# Acute Kidney Injury

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66 yr white male w/ DM, HTN, CAD admitted to an OSH w/ E Coli UTI on 7/24/16, developed E Coli bacteremia and Shock (on vaso + levo) transferred to BUMC 7/26/16 w/

- No UO x 12 hrs (despite IVF)
- Cr 2 (baseline 0.9)

# What’s going on?

- Is this AKI?
- Could this have been diagnosed earlier?
- How does this change his outcome?
- What’s happening at the level of the nephrons? What would a biopsy show?
- Can this be treated medically?
- Does this patient need dialysis?
- Will the patient survive after discharge?

Is this AKI?

# What is AKI?

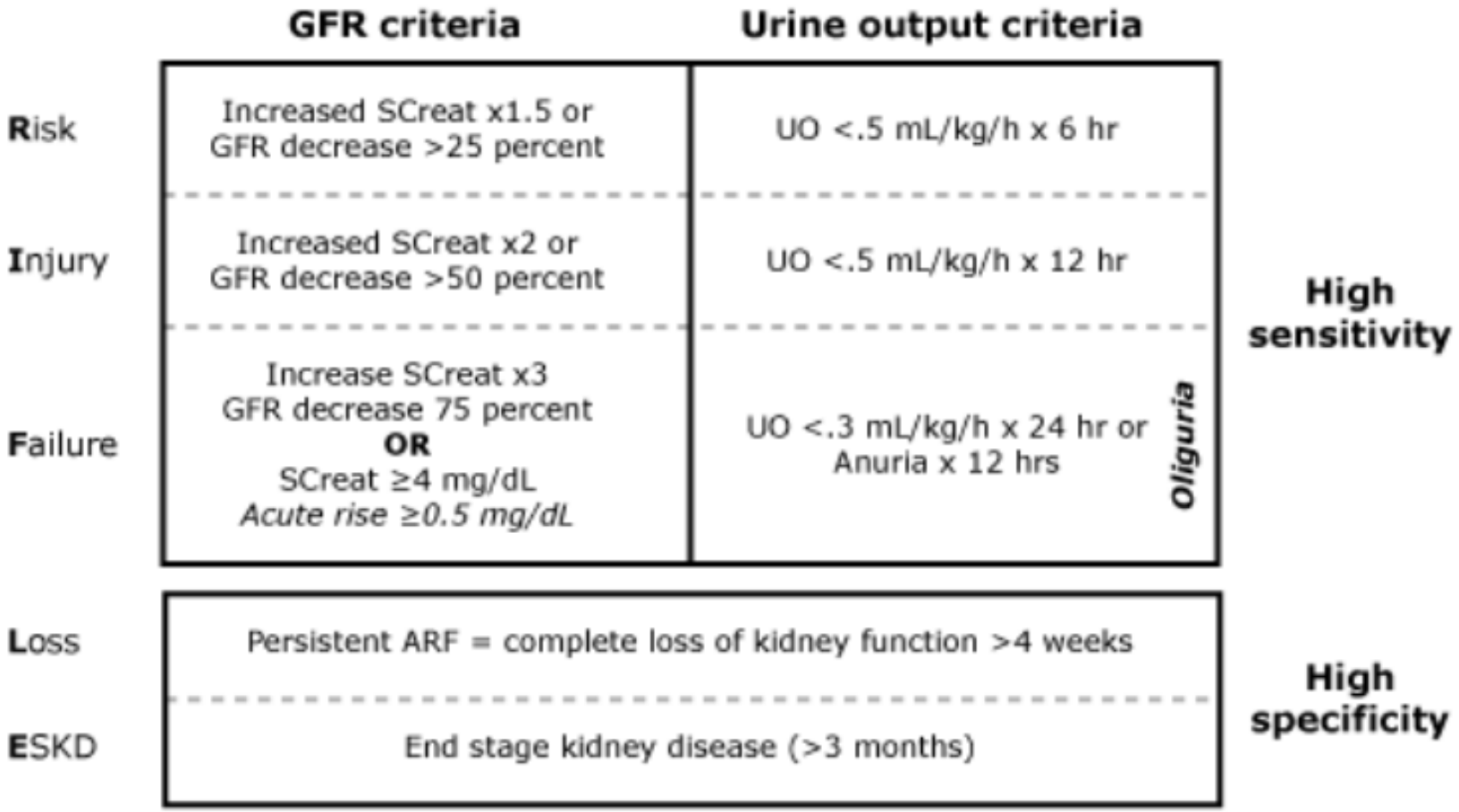
- abrupt (within 48 hours)
- absolute increase in Cr of ≥0.3 mg/dL
- increase in Cr of ≥50 percent
- oliguria of (< 0.5 mL/kg/hr) X >6 hrs

Caveats
1. only after volume status had been optimized
2. Urinary tract obstruction to be excluded (if oliguria was sole diagnostic criterion)

# What is Acute Kidney Injury?

- 2001 : Acute Dialysis Quality Initiative (ADQI)
  - Risk: 1.5x inc in SCr, GFR dec 25%, UOP<0.5 ml/kg/h x 6h
  - Injury: 2x inc SCr, GFR dec 50%, UOP<0.5 ml/kg/h x 12h
  - Failure: 3x inc SCr, GFR dec 75%, UOP<0.5/kg/h x 24h, anuria x 12 hr
  - Loss: complete loss (inc need for RRT) > 4 wks
  - ESRD: complete loss (inc need for RRT) > 3 months

- 2007: Acute Kidney Injury Network (AKIN)
  - Modified RIFLE to include ΔSCr 0.3 mg/dL from baseline, within 48hr, based on 80% mortality risk (Chertow, JASN 2005)




Bellomo, R, Ronco, C, Kellum, JA, et al. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8:B204.

Could this have been diagnosed earlier?

All the definitions (including RIFLE) depend on a surrogate marker ie creatinine

# functional versus biomarkers

| | Functional Marker | Biomarker |
|---|---|---|
| Liver damage | Hypoalbuminemia<br>Coagulopathy | SGOT<br>SGPT<br>GGT |

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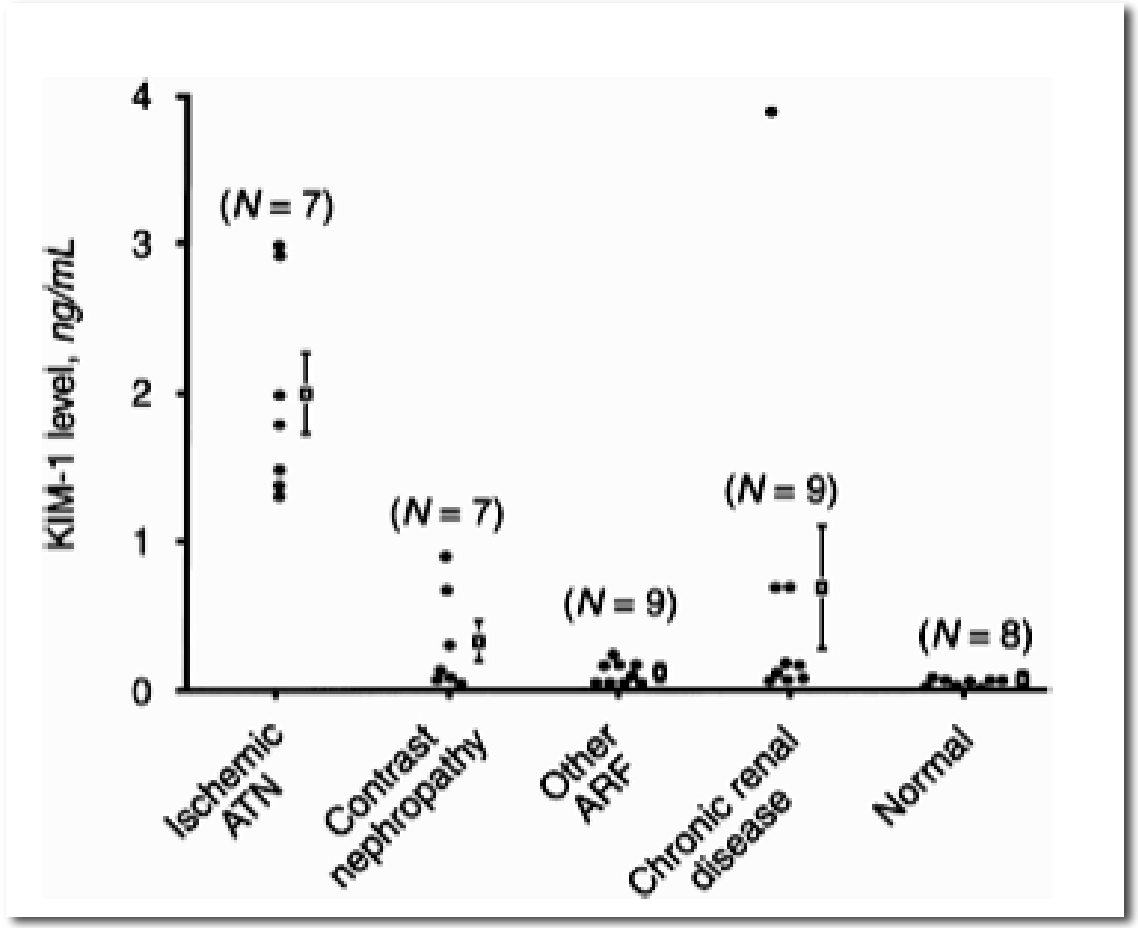
| Heart damage | Hypotension<br>Arrhythmia | Troponin I<br>Troponin T<br>CK-MB |
| Kidney damage | Creatinine<br>BUN<br>Cystatin C | KIM-1<br>NGAL |

# candidates for a renal troponin: kidney injury molecule-1 (kim-1)

- Transmembrane protein expressed in the proximal tubule.
- Expression is increased following ischemic damage
- Can be found 12 hours after renal insult



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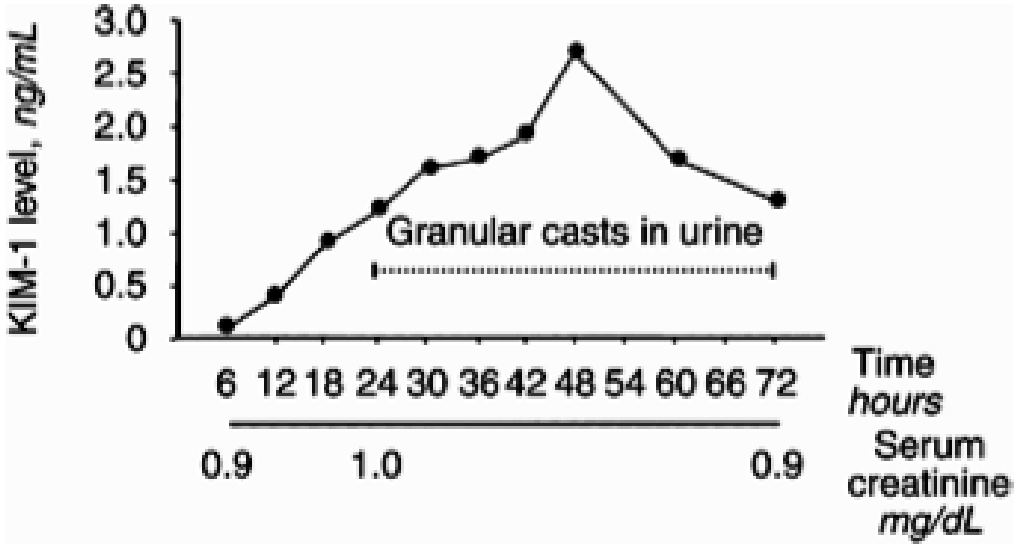
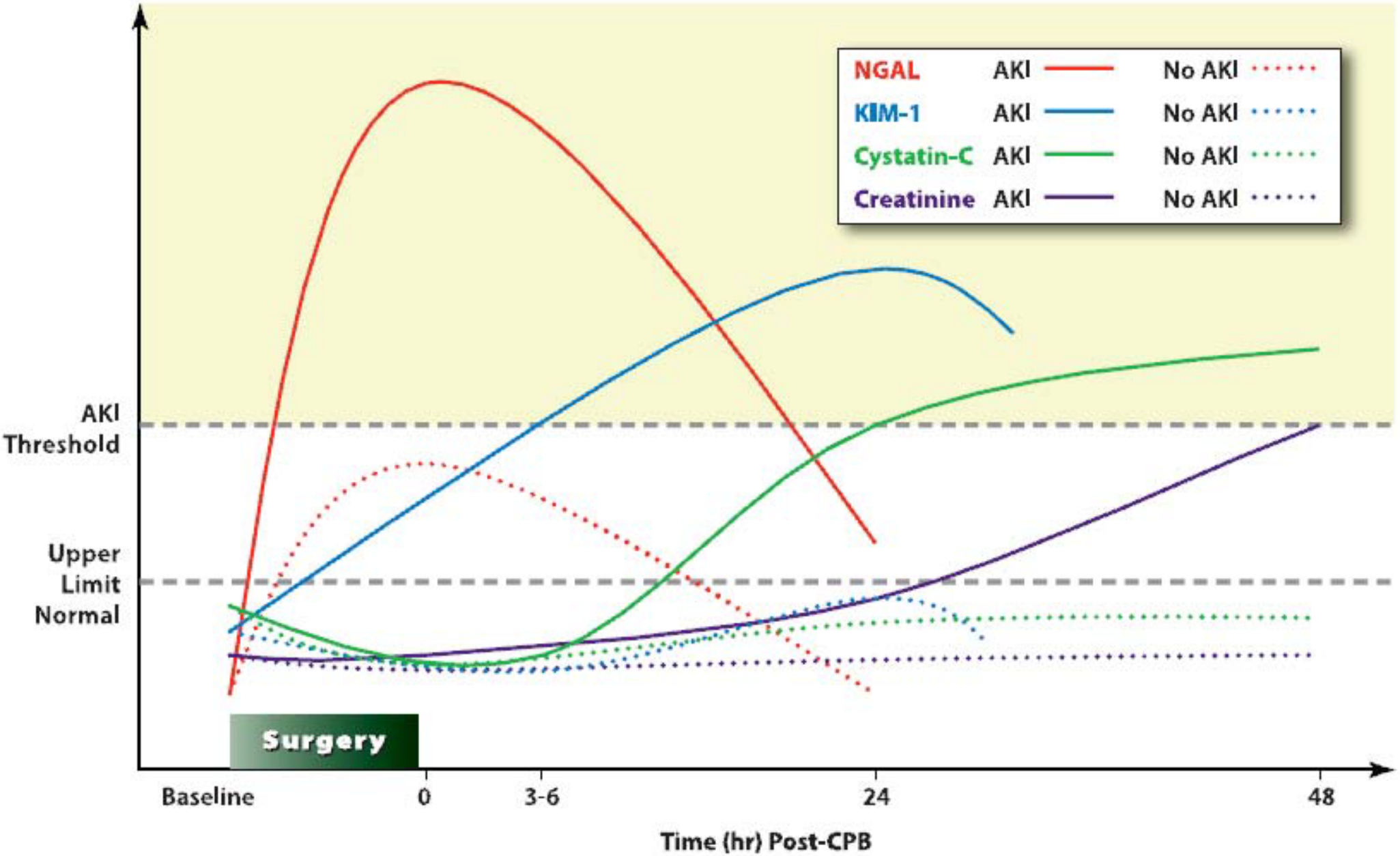
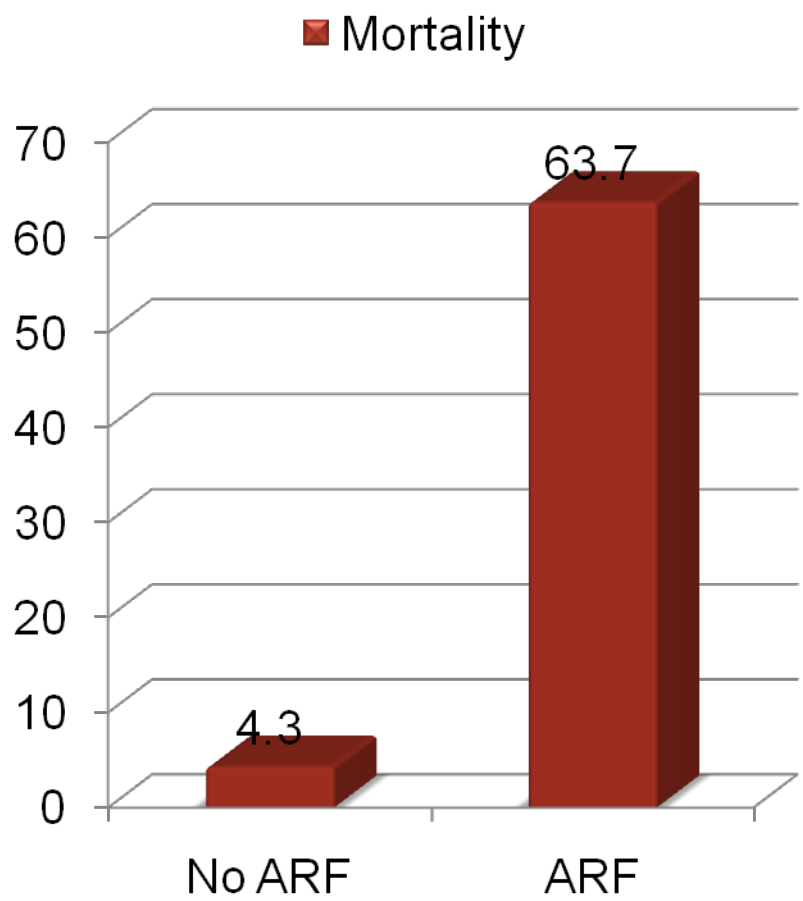
Time starts at aorta cross clamp.




NGAL AKI No AKI
KIM-1 AKI No AKI
Cystatin-C AKI No AKI
Creatinine AKI No AKI
AKI Threshold
Upper Limit Normal
Surgery
Baseline
0
3-6
24
48
Time (hr) Post-CPB

How does this change his outcome?

# Mortality following Cardiac Surgery




Odds-Ratio for Death

- Unadjusted: 39 (95% CI: 32-48)
- Adjusted for co-morbidities and postoperative complications: 7.9 (95% CI: 6-10)

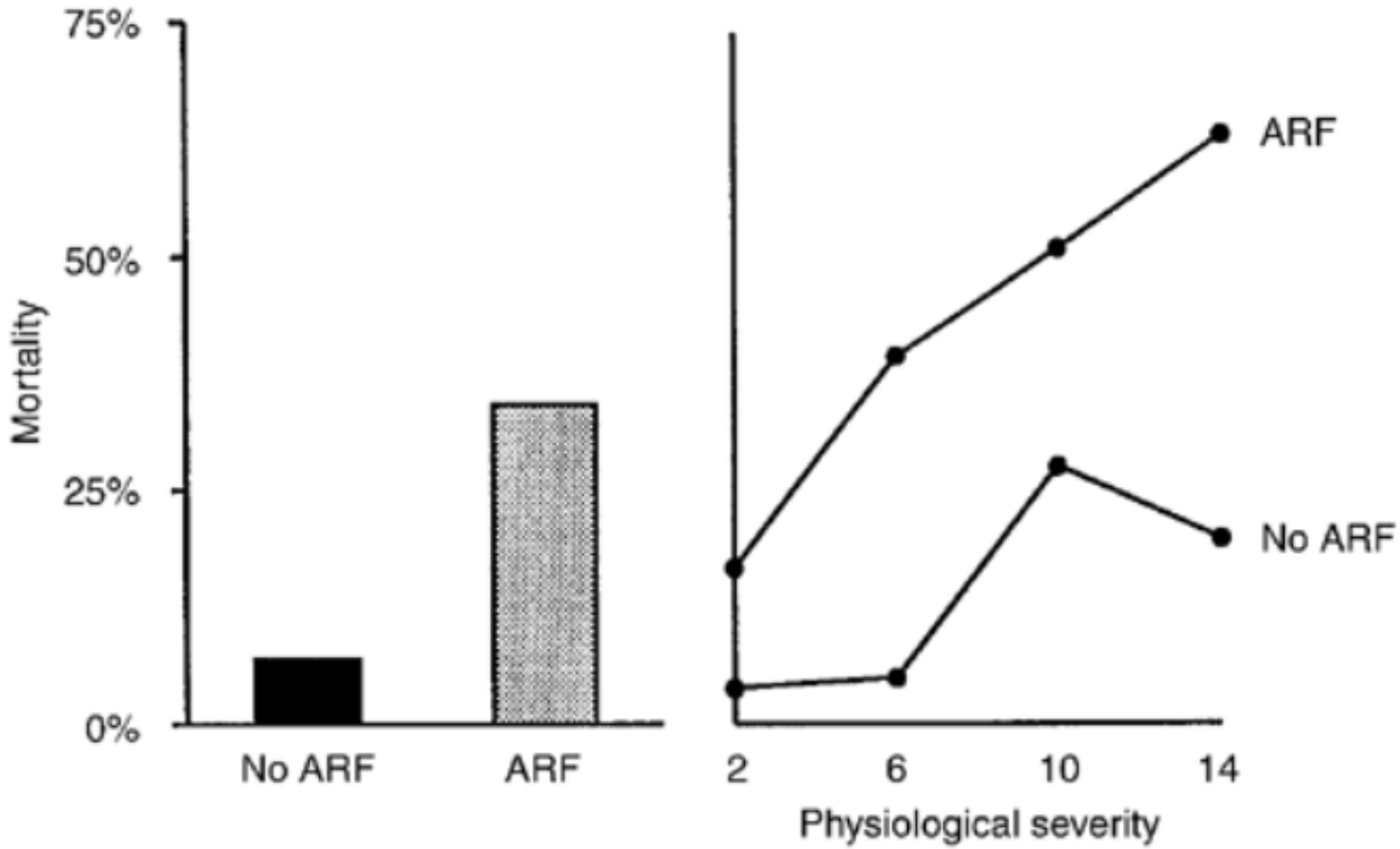
Chertow,GM et al Am J Med 1998;104:343

# AKI and Mortality(Brigham and Womens, 9210 adults)

Multivariable Odds Ratio for Death

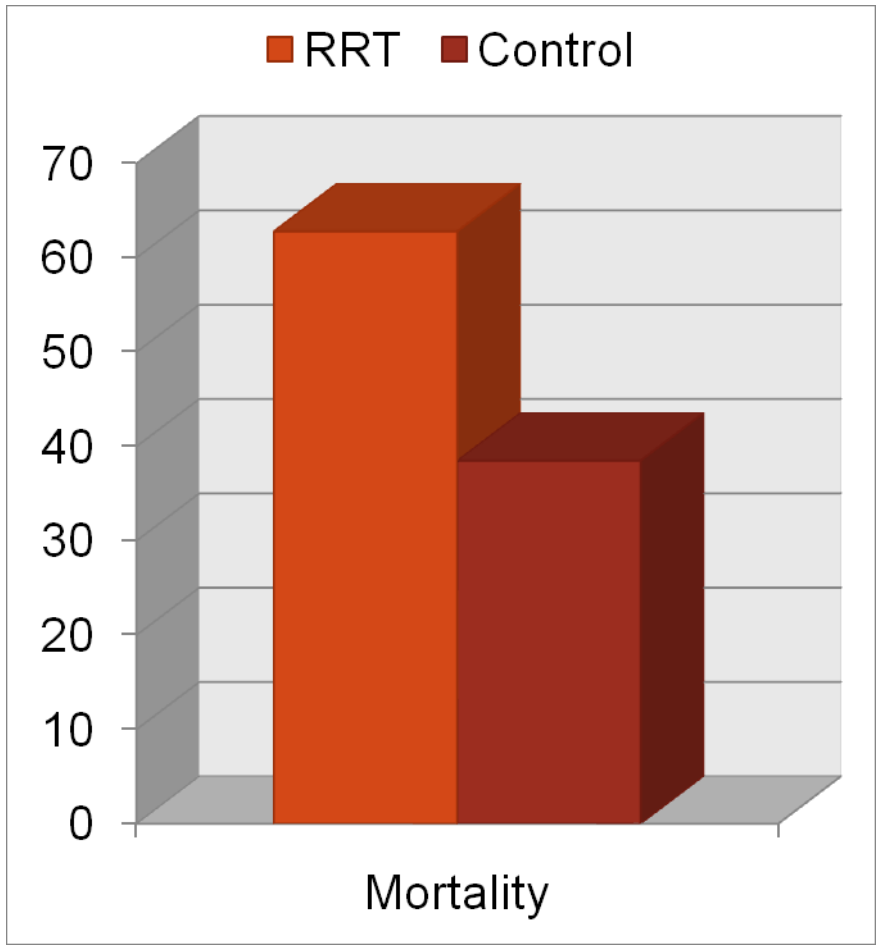
| | | |
|---|---|---|
| • **AKI (Δ in $S_{Cr}$ >0.5)** | **6.5** | **<0.0001** |
| •Age (per 10 yr) | 1.7 | <0.0001 |
| •CKD | 2.5 | <0.0001 |
| •CV dis. | 1.5 | <0.04 |
| •Respiratory dis | 3 | <0.0001 |
| •GI dis. | 2.4 | <0.001 |
| •Cancer | 2.9 | <0.0001 |
| •Infection | 7.5 | <0.0001 |

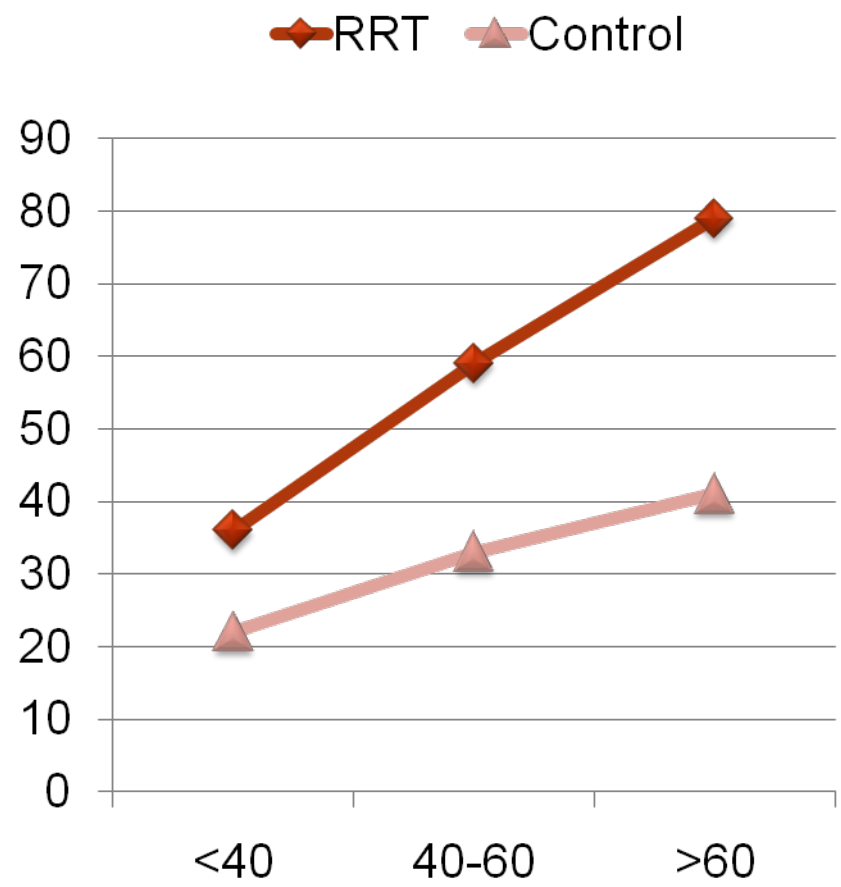
Chertow et al, JASN 16:3365-70; 2005




LEVY, EM, VISCOLI, CM, HORWITZ, RI: The effect of acute renal failure on mortality—A cohort analysis. **JAMA** 1996 **275**: 1489–1494

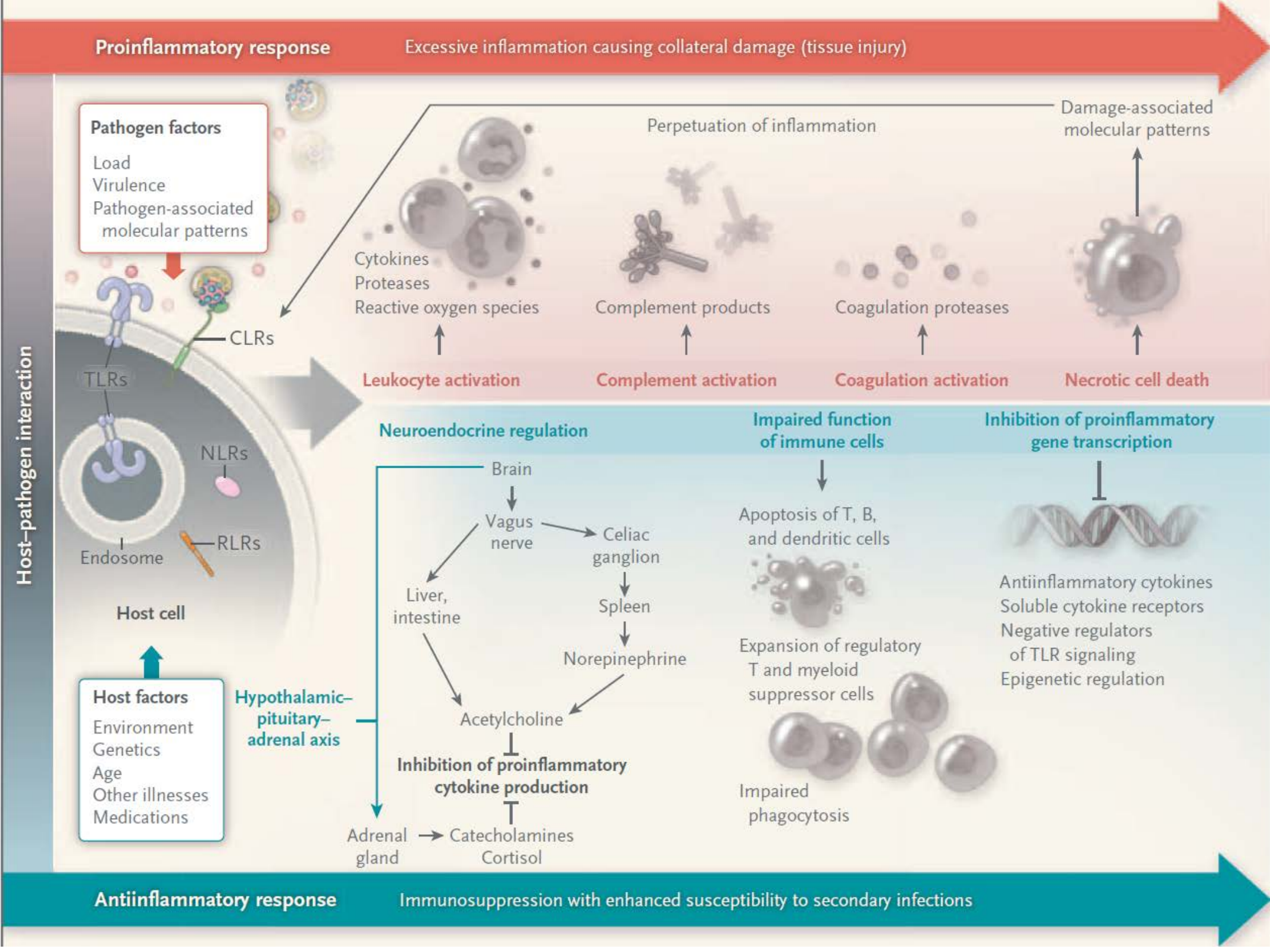
# Impact of ARF on Mortality in Critically Ill Patients

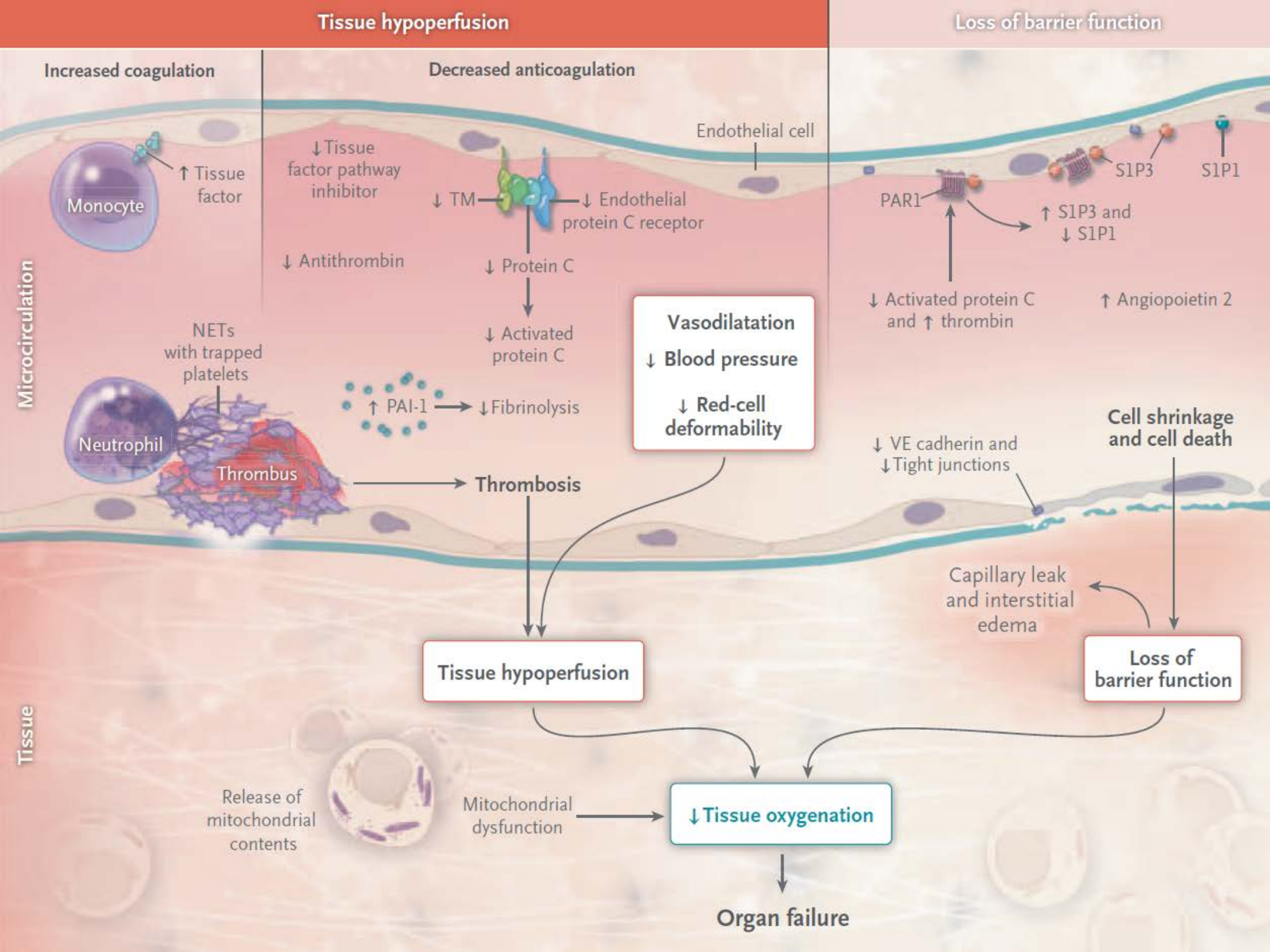


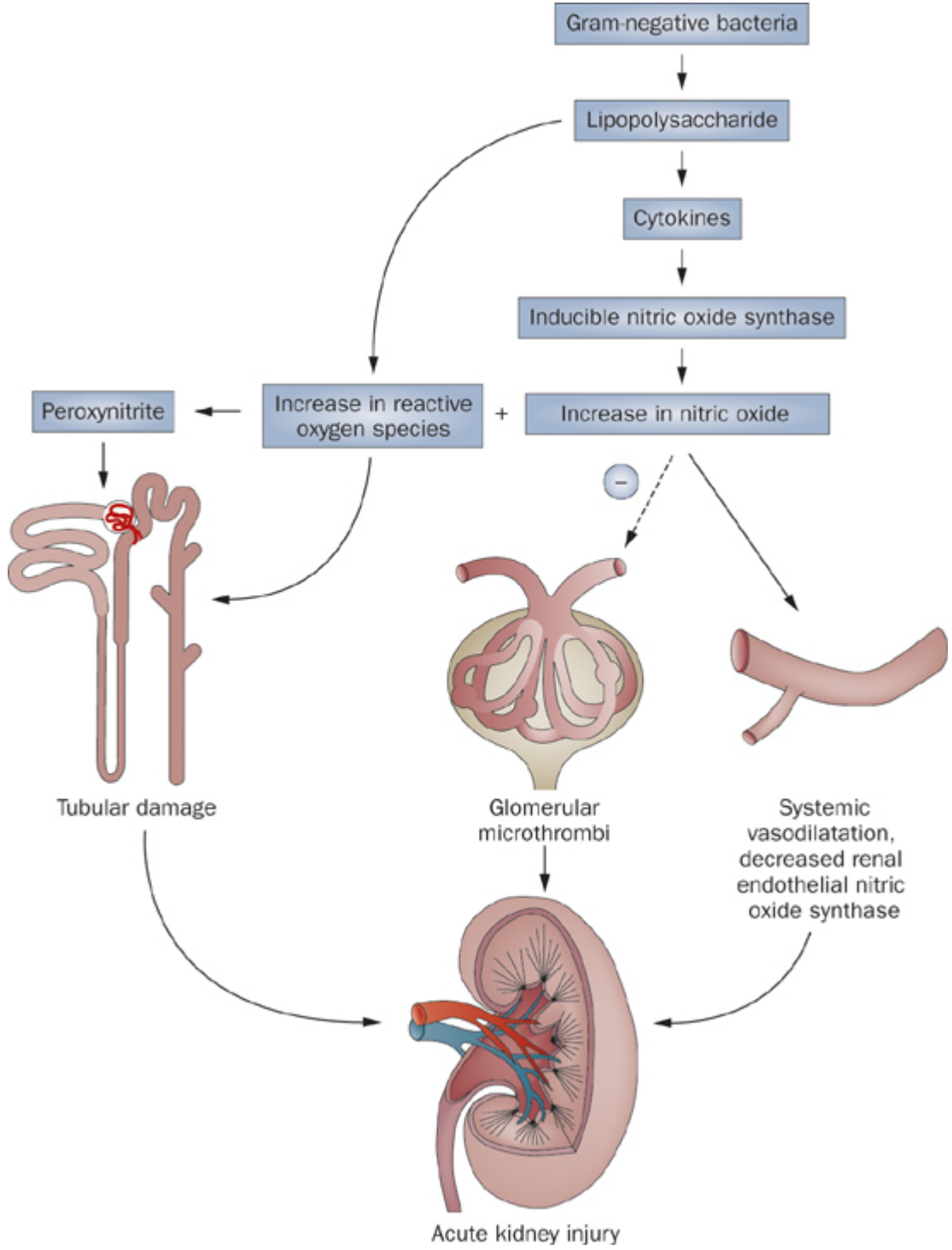



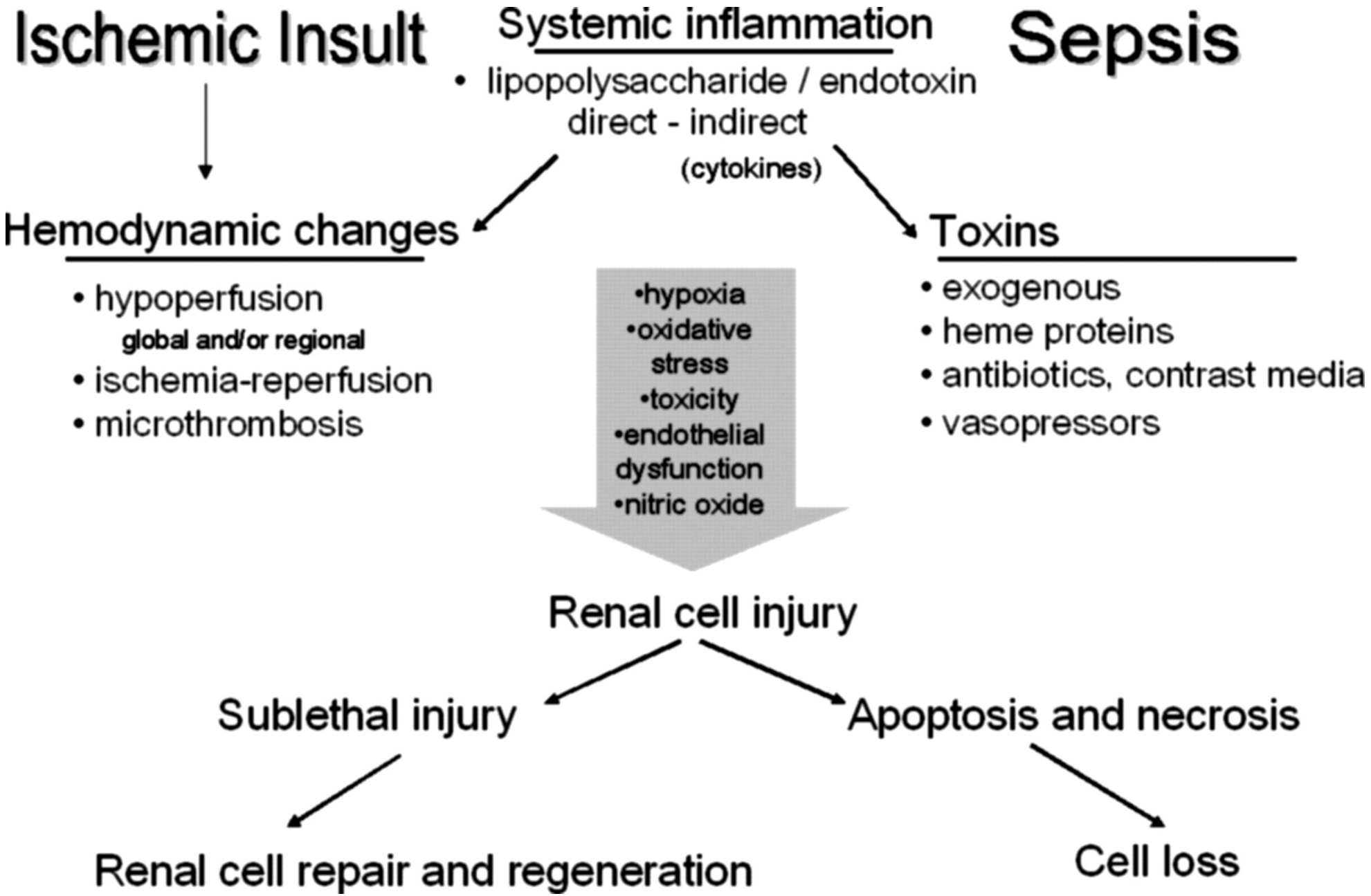

Metnitz,P et al Crit Care Med 2002;30:2051

What’s happening at the level of the nephrons?


Proinflammatory response
Excessive inflammation causing collateral damage (tissue injury)
Host–pathogen interaction
Pathogen factors
Load
Virulence
Pathogen-associated molecular patterns
CLRs
TLRs
NLRs
RLRs
Endosome
Host cell
Host factors
Environment
Genetics
Age
Other illnesses
Medications
Perpetuation of inflammation
Damage-associated molecular patterns
Cytokines
Proteases
Reactive oxygen species
Complement products
Coagulation proteases
Leukocyte activation
Complement activation
Coagulation activation
Necrotic cell death
Neuroendocrine regulation
Brain
Vagus nerve
Celiac ganglion
Liver, intestine
Spleen
Norepinephrine
Acetylcholine
Hypothalamic–pituitary–adrenal axis
Inhibition of proinflammatory cytokine production
Adrenal gland
Catecholamines
Cortisol
Impaired function of immune cells
Apoptosis of T, B, and dendritic cells
Expansion of regulatory T and myeloid suppressor cells
Impaired phagocytosis
Inhibition of proinflammatory gene transcription
Antiinflammatory cytokines
Soluble cytokine receptors
Negative regulators of TLR signaling
Epigenetic regulation
Antiinflammatory response
Immunosuppression with enhanced susceptibility to secondary infections


Tissue hypoperfusion
Loss of barrier function
Increased coagulation
Decreased anticoagulation
Endothelial cell
↑ Tissue factor
Monocyte
↓ Tissue factor pathway inhibitor
↓ TM
↓ Endothelial protein C receptor
↓ Antithrombin
↓ Protein C
↓ Activated protein C
S1P3
S1P1
PAR1
↑ S1P3 and ↓ S1P1
↓ Activated protein C and ↑ thrombin
↑ Angiopoietin 2
Microcirculation
NETs with trapped platelets
Neutrophil
Thrombus
↑ PAI-1
↓ Fibrinolysis
Vasodilatation
↓ Blood pressure
↓ Red-cell deformability
Thrombosis
↓ VE cadherin and ↓ Tight junctions
Cell shrinkage and cell death
Capillary leak and interstitial edema
Tissue hypoperfusion
Loss of barrier function
Tissue
Release of mitochondrial contents
Mitochondrial dysfunction
↓ Tissue oxygenation
Organ failure


Gram-negative bacteria
Lipopolysaccharide
Cytokines
Inducible nitric oxide synthase
Increase in nitric oxide
+
Increase in reactive oxygen species
Peroxynitrite
−
Tubular damage
Glomerular microthrombi
Systemic vasodilatation, decreased renal endothelial nitric oxide synthase
Acute kidney injury


Ischemic Insult
Systemic inflammation
• lipopolysaccharide / endotoxin
direct - indirect
(cytokines)
Sepsis
Hemodynamic changes
• hypoperfusion
global and/or regional
• ischemia-reperfusion
• microthrombosis
•hypoxia
•oxidative stress
•toxicity
•endothelial dysfunction
•nitric oxide
Toxins
• exogenous
• heme proteins
• antibiotics, contrast media
• vasopressors
Renal cell injury
Sublethal injury
Apoptosis and necrosis
Renal cell repair and regeneration
Cell loss

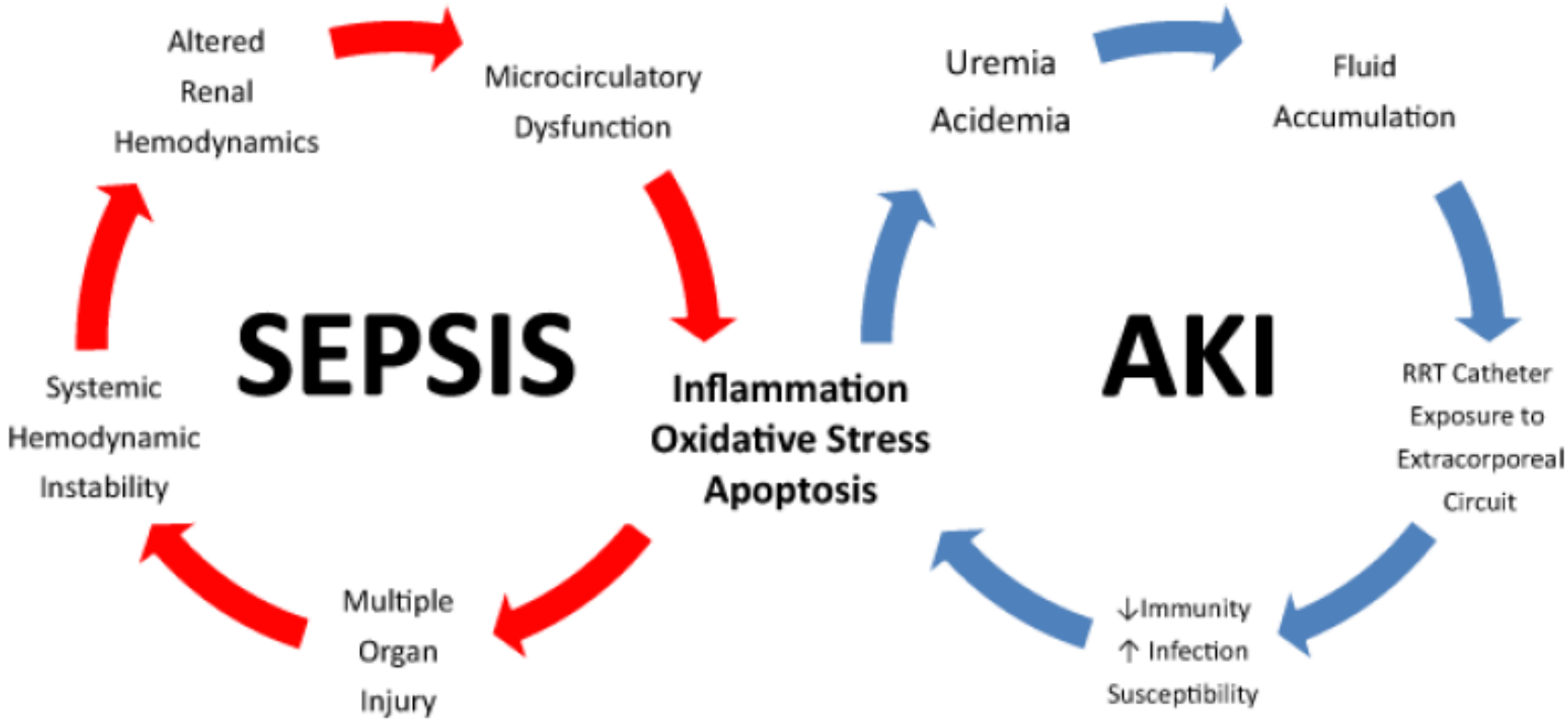
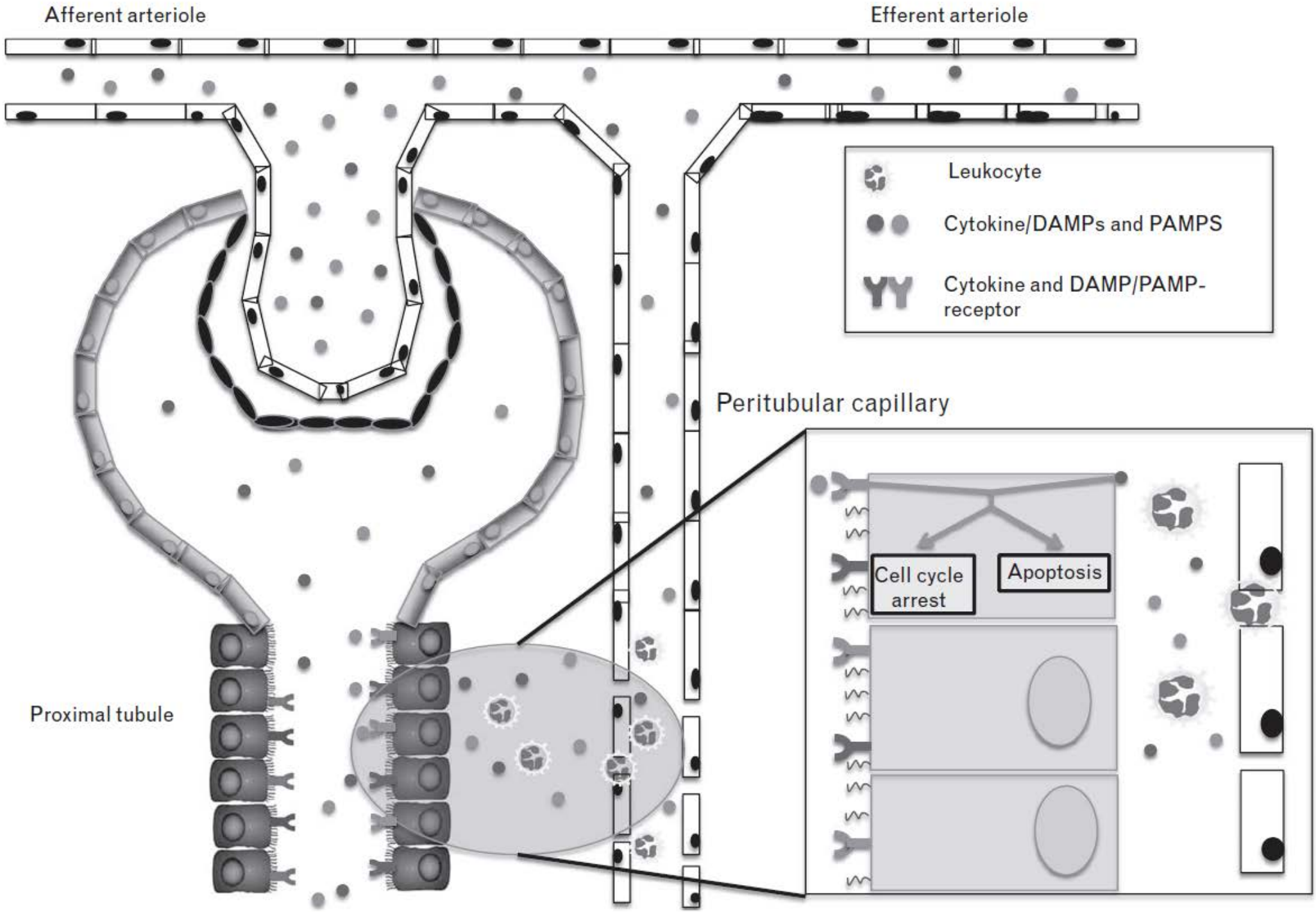



**Figure 1.**
Sepsis and AKI pathophysiological interaction in SA-AKI. Reprinted with permission from Romanovsky et al.[92]

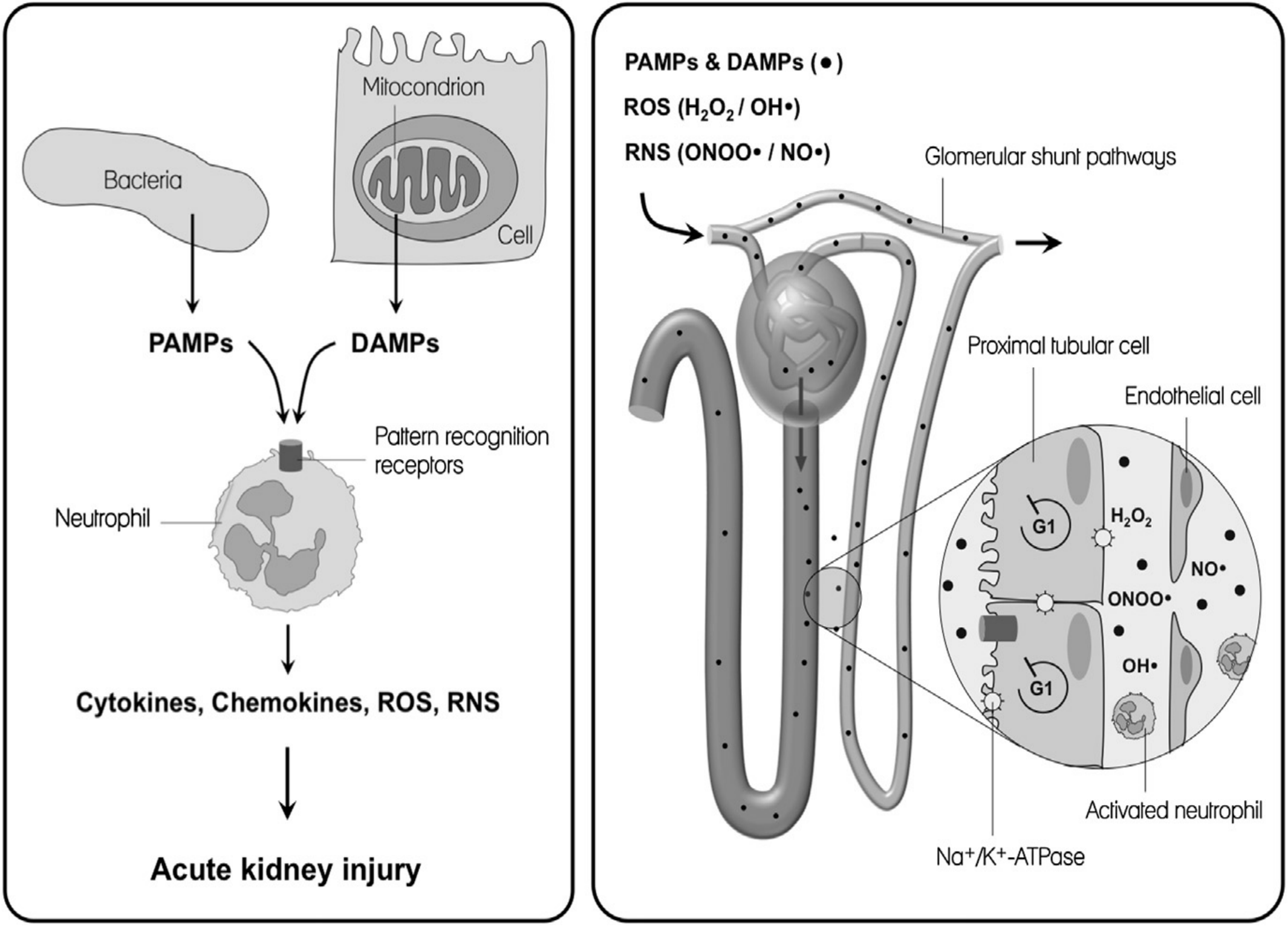
**Table 3** Potential pathophysiological mechanisms of septic AKI

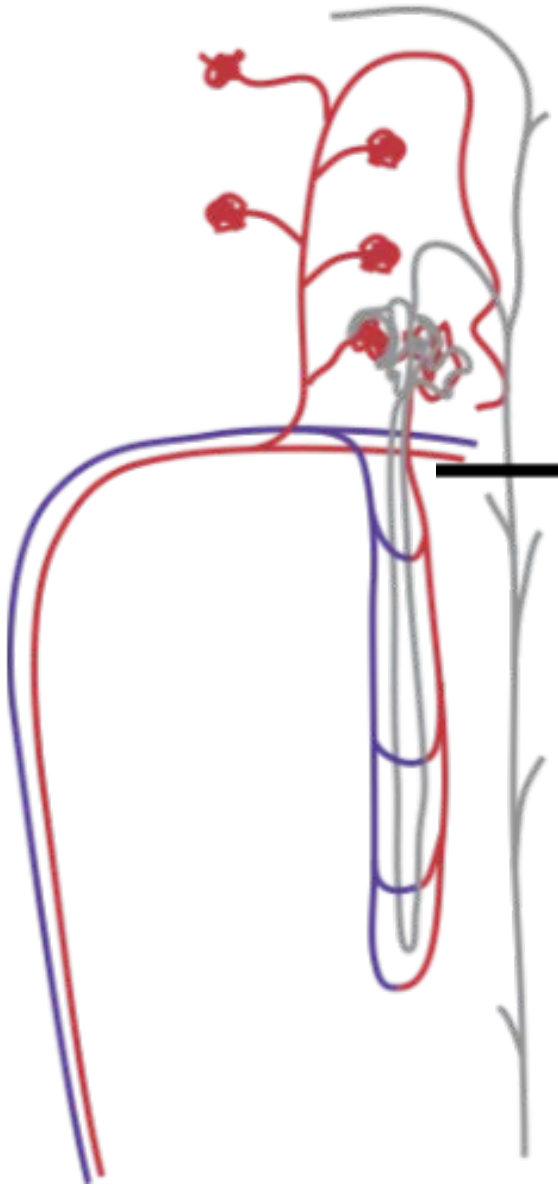
| |
|---|
| Pro-inflammatory state |
| Complement and coagulation activation |
| Protease activation (heparan sulfate, elastase) |
| Free radical formation |
| Pro-inflammatory cytokine production (IL-1, IL-6, IL-18, TNF-α) |
| Cell activation (neutrophil, macrophage, platelet, endothelial cell) |
| Anti-inflammatory state |
| Anti-inflammatory cytokine (IL-10) |
| Reduced phagocytosis and chemotaxis |
| Deranged immune function (lymphocyte apoptosis) |
| Dysregulation of microcirculation |
| Vasodilation-induced glomerular hypoperfusion |
| Abnormal blood flow within the peritubular capillary network |

*TNF* tumor necrosis factor




DAMPs damage associated molecular pattern, PAMPs pathogen associated molecular pattern


Mitocondrion
Cell
Bacteria
PAMPs
DAMPs
Pattern recognition receptors
Neutrophil
Cytokines, Chemokines, ROS, RNS
Acute kidney injury
PAMPs & DAMPs (●)
ROS ($H_2O_2$ / OH•)
RNS (ONOO• / NO•)
Glomerular shunt pathways
Proximal tubular cell
Endothelial cell
G1
$H_2O_2$
NO•
ONOO•
OH•
G1
Activated neutrophil
$Na^+/K^+$-ATPase



Cortex
70% $O_2$ requirement
90% Blood supply

S3 segment of PT

Medulla
30% $O_2$ requirement
10% Blood supply

↓ Renal Blood Flow

↑ Oxygen Demand

Ischemia

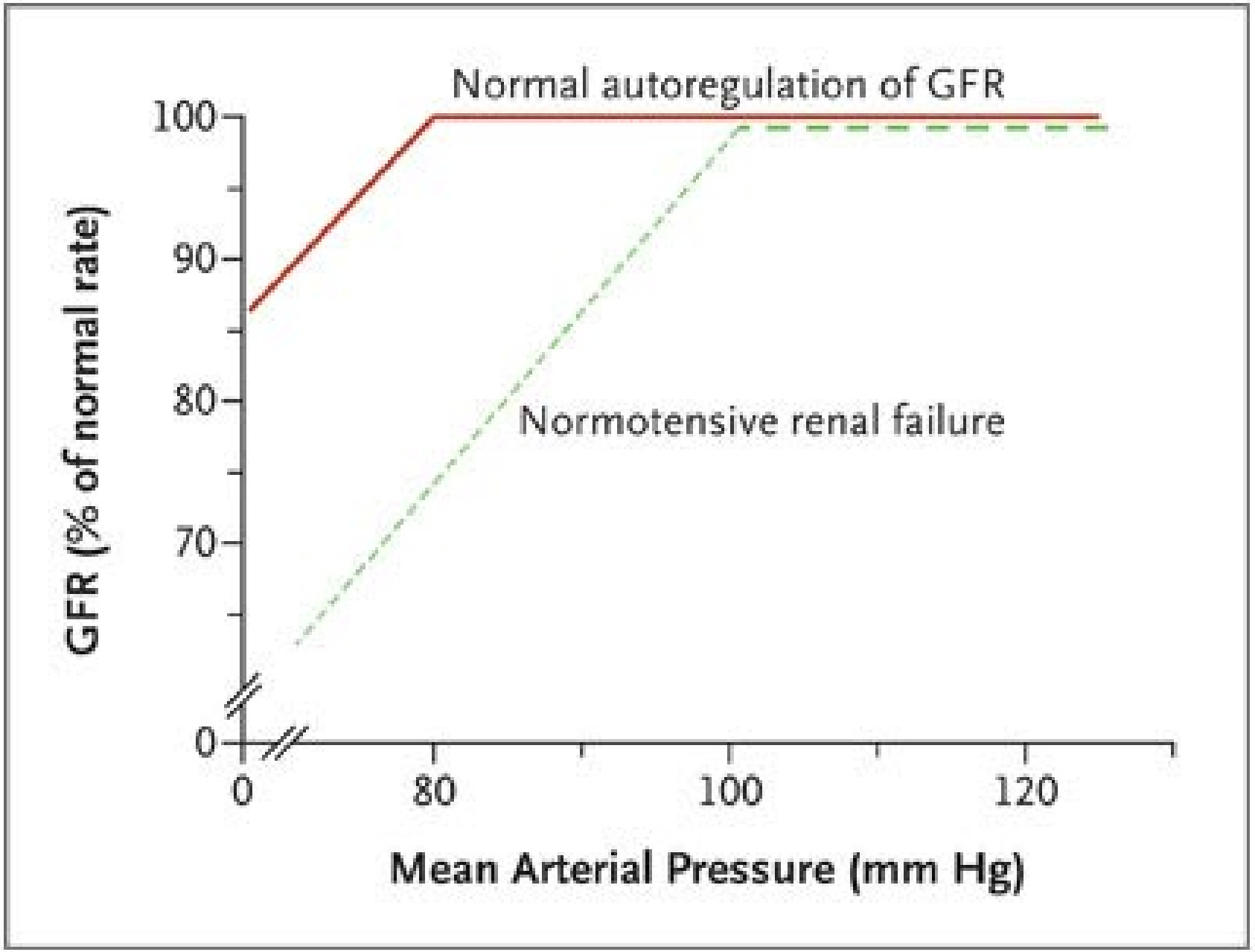
↑ Intracellular Calcium

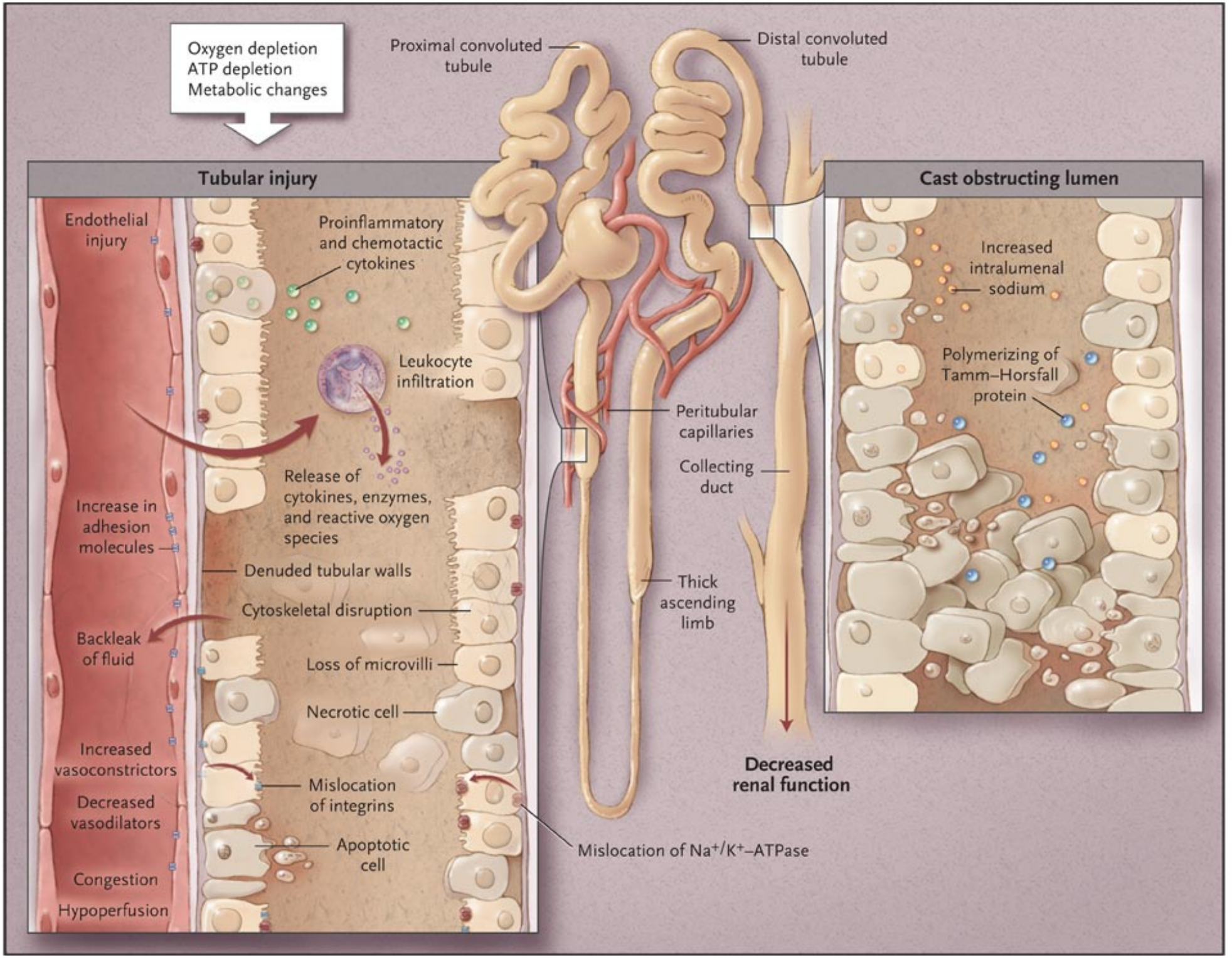
Endothelial injury

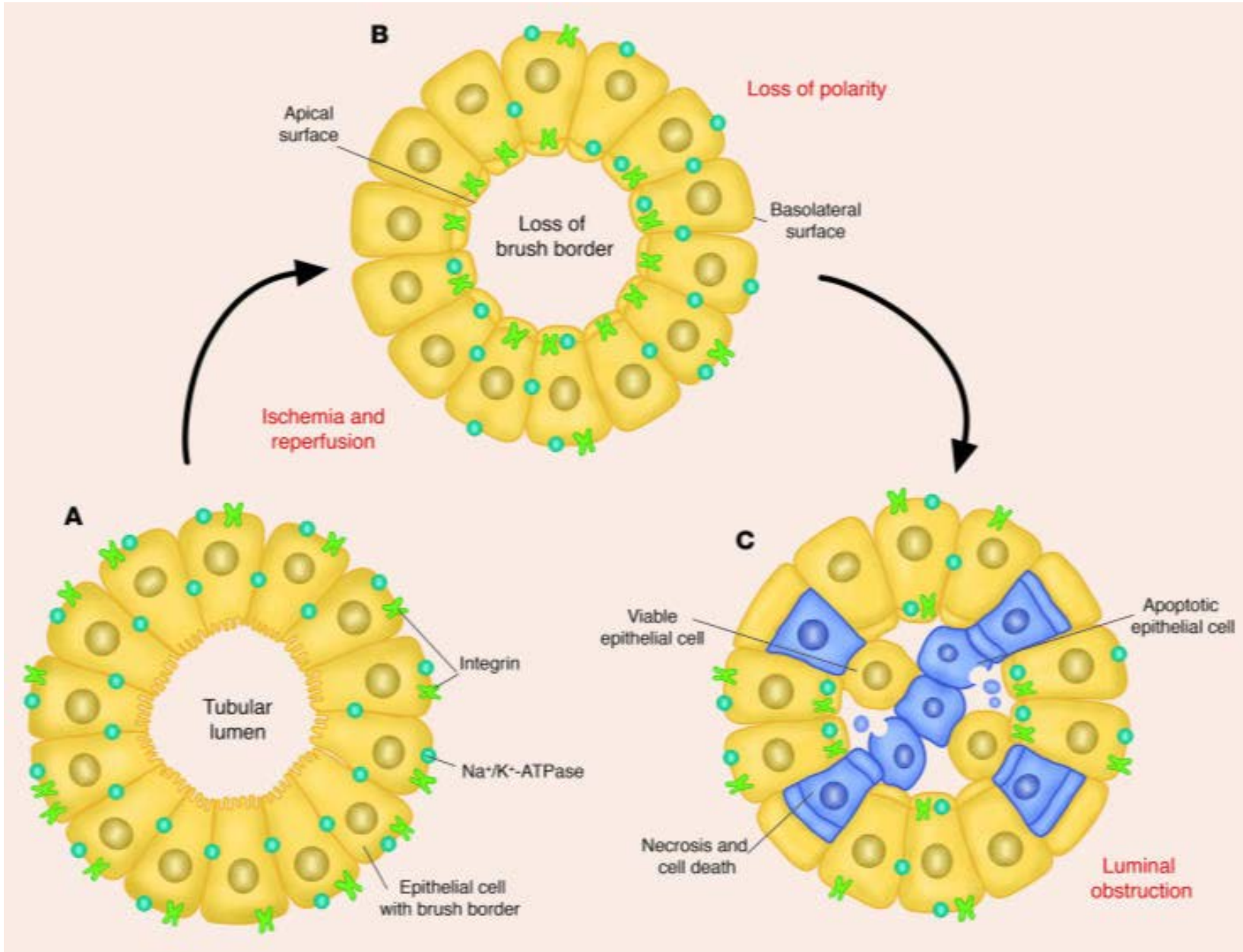
↓ PG; NO from eNOS
↑ TNF-a, IL-18

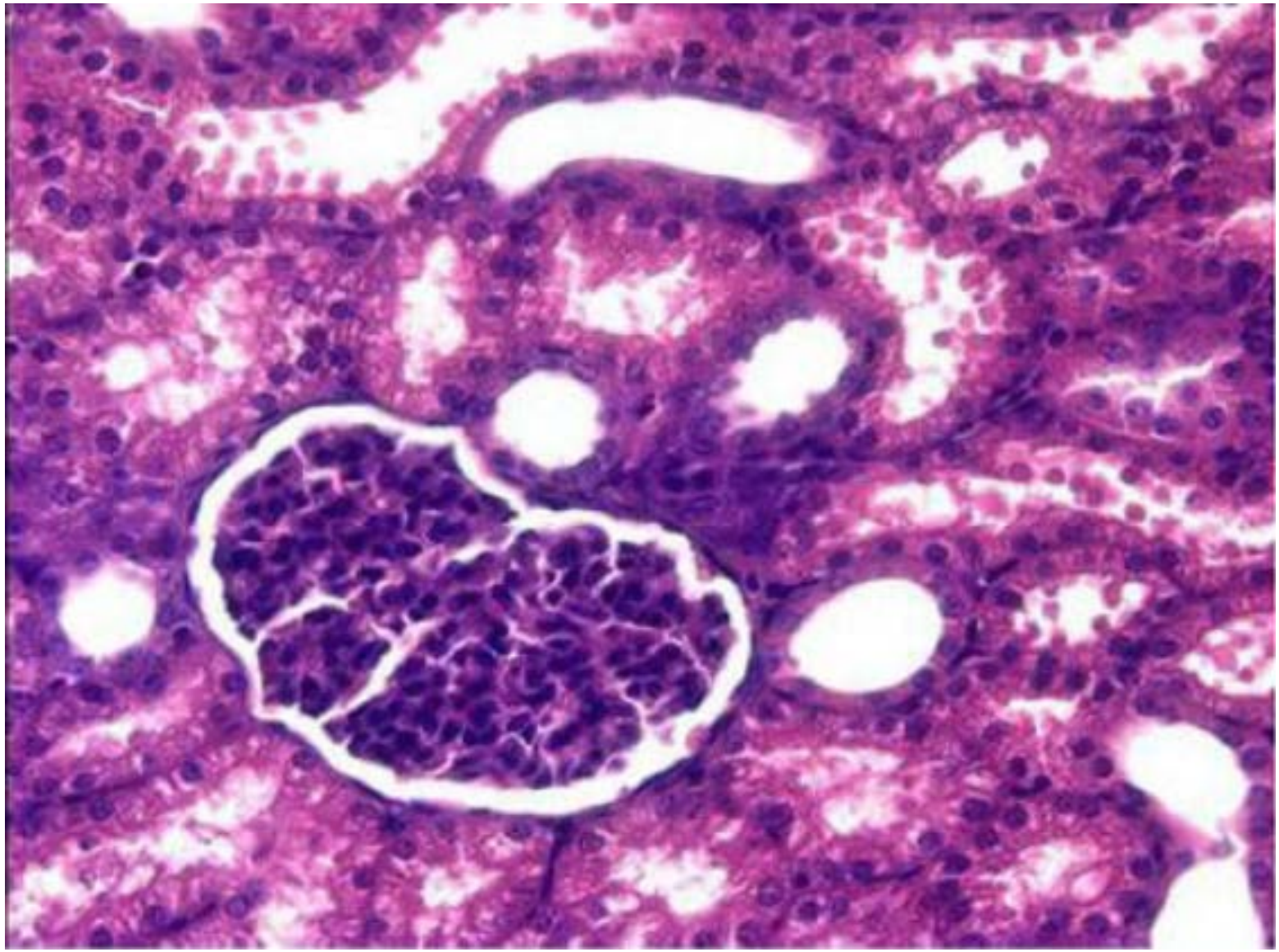
Loss of Autoregulation

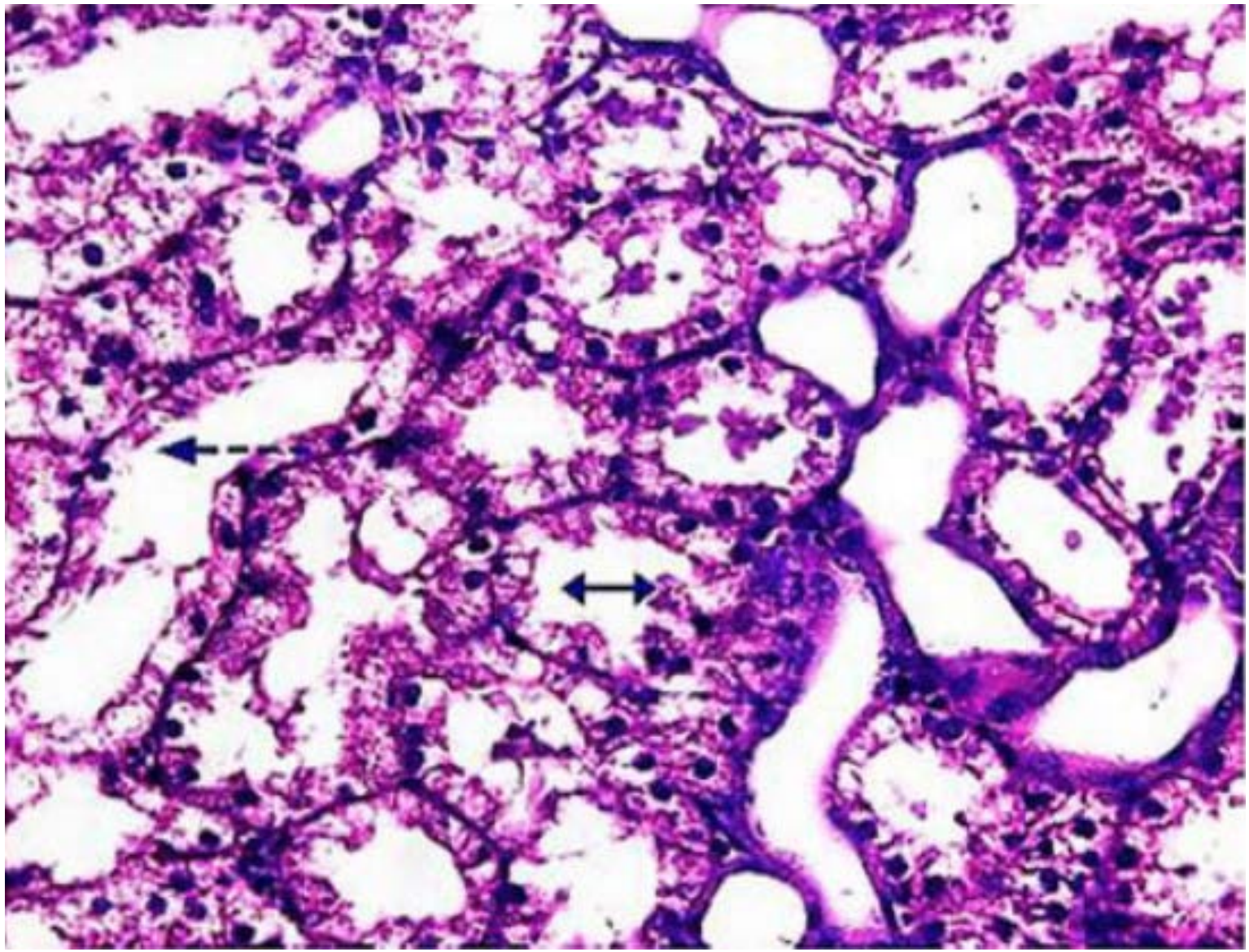
↓ GFR


Normal autoregulation of GFR
Normotensive renal failure
GFR (% of normal rate)
100
90
80
70
0
0
80
100
120
Mean Arterial Pressure (mm Hg)

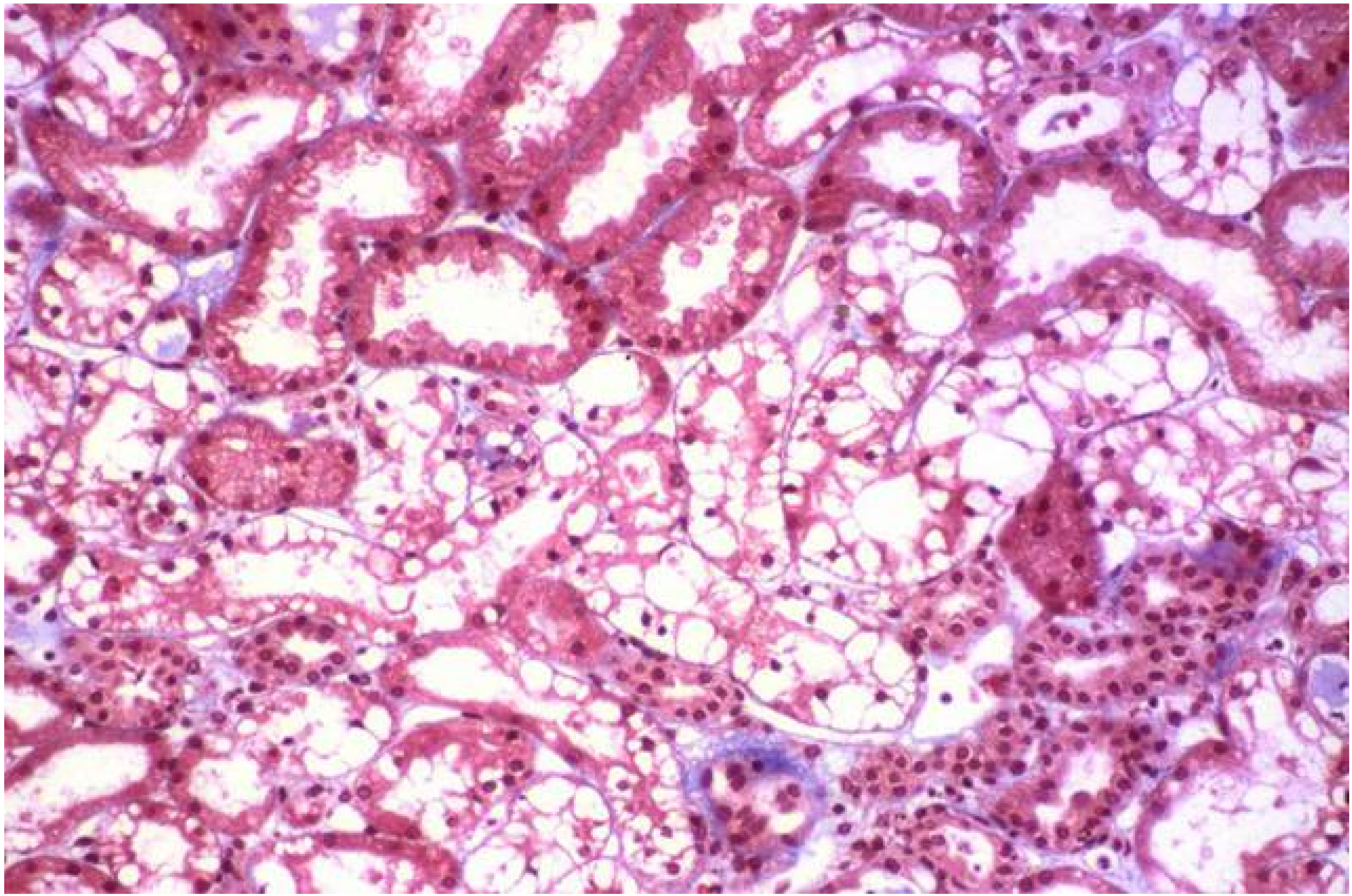

Oxygen depletion
ATP depletion
Metabolic changes
Proximal convoluted tubule
Distal convoluted tubule
Tubular injury
Endothelial injury
Proinflammatory and chemotactic cytokines
Leukocyte infiltration
Release of cytokines, enzymes, and reactive oxygen species
Increase in adhesion molecules
Denuded tubular walls
Cytoskeletal disruption
Backleak of fluid
Loss of microvilli
Necrotic cell
Increased vasoconstrictors
Mislocation of integrins
Decreased vasodilators
Apoptotic cell
Congestion
Hypoperfusion
Peritubular capillaries
Collecting duct
Thick ascending limb
Mislocation of Na+/K+–ATPase
Decreased renal function
Cast obstructing lumen
Increased intralumenal sodium
Polymerizing of Tamm–Horsfall protein

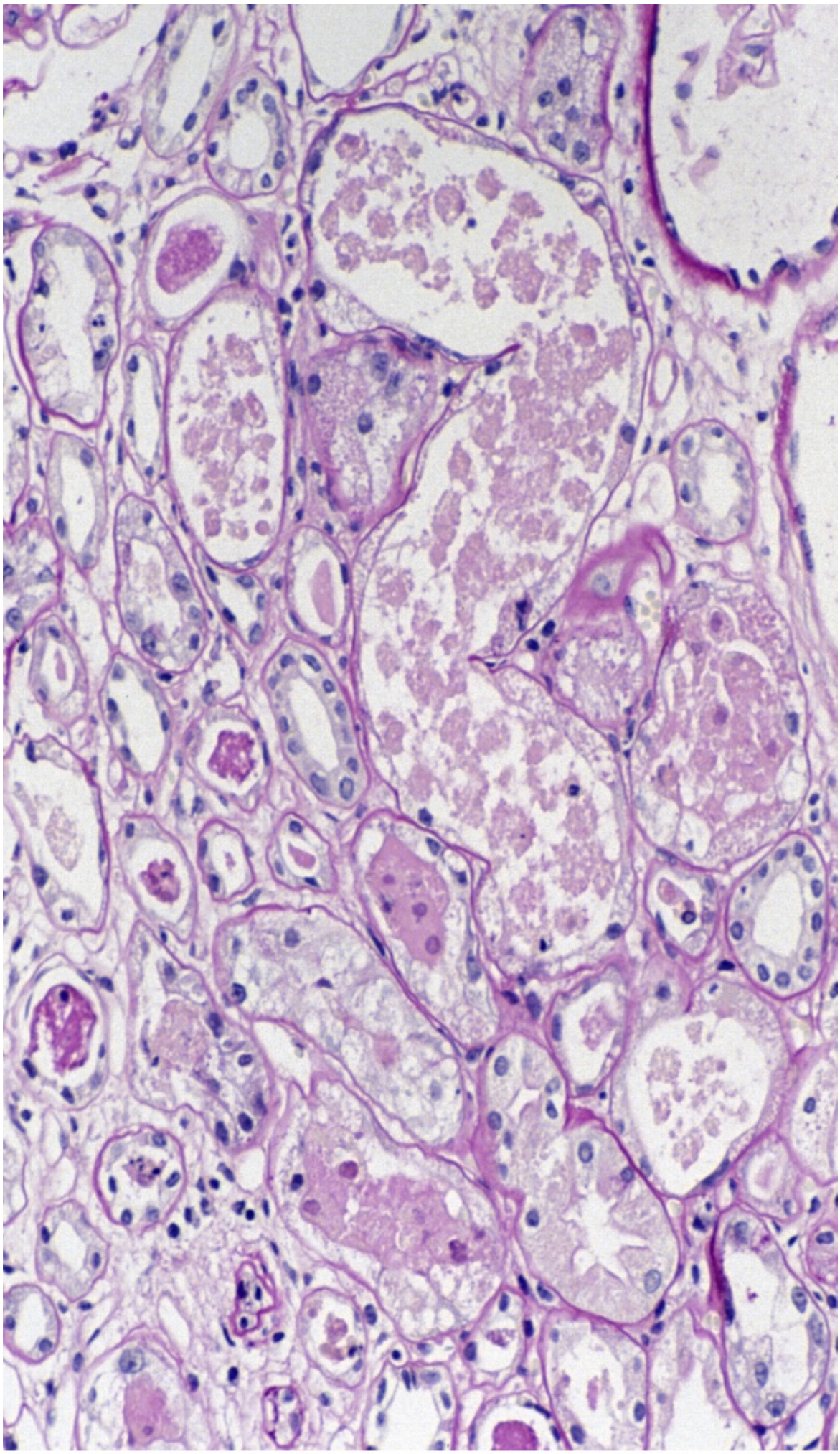

B
Loss of polarity
Apical surface
Basolateral surface
Loss of brush border
Ischemia and reperfusion
A
Integrin
Tubular lumen
Na+/K+-ATPase
Epithelial cell with brush border
C
Viable epithelial cell
Apoptotic epithelial cell
Necrosis and cell death
Luminal obstruction

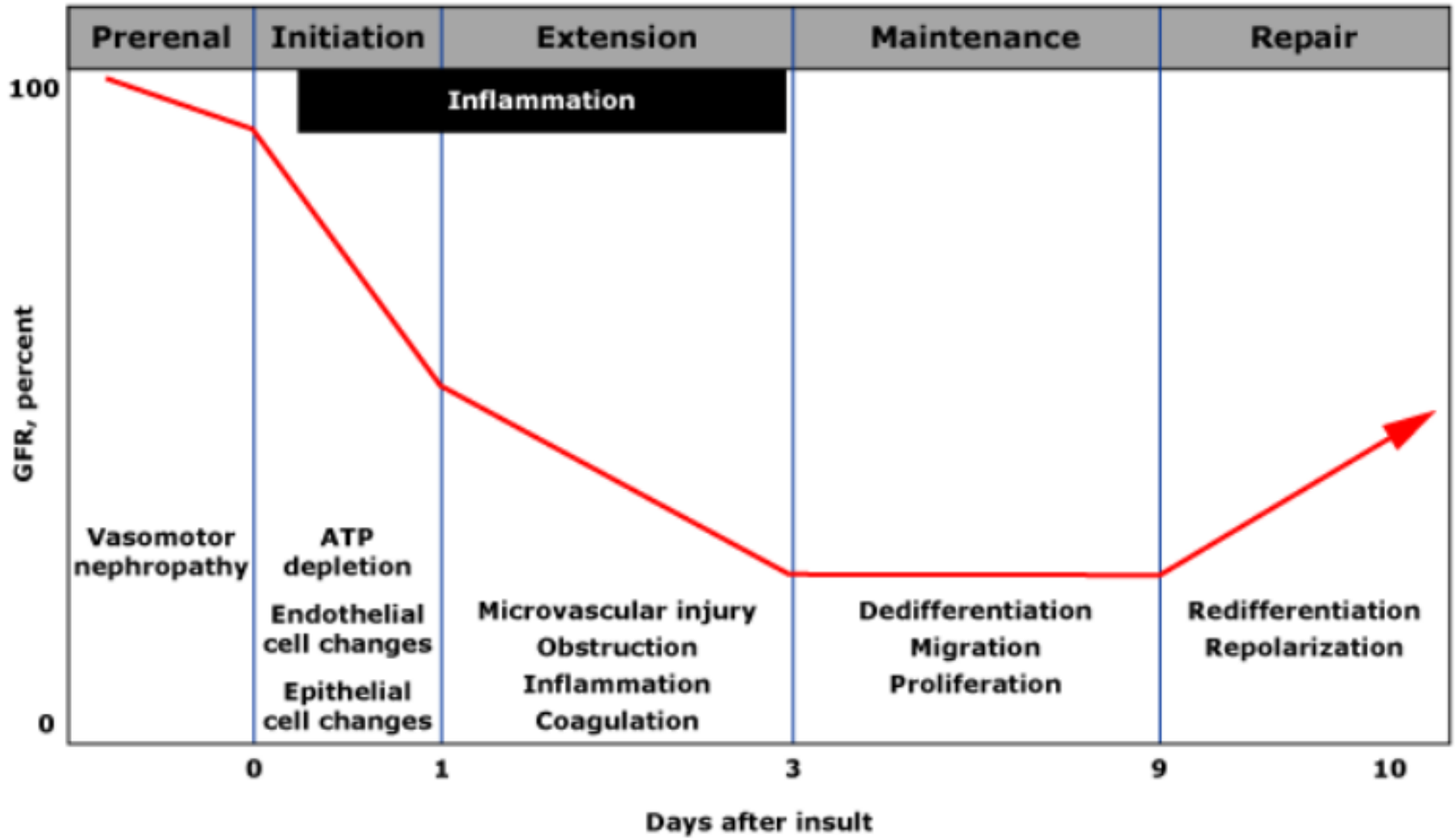




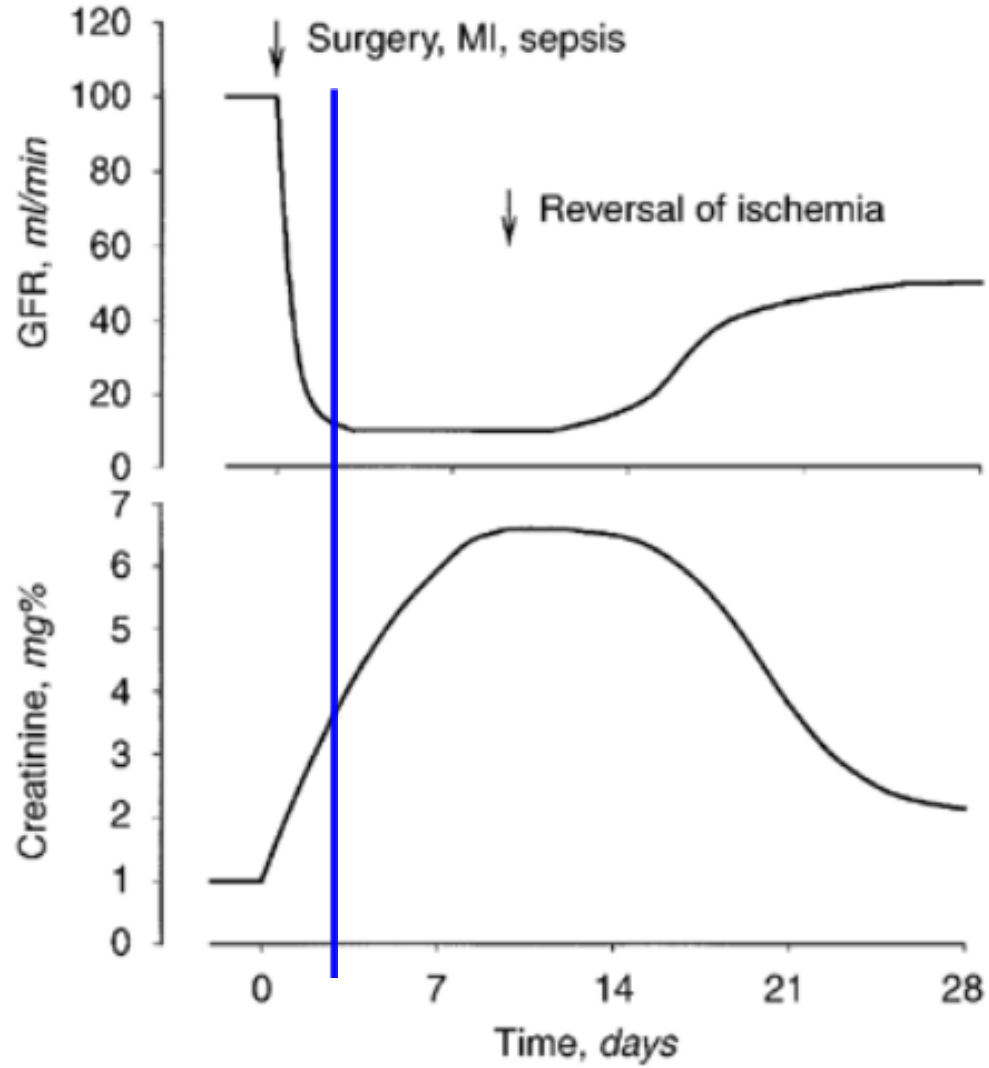
Arrows showing epithelial vacuolization with damage of brush border.

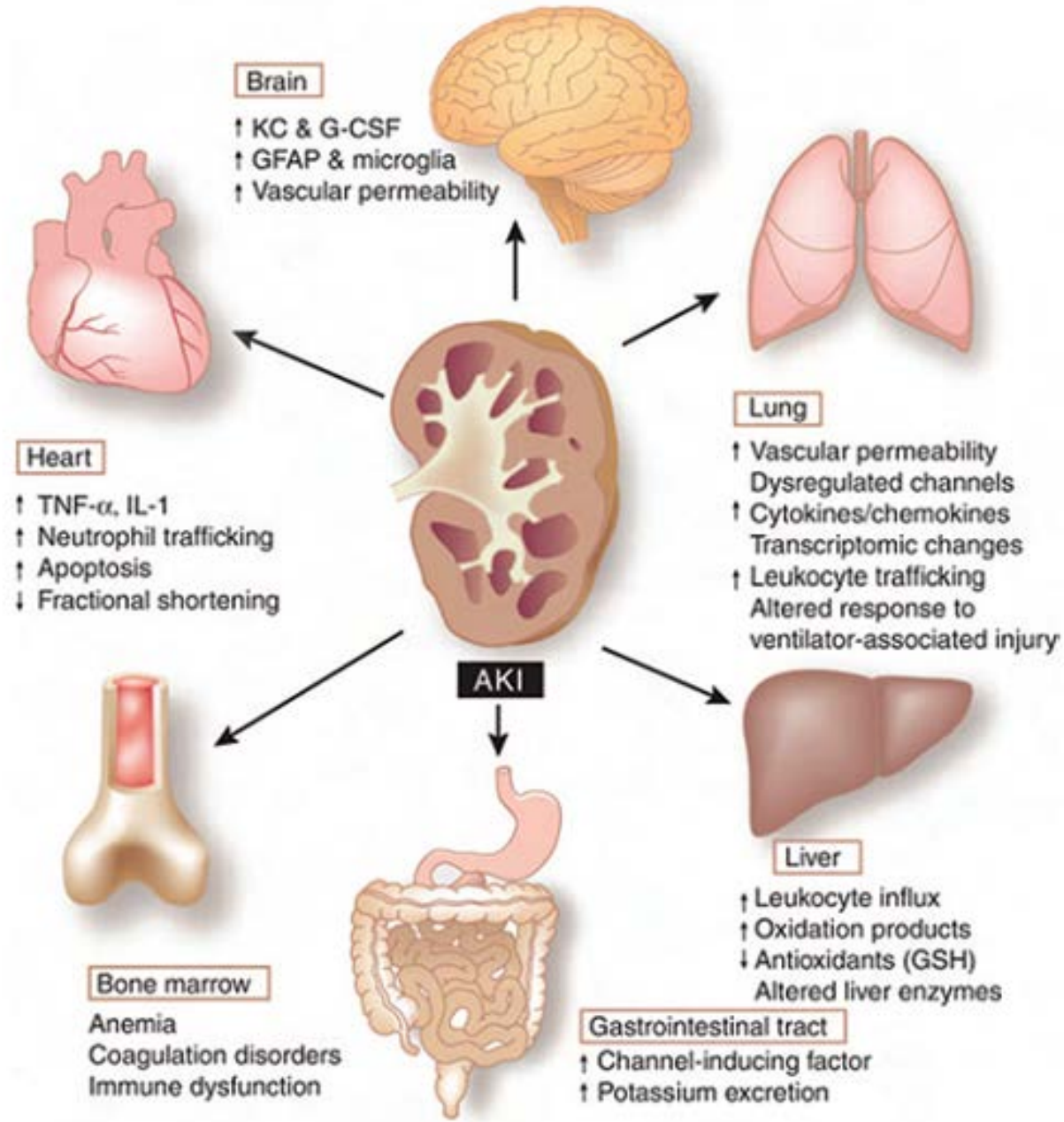






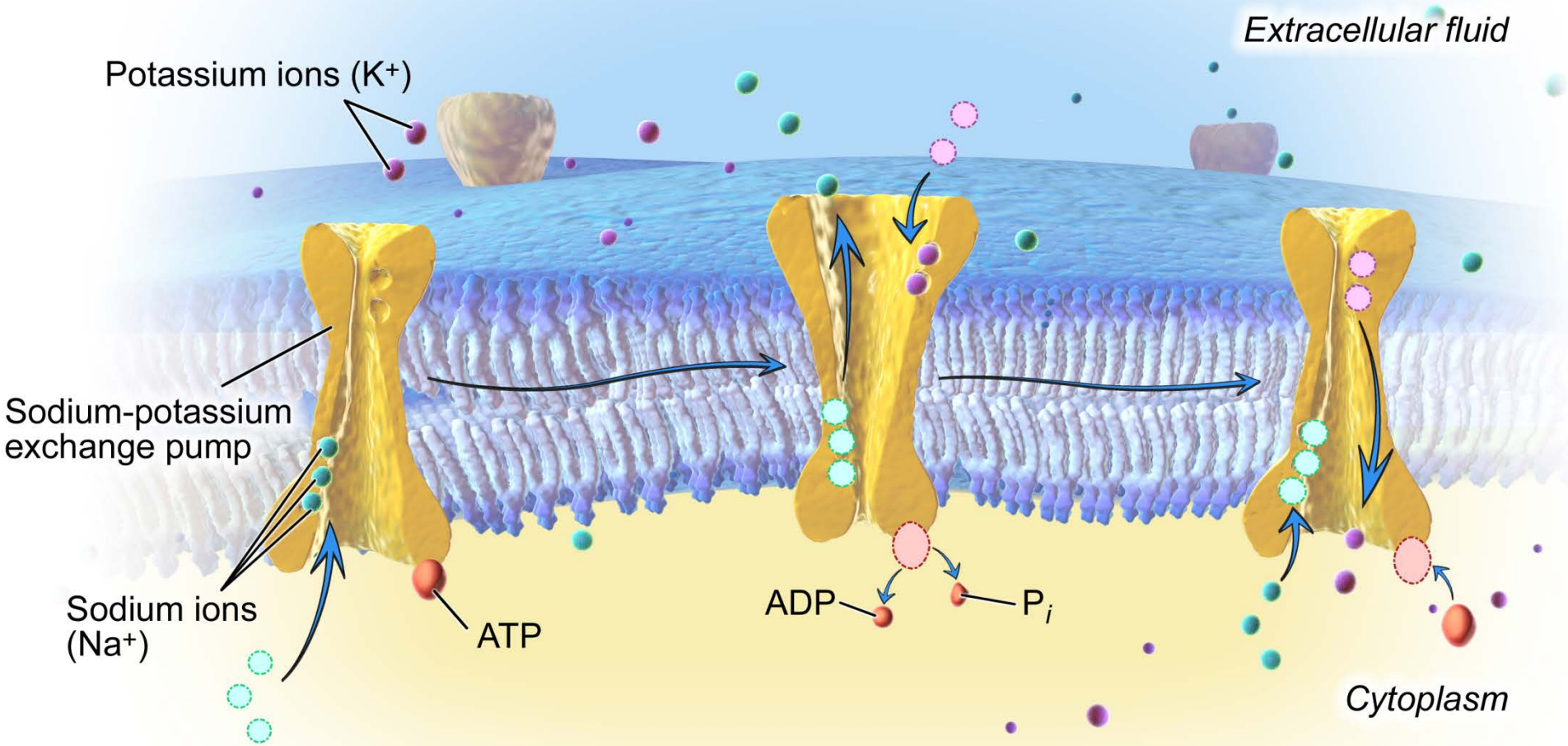

Adapted with permission from: Sutton, TA, Fisher, CJ, Molitoris, BA, et al. Microvascular endothelial injury and dysfunction during ischemic acute renal failure. Kidney Int 2002; 62:1539.


Surgery, MI, sepsis
Reversal of ischemia
GFR, ml/min
120
100
80
60
40
20
0
Creatinine, mg%
7
6
5
4
3
2
1
0
0
7
14
21
28
Time, days


Brain
↑ KC & G-CSF
↑ GFAP & microglia
↑ Vascular permeability
Heart
↑ TNF-α, IL-1
↑ Neutrophil trafficking
↑ Apoptosis
↓ Fractional shortening
Lung
↑ Vascular permeability
Dysregulated channels
↑ Cytokines/chemokines
Transcriptomic changes
↑ Leukocyte trafficking
Altered response to
ventilator-associated injury
AKI
Bone marrow
Anemia
Coagulation disorders
Immune dysfunction
Gastrointestinal tract
↑ Channel-inducing factor
↑ Potassium excretion
Liver
↑ Leukocyte influx
↑ Oxidation products
↓ Antioxidants (GSH)
Altered liver enzymes

Can this be treated medically?

# Loop diuretics

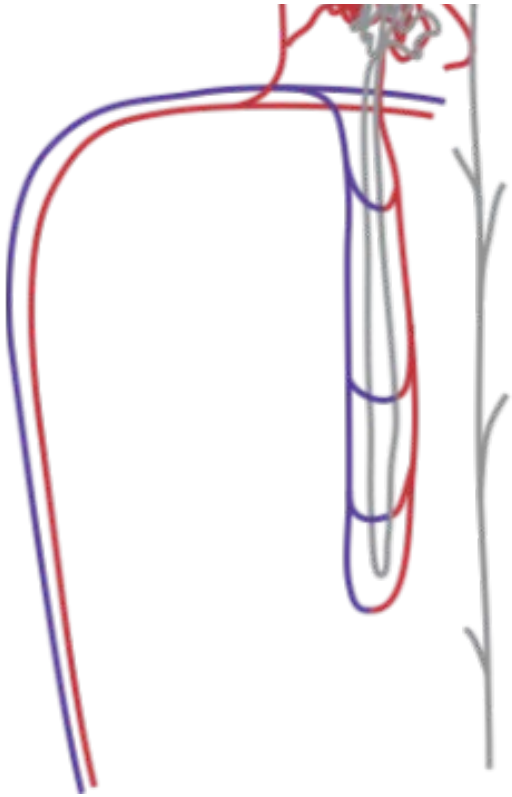



# The Sodium-Potassium Exchange Pump

↓ Renal Blood Flow

↑ Oxygen Demand

# The Na-K ATPase uses 80% of the ATP in the kidney (check)



Medulla

30% $O_2$ requirement

10% Blood supply

↑ Intracellular Calcium

Endothelial injury

↓ PG; NO from eNOS

↑ TNF-a, IL-18

Loss of Autoregulation

↓ GFR

# Furosemide

## I. Furosemide as an Innovative Therapeutic Agent

Furosemide and ethacrynic acid arrived on the clinical scene in the 1960s. They quickly became known as "loop diuretics" and "high-ceiling diuretics." The former appellation refers loosely to the site of action of these agents within the nephron—the loop of Henle—and the latter to the fact that the maximum diuresis achieved with these drugs far exceeded that obtained with the thiazide diuretics.

Before the loop diuretics, the thiazide and organic mercurial diuretics had been used to good effect as agents for mobilizing edema fluid in congestive heart failure, cirrhosis, and nephrosis. Furosemide and ethacrynic acid were found to be particularly effective in cases that were refractory to the thiazides and mercurials. They were also very effective as emergency intravenous treatments for pulmonary and cerebral edemas and in barbiturate poisoning: diuresis occurred within 15 min, whereas 1–3 h were required for thiazide and mercurial agents to take effect (Stason et al., 1966; Kirkendall and Stein, 1968; Cannon and Kilcoyne, 1969; Modell et al., 1976; Weiner and Mudge, 1985). Unlike the mercurial diuretics, furosemide and ethacrynic acid continued to be effective even when electrolyte and acid–base disturbances were present.

Furosemide has come to be prescribed much more frequently than ethacrynic acid, because of a considerably lower incidence of gastrointestinal side effects and a less steep dose–response curve (Weiner and Mudge, 1985). Loop diuretics, if not carefully administered, may be given in overdose and produce orthostatic hypoten-



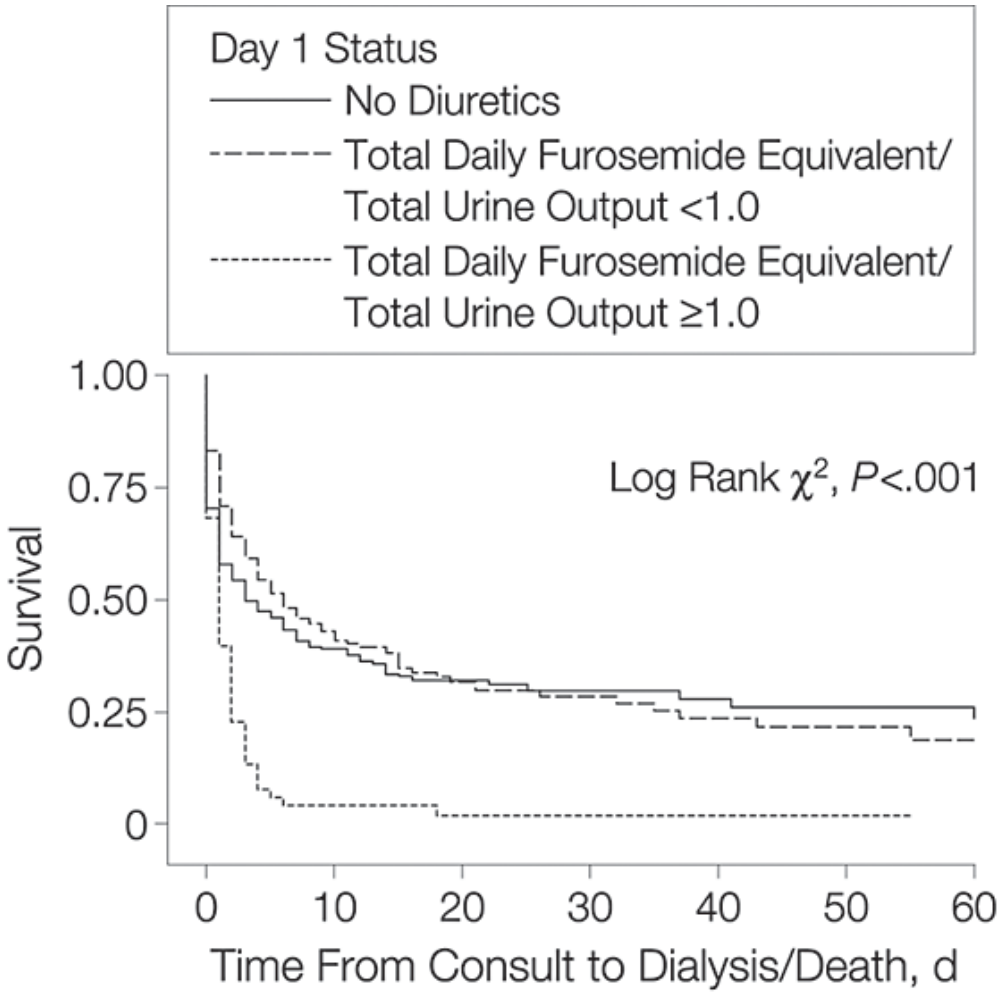
R. A. Maxwell et al., *Drug Discovery*

# furosemide

decreased activity of the ascending loop of Henle

decreases renal oxygen demand by the kidney

better align supply/demand in ischemia




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| No Diuretics | 170 | 63 | 31 | 18 | 14 | 10 |
| Total Daily Furosemide Equivalent/Total Urine Output | | | | | | |
| <1.0 | 188 | 73 | 28 | 21 | 12 | 9 |
| ≥1.0 | 53 | 2 | 1 | 1 | 1 | 1 |

Retrospective review of ICU patients

Diuretic responsiveness determined survival

Mehta, R. L. et al. JAMA 2002;288:2547-2553.

- 338 with dialysis dependent ARF
- Randomized to high dose furosemide (2,000 mg/day) vs placebo
- End-point length of dialysis
- No improvement of survival, length of dialysis, number of dialysis sessions
- Shorter time to 2 liters/day of urine output

Cantarovich F, Rangoonwala B, Et al. Am J Kidney Dis 2004; 44: 402-9.

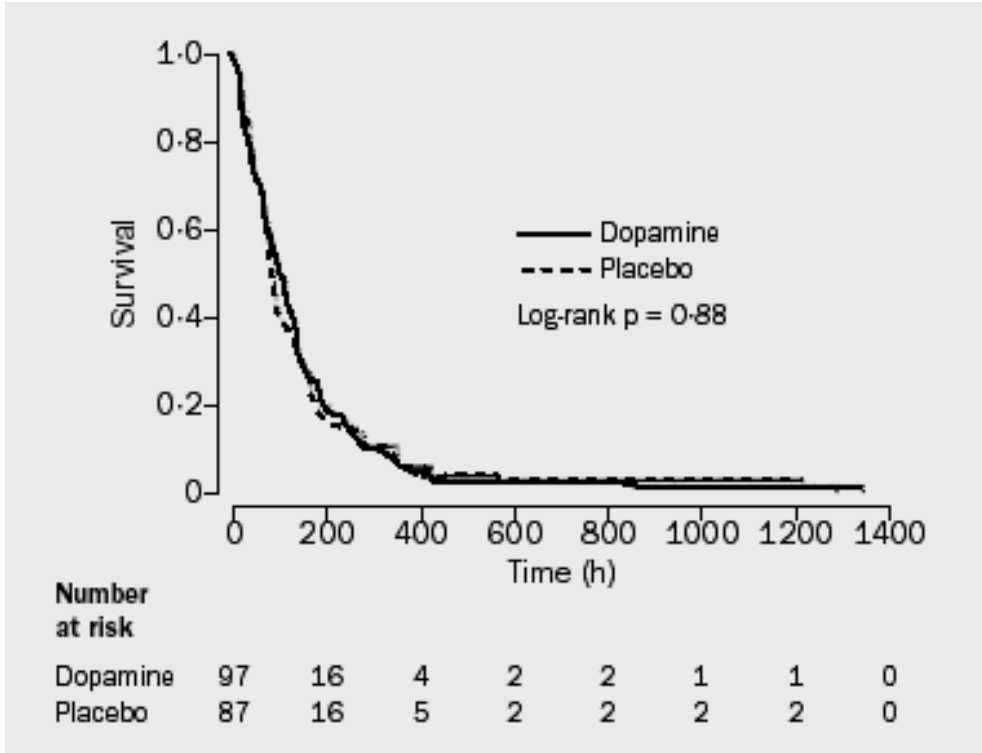
- In healthy volunteers low dose dopamine increases RBF and induces diuresis
- Patients in the intensive care unit do not respond this way.

| | Dopamine (n=161) | Placebo (n=163) | Difference (95% CI) |
|---|---|---|---|
| **Serum concentrations*** | | | |
| Peak creatinine (µmol/L) | 245 (144) | 249 (147) | 4 (−28 to 36) |
| Peak urea (mmol/L) | 20 (10) | 23 (12) | 3 (−0·8 to 6·8) |
| Increase in creatinine (µmol/L) | 62 (107) | 66 (108) | 4 (−21 to 29) |
| Increase in urea (mmol/L) | 6 (8) | 7 (9) | 1 ( (−1 to 3) |
| **Number of patients with event** | | | |
| Creatinine concentration >300 µmol/L | 56 | 56 | 0 (−16 to 16) |
| Renal replacement therapy | 35 | 40 | 5 (−10 to 20) |
| **Urine output (mL/h)*** | | | |
| Baseline | 37 (40) | 50 (59) | 13 (−1 to 27) |
| After 1 h | 71 (81) | 72 (77) | 1 (−20 to 22) |
| After 24 h | 96 (101)† | 92 (72)† | 4 (−19 to 27) |
| After 48 h | 99 (83)† | 109 (95)† | 10 (−11 to 31) |

*Mean (SD). †Significantly greater than baseline value (p=0·006).

ANZICS Clinical Trials Group. Lancet 2000;356:2139-47.
Kellum JA, Decker JM.Crit Care 2001; 29:1526-31.

- RCT of 380 ICU patients




ANZICS Clinical Trials Group. Lancet 2000;356:2139-47.
Kellum JA, Decker JM.Crit Care 2001; 29:1526-31.

# Dopamine

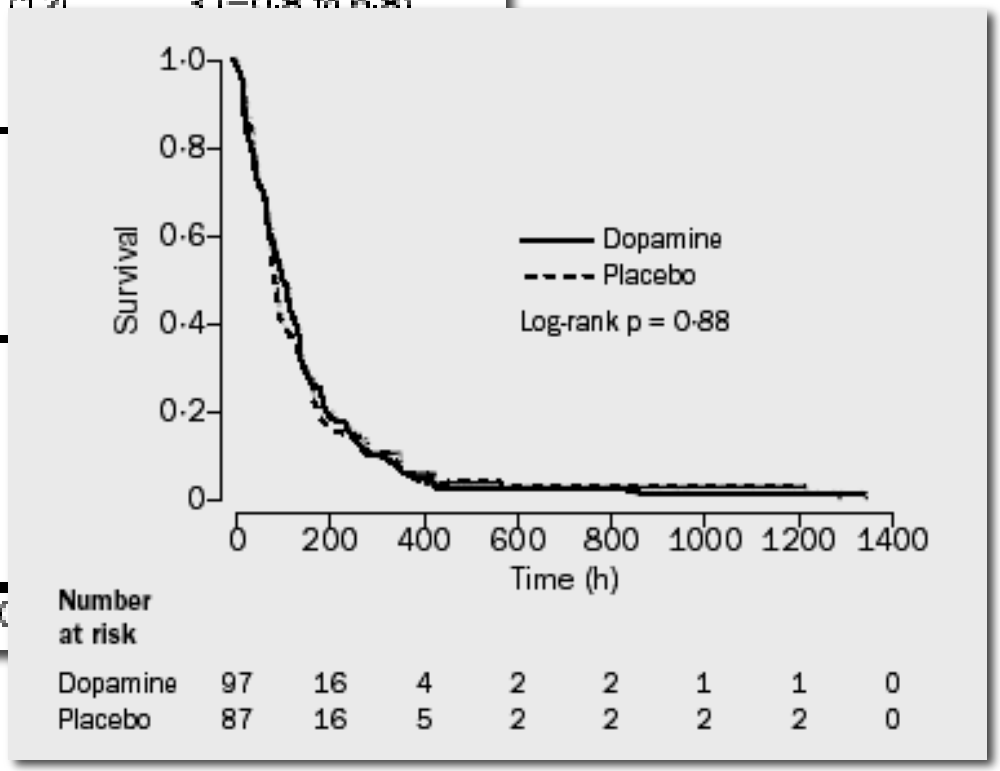
# dopamine: the RCT

- 328 ICU patients with SIRS
- Early signs of renal failure
  - < 0.5 cc/kg/hr
  - Cr > 1.7 mg/dL without a prior history of renal disease
  - A rise in serum Cr of 0.9 mg/dL in less than 24 hours
- The primary outcome was peak serum creatinine

ANZICS Clinical Trials Group. Lancet 2000;356:2139-47.

| | Dopamine (n=161) | Placebo (n=163) | Difference (95% CI) |
|---|---|---|---|
| **Serum concentrations*** | | | |
| Peak creatinine (µmol/L) | 245 (144) | 249 (147) | 4 (−28 to 36) |
| Peak urea (mmol/L) | 20 (10) | 23 (13) | 3 (−0·8 to 6·8) |
| Increase in creatinine (µmol/L) | 62 (107) | 66 | |
| Increase in urea (mmol/L) | 6 (8) | 7 | |
| **Number of patients with event** | | | |
| Creatinine concentration >300 µmol/L | 56 | 56 | |
| Renal replacement therapy | 35 | 40 | |
| **Urine output (mL/h)*** | | | |
| Baseline | 37 (40) | 50 | |
| After 1 h | 71 (81) | 72 | |
| After 24 h | 96 (101)† | 92 | |
| After 48 h | 99 (83)† | 109 | |

*Mean (SD). †Significantly greater than baseline value (p=




- Secondary end points:
  - Furosemide dose 192 mg vs 268 mg p=0.39
  - Duration of mechanical ventilation 10 vs 11 p=0.63
  - Duration of ICU stay 13 vs 14 p=0.67
  - Survival to hospital discharge 92 vs 97 p=0.66

# meta-analysis

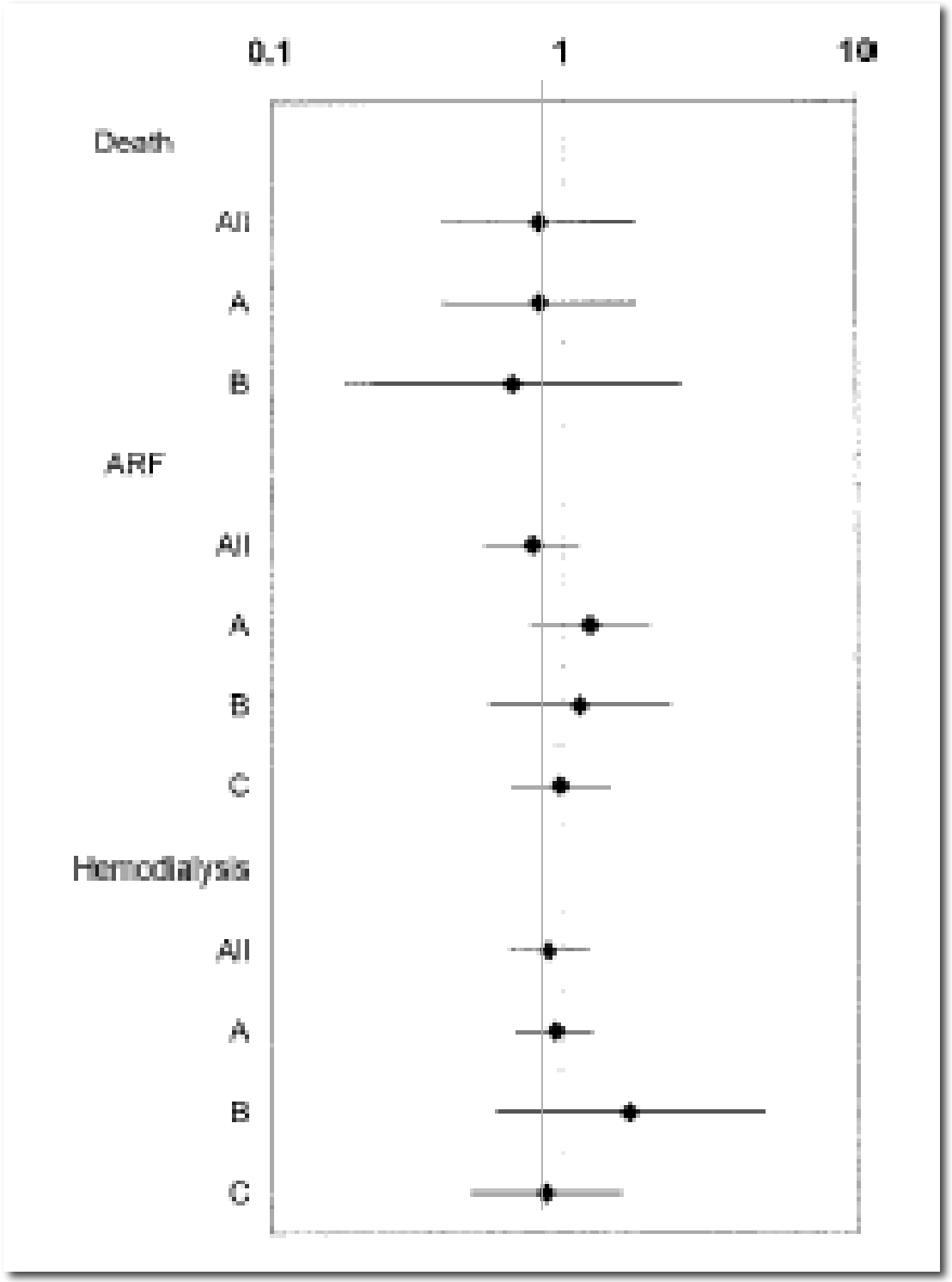
- Kellum and Decker searched MedLine (English and non-English literature) for every article on human trials with dopamine for the treatment or prevention of ARF from 1966 to 1999.
- They included 58 studies with 2149 patients

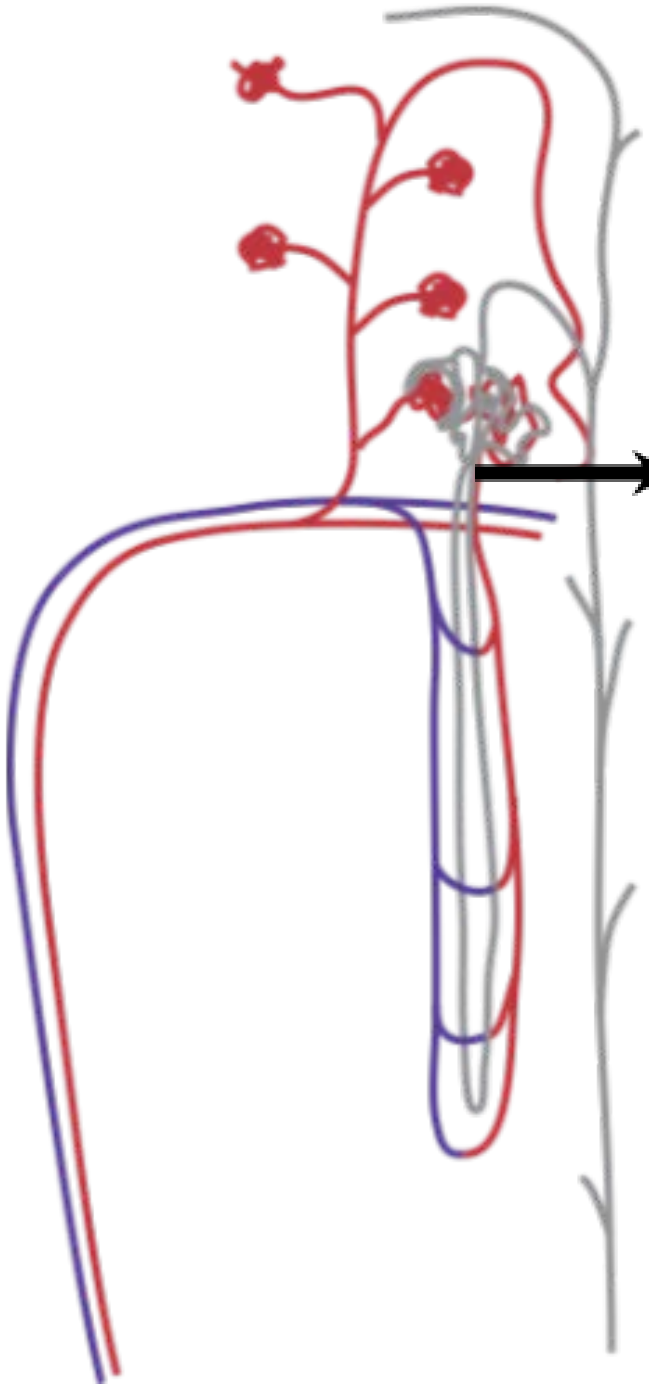
Kellum JA, Decker JM.Crit Care 2001; 29:1526-31.

A. Exclude radiocontrast studies

B. Limited to heart studies

C. Excludes studies in which had abnormal control groups or increased variance





Cortex
70% $O_2$ requirement
90% Blood supply

S3 segment of PT

Medulla
30% $O_2$ requirement
10% Blood supply

Dopamine

- increases cortical blood
- cortical blood flow increases GFR
- increases renal oxygen demand

# complications of low-dose dopamine

- Increase arrhythmias
- Increased myocardial oxygen demand
- Gut ischemia
- Suppressed respiratory drive
- Increased sensitivity to radiocontrast agents
- Decreases in T-cell activity

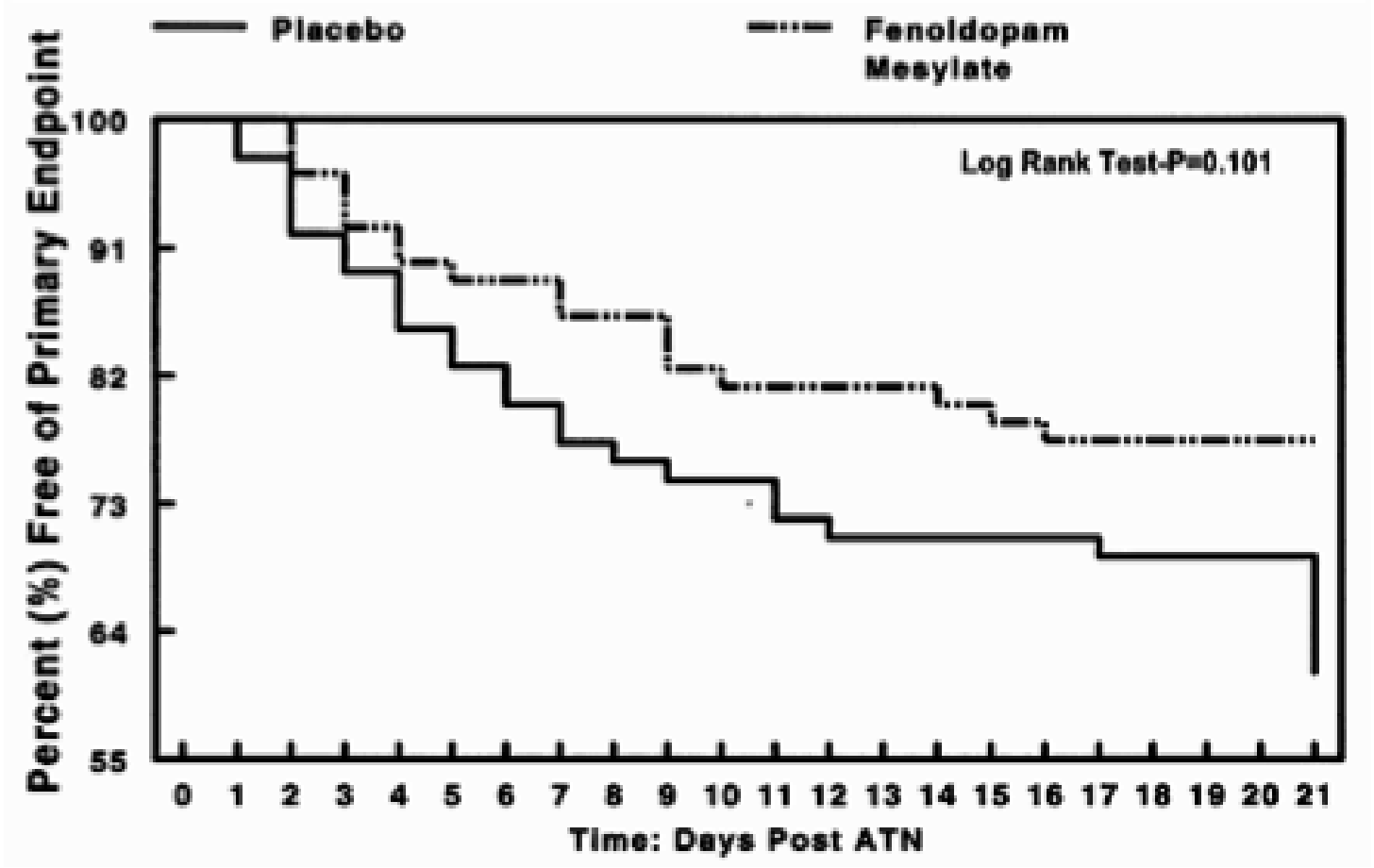
Fenoldapam

# dopamine 2.0: fenoldapam

- Isolated DA-1 activity
- Licensed as an IV anti-hypertensive
- Increases medullary blood flow more than cortical blood flow
  - Improved oxygenation
  - Does not increase renal work

- 155 patients randomized within 24 hours of 50% increase in Cr
- Primary end-point incidence of need-for-dialysis and/or survival at 21 days
- Fenoldapam or half normal saline for 72 hours
- Protocolized definition of need-for-dialysis

Tumlin JA, Finkel KW, Murray PT, Et al. Am J Kidney Dis. 2005; 46:26-34.

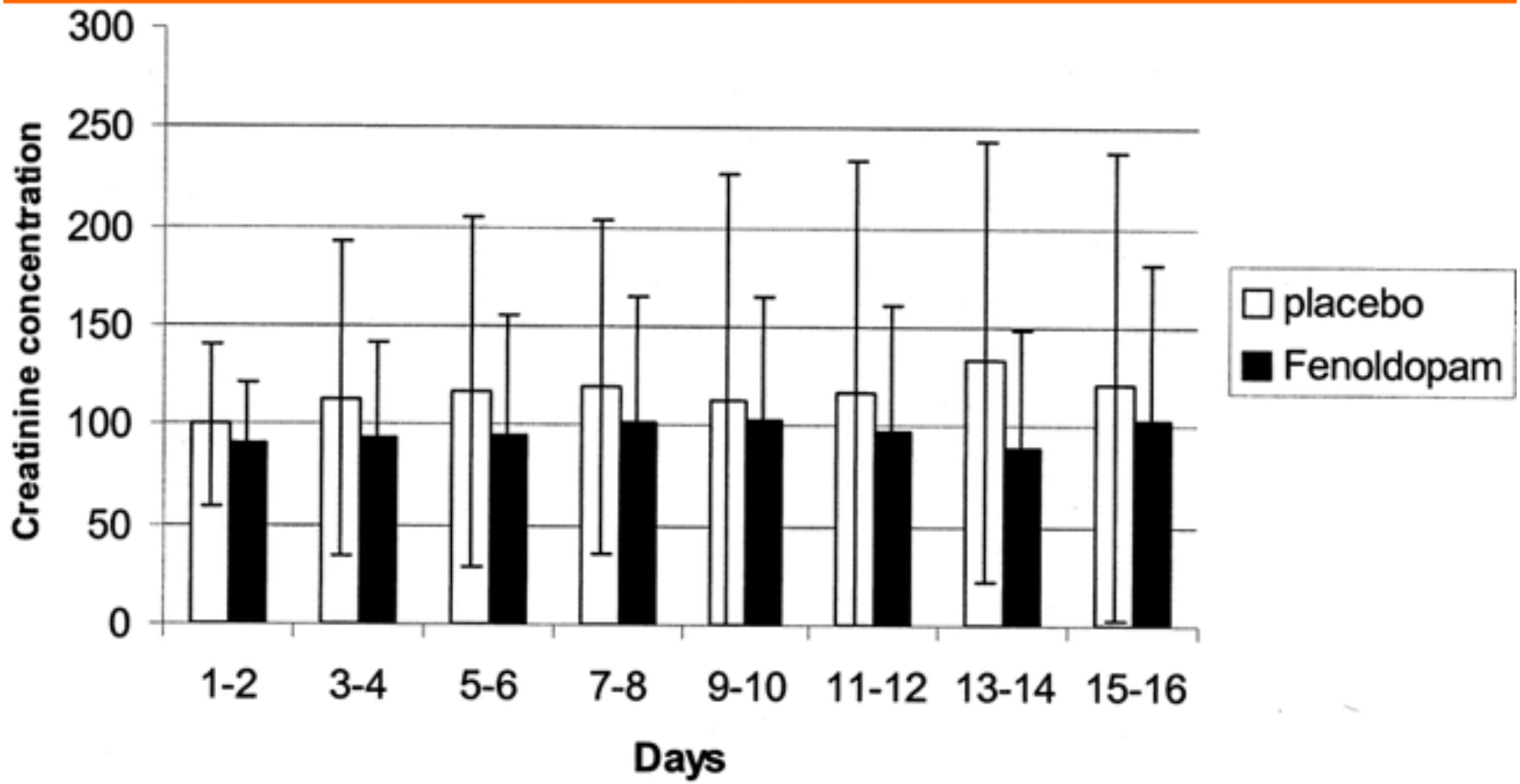


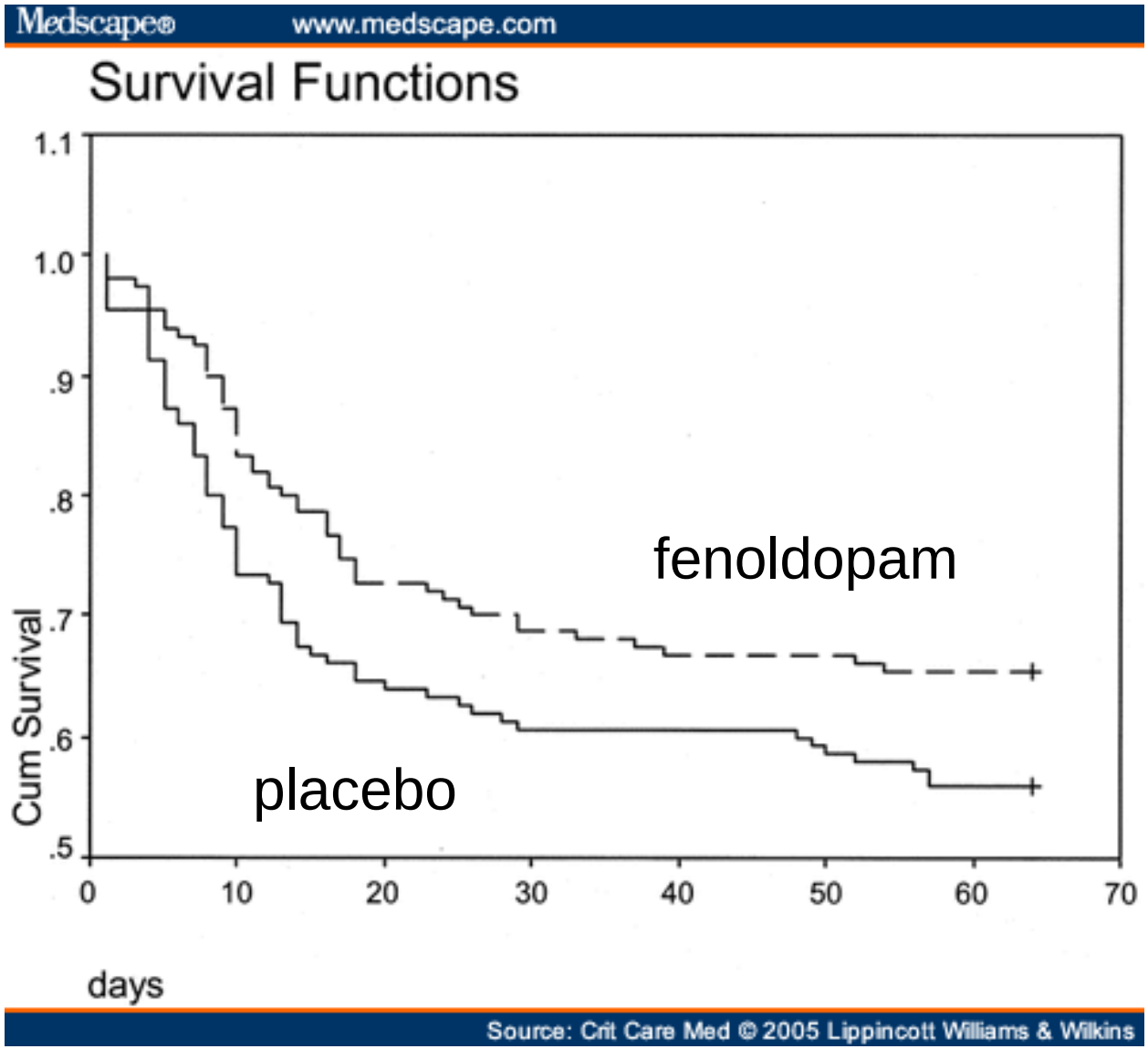

Tumlin JA, Finkel KW, Murray PT, Et al. Am J Kidney Dis. 2005; 46:26-34.

- 300 patients with SEPSIS and no signs of AKI
  - Non-oliguric
  - Cr < 1.7
- Randomized to **prophylactic** fenoldapam vs placebo

Morelli et al. Prophylactic Fenoldopam for Renal Protection in Sepsis: A Randomized, Double-Blind, Placebo-Controlled Pilot Trial.Crit Care Med. 2005;33(11):2451-2456.

Prophylaxis is a way to get around the problem of late diagnosis due to the lack of an established biomarker.





**Therapeutic targets in patients with or at risk of septic acute kidney injury, physiology, and current evidence**

| Targets | Physiologic Renal Effects | Clinical Renal Effects |
|---|---|---|
| MAP 80–85 vs 65–70 mm Hg | Higher MAP increases renal perfusion pressure and blood flow | SEPSISPAM trial: lower need for RRT with higher blood pressure target in patients with chronic hypertension[27] |
| CVP >12 mm Hg | Renal perfusion pressure (MAP – CVP) decreases when CVP increases. Elevated CVP increase intratubular pressure, which counteracts GFR | Elevated CVP (>12 mm Hg) is associated with the development or progression of AKI in observational studies[26,38] |
| Protocol-based EGDT[28] | NA | ARISE and ProCESS trials: no effect on mortality or RRT requirement compared with "usual care"[31,32] |
| Hemoglobin 90 vs 70 g/L | Increased oxygen delivery to kidney tubular cells | TRISS trial: no effect on dialysis-free survival with a target hemoglobin of 90 g/L compared with a target of 70 g/L[47] |
| Vasopressin | Increase MAP; maintain GFR by mainly contracting the efferent arteriole | VASST: no effect on mortality; Prevented AKI progression and need for RRT in post hoc analysis[39,40] |
| RRT | NA | Observational data; better renal recovery with continuous than with intermittent RRT; should be initiated when fluid balance cannot be managed with diuretics alone[48,54] |

**Future therapies**

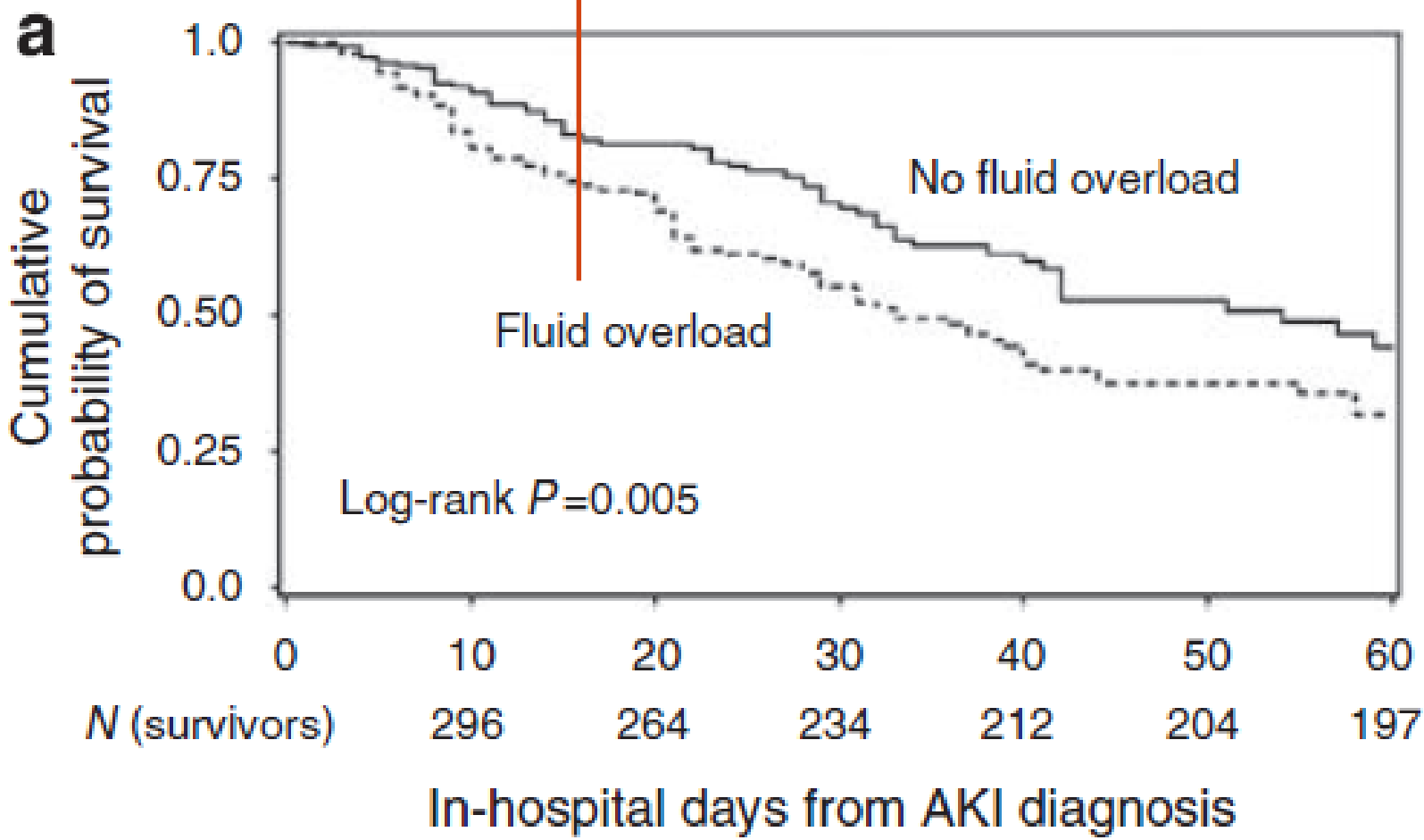
| Therapy | Mechanism | Evidence |
|---|---|---|
| Recombinant human soluble thrombomodulin | Reduce thrombin mediated clotting. Enhance protein C activation. Inactivate high-mobility group protein B1. | Phase 2b clinical trial in patients with sepsis and disseminated intravascular coagulation: Trend toward lower 28-day mortality. (Vincent 2013 2070–2079). |
| Acetylsalicylic acid | Induce synthesis of antiinflammatory molecules (lipoxins, resolvins, protectins). | Associated with reduced ICU mortality in observational studies.[62,63] Protected against endotoxin-induced AKI in animal model.[64] |
| Alkaline phosphatase | Endogenous enzyme. Detoxify endotoxins through dephosphorylation. iNOS inhibitor. | Phase 2a clinical trial: Improved creatinine clearance. Trend toward reduced RRT requirements. Decreased ICU duration of stay.[60] |
| Anti-histone antibody | Block cytotoxic extracellular histones released during sepsis. | Prevented death and AKI in experimental sepsis.[67] |
| Polymyxin B hemoperfusion | Polymyxin B adsorbed to a polystyrene fiber in a hemoperfusion device has the ability to bind and neutralize lipopolysaccharide. Inactivates circulating proapoptotic factors. | EUPHAS trial: Improved hemodynamics, lung function, SOFA score and survival at 28 d in patients with intraabdominal sepis.[68] |

Does this patient need dialysis?

# Accepted indications

- Refractory fluid overload
- Hyperkalemia (plasma potassium concentration >6.5 meq/L) or rapidly rising potassium levels
- Signs of uremia, eg pericarditis, neuropathy, or an otherwise unexplained AMS
- Metabolic acidosis (pH less than 7.1)
- Certain alcohol and drug intoxications
- Volume overload?
- BUN?

>10% from baseline at initiation of RRT




OR 2.07 (95% CI 1.27–3.37).

Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with AKI. KI 2009; 76:422.

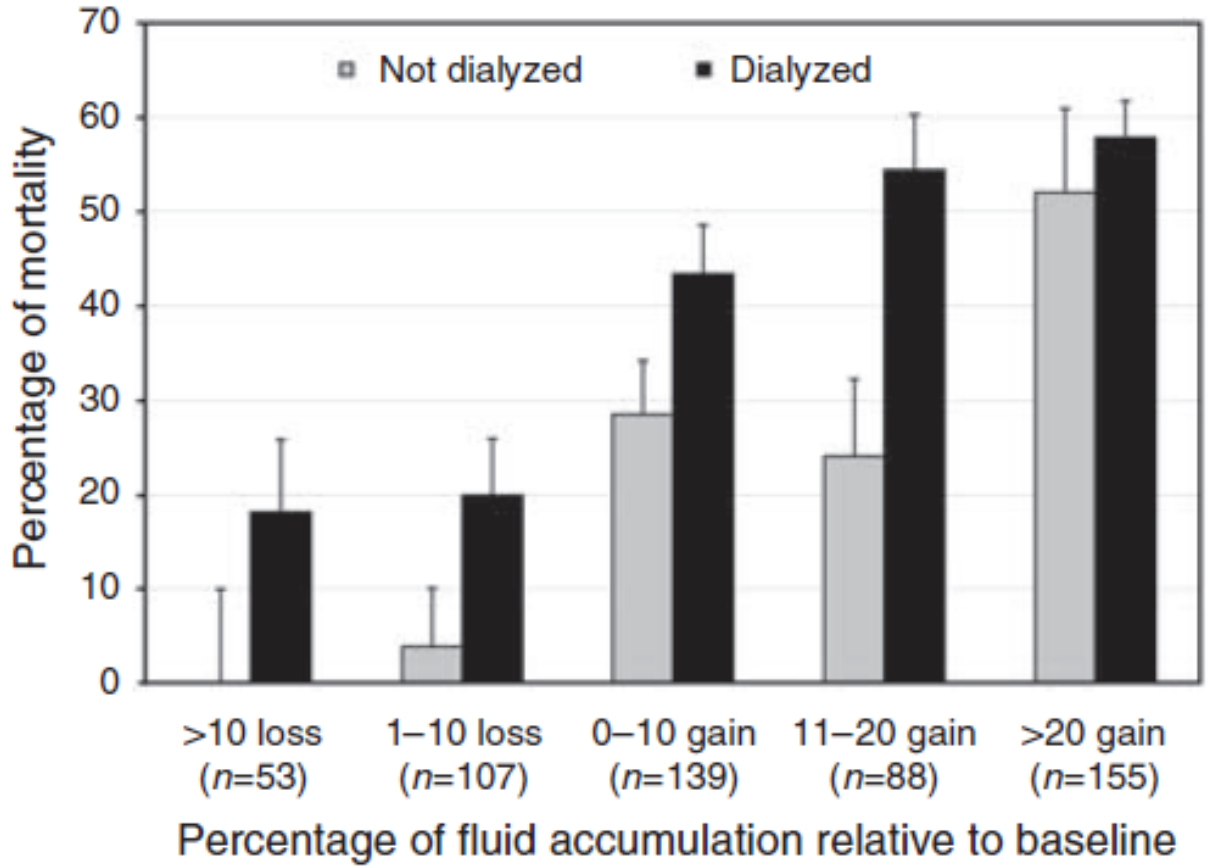



**Figure 2 | Mortality rate by final fluid accumulation relative to baseline weight and stratified by dialysis status.**

Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with AKI. KI 2009; 76:422.

# When should we start RRT?

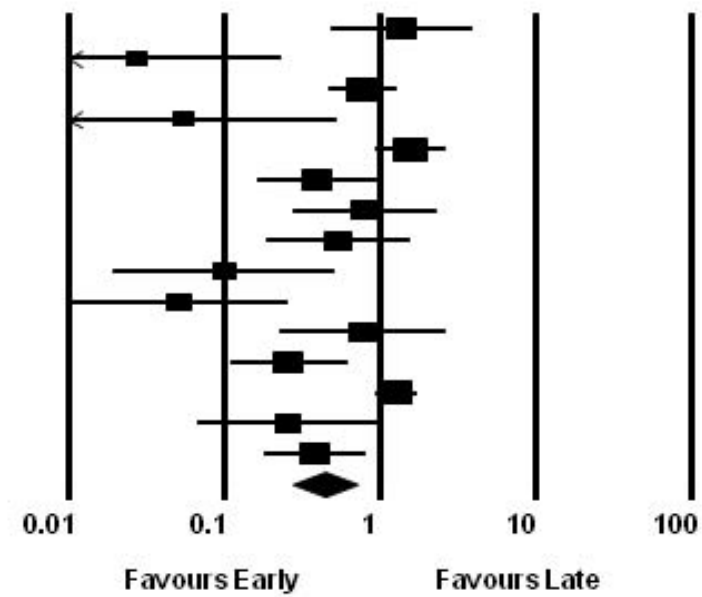
**Table 1 Clinical studies on timing of initiation of renal replacement therapy (RRT) in acute kidney injury (AKI) and patient outcome**

| | Study design | Clinical setting | Definition of timing | Confounding CRRT factors | Survival advantage early group |
|---|---|---|---|---|---|
| Bouman [8] | RCT ($n=105$) | Oliguric ARF and MOF | Early: creatinine clearance $<20$ ml/min and $<12$ h after onset of oliguria ($<180$ ml in 6 h)<br>Late: urea $\geq 40$ mmol/l or severe pulmonary edema[a] after onset of oliguria | No | No |
| Jiang [28] | RCT ($n=37$) | Severe pancreatitis renal function is not reported | Early: $<48$ h after onset of abdominal pain<br>Late: $>96$ h after onset of abdominal pain | No | Yes |
| Gettings [31] | Retrospective ($n=100$) | Post trauma | Early: urea $<60$ mg/dl[b]<br>Late: urea $\geq 60$ mg/dl | Various CRRT modes<br>Dose not reported | Yes |
| Piccini [32] | Retrospective ($n=80$) | Sepsis with oliguric ARF and ALI | Early: $<12$ h after ICU admission<br>Late: urea $>35$ mmol/l or creatinine $>600$ μmol/l | Dose early >> dose late | Yes |
| Elahi [30] | Retrospective ($n=64$) | Post cardiac surgery | Early: oliguria $<100$ ml in 8 h<br>Late: urea $>30$ mmol/l or sCr $>250$ μmol/l | Dose not reported | Yes |
| Demirkilic [29] | Retrospective ($n=61$) | Post cardiac surgery | Early: oliguria $<100$ ml in 8 h<br>Late: sCr $>5$ mg/dl[c] | Dose not reported | Yes |

- non-randomization of groups,
- differences in indications for initiation
- lack of inclusion in the analysis of patients with AKI who did not receive RRT because they recovered renal function or died

# Meta Analysis: All 15 studies

| Study name | Subgroup within study | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| Bouman 2002 | Mixed | 1.375 | 0.487 | 3.884 | 0.601 | 0.548 |
| Sugahara 2004 | Surgery | 0.028 | 0.003 | 0.231 | -3.318 | 0.001 |
| Liu 2006 | Mixed | 0.773 | 0.460 | 1.298 | -0.974 | 0.330 |
| Sabater 2008 | Mixed | 0.055 | 0.006 | 0.524 | -2.520 | 0.012 |
| Bagshaw 2010* | Mixed | 1.563 | 0.933 | 2.619 | 1.697 | 0.090 |
| Gettings 1999 | Surgery | 0.399 | 0.164 | 0.973 | -2.019 | 0.043 |
| Elahi 2004 | Surgery | 0.800 | 0.273 | 2.341 | -0.407 | 0.684 |
| Demirkilic 2004 | Surgery | 0.533 | 0.183 | 1.552 | -1.154 | 0.249 |
| Andrade 2007 | Mixed | 0.100 | 0.019 | 0.515 | -2.752 | 0.006 |
| Manche 2008 | Surgery | 0.051 | 0.010 | 0.256 | -3.623 | 0.000 |
| Iyem 2009 | Surgery | 0.778 | 0.229 | 2.644 | -0.403 | 0.687 |
| Shiao 2009 | Surgery | 0.260 | 0.110 | 0.614 | -3.075 | 0.002 |
| Bagshaw 2009 adj | Mixed | 1.250 | 0.915 | 1.708 | 1.401 | 0.161 |
| Wu 2007 adj | Surgical | 0.259 | 0.068 | 0.988 | -1.977 | 0.048 |
| Carl 2010 adj | Mixed | 0.380 | 0.177 | 0.816 | -2.482 | 0.013 |
| Meta Analysis | | 0.446 | 0.276 | 0.723 | -3.279 | 0.001 |

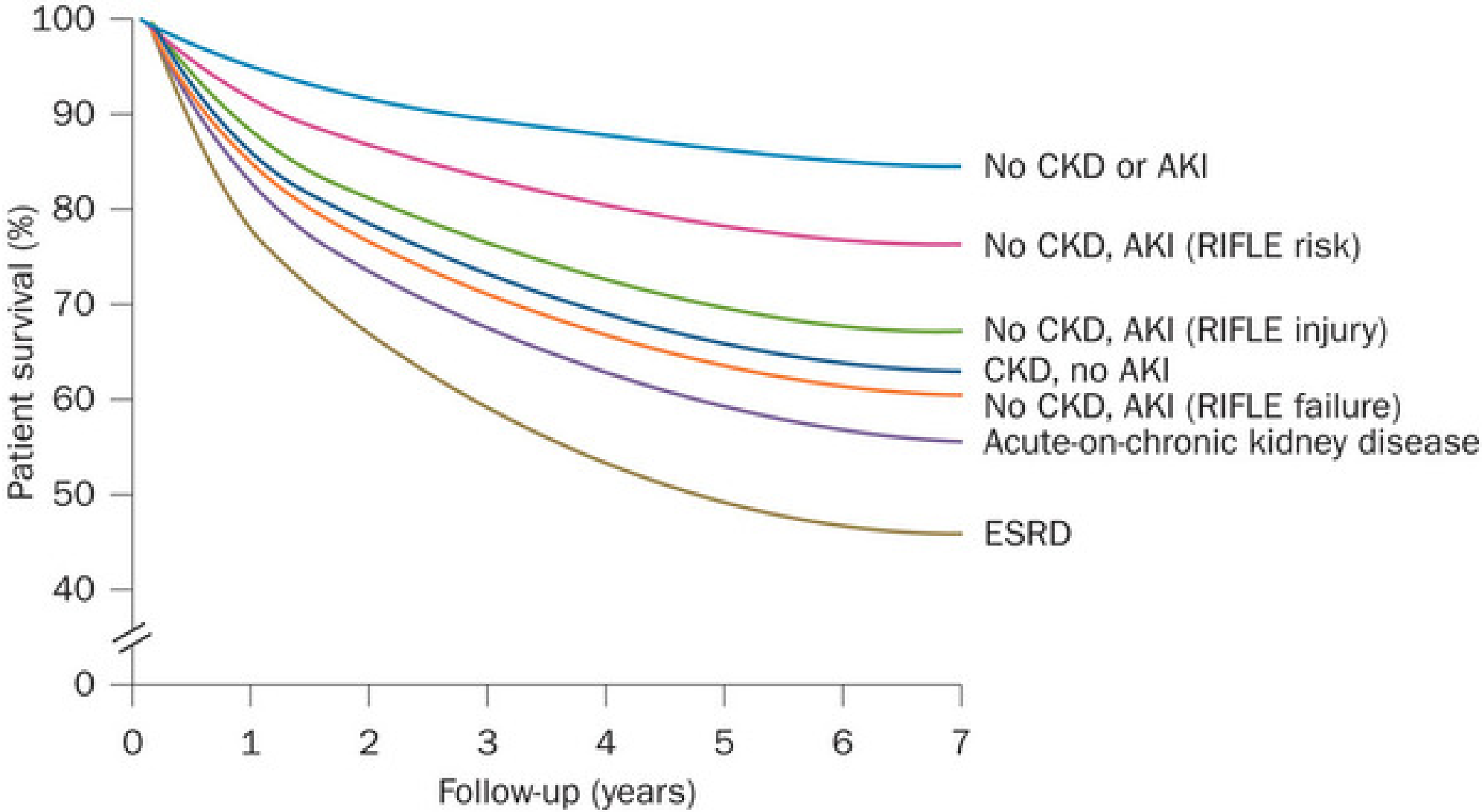



Karvellas, Constantine J., et al. "A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis." *Crit Care* 15.1 (2011): R72.

# So, when DO you start CRRT?

- No evidence based criteria
- Accepted criteria (hyperkalemia etc)
- Definitely before “overt” uremic signs and symptoms
- BUN 80-100….no hard data
- Fluid overload < 10%....no hard data

Will the patient survive after discharge?




Wu et al, acute on chronic kidney injury at hospital discharge is associated with long-term dialysis and mortality, KI, Aug 2011

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