Albumina in rianimazione: oltre il rimpiazzamento volemico

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Fondazione IRCCS – “Ospedale Maggiore Policlinico, 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 World War II:
7th December 1941, first case series of 7 patients very severely 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.

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Physiology and pathophysiology

Overview of evidences available

Recent findings besides volume replacement and new clinical trials...
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

O2 radicals / NO

SNO

S-nitrosylated protein

S

S-thiolated protein

SSG

O2

SO3H

NO

SH

reduced protein
2) Metabolic transport functions

### 3) Buffer functions – imidazole residuals

<table>
<thead>
<tr>
<th>Group</th>
<th>AH</th>
<th>$\leftrightarrow$</th>
<th>$A^- + H^+$</th>
<th>$pK$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu Asp</td>
<td>-COOH</td>
<td>$\rightarrow$</td>
<td>-COO⁻</td>
<td>$H^+$</td>
</tr>
<tr>
<td></td>
<td>$\leftrightarrow$</td>
<td>$\rightarrow$</td>
<td>$\leftrightarrow$</td>
<td></td>
</tr>
<tr>
<td>Lys</td>
<td>$\text{-NH}_3^+$</td>
<td>$\leftrightarrow$</td>
<td>-NH₂</td>
<td>$H^+$</td>
</tr>
<tr>
<td></td>
<td>$\leftrightarrow$</td>
<td>$\rightarrow$</td>
<td>$\leftrightarrow$</td>
<td></td>
</tr>
<tr>
<td>Arg</td>
<td>$\text{-N-C}$</td>
<td>$\leftrightarrow$</td>
<td>NH₂⁺</td>
<td>$H^+$</td>
</tr>
<tr>
<td></td>
<td>$\leftrightarrow$</td>
<td>$\rightarrow$</td>
<td>$\leftrightarrow$</td>
<td></td>
</tr>
<tr>
<td>Histidine</td>
<td>-CH₂</td>
<td>$\leftrightarrow$</td>
<td>NH⁺</td>
<td>$H^+$</td>
</tr>
<tr>
<td></td>
<td>$\leftrightarrow$</td>
<td>$\rightarrow$</td>
<td>$\leftrightarrow$</td>
<td></td>
</tr>
<tr>
<td>Cysteine</td>
<td>-SH</td>
<td>$\rightarrow$</td>
<td>-S⁻</td>
<td>$H^+$</td>
</tr>
</tbody>
</table>

*net fixed charge –21 mEq/mole*

*16 imidazole residuals – buffer function*

*binding function, NO, scavanger*
Which functions are important for the critically ill?

Primary

Oncotic properties

Secondary

Transport

Antioxidant

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

1 – ↓ production

2 – ↑ wasting
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

Interstitial space

Intravascular space
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, PCCM,* 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 Hygieia Associates, Grass Valley, California, U.S.A.

→ **Beneficial**
Epidemiology: “Tomb of intelligence”

Meta-analysis: “Sacking of tombs”

Point of view...

Reliability of meta-analysis
… finally, a prospective randomized study.

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.

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

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

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

**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.

*SAFE study – 2004*

SAFE study – 2004, subgroup analysis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Albumin Group</th>
<th>Saline Group</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>726/3473</td>
<td>729/3460</td>
<td>0.99 (0.91–1.09)</td>
</tr>
<tr>
<td>Trauma</td>
<td>81/596</td>
<td>59/590</td>
<td>1.36 (0.99–1.86)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>641/2831</td>
<td>666/2830</td>
<td>0.96 (0.88–1.06)</td>
</tr>
<tr>
<td>Yes</td>
<td>185/603</td>
<td>217/615</td>
<td>0.87 (0.74–1.02)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>518/2734</td>
<td>492/2720</td>
<td>1.05 (0.94–1.17)</td>
</tr>
<tr>
<td>No</td>
<td>607/3365</td>
<td>697/3354</td>
<td>0.93 (0.61–1.41)</td>
</tr>
<tr>
<td>ARDS</td>
<td>24/61</td>
<td>28/66</td>
<td>1.00 (0.91–1.09)</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Treated %</th>
<th>Control %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma patients</td>
<td>13.6</td>
<td>10.0</td>
</tr>
<tr>
<td>Severe sepsis patients</td>
<td>30.7</td>
<td>35.3</td>
</tr>
<tr>
<td>ARDS patients</td>
<td>39.3</td>
<td>42.4</td>
</tr>
</tbody>
</table>
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
"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;34:2536-40*
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
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
“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.”
Patients with severe sepsis – [SAFE study]

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
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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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

Data and Safety Monitoring Board

P.M. Suter, J.L. Vincent, M.G. Valsecchi, A. Santosuosso

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)
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 ($\geq 30$ 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 $\geq 30$ 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

Pz. con sepsi severa o shock settico

Incannulamento di un vaso arterioso e venoso centrale
(se non già in sede)

Randomizzazione

Rimpiazzo volemico
[Rivers]

Albumina
[300 ml al 20% in 3* hr]
+ cristalloidi

Cristalloidi
cristalloidi
dal giorno 1 al giorno 28 (o dimissione dalla TI)

Albumina

Controllare albuminemia

≥ 30 g/L

Nessuna infusione di Albumina

< 30 g/L e ≥ 25 g/L

Infusione di Albumina:
200 ml al 20% in 3* ore

< 25 g/L

Infusione di Albumina:
300 ml al 20% in 3* ore

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)