XXIX Congresso Nazionale SIFO
Società Italiana di Farmacia Ospedaliera
e dei Servizi Farmaceutici delle Aziende Sanitarie
Napoli, October 12th – 15th 2008

Albumina in rianimazione: oltre il rimpiazzo volemico

dott. Pietro Caironi,
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Mangiagalli, Regina Elena" di Milano,
Università degli Studi di Milano

Why do we care for albumin?
Why do we need to care for albumin?

Medline on pubmed

"albumin":	155.844 items
"hemoglobin":	125.396 items

last 10 years (1998 – 2008): 57.196 items [37 %]

Everything started during the Wold War II:
7th december 1941, first case series of 7 patients very severily burned patients injured during the Pearl Harbor attack

Actually, few months before,
the first clinical use of human albumin in traumatic shock

Case 4.—A 20-year-old man was admitted to Walter Reed General Hospital, Washington, D.C., in May 1941, 16 hours after he had sustained bilateral compound comminuted fractures of the tibia and fibula, fractures of five ribs; and associated pleural damage, pneumothorax, and subcutaneous emphysema. He was confused and irrational, with a blood pressure of 76/30 mm. Hg. After he had been given two units of albumin (each approximately 25 gm.), over a 30-minute period, the pressure rose to 106/70 mm. Hg, and two hours later, after insertion of a Kirschner wire, reduction of one of the fractures, and application of a cast, it was 130/80 mm. Hg. Over the next 12 hours, the patient received 1,250 cc. of fluid by mouth and 1,000 cc. of physiologic salt solution subcutaneously. The systolic pressure remained above 130 mm. Hg during this period, with occasional elevations to 150 mm. Hg. There was no evidence of circulatory failure at any time after the administration of the albumin.

"Office of Medical History" – http://history.amedd.army.mil

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"Office of Medical History" – http://history.amedd.army.mil

- Physiology and pathophysiology
- Overview of evidences available
- Recent findings besides volume replacement and new clinical trials...

Albumin structure - peculiarities

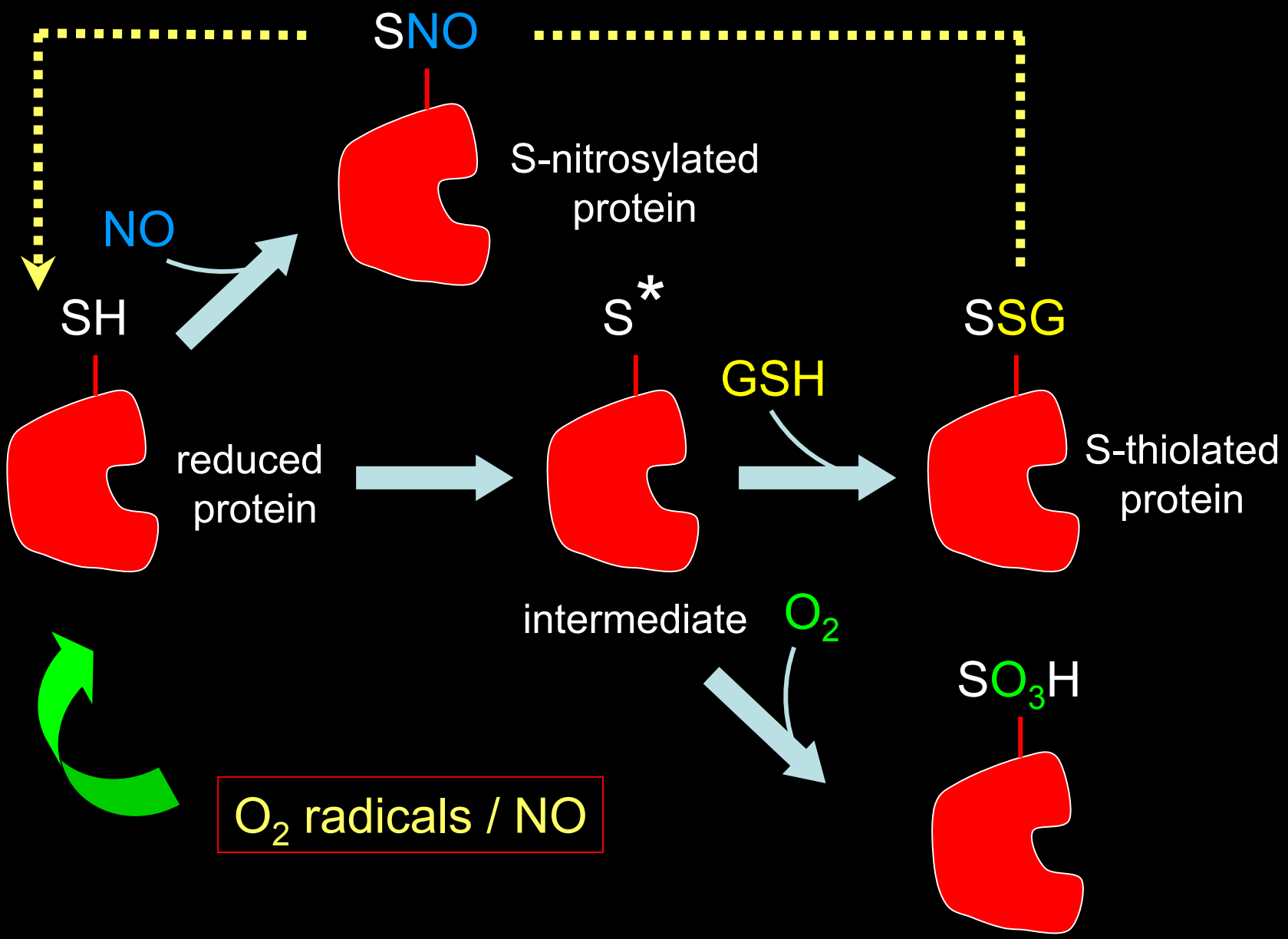
Molecular weight: 66.500 Da.

50% of plasmatic protein ⇨ responsible for 80% of oncotic pressure

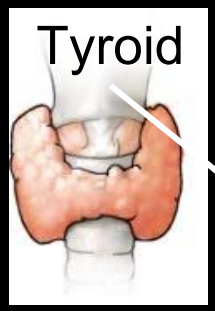
Important characteristics for the critically ill:

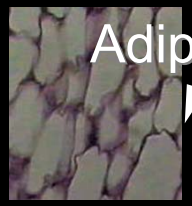
1) cystein residuals – thiol groups
2) domins I and II
3) histidin – imadozole residuals

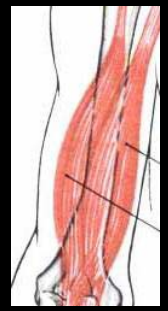
1) Oxygen radicals and NO scavenger



2) Metabolic transport functions







Muscle

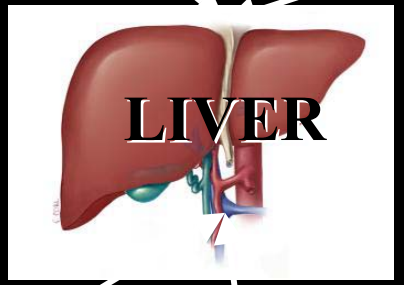
FA

(T4)

Phospholipids

Bone

Ca^{2+}



Cys

Trp

Steroids

FA

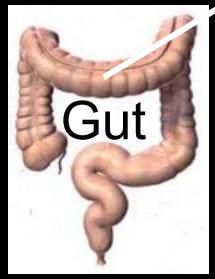
Trp

Cys

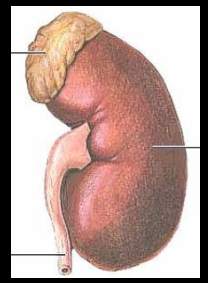
Ca^{2+}

Cu^{2+}

Bilirubin
(Heme)

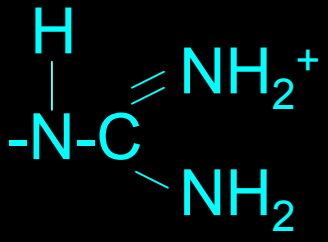
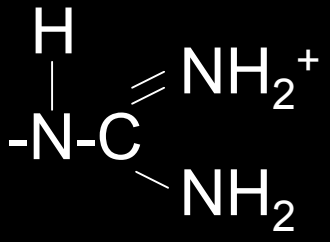


Adrenal

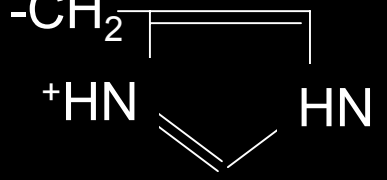
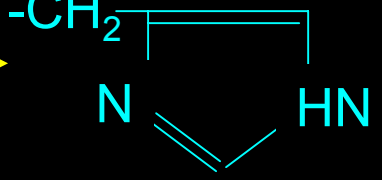


Gattinoni L, Carlesso E, and Caironi P. *Minerva Anestesiol* 2005;71:27-40

3) Buffer functions – imidazole residuals

Group	AH ⇌	A^- + H^+	*pK*
Glu Asp	-COOH →	$-COO^-$ + H^+	4.4
Lys	$-NH_3^+$ ←	$-NH_2$ + H^+	10
Arg	 ←	 + H^+	12

net fixed charge –21 mEq/mole

His	 ⇌	 + H^+	6.5

16 imidazole residuals – buffer functio

Cys	-SH ←	$-S^-$ + H^+	8.5

binding function, NO scavange

Which functions are important for the critically ill?

Primary ⇨ Oncotic properties

Secondary ⇨ Transport

⇨ Anti-oxydant

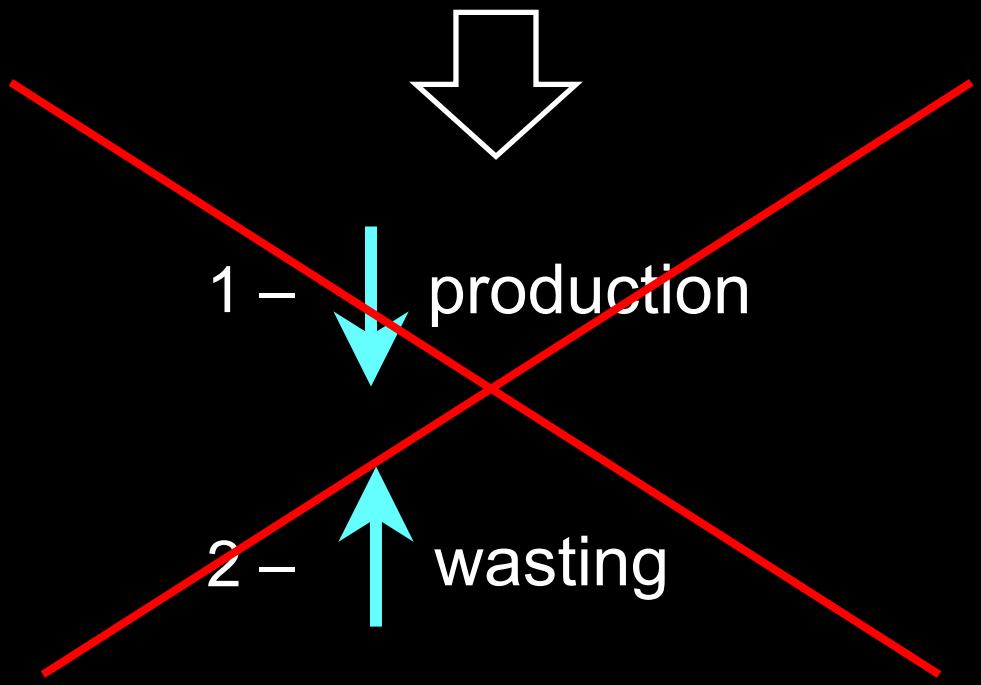
⇨ Nitric oxide modulation

⇨ Acid base status

What's the real problem for the critically ill ?

Hypoalbuminemia

(↓ plasma concentration, normal values ≈ 40 g/L)
is a symptom resulting from



What's the real problem for the critically ill ?

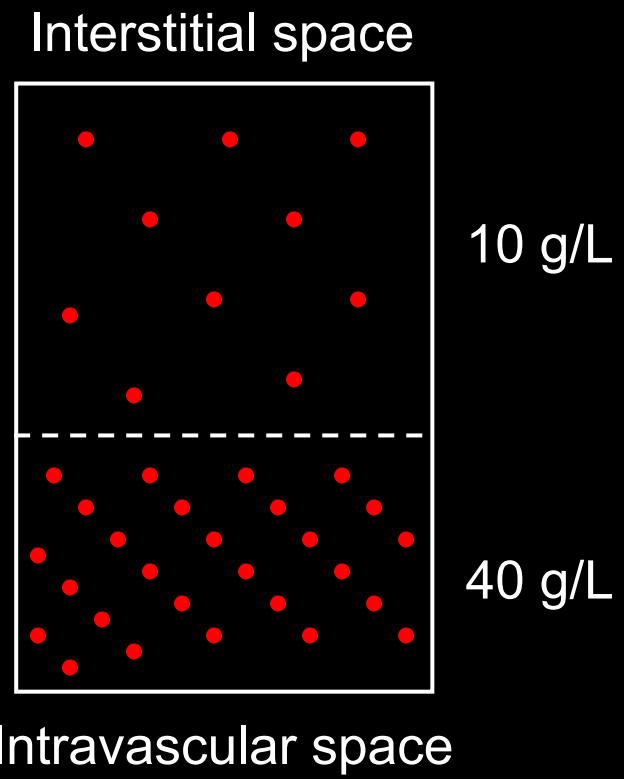
Hypoalbuminemia

(↓ plasma concentration, normal values ≈ 40 g/L)
is a symptom resulting from

1 – decreased absolute content

2 – altered water metabolism

3 – redistribution



Indeed, two main questions:

- Hypoalbuminemia *per se* causes morbidity and/or mortality?

- Do we need to treat it?
  What is the best cure for hypoalbuminemia?

- Physiology and pathophysiology
- Overview of evidences available
- Recent findings besides volume replacement and new clinical trials...

From 1998 to 2003: The era of meta-analysis...

Albumin infusion

Cochrane meta-analysis [1998]

Human albumin administration in critically ill patients: systematic review of randomised controlled trials

Cochrane Injuries Group Albumin Reviewers

⇨ Harmful

Wilkes' meta-analysis [2001]

Patient Survival after Human Albumin Administration

A Meta-Analysis of Randomized, Controlled Trials

Mahlon M. Wilkes, PhD, and Roberta J. Navickis, PhD

⇨ Indifferent

Vincent's meta-analysis [2003]

Hypoalbuminemia in Acute Illness: Is There a Rationale for Intervention?

A Meta-Analysis of Cohort Studies and Controlled Trials

Jean-Louis Vincent, MD, PhD, FCCM,* Marc-Jacques Dubois, MD,* Roberta J. Navickis, PhD,† and Mahlon M. Wilkes, PhD†

*From the *Department of Intensive Care, Université Libre de Bruxelles, Hôpital Erasme, Brussels, Belgium, and †Hygeia Associates, Grass Valley, California, U.S.A.*

⇨ Beneficial

Point of view...

Epidemiology:

"Tomb of intellingence"

Meta-analysis:

"Sacking of tombs"

? Reliability of meta-analysis

… finally, a prospective randomized study.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

ABSTRACT

BACKGROUND

It remains uncertain whether the choice of resuscitation fluid for patients in intensive care units (ICUs) affects survival. We conducted a multicenter, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU.

METHODS

We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization.

N Engl J Med 2004;350:2247-56

SAFE study – 2004

Prospective, randomized, double-blinded trial

16 ICU (Australia, New Zeland)

Intravascular fluid resuscitation by 4% albumin infusion (*treated group*) or saline NaCl 0.9% infusion (*control group*)

6997 patients
- Treated group: 3497 patients
- Control group: 3500 patients

Primary outcome:
death from any cause at 28-day period after randomization

N Engl J Med 2004, 350:2247-56

SAFE study – 2004

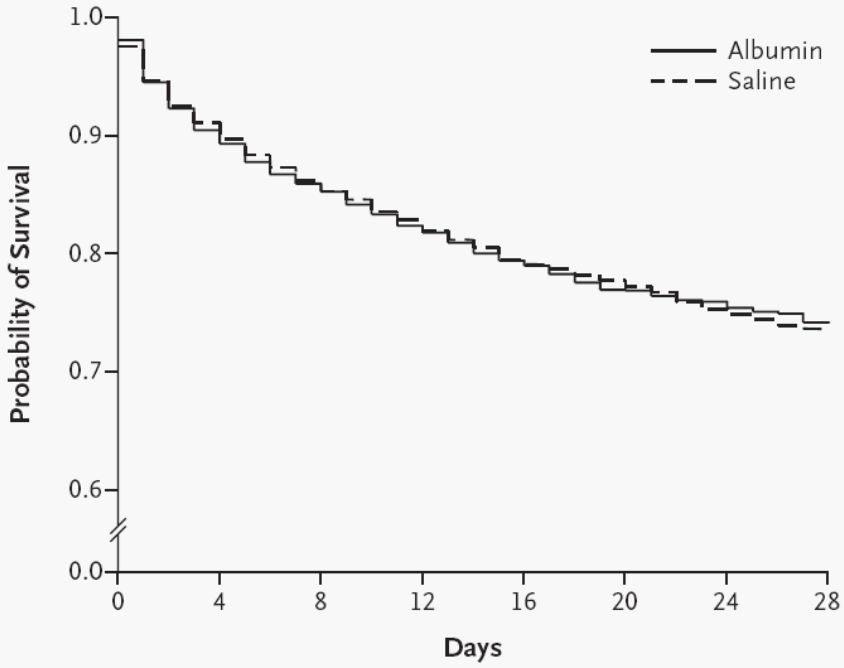


Figure 1. Kaplan–Meier Estimates of the Probability of Survival.
P=0.96 for the comparison between patients assigned to receive albumin and those assigned to receive saline.

Dead patients (%)
treated group 20.9% vs control group 21.1% (p=0.87)

CONCLUSIONS
In patients in ICU, use of either 4% albumin or normal saline for fluid resuscitation results in similar outcomes at 28 day

N Engl J Med 2004, 350:2247-56

SAFE study – 2004, subgroup analysis

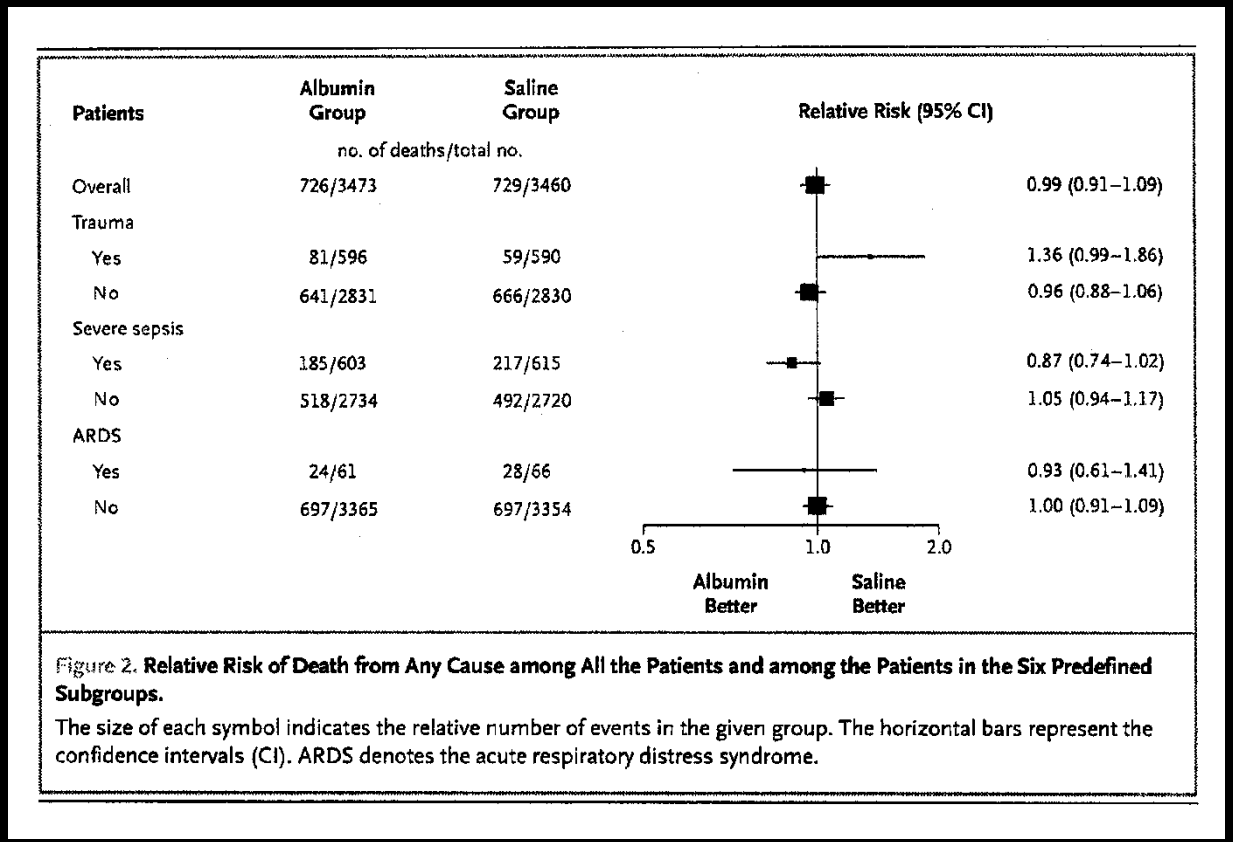


Figure 2. **Relative Risk of Death from Any Cause among All the Patients and among the Patients in the Six Predefined Subgroups.**

The size of each symbol indicates the relative number of events in the given group. The horizontal bars represent the confidence intervals (CI). ARDS denotes the acute respiratory distress syndrome.

	Treated %	Control %	P
Trauma patients	13.6	10.0	0.06
Severe sepsis patients	30.7	35.3	0.09
ARDS patients	39.3	42.4	0.72

Albumin administration improves organ function in critically ill hypoalbuminemic patients: A prospective, randomized, controlled, pilot study*

Marc-Jacques Dubois, MD, FRCPC; Carlos Orellana-Jimenez, MD; Christian Melot, MD, PhD, Msc (Stat); Daniel De Backer, MD, PhD; Jacques Berre, MD; Marc Leeman, MD, PhD; Serge Brimioulle, MD, PhD; Olivier Appoloni, MD; Jacques Creteur, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCP, FCCM

Crit Care Med 2006;34:2536-40

Prospective, controlled, randomized study

1 institution (Brussels) – 31 beds

100 patients, if < 30 g/L
- Treated group: 50 patients
- Control group: 50 patients

⇨ 300 ml + 200 ml 20% albumin, if < 30 g/L *vs.* no albumin

Dubois' study - 2006

Table 3. Baseline, last, and delta Sequential Organ Failure Assessment (SOFA) values in control and albumin groups

	Control Group (n = 50)	Albumin Group (n = 50)	*p* Value
Baseline SOFA	5.7 ± 0.8	6.3 ± 0.8	.31
Last SOFA	4.6 ± 1.2	4.1 ± 1.1	.65
Delta SOFA	1.4 ± 1.1	3.1 ± 1.0	.03

Last SOFA, SOFA score at day 7 or before if patient discharged or died; delta SOFA, difference between baseline and last SOFA.

Data are expressed as mean ± SD.

"The current pilot study also suggests that in the specific group of hypoalbuminemic critically ill patients, albumin may have beneficial effects on organ function, although the exact mechanisms remain undefined".

Crit Care Med 2006;34:2536-4

- Physiology and pathophysiology
- Overview of evidences available
- Recent findings besides volume replacement and new clinical trials...

Clinical indications – Recent findings

From evidence-based to individual-based medicine...!

- Patients with peripheral edema during recovery phase
- Patients with traumatic brain injury
- Patients with severe sepsis

1 Patients with traumatic brain injury

ORIGINAL ARTICLE

Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury

The SAFE Study Investigators*

ABSTRACT

BACKGROUND

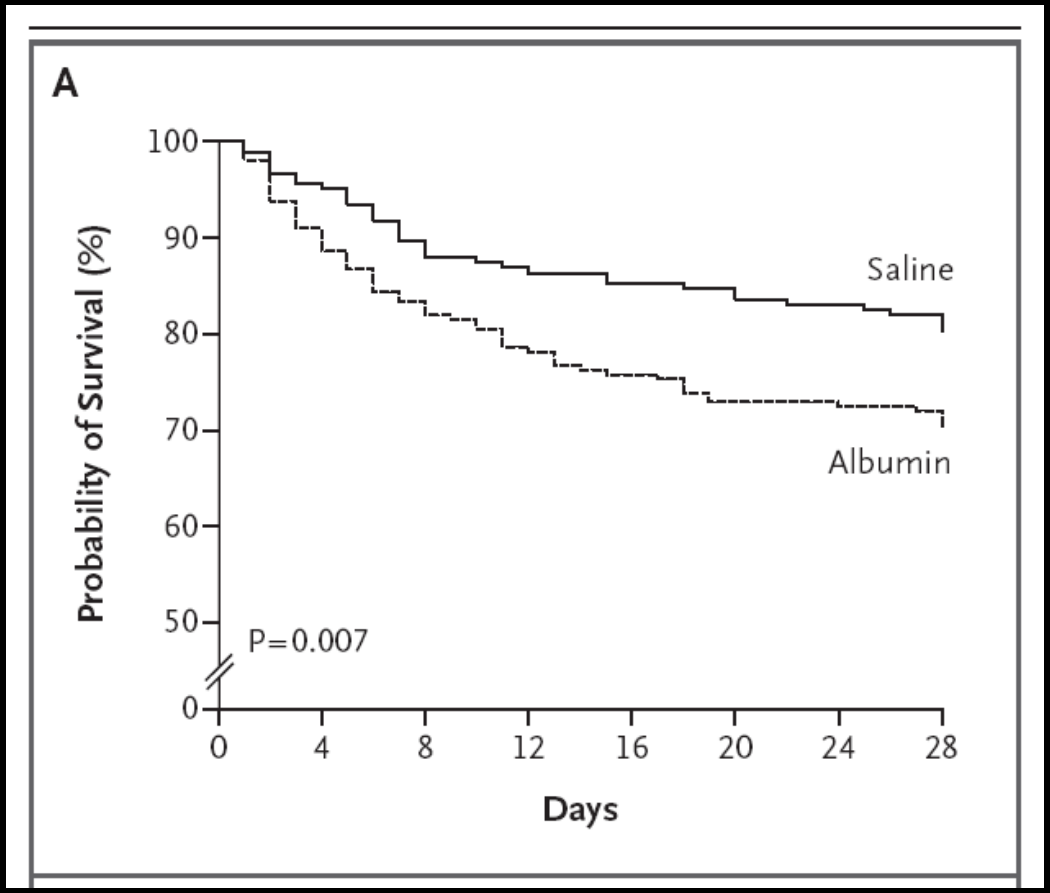
The Saline versus Albumin Fluid Evaluation study suggested that patients with traumatic brain injury resuscitated with albumin had a higher mortality rate than those resuscitated with saline. We conducted a post hoc follow-up study of patients with traumatic brain injury who were enrolled in the study.

METHODS

For patients with traumatic brain injury (i.e., a history of trauma, evidence of head trauma on a computed tomographic [CT] scan, and a score of ≤13 on the Glasgow Coma Scale [GCS]), we recorded baseline characteristics from case-report forms, clinical records, and CT scans and determined vital status and functional neurologic outcomes 24 months after randomization.

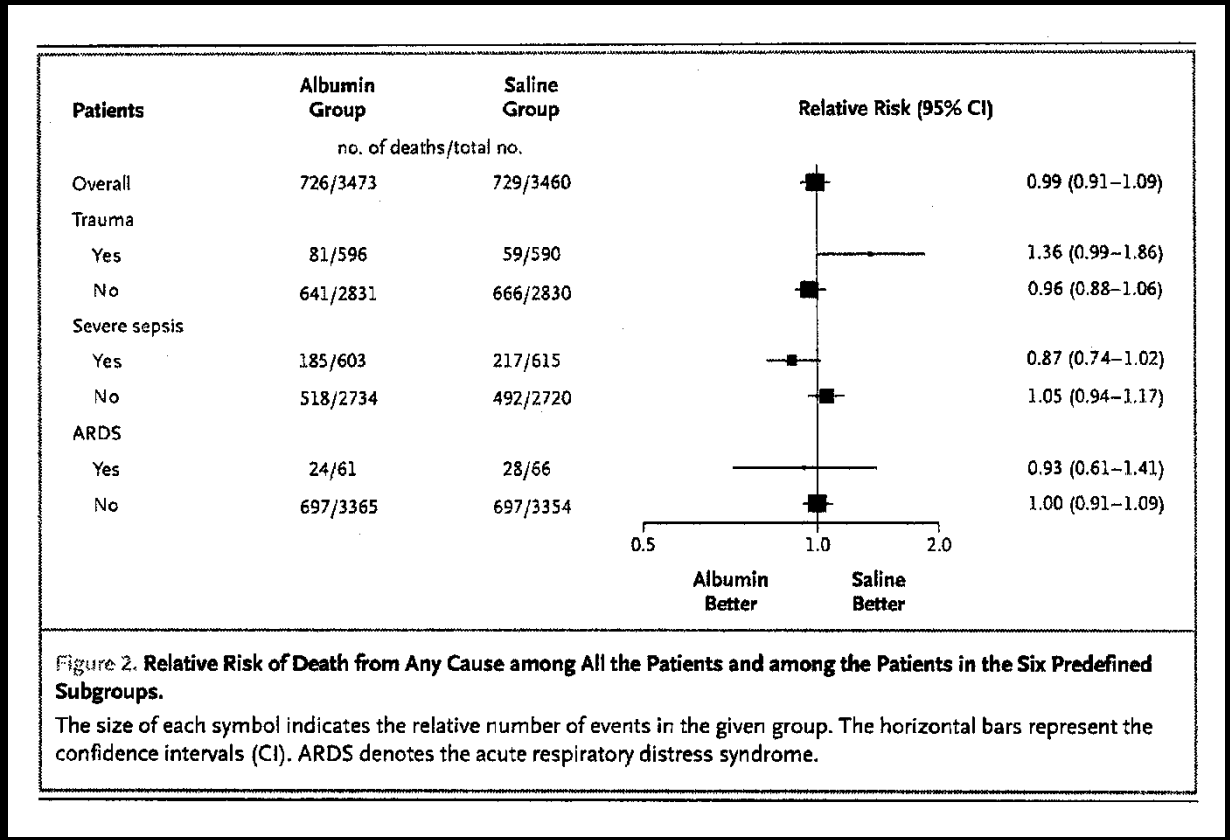
N Engl J Med 2007;357:874-84

1 Patients with traumatic brain injury



"In this post hoc study of critically ill patients with traumatic brain injury, fluid resuscitation with albumin was associated with higher mortality rates than was resuscitation with saline."

2 Patients with severe sepsis – [SAFE study]



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Uso dell'albumina nel rimpiazzo volemico di pazienti con sepsi severa o shock settico
(FARM6JS3R5)

finanziato dall'Agenzia Italiana del Farmaco
(bando AIFA 2006)

Steering Committee:

Luciano Gattinoni, Pietro Caironi, Antonio Pesenti, Roberto Fumagalli, Roberto Latini, Serge Masson, Marilena Romero, Gianni Tognoni

Steering Committee

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2) Dipartimento di Medicina Perioperatoria e Terapia Intensiva, A.O. San Gerardo di Monza: *A. Pesenti, R. Fumagalli*

3) Consorzio Mario Negri Sud, S. Maria Imbaro, Chieti: *G. Tognoni, M. Romero*

4) Istituto di Ricerche Farmacologiche Mario Negri, Milano: *R. Latini, S. Masson*

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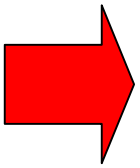
Good Clinical Practice Monitoring

Centro Studi SIFO (Società Italiana di Farmacia Ospedaliera)



Ipotesi

Efficacia della somministrazione di albumina durante sepsi severa o shock settico:

? nel rimpiazzo volemico

? come correzione dell'ipoalbuminemia *(funzioni secondarie)*

ALBIOS

Studio clinico multicentrico randomizzato di fase III

Obiettivo primario:

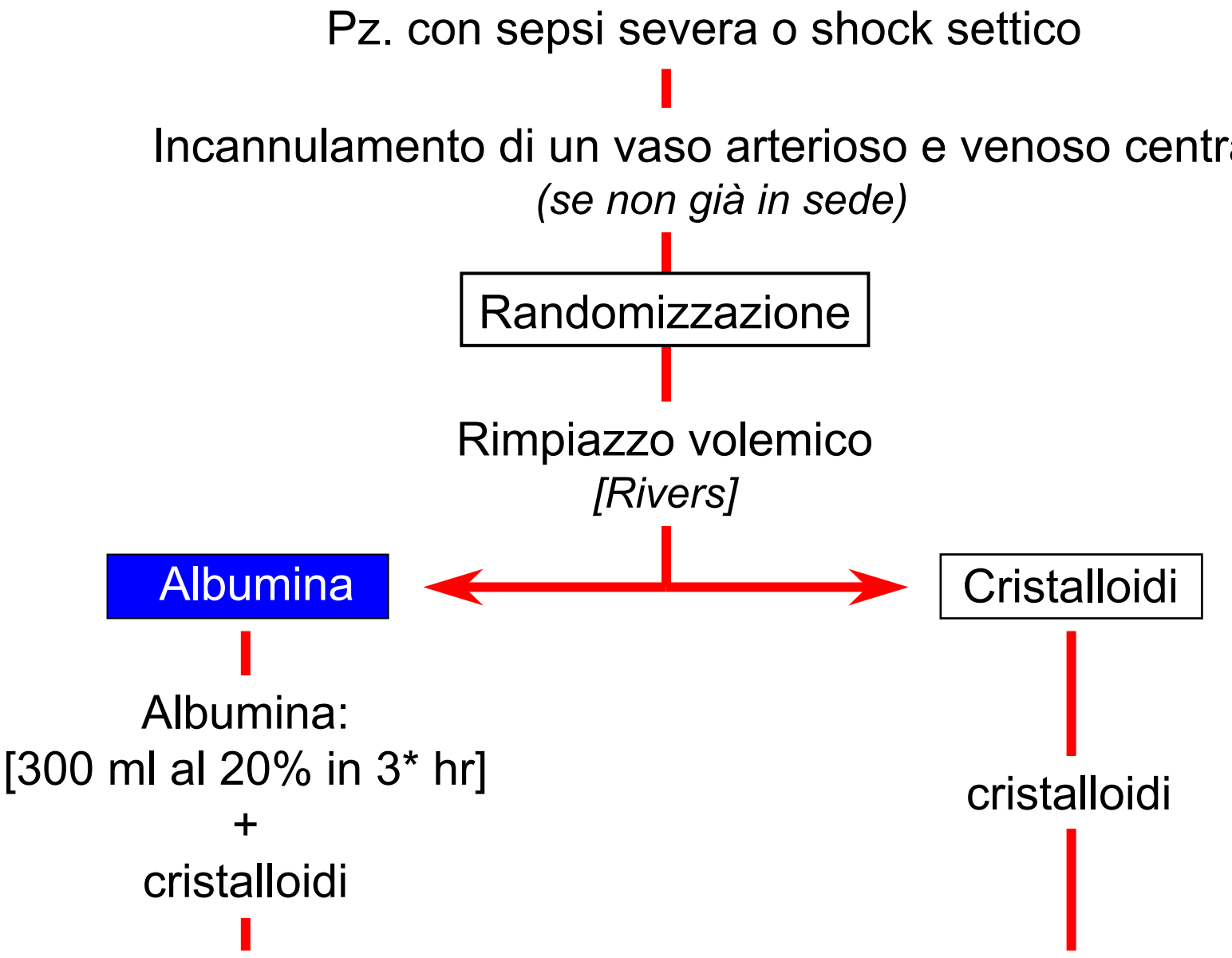
Verificare l'ipotesi che il rimpiazzo volemico con l'utilizzo di albumina e il mantenimento della sua concentrazione plasmatica entro un intervallo fisiologico (≥ 30 g/L) migliori la sopravvivenza a 28 e a 90 giorni dalla randomizzazione nello studio in pazienti con sepsi severa o shock settico, rispetto ad un rimpiazzo volemico con l'utilizzo di cristalloidi.

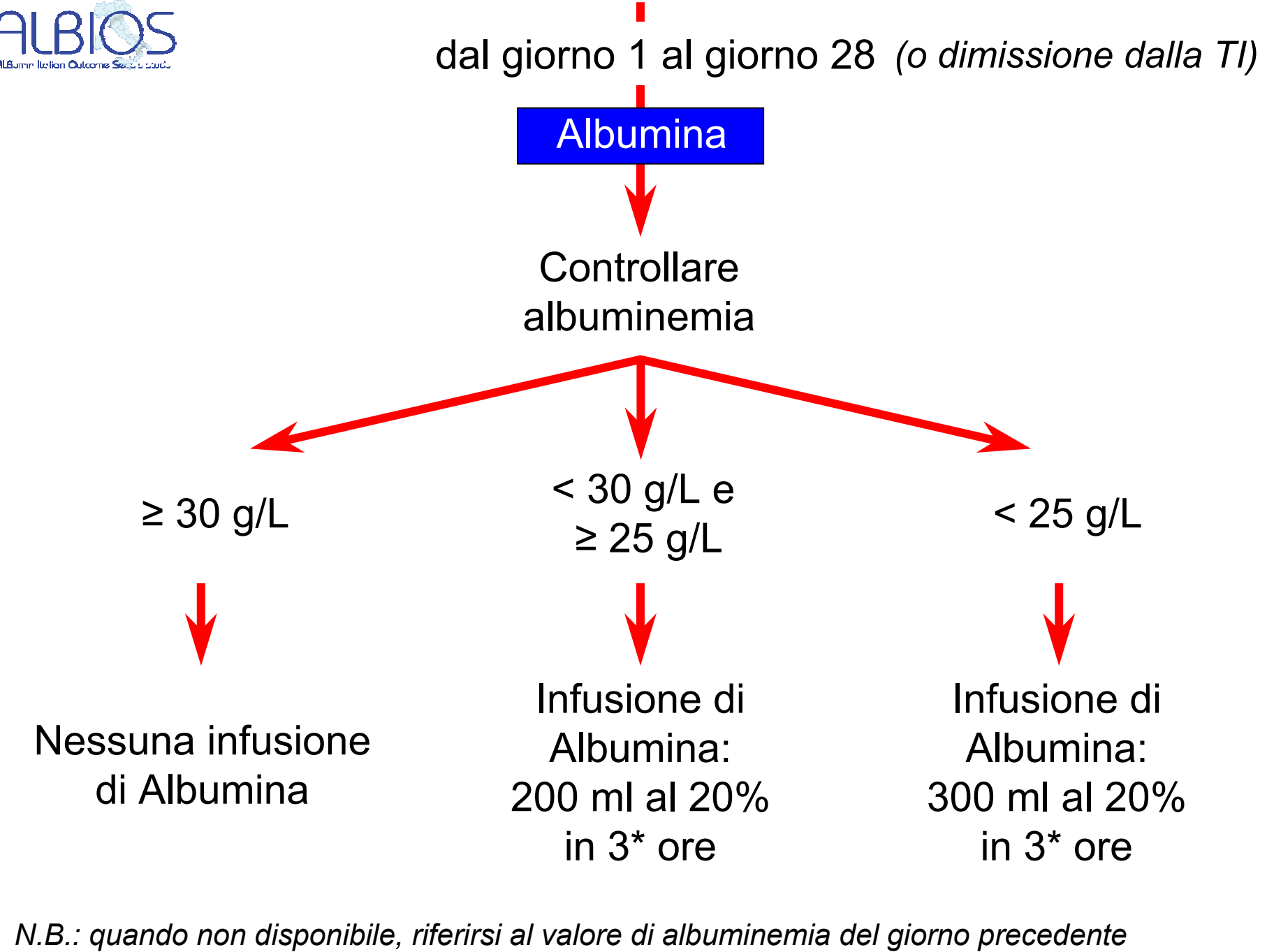
Obiettivi secondari:

Verificare l'ipotesi che il rimpiazzo volemico con l'utilizzo di albumina e il mantenimento della sua concentrazione plasmatica ≥ 30 g/L riduca:

1) Il numero e la gravità delle disfunzioni d'organo, come rilevato dal punteggio SOFA (*modificato*)*;*
2) la durata della degenza in Terapia Intensiva;
3) la durata della degenza ospedaliera.

Disegno dello studio





N.B.: quando non disponibile, riferirsi al valore di albuminemia del giorno precedente

dal giorno 1 al giorno 28 *(o dimissione dalla TI)*

Cristalloidi

Controllare
albuminemia

Se condizioni di estrema gravità
(es.: albuminemia < 15 g/L),
consentita l'infusione di Albumina
[in 3* ore]

**o in un periodo di tempo maggiore (se ritenuto clinicamente più utile), purché l'infusione termini entro il momento della compilazione della scheda giornaliera del giorno successivo*

Conclusions

- "Secondary functions" may be the most important in critically ill patients
- Evidence based: for routine volume replacement in mild critically ill, albumin is not recommended, and in patients with traumatic brain injury should not be employed.
- However: in hypoalbuminemic patients, it may be beneficial, especially in patients with peripheral edema during the recovery phase.
- In patients with severe sepsis, it may be beneficial (see in the next future... ALBIOS study)