

Hemoadsorption and cell-mediated immunity

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Athens, Greece
10th National Haemapheresis Association Conference
November 27th 2025



Conflicts of Interest

Scientific partnership with the following companies:

- Vantive
- BBraun
- Biomérieux
- Estor/Toray
- Exthera
- Fresenius Medical Care
- Infomed
- Jafron
- Cytosorbents
- Norrdia

Hemoadsorption and cell-mediated immunity

Focus for this talk:

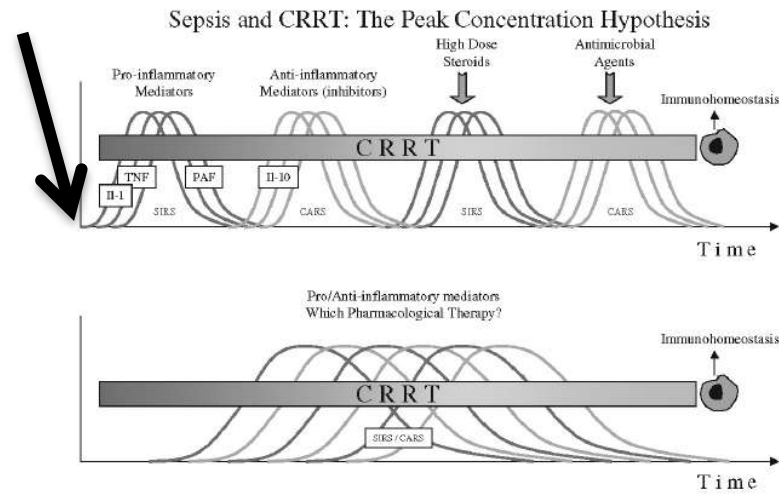
Can hemoadsorption do more than just removing from blood
cytokines and endotoxins?

=

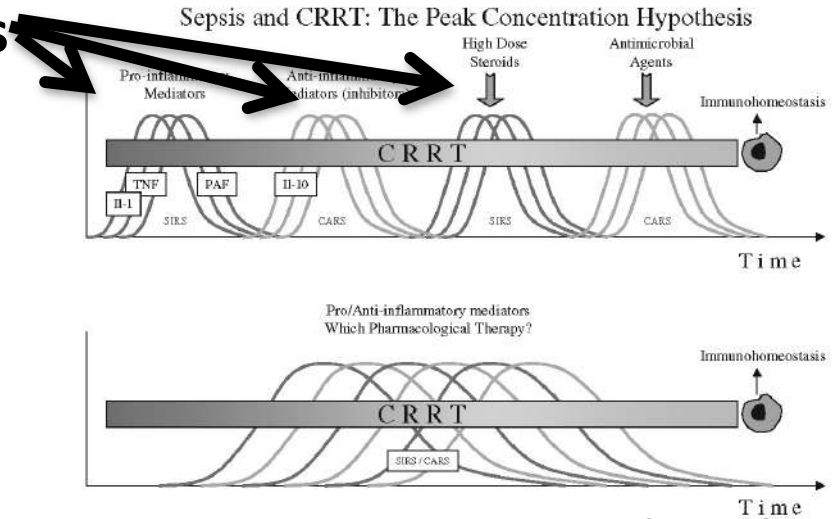
Can hemoadsorption also act at the cellular level?

HEMOADSORPTION: Possible mechanisms of action in sepsis

Endotoxins

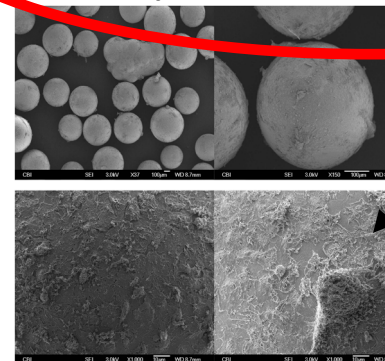


Cytokines



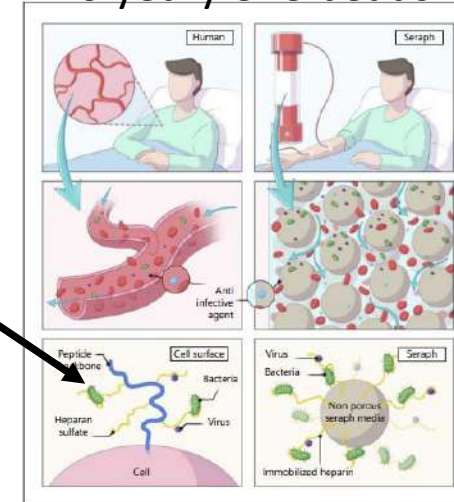
Ronco et al. Artificial Organs 2003

- Direct removal of activated leucocytes through adsorption
- Interaction sorbent-leucocyte leading to a modification of expression of leucocyte surface markers (ex: HLA-DR increase)



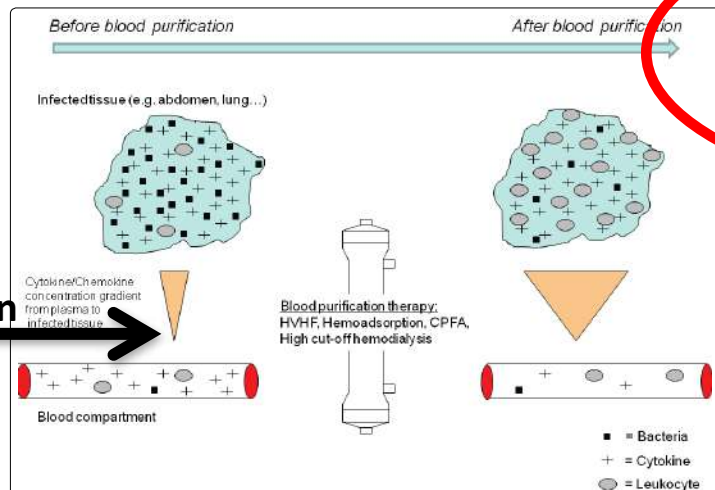
Rimmelé et al. Crit Care 2013

Polyethylene beads



Seffer et al. Blood Purif 2021

Chemokine concentration gradient



Peng et al. Critical Care 2014
Rimmelé et al. Anesthesiology 2012

Data to support this?

- 3 works
- 3 different teams
- 3 different continents
- 3 different hemoadsorption cartridges

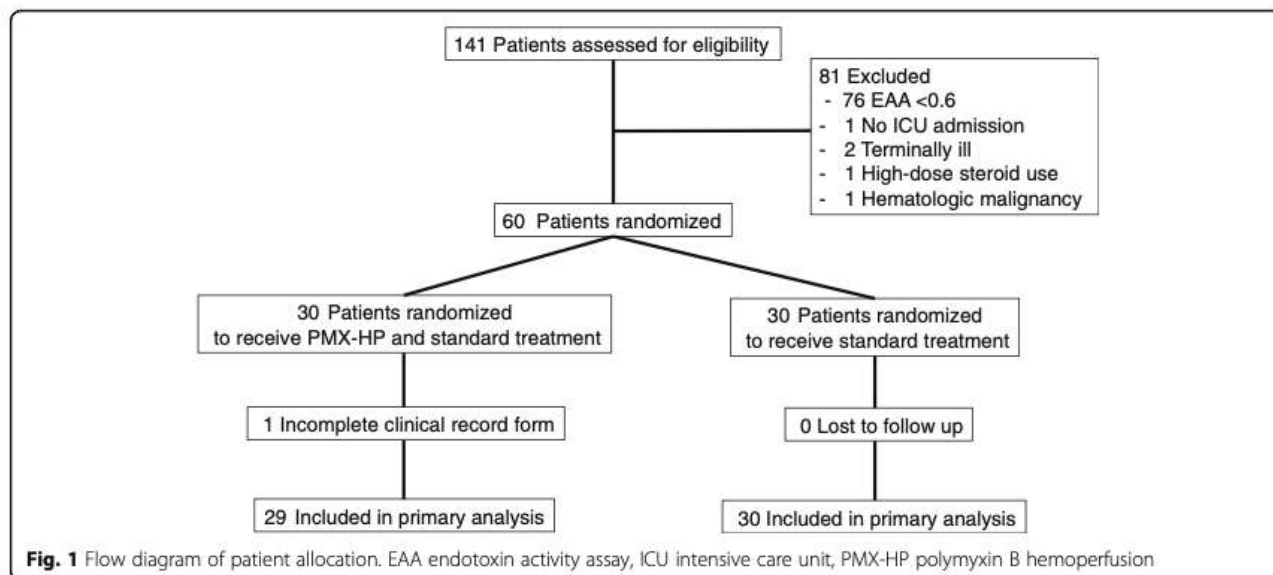
RESEARCH

Open Access



The effect of polymyxin B hemoperfusion on modulation of human leukocyte antigen DR in severe sepsis patients

Nattachai Srisawat^{1,2,3*}, Somkanya Tungsanga¹, Nuttha Lumlertgul^{1,2}, Chalermchai Kornaenthammasophon^{1,2}, Sadudee Peerapornratana^{1,2,3}, Nicha Thamrongsat^{1,2}, Khajohn Tiranathanagul¹, Karkiat Praditpornsilpa¹, Somchai Eiam-Ong¹, Kiang Tungsanga¹ and John A. Kellum³



- 59 septic patients randomized to receive either PMX-HP either standard ttt
- Expression of leukocyte surface markers at D1 and D3

Interaction sorbent-leucocyte leading to a modification of leucocyte surface markers expression (ex: HLA-DR increase)

Down regulate the activation of neutrophils expressed by the increase of CD11b in the standard group

= sort of “leucocyte reprogramming”

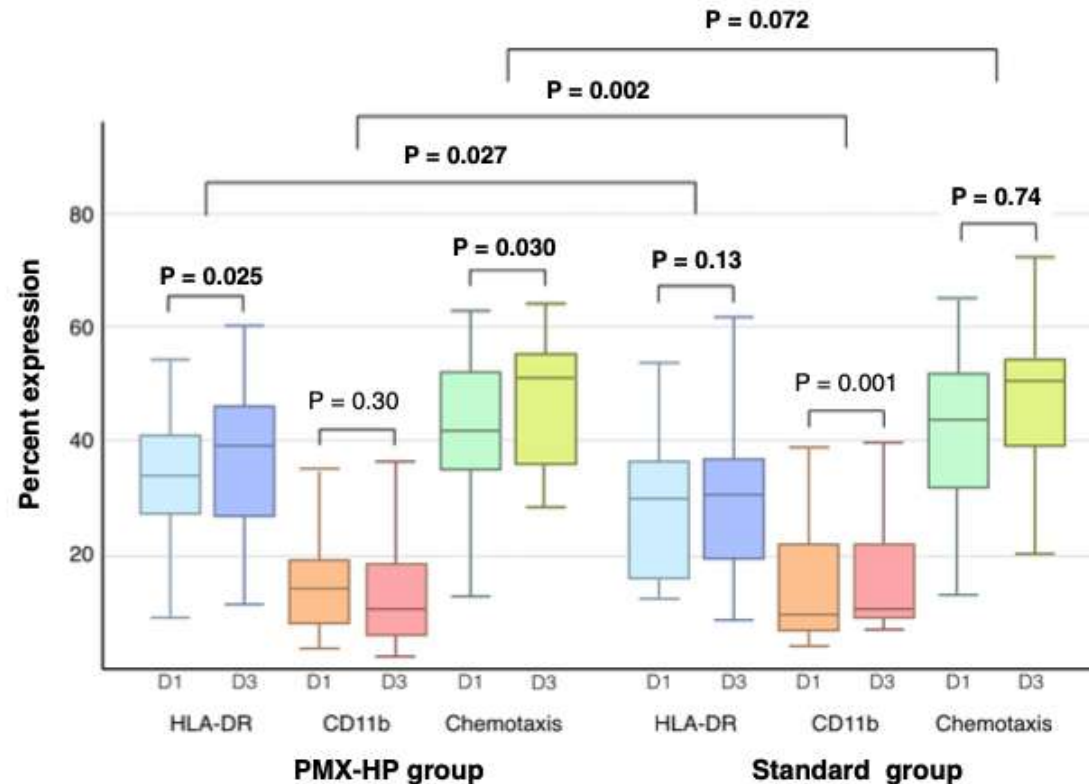


Fig. 2 Comparison of mHLA-DR expression, CD11b expression, and chemotaxis on neutrophil between PMX-HP group and non-PMX-HP group. D day, mHLA-DR monocytic human leukocyte antigen, PMX-HP polymyxin B hemoperfusion

RESEARCH

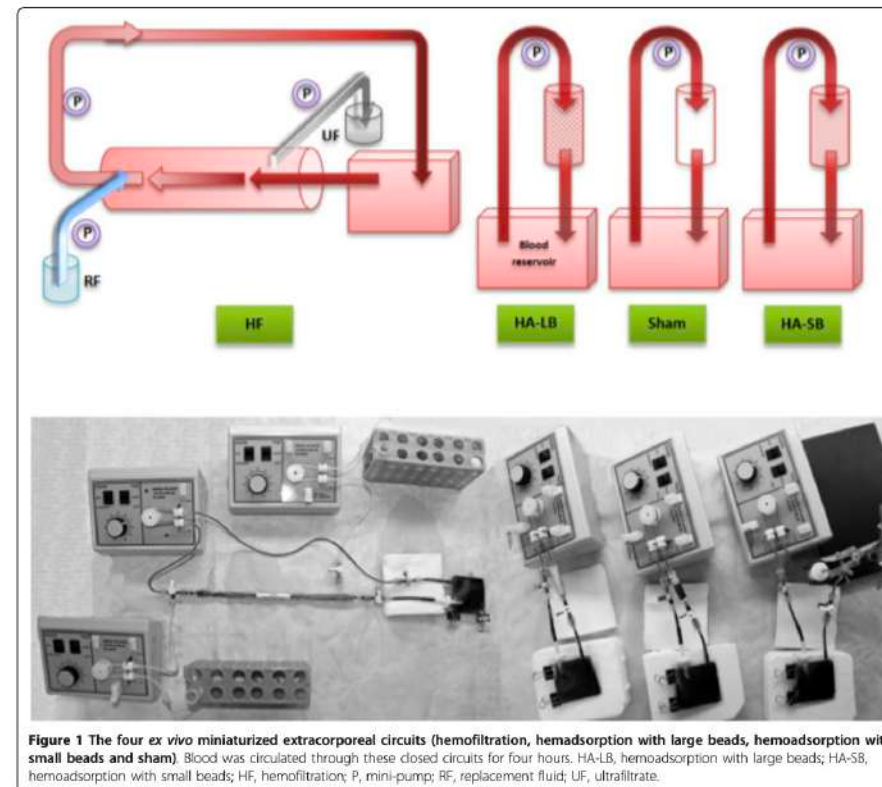
Open Access

Leukocyte capture and modulation of cell-mediated immunity during human sepsis: an *ex vivo* study

Thomas Rimmelé¹, Ata Murat Kaynar¹, Joseph N McLaughlin¹, Jeffery V Bishop¹, Morgan V Fedorchak², Anan Chuasuwan¹, Zhiyong Peng¹, Kai Singbartl¹, Daniel R Frederick¹, Lin Zhu¹, Melinda Carter¹, William J Federspiel^{1,2}, Adriana Zeevi³ and John A Kellum^{1,2*}

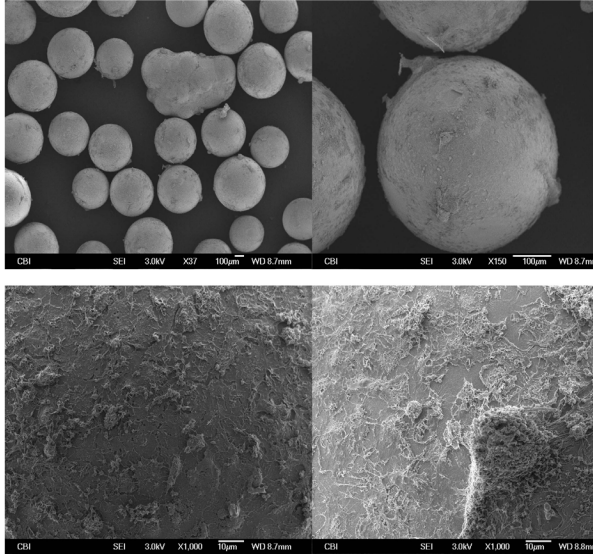
Rimmelé et al. *Critical Care* 2013, **17**:R59
http://ccforum.com/content/17/2/R59

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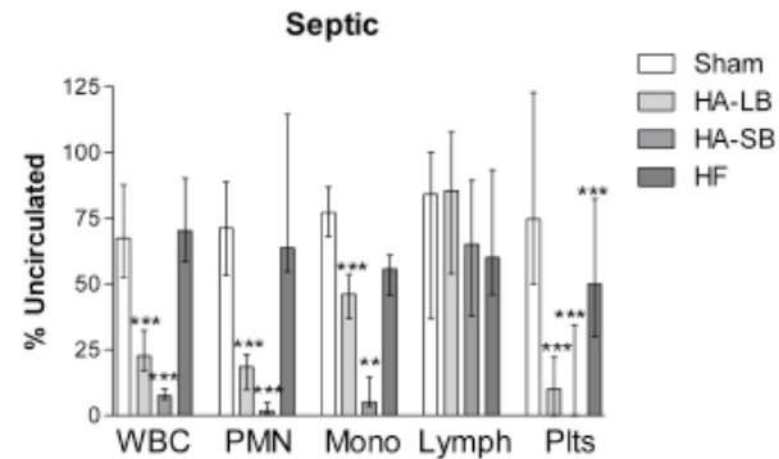
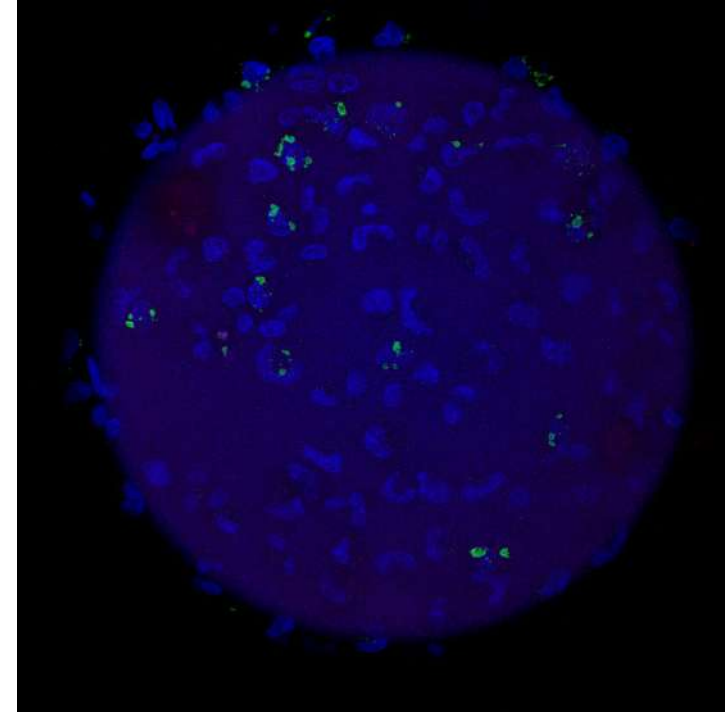


Leukocyte adsorption on the beads

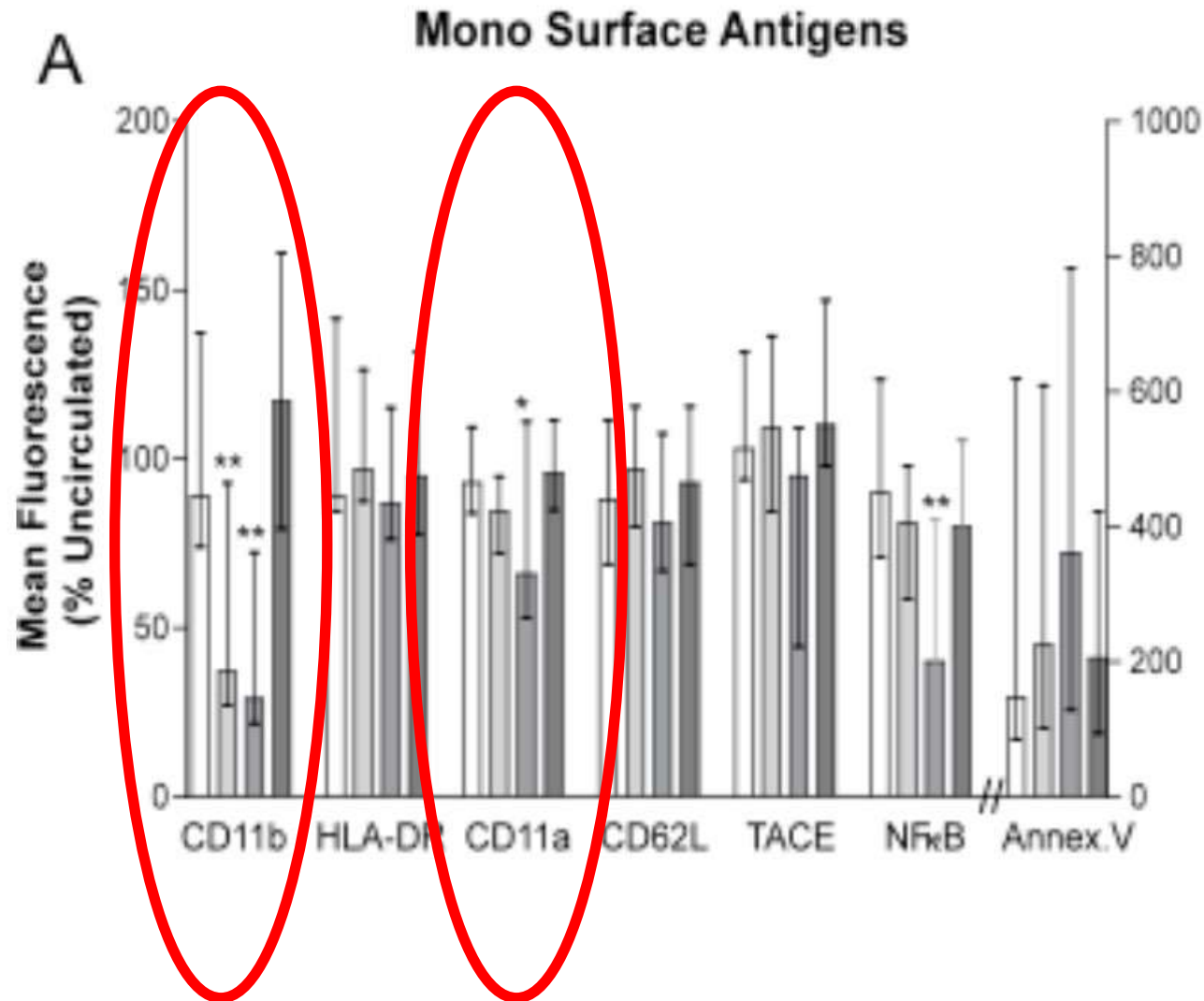
Regular Beads



Electronic microscopy
and immunofluorescence
pictures showing
leucocytes adsorption on
adsorptive polymer

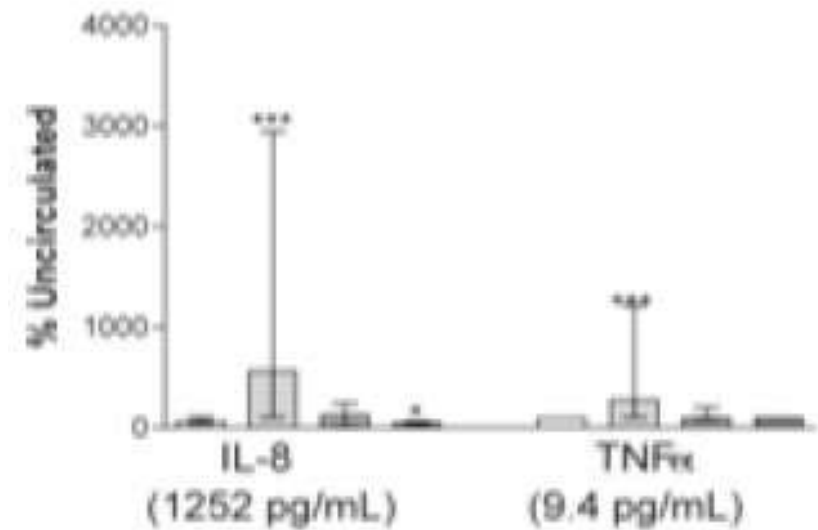
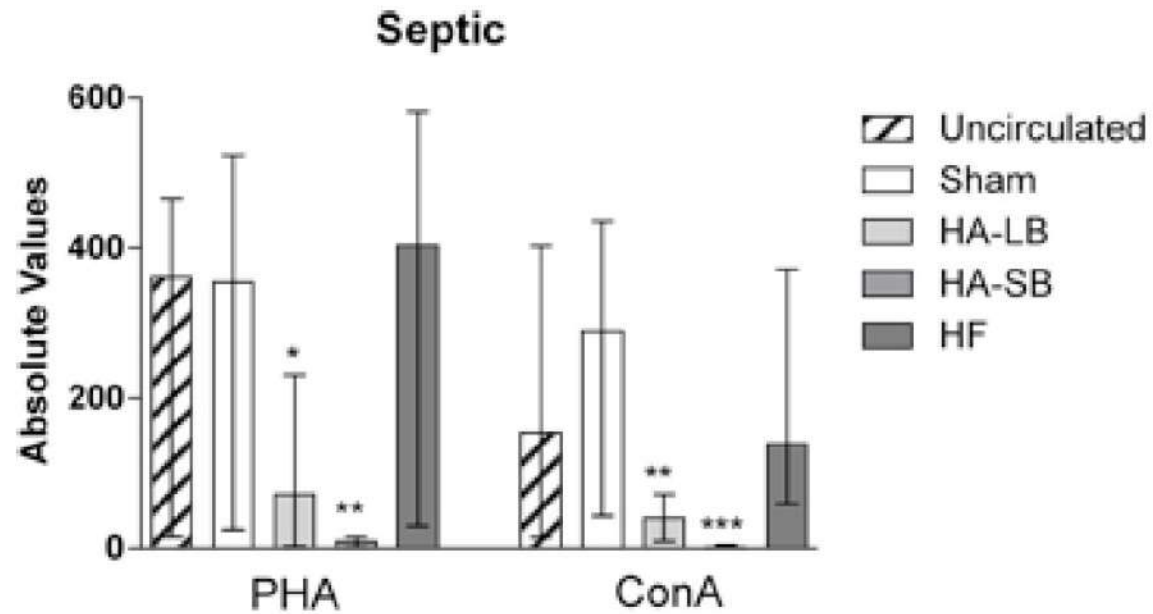


Activated cells are preferentially adsorbed on the beads



Modification of the lymphocyte function following
monocyte adsorption on the hemoadsorption beads with
IL-8 release

Lymph Intracellular ATP production



Effects on the lymphocyte function reversed when cells adsorption blocked by EDTA

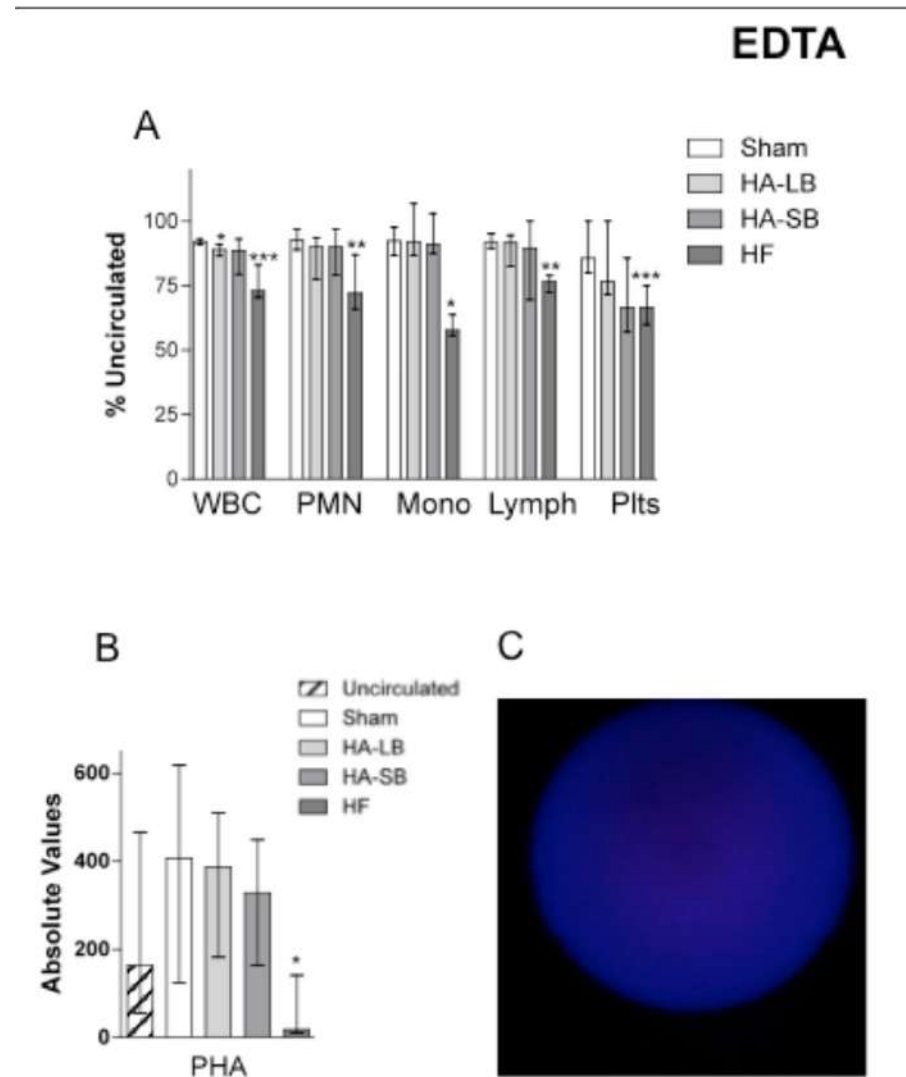


Figure 7 Experiments with EDTA. Effects of extracorporeal circuits on WBC count (A), cytokine Cell Memory assays (B), in healthy blood, when circuit anticoagulation was performed with EDTA/

RESEARCH

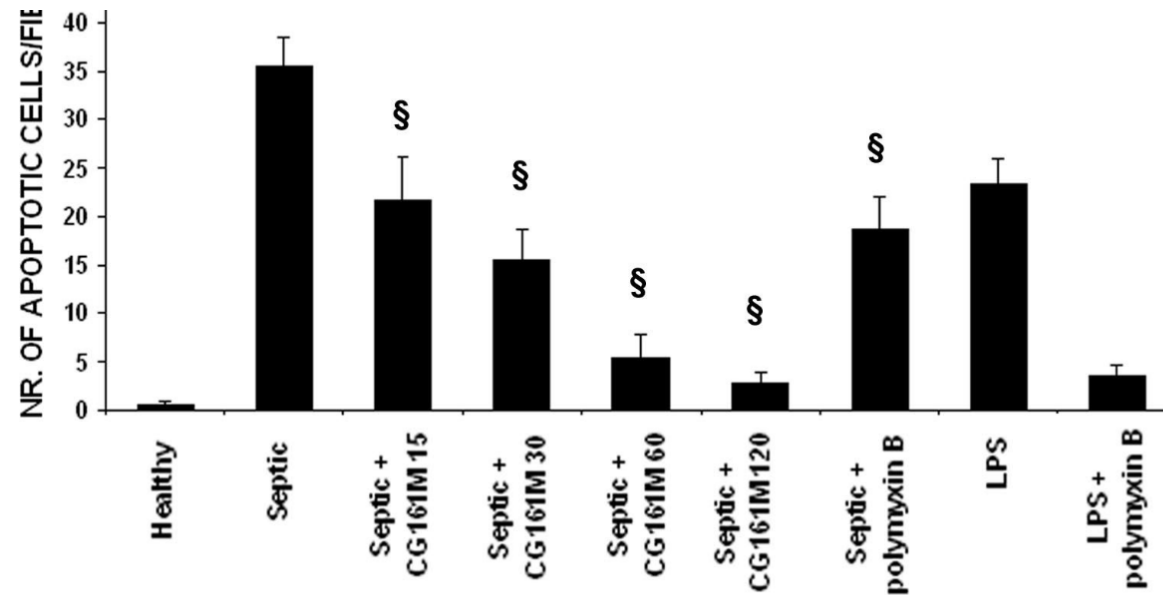
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Protective effect of resin adsorption on septic plasma-induced tubular injury

Vincenzo Cantaluppi^{1,2}, Viktoria Weber³, Carola Lauritano¹, Federico Figliolini¹, Silvia Beltramo¹, Luigi Biancone^{1,2}, Massimo De Cal⁴, Dinna Cruz⁴, Claudio Ronco⁴, Giuseppe Paolo Segoloni², Ciro Tetta⁵, Giovanni Camussi^{1,2,6*}

- 10 critically ill patients with sepsis-associated AKI
- Effects of their plasma on granulocyte adhesion, apoptosis and functional alterations of cultured human kidney tubular epithelial cells.
- In vitro model of plasma adsorption
- Assessment of the protective effect of unselective removal of soluble mediators by the Amberchrom CG161 M resin on septic plasma-induced tubular cell injury.

Decrease of the TEC apoptosis with hemoadsorption



Reversal of the septic plasma-induced alteration of TEC polarity with hemoadsorbent

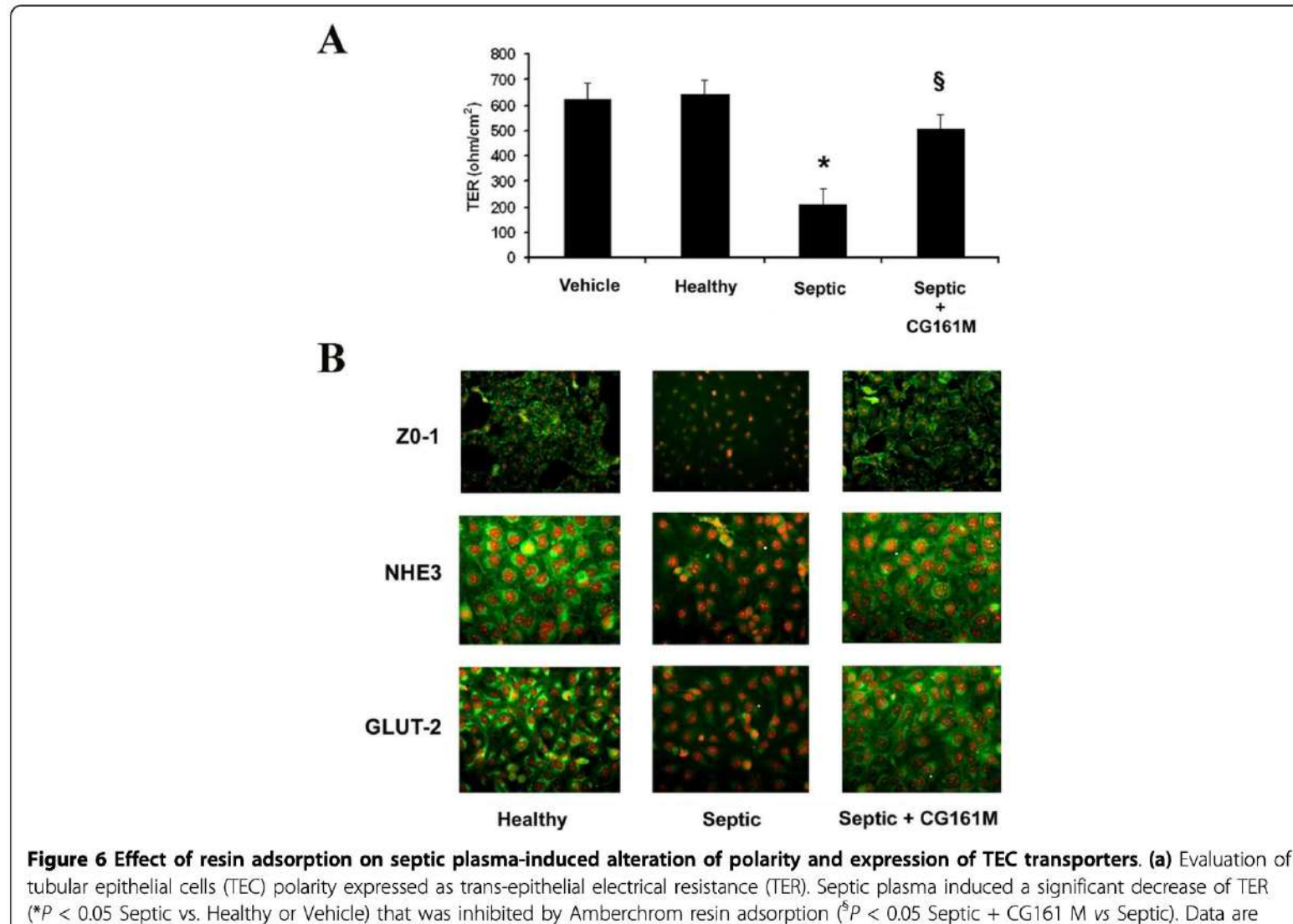


Figure 6 Effect of resin adsorption on septic plasma-induced alteration of polarity and expression of TEC transporters. (a) Evaluation of tubular epithelial cells (TEC) polarity expressed as trans-epithelial electrical resistance (TER). Septic plasma induced a significant decrease of TER (* $P < 0.05$ Septic vs. Healthy or Vehicle) that was inhibited by Amberchrom resin adsorption (§ $P < 0.05$ Septic + CG161 M vs Septic). Data are

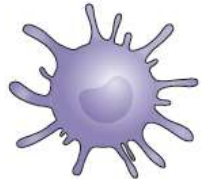
HA can interact with Innate immunity AND adaptive immunity!

a Effects of protracted sepsis on the innate immune system



Follicular dendritic cell

↑ Apoptosis
↓ Antigen presentation to B cells



Dendritic cell

↑ Apoptosis
↓ Antigen presentation to T cells
↓ Cytokine secretion



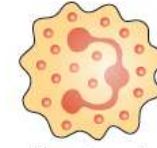
Macrophage

↑ Anti-inflammatory cytokine secretion
↓ HLA-DR expression
↓ Pro-inflammatory cytokine secretion
↓ Pathogen killing



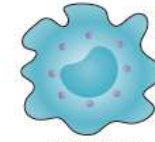
NK cell

↑ Apoptosis
↓ Cytotoxic function
↓ Cytokine secretion



Neutrophil

↑ Release of immature neutrophils
↑ IL-10 secretion
↓ Apoptosis
↓ Reactive oxygen species release
↓ Nitric oxide release
↓ Expression of adhesion markers



MDSC

↑ Apoptosis
↓ Cytotoxic function
↓ Cytokine secretion

b Effects of protracted sepsis on the adaptive immune system



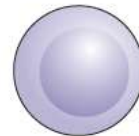
CD4⁺ T cell

• Cell exhaustion
↑ Apoptosis
↑ T_H2 cell polarization
↓ Adhesion molecule expression
↓ CD28 expression
↓ TCR diversity



CD8⁺ T cell

• Cell exhaustion
↑ Apoptosis
↓ Cytotoxic function
↓ Cytokine secretion
↓ TCR diversity



T_{Reg} cell

• Resistance to apoptosis
↑ Suppressive activities



B cell

↑ Apoptosis
↓ Antigen-specific antibody production

CONCLUSION

- 1) Hemoadsorption may be helpful in sepsis via the direct removal of DAMPS and PAMPS (LPS, cytokines)**
- 2) Thanks to technological improvements, new hemadsorption devices can adsorb leukocytes (monocytes and polynuclear cells +++) and pathogens**
- 3) Hemoadsorption does also act at the cellular level through complex mechanisms**
 - Modification of leukocyte surface markers**
 - Modification of leukocyte function**
 - Modification of other cells (TECs) function**
- 4) Both INNATE and ADAPTIVE immunity seem accessible to modulation via hemoadsorption**