Tecniche depurative speciali: aferesi, emoadsorbimento, quali indicazioni nel 2022 (2023)

Vincenzo Cantaluppi

SCDU Nefrologia e Trapianto Renale
Direttore Scuola di Specializzazione in Nefrologia
Dipartimento di Medicina Traslazionale (DIMET)
Università del Piemonte Orientale (UPO)
Responsabile Progetto Trapianti
AOU Maggiore della Carità di Novara

Nazionale ANTE Riccione, 17-19 Aprile 2023

ESRD

AKI

SEPSIS

MOF

LIVER FAILURE

LUNG FAILURE

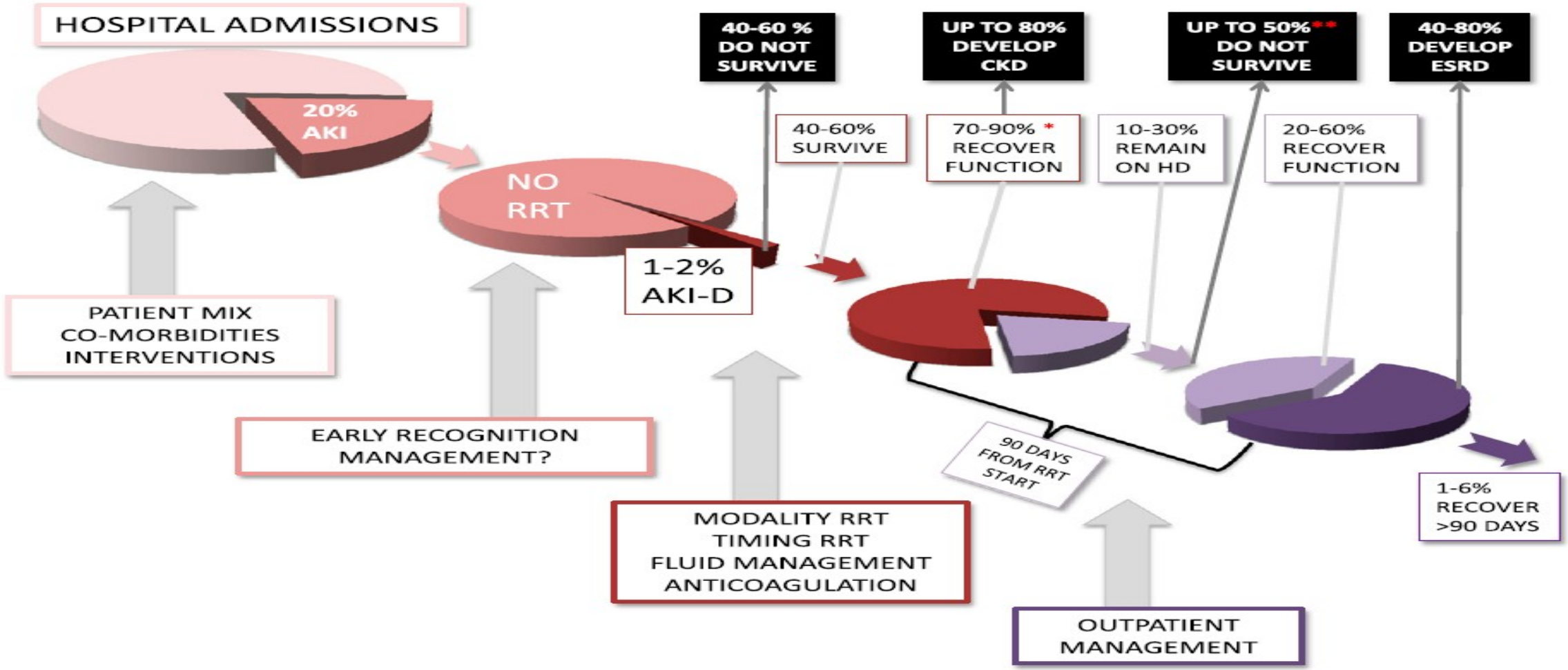
TRANSPLANTATION

……

……

Promoting Kidney Function Recovery in Patients with AKI Requiring RRT

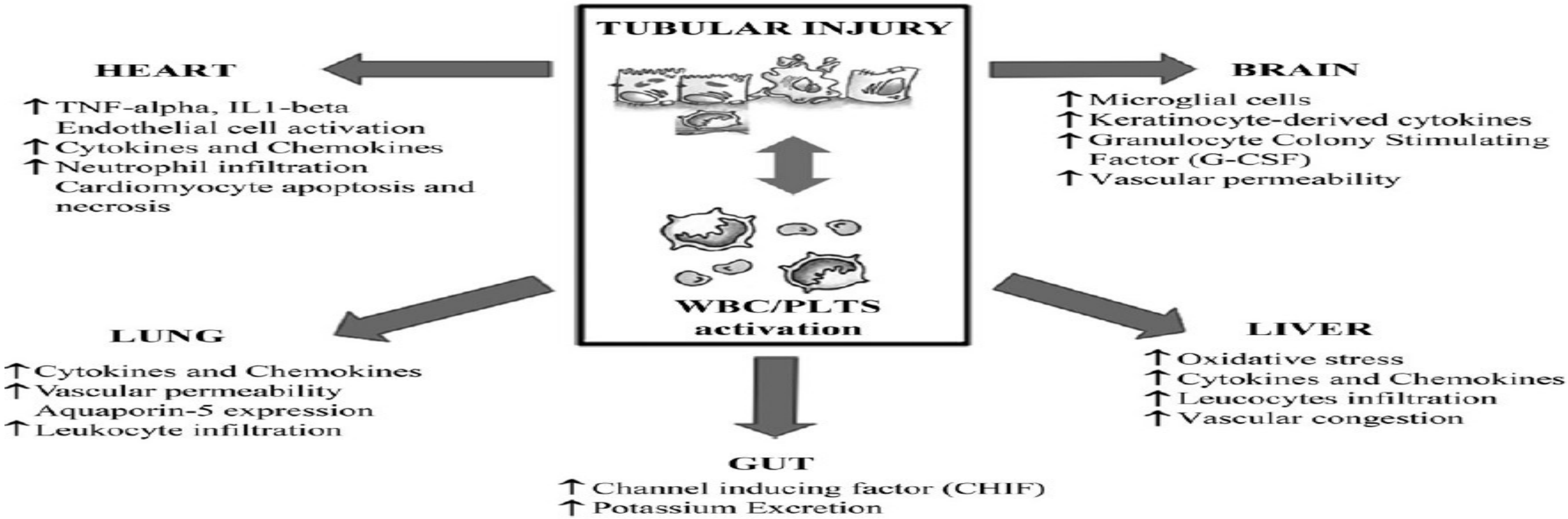
Jorge Cerdá, Kathleen D. Liu,† Dinna N. Cruz,‡ Bertrand L. Jaber,§ Jay L. Koyner,‖ Michael Heung,¶ Mark D. Okusa,** and Sarah Faubel†† for the AKI Advisory Group of the American Society of Nephrology*



Interaction between systemic inflammation and renal tubular epithelial cells

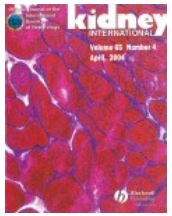
Vincenzo Cantaluppi, Alessandro Domenico Quercia, Sergio Dellepiane, Silvia Ferrario, Giovanni Camussi and Luigi Biancone

ndt
Nephrology Dialysis Transplantation



Plasma cytokine levels predict mortality in patients with acute renal failure

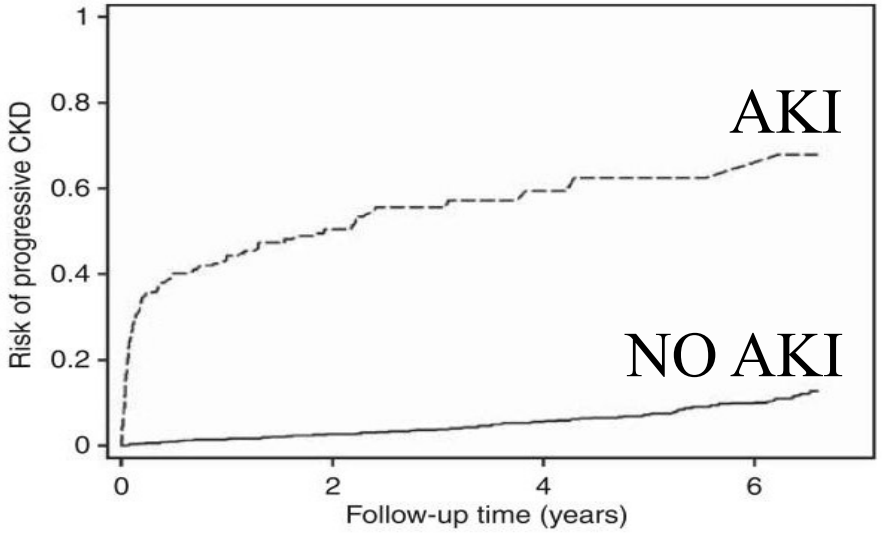
EDITH M. SIMMONS, JONATHAN HIMMELFARB, M. TUGRUL SEZER, GLENN M. CHERTOW, RAVINDRA L. MEHTA, EMIL P. PAGANINI, SHARON SOROKO, STEPHANIE FREEDMAN, KAREN BECKER, DANIEL SPRATT, YU SHYR, and T. ALP IKIZLER, FOR THE PICARD STUDY GROUP

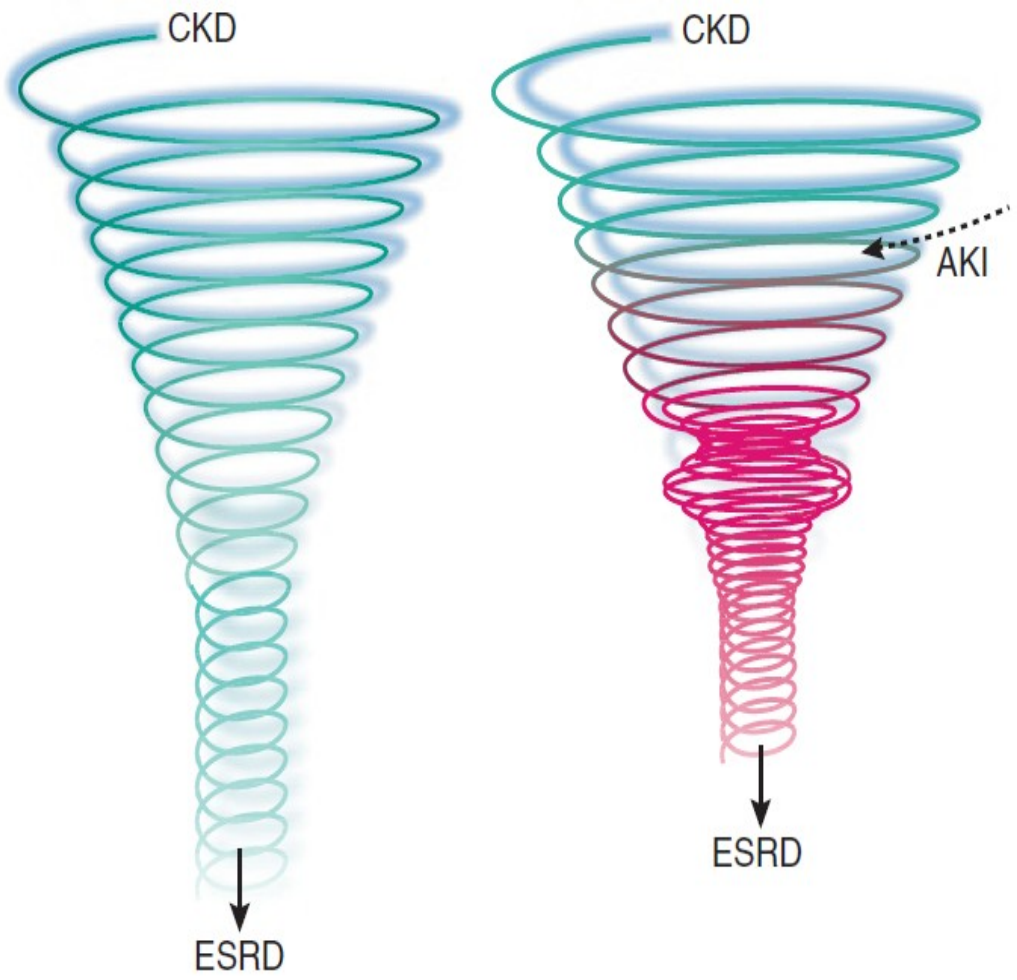


Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease

Lowell J. Lo[1], Alan S. Go[1,2,3], Glenn M. Chertow[4], Charles E. McCulloch[3], Dongjie Fan[2], Juan D. Ordoñez[5] and Chi-yuan Hsu[1,2]

AKI: progression toward CKD





2.1.2: AKI is staged for severity according to the following criteria (Table 2)

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

The growth of acute kidney injury: a rising tide or just closer attention to detail?

Edward D. Siew[1] and Andrew Davenport[2]

Kidney International (2015) **87**, 46–61

Table 2c | ICU-based incidences rates of AKI before and after RIFLE/AKIN/KDIGO

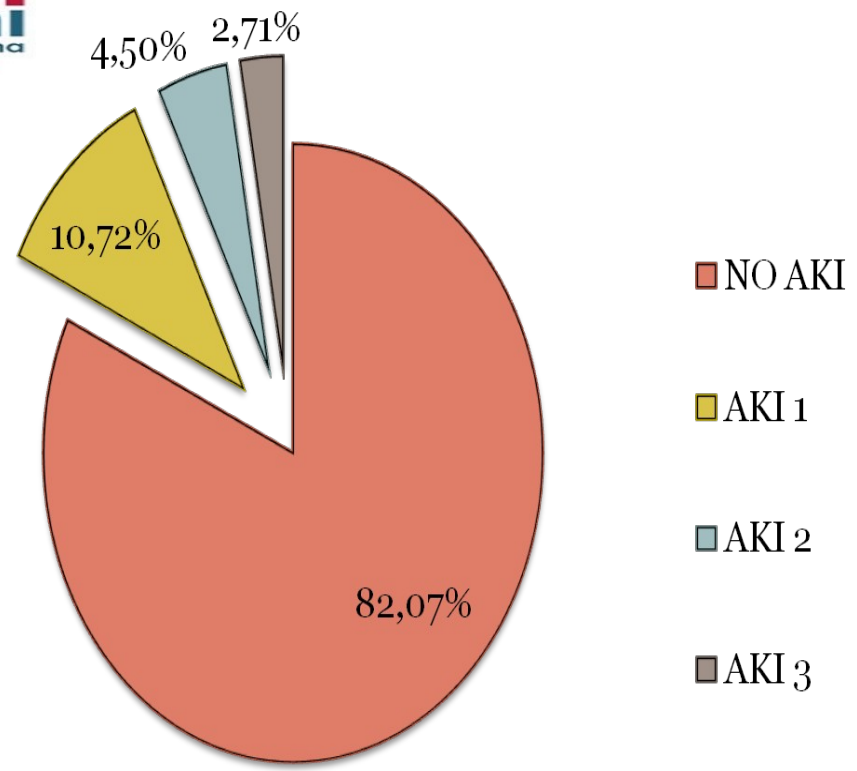
Study	Era	Country	Enrollment	Setting	Definition used	Incidence
Brivet *et al.*[143]	Before RIFLE AKIN KDIGO	France	1991	ICU	Increase in serum creatinine to >3.5 mg/dl or BUN >100 mg dl in non-CKD or 100% above baseline levels if CKD	7%
Uchino *et al.*[4]		Global	2000–2001	ICU	Severe AKI: urine output <200 ml per 12 h or BUN >84 mg/dl + RRT	5.7% (95% CI: 5.5–6.0%)
Hoste *et al.*[144]	After RIFLE AKIN KDIGO	USA (Pittsburgh)	2000–2001	ICU (single center)	RIFLE	67%
Osterman *et al.*[14]		United Kingdom and Germany	1988–1999	ICU (multicenter)	RIFLE	35.8%
Bagshaw *et al.*[146,147]		Australia/New Zealand	2000–2005	ICU (multicenter)	RIFLE on admission AKIN on admission	36.1% 37.1%
Bagshaw *et al.*[148]		Australia/New Zealand	2000–2005	ICU patients with sepsis (multicenter)	RIFLE on admission	42.1%
Cruz *et al.*[149]		Italy	2003	ICU (multicenter)	RIFLE	10.8% (95% CI: 9.5–12.1)
Nisula *et al.*[150]		Finland (Helsinki)	2011–2012	ICU (multicenter)	KDIGO	39.3% (95% CI: 37.5–41.1)

Abbreviations: ACRF, acute on chronic renal failure; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ARF, acute renal failure; ATN, acute tubular necrosis; BUN, blood urea nitrogen; CABG, coronary artery bypass surgery; CI, confidence interval; CKD, chronic kidney disease; ICD-9-CM, International Classification of Diseases, Clinical Modification; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss, and End-stage Kidney Disease; RRT, renal replacement therapy.

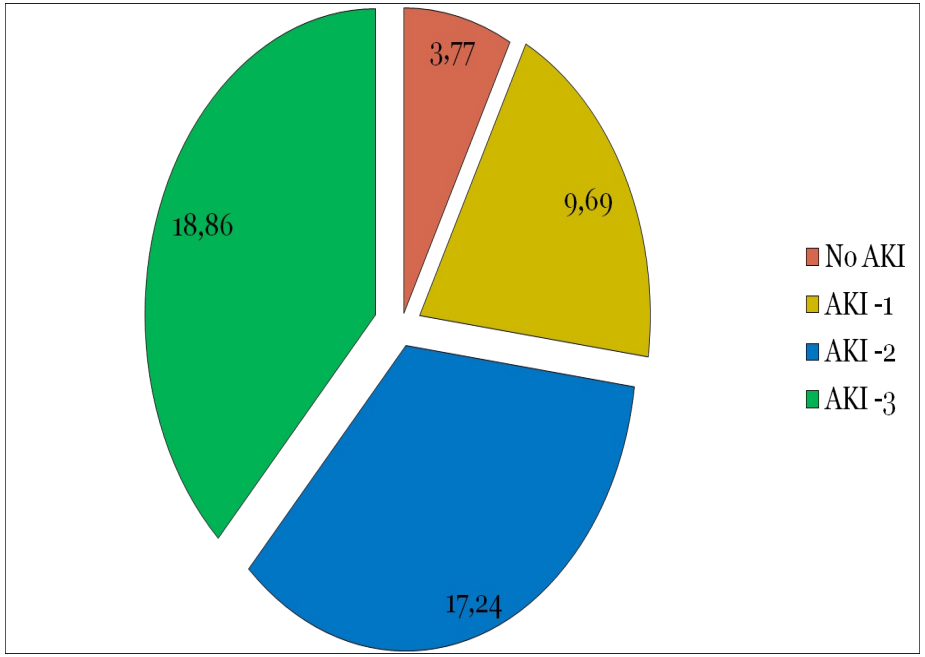
SIN-AKI study

A.O.U. “Maggiore della Carita’” di Novara- ITALY

RESULTS 2019: about 13000 hospital admissions



AKI incidence: about 18%



Outcome

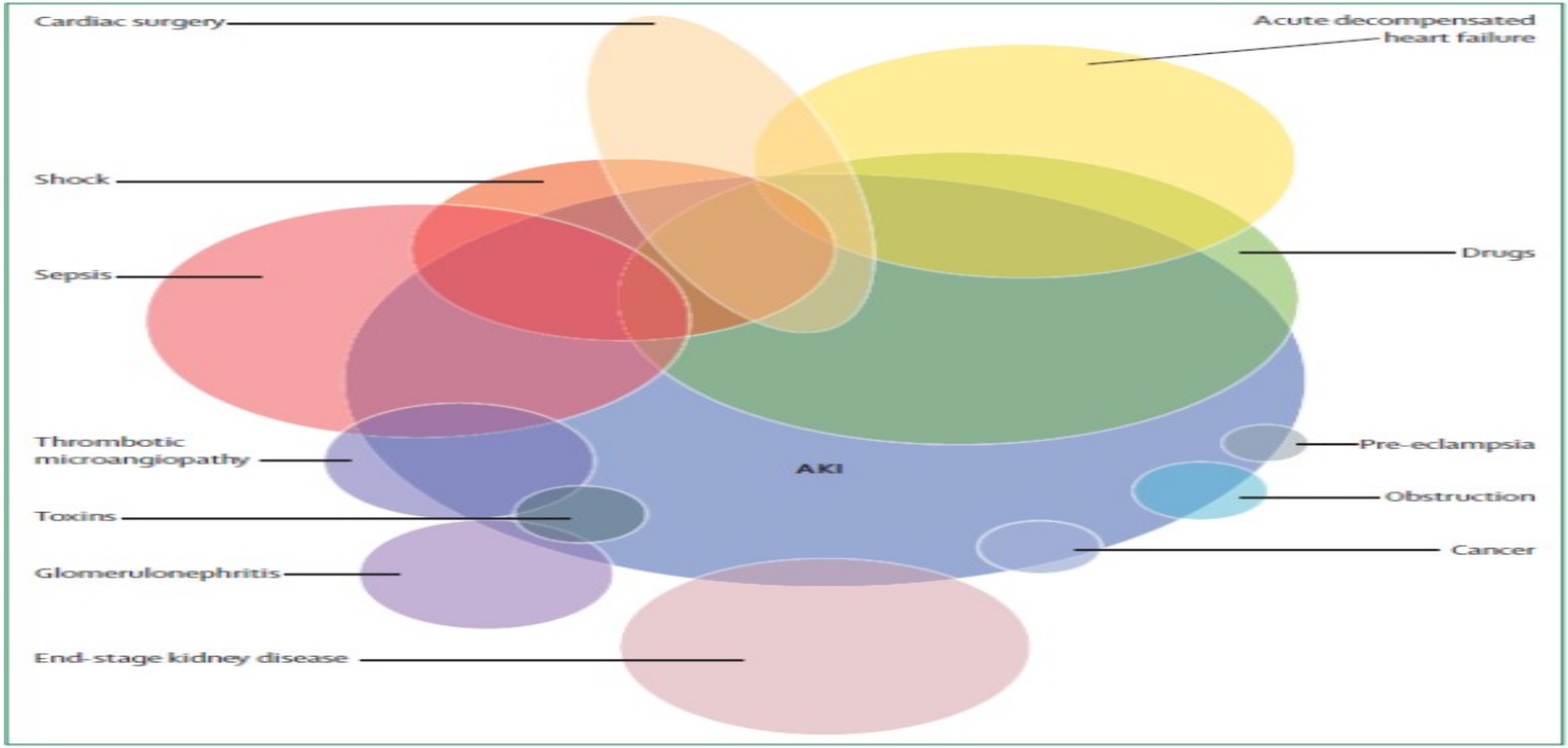
Acute kidney injury

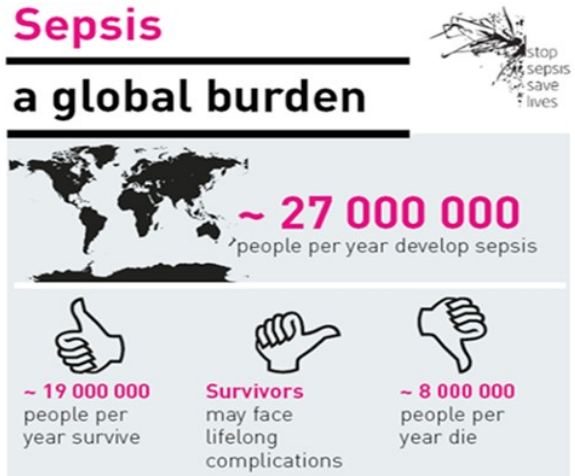
Claudio Ronco, Rinaldo Bellomo, John A Kellum

THE LANCET

Vol 394 November 23, 2019

The clinical spectrum of AKI syndrome





Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

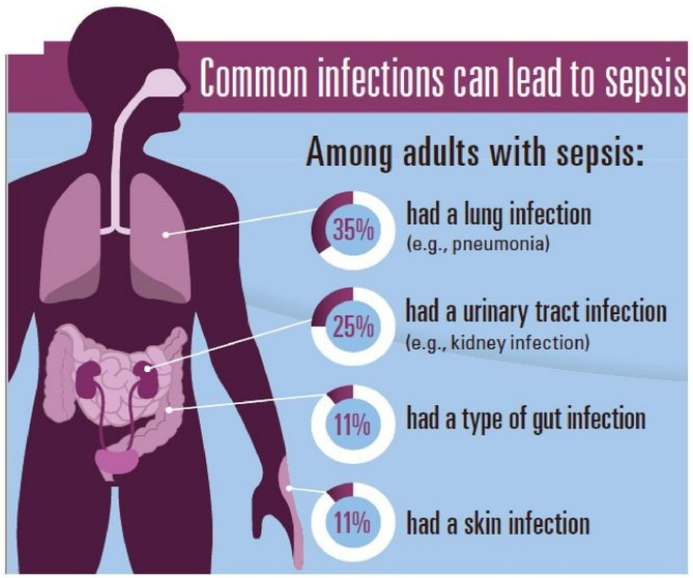
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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



SOURCE: CDC Vital Signs, August 2016.

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

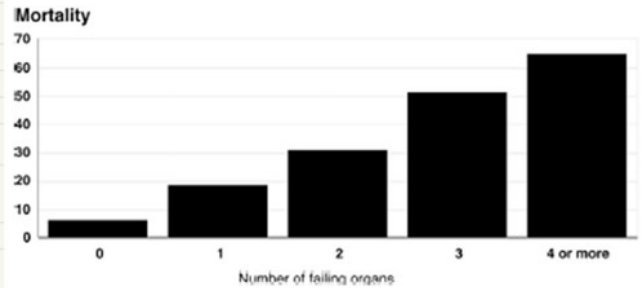
	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (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*

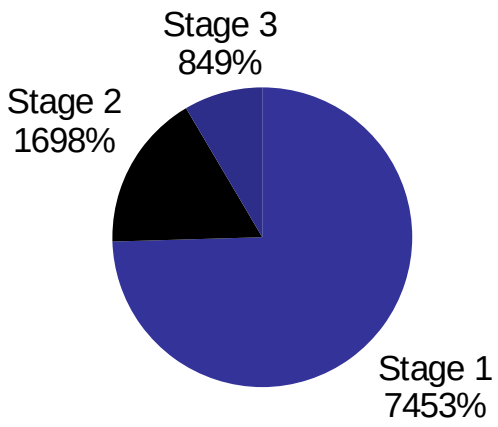
Jean-Louis Vincent, MD, PhD, FCCM; Yasser Sakr, MB, BCh, MSc; Charles L. Sprung, MD; V. Marco Ranieri, MD; Konrad Reinhart, MD, PhD; Herwig Gerlach, MD, PhD; Rui Moreno, MD, PhD; Jean Carlet, MD, PhD; Jean-Roger Le Gall, MD; Didier Payen, MD; on behalf of the Sepsis Occurrence in Acutely Ill Patients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

Crit Care Med 2006 Vol. 34, No. 2

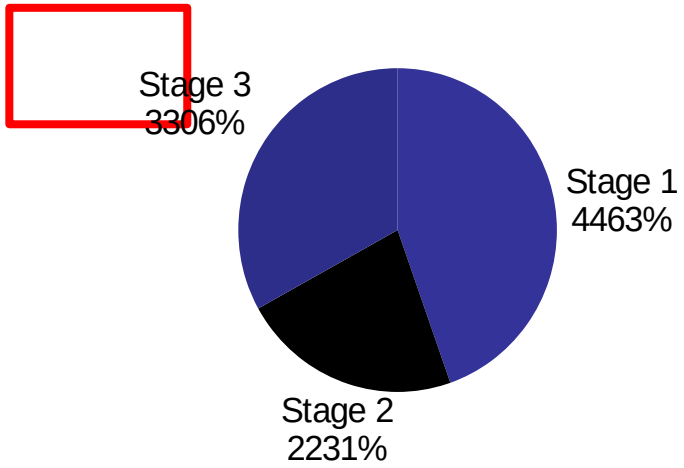
RESULTS: AKI SEVERITY AND PERSISTENCE

UNIVERSITÀ DEL PIEMONTE ORIENTALE

OC-AKI



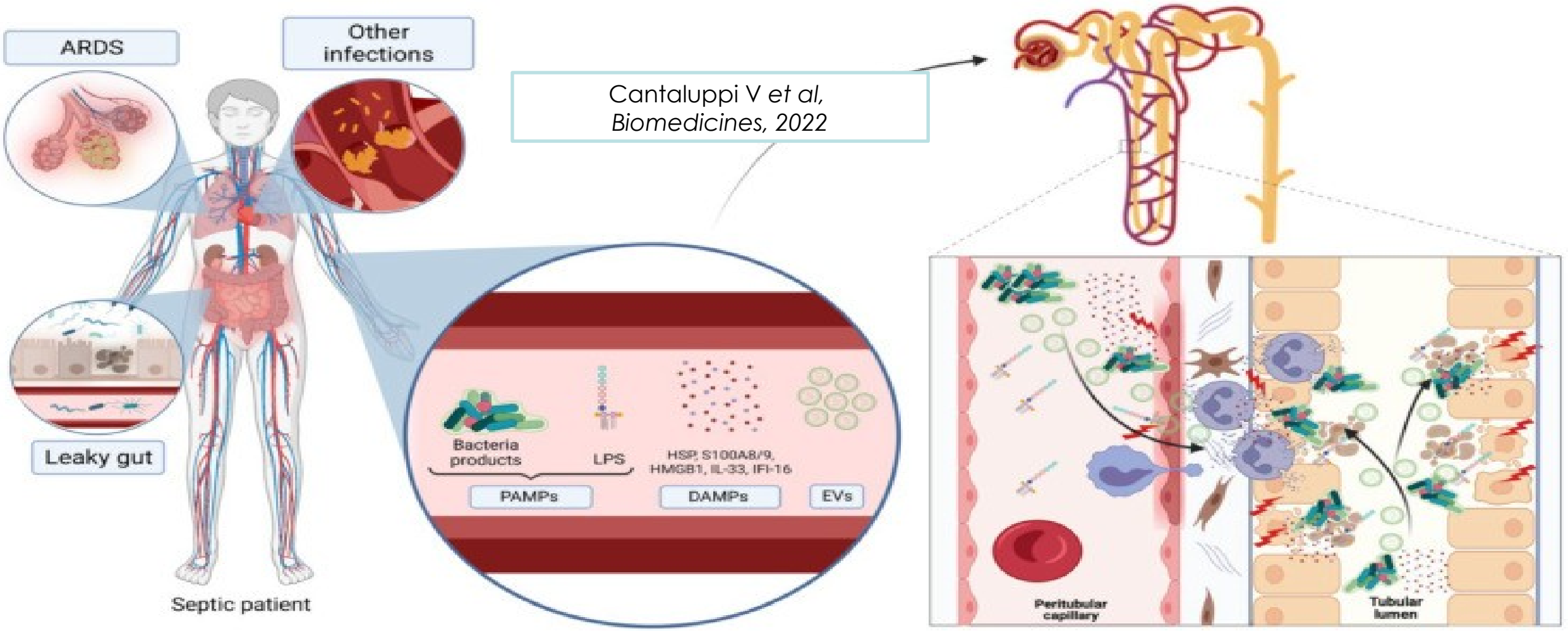
SA-AKI



- **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)**

BACKGROUND: SEPSIS-ASSOCIATED AKI



Cantaluppi V *et al*, *Biomedicines, 2022*

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

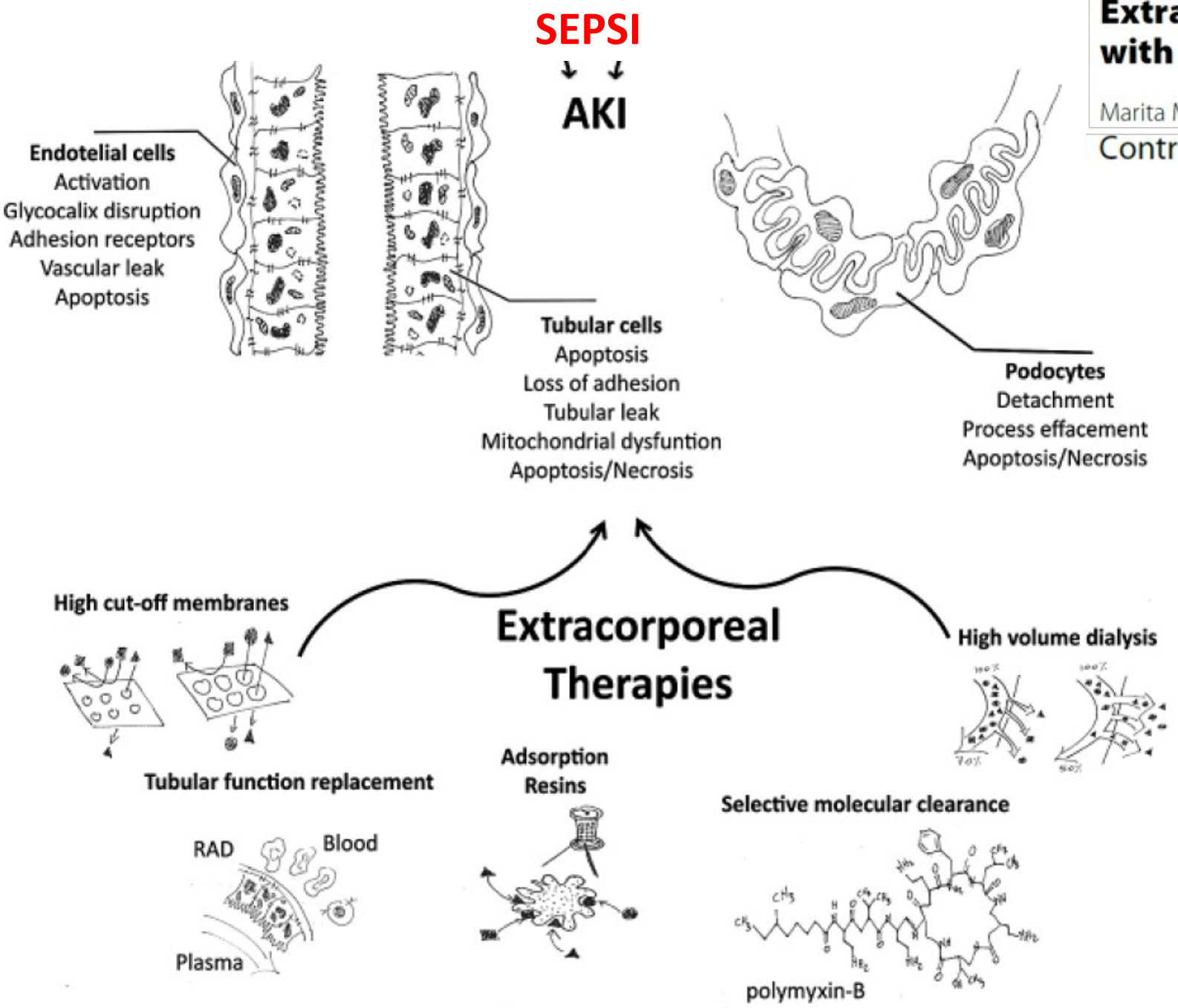
Alexander Zarbock[1,2,44], Mitra K. Nadim[3,44], Peter Pickkers[4], Hernando Gomez[5], Samira Bell[6], Michael Joannidis[7], Kianoush Kashani[8], Jay L. Koyner[9], Neesh Pannu[10], Melanie Meersch[1], Thiago Reis[11,12], Thomas Rimmelé[13], Sean M. Bagshaw[14], Rinaldo Bellomo[15,16,17,18], Vicenzo Cantaluppi[19],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

nature reviews nephrology

Extracorporeal Treatments in Patients with Acute Kidney Injury and Sepsis

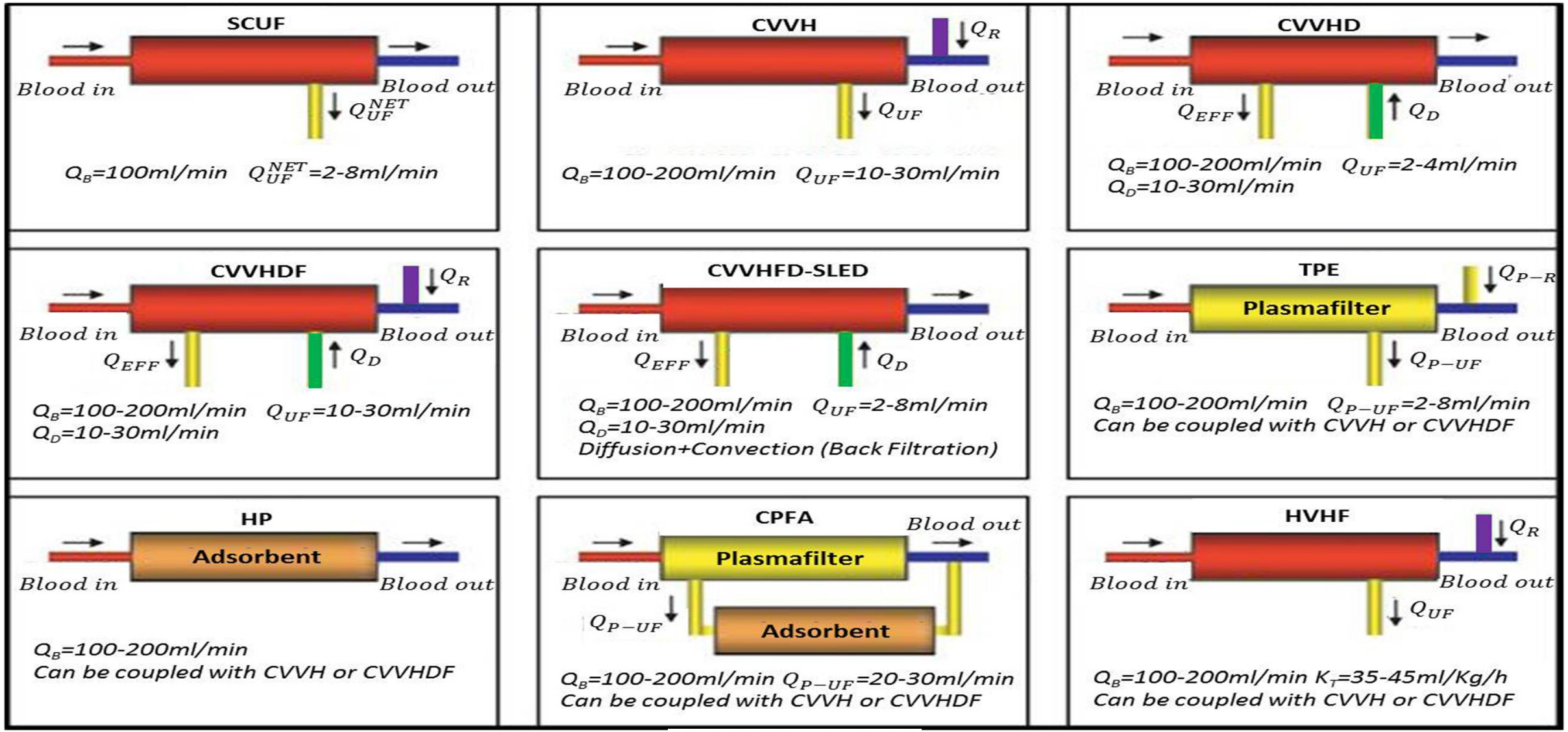
Marita Marengo[a] · Sergio Dellepiane[b] · Vincenzo Cantaluppi[c]

Contrib Nephrol. Basel, Karger, 2017, vol 190, pp 1–18



The main purpose of blood purification therapies should be to restore homeostasis, as a matter of facts, most sepsis mediators are water-soluble and fall into the "middle-molecular weight" category (about 5-50kDa) that can be theorically removed by RRT via

Come dializzare?



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

TIMING

Box 1. Factors to Consider for CRRT Initiation

Severity of illness and trajectory
- AKI severity and trend
- Levels of BUN and serum creatinine
- Electrolytes and acid-base disorders
- Fluid balance and evidence of fluid overload
- Urinary output in context of patient's fluid balance and fluid needs
- Presence of other significant organ dysfunction that will require renal support for optimizing care and promoting recovery

Necessity of the procedure
- Likelihood of recovery of kidney function without CRRT: cause and likelihood of reversibility of AKI, based on trend of kidney function parameters
- Both nature and timing of renal insult
- Underlying disease and comorbid conditions
- Presence of oliguria (consider effect of diuretic)
- Concurrent use of vasopressors and ventilator requirements

Risks associated with the procedure
- Vascular access complications: hemorrhage, thrombosis, bacteremia
- Complications of CRRT
- Intradialytic hypotension
- Hypersensitivity to the extracorporeal circuit
- Clearance of trace elements, and antibiotics
- Prolongation of AKI course

Futility
- Likelihood of patient surviving hospital admission
- Concerns about quality of life

Other considerations
- Family wishes
- Health costs
- Machine and nursing availability

The **optimal timing** of dialysis for AKI **is not clear**.
In the absence of an urgent need, clinicians tend to delay RRT initiation.

Earlier Start to RRT in AKI

Benefits	Risks
Azotemic control	CVC insertion
Electrolyte/acid-base homeostasis	Extracorporeal circuit
Fluid balance homeostasis	Anticoagulation
Prevent complications of AKI	Micronutrient depletion
Nutritional support	Added beside resources
Immunomodulation	Impaired/disrupted recovery

AJKD
Core Curriculum in Nephrology

Continuous Dialysis Therapies: Core Curriculum 2016

Etienne Macedo, MD, PhD,[1] and Ravindra L. Mehta, MD[2]

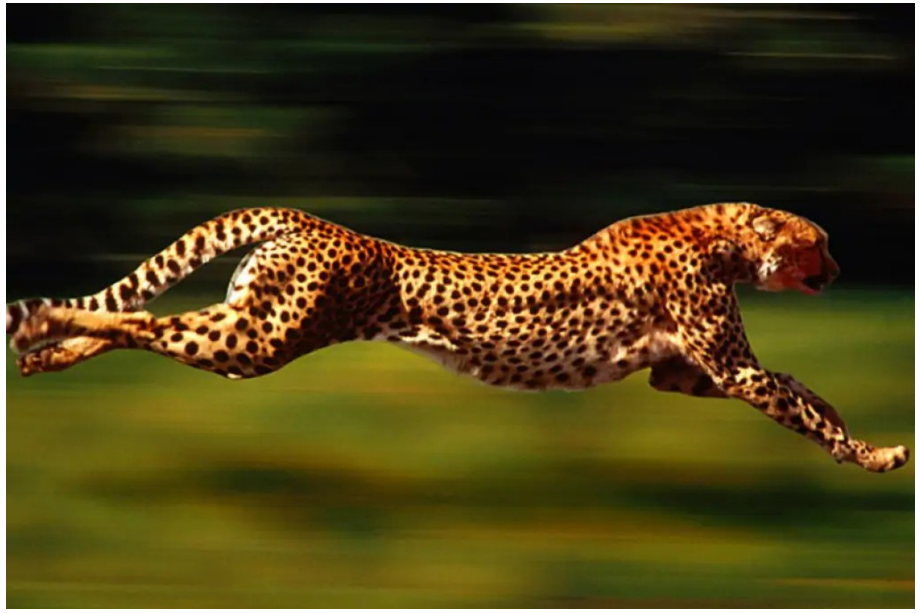
Am J Kidney Dis. 2016;68(4):645-657

TIMING

Extracorporeal therapy in sepsis: are we there yet?

Ashutosh M. Shukla[1]

Kidney International (2011) **81,** 336–338.



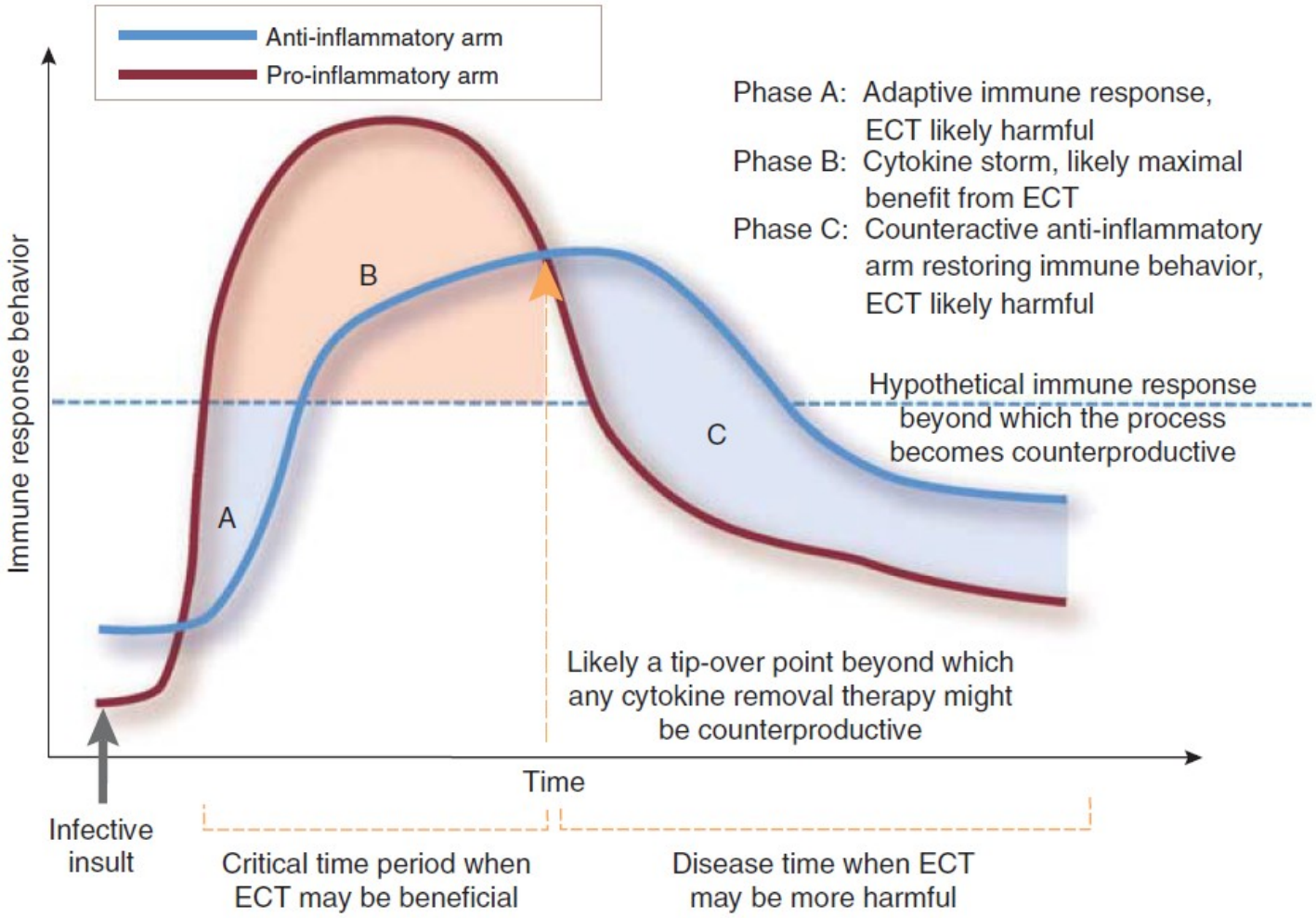
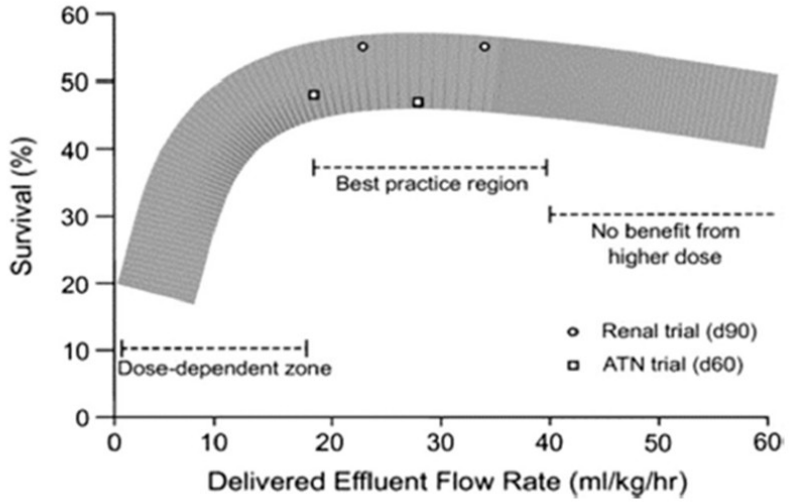


Figure 1 | Theoretical considerations of the likely impact of ECT in a single-hit model of sepsis, and its correlation to the stage and severity of disease. ECT, extracorporeal therapy.

DOSE

In many of these "high-volume" studies no correction was made for antibiotic flux and so patients may have been underdosed…

The actual delivery dose of RRT is approximately 70-90% of the prescription. Thus, prescribing a 25-30 be more useful in septic-AKI.



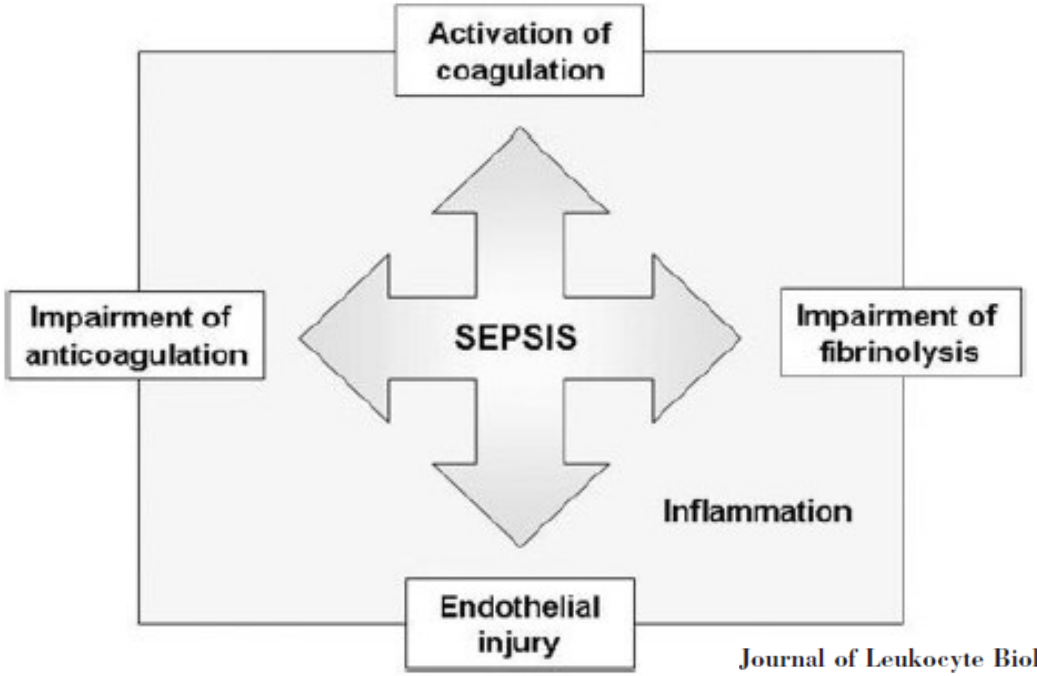
KDIGO Clinical Practical Guideline fro Acute Kidney Injury

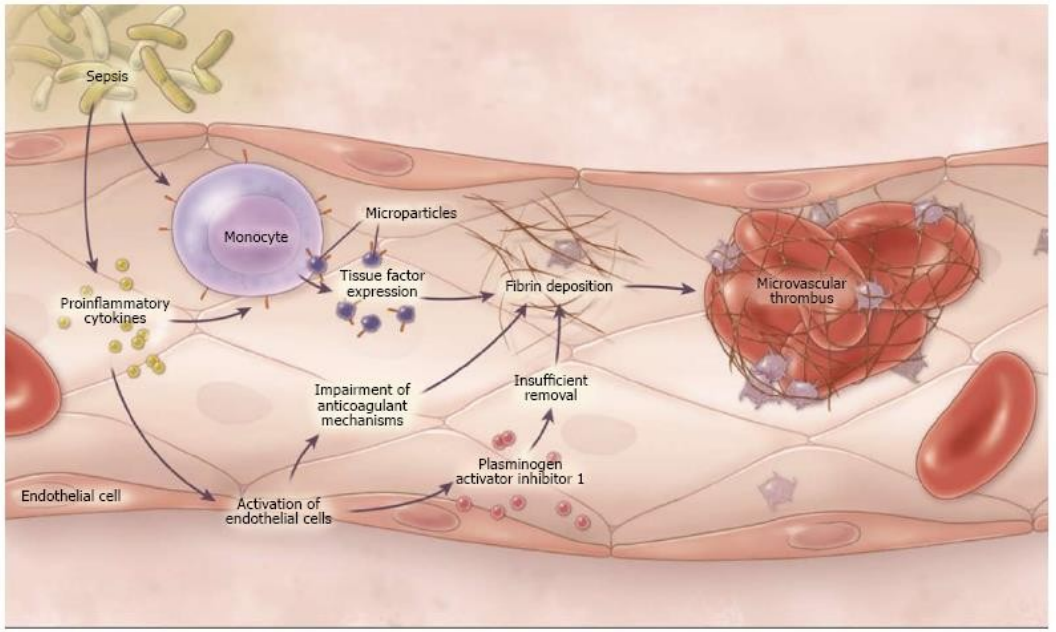
Chapter 5.8: Dose of renal replacement therapy in AKI

5.8.3: We recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. (*1A*)

5.8.4: We recommend delivering an effluent volume of 20–25 ml/kg/h for CRRT in AKI *(1A)*. This will usually require a higher prescription of effluent volume. (*Not Graded*)

ANTICOAGULATION



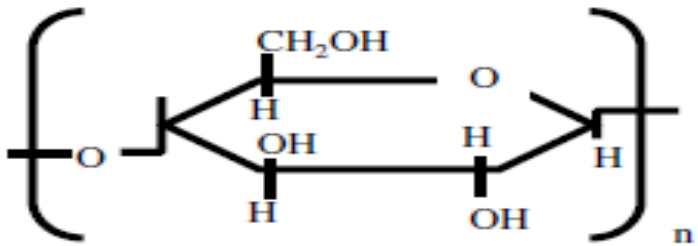


Journal of Leukocyte Biology Volume 83, March 2008

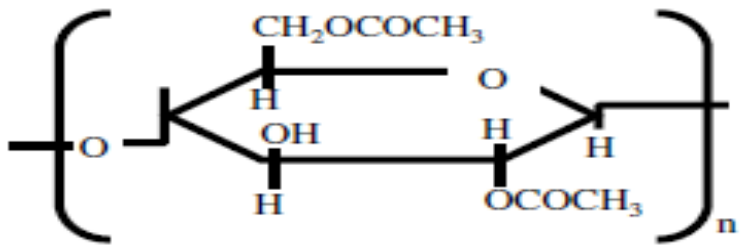
Extensive crosstalk exists between coagulation and inflammation during sepsis, which is characterized by inflammation-induced activation of coagulation with concurrent impairment of anticoagulation systems, fibrinolysis and endothelial function.

Chemical structures of cellulosic and synthetic polymeric membranes for blood purification

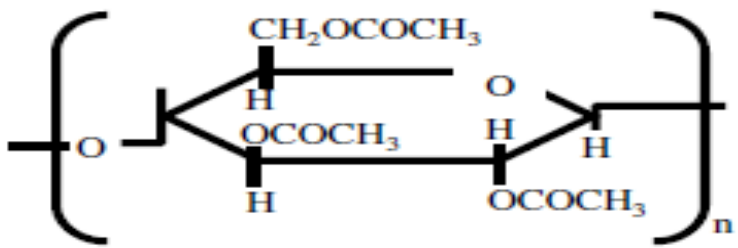
Cellulosic membranes



Regenerated cellulose

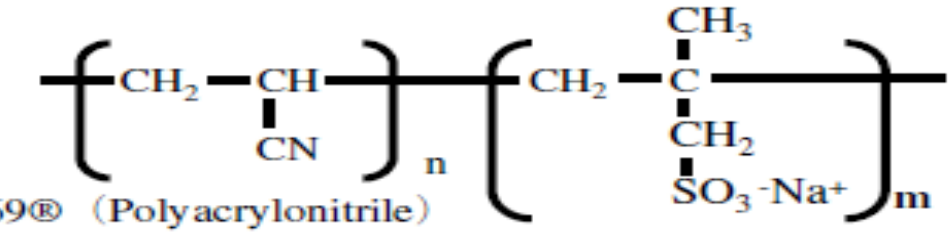


Cellulose diacetate （CDA）

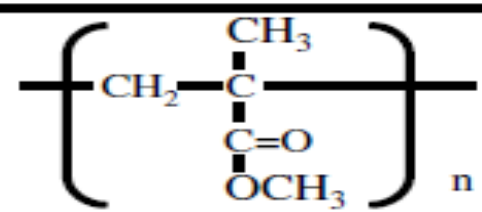


Cellulose triacetate （CTA）

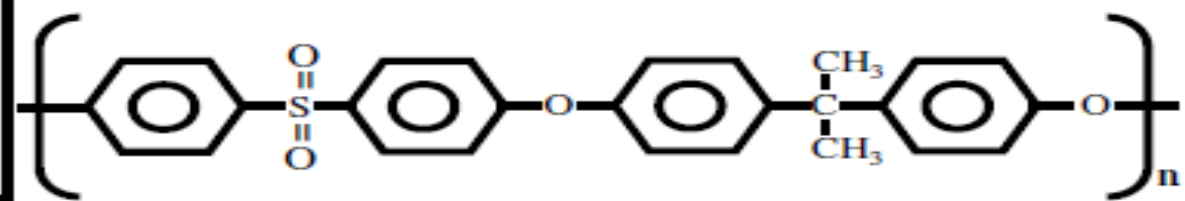
Synthetic polymeric membranes



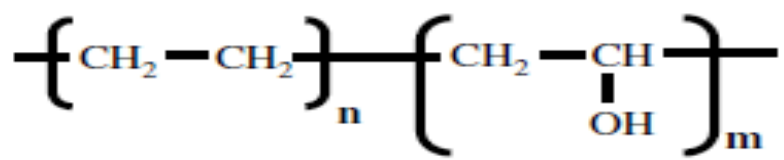
AN-69®（Polyacrylonitrile）



Polymethylmethacrylate （PMMA）



Polysulfone（PSf）



Ethylenevinylalcohol co-polymer （EVAL）

HIGH PERFORMANCE MEMBRANES (HPM)

hollow fiber dialyzers with an advanced level of performance

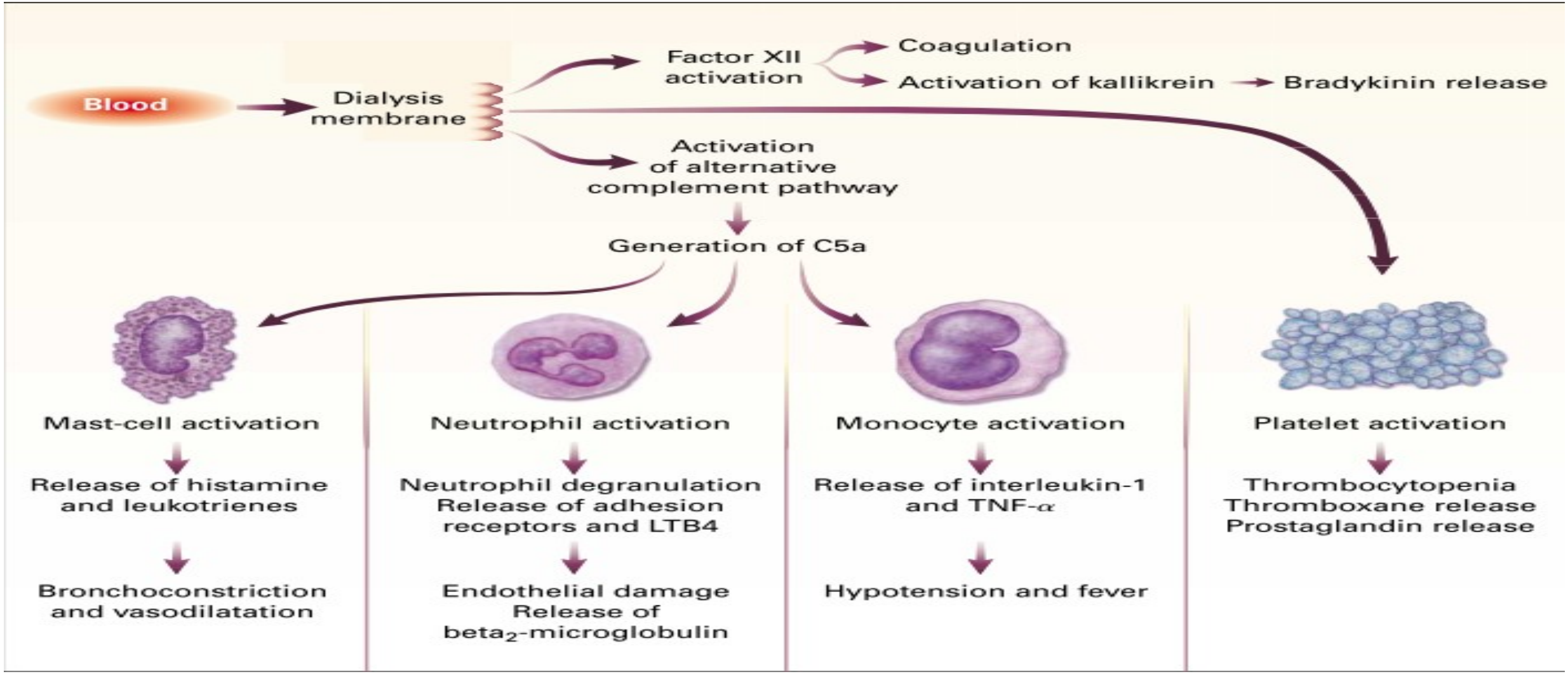
The criteria to identifie HPM:

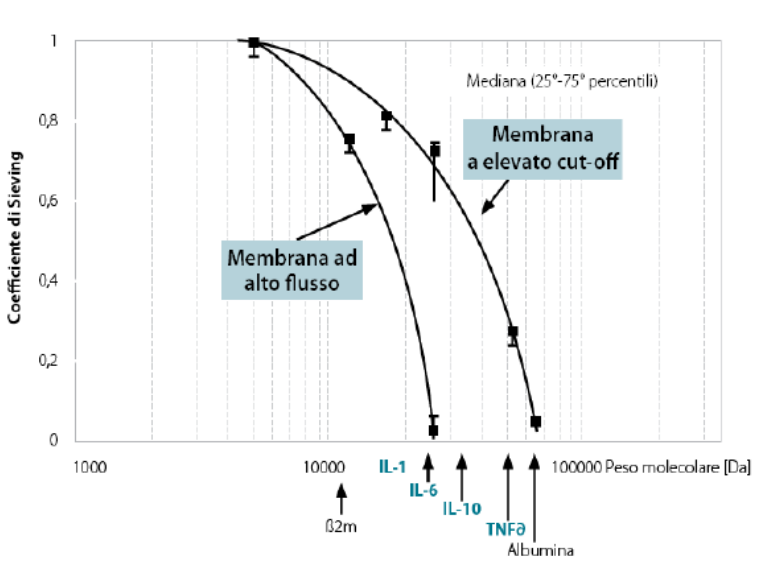
- excellent biocompatibility
- effective clearance of target solutes
- pore size larger than conventional hemodialysis (HD) membranes

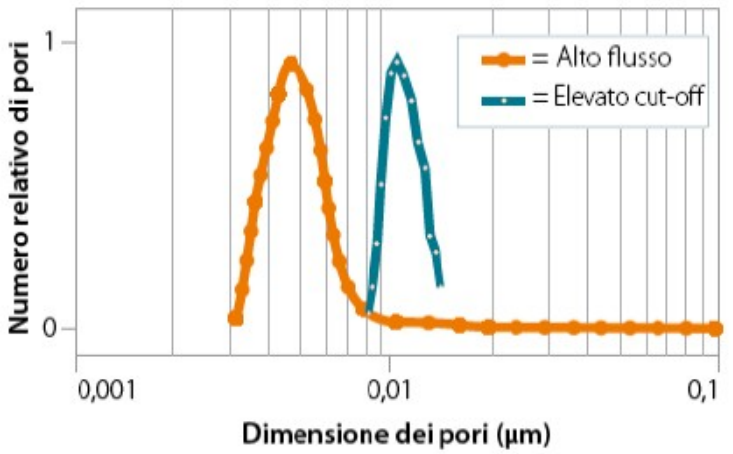
Promoting the removal of protein-bound uremic toxins, and middle to large molecular-weight solutes, including β2-microglobulin (β2-M).

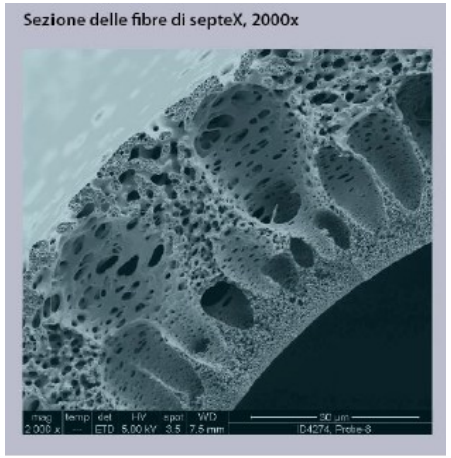
BIOCOMPATIBILITA'
La risposta del sangue
Attivazione della risposta immunitaria

The New England Journal of Medicine
Volume 338 Number 20









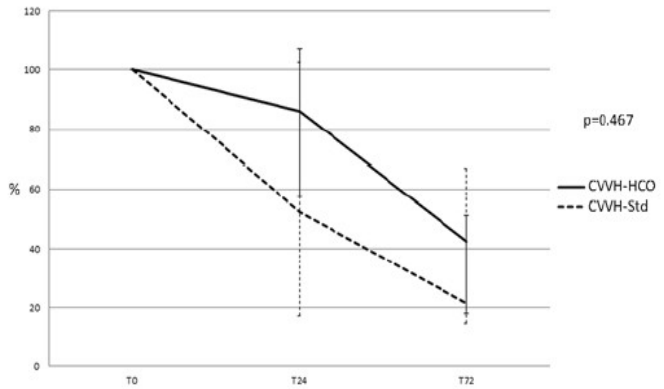
Porous enough to remove large molecules (15-60 kDa)

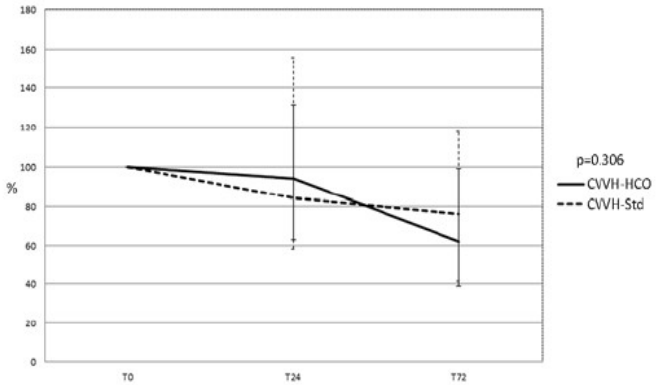
HCO

IJAO
ISSN 0391-3988
Int J Artif Organs 2016; 39(9): 479-486
DOI: 10.5301/ijao.5000527
ORIGINAL RESEARCH ARTICLE

High cut-off hemofiltration versus standard hemofiltration: effect on plasma cytokines

Rafidah Atan[1], Leah Peck[2], Kumar Visvanathan[3], Narelle Skinner[3], Glenn Eastwood[2], Rinaldo Bellomo[2,4], Markus Storr[5], Hermann Goehl[5]

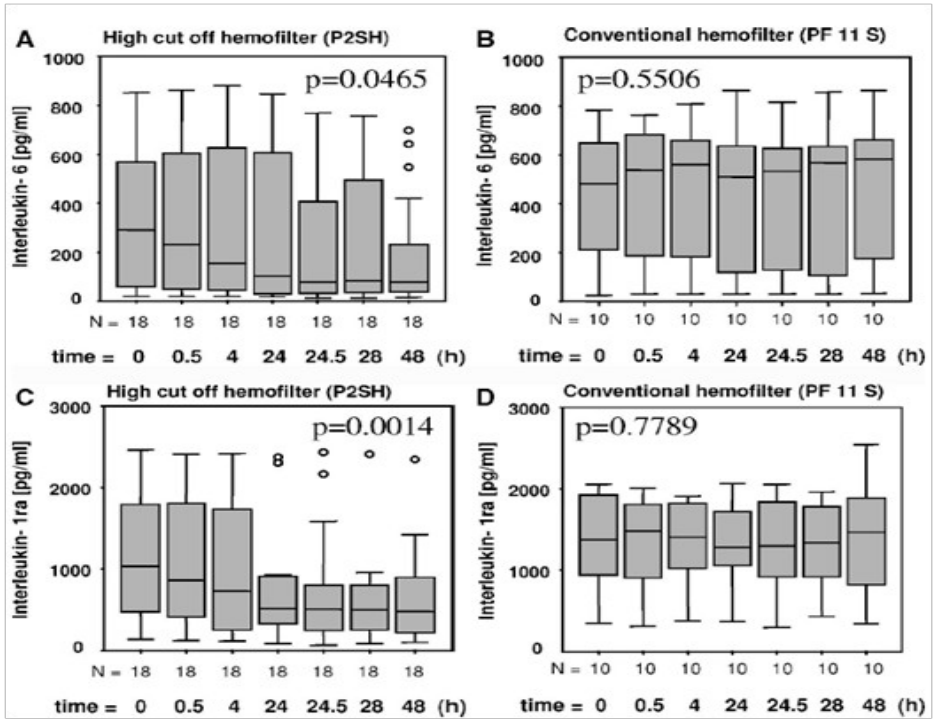


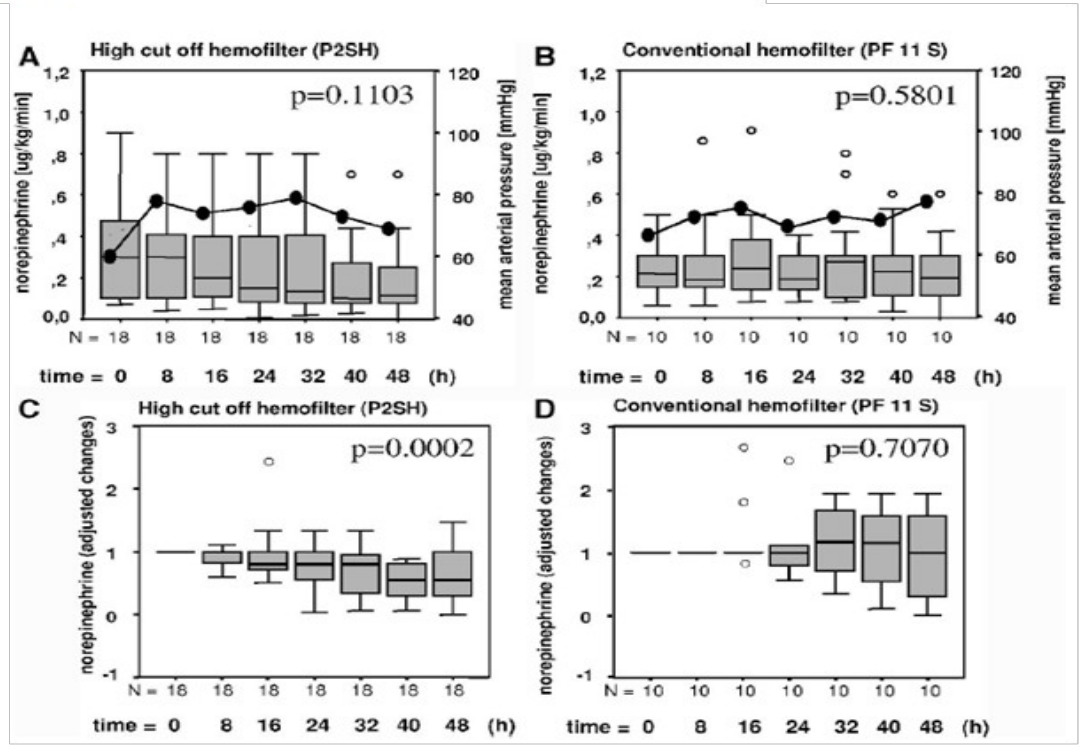


Conclusions: CVVH-HCO achieved greater combined sieving coefficient and mass removal rate by ultrafiltration for a group of key citokine than CVVH-Std. However, this effect did not differentially lower their plasma level over the first 72 hours.

Stanislao Morgera, MD; Michael Haase, MD; Thomas Kuss, MD; Ortrud Vargas-Hein, MD;
Heidrun Zuckermann-Becker, MD; Christoph Melzer, MD; Hanno Krieg, MD;
Brigitte Wegner, PhD; Rinaldo Bellomo, MD; Hans-H. Neumayer, MD

Crit Care Med 2006 Vol. 34, No. 8





High cut-off hemofiltration has been shown to exert a beneficial effect on the need for norepinephrine in septic patients with acute renal failure. In addition, we demonstrate that high cut-off hemofiltration is superior to conventional hemofiltration in the elimination of IL-6 and IL-1ra from the circulating blood of septic patients.

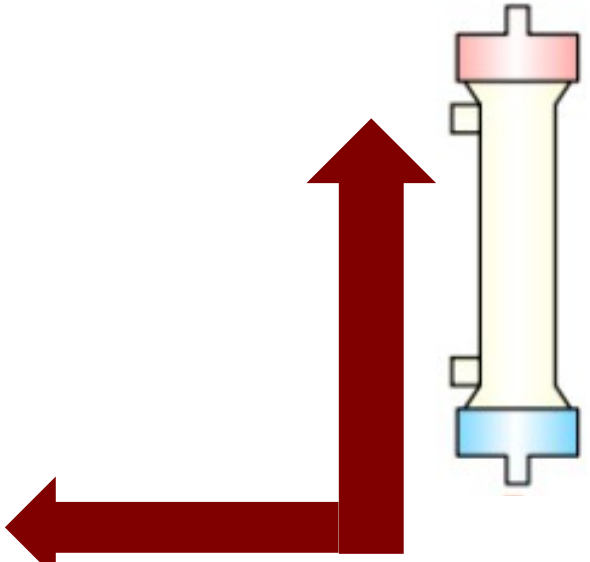
Caretteristiche Membrana Dialitica

Diffusione
Convezione

Diffusione
Convezione
Adsorbimento

DIFFUSIONE

Urea
Acido Urico
Creatinina



BIOCOMPATIBILITA'

CONVEZIONE

Beta2-Microglobulina
AGEs
Vit B12
Fosfati

Rimozione di tossine uremiche ad alto peso molecolare **> 50 kda**

ADSORBIMENTO

I DIALIZZATORI

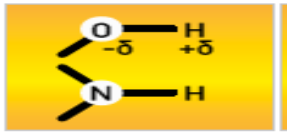
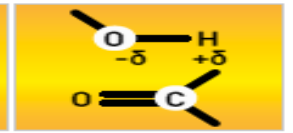
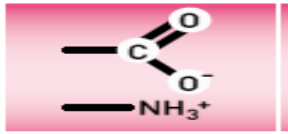
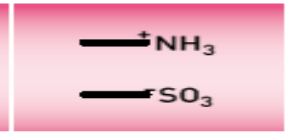
CRITERIO DI CLASSIFICAZIONE: CAPACITA' ADSORBENTI

Adsorbimento è un **meccanismo** attraverso cui un materiale lega a sé molecole mediante diversi processi fisico-chimici alquanto specifici. La specificità di tale adsorbimento è il risultato dei diversi gradi di affinità tra le molecole e i gruppi chimici del materiale (Cuq JL, Biochimie des protéines, 2006).

Un'interazione specifica determina l'eliminazione mirata di un minor numero di tossine senza inficiare lo stato proteico del paziente o le prestazioni della membrana e del trattamento

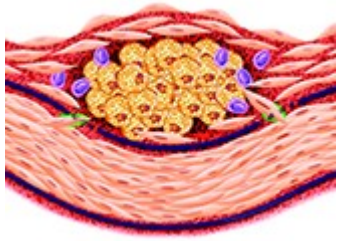
Le diverse membrane di dialisi hanno specificità e capacità di adsorbimento molto varie, a seconda della loro **composizione chimica** e della loro **microstruttura**.

Interazioni potenziali tra proteina e polimeri sintetici:

Tipi di interazioni	Breve definizione	Energia di legame (KJ/mol)	Esempi di interazioni tra gruppi chimici supportati: dalla proteina	dalla membrana
Bipolare o polare	Interazioni elettrostatiche tra gruppi con carica parziale (dipoli permanenti o indotti)	da 1 a 10 (da 8 a 40 nei legami idrogeno)		
Idrofobico	Interazioni tra gruppi non polari considerato il loro grado di repulsione verso le molecole d'acqua	da 4 a 12		
Ionico	Interazioni elettrostatiche tra gruppi con cariche opposte	da 35 a 90		

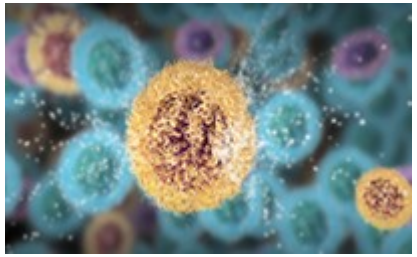
Perché l'adsorbimento è importante?

- Idealmente, cosa dovrebbe essere adsorbito da una membrana?



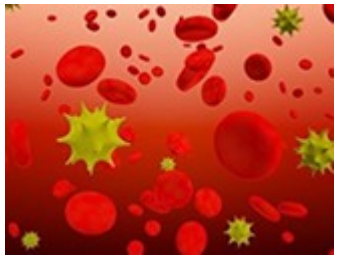
Mediatori dell'infiammazione

Fattori del complemento

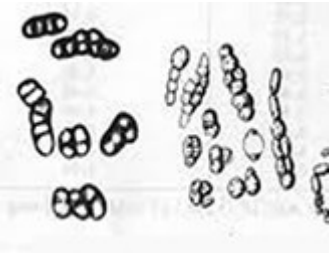


Citochine

Chemochine



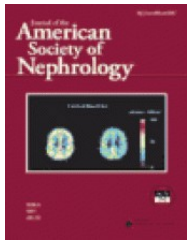
Tossine uremiche ($ß_2M$)

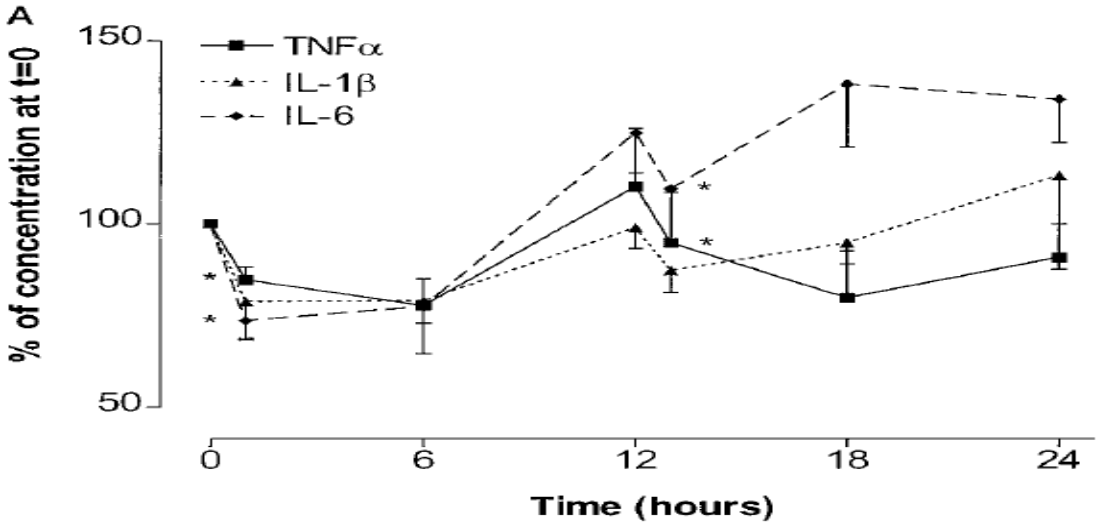


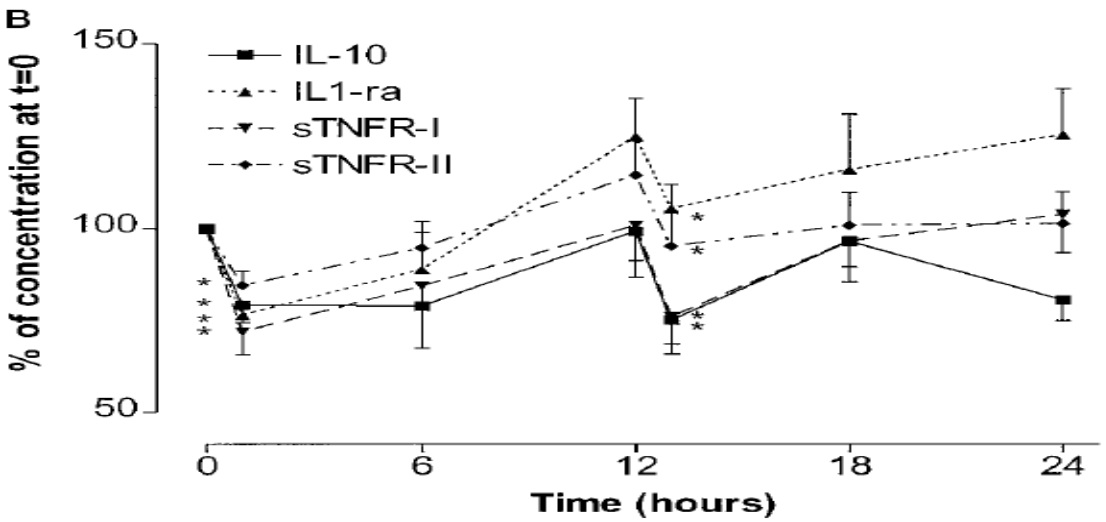
Frammenti batterici e sostanze che producono citochine

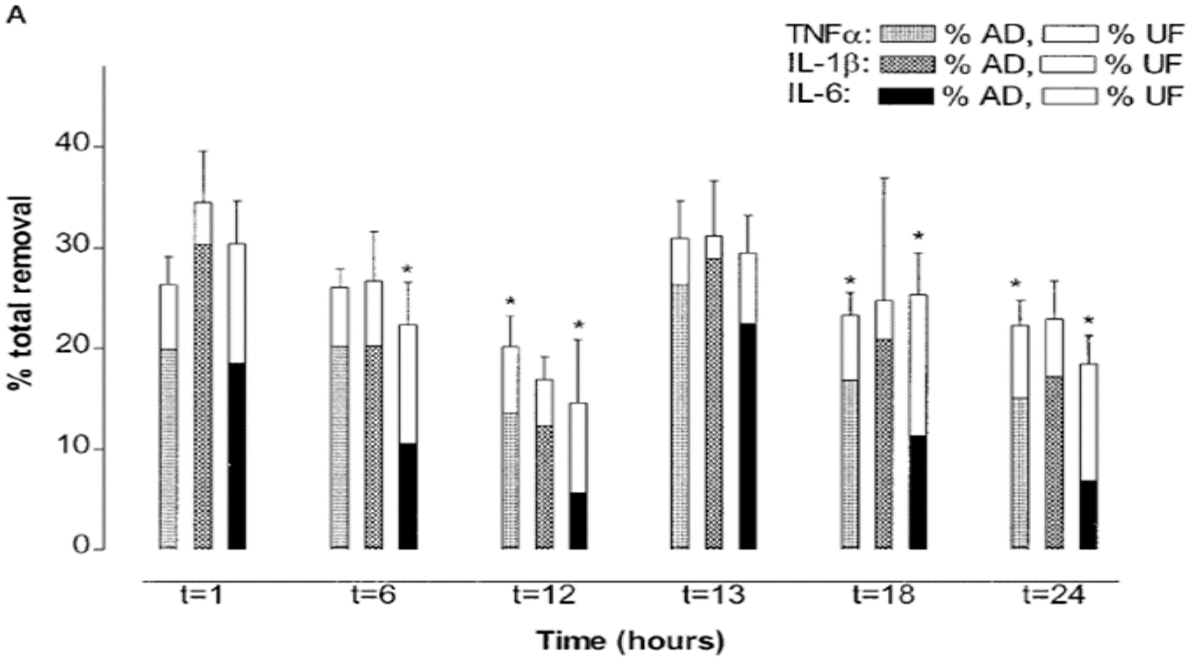
Cytokine Removal during Continuous Hemofiltration in Septic Patients

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







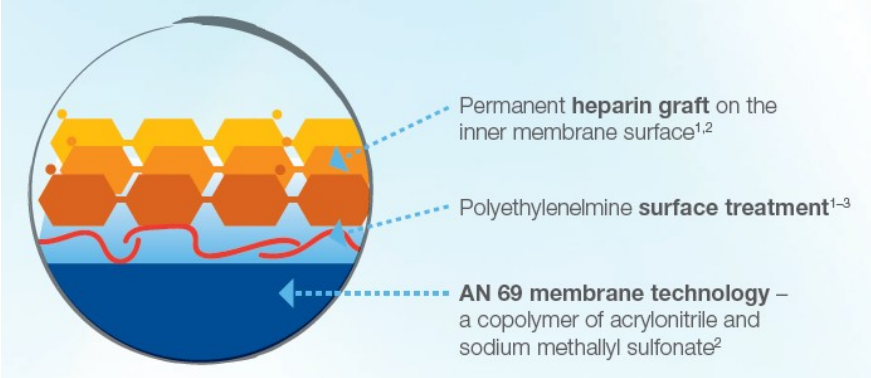


$$Q_I = Q_B(1 - \text{hematocrit}),\ Q_O = Q_I - Q_{UF},$$

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

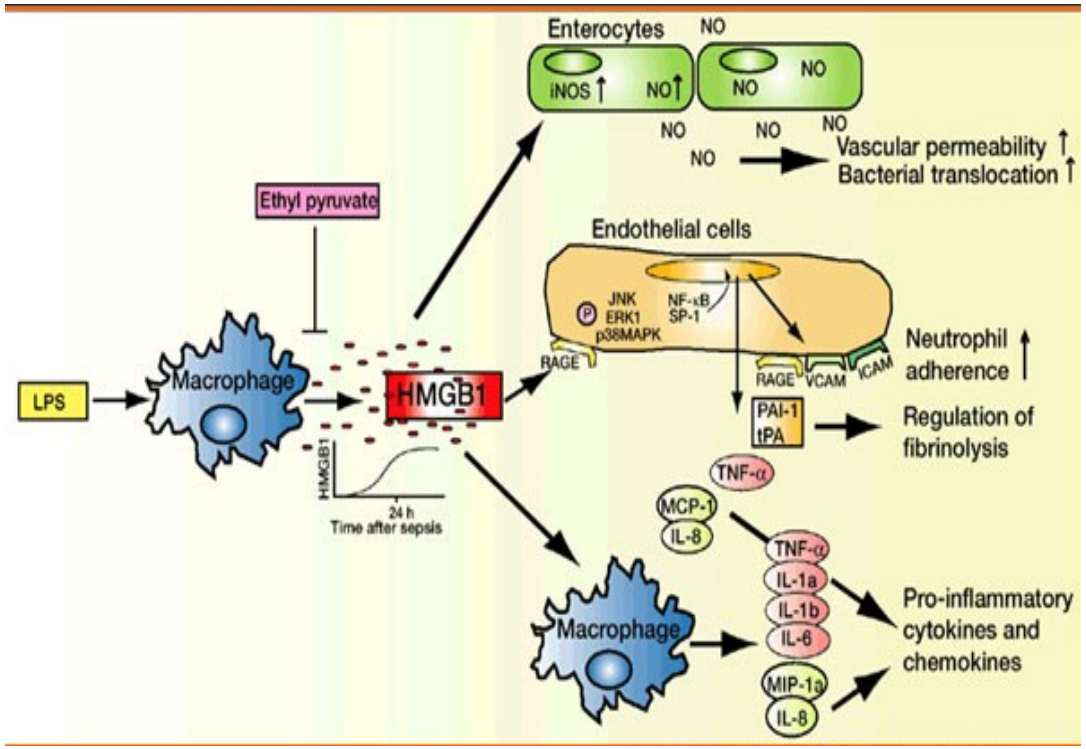
$$M_{TR} = M_I - M_O,\ M_{UF} = Q_{UF} \times C_{UF},\ M_{AD} = M_{TR} - M_{UF}$$

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



AN69ST is capable of adsorbing inflammatory mediators that are known to play a key role in the pathogenic mechanisms of S-AKI.

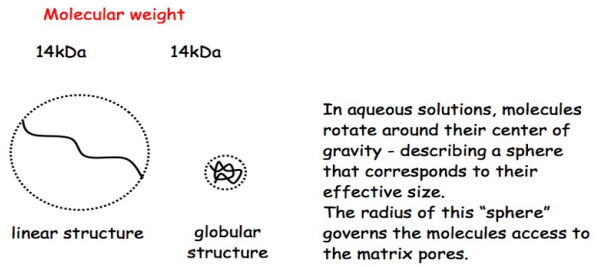
Rationale for AN-69 Membrane: HMGB-1



HMGB-1, despite small size (26 kDa), is not removed by convection but exclusively by

AN-69

Molecular Size - Stokes' radius



....moleculair weight is NOT the only specification we need to know, to determinate the accessibility for a molecule through a membrane....

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)

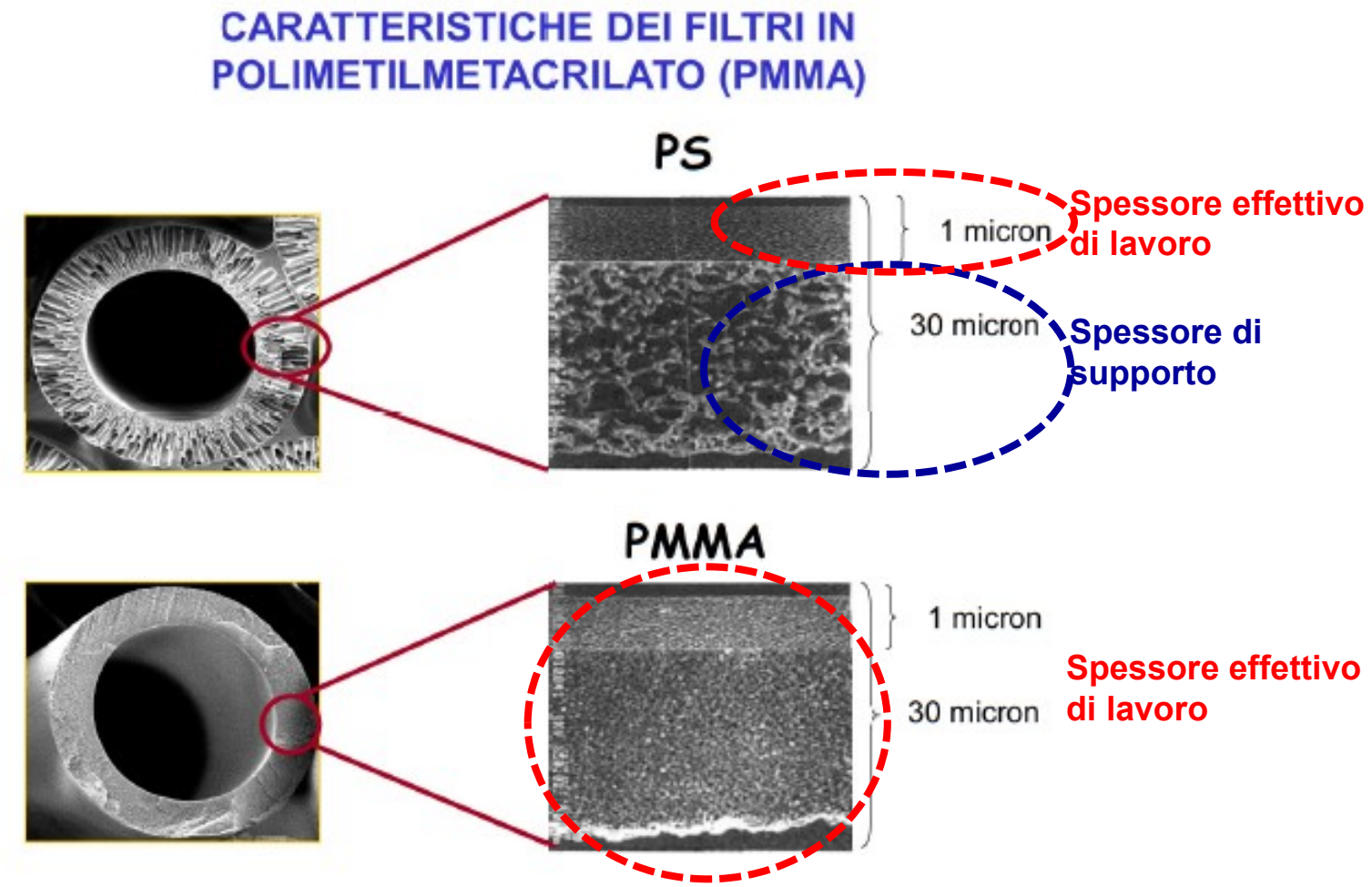
Group	Time-point	IL-6 (pg/ml)	IL-10 (pg/ml)	Endotoxin (EU/ml)
Observation group (n=23)	Before treatment	2187.47±528.37	674.82±125.46	64.72±12.10
	After treatment	128.30±40.22*	50.37±21.23*	16.47±3.26*
	t	18.637	23.536	18.465
	P	0.000	0.000	0.000
Control group (n=30)	Before treatment	2006±476.27	693.27±131.65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

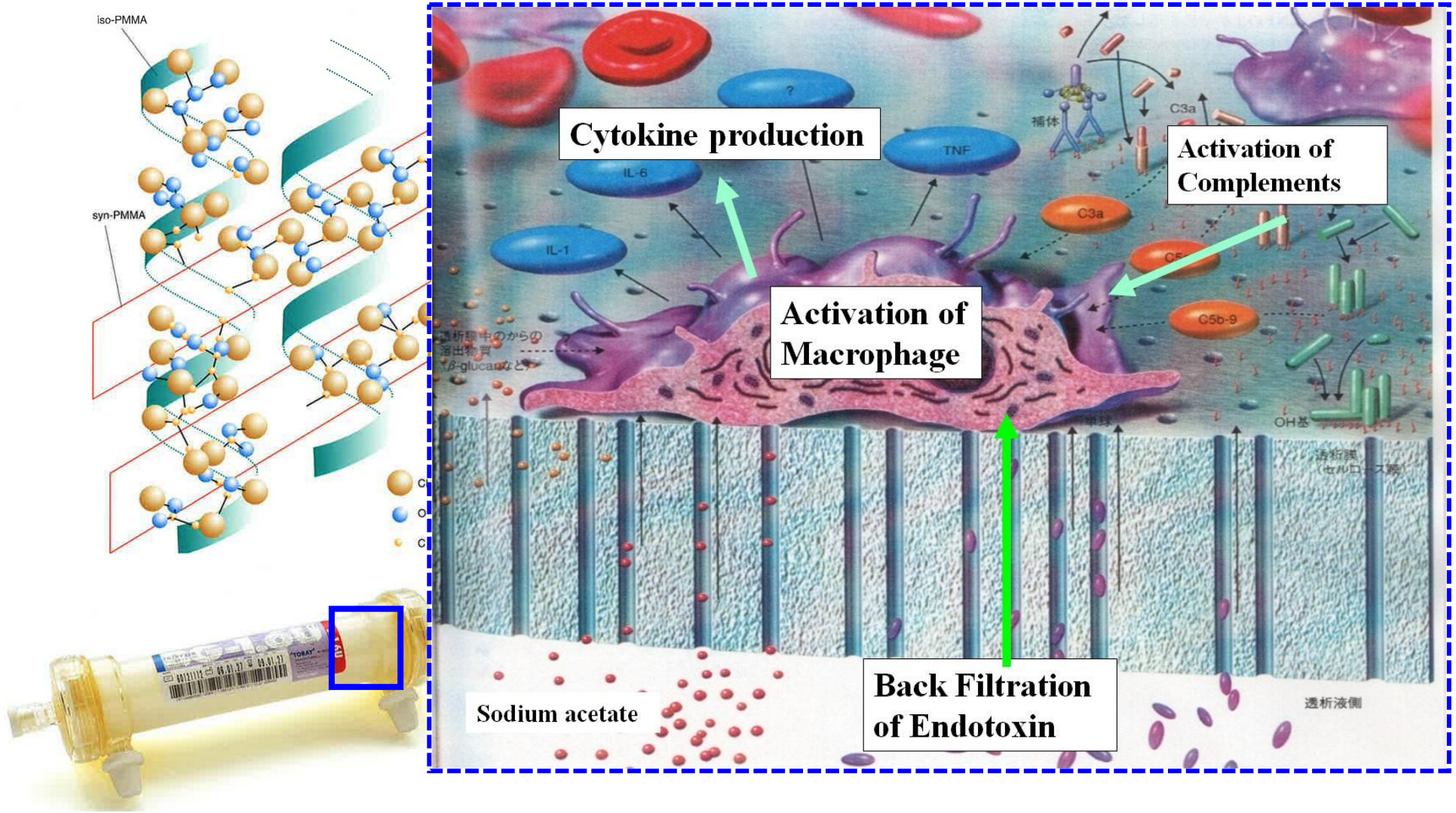
Group	Number of Cases	ICU stay (d, $\bar{x}$±sd)	Organ support duration (d, $\bar{x}$±sd)	Incidence of cardiovascular events [n (%)]
Observation Group	23	8.17±1.75	3.16±1.20	1 (4.35)
Control Group	30	10.21±2.18	4.85±1.39	9 (30.00)
t/X^2	-	3.667	4.650	4.046
P	-	0.001	0.000	0.044

Polimetilmetacrilato (PMMA) - Dal polimero al dializzatore



Polimetilmetacrilato (PMMA)

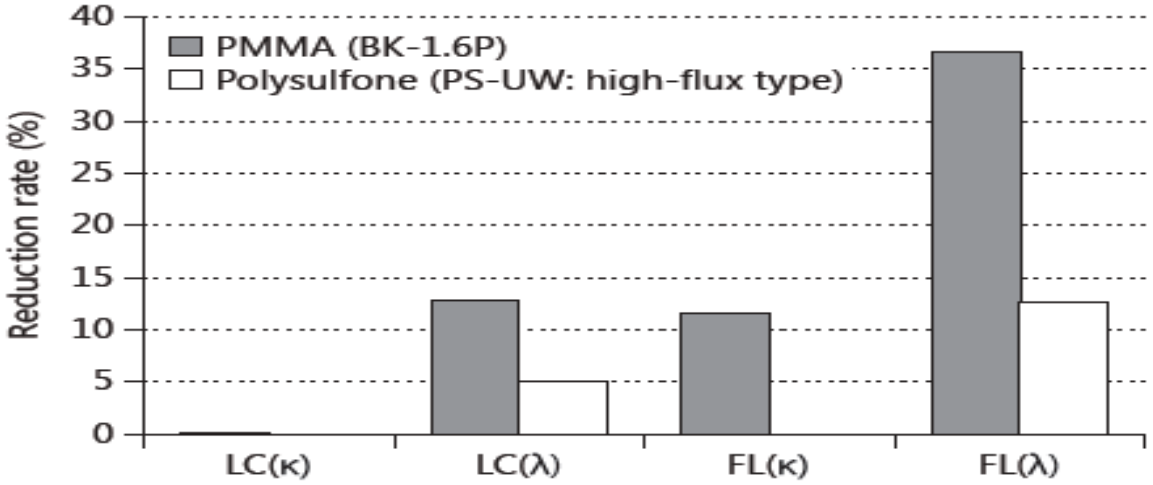
Emocompatibilità / Biocompatibilità

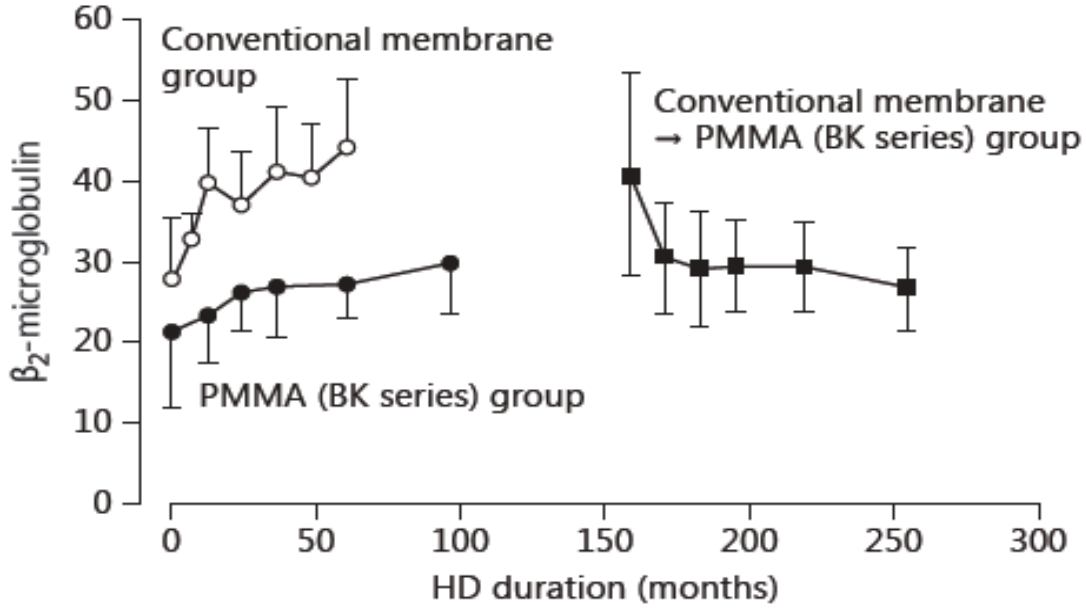


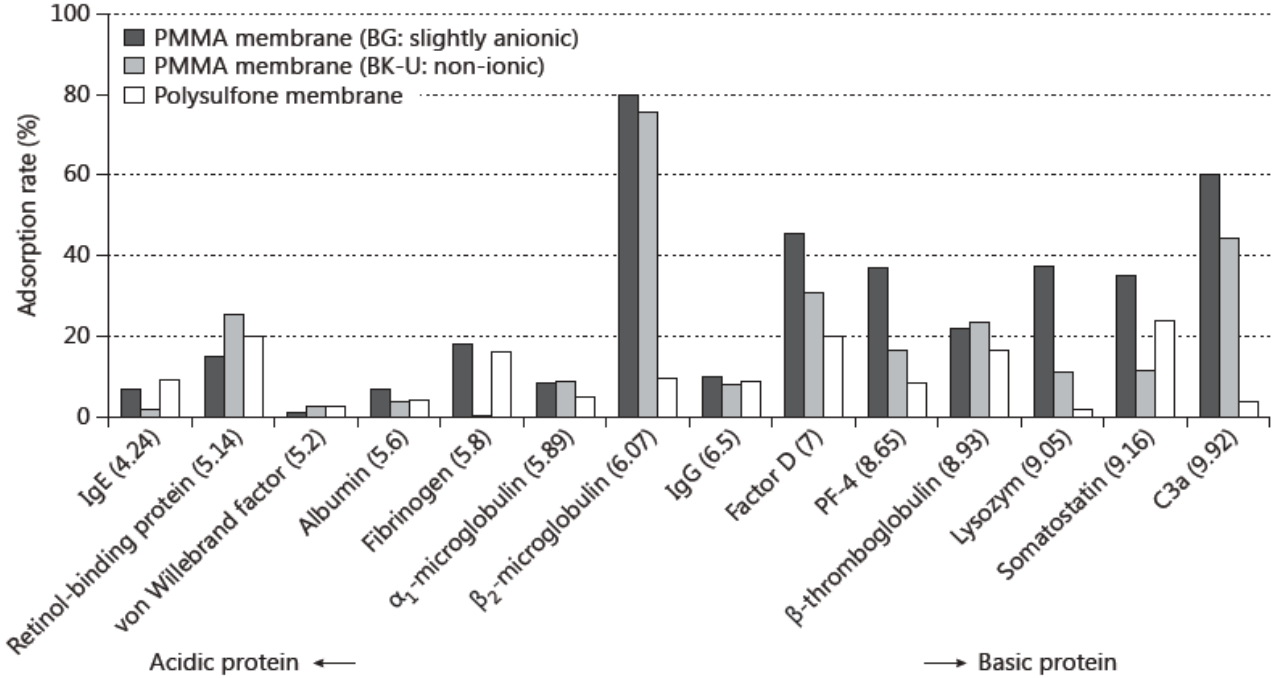
Adsorption Techniques: Dialysis Sorbents and Membranes

Angelo F. Perego

Blood Purification





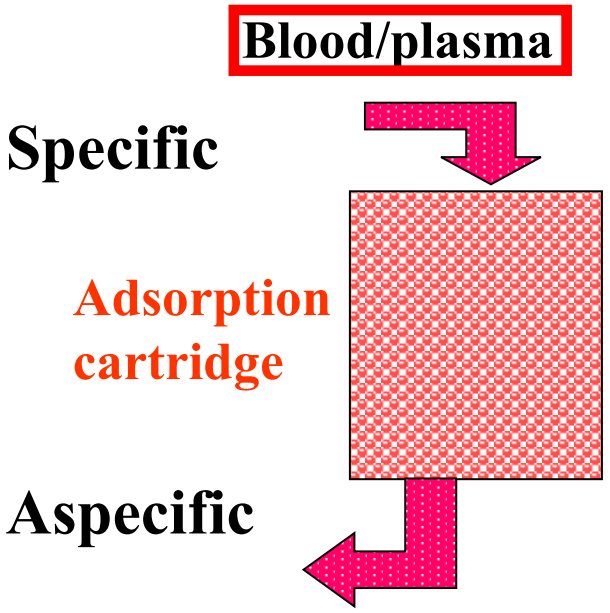


Adsorption is based on the attraction between the sorbent and the solute through hydrophobic interactions, ionic or electrostatic forces, hydrogen bonding or van der Waals forces. Adsorption is the adherence of molecules by the above-mentioned forces not only to the surface of the membrane but also to its interior.

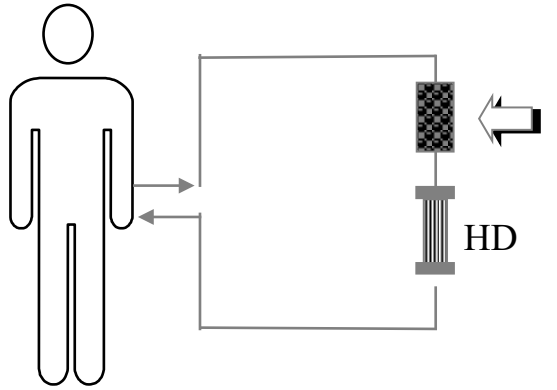
Since polymethylmethacrylate membranes have a much higher inside effective exchange surface than polysulfone membranes, these membranes are able to ensure a high level of adsorption, and therefore reduce the concentration of high-molecular-weight molecules and protein-bound uremic toxins.

Adsorption

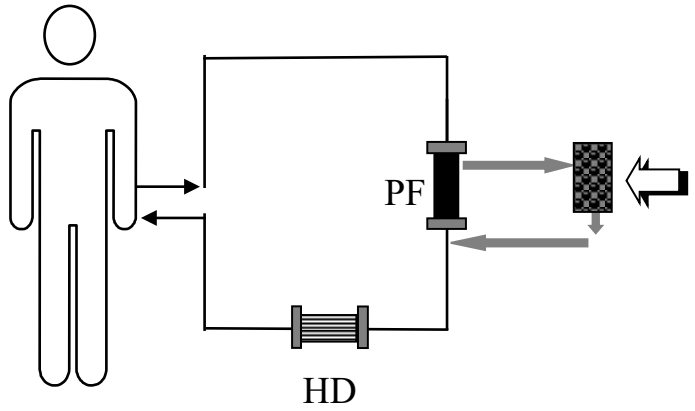
Adsorption = Chemical attachment of a specific element at the surface of another element with a molecular structure prepared to be complementary



Hemoperfusion



Plasma Filtration Adsorption



Blood/Plasma Adsorption

DEVICES DESIGNED TO REMOVE ENDOTOXIN AND CYTOKINES

Device	Company	Composition	Mechanism	Substance eliminated
Toraymyxin	Toray Industries, Japan	Polymyxin B covalently bound to polypropylene-polystirene fibers fabric	Adsorption	Endotoxin
LPS adsorber	Alteco Medical, Sweden	Synthetic polypeptide bound to porus polyethylene discs	Adsorption	Endotoxin
oXiris	Gambro-Hospal, France	AN69-based membrane, surgace treated with a polyethyleneimine (PEI) grafted with eparine	Adsorption Convection	Endotoxin Cytokines
MATISSE	Fresenius SE, Germany	Human serum albumin immobilised on polymethacrylate beads	Adsorption	Endotoxin
CPFA	Bellco, Italy	Polytersulfone plasma filter with adsorpion on sn unselective hydrophobicresin cartridge, and a synthetic high-permeability polyetersulfone hemofilter for continuos hemofiltration	Adsorption Plasma filtration	Cytokines
Cytosorb	Cytosorbents, USA	Polystyrenedivinylbenzene copolymer beads with a biocompatible polyvinilpirrolidone coating	Adsorption	Cytokines
HA330 HA380	Jafron, China	Polystyrenedivynlbenzene copolymer	Adsorption	Cytokines

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

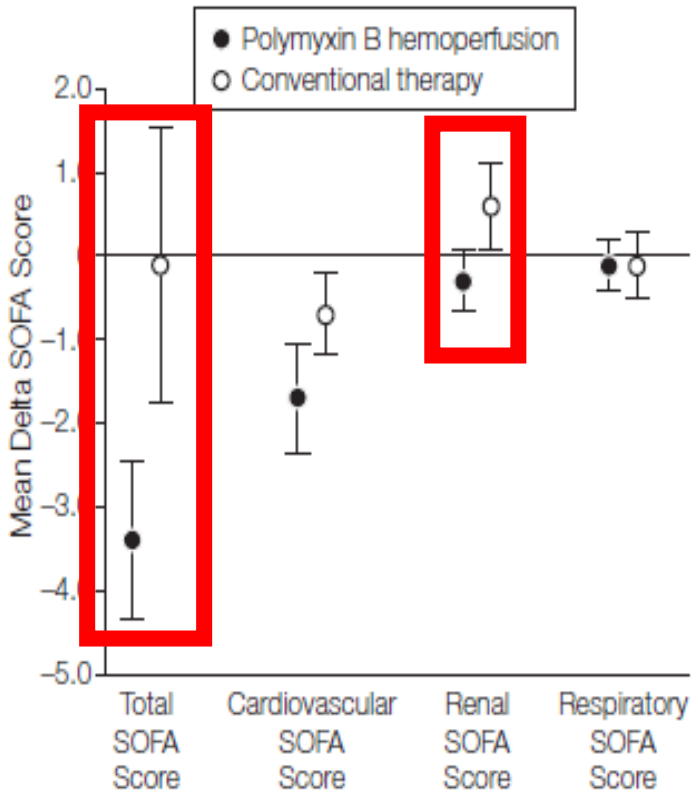
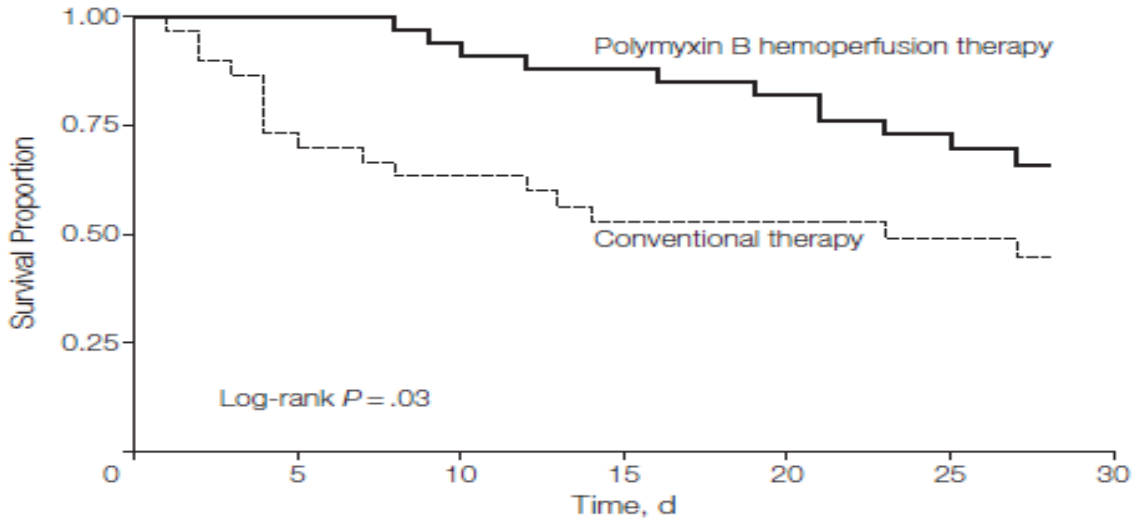


Figure 3. Estimation of Survival Rate According to Treatment Group



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.

Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level

The EUPHRATES Randomized Clinical Trial

R. Phillip Dellinger, MD, MSc; Sean M. Bagshaw, MD, MSc; Massimo Antonelli, MD; Debra M. Foster, BSc; David J. Klein, MD, MBA; John C. Marshall, MD; Paul M. Palevsky, MD; Lawrence S. Weisberg, MD; Christa A. Schorr, DNP, MSN, RN; Stephen Trzeciak, MD, MPH; Paul M. Walker, MD, PhD; for the EUPHRATES Trial Investigators

of 0.60 or higher enrolled between September 2010 and June 2016 at 55 tertiary hospitals in North America. Last follow-up was June 2017.

INTERVENTIONS Two polymyxin B hemoperfusion treatments (90-120 minutes) plus standard therapy completed within 24 hours of enrollment (n = 224 patients) or sham hemoperfusion plus standard therapy (n = 226 patients).

MAIN OUTCOMES AND MEASURES The primary outcome was mortality at 28 days among all patients randomized (all participants) and among patients randomized with a multiple organ dysfunction score (MODS) of more than 9.

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

[a] *P* values were calculated by χ^2 and were unadjusted.

[b] Multiple Organ Dysfunction Score (MODS)–measure of altered organ function in acutely ill patients using 6 organ systems with weighted scores (0, normal; 4, severe) of each organ system (MODS range, 0-24). A higher score is associated greater burden of organ dysfunction. A MODS of 9 to 12 points has a hospital mortality of approximately 50%. Prior to the protocol amendment, the MODS score was calculated at baseline (time of randomization to the initiation of the study treatment). After the amendment, MODS of more than 9 was included at the time of screening, prior to randomization.

ORIGINAL

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

Intensive Care Med (2018) 44:2205–2212

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

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.

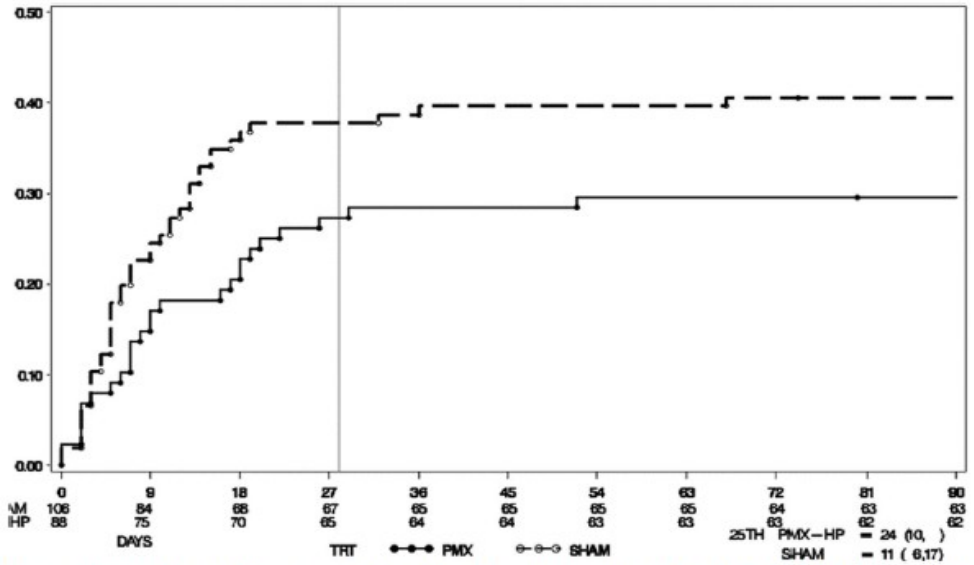


Fig. 2 Time to death within 90 days for PMX versus sham. Kaplan-Meier estimates of the probability of survival to day 90 among 194 per-protocol patients with MODS > 9 and EAA between 0.6 and 0.89, by treatment groups. The 90-day results of Cox proportional hazards adjusted for baseline MAP and APACHE 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

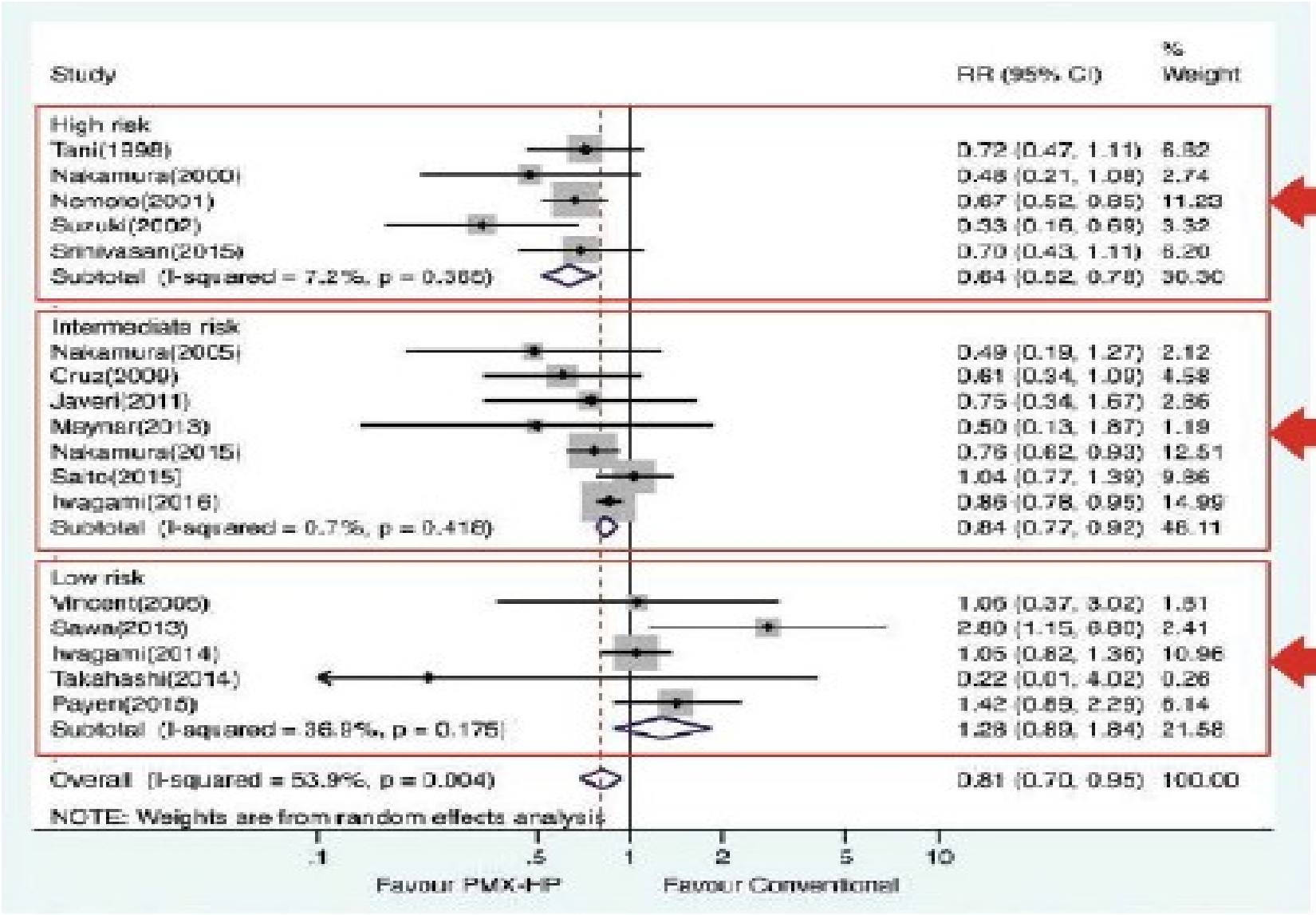
Treatment with PMX was associated with a significant change in median MAP (8 vs 4, p<0.05) and median (IQR) ventilator-free days to 28 days (20 vs 6, p=0.004).

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

Risk ratio of mortality by disease severity



High risk

High PMX benefit

Intermediate risk

PMX benefit

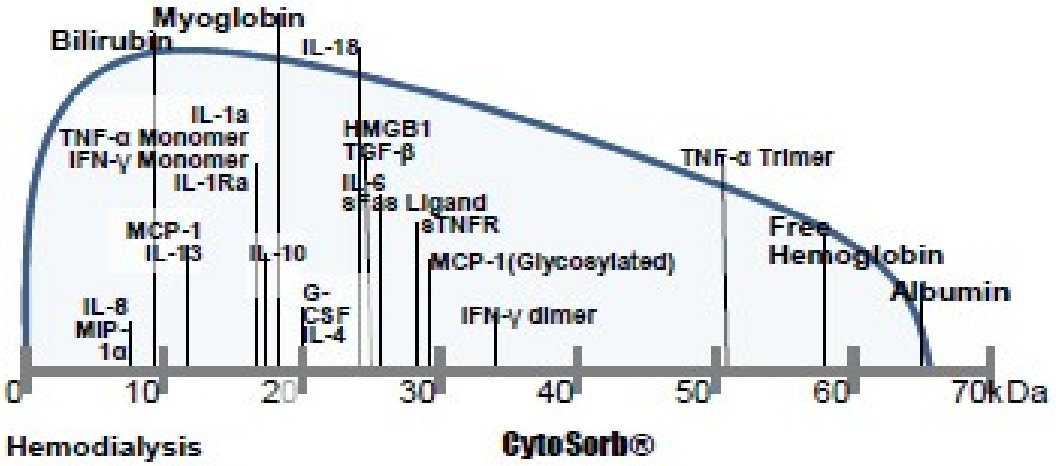
Low risk

Low PMX benefit

Chang et al, CCM 2017

- Rimozione delle **citochine**
- Riduzione della **produzione di citochine**
- Rimozione di altre medie molecole: **mioglobina, bilirubina, emoglobina libera**
- Perfusione di **Sangue intero**
- Adsorbimento continuo per **24 H**
- **Compatibilità** con tutte le macchine CRRT, Dialisi, Cuore- Polmone e ECMO
- Scoagulazione **Eparina o Citrato**
- Installazione ed utilizzo semplici e veloci

OVERALL SURFACE ≅ 40.000 - 45.000 m²

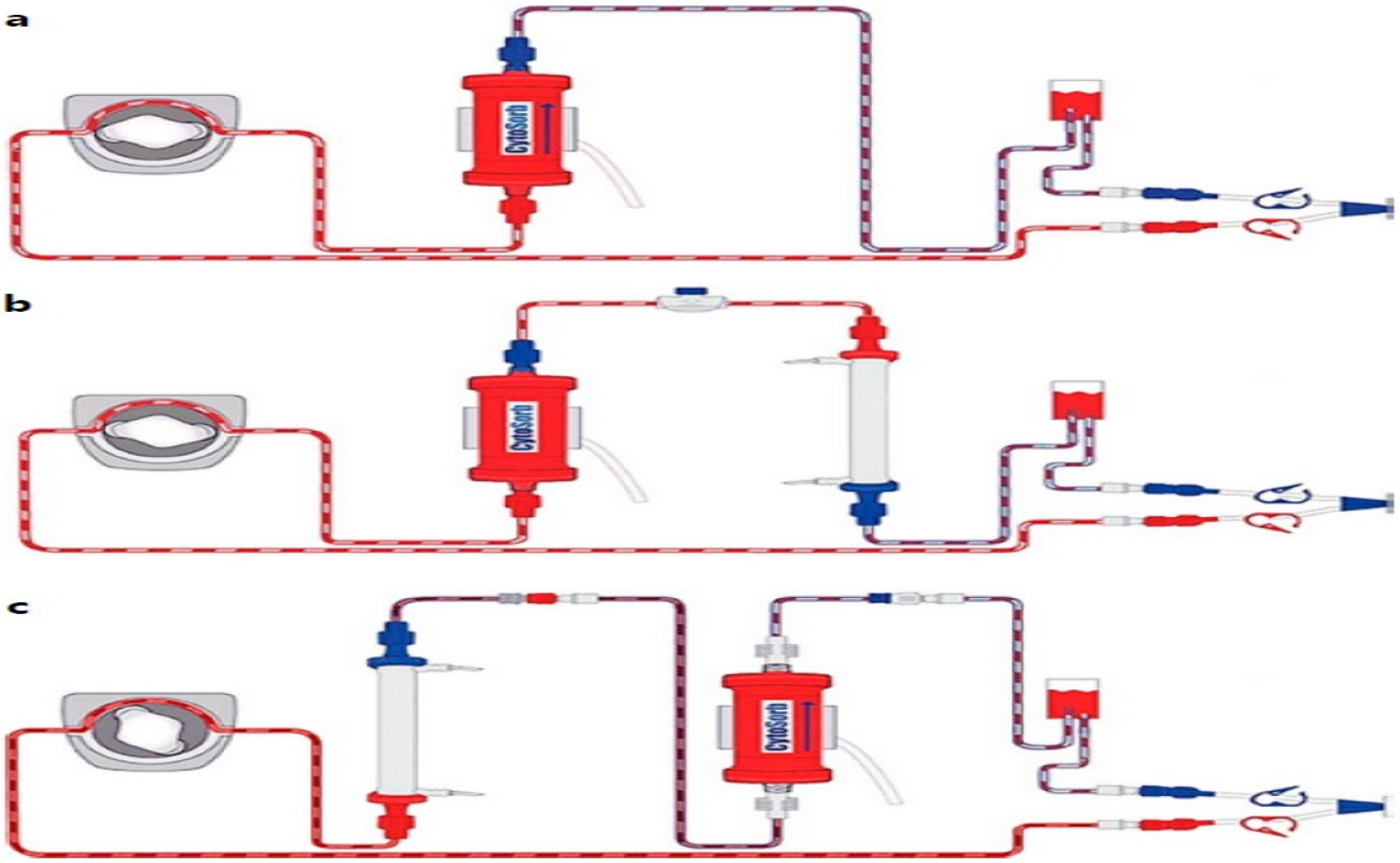


What Have We Learned about the Use of Cytosorb Adsorption Columns?

Ghada Ankawi[a, b] Yun Xie[a, c] Bo Yang[a, d] Yuanyuan Xie[a, e] Pan Xie[a, f]
Claudio Ronco[a, g]

Blood Purification

CytoSorb circuit: (a) as a stand-alone therapy, (b) in the pre-dialyzer mode, (c) in the post-dialyzer mode



Sorbents offer clear advantages compared to other extracorporeal techniques – first, the capacity for removal of a wide range of molecular weights and second, enhanced clearance due to large surface area of sorbents material. Sorbents do not rely on the removal of fluid for the clearance of toxins, potentially avoiding the time limitations of dialysis and the replacement fluid requirements of hemodiafiltration

Adsorption therapy may be of utmost benefit when, applied early in the course, for an adequate duration, and frequently repeated until hemodynamic stability is achieved

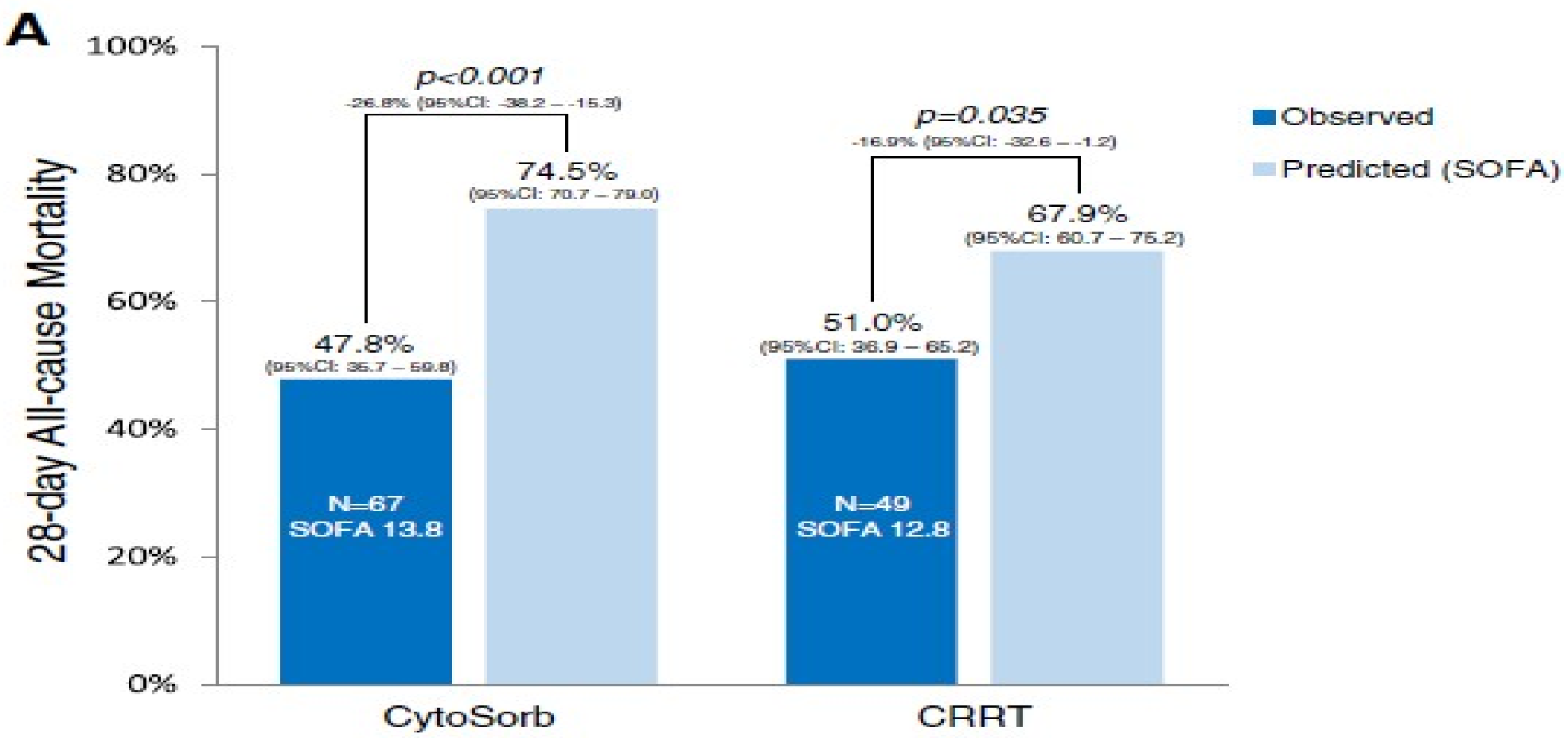
Adsorption therapy using CS columns seems to be safe and effective

Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study

Willem Pieter Brouwer[1,2*], Servet Duran[3], Martijn Kuijper[4] and Can Ince[5]

Critical Care

Observed versus predicted mortality rate according to the SOFA score for CytoSorb- and CRRT-treated patients

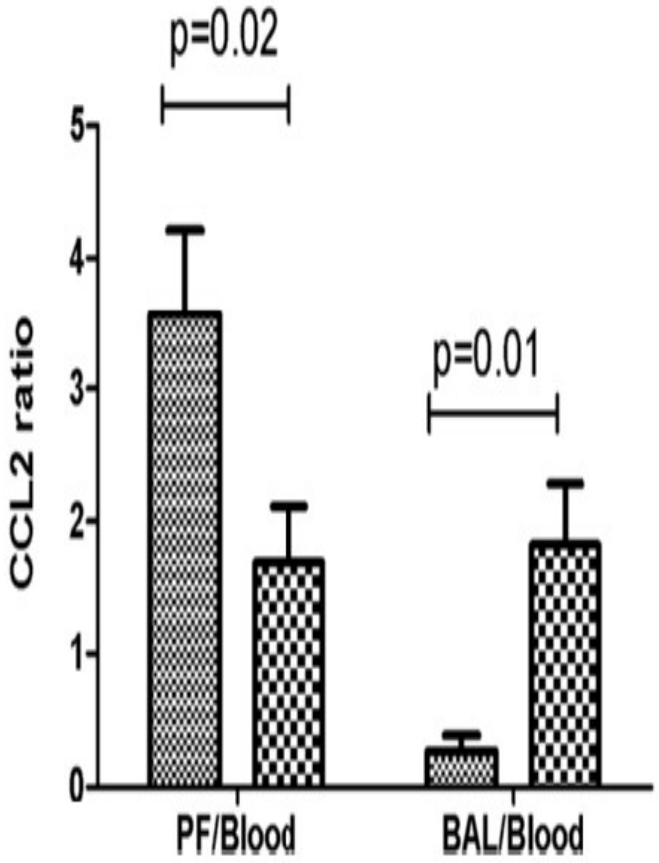


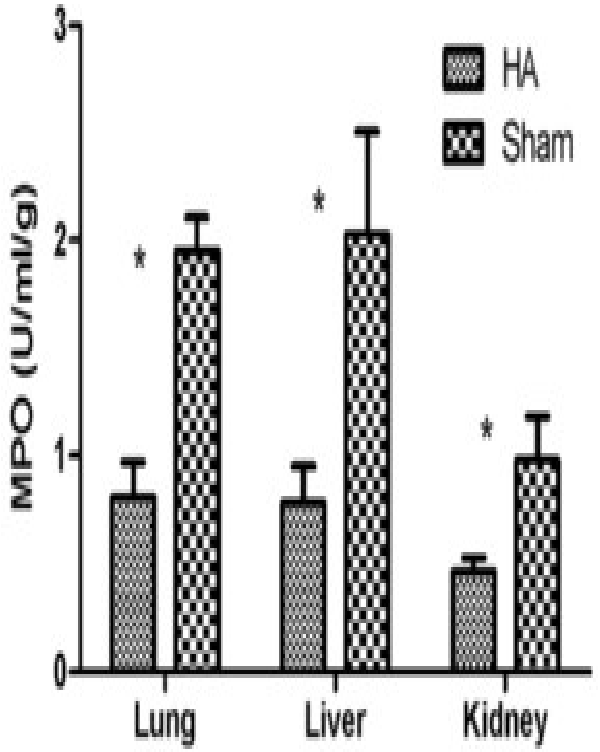
In the largest cohort of septic shock patients to date, that CytoSorb treatment may lead to an improved 28-day survival compared to CRRT alone

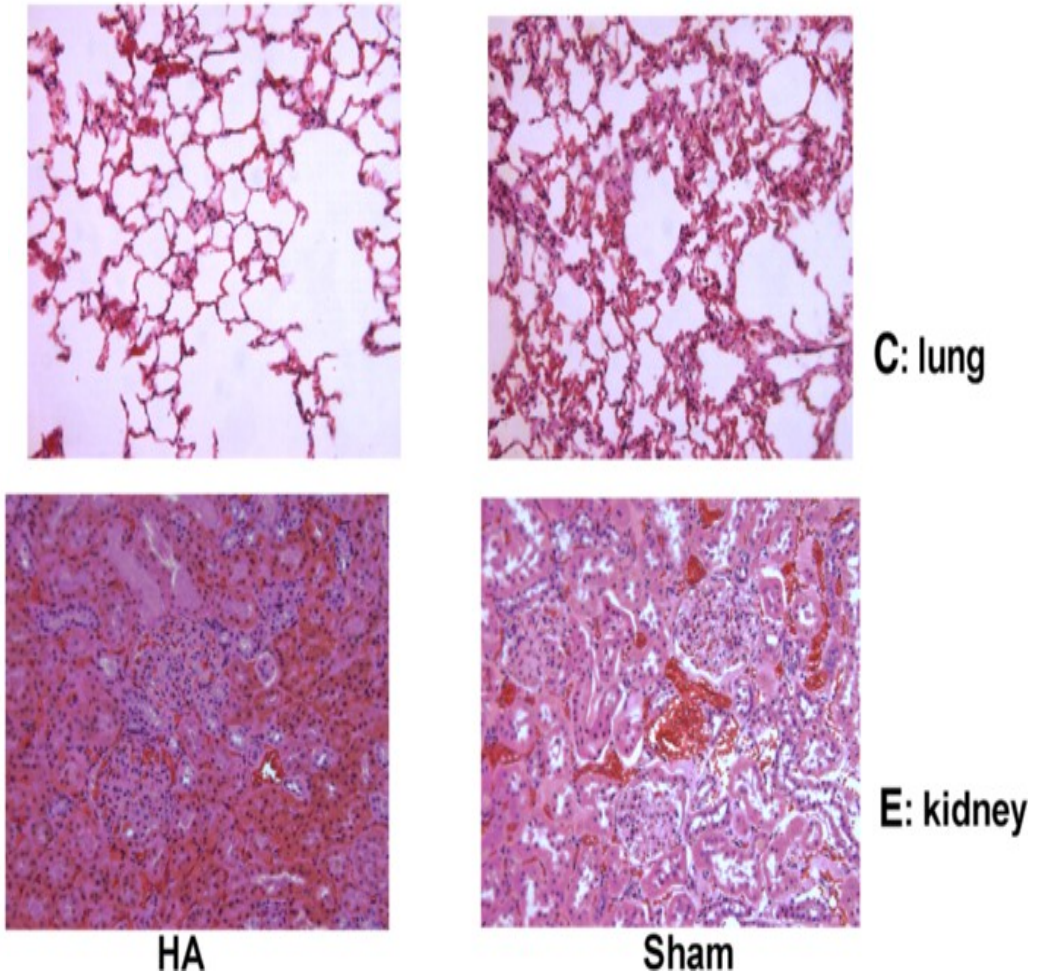
Modulation of chemokine gradients by apheresis redirects leukocyte trafficking to different compartments during sepsis, studies in a rat model

Zhi-Yong Peng[1,2], Jeffery V Bishop[2], Xiao-Yan Wen[1,2], Michele M Elder[1,2], Feihu Zhou[1,2], Anan Chuasuwan[1,2], Melinda J Carter[2], Jason E Devlin[3], A Murat Kaynar[1,2], Kai Singbartl[1,2], Francis Pike[1,2], Robert S Parker[1,2,5,6], Gilles Clermont[1,2,5,6], William J Federspiel[1,2,4,6] and John A Kellum[1,2,4,6,7*]

CRITICAL CARE







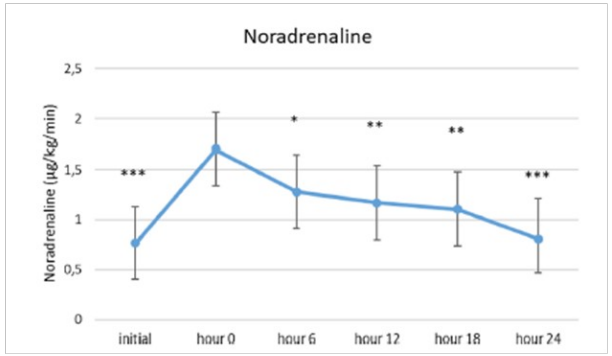
J Artif Organs (2017) 20:252–259
DOI 10.1007/s10047-017-0967-4

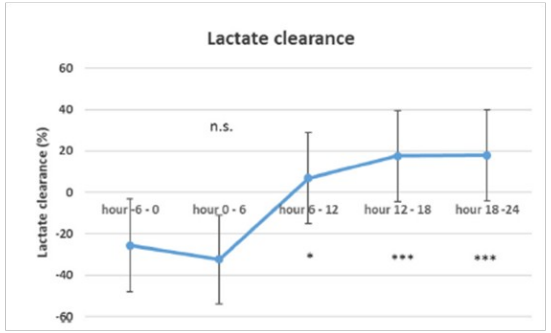
ORIGINAL ARTICLE

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]

20 consecutive patients with refractory septic shock were included: CytoSorb® treatment was started after 7.8 ± 3.7 h of shock therapy.





In severe septic shock unresponsive to standard treatment, haemodynamic stabilization was achieved using cytokine adsorption therapy, resulting in shock reversal in two-thirds of these patients.

Case Series: Efficacy and Safety of Hemoadsorption With HA-330 Adsorber in Septic Pediatric Patients With Cancer

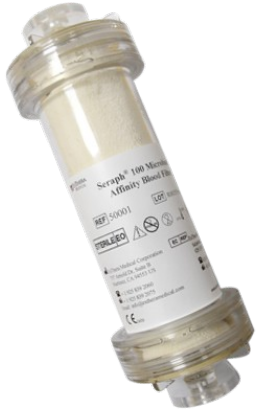
frontiers in Pediatrics

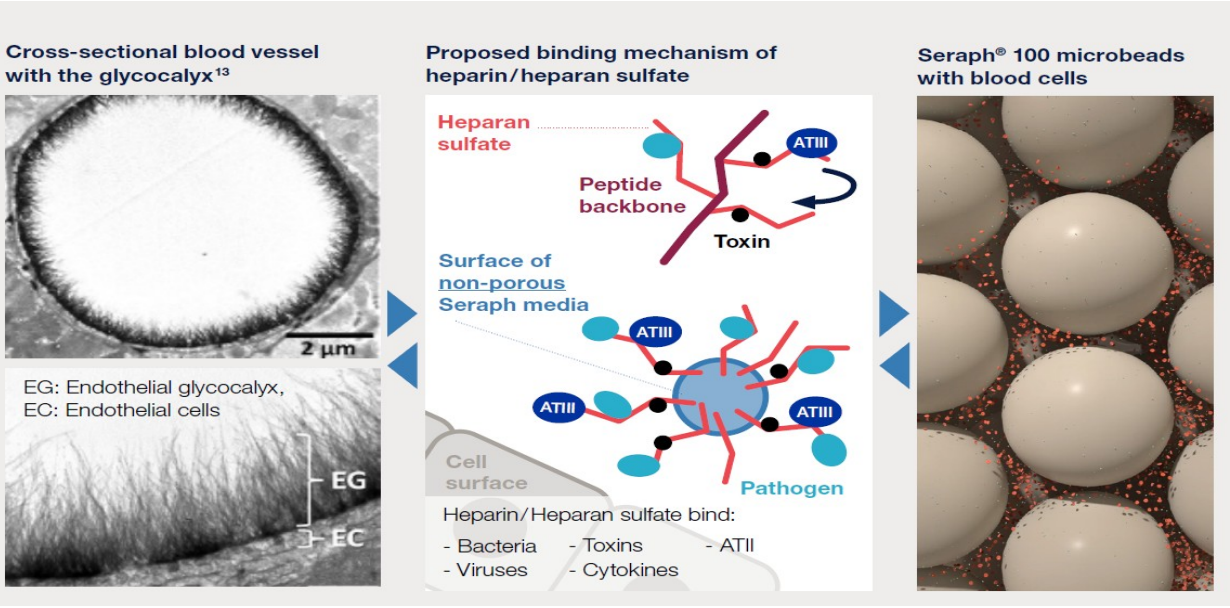
Vitaliy Sazonov[1,2], Ramazan Abylkassov[2,3], Zaure Tobylbayeva[2], Askhat Saparov[2], Olga Mironova[2] and Dimitri Poddighe[3,4]*

Case series: Here, we reported three septic children in whom we used extracorporeal blood purification therapy with hemoadsorption device HA330 (Jafron Biomedical Co., Ltd., China), aiming to scavenge and eliminate bacterial toxins and inflammatory mediators from the blood.

TABLE 4 | Plasma concentrations of CRP, procalcitonin, S100 protein, and IL-6 before and after blood purification procedure (mean ± SD, $n = 4$).

	Before	After	% of reduction
CRP, mg/L	376.32 ± 106.68	101.30 ± 64.13	−71.71 ± 20.32%
Procalcitonin, ng/L	260.65 ± 393.05	16.95 ± 21.78	−89.38 ± 7.07%
S100 protein, µg/L	7.54 ± 11.84	0.19 ± 0.08	−69.24 ± 44.77%
IL-6, pg/ml	806.88 ± 744.85	84.6 ± 69.99	−75.99 ± 23.74%





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.

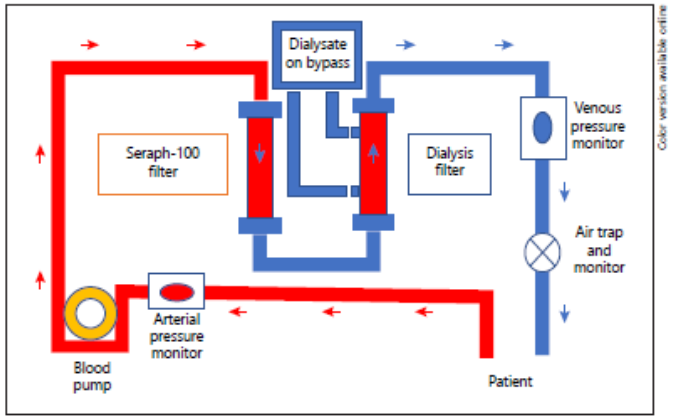
The surrogate glycocalyx can be expected to bind certain pathogens circulating in the bloodstream.[4]

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

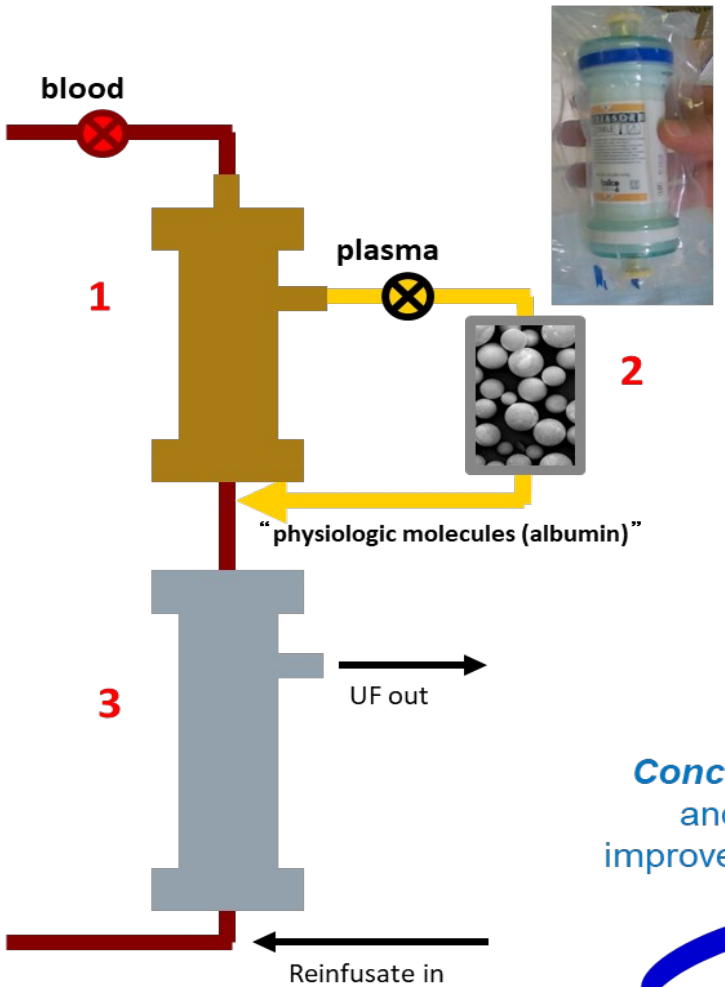
Reduction of Pathogen Load From the Blood in Septic Patients With Suspected, Life-threatening Bloodstream Infection

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.

Coupled Plasma Filtration Adsorption



1) PLASMAFILTER (POLYETHERSULPHONE 0.45 m^2 WITH A CUT-OFF OF 800 KDa)
2) SORBENT CARTRIDGE (HYDROPHOBIC STYRENIC RESIN)
3) HEMOFILTER/HEMODIAFILTER (POLYETHERSULPHONE 1.4 m^2)

BLOOD FLOW RATE 180-200 ml/min
PLASMA SEPARATION RATE 15-20%
ULTRAFILTRATION RATE 25-30 ml/Kg/hr

Hemodynamic response to CPFA in human septic shock — **Formica M et al.**

CRITICAL CARE

Conclusions: Coupled plasmafiltration-adsorption was a feasible and safe extracorporeal treatment and exerted a remarkable improvement in hemodynamics, organ function and outcome of septic shock patients with or without concomitant AKI.

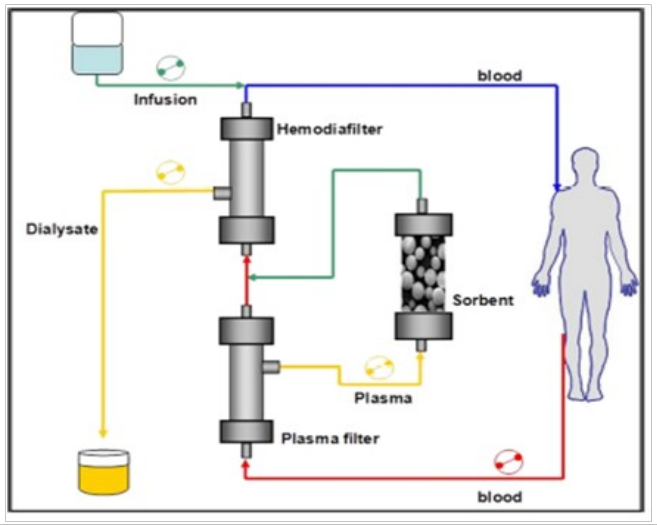
Simultaneous adsorption of several cytokines involved in systemic inflammation

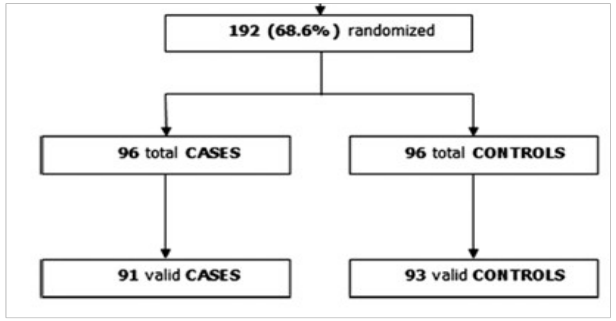
Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: A multicenter randomised controlled clinical trial

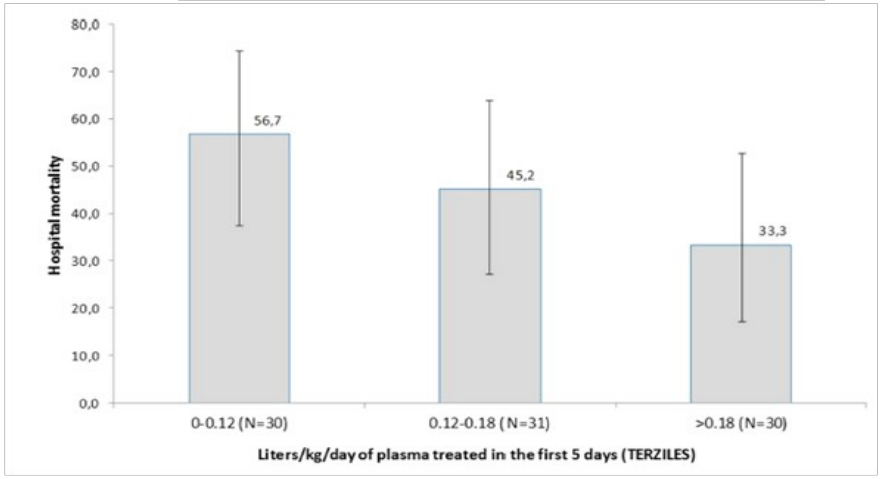
BMJ Open

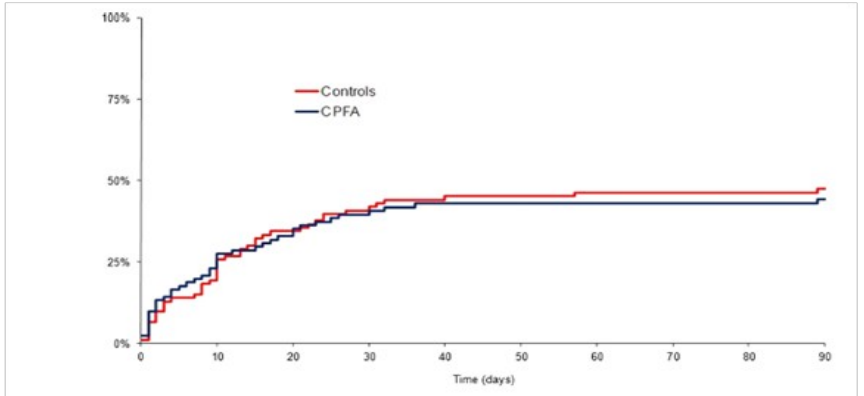
BMJ Open 2014;**4**:e003536.

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



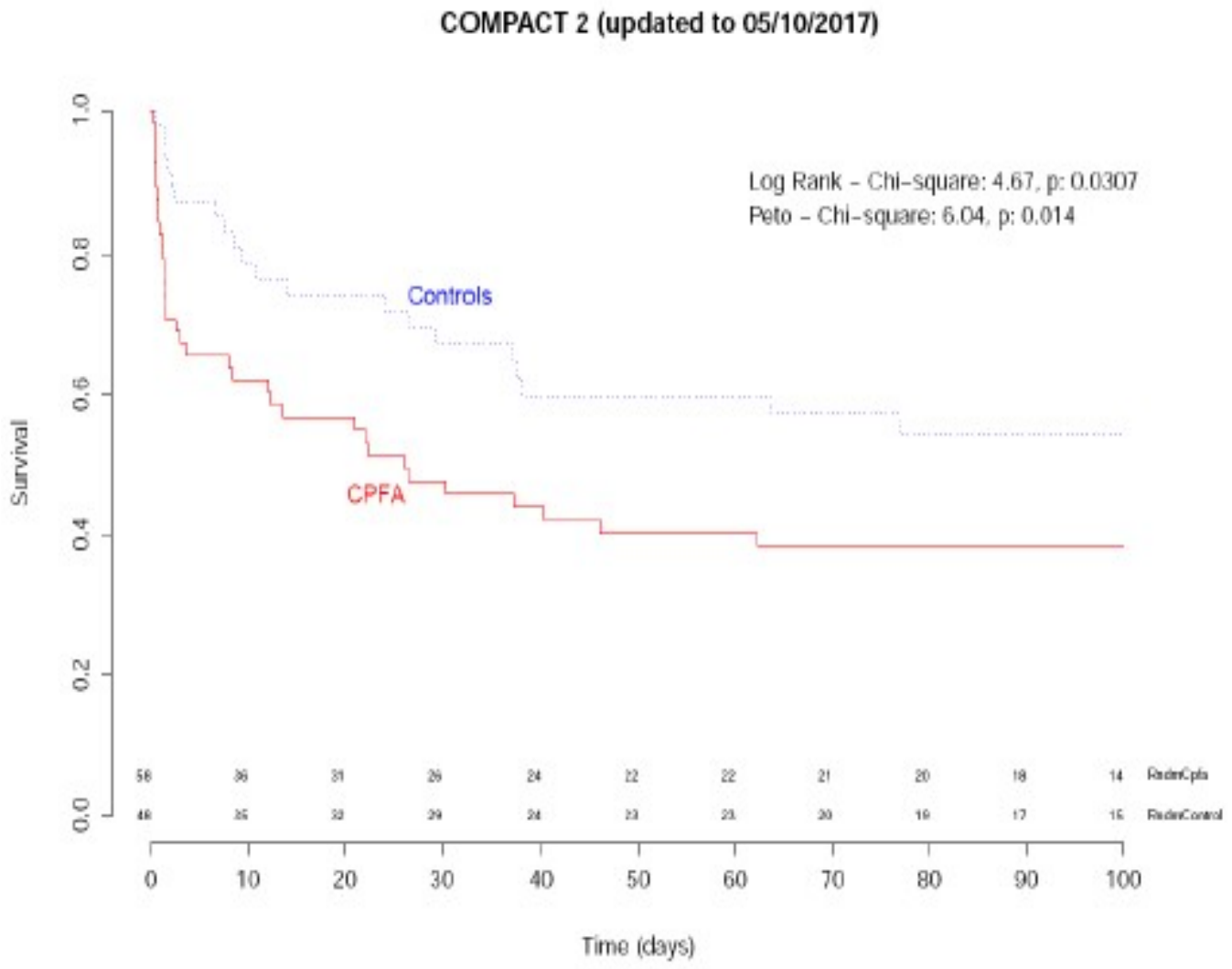






CPFA did not reduce mortality in patients with septic shock, nor did it positively affect other important clinical outcomes. A subgroup analysis suggested that CPFA could reduce mortality, when a high volume of plasma is treated.

EARLY STOP FOR COMPACT-2



Increased mortality in CPFA group vs control, expecially during the first days of treatment.

In septic shock patients enrolled in the study, a clinical poor outcome in the CPFA group was observed.

COMPACT-2 was prematurely interrupted and GiViTI did not reccomend the use of CPFA for septic shock patients.

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],

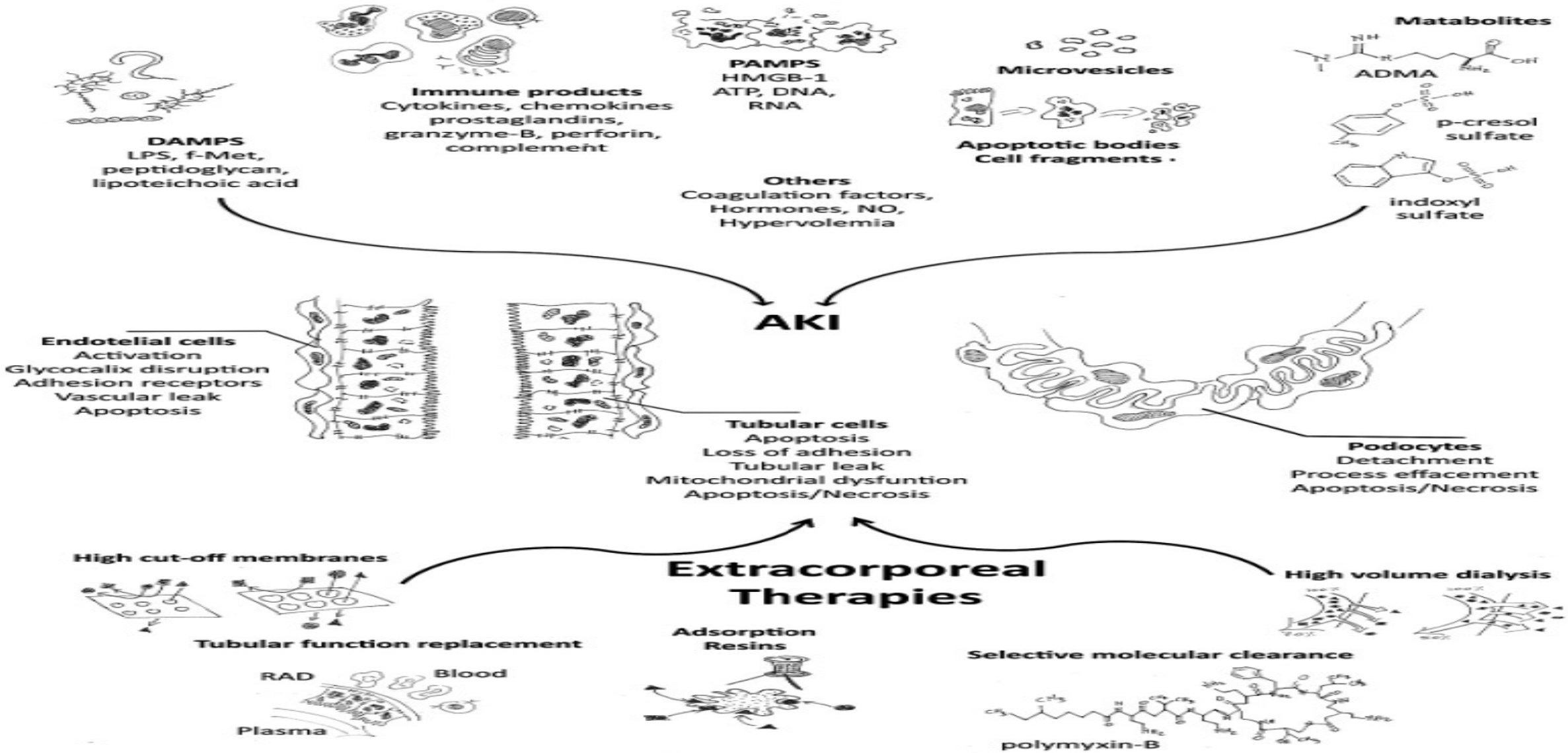
Characteristics of extracorporeal blood purification therapies available for sepsis and SA-AKI

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

Extracorporeal Treatments in Patients with Acute Kidney Injury and Sepsis

Marita Marengo[a] · Sergio Dellepiane[b] · Vincenzo Cantaluppi[c]

Blood Purification



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

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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).

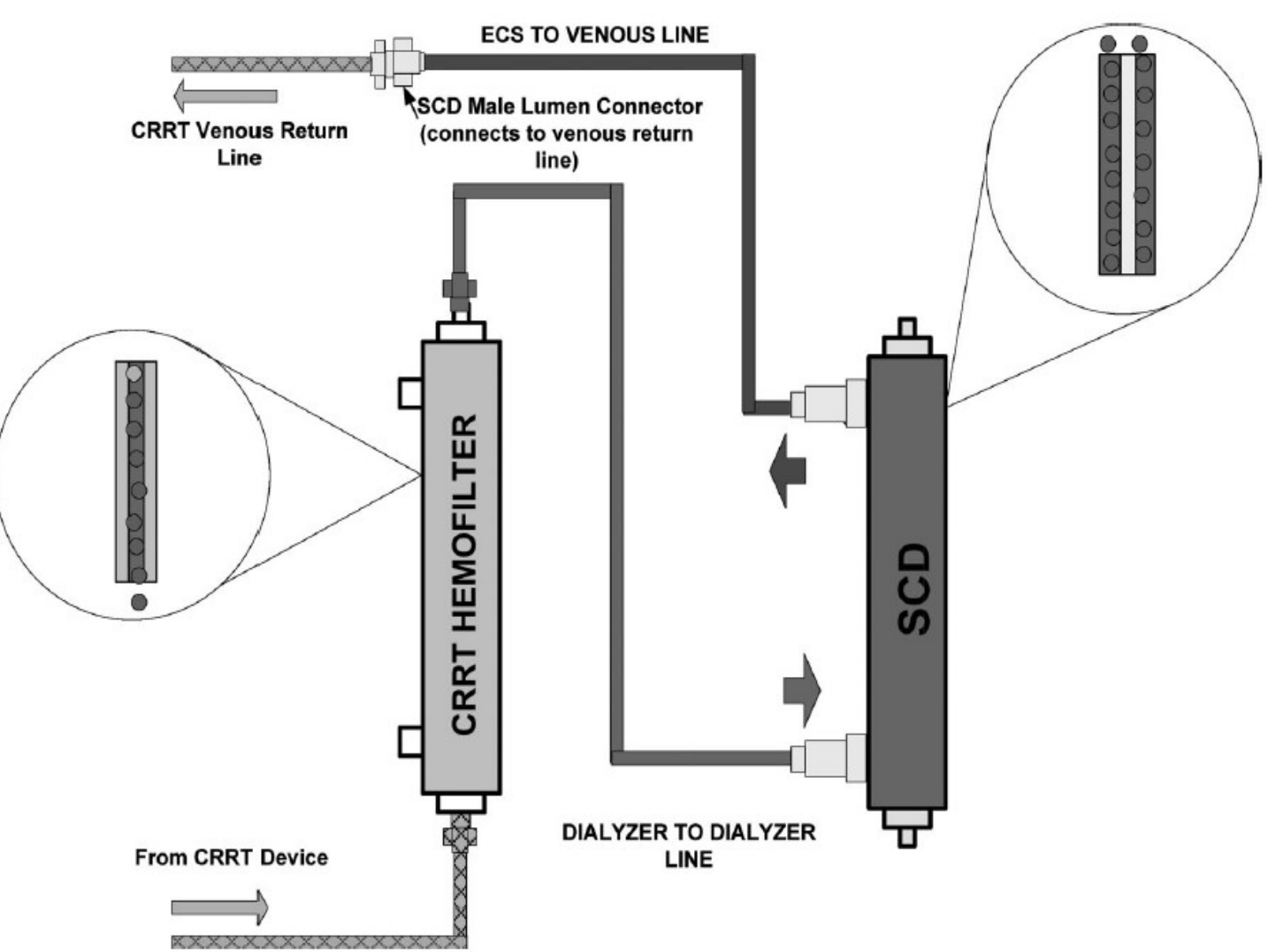
Consensus statement 5f

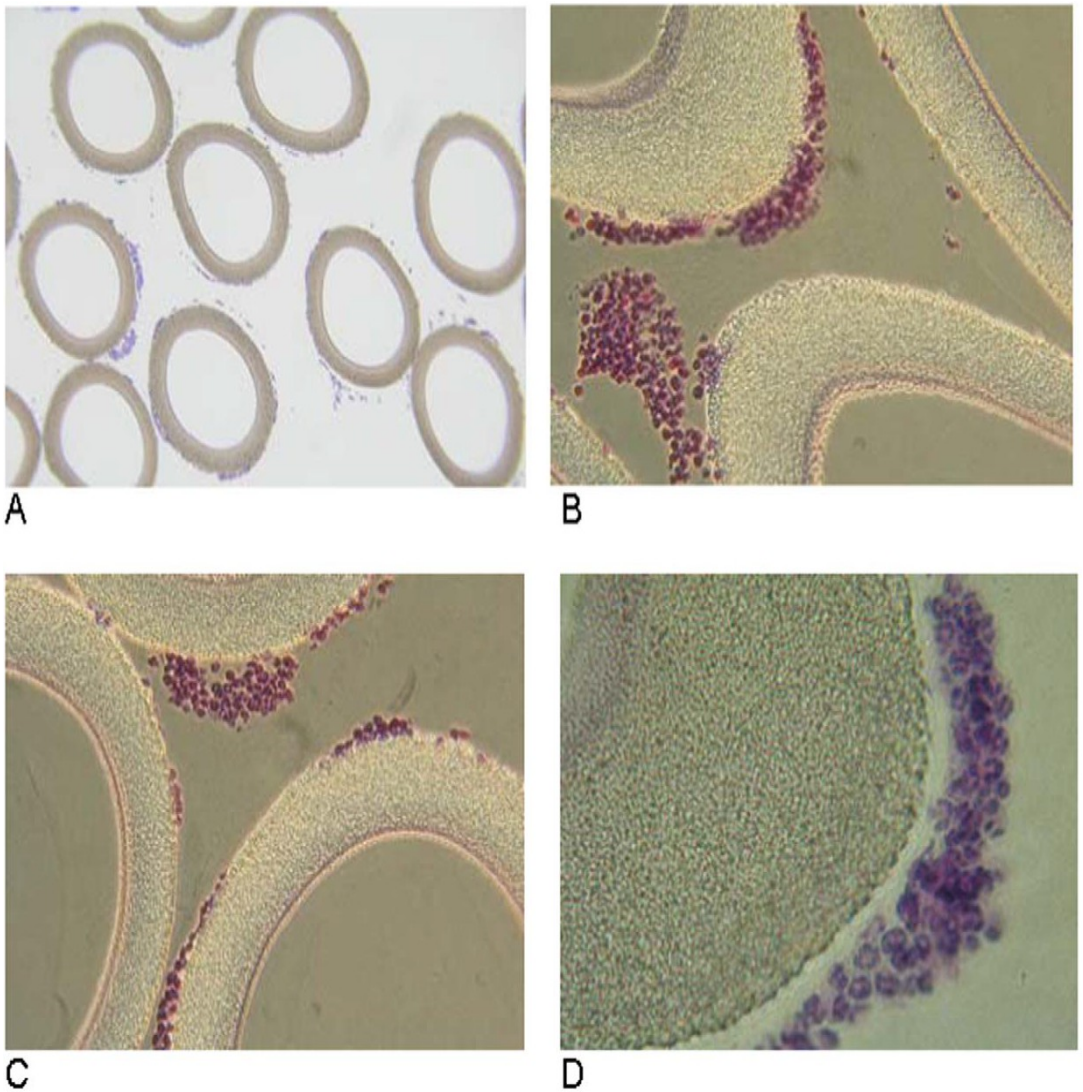
Safe and effective therapy requires objective indicators of treatment response, which must be evaluated throughout the therapy course with a focus on patient-centred care goals (grade 1B).

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





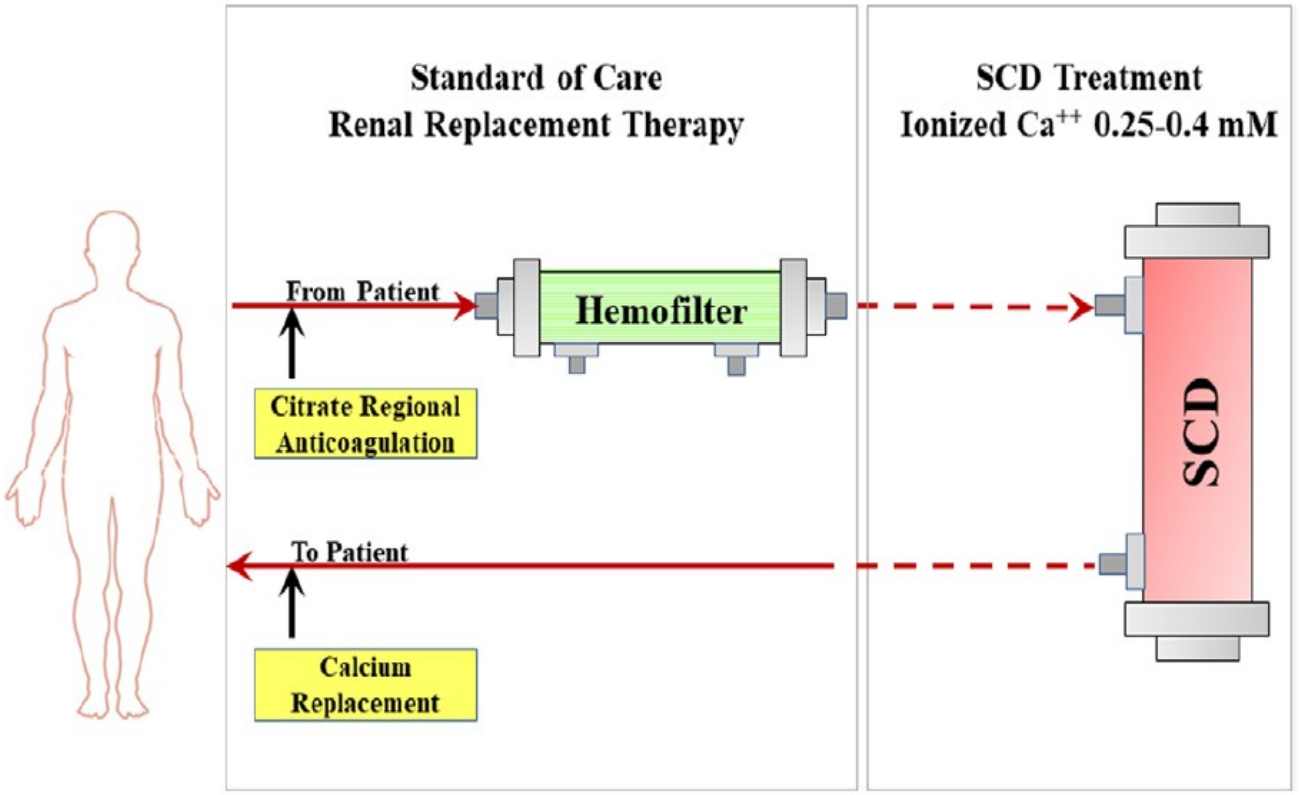
Extracorporeal Immunomodulation Treatment and Clinical Outcomes in ICU COVID-19 Patients

Balazs Szamosfalvi, MD[1]

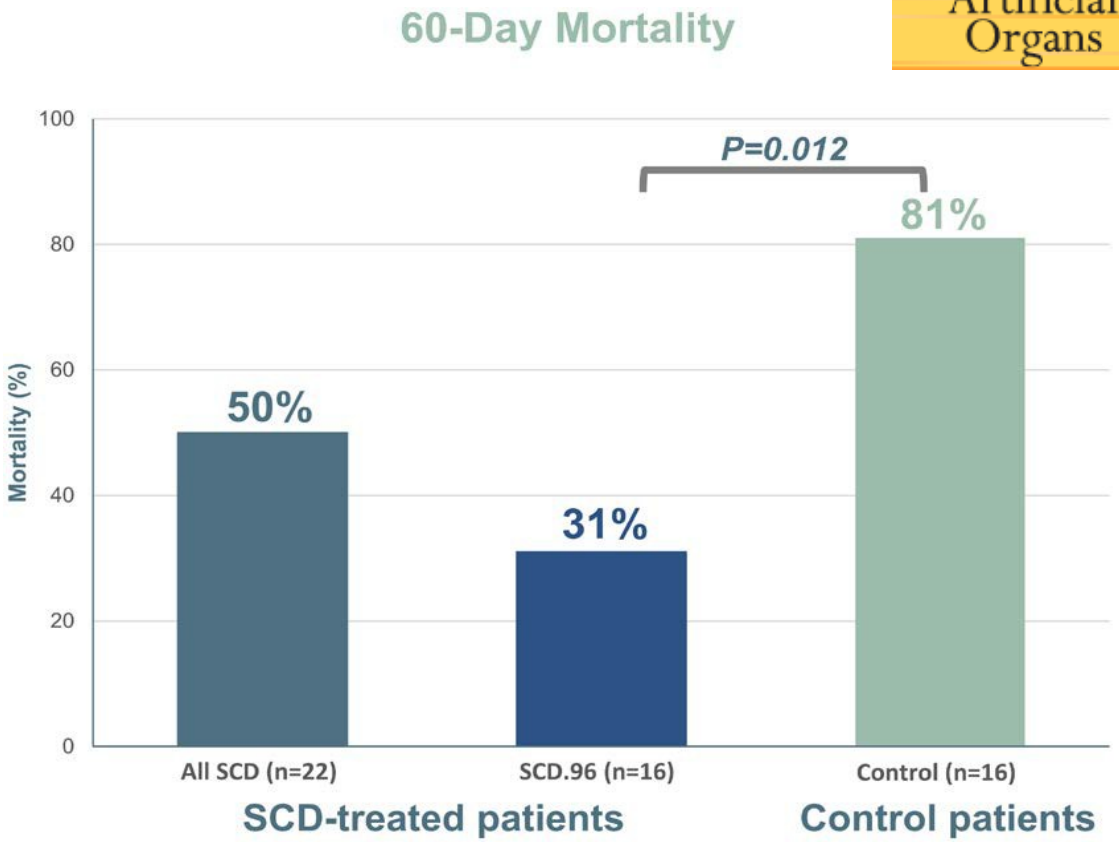
H. David Humes, MD[1,3]

Treatment of Cytokine Storm in COVID-19 Patients With Immunomodulatory Therapy

Lenar Yessayan,* Balazs Szamosfalvi,* Lena Napolitano,† Benjamin Singer,‡ Katsuo Kurabayashi,§¶ Yujing Song,§ Angela Westover,* and H. David Humes*



Artificial Organs



Extracorporeal immunomodulation therapy with an SCD demonstrated safety without any device-related serious adverse events. As a rescue therapy in COVID-19 ICU patients progressing to multiple organ failure despite maximal pharmacologic and organ support interventions, SCD treatment resulted in improved clinical outcomes. This autologous leukocyte cell processing technology may provide a new approach in the treatment of unremitting hyperinflammation of COVID-19

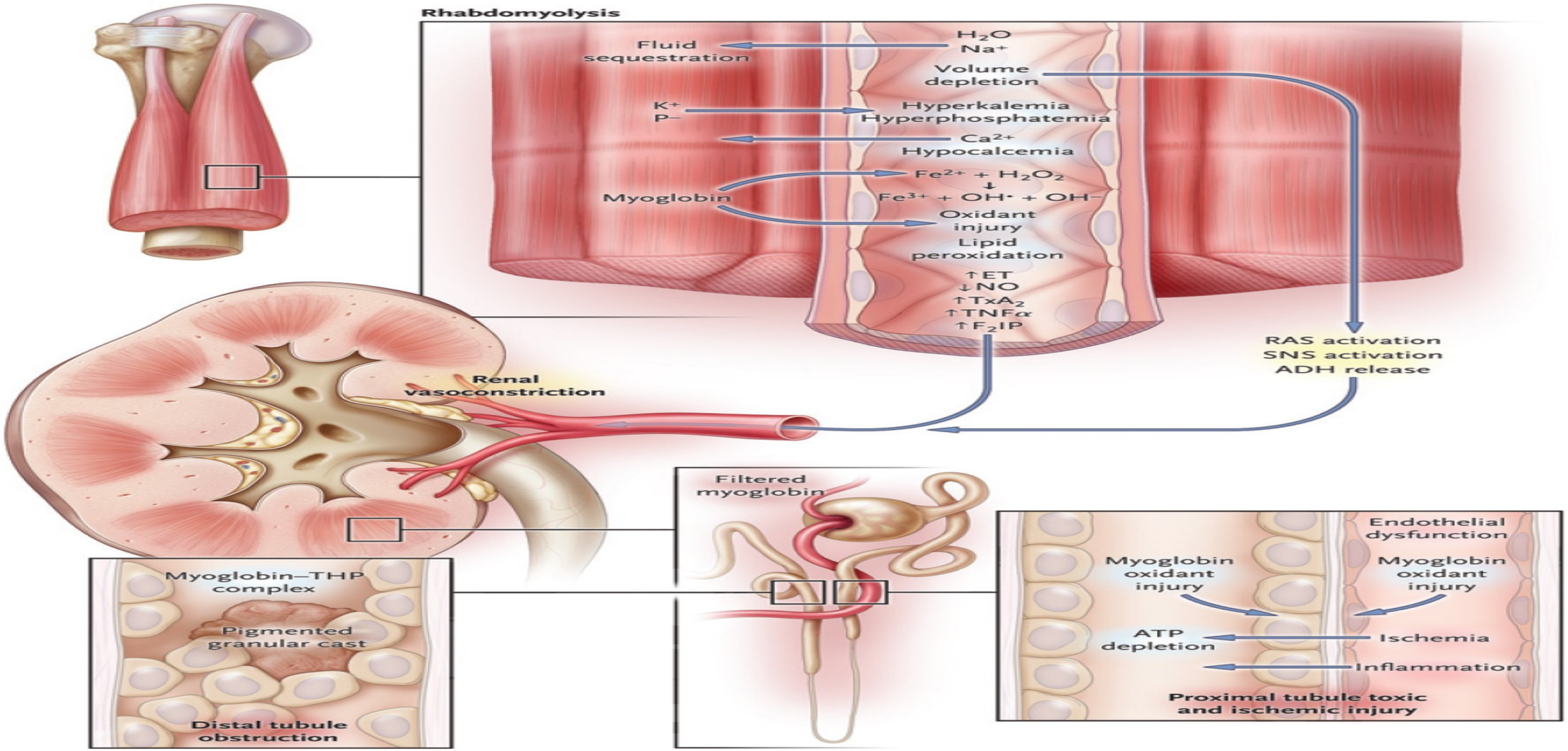

AKI:
other
causes?

Rhabdomyolysis and Acute Kidney Injury

The NEW ENGLAND JOURNAL of MEDICINE

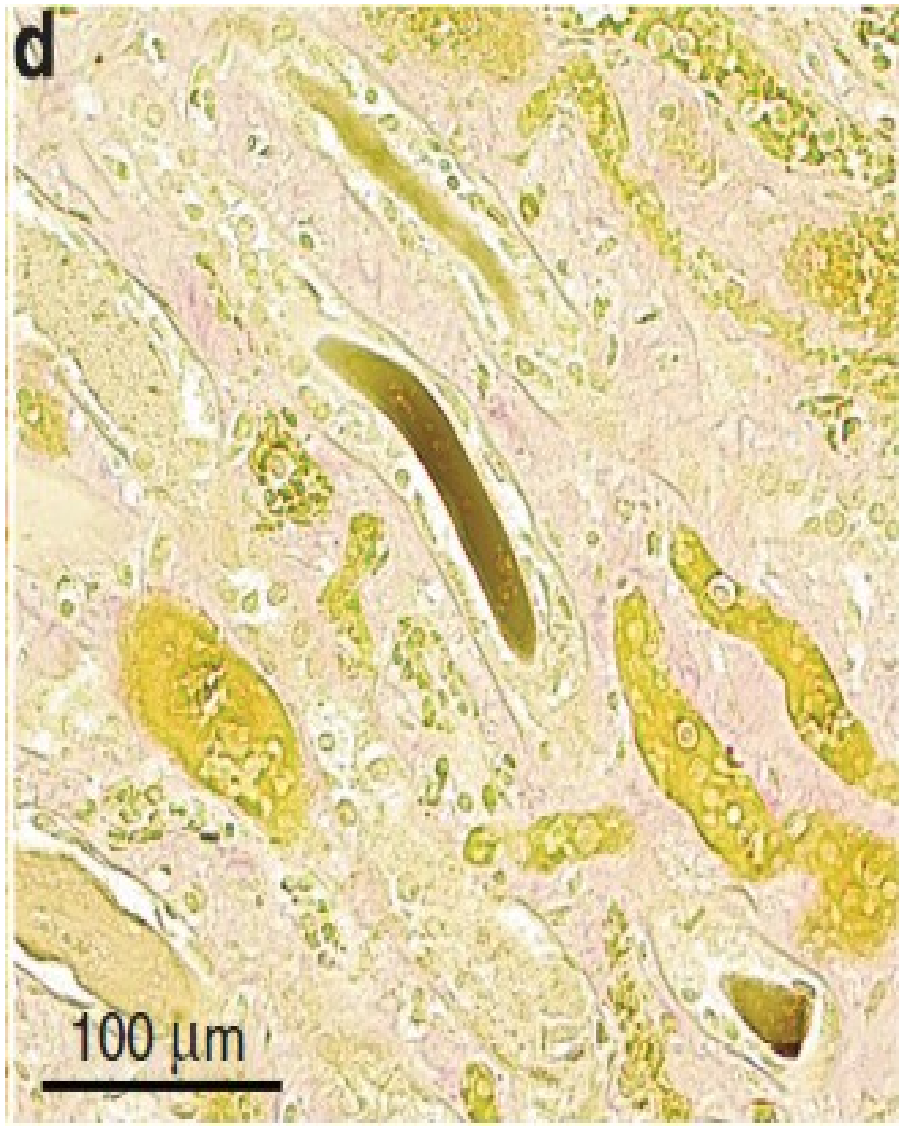
Xavier Bosch, M.D., Ph.D., Esteban Poch, M.D., Ph.D.,

Meccanismi di AKI indotta da rabdomiolisi (ischemia, cast nephropathy e danno tossico ossidativo propapoptotico).



Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction

Charles M. van Slambrouck[1], Fadi Salem[2], Shane M. Meehan[1] and Anthony Chang[1]



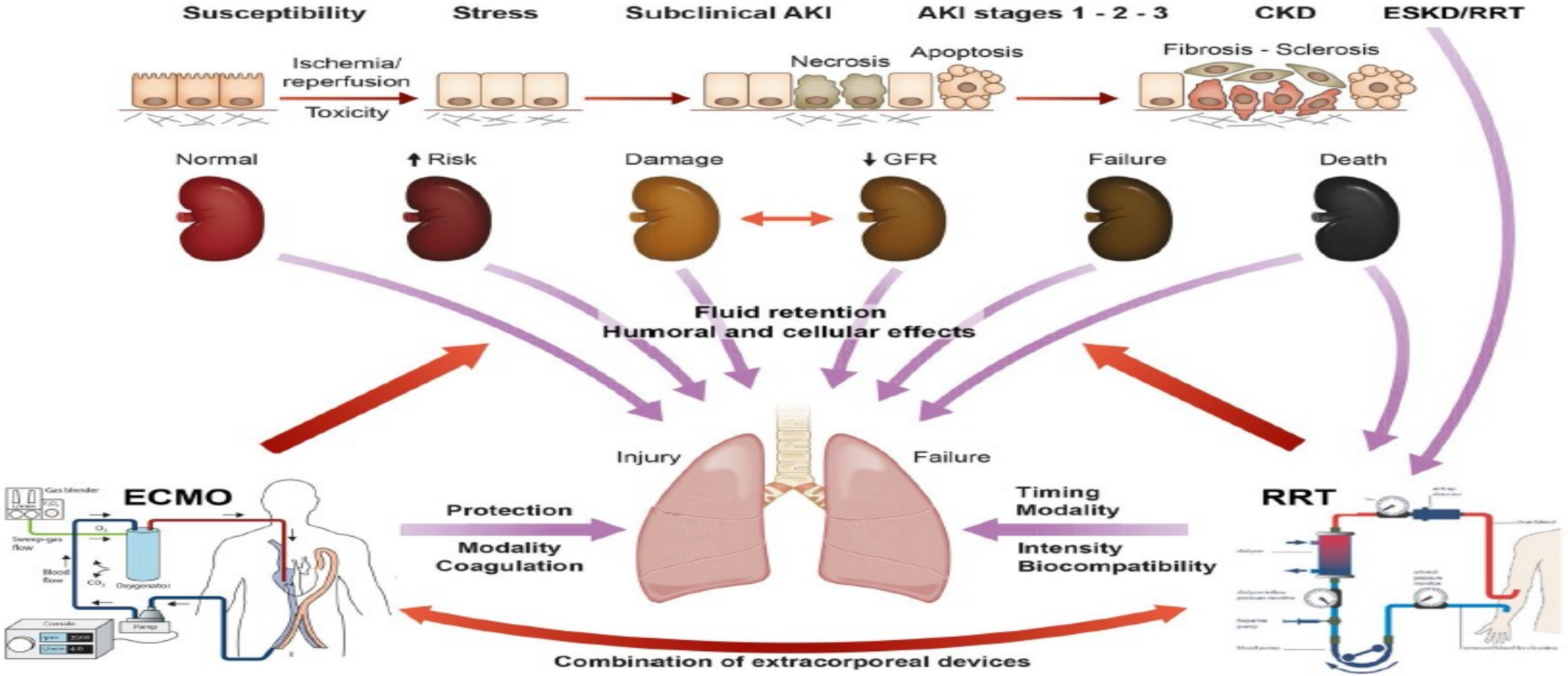
Bile-cast nephropathy: danno tubulare prossimale a seguito di formazione di cristalli biliari intrarenali riscontrati in pazienti con severa insufficienza epatica.

Effetto tossico diretto acidi biliary effetto tossico diretto (apoptosis TEC)

Entrambi i meccanismi di danno sono analoghi a quelli riscontrati nel danno da catene leggere nel mieloma o della mioglobina: ruolo del recettore endocitico della megalina

Lung–kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup

Michael Joannidis[1*], Lui G. Forni[2,3], Sebastian J. Klein[1,4], Patrick M. Honore[5], Kianoush Kashani[6], Marlies Ostermann[7], John Prowle[8,9], Sean M. Bagshaw[10], Vincenzo Cantaluppi[11], Michael Darmon[12,13,14], Xiaoqiang Ding[15], Valentin Fuhrmann[16,17], Eric Hoste[18,19], Faeq Husain-Syed[20], Matthias Lubnow[21], Marco Maggiorini[22], Melanie Meersch[23], Patrick T. Murray[24,25], Zaccaria Ricci[26], Kai Singbartl[27], Thomas Staudinger[28], Tobias Welte[29], Claudio Ronco[30,31,32] and John A. Kellum[33]



Acute kidney injury in SARS-CoV-2 infected patients

Vito Fanelli[1], Marco Fiorentino[2], Vincenzo Cantaluppi[3], Loreto Gesualdo[4], Giovanni Stallone[5], Claudio Ronco[6] and Giuseppe Castellano[7*]

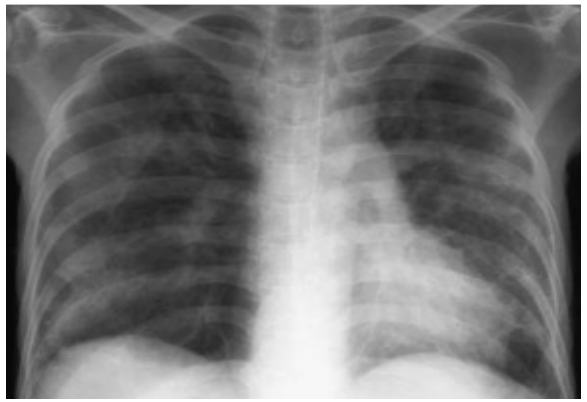
Critical Care

Courtesy by V. Fanelli, UNITO

ARDS
"Berlin definition"

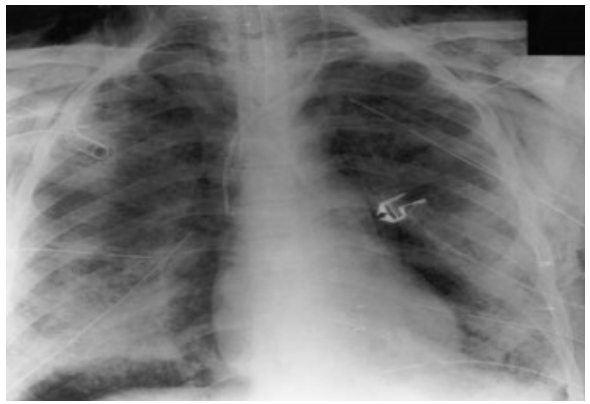
200mmHg < PaO2/FIO2 ≤ 300mmHg
with PEEP or CPAP ≥ 5cmH2O

MILD



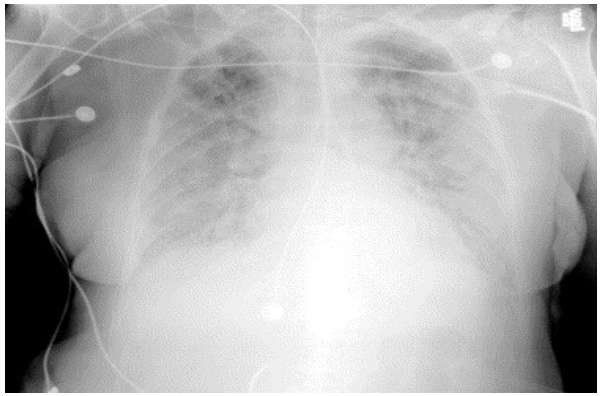
100mmHg < PaO2/FIO2 ≤ 200mmHg
with PEEP ≥ 5cmH2O

MODERATE

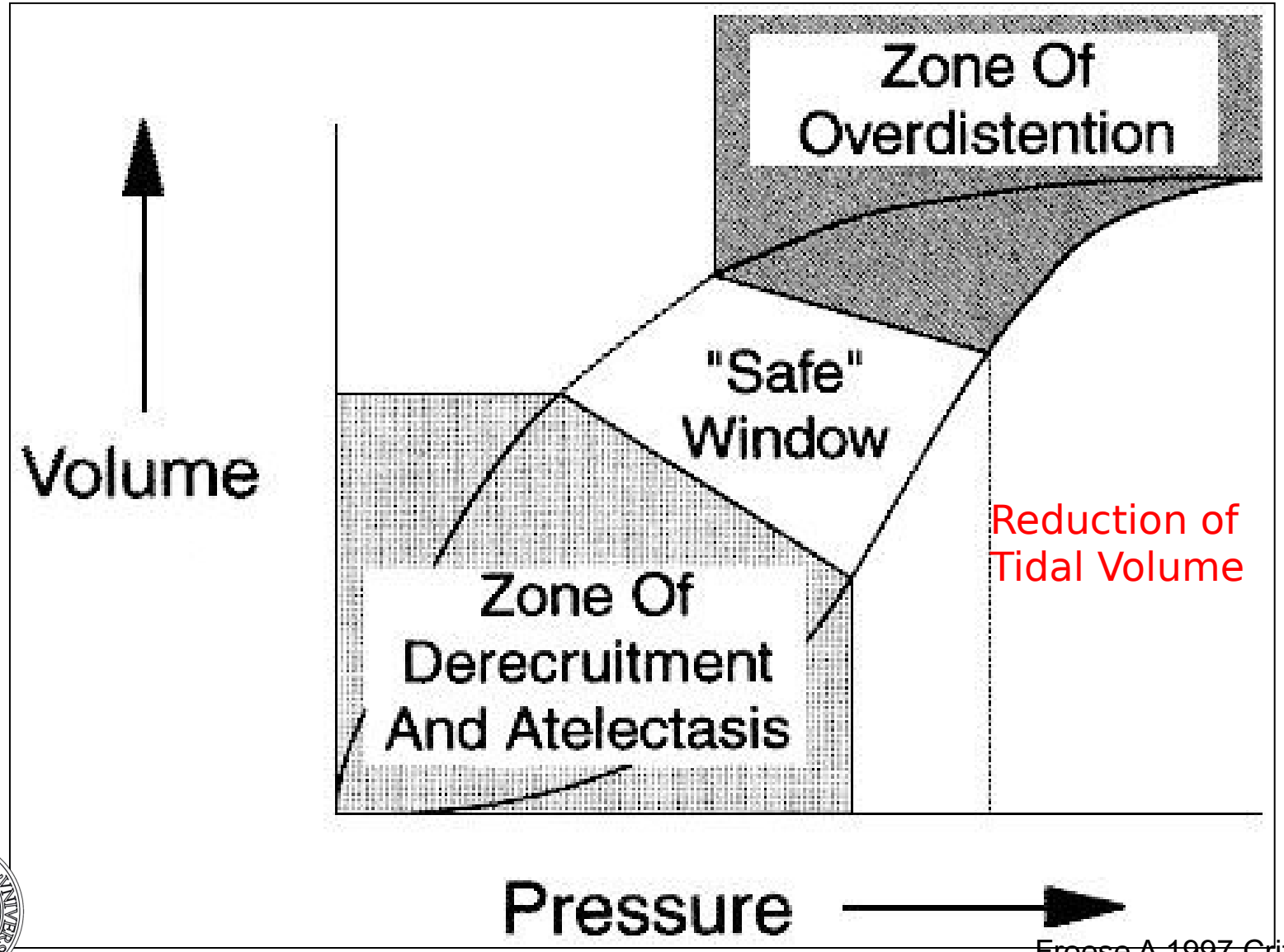


PaO2/FIO2 ≤ 100mmHg
with PEEP ≥ 5cmH2O

SEVERE



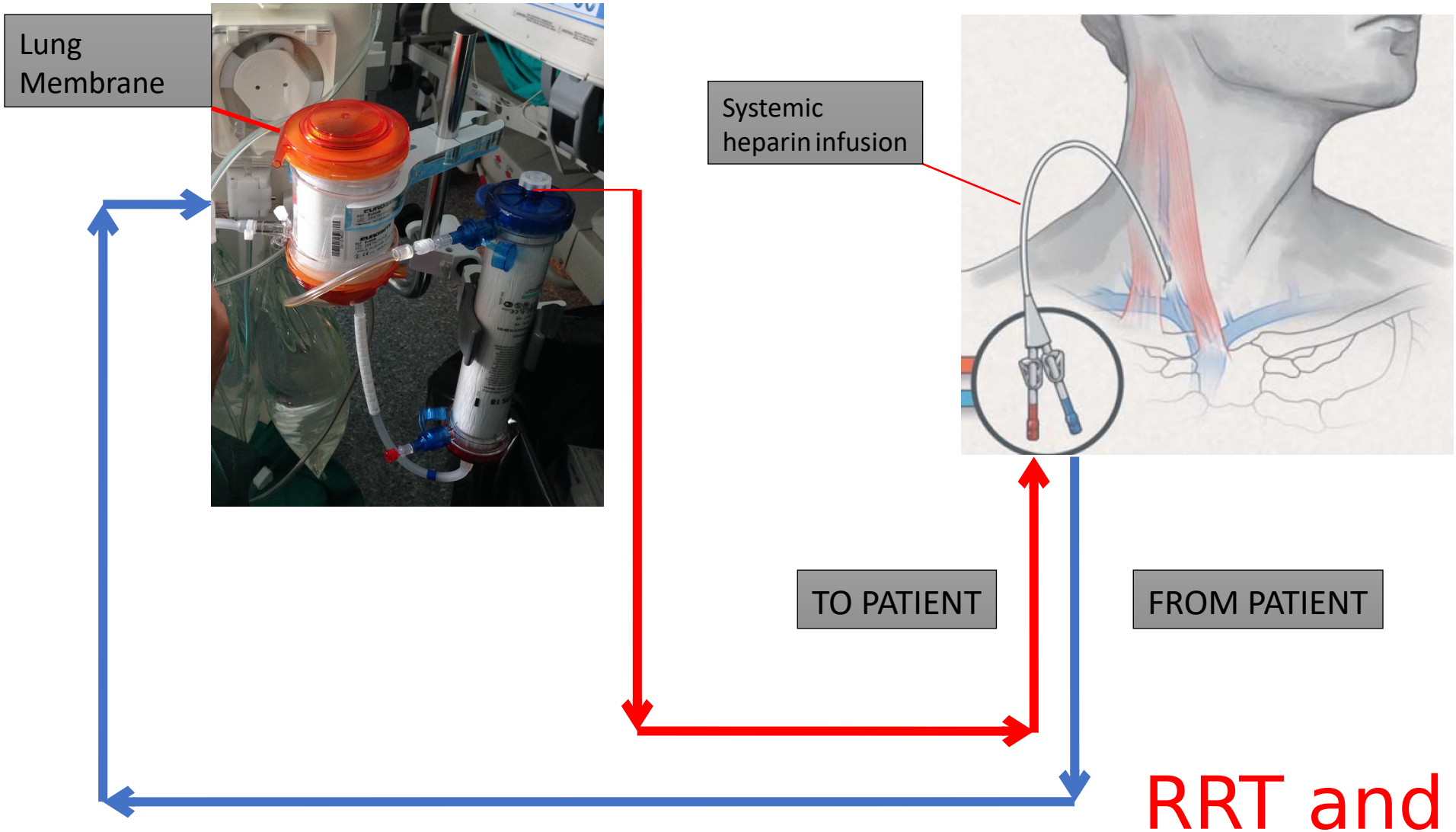
Risk of VILI and Death



Froese A 1997 Crit Care Med

Feasibility and safety of extracorporeal CO_2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study

Alain Combes[1], Vito Fanelli[2], Tai Pham[3], V. Marco Ranieri[4*] and On behalf of the European Society of Intensive Care Medicine Trials Group and the "Strategy of Ultra-Protective lung ventilation with Extracorporeal CO2 Removal for New-Onset moderate to severe ARDS" (SUPERNOVA) investigators

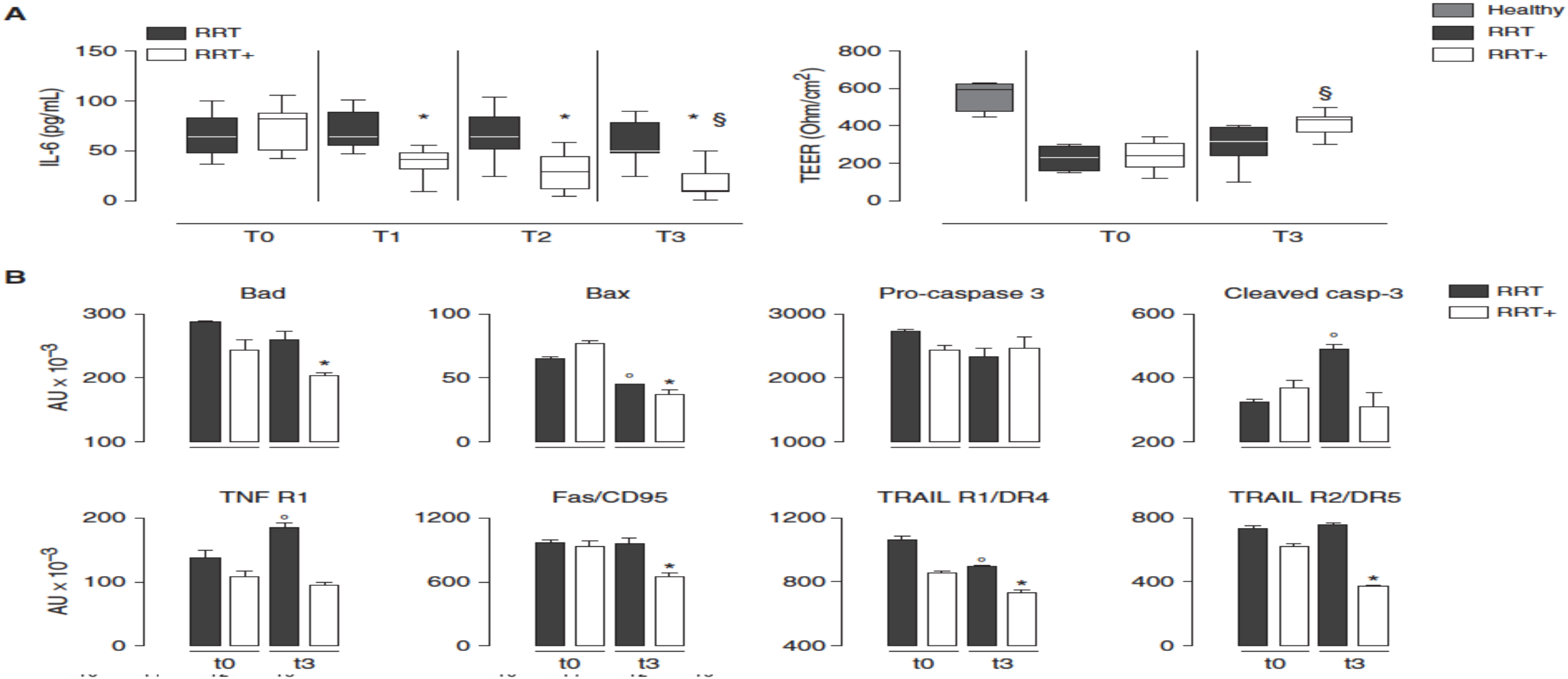


RRT and $ECCO_2$

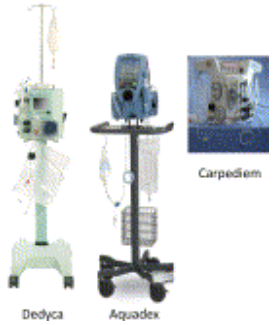
EXTRACORPOREAL CO_2 REMOVAL MAY IMPROVE RENAL FUNCTION OF PATIENTS WITH ARDS AND ACUTE KIDNEY INJURY

Vito Fanelli[1], Vincenzo Cantaluppi[2], Francesco Alessandri[3], Andrea Costamagna[1], Paola Cappello[4], Luca Brazzi[1], Francesco Pugliese[3], Luigi Biancone[5], PierpaoloTerragni[6],V. Marco Ranieri[3]

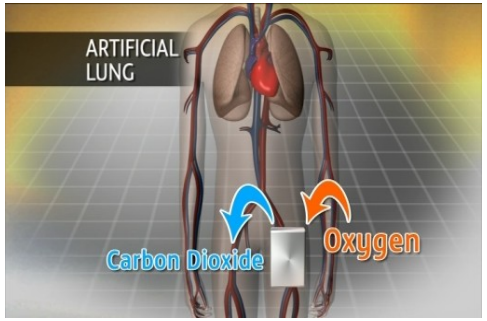
Running Title: ECCO$_2$R in patients with AKI and ARDS



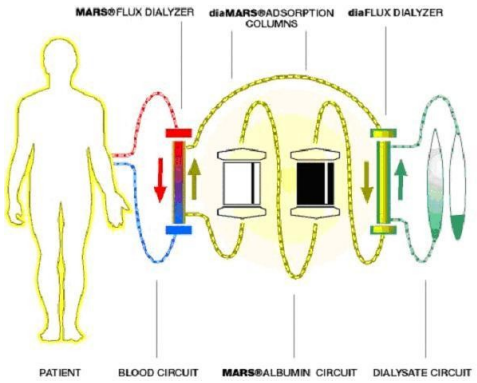
VAD



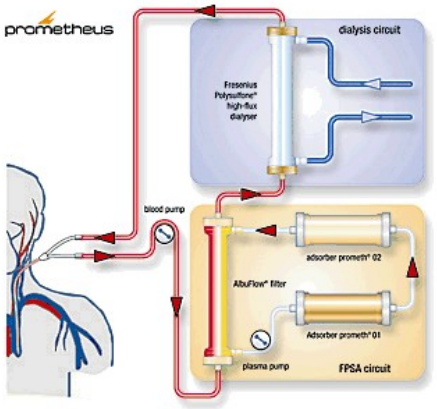
UF systems



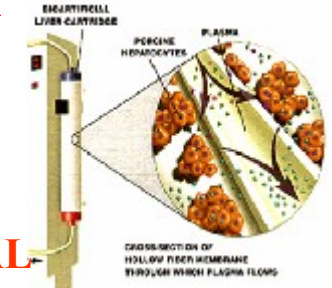
CO_2 removal



MARS



Prometheus



BAL

Brain

↑ Chemokines KC† and G-CSF*
↑ GFAP‡ and microglia
↑ Vascular permeability

Heart

↑ TNFα, IL-1
↑ Neutrophil trafficking
↑ Apoptosis

Lungs

↑ Vascular permeability
↑ Cytokines/chemokines
↑ Leukocyte trafficking
Transcriptomic changes

AKI

CRRT

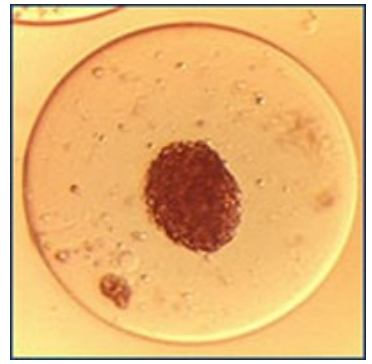
Liver

↑ Leukocyte influx
↑ Oxidation products
↓ Antioxidants (GSH)
Altered liver enzymes

Gut

↑ Channel-inducing factor
↑ Potassium excretion

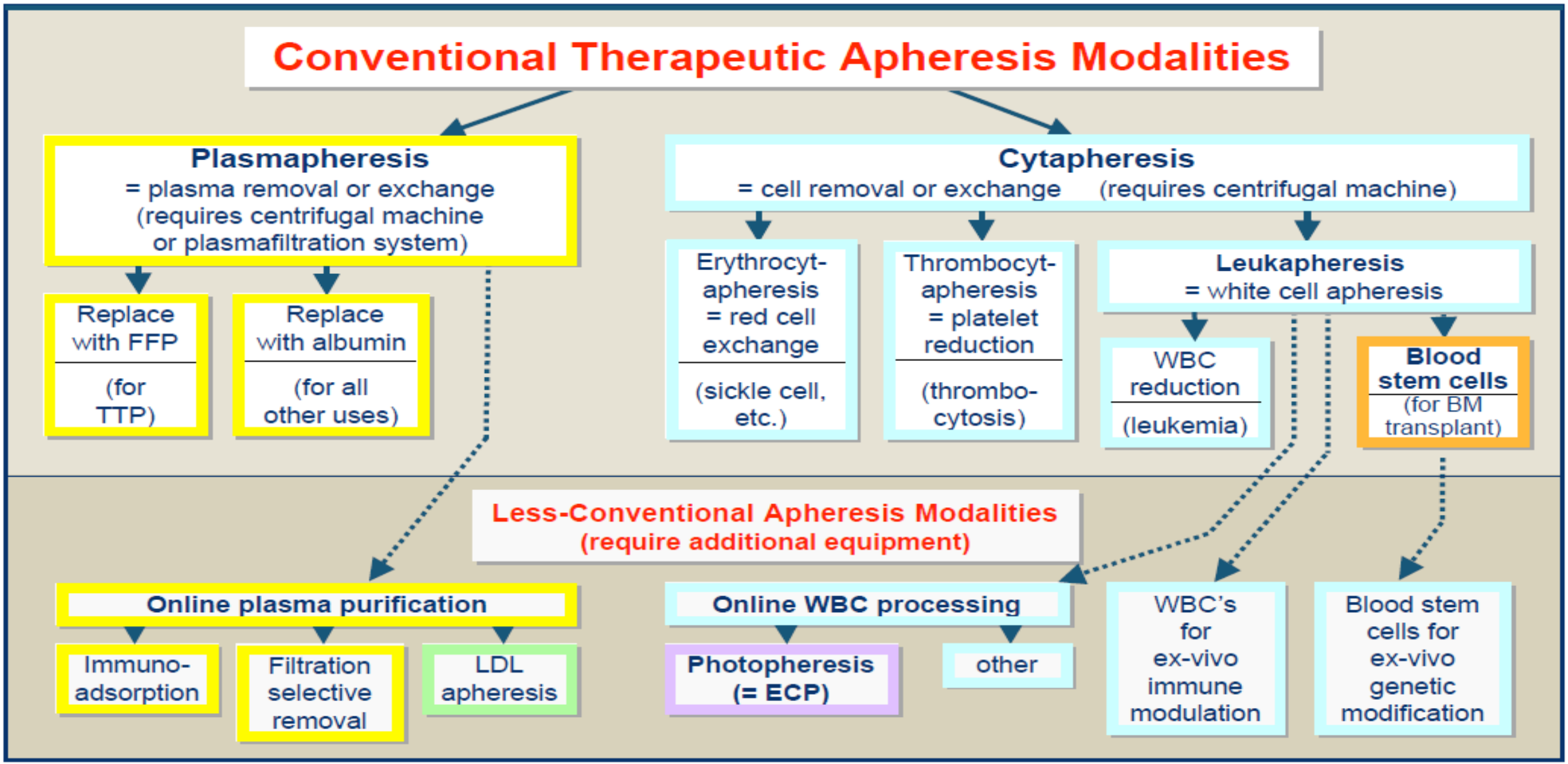
†A brain IL-8 homologue
*Granulocyte colony-stimulating factor
‡Glial fibrillary acidic protein
Glutathione



Islet encapsulation
Artifical pancreas

M.O.S.T
Multiple Organ Support therapy
Ronco C et al, Blood Purification, 2005

Apheresis modalities



Plasmapheresis applications

- **Autoantibody:** Anti-GBM GN (& Goodpasture's), Myasthenia gravis (MG), ANCA-nephritis (& Wegener's), Immune Thrombocytopenia (ITP), Thrombotic Thrombocytopenic Purpura (TTP), Antiphospholipid crisis, Guillain-Barré syndrome (GBS), Autoimmune Dilated Cardiomyopathy, Neuromyelitis Optica (NMO), Stiff Person syndrome, Pemphigus, etc.
- **Probable autoantibody:** Multiple sclerosis (also cell-mediated component), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), etc.
- **Antigen-Antibody complexes:** Hepatitis C vasculitis, S.L.E., etc.
- **Alloantibody:** Transplant sensitization, Transplant rejection (humoral), Transfusion reactions, etc.
- **Paraproteins:** Waldenstrom's, Hyperviscosity, Light-chain neuropathy, Light-chain glomerulopathy, Myeloma cast nephropathy, etc.
- **Non-Ig proteins:** Focal Segmental Glomerulosclerosis (FSGS), etc.
- **Endogenous toxins:** Hypercholesterolemia, Liver failure, Systemic Inflammatory Response Syndrome (SIRS), etc.
- **Exogenous poisons:** *Amanita*, drugs, etc.

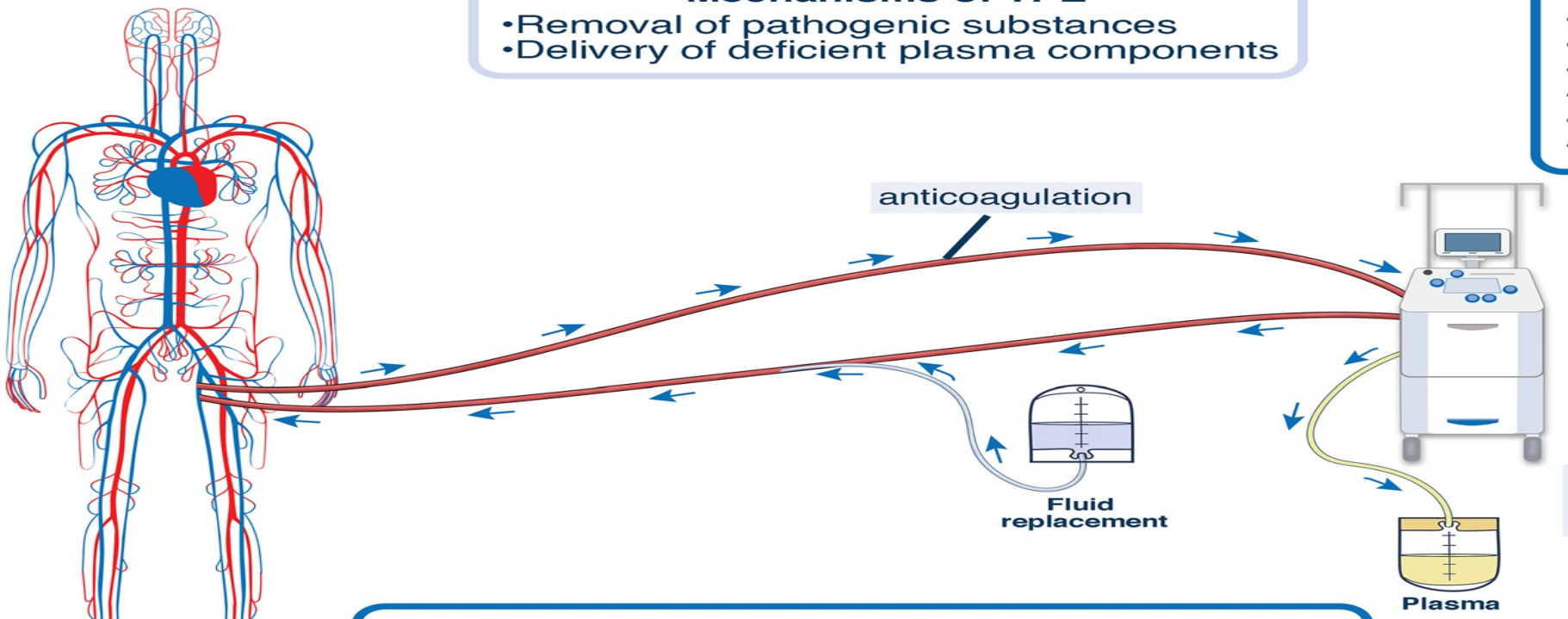
Plasma exchange in the intensive care unit: a narrative review

Philippe R. Bauer[2*], Marlies Ostermann[12], Lene Russell[15], Chiara Robba[14], Sascha David[6], Bruno L. Ferreyro[7], Joan Cid[5], Pedro Castro[4], Nicole P. Juffermans[8], Luca Montini[10], Tasneem Pirani[13], Andry Van De Louw[17],

Therapeutic plasma exchange: overview.

Mechanisms of TPE
- Removal of pathogenic substances
- Delivery of deficient plasma components

Prescription of TPE
- Vascular access
- Total plasma volume
- Number of sessions
- Interval between sessions
- Anticoagulation
- Type of replacement fluid
- Drug dosing



Apheresis (membrane- or centrifuge-based)

Removal of antibodies / inflammatory mediators

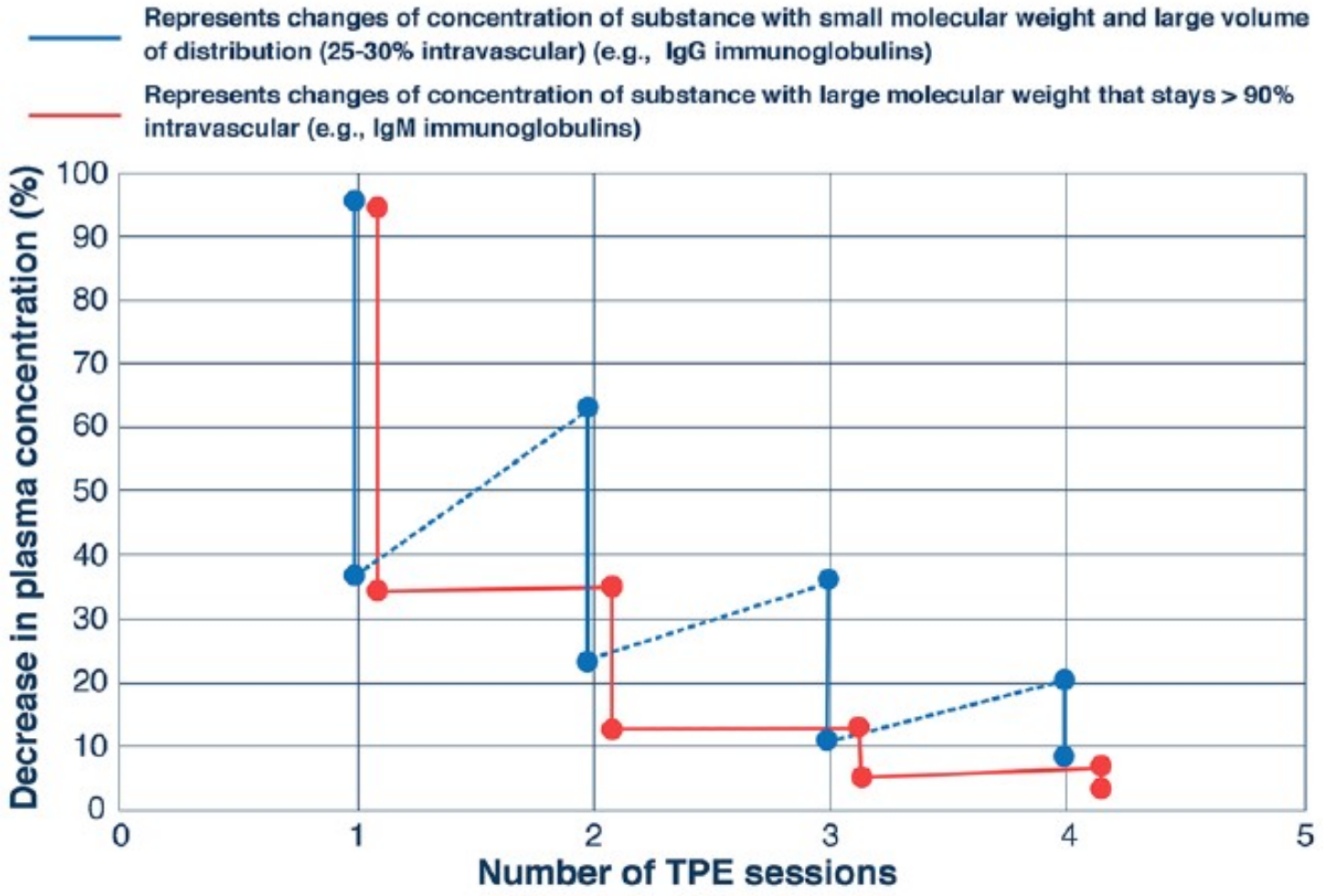
Diagnostic work-up before TPE
- Biochemistry (electrolytes, liver and renal function)
- Complete blood count
- Coagulation
- Disease-specific tests
- Infection status (HIV, hepatitis..)
- Blood type (ABO, Rhesus)

Monitoring during TPE
- Biochemistry
- Complete blood count
- Coagulation
- Disease-specific tests

Plasma exchange in the intensive care unit: a narrative review

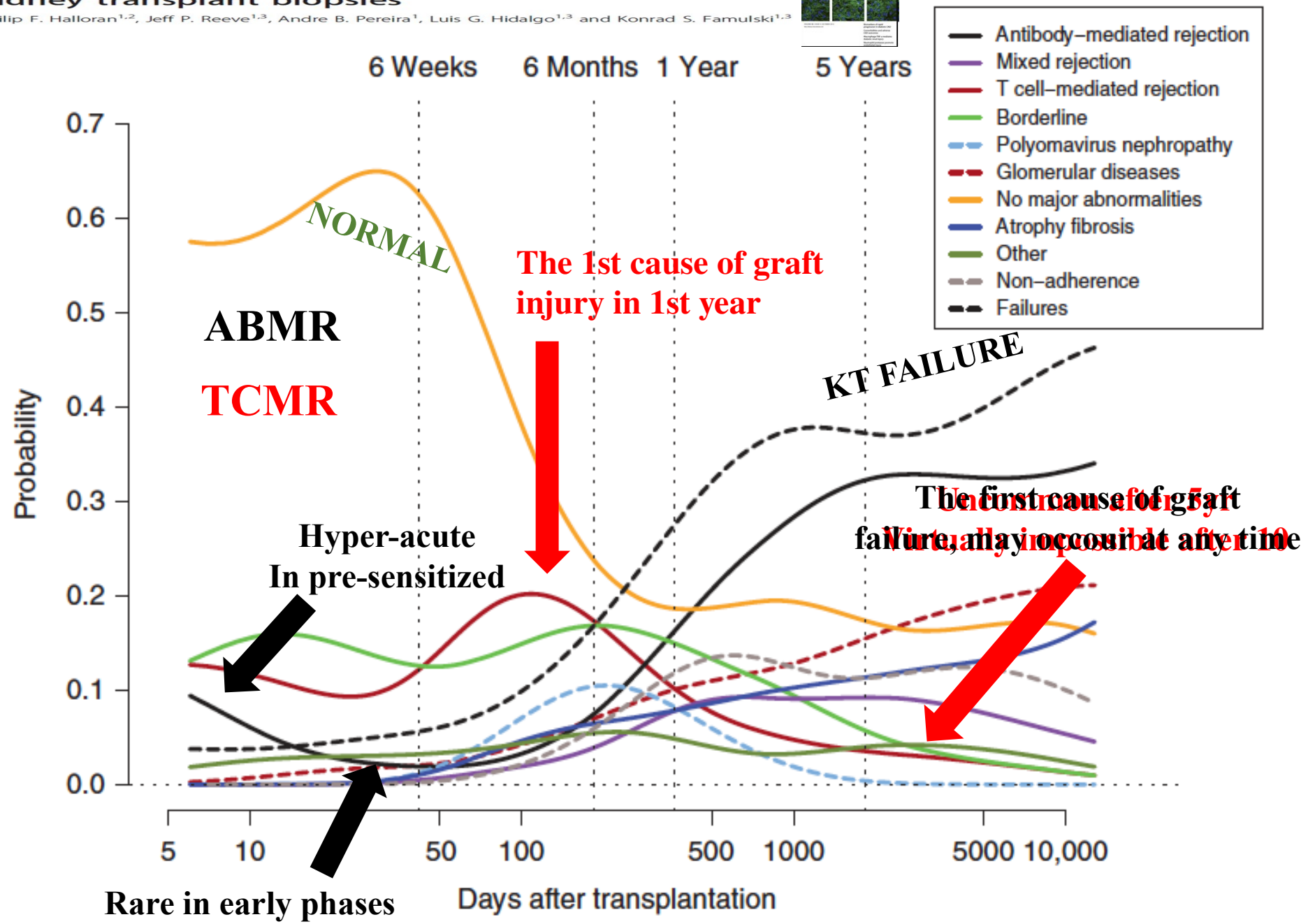
Philippe R. Bauer[2*], Marlies Ostermann[12], Lene Russell[15], Chiara Robba[14], Sascha David[6], Bruno L. Ferreyro[7], Joan Cid[5], Pedro Castro[4], Nicole P. Juffermans[8], Luca Montini[10], Tasneem Pirani[13], Andry Van De Louw[17],

Progressive decrease in plasma concentration of substance following four consecutive TPE treatments equaling 1.2 plasma volume each.



Antibody-mediated rejection, T cell–mediated rejection, and the injury-repair response: new insights from the Genome Canada studies of kidney transplant biopsies

Philip F. Halloran[1,2], Jeff P. Reeve[1,3], Andre B. Pereira[1], Luis G. Hidalgo[1,3] and Konrad S. Famulski[1,3]



TRAPIANTI IMMUNOLOGICAMENTE INCOMPATIBILI: CONDIZIONAMENTO PRE-TX

AB0i → incompatibilità di gruppo sanguigno

HLAi → presenza di DSA condizionanti XM CDC positivo o XM negativo ma (potenzialmente) patogeni (MFI based?)

RISCHI: AAMR, CAMR (?)

Categorie di pz a rischio di EARLY DAMAGE su graft:

-High risk: reTx, Ab classe I + II, MFI>5000

-Intermediate risk: primo Tx, Ab classe I o II, MFI > 3000

Strategies to overcome the ABO barrier in kidney transplantation

G.A. Böhmig, A.M. Farcas, F. Eskandary. T. Wekerle

Nature Reviews Nephrology - 1 september 2015

Elementi chiave nel trapianto renale ABO incompatibile

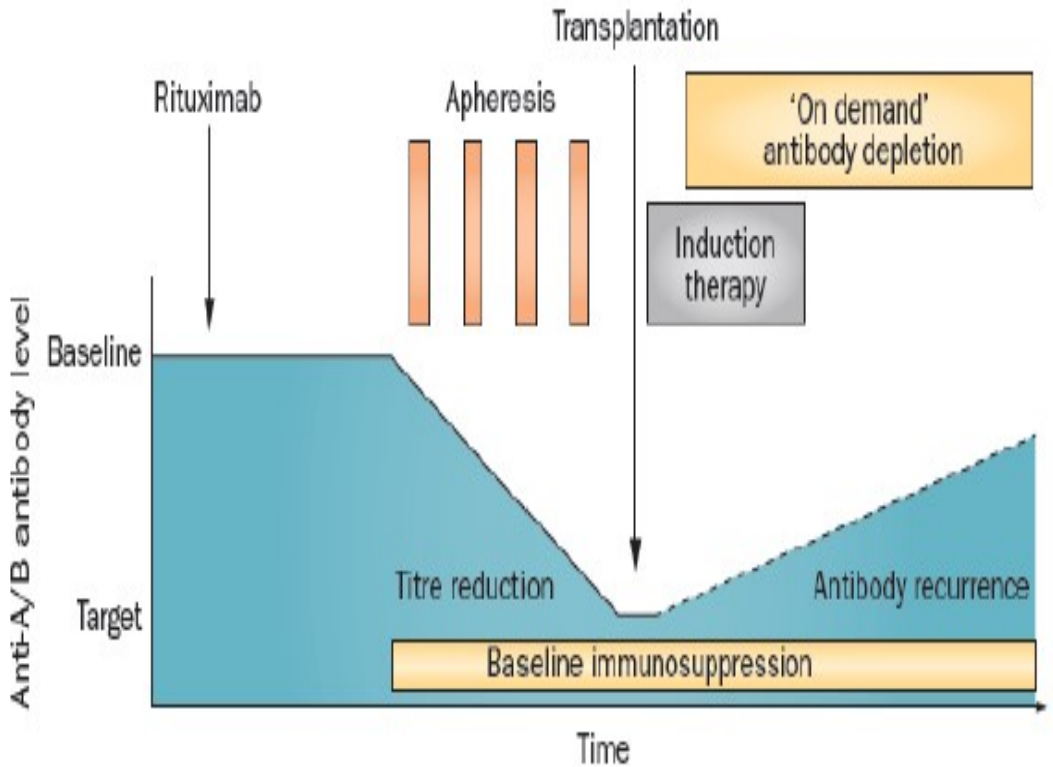


TABLE 1. The number of planned pre- and posttransplant PP/IVIg treatments correlate with the starting isohemagglutinin titer

Starting isoagglutinin AHG titer	Pretransplant PP/IVIG treatments	Posttransplant PP/IVIG treatments
<16	2	2
16–32	3	2–3
64	4	3
128	5–6	4
256	7–8	4
512	9–10	5
>512	>10	6

PP, plasmapheresis; AHG, anti-human globulin.

HLAi – letteratura recente

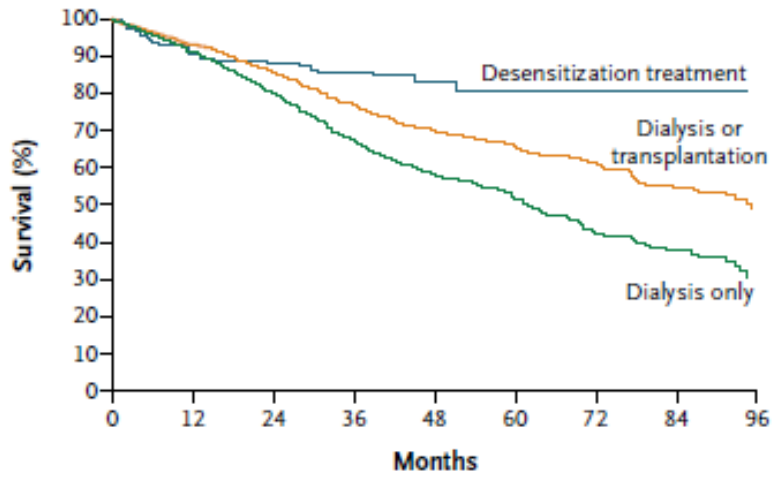
The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 365;4 NEJM.ORG JULY 28, 2011

ORIGINAL ARTICLE

Desensitization in HLA-Incompatible Kidney Recipients and Survival

Robert A. Montgomery, M.D., D.Phil., Bonnie E. Lonze, M.D., Ph.D.,



No. at Risk									
Desensitization treatment	210	170	143	110	75	58	42	28	14
Dual therapy	1027	854	688	497	321	230	157	96	41
Dialysis only	1012	822	626	419	250	159	93	54	17

Live-donor transplantation after desensitization provided a significant survival benefit for patients with HLA sensitization, as compared with waiting for a compatible organ. By 8 years, this survival advantage more than doubled. These data provide evidence that desensitization protocols may help overcome incompatibility barriers in live-donor renal transplantation.

ABOi e HLAi: dove siamo arrivati?

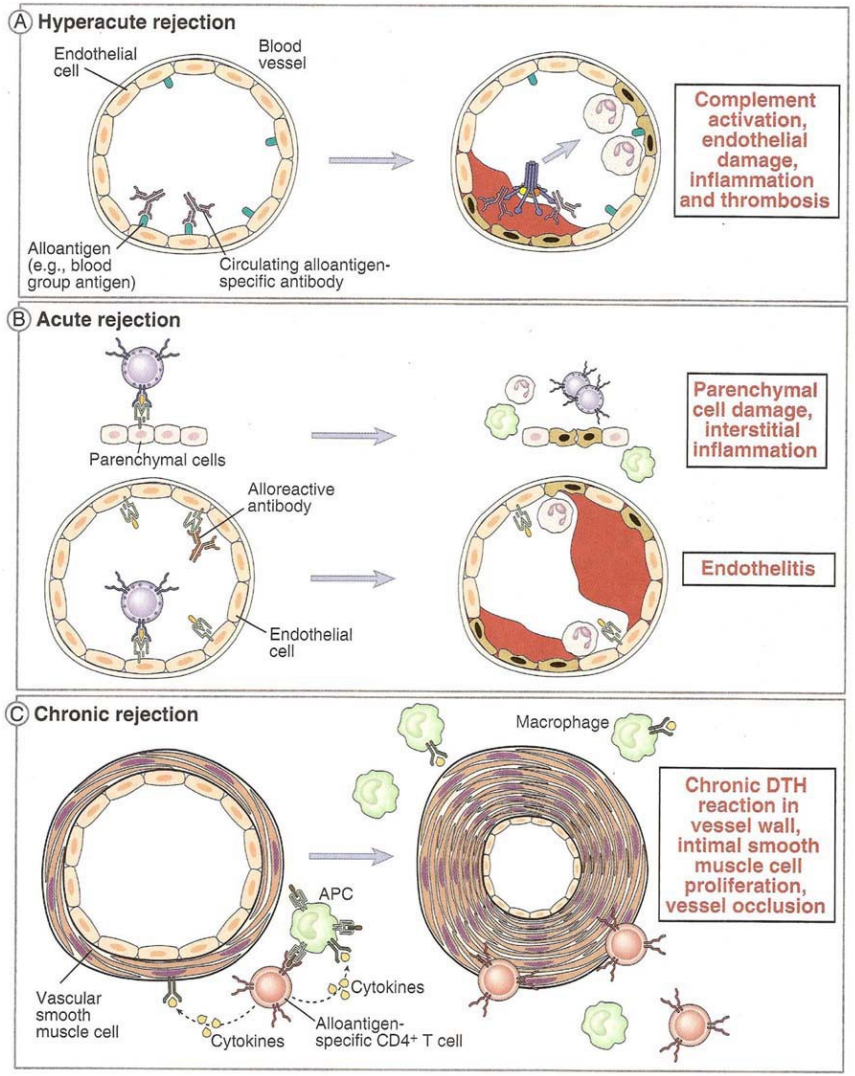
TARGET

AB0i → isoemoagglutinine ≤ 1:8

HLAi → CDC XM negativo

→ DSA < 1000 MFI

Rigetto anticorpo-mediato
fenotipi



ABMR fenotipo I
- Isoemoagglutinine
- DSA pre esistenti fissanti il complemento

PRE-TRAPIANTO

ABMR fenotipo II
- Sviluppo di DSA de novo (fissanti o no il complemento)

POST-TRAPIANTO

Anticorpi importanti nel trapianto di rene

- **Anti-ABO**
  >25% dei donatori viventi
  è AB0 incompatibile

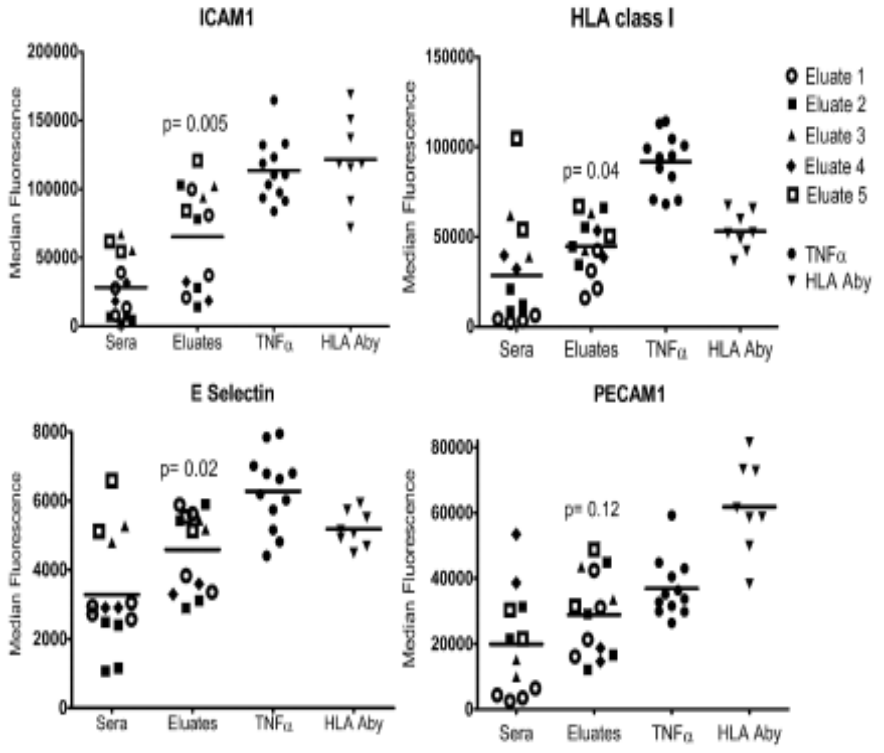
- **Anti-HLA -----DSA**

- **Anti- non-HLA:**

  - anti MICA/MICB
  - anti-AT_1R
  - anti-ET_AR
  - anti-Vimentina
  - Perlacan,
  - anti antigeni endoteliali

TO BE CONTINUED…….

Endothelial Cell Antibodies Associated with Novel Targets and Increased Rejection JACKSON, JASN 2015



Four antigenic targets expressed on endothelial cells were identified: endoglin, Fms-like tyrosine kinase-3 ligand,EGF-like repeats and discoidin I-like domains 3, and intercellular adhesion molecule 4;

Rigetto anticorpo-mediato terapia

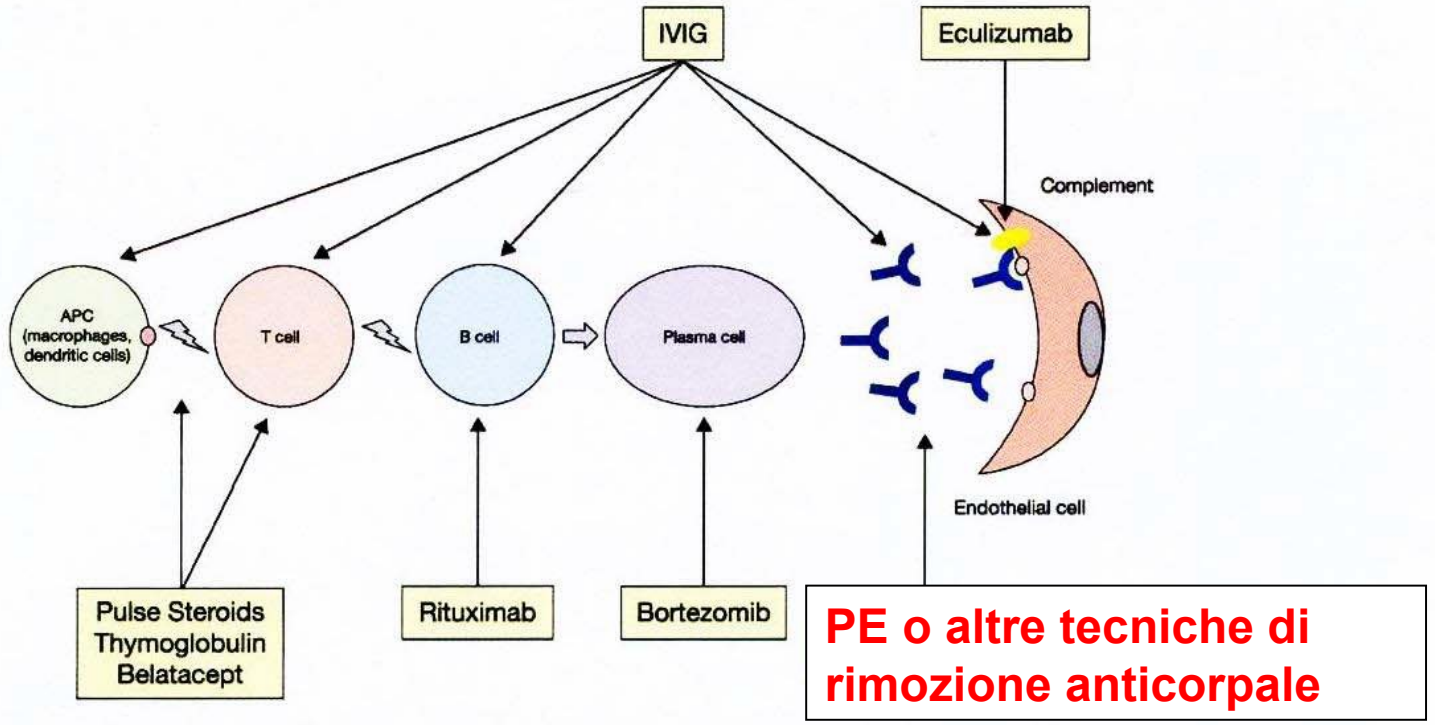


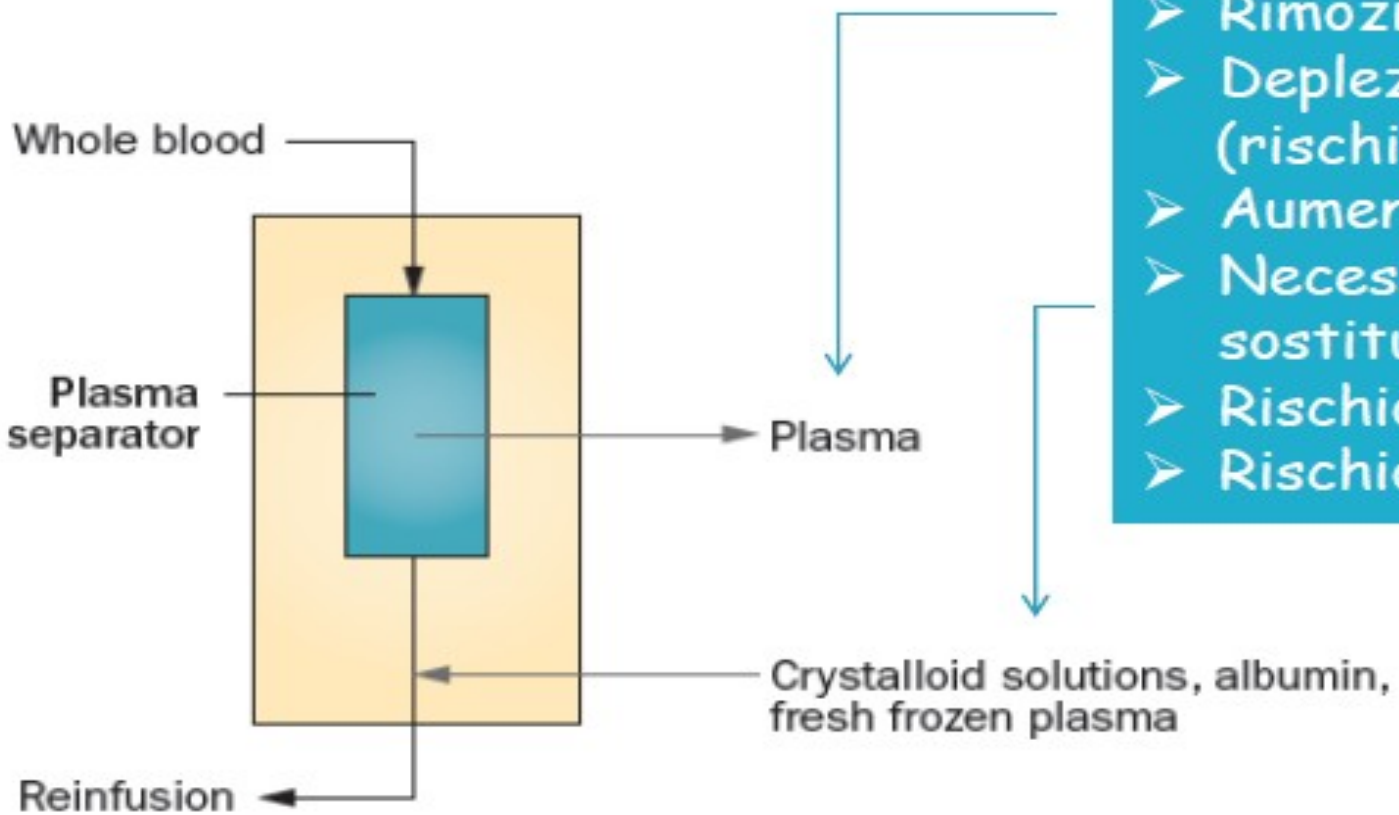
Figure 4: Therapeutic modalities for ABMR. ABMR, antibody-mediated rejection; APC, antigen-presenting cell; IVIG, intravenous immunoglobulins.

American Journal of Transplantation 2014; 14: 255–271

Tecniche di rimozione anticorpale

- **Plasmaferesi**

1 seduta: diminuzione Ab anti gruppo da **1 a 2 titoli**

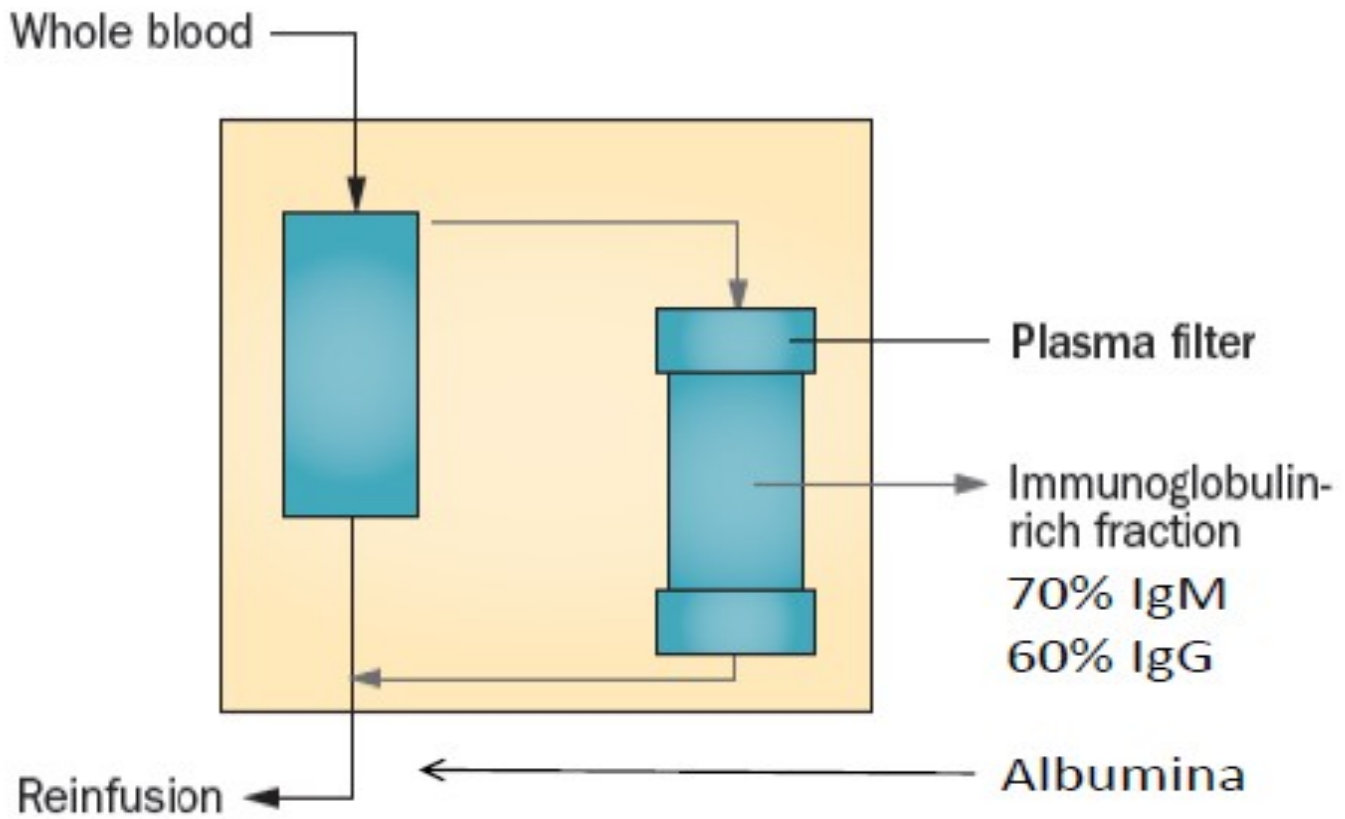


- Tecnica semplice
- Basso costo
- Rimozione non selettiva
- Deplezione fattori della coagulazione (rischio sanguinamento)
- Aumentato rischio infettivo
- Necessità di infusione di liquidi sostitutivi
- Rischio reazioni allergiche
- Rischio trasmissione infezioni virali

Tecniche di rimozione anticorpale

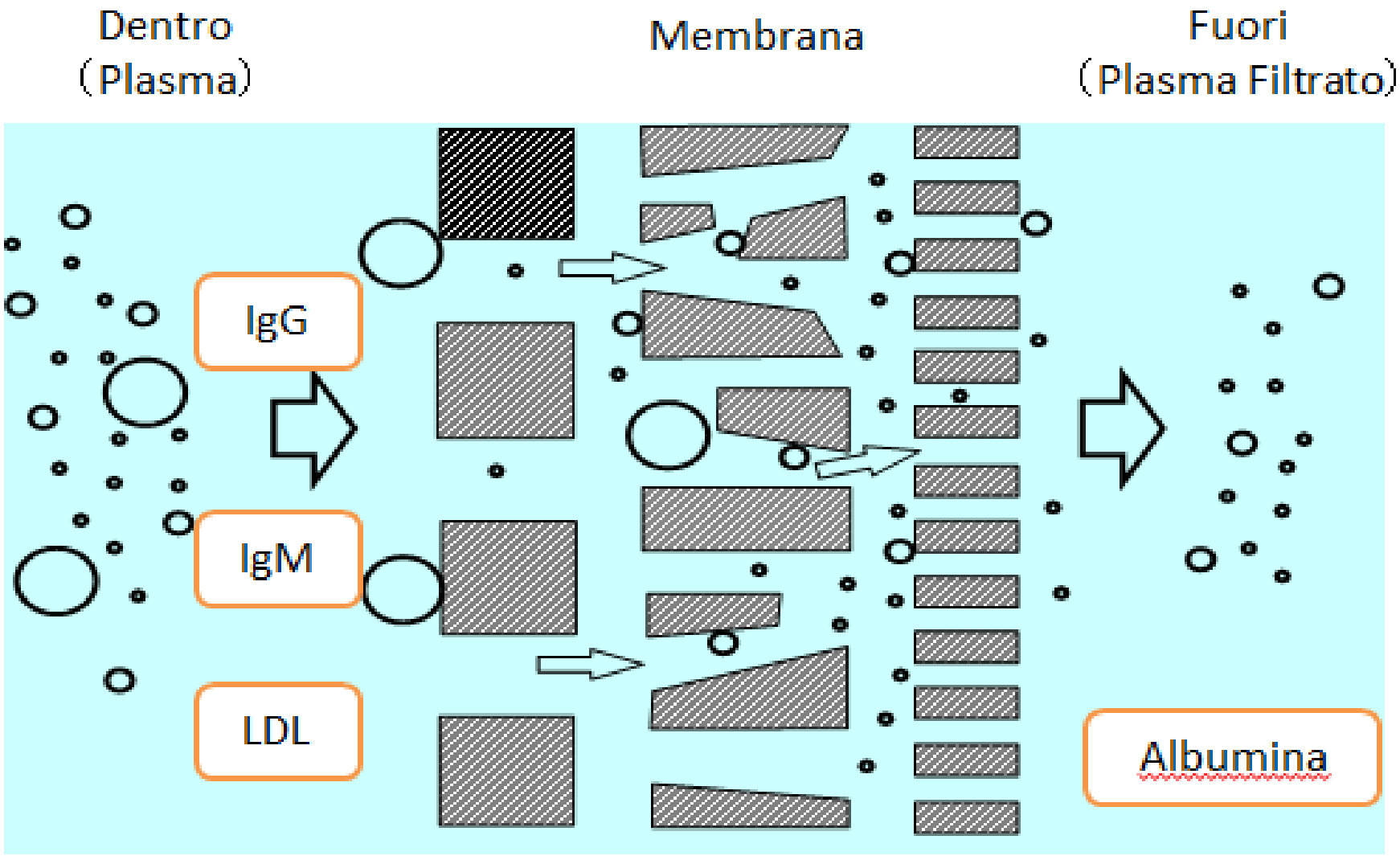
- **Doppia filtrazione a cascata**

1 seduta: diminuzione Ab anti gruppo da **1 a 2 titoli**



- Tecnica di filtrazione semi-selettiva
- Rimozione selettiva di sostanze ad alto peso molecolare (IgM, IgG, ICC, Crio, Fibrinogeno,fatt. VIII)
- Ridotta deplezione fattori della coagulazione vs PF
- Perdita albumina ~ 20-25%
- Necessità di infusione di liquidi sostitutivi << rispetto alla Plasmaferesi (0.5-1 vs 2.5-3 l in PE)
- Minor rischio infettivo e allergie

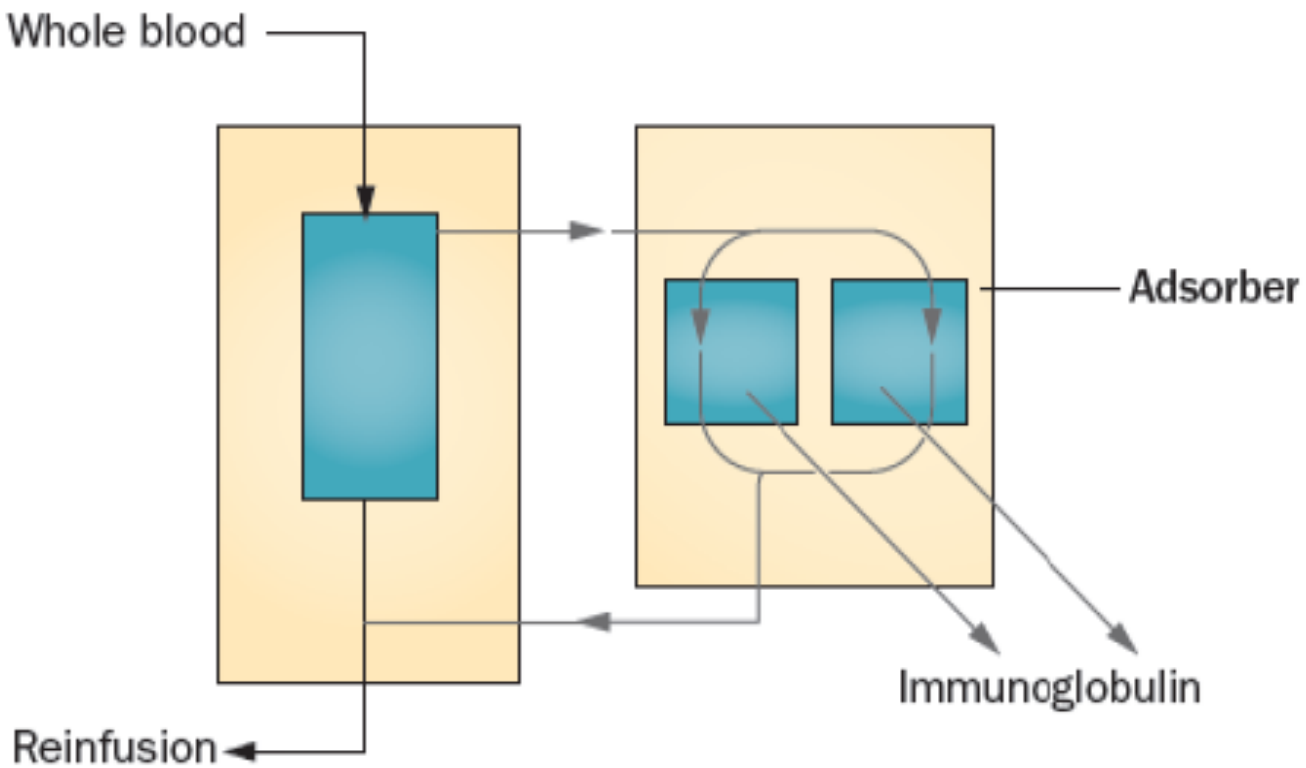
Aferesi Terapeutica: Filtro Frazionatore



Tecniche di rimozione anticorpale

Immunoadsorbimento semi-selettivo

1 seduta: diminuzione Ab anti gruppo da **2 a 4 titoli**



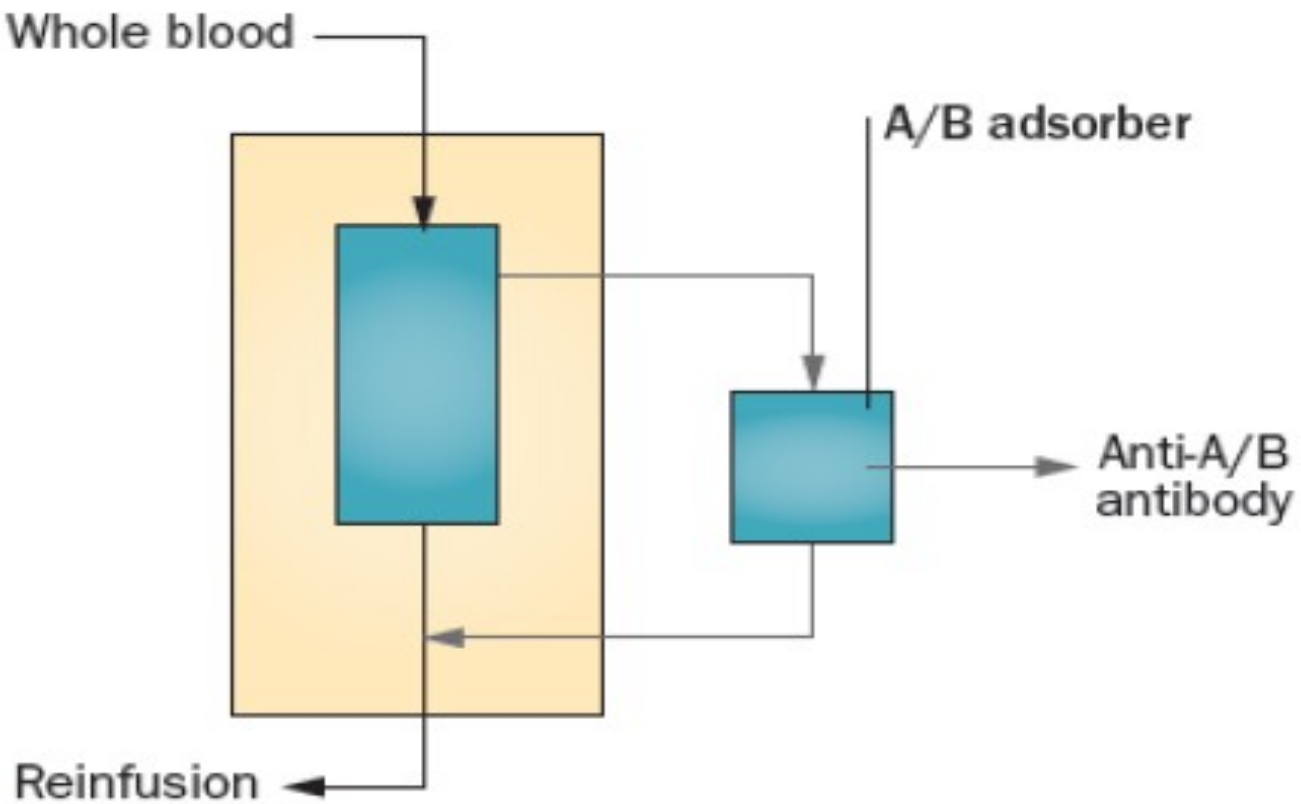
1.5 volume plasma = rimozione 61% IgG
2.5 volume plasma = rimozione 87% IgG

- Tecnica semi-selettiva
- Rimozione di immunoglobuline (IgG) , rimuove anticorpi anti gruppo A o B e anti HLA
- No deplezione fattori della coagulazione
- No necessità di infusione di liquidi sostitutivi
- No rischio infettivo virale
- Possibilità di processare alti volumi di plasma
- Costosa ma filtro riutilizzabile sino a 10 sedute per lo stesso paziente

Tecniche di rimozione anticorpale

- **Immunoadsorbimento selettivo**

1 seduta: diminuzione Ab anti gruppo da **2 a 4 titoli**



- Tecnica selettiva
- Rimozione selettiva di anticorpi anti gruppo A o B
- No deplezione fattori della coagulazione
- No necessità di infusione di liquidi sostitutivi
- No rischio infettivo virale
- Buona tolleranza
- Possibilità di processare alti volumi di plasma
- Molto costosa

The Treatment of Acute Antibody-Mediated Rejection in Kidney Transplant Recipients—A Systematic Review

Darren M. Roberts,[1,2,4] Simon H. Jiang,[1] and Steven J. Chadban[1,3]

Treatment of antibody-mediated rejection strenght of evidence supporting efficacy : THE GRADE SYSTEM

Therapy	Action	Evidence supporting the treatment[a]
Plasmapheresis (PP)[b]	Decrease the titer and block the effect of DSA	Low, benefit not consistently demonstrated
Immunoadsorption (column)	Decrease the titer of DSA	Low, seems beneficial
IVIG	Decrease the titer and block the effect of DSA	Very low
Bortezomib	Decrease production of DSA	Very low
Corticosteroids	Decrease inflammation caused by DSA in graft and decrease production of DSA, suppression of T cells	Very low
Anti-thymocyte preparations	Reduce production of DSA by decreasing Helper T cells, suppression of T cells	Very low
Eculizumab	Block complement activation resulting from DSA activation	Very low
Mycophenolate	Block the effect and decrease production of DSA, suppression of T cells	Very low
Rituximab	Decrease production of DSA	Very low
Cyclophosphamide	Decrease production of DSA	Very low
Deoxyspergualin	Decrease production of DSA, suppression of T cells	Very low
Splenectomy	Decrease production of DSA	Very low
Tacrolimus	Decrease production of DSA, Suppression of T cells	Very low

Key points for the non-TPE specialists

The organization of the TPE service differs between institutions. In many hospitals, specialist apheresis physicians and nurses provide TPE for ICU patients in close collaboration with intensivists. Since critically ill patients are highly vulnerable and at risk of hemodynamic instability, electrolyte disturbances, and coagulation disorders, close monitoring is needed during TPE. The choice of intravenous access (peripheral or central) should be carefully reviewed. TPE can be performed in the outpatient and inpatient setting. The decision regarding ICU admission rests on the clinical status and not on the need for TPE

The decision to initiate TPE should be based on the rationale that there is a presence of a substance causing a potentially life-threatening disruption that can be removed by TPE or the need for replacing a deficient substance to improve clinical outcomes. It should be evidence-based whenever possible although appropriate trials are lacking in most settings

The following tests must be performed before TPE: ABO Rh blood group and, if appropriate, an RBC antibody screen (in case plasma or RBC priming is needed); ionized calcium, magnesium, and potassium (which may be affected by citrate anticoagulation); complete blood cell count (to determine device settings and to exclude significant cytopenia that may require correction); and coagulation tests (activated partial thromboplastin time, partial thromboplastin time, prothrombin time, and fibrinogen)

The changes in hemostasis and coagulation tests induced by TPE must be considered when interpreting test results and making clinical decisions. For example, instituting oral anticoagulation regimens should be avoided during a string of TPE sessions, since dosing can be challenging given the removal of coagulation factors, combined with the potential addition of coagulation factors (in case of replacement with plasma)

Aside coagulation tests, TPE alters most laboratory variables, including serological tests, and inflammatory markers. Therefore, sample collection must be timed accordingly. Furthermore, circulating biomarkers such as troponin, brain natriuretic peptide, CRP, and LDH are no longer reliable for assessing the disease course

Ideally, repeated TPE requires therapeutic drug monitoring for antibiotics, anticoagulants, and several medications

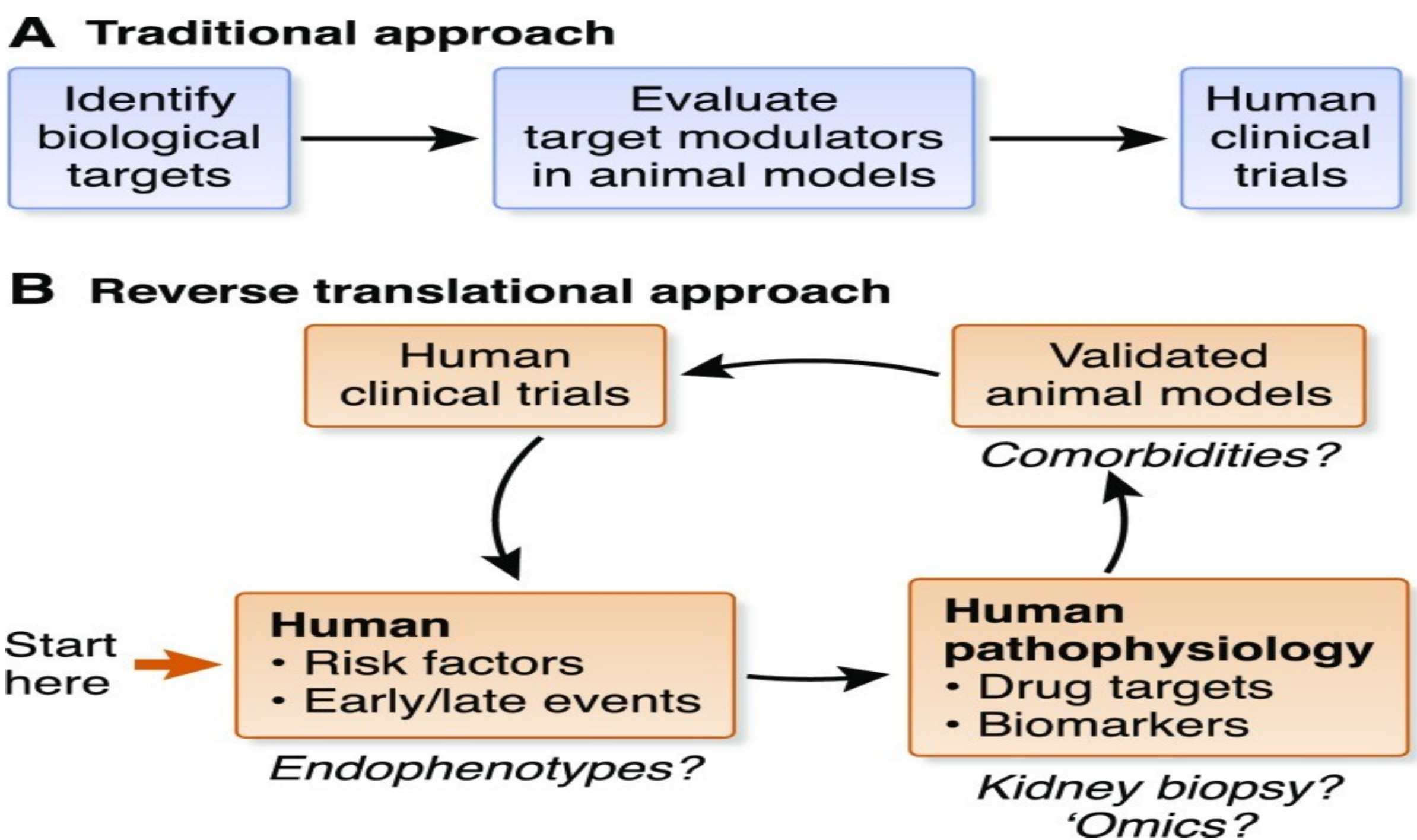
More is not necessarily better. Standard TPE replaces 1.0 to 1.5 times the TPV. Given removal kinetics, replacing two or three times more does not result in a two- or threefold increase in efficacy

In patients who also require renal replacement therapy (RRT), TPE should be performed first unless there are potentially life-threatening electrolyte disturbances mandating urgent RRT. The volume of replacement fluid given during TPE can be removed during RRT. In addition, fluid shifts that occur following RRT may result in hypotension when blood enters the extracorporeal circuit of the apheresis device during the TPE requiring fluid resuscitation which negates the benefit of volume removal during RRT. Tandem procedures combining TPE and RRT can also be performed in experienced centers

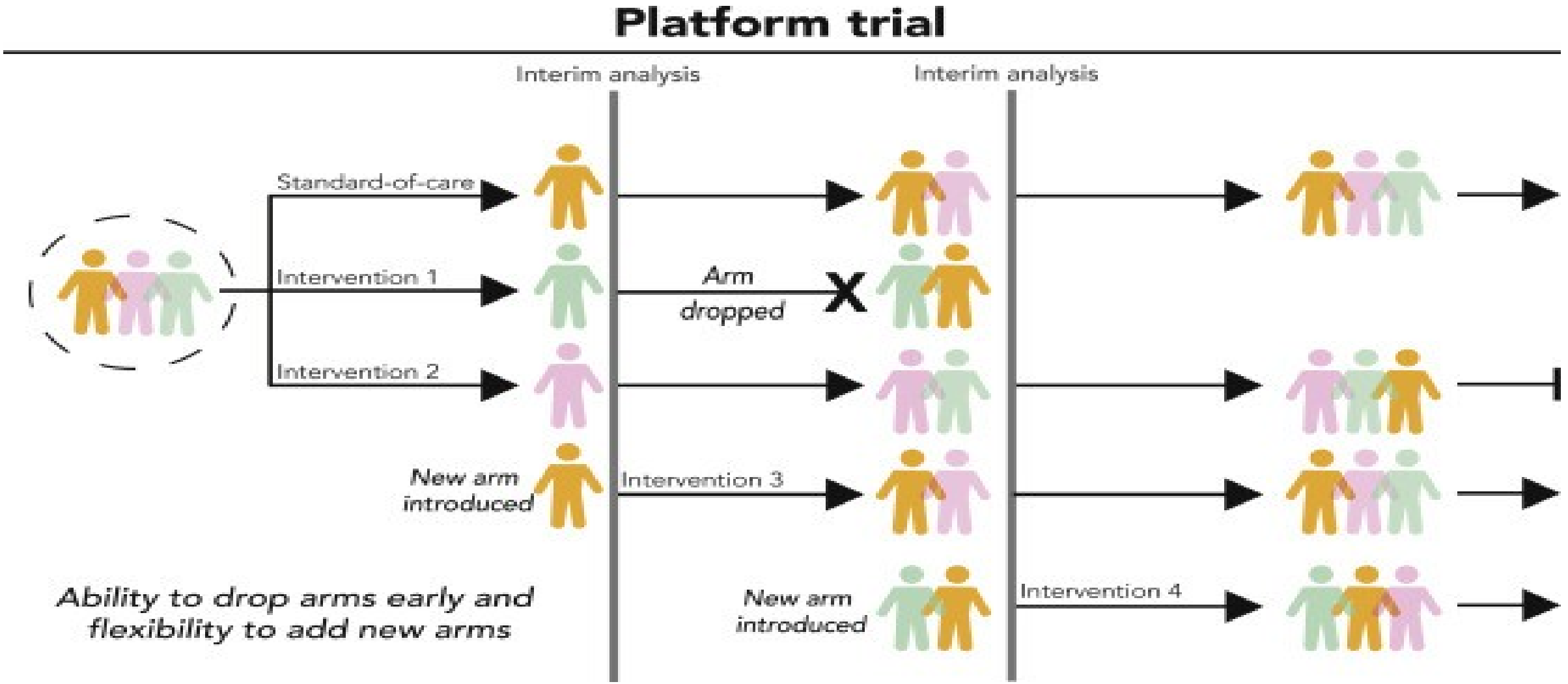
TPE involves replacement with colloids whose oncotic pressure is like the removed plasma. Therefore, in patients with volume overload before TPE, any decrease in the replacement fluid volume will decrease the intravascular volume and potentially cause hypotension. In contrast to dialysis, TPE cannot remove free water, which would lead to hemoconcentration and fluid shifts from the extravascular to the intravascular compartment

TPE has the potential to remove medications and there is limited pharmacokinetic data available. Practical recommendations to address this potential adverse effect include: once daily medications should be administered after TPE, not before; administration of IV medications should be avoided immediately prior to and during TPE; oral medications should be avoided within four hours prior to TPE to allow for adsorption and redistribution prior to the start of the TPE; chimeric antibodies, monoclonal antibodies, and IVIG are effectively removed and timing of administration of these agents and TPE must be coordinated to allow for maximum medication dwell time

In some clinical situations (e.g., Guillain–Barré syndrome), TPE and intravenous immunoglobulins (IVIG) have equivalent efficacy. Combining the two in these scenarios is not recommended and TPE may be reserved in case of failure to IVIG


A Traditional approach
Identify biological targets
Evaluate target modulators in animal models
Human clinical trials
B Reverse translational approach
Human clinical trials
Validated animal models
Comorbidities?
Start here
Human
• Risk factors
• Early/late events
Endophenotypes?
Human pathophysiology
• Drug targets
• Biomarkers
Kidney biopsy?
'Omics?

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



Tecniche depurative speciali: aferesi, emoadsorbimento, quali indicazioni nel 2022 (2023)

Vincenzo Cantaluppi

SCDU Nefrologia e Trapianto Renale
Direttore Scuola di Specializzazione in Nefrologia
Dipartimento di Medicina Traslazionale (DIMET)
Università del Piemonte Orientale (UPO)
Responsabile Progetto Trapianti
AOU Maggiore della Carità di Novara

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