RIMODULAZIONE DELLE CITOKINE. COME E PERCHE'

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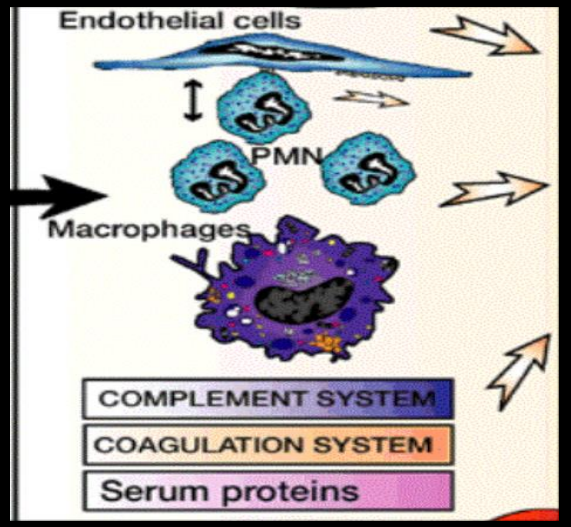
LEGENDA

~ Razionale della "blood purification"

~ Adsorbimento con Cytosorb: come rimuove e che cosa rimuove
~ Indicazioni al trattamento
~ Adsorbimento nella sepsi
~ Studi in vitro
~ Studi clinici
~ Conclusioni

INFEZIONE

Source control



SEPSI

DISFUNZIONE MULTIORGANICA

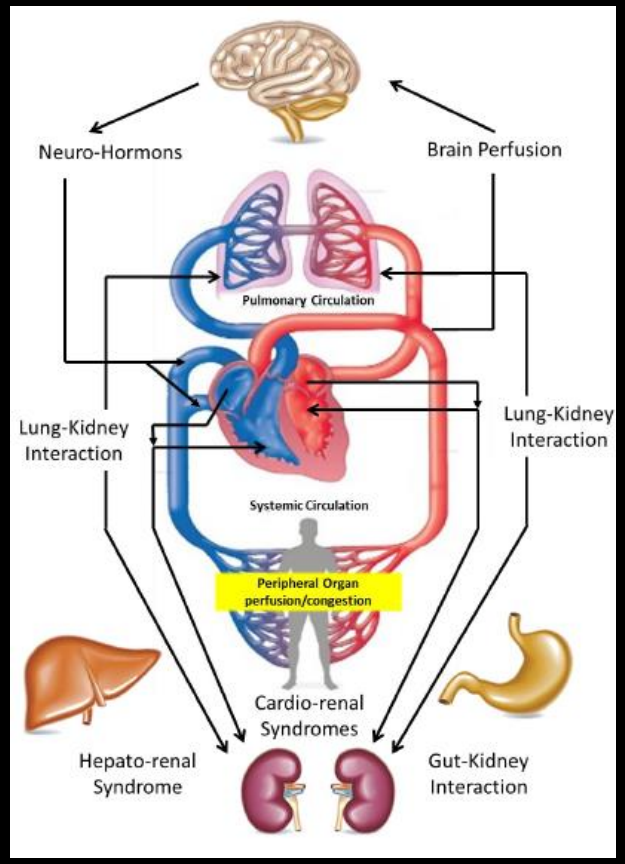
Blood purification

SHOCK SETTICO

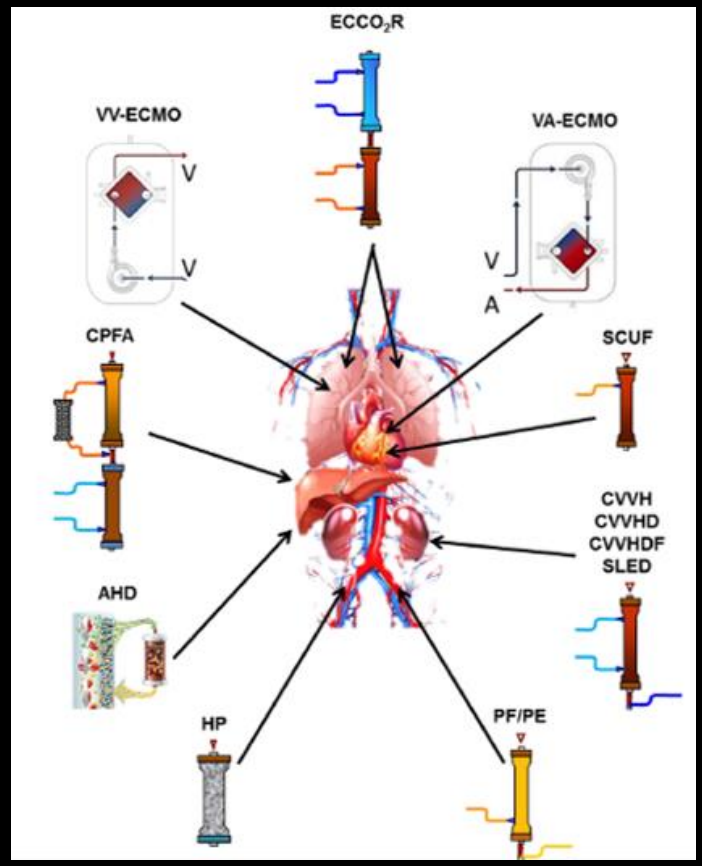
TERAPIA DI SUPPORTO
- Supporto emodinamico
- Supporto respiratorio
- Supporto metabolico

MORTE

Blood Purification: why?



MODS



BLOOD PURIFICATION

Sepsis and CRRT: The Peak Concentration Hypothesis

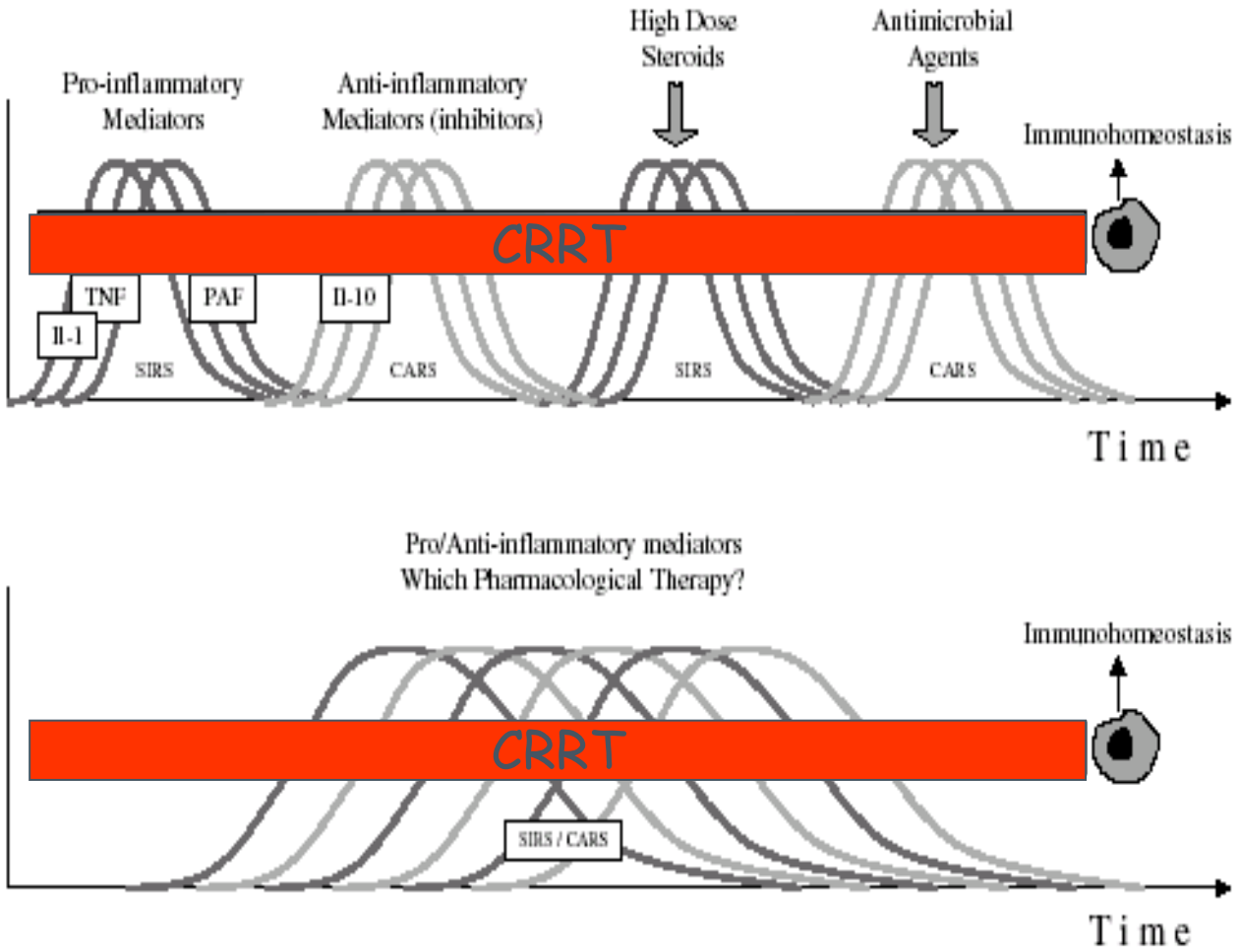


FIG. 3. In both theories (sequential and parallel), the concept introduced by the peak concentration hypothesis suggests that a nonselective control of the peaks of inflammation and immunoparalysis may contribute to bring the patient to a lesser degree of imbalance and close to the self-defenses induced by a nearly normal immunohomeostasis.

Terapie extracorporee per la modulazione citochinica

Table 1. Currently Available Extracorporeal Blood Purification Technologies

Treatment	Principle	Aim
CPFA	Convective with plasma filtration and adsorption	Volume removal Purification technique Cytokine removal
CVVH	Convective	Volume removal Purification technique
Continuous veno-venous hemodialysis (CVVHD)	Diffusive	Volume removal Purification technique
CVVHDF	Convective and diffusive	Volume removal Purification technique
Continuous veno-venous high-flux dialysis (CVVHFD)	Convective and diffusive	Volume removal Purification technique
HCO for hemofiltration or hemodialysis	Convective or diffusive	Cytokine removal Volume removal Purification technique
Hemoperfusion (HP)	Adsorption	Purification technique
HVHF	Convective	Cytokine removal Volume removal Purification technique
Pulse HVHF	Convective	Cytokine removal Volume removal Purification technique
Plasma adsorption (PA)	Filtration and adsorption	Cytokine removal
Plasma exchange (PEX)	Filtration with re-infusion	Cytokine removal
Slow continuous ultrafiltration (SCUF)	Ultrafiltration	Volume removal
SLED: sustained low efficiency dialysis	Diffusive	Volume removal Purification technique

Types of Blood Purification

- hemofilters
  - regular pore size (MW < 40,000D)
    - Low flux
    - High flux
  - large pore filtration (MW < 100,000D)
- open pore plasma filters
  - plasma exchange
  - plasmapheresis
- coupled plasma filtration/adsorption
- adsorption

Adsorbents

- non selective
  - charcoal
    - coated
    - uncoated
  - uncharged resins
  - liposomes (+ Vit C & Vit E)
- selective
  - hydrophobic resins
  - powdered adsorbent
  - microsphere based detoxification system
  - engineered matrices

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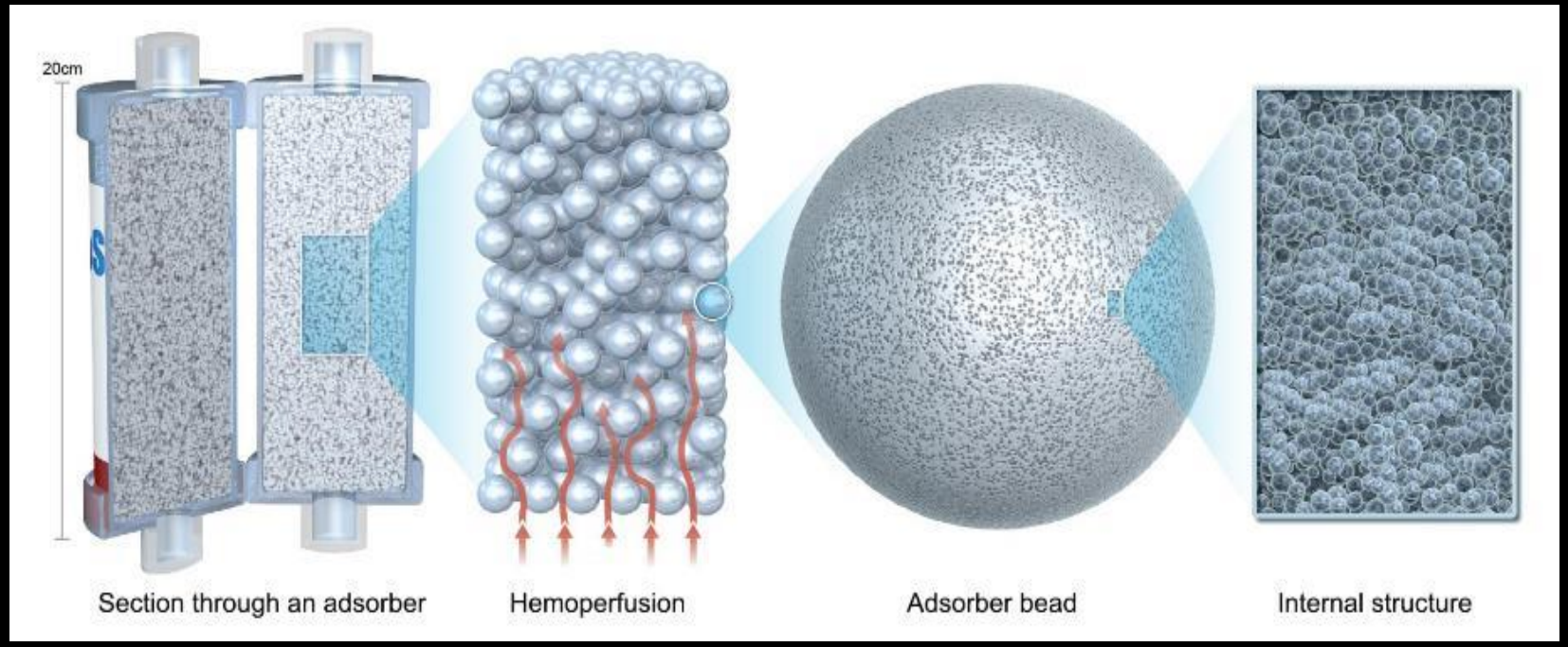
Adsorption with CytoSorb

CytoSorb is made of

Highly biocompatible, porous polymer beads

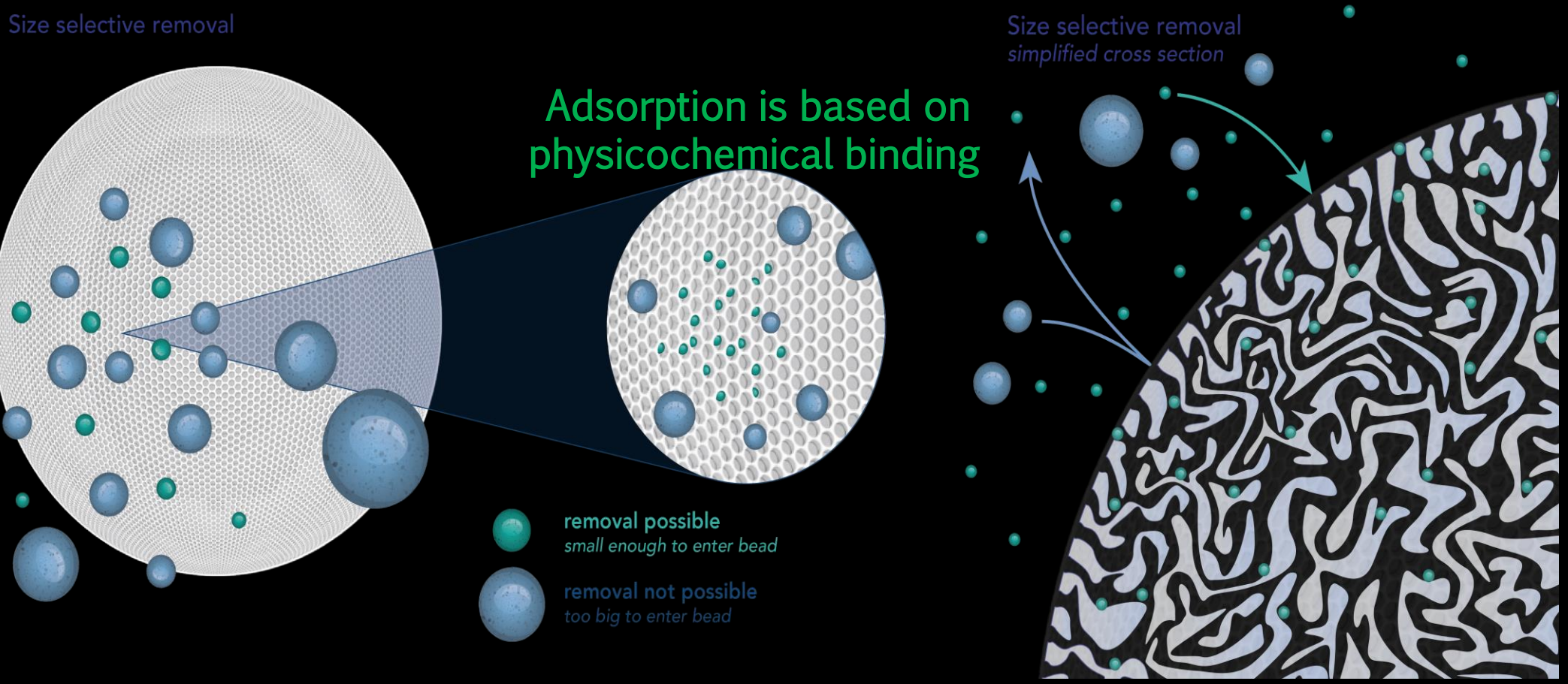


CytoSorb works directly with BLOOD

Adsorption with CytoSorb

CytoSorb removes hydrophobic substances due to:

- physicochemical properties
- pore size



Blood Purification

In-Depth Review

Blood Purif 2018;46:337–349
DOI: 10.1159/000492379

Received: July 6, 2018
Accepted: July 21, 2018
Published online: September 3, 2018

Clinical Utility of Extracorporeal Cytokine Hemoadsorption Therapy: A Literature Review

Anthony Bonavia[a] Andrew Groff[b] Kunal Karamchandani[a] Kai Singbartl[c]

of pores and channels, giving it a large effective surface area for binding of hydrophobic molecules between 5–60 kDa in size [90]. This size range (referred to as the "cytokine sweet spot") targets many of the key inflammatory mediators involved in the sepsis-triggered cytokine storm, such as: IL-1β, IL-6, TNF-α, IL-10, and potentially PAMPs and DAMPs [91]. Particles outside this size range, including larger immune cells and smaller serum electrolytes recirculate unchanged. While the manufacturer states that bacterial endotoxins are not removed with CytoSorb, a study has shown some efficacy in removing toxins within the 5–60 kDa range [92].

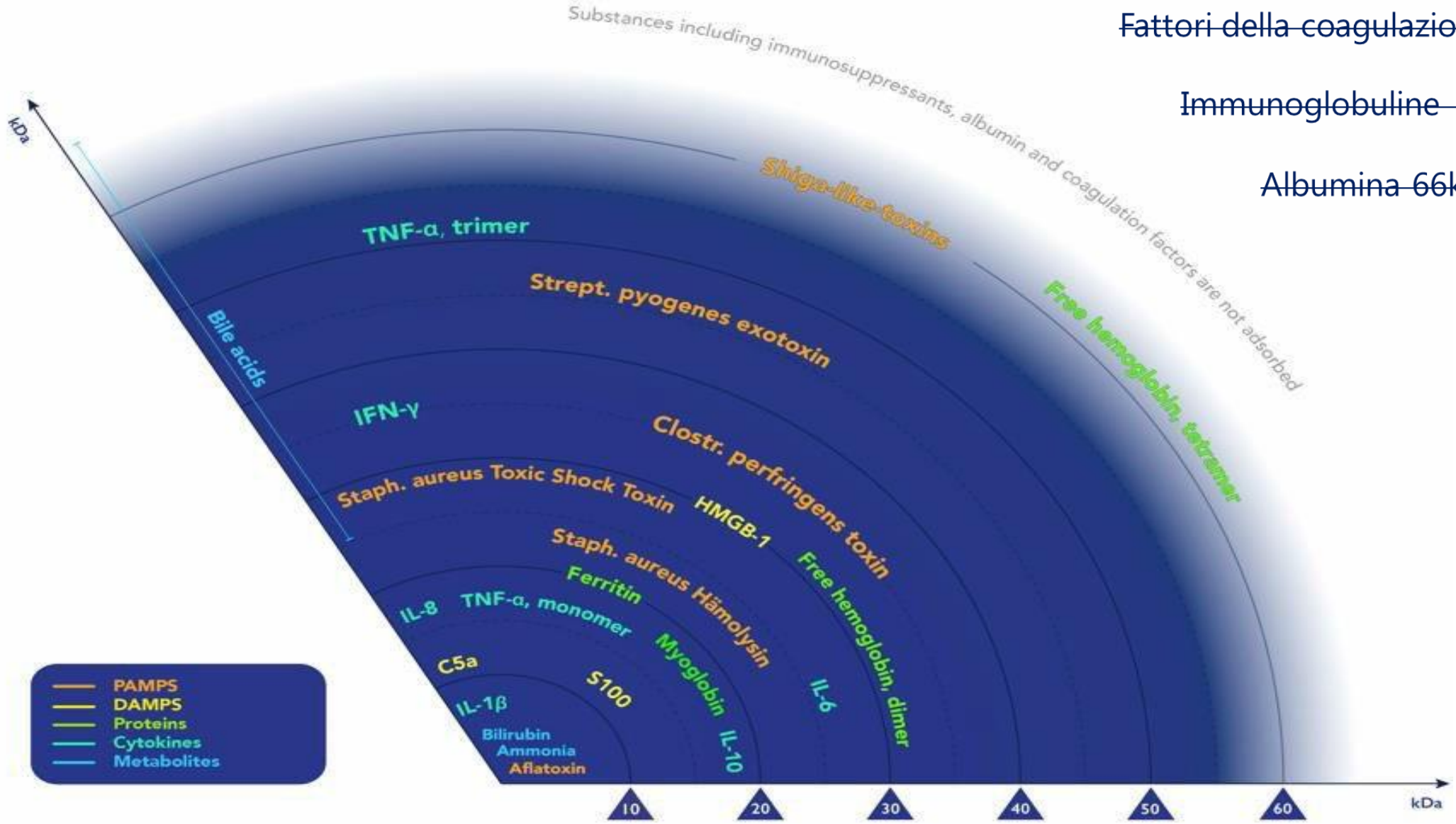
❖Molecole idrofobiche fino a 55-60 kDa

NON rimuove:

~~Fattori della coagulazione >100kDa~~

~~Immunoglobuline >150kDa~~

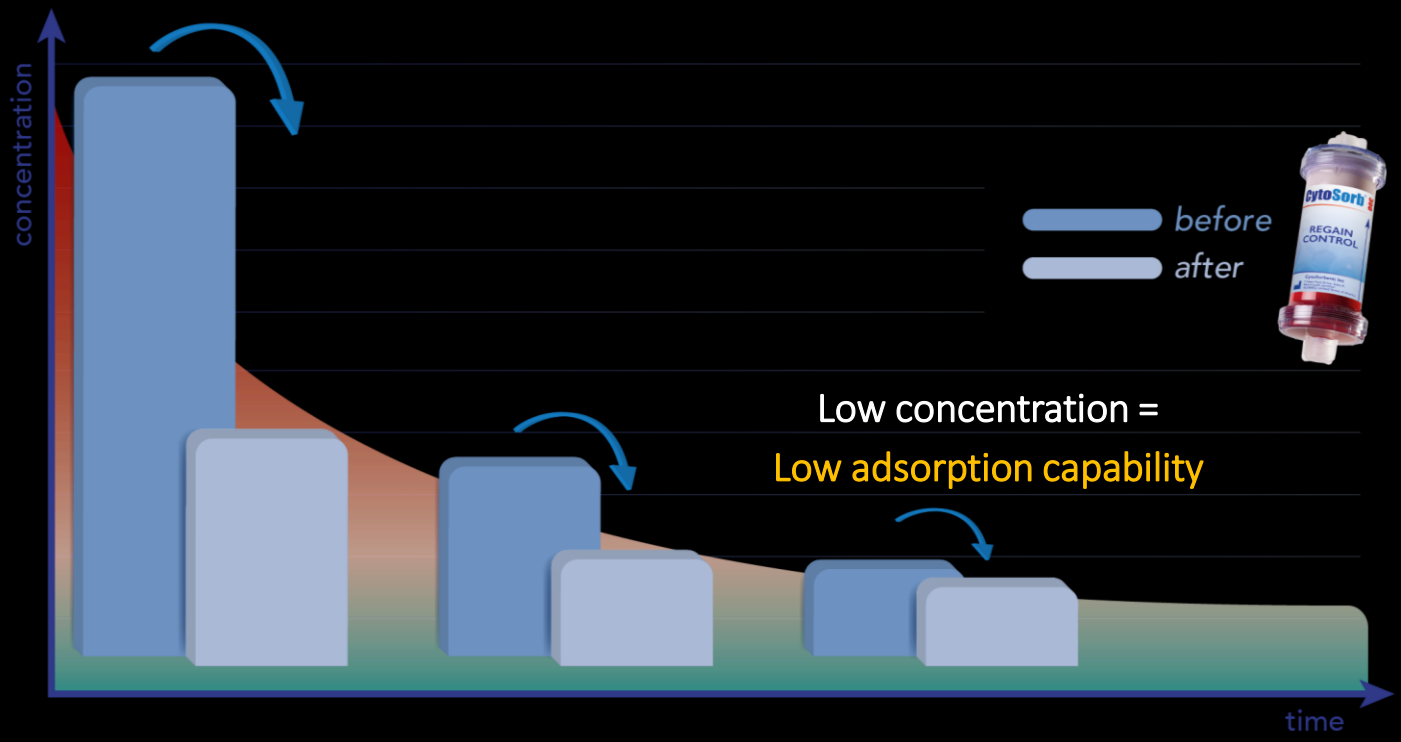
~~Albumina 66kDa~~



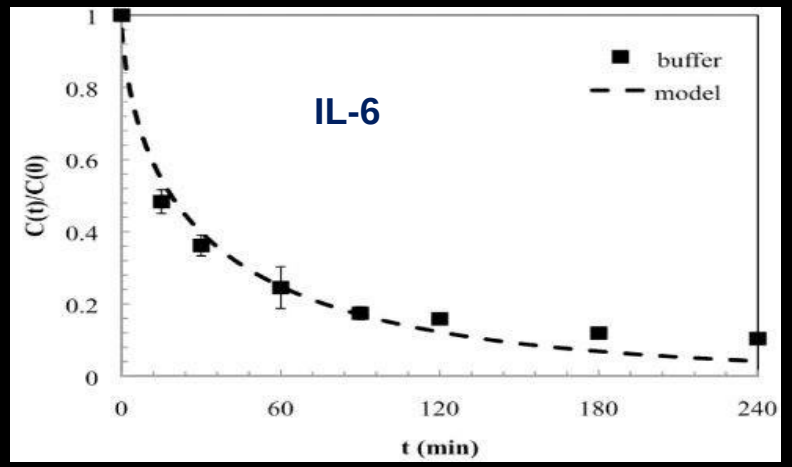
Adsorption with CytoSorb

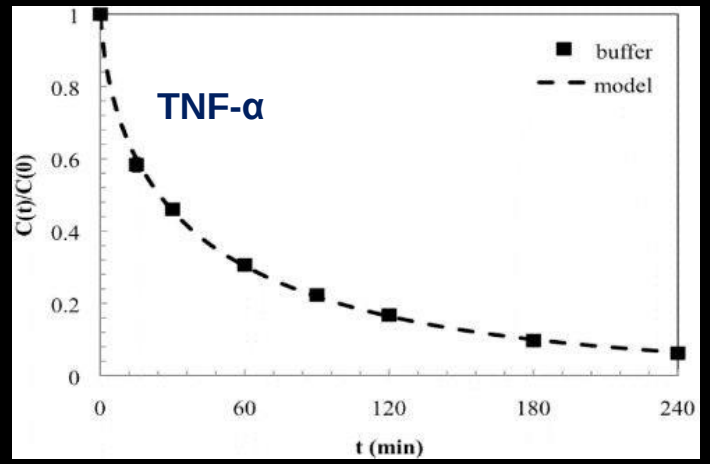
High concentration =

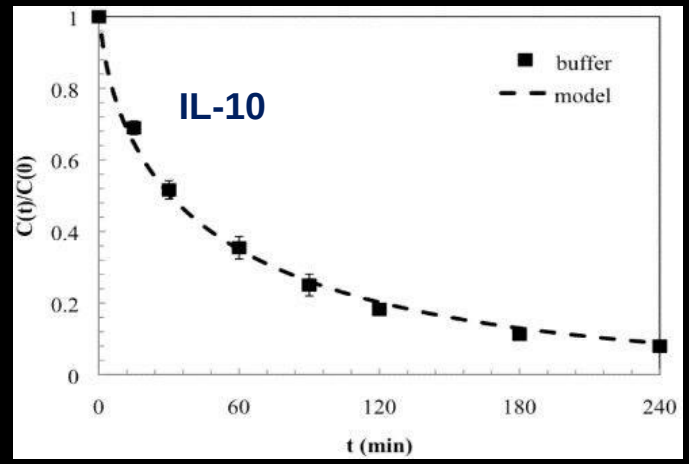
High adsorption capability

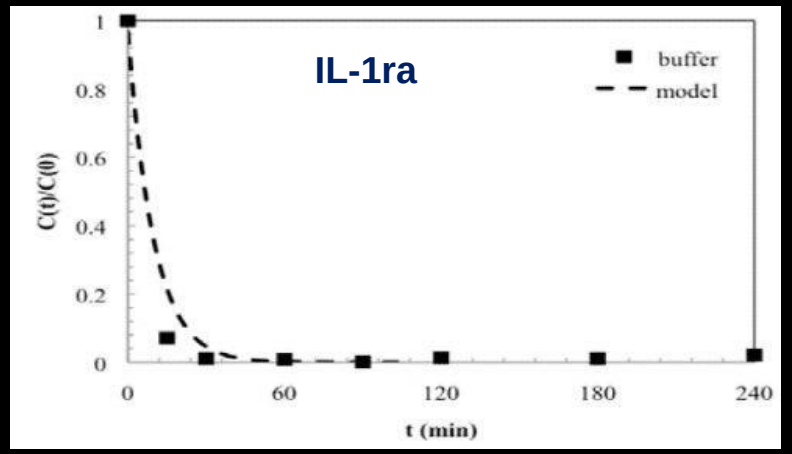


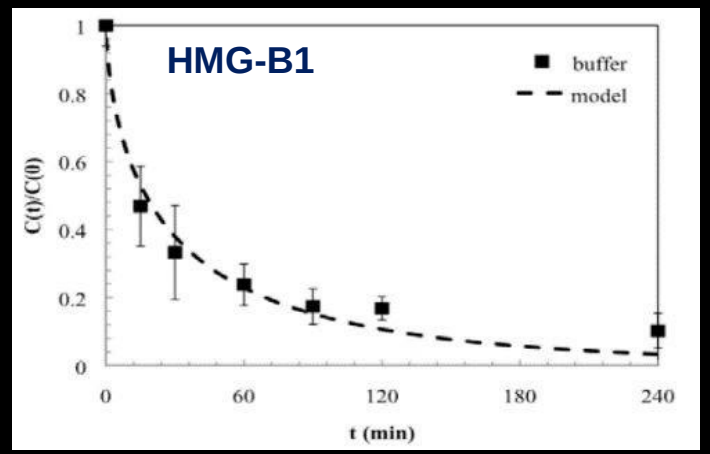
In vitro removal of cytokines

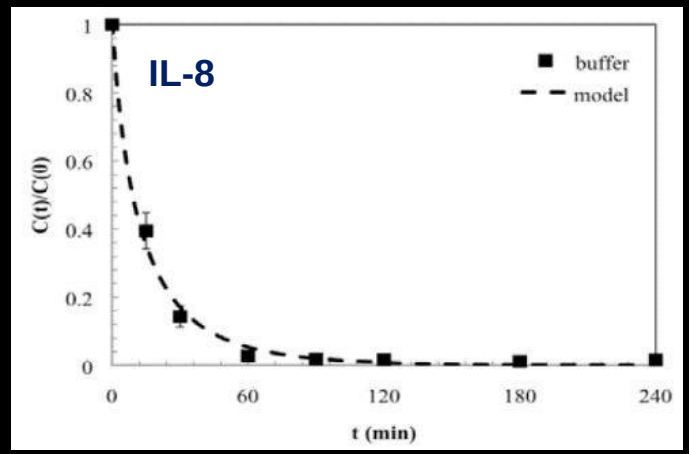












Valenti, I Kellum J A Characterization of a Novel Sorbent Polymer for the Treatment of Sepsis. Master Thesis 2008

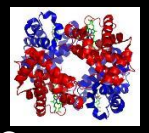
Adsorption with CytoSorb

Bilirubin

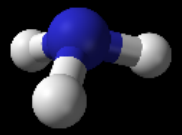
Infammatory mediators:

- Cytokines (IL-10, IL-6, IL-8, TNF-alfa and others)
- Inflammatory response triggers (PAMPS e DAMPS)

Bile Acids



Free hemoglobin



Ammonia

Myoglobin

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Adsorption with CytoSorb

SEPSIS

SEPTIC SHOCK

CARDIAC SURGERY

LIVER FAILURE

RHABDOMYOLYSIS

Rimozione In Vivo di Bilirubina Mediante un Nuovo Sorbente: Case Report.

S. Faenza[1], A. Siniscalchi[1], E. Pierucci[1], D. Ricci[2] E. Mancini[2]

[1] Dipartimento delle Insufficienze d'Organo e dei Trapianti
[2] Dipartimento di Nefrologia, Dialisi e Ipertensione.
Policlinico Sant'Orsola-Malpighi, Bologna

Male, 66 years old, **hepatitis C virus (HCV)-related cirrhosis, complicated by hepatocellular carcinoma (HCC),** in list for liver transplantation (MELD 10).

1. **First Liver Transplantation from a NHBD donor.**

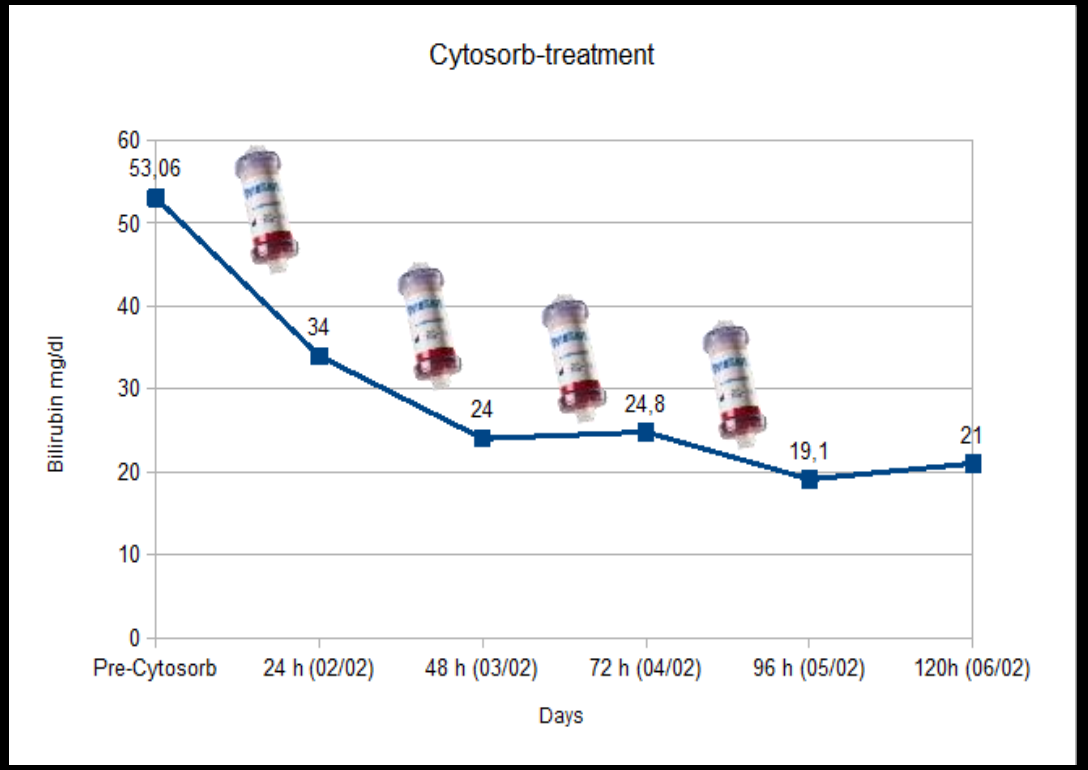
Post-reperfusion injury:

- High need of noradrenaline and adrenaline;
- Severe metabolic acidosis;
- Hyperlactatemia;
- Hypernatremia;
- Acute Renal Failure.

2. **Second Liver Transplantation after PNG of the first graft.**

- Acute renal failure
- Cytolysis (Myoglobin=23.118 ng/ml, CK=12.508 u/l)
- Hyperbilirubinemia (Bilirubina=53,06 mg/dl)
- Severe Sepsis (Enterobacter Cloache, PCT=70 ng/ml, PCR=11 mg/dl, GB=22000)

CVVHDF + 4 CytoSorb for 96 hours



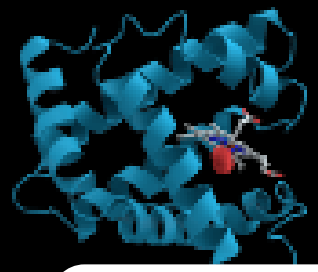
- Normalization of Bilirubin level
- Functional recovery of the graft
- Dismission of the patient from ICU

- No more need of inotropes after 2nd treatment
- Dramatic Reduction of Bilirubin
- Normalization of Mioglobin level

Adsorption with CytoSorb in rhabdomyolysis

Rhabdomyolysis

- Trauma
- Infection
- Hyperinflammation
- Drugs
- Toxines



Increase of myoglobin blood level

Myoglobin accumulation into renal tubules

Toxic and ischemic damage to renal tubules cells

Risk of ACUTE KIDNEY INJURY and hyperinflammation

Early CytoSorb treatment helps preventing or facilitating renal function recovery thanks to the adsorption of **myoglobin and muscle damage enzymes**

Purification Therapies L'evoluzione della cura

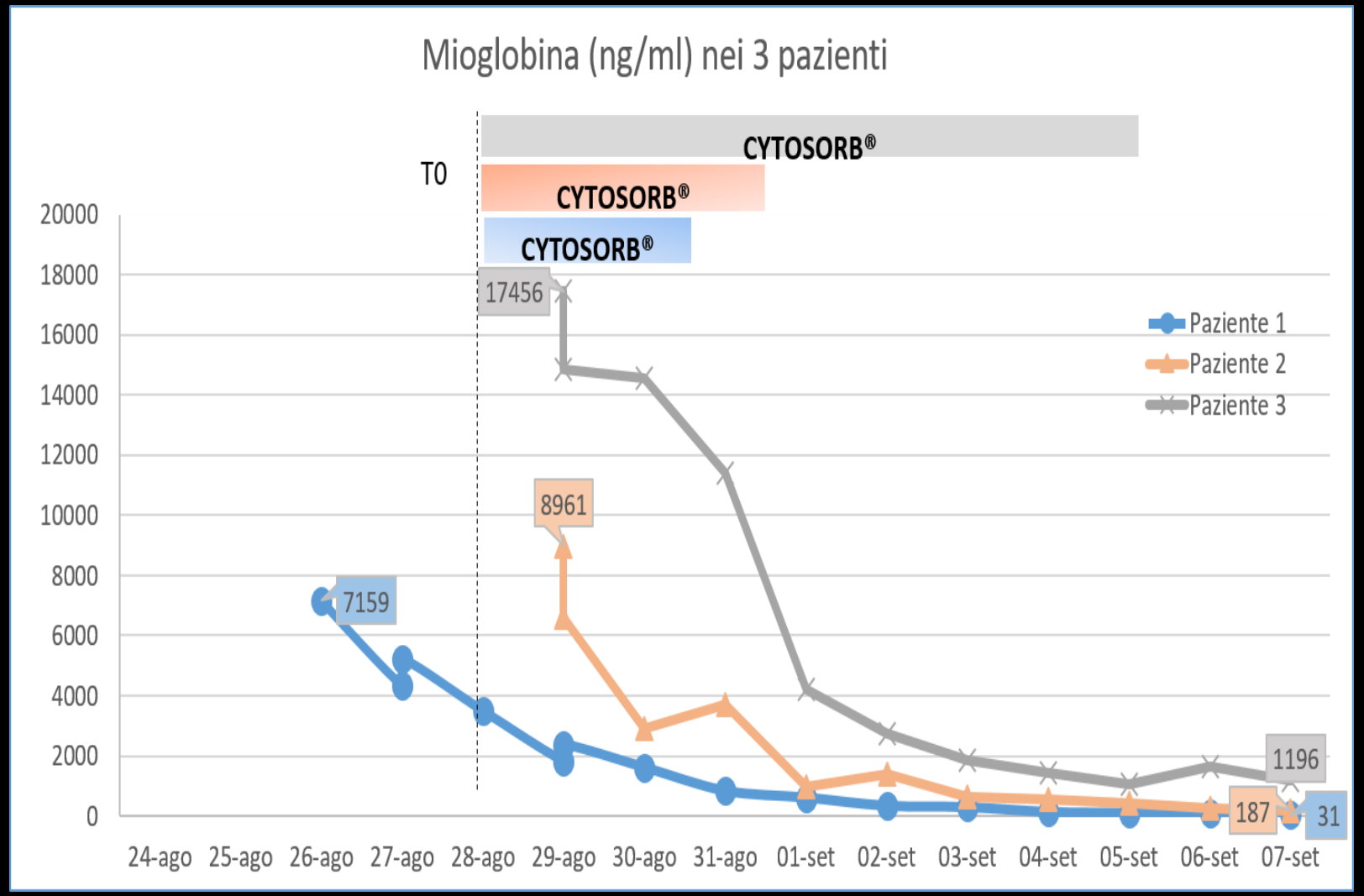
NUOVO TRATTAMENTO DELLA RABDOMIOLISI CON SEVERA IRA IN PAZIENTI COINVOLTI NEL TERREMOTO DEL CENTRO -ITALIA: LA NOSTRA ESPERIENZA.

Franca CERRONI, Fiorella FARAGLIA, Moreno ALEANDRI, Paola PEVERINI, Maria Lucia BROCCOLI, Claudia SAVIGNANI, Walter D. VALENTINI

U.O.C. Nefrologia e Dialisi, Direttore :Dr. W. D. Valentini – P.O. San Camillo de Lellis – Azienda USL- Rieti – Italia

- 3 patients with crush syndrome after middle-Italy earthquake
- At admission, high values of hematocrit, potassium, creatinin and muscle-damage markers. Low albumin level
- Myoglobin >> 12.000 (over the measurable limit)
- All 3 patients underwent CRRT with HCO filters without any improvement

- **Then CytoSorb therapy was initiated**



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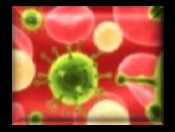
Adsorption with CytoSorb in septic patients

INFECTION



Batteric
Viral
Fungal

Pancreatitis

Trauma

Surgery

STERILE INFLAMMATION

PAMPS

DAMPS

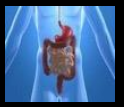
Inflammatory response

Nervous

Respiratory

Cardiovascular

Gastro-entheric



Renal

M
O
D
S

Triggers of the septic cascade

PAMPs

Pathogen-derived

Pathogen Associated Molecular Pathways

- Endotoxin
- Lipoteichoic acid
- Lipoproteins
- Peptidoglycans
- Bacterial DNA
- Et cet

DAMPs

Host-derived

Danger Associated Molecular Pathways
or Damage Associated Molecular Pathways
(and also known as alarmins)

- HMGB-1
- Heat shock proteins
- s100 protein
- Serum amyloid A
- Uric acid
- ATP, DNA
- Formyl peptides
- IL-1α, IL-18, etc.

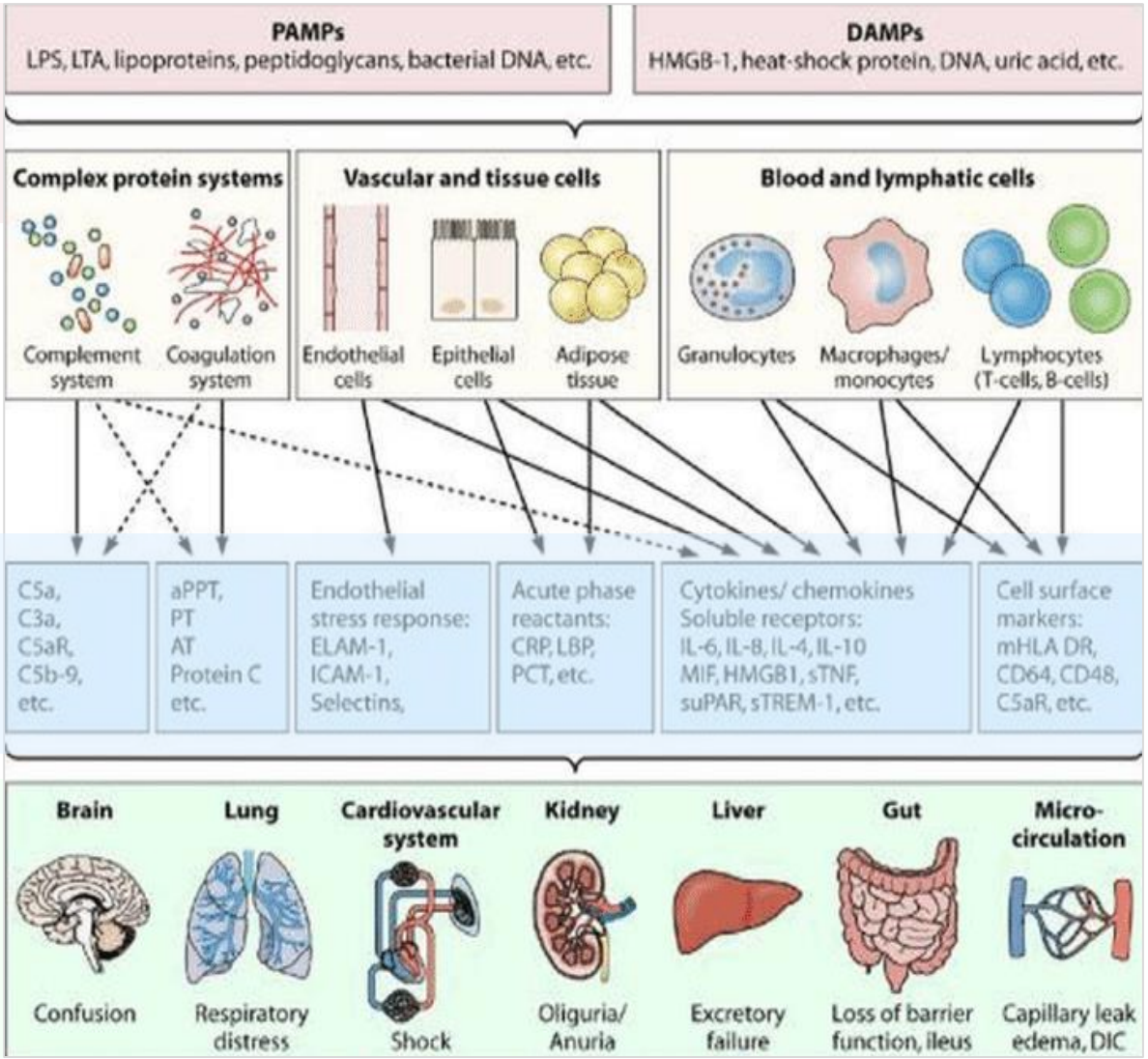
Sepsi e Shock Settico

PAMPs: Molecole pro-infiammatorie esposte o prodotte dai patogeni

DAMPs: Molecole endogene pro-infiammatorie prodotte o rilasciate dalle cellule danneggiate

Rilascio mediatori infiammatori

MODS

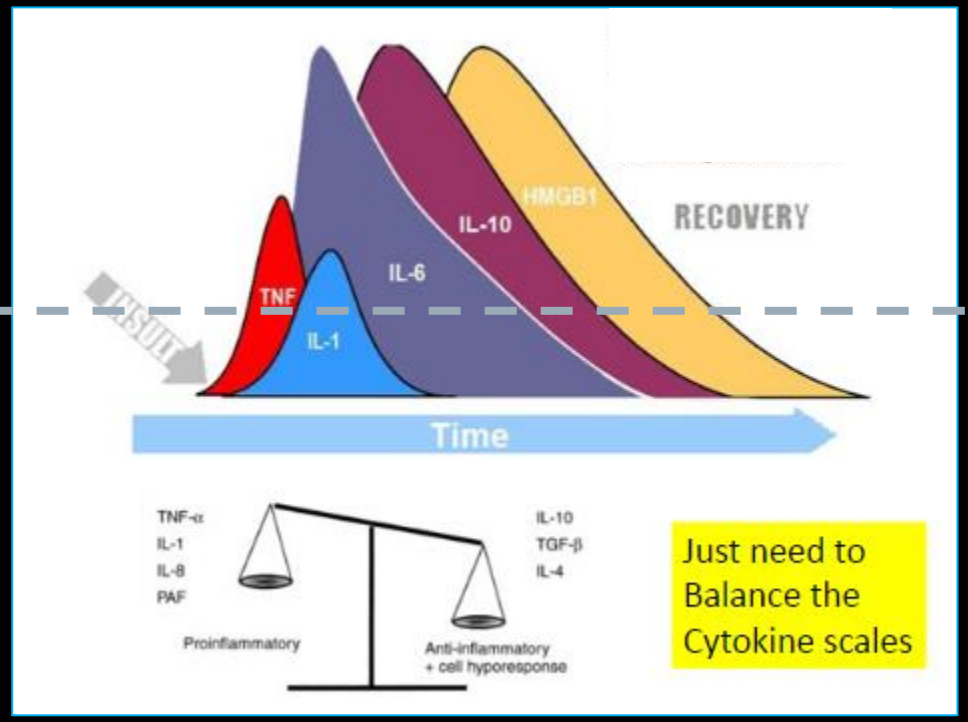


Immunol Rev. 2012 September ; 249(1): 158–175. doi:10.1111/j.1600-065X.2012.01146.x.

Adsorption with CytoSorb in septic patients

The rationale of cytokines adsorption

- **Modulation of cytokine storm** in order to facilitate organ recovery
  - Decrease of leucocytes-associated inflammatory response
  - Reduction of hyperinflammation
  - Improvement of microcirculation and hemodynamics



INFEZIONE

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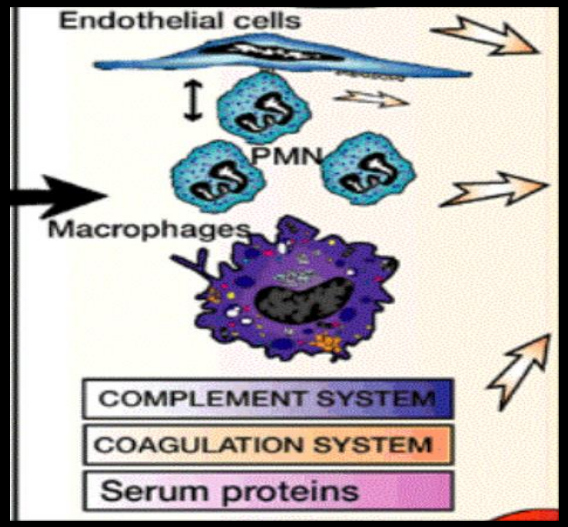

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RESEARCH ARTICLE

Broad adsorption of sepsis-related PAMP and DAMP molecules, mycotoxins, and cytokines from whole blood using CytoSorb® sorbent porous polymer beads

Maryann C. Gruda*, Karl-Gustav Ruggeberg, Pamela O'Sullivan, Tamaz Guliashvili, Andrew R. Scheirer¤, Thomas D. Golobish, Vincent J. Capponi, Phillip P. Chan

CytoSorbents Corporation, Monmouth Junction, New Jersey, United States of America

¤ Current address: Ethicon US, LLC, Somerville, New Jersey, United States of America
* mgruda@cytosorbents.com

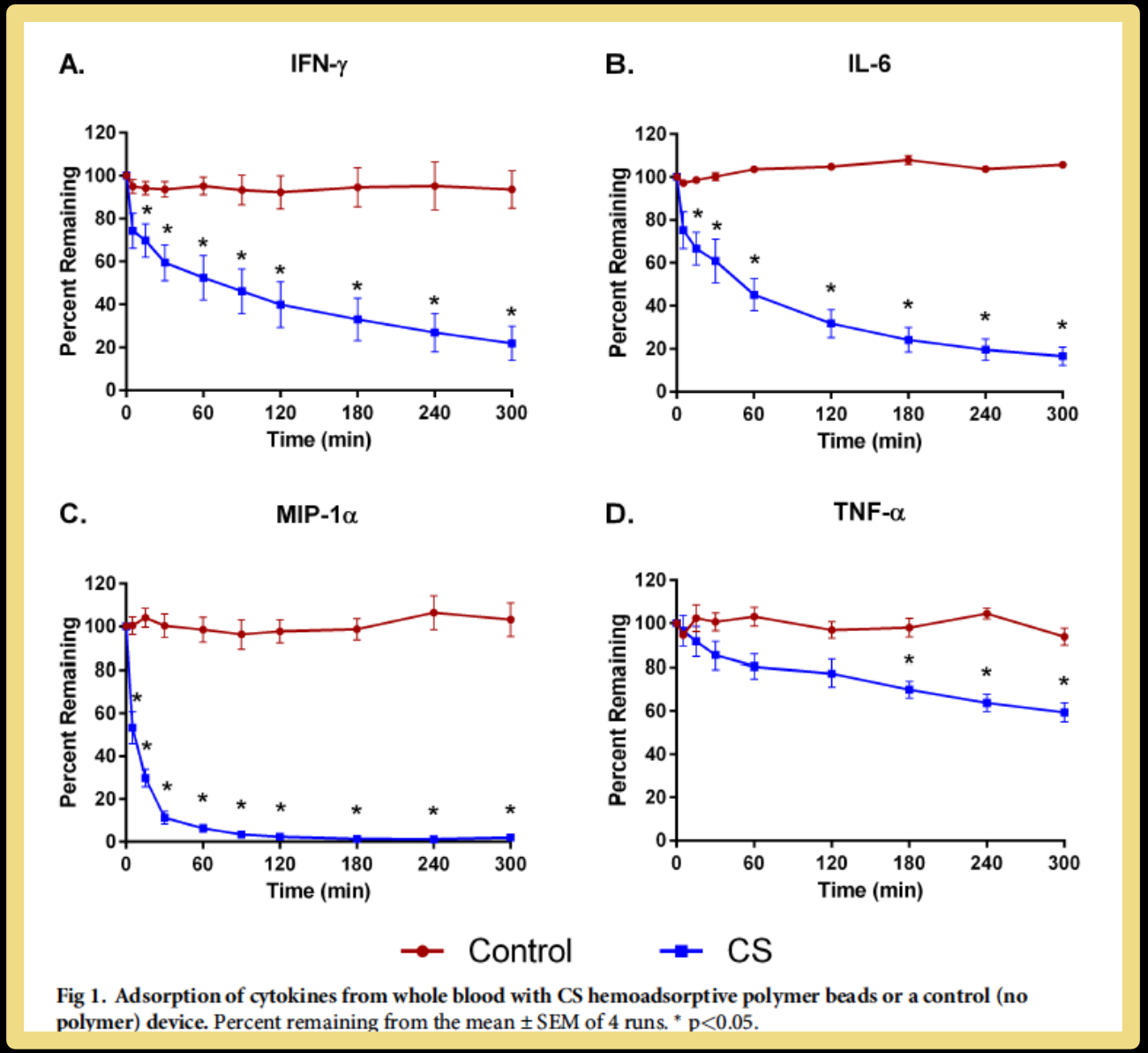


Fig 1. Adsorption of cytokines from whole blood with CS hemoadsorptive polymer beads or a control (no polymer) device. Percent remaining from the mean ± SEM of 4 runs. * $p<0.05$.

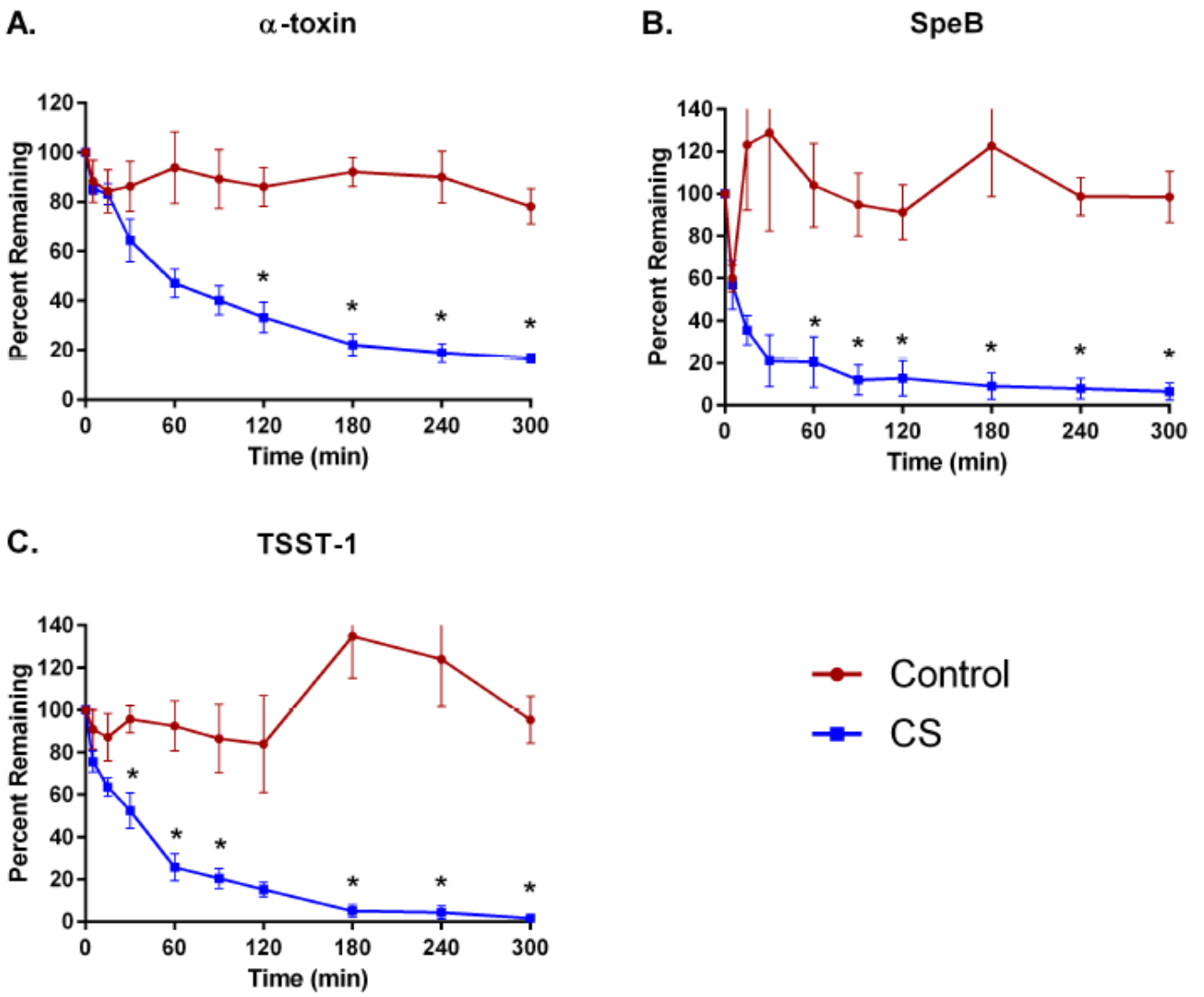


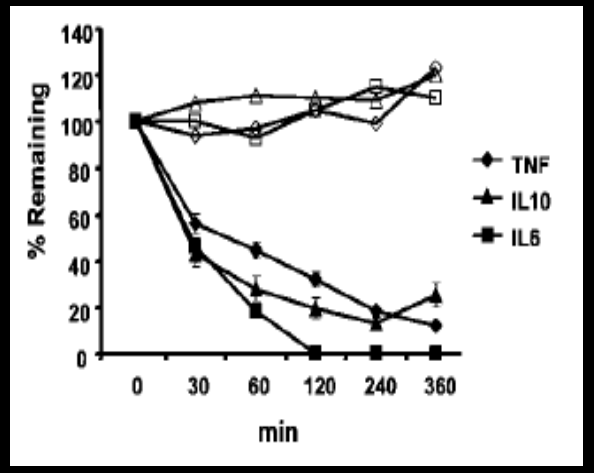
Fig 3. Adsorption of bacterial PAMPs with CS hemoadsorptive polymer beads or a control (no polymer) device from whole blood spiked with *S.* pyogenic exotoxin B, *Staph* TSST-1 or serum with *Staph aureus* alpha-toxin. Percent remaining from the mean ± SEM of 4 runs. * $p<0.05$.

Adsorption with CytoSorb in experimental sepsis

- Adsorption of cytokines, PAMPS and DAMPS
- Several in-vitro and in-animal studies

Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-κB DNA binding, and improves short-term survival in lethal endotoxemia*

John A. Kellum, MD, FCCM; Mingchen Song, MD, PhD; Ramesh Venkataraman, MD



ments, we studied 12 animals using the same protocol except that we killed all animals at 4 hrs and removed standardized sections of liver for analysis of nuclear factor-κB DNA binding.

Measurements and Main Results: Mean survival time among hemoadsorption-treated animals was 629 ± 114 vs. 518 ± 120 mins for sham-treated animals ($p < .01$). Overall survival (defined at 12 hrs) was also significantly better in the hemoadsorption group, seven of 20 vs. one of 20 ($p < .05$). Plasma interleukin-6 and interleukin-10 concentrations and liver nuclear factor-κB DNA binding were significantly reduced by hemoadsorption. *Ex vivo* experiments showed no endotoxin adsorption but strengthened our *in vivo* observations by showing rapid adsorption of tumor necrosis factor, interleukin-6, and interleukin-10.

Conclusions: Hemoadsorption was associated with reduced inflammation and improved survival in this murine model of septic shock. (Crit Care Med 2004; 32:801–805)

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CytoSorb in septic patiens: latest scientific results

Effects of hemoadsorption on cytokine removal and short-term survival in septic rats

Zhi-Yong Peng, MD, PhD; Melinda J. Carter, BS; John A. Kellum, MD, FCCM

Case Report

Cytokine Reduction in the Setting of an ARDS-Associated Inflammatory Response with Multiple Organ Failure

Karl Träger,[1] Christian Schütz,[1] Günther Fischer,[1] Janpeter Schröder,[1] Christian Skrabal,[2] Andreas Liebold,[2] and Helmut Reinelt[1]

Septic shock secondary to β-hemolytic streptococcus-induced necrotizing fasciitis treated with a novel cytokine adsorption therapy

Hubert Hetz[1], Reinhard Berger[1], Peter Recknagel[2], Heinz Steltzer[1]

F. Born, M. Pichlmaier, S. Peterß, N. Khaladj, C. Hagl

Herzchirurgische Klinik und Poliklinik an der LMU München Campus Großhadern

Herzklinik am Augustinum

(Direktor: Prof. Dr. med. Christian Hagl)

Systemic Inflammatory Response Syndrome in Heart Surgery: New possibilities for treatment through the use of a cytokine adsorber during ECC?

UKSH A multicenter randomized controlled study of an extracorporeal cytokine hemoadsorption device in septic patients

D Schädler[1], C Porzelius[2], A Jörres[3], G Marx[4], A Meier-Hellmann[5], C Putensen[6], M Quintel[7], C Spies[8], C Engel[9], N Weiler[1],M Kuhlmann[9]

Neurologic Critical Care

Feasibility study of cytokine removal by hemoadsorption in brain-dead humans*

John A. Kellum, MD, FCCM; Ramesh Venkataraman, MD; David Powner, MD, FCCM; Michele Elder, RN; Georgene Hergenroeder, RN; Melinda Carter, BS

IJAO

ISSN 0393-3660

SHORT COMMUNICATION

First report of cytokine removal using CytoSorb® in severe noninfectious inflammatory syndrome after liver transplantation

Observations in early vs. late use of CytoSorb® haemadsorption therapy in critically ill patients

IJAO

ISSN 0391-3988

SHORT COMMUNICATION

Treatment of post-cardiopulmonary bypass SIRS by hemoadsorption: a case series

Karl Träger, Daniel Fritzler, Guenther Fischer, Janpeter Schröder, Christian Skrabal, Andreas Liebold, Helmut Reinelt

Critical Care

LETTER Open Access

Hybrid blood purification strategy in pediatric septic shock

CASE REPORT Open Access

Effect of extracorporeal cytokine removal on vascular barrier function in a septic shock patient

Sascha David, Kristina Thamm, Bernhard M. W. Schmidt, Christine S. Falk and Jan T. Kielstein

CytoSorbents study ID	Category	Country	Site	Patient No.	Status
S20.122-1	Sepsis / ARDS	Germany	10 centers, lead: Klinikum Berlin Friedrichshain	100	publication phase
S20.122-2	Sepsis	Germany	6 centers, lead: Göttingen University	50	publication phase
S30.112-1	Pancreatitis	Germany	Munich Technical university, Weiden hospital	30	recruiting
S10.222-1	Cardiopulmonary bypass intraoperative	USA	8 sites	56	recruiting
S20.112-1	Septic shock	UK	coordinating center: University College London	130	in preparation

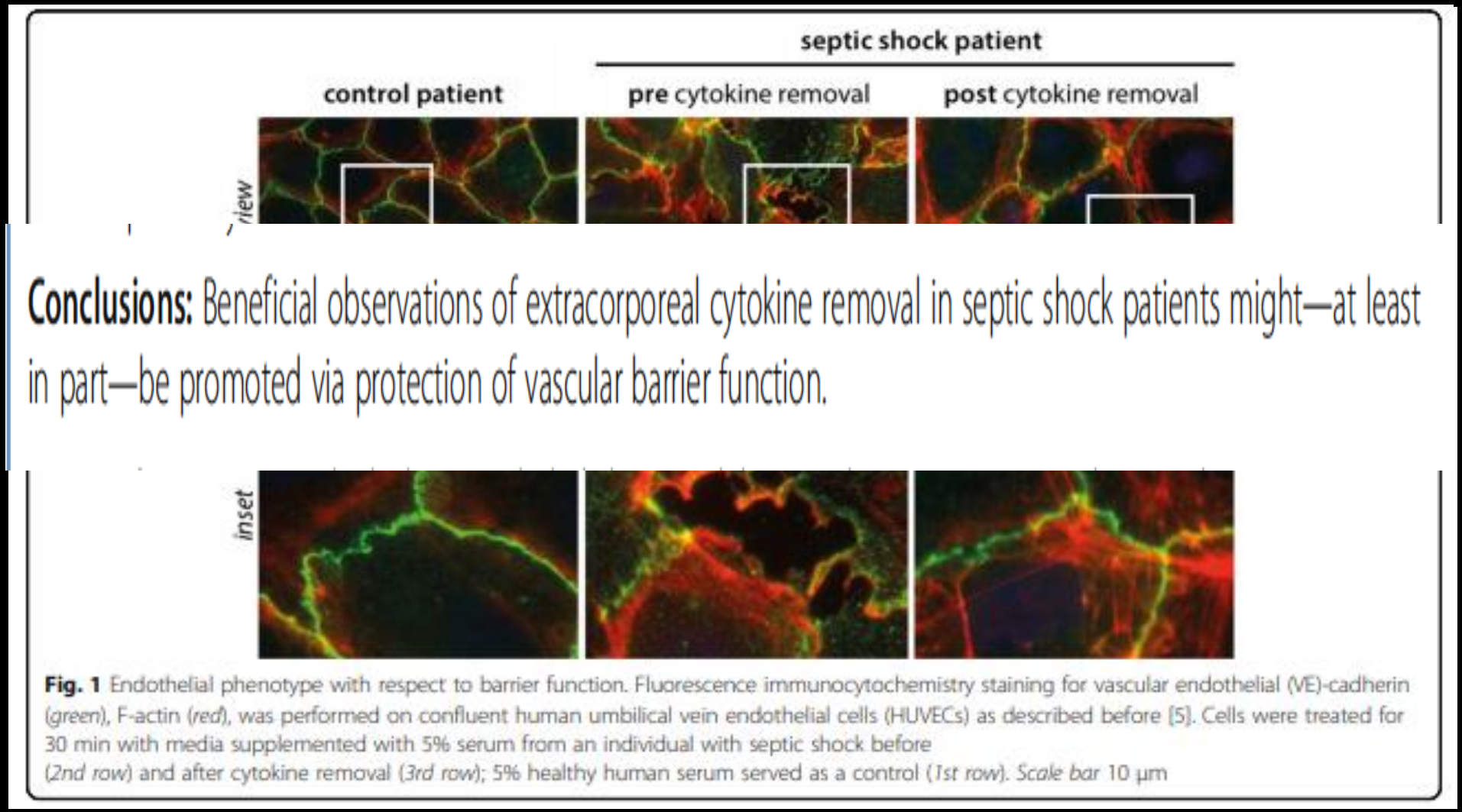
CytoSorbents study ID	Category	Country	Site	Patient No.	Status
S20.111-1	Septic shock	Germany	Greifswald University	20	publication phase
S20.111-2	Septic shock	Hungary	Szeged University	20	recruiting
S40.221-1	Rhabdomyolysis in trauma	US	San Antonio Military Medical Center	30	recruiting
S10.111-2	Cardiopulmonary bypass intraoperative	Germany	Hamburg University	40	data analysis
S10.111-3	Cardiopulmonary bypass intraoperative	Austria	Vienna University	40	published
S10.111-1	Cardiopulmonary bypass intraoperative	Germany	Cologne University	300	recruiting
S10.111-5	Cardiopulmonary bypass intraoperative	Germany	Bochum University	40	recruiting
S10.111-4	Cardiopulmonary bypass postoperative	Germany	Rostock University	10	recruiting
S10.111-7	Cardiopulmonary bypass intraoperative	Germany	Nuremberg hospital	40	in preparation
S50.111-1	influence on antibiotic/immunosuppressive therapy	Germany	Rostock University, Fraunhofer Institute	lab test	ongoing
S20.111-3	Septic shock/influence on antibiotic therapy	Germany	Munich University	20	recruiting
S30.111-1	Pancreatitis	Hungary	Debrecen University	24	recruiting
S20.111-5	Septic shock	Germany	Munich Technical University	124	recruiting
S20.111-4	Septic shock / influence on antibiotic therapy	Germany	Duesseldorf University	30	recruiting

CASE REPORT Open Access

Effect of extracorporeal cytokine removal on vascular barrier function in a septic shock patient

Sascha David[1*], Kristina Thamm[1], Bernhard M. W. Schmidt[1], Christine S. Falk[2] and Jan T. Kielstein[1]

- Cytokines effect on endothelium



Conclusions: Beneficial observations of extracorporeal cytokine removal in septic shock patients might—at least in part—be promoted via protection of vascular barrier function.

Fig. 1 Endothelial phenotype with respect to barrier function. Fluorescence immunocytochemistry staining for vascular endothelial (VE)-cadherin (*green*), F-actin (*red*), was performed on confluent human umbilical vein endothelial cells (HUVECs) as described before [5]. Cells were treated for 30 min with media supplemented with 5% serum from an individual with septic shock before (*2nd row*) and after cytokine removal (*3rd row*); 5% healthy human serum served as a control (*1st row*). *Scale bar* 10 μm

Blood Purification

In-Depth Review

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Clinical Utility of Extracorporeal Cytokine Hemoadsorption Therapy: A Literature Review

Anthony Bonavia[a] Andrew Groff[b] Kunal Karamchandani[a] Kai Singbartl[c]

Table 1. Literature summary of clinical reports relating to CytoSorb therapy in peer-reviewed and indexed medical journals

Authors	Disease or surgery	Number of Patients	Study type	Outcome		Control group (yes/no)	Comments
				primary	secondary		
Kogelmann et al. [83]	Sepsis with need for renal replacement therapy	26	Case series	Vasopressor requirement	Hospital mortality and blood lactate levels	No	Decreased catecholamine demand, predicted mortality (APACHE II), and lactate levels. No increased adverse effects
Friesecke et al. [104]	Refractory septic shock	20	Prospective single-center cohort	NE requirement after 6 and 12 h of CytoSorb	SOFA score, resolution of shock, and lactate clearance	No	Decrease in NE requirement and serum lactate. Improved mortality compared to predicted
Schadler et al. [107]	Sepsis or septic shock with ARDS	97	Randomized, controlled multicenter trial	Plasma IL-6 levels	Multiple organ dysfunction score, ventilation time, time course of oxygenation	Yes	No significant difference in primary and secondary outcomes
Nemeth et al. [134]	Orthotopic heart transplant	84	Prospective, observational	Hemodynamic stability, vasopressor demand (48 h post-operatively), and post-operative inflammatory response (CRP and PCT)	Volume of postoperative bleeding, rate or reoperation, need for blood products (first 24 h post-operatively), need for postoperative RRT	Yes	Significantly decreased vasopressor demand and less frequent RRT with CytoSorb. No difference in inflammatory response. No increased adverse events
Bernardi et al. [106]	CPB surgery	37	Randomized, single-center controlled trial	Serum IL-1β, IL-6, IL-18, TNF-α, and IL-10 levels during first 5 days post-operatively	Measurement of other inflammatory markers, 30-day mortality	Yes	No reduction in proinflammatory response or mortality following treatment. Strong inter-individual response to CytoSorb, suggesting some patients may have exaggerated inflammatory responses
Träger et al. [136]	CPB surgery complicated by infective endocarditis	39	Case series	Serum IL-6 and IL-8, vasopressor dose, MAP, lactate levels, and need for post-operative support	Postoperative and 24-h post-operative APACHE II score, and intensive care and hospital length of stay	Yes	Reduction in serum IL-6, IL-8, and lactate levels. Improvement in hemodynamic stability following CytoSorb compared to control.
Träger et al. [105]	CPB surgery complicated by SIRS	16	Case series	Not applicable	Not applicable	No	Overall reduction in cytokine levels and improvement in hemodynamic stability and organ function. No increased adverse effects

MAP, mean arterial pressure; NE, norepinephrine; PCT, procalcitonin; CPB, cardiopulmonary bypass.

Kogelmann et al. Critical Care (2017) 21:74
DOI 10.1186/s13054-017-1662-9

Critical Care

RESEARCH Open Access

Hemoadsorption by CytoSorb in septic patients: a case series

Klaus Kogelmann[1*], Dominik Jarczak[2], Morten Scheller[1] and Matthias Drüner[1]

Table 1 Patient characteristics, treatment modalities, clinical parameters and patient outcome

Case number	Sex	Age	Source	APACHE II	Abx	CytoSorb treatments (n)	Delay (h)	Cat-free days	Details on renal outcome/recovery on ICU	CRRT (days)	Ventilation (days)	Hospital stay (days)	ICU stay (days)	Predicted mortality	28-Day mortality	ICU mortality	Hospital mortality
1	M	76	Abd	45	Mero-Line-Cas	5	24	0	Non-recovery	15	17	17	17	97.5	Yes	Yes	Yes
2	M	58	Abd	48	Pip/T	3	24	7	Non-recovery	16	51	51	50	98.4	No	Yes	Yes
3	F	35	Abd	27	Pip/T-Clinda	2	24	28	Recovery	3	36	43	41	73.7	No	No	No
4	M	41	Abd	39	Mero-Fosfo	3	24	25	Recovery	13	27	36	36	94.2	No	No	No
5	F	58	Abd	27	Cefta-Levo	2	24	1	Non-recovery	2	3	4	4	73.7	Yes	Yes	Yes
6	M	75	Abd	37	Mero-Cas	3	24	0	Non-recovery	4	4	11	4	92.3	Yes	Yes	Yes
7	M	65	Abd	45	Mero	1	24	15	Non-recovery	3	3	18	18	97.5	Yes	Yes	Yes
8	M	54	Abd	37	Mero	4	24	1	Recovery	6	19	20	20	92.3	Yes	Yes	Yes
9	M	56	Abd	29	Pip/T-Clinda	3	36	3	Non-recovery	5	16	15	15	78.9	Yes	Yes	Yes
10	F	51	Abd	32	Levo-Cefta-Cas	1	48	0	Non-recovery	1	10	10	10	85.3	Yes	Yes	Yes
11	F	49	Abd	29	Mero-Line-Cas	3	48	18	Recovery	3	27	138	33	78.9	No	No	Yes
12	M	63	Abd	48	Cefta-Line-Cas	1	96	6	Non-recovery	3	14	14	14	98.4	Yes	Yes	Yes
13	M	72	Abd	34	Pip/T	2	72	4	Non-recovery	3	4	14	5	88.6	Yes	Yes	Yes
14	M	74	Pneu	33	Mero	5	24	0	Recovery	14	28	40	40	87	No	Yes	Yes
15	M	65	Pneu	33	Pip/T	3	24	0	Non-recovery	3	4	6	6	87	Yes	Yes	Yes
16	M	64	Pneu	56	Pip/T	3	24	31	Recovery	11	37	40	40	99.5	No	No	No
17	M	17	Pneu	29	Cefta-Clon	2	24	0	Unknown	2	2	2	2	78.9	No	No	No
18	F	72	Pneu	40	Pip/T-Ery	1	24	0	Non-recovery	1	1	1	1	94.9	Yes	Yes	Yes
19	M	58	Pneu	27	Pip/T-Ery	2	48	13	Chronic	9	16	43	21	73.7	Yes	Yes	Yes
20	F	79	Pneu	27	Pip/T-Ery-Cas	3	48	30	Recovery	20	34	46	40	73.7	No	No	No
21	M	62	Pneu	33	Mero-Line	3	48	2	Non-recovery	14	18	20	20	87	Yes	Yes	Yes
22	M	62	Pneu	54	Pip/T-Clinda	3	48	-	Recovery	19	33	35	35	99.3	No	Yes	Yes
23	F	53	Pneu	33	Pip/t-Ery	2	36	1	Non-recovery	3	3	4	4	87	Yes	Yes	Yes
24	M	64	Pneu	36	Mero	3	120	47	Recovery	16	45	88	72	91.2	No	No	Yes
25	M	43	Pneu	52	Pip/T-Ery-Cas	2	120	0	Chronic	3	12	12	12	99.1	Yes	Yes	Yes
26	M	46	Pneu	44	Pip/T	3	50	0	Non-recovery	7	7	7	7	97.1	Yes	Yes	Yes

M male, *F* female, *Cat-free* catecholamine-free, *CRRT* continuous renal replacement therapy, *Abd* abdominal focus, *Pneu* pneumonia, *Cefta* Ceftazidim, *Mero* Meropenem, *Pip/T* Piperacillin/Taz, *Clinda* Clindamycin, *Ery* Erythromycin, *Fosfo* Fosfomycin, *Cas* Caspofungin, *Line* Linezolid, *Levo* Levofloxacin, *Tyga* Tigecyclid

RESEARCH

Hemoadsorption by CytoSorb in septic patients: a case series

Klaus Kogelmann[1*], Dominik Jarczak[2], Morten Scheller[1] and Matthias Drüner[1]

Kogelmann K et al. Hemoadsorption by CytoSorb in septic patients: a case series
Critical Care (2017) 21:74

- 26 patients in septic shock in need of RRT.
- Amines and lactate reduction after 72h since the start of the therapy.
- Increase of survival rate in patient treated early within 24h since septic shock diagnosis, compared to expected mortality.

Table 3 Association between delay in start of therapy and mortality (i.e. predicted mortality, 28-day, ICU, and hospital mortality) in the overall patient population and in post-surgical and medical patients

		Predicted mortality	28-Day mortality	ICU mortality	Hospital mortality
Delay in starting therapy	<24 h ($n = 13$)	92.3	53.8	69.2	69.2
	<48 h ($n = 8$)	82.1	62.5	75.0	87.5
	>48 h ($n = 5$)	97.1	80.0	80.0	100.0
Focus	Abdominal/post-surgical	92.3	69.2	76.9	84.6
	Pneumonic/medical	87.0	53.8	69.2	76.9

Results are presented as median values

J Artif Organs
DOI 10.1007/s10047-017-0967-4
2017 Sep;20(3):252-259

ORIGINAL ARTICLE

Others

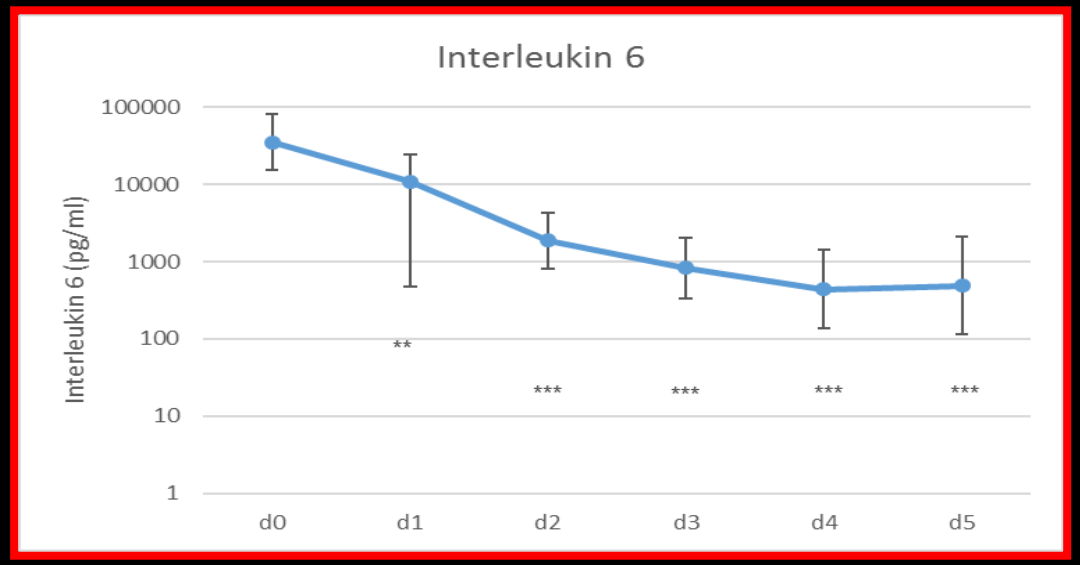
Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study

Sigrun Friesecke[1] · Stephanie-Susanne Stecher[1] · Stefan Gross[2] · Stephan B. Felix[1,2] · Axel Nierhaus[3]

- Single centre prospective study
- Refractory septic shock :
  - High lactate level > 2,8 mmol/L
  - High dosage of amines > 0,3 µg/kg/min
- **SOFA-Score (14,3±3)**

- Early application of CytoSorb + CRRT: after **7.8 ± 3.7 h** (mean) since septic shock diagnosis
- 3 CytoSorb (mean) for each patient
- CytoSorb change every **12-24 h**

- **Significant reduction of vasopressor dose after 6 hours**, since the beginning of the treatment
- **High lactate clearance after 6 hours**
- **Significant reduction of IL-6 after 24h** since the beginning of the treatment.
- **Shock reversal in 65% patients**



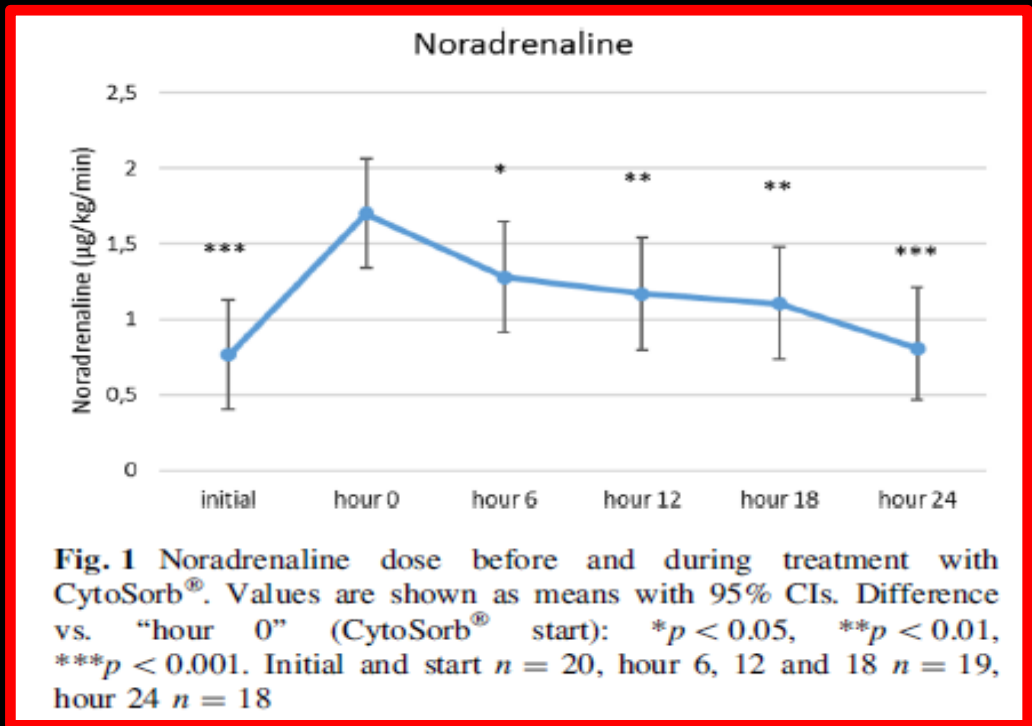


Fig. 1 Noradrenaline dose before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour 0" (CytoSorb® start): $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Initial and start $n = 20$, hour 6, 12 and 18 $n = 19$, hour 24 $n = 18$

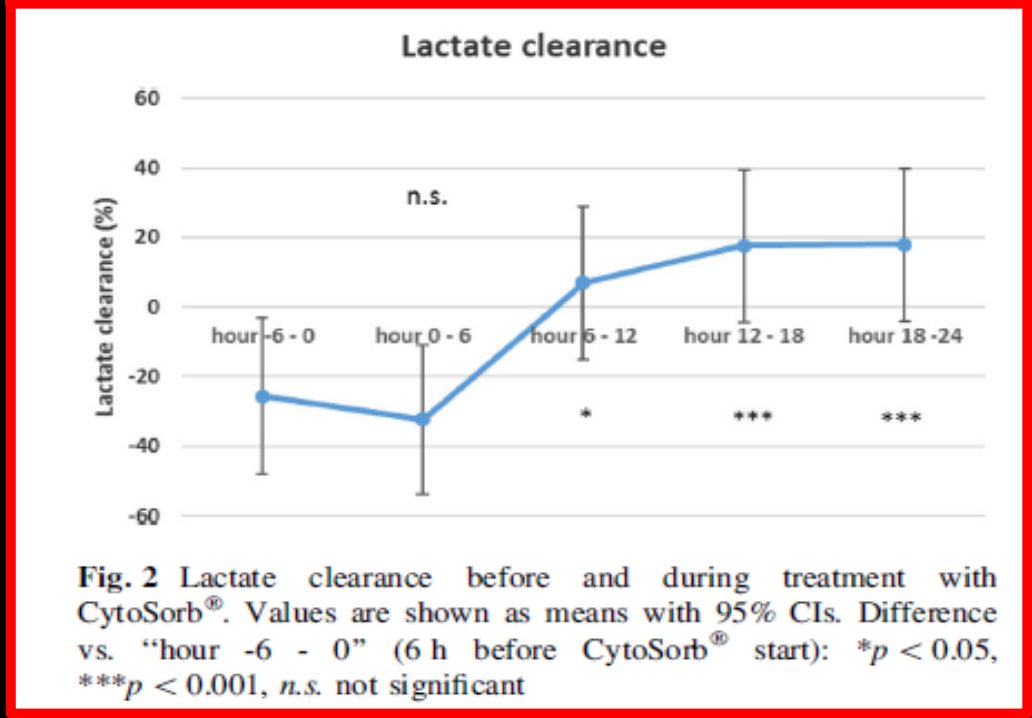


Fig. 2 Lactate clearance before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour -6 - 0" (6 h before CytoSorb® start): $*p < 0.05$, $***p < 0.001$, *n.s.* not significant

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]

1 Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany, **2** Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany, **3** Centre of Anaesthesiology, Emergency and Intensive Care Medicine, University Hospital Göttingen, Göttingen, Germany, **4** Department of Anesthesiology and Intensive Care Medicine, HELIOS Klinikum, Erfurt, Germany, **5** Department of Intensive Care Medicine, Helios Hospital Berlin-Buch, Berlin, Germany, **6** Department of Intensive Care and Intermediate Care, RWTH University Hospital Aachen, Aachen, Germany, **7** Department of Anesthesiology and Intensive Care Medicine, University of Bonn, Bonn, Germany, **8** Anaesthesiology and Intensive Care Medicine, Campus Charité Mitte and Campus Charité Virchow-Klinikum, Charité - University Medicine Berlin, Berlin, Germany, **9** Department of Medicine I - Nephrology, Transplantation & Medical Intensive Care, University Witten/Herdecke, Medical Center Cologne-Merheim, Cologne, Germany, **10** Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States of America, **11** Department of Nephrology, Vivantes Klinikum im Friedrichshain, Berlin, Germany

Methods

This was a randomized, controlled, open-label, multicenter trial. Mechanically ventilated patients with severe sepsis or septic shock and acute lung injury or acute respiratory distress syndrome were eligible for study inclusion. Patients were randomly assigned to either therapy with CytoSorb hemoperfusion for 6 hours per day for up to 7 consecutive days (treatment), or no hemoperfusion (control). Primary outcome was change in normalized IL-6-serum concentrations during study day 1 and 7.

RESEARCH ARTICLE

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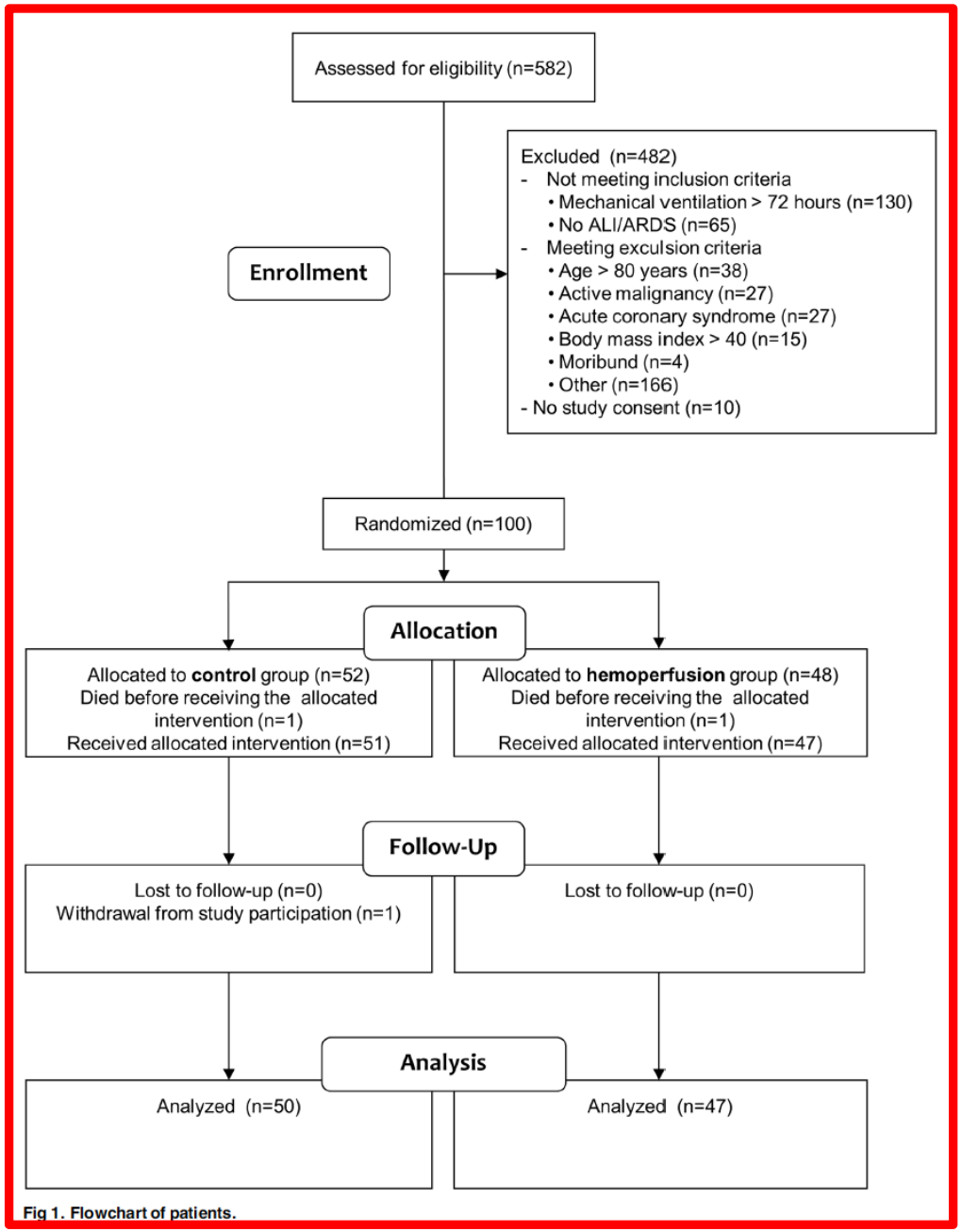

Fig 1. Flowchart of patients.

Table 1. Demographic data and baseline characteristics of all studied patients.

Variable	Treatment group (n = 47)	Control group (n = 50)
Age [years]	66.0 [55–73]	65 [56.5–71]
Male gender, no. (%)	35 (74.5%)	35 (70%)
Weight [kg]	77.8±13.7	84.5±17.9
Height [cm]	171.9±8.3	171.8±8.3
Body mass index [kg/m^2]	26.4±4.6	28.5±5.2
APACHE II score*	24.6±5.2	23.8±5.7
Renal replacement therapy, no. (%)	15 (31.9%)	8 (16.3%)
Diabetes mellitus, no. (%)	17 (36.2)	19 (38.8%)
White blood cell count (1/µl)	13.4 [8.6–18.1]	16.2 [12.4–21.3]
Creatinine (mg/dl)	1.7 [0.9–2.1]	1.9 [1.1–3.0]
Albumin (g/dl)	1.9 [1.5–2.4]	2.1 [1.8–2.2]
Total protein (g/l)	4.5 [4.0–5.1]	4.7 [4.3–5.1]
Lung injury category		
Sepsis		
Primary, no. (%)	17 (36.2%)	13 (26.0%)
Secondary, no. (%)	30 (63.8%)	37 (74.0%)
Trauma		
Primary, no. (%)	3 (6.7%)	3 (6.1%)
Secondary, no. (%)	1 (2.2%)	0 (0.0%)
Aspiration		
Primary, no. (%)	3 (6.5%)	6 (12.2%)
Secondary, no. (%)	0 (0.0%)	3 (6.1%)
Multiple transfusion		
Primary, no. (%)	0 (0.0%)	3 (6.2%)
Secondary, no. (%)	5 (11.1%)	2 (4.2%)
Pneumonia		
Primary, no. (%)	27 (57.4%)	23 (46.0%)
Secondary, no. (%)	10 (21.3%)	20 (40.0%)
Other		
Primary, no. (%)	5 (11.6%)	10 (20.8%)
Secondary, no. (%)	8 (18.6%)	5 (10.4%)
Other comorbid conditions, no. (%)	34 (72.3%)	41 (83.7%)

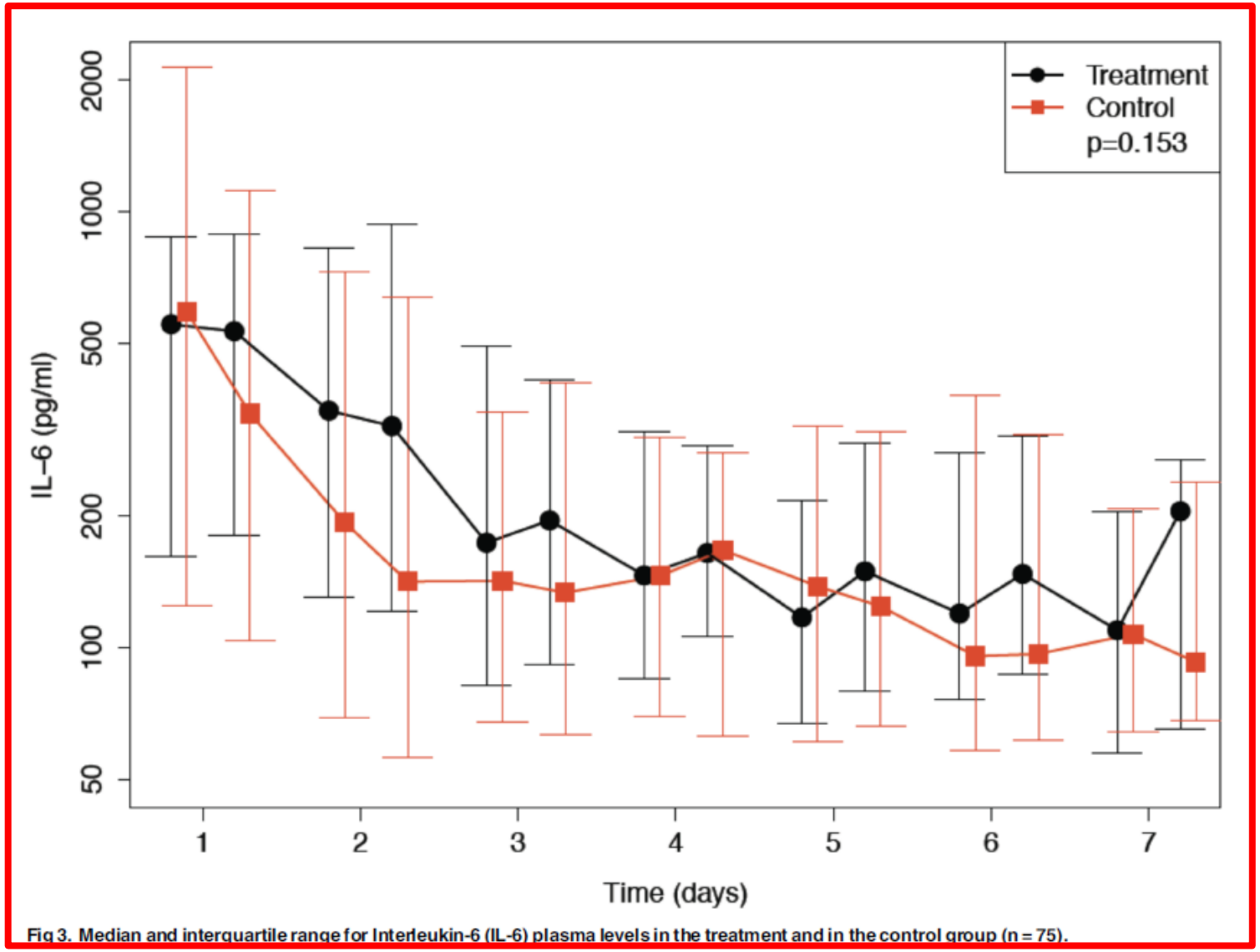

Fig 3. Median and interquartile range for Interleukin-6 (IL-6) plasma levels in the treatment and in the control group (n = 75).

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]

1 Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany, **2** Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany, **3** Centre of Anaesthesiology, Emergency and Intensive Care Medicine, University Hospital Göttingen, Göttingen, Germany, **4** Department of Anesthesiology and Intensive Care Medicine, HELIOS Klinikum, Erfurt, Germany, **5** Department of Intensive Care Medicine, Helios Hospital Berlin-Buch, Berlin, Germany, **6** Department of Intensive Care and Intermediate Care, RWTH University Hospital Aachen, Aachen, Germany, **7** Department of Anesthesiology and Intensive Care Medicine, University of Bonn, Bonn, Germany, **8** Anaesthesiology and Intensive Care Medicine, Campus Charité Mitte and Campus Charité Virchow-Klinikum, Charité - University Medicine Berlin, Berlin, Germany, **9** Department of Medicine I - Nephrology, Transplantation & Medical Intensive Care, University Witten/Herdecke, Medical Center Cologne-Merheim, Cologne, Germany, **10** Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States of America, **11** Department of Nephrology, Vivantes Klinikum im Friedrichshain, Berlin, Germany

treatment group (44.7%) compared to the control group (26.0%; p = 0.039). The proportion of patients receiving renal replacement therapy at the time of enrollment was higher in the treatment group (31.9%) when compared to the control group (16.3%). After adjustment for patient morbidity and baseline imbalances, no association of hemoperfusion with mortality was found (p = 0.19).

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Extracorporeal cytokine adsorption in septic shock: A proof of concept randomized, controlled pilot study

Fatime Hawchar [a], Ildikó László [a], Nándor Öveges [a], Domonkos Trásy [a], Zoltán Ondrik [b], Zsolt Molnar [a,*]

Therefore, the aim of this prospective, randomized, controlled, *proof of concept* (i.e.: *testing it as a standalone extracorporeal treatment without the need of renal replacement therapy*), pilot study was to investigate the effects of early (started within 24 h after ICU administration), 24-h long cytokine-adsorption therapy on organ dysfunction and inflammatory response in patients with septic shock, and to provide further data on safety.

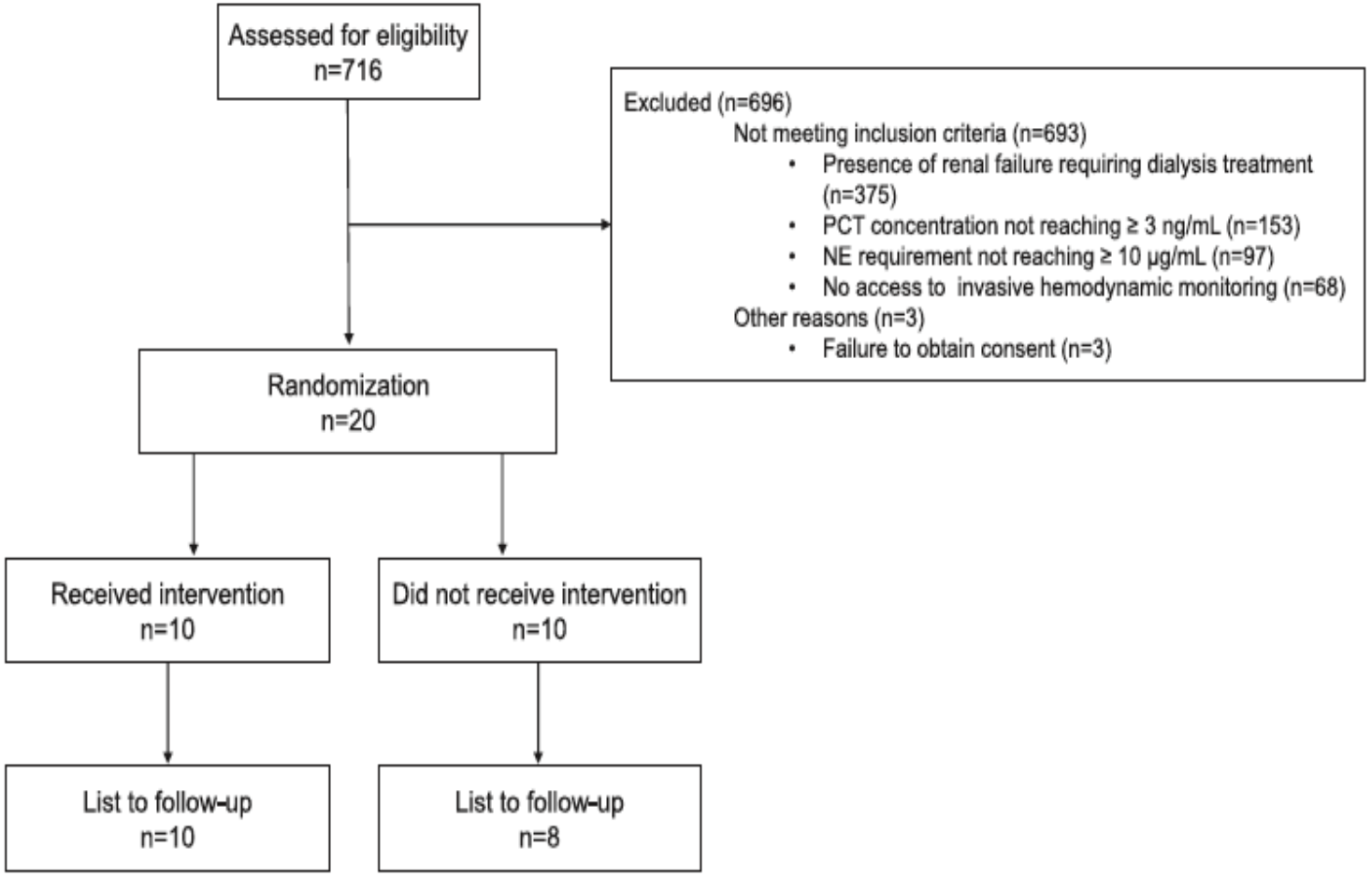
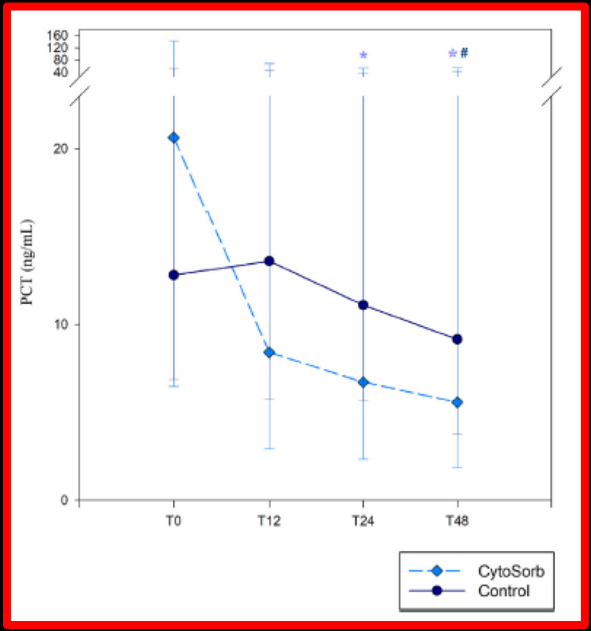


Fig. 1. Flowchart of patient screening and involvement according to CONSORT.

Table 1
Demographic data.

Parameters	All	CytoSorb	Control
N (male/female)	20 (13/7)	10 (7/3)	10 (6/4)
Age (years)	65.6 ± 12.9	60 ± 10	71 ± 14
Body Mass Index	28.8 ± 8.0	30.5 ± 10.2	26.9 ± 4.4
ICU length of stay (days)	10.1 ± 6.5	10.2 ± 8.5	10.0 ± 4.3
APACHE II	28 ± 7	26 ± 9	30 ± 6
Mortality within 48 h	2	0	2
Etiology (n)	–	Pneumonia (7) pancreatitis (1) toxic shock syndrome (1) urosepsis (1)	Pneumonia (6) meningococcus sepsis (2) cholangiosepsis (1) dermatomyositis (1)
Number of dialysis treatments	47	2.6 ± 1.5	2.1 ± 4.3

N: number of subjects, ICU: Intensive Care Unit, APACHE II: Acute Physiology and Chronic Health Evaluation II score. Data are presented as mean ± standard deviation.



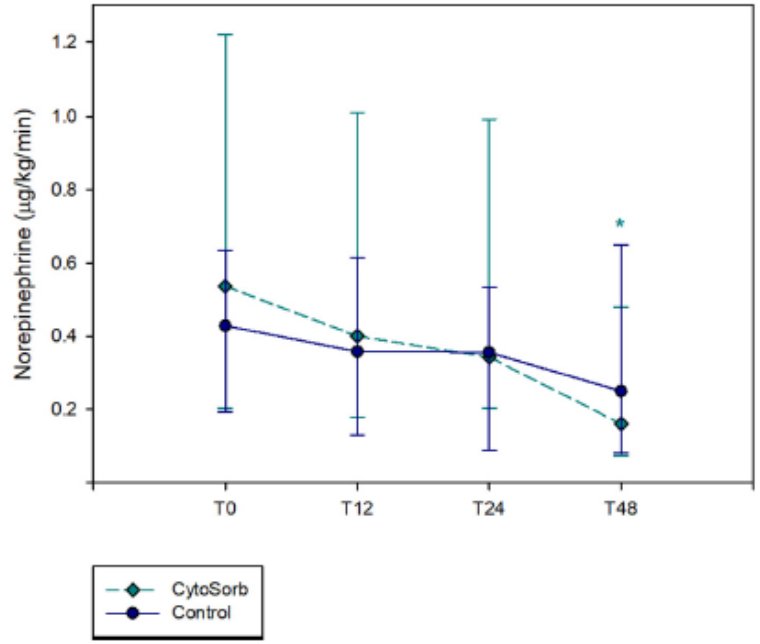


Fig. 2. Kinetics of norepinephrine need in the CytoSorb and in the Control group. Data are shown as median and interquartile ranges. *$p < .05$ vs. T_0.

Changes in cytokines, haemodynamics and microcirculation in patients with sepsis/septic shock undergoing continuous renal replacement therapy and blood purification with CytoSorb.
A prospective observational study on effects of blood purification with CytoSorb in septic patients.

Samuele Zuccari[1], Elisa Damiani[1], Roberta Domizi[1], Claudia Scorcella[1], Mario D'Arezzo[2], Andrea Carsetti[1], Simona Pantanetti[1], Sara Vannicola[1], Erica Adrario[1], A. Ranghino2 Abele Donati[1]

Pazienti:

- **10 pazienti con sepsi/shock settico**
- Pazienti con insufficienza renale e necessità di CRRT
- Uso di CytoSorb come terapia aggiuntiva per 24 ore

Obiettivi:

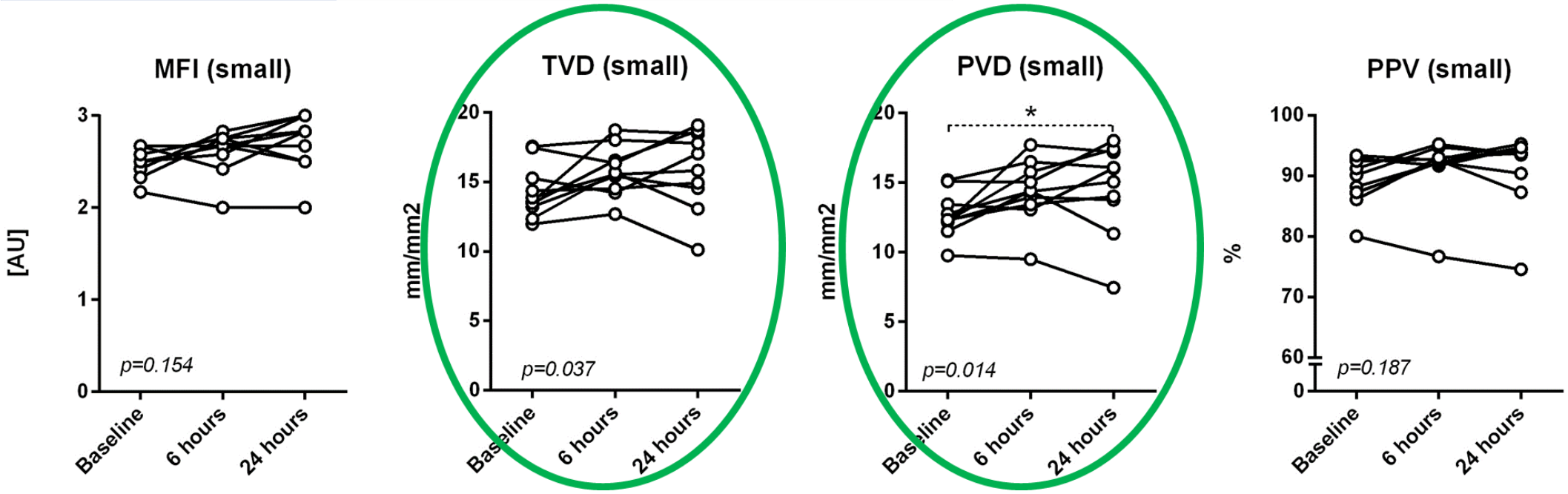
- Valutazione delle variabili del microcircolo (MFI, PPV, TVD, PVD)
- Valutazione dell'ossigenazione tissutale
- Valutazione dell'impatto sulle variabili della macroemodinamica (CI, GEDI, SVRI, MAP, HR, lactates, ScvO2) e dosaggio vasopressori

Blood Purification Sept 2019

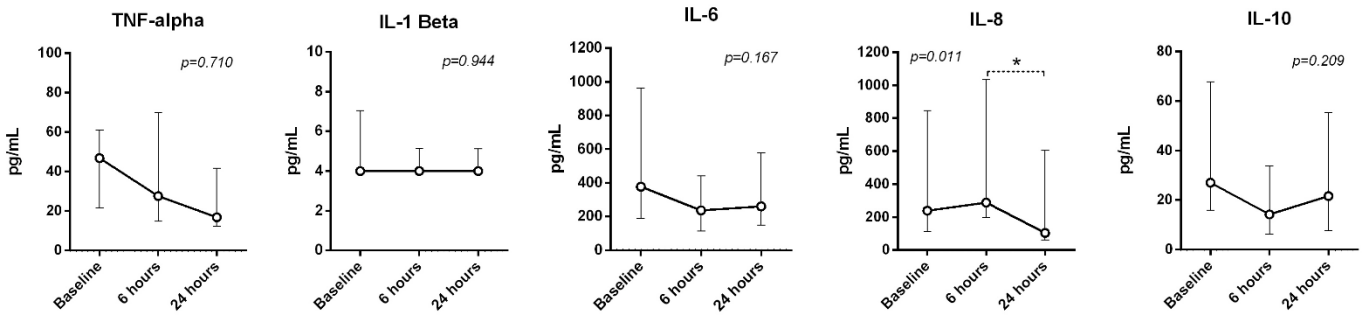
	Baseline	6 hours	24 hours	p*
Total small Vessel Density (mm/mm^2)	13.7 [13.0-15.8]	15.6 [14.4-16.9]	16.4 [14.2-18.5]	0.037
Perfused small Vessel Density (mm/mm^2)	12.3 [12.0-13.9]	14.4 [13.3-15.9]	15.5 [13.1-17.2]#	0.014
Microvascular Flow Index [AU]	2.50 [2.33-2.60]	2.67 [2.54-2.75]	2.83 [2.50-3.00]	0.154
Percentage of Perfused small Vessels (%)	89 [86-92]	92 [91-93]	93 [89-94]	0.187

Miglioramento del microcircolo statisticamente significativo in 24 ore:

- Densità piccoli vasi totale
- Densità piccoli vasi perfusi

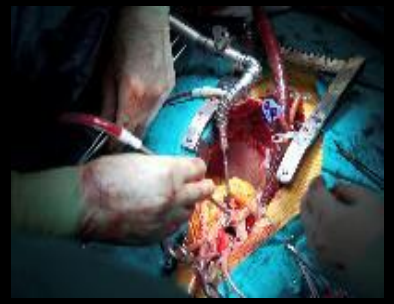


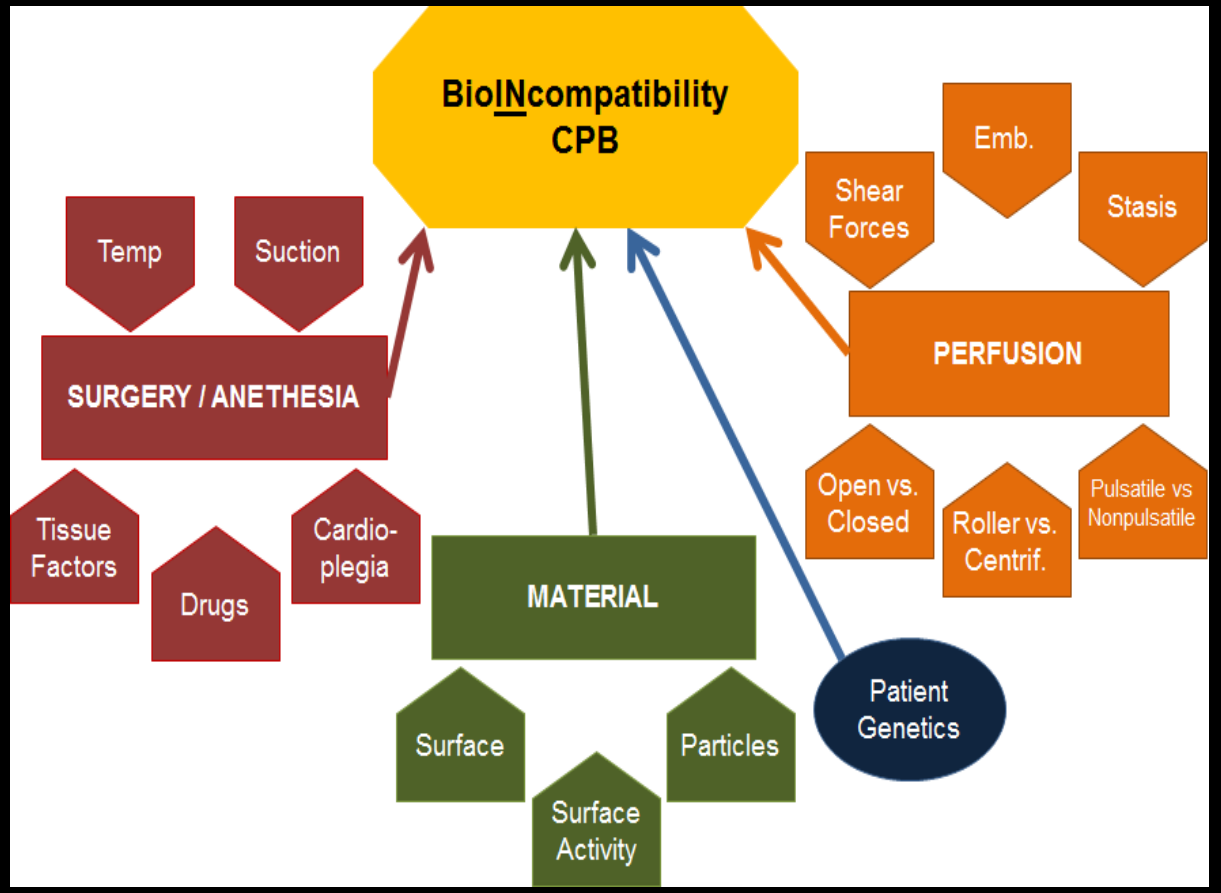
- **Riduzione citochinica in 24 ore, in particolare IL-8**
- **Stabilità dei valori di macroemodinamica**



Conclusioni:

- **La modulazione citochinica ha un impatto sul microcircolo, determinando un miglioramento delle variabili che lo caratterizzano;**
- **Si osserva una stabilità emodinamica senza peggioramenti;**
- **Vi è la necessità di un periodo di trattamento e di follow up più lungo di sole 24 h.**




BioINcompatibility
CPB
Temp
Suction
SURGERY / ANETHESIA
Tissue Factors
Drugs
Cardio-plegia
MATERIAL
Surface
Surface Activity
Particles
Patient Genetics
Shear Forces
Emb.
Stasis
PERFUSION
Open vs. Closed
Roller vs. Centrif.
Pulsatile vs Nonpulsatile

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SHORT COMMUNICATION

Hemoadsorption treatment of patients with acute infective endocarditis during surgery with cardiopulmonary bypass - a case series

Karl Träger[1], Christian Skrabal[2], Guenther Fischer[1], Thomas Datzmann[1], Janpeter Schroeder[1], Daniel Fritzler[1], Jan Hartmann[1], Andreas Liebold[2], Helmut Reinelt[1]

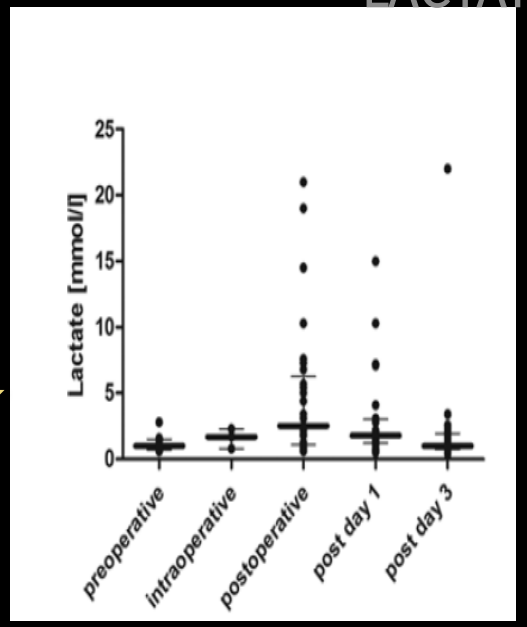
[1] Department of Cardiac Anesthesiology, University Hospital Ulm, Ulm - Germany
[2] Clinic of Cardiothoracic and Vascular Surgery, University Hospital Ulm, Ulm - Germany

67 patients with infective endocarditis

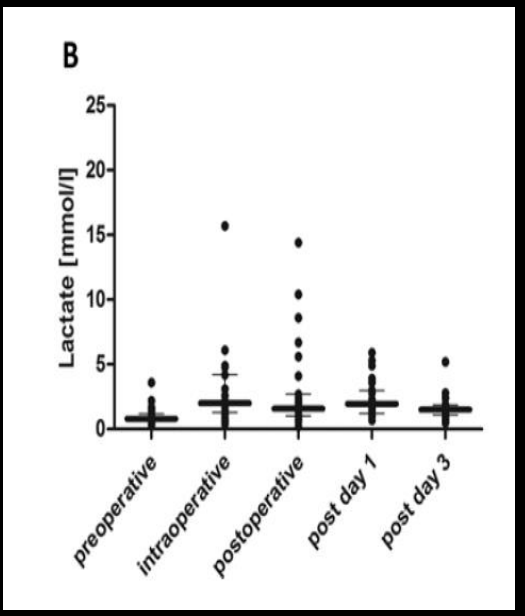
39 study group: CPB + CytoSorb

28 control grop: only CPB

LACTATE



Study group



Control group

- Hemodynamics improvement
- Reduction of noradrenaline dose

- Reduction of mean ICU stay:
5 days for study group vs 7,5 days for control group

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
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Original Article

Impact of intraoperative cytokine adsorption on outcome of patients undergoing orthotopic heart transplantation – an observational study

Endre Nemeth, Eniko Kovacs, Kristof Racz, Adam Soltesz, Szabolcs Szigeti, Nikolett Kiss, Gergely Csikos, Kinga B. Koritsanszky, Viktor Berzsenyi, Gabor Trembickij, Szabolcs Fabry, Zoltan Prohaszka, Bela Merkely, Janos Gal

84 patients undergoing orthotopic heart transplantation

24 study group: CPB+CytoSorb
60 control group: CPB only

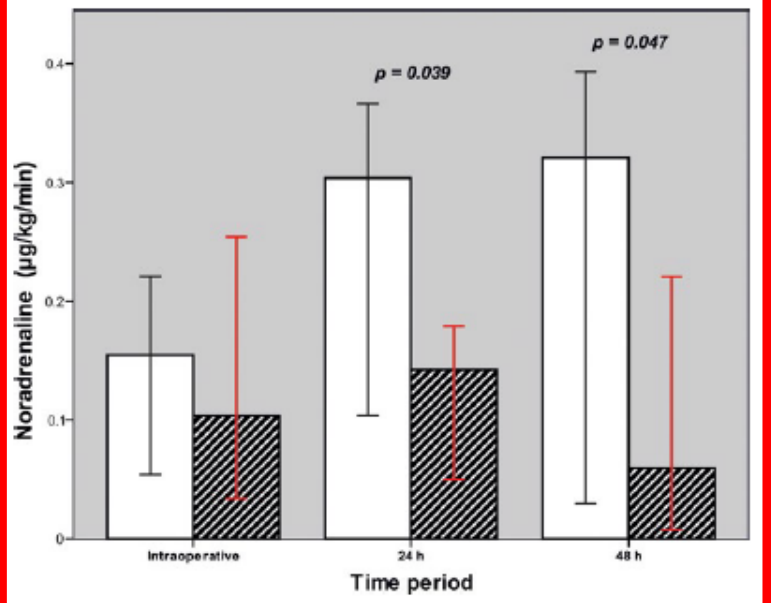
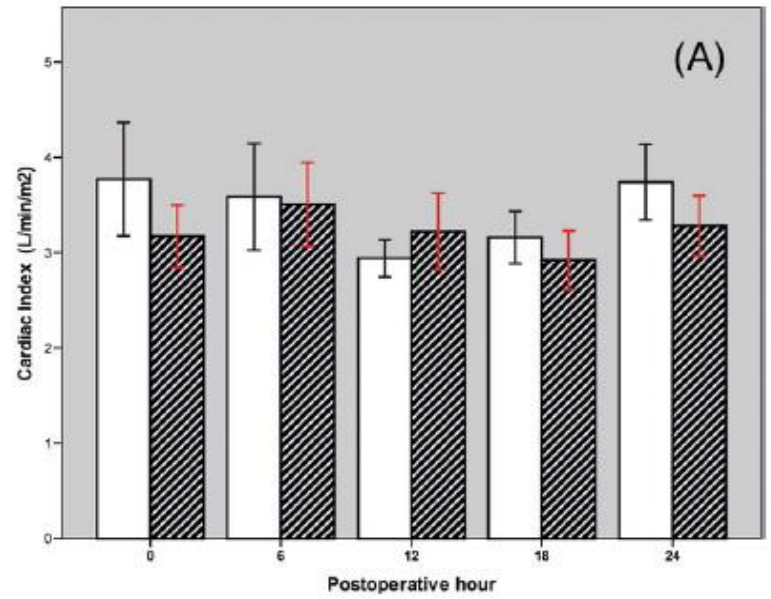


FIGURE 1 Comparison of noradrenaline requirements in the early postoperative period. Blank bar demonstrates control group and striped bar indicates CytoSorb™-treated patients. Data are presented as medians. Error bars show 95% confidence interval. Wilcoxon rank-sum test



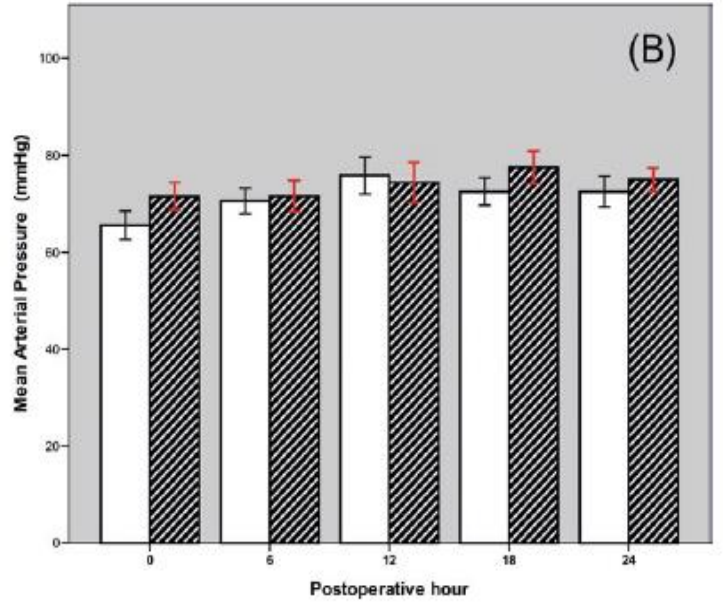


FIGURE 2 Cardiac index (A) and mean arterial pressure (B) during the first 24 h after orthotopic heart transplantation. Blank bar demonstrates controls and striped bar indicates CytoSorb™-treated patients. Data are presented as means. Error bars show standard error of the mean. Paired *t* test

Artificial Organs

Blood Purification With CytoSorb in Critically Ill Patients: Single-Center Preliminary Experience

*Maria Grazia Calabrò, *Daniela Febres, *Gaia Recca, *Rosalba Lembo, *Evgeny Fominskiy, *Anna Mara Scandroglio, *†Alberto Zangrillo, and *†Federico Pappalardo

*Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute; and †Vita-Salute San Raffaele University of Milan, Milan, Italy

40 heart patients with MOF

- 19 ECMO
- 11 IABP
- 9 IMPELLA
- 6 VAD
- 18 CRRT

Installed into ECMO or HP

40 heart patients with MOF

- 28 cardiogenic shock
- 2 septic shock
- 9 ARDS
- 1 liver failure

TABLE 3. *Peak and end treatment values*

Values	Peak during treatment	End of treatment	*P* value
Total bilirubin (mg/dL)	11.6 ± 9.2	6.8 ± 5.1	0.005
Lactate (mmol/L)	12.1 ± 8.7	2.9 ± 2.5	<0.001
CPK (U/L)	2416 (670–8615)	281 (44–2769)	<0.001
LDH (U/L)	1230 (860–3157)	787 (536–1148)	<0.001

Expected mortality 80%

Actual mortality 52,5%

Evidenze cliniche e diffusione della terapia con CytoSorb

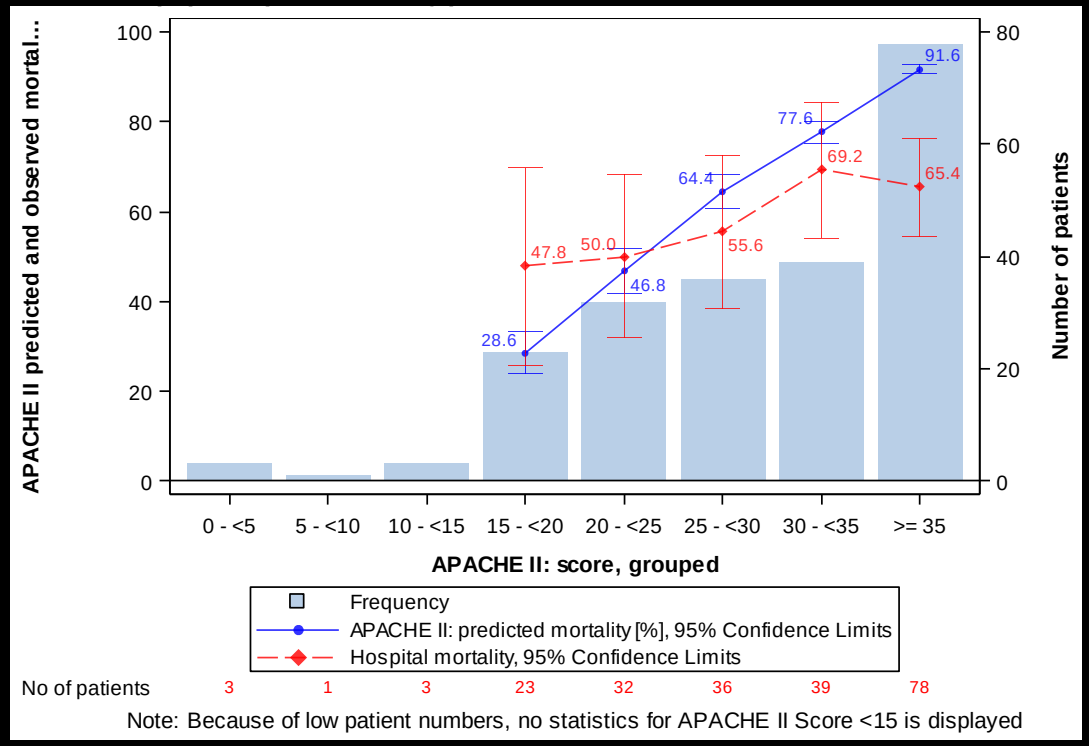
	Dic 18	Mag 18	Dic 17	Set 16	Ago 15
Trattamenti con CytoSorb					
Totale	51.000	40.000	31.000	14.000	5.500
Numero pazienti documentati/pubblicati	1.701	1.487	1.234	575	187
Trattamenti documentati/pubblicati	2.722	2.442	1.978	923	376
Publicazioni					
Totale (pubblicazioni, letture e *case of the week*)	242	207	177	92	20
Peer-reviewed	66	52	48	28	18
Totale trattamenti in pubblicazioni peer-reviewed	909	767	728	368	191
Registro CytoSorb					
Centri iscritti nel mondo	218	189	164	115	60
Pazienti inclusi	624	500	411	152	0
Trial Clinici					
Numero di studi su clinicaltrials.gov	31 / 14	30	15	12	10
Studi completati su clinicaltrials.gov	10 / 8	8	4	2	2

	Giugno 2019	Settembre 2018	Dicembre 2017	Agosto 2017	Settembre 2016	Agosto 2015
N° centri nel mondo	253	210	167	148	115	60
N° pazienti inclusi	748	574	426	369	152	0

Parameter	Sepsis / septic shock	N (296)	Cardiac surgery with CPB - preemptive	N (58)	Cardiac surgery with CPB - postoperative	N (43)	Other indication	N (98)
SOFA: score								
T1 Mean ± Std [Range]	16.0 ± 4.3 [3 – 24]	262	11.2 ± 3.9 [4 – 21]	40	16.5 ± 2.8 [9 – 21]	42	13.8 ± 5.0 [2 – 23]	82
T2 Mean ± Std [Range]	15.7 ± 5.0 [1 – 24]	178	12.8 ± 2.9 [7 – 19]	48	17.3 ± 2.4 [12 – 22]	40	14.0 ± 5.4 [2 – 23)	76
CRP [mg/L]								
T1 Mean ± Std [Range]	187.1 ± 140.8 [1 – 611]	261	73.5 ± 83.1 [0.1 – 300]	56	71.8 ± 98.7 [0.4 – 521]	43	107.8 ± 115.2 [1 – 495]	78
T2 Mean ± Std [Range]	159.0 ± 114.4 [2 – 626]	166	109.0 ± 80.2 [1 – 332]	56	117.6 ± 80.1 [1 – 290]	40	126.5 ± 98.8 [7 – 368]	64
PCT [ng/mL]								
T1 Mean ± Std [Range]	46.2 ± 99.2 [0 – 995]	254	2.5 ± 5.0 [0 – 17.4]	24	19.5 ± 23.8 [0.2 – 100.0]	33	16.6 ± 33.3 [0.1 – 179]	62
T2 Mean ± Std [Range]	30.9 ± 71.0 [0.4 – 605]	166	5.5 ± 8.4 [0.1 – 45]	31	20.3 ± 22.9 [0.7 – 100]	30	7.7 ± 16.2 [0.2 – 95]	54
IL6 [pg/mL]]*								
T1 Median [Range]	5000 [20 – > 10^7]	124	40 [2 – 5000]	36	432 [69 – 5000]	35	646 [65– 122500]	32
T2 Median [Range]	292 [0 – 22327]	85	288 [0 – 2232]	43	59 [12 – 2300]	30	106 [0.1 - 6263]	22
Length of ICU stay [days] Mean ± Std [Range]	29.8 ± 26.0 [2 – 165]	106***	6.2 ± 4.2 [1 – 20]	53***	14.8 ± 7.9 [7 – 43]	34***	27.6 ± 24.5 [2 – 116]	53***
Number (%) of deaths**	190 (64.2 %)	296	6 (10.3 %)	58	8 (18.6 %)	43	47 (48.0 %)	98

* Note: IL6 values measured outside the predefined 1 hour intevall included (later, or before cytosorb)

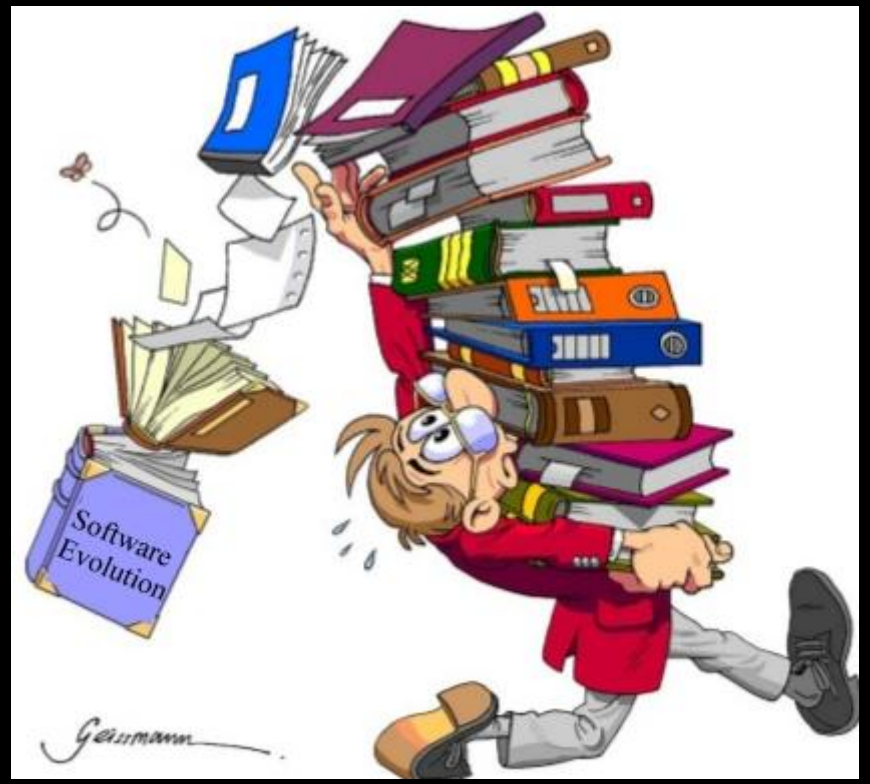
** Patients with unknown outcome at data base close have been counted as (still) alive



LEGENDA

~ Razionale della “blood purification”
~ Adsorbimento con Cytosorb: come rimuove e che cosa rimuove
~ Indicazioni al trattamento
~ Adsorbimento nella sepsi
~ Studi in vitro
~ Studi clinici

~ Conclusioni



- Many **extracorporeal therapies** have been investigated as adjuvant therapies for septic patients, especially for cytokines storm modulation.
- CytoSorb is an additional therapy potentially able to remove a **large spectrum of molecules**, alone and/or in **combination with any extracorporeal circuits, including CRRT**.

- CytoSorb might be a potential therapy for septic patients non responder to conventional treatments, especially when is used **early**.

- The adsorption of **bilirubin, bile acids and ammonia** can support liver function in patients with hyperbilirubinemia until liver spontaneous regeneration and functional recovery.

- The adsorption of **myoglobin and muscle dmage enzymes** can help treating rhabdomyolysis and preventing/solving AKI.

- Clinical patient's condition is important to define the length of CytoSorb treatment.