Sepsis & AKI
are the paradigm changing ?

Amir A. Nassiri, M.D, D.I.U

SBUMS

Tehran, Dec,14, 2023


CONFLICT
OF INTEREST

Overview

- Introduction
- Pathophysiology
- Hemodynamic
- Optimal management (*best way to protect the kidneys ?)*
- Heterogeneity & Sub-Phenotypes
- Biological therapies
- Possible “Mechanical” solutions

Facts

- AKI affects > 10% of Hosp pts & >50% in the ICU
- AKI is lethal problems in the ICU (Mortality 25%)
- AKI is costly (x2-x3 the cost)
- AKI is a sdrm that occurs in the presence of other acute illness
- Sepsis is the most common reason of AKI in the ICU (50% of AKI)
- SA-AKI has different trajectories

Criteria: Patients must have one of the following

- Increase in SCr ≥ 0.3 mg/dL within 48 h
- Increase in SCr ≥ 1.5 × baseline that is known o presumed to have occurred within the past 7 d
- Urine volume < 0.5 mL/kg/h for 6 h

Severity

Stage 1 1.5-1.9 × baseline SCr or ≥ 0.3-mg/dL increase in baseline SCr

Stage 2 2.0-2.9 × baseline SCr

Stage 3 3.0 × baseline SCr or increase in SCr to ≥ 4.0 or renal replacement therapy (eg, dialysis)

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

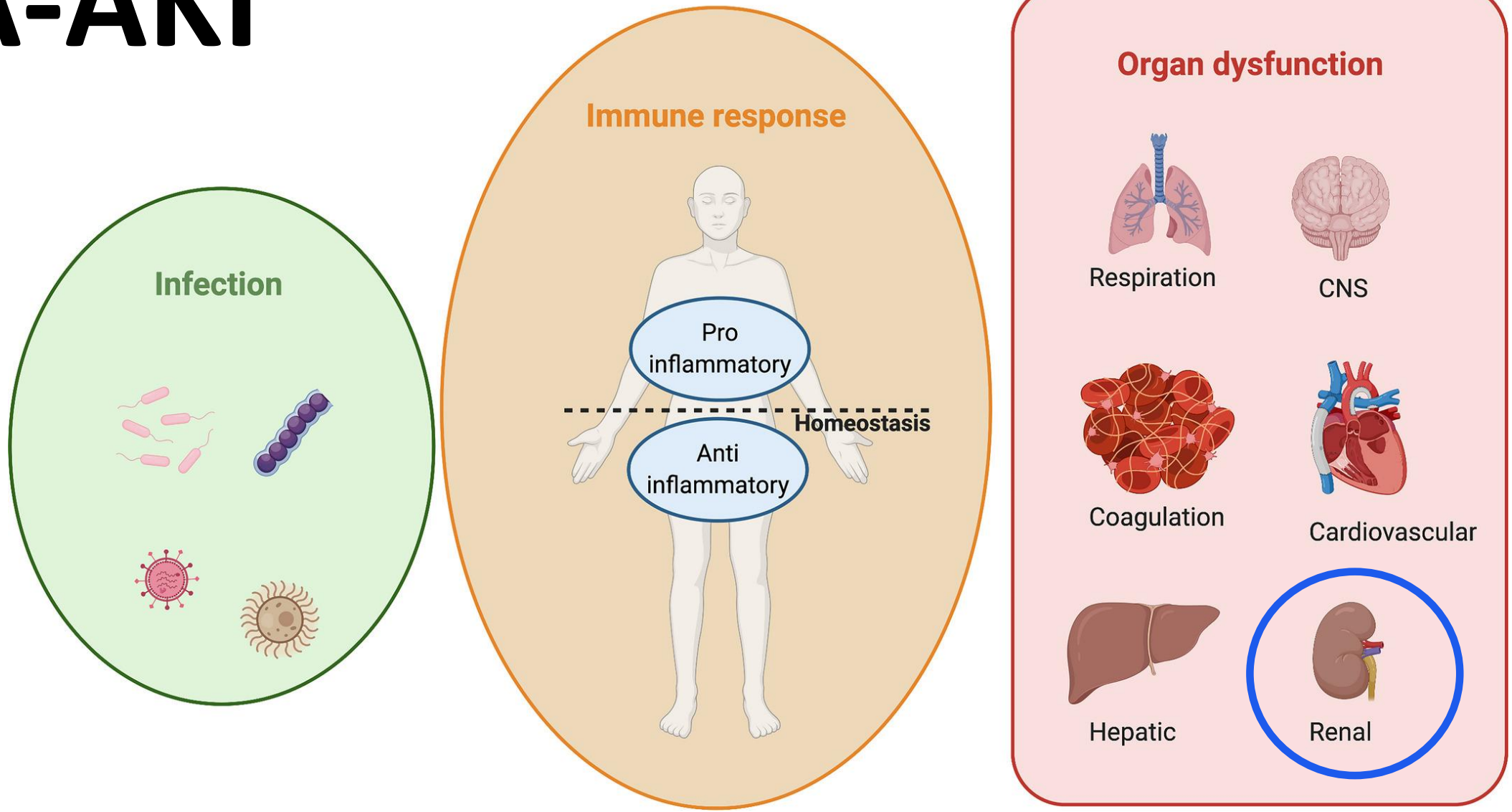
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

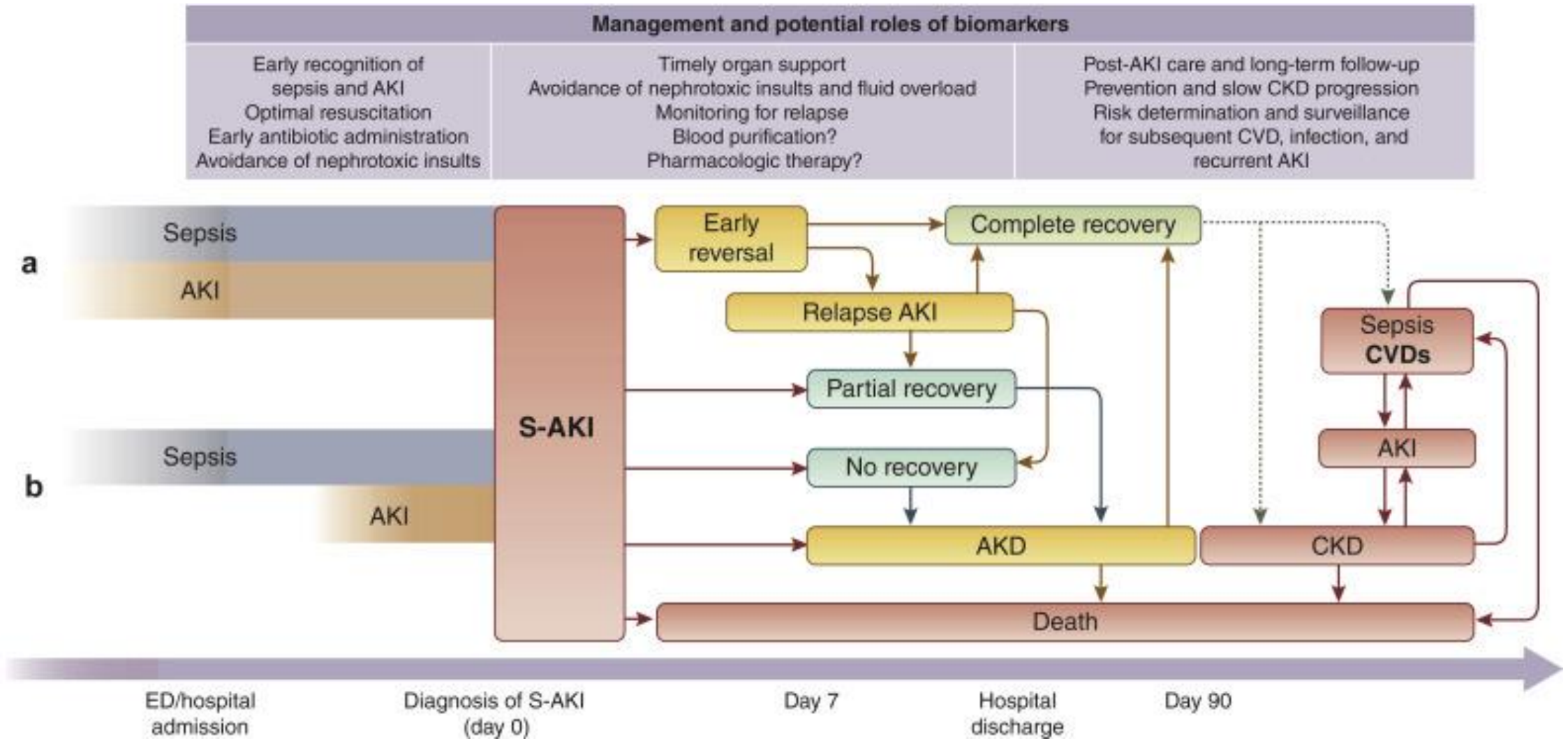
- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.

- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

SA-AKI

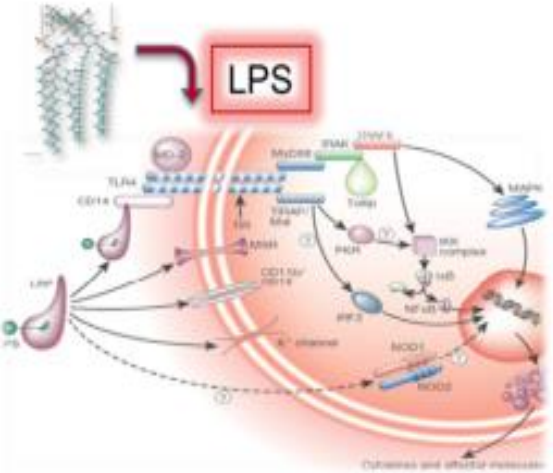

Infection
Immune response
Pro inflammatory
Homeostasis
Anti inflammatory
Organ dysfunction
Respiration
CNS
Coagulation
Cardiovascular
Hepatic
Renal

Sepsis & AKI

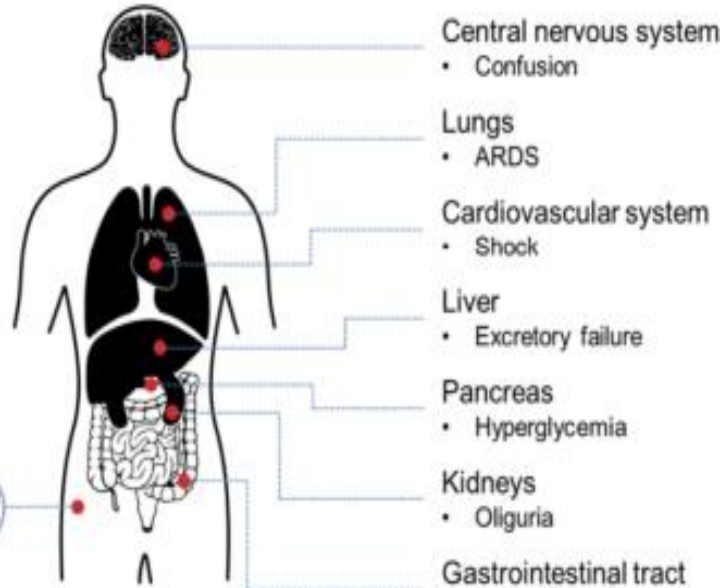

Management and potential roles of biomarkers
Early recognition of sepsis and AKI
Optimal resuscitation
Early antibiotic administration
Avoidance of nephrotoxic insults
Timely organ support
Avoidance of nephrotoxic insults and fluid overload
Monitoring for relapse
Blood purification?
Pharmacologic therapy?
Post-AKI care and long-term follow-up
Prevention and slow CKD progression
Risk determination and surveillance for subsequent CVD, infection, and recurrent AKI
a
Sepsis
AKI
b
Sepsis
AKI
S-AKI
Early reversal
Complete recovery
Relapse AKI
Partial recovery
No recovery
AKD
Death
Sepsis CVDs
AKI
CKD
ED/hospital admission
Diagnosis of S-AKI (day 0)
Day 7
Hospital discharge
Day 90

Sepsis & AKI are Dynamic w/ different trajectories

Infection >>> Immuno response >>> Organ Damage



Humoral
Cellular
Effectors



Central nervous system
- Confusion

Lungs
- ARDS

Cardiovascular system
- Shock

Liver
- Excretory failure

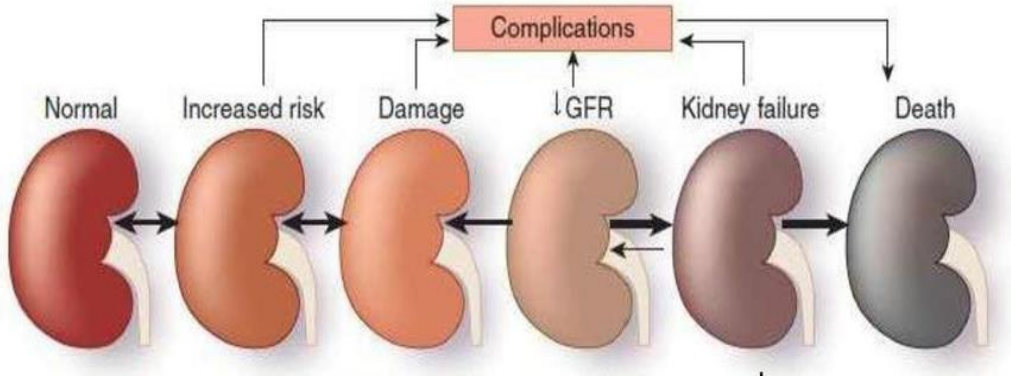
Pancreas
- Hyperglycemia

Kidneys
- Oliguria

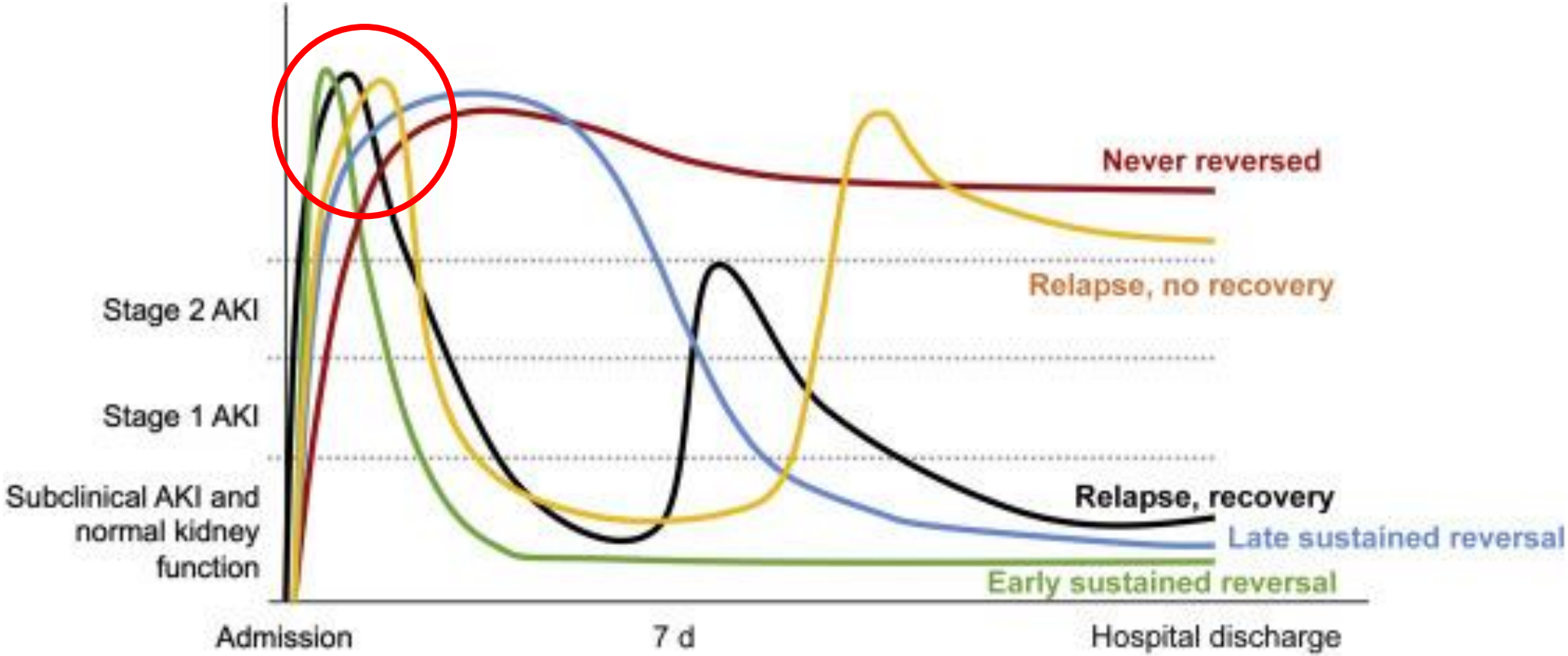
Gastrointestinal tract
- Loss of barrier function

LPS is opsonized and recognised by monocytes through CD14 leading to endothelial cell activation

Microcirculation
- Microvascular thrombosis



SA-AKI Trajectories



Sepsis-Associated Acute Kidney Disease

ProCESS Trial

1,341 Patients with Septic Shock

+ Biomarkers at 0, 6, 24 hours

598 Patients with Stage 2, 3 AKI

Early Death within 7 days (19.9%)

AKD (26.9%)

Early Reversal (53.2%)

Never Reversed (90.7%)
Late Reversal (9.3%)

Sustained Reversal (85.9%)
Relapse, Recovery (5.1%)
Relapse, No Recovery (9.0%)

Only 9.3% of patients with AKD recovered at hospital discharge

Prediction of Developing AKD at Day 7

Clinical Model	**AUC = 0.71**
Clinical Model + Urinary TIMP-2*IGFBP7 (6 hours)	**AUC = 0.72**
Clinical Model + Urinary NGAL (6 hours)	**AUC = 0.74**

AUC, area under the curve; IGFBP7, insulin-like growth factor binding protein 7; NGAL, neutrophil gelatinase-associated lipocalin; ProCESS, Protocolized Care for Early Septic Shock; TIMP-2, tissue inhibitor of metalloproteinase-2.

CONCLUSION:

AKD is common after septic shock. Existing AKI biomarkers have limited utility for predicting AKD but might be useful together with clinical variables.

KI REPORTS
KIReports.org

Peerapornratana et al, 2020

Current kidney function parameters overestimate kidney tissue repair in reversible experimental kidney disease

kidney INTERNATIONAL

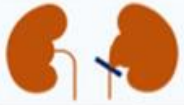
ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods:

Experimental models:

a) 2,8-dihydroxyadenine nephropathy

b) reversible unilateral ureteral obstruction

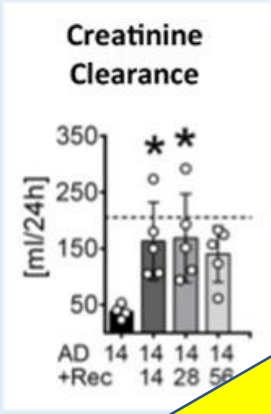


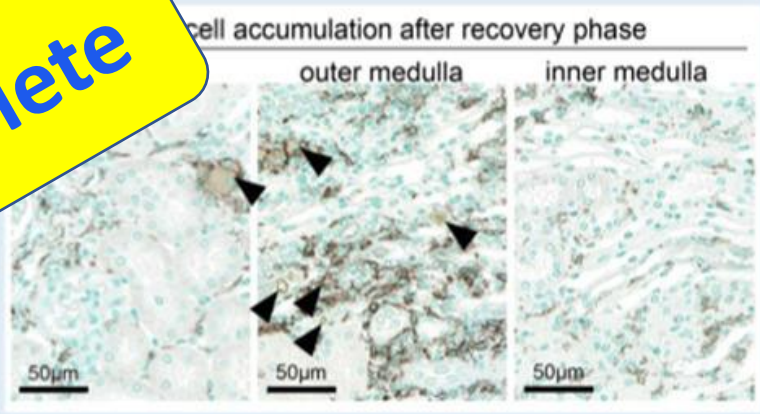
- *reversibility & regeneration*
- *therapeutic high fluid intake*

Results:

During recovery from CKD:

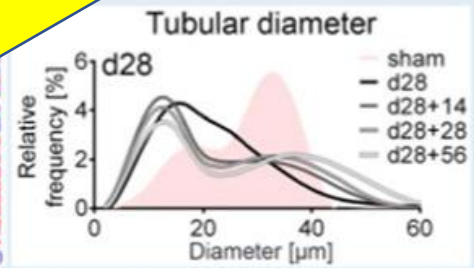
- kidney function improves
- tissue injury and fibrosis persist, particularly in the medulla





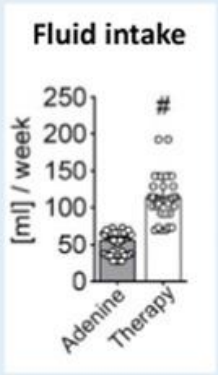
recovery is almost always incomplete

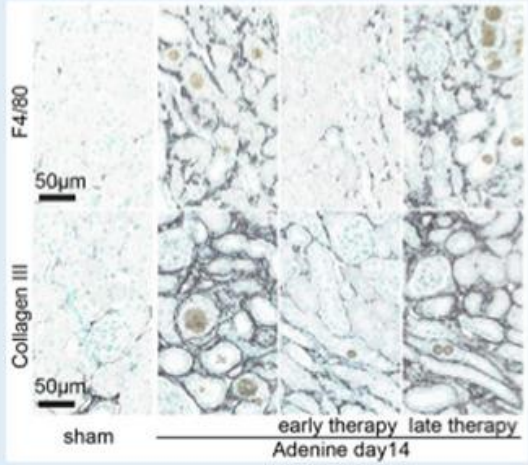
...ical
...bular fate:
..., dilation,
...phy or atrophy



Therapeutical increase of drinking volume:

- only effective in early but not advanced CKD
- effects are poorly reflected by kidney function





Klinkhammer et al., 2022

clinically invisible

CONCLUSION: *Recovery after crystal- or obstruction-induced CKD is characterized by ongoing tissue injury, fibrosis, and nephron loss, which is not reflected by standard kidney function parameters.*

the Inconvenient truth is that:

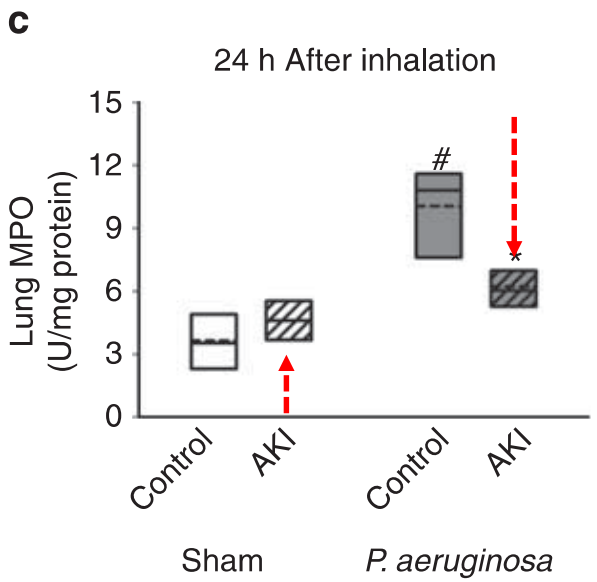
we can not recognize kidney “damage” clinically…until it is too late

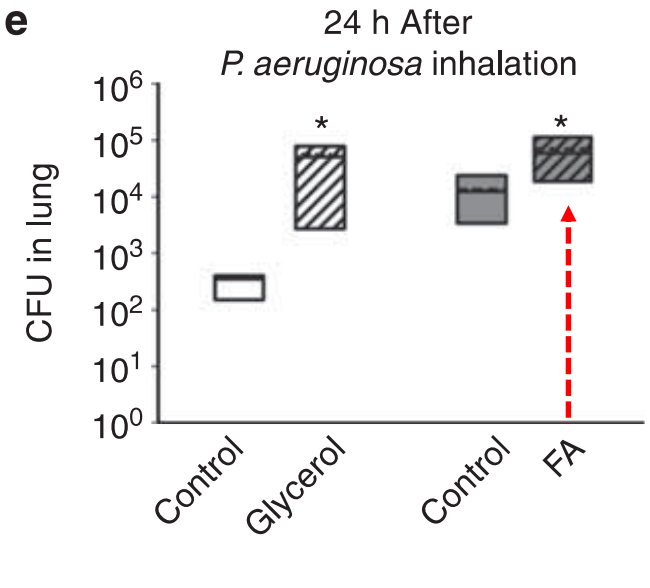
Kellum 2020

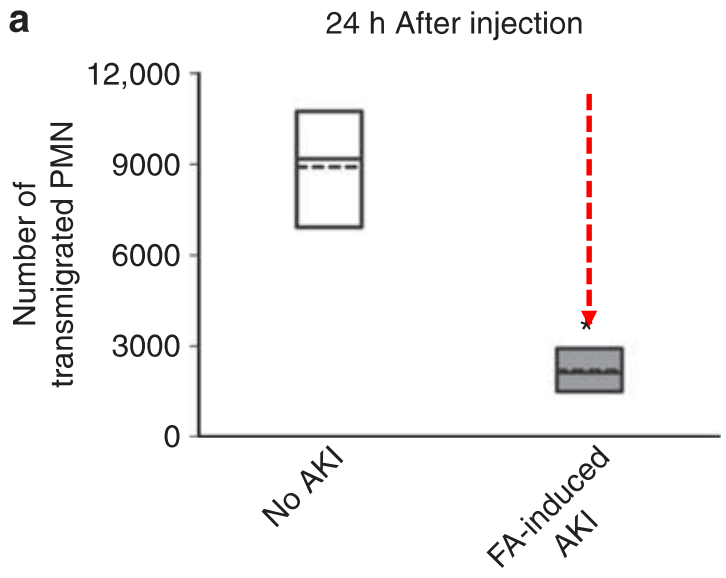
Differential effects of kidney–lung cross-talk during acute kidney injury and bacterial pneumonia

Kai Singbartl[1], Jeffery V. Bishop[1], Xiaoyan Wen[1], Raghavan Murugan[1], Saurabh Chandra[1], Marie-Dominique Filippi[2] and John A. Kellum[1]

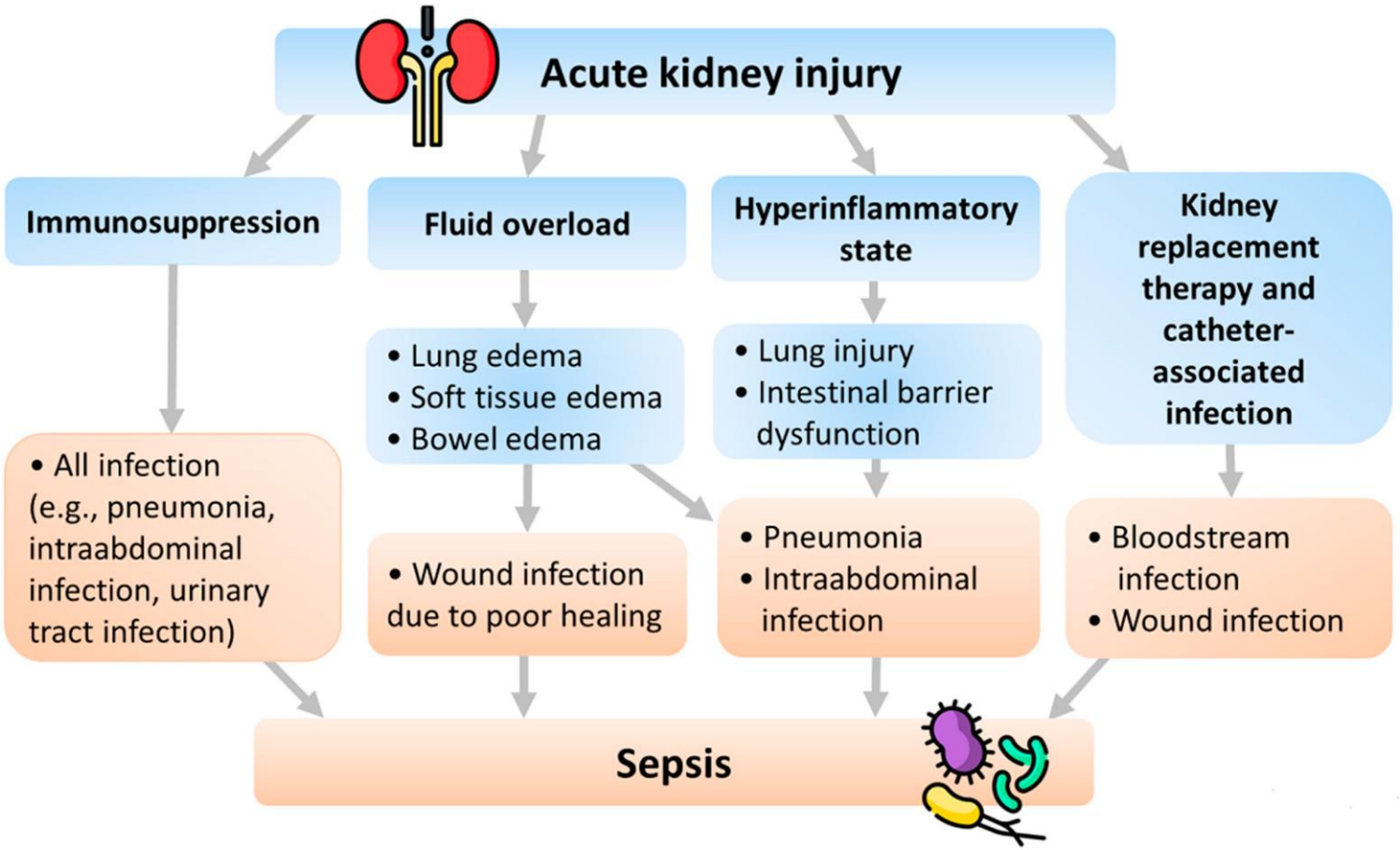
[1]*Department of Critical Care Medicine, CRISMA Center, University of Pittsburgh, Pittsburgh, Pennsylvania, USA and*







having AKI suffices to be susceptible to sepsis



even short periods of hypotension of < 5 min were independent associated w/ the onset of AKI

Time MAP <55 mmHg (min)	Adjusted Odds Ratio (95% CI)			
	Acute Kidney Injury	Myocardial Injury	Cardiac Complication	30-day Mortality
0	Referent			
1–5	1.18 (1.06–1.31)	1.30 (1.06–1.58)	1.35 (1.15–1.58)	1.16 (0.91–1.46)
6–10	1.19 (1.03–1.39)	1.47 (1.13–1.93)	1.46 (1.17–1.83)	1.16 (0.84–1.60)
11–20	1.32 (1.11–1.56)	1.79 (1.33–2.39)	1.50 (1.16–1.94)	1.26 (0.89–1.80)
>20	1.51 (1.24–1.84)	1.82 (1.31–2.55)	1.95 (1.46–2.60)	1.79 (1.21–2.65)

Estimates adjusted for patient age, sex, Charlson comorbidity index, emergency procedure status, type of surgery, preoperative hemoglobin, decrement in hemoglobin concentration, estimated blood loss, and volume of erythrocyte transfusions.

MAP = mean arterial pressure.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

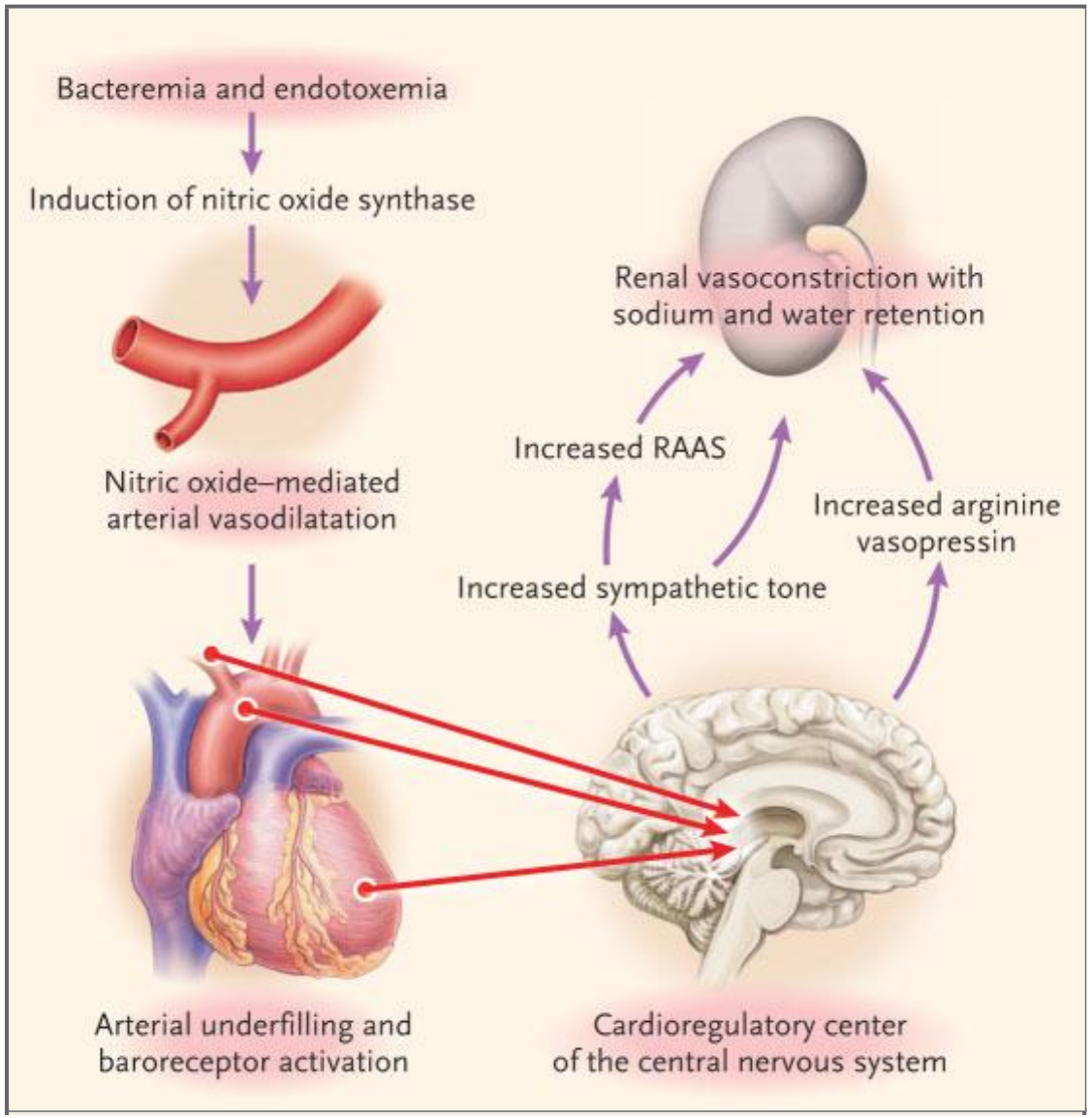
Acute Renal Failure and Sepsis

Robert W. Schrier, M.D., and Wei Wang, M.D.

ACUTE RENAL FAILURE OCCURS IN APPROXIMATELY 19 PERCENT OF patients with moderate sepsis, 23 percent with severe sepsis, and 51 percent with septic shock when blood cultures are positive (Tables 1 and 2).[1,2] A progressive increase in the acute respiratory distress syndrome also occurs with moderate and severe sepsis and septic shock. In the United States, an estimated 700,000 cases of sepsis occur each year, resulting in more than 210,000 deaths; this number accounts for 10 percent of all deaths annually and exceeds the number of deaths due to myocardial infarction.[3] The combination of acute renal failure and sepsis is associated with a 70 percent mortality, as compared with a 45 percent mortality among patients with acute renal failure alone. Thus, the combination of sepsis and acute renal failure constitutes a particularly serious medical problem in the United States.[4] Substantial progress has been made toward understanding the mechanisms whereby sepsis is associated with a high incidence of acute renal failure. Moreover, recently identified clinical interventions may be able to decrease the occurrence of acute renal failure and sepsis and the high associated mortality.

From the Department of Medicine, University of Colorado Health Sciences Center, Denver. Address reprint requests to Dr. Schrier at the Department of Medicine, University of Colorado Health Sciences Center, 4200 E. 9th Ave., Box C-281, Denver, CO 80262, or at robert.schrier@uchsc.edu.

N Engl J Med 2004;351:159-69.



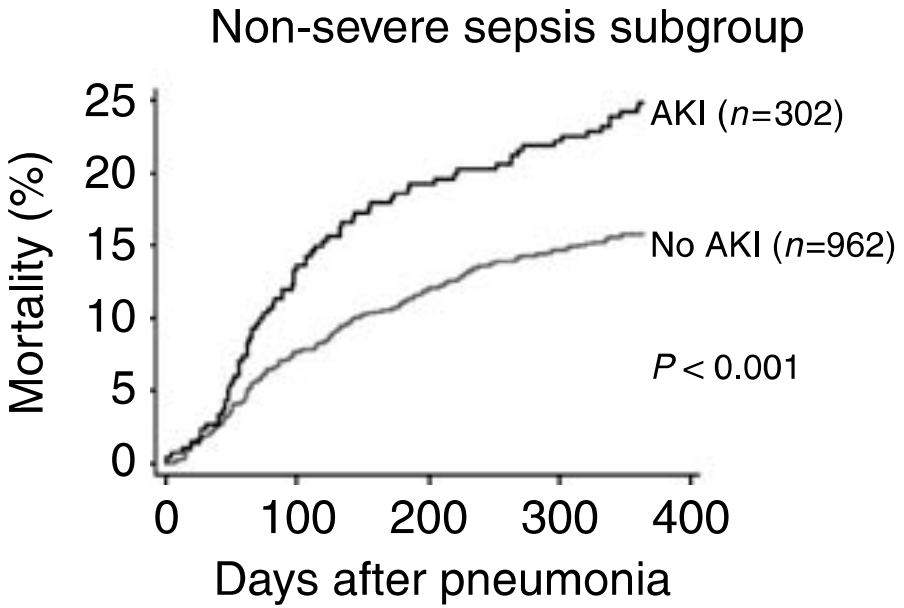
see commentary on page 485

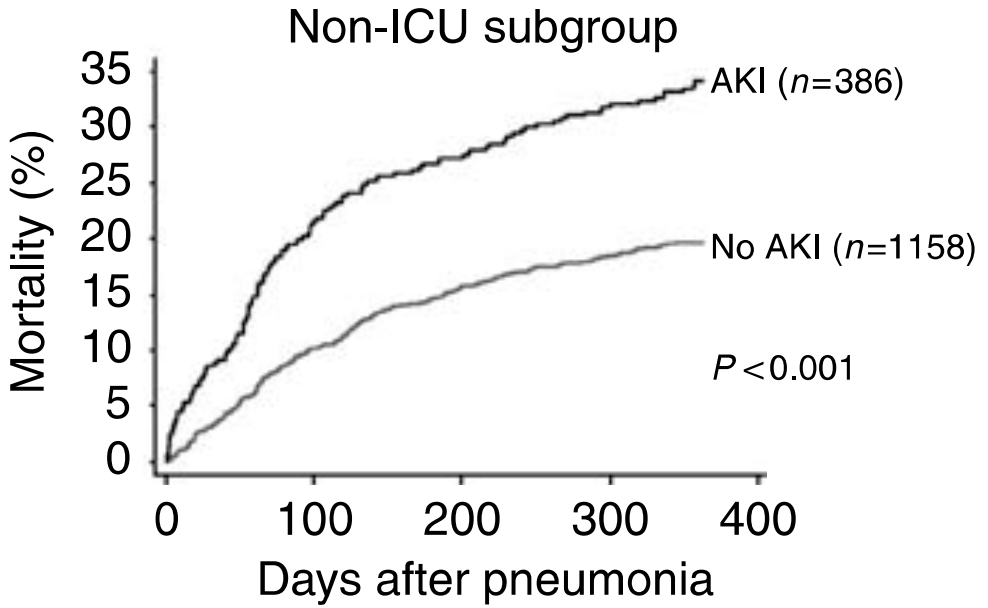
Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival

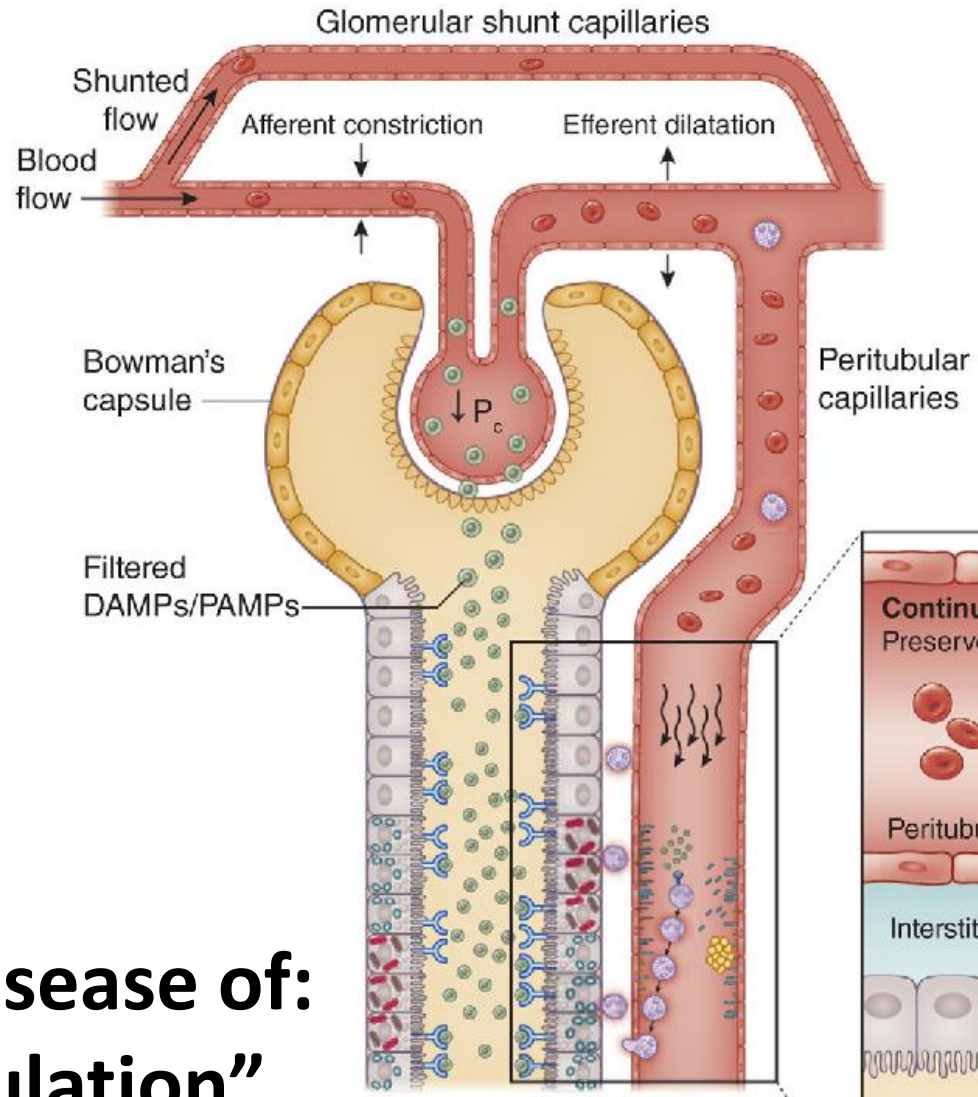
Raghavan Murugan[1], Vijay Karajala-Subramanyam[1], Minjae Lee[1,2], Sachin Yende[1], Lan Kong[1,2], Melinda Carter[1], Derek C. Angus[1] and John A. Kellum[1], on behalf of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Investigators

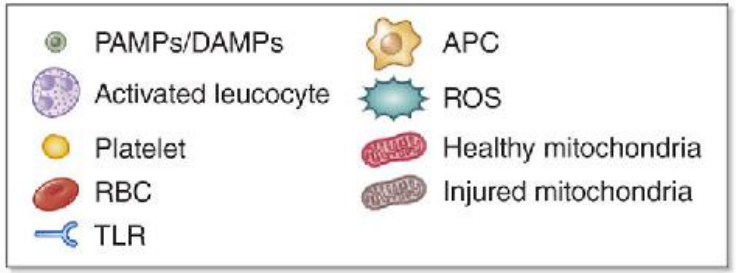
[1]*The CRISMA Laboratory, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA and* [2]*Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, USA*

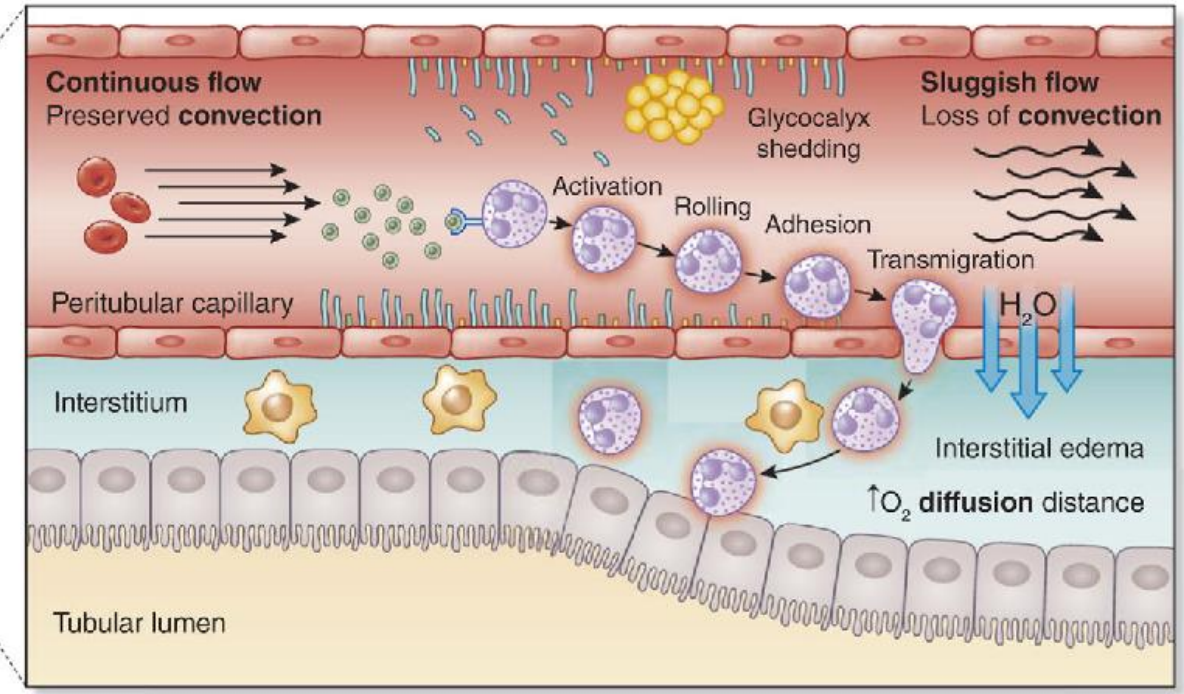
when there is AKI the mortality is higher but hypotension (severe sepsis) is not necessary for AKI in pts w/ pneumonia











SA-AKI is a disease of:

"micro-circulation"

"endothelium"

"mitochondrion"

Nephrol Dial Transplant (2014) 0: 1–7
doi: 10.1093/ndt/gfu052

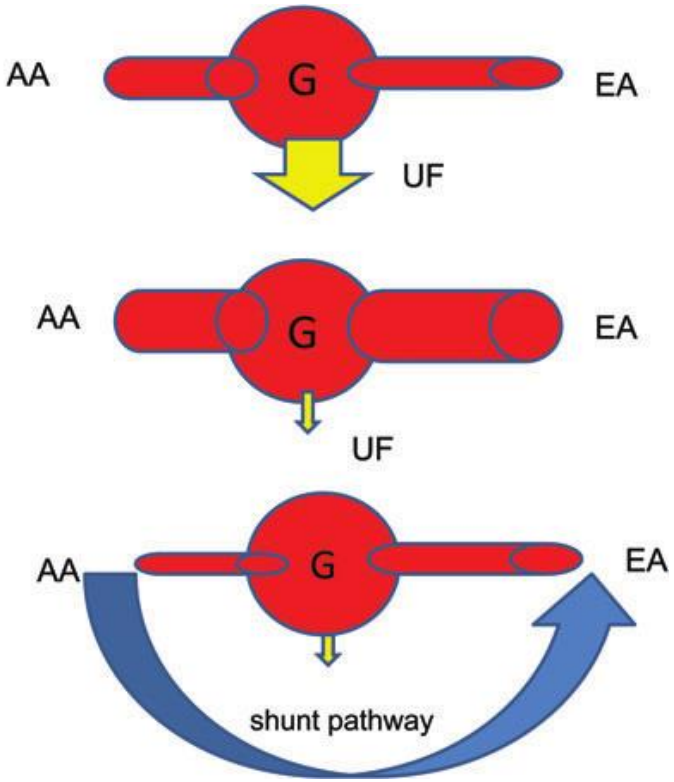
ndt
Nephrology Dialysis Transplantation

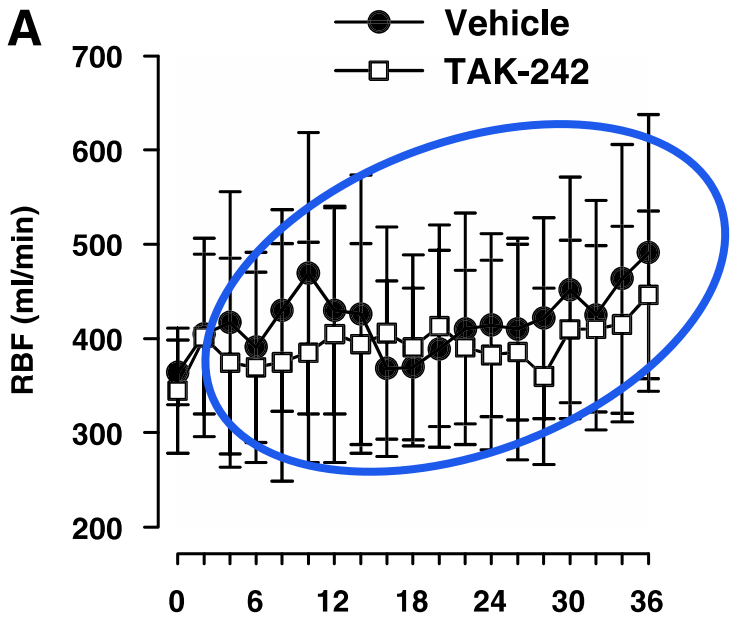
Editorial Review

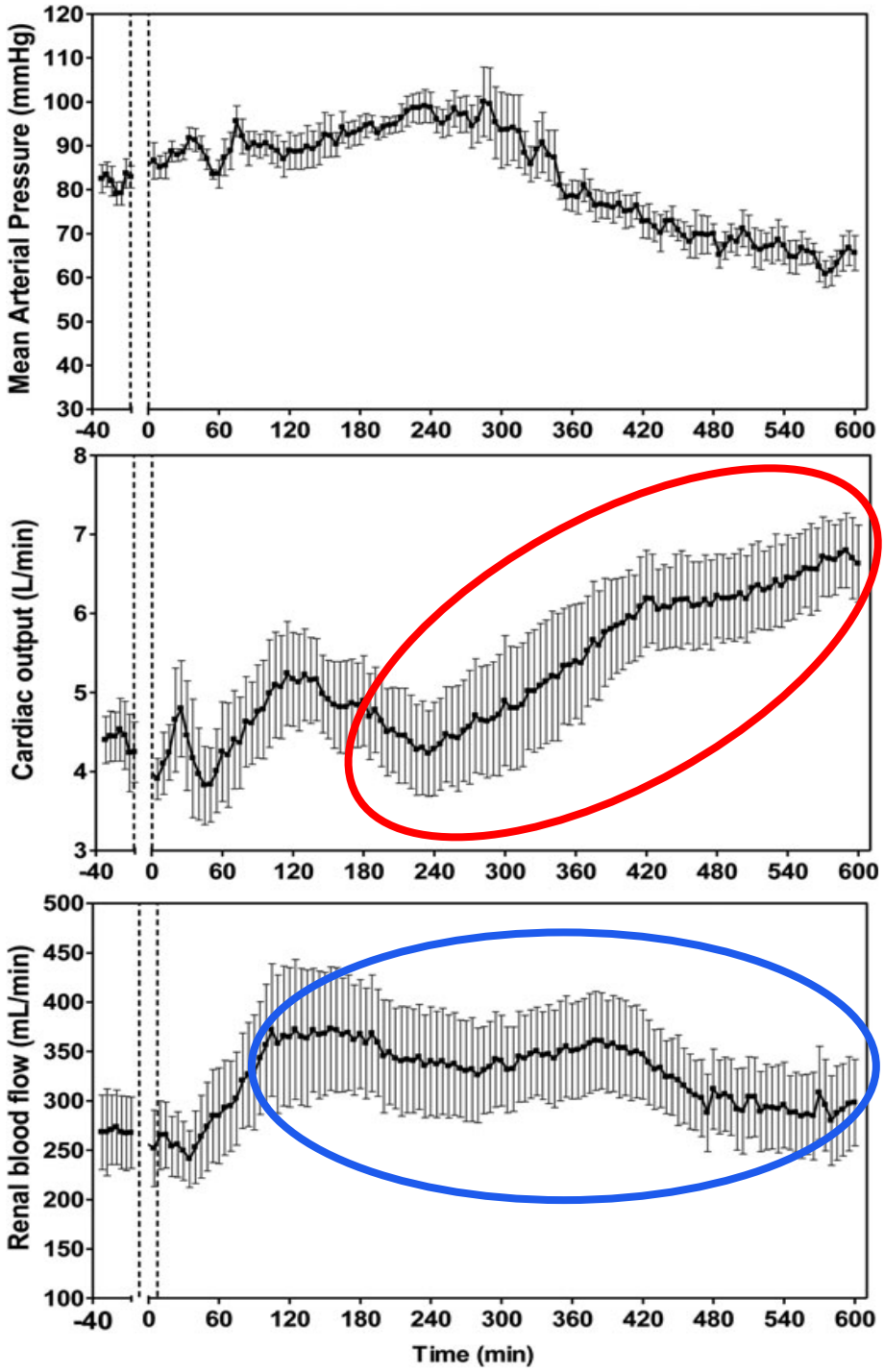
Glomerular haemodynamics, the renal sympathetic nervous system and sepsis-induced acute kidney injury

Paolo Calzavacca[1], Clive N. May[2] and Rinaldo Bellomo[3,4]

- Human sepsis is characterized by a 'hyper-dynamic' state with a high cardiac output;







Renal Histopathology During Experimental Septic Acute Kidney Injury and Recovery*

Christoph Langenberg, MD, PhD[1]; Glenda Gobe, PhD[2]; Sally Hood, MSc[1]; Clive N. May, PhD[1]; Rinaldo Bellomo, MD, PhD[3]

Objectives: Our understanding of septic acute kidney injury is limited. We therefore assessed renal histopathological changes induced by septic acute kidney injury and their evolution during recovery.

Design: Prospective experimental study.

Setting: Physiology Research Institute.

Subjects: Twenty-two Merino sheep.

Intervention: We induced septic acute kidney injury by continuous IV infusion of *Escherichia coli*. We studied histology, immunohistochemistry, markers of apoptosis, and expression of nitric oxide synthase isoforms and hypoxia-inducible factor-1α. Analysis was performed on kidneys from normal sheep, sheep with septic acute kidney injury, and sheep after recovery from septic acute kidney injury.

Measurements and Main Results: In normal, septic, and recovery sheep, respectively, serum creatinine was (median) 82 (interquartile range, 70–85), 289 (171–477), and 70 (51–91) μmol/L and renal blood flow was 270±42, 653±210, and 250±49 mL/min. There were no histological differences between baseline, acute kidney injury, and recovery sheep. There was no evidence of macrophage or myofibroblast infiltration, no evidence of caspase-3 cleavage to suggest activation of apoptotic pathways, and no increase in neutrophil gelatinase-associated lipocalin to suggest tubular injury. Similarly, quantification of apoptosis revealed no differences between the normal and septic groups (normal: median, 3; interquartile range, 0–5 cells per visual field and septic acute kidney injury: median, 3.5; interquartile range, 0–8 cells per visual field; $p = 0.618$), but in the recovery group, there was increased apoptosis (median, 14; interquartile range, 4–34 cells per visual field; $p = 0.002$). Expression of all nitric oxide synthase subtypes increased significantly in the renal cortex during septic acute kidney injury but tended to decrease in the medulla. Medullary hypoxia-inducible factor gene expression decreased from 1.00 (95% CI, 0.74–1.36) to 0.26 (95% CI, 0.09–0.76) in recovery ($p = 0.0106$). Both inducible nitric oxide synthase and neuronal nitric oxide synthase expressions correlated with renal blood flow.

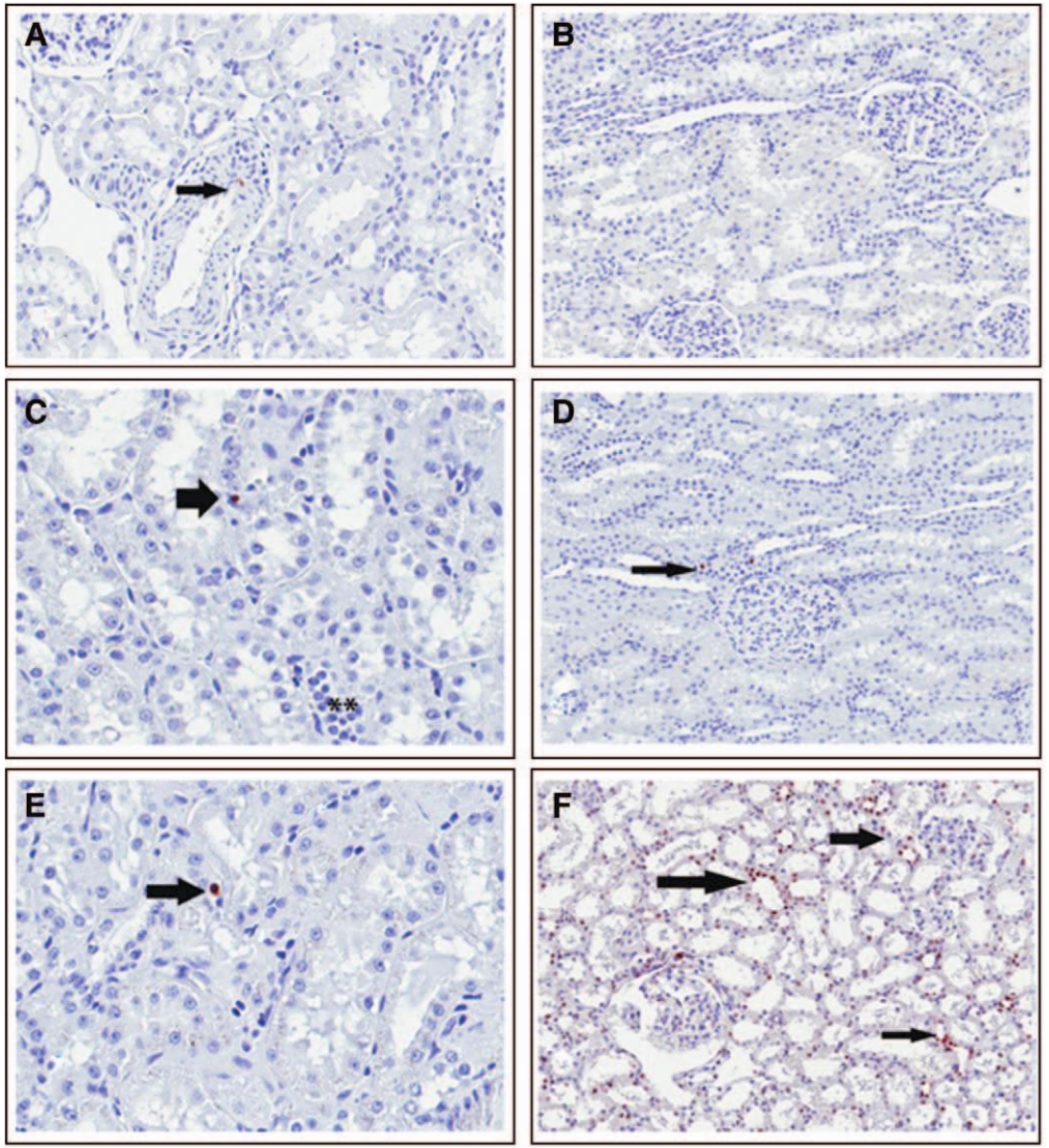
Conclusion: The lack of any tubular injury or increased apoptosis, the increased expression of all cortical nitric oxide synthase isoforms, and the link between inducible nitric oxide synthase and neuronal nitric oxide synthase with renal blood flow suggest in this experimental model that severe sepsis acute kidney injury can develop in the absence of histological or immunohistological changes and may be functional in nature. (*Crit Care Med* 2014; 42:e58–e67)

Key Words: acute kidney injury; apoptosis; histology; nitric oxide synthase; renal blood flow; sepsis

***See also p. 225.**

[1]Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia.

[2]University of Queensland School of Medicine, Princess Alexandra Hospital, QLD Australia.



severe SA-AKI w/ some “gentle” histologic changes

Research

Open Access

The histopathology of septic acute kidney injury: a systematic review

Christoph Langenberg[1,2], Sean M Bagshaw[1,3], Clive N May[1] and Rinaldo Bellomo[1,4]

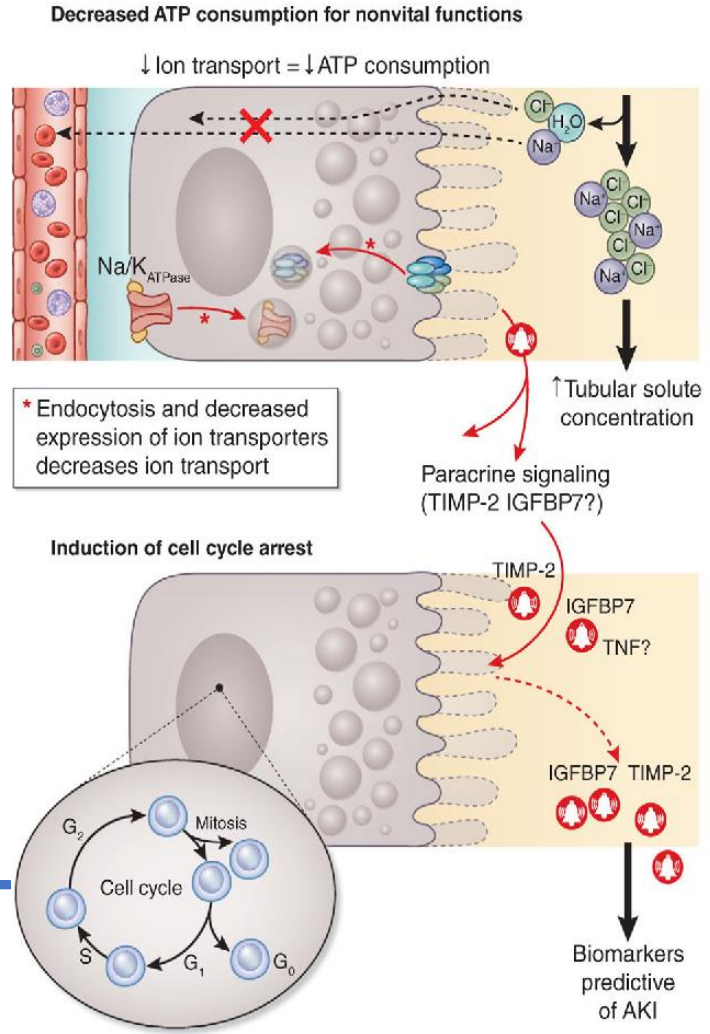
Human studies

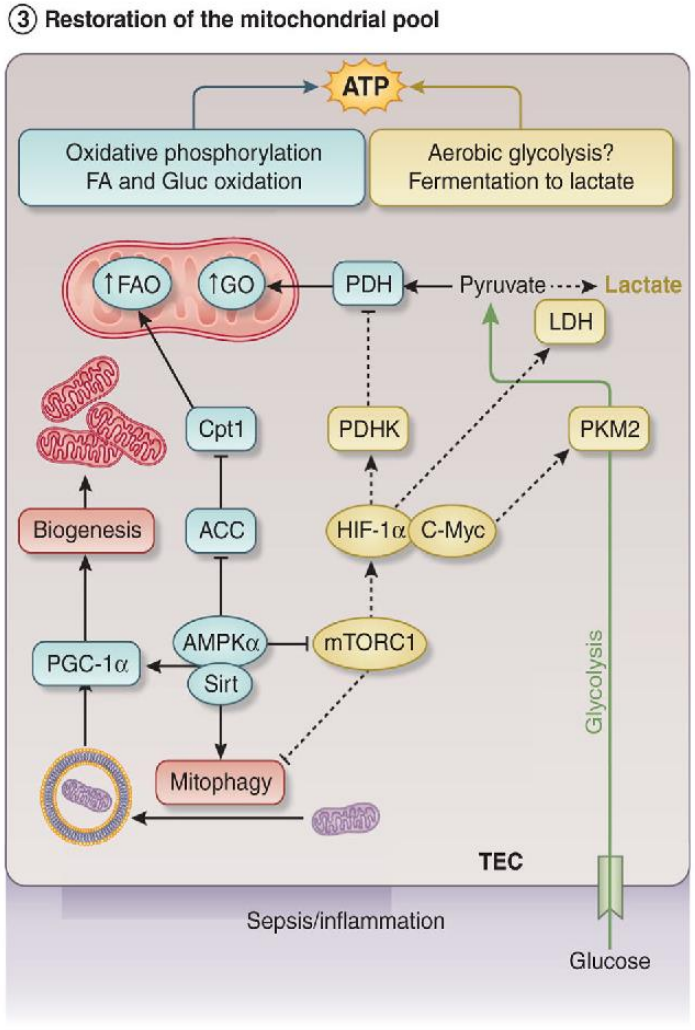
Study	Cause	Acute kidney injury definition	Method	Cases of AKI/number of patients (%)	Acute tubular necrosis (%)
Hotchkiss and colleagues [10]	Sepsis/septic shock	Serum creatinine >2 mg/dl and urine output <20 ml/kg/hour × 6 hours	Postmortem	12/20 (60)	1 (5)
Sato and colleagues [13]	Sepsis	Not available	Postmortem	6/6 (100)	1 (17)
Mustonen and colleagues [9]	Sepsis/shock/ hypovolemia	Not available	Biopsy	57/57 (100)	4 (7)
Rosenberg and colleagues [12]	Sepsis	Serum creatinine >3.5 mg/dl and urine/plasma osmolality >1	Biopsy	1/1 (100)	0 (0)
Zappacosta and Ashby [14]	Sepsis	Not available	Biopsy	1/1 (100)	0 (0)
Diaz de Leon and colleagues [11]	Severe sepsis	Serum creatinine, urine output, urine/plasma osmolality (not specified)	Biopsy	107/332 (32)	20 (50)[a]

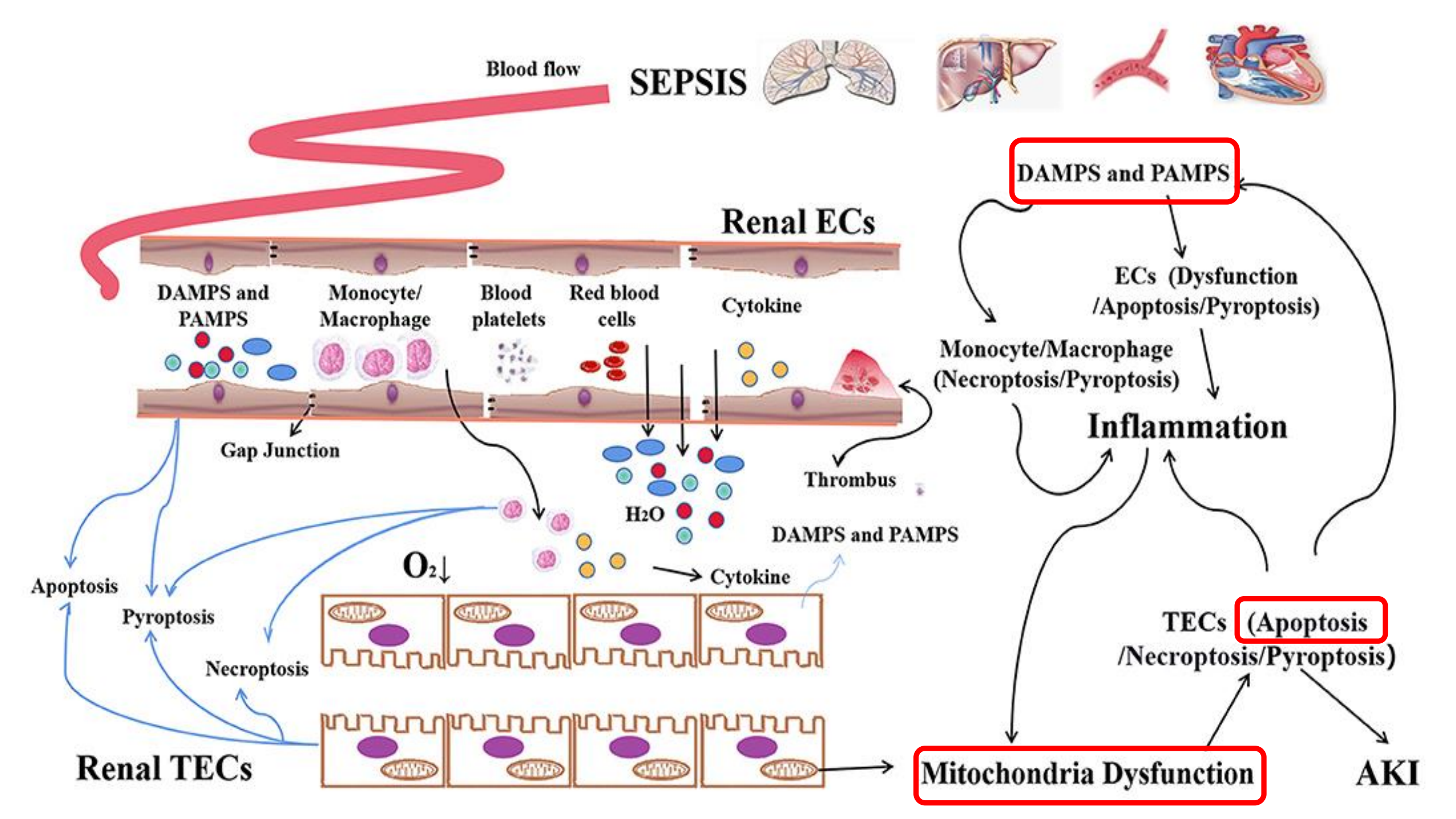
[a]Renal biopsy was only performed in 40 patients (37% of the acute kidney injury (AKI) cohort, 12% of the total cohort).

cell cycle arrest. >>> energy saving & avoiding DNA damage
the necessary functions for membrane potential, like Na/K ATPase, remains

Adaptation

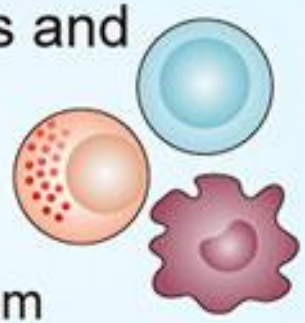





Blood flow
SEPSIS
Renal ECs
DAMPS and PAMPS
Monocyte/ Macrophage
Blood platelets
Red blood cells
Cytokine
Gap Junction
Thrombus
H2O
DAMPS and PAMPS
O2↓
Cytokine
Apoptosis
Pyroptosis
Necroptosis
Renal TECs
DAMPS and PAMPS
ECs (Dysfunction /Apoptosis/Pyroptosis)
Monocyte/Macrophage (Necroptosis/Pyroptosis)
Inflammation
TECs (Apoptosis /Necroptosis/Pyroptosis)
Mitochondria Dysfunction
AKI

Aestivation or *"Summer Sleep"*

Dysregulated immune responses and systemic inflammation

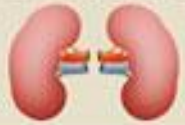


- Release of IL-1β, IL-6, IL-8, IL-18, TNF-α, chemokines and ROS
- Activation of the complement system
- Activation of the NLRP3 inflammasome

Dysfunction of renal microvascular endothelial cells

- Increase of microvascular permeability mediated by the VEGF/VEGFR2, ANG2/Tie2 and S1P/S1PR1 signaling pathways
- Shedding of endothelial glycocalyx

Sepsis-induced AKI

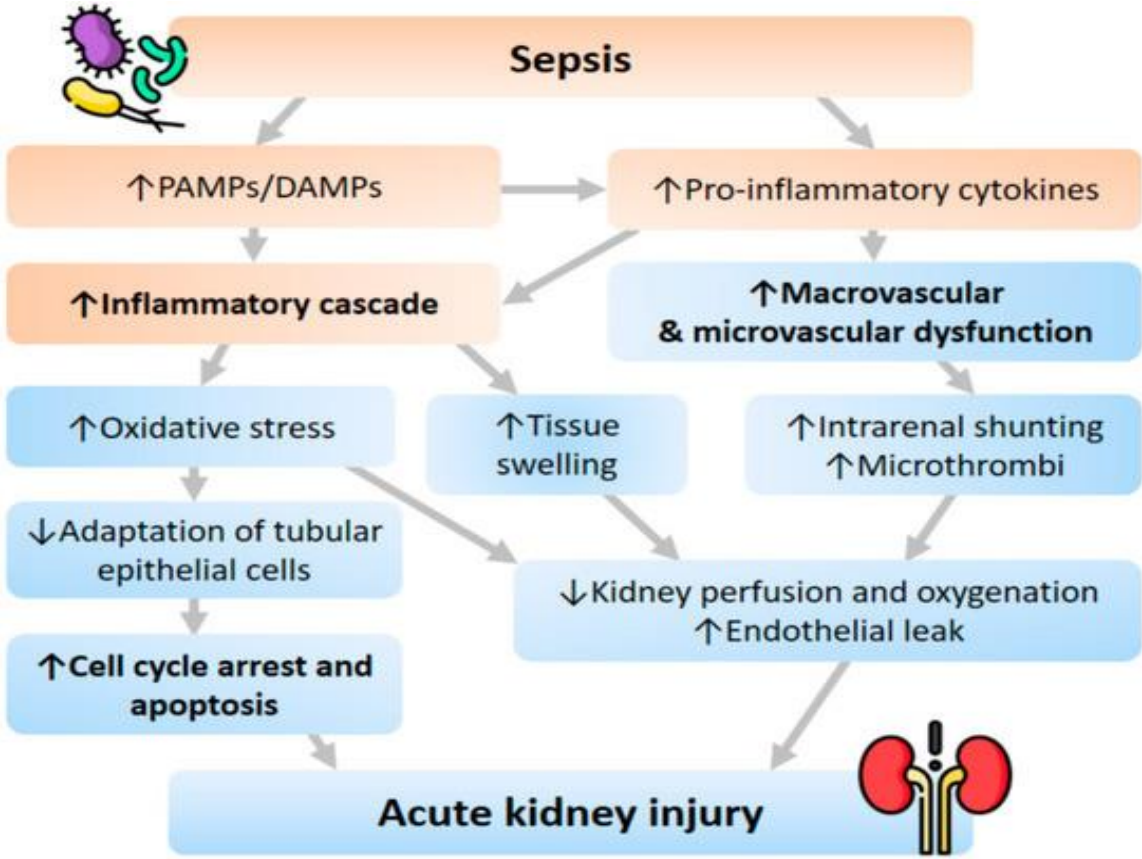


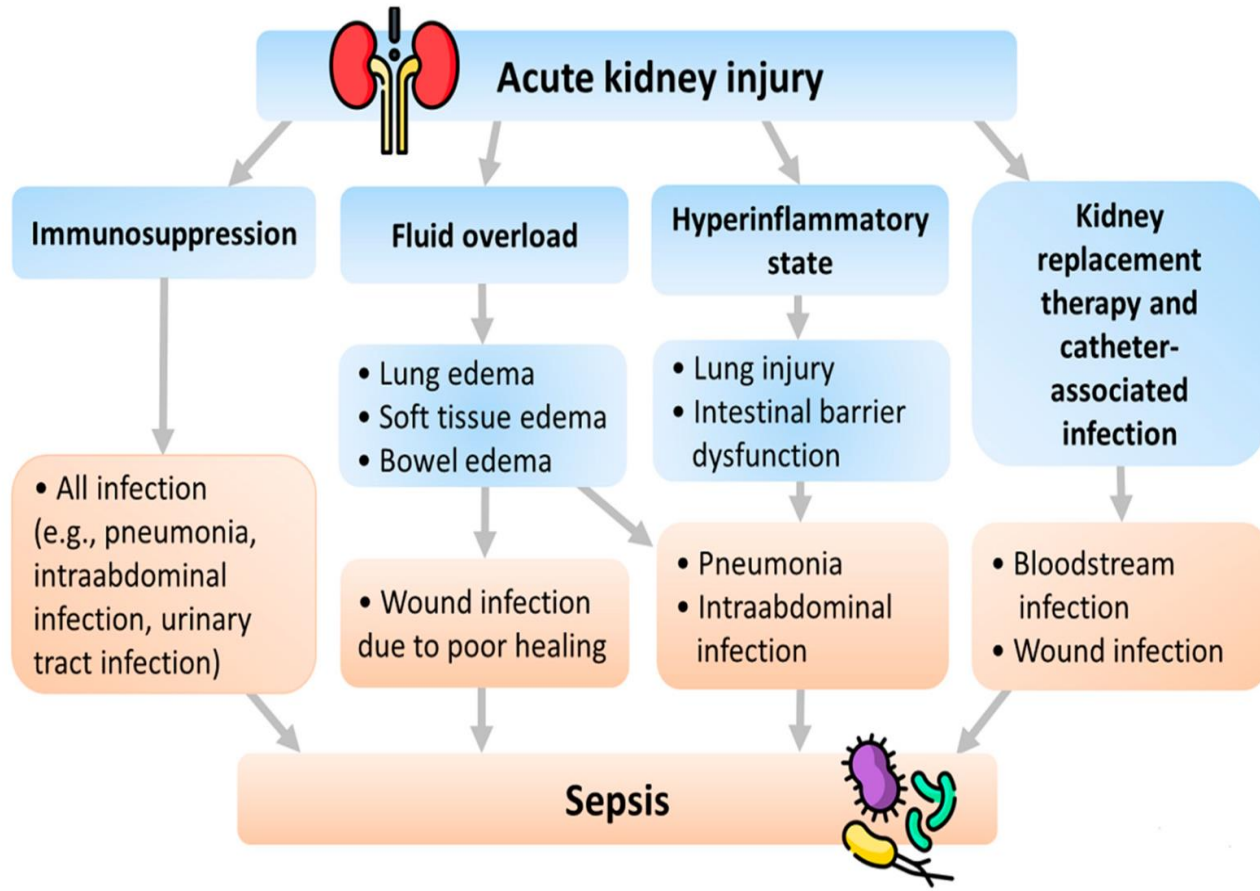
Hemodynamic changes

- Renal blood flow
- Macrocirculation
- Microcirculation

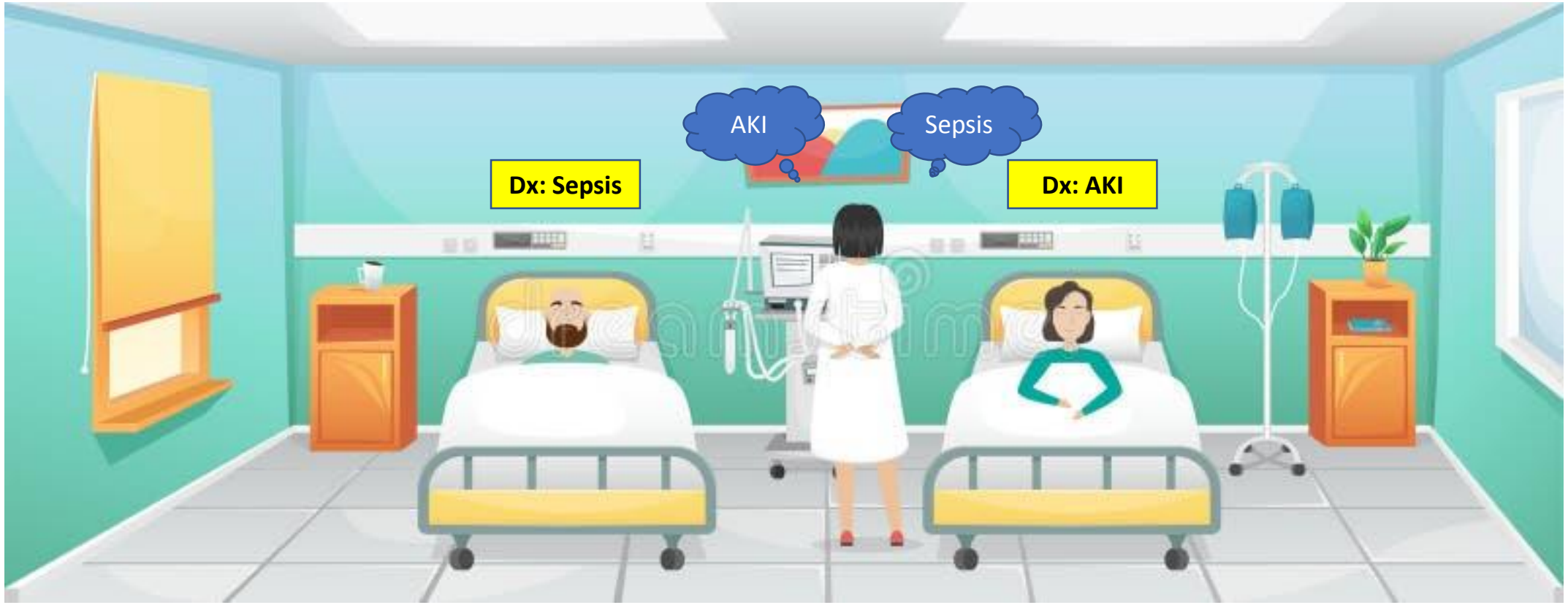
The injury of renal tubular epithelial cells

- TLRs/NF-kB
- Pro-inflammatory cytokines
- Over-production of ROS
- Mitochondrial injury
- Autophagy


Sepsis
↑PAMPs/DAMPs
↑Pro-inflammatory cytokines
↑Inflammatory cascade
↑Macrovascular & microvascular dysfunction
↑Oxidative stress
↑Tissue swelling
↑Intrarenal shunting
↑Microthrombi
↓Adaptation of tubular epithelial cells
↓Kidney perfusion and oxygenation
↑Endothelial leak
↑Cell cycle arrest and apoptosis
Acute kidney injury


Acute kidney injury
Immunosuppression
Fluid overload
Hyperinflammatory state
Kidney replacement therapy and catheter-associated infection
• All infection (e.g., pneumonia, intraabdominal infection, urinary tract infection)
• Lung edema
• Soft tissue edema
• Bowel edema
• Lung injury
• Intestinal barrier dysfunction
• Bloodstream infection
• Wound infection
• Wound infection due to poor healing
• Pneumonia
• Intraabdominal infection
Sepsis

Sepsis & AKI



it is so difficult to prevent/treat SA-AKI!

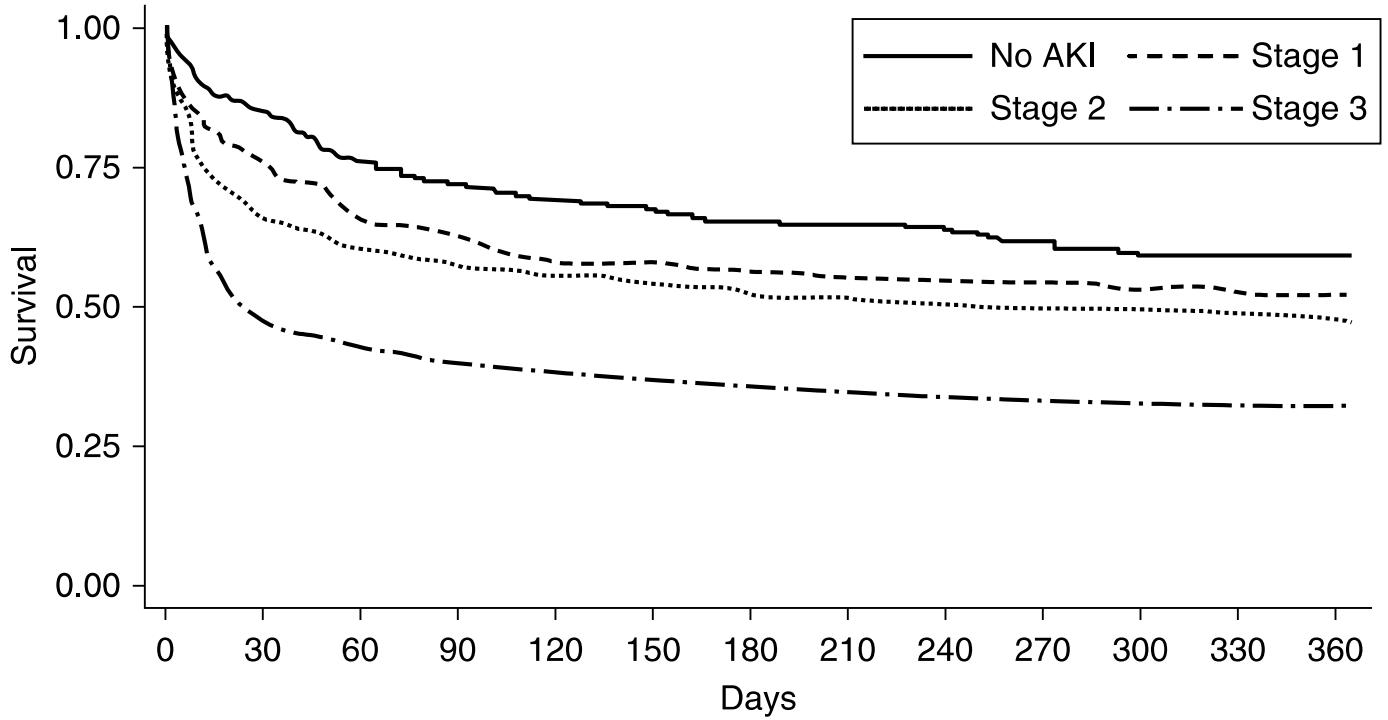
- Nephro-toxin / Tubular injury (due to add. of drugs; AMG, Acyclovir)
- Systemic hypotension (hemodynamic instability)
- Micro-thrombi
- Heart Failure (due to sepsis itself) LV HF
- Congestive Nephropathy: intra-renal congestion due to high renal vein pressures (simple fluid overload or Rt sided HF)
- Reduced renal reserve (CKD)
- …

in pts w/ Sepsis & AKI
the outcome is dramatically different

The Effects of Alternative Resuscitation Strategies on Acute Kidney Injury in Patients with Septic Shock

John A. Kellum[1,2], Lakhmir S. Chawla[2,3], Christopher Keener[1,4], Kai Singbartl[2,5], Paul M. Palevsky[2,6,7], Francis L. Pike[1], Donald M. Yealy[8], David T. Huang[1], and Derek C. Angus[1]; for the ProCESS and ProGReSS-AKI Investigators*

it is hard to die from SS w/o AKI



Hosp. mortality truncated @ 60 d was:

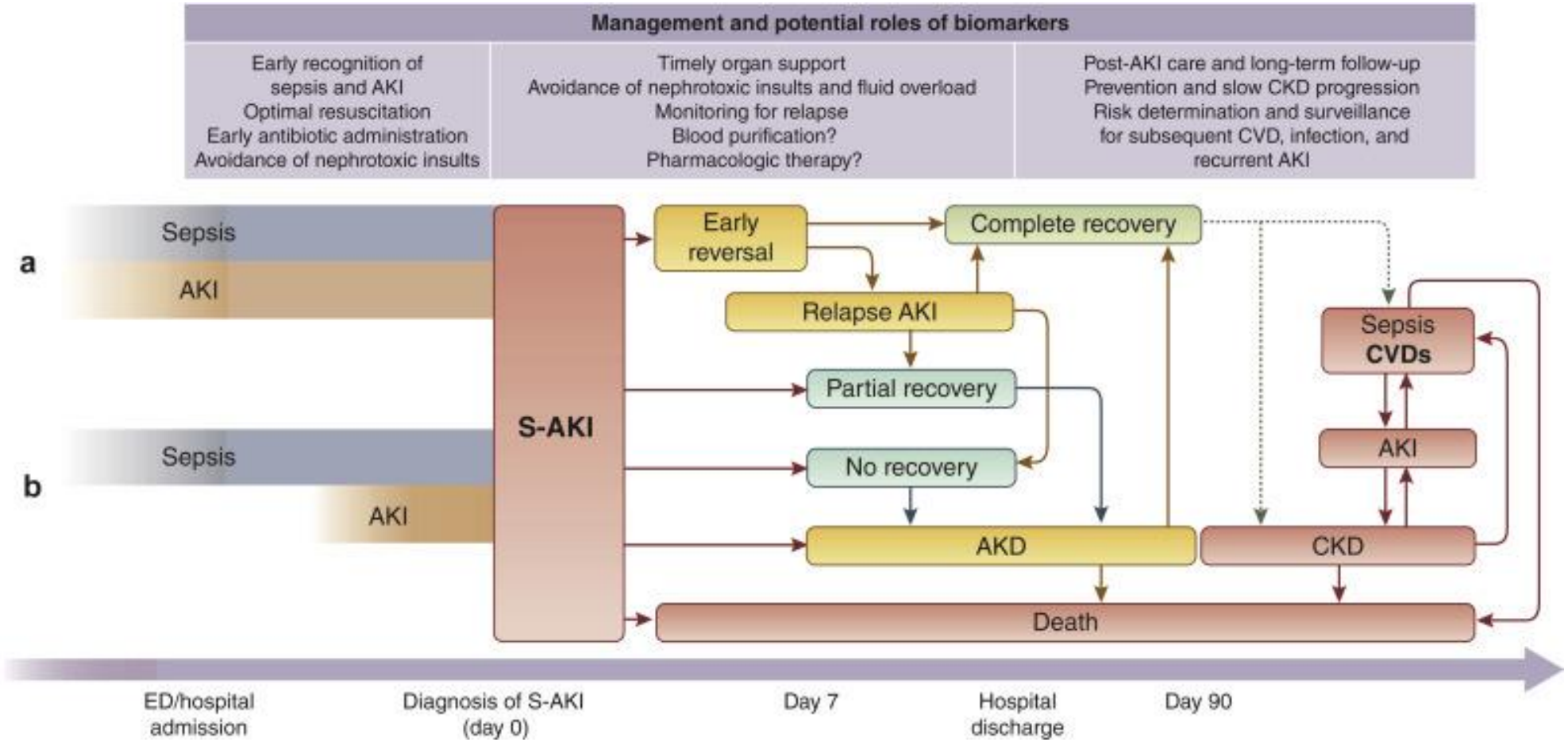
a-6.2% fpr pts w/o AKI

b-16.8% fpr pts w/ max AKI -1

c-27.7% for AKI-2 & 3 (p=0.0001)

Not All SA-AKI are the same

All these pts have ***the same form of AKI ?***



Optimal management ?

what is the best way to protect the kidneys ?

control the underlying cause

For the Primer, visit doi:10.1038/nrdp.2016.45

Sepsis has historically been difficult to define clinically. The condition is characterized by a dysregulated systemic inflammatory and immune response to infection that produces organ injury. Septic shock is characterized by persistent hypotension and substantially increases the risk of death.

EPIDEMIOLOGY

Estimating the burden of sepsis is complicated by the heterogeneous presentation of patients, controversy in clinical definitions, varying levels of awareness of sepsis as well as different coding systems for sepsis in hospital databases. An estimate in high-income countries suggests that 31.5 million cases of sepsis occur annually, with potentially 5.3 million deaths. Data are scant on incidence and mortality in low-income and middle-income countries.

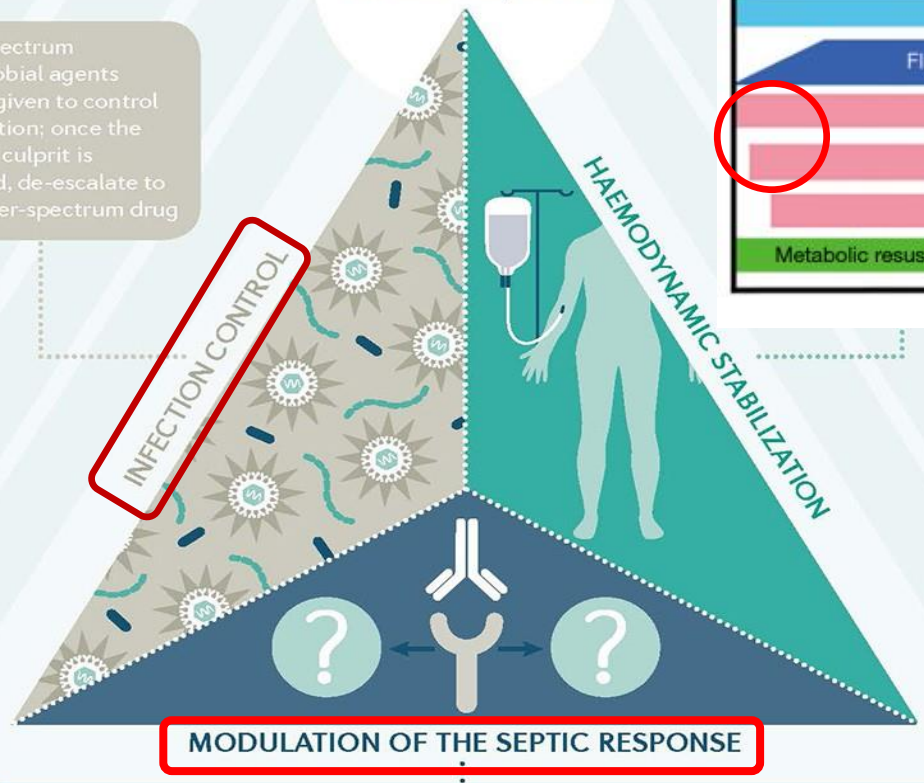
DIAGNOSIS

The symptoms of sepsis are variable and include mental alterations and difficulty breathing. Although infection is the precipitating event in sepsis, a causative pathogen is not identified in every patient. Rapid bedside assessment of early organ dysfunction is crucial to facilitate the diagnosis of sepsis. Septic shock is characterized by severe hypotension (which requires vasopressor therapy to maintain a mean arterial blood pressure of >65 mmHg) that is associated with an increased plasma lactate level of >2 mmol per l.

MANAGEMENT

Broad-spectrum antimicrobial agents must be given to control the infection; once the infective culprit is identified, de-escalate to a narrower-spectrum drug

Treatment of sepsis needs to be early and aggressive, and has three main components



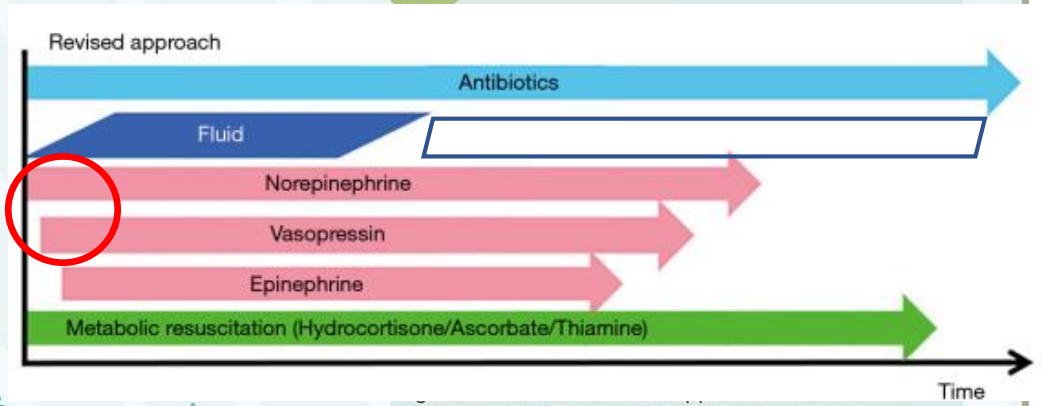
Many biological agents to modify the early septic response have been assessed; these include antibodies that target various components of the signalling cascades in sepsis. However, none has proven effective to date, although several are still in trials.

PREVENTION

Given that hospitalized patients are at high risk of developing sepsis, clean care and minimization of invasive procedures are effective preventive strategies. Hospitals should implement early warning systems that evaluate haemodynamics, urine output, body temperature and mental function in critically ill patients to prevent sepsis and its progression to septic shock and multiple organ failure.

However, a considerable number of patients develop sepsis outside of the hospital setting. In this regard, vaccination to reduce the burden of infectious disease can reduce the risk of sepsis.

MECHANISMS

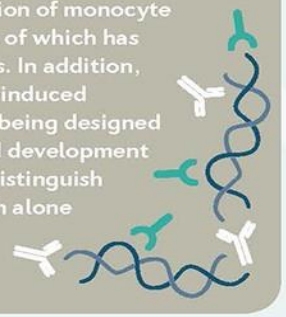


innate and the adaptive immune systems in spite of ongoing inflammation. This phase of sepsis is characterized by profound leukocyte apoptosis.

! Endothelial barrier dysfunction occurs early in sepsis and septic shock in particular, leading to hypotension and oedema

OUTLOOK

Defining the immunological state of the patient with sepsis or septic shock is of particular interest to better understand the syndrome, as well as to design and assess immunotherapies. Indeed, immunophenotyping of patients with sepsis is being explored and includes quantification of monocyte HLA-DR expression, loss of which has been implicated in sepsis. In addition, drugs to reverse sep–sis-induced immunosuppression are being designed and assessed. Continued development of biomarkers that can distinguish sepsis from inflammation alone also remains an area of active investigation.



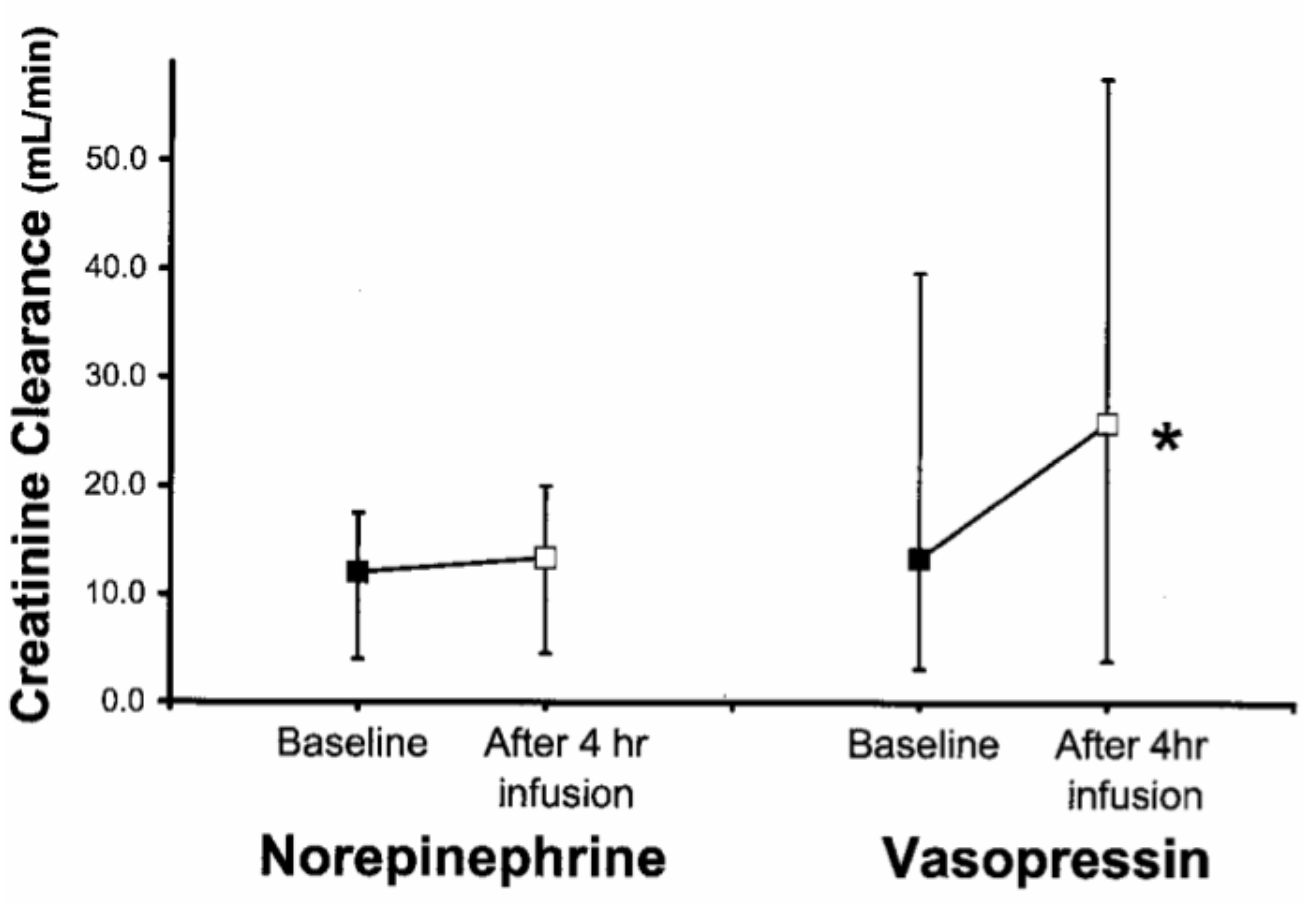
Designed by Laura Marshall

Article number: 16046; doi:10.1038/nrdp.2016.46; published online 30 June 2016

Hemodynamic Stability

- **Perfusion pressure is a key factor**
- +/- **Vasopressors**
- Different VC have different action point
- **Support of MAP with NE**
- ***Vasopressin allows reduction of norepinephrine doses, thereby reducing beta-adrenergic stimulation***

Vasopressin is associated with improved CrCl & increased UOP

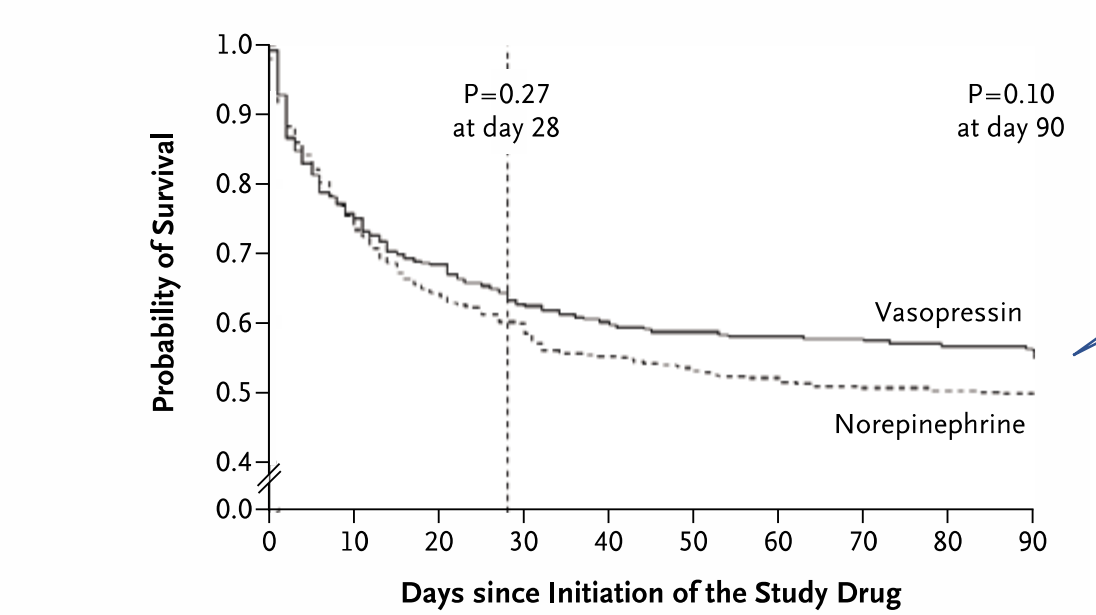


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2008 VOL. 358 NO. 9

Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D., Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D., John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D., and Dieter Ayers, M.Sc., for the VASST Investigators*



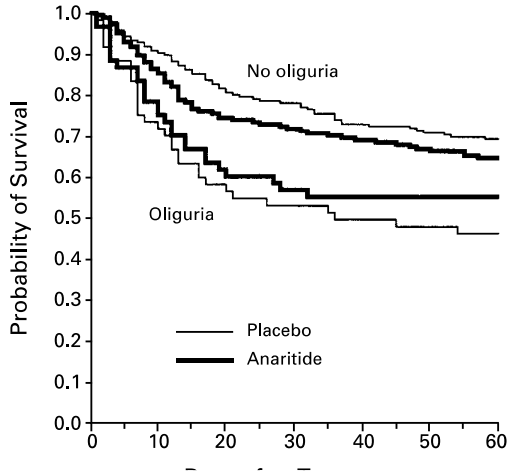
No. at Risk

Vasopressin	397	301	272	249	240	234	232	230	226	220
Norepinephrine	382	289	247	230	212	205	200	194	193	191

may be we are evaluating different groups of pts at the same time ?

ANARITIDE IN ACUTE TUBULAR NECROSIS

ROBIN L. ALLGREN, M.D., PH.D., THOMAS C. MARBURY, M.D., S. NOOR RAHMAN, M.D., LAWRENCE S. WEISBERG, M.D., ANDREW Z. FENVES, M.D., RICHARD A. LAFAYETTE, M.D., RICHARD M. SWEET, M.D., FREDRIC C. GENTER, PH.D., BRENDA R.C. KURNIK, M.D., JOHN D. CONGER, M.D., AND MOHAMED H. SAYEGH, M.D., FOR THE AURICULIN ANARITIDE ACUTE RENAL FAILURE STUDY GROUP*



Multicenter clinical trial of recombinant human insulin-like growth factor I in patients with acute renal failure.

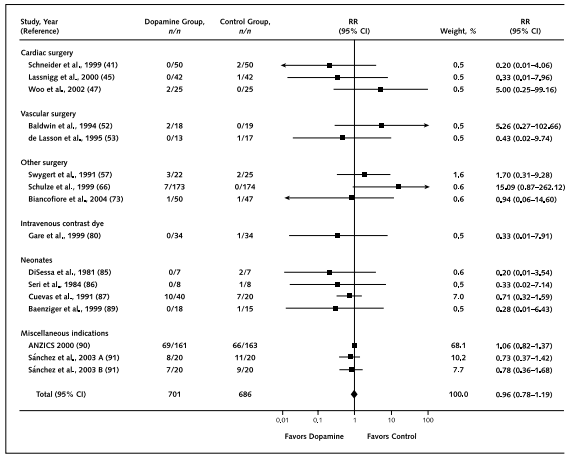
rhIGF-I does not accelerate the recovery of renal function in ARF patients with substantial comorbidity.

(Hirschberg R; Kopple J; Lipsett P; Benjamin E; Minei J; Albertson T; Munger M; Metzler M; Zaloga G: Murray M; Lowry S; Conger J; McKeown W; O'shea M; Baughman R; Wood K; Haupt M; Kaiser R; Simms H; Warnock D; Summer W; Hintz R; Myers B; Haenftling K; Capra W; et al; Kidney Int 1999 Jun; 55(6):2423-32)

High-Dose Furosemide for Established ARF: A Prospective, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

Félix Cantarovich, MD, Badrudin Rangoonwala, PhD, Horst Lorenz, DiplMath, Matti Verho, MD, and Vincent L.M. Esnault, MD, PhD, for the High-Dose Furosemide in Acute Renal Failure Study Group

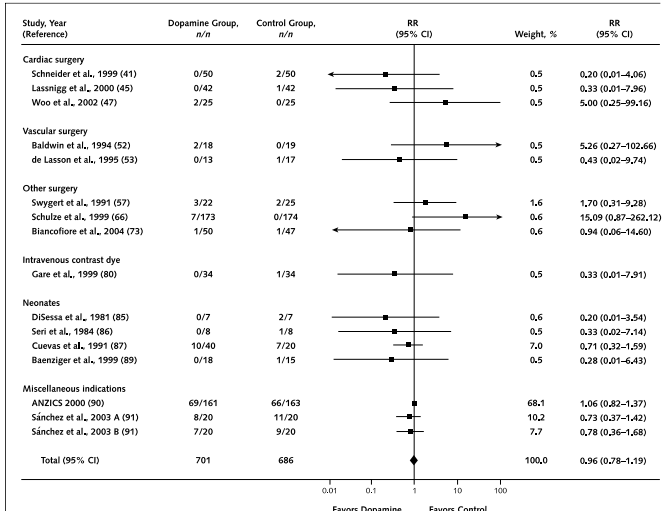
Figure 1. Effect of low-dose dopamine on mortality.



Meta-Analysis: Low-Dose Dopamine Increases Urine Output but Does Not Prevent Renal Dysfunction or Death

Jan O. Friedrich, MD, DPhil; Neill Adhikari, MD, CM; Margaret S. Herridge, MD, MPH; and Joseph Beyene, PhD

Figure 1. Effect of low-dose dopamine on mortality.



ORIGINAL ARTICLE

The Effects of Alternative Resuscitation Strategies on Acute Kidney Injury in Patients with Septic Shock

John A. Kellum[1,2], Lakhmir S. Chawla[2,3], Christopher Keener[1,4], Kai Singbartl[2,5], Paul M. Palevsky[2,6,7], Francis L. Pike[1], Donald M. Yealy[8], David T. Huang[1], and Derek C. Angus[1]; for the ProCESS and ProGReSS-AKI Investigators*

Conclusions: In patients with septic shock, AKI is common and associated with adverse outcomes, but it is not influenced by protocolized resuscitation compared with usual care.

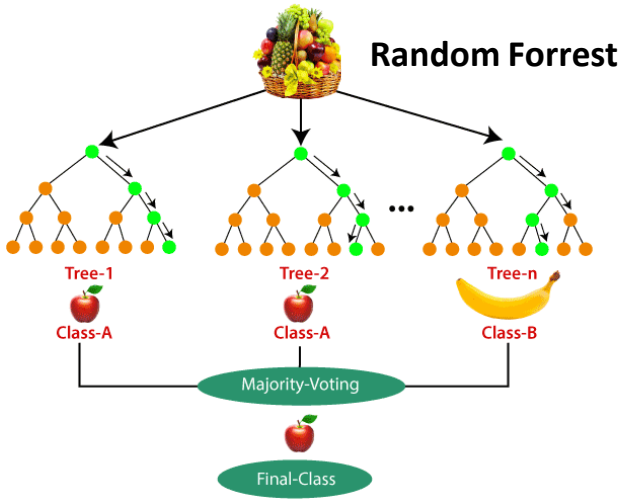
all these trials were negative in larger phase studies

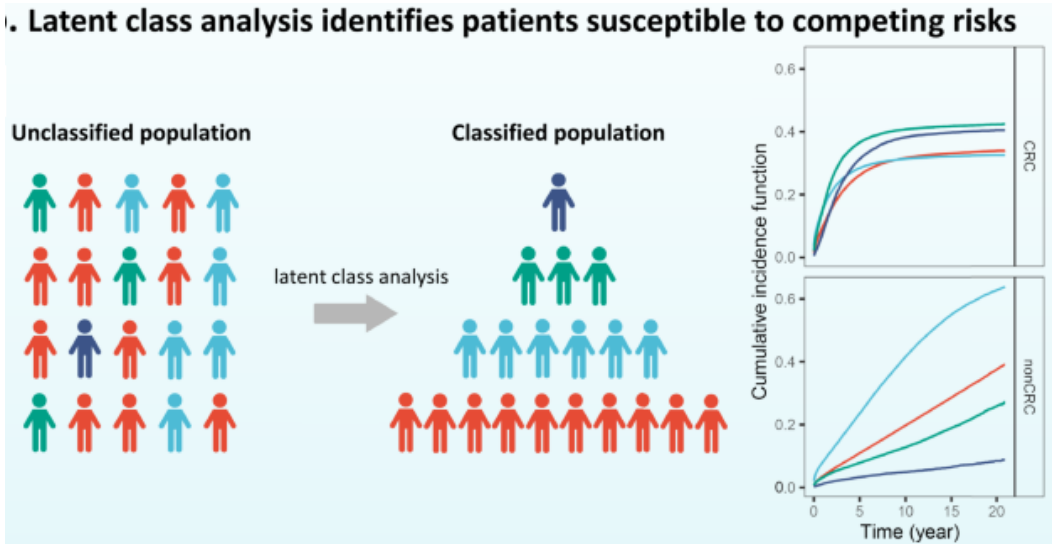
one of the potential reasons may be >>> we study a very different populations

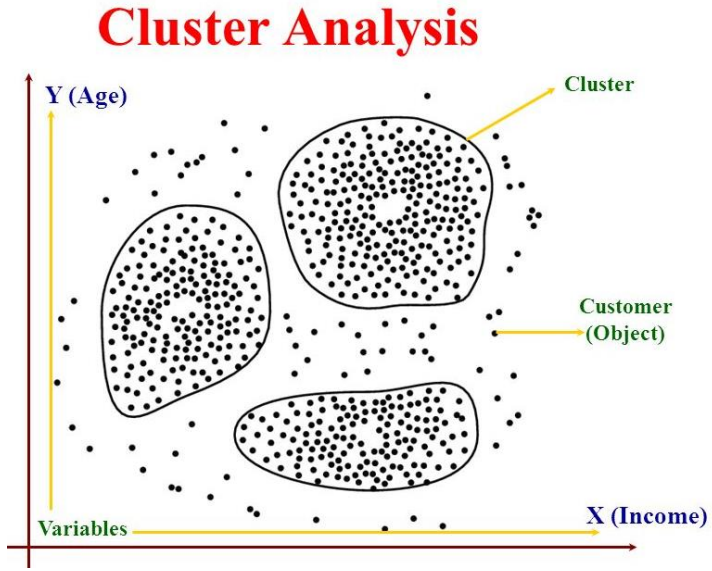
Heterogeneity may limit therapeutics

SA-AKI is a heterogeneous clinical sdrm, and this heterogeneity may obscure our attempts for an effective therapy.

Methods to identify distinct SA-AKI/SP



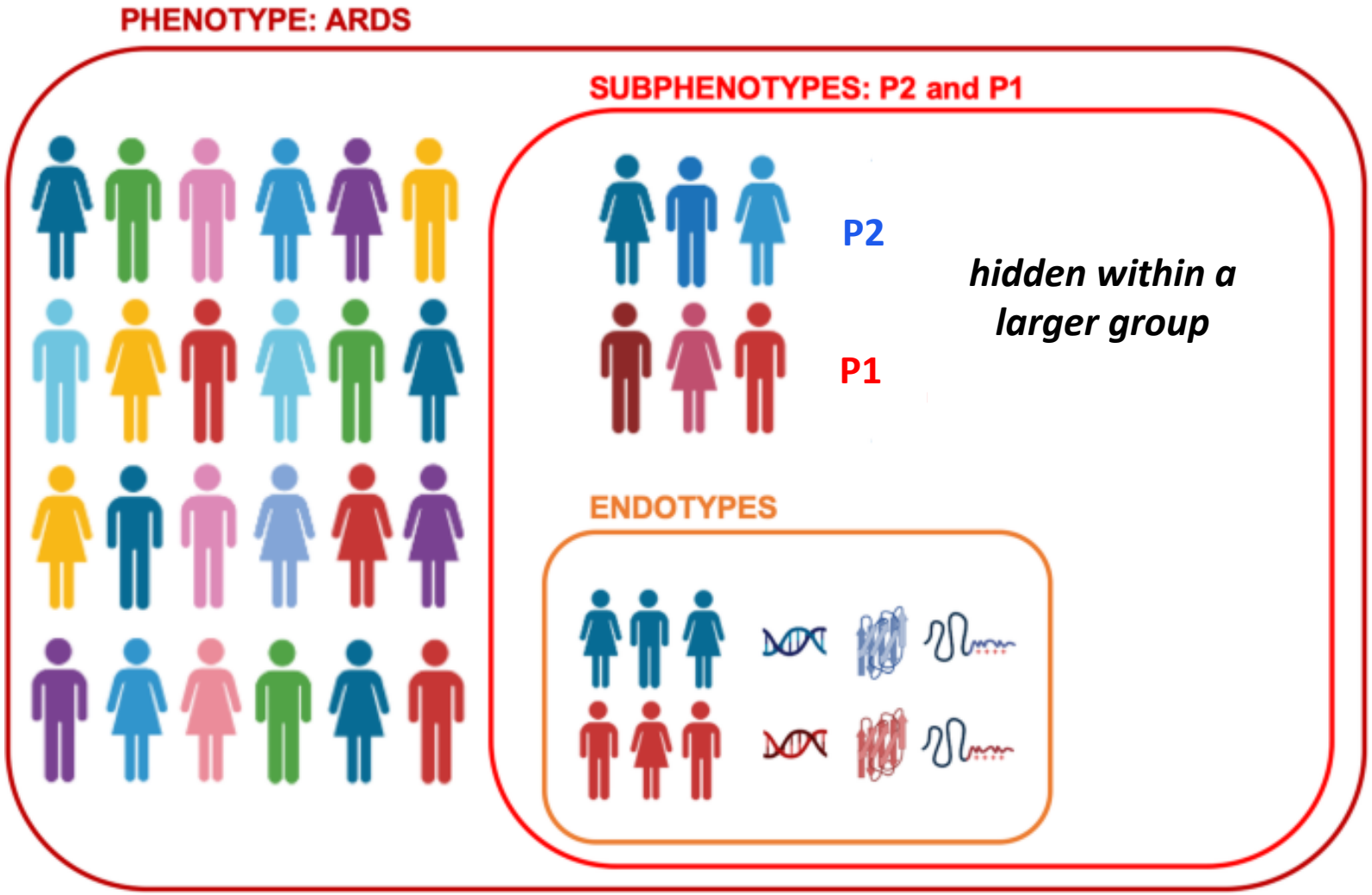




LCA is a good way to identify distinct AKI-SP

Latent Class Analysis

distinct subgroups of pts, within a larger population



Integrated Analysis of Blood and Urine Biomarkers to Identify AKI Subphenotypes and Associations With Long-term Outcomes

Setting & Participants

ASSESS-AKI:
Multicenter cohort study

N = 769 hospitalized adults with AKI and 769 without AKI

Dec 2009-Feb 2015

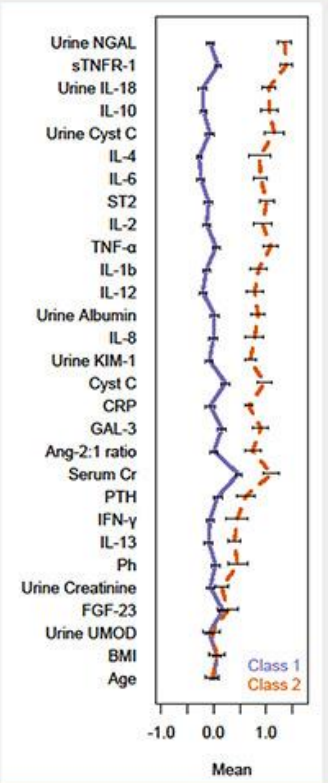
Latent class analysis and *k*-means to identify AKI sub-phenotypes

Two AKI Subphenotypes

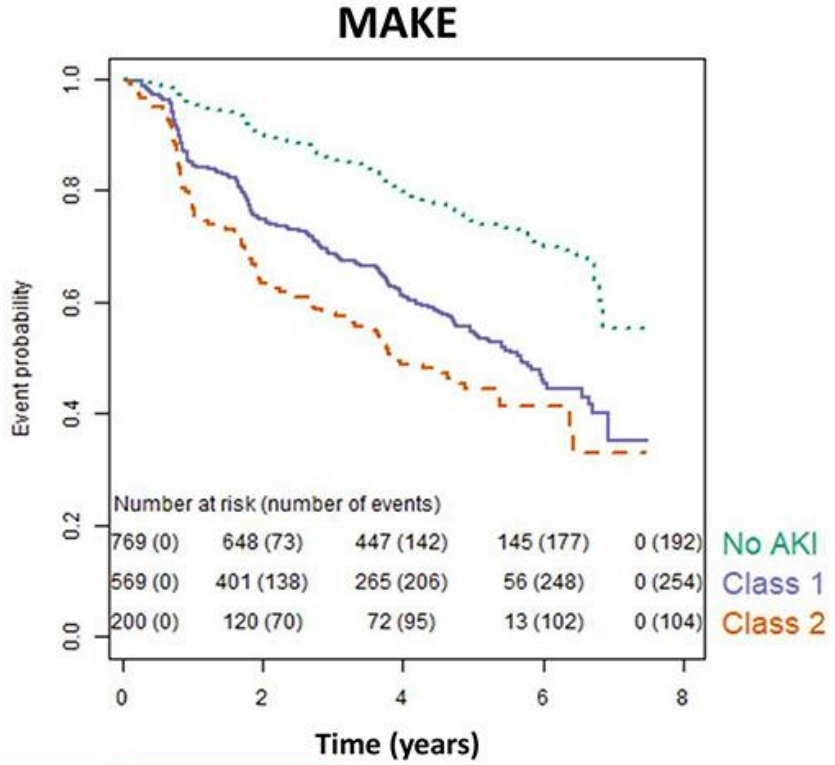
Two distinct AKI subphenotypes identified using levels from 29 clinical and molecular biomarkers

Class 1
N = 569 (74%)

Class 2
N = 200 (26%)



Class 2: Higher Risk of Major Adverse Kidney Events (MAKE)



Median follow-up: 4.7 years

CONCLUSION: We identify 2 molecularly distinct AKI subphenotypes with differing risk of long-term outcomes, independent of the current criteria to risk stratify AKI.

Pavan K. Bhatraju, David K. Prince, Sherry Mansour, et al.

@AJKDonline | DOI: 10.1053/j.ajkd.2023.01.449

AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES

identification of 2 types of AKI >>> 2 SP

different & very specific

A

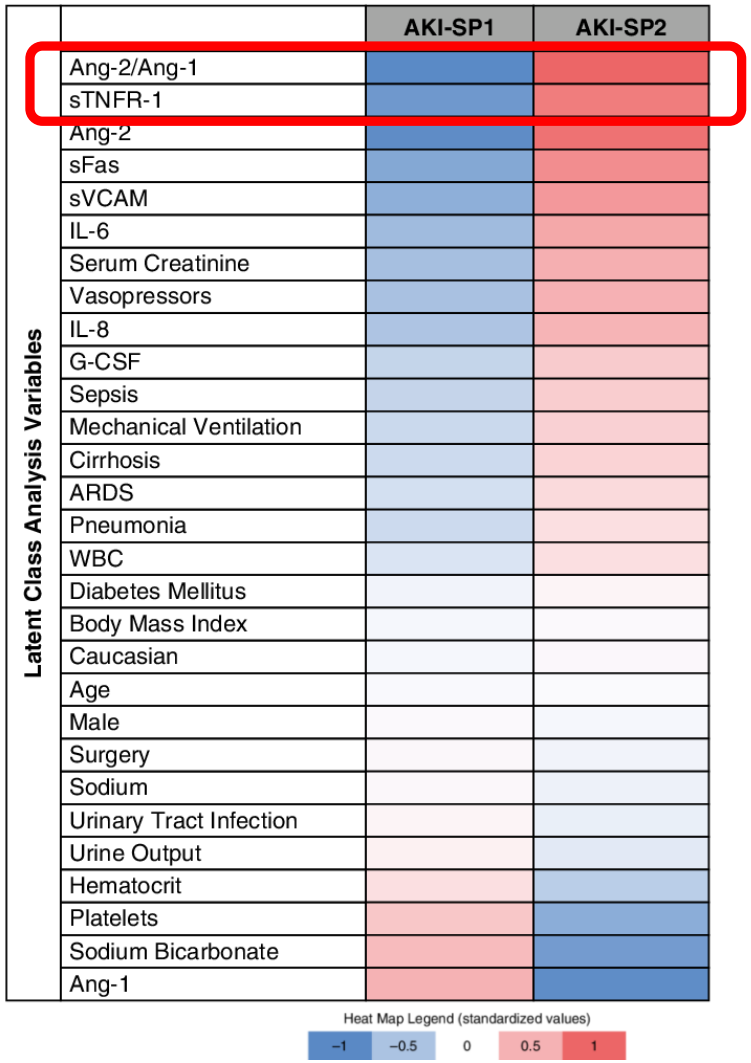
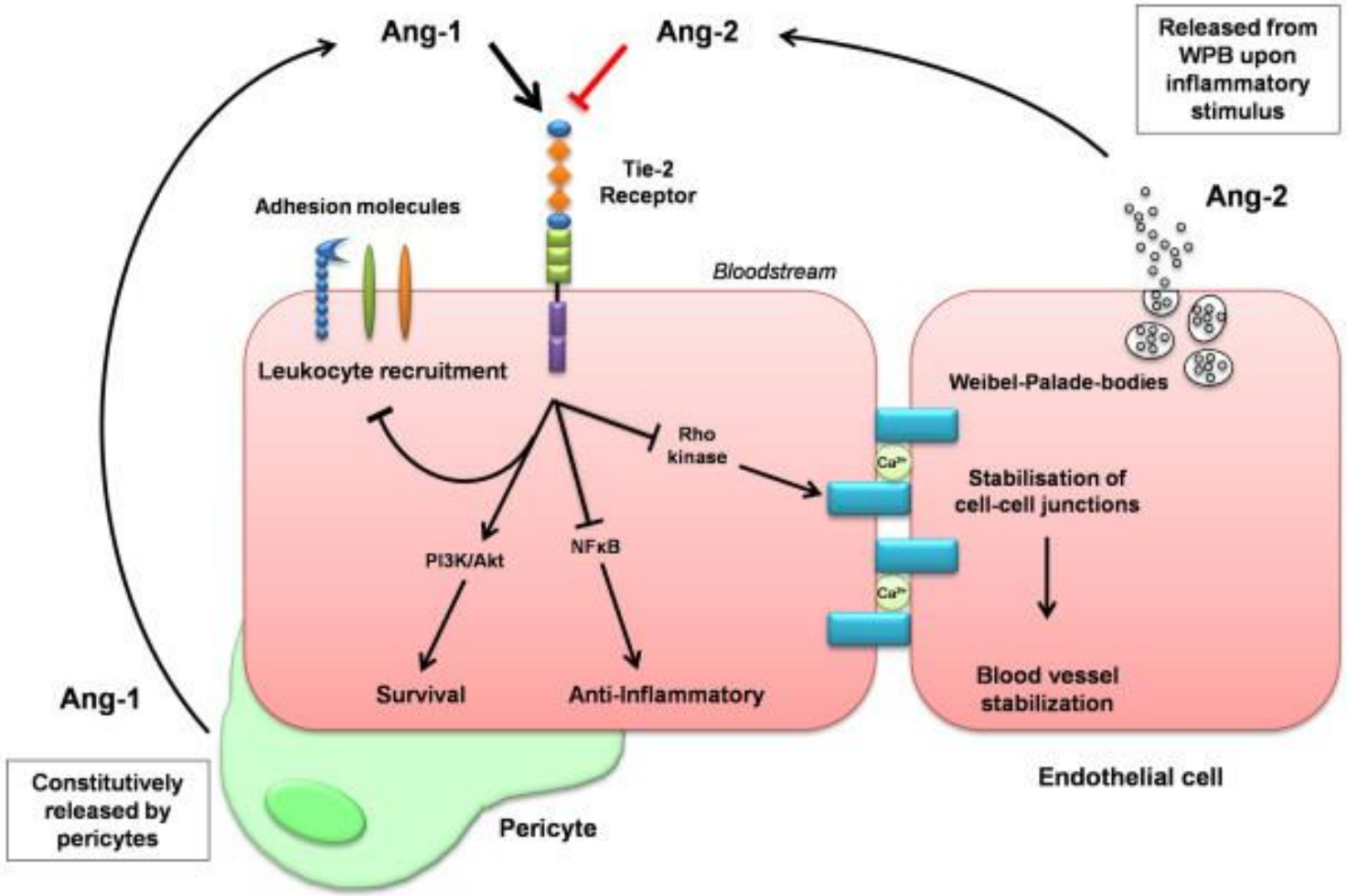


Table 2. Patient Characteristics and Outcomes Based on AKI Subphenotypes in the Discovery and Replication Populations

	Discovery			Replication		
	AKI-SP1	AKI-SP2	*P* Value	AKI-SP1	AKI-SP2	*P* Value
Subjects	462	332	—	268	157	—
Age, yr	55 ± 16	55 ± 16	0.80	57 ± 18	57 ± 18	0.95
Male	296 (65)	224 (66)	0.62	164 (61)	104 (39)	0.15
Race						
White	331 (76)	244 (78)	0.57	268 (100)	157 (100)	—
Comorbidities						
Diabetes mellitus	129 (28)	109 (32)	0.21	72 (27)	40 (26)	0.73
Cirrhosis	8 (2)	67 (20)	<0.01	6 (2)	14 (9)	<0.01
Chronic kidney disease	31 (7)	70 (21)	<0.01	—	—	—
ICU events*						
APACHE III scores	47 ± 21	72 ± 29	<0.01	74 ± 24	111 ± 26	<0.01
SOFA Day 1 scores	3 ± 2.3	7 ± 3.0	<0.01	8 ± 2	11 ± 3	<0.01
Sepsis-3	257 (46)	304 (54)	<0.01	178 (66)	132 (84)	<0.01
Acute respiratory distress syndrome	43 (9)	74 (22)	<0.01	107 (40)	103 (66)	<0.01
Vasopressors	66 (14)	166 (49)	<0.01	113 (42)	124 (79)	<0.01
Mechanical ventilation	286 (63)	280 (83)	<0.01	198 (74)	134 (85)	<0.01
KDIGO class 2 + 3	84 (19)	121 (36)	<0.01	48 (18)	45 (29)	<0.01
24-h urine output, ml	1,555 (910–2,565)	1,225 (486–2,089)	<0.01	1,680 (1,140–2,665)	1,199 (563–2,050)	<0.01
ICU laboratory values*						
Maximum white blood cell count, 10^9/L	14 ± 7	16 ± 10	<0.01	16 ± 8	17 ± 13	<0.01
Low hematocrit, %	30 ± 6	31 ± 6	0.77	30 ± 6	31 ± 6	0.77
Low sodium, mEq/L	137 ± 6	135 ± 5	<0.01	137 ± 6	135 ± 5	<0.01
Low albumin, g/dl	2.4 ± 0.6	2.2 ± 0.7	<0.01	2.4 ± 0.6	2.2 ± 0.7	<0.01
Low platelets, 10^9/L	184 ± 101	85 ± 75	<0.01	184 ± 101	85 ± 75	<0.01
Low sodium bicarbonate, mEq/L	22 ± 5	17 ± 5	<0.01	22 ± 5	17 ± 5	<0.01
Maximum serum creatinine, mg/dl	1.4 ± 0.8	3.1 ± 2.9	<0.01	1.9 ± 1.4	3.1 ± 1.7	<0.01
Biomarker concentrations						
Ang-2/Ang-1 ratio	1.4 (0.7–3.2)	18.1 (8.2–53.9)	<0.01	9.4 (3.3–25.5)	87.1 (35.7–266.1)	<0.01
sTNFR-1, pg/ml	6,798 (4,701–10,108)	18,772 (12,663–30,889)	<0.01	10,581 (6,828–15,742)	25,815 16,084–36,211)	<0.01
IL-8, pg/ml	10 (5–21)	22 (12–55)	<0.01	16 (10–26)	60 (28–149)	<0.01

in critical illnesses >>> Angpt-1 levels drops & Angpt-2 levels rises
the ratio Ang-2/Ang-1 is a better marker of "endothelial stability"



Do different SP, helps to chose a better ttt/strategy ?

ORIGINAL ARTICLE

Identification of Acute Kidney Injury Subphenotypes with Differing Molecular Signatures and Responses to Vasopressin Therapy

Pavan K. Bhatraju[1,2], Leila R. Zelnick[2], Jerald Herting[3], Ronit Katz[2], Carmen Mikacenic[1], Susanna Kosamo[1], Eric D. Morrell[1], Cassianne Robinson-Cohen[2], Carolyn S. Calfee[4,5,6], Jason D. Christie[7,8*], Kathleen D. Liu[9,10], Michael A. Matthay[4,5,6], William O. Hahn[11], Victoria Dmyterko[1], Natalie S. J. Slivinski[12], Jim A. Russell[13,14], Keith R. Walley[13,14], David C. Christiani[15,16,17], W. Conrad Liles[18], Jonathan Himmelfarb[2], and Mark M. Wurfel[1,2]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, [2]Kidney Research Institute, Division of Nephrology, and [11]Division of Allergy and Infectious Diseases, Department of Medicine, [3]Department of Sociology, and [18]Department of Medicine, University of Washington, Seattle, Washington; [4]Department of Medicine, [5]Department of Anesthesia and Perioperative Care, [6]Cardiovascular Research Institute, [9]Division of Nephrology, and [10]Division of Critical Care Medicine, University of California, San Francisco, San Francisco, California; [7]Division of Pulmonary, Allergy, and Critical Care and [8]Center for Clinical Epidemiology and Biostatistics, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [12]University of Leeds, Leeds, United Kingdom; [13]Centre for Heart Lung Innovation and [14]Division of Critical Care Medicine, Department of Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; [15]Department of Environmental Health and [16]Department of Epidemiology, Harvard School of Public Health, Harvard University, Boston, Massachusetts; and [17]Pulmonary and Critical Care Division, Department of Medicine, Massachusetts General Hospital/Harvard Medical School, Boston, Massachusetts

ORCID ID: 0000-0001-5151-9361 (S.K.).

Abstract

Rationale: Currently, no safe and effective pharmacologic interventions exist for acute kidney injury (AKI). One reason may be that heterogeneity exists within the AKI population, thereby hampering the identification of specific pathophysiologic pathways and therapeutic targets.

Objective: The aim of this study was to identify and test whether AKI subphenotypes have prognostic and therapeutic implications.

Methods: First, latent class analysis methodology was applied independently in two critically ill populations (discovery [$n = 794$] and replication [$n = 425$]) with AKI. Second, a parsimonious classification model was developed to identify AKI subphenotypes. Third, the classification model was applied to patients with AKI in VASST (Vasopressin and Septic Shock Trial; $n = 271$), and differences in treatment response were determined. In all three populations, AKI was defined using serum creatinine and urine output.

Measurements and Main Results: A two-subphenotype latent class analysis model had the best fit in both the discovery ($P = 0.004$) and replication ($P = 0.004$) AKI groups. The risk of 7-day renal nonrecovery and 28-day mortality was greater with AKI subphenotype 2 (AKI-SP2) relative to AKI subphenotype 1 (AKI-SP1). The AKI subphenotypes discriminated risk for poor clinical outcomes better than the Kidney Disease: Improving Global Outcomes stages of AKI. A three-variable model that included markers of endothelial dysfunction and inflammation accurately determined subphenotype membership (C-statistic 0.92). In VASST, vasopressin compared with norepinephrine was associated with improved 90-day mortality in AKI-SP1 (27% vs. 46%, respectively; $P = 0.02$), but no significant difference was observed in AKI-SP2 (45% vs. 49%, respectively; $P = 0.99$) and the P value for interaction was 0.05.

Conclusions: This analysis identified two molecularly distinct AKI subphenotypes with different clinical outcomes and responses to vasopressin therapy. Identification of AKI subphenotypes could improve risk prognostication and may be useful for predictive enrichment in clinical trials.

Keywords: acute kidney injury; endothelial dysfunction; mortality; subphenotypes

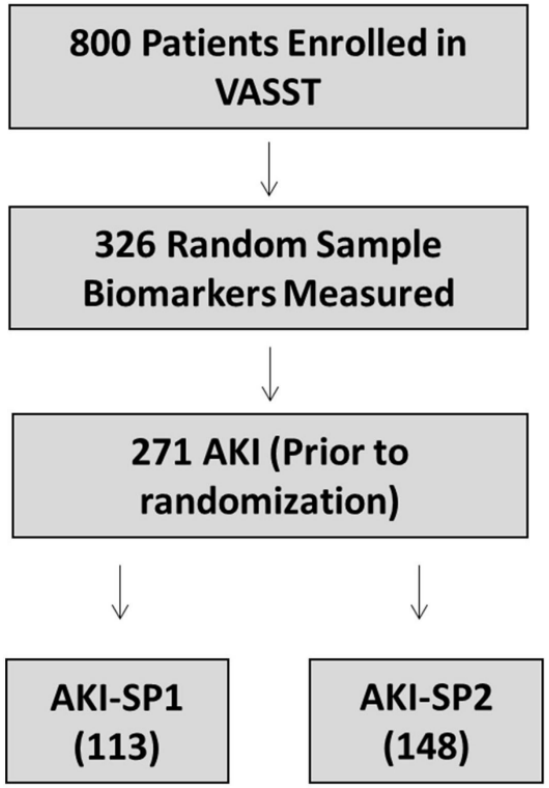
2 SP with different prognosis
AKI-SP 2 >>> much more worse prognosis

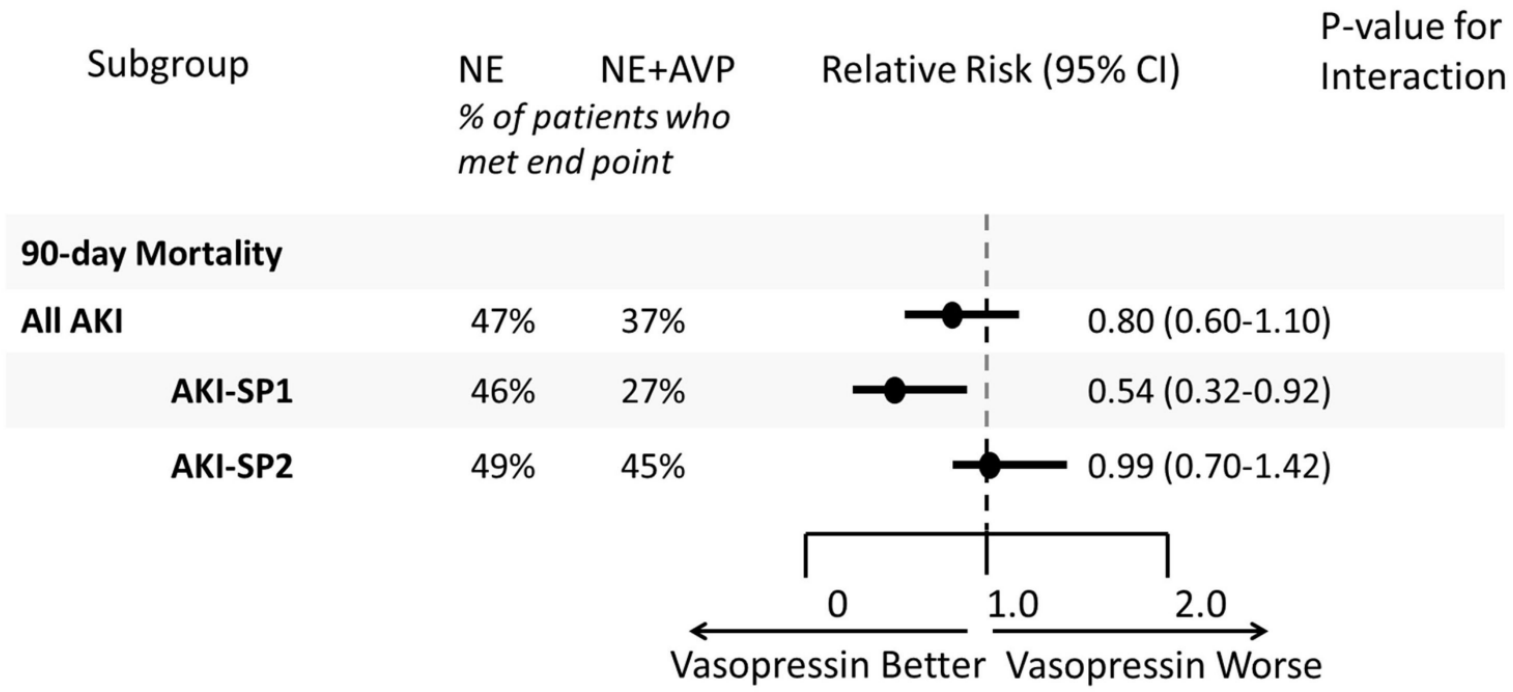
more risk of dying, more risk of "not recovery of kidney function"

	Discovery				Replication			
	AKI-SP1	AKI-SP2	RR (95% CI)†	*P* Value	AKI-SP1	AKI-SP2	RR (95% CI)†	*P* Value
Clinical outcomes								
7-d renal nonrecovery	16 (3)	78 (23)	4.4 (2.5–7.9)	<0.001	66 (25)	72 (46)	1.6 (1.1–2.2)	0.006
28-d mortality	28 (6)	83 (25)	2.5 (1.6–4.1)	<0.001	36 (13)	57 (36)	2.2 (1.3–3.5)	0.002

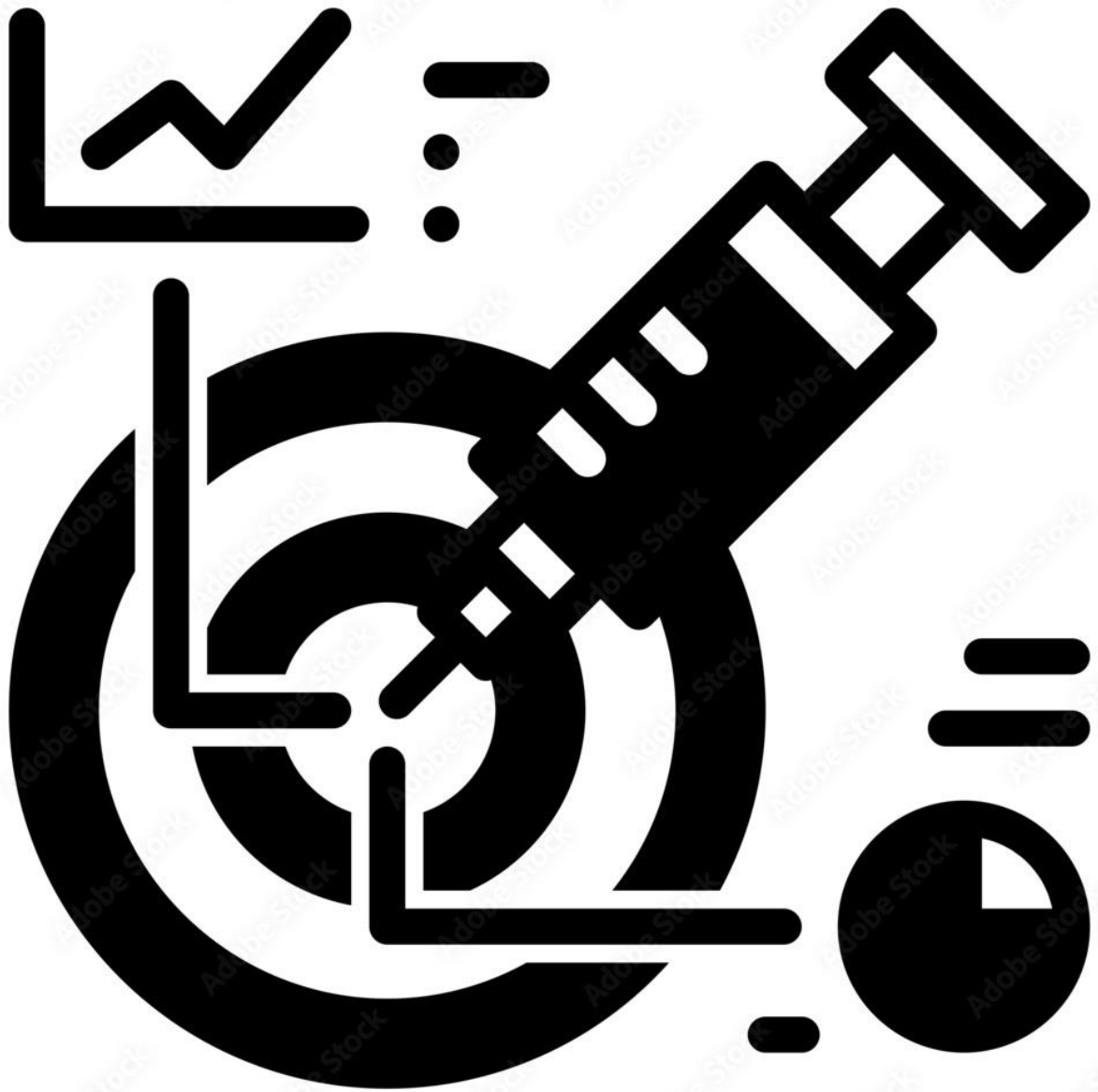
	AKI-SP1				AKI-SP2			
	Norepinephrine	Vasopressin	RR (95% CI)†	*P* Value	Norepinephrine	Vasopressin	RR (95% CI)†	*P* Value
Clinical outcomes								
7-d renal nonrecovery	24 (46)	23 (38)	0.80 (0.51–1.25)	0.32	44 (63)	44 (56)	0.99 (0.76–1.30)	0.96
28-d mortality	16 (31)	11 (18)	0.53 (0.30– 0.94)	0.03	30 (43)	31 (40)	1.03 (0.68–1.55)	0.88
90-d mortality	24 (46)	16 (27)	0.54 (0.32–0.92)	0.02	34 (49)	35 (45)	0.99 (0.70–1.42)	0.99

pts w/ AKI-SP 2 did not benefit from the addition of Vsp
pts w/ AKI-SP 1 had a clear benefit from receiving Vsp





trying to Identify the “right pts” for the “right therapy”



Do alternative AKI-SP exist ?
to identify other different SP

ORIGINAL ARTICLE

Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network*

ABSTRACT

BACKGROUND

Intravenous fluids and vasopressor agents are commonly used in early resuscitation of patients with sepsis, but comparative data for prioritizing their delivery are limited.

METHODS

In an unblinded superiority trial conducted at 60 U.S. centers, we randomly assigned patients to either a restrictive fluid strategy (prioritizing vasopressors and lower intravenous fluid volumes) or a liberal fluid strategy (prioritizing higher volumes of intravenous fluids before vasopressor use) for a 24-hour period. Randomization occurred within 4 hours after a patient met the criteria for sepsis-induced hypotension refractory to initial treatment with 1 to 3 liters of intravenous fluid. We hypothesized that all-cause mortality before discharge home by day 90 (primary outcome) would be lower with a restrictive fluid strategy than with a liberal fluid strategy. Safety was also assessed.

RESULTS

A total of 1563 patients were enrolled, with 782 assigned to the restrictive fluid group and 781 to the liberal fluid group. Resuscitation therapies that were administered during the 24-hour protocol period differed between the two groups; less intravenous fluid was administered in the restrictive fluid group than in the liberal fluid group (difference of medians, −2134 ml; 95% confidence interval [CI], −2318 to −1949), whereas the restrictive fluid group had earlier, more prevalent, and longer duration of vasopressor use. Death from any cause before discharge home by day 90 occurred in 109 patients (14.0%) in the restrictive fluid group and in 116 patients (14.9%) in the liberal fluid group (estimated difference, −0.9 percentage points; 95% CI, −4.4 to 2.6; P=0.61); 5 patients in the restrictive fluid group and 4 patients in the liberal fluid group had their data censored (lost to follow-up). The number of reported serious adverse events was similar in the two groups.

CONCLUSIONS

Among patients with sepsis-induced hypotension, the restrictive fluid strategy that was used in this trial did not result in significantly lower (or higher) mortality before discharge home by day 90 than the liberal fluid strategy. (Funded by the National Heart, Lung, and Blood Institute; CLOVERS ClinicalTrials.gov number, NCT03434028.)

The members of the CLOVERS writing committee (Nathan I. Shapiro, M.D., M.P.H., Ivor S. Douglas, M.D., Roy G. Brower, M.D., Samuel M. Brown, M.D., Matthew C. Exline, M.D., M.P.H., Adit A. Ginde, M.D., M.P.H., Michelle N. Gong, M.D., Colin K. Grissom, M.D., Douglas Hayden, Ph.D., Catherine L. Hough, M.D., Weixing Huang, M.S.P.H., Theodore J. Iwashyna, M.D., Ph.D., Alan E. Jones, M.D., Akram Khan, M.D., Poying Lai, M.S., Kathleen D. Liu, M.D., Chadwick D. Miller, M.D., Katherine Oldmixon, R.N., Pauline K. Park, M.D., Todd W. Rice, M.D., Nancy Ringwood, B.S.N., Matthew W. Semler, M.D., Jay S. Steingrub, M.D., Daniel Talmor, M.D., B. Taylor Thompson, M.D., Donald M. Yealy, M.D., and Wesley H. Self, M.D., M.P.H.) assume responsibility for the overall content and integrity of this article.

The affiliations of the members of the CLOVERS writing committee are listed in the Appendix. Dr. Shapiro can be contacted at nshapiro@bidmc.harvard.edu or at the Department of Emergency Medicine, Rosenberg 2, Beth Israel Deaconess Medical Center–Harvard Medical School, 330 Brookline Ave., Boston, MA 02216.

*The lists of the members of the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) Investigators and the National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury (PETAL) Network are provided in the Supplementary Appendix, available at NEJM.org.

Drs. Shapiro and Douglas contributed equally to this article.

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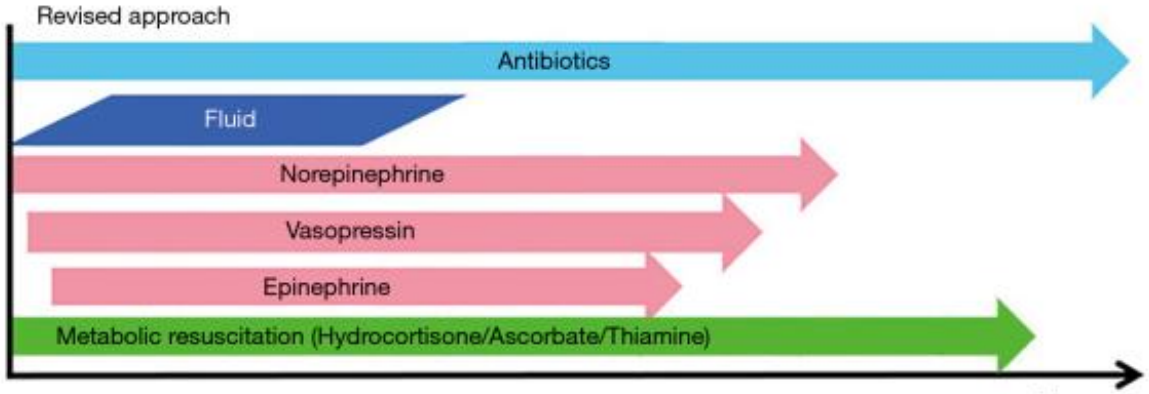
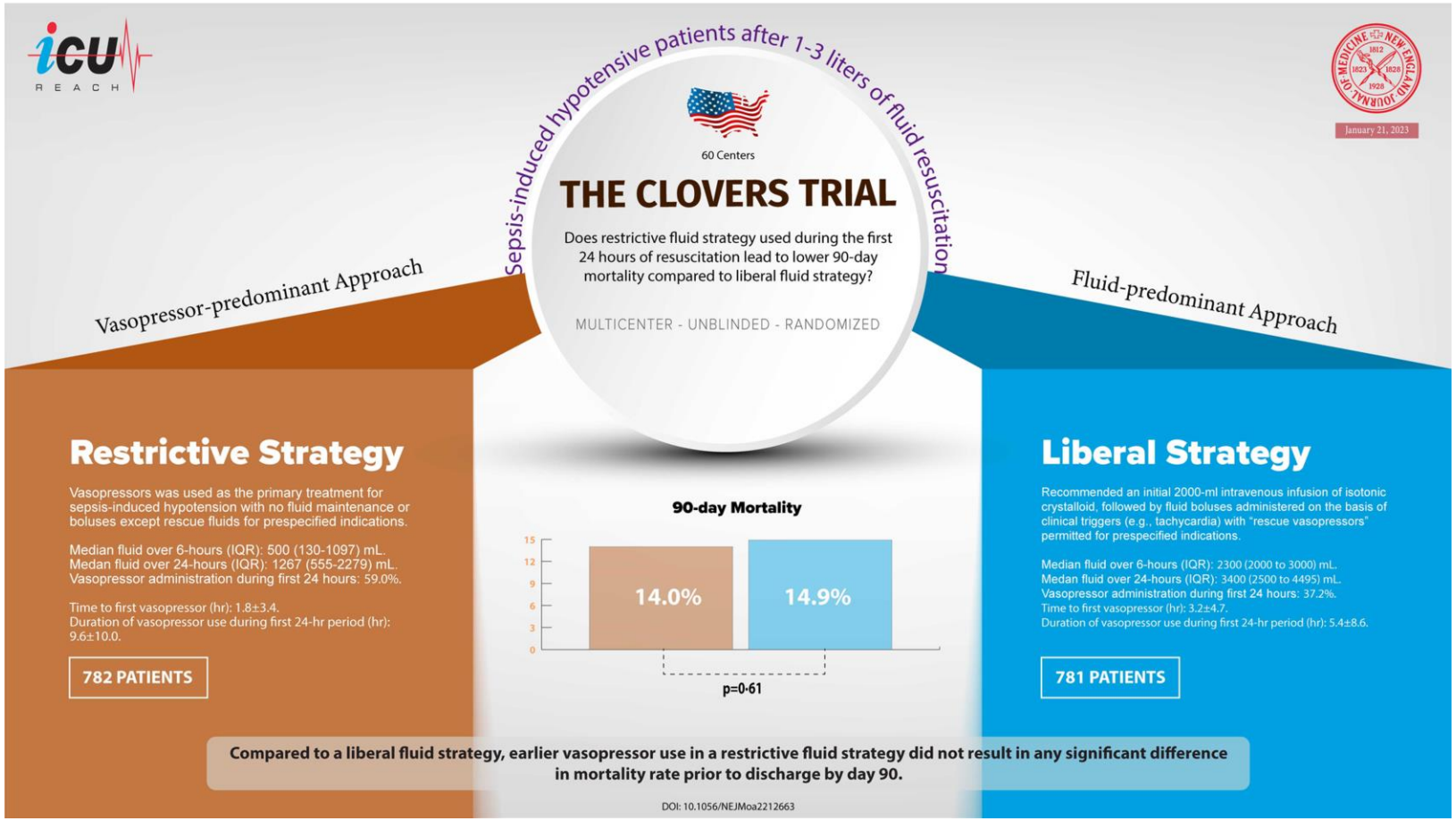


Paul Marik

- large RCT of 1400 pts
- crystalloids vs vasopressors early for resuscitation in sepsis
- a- restrictive resuscitation arm & early vasopressor arm
- b- liberal/usual care resuscitation (liberal resuscitation) and late vasopressors
- all pts early after the identification of septic shock (90% in ER)

Author's conclusions: A restrictive fluid strategy during *the first 24 hrs*, did *not results in reduced mortality* compared to a liberal fluid strategy in pts with sepsis-induced hypotension refractory to initial fluid resuscitation



the Q was
>>> potentially do these different AKI-SP, responds differently to the amount of fluid that they are receiving ?

The Interaction of Acute Kidney Injury with Resuscitation Strategy in Sepsis: A Secondary Analysis of a Multicenter, Phase 3, Randomized Trial (CLOVERS)

Authors: Ayesha Khader MD.[1]; Leila R. Zelnick PhD.[3]; Neha A. Sathe MD. MSc.[1]; Bryan R. Kestenbaum MD. MS.[3]; Jonathan Himmelfarb MD.[3]; Nicholas J. Johnson MD.[1,4]; Nathan I. Shapiro MD.[5]; Ivor S. Douglas MD.[6]; Catherine L. Hough MD. MSc.[7]; Pavan K. Bhatraju MD. MSc.[1-3] on behalf of the NHLBI PETAL Network

pts w/o prior AKI >>> liberal fluid may be better
pts w/ prior AKI >>> liberal fluid is harmful

Figure 1.

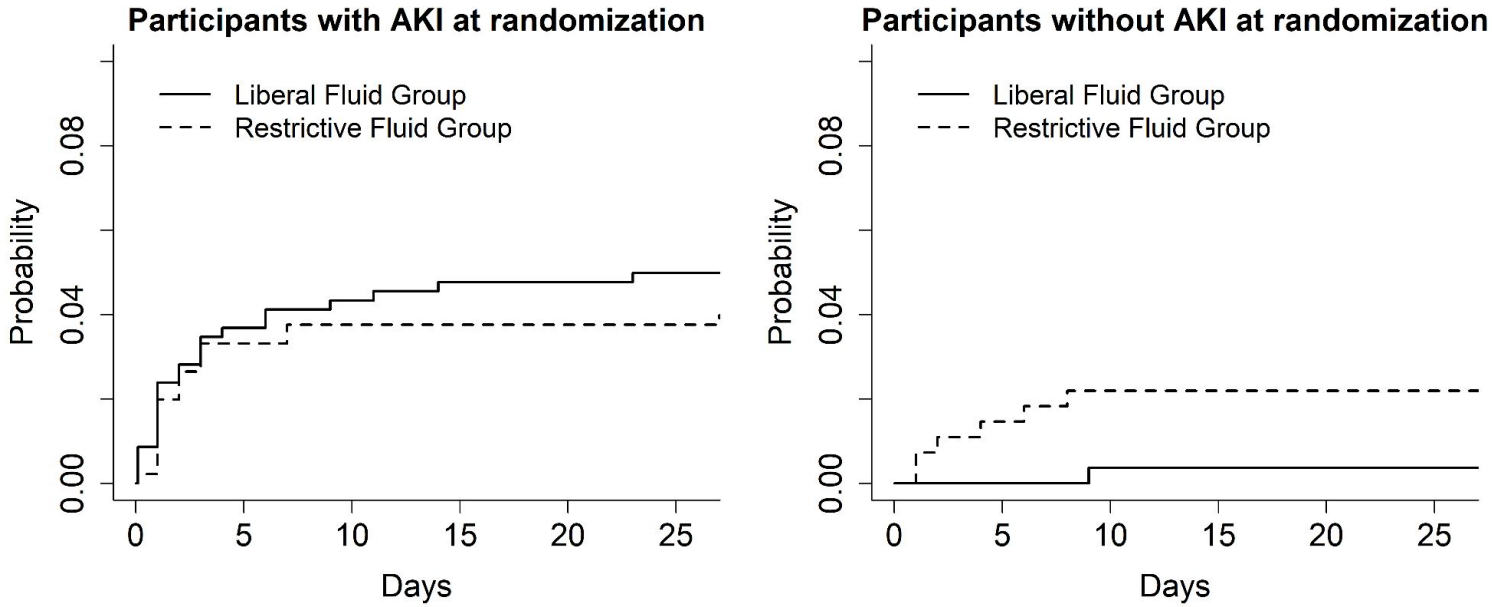
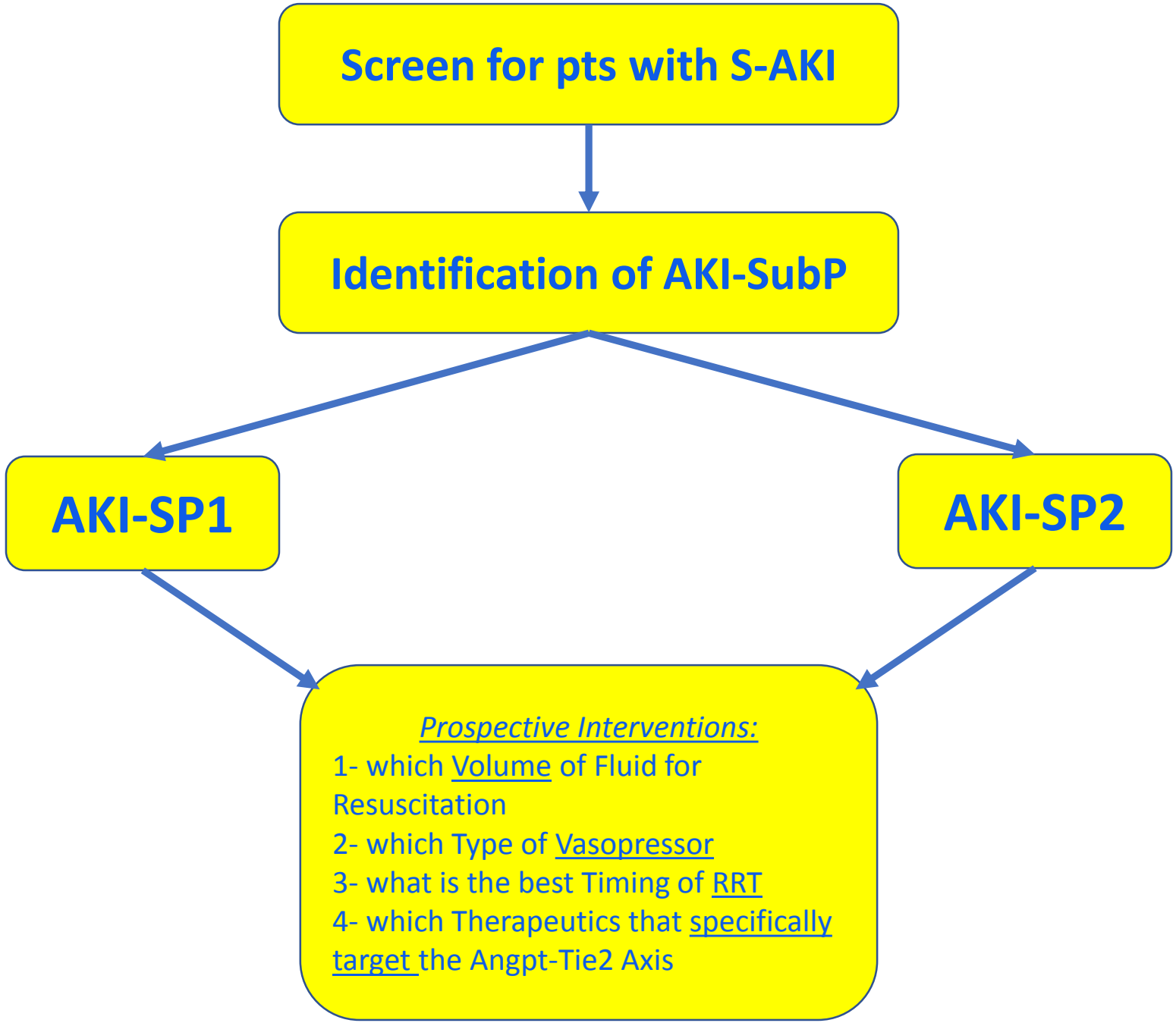


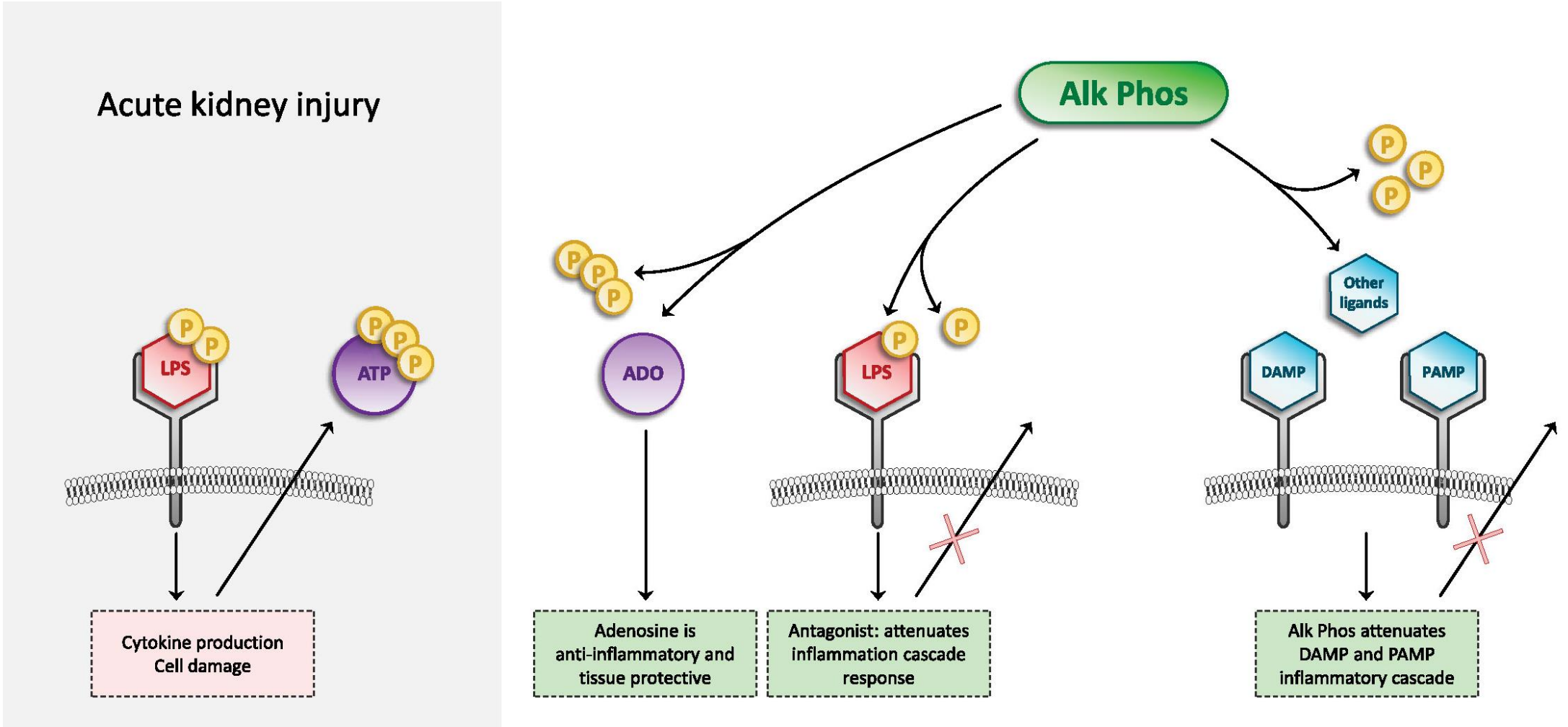
Figure Legend. Cumulative incidence plots of renal replacement therapy (RRT) in patients with and without AKI at study enrollment, randomized to a liberal or restrictive fluid strategy. Panel A demonstrates 18 RRT events within 28 days for patients with AKI who were randomized to a restrictive resuscitation strategy, and 23 RRT events in patients randomized to a liberal resuscitation strategy. Panel B demonstrates 6 RRT events within 28 days for patients without AKI who were randomized to a restrictive resuscitation strategy, and 1 RRT event in patients randomized to a liberal resuscitation strategy (*p-value* for interaction=*0.07)*.


Screen for pts with S-AKI
Identification of AKI-SubP
AKI-SP1
AKI-SP2
Prospective Interventions:
1- which Volume of Fluid for Resuscitation
2- which Type of Vasopressor
3- what is the best Timing of RRT
4- which Therapeutics that specifically target the Angpt-Tie2 Axis

is there a role for biological therapy in SA-AKI ?

anti-inflammatory biological with a *dual mechanism* of action

Alp is anti-inflammatory



rhAlp reduces:
need for RRT & the duration of RRT

Pickkers *et al. Critical Care* 2012, **16**:R14
http://ccforum.com/content/16/1/R14

CRITICAL CARE

RESEARCH Open Access

Alkaline phosphatase for treatment of sepsis-induced acute kidney injury: a prospective randomized double-blind placebo-controlled trial

Peter Pickkers[1*], Suzanne Heemskerk[1,2], Jeroen Schouten[3], Pierre-François Laterre[4], Jean-Louis Vincent[5], Albertus Beishuizen[6], Philippe G Jorens[7], Herbert Spapen[8], Michael Bulitta[9], Wilbert HM Peters[10] and Johannes G van der Hoeven[1]

Abstract

Introduction: To evaluate whether alkaline phosphatase (AP) treatment improves renal function in sepsis-induced acute kidney injury (AKI), a prospective, double-blind, randomized, placebo-controlled study in critically ill patients with severe sepsis or septic shock with evidence of AKI was performed.

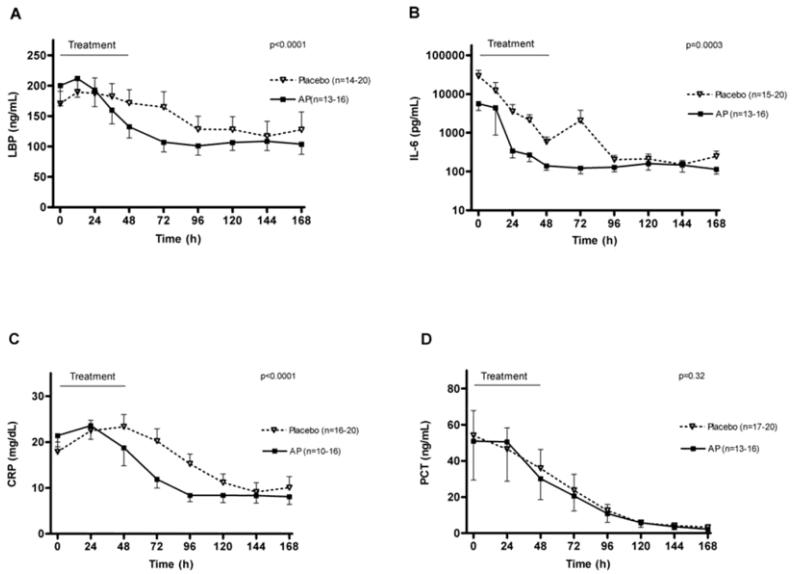
Methods: Thirty-six adult patients with severe sepsis or septic shock according to Systemic Inflammatory Response Syndrome criteria and renal injury defined according to the AKI Network criteria were included. Dialysis intervention was standardized according to Acute Dialysis Quality Initiative consensus. Intravenous infusion of alkaline phosphatase (bolus injection of 67.5 U/kg body weight followed by continuous infusion of 132.5 U/kg/24 h for 48 hours, or placebo) starting within 48 hours of AKI onset and followed up to 28 days post-treatment. The primary outcome variable was progress in renal function variables (endogenous creatinine clearance, requirement and duration of renal replacement therapy, RRT) after 28 days. The secondary outcome variables included changes in circulating inflammatory mediators, urinary excretion of biomarkers of tubular injury, and safety.

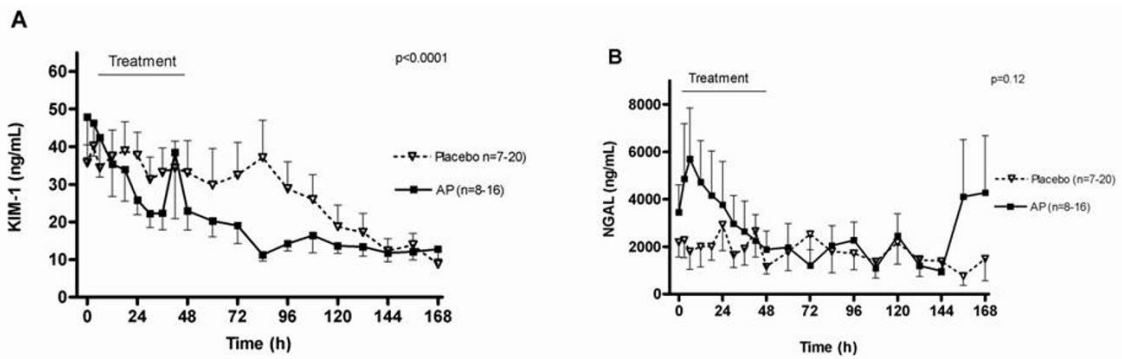
Results: There was a significant ($P = 0.02$) difference in favor of AP treatment relative to controls for the primary outcome variable. Individual renal parameters showed that endogenous creatinine clearance (baseline to Day 28) was significantly higher in the treated group relative to placebo (from 50 ± 27 to 108 ± 73 mL/minute (mean ± SEM) for the AP group; and from 40 ± 37 to 65 ± 30 mL/minute for placebo; $P = 0.01$). Reductions in RRT requirement and duration did not reach significance. The results in renal parameters were supported by significantly more pronounced reductions in the systemic markers C-reactive protein, Interleukin-6, LPS-binding protein and in the urinary excretion of Kidney Injury Molecule-1 and Interleukin-18 in AP-treated patients relative to placebo. The Drug Safety Monitoring Board did not raise any issues throughout the trial.

Conclusions: The improvements in renal function suggest alkaline phosphatase is a promising new treatment for patients with severe sepsis or septic shock with AKI.

Trial Registration: www.clinicaltrials.gov: NCTNCT00511186

Keywords: sepsis, systemic inflammatory response syndrome, septic shock, acute renal failure, therapy





BMJ Open

Study protocol for a multicentre randomised controlled trial: *S*afety, *T*olerability, efficacy and quality of life *O*f a human recombinant alkaline *P*hosphatase in patients with sepsis-associated *A*cute *K*idney *I*njury (STOP-AKI)

Esther Peters,[1,2] Ravindra L Mehta,[3] Patrick T Murray,[4] Jürgen Hummel,[5] Michael Joannidis,[6] John A Kellum,[7] Jacques Arend,[8] Peter Pickkers[1]

To cite: Peters E, Mehta RL, Murray PT, *et al*. Study protocol for a multicentre randomised controlled trial: *S*afety, *T*olerability, efficacy and quality of life *O*f a human recombinant alkaline *P*hosphatase in patients with sepsis-associated *A*cute *K*idney *I*njury (STOP-AKI). *BMJ Open* 2016;**6**:e012371. doi:10.1136/bmjopen-2016-012371

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-012371).

JA and PP share senior authorship.

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ABSTRACT

Introduction: Acute kidney injury (AKI) occurs in 55–60% of critically ill patients, and sepsis is the most common underlying cause. No pharmacological treatment options are licensed to treat sepsis-associated AKI (SA-AKI); only supportive renal replacement therapy (RRT) is available. One of the limited number of candidate compounds in clinical development to treat SA-AKI is alkaline phosphatase (AP). The renal protective effect of purified bovine intestinal AP has been demonstrated in critically ill sepsis patients. To build on these observations, a *human recombinant* AP (recAP) was developed, of which safety and efficacy in patients with SA-AKI will be investigated in this trial.

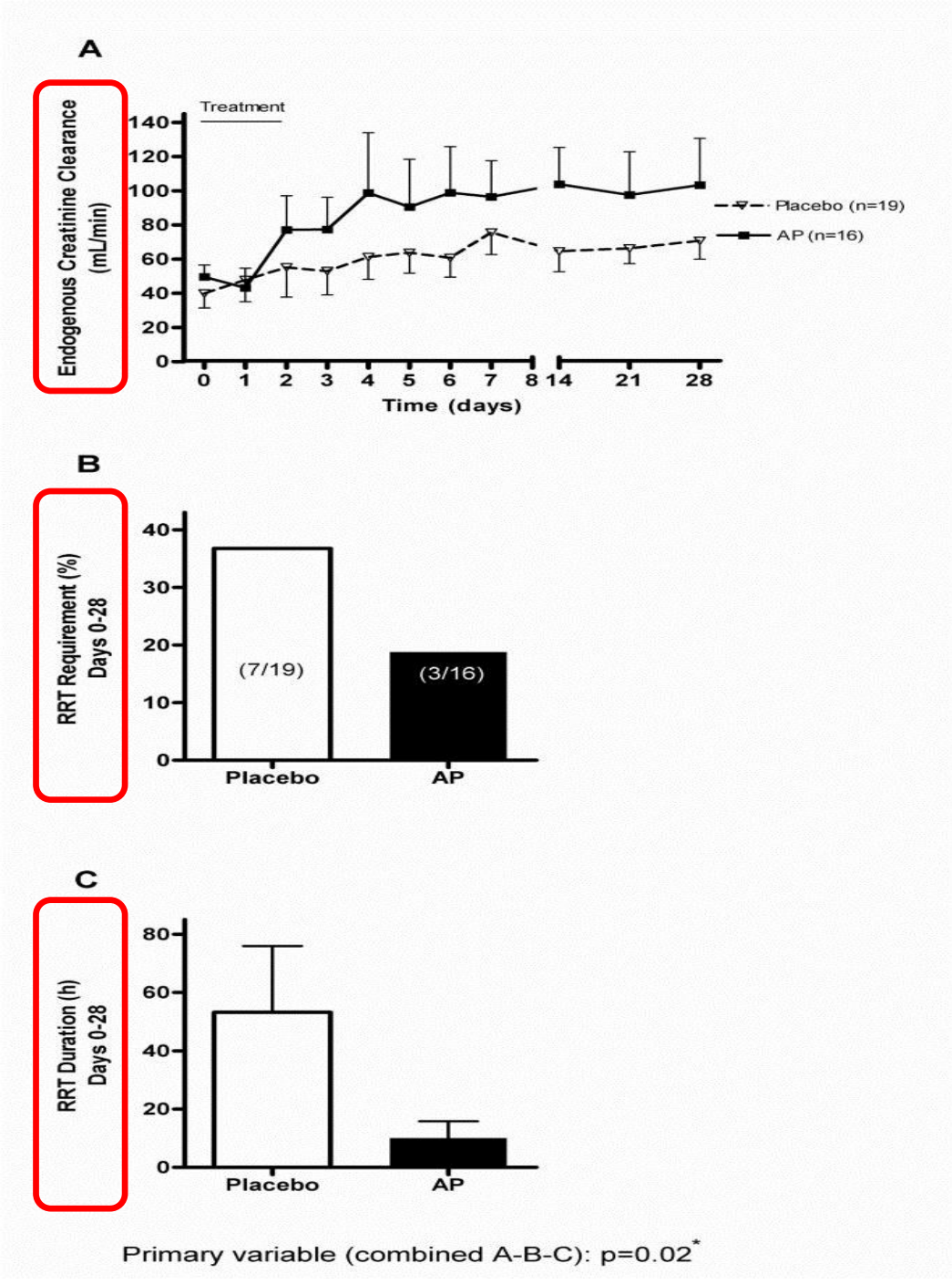
Methods: This is a randomised, double-blind, placebo-controlled, 4-arm, proof-of-concept, dose-finding adaptive phase IIa/IIb study, conducted in critically ill patients with SA-AKI. A minimum of 290 patients will be enrolled at ~50 sites in the European Union and North America. The study involves 2 parts. Patients enrolled during Part 1 will be randomly assigned to receive either placebo (n=30) or 1 of 3 different doses of recAP (n=30 per group) once daily for 3 days (0.4, 0.8 or 1.6 mg/kg). In Part 2, patients will be randomly assigned to receive the most efficacious dose of recAP (n=85), selected during an interim analysis, or placebo (n=85). Treatment must be administered within 24 hours after SA-AKI is first diagnosed and within 96 hours from first diagnosis of sepsis. The primary end point is the area under the time-corrected endogenous creatinine clearance curve from days 1 to 7. The key secondary end point is RRT incidence during days 1–28.

Ethics and dissemination: This study is approved by the relevant institutional review boards/independent ethics committees and is conducted in accordance with the ethical principles of the Declaration of Helsinki, guidelines of Good Clinical Practice, Code of Federal Regulations and all other applicable regulations. Results of this study will reveal the efficacy of recAP for the improvement of renal function in critically ill patients with SA-AKI and will be published in a peer-reviewed scientific journal.

Trial registration number: NCT02182440; Pre-results.

Strengths and limitations of this study

- This is the first randomised controlled trial in sepsis-associated acute kidney injury (SA-AKI) with well-controlled comparable standard of care, as participating institutions are required to adhere to the Surviving Sepsis Campaign and KDIGO Clinical Practice Guideline for AKI recommendations and to strictly defined renal replacement therapy starting and stopping criteria.
- The study was designed by a group of leading global experts in AKI and sepsis, with input from the US Food and Drug Administration, the European Medicines Agency and several local European country authorities, resulting in a dose-finding adaptive trial.
- Results of this trial will allow us to draw conclusions on the efficacy of human recombinant alkaline phosphatase in the improvement of renal function and related clinical parameters.
- Regardless of the outcome of the intervention, data from the placebo group will provide valuable information on clinical outcome in patients with SA-AKI.
- Strict inclusion criteria and time-windows may limit generalisation of the results to the entire population of critically ill patients with SA-AKI.



Systemic and renal inflammation with impaired microcirculation in sepsis-associated acute kidney injury.

AM-Pharma

Systemic inflammation

Gram-negative bacteria

LPS

AP

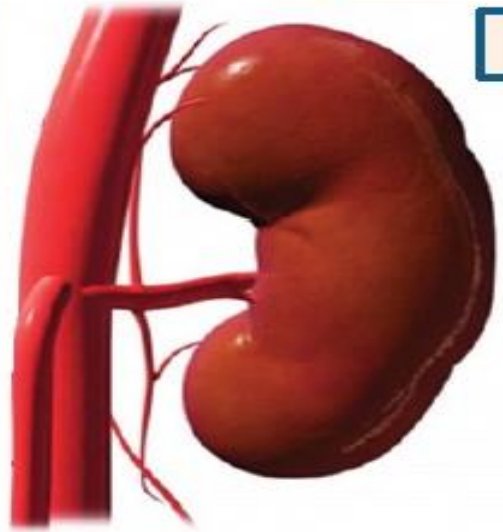
TLR4

Immune cells

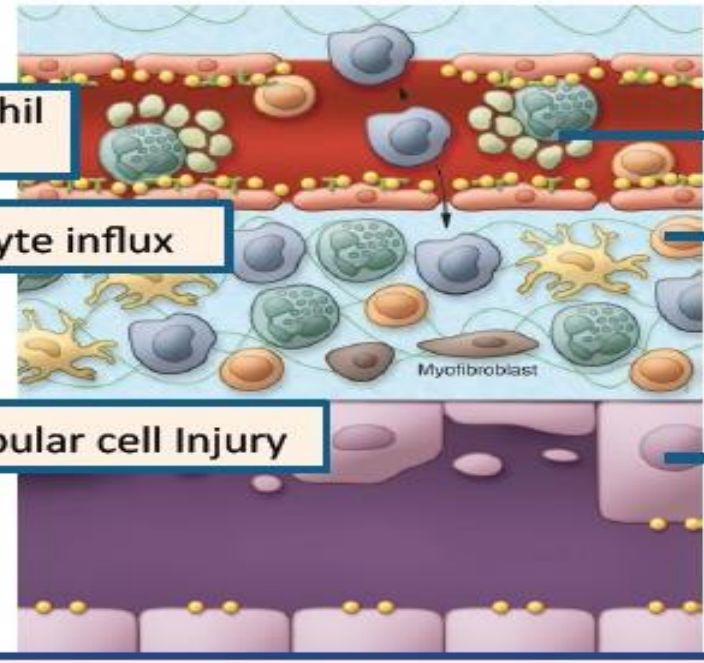
Inflammatory mediators
- Cytokines
- Extracellular ATP

ATP → ADP → AMP → Adenosine

AP AP AP



Local inflammation and injury



AP modulates the acute inflammatory process, resulting in clinical improvement of markers of inflammation, injury and function:
- Urine: KIM-1, IL-18, GSTa1, GSTp1, iNOS
- Plasma: creatinine, CRP, IL-6, LBP
- Creatinine Clearance (proxy for GFR)

BMJ Open

Study protocol of a randomised, double-blind, placebo-controlled, two-arm parallel-group, multi-centre phase 3 pivotal trial to investigate the efficacy and safety of recombinant human alkaline phosphatase for treatment of patients with sepsis-associated acute kidney injury

Peter Pickkers ,[1] Derek C Angus,[2] Jacques Arend,[3] Rinaldo Bellomo,[4,5] Erik van den Berg,[3] Juliane Bernholz,[3] Morten Bestle,[6,7] Kristine Broglio,[8] Jan Carlsen,[3] Christopher J Doig,[9] Ricard Ferrer,[10] Michael Joannidis,[11] Bruno Francois,[12] Kent Doi,[13] John A Kellum,[14] Pierre-François Laterre,[15] Kathleen Liu,[16] Ravindra L Mehta,[17] Patrick T Murray ,[18] Marlies Ostermann,[19] Ville Pettilä,[20] Sharon Richards,[21] Paul Young ,[22] Alexander Zarbock ,[23] Anne Louise Kjølbye[3]

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► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-065613).

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ABSTRACT

Introduction Sepsis, the leading cause of acute kidney injury (AKI), is associated with a high morbidity and mortality. Alkaline phosphatase (ALP) is an endogenous detoxifying enzyme. A recombinant human ALP compound, ilofotase alfa, showed no safety or tolerability concerns in a phase 2 trial. Renal function improvement over 28 days was significantly greater in the ilofotase alfa group. Moreover, a significant relative reduction in 28-day all-cause mortality of >40% was observed. A follow-up trial has been designed to confirm these findings.

Methods and analysis This is a phase 3, global, multi-centre, randomised, double-blind, placebo-controlled, sequential design trial in which patients are randomly assigned to either placebo or 1.6 mg/kg ilofotase alfa. Randomisation is stratified by baseline modified Sequential Organ Failure Assessment (mSOFA) score and trial site. The primary objective is to confirm the survival benefit with ilofotase alfa by demonstrating a reduction in 28-day all-cause mortality in patients with sepsis-associated AKI requiring vasopressors. A maximum of 1400 patients will be enrolled at ~120 sites in Europe, North America, Japan, Australia and New Zealand. Up to four interim analyses will take place. Based on predefined decision rules, the trial may be stopped early for futility or for effectiveness. In addition, patients with COVID-19 disease and patients with 'moderate to severe' chronic kidney disease are analysed as 2 separate cohorts of 100 patients each. An independent Data Monitoring Committee evaluates safety data at prespecified intervals throughout the trial.

Ethics and dissemination The trial is approved by relevant institutional review boards/independent ethics committees and is conducted in accordance with the ethical principles of the Declaration of Helsinki, guidelines of Good Clinical Practice, Code of Federal Regulations and all other applicable regulations. Results of this study will determine the potential of ilofotase alfa to reduce mortality in critically ill patients with sepsis-associated AKI and will be published in a peer-reviewed scientific journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Apart from the primary endpoint, results of this trial may also illustrate the efficacy of ilofotase alfa on renal endpoints and other organ-specific clinical outcomes.
⇒ The trial was designed with input from or review by the US Food and Drug Administration, the European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency and several national medicinal regulatory authorities in Europe, Australia and New Zealand.
⇒ The group sequential trial design allows for the results to be reported in case the trial is terminated prematurely for futility.
⇒ In the additional separate COVID-19 and 'moderate to severe' chronic kidney disease cohorts, therapeutic efficacy on clinical endpoints is likely underpowered to reach statistical significance.

REVIVAL

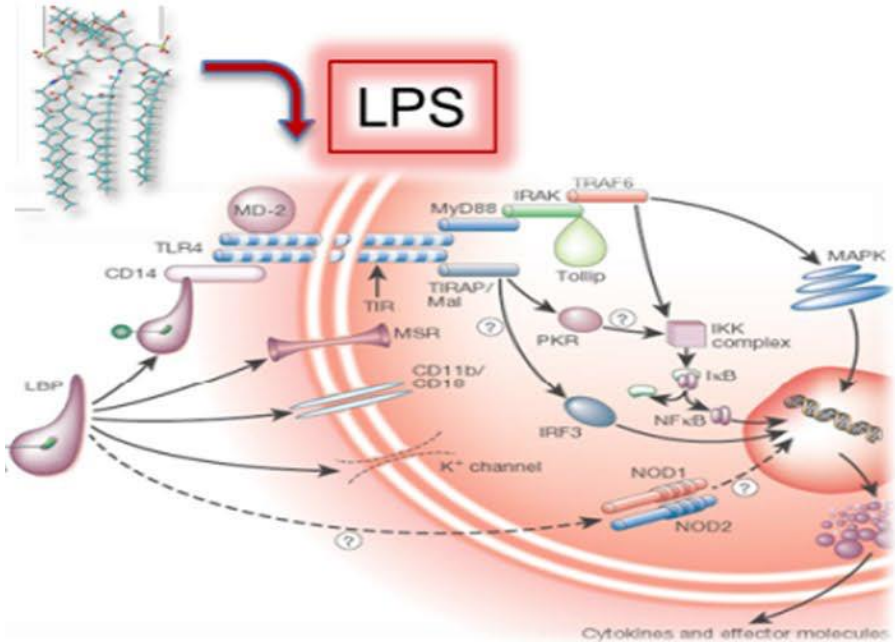
ICU pts w/ **sepsis + VC needs** (NE at least 0.1 microgram/kg/min) + **KDIGO criteria AKI**
interim-analysis >>> **411** pts in the main cohort
Mortality:
Ilofotase alpha >>> 29% & Placebo 26%
>>> Mort **not sig different** >>> the trial was stopped for futility !
BUT
a key **2nd endpoint** >>> **MAKE 90** >>> sig better w/ Ilofotase >>> **mainly for reducing the need for RRT** (28% vs 36%)

the renal therapeutic efficacy of Ilofotase alpha is more pronounced in

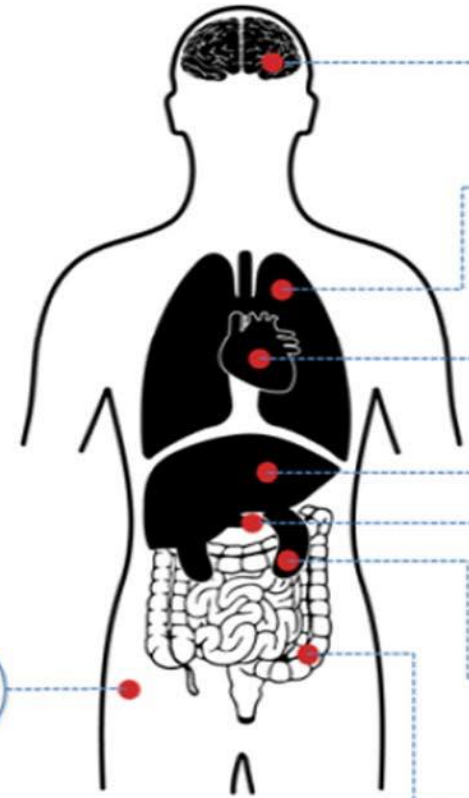
pts w/ a lower pre-AKI eGFR

“*mechanical*” possible solutions

Infection >>> Immuno response >>> Organ Damage



Humoral
Cellular
Effectors



Central nervous system
- Confusion

Lungs
- ARDS

Cardiovascular system
- Shock

Liver
- Excretory failure

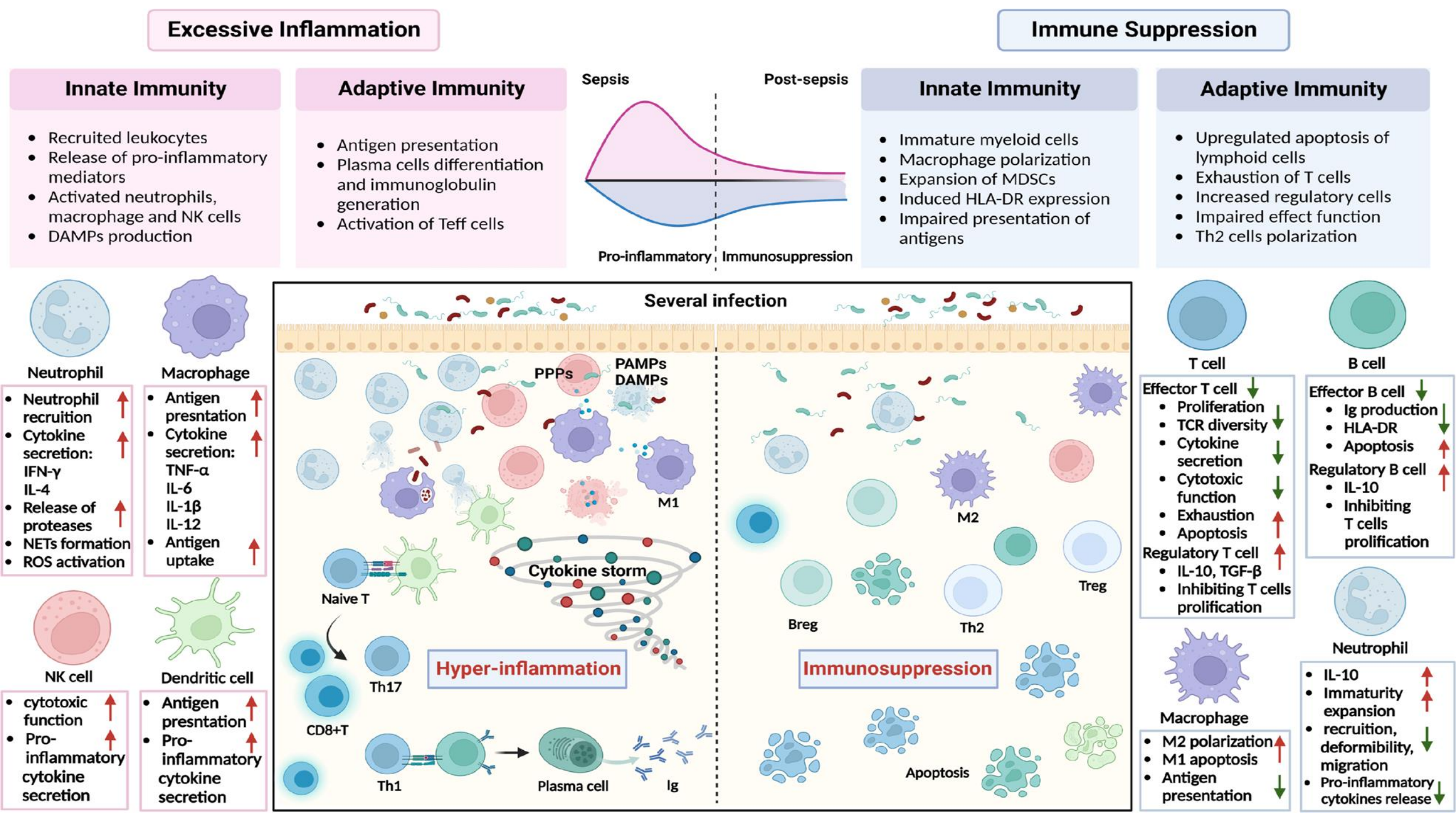
Pancreas
- Hyperglycemia

Kidneys
- Oliguria

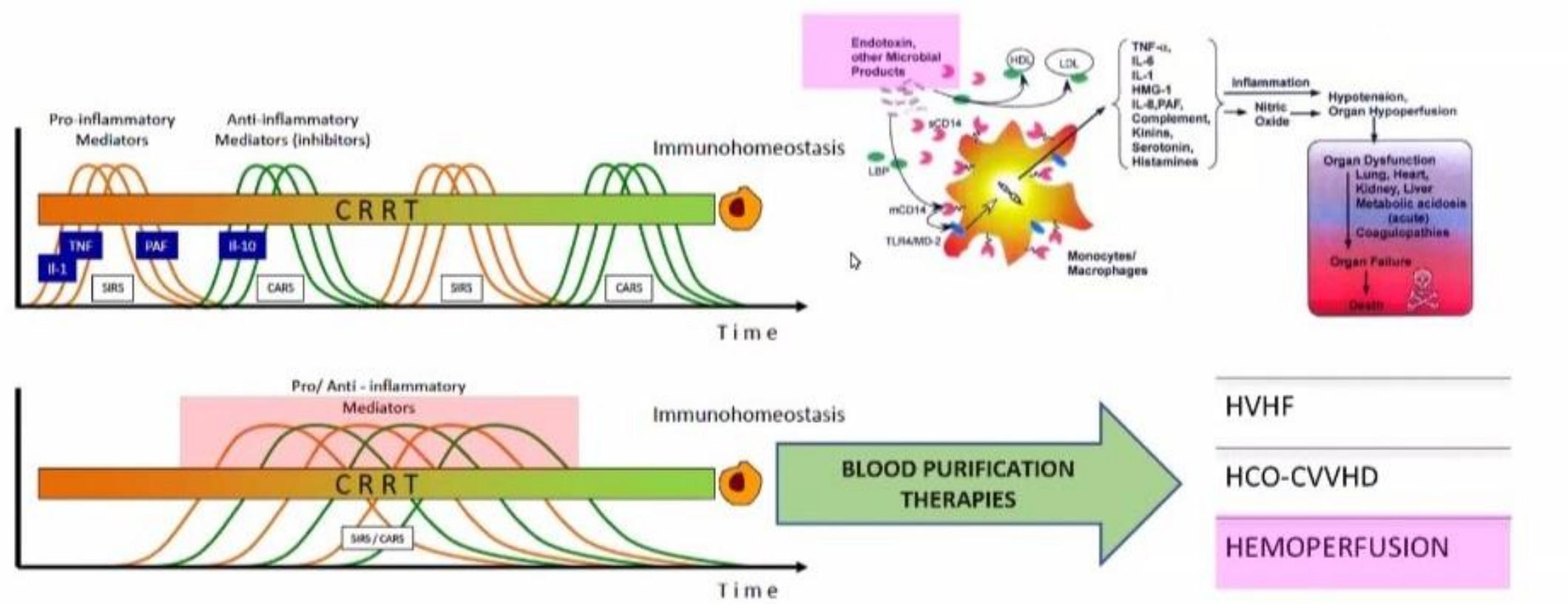
Gastrointestinal tract
- Loss of barrier function

LPS is opsonized and recognised by monocytes through CD14 leading to endothelial cell activation

Microcirculation
- Microvascular thrombosis


Excessive Inflammation
Immune Suppression
Innate Immunity
Recruited leukocytes
Release of pro-inflammatory mediators
Activated neutrophils, macrophage and NK cells
DAMPs production
Adaptive Immunity
Antigen presentation
Plasma cells differentiation and immunoglobulin generation
Activation of Teff cells
Sepsis
Post-sepsis
Pro-inflammatory
Immunosuppression
Innate Immunity
Immature myeloid cells
Macrophage polarization
Expansion of MDSCs
Induced HLA-DR expression
Impaired presentation of antigens
Adaptive Immunity
Upregulated apoptosis of lymphoid cells
Exhaustion of T cells
Increased regulatory cells
Impaired effect function
Th2 cells polarization
Neutrophil
Neutrophil recruition
Cytokine secretion: IFN-γ IL-4
Release of proteases
NETs formation
ROS activation
Macrophage
Antigen presntation
Cytokine secretion: TNF-α IL-6 IL-1β IL-12
Antigen uptake
NK cell
cytotoxic function
Pro-inflammatory cytokine secretion
Dendritic cell
Antigen presntation
Pro-inflammatory cytokine secretion
Several infection
PPPs
PAMPs
DAMPs
M1
Naive T
Cytokine storm
Th17
CD8+T
Th1
Plasma cell
Ig
Hyper-inflammation
M2
Treg
Breg
Th2
Immunosuppression
Apoptosis
T cell
Effector T cell
Proliferation
TCR diversity
Cytokine secretion
Cytotoxic function
Exhaustion
Apoptosis
Regulatory T cell
IL-10, TGF-β
Inhibiting T cells prolification
B cell
Effector B cell
Ig production
HLA-DR
Apoptosis
Regulatory B cell
IL-10
Inhibiting T cells prolification
Neutrophil
IL-10
Immaturity expansion
recruition, deformibility, migration
Pro-inflammatory cytokines release
Macrophage
M2 polarization
M1 apoptosis
Antigen presentation

the "peak concentration" hypothesis



a-specific removal of mediators

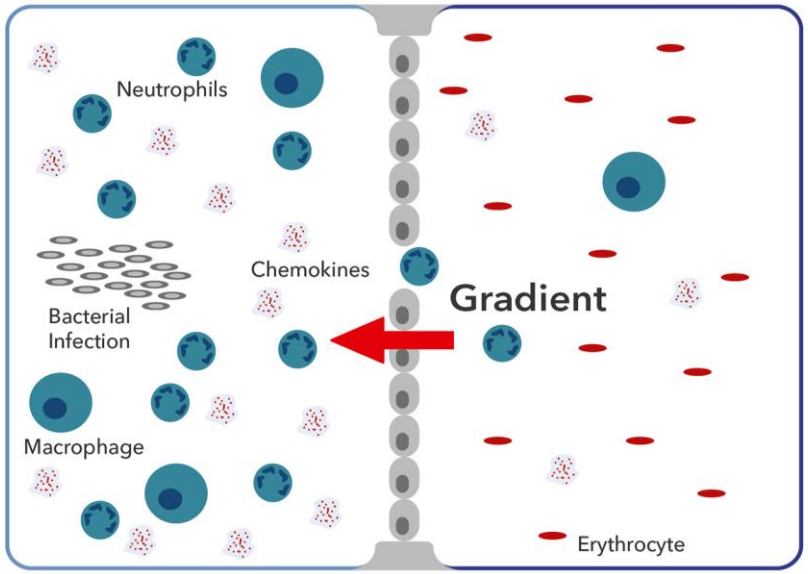
>>> **remove what is higher in concentration**

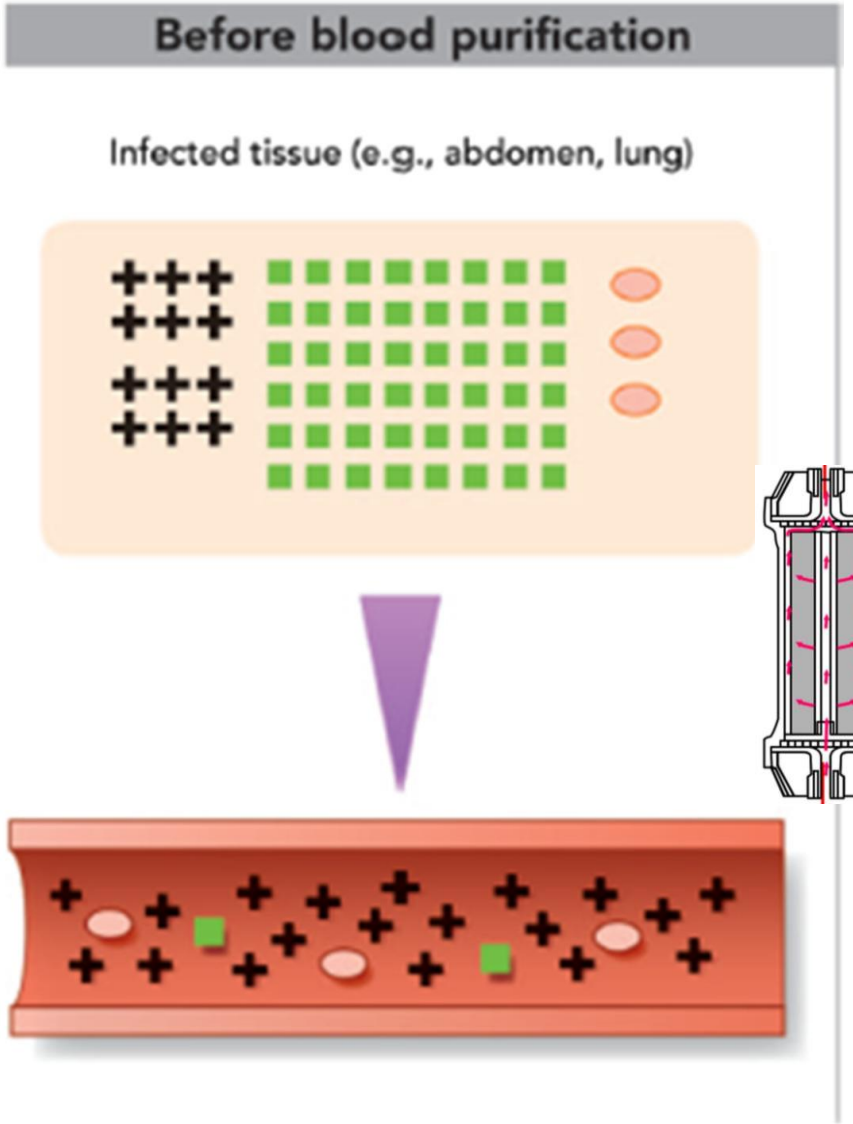
>>> trying to "equilibrate" the response

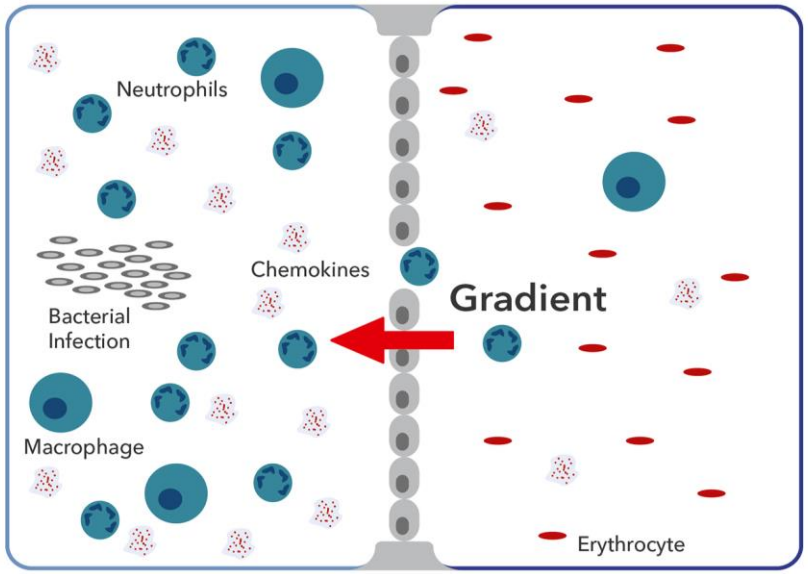
>>> slowing down the excess

>>> & so, the maximal "deviation" from the physiological pathways

Ronco C et al. Artif Organs 2003


Neutrophils
Chemokines
Gradient
Bacterial Infection
Macrophage
Erythrocyte


Before blood purification
Infected tissue (e.g., abdomen, lung)


Neutrophils
Chemokines
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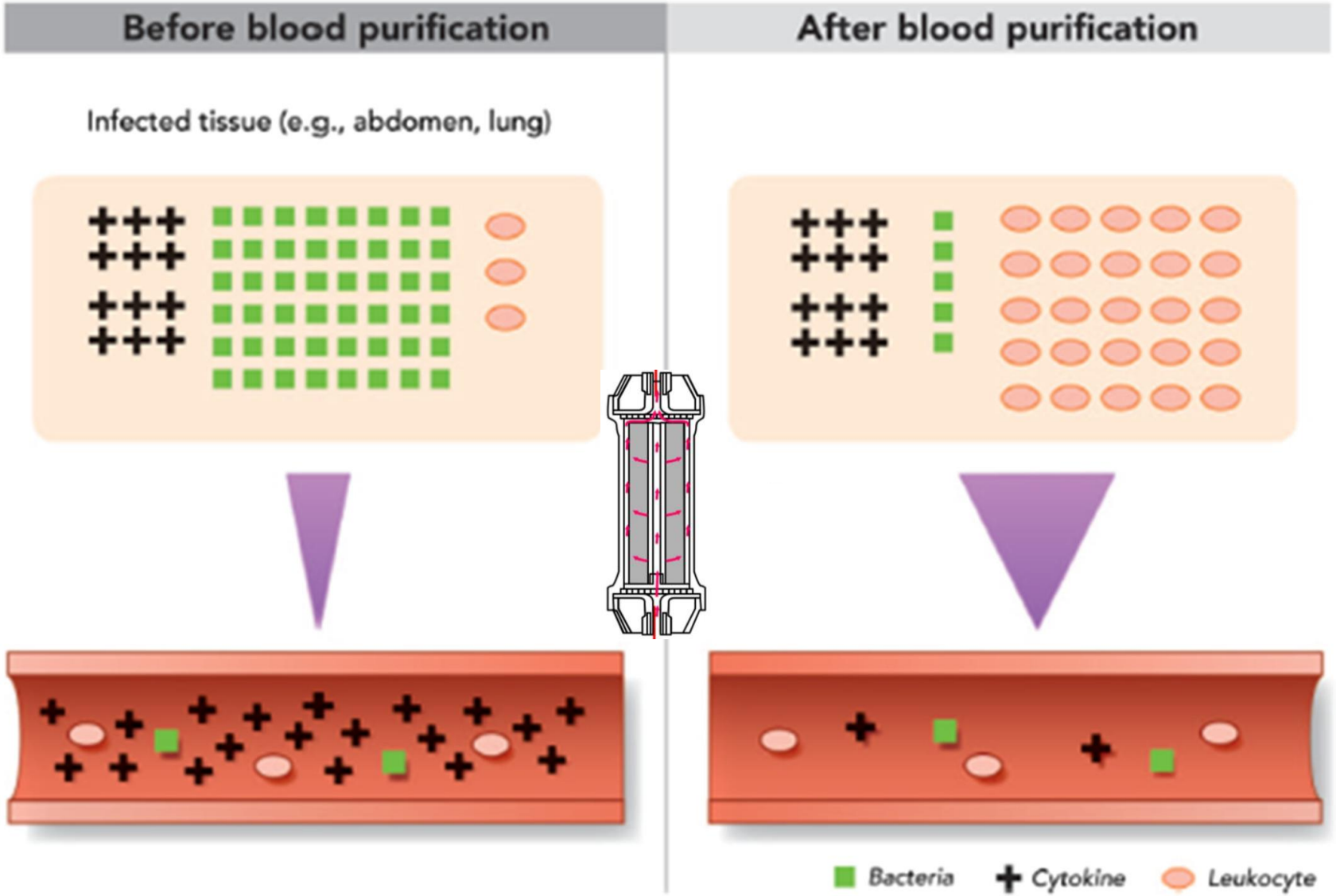
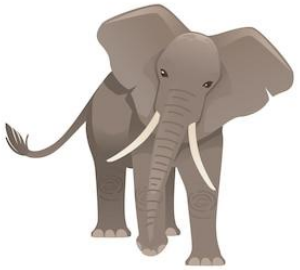

Before blood purification
After blood purification
Infected tissue (e.g., abdomen, lung)
Bacteria
Cytokine
Leukocyte

scientific evidence
decrease the mortality ?

Olivier Joannes-Boyau
Patrick M. Honoré
Paul Perez
Sean M. Bagshaw
Hubert Grand
Jean-Luc Canivet
Antoine Dewitte
Claire Flamens
Wilfried Pujol
Anne-Sophie Grandoulier
Catherine Fleureau
Rita Jacobs
Christophe Broux
Hervé Floch
Olivier Branchard
Stephane Franck
Hadrien Rozé
Vincent Collin
Willem Boer
Joachim Calderon
Bernard Gauche
Herbert D. Spapen
Gérard Janvier
Alexandre Ouattara

High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial



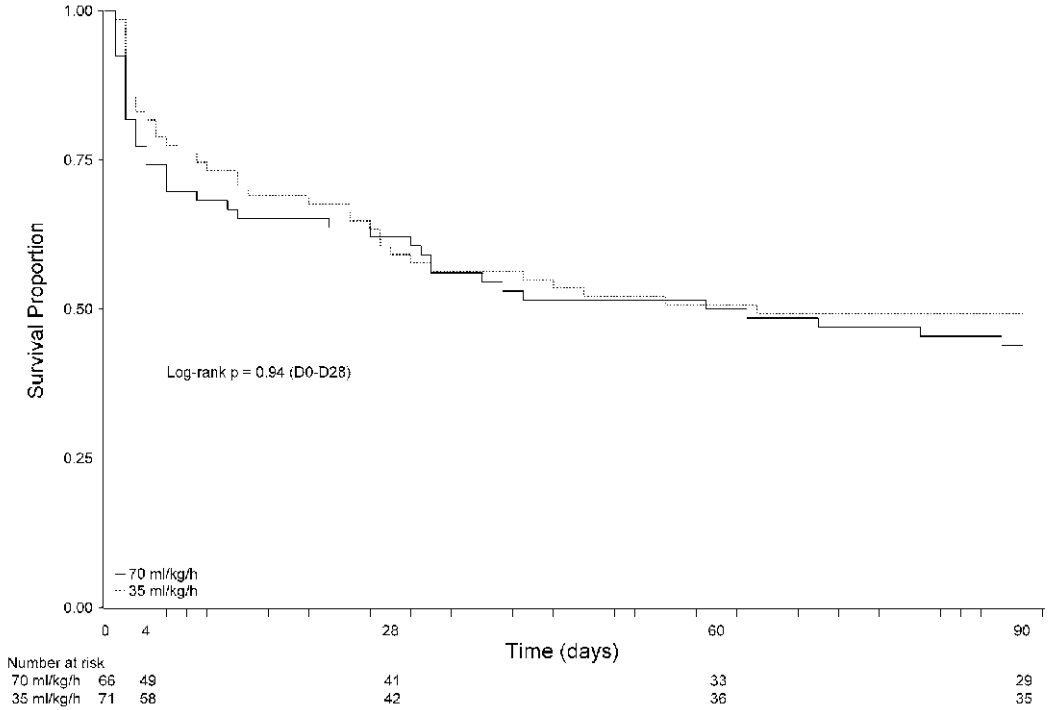
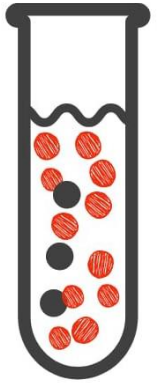


Fig. 2 Survival of participants in the IVOIRE (hIgh VOlume in Intensive caRE) trial. Participants in the HVHF group and SVHF group underwent haemofiltration at 70 mL/kg/h and 35 mL/kg/h of fluid exchange for 96 h, respectively



A Double-Blind Randomized Controlled Trial of High Cutoff Versus Standard Hemofiltration in Critically Ill Patients With Acute Kidney Injury

Rafidah Atan, PhD[1]; Leah Peck, GradCert(Crit Care)[2]; John Prowle, MD[3,4]; Elisa Licari, MD[5]; Glenn M. Eastwood, PhD[2]; Markus Storr, PhD[6]; Hermann Goehl, MSc[6]; Rinaldo Bellomo, MD[2,7]

NE dose = hemodynamic stability: not different between membranes

did not remove inflammatory mediators
did not measured any targets

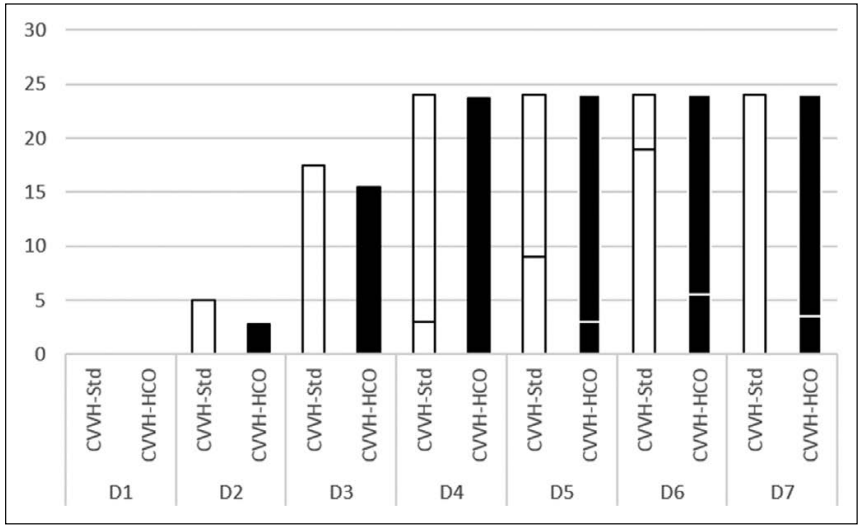


Figure 1. Norepinephrine-free time (hr) per day per group: day 1 to day 7. Values are median (*middle line*), Q1 (*lower margin*), and Q3 (*upper margin*). Continuous venovenous hemofiltration-high cutoff (CVVH-HCO): high cutoff group; continuous venovenous hemofiltration-standard (CVVH-Std): control/standard group. All patients contribute data. Nonsurvivors are recorded as having zero hours of norepinephrine-free time after death.

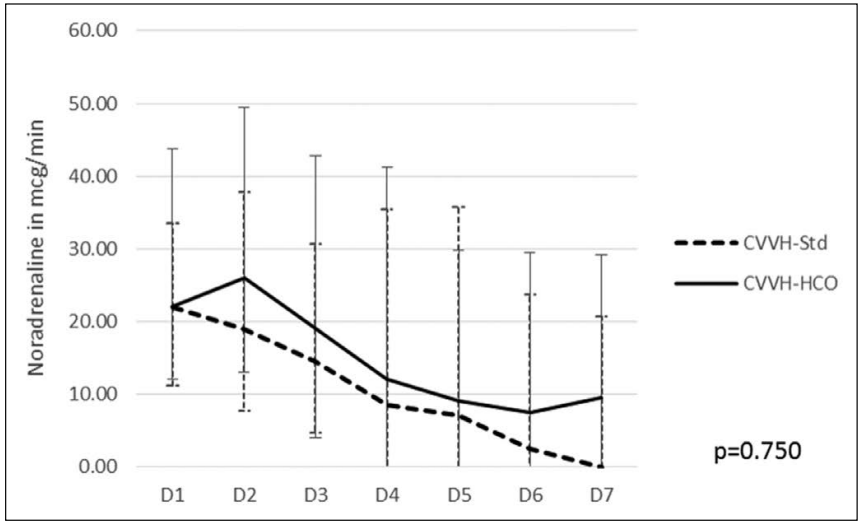
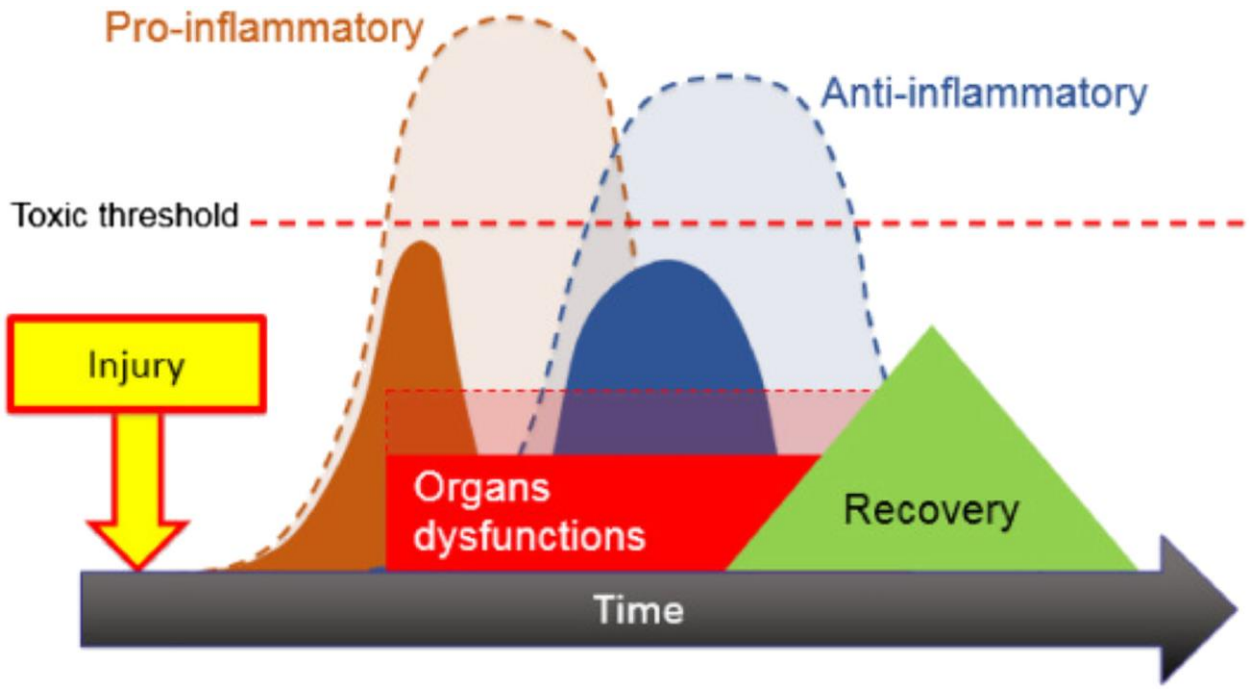
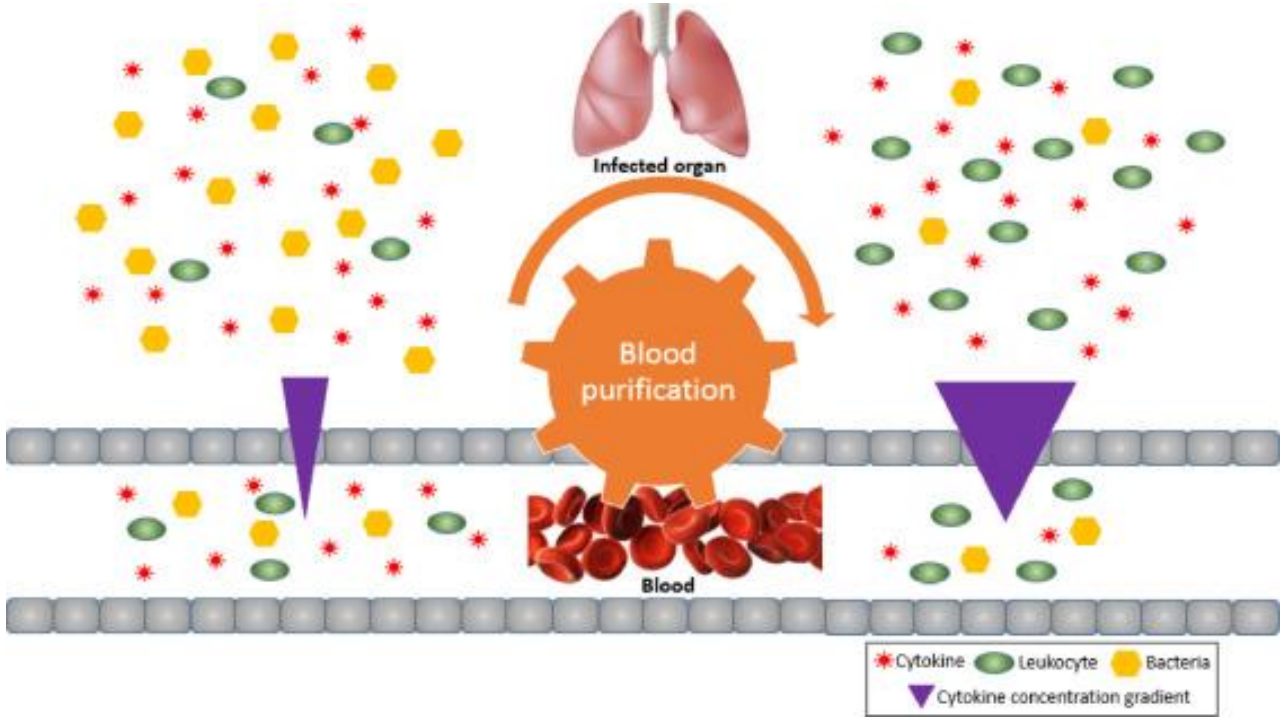


Figure 2. Median highest norepinephrine infusion rates per day. *Error bars* indicate interquartile ranges. Continuous venovenous hemofiltration-high cutoff (CVVH-HCO): high cutoff group; continuous venovenous hemofiltration-standard (CVVH-Std): control/standard group. $n = 36$ (CVVH-HCO); 38 (CVVH-Std).

cutting the peak & creating a gradient





Peng et al. Critical Care 2014, 18:R141
http://ccforum.com/content/18/4/R141

CRITICAL CARE

RESEARCH Open Access

Modulation of chemokine gradients by apheresis redirects leukocyte trafficking to different compartments during sepsis, studies in a rat model

Zhi-Yong Peng[1,2], Jeffery V Bishop[2], Xiao-Yan Wen[1,2], Michele M Elder[1,2], Feihu Zhou[1,2], Anan Chuasuwan[1,2], Melinda J Carter[2], Jason E Devlin[3], A Murat Kaynar[1,2], Kai Singbartl[1,2], Francis Pike[1,2], Robert S Parker[1,2,5,6], Gilles Clermont[1,2,5,6], William J Federspiel[1,2,4,6] and John A Kellum[1,2,4,6,7*]

Abstract

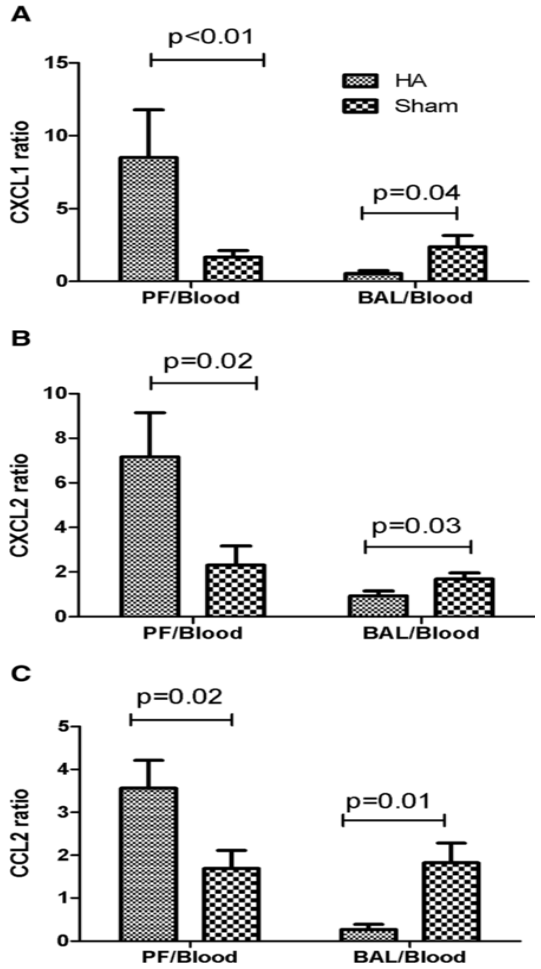
Introduction: Prior work suggests that leukocyte trafficking is determined by local chemokine gradients between the nidus of infection and the plasma. We recently demonstrated that therapeutic apheresis can alter immune mediator concentrations in the plasma, protect against organ injury, and improve survival. Here we aimed to determine whether the removal of chemokines from the plasma by apheresis in experimental peritonitis changes chemokine gradients and subsequently enhances leukocyte localization into the infected compartment, and away from healthy tissues.

Methods: In total, 76 male adult Sprague–Dawley rats weighing 400 g to 600 g were included in this study. Eighteen hours after inducing sepsis by cecal ligation and puncture, we randomized these rats to apheresis or sham treatment for 4 hours. Cytokines, chemokines, and leukocyte counts from blood, peritoneal cavity, and lung were measured. In a separate experiment, we labeled neutrophils from septic donor animals and injected them into either apheresis or sham-treated animals. All numeric data with normal distributions were compared with one-way analysis of variance, and numeric data not normally distributed were compared with the Mann–Whitney *U* test.

Results: Apheresis significantly removed plasma cytokines and chemokines, increased peritoneal fluid-to-blood chemokine (C-X-C motif ligand 1, ligand 2, and C-C motif ligand 2) ratios, and decreased bronchoalveolar lavage fluid-to-blood chemokine ratios, resulting in enhanced leukocyte recruitment into the peritoneal cavity and improved bacterial clearance, but decreased recruitment into the lung. Apheresis also reduced myeloperoxidase activity and histologic injury in the lung, liver, and kidney. These Labeled donor neutrophils exhibited decreased localization in the lung when infused into apheresis-treated animals.

Conclusions: Our results support the concept of chemokine gradient control of leukocyte trafficking and demonstrate the efficacy of apheresis to target this mechanism and reduce leukocyte infiltration into the lung.

if we can RESTORE the gradient we can get PMN to home to the site of infection (tissue) and clear the bacteria



think sepsis/think uremia
(think in the same way)

- Uremia: we still do not exactly know, what are the molecules that we want to remove !

- Sepsis: we are not completely sure that ,what we want really to remove !

- Both: we want rather “to remove things” to achieve a balance (re-equilibration)

Sequential Extra-corporeal Therapy (SET)

Drugs

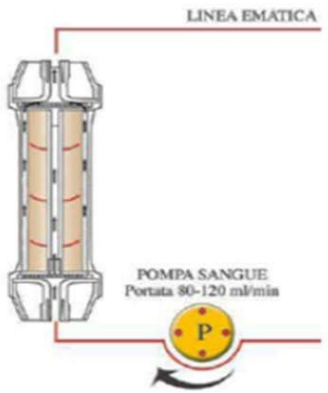
Drugs

Source control Endotoxin removal

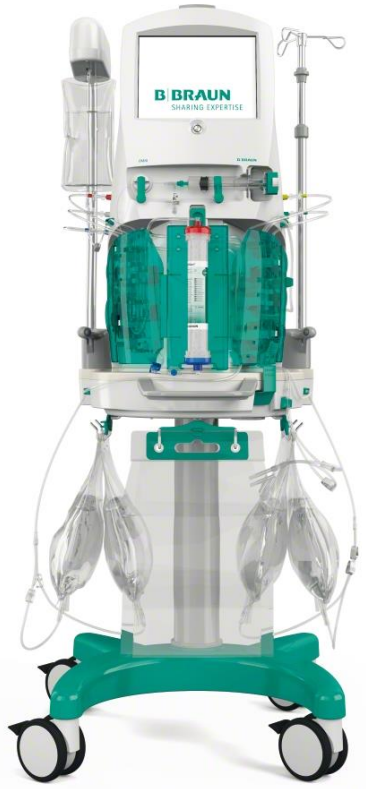
Immuno modulation Cytokine removal

Multiple Organ Support Therapy

Specific >>>>>> General Aspecific >>>>>> Specific



MOST ECOS



Concluding Thoughts

- SA-AKI has many features & many causes
- SA-AKI is not induced by hypo-tension
- Cells may not die but may “adapt” to their new critical situation
- It is difficult to choose the right and-point @ the right time
- By finding SA-AKI SP way have the chance of detection the right pt for the right treatment
- Insight into the pathophysiology offers opportunities for “targeted interventions” for SA-AKI prevention/ resolution
- Today there are NO specific therapies for SA-AKI & until then the management of SA-AKI (kidney protection), consist of good management of sepsis + possible some other solutions [mechanical (S.E.T)]

MERCI