XXX I Corso Nazionale di Aggiornamento

15—16—17 aprile Sala Congressi Hotel Corallo Riccione

Via Gramsci, 113 47838 Riccione RN

Corso Nazionale Ante 2024

Provider N° 354 E.C.M. Educazione Continua in Medicina

Programma Nazionale per la Formazione degli operatori della Sanità

Evento N. 370906 edizione N. 1

Crediti assegnati 9,8

Direttore Scientifico Vincenzo Cantaluppi

Presidente Ante Paolo Besati

Evoluzione tecnologica nei trattamenti dialitici cronici e acuti: dalla teoria alla pratica

UNIVERSITÀ DEL PIEMONTE ORIENTALE

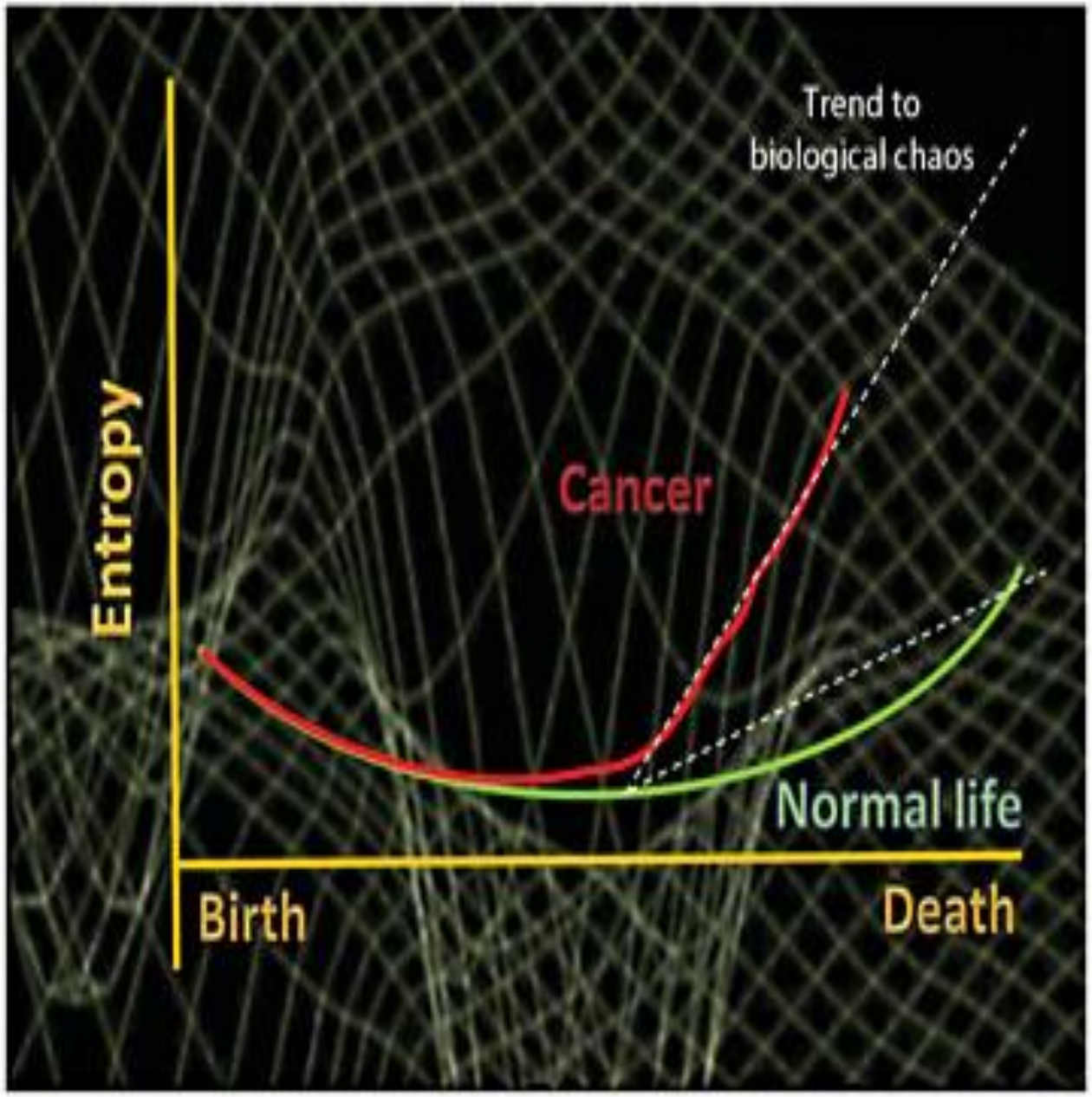
AKI associata a sepsi: ruolo dell'adsorbimento

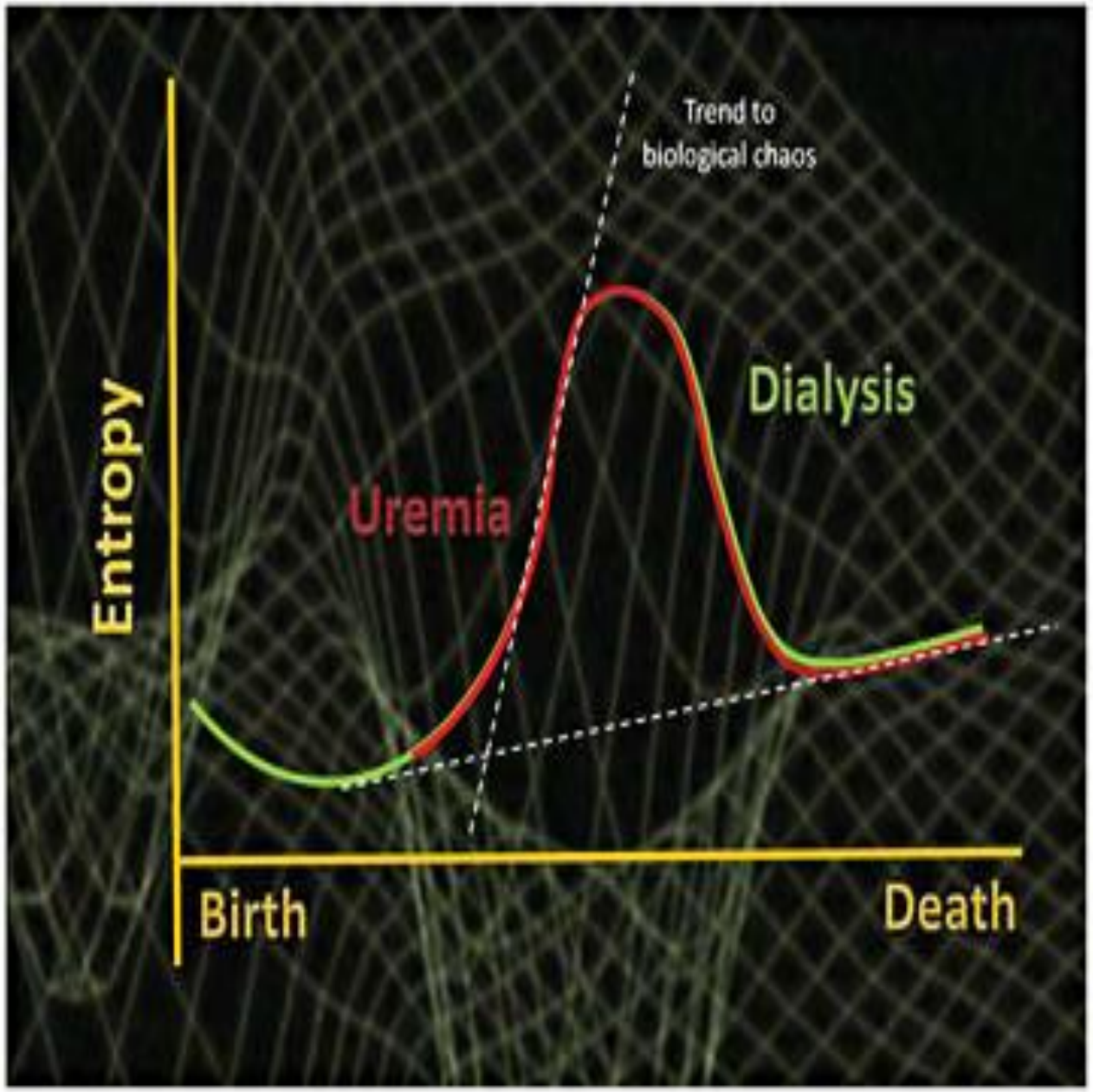
Vincenzo Cantaluppi

SCDU Nefrologia e Trapianto Renale, Dipartimento di Medicina Traslazionale e di Eccellenza su Aging (DIMET-AGING), Università del Piemonte Orientale (UPO), AOU Maggiore della Carità di Novara

Gruppo di Progetto AKI & CRRT SIN, Co-Chair ERAKI Working Group

From: **Entropy of Uremia and Dialysis Technology** **Ronco C.** Blood Purif. 2013;35(1-3):8-15. doi:10.1159/000345755

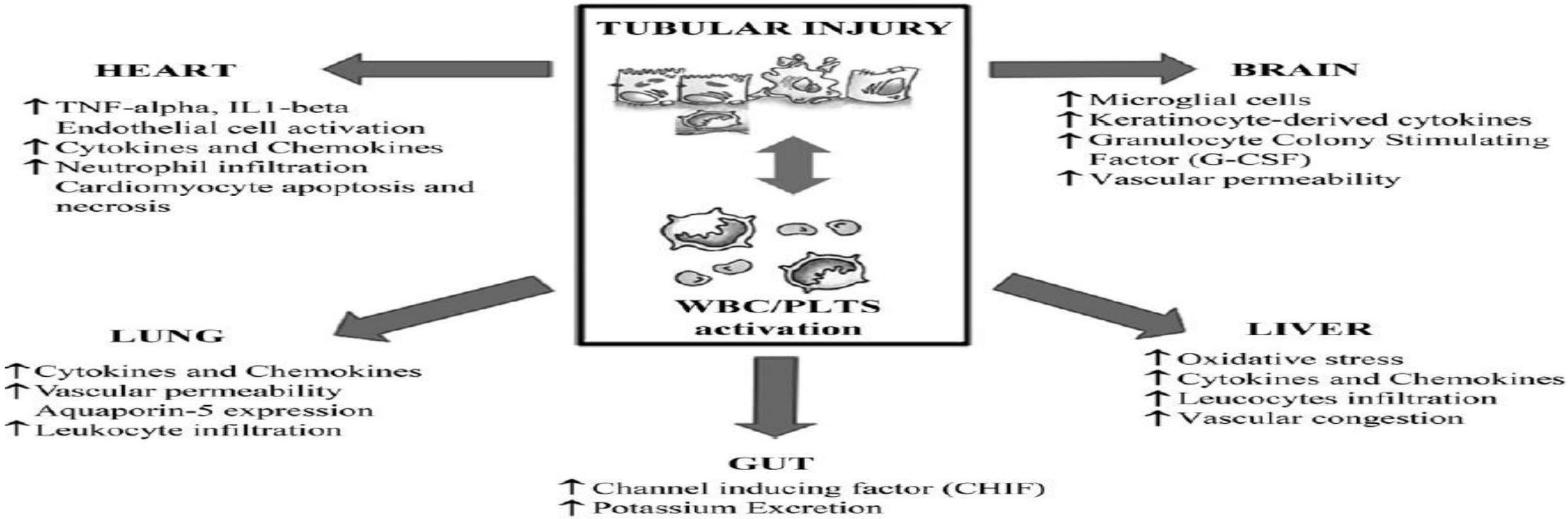




Interaction between systemic inflammation and renal tubular epithelial cells

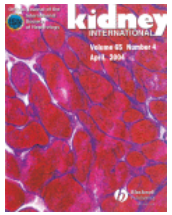
Vincenzo Cantaluppi, Alessandro Domenico Quercia, Sergio Dellepiane, Silvia Ferrario, Giovanni Camussi and Luigi Biancone

ndt
Nephrology Dialysis Transplantation



Plasma cytokine levels predict mortality in patients with acute renal failure

Edith M. Simmons, Jonathan Himmelfarb, M. Tugrul Sezer, Glenn M. Chertow, Ravindra L. Mehta, Emil P. Paganini, Sharon Soroko, Stephanie Freedman, Karen Becker, Daniel Spratt, Yu Shyr, and T. Alp Ikizler, for the PICARD Study Group



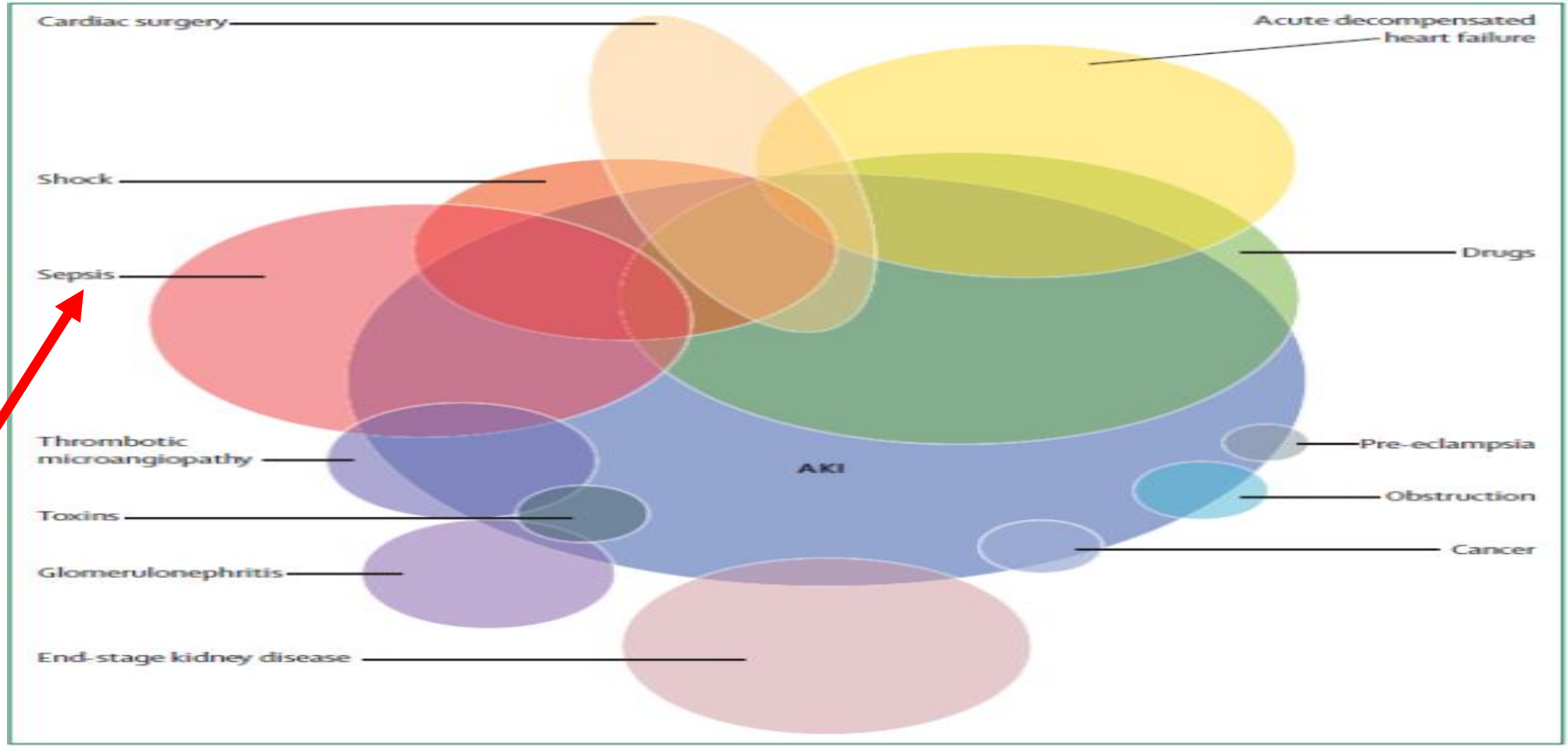
Acute kidney injury

Claudio Ronco, Rinaldo Bellomo, John A Kellum

THE LANCET

Vol 394 November 23, 2019

The clinical spectrum of AKI syndrome



SOURCE: CDC Vital Signs, August 2016.

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

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.

Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.

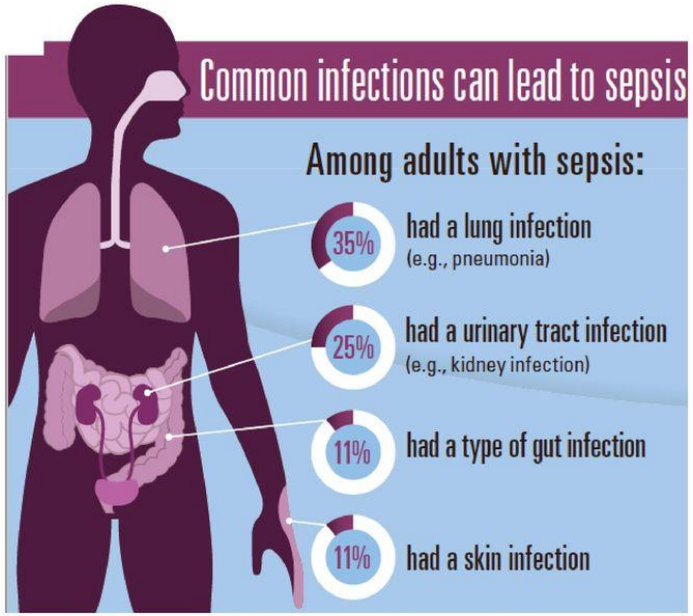


Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

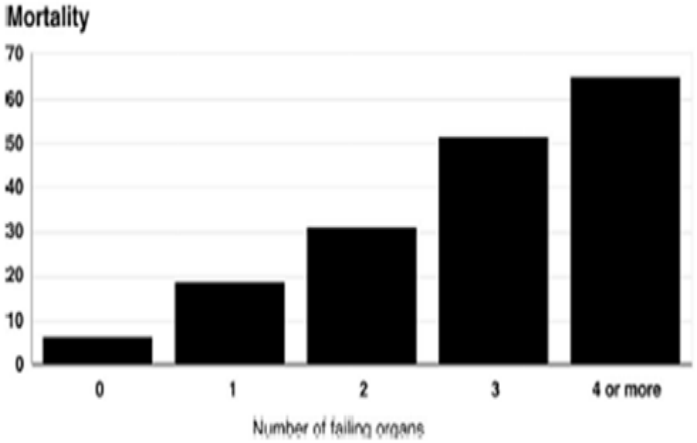
System	Score 0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.



Sepsis in European intensive care units: Results of the SOAP study*

Jean-Louis Vincent, MD, PhD, FCCM; Yasser Sakr, MB, BCh, MSc; Charles L. Sprung, MD; V. Marco Ranieri, MD; Konrad Reinhart, MD, PhD; Herwig Gerlach, MD, PhD; Rui Moreno, MD, PhD; Jean Carlet, MD, PhD; Jean-Roger Le Gall, MD; Didier Payen, MD; on behalf of the Sepsis Occurrence in Acutely Ill Patients Investigators

Crit Care Med 2006 Vol. 34, No. 2

Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup

nature reviews nephrology

Consensus statement 1a
We propose that sepsis-associated acute kidney injury (SA-AKI) be characterized by the presence of both consensus sepsis criteria (as defined by Sepsis-3 recommendations) and AKI criteria (as defined by Kidney Disease: Improving Global Outcomes recommendations) when AKI occurs within 7 days from diagnosis of sepsis (not graded).

Consensus statement 1b
We suggest that sepsis-induced AKI should be considered a subphenotype of SA-AKI in which sepsis is the predominant driver of tissue damage (not graded).

Consensus statement 1c
We suggest that AKI diagnosed within 48 h of the diagnosis of sepsis be defined as early SA-AKI, whereas AKI occurring between 48 h and 7 days of sepsis diagnosis be classified as late SA-AKI (not graded).

Consensus statement 1d
The epidemiology of SA-AKI varies and depends on the patient population and the criteria used to define AKI and sepsis (not graded).

Consensus statement 2a
Sepsis-associated acute kidney injury (SA-AKI) is a heterogeneous syndrome as multiple mechanisms contribute to injury with varying intensity between and within patients across the course of sepsis (not graded).

Consensus statement 2b
The relative contribution of one or more specific mechanisms that lead to injury defines distinct sepsis-induced AKI endotypes (not graded).

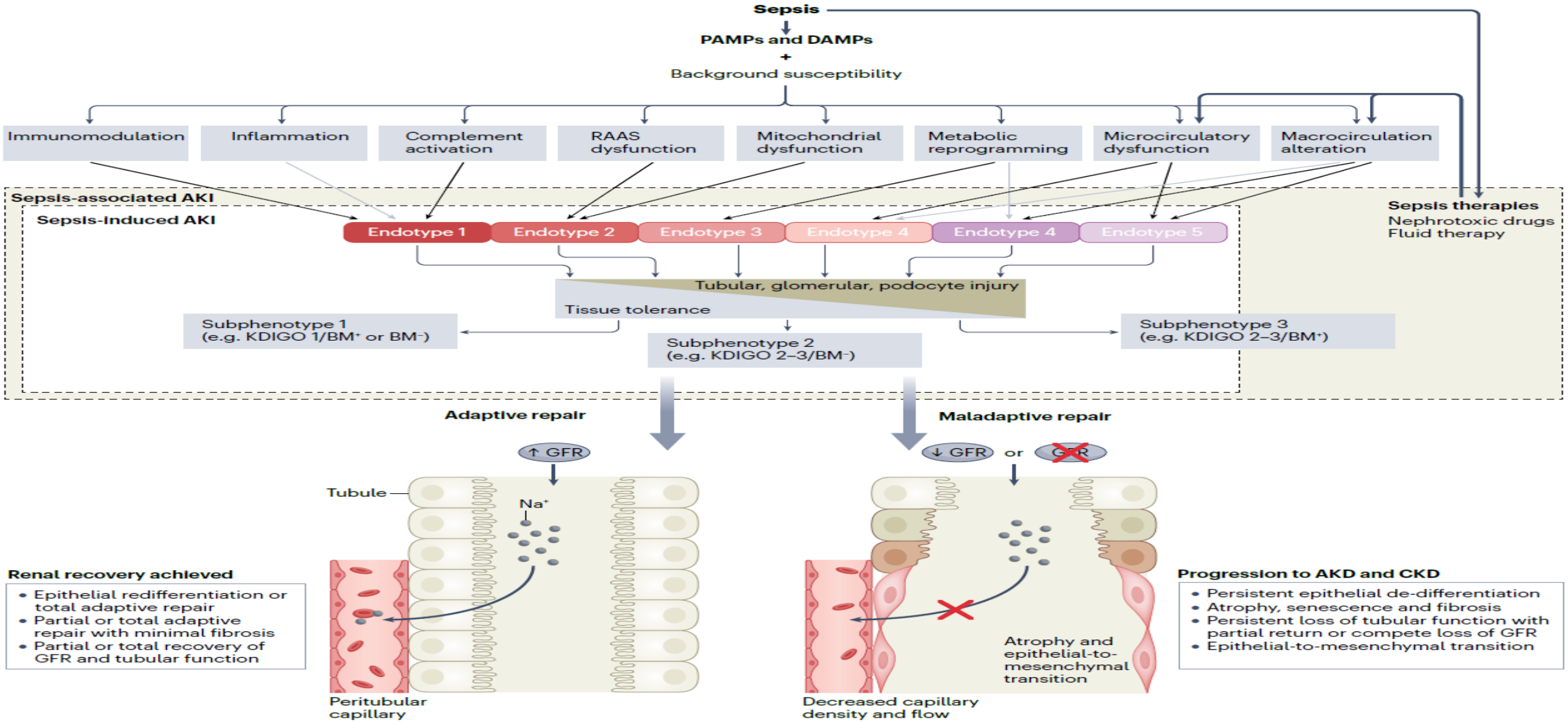
Consensus statement 2c
Modifiable and non-modifiable factors confer susceptibility to SA-AKI and determine the severity of AKI as well as the trajectory of recovery (not graded).

Consensus statement 2d
Integrating mechanism-specific biomarkers with clinical information will enable the identification of specific endotypes of SA-AKI (not graded).

Consensus statement 2e
Identifying distinct endotypes of SA-AKI might provide crucial prognostic information, help to define treatment responsiveness and enrich clinical trial populations (not graded).

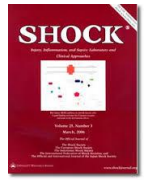
Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup

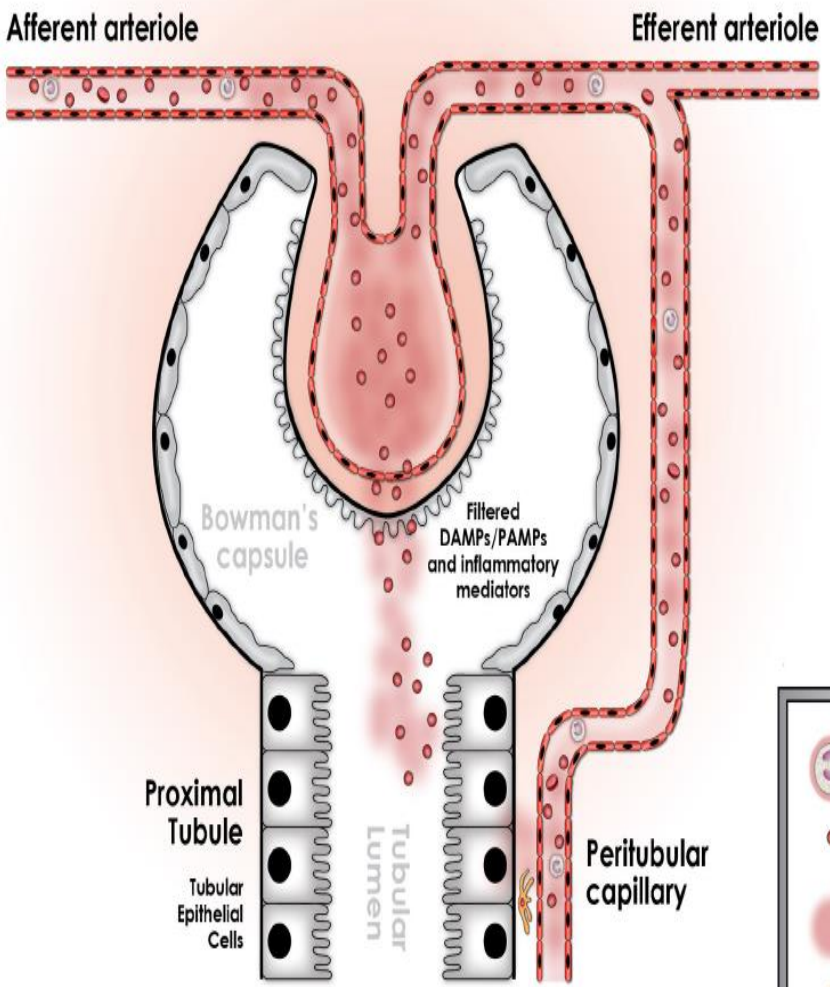
nature reviews nephrology

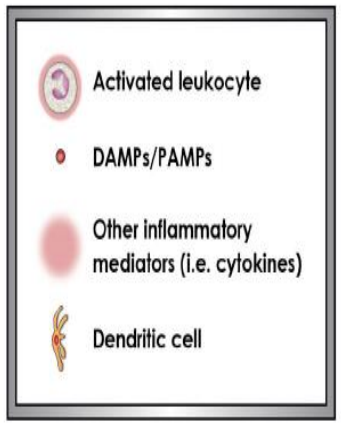


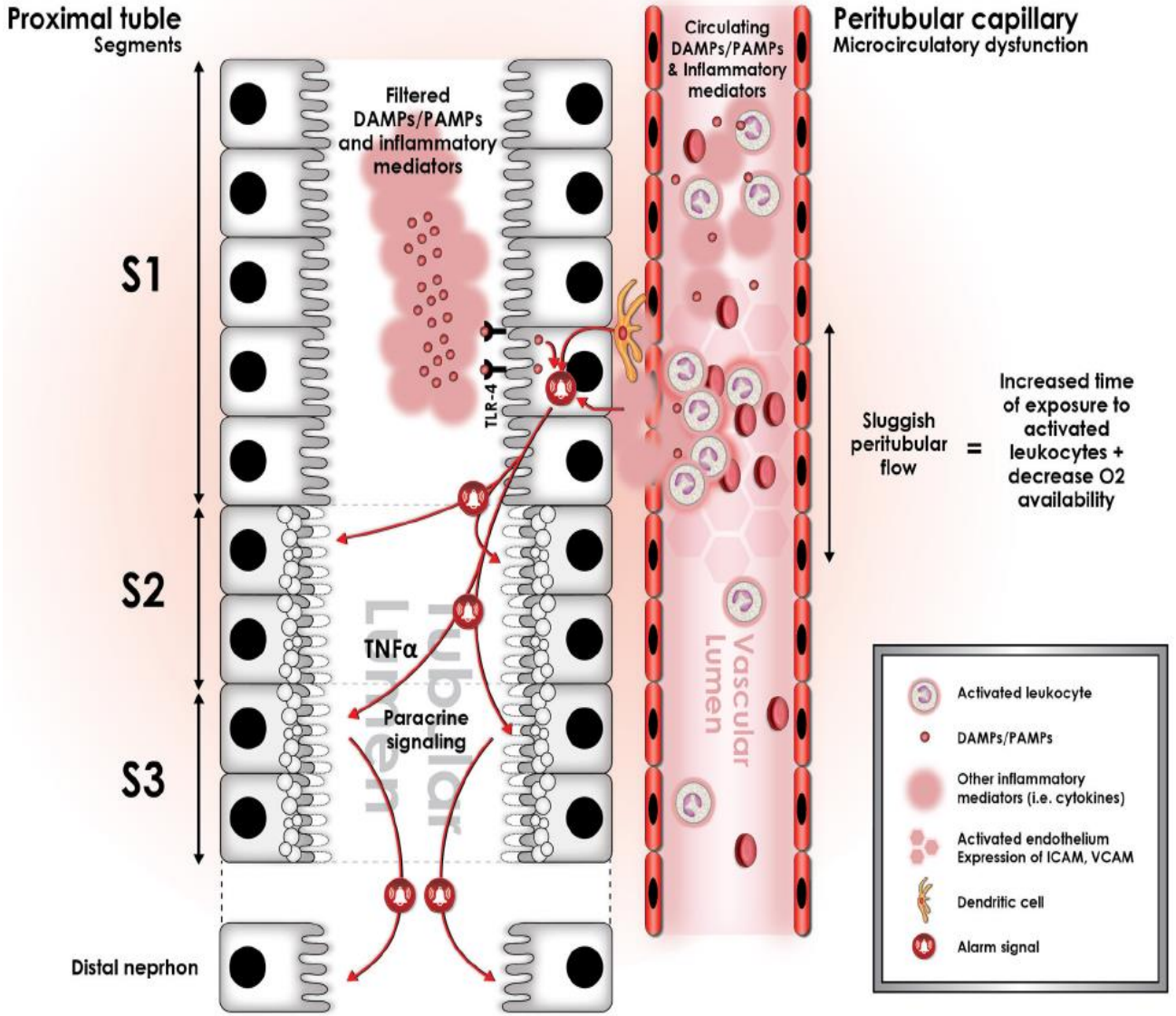
A Unified Theory of Sepsis-Induced Acute Kidney Injury: Inflammation, microcirculatory dysfunction, bioenergetics and the tubular cell adaptation to injury

Hernando Gomez, MD[*,†], Can Ince, PhD[†], Daniel De Backer, MD[‡], Peter Pickkers, MD[§], Didier Payen, MD[‖], John Hotchkiss, MD[*], and John A. Kellum, MD[*,†]





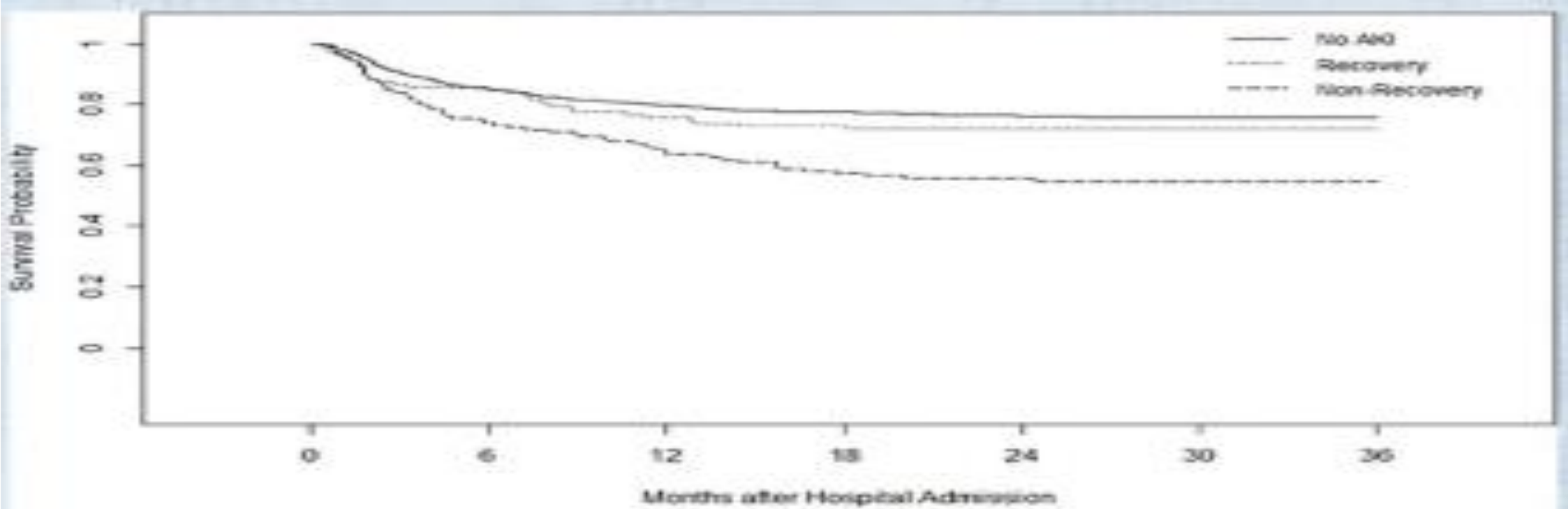




Long-term survival in patients with septic acute kidney injury is strongly influenced by renal recovery

Marco Fiorentino[1,2*], Fadi A. Tohme[1,3,4*], Shu Wang[1,5], Raghavan Murugan[1,3], Derek C. Angus[3], John A. Kellum[1,3,4*]

A multicenter study of pneumonia and sepsis
GenIMS
Genetic and Inflammatory Markers of Sepsis



Number of subjects at risk

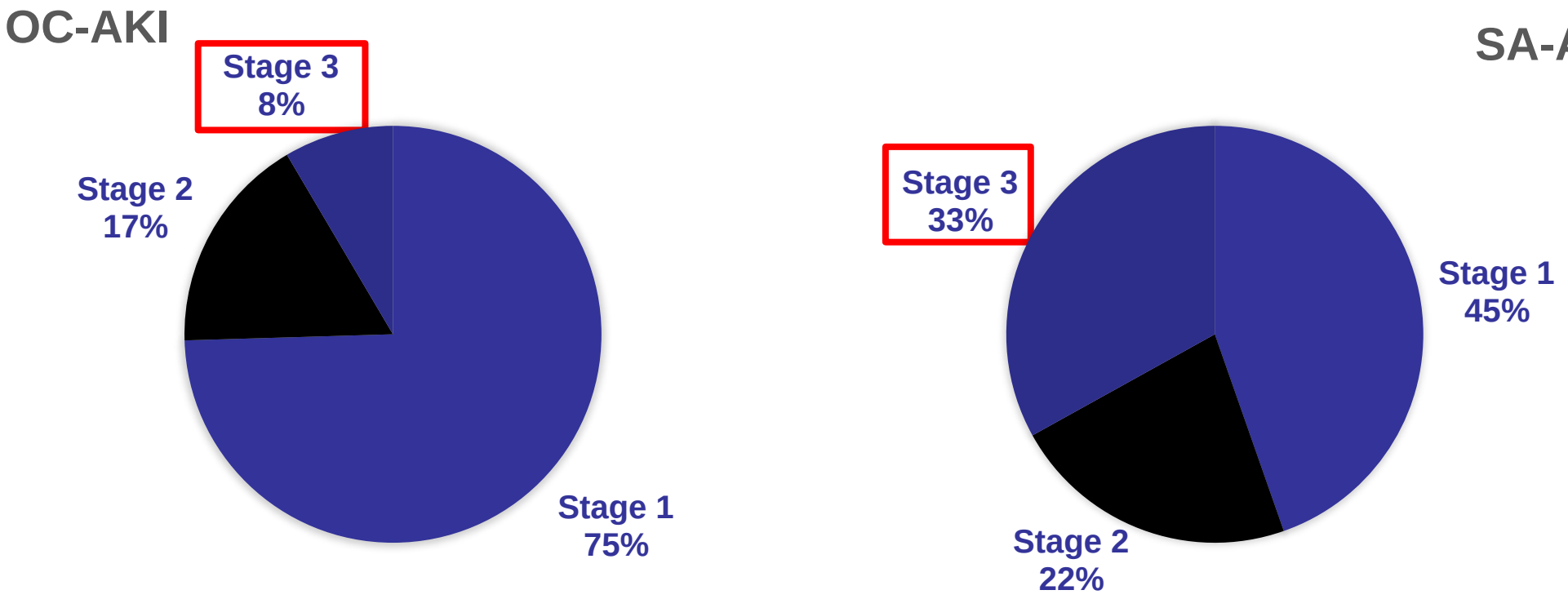
	0	6	12	18	24	30	36
No AKI	1480 (100%)	1261 (85%)	1180 (79.7%)	979 (66%)	496 (33.5%)	196 (13.2%)	25 (1.6%)
Recovery	111 (100%)	94 (84.6%)	84 (75.6%)	70 (63%)	37 (33.3%)	20 (18%)	6 (5.4%)
Non recovery	151 (100%)	112 (74.2%)	97 (64.2%)	77 (50.9%)	41 (27.1%)	14 (9.2%)	3 (1.9%)

SIN-AKI study

A.O.U. "Maggiore della Carita'" Novara- ITALY

UNIVERSITÀ DEL PIEMONTE ORIENTALE

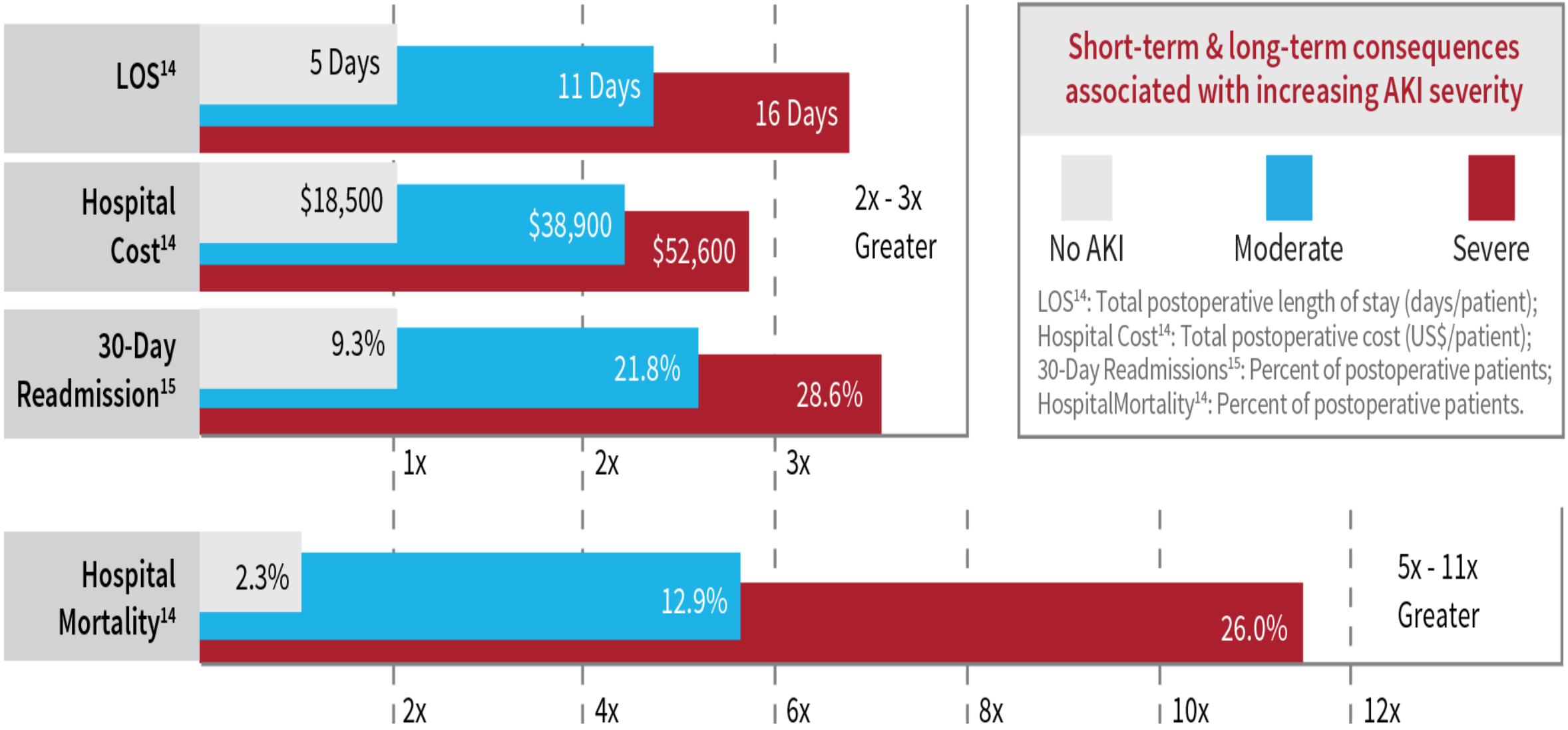
Società Italiana Nefrologia



- **The percentage of KDIGO Stage 3 is higher in the SA-AKI than in the OC-AKI cohort and characterized by a more frequent need of RRT (p < 0,001).**

- **Stage 3 AKI increased the risk of progression to Acute Kidney Disease (AKD) and Chronic Kidney Disease (CKD) in a follow-up period of 3 months (OR 8,19, p < 0,001)**

The Acute Kidney Injury Effect



Short-term & long-term consequences associated with increasing AKI severity

No AKI | Moderate | Severe

LOS[14]: Total postoperative length of stay (days/patient);
Hospital Cost[14]: Total postoperative cost (US$/patient);
30-Day Readmissions[15]: Percent of postoperative patients;
HospitalMortality[14]: Percent of postoperative patients.

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

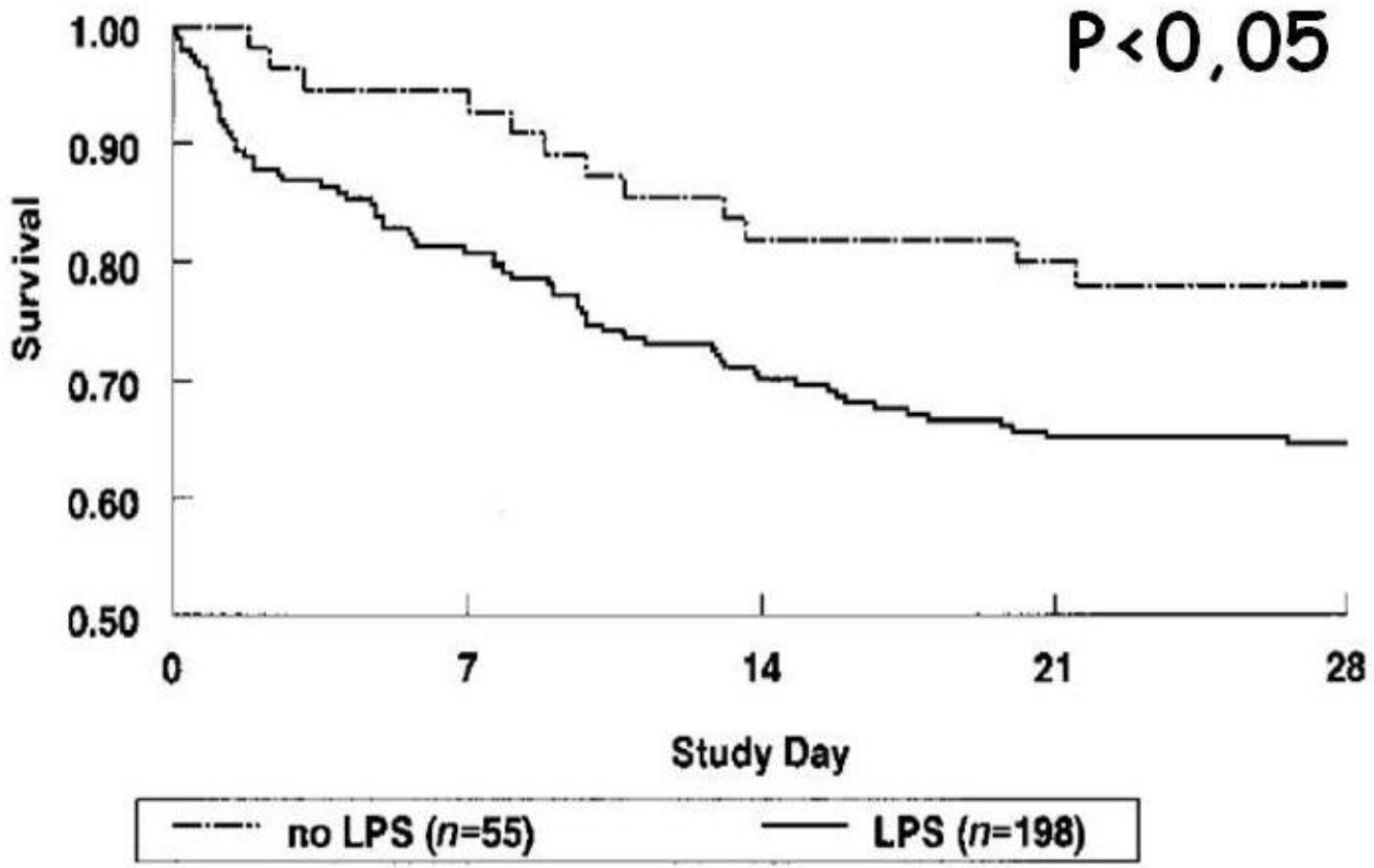
Pathway	Mediators	Treatment	Results of RCTs
	Superantigens: TSST-1	Anti-TSST-1	Not evaluated
	Streptococcal exotoxins (e.g., streptococcal pyrogenic exotoxin A)	Antistreptococcal exotoxins	Not evaluated
	Lipopolysaccharide (endotoxin)	Antilipopolysaccharide[9]	Negative
Innate immunity	TLR-2, TLR-4	TLR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

Table 1. (Continued.)

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

All negative!!!

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



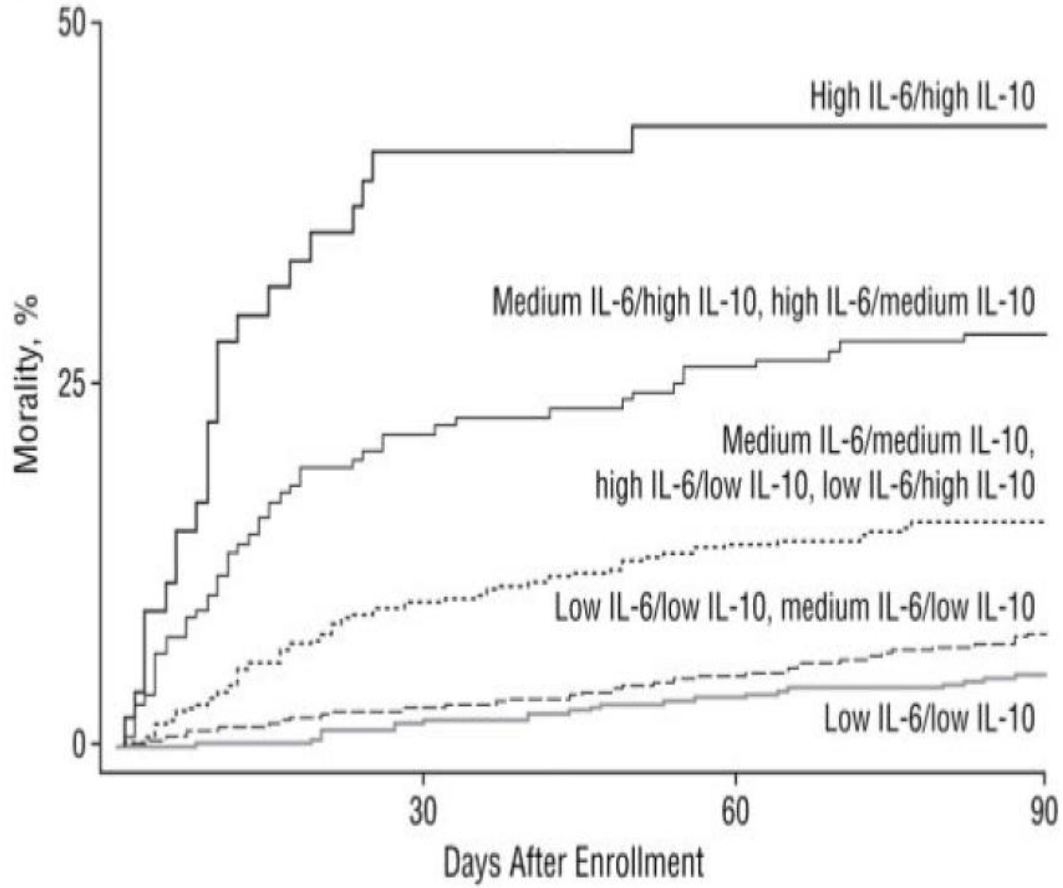
Opal SM, Infect Dis 1999

Understanding the Inflammatory Cytokine Response in Pneumonia and Sepsis

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

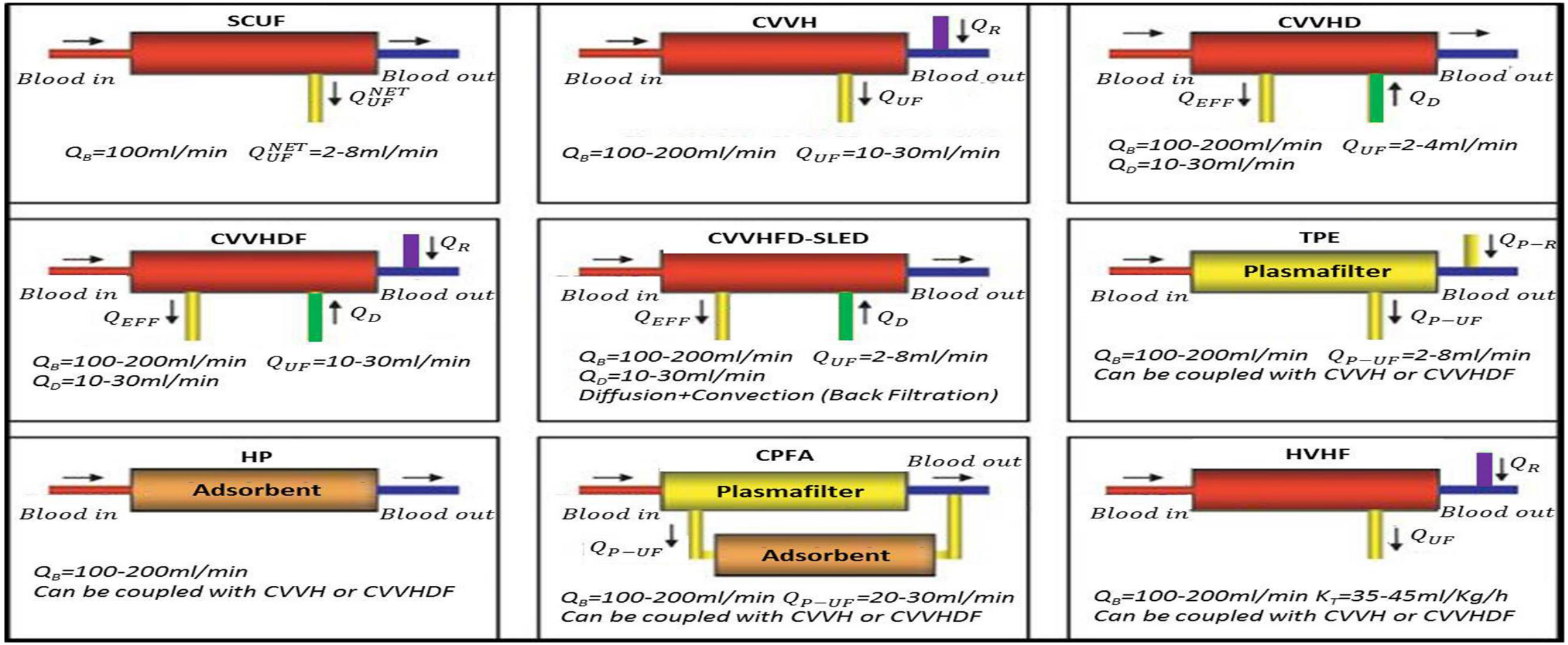
John A. Kellum, MD; Lan Kong, PhD; Mitchell P. Fink, MD; Lisa A. Weissfeld, PhD; Donald M. Yealy, MD; Michael R. Pinsky, MD; Jonathan Fine, MD; Alexander Krichevsky, PhD; Russell L. Delude, PhD; Derek C. Angus, MD, MPH; for the GenIMS Investigators

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



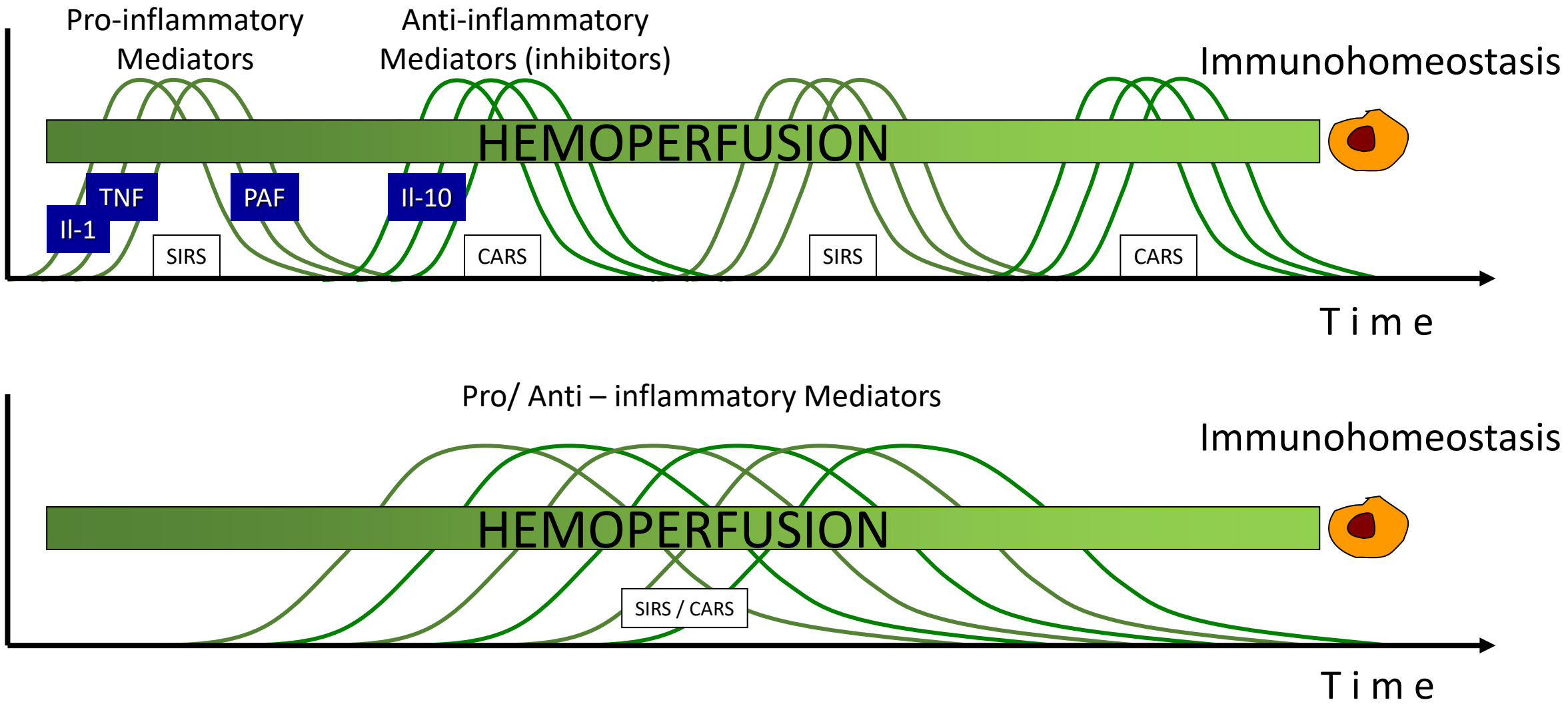
Come dializzare? Anarchia dai recenti RCTs

Villa *et al. Critical Care* (2016) 20:283



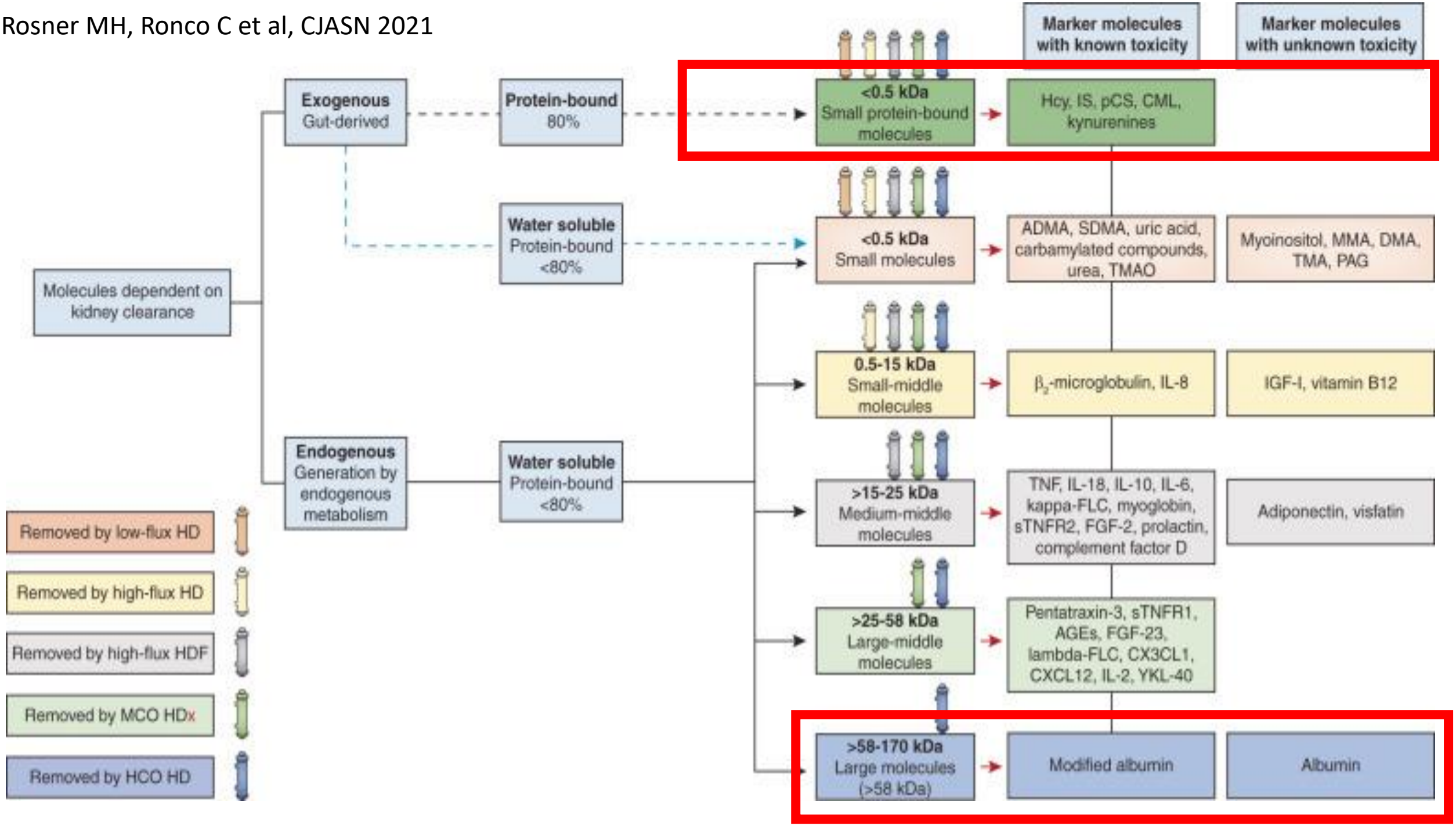
Timing.....Dose.....Anticoagulazione

The Peak Concentration Hypothesis

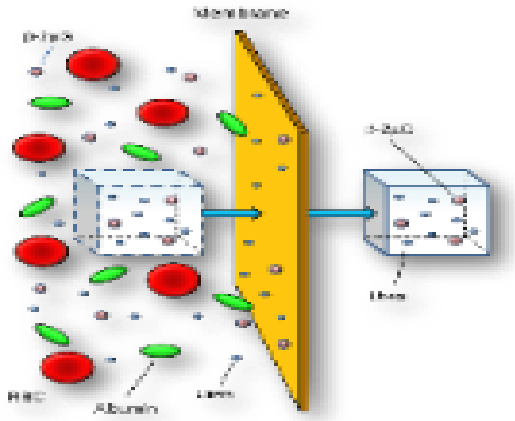


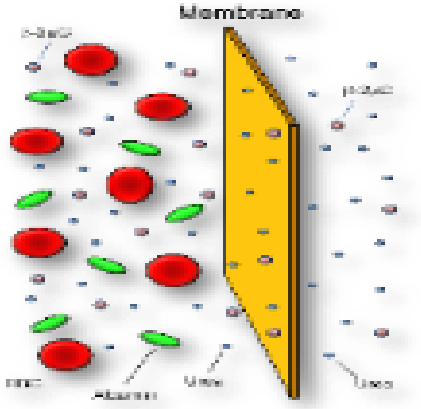
Ronco et Al Artif Organs 2003

Rosner MH, Ronco C et al, CJASN 2021



Mass Separation Processes



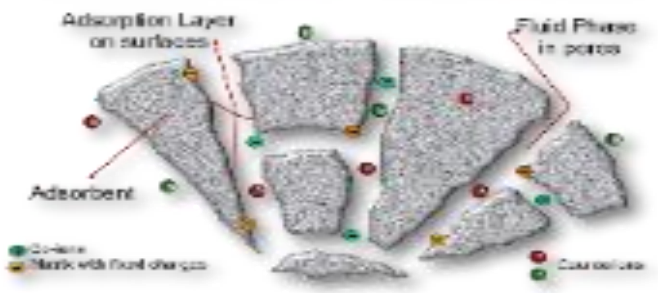


Diffusion
Hemodialysis
High Flux Dialysis

Blood Purification

Convection
Hemofiltration
Hemodiafiltration

Adsorption
Hemoadsorption
Hemoperfusion

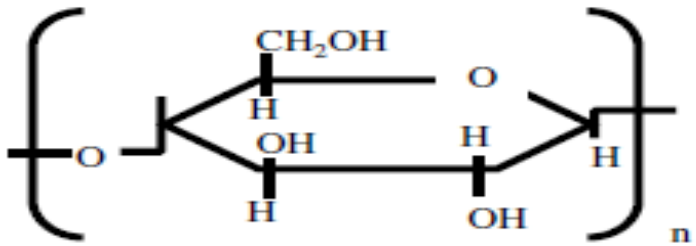


a) **Separation by barrier or membrane** (dialysis, ultrafiltration)

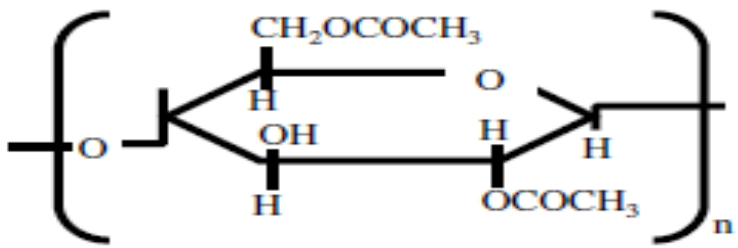
b) **Separation by solid agent or sorbent** (adsorption, ion exchange)

Chemical structures of cellulosic and synthetic polymeric membranes for blood purification: the concept of High Performance Membranes (enhanced clearances + biocompatibility)

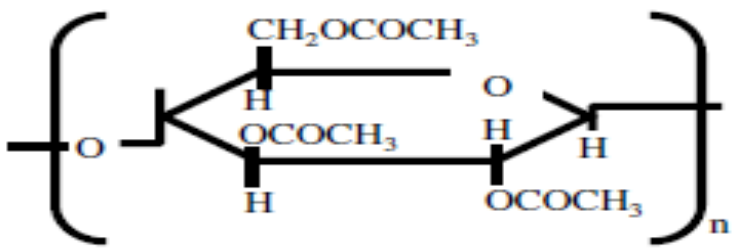
Cellulosic membranes



Regenerated cellulose

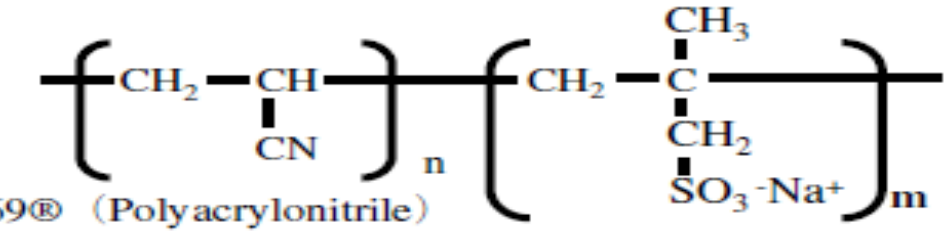


Cellulose diacetate (CDA)

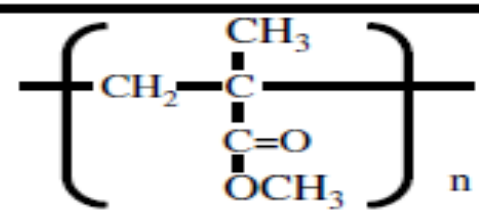


Cellulose triacetate (CTA)

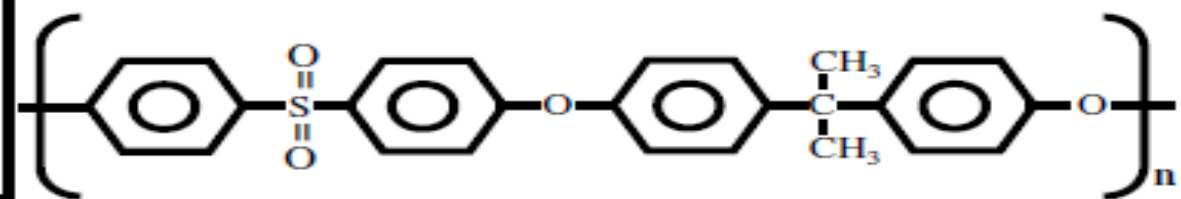
Synthetic polymeric membranes



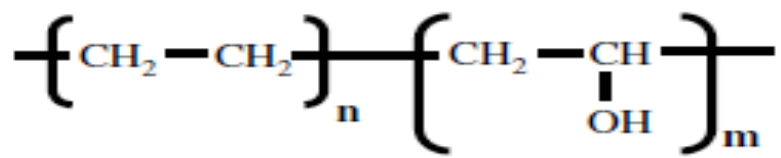
AN-69® (Polyacrylonitrile)



Polymethylmethacrylate (PMMA)



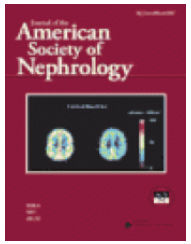
Polysulfone (PSf)

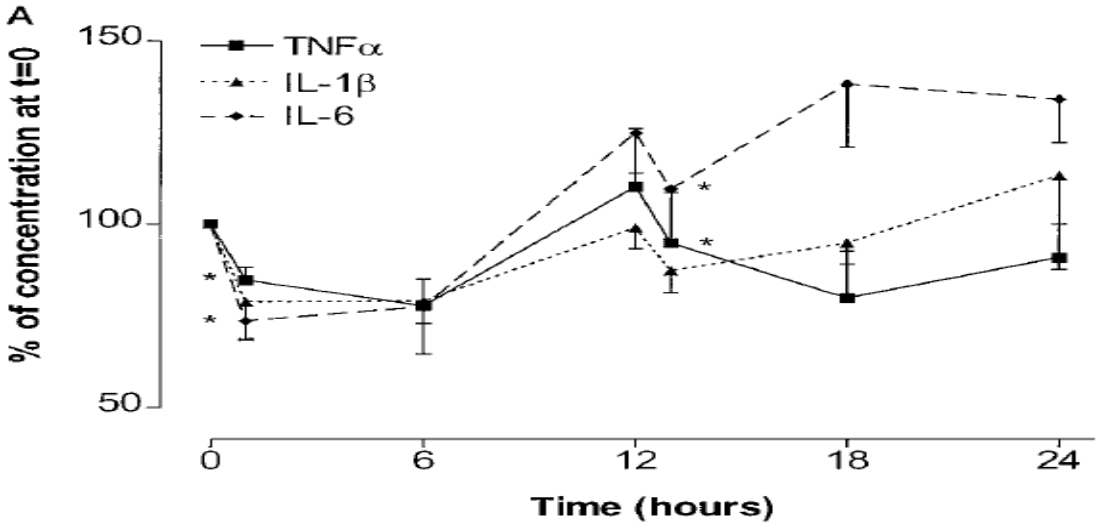


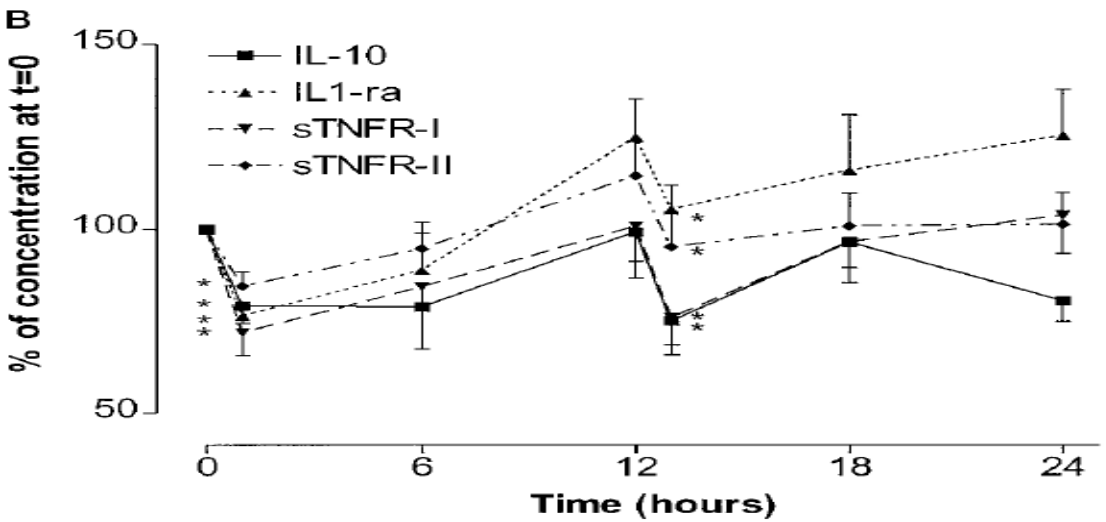
Ethylenevinylalcohol co-polymer (EVAL)

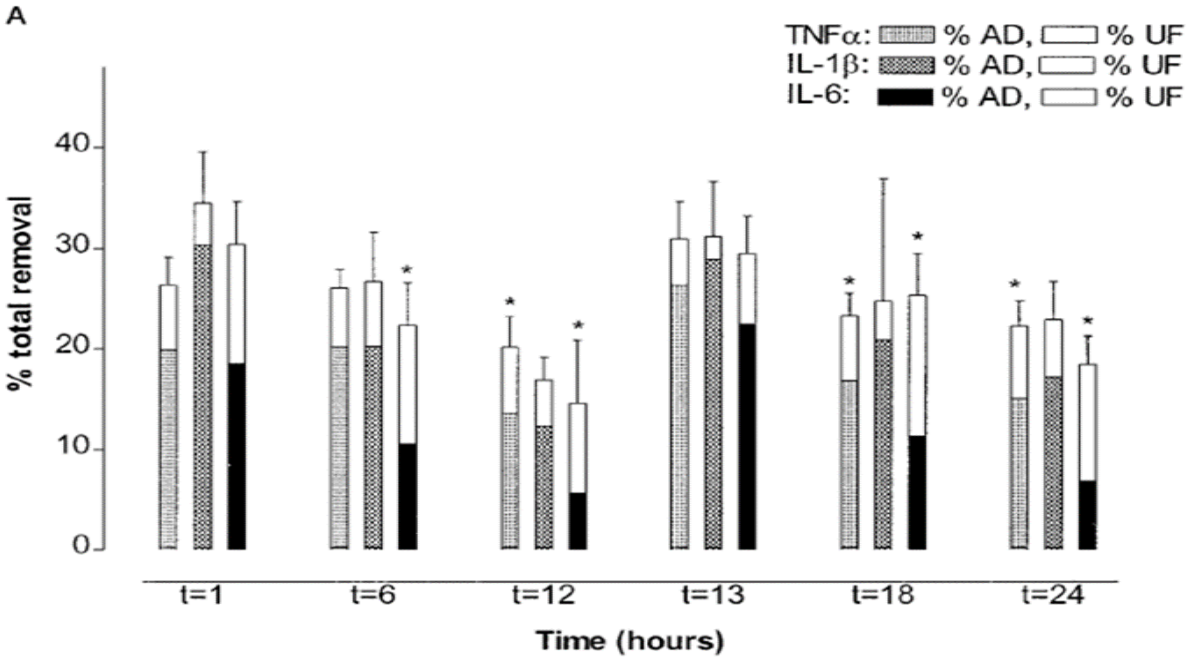
Cytokine Removal during Continuous Hemofiltration in Septic Patients

AN S. DE VRIESE,* FRANCIS A. COLARDYN,† JAN J. PHILIPPÉ,‡ RAYMOND C. VANHOLDER,* JOHAN H. DE SUTTER,† and NORBERT H. LAMEIRE*









$$Q_I = Q_B(1 - \text{hematocrit}),\ Q_O = Q_I - Q_{UF},$$

$$M_I = Q_I \times C_I,\ M_O = Q_O \times C_O$$

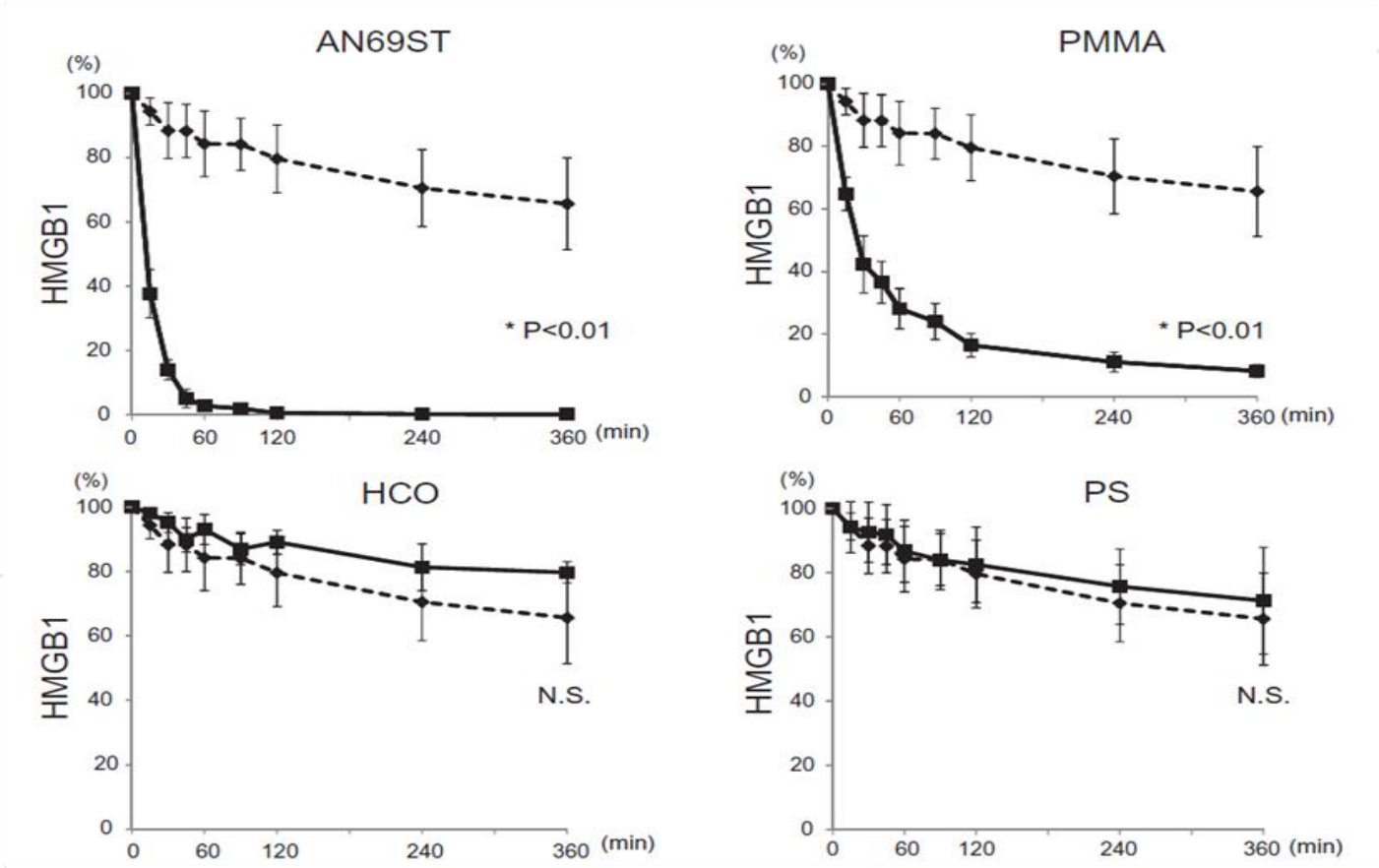
$$M_{TR} = M_I - M_O,\ M_{UF} = Q_{UF} \times C_{UF},\ M_{AD} = M_{TR} - M_{UF}$$

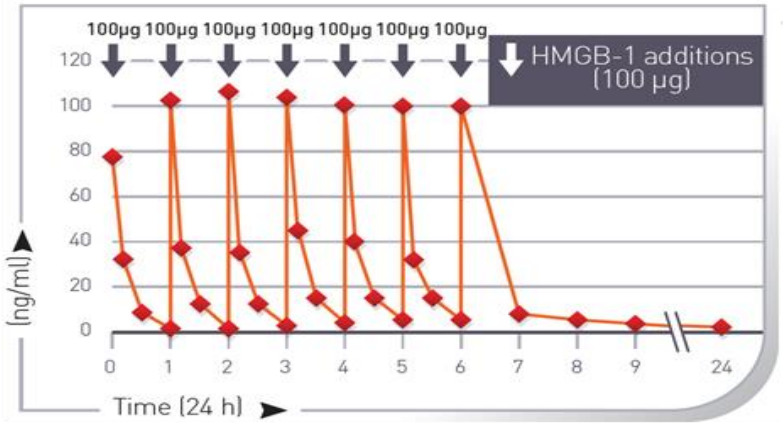
$$SC = 2 \times C_{UF}/C_I + C_O,$$

Protein Removal with Various Membranes for Continuous Hemofiltration

Miho Yumoto,[1] Osamu Nishida,[1] Kazuhiro Moriyama,[1] Yasuyo Shimomura,[1]
Tomoyuki Nakamura,[1] Naohide Kuriyama,[1] Yoshitaka Hara,[1] and Shingo Yamada[2]

Therapeutic Apheresis and Dialysis 15(4):385–393





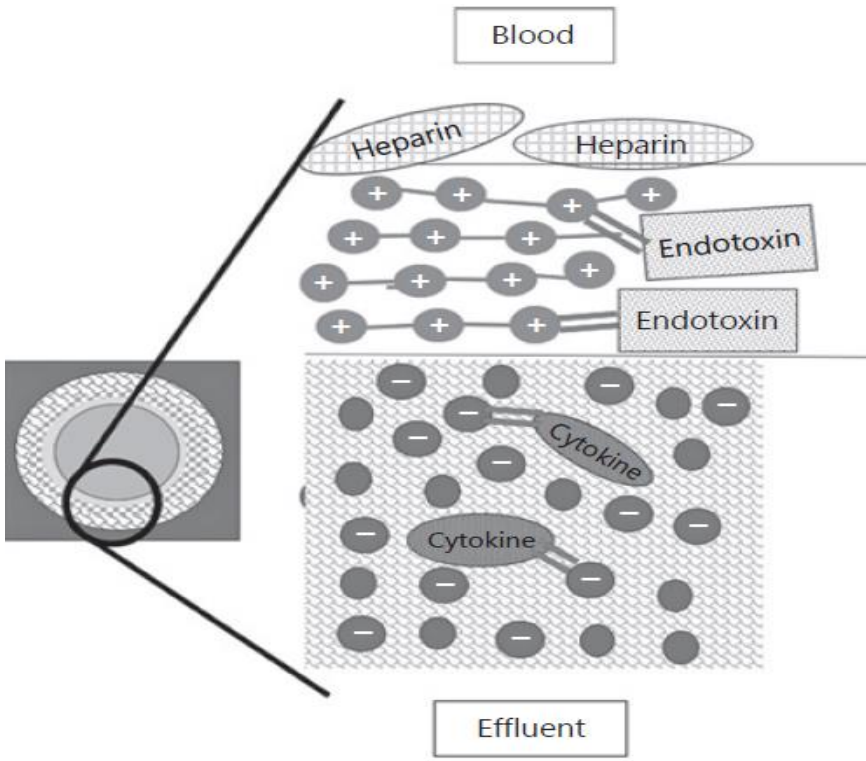
No saturation effect

Extracorporeal Blood Purification Therapies for Sepsis

Céline Monard[a, b] Thomas Rimmelé[a, b] Claudio Ronco[c–e]

Blood Purification

The 3 layers of the oXiris® membrane



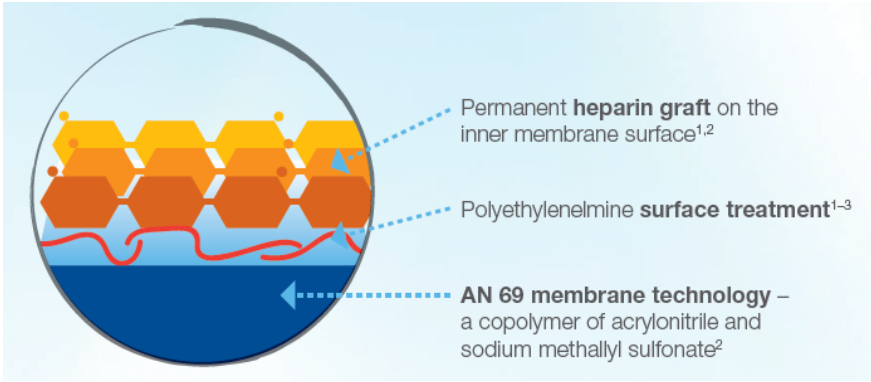
3rd layer	Heparin grafting	Reduce local thrombogenicity
2nd layer	Multiple layers of PEI	Improve biocompatibility Adsorb endotoxins
1st layer	AN69 copolymere hydrogel structure	Adsorb cytokines Remove solutes via convection through membrane pores (cut-off 40 kDa)

PEI molecules, positively charged

Adsorption due to polarity ionic charges

Acrylonitrile molecules
Methallylsulfonate molecules, negatively charged
} Polyacrylonitrile copolymere

Hydrogel structure



Am J Transl Res 2021;13(4):3839-3844
www.ajtr.org /ISSN:1943-8141/AJTR0126267

Original Article

The application value of oXiris-endotoxin adsorption in sepsis

Yanping Zhai, Jiayu Pan, Chunyun Zhang

23 sepsis patients hospitalized from January 2018 to September 2019 in our ICU center and received oXiris-endotoxin adsorption were enrolled as the observation group, and another 30 sepsis patients hospitalized during the same period were selected as the control group treated with routine continuous renal replacement therapy (CRRT). The study acquired the approval by hospital ethics committee.

Table 1. Comparison of clinical data between two groups of patients

Group	Number of Cases	Gender		Age (years old, $\bar{x}$±sd)	APACHE II score (points, $\bar{x}$±sd)	MAP (mmHg, $\bar{x}$±sd)	Urine volume (ml, $\bar{x}$±s)
		Male	Female				
Observation group	23	13	10	59.73±13.02	21.46±2.55	74.81±13.40	416.92±78.69
Control group	30	18	12	58.97±12.51	21.58±3.10	71.02±9.85	438.39±85.62
t/X^2	-	0.065		0.215	0.151	1.187	0.937
P	-	0.799		0.830	0.881	0.241	0.353

Table 2. Comparison of heart rate, respiratory rate and dosage of NE between the two groups before and after treatment ($\bar{x}$±sd)

Group	Phase	Heart rate (Times/min)	Respiratory rate (Times/min)	Dosage of NE (μg·kg·min)
Observation group (n=23)	Before treatment	113.62±18.95	25.84±3.94	1.09±0.57
	After treatment	76.48±10.13*	16.58±2.79*	0.38±0.23*
	t	9.177	10.018	6.209
	P	0.000	0.000	0.000
Control group (n=30)	Before treatment	115.02±19.27	25.18±3.75	1.17±0.42
	After treatment	85.62±10.85	19.27±2.66	0.61±0.32
	t	7.282	7.041	5.809
	P	0.000	0.000	0.000

Note: *$P<0.05$ compared with before treatment.

Table 3. Comparison of lactate, PCT, urine volume and SOFA score between the two groups before and after treatment ($\bar{x}$±sd)

Group	Phase	Lactate (mmol/L)	PCT (ng/ml)	Urine output (ml)	Sofa score (score)
Observation group (n=23)	Before treatment	4.83±1.25	41.62±13.98	416.92±78.69	12.64±2.85
	After treatment	1.79±0.63*	9.87±2.15*	1093.84±120.37*	8.93±1.52*
	t	10.415	10.765	22.574	5.509
	P	0.000	0.000	0.000	0.000
Control group (n=30)	Before treatment	5.02±1.52	40.27±15.20	438.39±85.62	12.97±3.01
	After treatment	2.54±0.71	15.64±4.29	891.25±117.58	10.22±1.20
	t	8.097	8.542	17.053	4.648
	P	0.000	0.000	0.000	0.000

Note: *$P<0.05$ compared with before treatment.

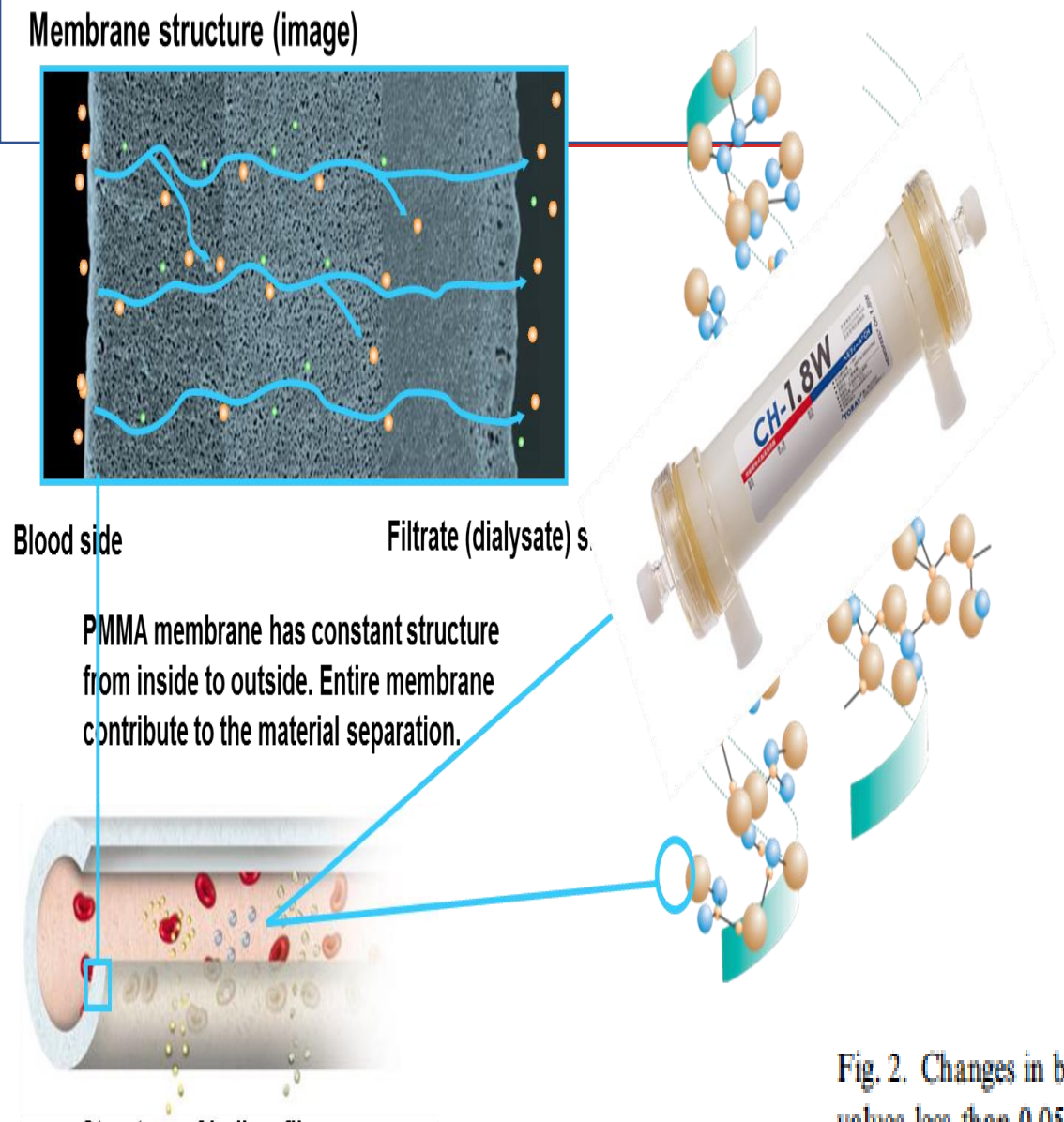
Table 4. Comparison of serum inflammatory factors and endotoxin degree between the two groups ($\bar{x}$±sd)

Group	Time-point	IL-6 (pg/ml)	IL-10 (pg/ml)	Endotoxin (EU/ml)
Observation group (n=23)	Before treatment	2187.47±528.37	674.82±125.46	64.72±12.10
	After treatment	128.30±40.22*	50.37±21.23*	16.47±3.26*
	t	18.637	23.536	18.465
	P	0.000	0.000	0.000
Control group (n=30)	Before treatment	2006±476.27	693.27±131.65	65.08±15.28
	After treatment	227.28±108.29	130.85±40.38	25.09±6.39
	t	17.465	19.589	11.580
	P	0.000	0.000	0.000

Note: *$P<0.05$ compared with before treatment.

Table 5. Comparison of ICU stay, organ support duration, and incidence of cardiovascular events between the two groups

Group	Number of Cases	ICU stay (d, $\bar{x}$±sd)	Organ support duration (d, $\bar{x}$±sd)	Incidence of cardiovascular events [n (%)]
Observation Group	23	8.17±1.75	3.16±1.20	1 (4.35)
Control Group	30	10.21±2.18	4.85±1.39	9 (30.00)
t/X^2	-	3.667	4.650	4.046
P	-	0.001	0.000	0.044



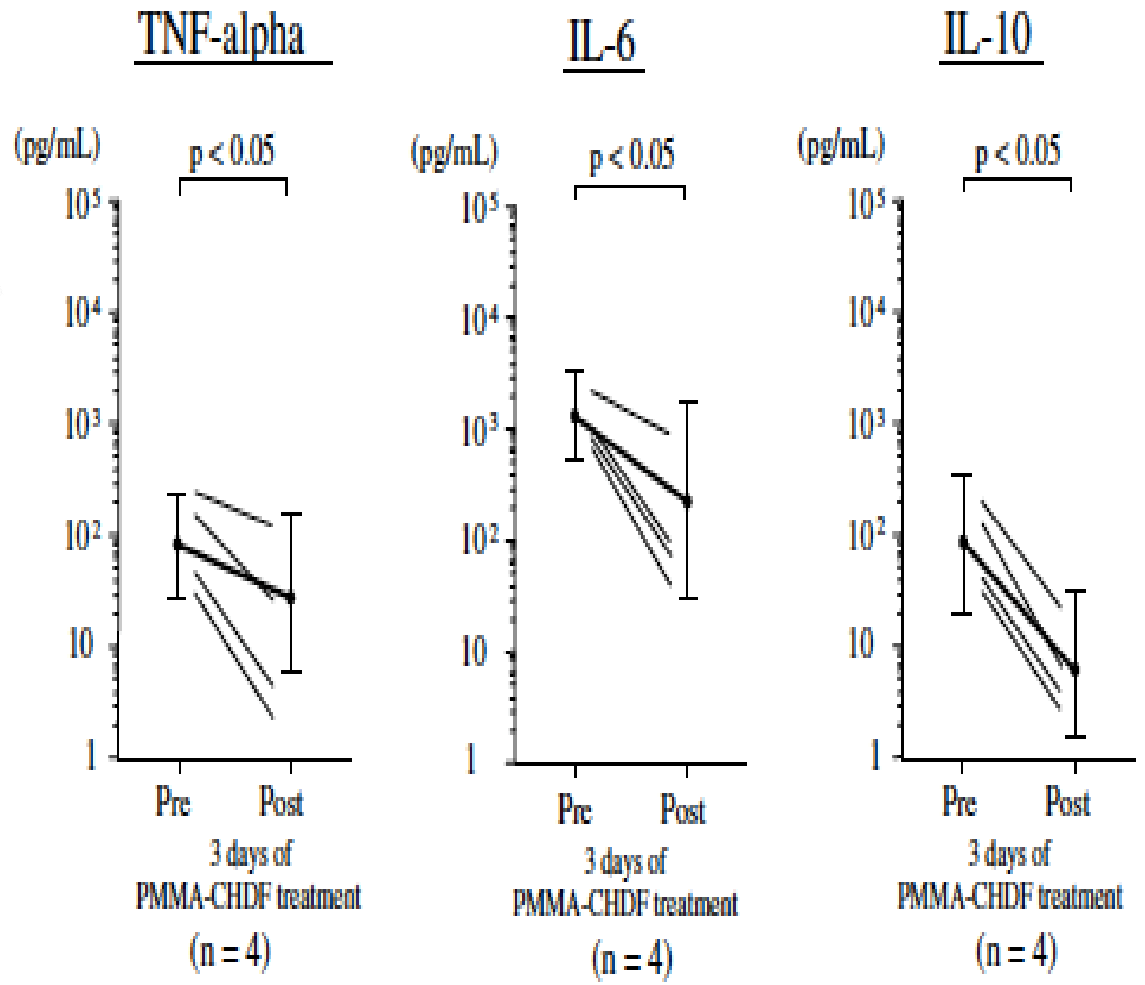


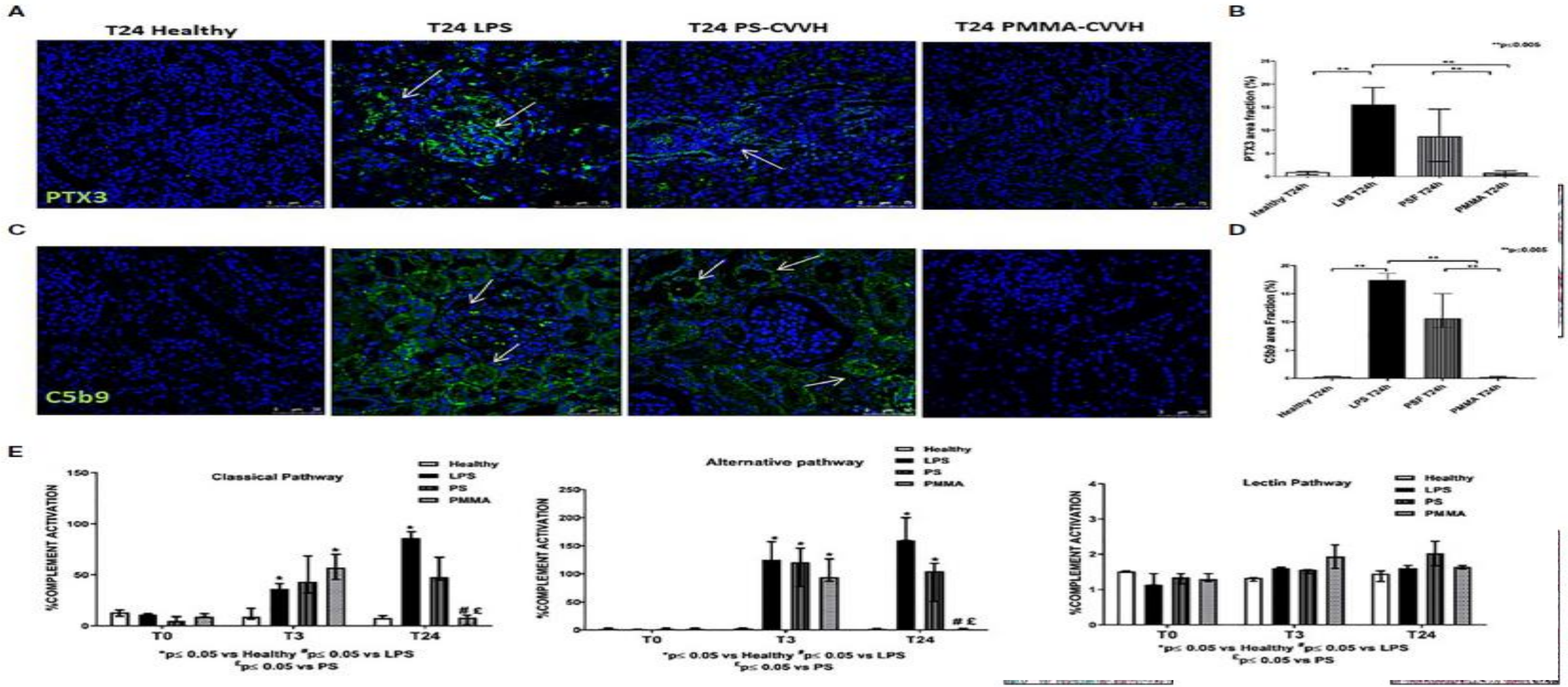
Fig. 2. Changes in blood levels of cytokines with three days of PMMA-CHDF treatment. All values are expressed as the mean ± SD. *P* values less than 0.05 were considered significant.

Nakamura, Transfusion and Apheresis Science, 2009

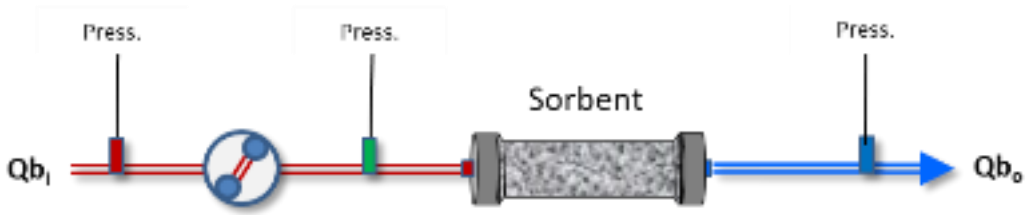
PMMA-Based Continuous Hemofiltration Modulated Complement Activation and Renal Dysfunction in LPS-Induced Acute Kidney Injury

Alessandra Stasi[1], Rossana Franzin[1], Chiara Divella[1], Fabio Sallustio[2], Claudia Curci[1],*

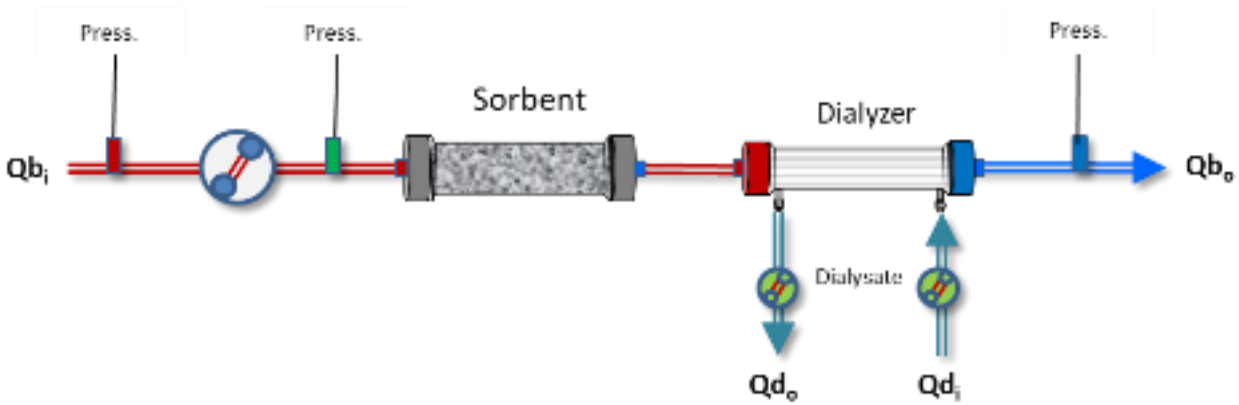
frontiers in Immunology



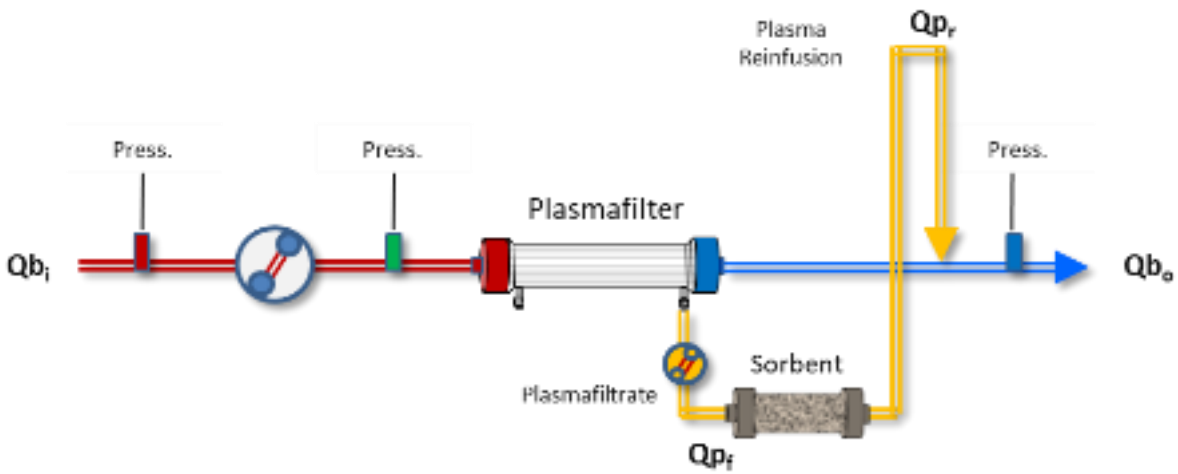
Direct Hemoadsorption



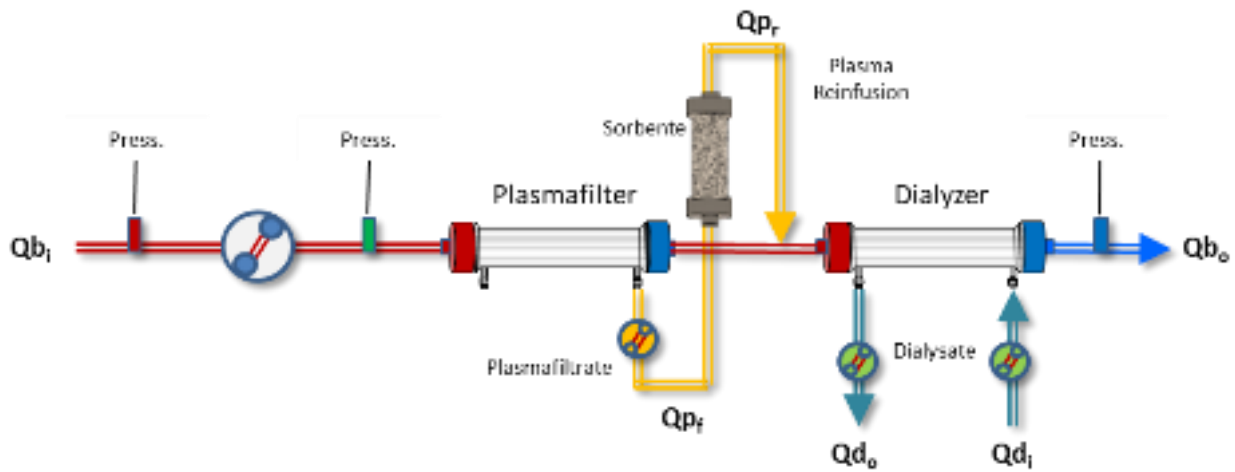
HP-HD or HP-CRRT



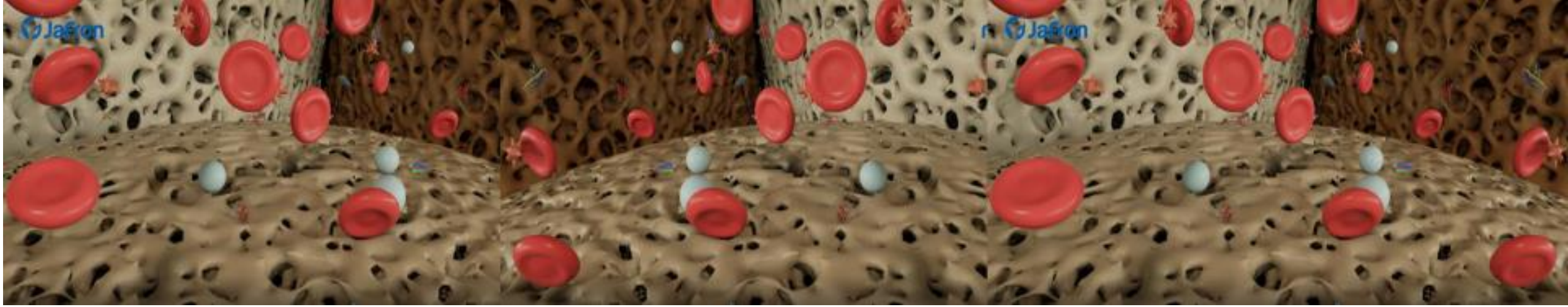
PFAD or CPFA



PFAD-HD or CPFA-CRRT



Ostermann M et al, BPU 2023: Rome consensus meeting on dialysis nomenclature



Fluid Phase (Blood) Pathways

1) Interparticle (Packing density)

2) Extraparticle (Bead design)

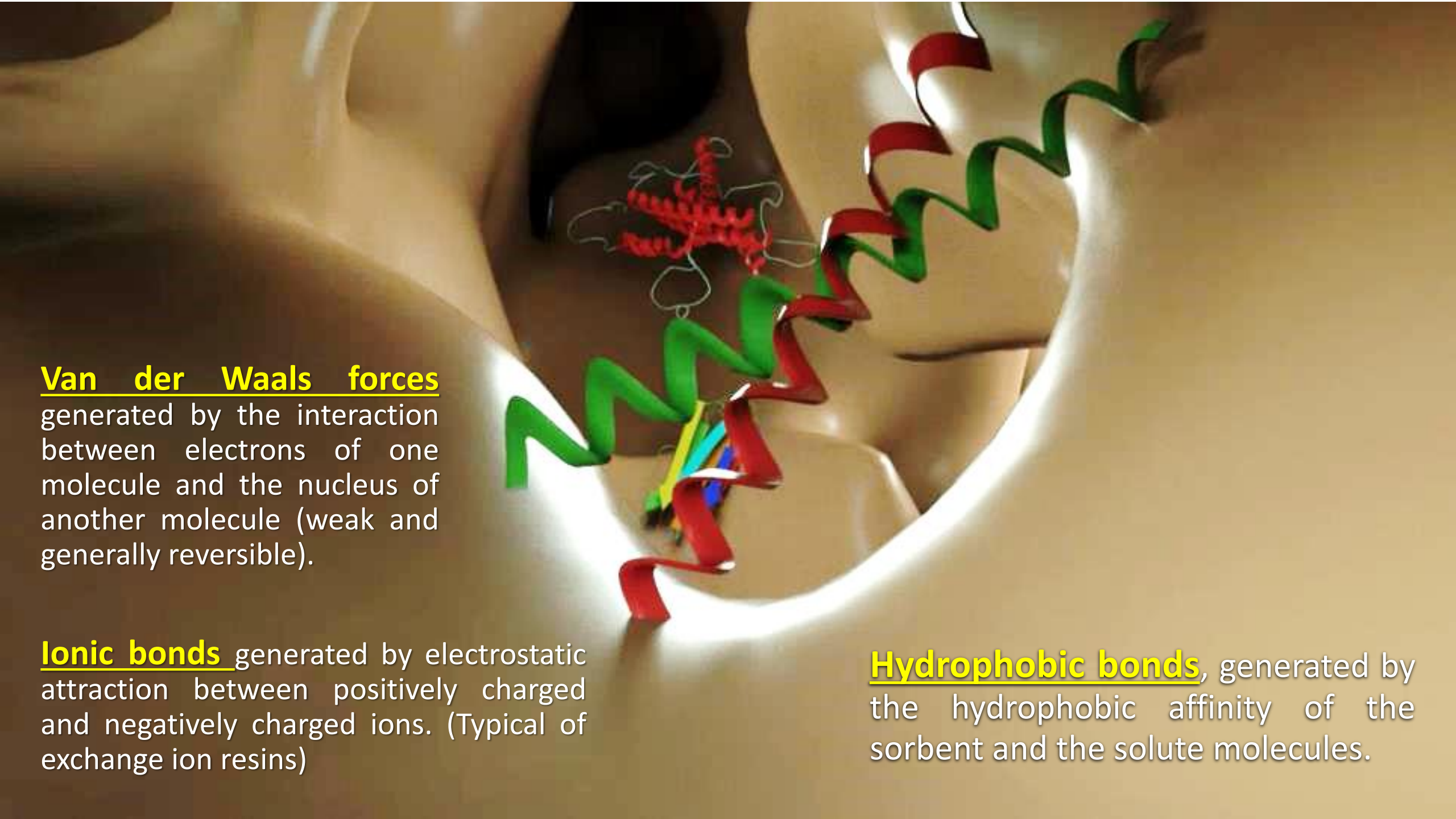
3) Intraparticle (Bead Porosity)

Darcy law

Kozeny Carman Eq.

Variables:

Particle diameter
Packing density
Interparticle porosity
Path Tortuosity
Length/diameter
Fluid Viscosity
Reynolds Number



Van der Waals forces generated by the interaction between electrons of one molecule and the nucleus of another molecule (weak and generally reversible).

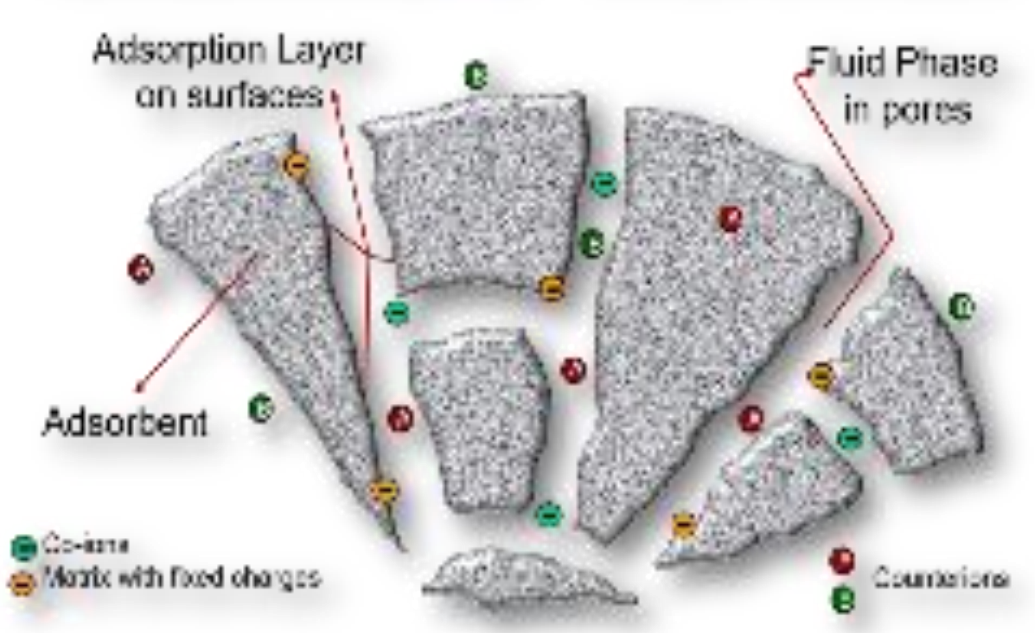
Ionic bonds generated by electrostatic attraction between positively charged and negatively charged ions. (Typical of exchange ion resins)

Hydrophobic bonds, generated by the hydrophobic affinity of the sorbent and the solute molecules.

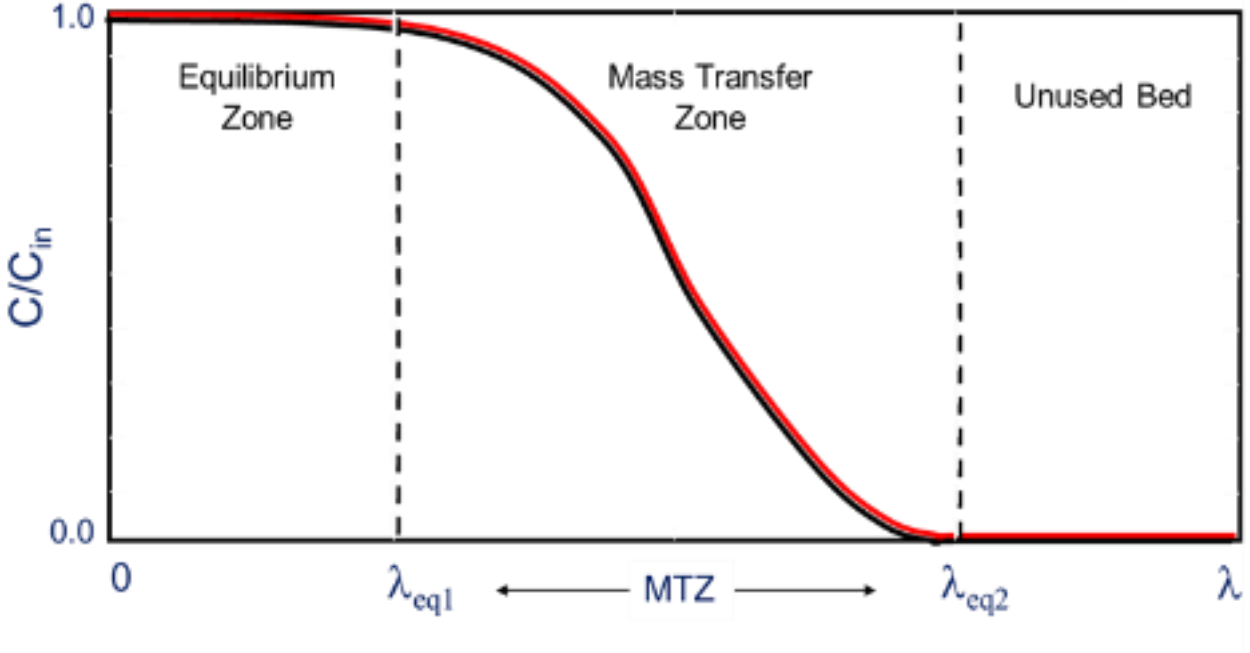
IRRIV International Renal Research Institute Vicenza

Courtesy by Claudio Ronco, IRRIV

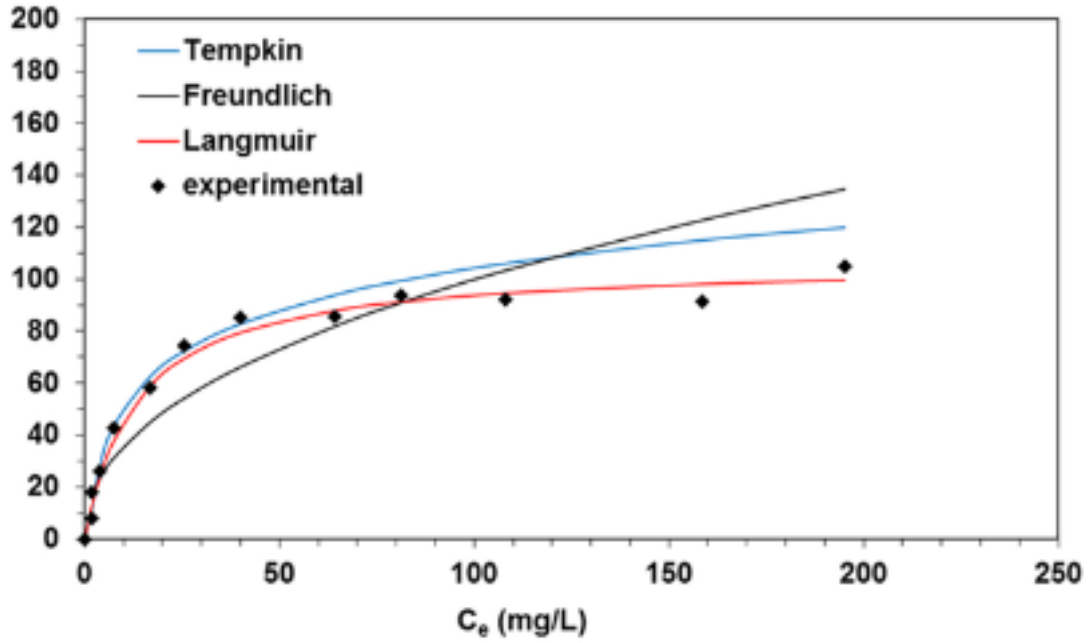
Sorbent



SOLUTE ONCENTRATION/DISTANCE PROFILE



SOLUTE ADSORPTION ISOTHERMS



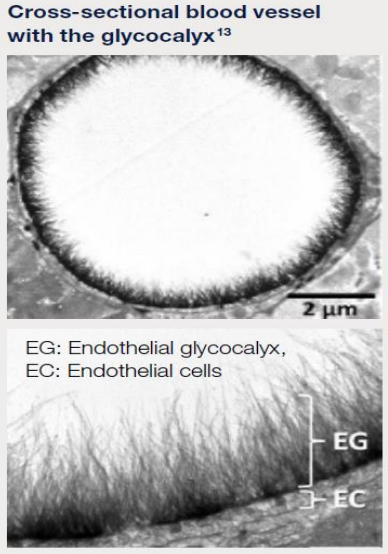
Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup

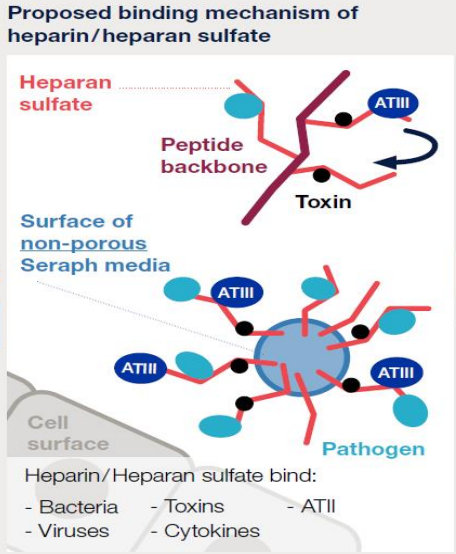
nature reviews nephrology

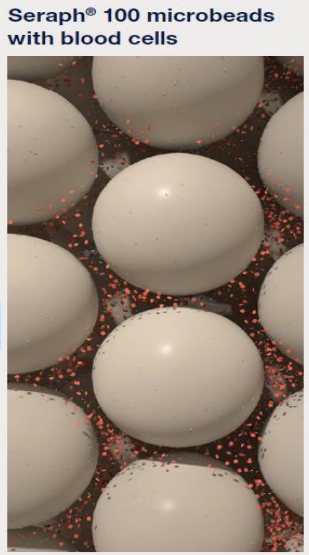
Alexander Zarbock[1,2,44], Mitra K. Nadim[3,44], Peter Pickkers[4], Hernando Gomez[5], Samira Bell[6], Michael Joannidis[7], Kianoush Kashani[8], Jay L. Koyner[9], Neesh Pannu[10], Melanie Meersch[1], Thiago Reis[11,12], Thomas Rimmelé[13], Sean M. Bagshaw[14], Rinaldo Bellomo[15,16,17,18], Vicenzo Cantaluppi[19], Akash Deep[20], Silvia De Rosa[21,22],

Characteristics of extracorporeal blood purification therapies available for sepsis and SA-AKI

Technology	Indication	Modality	Target of removal	Mass separation mechanism	Comments
PAES-PVP high-flux	KRT, hyperinflammation	HD, HFL, HDF	Fluids, electrolytes, middle molecules	Convection, diffusion	CRRT for kidney support
AN69-PEI-heparin	KRT, hyperinflammation, Gram-negative sepsis or endotoxaemia	HD, HF, HDF	Fluids, electrolytes, middle molecules, endotoxin	Adsorption, convection, diffusion	CRRT for kidney and immunomodulatory support
AN69-ST, PMMA	KRT, hyperinflammation	HD, HF, HDF	Fluids, electrolytes, middle molecules	Adsorption, convection, diffusion	CRRT for kidney and immunomodulatory support
PAES-PVP MCO and HCO	KRT, hyperinflammation	HD	Fluids, electrolytes, middle molecules	Diffusion	CRRT for kidney and immunomodulatory support
Plasmasulfone, polypropylene (for membrane plasmapheresis)	Hyperinflammation	Centrifugation or HF	Fluids, electrolytes, middle molecules, endotoxin	Convection (membrane); gravity sedimentation (centrifuge)	Immunomodulatory support
Heparin covalently bound to polyethylene	Viraemia, bacteraemia, fungaemia	Haemoadsorption	Bacteria, fungi, viruses	Adsorption	Selective immunomodulatory support
Porous polymer beads polystyrene divinylbenzene	Hyperinflammation	Haemopadsorption	Protein-bound compounds, middle molecules	Adsorption	Non-selective immunomodulatory support
PMX covalently bound to polypropylene–polystyrene fibre	Gram-negative sepsis or endotoxaemia	Haemoadsorption	Endotoxin	Adsorption	Selective immunomodulatory support







The endothelial glycocalyx

- Key constituents: glycoproteins, proteoglycans and glycosaminoglycans
- Multiple functions, including the regulation of vascular permeability[13]
- Many viruses and bacteria can bind to cell surface heparan sulfate proteoglycans, facilitating initial pathogen attachment and promoting infection[14]

A surrogate glycocalyx

The microbead broad-spectrum adsorption media of Seraph® 100 use chemically bonded heparin to mimic the natural endothelial cell surface.

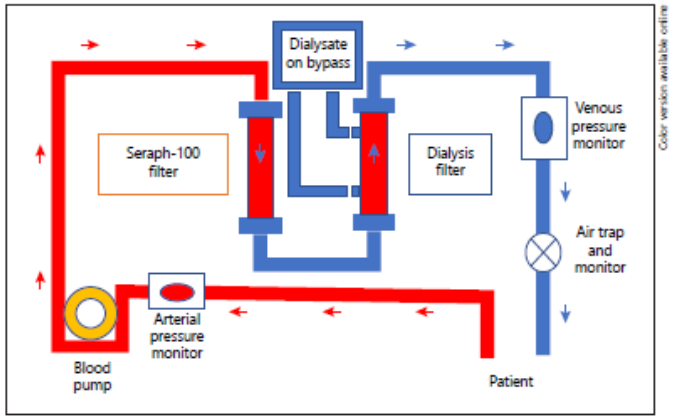
The surrogate glycocalyx can be expected to bind certain pathogens circulating in the bloodstream.[4]

Seraph-100 Hemoperfusion in SARS-CoV-2-Infected Patients Early in Critical Illness: A Case Series

Brian S. Rifkin[a] Ian J. Stewart[b]

[a]Hattiesburg Clinic Department of Nephrology, Hattiesburg, MS, USA; [b]Department of Medicine, Uniformed Services University, Bethesda, MD, USA

Blood Purification



NIH U.S. National Library of Medicine

ClinicalTrials.gov

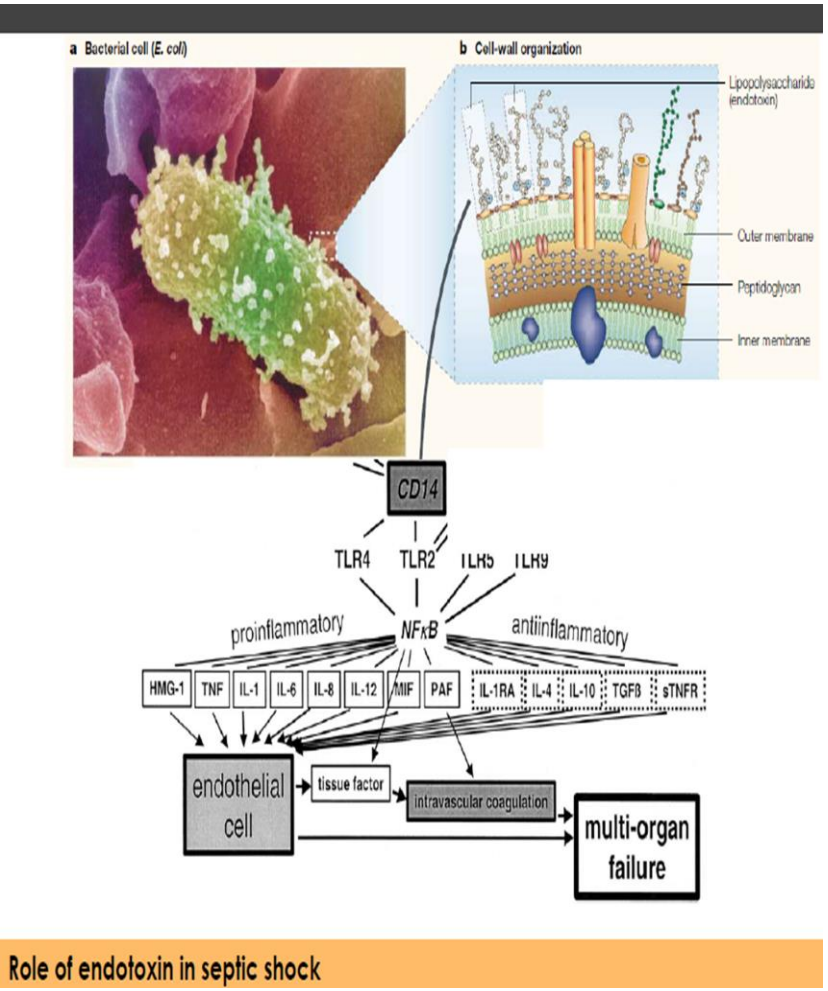
Reduction of Pathogen Load From the Blood in Septic Patients With Suspected, Life-threatening Bloodstream Infection

Table 1. Clinical characteristics of patients treated with Seraph-100 hemoperfusion filter

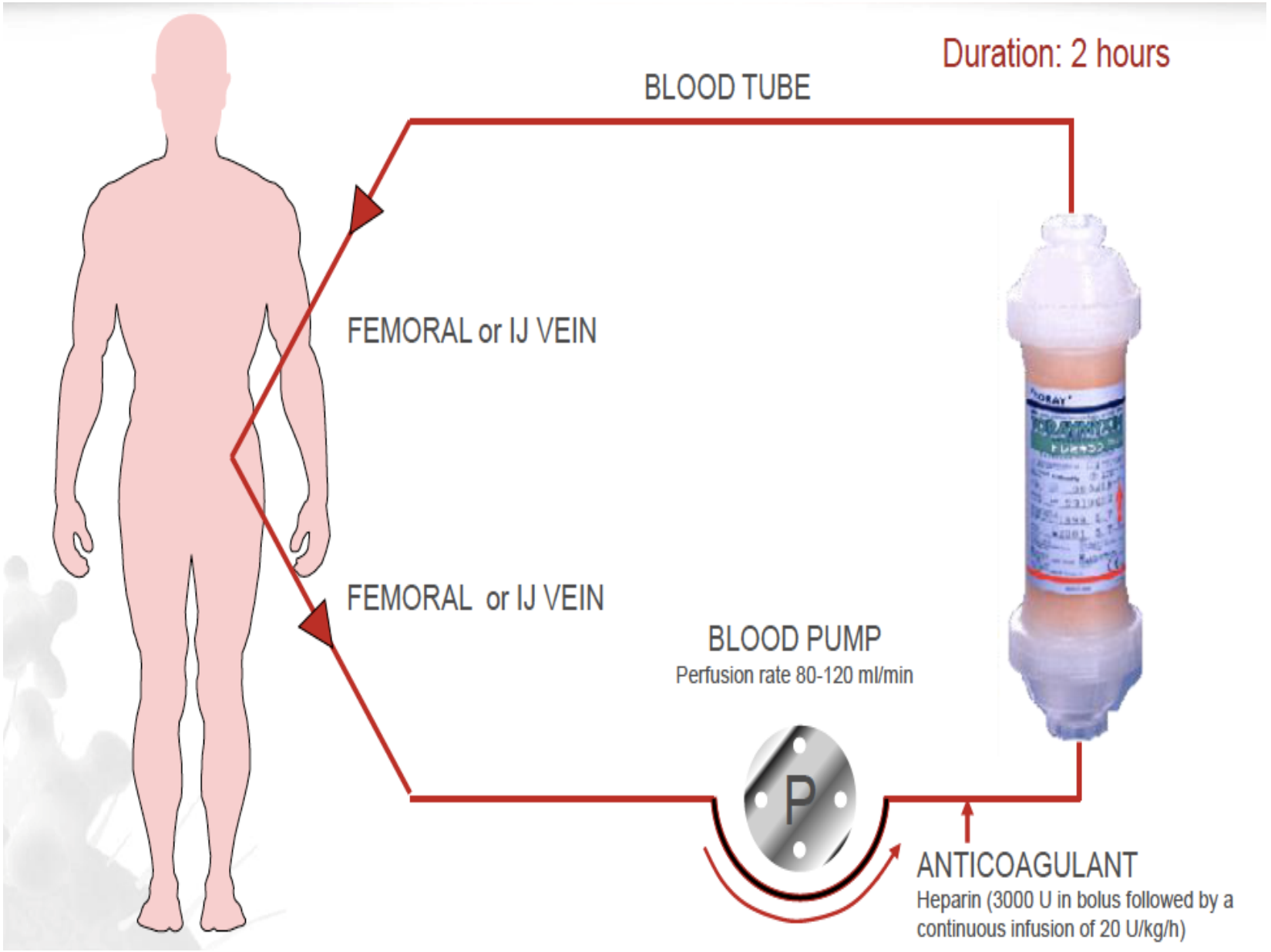
	Patient 1		Patient 2		Patient 3		Patient 4	
Age, years	38		65		61		54	
Sex	Male		Male		Male		Male	
BMI, kg/m^2	46		27		33		35	
Blood type	A+		A+		A+		A+	
Diabetes	Yes		Yes		No		Yes	
Hypertension	Yes		Yes		Yes		No	
COVID-positive test to treatment, days	19		7		6		7	
Hospital LOS	57		9		15		14	
ICU LOS	48		7		11		11	
Intubated	Yes		No		No		No	
Treatment time, min	425		435		380		370	
Blood pump, mL/min	400		450		400		400	
Blood volume, L processed/kg	1.01		2.45		1.42		1.48	
Apache II	15		17		9		10	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
CRP, mg/L[a]	209	157	47	14	198	33	137	74
Ferritin, ng/mL[a]	728	725	1,145	1,142	660	621	–	–
D-dimer, ng/mL[a]	989	725	422	370	643	645	592	285
Procalcitonin, ng/mL[a]	0.09	0.10	0.05	0.05	0.25	0.08	0.54	0.06
PaO_2/FiO_2 ratio[a]	71	297	54	252	137	92	64	98
Mean arterial pressure[b]	75	69	92	83	80	79	82	71
Temperature, F[b]	97.2	95.7	97.3	97.0	97.4	97.8	97.3	96.3
Disposition	LTAC-tracheostomy		Home		Home		Home	

[a] Values obtained between 6 and 12 h before and after Seraph treatment. [b] Values obtained within 1 h of start/finish of Seraph treatment.

Polymyxin-B hemoadsorption



Role of endotoxin in septic shock



Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock

The EUPHAS Randomized Controlled Trial

JAMA

Figure 2. Change in SOFA Scores at 72 Hours

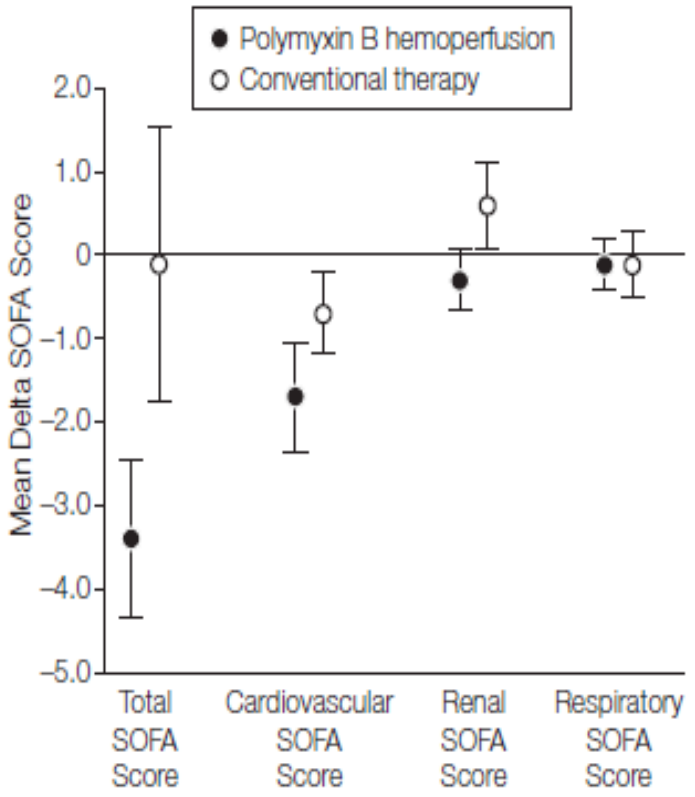
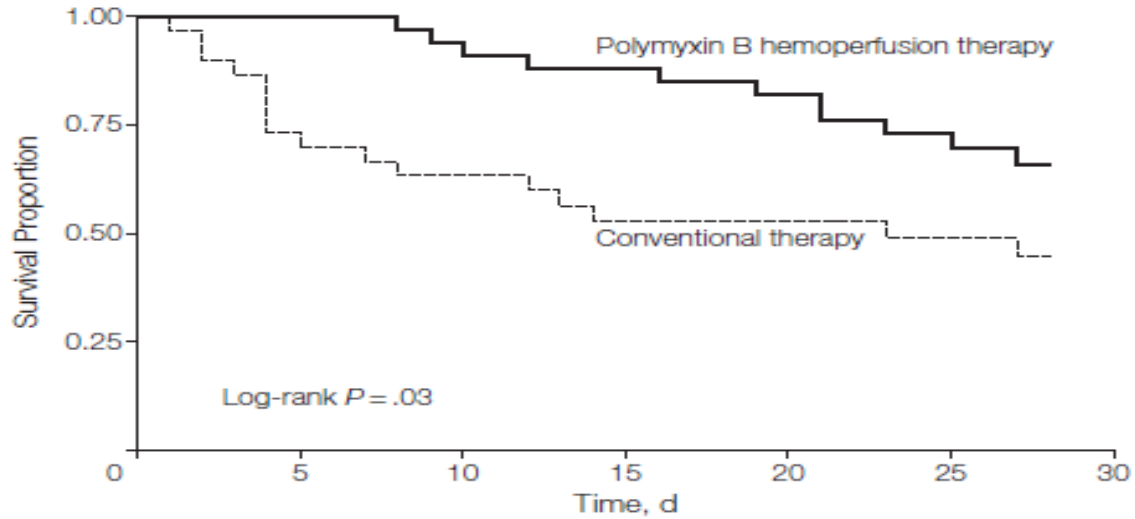


Figure 3. Estimation of Survival Rate According to Treatment Group



No. at risk							
Polymyxin B hemoperfusion therapy	34	34	32	30	27	22	18
Conventional therapy	30	22	19	15	15	12	11

Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy.

Polymyxin B hemoperfusion added to conventional therapy significantly improved hemodynamics and organ dysfunction and reduced 28-day mortality in a targeted population with severe sepsis and/or septic shock from intra-abdominal gram-negative infections.

ORIGINAL

Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial

D. J. Klein[1*], D. Foster[2], P. M. Walker[2], S. M. Bagshaw[3], H. Mekonnen[4] and M. Antonelli[5]

Intensive Care Med (2018) 44:2205–2212

Methods: Post-hoc analysis of the EUPHRATES trial for the 194 patients with EAA ≥ 0.6–0.89 who completed two treatments (PMX or sham). The primary end point was mortality at 28 days adjusted for APACHE II score and baseline mean arterial pressure (MAP). Additional end points included changes in MAP, cumulative vasopressor index (CVI), median EAA reduction, ventilator-free days (VFD), dialysis-free days (DFD) and hospital length of stay. Subpopulations analyzed were site and type of infection and those with norepinephrine dose > 0.1 mcg/kg/min at baseline.

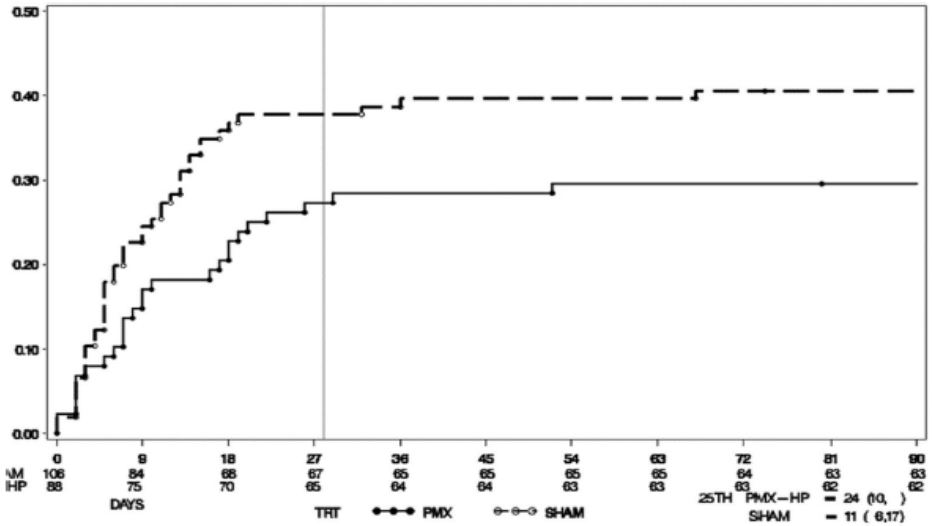


Fig. 2 Time to death within 90 days for PMX versus sham. Kaplan-Meier estimates of the probability of survival to day 90 among 194 per-protocol patients with MODS > 9 and EAA between 0.6 and 0.89, by treatment groups. The 90-day results of Cox proportional hazards adjusted for baseline MAP and APACHE II score are the hazard ratio [0.57, 95% CI (0.35, 0.93), *P* value = 0.02]. The vertical line represents the 28-day interval. The 28-day adjusted Cox proportional hazard ratio for death in the PMX group compared with the sham group is 0.58 (95% CI, 0.35 to 0.98; *P* = 0.04). *TRT* treatment, *25th* 25th percentile at 90 days

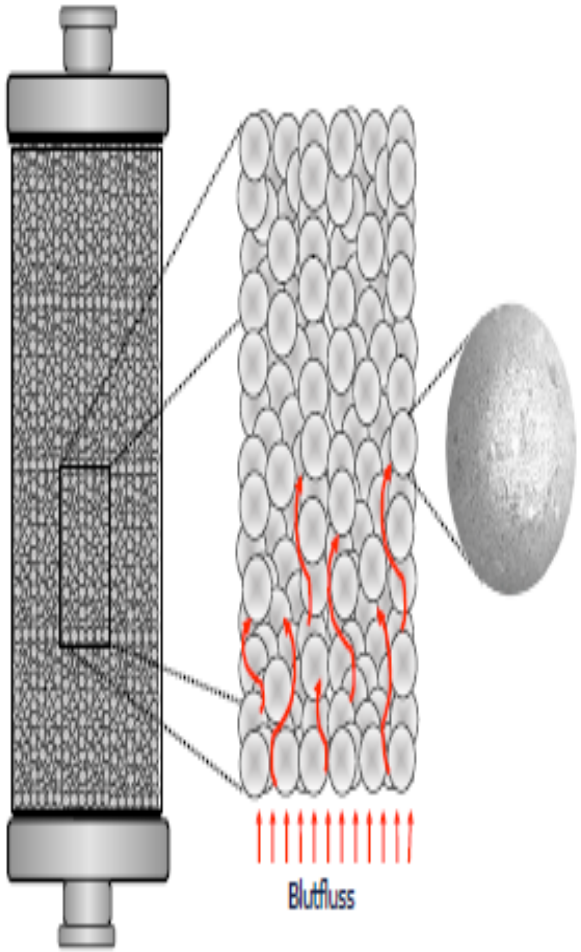
Treatment with PMX was associated with a significant change in median MAP (8 vs 4, p<0.05) and median (IQR) ventilator-free days to 28 days (20 vs 6, p=0.004).

The wind changed direction and the big river still flows: from EUPHRATES to TIGRIS

Toshiaki Iba[1*] and David J. Klein[2] *Journal of Intensive Care* (2019) 7:31

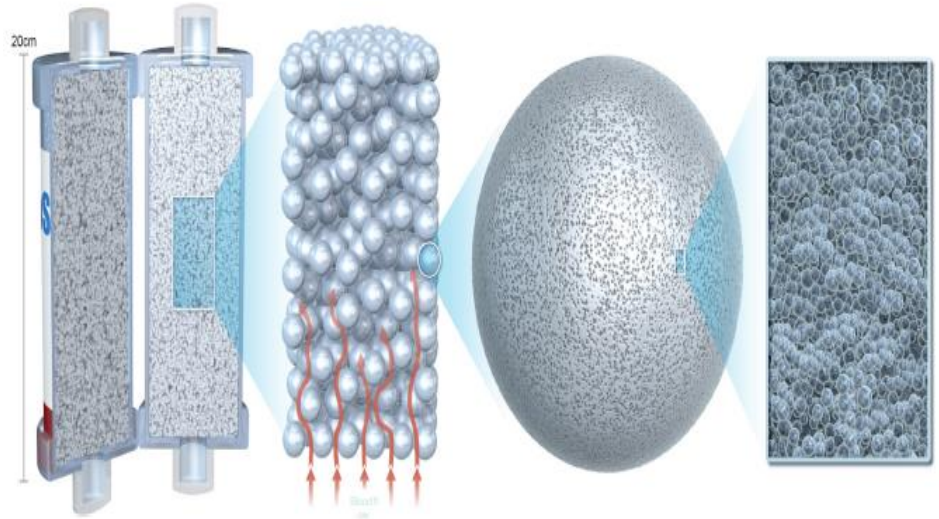
The study will be repeated…Using a precision medicine approach, eligibility have been modified in TIGRIS to include patients with MODS score > 9 and EAA levels between 0.60 and 0.89.

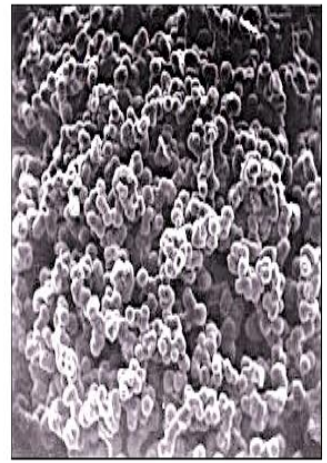
Polymer-Technology



- 300ml filter with a „bead"-design
- Hightech-polymer
- Size selection < 55kD
- Low flow resistance
- 120ml bloodvolume / filling volume
- Pre-filled with sodium-chlorid
- Gamma-steril, 3 year storage

Adsorber

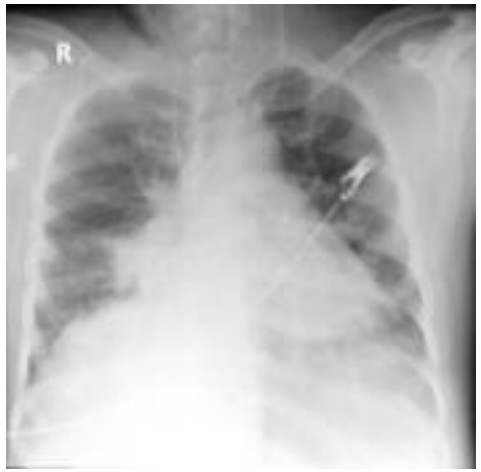


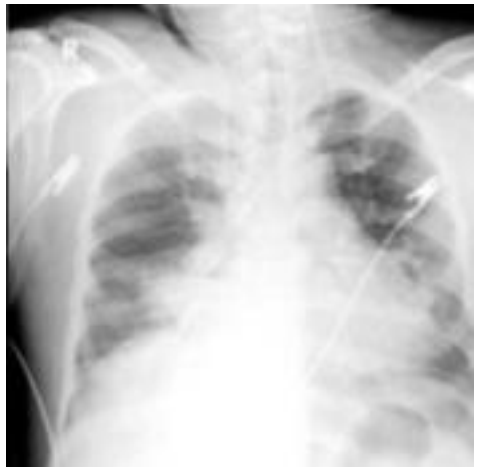


Case of COVID-19 patient with Cytokine Storm

Admission:
Fever
Hypotension
Respiratory failure
> Mech. Ventilation

Hemodynamic instability
High Cytokine Levels
High Ferritin
High CRP
Hypercoagulability





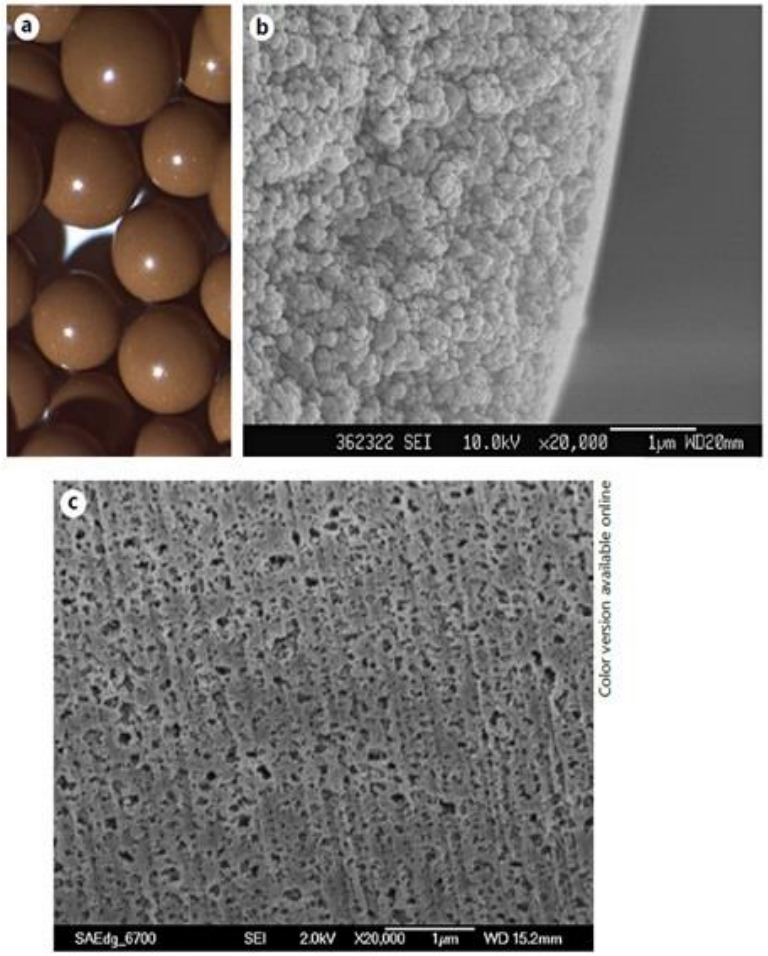
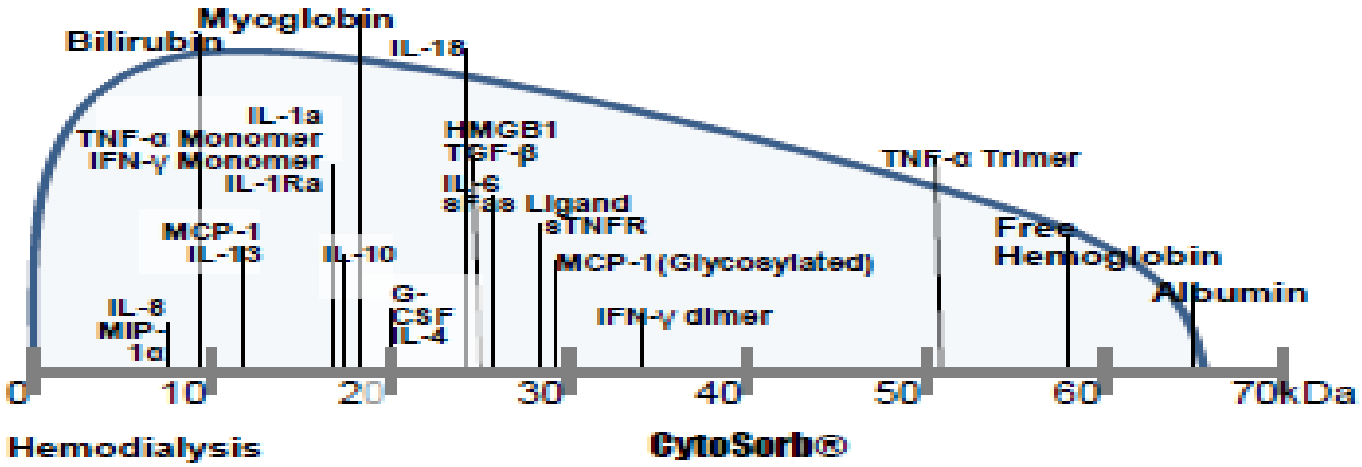


Fig. 1. Neutro-macroporous resin adsorbing beads made of styrene-divinylbenzene copolymer (**a**). In (**b**, **c**), pics made by transmission electron microscopy (TEM) of beats surface and section with the pore.

OVERALL SURFACE ≅ 40.000 - 45.000 m²



Jansen A, Pickkers P et Al:

la modulazione delle citochine

24 **soggetti sani** a cui sono state somministrate endotossine (LPS da E. Coli)

- LPS Giorno 0: per indurre risposta citochinica
- LPS Giorno 7: per controllare tolleranza immunologica
- 12 pazienti con Cytosorb (6h a 250ml/min in HP con Prismaflex)
- 12 pazienti senza Cytosorb

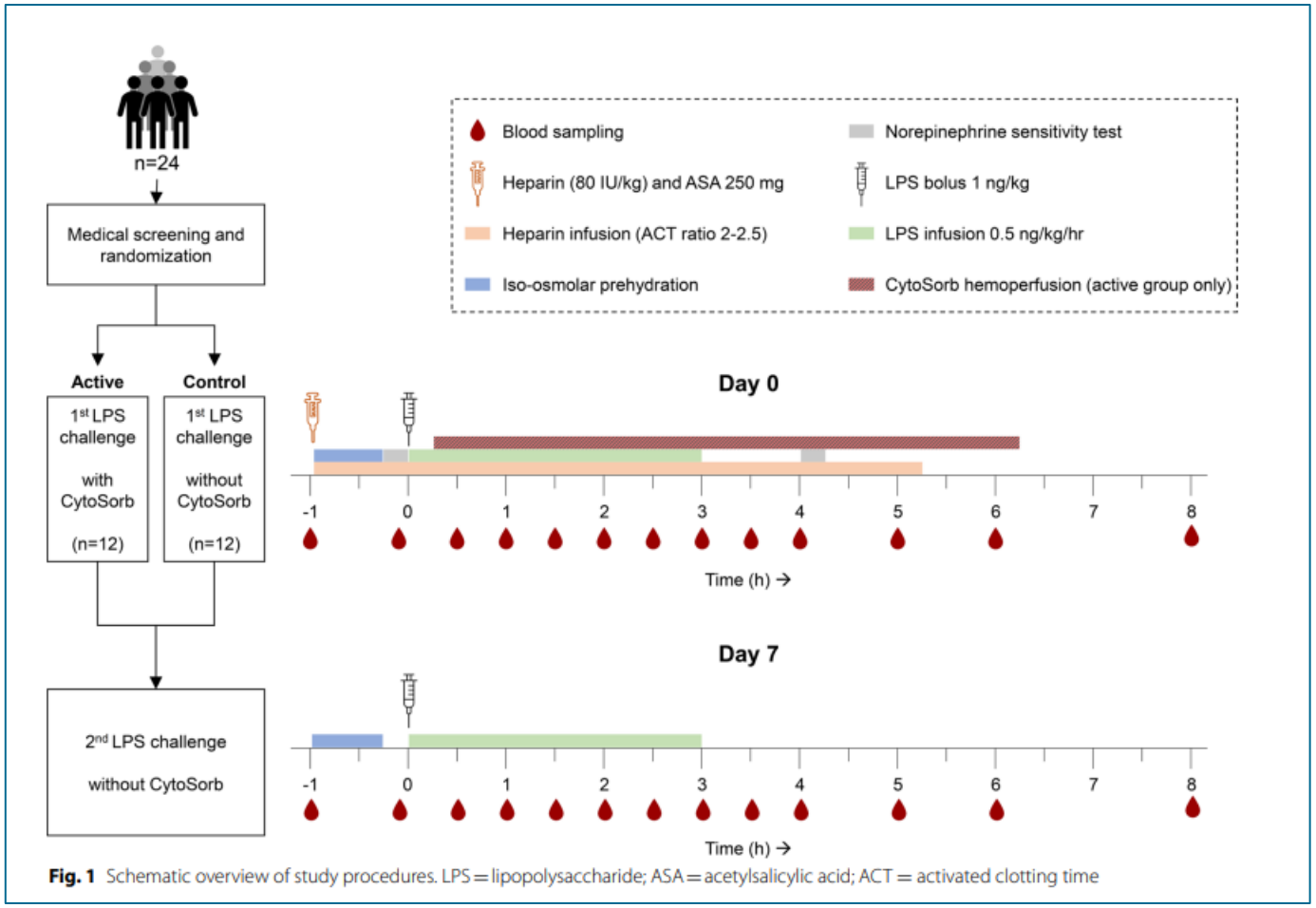
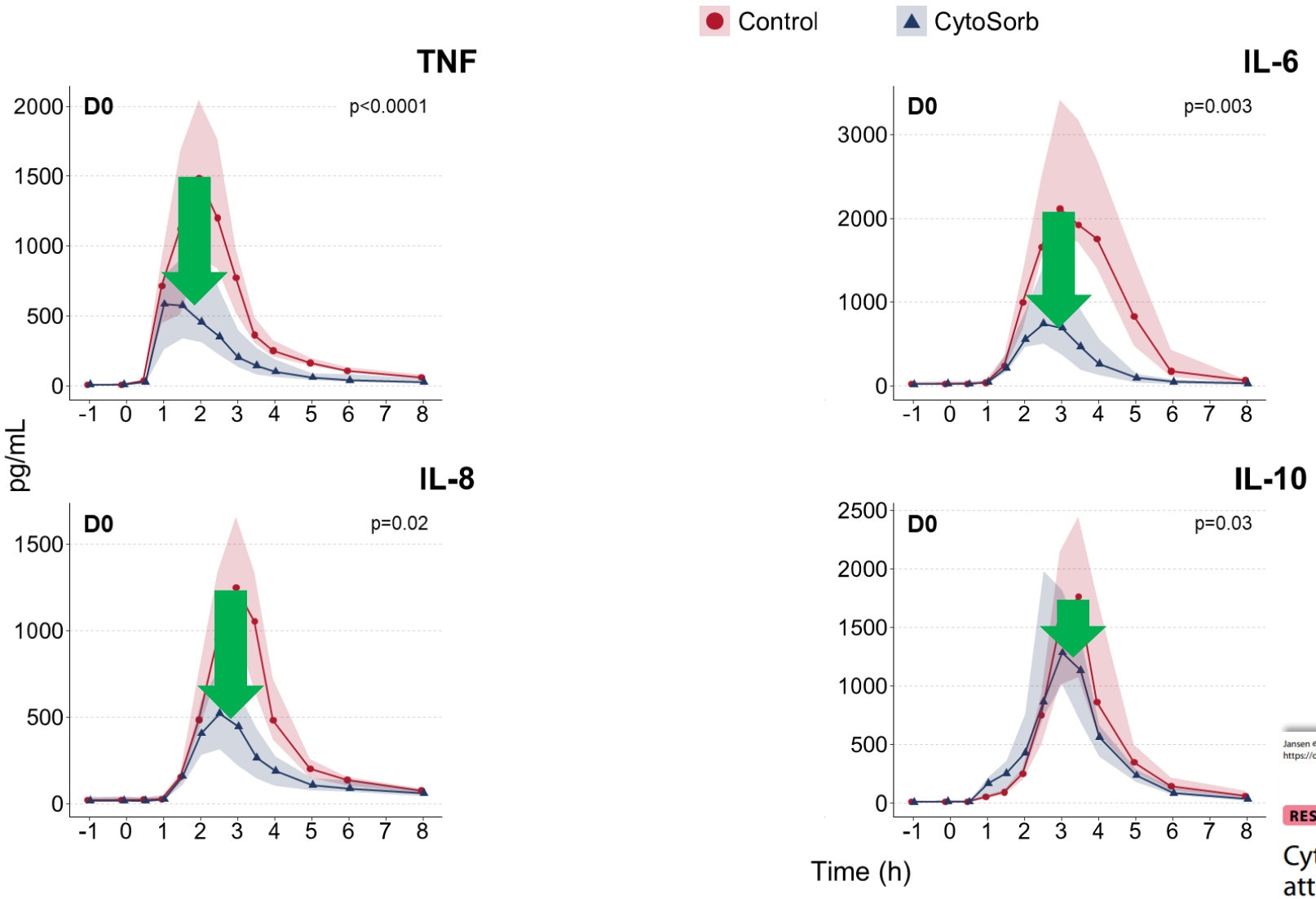


Fig. 1 Schematic overview of study procedures. LPS = lipopolysaccharide; ASA = acetylsalicylic acid; ACT = activated clotting time

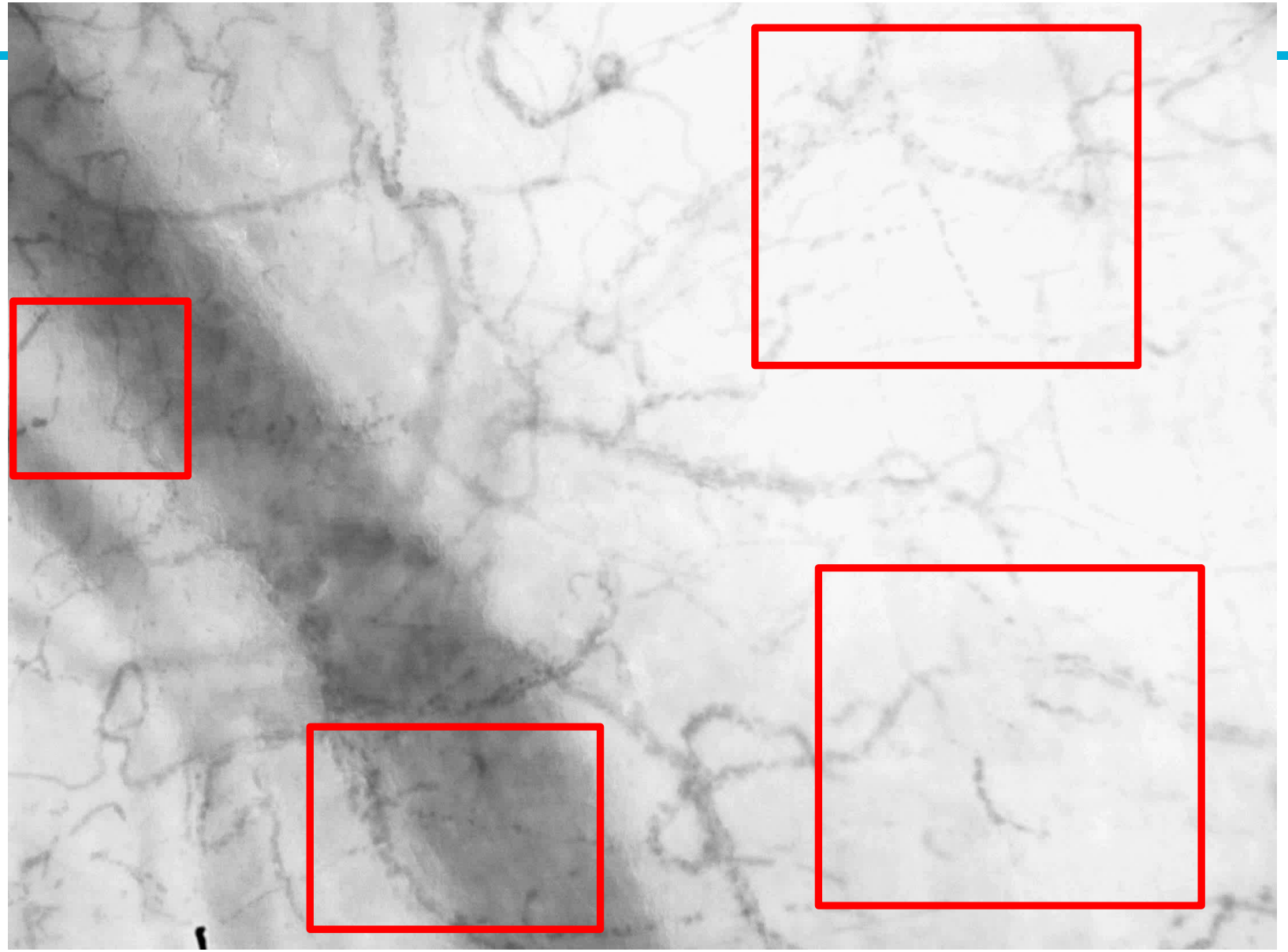
Plasma cytokines



Jansen et al. Critical Care (2023) 27:117
https://doi.org/10.1186/s13054-023-04391-z
Critical Care
RESEARCH
Open Access

CytoSorb hemoperfusion markedly attenuates circulating cytokine concentrations during systemic inflammation in humans in vivo

Aron Jansen[1,2*], Nicole J. B. Waalders[1,2†], Dirk P. T. van Lier[1,2†], Matthijs Kox[1,2] and Peter Pickkers[1,2*]



Slide 1: Sublingual microcirculation at baseline at time 0 before Cytosorb therapy of this septic patient. Note the plugged vessels highlighted in red.

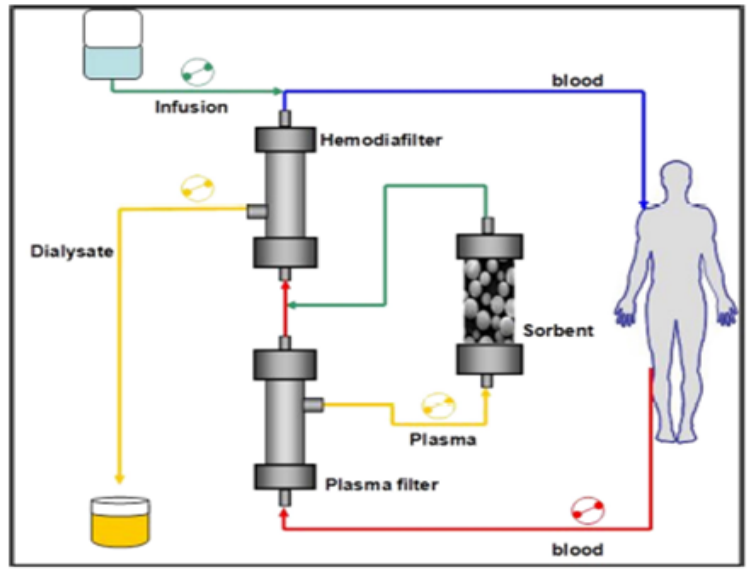
Radboudumc
Intensive Care

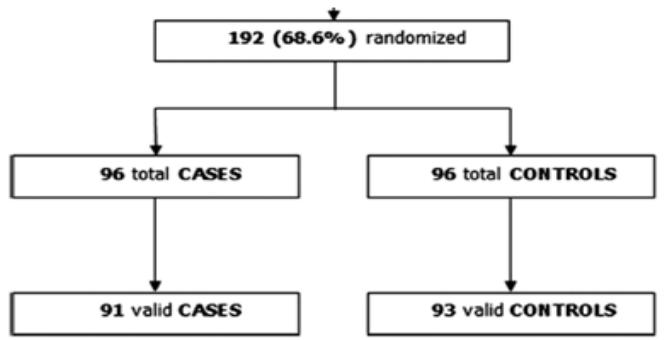
Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: A multicenter randomised controlled clinical trial

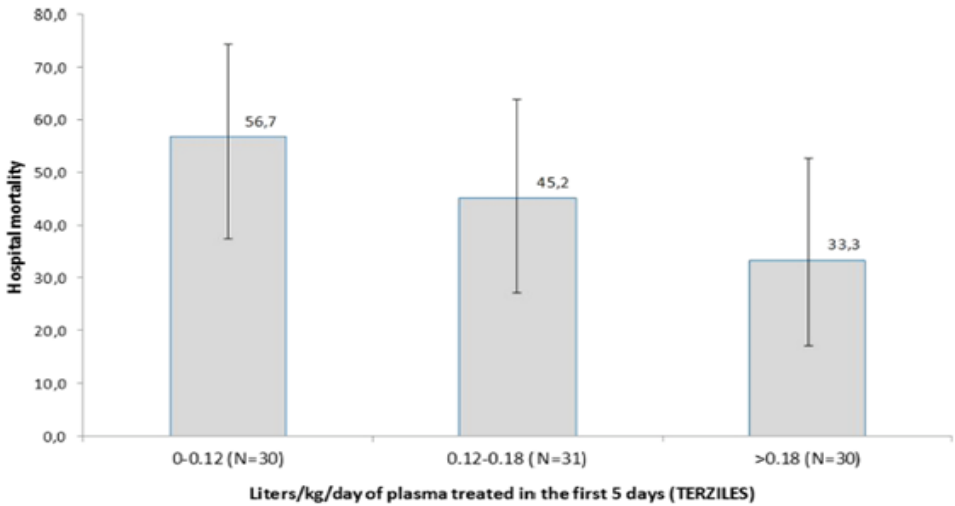
BMJ Open

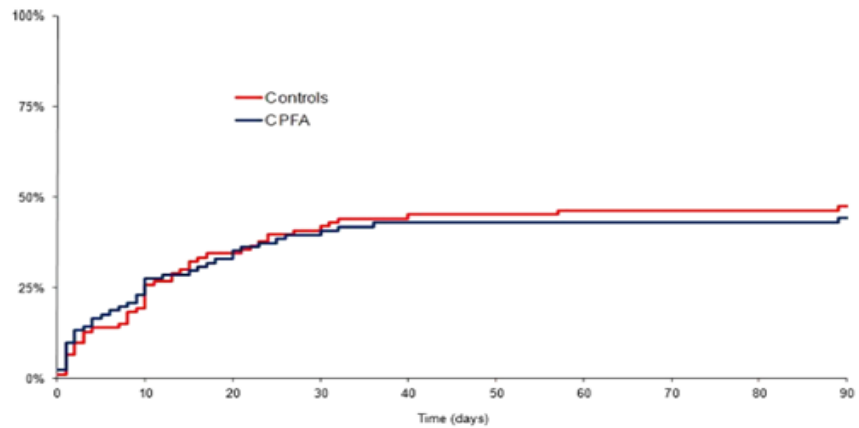
BMJ Open 2014;**4**:e003536.

Sergio Livigni,[1] Guido Bertolini,[2] Carlotta Rossi,[2] Fiorenza Ferrari,[1] Michele Giardino,[2] Marco Pozzato,[3] Giuseppe Remuzzi,[2] GiViTI: Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (Italian Group for the Evaluation of Interventions in Intensive Care Medicine) is an independent collaboration network of Italian Intensive Care units

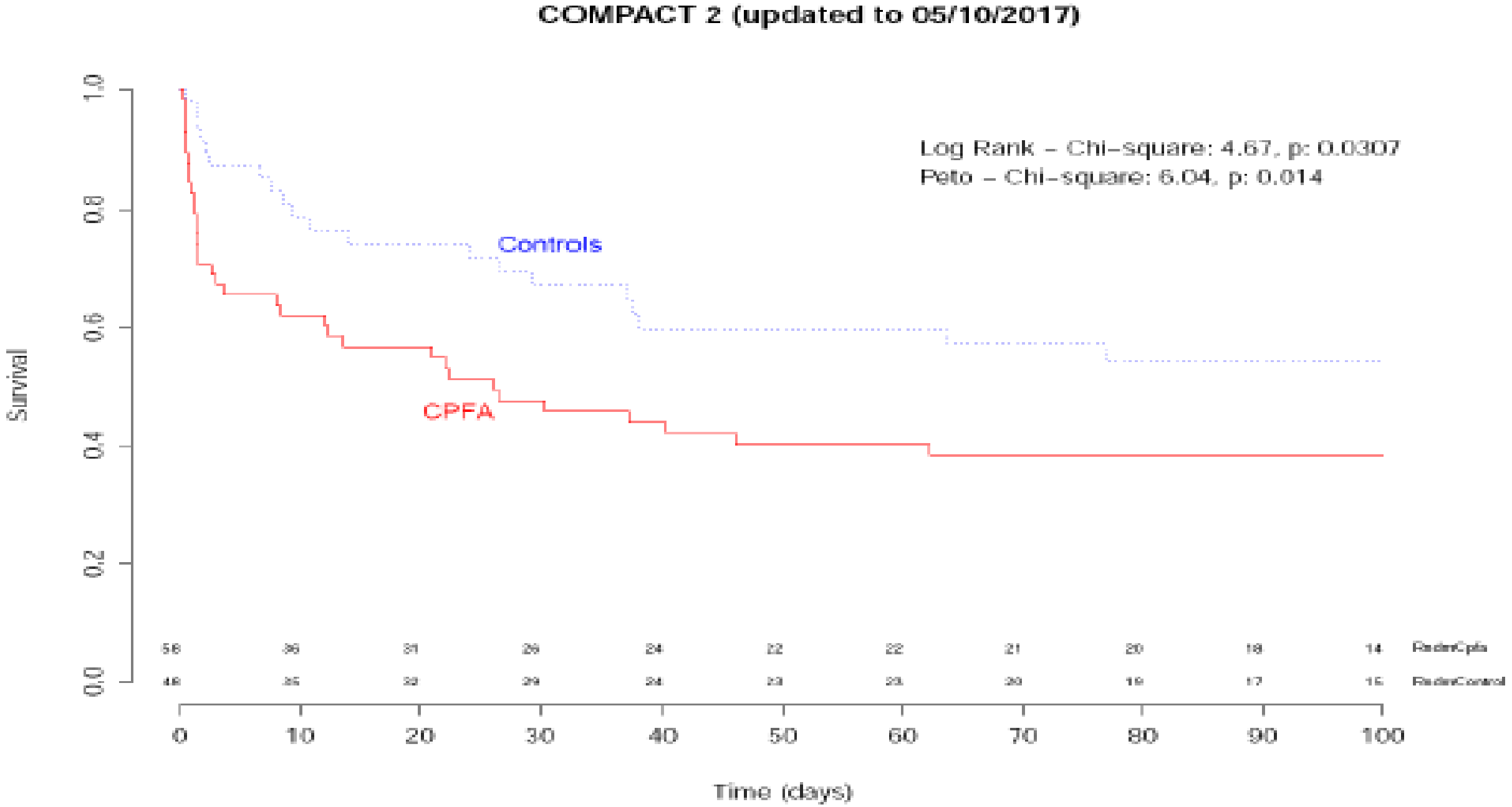








CPFA did not reduce mortality in patients with septic shock, nor did it positively affect other important clinical outcomes. A subgroup analysis suggested that CPFA could reduce mortality, when a high volume of plasma is treated.


COMPACT 2 (updated to 05/10/2017)
Log Rank – Chi-square: 4.67, p: 0.0307
Peto – Chi-square: 6.04, p: 0.014
Controls
CPFA
Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60
70
80
90
100
Time (days)
RadialCpfa
RadialControl

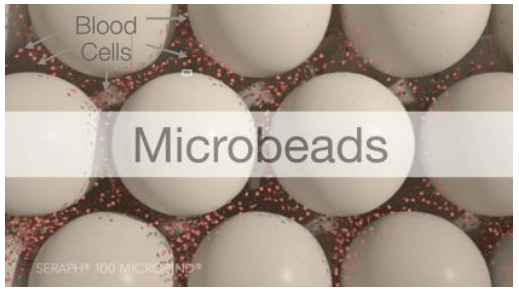
DIFFERENT TARGETS FOR EBP THERAPIES and Sequential Therapies……

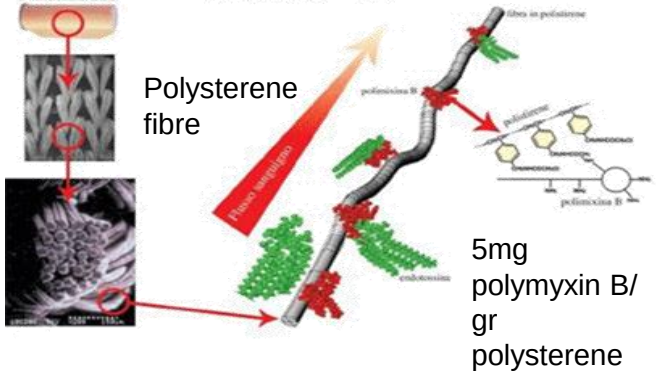
- **Seraph 100 HA**
- Binding of bacteria, virus, fungi
- No RRT

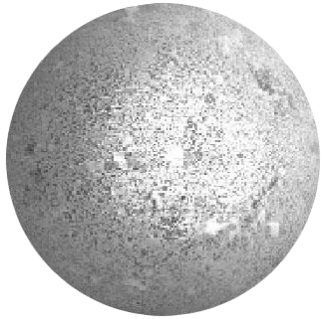
- **Polymyxin B HA**
- LPS binding
- No clearance of cytokines
- No RRT

- **Cytosorb/Jafron HA**
- Cytokines captured
- No clearance of LPS
- No RRT

- **oXiris membrane**
- LPS-adsorption
- Cytokine clearance
- RRT



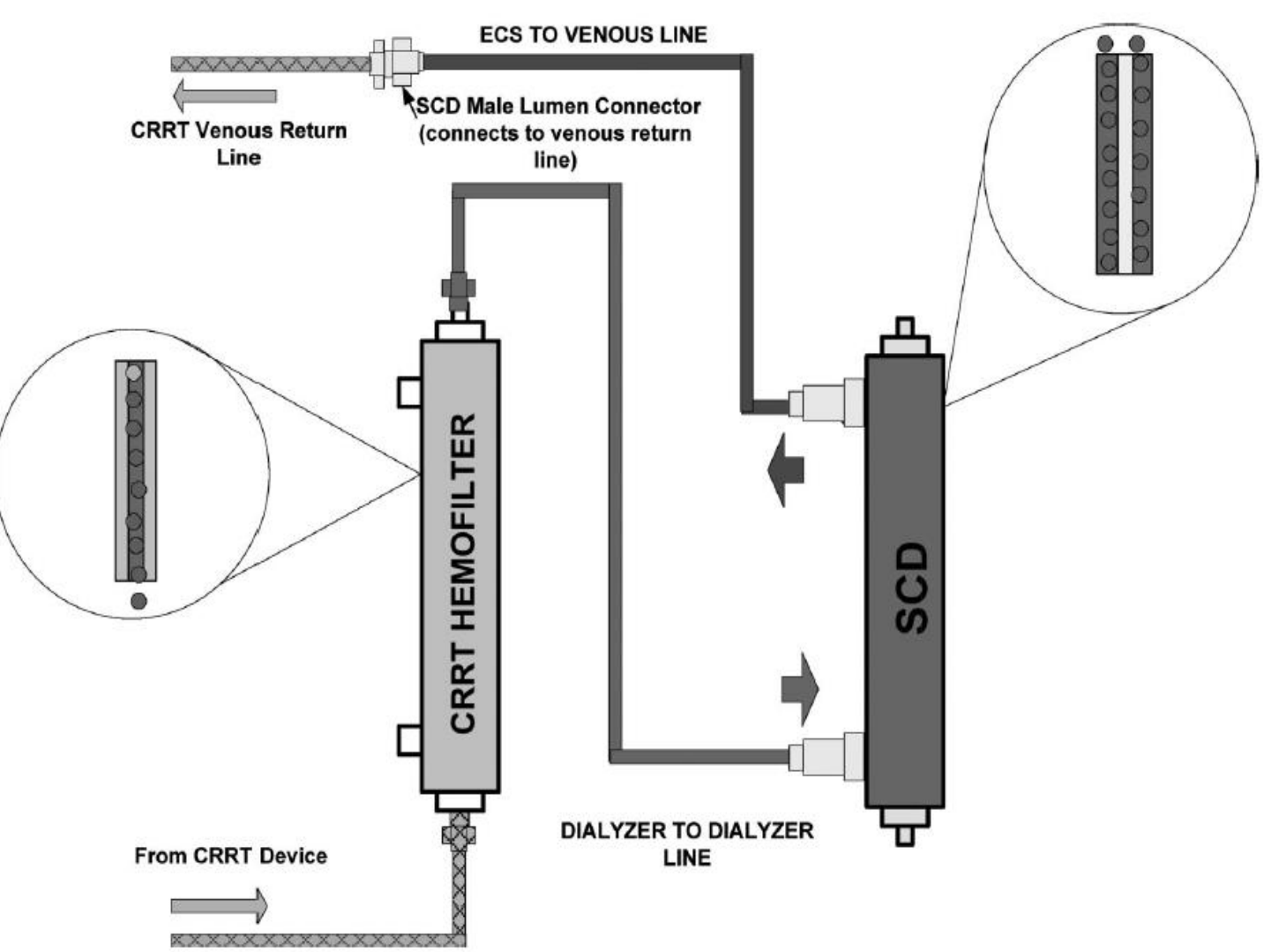


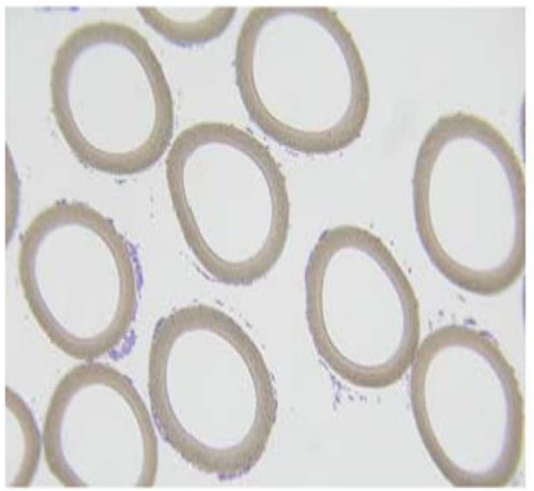


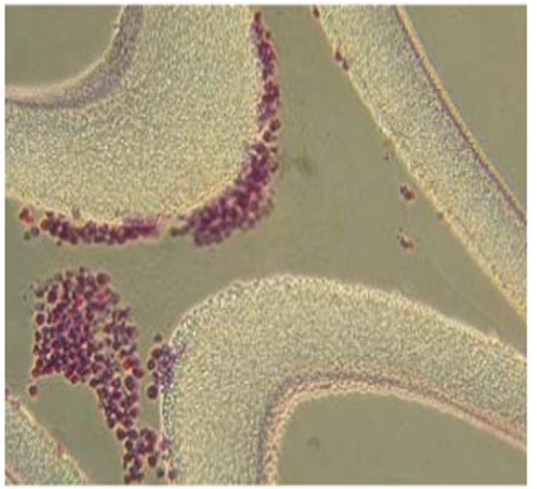
A Biomimetic Membrane Device That Modulates the Excessive Inflammatory Response to Sepsis

Feng Ding[1], Joon Ho Song[2], Ju Young Jung[3], Liandi Lou[4], Min Wang[4], Linda Charles[4], Angela Westover[4], Peter L. Smith[4], Christopher J. Pino[4], Deborah A. Buffington[4], H. David Humes[4,5]*

PLoS one




A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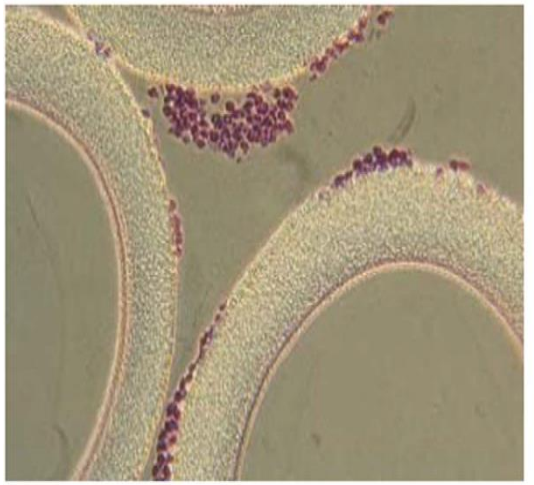
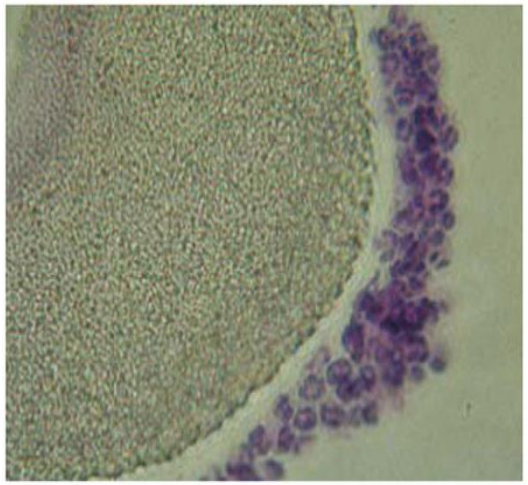

C


D


Adsorption:
what
to do?

ADQI # 30: Adsorption-based EBPT, Vicenza June 2023

Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup

nature reviews nephrology

Alexander Zarbock[1,2,44], Mitra K. Nadim[3,44], Peter Pickkers[4], Hernando Gomez[5], Samira Bell[6], Michael Joannidis[7], Kianoush Kashani[8], Jay L. Koyner[9], Neesh Pannu[10], Melanie Meersch[1], Thiago Reis[11,12], Thomas Rimmelé[13], Sean M. Bagshaw[14], Rinaldo Bellomo[15,16,17,18], Vicenzo Cantaluppi[19], Akash Deep[20], Silvia De Rosa[21,22],

Extracorporeal and novel therapies for SA-AKI

Consensus statement 5a

Extracorporeal blood purification (EBP) techniques can be used to remove pathogens, microbial toxins, inflammatory mediators and toxic metabolites from the blood as well as replenish solutes (grade 1A).

Consensus statement 5b

Kidney replacement therapy provides organ support through solute control, blood detoxification, and fluid balance via diffusion, convection and adsorption. Peritoneal dialysis can be used for kidney support when extracorporeal techniques are unavailable (grade 1A).

Consensus statement 5c

Emergent indications for initiating kidney replacement therapy do not differ between SA-AKI and other types of acute kidney injury (grade 1A).

Consensus statement 5d

Initiation of EBP in sepsis might be considered for immunomodulatory support in patients who meet explicit and timely clinical and/or biological criteria, such as high concentrations of damage-associated molecular patterns and pathogen-associated molecular patterns, as well as other targets of systemic inflammation (not graded).

Consensus statement 5e

Optimal delivery of extracorporeal therapies is determined by factors such as timely and safe initiation, treatment duration, appropriate vascular access placement and maintenance, individualized patient dose, safe and effective anticoagulation protocols, appropriate adjustments of medications (for example, antimicrobials or vasopressors) and nutrients, and a dynamic prescription of fluid removal (not graded).

Consensus statement 5f

Safe and effective therapy requires objective indicators of treatment response, which must be evaluated throughout the therapy course with a focus on patient-centred care goals (grade 1B).

ADQI

nature REVIEWS NEPHROLOGY

Consensus statement

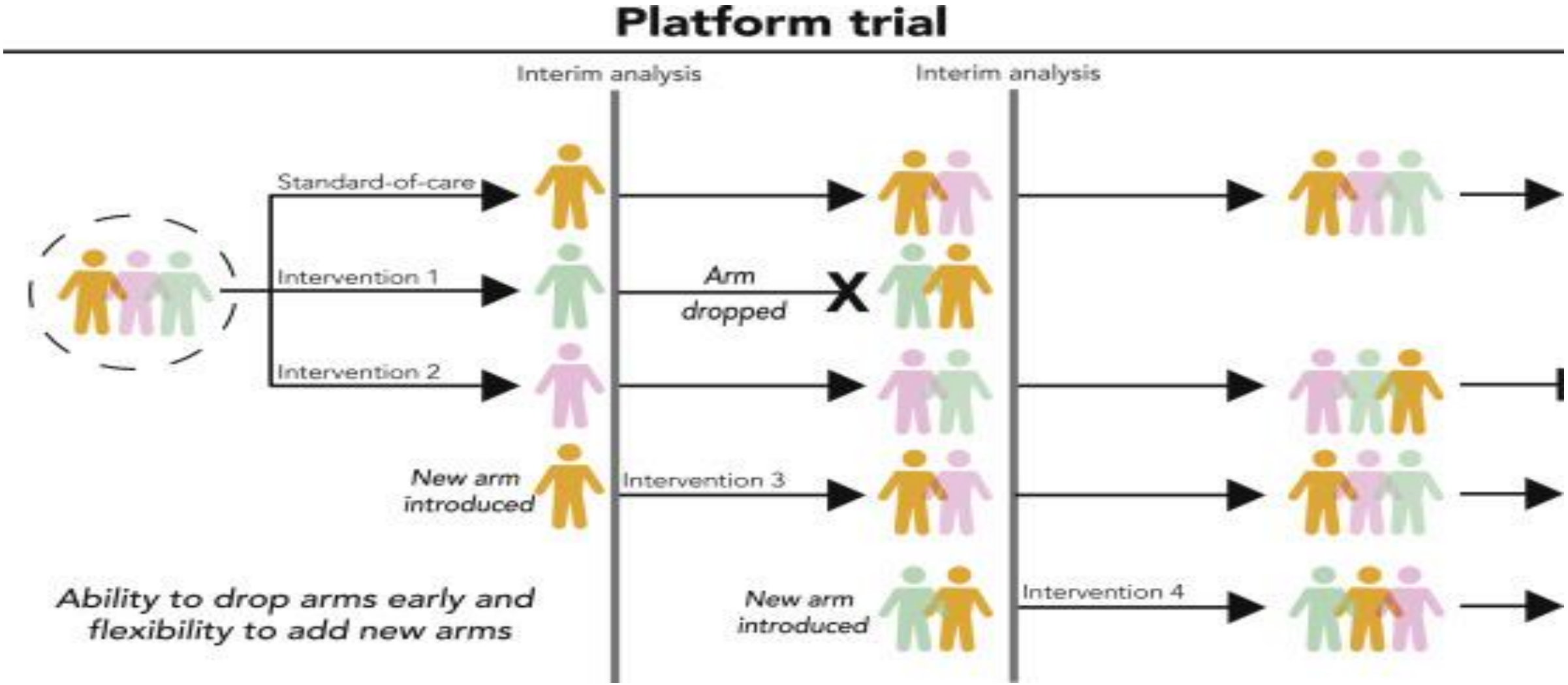
Check for updates

Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup

Research questions

1. How do the EBP therapies affect the pathophysiology of SA-AKI?
2. In which subgroup of patients, and when in the clinical course of the disease, might EBP therapies be beneficial?
3. Are EBP therapies safe, efficacious and cost-effective?
4. What meaningful target molecules can guide EBP therapy, and can their kinetics be employed to assess response to treatment?
5. What is the effect of EBP therapies on other organ systems during sepsis?

Platform trial: A type of randomized clinical trial design in which multiple interventions can be evaluated simultaneously against a common control group with flexibilities of allowing new interventions to be added and the control group to be updated throughout the trial



UNIVERSITÀ DEL PIEMONTE ORIENTALE

vincenzo.cantaluppi@med.uniupo.it

GdP AKI e Terapie Extracorporee in Area Critica

SIN Società Italiana Nefrologia

ERAKI European Acute Kidney Injury