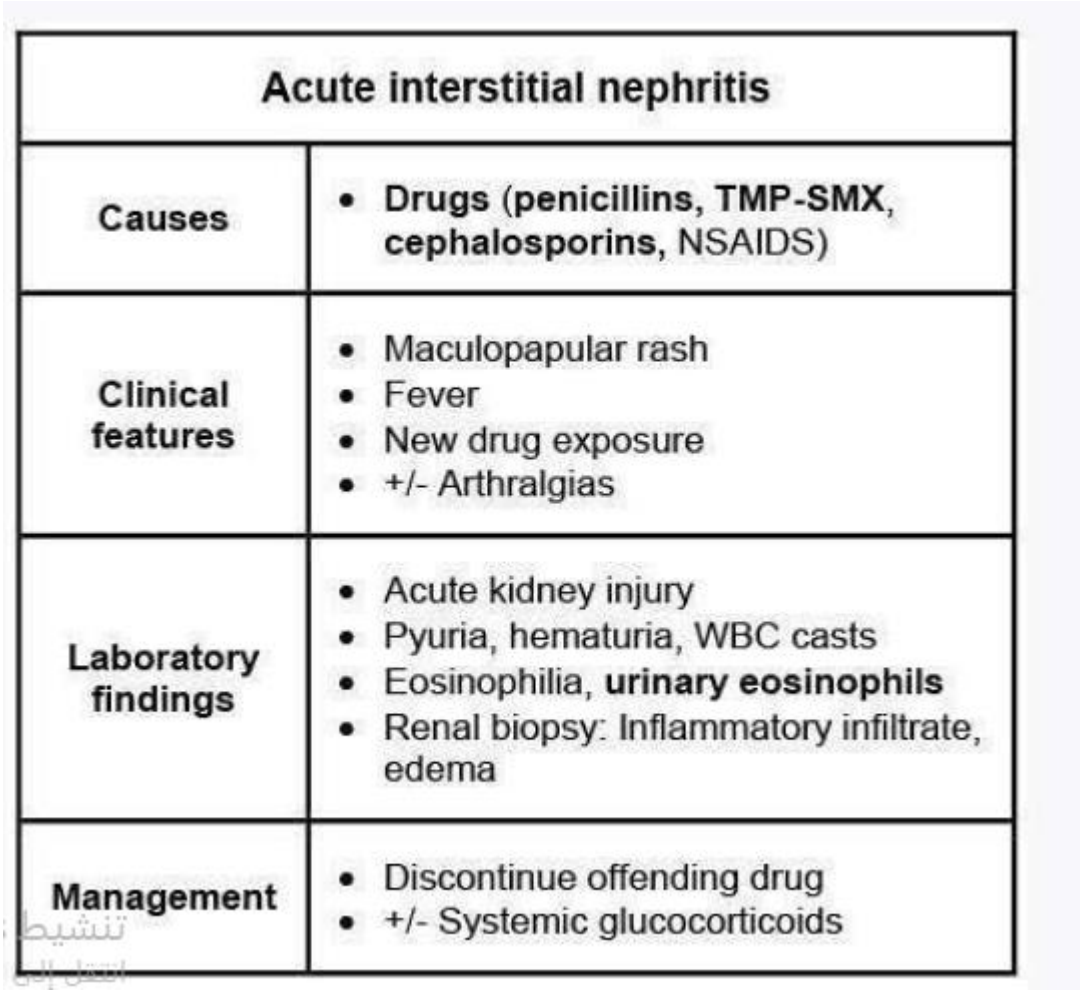
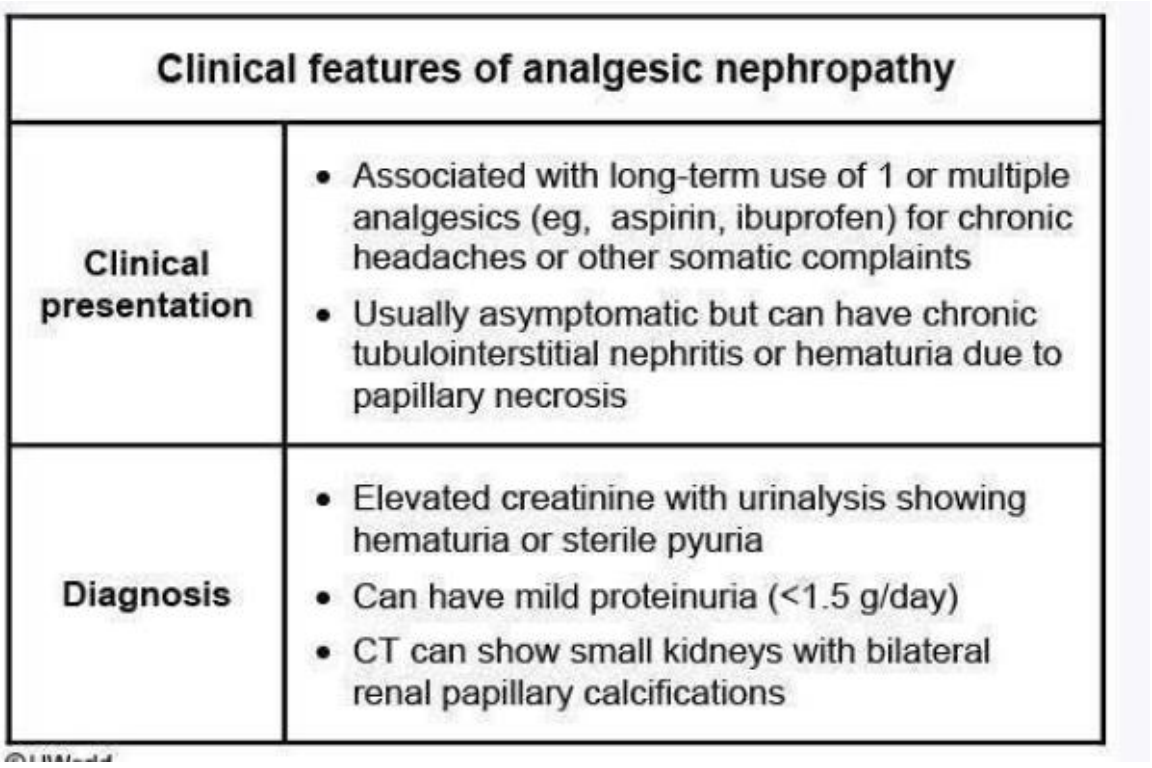
Renal

- 

Acute interstitial nephritis	
Causes	• **Drugs (penicillins, TMP-SMX, cephalosporins,** NSAIDS)
Clinical features	• Maculopapular rash • Fever • New drug exposure • +/- Arthralgias
Laboratory findings	• Acute kidney injury • Pyuria, hematuria, WBC casts • Eosinophilia, **urinary eosinophils** • Renal biopsy: Inflammatory infiltrate, edema
Management	• Discontinue offending drug • +/- Systemic glucocorticoids

- 

Clinical features of analgesic nephropathy	
Clinical presentation	• Associated with long-term use of 1 or multiple analgesics (eg, aspirin, ibuprofen) for chronic headaches or other somatic complaints • Usually asymptomatic but can have chronic tubulointerstitial nephritis or hematuria due to papillary necrosis
Diagnosis	• Elevated creatinine with urinalysis showing hematuria or sterile pyuria • Can have mild proteinuria (<1.5 g/day) • CT can show small kidneys with bilateral renal papillary calcifications

- Analgesic nephropathy is the most common form of drug-induced chronic renal failure. It accounts for 3-5% of end stage renal disease in the USA, and is most commonly seen in females (peak at age 50-55 years) who habitually use combined analgesics (e.g., aspirin and naproxen). It is generally seen after cumulative ingestion of 2-3 kg (4.4-6.6 lbs) of the index drug. Papillary necrosis and chronic tubulointerstitial nephritis are the most common pathologies seen. Polyuria and sterile pyuria (WBC casts may also be seen) are early manifestations. Microscopic hematuria and renal colic may occur following sloughing of renal papilla. Hypertension, mild proteinuria, and impaired urinary concentration commonly occur as the disease advances. In severe cases, nephrotic range proteinuria can be seen. Patients with chronic analgesic abuse are also more likely to develop premature aging, atherosclerotic vascular disease, and urinary tract cancer.
- Muddy brown granular cast - Acute tubular necrosis
  RBC casts - Glomerulonephritis
  WBC casts - Interstitial nephritis and pyelonephritis
  Fatty casts - Nephrotic syndrome
  Broad and waxy casts - Chronic renal failure
- **Clinical features of crystal-induced acute kidney injury**

Common etiologies	• Acyclovir • Sulfonamides • Methotrexate • Ethylene glycol • Protease inhibitors
Clinical presentation	• Usually asymptomatic • Elevated creatinine within 1-7 days of starting drug • Urinalysis can show hematuria, pyuria & crystals • ↑ Risk with underlying volume depletion, chronic kidney disease
Treatment	• Discontinue drug, volume repletion • Concurrent volume repletion while giving drug can prevent kidney injury

Large IV Doses

However, AIN usually occurs 7-10 days after drug exposure.

- Tuberculosis is a common cause of chronic primary adrenal insufficiency (Addison's disease) in endemic areas. Addison's disease causes aldosterone deficiency and presents with a non-anion gap and hyperkalemic and hyponatremic metabolic acidosis.

	AL amyloidosis	AA amyloidosis
Associated conditions	• Multiple myeloma • Waldenström macroglobulinemia	• Chronic inflammatory conditions: **rheumatoid arthritis**, inflammatory bowel disease • Chronic infections: osteomyelitis, tuberculosis
Composition of amyloid	• Light chains (usually lambda)	• Abnormally folded proteins: beta-2 microglobulin, apolipoprotein or transthyretin

AA amyloidosis = inflammatory amyloidosis; **AL amyloidosis** = amyloid light-chain amyloidosis.

- Rheumatoid arthritis is the most common cause of AA amyloidosis in the United States.
- Hyalinosis that affects both afferent and efferent arterioles is pathognomonic of diabetic nephropathy.
- Multiple myeloma is the most common cause of AL amyloidosis
- Aspirin intoxication should be suspected in a patient with the triad of fever, tinnitus, and tachypnea. Adults with aspirin toxicity develop a mixed respiratory alkalosis and anion gap metabolic acidosis. A normal pH in an acid-base disturbance typically signifies a mixed respiratory and metabolic acid-base disorder.

Acid-base disorders	
Primary disorder	**Appropriate compensation**
Metabolic acidosis	$PaCO_2 = 1.5$ (serum HCO_3^-) + 8 ± 2
Metabolic alkalosis	↑ $PaCO_2$ by 0.7 mm Hg for every 1 mEq/L rise in serum HCO_3^-
Acute respiratory acidosis	↑ Serum HCO_3^- by 1 mEq/L for every 10 mm Hg rise in $PaCO_2$
Acute respiratory alkalosis	↓ Serum HCO_3^- by 2 mEq/L for every 10 mm Hg decrease in $PaCO_2$

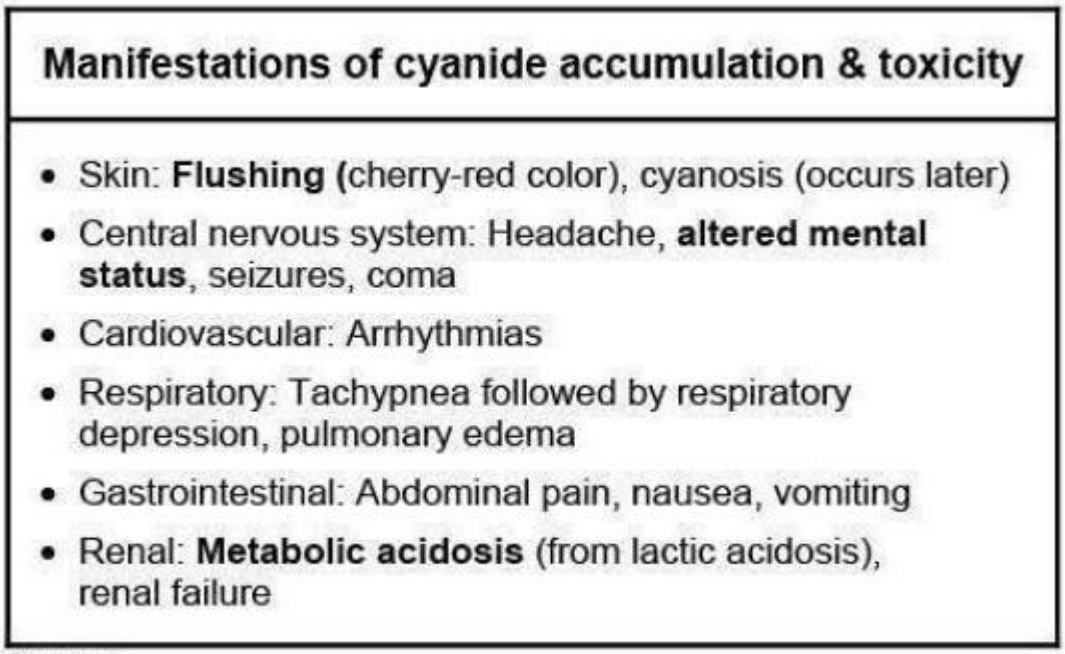
- **Educational Objective:**
  Platelet dysfunction is the most common cause of abnormal hemostasis in patients with CRF. PT, PTT, and platelet count are normal. BT is prolonged. DDAVP is usually the treatment of choice, if needed. DDAVP increases the release of factor VIII:von Willebrand factor multimers from endothelial storage sites. Platelet transfusion is not indicated because the transfused platelets quickly become inactive.

The advantages of renal transplantation over dialysis are:

1. Better survival and quality of life.
2. Anemia, bone disease, and hypertension persist in spite of dialysis; these are better controlled with transplantation.
3. Transplant patients have a return of normal endocrine, sexual, and reproductive functions, and enhanced energy levels; thus, returning to fulltime employment and more strenuous physical activity is possible.
4. In diabetics, autonomic neuropathy persists or worsens after dialysis; whereas, it stabilizes or improves with transplantation.
5. Expected survival rate after transplantation is 95% at one year and 88% at five years.

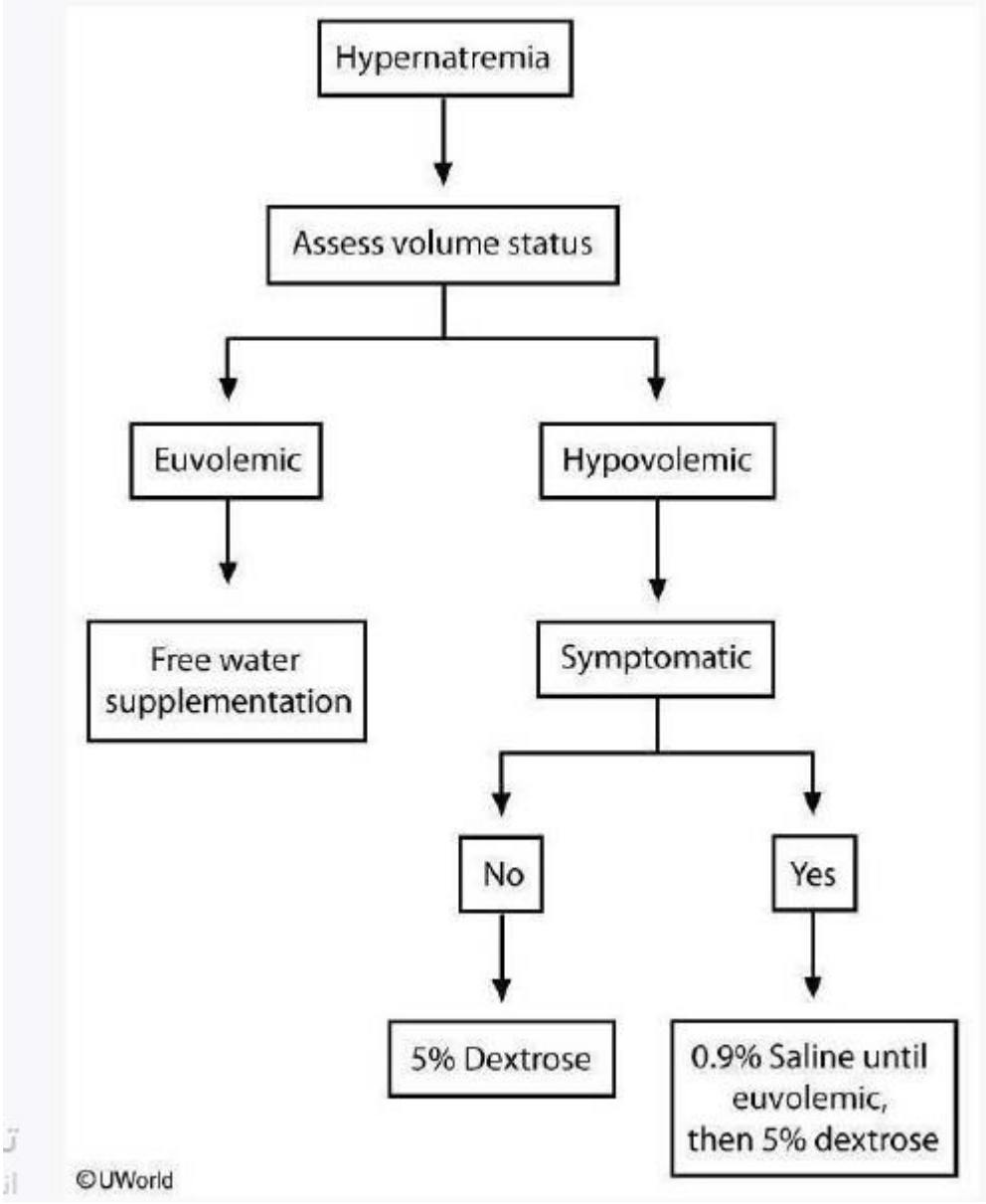
- The most common presentation is a spike in the creatinine within 24 hours of contrast administration, followed by a return to normal renal function within five days.
- Acute hypercarbia can be differentiated from chronic C02 retention in COPD by the associated acidosis and low bicarbonate level (chronic C02 retainers have normal pH and high serum bicarbonate).

- Risk factors not related to dialysis: A large number of patients on dialysis already have multiple risk factors for cardiovascular disease. These are:
  - Hypertension (96%)
  - Diabetes (54%)
  - Low serum HDL cholesterol (33%)
  - Left ventricular hypertrophy by ECG criteria (22%)
  - Coronary artery disease: Approximately 75% of patients with total end-stage renal disease have at least a 50% narrowing of at least one coronary artery.
  - Increased age: The average age of patients at the start of dialysis is about 60 years.
- Additional risk factors due to end stage renal disease and dialysis are:
  - End stage renal disease: This, by itself, is an independent risk factor for cardiovascular disease.
  - Anemia.
  - Metabolic abnormality, particularly hyperphosphatemia, and increased PTH levels.
  - Increased homocysteine levels: These are due to impaired metabolism and decreased removal.
  - Accelerated atherogenesis in dialysis patients: This is due to enhanced oxidant stress due to uremia and bio-incompatible renal replacement therapies.
  - Increased calcium intake (calcium is given to correct hyperphosphatemia in dialysis patients): This enhances coronary artery calcification.
  - Inhibition of NO: This is a common finding in dialysis patients, and can cause vasoconstriction and hypertension.



- Cyanide binds to cytochrome oxidase and inhibits mitochondrial oxidative phosphorylation. Cells then shift to anaerobic metabolism with decreased ATP production and eventual lactic acidosis. Patients can develop symptoms affecting the central nervous (eg, headache, confusion), cardiovascular (eg, arrhythmias), respiratory (eg, tachypnea followed by respiratory depression), and gastrointestinal (eg, vomiting) systems, and skin (eg, flushing).

  Sodium nitroprusside is a potent arterial and venous vasodilator often used for hypertensive emergencies. The drug contains 5 cyanide groups and undergoes rapid conversion to cyanide and eventually thiocyanate, which is eliminated by the kidneys. Prolonged infusion (>24 hours) at high rates (5-10 µg/kg/min) can lead to cyanide toxicity, especially in patients with chronic kidney disease. As a result, low infusion rates (<2 µg/kg/min), short-term use, and close monitoring are recommended. Treatment includes sodium thiosulfate.

- 

- Hemodialysis is usually indicated for serum lithium level >4 mEq/L or lithium level >2.5 mEq/L plus signs of significant lithium toxicity (eg, seizures, depressed mental status) or inability to excrete lithium (eg, renal disease, decompensated heart failure). Hemodialysis may be necessary in this patient once the lithium level is known and hypovolemia has been corrected.
- Diabetes insipidus (DI) is a leading cause of euvolemic hypernatremia.
- Based on urine osmolality, DI may be complete or partial.

  1. Complete DI - the urine osmolality is less than 300 mOsm/kg (often less than 100 mOsm/kg)
  2. Partial DI - urine osmolality ranges from 300-600 mOsm/kg.

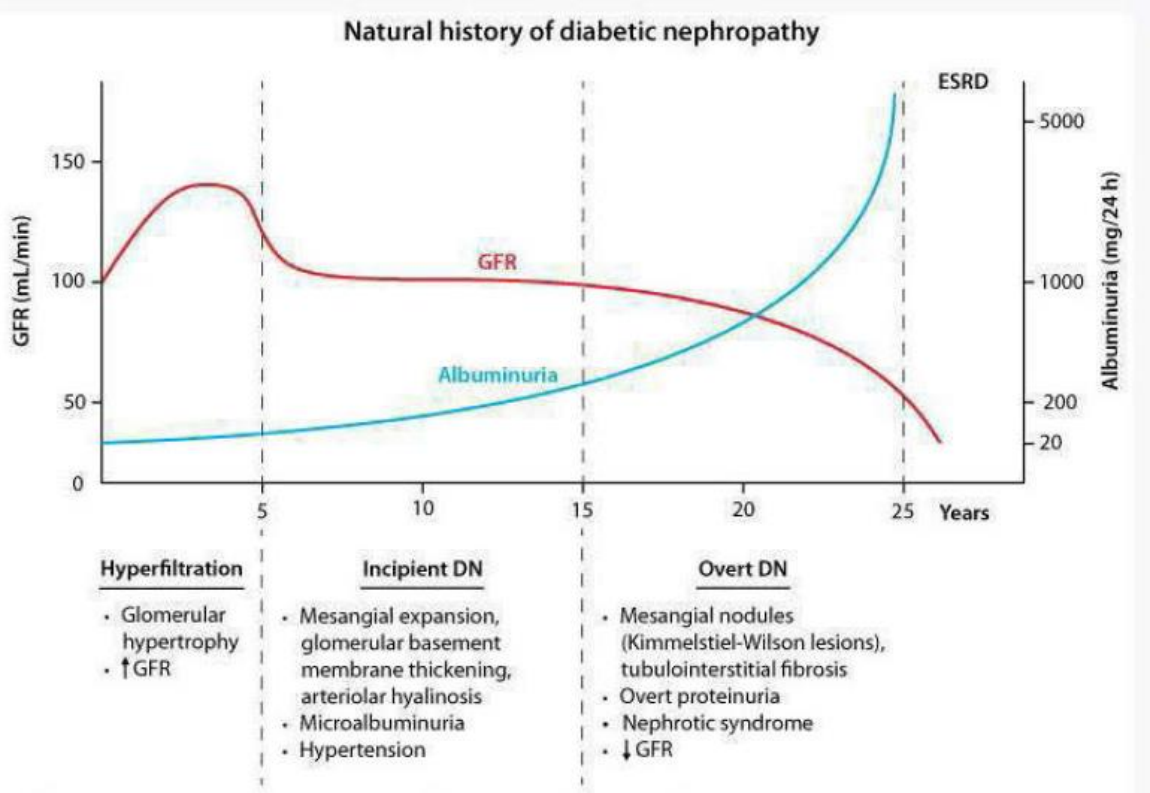
  The serum osmolality is elevated in both types.

  Based on etiology, DI may be central or nephrogenic.

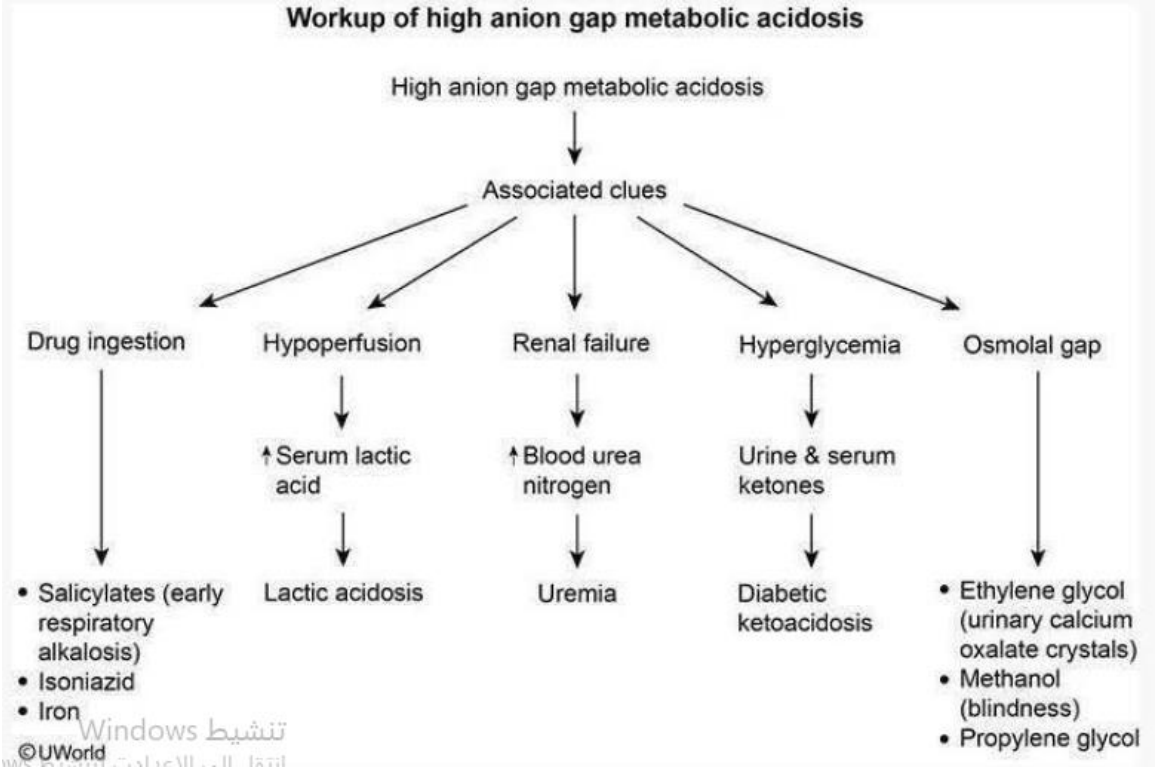
  1. Central DI is due to decreased production of antidiuretic hormone (ADH). Common causes include trauma, hemorrhage, infection, and tumors.
  2. Nephrogenic DI results from renal ADH resistance. Common causes include hypercalcemia, severe hypokalemia, tubulointerstitial renal disease, and medications. The most commonly implicated mediations are lithium, demeclocycline, foscarnet, cidofovir, and amphotericin.

Glomerular hyperfiltration is believed to be the earliest renal abnormality present in patients with diabetes mellitus. It can be detected as early as several days after the diagnosis of diabetes was made. Moreover, glomerular hyperfiltration is the major pathophysiologic mechanism of glomerular injury in these patients. It creates intraglomerular hypertension leading to progressive glomerular damage and renal function loss. You should remember that effectiveness of ACE inhibitors in diabetic nephropathy is related to their ability to *reduce intraglomerular hypertension* and, thereby, decrease glomerular damage.

(Choices A, B and C) Thickening of the glomerular basement membrane (GBM) is the first change that can be quantitated. This is followed by mesangial expansion. Nodular sclerosis is superimposed later and is specific for diabetic nephropathy.

- 

The urine dipstick for proteinuria (albumin)	
Trace	Between 15 and 30 mg/dL
1+	Between 30 and 100 mg/dL
2+	Between 100 and 300 mg/dL
3+	Between 300 and 1000 mg/dL
4+	>1000 mg/dL

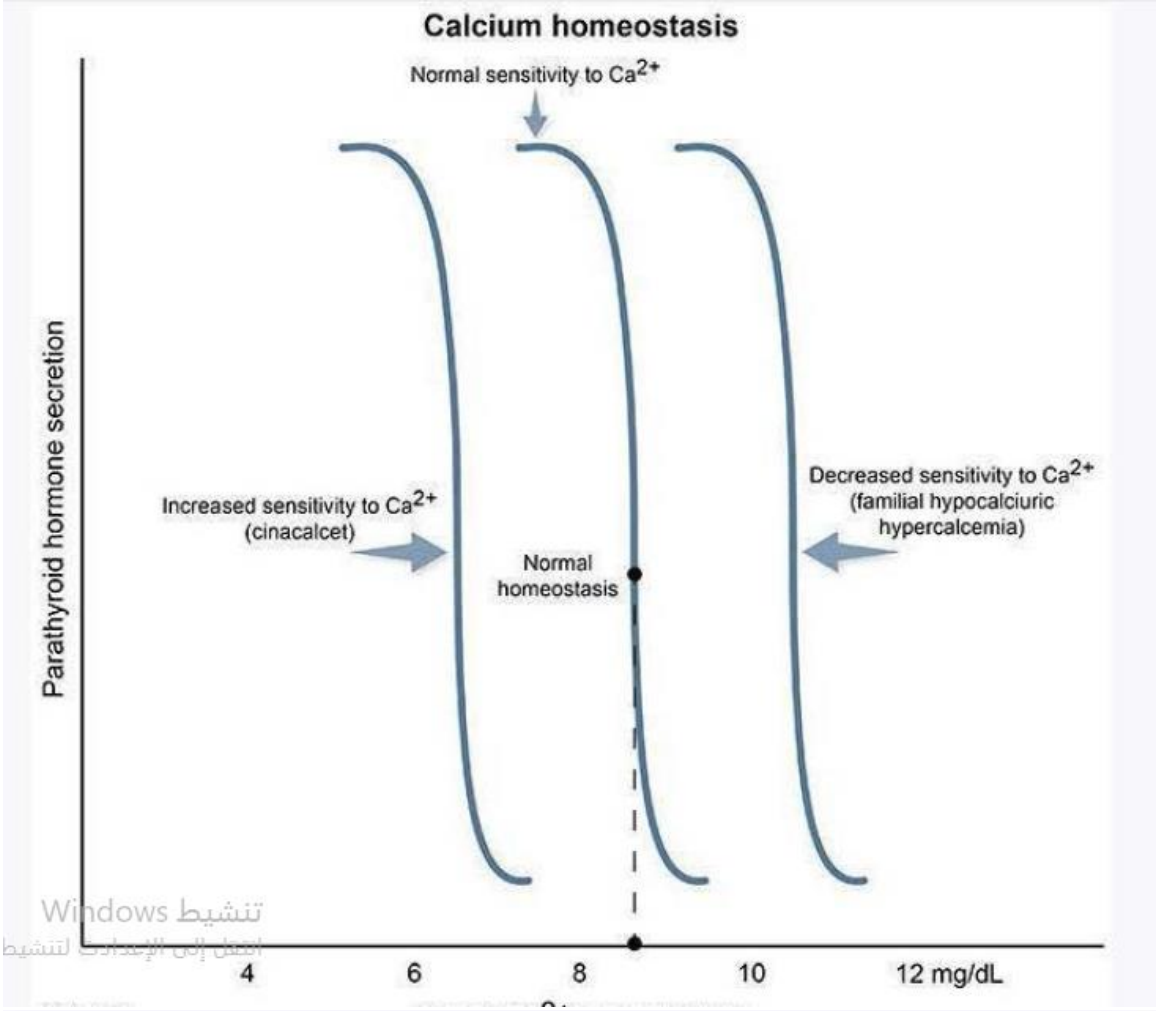
- The most common histologic lesion in diabetic nephropathy is diffuse glomerulosclerosis. Nodular glomerulosclerosis (with Kimmelstiei-Wilson nodules) is pathognomonic.
- 

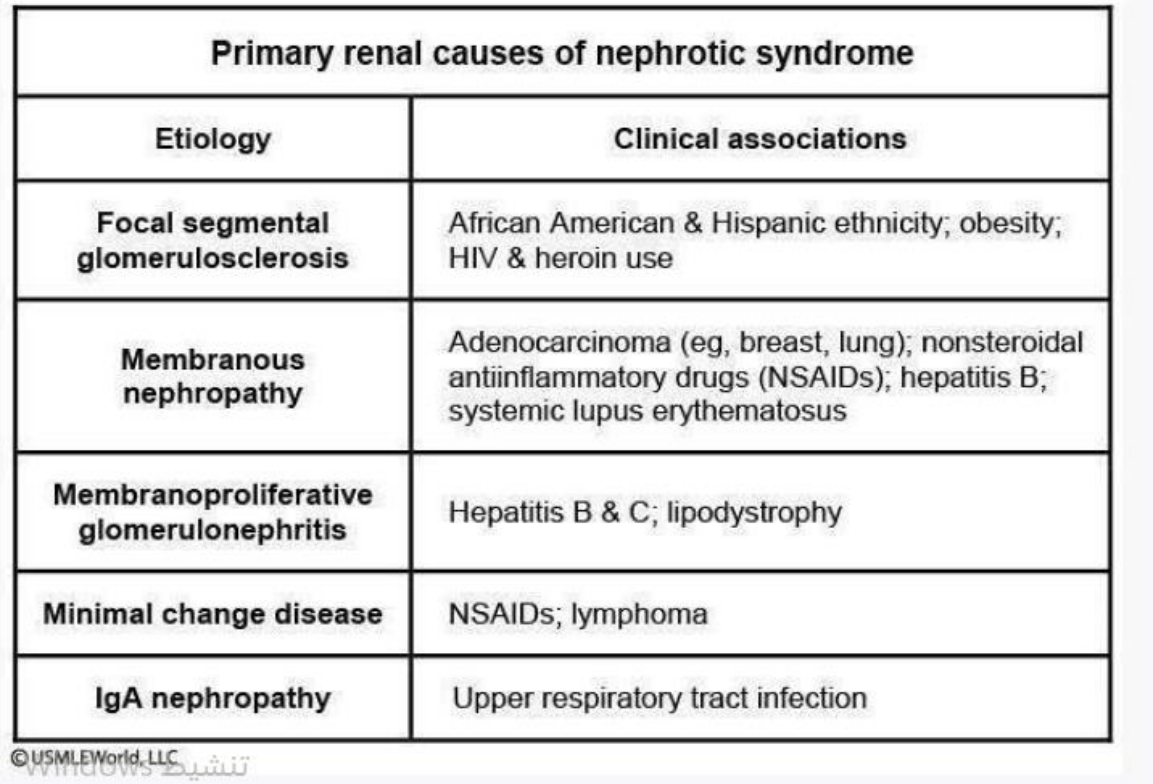
- A **combination** of high anion gap and osmolal gap metabolic acidosis is seen with acute ethanol (most common), methanol, or ethylene glycol poisoning. The patient's urinalysis shows rectangular, **envelope-shaped calcium oxalate crystals**, which are classically observed in patients with **ethylene glycol** poisoning, most commonly from **antifreeze** ingestion. **Acute renal failure** is the major complication of ethylene glycol intoxication (methanol intoxication can lead to blindness).
- **High anion gap metabolic acidosis**

  Anion gap = Sodium – (Chloride + Bicarbonate)
  (Normal = 10-14)

  Methanol
  Uremia
  Diabetic ketoacidosis
  Propylene glycol/**P**araldehyde
  Isoniazid/**I**ron
  Lactic acidosis
  Ethylene glycol (antifreeze)
  Salicylates (aspirin)

  Mnemonic: MUDPILES

- 

- 

Primary renal causes of nephrotic syndrome	
Etiology	**Clinical associations**
Focal segmental glomerulosclerosis	African American & Hispanic ethnicity; obesity; HIV & heroin use
Membranous nephropathy	Adenocarcinoma (eg, breast, lung); nonsteroidal antiinflammatory drugs (NSAIDs); hepatitis B; systemic lupus erythematosus
Membranoproliferative glomerulonephritis	Hepatitis B & C; lipodystrophy
Minimal change disease	NSAIDs; lymphoma
IgA nephropathy	Upper respiratory tract infection

- FSGS is the most common cause of nephrotic syndrome in adults. especially in African Americans
- It is interesting that focal segmental glomerulosclerosis can be manifested even if all the markers of HIV (CD4 count, viral load) are normal.

Causes of peripheral edema	
Primary mechanism	**Clinical examples**
Increased capillary hydrostatic pressure	• Heart failure (left ventricular & cor pulmonale) • Primary renal sodium retention (renal disease & drugs) • Venous obstruction (eg, cirrhosis & venous insufficiency)
Decreased capillary oncotic pressure (hypoalbuminemia)	• Protein loss (eg, nephrotic syndrome & protein-losing enteropathy) • Decreased albumin synthesis (eg, cirrhosis & malnutrition)
Increased capillary permeability	• Burns, trauma & sepsis • Allergic reactions • Acute respiratory distress syndrome • Malignant ascites
Lymphatic obstruction/increased interstitial oncotic pressure	• Malignant ascites • Hypothyroidism • Lymph node dissection

	Glomerular hematuria	**Non-glomerular hematuria**
Type of hematuria	Microscopic >gross hematuria	Gross >microscopic hematuria
Common etiologies	• Glomerulonephritis • Basement membrane disorders (eg, Alport syndrome)	• Nephrolithiasis • Cancer (eg, renal cell, prostate) • Polycystic kidney disease • Infections (eg, cystitis) • Papillary necrosis, renal infarction
Clinical presentation	• Nonspecific or no symptoms • Nephritic syndrome (hypertension, oliguria, elevated creatinine)	• Dysuria or symptoms of urinary obstruction (flank pain, renal or ureteral colic, anuria)
Urinalysis	• Blood **and** protein • RBC casts, dysmorphic RBCs	• Blood but **no** protein • Normal appearing RBCs

(Choice D) Papillary necrosis with sloughing of the renal papilla is a rare cause of non-glomerular hematuria. It may be seen with long-term acetaminophen abuse but not with light-intermittent use (mnemonic **NSAID**: **N**onsteroidal antiinflammatory drugs, **S**ickle cell disease, **A**nalgesic abuse, **I**nfection (pyelonephritis), and **D**iabetes mellitus).

- It is important to remember that rifampin causes red to orange discoloration of body fluids including urine, saliva, sweat, and tears. It can also cause discoloration of soft contact lenses.

Indications for urgent dialysis (AEIOU)	
Acidosis	• Metabolic acidosis ◦ pH <7.1 refractory to medical therapy

Electrolyte abnormalities	• Symptomatic hyperkalemia
	  ◦ ECG changes or ventricular arrhythmias
	• Severe hyperkalemia
	  ◦ K >6.5 mEq/L refractory to medical therapy

Ingestion	• Toxic alcohols (methanol, ethylene glycol) • Salicylate • Lithium • Sodium valproate, carbamazepine
Overload	Volume overload refractory to diuretics

Uremia	• Symptomatic:
	  ◦ Encephalopathy
	  ◦ Pericarditis
	  ◦ Bleeding

- Asterixis is seen in hepatic encephalopathy, uremic encephalopathy, and CO, retention.

Differential diagnosis of glomerular disease		
Classification	**Definition**	**Etiologies**
Mild GN	Nephritic urine sediment without renal insufficiency or nephrotic syndrome	• IgA nephropathy • Lupus nephritis • Thin basement membrane disease
Moderate to severe GN	Nephritic urine sediment, decreased GFR & variable proteinuria (can be nephrotic range)	• Postinfectious, lupus nephritis • MPGN, vasculitis (eg, cryoglobulinemia) • Rapidly progressive glomerulonephritis
Nephrotic syndrome	Bland urinary sediment, proteinuria >3.5 g/day, possible microscopic hematuria	• FSGS, minimal change disease • Diabetes, lupus nephritis • Membranous nephropathy • IgA nephropathy, primary amyloidosis

- Nephritic GN usually presents with red blood cells (can be dysmorphic), white blood cells, casts (red blood cell and/or white blood cell), and variable degrees of proteinuria. Mild GN presents with a nephritic sediment without renal insufficiency or nephrotic syndrome. Causes include IgA nephropathy, lupus nephritis, and thin basement membrane disease. Moderate-to-severe GN has nephritic sediment, decreased glomerular filtration rate, and variable degree of proteinuria (can be nephrotic syndrome). Etiologies include postinfectious, lupus, membranoproliferative GN (MPGN), rapidly progressive GN (RPGN), and vasculitis (eg, cryoglobulinemia).
- Mixed cryoglobulinemia is most commonly due to hepatitis C and presents with immune complex deposition in small blood vessels, leading to endothelial injury, inflammation, and end-organ damage. The immune complexes are IgM antibodies (similar to rheumatoid factor) that form complexes with IgG anti-hepatitis C virus antibodies, hepatitis C virus RNA, and complement. Patients can be asymptomatic or develop findings in the skin (eg, palpable purpura, Raynaud's phenomenon), kidney (eg, MPGN), nervous system (eg, motor sensory axonopathy), and musculoskeletal system (eg, arthralgias). Diagnosis can be confirmed serologically (serum cryoglobulins, low complement levels) or with kidney/skin biopsy. Treatment options in addition to addressing the underlying hepatitis C infection include plasmapheresis to remove cryoglobulins and immunosuppressants (eg, glucocorticoids, cyclophosphamide).
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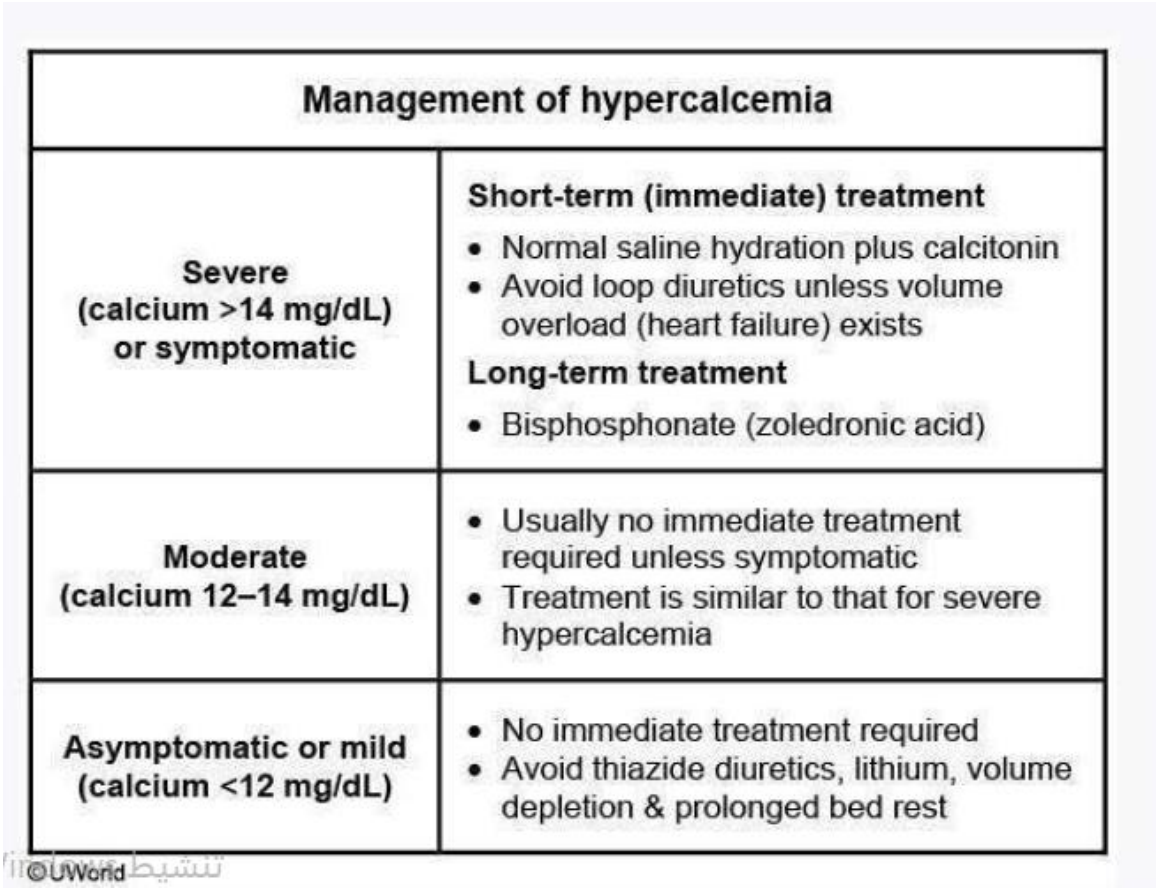
Hepatorenal syndrome	
Risk factors	• Advanced cirrhosis with portal hypertension & edema

Precipitating factors	• Reduced renal perfusion
	  ◦ GI bleed, vomiting, sepsis, excessive diuretic use, SBP
	• Reduced glomerular pressure & GFR
	  ◦ NSAID use (constricts afferent arterioles)

Diagnosis	• Renal hypoperfusion
	  ◦ FeNa <1% (or urine Na <10 mEq/L)
	• Absence of tubular injury
	  ◦ No RBC, protein, or granular casts in urine
	• No improvement in renal function with fluids

Treatment	• Address precipitating factors (eg, hypovolemia, anemia, infection) • Splanchnic vasoconstrictors (midodrine, octreotide, norepinephrine) • Liver transplantation



- Patients with severe hypercalcemia require aggressive **saline hydration** to restore intravascular volume and promote urinary calcium excretion. **Calcitonin**, by inhibiting osteoclast-mediated bone resorption, quickly reduces serum calcium concentrations and can be administered concurrently with saline. **Bisphosphonates** (eg, pamidronate, zoledronic acid) also inhibit bone resorption and provide a sustained reduction in calcium levels. However, the calcium-lowering effect of bisphosphonates is delayed, usually occurring over 2-4 days, and they are typically given after initial administration of saline and calcitonin **(Choice G)**.
- **(Choice C)** Hemodialysis is an effective treatment for hypercalcemia, but is typically reserved for patients with renal insufficiency or heart failure in whom aggressive hydration cannot be administered safely. This patient likely has confusion due to hypercalcemia not uremia.

Medications that can cause hyperkalemia	
Medication	**Mechanism**
Nonselective beta-adrenergic blockers	Interfere with beta-2-mediated intracellular potassium uptake
Angiotensin-converting-enzyme (ACE) inhibitors	Inhibition of angiotensin II formation with subsequent decrease in aldosterone secretion
Angiotensin II receptor blockers (ARBs)	Block the AT_1 receptor, thus decreasing aldosterone secretion
K^+-sparing diuretics	Block the epithelial sodium channel (ENaC) or aldosterone receptor
Cardiac glycosides (eg, digoxin)	Inhibition of the Na^+/K^+-ATPase pump
NSAIDs	Impaired local prostaglandin synthesis reduces renin and aldosterone secretion

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Clinical features of hyperkalemia	
Sequence of ECG changes	• Tall **peaked T waves** with shortened QT interval • **PR prolongation** & **QRS widening** • Disappearance of P wave • Conduction blocks, ectopy, or **sine wave** pattern
Cardiac membrane stabilization	• **Calcium** infusion
Rapidly acting treatment options	• Insulin with glucose • Beta-2 adrenergic agonists • Sodium bicarbonate
Removal of potassium from the body (slow-acting)	• Diuretics • Cation exchange resins • Hemodialysis

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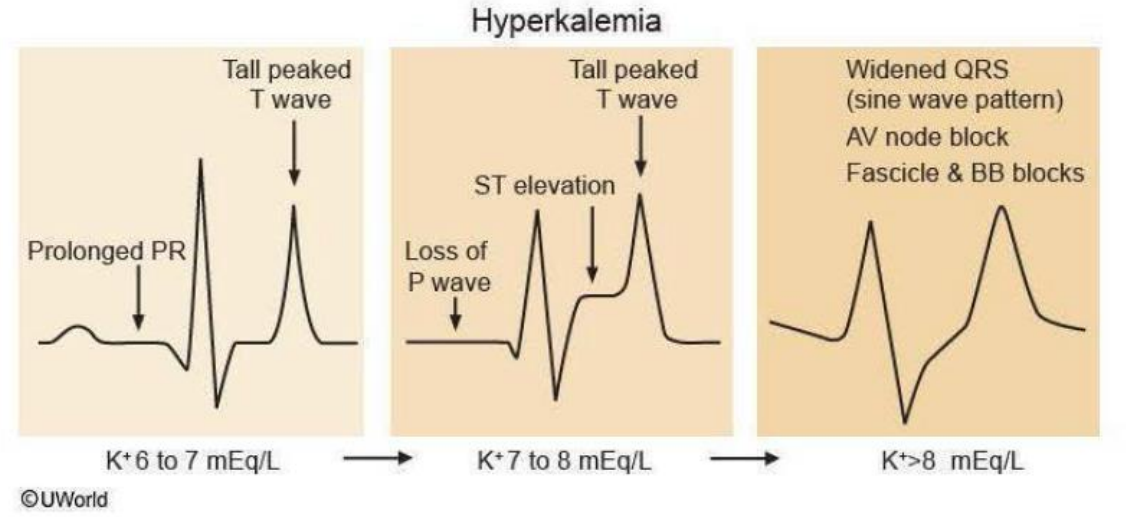

- Administration of intravenous calcium chloride or gluconate (not calcium carbonate, which is used as an oral calcium supplement) helps stabilize the cardiac membrane, making it resistant to the effects of hyperkalemia. However, calcium has no effect on serum potassium level

Medications that can cause hyperkalemia	
Medication	**Mechanism**
Nonselective beta-adrenergic blockers	Interferes with beta-2-mediated intracellular potassium uptake
ACE inhibitor, ARB, K^+ sparing diuretics	Inhibition of aldosterone or the ENaC channel
Digitalis	Inhibition of the Na-K-ATPase pump
Cyclosporine	Blocks aldosterone activity
Heparin	Blocks aldosterone production
NSAIDs	Decreases renal perfusion resulting in decreased K^+ delivery to the collecting ducts
Succinylcholine	Causes extracellular leakage of potassium through acetylcholine receptors

Trimethoprim can cause hyperkalemia by blocking the epithelial sodium channel in the collecting tubule, similar to the action of the potassium-sparing diuretic amiloride. This occurs more commonly in HIV-infected patients who are treated with high doses of trimethoprim, but even normal doses can produce a modest elevation in the plasma potassium concentration. Thus, patients treated with high-dose trimethoprim require serial monitoring of potassium to avoid serious complications. Trimethoprim also competitively inhibits renal tubular creatinine secretion and may cause an artificial increase in serum creatinine; however, glomerular filtration rate is unchanged.

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