

**2018 SCCM TEXAS CHAPTER 7TH  
ANNUAL SYMPOSIUM  
"LESS IS MORE"**

**RESTRICTIVE VS. LIBERAL FLUID  
RESUSCITATION**  
OCTOBER 19, 2018

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# OUTLINE

- Review Shock
- Understand the Role of Fluid Administration in the Treatment of Shock
- Review the Historical Perspective of Fluid Resuscitation in Shock
- Understand the Study and Assessment in Fluid Resuscitation
- Gain a Perspective to Recent Controversies in Resuscitation
- Explore Issues and Concerns Related to Fluid Resuscitation and De-resuscitation

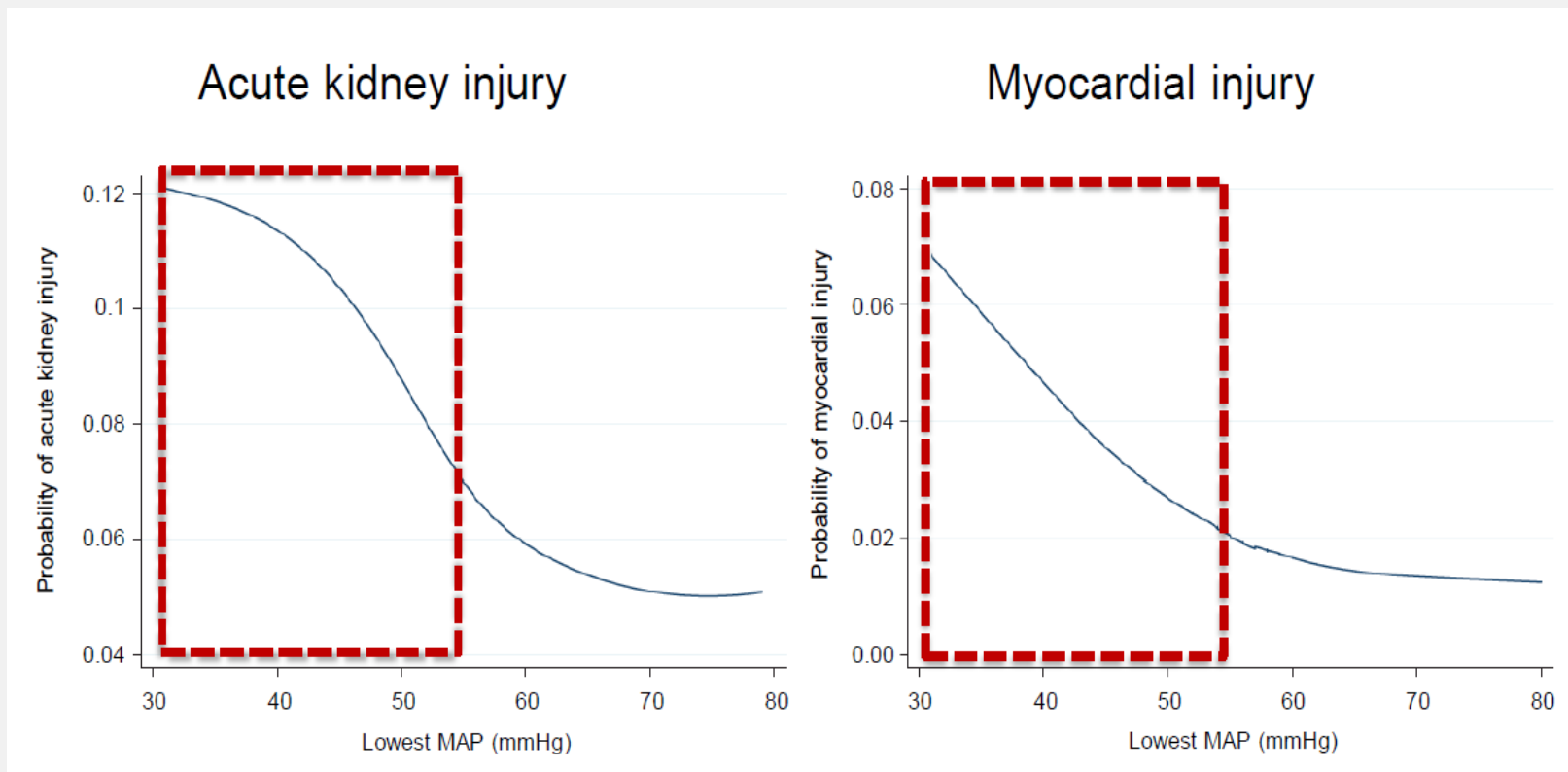
# OBJECTIVES

- 1. Describe pathophysiology of shock and role of fluid resuscitation
- 2. Discuss current evidence that evaluates restrictive versus liberal fluid resuscitation in shock

**QUESTION:**  
**WITH REGARD TO THE MANAGEMENT OF  
SHOCK...**

- A. One is allowed 3 hours to achieve a MAP > 65 mmHg given that no substantial damage can occur during this time window
- B. New evidence is suggesting that there is a preferable fluid type for resuscitation to minimize some of the detrimental effects of shock
- C. EGDT is a clear, well established and proven method for fluid resuscitation in patients with septic shock.
- D. There is no evidence that excess fluid can be harmful when the goal is to reverse shock and reestablish perfusion to vital organs

# LOW MAP IS ASSOCIATED WITH SERIOUS ADVERSE EVENT



Risk of both kidney and cardiac injury increases with decreasing MAP, particularly below 55 mmHg

# CURRENT TREATMENT OF SHOCK

Volume  
resuscitation

MAP <65 mmHg

Crystalloids (initial to minimum 30 mL/kg)

Albumin (in patients requiring substantial amount of crystalloids)

Unable to maintain MAP ≥65 mmHg

Vasopressor  
therapy

NE

Epinephrine (added to or substituted for NE)

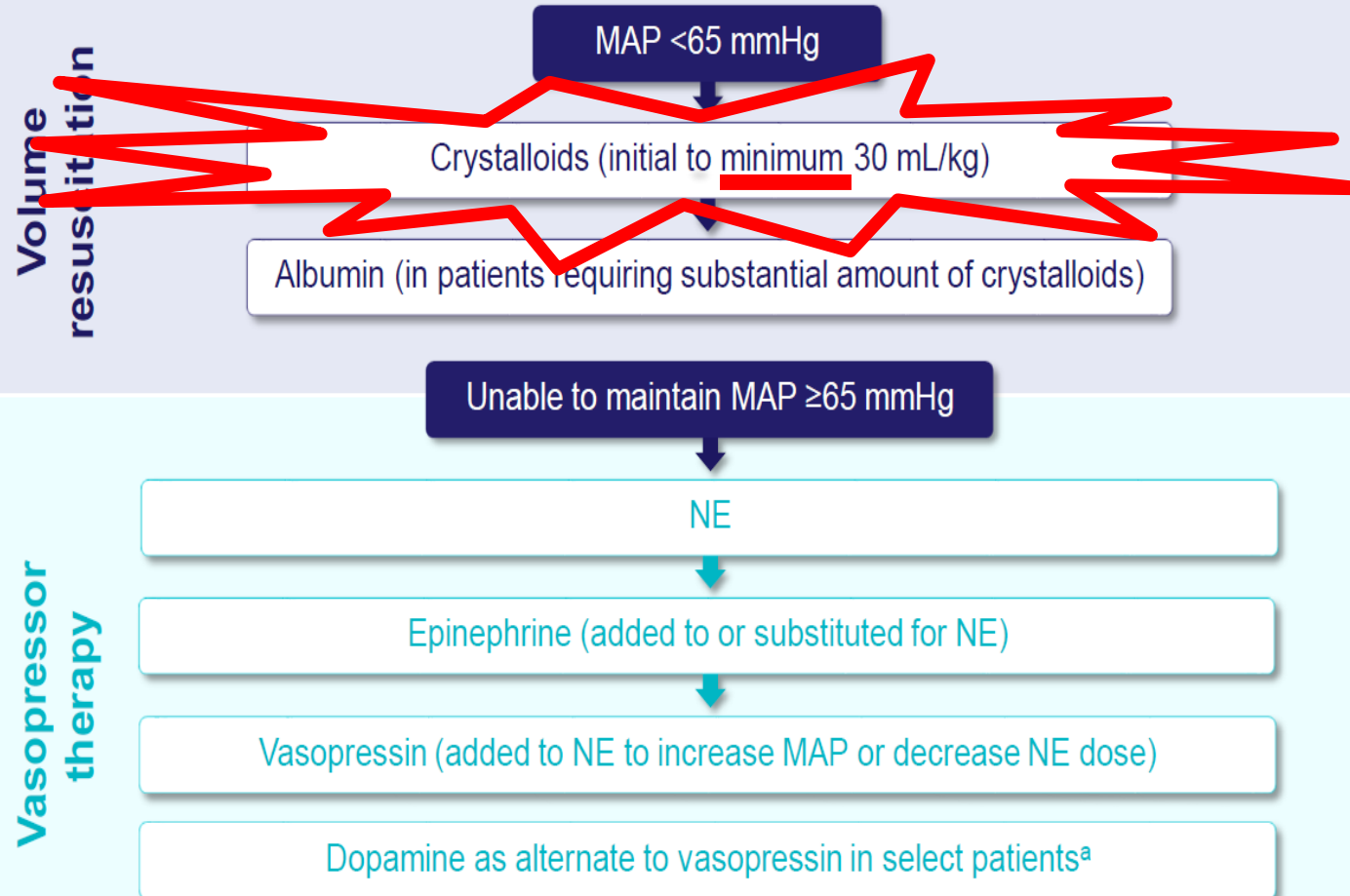
Vasopressin (added to NE to increase MAP or decrease NE dose)

Dopamine as alternate to vasopressin in select patients<sup>a</sup>

Phenylephrine is not recommended unless NE is contraindicated or all other interventions have failed to achieve MAP target.

<sup>a</sup>Patients with low risk of tachyarrhythmias and absolute or relative bradycardia.

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HOW DID WE GET HERE?



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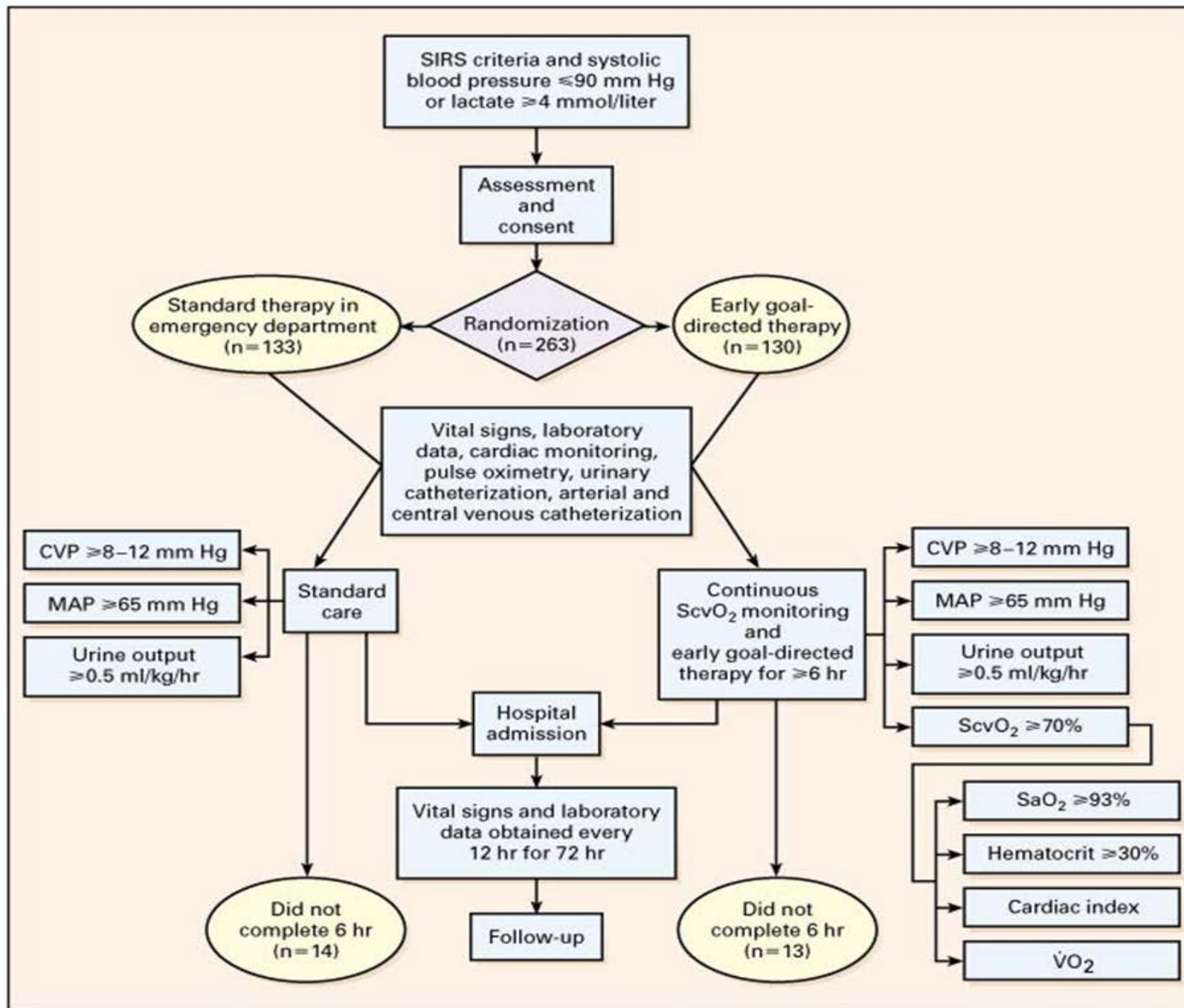
# Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock

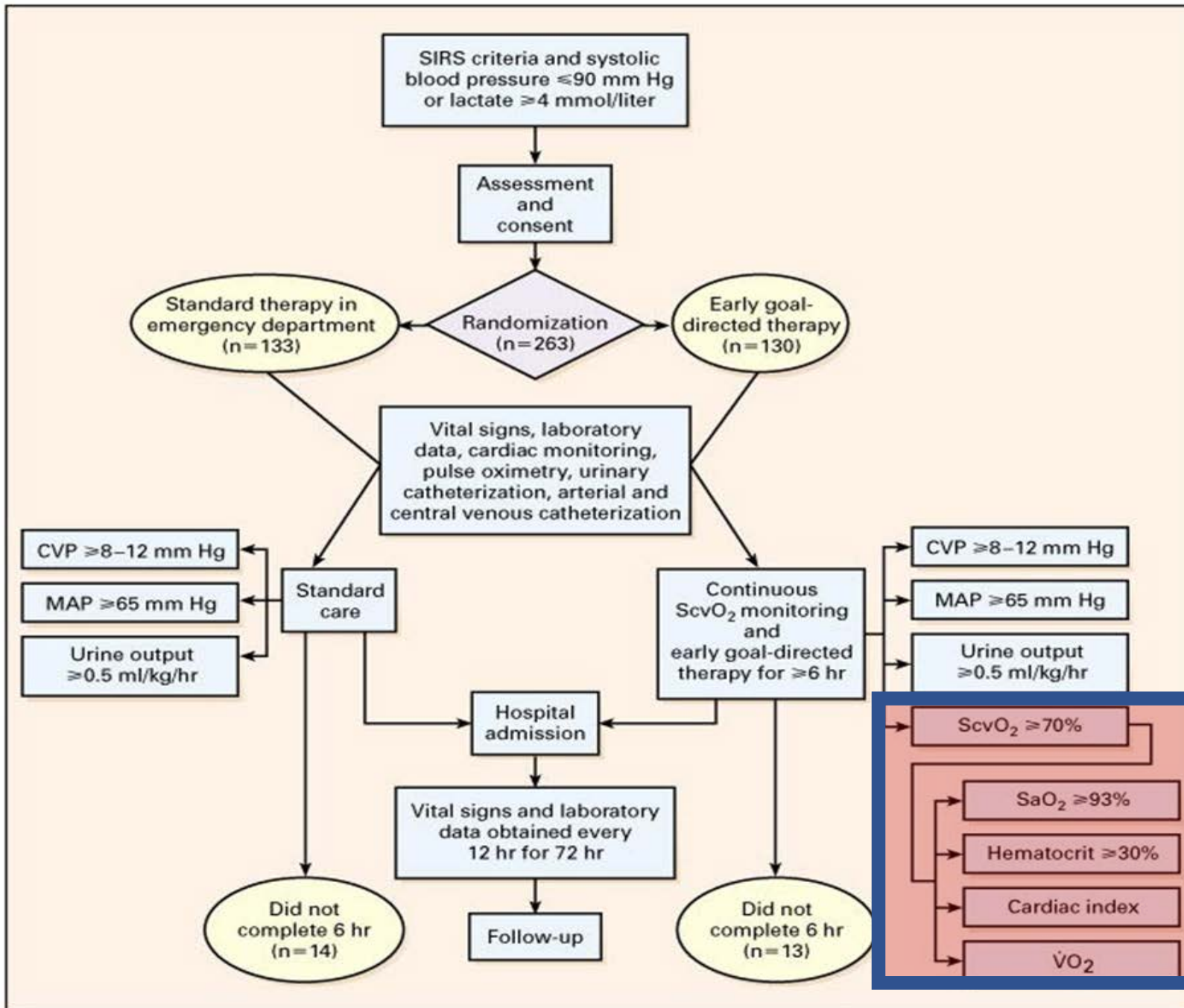


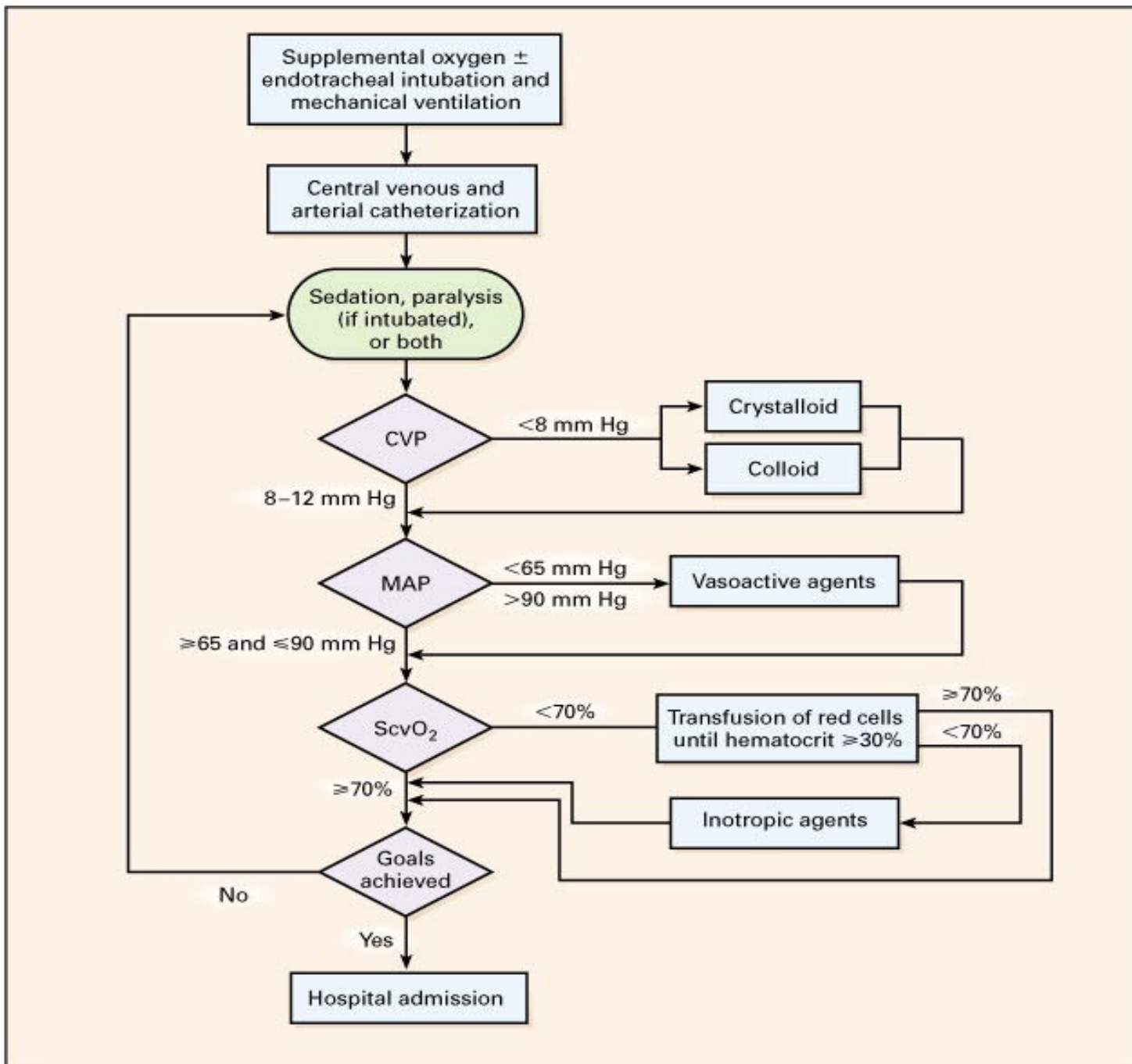
The NEW ENGLAND  
JOURNAL of MEDICINE

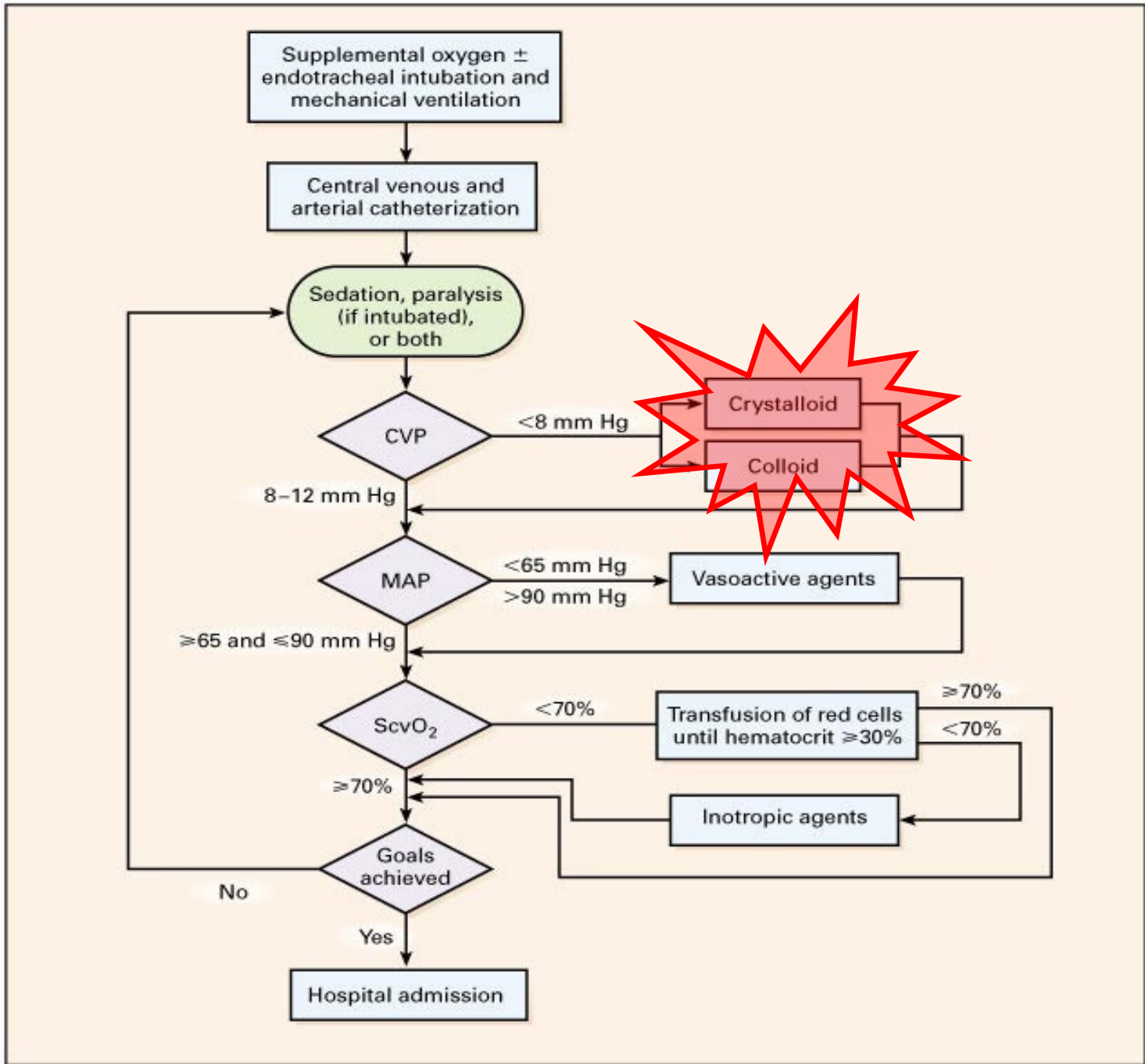
Rivers E. N Engl J Med 2001;345:1368-77.

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# EGDT Results

- 263 enrolled patients
  - 130 EGDT and 133 to standard therapy
    - No significant differences between the groups with respect to base-line characteristics
- In-hospital mortality:
  - **30.5% EGDT vs. 46.5% standard therapy**
- During the interval from 7 - 72 hrs,
  - EGDT patients:
    - Significantly **higher** mean (+/-SD) central venous oxygen saturation (70.4+/-10.7 percent vs. 65.3+/-11.4 percent)\*
    - **Lower** lactate concentration (3.0+/-4.4 vs. 3.9+/-4.4 mmol per liter)\*
    - **Lower** base deficit (2.0+/-6.6 vs. 5.1+/-6.7 mmol per liter)\*
    - **Higher** pH (7.40+/-0.12 vs. 7.36+/-0.12)\*
    - Mean APACHE II scores were **significantly lower**, indicating less severe organ dysfunction (13.0+/-6.3 vs. 15.9+/-6.4, P < 0.001).

\*(P < or = 0.02 for all comparisons)

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# Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock



Rivers E. N Engl J Med 2001;345:1368-77.

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**CONCLUSION:** Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock.



# Surviving Sepsis Campaign

- For patients with [tissue hypoperfusion from sepsis](#)
  - Advise **volume resuscitation should start immediately** and follow an institutional protocol
  - The goals during the **first 6 hours** of resuscitation should be (**Grade 1C**)
- MAP  $\geq$  65 mm Hg
- CVP: 8-12 mm Hg (12-15 mm Hg in patients receiving mechanical ventilation or with known preexisting decreased ventricular compliance)
- Urine output  $\geq$  0.5 mL/kg/hr (35 mL/hr for someone weighing 70 kg or 154 lbs)
- Central venous oxygen saturation (from the superior vena cava)  $\geq$  70%, or mixed venous oxygen saturation (from a pulmonary artery catheter)  $\geq$  65%
- **Crystalloid is recommended for initial fluid resuscitation for severe sepsis and septic shock (Grade 1B).** [Hydroxyethyl starch \(hetastarch\) should not be used as therapy for sepsis](#), according to [U.S. and European regulatory authorities \(Grade 1B\)](#).
- **A minimum of 30 ml/kg of crystalloids (1.5-3 liters) is advised for most patients to qualify as adequate fluid resuscitation (Grade 1C) but fluid should be aggressively infused for as long as the patient continues to improve hemodynamically (ungraded recommendation).**
  - A portion of resuscitation fluids may be given as "albumin-equivalent" (**Grade 1C**).
- Vasopressors should be begun within 6 hours for patients with hypotension despite aggressive initial fluid resuscitation (i.e., septic shock), to maintain a mean arterial pressure  $\geq$  65 mm Hg (**Grade 1C**).



"A randomized trial of protocol-based care for early septic shock."

N Engl J Med  
370(18): 1683-1693. Yealy, D. M., et al. (2014).  
*ProCESS Trial*

- METHODS:
  - 31 EDs randomly assigned 1341 patients with septic shock to one of three groups for 6 hours of resuscitation:
    - protocol-based EGDT (439)
    - protocol-based standard therapy that did not require the placement of a central venous catheter, administration of inotropes, or blood transfusions (446)
    - usual care (456)
  - Primary end point was 60-day in-hospital mortality.
  - Secondary outcomes included longer-term mortality and the need for organ support.
- RESULTS:
  - By 60 days
    - protocol-based EGDT – 92 Deaths (21%)
    - protocol-based standard therapy that did not require the placement of a central venous catheter, administration of inotropes, or blood transfusions – 81 Deaths (18.9%)
    - usual care 86 (19.9%)
  - Relative risk with protocol-based therapy vs. usual care, 1.04; 95% confidence interval [CI], 0.82 to 1.31; P=0.83
  - Relative risk with protocol-based EGDT vs. protocol-based standard therapy, 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.**
- CONCLUSIONS: In a multicenter trial conducted in the tertiary care setting, protocol-based resuscitation of patients in whom septic shock was diagnosed in the emergency department **did not improve outcomes.**

# "Goal-directed resuscitation for patients with early septic shock."

N Engl J Med 371(16): 1496-1506. Peake et al. 2014

## ARISE Trail

- **METHODS:** 51 centers randomly assigned 1600 patients presenting to the emergency department with early septic shock
  - EGDT (796)
  - Usual care (804)
  - Primary outcome was all-cause mortality within 90 days after randomization
- **RESULTS:**

Intervention	EGDT	Usual Care
Fluids – 1 <sup>st</sup> 6 hrs	1964 +/- 1415 ml	1713 +/- 1401 ml
Vasopressors	66.6%	57.8%
RBC transfusion	13.6%	7.0%
Dobutamine	15.4%	2.6%
90 Day – deaths	147 (18.6%)	150 (18.8%)

- Absolute risk difference with EGDT vs. usual care, -0.3 percentage points
  - 95% confidence interval, -4.1 to 3.6; P=0.90
- There was **no significant difference in survival time, in-hospital mortality, duration of organ support, or length of hospital stay.**
- **CONCLUSIONS:** In critically ill patients presenting to the emergency department with early septic shock, **EGDT did not reduce all-cause mortality at 90 days.**

“Trial of early,  
goal-directed  
resuscitation for  
septic shock”  
N Engl J Med  
2015; 372:1301-  
1311 Mounicy et  
al. 2015  
ProMISE Trial

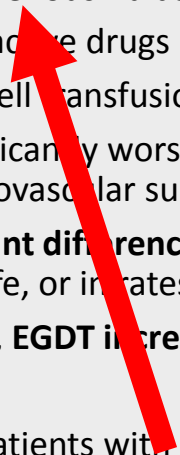
- Methods: 56 hospitals in England, 1260 patients
  - EGDT (630)
  - Usual care (630)
  - Primary clinical outcome was all-cause mortality at 90 days
- Results:
  - By 90 days
    - 184 of 623 patients (29.5%) in the EGDT group died
    - 181 of 620 patients (29.2%) in the usual-care group had died
      - RR in the EGDT group, 1.01; 95% confidence interval [CI], 0.85 to 1.20; P=0.90)
      - An ARR in the EGDT group of -0.3 percentage points (95% CI, -5.4 to 4.7).
  - Increased treatment intensity in the EGDT group was indicated by increased use of
    - intravenous fluids
    - vasoactive drugs
    - red-cell transfusions
    - significantly worse organ-failure scores, more days receiving advanced cardiovascular support, and longer stays in the intensive care unit.
  - **No significant differences in any other secondary outcomes**, including health-related quality of life, or in rates of serious adverse events.
  - On average, **EGDT increased costs**, and the probability that it was cost-effective was below 20%.
- Conclusions: In patients with septic shock who were identified early and received intravenous antibiotics and **adequate fluid resuscitation**, hemodynamic management according to a strict **EGDT protocol did not lead to an improvement in outcome**.

“Trial of early, goal-directed resuscitation for septic shock in England”  
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**MAYBE THEY NEED MORE FLUID?**

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"Early goal-directed resuscitation of patients with septic shock: current evidence and future directions."

Crit Care 19: 286. Gupta et al. 2015

- Three large randomized trials were undertaken to re-examine the effect of EGDT on morbidity and mortality:
  - ProCESS trial in the United States
  - ARISE trial in Australia and New Zealand
  - ProMISe trial in England.
- These trials showed that **EGDT did not significantly decrease mortality** in patients with septic shock compared with usual care.
  - Administration of antibiotics appeared to increase survival
  - Tailoring resuscitation to static measurements of CVP and SvO<sub>2</sub> did not confer survival benefit to most patients

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**SO THEN WHAT ABOUT FLUIDS???**

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  - Tailoring resuscitation to static measurements of CVP and SvO<sub>2</sub> did not confer survival benefit to most patients

Question: Since early goal directed therapy and the surviving sepsis guidelines, it is clear that generous fluid administration is an agreed upon standard of care in the treatment of shock.

A. True

B. False

# Literature to date... 2015

- “Management of septic shock: a protocol-less approach.” – *No difference*
  - Cabrera et al. Crit Care 19: 260.
- “A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators.” – *No difference*
  - Angus et al. Intensive Care Med 41(9): 1549-1560.
- “Early goal-directed therapy vs usual care in the treatment of severe sepsis and septic shock: a systematic review and meta-analysis.” - ?  
*Benefit*
  - Rusconi et al. Intern Emerg Med 10(6): 731-743.



# Literature to date... 2016

- “Early goal-directed therapy for severe sepsis and septic shock: A living systematic review.”
  - Simpson et al. J Crit Care 36: 43-48. –Benefit in populations with higher mortality
- “Effect of early goal-directed therapy on mortality in patients with severe sepsis or septic shock: a meta-analysis of randomised controlled trials.”
  - Yu et al. BMJ Open 6(3): e008330. – No benefit but not sufficiently homogenous pts
- “A Meta-Analysis of Randomized Clinical Trials.”
  - Xu et al. Anesth Analg 123(2): 371-381. –No long term benefit, but **increased immediate ICU survival**
- “The effect of early goal-directed therapy on mortality in patients with severe sepsis and septic shock: a meta-analysis.”
  - Lu et al. J Surg Res 202(2): 389-397. - **Suggests that EGDT can significantly reduce the mortality**
- “Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE.”
  - Nguyen, H. B. et al. Crit Care 20(1): 160. – REVIEW ARTICLE
- “Early goal-directed treatment versus standard care in management of early septic shock: Meta-analysis of randomized trials.”
  - Coccolini F. et al. J Trauma Acute Care Surg 81(5): 971-978. -EGDT seems **to increase the resource demand in terms of ICU admissions and cardiocirculatory support necessity without reducing mortality, renal and respiratory organ support necessity, respiratory and cardiocirculatory support duration, and length of hospital stay**

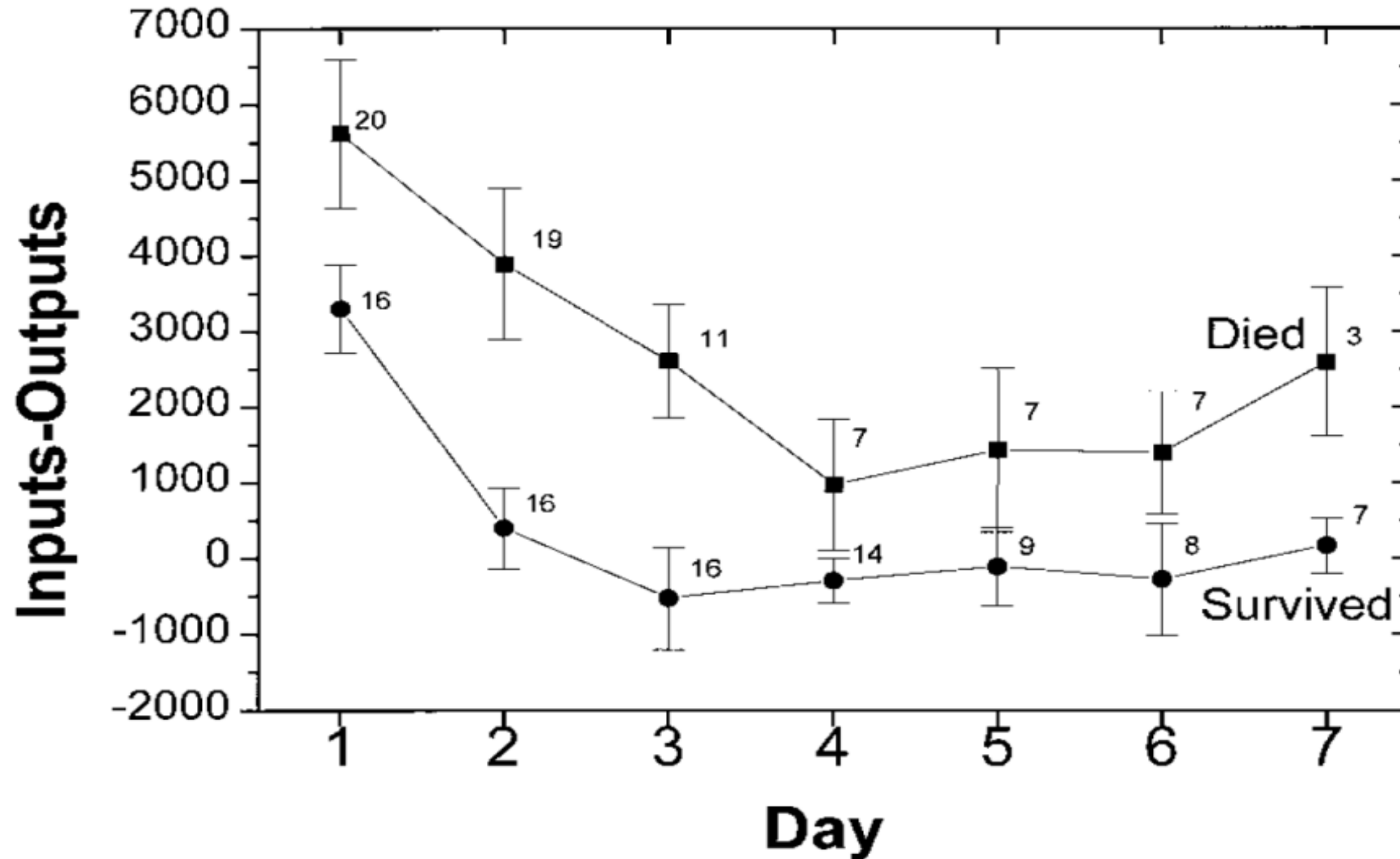
# Literature to date... 2017

- “Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis.”
  - Rowan, K. M. et al. N Engl J Med 376(23): 2223-2234. – *Outcome not better*
- “Potential Impact of the 2016 Consensus Definitions of Sepsis and Septic Shock on Future Sepsis Research.”
  - Peake, S. L. et al. Ann Emerg Med 70(4): 553-561.e551. – *Tested patients ability to meet new criteria*
- “The effect of early goal-directed therapy for treatment of severe sepsis or septic shock: A systemic review and meta-analysis.”
  - Park, S. K. J Crit Care 38: 115-122. – *Highlighted the potential bias on analysis of the 3 major trials*
- "The Physiology of Early Goal-Directed Therapy for Sepsis."
  - Lief, L. et al. J Intensive Care Med 32(10): 567-573. – **review of physiology to reconcile trial results**
- “Early goal-directed therapy versus usual care in the management of septic shock.”
  - Gottlieb, M Cjem 19(1): 65-67. – **EGDT associated with increase ICU admission, no other benefit**
- “Early outcome of early-goal directed therapy for patients with sepsis or septic shock: a systematic review and meta-analysis of randomized controlled trials.”
  - Chen, X. et al. Oncotarget 8(16): 27510-27519. – **“Neutral survival effect”**
- “Does Early Goal-Directed Therapy Decrease Mortality Compared with Standard Care in Patients with Septic Shock?”
  - Winters, M. E. et al. J Emerg Med 52(3): 379-384. - **No difference in mortality**
- “Protocolised early goal-directed therapy in patients with sepsis/septic shock does not result in improved survival compared with usual care with less invasive resuscitation strategies.”
  - Meyer, J. et al. Evid Based Med 22(6): 223. – **No improvement**

# Literature to date... 2018

- “Early Goal-Directed Therapy: The History and Ongoing Impact on Management of Severe Sepsis and Septic Shock.” – EGDT: **lower mortality**
  - Weisberg. A., et al. Surg Infect (Larchmt) 19(2): 142-146.
- “Early Goal-Directed Therapy in Severe Sepsis and Septic Shock: A Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials.”
  - Lu, Y. et al. J Intensive Care Med 33(5): 296-309.
    - *Original EGDT protocol is **unnecessary** for improved outcomes.*
    - *Some recommendations, such as **higher goal hemoglobin and hematocrit levels and liberal crystalloid fluid resuscitation, are likely harmful.***
    - *Despite controversy over a number of the recommendations, **early identification of sepsis, source control, and prompt empiric antibiotic administration** remain the mainstay of treatment for patients with sepsis and septic shock.*

# Daily fluid balance and Survival – CHEST 2000



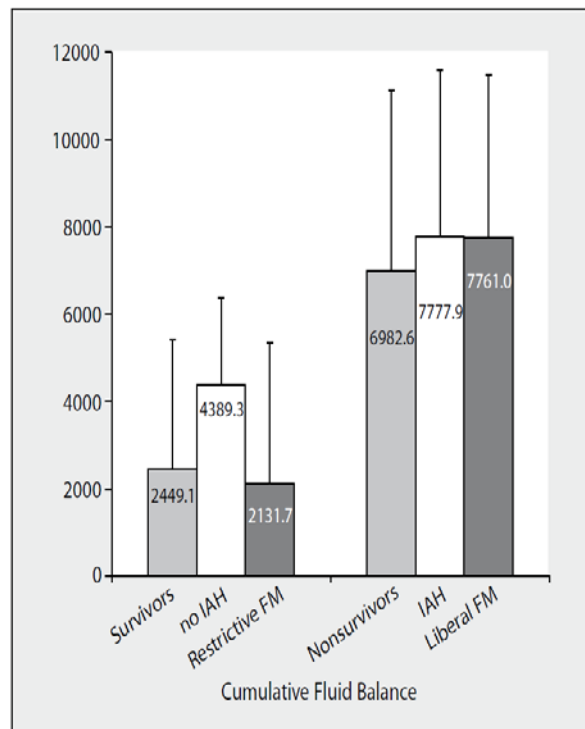
**Fluid overload, de-resuscitation, and outcomes  
in critically ill or injured patients: a systematic review  
with suggestions for clinical practice**

Manu L.N.G. Malbrain<sup>1</sup>, Paul E. Marik<sup>2</sup>, Ine Witters<sup>1</sup>, Colin Cordemans<sup>1</sup>, Andrew W. Kirkpatrick<sup>3</sup>,  
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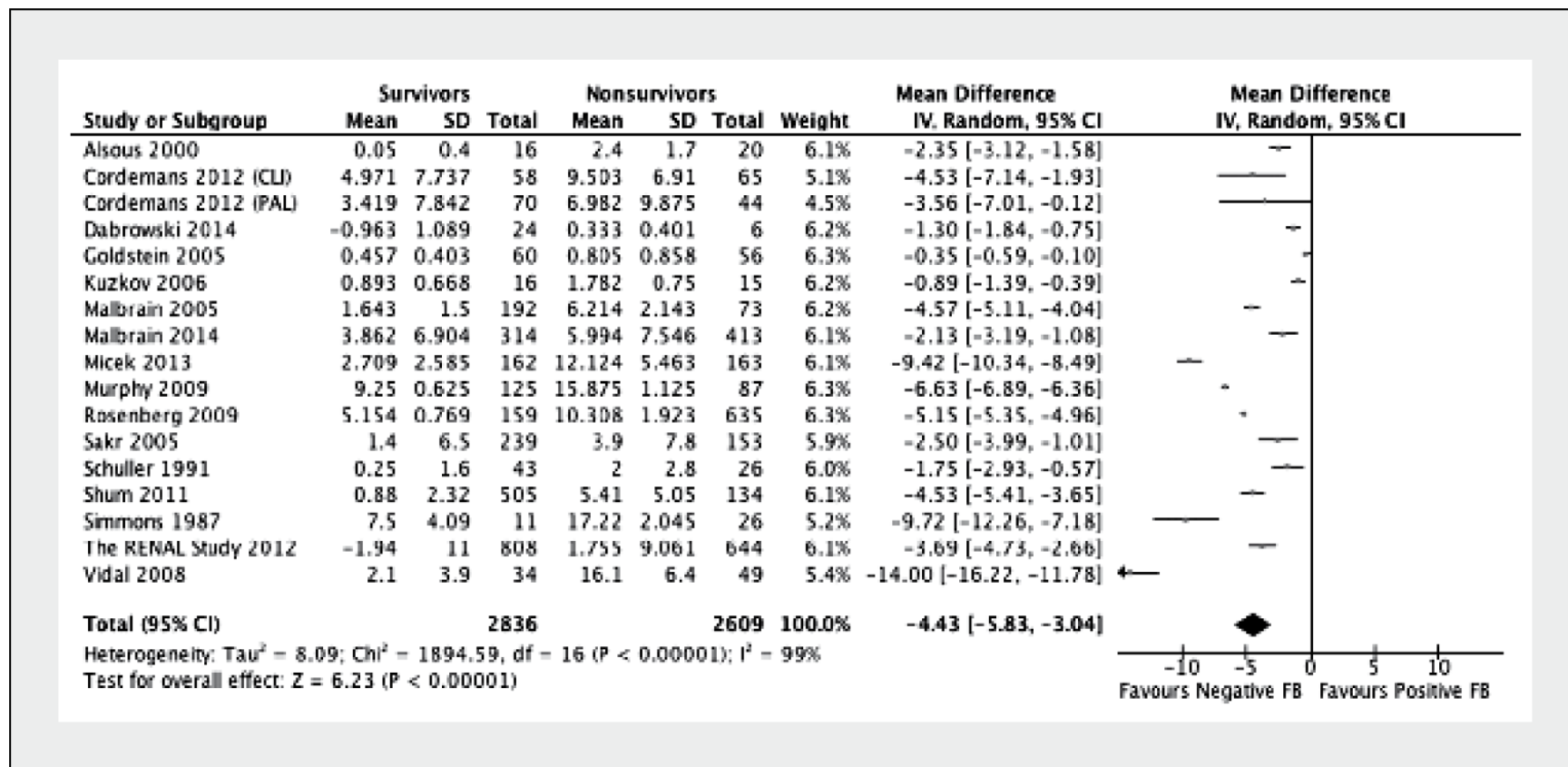
- Aim: systematically review assoc w/ + fluid balance/overload and outcomes in critically ill adults & if reduced, ? Better outcomes
- Methods: MEDLINE, PubMed, EMBASE, Web of Science, Cochrane Database, clinical trials registries etc...
  - Two independent reviews of each citations and studies
  - Examined assoc w/ fluid balance & outcomes or where interventions where a strategy or protocol attempted a negative or neutral fluid balance after 3 days
- Results: 1 meta-analysis, 11 RCT, 7 interventional studies, 24 observational studies, & 4 case series met inclusion criteria

# Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice

Manu L.N.G. Malbrain<sup>1</sup>, Paul E. Marik<sup>2</sup>, Ine Witters<sup>1</sup>, Colin Cordemans<sup>1</sup>, Andrew W. Kirkpatrick<sup>3</sup>,  
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**Figure 1.** Bar graph showing mean cumulative fluid balance after one week of intensive care unit (ICU) stay. Light grey bars showing cumulative fluid balance in survivors (left) vs nonsurvivors (right), white bars show data in patients without intra-abdominal hypertension, IAH (left) vs IAH (right), and dark grey bars data in patients with restrictive fluid management (left) vs liberal fluid management (right)



**Figure 3.** Forest plot looking at cumulative fluid balance after one week\* of ICU stay in survivors vs nonsurvivors. Updated and adapted from Malbrain et al. [61]; FB — fluid balance

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- Results:
  - Cumulative fluid balance after one week of ICU stay was **4.4 L more positive in non-survivors compared to survivors**.
  - A restrictive fluid management strategy resulted in a less positive cumulative fluid balance of 5.6 L compared to controls after one week of ICU stay.
  - **A restrictive fluid management was associated with a lower mortality compared to patients treated with a more liberal fluid management strategy (24.7% vs 33.2%; OR, 0.42; 95% CI 0.32–0.55; P < 0.0001).**
- Conclusions: A positive cumulative fluid balance is associated with IAH and worse outcomes. Interventions to limit the development of a positive cumulative fluid balance are associated with improved outcomes. In patients not transgressing spontaneously from the Ebb to Flow phases of shock, late conservative fluid management and late goal directed fluid removal (de-resuscitation) should be considered.

# Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the *CLASSIC* randomised, parallel-group, multicentre feasibility trial

- Purpose:

- assessed the effects of a **protocol restricting** resuscitation fluid vs. a standard care protocol after initial resuscitation in intensive care unit (ICU) patients with septic shock

- Methods:

- randomised 151 adult patients with septic shock who had received initial fluid resuscitation in nine Scandinavian ICUs
- In the fluid restriction group fluid boluses were permitted *only if signs of severe hypoperfusion occurred*, while in the standard care group fluid boluses were permitted as long as circulation continued to improve.



Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the *CLASSIC* randomised, parallel-group, multicentre feasibility trial

- Results
- The co-primary outcome measures, resuscitation fluid volumes at day 5 and during ICU stay, were **lower in the fluid restriction group** than in the standard care group [mean differences **-1.2 L** (95 % confidence interval -2.0 to -0.4);  $p < 0.001$  and **-1.4 L** (-2.4 to -0.4) respectively;  $p < 0.001$ ].
- **Neither *total fluid inputs and balances* nor serious adverse reactions differed statistically significantly between the groups.**
- Major protocol violations occurred in 27/75 patients in the fluid restriction group.

Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the *CLASSIC* randomized, parallel-group, multicentre feasibility trial

- Results
- Ischemic events occurred in 3/75 in the fluid restriction group vs. 9/76 in the standard care group (odds ratio 0.32; 0.08–1.27;  $p = 0.11$ ),
- Worsening of AKI in 27/73 vs. 39/72 (0.46; 0.23–0.92;  $p = 0.03$ )
- Death by 90 days in 25/75 vs. 31/76 (0.71; 0.36–1.40;  $p = 0.32$ )
- Conclusions
- A protocol restricting resuscitation fluid successfully reduced volumes of resuscitation fluid compared with a standard care protocol in adult ICU patients with septic shock. The patient-centered **outcomes all pointed towards benefit with fluid restriction, but our trial was not powered to show differences in these exploratory outcomes.**

# Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis

- Purpose: evaluate efficacy and safety of conservative or deresuscitative fluid strategies in adults and children with ARDS, sepsis or SIRS in the post-resuscitation phase of critical illness
- Methods: searched Medline, EMBASE and the Cochrane central register of controlled trials from 1980 to June 2016, and manually reviewed relevant conference proceedings from 2009 to the present.
- Results: 49 studies met the inclusion criteria. Marked clinical heterogeneity was evident.
- In a meta-analysis of 11 randomised trials (2051 patients) using a random-effects model
  - **No significant difference in mortality** with conservative or deresuscitative strategies compared with a liberal strategy or usual care [pooled risk ratio (RR) 0.92, 95 % confidence interval (CI) 0.82–1.02,  $I^2 = 0\%$ ].
  - A **conservative or deresuscitative strategy resulted in increased ventilator-free days** (mean difference 1.82 days, 95 % CI 0.53–3.10,  $I^2 = 9\%$ ) **and reduced length of ICU stay** (mean difference –1.88 days, 95 % CI –0.12 to –3.64,  $I^2 = 75\%$ )
- Conclusions: conservative or deresuscitative fluid strategy results in an increased number of **ventilator-free days and a decreased length of ICU stay** compared with a liberal strategy or standard care. **The effect on mortality remains uncertain. Large randomised trials are needed to determine optimal fluid strategies in critical illness.**

# Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database

- Purpose: optimal strategy of fluid resuscitation in the early hours of severe sepsis and septic shock
- Methods: 2013 Premier Hospital Discharge database to analyse the administration of fluids on the first ICU day,
  - 23,513 patients with severe sepsis and septic shock, who were admitted to an ICU from the ED
  - Day 1 fluid was grouped into categories 1 L wide, starting with 1–1.99 L up to  $\geq 9$  L, to examine the effect of day 1 fluids on patient mortality
- Results
  - Day 1 fluid administration averaged 4.4 L
    - Lowest: no mechanical ventilation and no shock (3.6 L)
    - Highest: receiving mechanical ventilation and in shock (5.4)
  - Mean ICU and hospital length of stay of 5.1 and 9.1 days, respectively

# Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database

## • Results

- In the entire cohort, low volume resuscitation (1–4.99 L) was associated with a small but significant reduction in mortality, of **-0.7% per litre** (95% CI -1.0%, -0.4%;  $p = 0.02$ ).
- However, in patients receiving high volume resuscitation (5 to  $\geq 9$  L), the mortality **increased by 2.3% for each additional litre above 5 L** (95% CI 2.0, 2.5%;  $p = 0.0003$ )
- Conclusion: The mean amount of fluid administered to patients with severe sepsis and septic shock in the USA during the first ICU day is **less than that recommended by the Surviving Sepsis Campaign guidelines**. **The administration of more than 5 L of fluid during the first ICU day is associated with a significantly increased risk of death and significantly higher hospital costs.**

# Deresuscitation of Patients With Iatrogenic Fluid Overload Is Associated With Reduced Mortality in Critical Illness

- **Objectives:** To characterize current practice in fluid administration and *deresuscitation* (removal of fluid using diuretics or renal replacement therapy), the relationship between fluid balance, deresuscitative measures, and outcomes and to identify risk factors for positive fluid balance in critical illness.
- **Design:** Retrospective cohort study.
- **Setting:** Ten ICUs in the United Kingdom and Canada.
- **Patients:** 400 adults receiving invasive mechanical ventilation for a minimum of 24 hours.
- **Interventions:** None.

# Deresuscitation of Patients With Iatrogenic Fluid Overload Is Associated With Reduced Mortality in Critical Illness

- **Measurements and Main Results:**

- Positive cumulative fluid balance occurred in 87.3%: **the largest contributions to fluid input were from medications and maintenance fluids rather than resuscitative IV fluids.**
- In a multivariate logistic regression model, **fluid balance on day 3 was an independent risk factor for 30-day mortality** (odds ratio 1.26/L [95% CI, 1.07–1.46]), whereas **negative fluid balance achieved in the context of deresuscitative measures was associated with lower mortality.**

- **Conclusions:** Fluid balance is a practice-dependent and potentially modifiable risk factor for adverse outcomes in critical illness. Negative fluid balance achieved with deresuscitation on day 3 of ICU stay is associated with improved patient outcomes. Minimization of day 3 fluid balance by limiting maintenance fluid intake and drug diluents, and using deresuscitative measures, represents a potentially beneficial therapeutic strategy which **merits investigation in randomized trials.**

# CLOVERS (“Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis”) trial

- Primary Hypothesis: Restrictive (vs liberal) fluid treatment strategy during the first 24 hours of resuscitation for sepsis-induced hypotension will **reduce 90-day in-hospital mortality**.
- We will emphasize early screening and protocol initiation, and enroll a maximum of 2320 patients with suspected sepsis-induced hypotension.
  - All patients will receive at least 1 liter of fluids prior to meeting study inclusion criteria (and no more than 3 liters prior to randomization).
  - Patients will be enrolled within 4 hours of meeting study inclusion criteria
  - Any type of isotonic crystalloid (normal saline, ringers lactate, or a balanced solution such as plasmalyte) is permitted.
- Restrictive Fluids (Early Vasopressors) Group
  - Norepinephrine will be used as preferred vasopressor and titrated to achieve mean arterial pressure (MAP) between 65 mmHg and 75 mmHg
  - "Rescue fluids" may be administered as 500ml boluses if predefined rescue criteria are met
- Liberal Fluids (Fluids First) Group
  - Additional 2 liter intravenous fluid bolus upon enrollment
  - Administer 500ml fluid boluses for fluid triggers until 5 liters administered or development of clinical signs of acute volume overload develop
  - "Rescue vasopressors" may be administered after 5 liters of fluid, for development of acute volume overload, or if other predefined rescue criteria are met



# CLOVERS (“Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis”) trial

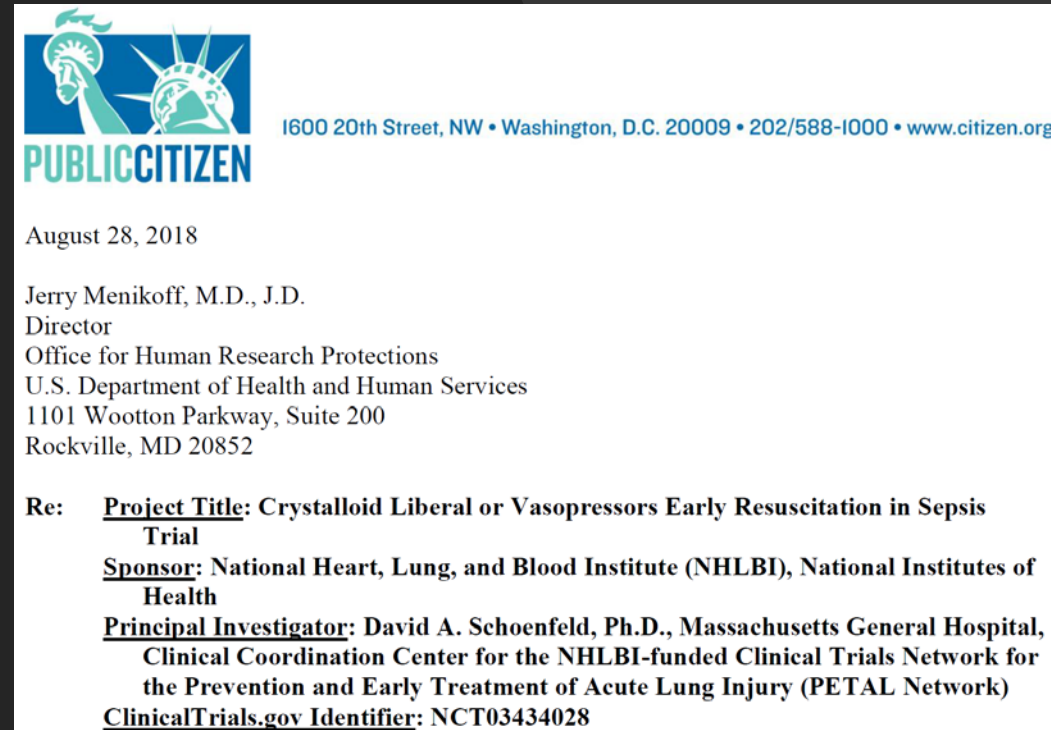
Patients to receive fluid resuscitation similar to those received in the ProCESS, ARISE, & ProMISE trials

## Criticism

Patients in the trial will get larger-than-usual volumes of IV fluids and in less time, and will receive “rescue vasopressors” only after getting about 5 quarts of fluids

# Request to NIH to “hault dangerous study”

- Risk of Getting Extra Fluids: possible that this could cause stress on your heart related to extra fluid, breathing difficulties, or increased swelling in your arms and legs.
- Risk of Getting Medicine to Raise Blood Pressure: Patients in the [restrictive fluids] group may receive earlier or more medicine to raise blood pressure. It’s possible that this could cause not enough oxygen to the heart, heart rhythm problems, not enough oxygen to the intestines, or not enough oxygen to arms, legs, toes, or fingers. The chances of these problems may be higher if the medicines are used early or before a larger amount of fluids are given. ...
- Risk of Death: We do not know whether your risk of dying from your serious infection will be changed by choosing to be in this study. ...



*Restrictive vs. Liberal Fluid*  
*Resuscitation –*  
*Is Less More?*

**Maybe Less is Less?**

- Less ventilator days
- Less ICU LOS
- ? Less mortality → The next step...

## Question:

With regard to the management of shock...

- A. One is allowed 3 hours to achieve a MAP > 65 mmHg given that no substantial damage can occur during this time window
- **B. New evidence is suggesting that there is a preferable fluid type for resuscitation to minimize some of the detrimental effects of shock**
- C. EGDT is a clear, well established and proven method for fluid resuscitation in patients with septic shock.
- D. There is no evidence that excess fluid can be harmful when the goal is to reverse shock and reestablish perfusion to vital organs

Question: Since early goal directed therapy and the surviving sepsis guidelines, it is clear that generous fluid administration is an agreed upon standard of care in the treatment of shock.

A. True

B. False