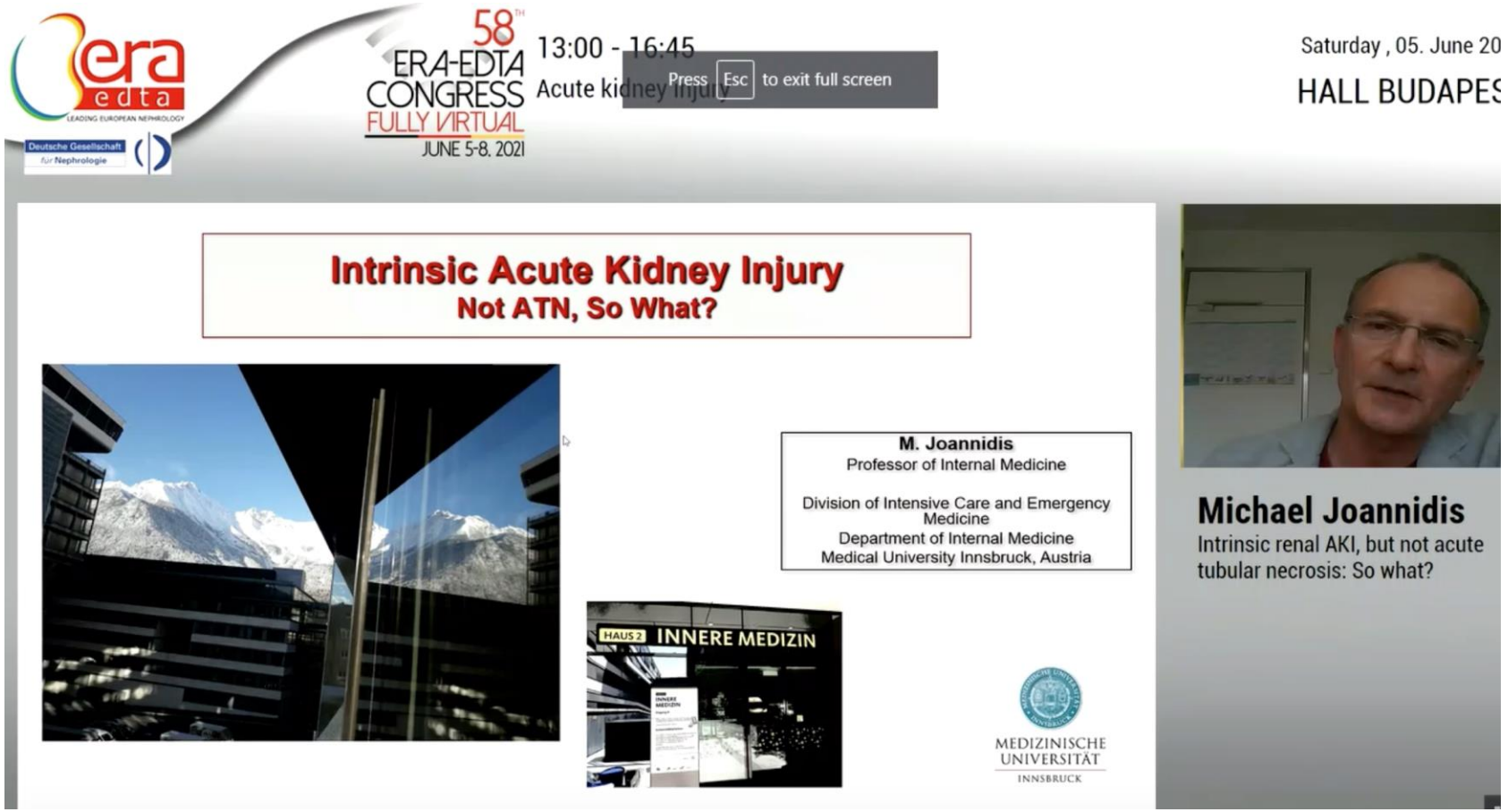
In the name of GOD

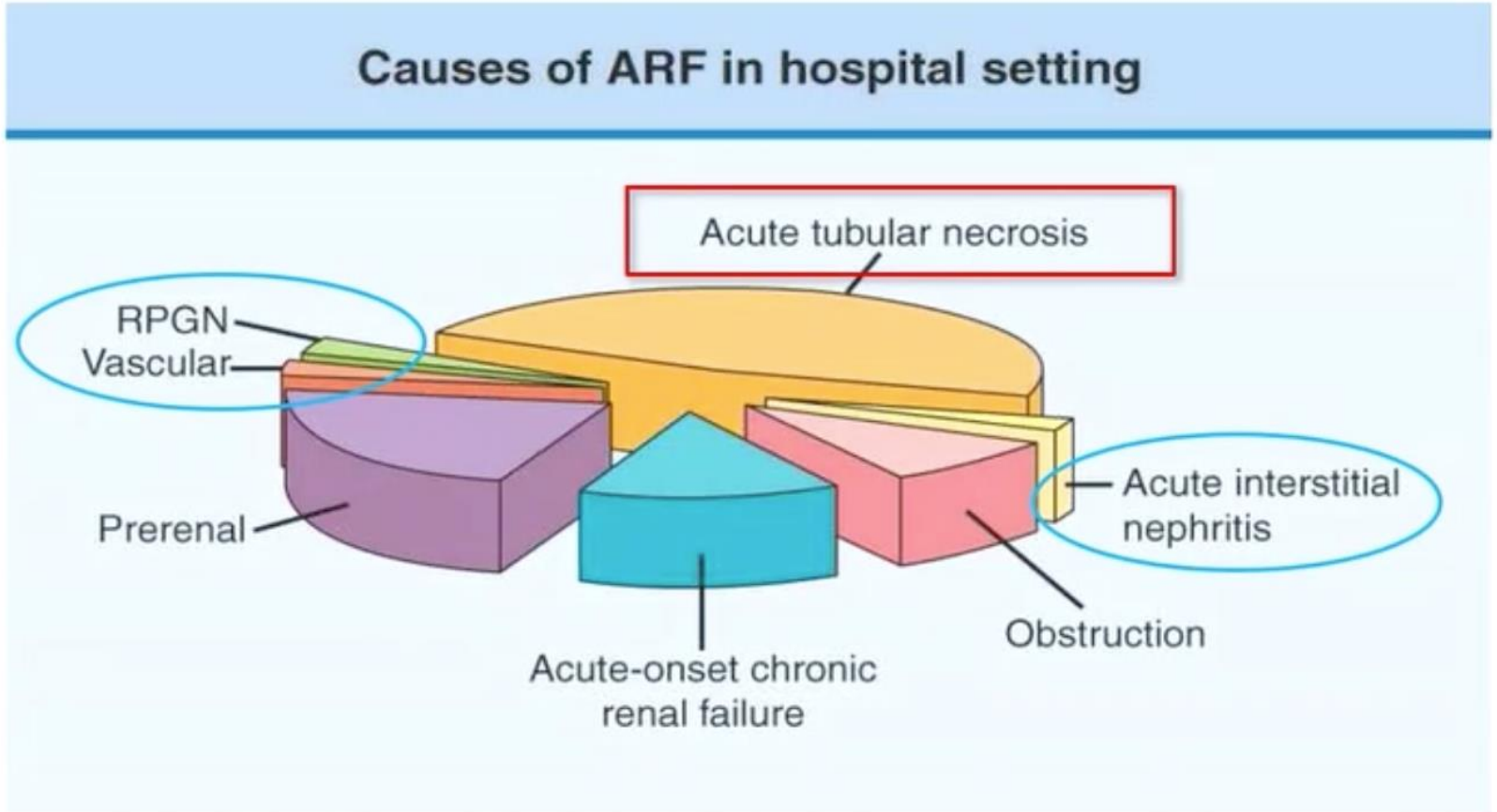


Fariba Samadian

Associate Professor of Shahid Beheshti University of Medical Sciences

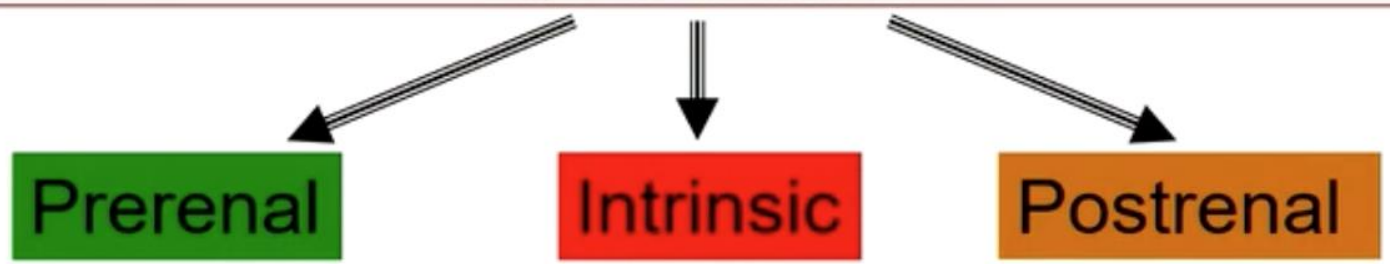
Labafinejhad Hospital

Is all AKI equal?



Liano F et al , Kidney International 1996, 50:811

A more pragmatic distinction of AKI….



50-60%

30-45%

<5%

- Large vessels
  - *e.g. bilateral thrombosis/dissection*
- Glomeruli/renal microvasculature
  - *e.g. acute GN, vasculitis, TMA*
- Tubules (“ATN”)
  - *e.g. toxins, ischemia*
- Tubulointerstitium
  - *e.g. acute interstitial nephritis*
- Everything
  - *e.g. sepsis*

Necrotising Renal Tubules in Severe Trauma

BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 22 1941

CRUSH INJURIES WITH IMPAIRMENT OF RENAL FUNCTION

BY

E. G. L. BYWATERS, M.B., B.S., M.R.C.P.

Beit Memorial Fellow

AND

D. BEALL, Ph.D. Toronto

(From the Departments of Medicine and Pathology, British Postgraduate Medical School)

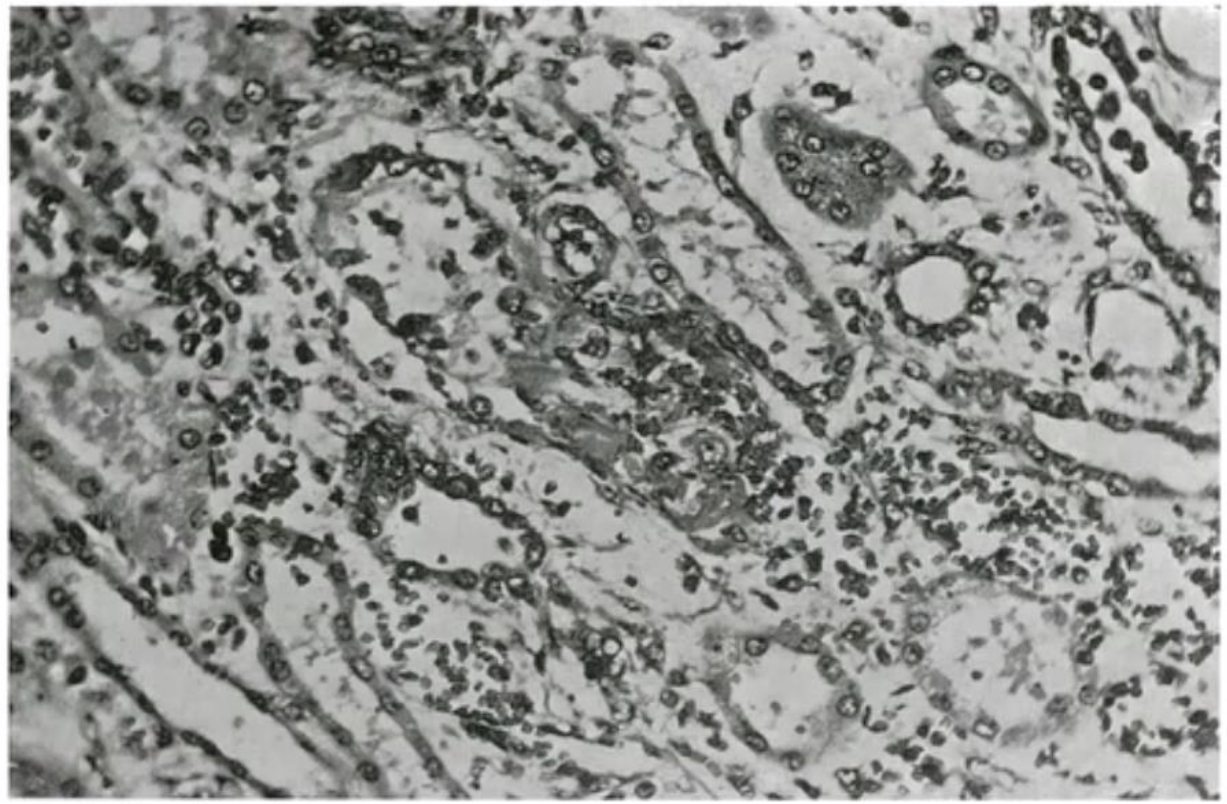
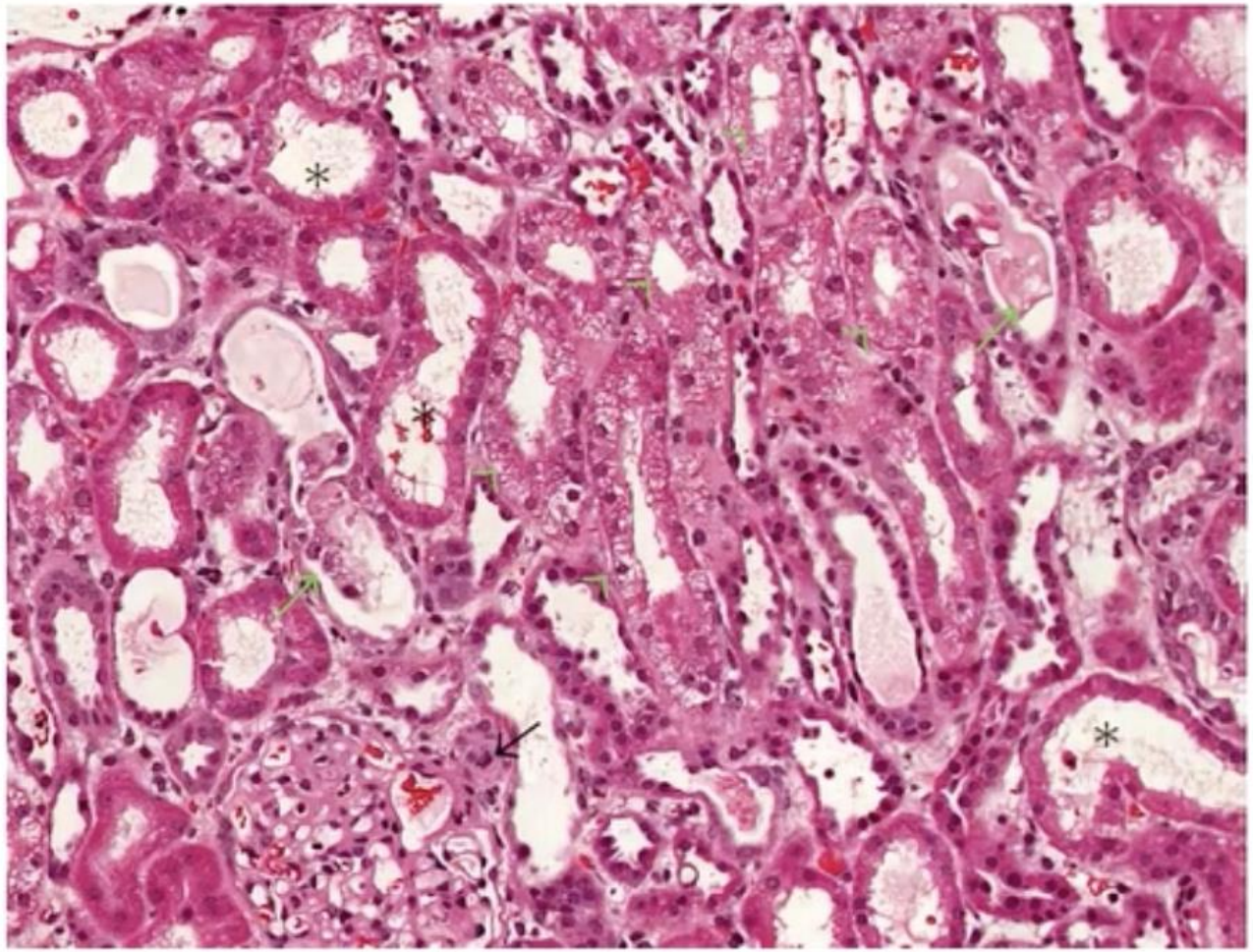


FIG. 2.—Photomicrograph of renal tubule from boundary zone, stained haematoxylin and eosin, showing necrosis of wall and commencing reactive changes. × 280.

Tubular cell necrosis occasionally detected in nephrotoxic AKI

Vancomycin induced AKI



Shah-Khan F et al, Int J Nephrol. 2011; 2011: 436856.

Case series of 10 native kidney biopsies in patients with COVID-19 and AKI

Cohort

10 patients with COVID-19

Mean age = 65 years

AKI, proteinuria ± hematuria

8 required dialysis

Kidney Biopsy Findings

Pathologic Findings

- All patients had varying degree of ATN
- 2 had TMA
- 1 had myoglobin cast nephropathy
- 1 had pauci-immune crescentic GN
- 1 had FSGS with features of collapsing glomerulopathy

SARS-CoV-2

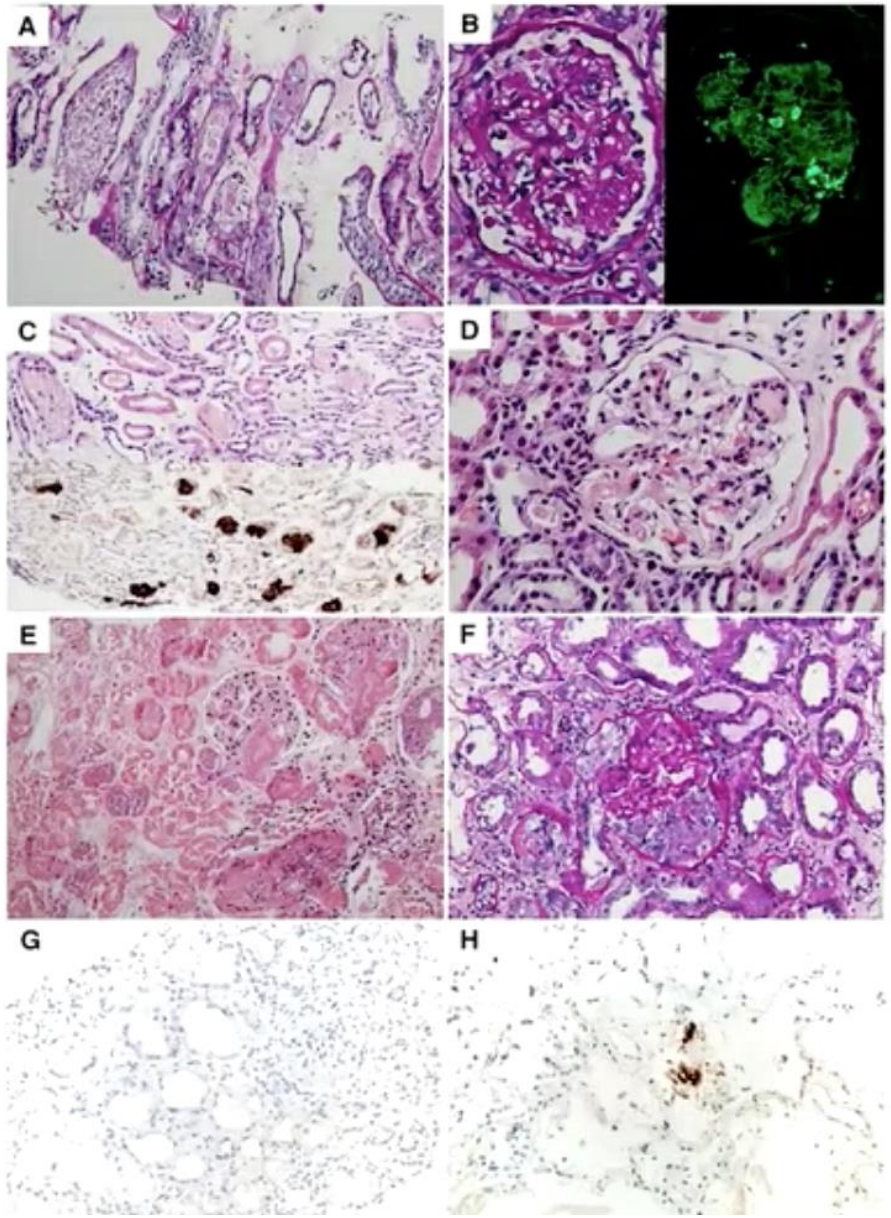
-All negative for SARS-CoV-2 by immunohistochemistry
-No viral particles identified via electron microscopy

Conclusion: This kidney biopsy series showed ATN as the most common finding in patients with COVID-19 and AKI. We found no evidence of significant viral presence in the kidney.

DOI: 10.1681/ASN.2020050699

Purva Sharma et al. JASN 2020;31:1948-1958

JASN



Case series of 10 native kidney biopsies in patients with COVID-19 and AKI

A variety of kidney histopathological findings seen in our patients with COVID-19 and AKI:

(A) ATN is often manifested by accumulation of cellular debris in lumens of distal tubules (periodic acid–Schiff [PAS]: ×200).
(B) Segmental glomerulosclerosis with features of healing collapse and protein reabsorption granules in podocytes (left, PAS; right, FITC IgG immunofluorescence stain: ×400).
(C) Red-brown casts in tubules in the patient with rhabdomyolysis, staining positively for myoglobin stain (upper, hematoxylin and eosin [H&E]; lower, myoglobin immunohistochemistry stain: ×200).
(D) Diffuse and early nodular diabetic glomerulosclerosis (H&E, ×400).
(E) Diffuse cortical necrosis in a patient with severe TMA (H&E, ×200).
(F) Cellular crescent in a glomerulus and surrounding acute tubular injury with flattening of the tubular epithelium in a patient with ANCA disease (PAS, ×200).
(G) Representative section of negative immunohistochemistry staining for SARS-CoV-2 nucleocapsid protein after antigen retrieval (×200).
(H) (H) Lung tissue as positive control for immunohistochemistry staining for SARS-CoV-2 (×200).

Purva Sharma et al. JASN 2020;31:1948-1958

ATN is rarely seen human sepsis

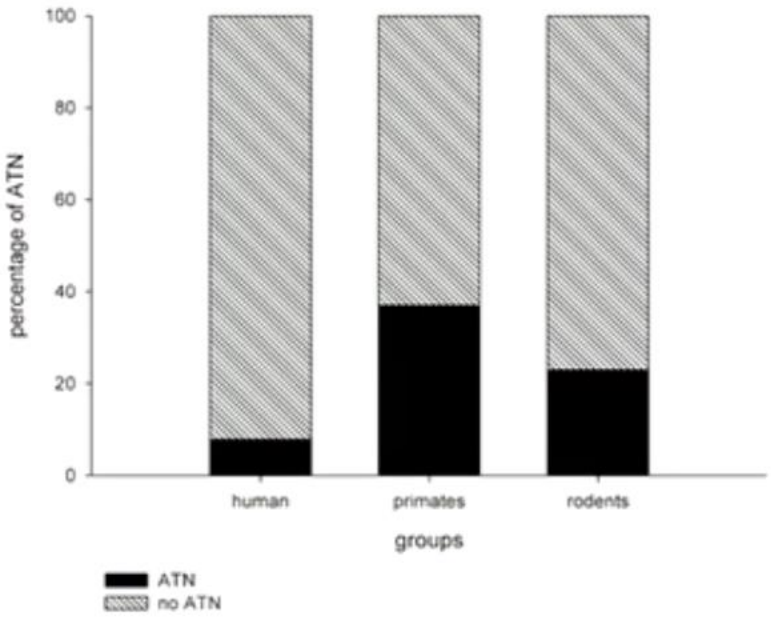


Table 1

Human studies

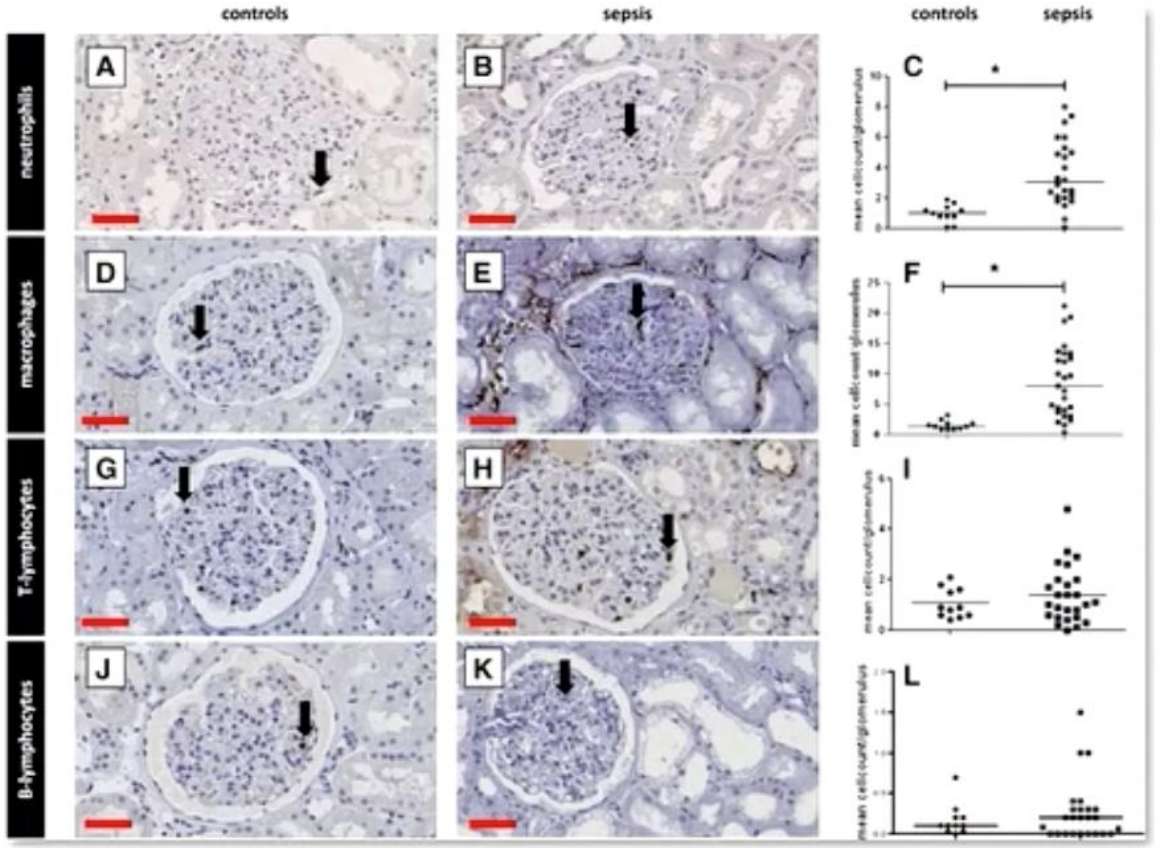
Study	Cause	Acute kidney injury definition	Method	Cases of AKI/number of patients (%)	Acute tubular necrosis (%)
Hotchkiss and colleagues [10]	Sepsis/septic shock	Serum creatinine >2 mg/dl and urine output <20 ml/kg/hour × 6 hours	Postmortem	12/20 (60)	1 (5)
Sato and colleagues [13]	Sepsis	Not available	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).

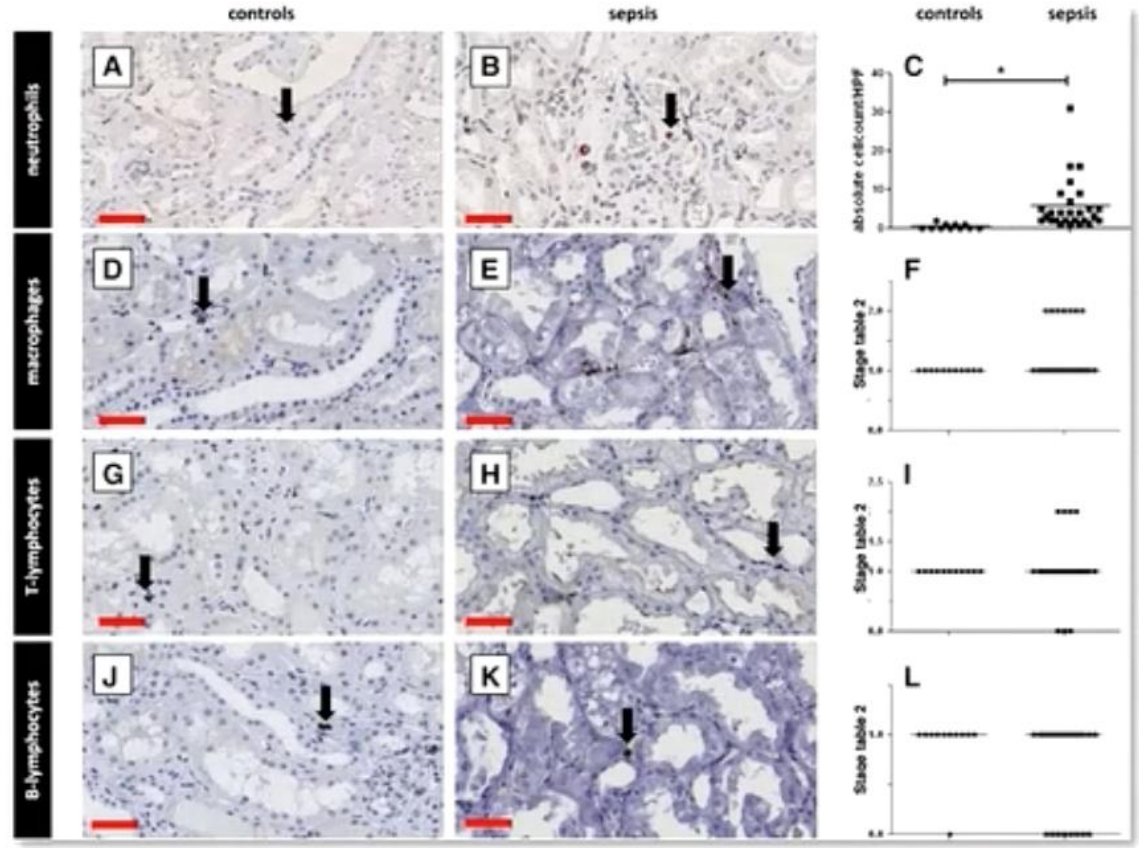
Langenberg C et al, Critical Care 2008, 12:R38 (doi:10.1186/cc6823)

Kidney histopathology in lethal human sepsis

Leukocyte infiltration in the glomeruli



Leukocyte infiltration in the tubulointerstitium

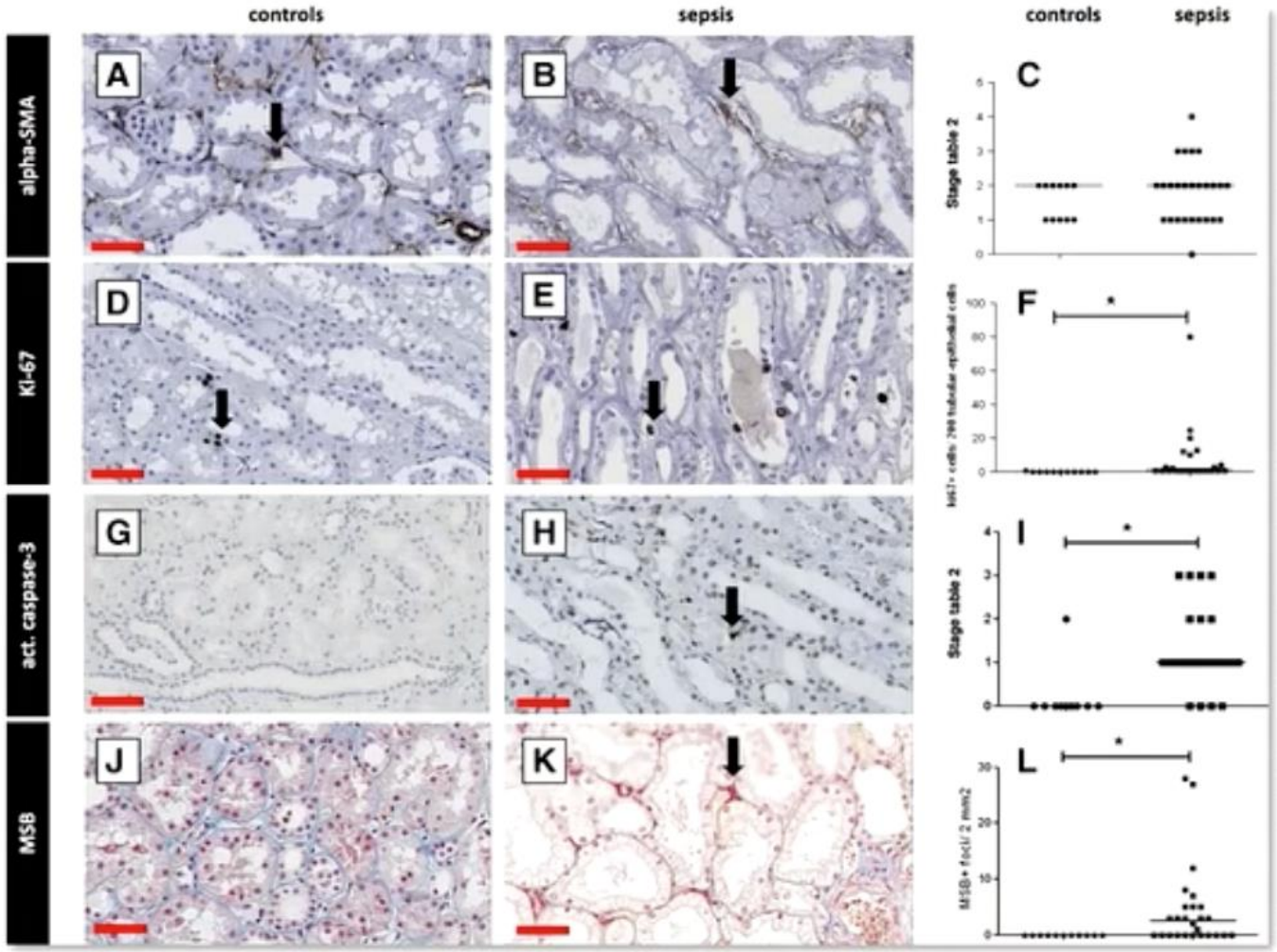


Sepsis (n=27): immediate post mortem biopsies
Controls: unaffected tissue from kidneys reoved for renal cell carcoinoma

Aslan et al. Critical Care (2018) 22:35

Kidney histopathology in lethal human sepsis

Proliferation, fibrin deposition and apoptosis in the tubulointerstitium



myofibroblasts

cell proliferation

apoptosis

fibrin deposition

Aslan et al. Critical Care (2018) 22:359

ATN – Fact Check

- ATN is frequently used as synonym for ischemic, nephrotoxic or septic AKI
- You hardly ever see isolated tubular necrosis in AKI
- Some degree of tubular damage may observed in all AKI

The concept of ATN as a distinct disease entity for (intrinsic) AKI is fundamentally wrong

If ATN is not the predominant mechanism in AKI …. what is it?

Frequent etiologies of AKI in the critically ill

- Sepsis
- Fluid overload
- Organ “cross-talk”
  - Cardiorenal syndrome
  - Lung-kidney interaction (ARDS)

Intensive Care Med (2015) 41:1411–1423
DOI 10.1007/s00134-015-3934-7

SEVEN-DAY PROFILE PUBLICATION

Eric A. J. Hoste
Sean M. Bagshaw
Rinaldo Bellomo
Cynthia M. Cely
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Charles D. Gomersall
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Ravindra L. Mehta
Paul Palevsky
Eric Roessler
Claudio Ronco
Shigehiko Uchino
Jorge A. Vazquez
Erick Vidal Andrade
Steve Webb
John A. Kellum

Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study

Etiology

Table 2 Variables at the time of acute kidney injury ($n = 666$)

Etiology of AKI	
Sepsis	271 (40.7 %)
Hypovolemia	227 (34.1 %)
Drug related	96 (14.4 %)
Cardiogenic shock	88 (13.2 %)
Hepatorenal syndrome	21 (3.2 %)
Obstruction of the urine outflow tract	9 (1.4 %)

Panel 3: Main exposures for acute kidney injury

Level 1 and 2 countries

- Sepsis
- Circulatory shock
- Trauma
- Cardiac surgery (especially with cardiopulmonary bypass)
- Major non-cardiac surgery
- Nephrotoxic drugs and agents
- Burns

Level 2 (some areas) and level 3 countries

- Diarrhoea
- Obstetric complications (including septic absorption)
- Infectious diseases (malaria, leptospirosis, dengue fever, cholera, yellow fever, tetanus, and Hantavirus)
- Animal venoms (snakes, bees and wasps, *Loxosceles* spp [recluse] spiders, and *Lonomia* spp caterpillars)
- Natural medicines
- Natural dyes
- Prolonged physically overwhelming work in an unhealthy environment

Ravindra L Mehta et al, Lancet 2015

Sepsis-associated AKI

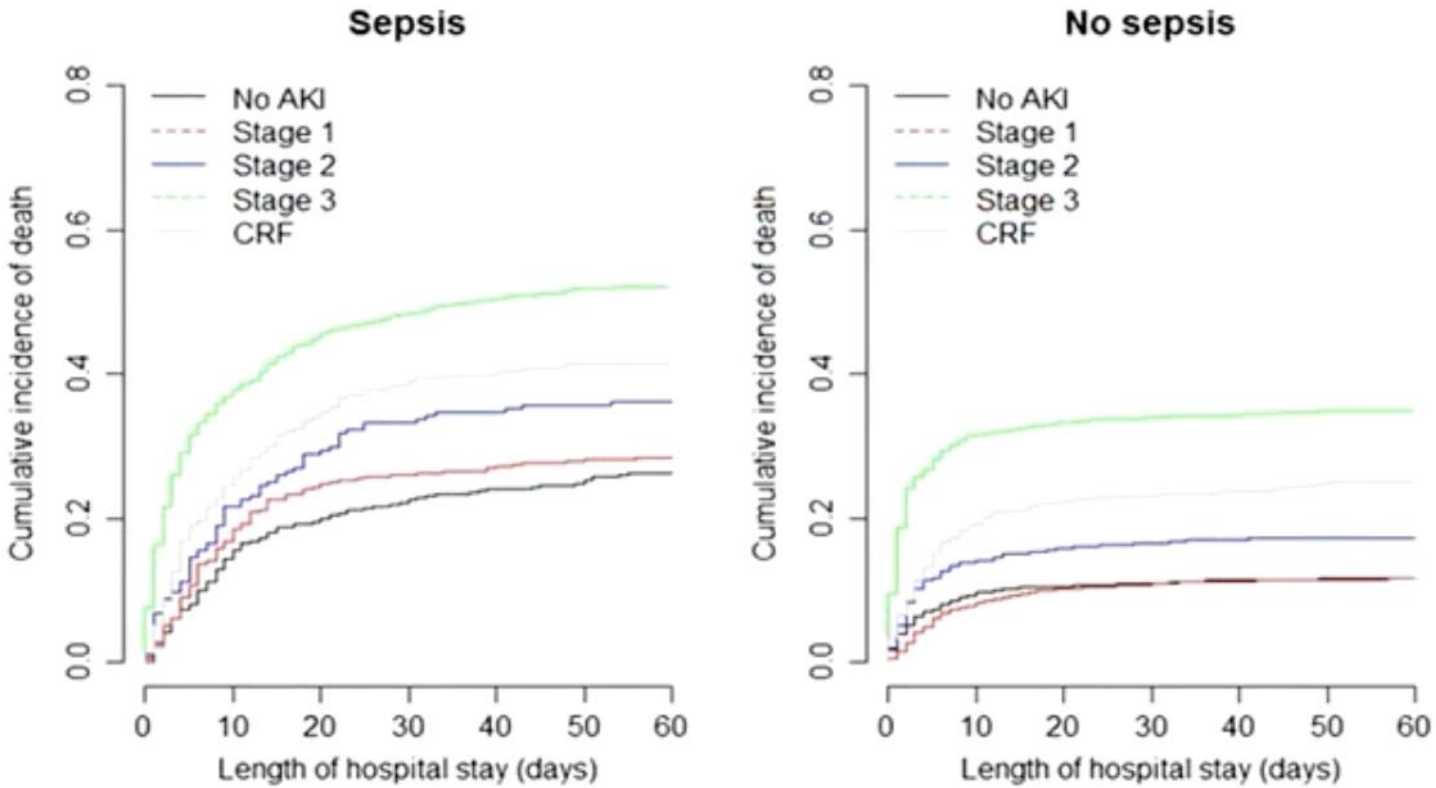
A worldwide multicentre evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from The Intensive Care Over Nations audit.

N=7970	Sepsis (N=1946)	No sepsis (n=6024)
AKI	68%	57%
AKI stage 3	40%	24%
RRT	20%	5%
Improvement to AKI<3 within 7days	21%	32%

Peters E. et al, Crit Care. 2018; 22: 188.

Sepsis-associated AKI

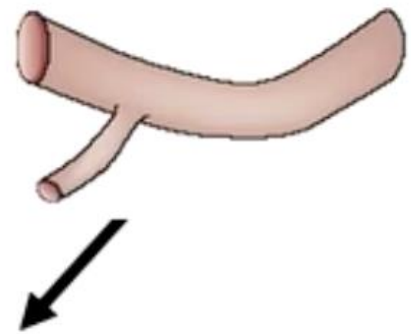
A worldwide multicentre evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from The Intensive Care Over Nations audit.



Peters E. et al, Crit Care. 2018; 22: 188.

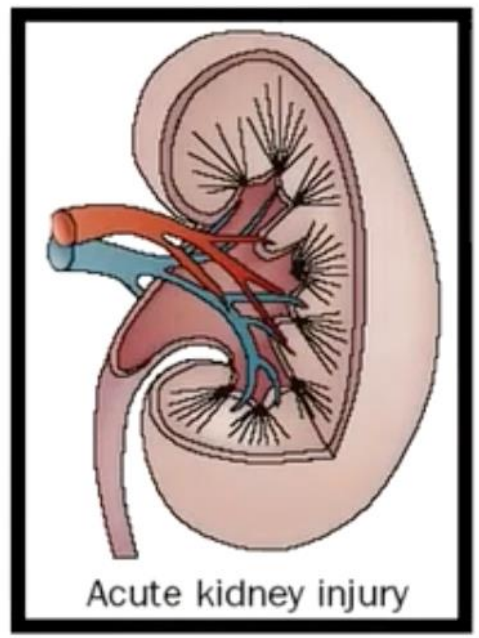
Mechanism of septic AKI is complex and not completely understood

Systemic vasodilation

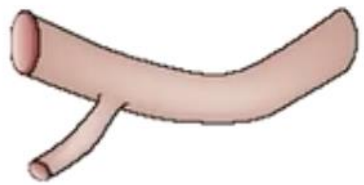


↑ GFR

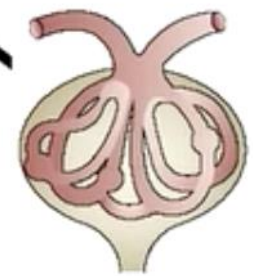
Mechanism of septic AKI is complex and not completely understood



Systemic vasodilation



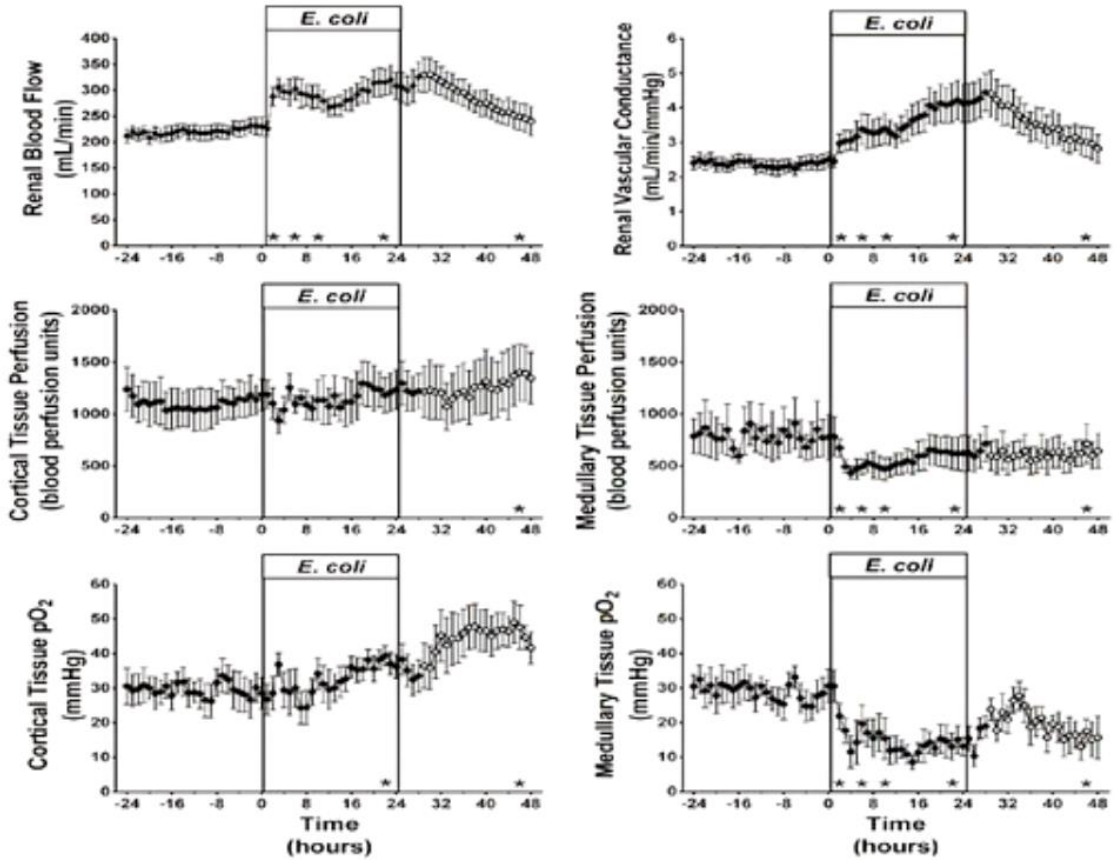
GFR ↓



Endothelial damage
and “microthrombi”

Cortical and Medullary Tissue Perfusion and Oxygenation in Experimental Septic Acute Kidney Injury

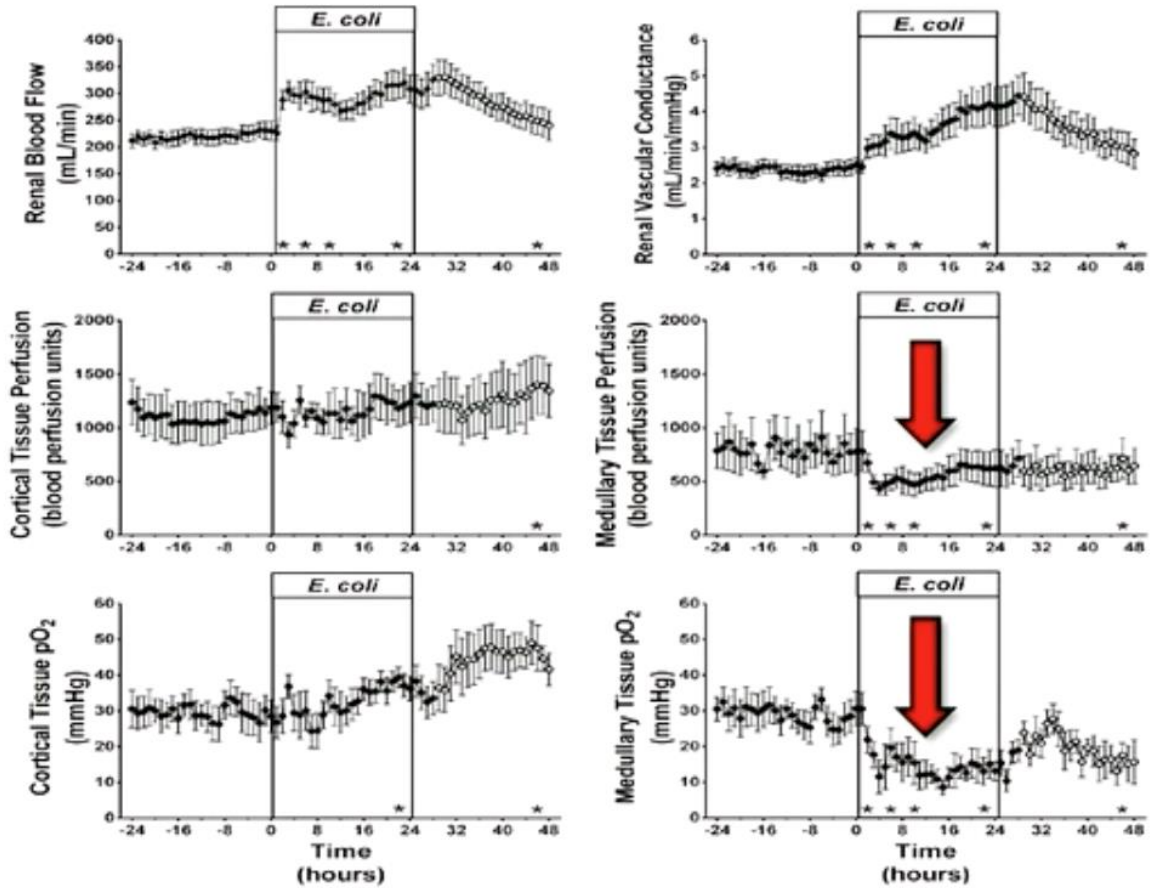
Hyperdynamic sepsis model in sheep



Calzavacca P et al, *Crit Care Med 2015; 43:e431–e439*

Cortical and Medullary Tissue Perfusion and Oxygenation in Experimental Septic Acute Kidney Injury

Hyperdynamic sepsis model in sheep



Cortical blood flow is slightly increased !

Medullary blood flow is decreased !

Calzavacca P et al, *Crit Care Med 2015; 43:e431–e439*

THE ANATOMICAL RECORD 201:237-248 (1981)

Shunting in Renal Microvasculature of the Rat: A Scanning Electron Microscopic Study of Corrosion Casts

D. CASELLAS AND A. MIMRAN
Department of Medicine D, CHR Saint-Charles, Montpellier, France

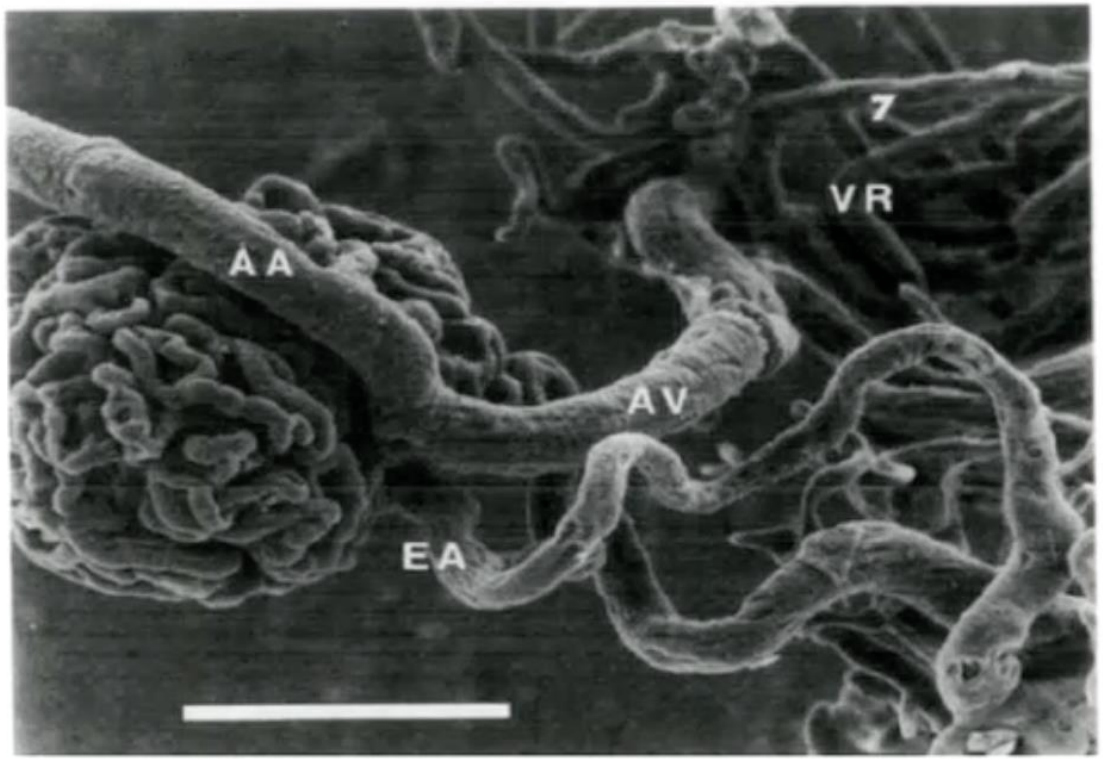
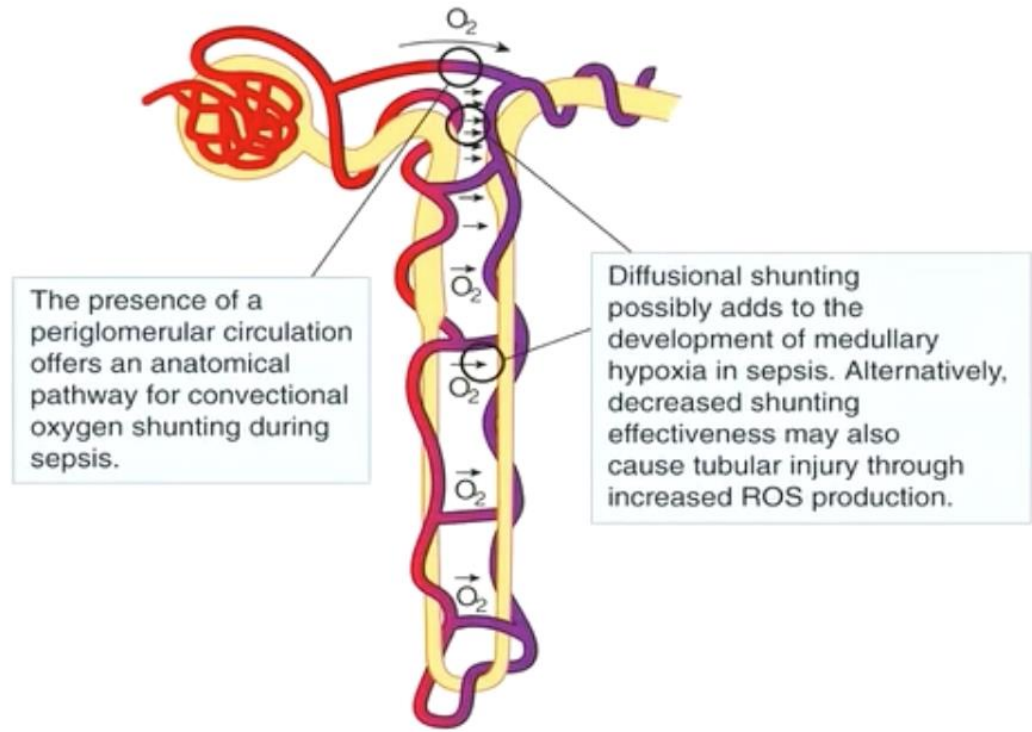
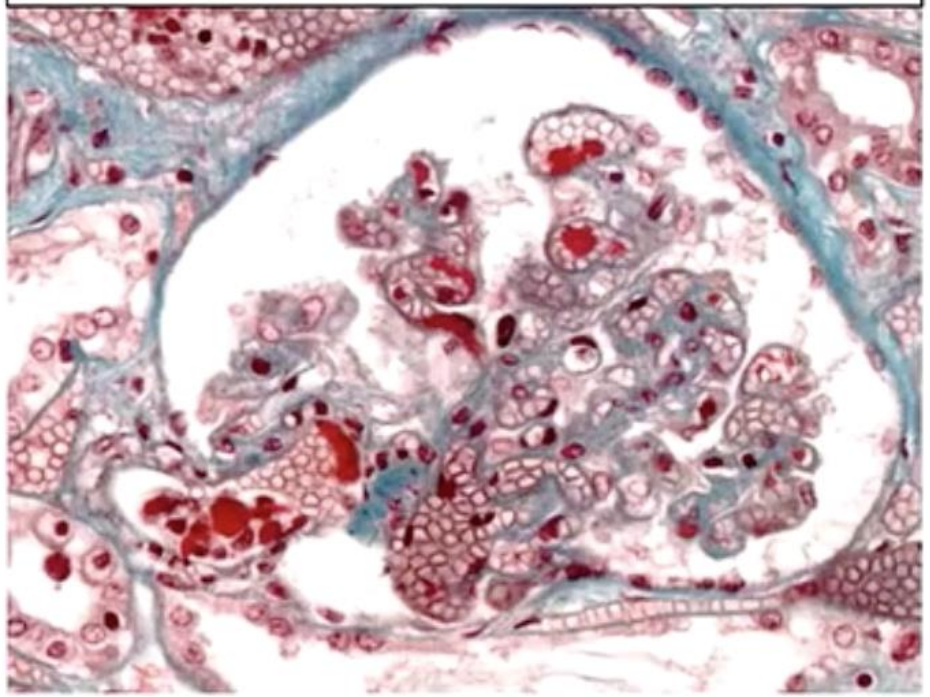


Fig. 7. Corrosion cast of a juxtamedullary glomerulus (539 g body weight). An aglomerular vessel (AV) arises from the afferent arteriole (AA) at the glomerular vascular pole. Note the presence of an efferent arteriole (EA). Bar: 100 μm. VR, vasa recta.

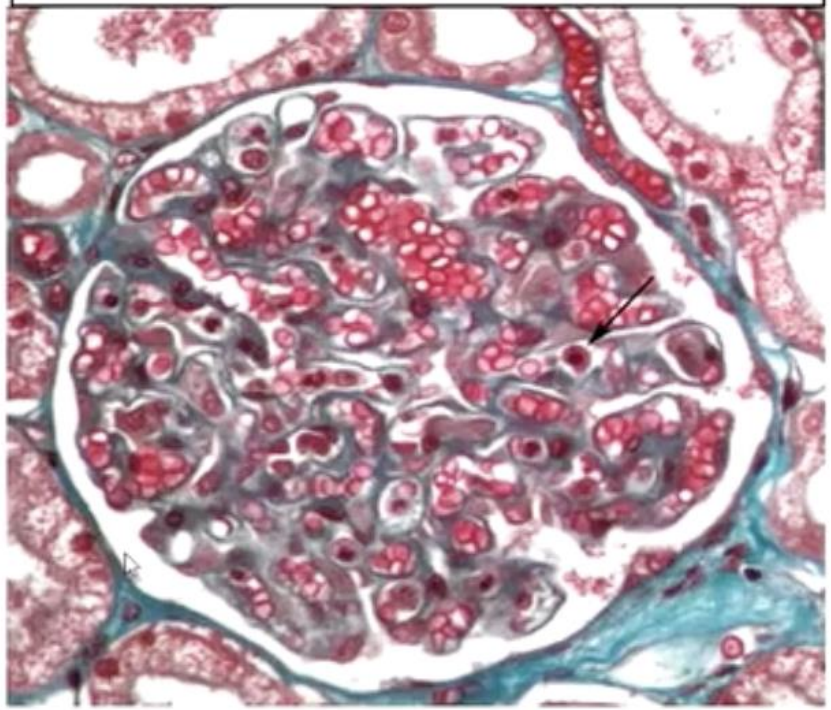


Histopathology of septic shock induced acute kidney injury: apoptosis and leukocytic infiltration

Partial thrombi in an afferent arteriole and glomerular capillaries

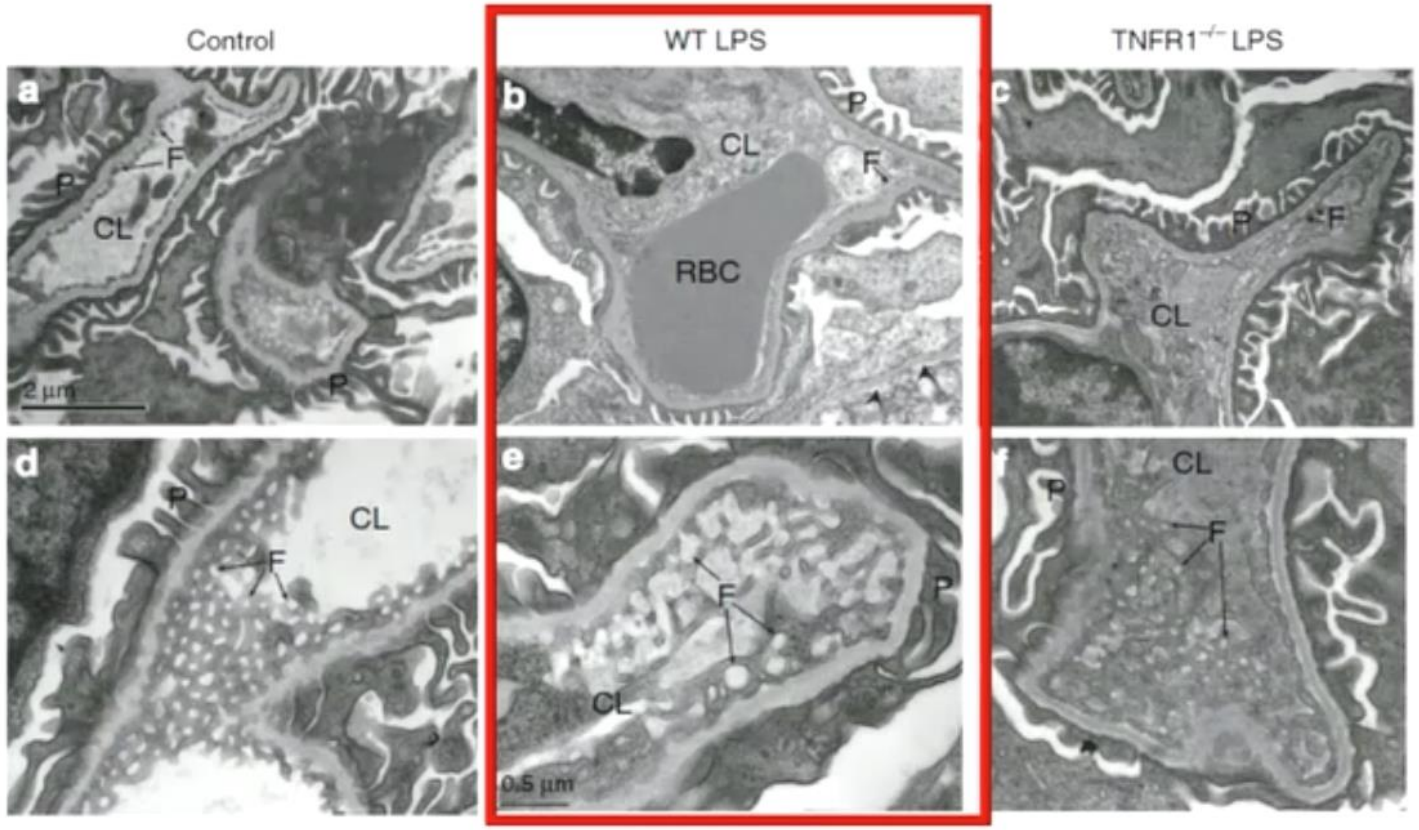


Glomerulus with extensive capillary leukocytic infiltration



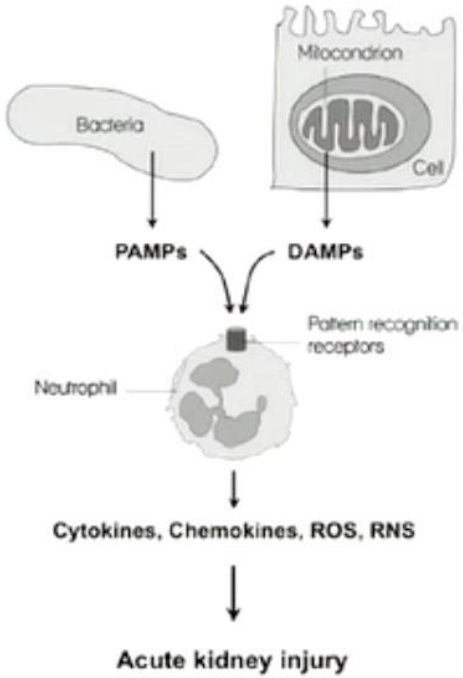
Lerolle N et al, Intensive Care Med. 2010 Mar;36(3):471-8.

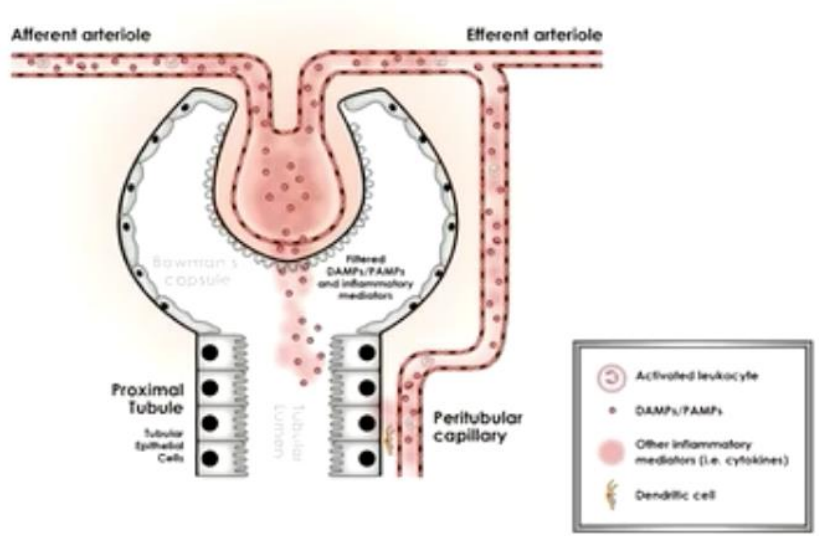
TNF-mediated damage to glomerular endothelium is an important determinant of acute kidney injury in sepsis



XU C et al, Kidney Int. 2013

A Unified Theory of Sepsis-Induced Acute Kidney Injury: Inflammation, microcirculatory dysfunction, bioenergetics and the tubular cell adaptation to injury

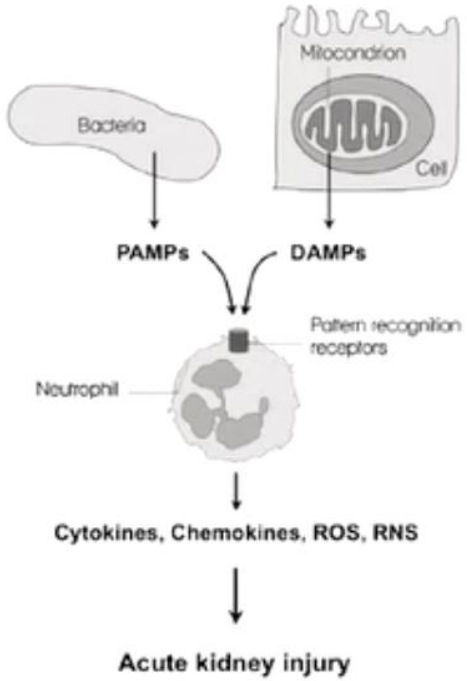


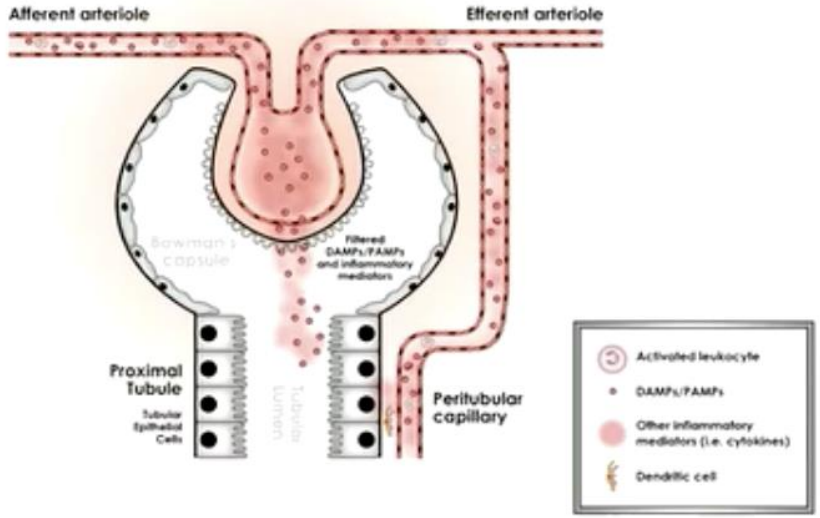


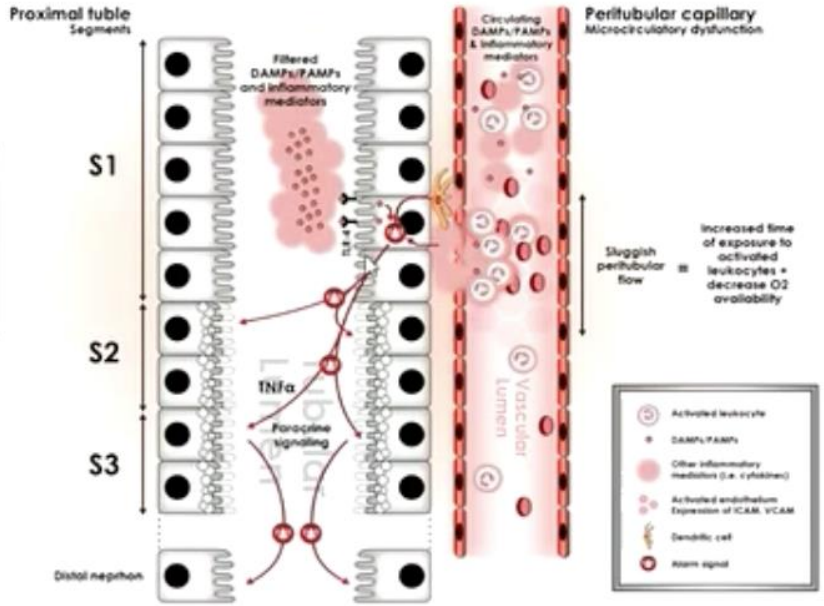
Martensson J et al,
Critical Care Clinics 2015 31, 649-660

Gomez H et al, Shock 2014 Jan; 41(1): 3–11.

A Unified Theory of Sepsis-Induced Acute Kidney Injury: Inflammation, microcirculatory dysfunction, bioenergetics and the tubular cell adaptation to injury







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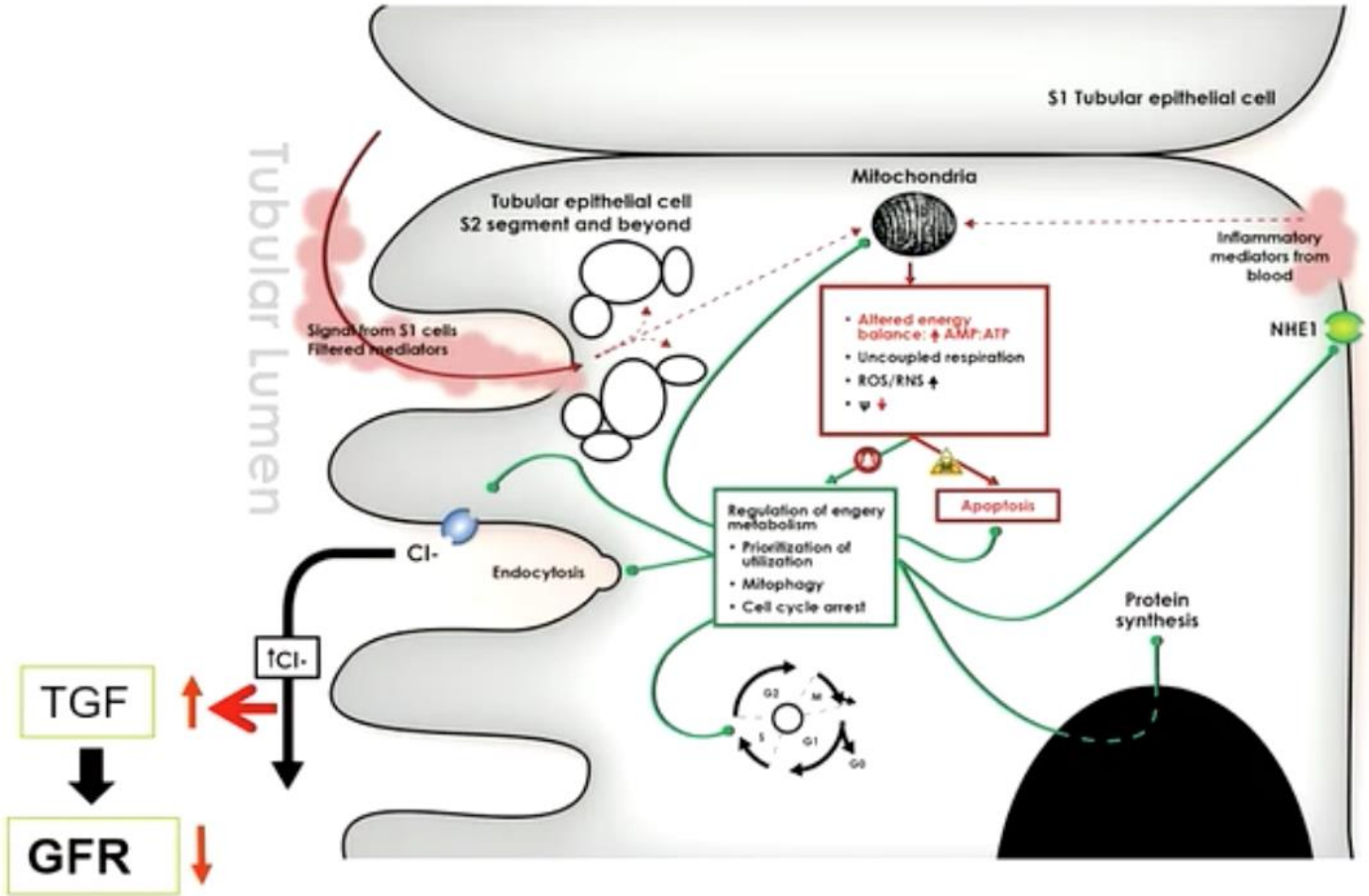

Gomez H et al, Shock 2014 Jan; 41(1): 3–11.

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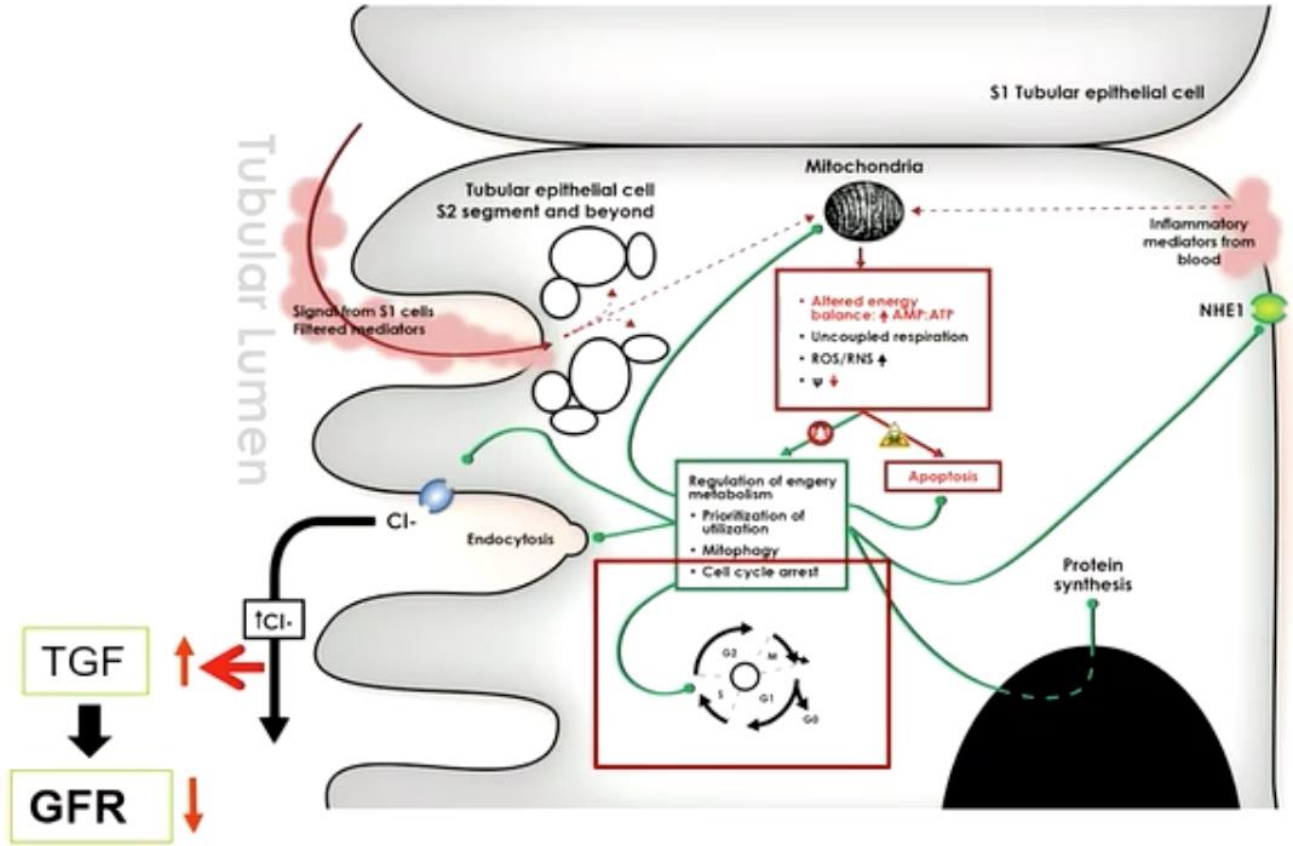
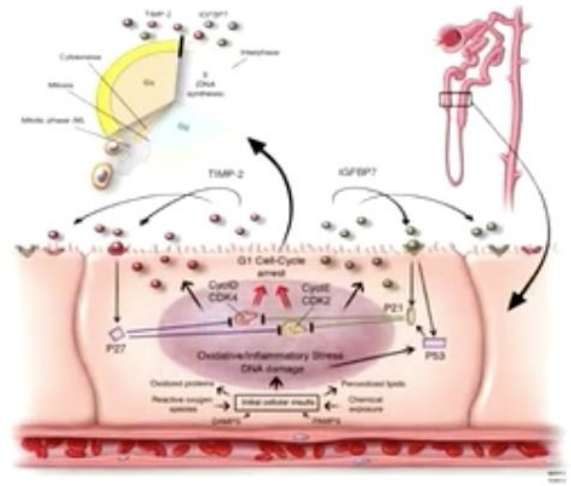


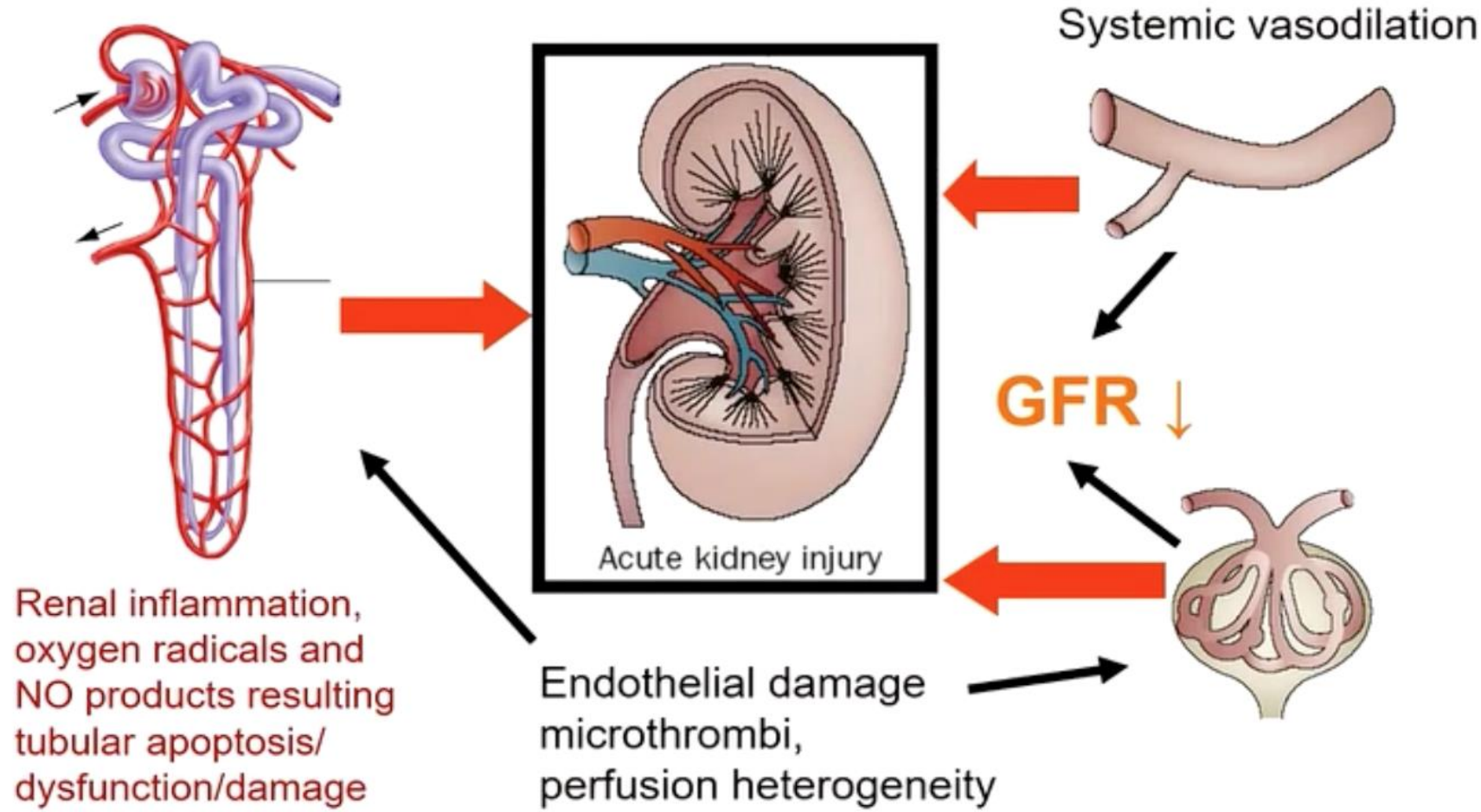
Gomez H et al, Shock 2014 Jan; 41(1): 3–11.

Cell cycle arrest proteins (TIMP-2, IGFBP7) as biomarkers for AKI



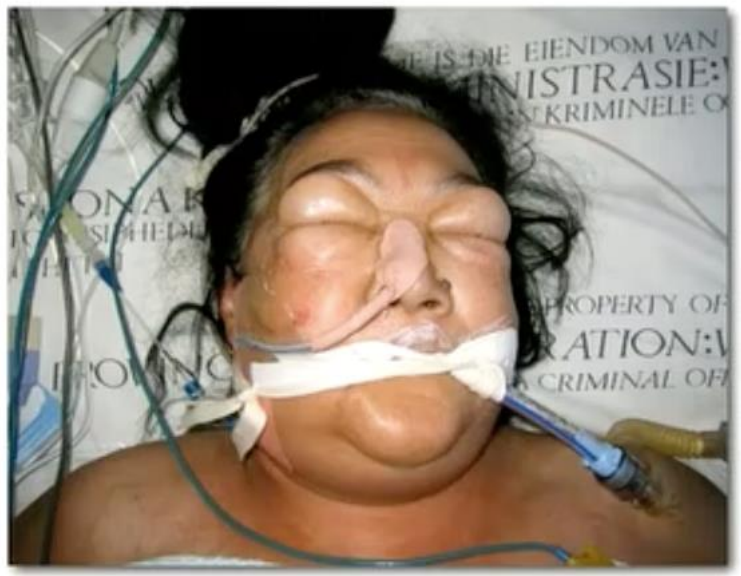
Kashani K et al, Crit Care 2013

Mechanism of septic AKI is complex and not completely understood



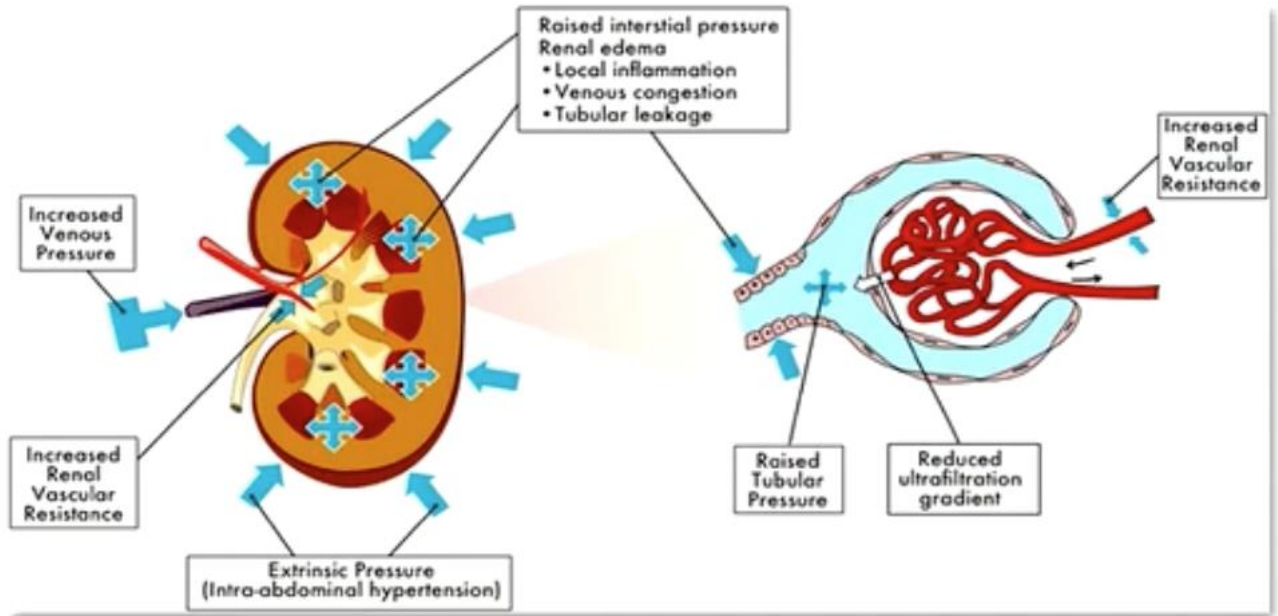
Fluid overload

Hospital acquired generalised interstitial edema



Lyons W. Crit Care Med 2000

Lyons W. J Trauma 2002



Perner A et al, *Intensive Care Med (2017) 43:807–815*

Peripheral Edema, Central Venous Pressure, and Risk of AKI in Critical Illness.

Incidence of AKI severity according to peripheral edema severity.

12,778 critically ill adult patients

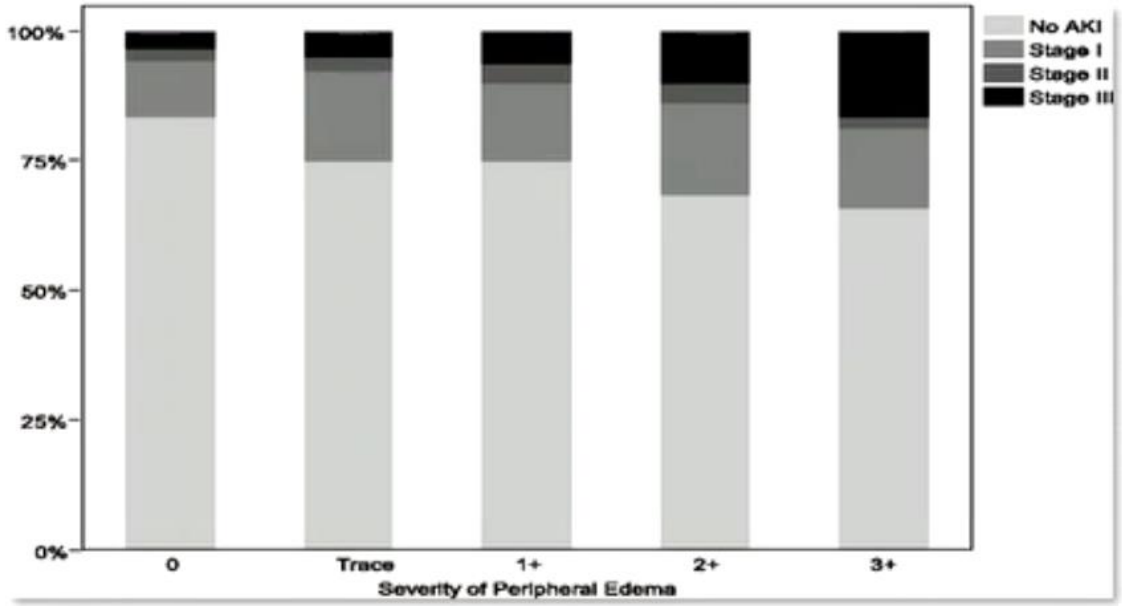
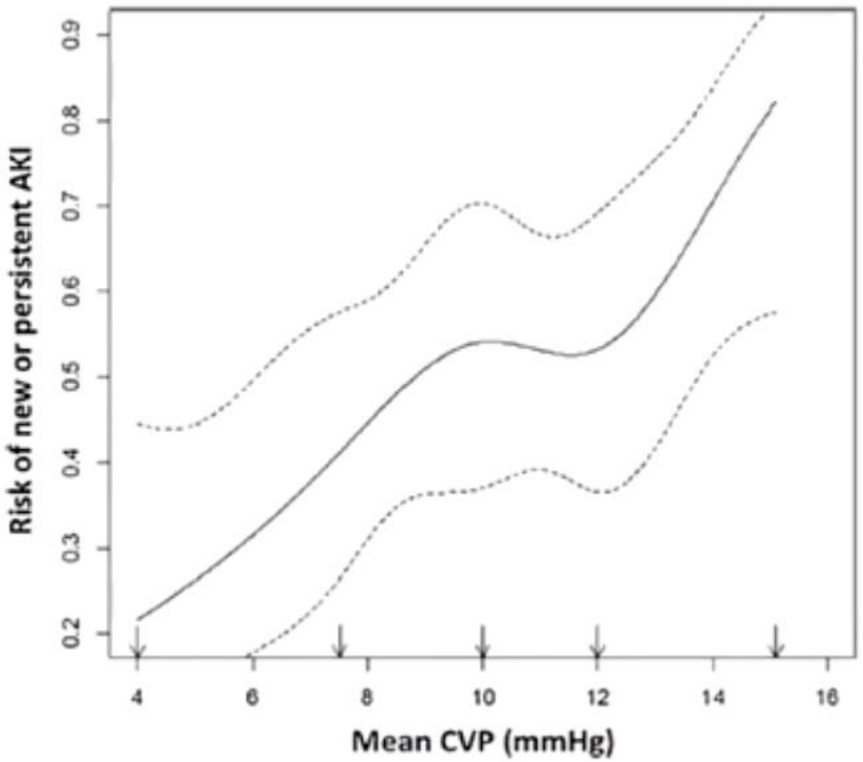


Table 4. Admission central venous pressure and subsequent risk of AKI

Risk	≤7 cm/H_2O	>7 to ≤10 cm/H_2O	>10 to ≤13 cm/H_2O	>13 cm/H_2O	Per 1 cm H_2O positive
N, % AKI	275 (21)	275 (22)	227 (23)	312 (26)	—
Odds ratio	Ref	1.06	1.08	1.18	1.02
95% CI		0.86 to 1.29	0.87 to 1.29	0.96 to 1.33	1.00 to 1.03
P value		0.57	0.46	0.09	0.02

Kenneth P. Chen et al. CJASN 2016;11:602-608

Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study

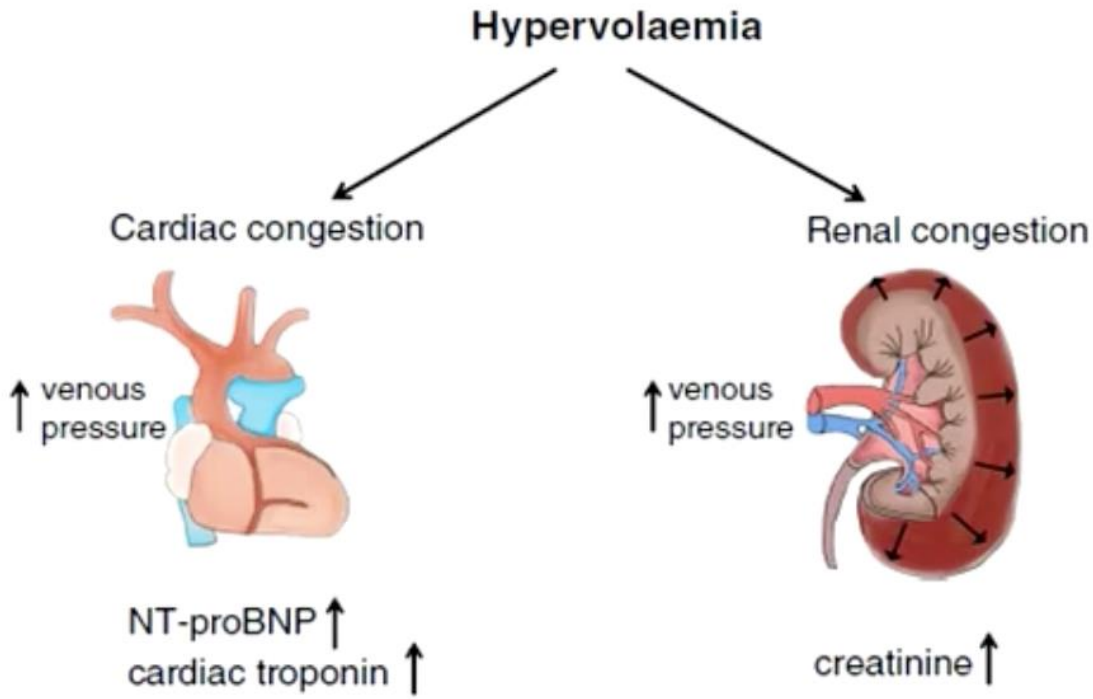


Statistical model of nonparametric logistic regression showing the relationship between mean central venous pressure during the first 24 hours after admission and the probability of new or persistent acute kidney injury.

Note the plateau for the incidence of acute kidney injury (AKI) when the lower limit of central venous pressure (CVP) was between 8 and 12 mmHg. Over this limit, the rise in CVP was associated with a sharp increase in new or persistent AKI incidence.

Legrand et al. Critical Care 2013, 17:R278

Cardiac biomarkers are associated with maximum stage of acute kidney injury in critically ill patients: a prospective analysis



Haines et al. Critical Care (2017) 21:88

Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population

Fluid Type	Volume			Sodium	Chloride
	%	Mean daily fluid volume in mL ± SD	Median daily fluid volume in mL (IQR)	Mean daily amount in mmol ± SD	Mean daily amount in mmol ± SD
Resuscitation fluids	6.5%	151 ± 439	0 (0-100)	21 ± 63	17 ± 49
Isotonic crystalloids (rate >1L/6h)	1.6%	36 ± 256	0 (0-0)	5 ± 36	4 ± 28
Colloids (mainly albumin and gelatins)	4.9%	114 ± 331	0 (0-98)	16 ± 48	13 ± 37
Blood products	3.2%	75 ± 318	0 (0-0)	11 ± 48	7 ± 29
Maintenance and replacement fluids	24.7%	574 ± 606	334 (150-894)	68 ± 78	79 ± 78
Glucose-containing crystalloids	22.3%	517 ± 506	296 (150-812)	59 ± 65	73 ± 70
Isotonic crystalloids (rate ≤1L/6h)	2.5%	57 ± 273	0 (0-0)	8 ± 39	6 ± 31
Nutrition	33.0%	766 ± 688	630 (0-1401)		
Enteral nutrition	19.0%	441 ± 593	0 (0-995)	20 ± 28	15 ± 21
Parenteral nutrition	7.8%	182 ± 492	0 (0-0)	0 ± 0[a]	0 ± 0[a]
Oral fluid intake	6.2%	143 ± 319	0 (0-150)	N/A	N/A
Fluid creep	32.6%	757 ± 608	645 (308-1039)		
Volume due to concentrated electrolytes	2.4%	56 ± 62	42 (22-72)	9 ± 50	10 ± 33
Volume used to keep venous access open	0.8%	20 ± 43	0 (0-28)	3 ± 7	3 ± 8
Intermittent and continuous medication	29.3%	681 ± 580	565 (251-946)	N/A	N/A
Total amount	100%	2,322 ± 1,315	2,296 (1,422-3,069)	131 ± 137	130 ± 111

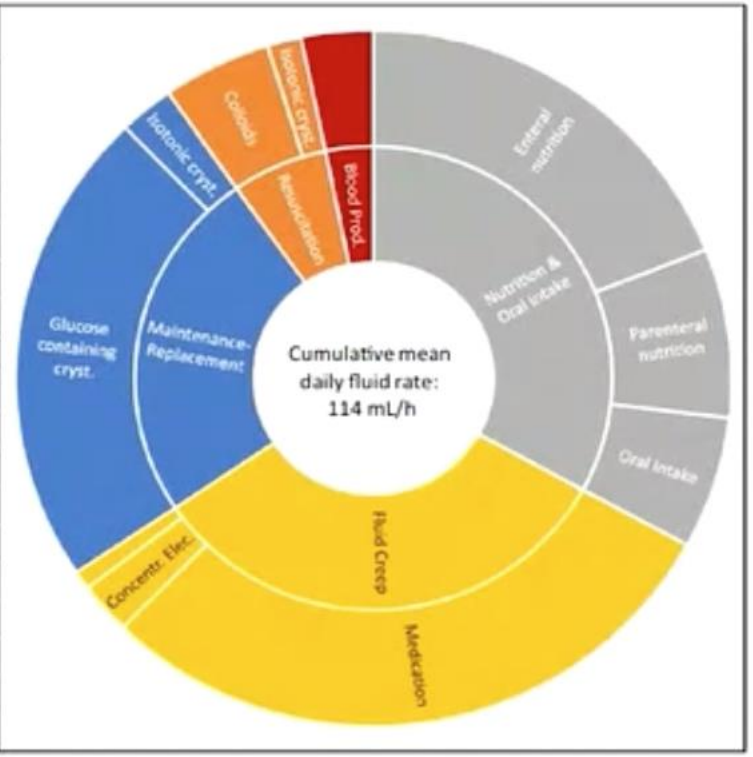


Fig. 1 Proportion, mean, and median fluid volumes, and mean sodium and chloride burdens of the different fluid types (average of 14,654 patients on their cumulative 103,098 days of ICU stay), including a graphic representation of the distribution of the different mean daily fluid volumes. Mean duration of one ICU day, 20.3 ± 6.7 h. SD standard deviation, IQR interquartile range, N/A data not available. [a]To ensure optimal electrolyte management in our ICU, only electrolyte-free formulas of parenteral nutrition are prescribed, with separate administration of electrolytes

Van Regenmortel N et al , *Intensive Care Med (2018) 44:409–417*

Restrictive fluid management versus usual care in acute kidney injury (REVERSE-AKI): a pilot randomized controlled feasibility trial

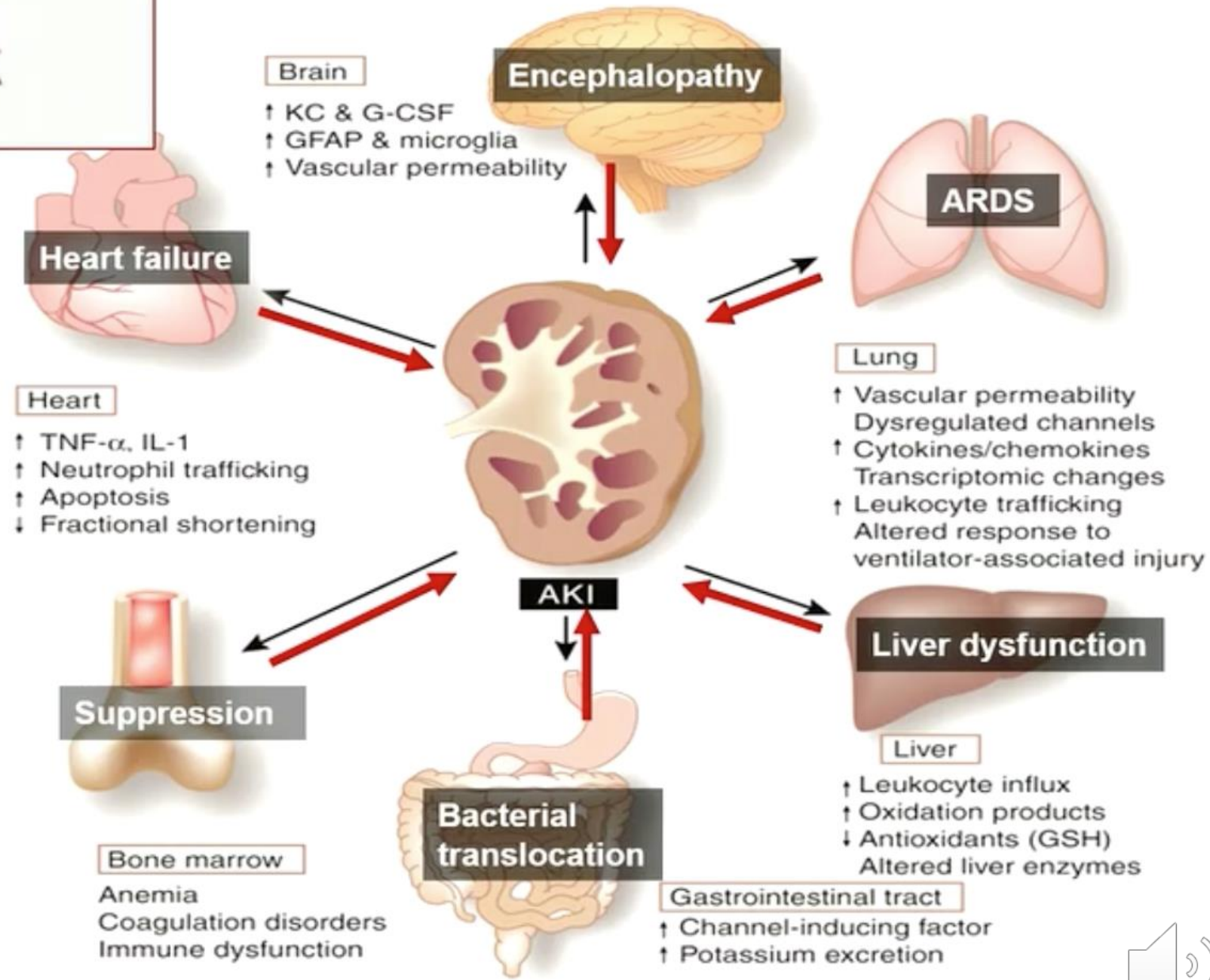
Table 2 Primary and secondary outcomes (adjusted for stratification variables)

Outcome	Restrictive fluid management ($n=49$)	Usual care ($n=51$)	Restrictive fluid management vs usual care (95% CI)[a]	*P* value[b]
Cumulative fluid balance at 72 h from randomization, mean (SD) mL[c]	−1080 (2003)	61 (3131)	−1148 (−2200; −97)	0.033
Duration of AKI (days), median [IQR][d]	2 [1–3]	3 [2–7]	−1 (−3; 0)	0.071
Number of patients-receiving RRT, n (%)[e]	6/46 (13)	15/50 (30)	0.42 (0.16; 0.91)	0.043
Cumulative fluid balance at 24 h from randomization, mean (SD) mL[c]	−416 (1194)	409 (1566)	−822 (−1381; −264)	0.004
Cumulative fluid balance at ICU discharge/day 7, mean (SD) mL[c]	−2166 (2988)	−650 (4469)	−1532 (−3036; −29)	0.046
Cumulative dose of furosemide per day, median [IQR] mg[f]	0 (0–19)	1.4 (0–26.2)	0 (−11; 5.7)	0.700

AKI acute kidney injury, *RRT* renal replacement therapy

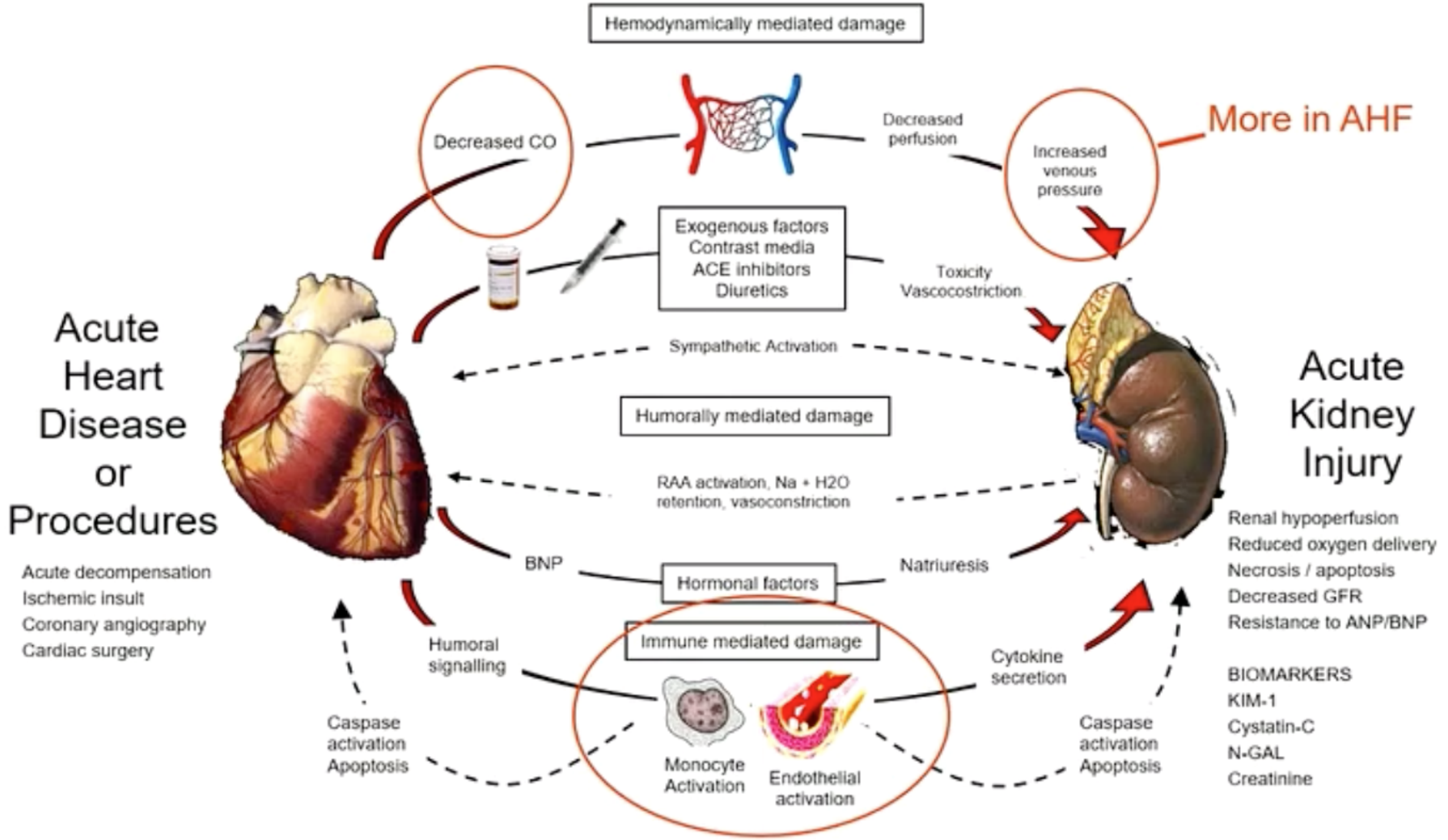
Vaara S et al , *Intensive Care Med (2021) epub*

Organ cross-talk



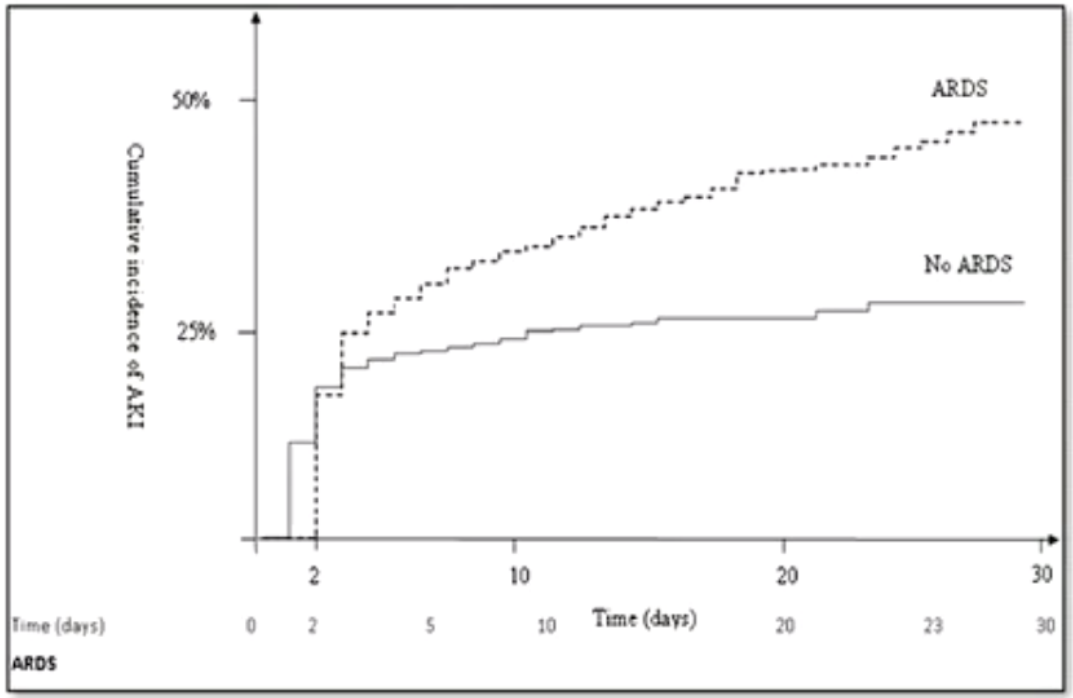
Scheel PJ et al, Kidney Int 2008

Pathophysiology of CRS Type 1



Acute Respiratory Distress Syndrome and Risk of AKI among Critically Ill Patients

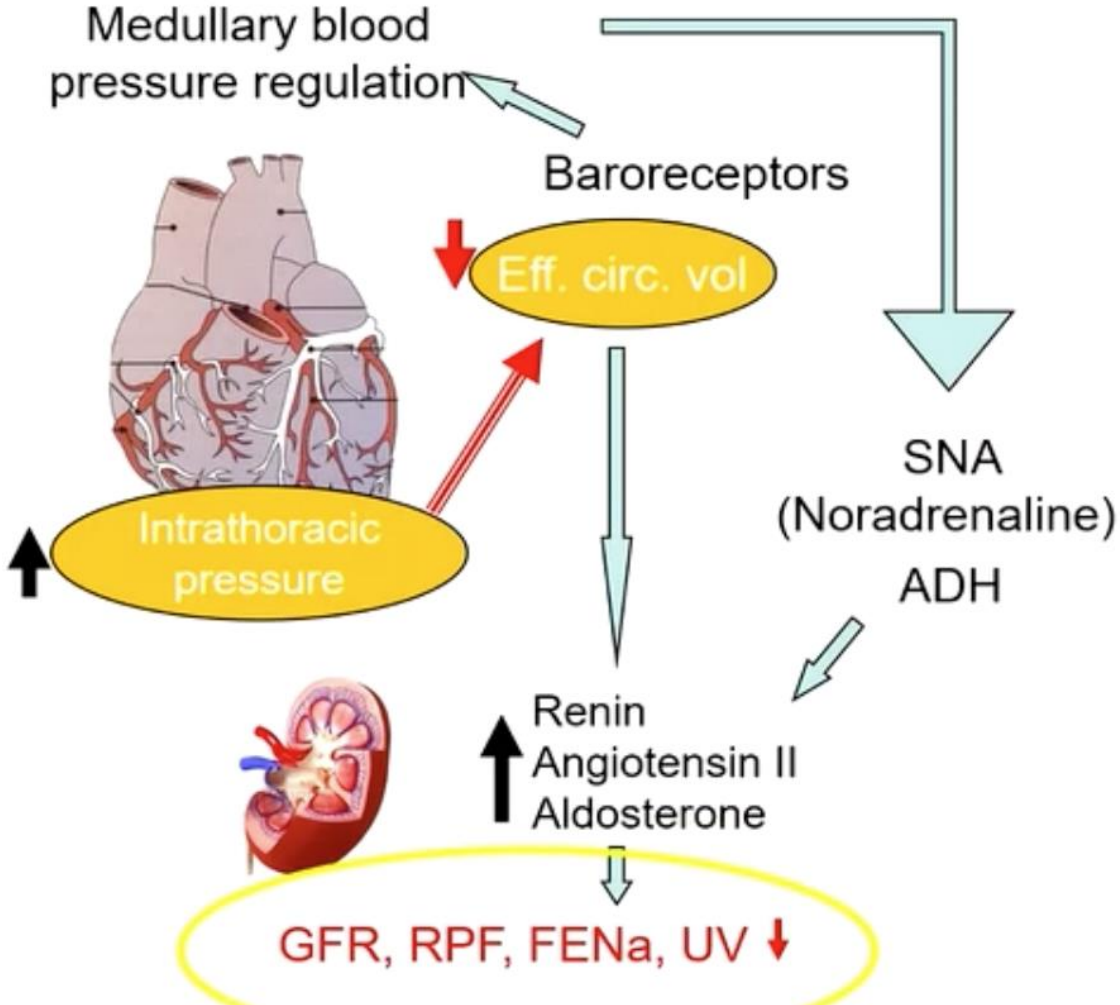
Cumulative risk of AKI in patients with and without ARDS



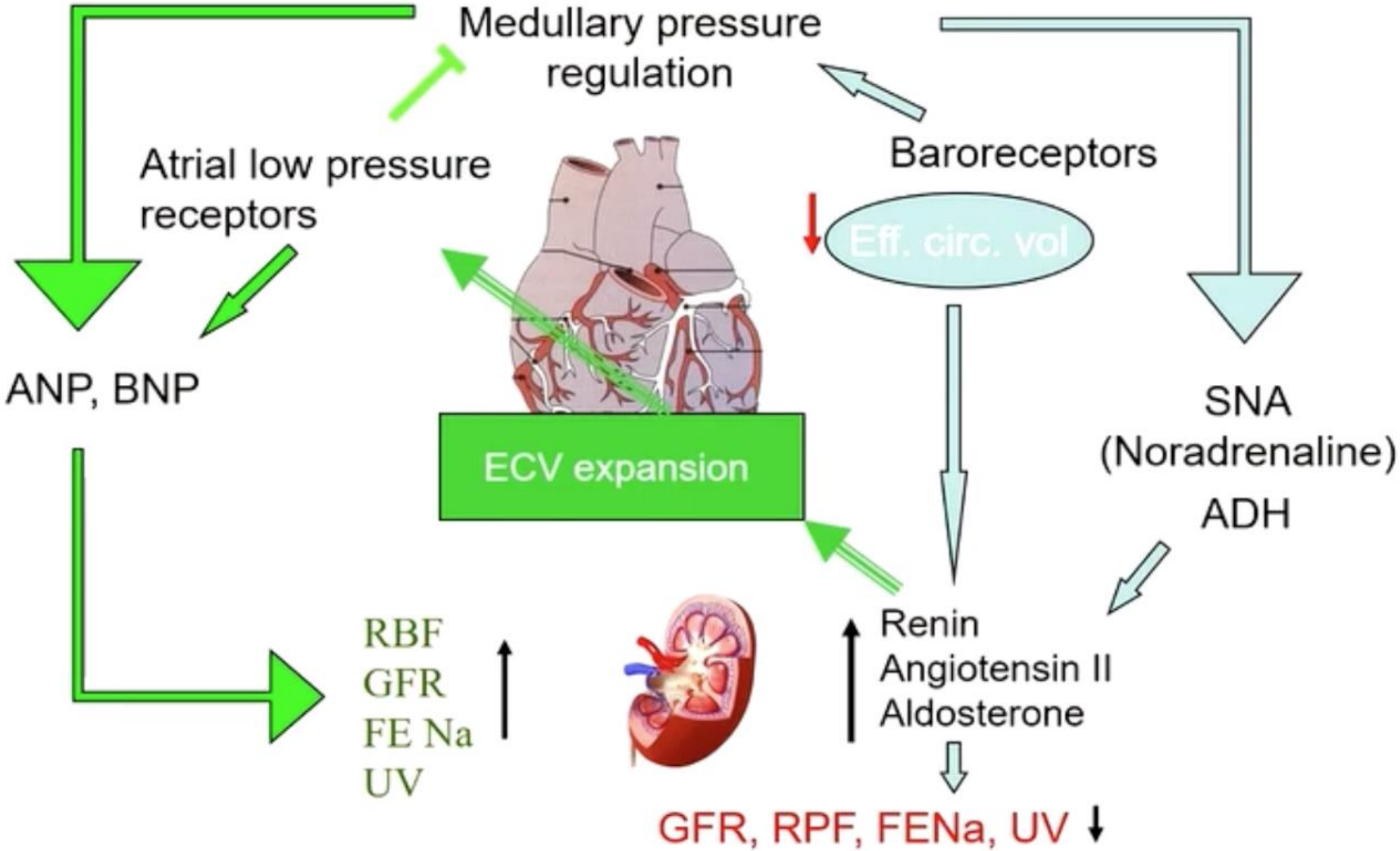
Patients with ARDS, who developed AKI had a higher hospital mortality rate than those without AKI (42.3% versus 20.2%; P<0.001)

Darmon M. et al. ***CJASN 2014; 9: 1347-53***

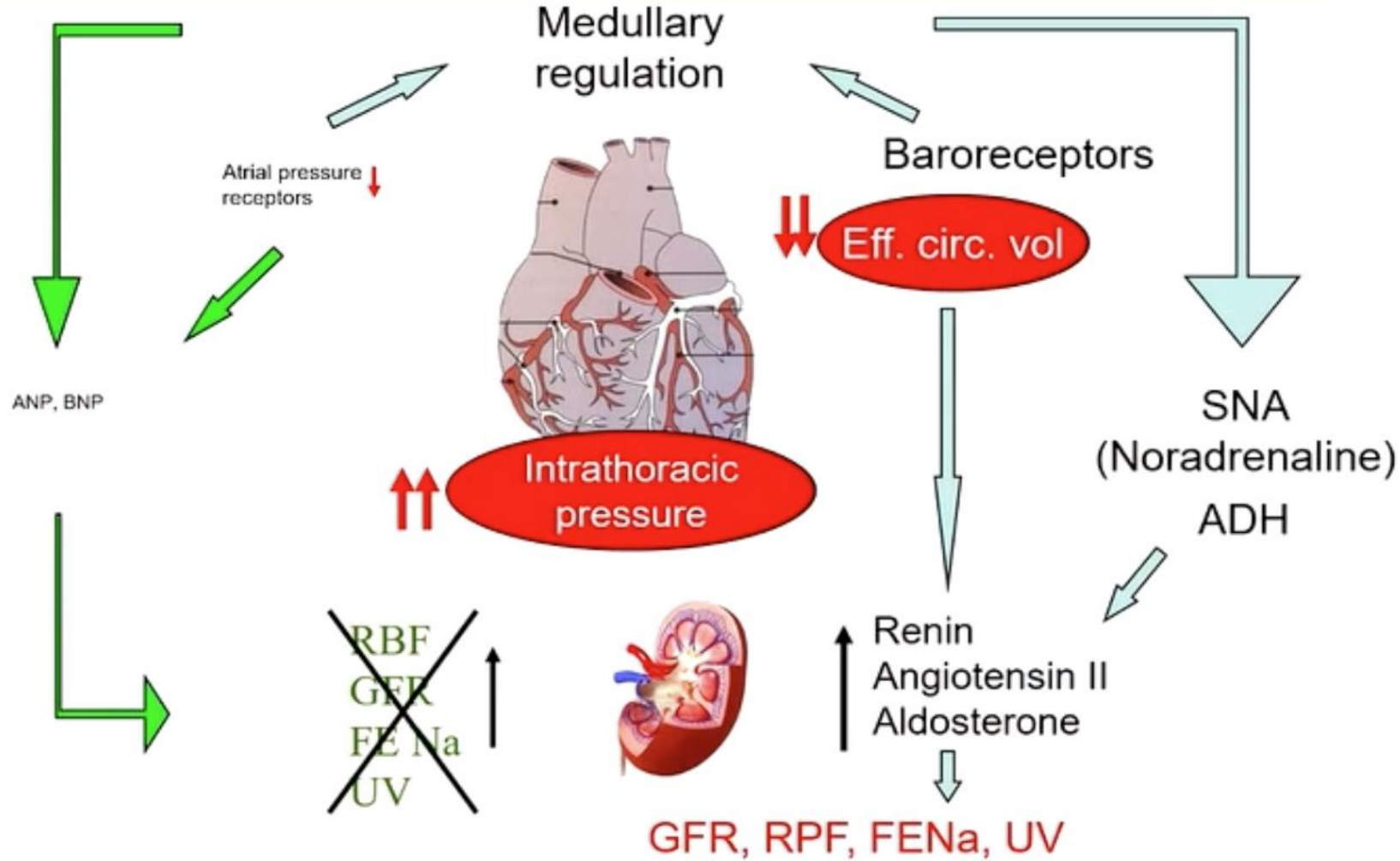
Effects of mechanical ventilation on renal function



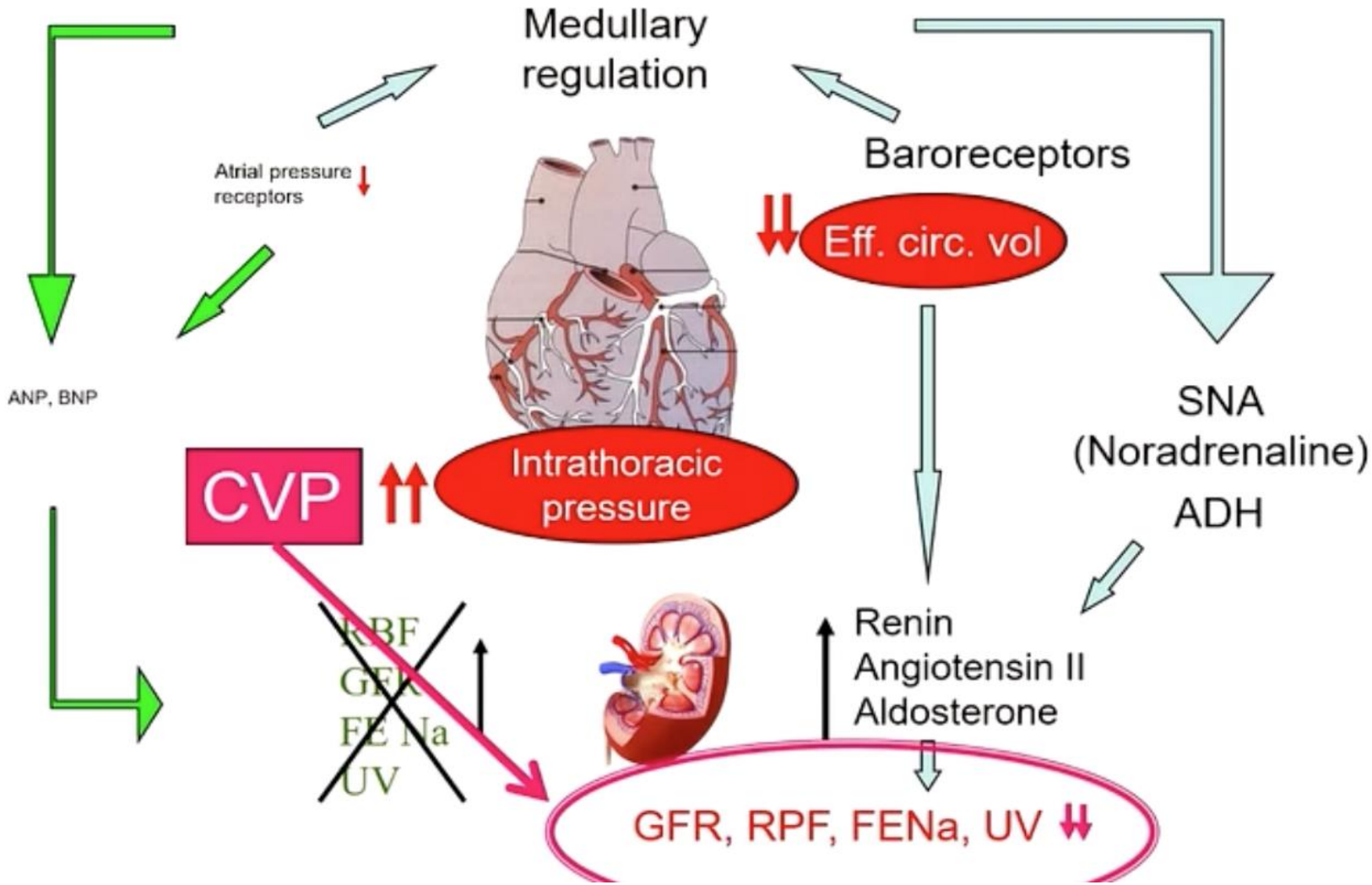
Effects of mechanical ventilation on renal function



Effects of mechanical ventilation on renal function (high airway pressures)

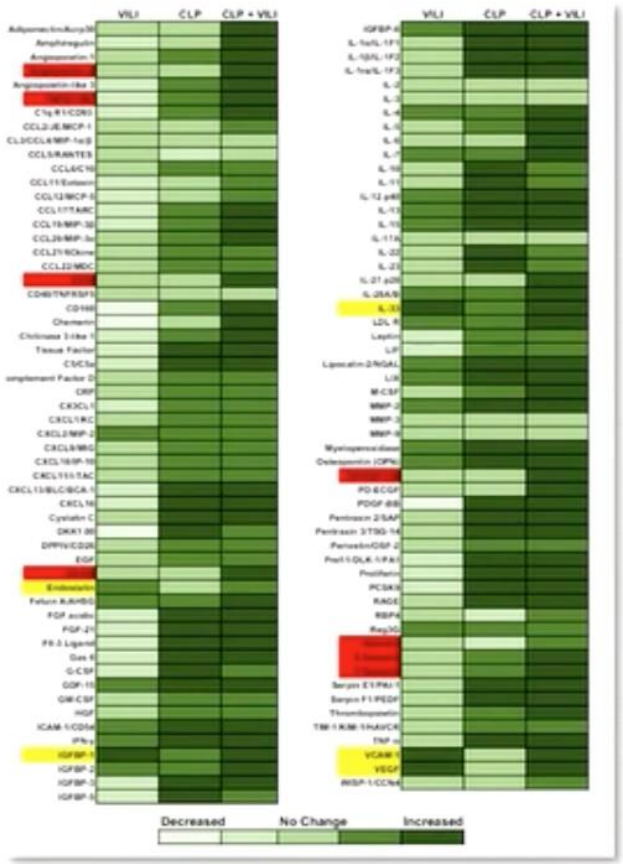


Effects of mechanical ventilation on renal function (high airway pressures)



Ventilator-induced lung injury increases expression of endothelial inflammatory mediators in the kidney

Proteome array analysis of inflammatory mediator levels in different injury models (mice)



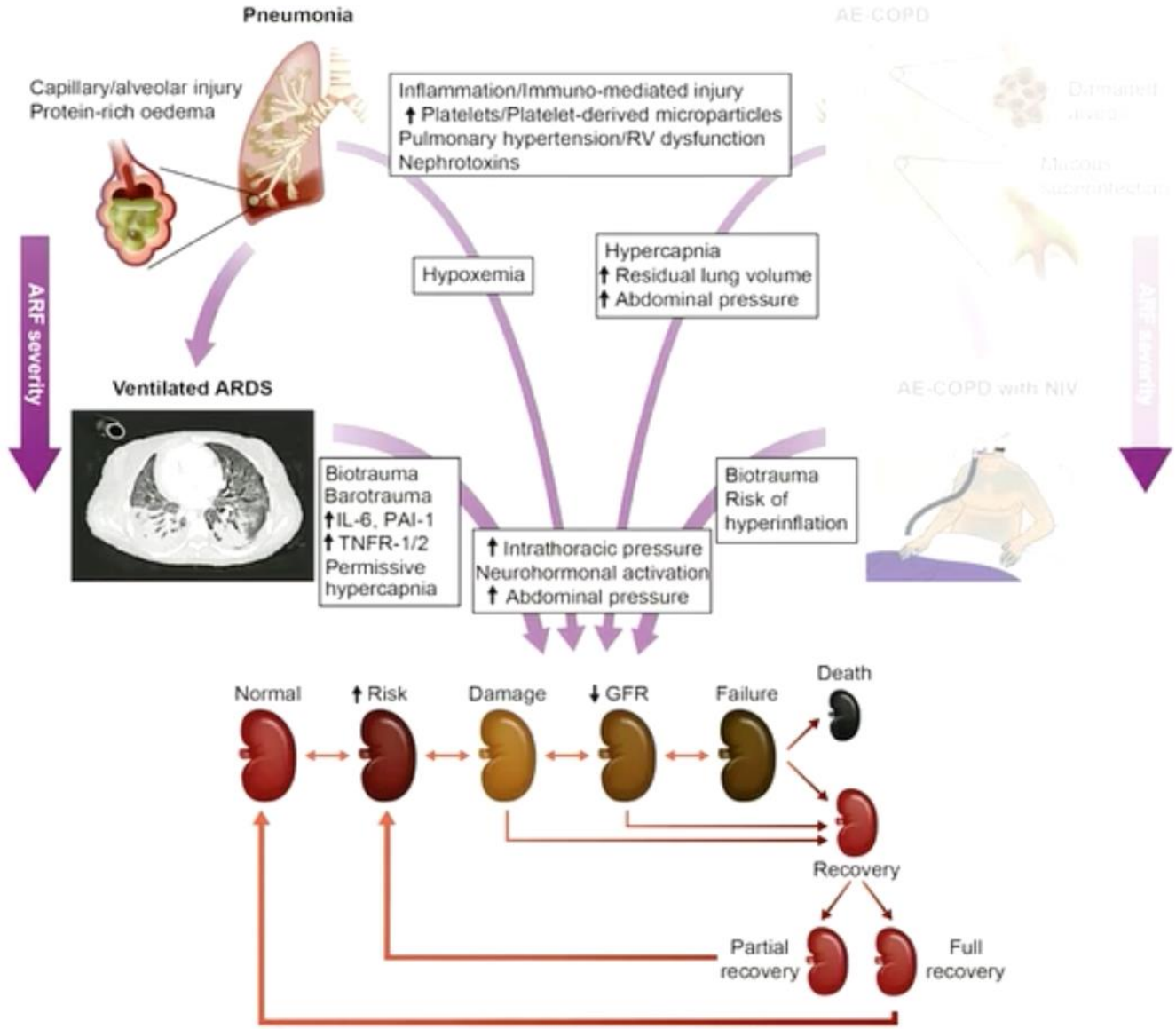
- sham
- ventilator induced lung injury (VILI)
- cecal ligation and puncture (CLP)
- CLP+VILI (*n* = 4 for each group)

2x upregulated proteins:
Resistin
E-Selectin
P-Selectin
Angiopoetin 2
TNFRSF11B
TNFRSF13B
CD14
CD105

Increased proteins:
IGFBP1
VCAM-1
VGEF
IL-33
CLCX2/MIP-2

Hepokoski M et al, Am J Physiol Renal Physiol. 2017 Apr 1; 312(4): F654–F660.

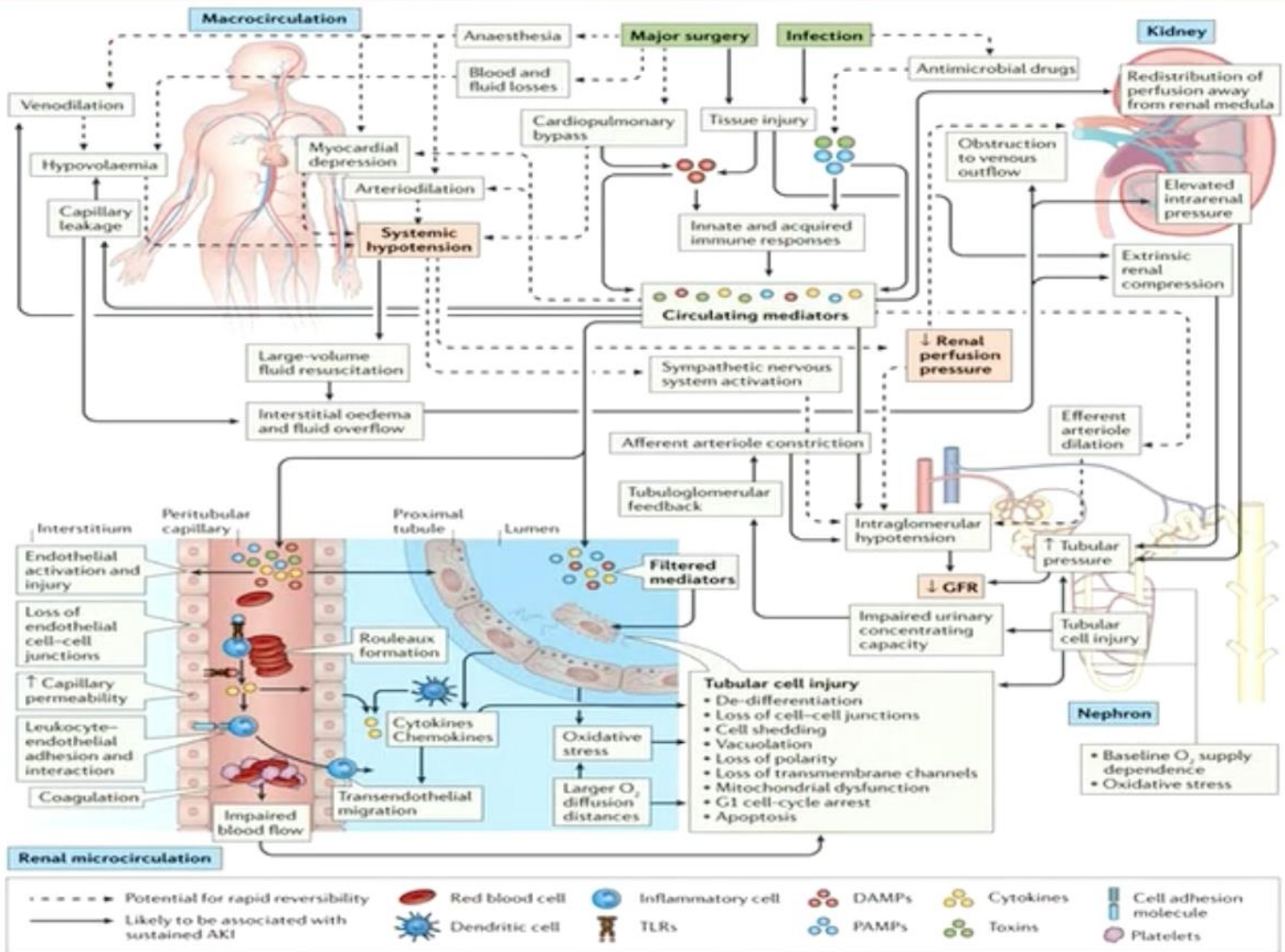
Possible effects of acute respiratory failure and invasive/non-invasive ventilation on renal function



ADQI 21, Lung-Kidney Interactions

Joannidis M et al. Intensive Care Medicine 20[illegible]

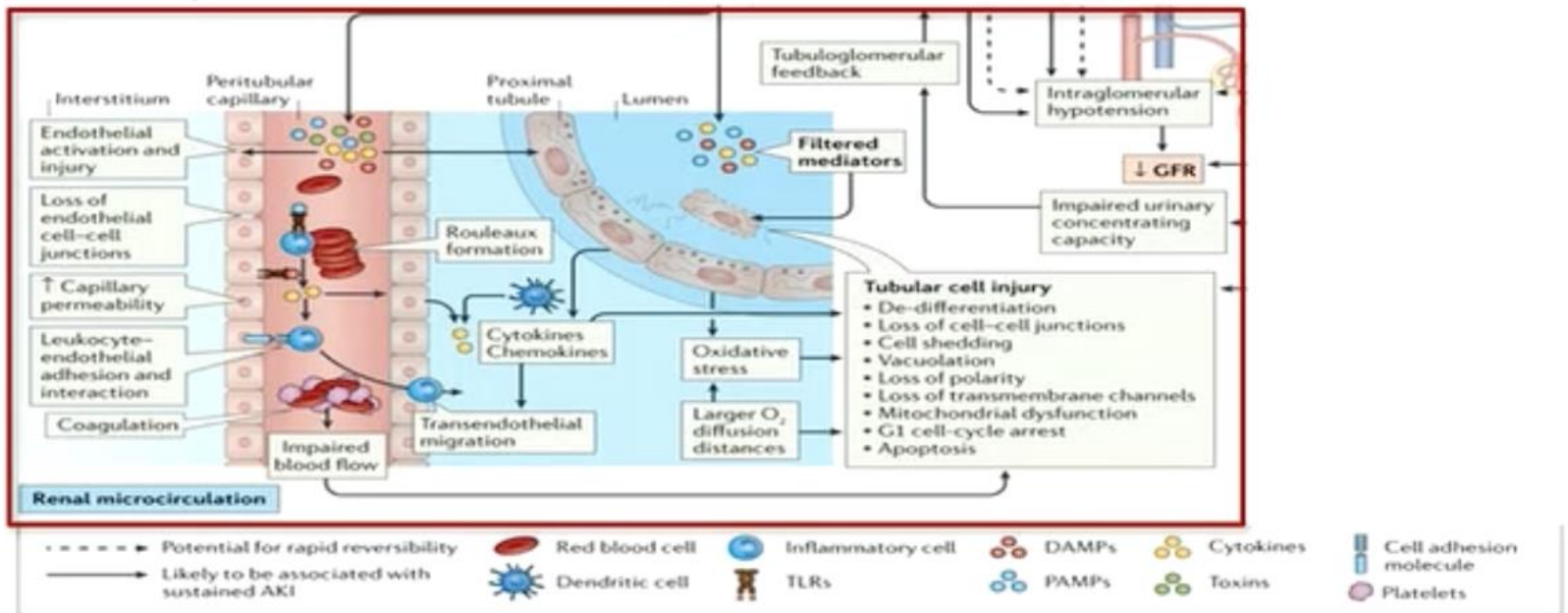
Pathophysiology of AKI



Kellum J & Prowle J Nature Reviews Nephrol 2018

Pathophysiology of AKI

- Tubular cell damage (hypoxia, toxins, DAMP/PAMPS, O_2 radicals)
- Tubulo-interstitial inflammation
- Impaired microcirculation

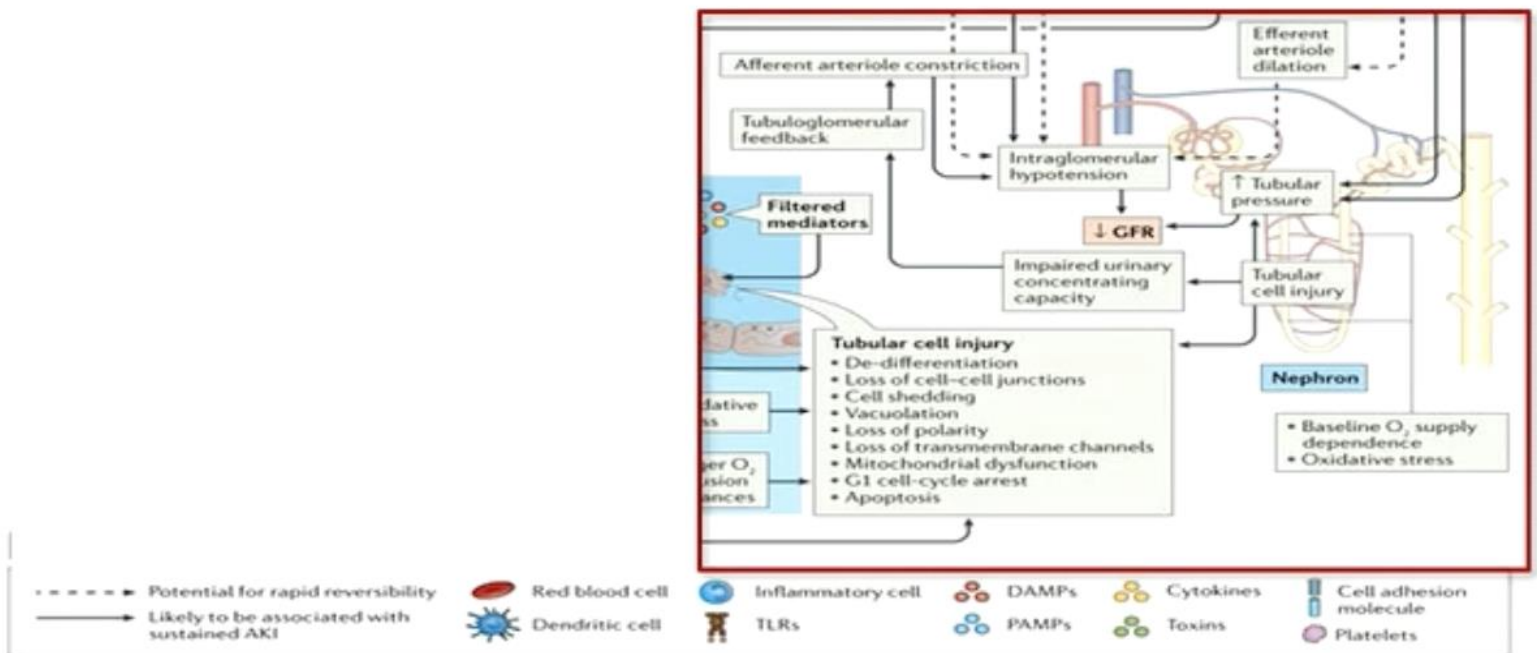


Kellum J & Prowle J Nature Reviews Nephrol 2018

Pathophysiology of AKI

Reduced GFR due to:

- Intraglomerular hypotension
- Increased tubular pressure
- Intrarenal edema
- Tubuloglomerular feedback (TGF)



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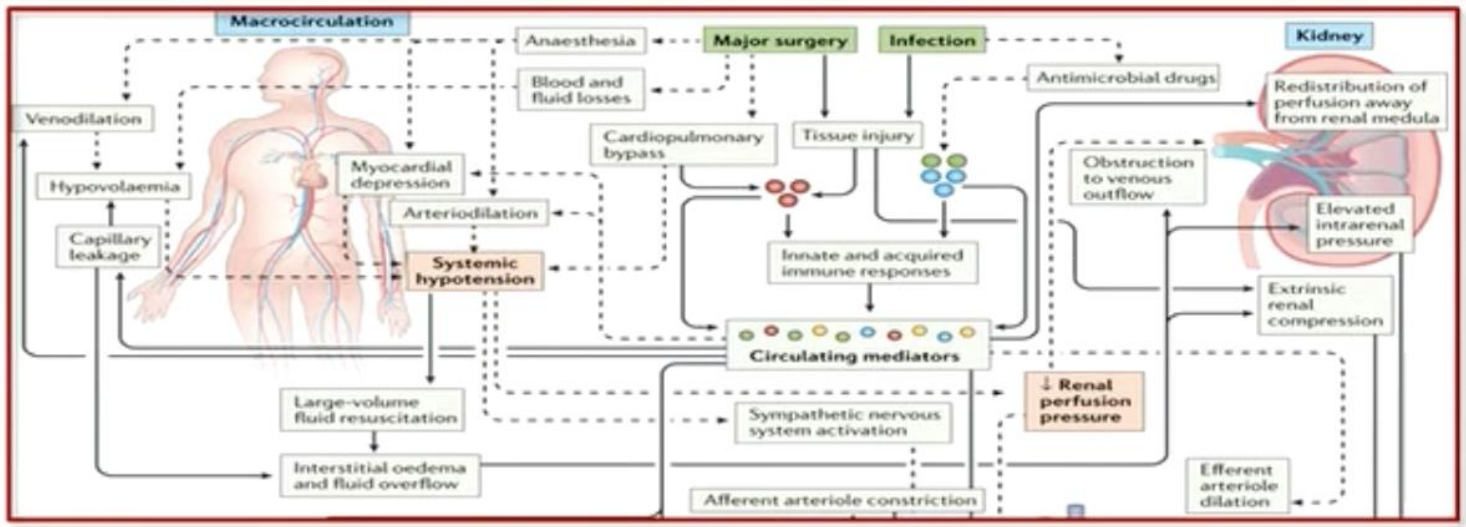
Pathophysiology of AKI

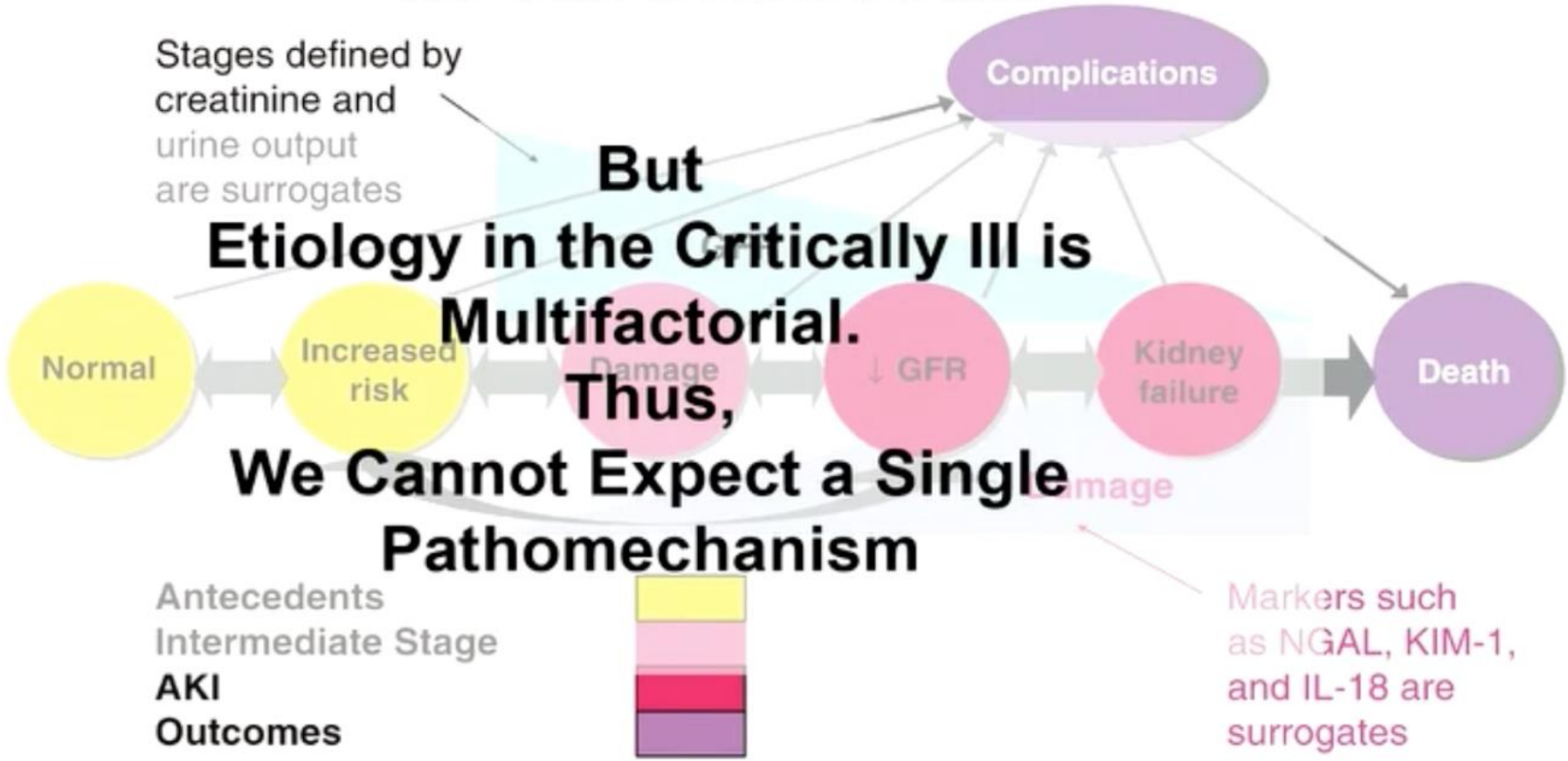


Reduced kidney perfusion (shock, cardiac failure)
and/or
Reduced perfusion of renal medulla

Kellum J & Prowle J Nature Reviews Nephrol 2018

AKI : A Broad Clinical Syndrome

We Can Define AKI…



But Etiology in the Critically Ill is Multifactorial. Thus, We Cannot Expect a Single Pathomechanism


Thank You