Acute kidney injury – it personal!

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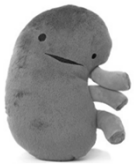


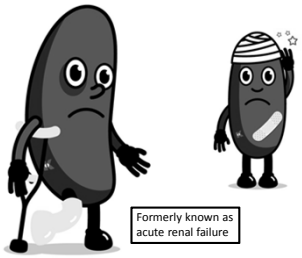
A 'cute' kidney

Objectives

- Differentiate between acute kidney injury and chronic kidney disease
- Describe RIFLE, AKIN, and KDIGO guidelines defining acute kidney injury
- Differentiate between prerenal, renal, and postrenal kidney injury.
- Describe the need for early markers of kidney injury.

Acute kidney injury (AKI)

- Abrupt decline in renal function occurring over a few hours or days
- Result of acute insult to kidneys
- Affects up to 20% of all hospitalized patients (up to 50% of critically ill patients)



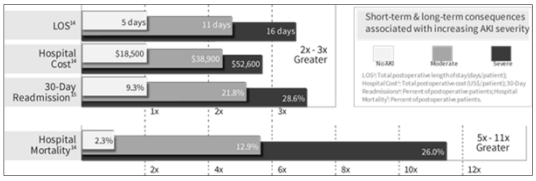
Formerly known as acute renal failure

Acute kidney injury (AKI)

- Risk factor for developing **or worsening** chronic kidney disease

It's personal!

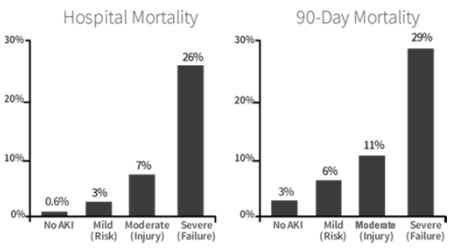
Acute kidney injury (AKI) costs

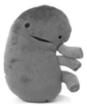


- One of costliest health issues worldwide
- Often preventable

AKI

- 'Silent killer'
- In-hospital complication of sepsis, heart conditions, and surgery
- Medical community slow to recognize AKI and implement standard of care





Acute vs. Chronic Kidney Disease

Acute
- Decline in function over hours or days
- Usually caused by an event (e.g., dehydration, blood loss from surgery, certain medications)
- **May be reversible**

Chronic
- Decline in function over months or years
- Usually caused by long-term disease (e.g., diabetes, high blood pressure)
- Not usually reversible

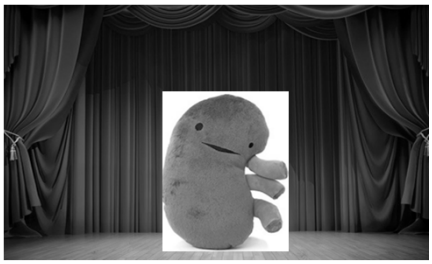
Chronic kidney disease

Staging based on GFR and albuminuria
- GFR < 60 for more than 3 months

Colors – risk of progression
Numbers – frequency of monitoring (times/year)

GFR Categories (mL/min/1.73 m²) Stage, Description, and Range				Persistent Albuminuria Categories, Description and Range: Normal to mildly increased (<30 mg/g (<3 mg/mmol))	Moderately increased (30-300 mg/g (3-30 mg/mmol))	Severely increased (>300 mg/g (>30 mg/mmol))
	1	Normal or high	≥90	1 if CKD	1	2
	2	Mildly decreased	60–89	1 if CKD	1	2
	3a	Mildly to moderately decreased	45–59	1	2	3
	3b	Moderately to severely decreased	30–44	2	3	3
	4	Severely decreased	15–29	3	3	4+
	5	Kidney failure	<15	4+	4+	4+

So what about Acute staging?



RIFLE

2002- Acute Dialysis Quality Initiative (ADQI) group met in Italy to develop a definition for AKI

2004- RIFLE definition and risk stratification published

Vicenza, Italy- life is tough.

RIFLE

Limitations

- Based on changes in serum creatinine; need baseline levels or must estimate

- Diuretics alter urine output

- Creatinine- marker of renal function, not renal injury

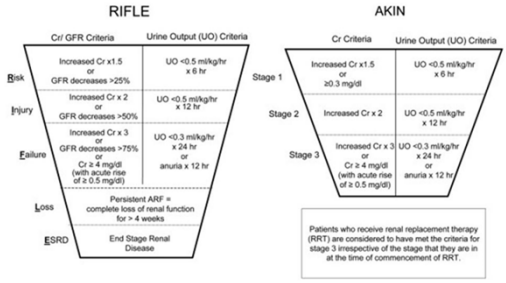
	GFR Criteria	Urine Output Criteria
Risk	↑ Cr_{serum} x1.5 or GFR ↓>25%	Urine output < 0.5ml/kg/h x 6hours
Injury	↑ Cr_{serum} x 2.0 or GFR ↓>50%	Urine output < 0.5ml/kg/h x 12hours
Failure	↑ Cr_{serum} x3.0 or GFR ↓>75% or Cr_{serum} >4mg/dl	Urine output < 0.3ml/kg/h x 24hours or anuria x 12 hours
Loss	Persistent AKI=complete loss of kidney function > 4 weeks	
ESRD	End Stage Renal Disease (ESRD)=complete loss of kidney function >3 months	

AKIN (Acute Kidney Injury Network)

2005- Working group met in Amsterdam to develop new classification,
2007- Published new classification

Poor things. Work, work, work.

RIFLE vs AKIN



KDIGO (Kidney Disease Improving Global Outcomes)

- Met in 2011
- Published staging guidelines in 2012 (based on RIFLE and AKIN)
- **Finally, also, prevention and treatment guidelines**

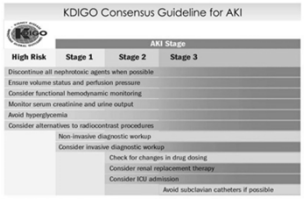


FIGURE 1: Stage-based management of AKI. Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases. AKI, acute kidney injury; ICU, intensive care unit. Source: www.KDIGO.org.

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Is this good enough?

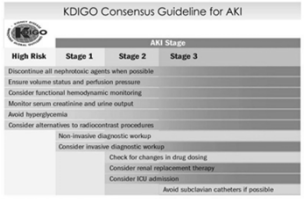


FIGURE 1: Stage-based management of AKI. Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases. AKI, acute kidney injury; ICU, intensive care unit. Source: www.KDIGO.org.

The need for new testing

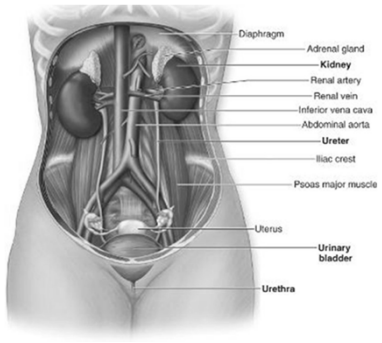
Timing - takes about 24-48 hours after injury to detect ↑ in serum creatinine. During this time, up to 50% of kidney function can be lost.

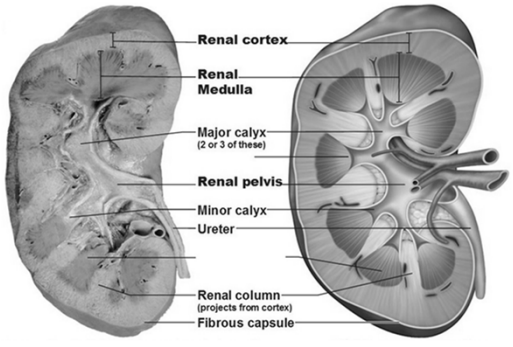
What are we measuring? - SCr and urine output → dysfunction, not injury.

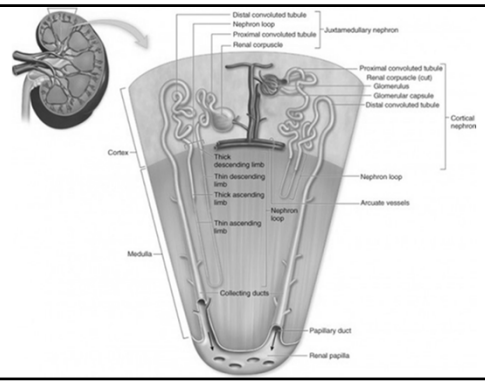
- Diagnosis ***after*** the kidney damaged → higher risk of mortality.

Earlier testing to ***detect injury*** - remove or treat the source of injury

So let's talk about the kidneys…



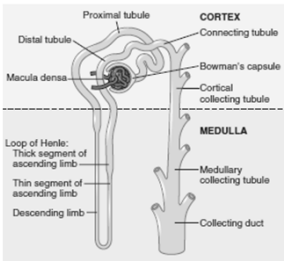


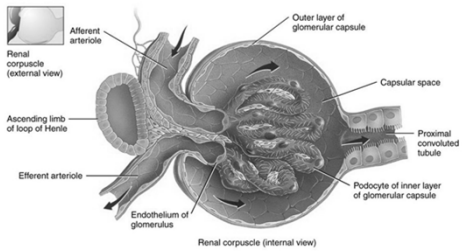


Nephron – functional unit of the kidney

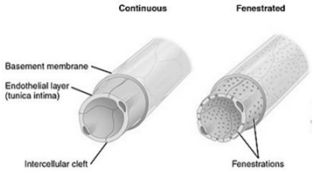
- Glomerulus + Bowman's capsule + tubules

Glomerulus = cluster of capillaries
Tubules = where urine is made



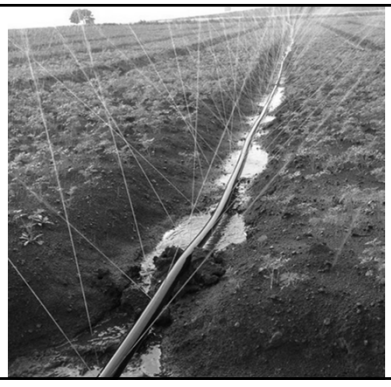


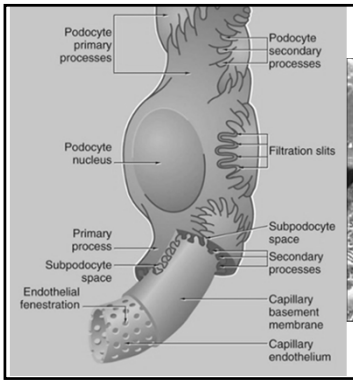
Filtration

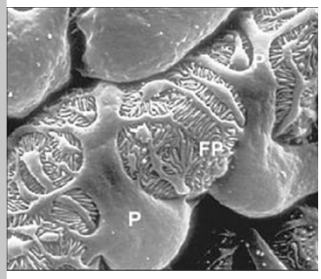


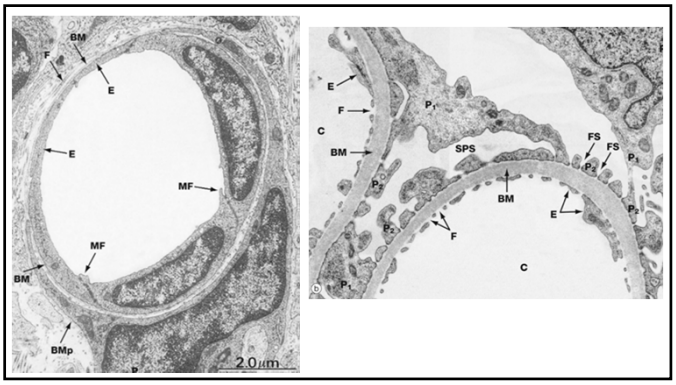
Glomerulus - special type of capillaries = fenestrated capillaries

- Endothelial lining - small openings that water and solutes can pass through
- Pressure in glomerular capillaries greater than in other capillaries→ pushes the water and solutes out



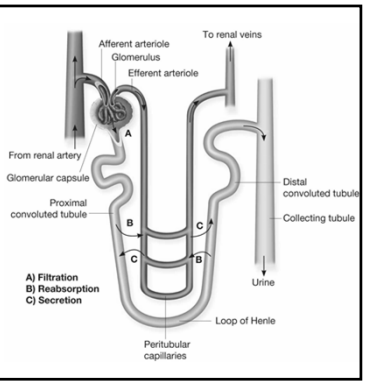






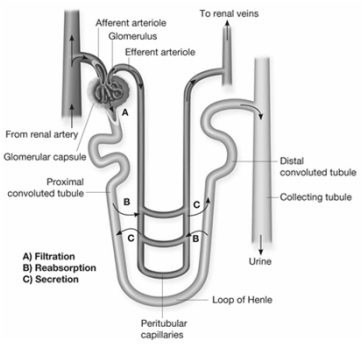
Reabsorption

- Process of moving solutes and fluid from the tubules back into the blood

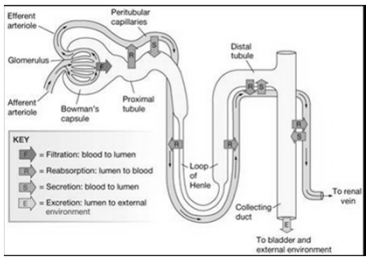


Secretion

- Process of transferring substances from the peritubular capillaries back to tubules (opposite of reabsorption)



Making of the urine



Filtration- movement of fluid + solutes from blood into Bowman's capsule, to tubules

Reabsorption- movement back into the blood

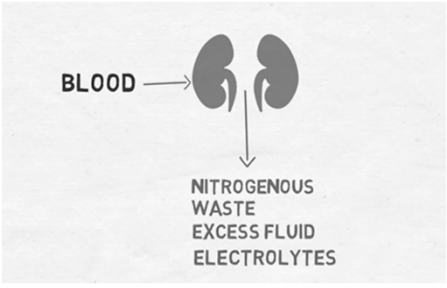
Secretion- transfer from peritubular capillaries into the tubules

Excretion- end result of urine

Amount **excreted** = amount **filtered** – amount **reabsorbed** + amount **secreted**

Kidneys and waste removal

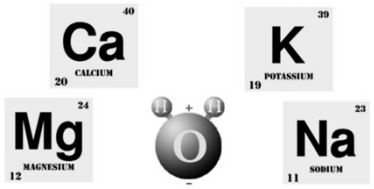
The function that we generally think of



Kidneys and water and electrolyte balance

Lab results may vary depending on cause of AKI

- Usually hyperkalemia



Kidneys and acid-base balance

Henderson-Hasselbach Equation

$$pH = pK + \log \frac{HCO_3^-}{H_2CO_3}$$

← think kidney

You want this ratio to be 20:1

← think lungs

Generally see a metabolic acidosis in AKI

$$pH = 6.1 + \log \frac{HCO_3^-}{H_2CO_3}$$

pKa of H_2CO_3 = 6.1

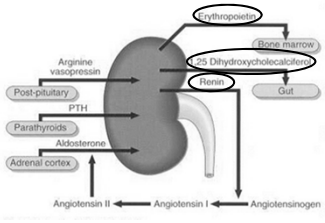
Kidneys and hormones

Produce

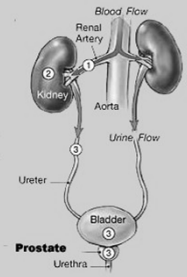
- **Renin** – part of renin-angiotensin-aldosterone system that regulates blood pressure and fluid balance
- **Erythropoietin**- promotes RBC production

Activate

- **Vitamin D**



Causes of Acute Renal Failure



① Prerenal
Sudden and severe drop in blood pressure (shock) or interruption of blood flow to the kidneys from severe injury or illness

② Intrarenal
Direct damage to the kidneys by inflammation, toxins, drugs, infection, or reduced blood supply

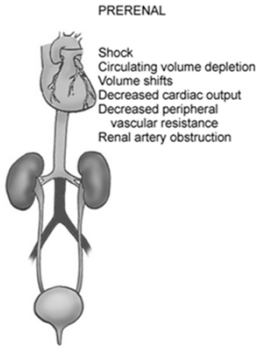
③ Postrenal
Sudden obstruction of urine flow due to enlarged prostate, kidney stones, bladder tumor, or injury

Most common!!!

Prerenal AKI

Results from **hypoperfusion** of kidney

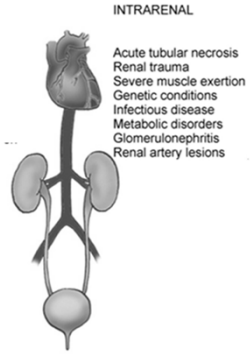
- ***Intravascular volume depletion***
  (dehydration, hemorrhage, leaky vessels as in sepsis)
- ***Decreased cardiac output***
  (CHF, infarct)
- ***Systemic vasodilation***
  (anaphylactic shock, sepsis)



Renal (Intrarenal) AKI

Results from direct damage to the kidney (e.g., nephrotoxic drugs, contrast dyes)

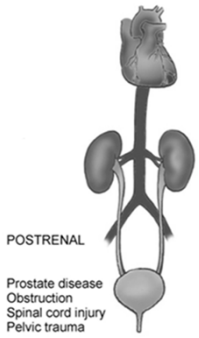
- ***Acute glomerulonephritis***
- ***Acute tubular necrosis***
- ***Acute interstitial nephritis***



Postrenal AKI

Results from **damage or obstruction 'past' the kidneys**

- ***Stones*** in ureter, bladder
- ***Tumors***
- ***Spinal cord injury***



Laboratory findings in Acute Kidney Injury (AKI)

Test	Pre renal	Intrinsic renal	Post renal
BUN/Cr	>20:1	<20:1	10-20:1
Urine specific gravity	>1.020	Variable	>1.010 early, <1.010 late
Uosm (mOsm/kg)	>500	<350	>400 early, ~300 late
U_{Na} (mEq/L)	<20	>40	<20 early, >40 late
FE_{Na} (%)	<1	>1	<1 early, >3 late
UCr/PCr ratio	≥40	≤20	>40 early, ≤20 late
Urine microscopy	Transparent hyaline cast	Granular cast, epithelial cast	Normal or red cells, white cells, crystals

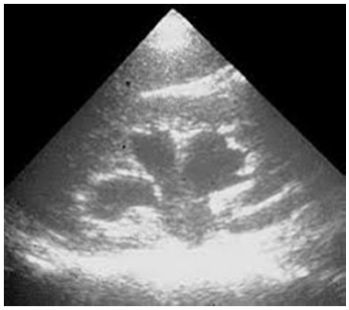
Findings helpful, but there are limitations with all of these, particularly with regard to timing.

Not useful as predictors.

Etiology	Prerenal Azotemia Poor renal perfusion	Postrenal Azotemia Obstruction of the urinary tract	Intrinsic Renal Disease Acute Tubular Necrosis (Oliguric or Polyuric) Ischemia, nephrotoxins	 Acute Glomerulonephritis Immune complex-mediated, pauci-immune, anti-GBM related	 Acute Interstitial Nephritis Allergic reaction; drug reaction; infection, collagen vascular disease
Serum BUN:Cr ratio	> 20:1	> 20:1	< 20:1	> 20:1	< 20:1
Urinary indices					
U_{Na} (mEq/L)	< 20	Variable	> 20	< 20	Variable
FE_{Na} (%)	< 1	Variable	> 1 (when oliguric)	< 1	< 1; > 1
Urine osmolality (mosm/kg)	> 500	< 400	250–300	Variable	Variable
Urinary sediment	Benign or hyaline casts	Normal or red cells, white cells, or crystals	Granular (muddy brown) casts, renal tubular casts	Red cells, dysmorphic red cells and red cell casts	White cells, white cell casts, with or without eosinophils

BUN:Cr, blood urea nitrogen:creatinine ratio; FE_{Na}, fractional excretion of sodium; U_{Na}, urinary concentration of sodium.

Clinicians also use ultrasound or other imaging techniques



Kidney of a Saints fan

So why is this personal?

- My cousin's daughter Kasi
- Ate Chinese buffet at the mall (not in Louisiana)
- Got food poisoning
- Ended up in the hospital

Disclaimer: This is not a full case study. Information was gathered from text messages, and Facebook posts- there are some gaps!

Kasi's progression

	11/13/17	11/15/17	11/16/17	11/18/18	11/20/17	11/27/17
Chem						
BUN (7-20 mg/dL)	16.0	21.0 ↑	??	??	14.0	21.0 ↑
SCr (0.6-1.2 mg/dL)	1.78 ↑	1.90 ↑	??	??	1.37 ↑	1.05
Heme						
WBC (4-10 K/mm^3)	12.3 ↑	11.5 ↑	??	10.5 ↑	12.2 ↑	6.0
RBC (3.80-4.80 M/mm^3)	3.09 ↓	**2.40 ↓**	??	**2.50 ↓**	2.86 ↓	3.14 ↓
Hgb (12.0-15.0 g/dL)	9.8 ↓	**7.7 ↓**	??	**7.9 ↓**	9.1 ↓	10.1 ↓
Hct (36.0-46.0 %)	27.5 ↓	21.5 ↓	??	22.7 ↓	28.0 ↓	31.0 ↓
Plt (150-400 K/mm^3)	40 ↓	**16 ↓**	??	77 ↓	262	440
		Rec'd RBCs + plts.	Felt better; ate ribs		Went home 11/19	

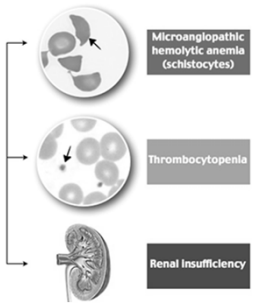
Campylobacter jejuni

- Common cause of food poisoning (usually isolated events, not outbreaks)
- Sources- undercooked **poultry** or beef, unpasteurized milk, contaminated water
- Symptoms- diarrhea (may be bloody), fever, vomiting

So why did she need to receive blood and platelets?

Hemolytic uremic syndrome

- Often associated with Shiga-like toxin-producing E. coli (but sometimes Campylobacter jejuni)
- Characterized by acute renal failure, microangiopathic hemolytic anemia, thrombocytopenia
- **Most common cause of acute kidney injury in children**

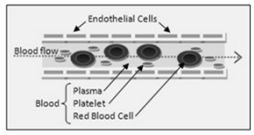


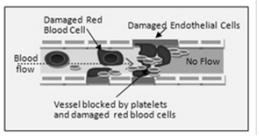
CDC reports as of 6/1/18

- 197 people infected with outbreak strain of *E. coli* O157:H7 (1 in Louisiana)
- 26 developed HUS
- 5 died

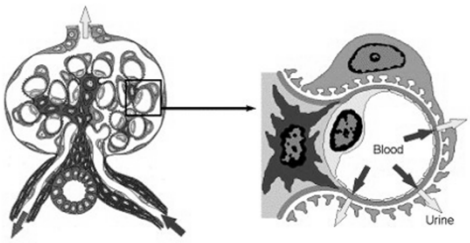
Hemolytic uremic syndrome

- Primary site of damage - vascular endothelial cells
- Micro clots form in vessels, particularly in kidney → blockages, thrombocytopenia, hemolysis





Glomerular Capillaries

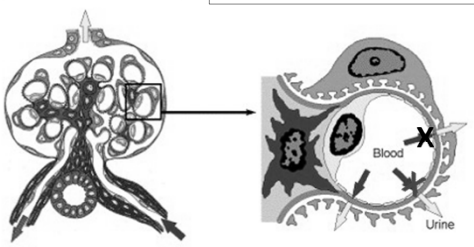


Drawing of a cross section of a glomerulus with arrows showing the flow of blood (red) and urine

Drawing of a cross section of one very small blood vessel called a capillary in a glomerulus showing the filtration of blood (red) into urine (yellow)

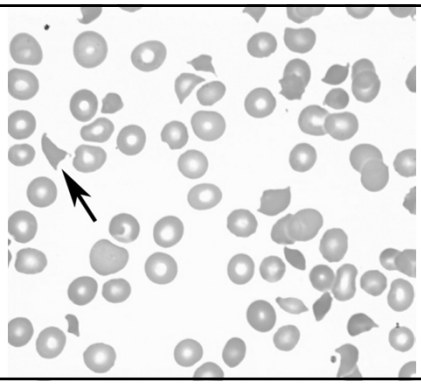
Glomerular Capillaries

HUS- clots block filtration



Drawing of a cross section of a glomerulus with arrows showing the flow of blood (red) and urine

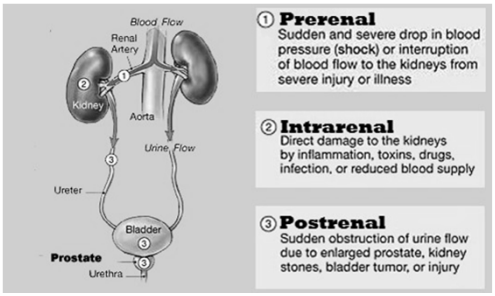
Drawing of a cross section of one very small blood vessel called a capillary in a glomerulus showing the filtration of blood (red) into urine (yellow)

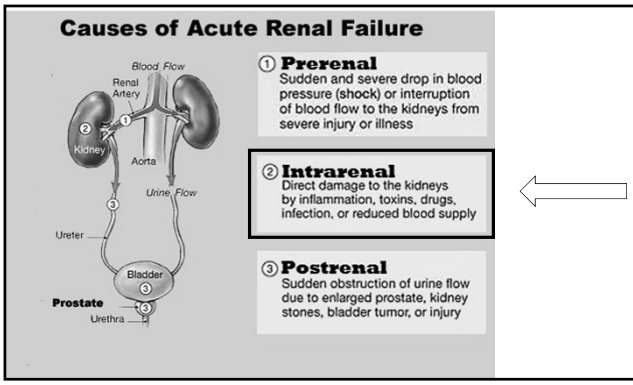


Kasi's message

Love you!!! Thank you!!! That's exciting! Tell people to stay away from chinese buffets and make sure their chicken is cooked lol
Happy Easter!!

Was Kasi's AKI Prerenal, Renal, or Postrenal?



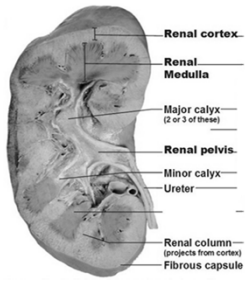


Case 1

- 2 year old girl
- Acute onset of anuria; no urine obtained via bladder catheterization
- Serum creatinine 6.8 mg/dL
- Metabolic acidosis (pH 7.2, HCO3 7.7 mEq/L)
- Hyperkalemia

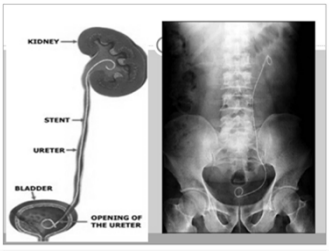
Case 1

- No recent diarrhea, infection, or cardiac problems
- No history of nephrotoxic drugs or chemical ingestion
- Ultrasound and x-ray confirmed - 29 mm stone in right renal pelvis; 27 mm stone in left ureter



Case 1

- Stents placed; re-established urine flow
- Serum creatinine normal by 48 hours post stent placement
- 24 hour urine- hyperoxaluria and cystinuria
- Laparoscopic stone removal performed

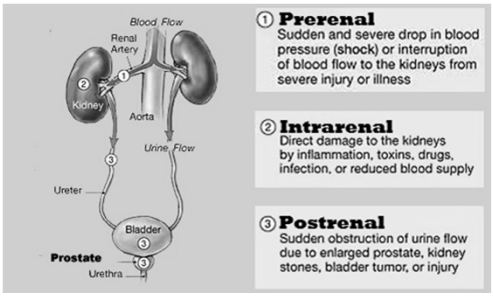


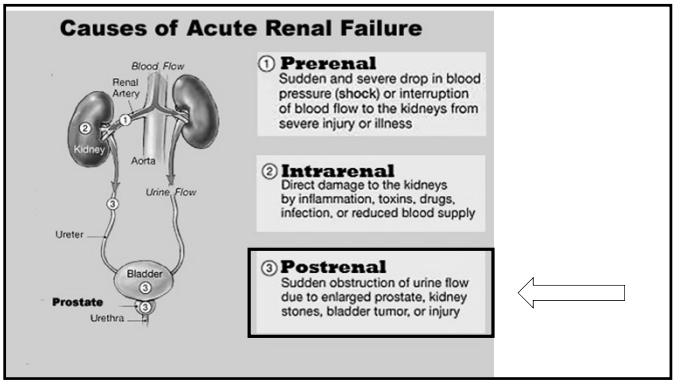
Case 1

- Cystine stones
- Prescribed Tiopronin to control cysteine precipitation and excretion

Personal- kidney stones

Was this Prerenal, Renal, or Postrenal?

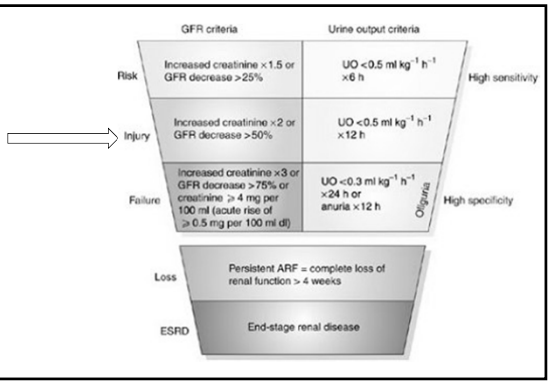


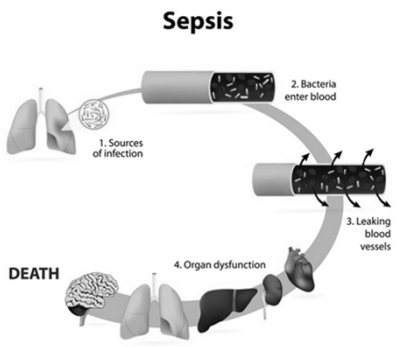


Case 2

A 57 year old female with a history of Type II diabetes and hypertension was admitted to ICU with urinary tract infection-related **sepsis**. On day 3 in the ICU, her lab results indicate AKI. Ultrasound indicates no urinary tract obstruction. Electrolytes are normal, and there is no history of nephrotoxic drugs.

	Day 1	Day 3	
Serum creatinine	1.0 mg/dL	2.1 mg/dL	↑ x 2
Urine output	1.4 mL/kg/hr	0.3 mL/kg/hr	< 0.5





Sepsis double whammy

- Vasodilation
- Increased permeability

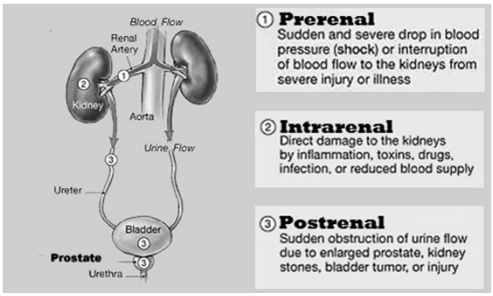
Decreased effective volume

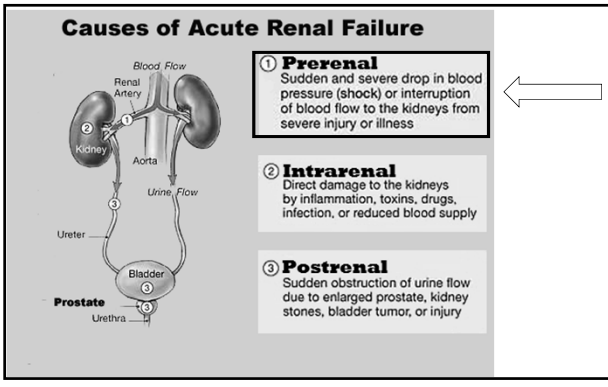
Hypoperfusion

Sepsis

- Most common cause of acute kidney injury in the ICU

Was this Prerenal, Renal, or Postrenal?





Case 3

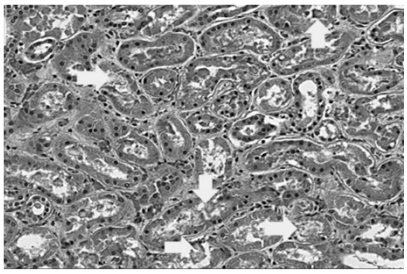
An 18 year year old male in the ER describes having nausea, vomiting, and abdominal pain for 2 days. Lab work and ultrasound reveals:

Metabolic acidosis	
Serum creatinine	2.4 mg/dL (0.6-1.2 mg/dL)
BUN	19 mg/dL (7-20 mg/dL)
Urinalysis	Hematuria with rare, amorphous crystals
Ultrasound	Enlarged kidneys

Case 3

An 18 year year old male in the ER describes having nausea, vomiting, and abdominal pain for 2 days. **Patient's condition grew progressively worse, and a biopsy was performed.**

Metabolic acidosis	
Serum creatinine	2.4 mg/dL (0.6-1.2 mg/dL)
BUN	19 mg/dL (7-20 mg/dL)
Urinalysis	Hematuria with rare, amorphous crystals
Ultrasound	Enlarged kidneys
Renal biopsy	**Acute tubular necrosis with calcium oxalate crystals**



Case 3

Diagnosis = ethylene glycol poisoning

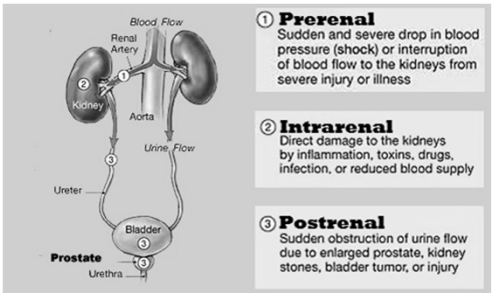
(Peak creatinine level = 11.9 mg/dL on day 5 of hospital stay)

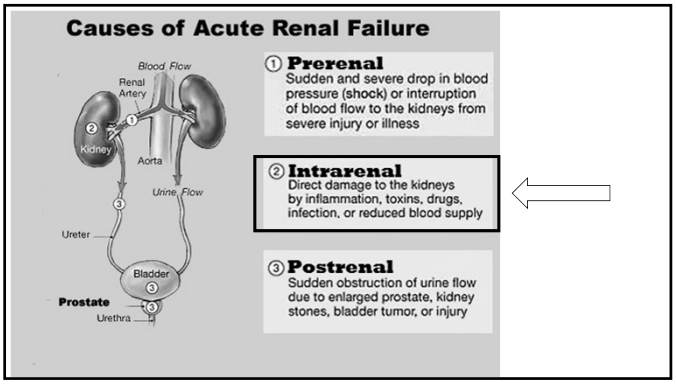
Treated with hemodialysis for 3 weeks

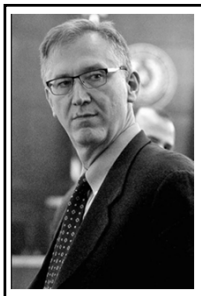
⇩

No evidence of renal dysfunction

Was this Prerenal, Renal, or Postrenal?







He now has 40% of his kidney function.

Texas oncologist poisoned by his mistress.

She put ethylene glycol in his coffee.

She got 10 years in prison.

Again, it's personal

Kenneth McMartin, PhD

- Friend and committee member
- Expert witness in case
- Studies antidotes to alcohol poisonings (methanol, ethylene glycol)- pretty famous in nerdy circles!

Case 4

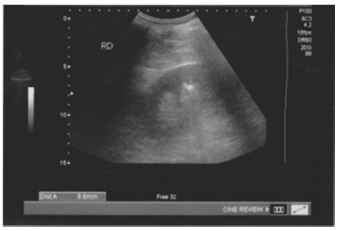
55 year old man - previously diagnosed nonsymptomatic kidney stones travels to Peru. He takes 2 doses of acetazolamide (ACZ) as prophylaxis to prevent acute mountain sickness prior to ascending to Ancash, Peru (4500 meters above sea level). He then took 3 more doses (at 12 hour intervals) at peak ascent. Patient had done so previously without incident. He developed headache, nausea, bilateral back pain, and oliguria.

Metabolic acidosis

Serum creatinine	9.5 mg/dL (0.6-1.2 mg/dL)
BUN	94 mg/dL (7-20 mg/dL)

Case 4

Ultrasound revealed small stones that did not appear to be causing blockages or other significant damage.

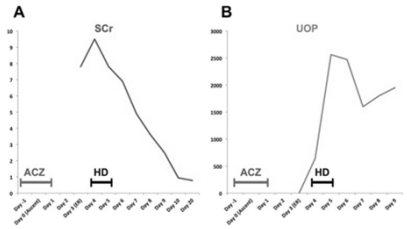


Case 4

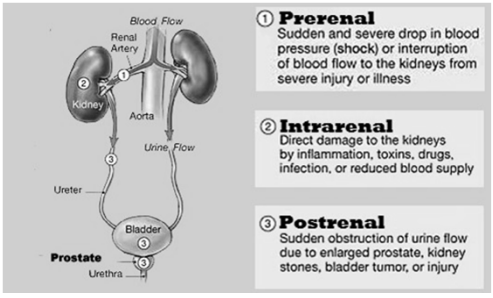
- Case complicated due to preexisting kidney stones
- ACZ - drug known to cause AKI.
- Kidney biopsy not performed; kidney stones not analyzed

Case 4

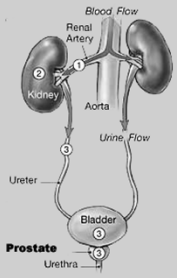
Patient was treated with hemodialysis and demonstrated marked improvement.



Was this Prerenal, Renal, or Postrenal?



Causes of Acute Renal Failure



① **Prerenal**
Sudden and severe drop in blood pressure (shock) or interruption of blood flow to the kidneys from severe injury or illness

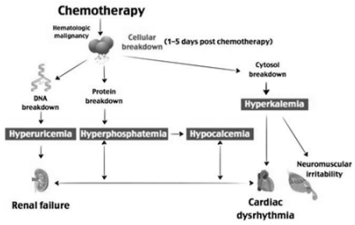
② **Intrarenal**
Direct damage to the kidneys by inflammation, toxins, drugs, infection, or reduced blood supply

③ **Postrenal**
Sudden obstruction of urine flow due to enlarged prostate, kidney stones, bladder tumor, or injury

It was personal to an audience member…

Her father had AML

- Intensive chemotherapy treatment
- Developed life-threatening complication characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and AKI
- Passed away

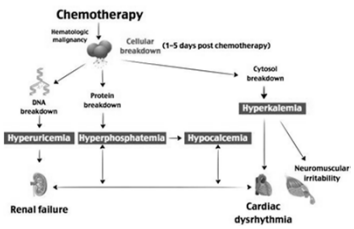


- Greatest risk in hematologic cancers
- May occur in solid tumors or even spontaneously

AKI – primarily due to precipitation of uric acid crystals in the tubules

Cardiac manifestations may lead to sudden death

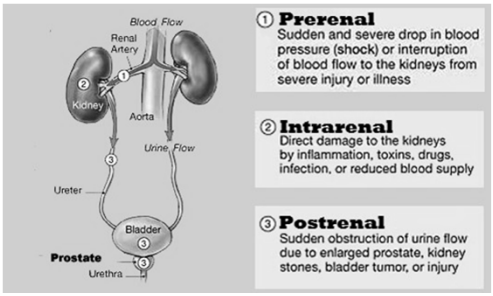
Acute Tumor Lysis Syndrome



Prophylaxis = IV fluids
+
allopurinol (prevents production of uric acid)
+
rasburicase (metabolizes uric acid substance easily excreted)

Monitor labs frequently!

Was this Prerenal, Renal, or Postrenal AKI?



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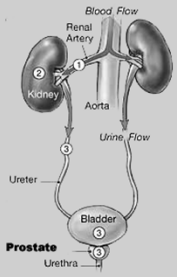

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The need for new testing

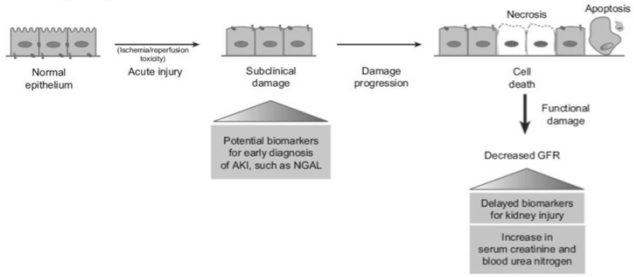
Earlier testing that can ***detect injury*** **-** clinicians can remove or treat the source of injury…

before irreversible damage is done!

Ideal biomarkers

- Noninvasive (blood or urine), easily measured, inexpensive
- Highly sensitive to allow early detection
- Highly specific – upregulated or downregulated in specific disease processes; unaffected by comorbidities
- Levels vary rapidly to reflect disease severity and response to treatment

Novel Biomarkers of Acute Kidney Injury

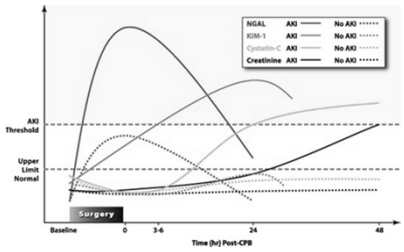


Biomarkers of tomorrow?

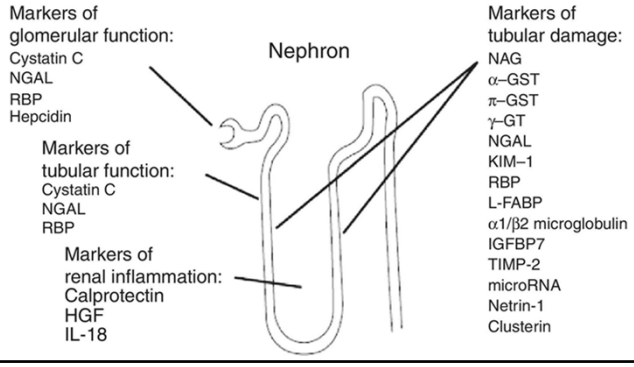
- Neutrophil gelatinase-associated lipocalin (NGAL)
- Interleukin-18 (IL-18)
- Kidney injury molecule 1 (KIM-1)
- Liver-type fatty acid-binding protein (L-FABP)
- Insulin-like growth factor-binding protein 7 (IGFBP7) X tissue inhibitor of metalloproteinases-2 (TIMP-2)
- Calprotectin
- Urinary angiotensinogen
- Cystatin C
- Proenkephalin

Biomarkers under investigation

These are predicted time course changes.



CPB = Cardiopulmonary bypass



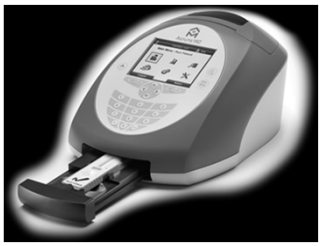
NephroCheck

- 2014- FDA approved
- Evaluates risk of patient developing AKI.
- Intended use- patients with acute CV and/or respiratory compromise (within the past 24 hrs) who are in ICU age 21 or older
- Detects TIMP-2 and IGFBP-7 in **urine**
- Results in 20 minutes
- Sandwich immunoassay (Lateral flow)
- Use in clinical laboratory; ***NOT*** a POCT

Nephro Check

Theoretically allows earlier intervention to prevent damage

- Sensitivity = 92% and 76% (2 studies)
- Specificity = 46% and 51% (2 studies)



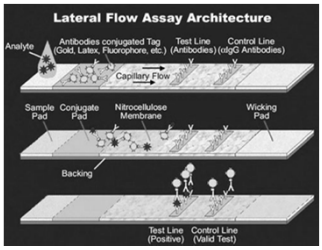
Result is AKI risk score.

NEPHROCHECK® Test Result (AKIRISK® Score) = $\frac{([TIMP\text{-}2]*[IGFBP\text{-}7])}{1000}$ (units = $(ng/ml)^2/1000$)

AKI RISK score > 0.3 → IDs patients who will likely develop moderate to severe AKI within 12 hours

Lateral flow immunoassay

Used in many POC tests (e.g., Home pregnancy tests)



sphingotest penKid

- Utilizes serum or plasma
- Immunoassay
- Measures proenkephalin, a stable surrogate marker for enkephalins (unstable)
- Enkephalins highly expressed in kidney; ↑in AKI
- Not FDA approved yet

sphingotec Announces Collaboration with Mayo Clinic for Evaluation and Use of Biomarkers to Improve Diagnosis of Certain Diseases, Including Kidney Disease, Breast Cancer, Sepsis, and Cardiovascular Disease

sphingotec

To assess kidney function in all clinical settings

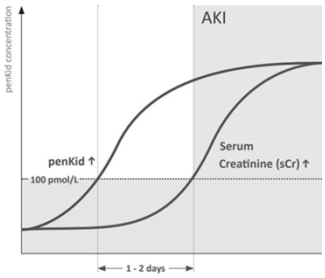
The level of penKid rises up to two days before serum creatinine (sCr) and can be used to predict, diagnose and monitor Acute Kidney Injury in critically ill patients, e.g. in

- Sepsis / Septic Shock
- Acute Heart Failure
- Acute Myocardial Infarction

penKid supports physicians in vital medical decisions, such as

- the use of nephrotoxic drugs
- renal replacement strategies

Prediction and diagnosis

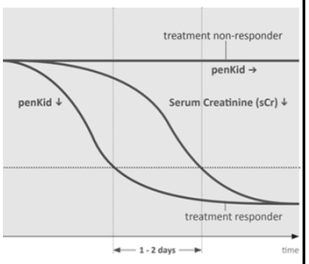


To improve AKI management and hospital outcomes

The level of penKid also declines up to two days before creatinine, making it possible to detect earlier that the medical treatment is succesfull and thereby supporting patient management and discharge decision.

In contrast to other kidney markers, penKid correlates with the severity of AKI, and is not influenced by systemic inflammation or comorbidities.

Monitoring



In conclusion

- At least in critical care- shifting from reactive to preventive medicine
- Early AKI markers necessary
- Only 1 test FDA approved to date; others in development
- Clinicians may be slow to implement