Cytokine removal in sepsis

Prof. Zsolt Molnár

zsoltmolna@gmail.com

Department of Anaesthesia and Intensive Therapy

University of Szeged, Hungary

Rationale of extracorporeal cytokine removal

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

Fatime Hawchar, Zsolt Molnar

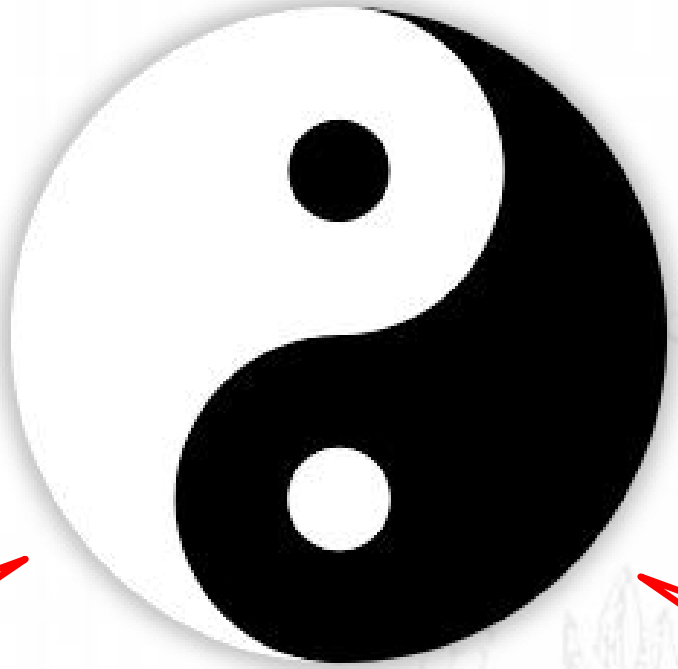
J Emerg Crit Care Med 2018;2:107

Acid

Pro-coagulation

Oxidants

Pro-inflammation



Base

Anti-coagulation

Anti-oxidants

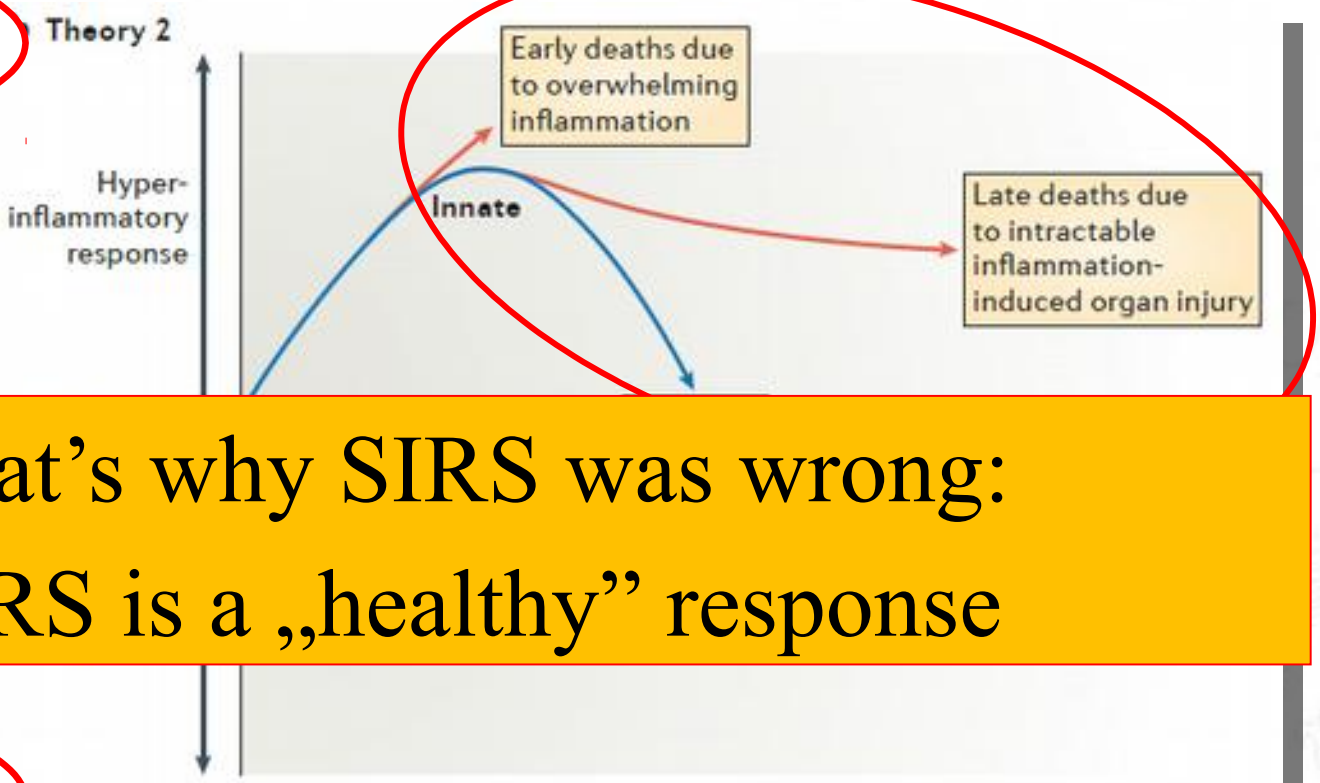
Anti-inflammation

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]

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

Pro-inflammation



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

Anti-inflammation

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

Organ dysfunction
+
dysregulated host response

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
...ical ...a	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]
...mended ...ary *ICD* ...des[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]	

Cytokine adsorbtion…

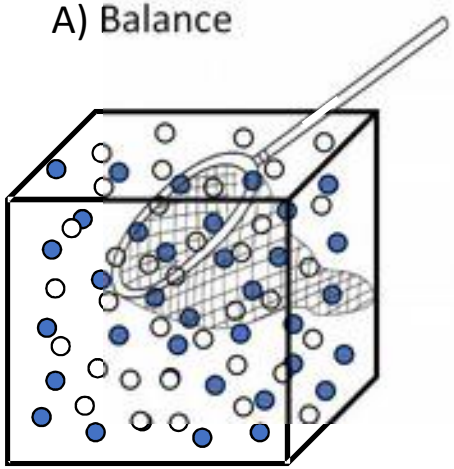
To regain balance!

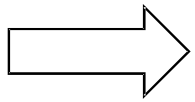
…and not only in septic patients but in any condition with a CYTOKINE STORM!

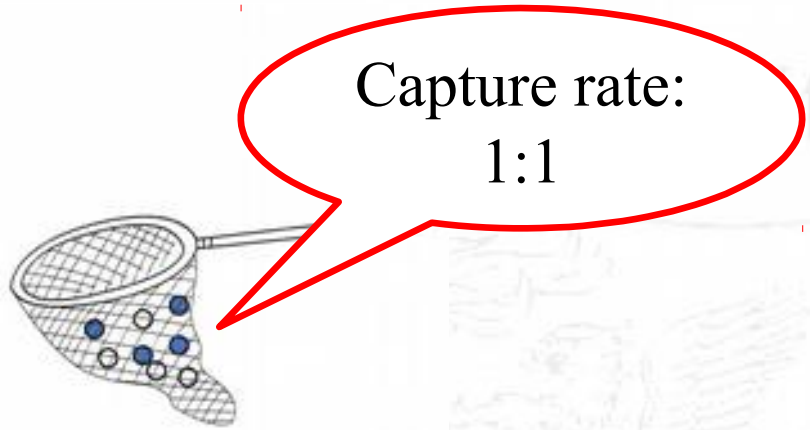
How does it work?

Let’s go fishing!

A) Balance



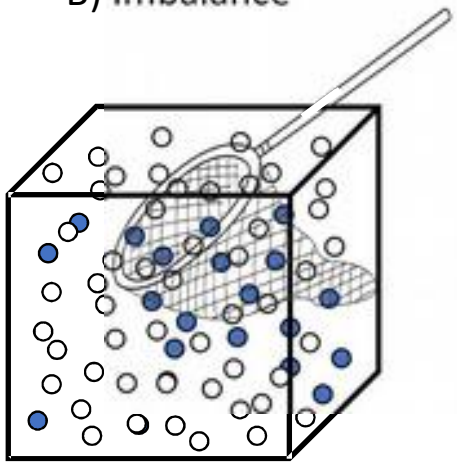




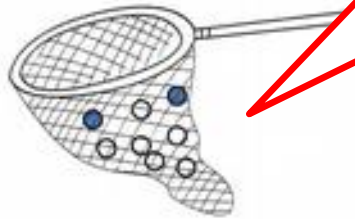
- Proinflammatory molecule
- Antiinflammatory molecule

Let’s go fishing!

B) Imbalance



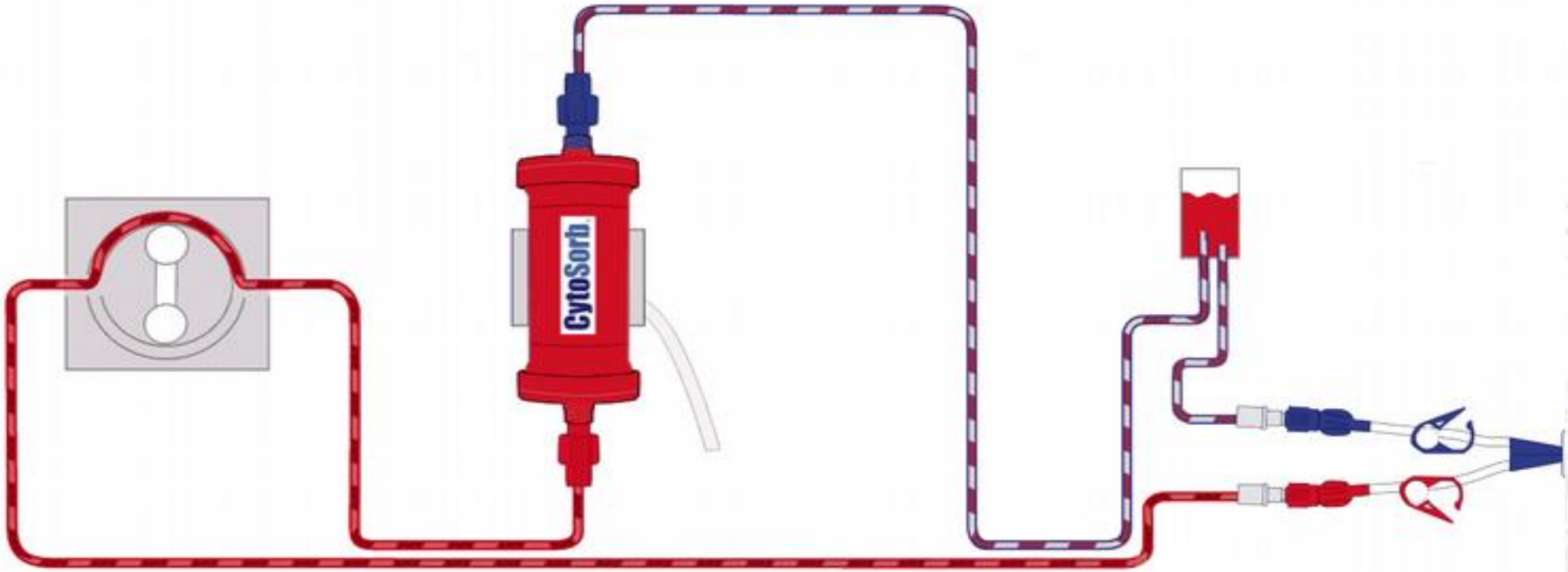
Capture rate:
Lot:Few



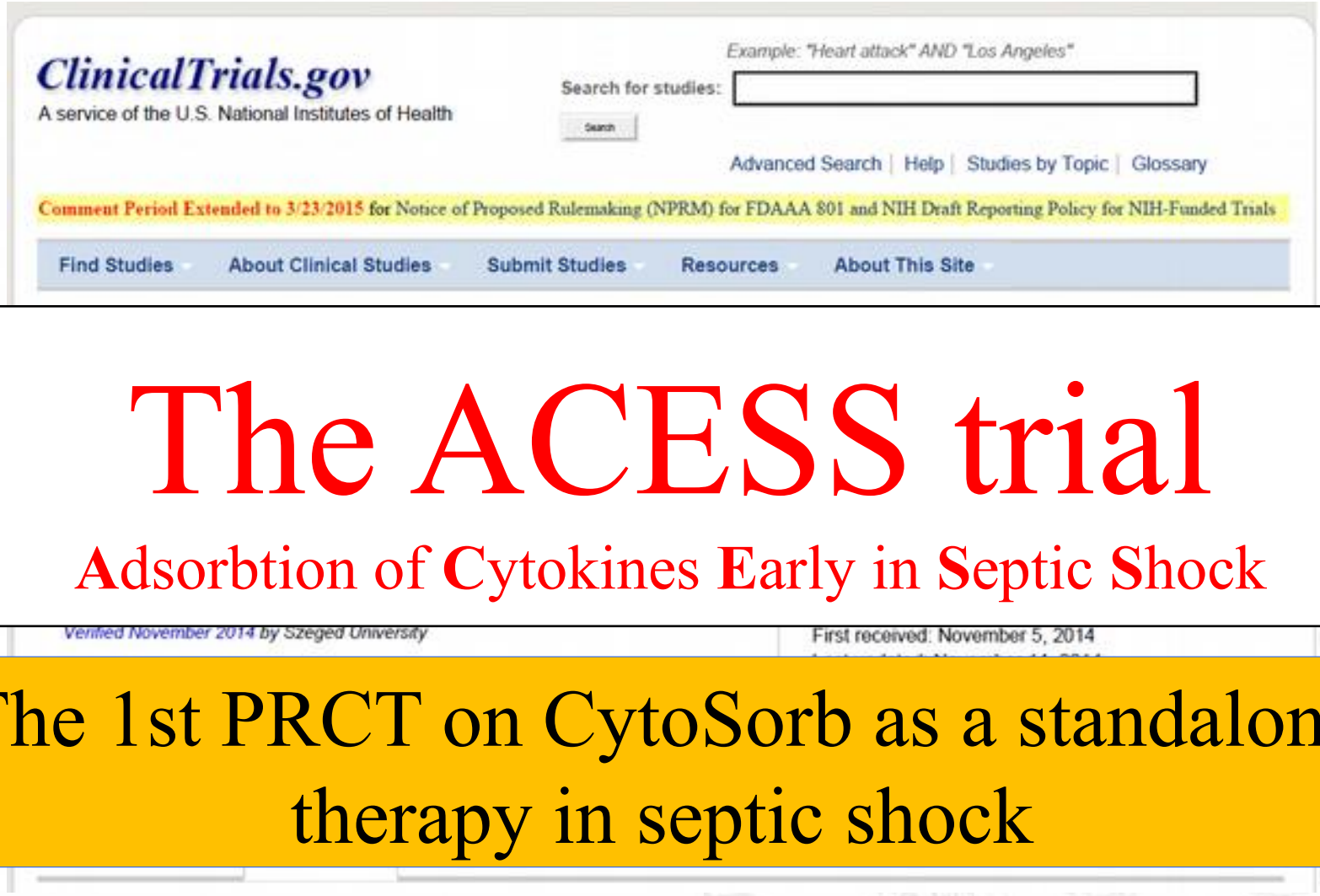
- Proinflammatory molecule
- Antiinflammatory molecule

Multiple support

How to apply? – CRRT or on its own



Attenuating the cytokine storm early?



The ACESS trial

Adsorbtion of **C**ytokines **E**arly in **S**eptic **S**hock

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

Journal of Critical Care 49 (2019) 172–178

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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!

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- Suspected sepsis of medical etiology < 24h
- IPPV
- PCT >3 ng/ml
- Norepinephrine ≥ 10 µg/min
- PiCCO confirmed normovolemia and CO
- Signs of hypoperfusion: $ScvO_2$, lactate, dCO_2, oliguria metabolic acidosis
- Exclusion: need of CRRT

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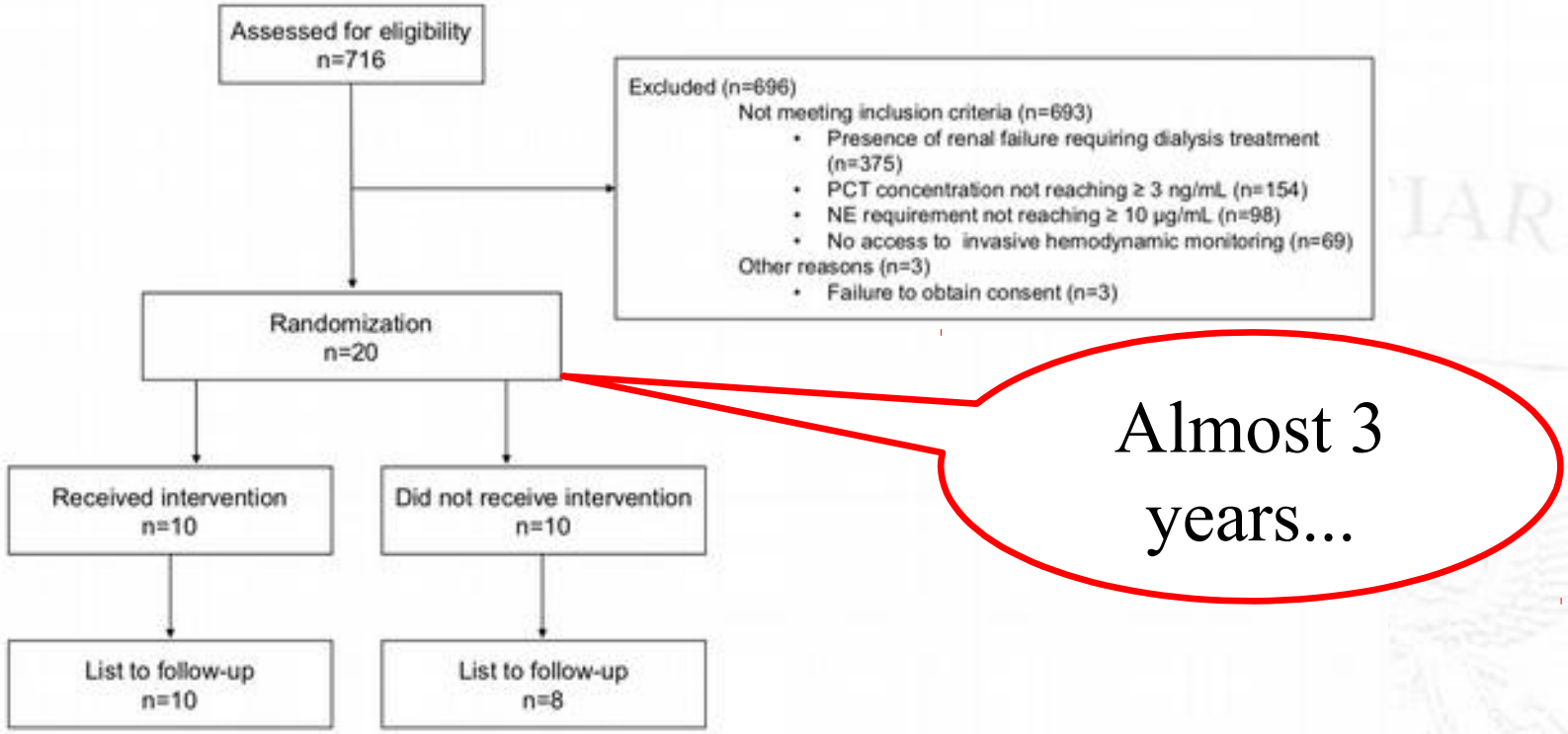

Almost 3 years...

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Is PCT an appropriate marker?

ACESS – 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)			Arterenol (ug/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	,037	,001	,569
	N	59	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**				,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			,576**	,330*	,512**
	Sig. (2-tailed)	,225	,488	,000	.			,000	,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	59	59	58
CRP (mg/l)	Sig. (2-tailed)	,569	,764	,123	,000	,416	,839	,001	,060	.
	N	58	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).

IL-10

IL-1ra

IL-6

IL-8

TNF-α

PCT may be an appropriate biomarker to monitor Cytokine Storm

ACESS results

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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.

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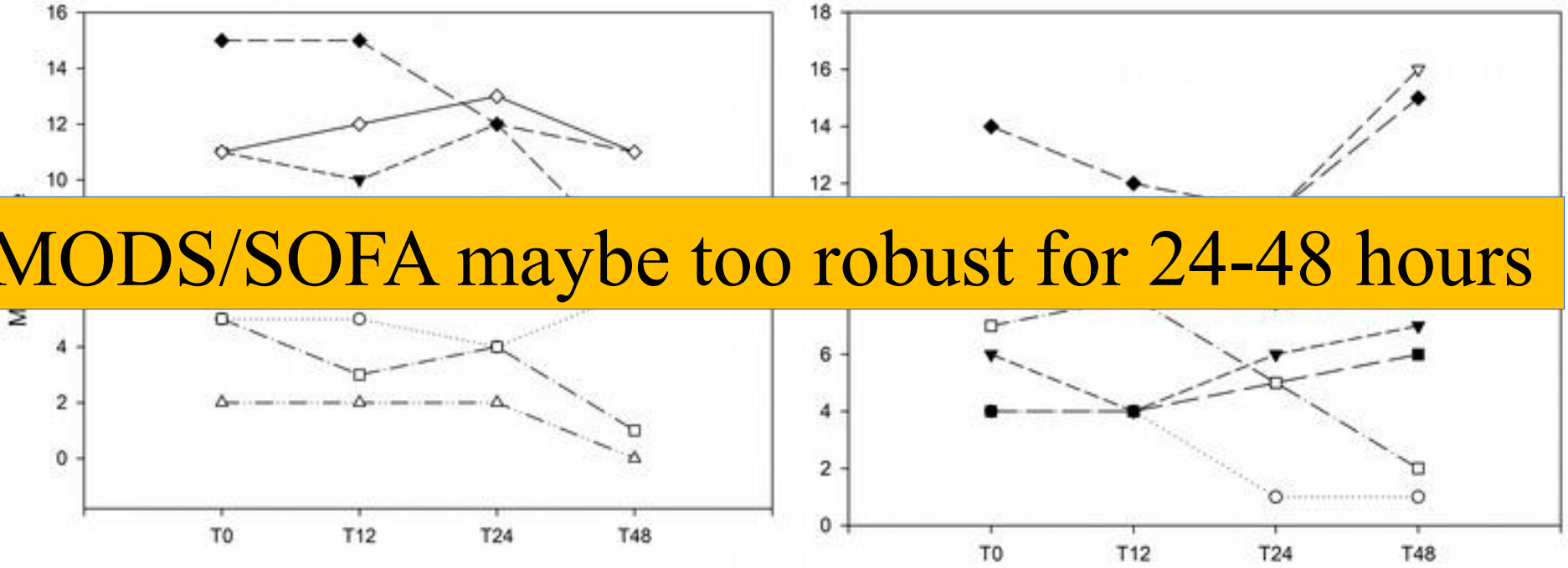
MODS

Control

CytoSorb



MODS/SOFA maybe too robust for 24-48 hours

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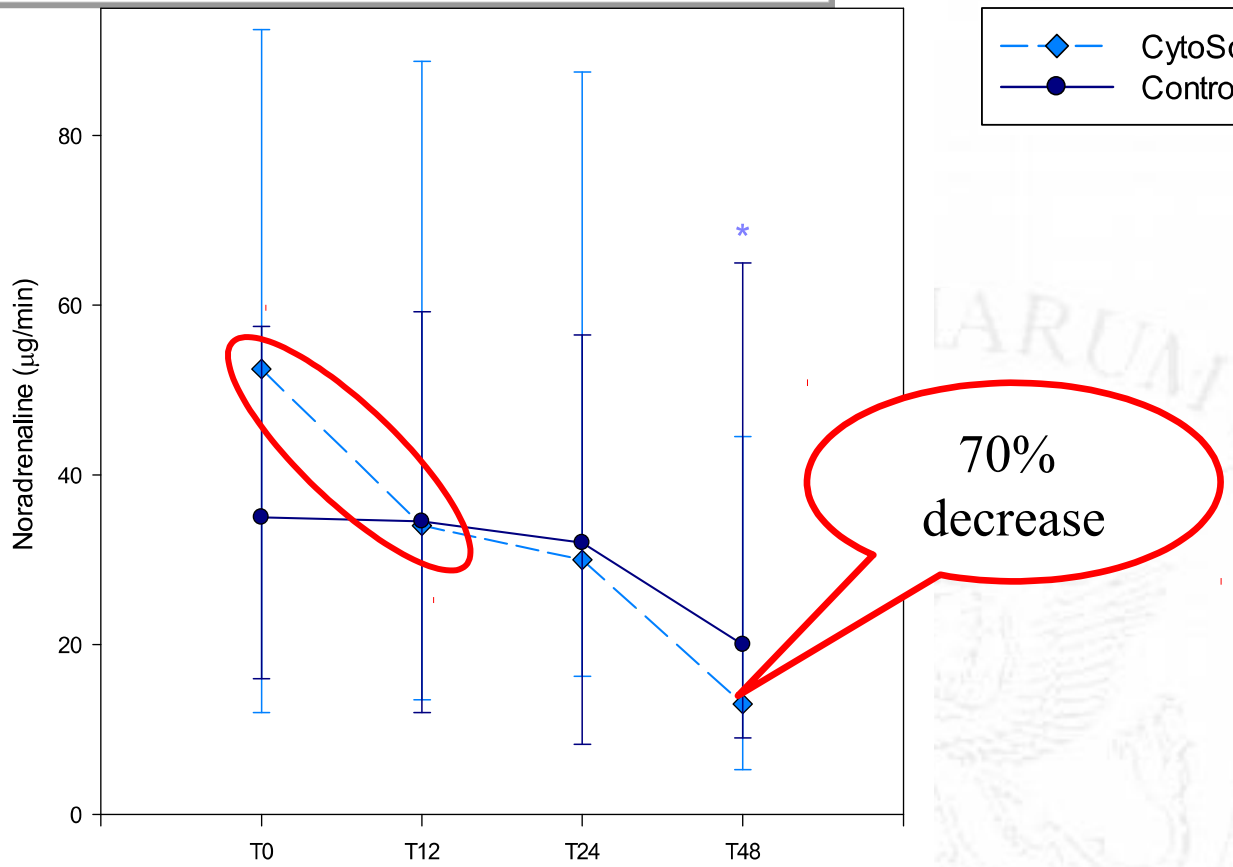
Vasopressor



Data are shown as median and interquartile ranges
*p<0.05 vs. T_0

J Artif Organs
DOI 10.1007/s10047-017-0967-4

CrossMark

ORIGINAL ARTICLE

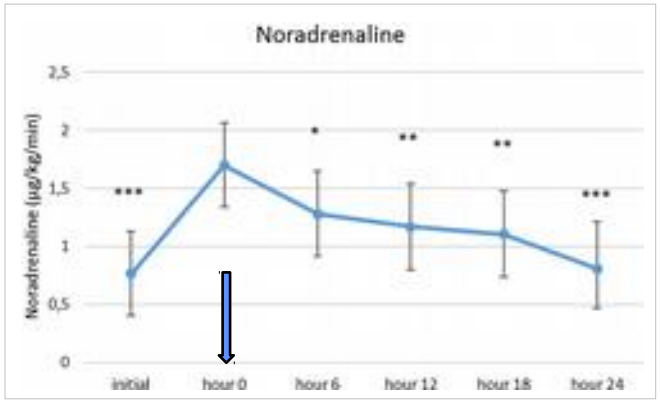
Others

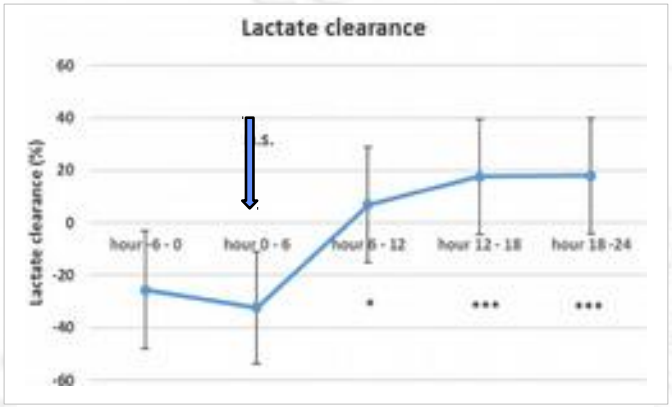
Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study

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

>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 Jarczak[2], Morten Scheller[1] and Matthias Drüner[1]

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.

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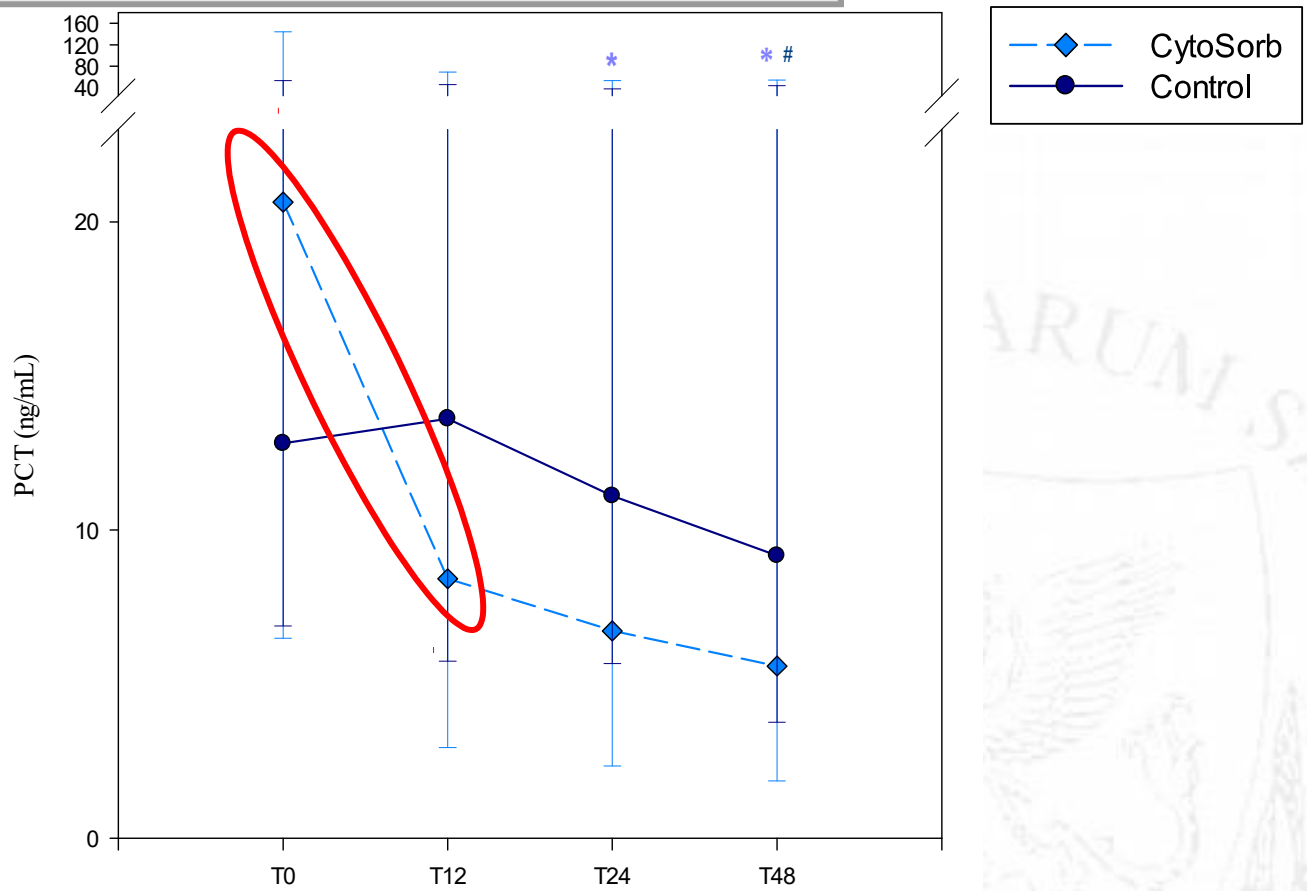
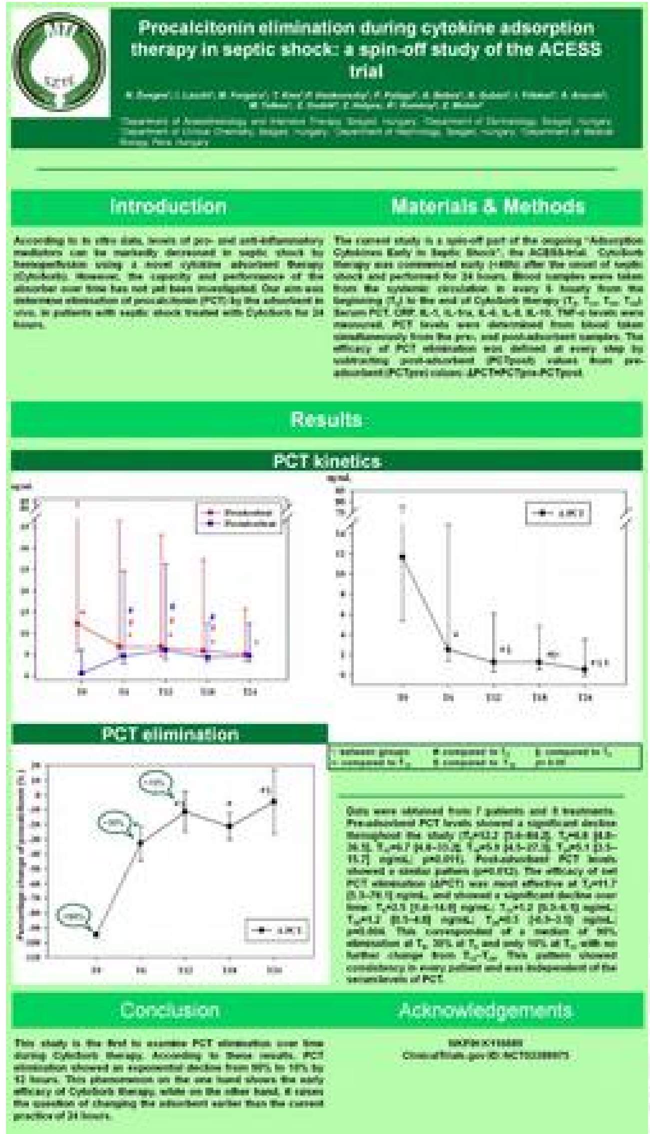
PCT



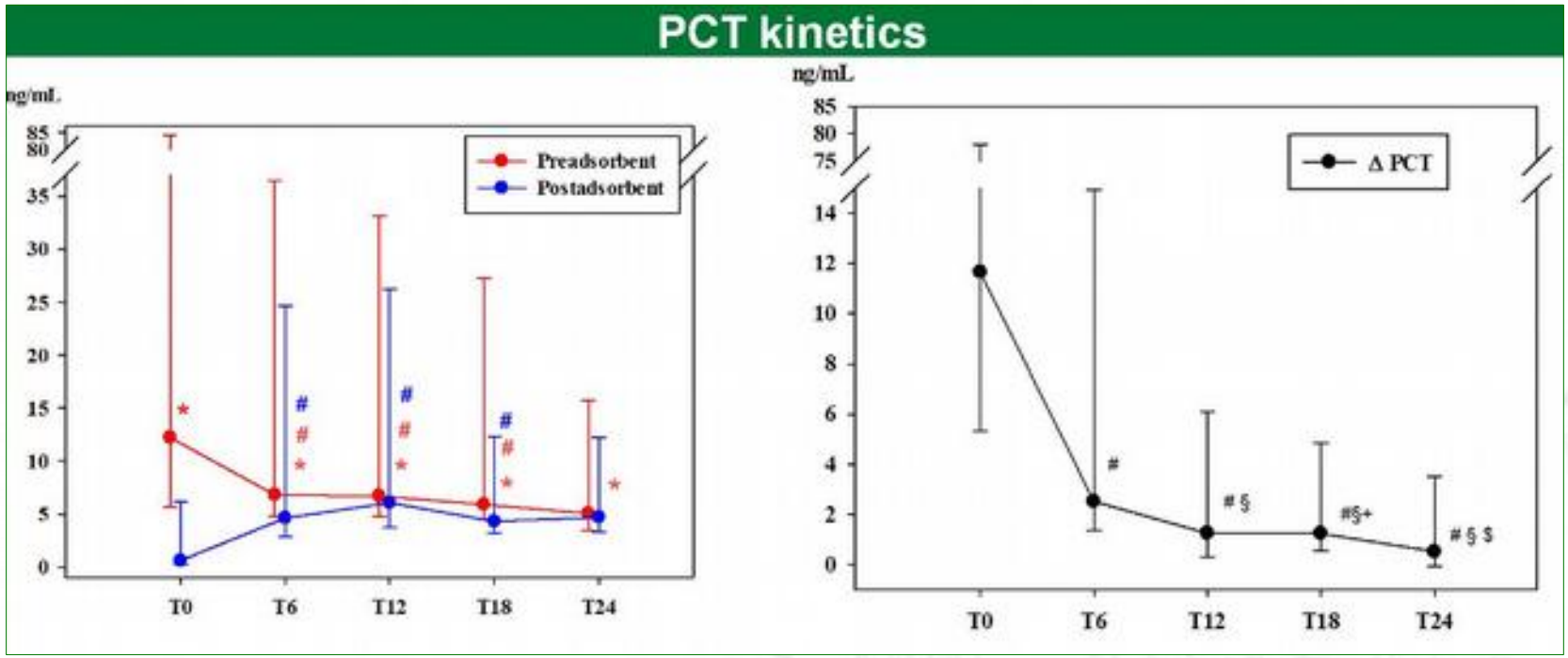
Data are presented as median and interquartile ranges
*p<0.05 vs. $T_{0CytoSorb}$, #p<0.05 vs. $T_{0Control}$

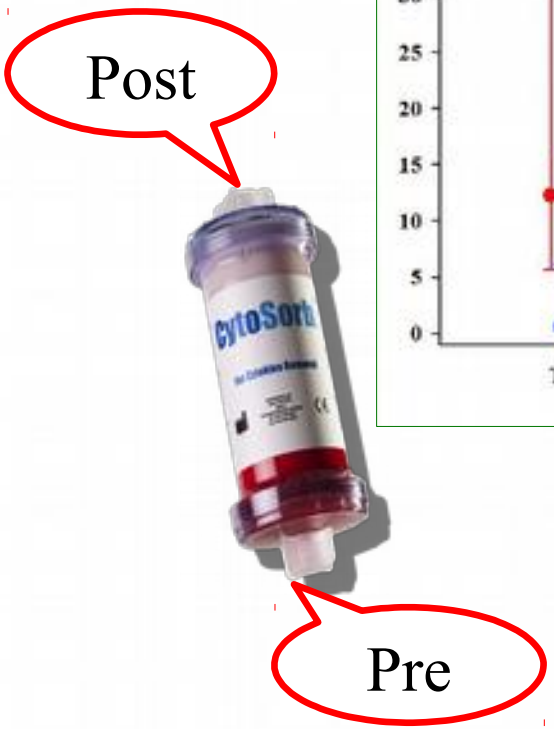
ACESS Spin Off – preliminary results



(ISICEM, 2017)

ACESS Spin Off – preliminary results

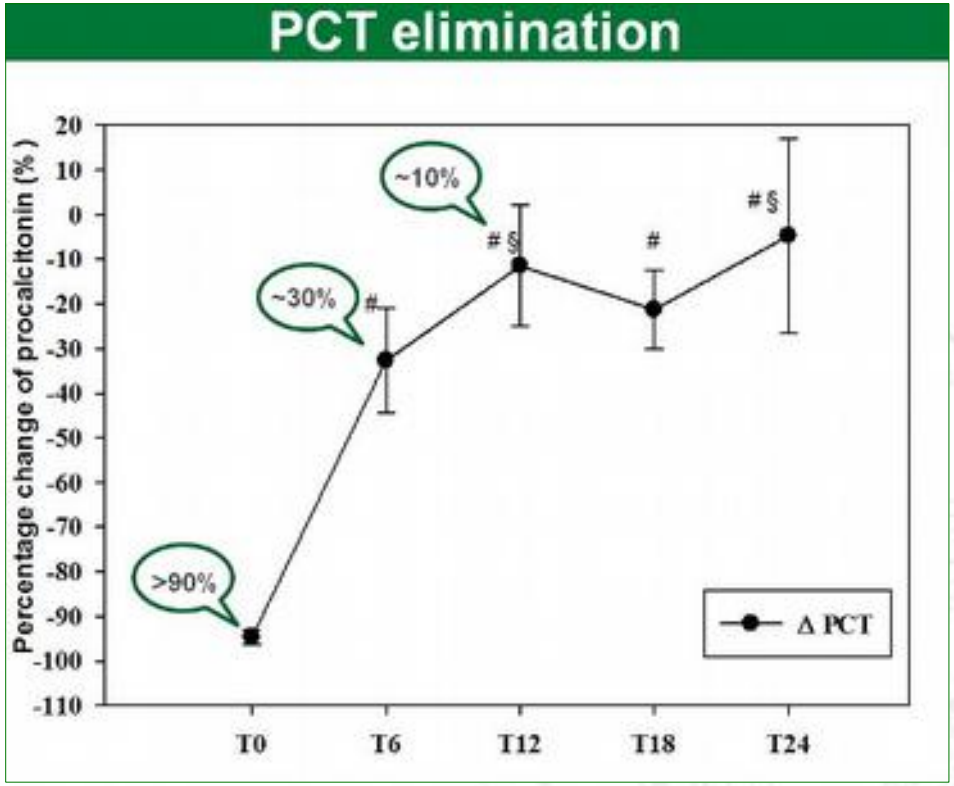




ACESS Spin Off – preliminary results

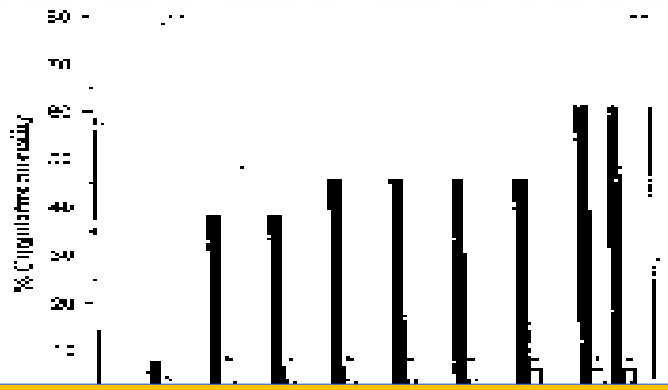
Post

Pre



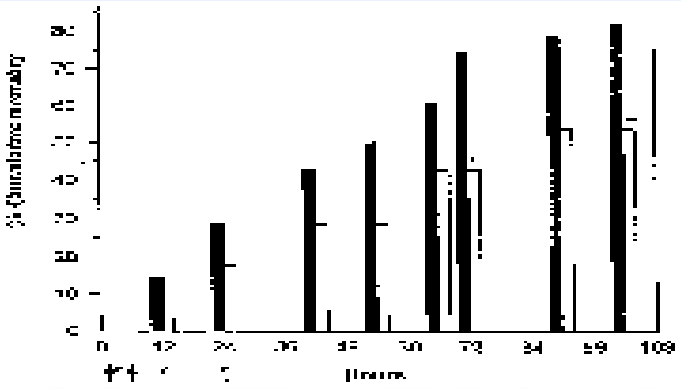
Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis.

(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

Intensive Care Med
https://doi.org/10.1007/s00134-018-5464-6

WHAT'S NEW IN INTENSIVE CARE

Hemoadsorption with CytoSorb®

Elettra C. Poli[1], 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 **R**emoval **I**n **S**eptic **S**hock (CRISS) trial