

# **Το παρόν και το μέλλον της εφαρμογής θεραπευτικής αφαίρεσης στις Μονάδες Εντατικής Θεραπείας**

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# Πλασμαφαίρεση σε μια τυπική ΜΕΘ στο Παρίσι.

## Indication for plasma exchange

Thrombotic microangiopathy	29 (58)
Thrombotic thrombocytopenic purpura	18 (36)
Hemolytic uremic syndrome, atypical	10 (20)
Thrombotic microangiopathy, drug associated	1 (2)
Hyperviscosity syndrome	12 (24)
ANCA-associated vasculitis	4 (8)
Kidney transplantation, antibody mediated rejection	3 (6)
Severe cryoglobulinemia	1 (2)
Catastrophic antiphospholipid syndrome	1 (2)

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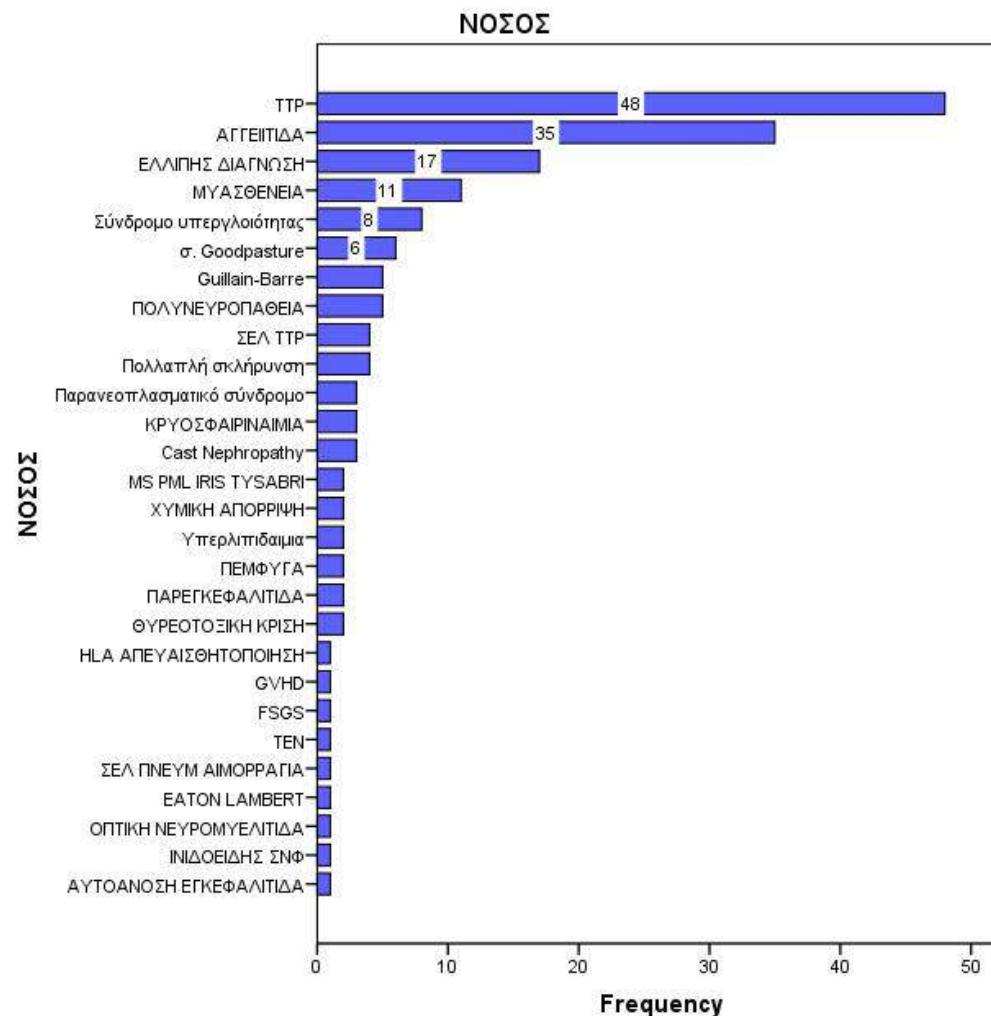
RESEARCH ARTICLE

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Journal of  
Clinical Apheresis

ASFA

# Πλασμαφαίρεση σε μια τυπική νεφρολογική κλινική στην Ελλάδα (ΠΝΗ)



## Pediatric Multiple Organ Dysfunction Syndrome: Promising Therapies

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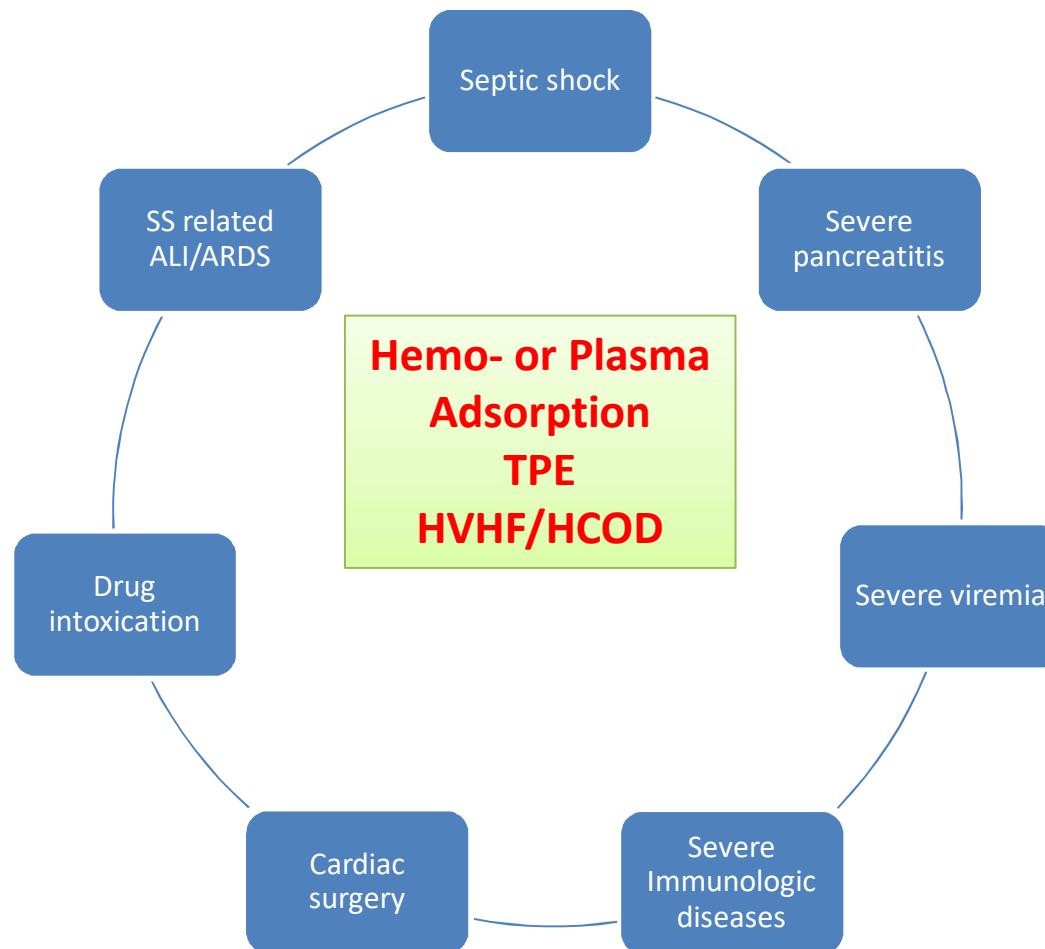
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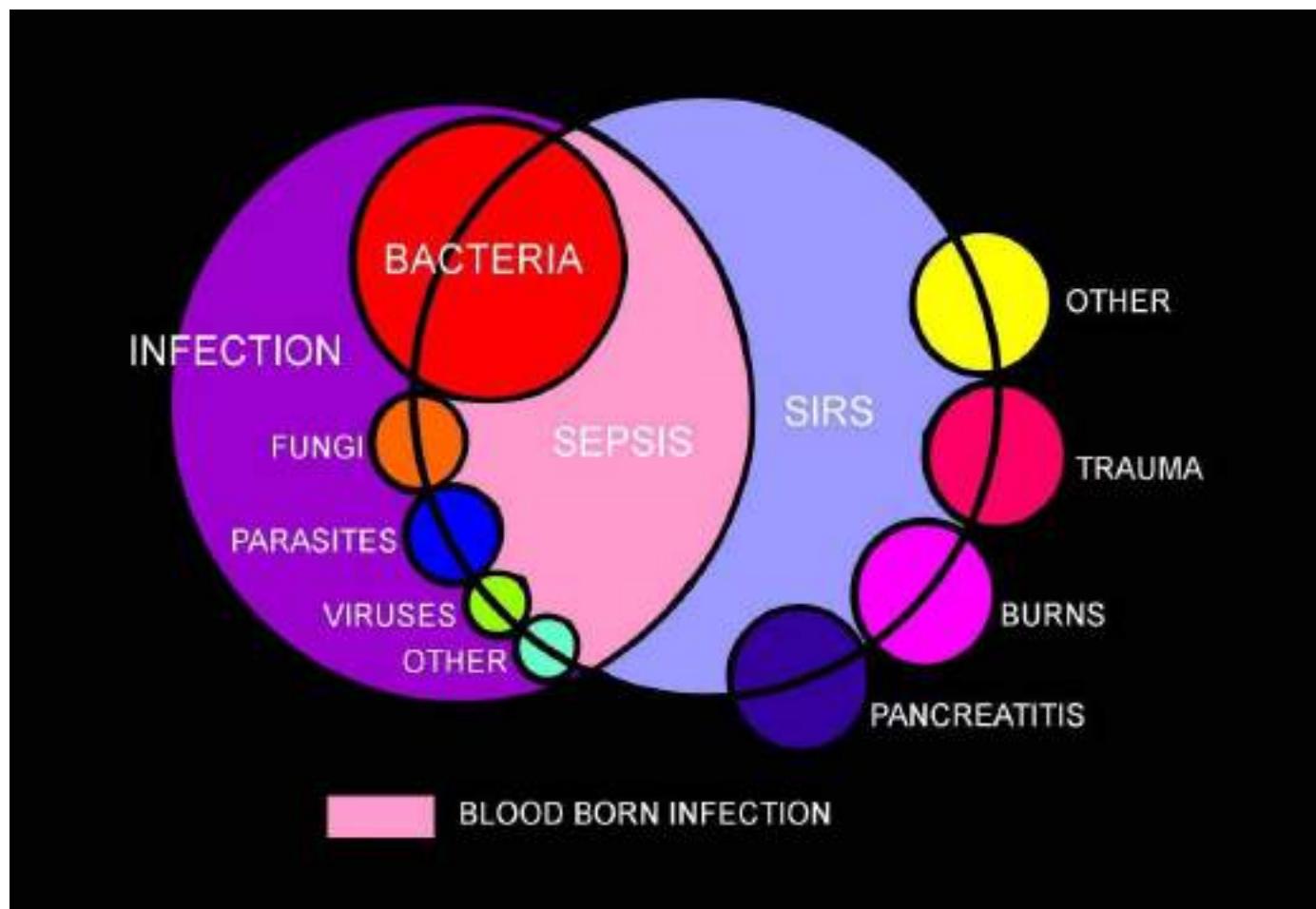
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**Promising therapies** either currently being implemented or developed: These include **extracorporeal therapies, anti-cytokine therapies, anti-toxin treatments**, anti-oxidant approaches and multiple forms of exogenous steroids. For the field to advance, these and other therapies must be assessed in rigorous manner and implemented accordingly.

# Μη παραδοσιακές Ενδείξεις Θεραπευτικής αφαίρεσης σε ΜΕΘ



# Ορισμοί



# Systemic inflammatory response syndrome (SIRS)

- SIRS is a nonspecific response to various clinical insults:  
**Infection, pancreatitis, ischemia, multiple trauma, tissue injury, hemorrhagic shock, or immune-mediated organ injury.**
- SIRS is defined by the presence of 2 or more of the following:
  - **Temperature**  $>38.0^{\circ}\text{C}$  or  $<36.0^{\circ}\text{C}$
  - **Heart rate**  $>90$  beats/min
  - **Respiratory rate**  $>20$  breaths/min or  $\text{aPCO}_2 < 32$  mm Hg
  - **WBC**  $>12,000/\mu\text{L}$ ,  $<4000/\mu\text{L}$ , or including more than 10% bands

# Ορισμός της σήψης

- Η σήψη είναι μια συστηματική φλεγμονώδης απάντηση ταυτόσημη με το SIRS, αλλά οφείλεται αποκλειστικά σε λοίμωξη.
- Ορίζεται ως η απειλητική για τη ζωή δυσλειτουργία των οργάνων λόγω μιας απρόσφορης απάντησης του ξενιστή στη λοίμωξη.
- Η υπερβολική απάντηση του ξενιστή δρα «αυτοκαταστροφικά» και συμβάλει σημαντικά στην αυξημένη νοσηρότητα και θνητότητα.
- Ως δυσλειτουργία των οργάνων ορίζεται η αύξηση του SOFA score (Sequential Organ Failure Assessment) κατά 2 ή περισσότερες μονάδες

# SOFA SCORE

<b>PaO<sub>2</sub>/FiO<sub>2</sub> (mmHg)</b>	<b>SOFA score</b>
≥ 400	0
< 400	+1
< 300	+2
< 200 and mechanically ventilated	+3
< 100 and mechanically ventilated	+4

<b>Bilirubin (mg/dl) [μmol/L]</b>	<b>SOFA score</b>
< 1.2 [< 20]	0
1.2–1.9 [20-32]	+1
2.0–5.9 [33-101]	+2
6.0–11.9 [102-204]	+3
> 12.0 [> 204]	+4

<b>Glasgow coma scale</b>	<b>SOFA score</b>
15	0
13–14	+1
10–12	+2
6–9	+3
< 6	+4

<b>Platelets × 10<sup>3</sup>/μl</b>	<b>SOFA score</b>
≥ 150	0
< 150	+1
< 100	+2
< 50	+3
< 20	+4

<b>Creatinine (mg/dl) [μmol/L] (or urine output)</b>	<b>SOFA score</b>
< 1.2 [< 110]	0
1.2–1.9 [110-170]	+1
2.0–3.4 [171-299]	+2
3.5–4.9 [300-440] (or < 500 ml/d)	+3
> 5.0 [> 440] (or < 200 ml/d)	+4

<b>Mean arterial pressure OR administration of vasopressors required</b>	<b>SOFA score</b>
MAP ≥ 70 mmHg	0
MAP < 70 mmHg	+1
dopamine ≤ 5 μg/kg/min or dobutamine (any dose)	+2
dopamine > 5 μg/kg/min OR epinephrine ≤ 0.1 μg/kg/min OR norepinephrine ≤ 0.1 μg/kg/min	+3
dopamine > 15 μg/kg/min OR epinephrine > 0.1 μg/kg/min OR norepinephrine > 0.1 μg/kg/min	+4

# quick SOFA

Assessment	qSOFA score
Low blood pressure ( <u>SBP</u> $\leq$ 100 mmHg)	1
High respiratory rate ( $\geq$ 22 breaths/min)	1
Altered mentation ( <u>GCS</u> $\leq$ 14)	1

Predictive validity similar to full SOFA score  
outside ICU

## **Stages of Sepsis Consensus Conference Definition**

- **Systemic Inflammatory Response Syndrome (SIRS)**

Two or more of the following:

- Temperature of  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$
- Heart rate of  $>90$
- Respiratory rate of  $>20$
- WBC count  $>12 \times 10^9/\text{L}$  or  $<4 \times 10^9/\text{L}$  or 10% immature forms (bands)

- **Sepsis**

SIRS plus a culture-documented infection

- **Severe Sepsis**

Sepsis plus organ dysfunction, hypotension, or hypoperfusion  
(including but not limited to lactic acidosis, oliguria, or acute mental status changes)

- **Septic Shock**

Hypotension (despite fluid resuscitation) plus hypoperfusion

# Multiple Organ Dysfunction Syndrome

- MODS είναι το κλινικό σύνδρομο που χαρακτηρίζεται από την ανάπτυξη προϊούσας αλλά αναστρέψιμης δυσλειτουργίας 2 ή περισσοτέρων οργάνων ή οργανικών συστημάτων, συνεπεία διαφόρων βλαπτικών παραγόντων-συμβαμάτων, περιλαμβανομένης της σήψης.

# Συνήθη όργανα που προσβάλλονται στο MODS

- Lungs (ARDS)
- Shocked Liver
- GI dysfunction (paralytic ileus, bacteria translocation, ulcers)
- AKI ( μειωμένος ΔΑΟ, αν και ↑ RBF)
- CNS dysfunction (brain hypoperfusion)
- Coagulopathy (subclinical to DIC)

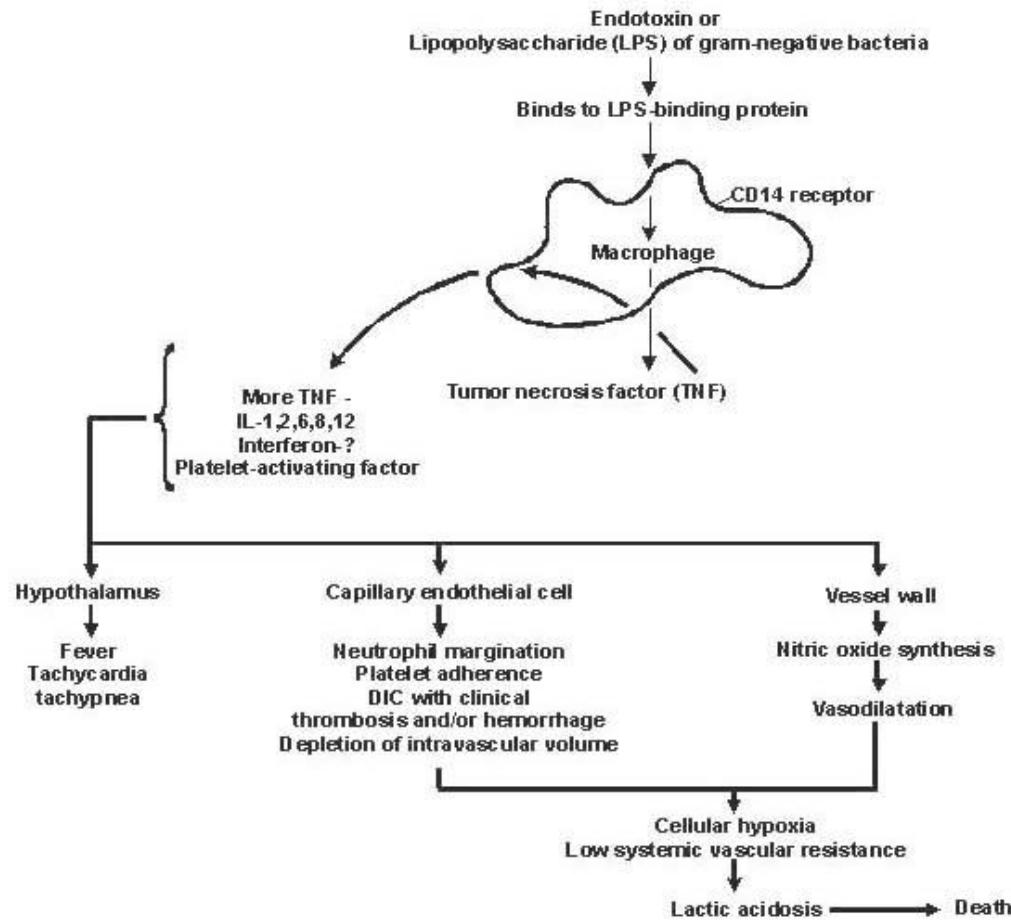
# Prognosis & Mortality

28-day mortality rates:

- SIRS 10%,
- Sepsis 20%,
- Severe sepsis 30%,
- ARDS alone 40%,
- Septic shock 50%,
- MODS 50-70%.

# Pathophysiology of sepsis

## *Malignant intravascular inflammation*

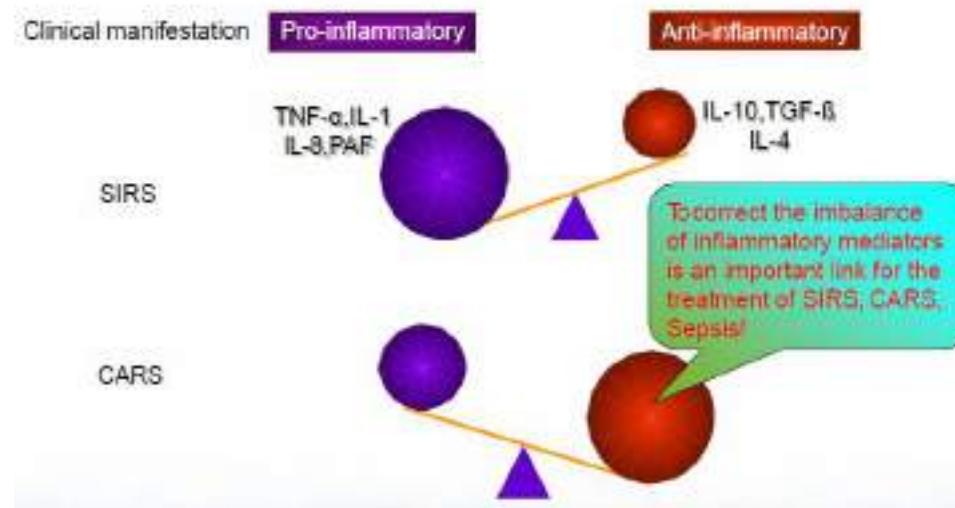


# Pathophysiology

- *Hypoxic hypoxia*: microcirculatory injury,
- *Direct cytotoxicity*, damage to mitochondrial electron transport, leading to disordered energy metabolism.
- *histotoxic anoxia*: inability to utilize oxygen even when it is present.
- *Apoptosis* (accelerated in gut epithelium etc)
- *Immunosuppression* (SIRS vs CARS)

# Η ουσία των SIRS & CARS βρίσκεται στην έλλειψη ισορροπίας προ-φελγμονωδών (SIRS) ή αντι- φλεγμονωδών (CARS) ουσιών

- SIRS: systemic **inflammatory** response syndrome
- CARS : compensatory **anti-inflammatory** response syndrome



**Box 1 Characterization of compensatory anti-inflammatory response syndrome**

**Cellular/molecular elements**

Lymphocyte dysfunction (ie, reduced proliferative and/or type 1 helper T-cell [Th1] cytokine production in response-defined antigens or specific T-cell stimuli)

Lymphocyte Apoptosis

Down-regulation of monocyte HLA receptors Monocyte deactivation (ie, reduced Th1/proinflammatory cytokine production in response stimuli)

IL-10 production

Transforming growth factor-beta production Prostaglandin E2 production

**Clinical elements**

Cutaneous anergy

Hypothermia

Leukopenia

Susceptibility to infection

Failure to clear infection

**Extracorporeal therapies** as adjunctive therapeutic intervention to traditional antimicrobials

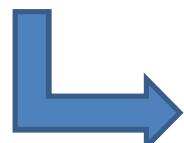


An effort to bring the inflammatory mediators to a homeostatic balance and to improve poor organ perfusion



### Imbalance

proinflammatory and anti-inflammatory cytokines, chemokines, antigens, endotoxins, procoagulant, and anticoagulant factors

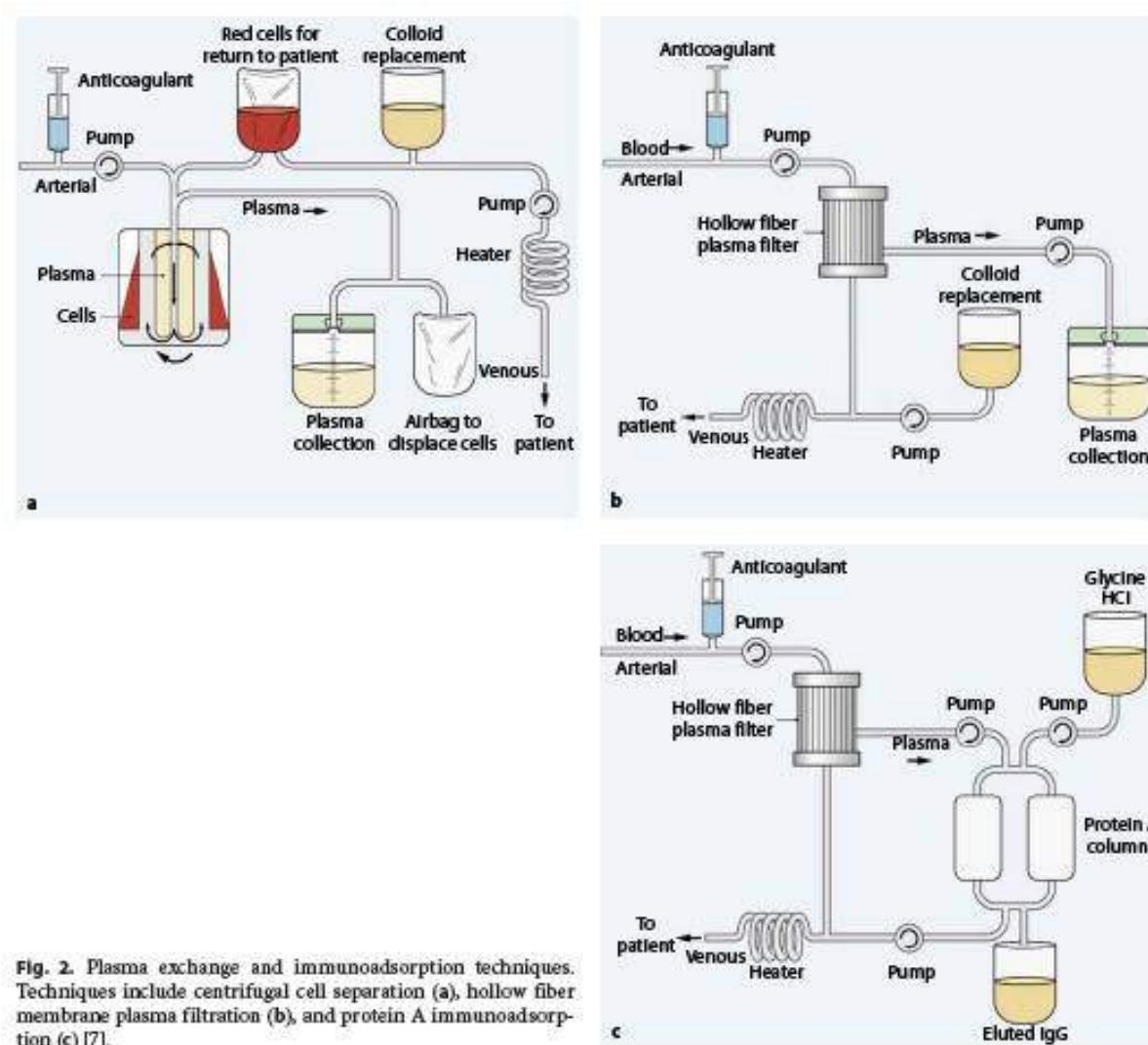


Κατηγορία	Ενδείξεις θεραπευτικής αφαίρεσης. Κατηγορίες κατά ASFA <u>2013 &amp; 2016</u> Περιγραφή
I	Διαταραχές για τις οποίες η αφαίρεση γίνεται δεκτή ως <b>θεραπεία πρώτης γραμμής</b> , είτε ως κύρια θεραπεία ή σε συνδυασμό με άλλες θεραπείες πχ: πλασμαφαίρεση στο σύνδρομο Guillain-Barre, ως μοναδικής θεραπείας 1ης γραμμής, πλασμαφαίρεση στη βαρεία μυασθένεια ως θεραπεία 1η γραμμής σε συνδυασμό με την ανοσοκαταστολή και αναστολείς χολινεστεράσης
II	Διαταραχές για τις οποίες αφαίρεση γίνεται δεκτή ως <b>θεραπεία δεύτερης γραμμής</b> , είτε ως κύρια θεραπεία ή σε συνδυασμό με άλλες θεραπείες πχ: πλασμαφαίρεση ως κύρια δεύτερη θεραπεία για <b>οξεία διάχυτη εγκεφαλομυελίτιδα</b> μετά την αποτυχία υψηλών δόσεων κορτικοστεροειδών, εξωσωματική φωτοφόρηση συμπληρωματική στα κορτικοστεροειδή για χρόνια <b>νόσου μοσχεύματος</b> <b>έναντι ξενιστή</b>
III	<b>Το όφελος από τη θεραπεία αφαίρεσης δεν είναι σαφές. Η λήψη αποφάσεων θα πρέπει να εξατομικεύεται. Πχ η εφαρμογή εξωσωματικής φωτοφόρησης για νεφρογενή συστηματική ίνωση, πλασμαφαίρεση <u>σε ασθενείς με σήψη και πολυοργανική ανεπάρκεια</u></b>
IV	Διαταραχές στις οποίες δημοσιευμένα στοιχεία δείχνουν ότι η αφαίρεση είναι αναποτελεσματικά ή επιβλαβής. Είναι επιθυμητή IRB έγκριση εάν η θεραπεία αφαίρεσης γίνεται σε αυτές τις περιπτώσεις, πχ: πλασμαφαίρεση για ενεργό ρευματοειδή αρθρίτιδα

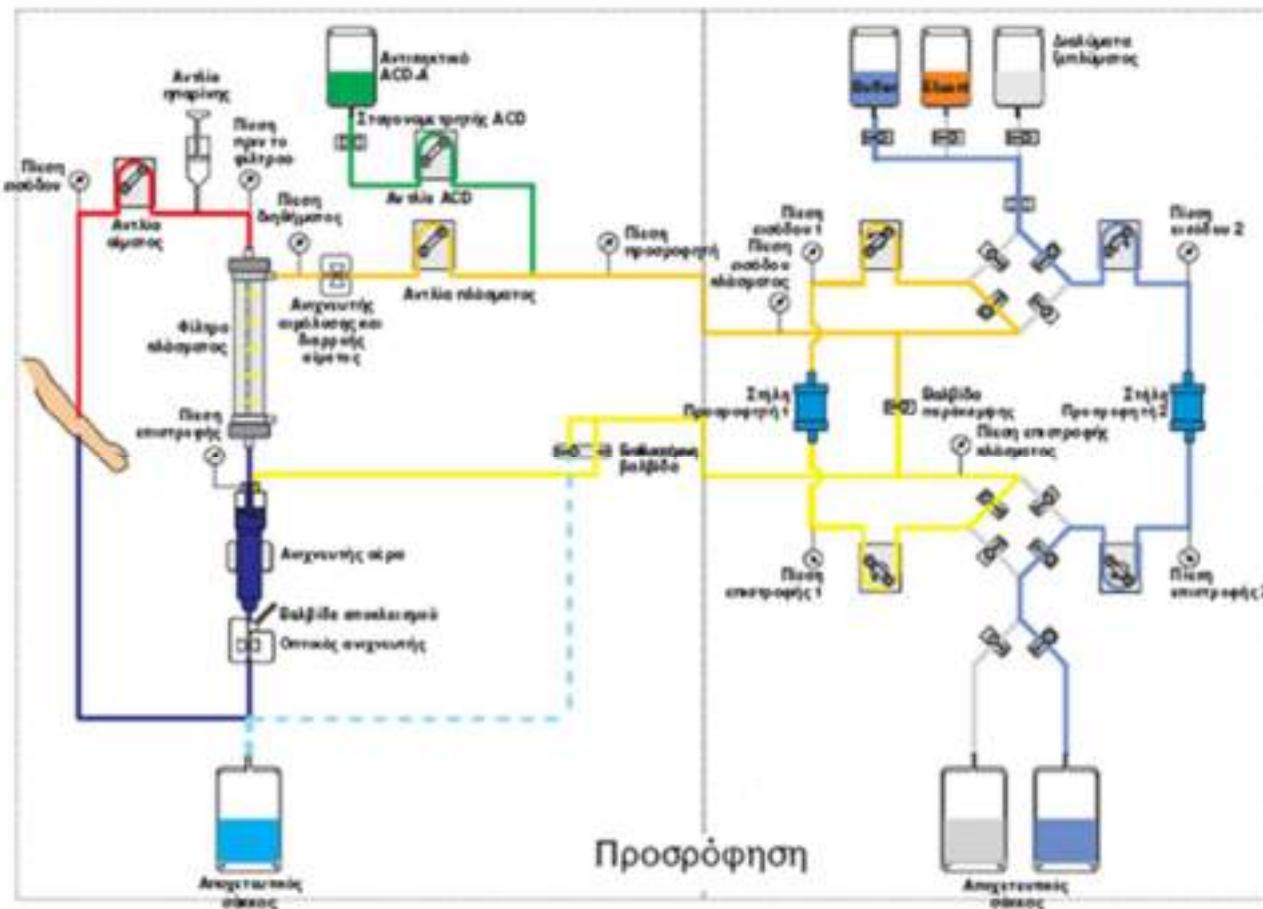
# Theoretical concept of TPE in sepsis

- 1) Removal of harmful circulating molecules that directly contribute to the manifestation of the disease (the injurious cytokine storm)
- 2) Replacement of protective plasma proteins important for coagulation (e.g., APC, AT-III, TF-inh), fibrinolysis (e.g., vWF cleaving proteases),
- 3) Replacement of protective plasma proteins that counteract inflammation and vascular leakage (e.g., angiopoietin-1, VEGF).

# Μεγάλη ποικιλία τεχνικών θεραπευτικής αφαίρεσης



# Μεγάλη ποικιλία τεχνικών θεραπευτικής αφαίρεσης - προσρόφησης



# Hybrid Blood Purification

## HD/CVVH...

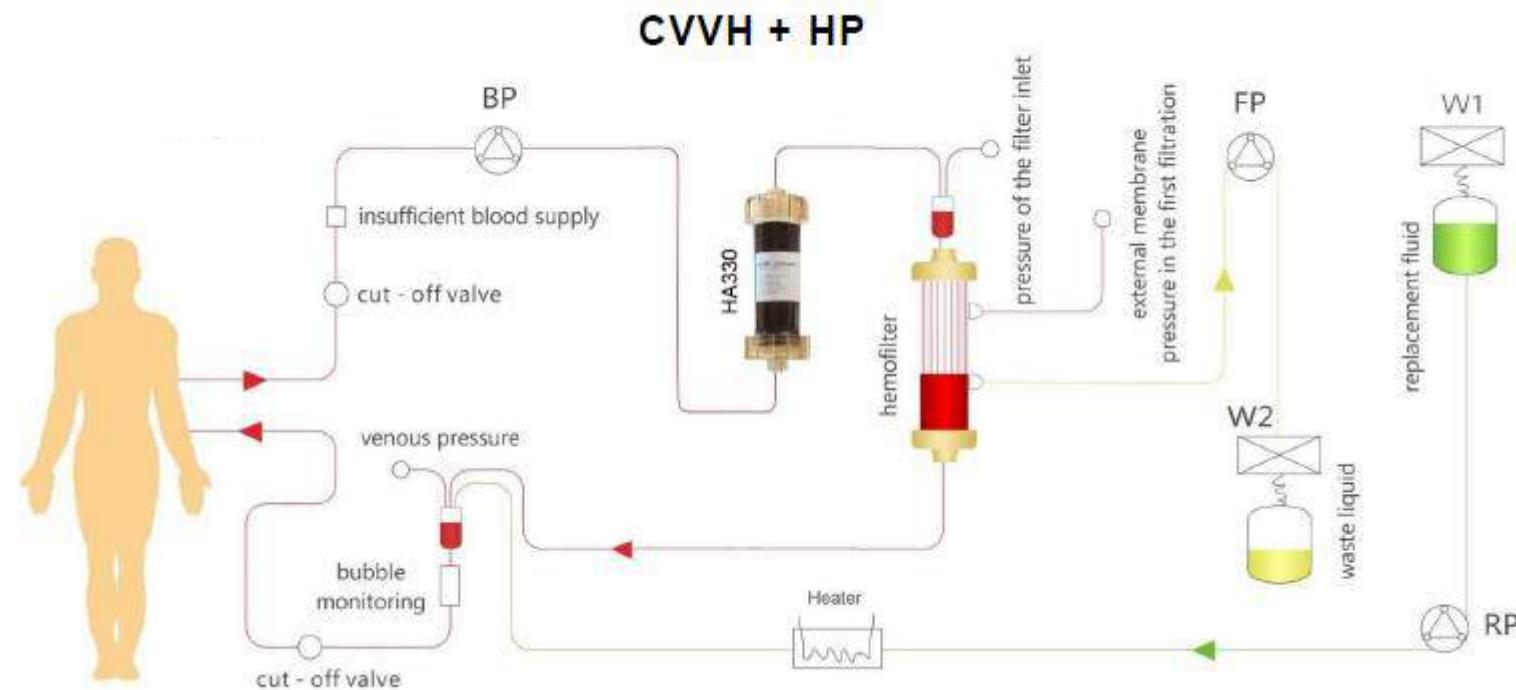
- Strengths: effective clearance of water-soluble and low protein substances, correct water-electrolyte imbalance.
- Weakness: inefficiency clearance of macro molecules and fat soluble toxins.



## Hemoperfusion

- Strength: effective clearance of medium-to-macro, protein-bound toxins and fat soluble substances.
- Weakness: it can not regulate water-electrolyte, acid-base balance.

# CVVH & Plasma or Hemo-perfusion

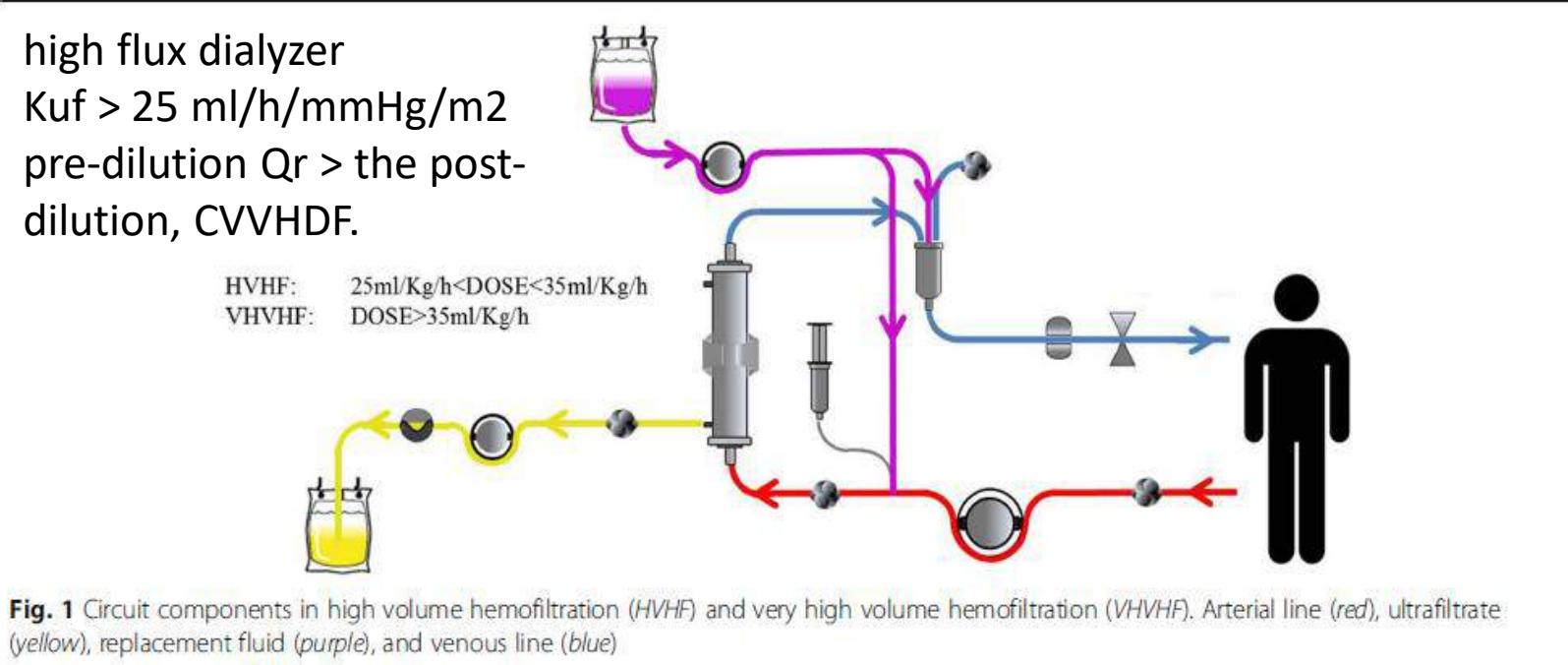


# Evolving strategies for sepsis

- Renal replacement therapy (RRT, CVVH, IHD) is recommended in septic patients who develop AKI to restore fluid, acid-base and electrolyte balance.
- Another application for RRT (CVVHF in particular) is the extracorporeal removal of inflammatory mediators.
- Several studies showed that **RRT alone is not sufficient to decrease serum cytokine levels,**
- Evolving strategies:
  - High volume hemofiltration (HVHF) or very high volume hemofiltration (VHVHF),
  - high cut-off (HCO) membranes,
  - adsorption alone, adsorption-CVVHF,
  - coupled plasma filtration adsorption (CPFA), CPFA-CVVHF

## High volume hemofiltration (HVHF) , very high volume hemofiltration (VHVHF) & pulse HVHF (PHVHF)

- HVHF convective target dose  $>35 \text{ ml/kg/h}$ .
- VHVHF convective target dose  $>45 \text{ ml/kg/h}$



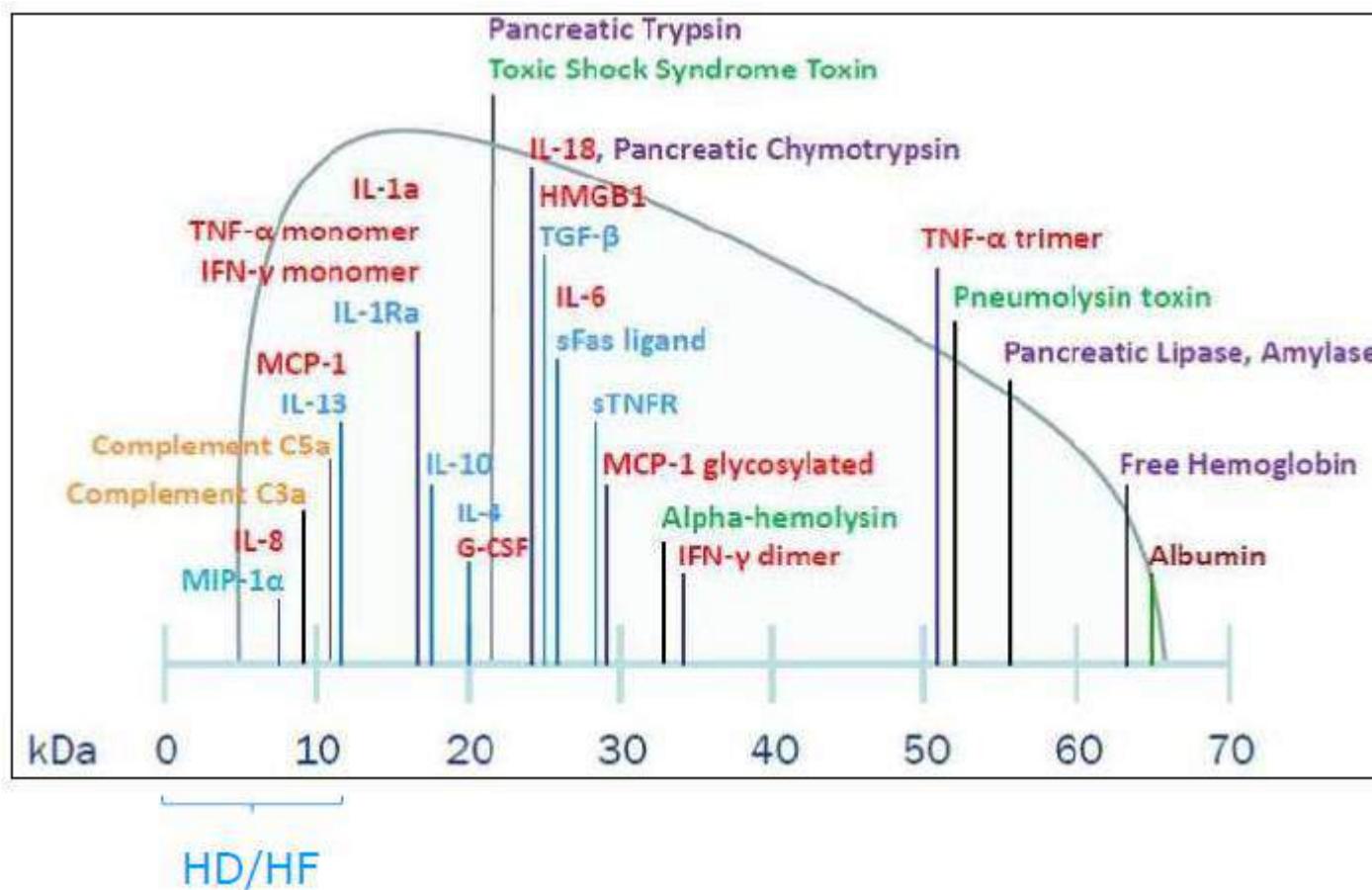
**Table 1** The main studies describing the effectiveness/limitations of high volume hemofiltration

	Honoré et al. 2000 [18]	Cole et al. 2001 [15]	Joannes-Boyau et al. 2004 [12]	Ratanaert et al. 2005 [19]	Correjo et al. 2006 [14]	Piccinni et al. 2007 [11]	Boussekky et al. 2008 [16]	Joannes-Boyau et al. 2013 [17] (VOIR)
Study design	Cohort; uncontrolled prospective	Randomized crossover	Cohort; uncontrolled prospective	Cohort; uncontrolled prospective	Cohort; uncontrolled prospective	Prospective randomized	Prospective, randomised, open, multicenter	Prospective, randomised, open, multicenter
Study population (n)	20 septic shock patients	11 septic shock patients	24 septic shock patients	15 severe sepsis patients	20 septic shock patients	10 septic shock patients and AKI	140 septic shock patients and AKI	140 septic shock patients and AKI
Prescribed dose	HVHF (4 h, 35 L of UF removed) followed by conventional CVVH for at least 4 days	8 h of HVHF (6 L/h) or 8 h of standard CWH (1 L/h)	40–60 mL/kg/h for 96 h	HVHF: 85 mL/kg/h for 6–8 h followed by CWH 35 mL/kg/h for 16–18 h	100 mL/kg/h for 24 h	70 mL/kg/h for 24 h	HVHF at 70 mL/kg/h vs SVHF at 35 mL/kg/h for 96 h	HVHF at 70 mL/kg/h vs SVHF at 35 mL/kg/h for 96 h
Survival/mortality	28-day observed survival of 45% compared to expected of 21% ( $p < 0.05$ )	Hospital mortality 54.5%	28-day survival 50% compared to 21% ( $p < 0.05$ )	28-day survival 55% compared to 27.5% in the conventional group ( $p < 0.05$ )	28-day survival 55% compared to 27.5% in the conventional group ( $p < 0.05$ )	+ ICU mortality of 33.3% in HVHF group vs 60% in LVHF group but not significantly different	+ 28 day mortality of 37.9% in HVHF vs 40.8% in SVHF, ( $p = 0.94$ ) + No difference in 60 and 90 days mortality	+ 28 day mortality of 37.9% in HVHF vs 40.8% in SVHF, ( $p = 0.94$ ) + No difference in 60 and 90 days mortality
Length of ICU stay	–	–	–	–	Significant improvement ( $p < 0.002$ )	No difference	No difference	No difference
Hemodynamics	Improvement in 11/20 patients	Improvement in 11/20 patients	Improvement in 11/20 patients	Significant improvement ( $p = 0.001$ )	Improvement in 11/20 patients	Significant improvement ( $p < 0.05$ )	Improvement in VP dose in the treatment group ( $p = 0.004$ )	No difference
Safety	–	–	–	–	–	No AE	Hypokalemia (30% in HVHF vs 20% in SVHF, ( $p = 0.1$ )) Hypophosphatemia 88% in HVHF vs 38 in SVHF ( $p = 0.01$ )	Hypokalemia (30% in HVHF vs 20% in SVHF, ( $p = 0.1$ )) Hypophosphatemia 88% in HVHF vs 38 in SVHF ( $p = 0.01$ )

NO SIGNIFICANT BENEFIT  
in RCTs & meta-analyses

HVHF high volume hemofiltration, LVHF low volume hemofiltration, SVHF standard volume hemofiltration, CVVH continuous veno-venous hemofiltration, UF ultrafiltrate, h hour, kg kilogram, NE norepinephrine, AE adverse events, VP vasopressor

# Molecular weight of common inflammatory mediators



# High cut-off membranes

- HCO membranes are characterized by a large pore size (average pore diameter (**20 nm**) compared with the standard high-flux membrane (10 nm)).
- HCO membranes have been used in the context of rhabdomyolysis, MM and sepsis.
- Loss of albumin in convective techniques.  
Diffusive preferable (CVVHD)

# High cut-off membranes

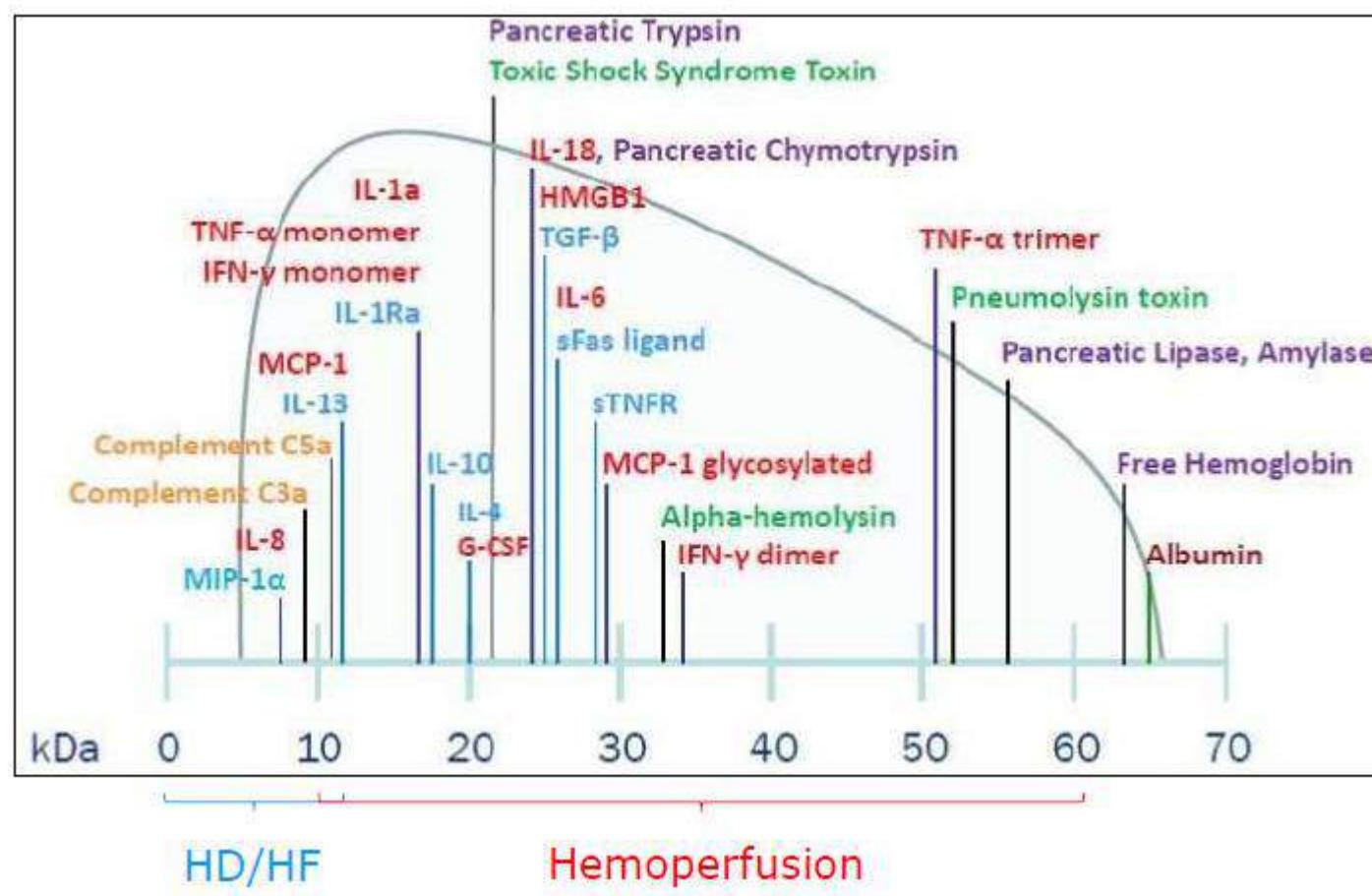
**Table 2** The main studies describing the effectiveness/limitations of high cut-off membranes

	Morgera et al. 2003 [28, 29]	Morgera et al. 2004 [27]	Morgera et al. 2006 [30]	Haase et al. 2007 [31]	Kade et al. 2016 [34]	Villa et al. 2017 [33]
Study design	Prospective single-center pilot trial	Prospective RCT	Prospective RCT	Double-blind RCT	Prospective, multicenter	Observational prospective multicenter study
Study population (n)	16 septic shock patients	24 patients with sepsis-induced AKI	30 septic patients with AKI	10 septic patients with AKI	30 patients with septic shock	38 patients with septic shock and AKI
Prescribed dose	Intermittent HP-HF over 5 days for 12 h/day alternating with conventional HF (12 h)	CWH (UF 1 L/h) vs CWH (UF 2.5 L/h) vs CWHDF (dialysate flow rate of 1 L/h) vs CWHD (dialysate flow rate of 2.5 L/h)	HCO vs conventional HF	–	HCO-CWHDF	HCO-CWHDF for 72 h
Results	High IL-6 elimination	Increasing UF volume or dialysate flow was significant in IL-1ra and IL-6 rates	Significant reduction in IL-8 plasma levels (p < 0.04) in the HCO group	ICU mortality rates were 37.5 and 87.5% for HCO and HF groups, respectively (p = 0.03) ICU LOS: 16 and 9 days (HCO- and HF-group; p = 0.03). Improvement of hemodynamics in the HCO group (p < 0.03)	Significant reduction in IL-10 and IL-12 levels	Significant reduction in circulating levels of TNFα and IL-6 among survivors
Safety or S/E	High cumulative protein loss (7.3 g; IQR 6.2–12.0)	–	Albumin loss of 7.7 g in the HCO group vs < 1.0 g (p < 0.01)	–	–	–

RCT randomized controlled trial, AKI acute kidney injury, CWH continuous veno-venous hemofiltration, CWHDF continuous veno-venous hemodialfiltration, CWHD continuous veno-venous hemodialysis, HCO-IHD high cut-off intermittent hemodialysis, HF-IHD high flux intermittent hemodialysis, HF hemofiltration, TNF tumor necrosis factor, IL interleukin, LOS length of stay, VP vasopressin, IQR interquartile range

NO PROVEN BENEFIT  
Reduction of IL-6

# Molecular weight of common inflammatory mediators



# Adsorbers

**Table 3** The commonly used adsorption cartridges and their prescriptions

	Toraymyxin	Cytosorb	Oxiris	LPS adsorber	HA 330
Composition	Polymyxin B-immobilized fiber blood-purification column	Porous polymer beads	AN69-based membrane, surface treated with PEI and grafted with heparin	Synthetic polypeptide bound to porous polyethylene discs	Styrene divinylbenzene copolymers
Indication	Severe sepsis and septic shock	Severe sepsis and septic shock Cardiac surgery with SIRS	Severe sepsis and septic shock	Severe sepsis and septic shock	Severe sepsis and septic shock
Toxins removed	Endotoxins	Cytokines/chemokines Anaphylatoxins Myoglobin Free hemoglobin Bilirubin/bile acids Toxins/metals Drugs	Endotoxin Cytokines	Endotoxins	Cytokines Complements Free hemoglobin
Prescription	2-h session daily for 2 consecutive days	Up to 24-h therapy daily for 2–7 consecutive days	Prescribed dose > 35 ml/kg/h (60% convective). Filter replacement after 24 h or if there is no reduction in VP dose by 50%. Treatment should be stopped if VP are reduced by > 50% or after 3 days of treatment in case of no-response	2–6 h. One session is usually sufficient to achieve improvement. Repeated procedures can be performed	2–6 h daily for 2 days
Blood flow rate (ml/min)	80–120	150–700	100–450	150± 50	100–300
Anticoagulation	Heparin	Heparin or citrate	Heparin	Heparin	Heparin or citrate
Additional features	Polymyxin B antimicrobial effect	Largest surface area	Lower risk of thrombogenicity by adsorbing antithrombin-III from the blood		

CRRT continuous renal replacement therapy, LPS lipopolysaccharides, PEI polyethylenimine, SIRS systemic inflammatory response syndrome, VP vasopressors

Adsorption is performed in the form of hemoperfusion (HP), plasma perfusion (PP), or coupled plasma filtration adsorption (CPFA)

# Αρχικές μελέτες με προσρόφηση

TABLE 2. Various clinical studies using adsorption techniques in the treatment of sepsis, severe sepsis, and in MODS

Study/adsorber	n	Main mode of therapy	Survival (%)	p
<b>Polymyxin B</b>				
Tani et al. (36)	37/33c	AdsPmx	54/36	< 0.05
Nemoto et al. (21)	98	AdsPmx	41/11c	< 0.05
Suzuki et al. (37)	24/24c	AdsPmx	75/25c	< 0.05
Vincent et al. (23)	17/19c	AdsPmx	71/72c	ns
Cruz et al. (22)	34/30	AdsPmx	68/47c	< 0.05
Albumin as adsorber				
Staubach et al. (19)	67/76c	Albumin adsorber	71/74	ns

AdsPmx, adsorption column using polymyxin B; c, control group; ns, not significant.

Nemoto, *Blood Purif* 2001; Cruz, *EUPHAS RCT, JAMA*, 2009; Vincent, *Shock*, 2005  
Suzuki, *Therap Apher* 2002; Tani, *Artif Organs* 1998; Staubach *Transfus Apher Sci* 2003

# Μελέτες προσρόφησης με polymyxin

**Table 4** The main studies describing the effectiveness/limitations of the polymyxin B-immobilized fiber column

	European pilot study (2005) [37]	EUPHAS (2009) [38]	Japan Registry (2014) [41]	ABDO-MIX (2015) [39]	Japan Registry (2016) [40]	EUPHAS 2 (2016) [42]
Study design	Multicenter, open-label, pilot, RCT	Multicenter, open-label, prospective RCT	Propensity-matched analysis	Multicenter, prospective RCT	Propensity-matched analysis	Retrospective study
Study population (n)	36 patients with intra-abdominal sepsis	64 patients with intra-abdominal sepsis or septic shock	PMX = 642 intra-abdominal sepsis patients vs 590 propensity score-matched pairs	232 patients with intra-abdominal septic shock/ peritonitis	Septic shock patients with CRRT-requiring AKI	357 patients with suspected Gram-negative sepsis
EAA assessment	Measured	Not measured	Not measured	Not measured	Not measured	Some centers
Prescribed dose	1 session (2 h)	2 sessions (2 h)	1–2 sessions	1–2 sessions (2 h)	1–2 sessions	1–2 sessions (2 h)
Timing (h)	24–48 (from diagnosis)	24 (from abdominal surgery)	24 (from surgery)	12 (from surgery)	24 (from starting CRRT)	24–48 (from diagnosis)
Survival/mortality	Mortality, 29% in the PMX group vs 28% in the control group ( $p=0.749$ )	<ul style="list-style-type: none"> <li>PMX group had a significant reduction in 28-day mortality (adjusted HR 0.36; 95% CI 0.16–0.80; <math>p=0.01</math>)</li> <li>P = benefit</li> </ul>	28-day mortality was 17.1% in the treatment group and 16.3% in the control group ( $p=0.696$ )	<ul style="list-style-type: none"> <li>28-day mortality 27.7% in the treatment group vs 19.5% in the control group (<math>p=0.14</math>)</li> <li>90-day mortality was 33.6% in 24 (P = benefit)</li> </ul>	<ul style="list-style-type: none"> <li>The 28-day mortality was 40.2% in the treatment group and 46.8% in the control group (<math>p=0.003</math>)</li> <li>28-day survival 54.5%</li> <li>ICU survival 55.2%</li> <li>Hospital survival 50%</li> <li>Patients with abdominal sepsis treated within 24 h survival 64.5%</li> </ul>	
Length of ICU stay	13.2 ± 9.4 days in the PMX vs 17.0 ± 9.4 days	No significant difference	–	No significant difference	–	–
Hemodynamics	Significant improvement in the PMX group	Significant reduction in VP dose in the treatment group	–	No significant difference	No significant difference	–
Other results	No significant difference in the change of IL-6 levels compared to baseline	–	–	–	–	–
Safety	Higher AE (mainly change in vitals in the treatment arm)	No adverse events reported	–	6 severe adverse events (hemorrhagic episodes in the treatment group) Platelet drop	–	Significant platelet drop with no clinical implications

CRRT continuous renal replacement therapy, EAA endotoxin activity assay, PMX polymyxin, AE adverse event, VP vasopressors

# Μελέτες προσρόφησης με cytosorb

**Table 5** The main studies describing the effectiveness/limitations of the Cytosorb cartridge

	Schädler et al. 2013 [51]	Friescke et al. 2017 [50]	Schädler et al. 2017 [52]	Kogelmann et al. 2017 [49]
Study design	Multicenter, open label, RCT	Prospective interventional single center	Multicenter, open label, RCT	Case series
Study population (n)	48 septic patients with ALI	25 septic shock patients	97 septic patients with ALI or ARDS	16 septic shock patients
IL-6 assessment (pg/ml)	>1000	One session in the pre-filter mode. Further treatments at the discretion of the study physicians	Assessments after up to 7 days of HP in the pre-filter mode (1-5 treatments)	- benefit
Prescribed dose	No benefit	Within 24 h	No benefit	HP in the pre-filter mode (1-5 treatments)
Timing	-	-	-	< 24 to > 48 h (outcomes better in the early group)
Survival	28-day mortality 28% in the treatment group vs 24% in the controls ( $p = 0.84$ ) 60-day mortality 39% in the treatment group vs 32% in the controls ( $p = 0.75$ )	benefit	28-day mortality 36.2% in the treatment group vs 18.0% in the controls ( $p = 0.073$ ) 60-day mortality of 44.7% in the treatment group vs 26.0% in the controls ( $p = 0.039$ )	The actual 28-day, ICU, and hospital mortality was 61.54%, 73.08%, and 80.77%, respectively, compared with 89.9% as predicted by APACHE II score
Hemodynamics	-	Significant reduction in VP requirements compared to baseline	-	Significant reduction in VP requirements compared with baseline
Other results	Significant reduction in IL-6	Significant reduction in IL-6	IL-6 reduction in the HP group compared with no HP	-
Safety	Modest reduction in platelet count (< 10%) and albumin (< 5%)	No AE	1 drop in platelets in the treatment group	No AE

RCT randomized controlled trial, ALI acute lung injury, ARDS acute respiratory distress syndrome, IL interleukin, ICU intensive care unit, AE adverse event, ST standard therapy, HP hemoperfusion, RRT renal replacement therapy, APACHE II Acute Physiology and Chronic Health Evaluation II, VP vasoressor

Δεν μειώνει την ενδοτοξινή και την IL-6. Μειώνει DAMPs & PAMPs.  
Συχνή χρήση στην καρδιοχειρουργική.

# Μελέτες προσρόφησης με LPS (Alteco)

**Table 7** The main studies describing the effectiveness/limitations of LPS adsorbers

	Yaroustovsky et al. 2009 [60]	Ala-Kokko et al. 2011 [61]	Adamik et al. 2015 [62]
Study design	Observational	Case series with matched controls	Observational
Study population (n)	13 Gram-negative sepsis	24 septic shock patients and endotoxaemia.	62 septic shock and suspected Gram-negative
EAA assessment	–	More than 0.3 considered endotoxaemia	EA [0.70 EA units (0.66–0.77)].
Prescribed dose	Two sessions with a maximum duration of 120 min/patient Alteco adsorber ( $n = 6$ ) and toraymyxin (–)	2-h LPS HP	LPS elimination + ST vs ST 1–2 sessions
Timing	–	Observational studies LPS reduction	Within 24 h
Survival	–	Improvement in survival No effect on survival	No effect
Length of ICU stay	–	Improvement in survival No effect on survival	No effect
Hemodynamics	Improved MAP Decrease in endotoxin and procalcitonin levels	Decreased endotoxin levels	Significant improvement in the treatment group
Other results	Decrease in endotoxin and procalcitonin levels	Decreased endotoxin levels	Decreased endotoxin levels
Safety	–	Low platelets, two patients requiring transfusion but no bleeding	–

EAA endotoxin activity assay, ST standard therapy, MAP mean arterial pressure, VP vasopressors, LPS lipopolysaccharide, HP hemoperfusion

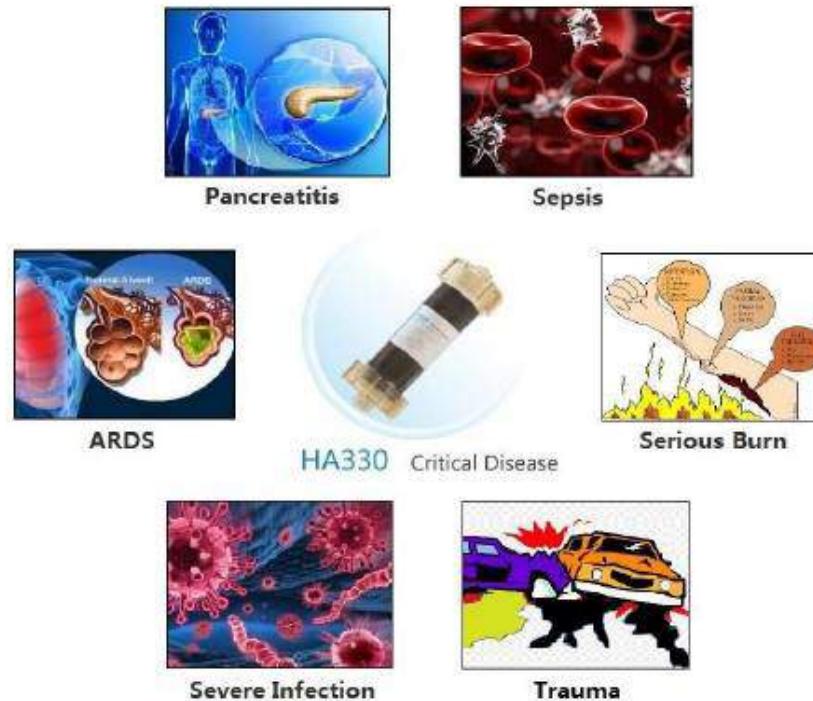
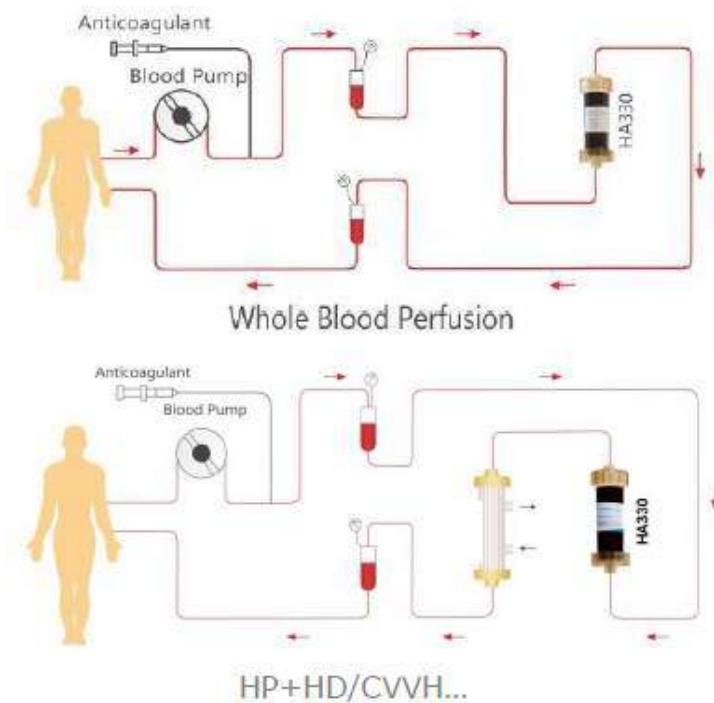
# Μελέτες προσρόφησης με HA330

**Table 6** The main studies describing the effectiveness/limitations of the HA 330 cartridge

	Huang et al. 2010 [56]	Huang et al. 2013 [57]
Study design	RCT	RCT
Study population (n)	44 sepsis or septic shock patients	46 ALI/extrapulmonary sepsis patients
EAA assessment	–	–
Prescribed dose	HP for 2 h for 3 days	HP for 2 h for 3 days
Survival	<ul style="list-style-type: none"><li>• ICU mortality 12.5% in HA vs 45.0% in the controls (<math>p = 0.02</math>)</li><li>• Hospital mortality 37.5% in HA vs 50.0% in the controls (<math>p = 0.81</math>)</li><li>• 28-day mortality 45.8% in HA vs 55.0% in controls (<math>p = 0.47</math>)</li></ul>	<ul style="list-style-type: none"><li>• ICU mortality 24% in HA vs 57.14% in the controls (<math>p = 0.02</math>)</li><li>• 28-day mortality 28% in HA vs 66.7% in the controls (<math>p = 0.009</math>)</li></ul>
Length of ICU stay (days)	$12.4 \pm 3.1$ in HA vs $19.5 \pm 4.0$ in controls ( $p = 0.03$ )	$15.5 \pm 4.0$ in HA vs $19.4 \pm 3.1$ in controls ( $p = 0.04$ )
Hemodynamics	Significant reduction in VP dose in the HA group vs increase in the control group ( $p = 0.01$ )	Significant reduction in VP dose in the HA group vs increase in the control group ( $p = 0.032$ )
Other results	Significant difference in IL-8 and IL-6 levels between the two groups at day 3 ( $p = 0.03$ and 0.01, respectively)	Significant difference in IL-1 and TNF- $\alpha$ in BAL fluid between the two groups ( $p = 0.02$ and 0.04, respectively)
Safety	<ul style="list-style-type: none"><li>• 1 patient died in the HA group</li><li>• Transfusions of platelet counts in the HA group</li></ul> <b>benefit</b>	<ul style="list-style-type: none"><li>–</li></ul> <b>benefit</b>

RCT randomized controlled trial, ALI acute lung injury, EAA endotoxin activity assay, HA hemoadsorption, HP hemoperfusion, ICU intensive care unit, TNF tumor necrosis factor, BAL broncho-alveolar lavage, VP vasopressor, IL interleukin

# Αιμοπροσρόφηση και CVVH



The HA330 resin cartridge has the ability to absorb various medium-sized factors, including most inflammatory cytokines (IL-1, IL-6, IL-8, TNF- $\alpha$ ), ranges from 6 kDa to 26 kDa.

## **Effect of hemoperfusion with neutral microporous resin column on extrapulmonary sepsis-induced Acute Lung Injury.**

**Design :** A prospective randomized, parallel controlled analysis.

**Study Subject:** patients with acute lung injury induced by extrapulmonary Sepsis

**Therapeutic Regimens:**

C Group (N=21): standard therapy including fluid resuscitation, vasopressors, antimicrobial therapy, ventilatory, etc.

H Group (N=25): standard therapy+**HA330 (1 time/day for 3days,**

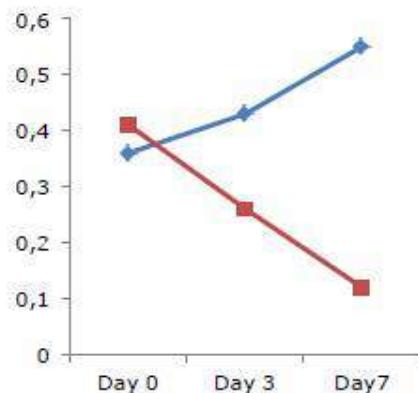
**2 hours each session. blood flow rate: 100-200ml/min)**

**Purpose:** investigate the effect of hemoperfusion on oxygenation improvement, removal of inflammatory cytokines in plasma and bronchoalveolar lavage, and mortality.

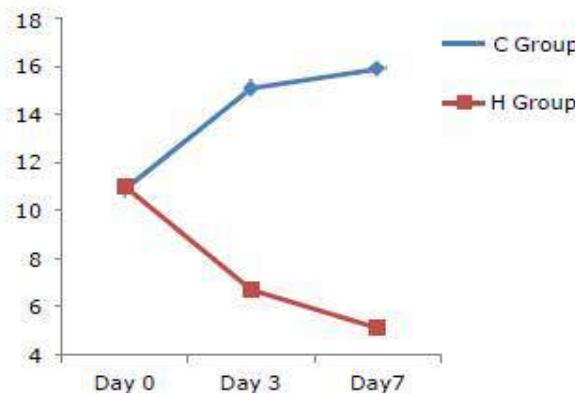
*Therapeutic Apheresis and Dialysis, 2012:1-8.*

# Effect of hemoperfusion with neutral microporous resin column on extrapulmonary sepsis-induced Acute Lung Injury.

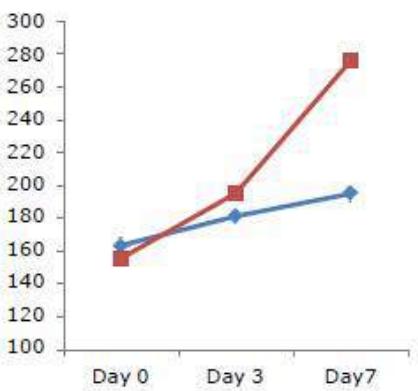
Noradrenaline (mg/kg per min)



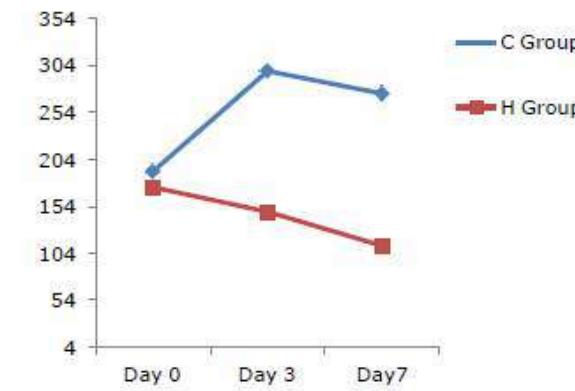
Dopamine (mg/kg per min)



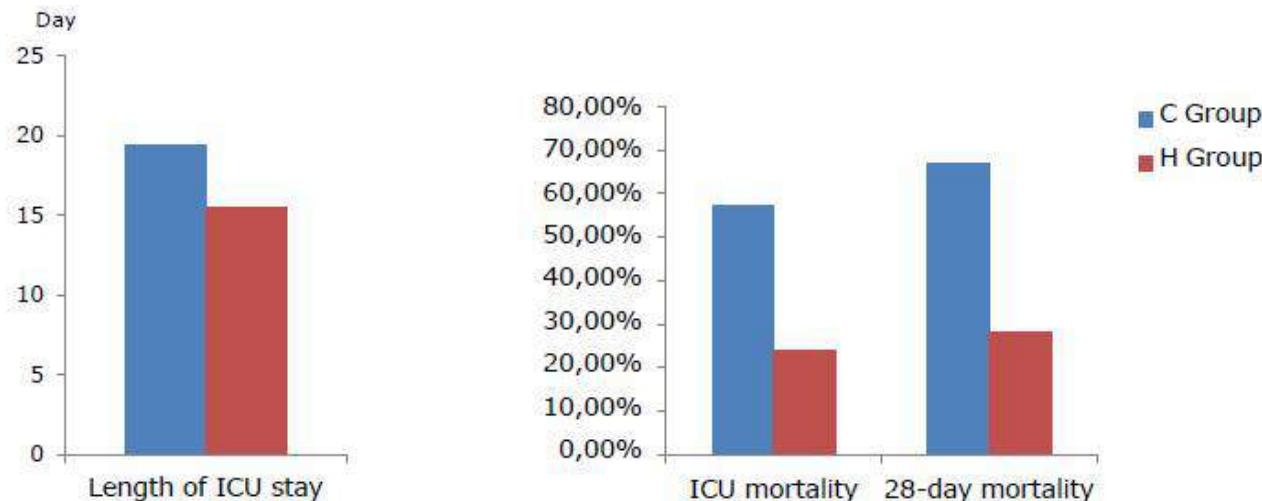
PaO<sub>2</sub>/FiO<sub>2</sub>



Creatinin (mmol/L)



## Effect of hemoperfusion with neutral microporous resin column on extrapulmonary sepsis-induced Acute Lung Injury.



**TABLE 5.** Duration of mechanical ventilation and length of stay in survivors; ICU and 28-day mortality

Variables	Control group	HA group	P-value
Duration of mechanical ventilation, days	$13.6 \pm 3.2$	$9.2 \pm 2.3$	0.01
Mechanical ventilation-free days to day 28	$14.7 \pm 5.5$	$19.6 \pm 4.7$	0.03
Duration of CRRT, hours	$65.7 \pm 14.6$	$18.6 \pm 5.1$	0.005
Length of ICU stay, day	$19.4 \pm 3.1$	$15.5 \pm 4.0$	0.04
ICU mortality No. (%)	12/21 (57.14)	6/25 (24)	0.02
28-day mortality No. (%)	14/21 (66.7)	7/25 (28)	0.009
SOFA at 14 day	$8.9 \pm 2.5$	$6.1 \pm 1.2$	0.047

CRRT, continuous renal replacement therapy; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

# Hemoperfusion with neutral microporous resin on Septic shock (RCT)

**Study Subject:** severe sepsis or septic shock patients

**Therapeutic Regimens:**

Hemoperfusion Group (N=24):

Standard therapy + HA330 hemoperfusion

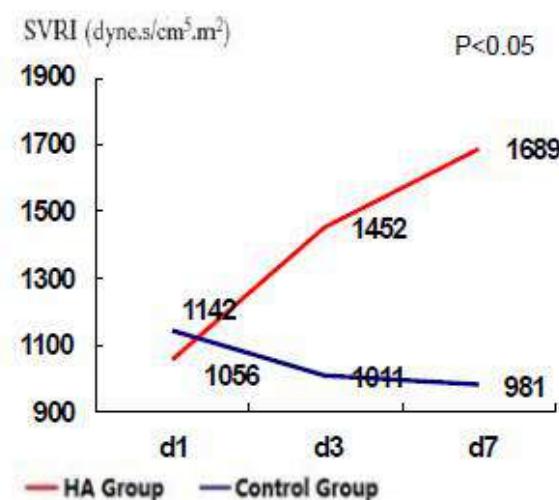
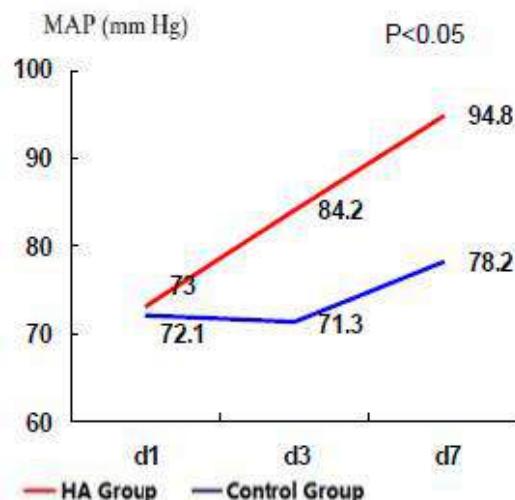
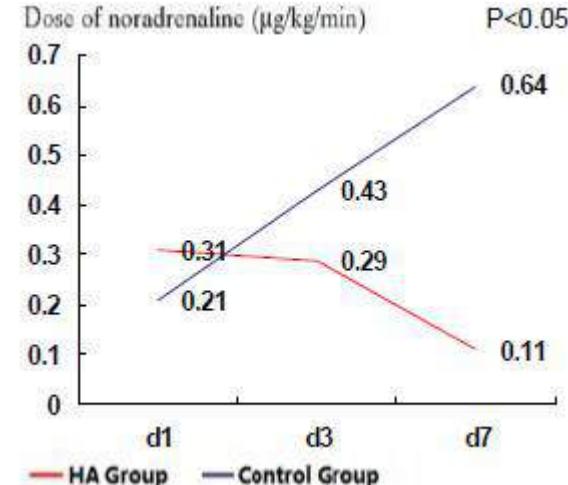
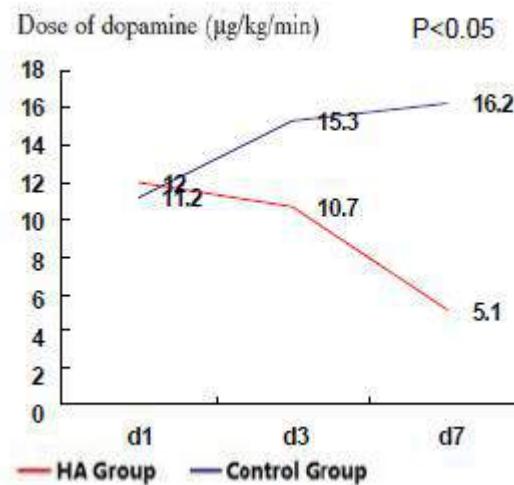
HA330 Regimen: 2 hours per treatment, once a day for 3 consecutive days  
blood flow rate 100~200ml/min

Control Group (N=20): Standard therapy

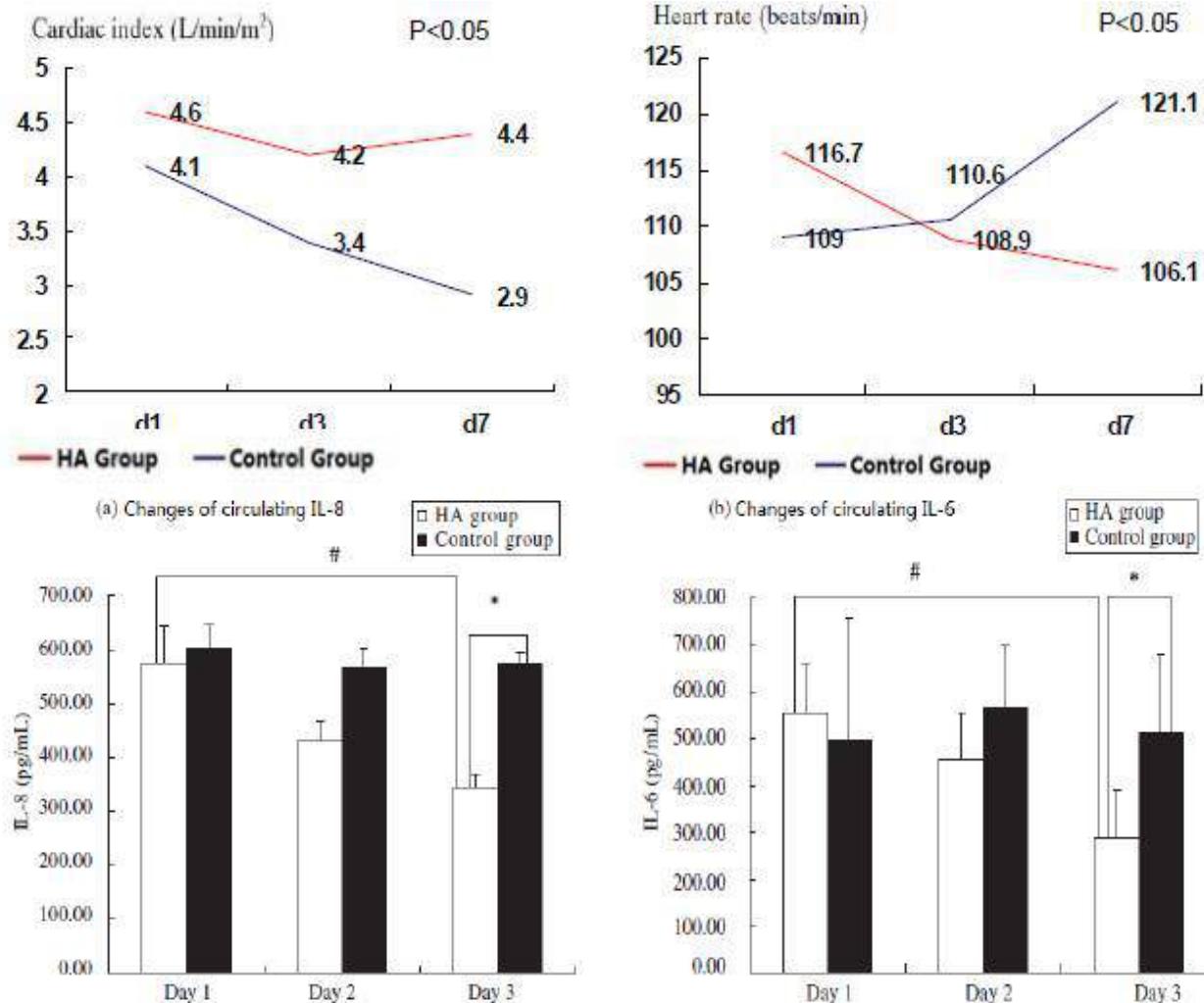
**Purpose:** Dynamic observation of daily testing index and 28-day survival rate between the control group and the HA group.

Zhao Huang, et al. Removal of Humoral Mediators and Effect on the Survival of Septic Patients by Hemoperfusion with Neutral Microporous Resin Column. *Therapeutic Apheresis and Dialysis*, 2010(8).

# Hemoperfusion with neutral microporous resin on Septic shock (RCT)



# Hemoperfusion with neutral microporous resin on Septic shock



Zhao Huang Therapeutic Apheresis and Dialysis, 2010

# Hemoperfusion with neutral microporous resin on Septic shock

Variables	HA group (N=24)	Control group (N=20)	P value
Length of ICU stay (days)	12.4 ± 3.1*	19.5 ± 4.0	0.03
Length of hospital stay (days)	27.9 ± 6.7	29.4 ± 4.4	0.76
ICU mortality	3 (12.5%)*	9 (45.0%)	0.02
Hospital mortality	9 (37.5%)	10 (50.0%)	0.81
28-day mortality	11 (45.8%)	11 (55.0%)	0.47
SOFA score at ICU admission			
>8	9/15 (60.0%)	8/13 (61.5%)	0.91
<8	2/9 (22.2%)*	3/7 (42.9%)	0.02

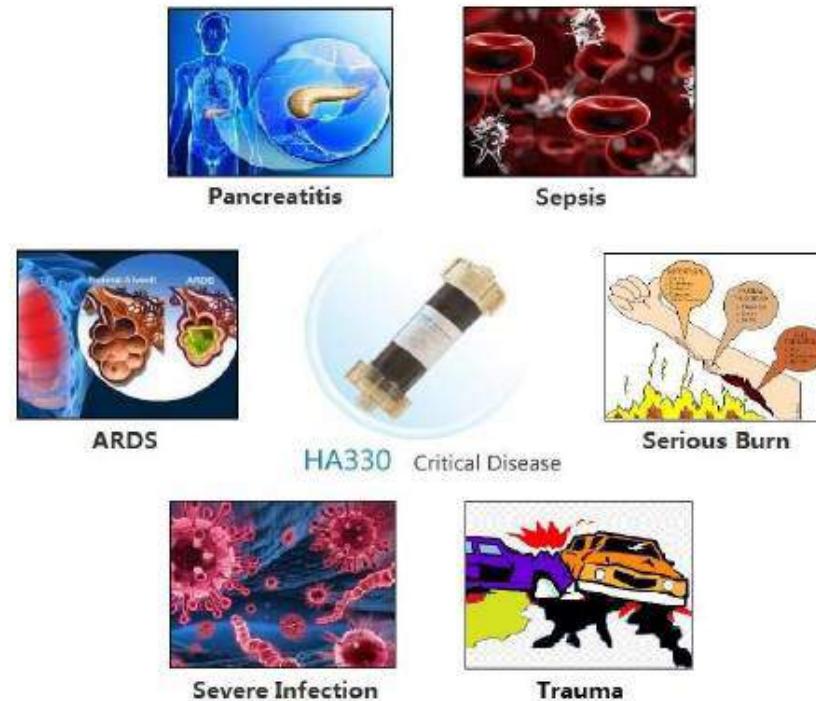
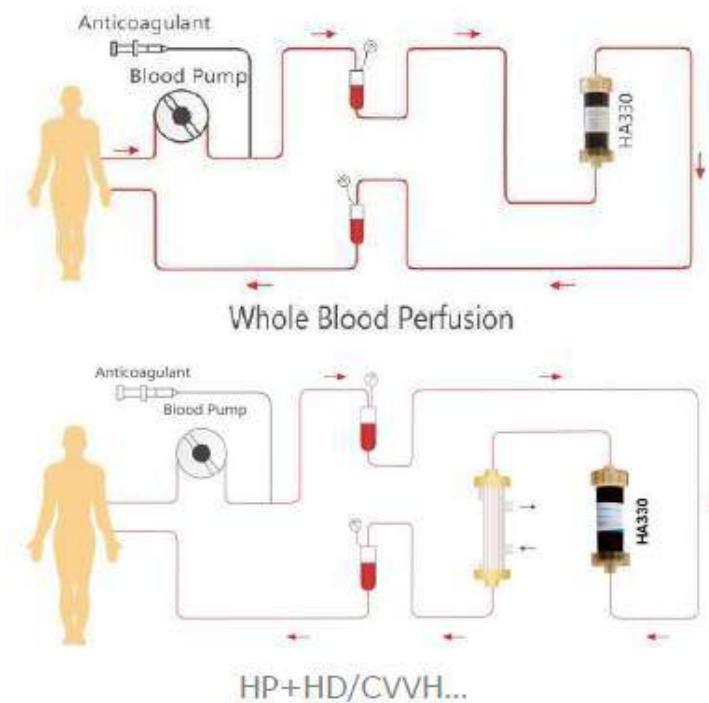
\*P < 0.05 vs. control group. ICU, intensive care unit; SOFA, sequential organ failure assessment.

## Conclusion:

Adopting HA330 disposable hemoperfusion cartridge on sepsis treatment has the following effects:

- (1) Improvement of hemodynamics;
- (2) Anti-inflammatory effect by the removal of inflammatory cytokines.
- (3) The improvement of organ dysfunction and ICU outcome.

# Αιμοπροσρόφηση και CVVH



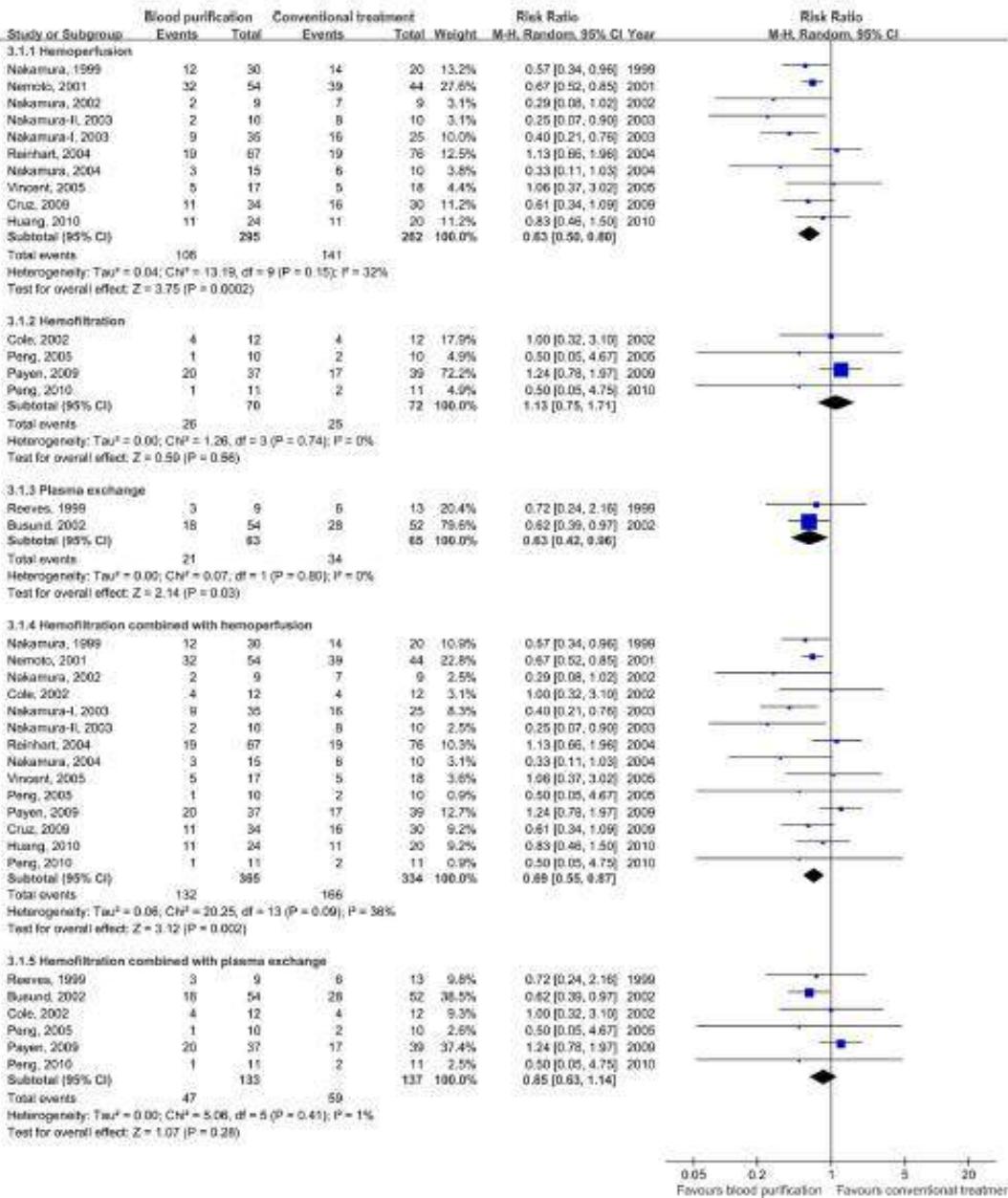
**The EUPHRATES trial 2018:**  
Preliminary reports suggest a 5% mortality  
benefit

# ΜΕΤΑ-ΑΝΑΛΥΣΗ ΓΙΑ ΟΛΕΣ ΤΙΣ ΤΕΧΝΙΚΕΣ ΑΦΑΙΡΕΣΗΣ

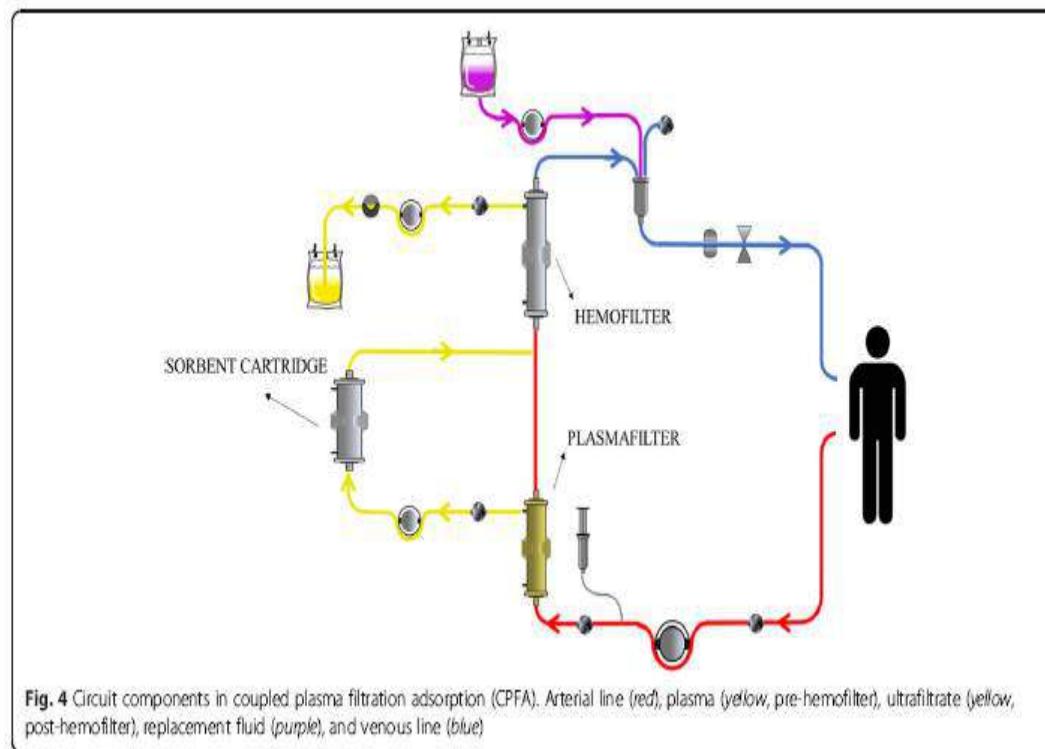
Zhou et al. Crit Care Med. 2013

## ΠΑΡΑΤΗΡΟΥΜΕ ΟΦΕΛΟΣ ΣΤΗΝ ΕΠΙΒΙΩΣΗ ΜΕ

- ΑΙΜΟΠΡΟΣΡΟΦΗΣΗ
- ΠΛΑΣΜΑΦΑΙΡΕΣΗ
- ΑΙΜΟΠΡΟΣΡΟΦΗΣΗ+  
ΑΙΜΟΔΙΗΘΗΣΗ
- ΟΧΙ ΟΦΕΛΟΣ ΑΠΟ  
ΤΕΧΝΙΚΕΣ ΑΠΛΗΣ  
ΑΙΜΟΔΙΗΘΗΣΗΣ



# Coupled plasma filtration adsorption (CPFA)= plasmapheresis-adsorption-CVVHF)



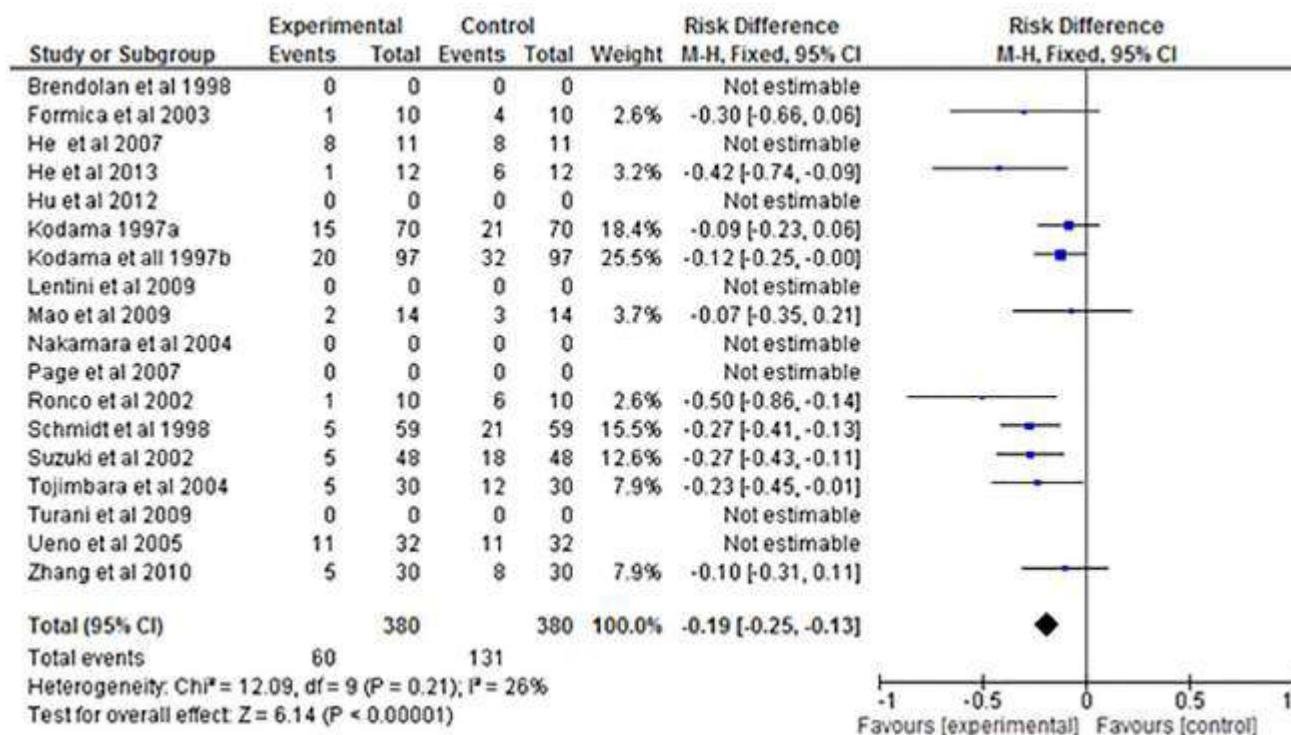
- Plasma flow rate: 17–20% of the blood flow rate (35–40 ml/min).
- Ultrafiltration rate: max 2500 ml/h (equivalent to 35 ml/kg/h in a 70 kg patient).
- Replacement fluid ( $Q_r$ ): usually in post-dilution mode.
- Duration: daily for five days lasting for at least 10 h/day.
- Anticoagulation: the typical anticoagulant used is heparin, but citrate has been used safely [63] and may represent an attractive alternative given the high rate of clotting with CPFA.

The advantage of CPFA is the lack of direct contact between blood cells with the sorbent material, which leads to improved biocompatibility

# CPFA in sepsis. meta-analysis 2015

Hazzard I, et al. J R Army Med Corps 2015

28-Day mortality pooled effect



Ongoing trials (COMPACT II and ROMPA) for feasibility and effectiveness of CPFA.

# HVHF-HP for hyperlipidemic severe acute pancreatitis (HL-SAP)

**Design :** A prospective controlled pilot study.

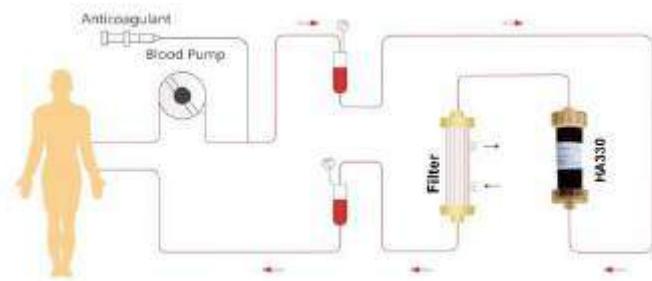
**Study Subject:** HL-SAP patients

**Therapeutic Regimens:**

C Group (N=10): conventional treatment

H Group (N=10): conventional treatment + HVHF&HP (two cycles,  
24 hours of HVHF + 2 hours of HP each cycle)

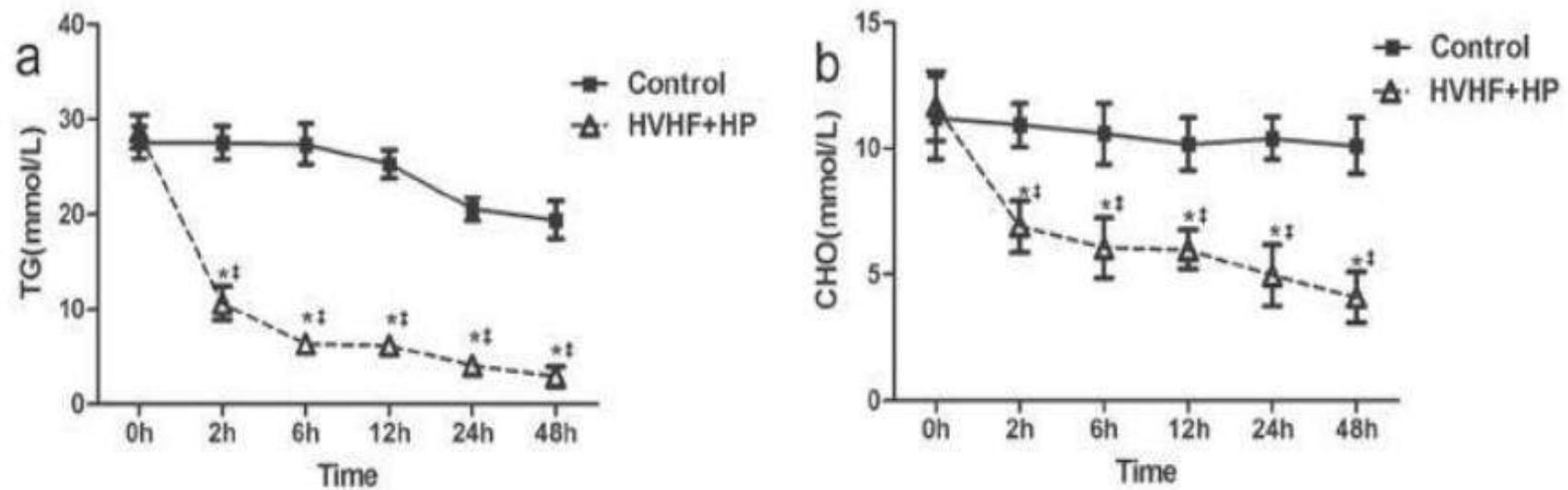
**Purpose:** evaluate the efficacy of HVHF&HP for HL-SAP in a prospective controlled study



*Shiren Sun, Lijie He, Ming Bai etc. High-volume hemofiltration plus hemoperfusion for hyperlipidemic severe acute pancreatitis: a controlled pilot study. Ann SaudiMed, 2015*

# HVHF-HP for HL-SAP

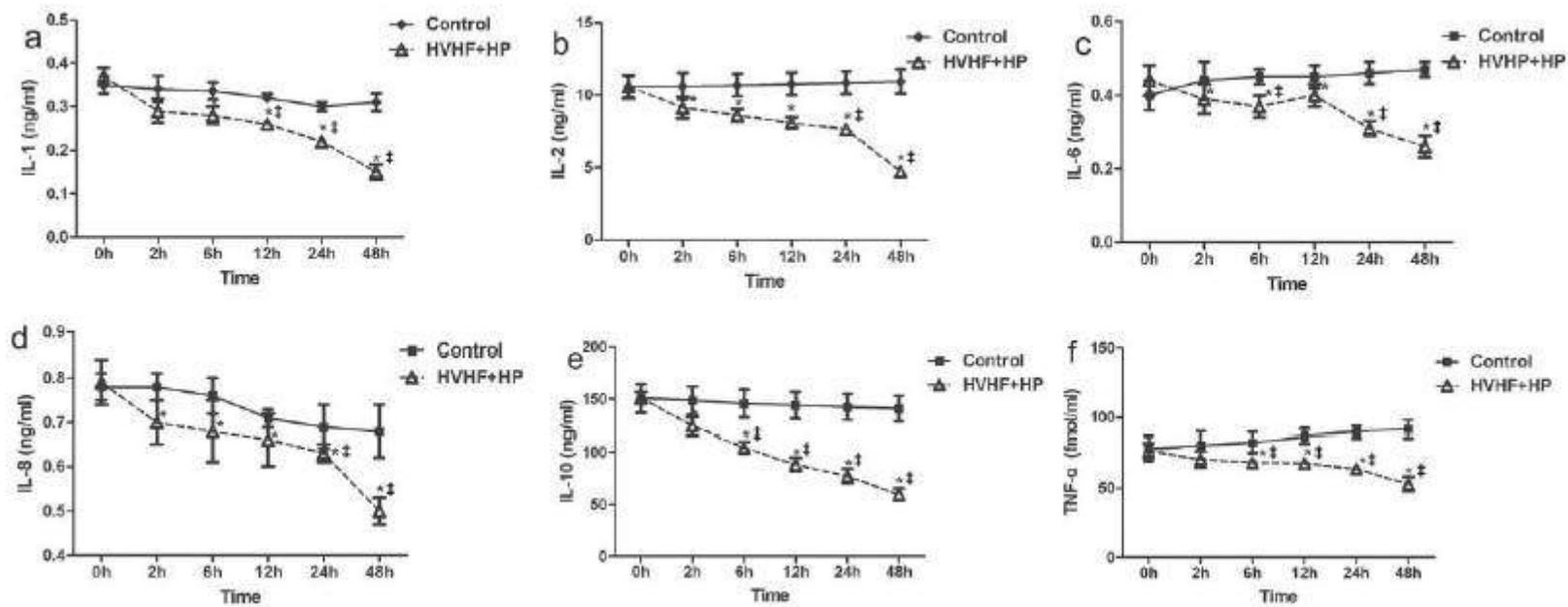
The serum lipid levels were significantly reduced after 48 hours



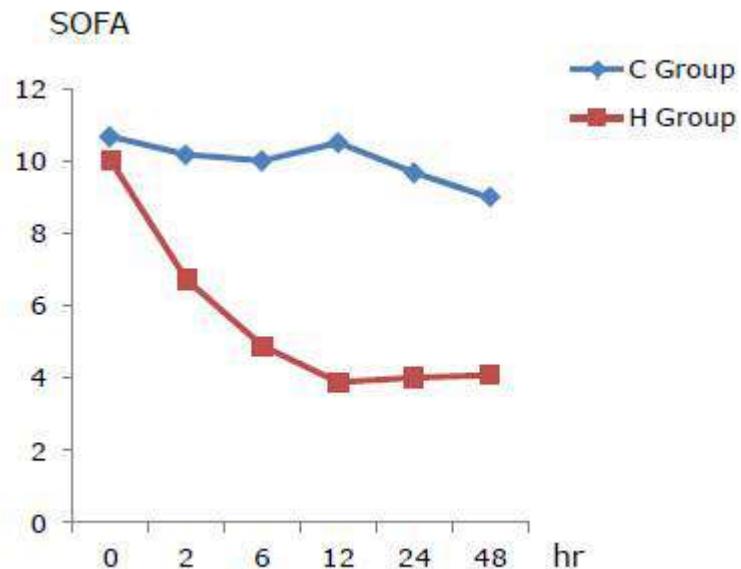
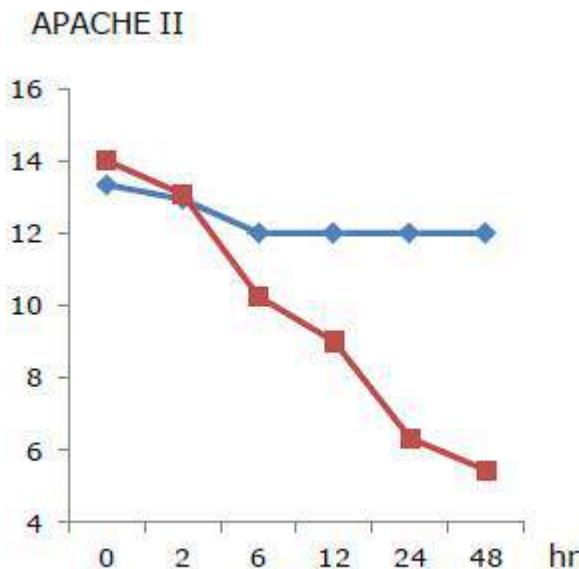
Shiren Sun, Ann Saudi Med, 2015

# HVHF-HP for HL-SAP

The serum concentrations of all tested cytokines were decreased to nearly normal after 48 hours of HVHF&HP treatment.



# HVHF-HP for HL-SAP



Shiren Sun, Ann Saudi Med, 2015

# Αρχικές μελέτες με πλασμαφαίρεση

Table 5. Comparison of outcome of the study and the literature

	Survivors %
This study	82 (survivors, 62; death, 14)
Average survival based on literature	20 <sup>a</sup>
Predicted survival based on APACHE II	33 <sup>b</sup>

APACHE, Acute Physiology and Chronic Health Evaluation.

<sup>a</sup>Relative risk, 0.055; confidence interval, 0.025–0.125;  $p < .0001$  (Fisher's exact test); <sup>b</sup>relative risk, 0.37; confidence interval, 0.26–0.52;  $p < .0001$  (Fisher's exact test).

Stegmayr, Crit Care Med, 2003

# Αρχικές μελέτες με πλασμαφαίρεση

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.

Reeves, Critical Care Med 1999; Busund, Intensive Care Med 2002; Nguyen, Crit Care Med 2008

*Nguyen, Crit Care Med 2008*

## Children with thrombocytopenia and multiple organ failure (TAMOF)

- The study was stopped early after interim analysis demonstrated a significant improvement in organ dysfunction scores with TPE.
- All TPE patients survived at 28 days, whereas 4/5 patients who received standard therapy died.
- Since the study's completion, patients meeting TAMOF criteria at Children's Hospital of Pittsburgh routinely have been offered plasma exchange.
- 60 patients have undergone plasma exchange with a 90% survival rate (at 28-day) and 80% at 1-year.
- 16 patients offered plasma exchange refused, with a 20% 28-day and a 15% 1-year survival rate (Joseph Carcillo MD, Ronco, personal communication).

# Προβλήματα κατά την TPE σε σηπτικούς ασθενείς

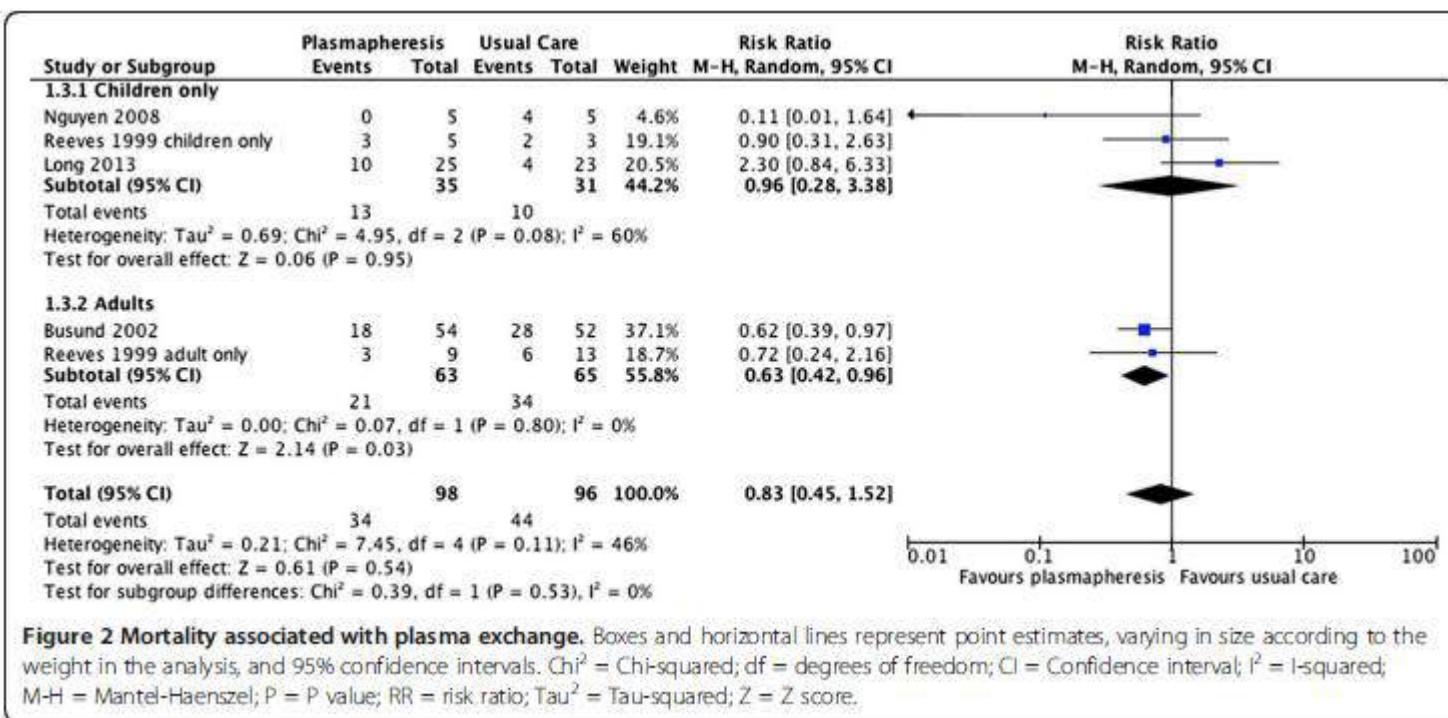
- Η αρχική πίεση είναι χαμηλή παρά τα ινότροπα, ο ασθενής υπερυδατωμένος στα όρια του ΟΠΟ και τα επινεφρίδια κατεσταλμένα.
- Κατά τη διάρκεια της TPE η ΑΠ αρχίζει να σταθεροποιείται και να μειώνονται τα ινότροπα. Σταδιακά αποκαθίσταται η διαβατότητα των αγγείων. Ποσότητες εξωκυττάριου υγρού επιστρέφουν ενδαγγειακά και αυξάνουν την συστηματική και πνευμονική ΑΠ.
- Η εμφάνιση πνευμονικού οιδήματος στη φάση αυτή είναι συχνή και υποδηλώνει βελτίωση της φλεβικής επιστροφής.
- Στη φάση αυτή απαιτείται υπερδιήθηση με αιμοκάθαρση. Η TPE συνεχίζεται έως ότου 2 από PT, APTT, DiDi, A-III κφ. Συνήθως απαιτούνται 2 TPE

**RESEARCH**

**Open Access**

# The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis

Emily Rimmer<sup>1,2</sup>, Brett L Houston<sup>3</sup>, Anand Kumar<sup>1</sup>, Ahmed M Abou-Setta<sup>4</sup>, Carol Friesen<sup>5</sup>, John C Marshall<sup>6</sup>, Gail Rock<sup>7</sup>, Alexis F Turgeon<sup>8</sup>, Deborah J Cook<sup>9,10</sup>, Donald S Houston<sup>1,2</sup> and Ryan Zarychanski<sup>1,2,4\*</sup>



RESEARCH

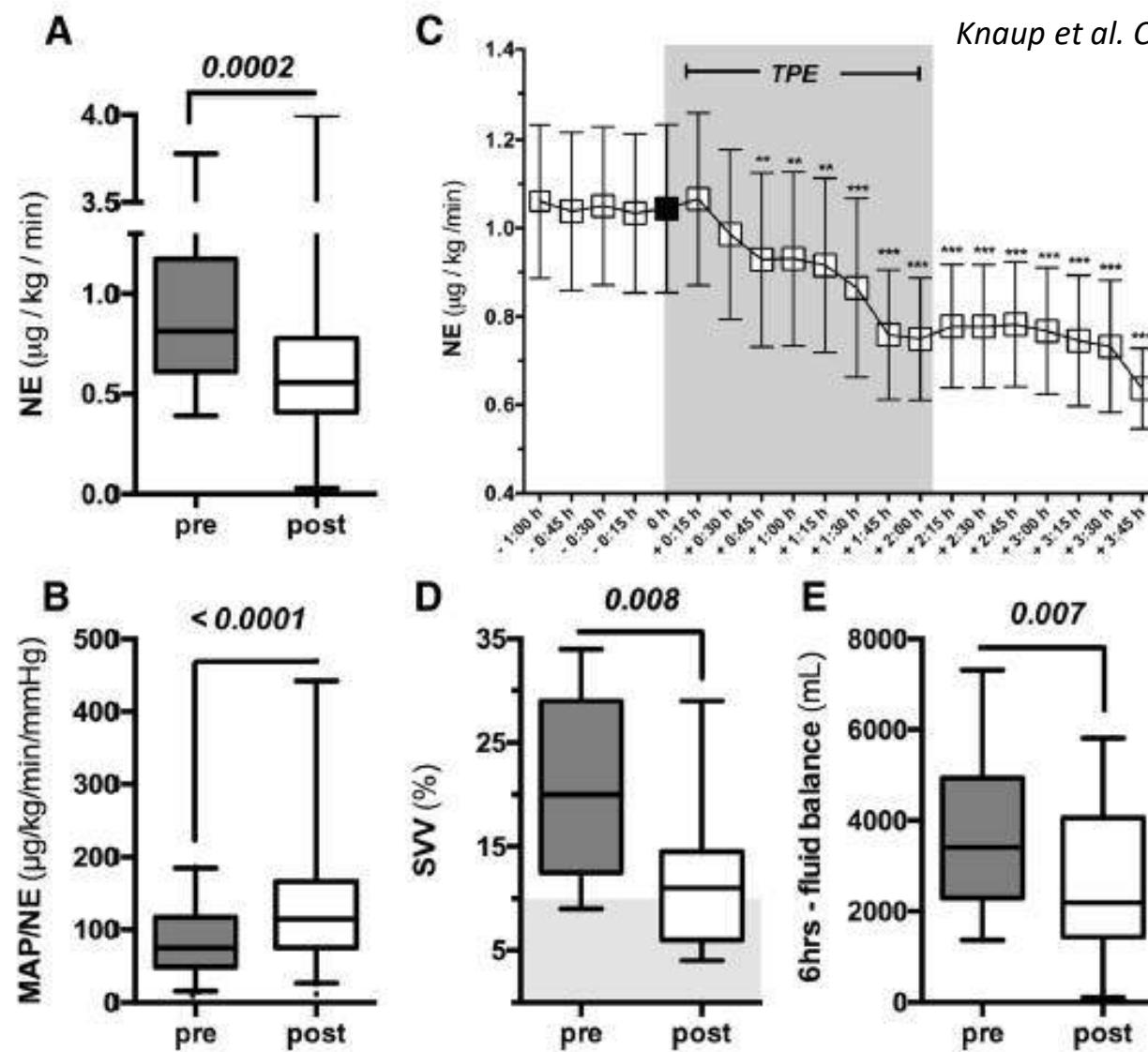
Open Access



# Early therapeutic plasma exchange in septic shock: a prospective open-label nonrandomized pilot study focusing on safety, hemodynamics, vascular barrier function, and biologic markers

Hannah Knaup<sup>1†</sup>, Klaus Stahl<sup>2†</sup>, Bernhard M. W. Schmidt<sup>1</sup>, Temitayo O. Idowu<sup>1</sup>, Markus Busch<sup>2</sup>, Olaf Wiesner<sup>3</sup>, Tobias Welte<sup>3</sup>, Hermann Haller<sup>1</sup>, Jan T. Kielstein<sup>4</sup>, Marius M. Hooper<sup>3</sup> and Sascha David<sup>1\*</sup>

- Rapid hemodynamic improvement and favorable changes in the cytokine profile in patients with septic shock were observed.
- 1 TPE only, 1.2PV, EARLY



**Fig. 2** Hemodynamic improvements upon TPE. Box and whisker plots showing **a** the dose of norepinephrine (NE;  $\mu\text{g}/\text{kg}/\text{min}$ ) immediately before the start of plasma exchange (pre) and after TPE (post) ( $p = 0.0002$ ), and **b** the ratio of mean arterial pressure (MAP) over NE dose ( $p < 0.0001$ ). **c** Peri-interventional ( $-60$  to  $+105$  min) longitudinal course of NE doses over the therapeutic plasma exchange (TPE) procedure assessed every 15 min ( $^{**}p < 0.001$ ,  $^{***}p < 0.0001$ , compared with time-point 0 highlighted in black). **d** Box and whisker plot of stroke volume variance (SVV) as a dynamic preload surrogate. Grey area highlights the reference range for healthy individuals ( $p = 0.008$ ). **e** Box and whisker plot for fluid requirements 6 h before (pre) plasma exchange and 6 h after (post) TPE ( $p = 0.007$ ).

**Table 2** Changes in clinical and biochemical parameters after TPE

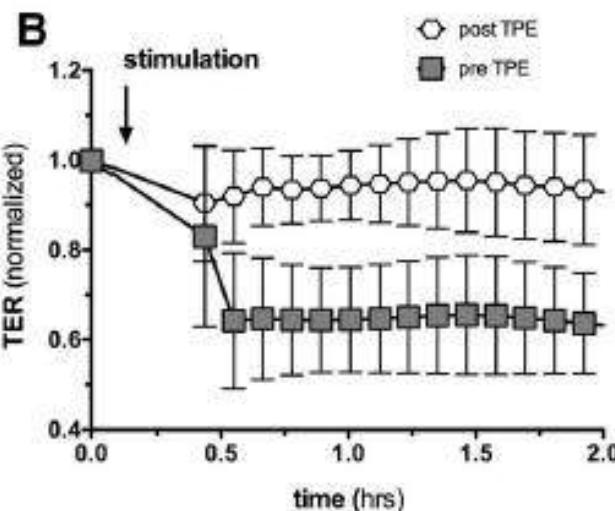
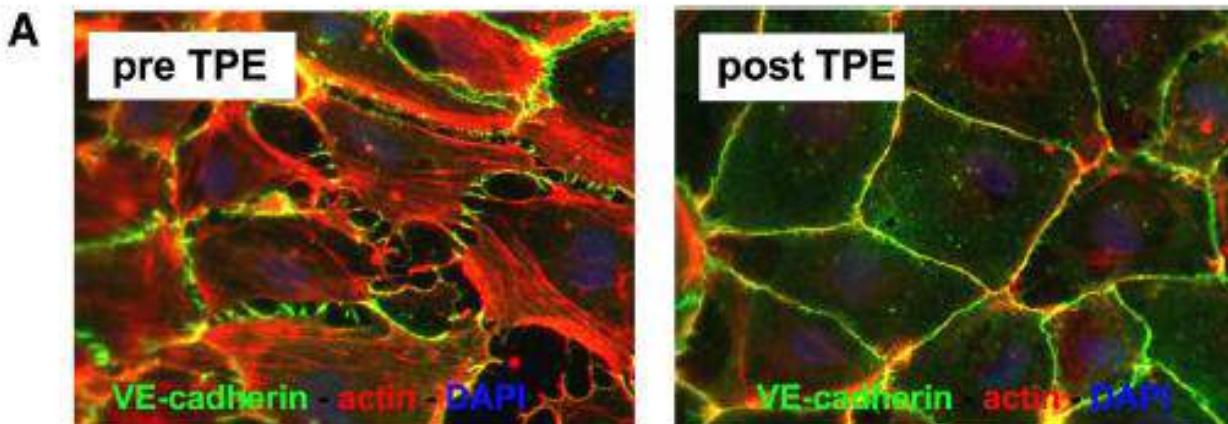
Variable	Therapeutic plasma exchange (TPE)		<i>p</i> value
	Before	After	
<b>Clinical parameters</b>			
MAP (mmHg)	65.5 (54.5–75.3)	69 (64–79.3)	0.07
NE dose ( $\mu\text{g}/\text{kg}/\text{min}$ )	0.82 (0.61–1.17)	0.56 (0.41–0.78)	0.0002*
MAP/NE (mmHg/ $\mu\text{g}/\text{kg}/\text{min}$ )	74.9 (48.5–116.8)	114.3 (75.3–166.7)	<0.0001*
HR (bpm)	110.5 (91.3–125.5)	103.5 (86.8–119)	0.11
SW (%)	20 (12.5–29)	11 (6–14.5)	0.008*
SVRI (dyne/s/cm <sup>5</sup> /m <sup>2</sup> )	1450 (980–1873)	1520 (1060–2126)	0.67
SVRI/NE (dyne/s/cm <sup>5</sup> /m <sup>2</sup> )/( $\mu\text{g}/\text{kg}/\text{min}$ )	1743 (1008–2921)	2547 (1213–3923)	0.06
EVLWI (mL/kg)	14 (8–17)	11.5 (8–16.5)	0.93
GEDI (mL/m <sup>2</sup> )	670 (483–909)	755 (622–998)	0.12
Cardiac index (L/min/m <sup>2</sup> )	2.85 (2.39–4.32)	3.42 (2.71–5.19)	0.39
Fluid balance/6 h (mL)	3411 (2295–4933)	2190 (1431–4060)	0.007*

	ICU	ED	<i>p</i>
Gas exchange			
Oxygenation index ( $\text{PaO}_2/\text{FiO}_2$ )	132 (96–229)	115 (102–212)	0.94
$\text{AaDO}_2$ (mmHg)	360 (251–541)	329 (247–489)	0.28
Inflammatory biomarkers			
CRP (mg/L)	236 (147–302)	174 (86–288)	0.07
PCT (ng/mL)	24.1 (16.9–83.7)	31 (14.8–87.3)	0.86
WBC (1/nL)	11.2 (0.93–34.8)	8.4 (1.2–25.6)	0.73
PLT (1/nL)	43.0 (16.8–112)	34.0 (20–66)	0.11
INR	1.76 (1.44–2.1)	1.43 (1.26–2.1)	0.16
Acid base balance			
pH	7.28 (7.19–7.34)	7.33 (7.23–7.38)	0.01*
$\text{pCO}_2$ (mmol/L)	44.5 (35.3–56.3)	46 (37–55)	0.99
$\text{HCO}_3^-$ (mmol/L)	20.0 (17–23.8)	22.0 (20–24.7)	0.001*
Lactate (mmol/L)	6.5 (2.8–11.3)	6.5 (3.2–10.8)	0.84
Cytokines			
IL-8 (ng/mL)	1.35 (0.6–10.81)	1.09 (0.4–7.1)	0.007*
IL-1 $\beta$ (pg/mL)	147.1 (57.1–241.6)	92.2 (42.9–184.8)	0.01*
IL-6 (ng/mL)	10.8 (2.54–27.6)	4.6 (0.9–13.7)	0.005*
IL-10 (pg/mL)	143.3 (65.5–259.2)	98.1 (59.6–180.4)	0.05
Vasoactive substances			
EVLWI	3.27 (2.01–5.36)	2.97 (1.42–5.15)	0.1
GEDI	9.51 (5.06–13.2)	5.14 (3.04–11.18)	<0.0001*
NE	1603 (10.91–19.51)	8.36 (6.67–12.85)	<0.0001*

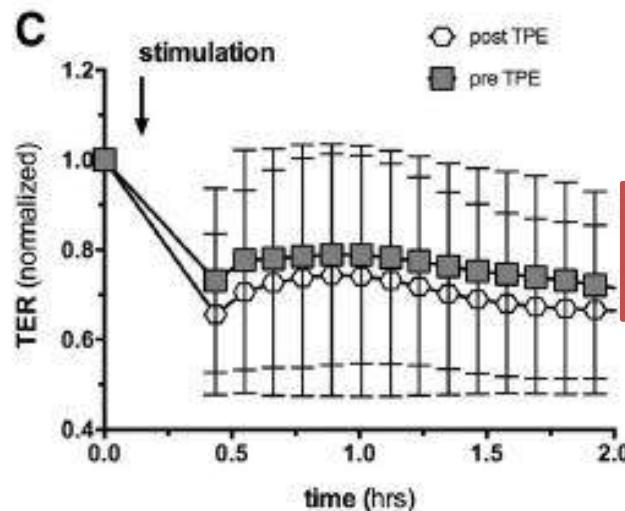
Values are shown as median (interquartile range)

$\text{AaDO}_2$  alveolar-arterial oxygen difference, CRP C-reactive protein, EVLWI extravascular lung water index, GEDI global end-diastolic index,  $\text{HCO}_3^-$  arterial bicarbonate concentration, HR heart rate, IL interleukin, INR international normalized ratio, MAP mean arterial pressure, NE norepinephrine,  $\text{pCO}_2$  arterial partial pressure of carbon dioxide, PCT procalcitonin, PLT platelet count, sTie2 soluble receptor of tyrosine kinase with immunoglobulin-like and EGF-like domains 2, SVRI systemic vascular resistance index, SVV stroke volume variance, WBC white blood cell count

\*Significant *p* values



Θνητότητα  
54%



Θνητότητα  
70%

**Fig. 4** Ex-vivo effect of plasma obtained from patients with septic shock on endothelial morphology and function. **a** HUVECs were incubated for 30 min with patients plasma obtained immediately before (left panel) and after (right panel) therapeutic plasma exchange (TPE) ex vivo. Immunofluorescent cytochemistry for the cell-cell contact protein VE-cadherin (green) and the cytoskeletal component f-actin (red) show severe alterations of the endothelial architecture and the formation of paracellular gaps (i.e., the cellular correlate of the clinical capillary leakage syndrome). Incubation of HUVECs with the same patients plasma obtained after TPE did not induce these changes any more. This assay was performed with plasma from all patients. Shown are images from a representative patient. **b** Transendothelial electrical resistance (TER), a highly quantitative method to assess permeability in real time *in vitro*, revealed that 60% (12/20) of patients plasma did induce a severe drop in resistance (grey dots). The same patients plasma after TPE did not induce permeability any more (white bars). **c** 40% (8/20) of patients did not show any response to therapeutic TPE with regard to TER before and after the procedure.

# Conclusions about TPE

- A major difference between TPE and modern adsorption strategies: TPE **replenishes protective factors** that had been consumed by the sepsis.
- TPE does not provide a cure for septic shock, but potentially an adjunctive therapeutic option with beneficial effects.

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All, glycosylated viruses. FDA approved, American Army

# Συμπεράσματα

- Η εφαρμογή HVHF, VHVF, HCOmHF, σε ασθενείς με σηπτικό σοκ είναι σχετικά εύκολη και απλή αλλά δεν προσφέρει κλινικό όφελος έναντι της απλής CVVHF
- Η αιμοπροσρόφηση (HP, PP) είναι καλά ανεκτή, βελτιώνει τις αιμοδυναμικές παραμέτρους και αυξάνει την επιβίωση (μετα-ανάλυση).
- Η πλασμαφαίρεση εάν εφαρμοστεί έγκαιρα σε βαριά περιστατικά με σηπτικό σοκ, εμφανίζει σημαντικό όφελος επιβίωσης.

# Συμπεράσματα

- Η CPFA φαίνεται να έχει καλά αποτελέσματα αλλά παρουσιάζει τεχνικές δυσκολίες, αυξάνει το φόρτο εργασίας και το κόστος.
- Όλες οι τεχνικές αφαίρεσης απαιτούν παρακολούθηση των επιπέδων των αντιβιοτικών, λόγου κινδύνου απομάκρυνσης τους και υποδοσολογίας.
- Επίσης απαιτούν, ανάλογα με την ακολουθούμενη τεχνική, παρακολούθηση των ηλεκτρολυτών, της αλβουμίνης, των PLTs και του μηχανισμού πήξης

# Συμπεράσματα

- Οι διάφορες τεχνικές αφαίρεσης (παλιές και νέες, σύνθετες και απλές) βρίσκουν σταδιακά νέα πεδία εφαρμογής, πολύ μακριά από τις παραδοσιακές ενδείξεις, σε σοβαρές και δυσίατες παθήσεις με μεγάλη θνητότητα
- Οι νεφρολόγοι πρέπει να γνωρίζουν και να συμμετέχουν στις εξελίξεις αυτές ώστε να διευρύνουν την κλινική πρακτική τους και να επιτύχουν ένα σημαντικό ρόλο στη νέα εποχή που διαγράφεται.

