Hemoadsorpcija pri septičnem šoku

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BREZ konflikta interesov

DEFINICIJA

Hemoadsorpcija - hemoperfuzija

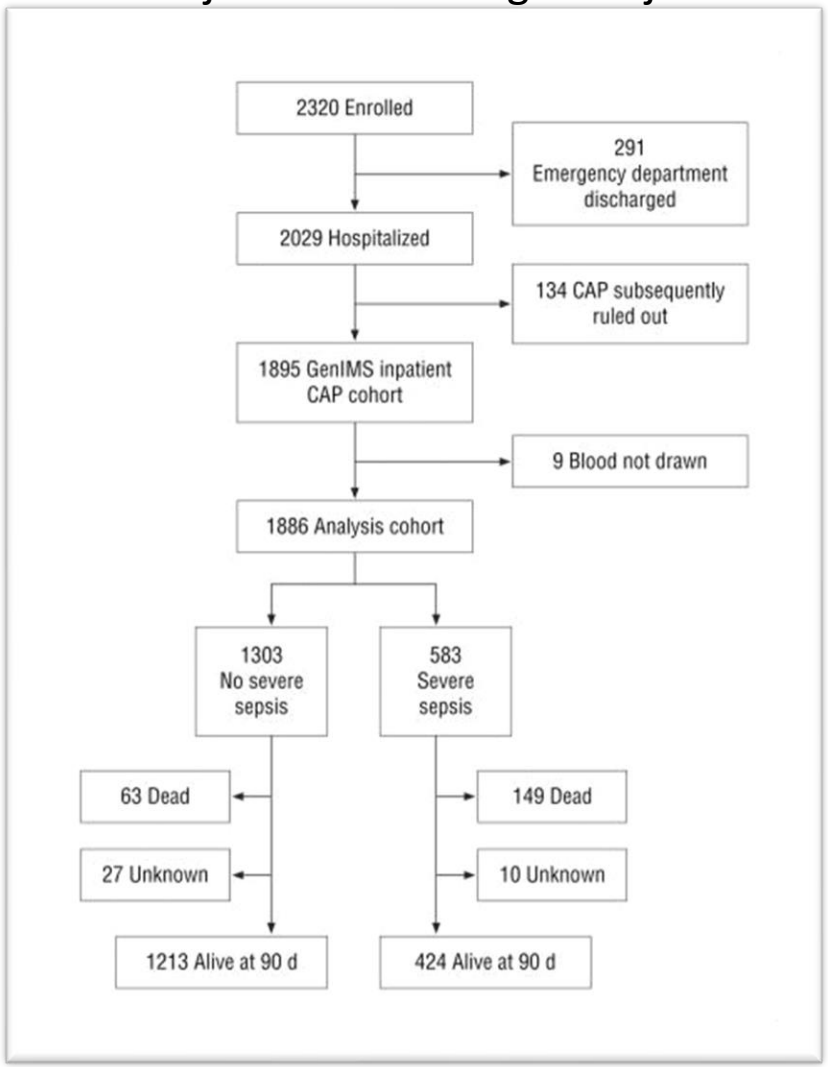
Ekstrakorporalna terapija za čiščenje krvi oz. plazme, ki omogoča selektivno ali širokospektralno odstranjevanje raztopljenih snovi / celic / patogenov, ki jih ni mogoče učinkovito odstraniti z difuzijo ali konvekcijo

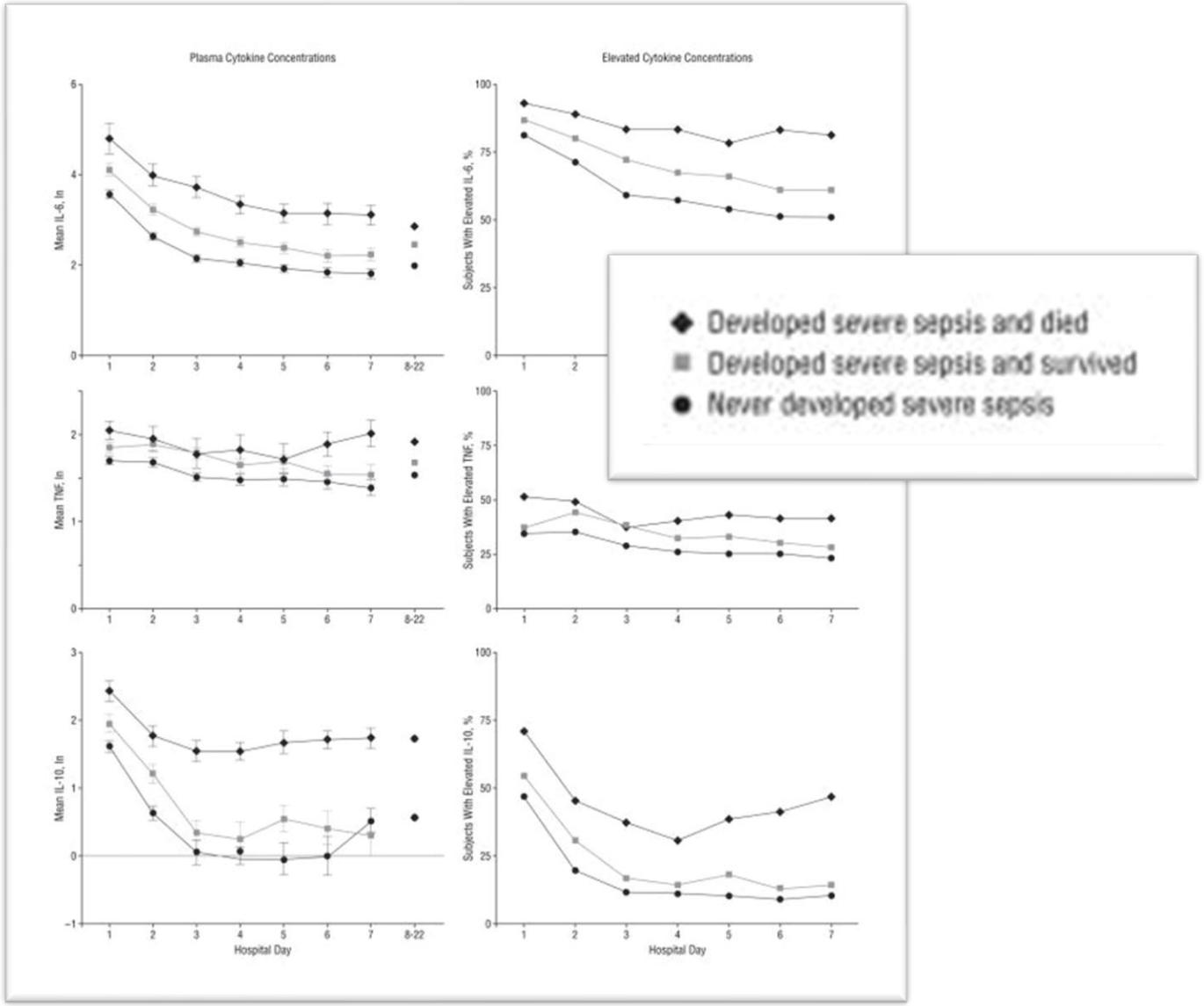
POTREBE / UTEMELJITEV

Kellum JA. GenIMS study. Arch Intern Med 2007

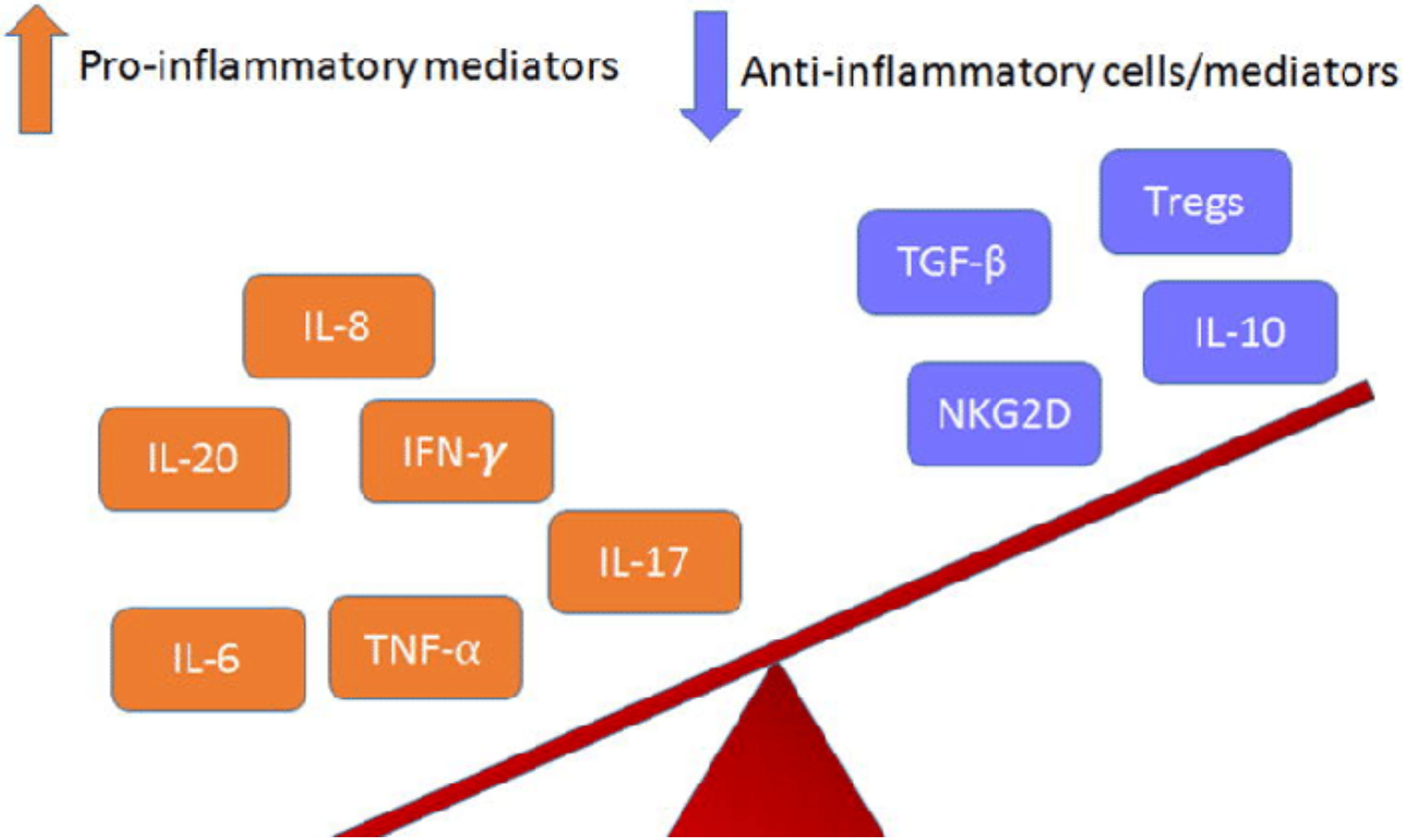
Preživeli bolniki s sepso imajo manjše breme vnetnih mediatorjev in hitreje razrešijo vnetje v primerjavi z umrlimi

Pljučnica domačega okolja





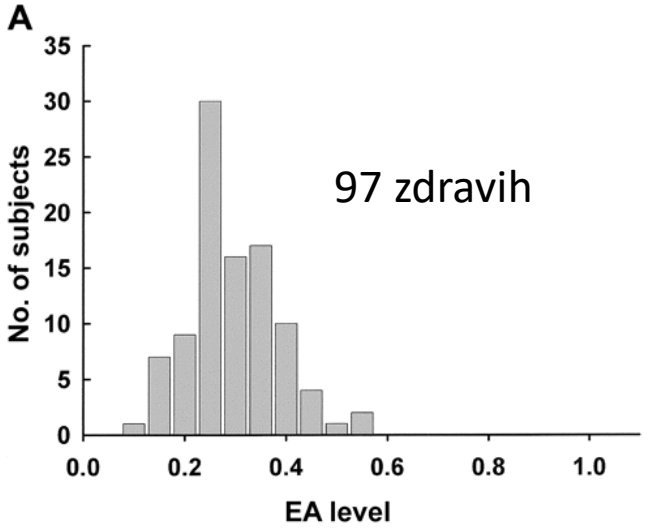
ZAKAJ PRI SEPSI?

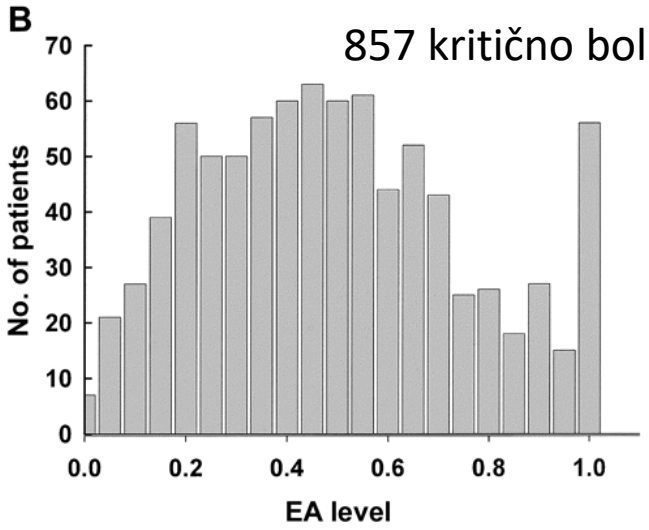


POTREBE / UTEMELJITEV

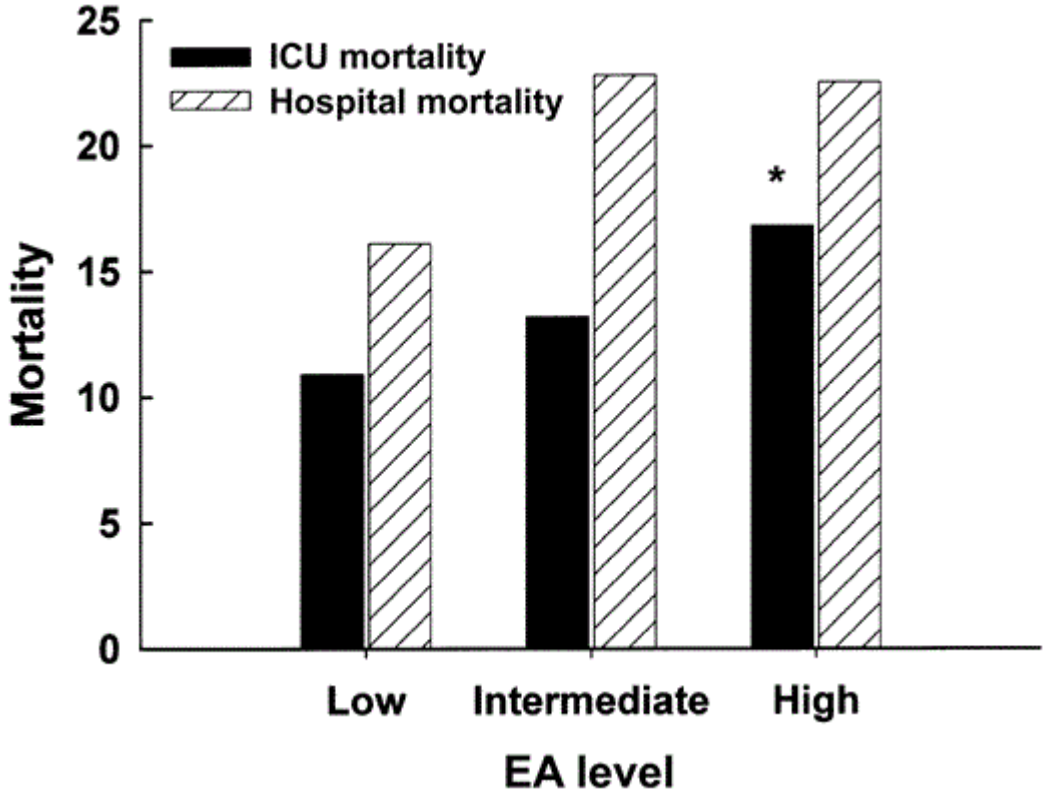
Marshall JC. MEDIC study. J Infect Dis 2004

Aktivnost endotoksinov v krvi je povezana s smrtnostjo v enoti intenzivne terapije

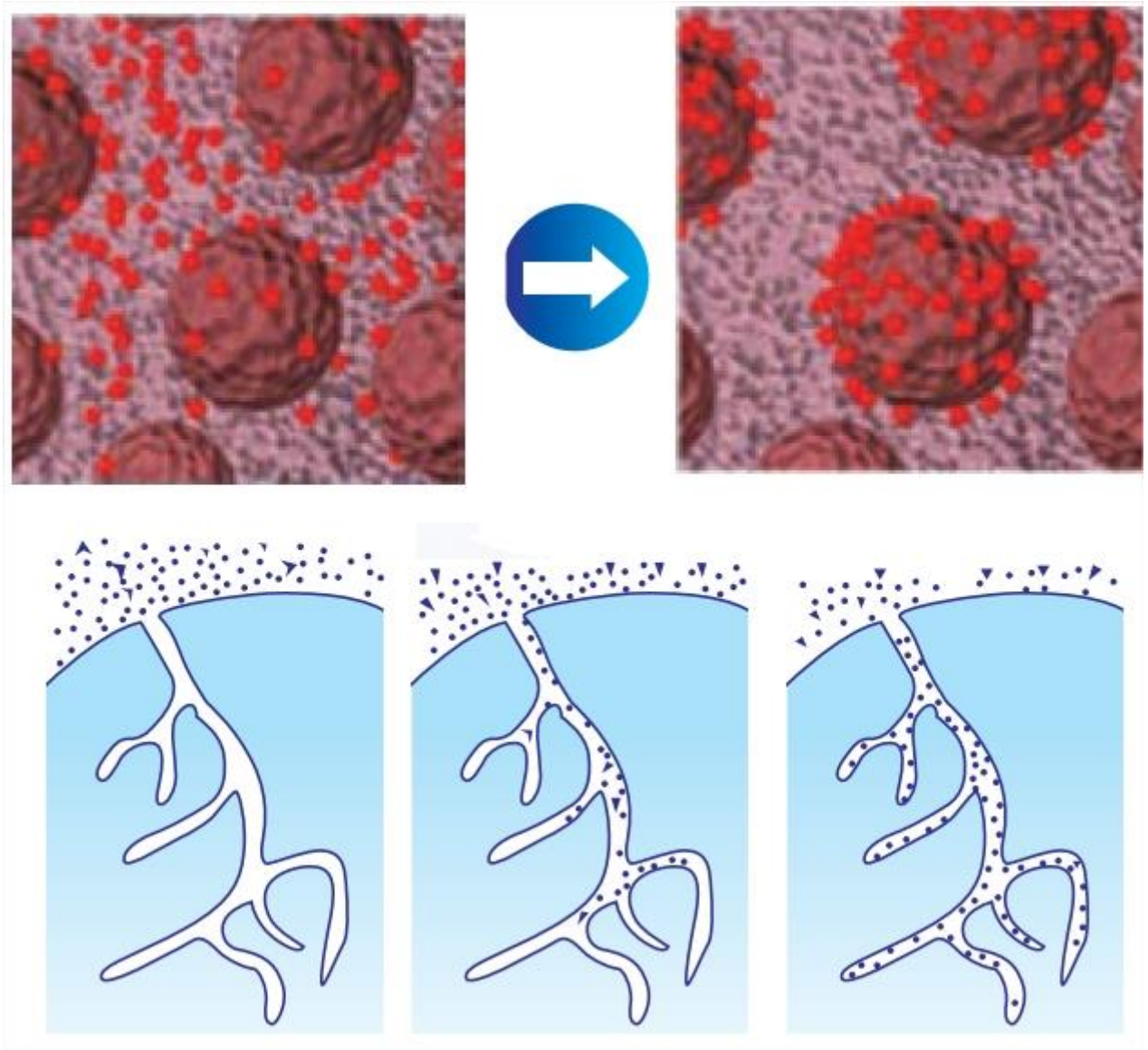




EA level	Risk of severe sepsis in first 24 h of ICU admission, % (no./total)	OR (95% CI)[a]	*P*
Low (<0.40)	4.9 (18/367)	…	…
Intermediate (0.40–0.60)	9.2 (21/228)	2.0 (1.0–3.8)	<.05
High (>0.60)	13.4 (35/262)	3.0 (1.7–0.5)	<.001



TEHNOLOGIJA



PODATKI

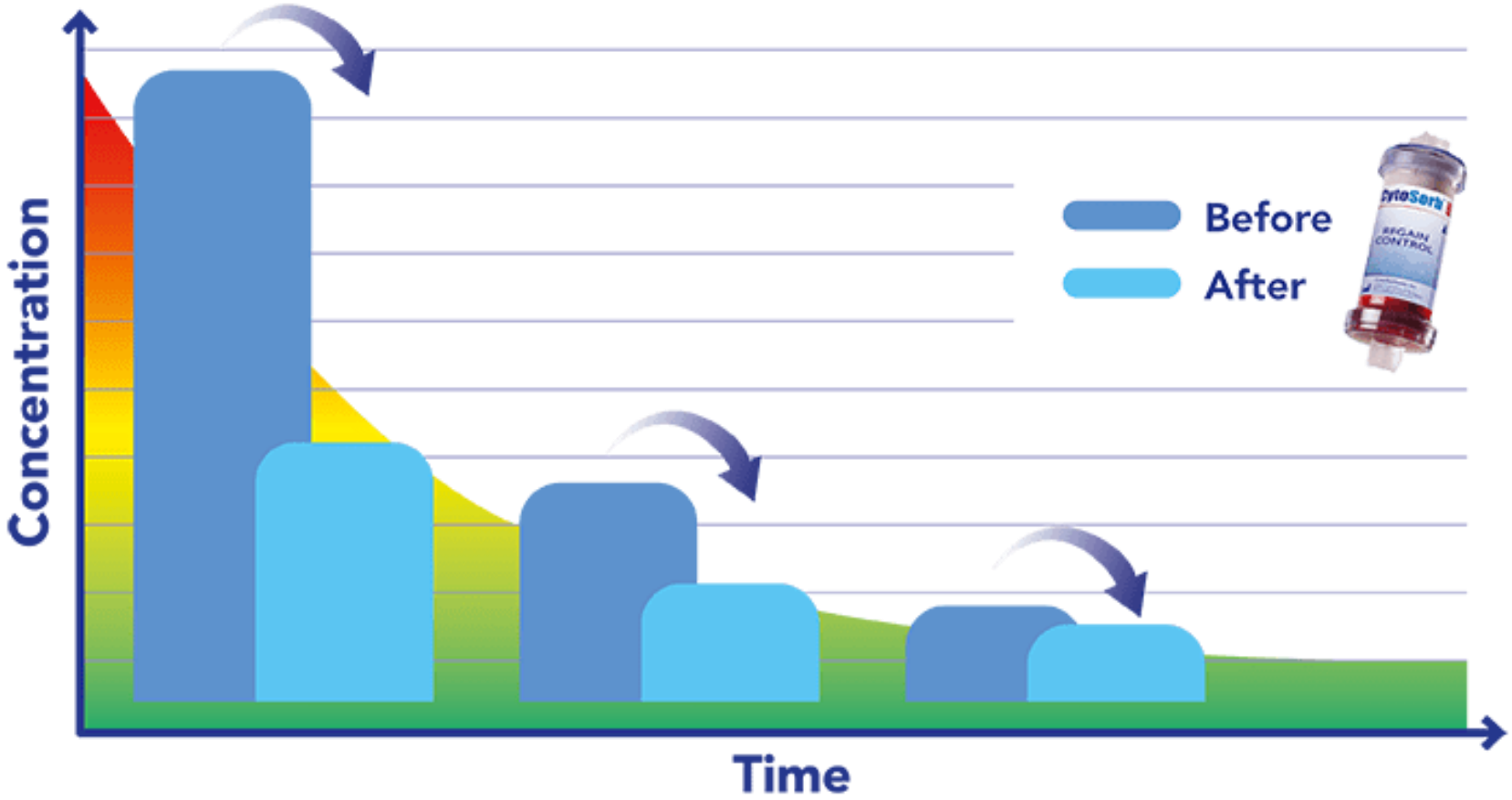
Hemoadsorpcija s pomočjo naprav s poroznimi polimernimi kroglicami zmanjša koncentracije citokinov ter molekularnih vzorcev povezanih s poškodbo in patogeni

Gruda MC. PLoS ONE 2018

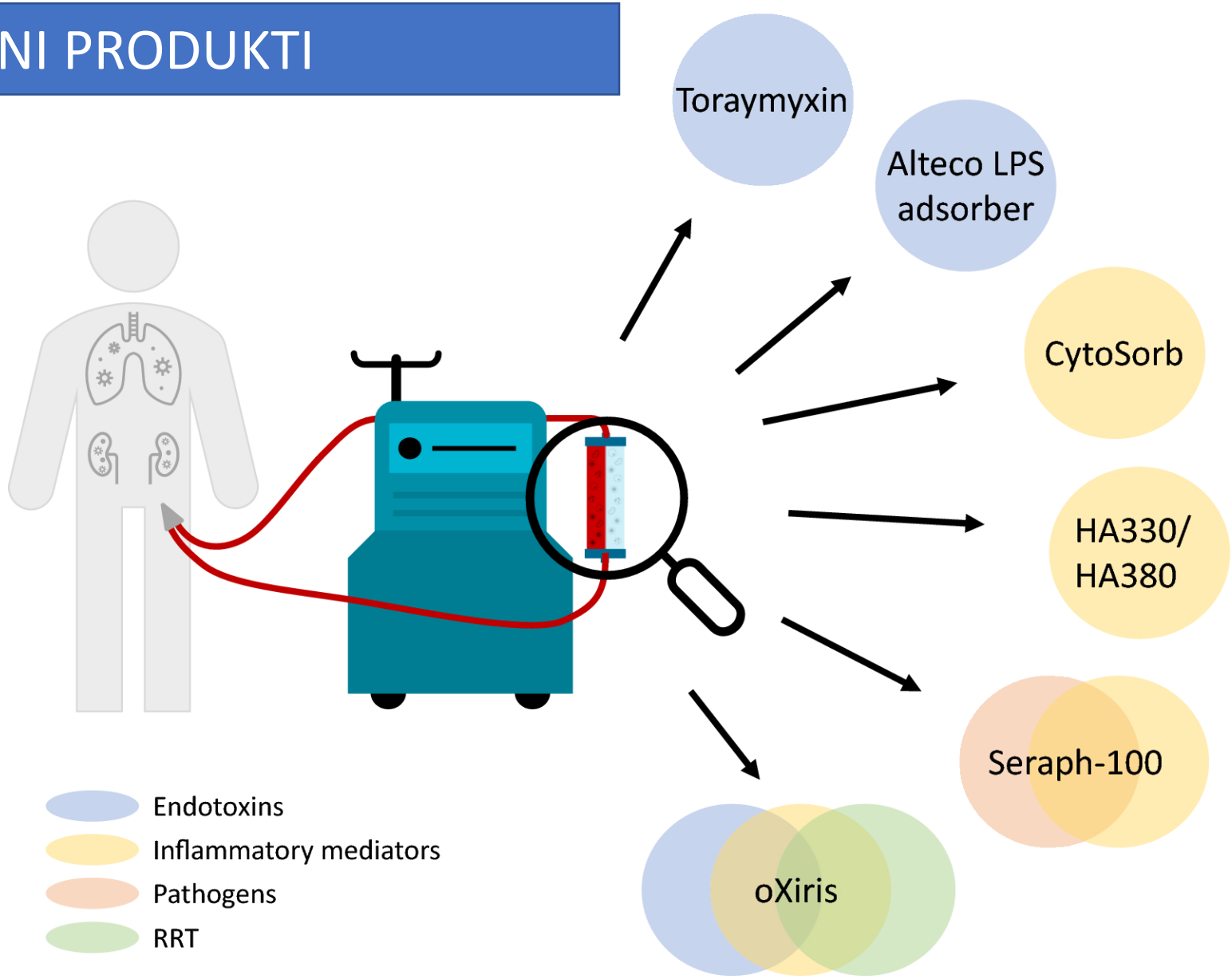
Stopnja odstranitve citokinov in endotoksinov je odvisna od vrste kartuše ter časa in intenzivnosti terapije

Malard B. Intensive Care Med 2018

PODATKI



KOMERCIALNI PRODUKTI



Waalders N. Intensive Care Med 2025

	tehnologija	Površina (m2)	tarča	Trajanje terapije	Specifične podskupine
NESELEKTIVNO ODSTR.	Porozne polimerne kroglice: **Cytosorb** (polistiren divinilbenzen) **Jafron** (stiren-divinil-benzen kopolimer)	 > 40.000 54.000	 Hidrofobne mol. do 60 kDa	 4 – 12 h 2 – 4 h	 hipercitokinemija
SELEKTIVNO	**Toraymyxin** (polimiksin vezan na polistirenska vlakna) **Seraph** (polietilenske kroglice s heparan sulfatom)	> 500 40	Endotoksin Bakterije, glive, virusi	2 h 6 h	EAA > 0.6 Bakteriemija, fungemija

POLIMIKSIN B HEMADSORPCIJA

Raziskava EUPHAS: 64 randomiziranih bolnikov z abdominalno sepso

Table 3. Physiological End Points by Treatment Group at Baseline and 72 Hours[a]

	Polymyxin B Hemoperfusion			Conventional Therapy		
	Mean (95% CI)			Mean (95% CI)		
Physiological End Points	Baseline (n = 34)	72 Hours (n = 34)	*P* Value	Baseline (n = 30)	72 Hours (n = 27)	*P* Value
Mean arterial pressure, mm Hg	76 (72-80)	84 (80-88)	.001	74 (70-78)	77 (72-82)	.37
Inotropic score	29.9 (20.4-39.4)	6.8 (2.9-10.7)	<.001	28.6 (16.6-40.7)	22.4 (9.3-35.5)	.14
Vasopressor dependency index, mm Hg^{-1}	4.3 (2.7-5.9)	0.9 (0.3-1.5)	<.001	4.1 (2.3-6.0)	3.3 (1.3-5.3)	.26
PaO_2/FIO_2	235 (206-265)	264 (236-292)	.049	217 (188-247)	228 (199-258)	.79
Renal replacement therapy, No. (%)	13 (38)	15 (44)	.50	6 (20)	8 (30)	.50

Abbreviations: CI, confidence interval; FIO_2, fraction of inspired oxygen.
[a]See "Methods" section for formulas for inotropic score and vasopressor dependency index. In the conventional therapy group, 3 patients died before 72 hours (n=27).

Cruz DN. JAMA 2009

POLIMIKSIN B HEMADSORPCIJA

ABDOMIX (243 pts), **EUPHRATES** (450 pts) RCT

Table 2. Summary of the Primary End Point of 28-Day Mortality for All Participants and for Patients With MODS of More Than 9

	No./Total (%)		(95% CI)		
	Polymyxin-B Hemoperfusion	Sham	Risk Difference	Risk Ratio	*P* Value[a]
All Participants	84/223 (37.7)	78/226 (34.5)	3.15 (−5.73 to 12.04)	1.09 (0.85 to 1.39)	.49
>9 MODS[b]	65/146 (44.5)	65/148 (43.9)	0.60 (−10.75 to 11.97)	1.01 (0.78 to 1.31)	.92

Post hoc analiza EUPHRATES: ugoden učinek pri 0.6 < EAA < 0.9

ZDA: TIGRIS RCT - septčni šok in EAA ≥0.60 and <0.90; 30-dnevno preživetje
Cca 150 pts – 2026

Payen DM. the EUPHRATES randomized clinical trial. JAMA 2018.
Payen DM. Abdomix. Intensive Care Med 2015

POLIMIKSIN B HEMADSORPCIJA

CRITICAL CARE MEDICINE

ANESTHESIOLOGY

Blood Purification and Mortality in Sepsis and Septic Shock

A Systematic Review and Meta-analysis of Randomized Trials

Alessandro Putzu, M.D., Raoul Schorer, M.D., Juan Carlos Lopez-Delgado, M.D., Ph.D., Tiziano Cassina, M.D., Giovanni Landoni, M.D.

ANESTHESIOLOGY 2019; 131:580–93

ABSTRACT

Background: Sepsis and septic shock are severe inflammatory conditions related to high morbidity and mortality. We performed a systematic review with meta-analysis of randomized trials to assess whether extracorporeal blood purification reduces mortality in this setting.

Methods: Electronic databases were searched for pertinent studies up to January 2019. We included randomized controlled trials on the use of hemoperfusion, hemofiltration without a renal replacement purpose, and plasmapheresis as a blood purification technique in comparison to conventional therapy in adult patients with sepsis and septic shock. The primary outcome was mortality at the longest follow-up available. We calculated relative risks and 95% CIs. The grading of recommendations assessment, development and evaluation methodology for the certainty of evidence was used.

Results: Thirty-seven trials with 2,499 patients were included in the meta-analysis. Hemoperfusion was associated with lower mortality compared to conventional therapy (relative risk = 0.88 [95% CI, 0.78 to 0.98], $P = 0.02$, very low certainty evidence). Low risk of bias trials on polymyxin B immobilized filter hemoperfusion showed no mortality difference *versus* control (relative risk = 1.14 [95% CI, 0.96 to 1.36], $P = 0.12$, moderate certainty evidence), while recent trials found an increased mortality (relative risk = 1.22 [95% CI, 1.03 to 1.45], $P = 0.02$, low certainty evidence); trials performed in the United States and Europe had no significant difference in mortality (relative risk = 1.13 [95% CI, 0.96 to 1.34], $P = 0.15$), while trials performed in Asia had a positive treatment effect (relative risk = 0.57 [95% CI, 0.47 to 0.69], $P < 0.001$). Hemofiltration (relative risk = 0.79 [95% CI, 0.63 to 1.00], $P = 0.05$, very low certainty evidence) and plasmapheresis (relative risk = 0.63 [95% CI, 0.42 to 0.96], $P = 0.03$, very low certainty evidence) were associated with a lower mortality.

Conclusions: Very low-quality randomized evidence demonstrates that the use of hemoperfusion, hemofiltration, or plasmapheresis may reduce mortality in sepsis or septic shock. Existing evidence of moderate quality and certainty does not provide any support for a difference in mortality using polymyxin B hemoperfusion. Further high-quality randomized trials are needed before systematic implementation of these therapies in clinical practice.

(ANESTHESIOLOGY 2019; 131:580–93)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Among patients with sepsis or septic shock, a variety of extracorporeal blood purification techniques are available
- Individual existing trials evaluating these options are underpowered to provide clear evidence

What This Article Tells Us That Is New

- Meta-analysis of very low-quality randomized controlled trial evidence demonstrates a potential benefit of hemoperfusion, hemofiltration, or plasmapheresis
- Additional high-quality trials demonstrating benefit in modern clinical practice are needed before recommending these therapies

Today, sepsis remains one of the main causes of morbidity and mortality in the intensive care unit. Despite recent advancement in intensive care unit and sepsis management, mortality still remains high.[1–4]

The pathogenesis of sepsis involves many complex cellular and biochemical interactions between leukocytes, platelets, endothelial cells, and the complement system that trigger an inflammatory response.[5] Inflammation is caused by the production of pro- and antiinflammatory mediators, such as cytokines, in the presence of infection and/or bacterial toxins, and the imbalance between these mediators or their excessive production may lead to multiorgan failure due to a prolonged or inadequate systemic inflammatory response syndrome.[5,6]

Extracorporeal blood purification techniques have been proposed as adjunctive therapy in sepsis. These techniques are based on the principle that removal and modulation of blood pro- and antiinflammatory mediators or bacterial toxins (or both) could attenuate the sepsis-related massive

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). For a downloadable PPT slide containing this article's citation information, please visit https://anesthesiology.pubs.asahq.org/ss/downloadable_slide.aspx.

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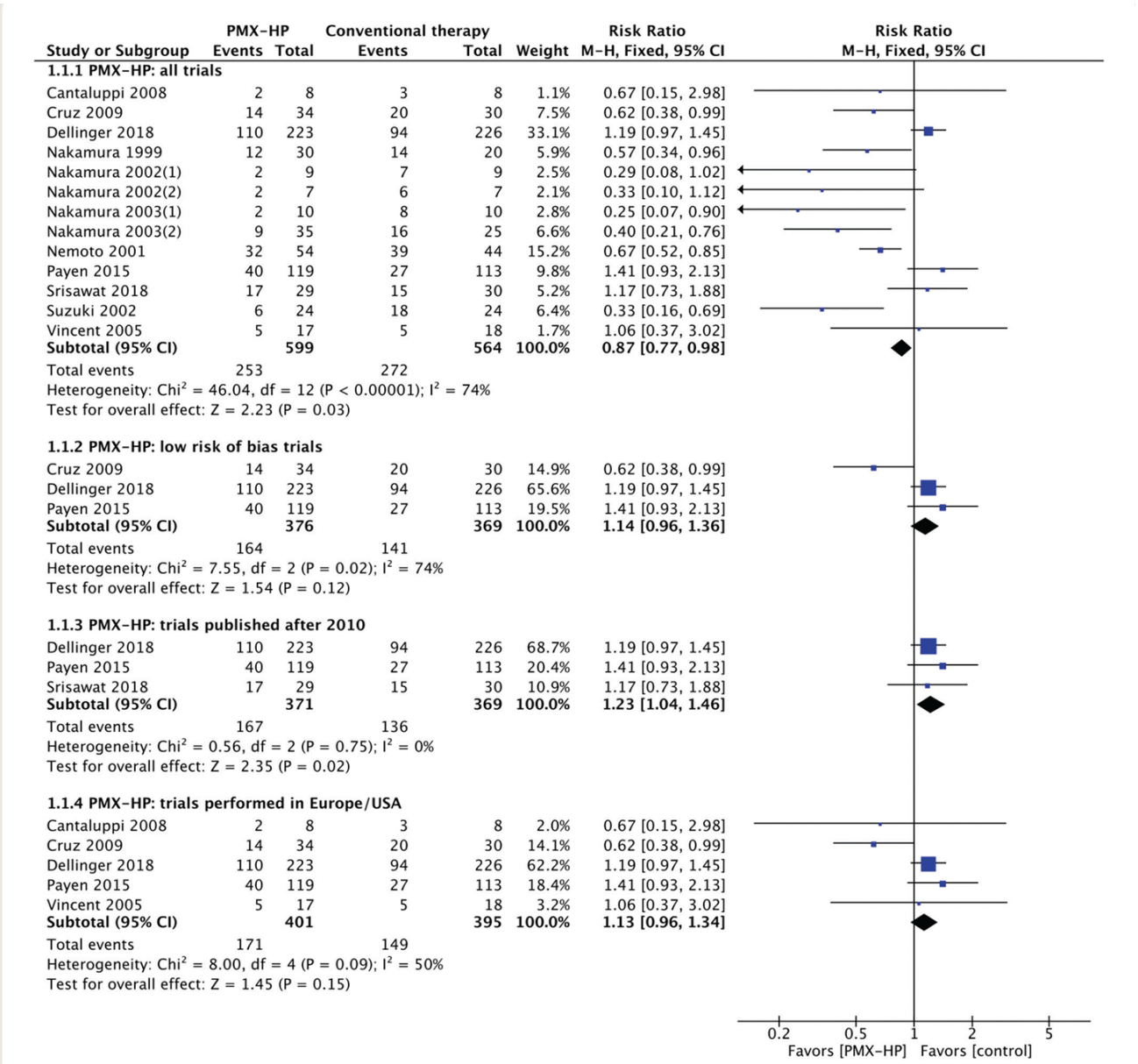
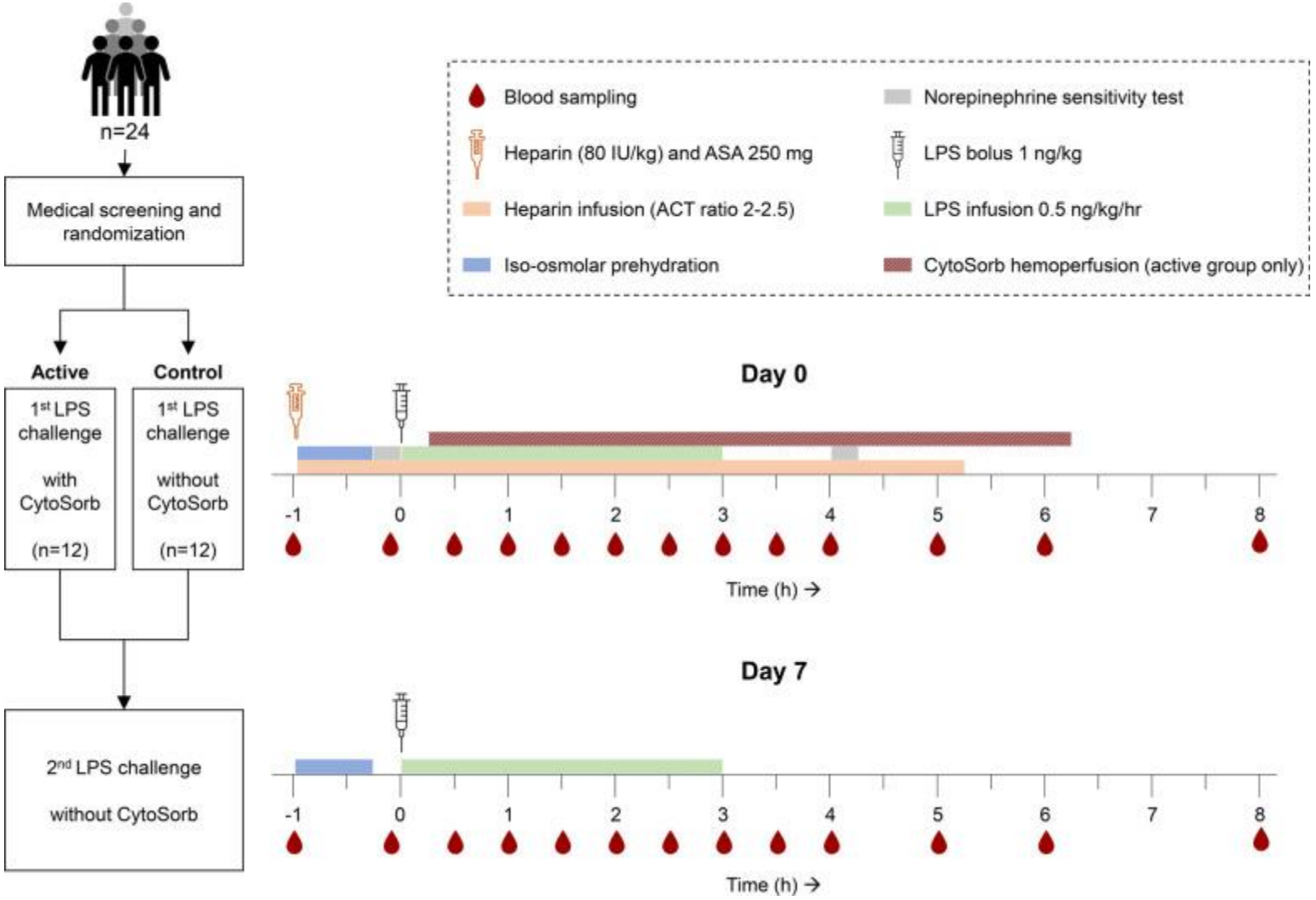
 Anesthesiology 2019; 131:580–93. DOI: 10.1097/ALN.0000000000002820



CYTOSORB



Jansen A. Crit Care 2023

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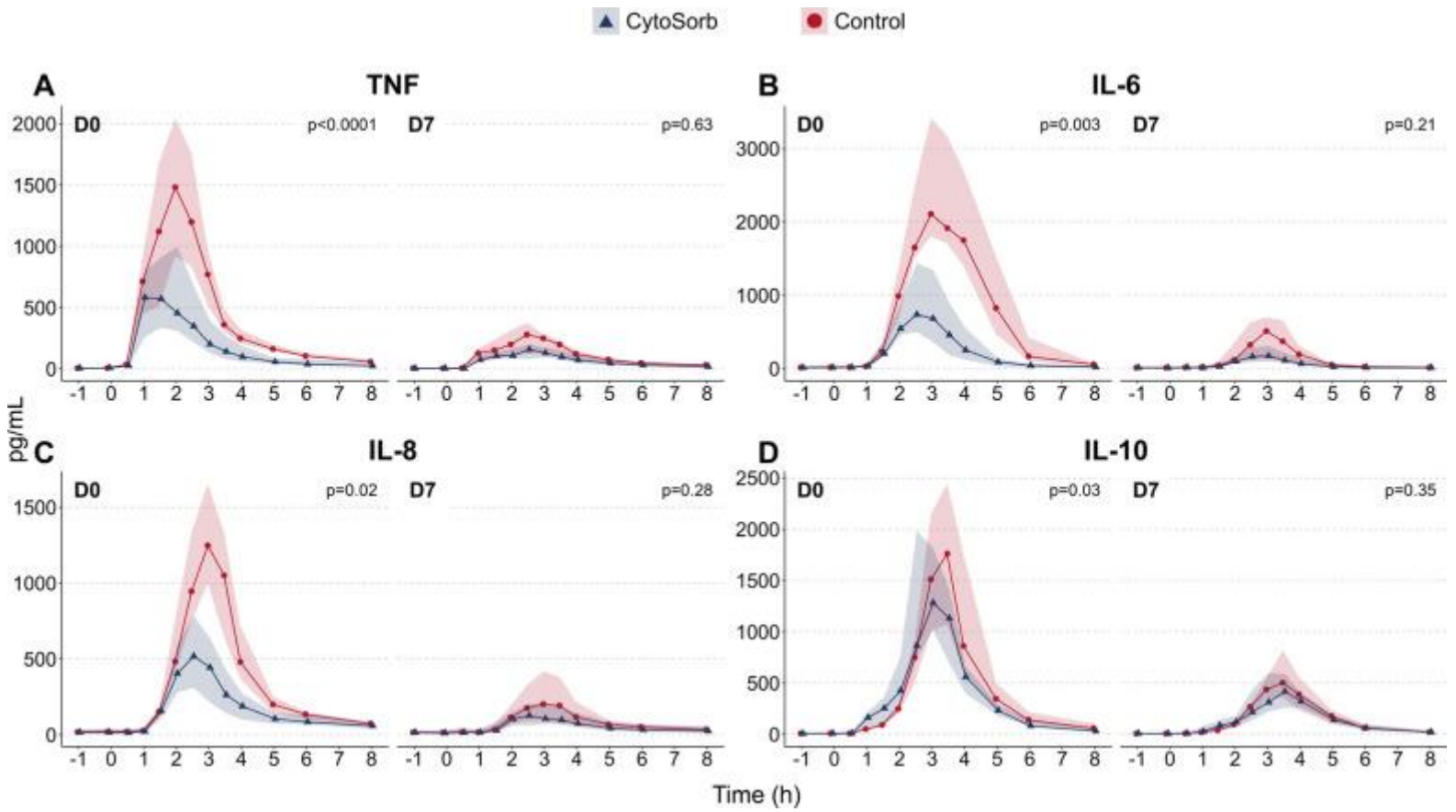

Jansen A. Crit Care 2023

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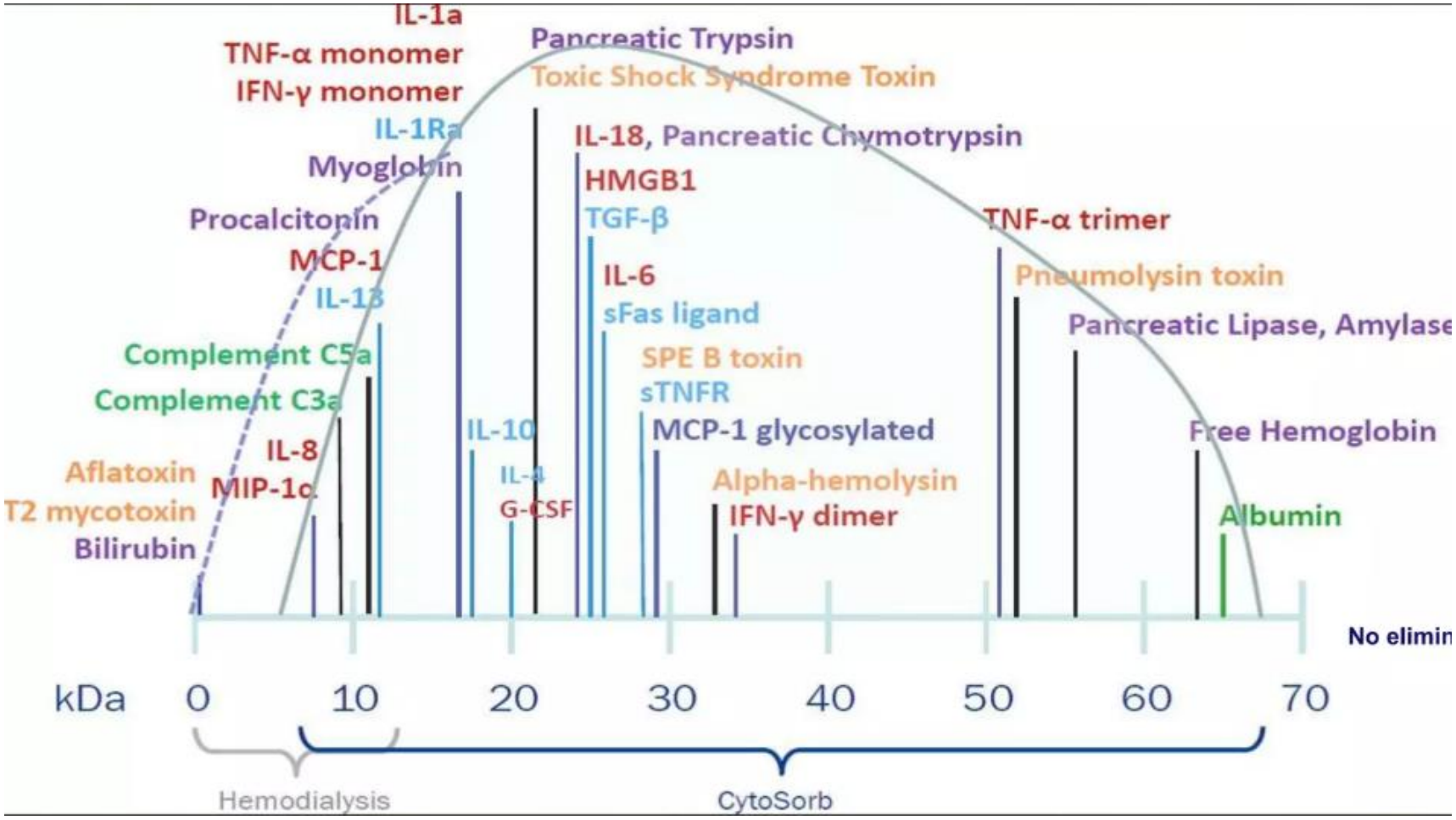

Waalders N. Intensive Care Med 2025

CYTOSORB

Becker *et al. Critical Care* (2023) 27:215
https://doi.org/10.1186/s13054-023-04492-9

Critical Care

RESEARCH Open Access

Efficacy of CytoSorb®: a systematic review and meta-analysis

Sören Becker[1†], Hannah Lang[1†], Clara Vollmer Barbosa[1], Zhejia Tian[1], Anette Melk[2] and Bernhard M. W. Schmidt[1*]

Abstract

Introduction Cytokine adsorption using the CytoSorb® adsorber has been proposed in various clinical settings including sepsis, ARDS, hyperinflammatory syndromes, cardiac surgery or recovery after cardiac arrest. The aim of this analysis is to provide evidence for the efficacy of the CytoSorb® adsorber with regard to mortality in various settings.

Methods We searched PubMed, Cochrane Library database and the database provided by Cytosorbents™ (01.1.2010–29.5.2022). We considered randomized controlled trials and observational studies with control groups. The longest reported mortality was defined as the primary endpoint. We computed risk ratios and 95%-confidence intervals and used DerSimonian and Lairds random effects model. We analysed all studies combined and divided them into the subgroups: sepsis, cardiopulmonary bypass surgery (CPB), other severe illness, SARS-CoV-2 infection and recovery from cardiac arrest. The meta-analysis was registered in advance (PROSPERO: CRD42022290334).

Results Of an initial 1295 publications, 34 studies were found eligible, including 1297 patients treated with CytoSorb® and 1314 controls. Cytosorb® intervention did not lower mortality (RR [95%-CI]: all studies 1.07 [0.88; 1.31], sepsis 0.98 [0.74; 1.31], CPB surgery 0.91 [0.64; 1.29], severe illness 0.95 [0.59; 1.55], SARS-CoV-2 1.58 [0.50; 4.94]). In patients with cardiac arrest, we found a significant survival advantage of the untreated controls (1.22 [1.02; 1.46]). We did not find significant differences in ICU length of stay, lactate levels, or IL-6 levels after treatment. Of the eligible 34 studies only 12 were randomized controlled trials. All observational studies showed moderate to serious risk of bias.

Interpretation To date, there is no evidence for a positive effect of the CytoSorb® adsorber on mortality across a variety of diagnoses that justifies its widespread use in intensive care medicine.

Introduction

Massive release of cytokines into the bloodstream is the pathophysiological culprit of many life-threating diseases. Pro-inflammatory cytokines lead to vasodilation, capillary leakage, and coagulopathy. Anti-inflammatory cytokines can cause relative immunosuppression leading to secondary nosocomial infections. The uncontrolled release of both types of cytokines has the potential to end in multiple organ failure [1].

Various blood purification techniques, such as dialysis using high cut-off membranes, hemoadsorption, high volume hemofiltration, and plasma exchange have been proposed to unselectively reduce cytokine levels [2]. CytoSorb® is one of the most widely used blood purification devices, which can reduce the level of hydrophobic molecules with a molecular mass up to 55 kDa. [3] Thus, the device adsorbs cytokines, bile acids, and myoglobin. CytoSorb® is in clinical use in patients with an excessive immune response such as in sepsis, ARDS, SARS-CoV-2

†Sören Becker and Hannah Lang contributed equally to this work.

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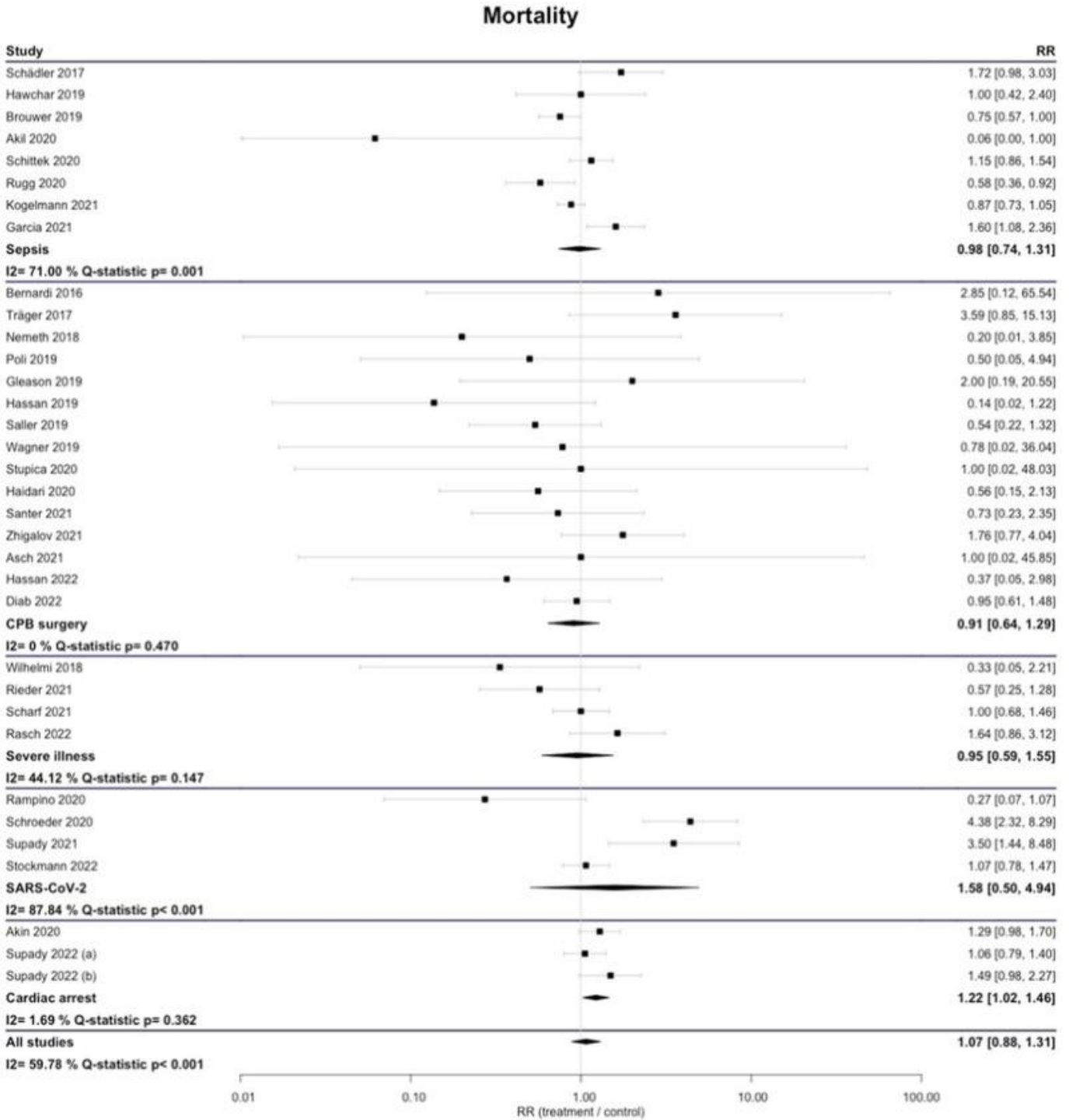

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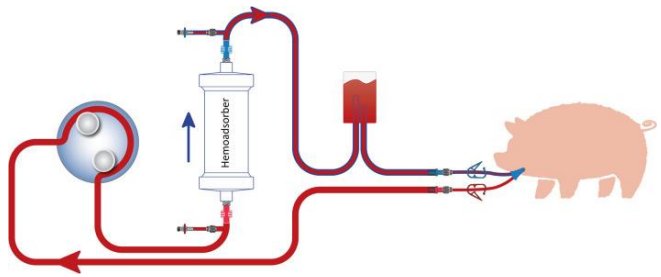

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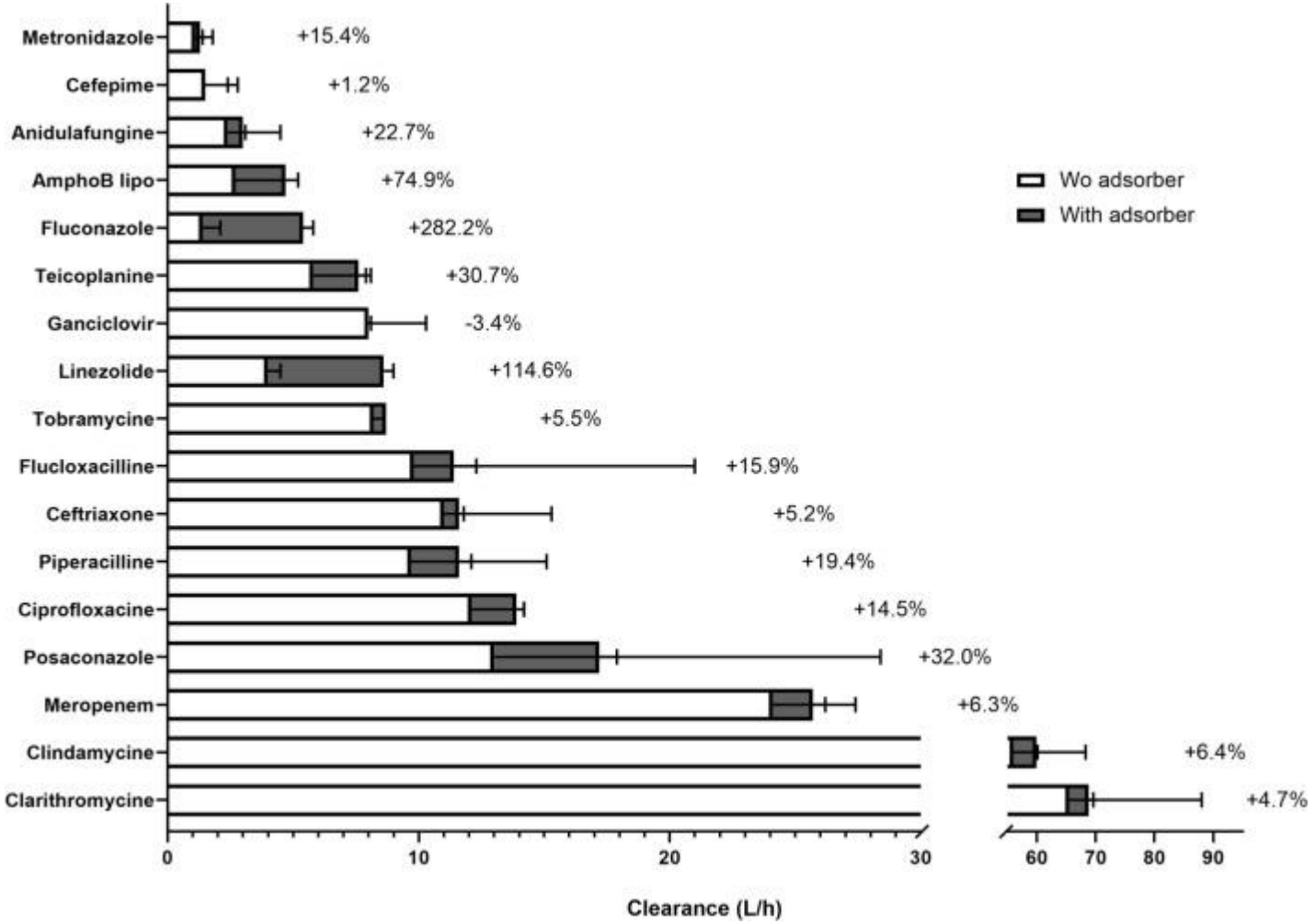


Schneider AG. J Antimicrob Chemother 2021

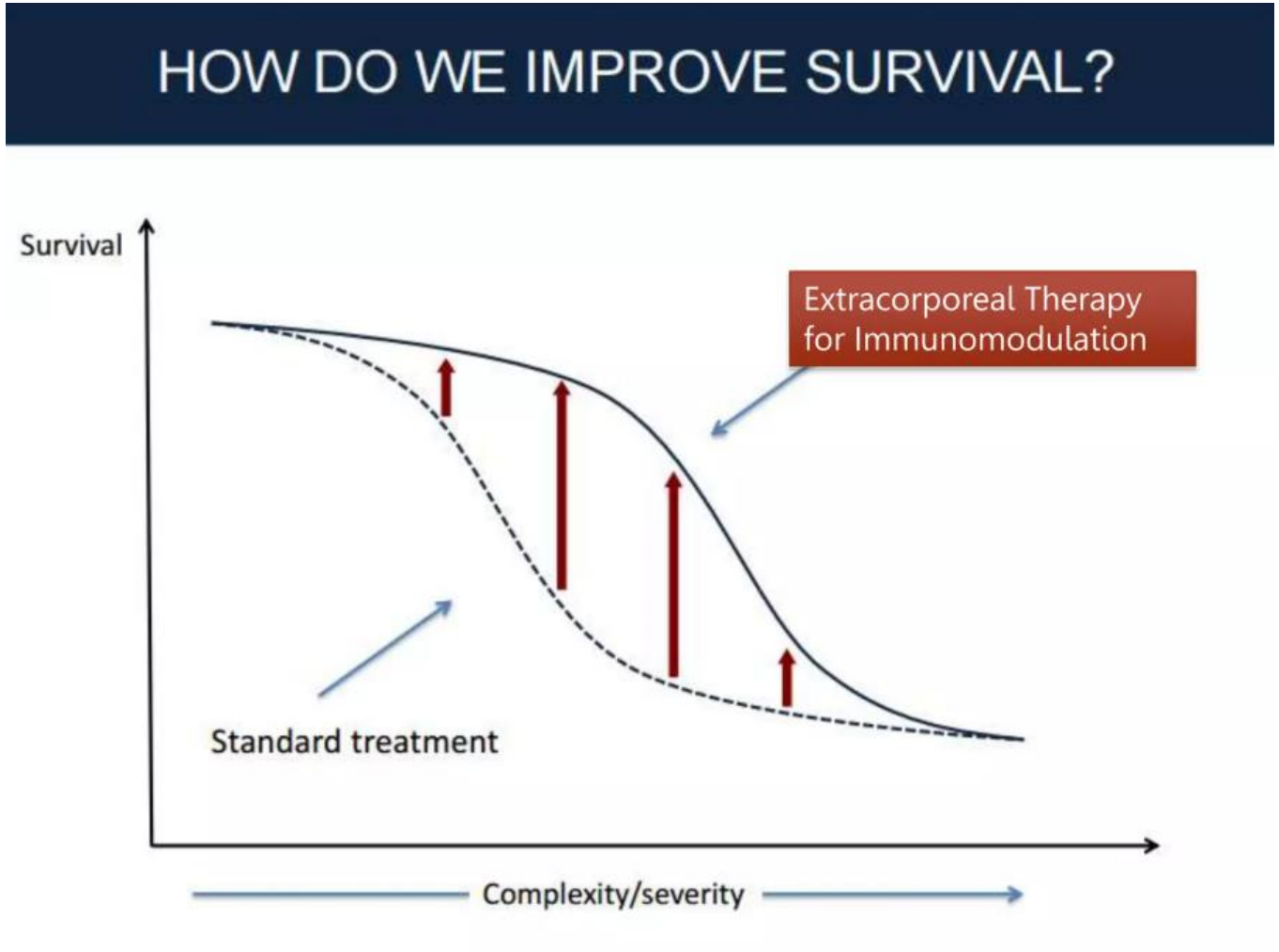
JAFRON (HA330/HA380)

Huang et al. [2010]	RCT	44	Severe sepsis	Attenuated circulating IL-6 and IL-8 concentrations. Improved hemodynamic parameters, lower SOFA score, shorter ICU LOS, and lower ICU mortality
Huang et al. [2013]	RCT	46	ARDS caused by extrapulmonary sepsis	Lower circulating IL-1 and TNF concentrations. Lower dopamine and norepinephrine requirements, shorter ICU LOS, lower ICU and 28-day mortality
He et al. [2022]	RCT	60	CPB surgery	Lower circulating TNF, IL-6, IL-8, and IL-10 concentrations and vasoactive inotropic score. Shorter ICU LOS and duration of mechanical ventilation
Wang et al. [2024]	Retrospective	117	Acute type A aortic dissection surgery	Lower circulating IL-6 concentrations and lower incidence of AKI and ARDS. No difference in postoperative complications and mortality

OXIRIS

Schwindenhammer et al.	Retrospective	None	31	Septic shock requiring RRT	Improvement of lactate and reduced norepinephrine requirement. Hospital mortality lower than expected for the most severe patients	
Broman et al.	RCT; crossover	Standard care	16	Septic shock and AKI	More pronounced decrease in circulating endotoxin and cytokine concentrations. Lower lactate levels and reduced norepinephrine requirement	
Wendel-Garcia et al.	RCT	Toraymyxin or standard care	30	Severe septic shock and EAA ≥ 0.6	No difference in reduction of EAA levels	No difference in other inflammatory markers, SOFA score and lactate levels
Pérez-Fernández et al.	RCT	Standard care	343	CPB surgery	Lower incidence of AKI	No difference in ICU LOS, hospital LOS, and mortality at day 7, 28 and 90

PRI KATERIH BOLNIKIH S SEPSO?



Yessayan L. Ren Fail. 2025

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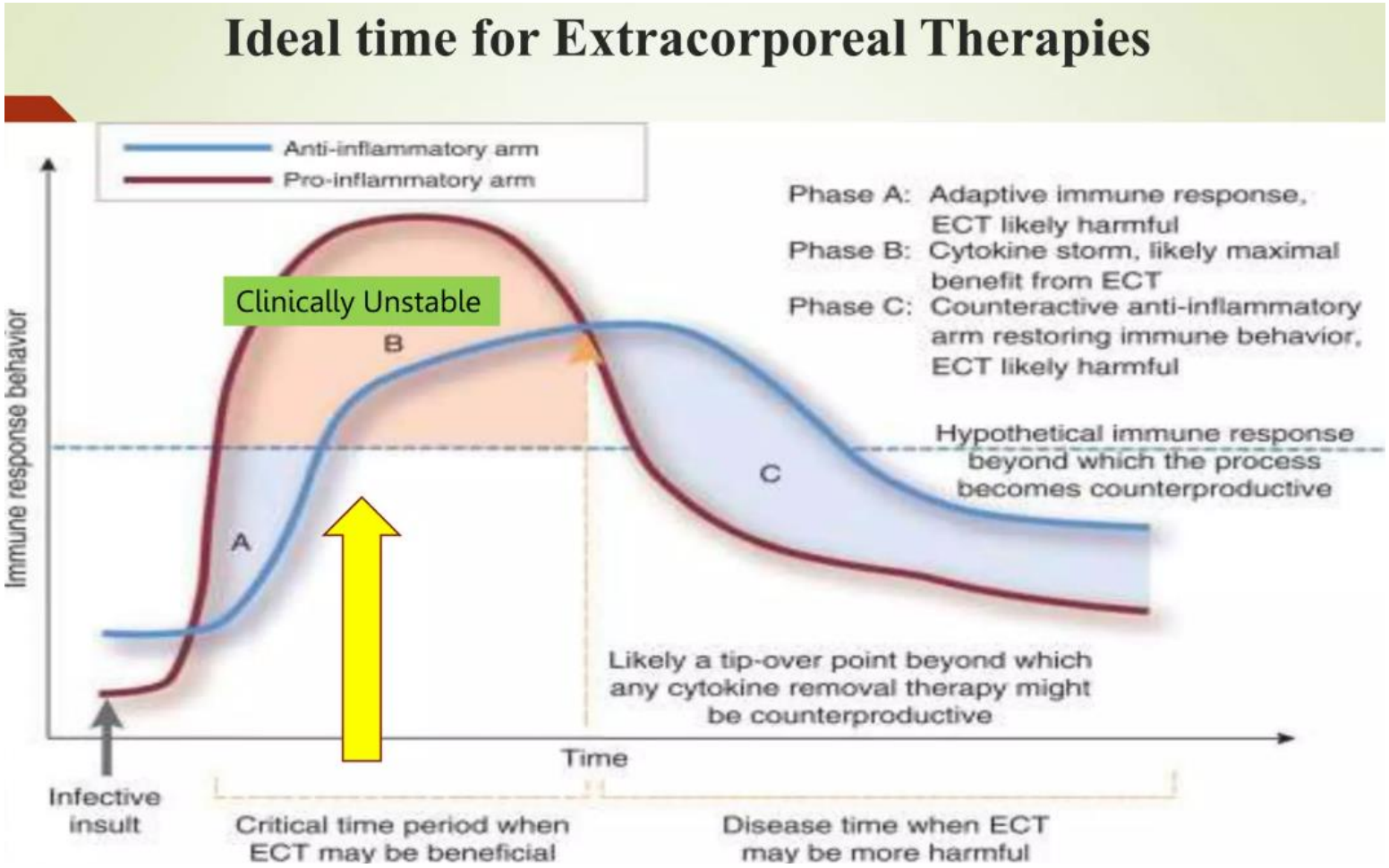
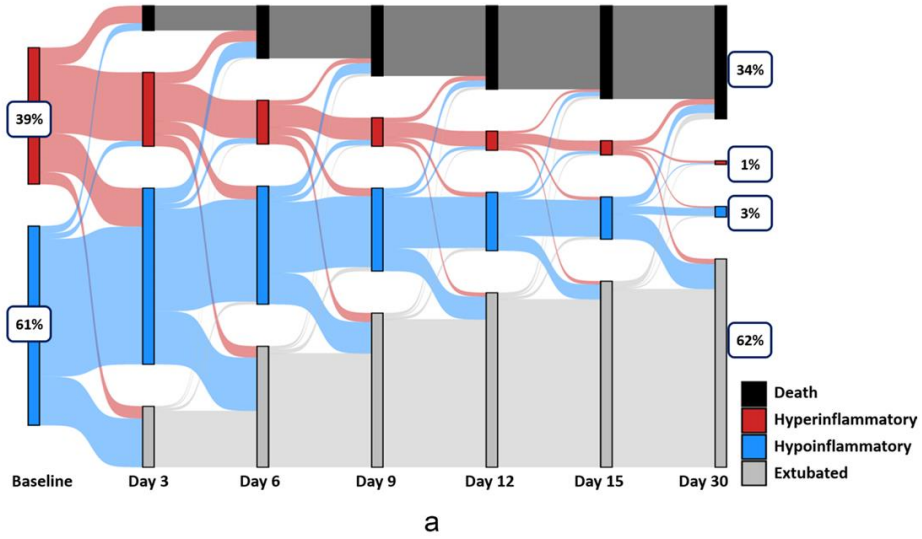


Mehta Y. World J Crit Care Med. 2023

SKLADNOST REZULTATOV



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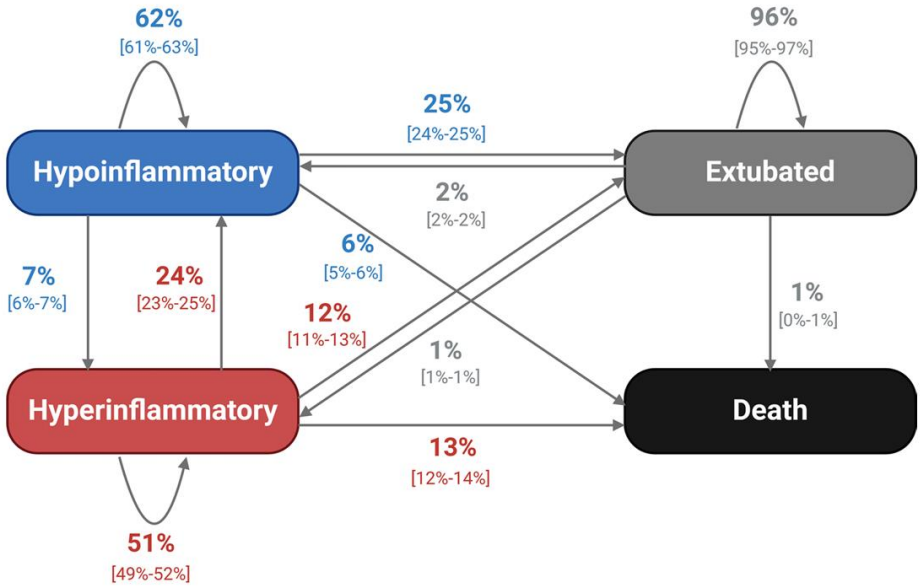
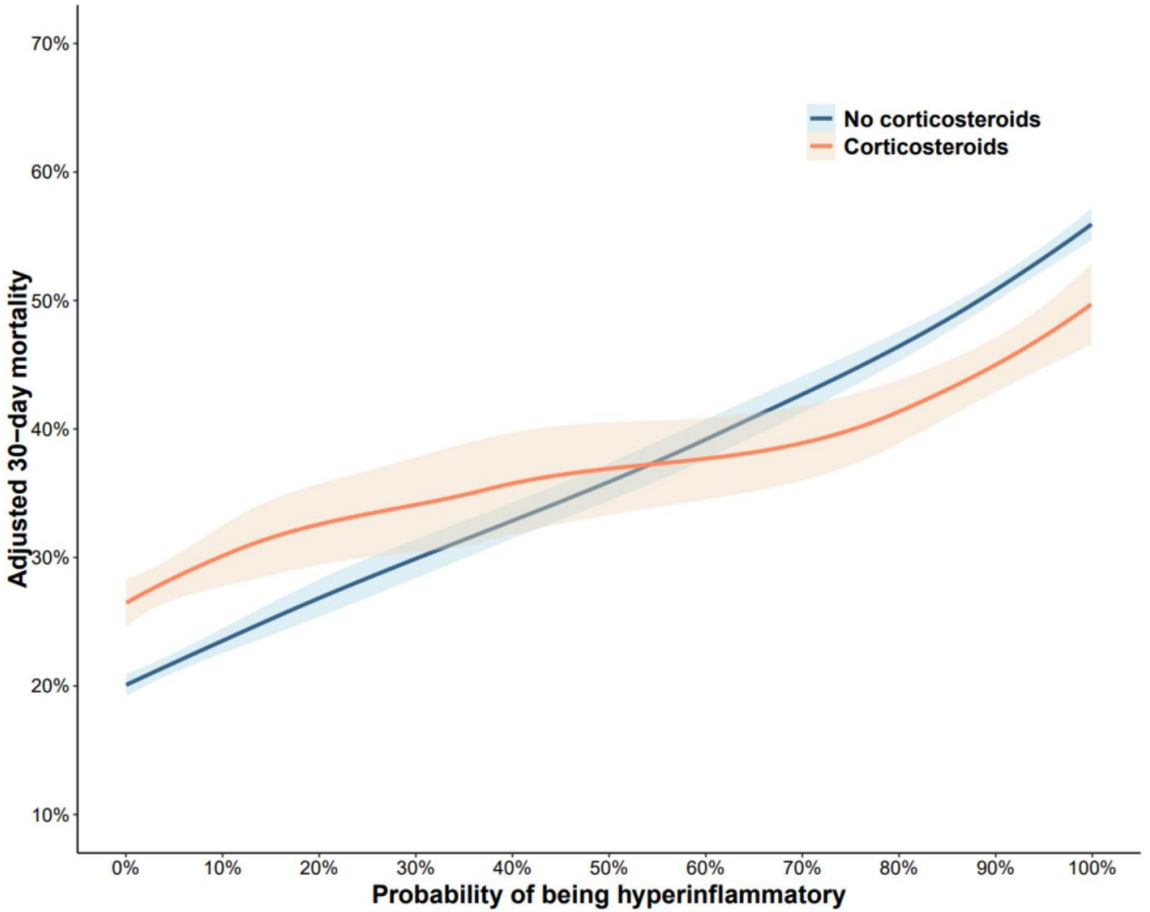
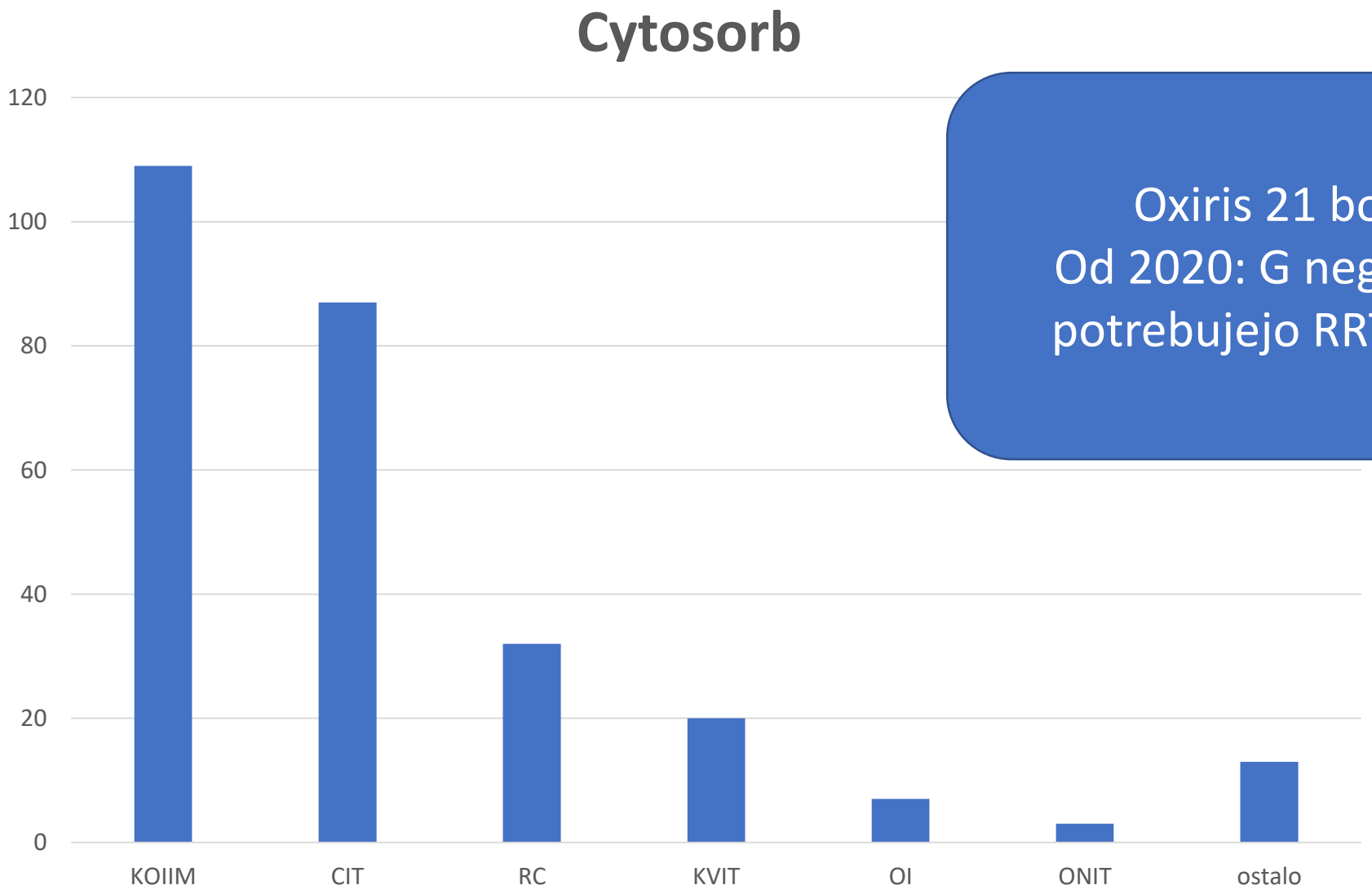




Pensier J. Intensive care med 2025

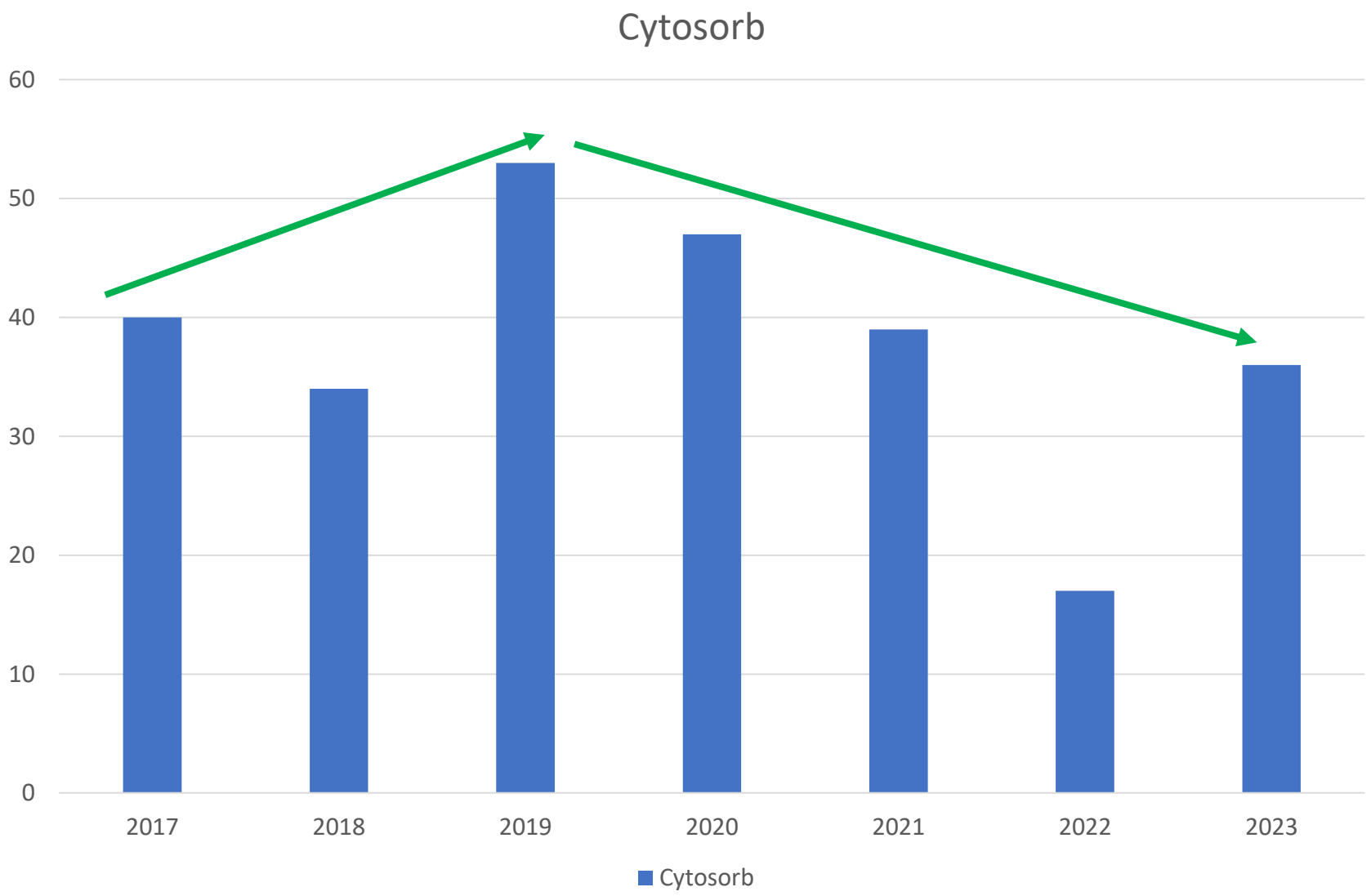
IZKUŠNJE UKCL 2017-2024



Oxiris 21 bolnikov
Od 2020: G neg. sepse, ki potrebujejo RRT (CVVHD)

Zahvala dr. Vanji Peršič

IZKUŠNJE UKCL 2017-2024



PODATKI KOIIM 2017-2022

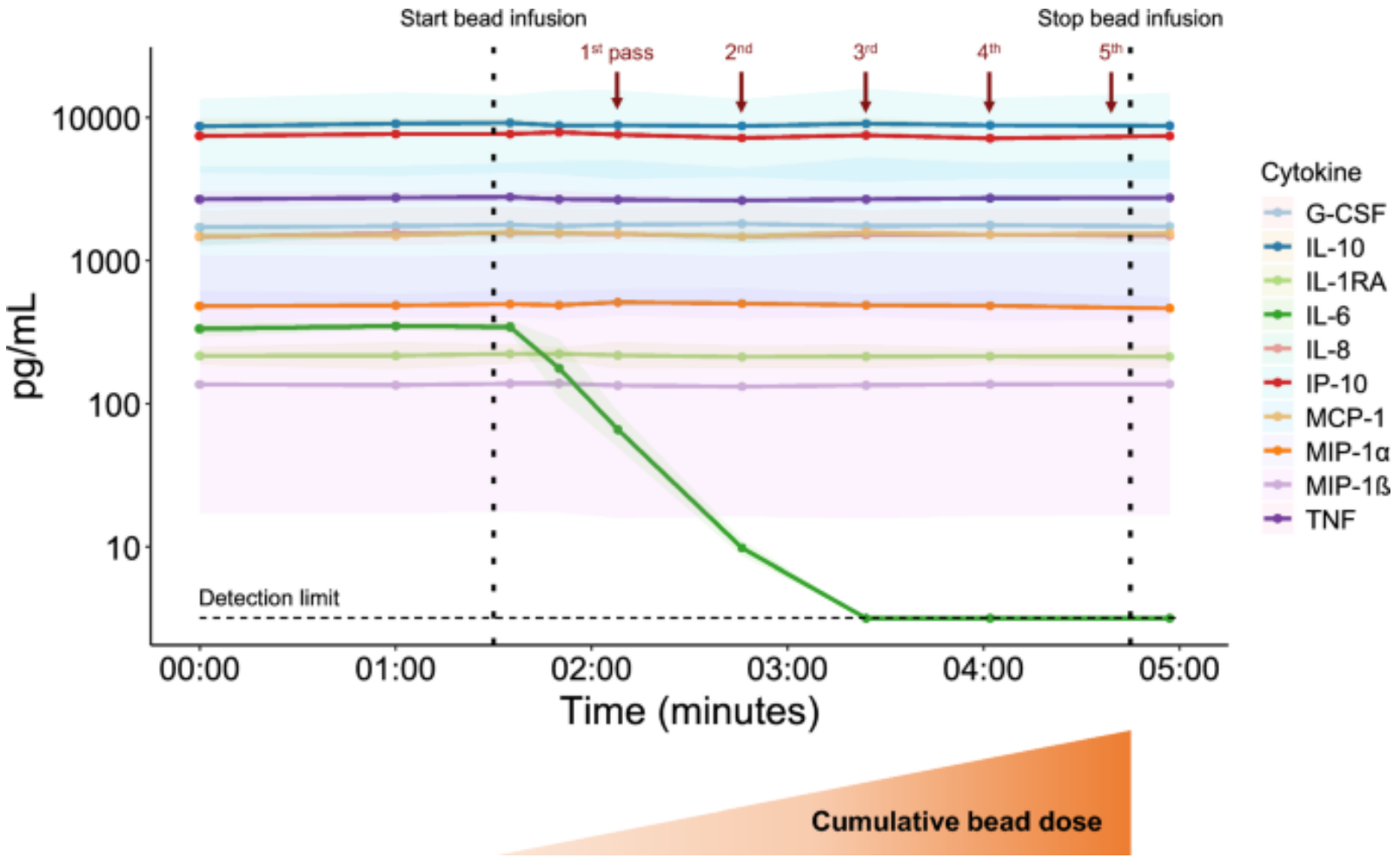
VIS pred	83 (75 – 106)
VIS po	40 (34 – 74)
Laktat pred (mmol/L)	7 (3 – 10)
Laktat po (mmol/L)	4 (2,6 – 8)
IL-6 pred (ng/L)	5000 (2300 – 13000)
IL-6 po (ng/L)	645 (170 – 1700)

	Septični šok N = 46
APACHE II	29 (27 – 33)
Predicted mortality	**68 (60 – 80)**
SAPS pred. mortality	**65 (48 – 87)**
SOFA	15 (12 – 18)
Predicted mortality	**70 (50 – 90)**

	SIRS po OHCA 18	Kardiogeni šok 12	**Septični šok 53**	Crush 3
• VV ECMO 1	• VA ECMO 7	• VA ECMO 6	• **VV ECMO 13**	• Preživeli 2/3
• Preživeli 3/4	• Preživeli 5/18	• Preživeli 1/12	• **Preživeli 14/53**	• Mortaliteta 33%
• Mortaliteta 25%	• Mortaliteta 72%	• Mortaliteta 92%	• **Mortaliteta 74%**	

Zahvala dr. Jerneju Berdenu

V PRIHODNJE?



Waalders N. Sci report 2024

V PRIHODNJE?

The score can be taken 6 hrs. after diagnosis of septic shock/start of standard therapy to define severity and support decision making in regard to initiation of CytoSorb Therapy.

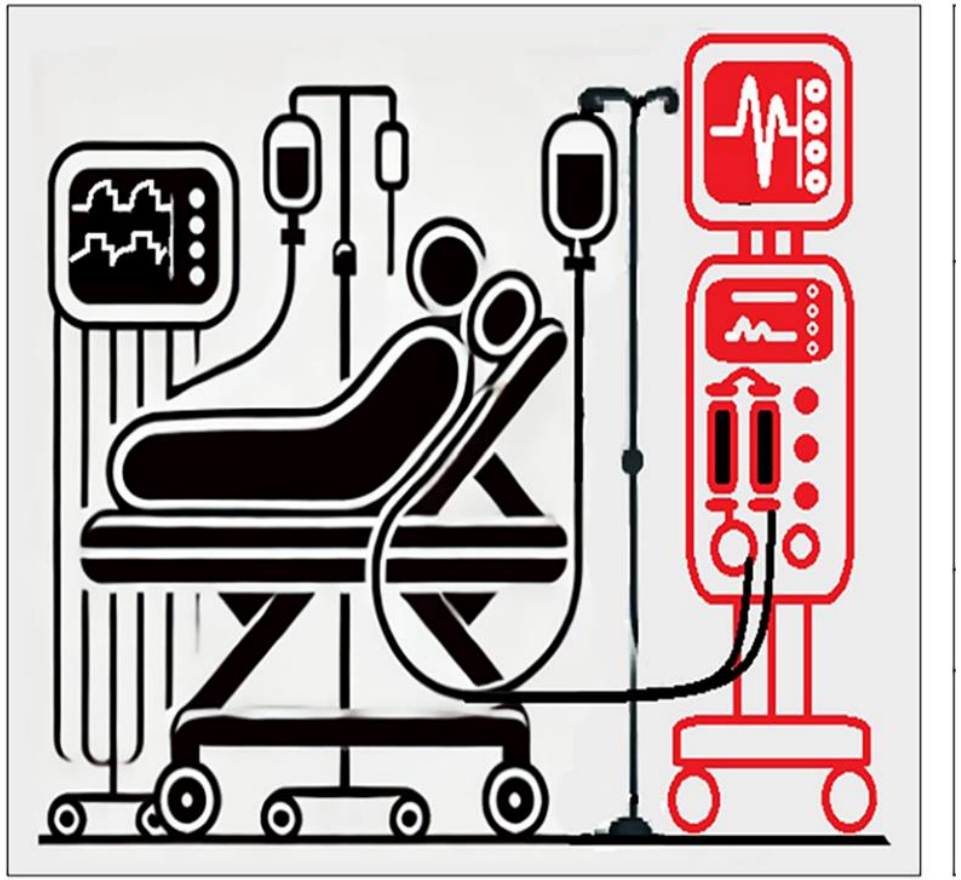
1 Lactate mmol/l	< 2.0		≥ 2.0
2 Lactate change / 6hrs	decreased	≤ 50 %	> 50 %
3 NE* µg/kg/min (MAP** ≥ 65)	< 0.1		≥ 0.1
4 NE change / 6hrs	decreased	≤ 50 %	> 50 %
5 2nd catecholamine / vasopressor	No	Yes	
6 Hydrocortisone use	No	Yes	
7 Volume bolus 30 ml/kgbw***	No	< 2.0 boli	≥ 2.0 boli

* Norepinephrine \ ** Mean Arterial Pressure \ *** Kilogram Body Weight

„this easy-to-apply scoring system would **require validation** in a prospective manner to learn whether patients to be treated with hemoadsorption therapy in the course of septic shock could thereby be identified“

Kogelmann K. J Clin Med 2021

POVZETEK



- Učinek odvisen od bolnikovega fenotipa / časa aplikacije
- Neselektivnost
- Pomanjkanje dokazov (večjih RCT)
- Potencialna škoda (odstranjevanje zdravil)
- Ne rutinsko – raziskave / registri