WEBINAR SERIES

11 OCTOBRE 2022

de 18h00 à 19h00

LE FLASH BIBLIO Soins Intensifs

Traiter l'hypoalbuminémie en réanimation, le débat reste ouvert : **l'albumine pour ou contre**

LE PROGRAMME

#1 18H00 - 18H20 : Pour

Pr Karim Asehnoune - CHU Nantes

#2 18H20 - 18H40 : Contre

Pr Didier Payen - Université Paris 7

#3 18H40 - 19H00 : Synthèse et réponse aux questions

Pr Karim Asehnoune
CHU de Nantes

Pr Didier Payen
Université Paris 7

J A R C A Novembre 2022

Seul conflit d intérêt reel: mon amitié pour Karim

Autrement **contrat de presentation avec LFB**

Pr Karim Asehnoune
CHU de Nantes

Pr Didier Payen
Université Paris 7

Contre l'albur

Pr Didier Payen

Comment?

Plutôt le volume plasmatique?

Comment le savoir?

…on de l'albumine *est in… …ntien* ***du volume sanguin circulant*** *lorsque la* ***perte … démontrée et que l'utilisation d'un colloïde est appropriée*** *; le* ***choix de l'albumine*** *par rapport aux autres colloïdes devant* ***dépendre de la situation clinique*** *de* ***chaque patient****, selon les* ***recommandations officielles de chaque pays*** *»*

Plutôt vague!!!

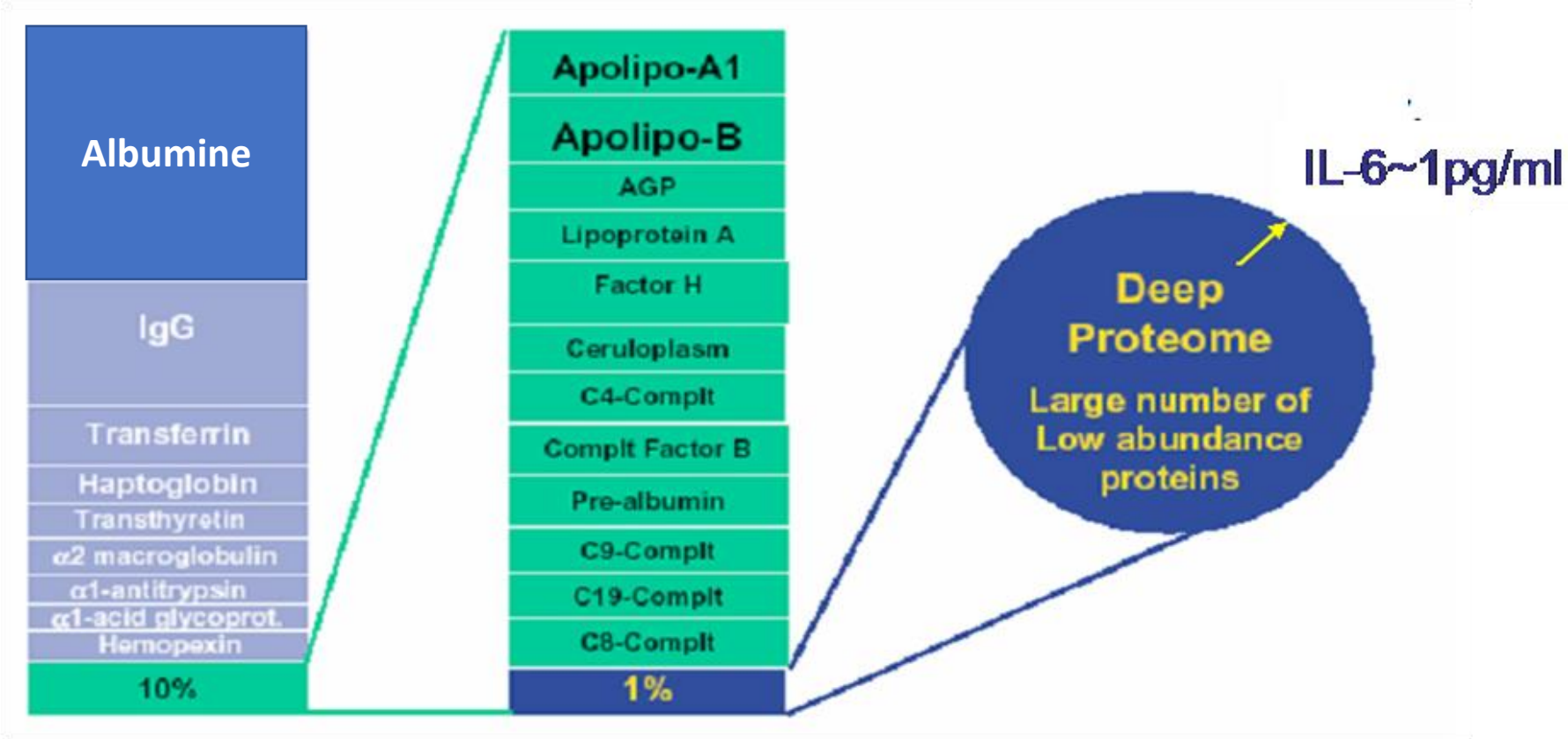
EMA 2002

2

Contre l'albumine

Pr Didier Payen

PREOTEIN-PROTEOME



10% of proteins are 99 % of the protein mass. Role is <u>independent</u> from mass

Contre l'albumine

Pr Didier Payen

What is Albumin?
A protein… from proteasome

550 AAcids; 68.5 KD; ½ life 21 Days

Synthesized by the liver (14g/D)

Plasma pool of albumine
150 G or 42g/l

⟶
⟵

Interstitial pool
230 g or 21 g/l

Contre l'albumine

Pr Didier Payen

What is Albumine?

Fasting
Acute Phase Response

Synthetized by the liver (14g/D)

Plasma pool of albumine
150 G or **42g/l**

Interstitial pool
230 g or **21 g/l**

Endoth C lesions → Leak

Nephrotic Synd
Crohn dis
Burn

Increase catabolism

Pr Didier Payen

Hypo-albuminémie

- **Toujours associée à un mauvais pronostique ≠ causalité**
- **Baisse de production** (maladie hépatique…)
- **Perte anormale**
- **Transfert interstitiel anormal**

2

Contre l’albumine

Pr Didier Payen

Question naive: puis-je survivre sans albumine?

2

Contre l'albumine

Pr Didier Payen

Congenital Analbuminemia attributable to Compound Heterozygosity for Novel Mutations in the Albumin Gene, *Filomena Campagna,[1] Francesca Fioretti,[1] Marco Bu-*

Il s'agit donc d'une question **d'équilibre** et de **vitesse d'installation**, plus que **de valeur elle-même**.

Il faut donc discuter:

- ***l'albumine*** **iso-oncotique (4%; 5%)**
- ***l'albumine*** **hyper-oncotique (20%; 25%)**

- **Quels sont les buts pour donner de l'albumine?**

2005

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Contre l'albumine

Pr Didier Payen

Serum Albumin Levels: Who Needs Them?

Brian L. Erstad, PharmD, MCCM[1]

Annals of Pharmacotherapy
1–7

DOI: 10.1177/1060028020959348

Objectives: to **discuss indications** for **ordering serum albumin levels** in **ICU adult** and to **provide recommendations** for ordering of SA levels

Data Synthesis: **Serum Alb**: a **marker of severity of illness**, and **hypoalbuminemia associated with poor patient outcome**, but **albumin is an acute phase protein**, ➔ **levels varies with illness fluctuations**.

U are:

d

costs.

Conclusions: **there is little evidence or justification for routinely ordering levels in critically ill patients**.

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Contre l'albumine

Pr Didier Payen

Serum Albumin Levels: Who Needs Them?

Brian L. Erstad, PharmD, MCCM[1]

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DOI: 10.1177/1060028020959348

Why albumin is administered? for fluid resuscitation

In the majority of clinical trials, **albumin administration** was based on **common resuscitation parameters** related **to HDyn stability, rather than serum alb levels**

3 largest, multicenter RCTs Saline vs Albumin (**4%**) Fluid Evaluation **(SAFE),** Albumin (**20%**) Italian Outcome Sepsis (**ALBIOS**),[9] and Early Albumin Resuscitation for Sepsis and Septic Shock (**EARSS**):

Alb did not reduce mortality when compared with crystalloid resuscitation.

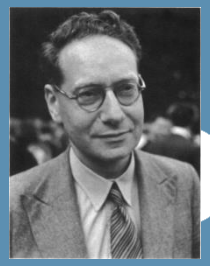
The NEW ENGLAND JOURNAL of MEDICINE

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*

- The **only trial titrating Alb administration on SA level;**
- Patients: **severe sepsis or septic shock**
- **Low level limit 30g/L** (arbitrary)
- **No demonstration of a critical level of SA related to outcome**



Contre l'albumine

Pr Didier Payen

ON THE ABSORPTION OF FLUIDS FROM THE CONNECTIVE TISSUE SPACES. By ERNEST H. STARLING. (Two Figures in Text.)

(*From the Physiological Laboratory, Guy's Hospital.*)

Loi de Starling ➔ Flux trans-microvasculaire

Hydro P — Colloido Osm P

$$Q = Kf [(Pmv – Ppmv) – \sigma (PCOmv – PCOpmv)]$$

Kf : *Coefficient de filtration*

Pmv : *Pression **hydrostatique** microvasculaire*

Ppmv : *Pression **hydrostatique** péri microvasculaire*

σ : ***Coefficient de reflection** aux protéines*

PCOmv *: Pression **colloido-osmotique** microvasculaire*

PCOpmv : *pression **colloïdo-osmotique** péri microvasculaire*

A l'équilibre :

Q = Débit lymphatique

Starling et al. J Physiol. 1896.

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Contre l'albumine

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Qu'est ce que la Pression Oncotique (PCO) ?

La PCO d'une solution contenant un soluté **non diffusible = Pression hydrostatique à appliquer pour empêcher la diffusion** ***(de part et d'autre d'une membrane semi-perméable)***

Pression Oncotique ou Pression Colloïdo-Osmotique (PCO) :

⇒ **Pression liée à la présence de macromolécules (protéines)**

PCO dépend : **Poids moléculaires des molécules dissoutes**
Nombres de molécules osmotiquement active
De la charge électrique

Albumine : 65 %	**(PM = 69 000 Da)**
Globulines : 15 %	**(PM = 140 000 Da)**
Fibrinogène : 10 %	**(PM = 400 000 Da)**

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Contre l’albumine

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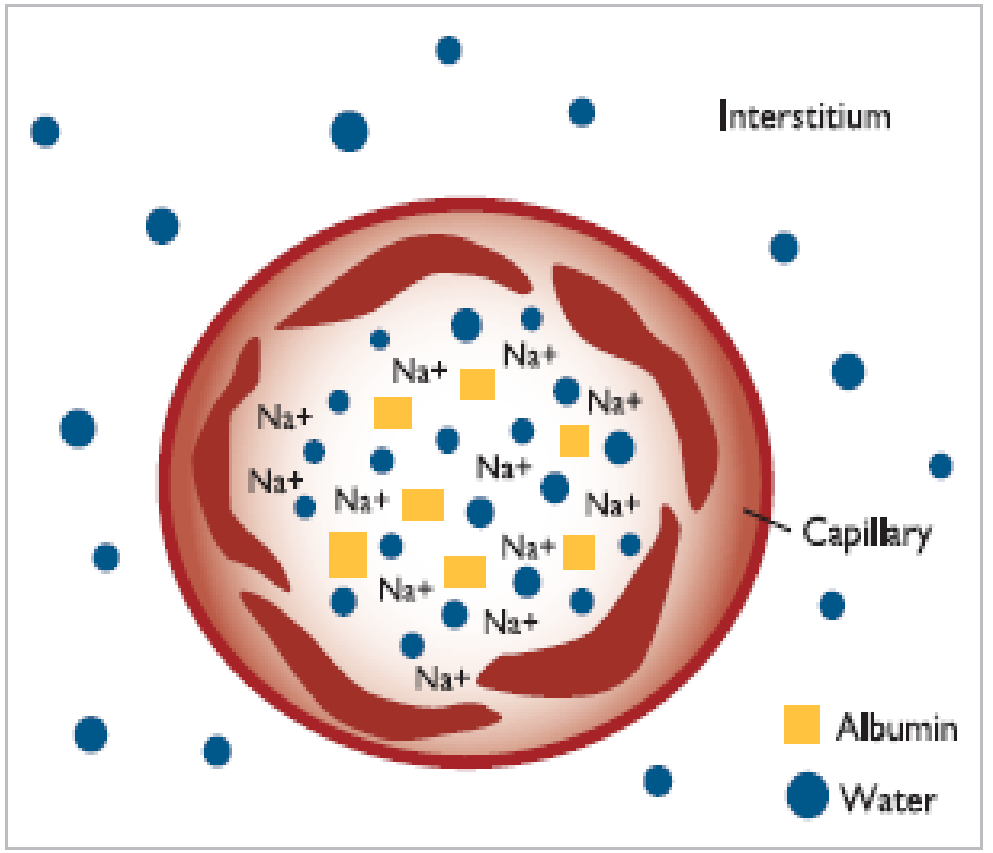
ONCOTIC PRESSURE



The **protein’s high net negative charge** attracts **cations** such as sodium (*Na+), causing* **water to follow** and **move across the semi-permeable capillary membrane** into the intravascular space.

2

Contre l'albumine

Pr Didier Payen

The Efficacy and Safety of Colloid Resuscitation in the Critically Ill

Christiane S. Hartog, MD, Michael Bauer, MD, and Konrad Reinhart, MD

(Anesth Analg 2011;112:156–64)

4 main arguments for colloids:

1. Colloids are more effective plasma expanders than crystalloids,
2. Synthetic colloids, i.e., dextran, gelatin, and HES are equally effective and safe but costless than albumin,
3. HES solutions have the best risk/benefit profile among the synthetic colloids, and
4. The third-generation HES 130/0.4 is safer than older generation HES solutions.

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Contre l'albumine

Pr Didier Payen

The Efficacy and Safety of Colloid Resuscitation in the Critically Ill

Christiane S. Hartog, MD, Michael Bauer, MD, and Konrad Reinhart, MD

(Anesth Analg 2011;112:156–64)

Meta-analyses failed to find a mortality benefit of any type of colloid in critically ill patients.

- ✓In a subgroup of **1218 patients** from **the SAFE study with severe sepsis**, albumin **tended to decrease mortality (30.7% vs 35.3%, *P = 0.09*) and *did not increase* rates of RRT.**
- ✓In **patients** with **spontaneous bacterial peritonitis complicating cirrhosis**, fluid therapy with **albumin** was associated with **less renal failure** and **reduced mortality**.
- ✓**Albumin** may be **harmful in patients with traumatic brain injury**.
- ✓**Mortality in brain injury was higher in the alb (4%) than in the saline group** (*P = 0.009*).

Perel P, Roberts I. *Colloids versus crystalloids for fluid resuscitation in critically ill patients.* ***Cochrane Database Syst Rev 2009;4:CD000567***

Bunn F, Trivedi D, Ashraf S. *Colloid solutions for fluid resuscitation.* ***Cochrane Database Syst Rev 2008;1:CD001319***

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Contre l'albumine

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The Efficacy and Safety of Colloid Resuscitation in the Critically Ill

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(Anesth Analg 2011;112:156–64)

✓**colloids lessen the risk of edema (**increase intravascular colloid oncotic pressure),

✓**For crystalloid proponents: the colloids may increase the risk because they leak into the interstitium**.

✓**Crystalloid-Colloid Volume Ratio Resuscitation** with crystalloids in critically ill patients **requires more fluid volume. T**extbooks recommend **a 3-fold or even higher ratio** of **crystalloid than colloid volumes** to achieve resuscitation to comparable endpoints.

✓In several thousand critically ill patients, **the volume of normal saline** needed for resuscitation **on day 1 was only 1.3-fold larger than the volume of 4% albumin**, and **over the first 4 days, the ratio was 1.4.**

Zarychanski R, Turgeon AF, Fergusson DA, Cook DJ, Hebert P, Bagshaw SM, Monsour D, McIntyre LA.. Open Med 2009;3:E196–209

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Contre l'albumine

Pr Didier Payen

Is albumin administration in the acutely ill associated with increased mortality? Results of the SOAP study

Jean-Louis Vincent[1], Yasser Sakr[1], Konrad Reinhart[2], Charles L Sprung[3], Herwig Gerlach[4], V Marco Ranieri[5] for the 'Sepsis Occurrence in Acutely Ill Patients' investigators

'cc3895)

Key messages

- In this observational study of 3,147 patients, albumin administration was independently associated with a lower 30-day survival, using a Cox proportional hazard model.
- Moreover, in 339 pairs matched according to a propensity score, ICU and hospital mortality rates were higher in patients who received albumin than in those who did not.
- While albumin administration may be safe in patients requiring fluid for intravascular volume depletion, these results suggest it may not be harmless in all ICU patients.

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Contre l’albumine

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POUR RESTAURER LA PRESSION DE PERFUSION RENALE?

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Contre l'albumine

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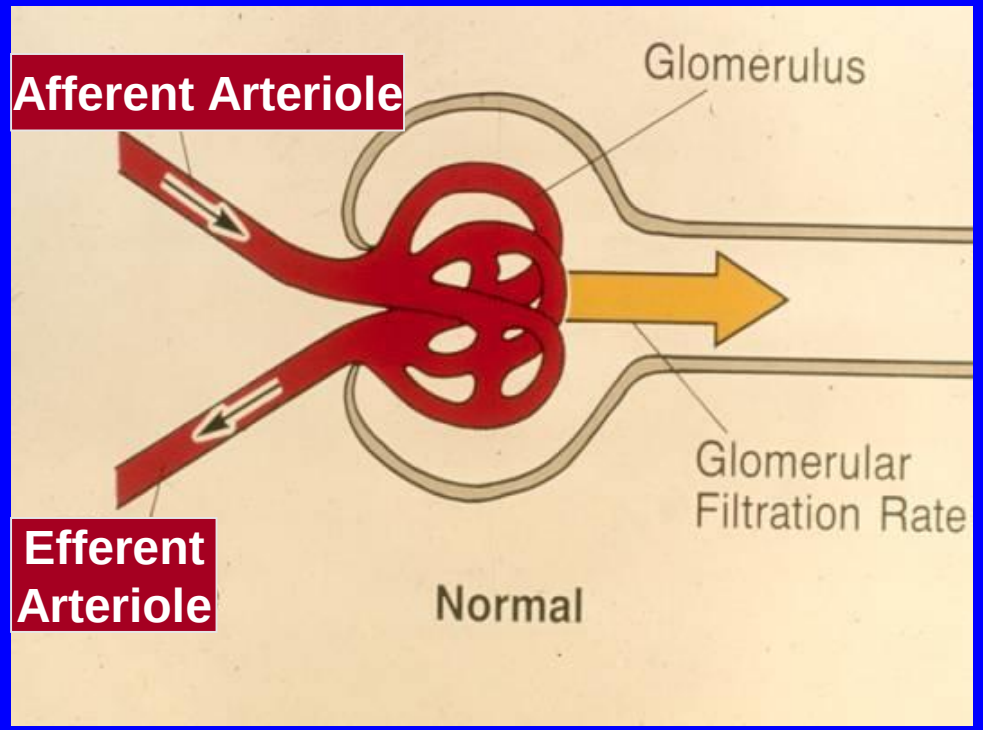
Glomerular filtration rate



$$Jv = Kf\,[(P_{capillary} - P_{Bowman}) - \sigma\,(\Pi_{capillary} - \Pi_{Bowman})]$$

$$= \underbrace{Kf\,(P_{capillary} - \Pi_{capillary})}$$

Net filtration pressure

2

Contre l'albumine

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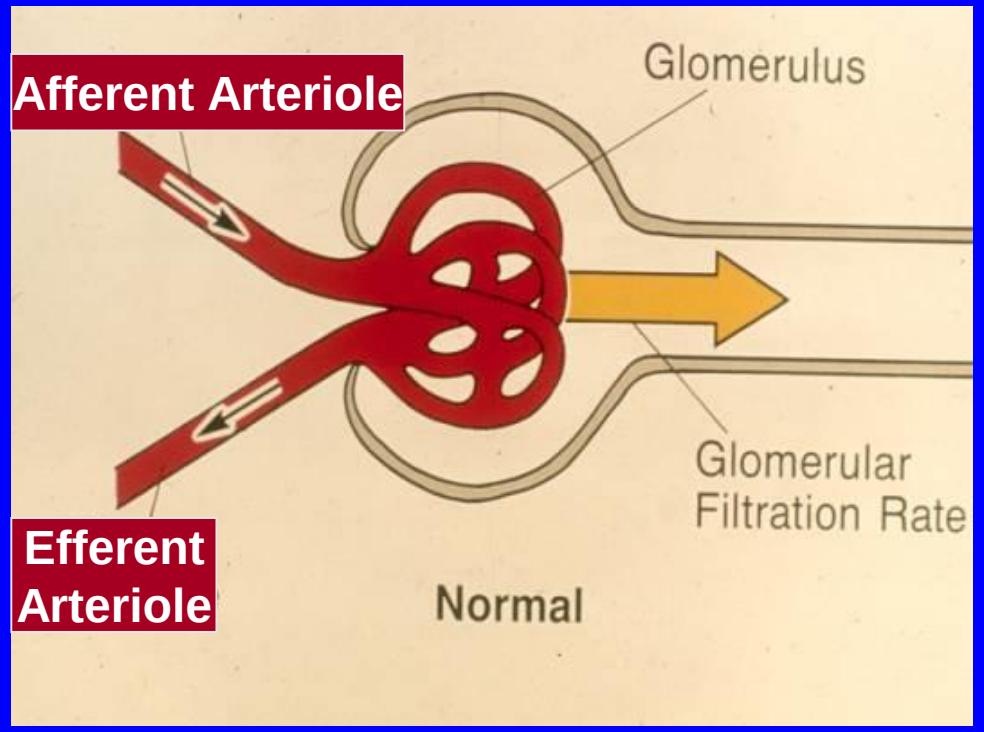
Glomerular filtration rate crystalloid



$$Jv = Kf\ (P_{capillary} - \downarrow \Pi_{capillary})$$

↑Net filtration pressure

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Contre l’albumine

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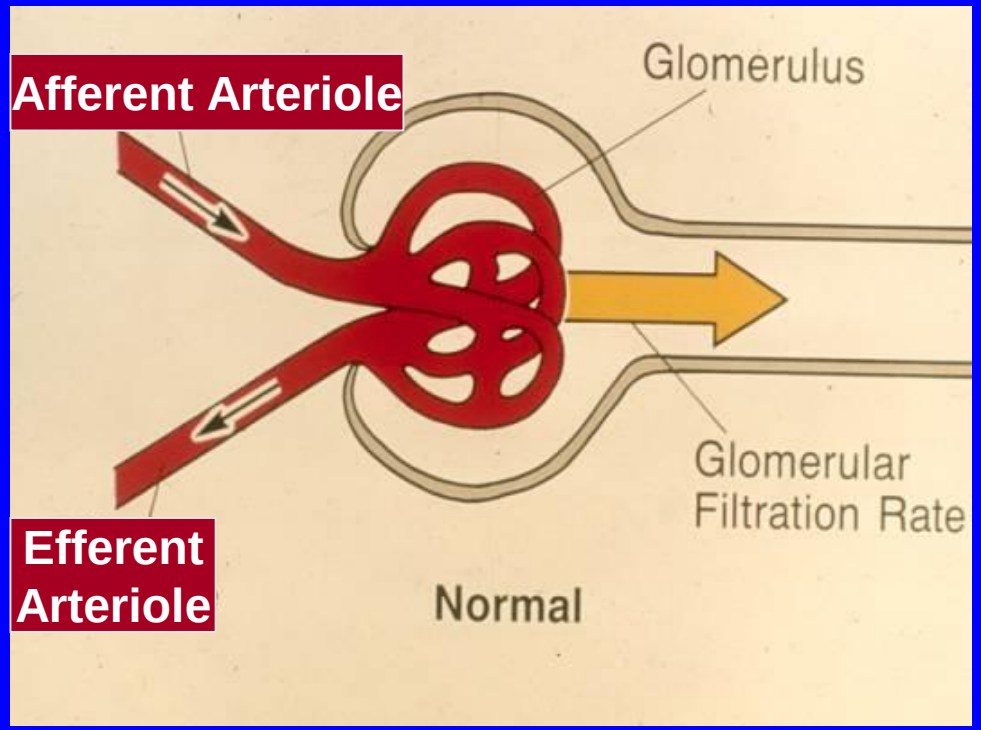
Glomerular filtration rate colloids



$$Jv = Kf\ (P_{capillary} - \nearrow \Pi_{capillary})$$

↙Net filtration pressure colloïds

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Contre l'albumine

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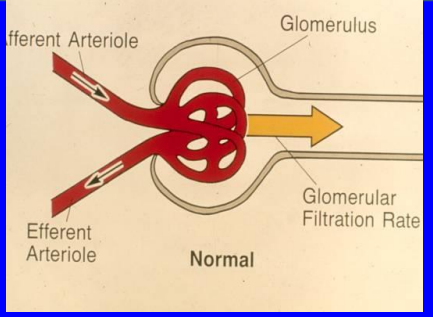
Effective Glomerular Filtration Pressure and Single Nephron Filtration Rate during Hydropenia, Elevated Ureteral Pressure, and Acute Volume Expansion with Isotonic Saline

VITTORIO E. ANDREUCCI, JAIME HERRERA-ACOSTA, FLOYD C. RECTOR, JR., and DONALD W. SELDIN

The Journal of Clinical Investigation Volume 50 1971



π aff, cm H2O	26.3	Volume expansion: Crystalloids	13.2
π G, cm H2O	36.3		16.5
π eff, cm H2O	46.1		19.7
PG, cm H2O	71.3		70.9
SNGFR, nl/min	32.5		46.0 *

$Jv = Kf (P_{capillary} - \downarrow \Pi_{capillary})$

2

Contre l'albumine

Pr Didier Payen

Intensive Care Med
DOI 10.1007/s00134-008-1225-2

ORIGINAL

CRYCO Study

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

The risk associated with hyperoncotic colloids in patients with shock

822 patients needing fluid resuscitation for shock

Crystalloids only	Hypo-oncotic colloids	Artificial hyperoncotic colloids	Hyperoncotic Albumin
N=127	Gelatins 4% albumin N=189	Starches Dextrans N=401	N=105
ARF: 11%	**10%**	18%	**35%**

2

Contre l’albumine

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POUR LE REIN:

On peut conclure: PAS UTILE VOIR DANGEREUX!!!

2

Contre l’albumine

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OUI? MAIS SI JE COMBINE ALBUMINE-FUROSEMIDE?

- **JE DOIS MIEUX CONTROLLER LA BALANCE HYDROSODEE…**

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Contre l'albumine

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Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury*

Greg S. Martin, MD; Robert J. Mangialardi, MD; Arthur P. Wheeler, MD; William D. Dupont, PhD; John A. Morris, MD; Gordon R. Bernard, MD

(Crit Care Med 2002; 30:2175–2182)

Patients: Thirty-seven mechanically-ventilated patients with acute lung injury and serum total protein ≤5.0 g/dL.

Interventions: Five-day protocolized regimen of 25 g of human serum albumin every 8 hrs with continuous infusion furosemide, or dual placebo, targeted to diuresis, weight loss, and serum total protein.

Conclusions: Albumin and furosemide therapy improves fluid balance, oxygenation, and hemodynamics in hypoproteinemic patients with acute lung injury. Determining the effect of this simple therapy on cost, outcomes, and other patient populations requires further study. (Crit Care Med 2002; 30:2175–2182)

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Contre l’albumine

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ALBUMINE ET CERVEAU

2

Contre l'albumine

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CONCLUSIONS

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. (Current Controlled Trials number, ISRCTN76588266.)

460 patients; 231 (50.2%) received albumin; 229 (49.8%) received saline.

Subgroup with GCS scores of 3 to 8 (severe brain injury).

- ✓ At **24 months**, **33.2% died in the albumin group / 20.4% in the saline group** (RR 1.63; 95% [CI], 1.17 to 2.26; **P = 0.003**).
- ✓ Among **severe brain injury**, **41.8% died in the albumin group / 22.2% in the saline group**, (RR 1.88; 95% CI, 1.31 to 2.70; **P<0.001**);
- ✓ **Among patients with GCS scores of 9 to 12, death rate P = 0.50.**

Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai Lo S, Vallance S.
N Engl J Med 2007;357:874–84

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Contre l’albumine

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ALBUMINE ET IMMUNITE

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Contre l'albumine

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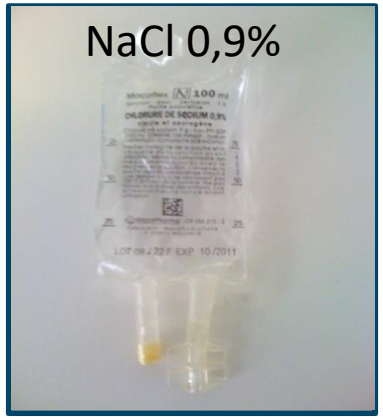
Physico-chemical characteristics: saline is everywhere… ➔ is only the difference dangerous?

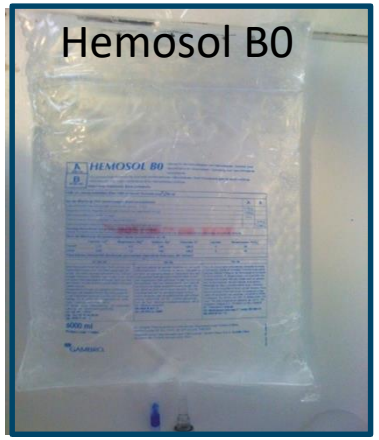
crystalloids

Colloids = crystalloids + macromolecules



153 Na+
153 Cl-
pH 5.4

130 Na+ 150
112 Cl- 100
pH 5.1 Lactate 30
pH 6.8



140 Na+
109 Cl-
HCO3- 32
Lact 3

pH 7.4

Albumine 20%

ΔNa or Cl- = 25 mM/l

Contre l'albumine

Pr Didier Payen

GOALS

✓To study ***in vitro*** the effect of the **blood dilution** by fluids on **cell surface molecules** and **radical oxygen species (ROS) production**

✓To **compare** the effects of **different fluids INCLUDING ALBUMIN**

✓To analyze the effects of these fluids **in stimulated conditions**

2

Contre l'albumine

Pr Didier Payen

PROTOCOL & METHODS

Healthy donors **whole blood incubated 3hrs (37°C, 5% CO_2) with:**

Cristalloids: **NaCl , Hemosol® (CRRT fluid replacement)**

Colloids: **20% Alb, Gelatin (Plasmion®), HEA (Voluven®)**

Control: incubation with **autologous plasma**

Two dilutions levels:

1) ➔ 8-9 g/dl Hb;

2) ➔ 4-5 g/dl Hb

stimulation by **LPS 100ng/ml) or LPS + PMA 10^{-8}M)**

FLOW CYTOMETRY

Monocytes: expression of **HLA-DR, CD11b, CD18**

Neutrophils (PMNs): expression of **CD11b, CD18**

Monocytes and PMNs: **ROS production** (Dihydro-Rhodamine 123)

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Contre l'albumine

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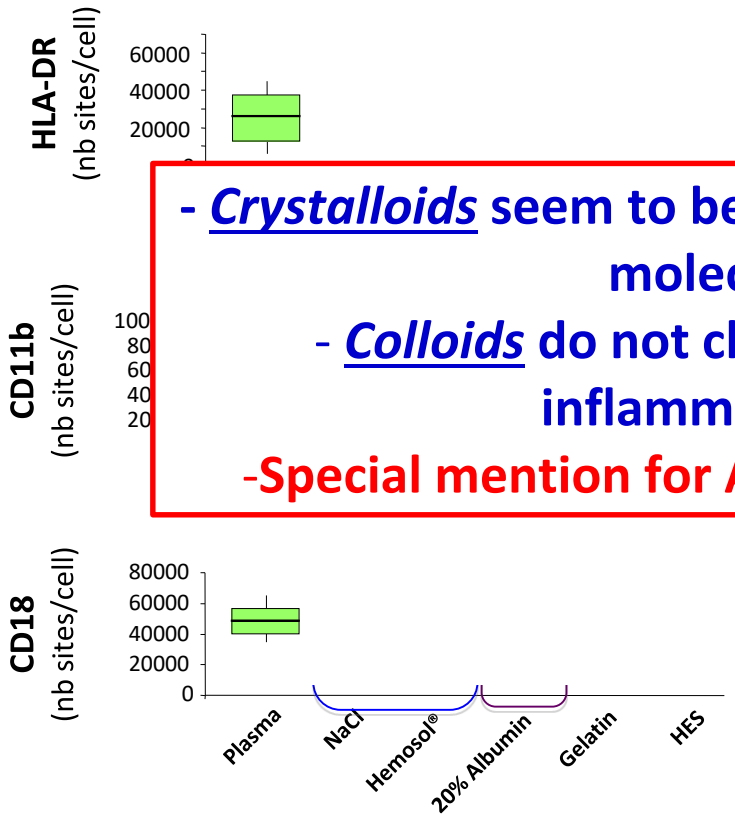
EFFECTS OF BLOOD DILUTION WITH FLUID

MONOCYTES ***PMNs***



- *Crystalloids* seem to be « anti-inflammatory » molecules

- *Colloids* do not change or increase inflammation….

-Special mention for Alb: a cryst/colloïds?

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Contre l’albumine

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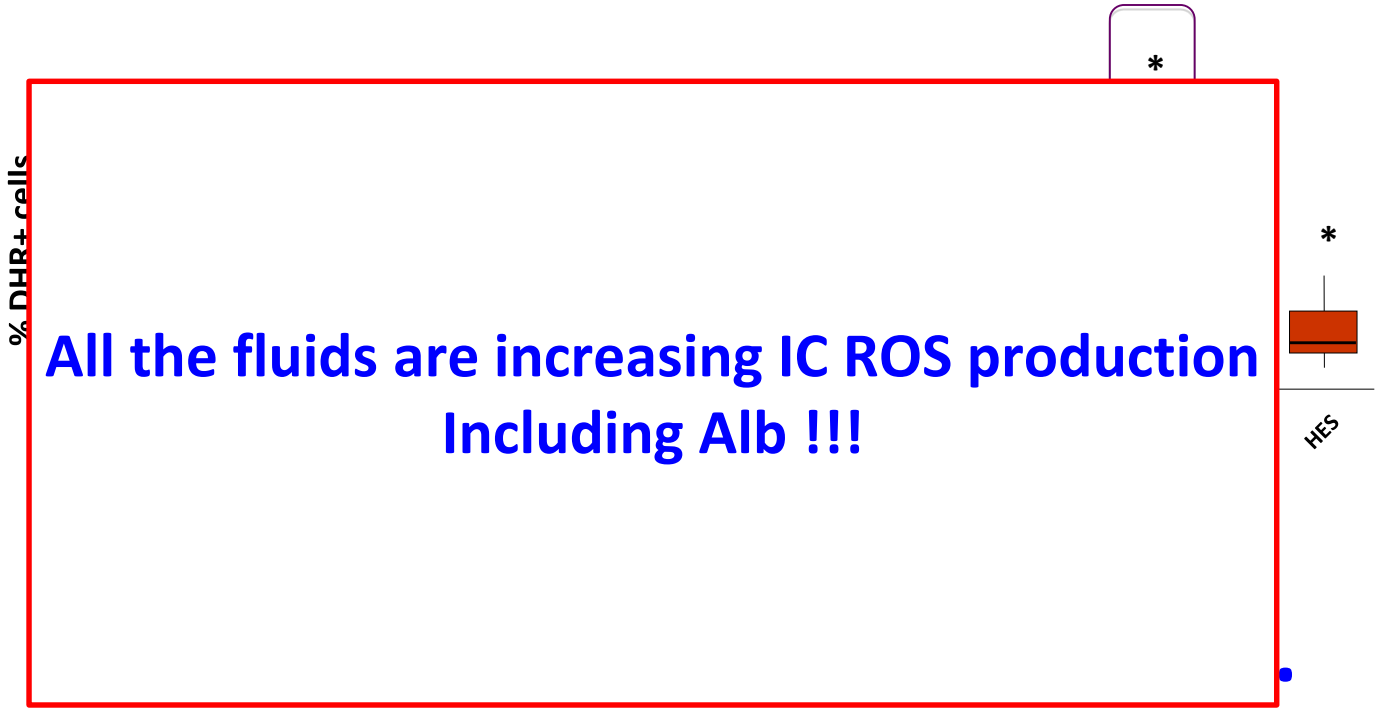
EFFECTS OF BLOOD DILUTION WITH FLUID

MONOCYTES ***PMNs***



All the fluids are increasing IC ROS production
Including Alb !!!

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Contre l'albumine

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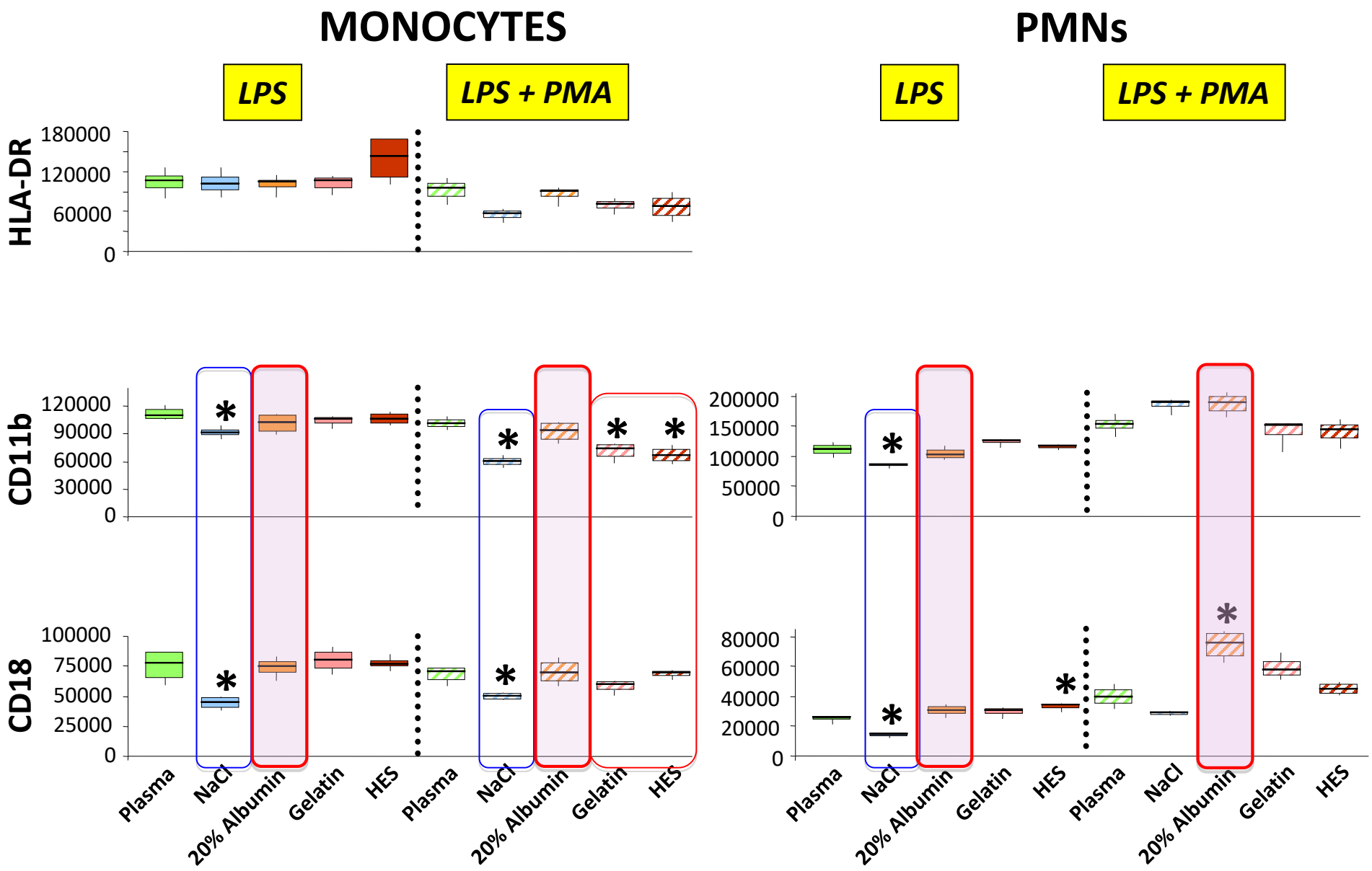
EFFECTS OF STIMULATION ON BLOOD DILUTED WITH FLUID



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Contre l'albumine

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DISCUSSION - CONCLUSION

- Crystalloids seemed to limit adhesion capacities in circulating immune cells, in basal and stimulated conditions
- Colloids had cell-specific effects

- increasing the ROS

Albumin has complex and discordant effects with mixed pro / anti-inflammatory effects

CAUTIOUS USE IN CLINIC

2

Contre l'albumine

Pr Didier Payen

Pour conclure…

- **Albumine OUI** dans des **indications restreintes**, et que **hyper concotique**
- **Albumine NON** pour le **rein**, pour le **cerveau**
- **Albumine** sur **immunité**: comme un crystalloïde mais **stimule la production de ROS!**
- **Coût reste elevé**, et donc utile pour des patients bien particulier… **Médecine personalisée**…
- **Qs:** doit-on se servir de l '**EBM** pour une **médecine personnalisée?**