke volume, pulse pressure, variation).

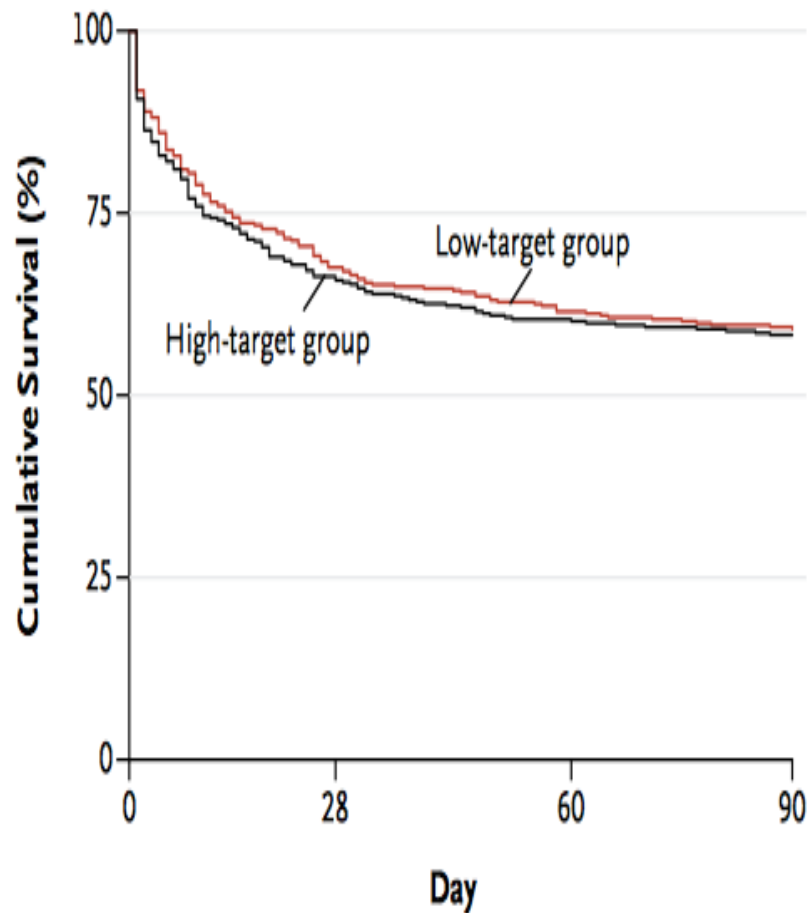
Try to reach a MAP of 65 mmHg, with vasoactive drug.

Try to normalise the level of lactate.

# High versus Low Blood-Pressure Target in Patients with Septic Shock

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Group PAM 80-85 mmHg  
vs  
Group PAM 65-70 mmHg



No difference:  
1. Survival at 28 day;  
2. Organ dysfunction  
3. Mortality at 90 days





# Vasopressors

Norepinephrine is the first choice vasoactive drug

It can be associated with adrenaline or vasopressin to reach the target MAP or to reduce the dosage of norepinephrine



# Blood

Tranfufion is needed for  $\text{Hb} < 7 \text{ g/dl}$  (absence of miocardial infartion...)

No eritropietin in case of acute anemia

No fresch frozen plasma in absence of hemorragia.

# NUTRITION

**We recommend against the administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with sepsis or septic shock who can be fed enterally (strong recommendation, moderate quality of evidence).**

This may represent an advantage over enteral nutrition, especially when patients may be underfed due to GI intolerance, which may be pertinent over the first days of care in the ICU. However, parenteral delivery is more invasive and has been associated with complications, including an increased risk of infections

# Conclusioni

- La sepsi e lo shock settico sono ancora molto frequenti e associati ad elevata mortalità
- La diagnosi precoce è fondamentale per intraprendere la corretta terapia
- Dalla rapidità di «azione» anche nel gestire il «source control» dipende la sopravvivenza dei pazienti
- Il qSOFA o il MEWS dovrebbero essere considerato in tutti i reparti ospedalieri
- Le strategie terapeutiche di maggiore impatto clinico sono la somministrazione dell'antibiotico (a dose corretta!) e dei fluidi (cristalloidi) fatti nella corretta dose
- *La semplificazione della definizione di sepsi / shock settico deve permettere una compilazione corretta di quanto ci viene richiesto*