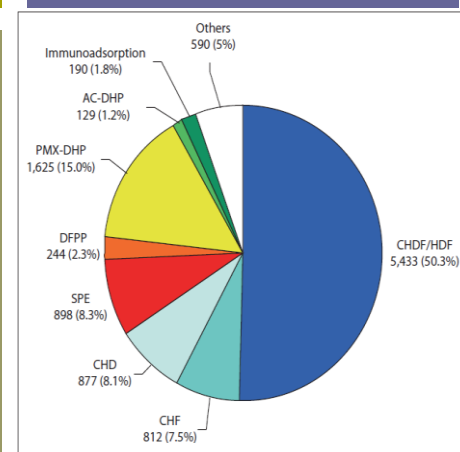




Άλλοι μέθοδοι Αφαίρεσης στην ΜΕΘ

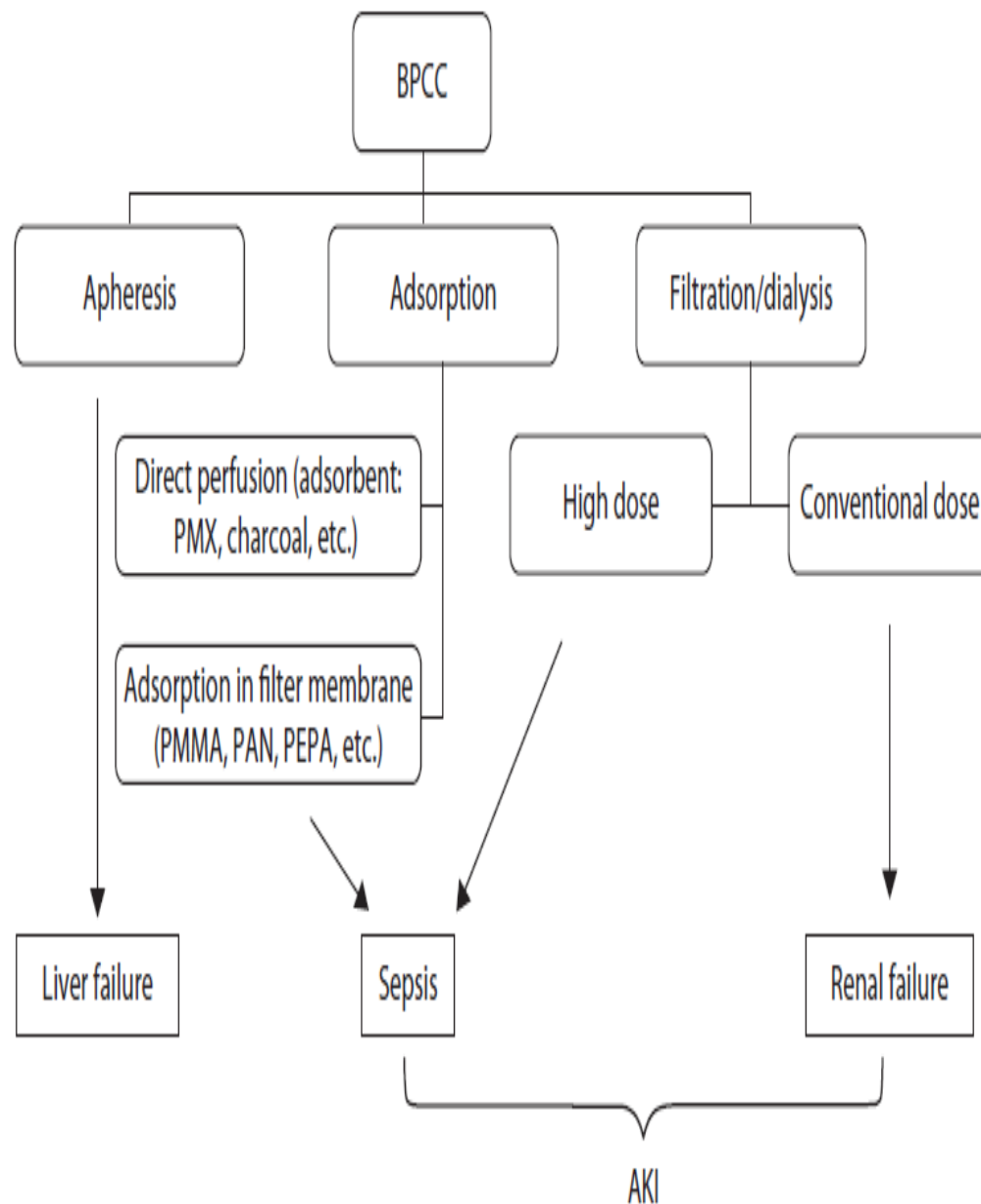
Ιωάννης Γ. Γριβέας

Νεφρολογικό Τμήμα 401 ΓΣΝΑ



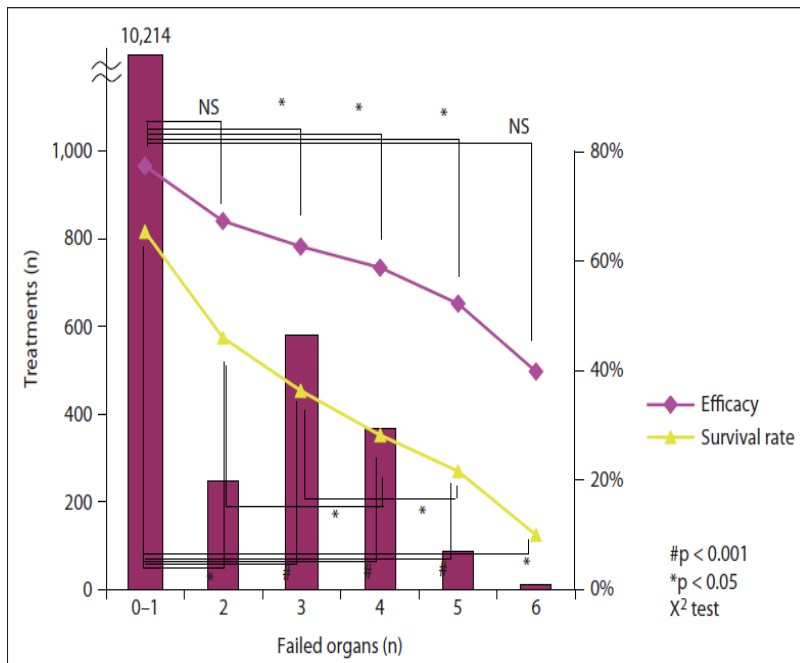


Classification of blood purification in critical care



+ Therapeutic Apheresis

- ◆ Extracorporeal procedure in removing abnormal blood cells and plasma constituents.
- ◆ Plasmapheresis, leukapheresis, erythrocytapheresis and thrombocytapheresis.
- ◆ Membrane or centrifugation.



Immune Cells as an Organ



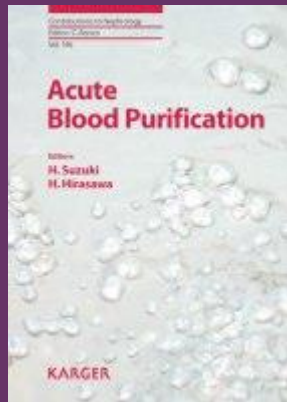
Mass of immune cells = 2×10^{12} cell = about 2 kg

Lined up gives this a distance of $2 \times 10^{12} \times 10 \mu =$

20.000 km !



Application of Blood Purification in Critical Care



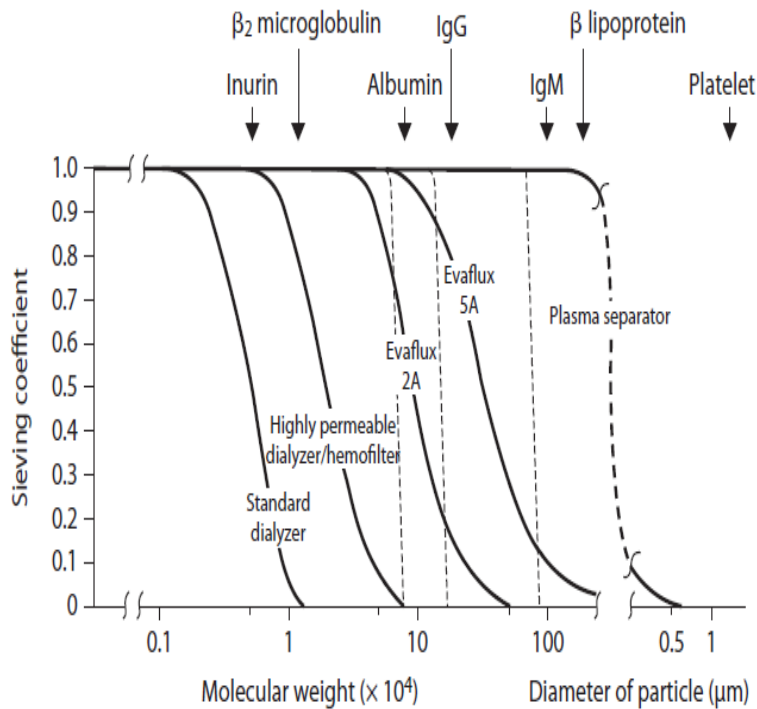
- Blood purification treatments, are used in emergency rooms and ICU because critically ill patients are treated using total life support, including extracorporeal circulation.
- The quick removal of toxic/pathogenic substances by blood purification can improve survival rate or at least ensure that the healing time is shortened compared to that required for conventional treatments.
- Because each method has a distinct technique for the removal of accumulated substances and improves homeostasis in critically ill patients to different extents, the method that is most appropriate for treatment has to be chosen and used in a timely manner, depending on the condition of the patient.



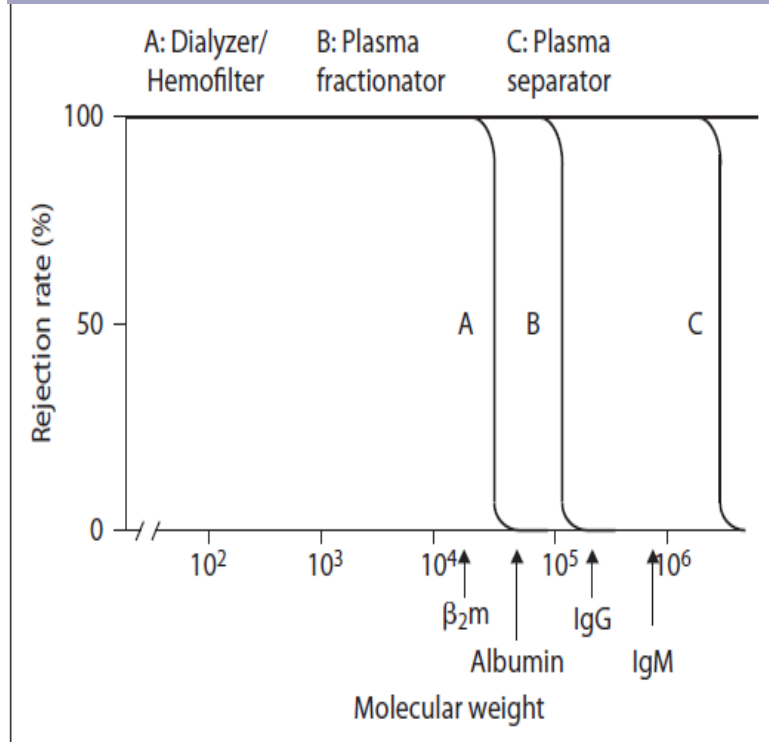
Membranes for Blood Purification



5 kinds of blood purification membranes



Ideal blood purification membrane



+ Selective apheresis



TABLE 3. *Devices and Indications for Selective Apheresis*

Device/procedure	Ligand/principle	Indications (examples)
Ig-Immunoabsorption Prosorba	Anti-Ig-ab; SPA-sepharose (Ig-Therasorb; Immunosorba)	Kidney transplantation, DCM, SLE, anti-FVIII-ab
Coraffin	SPA-silica	Rheumatoid arthritis
LDL-Immunoabsorber (LDL-Therasorb)	Peptides PDCM349, PDCM075	DCM
Liposorber	Anti-apoprotein B100-ab	Hypercholesterolemia
DALI	Dextran sulfate-cellulose	Hypercholesterolemia, SLE
HELP	Polyacrylate-Eupergit	Hypercholesterolemia
Leukocyte apheresis	Heparin precipitation	Hypercholesterolemia, sudden hearing loss
Liver albumin dialysis	Cellulose acetate, polyester fibres (ADA column, Cellsorba)	Ulcerative colitis, Crohn's disease
Double filtration	Albumin, FPSA (MARS, Prometheus)	Liver failure
Glycosorb	Polyvinyl-alcohol, polypropylene	AMD, Waldenström's disease, HC
Lixelle	Blood group antigen A or B	ABO incompatible kidney transplantation
Toraymyxin	Hydrophobic ligands	AB-amyloidosis
IM-TR, IM-PH	Polymyxin B	Sepsis
Cryofilter	Tryptophane, phenylalanine	Myasthenia gravis, Guillain-Barré syndrome
	Cryofiltration	Cryoglobulinemia

Ab, antibody; AMD, age-related macular degeneration; DALI, direct adsorption of lipids; DCM, dilative cardiomyopathy; FVIII, coagulation factor VIII; FPSA, fractionated plasma separation and adsorption; HC, hypercholesterolemia; HELP, heparin induced extra-corporeal LDL precipitation; Ig, immunoglobulin; MARS, molecular adsorbent and recirculation system; SLE, systemic lupus erythematosus; SPA, staphylococcal protein A.

+ Possible mechanisms

- ◆ Removal of abnormal circulating factors:
 - Ab e.g. anti-GBM disease
 - monoclonal protein e.g. Waldenstrom macroglobulinemia
 - circulating immune complexes e.g. SLE
- ◆ Replenishment of specific plasma factor:
 - TTP
- ◆ Other effects on immune system:
 - improvement in function of RE system
 - removal of inflammatory mediators
 - shift in Ab-to-antigen ratio, resulting in more soluble forms of immune complexes
 - stimulation of lymphocyte clones to enhance cytotoxic therapy

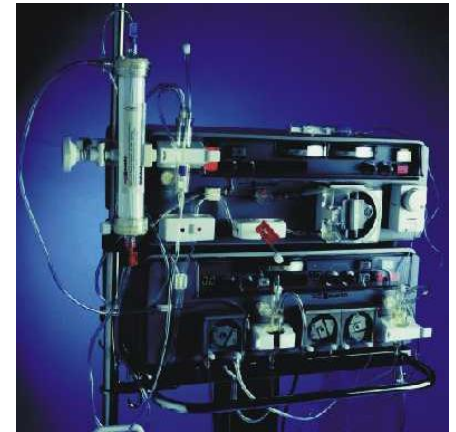




Therapeutic Plasma Exchange (TPE)

Therapeutic plasma exchange (TPE) is the automated removal of a patient's plasma and its replacement (exchange) with a suitable alternative fluid such as a solution containing albumin or fresh frozen plasma.

Its intended use is not only depletion of pathogenic, large molecular weight substances (>30–50,000 daltons) present in blood plasma, but also replacement of depleted normal/beneficial substances.



+ Rationale for TPE

- ◆ Relatively large molecules ($MW > 15000$) so that it cannot be easily removed by less expensive techniques e.g. hemofiltration.
- ◆ Long $T_{1/2}$ so that extracorporeal removal is much more rapid than endogenous clearance.
- ◆ Acutely toxic substance so that rapid elimination is indicated.



The decision to utilize TPE



- What is the pathophysiological role of the target macromolecule in the clinical disorder?
- Is there an evidence of acute toxicity caused by the substance?
- Is the patient resistant to the usual medical and/or pharmacologic therapy or does the clinical urgency demand more immediate action?
- Can the substance be efficiently removed by TPE? Generally, this applies to large molecules with relatively long half-lives (reduced synthetic rate).
- Is there evidence that reduction in levels of the offending substance is associated with improved clinical outcomes?

+ The Principles



- ◆ Use of concomitant immunosuppression:
 - reduction in plasma factors should be coupled with immunosuppressant to reduce the rate of re-synthesis.
- ◆ Treat early.
- ◆ Alternative treatment, if available, should be used first.



Table 21.1 Decision making in therapeutic plasma exchange

	Considerations
Rationale	Disease pathogenesis, published efficacy, and quality of evidence
Technical issues	Vascular access, volume of plasma to process, replacement solution
Management plan	Timing (emergent, urgent), number, and frequency of treatments
Endpoint	Clinical and/or laboratory response

Table 21.2 Consensus indications for plasma exchange

ASFA category	Interpretation	Remarks
I	Standard acceptable therapy	Proven in controlled trials
II	Available evidence supports efficacy	Case series, second line, adjunctive therapy
III	Available evidence suggests efficacy but is inconclusive	Anecdotal data, for example case reports
IV	Ineffective in controlled trials	



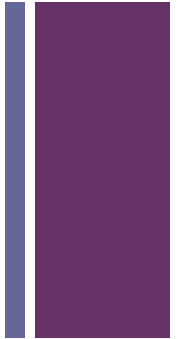
Table 21.3 Clinical examples where plasma exchange is used

Substances removed	Clinical examples	ASFA category
Autoantibodies	Goodpasture's syndrome (antiglomerular basement membrane autoantibodies)	I
Alloantibodies	Solid organ transplant (e.g., anti-HLA)	II
Immunoglobulins causing hyperviscosity	Waldenstrom's macroglobulinemia	I
Cryoglobulins	Cryoglobulin-associated skin ulceration, renal dysfunction	I
Protein-bound toxins	Amanita (mushroom) poisoning	II
Substances replenished		
ADAMTS13 (von-Willebrand factor cleaving protease)	Thrombotic thrombocytopenic purpura (TTP)	I
Coagulation factors	Hepatic failure	III



+ TPE prescription – the theoretical considerations

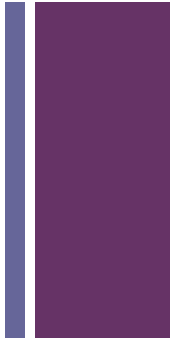
- ◆ What is being removed?
 - IgG vs IgM
- ◆ What is the desired endpoint?
 - clinical improvement or a reduction in the plasma level of a specific measurable pathologic moiety





Indications for emergency TPE

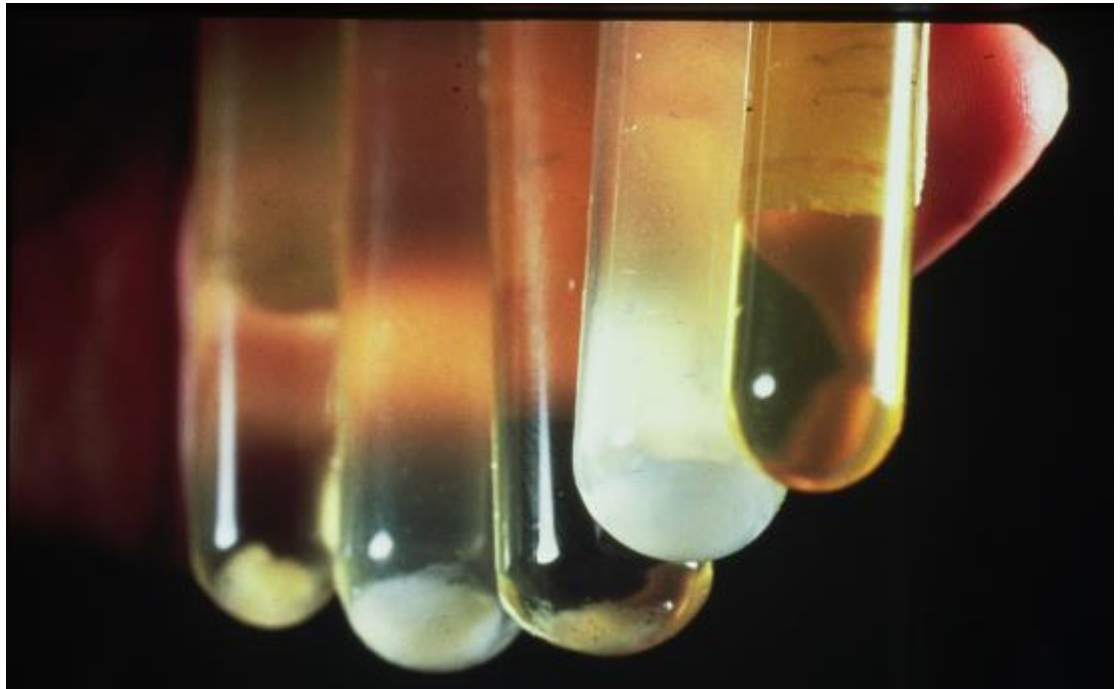
- ◆ Anti-GBM disease
- ◆ Symptomatic hyperviscosity syndrome
- ◆ TTP/HUS
- ◆ Pre-op for pts with high factor VIII inhibitor levels
- ◆ Guillain-Barre synd with resp insufficiency
- ◆ MG with resp compromise
- ◆ Acute poisoning with certain mushrooms or with other strongly protein-bound poisons e.g. paraquat





Anti-GBM disease

- ◆ For renal indication, only when S.Cr is still low and before the onset of oliguria.
- ◆ Initial high vol and freq exchanges so as to rapidly decrease the Ab titre e.g. 2 PVs daily for 7 days, followed by e.g. alternate day schedule.
- ◆ Duration dictated by clinical status and anti-GBM titres.

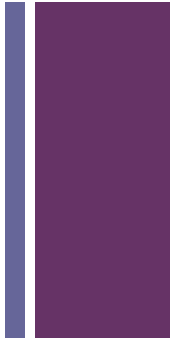


+ TTP/HUS

- ◆ Daily TPE until normalization of plt counts.
- ◆ 1.0-1.5 PVs for 1st 3 treatments followed by 1 PV exchange thereafter.
- ◆ Replace with 50-100% FFP.
- ◆ Relapse may occur within a few days of stopping the treatment.

+ Guillain-Barre syndrome

- ◆ IVIG equally effective.
- ◆ 1.0-1.5 PVs 2-3 times per week. For mild cases, 2 exchanges may suffice.
- ◆ 5% albumin as replacement.





Sepsis and MODS

- ◆ Extremely complex nature of inflammatory response in sepsis.
- ◆ Unlikely a single agent (e.g. anticytokine Rx) would work.
- ◆ Ronco proposed that ‘...unspecific removal of soluble mediators, be they pro or antiinflammatory, without completely eliminating their effect, may be the most logical and adequate approach to a complex and long-running process such as sepsis.’



+ Sepsis and MODS

- ◆ Observational studies showed no effect of exchange or plasmafiltration on cardiovascular parameters or mortality.

Ataman K et al Intensive Care Med 2002

Reeves JH et al Crit Care Med 1999

- ◆ One RCT demonstrated a 20.5% reduction in the 28-day all-cause mortality among patients with severe sepsis or septic shock treated with 1 or 2 daily plasma exchanges compared to untreated control.

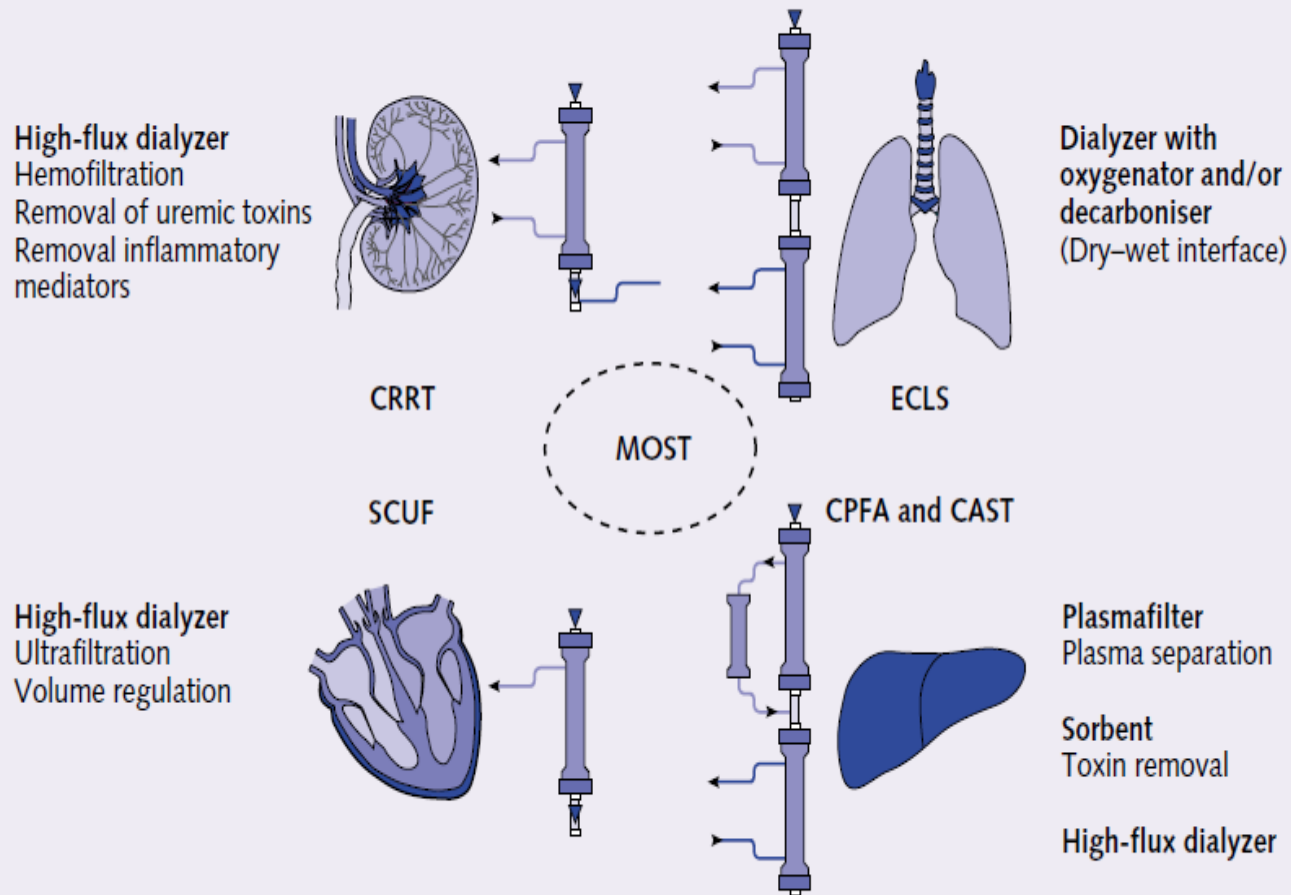
Busund R et al Intensive Care Med 2002



INTENSIVE CARE MEDICINE

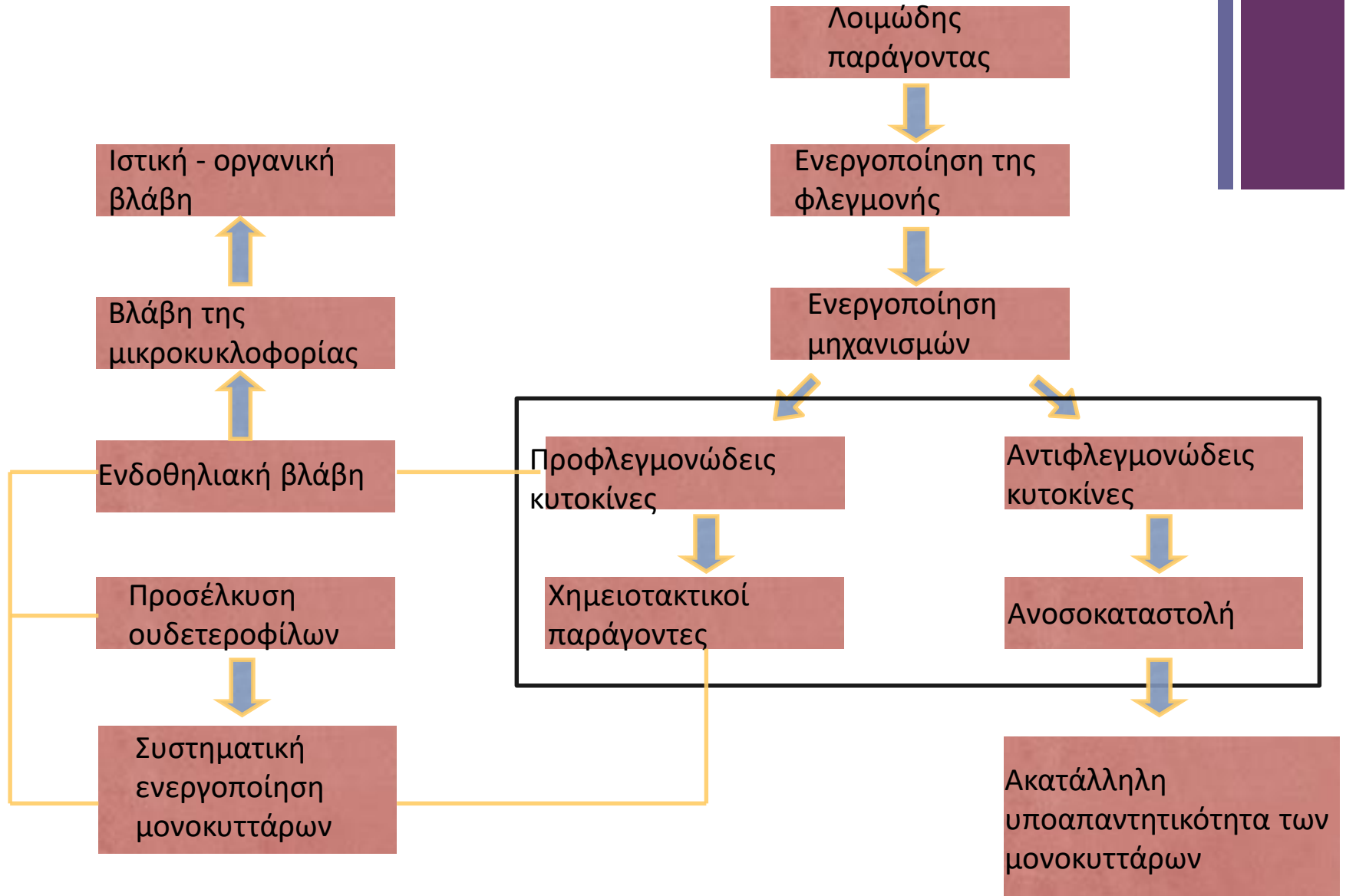
OFFICIAL JOURNAL OF THE
EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE
AND THE
EUROPEAN SOCIETY OF PAEDIATRIC & NEONATAL INTENSIVE CARE

Figure 4. The concept of MOST. Different organs can be supported by special modifications to the extracorporeal circuit. The kidney is supported by dialysis, the lung by extracorporeal CO₂ removal, the heart by optimal ultrafiltration and fluid balance, and the liver by specific filters and sorbents to remove liposoluble toxins.



CAST: counter anti-inflammatory support therapy; CPFA: coupled plasmafiltration-absorption; CRRT: continuous renal replacement therapy; ECLS: extracorporeal life support; MOST: multiorgan support therapy; SCUF: slow continuous ultrafiltration.

+ Διαφορετικά στάδια στην εξέλιξη της σήψης



Προφλεγμονώδης και αντιφλεγμονώδης φάση της σήψης

Κλινική
εικόνα

TNF
IL-1
IL-8
PAF

IL-10
TGF-β
IL-4

Βιολογικές
συνέπειες



Σήψη, SIRS

προφλεγμονώδεις
κυτοκίνες

Ενεργοποίηση των
μονοκυττάρων

Σηπτική
καταπληξία

IL-10
TGF-β
IL-4

TNF
IL-1
IL-8
PAF

Αδρανοποίηση
μονοκυττάρων



αντιφλεγμονώδεις
κυτοκίνες

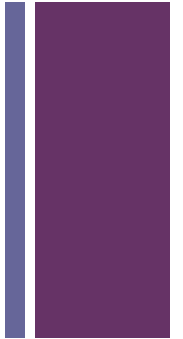
προφλεγμονώδεις
κυτοκίνες



Εφαρμογή θεραπευτικής αφαίρεσης στη σήψη

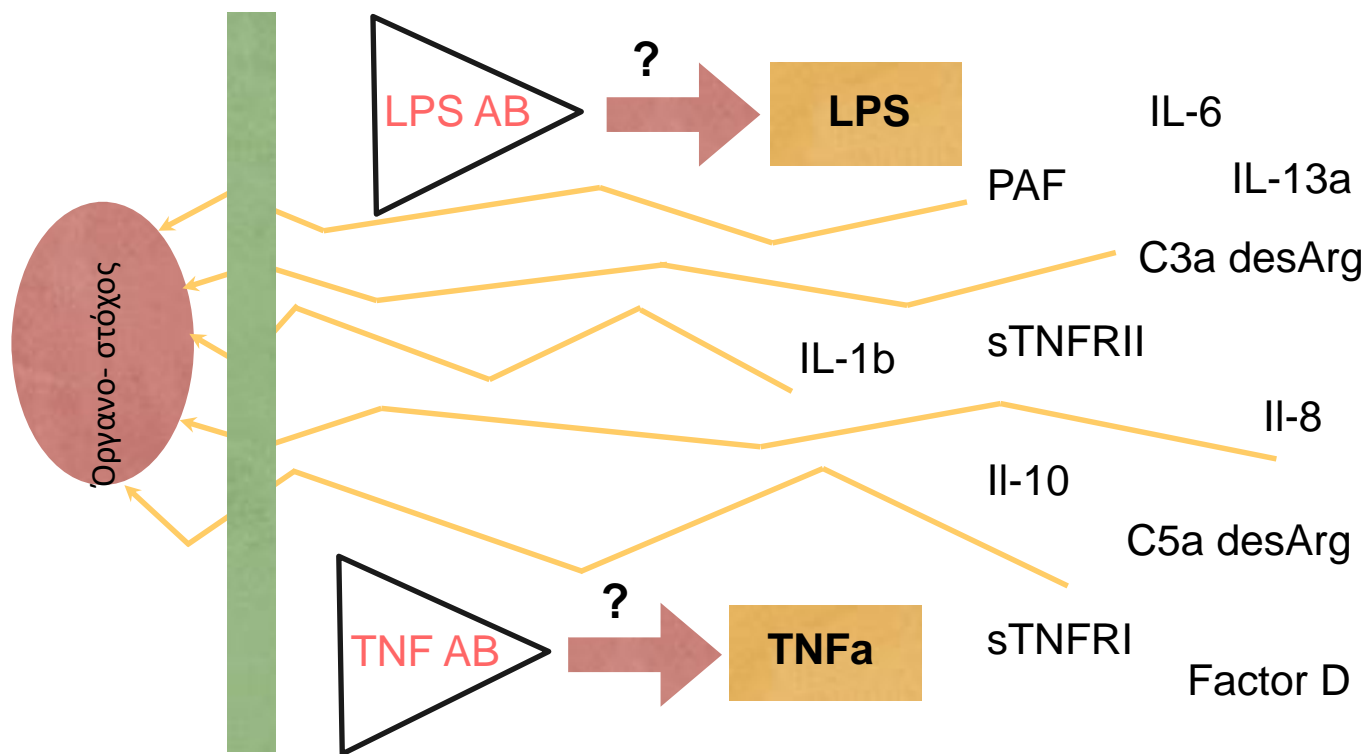
Μια ιδέα που έφτασε η ώρα της εφαρμογής της

- ❑ Καλύτερη κατανόηση της σήψης και γνώση όλο και περισσότερων μεσολαβητών - παραγόντων που συμμετέχουν ενεργά στην παθοφυσιολογία του συνδρόμου
- ❑ Ποικίλλες θεραπευτικές προσεγγίσεις: “Μαγική σφαίρα” εναντίον συγκεκριμένου παράγοντα ή “μαγική ασπίδα” που προστατεύει από πολλαπλές ουσίες που ενέχονται στην εκδήλωση του συνδρόμου
- ❑ Η ιδέα της “αποτοξίνωσης” του αίματος σε ασθενείς με σήψη έχει ήδη συμπληρώσει μια δεκαετία



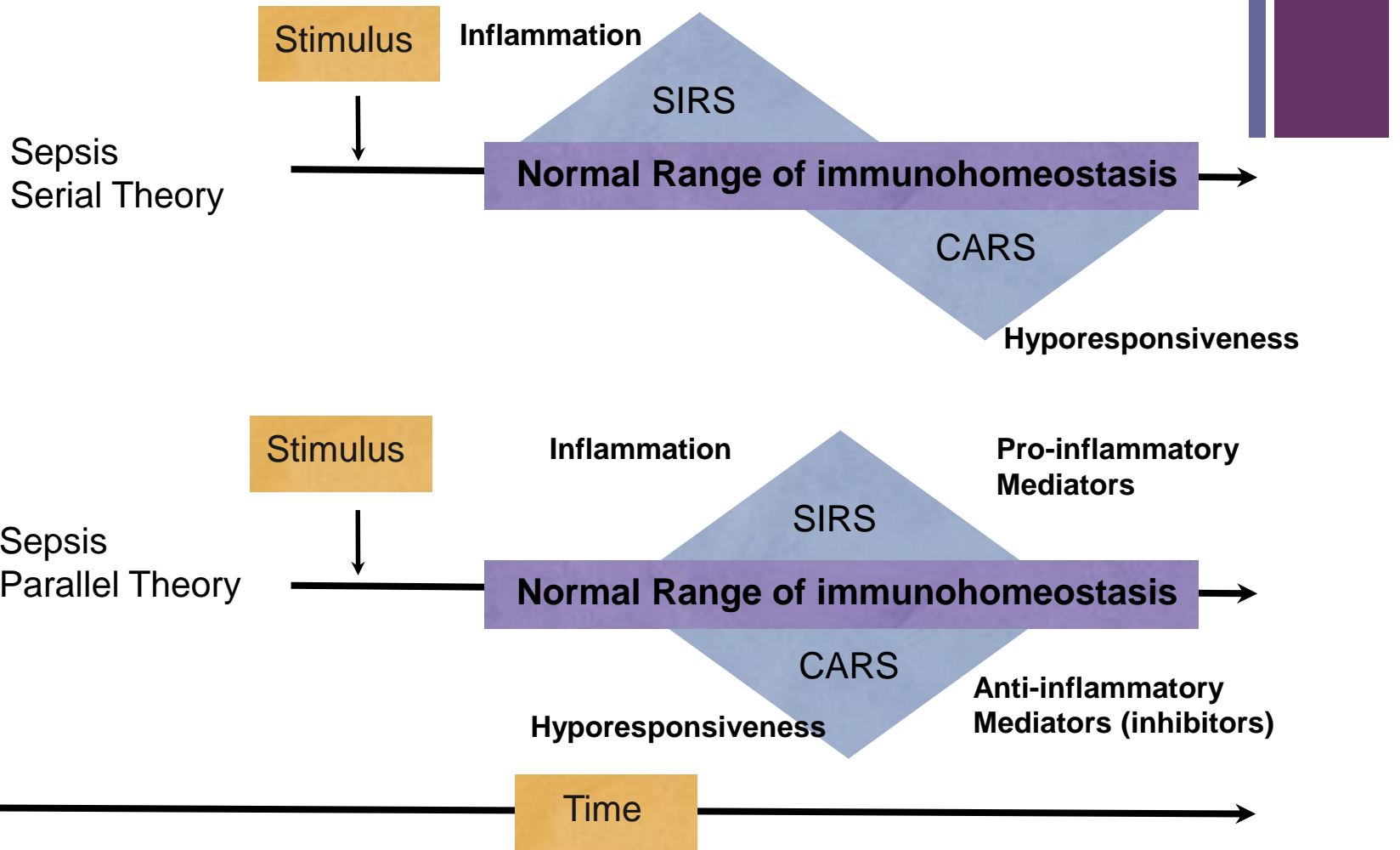


“Καταιγίδα κυτοκινών” στη διαδικασία της σήψης: “μαγική σφαίρα” ή “μαγική ασπίδα”

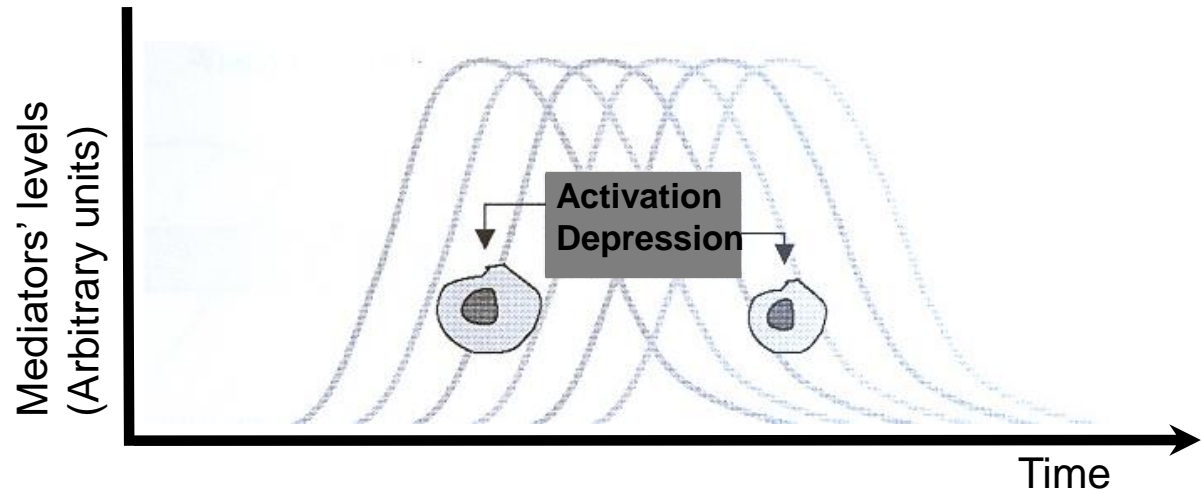
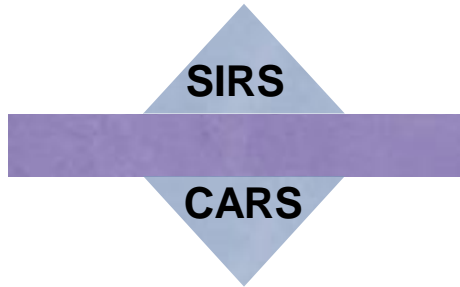
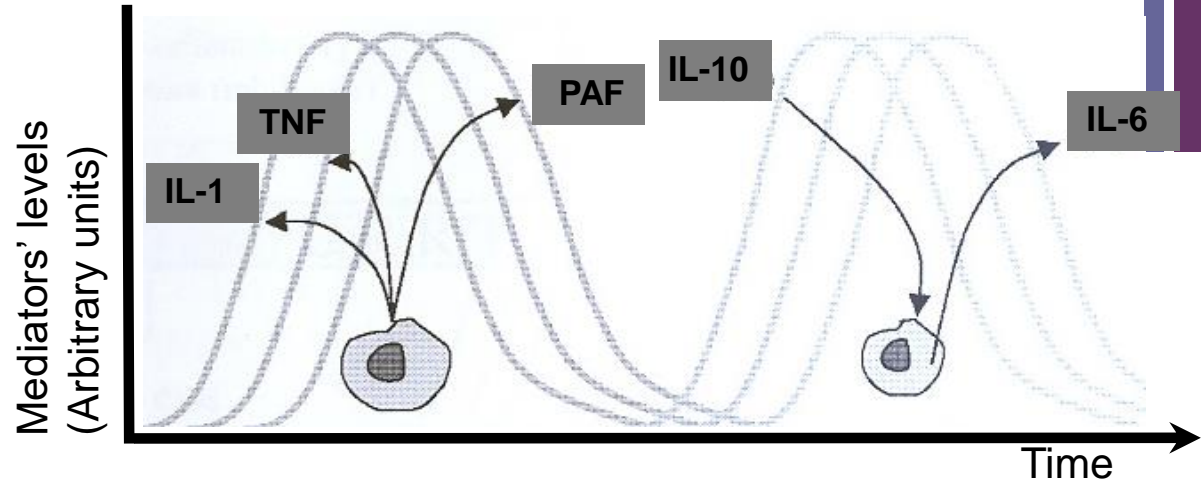
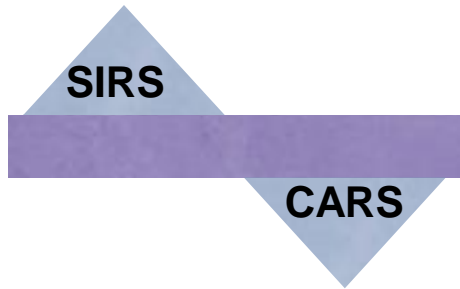




“Κατά σειρά” και “παράλληλη” θεωρία της σήψης

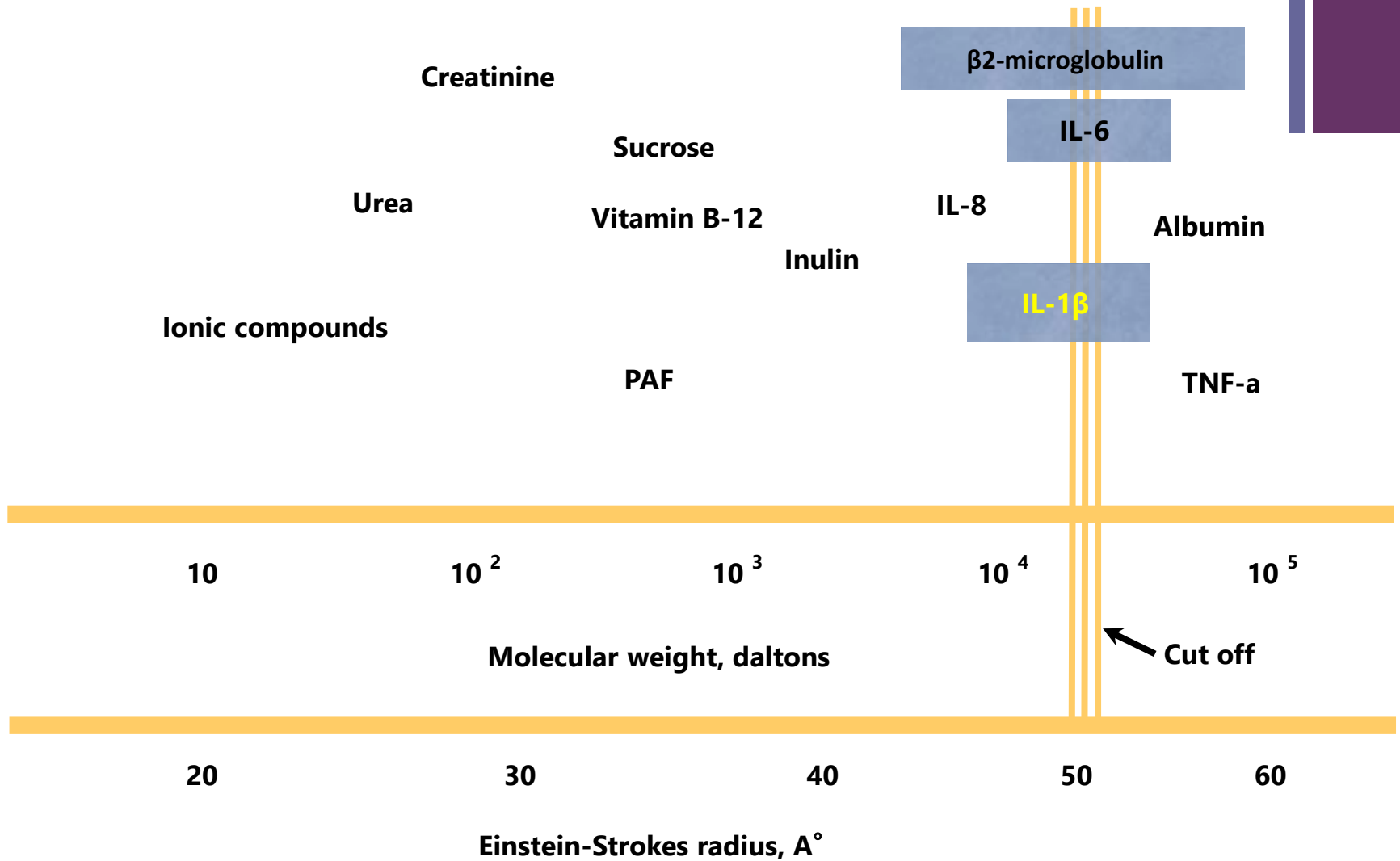


+ The Peak Concentration Hypothesis





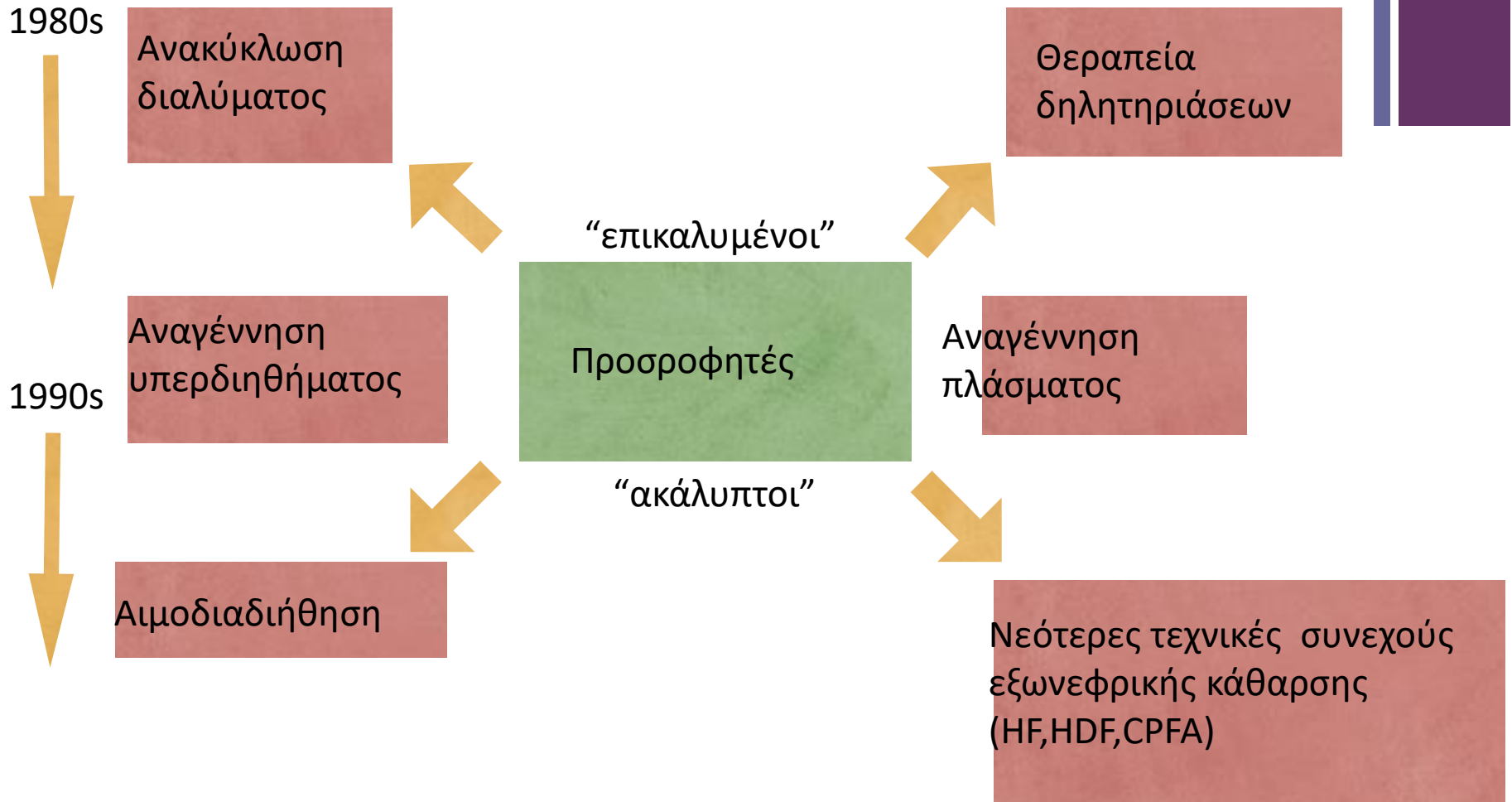
Μοριακά βάρη μεσολαβητών στη σήψη συγκριτικά με το cut off των μεμβρανών υψηλής διαπερατότητας



+ Πλασμαφαίρεση στη θεραπεία της σήψης

		Αρ. ασθενών	% επιβίωση
Bjorvatn	1984	4	100
Brandtzaeg	1985	8	75
Graf	1987	2	100
Hauser	1987	4	0
Stegmayer	1987	4	100
Asanuma	1989	19	69
Stegmayer	1990	13	69
McClelland	1990	2	100
van Deuren	1992	15	60
Stegmayer	1995	27	81
Stegmayer	1998	56	79
Koyklin	1998	100 (rand.)	66

+ Η χρήση των προσροφητών στις θεραπείες εξωσωματικής κάθαρσης



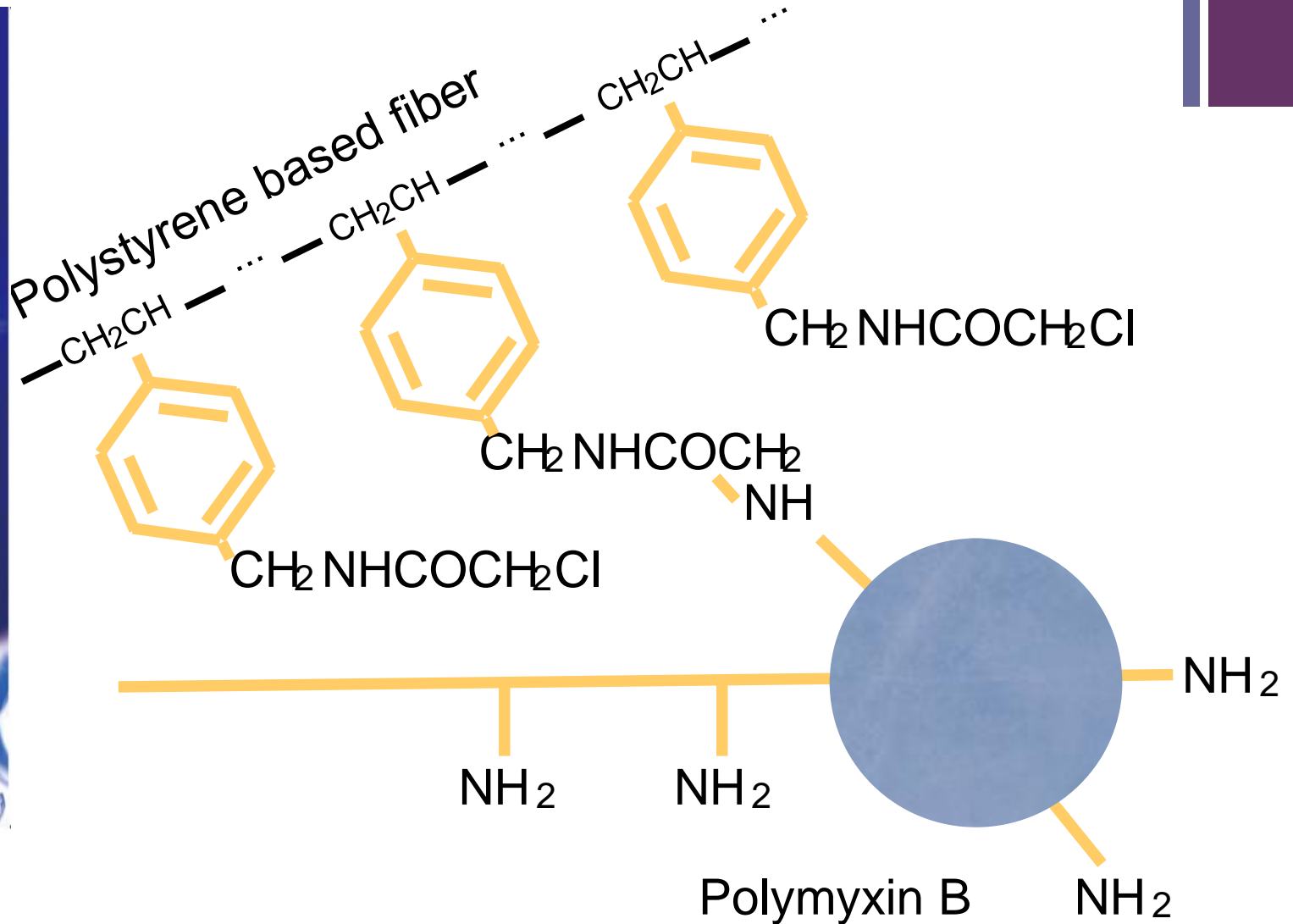
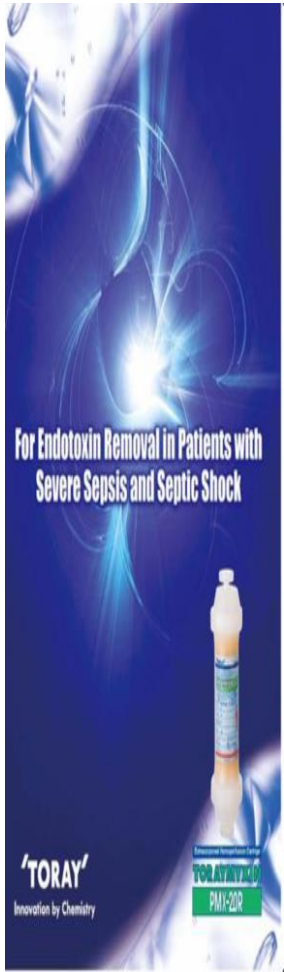
Προβλήματα βιοασυμβατότητας, απελευθέρωση μετάλλων, έκλυση μικροσωματιδίων, χαμηλή ομογενοποίηση, πυρετογόνες αντιδράσεις, ηλεκτρολυτικές δχ, αιμόλυση



Αιμοπροσρόφηση με τη χρήση πολυμυξίνης Β (PL-B)

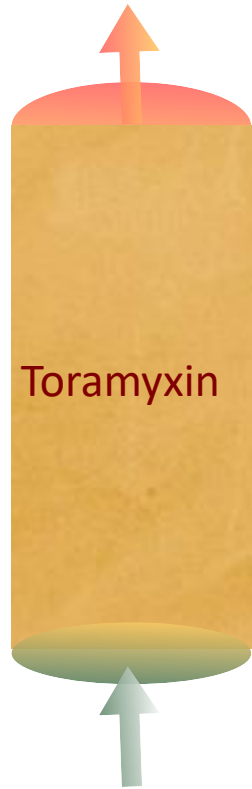
- ❑ Πολυκατιονικό αντιβιοτικό που συνδέει την ενδοτοξίνη και την αδρανοποιεί. Αντεδείκνυται η ενδοφλέβια χορήγηση λόγω νεφρο- και νευροτοξικότητας
- ❑ Συνδεδεμένα ινίδια **πολυστερένιου** και **πολυπροπυλένιου**: υλικό - φορέας που συνδέει και ακινητοποιεί την PL-B προσδίδοντας μεγαλύτερη σταθερότητα
- ❑ 30.000 ασθενείς έχουν υποβληθεί σε αιμοπροσρόφηση με PL-B από το 1994 στην Ιαπωνία
- ❑ Χωρίς ιδιαίτερες παρενέργειες εκτός από υποτασικά επεισόδια και θρομβοπενία

+ Πολυμυξίνη Β συνδεδεμένη ομοιοπολικά με το πολυστερένιο σε μορφή ινιδίων



+ Χαρακτηριστικά των φίλτρων πολυμυξίνης B

Έξοδος αίματος



Είσοδος αίματος

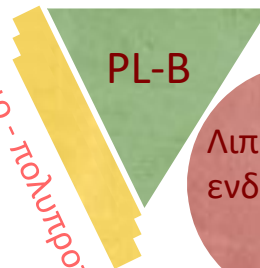
Μήκος σε mm 225

PL-B:
πολυανιονικό
αντιβιοτικό

Διάμετρος σε mm 49

Αποστείρωση με Priming volume: 135 ml
ατμό

Πολυστερένιο - πολυπροπυλένιο



Λιπίδιο A της
ενδοτοξίνης

Διάρκεια 2h με ροή αίματος συνήθως
80-100ml/min

Polymyxin B Hemoperfusion

EUPHAS Clinical Trial

- Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis (EUPHAS)
 - Randomized 64 patients @ 10 Italian tertiary care ICUs
 - Significant improvements:
 - Cardiac index; Left ventricular stroke index; Oxygen delivery index
 - Shorter hospital stay and better 28-day survival (32% in the hemo-adsorption group compared with 53% in the control group ($P = 0.03$)).
 - Not different:
 - Endotoxin and IL-6 levels pre-post treatment
 - Organ dysfunction (SOFA) between control and treatment group
 - The study was prematurely stopped because
 - It was judged to be unethical to deprive patients of hemo-adsorption
 - Inability to blind treating physicians

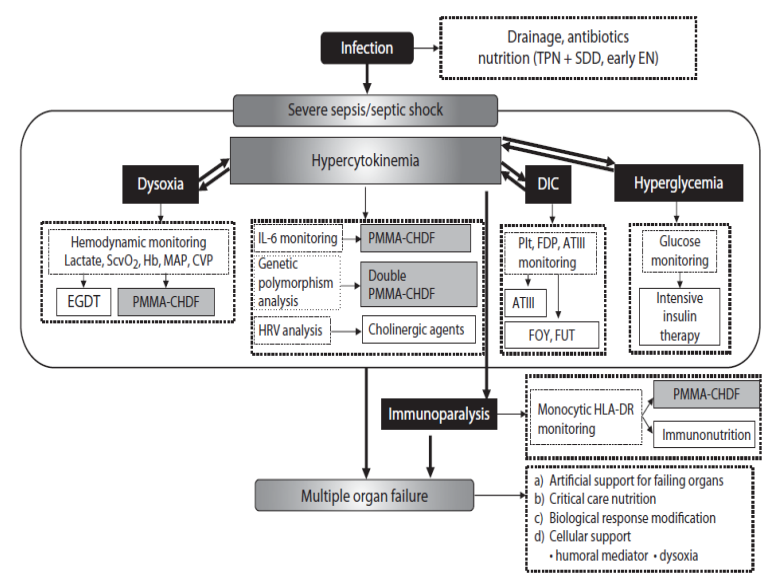
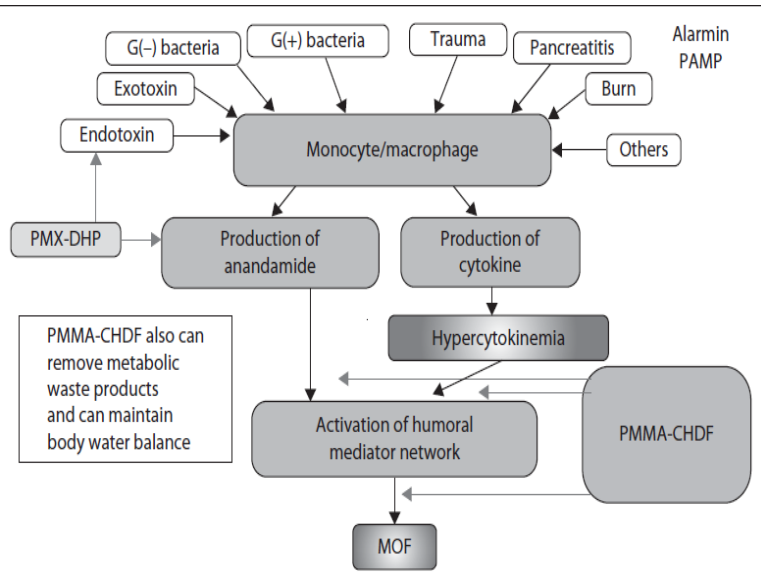
Polymyxin B Hemoperfusion

EUPHRATES Clinical Trial

- Evaluating the Use of Polymyxin B in Randomized controlled trial of Adults Treated for Endotoxemia and Septic Shock (EUPHRATES)
 - 360 patients in 15 centers in the United States
 - primary end point of 28-day mortality

Conclusions re Hemoperfusion with Polymyxin-B:

- “No large-scale randomized trials have been completed and lower mortality has not yet been sufficiently demonstrated.” (JC Schefold).
- 3 authors conclude that single LPS adsorption did not improve morbidity or organ dysfunction (Amoureaux et al; Staubach et al; Cruz et al).





Blood purification technique	Indication
Continuous hemofiltration/ continuous hemodiafiltration	Acute kidney injury Severe sepsis/septic shock Severe acute pancreatitis Fulminant hepatic failure
Plasma exchange	Fulminant hepatic failure Thrombotic thrombocytopenic purpura Toxic epidermal necrolysis
Direct hemoperfusion	Drug intoxication (charcoal DHP) Endotoxic shock (PMX-DHP)

Table 2. Blood purification techniques for cytokine removal in non-renal indications

PMMA-CHDF
Plasma diafiltration
High-flow-volume CHDF
Online CHDF
Cytokine adsorbing column

Table 1. Structures, adsorption rates of cytokines in vitro, and animal study in cytokine adsorbing columns

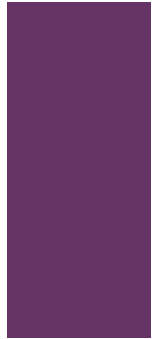
	Column				
	CytoSorb	CYT-860-DHP	Lixelle	CTR-001	MPCF-X
Structure	polystyrene divinyl co-polymer beads	polystyrene-based conjugated fiber	porous cellulose beads	porous cellulose beads	cellulose beads
<i>Adsorption rate</i>					
Methods	in vitro circuit (1 h)	batchwise (2 h)	batchwise (2 h)	batchwise (2 h)	batchwise (1 h)
TNF- α	<50%	20%	31.2%	53%	100%
IL-1 β		97%	98.5%	98%	
IL-6	<50%	92%	82.9%	80%	98.9%
IL-8		99%	99.9%	80%	70%
<i>Animal study</i>					
Animal	rat		rat	rat	
Methods	endotoxin injection, cecal ligation and puncture		endotoxin injection	endotoxin injection	
Time	240 min		120 and 180 min	120 min	



Cytokine Adsorbing Columns

(Non-selective)

Company	Cytosorbents	Toray	Kaneka	Kaneka
Product	Cytosorb	Cyt-860-DHP	Lixelle	CTR-001
Structure	Polystyrene divinyl co-polymer beads	Polystyrene conjugated fiber	Porous cellulose beads	Porous cellulose beads
Methods	In vitro circuit	Batch	Batch	Batch
TNF- α	<50%	20%	31.2%	53%
IL-1 β		97%	98.5%	98%
IL-6	<50%	92%	82.9%	80%
IL-8		99%	99.9%	80%
Animal	Rat		Rat	Rat
Method	Endotoxin injection, CLP		Endotoxin injection	Endotoxin injection



CytoSorb Cytokine Extractor



CytoSorbent's products are comprised of porous, adsorbent polymer beads that target molecules up to 50,000 Daltons, such as pro-inflammatory and anti-inflammatory cytokines i.e. IL-1, IL-6, TNF and Il-10, which are associated with sepsis.

The beads contain pores that are large enough to allow toxins to enter the beads and adhere to the bead through hydrophobic interactions while allowing large proteins to pass around the beads, back into the patient.



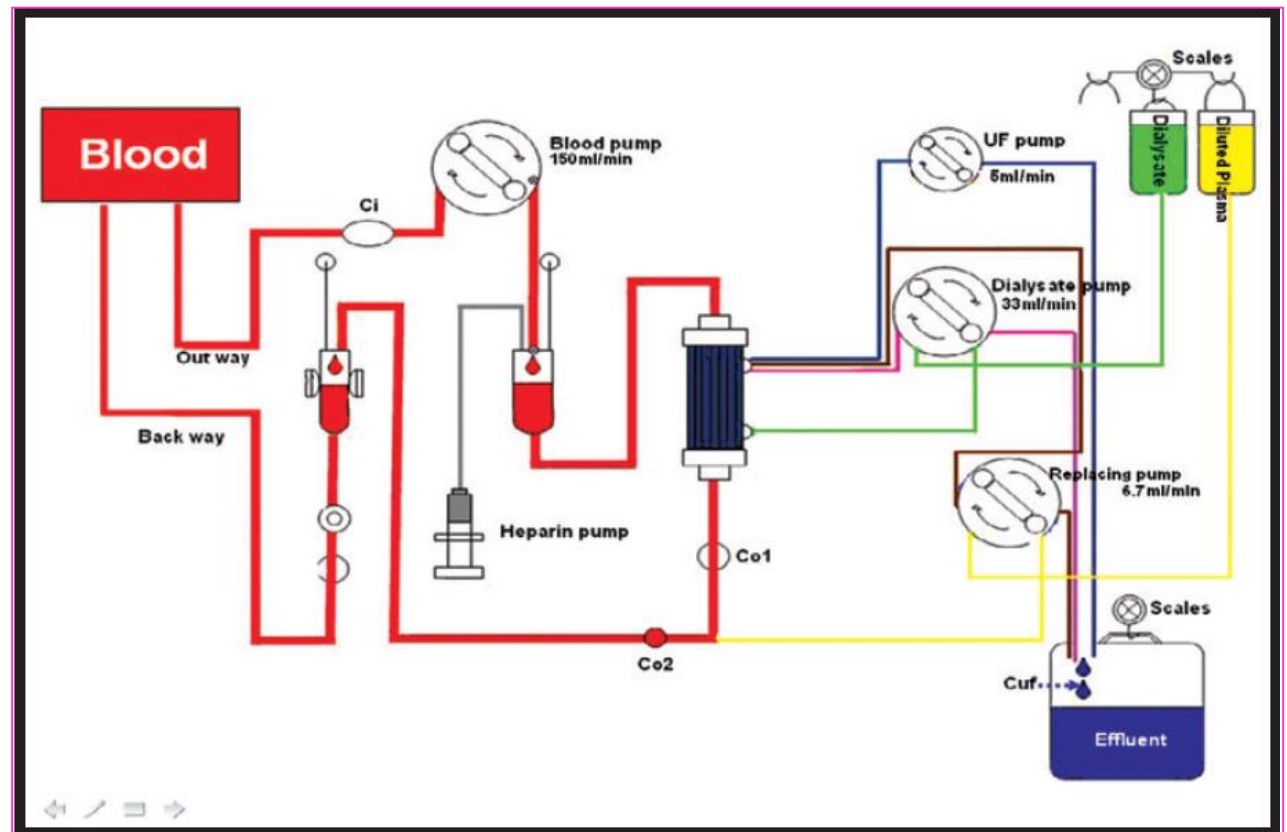
Cytosorbents Cytosorb®

Clinical Trial Results

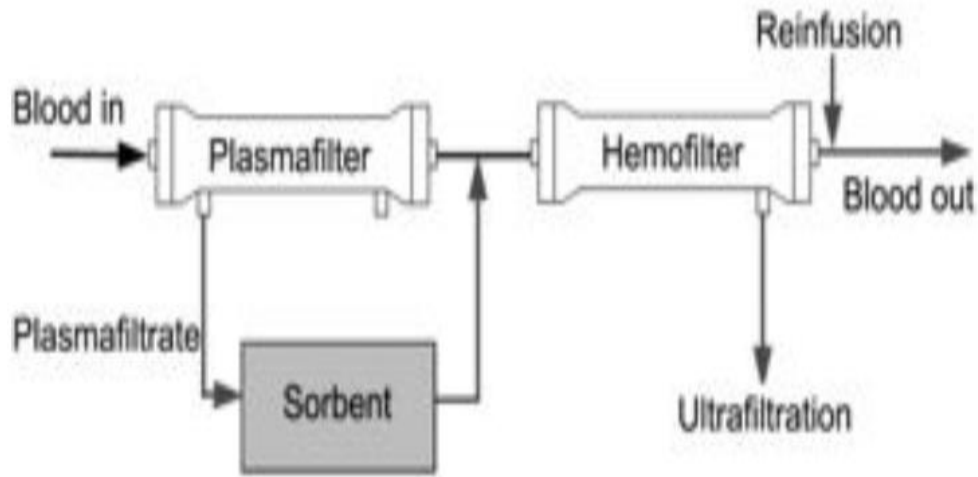
- 43 patients (25 control, 18 treated)
- Only the >65 year old cohort showed a statistical difference;
 - significant improvement in 14-day mortality (0% vs 36% control, $p = 0.04$, $n = 21$)
 - with trends to benefit in 28-day mortality (40% vs 45% control)
- Fewer mechanically ventilated patients at 28 days (60% vs 73% control)



Plasma diafiltration (PDF) is a blood purification therapy in which simple plasma exchange (PE) is performed using a selective membrane plasma separator while the dialysate flows outside the hollow fibers.



Coupled Plasma Filtration with Adsorption (CPFA)



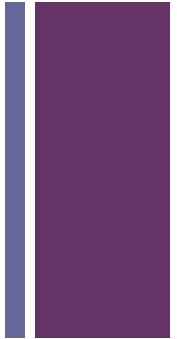
Selective or non-selective





Βασικά σημεία της μεθόδου CPFA (coupled plasma filtration adsorption)

- ❑ Συνδυασμός πλασμαφαίρεσης, αιμοπροσρόφησης και αιμοδιαδιήθησης
- ❑ Διαδικασίες ανάλογες μιας κλασσικής χρωματογραφίας: “κινητή φάση” είναι το πλάσμα του ασθενή και “σταθερή” η χρησιμοποιούμενη ρητίνη
- ❑ Στόχος της μεθόδου είναι η συγκράτηση των διαφόρων μεσολαβητών πάνω στη ρητίνη, η επαναφορά των φυσιολογικών μορίων και η αποφυγή χορήγησης πλάσματος εξωγενώς
- ❑ Η χρησιμοποιούμενη ρητίνη είναι ανάστροφης φάσης και αλληλεπιδρά μέσω υδρόφοβων περιοχών πάνω στα ζητούμενα μόρια



Advantages of CPFA

- No direct blood contact with adsorbents
- Avoids biocompatibility issues:
 - Coagulation (use of anticoagulants)
 - Platelet aggregation
 - Hemolysis
 - Thrombocytopenia
- Can provide increased contact between target mediators and adsorbents
 - total removal rates of target mediators far surpass conventional hemodialysis or hemofiltration
- Plasma is returned to patient avoiding expensive and allergenic replacement solutions

CFPA Clinical Trials

- 2002 pilot study (Ronco et al)
 - Cross-linked styrenic divinylbenzene resin (**non-selective**).
 - 10 patients; CPFA + HD vs CVVH; 10 hrs.
 - MAP \uparrow 11.8 vs 5.5 mmHg ($p=.001$)
 - Norepinephrine \downarrow 0.08 vs 0.0049 $\mu\text{g}/\text{kg}/\text{min}$ ($p=.003$)
- Pre-resin plasma suppressed LPS-stimulated production of TNF- α . This suppressive effect was significantly reduced after passage of plasma through the resin ($p = .019$)
- Conclusions:
 - CPFA improved hemodynamics
 - CPFA restored leukocyte responsiveness to LPS

CPFA Clinical Trials

- Hu et al; The First Affiliated Hospital of Nanjing Medical University, China
 - 14 patients; CPFA vs HVHF; 10 hrs
 - Both the SOFA and the APACHE II scores were markedly reduced after CPFA ($p < 0.01$),
 - MAP and oxygen index (P_aO_2/FiO_2) were significantly higher than those at 0 h
 - Serum levels of HMGB-1, ICAM-1, and TNF- α decreased after 10 h of CPFA ($p < 0.05$); whereas...
 - Serum levels of TNF- α and ICAM-1 showed no significant change after treatment with HVHF
- Conclusions:
 - CPFA could be superior to HVHF in improving the clinical manifestations and eliminating inflammatory mediators

CPFA

Selective; Multi-target

SHOCK, Vol. 28, No. 4, pp. 418Y425, 2007

A NOVEL SELECTIVE EXTRACORPOREAL INTERVENTION IN SEPSIS: IMMUNOADSORPTION OF ENDOTOXIN, INTERLEUKIN 6, AND COMPLEMENT-ACTIVATING PRODUCT 5A

Joerg C. Schefold,* Stephan von Haehling,† Malte Corsepius,* Cosima Pohle,* Peter Kruschke,‡
Heidrun Zuckermann,§ Hans-Dieter Volk,|| and Petra Reinke*

*Department of Nephrology and Intensive Care Medicine, University Medicine Berlin, Charité´
Campus Virchow Clinic, Berlin, Germany; †National Heart and Lung Institute, Department of Clinical
Cardiology, Imperial College School of Medicine, London, United Kingdom; ‡Adexter GmbH,
Rostock; and Departments of §Surgery and ||Medical Immunology, University Medicine Berlin,
Charité´ Campus Mitte, Berlin, Germany

“...these sepsis trials taught a very im-portant lesson as they suggested
that the modulation of a single inflammatory molecule or a single
immunologic pathway may not lead to significant clinical benefits in
pa-tients with sepsis.”

RESEARCH

Open Access

Extracorporeal cell therapy of septic shock patients with donor granulocytes: a pilot study

Jens Altrichter¹, Martin Sauer², Katharina Kaftan¹, Thomas Birken², Doris Gloger³, Martin Gloger⁴, Jörg Henschel⁴, Heiko Hickstein¹, Ernst Klar⁵, Sebastian Koball¹, Annette Pertschy⁵, Gabriele Nöldge-Schomburg², Dierk A Vagts² and Steffen R Mitzner^{1*}

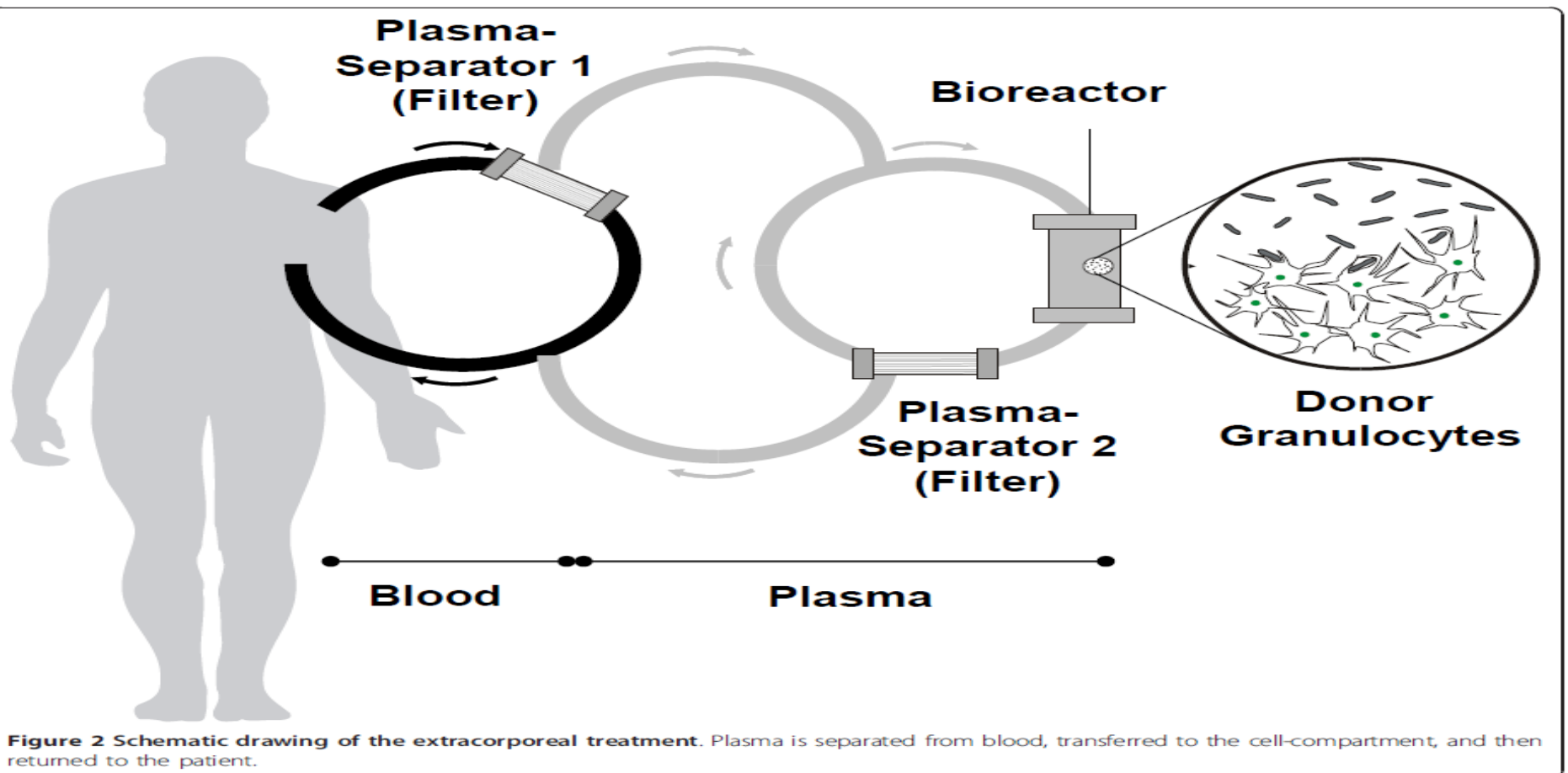


Figure 2 Schematic drawing of the extracorporeal treatment. Plasma is separated from blood, transferred to the cell-compartment, and then returned to the patient.



15TH INTERNATIONAL CONFERENCE ON DIALYSIS

ADVANCES IN CKD 2013

RENAL
RESEARCH
INSTITUTE



January 23-25, 2013


Wyndham Rio Mar
Rio Grande, Puerto Rico

Leukocyte Modulation Hypothesis

Univ. of Michigan; CytoPherx, Inc.

- A biomimetic membrane device (the SCD) *preferentially* binds activated leukocytes
- Regional citrate anticoagulation promotes a lower systemic leukocyte activation profile due to a decline in iCa which inhibits key leukocyte activation processes





The effects of a novel therapeutic device on acute kidney injury outcomes in the intensive care unit: a pilot study.

Ding F, et al. ASAIO Journal 2011 Sep-Oct;57(5):426-32.

Division of nephrology, Huashan Hospital, Fudan University, Shanghai, China.

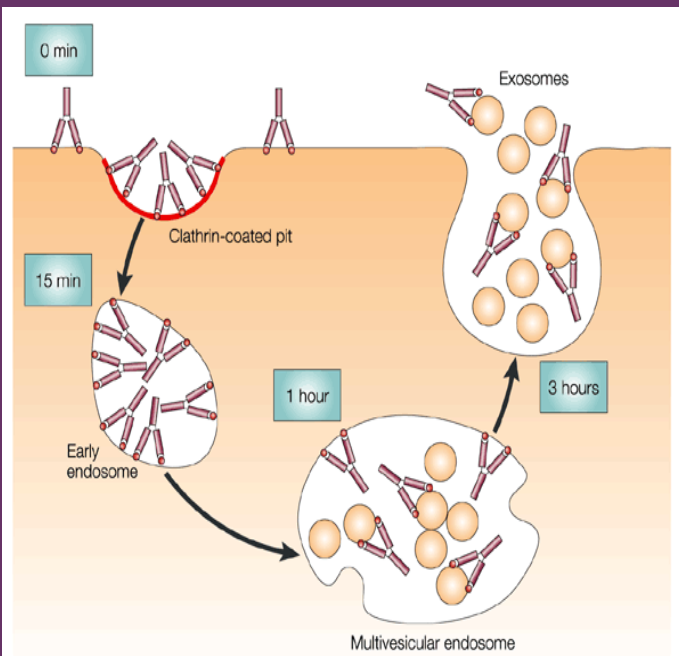
- A prospective, single-arm, single-center study designed to evaluate the SCD device on clinical outcomes in AKI in the ICU.
- The mortality for the case-matched controls was 77.78%, whereas the mortality in the SCD treatment group was 22.22% ($p = 0.027$).

The Effect of the Selective Cytopheretic Device on Acute Kidney Injury Outcomes in the Intensive Care Unit: A Multicenter Pilot Study

James A. Tumlin,* Lakhmir Chawla,† Ashita J. Tolwani,‡ Ravindra Mehta,§ John Dillon,– Kevin W. Finkel,** J. Ricardo DaSilva,†† Brad C. Astor,§§ Alexander S. Yevzlin§§ and H. David Humes.

- A single-arm, open-label, multicenter pilot study to assess the safety and efficacy of a selective cytopheretic device (SCD) in patients with AKI.
- 60-day mortality rate of 31.4%.
- Among the 22 patients who survived to day 60 in, 100% recovered kidney function and did not need dialysis.
- A pivotal trial of SCD therapy is underway in the US.



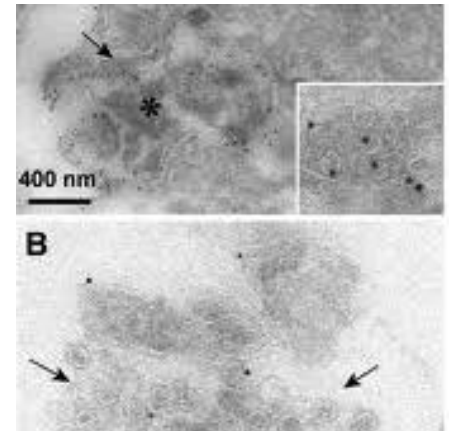
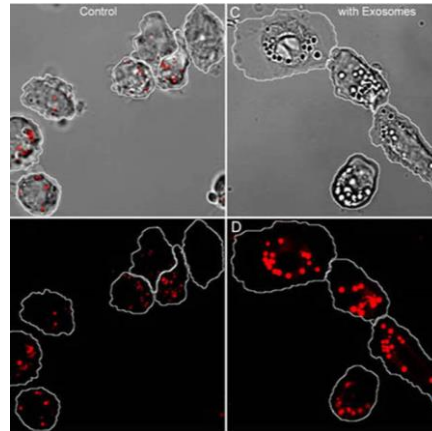


Exosomes

- A specific subset of membrane-bounded vesicles formed intracellularly within vesicular endosomes.
- Released into the extracellular environment by many cells from different tissues and organs.
- Exist in a wide range of biological fluids, including blood and urine.
- Between 30 and 100 nm in diameter.

Exosomes

- Have a molecular envelope structure that is remarkably similar to that of viruses.
- Have a hydrophilic core containing proteins, mRNAs and microRNAs (miRNA).
- Originally thought to be “cellular trash bags”
- Now, widely believed to be involved with intercellular communications.



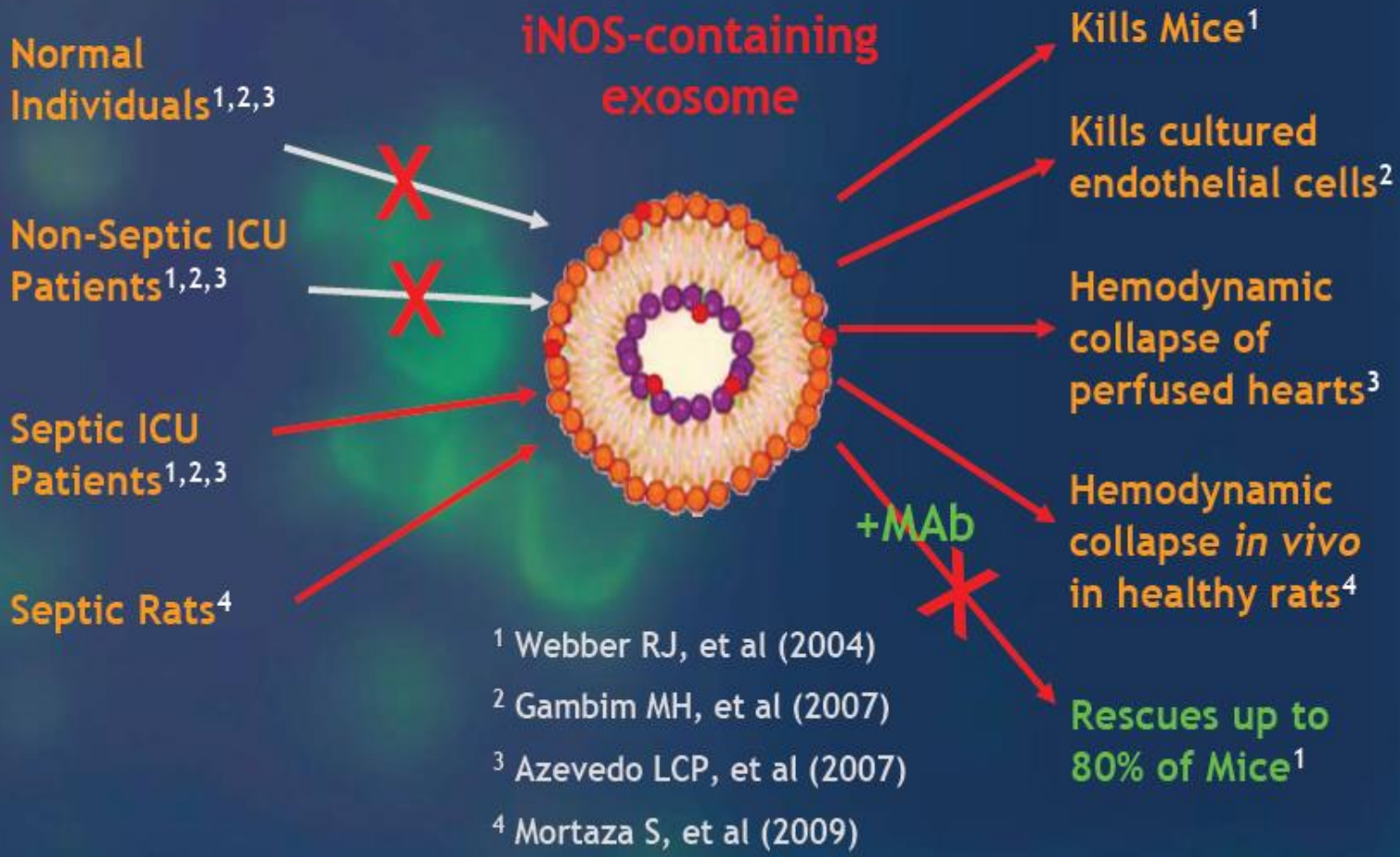
Exosomes

- Both mRNAs and miRNAs present in the exosomal fraction maintain their function when transferred to other cells demonstrating that exosomal RNA transfer may be an important route for epigenetic signaling between cells.
- Transferred RNAs can affect protein production and gene expression in target cells.
- The dissemination of pro-cancer cargo by exosomes has been identified as promoting several critical aspects of cancer pathogenesis, including:
 - signaling for tumor growth,
 - metastasis,
 - angiogenesis, and
 - resistance to chemo- and immunotherapeutic agents.

Exosomes

- The generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), plays a major role in endothelial activation and vascular failure.
- Two main enzymatic sources of ROS/RNS (NADPH oxidase & NO synthase) are expressed by platelets.
- Exosomes generated from platelets exposed to LPS are quite similar to those found in septic patients w/r/t protein content, phosphatidylserine exposure, and redox activity.
- Platelet-derived exosomes from septic patients induce vascular cell apoptosis and contain inducible nitric oxide synthase (iNOS).

Evidence that platelet-derived iNOS-Containing Exosomes Cause Organ Damage/Dysfunction in Sepsis





Current Military-funded Anti-sepsis Project

- Goal: Reduce sepsis-related mortality in wounded warfighters.
- Approach: Extracorporeal Blood Purification (Dialysis-like Therapeutic)
- Multi-company consortium

CPFA

Selective, Multi-target plus Semi-selective

- In addition to the potential to restore immune homeostasis and extract sepsis-inducing viruses, this therapeutic intervention has the ability to extract dormant viruses that may bloom during immunoparalysis.
- This may well lead to a reduction in the mortality resulting from secondary viral infections.



● **Hemoperfusion** is the passage of blood across material that adsorbs various solutes or substances



Table 1. Features of blood purification

	Substances removed	Target substances
Hemoperfusion	substances adsorbed on activated carbon	phenytoin; theophylline; phenobarbital
Hemodialysis	MW <2,000; water-soluble substances; $V_D < 1$ l/kg; protein-binding rate: low	alcohol; lithium; acetylsalicylic acid
Hemofiltration	MW <40,000; $V_D < 1$ l/kg; protein-binding rate: low	aminoglycoside
PE	protein-binding rate: high	protein-bound toxins

MW = Molecular weight.

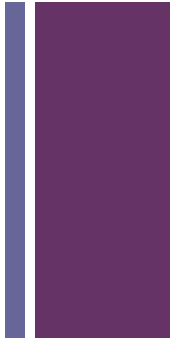
Table 2. Blood purification for albumin-bound substances

	Sieving coefficient for albumin	Continuous performance	Renal replacement therapy
Plasma exchange	1.0	impossible	impossible
Extracorporeal albumin dialysis			
MARS®	0.01	possible (6-8 h in practice)	good
Prometheus®	0.6	5-6 h	good
PDF	0.3	possible	good



Consensus of Conference on Biocompatibility

+ Questions

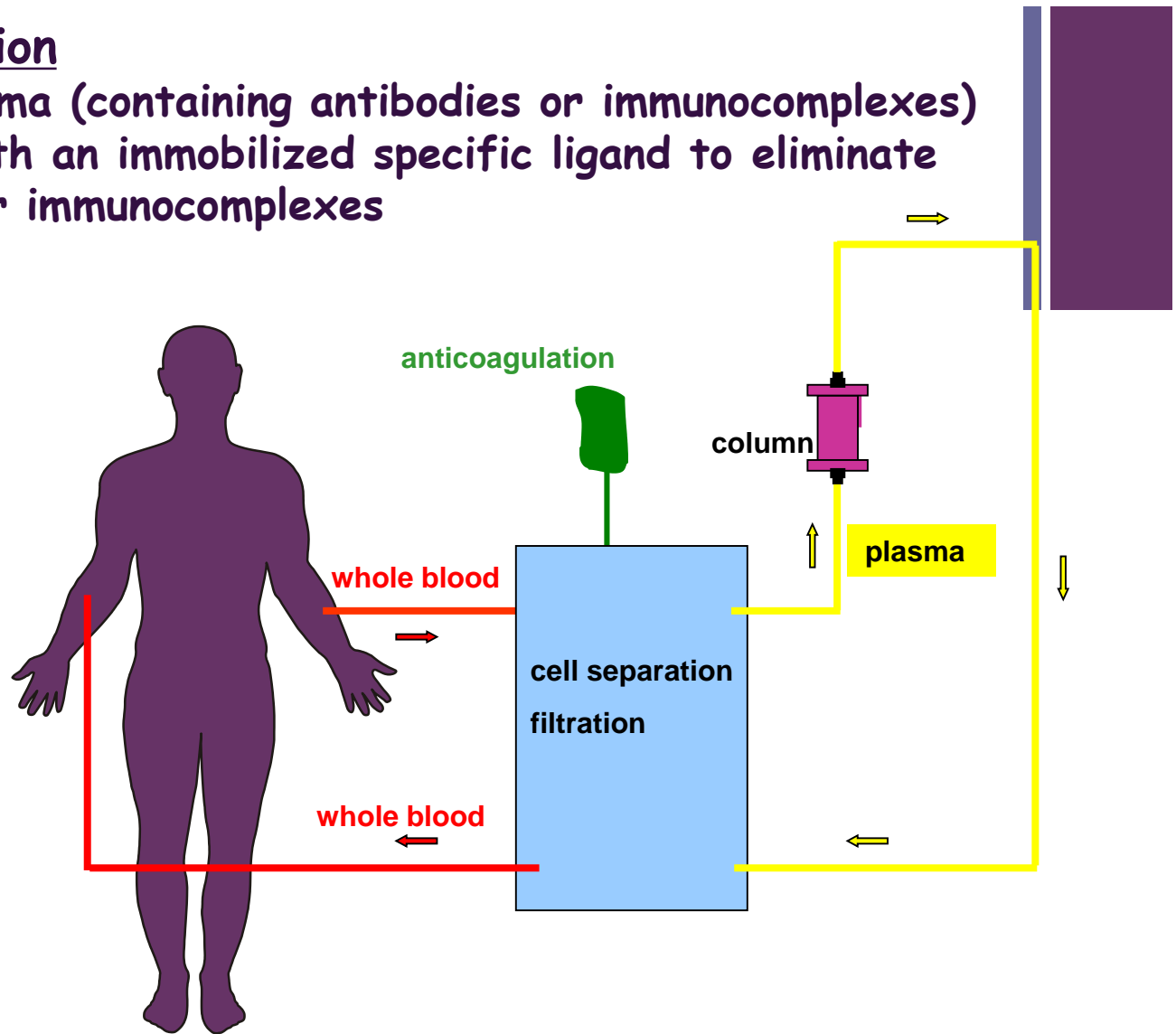


- ✿ Do the sorbents influence the biocompatibility of the system?
- ✿ A series of beneficial substances are eliminated with regeneration through sorbents?
- ✿ Whether continuous renal replacement therapy (CRRT) is better at removing dialyzable toxins than classic hemodialysis?
- ✿ Whether charcoal hemoperfusion is at all useful in treating paraquat poisoning?
- ✿ Is any modality of extracorporeal treatment useful in the treatment of amatoxin poisoning?

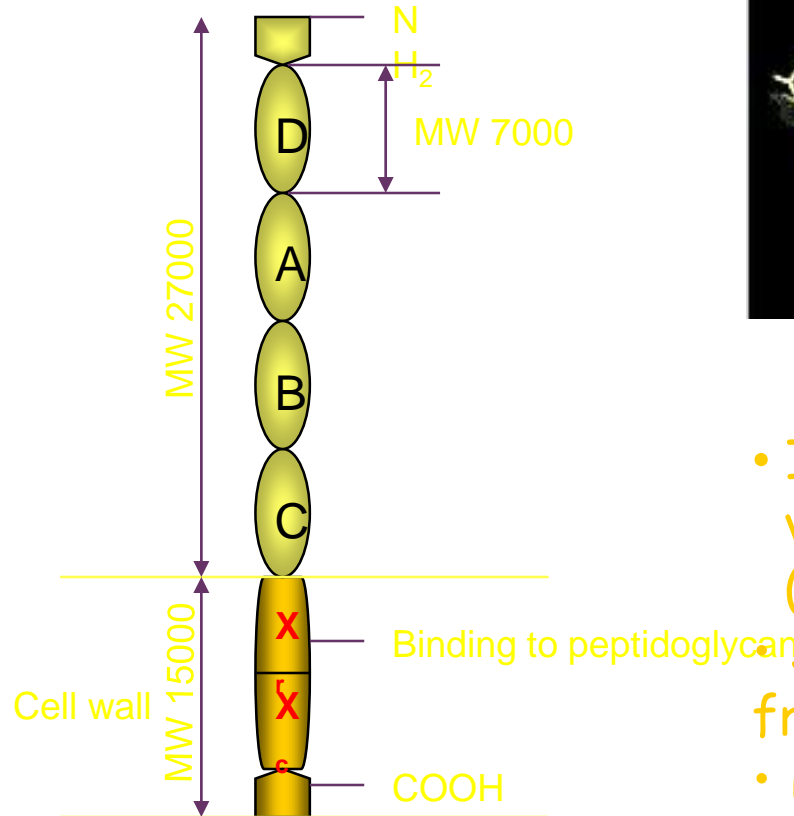


Immunoabsorption

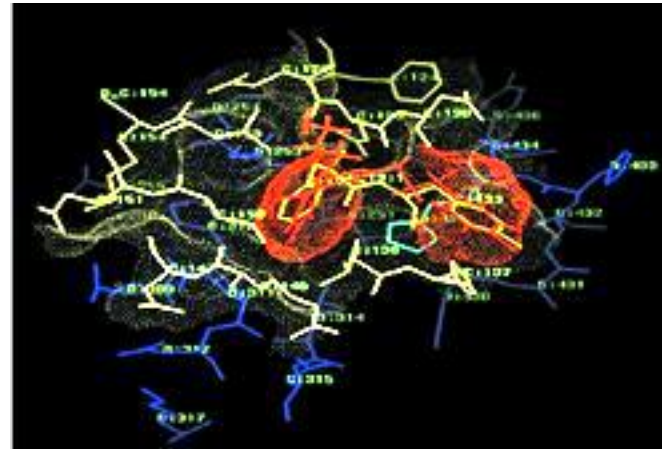
Perfusion of plasma (containing antibodies or immunocomplexes) over a matrix with an immobilized specific ligand to eliminate antibodies and/or immunocomplexes



Protein A



Staphylococcus
protein a (SPA)



Protein a

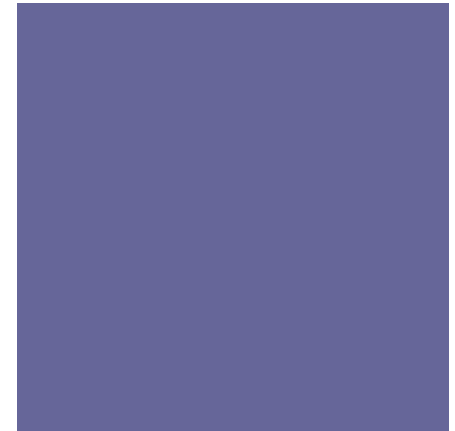
IgG

Biomimetic

- Interaction between IgG protein a via CH₂ and CH₃ domain of IgG (F_c-fragment)
- Some binding affinity to the Fab-fragment
- Binds IgG(1,2,4) not IgG3
- Binds some IgM and IgA (Fab fragment)
- High affinity to CIC

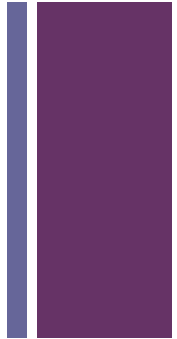


Immunoadsorption in Lupus Myocarditis






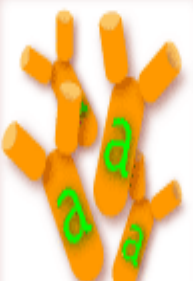



**Griveas I.¹, Visvardis G.¹, Zarifis I.², Papadopoulou D.¹,
Manou E.¹, Kyriklidou P.¹, Nouskas I.², Mitsopoulos E.¹,
Sourgounis A.², Meimaridou D.¹, Ginikopoulou E.¹,
Sakellariou G.¹**

**Departments of Nephrology¹ and Cardiology²,
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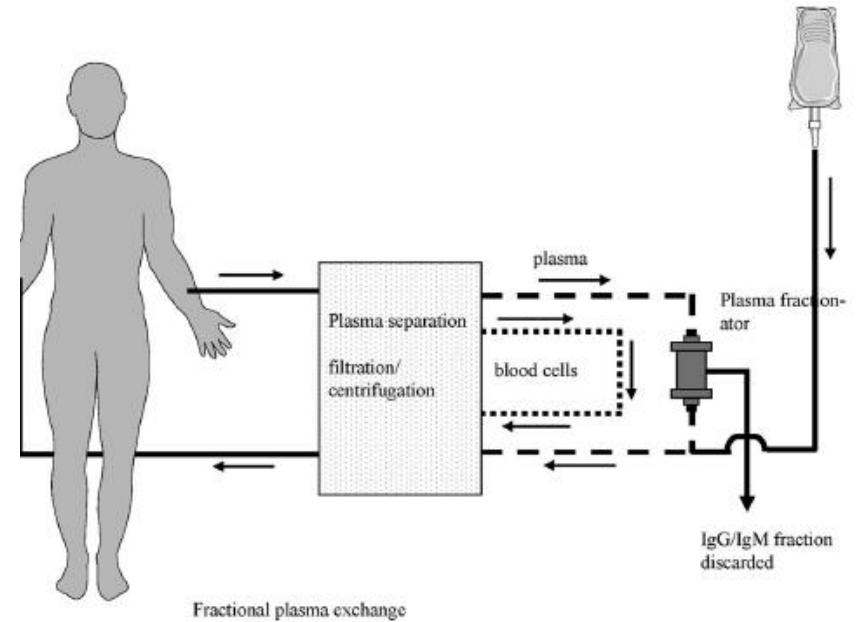
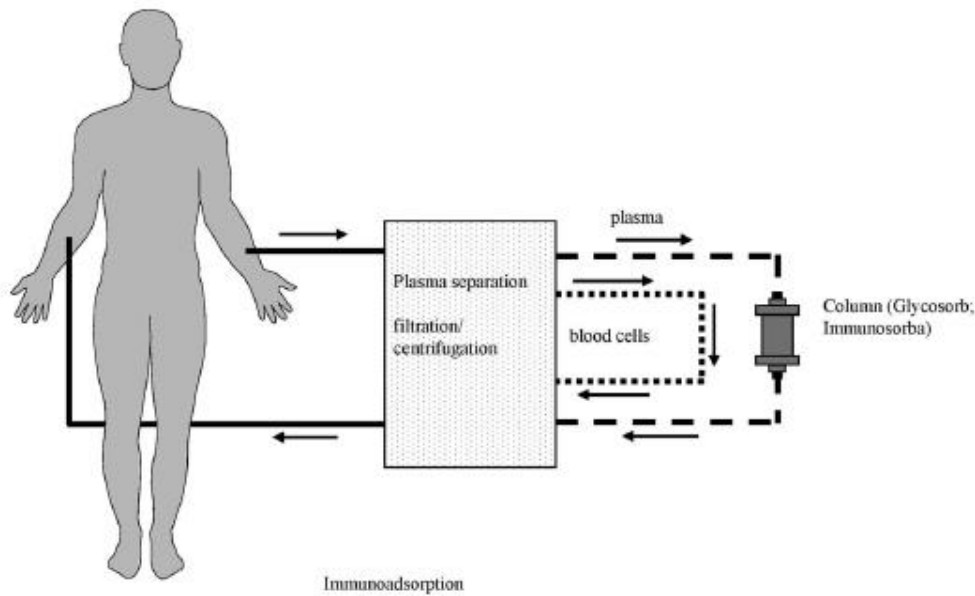
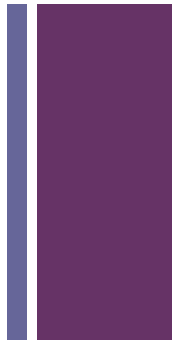


The ABO Blood System

Blood Type (genotype)	Type A (AA, AO)	Type B (BB, BO)	Type AB (AB)	Type O (OO)
Red Blood Cell Surface Proteins (phenotype)	 <p>A agglutinogens only</p>	 <p>B agglutinogens only</p>	 <p>A and B agglutinogens</p>	 <p>No agglutinogens</p>
Plasma Antibodies (phenotype)	 <p>b agglutinin only</p>	 <p>a agglutinin only</p>	<p>NONE.</p> <p>No agglutinin</p>	 <p>a and b agglutinin</p>

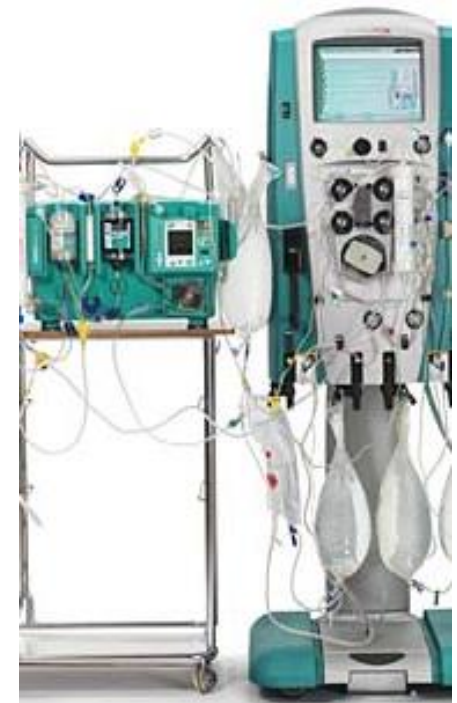
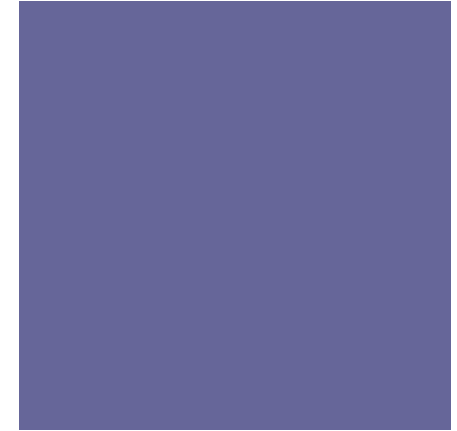
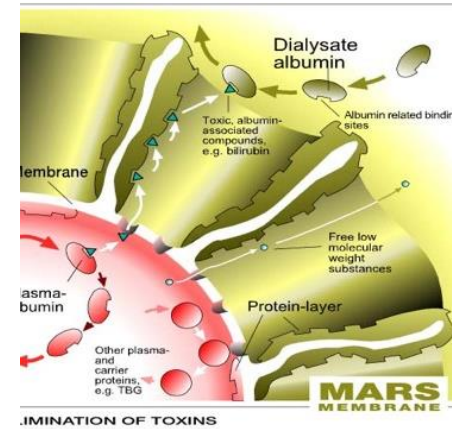
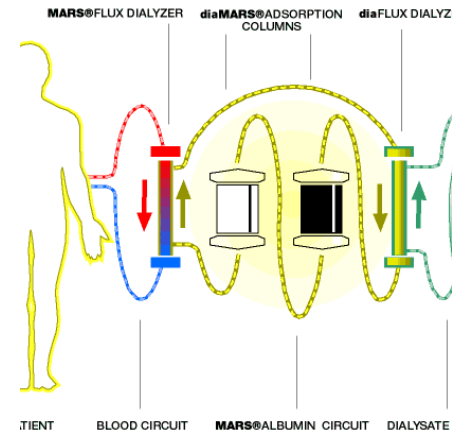


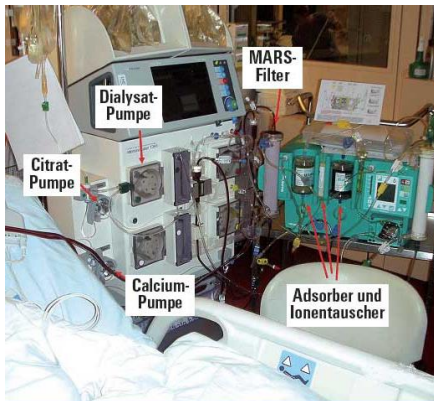
+ Extracorporeal Antibody Removal Techniques (EART)



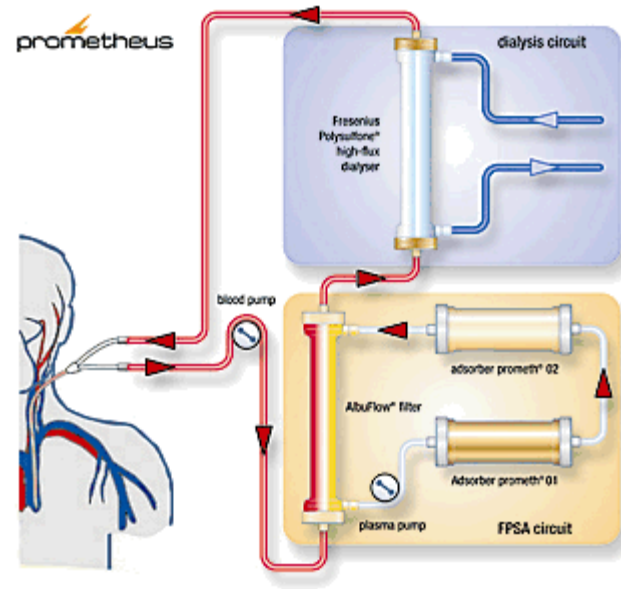


Molecular Adsorbents Recirculating System

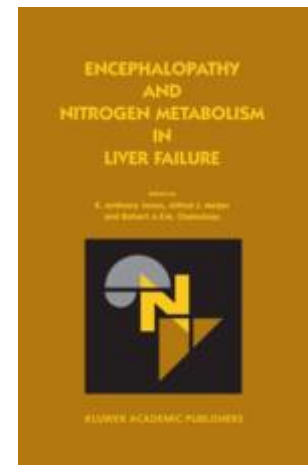




iCa-HD MARS, funktionelle Beschreibung



+

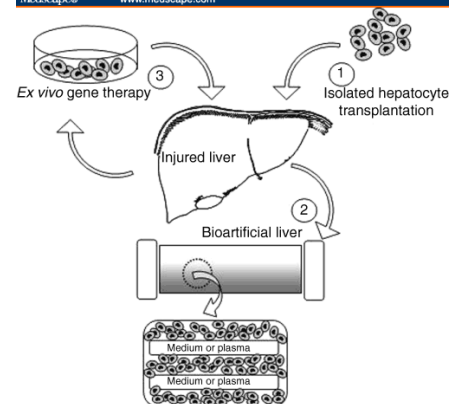




Bioartificial Liver Devices

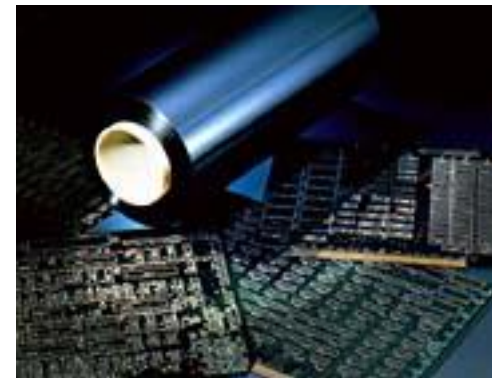
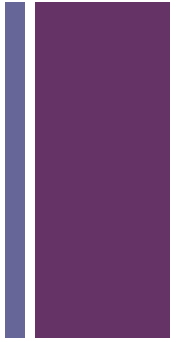


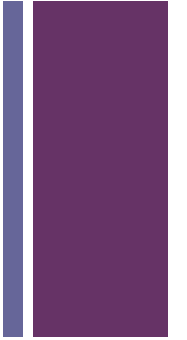
Medscape www.medscape.com



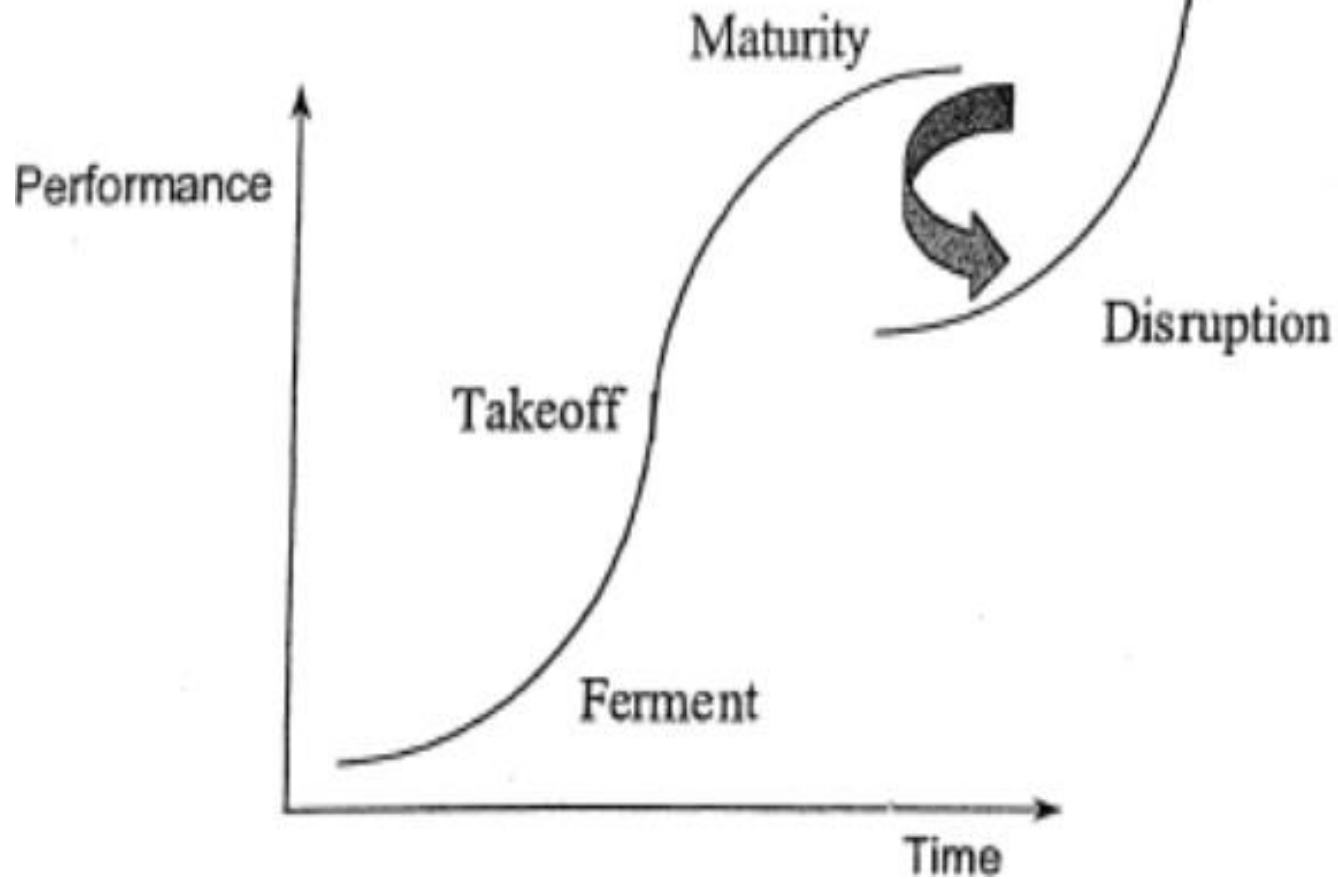
Source: Alment Pharmacol Ther © 2003 Blackwell Publishing

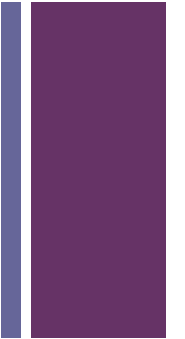
+





The Industry life cycle as an S-curve





Quality



- Smart Goals
 - Specific
 - Measurable
 - Attainable
 - Relevant
 - Time based

+ Selective apheresis



TABLE 3. *Devices and Indications for Selective Apheresis*

Device/procedure	Ligand/principle	Indications (examples)
Ig-Immunoabsorption Prosorba	Anti-Ig-ab; SPA-sepharose (Ig-Therasorb; Immunosorba)	Kidney transplantation, DCM, SLE, anti-FVIII-ab
Coraffin	SPA-silica	Rheumatoid arthritis
LDL-Immunoabsorber (LDL-Therasorb)	Peptides PDCM349, PDCM075	DCM
Liposorber	Anti-apoprotein B100-ab	Hypercholesterolemia
DALI	Dextran sulfate-cellulose	Hypercholesterolemia, SLE
HELP	Polyacrylate-Eupergit	Hypercholesterolemia
Leukocyte apheresis	Heparin precipitation	Hypercholesterolemia, sudden hearing loss
Liver albumin dialysis	Cellulose acetate, polyester fibres (ADA column, Cellsorba)	Ulcerative colitis, Crohn's disease
Double filtration	Albumin, FPSA (MARS, Prometheus)	Liver failure
Glycosorb	Polyvinyl-alcohol, polypropylene	AMD, Waldenström's disease, HC
Lixelle	Blood group antigen A or B	ABO incompatible kidney transplantation
Toraymyxin	Hydrophobic ligands	AB-amyloidosis
IM-TR, IM-PH	Polymyxin B	Sepsis
Cryofilter	Tryptophane, phenylalanine	Myasthenia gravis, Guillain-Barré syndrome
	Cryofiltration	Cryoglobulinemia

Ab, antibody; AMD, age-related macular degeneration; DALI, direct adsorption of lipids; DCM, dilative cardiomyopathy; FVIII, coagulation factor VIII; FPSA, fractionated plasma separation and adsorption; HC, hypercholesterolemia; HELP, heparin induced extra-corporeal LDL precipitation; Ig, immunoglobulin; MARS, molecular adsorbent and recirculation system; SLE, systemic lupus erythematosus; SPA, staphylococcal protein A.

Immune Cells as an Organ



Mass of immune cells = 2×10^{12} cell = about 2 kg

Lined up gives this a distance of $2 \times 10^{12} \times 10 \mu =$

20.000 km !

Life Time



- **Granulocytes** **8 hours**
- **Monocytes** **days....weeks**
- **Lymphocytes** **weeks....years**
(Memory cells) **partly lifelong?**

Dichotomy of Immune System



Humoral:

- Immunoglobulins
- Complement system

Cellular:

- Lymphocytes

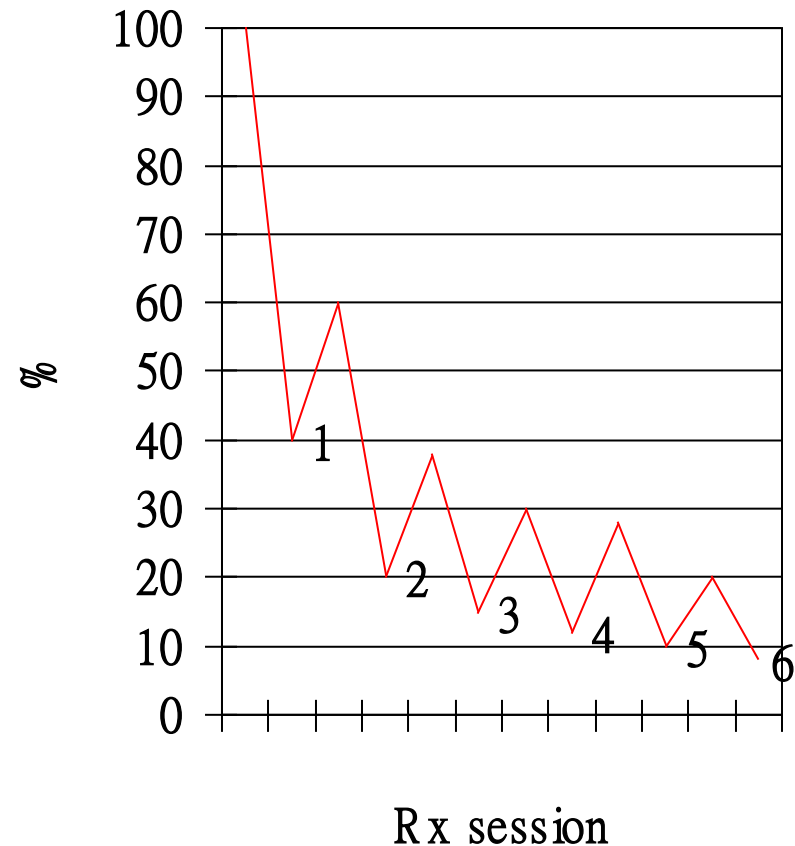
Pharmacokinetic considerations

- ◆ 70-kg patient with a plasma volume of 2800 ml.
assume removal from a single compartment.

PV exchanged	Volume exchanged (ml)	Removal ratio (%)
0.5	1400	39
1.0	2800	63
1.5	4200	78
2.0	5600	86
2.5	7000	92
3.0	8400	95

Pharmacokinetic considerations

- ◆ Reaccumulation
 - From lymphatic drainage
 - Endogenous synthesis
- ◆ After 4 or 5 TPEs, the conc would be oscillating between 10% to 20-25%.



+ The regimen

- ◆ Numbers of PV q X days for Y sessions.
- ◆ Membrane vs centrifugal separator.
- ◆ Anticoagulation.
- ◆ Replacement solutions.

Table 21.4 Removal of a substance by TPE

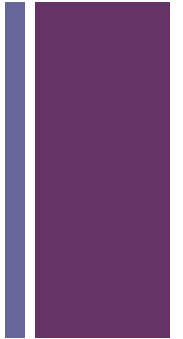
- Efficiency:
 - 1 PV = 65% removal
 - 1.5 PV = 75%
 - 2 PV = 87%
 - 3 PV = 95%
- IgM—80% Intravascular (efficiently depleted due to limited reequilibration)
- IgG—both Intravascular (40%) and In tissues (removal less efficient, redistribution into plasma postapheresis over 24–48 hour period)

+ Estimation of plasma volume

- ◆ 35-40 ml/kg

- ◆ Kalpan's simplified equation :

$$[0.065 \times \text{weight (kg)}] \times (1 - \text{Hct})$$



	Advantages	Disadvantages
Membrane apheresis	<ul style="list-style-type: none"> -fast and efficient -no citrate requirements -can be adapted for cascade filtration 	<ul style="list-style-type: none"> -limited by sieving coefficient -no cytapheresis -high BFR, central access -requires heparin
Centrifugal devices	<ul style="list-style-type: none"> -cytapheresis -no heparin requirement -more efficient removal of all plasma components 	<ul style="list-style-type: none"> -expensive -requires citrate -loss of platelets

Solution	Adv	Disadv
Albumin	<ul style="list-style-type: none">-no viral transmission-room temp-allergic reactions rare-no blood gp concern-depletes inflammation mediators	<ul style="list-style-type: none">-expensive-no coagulation factors-no Igs
FFP	<ul style="list-style-type: none">-coagulation factors-Igs-'beneficial' factors-complement	<ul style="list-style-type: none">-viral transmission-allergic reactions-hemolytic reactions-must be thawed-ABO-compatible-citrate load

+ Replacement solutions

- ◆ 5% albumin, albumin-saline or FFP.
- ◆ With albumin-saline combination, albumin should not be < 50% of the total volume. An appropriate combination would be 60-80% colloid and 20-40% crystalloid.

