The fluid debate.

Enough is enough.

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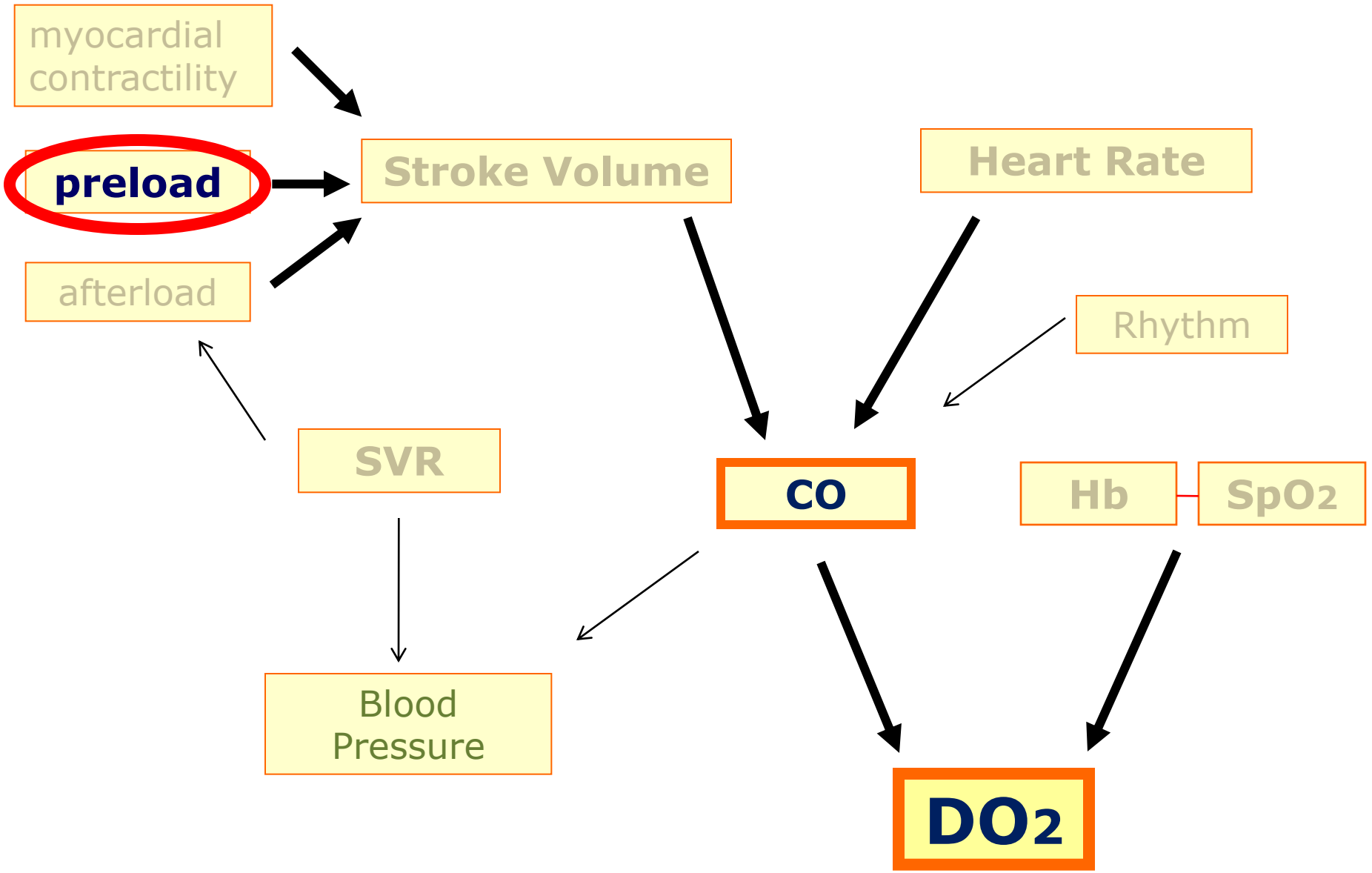
SIMEU 2012, Rimini

Fluid Therapy Might Be

More Difficult Than You Think

Hahn RG Anesthesia & Analgesia (2007) 105;2:304-5


myocardial contractility
preload
afterload
Stroke Volume
Heart Rate
Rhythm
SVR
CO
Hb
SpO2
Blood Pressure
DO2

My (and maybe your) problems

- basic physiology
- what patient
- what target
- how guide replacement
- colloids or crystalloids
- transfusion
- vasopressors

- ***Volume overload*** is increasingly recognized as contributing to both morbidity and mortality

- The **ideal *amount*** and ***type*** of i.v. fluids would *avoid both hypovolemia* (impaired perfusion), and *hypervolemia*.

Septic shock

A positive fluid balance and elevated CVP are associated with increased mortality

Crit Care Med 2011; 39:259 –265

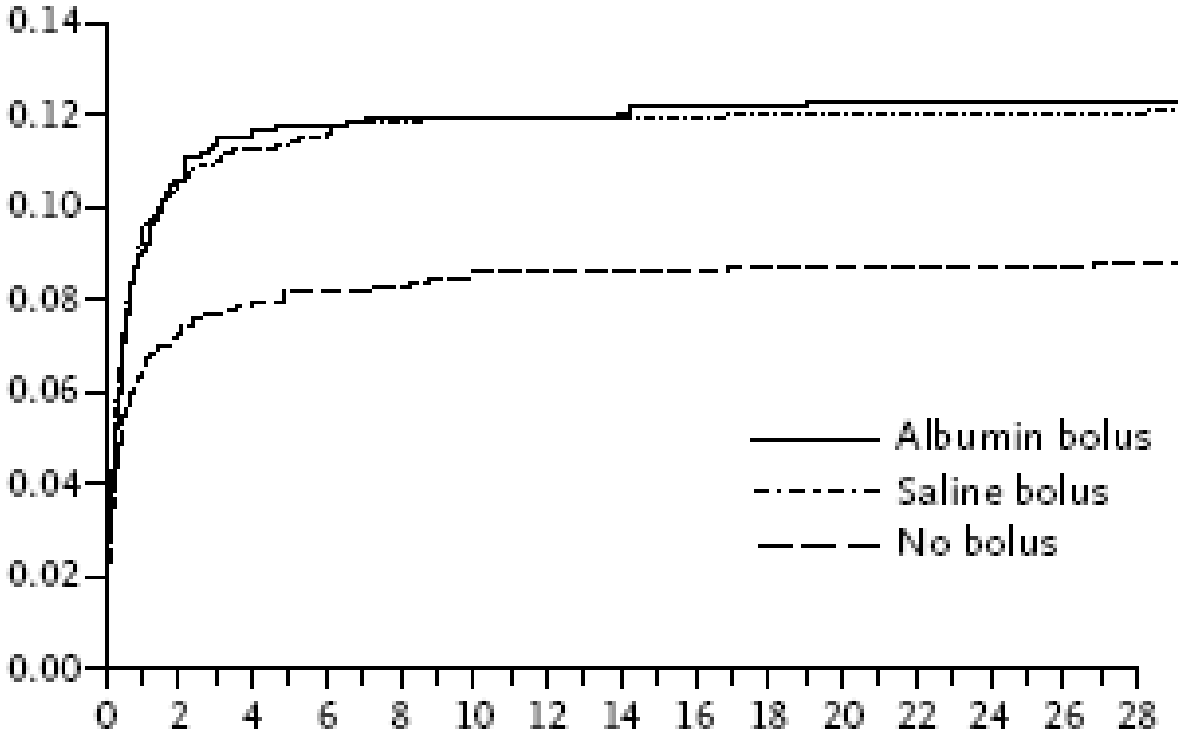
Trauma patients

High-volume resuscitations associated with high-mortality (elderly!)

Ley EJ et al J Trauma 2011 Feb;70(2):398-400

Fluid Expansion as Supportive Therapy

(FEAST) trial



Maitland K, Kiguli S, Opoka RO, et al.
Mortality after fluid bolus in African children with severe infection.
N Engl J Med 2011; 364:2483-2495

Fluid Resuscitation in Acute Illness
Time to Reappraise the Basics

Myburgh JA N Engl J Med 2011;364:2543-44

…**discontinuation of the practice of bolus- fluid resuscitation** in patients with febrile illness due to medical causes and impaired perfusion or compensated shock **must be recommended**.

Potential mechanisms may include **the interruption of genetically determined catecholamine-mediated host defense responses** by the rapid increase in plasma volume, which might result in a ***reperfusion injury.***

Similarly, transient hypervolemia or hyperosmolality **might exacerbate capillary leak** in patients who are susceptible to intracranial hypertension or pulmonary edema, with fatal consequences.

Myburgh JA N Engl J Med 2011;364:2543-44

A critique of fluid bolus resuscitation in severe sepsis

Hilton and Bellomo Critical Care 2012, 16:302

…. recommendations are only based on **expert opinion** and **lack adequate experimental or controlled human evidence**.

Emerging data from basic and clinical science have *challenged* the **dogma of large-volume fluid resuscitation** in ***trauma***.

Douzinas EE Crit Care Med 2012 Vol. 40, No. 4

Early fluid resuscitation in severe trauma

Harris T et al BMJ 2012;345:e5752

- **strategy of permissive hypovolaemia** (hypotension)

- **crystalloid or colloid** based resuscitation **associated with worse outcome**

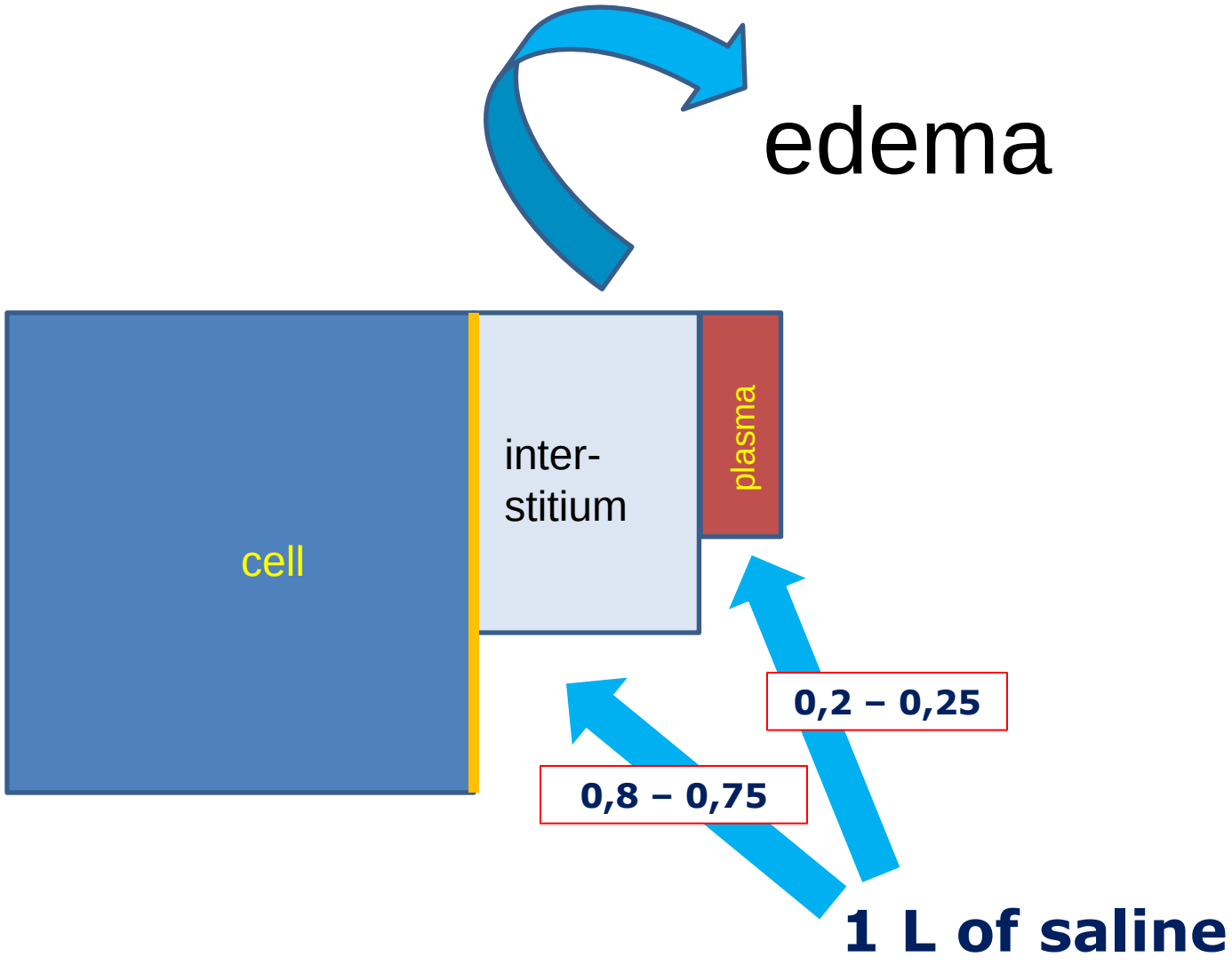
- **avoidance of crystalloids** , **colloid**s and **vasopressors**.

The fluid of my (and your) dreams

- rapid achievement of normovolemia
- long maintenance of normovolemia
- low volume
- no effects on SIRS
- quite similar to blood
- no adverse reactions
- low cost

The end of the crystalloid era?

Twiglwy AJ, Hillman KM Anaesthesia 1985;40(9):860-71


edema
cell
inter-
stitium
plasma
0,2 – 0,25
0,8 – 0,75
1 L of saline

…***classic model*** would expect

colloids to distribute into the IV and, by

raising oncotic pressures, recruit fluids into

the circulation from the ISF

However, **this model is not consistent with the observed effects**

Raghunathan K et al. Curr Opin Crit Care 2012, 18:350–357

The common belief that **3 to 4 times more crystalloids than colloids are needed** to achieve similar hemodynamic effects is **not supported by this clinical observation**

Schortgen F, Brochard L Crit Care Med 2012 40;9:2709-10

1.4 : 1 (crystalloids to HES)

1.1 : 1 (crystalloids to gelatin)

Bayer 0 et al. Crit Care Med 2012; 40:2543–25

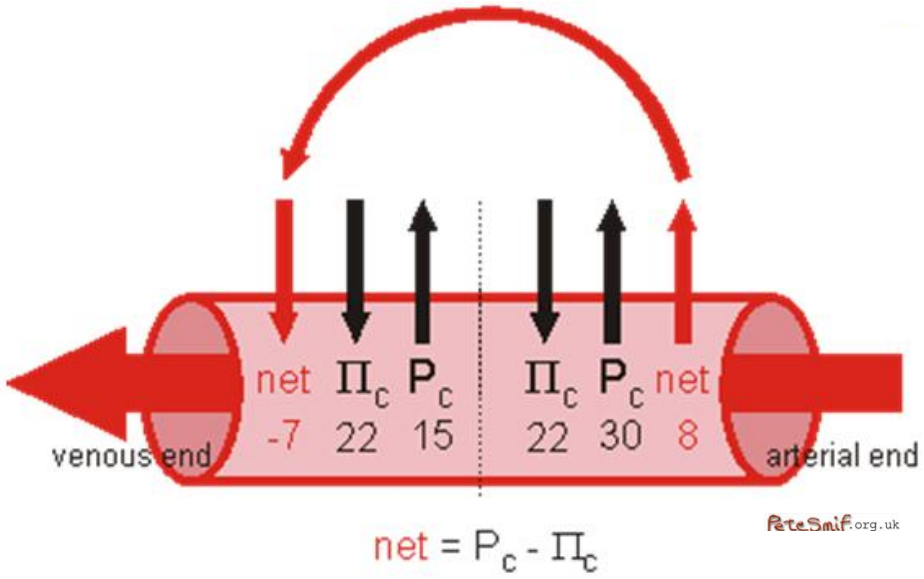
Evidence that colloids provide better survival is lacking

Consensus statement of the ESICM task force
on colloid volume therapy in critically ill patients

Intensive Care Med 2012; 38:368–383

Bye, bye Starling?

RSE&GM



$$J = K_f ([P_c - P_i] - \sigma [\Pi_c + \Pi_i])$$

P_c= hydrostatic capillary pressure

P_i= hydrostatic interstitial pressure

Π_c = oncotic capillary pressure

Π_i= oncotic interstitial pressure

K_f = filtration co-efficient

σ = reflection co-efficient

Revised Starling equation (RSE) and the **glycocalyx model (GM) of transvascular fluid exchange**:

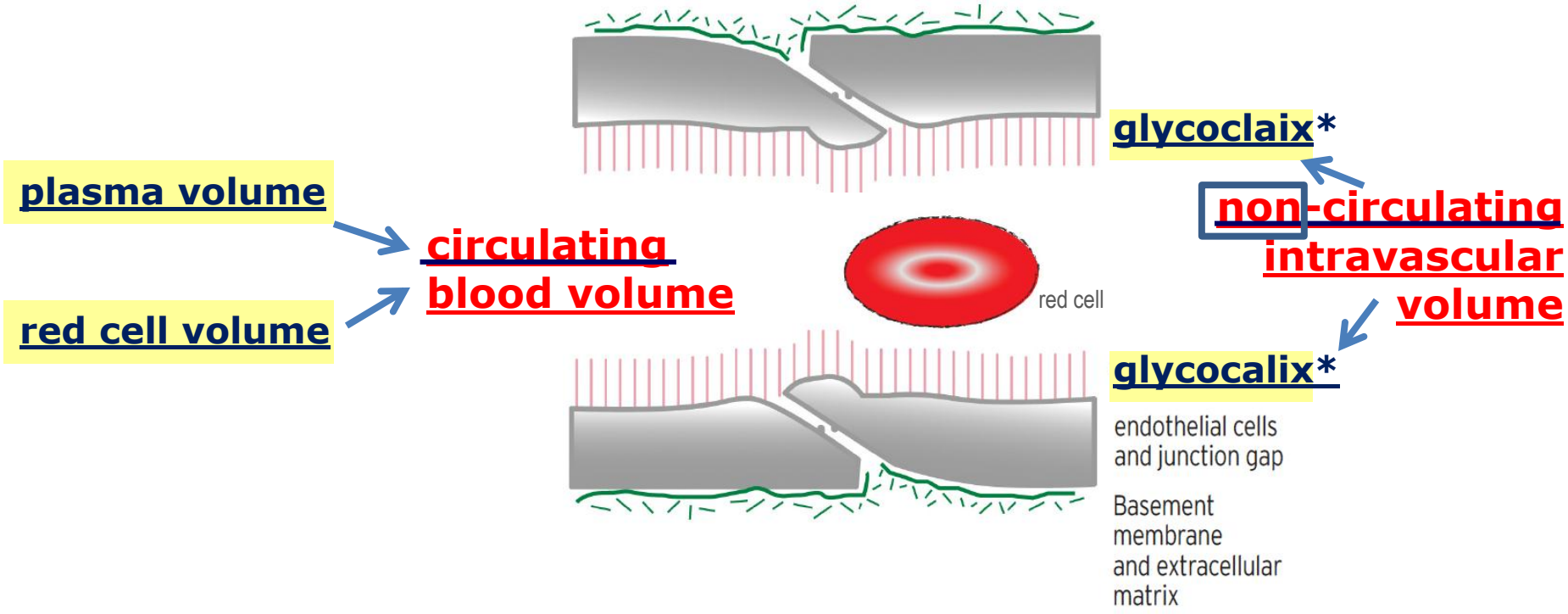
an improved paradigm for prescribing intravenous fluid therapy

WoodcockTE, Woodcock TM
British Journal of Anaesthesia 108 (3): 384–94 (2012)

Levick R, Michel CC
Cardiovascular Research (2010) 87, 198–210

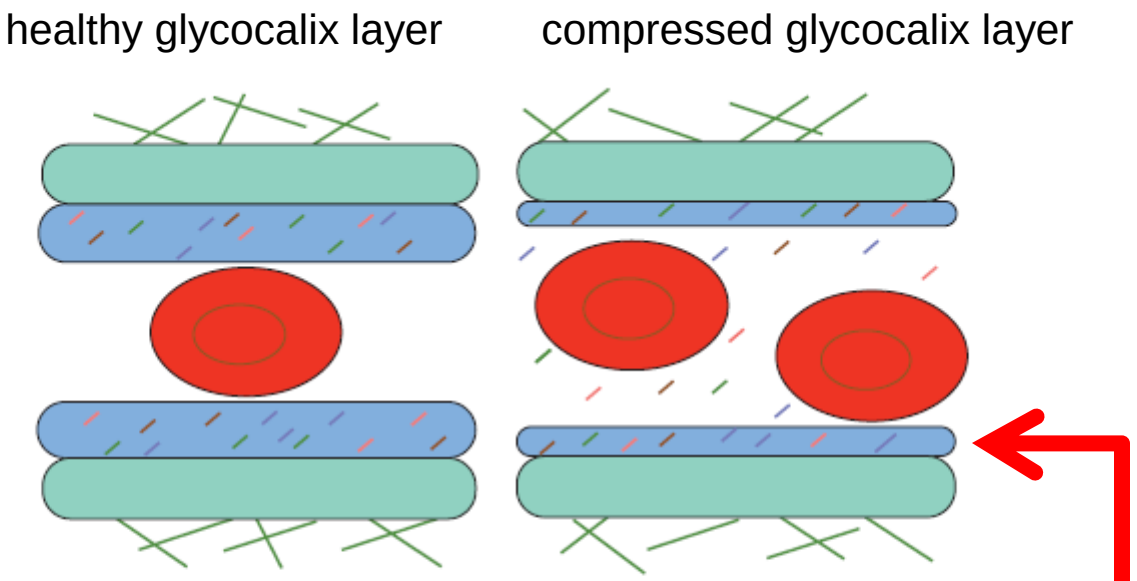
There are three intravascular volumes:

- **plasma volume**
- **red cell volume**
- **glycocalix**



** 1.5 litres of the intravascular volume in health*

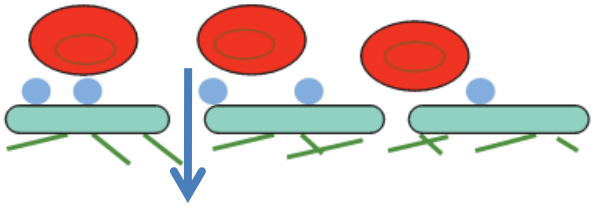
from Woodcock, modified



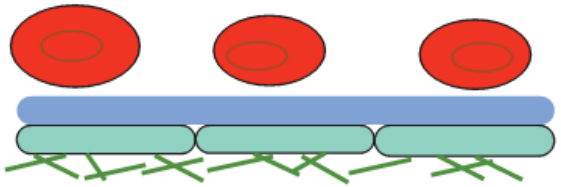
Compaction of the glycocalyx layer increases plasma volume and the red cell dilution volume independently of changes in intravascular volume.

Woodcock TE, Woodcock TM British Journal of Anaesthesia 108 (3): 384–94 (2012)

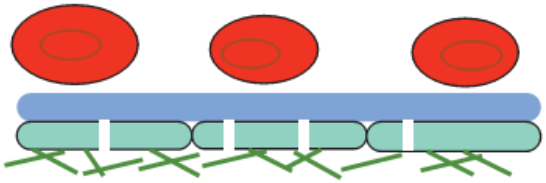
Sinusoidal capillary
(*liver*, spleen, marrow)



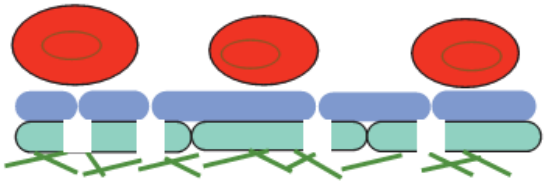
Non-fenestrated capillary
(*CNS*, muscle, connective, *lung*)



Fenestrated capillary
(endocrine, choroid plexus, *gut mucosa*)



Fenestrated capillary
(*glomerular*)



Woodcock TE, Woodcock TM British Journal of Anaesthesia 108 (3): 384–94 (2012)

- ***nonfenestrated capillaries*** normally ***filter fluid*** to the ISF throughout their length.

- ***absorption*** through venous capillaries and venules ***does not occur***.

- ***COP*** *opposes, but* ***does not reverse, filtration***.

- most of the filtered fluid returns to the circulation as ***lymph***.

British Journal of Anaesthesia 108 (3): 384–94 (2012)

Plasma proteins, including albumin, escape to the interstitial space by a relatively small number of large pores, which are responsible for the **increased transcapillary flow (Jv**) observed in the early stage of **inflammation**.

British Journal of Anaesthesia 108 (3): 384–94 (2012)

A context-sensitive view

Albumin

SAFE: use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days

N Engl J Med 2004; 350: 2247–56

Human serum albumin as a resuscitation fluid: Less SAFE than presumed?

Crit Care Med 2011 Vol. 39, No. 6:1584-85

The role of albumin as a resuscitation fluid for patients with sepsis.

Crit Care Med 2011 Feb;39(2):386-91

…in view of the

- ***absence of evidence of a mortality benefit***

- **increased cost** compared to alternatives such as saline,

it would seem reasonable that ***albumin*** **should only be used within the context** of well concealed and adequately powered **randomised controlled trials.**

Cochrane Database of Systematic Reviews. 11, 2012

HES

The VISEP trial *stopped early for safety reasons*.

N Engl J Med. 2008;358:125-139

…from 6% HES 130/0.4 **to** 4% gelatins **to** crystalloids only. *A prospective sequential analysis*.

Crit Care Med 2012; 40:2543–2551

HES 130/0.42 versus Ringer's Acetate in Severe Sepsis (6S)

N Engl J Med 2012;367:124-34.

We **recommend not to use HES** with molecular weight ≥200 kDa and/or degree of substitution 0.4 in patients with ***severe sepsis or risk of acute kidney injury*** and **suggest not to use 6% HES 130/0.4 or gelatin** in these populations.

…**not to use colloids in patients with head injury** and not to administer gelatins and HES in organ donors.

We suggest **not to use hyperoncotic solutions** for fluid resuscitation.

ESICM
Intensive Care Med (2012) 38:368–383

We conclude and recommend that

any new colloid should introduced into clinical practice **only after its patient-important safety parameters are established**.

ESICM Intensive Care Med (2012) 38:368–383

……it is hard to see how their continued use in these patients can be justified outside the context of RCTs.

Colloids versus crystalloids for fluid resuscitation in critically ill patients
Perel P, Roberts I
Cochrane Database of Systematic Reviews. 6, 2012

…….**HES solution** resulted in **reduced inflammation**, **less endothelial damage**, and **fewer alterations in renal tubular integrity** compared with an albumin-based priming.

Boldt J, Anesth Analg 2009;109:1752–62

The Boldt debacle

Cardiopulmonary Bypass Priming Using a High Dose of a Balanced Hydroxyethyl Starch Versus an Albumin-Based Priming Strategy

Joachim Boldt, MD
Stephan Suttner, MD
Christian Brosch, MD
Andreas Lehmann, MD
Kerstin Röhm, MD
Andinet Mengistu, MD

BACKGROUND: The optimal priming solution for cardiopulmonary bypass (CPB) is unclear. In this study, we evaluated the influence of high-volume priming with a modern balanced hydroxyethyl starch (HES) preparation on coagulation, inflammation, and organ function compared with an albumin-based CPB priming regimen.

METHODS: In 50 patients undergoing coronary artery bypass grafting, the CPB circuit was prospectively and randomly primed with either 1500 mL of 6% HES 130/0.42 in a balanced electrolyte solution (Na^+ 140 mmol/L, Cl^- 118 mmol/L, K^+ 4 mmol/L, Ca^{2+} 2.5 mmol/L, Mg^{++} 1 mmol/L, acetate$^-$ 24 mmol/L, malate$^-$ 5 mmol/L) (n = 25) or with 500 mL of 5% human albumin plus 1000 mL 0.9% saline solution (n = 25). Inflammation (interleukins [IL]-6, -10), endothelial damage (soluble intercellular adhesion molecule-1), kidney function (kidney-specific protein α-glutathione *S*-transferase, neutrophil gelatinase-associated lipocalin), coagulation (measured by thromboelastometry [ROTEM®, Pentapharm, Munich, Germany]), and platelet function (measured by whole blood aggregometry [Multiplate® analyzer, Dynabyte Medical, Munich, Germany]) were assessed after induction of anesthesia, immediately after surgery, 5 h after surgery, and on the morning of first and second postoperative days.

RESULTS: Total volume given during and after CPB was 2090 ± 340 mL of balanced HES and 3110 ± 450 mL of albumin. Base excess after surgery was lower in the albumin-based priming group than in the balanced HES priming group (−5.9 ± 1.2 mmol/L vs −0.2 ± 0.2 mmol/L, P = 0.0003). Plasma levels of IL-6, IL-10, and intercellular adhesion molecule-1 were higher after CPB in the albumin-based priming group compared with the HES priming group at all time periods (P = 0.0032). Urinary concentrations of α-glutathione *S*-transferase and neutrophil gelatinase-associated lipocalin were higher after CPB through the end of the study in the albumin group compared with the balanced HES group (P = 0.00004). After surgery through the first postoperative day, thromboelastometry data (clotting time and clot formation time) revealed more impaired coagulation in the albumin-based priming group compared with the HES priming group (P = 0.004). Compared with baseline, platelet function was unchanged in the high-dose balanced HES priming group after CPB and 5 h after surgery, but it was significantly reduced in the albumin-based priming group.

CONCLUSIONS: High-volume priming of the CPB circuit with a modern balanced HES solution resulted in reduced inflammation, less endothelial damage, and fewer alterations in renal tubular integrity compared with an albumin-based priming. Coagulation including platelet function was better preserved with high-dose balanced HES CPB priming compared with albumin-based CPB priming.

The ideal strategy for priming of the cardiopulmonary bypass (CPB) circuit in adult cardiac surgery is still a matter of debate.[1–8] In many institutions, either albumin or nonprotein synthetic colloids (gelatins, dextrans, hydroxyethyl starch [HES]) are added to the crystalloid-based prime. HES preparations are classified based on their mean molecular weight (MW; low MW HES: 70 kD; medium MW HES: from 130 to 260 kD; high MW [HMW] HES: >450 kD), their molar substitution (MS; high MS: >0.7; medium MS: >0.5; low MS: >0.5), and their ratio of the C_2/C_6 hydroxyethylation. The importance of the diluent solution of HES has been recently emphasized.[7,8] Most colloids (including albumin) are diluted in 0.9% normal saline that contains nonphysiologically high concentrations of sodium (154 mmol/L) and chloride (154 mmol/L) that might contribute to hyperchloremic acidosis.[9] Modern HES preparations are dissolved in an electrolyte solution closer in composition to plasma ("balanced" or "plasma adapted" solutions). The purpose

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Accepted for publication June 12, 2009.

Supported by a hospital grant.

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Happy dawn.

A gift from NEJM.

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

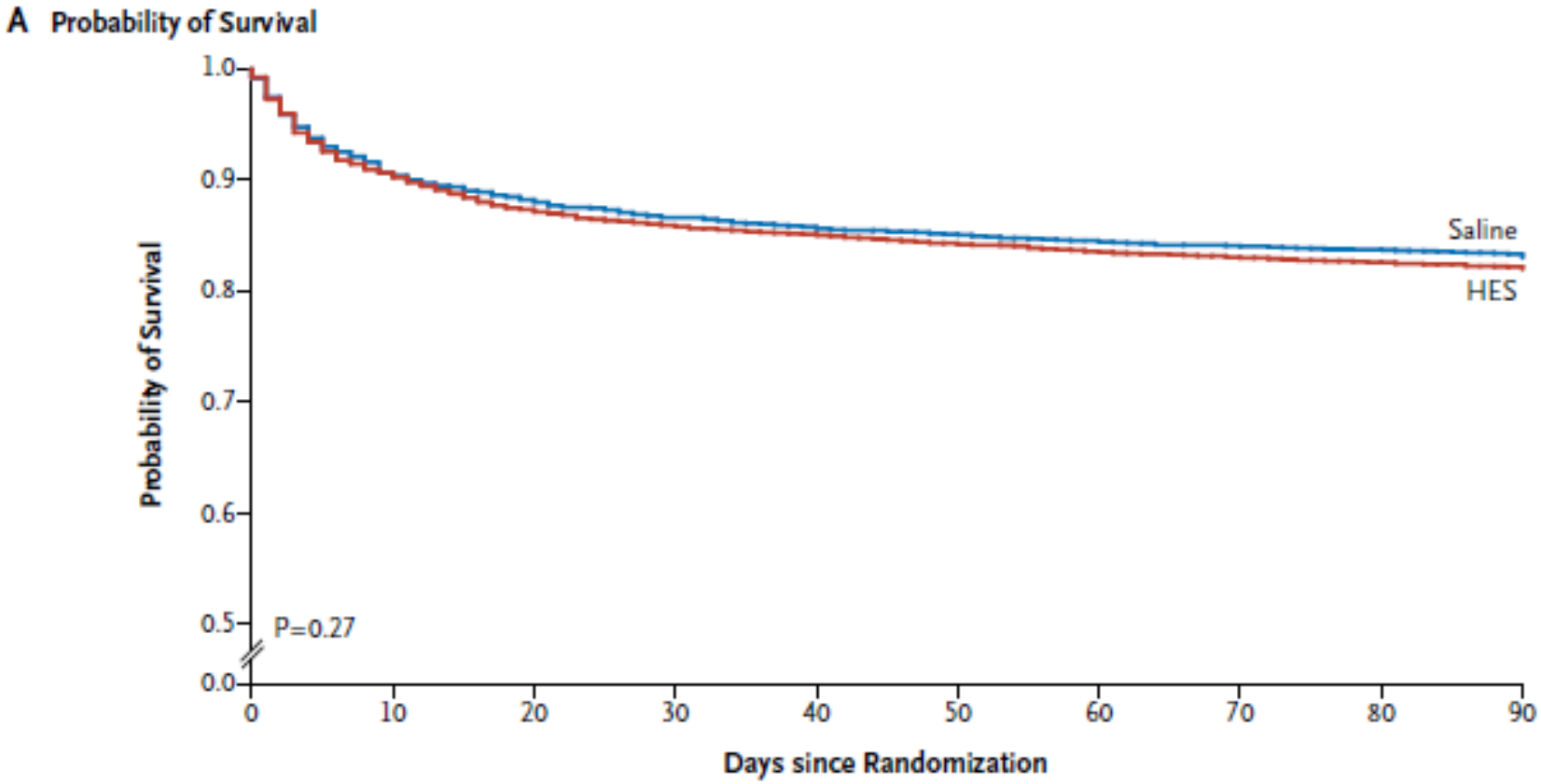
John A. Myburgh, M.D., for the **CHEST** Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group

NEJM October 17, 2012
DOI: 10.1056/NEJMoa1209759

In patients in the ICU, there was no significant difference in 90-day mortality between patients resuscitated with 6% HES (130/0.4) or saline.

However, more patients who received resuscitation with HES were treated with renal-replacement therapy.

NEJM October 17, 2012
DOI: 10.1056/NEJMoa1209759



NEJM October 17, 2012
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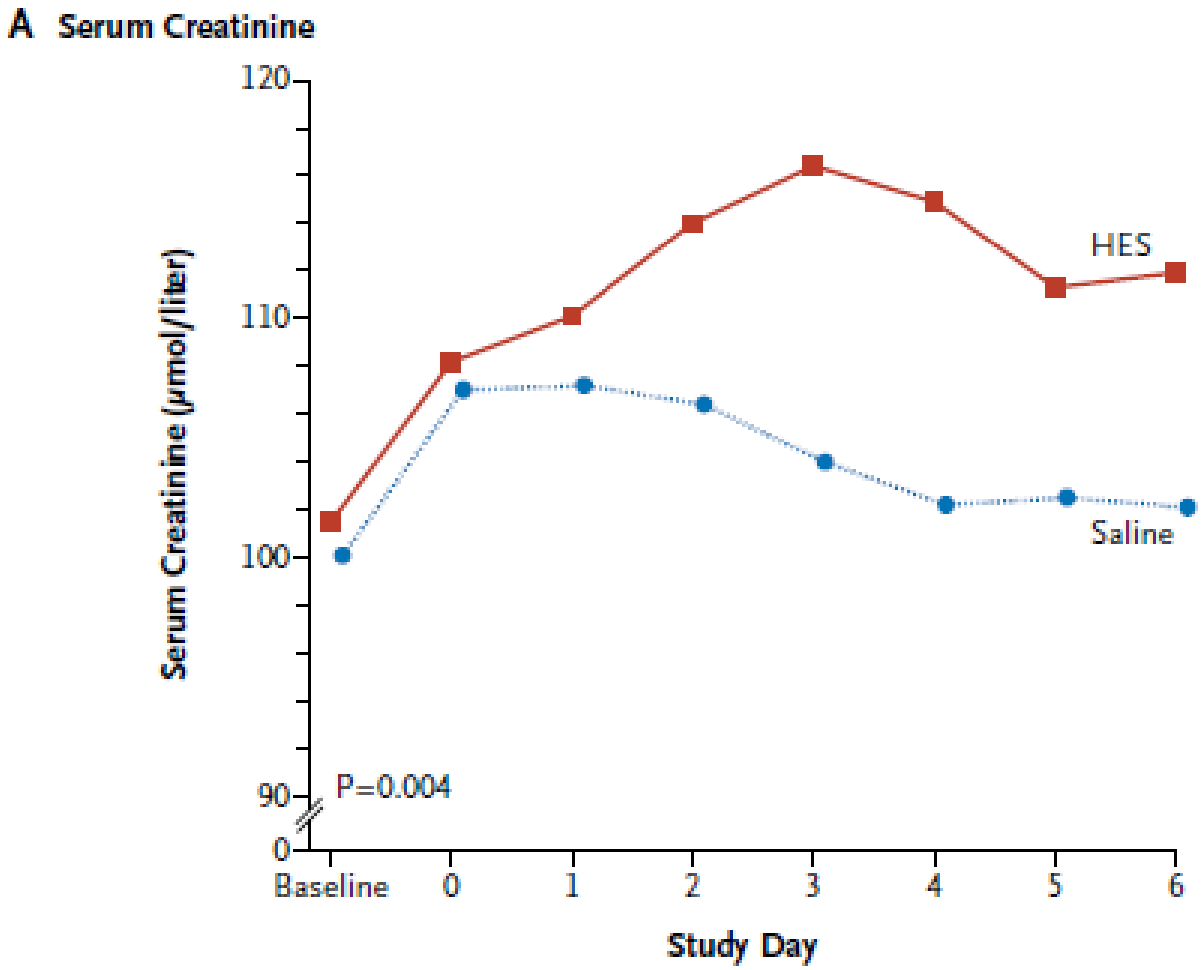


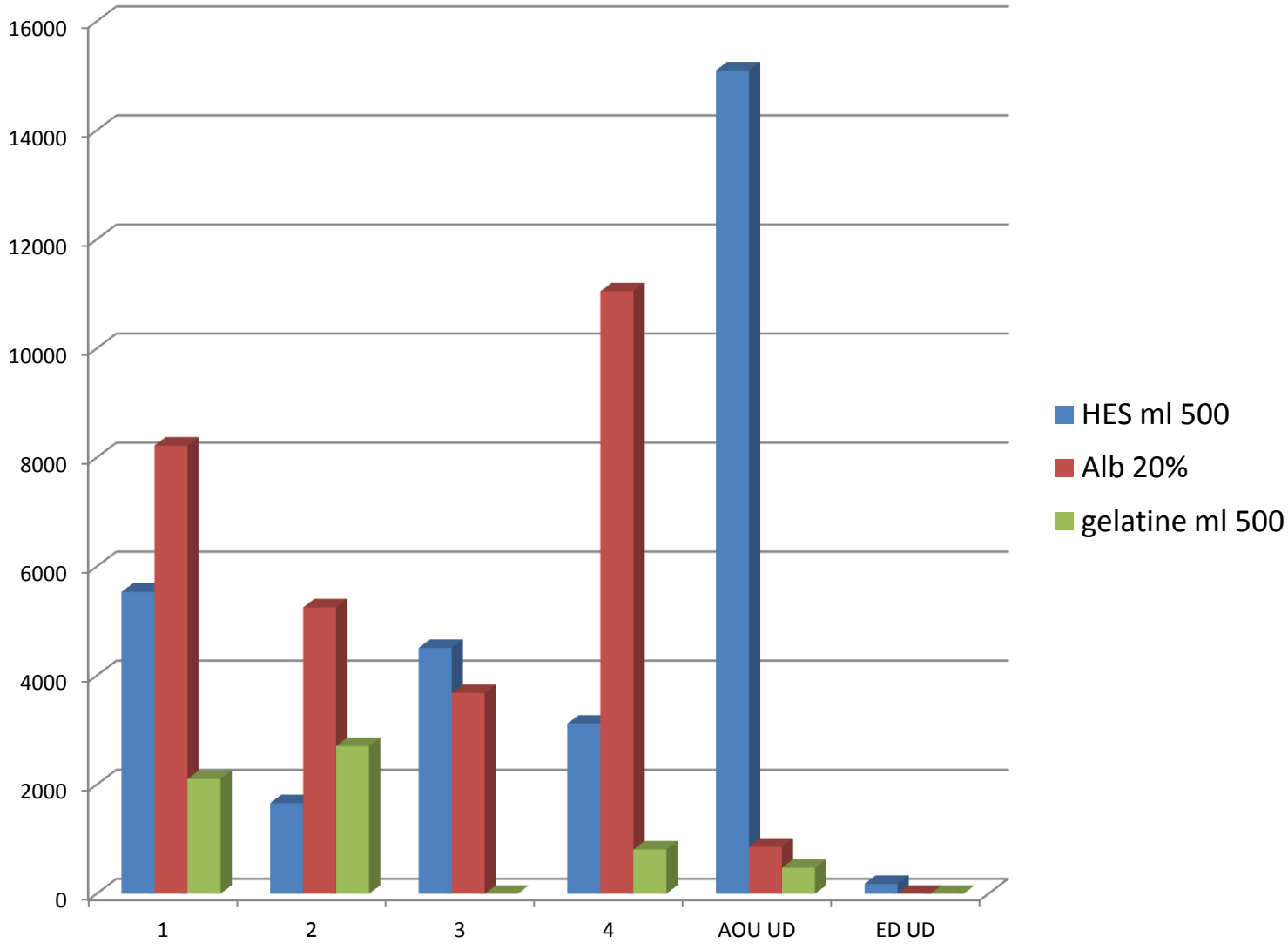
NEJM October 17, 2012
DOI: 10.1056/NEJMoa1209759

In conclusion, our study **does not provide evidence that resuscitation with 6% HES (130/0.4), as compared with saline, in the ICU provides any clinical benefit to the patient.**

Indeed, the use of HES resulted in an **increased rate of renal replacement therapy**.

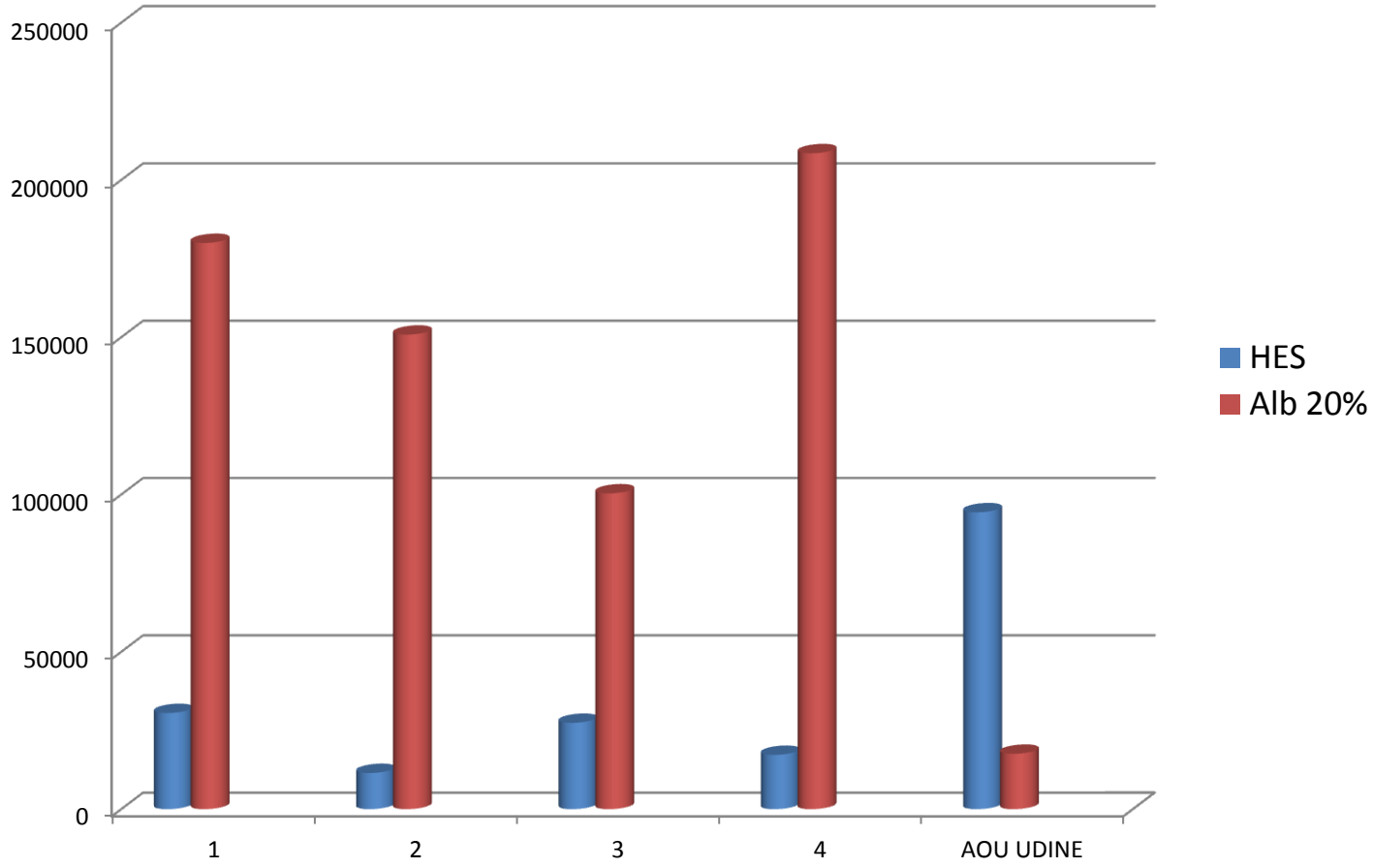
Thus, the selection of resuscitation fluid in critically ill patients requires careful consideration of its **safety**, its potential effect on patient-centered outcomes, and its **cost**.

NEJM October 17, 2012
DOI: 10.1056/NEJMoa1209759


16000
14000
12000
10000
8000
6000
4000
2000
0
1
2
3
4
AOU UD
ED UD
HES ml 500
Alb 20%
gelatine ml 500

2011

€


250000
200000
150000
100000
50000
0
1
2
3
4
AOU UDINE
HES
Alb 20%

2011

courtesy of Chiara Paccagnella,RN

…if the ideal randomized, controlled trial definitively reported the truth, **would clinical practice change?**

Han J, Martin GS Critical Care 2010, 14:1006

The difficulty lies, not in new ideas, but in escaping old ones, which ramify, for those brought up with them, as most of us have been, into every corner of our minds.

John Maynard Keynes