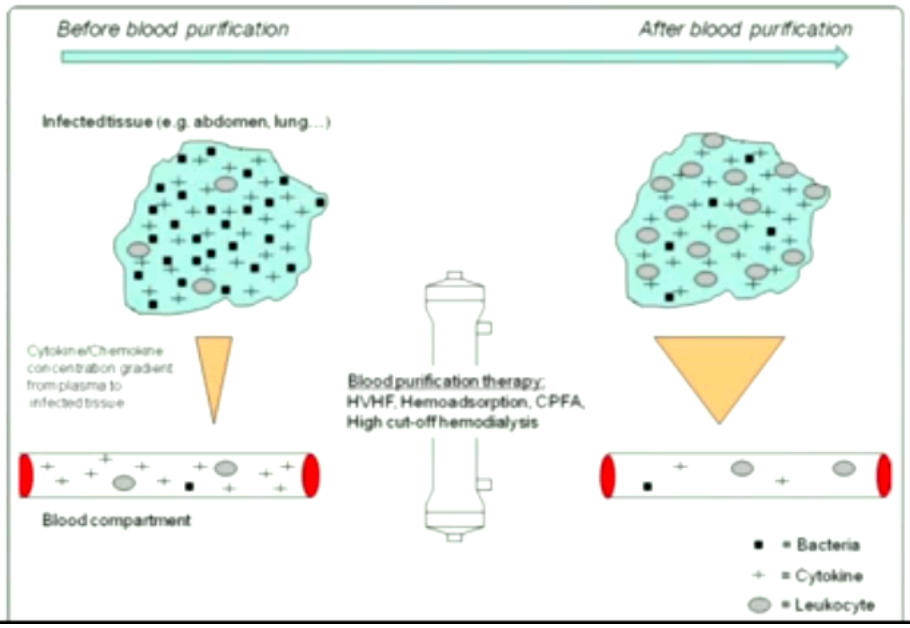
Peng et al. Critical Care 2014, 18:R141
http://ccforum.com/content/18/4/R141

CRITICAL CARE

RESEARCH Open Access

Modulation of chemokine gradients by apheresis redirects leukocyte trafficking to different compartments during sepsis, studies in a rat model

Zhi-Yong Peng[1,2], Jeffery V Bishop[2], Xiao-Yan Wen[1,2], Michele M Elder[1,2], Feihu Zhou[1,2], Anan Chuasuwan[1,2], Melinda J Carter[2], Jason E Devlin[3], A Murat Kaynar[1,2], Kai Singbartl[1,2], Francis Pike[1,2], Robert S Parker[1,2,5,6], Gilles Clermont[1,2,5,6], William J Federspiel[1,2,4,6] and John A Kellum[1,2,4,6,7*]



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

EXTRACORPOREAL BLOOD PURIFICATION TECHNIQUES AVAILABLE IN 2019

- High-volume hemofiltration and Cascade hemofiltration
- Plasma exchanges
- Coupled Plasma Filtration Adsorption
- Hemoperfusion: PMX-B (Toray), Cytosorb (Cytosorbents), LPS adsorber (Alteco), HA330 (Biosun), MG350 (Jafron)
- New CRRT membranes: high adsorptive hemofiltration (oXiris, Baxter) and high cut-off membranes (Emic2, Fresenius Medical Care)

Hemoperfusion devices

Device	Company	Composition	Substance eliminated
PMX	Toray, Japan	PMX covalently bound to polypropylene-polystyrene fiber	Endotoxin
HA330	Jafron, China	Neutral resin	Cytokines
MG350	Biosun, China	Neutral resin	Cytokines
Cytosorb	Cytosorbents, USA	Polystyrenedivinyl benzene copolymer beads with biocompatible polyvinylpyrrolidone coating	Cytokines
LPS adsorber	Alteco, Sweden	Synthetic polypeptide bound to porous polyethylene discs	Endotoxin

Courtesy of Dr Srisawat

Review Article

Blood Purification and Mortality in Sepsis: A Meta-Analysis of Randomized Trials*

Feihu Zhou, MD, PhD[1,2]; Zhiyong Peng, MD, PhD[1]; Raghavan Murugan, MD, MS, FRCP[1]; John A. Kellum, MD, MCCM[1]

Study or Subgroup	Favours blood purification Events	Total	Conventional treatment Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
2.1.1 Total mortality							
Reeves, 1999	3	9	6	13	2.7%	0.72 [0.24, 2.16]	1999
Nakamura, 1999	12	30	14	20	9.2%	0.57 [0.34, 0.96]	1999
Nemoto, 2001	32	54	39	44	21.7%	0.67 [0.52, 0.85]	2001
Cole, 2002	4	12	4	12	2.5%	1.00 [0.32, 3.10]	2002
Nakamura, 2002	2	9	7	9	2.0%	0.29 [0.08, 1.02]	2002
Busund, 2002	18	54	28	52	11.3%	0.62 [0.39, 0.97]	2002
Nakamura-II, 2003	2	10	8	10	2.0%	0.25 [0.07, 0.90]	2003
Nakamura-I, 2003	9	35	16	25	6.9%	0.40 [0.21, 0.76]	2003
Nakamura, 2004	3	15	6	10	2.5%	0.33 [0.11, 1.03]	2004
Reinhart, 2004	19	67	19	76	8.7%	1.13 [0.66, 1.96]	2004
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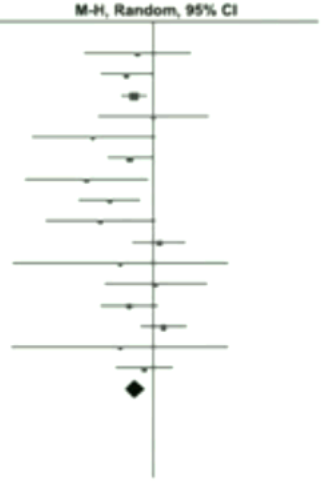
Huang, 2010	11	24	11	20	7.7%	0.83 [0.46, 1.50]	2010
Subtotal (95% CI)		**428**		**399**	**100.0%**	**0.69 [0.56, 0.84]**	
Total events	153		200				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 20.54$, df = 15 (P = 0.15); $I^2 = 27\%$

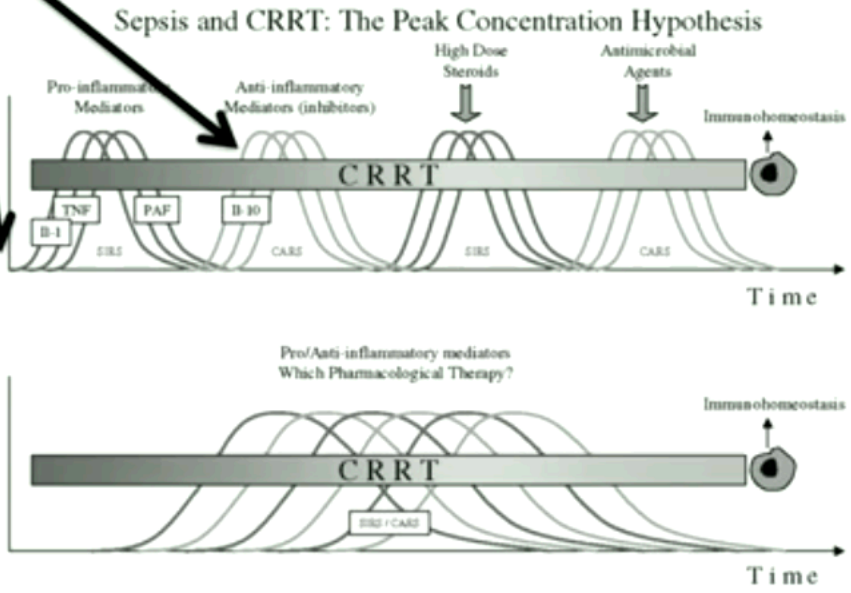
Test for overall effect: Z = 3.71 (P = 0.0002)



Zhou et al. *Crit Care Med* 2013;41(10):1-12.

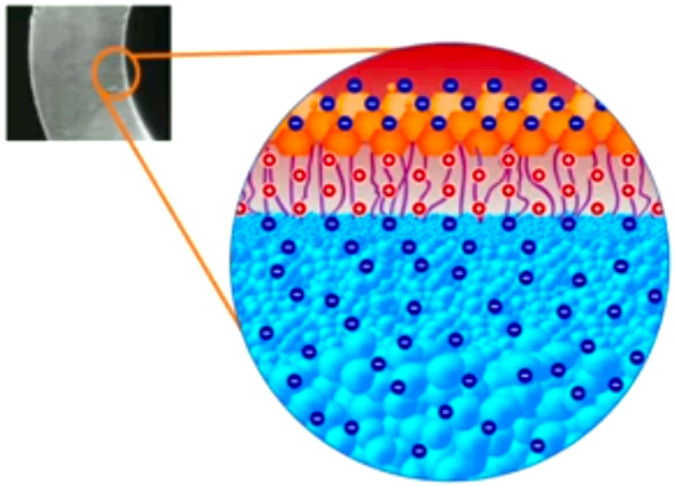
OXIRIS set : pathophysiology

Endotoxins and cytokines



Ronco et al. *Artificial Organs* 2003

OXIRIS set



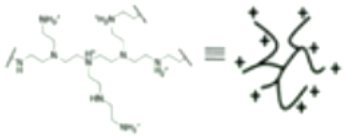
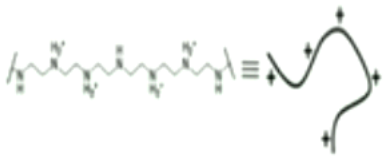
Heparin coating reduces membrane thrombogenicity

PEI surface treatment adsorbs endotoxin (interaction with lipid A groups)

AN69 base membrane adsorbs cytokine and toxins whilst providing continuous renal support. Cytokine adsorption occurs throughout the entire membrane thickness

No influence of surface coating on AN69 based adsorption properties

Courtesy of Baxter

	AN69ST	oXiris
Membrane	AN69 hollow fiber with high ionic adsorptive capacity in the bulk thickness	AN69 hollow fiber with high ionic adsorptive capacity in the bulk thickness
Surface treatment	PEI (-)	PEI Heparin
Initial heparin quantity	(-)	~ 4500 UI/m^2
Priming recommendation	Heparin solution (w/5000UI per L) to minimize residual adsorption capacities	
Heparin quantity grafted during priming	~ 500 UI/m^2	~ 1500 UI/m^2
Endotoxin adsorption	Low affinity for endotoxin removal	High affinity. Fast removal of a pathological concentration shown *in vitro* (> 50 EU/ml)
PEI free amine quantity	Approx 0.2 µmol/g of fiber	Approx 3.5 µmol/g of fiber
PEI resulting conformation		
	Low accessibility of PEI positive PEI groups at the surface	**High accessibility of PEI positive groups at the surface**

Courtesy of Baxter

OXIRIS set | Latest functional data

Malard *et al. Intensive Care Medicine Experimental* (2018) 6:12
https://doi.org/10.1186/s40635-018-0177-2

Intensive Care Medicine Experimental

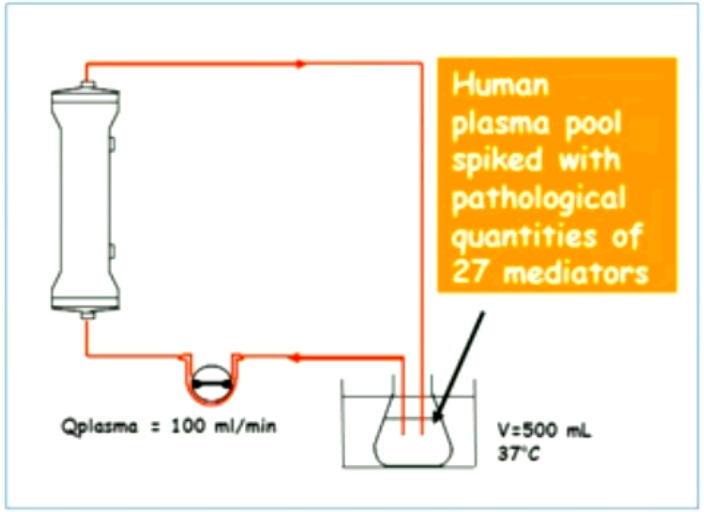
RESEARCH Open Access

In vitro comparison of the adsorption of inflammatory mediators by blood purification devices

Benjamin Malard[1*], Corine Lambert[1] and John A. Kellum[2]

- In vitro side by side comparison of **oXiris** set, Toraymyxin and Cytosorb for inflammatory mediators removal

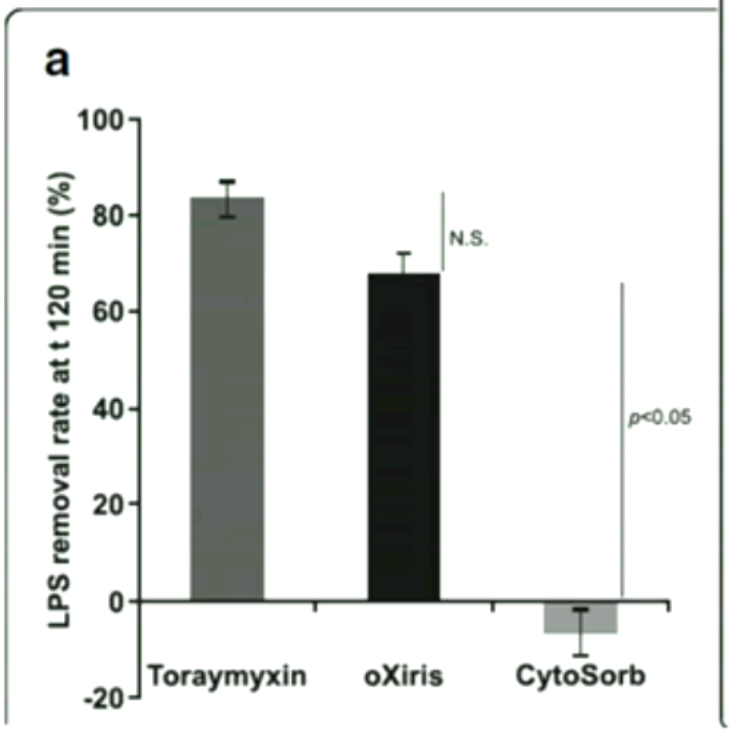
In vitro selected model



Time of experiment 2h. N=3 circulations with each device.

Malard et al. *Intensive Care Med Exp* 2018

OXIRIS set | Latest functional data



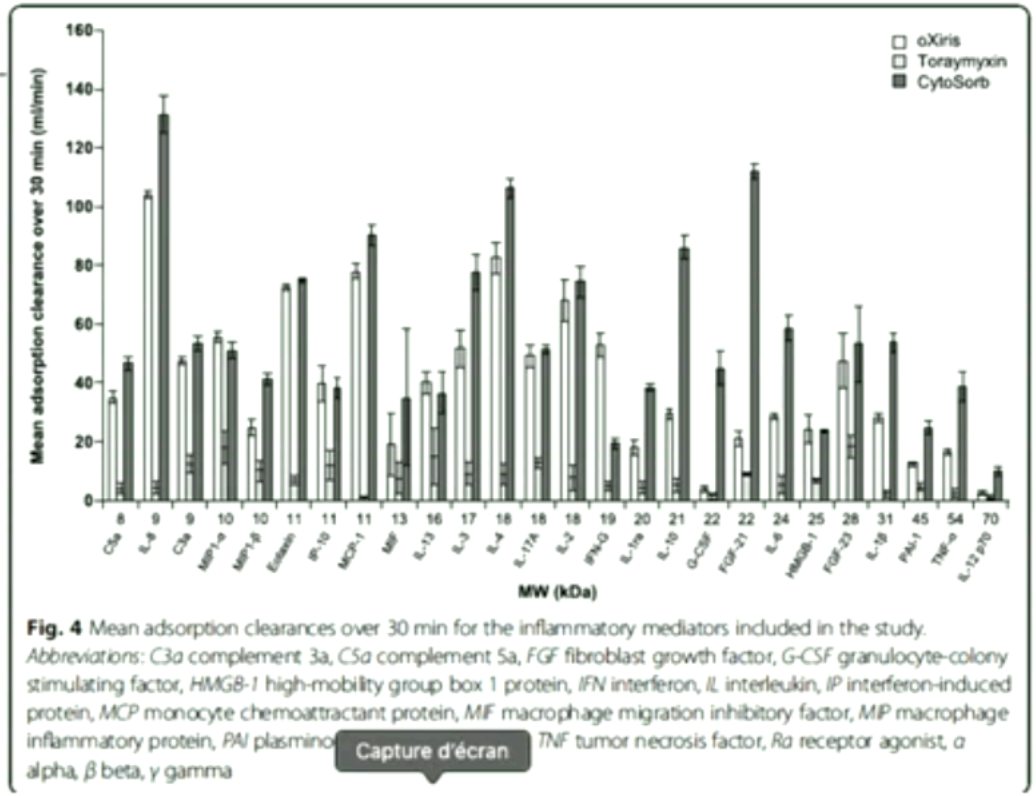
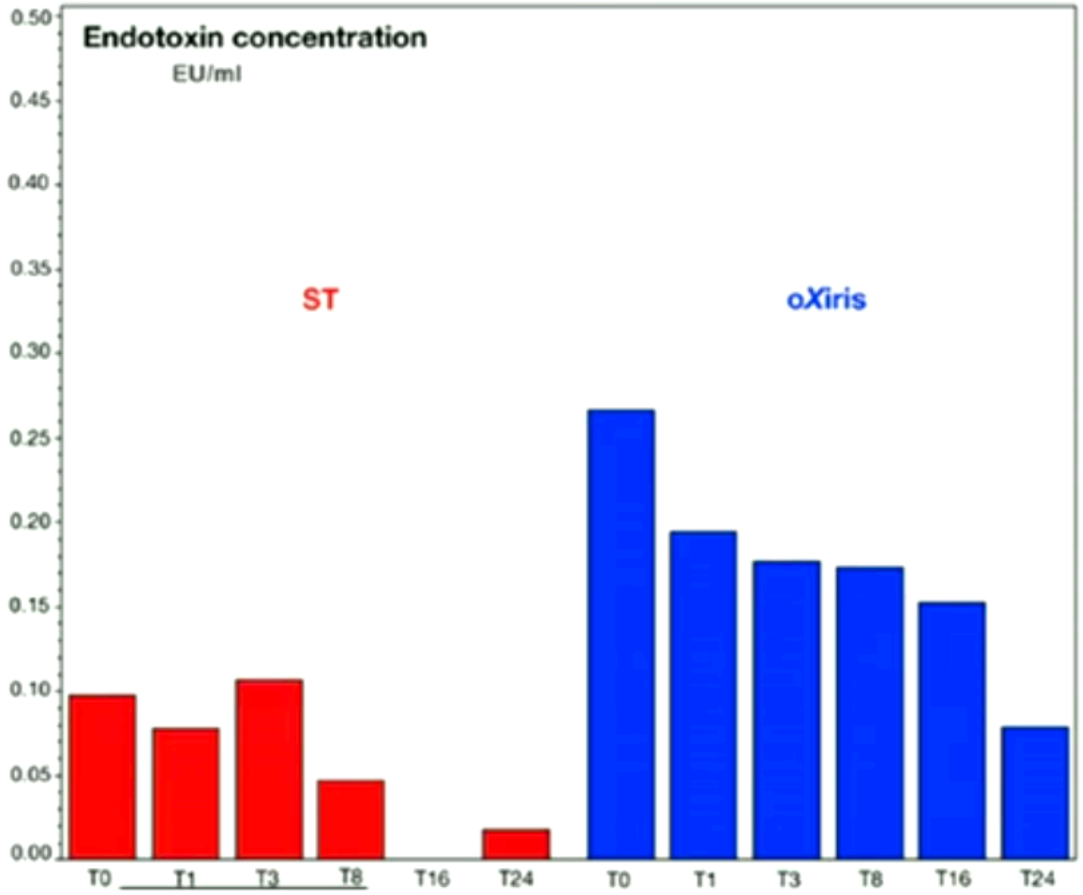


Fig. 4 Mean adsorption clearances over 30 min for the inflammatory mediators included in the study. *Abbreviations*: *C3a* complement 3a, *C5a* complement 5a, *FGF* fibroblast growth factor, *G-CSF* granulocyte-colony stimulating factor, *HMGB-1* high-mobility group box 1 protein, *IFN* interferon, *IL* interleukin, *IP* interferon-induced protein, *MCP* monocyte chemoattractant protein, *MIF* macrophage migration inhibitory factor, *MIP* macrophage inflammatory protein, *PAI* plasmino *TNF* tumor necrosis factor, *Ra* receptor agonist, *α* alpha, *β* beta, *γ* gamma

Capture d'écran

Malard et al. *Intensive Care Med Exp* 2018



Broman et al. *Plos One* 2019

1) Some (limited) evidence, not no evidence!

Blood Purification and Mortality in Sepsis: A Meta-Analysis of Randomized Trials*

Feihu Zhou, MD, PhD[1,2]; Zhiyong Peng, MD, PhD[1]; Raghavan Murugan, MD, MS, FRCP[1]; John A. Kellum, MD, MCCM[1]

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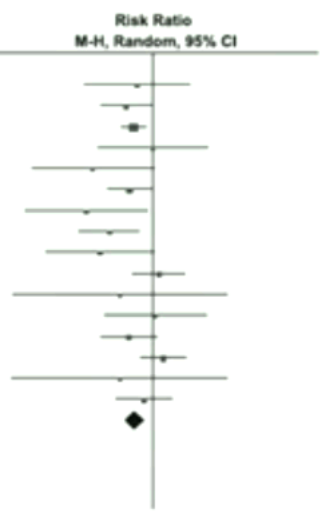
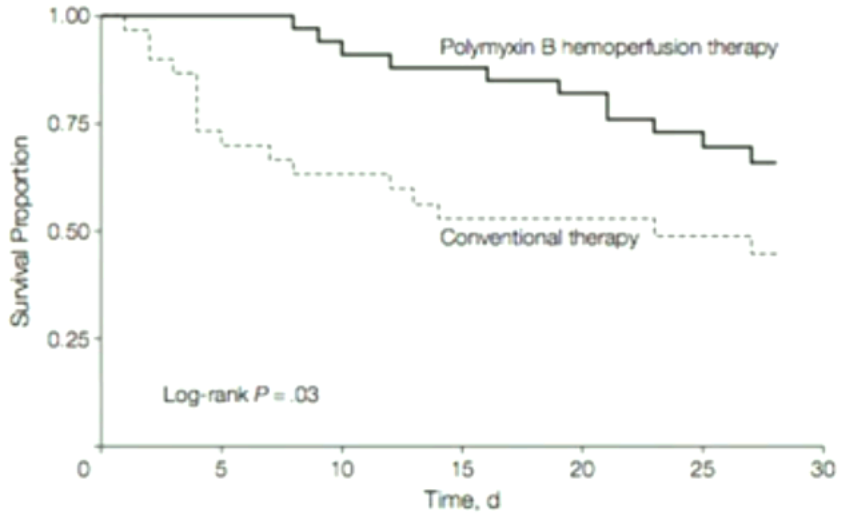


Zhou et al. *Crit Care Med* 2013

EUPHAS study

- Multicenter RCT performed in 10 Italian ICUs from 2004 to 2007
- 64 patients in septic shock, randomized in 2 groups:
  - Conventional treatment
  - Conventional treatment + 2 polymyxin B hemoadsorption sessions
- Improvement of hemodynamics, PaO2 / FiO2 and SOFA score



Cruz et al. *JAMA* 2009

2) Any limits with these trials…?

IVOIRE

ABDOMIX

COMPACT 1

EUPHRATES

Intensive Care Med
DOI 10.1007/s00134-013-2967-z

ORIGINAL

Olivier Joannes-Boyau
Patrick M. Honoré
Paul Perez
Sean M. Bagshaw
Hubert Grand
Jean-Luc Canivet
Antoine Dewitte
Claire Flamens

High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial

Intensive Care Med
DOI 10.1007/s00134-015-3751-z

SEVEN-DAY PROFILE PUBLICATION

Didier M. Payen
Joelle Guilhot
Yoann Launey
Anne Claire Lukaszewicz
Mahmoud Kaaki
Benoit Veber

Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial

Open Access Research

BMJ Open

Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: A multicenter randomised controlled clinical trial

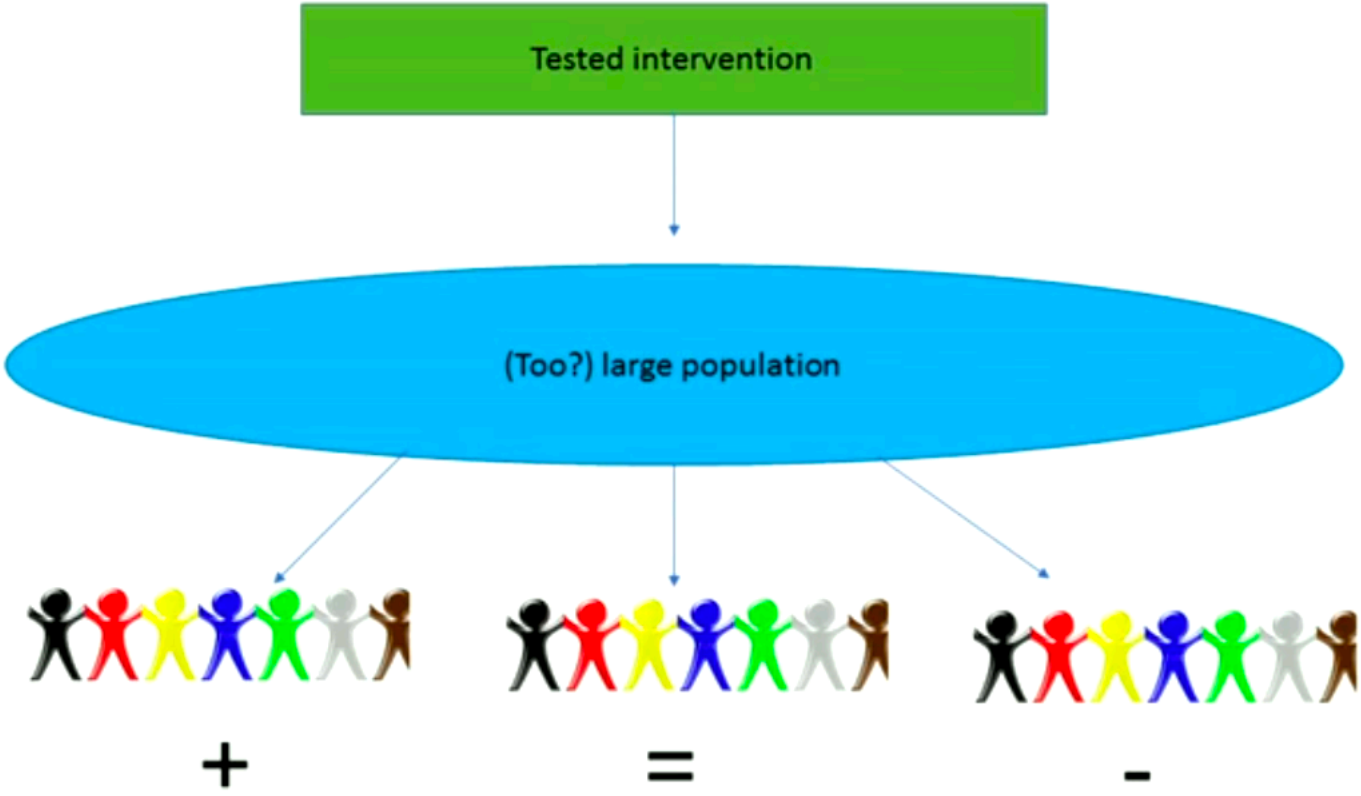
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level
The EUPHRATES Randomized Clinical Trial

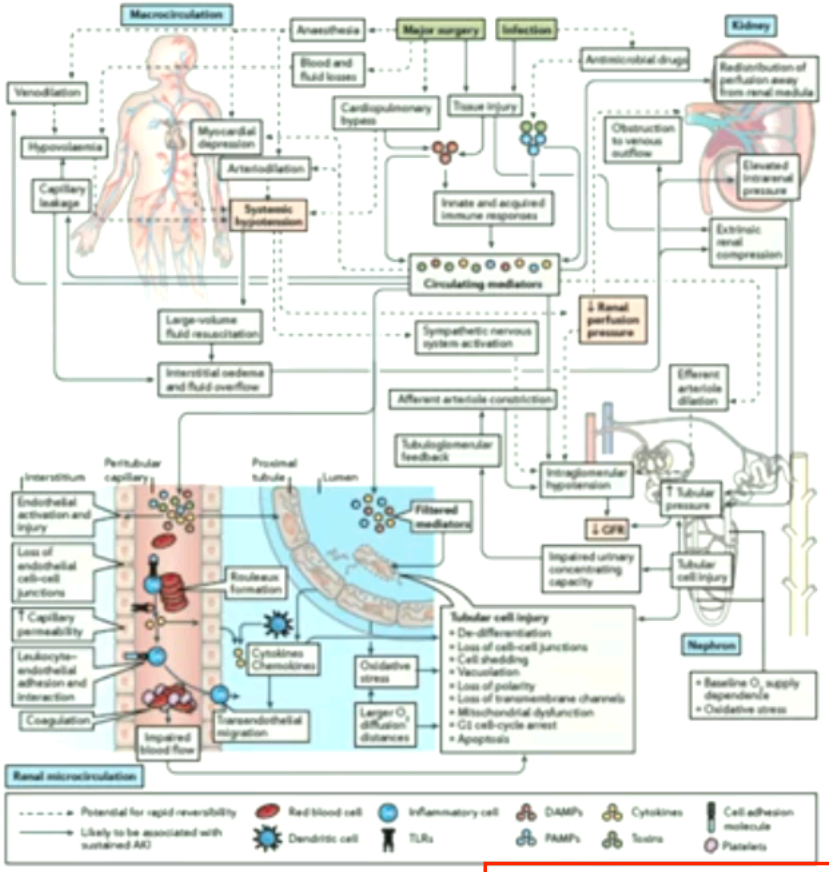
R. Phillip Dellinger, MD, MSc; Sean M. Bagshaw, MD, MSc; Massimo Antonelli, MD; Debra M. Foster, BSc; David J. Klein, MD, MBA; John C. Marshall, MD; Paul M. Palevsky, MD; Lawrence S. Weisberg, MD; Christa A. Schorr, DNP, MSN, RN; Stephen Trzeciak, MD, MPH; Paul M. Walker, MD, PhD; for the EUPHRATES Trial Investigators

Joannes-Boyau et al. *Intensive Care Med* 2013
Payen et al. *Intensive Care Med* 2015
Livigni et al. *BMJ Open* 2014
Dellinger et al. JAMA 2018

4) Negative large RCTs: importance of the studied population



1-How do these therapies exactly interfere with sepsis pathophysiology?



Kellum et al. Nature Rev Nephrol 2018

2-Which patients?

- Better selection of the study population : not all different types of sepsis together (more homogeneous population)
- Stratification with sepsis biomarkers (stratification on severity, lactate, endotoxin levels/activity) in order to work on a more homogeneous population
- **Extracorporeal BP therapy as an adjuvant treatment of sepsis most likely interesting in very particular/specific clinical situations and not in all septic patients**

Mortality as an Endpoint in Septic Shock Trials

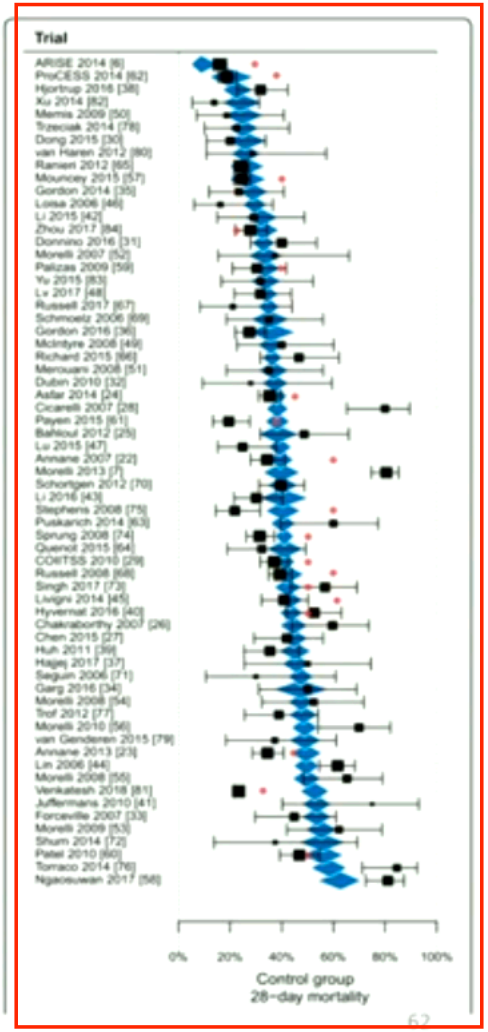
SYSTEMATIC REVIEW

Unexplained mortality differences between septic shock trials: a systematic analysis of population characteristics and control-group mortality rates

Harm-Jan de Grooth[1,2*], Jonne Postema[2], Stephan A. Loer[2], Jean-Jacques Parienti[3,4], Heleen M. Oudemans-van Straaten[1] and Armand R. Girbes[1]

- Blue Diamond – predicted mortality rate
- Black Square – observed real mortality
- Control-group mortality demonstrates rate variability
- Septic shock : heterogenic syndrome
- Different trial populations

Intensive Care Med (2018) 44:311–322
https://doi.org/10.1007/s00134-018-5134-8



Challenges with RCTs in the ICU

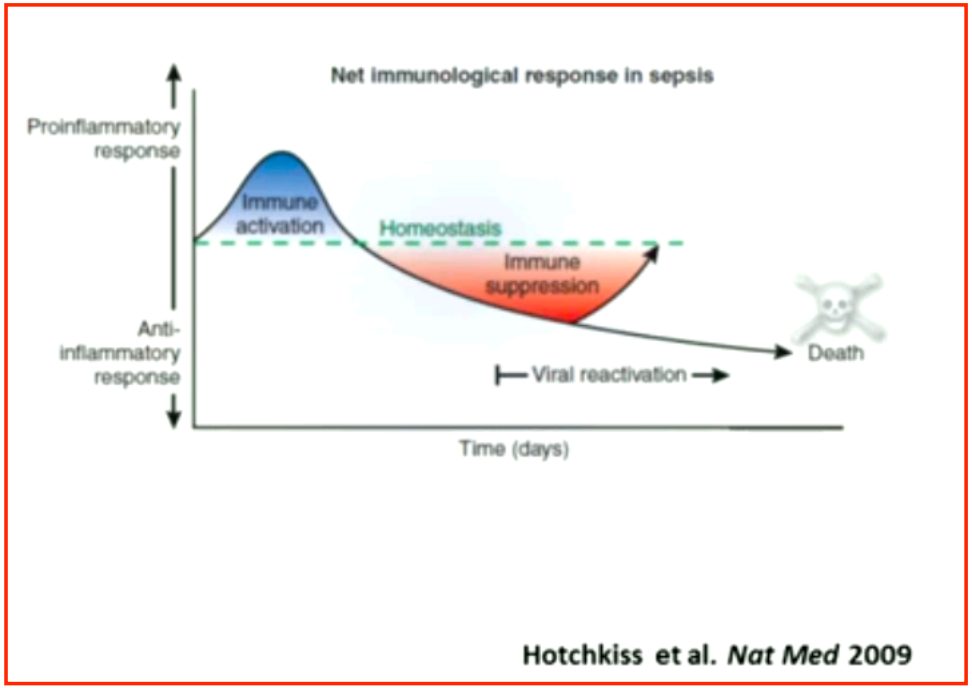
Crit Care Med 2010 Vol. 38, No. 10 (Suppl.)

We should abandon randomized controlled trials in the intensive care unit

Jean-Louis Vincent, MD, PhD, FCCM

- RCT is the standard for evidence based medicine.
- In the ICU, confounding factors often result in studies that are challenging to conduct, and results are often difficult to interpret and apply.
- There are many reasons for these negative results including problems with **timing, end point selection, and heterogeneous** populations.
- Due to these complexities, alternate study designs should be considered in the challenging intensive care unit environment.

3- Which timing?



Hotchkiss et al. *Nat Med* 2009

SHOCK, Vol. xx, No. x, pp. x–xx, 2015

Review Article

IMMUNE CELL PHENOTYPE AND FUNCTION IN SEPSIS

Thomas Rimmelé,* Didier Payen,† Vincenzo Cantaluppi,‡ John Marshall,§ Hernando Gomez,¶ Alonso Gomez,‖ Patrick Murray,** and John A. Kellum¶,
On behalf of the ADQI XIV Workgroup

*Anesthesiology and Critical Care Medicine, Edouard Herriot Hospital, Hospices Civils de Lyon, University Claude Bernard Lyon 1, Lyon; †Department of Anesthesiology and Critical Care and UMR INSERM 1160 Lariboisière Hospital, AP-HP and University Paris 7, Sorbonne Paris Cité, Paris, France; ‡Nephrology, Dialysis and Kidney Transplantation Unit, Department of Medical Sciences, "Città della Salute e della Scienza di Torino-Molinette" University Hospital, Torino, Italy; §Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, Ontario, Canada; ¶Center for Critical Care Nephrology, The CRISMA (Clinical Research, Investigation, and Systems Modeling of Acute Illness) Center, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; ‖Academia Colombiana de Medicina Crítica (ACOMEC); **Division of Critical Care Medicine, Clínica Palermo, Bogotá, Colombia; and ††University College Dublin, Dublin, Ireland

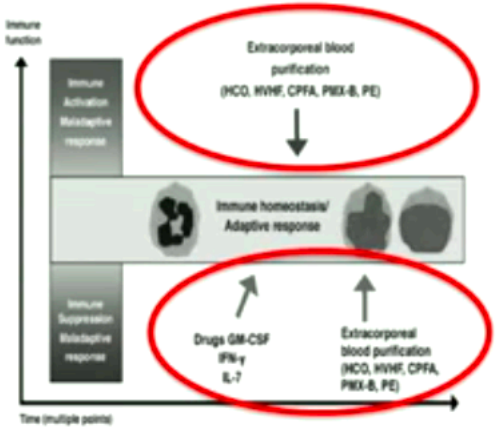


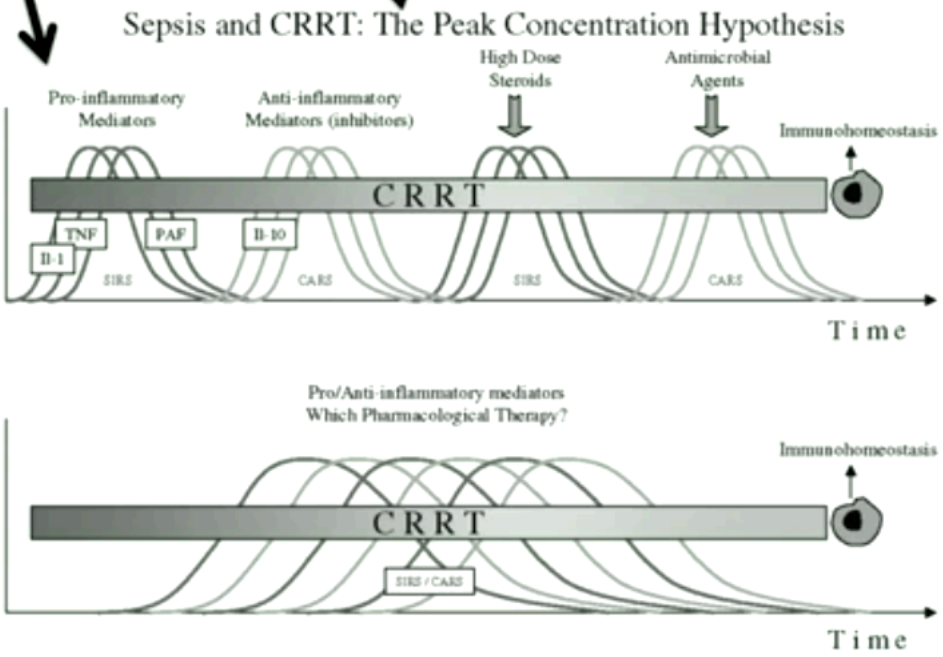
FIG. 3. **Possible biological effects of different drugs and of extracorporeal blood purification therapies on immune system activation, suppression, and homeostasis.** CPFA indicates coupled plasma filtration adsorption; GM-CSF, granulocyte-macrophage colony-stimulating factor; HCO, high cutoff; HVHF, high-volume hemofiltration; IFN-γ, interferon gamma; IL-7, interleukin 7; PE, plasma exchange; PMX-B, polymyxin B hemoperfusion. Source: Acute Dialysis Quality Initiative 14, www.ADQI.net 2014; used with permission.

Rimmelé et al. *Shock* 2016

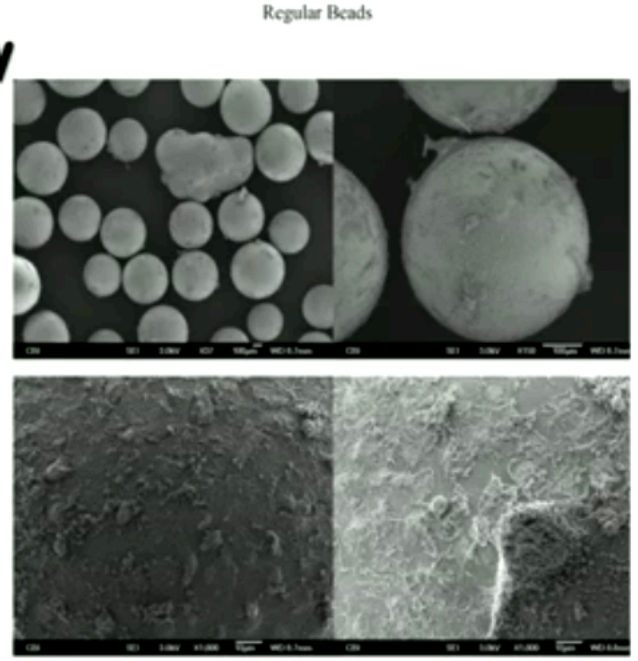
4- What to ultimately remove?

Endotoxins?

Cytokines?



Leulocytes adsorbed on the blood purification device?



Ronco et al. *Artificial Organs* 2003

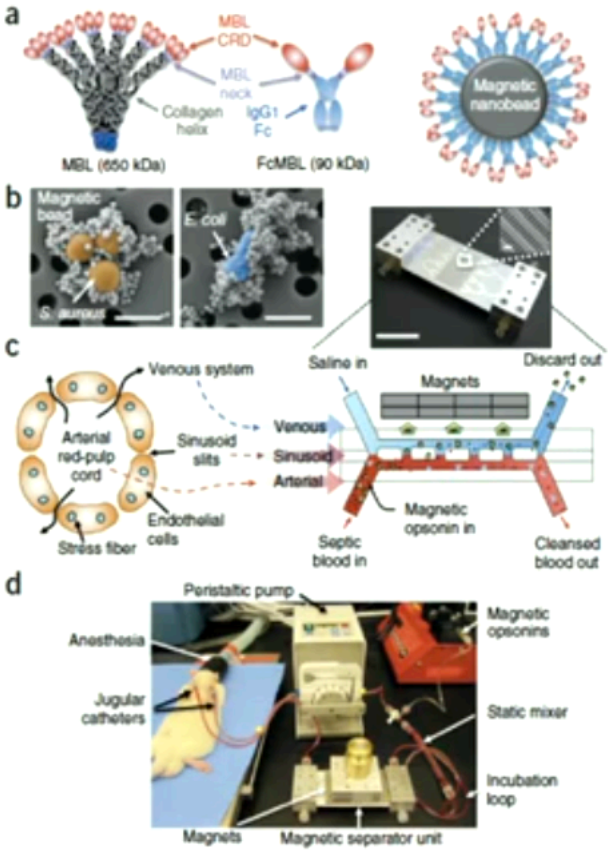
4- What to ultimately remove?

TECHNICAL REPORTS

nature medicine

An extracorporeal blood-cleansing device for sepsis therapy

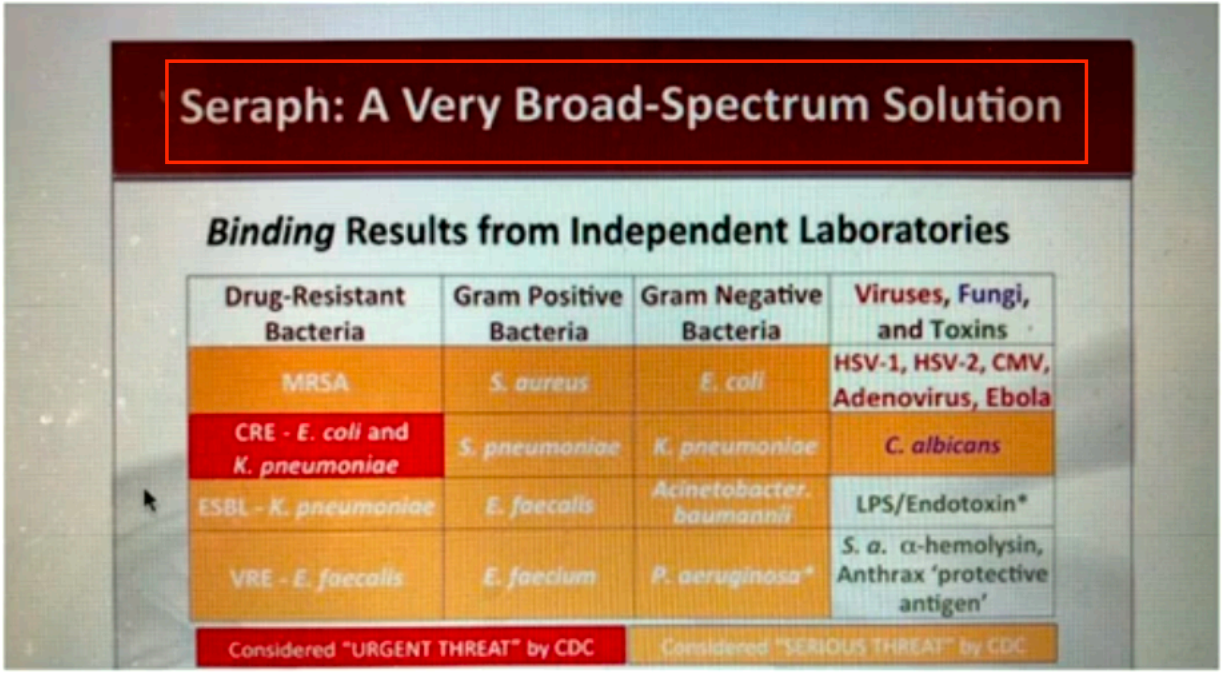
Joo H Kang[1–3,7], Michael Super[1,7], Chong Wing Yung[1,2], Ryan M Cooper[1,2,4], Karel Domansky[1], Amanda R Graveline[1], Tadanori Mammoto[2], Julia B Berthet[1], Heather Tobin[2], Mark J Cartwright[1], Alexander L Watters[1], Martin Rottman[1,6], Anna Waterhouse[1], Akiko Mammoto[2], Nazita Gamini[1], Melissa J Rodas[1], Anxhela Kole[1], Amanda Jiang[2], Thomas M Valentin[1], Alexander Diaz[1], Kazue Takahashi[5] & Donald E Ingber[1–3]



Kang et al. *Nature Medicine* 2014

Ongoing research from Harvard University, Boston, USA

4- What to ultimately remove?



Courtesy of Exthera

4- What to ultimately remove?

Blood Purification

Blood Purif 2009;27:64–69
DOI: 10.1159/000167011

Published online: January 23, 2009

Reduction of Hepatitis C Virus Using Lectin Affinity Plasmapheresis in Dialysis Patients

Richard H. Tullis[a] R. Paul Duffin[a] Harold H. Handley[a] Puneet Sodhi[b]
Jeevan Menon[a] James A. Joyce[a] Vijay Kher[b]

[a]Aethlon Medical Inc., San Diego, Calif., USA; [b]Fortis Flt. Lt. Rajan Dhall Hospital, New Delhi, India

Marleau et al. Journal of Translational Medicine 2012, 10:134
http://www.translational-medicine.com/content/10/1/134

JOURNAL OF TRANSLATIONAL MEDICI

COMBINATION STRATEGIES Open Acce

Exosome removal as a therapeutic adjuvant in cancer

Annette M Marleau[1*], Chien-Shing Chen[2], James A Joyce[1] and Richard H Tullis[1]

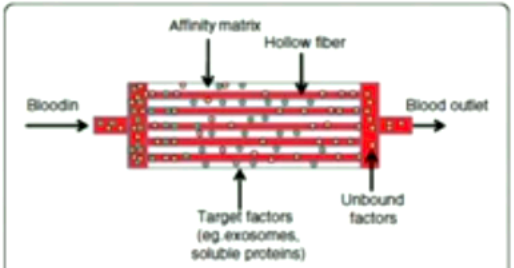


Figure 3 Schematic of Aethlon's ADAPT™ device platform. This technology consists of plasmapheresis cartridges that allows blood cells to pass through the hollow fibers while serum components < 200 nm in size fit through the hollow fiber pores to interact with the affinity matrix. The matrices can be customized with one or more affinity substrates comprising monoclonal antibodies, lectins, aptamers or other affinity agents to specifically capture and remove tumor-derived exosomes and other soluble oncoproteins from the bloodstream using kidney dialysis or CRRT units.

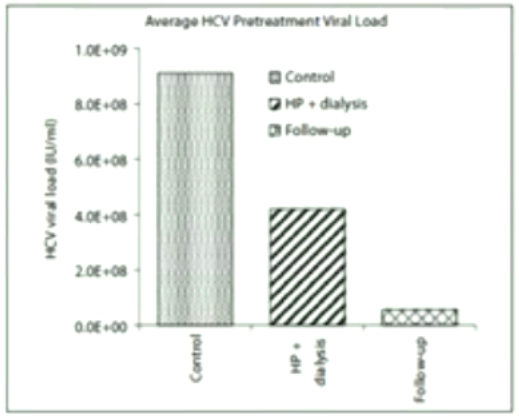


Fig. 2. Average HCV viral load in patients prior to treatment comparing control dialysis to Hemopurifier + dialysis and final values in the week after treatment was stopped. Final values represent the average of HCV viral load for the week after treatment was stopped (follow-up phase).

Tullis et al. *Blood Purification* 2009
Marleau et al. *Journal of Translational Medicine* 2012
The Aethlon Hemopurifier®: Ongoing research from San Diego University, USA.

Conclusions

1) 2019: Immunology is now part of a- the sepsis definition b- our daily clinical practice
2) Patients die of septic shock because of immununosuppression
3) Will extracorporeal blood purification be one day part of sepsis management?

Extracorporeal blood purification techniques under investigation

5) Multicenter RCTs = negative studies… but were they well-designed?
6) Many unanswered questions that should be addressed in the future:

How do these therapies interfere with sepsis pathophysiology?
Which patients exactly?
Which Timing?
What to ultimately remove (cytokines, endotoxins, leukocytes, bacteria or viruses)?

7) Research in this field should definitely continue with well-designed experimental and clinical trials

Table 1. Pathways and Mediators of Sepsis, Potential Treatments, and Results of Randomized, Controlled Trials (RCTs).*

Pathway	Mediators	Treatment	Results of RCTs
	Superantigens: TSST-1	Anti-TSST-1	Not evaluated
	Streptococcal exotoxins (e.g., streptococcal pyrogenic exotoxin A)	Antistreptococcal exotoxins	Not evaluated
	Lipopolysaccharide (endotoxin)	Antilipopolysaccharide[9]	Negative
Innate immunity	TLR-2, TLR-4	TLR agonists[10] and antagonists	Not evaluated
	Monocytes, macrophages	GM-CSF, interferon gamma[11]	Not evaluated
	Neutrophils	G-CSF†	Not evaluated
Adaptive immunity	B cells (plasma cells and immunoglobulins)	IgG	Not evaluated
	CD4+ T cells (Th1, Th2)		
Proinflammatory pathway	TNF-α	Anti–TNF-α[13,14]	Negative
	Interleukin-1β	Interleukin-1–receptor antagonist[15]	Negative
	Interleukin-6	Interleukin-6 antagonist	Not evaluated
	Prostaglandins, leukotrienes	Ibuprofen,[16] high-dose corticosteroids[17]	Negative
	Bradykinin	Bradykinin antagonist[18]	Negative
	Platelet-activating factor	Platelet-activating factor acetyl hydrolase[19]	Negative
	Proteases (e.g., elastase)	Elastase inhibitor‡	Negative
	Oxidants	Antioxidants (e.g., *N*-acetylcysteine)[20]	Not evaluated
	Nitric oxide	Nitric oxide synthase inhibitor[21]	Negative

Table 1. (Continued.)

Pathway	Mediators	Treatment	Results of RCTs
Procoagulant pathway	Decreased protein C	Activated protein C[5]	Positive ⟶ Negative
	Decreased protein S	Protein S[22]	Not evaluated
	Decreased antithrombin III	Antithrombin III[23]	Negative
	Decreased tissue factor–pathway inhibitor	Tissue factor–pathway inhibitor[24]	Negative
	Increased tissue factor	Tissue factor antagonist[25]	Not evaluated
	Increased plasminogen-activator inhibitor 1	Tissue plasminogen activator	Not evaluated
Antiinflammatory	Interleukin-10	Interleukin-10§	Not evaluated
	TNF-α receptors	TNF-α receptors[13]	Negative
Hypoxia	Hypoxia-inducing factor 1, vascular endothelial growth factor	Early, goal-directed therapy[2]	Positive
		Supernormal oxygen delivery	Negative
		Erythropoietin[26]	Not evaluated
Immunosuppression or apoptosis	Lymphocyte apoptosis	Anticaspases[27]	Not evaluated
	Apoptosis of intestinal epithelial cells	Anticaspases[27]	Not evaluated
Endocrine	Adrenal insufficiency	Corticosteroids[28]	Mixed results¶
	Vasopressin deficiency	Vasopressin[29]	Not evaluated
	Hyperglycemia	Intensive insulin therapy[30,31]	Not evaluated‖

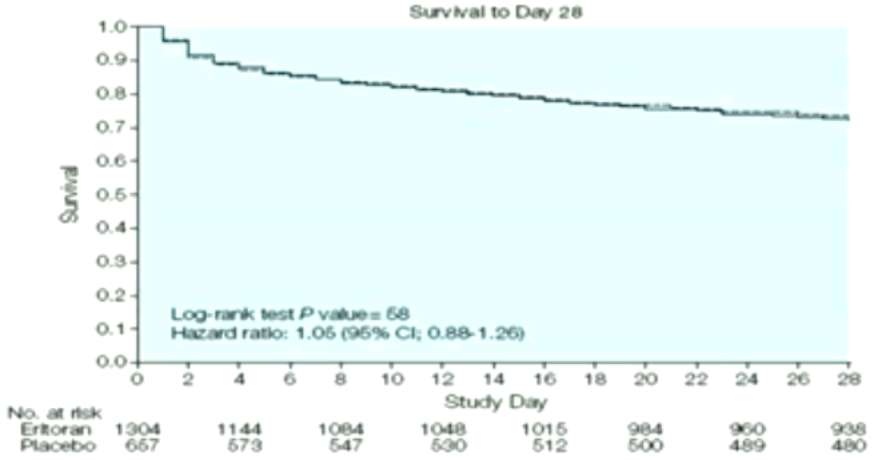
All negative!!!

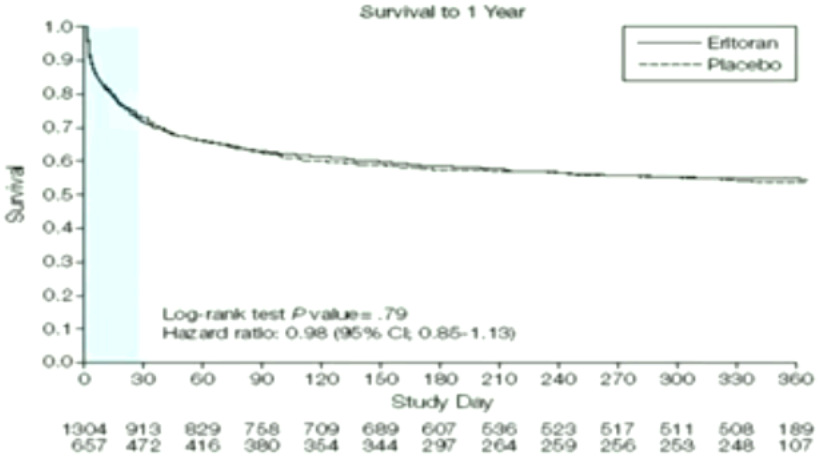
N Engl J Med 2006;355:1699-713.

CARING FOR THE
CRITICALLY ILL PATIENT

Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients With Severe Sepsis

The ACCESS Randomized Trial



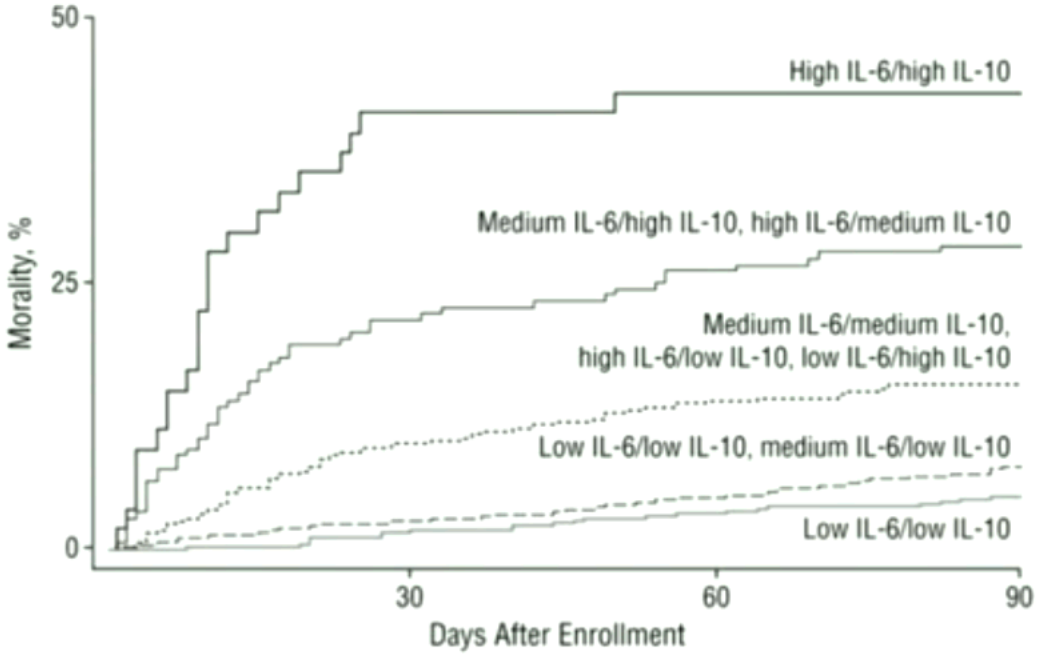


Understanding the Inflammatory Cytokine Response in Pneumonia and Sepsis

Results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study

John A. Kellum, MD; Lan Kong, PhD; Mitchell P. Fink, MD; Lisa A. Weissfeld, PhD; Donald M. Yealy, MD; Michael R. Pinsky, MD; Jonathan Fine, MD; Alexander Krichevsky, PhD; Russell L. Delude, PhD; Derek C. Angus, MD, MPH, for the GenIMS Investigators

Arch Intern Med. 2007;167(15):1655-1663



Hypothesis

"Instead of inhibiting very specific inflammatory pathways

(that are then bypassed from left and right),

a more unspecific approach

may be more likely to yield a beneficial effect"

“Blood-purification”

- Polymyxin B filter
- LPS binding
- No clearance of cytokines
- No RRT

- Cytosorb-filter
- Cytokines captured
- No clearance of LPS
- No RRT

- oXiris-filter
- LPS-adsorption
- Cytokine clearance
- RRT

Euphas vs Abdomix vs Euphrates

- ***Euphas*** (Italy)
  - Improvement within the treatment group, but no differences between groups in hemodynamics and mortality
  - Unfortunate early termination
  - Baseline mortality 53%

- ***Abdomix*** (France)
  - 19.5% mortality in control group
  - Completely/partial succesful surgery
  - Incomplete PMX sessions
  - Enrollment not based on EAA

- ***Euphrates*** (USA, Canada)
  - Blinded
  - Population enrichment using EAA
  - Primary end-point negative, post-hoc subgroup positive?
  - Control group mortality 36%

Rationale

- Inclusion criterium was EAA>0.6
- Some patients with 'extreme endotoxemia' are beyond salvage, the levels are too high for the filter
- Therefore: subgroup analysis in patients with 'addressable LPS levels'

Results: At 28 days, 23 patients of 88 (26.1%) in the PMX group died versus 39 of 106 (36.8%) in the sham group [risk difference 10.7%, OR 0.52, 95% CI (0.27, 0.99), $P = 0.047$]. When unadjusted for baseline variables, $P = 0.11$. The 28-day survival time in the PMX group was longer than for the sham group [HR 0.56 (95% CI 0.33, 0.95) $P = 0.03$]. PMX treatment compared with sham showed greater change in MAP [median (IQR) 8 mmHg (− 0.5, 19.5) vs. 4 mmHg (− 4.0, 11) $P = 0.04$] and VFD [median (IQR) 20 days (0.5, 23.5) vs. 6 days (0, 20), $P = 0.004$]. There were no significant differences in other end points. There was a significant difference in mortality in PMX-treated patients with no bacterial growth on culture [PMX, 6/30 (20%) vs. sham, 13/31 (41.9%), $P = 0.005$]. The median EAA change in the population was − 12.9% (range: increase 49.2%–reduction 86.3%). The mortality in the above median EAA change group was PMX: 6/38 (15.7%) vs. sham 15/49 (30.6%), $P = 0.08$.

In summary:

- Lower 28-day mortality
- Longer survival time
- Better blood pressure
- Shorter LOS on mechanical ventilation
- Endotoxin concentrations decrease
- 'Above median LPS group' borderline significant effect on mortality

Discussion

illness (MOD score > 9) and an endotoxin activity level as measured by EAA between 0.6 and 0.89, PMX use is associated with an absolute mortality benefit over sham patients of 10.7% at 28 days. This finding is supported

Intensive Care Med (2018) 44:167–178
https://doi.org/10.1007/s00134-017-5004-9

SYSTEMATIC REVIEW

Polymyxin B-immobilized hemoperfusion and mortality in critically ill adult patients with sepsis/septic shock: a systematic review with meta-analysis and trial sequential analysis

Tomoko Fujii[1,2], Riki Ganeko[3], Yuki Kataoka[4], Toshi A. Furukawa[5], Robin Featherstone[6], Kent Doi[7], Jean-Louis Vincent[8], Daniela Pasero[9], René Robert[10], Claudio Ronco[11] and Sean M. Bagshaw[12*]

Conclusions: There is currently insufficient evidence to support the routine use of PMX-HP to treat patients with sepsis or septic shock.

Conclusions of post-hoc analysis

- Post-hoc analysis of a RCT should not be an adjusted analysis
- If you adjust for baseline variables post-hoc, there needs to be a reason.

  There was no dysbalance between groups
- Unadjusted mortality: p=NS
- There was no difference in absolute mortality
- Authors mention that 'a decrease in [LPS] is associated with better outcome'.

  ("Implying that the hypothesis of the PMX-filter is correct")
- Was [LPS] decrease more pronounced? (as proof of principle?)
  - Authors: 'there was little difference…' , supplemental file: No effect of PMX-filter op [LPS]

Intensive Care Med (2018) 44:167–178
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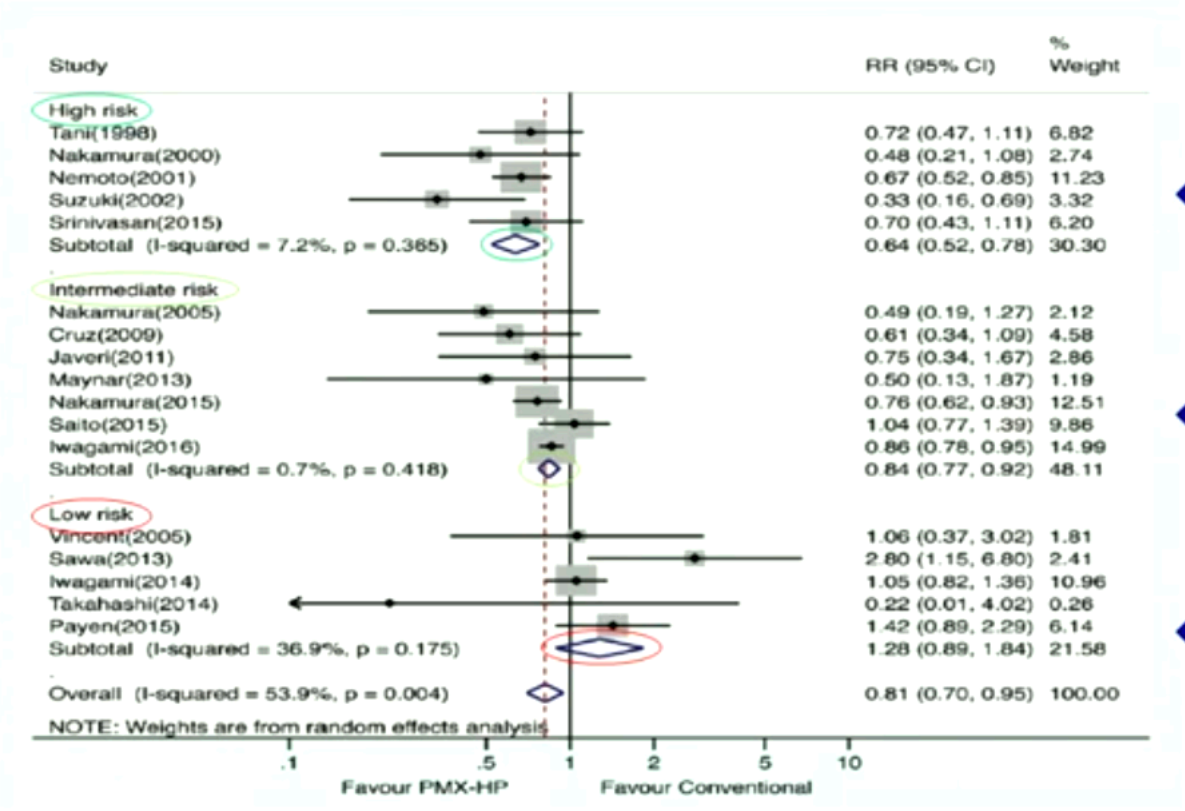
OPEN

Effects of Polymyxin B Hemoperfusion on Mortality in Patients With Severe Sepsis and Septic Shock: A Systemic Review, Meta-Analysis Update, and Disease Severity Subgroup Meta-Analysis

Tzu Chang, MD[1]; Yu-Kang Tu, PhD[2]; Chen-Tse Lee, MD[1]; Anne Chao, MD[1]; Chi-Hsiang Huang, MD[1]; Ming-Jiuh Wang, MD, PhD[1]; Yu-Chang Yeh, MD, PhD[1]

(*Crit Care Med* ; 45:e858–e864)

Risk ratio of mortality by disease severity



High risk
High PMX benefit

Intermediate risk
PMX benefit

Low risk
Low/no PMX benefit

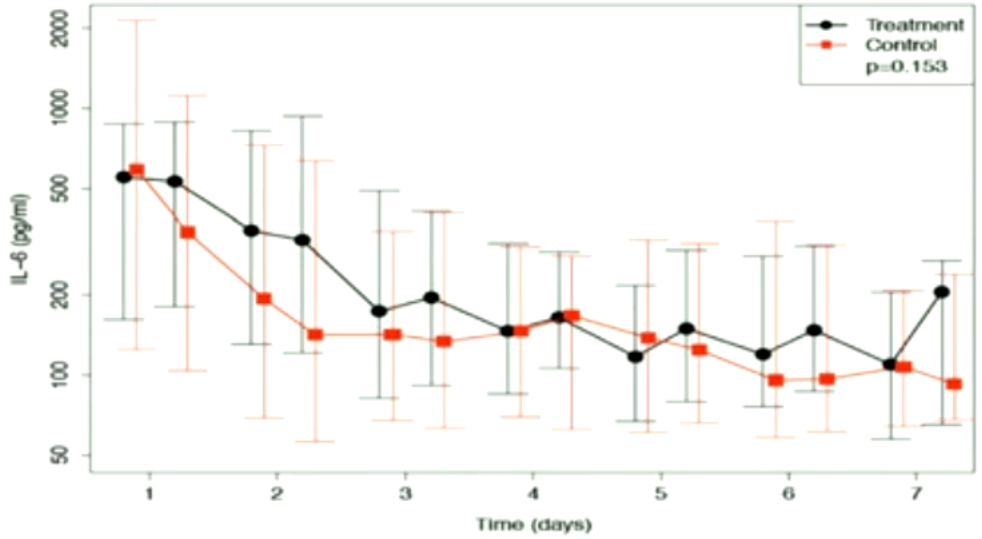
Chang et al., Critical Care Med 2017

PLOS | ONE

RESEARCH ARTICLE

The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial

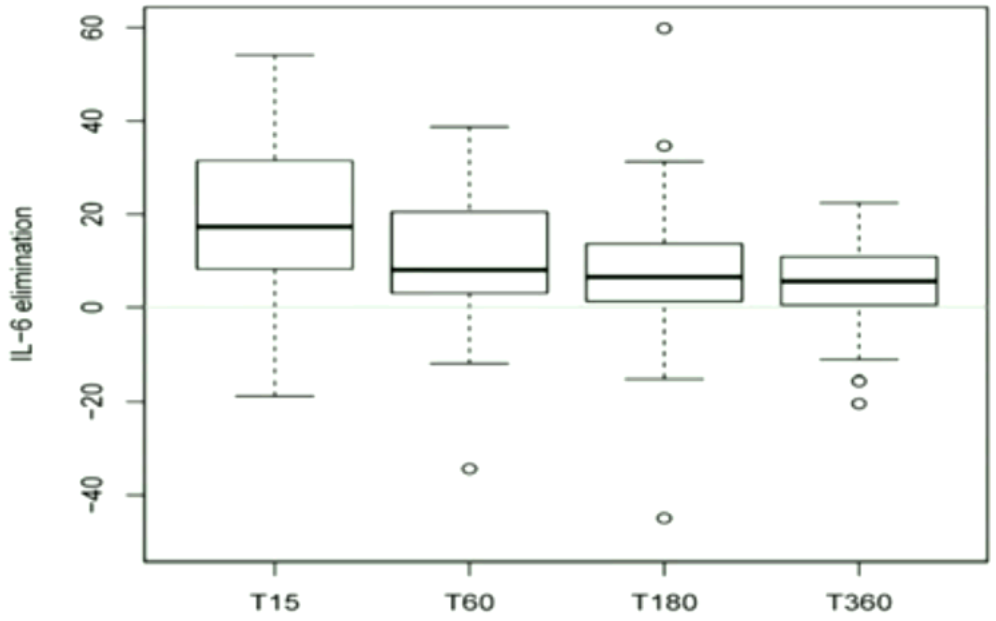
Dirk Schädler[1]*, Christine Pausch[2]*, Daniel Heise[3], Andreas Meier-Hellmann[4], Jörg Brederlau[5], Norbert Weiler[1], Gernot Marx[6], Christian Putensen[7], Claudia Spies[8], Achim Jörres[9], Michael Quintel[3], Christoph Engel[2], John A. Kellum[10], Martin K. Kuhlmann[11]



RCT, n=97
6 hr/d for 7 days

"No effect of Cytosorb on circulating cytokines…"

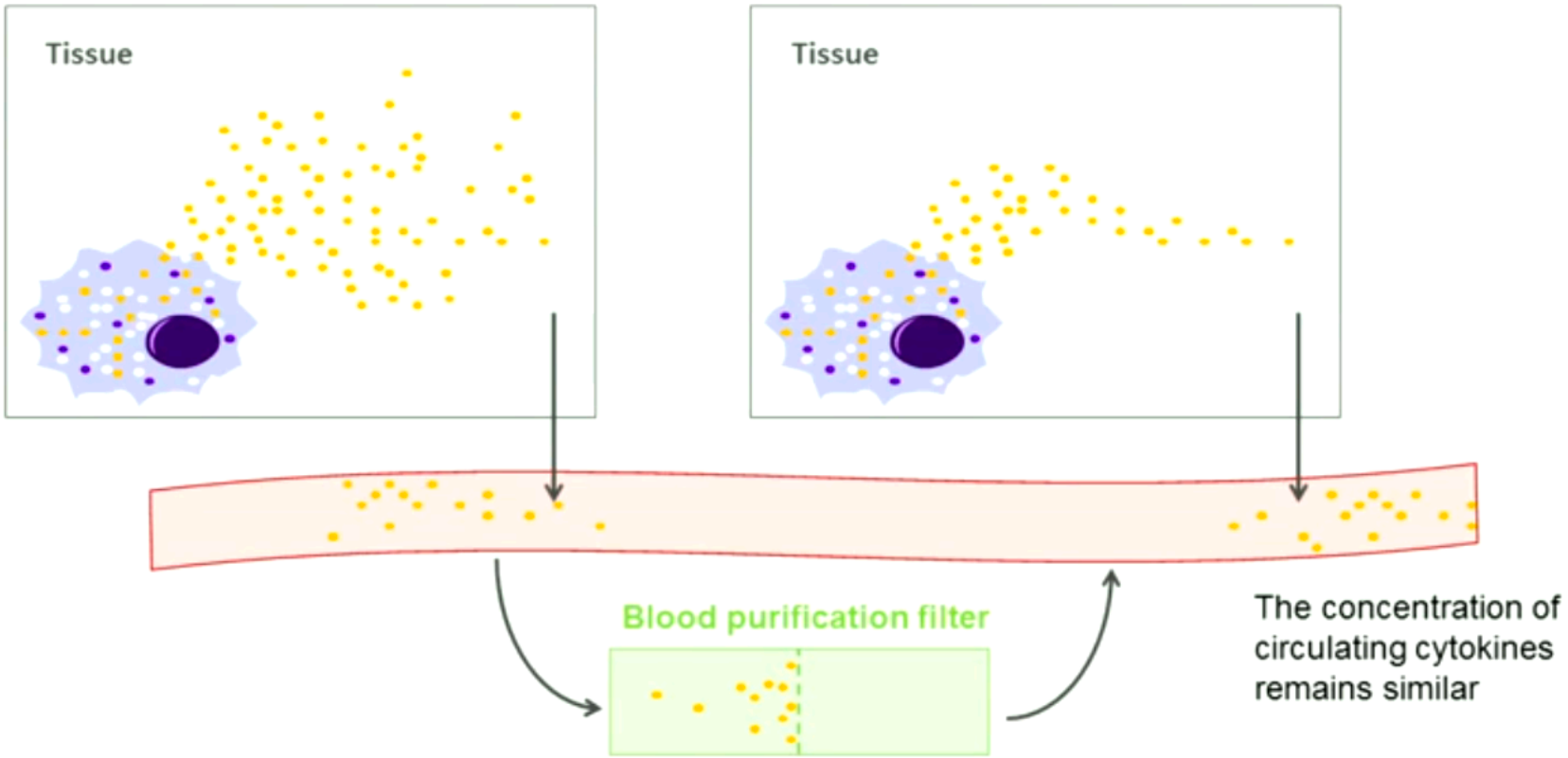
Nevertheless, there is clearance of cytokines

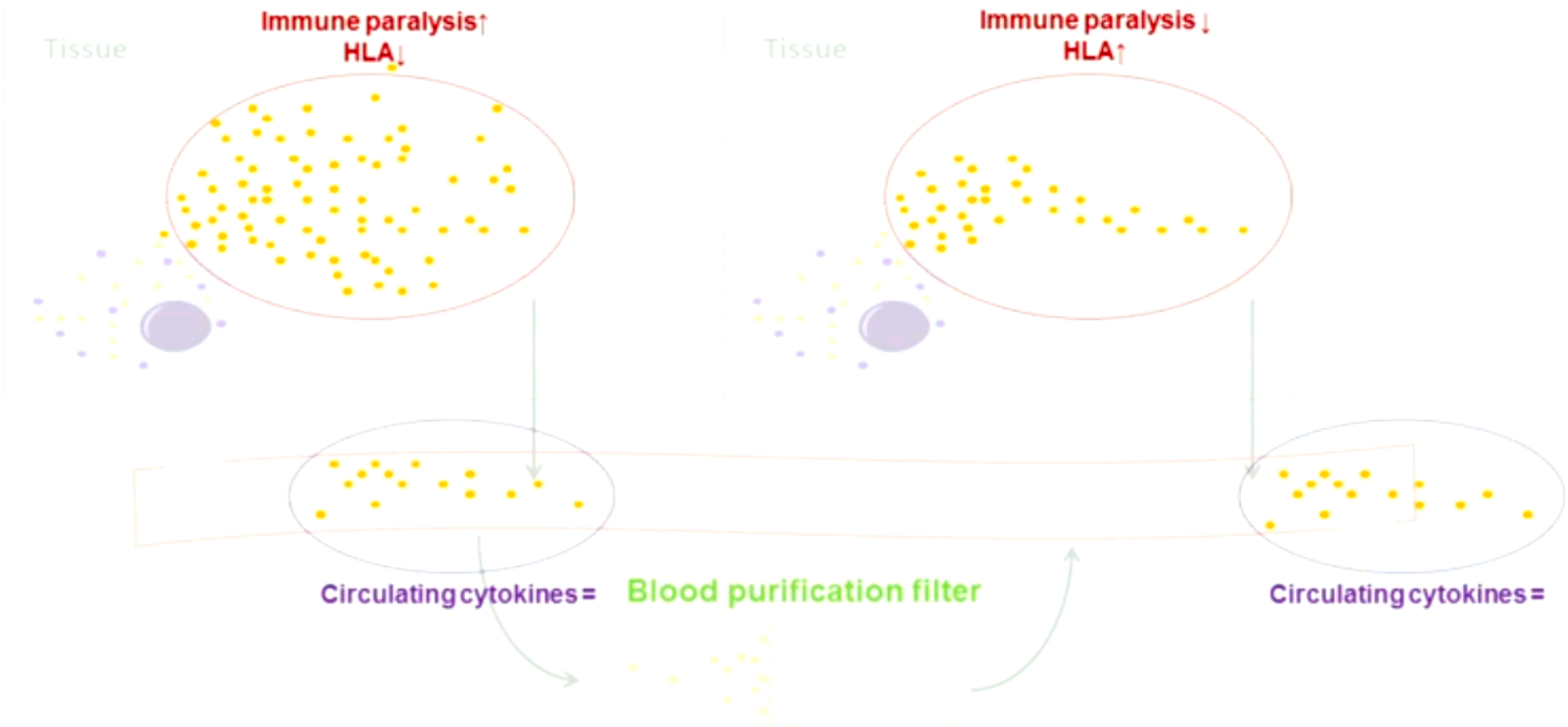


Importantly:

- Cytokines are mainly produced by tissue-resident macrophages, not by circulating immune cells

- There is spill-over to the circulation


Tissue
Tissue
Blood purification filter
The concentration of circulating cytokines remains similar
The filter clears circulating cytokines, and thereby drains the tissues


Tissue
Immune paralysis↑
HLA↓
Tissue
Immune paralysis ↓
HLA↑
Circulating cytokines =
Blood purification filter
Circulating cytokines =

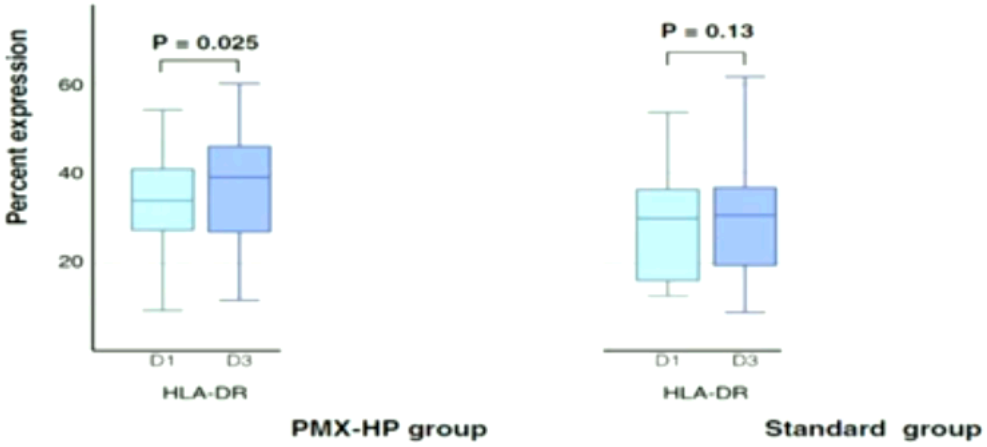
Srisawat et al. Critical Care (2018) 22:279
https://doi.org/10.1186/s13054-018-2077-y

Critical Care

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 Tungsanga[1], Nuttha Lumlertgul[1,2], Chalermchai Komaenthammasophon[1,2], Sadudee Peerapornratana[1,2,3], Nicha Thamrongsat[1,2], Khajohn Tiranathanagul[1], Kearkiat Praditpornsilpa[1], Somchai Eiam-Ong[1], Kriang Tungsanga[1] and John A. Kellum[3]



- PMX-filter (capturing LPS only) prevents immunoparalysis
- Filters also capturing cytokines may have a more pronounced effect in prevention of immunoparalysis, as immunoparalysis is mainly induced by cytokines

Why is this of relevance?

- Prevention of immunoparalysis is now considered more relevant than suppression of circulating cytokines.
- The results may provide evidence for a novel mode of action: prevention of immunoparalysis.
- This would be an unique feature of this device

Conclusions

- Blood purification in sepsis:
  - A valid theory
  - There is a tendency to biased reporting
  - Up to now, there is insufficient evidence for an overall survival benefit
  - There might be a benefit in the sickest patients
  - For now: No standard treatment, may be considered as 'last resort therapy'
  - **Urgent need for further evidence in the form of RCTs and/or high-quality prospective studies to help guide decision making**

Things to consider, to find the ideal patient

- Selection of the hyperinflamed/sustained inflammatory patient: Which marker to use?
- Timing of treatment
- Dosing/duration of treatment
- What end-points