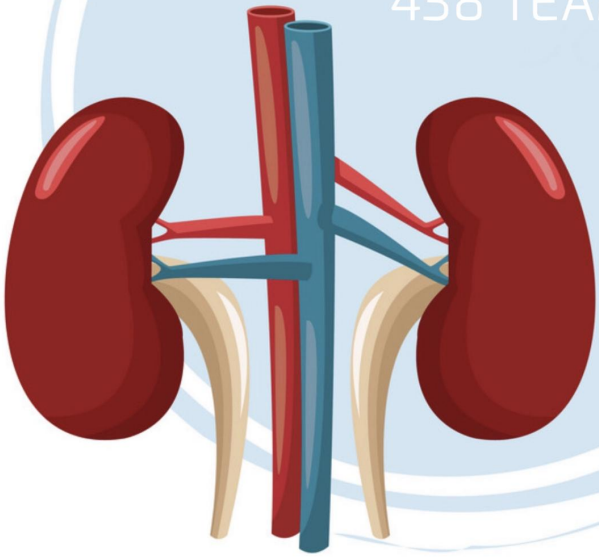
Editing file

Pathology

438 TEAM



Acute kidney injury
(Acute renal failure)

Objectives:

- Describe the guidelines of the renal biopsy.
- Recognize the types of acute kidney injury.
- Recognize the clinical manifestations of acute kidney injury.
- Describe the pathological findings in acute kidney injury.

Color index:

Black: original content.
Red: Important.
Light Purple: From Robbin's.
Blue: only found in boys slides.

Green: Boy's doctor notes .
Dark orange: Girl's Doctor notes.
Grey: Explanation.
Pink: Only found in girls slides.

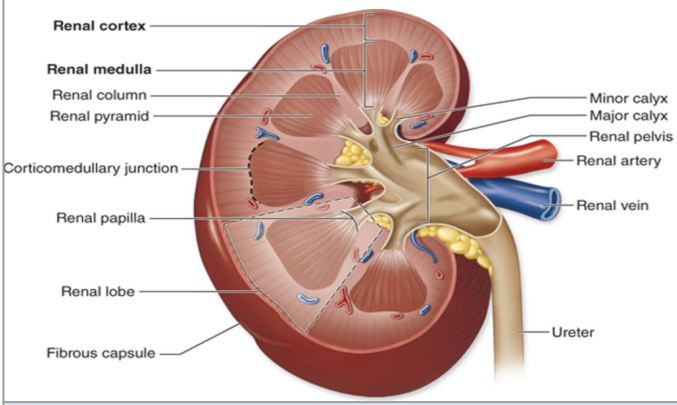
Pathology

Reviewed by: Rezan AlRabah & Ibrahim AlBabah

Introduction

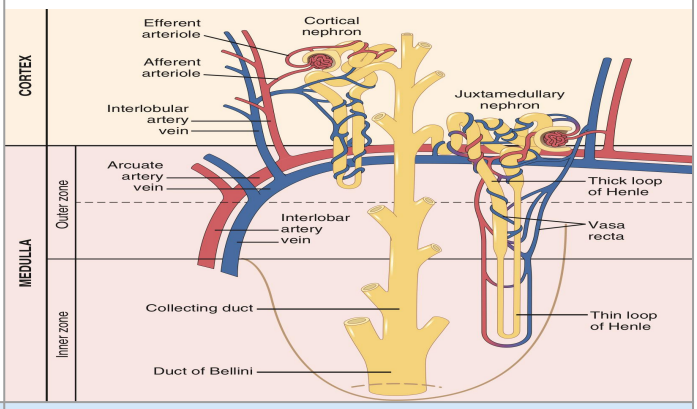
Normal anatomy and histology of kidney:

Kidney-cross section

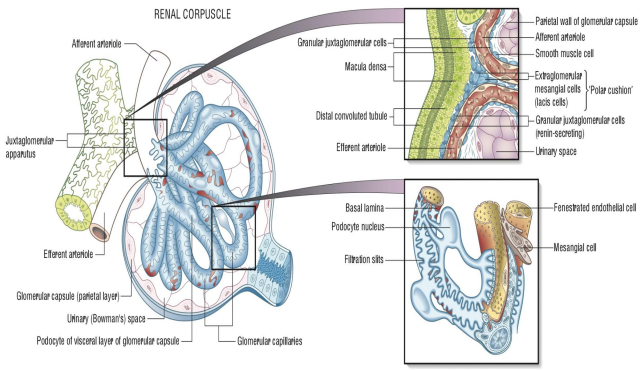


Nephron

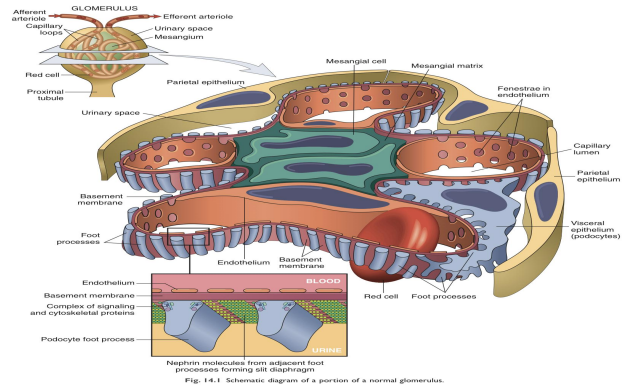
"the functional unit of the kidney"



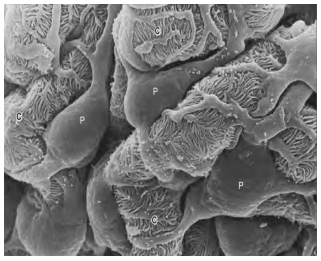
Renal corpuscle



Glomerulus-cross section

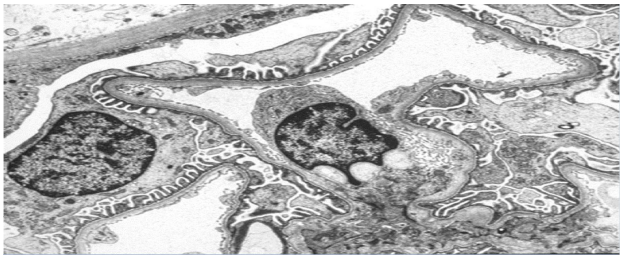


A **scanning electron micrograph** showing podocytes forming the visceral layer of Bowman's capsule in the renal corpuscle.
"scanning electron micrograph is used for research only"

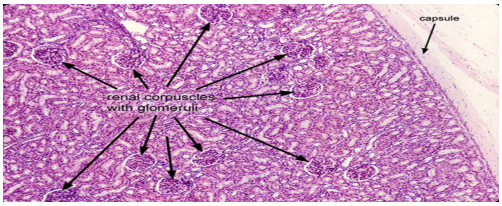


Their cell bodies (P) send out primary processes that branch several times and end in fine pedicels, which wrap tightly around the glomerular capillaries (C), and interdigitate with similar pedicels from a neighbouring podocyte.

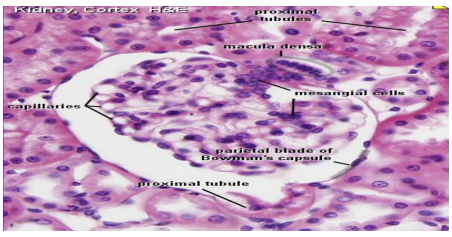
Transmission electron micrograph showing glomerulus
"Transmission EM is used in daily practice"



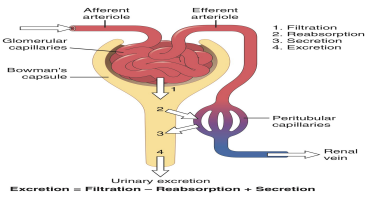
Cortex of kidney showing many renal corpuscles



Biopsy section showing normal glomerulus



Introduction (cont.)



Functions of normal kidney:

1- Excretory function:

- Detoxify blood, removal of toxins, nitrogenous wastes (urea and creatinine), drugs etc.

2- Homeostatic function:

- Maintain and regulate water balance and osmolality.
- Regulate electrolyte balance (Na+, K+, Ca2+, Cl-, Mg2+ ions etc.)
- Maintain and regulate acid-base balance (pH, H+ and HCO3- ions).

3- Endocrine function:

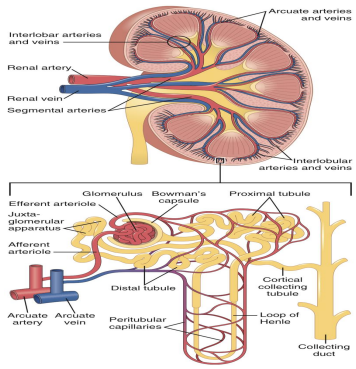
- Secretes **renin** from the *JGA cells* to regulate BP and electrolyte balance.
- Secretes **erythropoietin** from the *endothelial cells lining the cortical peritubular capillaries* to stimulate the bone marrow to produce RBCs.
- Converts inactive Vit D3 to active 1,25- dihydroxycholecalciferol by *alpha one hydroxylase enzyme* under the influence of PTH (Parathyroid hormone) → increases calcium absorption.

Introduction to Renal Pathology

EXTRA from Robbins

Diseases of the kidney are as complex as its structure, but their study is facilitated by dividing them into those that affect its four components:

1- glomeruli.
2- tubules.
3- interstitium.
4- blood vessels.



However, some disorders affect more than one structure, and functional interdependence of structures in the kidney means that damage to one component almost always affects the others.

For example:

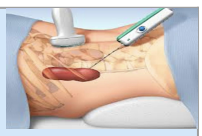
Severe glomerular damage impairs blood flow through the peritubular vascular system; conversely, tubular destruction, by increasing intraglomerular pressure and inducing the production of cytokines and chemokines, may lead to glomerular sclerosis.

Introduction to Renal Pathology cont.

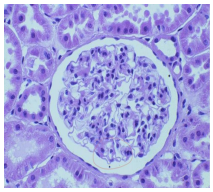
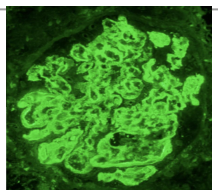
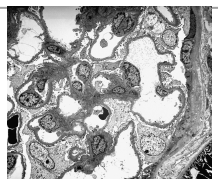
Some important terminology:

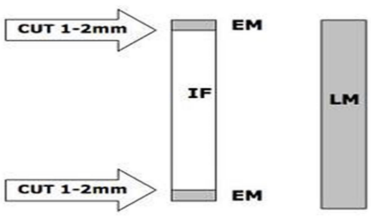
Terminology	Definition
Azotemia Azot=nitrogen emia=blood	• An abnormally high levels of nitrogen-containing compounds (such as urea, creatinine etc) in the blood, usually reflects a decreased GFR. • It can lead to uremia if not controlled. • When azotemia gives rise to clinical manifestations and systemic biochemical abnormalities, it is termed uremia.
Uremia "The word uremia means urine in the blood."	• A clinical syndrome associated with fluid, electrolyte, and hormone imbalances and metabolic abnormalities, which develops with deterioration of renal function. • It is due to the accumulation of organic waste products that are normally cleared by the kidneys. • Uremia can be seen in both chronic kidney disease and acute kidney injury.
Oliguria Oligo=little Uria=urine	• urine output less than 400 ml/24 hours
Anuria An= almost absent uria=urine	• urine output less than 200 ml/24 hours

Kidney biopsy



"Only with this combination of methods we can diagnose a kidney disease"

Light microscopy (LM)	• To study the histology in renal cortex & medulla,	 LM
Immunofluorescence (IF)	• To detect the presence of immunoglobulins (IgA, IgG, IgM) and complements (C3 and C1q) in the glomerular mesangium or in the wall of the glomerular capillary loops.	 IF "positive for IgA"
Electron microscopy (EM)	• To detect the presence or absence of effacement of the epithelial cell (podocytes) foot processes. • electron dense immune complex deposits. • If deposits are present then to identify the location of the deposits in the glomeruli (mesangial/paramesangial, subepithelial.)	 EM



In kidney biopsy we usually take 2 cores:

- One for LM
- One for EM and IF.

Renal failure

Definition

- Renal failure or kidney failure (renal insufficiency): is when the kidneys fail to adequately filter toxins and waste products **(decrease in GFR)** from the blood. It can be acute (acute kidney injury) or chronic (chronic kidney disease). Biochemically, renal failure is typically detected by an elevated serum creatinine level.
- Note: Creatinine clearance or filtration is *dependent* on the glomerular filtration rate (GFR).

Renal failure can be classified based on:

Duration	**Acute:** • sudden onset • rapid reduction in urine output • usually reversible.
	Chronic: • gradually progressive with nephron loss • usually not reversible
Etiology	**Pre-renal** (before the kidney), **renal** (within the kidney) or **post-renal** (after the kidney)
Urine output	**Oliguric:** urine output less than 400cc/24hr.
	Non-oliguric: urine output greater than 400cc/24hr.
	Anuric: urine output less than 100cc/24hr. "It's different from the one mentioned before, those numbers are always changing so just know the range and the concept"

Note: sometimes more than 70% of renal function (of both kidneys) can be lost before it is clinically noticeable

Case by the Doctor:

A patient comes to ER bleeding after a trauma, you will find that his urine output is decreased and his creatinine and urea levels are high.

Diagnosis?

Acute kidney injury(Acute renal failure)

Etiology in this case?

Pre-renal, Hypovolemia.

Why did he have increased Cr and urea?

Because this patient is losing his blood(due to the trauma), so less blood is filtered leading to increased creatinine and urea concentration in blood.

How do we treat him?

Replace blood and electrolytes immediately, and the problem will be solved(reversible)

ACUTE KIDNEY INJURY

Definition

AKI (also known as Acute renal failure) is a syndrome defined by a sudden loss of renal function over several hours to days resulting in the accumulation of nitrogenous compounds such as urea and creatinine. It can result from glomerular injury, interstitial injury, vascular injury, or acute tubular epithelial cell injury.

Characteristics

- Sudden decrease in GFR (hours to days)
- Accumulation of nitrogenous waste products. (Rapid rise in serum creatinine.)
- Oliguria: the urine output is markedly decreased (usually it is less than 400 ml/day).
  "Could be associated with anuria as well"
- Fluid imbalance; electrolyte imbalance; acid-base disturbance; and mineral disorders.

Pathogenesis Of Acute Kidney Injury:

The pathogenesis depends on the etiology, this one is just an example

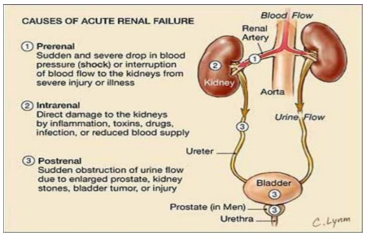
1. Reduction in renal blood flow/ renal perfusion.
2. Decrease in glomerular filtration rate (this is the common pathologic pathway for AKI regardless of the cause).
3. Activation of renin-angiotensin-aldosterone system.
4. Increased sodium reabsorption, increased water retention.
5. Increased urinary creatinine concentration.
6. Increased urine specific gravity[1] and increased urine osmolality.
7. Acids are retained and HCO_3 is excreted.

1- A urine specific gravity test compares the density of urine to the density of water. This quick test can help determine how well your kidneys are diluting your urine.

ACUTE KIDNEY INJURY

Etiology

- **Pre-renal (55-60%)** — the renal tubular and glomerular functions are normal. Here the GFR is decreased due to reduced renal perfusion.
- **Renal (35-40%)** — is due to diseases of the kidney itself (which is associated with release of renal afferent vasoconstrictors).
- **Post-renal (5-10%)** — occurs when an obstruction in the urinary tract below the kidneys causes waste to build up in the kidneys.



A) Pre-renal causes of ARF (Pre-renal azotemia)

Pre-renal pathology is the most common cause of ARF

It **results from decreased renal perfusion/ hypoperfusion** (i.e. decreased effective blood flow to the kidney).

Normally there are compensatory mechanism but in severe hypoperfusion → GFR is markedly decreased → AKI.

The treatment of the cause restores the renal function. (reversible)

***(Important to know all of them because it may come as cases)**

Pre-renal causes of ARF

- **Hypovolemia:** e.g. hemorrhage, volume depletion (dehydration or GIT fluid loss in vomiting, diarrhea), hypoalbuminemia, diuretics, third space losses (burns, peritonitis, muscle trauma, hypoalbuminemia), Renal losses (Drug-induced or osmotic diuresis, diabetes insipidus) etc.
- **Impaired cardiac function:** cardiac failure, myocardial infarction, massive pulmonary embolism, pulmonary HTN, vascular disease, systemic vasodilation, liver failure.
- **Sepsis, septic shock:** AKI can occur in patients with sepsis. Combination of AKI & sepsis has a high mortality rate.
- **Cirrhosis**[1]: cirrhotic patients can develop a type of kidney injury that is secondary to renal vasoconstriction known as *hepatorenal syndrome*.
- Other causes: Anaphylaxis,surgery, NSAIDS , ACEIs, ARBs, etc.

1-cirrhosis=chronic damage of liver,damaged liver secretes NO>dilation>hypotension>decrease in RBF>increase RAAS>constriction

B) Post-Renal causes

Any obstruction to the outflow of urine:

1. **In young**
   congenital or structural abnormality
2. **Older male**
   prostatic enlargement (benign prostatic hyperplasia)
3. **Obstruction by stones**
   Obstruction by stones in the urinary tract (e.g. bilateral renal calculi)
4. **Tumors**
   Any tumor in the ureters, bladder, prostate, urethra causing obstruction of the urinary tract.
5. **External compression**
   External compression (from the outside) of the urinary tract by retroperitoneal fibrosis or tumors (e.g. carcinoma of cervix).
6. **Others**
   - **Bladder outlet obstruction:** BPH,Malignancy, anticholinergic drugs,displaced bladder catheter
   - **Ureteral obstruction:** Malignancy,retroperitoneal fibrosis,nephrolithiasis
   - **Renal pelvis/tubular obstruction:** Nephrolithiasis, drugs.

C) Renal (Intrinsic) causes

- **The renal causes of ARF are divided into glomerular, tubular, vascular and interstitial causes.**
- **The disease may involve one or more of the above mentioned renal compartments.**

Causes	Glomerular causes	Vascular causes	interstitial causes	tubular causes
Pathogenesis	**Severe forms of active glomerulonephritis (GN) has glomerular injury→reduction in total filtration area→reduction in GFR.**	**Various forms of vasculitis and emboli lead to reduced renal blood flow due to vascular obstruction or destruction, thus lowering the GFR.**	-	**Acute Tubular Injury/Necrosis** (explained in next page)
Examples	-Post infectious GN -Rapidly progressive crescentic GN - Active autoimmune GN,Etc	• Vasculitis;ex:wegeners and polyarthritis nodosa • Thromboembolic disease (renal artery/ renal vein thrombosis) • **Thrombotic microangiopathies (HUS/TTP)** • Malignant hypertension • atherothromboembolism	- Malignant infiltration in interstitium (Rare) - **Acute Tubulo-interstitial Nephritis (TIN),e.g.** • Drug induced TIN (NSAIDs, Certain antibiotics) • Autoimmune TIN • Infections TIN	

The kidney biopsy of a patient with AKI can show any of the previously mentioned causes but the most common causes are:

- **Tubular cause:**
  - acute tubular injury or acute tubular necrosis(coagulative necrosis)
- **Glomerular cause:**
  - Post infectious glomerulonephritis (later lectures)
  - Rapid progressive crescentic glomerulonephritis (later lectures)
- **Interstitial cause:**
  - acute tubulointerstitial nephritis (later lectures)

Acute Tubular Injury/Necrosis

Acute Tubular Injury/Necrosis

In acute tubular injury/necrosis there is damage to the **epithelial** cells of the renal tubule and it leads to rapid decline of renal function (i.e. AKI) and presence of **granular casts** and **tubular cells** in urine. The damage can be induced by 2 ways:

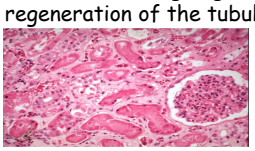
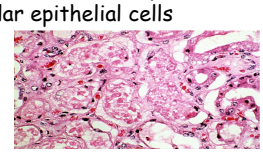
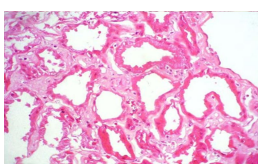
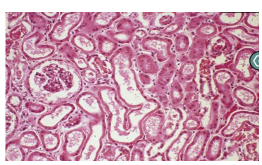
	1) Ischemia	2) Nephrotoxic
Definition	Any condition that causes prolonged and persistent **hypovolemia** or **circulatory shock** can lead to ischemic injury. **The straight segment of the proximal tubule is most vulnerable to ischemia.**	toxicity to nephrons leads to **tubular injury & necrosis (direct injury to the tubules by toxins)**
P.G	Significant ischemia to the kidney → vasoconstriction of afferent arteriole → ↓ GFR → acute tubular injury/necrosis.	direct injury of the tubules by toxins → acute tubular injury/necrosis (death of cells) → cells plugg the tubule → ↑Bowman's capsule hydrostatic pressure → ↓ GFR

Examples	• extensive trauma
	• burns
	• hemorrhage
	• pancreatitis
	• incompatible blood transfusions
	• dehydration
	• septic shock
	• hypotension
	• sepsis
	
	1-indicating Lysed blood in urine
	2-a cancer of plasma cells
	3-calcineurin=calcium that activate T-cells
		1) Endogenous toxins
		• **Pigments and casts:**
		  • **Myoglobinuria**:by breaking down to substances that cause damage to kidney cells(results from damaged cells. E.g. Rhabdomyolysis)
		  • **Hemoglobinuria**[1]
		  • **Myeloma casts**
		  • uric acid
		  • myeloma light chains
		
		2) Exogenous toxins
		• **Nephrotoxic drugs:**
		- **Antibiotics (Aminoglycosides**, Tetracyclines, Amphotericin, Cephalosporins etc.)
		- **Amphotericin B**
		- **Calcineurin**[3] **inhibitors** (e.g.,tacrolimus)
		• **Miscellaneous:** Cisplatin, Doxorubicin,Carbon tetrachloride, **contrast medium/dye used in various radiological tests.**
		• **Heavy metals:** Mercury, **Lead**, Arsenic, Gold salts, Barium
		
		*You **must** remember all it will come as a case e.g.A patient was exposed to arsenic...

Morphology of Acute tubular injury/necrosis

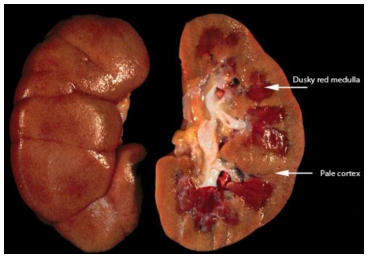
Histological morphology:

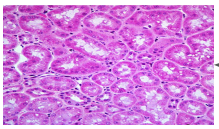
- Ranges from tubular epithelial cell swelling (mild injury) to tubular epithelial cell necrosis (severe injury).
- The proximal tubules are dilated with thinning of tubular wall.
- The tubular epithelial cells are flattened and show loss of brush border
- Hyaline, granular and pigmented casts are present in the lumen of the distal tubules.
- The interstitium has mild edema.
- Later as healing begins there is subsequent regeneration of the tubular epithelial cells

Gross morphology:

- bilaterally enlarged & swollen kidneys (due to edema).
- Cut surface shows a pale cortex and a dark & congested medulla.
- Note that in chronic renal failure the kidney will get shrunken not enlarged.





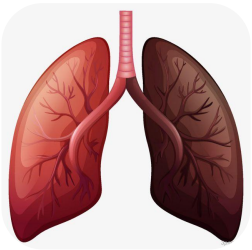
Normal tubule

Clinical features of AKI

01

Pulmonary edema

Pulmonary edema (shortness of breath due to extra fluid on the lungs) during this phase.



02

Defective elimination

Defective elimination of metabolic waste, water, electrolytes, and acids from the body. Waste material is accumulated in the body which causes azotemia (→ vomiting), acid-base imbalance (→ acidosis) and electrolyte imbalance like hypernatremia and hyperkalemia (→ abnormal heart rhythms, risk of heart failure, weakness and muscle paralysis).

03

Peripheral edema

Salt and water retention → starting with swelling in legs, ankles or feet → generalized edema.

04

Oliguria

Decreased urine output (occasionally urine output remains normal). Typically the urinary output is **< 400 ml/day**.

05

Other features include

- Hypotension
- Tachycardia
- Nephritic syndrome
- Nausea, vomiting, flank pain
- Fatigue
- Uremic encephalopathy, confusion, seizures or coma in severe cases
- Sometimes acute kidney failure causes no signs or symptoms and is detected through lab tests done for another reason.

Diagnosis

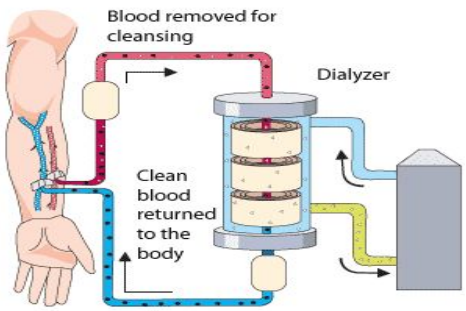
Diagnosis:

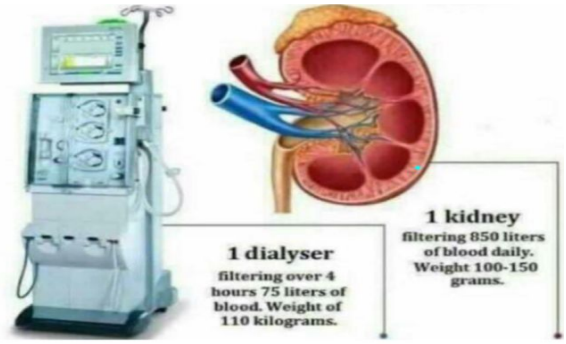
- Based on Kidney Disease Improving Global Outcomes (KDIGO)[1] AKI can be diagnosed if any one of the following is present:

1. Increase in sCr ≥ 0.3 mg/dL (≥26.5 µmol/L) within 48 hours.
2. Increase in sCr ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.
3. Urine volume < 0.5 mL/kg/h for 6 hours.

Treatment

1. Treat the underlying etiology.
   E.g.: hypovolemia → blood transfusion
2. Correction of acidosis and electrolyte imbalance e.g. hyperkalemia
3. Correction of fluid imbalance.
4. Dialysis.





1-KDIGO is the global nonprofit organization developing and implementing evidence-based clinical practice guidelines in kidney disease

Summary

Characterized by:
- Sudden decrease in GFR.
- Accumulation of nitrogenous waste.
- Rapid rise in serum creatinine.
- Oliguria.
- Fluid/ electrolyte imbalance.

Acute Kidney Injury (AKI) -

syndrome defined by a sudden loss of renal function over several hours to days resulting in the accumulation of nitrogenous compounds such as urea and creatinine

Defined by one of:
- ↑ in sCr ≥ 0.3 mg/dL within 48 hrs.
- ↑ in sCr ≥ 1.5 times baseline within the prior 7 days.
- urine volume < 0.5 mL/kg/h for 6 hrs.

Prerenal (55-60%)

- Renal tubular and glomerular functions are normal.
- GFR is decreased due to reduced renal perfusion.
- **Causes**: (anything that leads to renal hypoperfusion)
  1) Hypovolemia (*eg*, Hemorrhage)
  2) Impaired cardiac function (*eg*. Cardiac failure)
  3) Sepsis/ Septic shock
  4) Cirrhosis
  5) Anaphylaxis
  6) Other causes: surgery, NSAIDS and nephrotoxicity.

Renal/Intrinsic (35-40%)

due to diseases of the kidney itself (associated with release of renal afferent vasoconstrictors)

Glomerular damage:
eg. Acute glomerulonephritis

Tubular damage:
(acute injury or necrosis)

Ischemic

Vascular damage:
(vascular obstruction → reduced perfusion → ↓ GFR)
eg. Vasculitis, Thrombosis.

Toxic:
→ Exogenous (Nephrotoxic drugs)
→ Endogenous (Pigments and casts)
→ Radiographic contrast medium/dyes

Interstitial damage: (Acute Tubulointerstitial Nephritis - TIS)
eg. Drug induced TIN, Autoimmune TIN, infectious TIN.

Postrenal (5-10%)

- Any obstruction to the outflow of urine.
- **Causes**:
  1) Young → congenital abnormality.
  2) Older male → benign prostatic hyperplasia.
  3) Obstruction by stones → bilateral renal calculi.
  4) Tumor
  5) External compression

Quiz

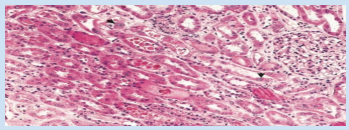
Answer key: Answers Explanation File!

1) B ; 2) A ; 3) A ; 4) E ; 5) A ; 6)

1) AT is a 54-year-old female presenting to the emergency department with acute kidney injury (AKI) secondary to dehydration. Her labs indicate the following: Na 133 mEq/L (133 mmol/L), K 5.8 mEq/L (5.8 mmol/L), Cl 101 mEq/L (101 mmol/L), CO2 22 mEq/L (22 mmol/L), PO4 5.3 mg/dL (1.71 mmol/L), Ca 7.8 mg/dL (1.95 mmol/L), BUN 33 mg/dL (11.8 mmol/L), and Scr 2.2 mg/dL (194 µmol/L). Which of the following electrolyte abnormalities does AT have that are commonly found in patients with AKI?

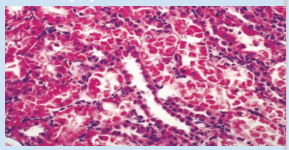
A	hypophosphatemia
B	hyperkalemia
C	Hyponatremia
D	Hypocalcemia
E	One of the above since Electrolytes usually unaffected

2) A 60-year-old man undergoes resection of an abdominal aneurysm, which is complicated by massive hemorrhage. Two days after surgery, the patient develops acute renal insufficiency. He is placed on dialysis but suffers a massive heart attack and dies. Microscopic examination of the kidneys at autopsy reveals necrotic epithelial cells within the lumina of some tubules (shown in the image). The arrows identify enlarged, regenerative epithelial cells. What is the appropriate diagnosis?



A	Acute interstitial nephritis
B	Acute tubular necrosis
C	Eosinophilic interstitial nephritis
D	Fanconi syndrome
E	Polyarteritis nodosa

3) A 60-year-old man presents with acute renal insufficiency. He treated his garden last week with a number of herbicides and insecticides, some of which may have contained heavy metals. Laboratory studies confirm oliguria and increased levels of BUN (54 mg/dL) and creatinine (3.7 mg/dL). A renal biopsy is shown. What is the most likely diagnosis?



A	Acute tubular necrosis (ATN)
B	Bilateral cortical necrosis
C	Papillary necrosis
D	Rapidly progressive glomerulonephritis
E	Tubulointerstitial nephritis

4) Acute tubular necrosis can be caused by all of the following except:-

A	Pancreatitis
B	Contrast dyes
C	Hemorrhage
D	Hypotension
E	Amyloidosis

5) A patient with acute renal injury has a GFR (glomerular filtration rate) of 40 mL/min. Which signs and symptoms below may this patient present with? Select all that apply:

A	Hypervolemia
B	Hypokalemia
C	Increased BUN level
D	Decreased Creatinine level
E	A & C

6) A 55 year old male patient is admitted with a massive GI bleed. The patient is at risk for what type of acute kidney injury?

A	Pre-renal
B	Intra-renal
C	Post-renal
D	Perirenal
E	B & C

Thank you

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