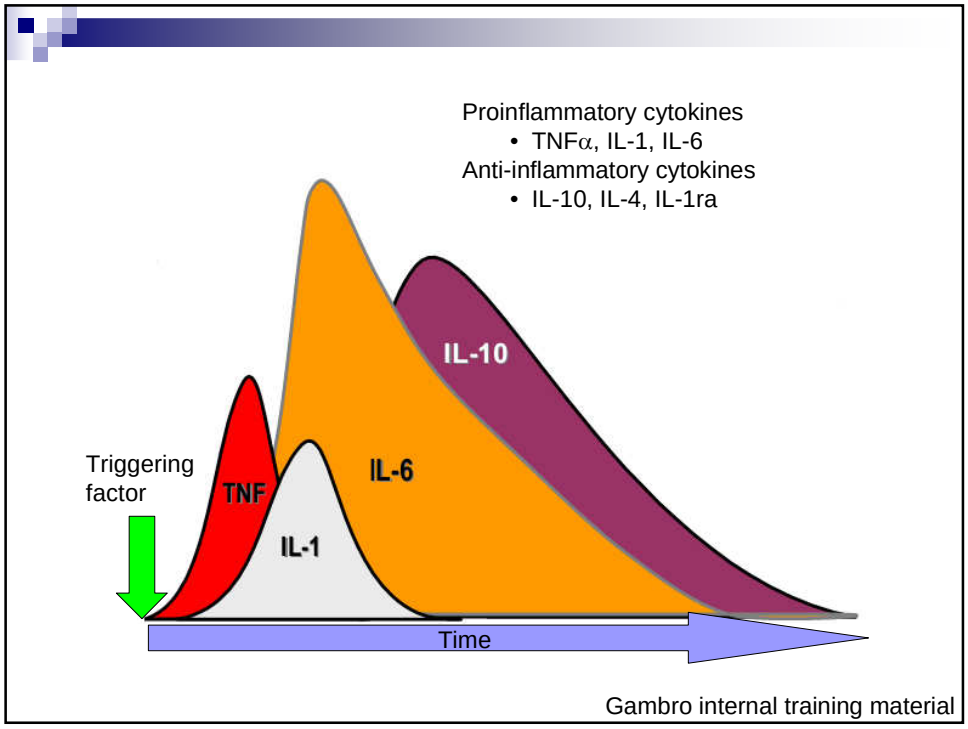
Extra-corporeal Blood Purification in Sepsis

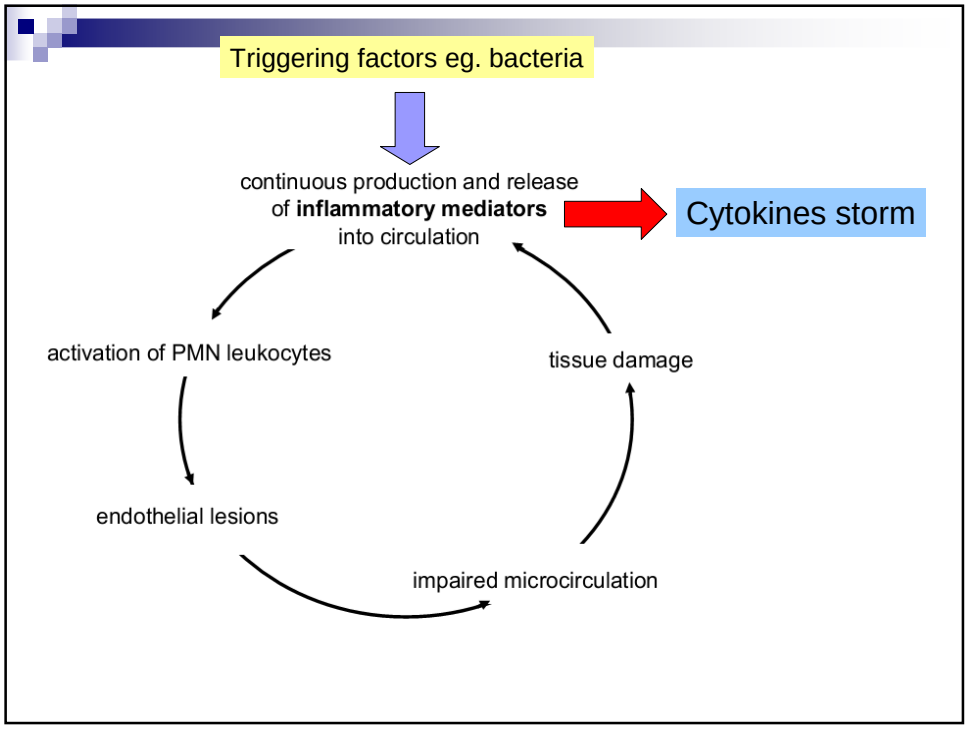
Dr. HP Shum
Nephrologist and Critical Care Physician
Department of Intensive Care
Pamela Youde Nethersole Eastern Hospital

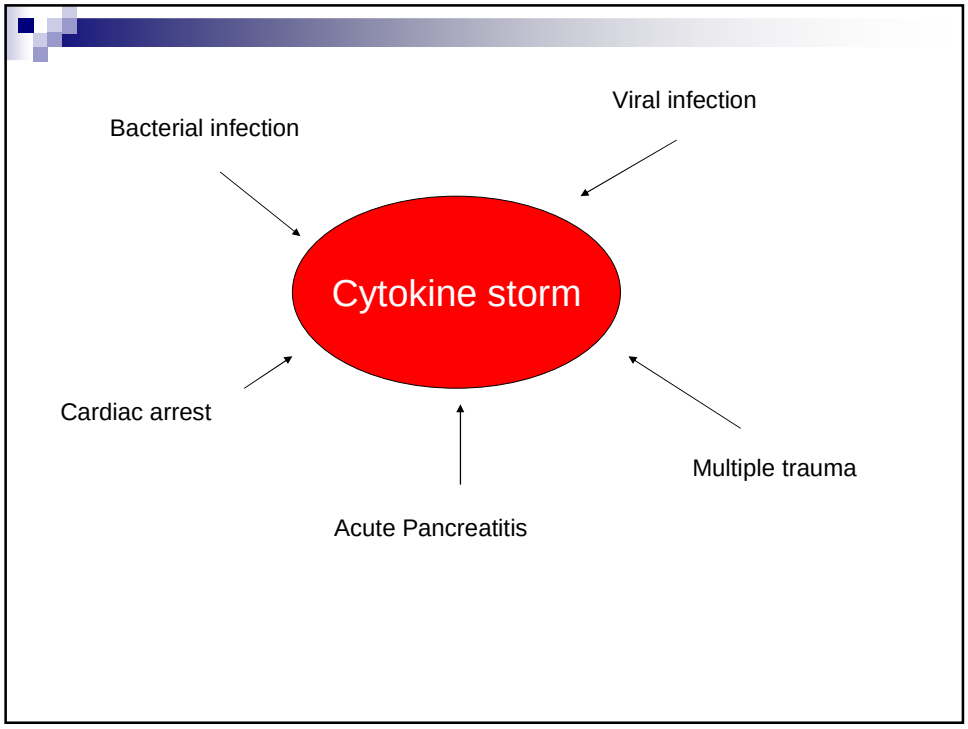
Bacteria Virus

Cytokine release

- Cell signaling protein/ glycoprotein/ peptides
- Chemotactic effect on different types of WCC


Proinflammatory cytokines
• TNFα, IL-1, IL-6
Anti-inflammatory cytokines
• IL-10, IL-4, IL-1ra
IL-10
IL-6
TNF
IL-1
Triggering factor
Time
Gambro internal training material


Triggering factors eg. bacteria
continuous production and release of inflammatory mediators into circulation
Cytokines storm
activation of PMN leukocytes
tissue damage
endothelial lesions
impaired microcirculation



Why bother to control the cytokine storm?

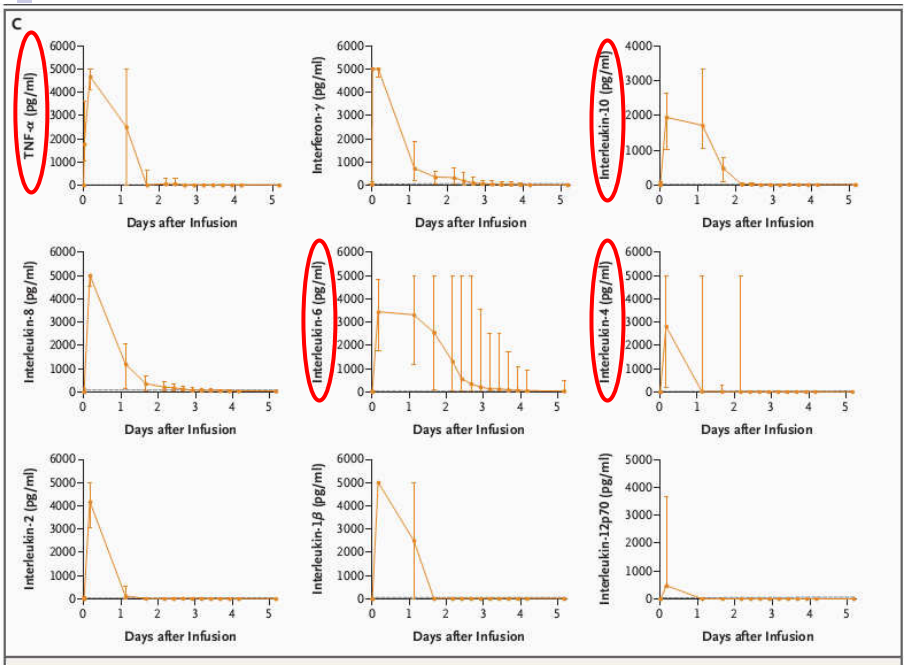
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

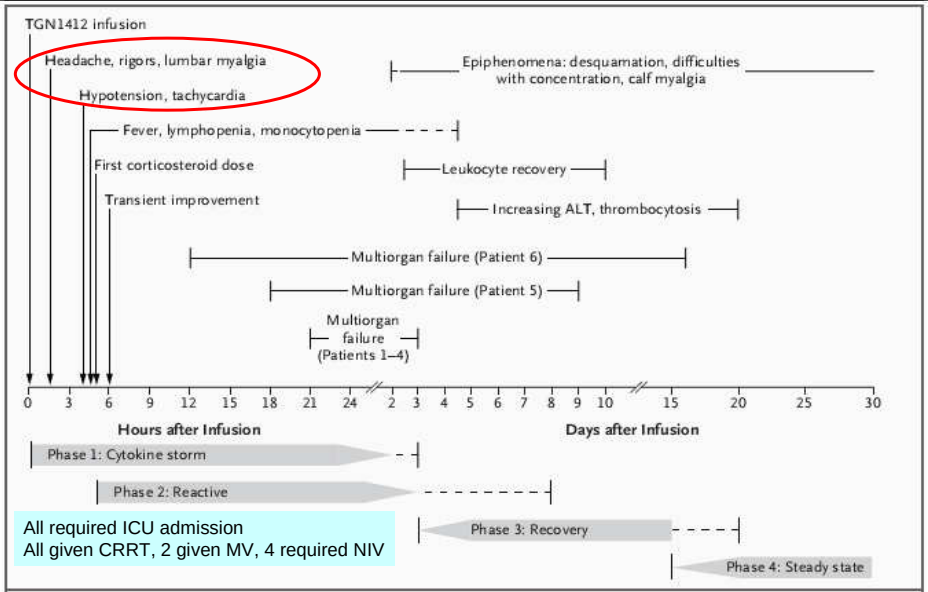
Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

Suntharalingam G et al; N Engl J Med. 2006 Sep 7;355(10):1018-28.



Suntharalingam G et al; N Engl J Med. 2006 Sep 7;355(10):1018-28.



All required ICU admission
All given CRRT, 2 given MV, 4 required NIV

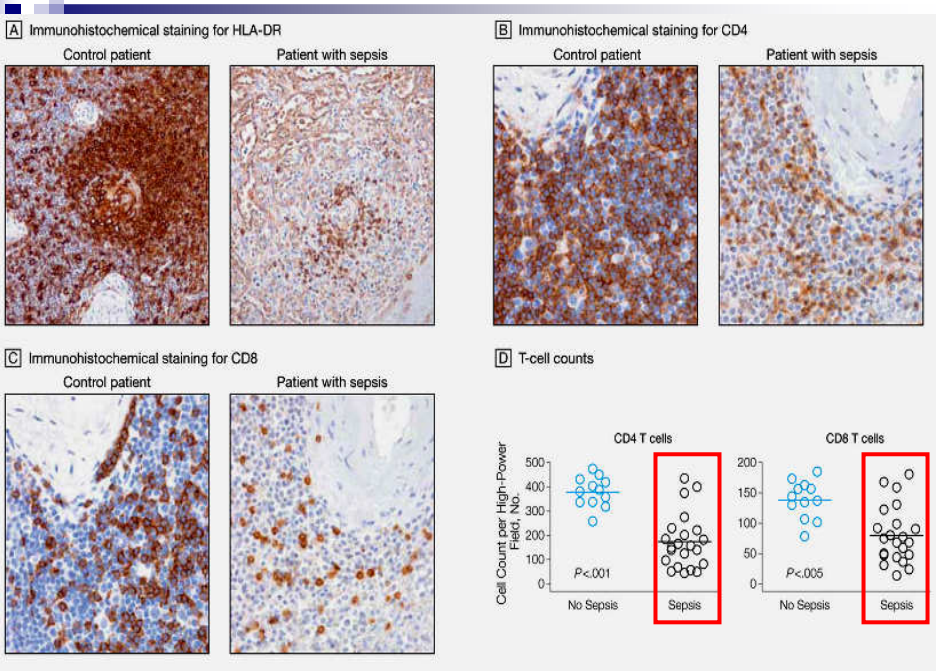
Figure 1. Summary Timeline of the Main Events after Infusion of TGN1412.
The course is divided into four phases: cytokine storm, reactive, recovery, and steady state. ALT denotes alanine aminotransferase. Dashed lines represent the responses of Patients 5 and 6 (who were the most seriously ill).

Suntharalingam G, et al; N Engl J Med. 2006 Sep 7;355(10):1018-28.

Immunoparalysis

- 40 patients who died in ICU due to severe sepsis
- Rapid postmortem spleen and lung tissue
- Control spleens (n=29) were obtained from patients who were declared brain-dead or had emergent splenectomy due to trauma

Boomer JS et al; JAMA. 2011 Dec 21;306(23):2594-605



Boomer JS et al; JAMA. 2011 Dec 21;306(23):2594-605

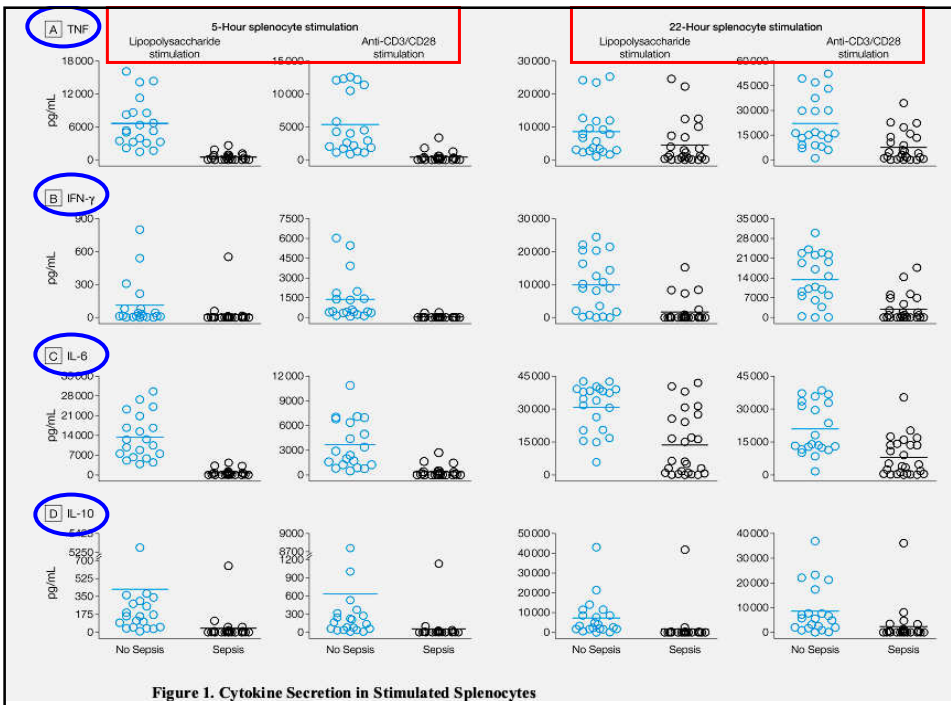


Figure 1. Cytokine Secretion in Stimulated Splenocytes

Boomer JS et al; JAMA. 2011 Dec 21;306(23):2594-605

Should every septic patients being treated with cytokines modulation technique?

Understanding the Inflammatory Cytokine Response in Pneumonia and Sepsis

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

Kellum JA et al; Arch InternMed. 2007;167(15):1655-1663

- Cohort study of 1886 subjects hospitalized for CAP
- TNFα, IL-6, IL-10 were checked daily for 1st wk and then wkly
- 583 patients (31%) developed severe sepsis
- 149 died (26%)

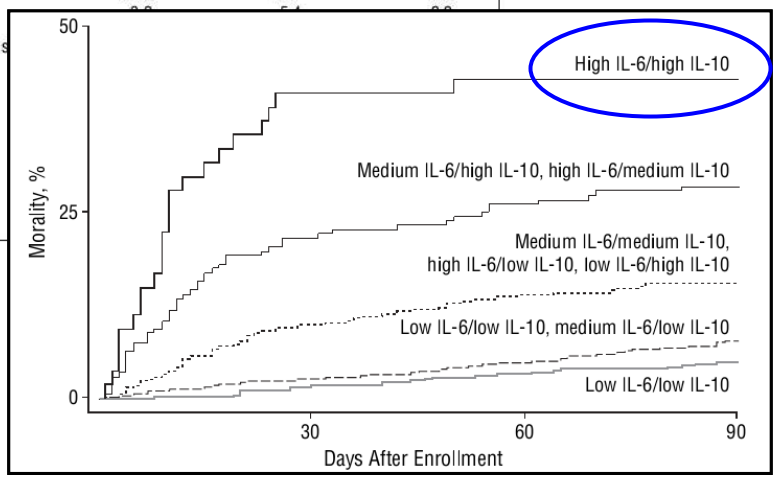
Table 2. Cytokine Concentrations at Presentation to the Emergency Department[a]

Cytokine	All			No Severe Sepsis on Day 1			Severe Sepsis During Hospitalization		
	Severe Sepsis on Day 1	No Severe Sepsis on Day 1	*P* Value	Developed Subsequent Severe Sepsis	Never Developed Severe Sepsis	*P* Value	Dead at 90 d	Alive at 90 d	*P* Value
IL-6 (n = 1426)									
Level	98.7	38.7	<.001	51.4	36.5	.03	109.4	59.6	.01
Elevated	89.9	82.3	.01	87.4	81.1	.03	92.2	87.1	<.001
IL-10 (n = 1423)									
Level	10.4	5.1	<.001	5.1	5.0	.91	10.7	6.5	.01
Elevated	55.1	34.5	<.001	33.6	34.7	.75	53.0	41.1	.03
TNF (n = 1424)									
Level	7.5	5.5	<.001	6.0	5.5	.20	7.3	6.3	.22
Elevated	45.9	34.3	.001	35.9	33.9	.58	38.4	47.0	.11

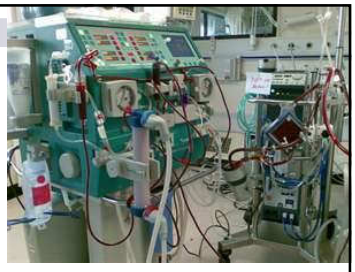
Kellum JA et al; Arch InternMed. 2007;167(15):1655-1663

Group Membership for IL-6 and IL-10 Patterns Based on Trajectory Analysis

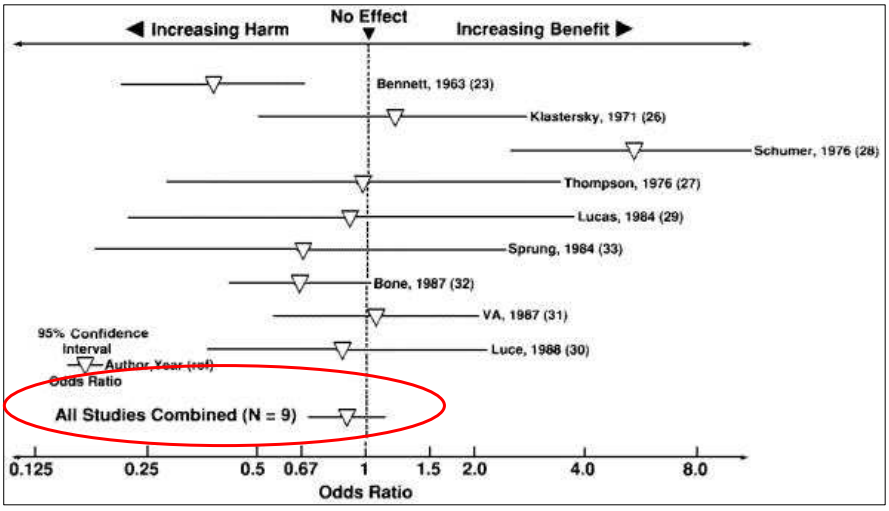
Group	Low IL-10	Medium IL-10	High IL-10
Overall frequency, %			
Low IL-6	26.1	7.9	1.4
Medium IL-6	35.6	13.7	3.8
High IL-6			
Developing severe s			
Low IL-6			
Medium IL-6			
High IL-6			
Dead at 90 d, %			
Low IL-6			
Medium IL-6			
High IL-6			



Kellum JA et al; Arch InternMed. 2007;167(15):1655-1663

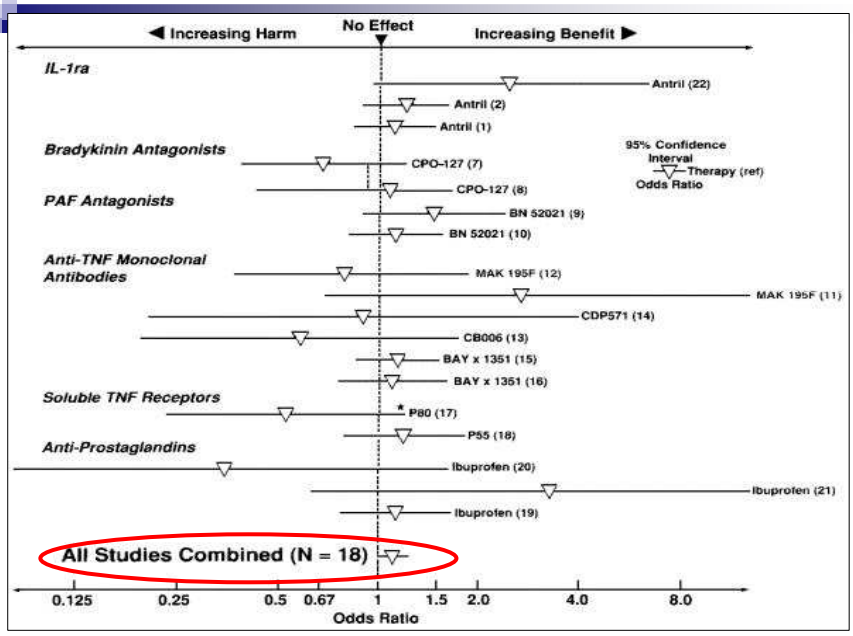


Why should we use Blood Purification in septic patients?



9 steroid trials on sepsis and septic shock

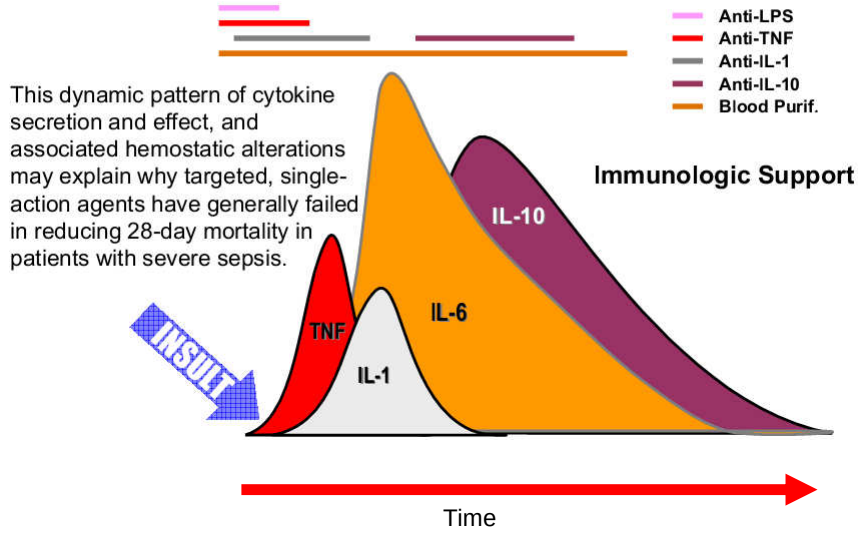
Zeni D et al; Crit Care Med 1997; 25: 1095-1100



18 non-steroid anti-inflammatory agents for sepsis and septic shock

Zeni D et al; Crit Care Med 1997; 25: 1095-1100

Immunomodulation in Sepsis

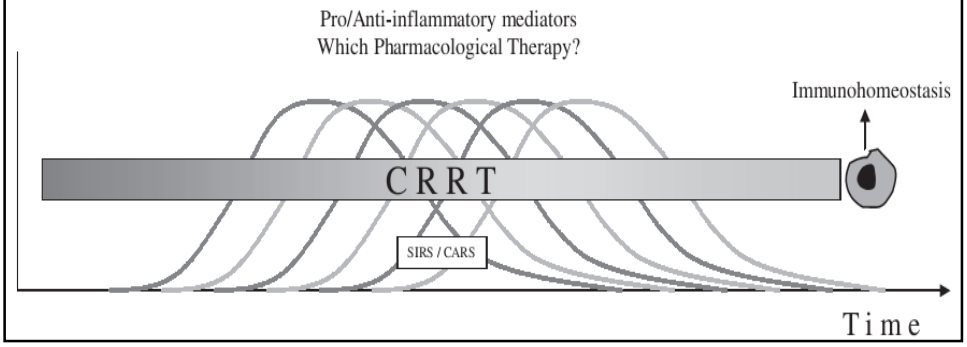


Gambro internal training material

In fact, only blood purification provides non-specific cytokines clearance

Peak concentration hypothesis

- Ronco et al (Artif Organ 2003, 27:792-801)
- Elimination of peaks of cytokine blood concentrations during early phase of sepsis
- Stop inflammatory cascade
- Limit organ damage
- Decrease MOFS



Threshold immunomodulation hypothesis

- Honore et al (Crit Care Med 2004, 32:896-897)
- Cytokine removed from blood compartment leads to removal of cytokines at tissue level
- Explained why no modification of blood cytokine level during blood purification but patient's outcome improved

Mediator delivery hypothesis

- Di Carlo and Alexander et al (Int J Artif Organs 2005 28:777-786)
- HVHF responsible for increase lymphatic flow
- Drag and displacement of inflammatory mediators to the blood compartment, so available for removal

Cellular level theory

- Peng et al (Contrib Nephrol 2010, 165:322-328)
- Blood purification act on inflammatory cell level
- Restore immune function through the regulation of monocytes, neutrophils and lymphocytes

Cytokinetic hypothesis

- Kellum et al (Crit Care 2011, 15:205-213)

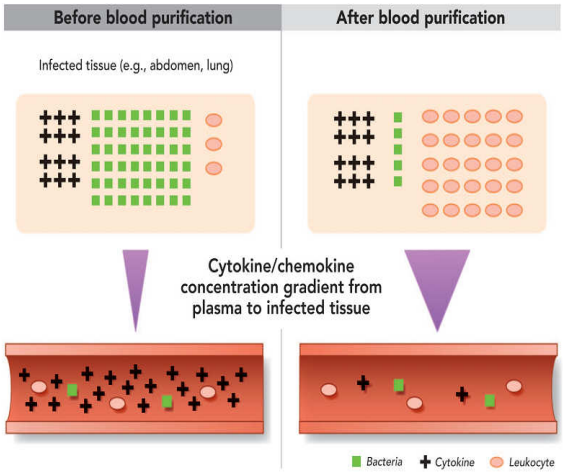


Fig. 2. The "cytokinetic" model. By removing inflammatory mediators from the blood compartment, blood purification therapies increase the cytokine/chemokine concentration gradient from plasma to infected tissue. Leukocyte trafficking is therefore driven toward the nidus of infection, increasing local bacterial clearance.

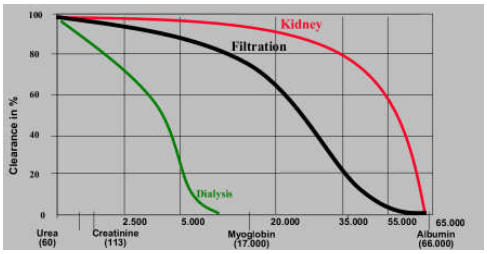
Rimmelé T et al; Anesthesiology. 2012 Jun;116(6):1377-87.

What kind of techniques currently available?

High volume hemofiltration

- Circulating inflammatory mediators are mostly water soluble
- Middle molcules (5-60kDa)
- Membrane carry some adsorption capacity

	Protein Binding	MW
C3a desArg	no	8900
C5a desArg	no	10000
Il-1a	no	31000
Il-1ra	no	18000
TNFα	Partly	17000 x 3
HMGB1	yes	25000
Il-6	no	24400
Il-8	no	8400
Il-10	no	20600
Factor D	yes	23700



HVHF

- Definition
  - 50-70ml/kg/hr for continuous HVHF or 100-120ml/kg/hr for pulse HVHF (Honore et al)
  - >35ml/kg/hr (ADQI workgroup)

Table 1. Most Important Recent Human Studies that Assessed the Effects of HVHF as a Blood Purification Technique on Hemodynamics and Survival

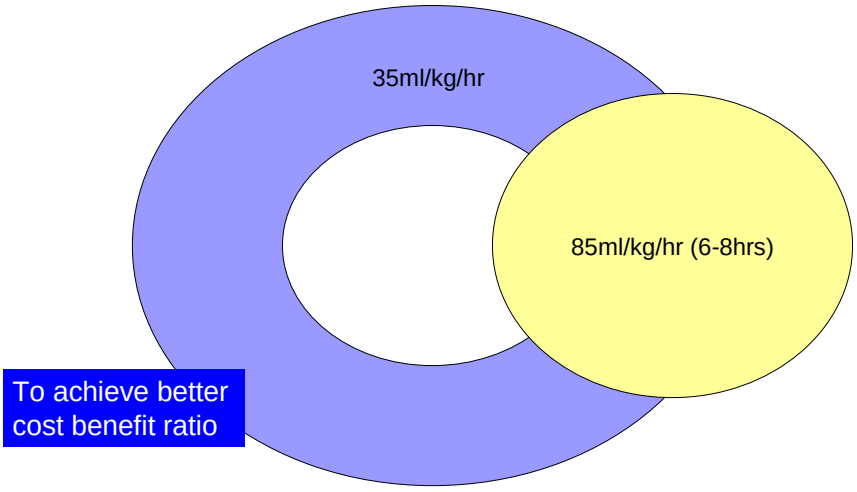
Design	First Author, Year	Number of Patients	Clinical Setting	Dose (ml · kg^{-1} · h^{-1})	Improved Hemodynamics with HVHF	Improved Survival with HVHF	*P* Value (Survival)
Randomized, controlled trials	Laurent, 2005[75]	61	Resuscitated cardiac arrest	200	Yes	Yes; 6-mo survival: 21–45%	0.026
	Jiang, 2005[77]	37	Severe acute pancreatitis	4,000 ml/h	Yes	Yes; 14-day survival: 68.4–94.4%	<0.01
	Boussekey, 2008[14]	20	Septic shock	65	Yes	No	0.65
	IVOIRE study, on going	~150	Septic shock	70	—	—	—
Randomized, crossover trial	Cole, 2001[58]	11	Septic shock with multiorgan failure	6,000 ml/h	Yes	Not assessed	N/A
Prospective, cohort, uncontrolled trials	Honoré, 2000[70]	20	Refractory septic shock	115	Yes	Yes; 28-day survival: (Expected) 21–(Observed) 45%	<0.05
	Joannes-Boyau, 2004[71]	24	Septic shock	40–60	Yes	Yes; 28-day survival: (Expected) 30–(Observed) 54%	<0.075
	Ratanarat, 2005[74]	15	Severe sepsis	85 (pulse HVHF)	Yes	Yes; 28-day survival: (Expected) 30%–(Observed) 53%	N/A
	Cornejo, 2006[69]	20	Refractory septic shock	100	Yes	Yes; Hospital survival: (Expected) 37–(Observed) 60%	<0.03
Retrospective trials	Piccinni, 2006[73]	80	Septic shock	45	Yes	Yes; 28-day survival: 27.5–55%	0.005
	Zhu, 2009[88]	63	Severe acute pancreatitis	60–80	No	Yes; 28-day survival: 65.5–91.2%	0.014

Rimmelé T et al; Anesthesiology. 2012 Jun;116(6):1377-87.

HVHF – clinical consideration

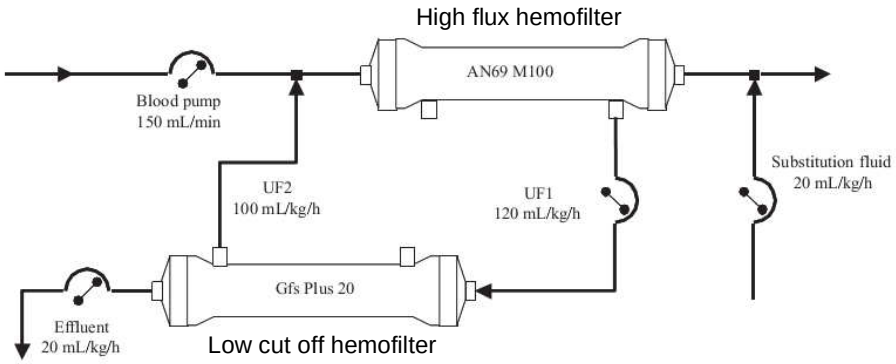
- Increase blood flow in order to keep filtration fraction <25%
  - 250ml/min BF, HCT 0.35 -> Qp = 162.5ml/min -> if 20% FF -> 32.5ml/kg/hr for 60kg patient (post dilution)
  - Consider pre + post dilutional
- Using hemofilter with high KUF (>20ml/hr/mmHg)
- Loss of small molcules including micro-nutrients, amino-acids, vitamin, trace element
- Antibiotic dosing adjustment
- Cost
- Nursing workload

Pulse HVHF



Ratanarat R et al: Semin Dial. 2006 Jan-Feb;19(1):69-74.

Cascade HF



Rimmelé T et al: Ther Apher Dial. 2009 Feb;13(1):63-70.

Prismaflex

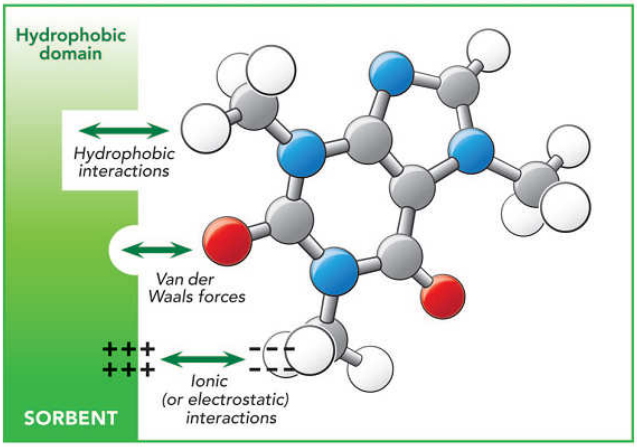
Multifiltrate

Diapact

AK200US

5008

Hemoadsorption

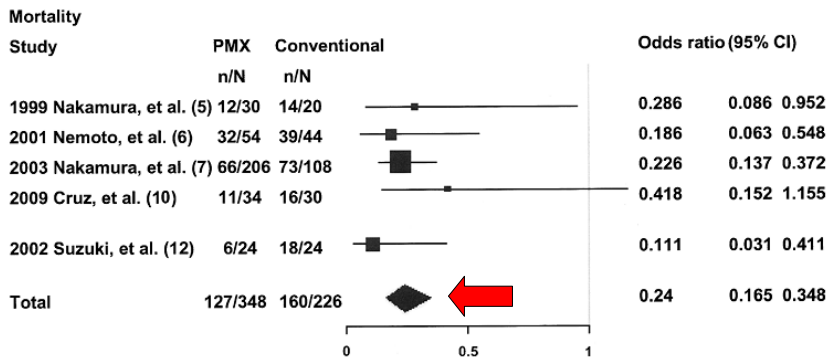


Selective or non-selective removal of endotoxin / cytokines/ superantigens etc

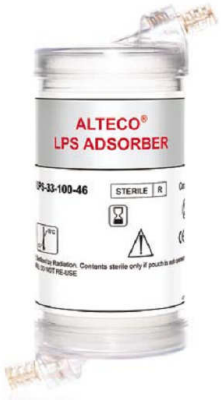
Rimmelé T et al; Anesthesiology. 2012 Jun;116(6):1377-87.

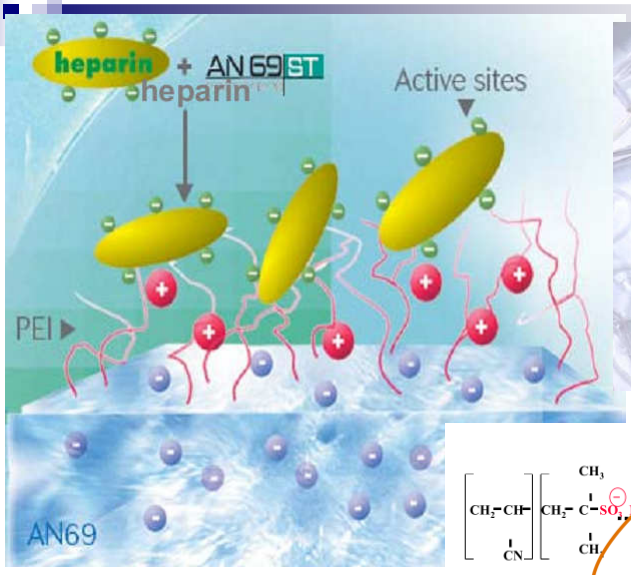
	PMX						Conventional				
Study	n	PMX duration	APACHE II score	BP	Vasopressor	Mediator	Pao_2/Fio_2 ratio	n	APACHE II score	BP	Mediator	Pao_2/Fio_2 ratio
Nakamura et al. (5)	30	2 h × 1	24.8	↑	↓	Endotoxin ↓, PF-4 ↓ P-selectin ↓, β-TG ↓		20			Endotoxin → PF-4 →, β-TG → P-selectin →	
Nemoto et al. (6)	54	4 h × 1 or 2	22	↑→*		Endotoxin ↓		44	23			
Nakamura et al. (7)	206	2 h × 2	24.6	↑		Endotoxin ↓, IL-6 ↓ TNF-α ↓, sIL-2 receptor ↓ Endothelin ↓, PF-4 ↓ (survivor)	↑	108	24			
Nakamura et al. (8)	15	2 h × 2	28.4			Endotoxin ↓ Urinary NOx ↓		10	28		Endotoxin → Urinary NOx →	
Vincent et al. (9)	17	2 h × 1	18.7	↑	→	Endotoxin → IL-6 →		19	16.7	↑	Endotoxin → IL-6 →	
Cruz et al. (10)	34	2 h × 2	21	↑	↓		↑	30	20	→		→

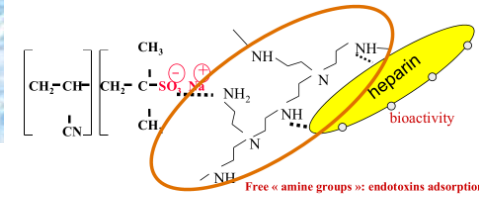
Mitaka C et al; Shock. 2011 Oct;36(4):332-8.



Mitaka C et al; Shock. 2011 Oct;36(4):332-8.







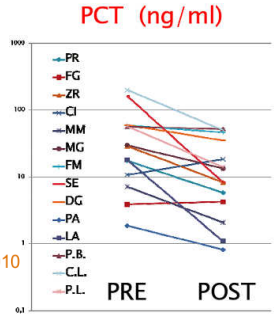
Gambro internal training material

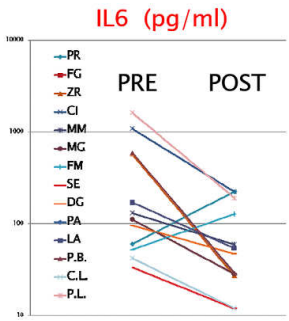
AN69 | Polyethylene-imine | heparin

Treatments:

- oXiris used in **CVVHDF**, effluent dose **50 ml/kg/h** (40% diffusive, 60% convective)

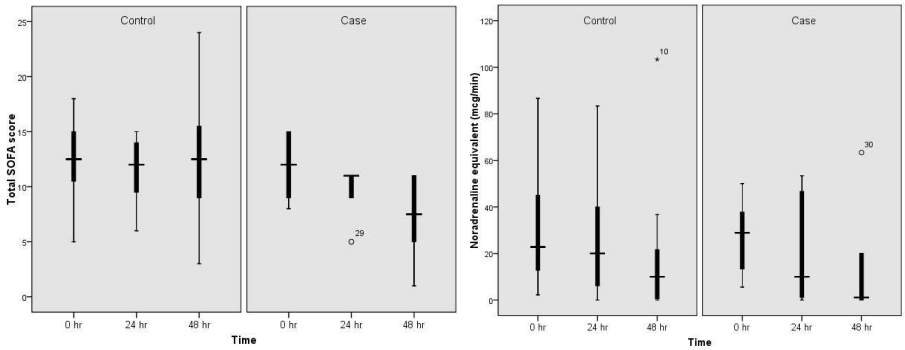
	PRE TREATMENT (mean ± std)	POST TREATMENT (mean ± std)	T-TEST STATISTICS
SOFA	13.4±2.4	8.7±3.9	p<0.001
MAP (mmHg)	64±20	82±16	p<0.01
URINE OUTPUT (ml/12H)	550±380	840±650	p<0.05
NOREPINEPHRINE (γ/kg/h)	0.35±0.35	0.02±0.03	p<0.001





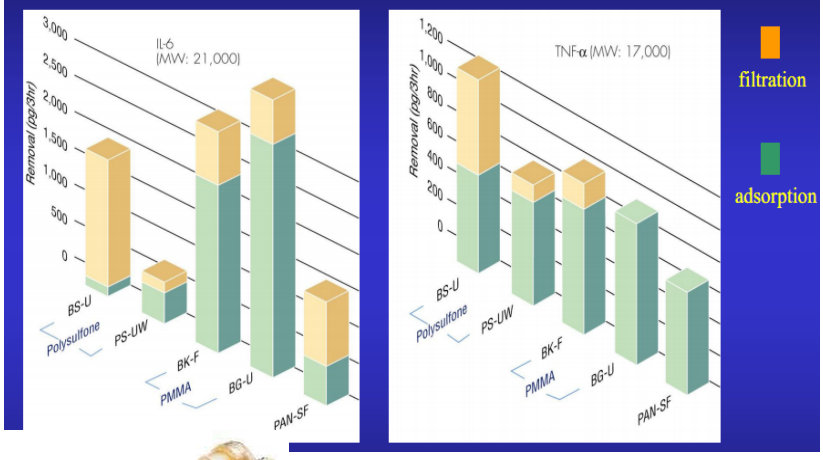
Caravetta et Al. SMART congress 2010

6 patients with septic shock due to Gram negative bacterial infection
Compare with 24 histological controls



	Case (N=6)	Control (N=24)	P value
ICU LOS (days)	6.2 (4.0, 18.5)	7.5 (5, 18)	0.716
Hospital LOS (days)	21.0 (17.5, 25.8)	19.5 (10.5, 51.5)	0.876
ICU mortality	2 (33.3%)	10 (41.7%)	1.0
Hospital mortality	3 (50%)	12 (50%)	1.0

Comparison of removal for several cytokines (*in vitro*)



Polymethylmethacrylate (PMMA) membrane hemofilter remove cytokines from blood mainly by adsorption to membrane matrix of the hemofilter

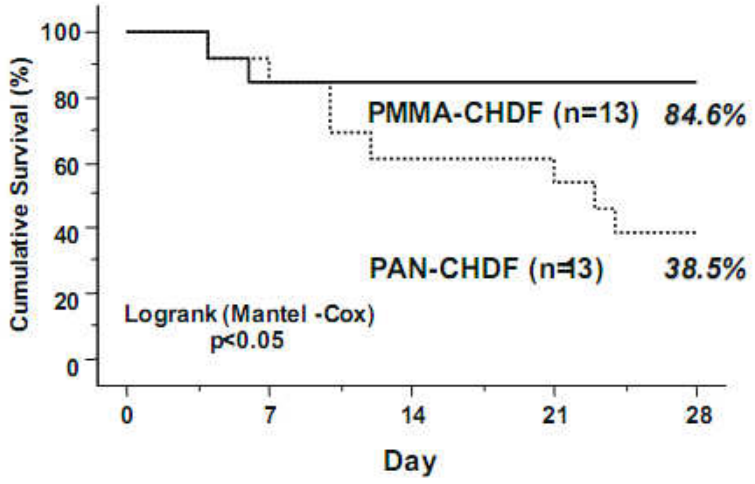
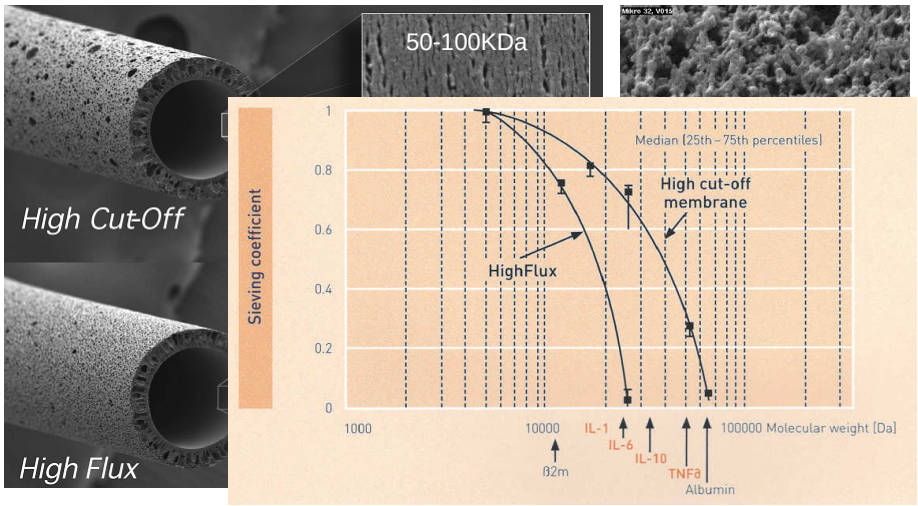


Fig. 3. Comparison of cumulative survival of septic ARF patients between PAN–CHDF group and PMMA–CHDF group and PMMA–CHDF group.

Matsuda K et al: Transfus Apher Sci. 2009 Feb;40(1):49-53

High cut-off HF/ HD



Haase M et al; Int J Artif Organs. 2007 Dec;30(12):1031-41

Comparison on High Permeability Filters

Company	Fresenius	Gambro	Gambro
Filter name	EMiC2	septeX/HCO1100	Theralite
Membrane material	Fresenius Polysulfone®	(PAES Membrane) HCO Membrane	PAES Membrane
Therapy mode	CVVHD/SLEDD	CVVHD	CVVHD
Effective Surface	1.8 m2	1.1 m2	2.1 m2
Cut-off	circa 40 kDa	45 kDa	45 kDa
Target molecules	Middle molecules, Immunglobulin Light Chains, Myoglobin	Cytokines in septic patients	Immunglobulin Light Chains
Sieving coefficient for albumin	0.01	0.1	0.2
Machine	multiFiltrate	PrismafleX	e.g. AK200
Blood flow	100-350 ml/min	80-400 ml/min	200-500 ml/min
max. Treatment time	72h	24h	?

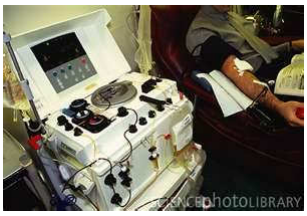


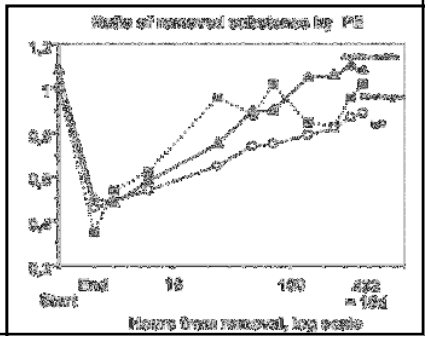
Plasmapheresis

TABLE 3. Various randomized studies using plasma exchange/plasmapheresis in the treatment of severe sepsis and in MODS

Study	*n*	Main mode of therapy	Survival (%)	*p*
Reeves et al. (26)	14/16c	PF	57/50	ns
Busund et al. (27)	54/52c	PE	67/44	0.05
Nguyen et al. (28)	5/5c	PE	100/20	< 0.05

PE, plasma exchange by centrifugation technique; PF, plasma exchange by filtration; c, control.





Stegmayr B et al: Semin Dial. 2012 Mar-Apr;25(2):171-5

Coupled plasma filtration adsorption (CPFA)

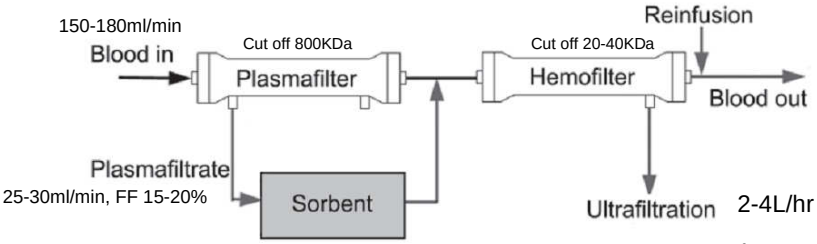


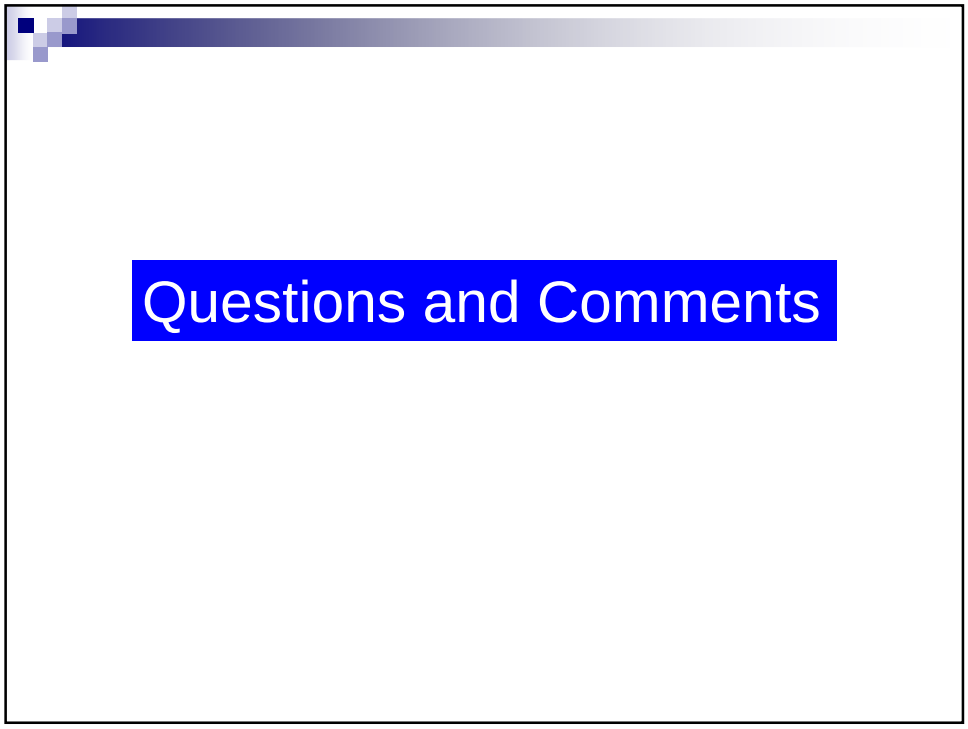
Figure 3. Coupled plasma filtration adsorption circuit.

- Advantage:
  - lower flow of plasma allows a longer contact time with the sorbent
  - biocompatibility problems avoided

Formica M et al; Contrib Nephrol. 2007;156:405-10

Take home message

- Septic source control and early appropriate antibiotic are the most important component for sepsis
- Blood purifications are supportive treatment
- Recent researches on blood purification for sepsis produce encouraging results
- Cytokines +/- endotoxin removal may offer extra clinical benefit in severe sepsis / septic shock cases when compared with traditional CRRT


Questions and Comments