



Cytokine removal in sepsis

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Rationale of extracorporeal cytokine removal





Interpreting biomarkers in infectious diseases in intensive care unit: the potential role of procalcitonin

Fatime Hawchar, Zsolt Molnar

J Emerg Crit Care Med 2018;2:107

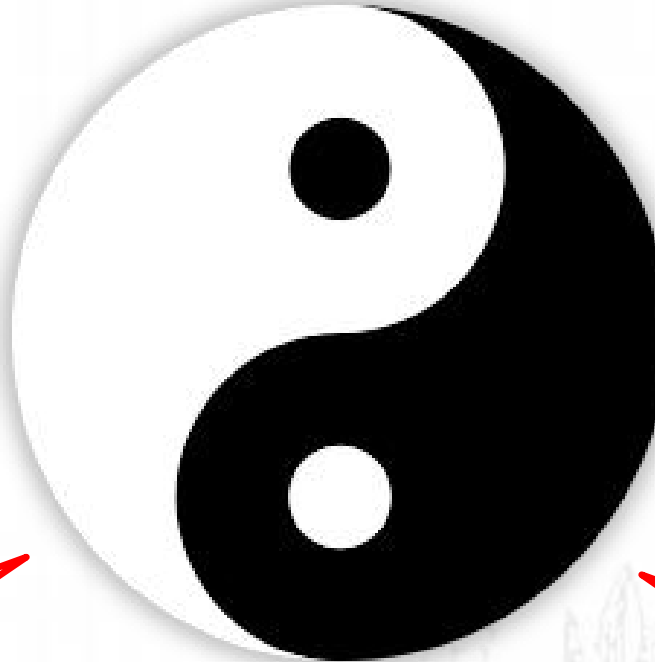


Acid

Pro-coagulation

Oxidants

Pro-inflammation



Base

Anti-coagulation

Anti-oxidants

Anti-inflammation

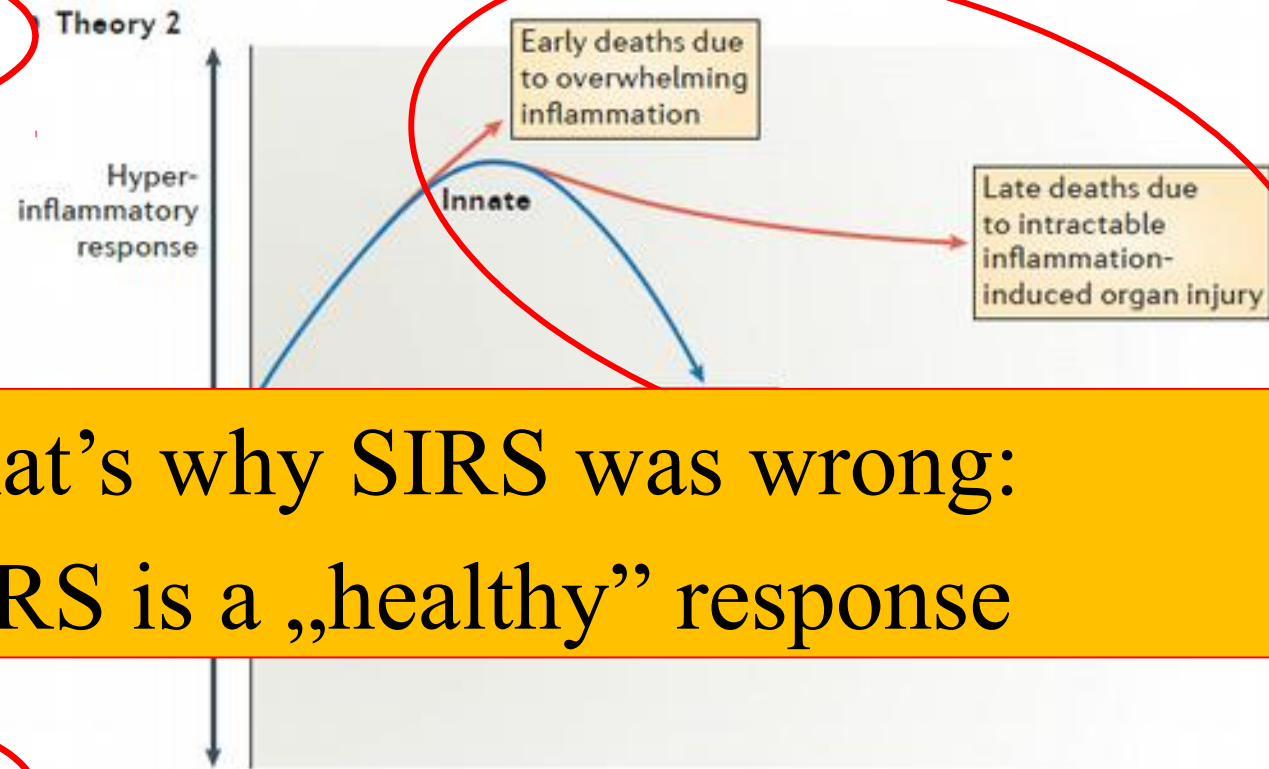


Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss¹, Guillaume Monneret² and Didier Payen³

Nature Reviews | Immunology Volume 13 | December 2013 | 862-874

Pro-
inflammation



That's why SIRS was wrong:
SIRS is a „healthy” response

Anti-
inflammation



The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH



Table 2. Terminology and International Classification of Diseases Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology ^{9,10}	Severe sepsis Sepsis-induced hypoperfusion	Septic shock ^{1,3}
2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
Clinical	Suspected or documented infection and an acute increase of ≥ 2 SOFA points (a proxy for organ dysfunction)	Sepsis ^a and vasopressor therapy needed to elevate MAP ≥ 65 mm Hg and lactate > 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation ^{1,3}
Recommended primary ICD codes ^a		
ICD-9	995.92	785.52
ICD-10 ^a	R65.20	R65.21
Framework for implementation for coding and research	Identify suspected infection by using concomitant orders for blood cultures and antibiotics (oral or parenteral) in a specified period ^b Within specified period around suspected infection ^c : 1. Identify sepsis by using a clinical criterion for life-threatening organ dysfunction 2. Assess for shock criteria, using administration of vasopressors, MAP < 65 mm Hg, and lactate > 2 mmol/L (18 mg/dL) ^d	

Organ dysfunction
+
dysregulated host
response





Cytokine adsorbtion...



To regain balance!

**...and not only in septic patients but in any condition with a
CYTOKINE STORM!**



How does it work?

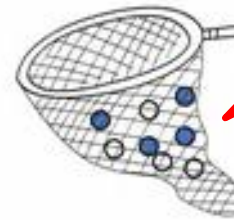
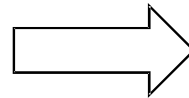
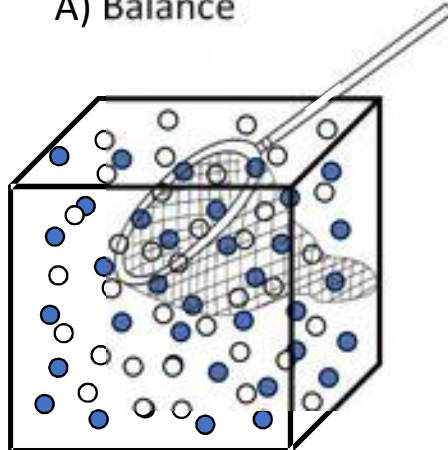




Let's go fishing!



A) Balance



Capture rate:
1:1

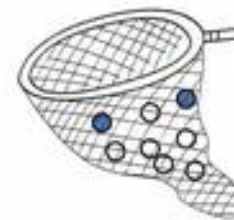
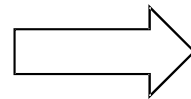
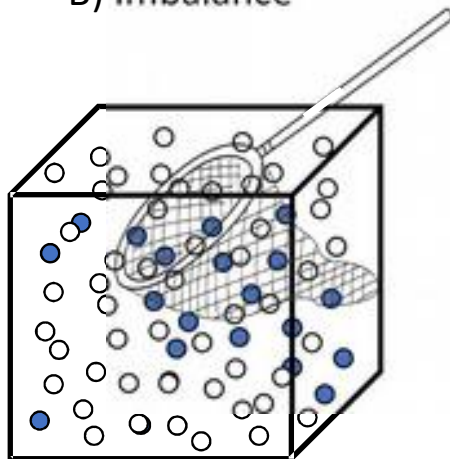
- Proinflammatory molecule
- Antiinflammatory molecule



Let's go fishing!



B) Imbalance



Capture rate:
Lot:Few

- Proinflammatory molecule
- Antiinflammatory molecule



Multiple support

CRRT

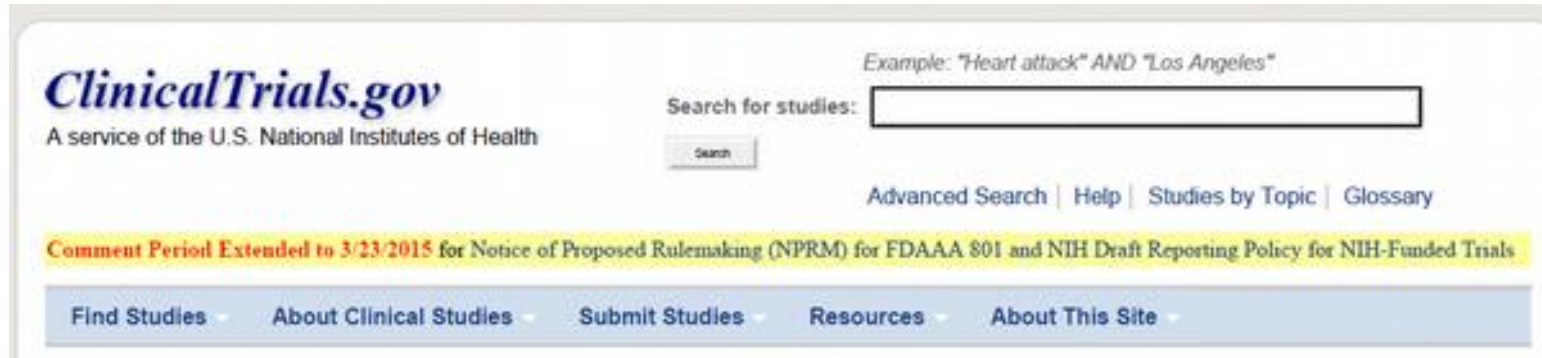
CytoSorb

ECMO





Attenuating the cytokine storm early?



The ACCESS trial

Adsorption of Cytokines Early in Septic Shock

Verified November 2014 by Szeged University

First received: November 5, 2014

The 1st PRCT on CytoSorb as a standalone therapy in septic shock



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,*}

Nándor Öveges



Ildiko Laszlo



Fathime Hawchar

Thank you!



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



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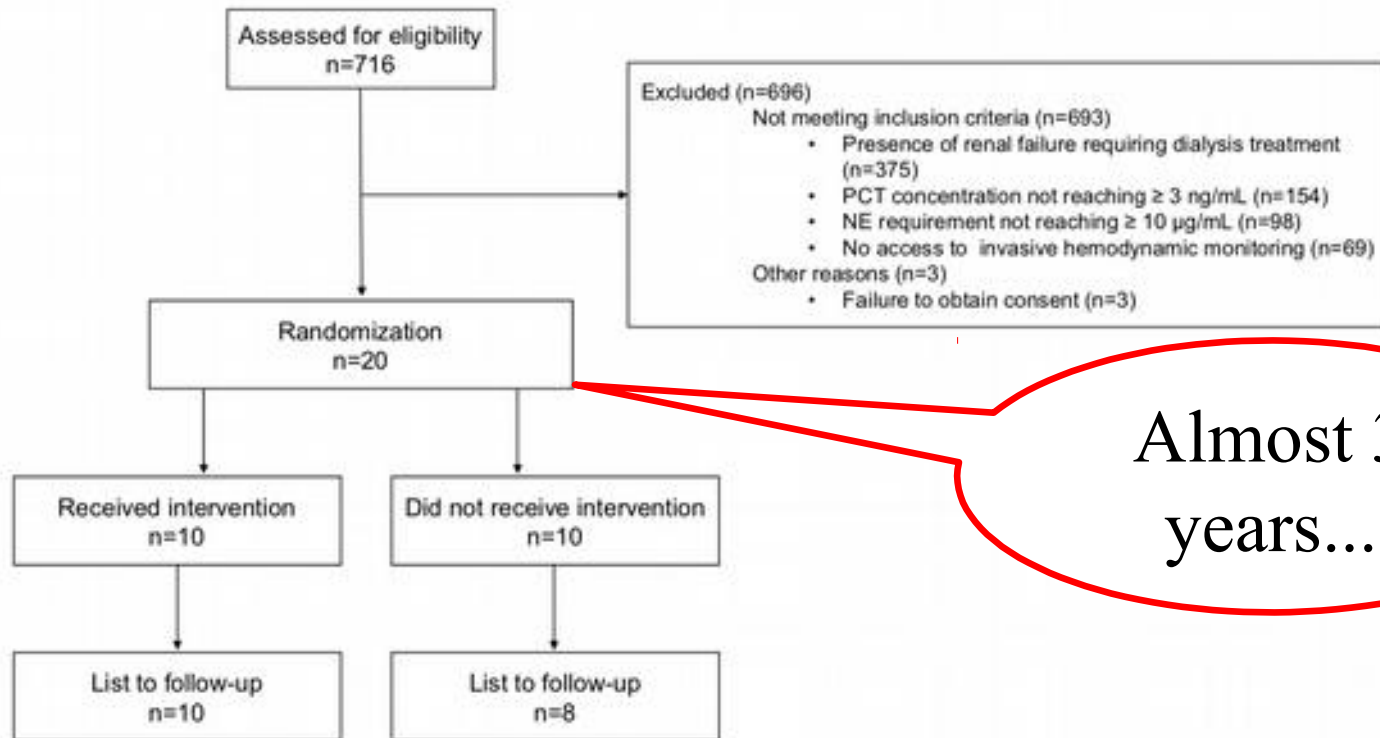
- Suspected sepsis of medical etiology < 24h
- IPPV
- PCT >3 ng/ml
- Norepinephrine $\geq 10 \mu\text{g}/\text{min}$
- PiCCO confirmed normovolemia and CO
- Signs of hypoperfusion: ScvO₂, lactate, dCO₂, oliguria metabolic acidosis
- Exclusion: need of CRRT



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



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Almost 3 years...



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

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Check for updates

- Suspected sepsis of medical etiology
- IPPV
- PCT ~~> 3~~ ng/ml
- Norepinephrine $\geq 10 \mu\text{g}/\text{min}$
- PiCCO confirmed normovolemia and CO
- Signs of hypoperfusion: ScvO₂, lactate, dCO₂, oliguria metabolic acidosis
- Exclusion: need of CRRT

Is PCT an appropriate marker?



ACCESS – PCT and cytokines

(Laszlo I, et al. Unpublished data)

Spearman's rho		hIL-10 (pg/ml)	hIL-1a (pg/ml)	hIL-1ra (pg/ml)	hIL-6 (pg/ml)	IL-10	Arterenol (µg/min)	PCT (ng/ml)	CRP (mg/l)
hIL-10 (pg/ml)	Correlation Coefficient	1,000	,064	,383**	,160	,458*	,383**	,421**	,076
	Sig. (2-tailed)		,631	,003	,225	,000	,003	,001	,569
	N	59	59	59	59	59	59	59	58
hIL-1a (pg/ml)	Correlation Coefficient	,064	1,000	-,076	-,092		-,097	,009	-,040
	Sig. (2-tailed)	,631		,569	,488		,465	,944	,764
	N	59	59	59	59		59	59	58
hIL-1ra (pg/ml)	Correlation Coefficient	,383**	-,076	1,000	,660**		,383**	,256	,205
	Sig. (2-tailed)	,003	,569		,000		,000	,050	,123
	N	59	59	59	59		59	59	58
hIL-6 (pg/ml)	Correlation Coefficient	,160	-,092	,660**	1,000		,160	,330*	,512**
	Sig. (2-tailed)	,225	,488	,000			,576**	,011	,000
	N	59	59	59	59		59	59	58
hIL-8 (pg/ml)	Correlation Coefficient	,458**	-,240	,544**	,312*		,430**	,473**	-,109
	Sig. (2-tailed)	,000	,067	,000	,016		,001	,000	,416
	N	59	59	59	59		59	59	58
hTNF-a (pg/ml)	Correlation Coefficient	,383**	,005	,295*	,295*		,123	,300*	,027
	Sig. (2-tailed)	,003	,970	,023	,024		,003	,021	,839
	N	59	59	59	59		59	59	58

IL-10

IL-1ra

IL-6

IL-8

TNF-α

PCT may be an appropriate biomarker to monitor Cytokine Storm

CRP (mg/l)	Correlation Coefficient	,076	-,040	,205	,512**	,109	,027	,000	1,000
	Sig. (2-tailed)	,569	,764	,123	,000	,416	,839	,001	,000
	N	58	58	58	58	58	58	58	58

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)



ACCESS results





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,*}

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.



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

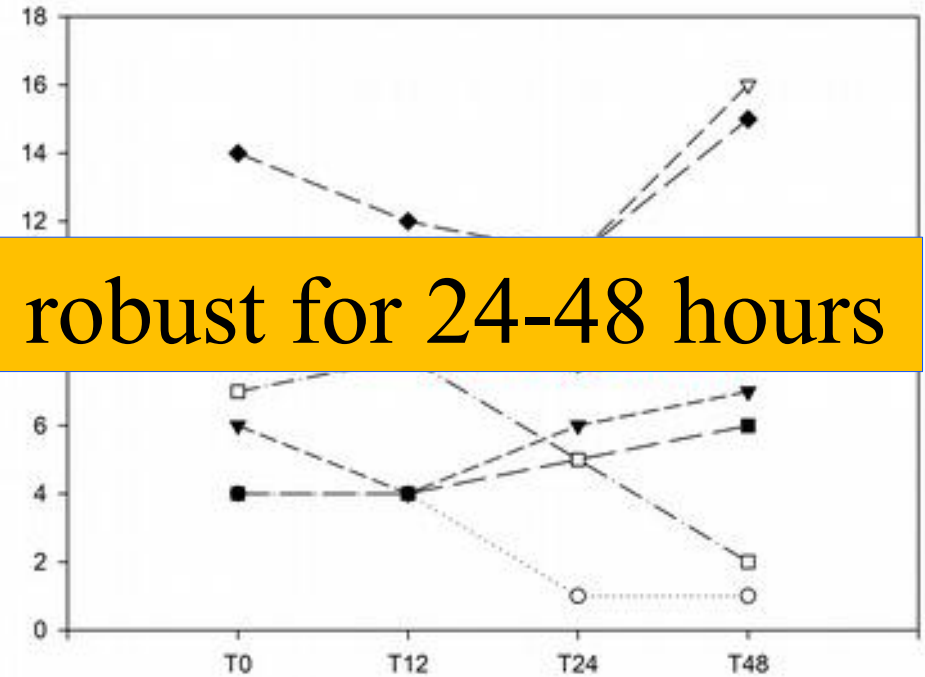
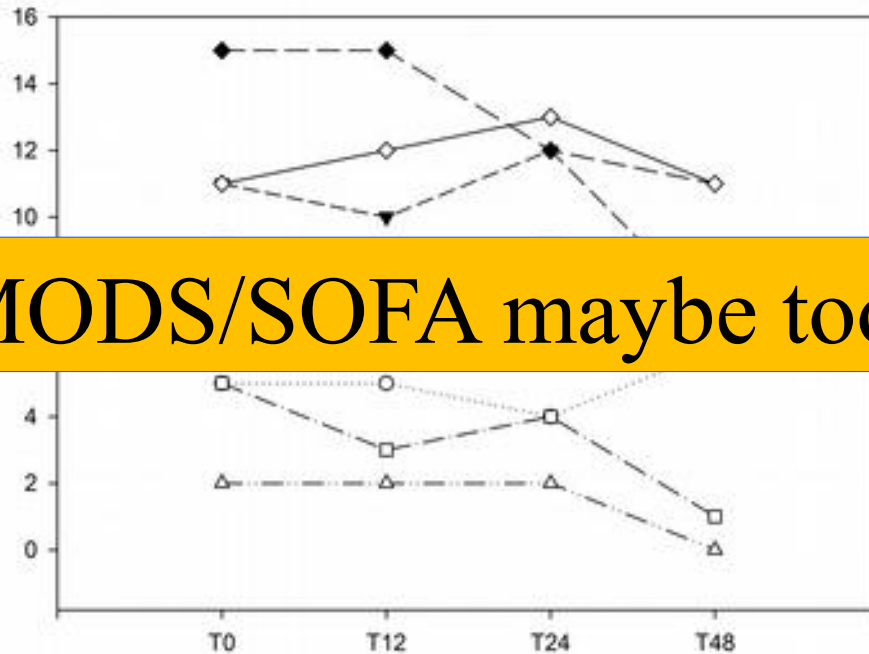


Fatime Hawchar ^a, Ildikó László ^a, Nándor Öveges ^a, Domonkos Trásy ^a, Zoltán Ondrik ^b, Zsolt Molnar ^{a,*}

MODS

Control

CytoSorb



MODS/SOFA maybe too robust for 24-48 hours

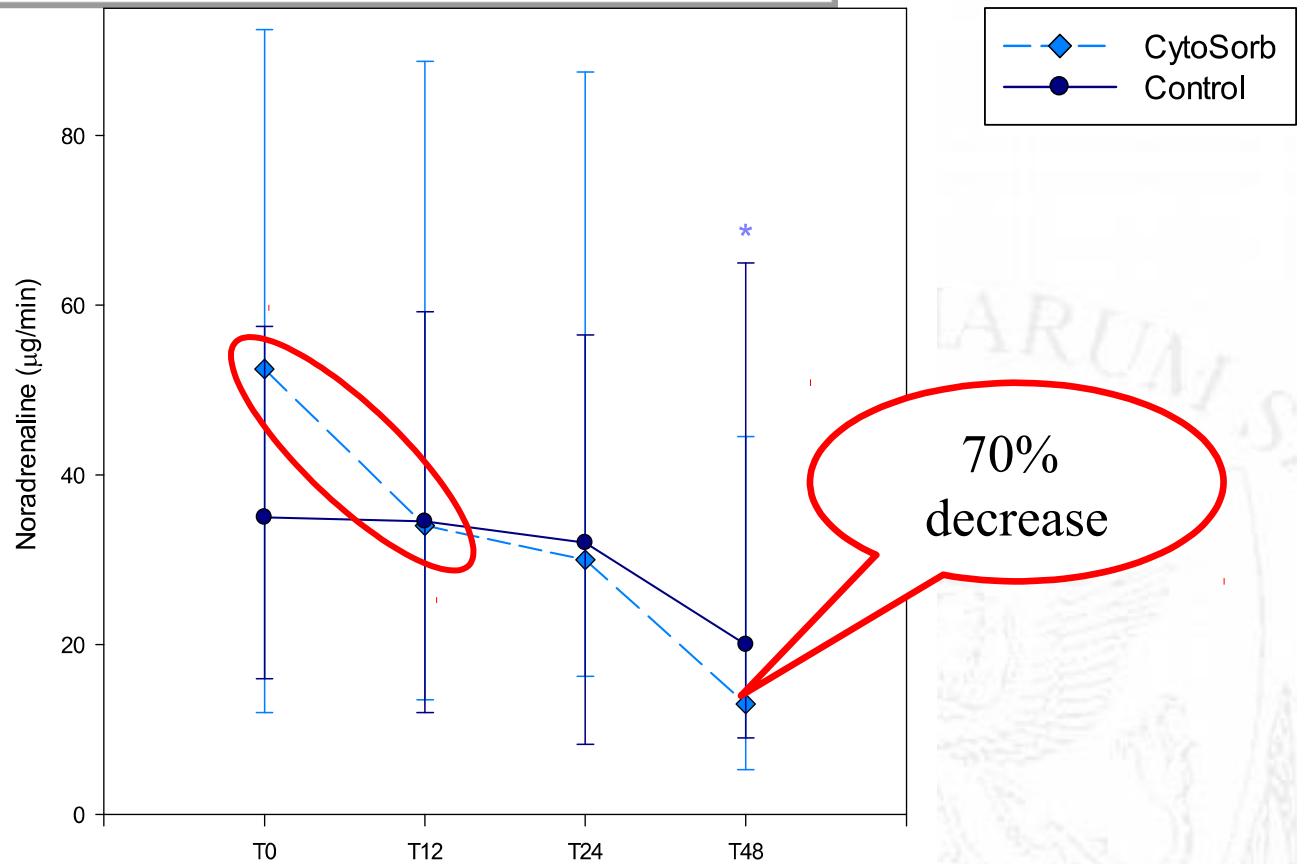


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Vasopressor



Data are shown as median and interquartile ranges
*p<0.05 vs. T₀

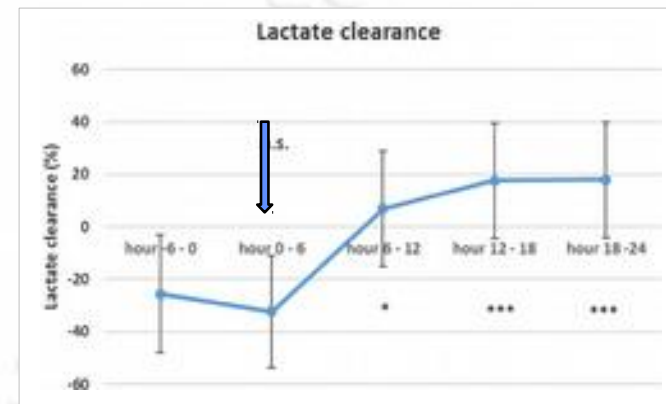
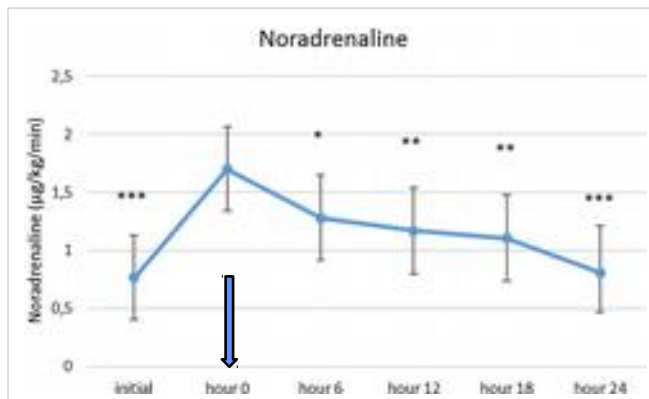


Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study

Sigrun Friesecke¹ · Stephanie-Susanne Stecher¹ · Stefan Gross² · Stephan B. Felix^{1,2} · Axel Nierhaus³

>80% risk

SOFA score	14.3 ± 3.0
SAPS II	70.4 ± 10.9
Interleukin-6 (ng/l)	25,523 (1052/491260)
Procalcitonin (µg/l)	16 (1.3/776)



Shock reversal 65% & observed mortality: 55%



Case series 13 surgical 13 medical on CRRT

RESEARCH

Open Access



Hemoadsorption by CytoSorb in septic patients: a case series

Klaus Kogelmann^{1*}, Dominik Jarczak², Morten Scheller¹ and Matthias Drüner¹

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

Conclusion: Hemoadsorption using CytoSorb resulted in rapid hemodynamic stabilization and increased survival, particularly in patients in whom therapy was started early. Given the positive clinical experience of this case series, randomized controlled trials are urgently needed to define the potential benefits of this new treatment option.

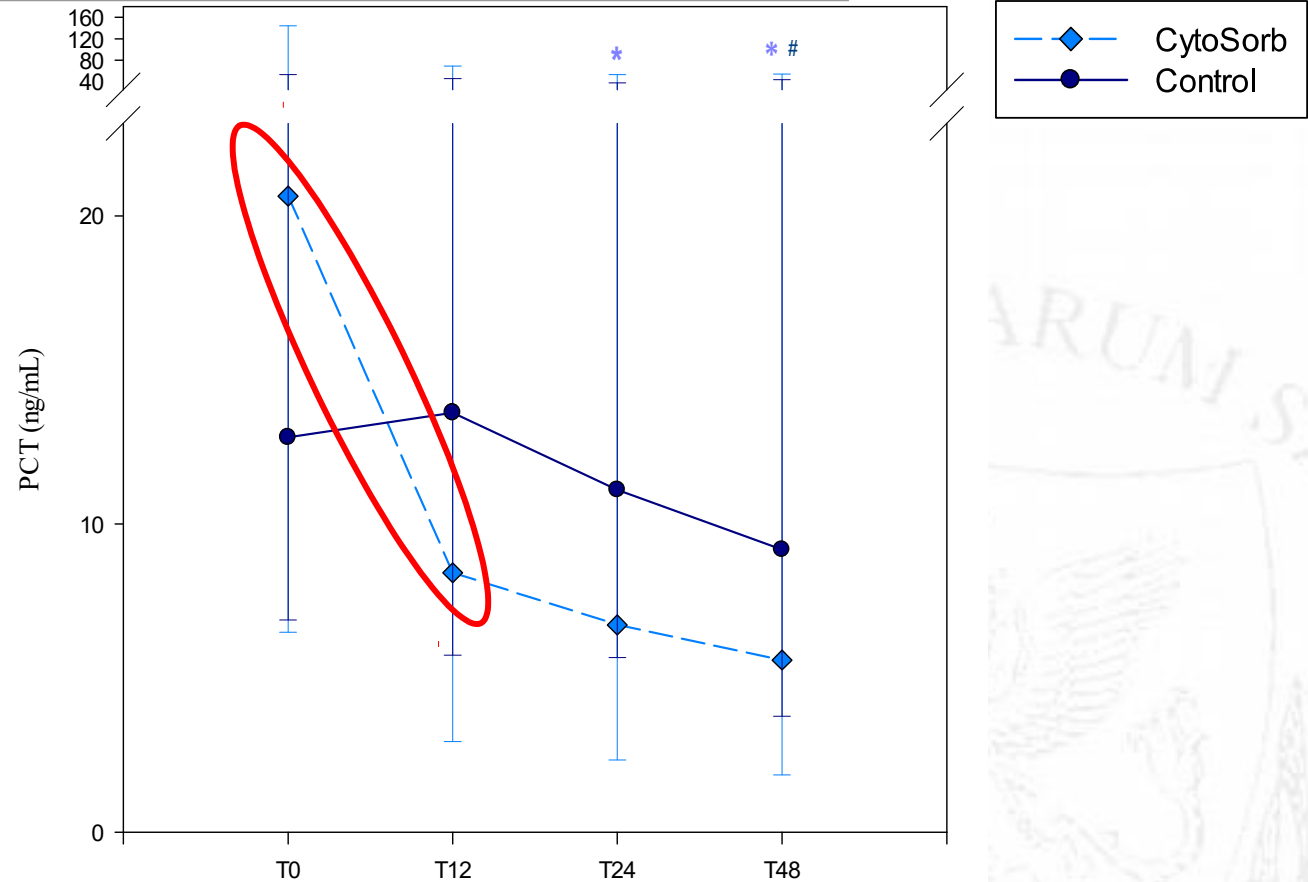


Extracorporeal cytokine adsorption in septic shock: A proof of concept randomized, controlled pilot study



Fatime Hawchar ^a, Ildikó László ^a, Nándor Öveges ^a, Domonkos Trásy ^a, Zoltán Ondrik ^b, Zsolt Molnar ^{a,*}

PCT



Data are presented as median and interquartile ranges

*p<0.05 vs. T₀CytoSorb, #p<0.05 vs. T₀Control



ACCESS Spin Off – preliminary results



Procalcitonin elimination during cytokine adsorption therapy in septic shock: a spin-off study of the ACCESS trial

R. Szegedi, L. Lakatos, M. Fogarasi, T. Kósa, P. Harkányi, P. Pálfi, A. Békési, B. Csabai, I. Földes, A. Árkai, B. Tóth, E. Góspál, Z. Major, P. Kóvacs, E. Bócskó

Department of Anesthesiology and Intensive Therapy, Semmelweis University, Department of Geriatrics, Semmelweis University, Department of Clinical Chemistry, Semmelweis University, Department of Hematology, Semmelweis University, Department of Internal Medicine, Semmelweis University

Introduction

According to *in vitro* data, levels of pro- and anti-inflammatory mediators can be markedly decreased in septic shock by hemoperfusion using a novel cytokine adsorbent Resay (CytoSort). However, the capacity and performance of the adsorbent over time has not yet been investigated. Our aim was determine elimination of procalcitonin (PCT) by the adsorbent *in vivo*, in patients with septic shock treated with CytoSort for 24 hours.

Materials & Methods

The current study is a spin-off part of the ongoing "Adsorption Cytokines Early in Septic Shock", the ACCESS trial. Cytokine therapy was commenced early (1-6h) after the onset of septic shock and performed for 24 hours. Blood samples were taken from the systemic circulation at every 6 hourly from the beginning (T₀) to the end of Cytokine therapy (T₆, T₁₂, T₁₈, T₂₄). Serum PCT, CRP, IL-6, IL-1ra, IL-6, IL-8, IL-10, TNF- α levels were measured. PCT levels were determined from blood taken simultaneously from the pre- and post-adsorbent samples. The efficacy of PCT elimination was defined at every step by subtracting post-adsorbent (PCT_{post}) values from pre-adsorbent (PCT_{pre}) values: $\Delta PCT = PCT_{pre} - PCT_{post}$.

Results

PCT kinetics

PCT elimination

*Legend: * between groups, # compared to T₀, % compared to T₀, & compared to T₆, & compared to T₁₂, & compared to T₁₈, & compared to T₂₄, p < 0.05*

Only were obtained from 7 patients and 8 treatments. Pre-adsorbent PCT levels showed a significant decline throughout the study (T₀:412 [18-842], T₆:468 [18-363], T₁₂:467 [48-102], T₁₈:59 [45-122], T₂₄:53 [15-112] ng/ml, p<0.01). Post-adsorbent PCT levels showed a similar pattern (p<0.02). The efficacy of net PCT elimination (ΔPCT) was most effective at T₆:117 [33-78] ng/ml, and showed a significant decline over time: T₆:23 [2-149] ng/ml, T₁₂:42 [32-63] ng/ml, T₁₈:41 [25-62] ng/ml, T₂₄:23 [0-23] ng/ml, p<0.04. This corresponded of a median of 50% elimination at T₆ 20% at T₂₄ with no further change from T₆-T₂₄. This pattern showed consistency in every patient and was independent of the vancomycin of PCT.

Conclusion

This study is the first to examine PCT elimination over time during CytoSort therapy. According to these results, PCT elimination showed an exponential decline from 50% to 10% by 24 hours. This phenomenon on the one hand shows the early efficacy of CytoSort therapy, while on the other hand, it raises the question of changing the adsorbent earlier than the current practice of 24 hours.

Acknowledgements

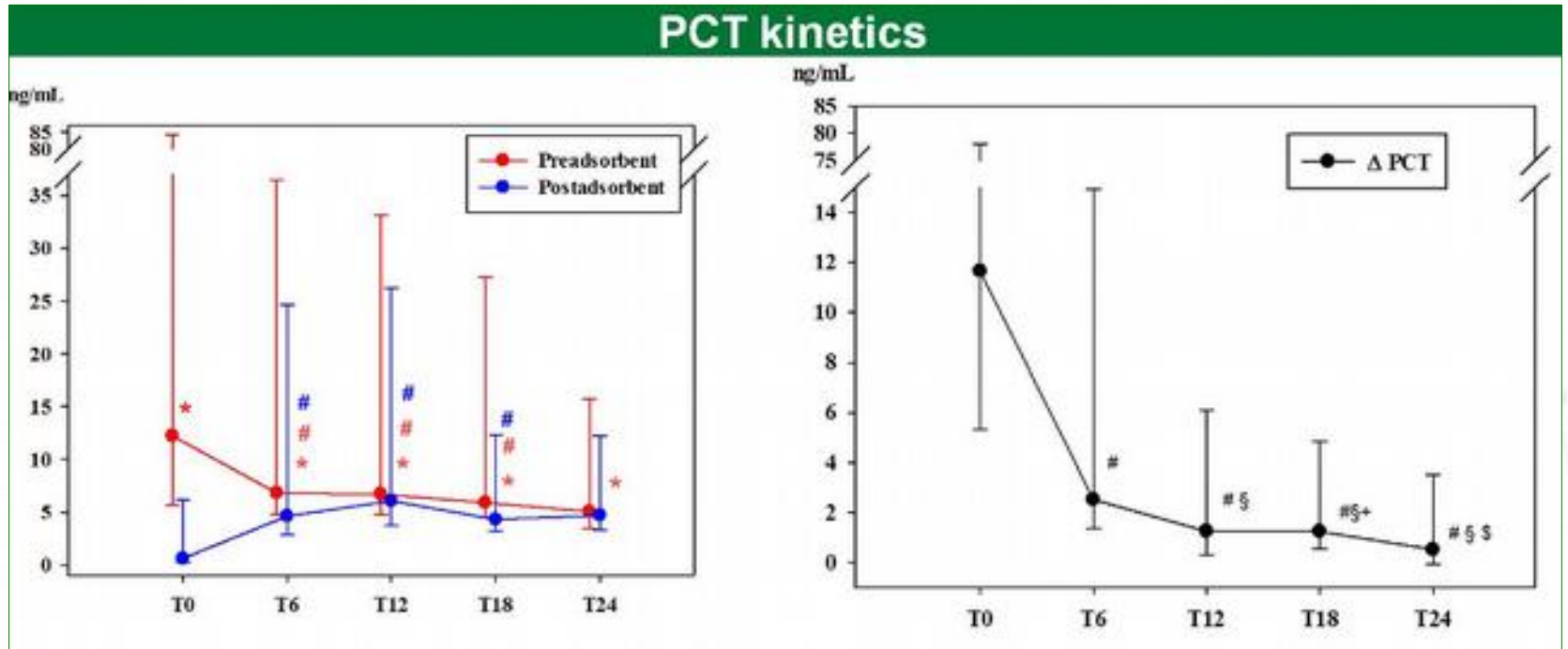
INNOVATION
ClinicalTrials.gov ID: NCT02388975



(ISICEM, 2017)



ACCESS Spin Off – preliminary results



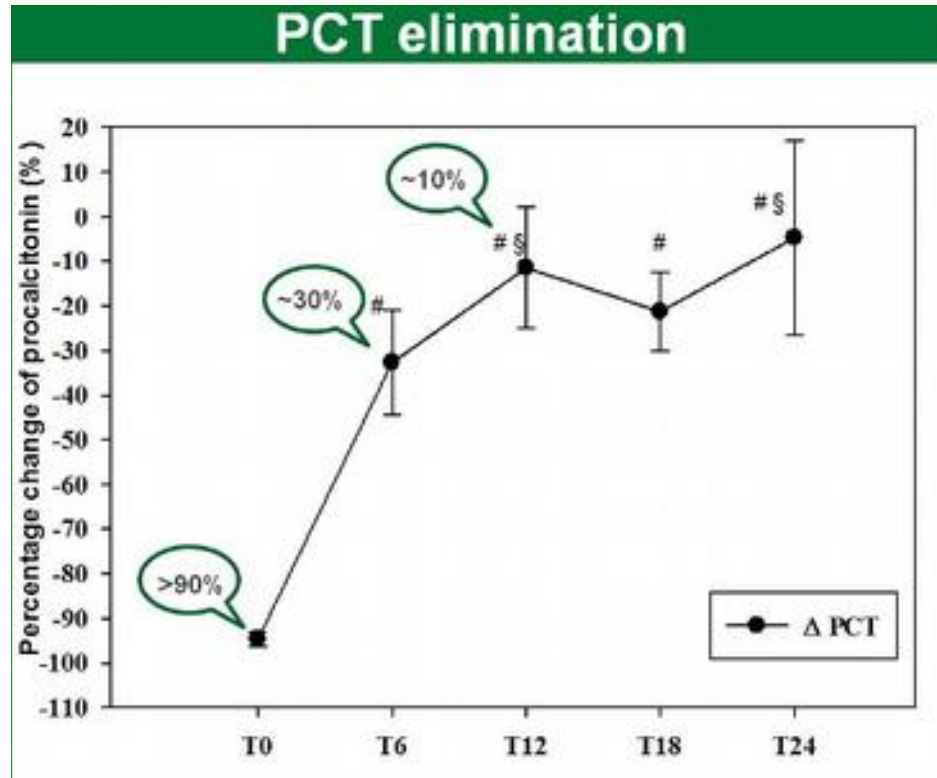
Post

Pre

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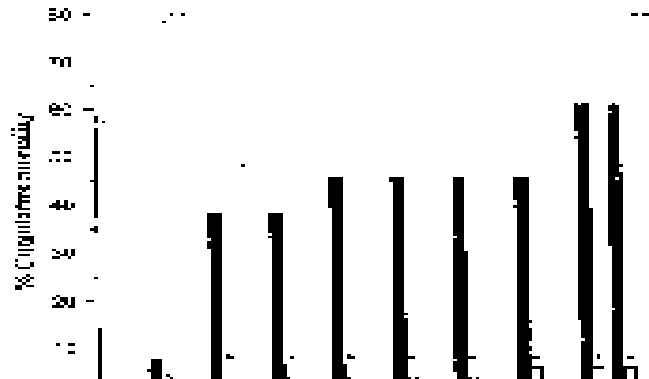
ACCESS Spin Off – preliminary results





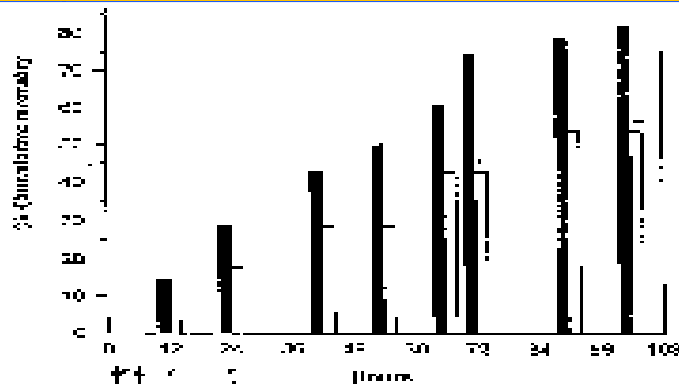
Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis.

(Nylen ES et al, *Crit Care Med* 1998; 26: 1001)



- Black column: control (*E. coli*)
- White: PCT-AS pretreatment + *E. coli*

PCT is toxic – removal maybe beneficial

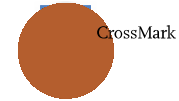


- Black: control (*E. coli*)
- White: *E. coli* + PCT-AS treatment



WHAT'S NEW IN INTENSIVE CARE

Hemoadsorption with CytoSorb[®]



Elettra C. Poli¹, Thomas Rimmelé^{2,3} and Antoine G. Schneider^{1*}

Conclusions and considerations for future studies

Numerous publications have assessed the efficacy of CytoSorb[®] HA in various clinical situations. Experimental models and observational series have suggested dramatic clinical improvement, while RCTs have not demonstrated any clinical benefit so far. However, their limited number and size as well as the relatively low severity of included patients preclude any final conclusion being drawn. Hence, further studies should focus on populations with very high inflammatory response ideally enriched with a pre-intervention test. Adequate target population determination is essential for future assessment of the device in order to prevent either abuse of its use or its fallacious abandonment. While we wait more evidence from these RCTs, the use of Cytosorb in clinical practice should take into account the absence of clear evidence for benefit, the potential for adverse effects and the cost.



The future:
**Cytokine Removal In Septic Shock
(CRISS) trial**

