22° Tuscany Critical Care Group

Firenze, September 25-26, 2019

Albumina: 20% vs. 5%. Indicazioni e differenze

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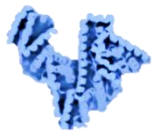
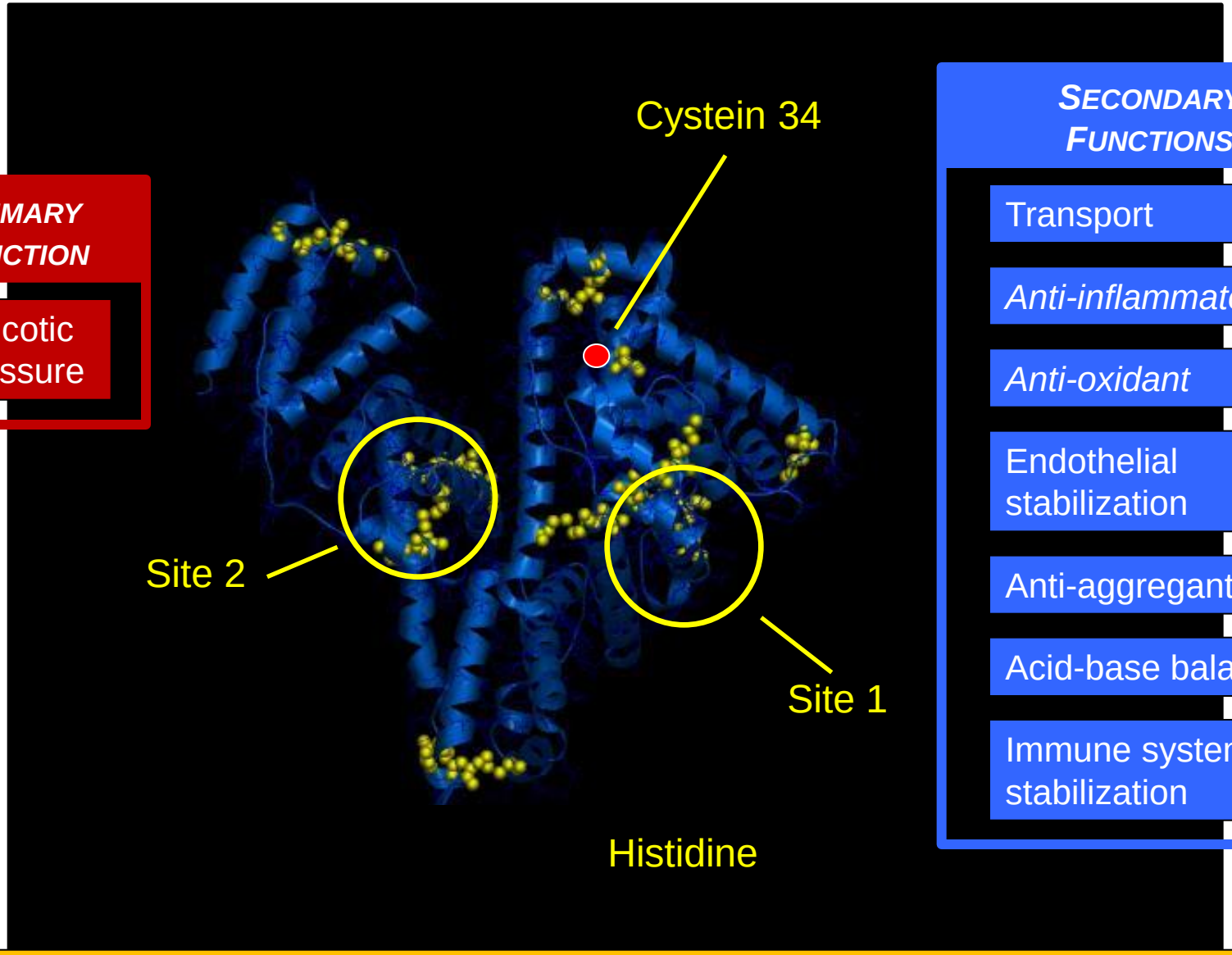


PRIMARY FUNCTION

Oncotic Pressure



SECONDARY FUNCTIONS

- Transport
- *Anti-inflammatory*
- *Anti-oxidant*
- Endothelial stabilization
- Anti-aggregant
- Acid-base balance
- Immune system stabilization

***imary** and **Secondary** functions of ALBUMIN, as potentially clinically relevant in hospitalized patien*

- General overview
  (composition, rationale, caveats, efficacy)
- Specific indications and clinical evidence
  (20% and 4-5% albumin)
- Comparison of efficacy (4-5% vs. 20% albumin)
- Specific aspects and open questions

Composition of different Albumin-containing solutions

Table 2 | **Composition of commonly used colloid intravenous fluids**

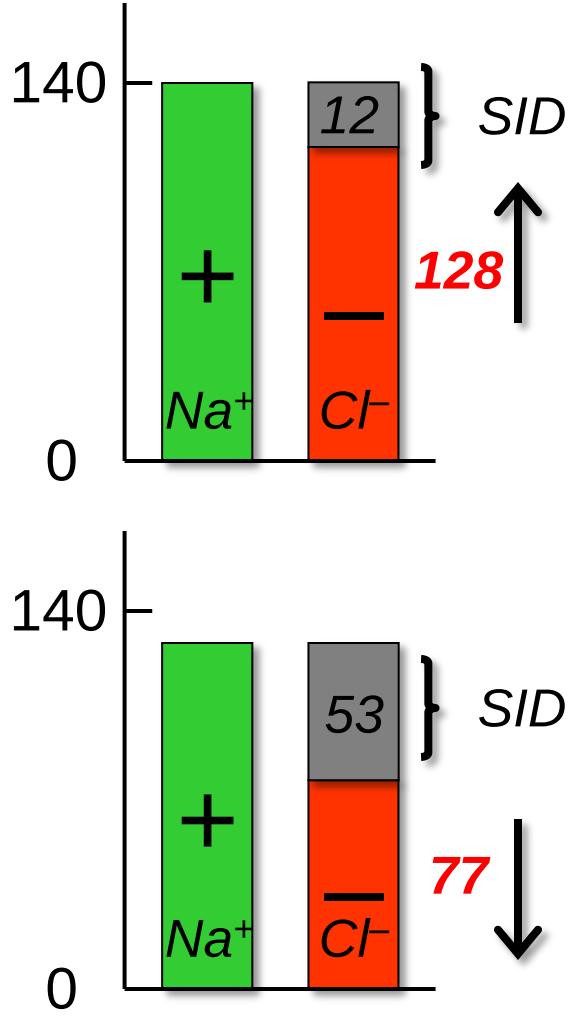
Solution	Characteristics and composition (per litre)
Albumin 4%	• Osmolarity: 250 mOsm/l (calculated) • Osmolality: 260 mOsm/kg (measured) • pH 6.7–7.3 • Na^+ 140 mmol, Cl^- 128 mmol and octanoate 6.4 mmol
Albumin 5%	• Osmolarity: 309 mOsm/l (calculated) • Osmolality: 309 mOsm/kg (measured) • pH 6.4–7.4 • Na^+ 130–160 mmol, K^+ <2 mmol, Cl^- ~130 mmol, sodium caprylate 4 mmol and sodium N-acetyl tryptophanate 4 mmol
Albumin 20%	• Osmolarity: 130 mOsm/l (calculated) • Osmolality: 130 mOsm/kg (measured) • pH 6.7–7.3 • Na^+ 48–100 mmol and octanoate 32 mmol
Albumin 25%	• Osmolarity: 312 mOsm/l (calculated) • Osmolality: 312 mOsm/kg (measured) • pH 6.4–7.4 • Na^+ 130–160 mmol, K^+ <1 mmol, Cl^- ~130 mmol, sodium caprylate 4 mmol and sodium N-acetyl tryptophanate 4 mmol

Iso-oncotic

Hypo-tonicity

Iso-tonicity

Hyper-oncotic



Finfer S et al., Nat Rev 2018;14:541-557

Albumin vs. Volume administration – DIFFERENCES and CAVEATS

1 *Dissociation of the two effects*

Albumin 20%

Albumin + Volume

Supplementation

Albumin 4/5%

Albumin + Volume

Volume

2 *Similarity of the final effect*

5% albumin = 20% albumin + crystalloids

100 ml 20% albumin + 500 ml crystalloid

20% albumin = 20 gr / 100 ml = 10 gr / 50 ml

4% albumin = 4 gr / 100 ml = 20 gr / 500 ml

100 ml with 20 gr + 400 ml = 20 gr / 500 ml

500 ml (4 gr/100 mL) = 500 ml 4% albumin

- General overview
  (composition, rationale, caveats, efficacy)
- Specific indications and clinical evidence
  (20% and 4-5% albumin)
- Comparison of efficacy (4-5% vs. 20% albumin)
- Specific aspects and open questions

Evidence for Hemodynamic Advantage

Crystalloids vs. colloids for fluid resuscitation in the Intensive Care Unit: A systematic review and meta-analysis

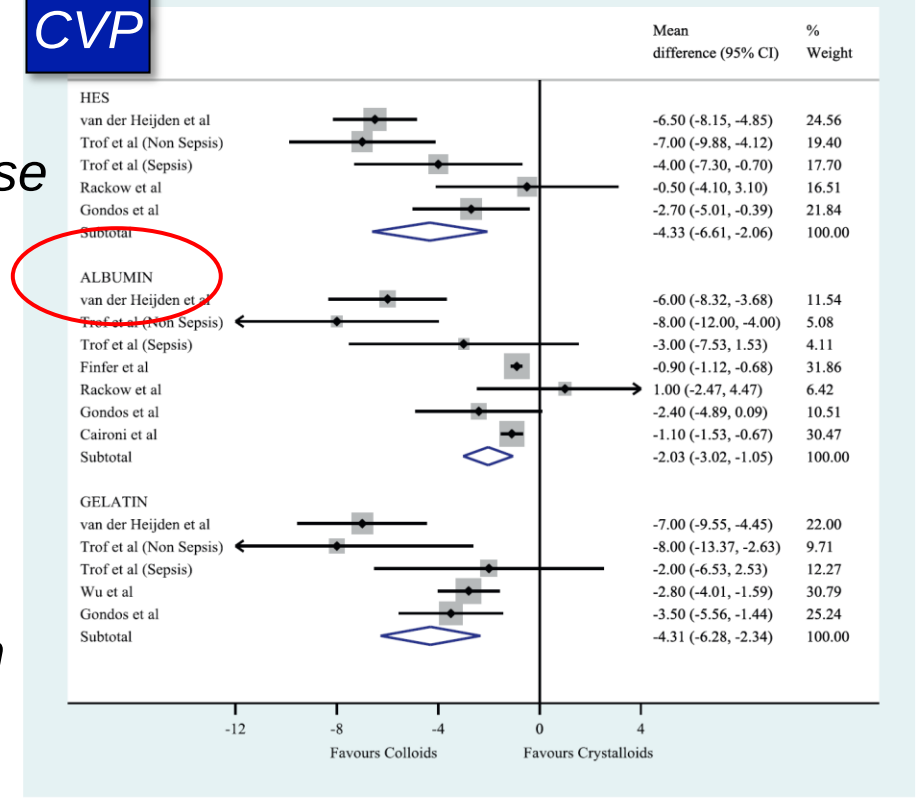
Greg S. Martin [a,*], Paul Bassett [b]

[a] Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine, Emory University School of Medicine, Grady Memorial Hospital, Atlanta, GA, USA
[b] Meridian HealthComms, Plumley Moor Road, Plumley, UK

- *Hemodynamic response to crystalloids/colloids (critically ill pts)*
- *55 RCTs 27,036 pts*
- *HES, Albumin, Gelatin vs. Crystalloids*

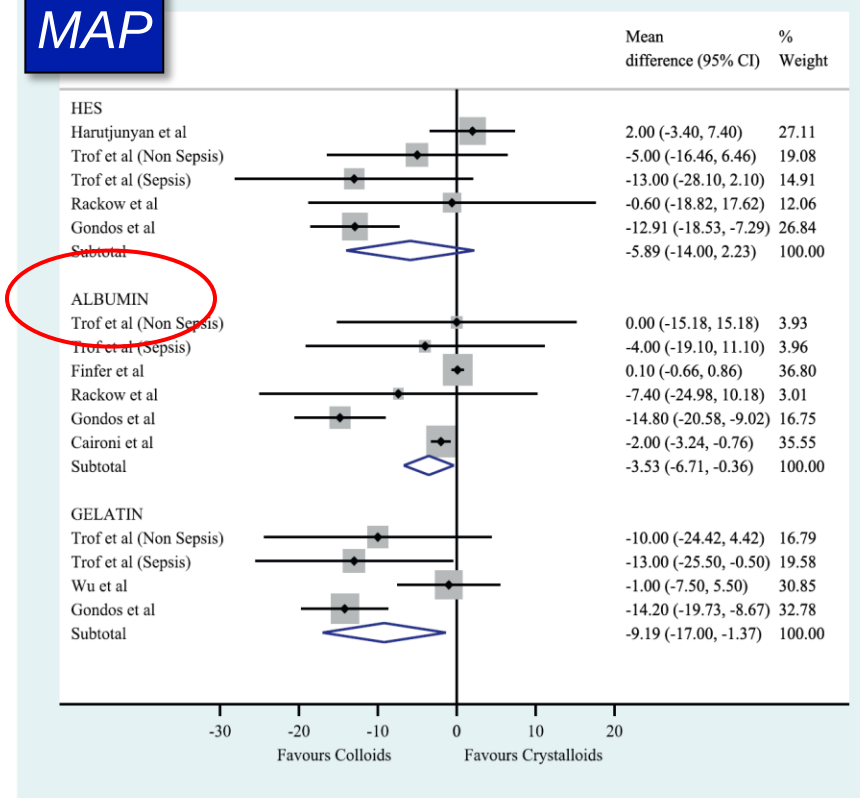
A

CVP



B

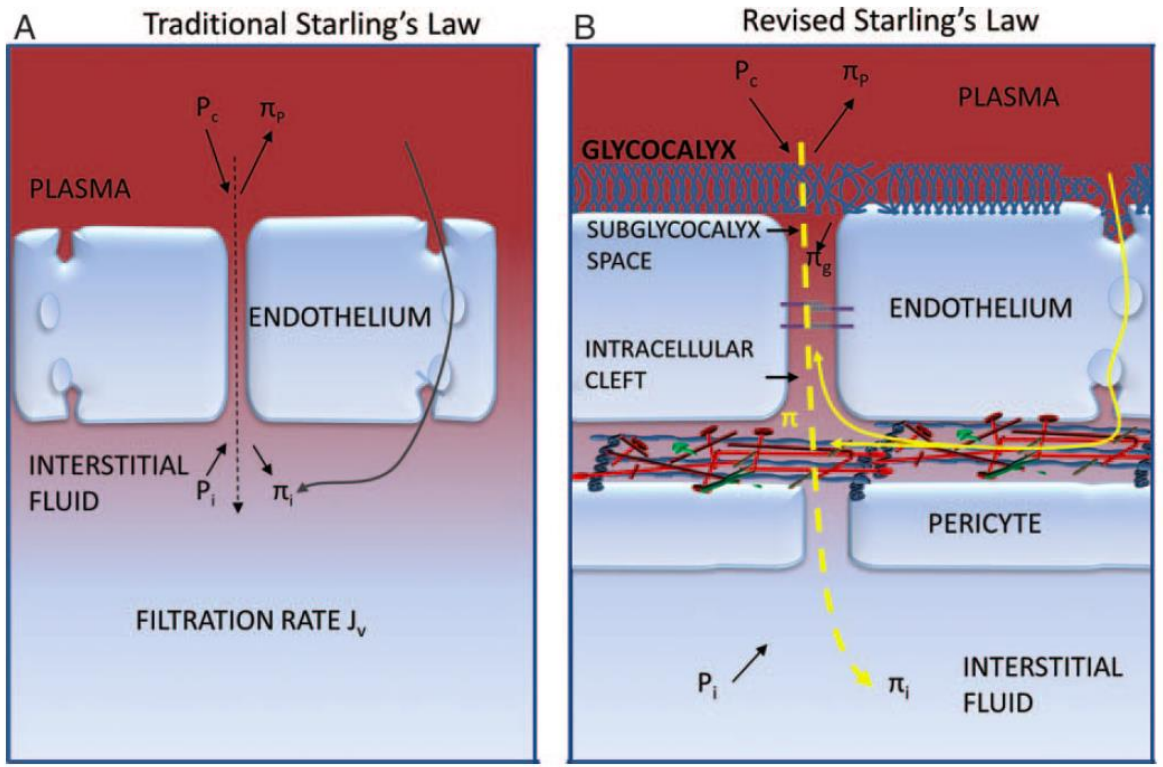
MAP



J Crit Care 2019;50:144-154

Capillary hemodynamics – Glycocalyx and Vascular Permeability

Oncotic gradient shift (from interstitium to sub-glycocalyx space)



A $Filtration\ rate = K_f\,[(P_c - P_i) - \sigma\,(\pi_c - \pi_i)]$

B $Filtration\ rate = K_f\,[(P_c - P_i) - \sigma\,(\pi_c - \pi_g)]$

σ reflection coefficient
P hydrostatic pressure
Π oncotic pressure

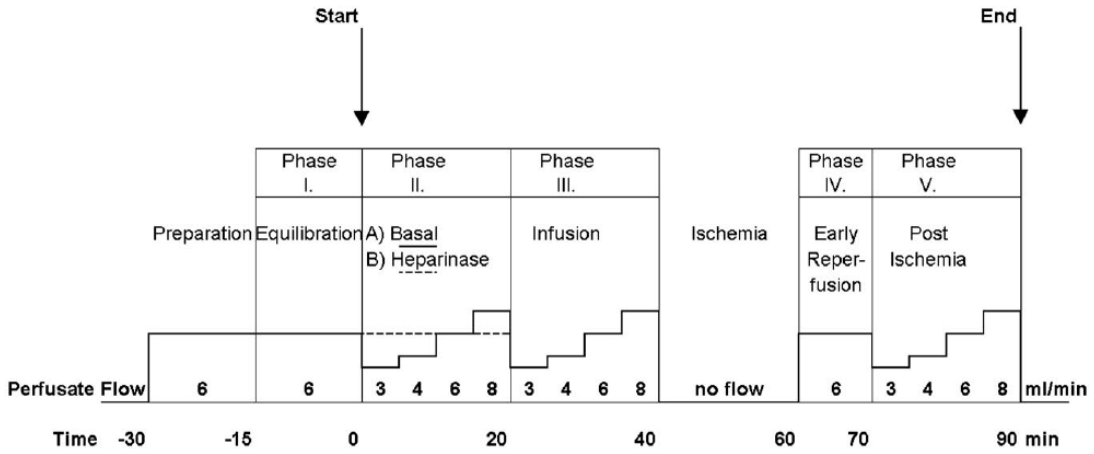
Melissa A et al., Shock 2016;46:20-36

Contrasting Effects of Colloid and Crystalloid Resuscitation Fluids on Cardiac Vascular Permeability

Matthias Jacob, M.D., Dirk Bruegger, M.D.,* Markus Rehm, M.D.,† Ulrich Welsch, M.D., Ph.D.,‡ Peter Conzen, M.D.,§ Bernhard F. Becker, M.D., Ph.D.‖*

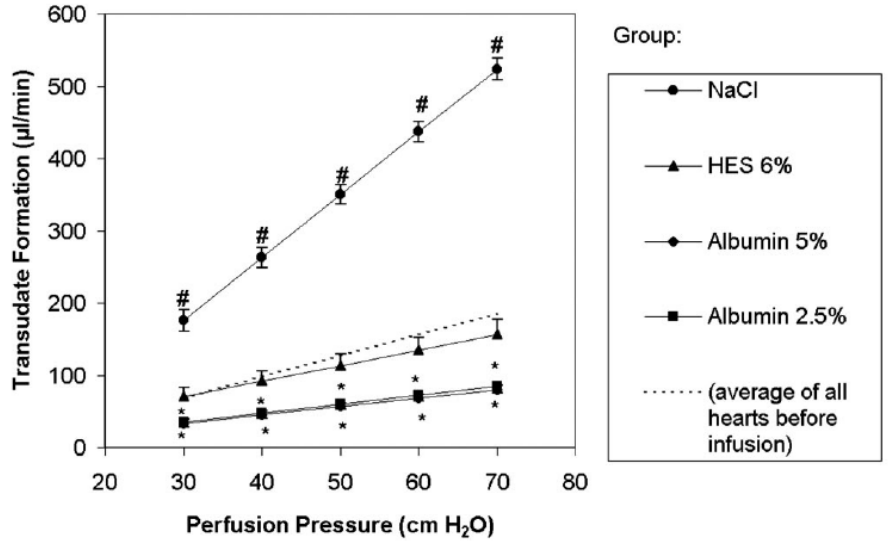
FLUIDS: In-vitro Isolated model

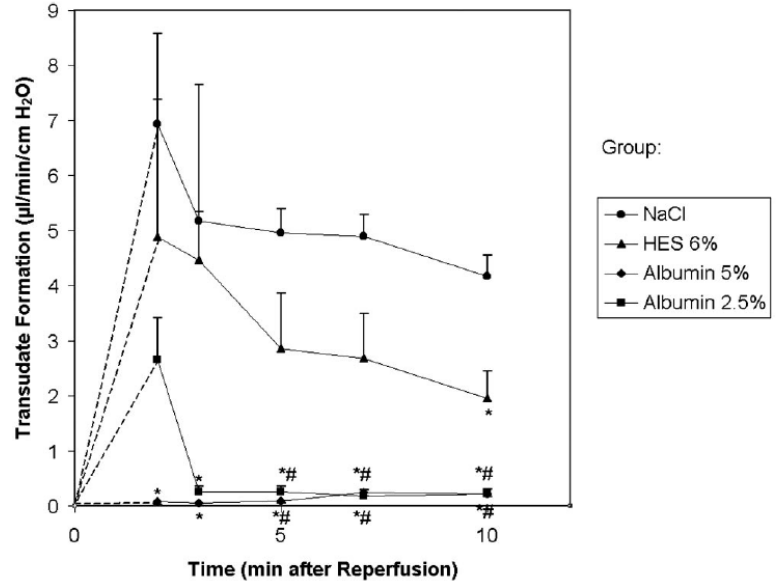
Anesthesiology 2006;104:1223-31

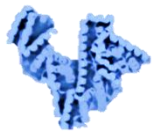


- *Isolated perfused heart model (guinea pig) of IR-injury*
- *Perfusion pressure vascular fluid filtration (different flow rates)*

***Albumin** more effectively prevented fluid extravasation than crystalloid and synthetic colloids*







20% Albumin

- 1818 patients with severe sepsis or septic shock
- Albumin + Crystalloids *vs*. Crystalloids during the first 28 days
- 28-day and 90-day mortality
- Funded by Italian Medicines Agency (AIFA)

The NEW ENGLAND JOURNAL of MEDICINE

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*

ABSTRACT

BACKGROUND

Although previous studies have suggested the potential advantages of albumin administration in patients with severe sepsis, its efficacy has not been fully established.

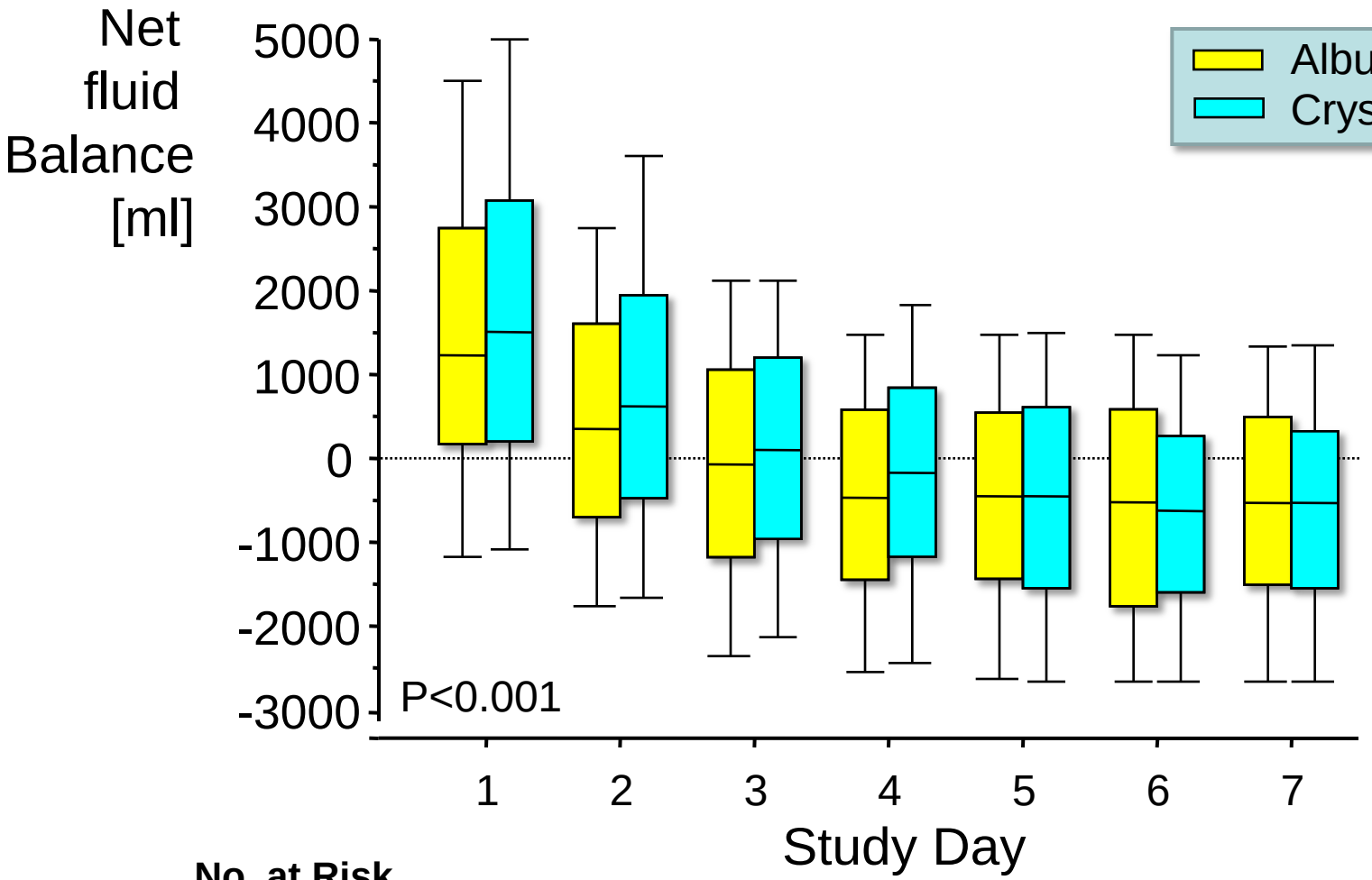
METHODS

In this multicenter, open-label trial, we randomly assigned 1818 patients with severe sepsis, in 100 intensive care units (ICUs), to receive either 20% albumin and crystalloid solution or crystalloid solution alone. In the albumin group, the target serum albumin concentration was 30 g per liter or more until discharge from the ICU or 28 days after randomization. The primary outcome was death from any cause at 28 days. Secondary outcomes were death from any cause at 90 days, the number of patients with organ dysfunction and the degree of dysfunction, and length of stay in the ICU and the hospital.

N Engl J Med 2014;370:1412-21

From ALBIOS trial: net daily fluid balance

20% Albumin



No. at Risk

Albumin	840	789	742	701	639	586	542
Crystalloids	844	795	735	685	635	587	529

"Using albumin in addition to crystalloids when pts require substantial amount of crystalloids"

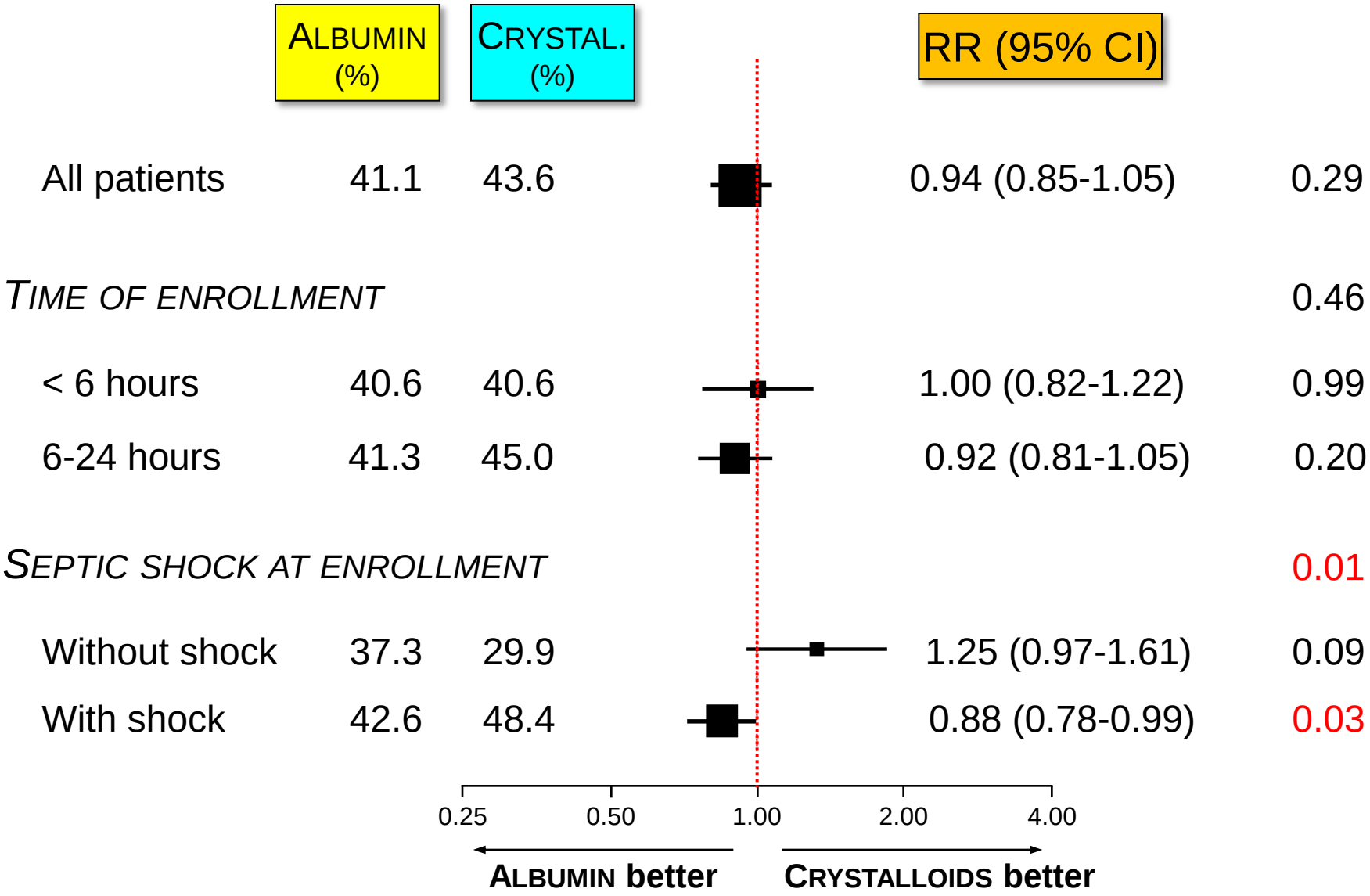
Weak recommendation
Low quality of evidence

SSC 2017
Crit Care Med 2017;45:486-552

Caironi P et al., N Engl J Med 2014;370:1412-21

Results of main study – Subgroup post-hoc analysis

20% Albumin



Caironi P et al., N Engl J Med 2014;370:1412-21

Future RCTs upcoming…

ALBIOSS-BALANCED trial

(*Efficacy of Albumin Replacement and Balanced Solutions in Patients with Septic Shock*)

20% Albumin

ALBIOS 2

ALBumin Italian Outcome Sepsis study

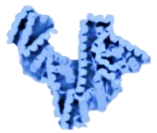
Pietro Caironi (PI), Antonio Pesenti (co-PI)

ARISS trial

(*A Randomized Controlled Multicenter Trial on Albumin Replacement in Septic Shock*)

Yasser Sakr (PI), Luciano Gattinoni and Michael Quintel (co-PI)

IPDMA pre-planned



Lactated Ringer's Versus 4% Albumin on Lactated Ringer's in Early Sepsis Therapy in Cancer Patients: A Pilot Single-Center Randomized Trial

Clarice Hyesuk Lee Park, MD[1]; Juliano Pinheiro de Almeida, PhD[1]; Gisele Queiroz de Oliveira, MD[1]; Stéphanie Itala Rizk, MD[1]; Julia Tizue Fukushima, MSc[1]; Rosana Ely Nakamura, MD[1]; Matheus Moraes Mourão, MD[1]; Filomena Regina Barbosa Gomes Galas, PhD[2]; Edson Abdala, PhD[3]; Maristela Pinheiro Freire, PhD[3]; Roberto Kalil Filho, PhD[4,5]; Jose Otavio Costa Auler Jr, PhD[2]; Pasquale Nardelli, MD[6]; Greg S. Martin, MD[7]; Giovanni Landoni, MD[6,8]; Ludhmila Abrahao Hajjar, PhD[1,4,5]

4% Albumin

- *Albumin role as a resuscitation fluid in the early phase of sepsis never investigated*
- *Single-center, double blind, RCT, in 360 pts with cancer admitted to ICU with sepsis or septic shock*
- *500 mL of either 4% albumin + RL or RL in < 10 min after analysis of fluid status (physical examination)*
- *Primary outcome: death from any cause within 7 days*

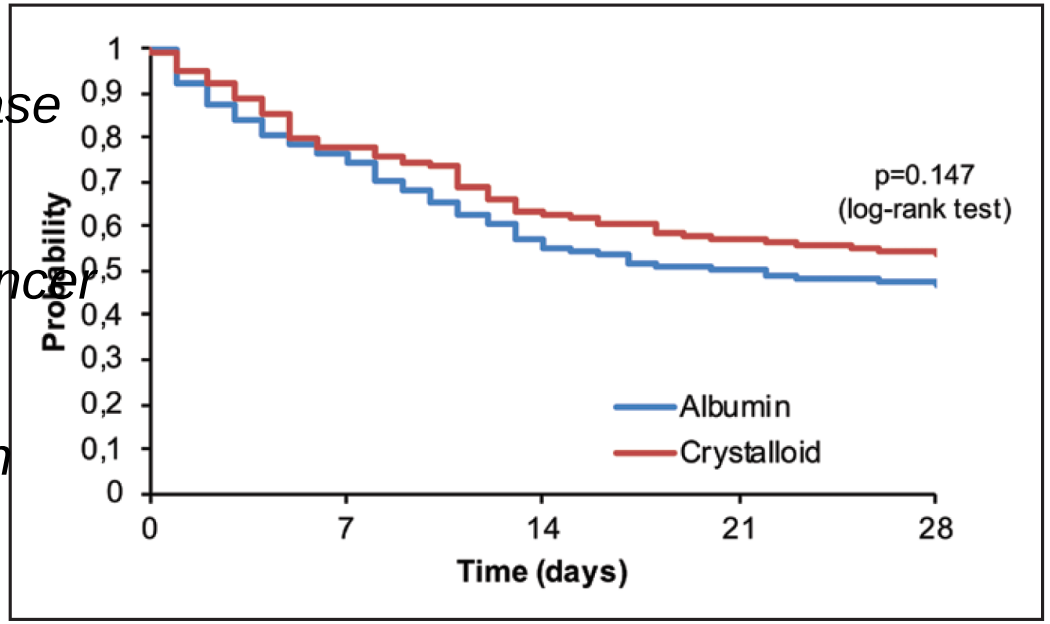


Figure 1. Twenty-eight–day mortality Kaplan-Meier curve.

Crit Care Med 2019;47:e798-e805

- General overview
  (composition, rationale, caveats, efficacy)
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  (20% and 4-5% albumin)
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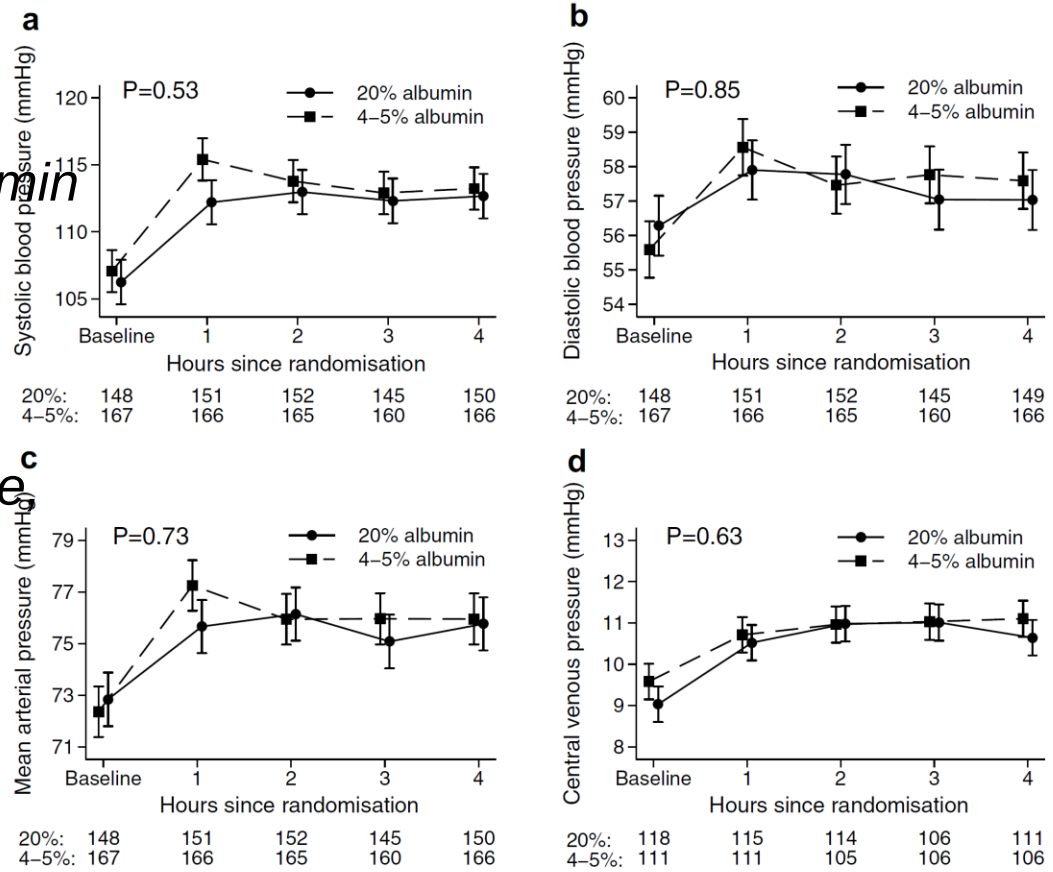
Comparison of 4-5% vs. 20% Albumin

ORIGINAL

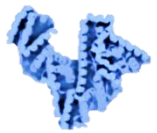
Small volume resuscitation with 20% albumin in intensive care: physiological effects

The SWIPE randomised clinical trial

- *Resuscitation fluid requirements of ICU pts resuscitated with 20% albumin vs. 4-5% albumin*
- *Inclusion criteria*
  Adult pts hemodynamic unstable requiring fluid bolus within 48 h of ICU admission (hypotension, vasopressor need, PPV positive or CI, HR, UO, lactate, refill time)
- *Fluid resuscitation with 20% or 4-5% albumin during the first 48 h for hemodynamic target*
- *Primary outcome:*
  cumulative volume of resuscitation fluid



Martensson J et al., Intensive Care Med 2018;44:1797-1806



4-5% vs. 20% Albumin

Table 2 Primary and secondary outcomes in the first 48 h after randomisation

Outcome	20% albumin group ($n = 153$)	4–5% albumin group ($n = 168$)	20% albumin vs. 4–5% albumin (95% CI)	*P* value[a]
Volume of resuscitation fluid, median (IQR), ml	300 (200, 500)	900 (500, 1250)	− 600 (− 800 to − 400)	< 0.001
Volume of study fluid, median (IQR), ml	300 (200, 400)	750 (500, 1250)	− 450 (− 547 to − 353)	< 0.001
Total fluid input, median (IQR), ml	3429 (2132, 4937)	4217 (2634, 5847)	− 801 (− 1634 to 31.8)	0.06
Total fluid output, median (IQR), ml	2995 (1850, 4409)	3353 (2180, 4781)	− 360 (− 836 to 116)	0.14
Total urine output, median (IQR), ml	2235 (1235, 3450)	2407 (1429, 3580)	− 188 (− 727 to 351)	0.49
Cumulative fluid balance, mean (SD), ml	354 (2124)	930 (2038)	− 576 (− 1033 to − 119)	0.01
Maximum norepinephrine infusion rate, median (IQR), µg/min	2 (0, 6)	4 (0, 10)	− 2 (− 5 to 1)	0.19
Maximum albumin level, mean (SD), g/l	35 (6.2)	32 (5.4)	2.5 (1.2–3.8)	< 0.001

***Small** volume resuscitation with **20% albumin** reduced resuscitation fluid requirement and **minimized fluid accumulation** compared with resuscitation with 4-5% albumin*

***Small** volume resuscitation with **20% albumin** did **not negatively impact kidney function** or other key clinical outcomes*

Martensson J et al., Intensive Care Med 2018;44:1797-1806

Possible Limitations of the SWIPE trial

- *Study population* (most postoperative pts, only 11% of septic pts)
- *Heterogeneity of the effect*
  (possible different effect in septic pts; P = 0.05 – not discussed…)
- *Data collection*
  (infusion rate and dosage not fixed; no data on infusion rate)
- *Short follow-up period*
  (only 48 hours – inadequate follow-up period for renal injury / intravascular effect)

Open question: more severe patients (or pts with sepsis)?

- General overview
  (composition, rationale, caveats, efficacy)
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  (20% and 4-5% albumin)
- Comparison of efficacy (4-5% vs. 20% albumin)
- Specific aspects and open questions

Possible risk of Renal Hyper-oncotic Injury

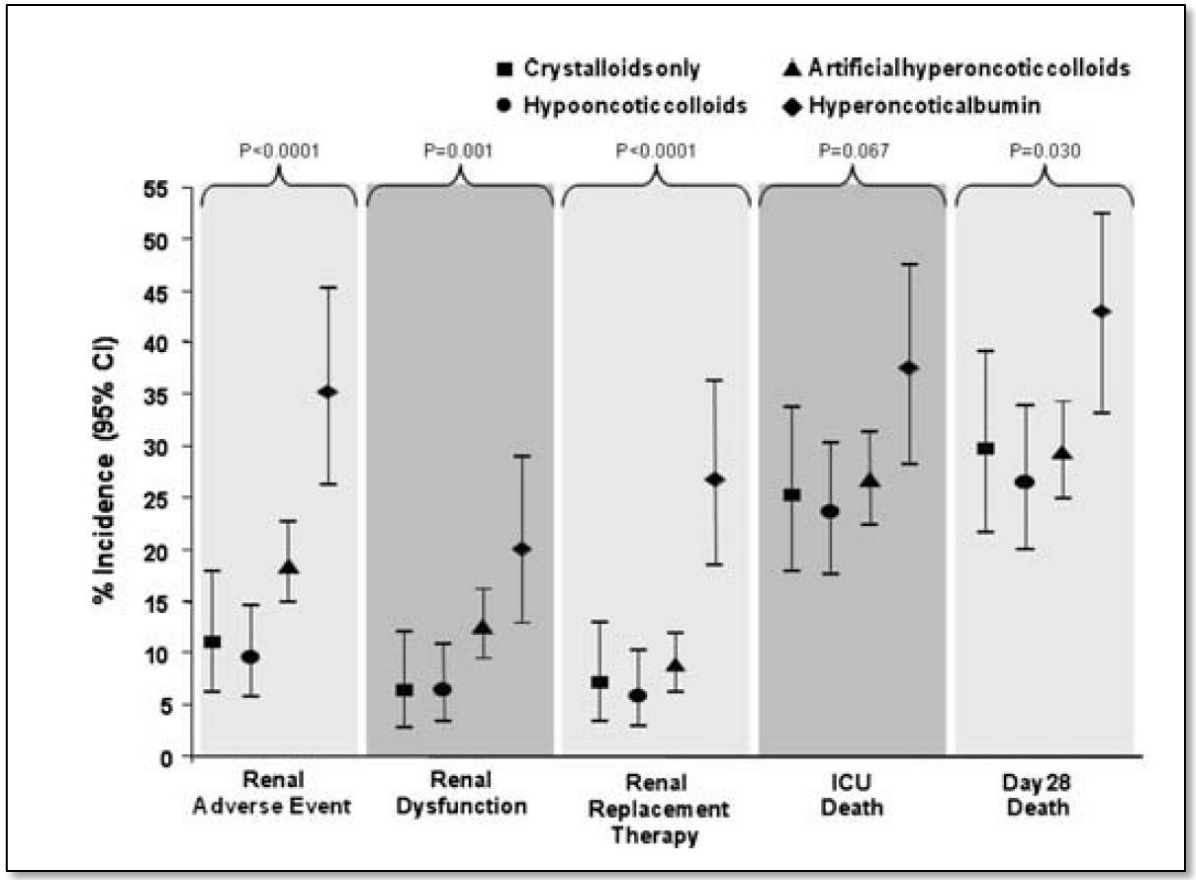
Frédérique Schortgen
Emmanuelle Girou
Nicolas Deye
Laurent Brochard
for the CRYCO Study Group

The risk associated with hyperoncotic colloids in patients with shock

Intensive Care Med 2008;34:2157-2168

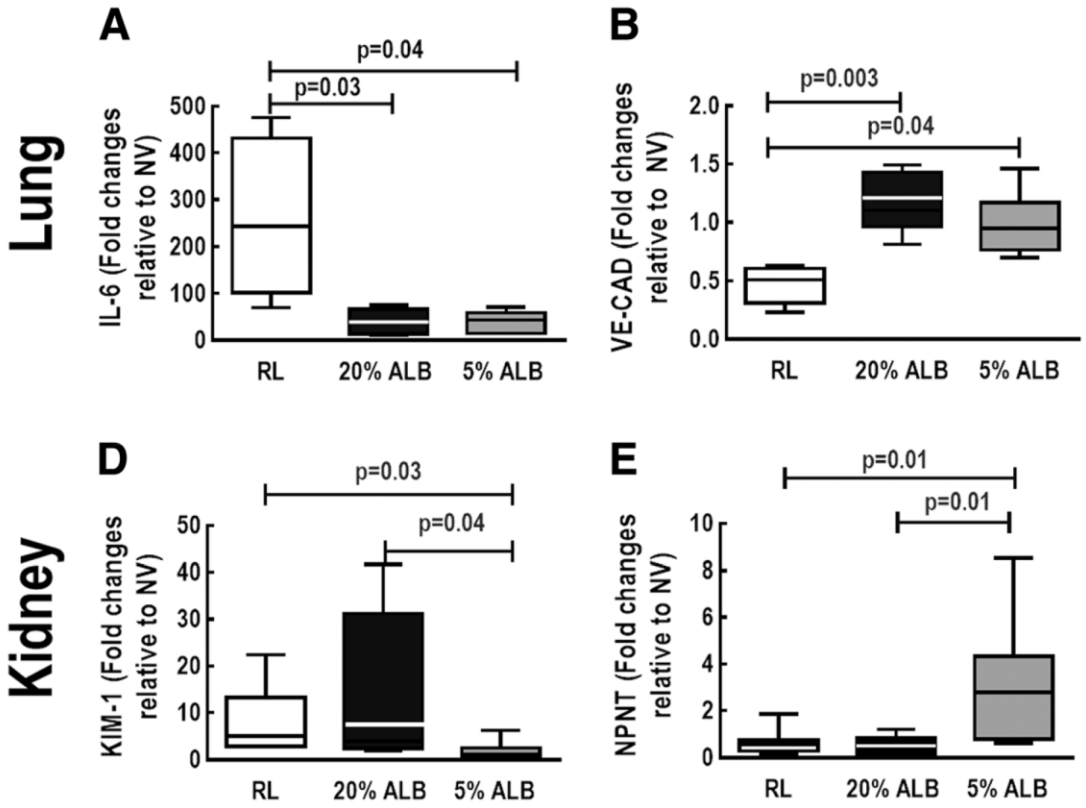
Multicenter, prospective, cohort study

- *1013 ICU pts*
- *needing fluids for shock*
- *rapid administration*
- *renal events / mortality*



RESEARCH Open Access

Effects of crystalloid, hyper-oncotic albumin, and iso-oncotic albumin on lung and kidney damage in experimental acute lung injury



- *Experimental in-vivo model of LPS-induced ALI*
- *Hemodynamic resuscitation With RL, 20%ALB, or 5%ALE*

Iso-oncotic and hyper-oncotic ALB solutions were associated with less lung injury compared to RL Hyper-oncotic ALB resulted in a greater AKI than iso-oncotic ALB

S. Mendes et al., Respiratory Research 2019;20:155

Possible importance of infusion rate – Hypothesis…

Study	Dosage and time	Infusion rate	Intravascular expansion	AKI	Healthy?
ALBIOS (NEJM 2014)	300 mL 20% ALB in 3h	4.7 mg/kg/min	Yes	No	
RASP (CCM 2019)	500 mL 4% ALB in < 10 min	30 mg/kg/min	No	No	
De S. Mendes (RR 2019)	2 mL/kg 20% ALB as bolus *(flush)*	420 mg/kg/min	~	Yes	
Bihari S (JAP 2019)	480 mL 20% ALB in 20 min	60 mg/kg/min	Yes	No	

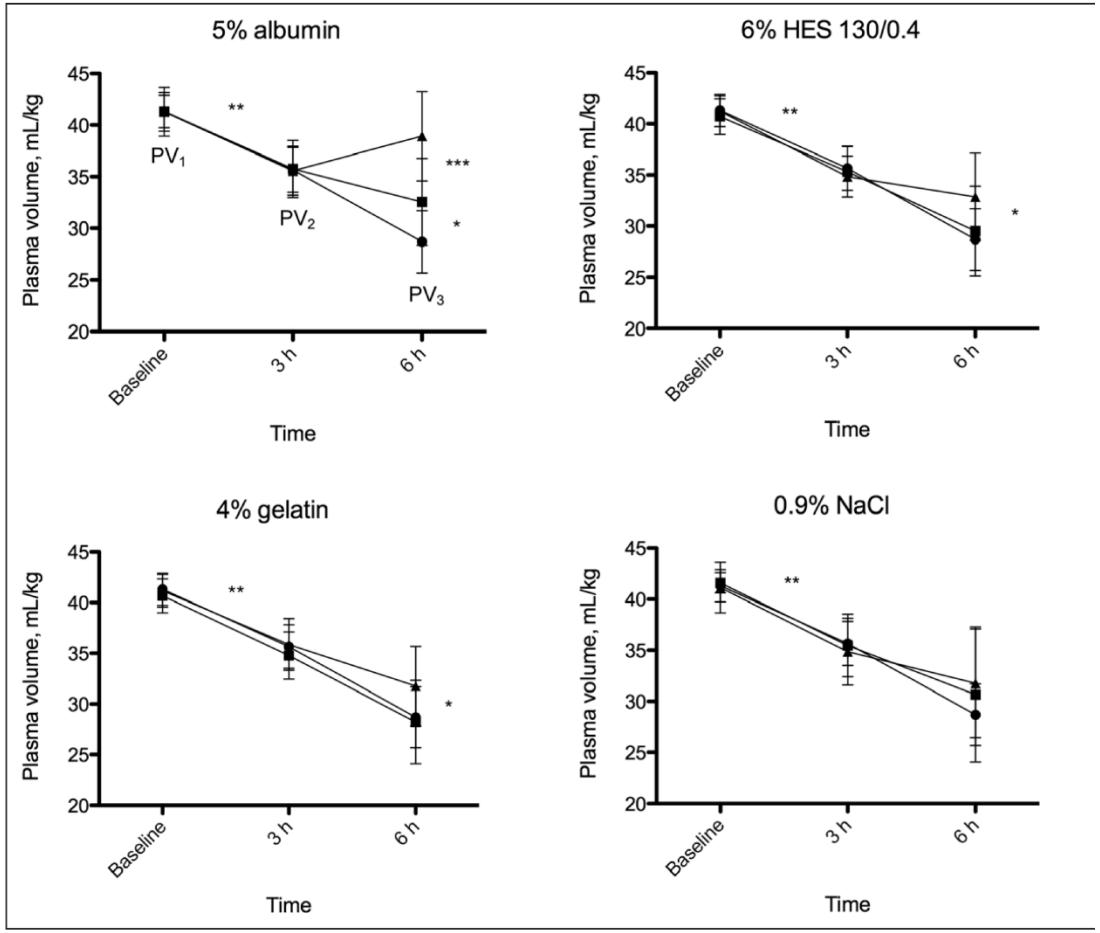
Possible importance of infusion rate

Importance of the Infusion Rate for the Plasma Expanding Effect of 5% Albumin, 6% HES 130/0.4, 4% Gelatin, and 0.9% NaCl in the Septic Rat*

Björn P. Bark, MD; Johan Persson, MD, PhD; Per-Olof Grände, MD, PhD

Crit Care Med 2013; 41:857-866

- 112 adult male rats with sepsis (*cecal ligation model*)
- Volume replacement:
  1) 5% albumin
  2) 6% HES 130/0.4 — 12 mL/kg
  3) 4% gelatin
  4) 0.9% NaCl — 48 mL/kg
- 15-*min* vs. 3-*hrs* infusion
- Plasma Volume measurement with ^{125}I-albumin



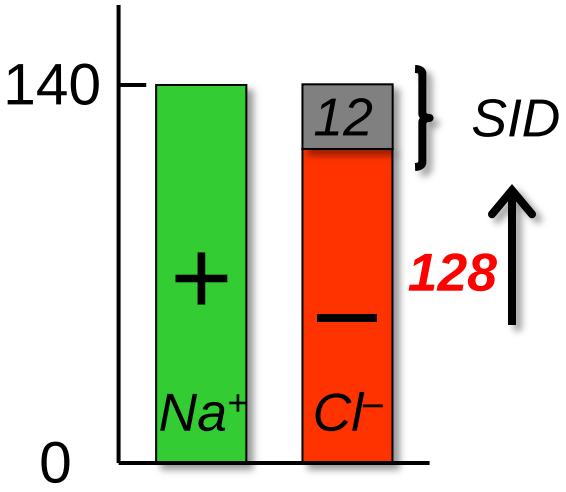
Efficacy of low-Cl content fluid therapy

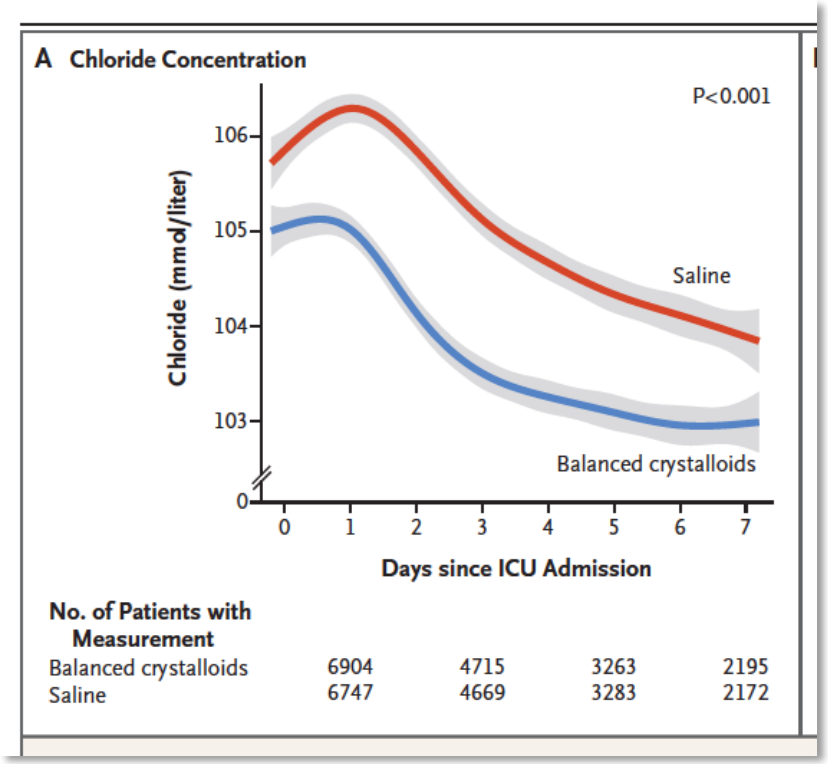
ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

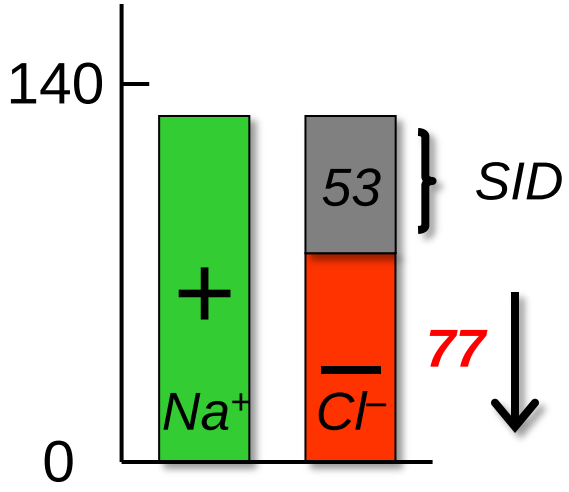
Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H., Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H.,

4-5% Albumin





20% Albumin



N Engl J Med 2018;378:829-39

CONCLUSIONS – Take-Home Messages

- *20% ALB reduces resuscitation **fluid requirement***
  (solid evidence in post-operative ICU pts; not clear in sicker patients)
- *20% ALB do not have beneficial effects in **sepsis**,*
  *while 20% ALB might be beneficial in patients with **septic shock***
- *4-5% ALB may be employed as a **colloid**, keeping in mind limitations*
  *(volume effects, fluid accumulation / NO in **TBI**)*
- *NO clinical data whatsoever supporting the hypothesis of **renal damag***
  associated with ALB administration (either 4-5% or 20%)
- *Be careful to **infusion rate** (necessary more data)*
- *20% ALB as included in a **low-chloride** content fluid therapy*

Future trial in patients after abdominal surgery

STUDY PROTOCOL Open Access

The importance of albumin infusion rate for plasma volume expansion following major abdominal surgery – AIR: study protocol for a randomised controlled trial

Svajunas Statkevicius[1], Johan Bonnevier[1], Björn P. Bark[1], Erik Larsson[2], Carl M. Öberg[3], Päivi Kannisto[4], Bobby Tingstedt[5] and Peter Bentzer[6*]

- *Single center, assessor-blinded, parallel group, randomized prospective trial*

- *Adult patients, after abdominal surgery, presenting signs of hypovolemia will be randomized (.*
  1) *Rapid administration (30 min) – 5% albumin, 10 ml/kg IBW*
  2) *Slow administration (180 min) – 5% albumin, 10 ml/kg IBW*

- *Primary end-point: change in plasma volume (^{125}I-HSA) after 180 min*

- *Secondary end-point: transcapillary escape rate, other clinically relevant outcomes*

Trials 2016;17:578