PATHOLOGY TEAM
439

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Acute Kidney Injury

Recommended videos for explanation :

Osmosis
Armando

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.

Key outlines:

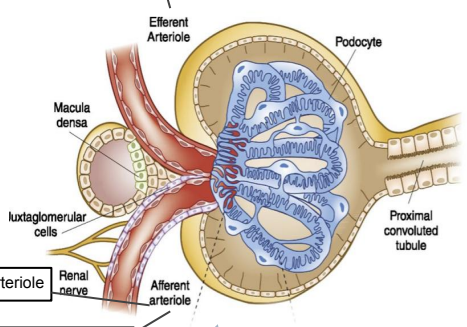
- Brief review of the normal anatomy and histology of the kidney and urinary tract.
- Terminology
- Etiology
- Pathophysiology
- Clinical manifestations with diagnostic approach.
- Pathological evaluation: The four elements possibly implicated: Gross and histological findings.
- Conclusion.

Index:
Important
NOTES
Extra Information

Introductory slide

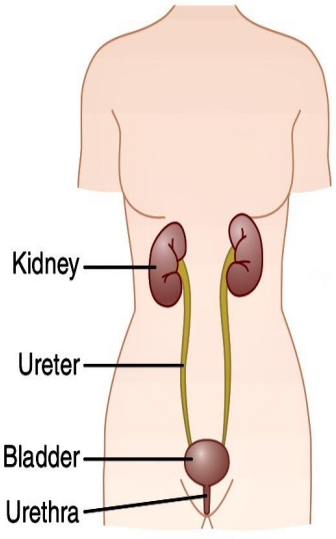
Anatomy of the kidney

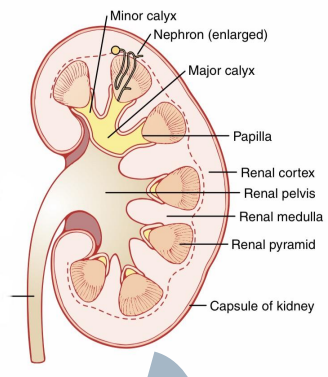
Efferent arteriole = High-resistance outflow pathway
Plus vasa recta

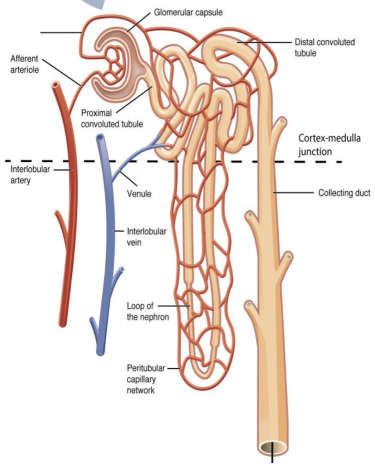


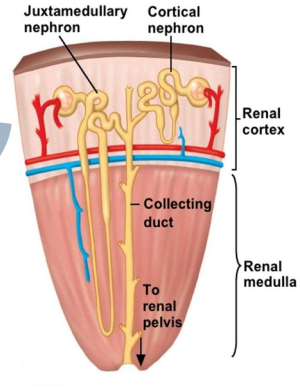
Flow controlled by vasoconstriction of afferent arteriole

Short , wide Afferent arteriole = Low-resistance input pathway





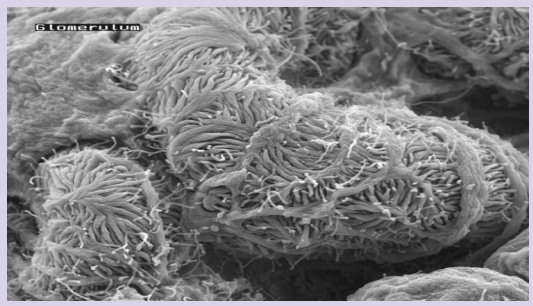




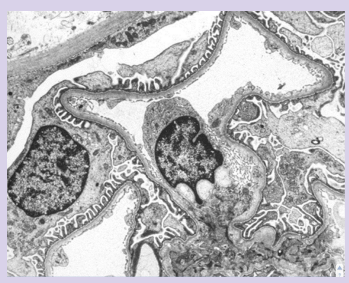
Histology of the glomerulus

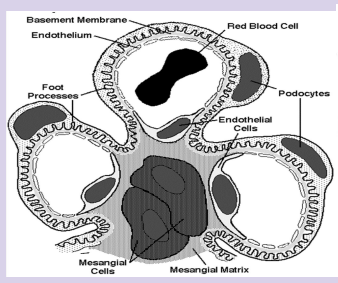
Glomerulus under the (EM)

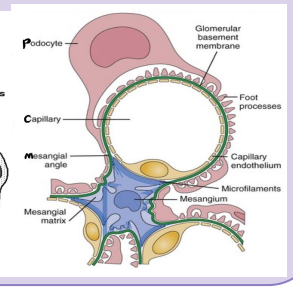
Scanning EM



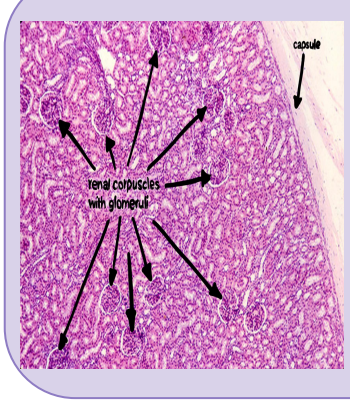
Transmission (cross section) EM

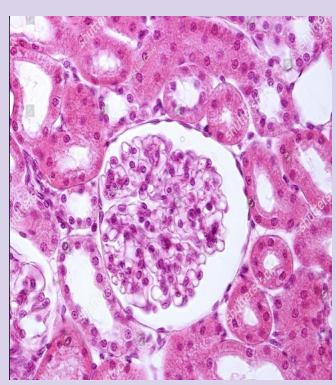


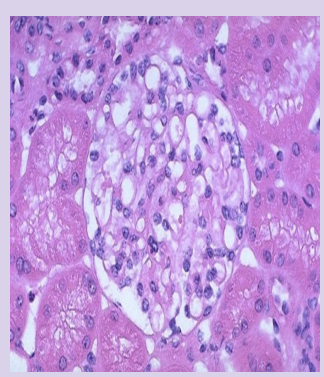


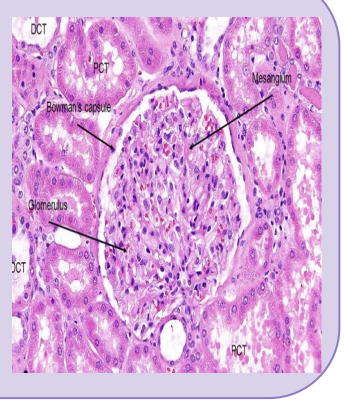


Glomerulus under the (LM)

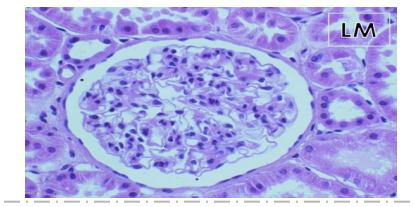
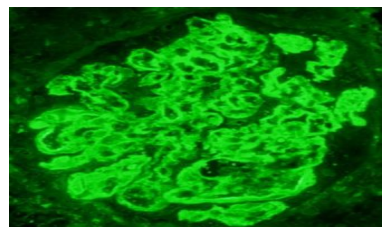


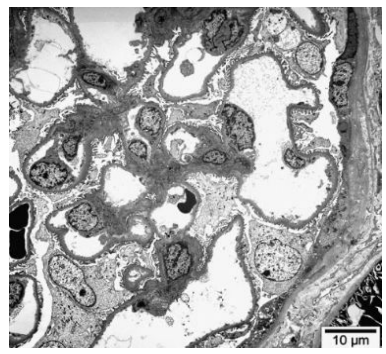






Kidney biopsy

Light microscopy (LM)	- Study the histology in renal cortex & medulla.	
Immunofluorescence (IF)	- Study is 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.	

Electron microscopy (EM) (ultrastructural)	- study is 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, subendothelial).
		

The kidney biopsy of a patient with AKI can show any of the previously mentioned causes. The common causes are:	• **Tubular cause:** acute tubular injury/ acute tubular necrosis
	• **Interstitial cause**: acute tubulointerstitial nephritis (later lectures)
	• Glomerular cause:
	  ○ Post infectious glomerulonephritis (later lectures)
	  ○ Rapid progressive crescentic glomerulonephritis (later lectures)	

Renal failure classification

Based on Duration

Acute	Chronic
• Sudden onset • Rapid reduction in urine output • Usually reversible	• Gradually progressive with nephron loss • Usually NOT reversible

based on Etiology

1- Pre-Renal (55-60%)	2- Renal (35-40%) :	3- Post-Renal (5-10%)
The renal tubular and **glomerular function are normal.** Here the **GFR is decreased** due to reduced renal perfusion.	Is due to diseases of the **kidney itself** (which is associated with release of renal afferent vasoconstrictors).	Occurs when obstruction in the urinary tract below the kidneys causes waste to build up in the kidneys.

based on Urine output

Oliguric	Non-oliguric	Anuric
Urine output **less** than 400cc/24hr	Urine output **greater** than 400cc/24hr	Urine output **less** than 100cc/24hr

NOTE: Sometimes more than 70% of renal function can be lost before it is clinically noticeable

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.

Important terminology	
Uremia	-is 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. -The word uremia means urine in the blood. Uremia can be seen in both chronic kidney disease and acute kidney injury.
Azotemia	-Is abnormally high levels of nitrogen-containing compounds (such as urea, creatinine etc) in the blood. -It can lead to uremia if not controlled. -It is an elevation of blood urea nitrogen (BUN) and serum creatinine levels.
Oliguria	-Urine output is markedly less than 400 ml/24 hours
Anuria	-Urine output less than 200 ml/24 hours
Renal Failure	• **Renal failure (Renal insufficiency)**: Is when the kidneys fail to adequately filter toxins and waste products from the blood. • In renal failure there is decrease in glomerular filtration rate(GFR) and an elevated serum creatinine level. (creatinine clearance or filtration is dependent on the GFR)

Acute kidney injury

Definition

AKI (previously called acute renal failure) is a syndrome defined by a sudden loss of renal function over several hours to days resulting in accumulation of nitrogenous compounds such as urea and creatinine.

AKI Characteristics

Sudden **decrease** in GFR (hours to days)
Accumulation of nitrogenous waste products
Rapid **rise** in serum creatinine
Oliguria
Fluid imbalance; electrolyte imbalance; acid-base disturbance; and mineral disorders

Pathogenesis Of Acute Kidney Injury

(The common pathological pathway for AKI regardless of the cause)

1-Reduction in renal blood flow/renal perfusion

→ 2-**Decrease in Glomerular filtration rate(GFR)**

↓ 3-activation of renin-angiotensin-aldosterone system(RAAS)

← 4-Increase urine Creatinine concentration

↓ 5-Increase sodium reabsorption and water retention

→ 6-Increase urine specific gravity and increase urine osmolarity

↓ 7-Acid are retained and HCO_3 is excreted

Based on Kidney Disease Improving Global Outcomes(KDIGO) **AKI is defined by the presence of any <u>one</u> of the following:**

- Increase in serum creatinine >=0.3mg/dL(26.5µmol/L) within 48 hours
- Increase in serum creatinine >= 1.5 times baseline, which is presumed to have occured within the prior 7 days.
- Urine volume <0.5mL/kg/h for 6 hours

1- Pre Renal (Pre-Renal azotemia)

Is the most common cause of Acute renal failure.

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

Initially the body tries to compensate but in **severe hypoperfusion** → GFR is markedly decreased → AKI

The treatment of the cause **restores** the renal function.

Pre Renal causes of ARF are: Anything that leads to renal Hypoperfusion:	
	Hypovolemia: e.g. hemorrhage, volume depletion (dehydration or GIT fluid loss in vomiting, diarrhea), hypoalbuminemia, diuretics, third space losses (burns, peritonitis, muscle trauma) etc.
	Impaired cardiac function (cardiac failure, myocardial infarction, massive pulmonary embolism).
	Sepsis, septic shock.
	Cirrhosis (it can cause renal vasoconstriction à kidney injury called "hepatorenal syndrome")
	Anaphylaxis
	Other causes: surgery, NSAIDS and other nephrotoxic drugs etc.

2- Renal Causes of AKI (Intrinsic causes)

Glomerular Diseases	in severe forms of active **glomerulonephritis (GN)** leads to reduction in total filtration area reduction in GFR. **Examples:** • -Post infectious GN • -Rapid progressive crescentic GN • -Active autoimmune GN • -Etc.	
Tubular Diseases Acute tubular injury/ Necrosis	**Ischemic cause:** prolonged ischemia to nephrons leads to tubular injury and necrosis.	**Nephrotoxic cause:** Toxicity to nephrons leads to tubular injury & necrosis. **Endogenous toxin** **Pigments and casts:** - Myoglobinuria (in Rhabdomyolysis) - Hemoglobinuria - Myeloma casts etc. **Exogenous toxin** **Nephrotoxic drugs**: - Aminoglycosides (antibiotic). - Amphotericin B - Calcineurin inhibitors (e.g.,tacrolimus) etc. **Radiographic contrast medium (dyes induced toxicity)**
Vascular Diseases	Various forms of vasculitis and emboli lead to reduced renal blood flow due to vascular obstruction or destruction, thus lowering the GFR. **Examples**: • Vasculitis • Thromboembolic disease (renal artery/ renal vein thrombosis) • Thrombotic microangiopathies (HUS/ TTP) • Malignant hypertension.	
Interstitial Diseases	Acute Tubulointerstitial Nephritis (TIN) **Examples:** • Drug induced TIN • Autoimmune TIN -Infections TIN Rarely malignant infiltration in interstitium can cause AKI	

3- Post Renal Causes of AKI/ARF

Any obstruction to the outflow of urine

Any obstruction to the outflow of urine:

1. Congenital or structural abnormality
2. Benign prostatic hyperplasia (older men)
3. Stones in the urinary tract
4. A tumor in the urinary tract (e.g. ureter, bladder, prostate, urethra).
5. Benign prostatic hyperplasia (older men)

Acute Tubular Injury/Necrosis

tubular cause of AKI (Acute kidney injury)

Definition

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 :

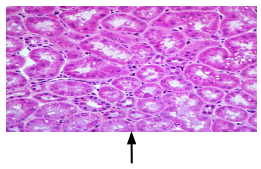
1. Ischemia leading to renal ischemic injury
2. Substances toxic to the kidney leading to nephrotoxic injury

Ischemia	Nephrotoxicity
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**	direct injury of the tubules by toxins → acute tubular injury/necrosis (death of cells) → cells plugg the tubule → ↑Bowman's capsule hydrostatic pressure → ↓ GFR
Significant ischemia to the kidney → vasoconstriction of afferent arteriole → ↓ GFR → acute tubular injury/necrosis	
· Extensive trauma · Burns · Hemorrhage · Pancreatitis · Incompatible blood transfusions · Dehydration · Septic shock · Hypotension · Sepsis	Causes include: ● *Antibiotics*: Aminoglycosides, Tetracyclines, amphotericin, Cephalosporins etc. ● *Heavy metals:* mercury, lead, arsenic, gold salts, barium etc. ● Others: cisplatin, doxorubicin, carbon tetrachloride, radiographic contrast agents, etc.

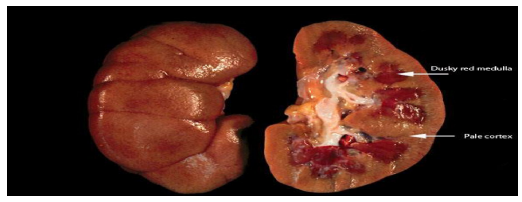
Gross morphology:

- 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

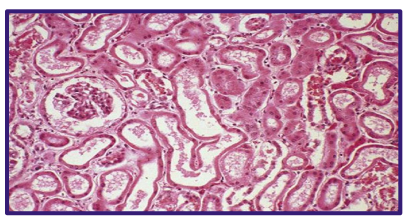
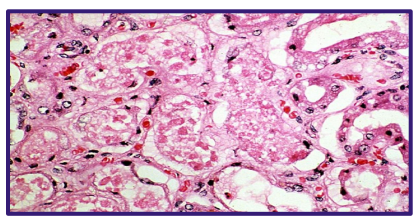
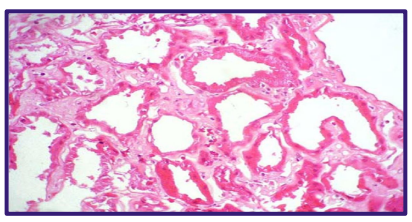
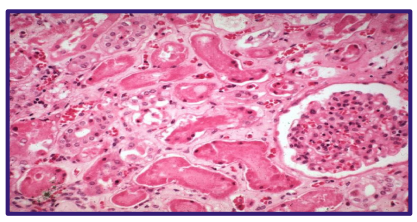


Normal tubule



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

Clinical features of AKI

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

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

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

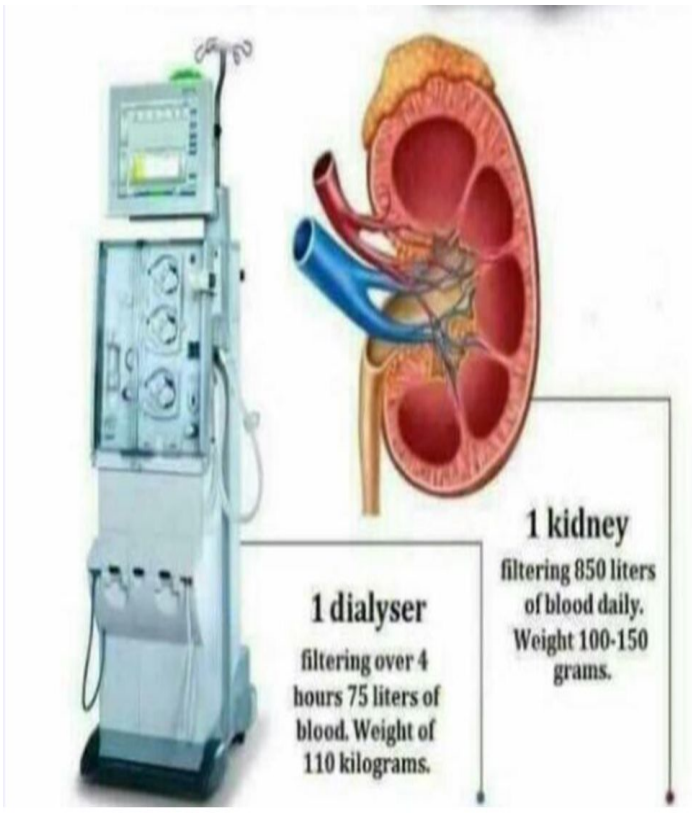
Oliguria Decreased urine output (occasionally urine output remains normal). Typically the urinary output is < 400 ml/day.

Other:
hypotension, nephritic syndrome, 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.

Treatment

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



Qulz

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 , what is the appropriate diagnosis			
a-Acute interstitial nephritis	b-Acute tubular necrosis	c-Eosinophilic interstitial nephritis	d-Polyarteritis nodosa
2-60-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). What is the most likely diagnosis?			
a-Acute tubular necrosis (ATN)	b-Bilateral cortical necrosis	c-papillary necrosis	d-non
3-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-post renal	c-intra renal	d-A+B
4-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-hyperkalemia	b-hyponatremia	c-Hypocalcemia	d-hypophosphatemia

1-B , 2-A , 3-A , 4-A

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