Dipartimento gravi insufficienze
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Bologna - ITALY

Tecniche di depurazione extracorporea nel paziente settico

Antonio Santoro, MD,FERA

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

- **Consensus Definitions:**

– Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection

– Septic shock: Sepsis with circulatory and cellular/metabolic abnormalities profound enough to substantially increase mortality

- **Clinical Criteria:**

– Sepsis: Suspected or documented infection and an acute increase of ≥ 2 SOFA points (a proxy for organ dysfunction)

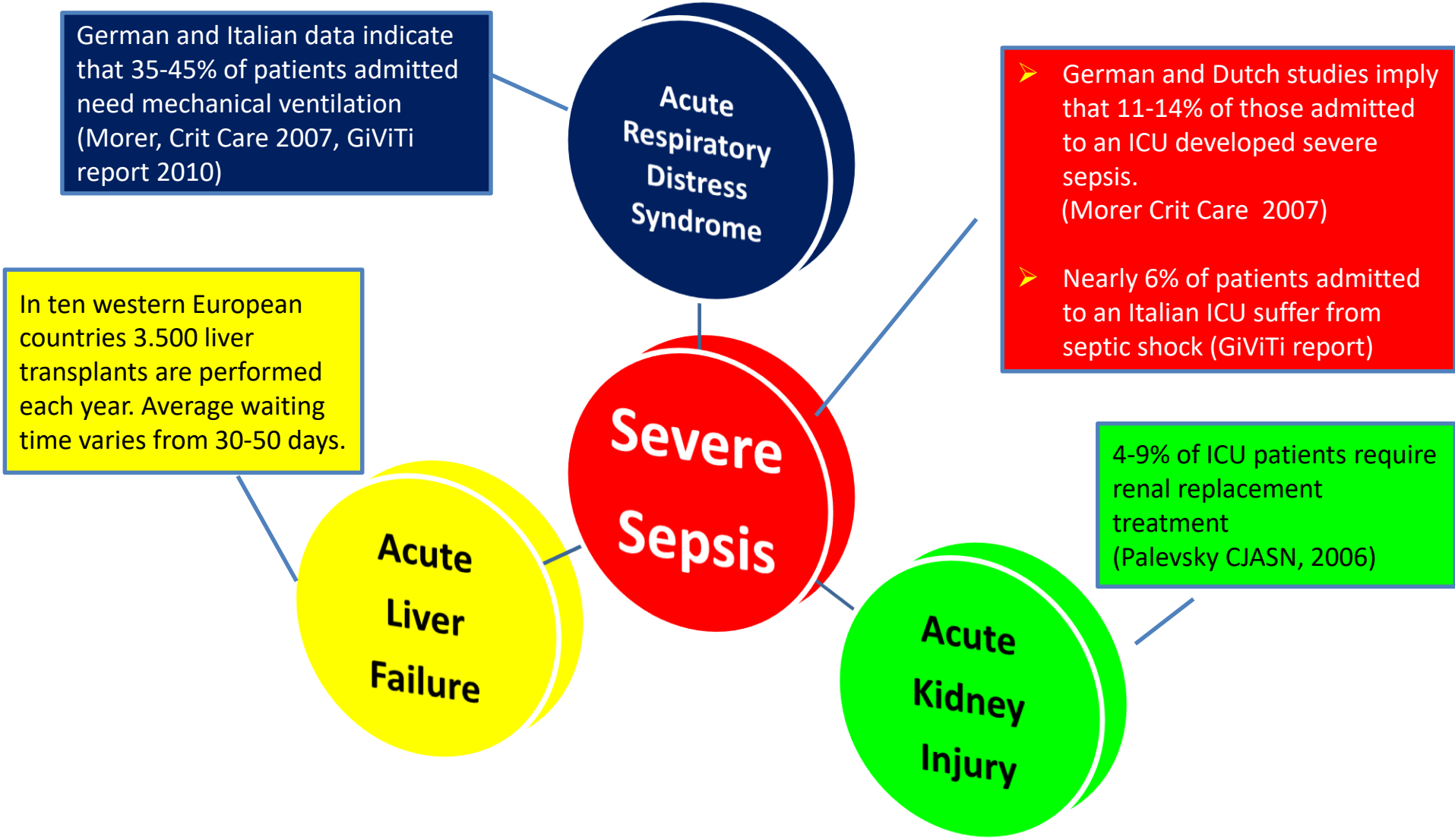
– Septic Shock: Sepsis and vasopressor therapy needed to elevate MAP ≥65 mmg Hg and lactate > 2 mmol/L (18 mg/dL) after adequate fluid resuscitation

Singer M et al, JAMA 2016; 315: 801-810

Sepsis – Organ dysfunction

- Circulatory failure: ↓organ perfusion; metabolic acidosis
- Kidney failure: overhydration; uremic intoxication
- ALI / ARDS: ↓oxygen supply; respiratory acidosis
- Liver failure: hepatic coma; ↓ protein synthesis
- BM depression: platelet / leukocyte loss or dysfunction
- CNS dysfunction: coma

Incidence of severe clinical complications (non CV) and sepsis in ICU

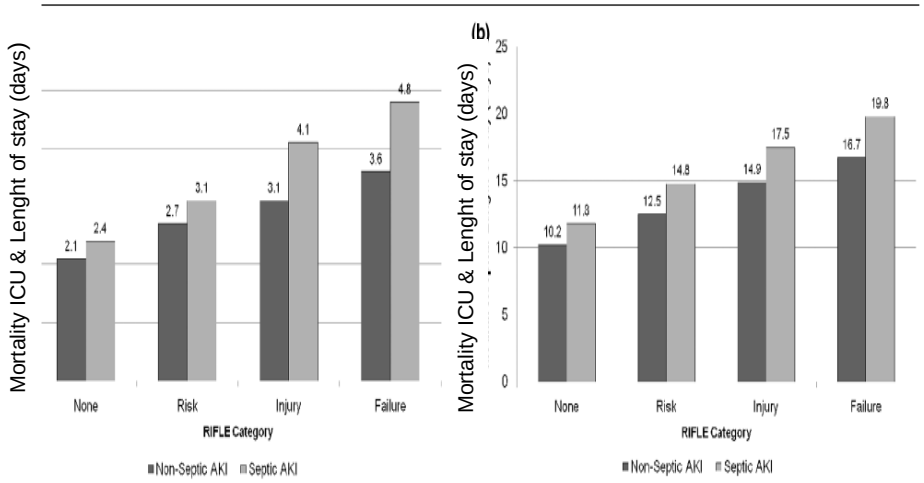


Early acute kidney injury and sepsis: a multi-centre evaluation

Sean M Bagshaw *et al* for the ANZICS Database Management Committee

Total ICU patients - 120,123

- Patients with sepsis - 33,375 (27.8%).
- Patients with septic AKI - 14,039 (42.1%)



ICU and hospital length of stay. **(a)** Intensive care unit (ICU) length of stay for acute kidney injury (AKI) patients stratified by sepsis and RIFLE category. For each comparison of nonseptic versus septic AKI, $P < 0.0001$. **(b)** Hospital length of stay for AKI patients stratified by sepsis and RIFLE category. For each comparison of nonseptic versus septic AKI, $P < 0.0001$. RIFLE, risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function and end-stage kidney disease.

Stratification by RIFLE

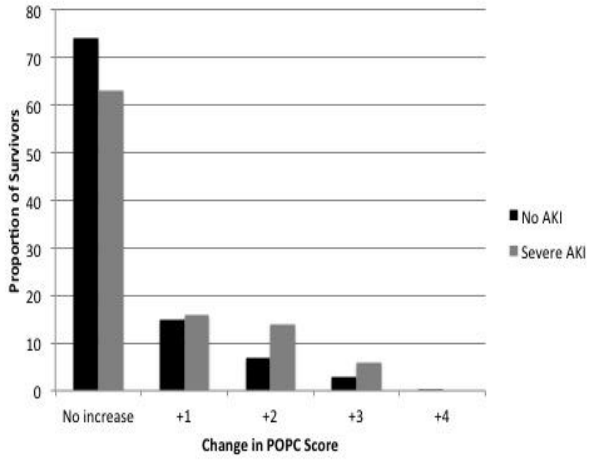
- Risk Category - 38.5%
- Injury Category - 38.8%
  Failure Category-22.7%

493 patients enrolled in the SPROUT study with severe sepsis had AKI
21% had severe AKI

Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study

Crit Care Med. 2016 Aug 10.

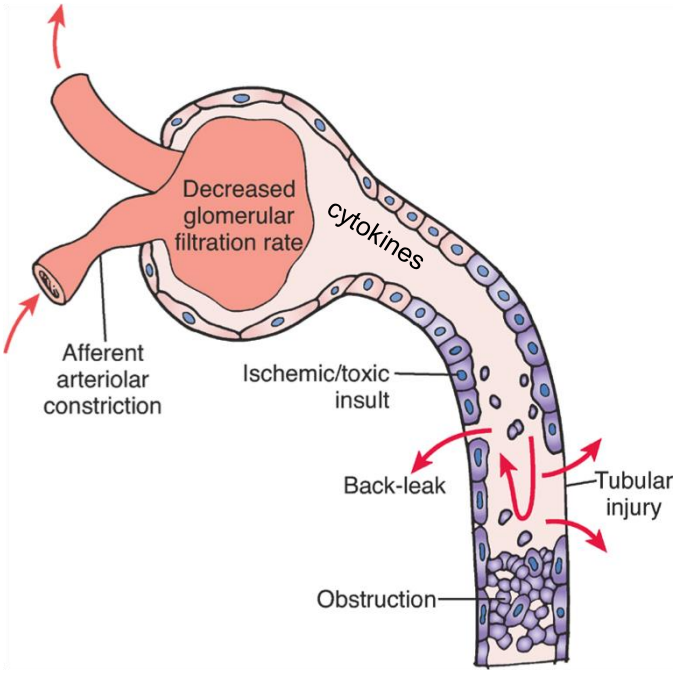
Acute Kidney Injury in Pediatric Severe Sepsis: An Independent Risk Factor for Death and New Disability



Patient Outcomes

Outcome Measure	No AKI/Stage 1 AKI (n=391)	Stage 2-3 AKI (n=102)	p-value
Death or moderate disability, n (%)	119 (30)	65 (64)	<0.001
Hospital mortality, n (%)	70 (18)	53 (52)	<0.001
PICU mortality, n (%)	66 (17)	51 (50)	<0.001
Hospital LOS (days), median (IQR)	25 (12, 51)	27 (15, 51)	0.767
PICU LOS (days), median (IQR)	14 (6, 32)	18 (10, 32)	0.105
Vasoactive-free days, median (IQR)	25 (19, 28)	20.5 (11, 24)	<0.001
Ventilator-free days, median (IQR)	20 (2, 26)	14.5 (0, 21)	0.0013

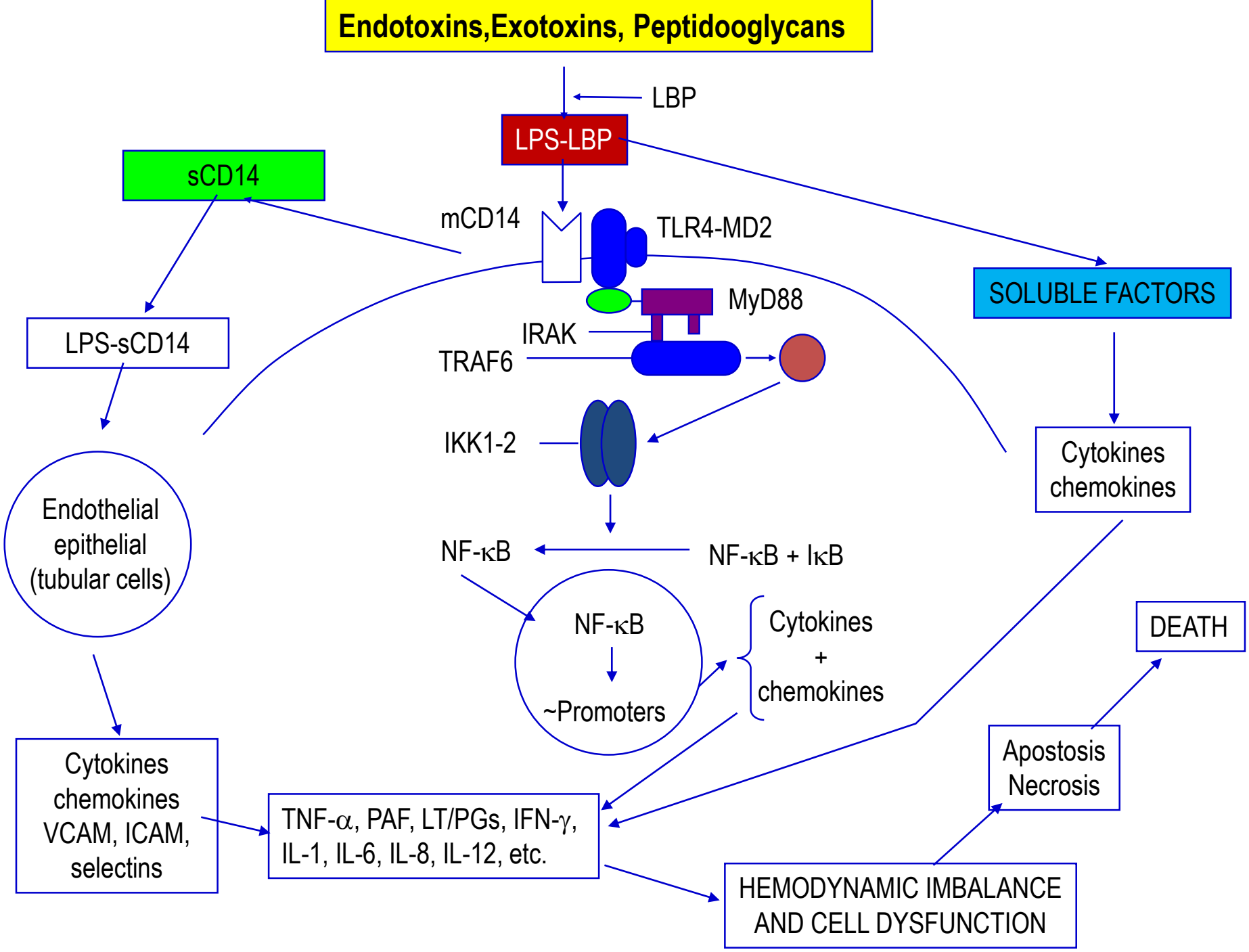
Julie C. Fitzgerald, Rajit K. Basu, Akash Deep, for the Sepsis PRevalence, OUtcomes, and Therapies Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators Network



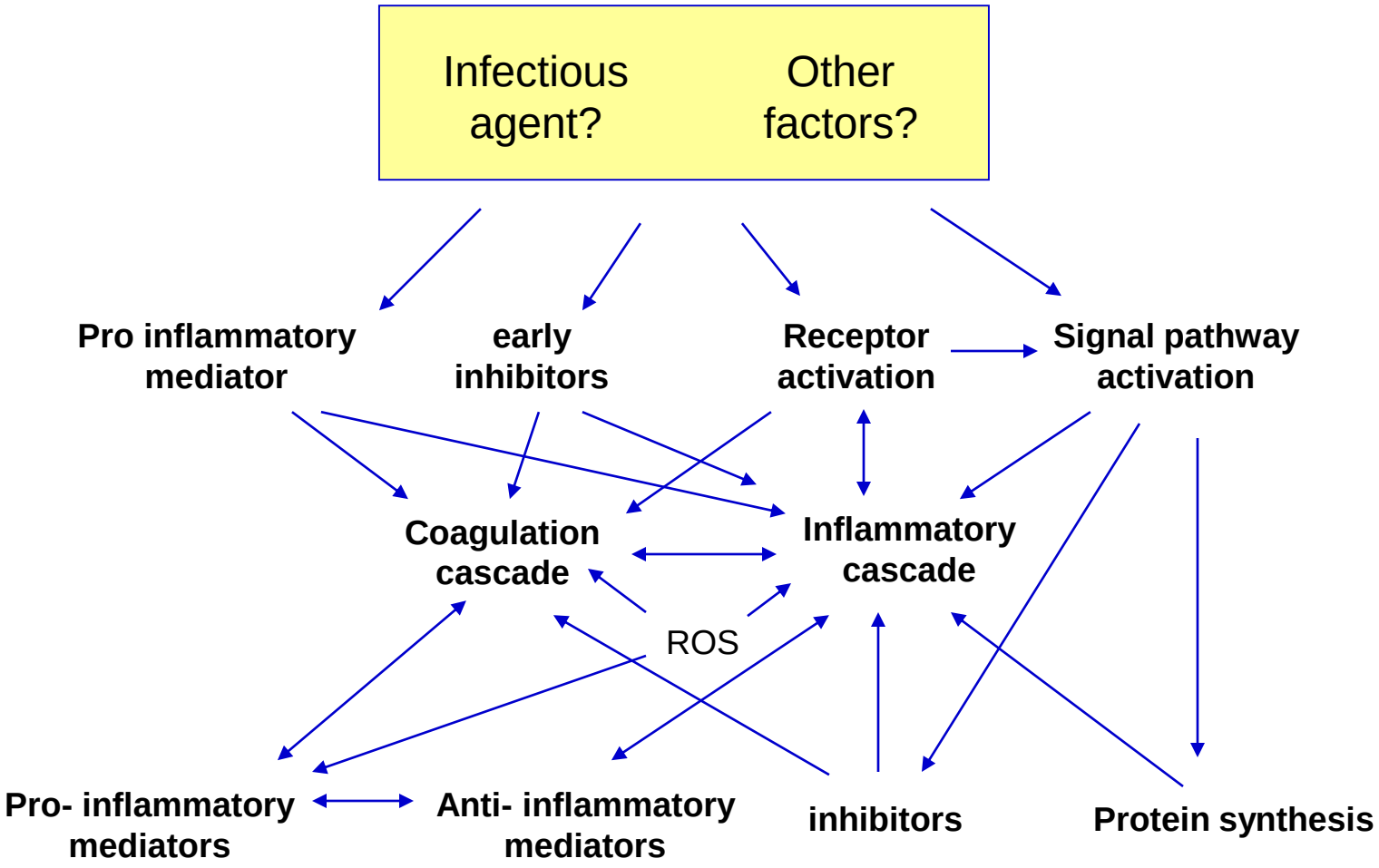
- The Heterogeneous distribution of renal blood flow induced by the microcirculatory dysfunction probably causes patchy tubular cell injury during sepsis-induced AKI, whereas hypoxia and hypoperfusion may amplify inflammation and contributes to an adaptive response of tubular epitelial cells

- Pro-inflammatory cytokines released during sepsis are filtered in the glomerulus, entered the proximal tubulus and can directly activate tubular epithelial cells resulting in a change of the metabolic and functional state of these cells.

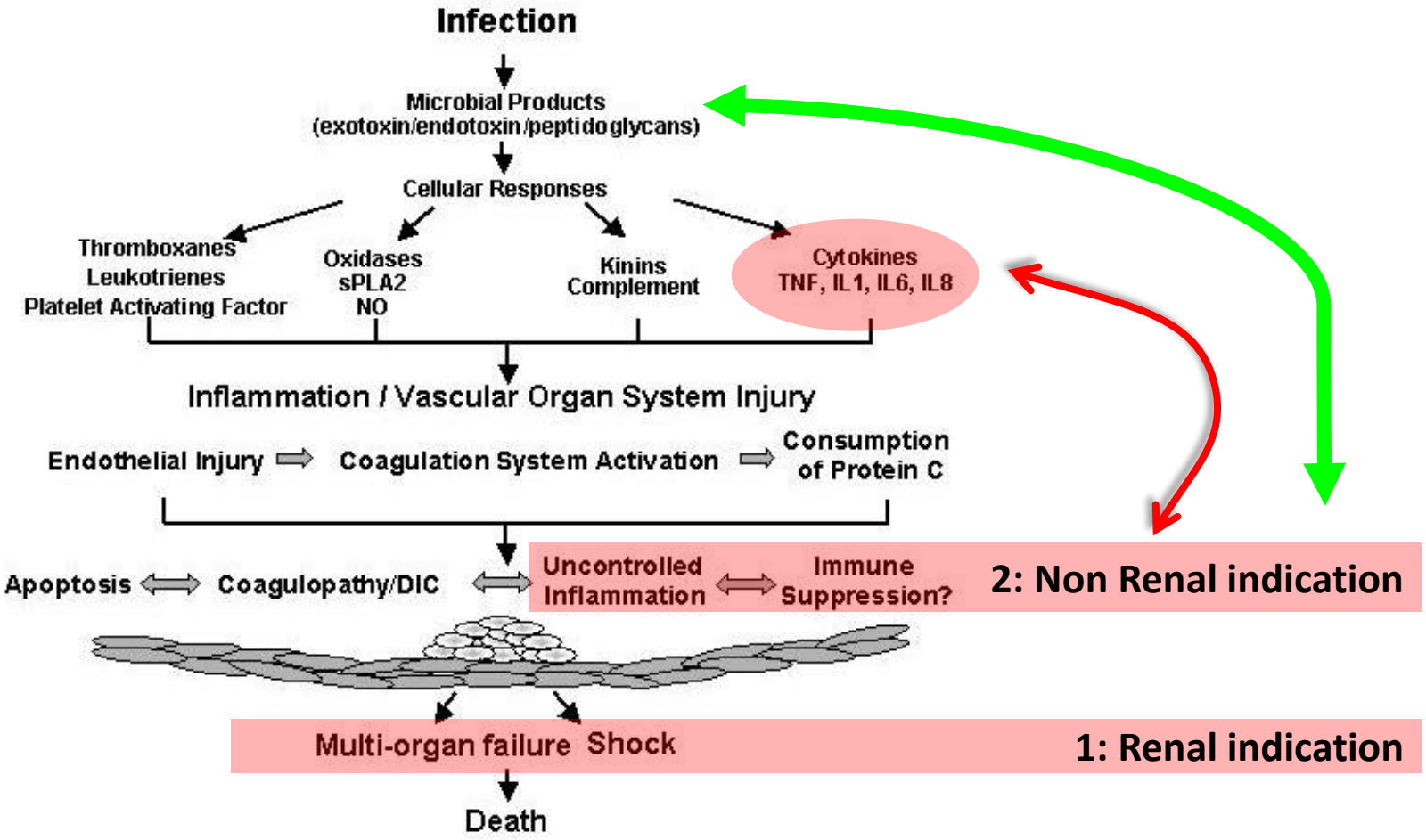
- G1 cell cycle arrest of tubular epithelial cells may occur


Endotoxins,Exotoxins, Peptidooglycans
LBP
LPS-LBP
sCD14
mCD14
TLR4-MD2
MyD88
IRAK
TRAF6
SOLUBLE FACTORS
LPS-sCD14
IKK1-2
Cytokines
chemokines
Endothelial
epithelial
(tubular cells)
NF-κB
NF-κB + Iκ B
NF-κB
~Promoters
Cytokines
+
chemokines
DEATH
Apostosis
Necrosis
Cytokines
chemokines
VCAM, ICAM,
selectins
TNF-α, PAF, LT/PGs, IFN-γ,
IL-1, IL-6, IL-8, IL-12, etc.
HEMODYNAMIC IMBALANCE
AND CELL DYSFUNCTION

Sepsis is very complex!



Rationale for extracorporeal therapies in sepsis

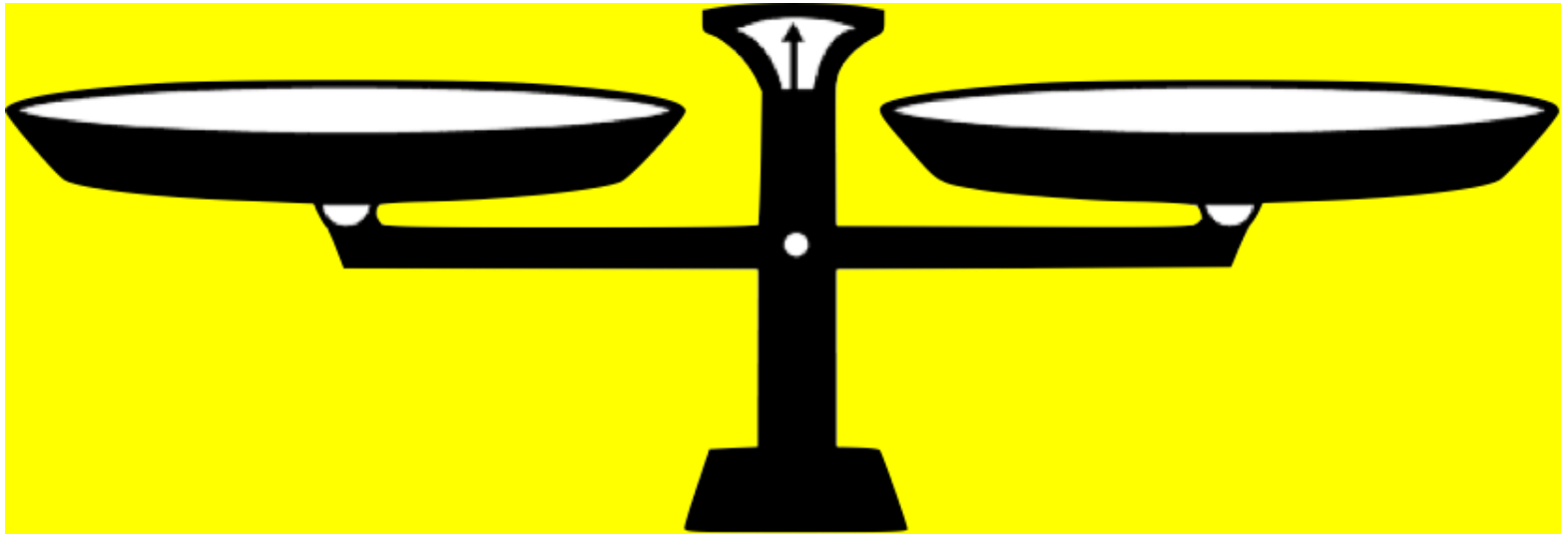


Lee A O'Brien, Frontiers in Bioscience, 2006, 11, 676-98

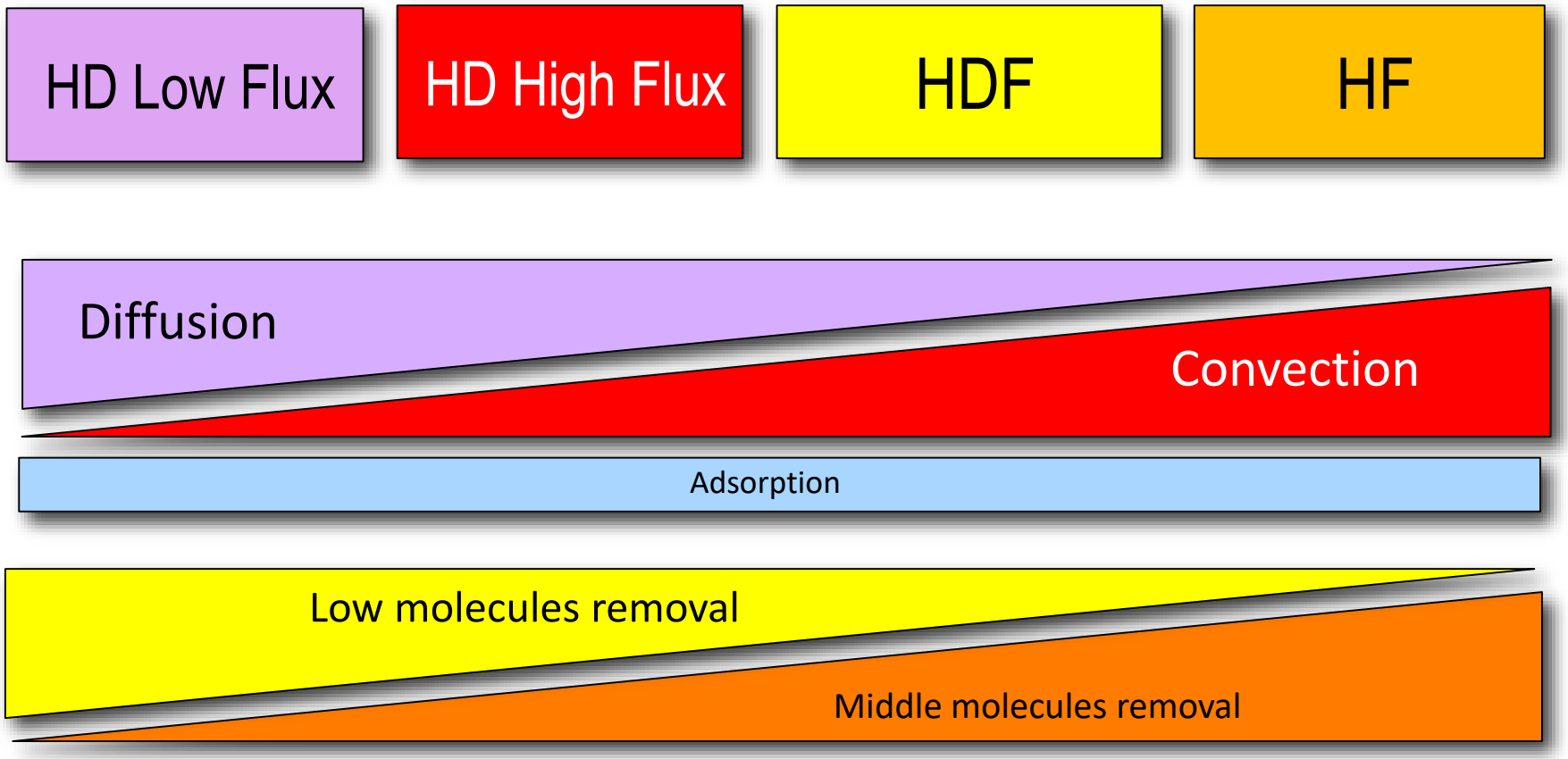
Extracoporeal Therapies

Restores physiology

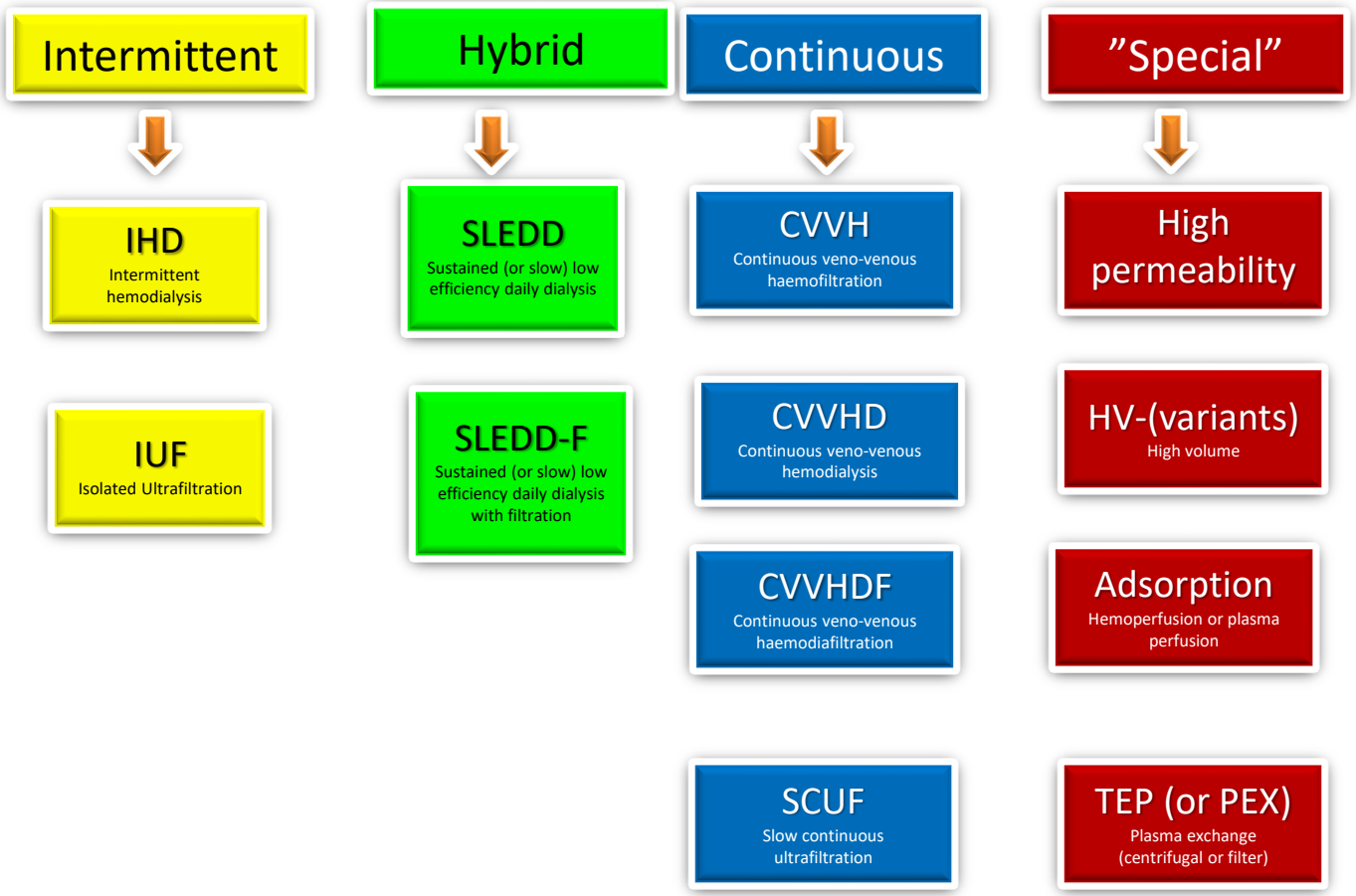
remove toxins
decrease fluid overload
restore electrolyte balance



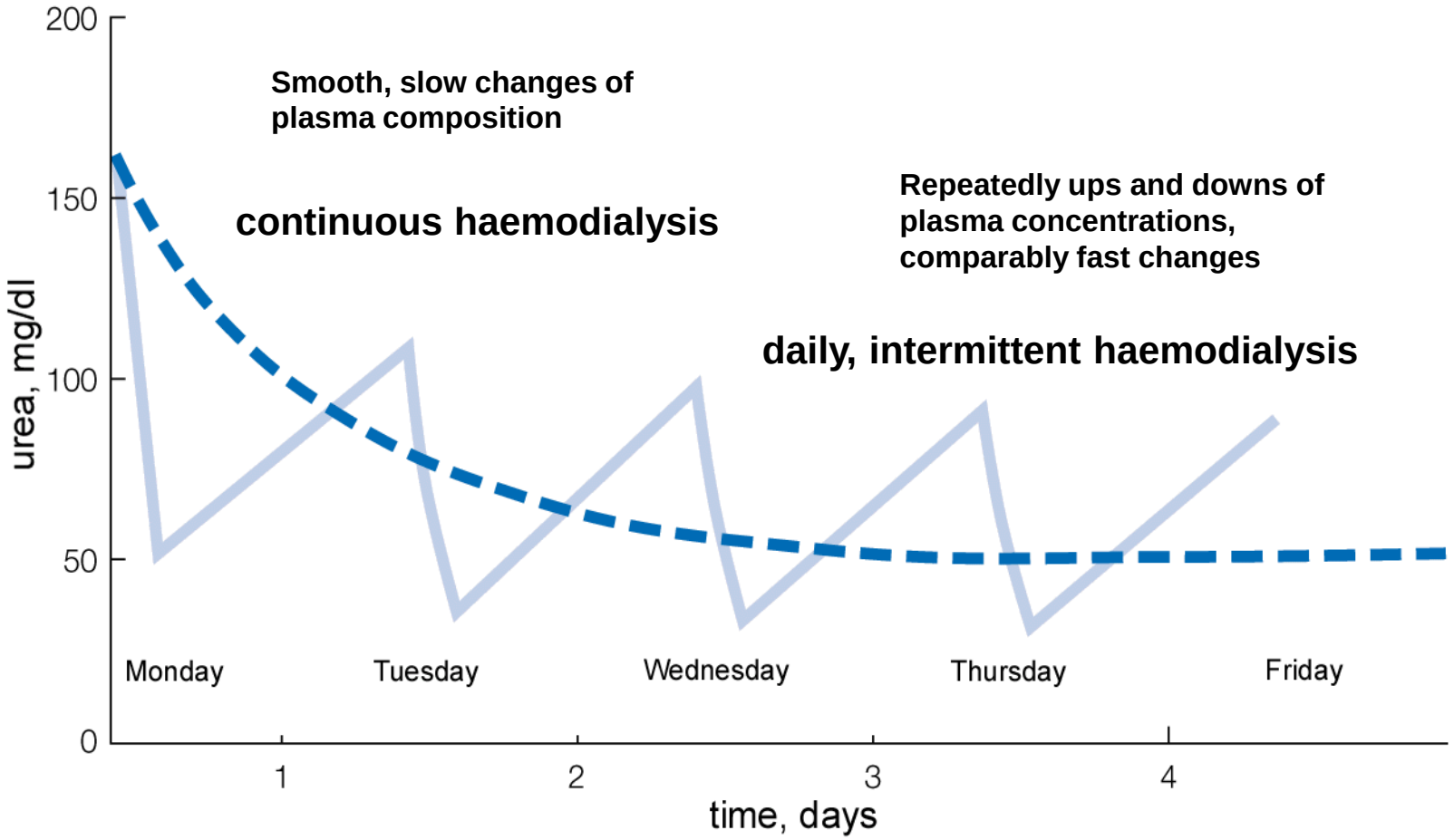
Renal replacement therapy options: impact on solute clearances

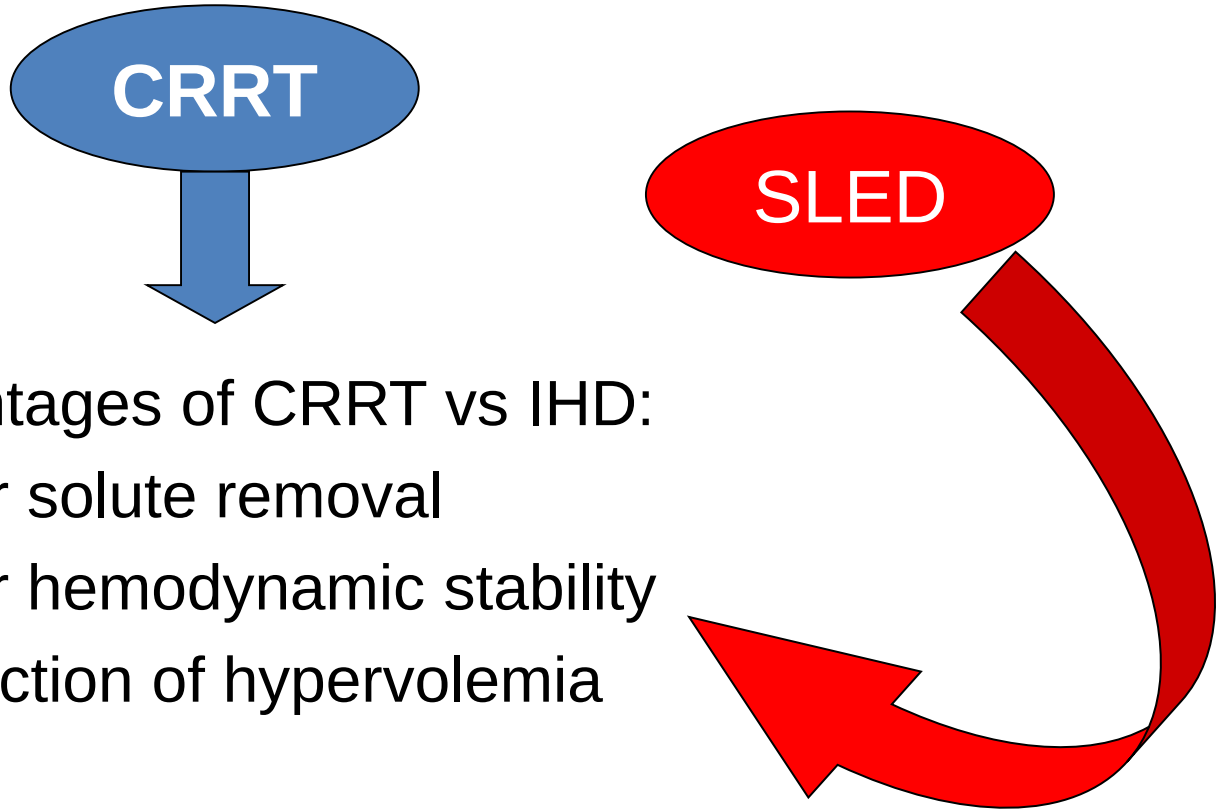


Types of acute RRT



The „saw tooth profile“ with intermittent haemodialysis

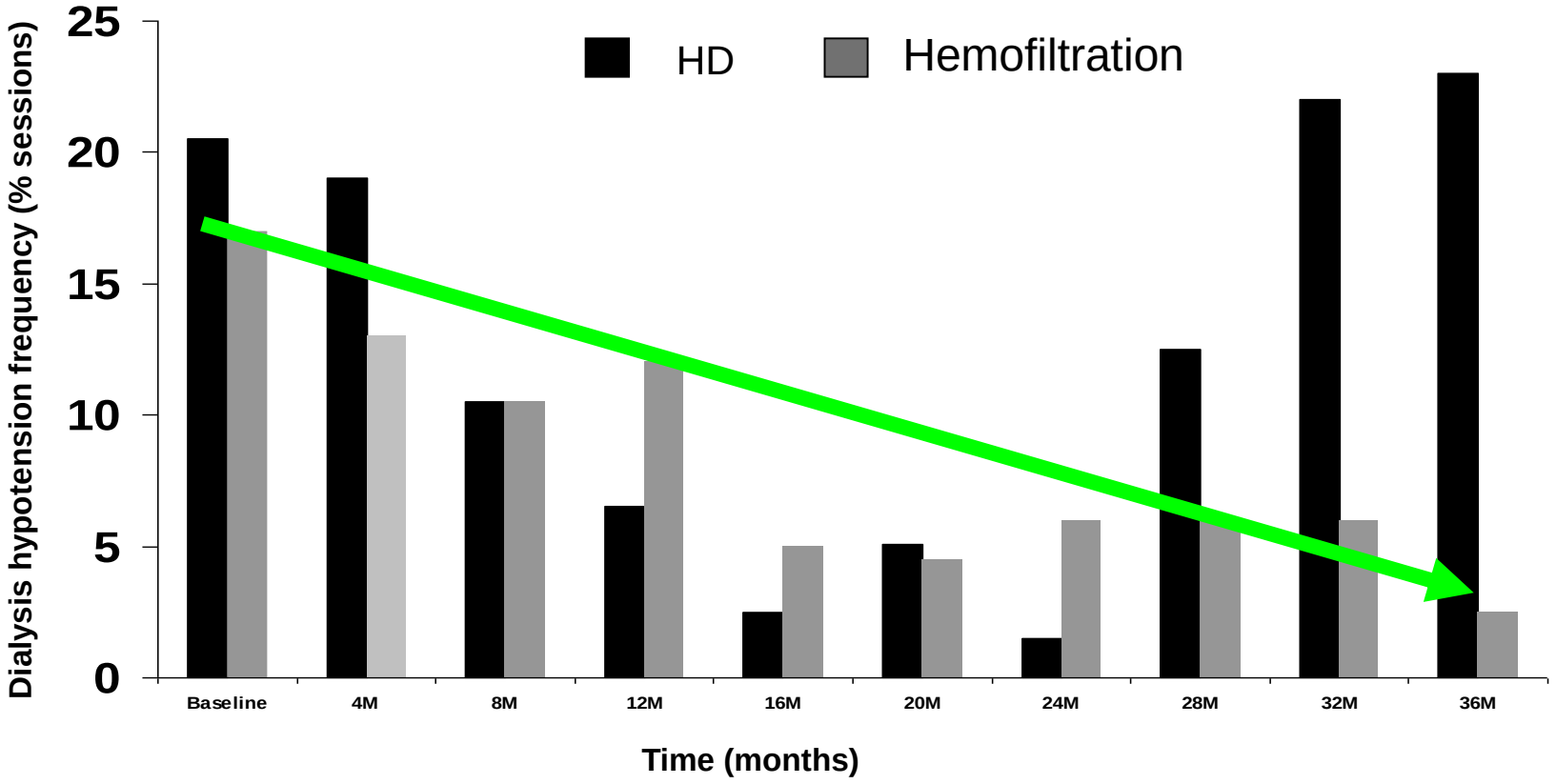




Real advantages of CRRT vs IHD:

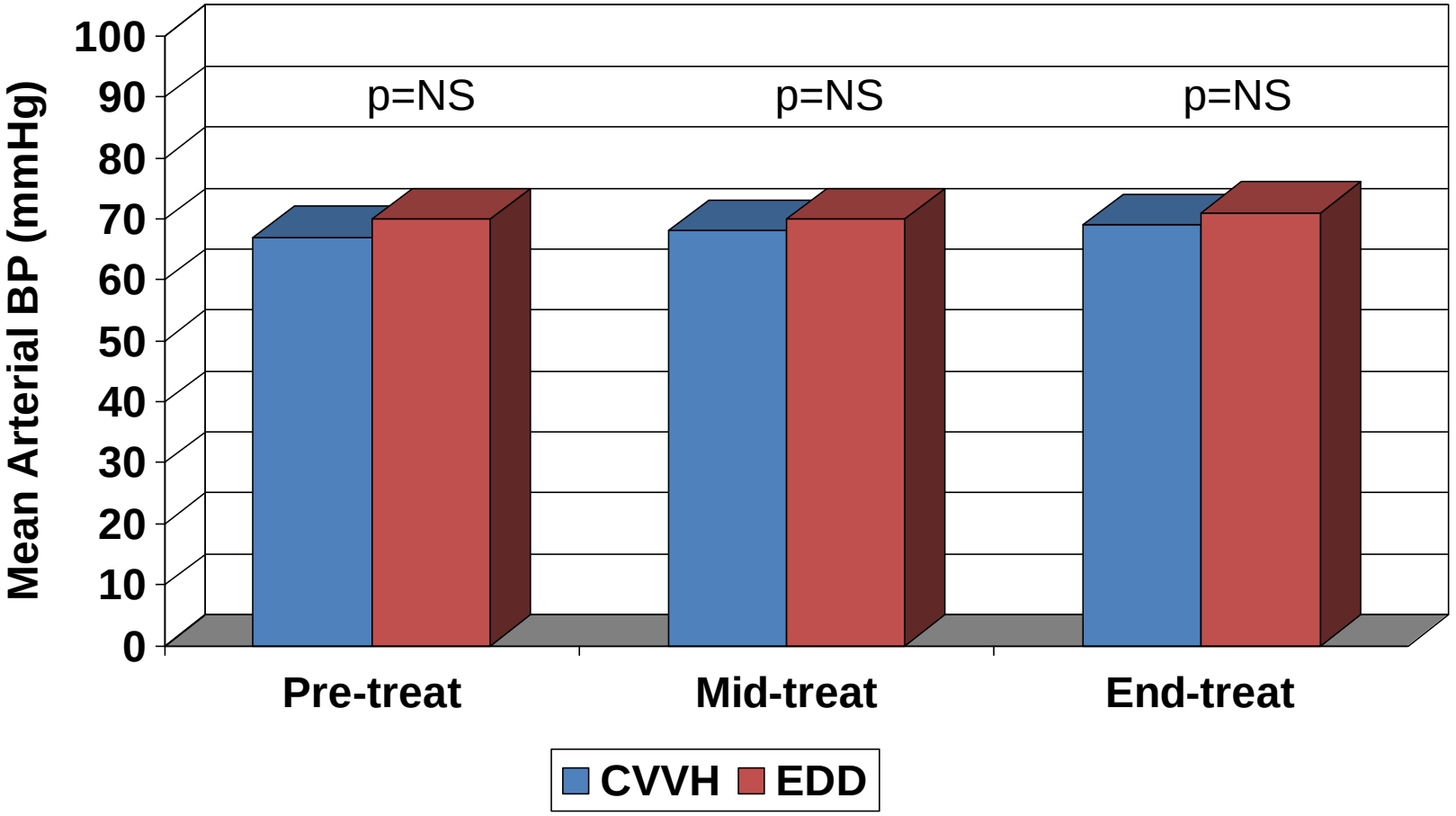
- Better solute removal
- Better hemodynamic stability
- Correction of hypervolemia

Frequency of dialysis hypotension during the trial in patients completing the study



Santoro A. et al. *Am J Kidney Dis 2008;*52:507-518

Comparison of MAP during EDD versus CVVH



Kumar, Am J K Dis 2000;36:294-300

Inotropic support during treatments

	Hypotension Episodes (n.)	Inotropes/ vasoconstrictors (n. of treatment)	Inotropes/ vasoconstrictors (%)
EDD	358	220	59.9%
CVVH	165	79	69.9%

Kumar, Am J K Dis 2000;36:294-300

	CRRT	SLED	IHD
Treatment week	7 days	5-6 days	3-5 sessions
Hours/day	24 hrs	6-12 hrs	4 hrs
Blood flow ml/min	100-200	150-250	300-400
Dialysate flow ml/min	20-30	300-350	500-800
Anticoagulation	Heparin or citrate	Heparin or cytrate or notting	Heparin or notting
Hemodynamic stability	+++-	++--	+---
Mobilization	Absent	Possible	Possible

Treatment parameters in convective therapies

For convection : Q_{UF} S

For ultrafiltration : Q_B TMP K_{UF}

For infusion : Q_{UF} Q_{WL}

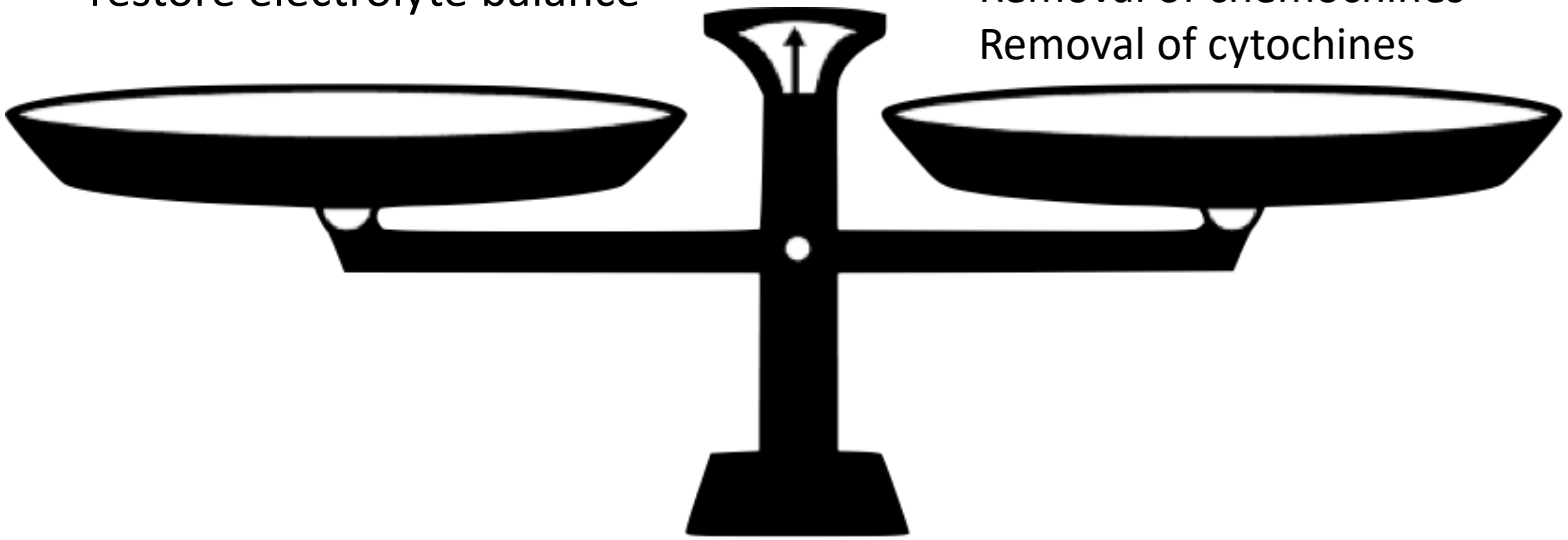
Extracoporeal Therapies

Restores physiology

remove toxins
decrease fluid overload
restore electrolyte balance

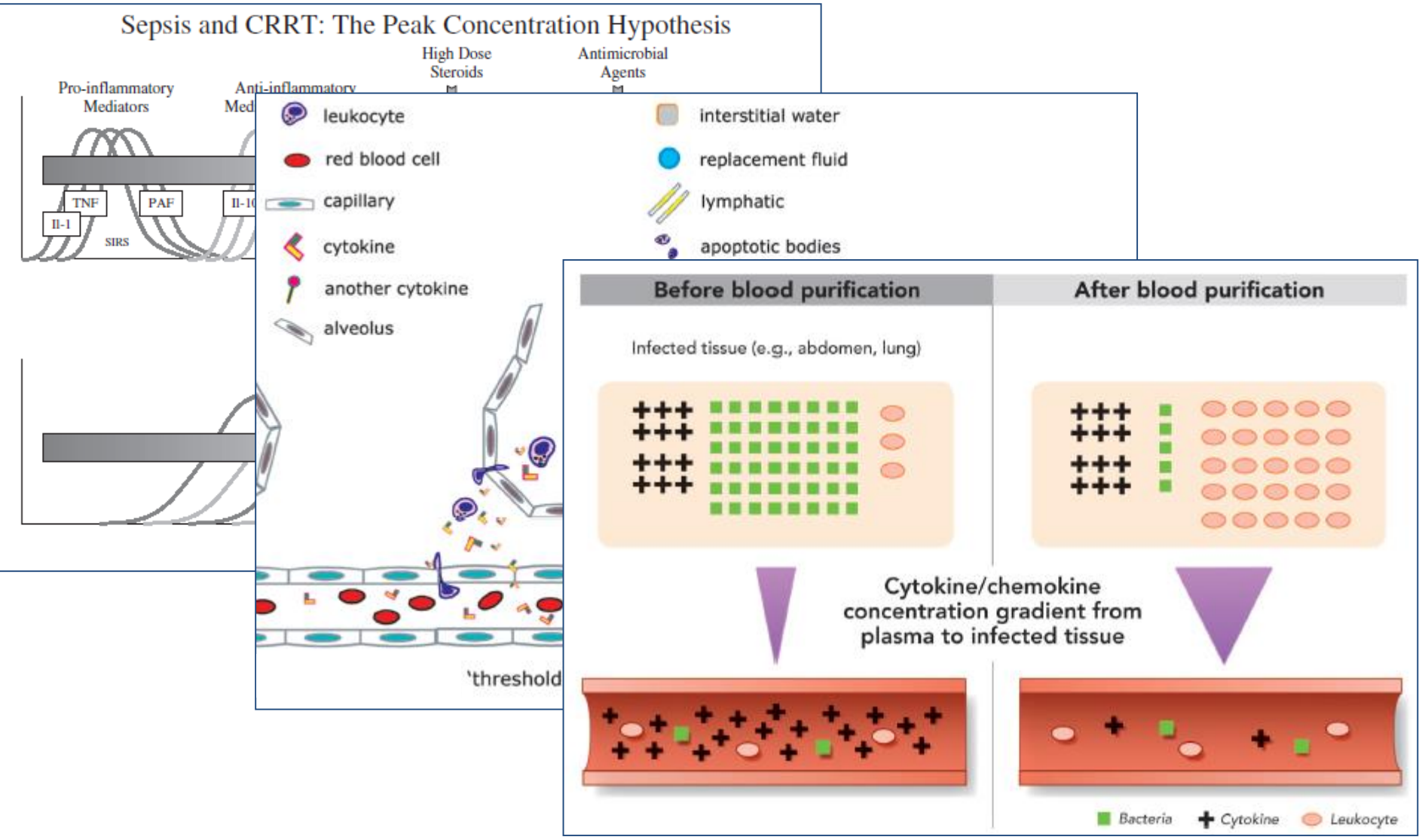
Contributes to resolve inflammation

Removal of endotoxins
Removal of chemochines
Removal of cytochines



Blood Purification for Systemic Inflammation

«...from Cytotoxic Model to Cytokinetic model»



Intensive Care Med (1999) 25: 903–910

REVIEW

A. S. De Vriese
R. C. Vanholder
M. Pascual
N. H. Lameire
F. A. Colardyn

Can inflammatory cytokines be removed efficiently by continuous renal replacement therapies?

Table 1 Clinical studies on mediator removal with CRRT

Author [Ref]	Study Population	Treatment	Membrane	Q_B[a] ml/m	Q_D[a] l/h	UFR[b] l/h	Mediator	Assay	UF[b]	PC[c]
Gotloib [29]	24 sepsis, ARDS	CAVH	CU	300			TXB_2	RIA[d]	+	
Cosimi [30]	36 respiratory failure post cardiac surgery	CAVH	PS			0.85	Myocardial Depressant Factor	Bioassay	+	+
Staubach [31]	15 shock	CAVH	PA				6-keto$PGF_1\alpha$ TXB_2	RIA	+ +	
McDonald [32]	12 sepsis, acute renal failure	CAVHD	AN69	116		0.6	TNFα TNFα IL-1β	Bioassay EIA[e] RIA	+ – +	– – –
Kierdorf [33]	10 MOF	CVVH	AN69			1.2	TNFα	EIA	+	–
Cotrell [34]	5 sepsis, acute renal failure	CVVHD	AN69				TNFα	Bioassay + IRMA[f]	+	
Byrick [35]	1 MOF, ARF	CAVHD	PS		2	0	TNFα	RIA	–	–
Tomasson [36]	9 septic shock, acute renal failure	CAVH	PS			0.4–0.75	TNFα IL-1β, IL-6	EIA EIA	+ +	– –
Bellomo [37]	18 sepsis, acute renal failure	CVVHD	AN69	150	1		TNFα IL-1β	Bioassay EIA	+ +	– –
Andreasson [38]	9 cardiopulmonary bypass	HF[a]	PA				C3a C5a TCC[g]	RIA RIA EIA	+ +	– + –
Millar [39]	18 cardiopulmonary bypass	9 HF 9 no HF	PA				TNFα IL-6, IL-8	Bioassay EIA	+ +	+ –
Journois [40]	32 cardiopulmonary bypass	16 HF 16 no HF	PS				TNFα, IL-6 IL-8 C3a, C5a	EIA EIA RIA		+ – +
Gueugniaud [41]	4 burns, sepsis, acute renal failure	CVVHD					TNFα IL-1β, IL-2R IL-6	EIA EIA EIA	– + +	– – +
Elliott [42]	77	CAVHD/ CVVHD			0.9	0.56	TNFα IL-1β		+ +	
Bellomo [43]	10 sepsis, ARF	CVVHD	AN69	150	1		IL-6 IL-8	EIA EIA	+ +	– –
Styrus [44]	20 sepsis, acute renal failure	CVVH					TNFα IL-6	EIA EIA	+ +	– –
Hoffmann [45]	16 MOF	CVVH	PA	150		2	TNFα, IL-6 IL-1β, IL-8, C5a, C3 C3a TCC	Bioassay EIA EIA EIA	– + + –	– – + –
Braun [46]	30 SIRS	15 CVVHD 15 conservative	PA/ AN69	100–120			TNFα, C3a IL-6, TCC	EIA EIA		– +
Boldt [47]	14 SIRS, acute renal failure	CVVH	PS	120–150			sELAM-1, sICAM-1 sVCAM-1, sGMP-140	EIA EIA EIA EIA		– – – –
Wakabayashi [48]	6 SIRS	CVVH					IL-6 IL-8			+ +
Gasche [49]	7 critically ill, acute renal failure	CVVH	AN69 PA	250 250		1–1.5 1–1.5	Factor D Factor D		–/+	+ –
Journois [50]	20 cardiopulmonary bypass	10 ZHVHF +HF[h] 10 HF	AN69	200[i]			TNFα, IL-1β, IL-6, IL-8 IL-10, C3a	EIA EIA EIA		+ + +
Heering [51]	33 acute renal failure (septic/ cardiovascular)	CVVH	PS	150–200		1	TNF-α, IL-1β, IL-6, IL-8 IL-2, IL-10 TNF-RI1, IL-1rn IL-2R, IL-6R	EIA EIA EIA	+ + +	– – –

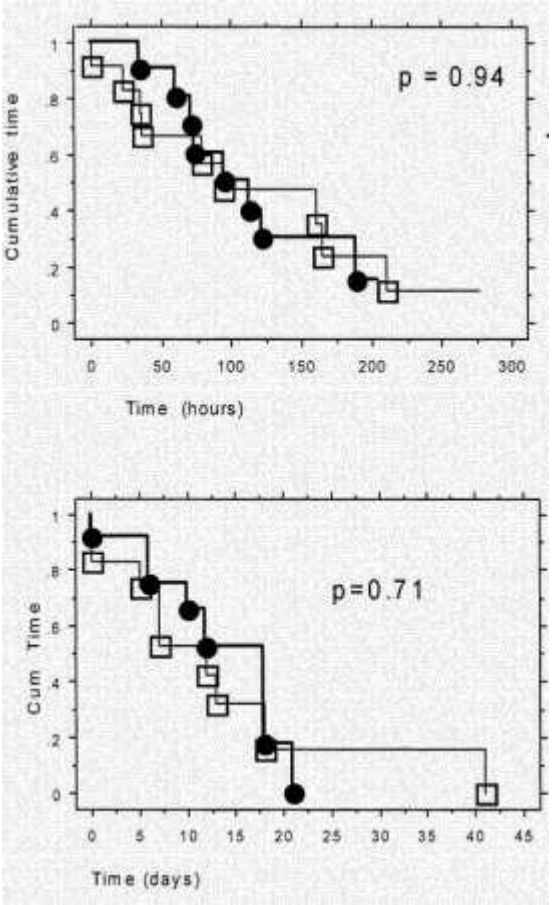
- Several (small) studies
- Contradictory results
- Several studies report a certain amount of cytokine clearance via convection / diffusion, but:

overall **no** significant lowering of plasma levels

A phase II randomized, controlled trial of continuous hemofiltration in sepsis

Louise Cole, MBBS, FFICANZCA; Rinaldo Bellomo, MBBS, MD, FRACP; Graeme Hart, MD, FFICANZCA; Didier Journois, MD, PhD; Piers Davenport, BSc; Peter Tipping, MBBS, PhD; Claudio Ronco, MD

- 24 Pat. with septic shock
- Prospective, randomised:
  48 h CVVH with 2 L/h vs. no CVVH
- Result: no difference regarding circulating cytokines and complement factors; no improvement of organ function with CVVH

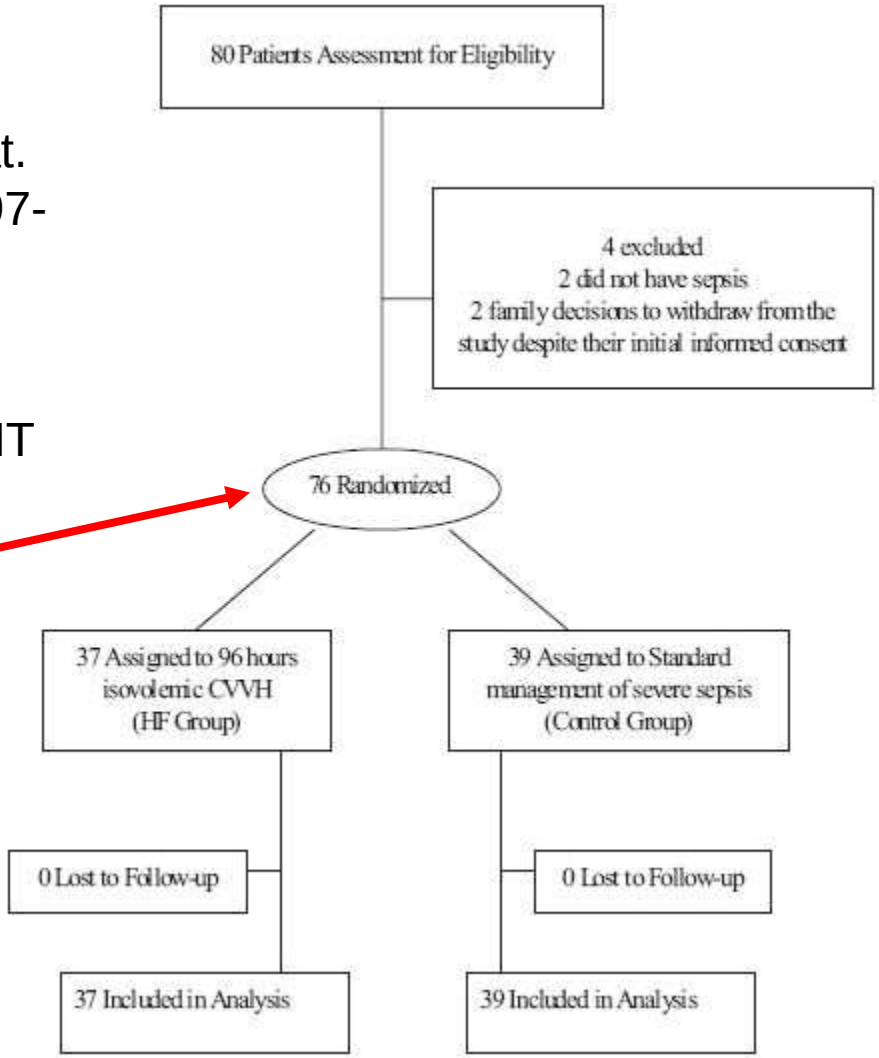


Crit. Care Med. 2002; 30: 100-106

Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: A randomized controlled trial*

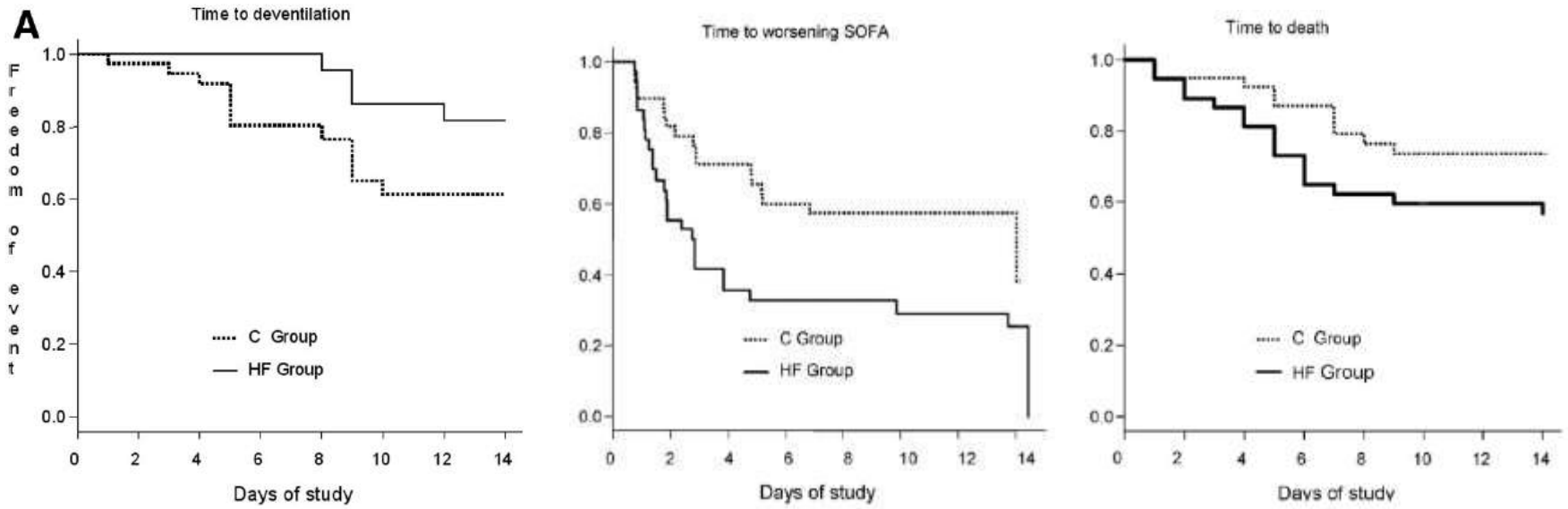
- Prospective multicenter RCT in 80 pat. With Sepsis/sept. shock (France) 1997-1999
- Inclusion within 24h after first organ failure
- CVVH for ≥96h with 25 ml/kg×h vs. SMT

Study stopped following Interim analysis !



Payen D. et al., *Crit. Care Med.* 2009; 37: 803-10

Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: A randomized controlled trial*



CHHV group:

- Number and severity of organ complications higher
- More / prolonged ARF (need for CVVH after 96h)
- No reduction of plasma cytokines

Payen D. et al., *Crit. Care Med.* 2009; 37: 803-10

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

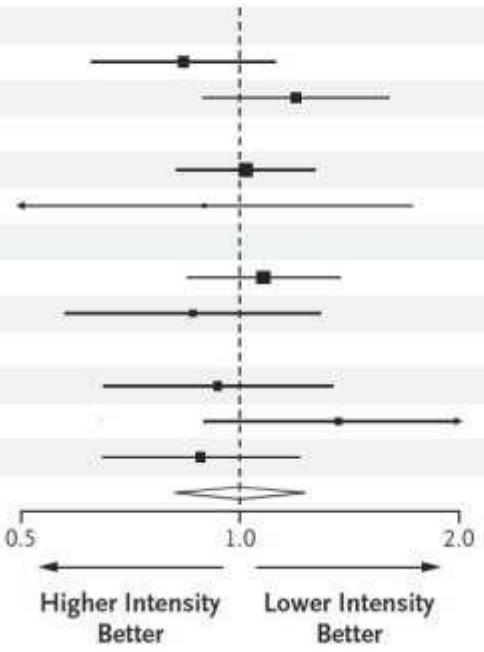
The RENAL Replacement Therapy Study Investigators*

NEJM 2009; 361: 1627-38

40 ml per kilogram of body weight per hour (higher intensity) or 25 ml per kilogram per hour (lower intensity).

A question of dose?

Prespecified Subgroup	Higher Intensity (N=721)	Lower Intensity (N=743)	Odds Ratio (95% CI)
	no. of deaths/no. of patients (%)		
Patients with criteria for sepsis			
Yes	168/359 (46.8)	186/363 (51.2)	0.84 (0.62–1.12)
No	154/362 (42.5)	145/379 (38.3)	1.19 (0.89–1.60)
Patients with at least one nonrenal organ failure			
Yes	299/628 (47.6)	306/649 (47.2)	1.02 (0.82–1.27)
No	23/93 (24.7)	25/93 (26.9)	0.89 (0.46–1.72)
Patients with SOFA cardiovascular score of 3 or 4			
Yes	247/510 (48.4)	254/546 (46.5)	1.08 (0.85–1.37)
No	74/210 (35.2)	75/194 (38.7)	0.86(0.58–1.29)
Patients with eGFR <60 ml/min			
Yes	114/250 (45.6)	105/222 (47.3)	0.93 (0.65–1.34)
No	81/157 (51.6)	81/185 (43.8)	1.37 (0.89–2.10)
Missing	127/314 (40.5)	146/336 (43.5)	0.88 (0.65–1.21)
Death from any cause by day 90	322/721 (44.7)	332/743 (44.7)	1.00 (0.81–1.23)



CONCLUSIONS:

In critically ill patients with acute kidney injury, treatment with higher-intensity continuous renal-replacement therapy did not reduce mortality at 90 days also in septic patients..

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Patrick M. Honoré
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Sean M. Bagshaw
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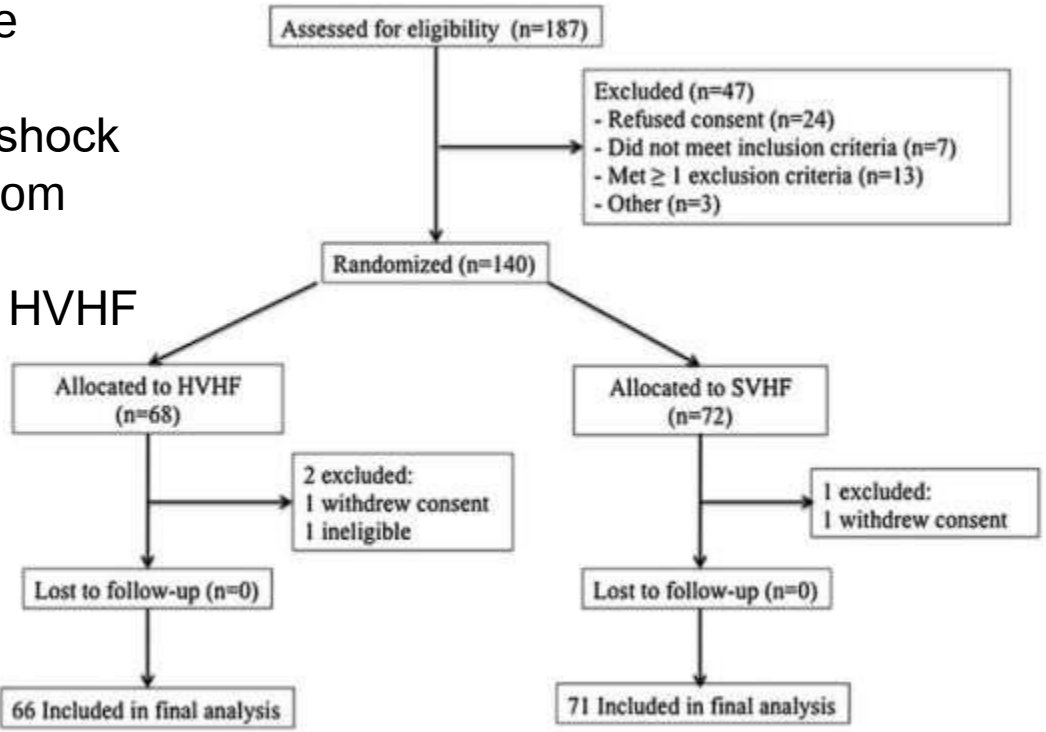
Jean-Luc Canivet
Antoine Dewitte

High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial

Prospective multicentre RCT, 18 intensive care units in France, Belgium and the Netherlands.

- 140 critically ill patients with septic shock and AKI for less than 24 h enrolled from October 2005 through March 2010.
- Patients were randomized to either HVHF at 70 mL/kg/h or standardvolume CVVH at 35 mL/kg/h for 96 h.



Joanes-Boyeau , *Intensive Care Med.* 2013; 39: 1535-46

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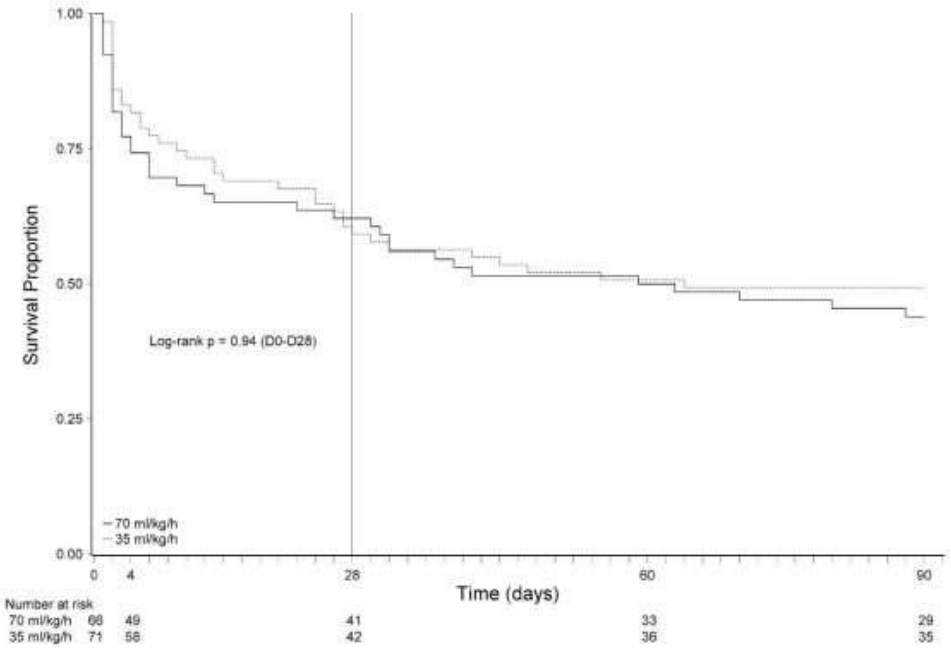
High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial

Trial was stopped prematurely after enrolment of 140 patients (slow patient accrual and resources no longer being available)

• Mortality at 28 days was lower than expected but not different between groups (HVHF 37.9 % vs. SVHF 40.8 %, log-rank test p = 0.94).

• There were no statistically significant differences in any of the secondary
endpoints between treatment groups.



Joanes-Boyeau , *Intensive Care Med.* 2013; 39: 1535-46

High Volume HemoFiltration

- Definition of HVHF:
  1. Proc 2° Conference on Crit Care Nephrology (Czhech Repub, 2007)
  – Continuous HVHF with 50 – 70 mL/Kg/h for 24 h

     OR

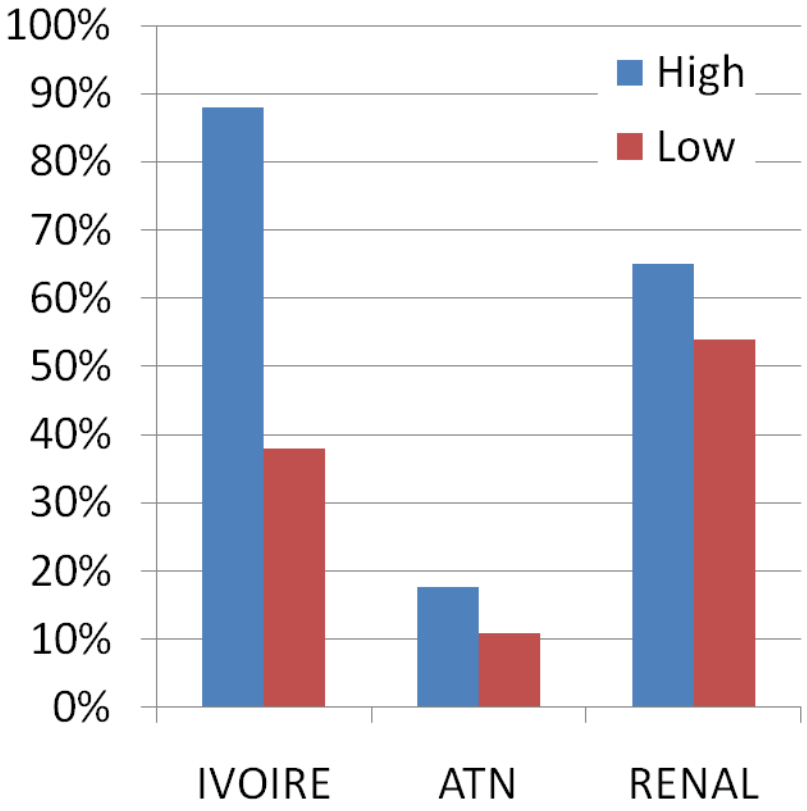
  – Intermittent HVHF 100 – 200 mL/Kg/h for 4-8 h followed by conventional CVVH
  1. ADQI
  – HVHF when > 35 mL/Kg/h

Potential drawbacks:

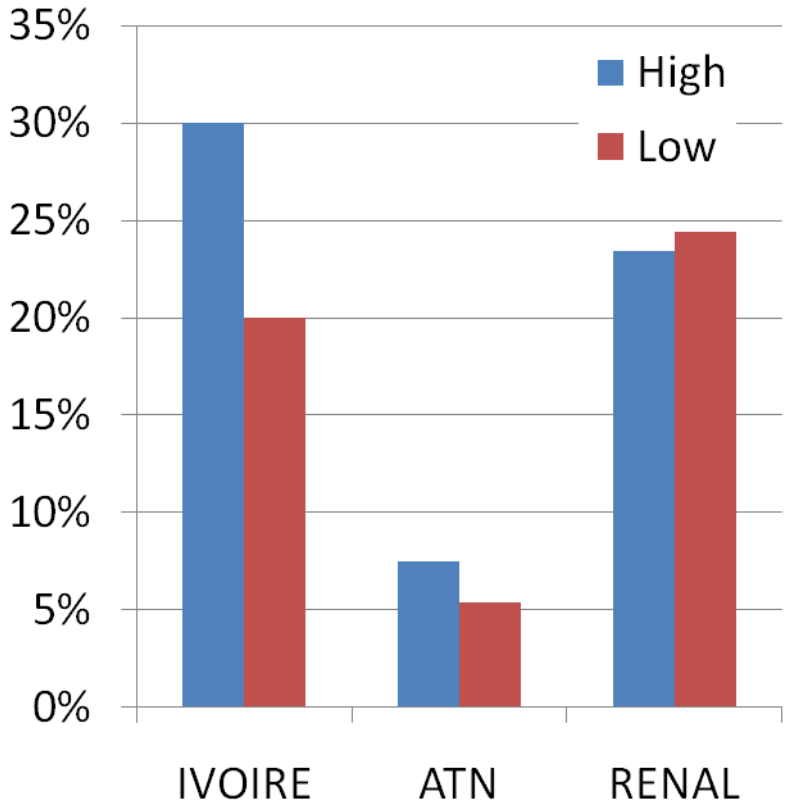
- Hyposphatemia (RENAL, ATN, IVOIRE)
- Hypokalemia
- Hypoalbuminemia
- Drugs clearances

HVHF: risk of electrolytes dysbalance

Hypophosphatemia



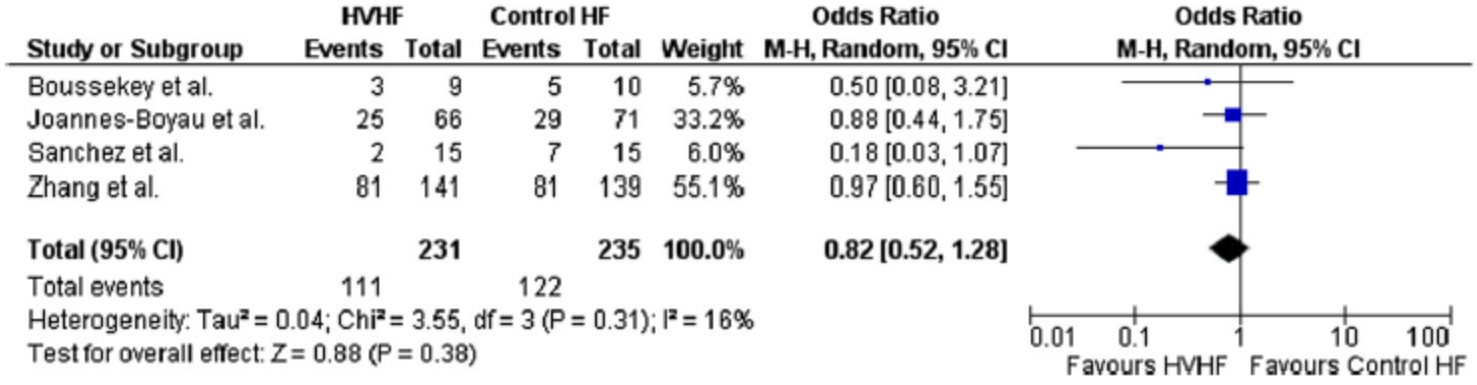
Hypokalemia



HVHF for septic acute kidney injury: a systematic review and meta-analysis

Study	Modality	Prescribed effluent rate (ml/kg/hr)		Delivered effluent rate (ml/kg/hr)		Days in ICU before Enrolment		Duration of HF (days)	
		HVHF	Control HF	HVHF	Control HF	HVHF	Control HF	HVHF	Control HF
Boussekey (2008) [25]	CVVH	65	35	62	32	Not stated[a]	Not stated[a]	7	6
Sanchez (2010) [27]	CVVH	55	35	-	-	-	-	5.7	6.4
Zhang (2012) [28]	CVVH	85	50	87.54	49.99	5.4	6.2	9.38	8.88
Joannes-Boyau (2013) [26]	CVVH	70	35	65.6	33.2	2.4	1.9	6[b]	7[b]

CVVH, continuous veno-venous hemofiltration. [a]Boussekey *et al.* [25] reported "time from shock to hemofiltration": 21 hours for HVHF; 15.5 hours for SVHF. [b]This was estimated according to the outcome "RRT-free days at day 90".



Clark E et al, Crit Care, 2014, 18, R7

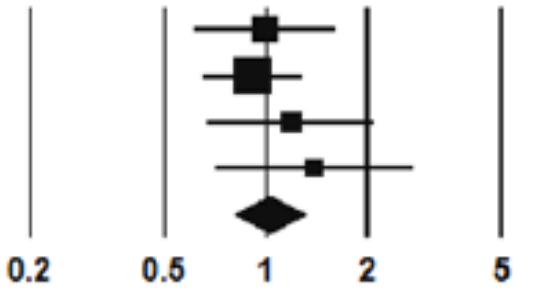
BMJ Open

High-dose versus low-dose haemofiltration for the treatment of critically ill patients with acute kidney injury: an updated systematic review and meta-analysis

Li P, *et al*. *BMJ Open* 2017;7:e014171. doi:10.1136/bmjopen-2016-014171

(C) Hospital mortality

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zhang (2012)	0.99	0.61	1.61	-0.03	0.98
Bellomo (2009)	0.91	0.65	1.29	-0.52	0.60
Tolwani (2008)	1.19	0.67	2.10	0.58	0.56
Bouman (2002)	1.39	0.71	2.74	0.96	0.34
Pooled	1.02	0.81	1.30	0.20	0.84

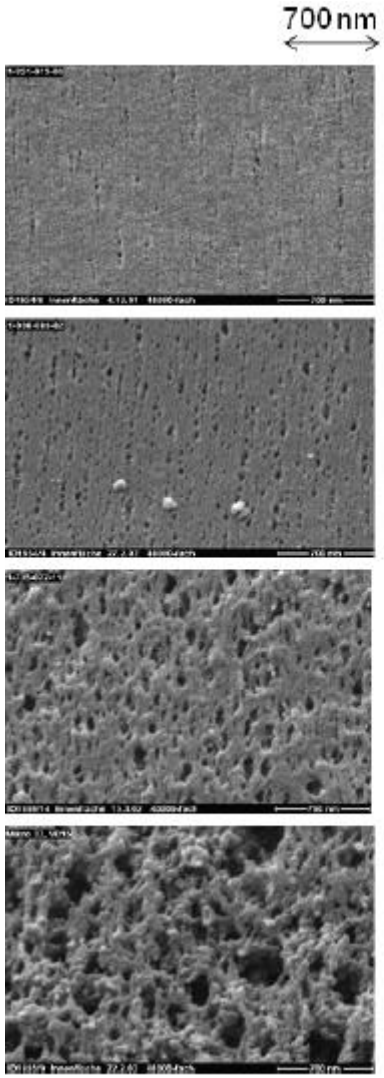


Heterogeneity test: Q = 1.49, P = 0.69, I^2 = 0%

Metaregression analysis indicated that the results were not affected by the percentage of patients with sepsis or septic shock.

High Cut-Off membrane

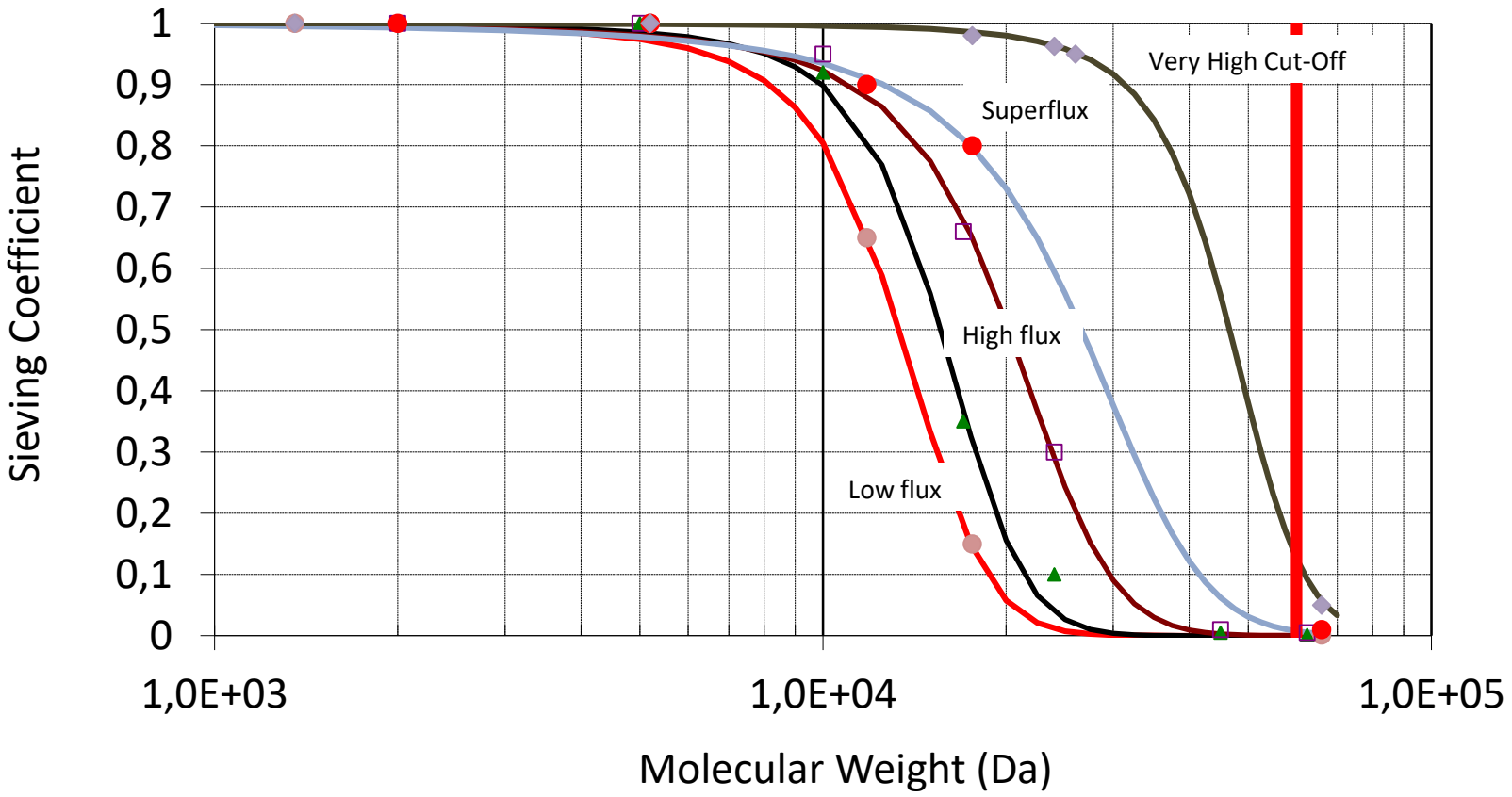
Inner surface electronic microscopy of of different membranes



Pore diameter	Type of membrane
< 0.01 µm	High flux
< 0.02 µm	High cut-off
0.09 µm	For protein separation
0.30 µm	Plasma filter

Rimmelé T, Kellum J, Crit Care, 2011, 15, 205

Membrane: nomenclature and classification



Cytokine clearances by HCO filters

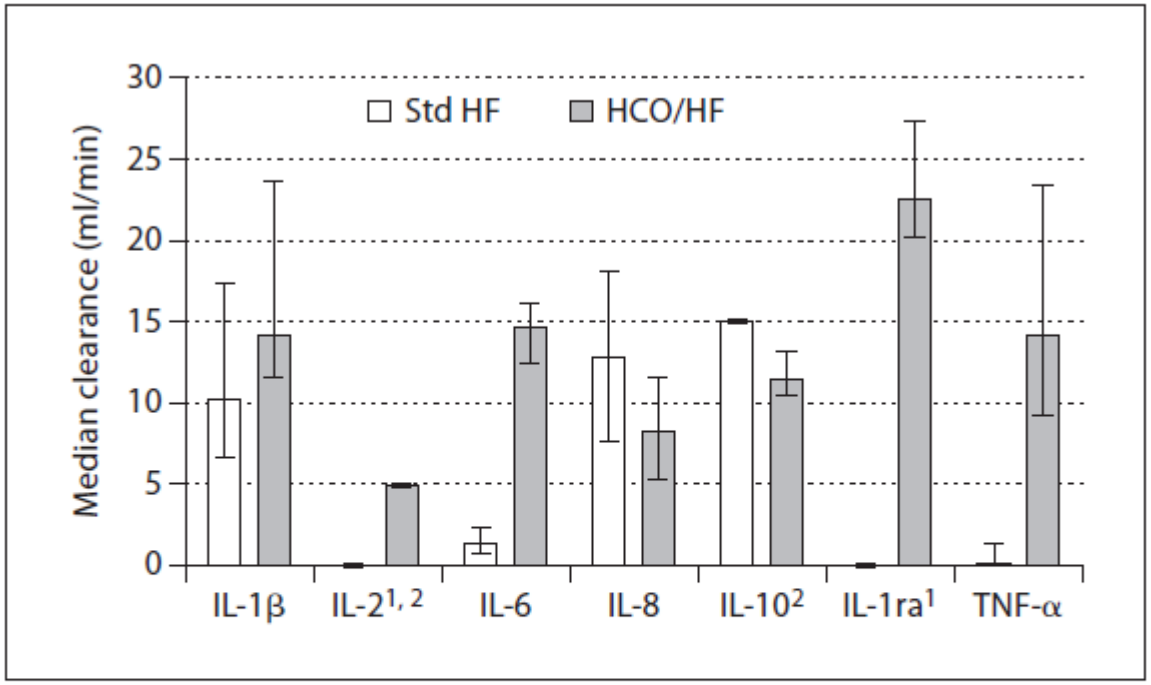
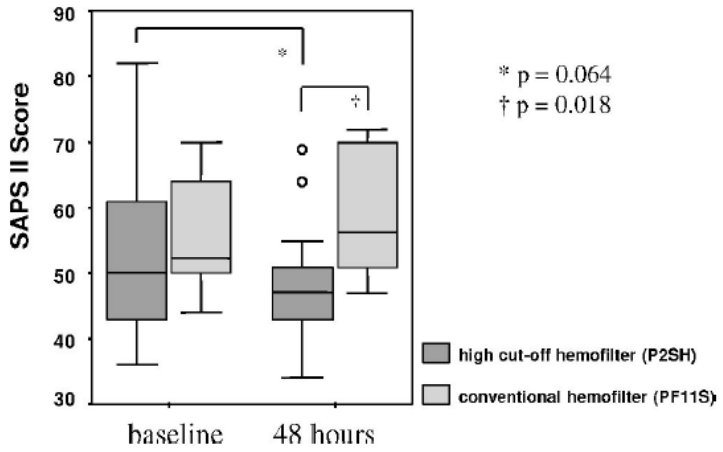


Fig. 2. Median cytokine clearance by Std HF versus HCO/HF, with whiskers indicating interquartile range. [1] No values recorded for IL-2 and IL-1ra for Std HF. [2] No whiskers shown when only one value recorded.

Atan R, Bellomo R, et al, Blood Purif, 2012, 33, 88-100

Amines doses: pilot study comparison between HCO vs standard CVVH



Morgera S et al, Crit Care Med, 2006, 34 (8), 2099-

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 4338-4344
DOI: 10.12659/MSM.896819

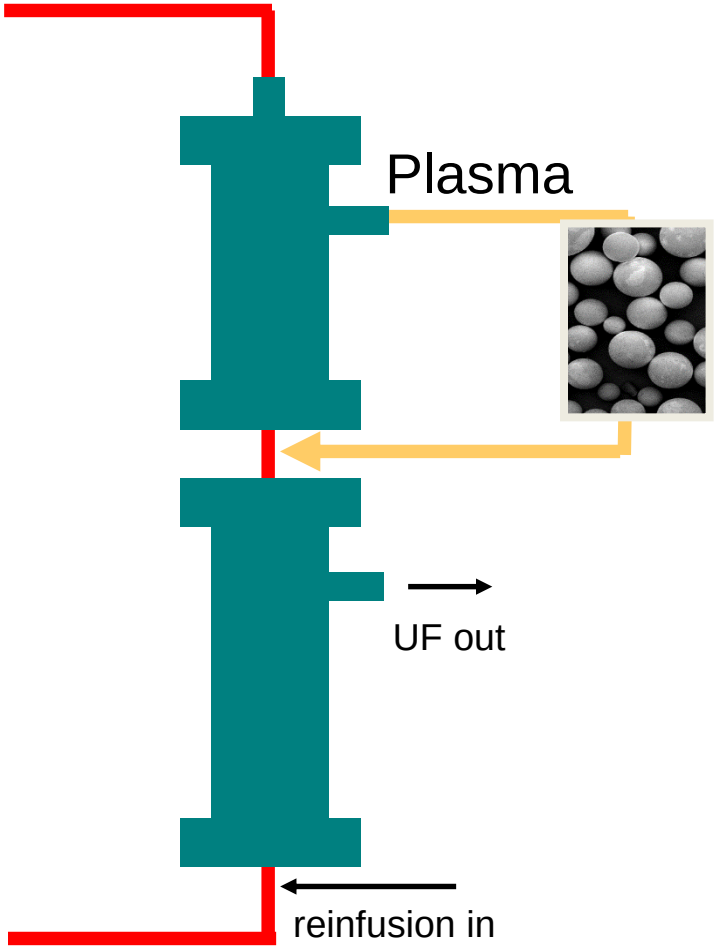
Effectiveness of High Cut-Off Hemofilters in the Removal of Selected Cytokines in Patients During Septic Shock Accompanied by Acute Kidney Injury-Preliminary Study

Table 2. Average cytokine concentrations in serum, initially and after 24 hours of treatment.

Cytokine	C_0 [pg/ml]	C_{24} [pg/ml]	p-Value (C_0: C_{24})
INF-α	2.49*±0.00	2.49*±0.00	n/a*
INF-γ	6.01*±0.0	6.01*±0.0	n/a*
TNF-α	4.74*±0.0	4.74*±0.0	n/a*
IL-1β	0.36*±0.00	0.36*±0.00	n/a*
IL-2	0.20*±0.0	0.20*±0.0	n/a*
IL-6#	78.73 [1.66; 2634.98]	141.17 [1.66; 2177.41]	0.340
IL-10#	39.22 [0.61; 156.88]	10.07 [0.61; 144.15]	0.004
IL-12	7.64±6.18	6.86±4.63	0.043

C_0 – concentration before HCO-CVVHD; C_{24} – concentration and after 24hrs of HCO-CVVHD; n/a – non-available;
median; * concentrations below or on the level of the detection limit.

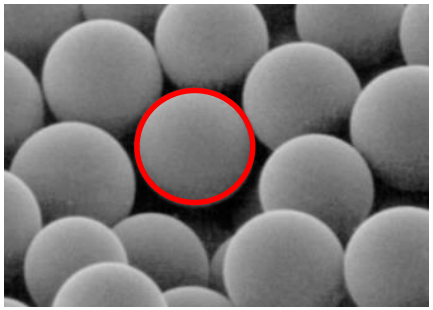
Coupled Plasma Filtration-Adsorption

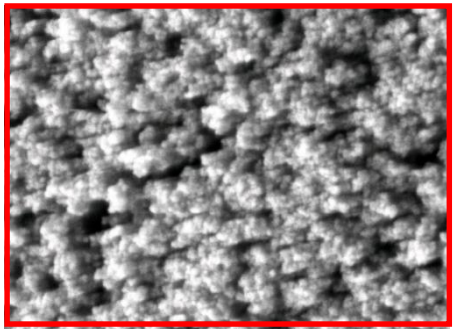


Selective removal of cytokines and inflammatory mediators

High surface area

1.2 to 2.4 m^2

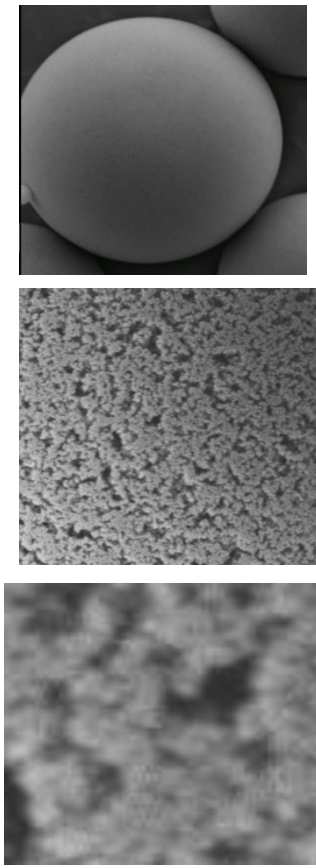




700 m^2/g resin

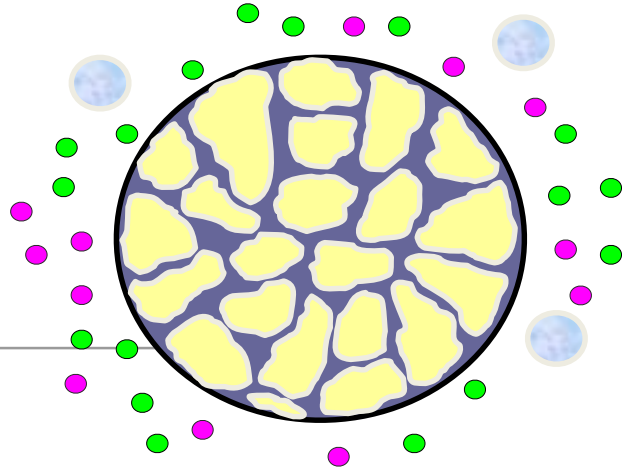
50,000 m^2/cartridge

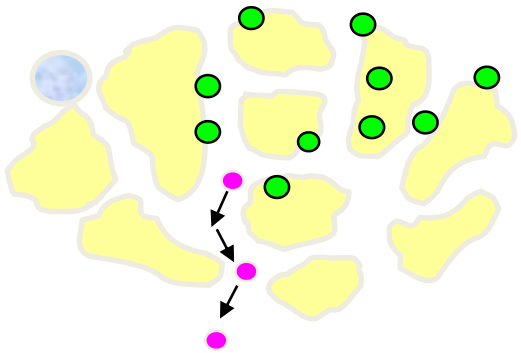
How does the resin work?



From micro

To nano



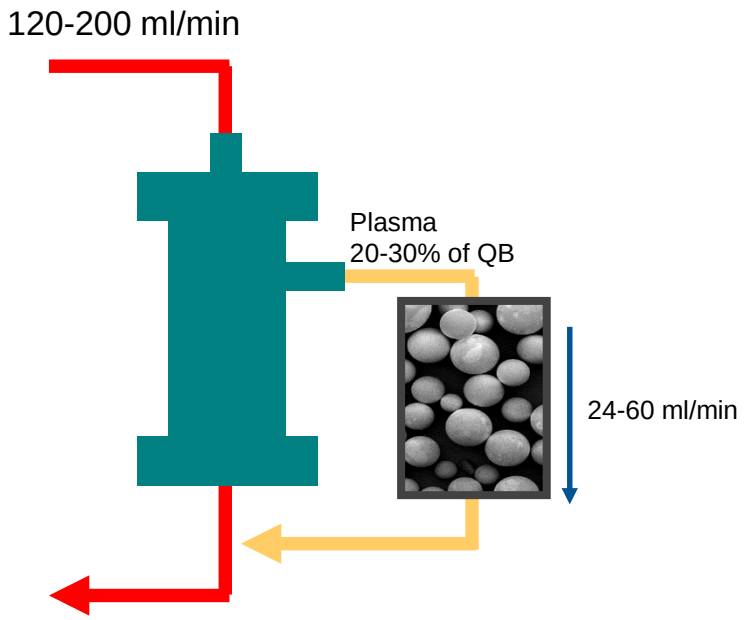


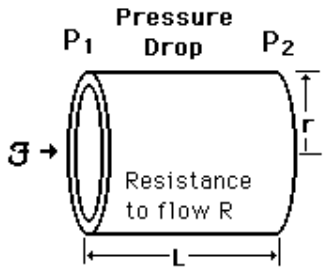
1. Interphase
2. Intraphase
3. Thin surface film

4. Large molecules bind only at surface
5. Small solutes enter by diffusion
6. Adsorption or elution

Plasmaperfusion

- Slower plasma flow allows more contact time with resin
  = better adsorption efficiency
- less fouling of resin surface
- no interaction of cells with resin
- Anticoagulation is sometimes more difficult





$R = \frac{8\eta L}{\pi r^4}$ where η = viscosity

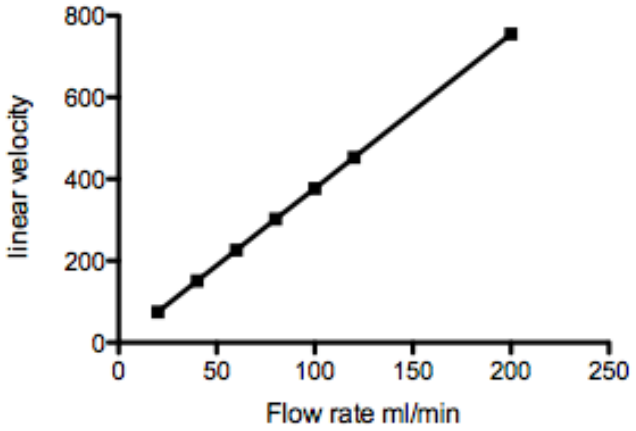
Suppose the original flowrate is 100 cm^3/sec. The effect of changes in the parameters is as follows:

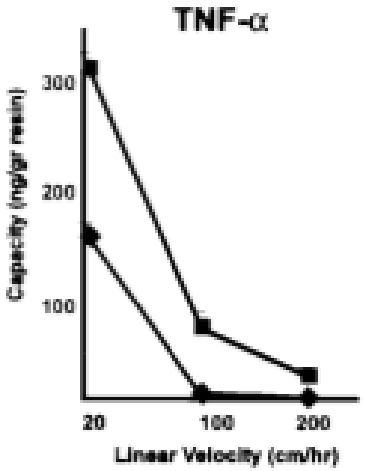
*Double length	→ 50	cm^3/sec
Double viscosity	→ 50	cm^3/sec
Double pressure	→ 200	cm^3/sec
Double radius	→ 1600	cm^3/sec

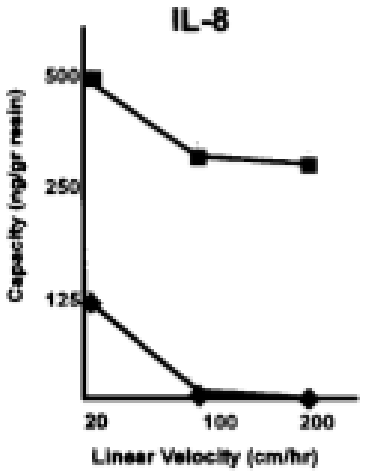
* With other parameters held at original values

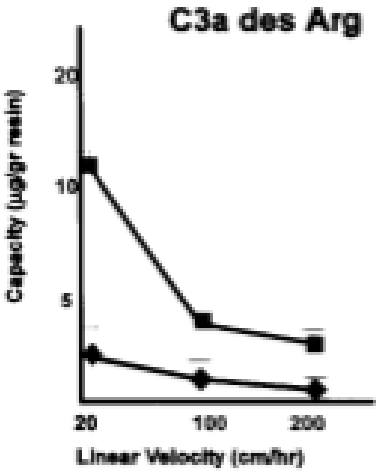
$$\text{Volume Flowrate} = \mathfrak{F} = \frac{P_1 - P_2}{R} = \frac{\pi(\text{Pressure difference})(\text{radius})^4}{8(\text{viscosity})(\text{length})}$$

A 19% increase in radius will double the volume flowrate!



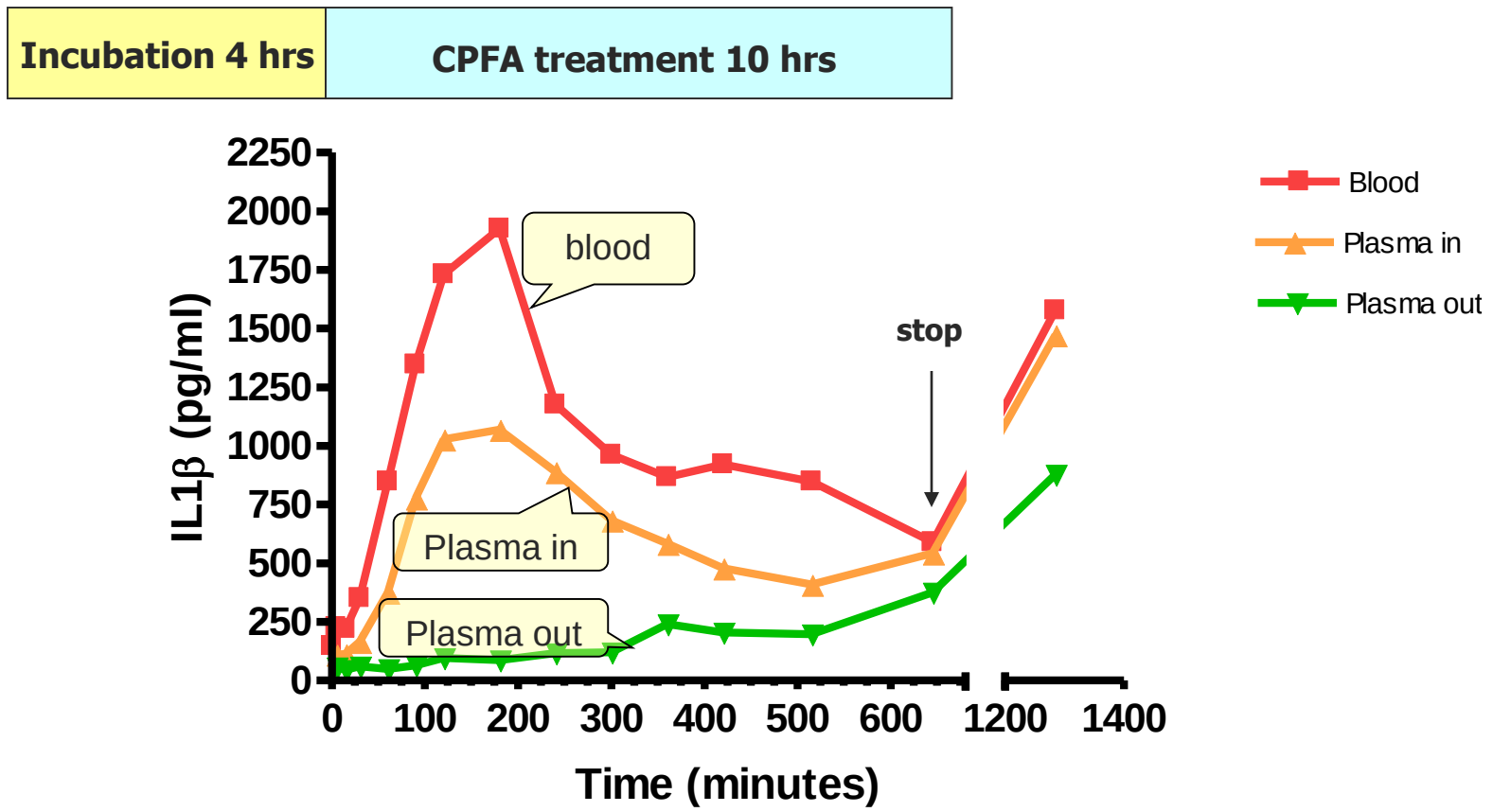






Tetta C. Nephrol Dial Transplant 1998

In vitro LPS + healthy human blood



CPFA: main results

Author	Target population	Study Design	Major Results of CPFA trials	P
Tetta et al, 2000	Animal model	Prospective RCT w. out CPFA - CPFA	- Survival @ 2 days 85% in CPFA - Survival @ 2 days 25% w.out CPFA	0.041
Ronco et al, 2000	Septic pts N=?	Prospective RCT CPFA – CVVH CVVH - CPFA	- ↑ Hemodynamic response - ↓ Norepinephrine dose	
Formica et al, 2003	Septic shock pts N= 12	Prospective Longitudinal CPFA	- ↑MAP - ↓Cardiac Index - ↑ Syst Vasc Res Index - PaO2/FiO2 - No change extracvasc lung water - intra-thoracic blood index - Survival @ 28 days 90% - Survival at 90 days 70%	<0.001 <0.001 <0.001 <0.001 Ns Ns
Ronco et al, 2002	Septic shock pts N= 10	Prospective pilot CPFA (10h) – CVVHDF (10h) CVVHDF (10h) – CPFA (10h)	- ↑ MAP 11.8 vs 5.5 mmHg - ↓ Norepinephrine 0.08 vs 0.0049 ug/Kg/min	0.001 0.003
Mariano et al, 2004	Septic shock, ARF N=13	Parallel group CPFA + Hep CPFA + Citrate	- Kit survival Hep: 8.40±0.39 h - Kit survival Cit: 7.79±0.19 h	ns
Lentini et al, 2009	Septic shock, AKI N=8	Prospective RCT HVHF-CVVH-CPFA-CVVH CPFA-CVVH-HVHF-CVVH	- No change MAP - No change Norepinephrine - No change Vasopressor - No change PaO2/FiO2	0.29 0.18 0.22 0.08

CPFA: main results

Author	Target population	Study Design	Major Results of CPFA trials	P
Caroleo et al, 2010	Case report Liver Failure	CPFA	-Bilirubin levels (RR 47.8%, 53.8%, 59.3%)	
Lucisano et al, 2011	Case Report ARDS	Case Report	-↑ IL-6 vs baseline -↑ TNF vs baseline -↑ PCT vs baseline -↑ PC-R vs baseline	
Mao et al, 2011	Septic shock, MOF N=7	RCT CPFA (10h) – HVHF (10h) HVHF (10h) – CPFA (10h)	-↑ MAP 120.75±20 vs 115.3±18.5 mmHg -paO2/FiO2 297.3±204 vs 265.45±173.7 -↑ Citokines	<0.05 <0.05
Berlot et al, 2011	Case report Septic shock	CPFA	-↑ Vessels perfusions in the microcirculation	
Moretti et al, 2011	Case report Weil's syndrome	CPFA	-Patient's survival	

CPFA: largest RCT, COMPACT

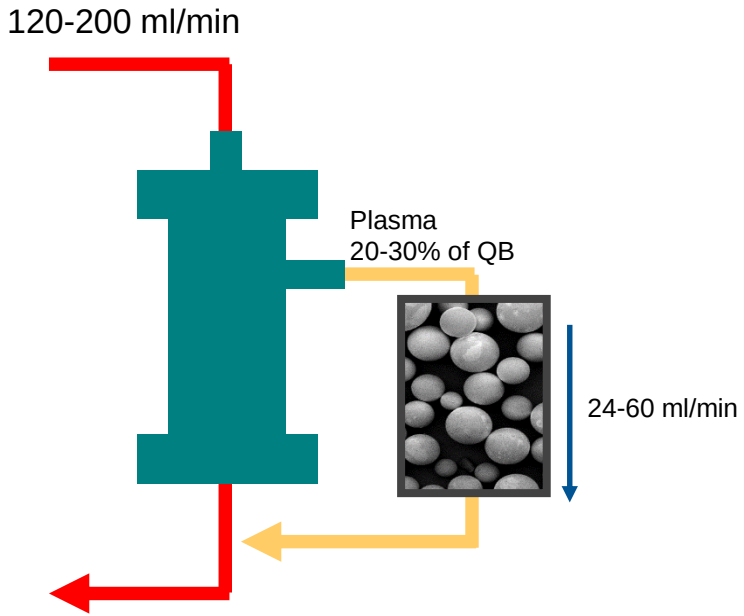
Livigni S et al, 2014, BMJ Open

	Mortality in Internal Medicine / Nephrology Unit
CPFA	44.0 %
Stadard care	47.3 %

An a priori planned subgroup analysis showed those receiving a CPFA dose >0.18 L/kg/day had a lower mortality compared with controls (OR 0.36, 95% CI 0.13 to 0.99).

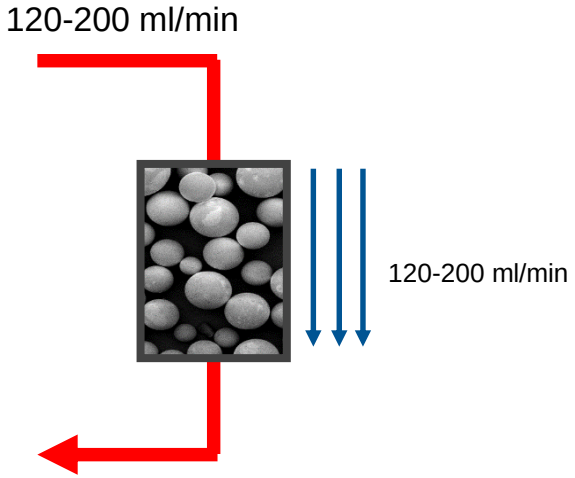
Plasmaperfusion

- Slower plasma flow allows more contact time with resin
  = better adsorption efficiency
- less fouling of resin surface
- no interaction of cells with resin
- Anticoagulation is sometimes more difficult

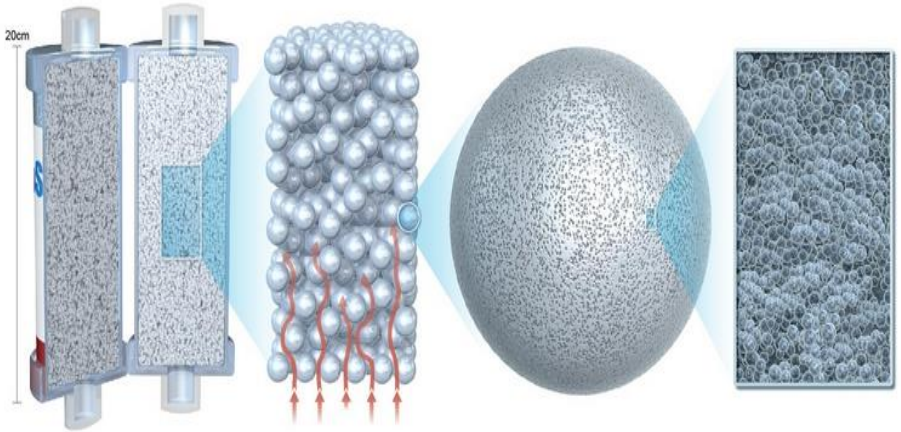


Hemoperfusion

- Faster blood flow allows more blood to be treated.
- Results depend strongly on adsorption efficiency under high linear velocity - and eventual decrease of resin efficiency after fouling.
- More likely to have “channeling”



- Highly biocompatible, porous polymer beads
- Removal of hydrophobic substances due to
  - physicochemical properties
  - pore size



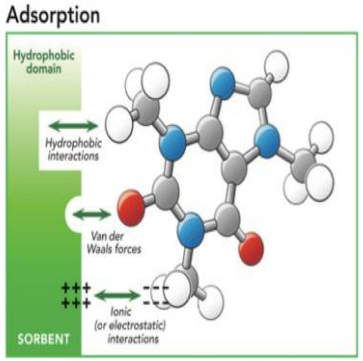
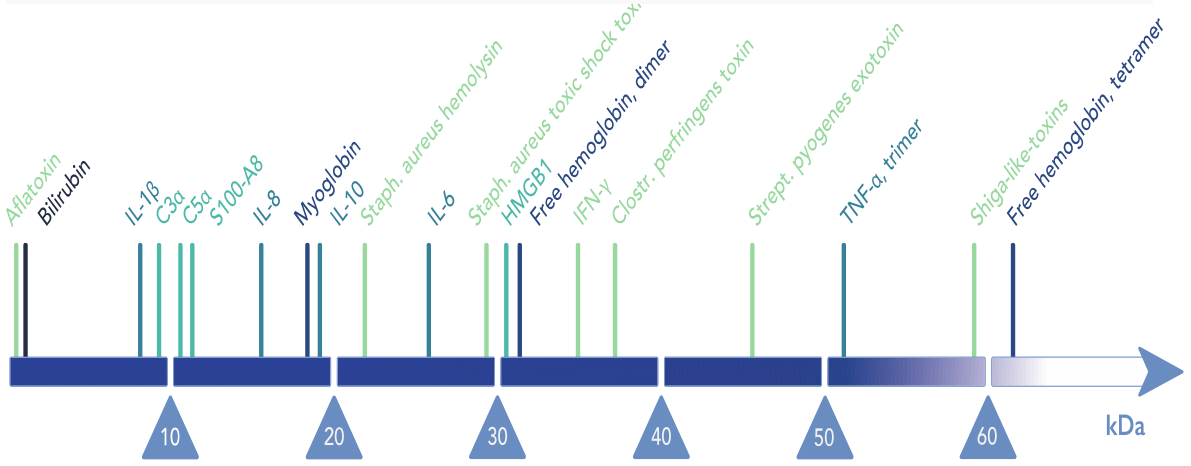


Fig. 3. Adsorption corresponds to the saturable fixation of some molecules directly on a sorbent or a membrane along an affinity gradient depending on ionic, hydrophobic, and van der Waals interactions.

Size-selective removal

Controlled and effective adsorption of numerous substances

- PAMPS (Pathogen Associated Molecular Patterns) e.g. enterotoxins [12]
- DAMPS (Damage Associated Molecular Patterns) [12,13]
- Cytokines [1,2,3,4,5]
- Myoglobin [4,11]
- Metabolites (e.g. Bilirubin, Bile acids, Ammonia) [9,10]



Data for septic shock II (Crit Care 2017)

Kogelmann *et al. Critical Care* (2017) 21:74
DOI 10.1186/s13054-017-1662-9

Critical Care

RESEARCH Open Access

Hemoadsorption by CytoSorb in septic patients: a case series

Klaus Kogelmann[1*], Dominik Jarczak[2], Morten Scheller[1] and Matthias Drüner[1]

- 26 consecutive patients fulfilled the inclusion criteria (post-surgical; 13, pneumonic; 13)
- Both vasopressor and lactate levels showed a sustained reduction even beyond 72 hrs. after the last CytoSorb treatment
- **Actual mortality was lower than the mortality predicted by APACHE II**. These favorable effects seem to be more pronounced in patients where therapy started within 24 hours after the septic shock

Data for postop cardiac surgery SIRS (IJAO 2016)

IJAO
ISSN 0391-3988

Int J Artif Organs 2016; 00(00): 000-000
DOI: 10.5301/ijao.5000492

SHORT COMMUNICATION

Treatment of post-cardiopulmonary bypass SIRS by hemoadsorption: a case series

Karl Träger[1], Daniel Fritzler[1], Guenther Fischer[1], Janpeter Schröder[1], Christian Skrabal[2], Andreas Liebold[2], Helmut Reinelt[1]

[1] Department of Cardiac Anesthesiology, University Hospital Ulm, Ulm - Germany
[2] Clinic of Cardiothoracic and Vascular Surgery, University Hospital Ulm, Ulm - Germany

- Reduction of elevated cytokine levels
- Associated with a **clear stabilization of deranged hemodynamic, metabolic and organ function parameters**.
- Treatment was well tolerated and safe and no device related adverse events were occurring

Data for ECMO (J Thoracic Disease 2017)

Review Article

Extracorporeal membrane oxygenation and cytokine adsorption

Thomas Datzmann, Karl Träger

Department of Cardiac Anesthesiology, University Hospital Ulm, Ulm, Germany

Contributions: (I) Conception and design: None; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

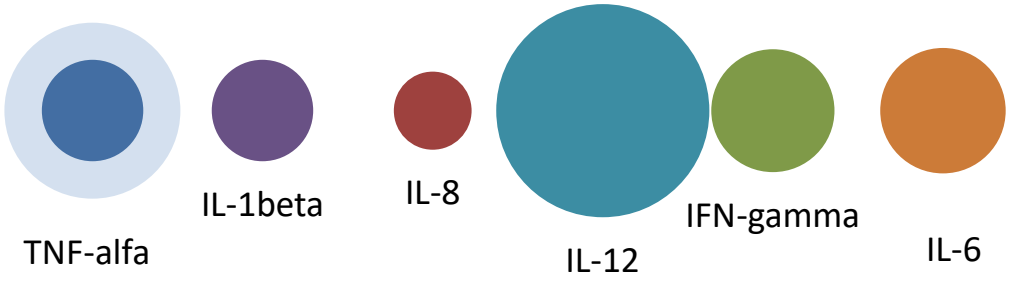
Correspondence to: Dr. Thomas Datzmann. Department of Cardiac Anesthesiology, University Hospital Ulm, Albert-Einstein-Allee 23, 89081 Ulm, Germany. Email: thomas.datzmann@gmx.de.

- Hemoadsorption therapy seems to offer a promising new option for the treatment of patients with overwhelming inflammatory response leading to **faster hemodynamic and metabolic stabilization** finally resulting in **preserved organ functions.**

The removal of cytokines in the patient with sepsis by means of extracorporeal techniques is appealing, but……

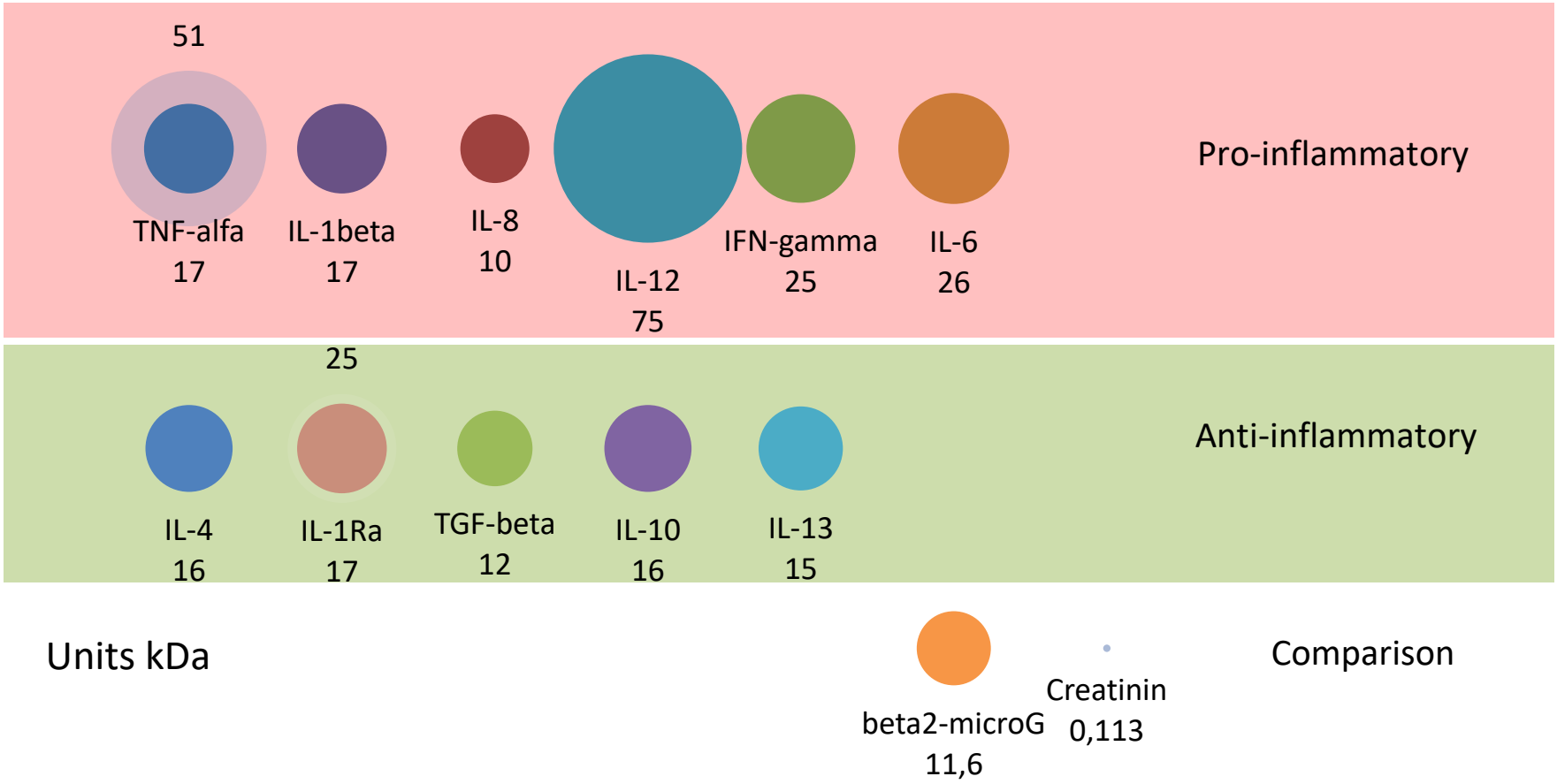
Cytokines

Pro-inflammatory



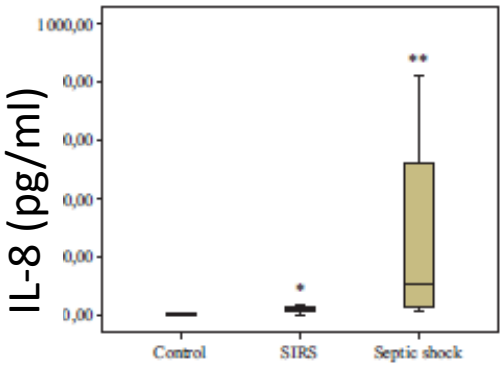
Cytokine molecular characteristics

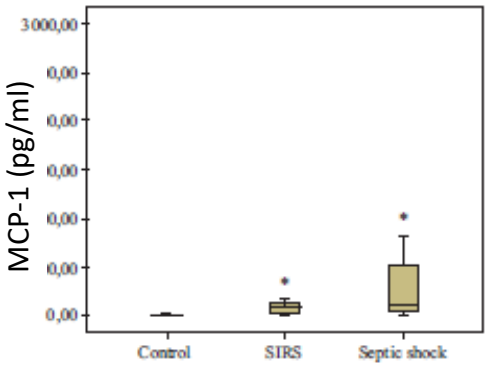
Cytokine molecular size

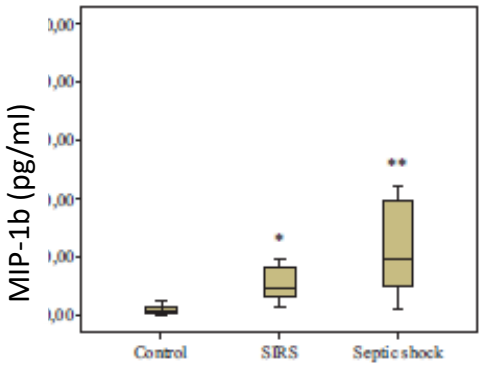


Cytokine are water soluble compounds

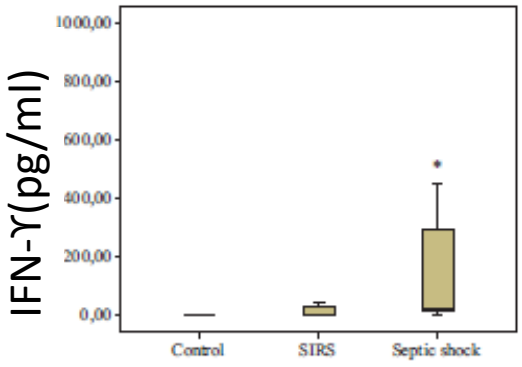
Pro- and anti-inflammatory simultaneous response to septic shock: in vivo study

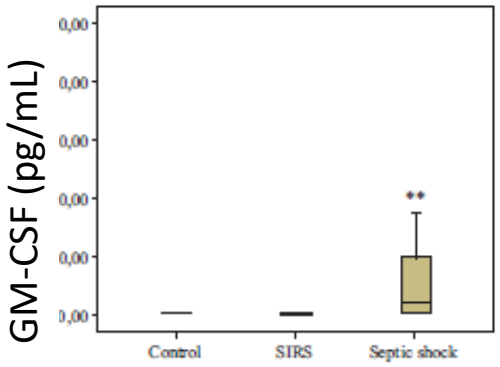


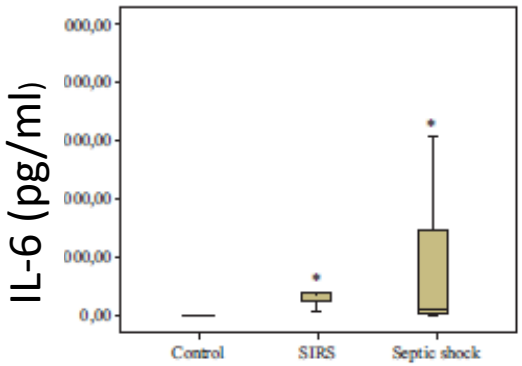


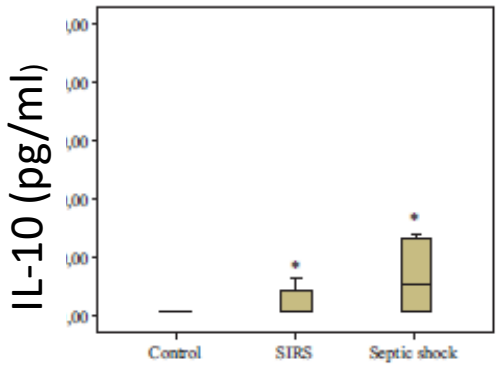


N= 31 ICU pts
20 septic shock, 11 SIRS
15 abdominal surgery
Blood samples within 24 h from diagnosis

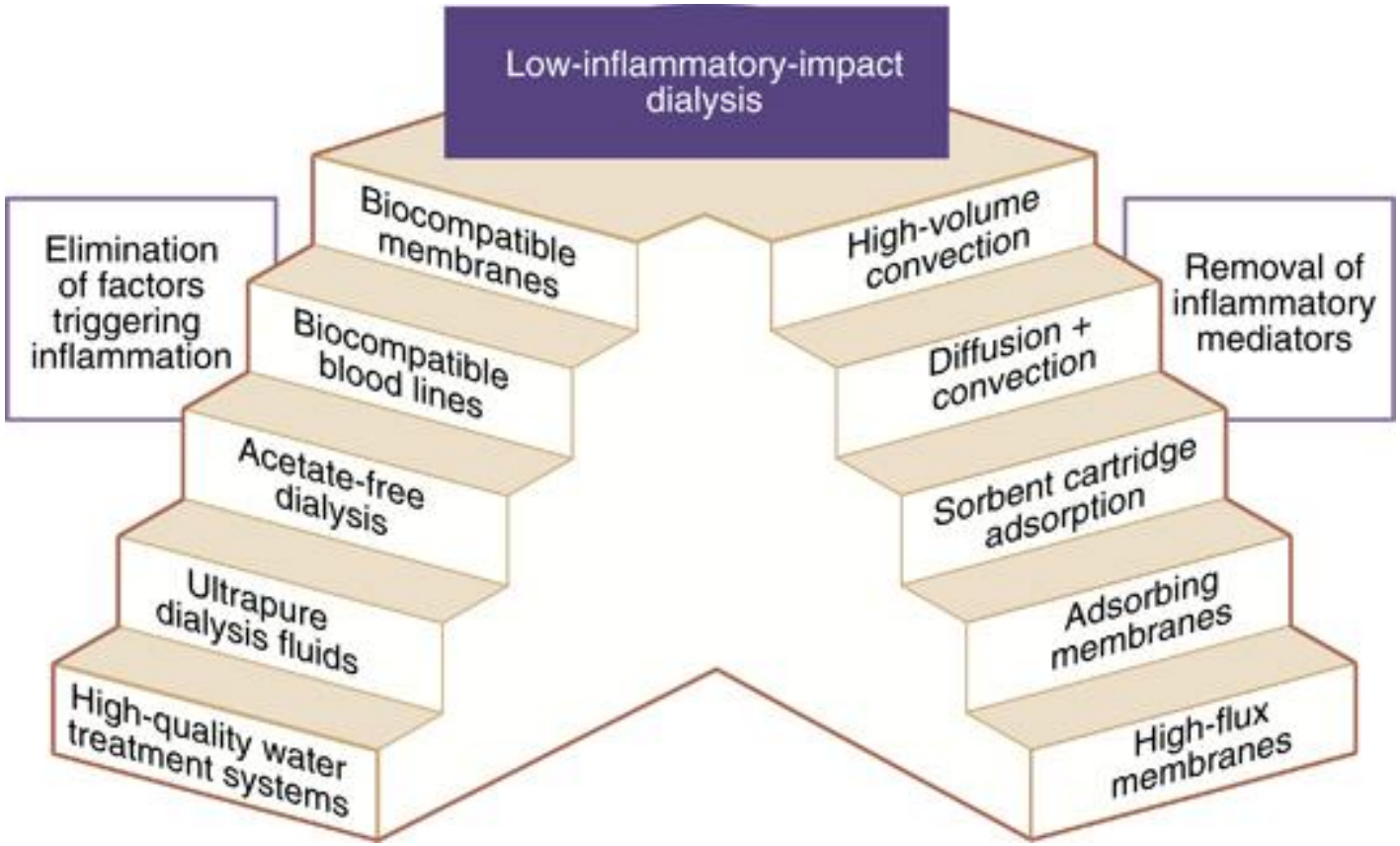








Tamayo et al , Eur Cytok Net, 2011, 22 (2), 82-7



Santoro A, E,Mancini .Kidney International (2014) **86,** 235–237; doi:10.1038/ki.2014.81

Kinetics of plasma constituents

Costituent	Half life (days)
IgG (1,2,3)	22
IgG 3	7
IgM	5
IgA	6
IgD	2.8
IgE	2.5
Albumin	17
C_3	2
C_4	2
Fibrinogen	4.2
TNF	6-20 minutes
Cytokines	minutes

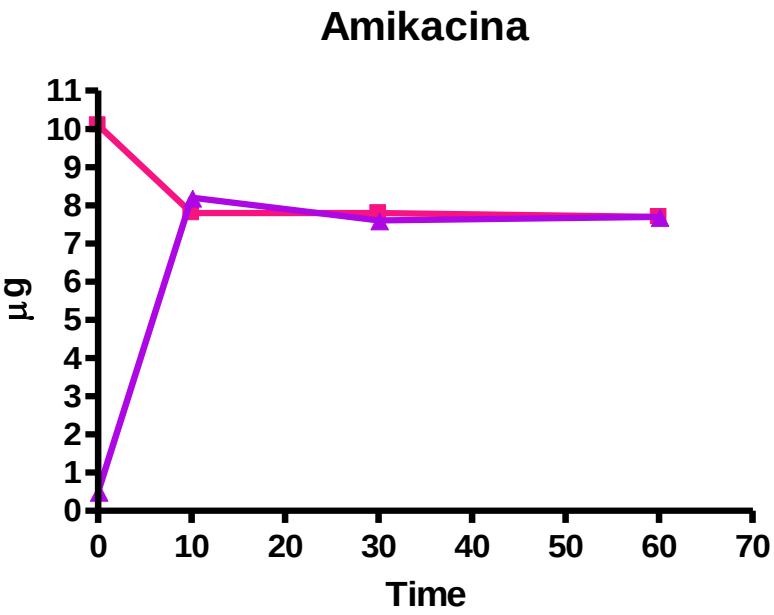
Common Antibiotics and CRRT

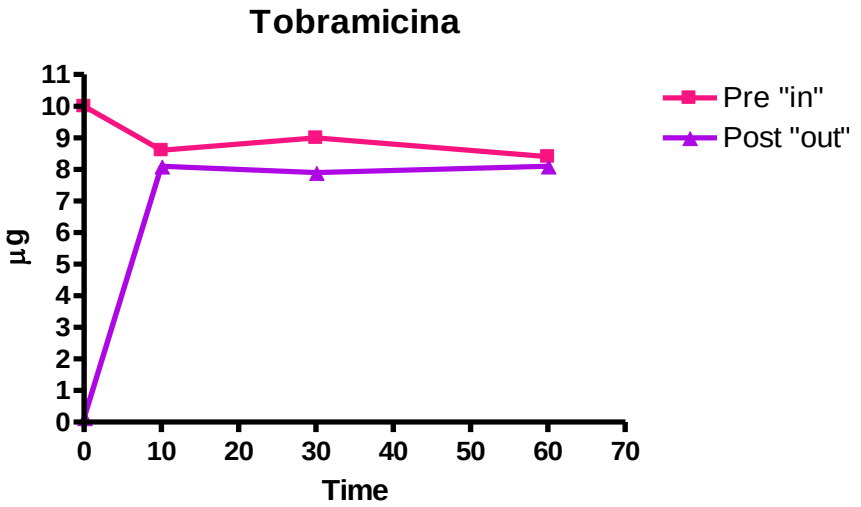
TABLE I - ANTIBIOTIC CLEARANCE ADAPTATION DURING THE FIRST THREE DAYS OF ICU ADAPTED TO INCREASED UF EXCHANGED RATE

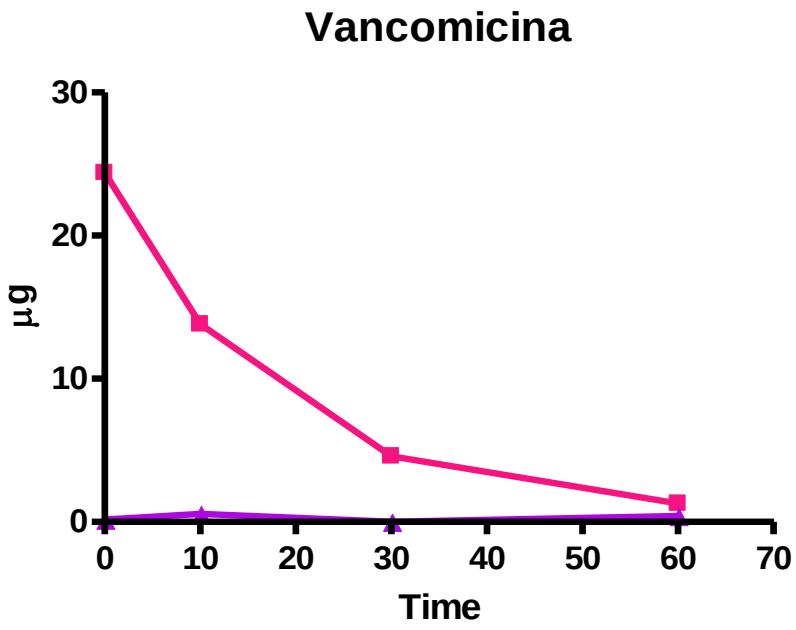
	Vancomycin	Teicoplanin	Flucloxacilline	Carbapenem (Imipenem)	Fluconazole	Cefepime	Piperacilline Tazobactan	Quinolones (Ciprofloxacin)
MW	1448 KDa	1900 KDa	-	383.5 KDa	-	-	-	-
Protein bounding	Moderate (30%)	High	High	Low	Low	-	-	-
Volume of distribution	Low	Low	Low	High	Moderate	-	-	-
Administration	Continuous infusion	Bolus	Bolus	Bolus	Bolus	Bolus	Bolus	Bolus
Dose if 20 ml/kg/hour	10-15 mg/kg/day	5-7 mg/kg/day	2 g Q DS	500 mg BD	400 mg OD	500 mg OD	4 g BD	200 mg TDS
Dose if 35 ml/kg/hour	25-30 mg/kg/day	10-15 mg/kg/day	4 g TDS	1 g TDS	600 mg BD	500 mg TDS	4 g TDS	400 mg BD
Monitoring	Easy	Easy	Difficult	Difficult	Difficult	Difficult	Difficult	Difficult
Elimination by CRRT	High	Moderate	Low	High	Moderate	Moderate	High (70%) !	Moderate

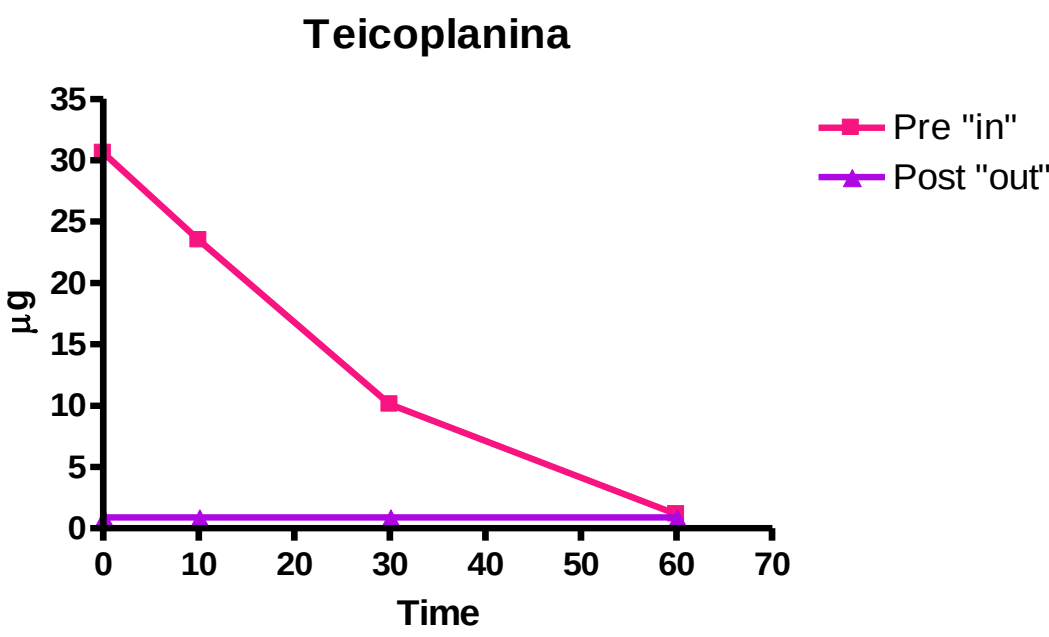
These effects will be even more dramatic with HVHF

Honore, PM *et al*. Int J Artif Organs 2006; 29: 649-659









CPFA : in vitro study

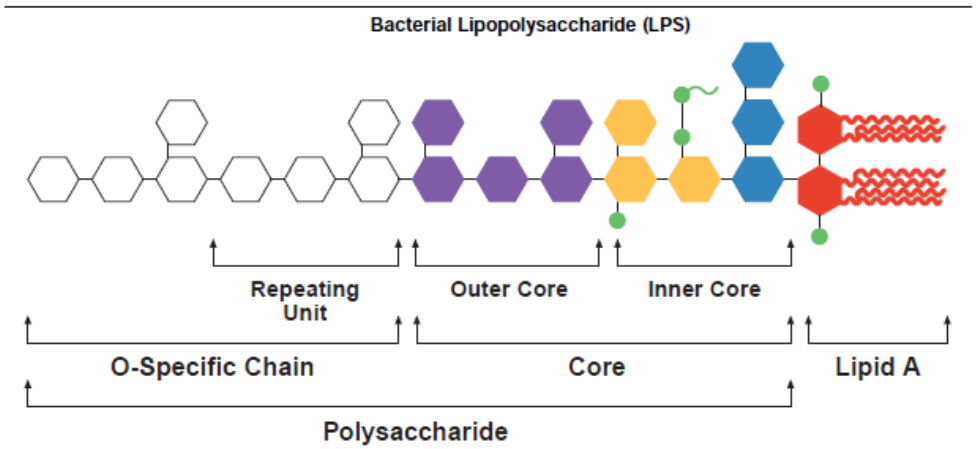
Extracorporeal therapies for sepsis

Endotoxins Bacterial fragments	• Hemoadsorption • Plasma Exchange
Cytokine removal	• HVHF • CPFA • High cut-off / superflux CVVHD

Other extracorporeal therapies

Endotoxins

- Molecular weight 10 ÷ 20 kDa in acqueous solutions
- Molecular weight > 100 kDa in non acqueous solutions (protein containing solutions)
- It complexes with protein forming LPS binding proteins which makes difficult to remove by ultrafiltration
- Highly stable in temperature and pH.



Adapted from Rietschel, *et al.*, *Progress in Clinical & Biological Research* 189:31-51, 1985

Polymixin B

- Polymyxin B is a cyclic cationic polypeptide antibiotic derived from *Bacillus polymyxa* with bactericidal action against Gram-negative bacteria.

- Polymyxin B binds to the cell membrane and alters its structure, increasing permeability. The resulting water uptake leads to cell death.

- Only used as topic antibiotic, not for systemic administration (toxicity)
- Binds endotoxin
  - Direct electrostatic interaction with lipid A region
  - Binding via primary amino groups
- Binds cytokine-inducing substances (peptidoglycans, lipoteichoic acid)

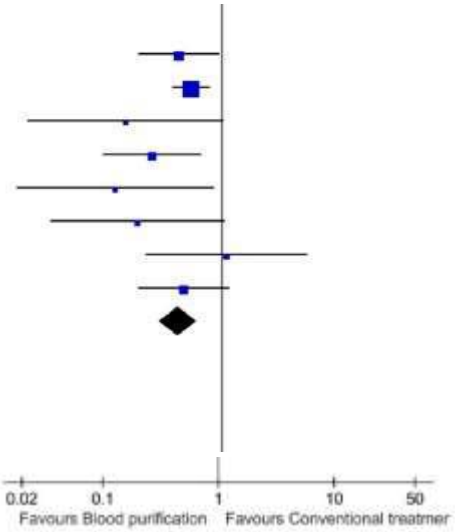
Blood Purification and Mortality in Sepsis: A Meta-analysis of Randomized Trials

Feihu Zhou, MD, PhD[1,2], Zhiyong Peng, MD, PhD[1], Raghavan Murugan, MD, MS, FRCP[1], and John A. Kellum, MD, FCCM[1]

3.1.9 Hemoperfusion with PMX-B							
Nakamura, 1999	12	30	14	20	17.2%	0.57 [0.34, 0.96]	1999
Nemoto, 2001	32	54	39	44	37.1%	0.67 [0.52, 0.85]	2001
Nakamura, 2002	2	9	7	9	3.9%	0.29 [0.08, 1.02]	2002
Nakamura-I, 2003	9	35	16	25	13.0%	0.40 [0.21, 0.76]	2003
Nakamura-II, 2003	2	10	8	10	3.9%	0.25 [0.07, 0.90]	2003
Nakamura, 2004	3	15	6	10	4.9%	0.33 [0.11, 1.03]	2004
Vincent, 2005	5	17	5	18	5.6%	1.06 [0.37, 3.02]	2005
Cruz, 2009	11	34	16	30	14.5%	0.61 [0.34, 1.09]	2009
Subtotal (95% CI)		**204**		**166**	**100.0%**	**0.57 [0.45, 0.72]**	
Total events	76		111				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.16$, df = 7 (P = 0.32); $I^2 = 14\%$

Test for overall effect: Z = 4.74 (P < 0.00001)



Apparent benefit for PMX Hemoperfusion, but low patient number

Zhou F. et al, *Crit Care Med* 2013; 41: 2209-20

Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock

The EUPHAS Randomized Controlled Trial

Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis [EUPHAS]

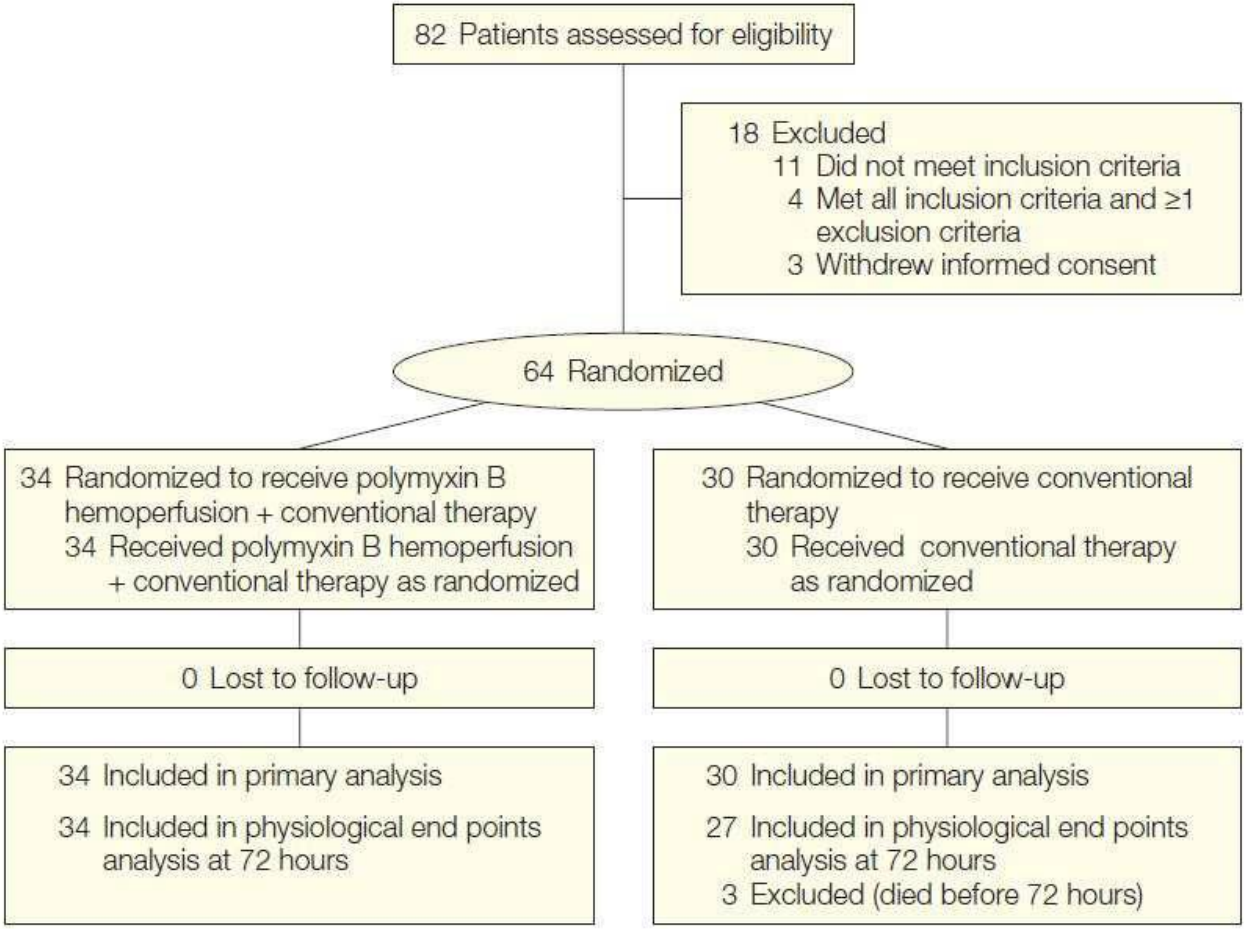
- Prospective randomised study, 12/2004 – 12/2007 in 10 centres (Italy)
- Patients were eligible for enrollment if they had severe sepsis or septic shock due to intra-abdominal cavity infection requiring emergency abdominal surgery and had to be included within 6 hours of surgery (treatment within 24 hours)
- Conventional therapy (n=30) vs conventional therapy plus 2 treatments with Polymyxin B haemoperfusion (n=34).
- Primary endpoints: MAP and vasopressor requirement
- Secondary endpoints : PaO_2/FIO_2 ; SOFA scores; 28-day mortality.

- Trial was stopped early after an interim analysis showed the mortality difference in a secondary endpoint

Cruz D. et al, *JAMA* 2009; 301: 2445-52

Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock

The EUPHAS Randomized Controlled Trial



Cruz D. et al, *JAMA* 2009; 301: 2445-52

Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock

The EUPHAS Randomized Controlled Trial

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

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

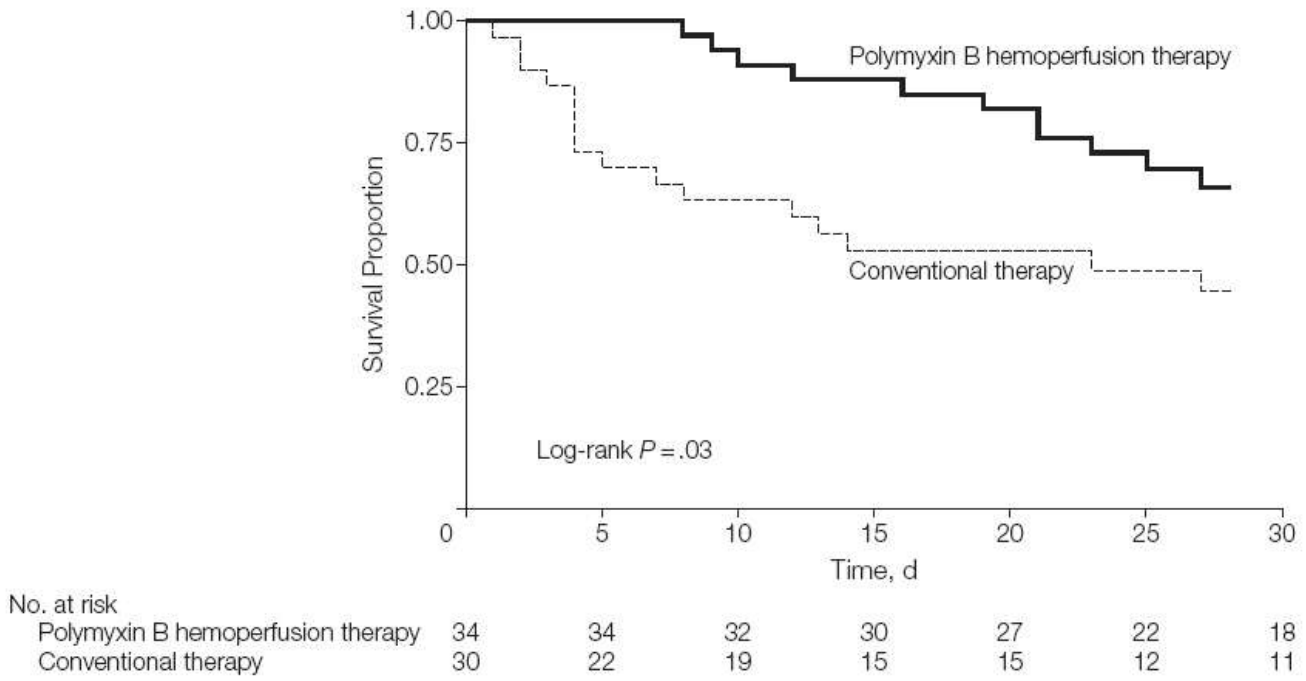
Significant improvement of circulatory stability and oxygenation within 72 h with haemoperfusion, not with standard therapy

Cruz D. et al, *JAMA* 2009; 301: 2445-52

Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock

The EUPHAS Randomized Controlled Trial

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

28-day mortality was 32% (11/34 patients) in the polymyxin B group and 53% (16/30 patients) in the conventional therapy group (unadjusted hazard ratio, 0.43; 95% confidence interval, 0.20-0.94

Cruz D. et al, *JAMA* 2009; 301: 2445-52

EUPHAS study: critique

- *Primary endpoint SOFA, not survival*
- *Study stopped prematurely; 1 or 2 patients may have prevented significant result*
- *High mortality in control group (53%)*

Polymyxin B Hemoperfusion in Clinical Practice: The Picture from an Unbound Collaborative Registry

The Early Use of Polymyxin B Hemoperfusion in the Abdominal Sepsis 2 (EUPHAS2) Collaborative Group

- Collaborative web-based registry of clinical data among users of Toraymyxin
- Data collection included patients with severe sepsis and septic shock treated with Toraymyxin over the last 3 years, up to July 2013.
- Thirty-one hospitals collected data on 306 patients with abdominal (41.8%) and non-abdominal (58.2%) sepsis
- In patients with abdominal sepsis, 28-day mortality rate was 35% with a significant reduction of the SOFA score after 72 h of treatment ($p < 0.001$).
- In patients with non-abdominal sepsis 28-day mortality rate was 49% and the SOFA score did not significantly change before and after treatment.

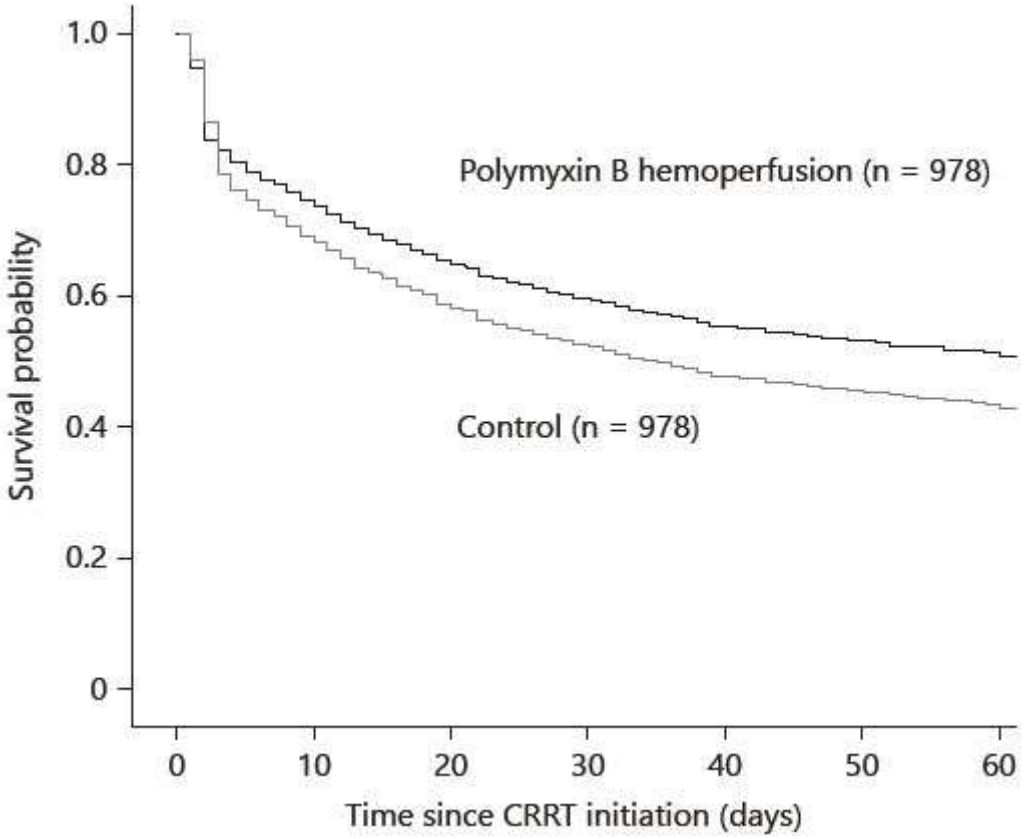
Blood Purif 2014; 37(suppl 1): 22–25

Postoperative Polymyxin B Hemoperfusion and Mortality in Patients With Abdominal Septic Shock: A Propensity-Matched Analysis*

- Patients with abdominal septic shock triggered by lower gastrointestinal tract perforation
- Retrospective analysis (nationwide inpatient database in Japan) of outcomes comparing patients
- Of 2,925 eligible patients, 642 received one or two polymyxin B hemoperfusion sessions, starting the first one on day 0 or 1.
- Propensity score matching created a matched cohort of 1,180 patients (590 pairs with and without polymyxin B hemoperfusion).
- Postoperative polymyxin B hemoperfusion did not show any survival benefit for the overall study population or any of the studied subgroups of patients with abdominal septic shock.

Iwagami M et al, *Crit. Care Med.* 2014; 42: 1187-93

Postoperative Polymyxin B Hemoperfusion and Mortality in Patients With Abdominal Septic Shock: A Propensity-Matched Analysis*

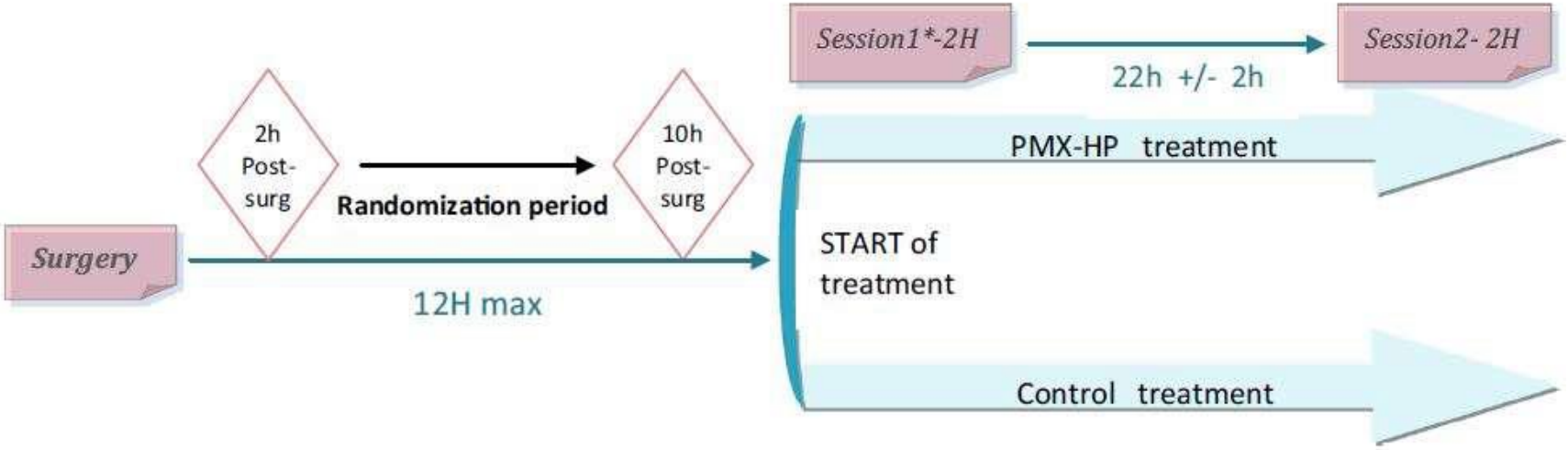


The 28-day mortality was 40.2% (393/978) in the PMX group and 46.8% (458/978) in the control group (p = 0.003)

Iwagami M et al, *Blood Purif.* 2016; 42: 9-17

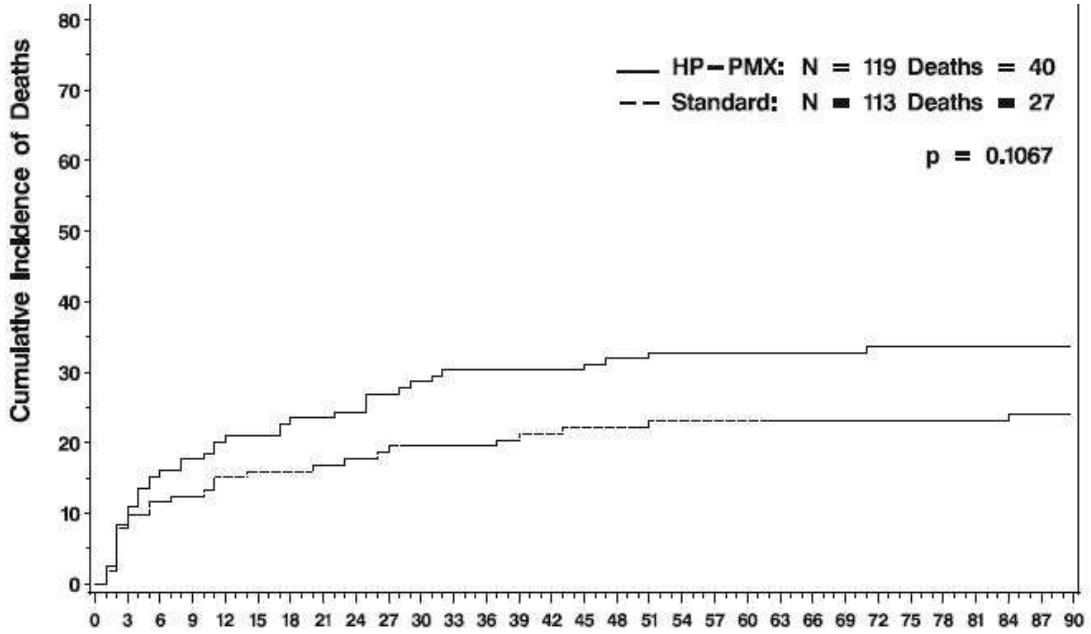
Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial

- Prospective multicenter RCT in 18 ICUs (France); October 2010 – March 2013
- 243 Patients with septic shock within 12 h after emergency surgery for peritonitis related to organ perforation
- Primary outcome: Mortality on day 28.



Payen DM et al, *Intensive Care Med* 2015; 41: 975-84

Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial



33/119 patients (27.7 %) died until day 28 in the PMX-HP group versus 22/113 patients (19.5 %) in the control group (p = 0.14, OR 1.5872, 95 % CI 0.8583–2.935).

- 2 completed PMX treatments only in 81 / 119 patients (69.8 %)
- Only 75% gram negative infections

Payen DM et al, *Intensive Care Med* 2015; 41: 975-84

Iba and Fowler *Journal of Intensive Care* (2017) 5:40
DOI 10.1186/s40560-017-0236-x

Journal of Intensive Care

LETTER TO THE EDITOR Open Access

Is polymyxin B-immobilized fiber column ineffective for septic shock? A discussion on the press release for EUPHRATES trial

Toshiaki Iba[1*] and Lucy Fowler[1,2]

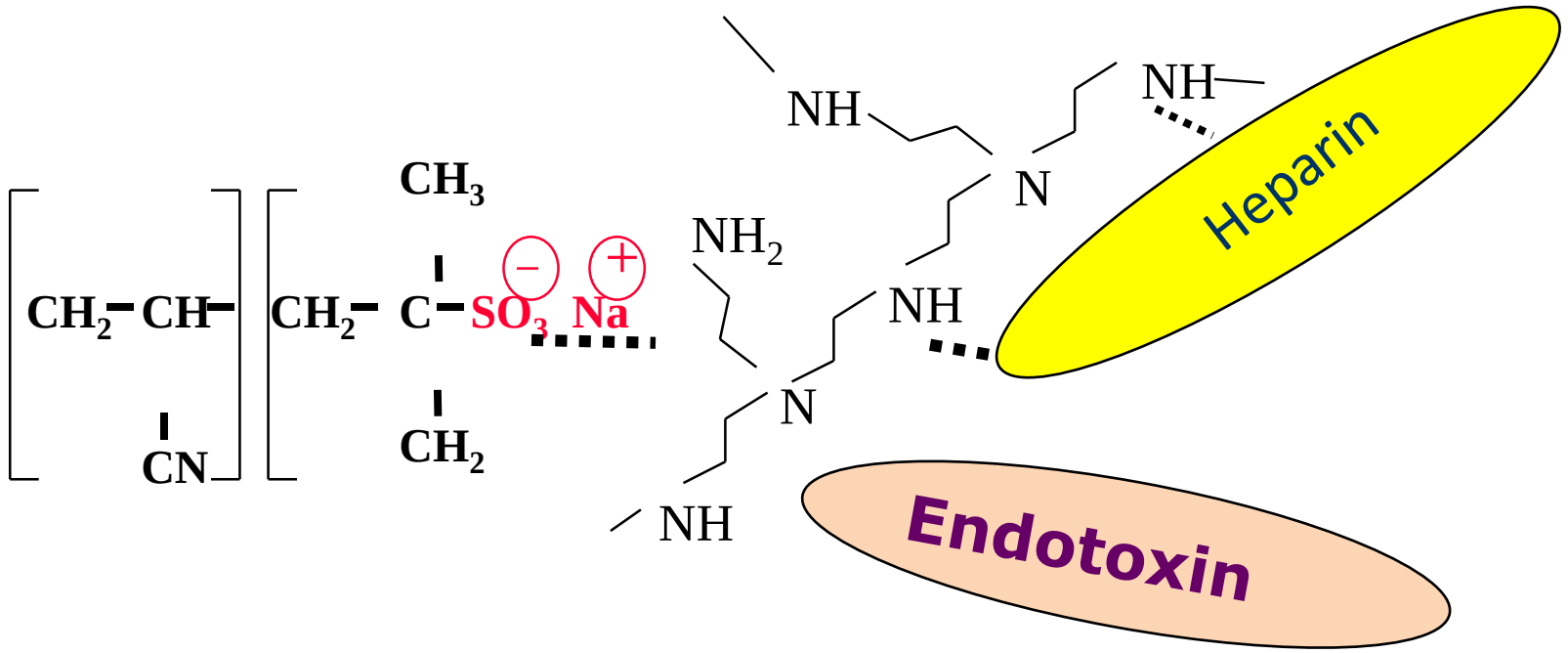
Abstract

The efficacy of polymyxin B-immobilized (PMX) fiber column on septic shock is still under debate. Recently, the result from "Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock (EUPHRATES)" trial has been announced as a press release. According to that report, less than a 5% mortality difference was recognized in the "per protocol population" ($n = 244$, 31.9 vs. 36.9%) and the decrease was not statistically significant. However, among the patients in refractory shock with a multiple organ dysfunction score of more than 9 and an EAA between 0.6 and 0.9, a 10.7% reduction in 28-day mortality was recognized ($p = 0.0474$) when they received two sessions of hemoperfusion using the PMX fiber column. Since this favorable effect was obtained from "post hoc" analysis, further study is expected.

Keywords: Polymyxin B-immobilized fiber column, Sepsis, Septic shock, Randomized controlled trial, Endotoxin activity assay

- Primary survival end-point failed again (´´per protocol analysis´´)
- Post-hoc analysis found a 10.7% mortality reduction for patients with 0.6 <Enotoxin Activity Assay <0.9.
- Further studies are needed.... Once again

Oxiris®



Basis structure (polyacrylonitrile)

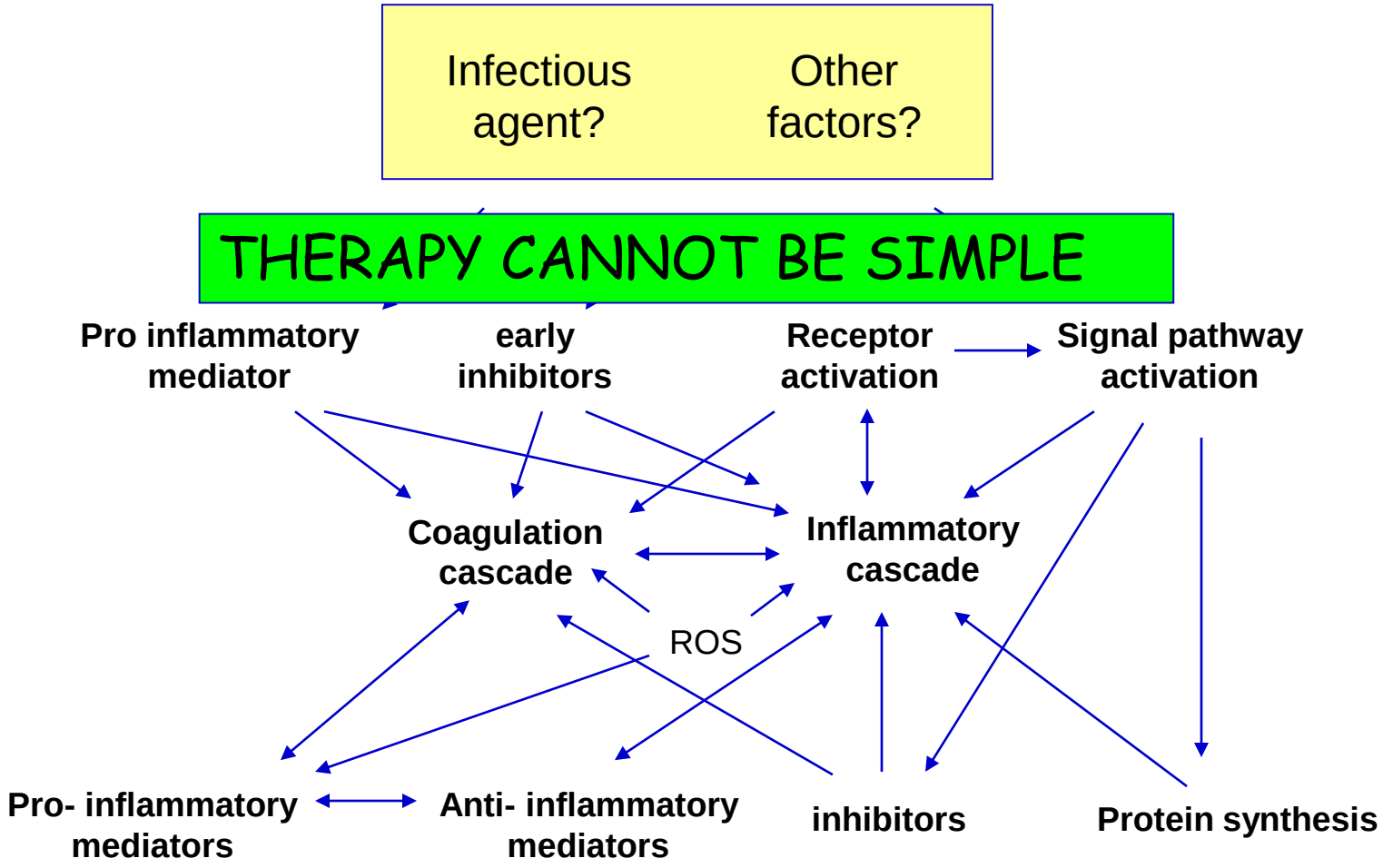
Polycation : Polyethyleneimine

Endotoxin adsorption (negatively charged)

Oxiris membrane: adsorption

- **Cytokine adsorption : adsorption takes place in the membrane bulk mainly on the sulfonic groups (negligible influence of the surface treatment) ;**
- **Endotoxin adsorption: adsorption only due to the surface treatment (interaction between amine groups of high concentrated PEI and phosphate groups of lipid A).**

Sepsis is very complex!



Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016.

Rhodes et al

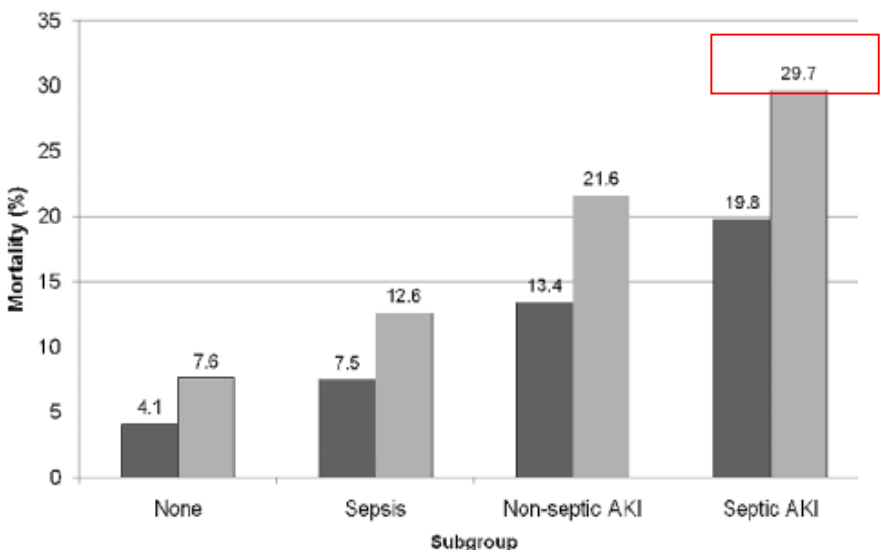
APPENDIX 2. (*Continued*). Comparison of Recommendations From 2012 to 2016

2012 RECOMMENDATIONS	2016 RECOMMENDATIONS
J. IMMUNOGLOBULINS	**J. IMMUNOGLOBULINS**
1. Not using IV immunoglobulins in adult patients with severe sepsis or septic shock (grade 2B).	1. We suggest against the use of IV immunoglobulins in patients with sepsis or septic shock (weak recommendation, low quality of evidence).
K. BLOOD PURIFICATION	**K. BLOOD PURIFICATION**
Not applicable.	1. We make no recommendation regarding the use of blood purification techniques.

Conclusions

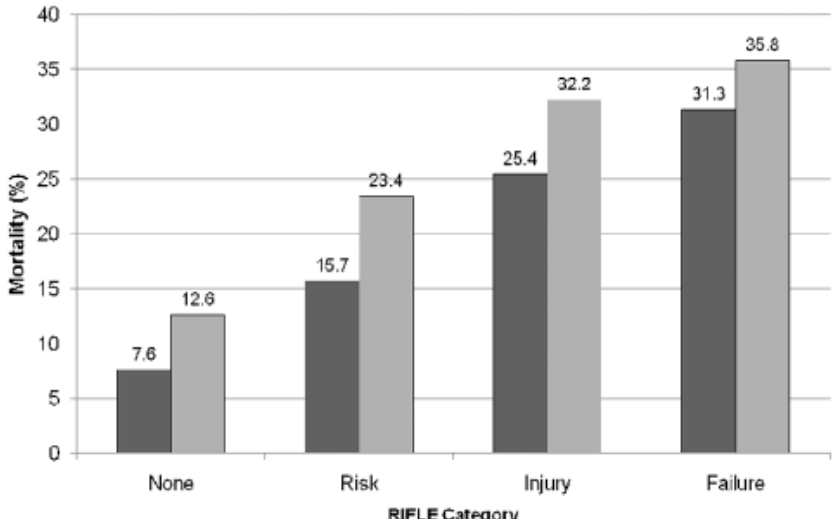
- Septic shock often complicates with AKI and still show a high mortality rate
- Its underlying mechanisms are still debated
- The ideal RRT for AKI should be tailored with the purpose to
  - control of intra/extravascular volume
  - correct acid-base disturbances
  - correct uraemia & effectively clears “toxins”
- PMX-B, Cytosorb, CPFA, HCO filters efficacy is still not proofed... Maybe different surrogate end-points (not mortality) should be looked for not to spoil these potential aids

Crude ICU and hospital mortality stratified by subgroups



Crude ICU and hospital mortality stratified by subgroups. The subgroups of patients were control, sepsis, acute kidney injury (AKI) and septic AKI. ICU, intensive care unit.

Crude hospital mortality for septic AKI estimated by Rifle criteria



Crude hospital mortality for septic and non-septic AKI stratified by RIFLE category. For each comparison of nonseptic versus septic acute kidney injury (AKI), $P < 0.0001$. RIFLE, risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function and end-stage kidney disease.

High Volume HemoFiltration

Definition of HVHF:

1. Proc 2° Conference on Crit Care Nephrology (Czhech Repub, 2007)
   - Continuous HVHF with 50 – 70 mL/Kg/h for 24 h

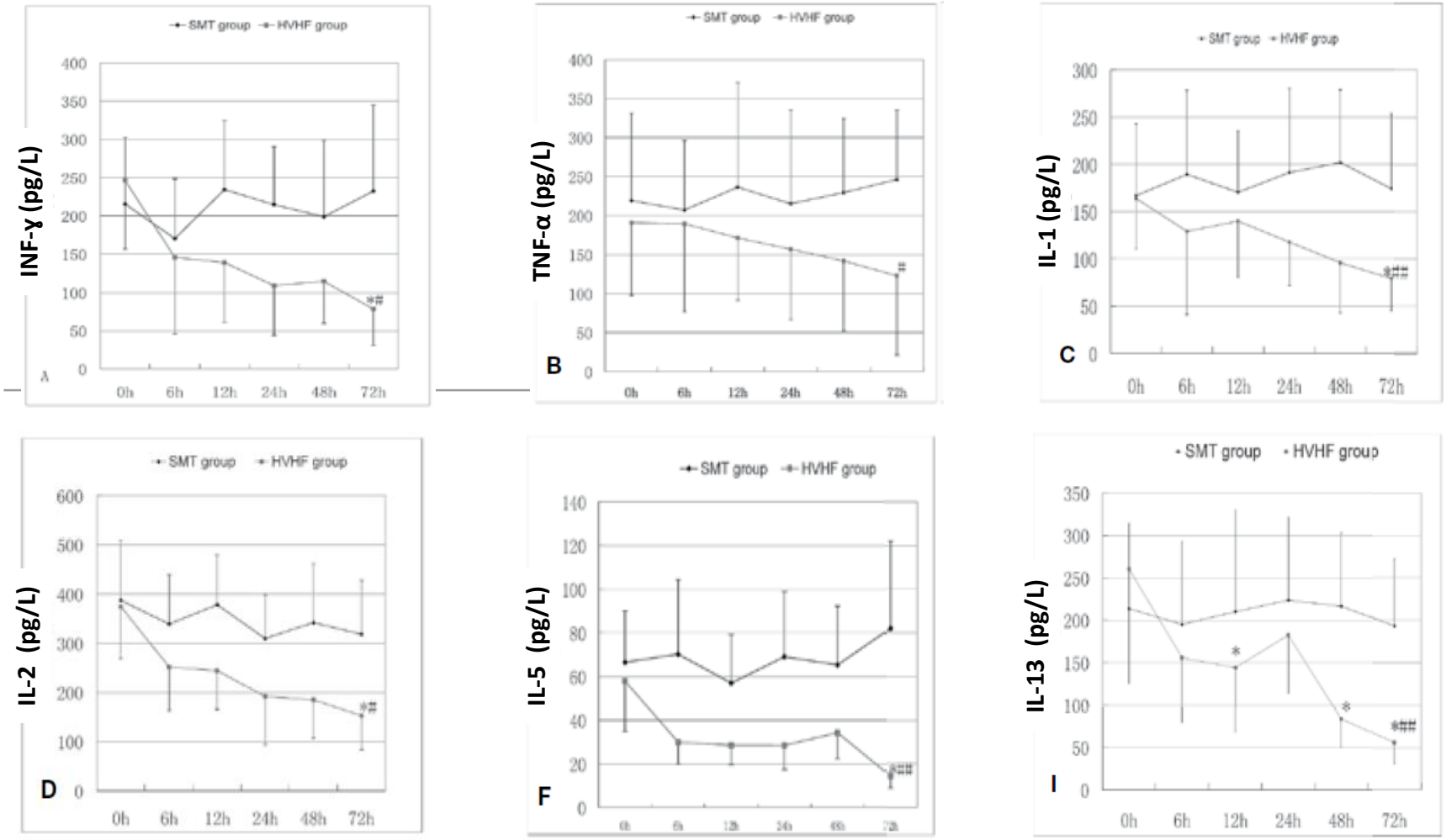
   OR

   - Intermittent HVHF 100 – 200 mL/Kg/h for 4-8 h followed by conventional CVVH
1. ADQI
   - HVHF when > 35 mL/Kg/h

PROs

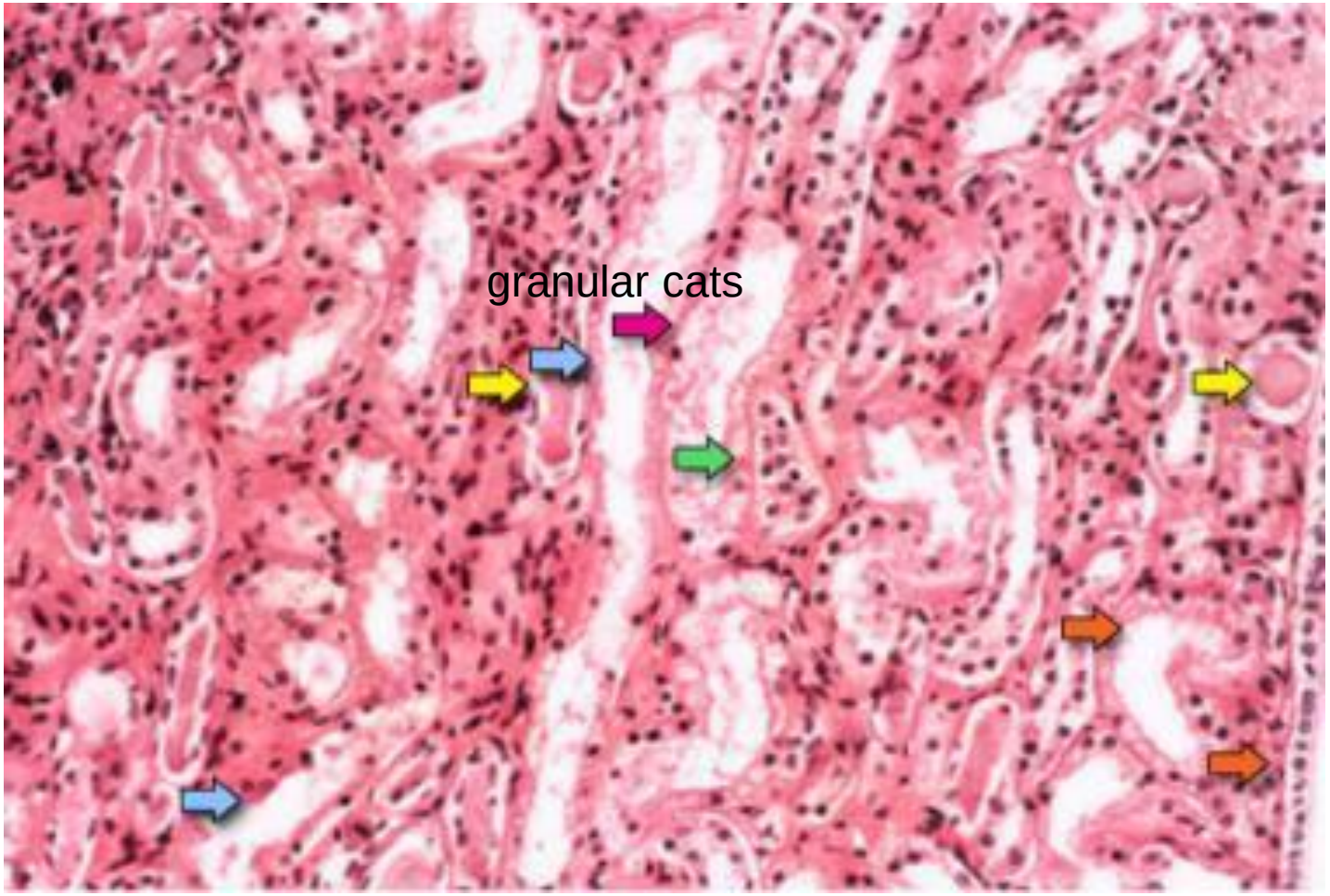
- **High KT/V of urea, great removal of middle (beta-2 microglobulin)and large molecule**
- **New concepts on cytokines compartimentalization**

“Improvement of immune dysfunction in patients with severe acute pancreatitis by high-volume hemofiltration”



Medical therapy vs High-Volume HF (4000 ml/h)

Gong D. Int J Artif Organs 2010


granular cats