03/04/2025

Acute Kidney Injury

Nephrology Course, Medical School, EKPA

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Definition

- Acute kidney injury(AKI) refers to an abrupt decrease in kidney function and loss of GFR, resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes.

- How fast? Hours and days.

- The term AKI has largely replaced acute renal failure (ARF), reflecting the recognition that smaller decrements in kidney function that do not result in overt organ failure are of substantial clinical relevance and are associated with increased morbidity and mortality.

Stages of AKI

KDIGO definition of acute kidney injury

Stage	Creatinine Criteria	Urine Output Criteria
1	Cr 1.5-1.9 times baseline, OR Cr increase >0.3 mg/dL	< 0.5 ml/kg/hr x 6-12 hours
2	Cr 2-2.9x baseline	<0.5 ml/kg/hr for >12 hours
3	Cr > 3x baseline, OR Cr > 4 mg/dL, OR Initiation of dialysis	<0.3 ml/kg/hr for >24 hours, OR Anuria > 12 hours

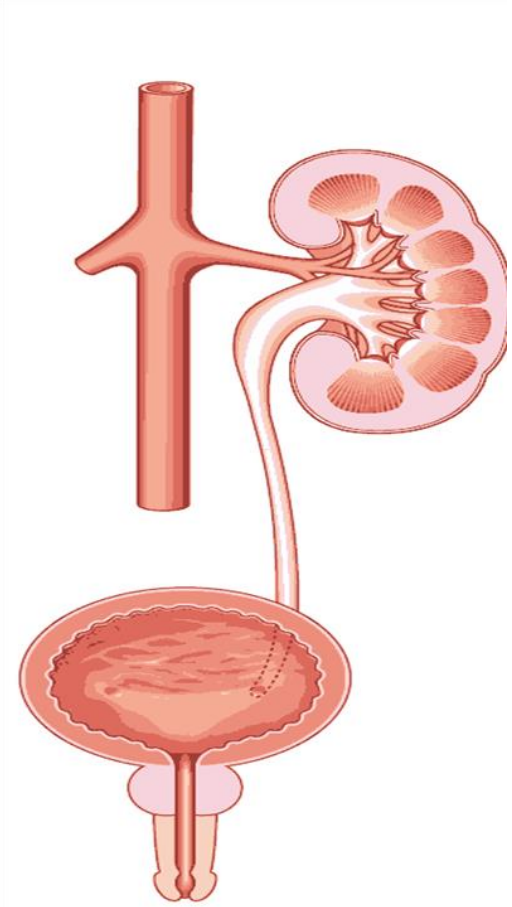
Patients are staged based on the single most concerning feature.

Epidemiology

- 10-15% of hospital admissions have AKI.
- 50% of patients in the ICU.

Ronco C et al, Lancet 2019

AKI classification based on anatomy



Hemodynamic("Prerenal")
Reduced renal arterial perfusion
Renal venous congestion
Drugs affecting glomerular hemodynamics

Intrinsic
Renal vascular disease
Glomerular disease
Tubular diseases
Interstitial diseases

Obstructive
Obstruction may occur anywhere in the urinary tract.

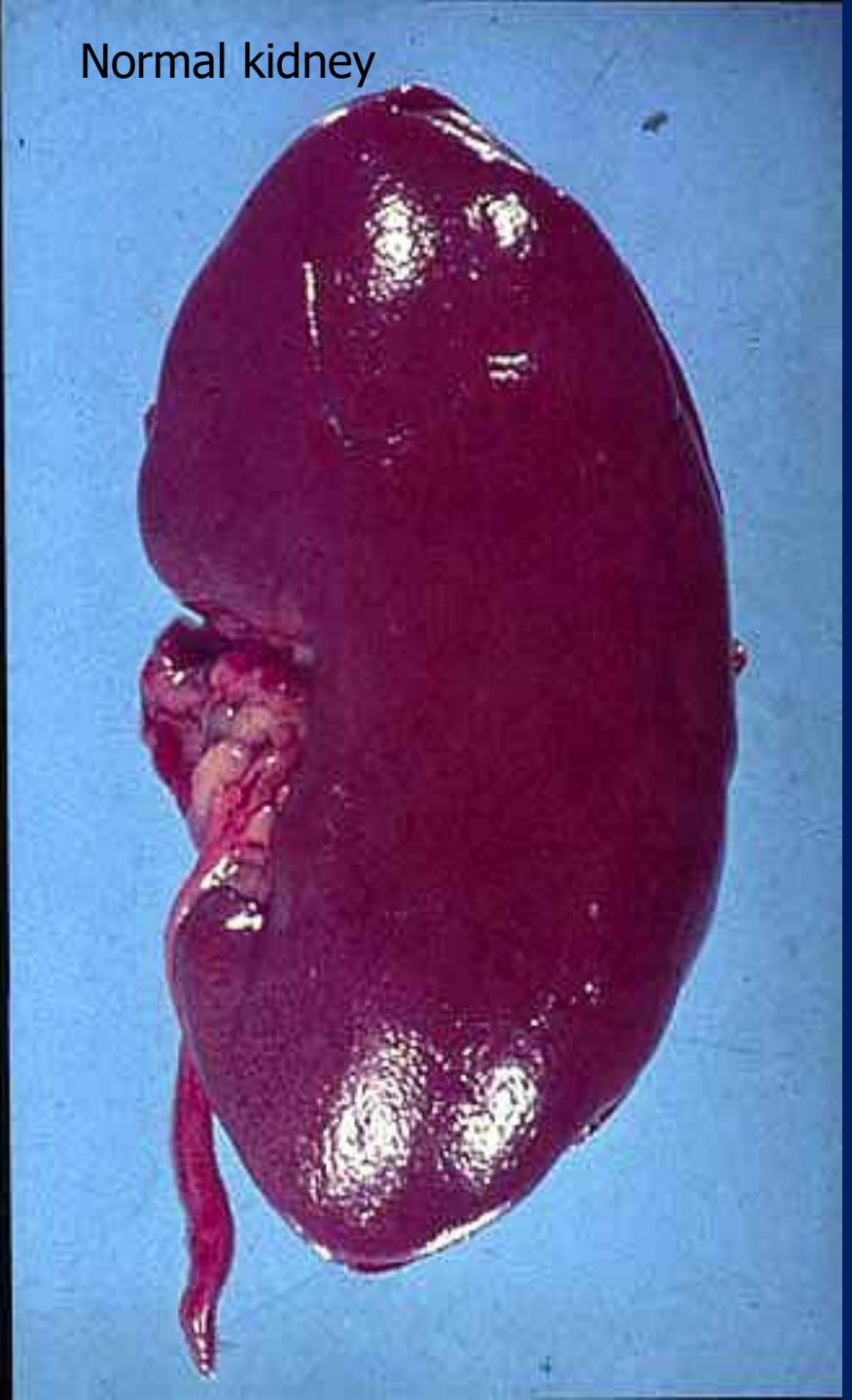
ACUTE RENAL FAILURE

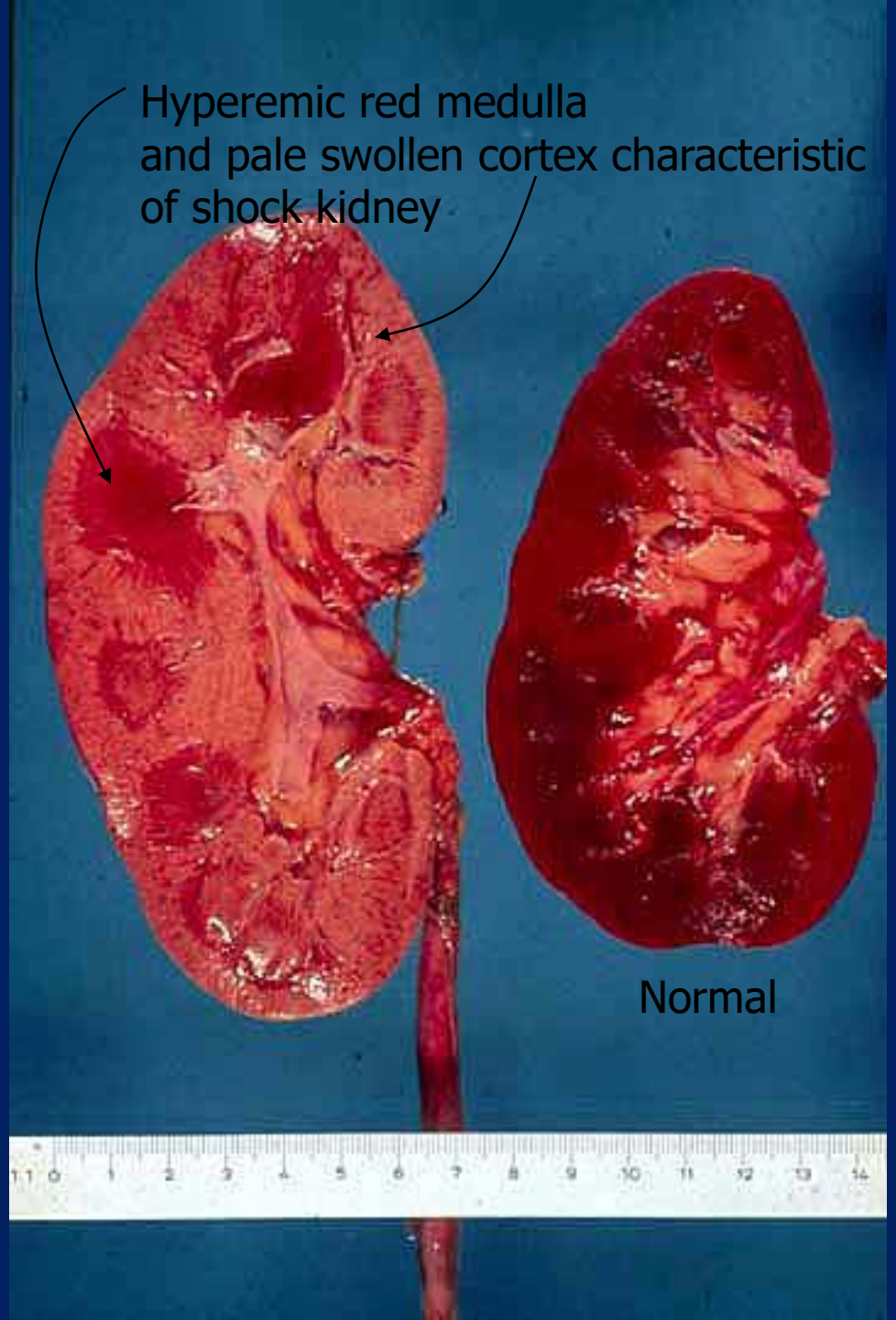
- Prerenal Acute Renal Failure
  - Reduced perfusion or oxygenation
- Intrarenal Acute Renal Failure
  - Renal parenchymal disease
- Postrenal Acute Renal Failure
  - Urinary tract obstruction

Shock kidney

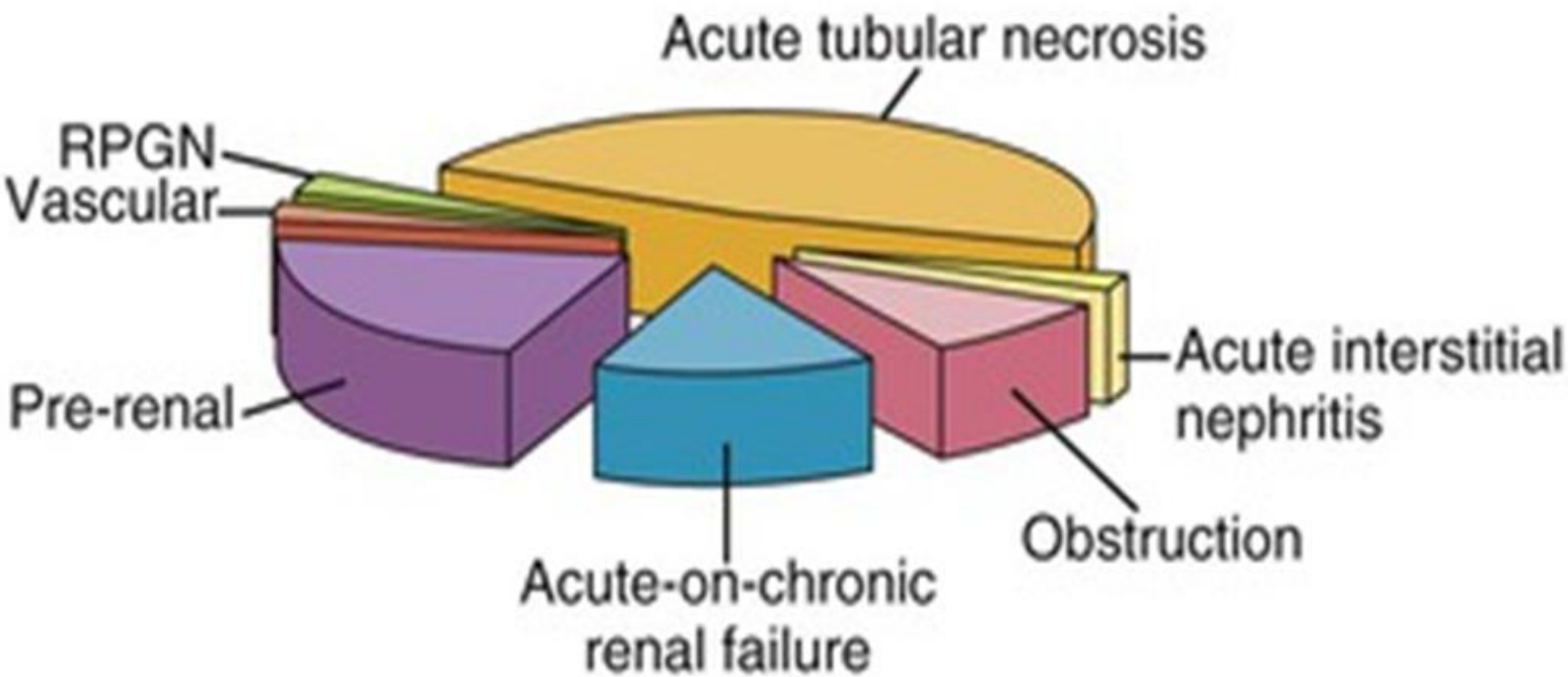
Swollen pale gross appearance to cortex

Normal kidney




Hyperemic red medulla
and pale swollen cortex characteristic
of shock kidney
Normal

Causes of AKI in Hospital Setting



Hemodynamic/Prerenal AKI

Reduced renal arterial perfusion

Total body volume depletion

(diarrhea, vomiting, acute bleeding, unreplenished insensible losses, excessive diuretic therapy, third-space sequestration (eg, crush injury or acute pancreatitis)

Normal or variable total body volume

(sepsis or anaphylaxis. overtreatment with antihypertensive medication)

Total body volume overload

(severe heart failure with reduced ejection fraction, hepatorenal syndrome).

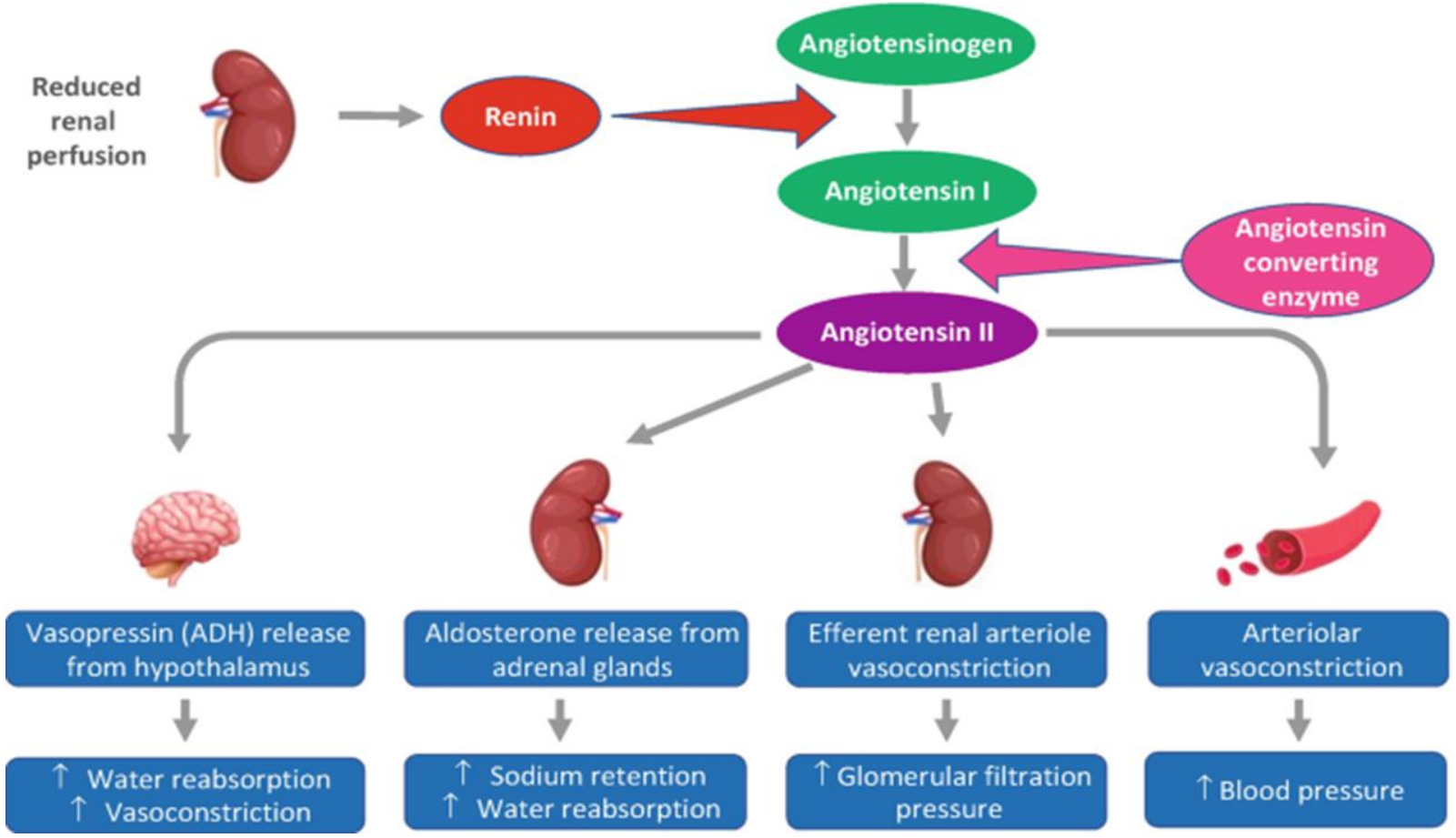
Renal venous congestion

Severe heart failure with preserved ejection fraction, abdominal compartment syndrome

Drugs affecting glomerular hemodynamics

NSAIDs, Angiotensin blockade

Pathophysiology of prerenal AKI



Loss of compensation by BP<80mmHg leads to reduction of GFR

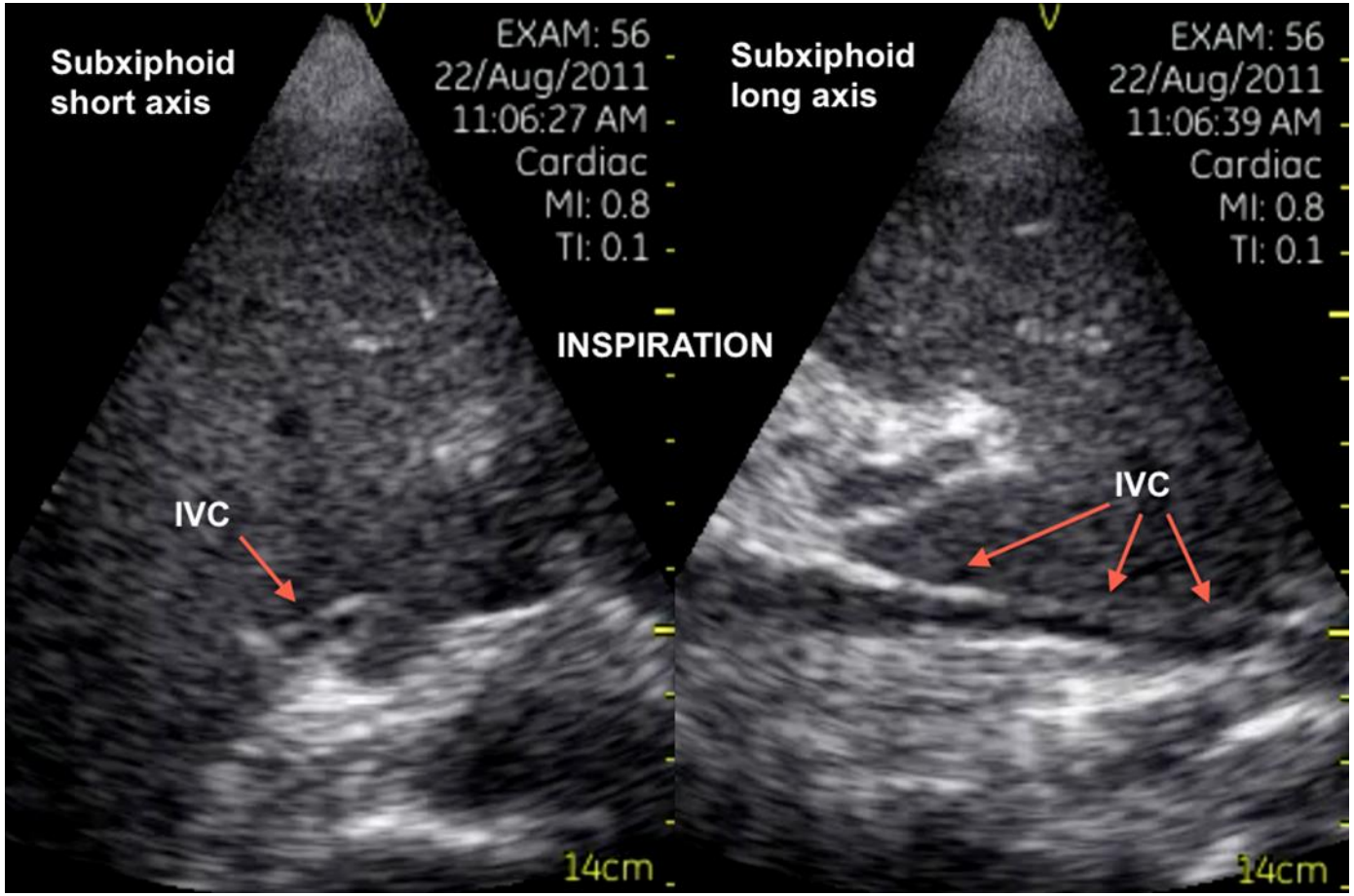
Pre-renal: true volume depletion

- Common causes are hemorrhage, diarrhea, excessive diuretics (endogenous or exogenous)
- Physical signs of decreased extracellular volume: hypotension, tachycardia, orthostasis, poor skin turgor, dry mouth, etc.
- Lab signs: oliguria, high urine specific gravity, low urine sodium, low fractional excretion of sodium and/or urea, elevated BUN to creatinine ratio. Urine sediment is normal.
- Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and non-steroidal anti-inflammatory agents will all increase susceptibility to pre-renal azotemia.

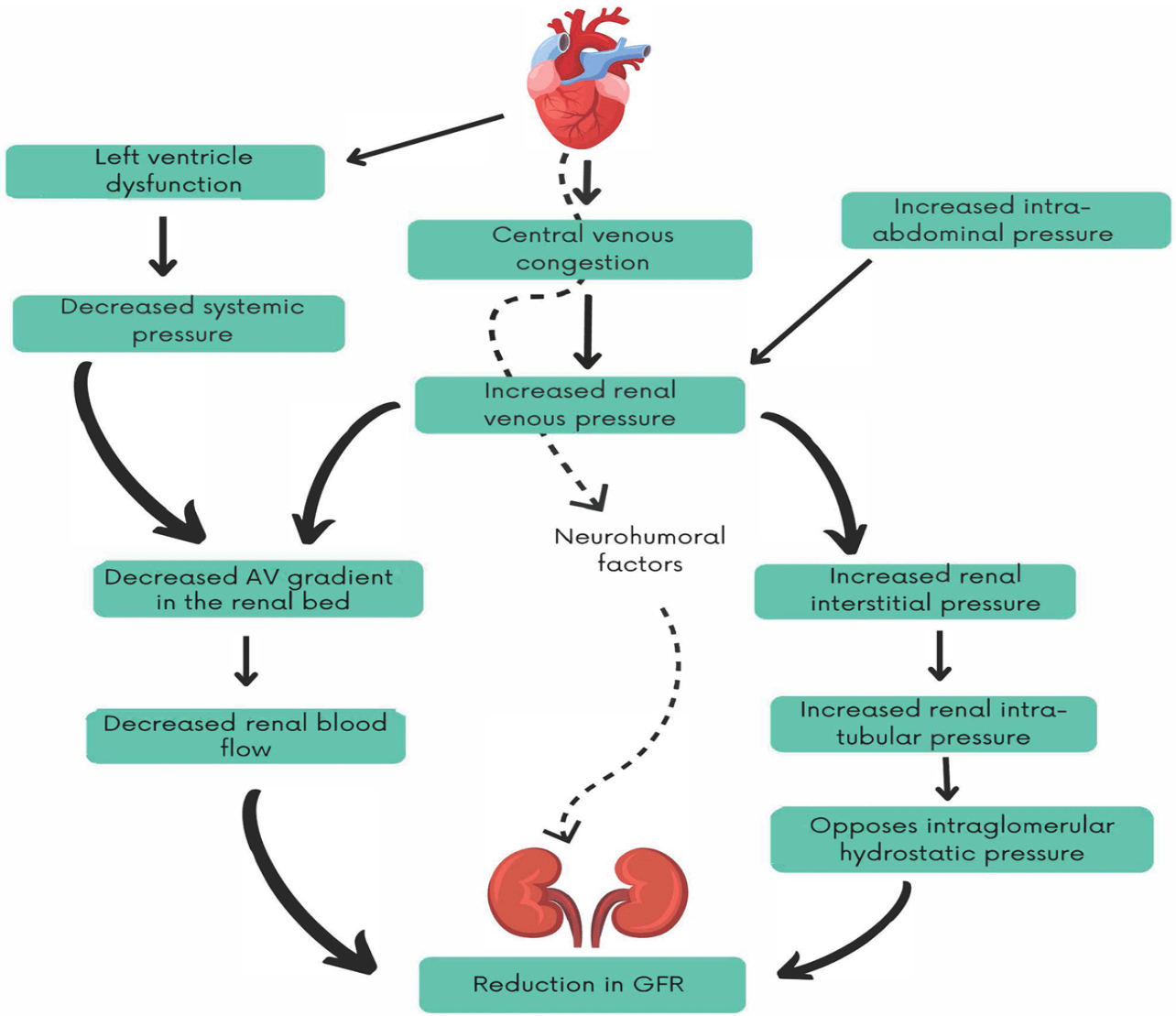
Pre-renal: decreased effective circulating volume

- Conditions of heart failure or liver failure where filling of the arterial circulation is inadequate despite expanded extracellular volume.
- These patients may have evidence of volume expansion on physical exam, but kidney will behave as if there is volume depeletion with avid sodium retention reflected in low urine sodium, low FE, high BUN/creat ratio.

Prerenal AKI



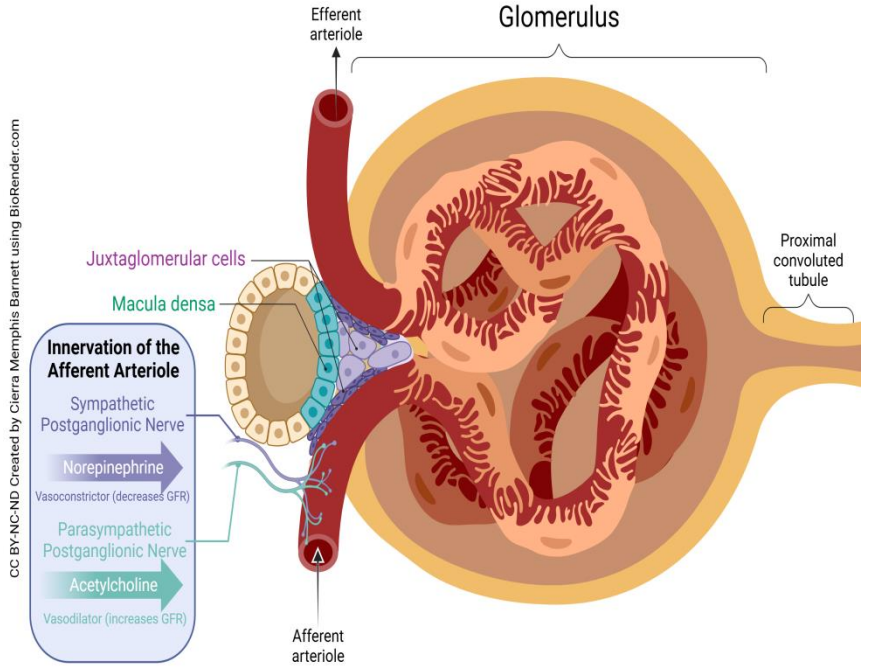
Cardiorenal - Two ways to AKI



Classic clinical paradigm I

Diarrhea

\+ **RAAS blockade**



RAAS blockade inhibits efferent arteriole constriction

↓

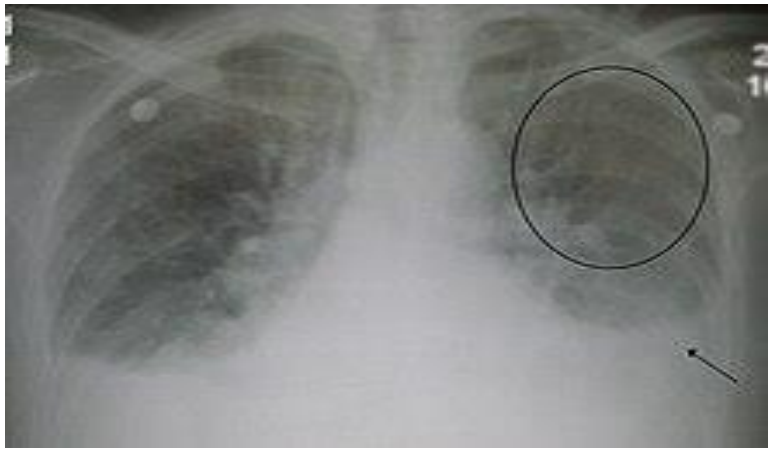
Kidney can not hold normal GFR. GFR falls.

↓

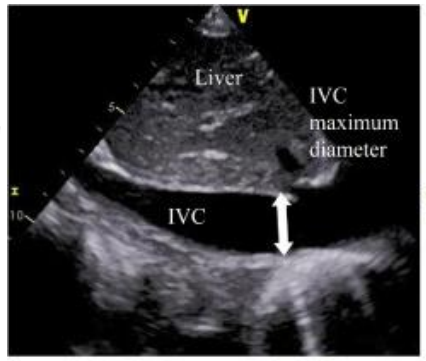
AKI

Classic clinical paradigm II

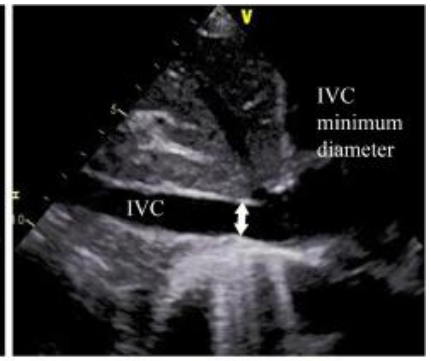
Decompensated heart failure



Fluid overload



End-expiratory period



After brief sniff

Increased renal venous pressure

Oliguria. AKI

Intristic AKI

Renal vascular disease

Small vessels: vasculitides, atheroembolic disease, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP/HUS), scleroderma, and malignant hypertension.

Large vessels: renal infarction from aortic dissection, systemic thromboembolism, renal artery abnormality (such as aneurysm), and acute renal vein thrombosis.

Glomerular disease

Rapidly progressive glomerulonephritis(RPGN)

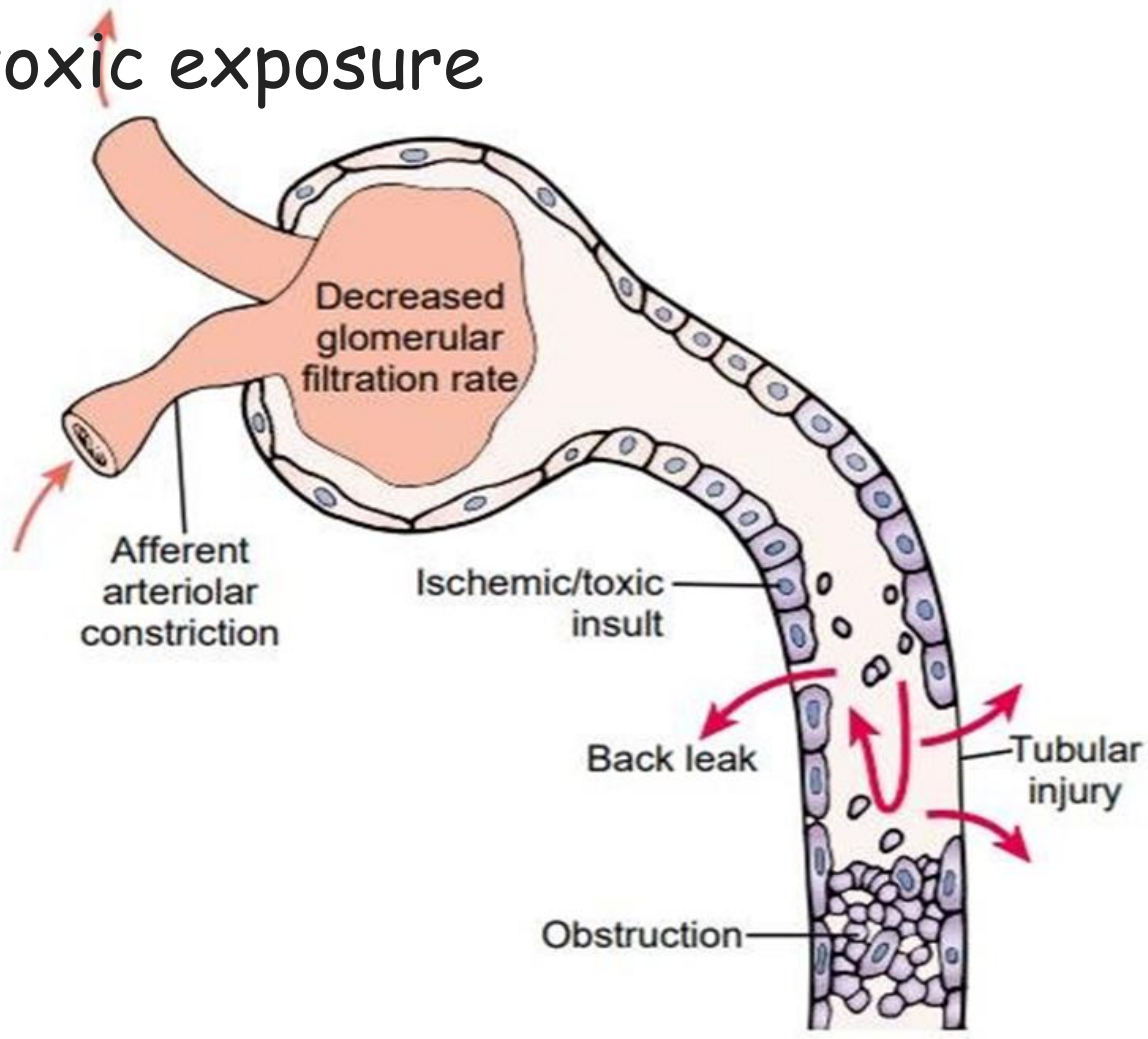
Tubular and interstitial diseases

Acute tubular necrosis

Acute interstitial nephritis

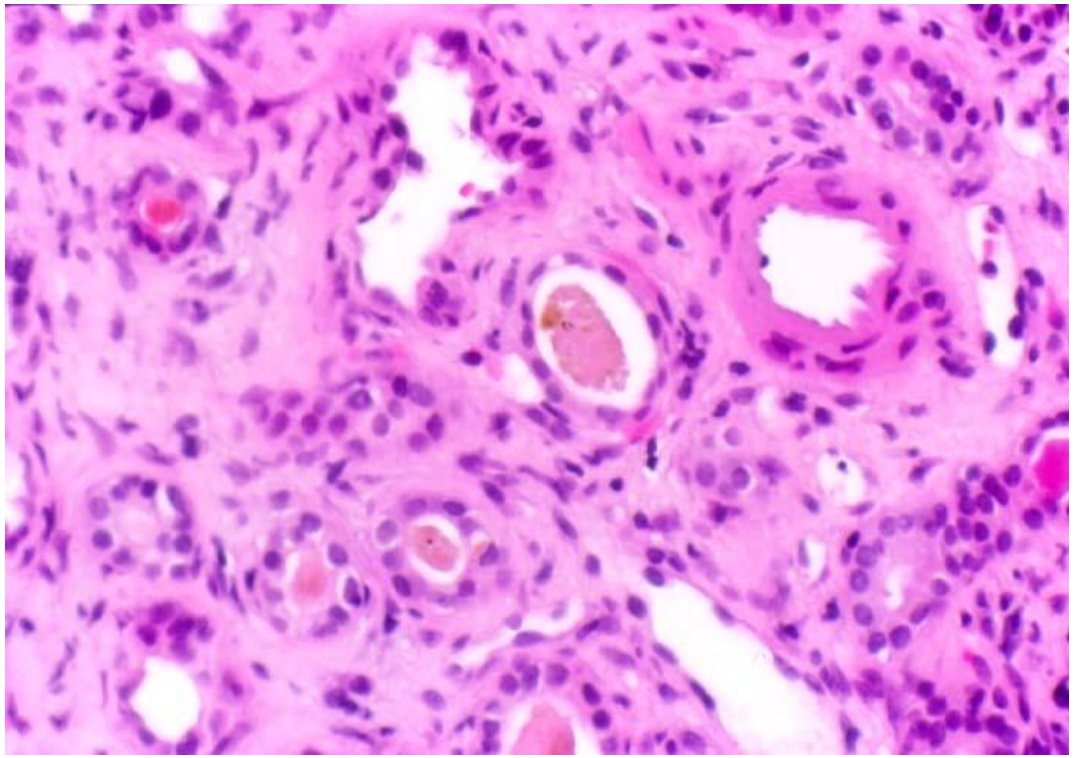
Acute tubular necrosis(ATN)

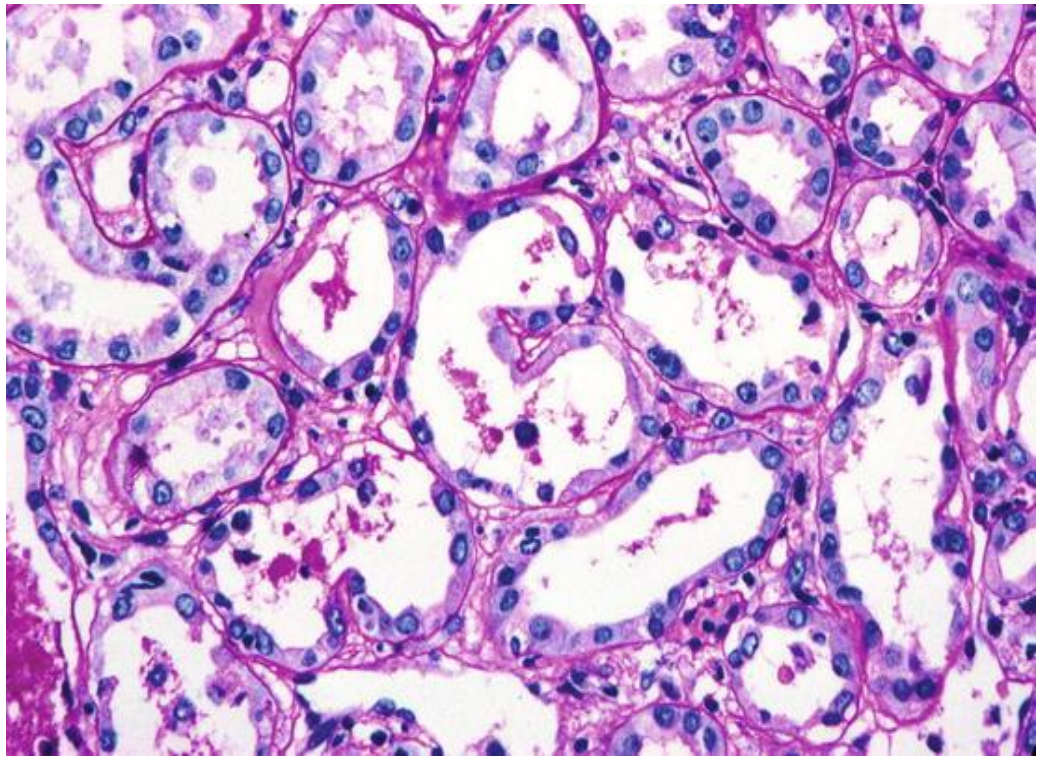
- Prolonged Ischemia or a nephrotoxic exposure



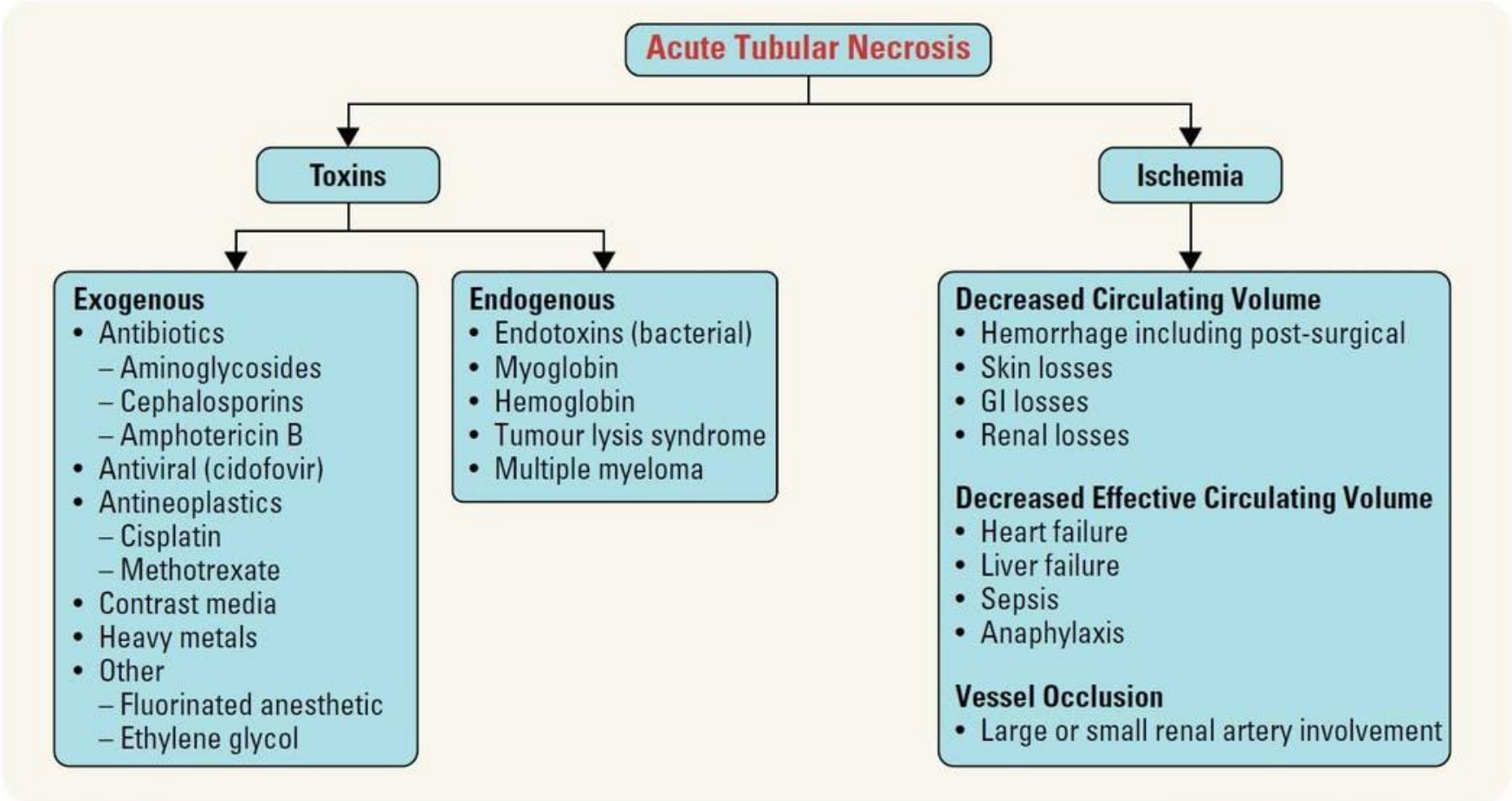
Acute tubular necrosis(ATN) - Histology

- Attenuation or simplification of tubular epithelium with loss of brush borde.
- Tubular lumens filled with sloughed off necrotic tubular epithelial cells.





Acute tubular necrosis(ATN)



Etiology of ATN

Source: Toronto Notes 2021

Acute tubular necrosis(ATN)

Exogenous toxins
Antibiotics(Aminoglycosides, Colimycin)
Iodinated Contrast
NSAIDs
Chemotherapy(Platinum)
Crystals(Acyclovire)

Endogenous toxins
Tumor lysis syndrome (acute uric acid nephropathy)
CAST nephropathy(myeloma kidney, κ and λ free light chains)
Rahbdomyolysis(myoglobin)

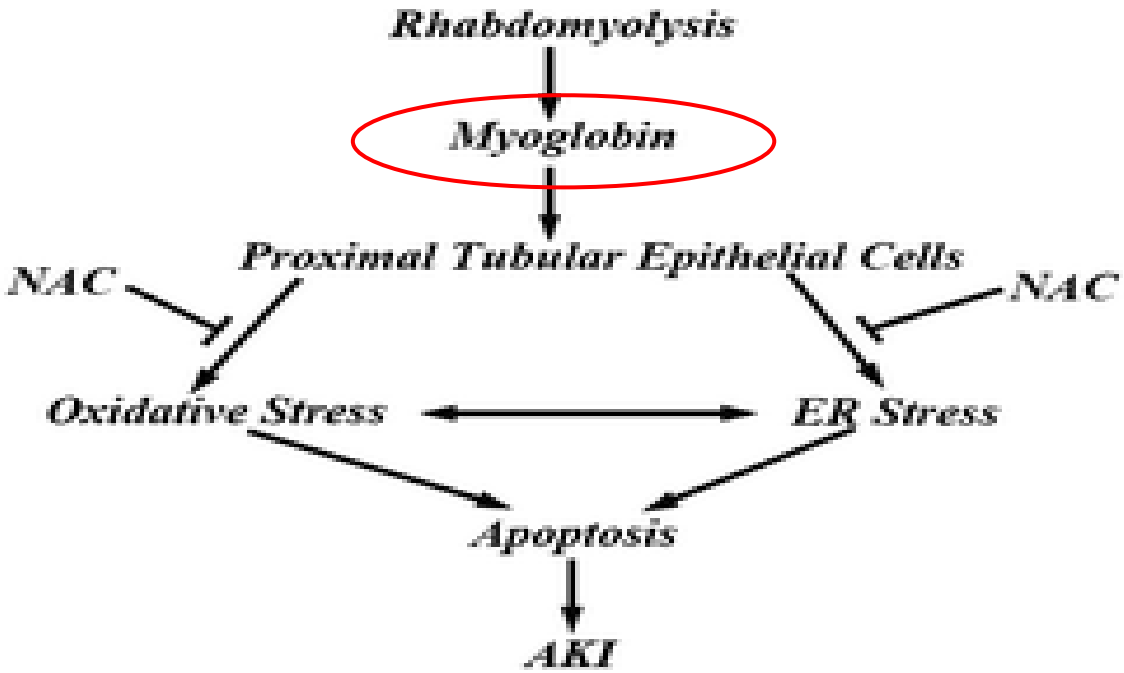
Contrast induced nephropathy

- AKI may develop after administration of iodinated contrast material(CT scan).
- The mechanism by which ATN occurs is not well understood, propably renal vasoconstriction resulting in medullary hypoxia.
- Increase in serum creatinine that is generally observed within 24 to 48 hours after the iodinated contrast exposure and that is usually mild.
- Most patients are nonoliguric.
- Prevention is very important!!! Patients with CKD at higher risk.
- Preventive intravenous volume administration is commonly used in high-risk patients.

Rhabdomyolysis

Traumatic	Non-traumatic
• Crush injury • Entrapment • Prolonged immobilisation • Electrical injury • Excessive muscle activity – marathon running, status epilepticus, MH • Heat-related – heat stroke, neuroleptic malignant syndrome (NMS), hypothermia (rarely)	• Ischaemic insult • Substance misuse – alcohol, cocaine amphetamine, ecstasy • Drugs – statins, fibrates, cocaine, antipsychotics, antidepressants (NMS) • Toxins – carbon monoxide, heavy metals, snake venom • Infection – tetanus, legionella, viral, sepsis syndrome • Electrolyte disturbance – hypokalaemia, hypo/hypernatraemia, hypocalcemia, hypophosphataemia, HONK, DKA, hypo/hyperthyroidism • Muscle enzyme deficiencies • Autoimmune – dermatomyositis, polymyositis

Rhabdomyolysis



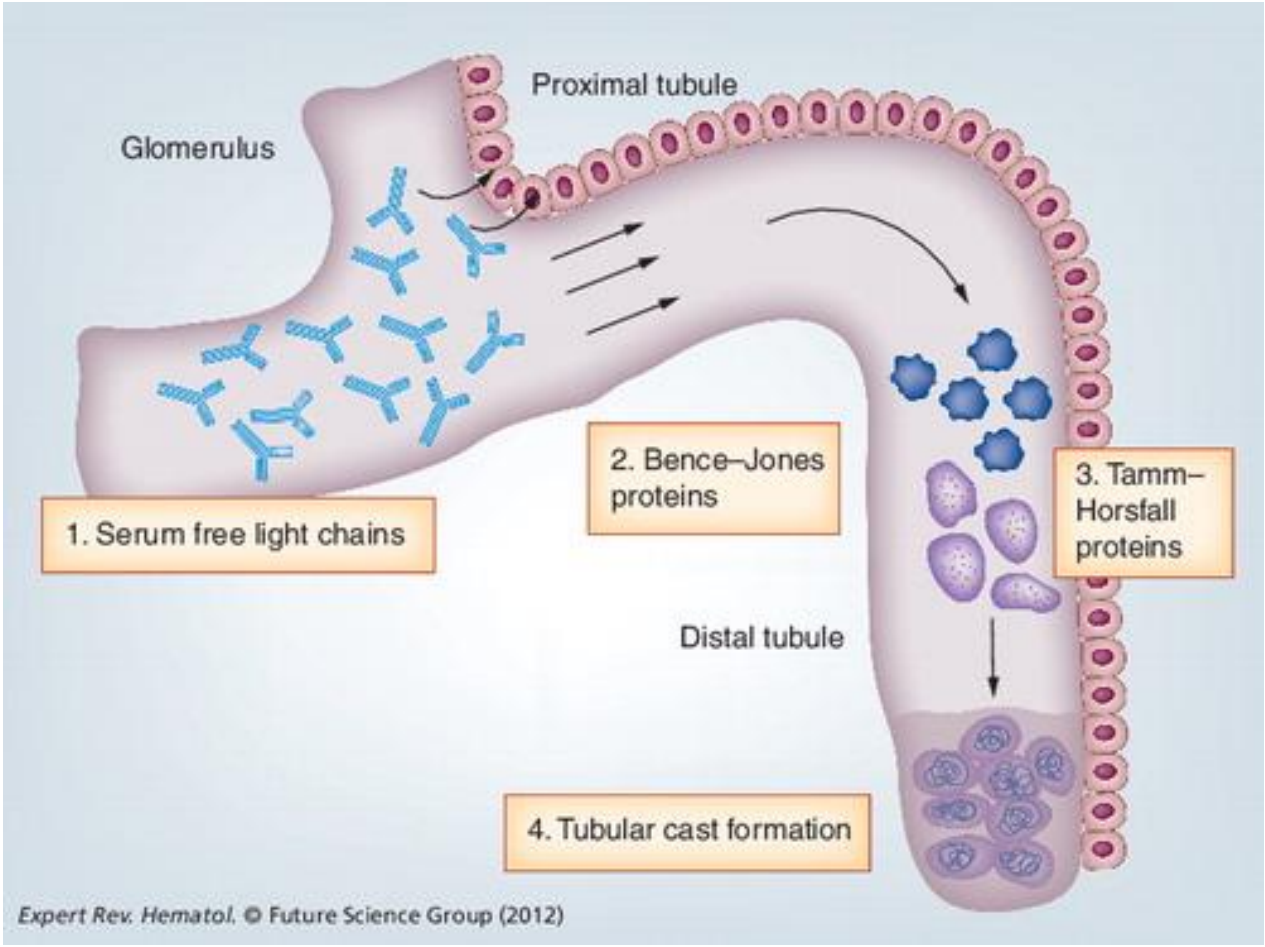
Rhabdomyolysis

Muscle pain and weakness

Red/Brown urine.
AKI

Elevated creatine kinase

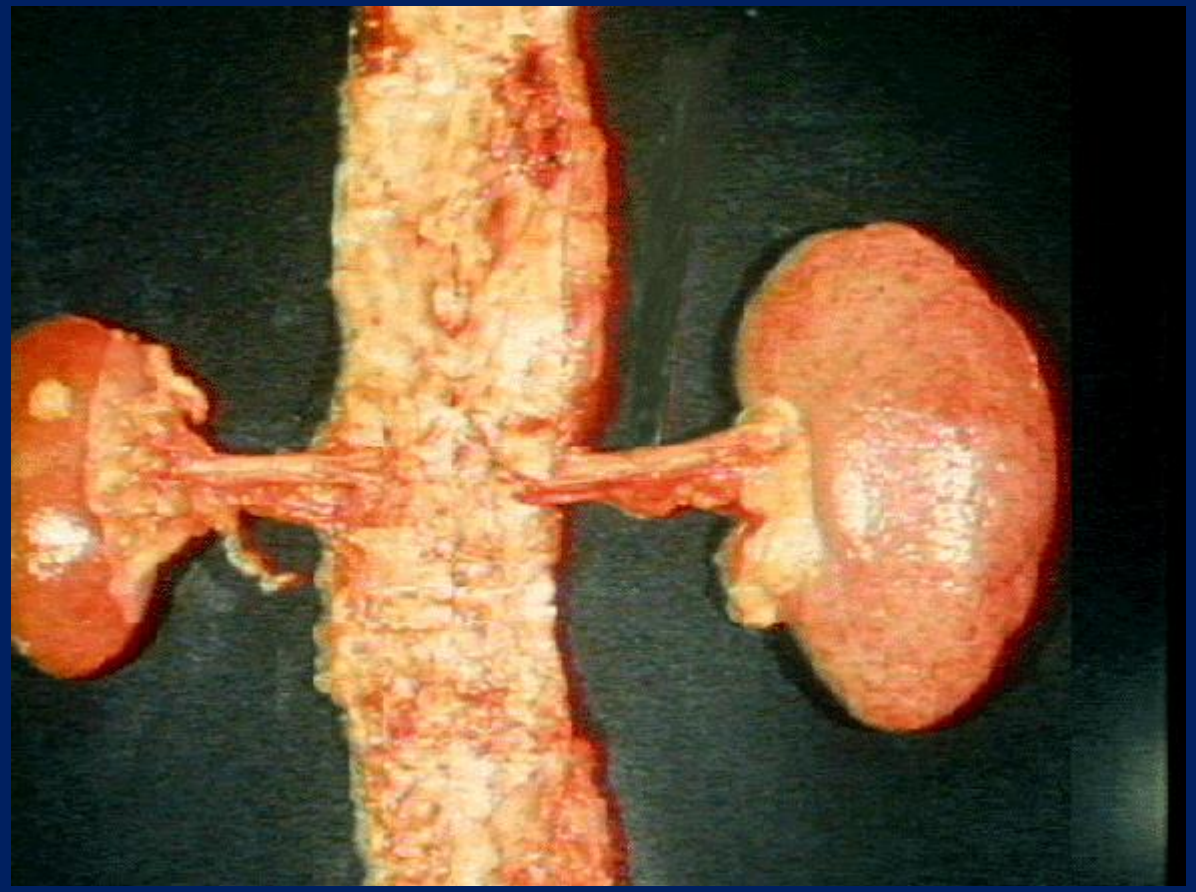
Myeloma kidney



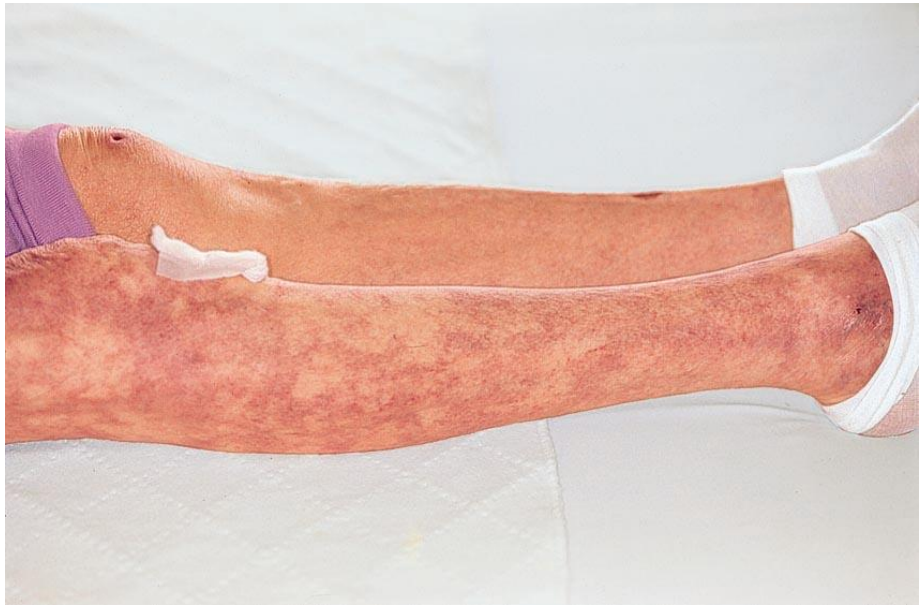
Atheroemboli

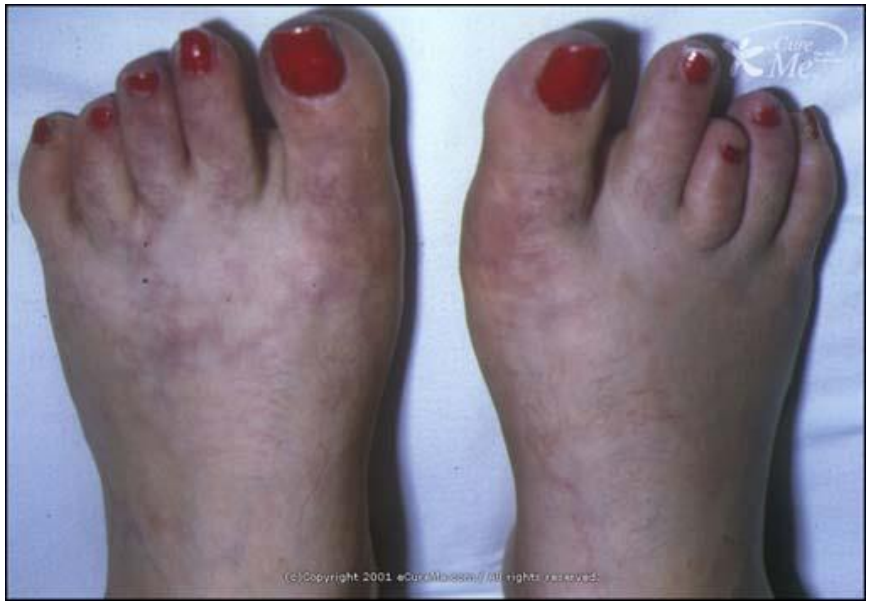
- Atherosclerotic plaques on inner surface of aorta become unstable and shower lipid-rich particles into distal circulation.
- May occur spontaneously, but often follows instrumentation of the aorta.
- May be triggered by anticoagulation.
- Particles lodge in small arterioles, causing local inflammation and distal ischemia.
- Multi-system involvement common: skin (livedo reticularis and digital infarcts), gut, eyes, brain.
- Hypertension, dysmorphic hematuria, eosinophilia, and depressed complement levels may be seen during episodes of embolization.

Atherosclerosis of Aorta and Renal Arteries



Livedo Reticularis associated with atheroembolization





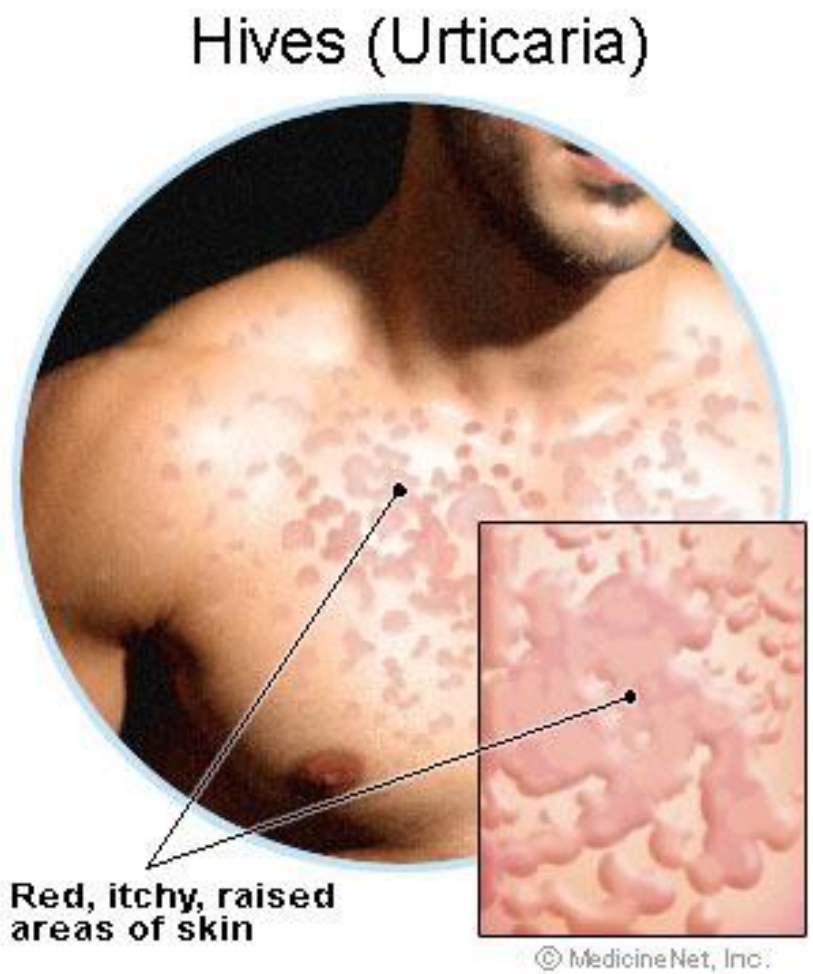
Atheroemboli: prognosis and treatment

- Renal disease tends to follow stuttering course with waves of embolization causing stepwise decline in renal function.
- Usually progresses to end stage kidney disease over many months.
- Treatment is supportive. Important to avoid anticoagulation, which accelerates embolization.

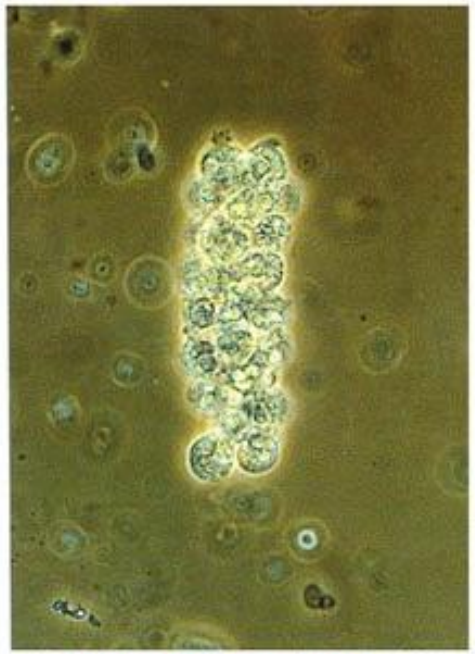
Intrarenal Acute Kidney Injury: Acute Interstitial Nephritis

- Most commonly due to allergic reaction to a drug, but also may be seen as part of immunologic reaction to a systemic infection or part of multi-system auto-immune disorders.
- Allergic Interstitial Nephritis typically presents with acute azotemia in context of eosinophilia, fever, and rash. Urine sediment may have white cell casts, hematuria, and low grade proteinuria. Eosinophils in the urine are a classic sign that has limited positive or negative predictive value.

Typical Drug Eruption: macuolo-papular blanching rash, often starting on upper chest and back



WBC casts in urine sediment



Intrarenal Acute Kidney Injury: Acute Interstitial Nephritis

- Virtually any drug may cause interstitial nephritis, but antibiotics are most commonly encountered offenders
- NSAIDS cause an unusual interstitial nephritis. Typically there is no rash, fever or esoinphilia, and proteinuria may be in nephrotic range.

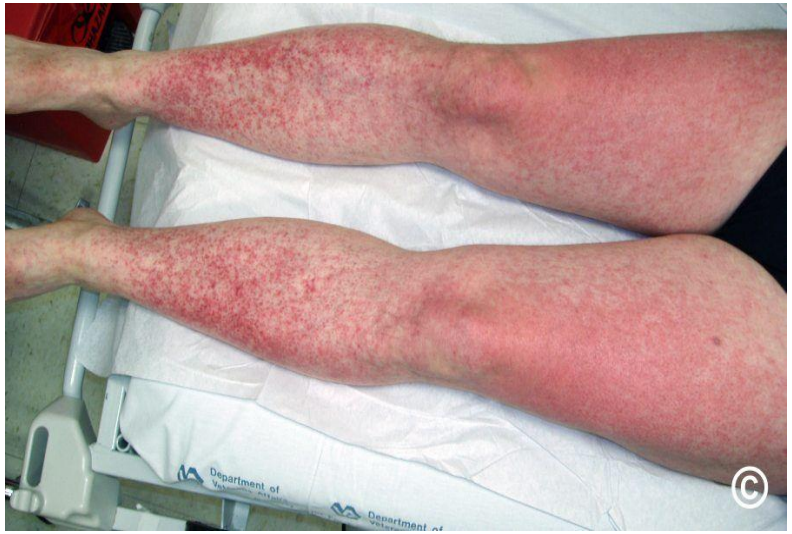
Intrarenal Acute Kidney Injury: Acute Interstitial Nephritis

- Treatment is to remove the offending agent.
- Course of corticosteroids may shorten the time of renal recovery, but probably has little effect on long term outcome.

Classic clinical paradigm III

DRESS Syndrom

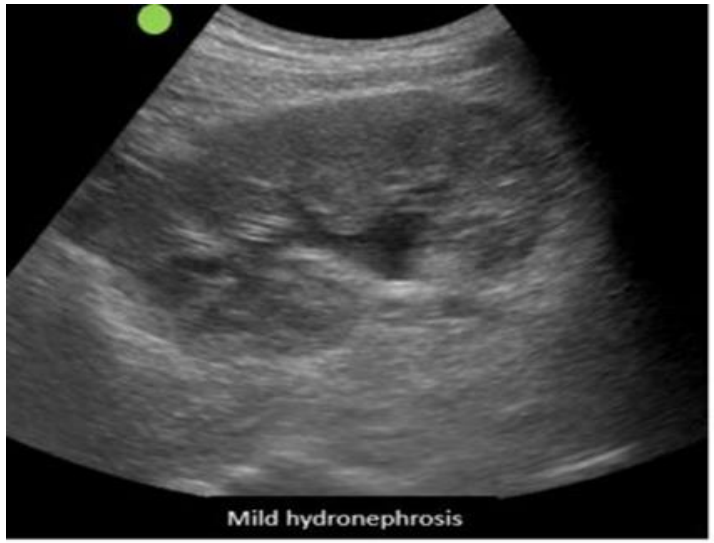
Drug Rush(maculo-papular)
Eosinophilia
Systemic Symptoms

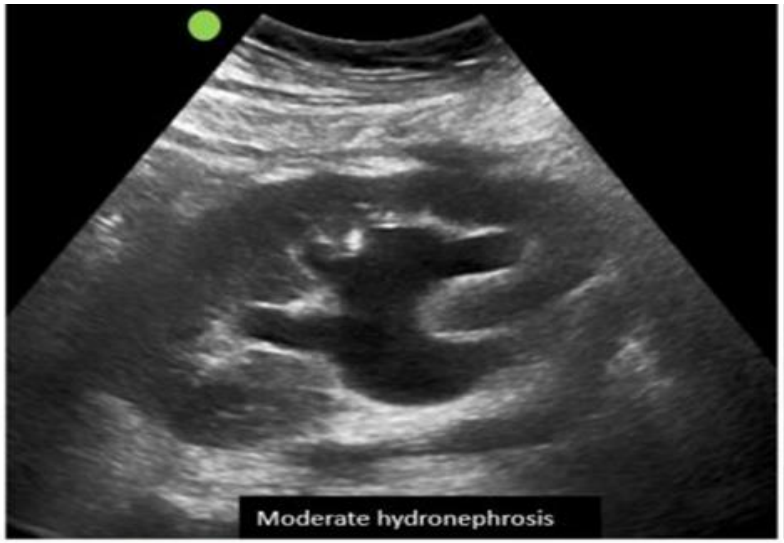


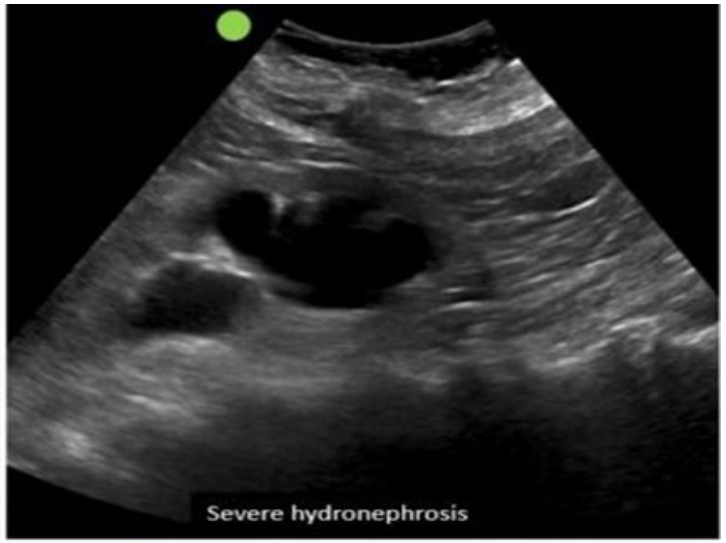
Obstructive AKI

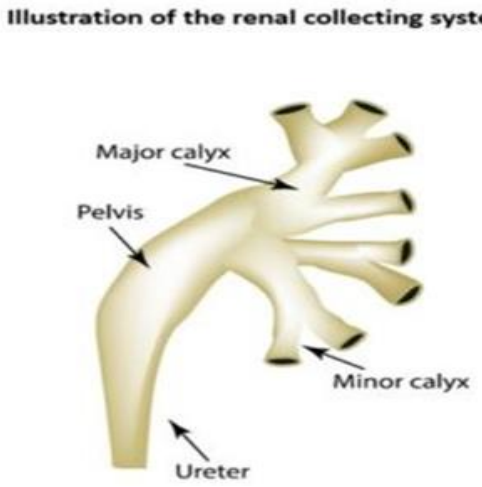
- Obstruction may occur anywhere in the urinary tract.
- This is most commonly due to prostatic disease (hyperplasia or cancer), urothelial carcinoma, gynecologic/metastatic cancer, or renal stones. Retroperitoneal fibrosis is a rare cause of progressive ureteral obstruction.
- Bilateral obstruction or unilateral obstruction of a single functioning kidney.

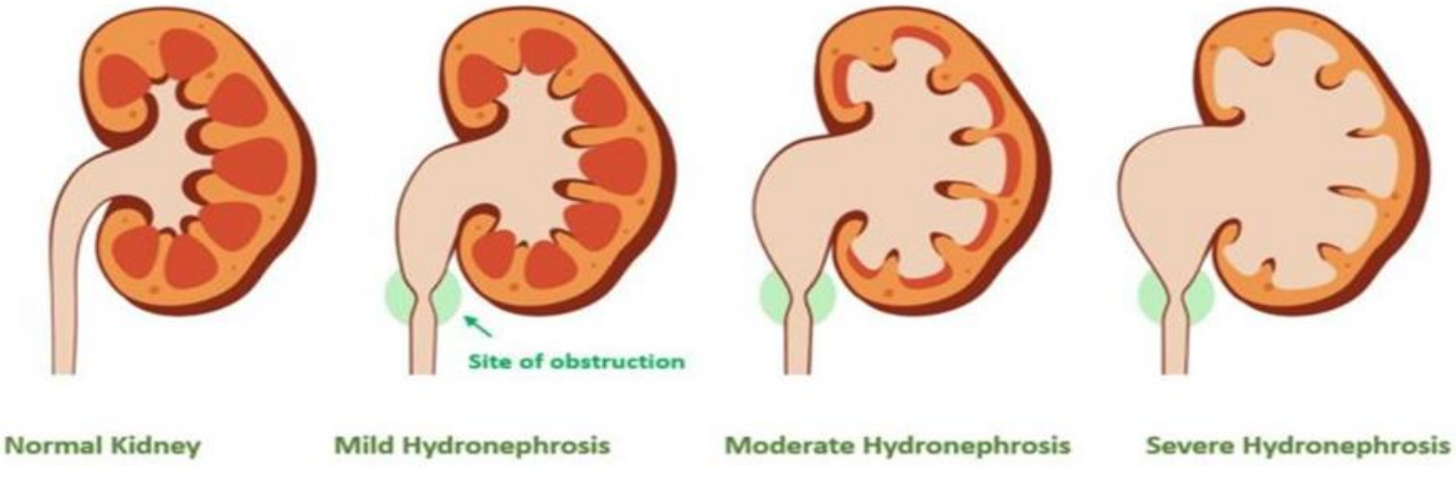
Hydronephrosis





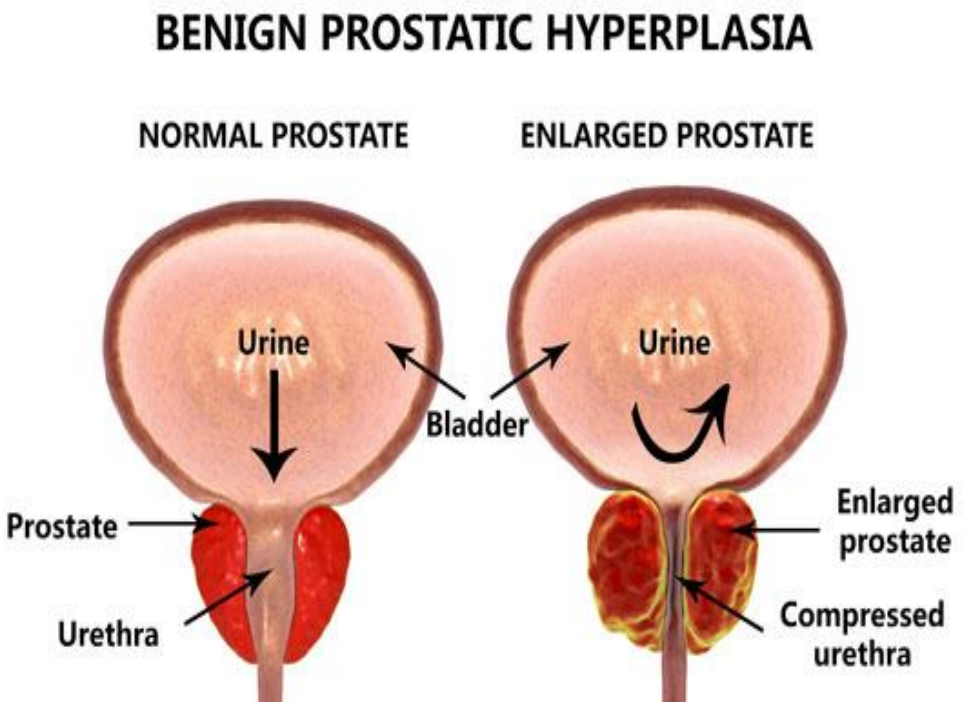






Classic clinical paradigm IV

- Male about 70 years old complains about oliguria and pain at his abdomen.
- Clinical examination shows dilated lower abdomen.
- Point of care Ultrasound shows urinary retention and mild hydronephrosis.
- Patient propably has benign prostatic hyperplasia and only needs a bladder catheter.



Clinical Manifestations of AKI

- Acute kidney injury (AKI) develops over hours to days and is usually diagnosed in the emergency department, in hospitalized patients, or following a procedure.

- Hallmark of AKI is increase of creatinine.

- **Symptoms and signs**

  Decreaded urine output

  Hypertension

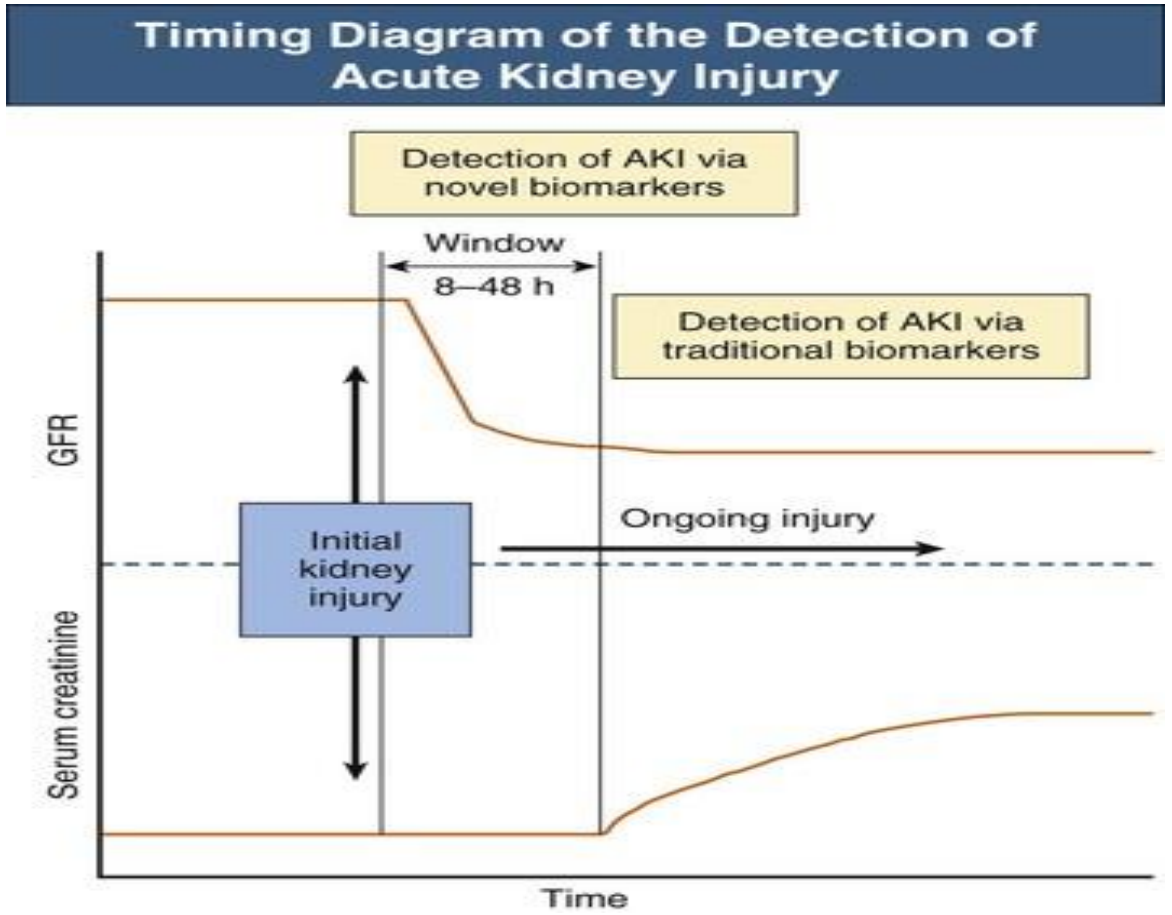
  Edema

  Dyspnoe

- However, many patients with early or mild AKI have no clinical symptoms, and an increase in creatinine is detected by the frequent laboratory testing common among hospitalized patients.

Creatinine - AKI

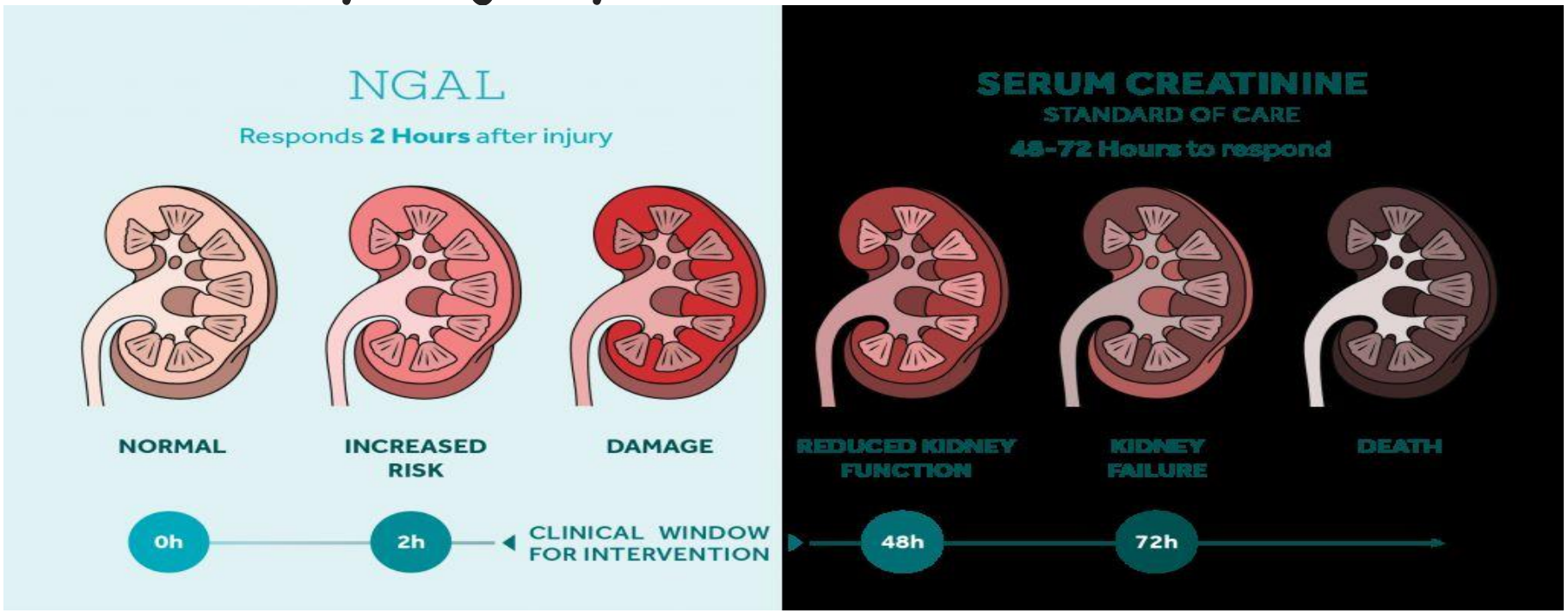
- Serum creatinine remains the only laboratory value used in formal definitions of AKI.
- Serum creatinine is the laboratory test most used in clinical practice.
- Well known limitations regarding body mass, diet etc., not so concerning in AKI.
- It is a lagging marker of change in kidney function.



Investigational biomarkers and the evaluation of acute kidney injury

- Possible biomarkers for the early diagnosis of ATN.
- There are promising candidate biomarkers that detect an early tubular epithelial cell injury, and distinguish prerenal disease from ATN.
- Some biomarkers are detected in the urine of patients without a diagnostic increase in serum creatinine, which defines a group of patients with "subclinical AKI" who are at risk for adverse outcomes.
- **Diagnostic biomarkers:** Neutrophil gelatinase-associated lipocalin (NGAL), Urinary tubular enzymes, KIM-1, urinary interleukin IL-18.
- **Prognostic Biomarkers:**Urinary insulin-like growth factor-binding protein 7 (IGFBP7), tissue inhibitor of metalloproteinases-2 (TIMP-2),Soluble urokinase plasminogen activator receptor (suPAR).

Investigational biomarkers and the evaluation of acute kidney injury



NGAL is markedly upregulated and abundantly expressed in the kidney after kidney ischemia

Diagnostic approach in AKI

- **Timing of onset.** Most easily found with hospitalized patients.
- **Concurrent illness.** Diarrhea? Sepsis? Fever ?Crush injury? Contrast? Etc.
- **Medication review.** Angiotensin blockade? SGLT2s? NSAIDs? Antimicrobials?
- **Physical examination.** Volume status is the most important for diagnosis and management!!! Very difficult sometimes!!

  Volume depletion?(Hypotension, fatigue, postural diziness, diminished skin turgor)

  Volume overload(Edema, dyspnoe, rales, increased jugular venous pressure)

Diagnostic approach

Is it really AKI or maybe it is Chronic Kidney Disease(CKD)?

- Recent normal kidney function with normal values of creatinine and normal urinanalysis.
- No signs and symptoms of CKD.
- ECHO with normal kidney size.

Patient with creatinine value of 3mg/dl.

AKI. Hospital admission!

CKD. Appointment after one month.

Diagnostic approach – Urine output

- Oliguria (typically defined as <0.3 mL/kg per hour or <500 mL/day of urine output) occurs often.
- Normal urine output can be maintained in non oliguric AKI.
- Non oliguric better than oliguric.
- Anuria is rare. Severe ATN due to prolonged shock, Bilateral urinary tract obstruction, or unilateral obstruction with one kidney, Bilateral renal artery obstruction as seen in abdominal aortic dissection.

Laboratory tests

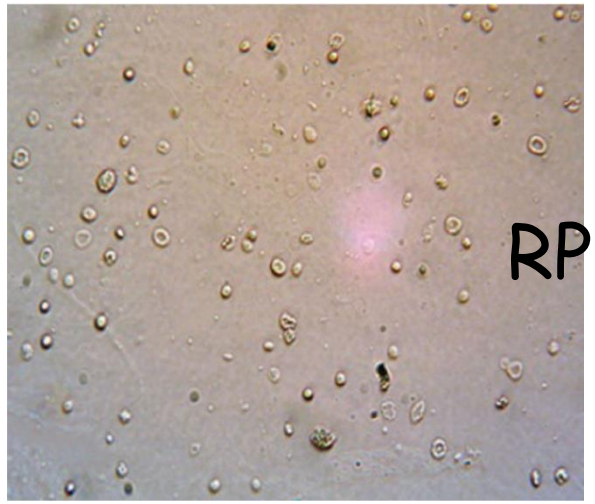
- Urinanalysis. Blood, SG, protein, pyuria, hemoglobin(or myoglobin), ph.
- Protein excretion.
- Calcium, complete blood count, PTH, uric acid.

Urine Sediment microscopy

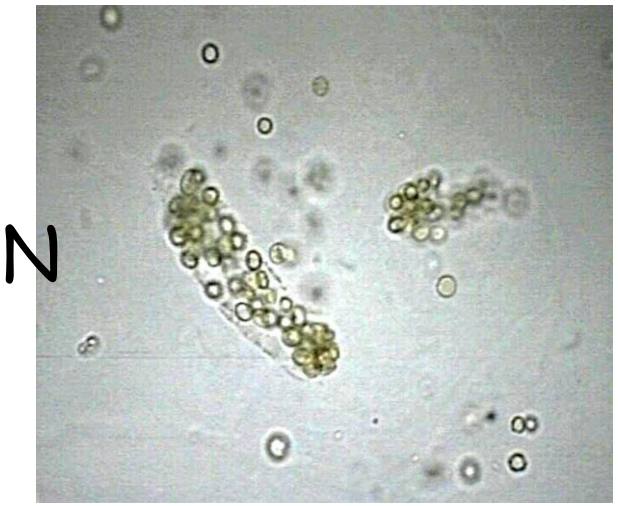
Urinary patterns associated with different kidney diseases

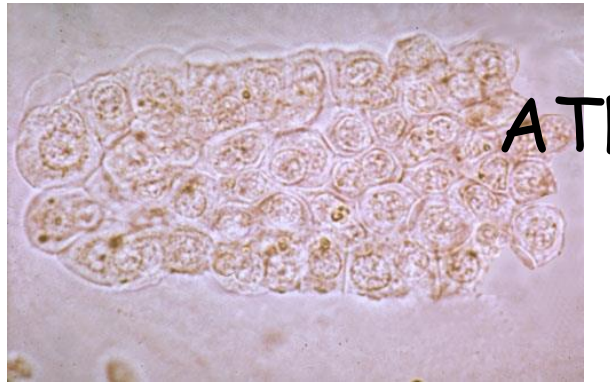
Urinary pattern	Kidney disease suggested by pattern
Hematuria with dysmorphic red blood cells, red blood cell casts, varying degrees of albuminuria	Proliferative glomerulonephritis (eg, IgA nephropathy, ANCA-associated vasculitis, lupus nephritis)
Heavy albuminuria with minimal or absent hematuria	Nonproliferative glomerulopathy (eg, diabetes, amyloidosis, membranous nephropathy, focal segmental glomerulosclerosis, minimal change)
Multiple granular and epithelial cell casts with free epithelial cells	Acute tubular necrosis in a patient with underlying acute kidney injury
Isolated pyuria	Infection (bacterial, mycobacterial) or tubulointerstitial disease
Abnormal kidney function with normal dipstick and sediment containing few cells, no casts, and no or minimal proteinuria	▪ Prerenal acute kidney injury due to either volume contraction or an effective decrease in circulating volume (eg, heart failure, liver disease) ▪ Hypercalcemia ▪ Light chain cast nephropathy in multiple myeloma ▪ Tumor lysis syndrome ▪ Vascular disease that produces glomerular ischemia but not infarction (eg, hypertensive emergency, scleroderma, thrombotic microangiopathies) or that affects extraglomerular vessels (eg, cholesterol atheroemboli, polyarteritis nodosa) ▪ Urinary tract obstruction

ANCA: antineutrophil cytoplasmic antibody; IgA: immunoglobulin A.

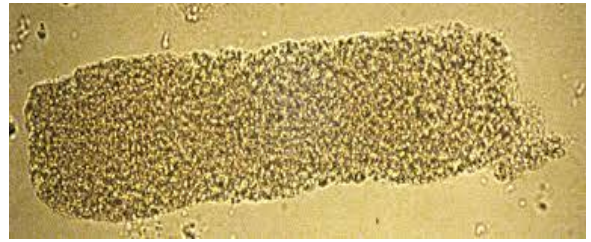


RPGN





ATN



Biochemical markers urine

Test	**Pre-renal azotaemia**	**Intrinsic AKI**
Sediment	Normal or hyaline casts	Casts, tubular epithelial cells
Sp. gravity	High >1.020	Low <1.020
uNa	Low <20 mmol/L	High>40mmol/L
FeNa	<1%	>1%
FeUr	<35%	>35%
Urine osmolality (mOsm/Kgr H_2O)	High>500	Near serum (<300)
uCr/sCr ratio	High>40	Low<10

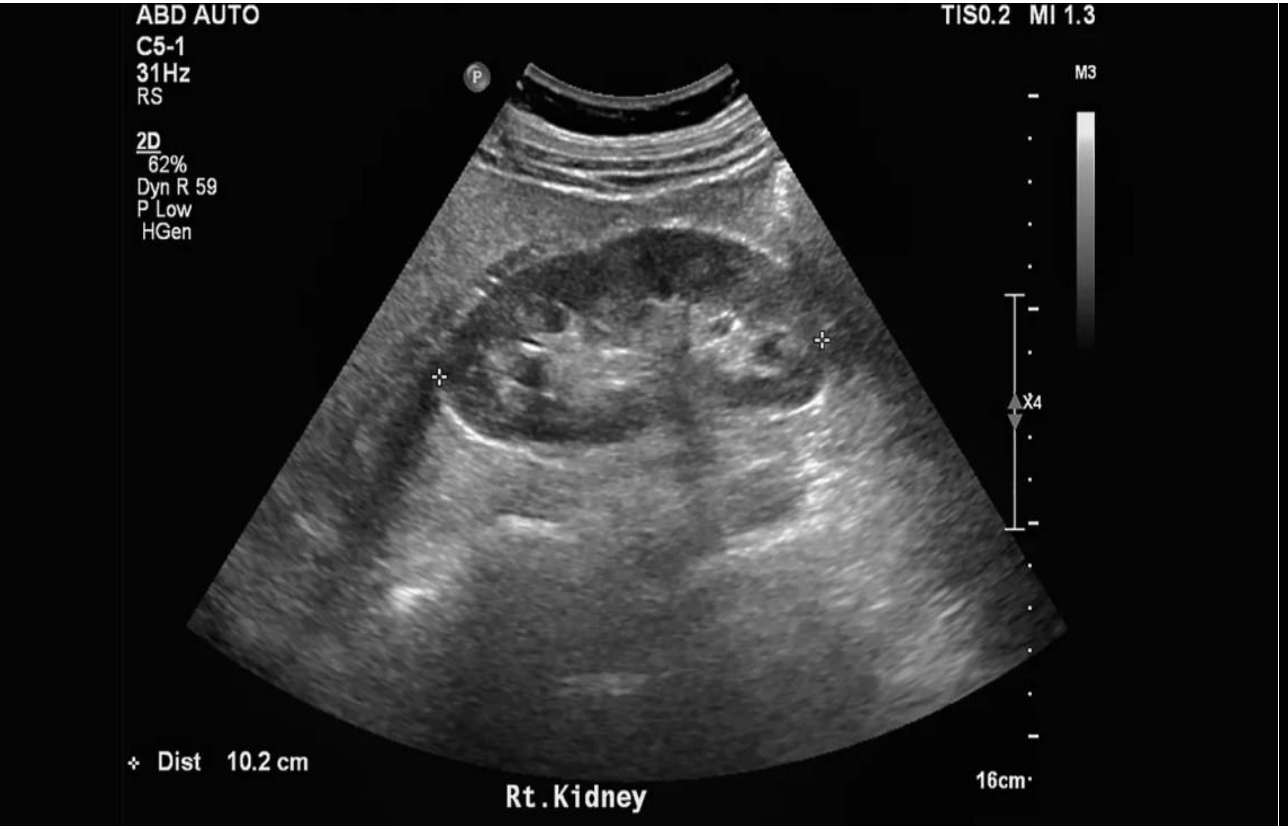
uNa=urinary Sodium, FeNa=fractional excretion of sodium, FeUr=fractional excretion of urea, uCr=urinary creatinine, sCr=serum creatinine

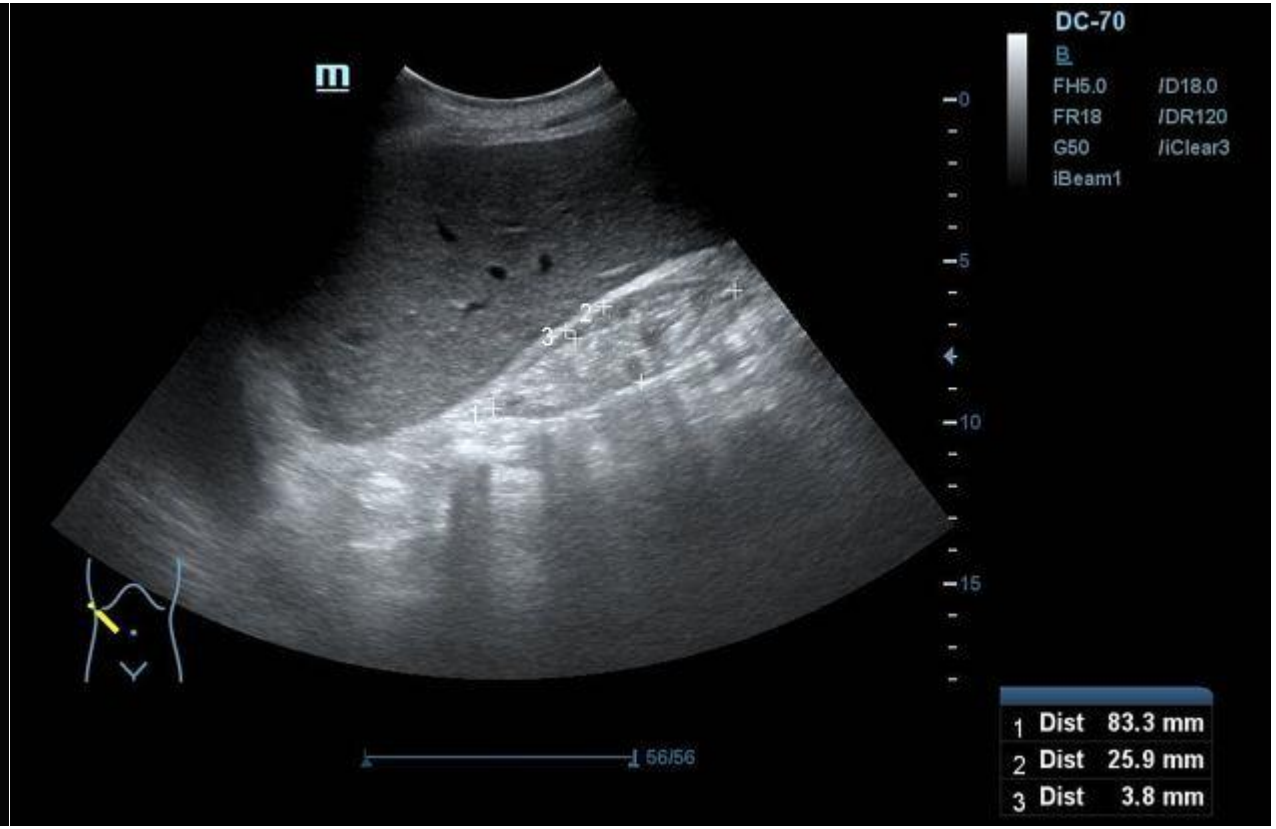
What about imaging studies?

- Almost everyone needs an **ultrasound** to diagnose/exclude an obstruction or CKD.
- Some will need a **CT scan** to better differentiate the reason of obstruction(Stone, cancer).
- Other modalities such as triplex, scintigram, angiography are rarely needed for assessment of vascular problems.

Ultrasound - CKD

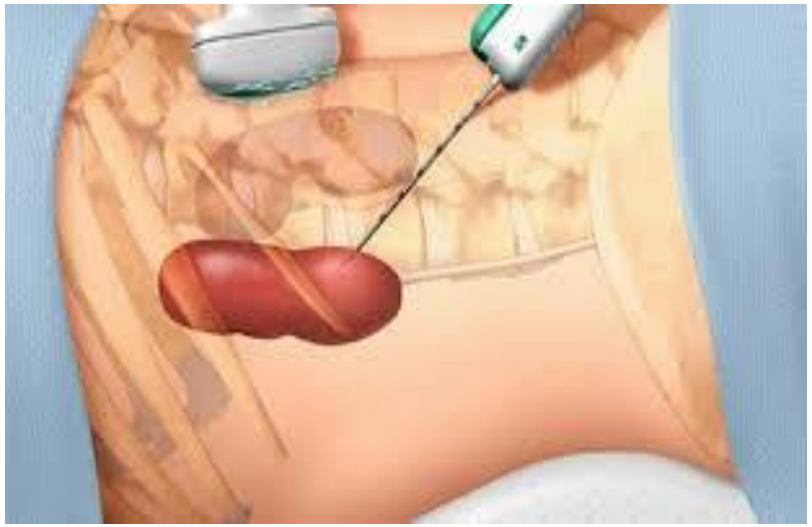
Small kidneys(<9cm), hyperechogenic, reduced cortical thickness(<1cm)





Kidney biopsy

- Prolonged AKI
- Unknown diagnose, no obvious cause.
- Evidence of glomerular or interstitial injury.



Complications

- Fluid retention that leads to volume overload/pulmonary edema
- Hyperkaliemia
- Metabolic acidosis
- Uremia(vomiting, pericarditis, neurological complications, GI hemorrhage)
- Infection/Sepsis

Therapies related to the cause

- Volume depletion. IV fluid therapy.
- Urinary tract obstruction. Treat the obstruction.
- Sepsis. Treat the infection, hypotension, IV fluid therapy.
- Heart failure with edema. Diuresis.
- Rhabdomyolysis. IV fluid therapy, alkaline urine.
- Acute interstitial nephritis. Corticosteroids.
- Acute tubular necrosis. Wait.
- Myeloma Kidney. Chemotherapy.
- RPGN. Immunsupression.

Subsequent management

- Stop medications(NSAIDs, RAAS blockades, SGLT2 inhibitors).
- Correct dosing of medications based on GFR.
- Treat hypotension.
- Treat hyperkalemia, hyperphosphatemia, metabolic acidosis.
- Care about the nutrition.
- Polyuria after lysis of AKI, particularly by ATN and obstructive AKI.

Dialysis?

We dialyze to manage the complications, not to reverse the AKI!
We don't dialyze because of high creatinine(most of the times).

Indications:

- Pulmonary edema
- Severe hyperkaliemia(>6,5meQ/L) or symptoms and signs
- Severe metabolic acidosis(ph<=7.1)
- Life-threatening uremic symptoms(seizures, pericarditis, somnolence)

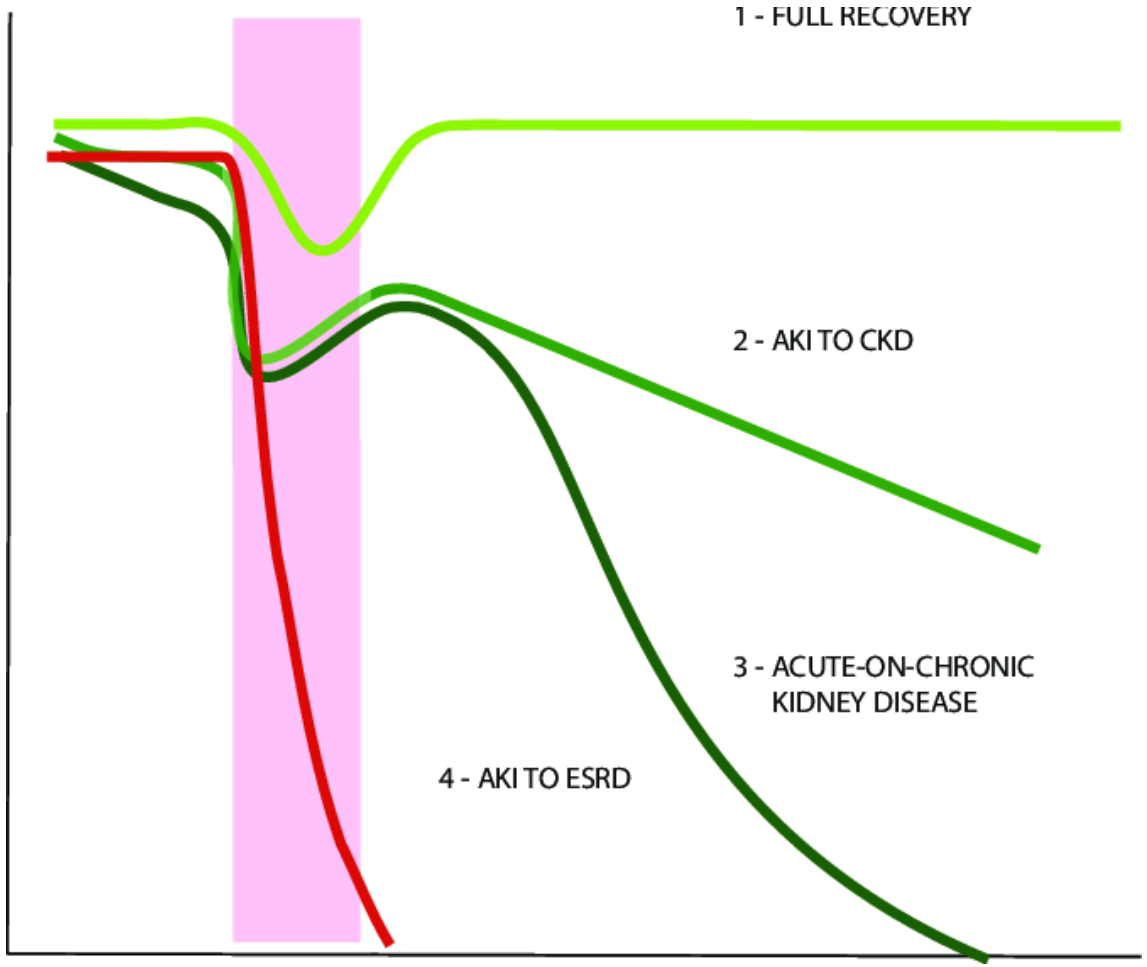
Dialysis Mini Quiz

	Dialysis?	
• Patient with Creatinine 10mg/dl, Urea 400mg/dl, K 5,6meQ/L, volume depletion, Diuresis 300ml/24h .	Y	N
• Patient with heart failure, edema, dyspnoe, creatinine 3mg/dl, urea 210mg/dl, Diuresis 2lt/24h with diuretics.	Y	N
• Patient with rhabdomyolysis, creatinine 5mg/dl, urea 200mg/dl, K 5,9 meQ/L, T waves in ECG Diuresis 2lt/24h.	Y	N
• Patient with metastatic cancer, DNR, creatinine 8mg/dl, hypovolemia, sepsis, K 7,3meQ/L, ph 7,08, Diuresis 400ml/24h.	Y	N
• Patient with hydronephrosis by prostatic cancer, K 6 meQ/L, creatinine 12mg/dl, anuria.	Y	N

Outcomes

- Patients with acute kidney injury (AKI) have a maintenance phase that typically lasts between 7 and 21 days but can last to 3 months.
- Whereas some patients recover within days, others require kidney replacement therapy (KRT) for weeks to months.
- Patients who recover from AKI may not return to their baseline kidney function, thus they develop CKD.

Outcomes


1 - FULL RECOVERY
2 - AKI TO CKD
3 - ACUTE-ON-CHRONIC KIDNEY DISEASE
4 - AKI TO ESRD

Thanks!