



What Can Hemofiltration Teach us About Sepsis?

John A. Kellum, MD

**Professor of Critical Care Medicine, Medicine,
Bioengineering and Clinical and Translational Science
Vice Chair for Research**

The CRISMA Center

**Department of Critical Care Medicine
School of Medicine**

**Center for Inflammation and Regenerative Modeling
McGowan Institute for Regenerative Medicine**

**Health Policy and Management
Graduate School of Public Health**

University of Pittsburgh

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Monica



- ⊕ 51 y.o. artist
- ⊕ Admitted on New Years Day with abdominal pain
- ⊕ Underwent open cholecystectomy



⊕ 24 hours after surgery

- ✱ Despite antibiotics...
- ✱ Fever, shortness of breath, decreased urine output
- ✱ Admitted to ICU

⊕ 12 hours later

- ✱ Confused and low blood oxygen
- ✱ Requires mechanical ventilation
- ✱ Blood pressure is low

⊕ 6 hours later

- ✱ Cardiac arrest
- ✱ Pronounced dead

Howard



- ✦ 70 y.o. retired school teacher
- ✦ Mild emphysema, hypertension
- ✦ Admitted to hospital with pneumonia
- ✦ Developed respiratory failure, circulatory shock, acute renal failure
- ✦ 22 days in ICU, 35 days in hospital, 16 days in rehab
- ✦ Discharged to home
- ✦ Readmitted two weeks later, fever and shortness of breath



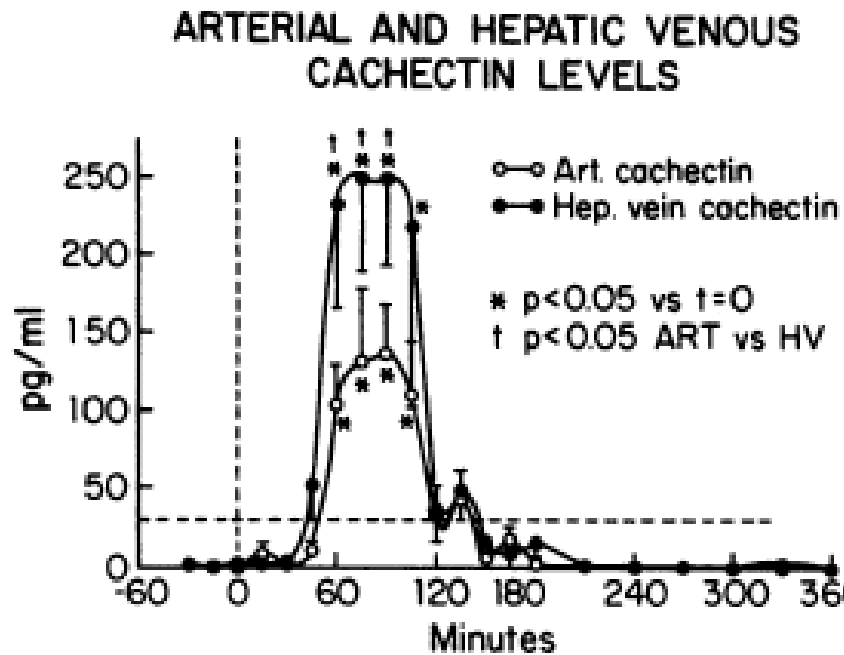
- ⊕ **Requires mechanical ventilation and hemodialysis**
- ⊕ **Requests discontinuation of life support after 5 days in ICU**

Cytokine response to endotoxin

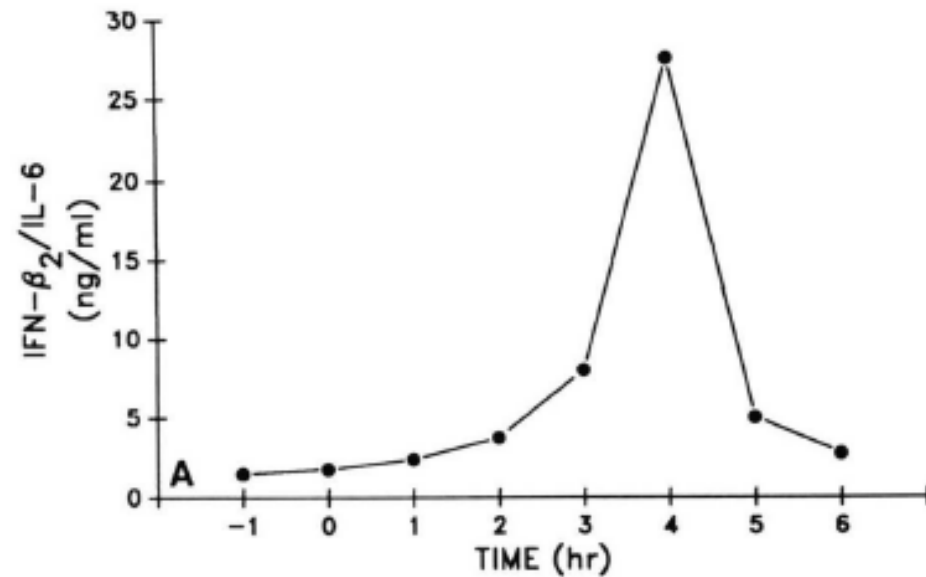


TNF

IL-6



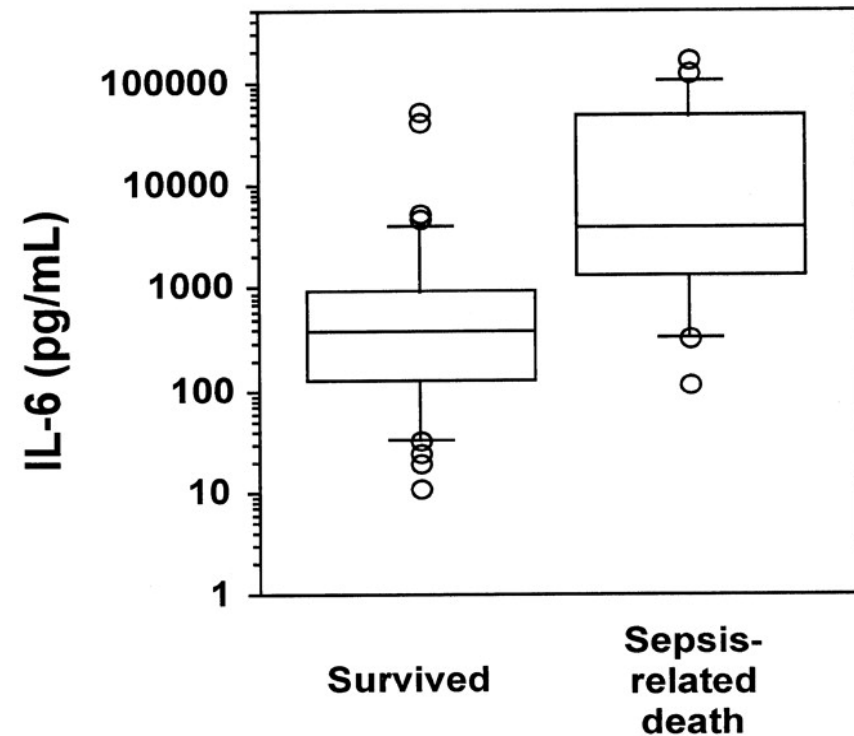
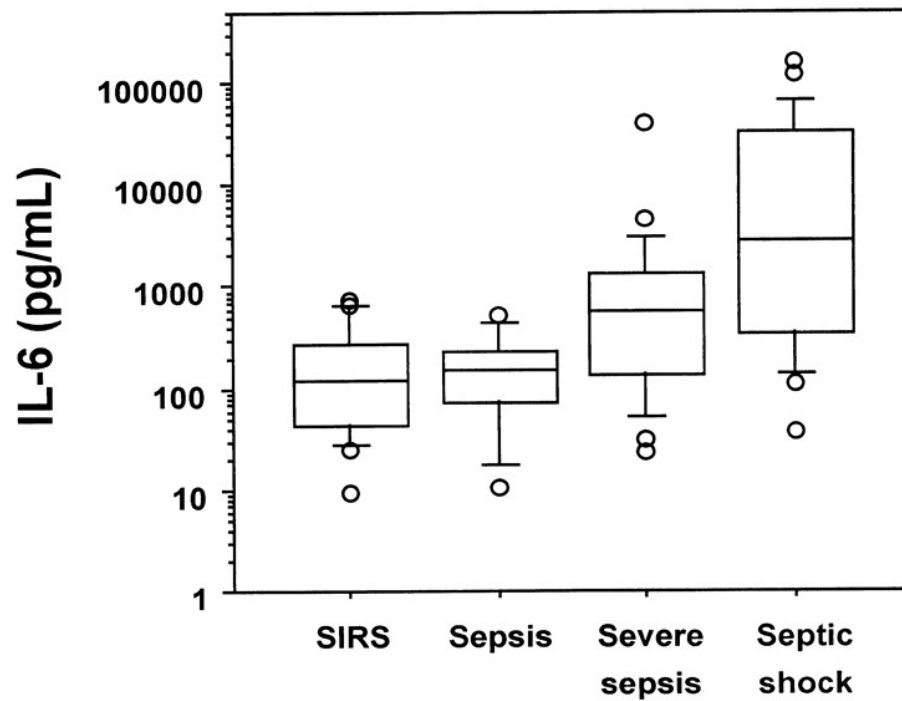
Fong et al. *J Clin Invest* 1990;85:1896



Fong et al. *J Immunol* 1989;142:2321

6 healthy volunteers

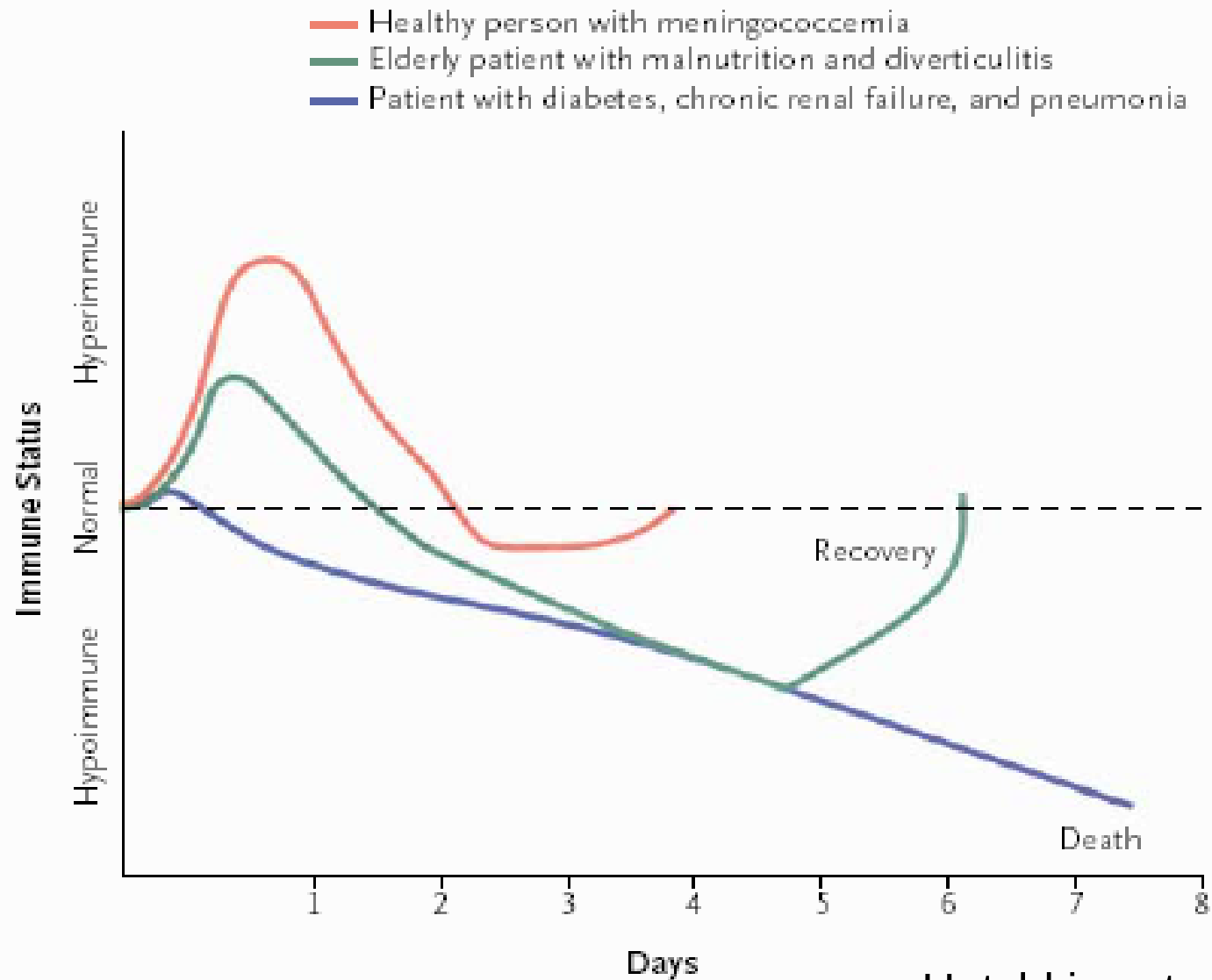
IL-6 in sepsis



N=78

Harbarth AJRCCM 2001

The course of sepsis



Hotchkiss et al. NEJM 2003

Genetic and Inflammatory Markers of Sepsis (GenIMS)



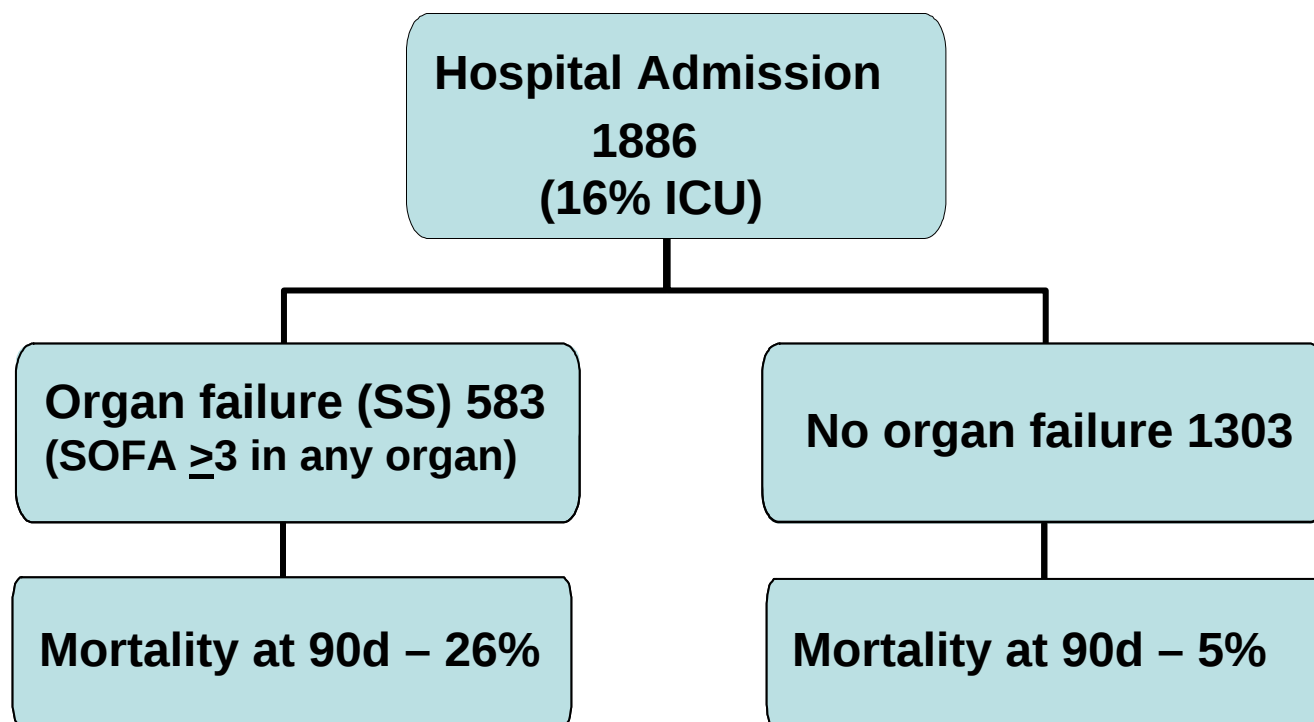
A multicenter study of pneumonia and sepsis

GenIMS

Genetic and Inflammatory Markers of Sepsis

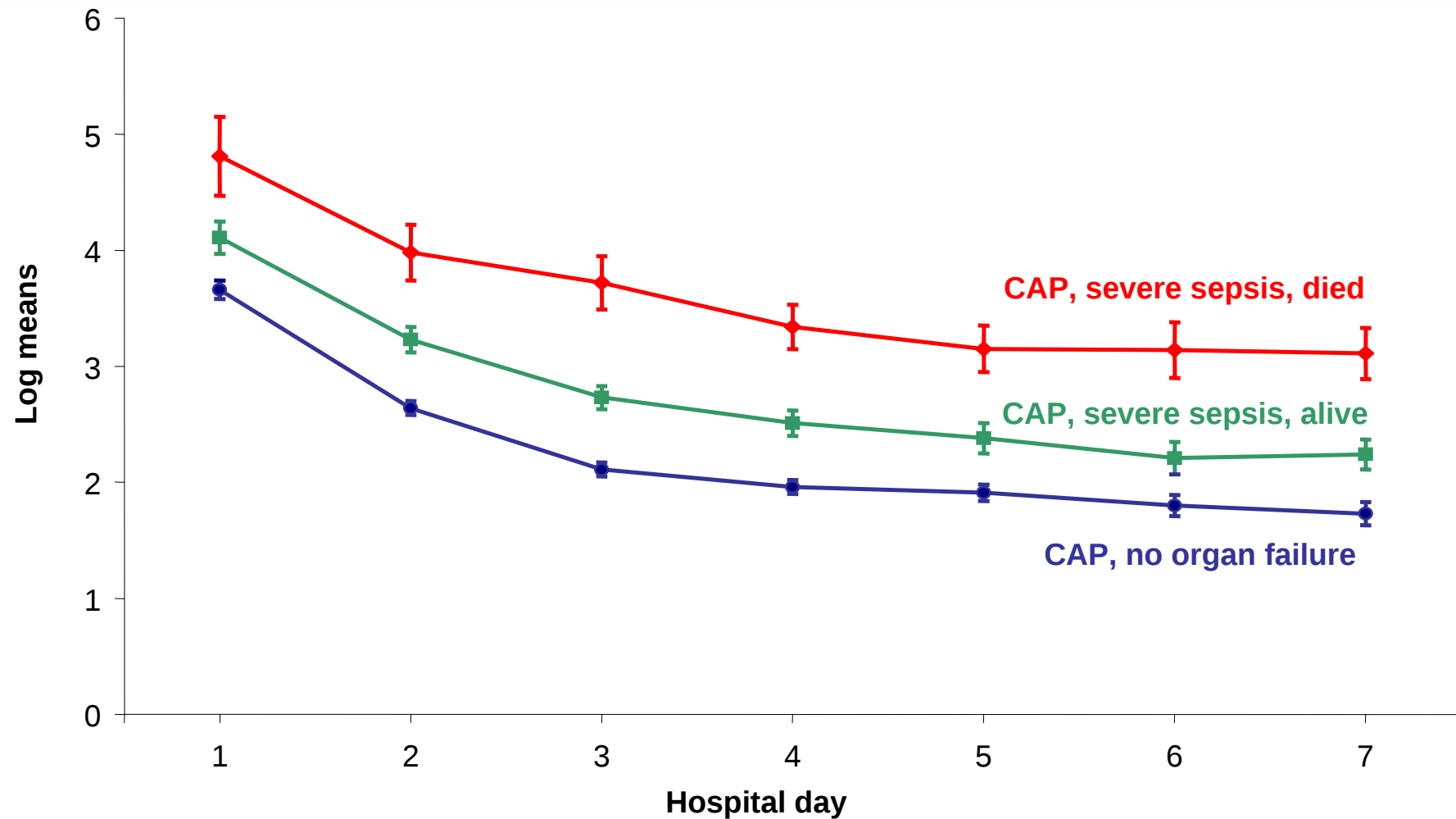
- ✚ **Inception cohort study of patients presenting to ED with CAP**
 - ✚ 28 hospitals clustered in 4 regions
 - ✚ Pennsylvania (SW)
 - ✚ Connecticut
 - ✚ Michigan (Detroit area)
 - ✚ Tennessee (Memphis area)
- ✚ **Serial blood sampling and clinical data collection**
- ✚ **Characterize genotype, serum inflammatory markers, and clinical outcomes**
 - ✚ CAP but no progress to severe sepsis
 - ✚ CAP progressing to severe sepsis

The GenIMS study of Sepsis in Community Acquired Pneumonia



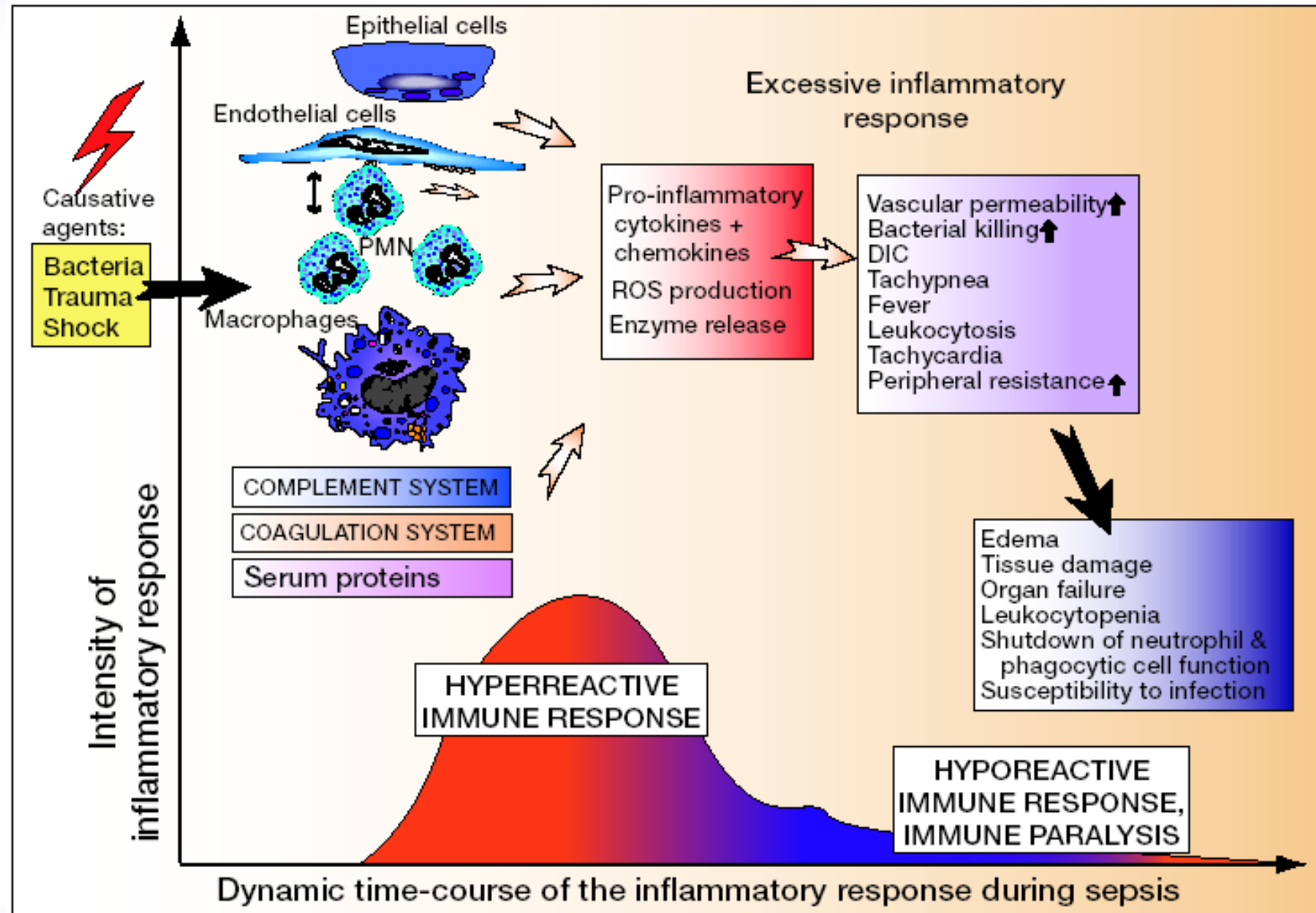
Kellum JA et al. Arch Intern Med 2007; 167(15):1655-63

IL-6 and severe sepsis

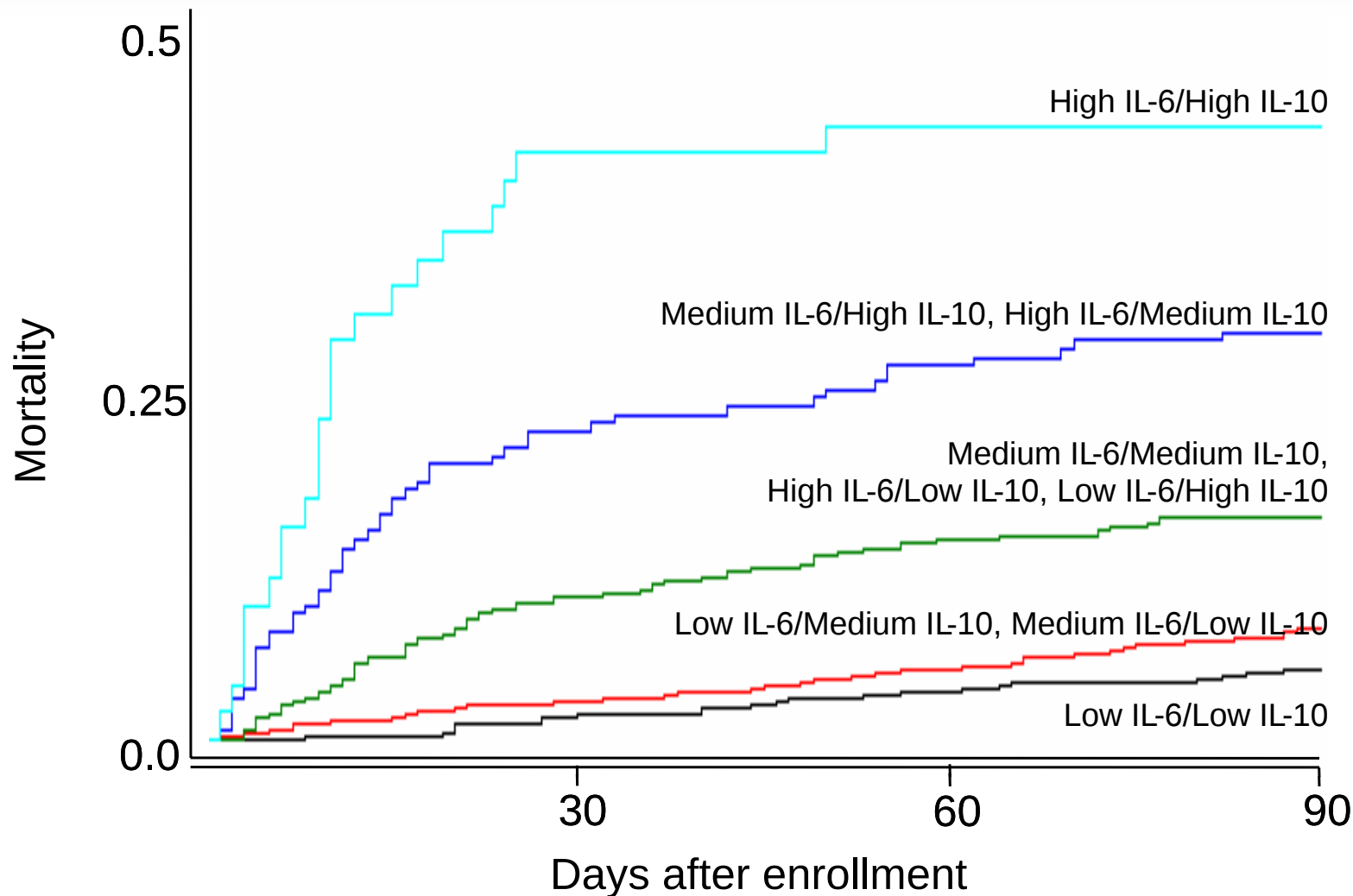


Kellum JA et al. Arch Intern Med 2007; 167(15):1655-63

Reidemann, et al Nature Med. 2003



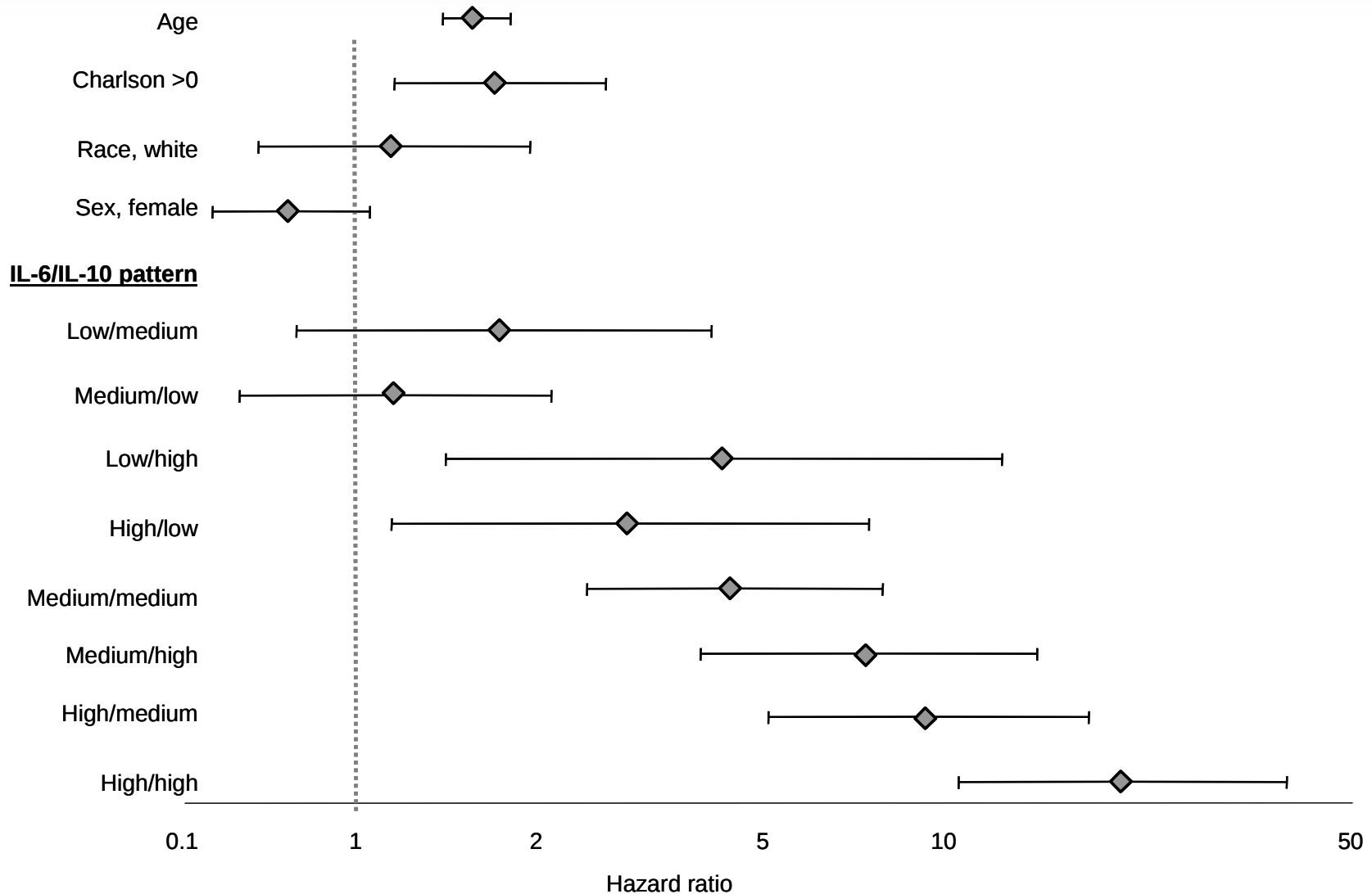
Cytokine Patterns and Survival



N= 1886

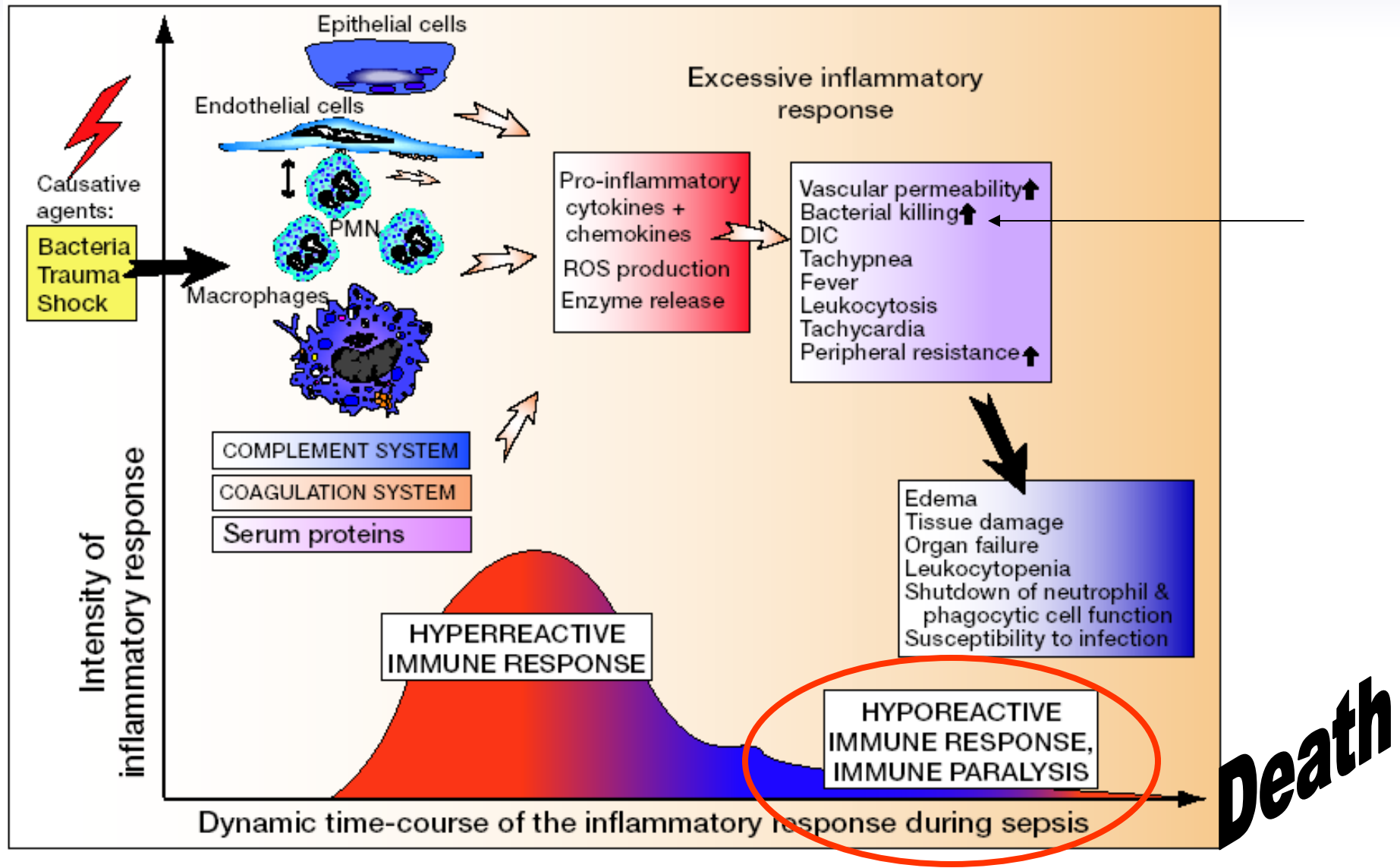
Kellum JA et al. Arch Intern Med 2007; 167:1655-63

Cox model

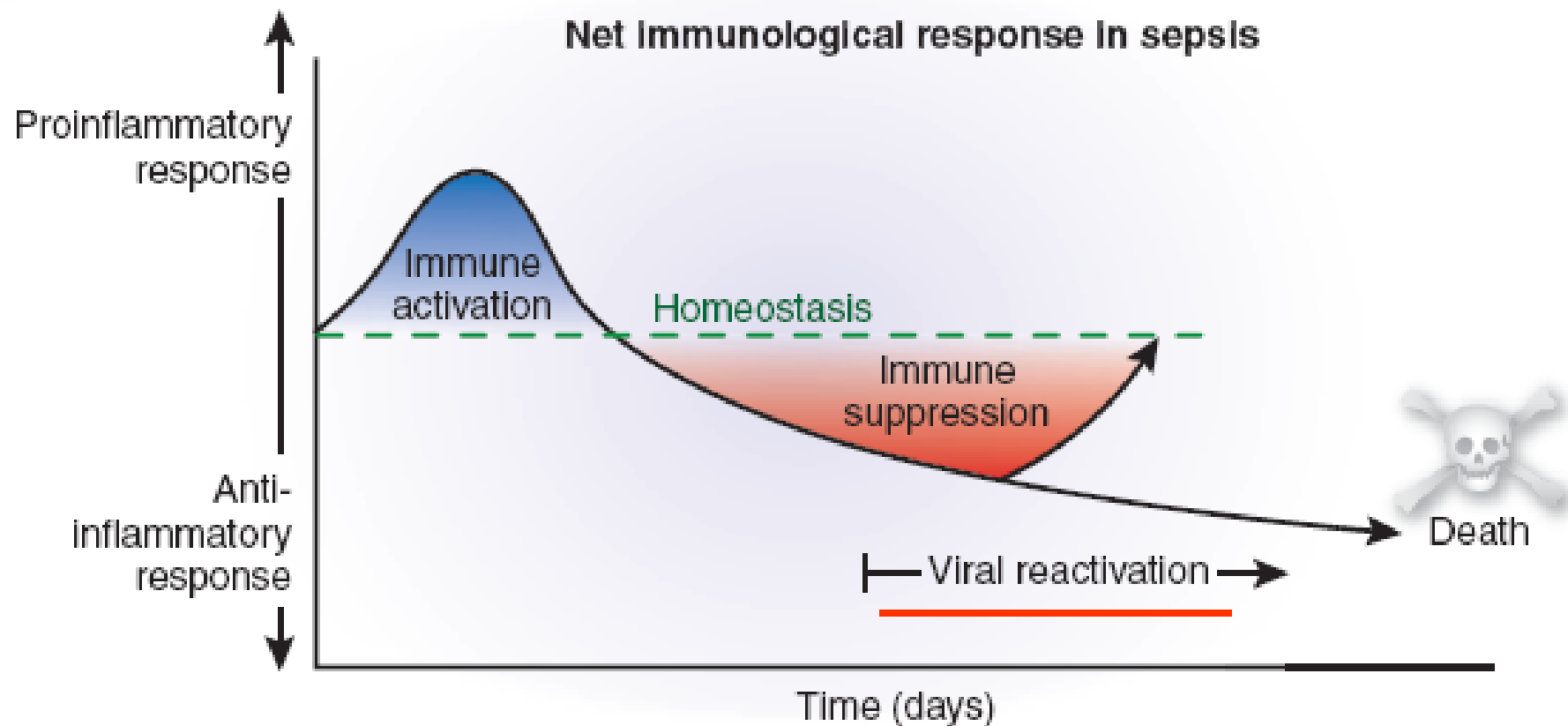


Kellum JA et al. Arch Intern Med 2007; 167:1655-63

Reidemann, et al Nature Med. 2003



Sepsis = immune suppression



Hotchkiss et al. Nat Med 2009

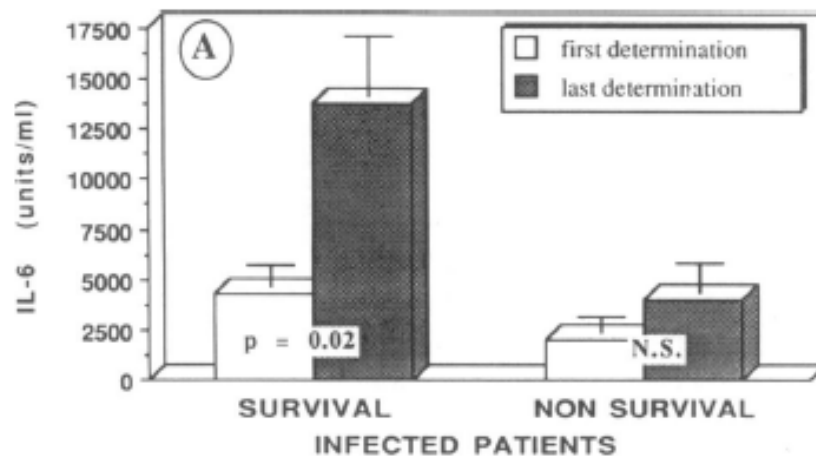
Immunoparalysis



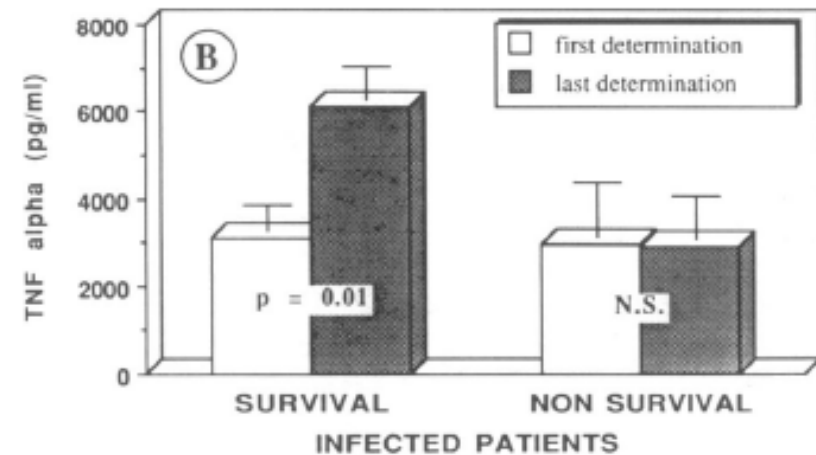
Munoz, et al. J. Clin. Invest. 1991. 88:1747-1754

Whole blood response to LPS stimulation

IL-6

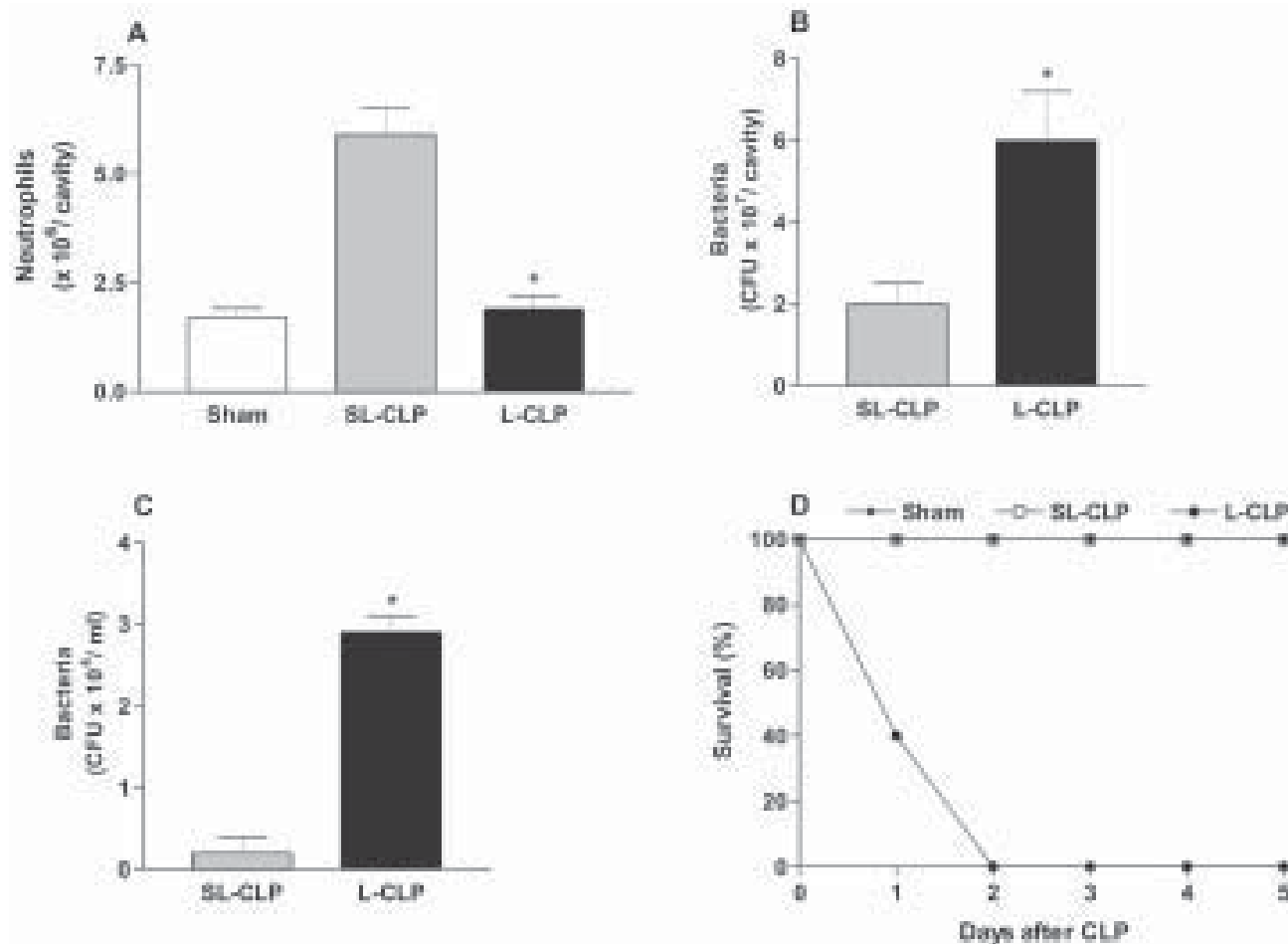


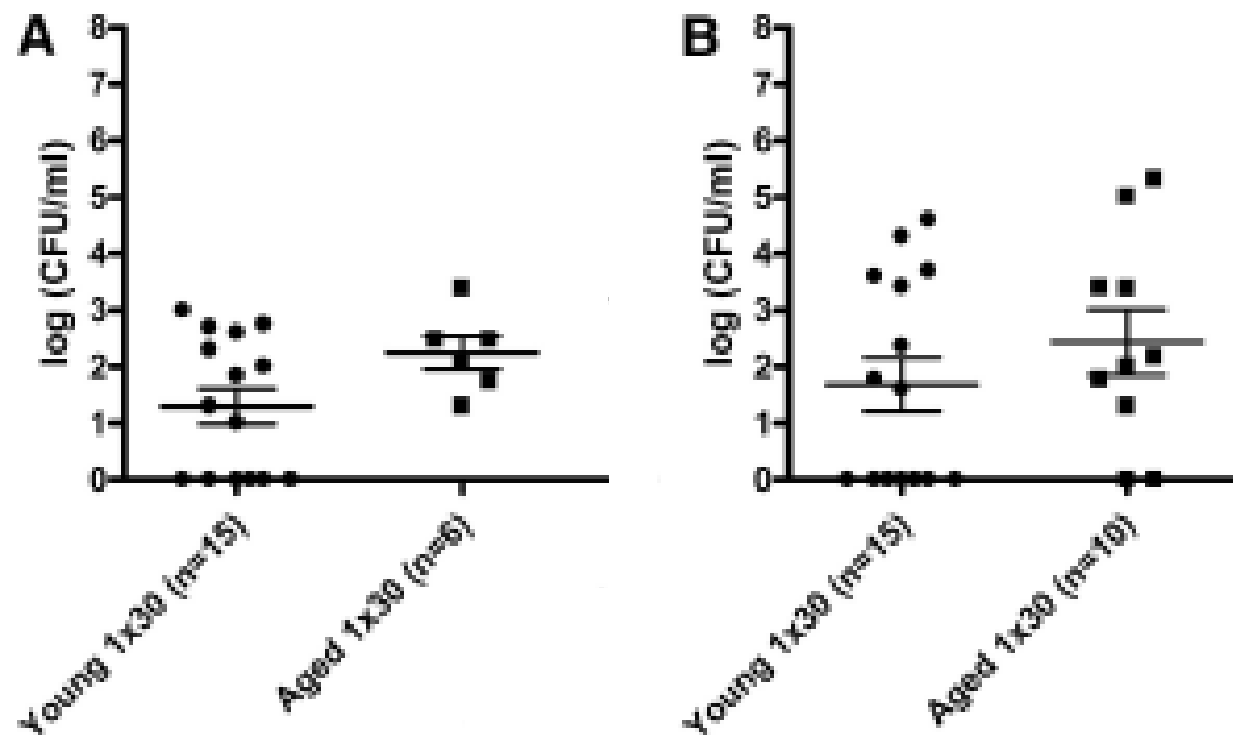
TNF



Alves-Filho JC et al.

Mem Inst Oswaldo Cruz, Rio de Janeiro, Vol. 100(Suppl. I): 223-226, 2005



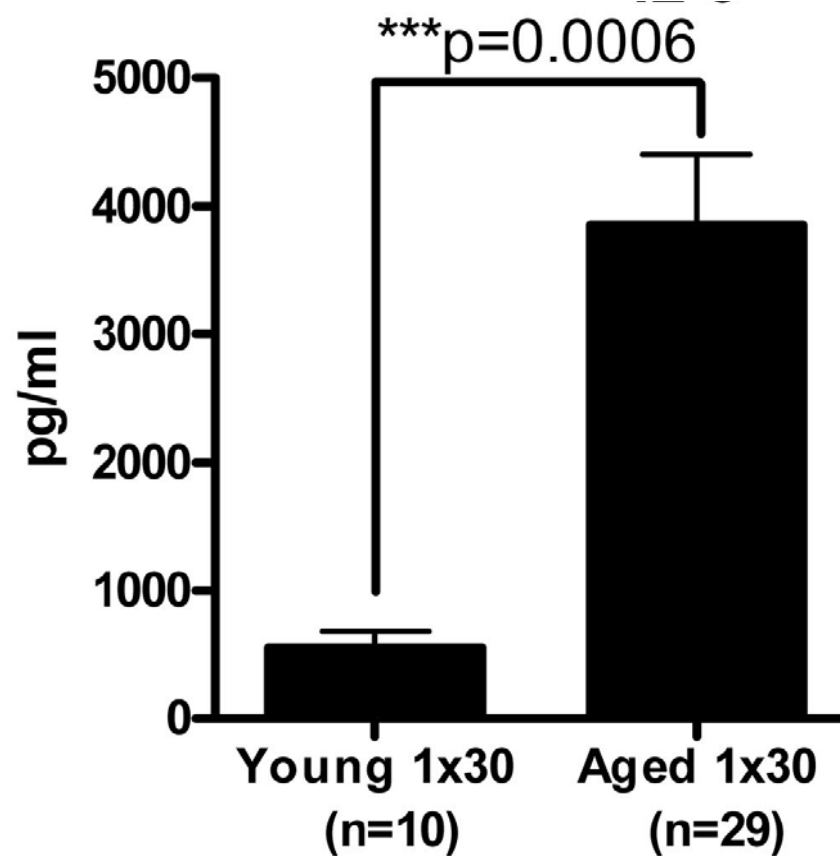


Turnbull et al. (Crit Care Med 2009; 37: 1018–1023

...and yet systemic inflammation is greater



IL-6



Do high systemic concentrations of cytokines “distract” the leukocytes from source of infection?



This information is current as
of December 6, 2010

Early Enhanced Local Neutrophil Recruitment in Peritonitis-Induced Sepsis Improves Bacterial Clearance and Survival

Florin L. Craciun, Elizabeth R. Schuller and Daniel G.
Remick

J Immunol 2010;185:6930-6938; Prepublished online 1
November 2010;

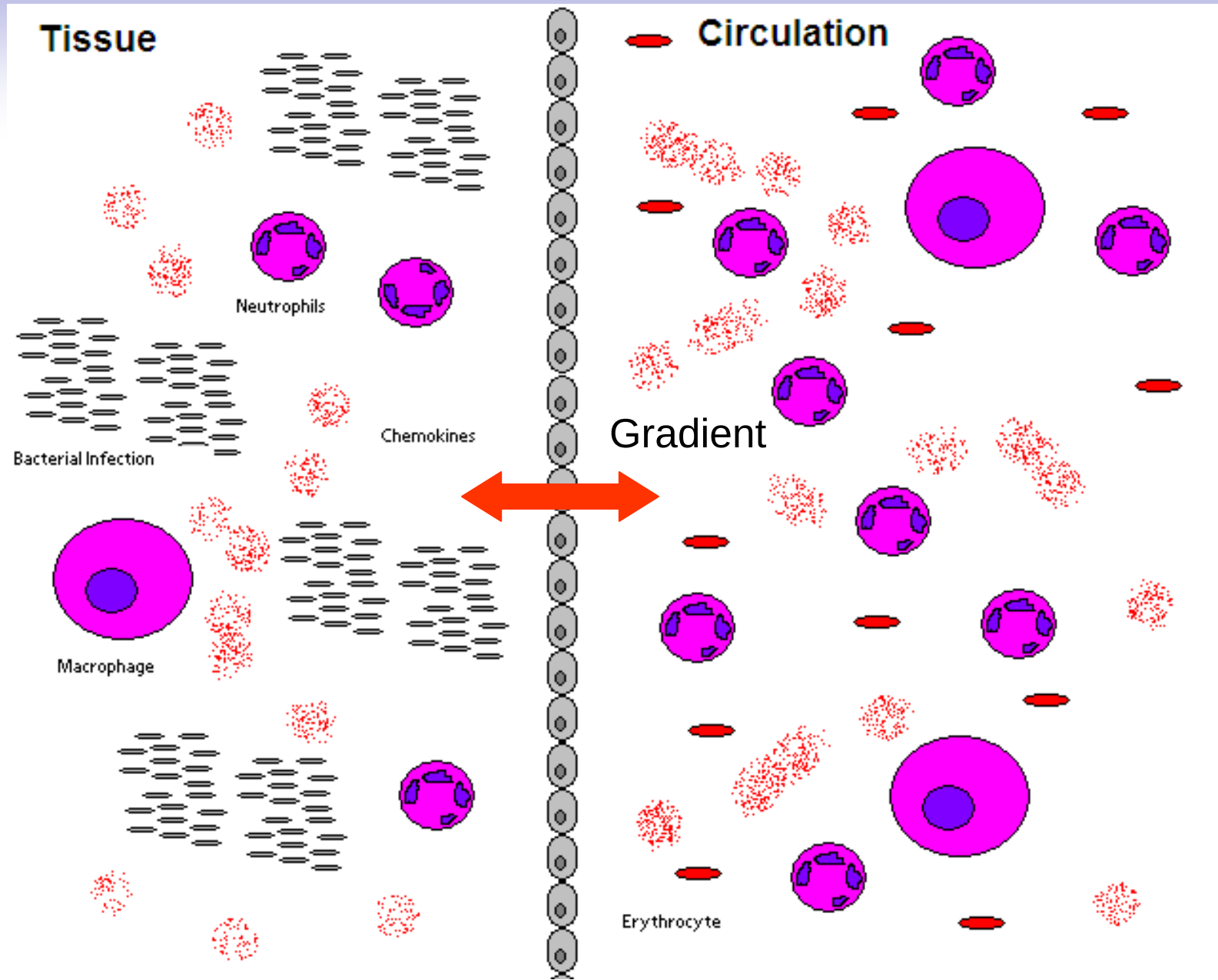
doi:10.4049/jimmunol.1002300

<http://www.jimmunol.org/content/185/11/6930>



Cytokine

cyto- (cell) -kinos (movement)





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affiliated with

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McGOWAN INSTITUTE FOR REGENERATIVE MEDICINE

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 **immunetrics**

Systems Engineering of a Pheresis Intervention for Sepsis (SEPsIS)

John A. Kellum, MD
Principal Investigator
Director, Molecular Core Laboratory, CRISMA
Vice Chair for Research
Professor, Department of Critical Care Medicine



National Heart
Lung and Blood Institute

⊕ the Clinical Research, Investigation, and Systems Modeling of Acute illness ⊕

The SEPsis Team



⊕ CRISMA

- ✱ John Kellum
- ✱ Kai Singbartl
- ✱ Zhiyong Peng
 - ⊕ Michele Elder
 - ⊕ Melinda Carter
 - ⊕ Lisa Weissfeld
 - ⊕ Lan Kong
 - ⊕ David DelGrosso
 - ⊕ Xia Tang
- ✱ Gilles Clermont
 - ⊕ Silvia Daun
 - ⊕ Justin Haug

⊕ Chemical/Industrial Engineering

- ✱ Bob Parker

⊕ Immunetrics

- ✱ Steven Chang
- ✱ John Bartels

⊕ McGowan/Bioengineering

- ✱ William Federspeil
 - ⊕ Morgan DiLeo
 - ⊕ Patrick Bartlow
 - ⊕ Brian Frankowski
 - ⊕ Emily Ciak
- ✱ William Wagner
 - ⊕ Josh Woolley
 - ⊕ Mustafa Kocakulak

⊕ McGowan/Surgery

- ✱ Yoram Vodovotz
 - ⊕ Claudio Lagoa
 - ⊕ Derek Barclay

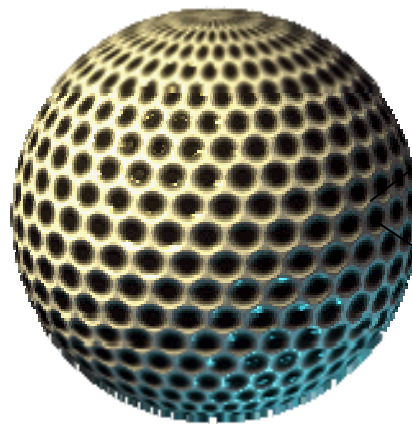
⊕ MedaSorb/CytoSorbents

- ✱ Vincent Capponi
- ✱ James Winchester
- ✱ Phil Chan

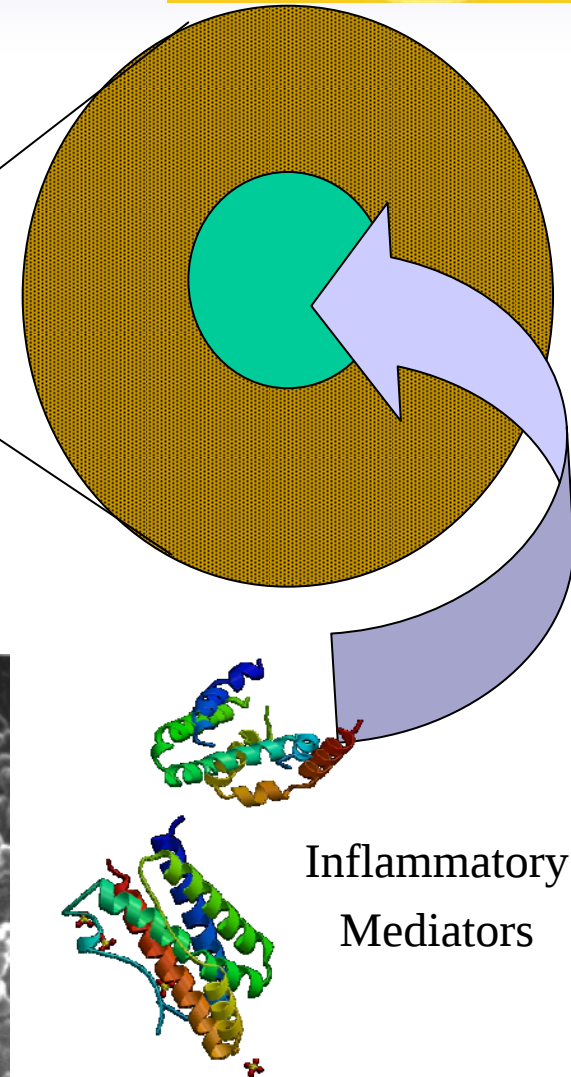
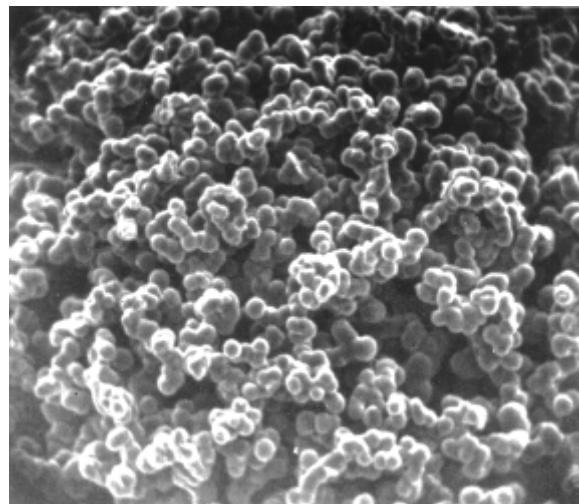
CytoSorb™



- Polystyrene divinyl benzene copolymer beads
- A biocompatible coating
- 300-800 microns diameter
- Each gram of material has a surface area of 850 m²
- Cartridge containing 10g of material



Pore-size
8-50 Å

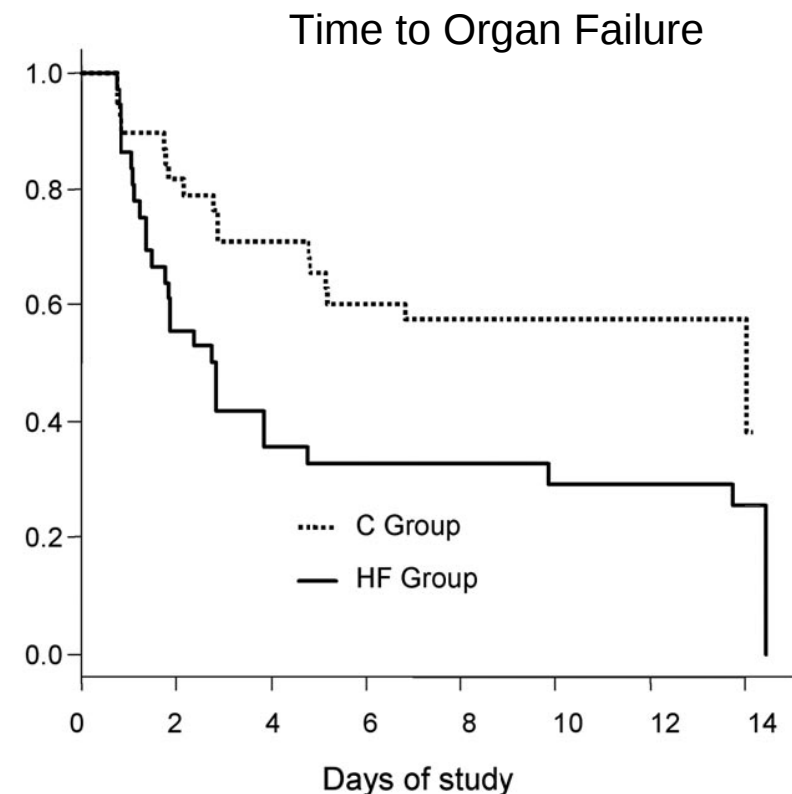
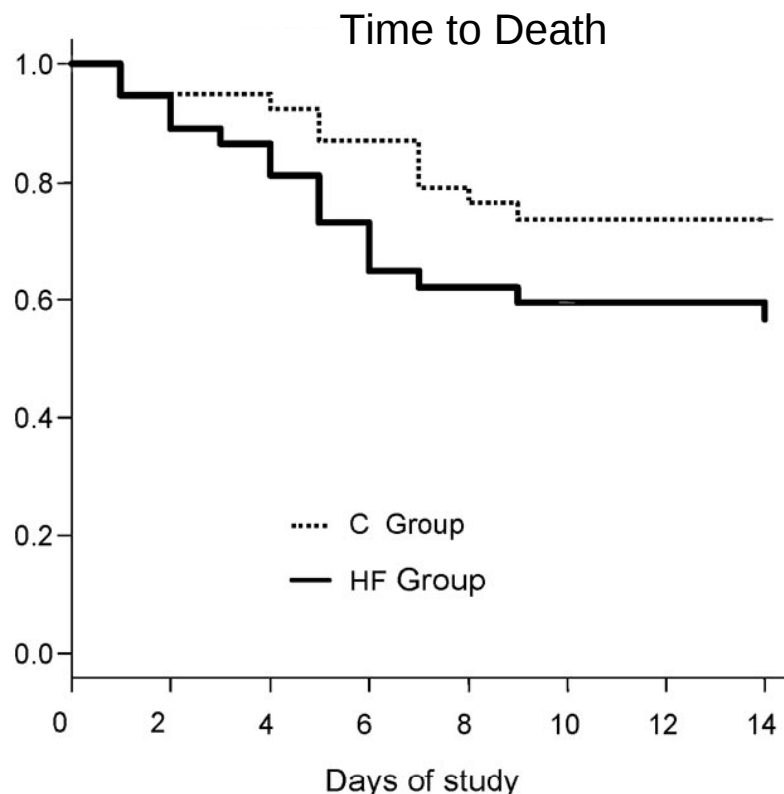


MedaSorb™
TECHNOLOGIES, LLC



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

Didier Payen, MD, PhD; Joaquim Mateo, MD; Jean Marc Cavaillon, PhD; François Fraisse, MD; Christian Floriot, MD; Eric Vicaut, MD, PhD; for the Hemofiltration and Sepsis Group of the Collège National de Réanimation et de Médecine d'Urgence des Hôpitaux extra-Universitaires

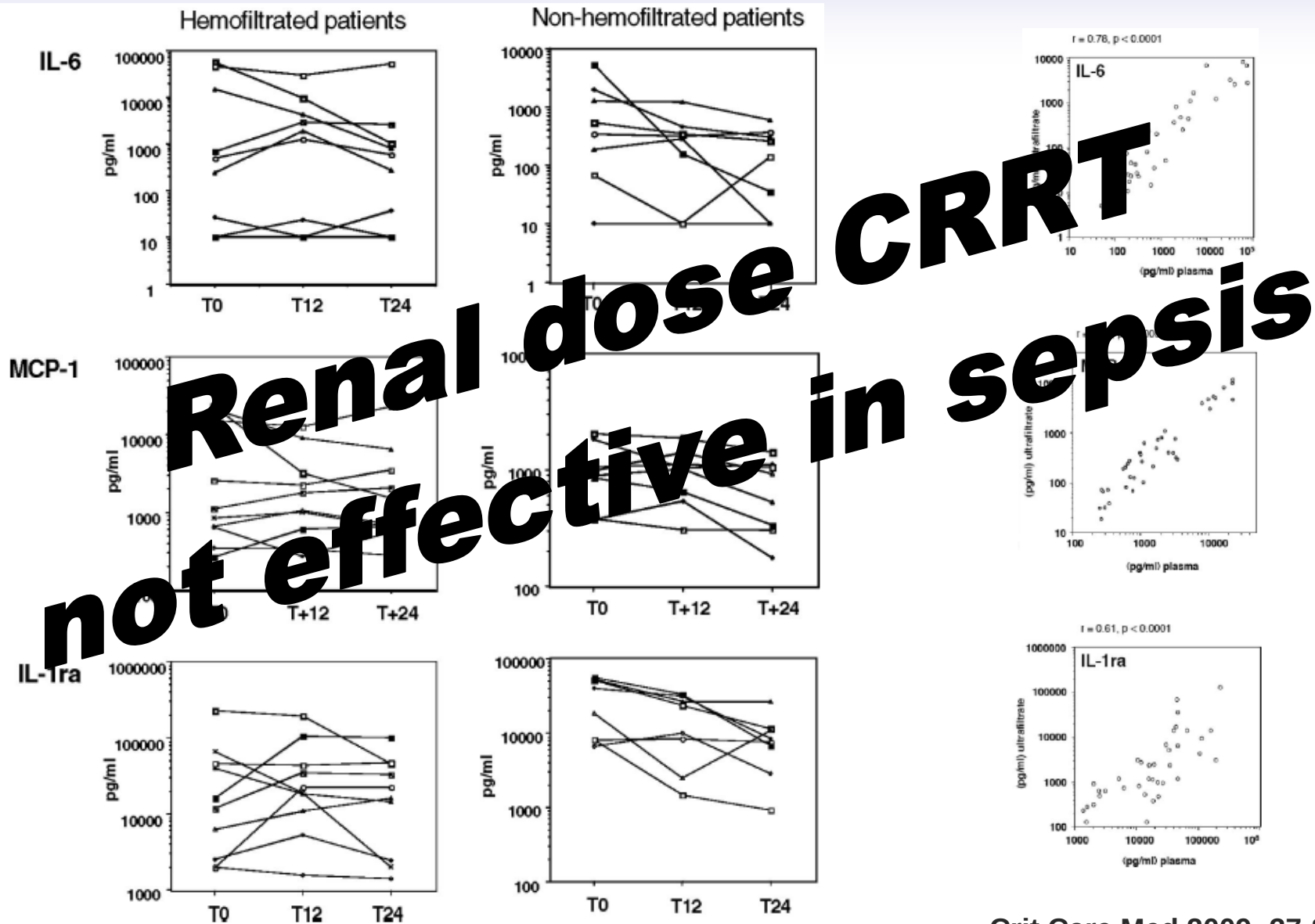


N=76

Crit Care Med 2009; 37:803– 810

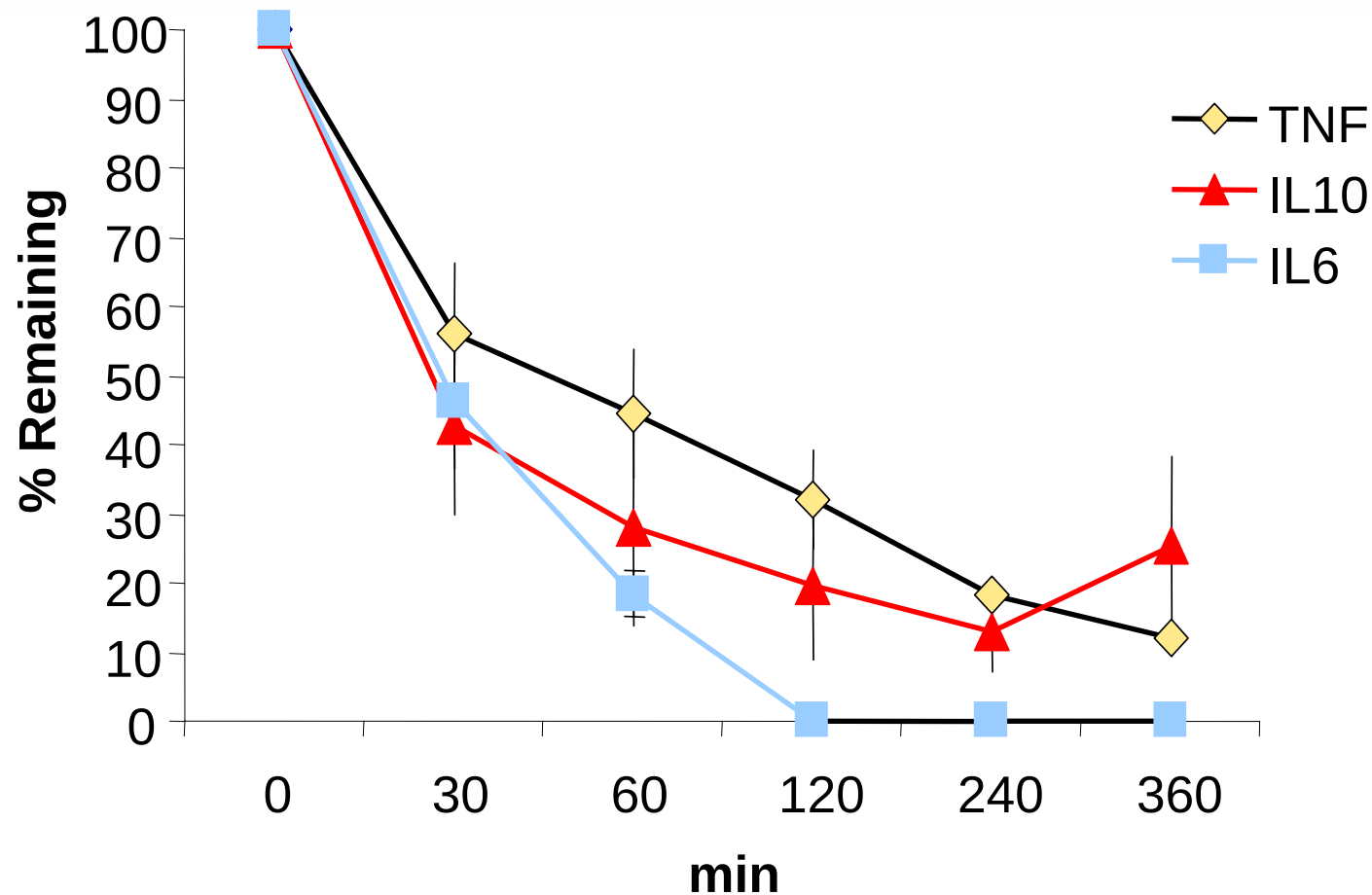


No effect on Cytokines



Crit Care Med 2009; 37:803– 810

In Vitro Cytokine Elimination with CytoSorb™



CytoSorb 10g
Blood Reservoir 24cc
Blood Flow Rate 0.8cc/min

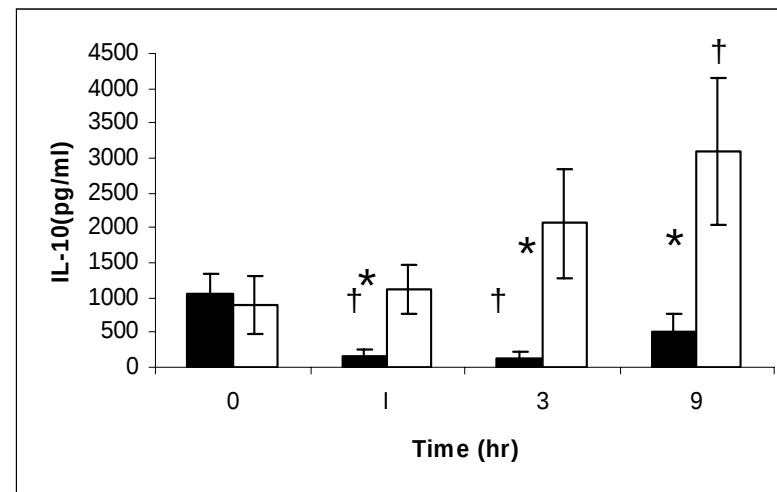
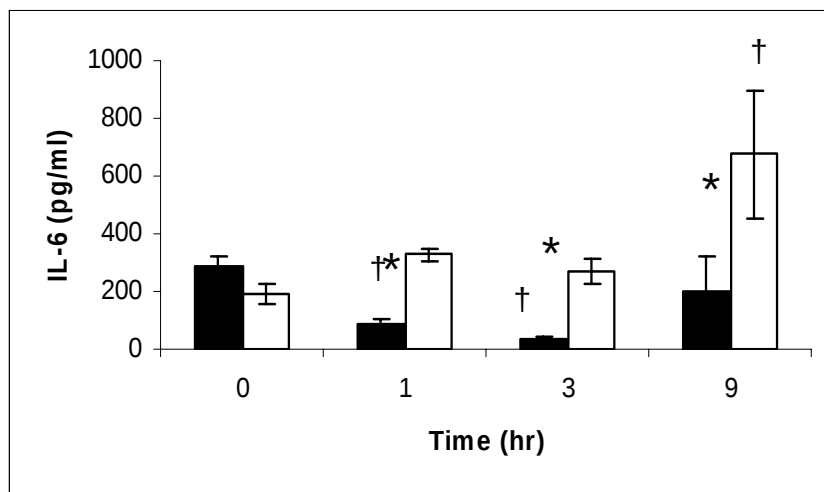
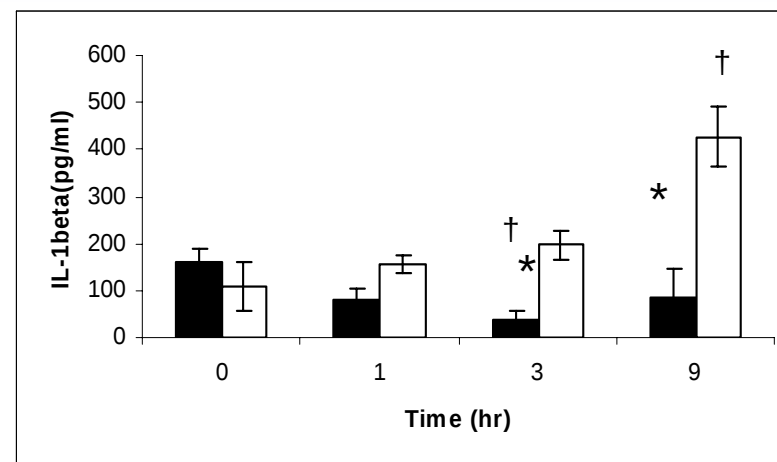
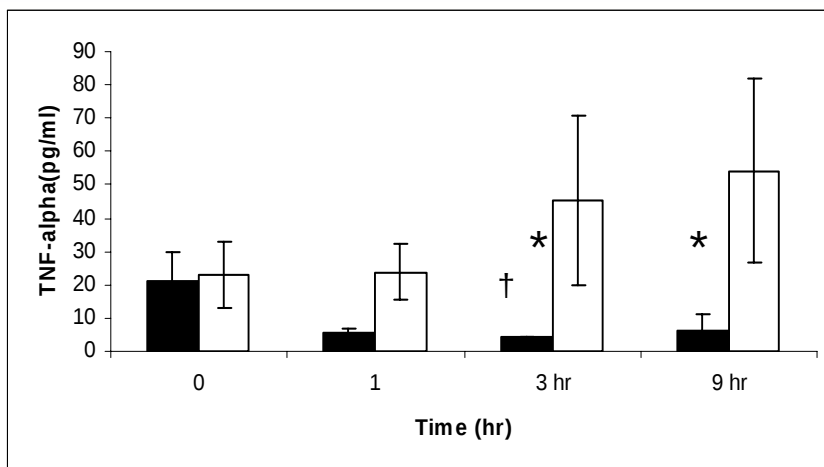
Time 0 Concentrations
TNF: 5,984 pg/ml
IL-10: 9,584 pg/ml
IL-6: 118,284 pg/ml

Hemoadsorption: CLP sepsis



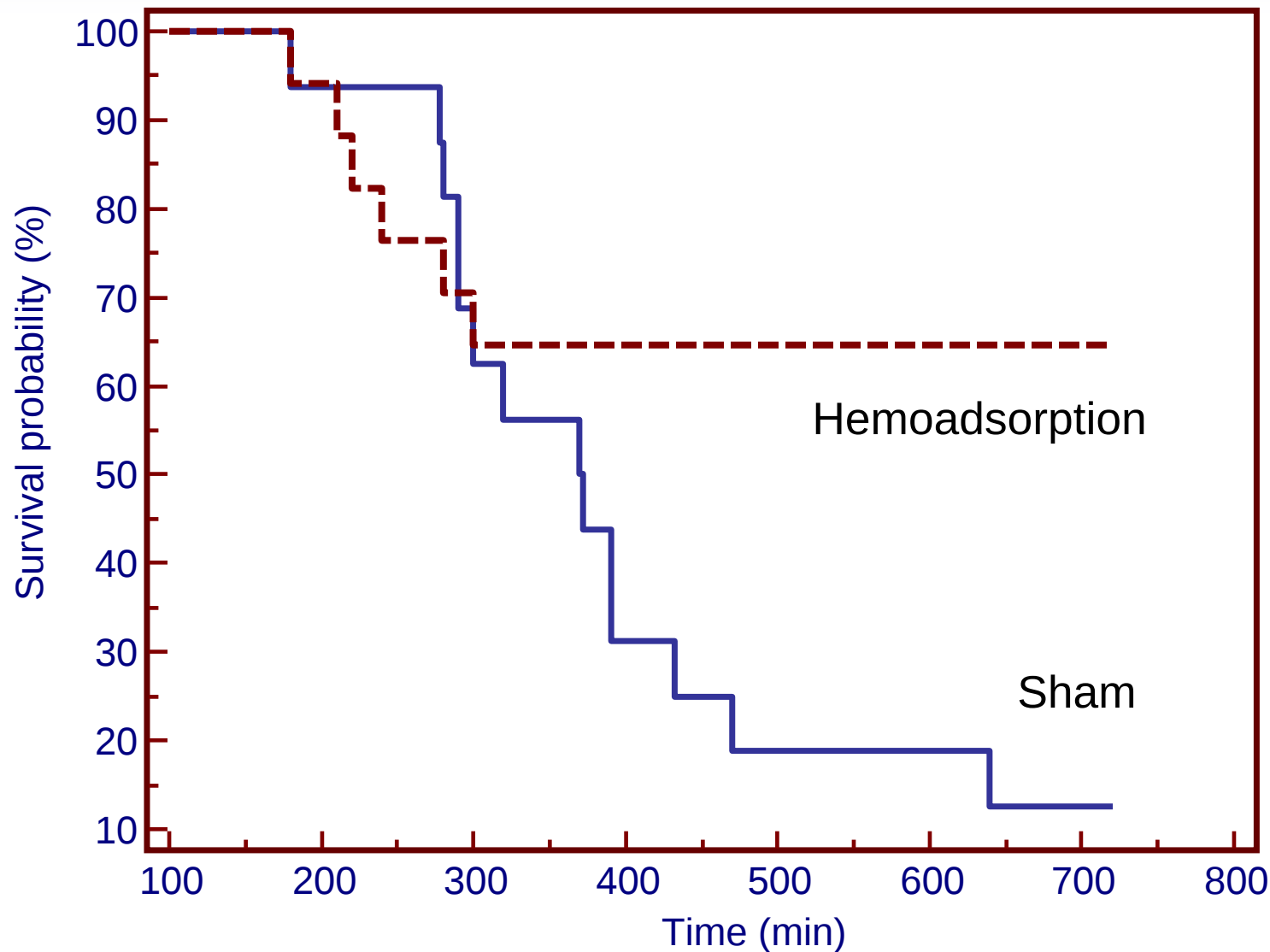
HA

Sham



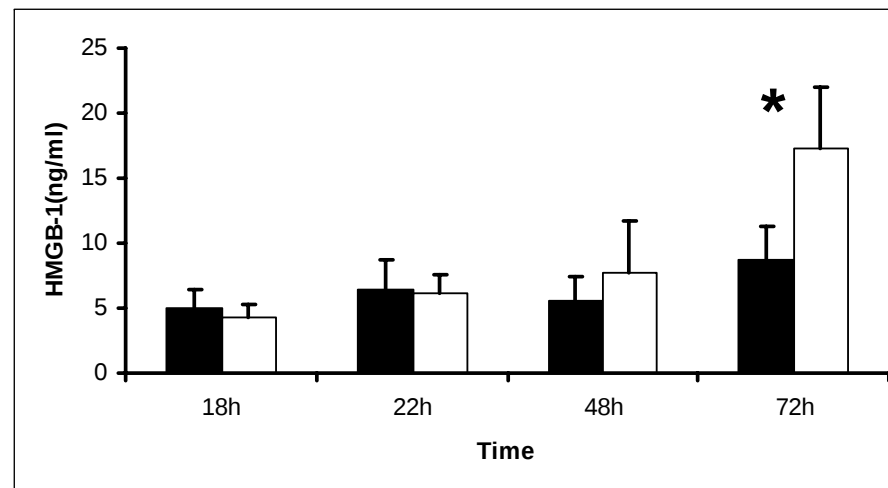
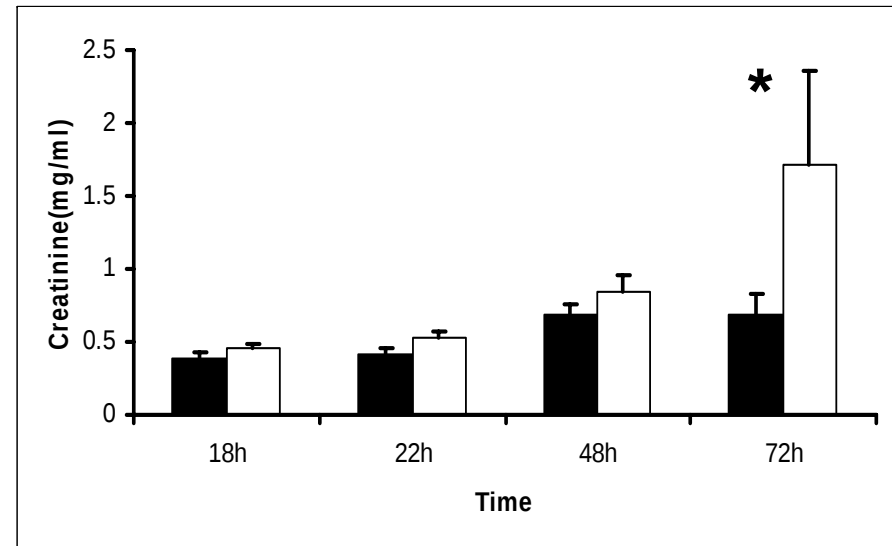
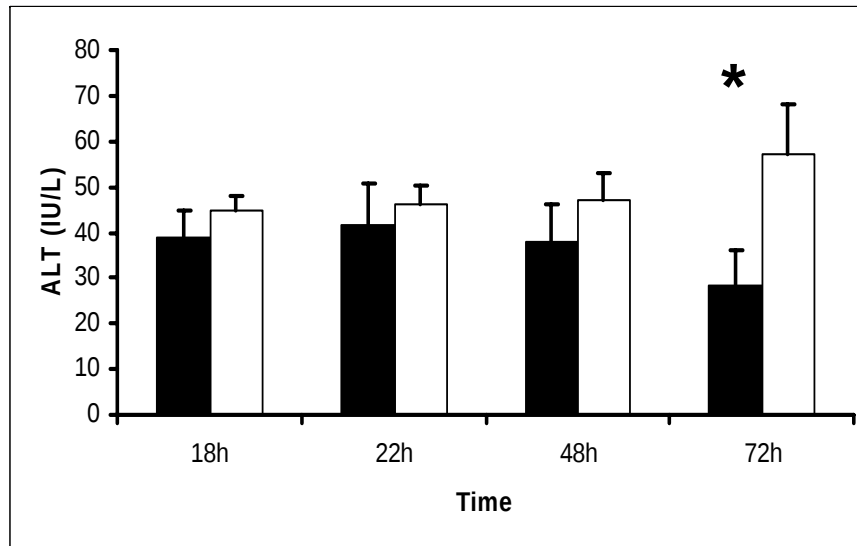
Peng Z, et al. Crit Care Med 2008; 36(5):1573-7

Hemoadsorption improves survival



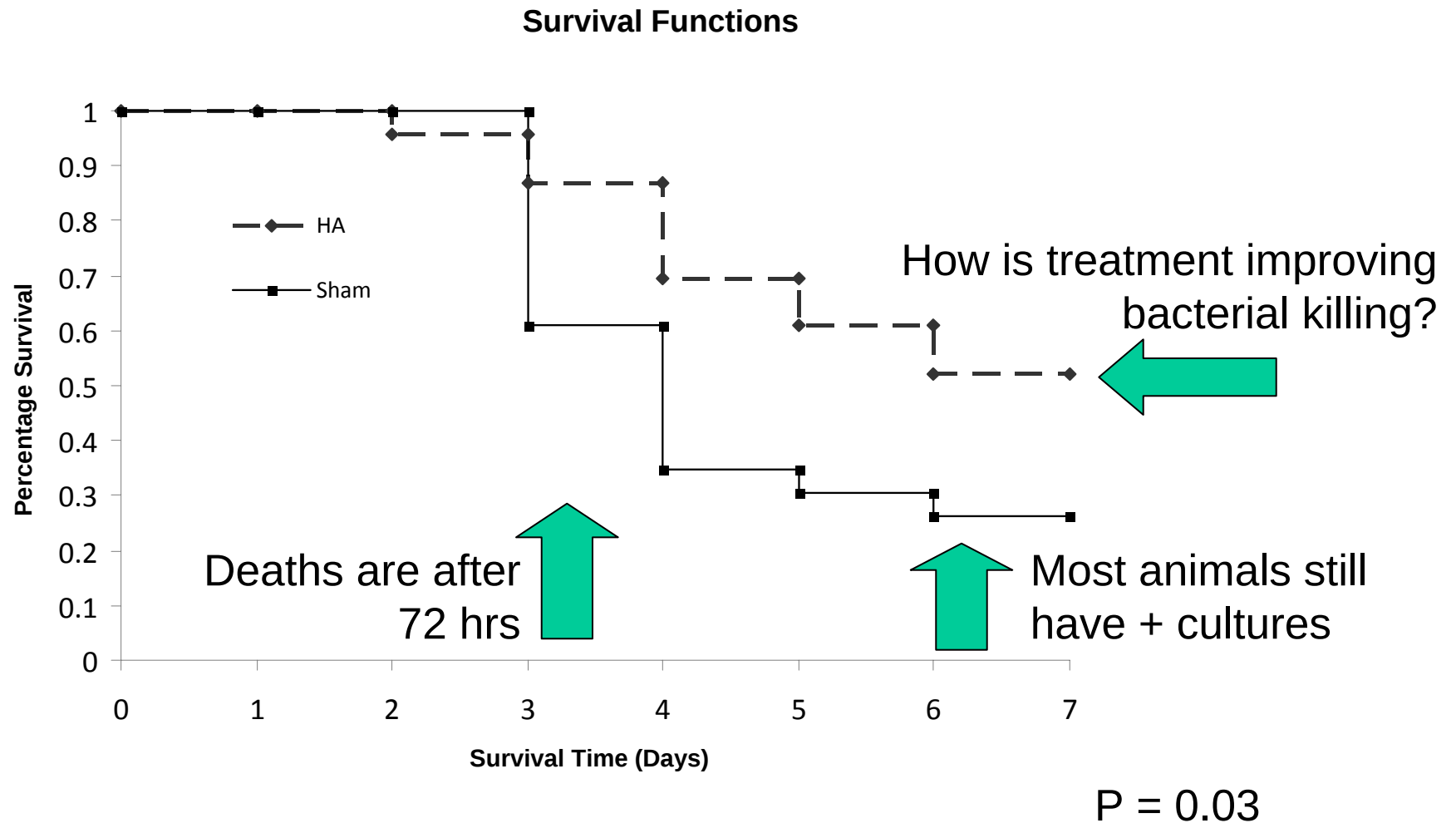
Peng Z, et al. Crit Care Med 2008; 36(5):1573-7

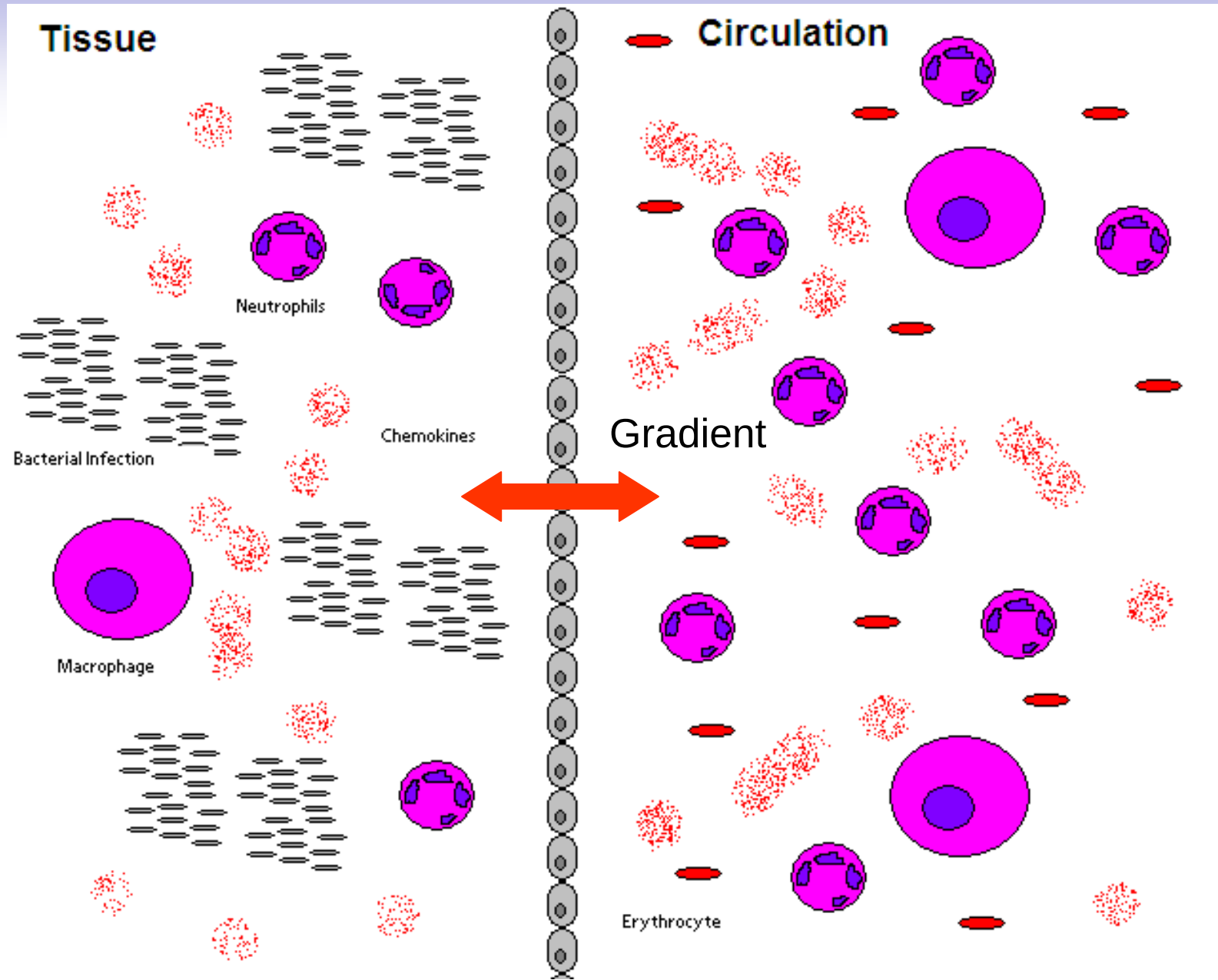
Organ injury is reduced

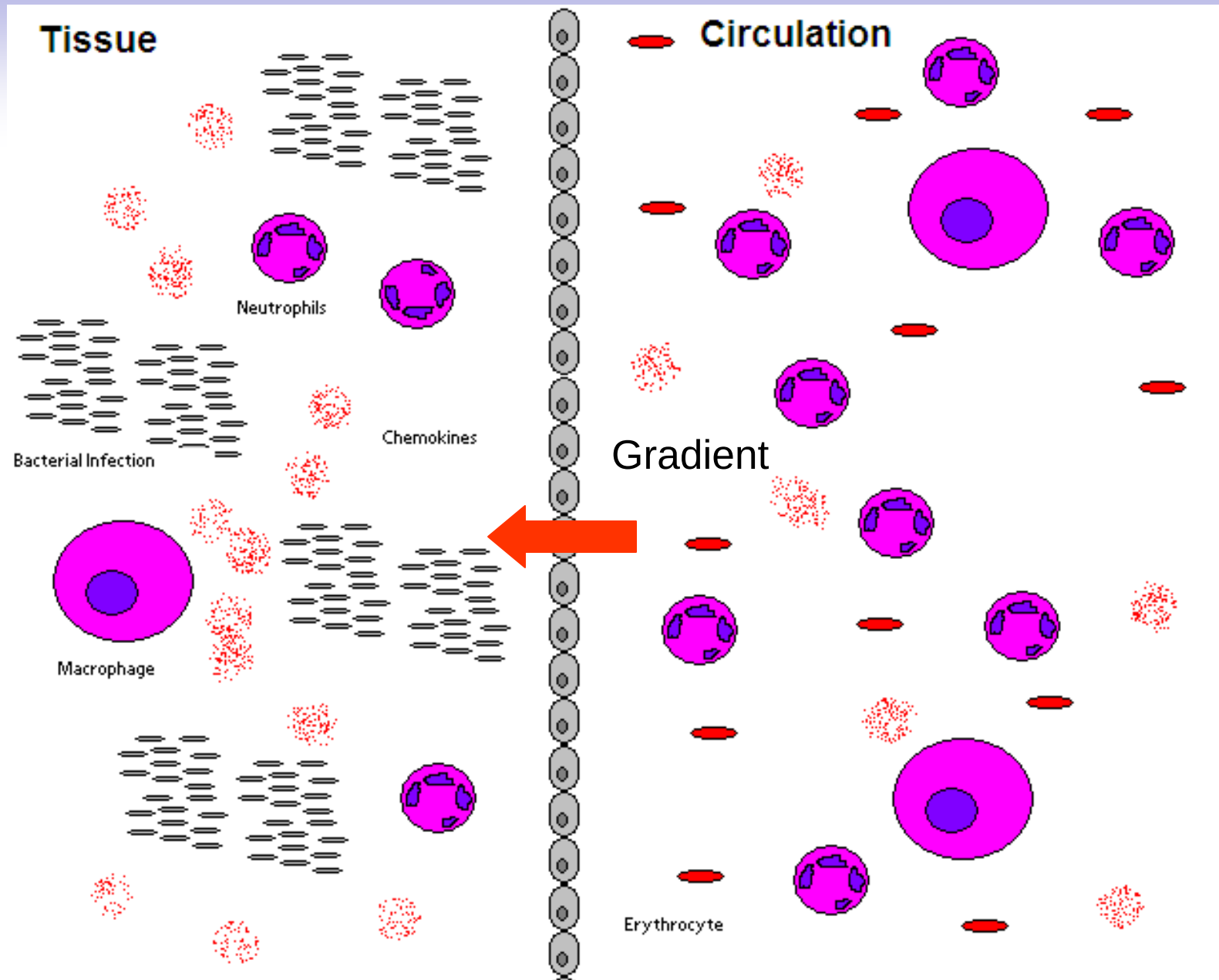


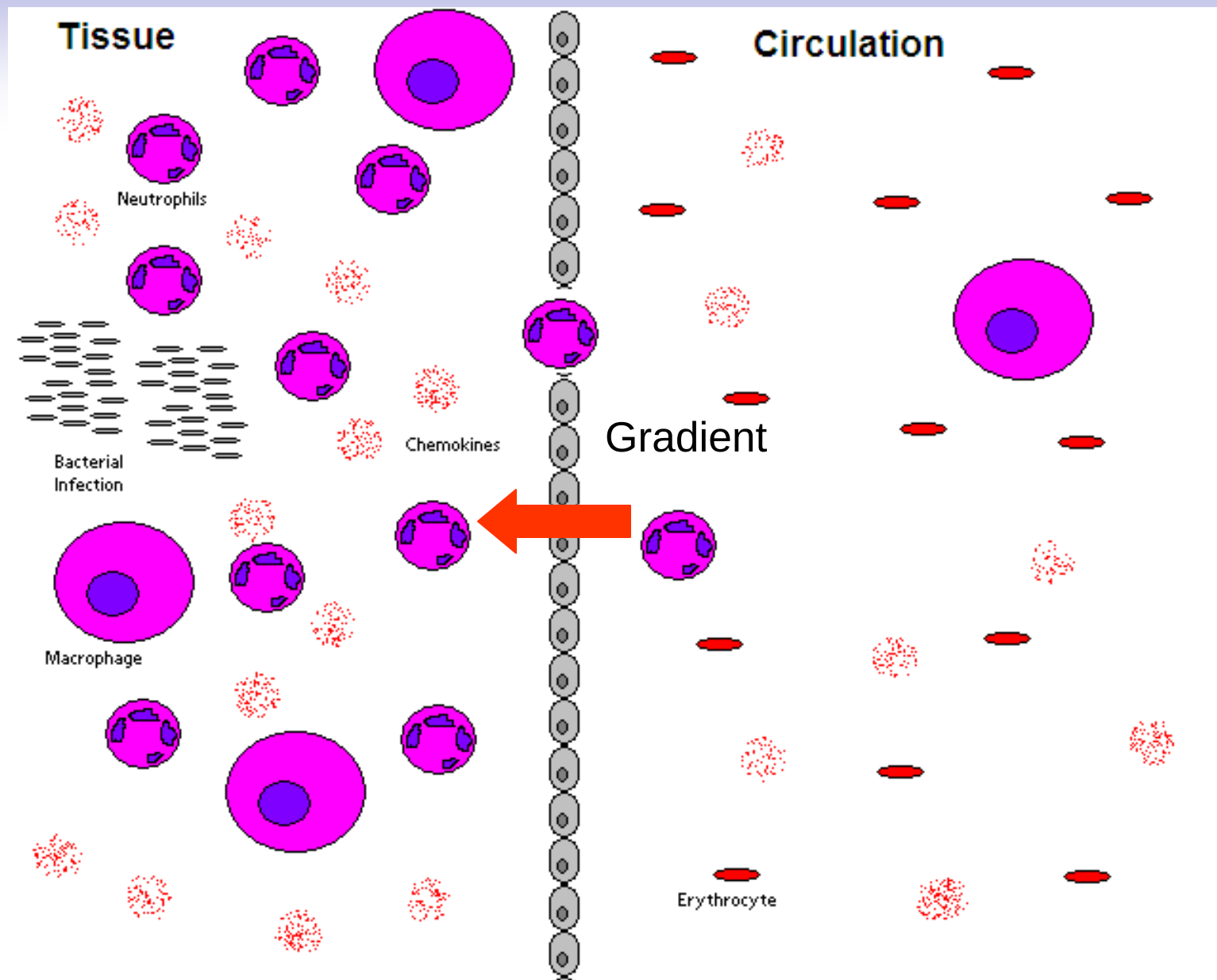
Peng Z, et al.
Submitted

Long term survival

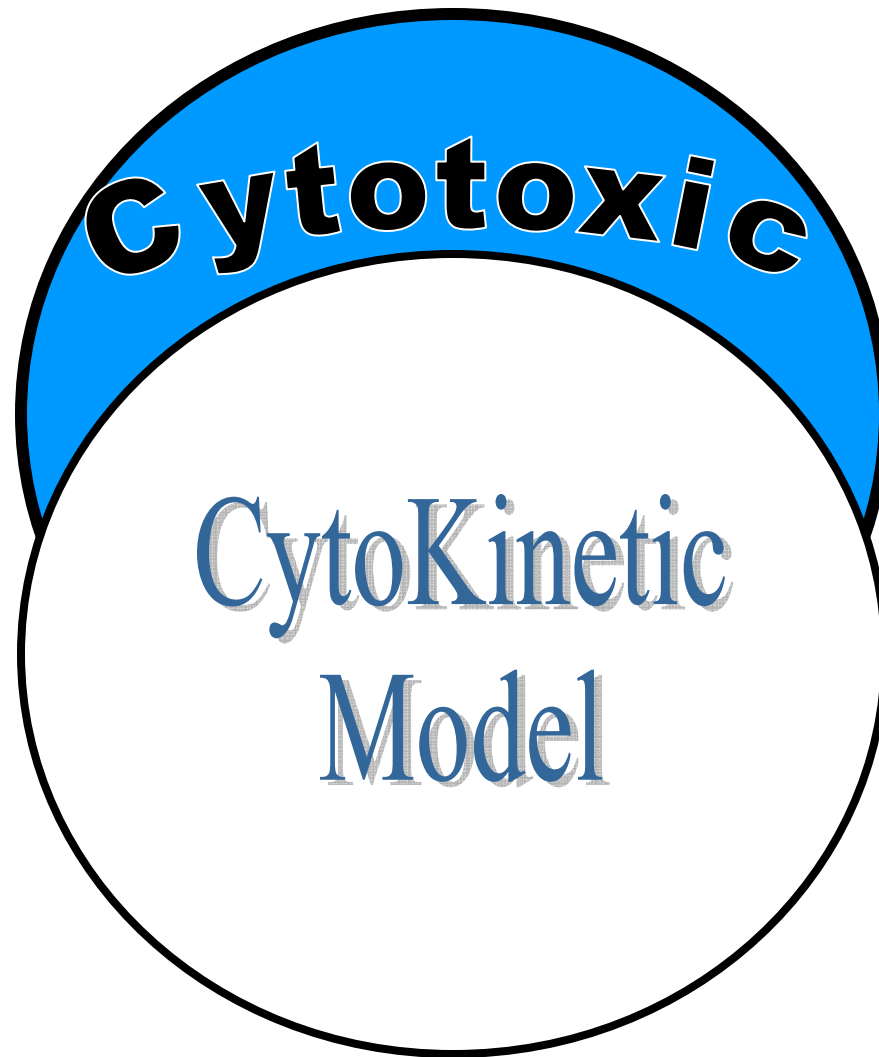








Blood Purification for Sepsis





Conclusions

✚ Inflammation continues for many days after clinical signs/symptoms have abated

- ✚ Immune suppression may last for weeks and may have long term consequences

✚ Goal to have sepsis patients survive

- ✚ Can we bolster the immune system?
- ✚ Can we control secondary infection?

✚ ...and survivors live, function and feel well

- ✚ Rich research agenda
- ✚ Clear opportunities to improve care now

Conclusions



✚ The Cytotoxic model of sepsis is inadequate

- ✚ ...in terms of observations in humans
- ✚ ...to explain the effects seen in animal studies of immunomodulation

✚ The Cytokinetic model explains

- ✚ ...how certain interventions might improve outcome in infection
- ✚ ...fits the existing data from multiple laboratories

✚ Studies of sepsis interventions will need to be designed differently

- ✚ Measurement of enhance immune effector cell function
- ✚ Improving “signal to noise ratio” for systemic vs. local inflammation
- ✚ Studies on bacterial clearance
- ✚ Resistant infection?
- ✚ “Chronic” sepsis?