Pathogenesis of Acute Kidney Injury

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From the pathogenesis point of view

Definition

Epidemiology

Causes

Post- renal

Pre- renal

Intrinsic renal failure

RBF regulation

molecular level response

Cellular response

mitochondrial response

Repair

Biomarkers

AKI in special conditions

AKI and extra-renal organ dysfunction

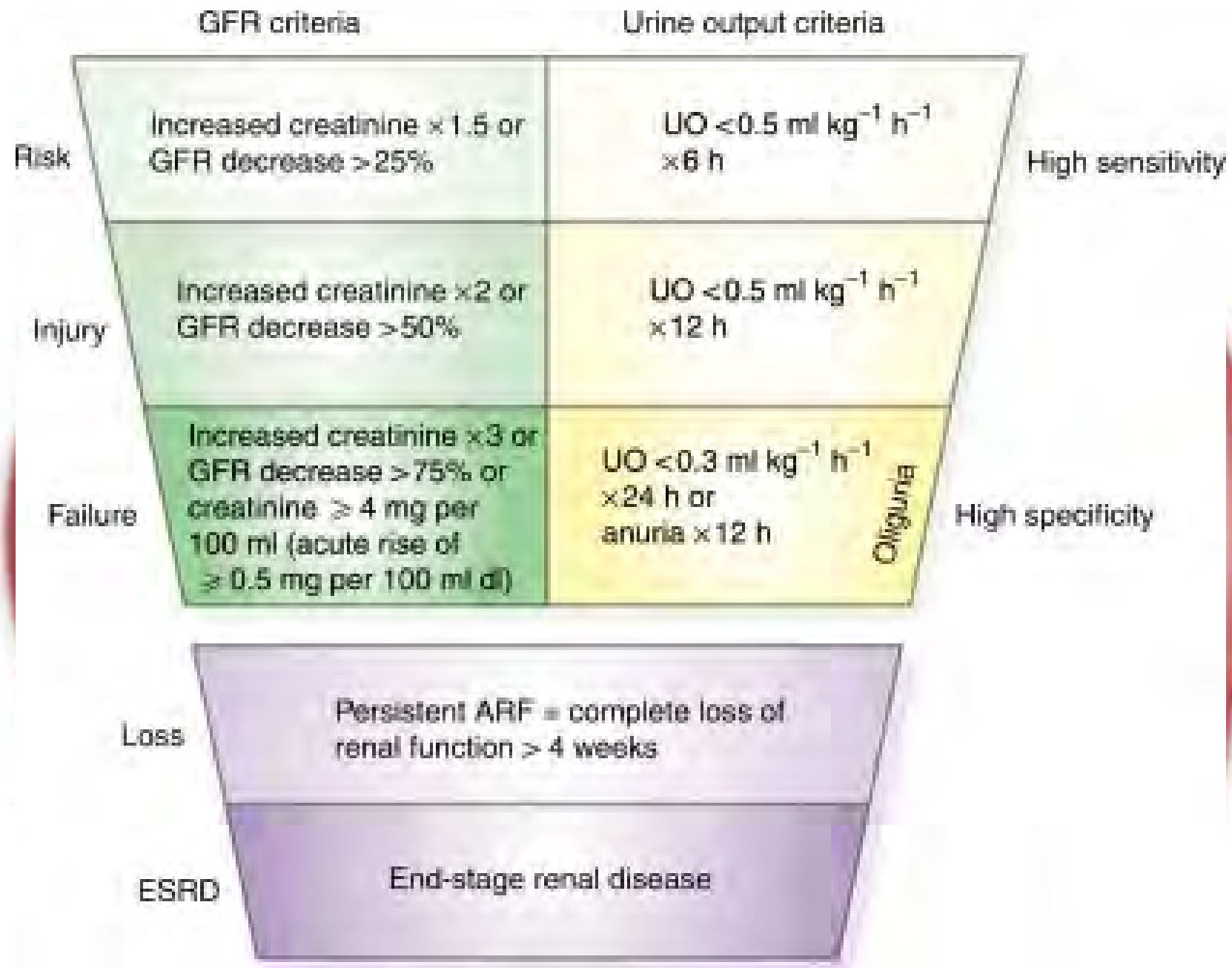
The Problematic Definition of AKI

- Over **30** published AKI definitions
- All based on increased serum creatinine levels
- Pediatric AKI definition: a moving target
- Infants Cr in the first few weeks of life may reflect maternal values
- Children Low baseline Cr makes 0.2-0.3 changes in Cr significant
- Varying muscle mass
- Changes in SCr may lag changes in GFR and may be a very late indicator of renal injury

Definition

- Sudden interruption of kidney function results in retention of toxins, fluids, and end products of metabolism, Usually **reversible** with medical treatment, May progress to **ESRD**, uremic syndrome, and **death** without treatment

Earlier diagnosis of AKI represents an important area in treating patients with AKI


GFR criteria
Urine output criteria
Risk
Increased creatinine ×1.5 or GFR decrease >25%
UO <0.5 ml kg⁻¹ h⁻¹ ×6 h
High sensitivity
Injury
Increased creatinine ×2 or GFR decrease >50%
UO <0.5 ml kg⁻¹ h⁻¹ ×12 h
Failure
Increased creatinine ×3 or GFR decrease >75% or creatinine ≥ 4 mg per 100 ml (acute rise of ≥ 0.5 mg per 100 ml dl)
UO <0.3 ml kg⁻¹ h⁻¹ ×24 h or anuria ×12 h
Oliguria
High specificity
Loss
Persistent ARF = complete loss of renal function > 4 weeks
ESRD
End-stage renal disease

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Epidemiology

The largest epidemiological study of pediatric AKI 2 644 263 hospital admissions (encompassing both general and critical care populations) in hospitals throughout the USA, and reported an AKI incidence of **3.9 cases per 1000 admissions.**

(Proulx et al: Crit Care Med 22:1025, 1994)

Renal Function at Hospital Discharge

(**66**%) survivors completely **recovered**

(**29**%) had improved renal function or **chronic renal insufficiency**

(**5**%) required **RRT**

Stickle SH et al: Am J Kid Dis 45:96-101, 2005

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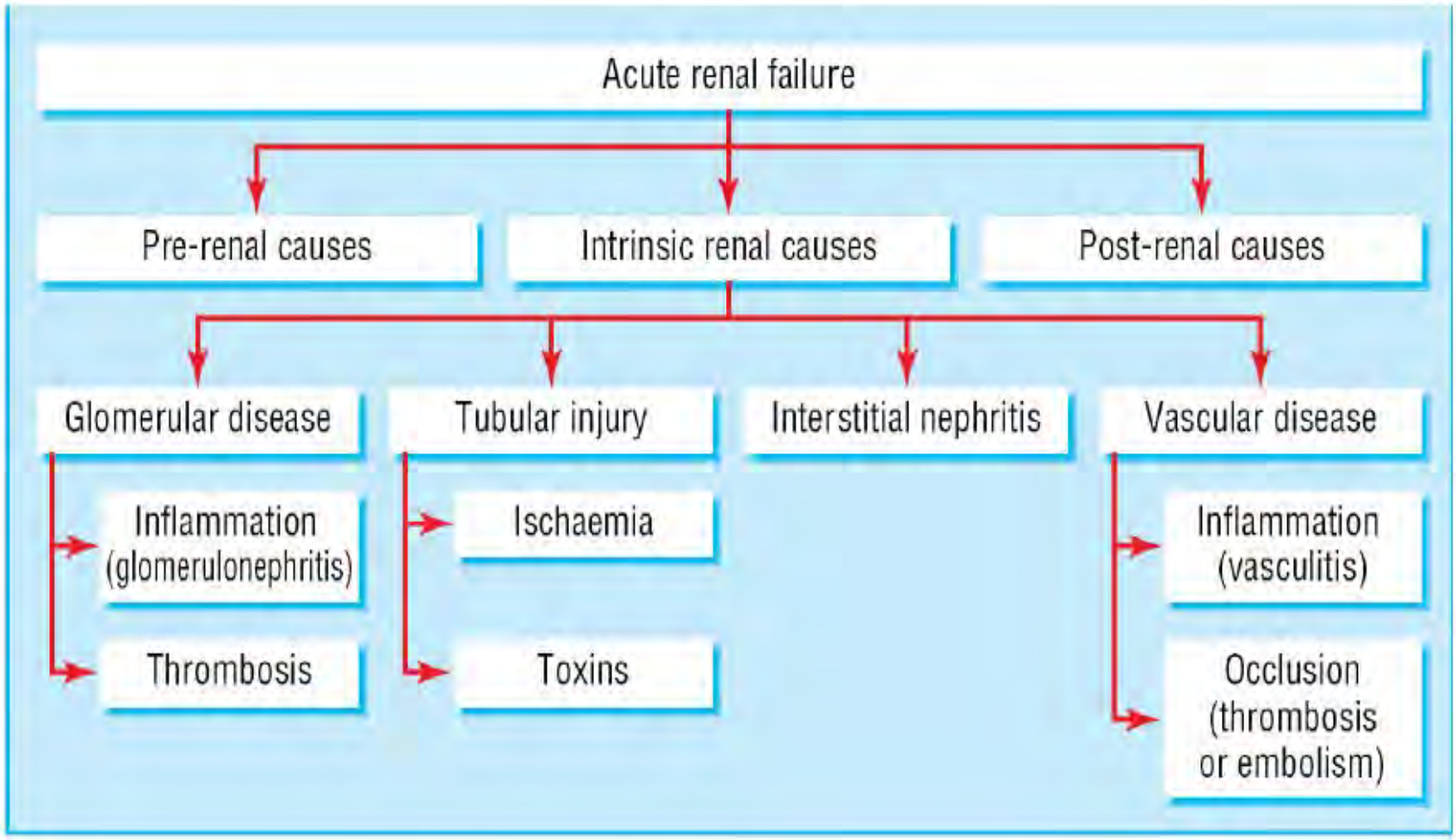
CAUSES of AKI



Hilton: BMJ 2006; 333: 786-790

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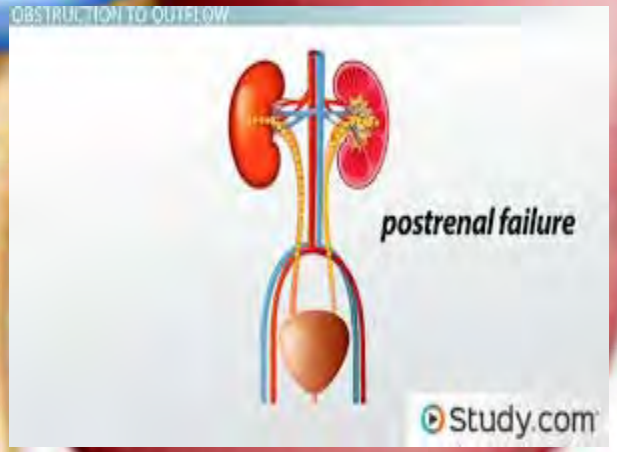

AKI in special conditions

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Post-renal AKI

Characterized by **acute obstruction** to urinary flow.

Increases intra-tubular pressure and thus decreases GFR

In addition, it can lead to **impaired renal blood flow and inflammatory** processes that also contribute to diminished GFR

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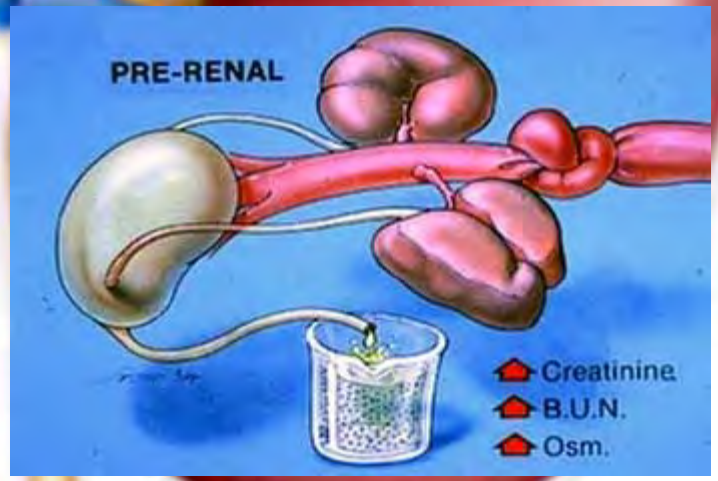

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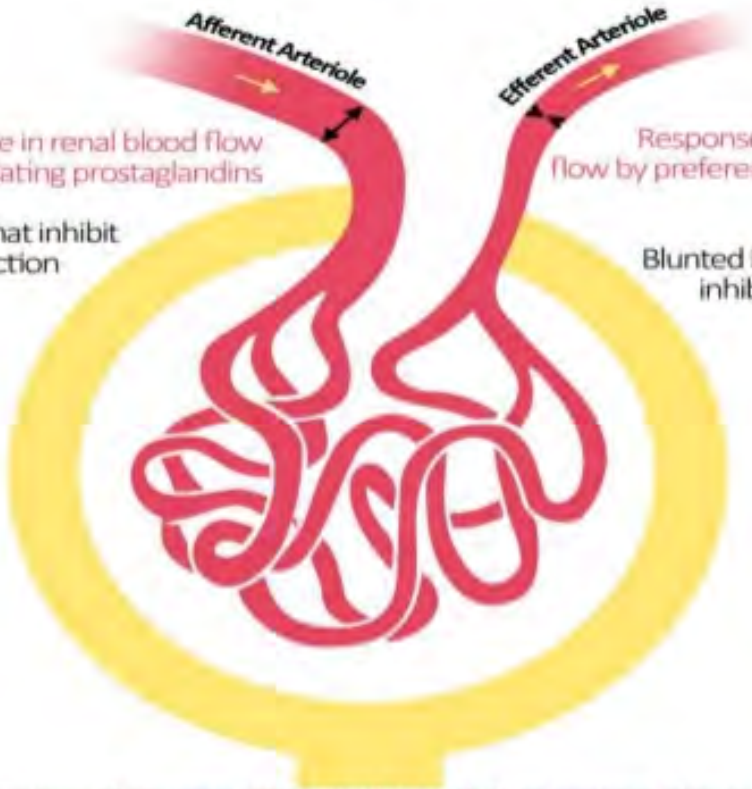
Prerenal azotemia

25% of the cardiac output , a **decrease in GFR** due to a **decrease in renal perfusion pressure without** damage to the renal parenchyma

The normal response of the kidney to prerenal conditions is to **concentrate** the urine maximally and **avidly reabsorb sodium** in an effort **to maintain/increase intravascular volume and normalize renal perfusion**

It is important to appreciate that **prolonged** or **profound** prerenal azotemia can result in **ischemic** damage to the kidney and thus there is spectrum from prerenal azotemia to ischemic AKI.

Pathophysiology of Prerenal AKI



Response to decrease in renal blood flow by increase in vasodilating prostaglandins

Blunted by NSAIDS that inhibit prostaglandin production

Response to decrease in renal blood flow by preferential constriction of efferent arteriole by Angiotensin II

Blunted by ACE Inhibitors/ARBs that inhibit Angiotensin II production

Both mechanisms of compensation work together to increase glomerular blood flow and maintain intraglomerular hydrostatic pressure required for proper filtration

Both mechanisms may be overcome by severe hypovolemia

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Pathophysiology

- **Functional** alterations lead to injury

  Failure of autoregulation

- **Injury** precedes functional change

  Direct Nephrotoxicity 30%

  Ischemia Reperfusion 60%

  Inflammation, AKI Related Sepsis

- **Injury** and **functional** change are **concurrent**

  Complete vascular occlusion

- **Extension** phase represents an area potential of treatment with the greatest possible impact

Maintaining a normal GFR is dependent on adequate renal perfusion

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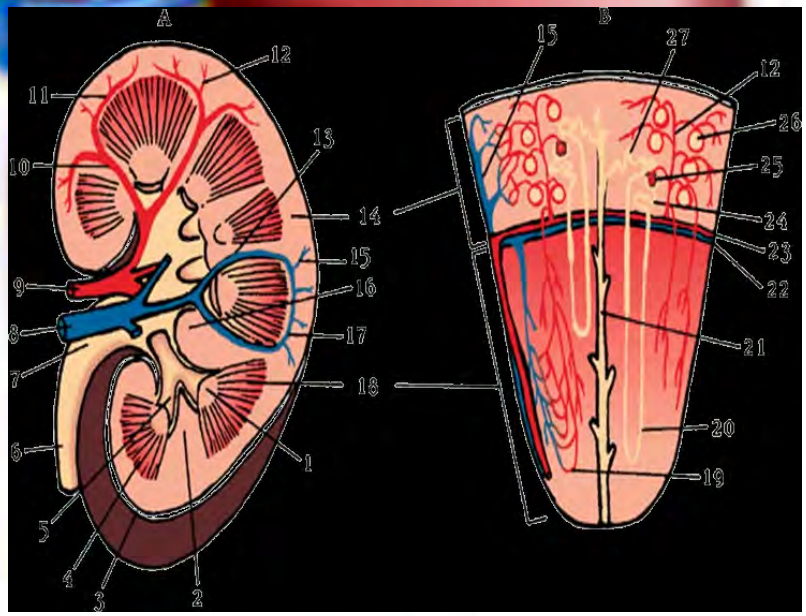

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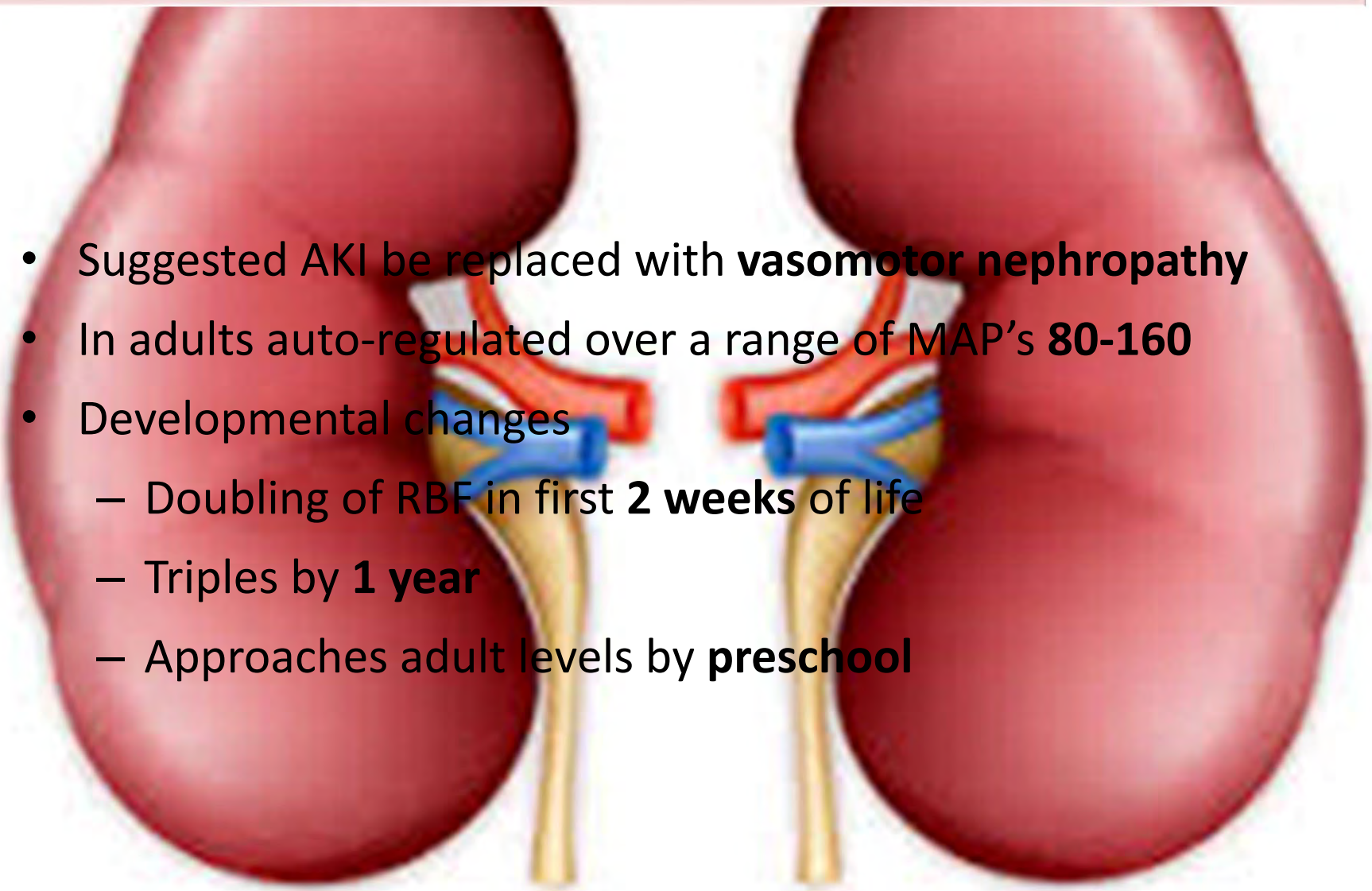
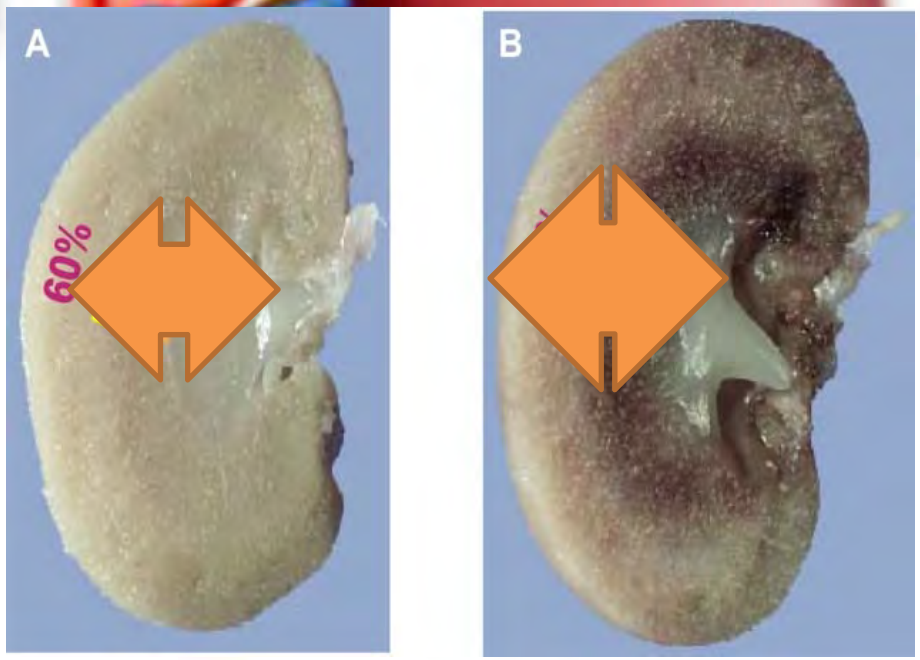
Regulation of RBF and its controller



- Suggested AKI be replaced with **vasomotor nephropathy**
- In adults auto-regulated over a range of MAP's **80-160**
- Developmental changes
  - Doubling of RBF in first **2 weeks** of life
  - Triples by **1 year**
  - Approaches adult levels by **preschool**

- **Hypo-perfusion**
  - Well perfused kidney – 90% of blood to cortex
  - Ischemia – **increased** blood flow to **medulla**
  - profound reduction of the blood flow to the **outer stripe of the outer medulla**
  - Outcome may be able to be influenced by restoration of energy/supply demands
    - Lasix example
  - Leads to **tubular** damage



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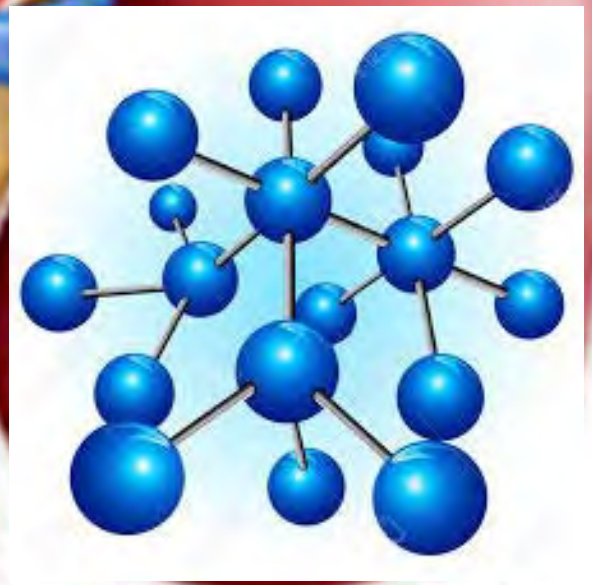


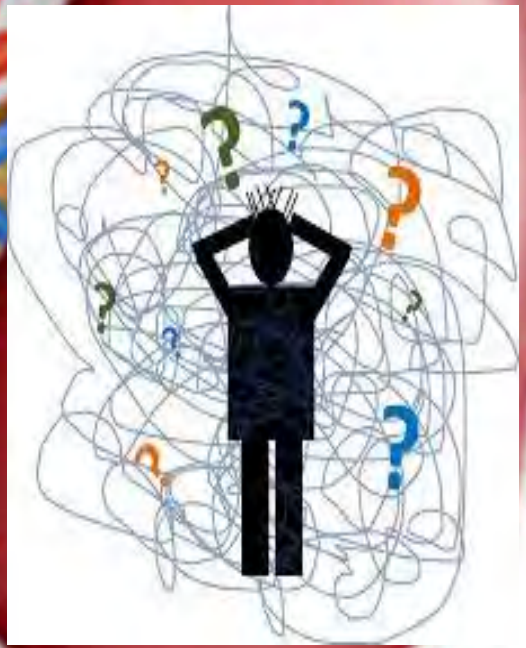
AKI in special conditions

AKI and extra-renal organ dysfunction

Renal blood flow regulation is complex No one system accounts for everything…..

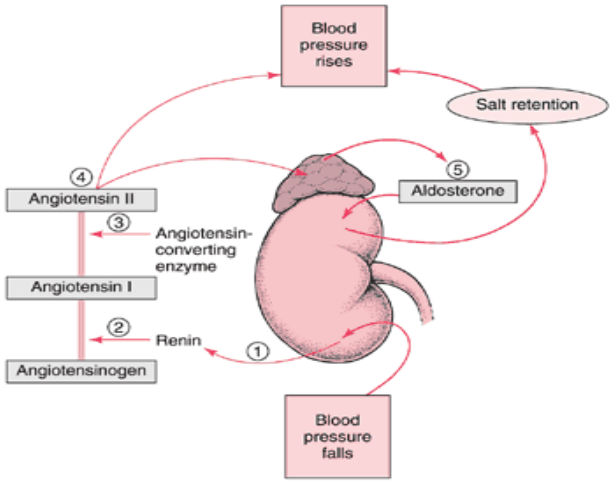
Insult to tubular epithelium causes release of vasoactive molecules which cause the constriction

Angiotensin II,
endothelin,
NO,
adenosine,
prostaglandins,
etc.



Renin Angiotensin Axis

- Renin's role in pathogenesis of AKI
  - **Hyperplasia** of JGA with increased renin granules seen in patients and experimental models of AKI
  - **Increased** plasma renin activity in AKI patients
  - Changing intra-renal renin content modifies degree of damage



Prostaglandins

PGE 2 and PGI

Very important for renal **vasodilation**, especially in the injured kidney

Act as a **buffer** against uncontrolled A2 mediated constriction

The RAS and Prostaglandin pathways account for ~60% of RBF auto-regulation…

Adenosine

- Potent **renal vasoconstrictor**
  - **Peripheral vasodilator**
- Infusion of **methylxanthines** (adenosine receptor blockers) **inhibits** the **decrease** in GFR that is seen with **tubular damage**

- But…. Likely not a major factor in AKI
  - Methylxanthines have lots of **other actions** besides adenosine blockade
  - Adenosine is **rapidly degraded** after production
  - **Intra-renal** adenosine levels diminish **very rapidly** after reperfusion, but the **vasocontraction** remains for a **longer** period

Endothelin

- 21 amino acid peptide that is one of the **most potent vasoconstrictors**
- Can be used as a **pressor**
- Its role in unclear in normal state
- In AKI, **overproduction** by cells (both in and outside of the kidney) leads to **decreased afferent flow** and thus decreased RBF and GFR
  - Endothelin increases **mesangial cell contraction** which reduces glomerular ultrafiltration
- Anti-endothelin **antibodies** or endothelin **receptor antagonists** decrease AKI in experimental models

Nitric Oxide

- Produced by multiple isoenzymes of NOS
- In addition to its role in **vasodilation**, likely has a role in **sodium reabsorption**
  - Give a NOS **blocker** and you get **naturesis**
- Exact mechanisms not worked out completely…

- Confusing results
  - Ischemic rat kidney model – inducing **NOS** causes **increasing injury**
  - But if you **block NOS** production, you get **worsening** of renal function and severe **vasoconstriction**

Dopamine

- Dopamine receptors in the **afferent** arteriole
- **Dilation** of renal vasculature at **low** doses, **constriction** at **higher** doses
- Also causes naturesis (? Reason for increased UOP after starting)
- Renal dose dopamine controversy…….

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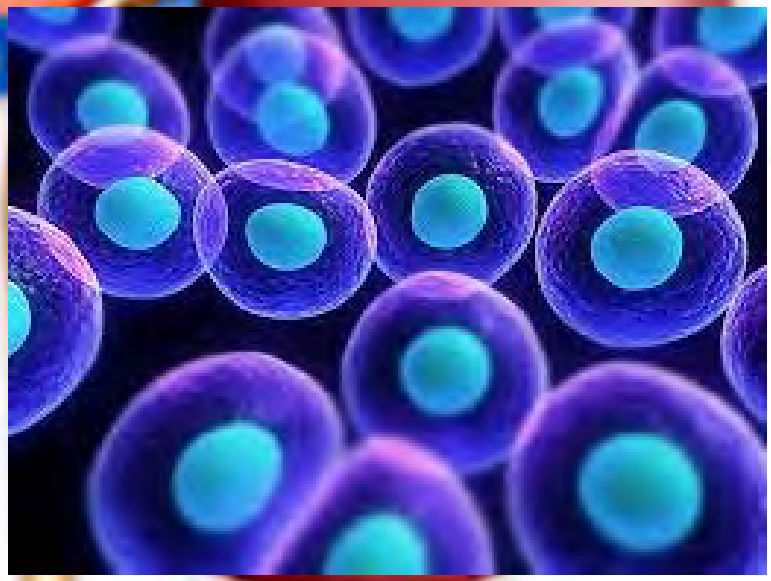

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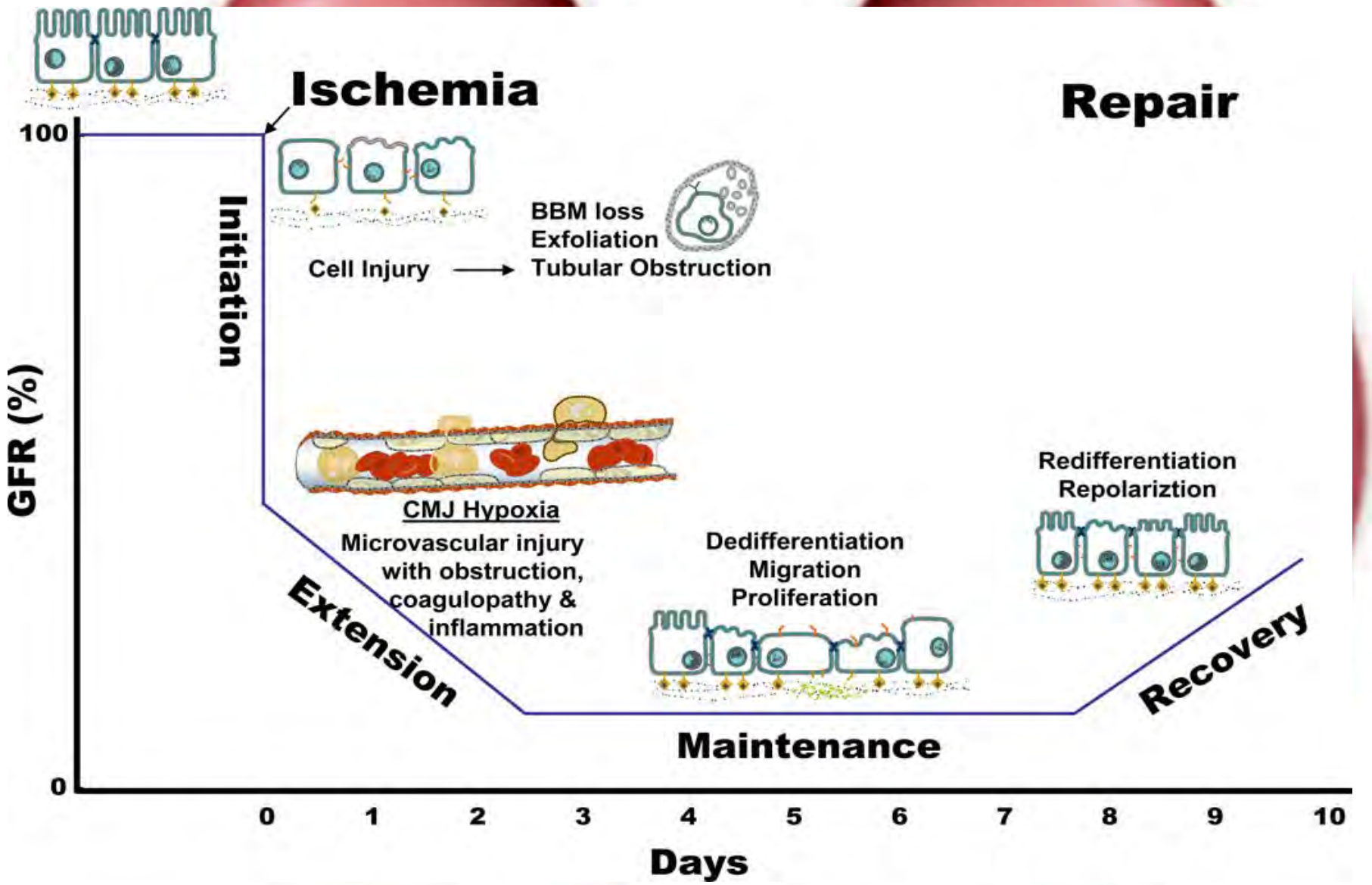
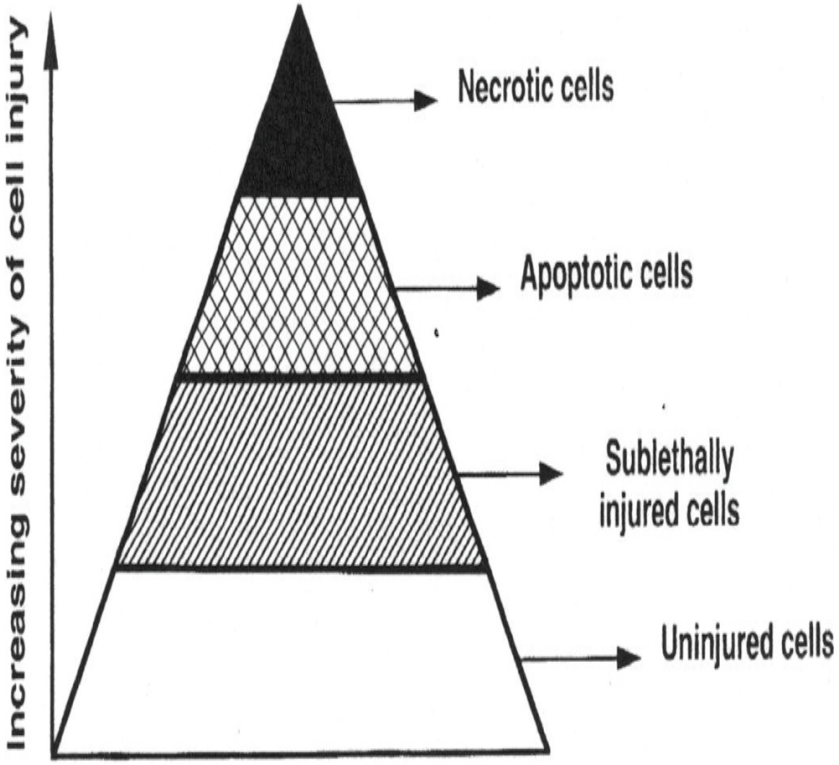
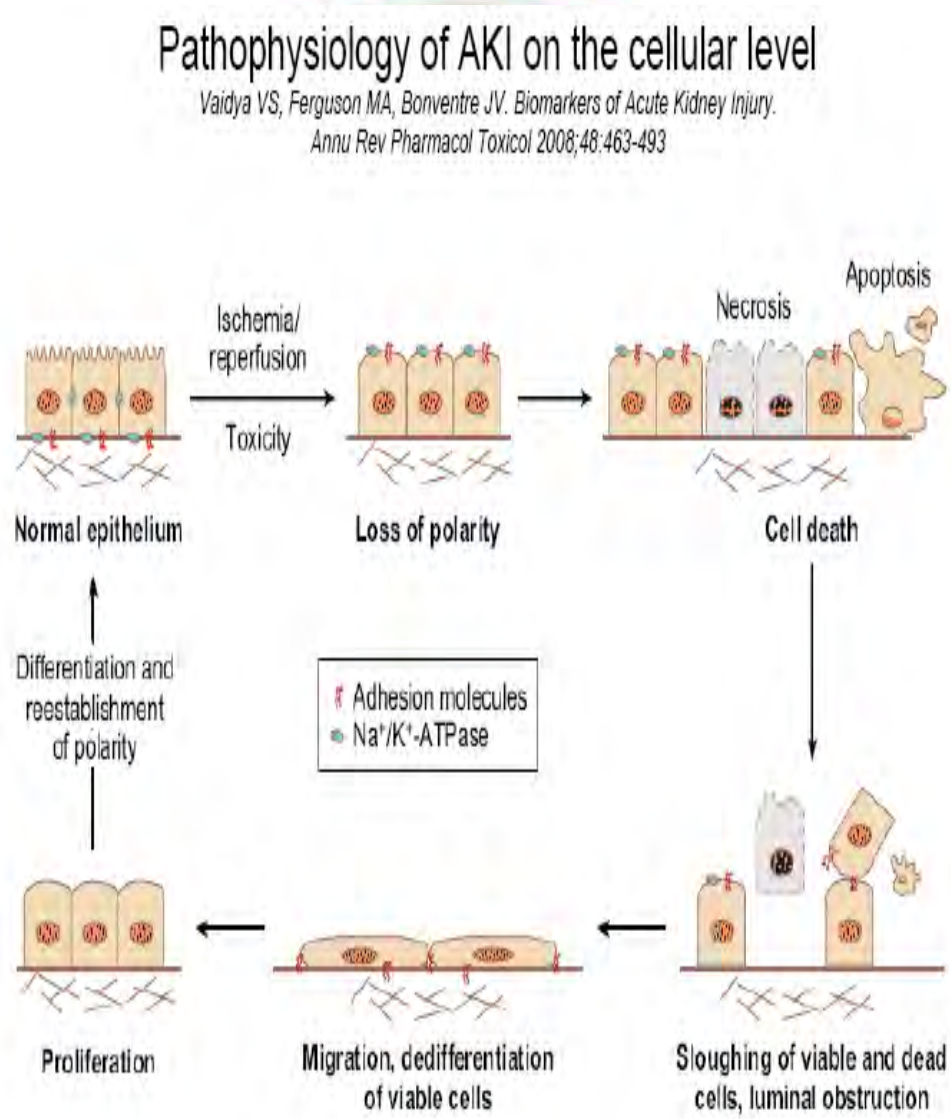
Cellular Injury







The continuum of renal cell damage

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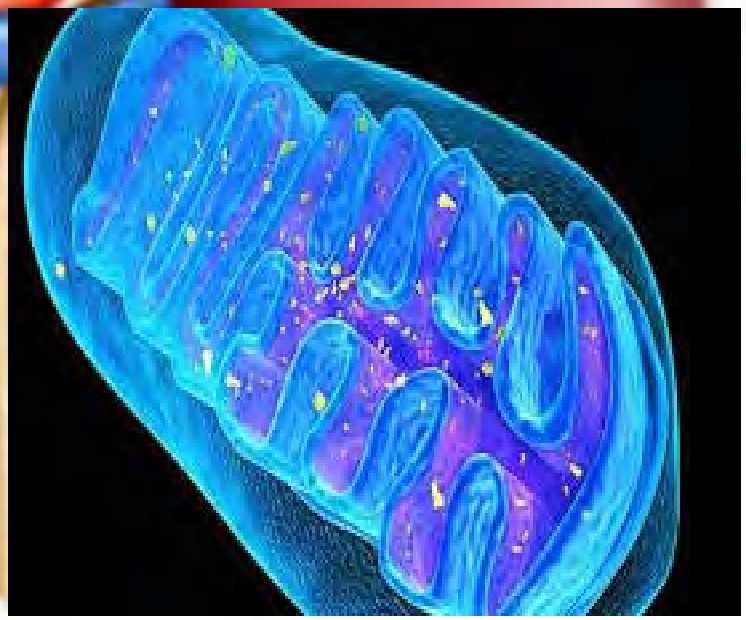

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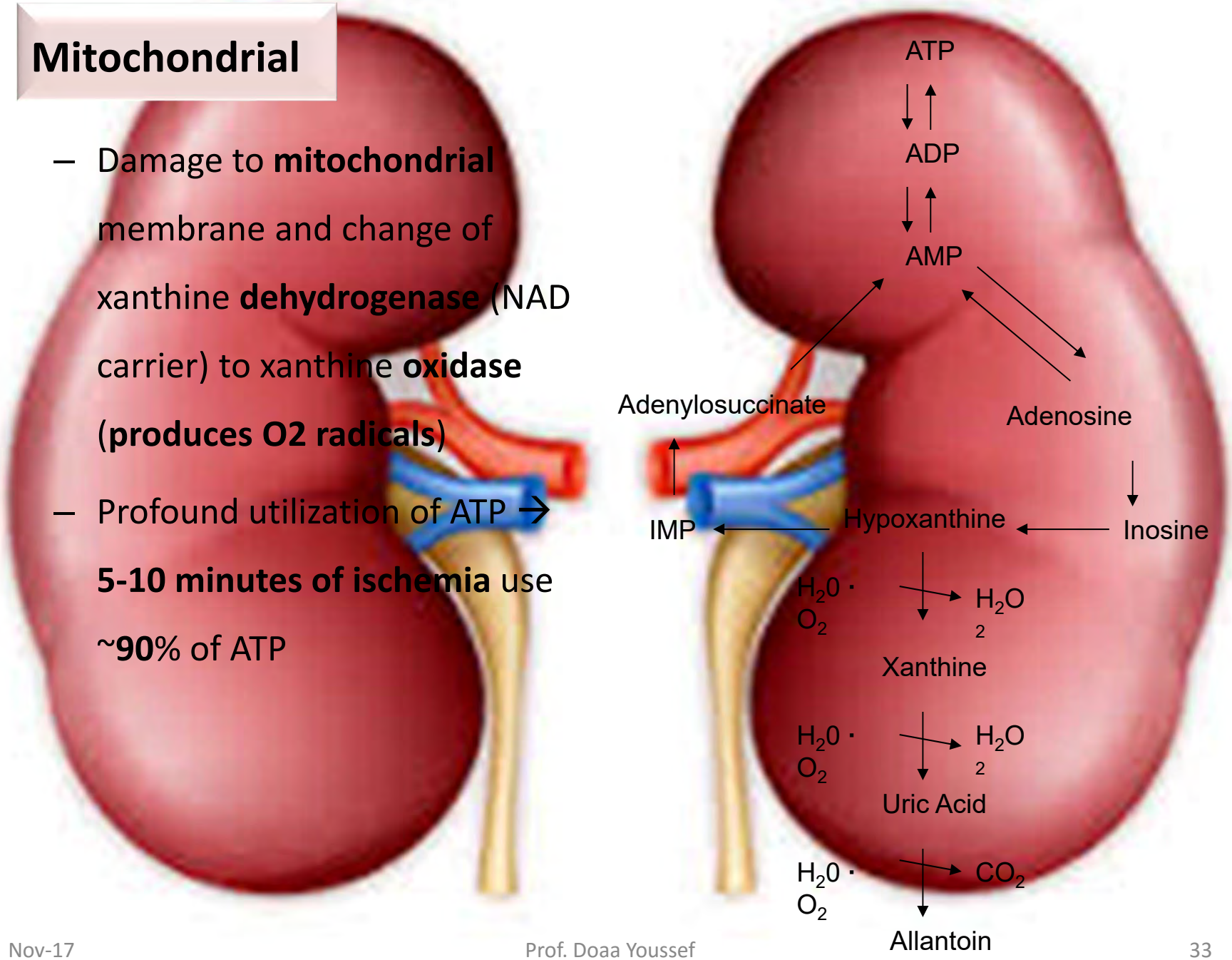
Mitochondrial

- Damage to **mitochondrial** membrane and change of xanthine **dehydrogenase** (NAD carrier) to xanthine **oxidase** (**produces O2 radicals**)
- Profound utilization of ATP → **5-10 minutes of ischemia** use ~**90**% of ATP



Oxidative damage

- Especially during **reperfusion** injuries
- Main players
  - Super-oxide anion, hydroxyl radical – highly ionizing
  - Hydrogen peroxide, hypochlorous acid – not as reactive, but because of that have a longer half life and can travel farther and cause injury distal to the site of production

- Amount of damage depends on ability to **replete ATP stores**
  - Continued low ATP leads to **disruption** of cell **cytoskeleton**, increased **intracellular Ca**, activation of **phospholipases** and subsequently the **apoptotic** pathways
- This endothelial cell injury sparks an immune response….that can't be good….

The term ATN is a misnomer

NOT ONLY TUBULAR

Alterations of the **interstitium**, **vasculature**, and **glomeruli** have also been documented in ATN

- **Interstitial edema** is often observed and may develop from leakage of fluid from increased microvascular permeability or back-leak of tubular filtrate
- Peritubular accumulation of **leukocytes** in the **interstitium**

- Congestion of the **peritubular capillaries** in the outer medullary region is a salient feature of ATN that may play an important role in **regional alterations of blood flow** and exacerbating tubular injury during the extension phase.
- Additionally the accumulation of **leukocytes in the vasa recta**,

- As may be expected, the most noted **glomerular** alteration in ATN is **collapse** of the glomerular tuft due to **hypoperfusion**.
- Alterations in glomerular **foot processes** have also been described , but this has not been a consistent finding.

NOT ONLY NECROSIS

contradiction between the **degree** of **histological abnormalities** on human biopsy samples and the extent of **GFR depression** has served as a one of the main paradoxes in AKI.

Outside of **rare frankly necrotic** tubular cells that occur, the prominent findings in human biopsies include **detachment of renal tubular epithelial cells** from the basement membrane, **sloughing** of cells into the tubular lumen, **effacement** and **loss of brush border in proximal tubular segments**, and the formation of tubular casts derived from **sloughed cells, tubular debris, and protein**

While evidence of tubular **injury** is apparent, evidence of tubular **cell regeneration** can also been seen alongside the injury .

Tubular cells with **basophilic cytoplasm and hyperchromatic** nuclei consistent with **regenerating** epithelial cells and even tubular cells undergoing active **mitosis** have been observed in many human biopsies of patients with ATN

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Repair and Regeneration

mammalian kidney has no **portal** blood supply (unlike fish).

The **proximal tubule** is particularly sensitive to ischemia because it relies predominantly on aerobic **adenosine triphosphate production(mitochondrial Krebs cycle**) and it cannot use the ischemic salvage pathway of glycolysis

the proximal tubule **reabsorbs** most of the filtered substances including toxins, in part by **endocytosis**.

For example, gentamycin is taken up by the cubilin megalin complex and gentamycin toxicity is **increased** in a water-retaining kidney

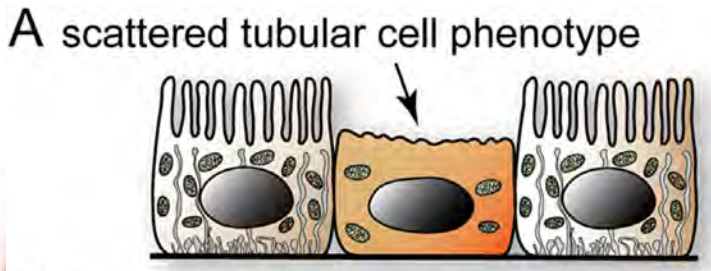
Tubules have a remarkable capacity to regenerate lost cells, usually within less than a week

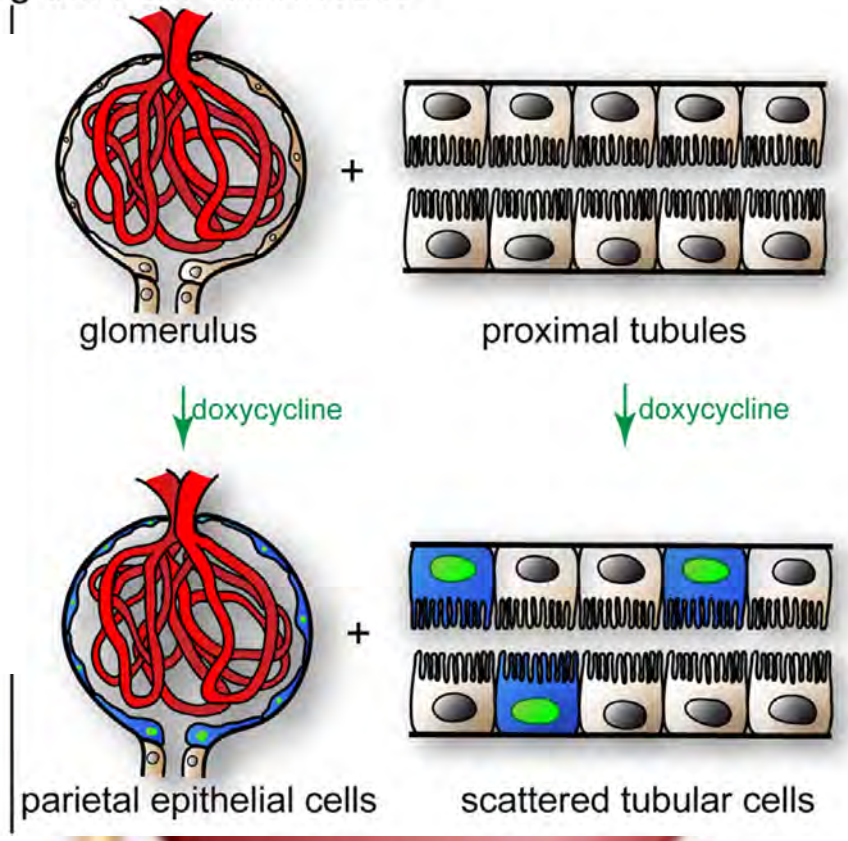
the role of a recently discovered subpopulation of tubule cells is discussed: **scattered tubular cells (STCs)**.
These cells become abundant in response to AKI and likely play a major role in the regenerative process.

In **2011, a** novel subpopulation of proximal tubular cells was described. Because these cells showed a distinct morphology and were **scattered** as single cells among fully differentiated inconspicuous tubular cells throughout the **entire** proximal tubule, these cells were termed scattered tubular cells.

It is an open question whether the STC phenotype reflects cellular **dedifferentiation** or an **alternative cellular program** that is activated specifically upon injury.

STCs are **not a fixed** progenitor population and that STCs can arise from **any** surviving proximal tubular cell





STCs show very characteristic morphologic and ultra-structural features .

They generally are **smaller** than fully differentiated tubular cells and may have **different** shapes.

In the normal kidney, they occur as ***single*** cells or, less often ,as ***doublets*** or ***triplets***.

They are **surrounded** by fully **differentiated** tubular cells, mostly with an abrupt transition.

In this setting, STCs often show an **arrow flask-like** shape.

Importantly, STCs show a **dramatic decrease in mitochondria** compared with neighboring proximal tubule cells

STCs **do not have apronounced apical brush** border.

STCs also express **only very low** levels of the classic multitarget protein endocytic transporter **megalin**.

STCs also **lack the basolateral** labyrinth of extensive membrane infoldings

Because Kim-1 is expressed by STCs, it may be regarded as a marker for kidney regeneration rather than kidney injury.

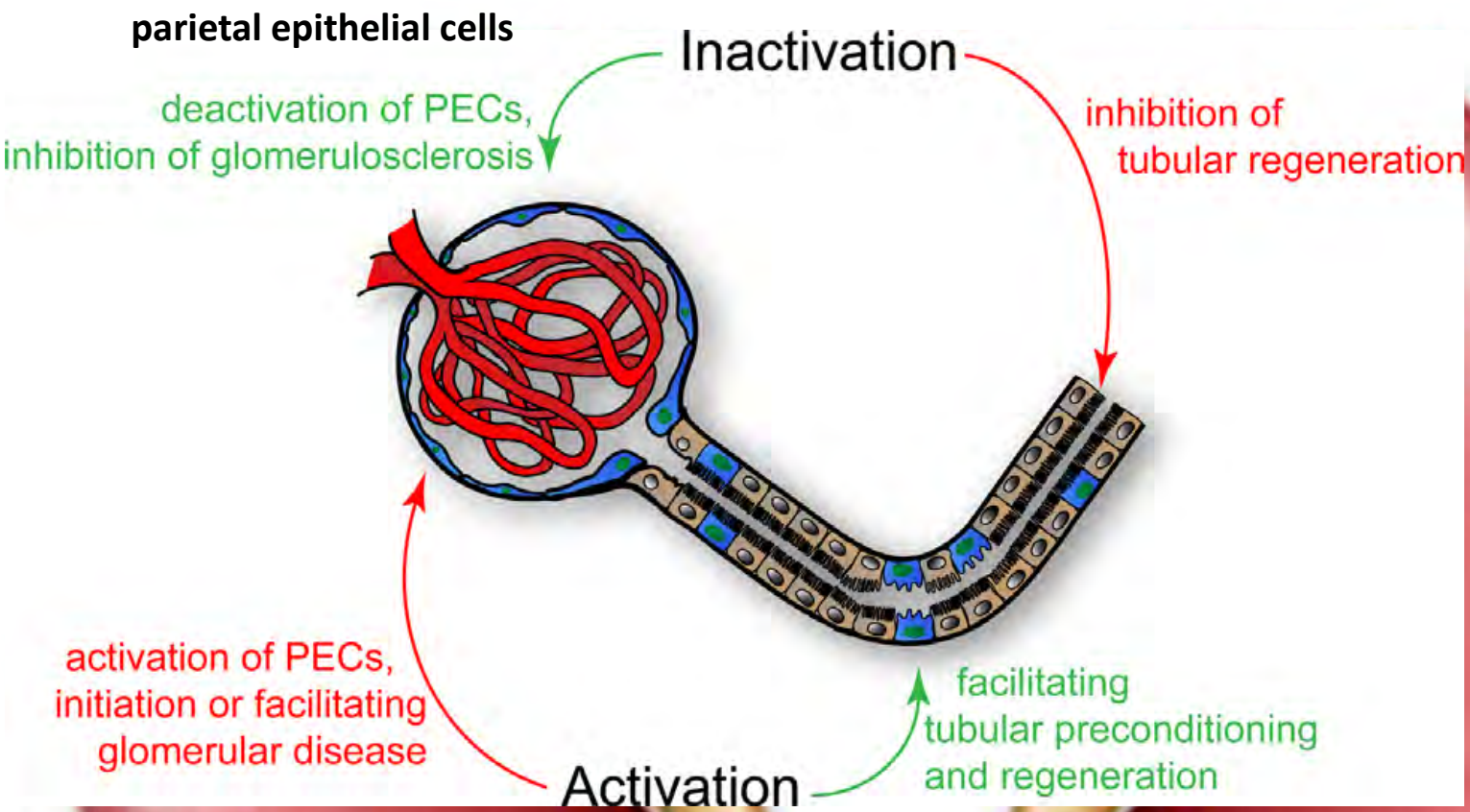
Several observations support this notion: STCs become more numerous after AKI, they express **similar antigens as hematopoietic stem cells** (eg,glyCD133,CD24,and vimentin), and they show a higher proliferation index

STCs MAY RENDER THE KIDNEY MORE RESISTANT TO INJURY

STCs may be more resistant to ischemia because they contain significantly **fewer mitochondria**.

This suggests that **STCs may be able to derive their adenosine triphosphate also from glycolysis,** but this still needs further investigation.

Targeting the STC subpopulation of proximal tubule cells therapeutically is a promising novel approach to develop a specific therapy for prevention and amelioration of AKI.



The fact that PECs and STCs have a similar protein expression pattern. STCs AS THERAPEUTIC TARGET: WHAT MAY BE GOOD FOR THE TUBULE MAY BE BAD FOR THE GLOMERULUS AND VICE VERSA e.g doxycycline

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Biomarkers for Acute Kidney Injury

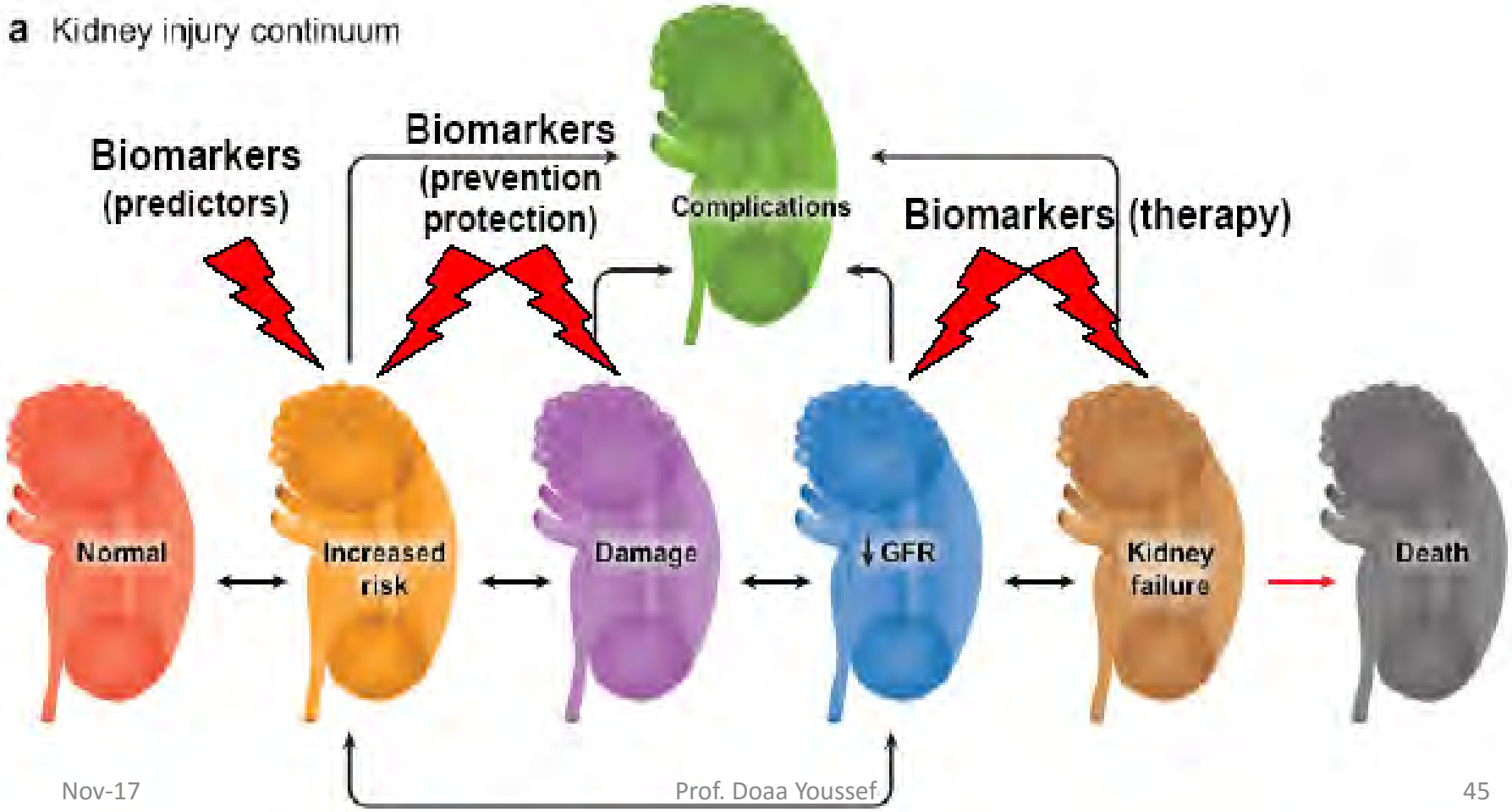
- Ideally AKI would have a biomarkers like myocardial infarction
  - (i.e. troponin-1)

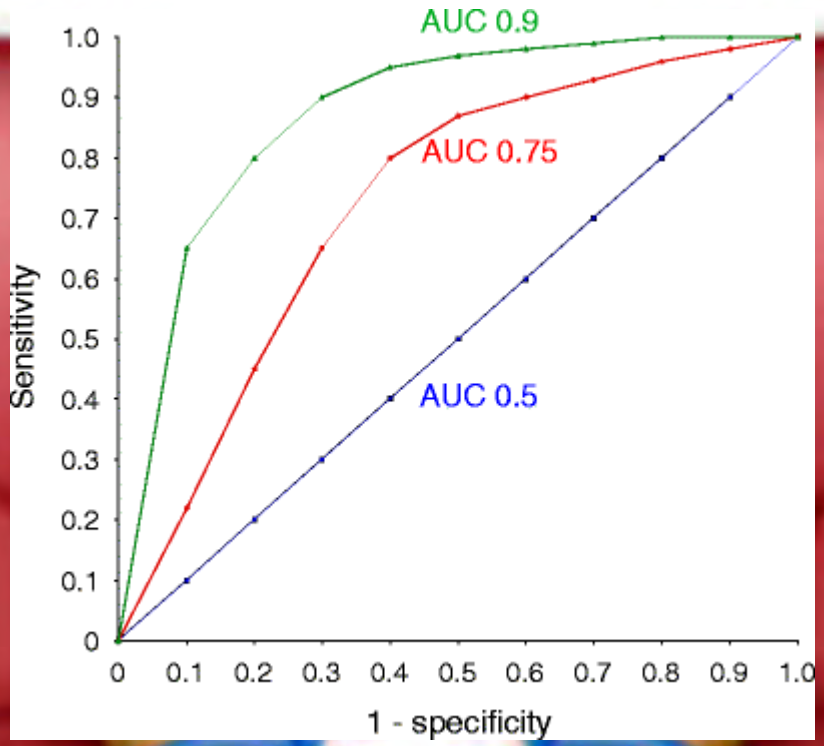
- Currently no Troponin-I like marker to identify the site or severity of injury, although various markers are being evaluated
  - (KIM-1)
  - (NGAL)
  - IL-18
  - Cystatin C

Conceptual Model for AKI

Kidney Injury Continuum

Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of Acute Kidney Injury. Annu Rev Pharmacol Toxicol 2008;48:463-493





Three hypothetical receiver-operating characteristic (ROC) curves are shown.

The *blue* (*straight*) *line* represents a biomarker with an area under the curve (AUC) of 0.5, which indicates a result that is no better than expected by random chance.

The *red* (*middle*) *curve* yields an AUC of about 0.75, which is generally considered a good biomarker.

The *green* (*top*) *curve* gives an AUC of approximately 0.9, which would represent an excellent biomarker

Current status of promising (AKI) biomarkers in various clinical situations

Biomarker Name	Sample Source	Cardiac Surgery	Contrast Nephropathy	Sepsis or ICU	Kidney Transplant	Commercial Test?
NGAL	Plasma	Early	Early	Early	Early	Biosite[a]
Cystatin C	Plasma	Intermediate	Intermediate	Intermediate	Intermediate	Dade-Behring
NGAL	Urine	Early	Early	Early	Early	Abbott[a]
IL-18	Urine	Intermediate	Absent	Intermediate	Intermediate	None
KIM-1	Urine	Intermediate	Not tested	Not tested	Not Tested	None

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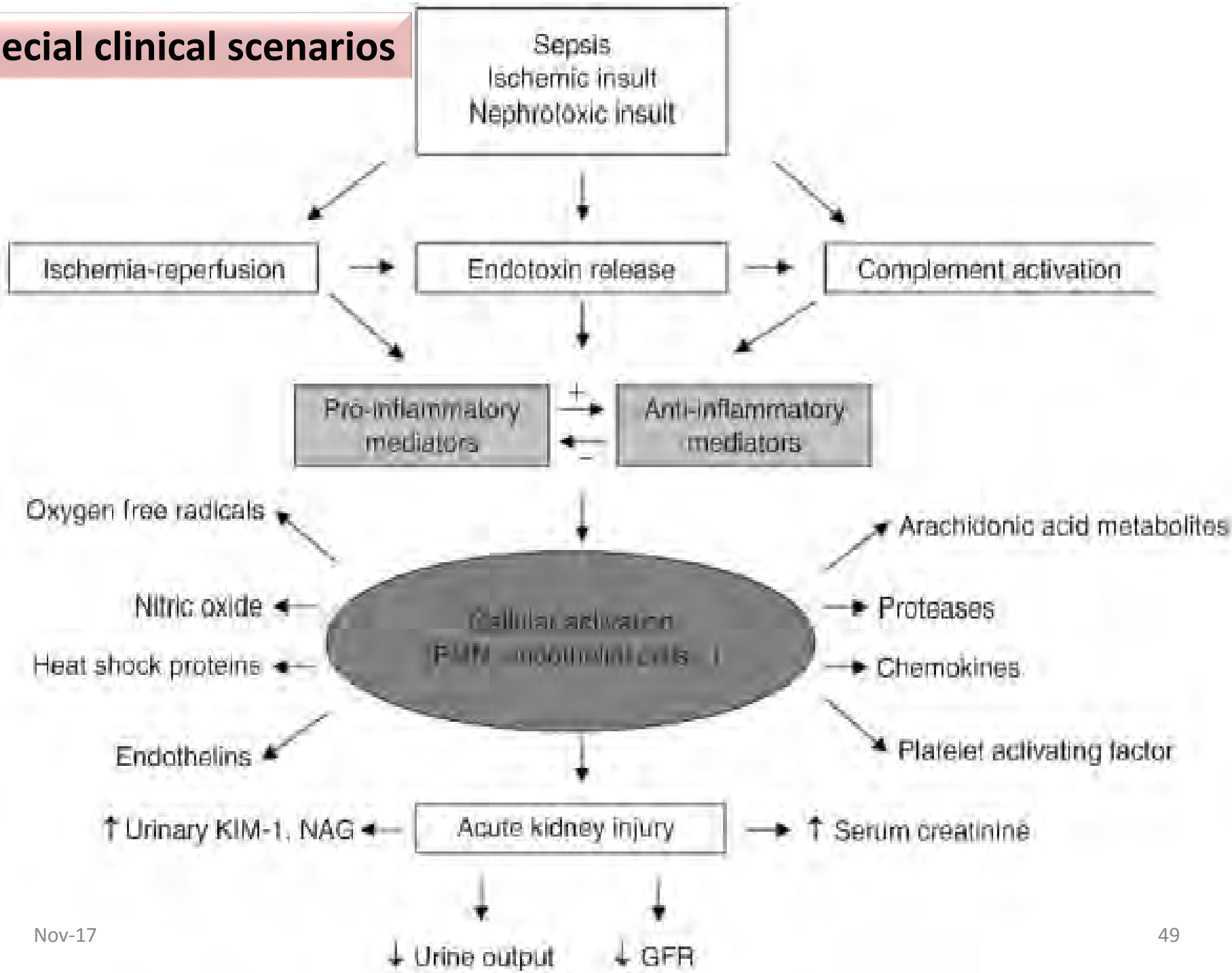
AKI and extra-renal organ dysfunction

Special clinical scenarios



Rhabdomyolysis

- the breakdown and necrosis of damaged skeletal muscle and subsequent release of its contents (i.e. myoglobin, sarcoplasmic proteins) into extracellular fluid and circulation.
- These products may be filtered through the glomeruli, leading to AKI via different mechanisms,
- such as **intratubular** obstruction secondary to protein precipitation,
- renal **vasoconstriction**,
- **inflammation** and
- tubular damage associated with **reactive oxygen species** production.
- Rhabdomyolys is usually develops in the setting of one or more of the following situations:
- disruption of the substrates and/or oxygen for metabolism (i.e. ischaemia, hypoxia, crush injuries),
- excessive metabolic demand (i.e. strenuous exercise),
- impaired cellular energy production (i.e. hereditary enzymatic disorders, toxins),
- and/or increased intracellular calcium influx

Drug-induced AKI

- Medications frequently show toxic effects on the kidney as **glomerular**, **interstitial** and **tubular** cells encounter significant concentrations of medications and their metabolites, which can induce changes in kidney **function** and **structure**.
- **Renal tubular cells** are **particularly** vulnerable to the toxic effects of drugs because of their role in concentrating and reabsorbing glomerular filtrate, which exposes them to high levels of circulating toxins.
- **Renal toxicity can be a result of**

- hemodynamic changes,
- direct injury to cells and tissue,
- inflammatory tissue injury and
- obstruction of renal excretion.

Contrast Induced Acute Kidney Injury (CI-AKI)

- Contrast agents are used widely for diagnostic and therapeutic purposes.
- Their nephrotoxic potential was first suggested at least **50** years ago and today are considered one of the most common causes of AKI among hospitalised patients. The risk of CIN has long been assumed to be proportional to the **degree of preexisting renal dysfunction**
- and it is associated with extended length of hospital stay, accelerated onset of end stage renal disease, need for dialysis, increased mortality and increased costs.
- The pathophysiology of CI-AKI is **not very well defined**.

From the pathogenesis point of view

Definition

Epidemiology

Causes

Post- renal

Pre- renal

Intrinsic renal failure

RBF regulation

molecular level response

Cellular response

mitochondrial response

Repair

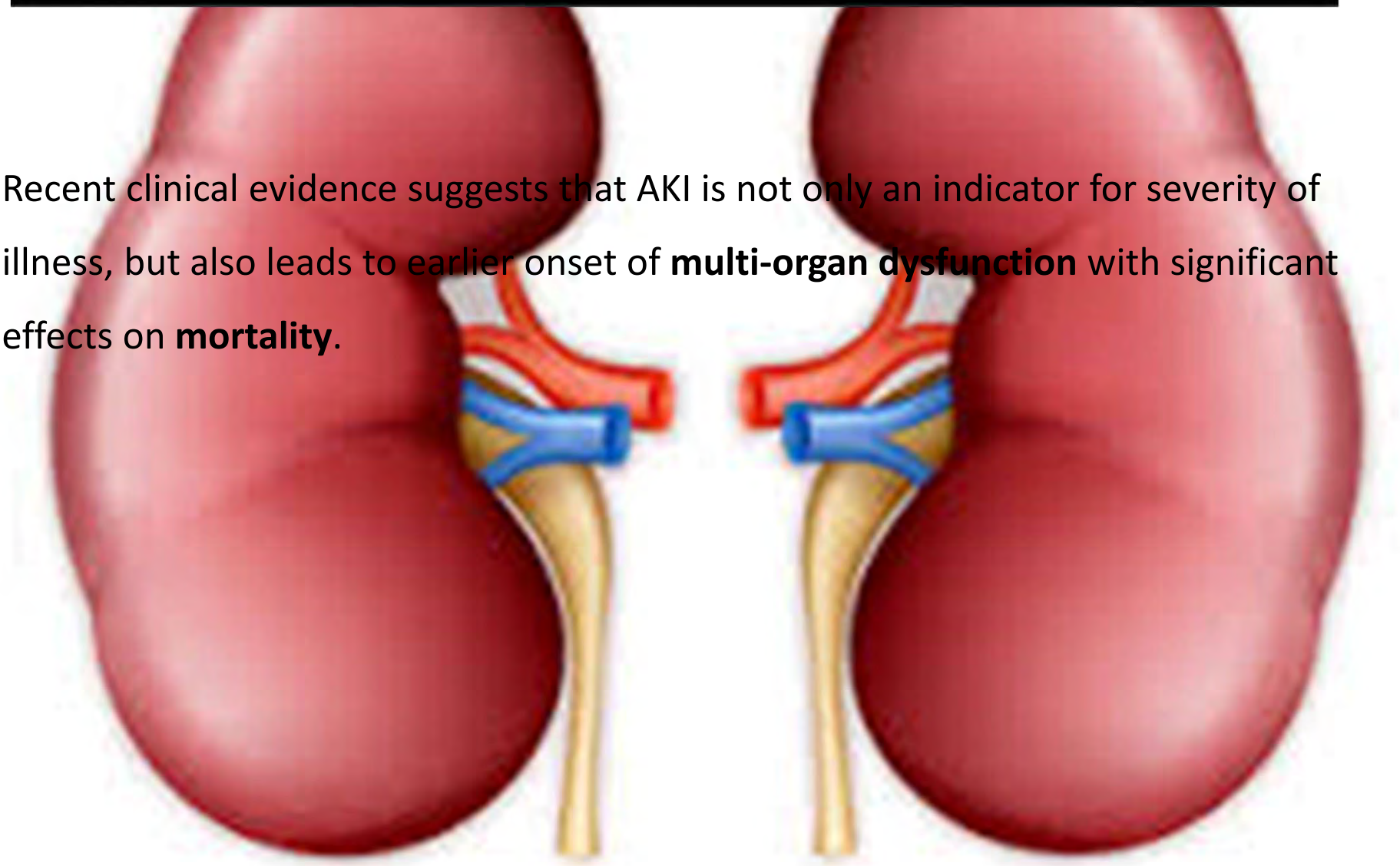
Biomarkers

AKI in special conditions

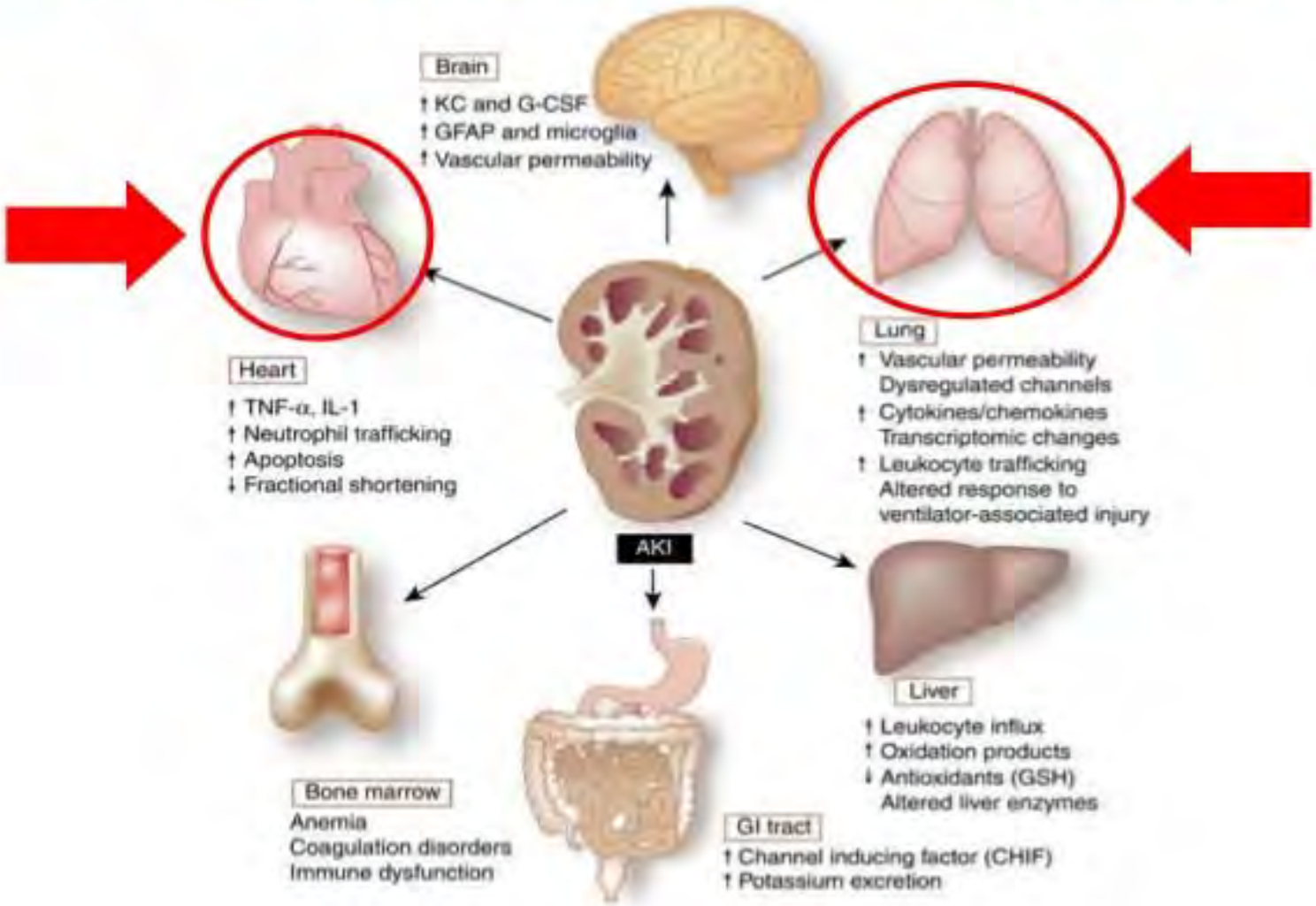
AKI and extra-renal organ dysfunction

AKI and extra-renal organ dysfunction

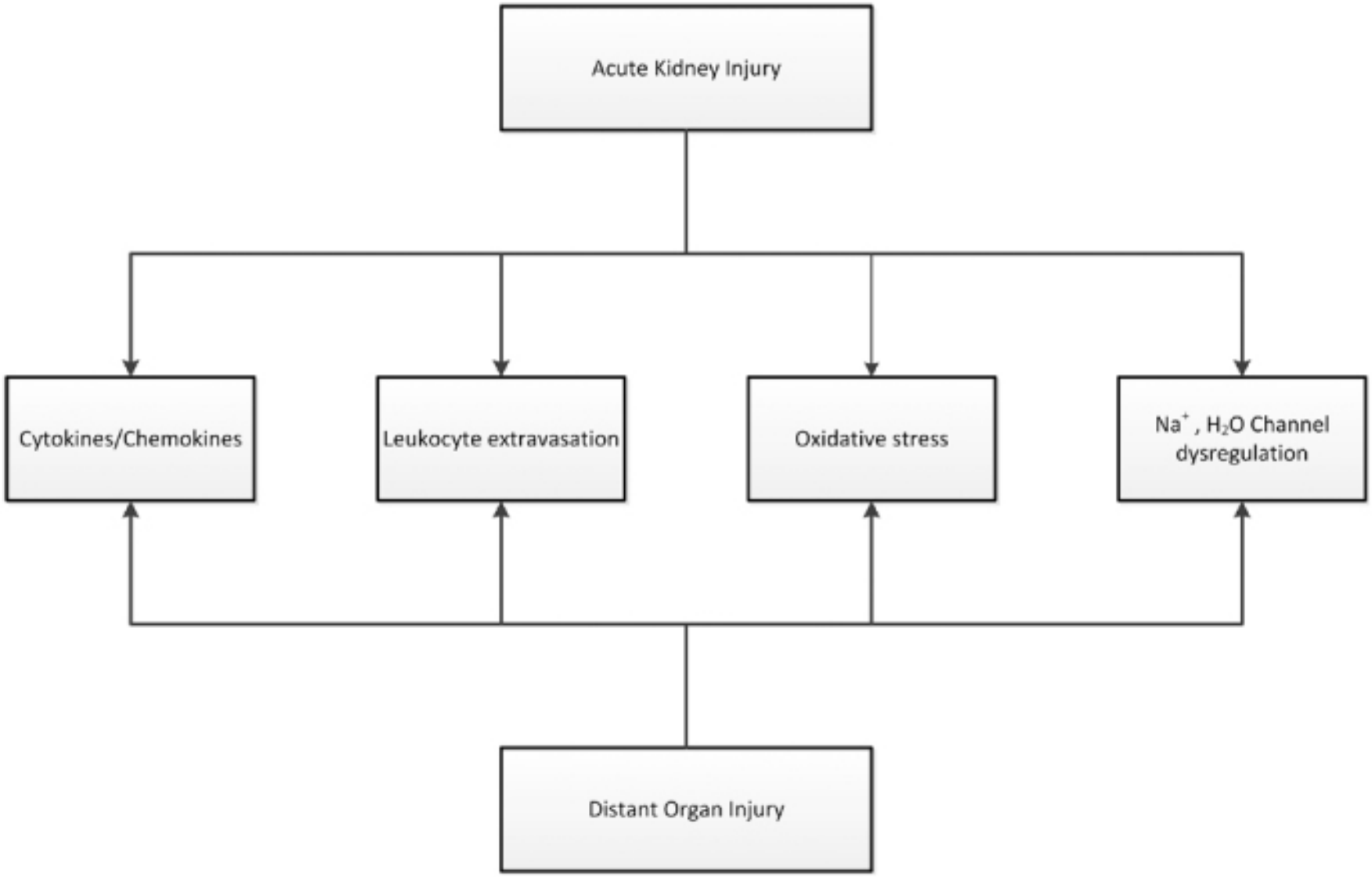
Recent clinical evidence suggests that AKI is not only an indicator for severity of illness, but also leads to earlier onset of **multi-organ dysfunction** with significant effects on **mortality**.



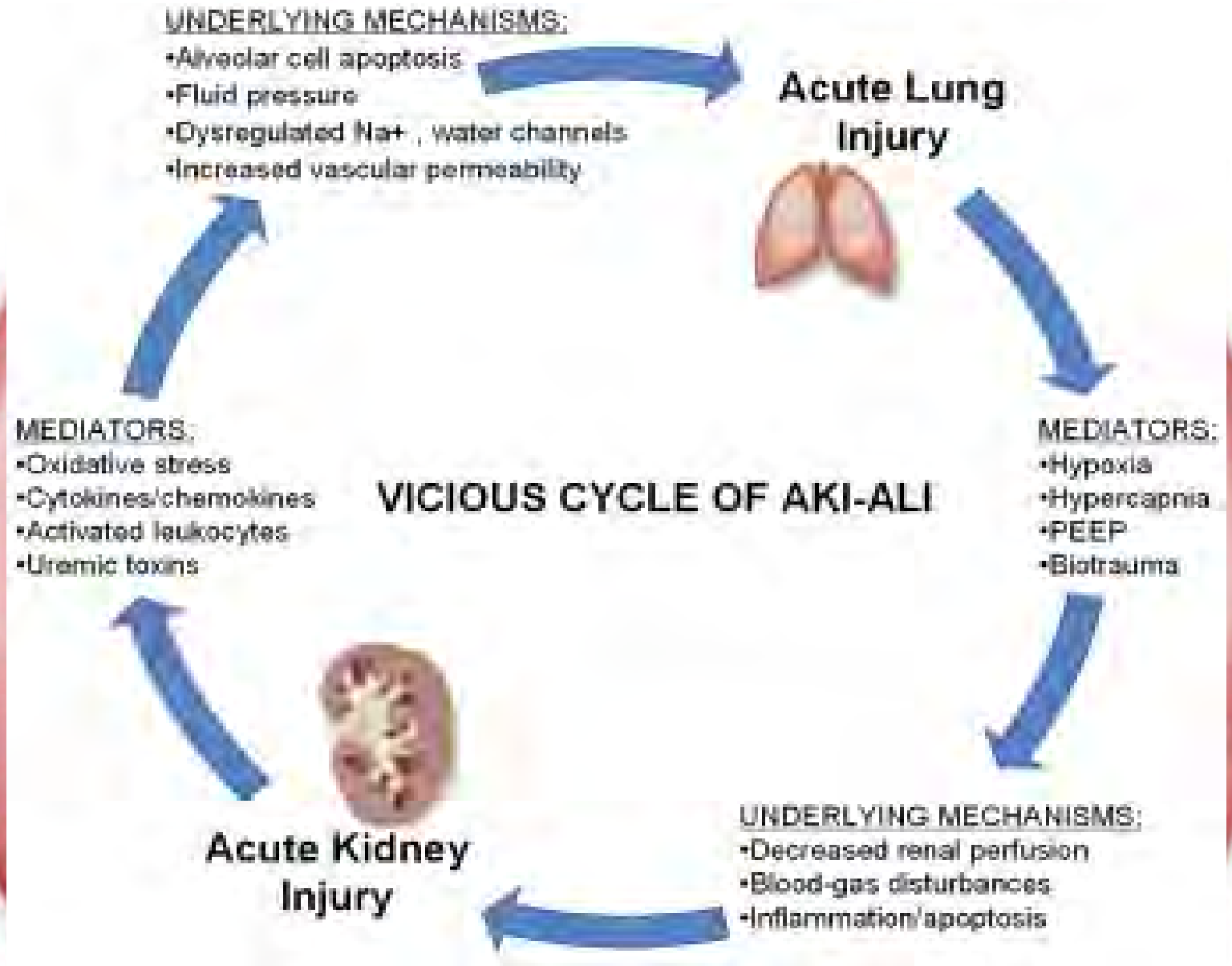
AKI hurts other organ systems



Grams ME, Rabb H. Kidney International 2011; advance online publication, 3 August 2011

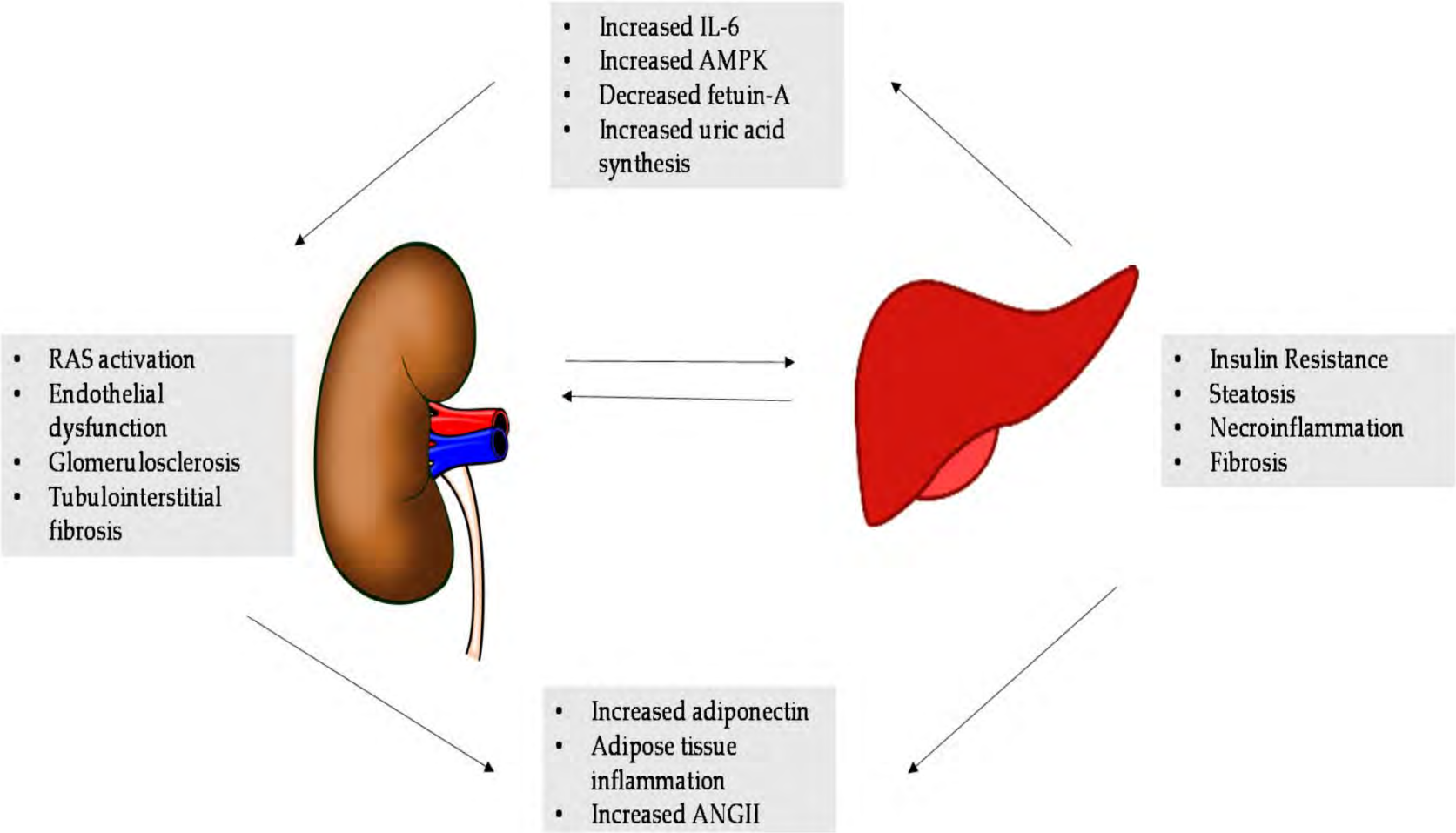


Proposed mechanism of distal organ injury.



Kidney-lung crosstalk in the critically ill patient

Kidney-liver interactions: Hepato-renal syndrome

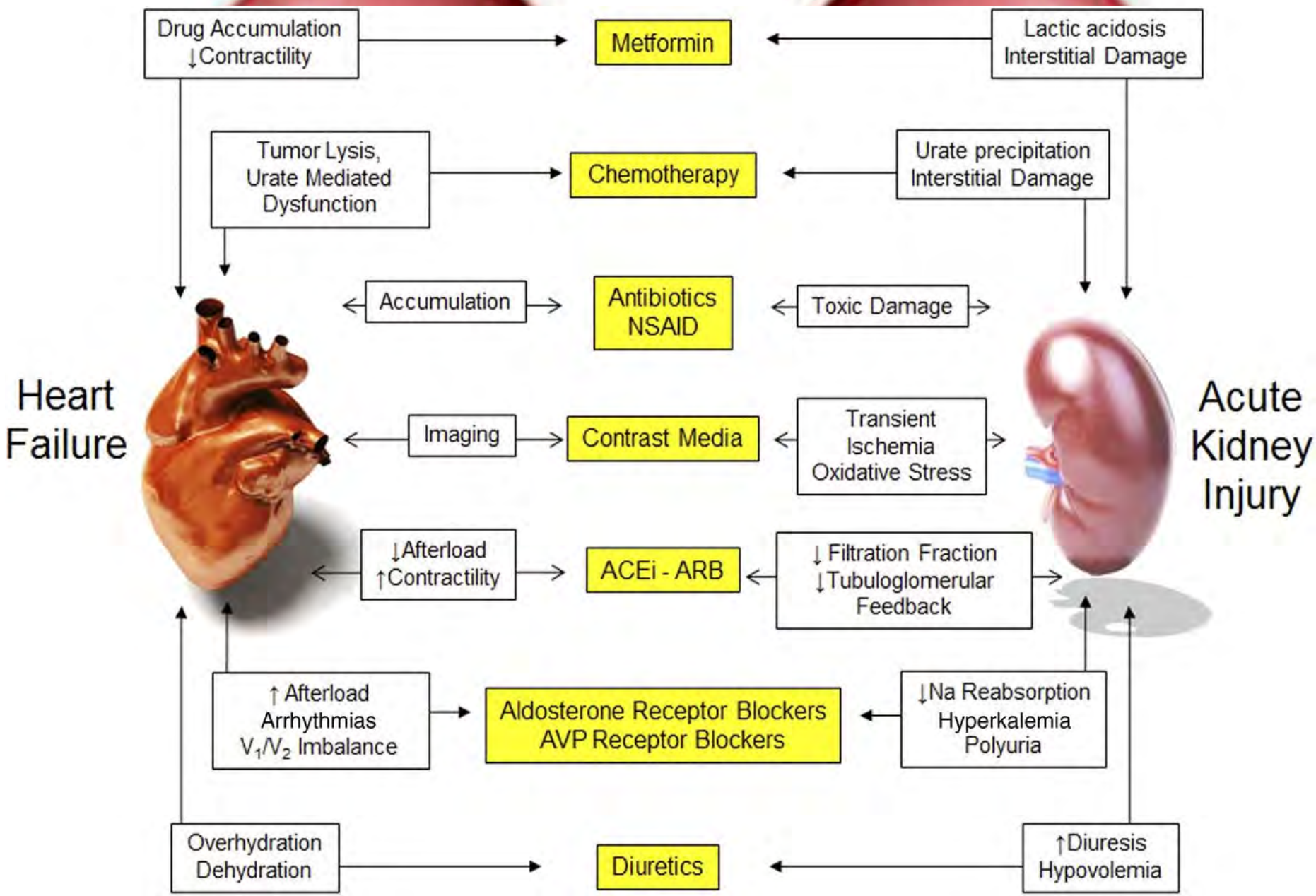


Acute-on-chronic kidney disease	Rise in serum creatinine of ≥ 50% from baseline in <48 h in a patient with cirrhosis whose glomerular filtration rate is <60 ml/min for >3 months

Heart-kidney crosstalk: the cardiorenal syndrome

Classification	Abbreviation	Characteristic	Primary Event	Secondary Event
Acute cardio-renal syndrome	CRS type1	Abrupt worsening of cardiac function leading to AKI	AHF, ACS cardiogenic shock	AKI
Chronic cardio-renal syndrome	CRS type2	Chronic worsening of cardiac function leading to progressive and permanent chronic kidney disease	CHD	CKD
Acute reno-cardiac syndrome	CRS type3	AKI causing acute cardiac dysfunction	AKI	AHF, ACS arrhythmias shock
Chronic reno-cardiac syndrome	CRS type4	CKD leading to impairment of cardiac function and/or increased risk of adverse cardiovascular events	CKD	CHD, AHF ACS
Secondary cardio-renal syndrome	CRS type5	Systemic disorders causing both cardiac and renal dysfunction (i.e. septic shock, vasculitis)	Systemic disease (i.e. sepsis)	AKI, CKD AHF, CHD ACS

Cardiorenal Syndrome Type 1



MCQ

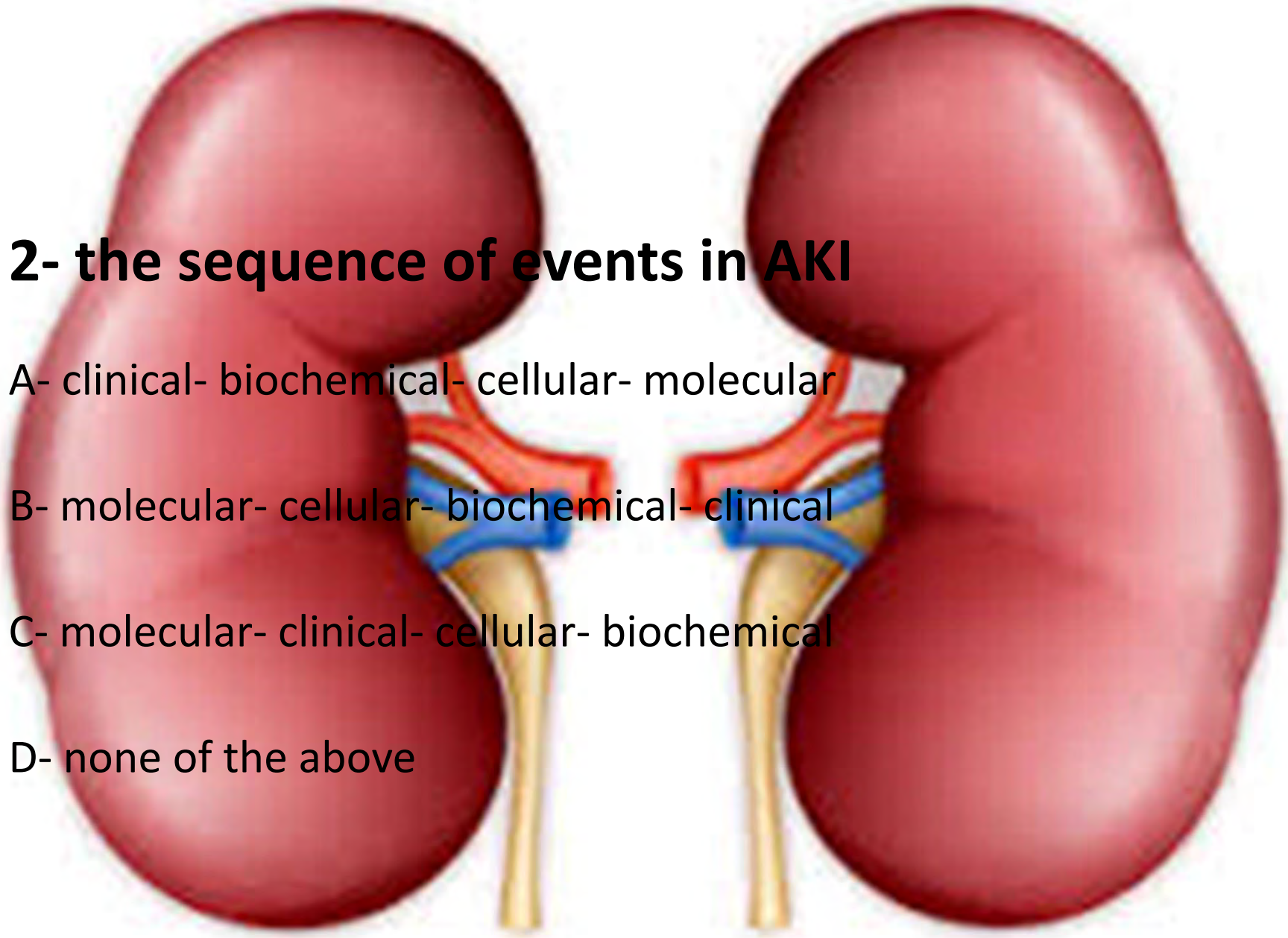
1. **With decreases renal perfusion which of the following is right:**

A- PGs mediate vasoconstriction on efferent arterioles

B- angiotensin II mediate vasodilatation on afferent arterioles

C- angiotensin II enhances vasoconstriction on afferent arterioles

D- PGs mediates vasodilatation on afferent arterioles



2- the sequence of events in AKI

A- clinical- biochemical- cellular- molecular

B- molecular- cellular- biochemical- clinical

C- molecular- clinical- cellular- biochemical

D- none of the above

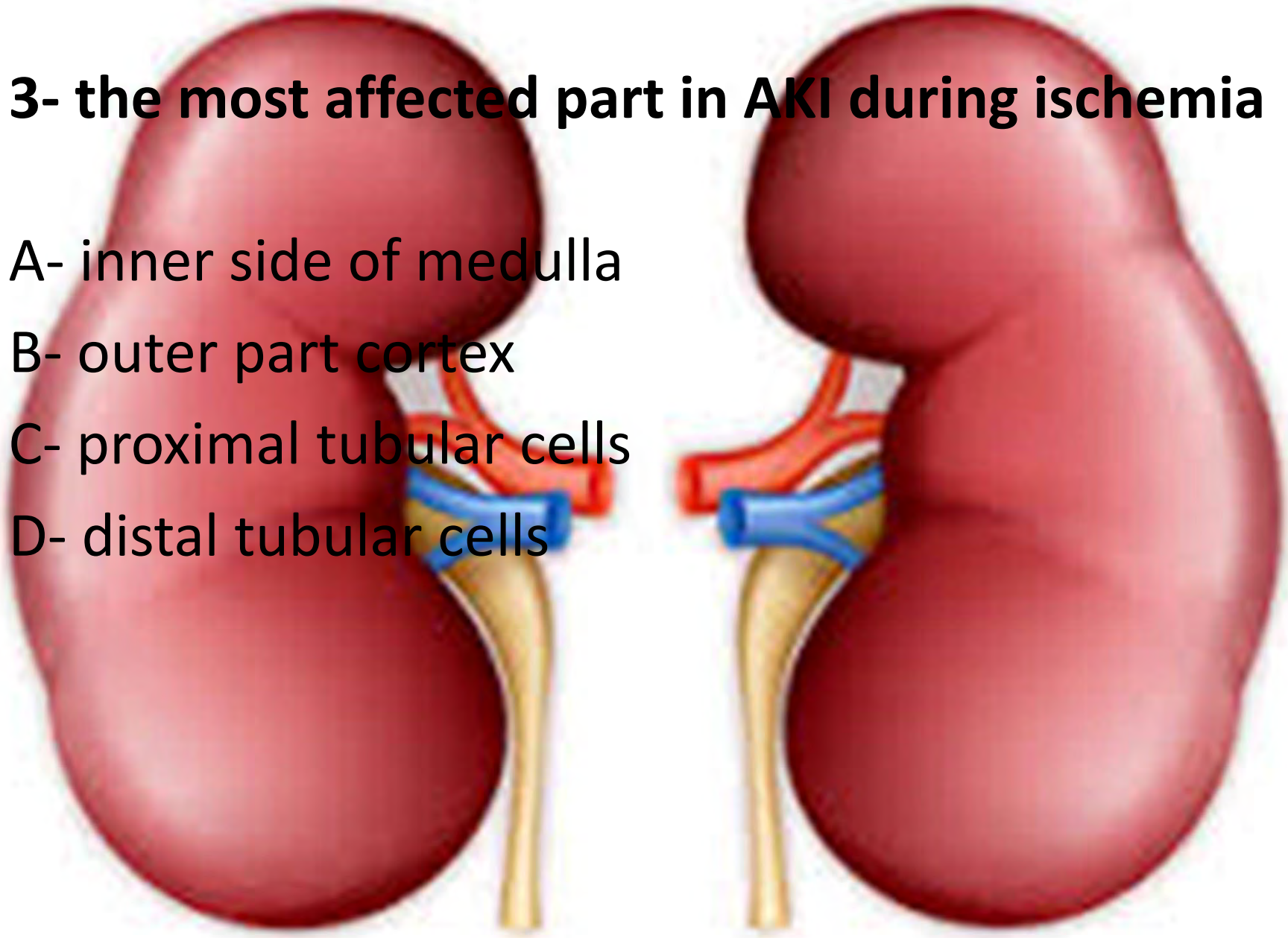
3- the most affected part in AKI during ischemia

A- inner side of medulla

B- outer part cortex

C- proximal tubular cells

D- distal tubular cells



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Thank
You!