Extracorporeal Approaches to Immunomodulation in Septic Conditions

William R. Clark, M.D.

Gambro Intensive Care

Indiana University School of Medicine

Indianapolis, Indiana USA

Gambro Symposium

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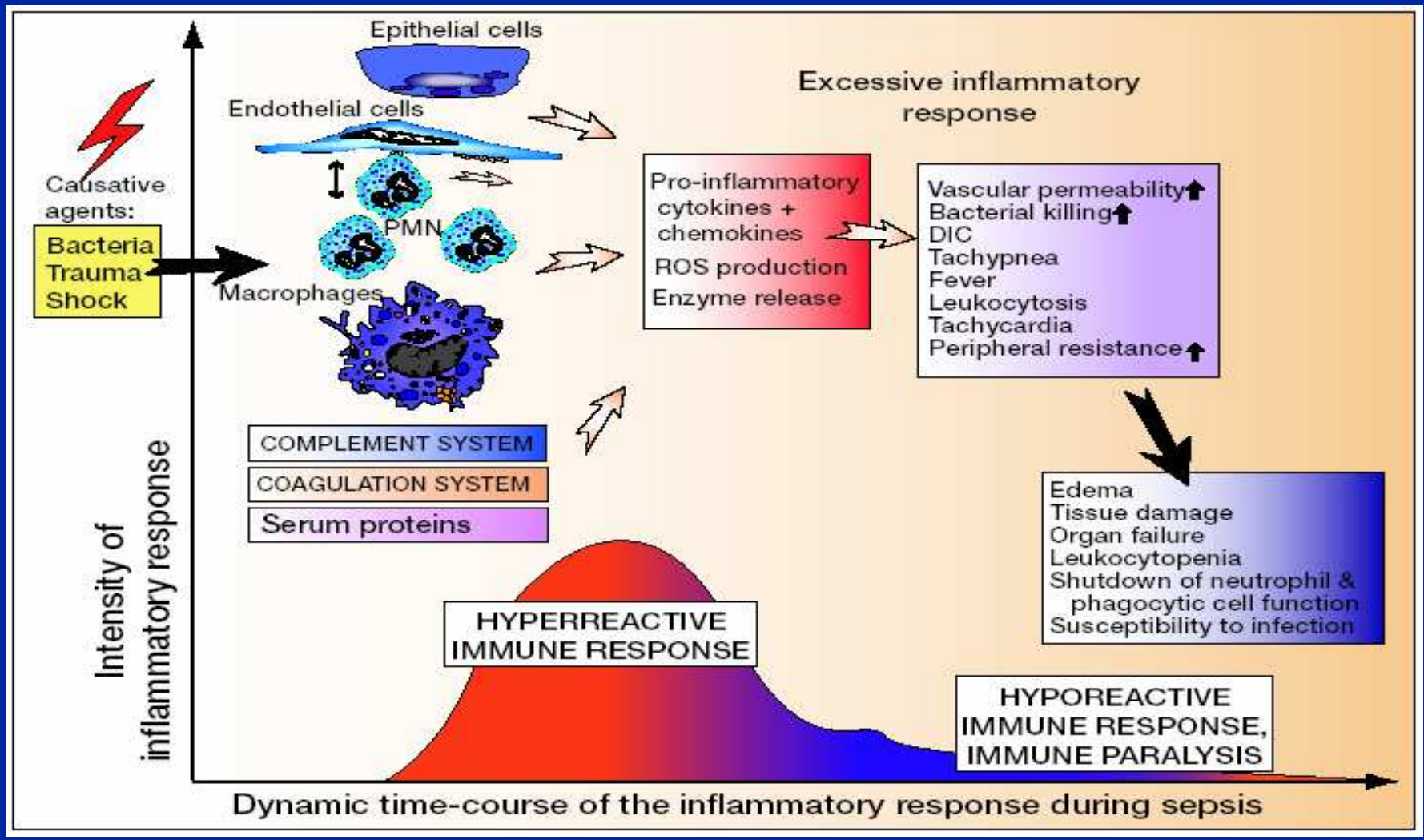
Outline

- General Principles
- Dose vs outcome in CRRT (focus on ATN and RENAL trials)
- Adapted CRRT techniques for septic conditions
  - High-volume hemofiltration
  - Adsorption-based approaches (Oxiris)
  - Large pore membranes (Septex)

General Principles

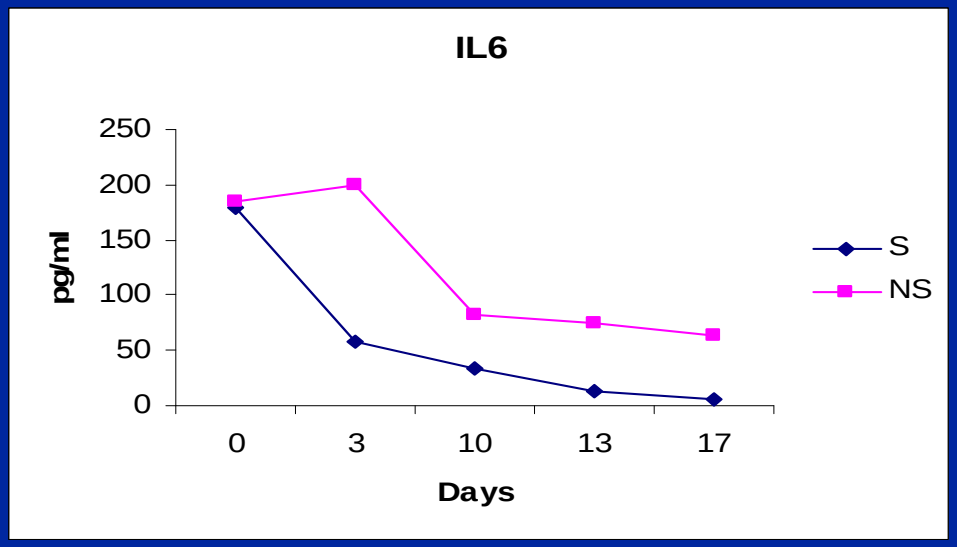
Sequence of Events in Sepsis

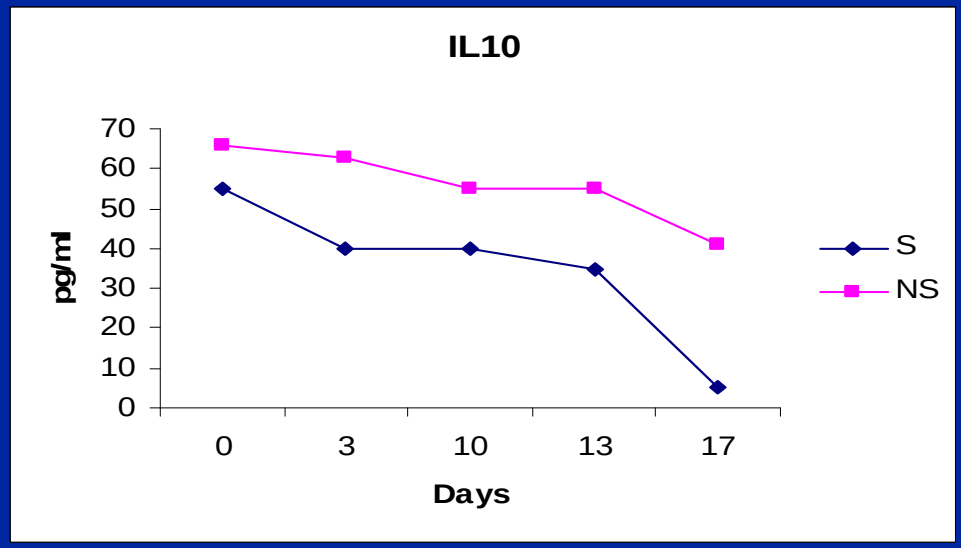
Reidemann et al, Nature Med. 2003

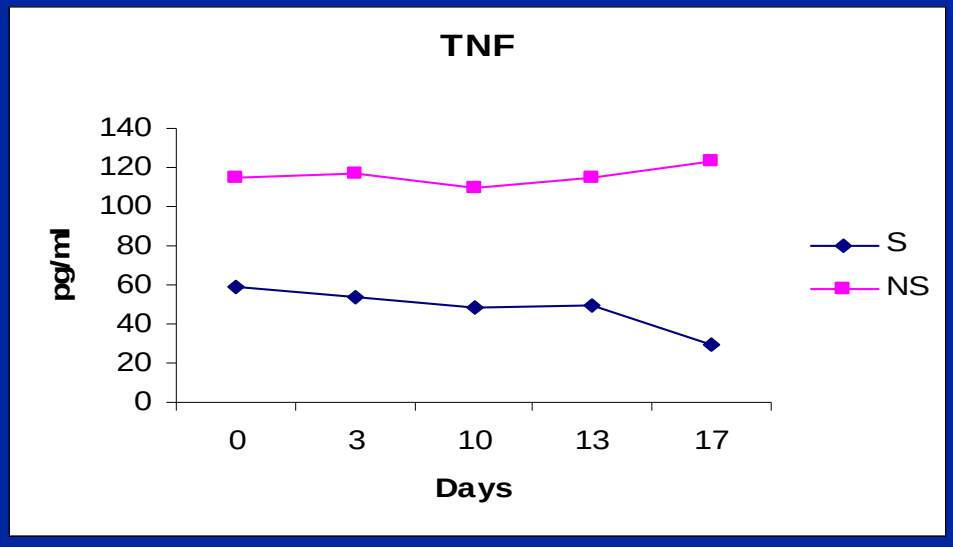


Cytokine Profiles in Severe Sepsis

Lekkou et al, Clin Diag Lab Immunol 2004

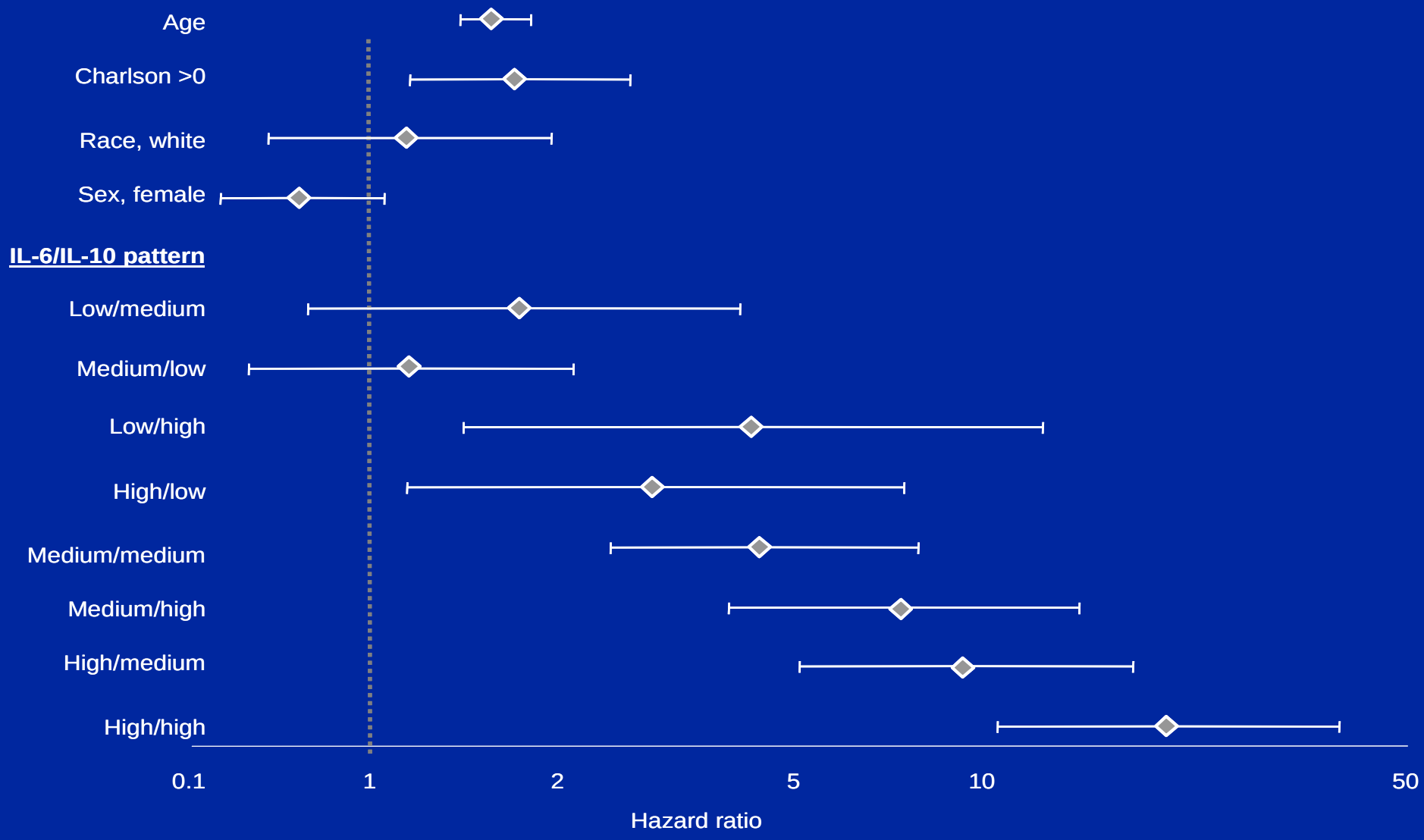




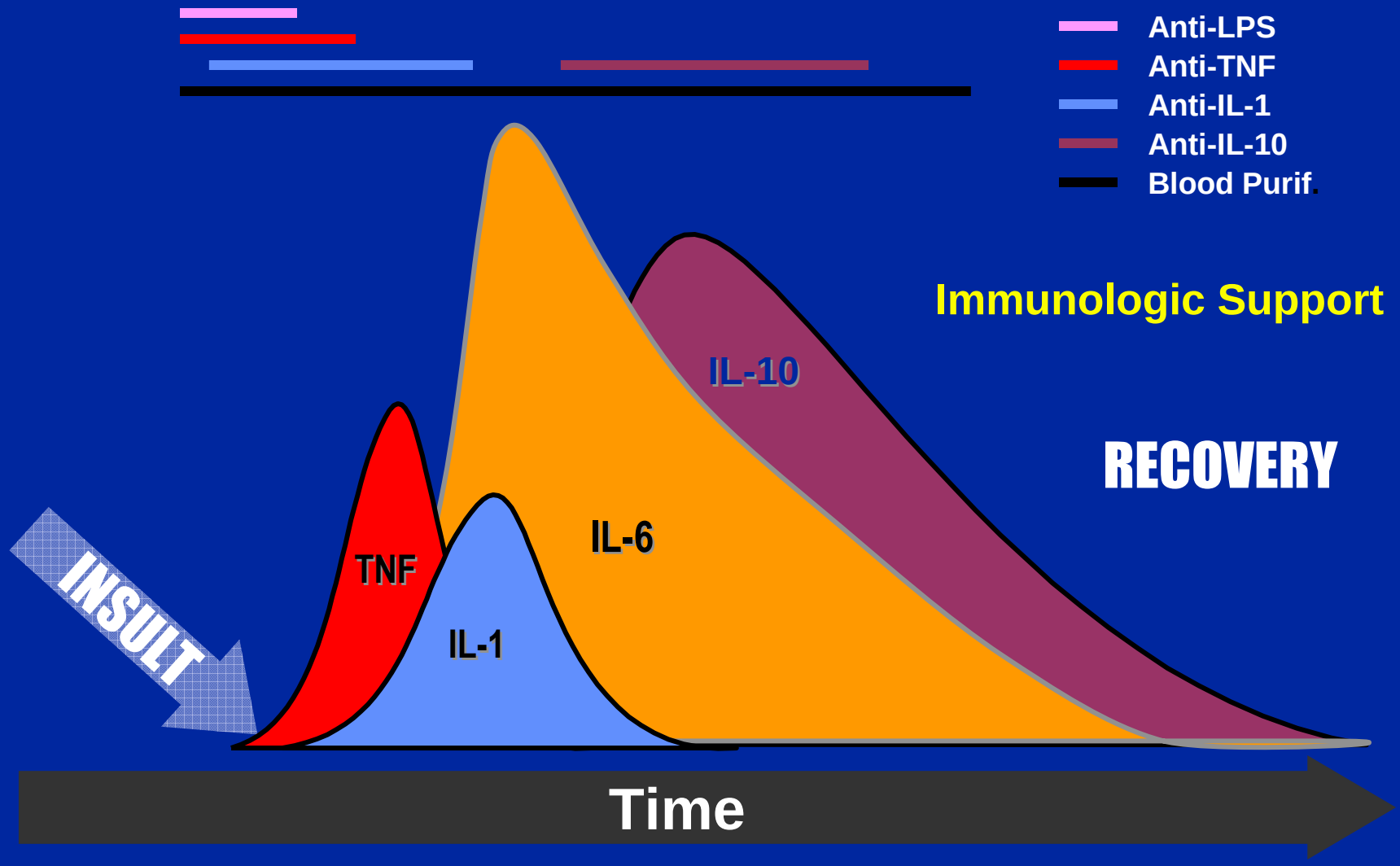


Cox Model in GenMS Study

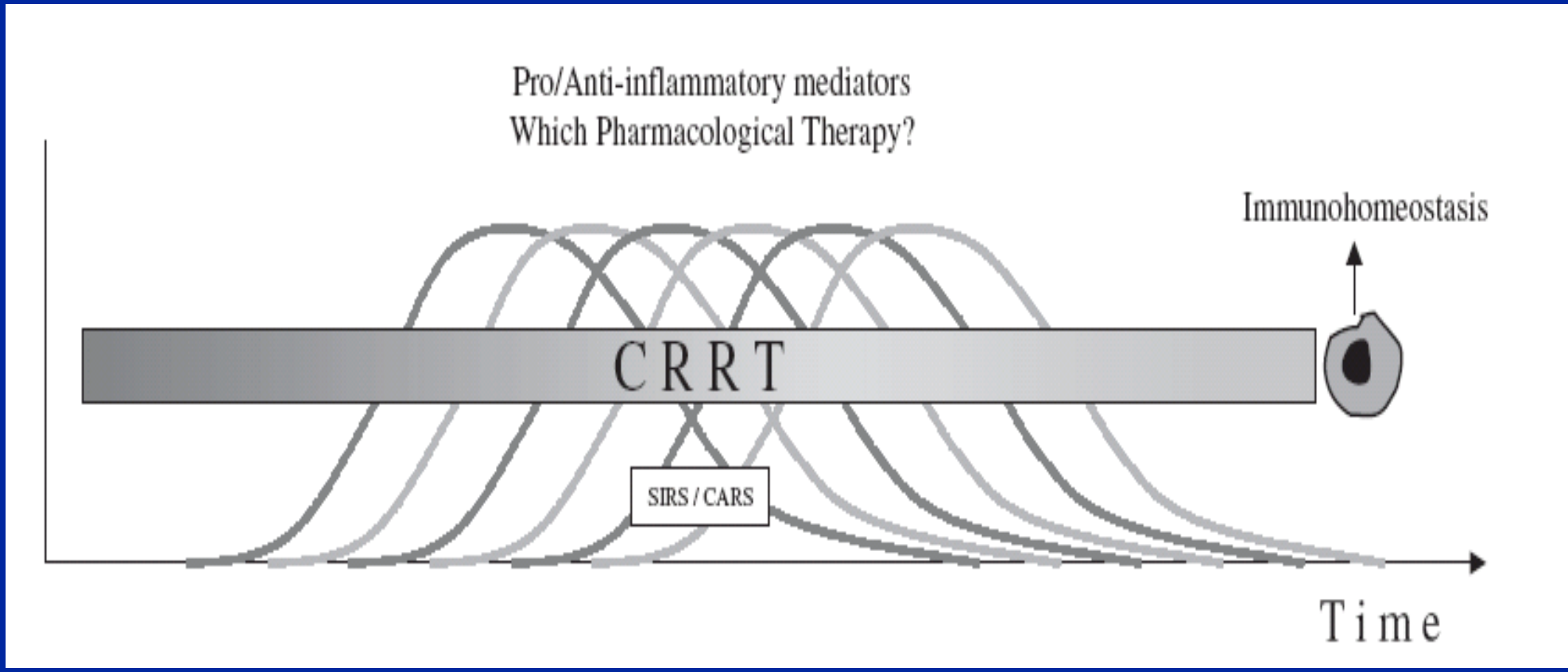
Kellum et al, Arch Intern Med 2007



Immunomodulation in Sepsis

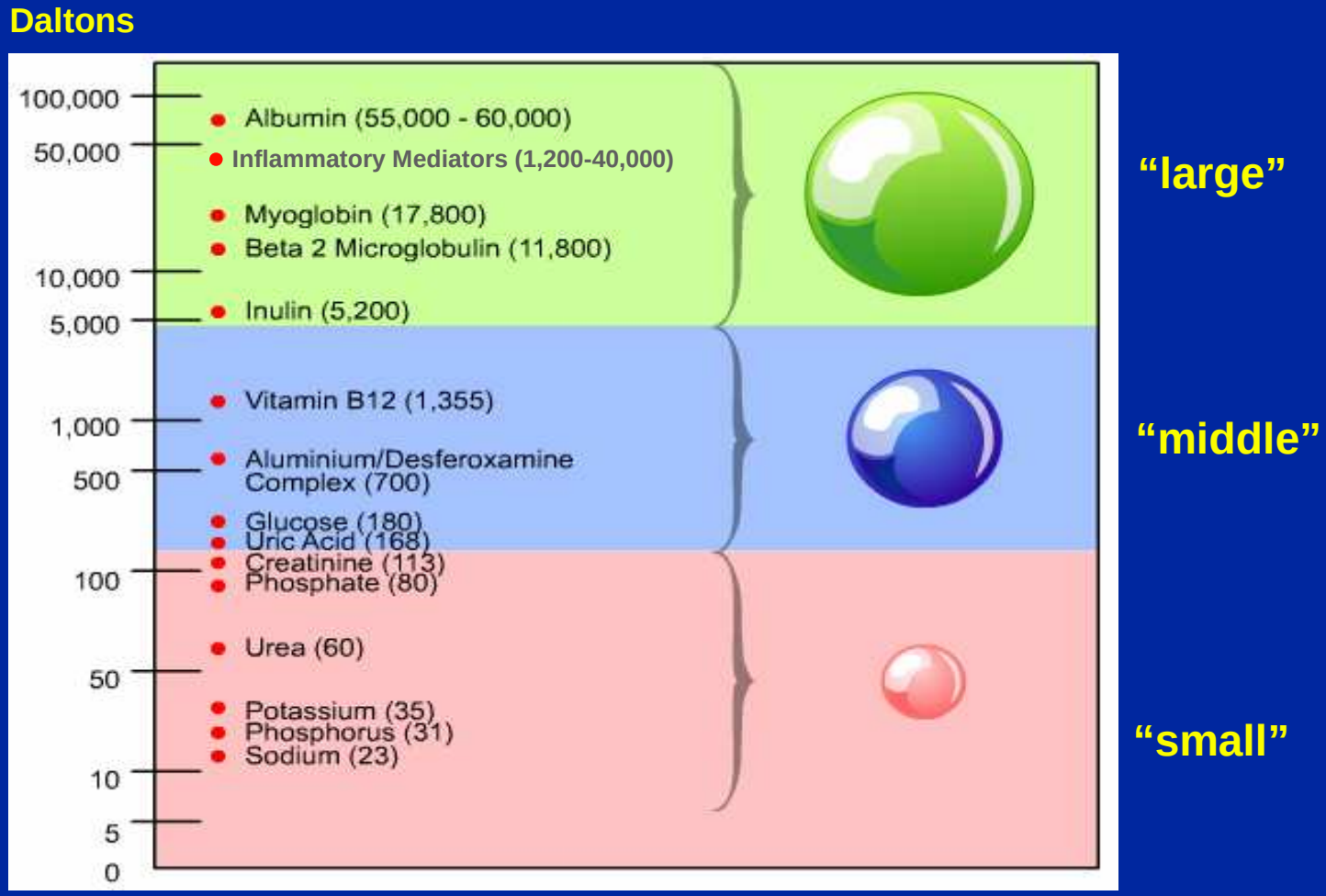


CRRT for Sepsis - Theoretical Rationale: Peak Concentration Hypothesis



Adapted from Ronco C, et al, Artif Organs 2003

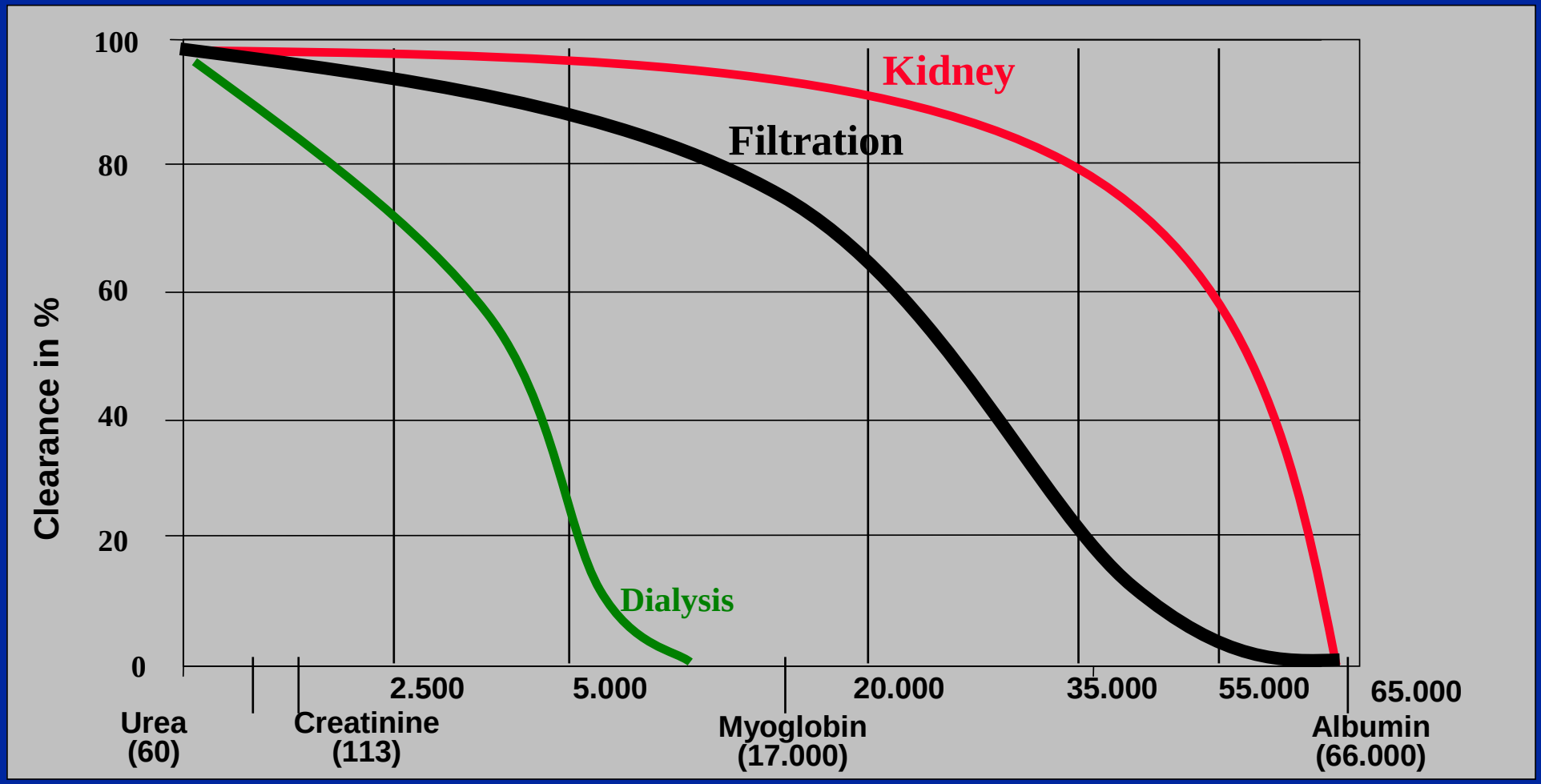
Solute Classes by Molecular Weight



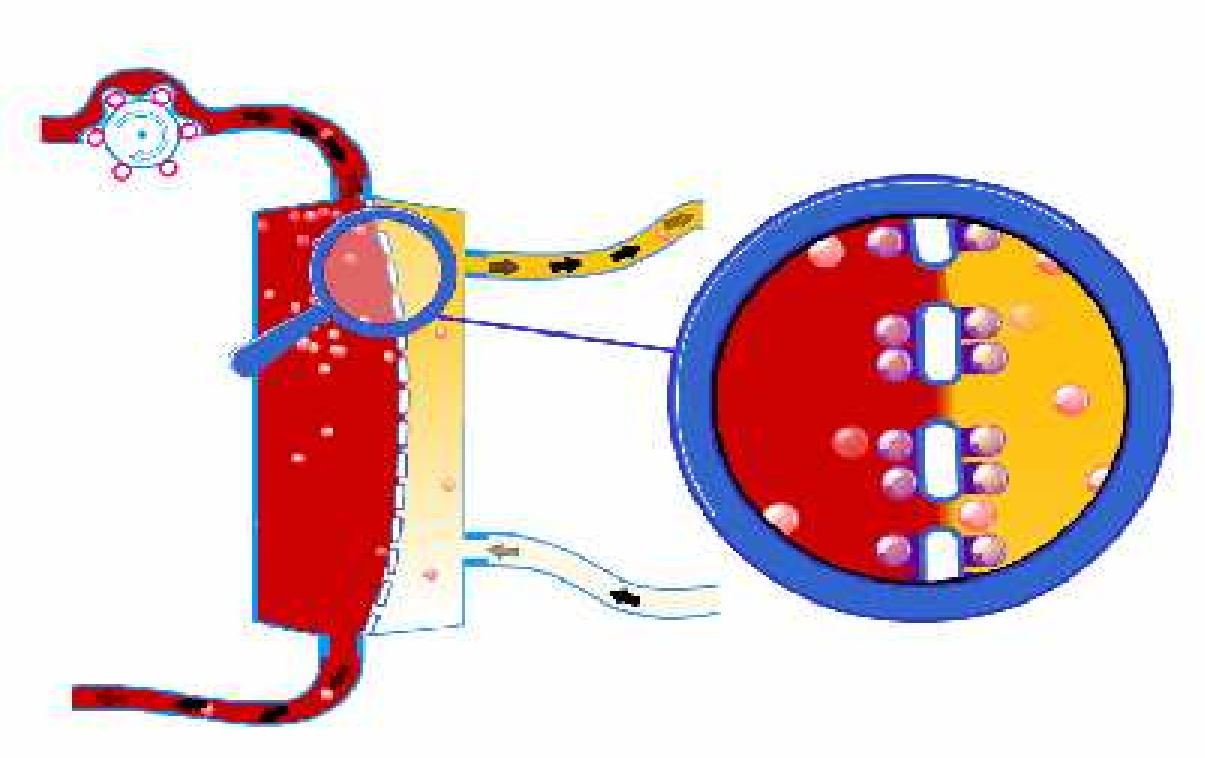
Mediators: Physical Properties

	Protein Binding	MW
C3a desArg	no	2500
C5a desArg	no	2800
Il-1a	no	17000
Il-1Ra	no	14000
TNFα	Partly	17,500 x 3
sTNFRI	yes	55000
sTNFRII	yes	75000
Il-6	no	25000
Il-8	no	9000
Il-10	no	18000
P A F	Partly	450
Factor D	yes	23000

Small vs. Large Molecule Clearance



Adsorption

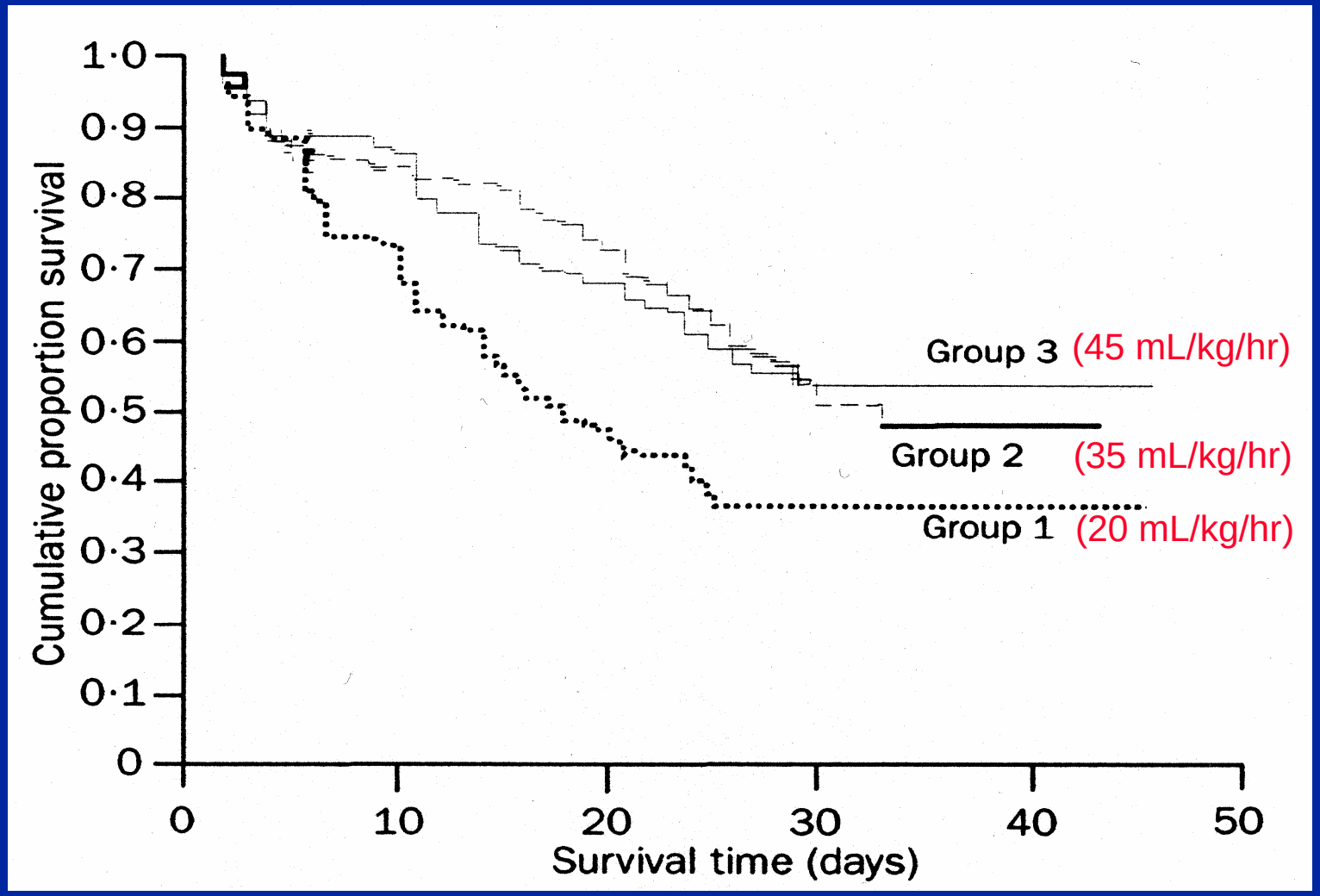


Molecular adherence to the surface or interior of the membrane.

Dose vs Outcome in CRRT

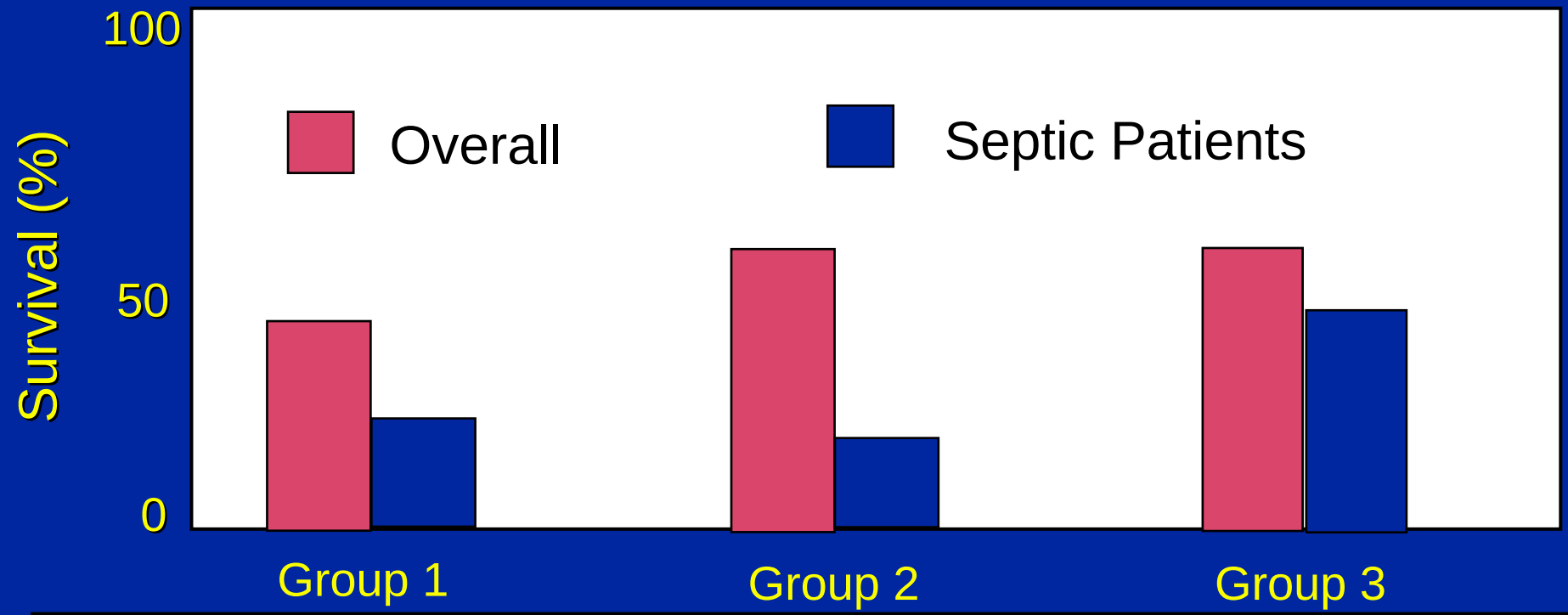
Dose vs Outcome in Post-Dilution CVVH

Ronco *et al.*, Lancet 2000



“Sepsis Dose” in AKI?

Ronco et al., Lancet 2000



Trial Group	No Sepsis (%)	Sepsis (%)	p-value
Group1	55/126 (44%)	5/20 (25 %)	0.90
Group 2	76/122 (62 %)	3/17 (18 %)	0.001
Group 3	74/125 (59 %)	7/15 (47 %)	0.256

VA/NIH Acute Renal Failure Trial Network (ATN) Study

1124 patients
27 sites
3 years

Randomization

	Intensive Management Strategy (561 patients)	**Less Intensive Management Strategy (563 patients)**
Stable hemodynamics *(SOFA 0-2)*	• IHD 6x/week @ Kt/V of ~1.2/session	• IHD 3x/week @ Kt/V of ~1.2/session
Unstable hemodynamics *(SOFA 3-4)*	• CVVHDF @ 35 mL/kg/hr, or • SLED/EDD 6x/week	• CVVHDF @ 20 mL/kg/hr, or • SLED/EDD 3x/week

Modality Prescription in ATN Study

VA/NIH Trial Group, NEJM 2008

Hemodynamic Status	Modality	Number of Treatments	Percentage of Treatments
Stable*	IHD	5077	100%
Unstable**	CRRT	5967	95.2%
	SLED	299	4.8%

*: SOFA score: 0, 1, or 2

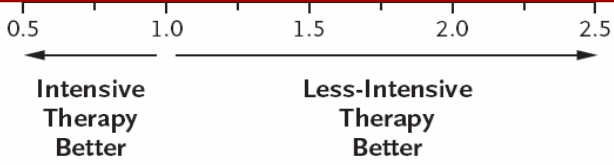
**: SOFA score: 3 or 4

ATN Study: Primary Outcomes

VA/NIH Trial Group, NEJM 2008

B

Baseline Characteristic	No. of Patients	Intensive Therapy	Less-Intensive Therapy	Odds Ratio for Death at 60 Days (95% CI)	P Value for Interaction
Overall	1124	53.6	51.5	1.09 (0.86–1.40)	
SOFA cardiovascular score					0.15
0–2	509	43.9	37.8	1.33 (0.93–1.91)	
3–4	615	61.7	62.9	0.93 (0.66–1.29)	
Oliguria					0.45
No	247	41.1	36.6	1.31 (0.77–2.21)	
Yes	877	57.2	55.7	1.04 (0.79–1.37)	
Sex					0.30
Female	330	50.7	52.8	0.90 (0.57–1.41)	
Male	793	54.8	50.8	1.19 (0.89–1.60)	
Sepsis					0.36
No	416	47.8	49.8	0.94 (0.63–1.41)	
Yes	708	57.0	52.6	1.19 (0.88–1.62)	



ATN Study: Hypotension in IHD Group

VA/NIH Trial Group, NEJM 2008

Supplementary Table 6. Hypotension During Intermittent Hemodialysis*

	Intensive Management Strategy	Less-Intensive Management Strategy
Total number of IHD treatments	3241	1836
IHD treatments reported as complicated by hypotension; No. (%)	601 (18.5)	347 (18.9)
Hypotension requiring initiation of vasopressor support; No. (%)	55 (1.7)	27 (1.5)
Hypotension requiring discontinuation of treatments; No. (%)	51 (1.6)	35 (1.9)
Hypotension requiring other intervention; No. (%)	495 (15.3)	285 (15.5)
Blood Pressure at Initiation of IHD (mm Hg)		
Systolic	129±23	130±24
Diastolic	64±15	64±16
Mean	86±15	86±16
Lowest Blood Pressure During IHD (mm Hg)		
Systolic	109±22	108±22
Diastolic	58±15	57±15
Mean	75±16	74±16
Maximal Change in Blood Pressure During IHD (mm Hg)		
Systolic	-20±18	-22±19
Diastolic	-6±12	-7±12
Mean	-11±12	-12±13

*IHD denotes intermittent hemodialysis; Percent calculated based on total number of IHD treatment

Comparison of Major CRRT Dose Trials

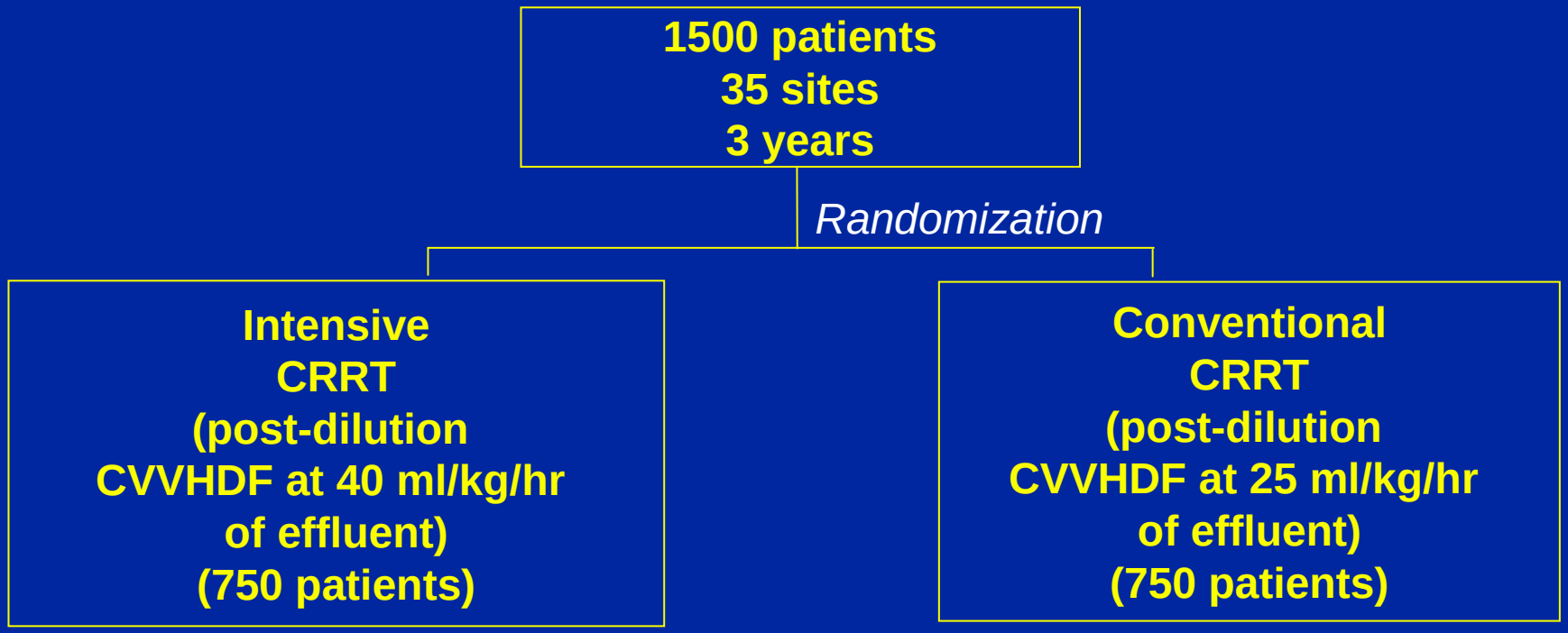
	Ronco[1]	Saudan[2]	Tolwani[3]	ATN[4]
Number of patients	425	206	200	1124
Multi-center RCT	No	No	No	Yes
CKD (%)	NA	33	42	Exclusion
Predominant AKI cause	Surgical	Sepsis	Sepsis	Ischemia
APACHE II	~23	25	26	~29
Initiation BUN (mg/dL)	53	83	75	65
Modality	post CVVH	pre CVVHDF	pre CVVHDF	pre CVVHDF
% Convective	100	~60	43-44	50
Prescribed dose (mL/kg/h)	20/35/45	25/42	20/35	20/35
“Diluted” dose (mL/kg/h)	20/35/45	~20/37	~17/29	~17/27
ICU wait (days)	NA	NA	8	6.9

1: Lancet 2000; 2: Kidney Int 2006; 3: JASN 2008; 4: NEJM 2008

Major Criticisms of Study

- Approach to IHD prescription/delivery not applicable in “real world”
- Effective CRRT dose was significantly lower than Ronco (Lancet 2000) and Saudan (Kidney Int 2006) studies
- Late initiation of RRT
- Potential independent effect of fluid balance on outcome
- High percentage of patients with RRT “pre-exposure” (when patients were most critically ill)
- Low rate of renal recovery (despite exclusion of patients with moderate/advanced CKD) – likely contribution from IHD-induced hypotension

R.E.N.A.L. Trial


1500 patients
35 sites
3 years
Randomization
Intensive
CRRT
(post-dilution
CVVHDF at 40 ml/kg/hr
of effluent)
(750 patients)
Conventional
CRRT
(post-dilution
CVVHDF at 25 ml/kg/hr
of effluent)
(750 patients)

RENAL Trial: Study Design

- RCT involving 1508 patients (35 centers) in Australia/New Zealand conducted from December 2005 to September 2008
- Two groups treated with post-dilution CVVHDF
  - Group 1: 40 mL/kg/hr
  - Group 2 (standard of care in AUS/NZ): 25 mL/kg/hr (both groups: BFR = 150 mL/min; D:R=1:1)
  - Exclusively with AN69 filters
- CRRT was initial treatment in all patients and applied almost exclusively while patients in ICU
- Primary outcome: 90-day mortality
- Major secondary outcomes
  - 28-day mortality
  - ICU and hospital length of stay (LOS)
  - Renal recovery rate

RENAL Trial: Major Results

- Two groups well matched with respect to illness severity and all measured clinical parameters
- 90-day mortality (45%) in both groups was identical and substantially lower than ATN Trial and most previous RCTs
- Renal recovery rate at 90 days was 93% in both groups (again, substantially better than ATN)
- No significant differences in any of secondary outcomes
- Other significant findings
  - CRRT was initiated early in both groups (average ~50 hrs after ICU admission)
  - Delivered dose (average) ~85% of prescribed dose

Comparison of ATN and RENAL Trials

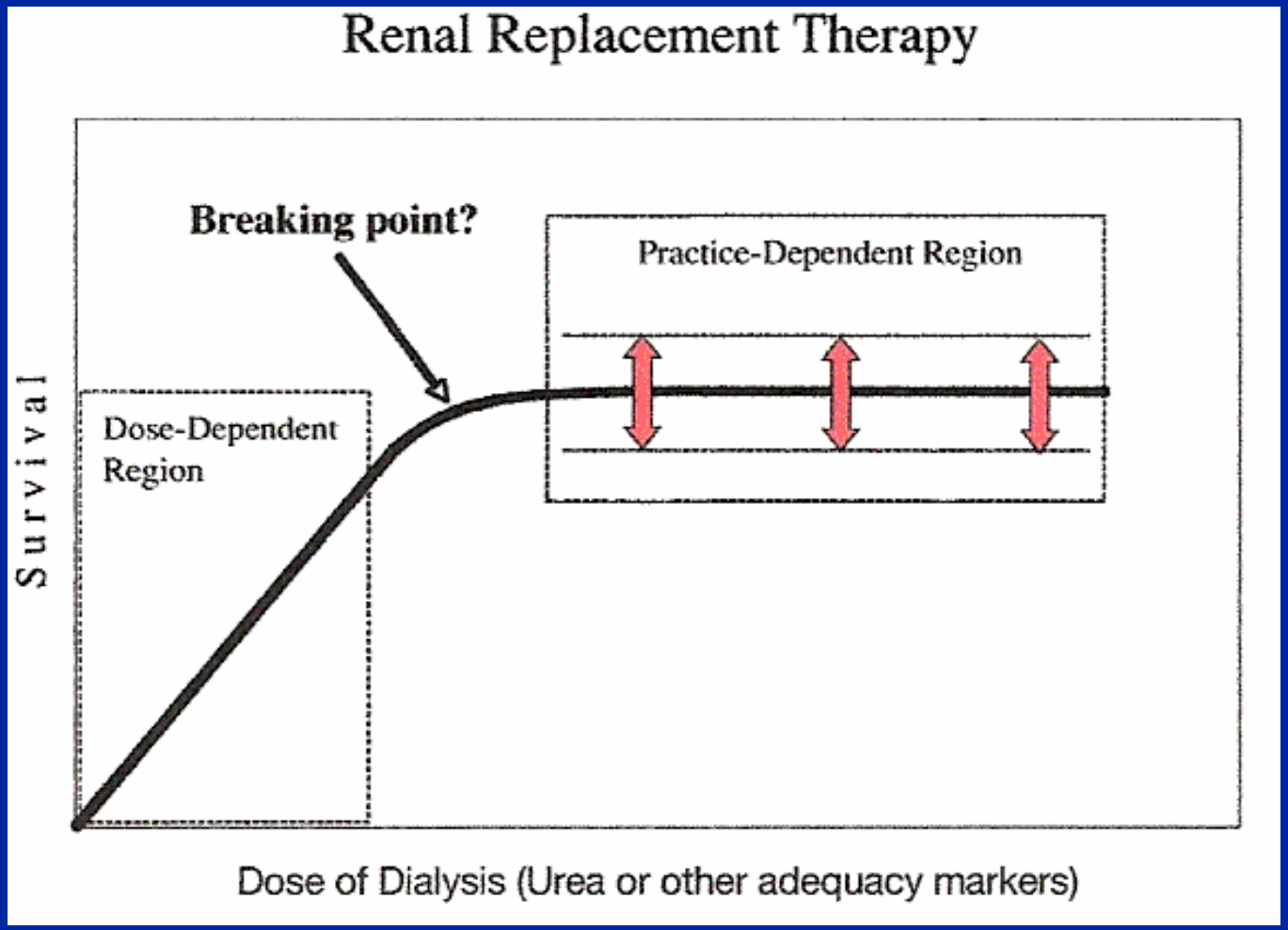
Clinical Factor	ATN	RENAL
Initiation Timing (hrs)	150	50
Initial CRRT Use (%)	55	100
Exclusion of advanced CKD patients	Yes	No
60-day Mortality (%)	53	---
90-day Mortality (%)	---	45
60-day Renal Recovery (%)	75	---
90-day Renal Recovery (%)	---	93

RENAL Trial: Preliminary Main Takeaways

- The RENAL design and results are fundamentally different from those of ATN – in RENAL:
  - CRRT was initial treatment (when patients were most critically ill) in all patients
  - CRRT was almost exclusively applied while patients were in the ICU
  - Survival and renal recovery outcomes were substantially improved
- The results seems to confirm that early CRRT initiation is an important factor influencing patient outcome
- Compensation for therapy downtime requires “over-prescription” to achieve the target doses
- Based on the excellent overall outcomes achieved in RENAL with CRRT, the relevance of other modalities for critically ill AKI patients is an open question

Effect of Dialysis Dose on Patient Outcome

Ronco, Int J Artif Organs 2008



Adapted CRRT Approaches for Septic Conditions: High-Volume Hemofiltration

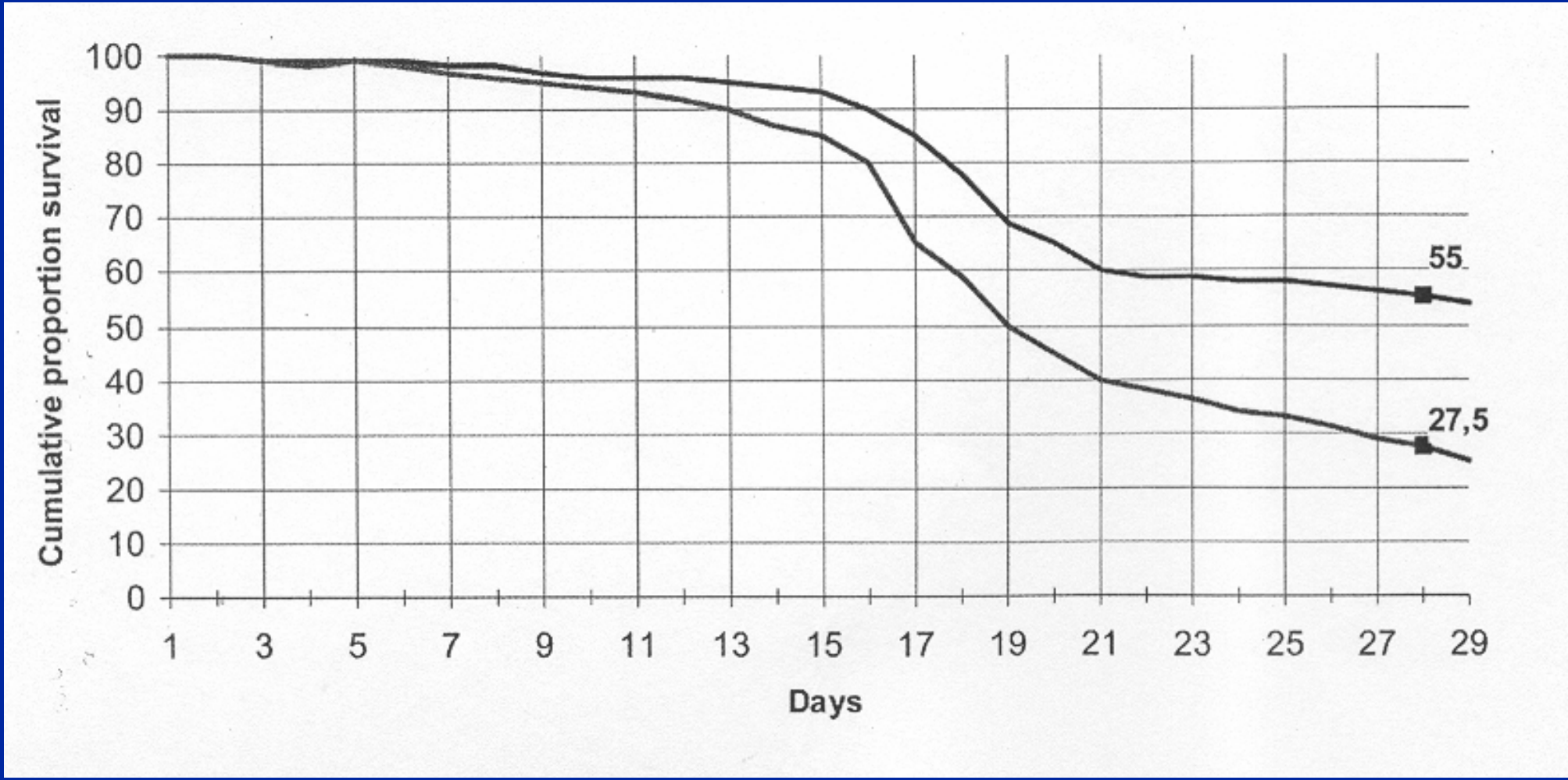
Effect of Early Isovolemic Hemofiltration (EIHF) on Outcome in Patients with Septic Shock

Piccinni et al, Intensive Care Med 2006

	EIHF (n=40)	Control (n=40)	p
Successful weaning	28 (70%)	15 (37%)	<0.001
Duration of MV(days)	11±3	20±5	<0.001
Independence from vasopressor support	30 (75%)	10 (25%)	<0.001
ICU stay (days)	12±5	16±4	0.002
Hospital stay (days)	19±5	34±4	<0.001
ICU survival	28 (70%)	16 (40%)	0.003
(predicted survival based on individual risk of death)	(41±12)	(40± 10)	n.s.
28-day survival	22 (55%)	11 (27.5%)	0.005
(predicted survival based on individual risk of death)	(41±12)	(40± 10)	n.s.

Effect of Early Isovolemic Hemofiltration (EIHF) on Survival in Patients with Septic Shock

Piccinni et al, Intensive Care Med 2006



High-Volume Hemofiltration: Pilot Study

Honore et al, Crit Care Med 2002

1° Hemodynamic status	
- MAP	- < 55 mmHg
- Inotropic support : after failure of maximal dosages of dopamine and dobutamine-norepinephrine	- Epinephrine not for more than 2 hours
- Cardiac index	- < 2 l/min/m^2
- Wedge pressure	- > 14 < 18 mm Hg
2° Acid-base balance	
- Arterial pH	- < 7.15
- Serum lactate	- > 5 mmol/L
3° Septic status	
- SIRS criteria (ACCP/SCCM criteria)	- 3 out of 4
- Objective source of sepsis	- Always present
4° Respiratory support	
- Mechanical ventilation	- All the patients
- paO_2/FIO_2 ratio	- < 100
5° Renal status	No incidence at study inclusion

Dopamine : up to 20 mg/Kg/min

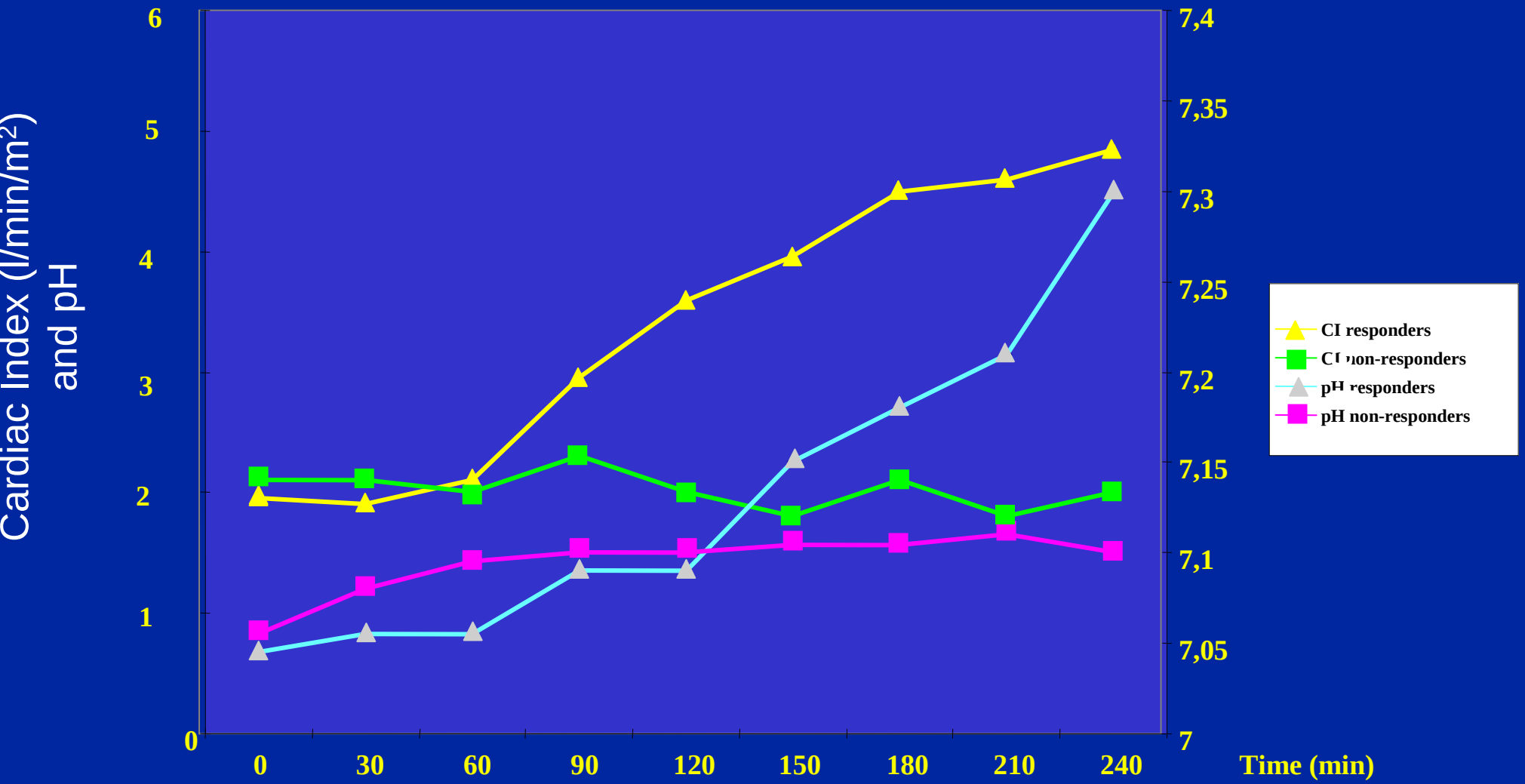
Norepinephrine : up to 2 mg/Kg/min

Dobutamine : up to 14 mg/Kg/min

Epinephrine : up to 0.5 mg/Kg/min

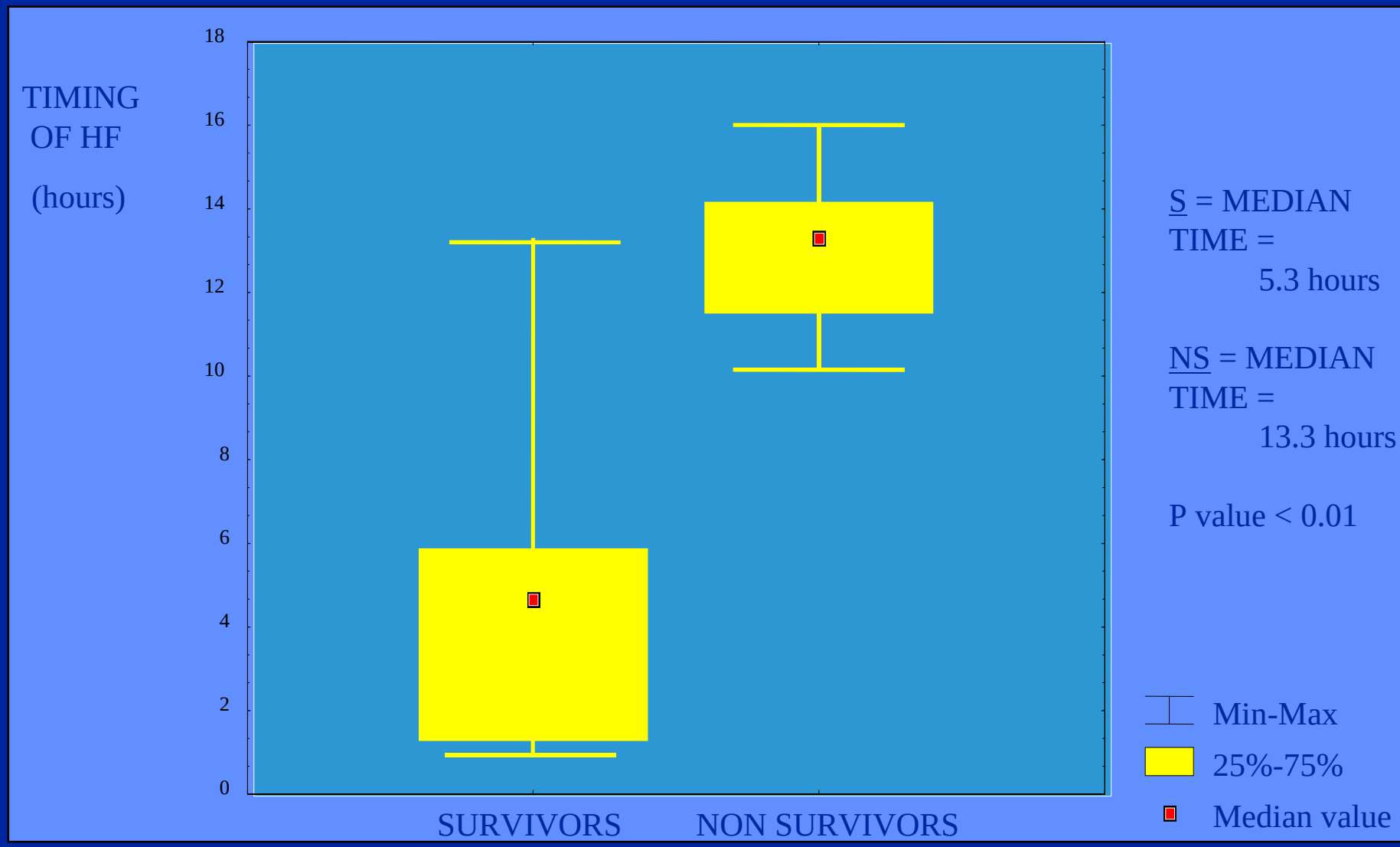
High-Volume Hemofiltration: Pilot Study

Honore et al, Crit Care Med 2002



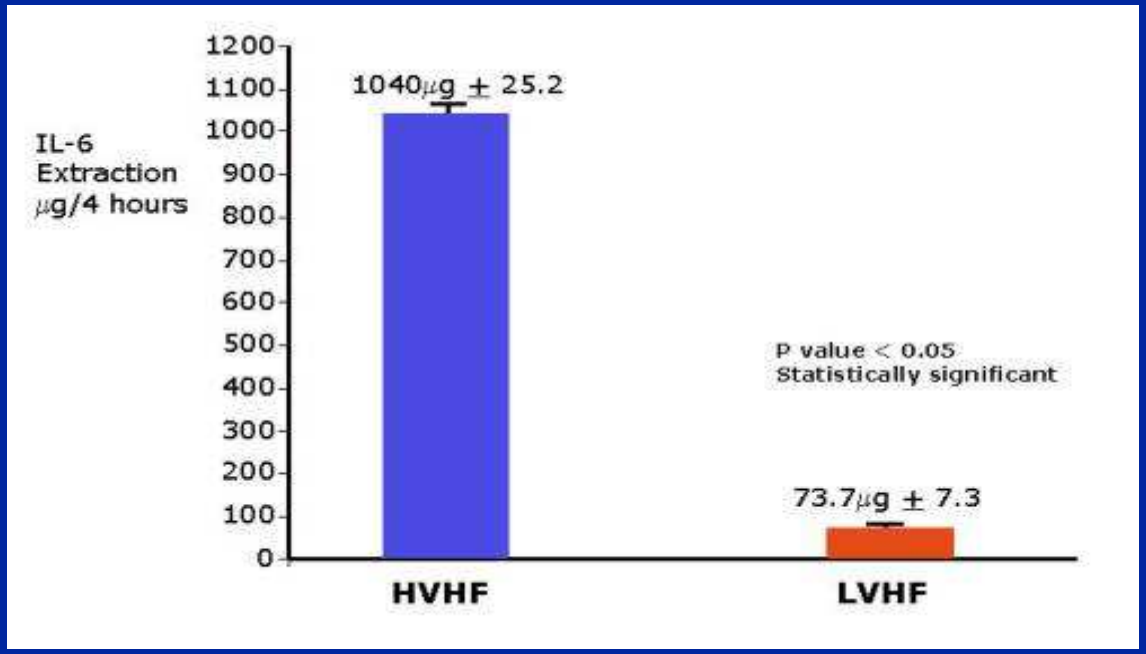
High-Volume Hemofiltration: Pilot Study

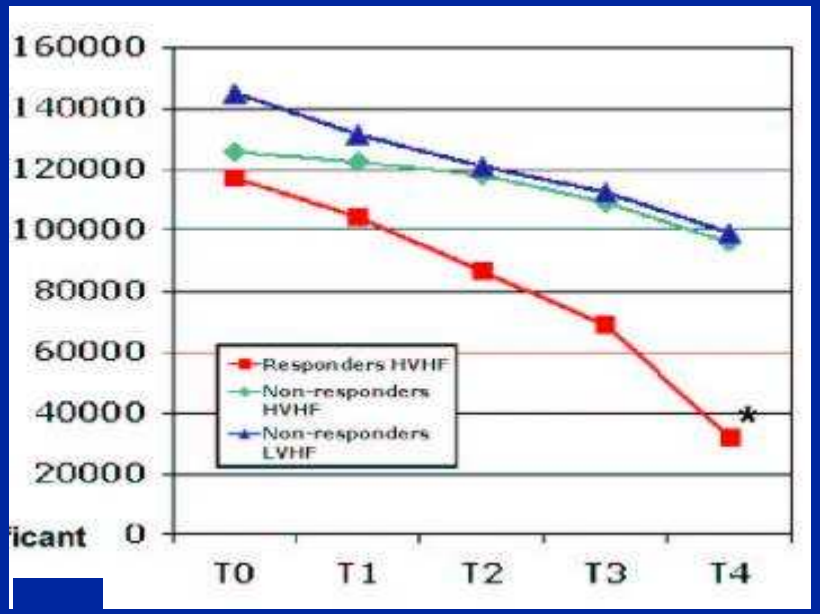
Honore et al, Crit Care Med 2004



IL-6 Removal in Refractory Septic Shock

Honoré et al, Crit Care Med 2000



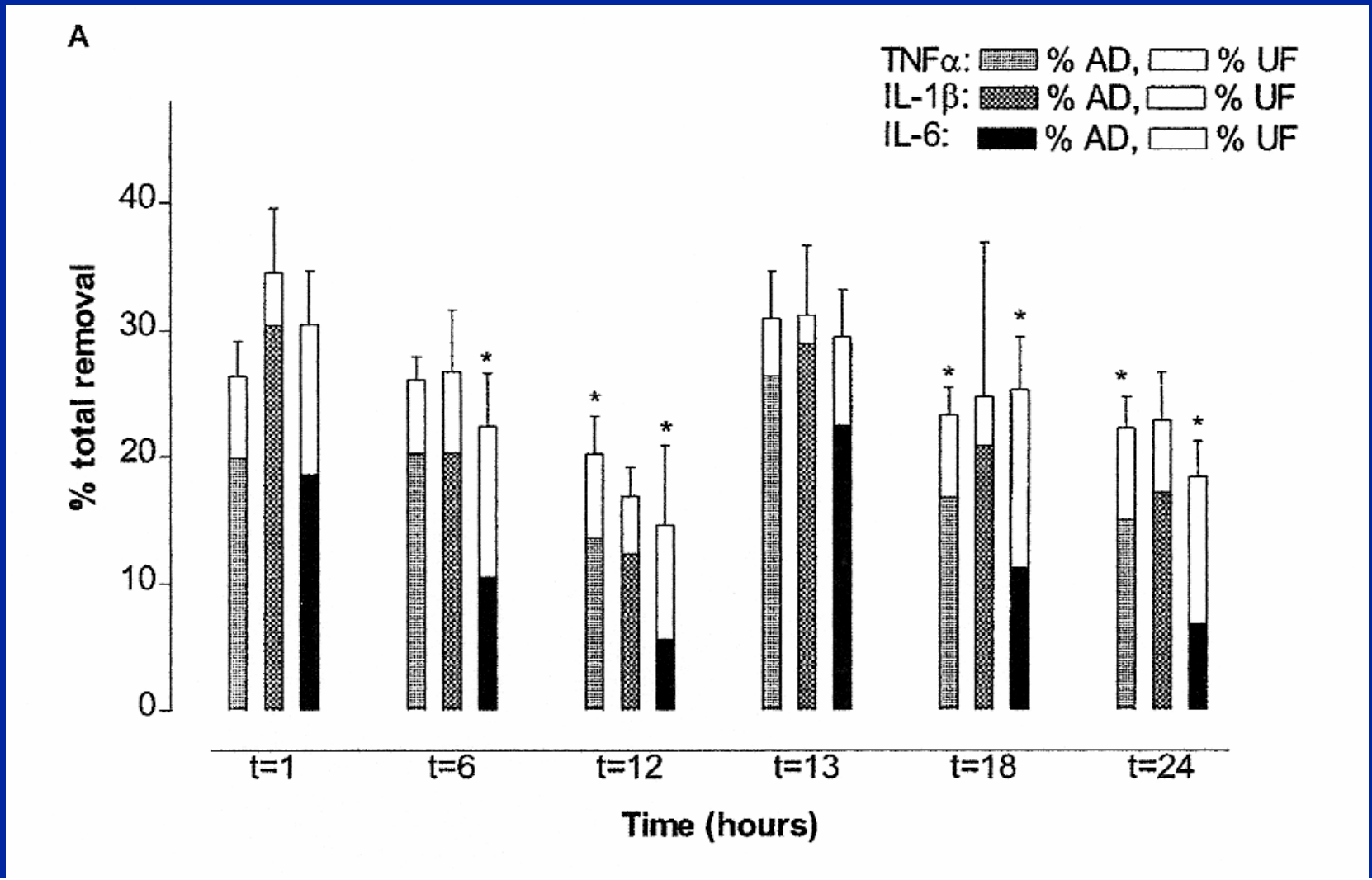


All 8 LVHF patients died
4/8 HVHF patients “responded” (shock resolved)
2/4 responders survived

Adapted CRRT Approaches for Septic Conditions: Adsorption (Oxiris)

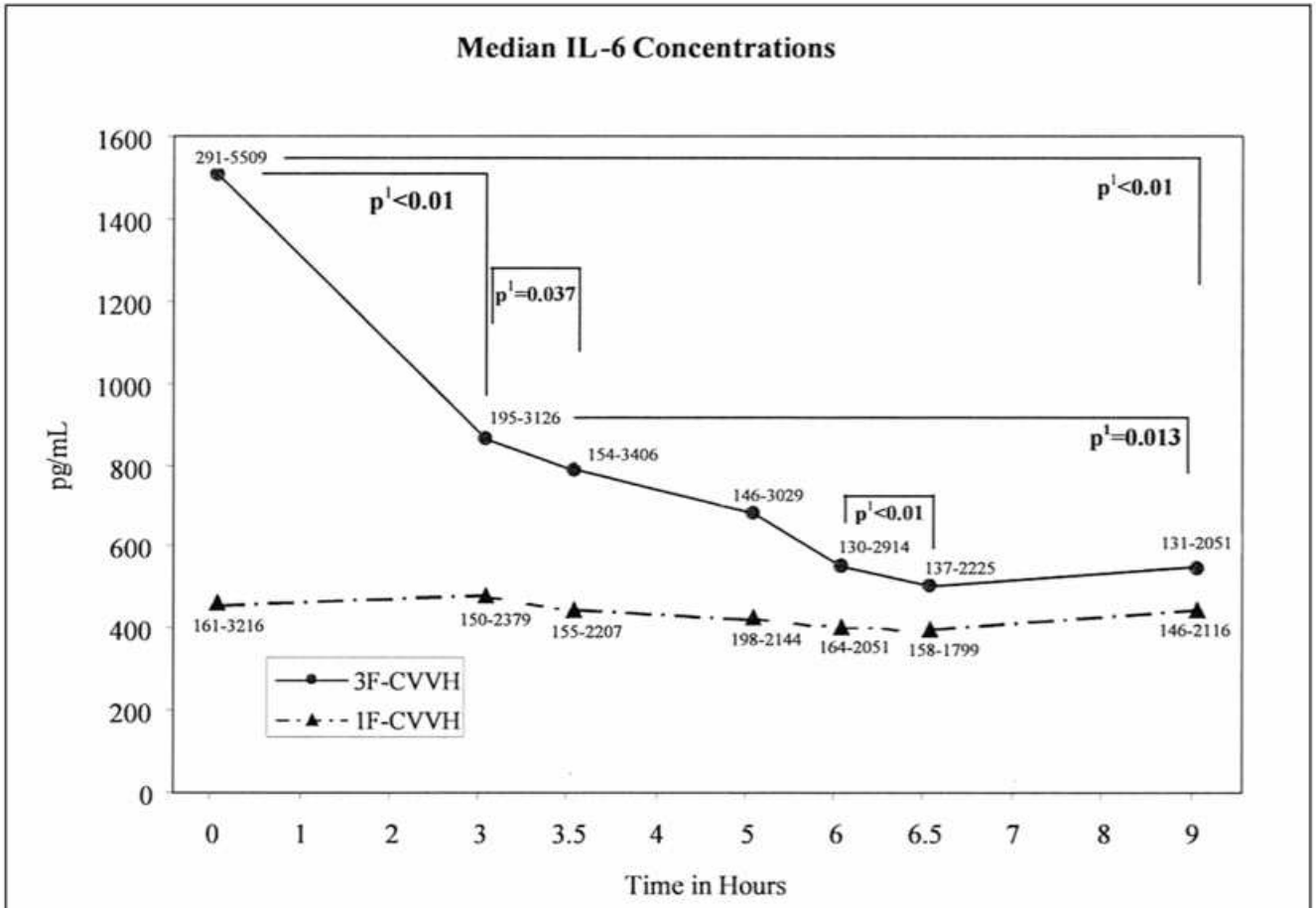
Cytokine Removal During "Standard" CRRT

De Vriese et al, JASN 1999



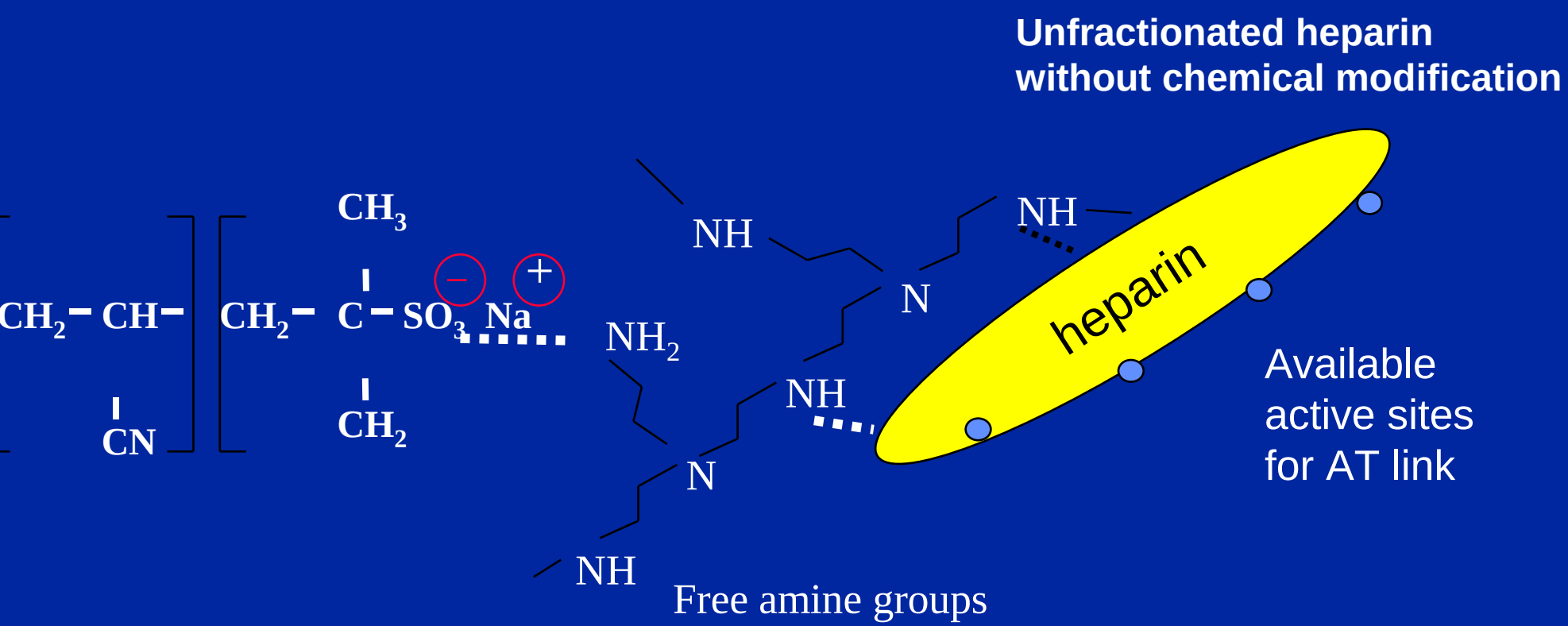
IL-6 Concentration Changes – AN69

Haase et Al., Int J Artif Organs 2007



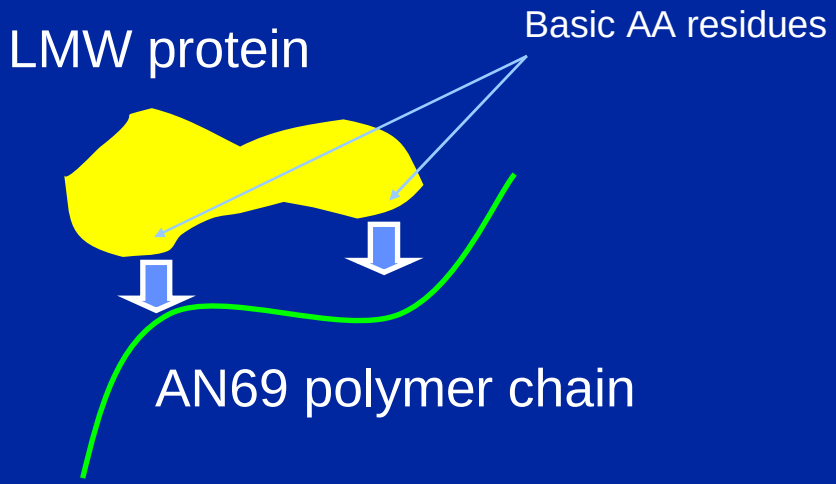
Median IL-6 concentrations during 3F-CVVH and 1F-CVVH (CVVH Continuous Veno-Venous Hemofiltration; 3F-CVVH 3Filter-high-adsorption CVVH, 1F-CVVH 1Filter-standard CVVH, numbers next to triangles and circles indicate interquartile ranges)

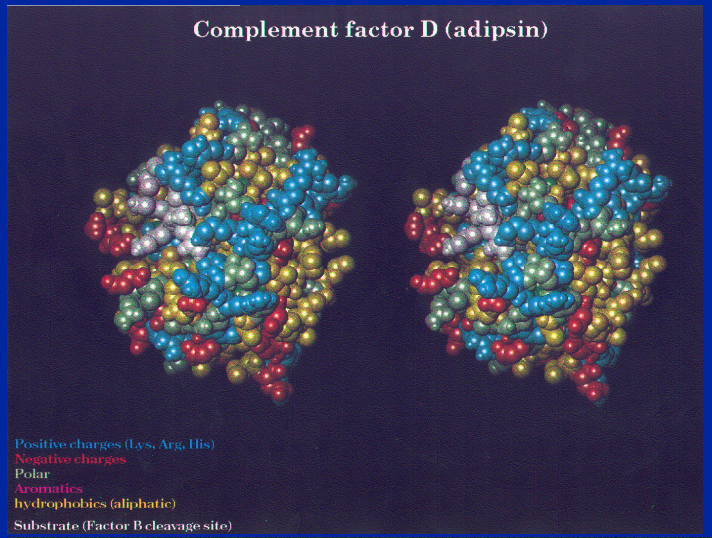
Oxiris: grafting mechanism (Heparin)

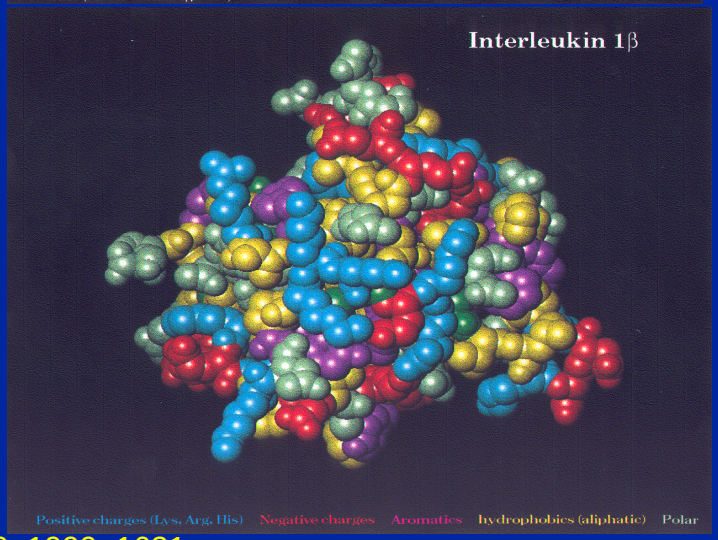


Oxiris: action mode

Low molecular weight protein adsorption properties







- *Adsorption of low molecular weigt proteins to hemodialysis membranes: experimental results and simulations* - P. Valette, M. Thomas, P. Déjardin Biomaterials, 20, 1999, 1621
- *Influence of the charge of low molecular weight proteins on their efficiency of filtration and / or adsorption on dialysis membranes with different intrinsic properties* - N. Moachon, M. Thomas, G. Quash Biomaterials, 23, 2002, 651

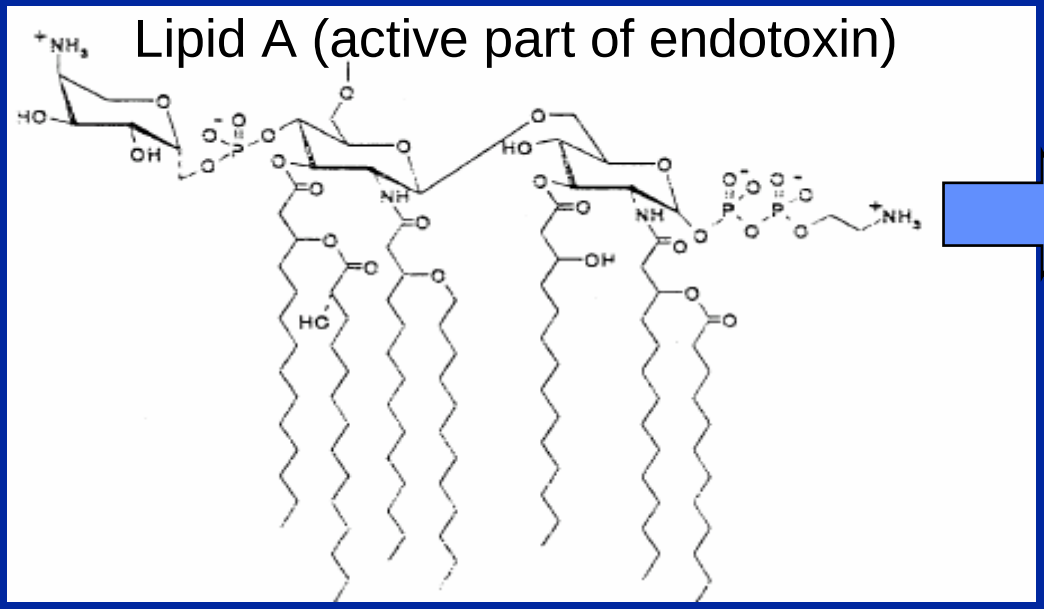
Oxiris: action mode

Endotoxin adsorption

Endotoxin:

- large MW molecule (100 000 to 5M)
- major component of gram – bacteria
- chemical composition: polysaccaride, carbohydrate and lipid A (LPS)

Lipid A (active part of endotoxin)



Ionic bonding with free amine groups of PEI

** S. Morimoto et al, Polymer journal, vol.27, 8, 1995, 831

S. Mitzner et al, Artificial organs, 17 (9), 1993, 775

Oxiris membrane: adsorption

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

Endotoxin Concentration - oxiris

Rimmele et al., Nephrol Dial Transplant 2008

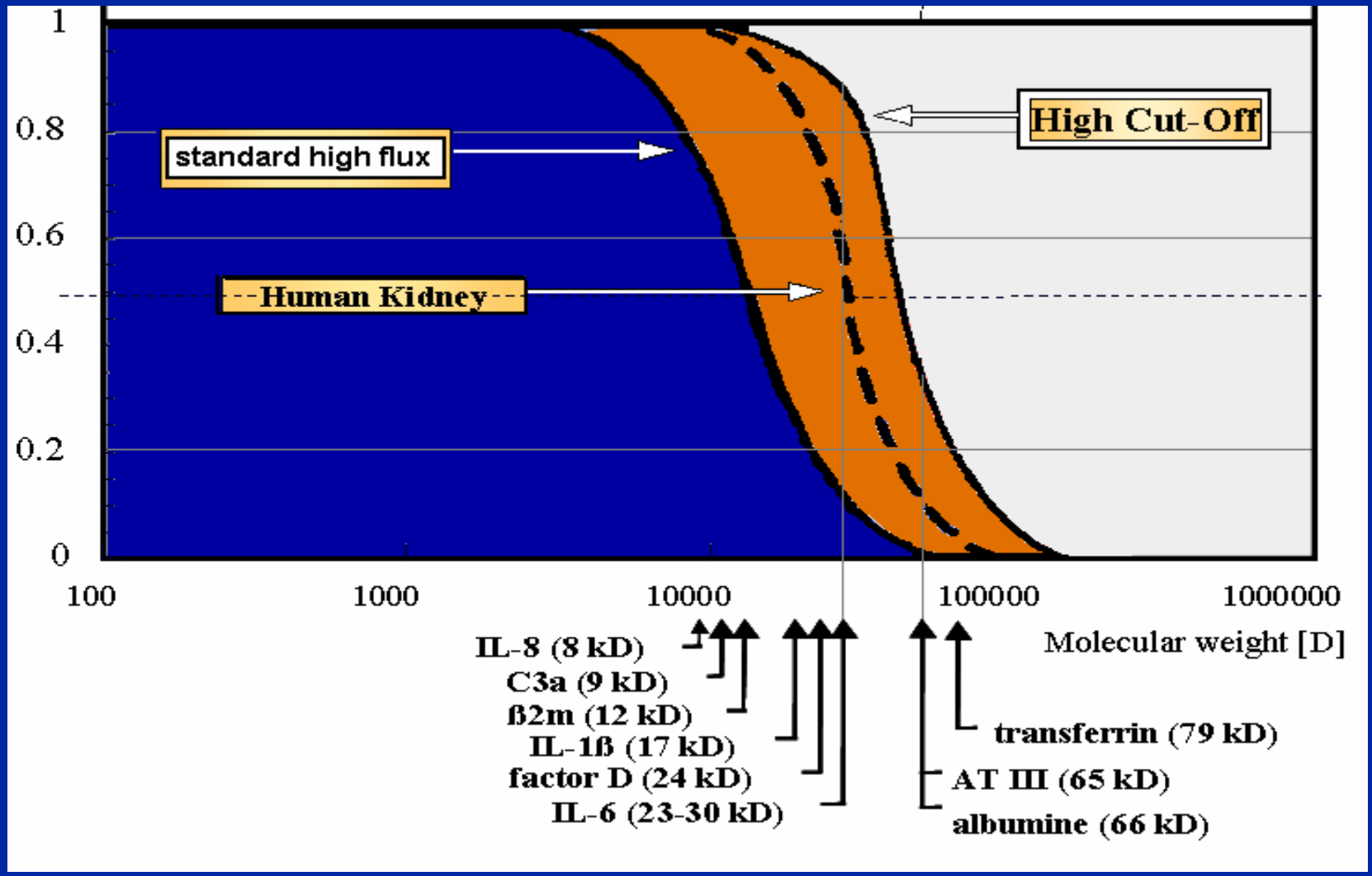
	AN69 membrane (*n* = 10)	Treated membrane (*n* = 10)
T0	**3.98** ± 3.31	**4.26** ± 7.68
T1	**11.07** ± 10.64	**1.91** ± 1.19[a]
T6	**2.96** ± 2.75	**2.26** ± 2.39

T0 = beginning of HVHF, T1 = time after 1 h of HVHF, T6 = time after 6 h of HVHF.

Statistics: ANOVA for repeated measurements followed by a Duncan post test. *P* = 0.014 for the time factor, *P* = 0.064 for the type of membrane.

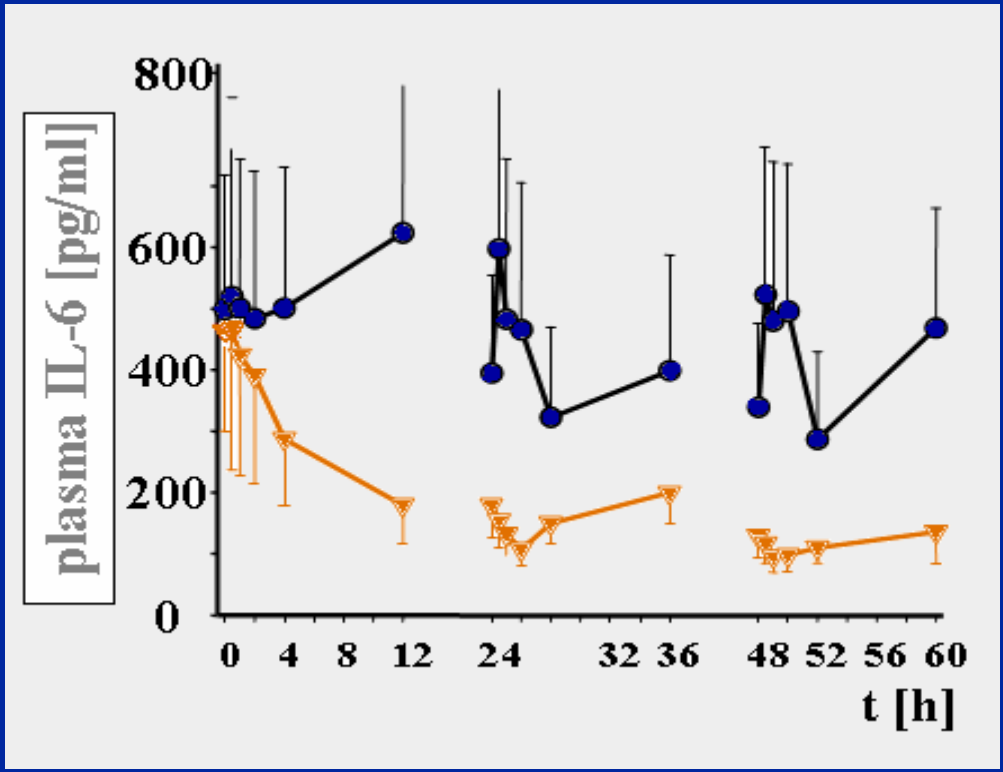
Adapted CRRT Approaches for Septic Conditions: Large Pore Membranes

HCO Membrane with Increased Permeability for Inflammatory Mediators



Substantial Reduction of Plasma IL-6 Levels

HCO treatment reduces interleukin-6 plasma levels from ~500 pg/ml to ~100 pg/ml

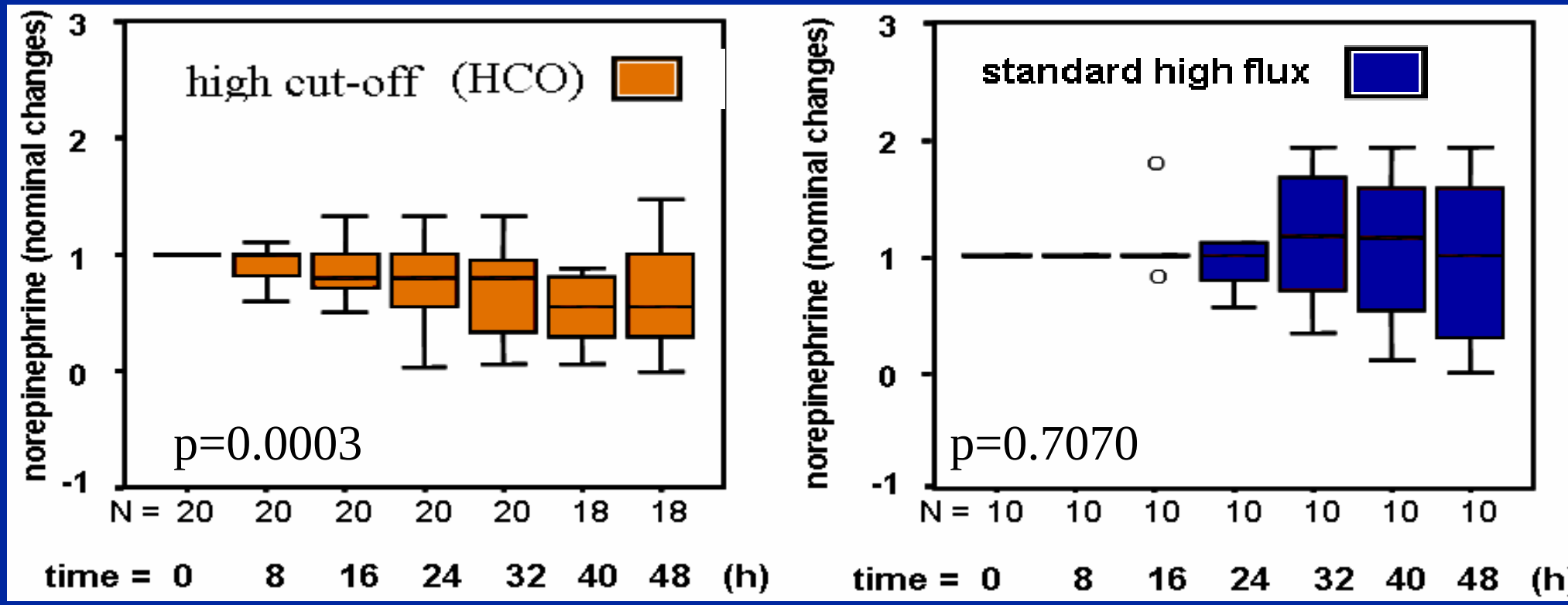


high cut-off (HCO)

standard high flux

Intensive Care Med 2003;29:1989-95

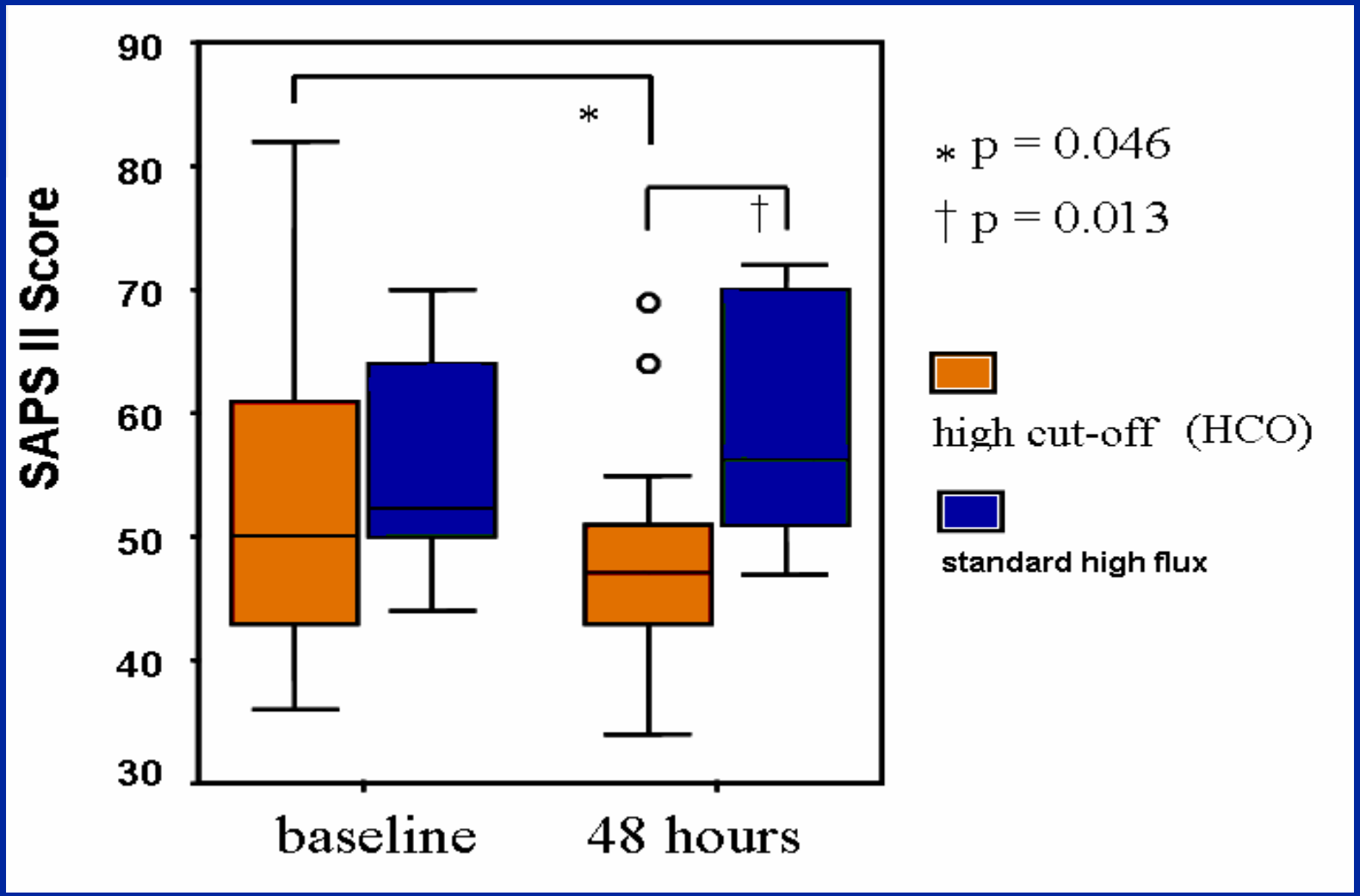
Norepinephrine
- relative values -



p=0.0303 between HCO and standard high flux

Crit Care Med. 2006;34:2099-04.

Simplified Acute Physiology Score (SAPS) II



Crit Care Med. 2006;34:2099-04.

Summary

- Based on the excellent overall outcomes achieved in RENAL with CRRT, the relevance of other modalities for critically ill AKI patients is an open question
  - The results seems to confirm that early CRRT initiation is an important factor influencing patient outcome
- Extracorporeal techniques represent an opportunity to achieve immunomodulation in sepsis – these techniques include:
  - High-volume hemofiltration
  - Adsorption-based approaches
  - Large pore membranes
- Oxiris and Septex are innovative new approaches providing the possibility to achieve immunomodulation