Stanford HEALTH CARE

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Acute Tubular Necrosis

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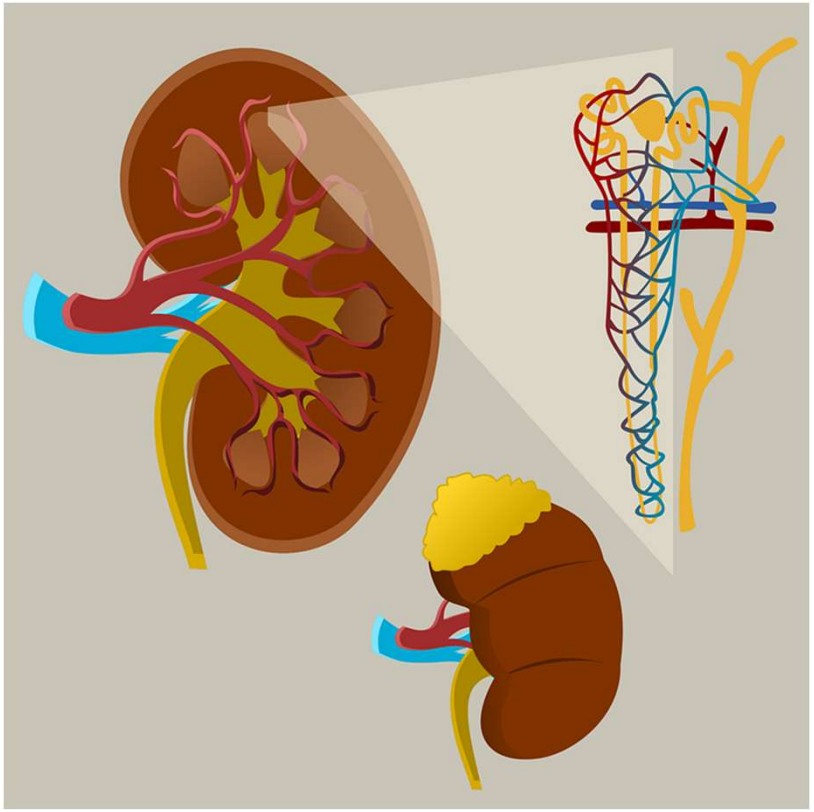


Disclosures:

I have no relevant relationships with ineligible companies to disclose within the past 24 months.

Objectives

- Why do we care about ATN
- Understand that prerenal and ATN are on a continuum
- Identify the major causes of ATN
- Distinguishing between prerenal and ATN with objective data
- Treatment of ATN and when dialysis is indicated

Question:

- 70 year old gentleman with normal renal function at baseline (Cr 1.0) presents to the hospital with Cr at 5.8.
- Given what you know about the most common cause of AKI in the inpatient setting, what is the most likely cause of his AKI without more information?

A) Prerenal

B) Acute Tubular Necrosis (ATN)

C) Urinary tract obstruction

D) Glomerulonephritis or vasculitis

E) Acute interstitial nephritis

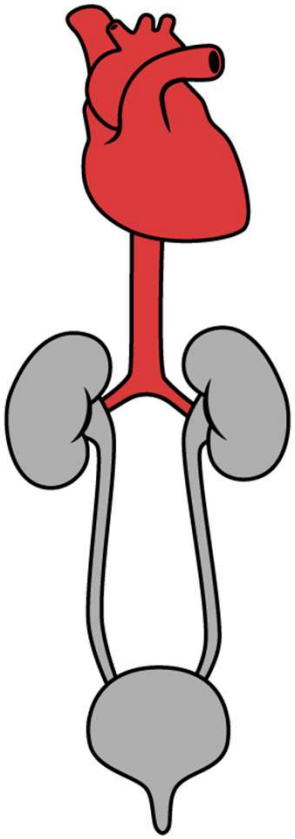
F) Atheroembolic disease

Why care about ATN?

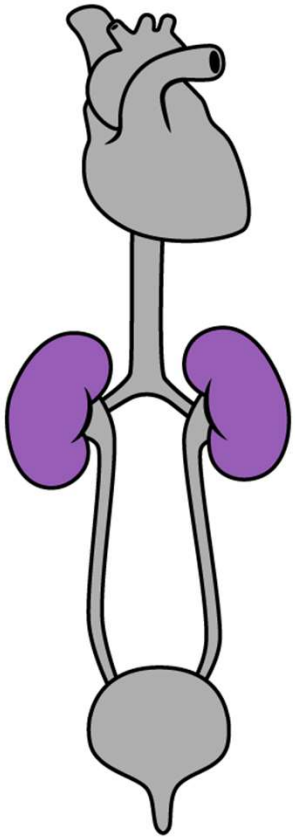
- Approx 65-75% of cases of AKI in the hospital are either pre-renal or ATN
- **Frequent causes of AKI**
- **ATN- 45%**
- **Prerenal- 21%**
- **Acute on chronic renal failure- 13% (most due to ATN or prerenal disease)**
- Urinary tract obstruction- 10%
- Glomerulonephritis or vasculitis- 4%
- Acute interstitial nephritis- 2%
- Atheroemboli- 1%

Approach to AKI, 3 major categories:

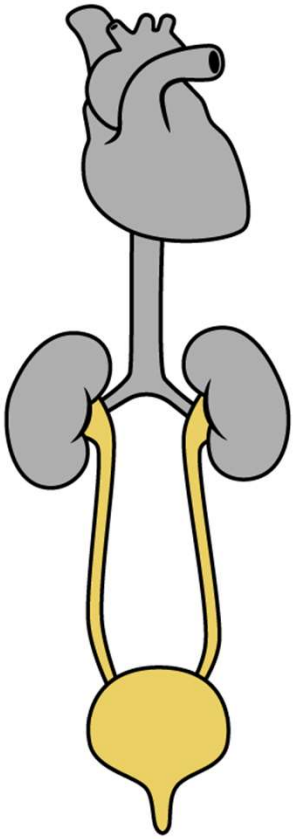
PRERENAL



INTRARENAL



POSTRENAL

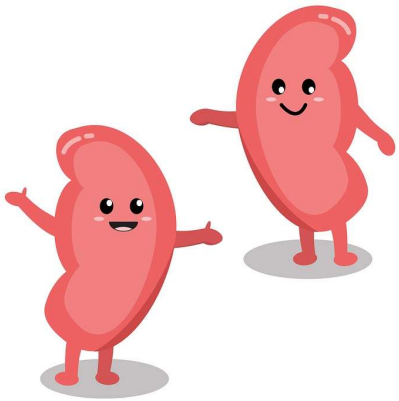


What is the difference between prerenal and ATN?

- Both with decrease in glomerular filtration due to renal hypoperfusion

- **Prerenal:**

-Integrity of the renal parenchyma is **not** disrupted. Without glomeruli or tubular injury



- **ATN (Part of intrinsic/intrarenal) AKI:**

-WITH direct tubular injury

QUESTION:

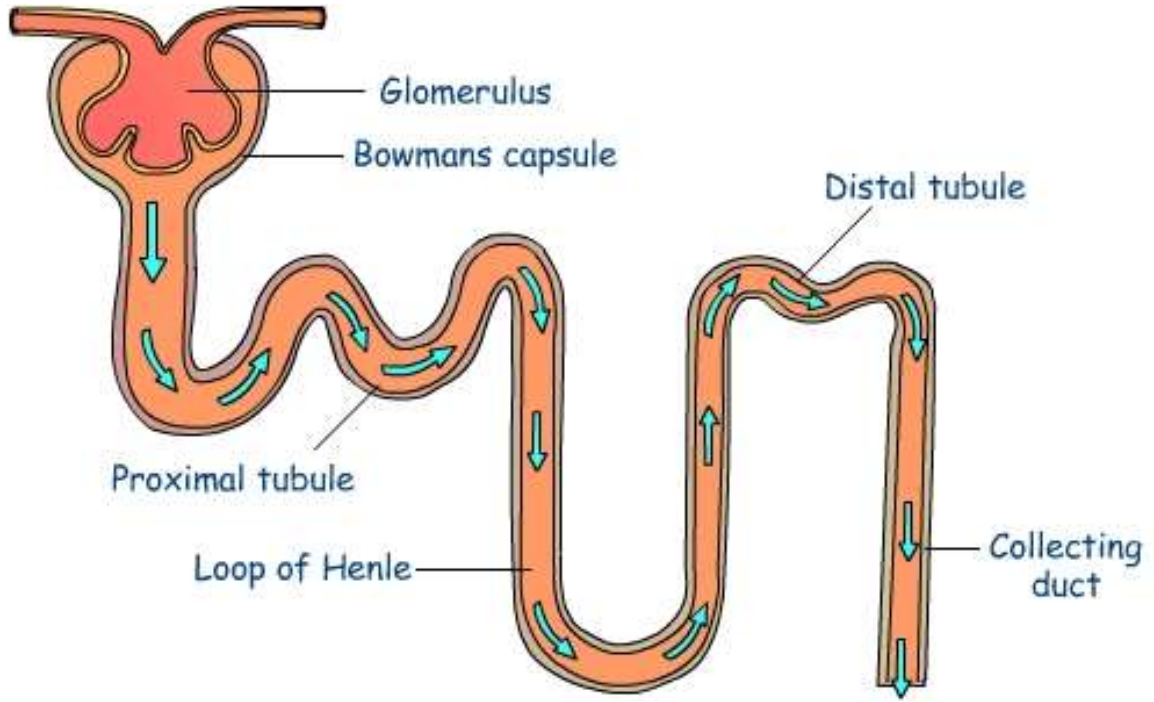
- Can someone have both pre-renal and ATN at the same time?

A) Yes

B) No

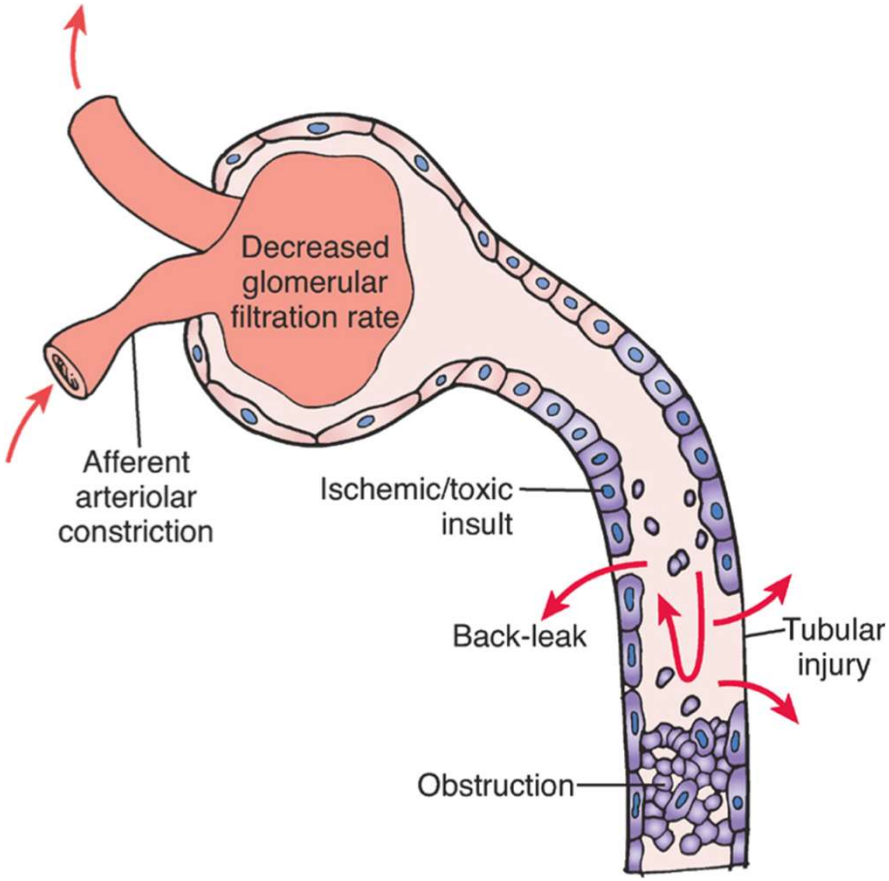
- Yes!

- ATN is not “all or none” phenomenon and many nephrons of the kidney can endure in a prerenal functional state whereas others are injured.

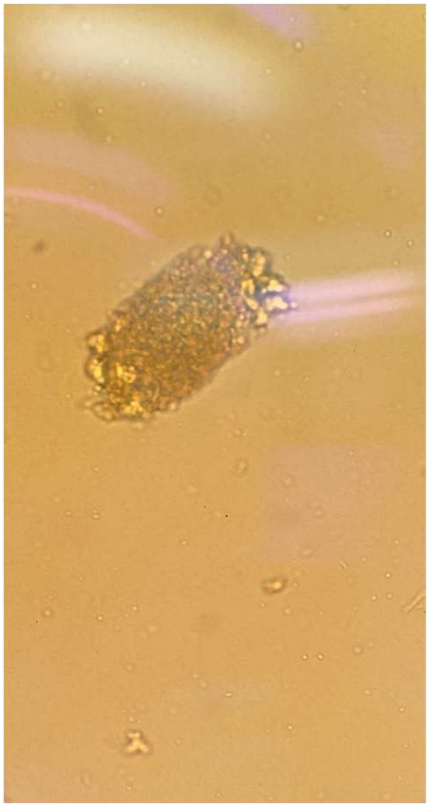


Acute Tubular Necrosis (ATN) definition

- Sudden decline in kidney function resulting from ischemic or toxic-related damage to the renal tubular epithelium
- Histologic Changes: Necrosis, with denuding of the epithelium and occlusion of the tubular lumen by casts and cell debris. Not universal.



Muddy Brown Cast

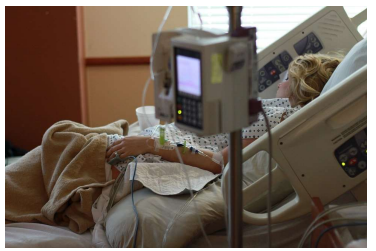


Acute Tubular Necrosis (ATN)

3 major causes of ATN:

- **Ischemic**- Any process associated with prerenal but severe.

- **Septic**- Decreased renal perfusion from systemic vasodilation. Endotoxins and inflammatory cytokine release with activation of neutrophils.



- **Nephrotoxic**- Toxins that directly damage renal tubules

Ischemic ATN

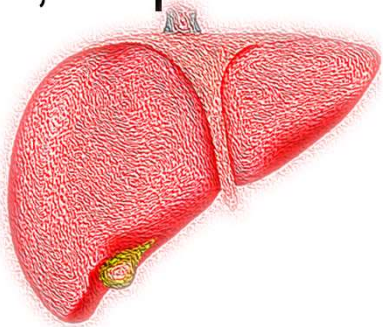
SYSTEMIC

True volume depletion:

- Gastrointestinal fluid loss
- Renal losses
- Skin/respiratory losses
- Acute blood loss/Hemorrhage

Effective circulating volume depletion:

- Edematous stages: Heart failure, Cirrhosis, nephrotic syndrome.



Ischemic ATN

Post-operative patients at increased risk for ATN

<u>3 surgical procedures that has highest risk for ATN</u>

1) Abdominal aortic aneurysm surgery

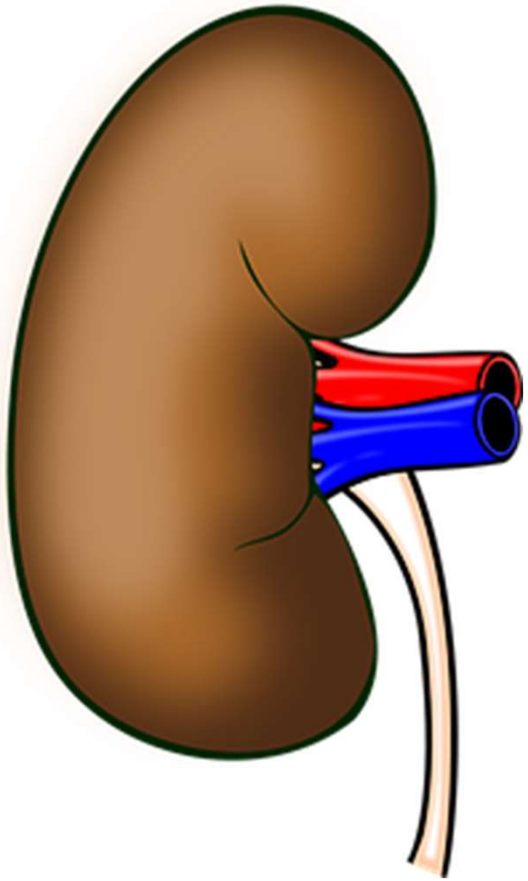
2) Surgery to correct obstructive jaundice

3) Cardiac surgery, particularly coronary artery bypass graft (CABG) with valve surgery.

Ischemic ATN

LOCALIZED TO RENAL VASCULATURE

- Bilateral renal artery stenosis
- Unilateral stenosis in solitary functioning kidney- made worse with impairment of renal autoregulation (ie. ACEI or ARB)



Question

Most causes of ATN are due to one insult:

A) True

B) False

Ischemic ATN

- Nearly two-thirds of patients who develop ATN have been exposed to more than one insult.

Question

Overt hypotension (ie SBP<110mmHg) must be observed for ischemic ATN to happen?

A) True

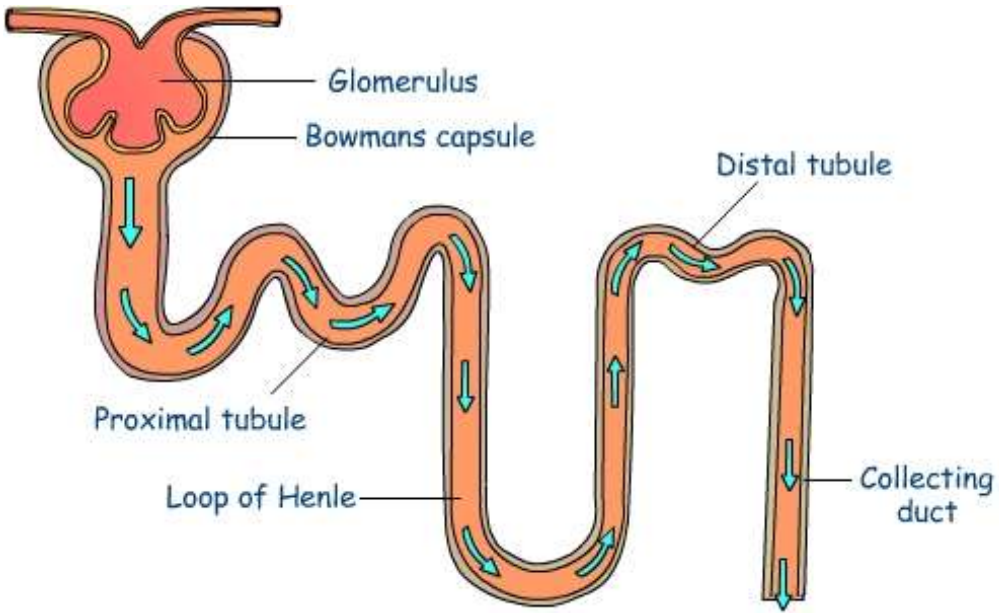
B) False

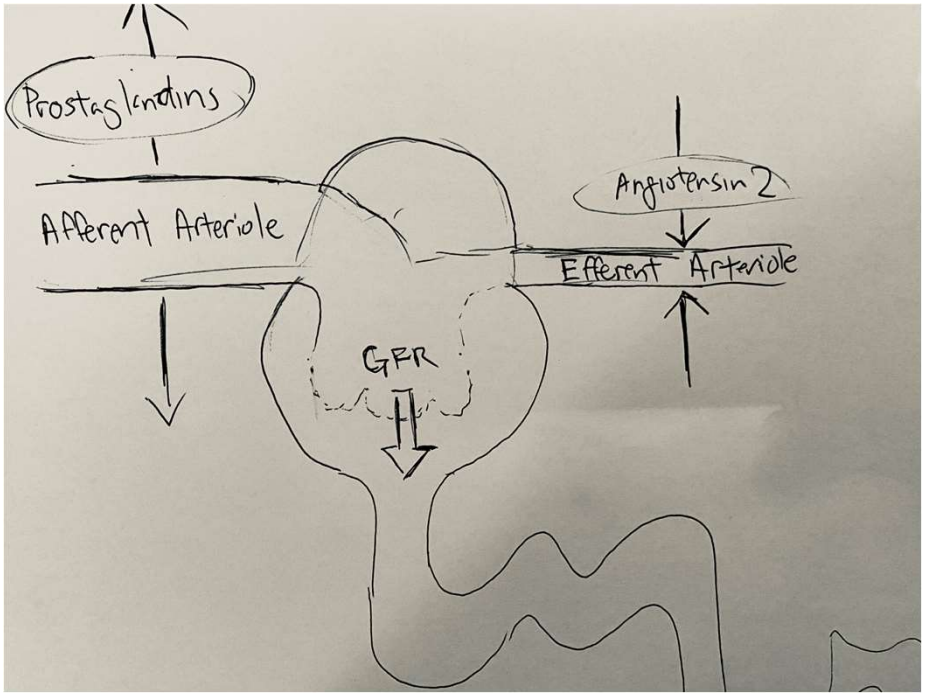
Ischemic ATN

- Ischemic ATN may also occur in the absence of overt hypotension in conditions in which renal autoregulation is impaired.

What is renal autoregulation?

- Changes in the renal microvasculature to maintain stable hemodynamics despite fluctuations in systemic arterial pressures.





Ischemic ATN

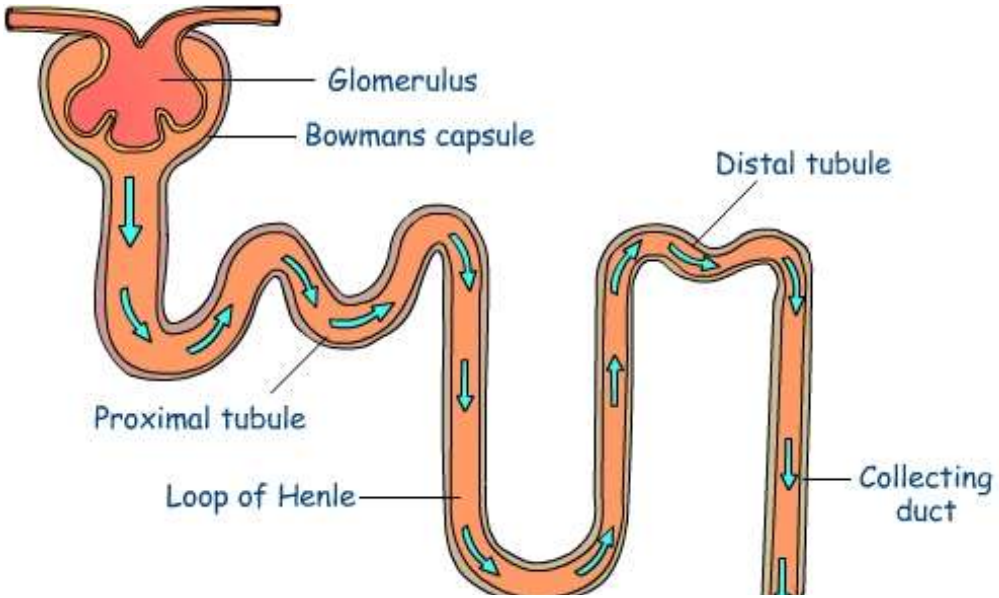
Impaired Renal Autoregulation

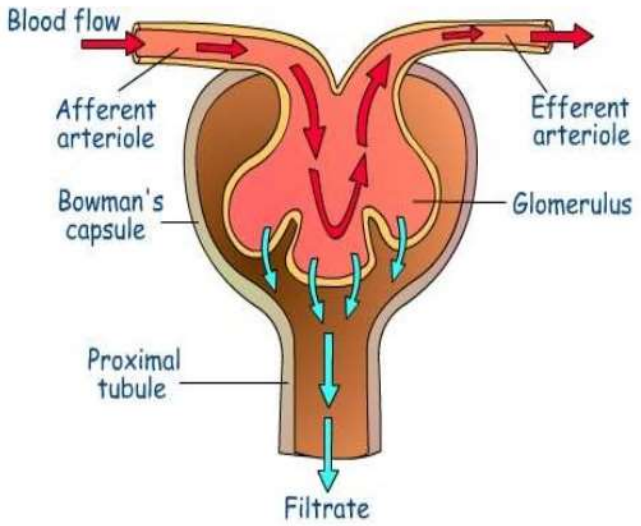
Conditions:

- Chronic kidney disease
- Liver failure
- Heart failure
- Longstanding hypertension

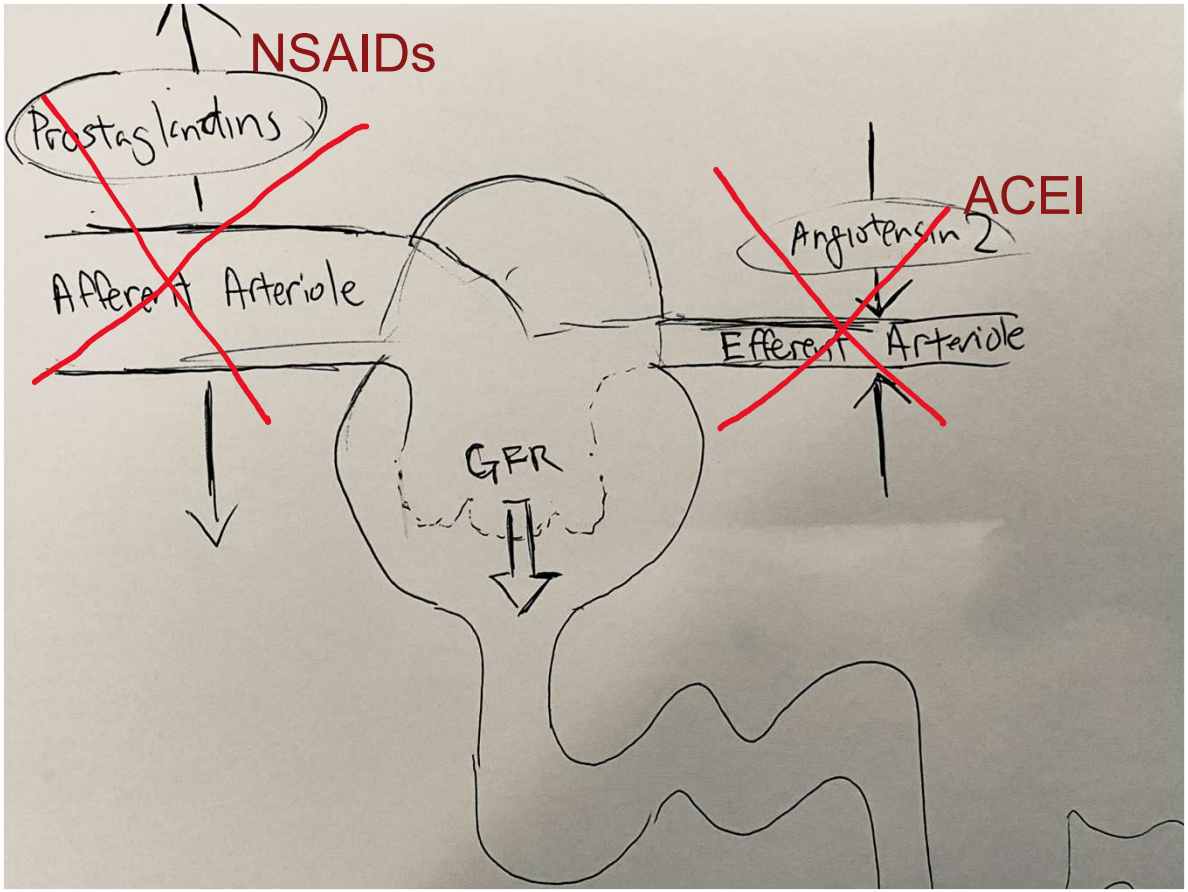
Medications:

- Angiotensin-converting enzyme inhibitors (ACEI)
- Angiotensin receptor blockers (ARBs)
- NSAIDs.





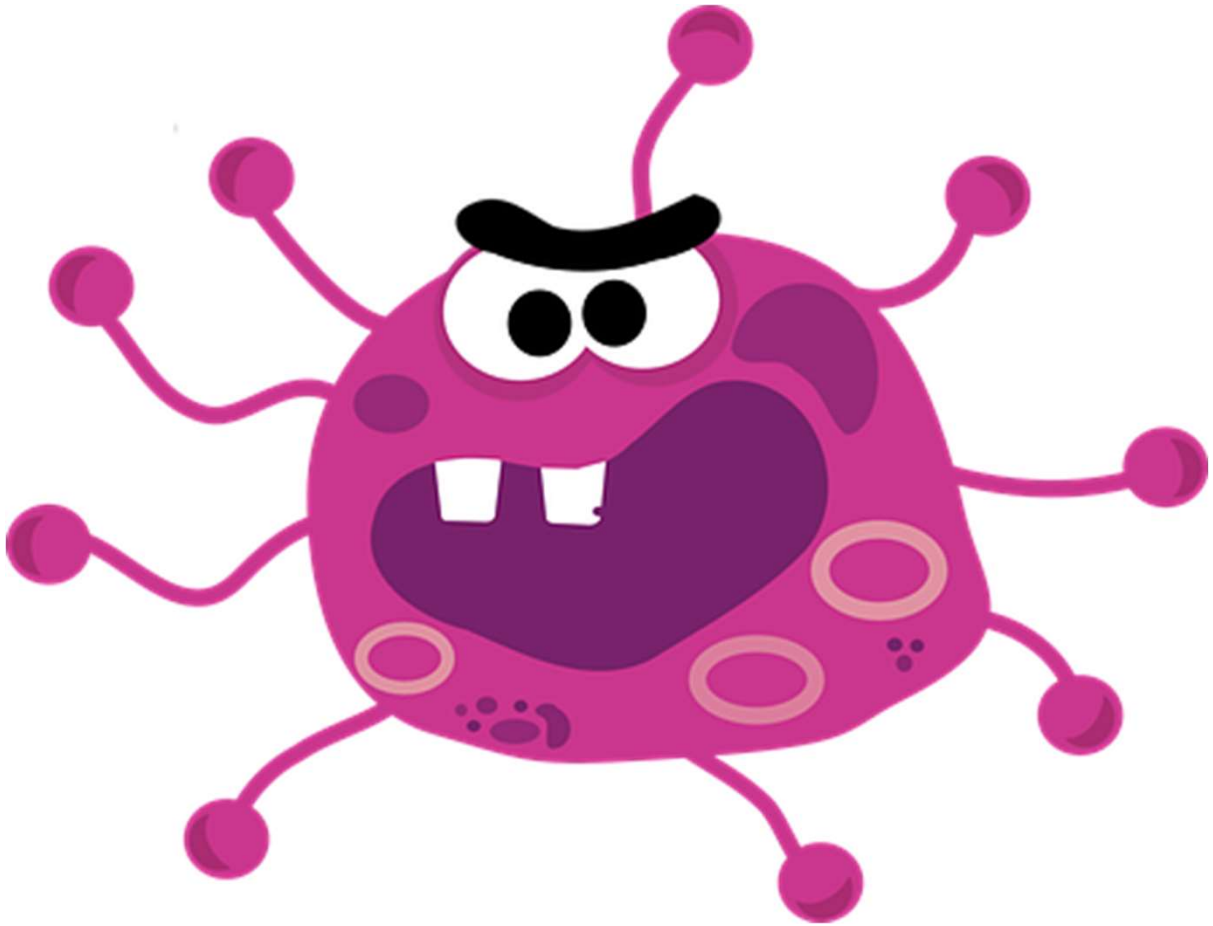
Ischemic ATN



- Decreasing afferent (preglomerular) arterial dilatation
  - ie. NSAIDs or calcineurin inhibitors
- Decreasing efferent (postglomerular) vasoconstriction
  - ie. ACEI or ARB

Septic ATN

- Overt or intermittent endotoxemia may play an important role in AKI
- The release of elastase and oxidants from neutrophils may also contribute to tubular damage in this setting.



Nephrotoxic ATN

- Kidneys are vulnerable to toxicity due to high blood flow, and they are the major elimination/ metabolizing route of many of these elements

- Endogenous Toxins
- Exogenous Toxins

Nephrotoxic ATN: Endogenous Toxins

Rhabdomyolysis- clinical syndrome associated with muscle necrosis and release of intracellular contents into the extracellular space

- Physical Injury- trauma, crush injuries, immobilization
- Muscle-Fiber Exhaustion- Excessive exercise, Seizures, Heat Stroke
- Medications/Drugs- SSRIs, Statins, Fibrates, Amphetamines, Cocaine, Alcohol

- **Toxin: Myoglobin**

(direct tubular toxin)

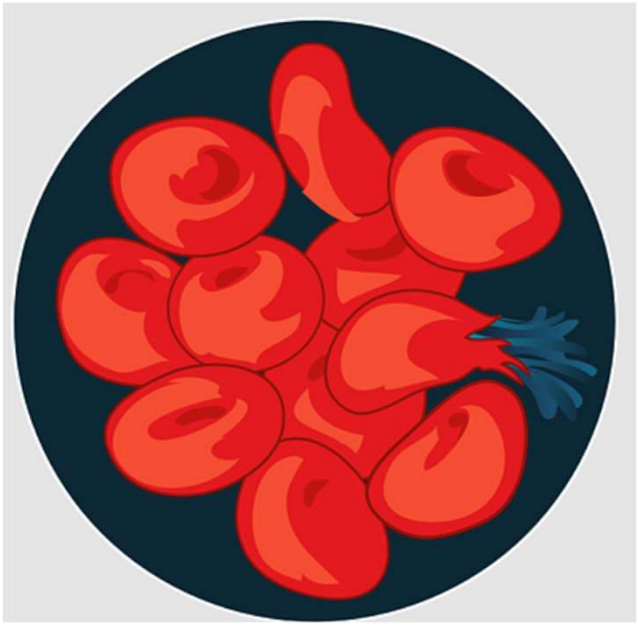
- Blood tests:

Elevated creatine kinase (CK).

Nephrotoxic ATN: Endogenous Toxins

Hemoglobinuria- Free circulating hemoglobin occurs in the setting of intravascular hemolysis

- Mechanical- prosthetic valves, microangiopathic hemolytic anemia, extracorporeal circulation
- Immunologic- transfusion reaction
- Genetic- G6PD deficiency
- Drugs



Toxin: Hemoglobin

Nephrotoxic ATN: Endogenous Toxins

Rhabdo and hemolysis causes:

Pigment nephropathy

UA, MACROSCOPIC		
Specimen	CLEAN CATCH	
Color	Yellow	
Clarity	Hazy	!
Specific Gravity	1.027	
Glucose	Negative	
Ketone	Negative	
Blood	1+	!
pH	5.0	
Protein	Negative	
Nitrite	Negative	
Leuk esterase	Negative	
UA, MICROSCOPIC		
RBC, urine	0-3	
WBC, urine	0-2	
Squamous cells		
Mucous threads	Rare	
Bacteria	No significant ...	
Urine comment	Automated urine...	

DX: UA with significant positivity for heme protein but no RBCs seen on microscopy.

Treatment is similar for both rhabdomyolysis and hemoglobinuria

- Early aggressive fluid repletion is the most important factor.

Nephrotoxic ATN: Endogenous Toxins

Tumor lysis syndrome

- Results from release of a large amount of intracellular contents into the ECF following massive necrosis of tumor cells.
  - Elevated serum potassium, phosphate and uric acid
- **AKI due to uric acid or calcium-phosphate crystal precipitation within the renal tubules**

RX: IVF to induce high urine flows

- Allopurinol inhibit formation of uric acid
- Rasburicase increase breakdown of uric acid to allantonin
- Sodium bicarb for uric acid level >12 mg/dl

Nephrotoxic ATN: Endogenous Toxins

Others

Multiple Myeloma- Serum free light chains

Oxalate

Genetic, gastric bypass surgery and other causes of malabsorption (pancreatitis, Crohn's disease) which causes increased gut absorption of oxalate from dietary sources

Nephrotoxic ATN: Exogenous Toxins

Antibiotics

Aminoglycosides- low therapeutic dose and single daily dose

Amphotericin B

Antiviral agents- acyclovir, foscarnet

Vancomycin

Chemotherapy- Cisplatin, Ifosfamide, Methotrexate

Calcineurin Inhibitors- Cyclosporin, Tacrolimus

MISC: Radiocontrast media, NSAIDs, Oral phosphate bowel preparations

Nephrotoxic ATN: Exogenous Toxins

IV Contrast

- Big fus about nothing?

Question: What is the most likely cause of his AKI?

- 70 year old gentleman with h/o **CKD (Cr baseline ~2),** CHF, IDDM2, HTN, HLD who presented with syncopal event on toilet and **melena.**
- On presentation **Cr was 5.8.** BUN 132. **Hgb 6.8, down from 8.9, 2 weeks ago**. At home he was also **on Lisinopril and Lasix for CHF**. **UA bland without hematuria, proteinuria or pyuria. Renal ultrasound was without hydronephrosis.**
- Vitals: Afebrile. **BP 100s/60s. HR 120s.** RR 25. RA
- Physical exam: NAD. **EENT: Dry mucous membranes. Cardiac: Sinus Tachycardia**. No m/r/g. Pulm: CTAB. Abdomen: BS active. Soft. Non-tender**. Extremities: Cool, no edema. Skin: Decreased skin turgor.**

A) Prerenal

B) Acute Tubular Necrosis (ATN)

C) Urinary tract obstruction

D) Glomerulonephritis or vasculitis

E) Acute interstitial nephritis

F) Atheroemboli

- **Prerenal**
- **Acute Tubular Necrosis (ATN)**
- Urinary tract obstruction- No hydro on renal ultrasound
- Glomerulonephritis or vasculitis- Unlikely without hematuria and proteinuria
- Acute interstitial nephritis- Abx can cause but less likely without pyuria.
- Atheroemboli- usually common after cardiac procedures

Question

What is the gold standard for distinction between pre-renal disease secondary to volume depletion and ischemic or nephrotoxic ATN?

A) FENa or FEUrea

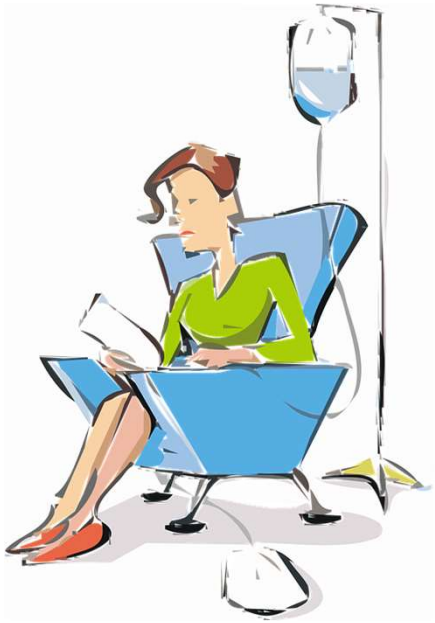
B) BUN/Cr ratio

C) Fluid repletion

D) UA or urine microscopy

Prerenal vs ATN: Response to fluid repletion

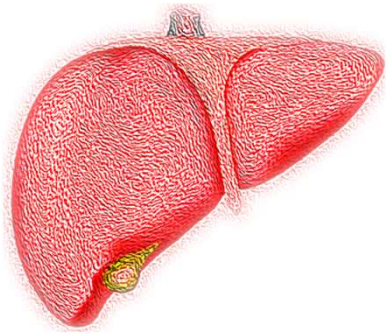
- **Gold standard for distinction between pre-renal disease secondary to volume depletion and ischemic or nephrotoxic ATN is response to fluid repletion**



- Return of serum Cr to previous baseline within 24-72 hrs is considered to represent correction of prerenal, whereas persistent AKI is ATN

Prerenal vs ATN- diagnostics

- Response to fluid repletion in patients who have evidence of volume depletion
  - Caution: Heart failure and cirrhosis

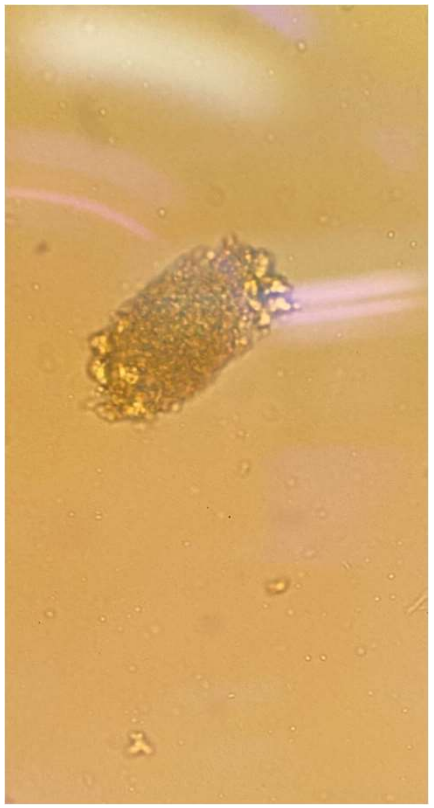


- Urine microscopy
- Fractional excretion of sodium (FENa) or fractional excretion of urea (FEUrea) in patients with diuretics.
- Other parameters: BUN/Serum Cr ratio; rate of rise of serum Cr concentration, urine osmolality and urine volume

Prerenal vs ATN: Urine microscopy

- Prerenal: Normal or near normal. Hyaline casts may be seen
- ATN: Muddy brown granular casts, renal tubular epithelial cells.

Muddy Brown Cast



Prerenal vs ATN: Fractional excretion of sodium (FENa) and urine sodium concentration

Definition: The fraction of filtered sodium that is excreted.

Prerenal: <1%

ATN: >2%

Question:

- 70 year old gentleman with h/o CKD (Cr baseline ~2), CHF, IDDM2, HTN, HLD who presented with syncopal event on toilet and **melena.**
- On presentation Cr was 5.8. BUN 132. Hgb 6.8, down from 8.9, 2 weeks ago. At home he was also **on Lisinopril and Lasix for CHF**. UA bland without hematuria, proteinuria or pyuria. Renal ultrasound was without hydronephrosis.

His FENa was 2%, does this mean he has ATN?

A) Yes

B) No

- FENa will be elevated with diuretic use (physiology of diuretics is to excrete sodium in the urine).

Limitations of FENa:

- Diuretics affect FENa. Use fractional excretion of urea (FEUrea) instead.
  - FEUrea <35%= Prerenal
  - FEUrea >50%= ATN

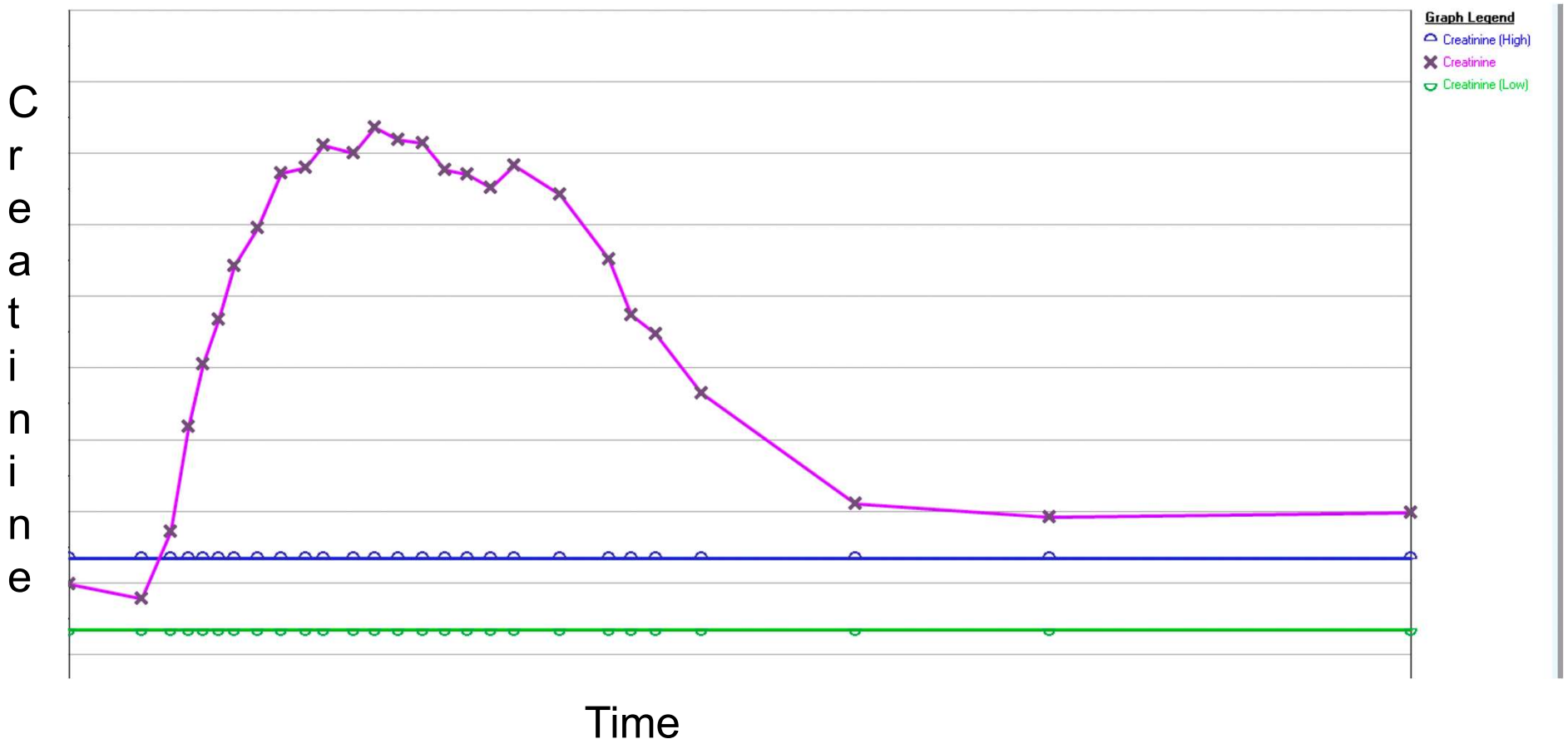
Other useful tests:

- Blood urea nitrogen/serum Cr ratio:
  - Prerenal: Elevated at >20:1
  - ATN: Normal at 10 to 15:1
- Urine osmolality:
  - Prerenal: usually > 500 mosmol/kg
  - ATN: usually < 350 mosmol/kg
- Urine volume:
  - Prerenal: Low (limit fluid loss)
  - ATN: Varies

Other useful tests:

Rate of rise of serum Cr concentration:

- In ATN, serum Cr tends to rise progressively and usually at a daily rate greater than 0.3 to 0.5mg/dL



Question: Back to case…

- Our patient with GIB who is either prerenal or ATN. His labs:

-Urine microscopy:

No muddy brown casts

-FEUrea: Equivocal at 35%

-BUN/Cr: 23 but with GIB

Sodium, Ser/Plas	134	
Potassium, Ser/Plas	6.2 *	c
Chloride, Ser/Plas	105	
CO2, Ser/Plas	17	
Urea Nitrogen,Ser/...	132	
Creatinine, Ser/Plas	5.79 *	
eGFR	9 *	
eGFR (African Amer...	10 *	
Fasting	See Comment *	
Glucose, Ser/Plas	195 *	
Anion Gap	12	
Calcium, Ser/Plas	7.8	

Assuming excellent urine output and no signs of volume overload. What type of IVF would you challenge him with to eliminate pre-renal AKI as a cause?

A) Normal Saline

B) Lactated Ringers

C) D5W with 3amps of bicarb

Answer:

D5W with 3 amps of bicarb!

- Metabolic acidosis
- Hyperkalemia

Sodium, Ser/Plas	134	
Potassium, Ser/Plas	6.2 *	c
Chloride, Ser/Plas	105	
CO2, Ser/Plas	17	
Urea Nitrogen,Ser/...	132	
Creatinine, Ser/Plas	5.79 *	
eGFR	9 *	
eGFR (African Amer...	10 *	
Fasting	See Comment *	
Glucose, Ser/Plas	195 *	
Anion Gap	12	
Calcium, Ser/Plas	7.8	

- Caution: Watch urine output and signs of volume overload before any IVF challenge!

Question:

- After receiving isotonic IVF (prior to renal consult):

Sodium, Ser/Plas	134
Potassium, Ser/Plas	6.2 * c
Chloride, Ser/Plas	105
CO2, Ser/Plas	17
Urea Nitrogen,Ser/...	132
Creatinine, Ser/Plas	5.79 *
eGFR	9 *
eGFR (African Amer...	10 *
Fasting	See Comment *
Glucose, Ser/Plas	195 *
Anion Gap	12
Calcium, Ser/Plas	7.8

Sodium, Ser/Plas	136 *
Potassium, Ser/Plas	6.2 * c
Chloride, Ser/Plas	108 *
CO2, Ser/Plas	14 *
Urea Nitrogen,Ser/...	>150 *
Creatinine, Ser/Plas	5.85 *
eGFR	
eGFR (African Amer...	
Fasting	See Comment *
Glucose, Ser/Plas	314 *
Anion Gap	14 *
Calcium, Ser/Plas	7.9 *

Confirmed ATN.

Vitals stable and resolving GIB/BRBPR. Nonoliguric.

On exam: NAD. HR:RRR. Lung: CTAB. Abd: BS active. Non-TTP. Extremities: No edema.

Does he need dialysis based on what you know?

Need dialysis

A) Yes

B) No

ATN Treatment

- Supportive care!
- Dialysis only IF indications for dialysis

Indications for dialysis

- Acidosis
- Electrolyte Disturbances
- Intoxication
- Overload
- Uremia

Sodium, Ser/Plas	*136 **	
Potassium, Ser/Plas	*6.2 **	c
Chloride, Ser/Plas	*108 **	
CO2, Ser/Plas	*14 **	
Urea Nitrogen,Ser/...	*>150 **	
Creatinine, Ser/Plas	*5.85 **	
eGFR		
eGFR (African Amer...		
Fasting	*See Comment **	
Glucose, Ser/Plas	*314 **	
Anion Gap	*14 **	
Calcium, Ser/Plas	*7.9 **	

Uremia

- Absolute indications for dialysis
- Overt uremic symptoms such as encephalopathy, pericarditis, uremic bleeding diathesis
- A precise correlation does not exist between the BUN level and the onset of uremic symptoms
  - Although the longer the duration and greater the severity of azotemia, the more likely that overt symptoms will develop

Takeaways

- ATN is the most common cause of AKI in the hospital setting
- The three major causes of ATN are: Ischemic, Septic and nephrotoxic
- Fluid repletion is the best way to distinguish between prerenal and ATN
- The treatment of ATN is supportive care
- There is no benefit to early dialysis

- You are awesome! Thank you for listening

Thank you!!

Questions:
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Special Thanks:

- Dr. Pedram Fatehi
- Dr. Tara Chang
- Shira Roth PA-C

Sources

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