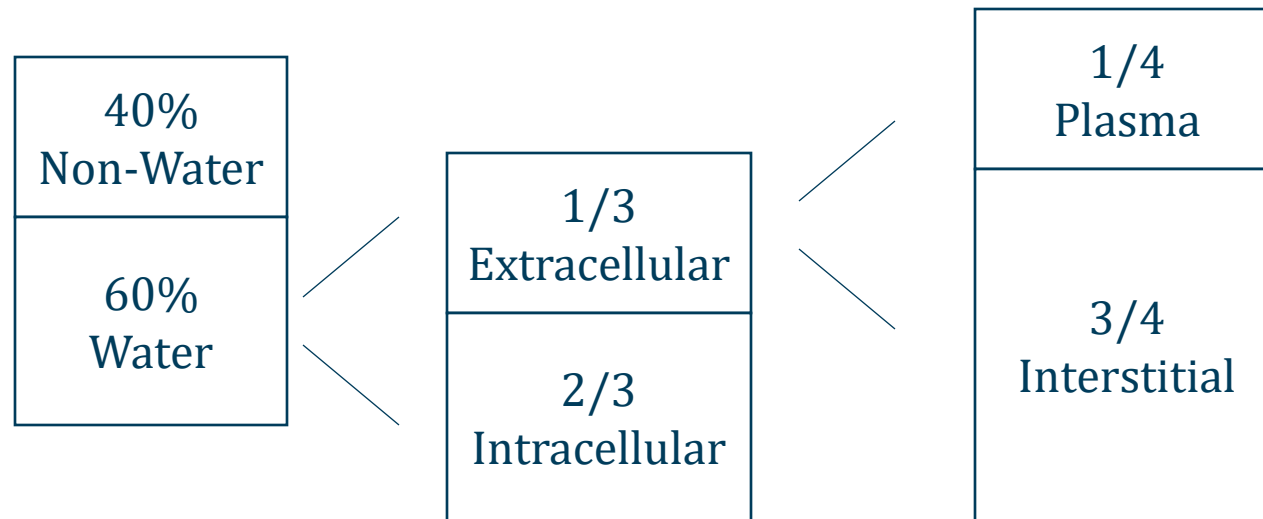


# Fluids

Jason Ryan, MD, MPH



# Fluid Compartments



# Fluid Intake and Output

- Normal oral intake  $\sim 2$  L/day
- Output:
  - Urine: 1.0 L/day
  - Stool: 0.25 L/day
  - Insensible losses: 0.75 L/day
- Insensible losses:  $\uparrow$  pathologic states
  - Fever
  - Burns



# Intravenous Fluids

- Normal saline
- Lactated ringers
- D5 ½ normal saline
- D5W
- Hypertonic saline

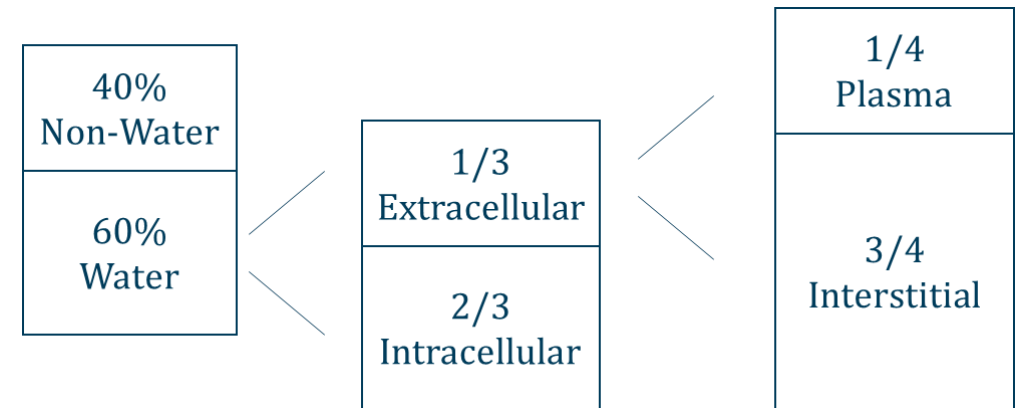




# Normal Saline

## 0.9% Normal Saline

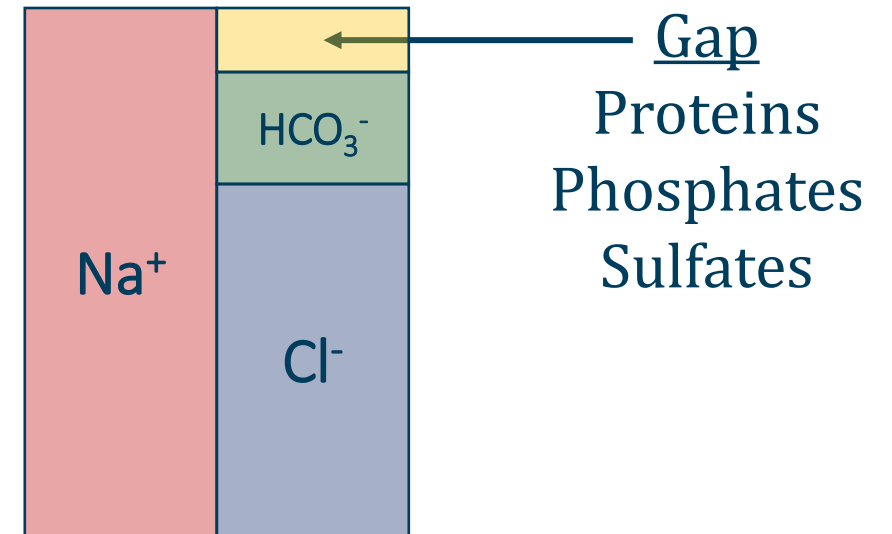
- Approximately same osmolarity as plasma
  - 154 mEq/L sodium chloride vs. 140 mEq/L plasma
  - 308 mOsmol/liter vs. 285 mOsm/L plasma
- 25% remains in intravascular space
- Used for **volume replacement**
  - Hypovolemic shock
  - Septic shock



# Normal Saline

## 0.9% Normal Saline

- Results in influx of chloride ions ( $\text{Cl}^-$ )
- Causes shift of bicarbonate ions ( $\text{HCO}_3^-$ ) into cells
- **Causes acidosis ( $\downarrow\text{pH}$ )**
- Acidosis  $\rightarrow$  potassium shift out of cells
- **$\uparrow$  serum potassium**



# Lactated Ringers

- Sodium, chloride, potassium, calcium, and lactate
- “Balanced fluid”
- Isotonic: osmolarity 286 mOsm/L
- Lactate metabolized to bicarbonate
- Acts as buffer in acidotic states
- Most common use: trauma resuscitation
- Does NOT cause hyperkalemia
  - Low concentration of potassium



# SMART Trial

## Isotonic Solutions and Major Adverse Renal Events Trial

- March 2018
- 15,802 critically ill patients
- Normal saline versus lactated ringers
- Improved outcomes with LR
  - Death from any cause
  - New renal-replacement therapy
  - Persistent renal dysfunction

*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

### Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H.,  
Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H.,  
Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D.,  
Avinash B. Kumar, M.D., Christopher G. Hughes, M.D.,  
Antonio Hernandez, M.D., Oscar D. Guillaumondegui, M.D., M.P.H.,  
Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D.,  
Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D.,  
and Todd W. Rice, M.D., for the SMART Investigators  
and the Pragmatic Critical Care Research Group\*


# Half Normal Saline

## 0.45% Normal Saline

- Hypotonic solution concentration of sodium chloride
- Does not remain intravascular
- Used as **“maintenance fluids”**
- Replaces daily losses of sodium and water
- 5% dextrose often added: D5 ½ NS
- Potassium can be added: D5 ½ NS with 20mEq K
- Often used when oral intake is low

# D5W

- Dextrose metabolized leaving only free water
- Used to correct **hyponatremia**

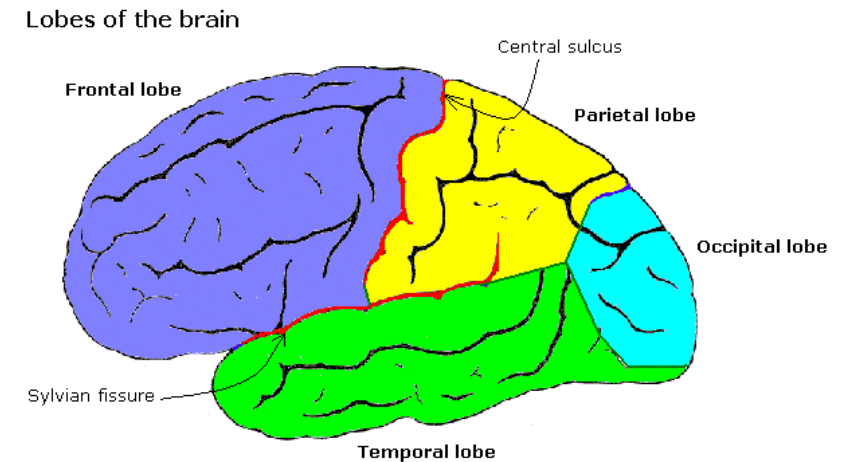


1 H			
3 Li	4 Be		
11 Na	12 Mg		
19 K	20 Ca	21 Sc	22 Ti
37 Rb	38 Sr	39 Y	40 Zr

# Hypertonic Saline

## 3% Saline

- Hypertonic:  $\sim 900$  mOsm/liter
- Draws fluid out of tissues into vascular space
- Used in two circumstances:
  - Elevated intracerebral pressure
  - Severe hyponatremia



Public Domain

# Crystalloids and Colloids

- Crystalloid solutions
  - Contain water and salts
  - Normal saline, half normal saline etc.
- Colloid solutions
  - Contain water and large molecules
  - Example: albumin
  - Expensive
  - No proven benefit over crystalloid



# Hypovolemia

- Many causes
  - Vomiting/diarrhea
  - Poor oral intake
  - Third spacing/fluid leak: sepsis, trauma
- Clinical features
  - **Decreased urine output**
  - Dry mucous membranes
  - Poor skin turgor
  - Hypotension
- Treatment: oral intake, IV fluids



Pixabay/Public Domain

# Hypervolemia

- Classic causes
  - Heart failure
  - Cirrhosis
  - Nephrotic syndrome
- Clinical features
  - Weight gain
  - Pitting edema
  - Elevated jugular venous pressure
  - Pulmonary edema
- Treatment: diuretics



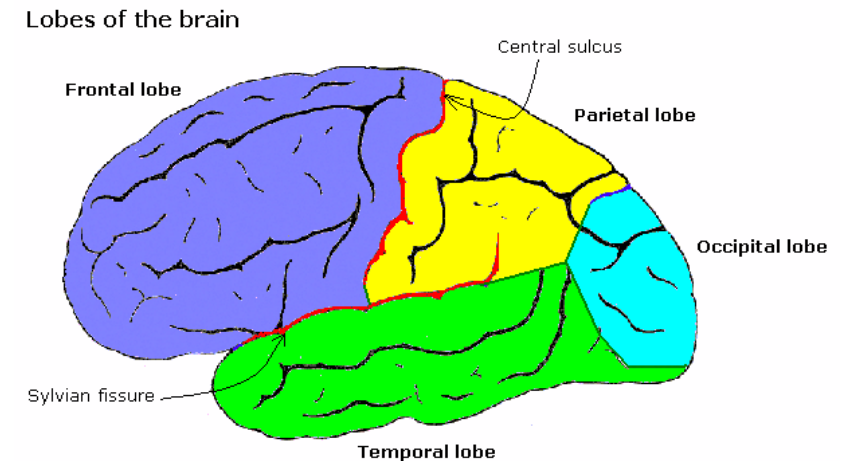
# Hyponatremia

Jason Ryan, MD, MPH



# Sodium

- **Normal Na = 135 to 145 mEq/L**
- Hypo and hypernatremia affect **brain**
- Low sodium = low plasma osmotic pressure
  - Fluid into cells → brain swells
- High sodium = high plasma osmotic pressure
  - Fluid out of cells → brain shrinks
- Symptoms
  - Malaise, stupor, coma
  - Nausea



Public Domain

# Hyponatremia

## Plasma Osmolality

- Amount of solutes present in plasma
- Key solute: sodium
- Osmolality should be LOW in HYPOnatremia
- 1<sup>st</sup> step in hyponatremia is to make sure it's low

$$\text{Serum Osmolality} = 2 * [\text{Na}] + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8}$$

Normal = 285 (275 to 295)


# Hyponatremia

## Plasma Osmolality

- Hyponatremia with **HIGH** osmolality
  - Hyperglycemia or mannitol
  - Glucose or mannitol = osmoles
  - Raise plasma osmolality
  - Water out of cells → hyponatremia

$$\text{Serum Osmolality} = 2 * [\text{Na}] + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8}$$

Normal = 285 (275 to 295)



1 H			
3 Li	4 Be		
11 Na	12 Mg		
19 K	20 Ca	21 Sc	22 Ti
37 Rb	38 Sr	39 Y	40 Zr


# Hyponatremia

## Plasma Osmolality

- Hyponatremia with **NORMAL** osmolality
  - Artifact in serum Na measurement
  - Hyperlipidemia
  - Hyperproteinemia (multiple myeloma)
  - “Pseudohyponatremia”

$$\text{Serum Osmolality} = 2 * [\text{Na}] + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8}$$

Normal = 285 (275 to 295)

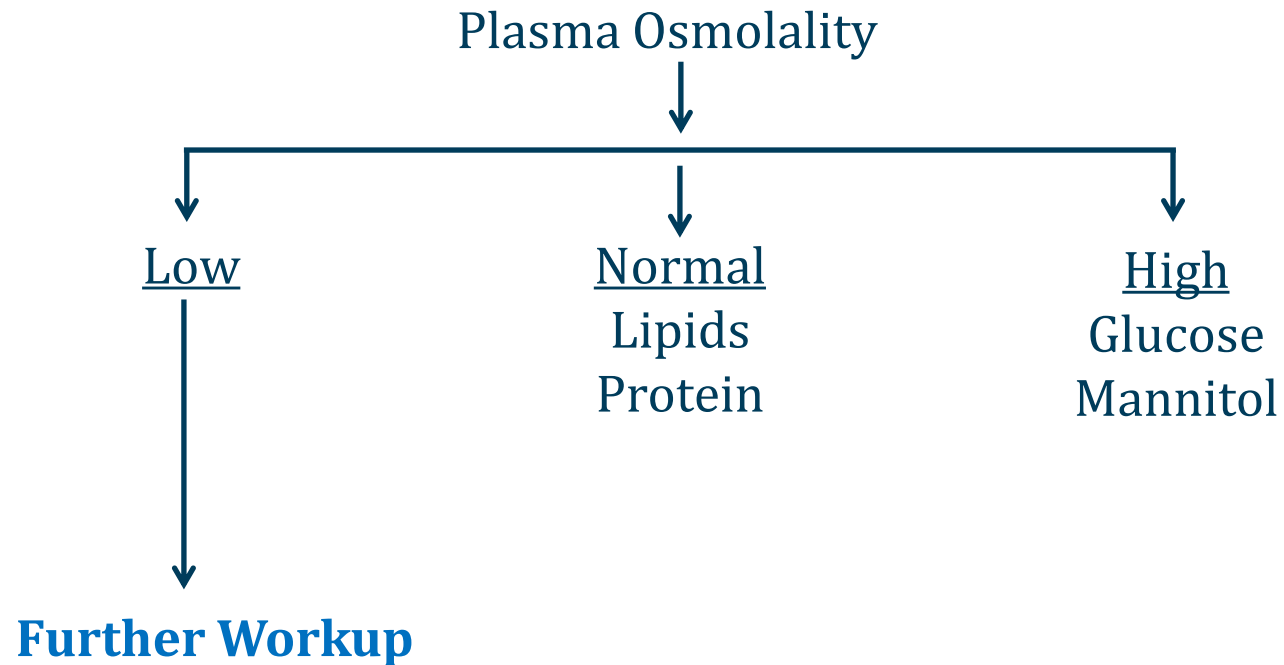


1 H			
3 Li	4 Be		
11 Na	12 Mg		
19 K	20 Ca	21 Sc	22 Ti
37 Rb	38 Sr	39 Y	40 Zr

# Hyponatremia

## Plasma Osmolality

- 1<sup>st</sup> step in evaluation of hyponatremia unknown cause





# Hyponatremia

## General Points

- Urine should be **diluted**
  - More free water than solutes
  - Normal osmolality 50 to 1200 mOsm/kg
  - Low urine osmolality ( $< 100$  mosm/kg)
  - Low urinary sodium ( $< 30$  meq/L)

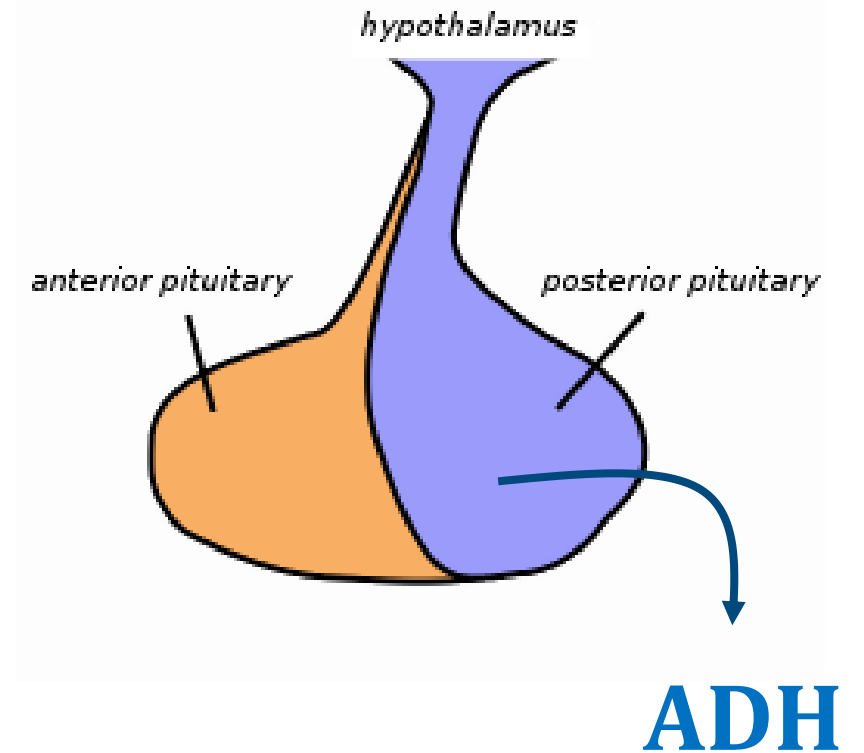


Wikipedia/Public Domain

# Antidiuretic Hormone

ADH; Vasopressin

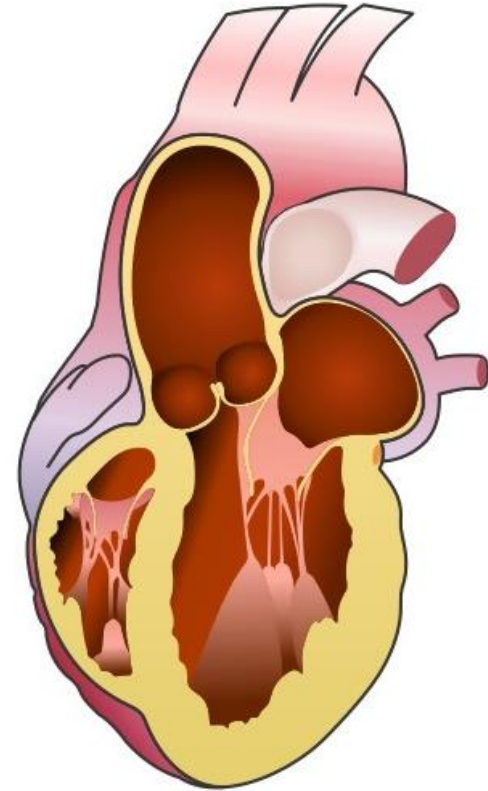
- Controls plasma **sodium** concentration
- Any cause of high ADH can cause hyponatremia
  - Sodium no longer controlled by ADH (always high)
  - Plasma free water varies with intake
  - Water intake → hyponatremia
- High ADH → concentrated urine
  - Osmolality 50 to 1200 mOsm/kg
  - Should be low in hyponatremia
  - Concentrated = high ADH



# Hypovolemia

Causes High ADH

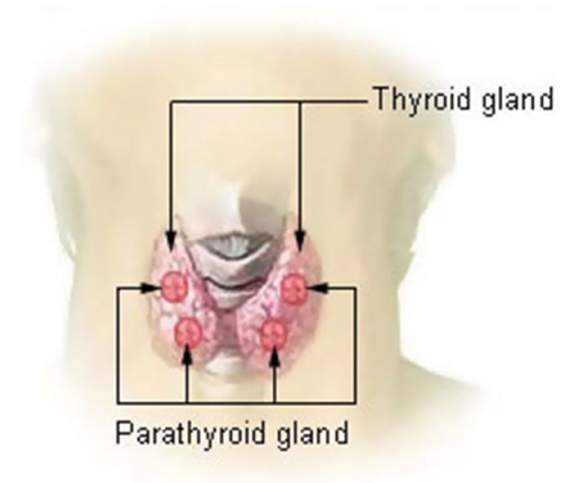
- Perceived hypovolemia
  - Under-filled arterial system
  - Hypervolemia: total body fluid overloaded
  - Heart failure
  - Cirrhosis
- True hypovolemia
  - Diuretics (thiazides)
  - GI losses (vomiting, diarrhea)
  - Sweating/exercise



# High ADH

## Other rare causes

- Adrenal insufficiency
  - Cortisol normally suppresses ADH release
  - Loss of cortisol (primary/secondary) → ↑ ADH
  - Loss of aldosterone (primary) → loss of salt/water → ↑ ADH
- Hypothyroidism
  - Can increase ADH



Wikipedia/Public Domain

# SIADH

## Syndrome of Inappropriate Antidiuretic Hormone Secretion

- Hyponatremia due to inappropriate ADH release
- Absence of other causes for high ADH
  - Heart failure
  - Cirrhosis
  - Volume depletion
  - Thyroid/adrenal disease
- Normal renal function
- Euvolemia
- High urinary osmolality ( $>100$  mOsm/kg)

# SIADH

## Causes

- Drug-induced (carbamazepine, cyclophosphamide)
- Paraneoplastic (small cell lung cancer)
- CNS disorders (stroke, trauma, infection)
- Pulmonary disease (pneumonia)

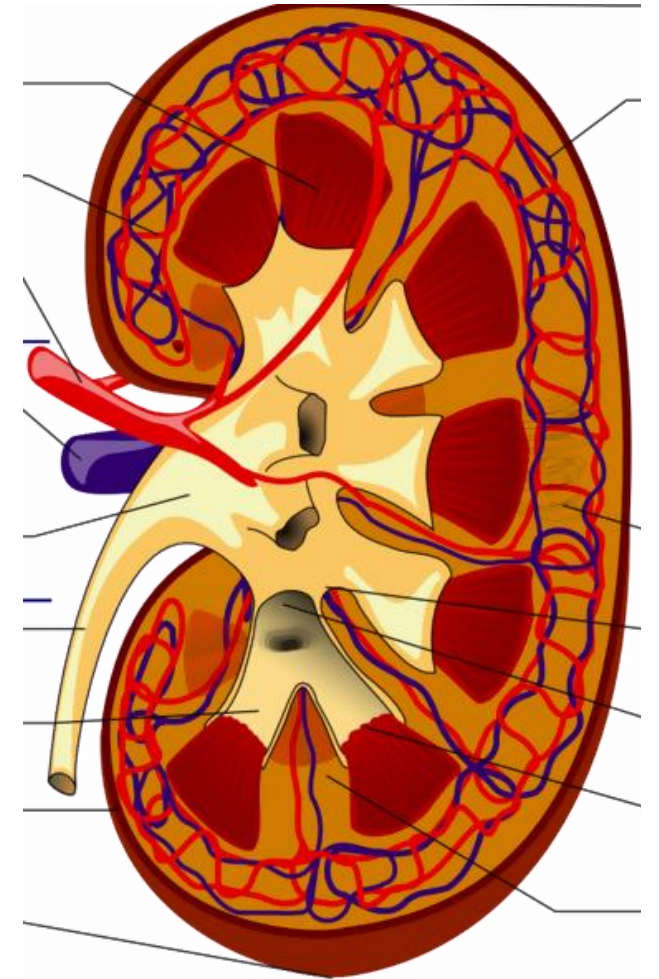
# Hyponatremia

## Non-ADH Causes

- Renal failure
- Psychogenic polydipsia
- Special diets

# Renal Failure

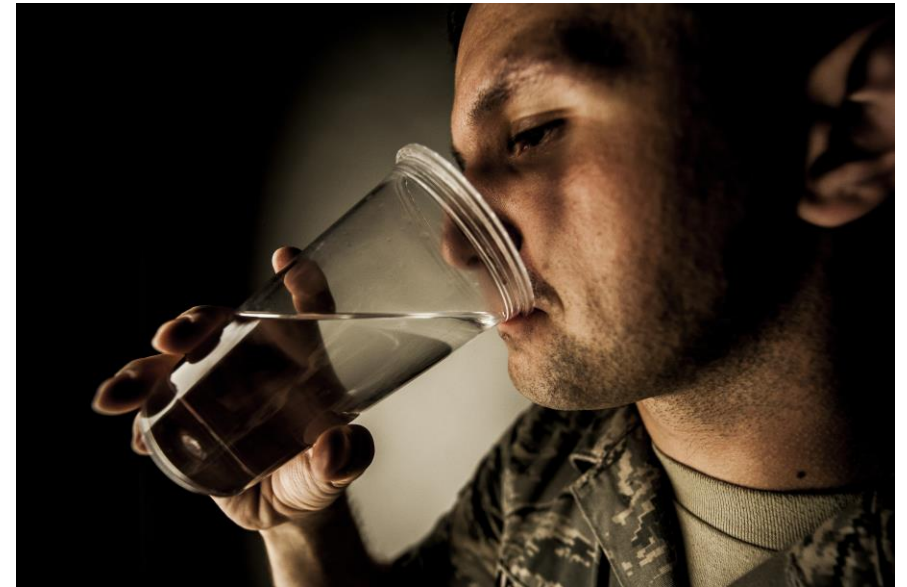
- **Advanced chronic kidney disease**
  - Kidneys cannot excrete free water normally
  - Urine cannot be diluted
  - Minimum Uosm rises even with low ADH
  - Normal < 100 mOsm/kg
  - Greater than 200 to 250 mOsm/kg with renal failure
  - Key point:  $\uparrow$  Uosm indicates abnormal response to  $\downarrow$ Na
- May occur with euvolemia or hypervolemia





# Psychogenic Polydipsia

- Consumption of  $> 18$  L/day  $\rightarrow$  hyponatremia
- Occurs in psychiatric patients (compulsive)
- Low urine osmolality ( $< 100$  mOsm/kg)
  - Indicates kidneys working
  - Kidneys trying to eliminate free water
- Water restriction resolves hyponatremia



Public Domain

# Special Diets

- Tea and toast
- Beer drinkers (“beer potomania”)
- Very little sodium ingestion
- Minimum urine osmolality  $\sim 50 \text{ mOsm/kg}$
- Minimal sodium intake limits free water excretion
- Free water intake  $>$  output
- Result: hyponatremia



Wikipedia/Public Domain

# Special Diets

- **Low urine osmolality** ( $< 100 \text{ mOsm/kg}$ )
  - Indicates kidneys working
  - Kidneys trying to eliminate free water
- Free water excretion limited by solute availability



Alexa\_Fotos/Pixabay/com

# Psychogenic Polydipsia or Special Diets

- **Hyponatremia with low Uosm ( $< 100$  mOsm/kg)**
  - Indicates ADH is low
  - Psychogenic polydipsia
  - Special low solute diet
- All other causes: Uosm  $> 100$  mOsm/kg



Alexa\_Fotos/Pixabay/com

# Causes by Volume Status

Hypervolemic	Euvolemic	Hypovolemic
Heart failure Cirrhosis	SIADH Polydipsia Special diets Hypothyroidism	Volume depletion Diuretics Addison's disease

# Hyponatremia

## Workup

- History and physical exam
  - Heart failure
  - Cirrhosis
  - Diuretic use
  - Volume loss (vomiting/diarrhea)
- Serum glucose
- BUN and Cr
- Euvolemic with high urinary osmolality and  $\text{Na} = \text{SIADH}$

# Hyponatremia

## Treatment

- **Identify and treat underlying cause**
  - PNA, heart failure, volume depletion
- Free water restriction
- Sodium chloride tablets
  - Only for euvolemic hyponatremia



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# Hyponatremia

## Treatment

- **Hypertonic (3%) saline**
  - Used only in severe, symptomatic cases
- Vaptan drugs (tolvaptan, lixivaptan, and conivaptan)
  - Block ADH
  - Main use is in severe hyponatremia of heart failure
  - Only used on hospitalized patients



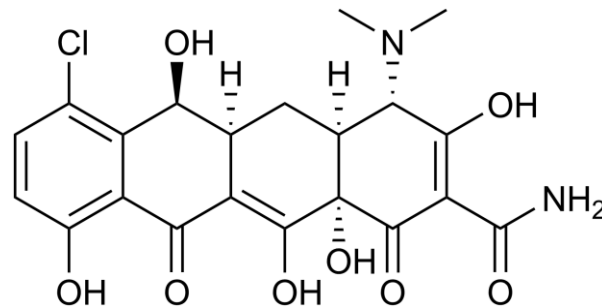
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# SIADH

## Special Treatments

- **Normal saline worsens hyponatremia**
  - Excess ADH causes retention of free water
  - Urinary sodium concentration > normal saline
- Chronic SIADH: demeclocycline
  - Tetracycline antibiotic
  - ADH antagonist



Demeclocycline

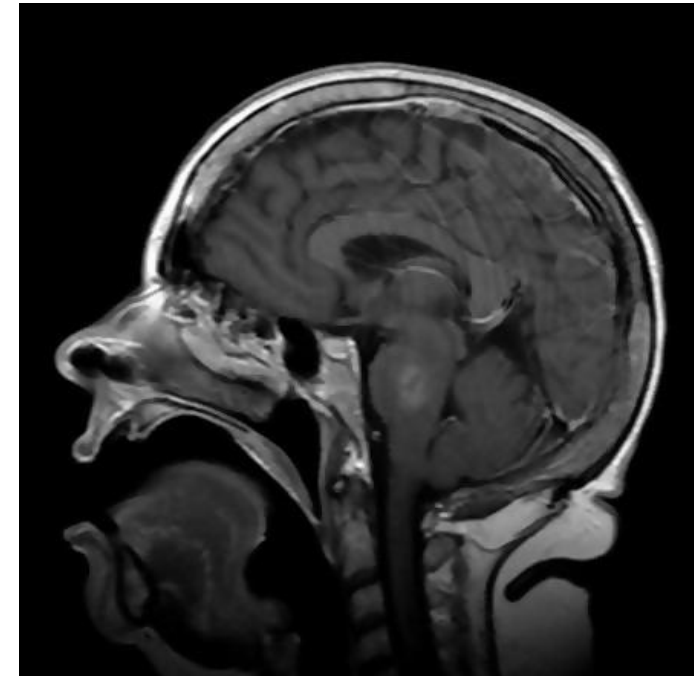


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# Central Pontine Myelinolysis

“Osmotic demyelination syndrome”

- Associated with overly rapid correction of hyponatremia
  - Usually  $> 10$  meq per 24 hours
- Demyelination of central pontine axons
- Lesion at base of pons
- Loss of corticospinal and corticobulbar tracts
- Quadriplegia
- Can be similar to locked-in syndrome



Dr Bruno Di Muzio/Radiopedia.org

# Hypernatremia

Jason Ryan, MD, MPH



# Hypernatremia

## Causes

- Normal Na = 135 to 145 mEq/L
- Hypernatremia > 145 mEq/L
- **Lack of access to free water**
- **Free water loss >> sodium loss**
  - Febrile illness, burns, diarrhea, diuretics



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# Hypernatremia

## Causes

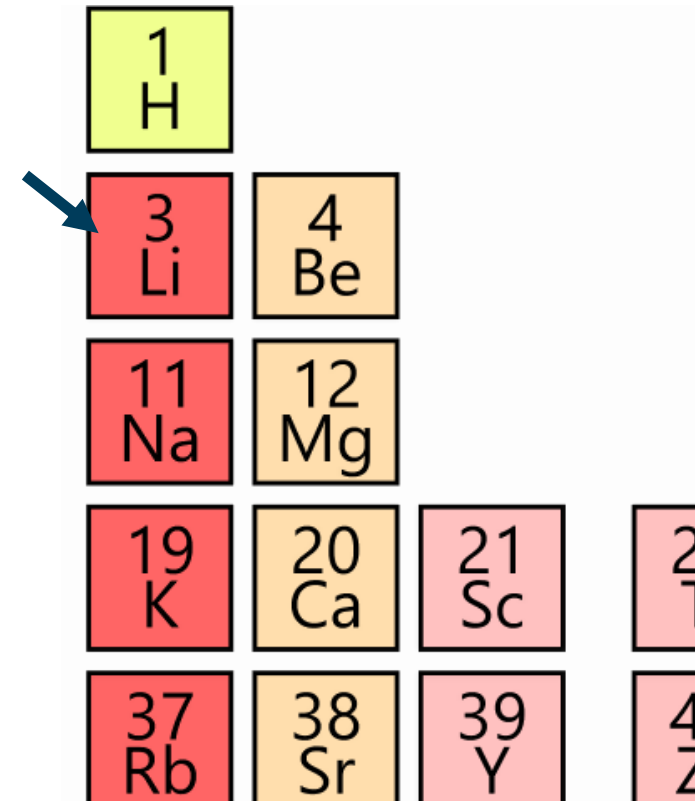
- **Diabetes insipidus**
  - Loss of ADH effects
  - Excessive free water loss
  - Central: trauma, tumors
  - Nephrogenic: many causes
- **Polyuria and polydipsia**
  - Similar to diabetes mellitus via different mechanism
  - Babies: frequent wet diapers
  - Adults: frequent thirst, nocturia



Wikipedia/Public Domain

# Nephrogenic Diabetes Insipidus

- Hypercalcemia
- Hypokalemia (severe;  $< 3.0$  meq/L)
- Drugs
  - Lithium
  - Amphotericin B



1 H			
3 Li	4 Be		
11 Na	12 Mg		
19 K	20 Ca	21 Sc	22 Ti
37 Rb	38 Sr	39 Y	40 Zr

# Diabetes Insipidus

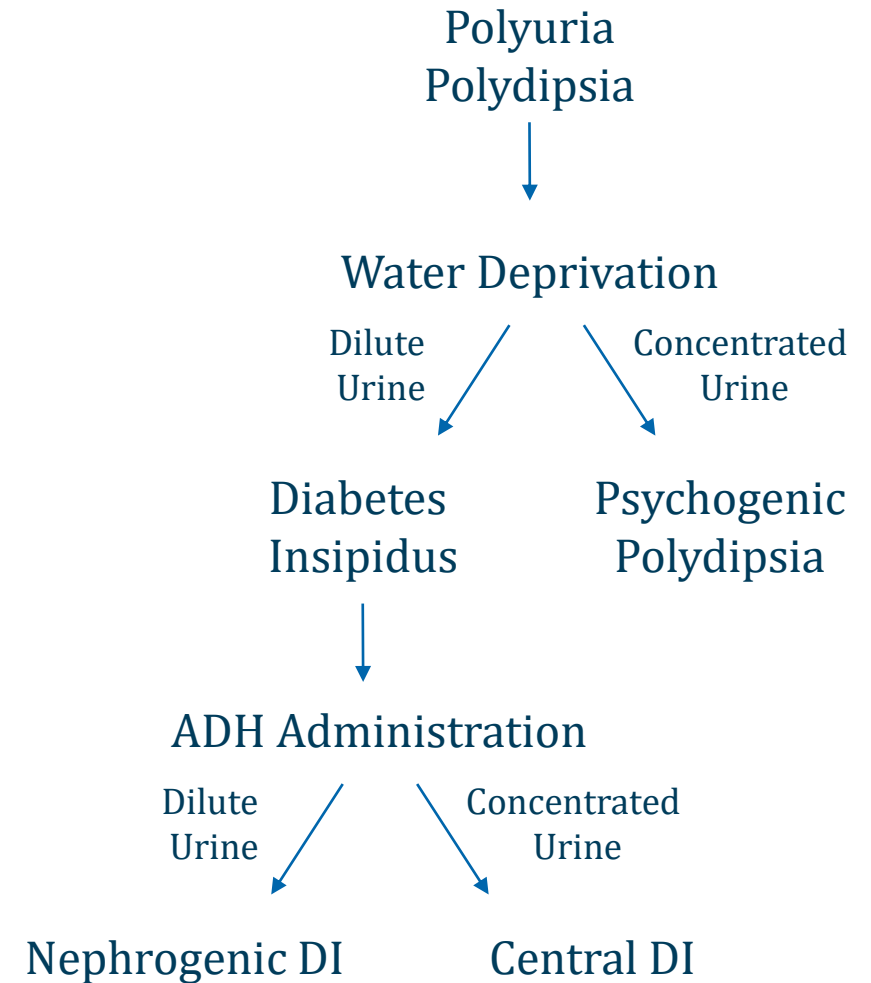
## Symptoms and Diagnosis

- Polyuria and polydipsia
- **Hypernatremia or normal sodium**
  - Water loss stimulates thirst
  - Hypernatremia occurs if not enough water
  - Central lesion (central DI) can impair thirst
- Urine osmolality low (50-200 mOsm/L)

# Diabetes Insipidus

## Diagnosis

- Best first test: **water deprivation**
  - After 8 hours of no fluid, urine should be concentrated
  - If urine is dilute → absent/ineffective ADH
- Administration of **desmopressin**
  - Activates renal ADH receptors (V2)
  - Should concentrate urine if kidneys work
  - If no concentration → nephrogenic DI
  - If concentration → central DI





# Hypernatremia

## Treatment

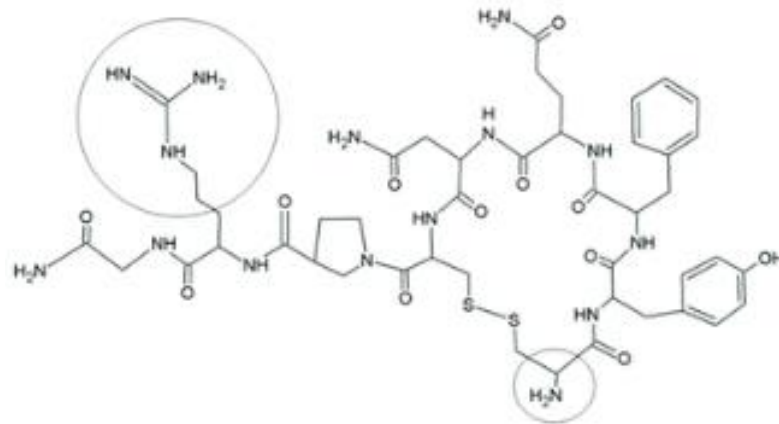
- Water (ideally PO)
- IV Fluids (D5W)
- Caution: **cerebral edema**
  - Occurs with overly-rapid correct of hypernatremia
  - Maximum correction: 12 mEq/L/day



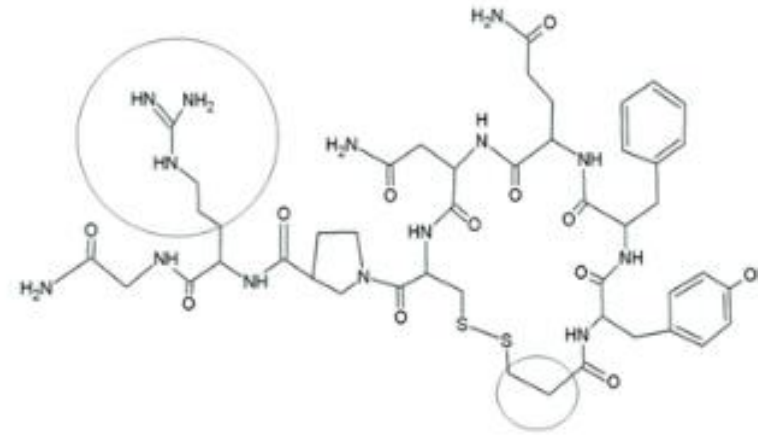
# Central Diabetes Insipidus

## Treatments

- Desmopressin (DDAVP)
  - ADH analog
  - No vasopressor effect (contrast with vasopressin)



Vasopressin (ADH)

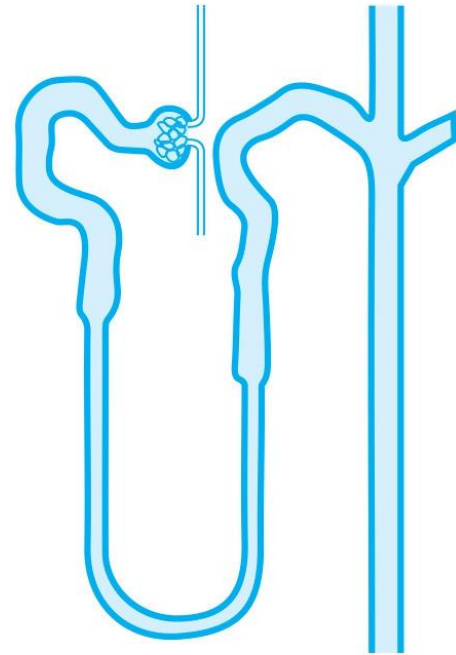


Desmopressin

# Nephrogenic Diabetes Insipidus

## Treatments

- Treat hypercalcemia or hypokalemia
- **Thiazide diuretics**
  - Increase in proximal Na/H<sub>2</sub>O reabsorption
  - Less H<sub>2</sub>O delivery to collecting tubules
  - Paradoxical antidiuretic effect
- NSAIDs
  - Inhibit renal synthesis of prostaglandins (ADH antagonists)



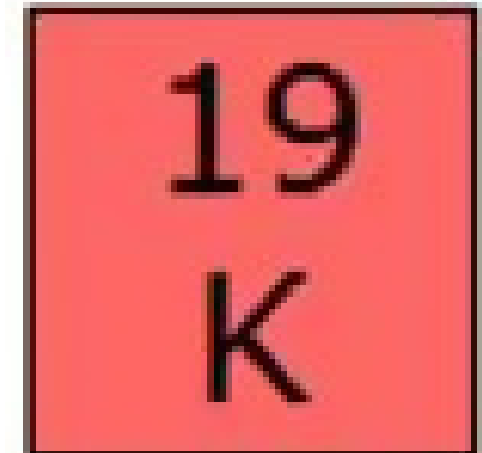
# Potassium Disorders

Jason Ryan, MD, MPH



# Potassium

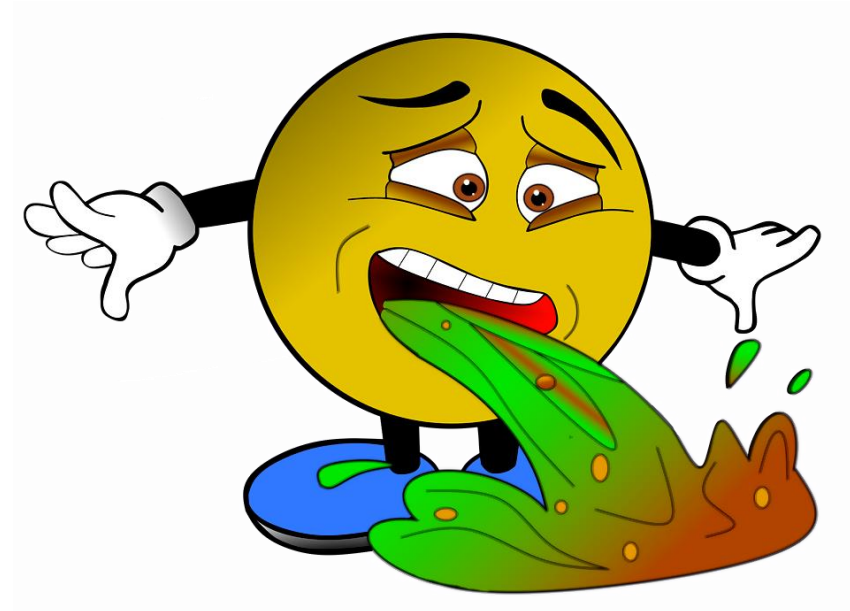
- Normal serum potassium: **3.5 – 5.0 mEq/L**
- Needed for HEART and SKELETAL MUSCLES
- Hypo/hyper effects:
  - EKG changes
  - Arrhythmias
  - **Weakness**



# Hypokalemia

## Selected Causes

- Gastrointestinal losses
  - **Vomiting**
  - **Diarrhea**
- Renal losses
  - **Diuretics**
  - Type I and II RTAs
- **Hypomagnesemia**
  - Promotes urinary K loss
  - Cannot correct K until Mg is corrected!!

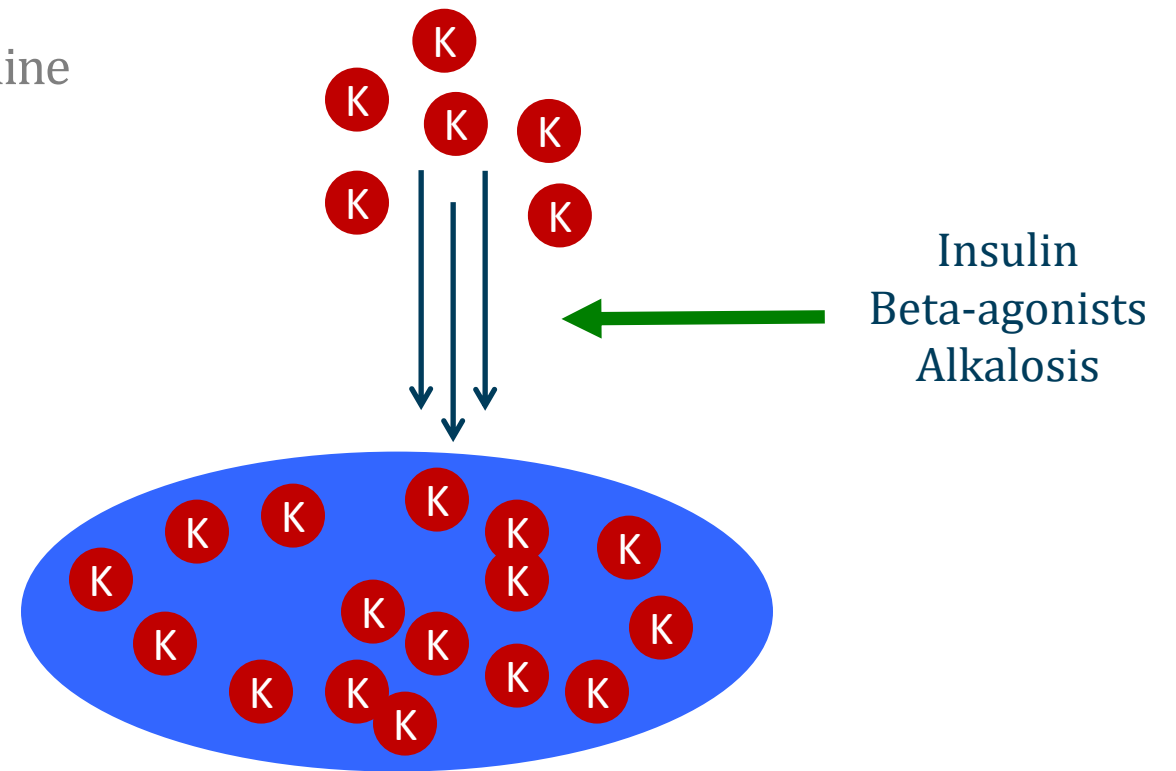


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# Hypokalemia

## Selected Causes

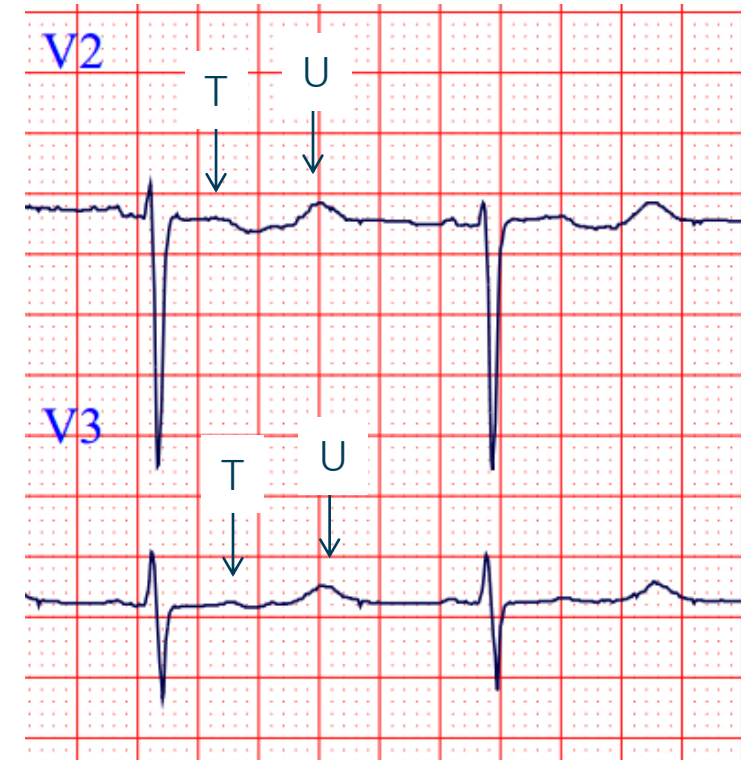
- **Redistribution into cells**
  - Insulin
  - Beta-agonists: albuterol, terbutaline, dobutamine
  - Alkalosis



# Hypokalemia

## Signs/Symptoms

- **Muscle weakness** → paralysis
  - Lower extremities → trunk → upper extremities
- Arrhythmias
  - PACs, PVCs
  - Bradycardia
- EKG changes
  - U waves
  - Flattened T waves
- Increased sensitivity to digoxin toxicity





# Hypokalemia

## Treatment

- Oral or IV potassium
  - IV potassium: phlebitis or arrhythmias at high infusion rates
- Potassium-sparing diuretics (spironolactone, eplerenone)
- Treat **hypomagnesemia** if present

Potassium	Treatment
3.0 – 3.5 mEq/L	Oral potassium
< 3.0 mEq/L or symptomatic	Oral or IV potassium

# Hyperkalemia

## Selected Causes

- Most cases: **↓ K excretion in urine**
  - Acute and chronic kidney disease
  - Type IV RTA (aldosterone resistance)
  - Drugs

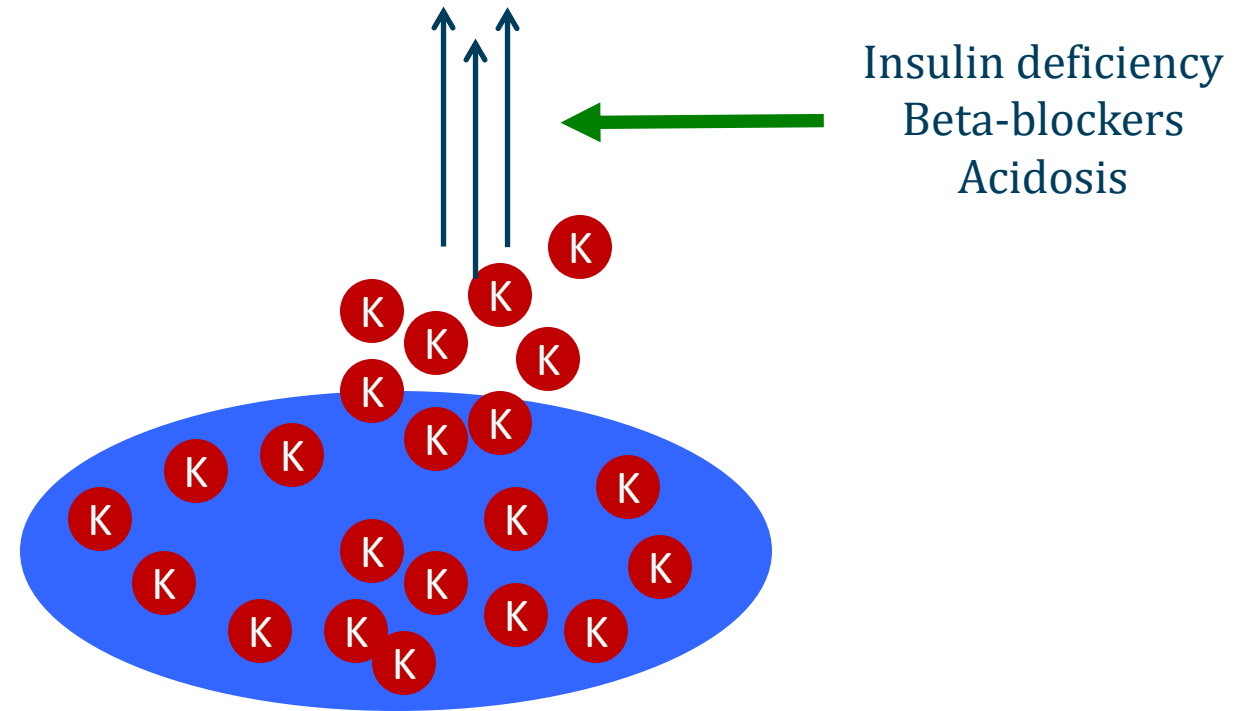


Wikipedia/Public Domain

# Hyperkalemia

## Selected Causes

- **Increased K release from cells**
  - Insulin deficiency
  - Beta-blockers
  - Acidosis
  - Digoxin toxicity
  - Lysis of cells (tumor lysis syndrome)
  - Hyperosmolarity (DKA, mannitol)

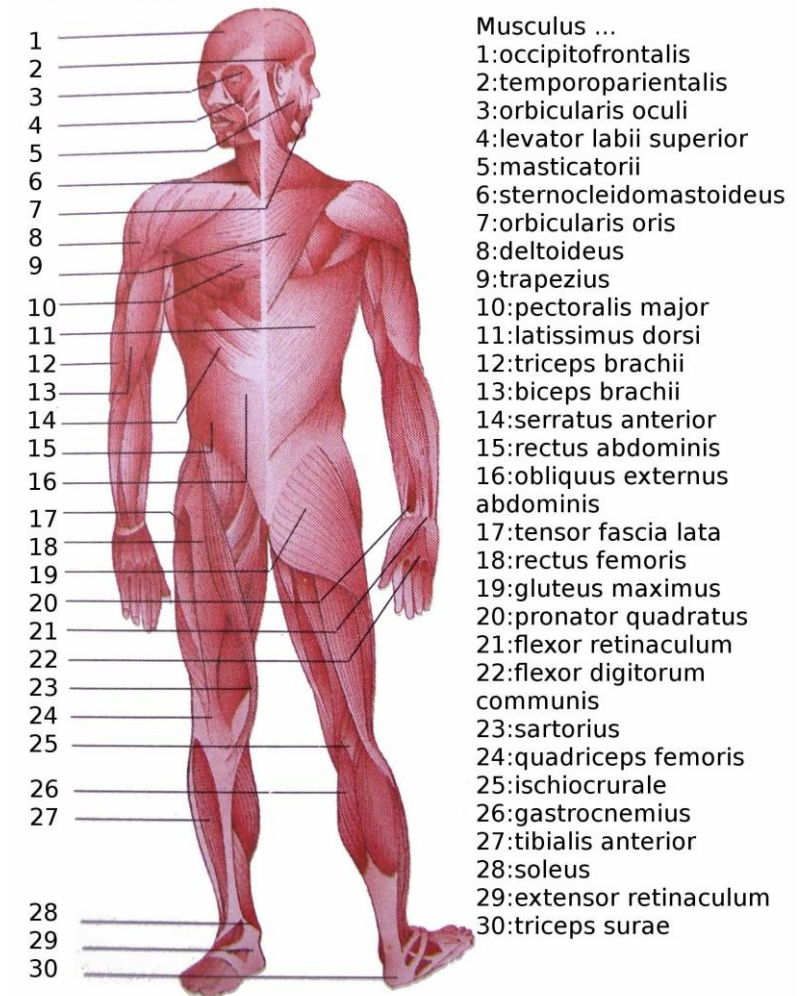


# Hyperkalemia

## Selected Causes

- **Rhabdomyolysis**
  - Breakdown of muscle tissue
  - Release of potassium

Skeletal muscles



Wikipedia/Public Domain

# Hyperkalemia

## Medication Causes

- **ACE-inhibitors, Angiotensin Receptor Blockers (ARBs)**
  - Limit aldosterone secretion
- **Potassium-sparing diuretics**
  - Block aldosterone effects
- Others (rare)
  - Non-selective beta-blockers (block K cellular uptake)
  - Digoxin (Inhibit Na/K ATPase)
  - NSAIDs (decrease prostaglandin-mediated aldosterone release)

# Hyperkalemia

## Signs/Symptoms

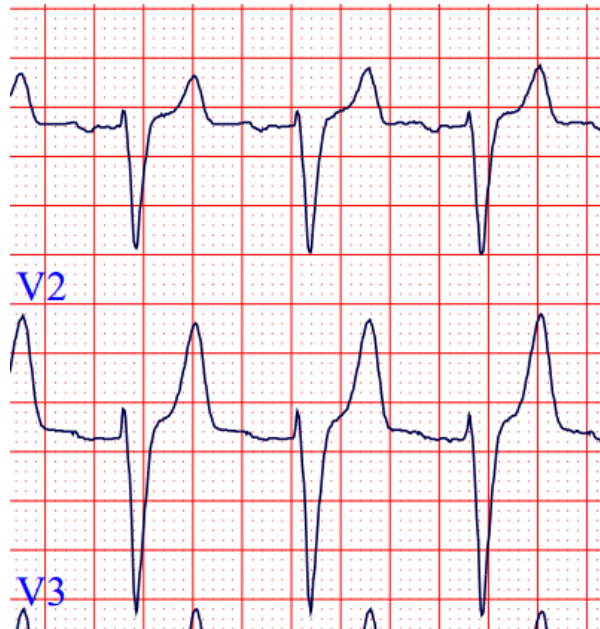
- Muscle weakness → paralysis
  - Lower extremities → trunk → upper extremities
- Arrhythmias
  - Sinus arrest
  - AV block



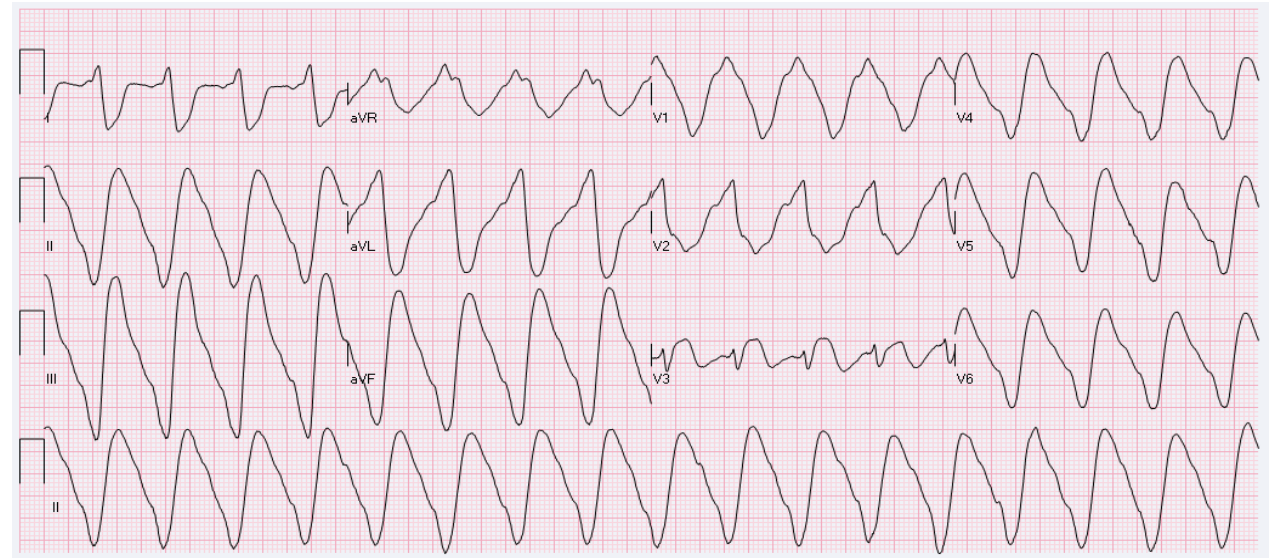
# EKG Changes

- **Key diagnostic test: EKG**

Peaked T Waves



Widened QRS



# Hyperkalemia

## Treatment

- Mild elevations without symptoms/EKG changes
  - Treat underlying cause
- Severely elevated K ( $>6.0$  mEq/L) or symptomatic/EKG changes
  - **IV calcium gluconate** (stabilizes myocardium – key with EKG changes)
  - Insulin with D5W (drives potassium into cells)
  - Bicarbonate (drives potassium into cells)
  - Potassium-binding resins (sodium polystyrene or patiromer)
  - Hemodialysis



# Calcium, Magnesium and Phosphate Disorders

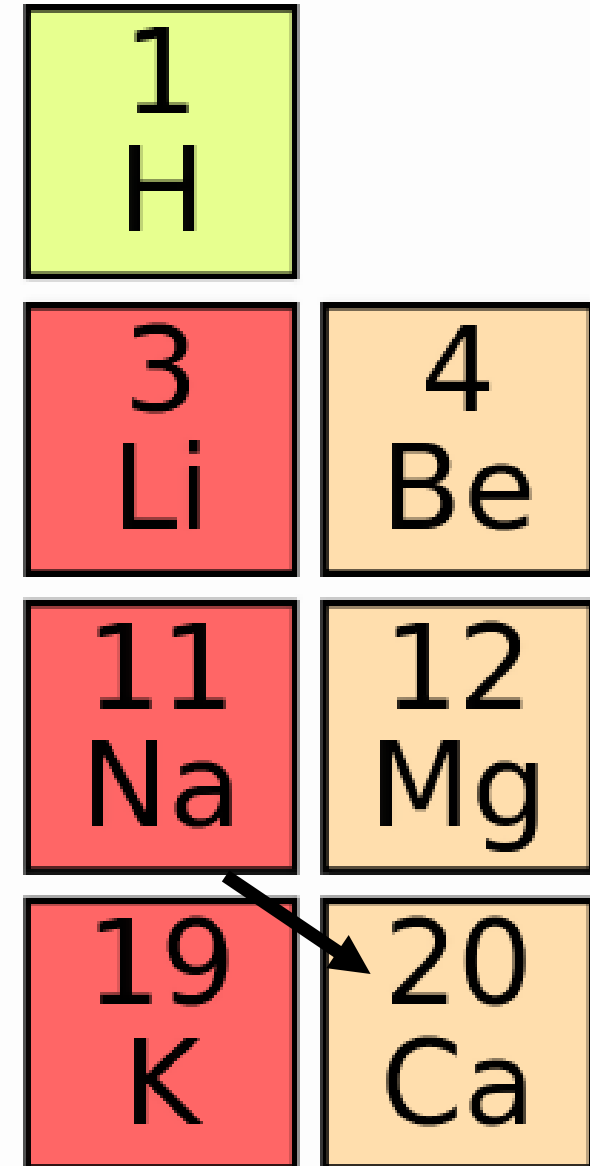
Jason Ryan, MD, MPH



# Calcium

- Total serum calcium: 8.5 to 10.0 mEq/L
- Corrected based on **serum albumin**
  - Normal albumin 3.4 to 5.4 g/dL
  - Every 1 below 4.0 albumin, add 0.8 to calcium
- Can measure **ionized (free) calcium**
  - Affected by pH
  - High in acidosis
  - Low in alkalosis

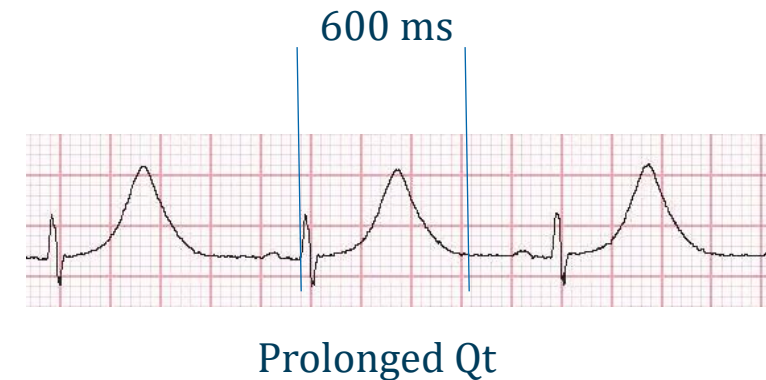
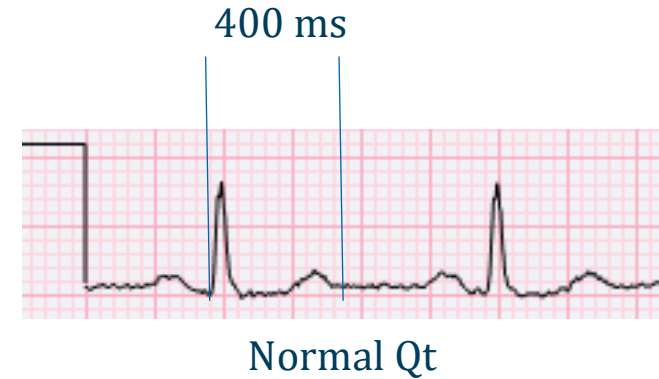
1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca



# Hypocalcemia

## Signs/Symptoms

- **Tetany**
  - Muscle twitches
  - Hyperactive reflexes
  - Trousseau's sign: Hand spasm with BP cuff inflation
  - Chvostek's sign: Facial contraction with tapping on nerve
- **Seizures**
- Prolonged Qt interval ( $> 470$  ms)



# Hypocalcemia

## Selected Causes

- Low parathyroid hormone levels
  - **Hypoparathyroidism (↓ PTH)**
- High parathyroid hormone levels
  - Vitamin D deficiency
  - Chronic kidney disease (↓ active vitamin D)
  - Pancreatitis (saponification of Mg/Ca in necrotic fat)
- Hypomagnesemia
  - Very low Mg → inhibits PTH release

12  
Mg

20  
Ca

# Hypocalcemia

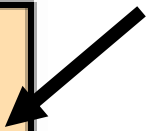
## Treatment

- Correct magnesium deficiency
- Vitamin D supplementation
- Mild deficiency (7.5 to 8.4 mg/dL): oral calcium
- Severe deficiency ( $< 7.5$  mg/dL)/highly symptomatic: **IV calcium gluconate**

# Hypercalcemia

- Calcium > 10.0 mg/dL
- Often asymptomatic unless Ca > 12.0 mg/dL
- Often identified on routine blood work
- May cause **recurrent kidney stones**
- Acute hypercalcemia → **polyuria**
  - Nephrogenic diabetes insipidus
  - Loss of ability to concentrate urine
  - Excessive free water excretion
  - ↓ GFR → acute renal failure

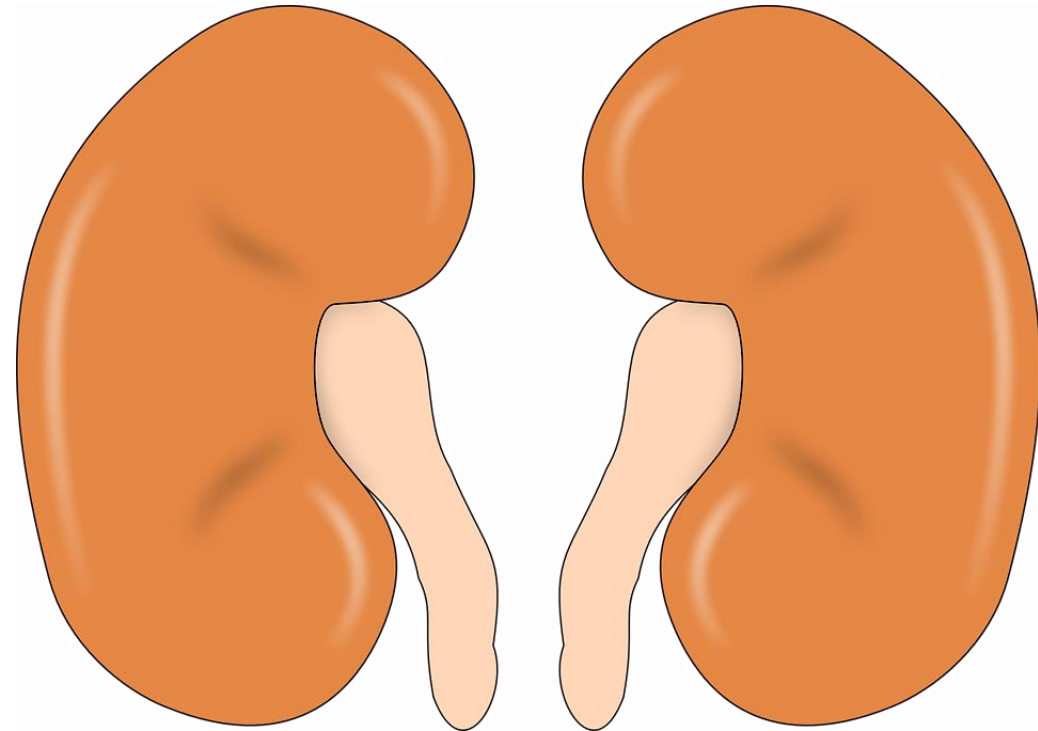
1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca



# Hypercalcemia

## Symptoms

- Stones (kidney)
  - Polyuria
  - Kidney stones
  - Renal failure
- Bones (bone pain)
- Groans (abdominal pain)
  - Constipation, anorexia, nausea
- Psychiatric overtones
  - Anxiety, altered mental status

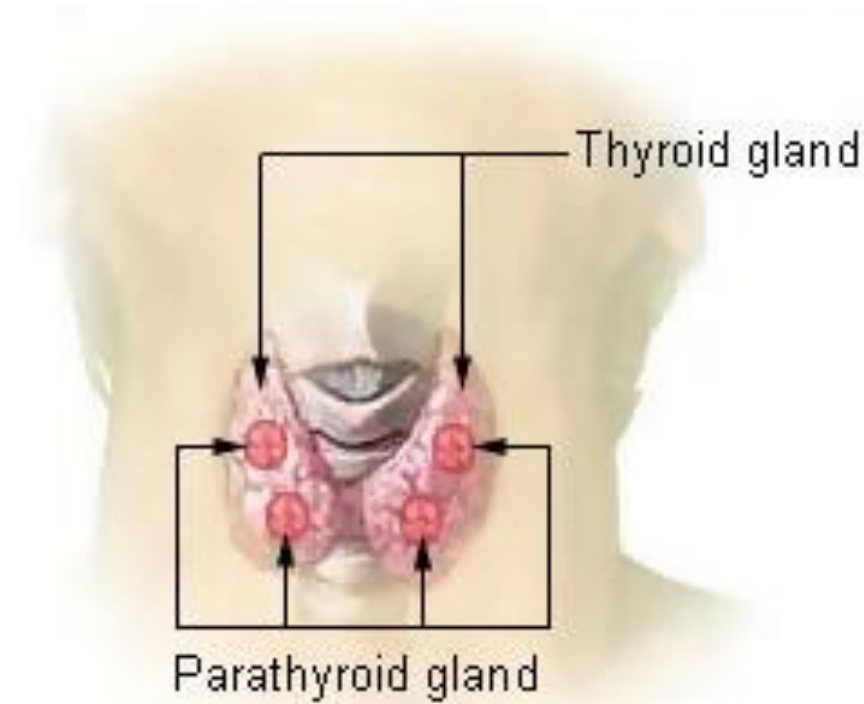


Public Domain

# Hypercalcemia

## Selected Causes

- **Hyperparathyroidism**
- **Malignancy**





# Hypercalcemia

## Selected Causes

- **Hypervitaminosis D**
  - Massive consumption calcitriol supplements
- **Sarcoidosis:** granulomatous macrophages  $1\alpha$ -hydroxylase
- **Milk alkali syndrome**
  - Largely historical
  - High intake calcium carbonate (ulcers)
  - Excess calcium and alkali intake
  - Hypercalcemia
  - Metabolic alkalosis
  - Renal failure



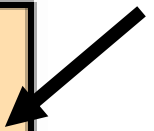
Wikimediacommons

# Hypercalcemia

## Treatment

- Treat underlying condition
- If severe ( $>14$  mg/dL) or symptomatic
  - Intravenous normal saline
  - Calcitonin
  - Bisphosphonates

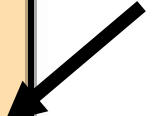
1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca



# Hypomagnesemia

- Normal: 1.8 to 2.5 mEq/L
- Neuromuscular excitability
  - Tetany, tremor
- Prolonged Qt interval
- Cardiac arrhythmias
- **Hypocalcemia**
- **Hypokalemia**

1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca



# Hypomagnesemia

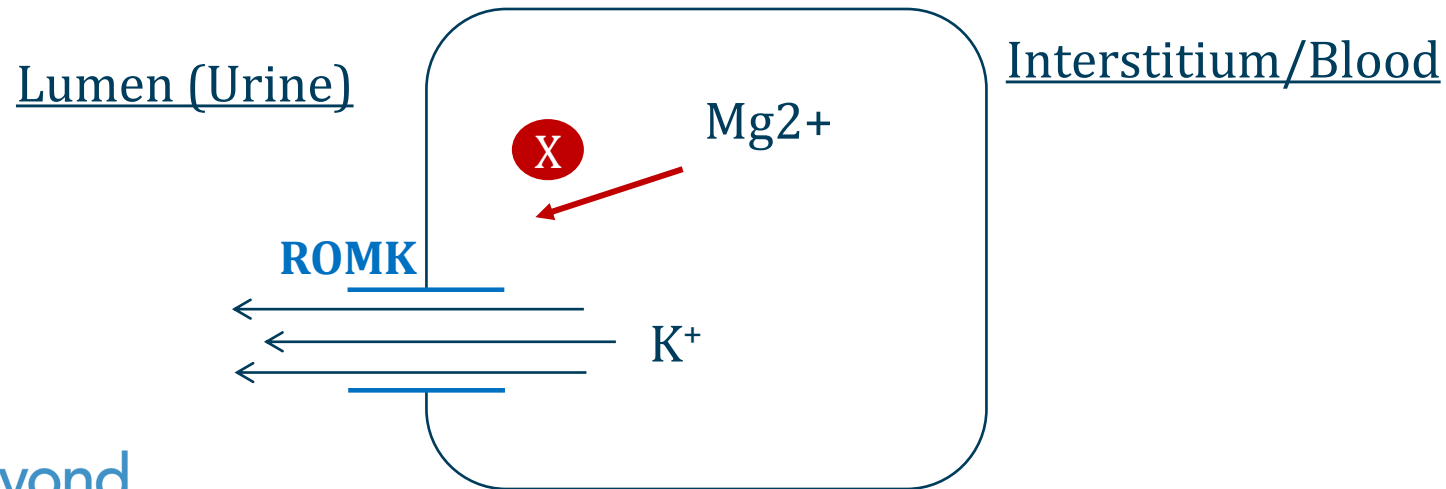
## Parathyroid Gland

- Low Mg
  - ↑ PTH release (same effect as calcium)
  - ↑ GI and renal magnesium along with calcium
- Very low Mg → inhibits PTH release
  - Some Mg required for normal CaSR function
  - Abnormal function → suppression of PTH release
  - **Hypocalcemia often seen in severe hypomagnesemia**

# Hypomagnesemia

## Potassium

- Magnesium inhibits potassium excretion
- **ROMK**
  - Renal outer medullary potassium channel
  - Found in cortical collecting duct
- **K won't correct until Mg corrected**



# Hypomagnesemia

## Selected Causes

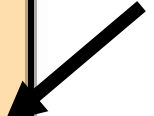
- GI losses (secretions contain Mg)
  - Diarrhea
- Renal losses
  - Loop and thiazide diuretics
- Malnutrition
  - **Alcohol use** (alcohol-induced tubular dysfunction)

# Hypomagnesemia

## Treatment

- Oral or intravenous magnesium

1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca

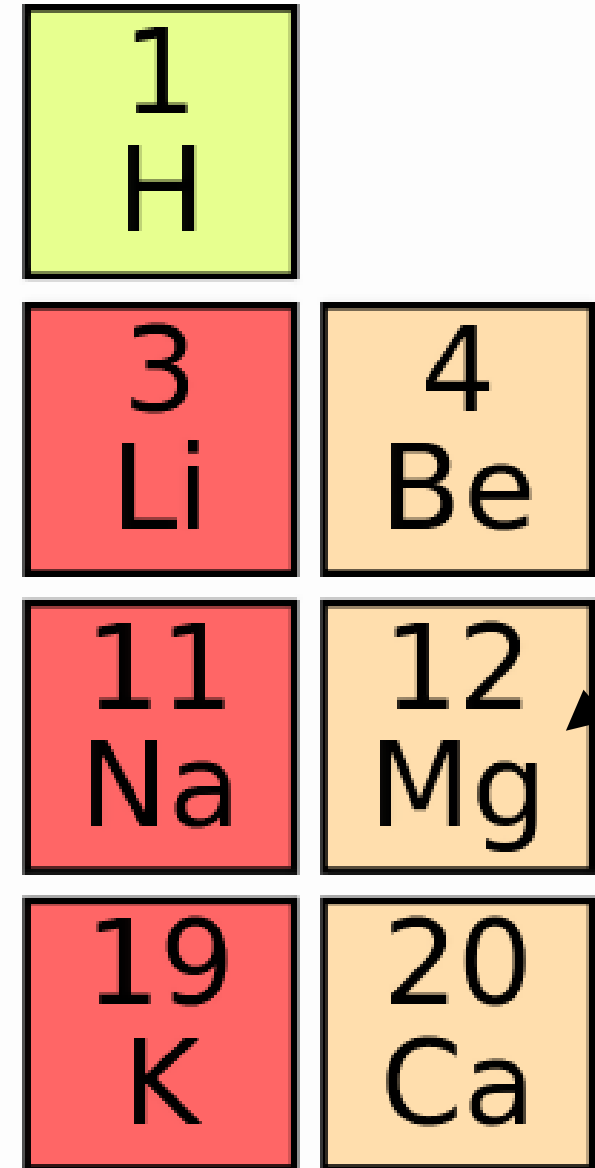


# Hypermagnesemia

- Magnesium > 2.5 mEq/L
- Mg blocks Ca and K channels
- Neuromuscular toxicity
  - ↓ reflexes
  - Paralysis
- Bradycardia, hypotension, cardiac arrest
- Hypocalcemia (inhibits PTH secretion)

↑ Mg → ↓PTH → ↓Ca

1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca

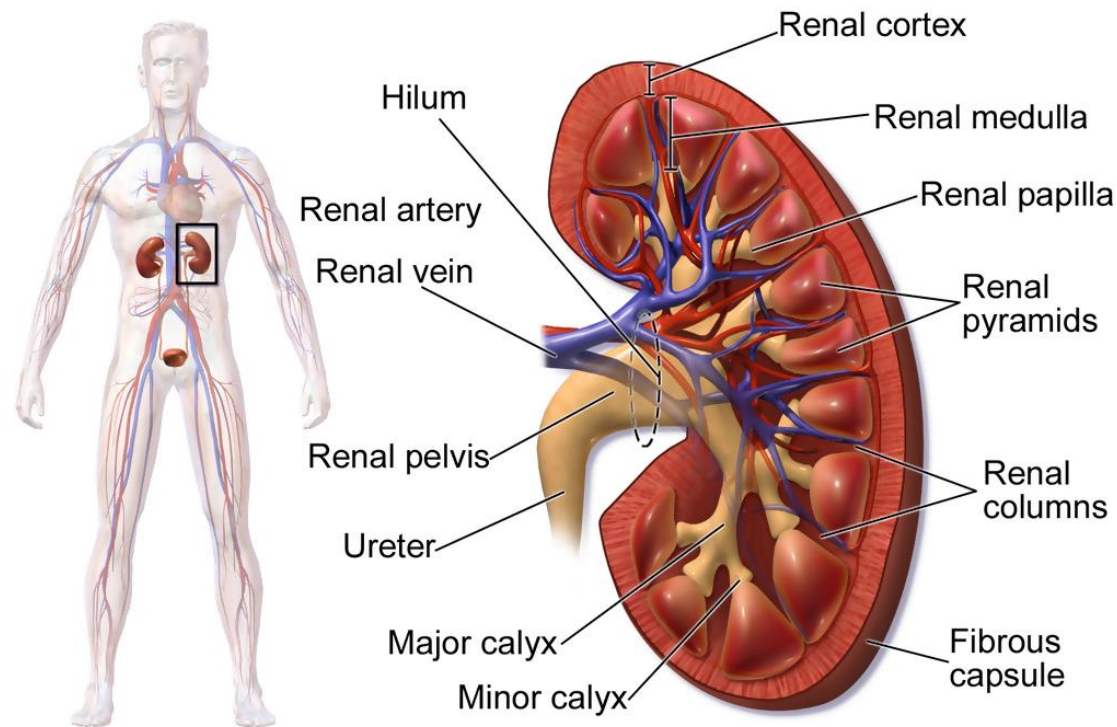




# Hypermagnesemia

## Selected Causes

- **Renal insufficiency**



## Kidney Anatomy

BruceBlais

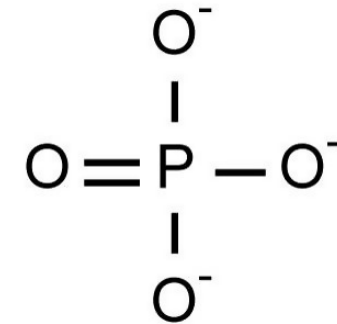
# Hypermagnesemia

## Treatment

- Stop magnesium-containing drugs
- Normal saline and loop diuretics
- Calcium gluconate
- Severe renal insufficiency: dialysis

# Hypophosphatemia

- Normal phosphate: 2.5 to 4.5 mg/dL
- Main acute symptom is **weakness**
  - ATP depletion
  - Often presents are **respiratory muscle weakness**
- If chronic: bone loss, osteomalacia

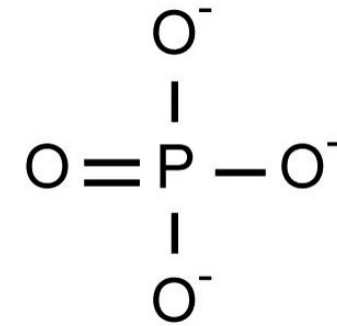


$\text{PO}_4^-$

# Hypophosphatemia

## Selected Causes

- Primary hyperparathyroidism
- Diabetic ketoacidosis (DKA)
  - Glucose induced diuresis → ↑ PO<sub>4</sub> excretion
- Refeeding syndrome
  - Low PO<sub>4</sub> from poor nutrition
  - Food intake → metabolism → further ↓ PO<sub>4</sub>

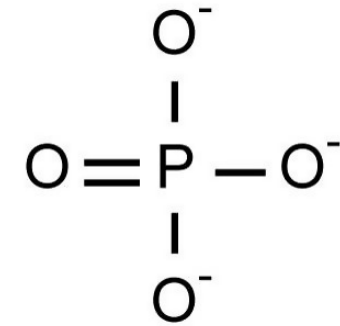


PO<sub>4</sub><sup>-</sup>

# Hypophosphatemia

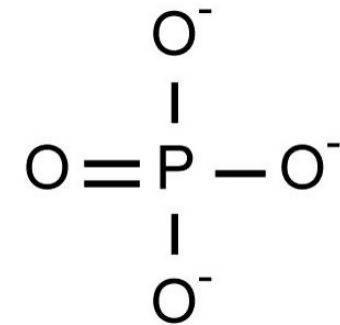
## Treatment

- Oral or IV phosphate replacement



# Hyperphosphatemia

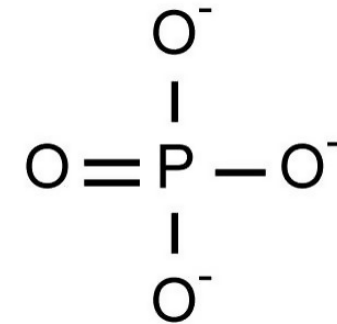
- Phosphate > 4.5mg/dL
- Most patients asymptomatic
- Signs and symptoms usually from **hypocalcemia**
- Phosphate precipitates serum calcium



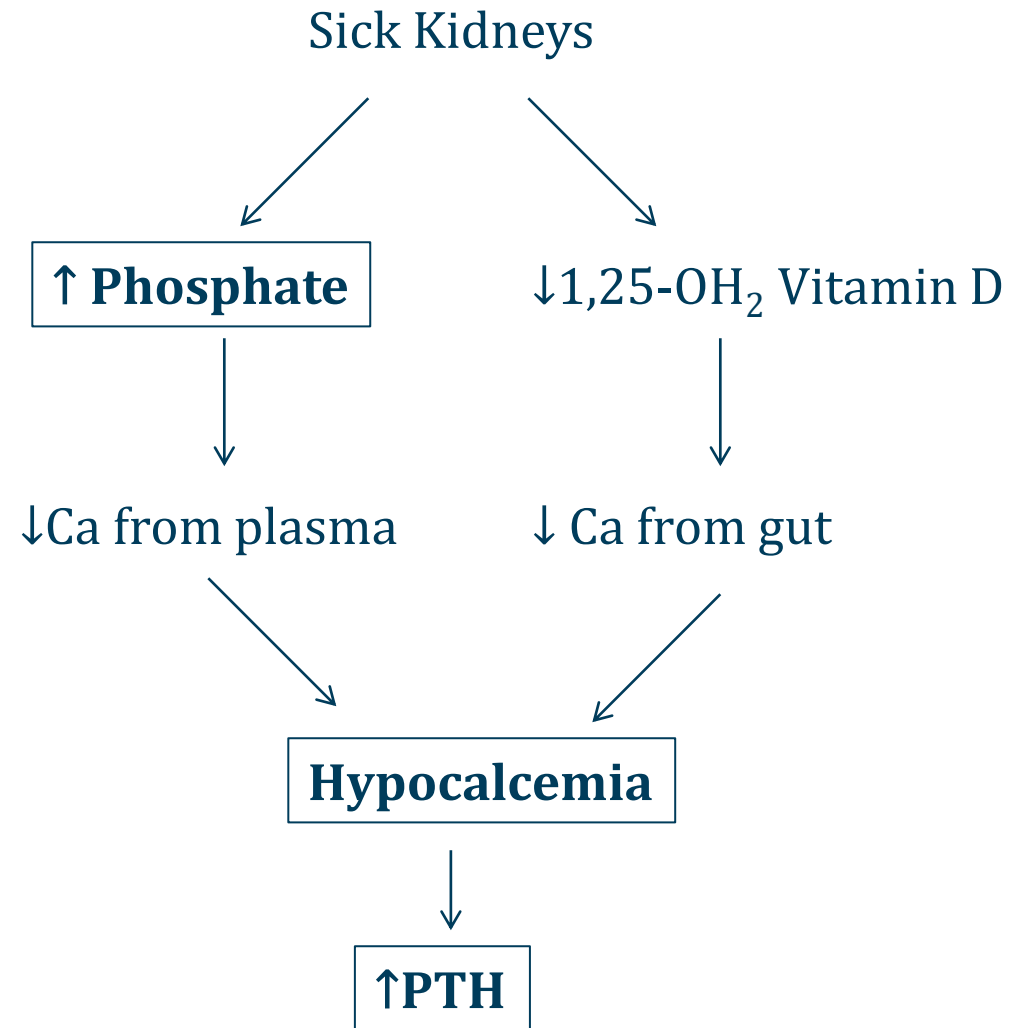
# Hyperphosphatemia

## Selected Causes

- **Acute and chronic kidney disease**
- Hypoparathyroidism
  - PTH inhibits phosphate reabsorption
  - Low PTH → increased phosphate reabsorption
- Phosphate load
  - Tumor lysis syndrome
  - Rhabdomyolysis
  - Large amount of phosphate laxatives (Fleet's Phospho-soda)



# Calcium-Phosphate in Chronic Renal Failure

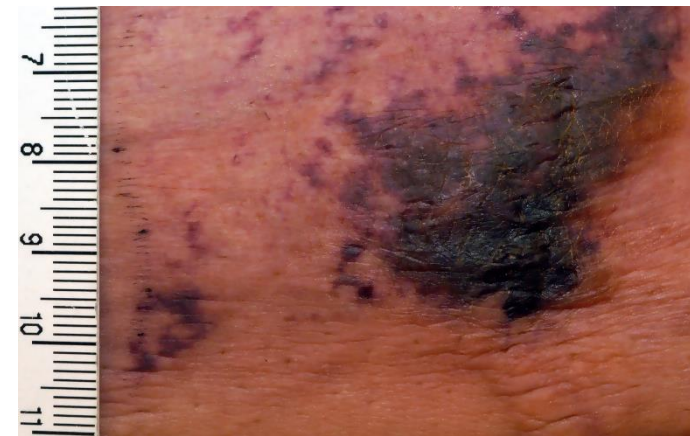




# Hyperphosphatemia

## Symptoms

- **Metastatic calcifications**
  - “Calciophylaxis”
  - Seen in chronic hyperphosphatemia in CKD
  - Excess phosphate taken up by vascular smooth muscle
  - Smooth muscle osteogenesis
  - **Vascular wall calcification**
  - Increased systolic blood pressure
  - Small vessel thrombosis
  - Painful nodules, skin necrosis

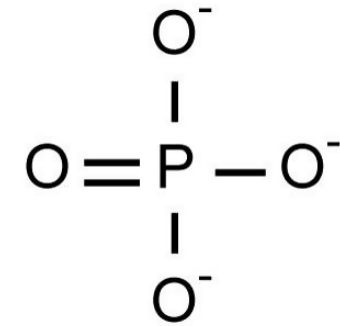


Niels Olsen/Wikipedia

# Hyperphosphatemia

## Treatment

- Low phosphate diet
- Phosphate binders
  - Used in patients with chronic kidney disease
  - Calcium carbonate
  - Calcium acetate (Phoslo)
  - Sevelamer (Renagel)
  - Lanthanum



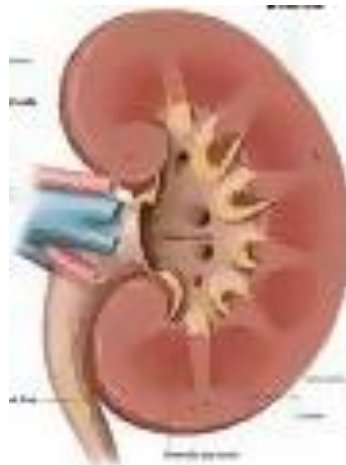
# Acid-Base Principles

Jason Ryan, MD, MPH

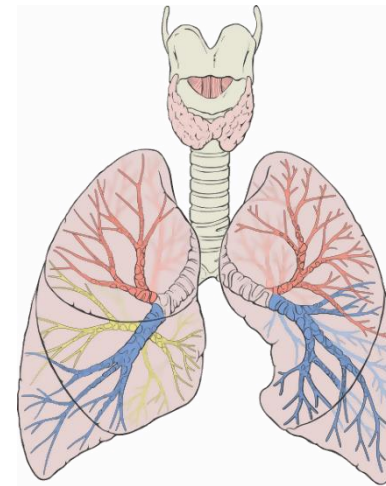


# Acid-Base Balance

- Normal arterial pH: 7.37 to 7.42
- Tightly controlled
- **Lungs**: excrete carbon dioxide
- **Kidneys**: excrete acid & produce bicarbonate



Public Domain



Patrick J. Lynch, medical illustrator

# Henderson-Hasselbalch Equation

Maintained by kidneys



$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$



Maintained by lungs

# Arterial Blood Gas

- Normal  $\text{HCO}_3^- = 22 - 26 \text{ mEq/L}$
- Normal  $\text{pCO}_2 = 35 - 45 \text{ mmHg}$
- Normal  $\text{pH} = 7.37-7.42$

**$\text{HCO}_3^-$ : 24**  
 **$\text{PCO}_2$ : 40**  
**pH: 7.4**

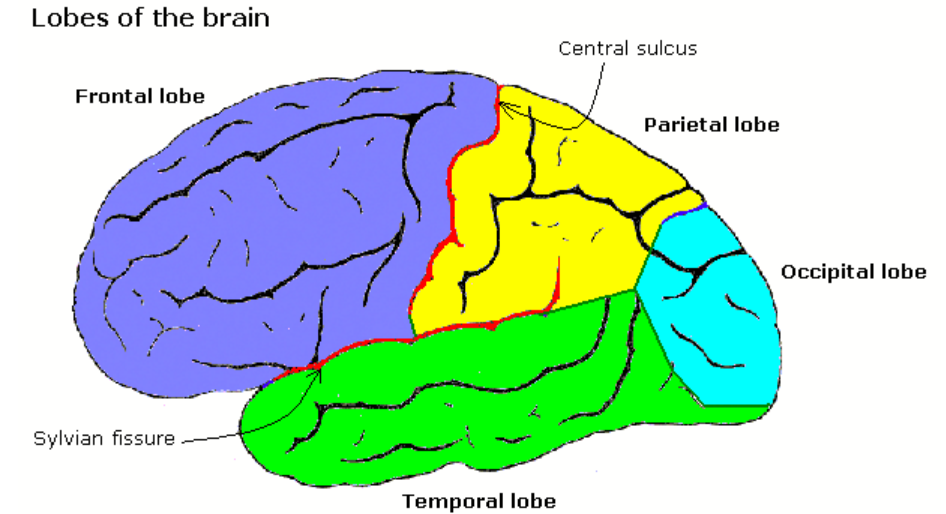


# Acid-Base Disorders

- Acidosis/alkalosis
  - Disorder-altering  $H^+$  levels
- Acidemia/alkalemia
  - Presence of low or high pH in bloodstream
- Acidosis without acidemia occurs in mixed disorders
  - i.e. acidosis + alkalosis at same time

# Acidosis Effects

- Hyperventilation
- Myocardial depression (↓ contractility)
- Cerebral vasodilation
  - CO<sub>2</sub>: major cerebral autoregulator
  - CO<sub>2</sub> → ↓ pH: increased cerebral blood flow
  - Increased intracranial pressure → headaches
- **Hyperkalemia**
  - High H<sup>+</sup> shifts into cells in exchange for K<sup>+</sup>



RobinH/Wikipedia

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$



# Alkalosis Effects

- Hypoventilation
- **Cerebral vasoconstriction**
  - Decrease in cerebral blood flow
- Hypokalemia

# Acid-Base Disorders

- **Metabolic Disorders**

- Excess or insufficient  $\text{HCO}_3^-$
- Metabolic acidosis ( $\downarrow \text{HCO}_3^-$ )
- Metabolic alkalosis ( $\uparrow \text{HCO}_3^-$ )

- **Respiratory disorders**

- Excess or insufficient  $\text{CO}_2$
- Respiratory acidosis ( $\uparrow \text{CO}_2$ )
- Respiratory alkalosis ( $\downarrow \text{CO}_2$ )

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$

# Acid-Base Problems

- Given pH,  $\text{CO}_2$ ,  $\text{HCO}_3^-$
- What is the disorder?



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# Acid-Base Problems

## 1. Check the **pH**

- $\text{pH} < 7.37$  = acidosis
- $\text{pH} > 7.42$  = alkalosis

## 2. Check the **$\text{HCO}_3^-$** and **$\text{pCO}_2$**

- Increased or decreased?
- $\text{HCO}_3^-$ : normal 22-26 mEq/L
- $\text{pCO}_2$  from ABG: normal 35-45mmHg

# Acid-Base Problems

## 3. Determine acid-base disorder

- Acidosis +  $\downarrow \text{HCO}_3^-$  = metabolic acidosis
- Acidosis +  $\uparrow \text{pCO}_2$  = respiratory acidosis
- Alkalosis +  $\uparrow \text{HCO}_3^-$  = metabolic alkalosis
- Alkalosis +  $\downarrow \text{pCO}_2$  = respiratory alkalosis

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$

# Acid-Base Problems

4. Calculate anion gap (metabolic acidosis)
5. Use special formulas to check for mixed disorders
  - Combined respiratory/metabolic
  - Two metabolic disorders

# Compensatory Changes

- $\text{HCO}_3^-$  and  $\text{CO}_2$  are not independent
- Abnormal  $\text{HCO}_3^- \rightarrow$  Abnormal  $\text{CO}_2$
- Abnormal  $\text{CO}_2 \rightarrow$  Abnormal  $\text{HCO}_3^-$
- This is called **compensation**

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$

# Compensatory Changes

- Respiratory disorders → abnormal  $\text{CO}_2$ 
  - Compensation:  $\text{HCO}_3^-$  (renal)
- Metabolic disorders → Abnormal  $\text{HCO}_3^-$ 
  - Compensation  $\text{CO}_2$  (respiratory)

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$



# Compensatory Changes

Acid-Base Disorder	Primary Abnormality	Compensation
Metabolic Acidosis	$\downarrow \text{HCO}_3^-$	$\downarrow \text{CO}_2$
Metabolic Alkalosis	$\uparrow \text{HCO}_3^-$	$\uparrow \text{CO}_2$
Respiratory Acidosis	$\uparrow \text{CO}_2$	$\uparrow \text{HCO}_3^-$
Respiratory Alkalosis	$\downarrow \text{CO}_2$	$\downarrow \text{HCO}_3^-$

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$

# Compensatory Changes

- Most acid-base disorders:  $\text{HCO}_3^-$  and  $\text{CO}_2$  abnormal
- One is “culprit” causing disorder
- Other is compensatory change

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$

# Compensatory Changes

- Simple disorders
  - Culprit and compensatory change: same direction
  - $\text{HCO}_3^-$  and  $\text{pCO}_2$  both increased or both decreased

## Example 1

pH = 7.30 (acidosis)

$\text{HCO}_3^-$  = low

$\text{pCO}_2$  = low

Metabolic acidosis with respiratory compensation

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$

# Compensatory Changes

- Simple disorders
  - Culprit and compensatory change: same direction
  - Both increased or both decreased

## Example 2

pH = 7.30 (acidosis)

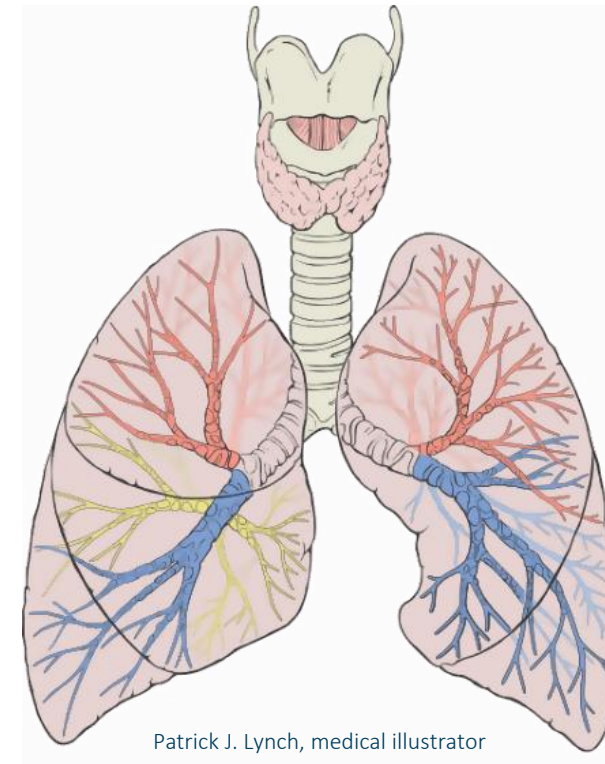
$\text{HCO}_3^-$  = high

pCO<sub>2</sub> = high

Respiratory acidosis with metabolic compensation

# Respiratory Compensation

- Hyperventilation or hypoventilation
- Alters  $\text{CO}_2$
- Compensates for metabolic disorders ( $\text{HCO}_3^-$ )
- **Hyperventilation**
  - Physiologic response to metabolic acidosis
  - Kussmaul breathing = deep, labored breathing
  - Trying to blow off  $\text{CO}_2$



# Respiratory Compensation

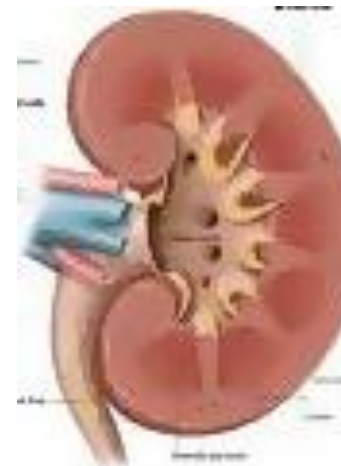
- Hyperventilation
  - Blows off CO<sub>2</sub>
  - Plasma CO<sub>2</sub> level falls
  - Less H<sup>+</sup> in blood
  - pH rises
- Hypoventilation
  - Retains CO<sub>2</sub>
  - Plasma CO<sub>2</sub> level rises
  - More H<sup>+</sup> in blood
  - pH falls

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$

# Renal Compensation

- Acidosis
  - **Serum bicarbonate increases**
  - Excess H<sup>+</sup> filtered/secreted
  - Bicarbonate reabsorbed
  - Bicarbonate generated
- Alkalosis
  - Reverse of acidosis

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$



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# Compensation Timeframe

- Respiratory compensation to metabolic disorders
  - Occurs in **minutes**
  - Rapid change in respiratory rate
- Metabolic compensation to respiratory disorders
  - Chronic, significant compensation in **days** from kidneys



Public Domain



# Mixed Disorders

- **Two disorders** at same time
  - Metabolic acidosis AND respiratory acidosis
  - Metabolic acidosis AND metabolic alkalosis
  - Two metabolic acidoses
  - Occurs in many pathologic states
  - Example: vomiting and diarrhea

# Mixed Disorder Recognition

- Determine “**expected**” response
  - Expected  $\text{HCO}_3^-$  for respiratory disorder
  - Expected  $\text{CO}_2$  for metabolic disorder
- If actual  $\neq$  expected  $\rightarrow$  2<sup>nd</sup> disorder present
- Compensation back to normal pH ***very rare***
  - Normal pH usually implies a mixed disorder

# Mixed Disorder Recognition

- If actual  $\neq$  expected, determine abnormality
  - Example:  $\text{CO}_2$  higher than expected
  - Example:  $\text{HCO}_3^-$  lower than expected
- Usual rules then apply for determining 2° disorders:
  - $\uparrow \text{CO}_2$  = respiratory acidosis
  - $\downarrow \text{CO}_2$  = respiratory alkalosis
  - $\downarrow \text{HCO}_3^-$  = metabolic acidosis
  - $\uparrow \text{HCO}_3^-$  = metabolic alkalosis

# Compensation Formulas

- **Winter's Formula**
- Metabolic Alkalosis Formula
- Acute/Chronic Respiratory Equations
- Delta-Delta

# Metabolic Acidosis

- Compensatory respiratory alkalosis ( $\downarrow \text{CO}_2$ )
- Hyperventilation
- **Winter's Formula:**
  - Calculates expected  $\text{CO}_2$
  - If actual  $\text{CO}_2 \neq$  expected, mixed disorder

$$\text{pCO}_2 = 1.5 (\text{HCO}_3^-) + 8 + /- 2$$

# Metabolic Acidosis

- Compensatory respiratory alkalosis ( $\downarrow \text{CO}_2$ )
- Hyperventilation
- **Winter's Formula:**
  - Calculates expected  $\text{CO}_2$
  - If actual  $\text{CO}_2 \neq$  expected, mixed disorder

$$\text{pCO}_2 = 1.5 (\text{HCO}_3^-) + 8 \pm 2$$

## Example 1

pH = 7.23 (acidosis)

$\text{HCO}_3^- = 9 \text{ mEq/L}$  (nl = 24)

$\text{pCO}_2 = 22 \text{ mmHg}$  (nl=40)

Expected  $\text{pCO}_2 = 1.5 (9) + 8 = 22 \pm 2$

# Metabolic Acidosis

- Compensatory respiratory alkalosis ( $\downarrow \text{CO}_2$ )
- Hyperventilation
- **Winter's Formula:**
  - Calculates expected  $\text{CO}_2$
  - If actual  $\text{CO}_2 \neq$  expected, mixed disorder

$$\text{pCO}_2 = 1.5 (\text{HCO}_3^-) + 8 \pm 2$$

## Example 2

pH = 7.10 (acidosis)

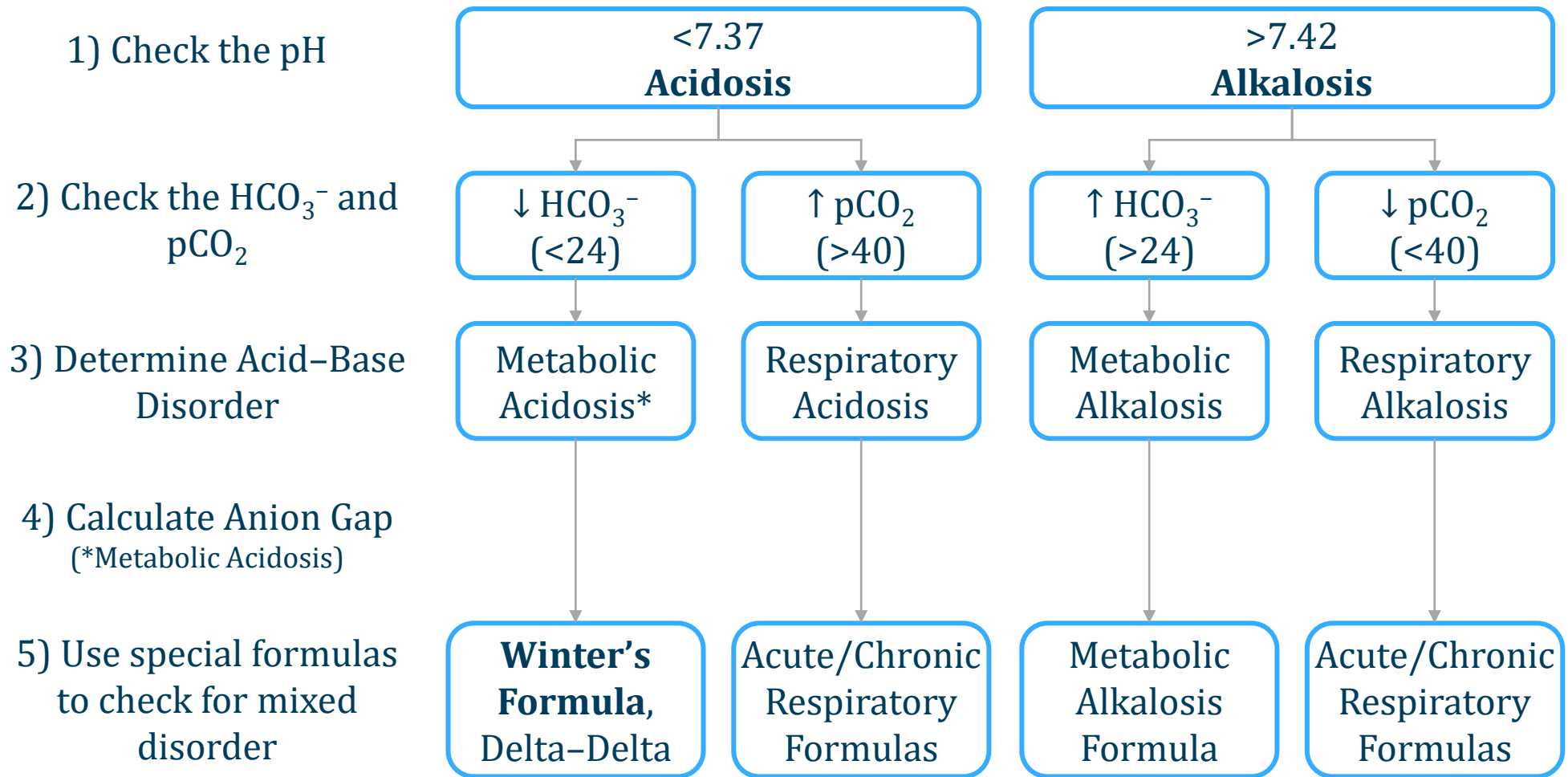
$\text{HCO}_3^- = 12 \text{ mEq/L}$  (nl = 24)

$\text{pCO}_2 = 40 \text{ mmHg}$  (nl=40)

Expected  $\text{pCO}_2 = 1.5 (12) + 8 = 26 \pm 2$

$\text{pCO}_2 > \text{expected}$

Concomitant Respiratory Acidosis





# Metabolic Alkalosis

Jason Ryan, MD, MPH



# Acid-Base Disorders

1. Respiratory alkalosis
2. Respiratory acidosis
3. Metabolic alkalosis
4. Metabolic acidosis

# Metabolic Alkalosis

$$\text{pH} > 7.42$$
$$\uparrow \text{HCO}_3^-$$

Increased **pH** =  $6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$

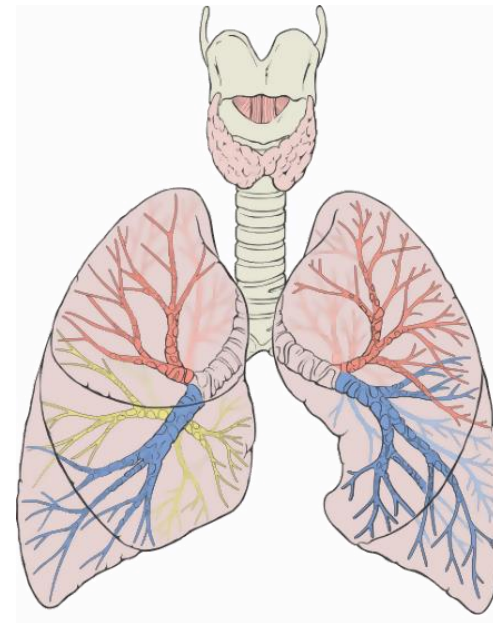
$\uparrow$  = primary abnormality

$\uparrow$  = respiratory compensation

# Hypoventilation

- Respiratory compensation in metabolic alkalosis
- Increased  $p\text{CO}_2$
- Lowers pH

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * p\text{CO}_2}$$



Patrick J. Lynch, medical illustrator

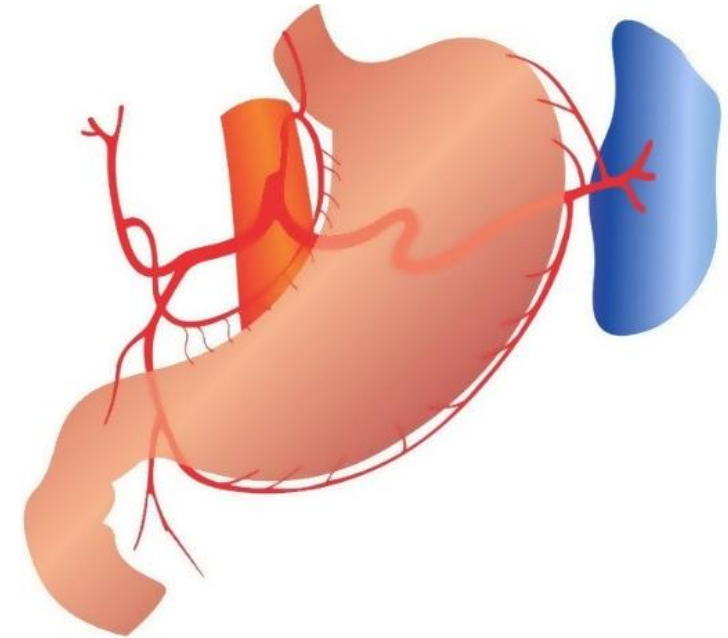
# Metabolic Alkalosis

1. Gastrointestinal acid loss
2. Contraction alkalosis
3. Hypokalemia
4. Milk-alkali syndrome
5. Hyperaldosteronism
6. Rare renal syndromes

**pH > 7.42**  
**↑ HCO<sub>3</sub><sup>-</sup>**

# Gastrointestinal Acid Loss

- Vomiting
- Gastric suction
- Parietal cells secrete HCl
- Loss of stomach contents → **alkalosis**
- **Hypochloremia** ( $\text{Cl}^-$  loss)
- **Hypokalemia** ( $\text{K}^+$  loss)
- Hypochloremic, hypokalemic metabolic alkalosis



Stomach

# Contraction Alkalosis

- Loss of fluid with Na and Cl
- ↓ Effective Circulating Volume (ECV)
- Renin-Angiotensin-Aldosterone System (RAAS) activation
- Sympathetic nervous system (SNS) activation
- ↑  $\text{HCO}_3^-$  resorption proximal tubule
- ↑  $\text{H}^+$  secretion collecting duct
- New data suggest **chloride depletion** is true cause
  - Low volume → low NaCl
  - Chloride repletion resolves alkalosis

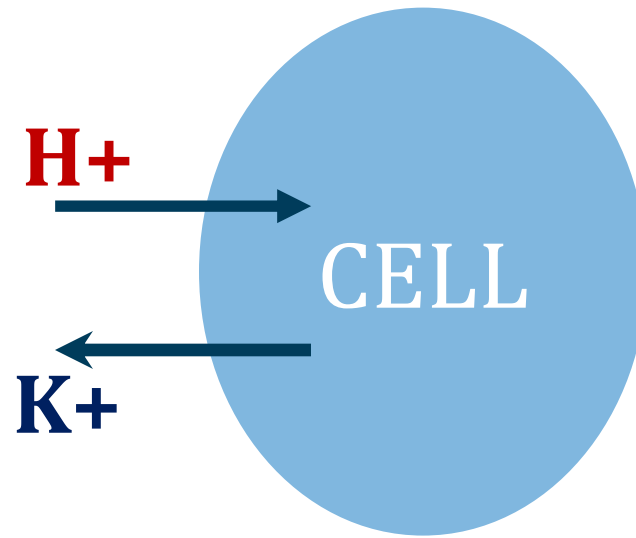
# Contraction Alkalosis

- Vomiting
- Diuretics
- Heart failure
- Cirrhosis



# Hypokalemia

- $K^+$  exchanges with  $H^+$
- **Shifts in and out of cells**
- $\downarrow K^+ \rightarrow$  shift  $K^+$  out of cells  $\rightarrow H^+$  into cells
- Hypokalemia  $\rightarrow$  alkalosis (vice versa)



# Milk-alkali Syndrome

- Hypercalcemia, metabolic alkalosis, renal failure
- Excessive intake:
  - Calcium
  - Alkali (base)
- Usually **calcium carbonate** and/or milk
  - Alkaline  $\text{CaCO}_3$
- Often taken for dyspepsia



Midnightcomm

# Milk-alkali Syndrome

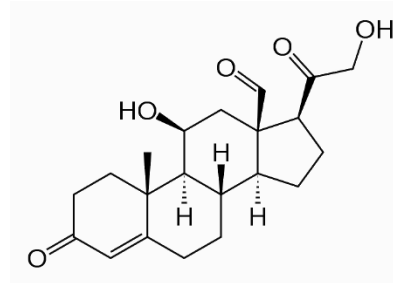
- Increased Ca intake → hypercalcemia
- Hypercalcemia → **polyuria**
  - Inhibition Na-K-2Cl in TAL
  - Blockade (ADH)-dependent water reabsorption collecting duct
- Results in volume contraction
- Contraction + alkali = **metabolic alkalosis**
- ↓ GFR from volume contraction
  - ↑ BUN, Cr

**Hypercalcemia**  
**Metabolic alkalosis**  
**Renal failure**

# Hyperaldosteronism

## Primary Aldosteronism

- Adrenal overproduction of aldosterone
- Adrenal hyperplasia
- Adrenal adenoma (Conn's syndrome)
- Increased secretion  $H^+$
- **Metabolic alkalosis**
- Hypokalemia
- **Hypertension**



Aldosterone

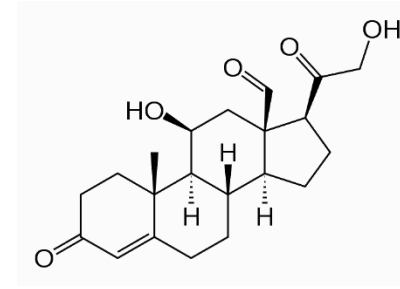


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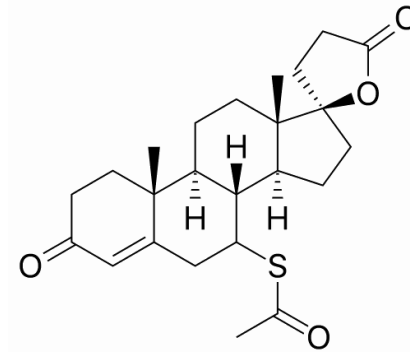
# Hyperaldosteronism

## Primary Aldosteronism

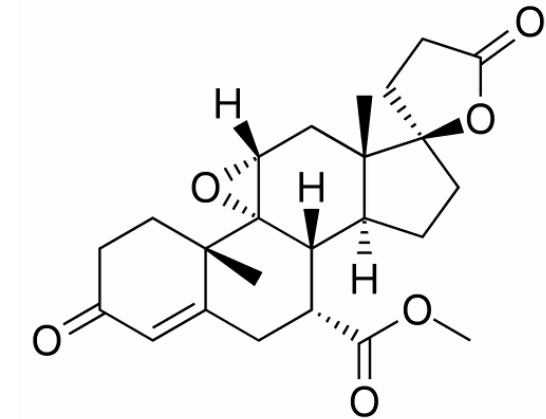
- Diagnosis
  - High plasma aldosterone concentration
  - Low plasma renin activity
- Treatment
  - Spironolactone
  - Eplerenone
  - Surgery for adrenal adenoma



Aldosterone



Spironolactone



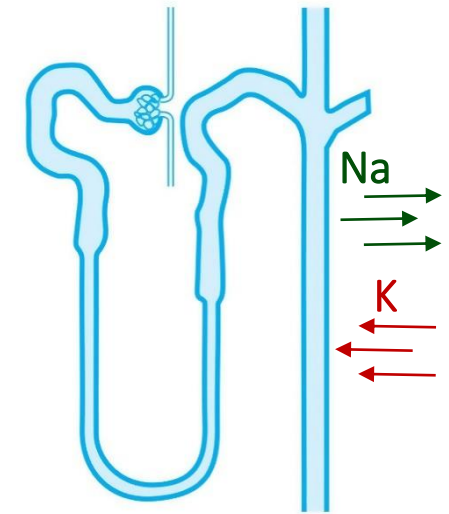
Eplerenone

# Low Renin Hypertension

- Primary aldosteronism
- Liddle syndrome
- SAME
- Licorice consumption

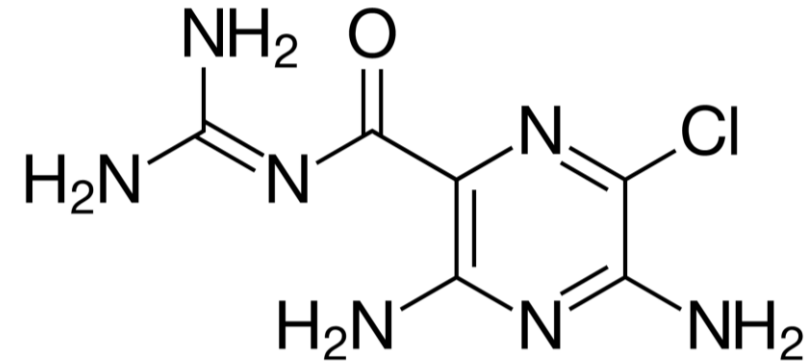
# Liddle Syndrome

- Genetic disorder of **increased activity of ENaC**
  - Epithelial sodium channel
  - Activity increased by aldosterone
- Presents in juveniles
- Similar clinical syndrome to hyperaldosteronism
  - Hypertension
  - Hypokalemia
  - Metabolic alkalosis



# Liddle Syndrome

- Young patient with hypertension, hypokalemia
- **Aldosterone levels low**
- **Treatment: amiloride**
  - Potassium-sparing diuretic
  - Inhibits ENaC activity



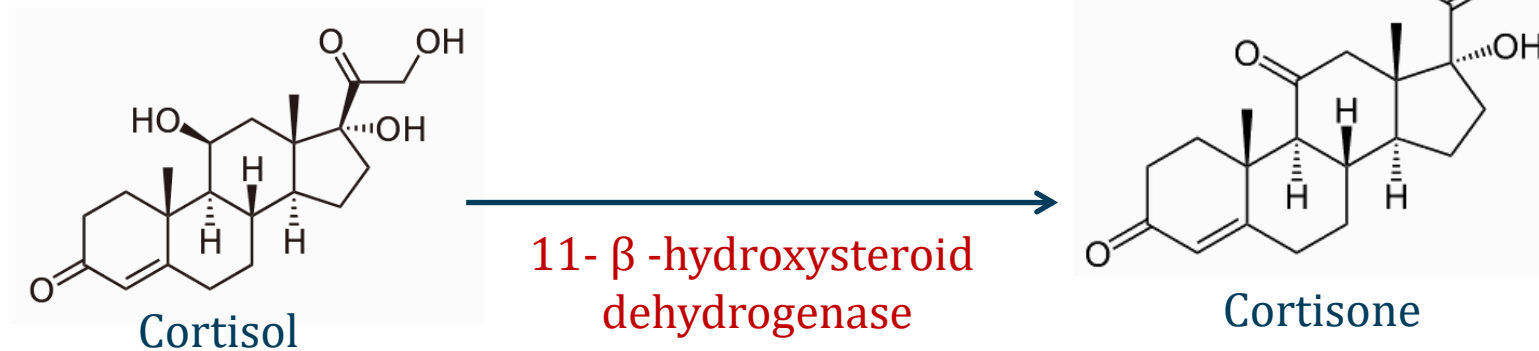
**Amiloride**



# SAME

## Syndrome of Apparent Mineralocorticoid Excess

- Renal aldosterone receptors bind cortisol
- Cortisol → cortisone by renal cells
- Enzyme: **11- $\beta$ -hydroxysteroid dehydrogenase**
- SAME: deficiency 11- $\beta$ -hydroxysteroid dehydrogenase
- Cortisol produces **aldosterone effects**



# SAME

## Syndrome of Apparent Mineralocorticoid Excess

- Presents in children/adolescents
- Similar clinical syndrome to hyperaldosteronism
  - Hypertension
  - Hypokalemia
  - Metabolic alkalosis
- **Aldosterone levels low**
- Treatment:
  - Potassium-sparing diuretics (amiloride, spironolactone)
  - Dexamethasone

# Licorice

- Contains **glycyrrhetic acid** (a steroid)
  - Weak mineralocorticoid effect
  - Inhibits renal 11-beta-hydroxysteroid dehydrogenase
- Large amounts may cause disease
- Hypertension, hypokalemia, metabolic alkalosis
- Plasma aldosterone level low



[Pikaluk/Flickr](#)

# Bartter and Gitelman Syndromes

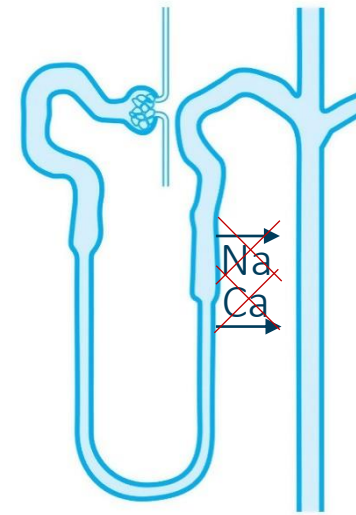
- Congenital disorders
- Occur in children
- Impaired sodium resorption in nephron
- Polyuria
- Hypokalemia (muscle cramps)
- Metabolic alkalosis
- Do not cause hypertension



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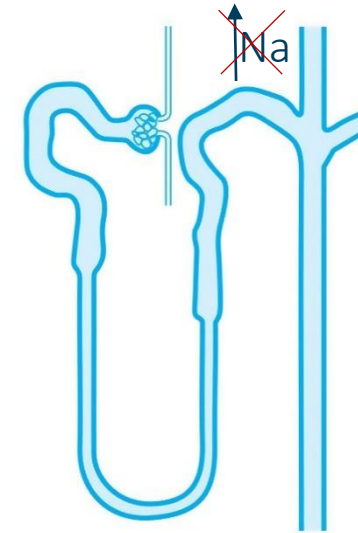
# Bartter Syndrome

- Defective sodium resorption thick ascending limb
- Similar to administration of **loop diuretic**
- Presents in childhood
- Polyuria, polydipsia or nocturia
- Contraction alkalosis
- Hypokalemia
- **High urinary calcium**
  - TAL cannot absorb Ca



# Gitelman Syndrome

- Defective sodium resorption distal tubule
- Similar to administration of **thiazide diuretic**
- Presents in childhood
- Polyuria, polydipsia or nocturia
- Contraction alkalosis
- Hypokalemia
- **Low urinary calcium**
  - Distal tubule cannot secrete Ca



# Urinary Chloride

- Rarely used test in metabolic alkalosis
- Low ( $< 20$  mEq/L) with **gastric acid loss (HCl)**
  - Vomiting
  - Nasogastric suction
- Variable findings with other causes
- High immediately after diuretic administration



# NaCl Fluid Administration

- Contains sodium, chloride and water
- Resolves many forms of metabolic alkalosis
  - **“Chloride responsive”**
  - Diuretics
  - Vomiting
- Exceptions:
  - Hyperaldosteronism
  - Bartter, Gitelman
  - Heart failure, cirrhosis
- Key step in evaluation: **determination of volume status**





# Metabolic Acidosis

Jason Ryan, MD, MPH



# Acid-Base Disorders

1. Respiratory alkalosis
2. Respiratory acidosis
3. Metabolic alkalosis
4. Metabolic acidosis

# Metabolic Acidosis

- Most complex set of acid-base disorders
- Reduced pH (acidosis)
- Reduced  $\text{HCO}_3^-$  (metabolic acidosis)
- Causes categorized by **anion gap**

**pH < 7.37**  
**↓  $\text{HCO}_3^-$**

$$\text{Decreased pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$

↓ = primary abnormality

↓ = respiratory compensation

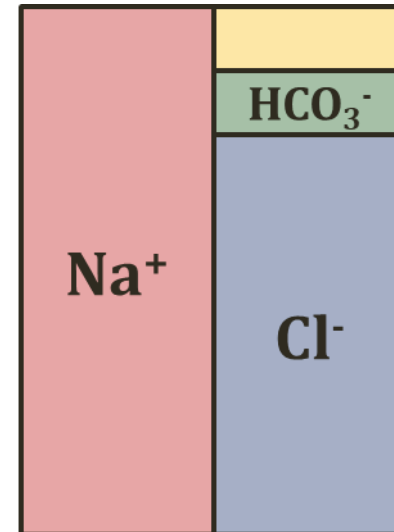
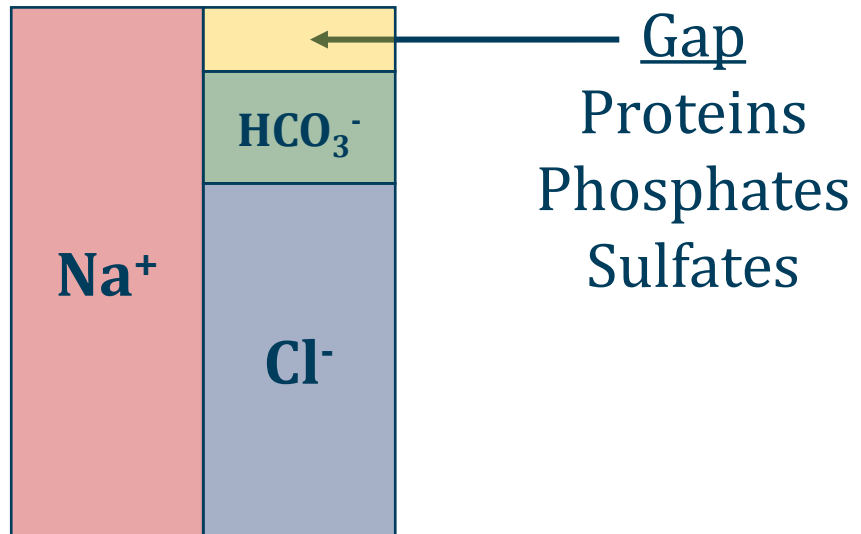
# The Anion Gap

- Anion Gap =  $\text{Na} - (\text{Cl}^- + \text{HCO}_3^-)$
- Normal: **8 to 12**
- Metabolic acidosis subtypes:
  - Normal anion gap
  - Increased anion gap

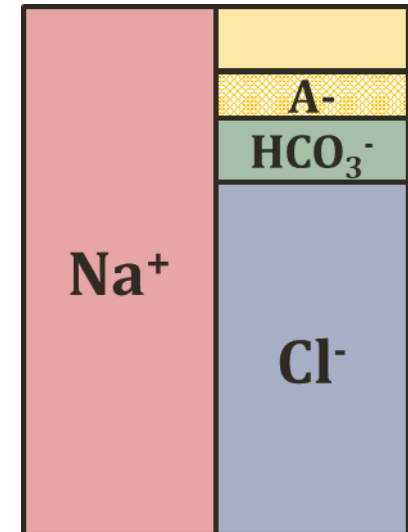
Measurement	Value
Sodium ( $\text{Na}^+$ )	140 mEq/L
Chloride ( $\text{Cl}^-$ )	103 mEq/L
Bicarbonate ( $\text{HCO}_3^-$ )	17 mEq/L

$$\text{Anion Gap} = 140 - (103 + 17) = 20$$

# The Anion Gap



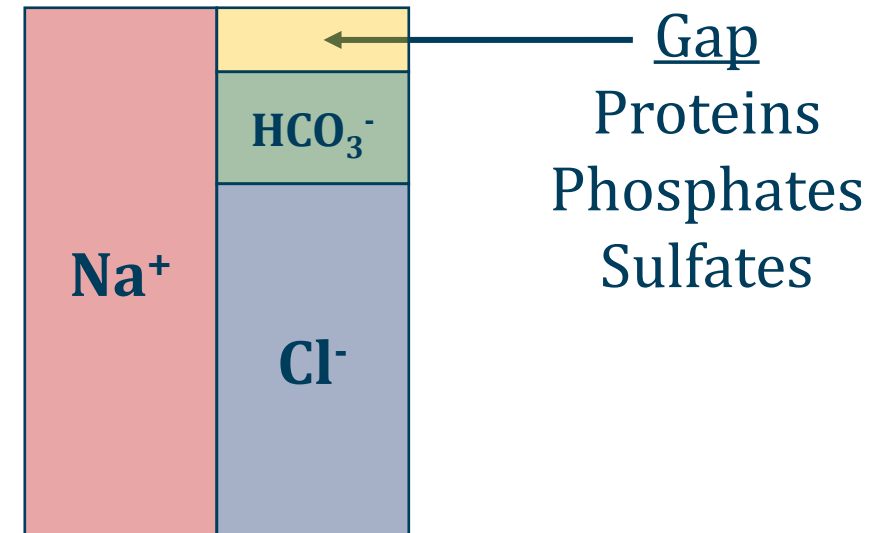
Non-AG acidosis



High AG

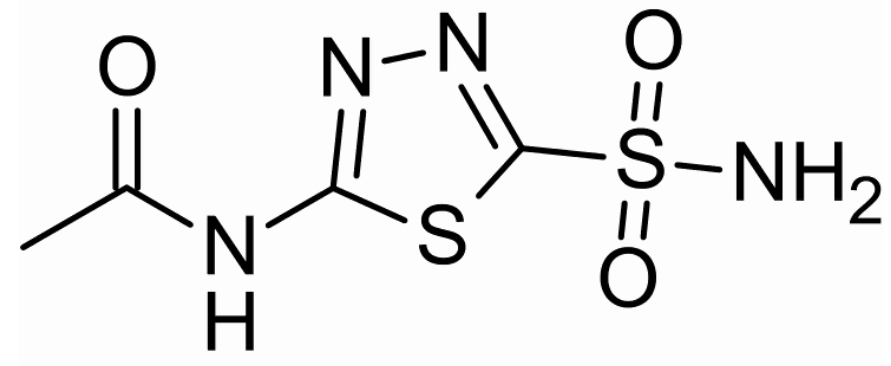
# Non-Anion Gap Metabolic Acidosis

- **Diarrhea**
  - Loss of  $\text{HCO}_3^-$  in stool
  - Occurs with any fluid loss from bowel (fistula)
- **NaCl (saline) infusion**
  - Influx of chloride ions ( $\text{Cl}^-$ )
  - Shift of bicarbonate ions ( $\text{HCO}_3^-$ ) into cells
  - Does not occur with lactated ringers (contains  $\text{HCO}_3^-$ )



# Non-Anion Gap Metabolic Acidosis

- Acetazolamide
  - Blocks formation and resorption  $\text{HCO}_3^-$
- Loss of aldosterone effects
  - Addison's disease
  - Potassium-sparing diuretics
- Renal tubular acidosis



Acetazolamide

# Non-Anion Gap Metabolic Acidosis

- Diagnosis by history, exam, labs
- Treat underlying cause



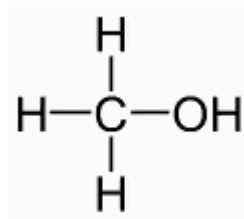
# Anion Gap Metabolic Acidosis

- **M**ethanol
- **U**remia
- **D**iabetic ketoacidosis
- **P**ropylene glycol
- **I**ron tablets or INH
- **L**actic acidosis
- **E**thylene glycol
- **S**alicylates

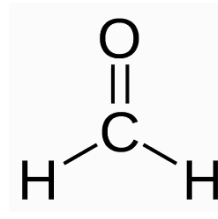
**MUD PILES**

# Methanol

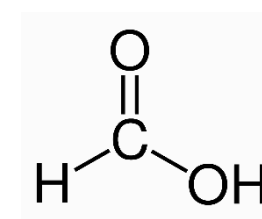
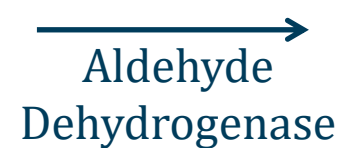
- Antifreeze, industrial cleaners, windshield wiper fluid
- Metabolized to **formic acid**
- Central nervous system poison
- Visual loss, coma



Methanol



Formaldehyde



**Formic Acid**

# Methanol

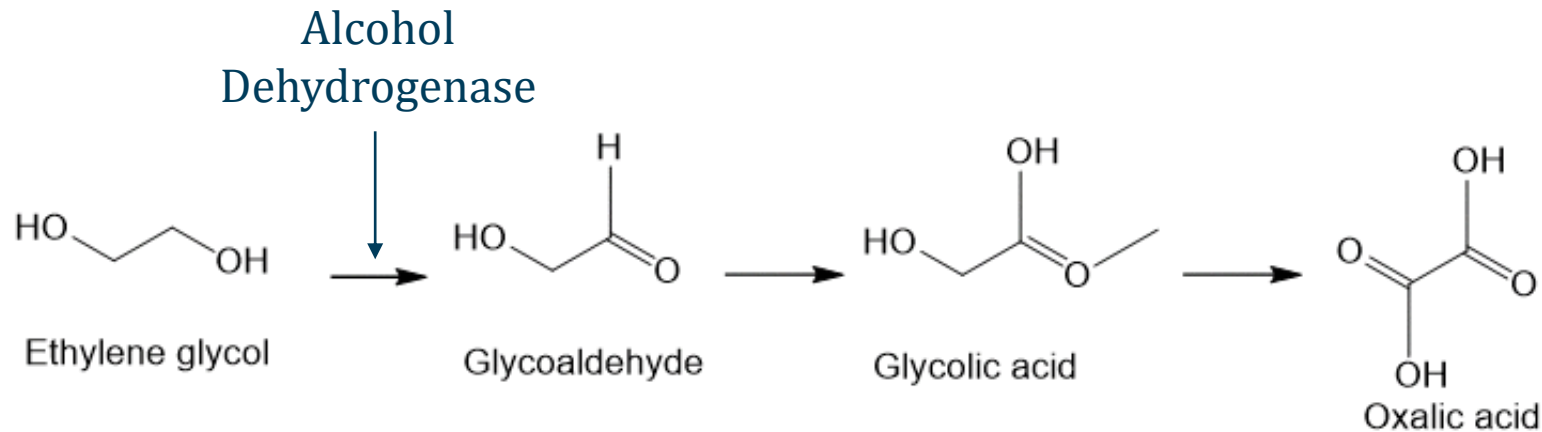
- Classic scenario:
  - Suspected ingestion (accidental, suicide, alcoholic)
  - Confusion (may appear inebriated)
  - **Visual symptoms**
  - High AG metabolic acidosis
- Diagnosis: serum methanol level
- Treatment:
  - Inhibit alcohol dehydrogenase
  - Fomepizole (Antizol)
  - Ethanol



Petr Novák, Wikipedia

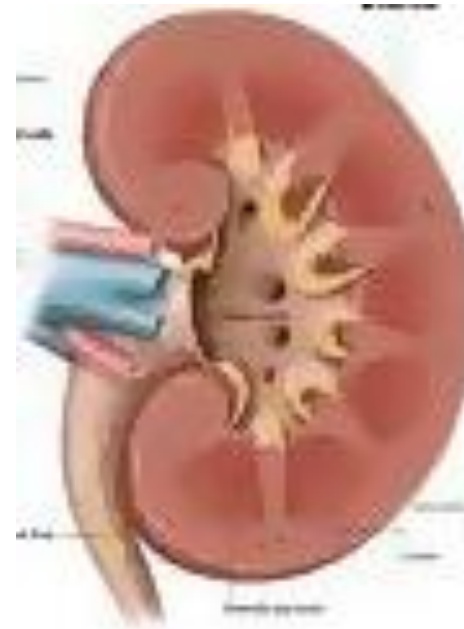
# Ethylene Glycol

- Antifreeze, industrial cleaners, windshield wiper fluid
- Metabolized to glycolate and oxalate
- **Kidney toxins**
- Glycolate: toxic to renal tubules
- Oxalate: precipitates calcium oxalate crystals



# Ethylene Glycol

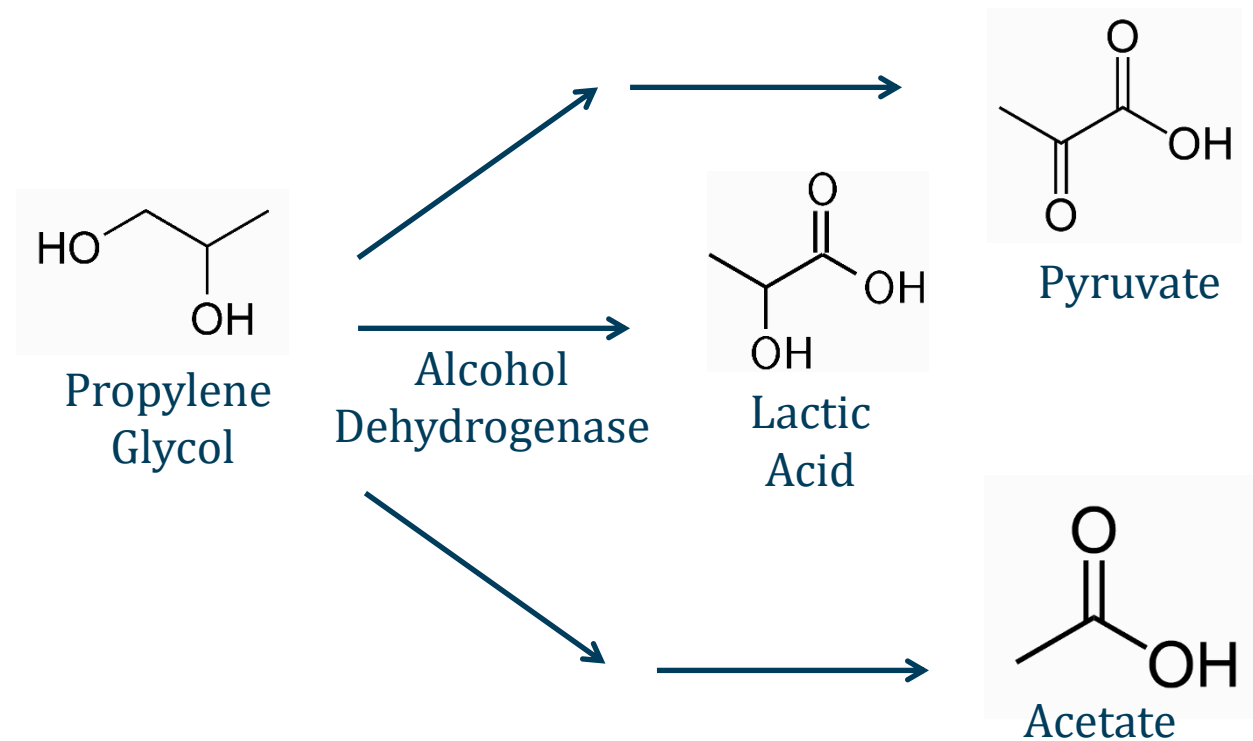
- Classic scenario:
  - Suspected ingestion (accidental, suicide, alcoholic)
  - Flank pain, oliguria, anorexia (acute renal failure)
  - High AG metabolic acidosis
- Diagnosis: serum ethylene glycol
- Treatment:
  - Inhibit alcohol dehydrogenase
  - Fomepizole (Antizol)
  - Ethanol
  - Dialysis



Public Domain

# Propylene Glycol

- Antifreeze (lowers freezing point of water)
- Solvent for **IV benzodiazepines**
- Metabolized to pyruvic acid, acetic acid, lactic acid



# Propylene Glycol

- Main clinical feature of overdose is **CNS depression**
- High AG metabolic acidosis from lactate & other acids
- Many other adverse effects:
  - Hemolysis
  - Seizure, coma, and multisystem organ failure
- No visual symptoms or nephrotoxicity
- Treatment: dialysis +/- fomepizole
  - Little data for fomepizole



# Dialysis in Poisoning

- Methanol
- Ethylene glycol
- Propylene glycol

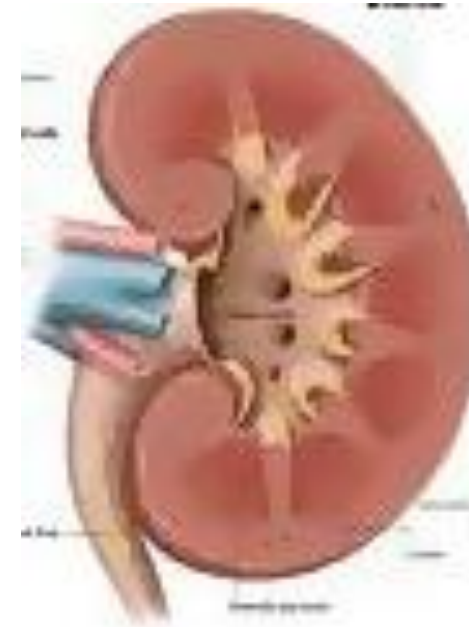


# Osmolar Gap

- Serum osmolarity mostly determined by sodium, glucose and urea
- Calculated osmolarity =  $(2 \times [\text{Na}^+]) + [\text{glucose}]/18 + [\text{urea}]/2.8$
- Calculated osmolarity should be close to measured osmolarity
- Osmolar Gap = measured osmolarity – calculated osmolarity
  - Normal  $\leq 10$
- Causes of elevated osmolar gap:
  - Mannitol
  - **Methanol**
  - **Ethylene glycol**

# Uremia

- Advanced kidney disease
  - Early kidney disease can have non-AG acidosis
  - Reduction in  $H^+$  excretion (loss of tubule function)
- Kidneys cannot excrete **organic acids**
- Retention of phosphates, sulfates, urate, others
- Increased anion-gap acidosis
- Treatment: dialysis

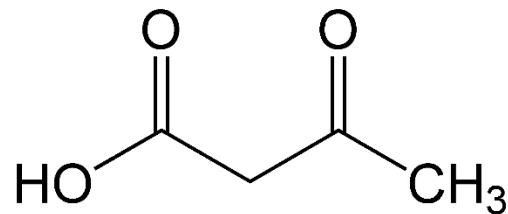


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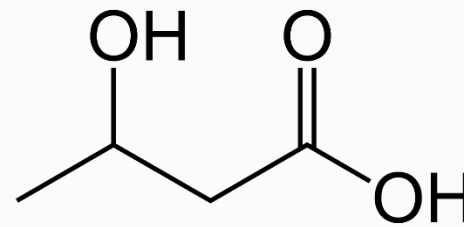
# Diabetic Ketoacidosis

## DKA

- Usually occurs in **type I diabetics**
- Insulin requirements rise → cannot be met
  - Often triggered by infection
- Fatty acid metabolism → **ketone bodies**
  - $\beta$ -hydroxybutyrate
  - Acetoacetate



Acetoacetate



$\beta$ -hydroxybutyrate

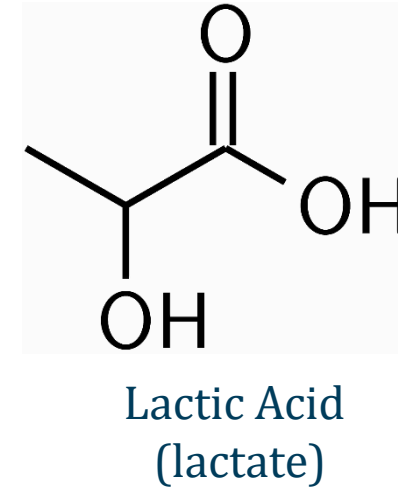
# Diabetic Ketoacidosis

## DKA

- Polyuria, polydipsia ( $\uparrow$ glucose  $\rightarrow$  diuresis)
- Abdominal pain, nausea, vomiting
- **Kussmaul respirations**
  - Deep, rapid breathing
  - From acidosis
- High AG metabolic acidosis from ketones

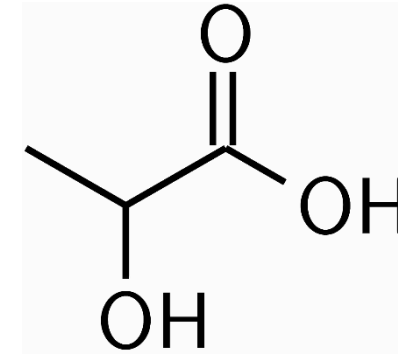
# Lactic Acidosis

- Low tissue oxygen delivery
- Pyruvate converted to lactate
- High levels ( $> 4.0$  mmol/L)  $\rightarrow$  lactic acidosis
- Anion gap metabolic acidosis
- Clinical scenarios:
  - Shock ( $\downarrow$  tissue perfusion)
  - Ischemic bowel
  - Metformin therapy (especially with renal failure)
  - Seizures



# Lactic Acidosis

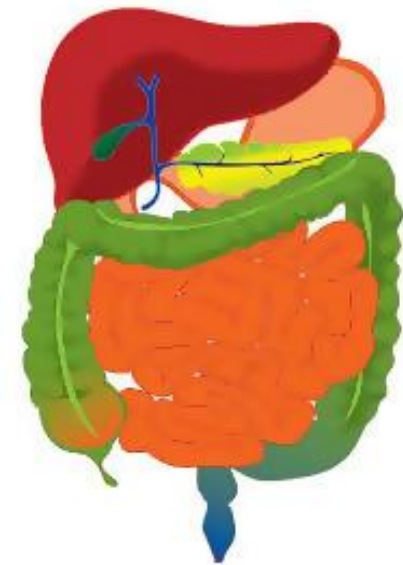
- Usually no specific therapy
- **Treat underlying condition**
  - Shock: fluids, vasopressors, inotropes
  - Ischemic bowel: surgery
  - Metformin: stop drug
- Post-ictal acidosis: no treatment required



Lactic Acid  
(lactate)

# Iron

- Acute iron poisoning
- Initial gastrointestinal phase (0 to 6 hours)
  - Iron toxic to GI mucosal cells
  - **Abdominal pain**
- Weeks later: bowel obstruction (scarring)



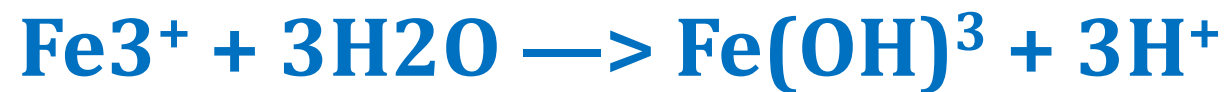
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# Iron



Tomihahndorf

- Later (24 hours)
  - Cardiovascular toxicity: **shock**
  - Coagulopathy: iron inhibits thrombin formation/action
  - Hepatic dysfunction: worsening coagulopathy
  - Acute lung injury
- Anion-gap metabolic acidosis
  - From **ferric irons ( $\text{Fe}^{3+}$ )**
  - Also lactate (hypoperfusion)



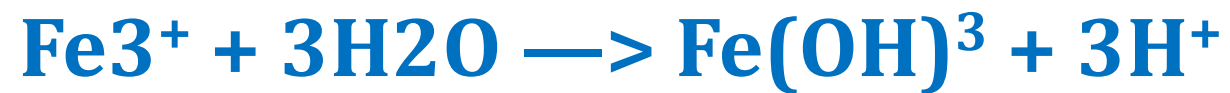


# Iron

- Diagnosis: serum iron level
- Treatment:
  - GI decontamination
  - Defuroxamine
    - Iron chelating agent
    - Binds ferric iron ( $\text{Fe}^{3+}$ )
    - Forms water-soluble ferrioxamine  $\rightarrow$  excreted by kidneys



Tomihahndorf



# Isoniazid

INH

- Tuberculosis antibiotic
- Overdose causes **seizures**
  - Often severe, refractory (status epilepticus)
- Seizures cause **lactic acidosis**
- Anion gap metabolic acidosis
- Treatment: anti-seizure drugs

*M. tuberculosis*

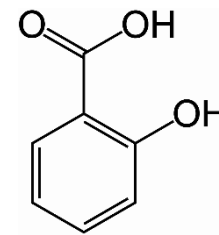


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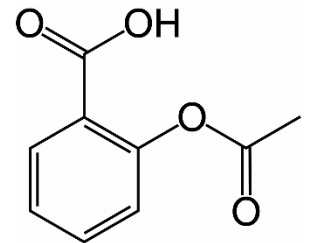
# Aspirin Overdose



- Two acid-base disorders
- Shortly after ingestion: **respiratory alkalosis**
  - Salicylates stimulate medulla
  - Hyperventilation
- Hours after ingestion: **AG metabolic acidosis**
  - Salicylates uncouple oxidative phosphorylation
  - Accumulation of pyruvate, lactate, ketoacids
- Diagnosis: serum salicylate level
- Treatment: urinary alkalinization



Salicylic Acid  
(salicylate)



Acetylsalicylic Acid  
(aspirin)

# Anion-Gap Metabolic Acidosis

Cause	Mechanism	Diagnosis	Treatment
Methanol	Ingestion	Methanol level	Fomepizole/dialysis
Uremia	Renal failure	BUN/Cr	Dialysis
DKA	Insulin deficiency	Serum ketones	Insulin, fluids
Propylene Glycol	Ingestion	Propylene glycol level	Dialysis
Iron	Ingestion	Serum iron level	Deferoxamine
Lactic Acidosis	Hypoperfusion	Serum lactate	Restore perfusion
Ethylene Glycol	Ingestion	Ethylene glycol level	Fomepizole/dialysis
Salicylates	Aspirin overdose	Aspirin level	Urine alkalization

# Anion Gap Metabolic Acidosis

## MUD PILES

- **M**ethanol
- **U**remia
- **D**iabetic ketoacidosis
- **P**ropylene glycol
- **I**ron tablets or INH
- **L**actic acidosis
- **E**thylene glycol
- **S**alicylates

## GOLD MARK

- **G**lycols (ethylene or propylene)
- **O**xoproline
- **L**-lactate
- **D**-lactate
- **M**ethanol
- **A**spirin
- **R**enal failure
- **K**etones

# Hyperventilation

- **Respiratory compensation** to metabolic acidosis
- Lowers  $p\text{CO}_2$
- Increases pH

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * p\text{CO}_2}$$

# Winter's Formula

- Acidosis: compensatory **respiratory alkalosis**
  - $\downarrow$  pCO<sub>2</sub>
  - Hyperventilation
- Winter's Formula gives expected pCO<sub>2</sub>
- If actual CO<sub>2</sub>  $\neq$  expected  $\rightarrow$  mixed disorder
- Check Winter's formula for all metabolic acidoses

$$\text{pCO}_2 = 1.5 (\text{HCO}_3^-) + 8 + /- 2$$

# Respiratory Acid-Base Disorders

Jason Ryan, MD, MPH





# Acid-Base Disorders

1. Respiratory alkalosis
2. Respiratory acidosis
3. Metabolic alkalosis
4. Metabolic acidosis

# Respiratory Alkalosis

$$\text{pH} > 7.42$$
$$\downarrow \text{pCO}_2$$

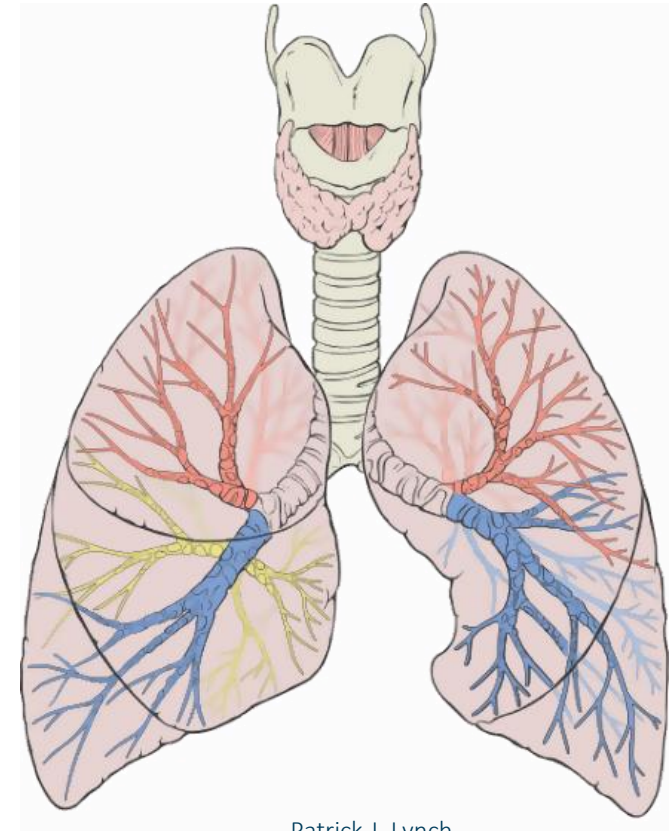
$$\text{Increased pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$

↓ = compensation

↓ = primary abnormality

# Respiratory Alkalosis

- Caused by **hyperventilation**
  - Pain
  - Anxiety
  - Mechanical ventilation
  - High-altitude exposure
  - Aspirin overdose
- Normal respiratory rate 12 to 20 breaths/min



Patrick J. Lynch

# High Altitude

- **Lower atmospheric pressure**
  - Sea level: 760 mmHg
  - Machu Picchu = 560 mmHg
- **Lower  $pO_2$** 
  - $P_{AO_2}$  sea level = 100 mmHg
  - $P_{AO_2}$  Machu Picchu = 75 mmHg



Wikipedia/Public Domain

# High Altitude

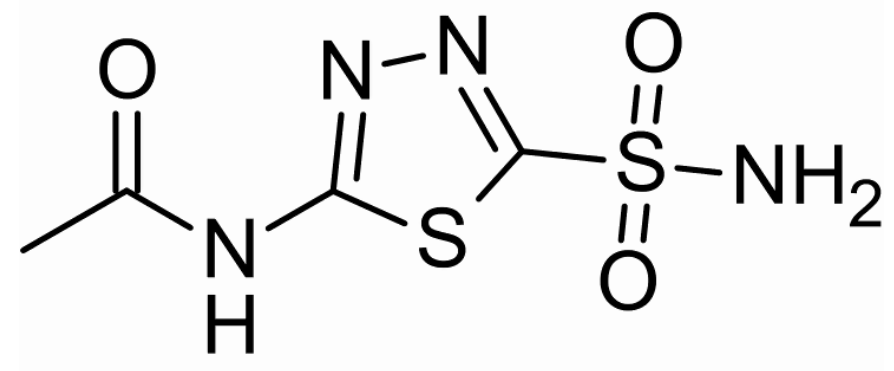
- Hypoxia → **hyperventilation**
- ↓ pCO<sub>2</sub> → respiratory alkalosis (pH rises)

Parameter	Change
P <sub>02</sub> (alveoli, artery)	Decrease
Respiratory rate	Increase
Carbon dioxide	Decrease
pH	Increase

# High Altitude

## Acclimatization

- Renal response
  - After 24-48 hours: kidneys **excrete  $\text{HCO}_3^-$**
  - pH will fall back toward normal
  - **Acetazolamide** increases  $\text{HCO}_3^-$  excretion
- Red cell response to hypoxemia
  - Synthesis of **2,3-Bisphosphoglycerate**
  - Unloading of oxygen from hemoglobin



Acetazolamide

# Aspirin Overdose

- Two acid-base disorders
- Shortly after ingestion: **hyperventilation**
  - Salicylates stimulate medulla
  - **Respiratory alkalosis**
- Hours after ingestion: **AG metabolic acidosis**
  - Salicylates ↓ lipolysis, uncouple oxidative phosphorylation
  - Inhibits citric acid cycle
  - Accumulation of pyruvate, lactate, ketoacids



# Aspirin Overdose

- pH
  - Variable due to mixed disorder
  - Acidotic, alkalotic, normal
- $p\text{CO}_2$ 
  - Low due to hyperventilation
- $\text{HCO}_3^-$ 
  - Low due to acidosis
- Winter's formula predicts  $\text{CO}_2$  higher than actual
- $\text{CO}_2$  lower than expected for compensation





# Aspirin Overdose

- Sample case: pH 7.36,  $p\text{CO}_2$  20,  $\text{HCO}_3^-$  11
- Metabolic acidosis
- Winter's formula
  - $p\text{CO}_2 = 1.5 (\text{HCO}_3^-) + 8 \pm 2$
  - $p\text{CO}_2 = 1.5 (11) + 8 \pm 2 = 25$
- $p\text{CO}_2 < \text{expected}$
- Concomitant respiratory alkalosis



# Aspirin Overdose

- Diagnosis: serum salicylate level
- Treatment: **urinary alkalization**
  - Sodium bicarbonate
  - Goal urine pH > 7.5
  - Alkaline urine favors ionization of salicylates
  - Negatively charged molecules remain in urine



# Respiratory Acidosis

$$\text{pH} < 7.37$$
$$\uparrow \text{pCO}_2$$

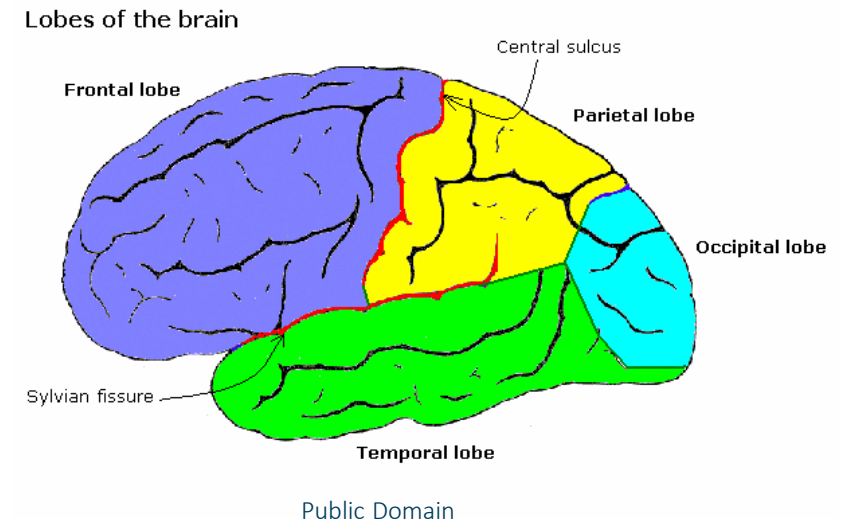
$$\text{Decreased pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$

↑ = compensation

↑ = primary abnormality

# Respiratory Acidosis

- Caused by **hypoventilation**
- Decreased CNS respiratory drive
  - Opiates, barbiturates
- Respiratory muscle diseases
  - Guillain-Barre
  - Polio
  - Multiple sclerosis
  - Amyotrophic lateral sclerosis



# Respiratory Acidosis

- Impaired gas exchange
  - Pneumonia
  - Pulmonary edema
  - Acute respiratory distress syndrome
  - COPD
- Airway obstruction
  - Aspiration
  - Obstructive sleep apnea

## ARDS

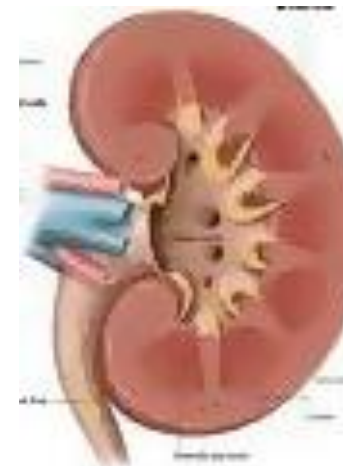


# Respiratory Acidosis

## Renal Compensation

- Excess H<sup>+</sup> filtered/secreted
- **Bicarbonate** reabsorbed
- Bicarbonate generated
- **Metabolic alkalosis**
- Classic example: COPD
  - Chronic increase pCO<sub>2</sub>
  - Chronic respiratory acidosis
  - Compensation: **increased HCO<sub>3</sub><sup>-</sup>**

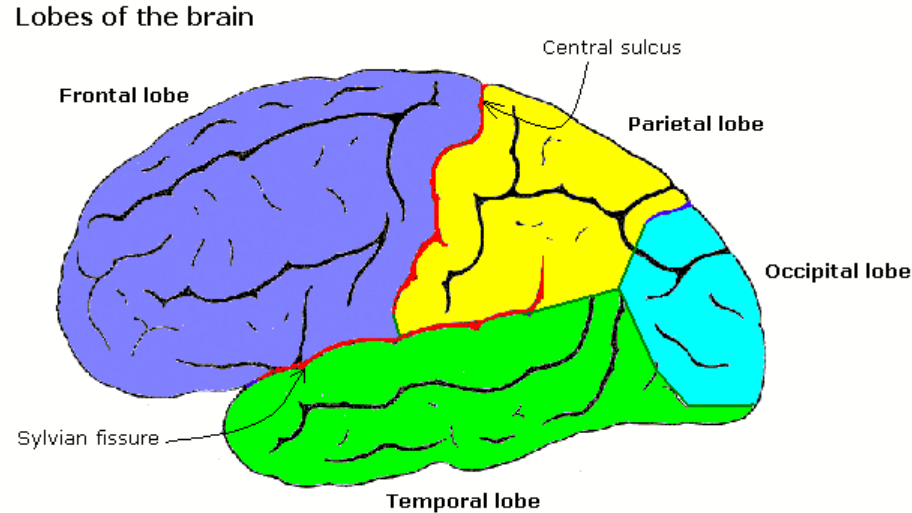
$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 * \text{pCO}_2}$$



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# Acute hypercapnia

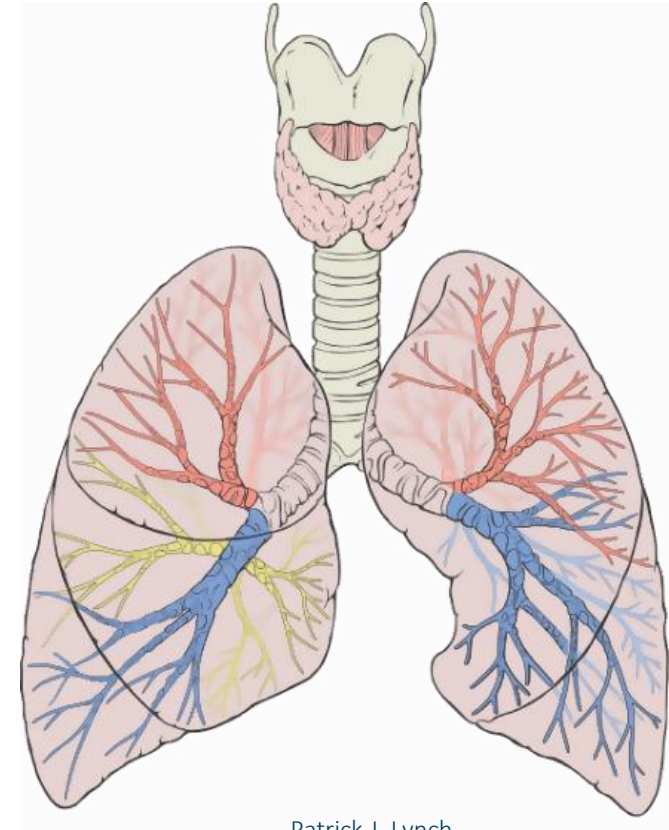
- Hypercapnia can affect **CNS system**
- **$\uparrow \text{CO}_2 \rightarrow \uparrow \text{cerebral blood flow} \rightarrow \uparrow \text{ICP}$**
- Mild to moderate: anxiety, headaches
- Severe: delirium, eventually coma



$\text{CO}_2$

# Carbon Dioxide Level

- Determined by **alveolar ventilation**
- $\uparrow$  PaCO<sub>2</sub>: hypoventilation
  - Drugs
  - Neuromuscular disease
  - Lung disease
- $\downarrow$  PaCO<sub>2</sub>: hyperventilation
  - Anxiety
  - High altitude
  - Aspirin



Patrick J. Lynch



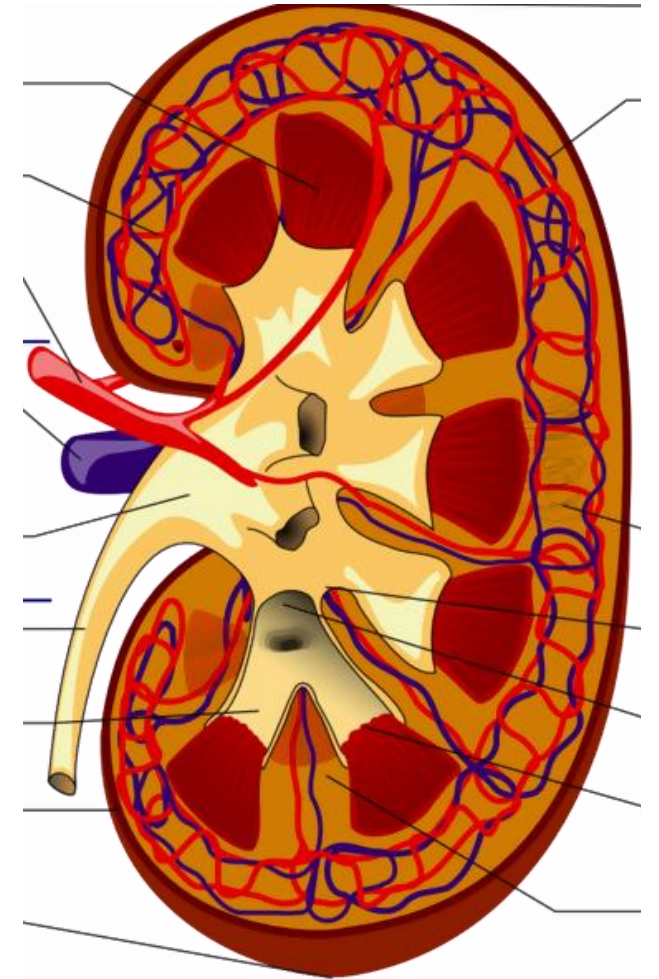
# Acute Renal Failure

Jason Ryan, MD, MPH



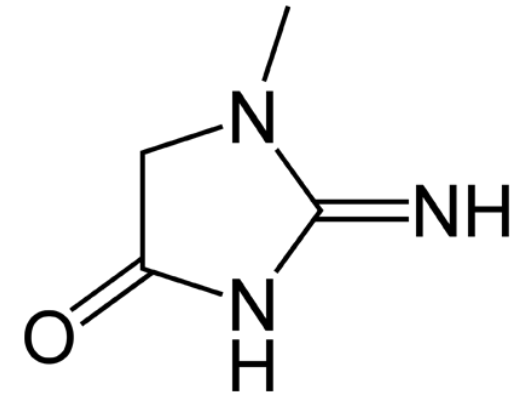
# Terms

- **Acute renal failure(ARF)/Acute kidney injury (AKI)**
  - Abrupt decrease in renal clearance over days
  - Sometimes associated with symptoms
  - Many causes
  - Most cases resolve
- **Chronic kidney disease/Chronic renal failure**
  - Slow, steady deterioration of renal function (years)
  - Usually due to diabetes, hypertension
  - Symptoms only in most severe stages
  - Usually irreversible

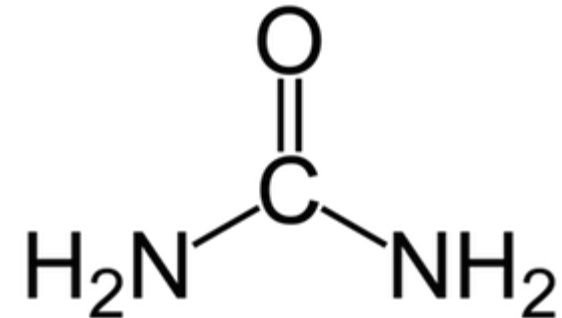


# Terms

- Azotemia
  - Elevated BUN and Cr
  - Indicates insufficient filtering of blood by kidneys
- Uremia
  - Azotemia + “uremic” symptoms
- Types of AKI
  - Oliguric
  - Non-oliguric
  - Anuric



**Creatinine**



**Urea**

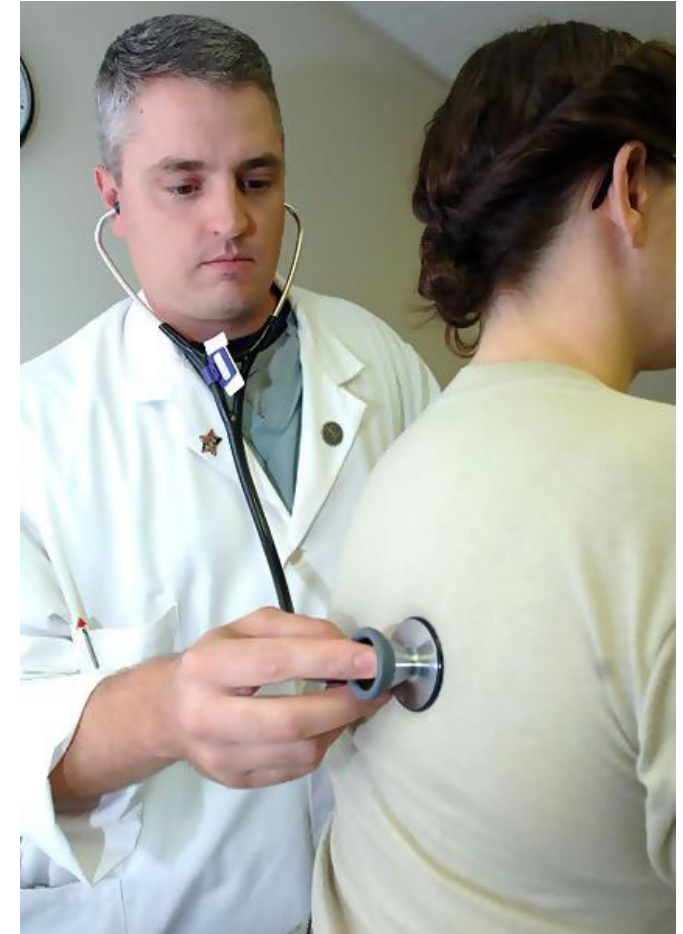
# KDIGO Clinical Definitions

## Kidney Disease: Improving Global Outcomes

- **Acute kidney injury**
  - Increase in Cr of  $\geq 0.3$  over 48 hours
  - Increase  $\geq 1.5$ x the baseline within past 7 days
  - Oliguria
- **Oliguria**
  - Urine output  $< 0.5$  ml/kg/hr

# Uremic Symptoms

- Anorexia
- Nausea, vomiting
- Platelet dysfunction (bleeding)
- Pericarditis
- Asterixis
- Encephalopathy
- **Most patients with AKI asymptomatic**
- **No history or exam finding is very specific**



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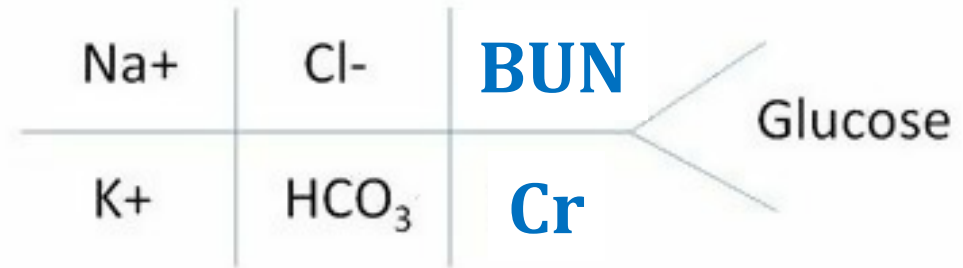
# Key Labs

- **Creatinine**

- Freely filtered
- Small amount of secretion

- **Blood urea nitrogen**

- Freely filtered
- Reabsorbed when kidney reabsorbs water
- In acute renal failure both rise (less filtered)
- If kidneys under-perfused: BUN rises more (less filtered, more reabsorbed)



# Acute Renal Failure

- **Pre-renal failure:** 60 to 70% cases
  - Insufficient blood flow to kidneys
  - Volume depletion, shock, heart failure
- **Post-renal failure:** 5 to 10% cases
  - Obstruction of urine outflow
  - Need bilateral obstruction
  - Kidney stones, BPH, tumors, congenital anomalies
- **Intrinsic renal failure:** 25 to 40% cases
  - Acute tubular necrosis
  - Glomerulonephritis

# Pre-Renal Failure

## Serum BUN/Cr

- Decreased blood flow to kidneys
- Less BUN/Cr filtered
- Rising BUN/Cr in blood
- More resorption H<sub>2</sub>O
- BUN resorbed with H<sub>2</sub>O
- BUN rises >> Cr rises
- Result
  - ↑ Cr
  - ↑↑ BUN
  - ↑ BUN/Cr ratio

Na <sup>+</sup>	Cl <sup>-</sup>	<b>BUN</b>	Glucose
K <sup>+</sup>	HCO <sub>3</sub> <sup>-</sup>	<b>Cr</b>	



# Renal Measurements

- **Urinary sodium ( $U_{Na}$ )**
  - Varies based on intake of sodium and water
  - Low when retaining salt/water
  - $< 20$  mEq/L is low
- **Fractional excretion of Na ( $Fe_{Na}$ )**
  - Amount of filtered Na that is excreted
  - Low when kidney retaining salt/water
  - $< 1\%$  is low
- **Urinary osmolarity ( $U_{osm}$ )**
  - Measure of concentrating ability of kidney
  - High when kidney retaining water
  - $> 500$  mOsm/kg is high

$$Fe_{Na} = \frac{P_{Cr} * U_{Na}}{P_{Na} * U_{Cr}}$$

**\*\*Na measurements not useful  
in patients on diuretics**

# Pre-Renal Failure

## Urinary Findings

- Lots of H<sub>2</sub>O and Na resorbed
- Concentrated urine
  - ↑U<sub>osm</sub>
- Low sodium excretion
  - ↓U<sub>Na</sub>
  - ↓Fe<sub>Na</sub>
- Bland sediment
  - No protein
  - No cells
  - Rarely hyaline casts



Wikipedia/Public Domain

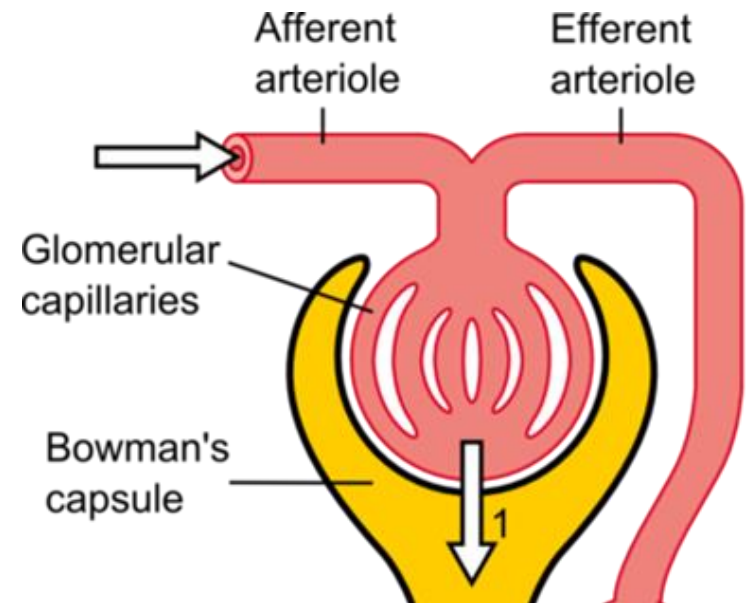
# Pre-Renal Failure

	Normal	Pre-Renal Failure
BUN (mg/dl)	20	60
Cr (mg/dl)	1.0	2.0
BUN:Cr	20:1	> 20:1
UNa (mEq/L)	variable	< 20
FeNa (%)	variable	< 1
Uosm (mOsm/kg)	variable	> 500

# Pre-Renal Failure

## Selected Causes

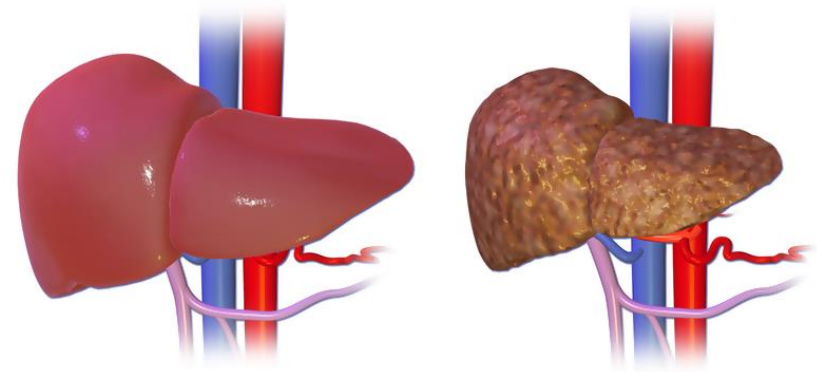
- Hypotension
  - Sepsis, bleeding, anaphylaxis
- Hypovolemia
  - Diuretics, burns
- Renal artery stenosis
- NSAIDs
  - Afferent arteriolar vasoconstriction
- ACE inhibitors
  - Efferent arteriolar vasodilation



Madhero88/Wikipedia

# Cardiorenal and Hepatorenal Syndromes

- Occurs with heart failure or cirrhosis
- Renal failure with some pre-renal features
  - Often low urinary sodium
- Normal/bland urinalysis
  - No protein
  - No/few red or white cells
- **Does not respond to fluid administration**



Normal Liver

Liver Cirrhosis

Wikipedia/Public Domain

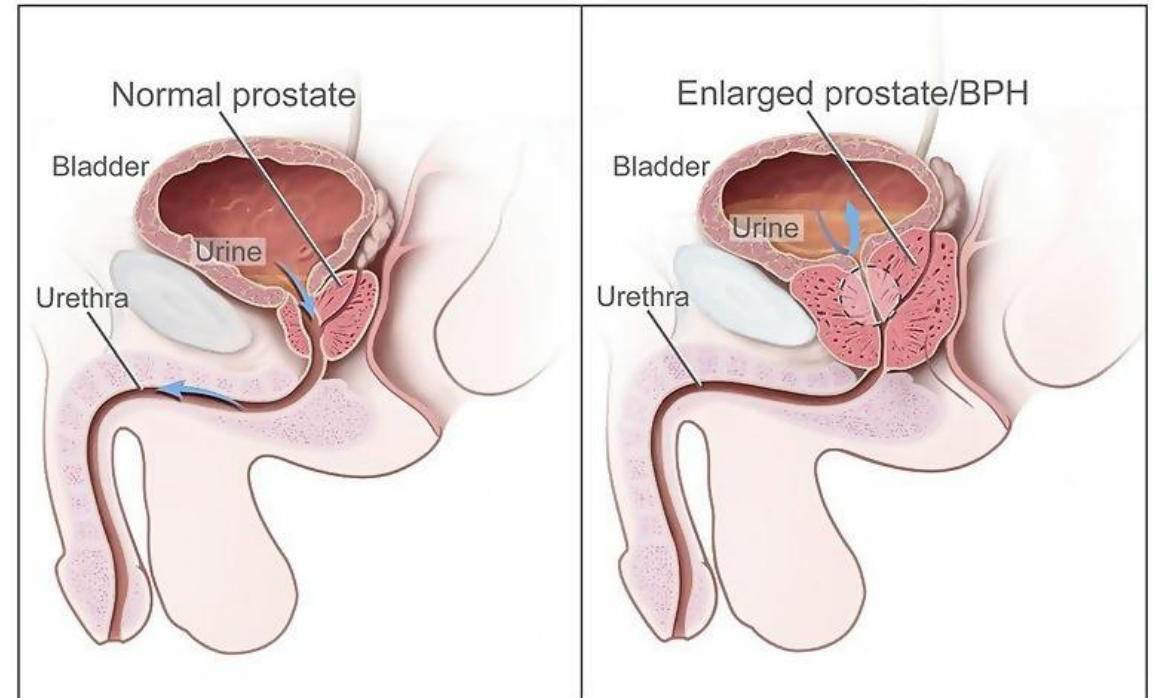
# Post-Renal Failure

- Obstruction to outflow
- Urine backs up
- High pressure in tubules
- Kidney cannot filter blood
- Kidney's resorptive mechanisms damaged/destroyed

# Post-Renal Failure

## Selected Causes

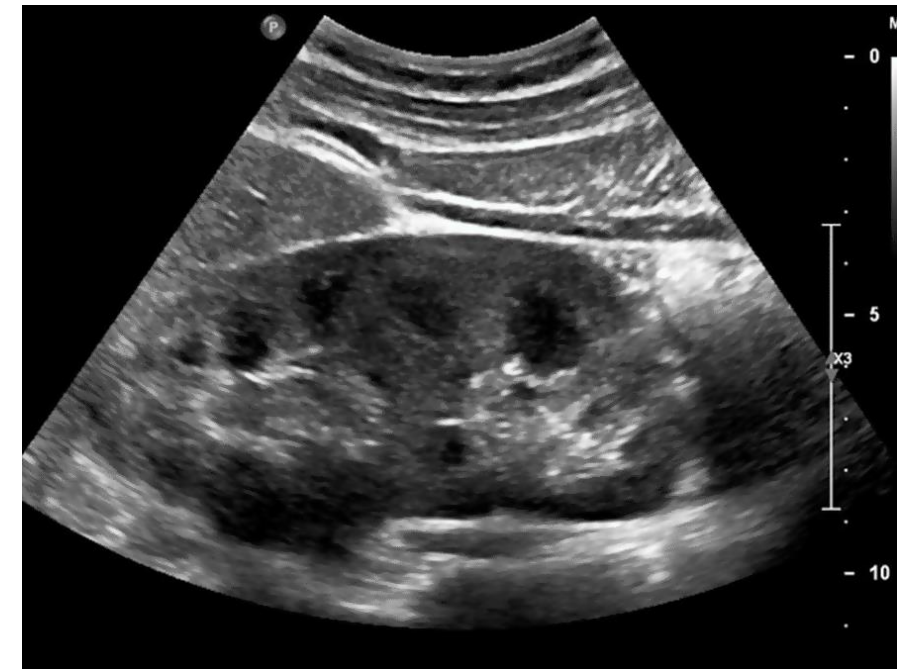
- Prostate enlargement
- Prostate cancer
- Ureteral stones
- Neurogenic bladder
- Medications



National Cancer Institute

# Post-Renal Failure

- Key clinical feature: anuria
- **Test of choice: ultrasound**
  - Bladder ultrasound (bedside)
  - Renal ultrasound
  - Bilateral hydronephrosis
  - Hydroureter
- **Urinary catheterization**
  - Diagnostic and therapeutic
  - Relieves bladder outlet obstruction





# Post-Renal Failure

- Lots of variation in lab values based on tubules
- Early post renal → tubular function intact
- Late → high pressure disrupts tubular resorption
- Urine chemistries variable

Na+	Cl-	<b>BUN</b>	Glucose
K+	HCO <sub>3</sub>	<b>Cr</b>	

# Intrinsic Renal Failure

## Serum BUN/Cr

- Kidney cannot filter blood normally
- Less BUN/Cr filtered
- Rising BUN/Cr in blood
- No extra rise in BUN from  $\uparrow$  resorption
- Normal ratio BUN:Cr (20:1)

Na+	Cl-	BUN	Glucose
K+	HCO <sub>3</sub>	Cr	

# Intrinsic Renal Failure

## Urinary Findings

- Urine: kidney cannot resorb water/Na
- U<sub>osm</sub> not high (can't concentrate urine)
- U<sub>Na</sub> high (can't resorb Na)
- Fe<sub>Na</sub> high (can't resorb Na)
- Often abnormal sediment
  - Protein
  - Red/white cells
  - Casts



Wikipedia/Public Domain

# Intrinsic Renal Failure

	Normal	Intrinsic Failure	Pre-Renal Failure
BUN (mg/dl)	20	40	60
Cr (mg/dl)	1.0	2.0	2.0
BUN:Cr	20:1	20:1	> 20:1
UNa (mEq/L)	variable	> 40	< 20
FeNa (%)	variable	> 2	< 1
Uosm (mOsm/kg)	variable	< 350	> 500

# Intrinsic Renal Failure

## Selected Causes

- **Acute tubular necrosis (most common)**
  - Often caused by underperfusion → prerenal → ATN
- Toxins
  - Contrast agents
  - NSAIDs
  - Cisplatin
  - Amphotericin
  - Cyclosporine

# Pre, Intrinsic, Post Problems

- Diseases often cross boundaries
  - Pre-renal → ATN
- Diuretics obscure urine findings
- Pre-existing chronic renal disease

# Acute Renal Failure

## Management

- Pre- and Post-Renal Failure: **correct underlying cause**
  - Volume depletion
  - Heart failure
  - Ureteral obstruction
- Monitor for dialysis indications

# Acute Renal Failure

## Management

- **Stop/hold drugs that alter renal function**
  - Diuretics
  - ACEi and ARBs
  - NSAIDs
- Metformin: risk of lactic acidosis in ARF



# Indications for Dialysis

- Acidemia
- **Electrolytes (hyperkalemia)**
- Intoxication (overdose dialyzable substance)
- **Overload of fluid (CHF)**
- Uremic symptoms
- Must be refractory to medical therapy



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# AKI of Unclear Etiology

## Evaluation

- **History and physical exam**
  - Known heart failure/cirrhosis
  - Volume depletion/overload
- Medication review
- Identify baseline Cr

# AKI of Unclear Etiology

## Evaluation

- Bladder or renal ultrasound
- Urinalysis
  - Bland = no casts, few cells
- Urine sodium
- Urine osmolarity
- Fractional Excretion of Na (FeNa)
  - Serum Na and Cr
  - Urine Na and Cr

$$Fe_{Na} = \frac{P_{Cr} * U_{Na}}{P_{Na} * U_{Cr}}$$

# Acute Renal Failure

## Monitoring

- BUN/Cr
- Daily weight
- Ins and outs
- Blood pressure
- Electrolytes

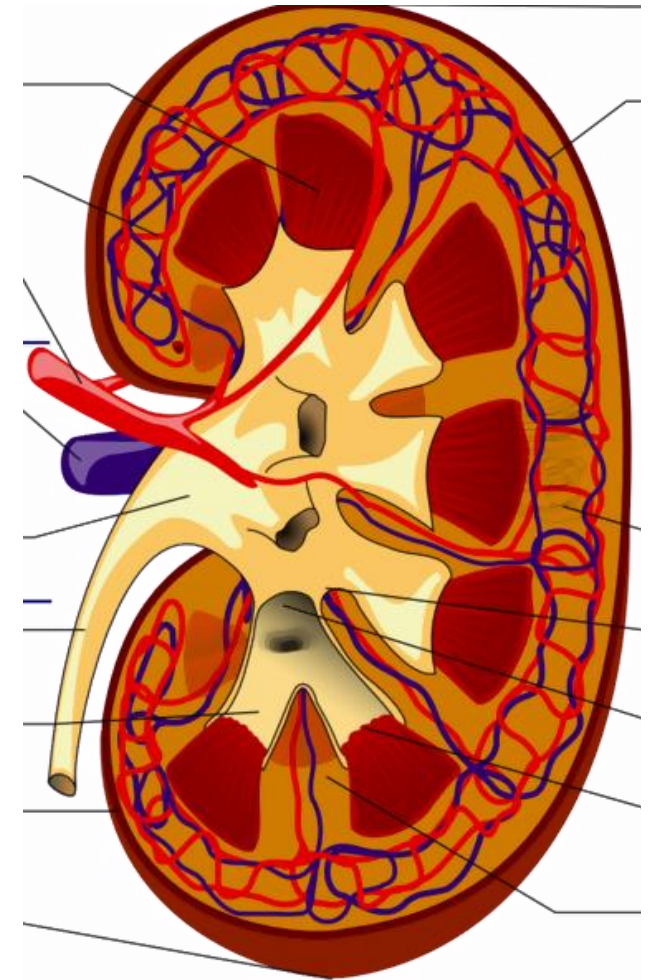
# Chronic Kidney Disease

Jason Ryan, MD, MPH



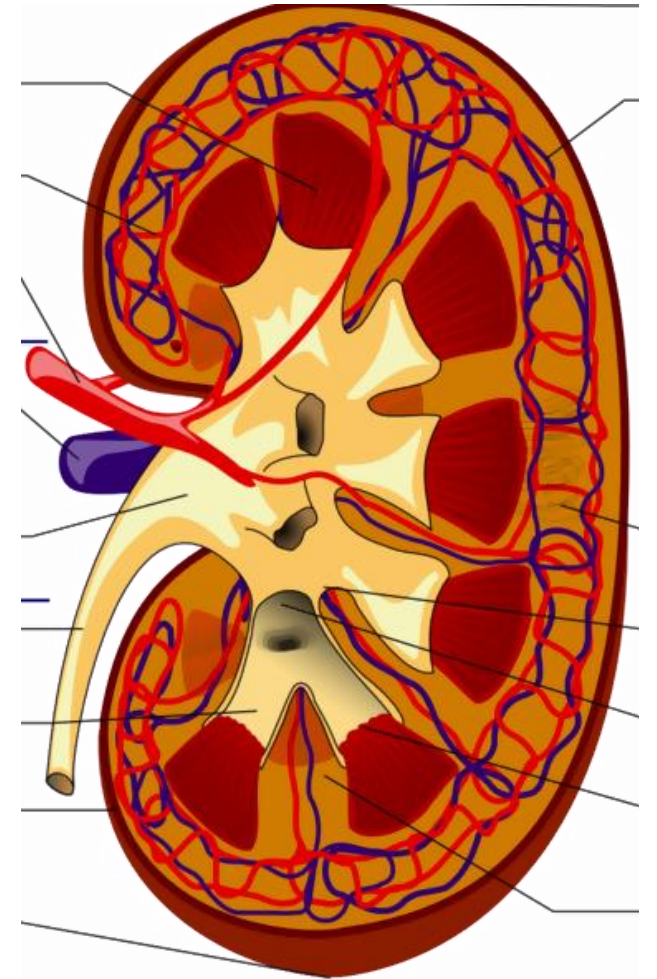
# Chronic Kidney Disease

- Slow, steady fall in creatinine clearance
  - Blood tests show  $\uparrow$  BUN/Cr
- Eventually progresses to dialysis for many patients
- Most common causes diabetes and hypertension
  - Diabetic nephropathy
  - Hypertensive nephrosclerosis
- Rarely other causes:
  - Glomerulonephritis
  - Cystic kidney disease



# Stages of Chronic Kidney Disease

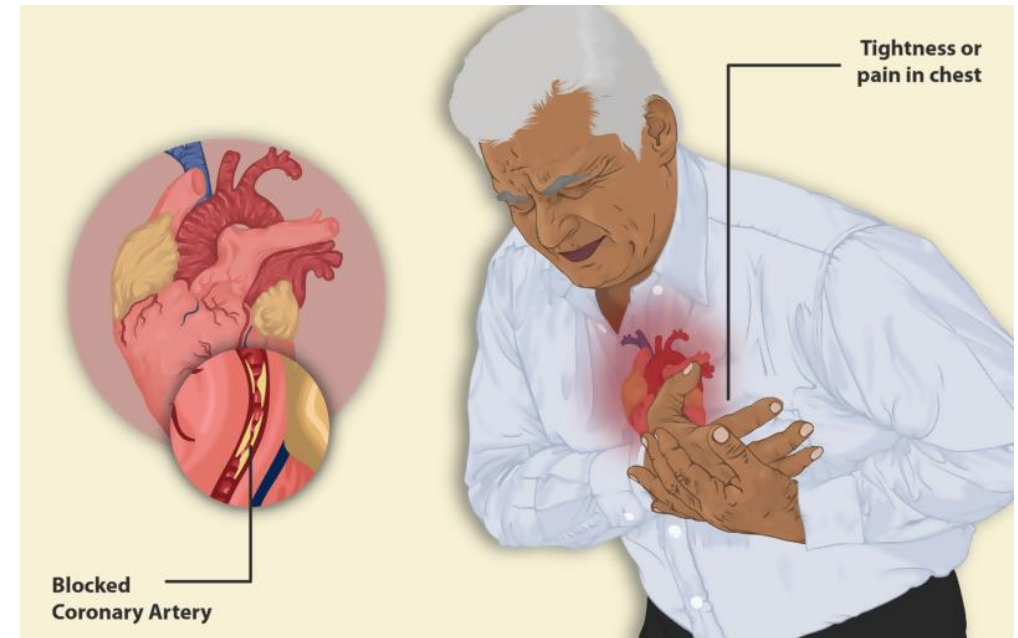
- Stage 1 → GFR > 90 (↑BUN/Cr, proteinuria)
- Stage 2 → GFR 60-89
- Stage 3 → GFR 30-59
- Stage 4 → GFR 15-29 (approaching dialysis)
- Stage 5 → GFR < 15 (usually on dialysis)



# Chronic Kidney Disease

## Risks

- Progression to dialysis
- **Cardiovascular disease**
  - Stroke, MI
  - CKD → accelerated atherosclerosis
  - Most common cause of death in adults
- **Infection**
  - Most common cause of death in children
  - Most common cause of death with transplants



myupchar.com/Public Domain

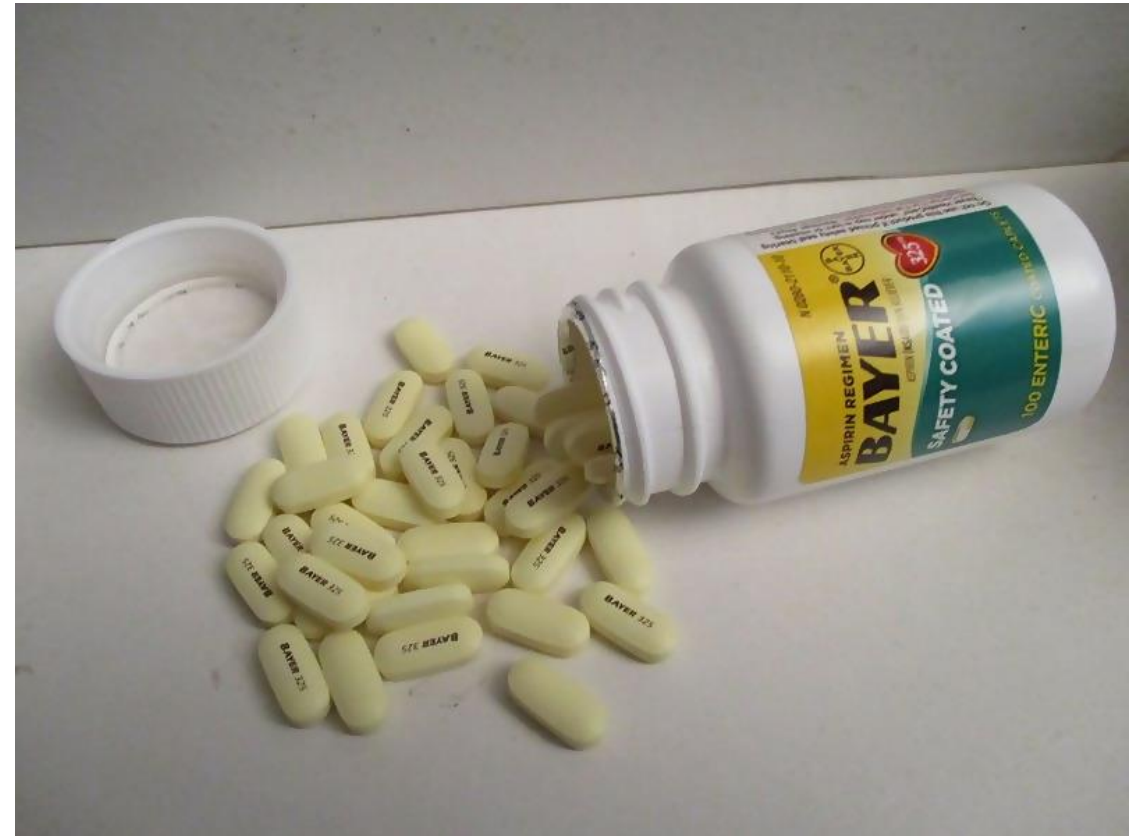


# Renal Replacement Therapy

- GFR < 5 ml/min
- GFR 5 – 15 ml/min with AEIOU
  - Acidemia
  - Electrolytes (hyperkalemia)
  - Intoxication (**overdose** dialyzable substance)
  - Overload of fluid (CHF)
  - Uremic symptoms (pericarditis, encephalopathy)
- Most common indications: **hyperkalemia and volume overload**

# Dialyzable Substances

- Salicylates (aspirin)
- Lithium
- Isopropyl alcohol
- Magnesium laxatives
- Ethylene glycol



Bodhi Peace/Wikipedia

# Dialysis Methods

## Hemodialysis

- Requires vascular access
- Blood pumped from body → filter → back to body
- Done in “sessions” of few hours at a time
- Usually 3 days per week
- Can be done emergently
- Risk of hypotension

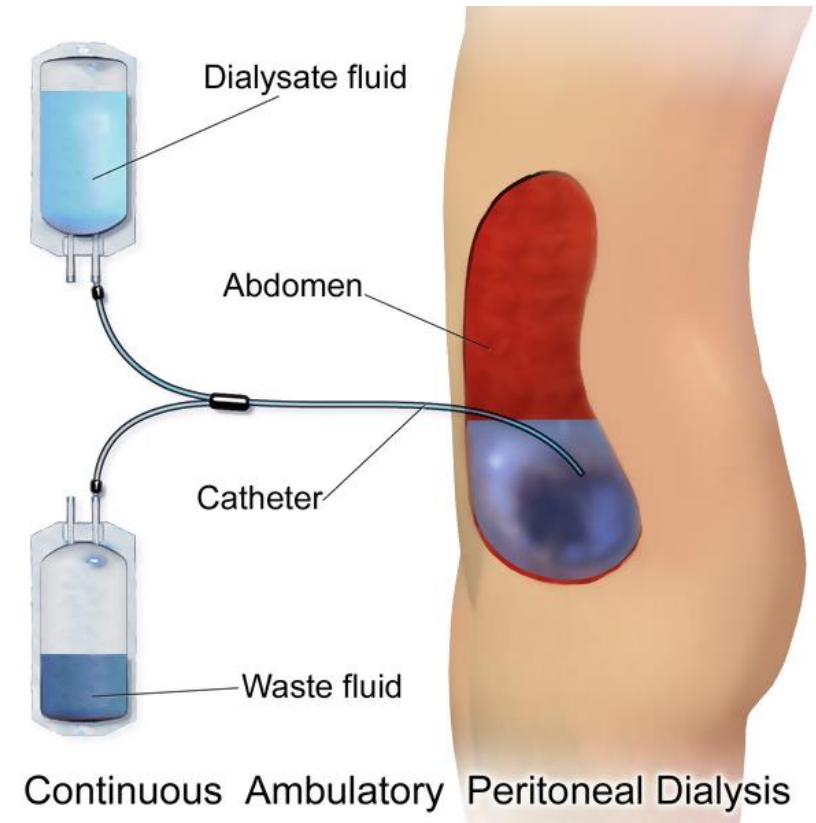


Wikipedia/Public Domain

# Dialysis Methods

## Peritoneal Dialysis

- Fluid cycled through peritoneal cavity
- Peritoneum used as dialysis membrane
- Cycles for 4-6 hours per day
- Usually done at home during sleep
- Major risk: peritonitis



Burce Blaus/Public Domain

# Dialysis Methods

## Hemofiltration

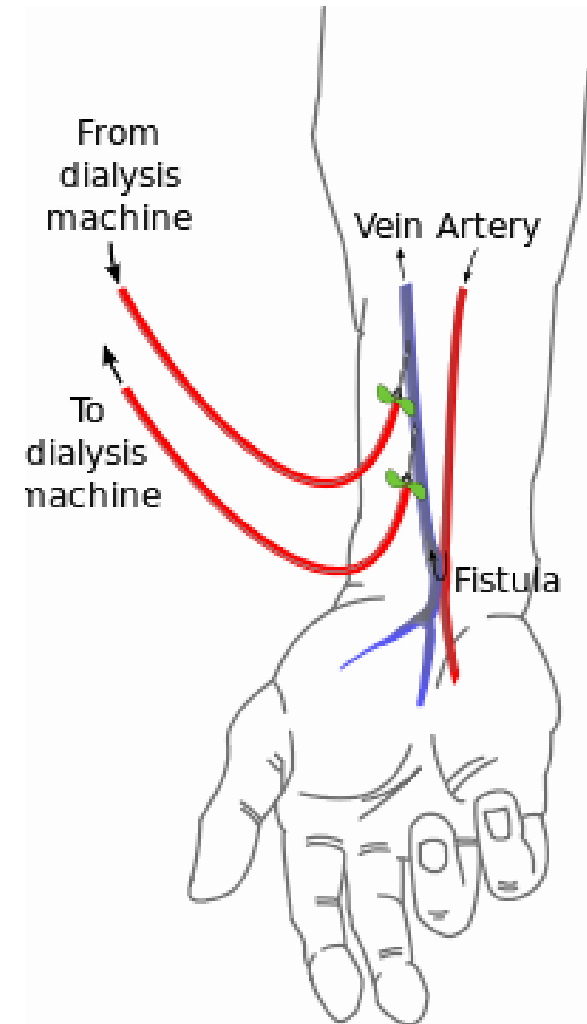
- Constant filtering of blood
- Usually done at bedside for critically-ill patients



Ringer21/Slideshare.net

# Vascular Access

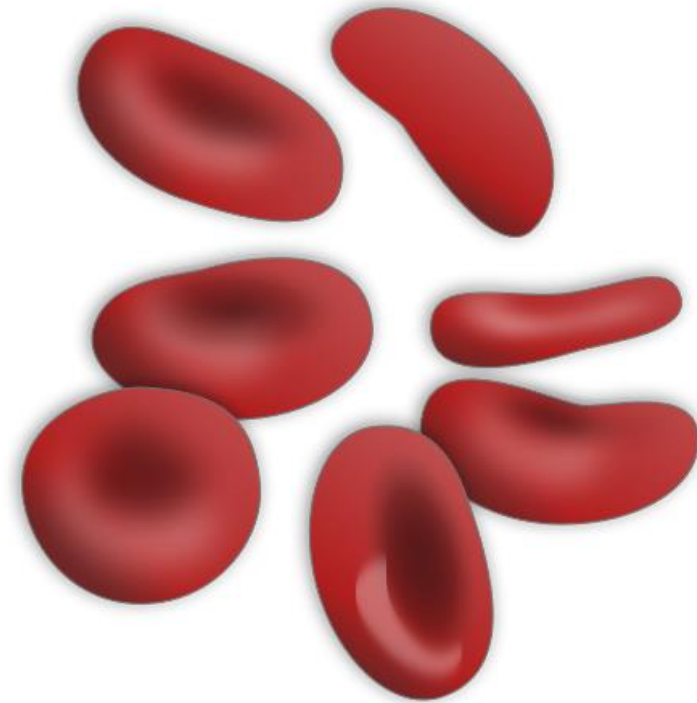
- For acute dialysis, central line can be placed
- Ideal method is **fistula**
  - Connection between artery and vein
  - Placed surgically, usually in arm
  - Lowest rates of thrombosis, infection
- Fistula must “mature” for use
- Ideally placed several months before dialysis



Kbk/Wikipedia

# Complications CKD

- Anemia
  - Loss of EPO
- Bleeding
  - Abnormal platelet function
- Infection
  - Abnormal neutrophil function



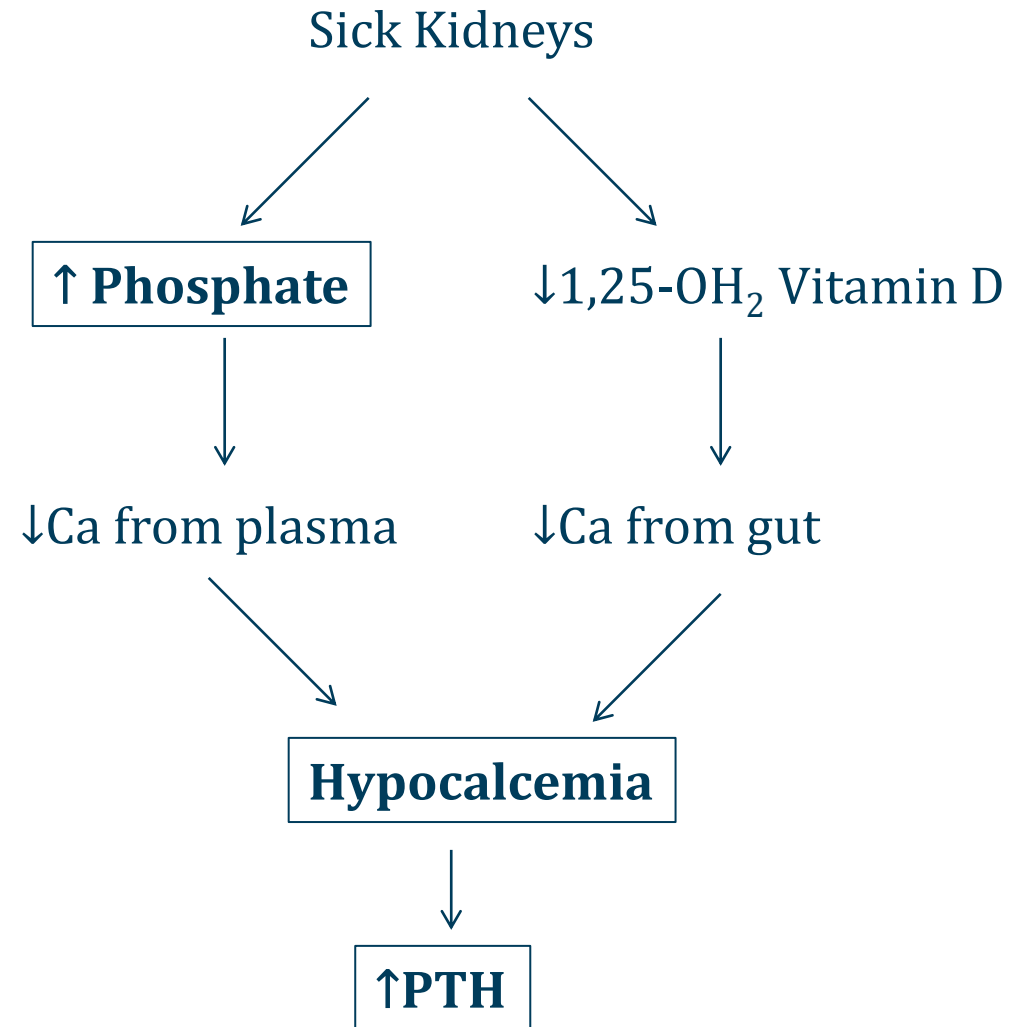
Jessica Polka/Wikipedia

# Complications CKD

- Dyslipidemia
  - Mostly triglycerides
  - Protein loss in urine → stimulation of liver synthesis
  - Impaired clearance of chylomicrons and VLDL
- Sexual dysfunction
  - Erectile dysfunction
  - Anovulation
- Abnormal calcium and phosphate

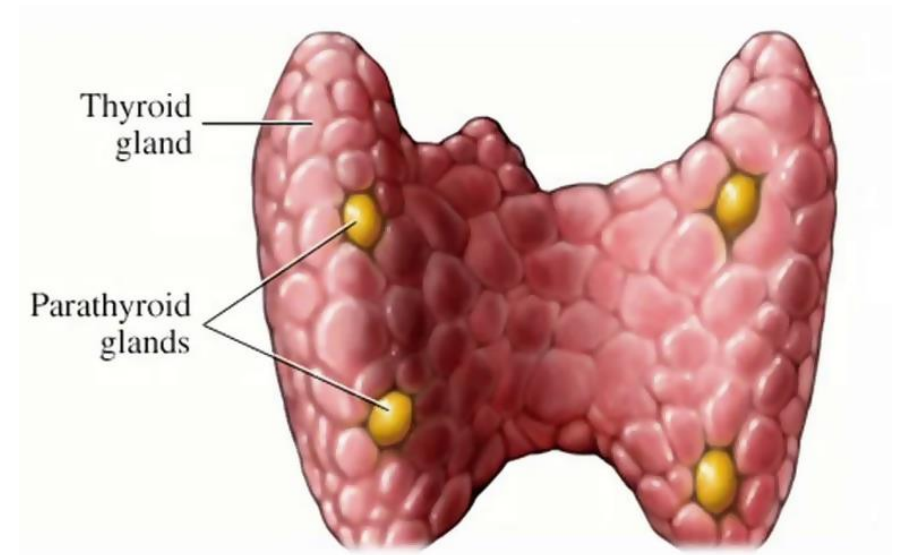


# Calcium-Phosphate in CKD



# Calcium-Phosphate in CKD

- Secondary hyperparathyroidism
  - Parathyroid stimulation in renal failure
- Tertiary hyperparathyroidism
  - Autonomous hormone release from constant stimulation
  - VERY high PTH levels
  - Calcium becomes elevated
  - Often requires parathyroidectomy



Lee Health/Vimieo

# Bone Disease in CKD

- Untreated hyperparathyroidism leads to **renal osteodystrophy**
  - Bone pain (predominant symptom)
  - Fracture (weak bones 2° chronic high PTH levels)
- Osteitis fibrosa cystica
  - Untreated, severely elevated **PTH levels**
  - Bone cysts
  - Brown tumors (osteoclasts w/fibrous tissue)



# Chronic Kidney Disease

## Treatment

- **ACE Inhibitors**
  - Used in early CKD
  - Limit progression
- **Renal diet**
  - Advanced CKD
  - Low protein (limits urea production)
  - Low potassium, phosphate and magnesium
  - Low salt if HTN, CHF or oliguria

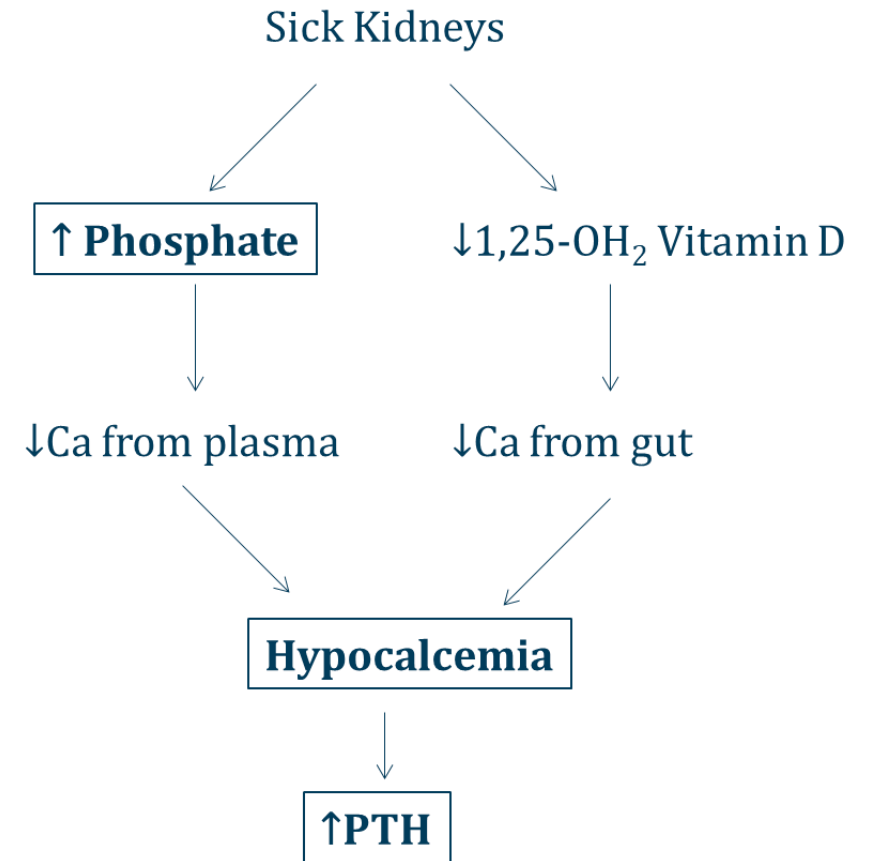


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# Chronic Kidney Disease

## Treatment

- **Vitamin D and calcium supplementation**
- Phosphate binders
  - Bind phosphate in GI tract
  - Calcium carbonate
  - Calcium acetate (Phoslo)
  - Sevelamer (Renagel)
  - Lanthanum



# Drugs and Renal Function

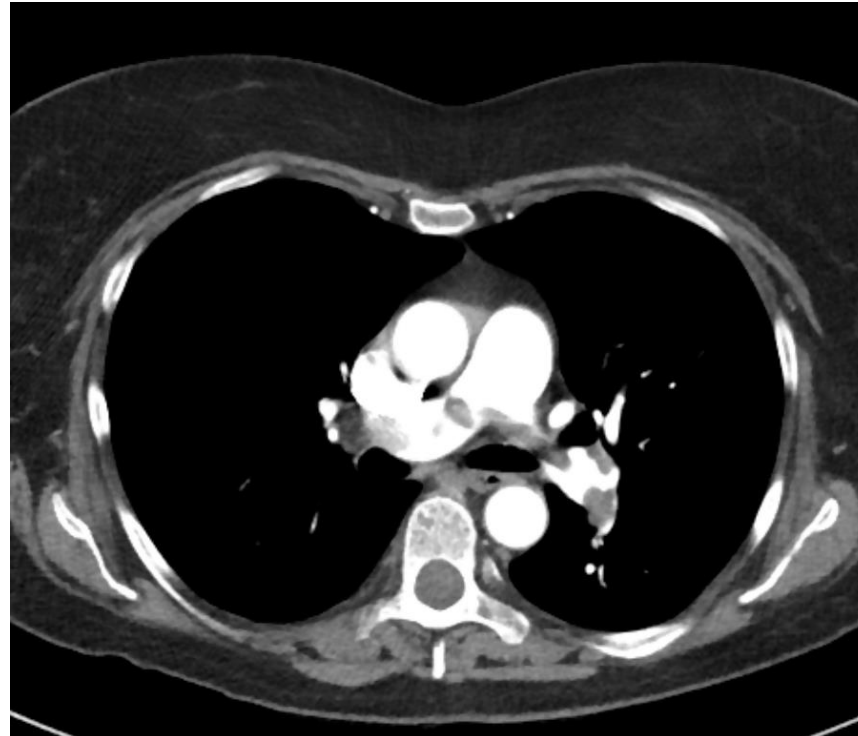
- Many drugs worsen renal function
- Decrease GFR
- Associated with  $\uparrow$  BUN/Cr
- Loop, Thiazide, and K-sparing diuretics
- NSAIDs



Pixabay/Public Domain

# Contrast Nephropathy

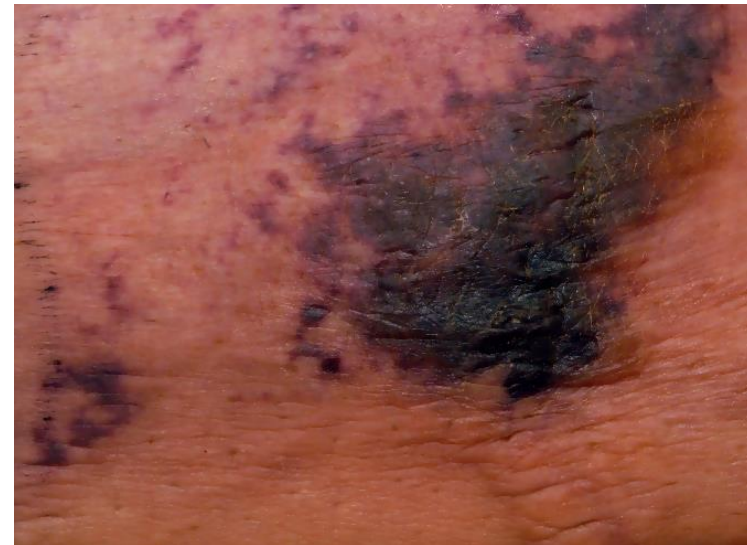
- CT radiocontrast dye may lead to acute kidney injury
- Avoided in patients with CKD



# Calciophylaxis

## Calcific Uremic Arteriopathy

- Seen in chronic **hyperphosphatemia in CKD**
- Excess phosphate taken up by vascular smooth muscle
- Smooth muscle osteogenesis
- Vascular wall calcification
- Increased systolic blood pressure
- Small vessel thrombosis
- Painful nodules, skin necrosis



Niels Olsen/Wikipedia



# Nephrogenic Systemic Fibrosis

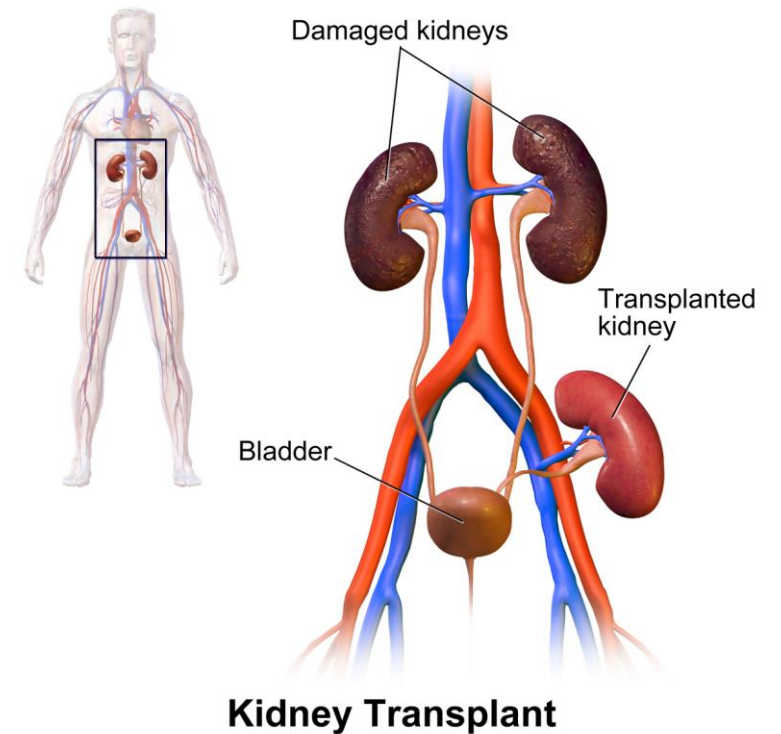
- Diffuse fibrosis of skin
  - Induration, thickening, hardening
- “Brawny” hyperpigmentation
  - Shiny skin
- Gadolinium: MRI contrast agent
- Renal disease + exposure to gadolinium
- **Gadolinium contraindicated in CKD patients**
- No treatment



Public Domain

# Kidney Transplantation

- **Reduces mortality compared with dialysis**
- Improves quality of life
- Usually reserved for younger patients (< 55)
- Requires post-transplant immunosuppression therapy



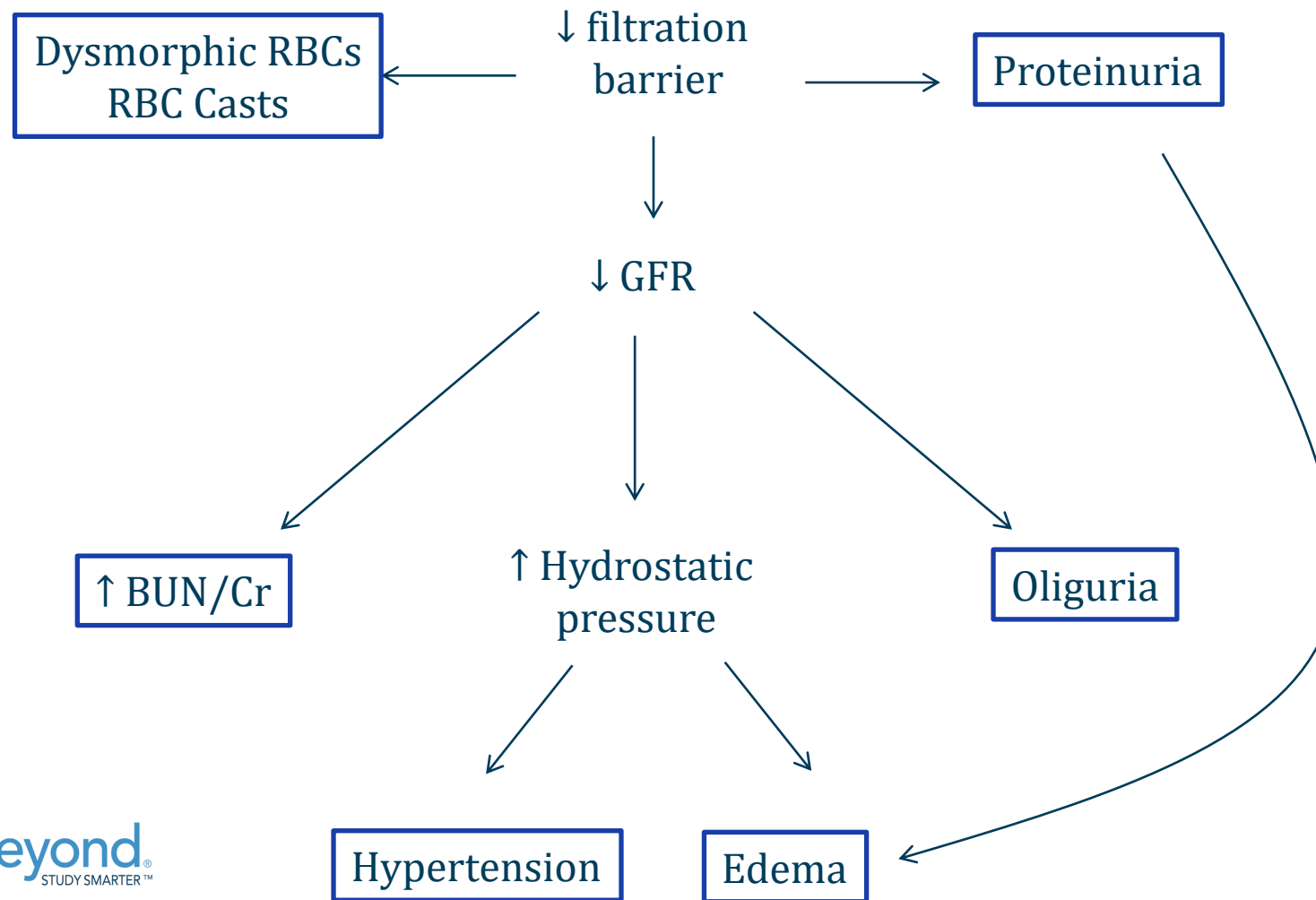
BruceBlaus/Wikipedia

# Nephritic Syndrome

Jason Ryan, MD, MPH

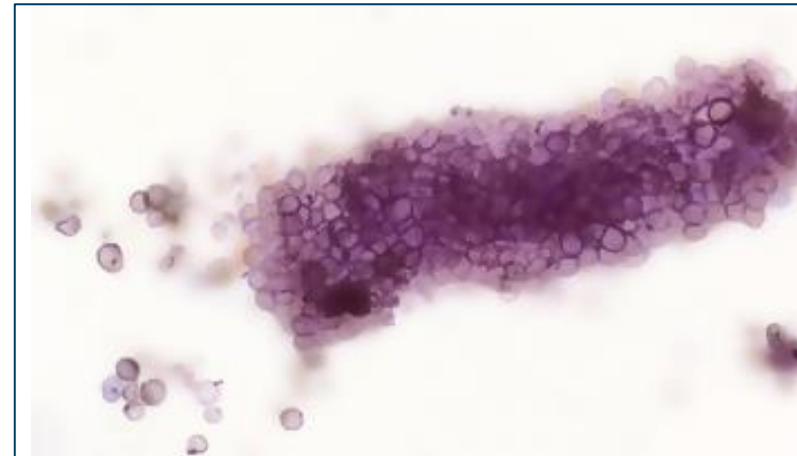


# Nephritic Syndrome



# Nephritic Syndrome

- Hematuria/dark urine
- Dysmorphic RBCs
- RBC Casts
- ↑ BUN/Cr
- Hypertension
- Swelling/edema
- Fatigue (uremia)
- Proteinuria (< 3.5g/day)



Red Cell Cast  
crystal-violet/safranin stain

# Nephritic Syndrome

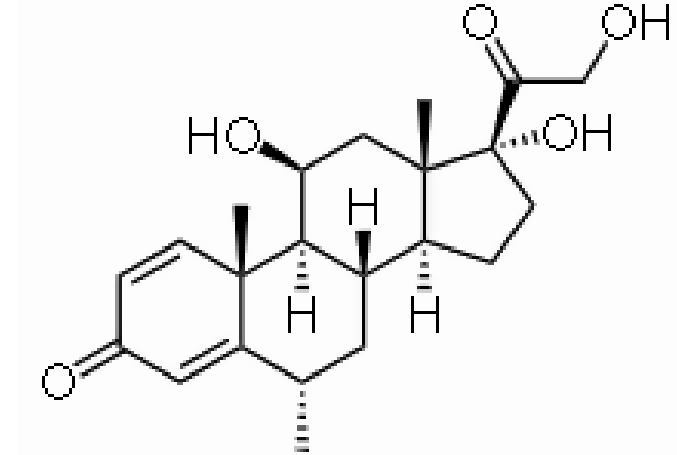
## Major Causes

1. Post-streptococcal
2. Berger's (IgA) nephropathy
3. Diffuse proliferative glomerulonephritis
4. Rapidly-progressive glomerulonephritis (RPGN)
5. Alport syndrome
6. Membranoproliferative glomerulonephritis

# Nephritic Syndrome

## General Points

- Diagnosis:
  - Urinalysis (casts, protein)
  - BUN/Cr
  - **Renal biopsy**
- Hypertension/proteinuria: treat with ACEi/ARB
- Treatment: usually **immunosuppression**
  - Glucocorticoids
  - Cyclophosphamide
  - Mycophenolate



Methylprednisolone

# Postinfectious GN

- Usually follows **group A  $\beta$ -hemolytic strep infection**
  - Impetigo (skin)
  - Pharyngitis
- Immune complex deposition
- Diagnosis:
  - Biopsy most accurate but not routinely done
  - **Antistreptolysin O antibodies**
  - Hypocomplementemia (also lupus, MPGN)

**Streptococcal Pharyngitis**



Dake/Wikipedia



# Postinfectious GN

- Common in children (can also occur in adults)
- Classic case
  - Child
  - 2-3 weeks following strep throat infection
  - Nephritic syndrome

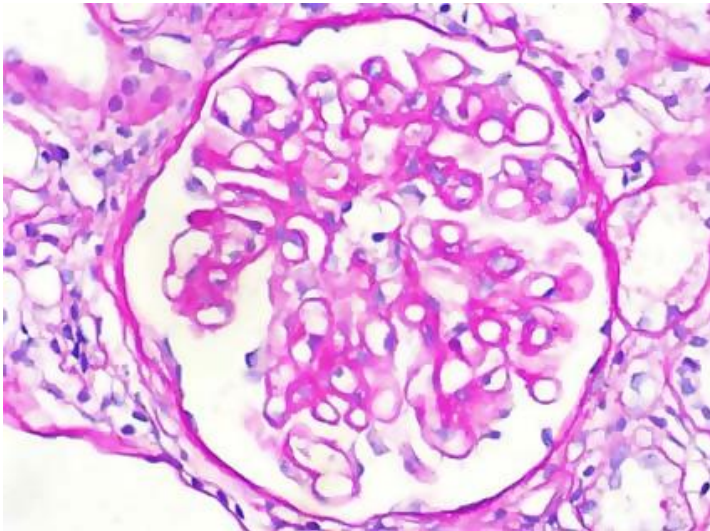


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# Postinfectious GN

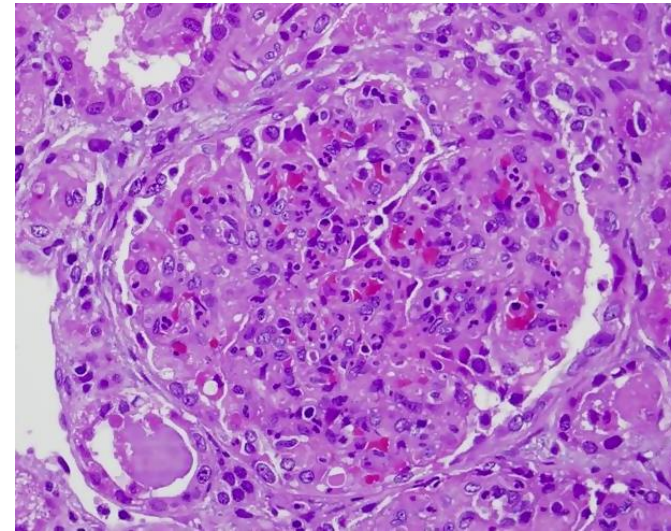
- Glomeruli: Enlarged, hypercellular

Normal



Public Domain

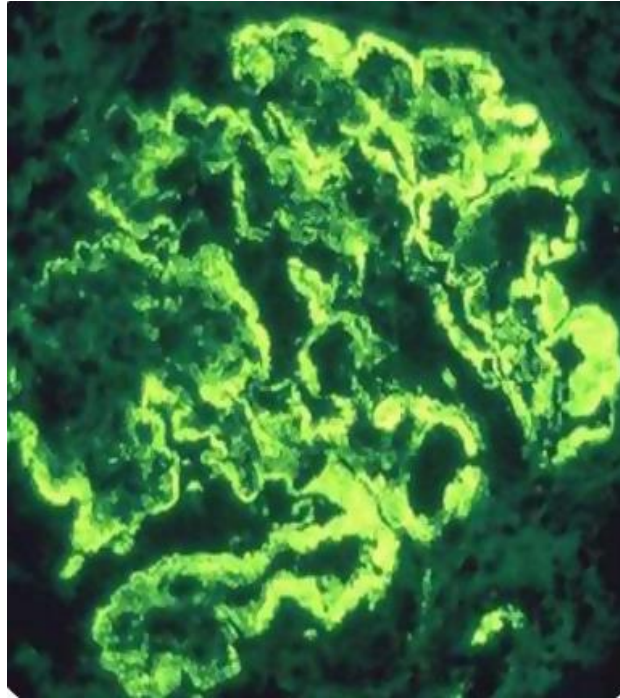
Postinfectious GN



Boonyarit Cheunsuchon/Flickr

# Postinfectious GN

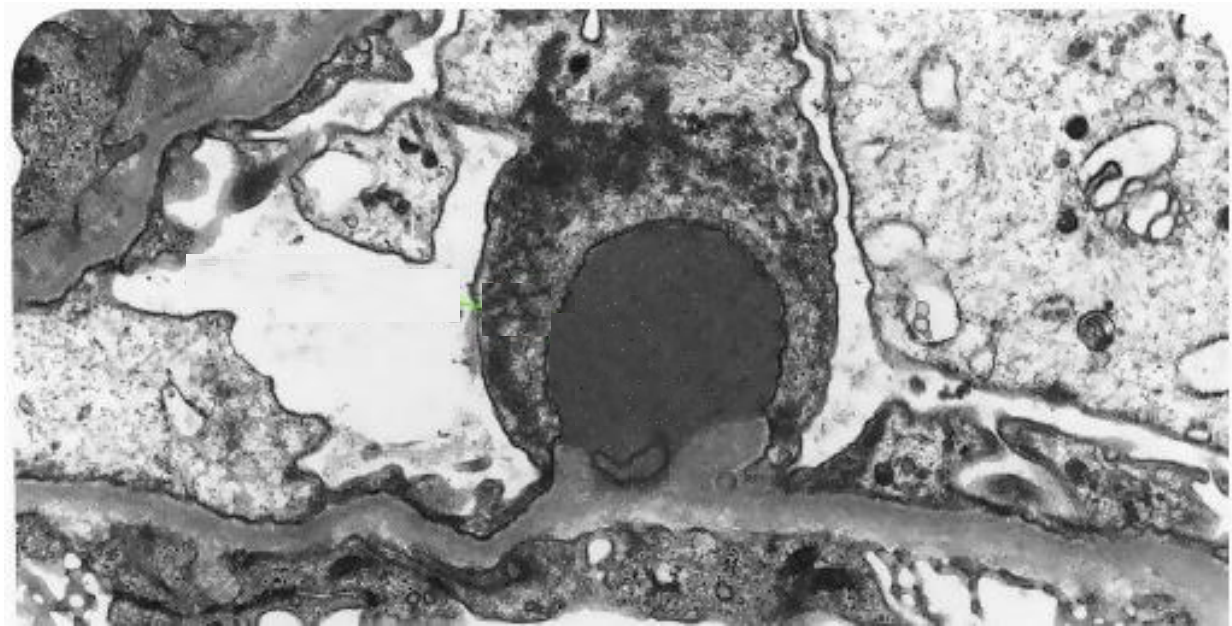
- Subendothelial antibodies/complexes
- Granular IF (IgG, C3)



Images courtesy of bilalbanday

# Postinfectious GN

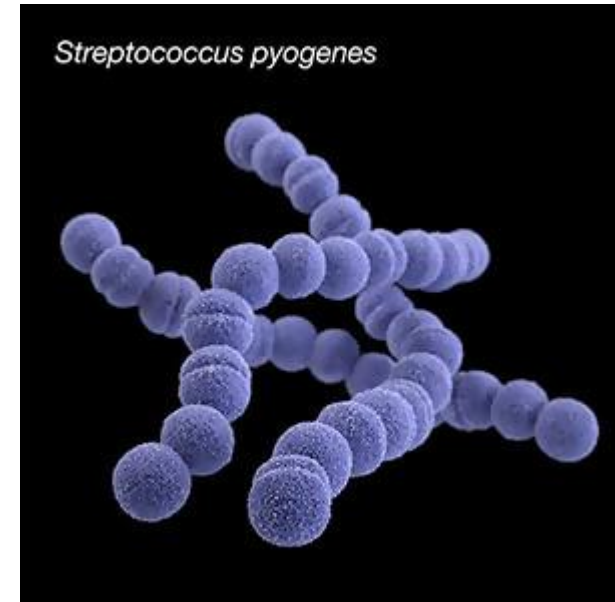
- Electron microscopy: **subepithelial “humps”**
  - Immune complexes (IgG/C3)





# Postinfectious GN

- No specific therapy (supportive)
- Spontaneous resolution
- Good prognosis in children
  - 95% recover completely
- Adults have worse prognosis
  - About 60% recover
  - Many develop renal insufficiency
  - Can be late: 10 to 40 years after initial illness
  - Can develop RPGN

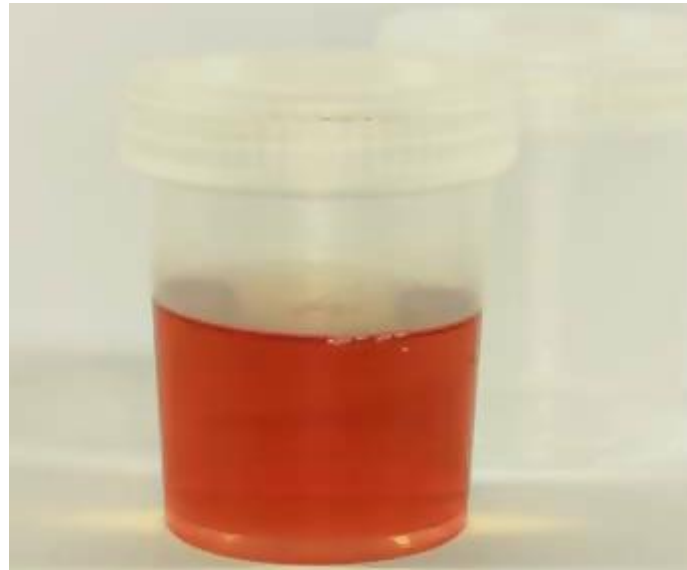


CDC/Public Domain

# IgA Nephropathy

## Berger's Disease

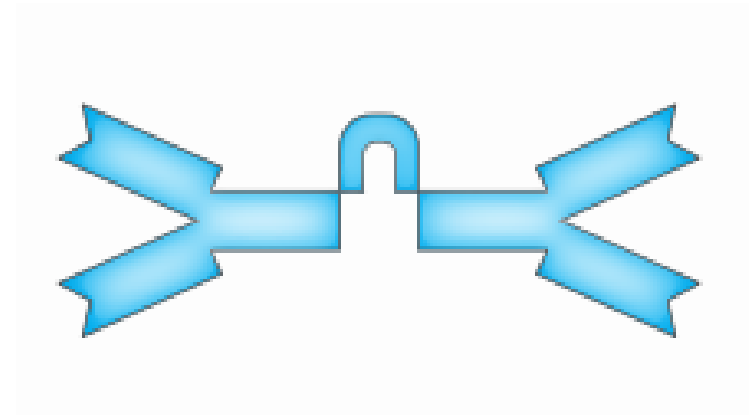
- Most common form glomerulonephritis in the developed world
- **Repeated episodes of hematuria**
- Over time leads to ESRD and HD (50% patients)



# IgA Nephropathy

## Berger's Disease

- Overactive immune system
- **↑ IgA synthesis** in response to triggers
  - Respiratory infection
  - GI infection
- IgA immune complexes → glomerular injury

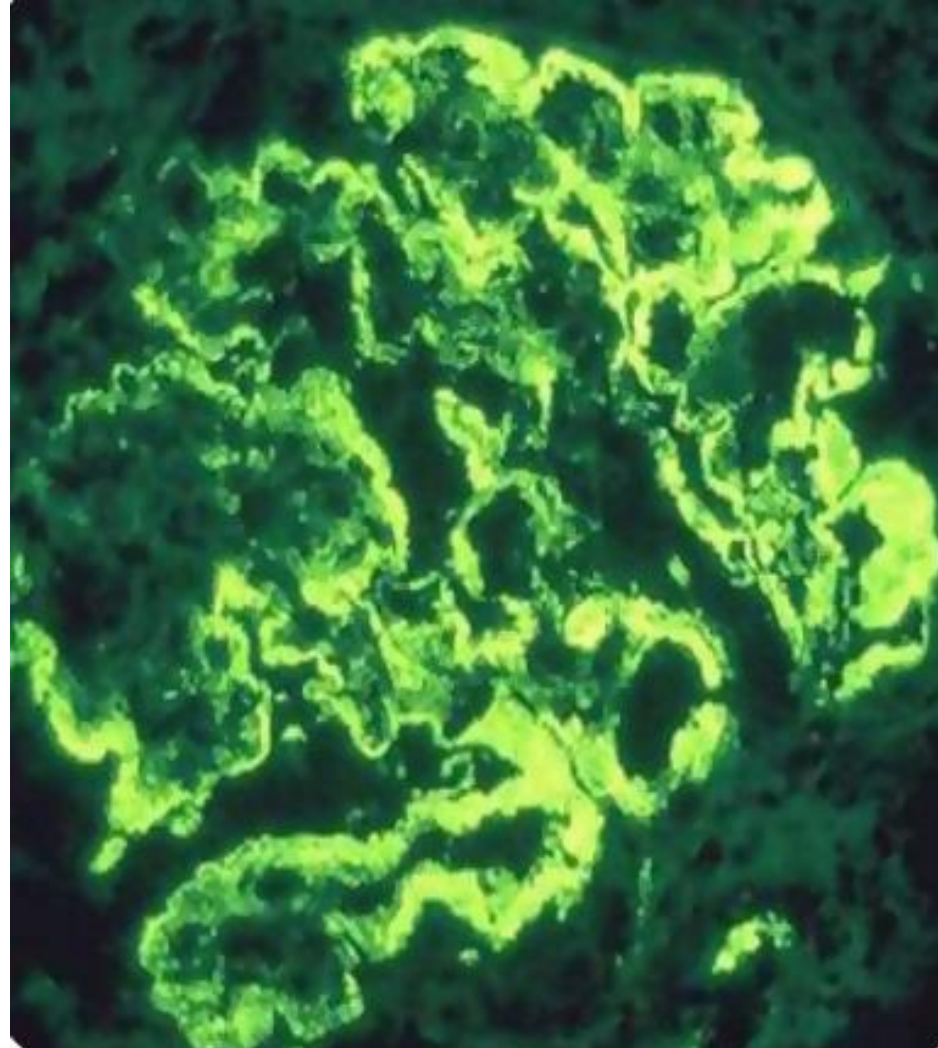


**IgA Antibody**

# IgA Nephropathy

Berger's Disease

- Granular IF
- Stained for IgA



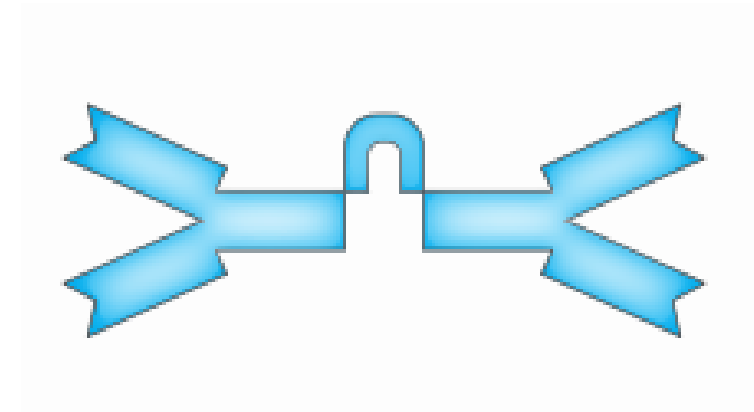
Images courtesy of bilalbanday



# IgA Nephropathy

## Berger's Disease

- Classic case
  - Recurrent episodes hematuria since childhood
  - Episodes follow days after URI or diarrheal illness
- Don't confuse with other glomerular disorders
  - Post-strep GN: weeks after infection
  - IgA GN: days after infection
  - Minimal change: nephrotic syndrome after URI

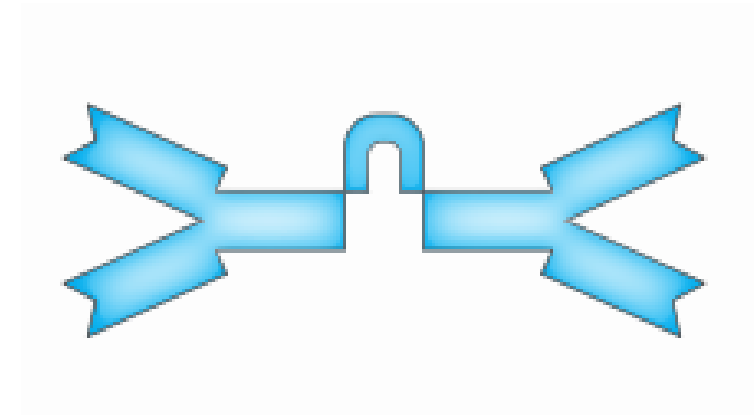


**IgA Antibody**

# IgA Nephropathy

## Berger's Disease

- Diagnosis:
  - Serum IgA levels increased in ~ 50% of cases
  - Renal biopsy usually required
- Treatment:
  - No treatment proven to reverse disease
  - Glucocorticoids in patients with high level proteinuria
- Prognosis:
  - Recurrent episodes, often persistent proteinuria
  - 50% patients progress to ESRD over 20-25 years



**IgA Antibody**

# Henoch-Schonlein Purpura

- IgA nephropathy with extra-renal involvement
- Most common **childhood** systemic vasculitis
- Skin: palpable purpura on buttocks/legs
- GI: abdominal pain, melena
- Joint pains
- **Diffuse IgA deposition**
- Tissue biopsy: demonstrates IgA



Peter Rammstein/Wikipedia

# DPGN

## Diffuse proliferative glomerulonephritis

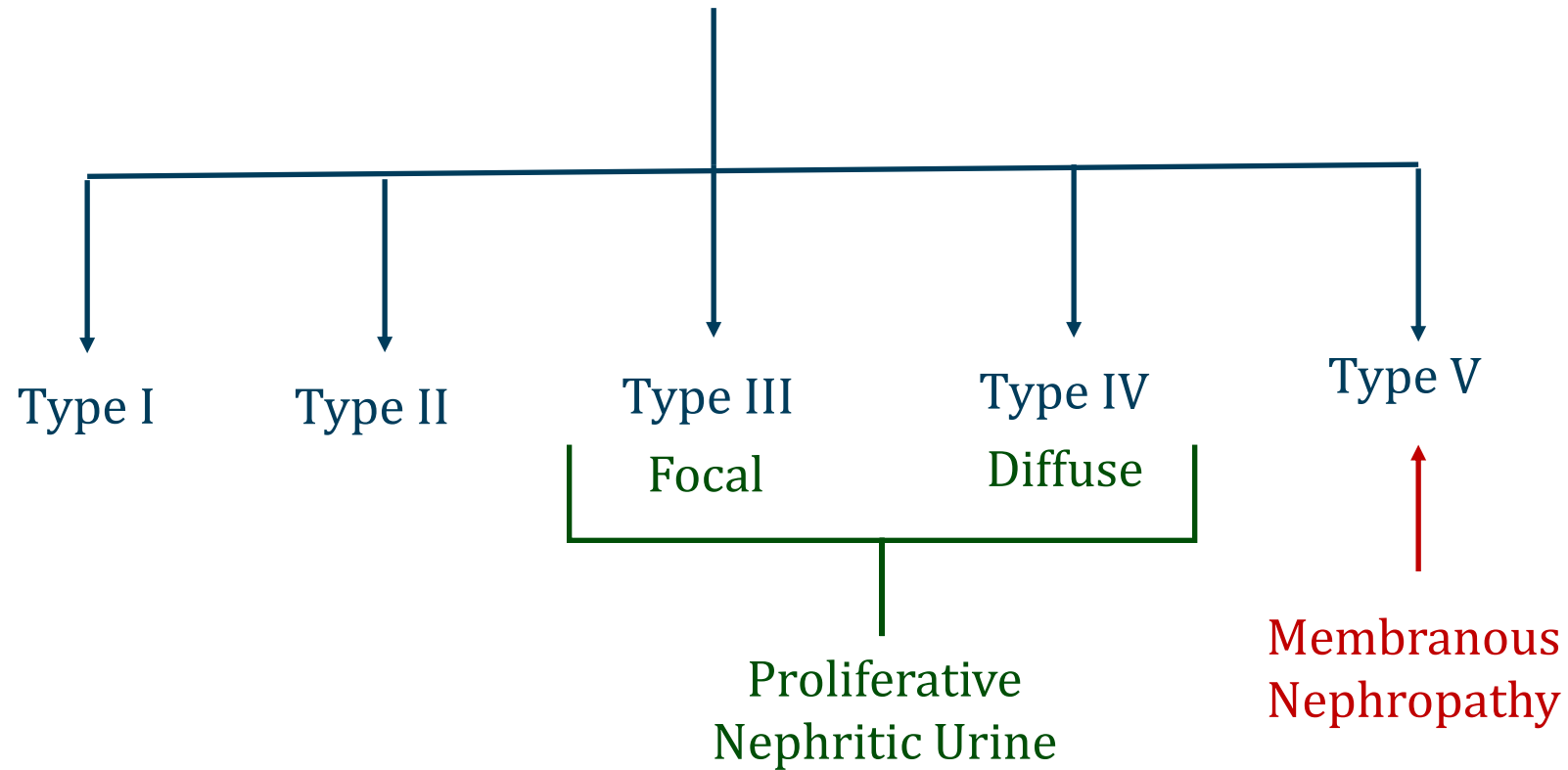
- Systemic lupus erythematosus (SLE)
  - Most common subtype of SLE renal disease
  - “Type IV Lupus Nephritis”
  - Often presents with other SLE features: fever, rash, arthritis
- **Immune complex deposition** in glomeruli
  - IC → inflammatory response

Lupus Malar Rash



M. Sand, D. Sand, C. Thrandorf, V. Paech, P. Altmeyer, F. G. Bechara:  
*Cutaneous lesions of the nose. In: Head & face medicine Band 6, 2010, S. 7*

# Lupus Nephritis



# DPGN

## Diffuse proliferative glomerulonephritis

- Diffuse: More than 50% glomeruli affected
- Proliferative:
  - Increase in cellularity of glomeruli
  - Mesangial cells
  - Endothelial cells
  - Monocyte/neutrophil infiltration

## Lupus Malar Rash



M. Sand, D. Sand, C. Thrandorf, V. Paech, P. Altmeyer, F. G. Bechara:  
*Cutaneous lesions of the nose. In: Head & face medicine Band 6, 2010, S. 7*



# DPGN

## Diffuse proliferative glomerulonephritis

- Subendothelial deposits drive immune response
  - Anti-dsDNA
  - Hypocomplementemia (also post-strep, MPGN)
- Classic finding: **capillary loops thickened**
  - “Wire looping”

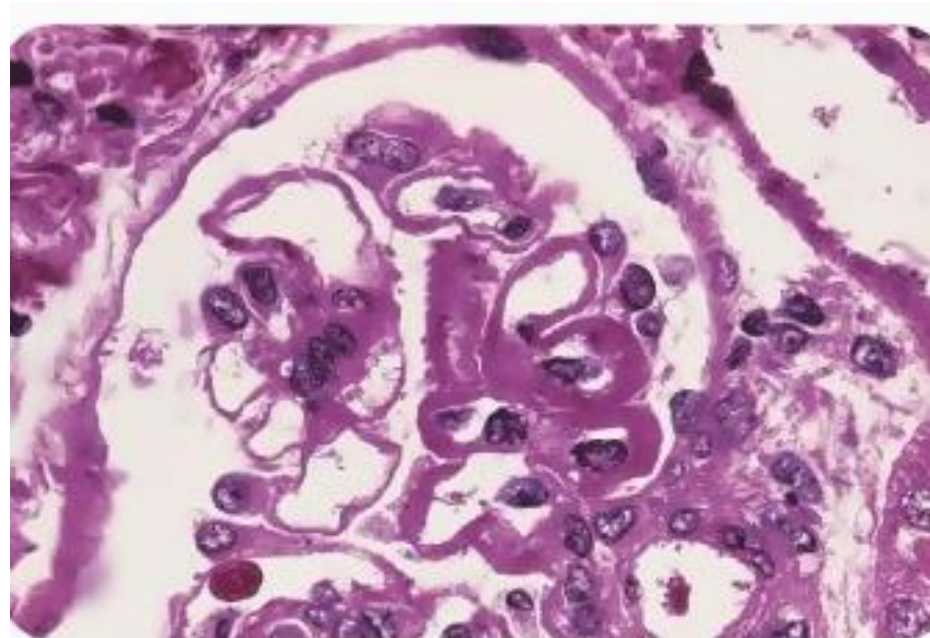


Image courtesy of bilalbanday

# DPGN

Diffuse proliferative glomerulonephritis

- **Granular IF**
- “Full house” immunofluorescence
  - IgG, IgA, IgM, C3, C1q

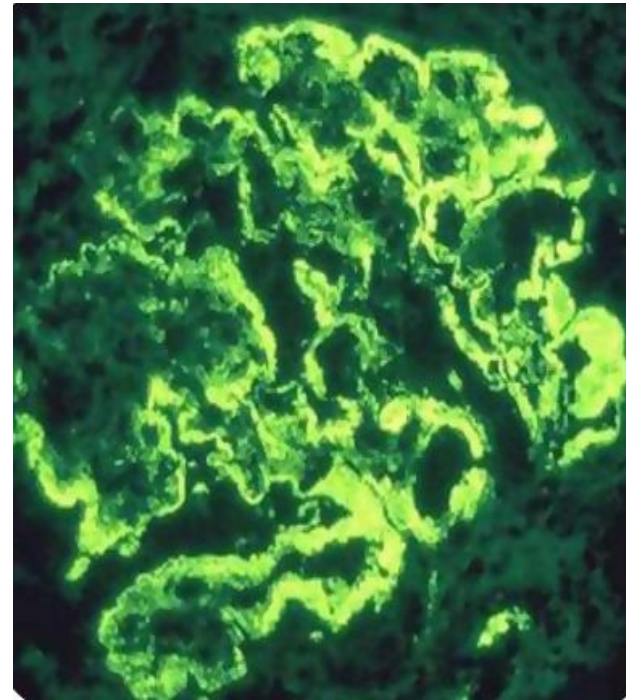


Image courtesy of bilalbanday



# DPGN

## Diffuse proliferative glomerulonephritis

- Clinical presentation
  - Hematuria
  - Reduced GFR
  - Heavy proteinuria (sometimes nephrotic)
- Severe, often leads to ESRD and HD
- Treatment: **glucocorticoids plus cyclophosphamide** (or mycophenolate)

# Alport Syndrome

## Hereditary Nephritis

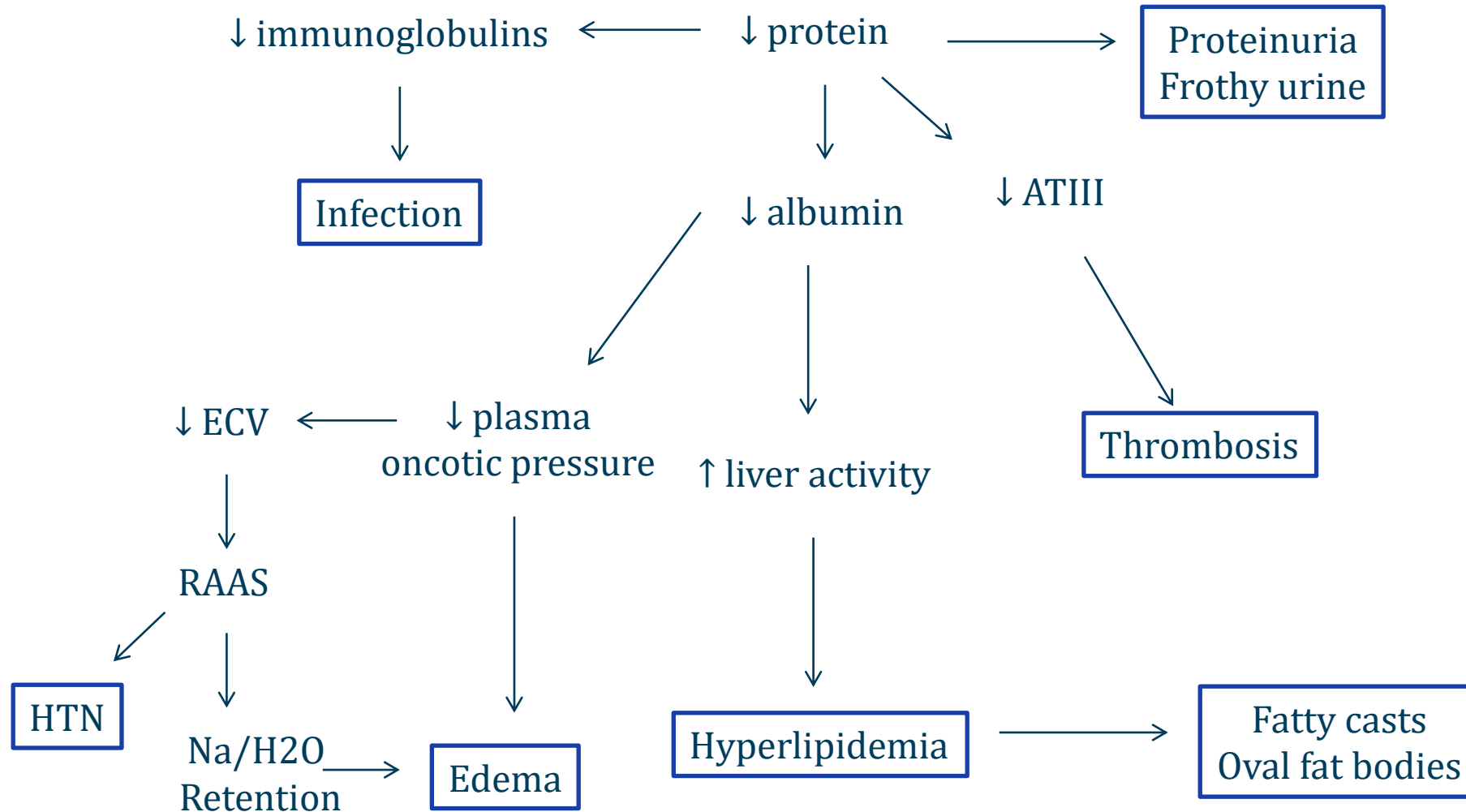
- Genetic **type IV collagen** defect
  - Mutations in **alpha-3, alpha-4, or alpha-5** chains
  - Chains found in basement membranes kidney, eye, ear
- Inherited: X-linked
- Classic triad:
  - Hematuria
  - Hearing loss
  - Ocular disturbances
- Look for child with triad and family history
- No specific treatments available
- Often progresses to ESRD or transplant

# Nephrotic Syndrome

Jason Ryan, MD, MPH



# Nephrotic Syndrome



# Nephrotic Syndrome

- Frothy urine
- Swelling of ankles
- Swelling around eyes (periorbital)
- Serum total cholesterol > 300 mg/day
- Proteinuria (> 3.5 g/day)
- Increased risk of infection
- Increased risk of thrombosis



James Heilman, MD/Wikipedia

# Nephrotic Syndrome

## General Diagnostic Points

- Best initial test: **urinalysis**
  - Defines protein losses in nephrotic range
  - Preferentially detects **albumin**
  - Less sensitive to immunoglobulins
- Definitive test: renal biopsy

Urinalysis Finding	Protein Excretion g/24hr
Negative	< 0.1
Trace	0.1-0.2
1+	0.2-0.5
2+	0.5-1.5
3+	2.0-5.0
4+	>5.0

# Nephrotic Syndrome

## General Diagnostic Points

- 24-hour urine collection
  - Normal protein excretion < 150 mg/day
  - Nephrotic range: > 3500 mg/day (3.5 g/day)
- **Urine protein to creatinine ratio (UPr/Cr)**
  - Estimates 24-hour protein excretion
  - Easier to obtain than 24-hour collection
  - Ratio 3.5:1 = 3.5 grams per 24-hours
- Nephrotic range = **glomerular problem**



Wikipedia/Public Domain

# Nephrotic Syndrome

## General Treatment Points

- Hypertension and proteinuria: ACEi and ARB
- Hyperlipidemia: statins
- Edema: sodium restriction



Flickr/Public Domain

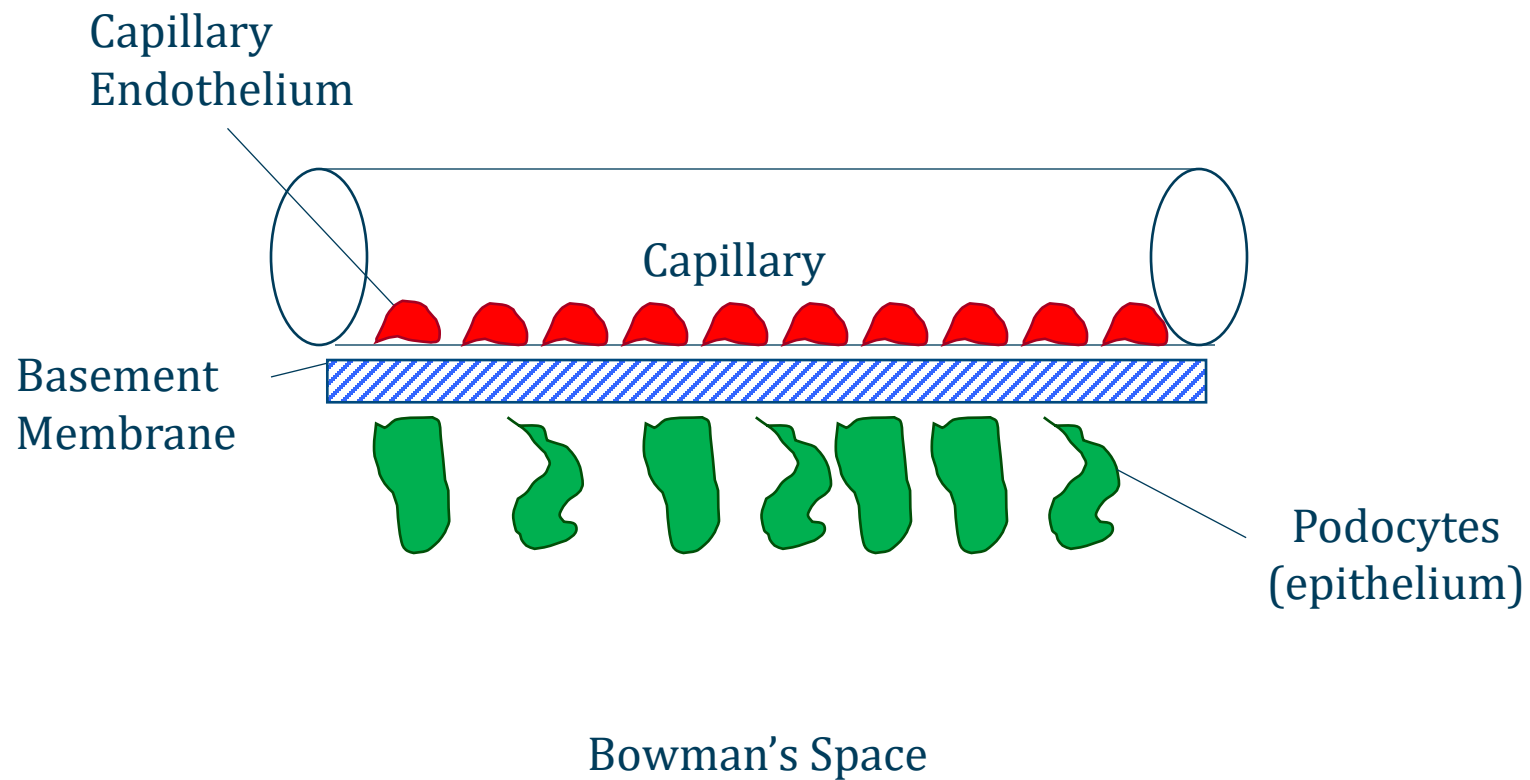


# Nephrotic Syndrome

## Major Causes

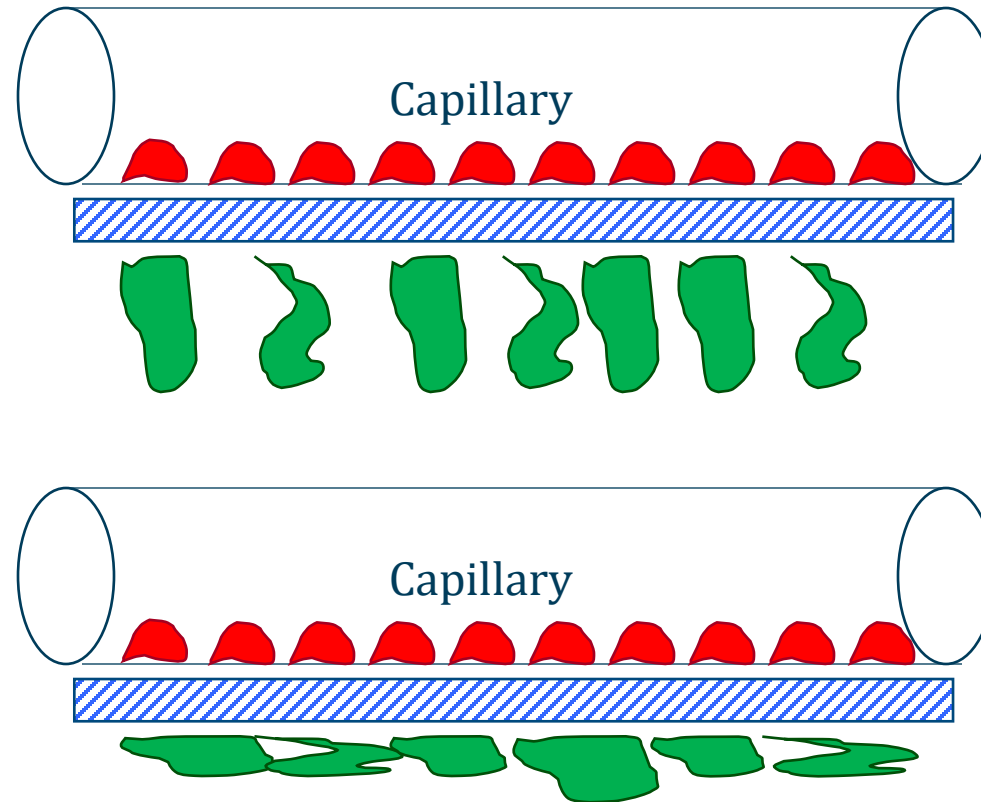
1. Minimal change disease
2. Focal segmental glomerulosclerosis (FSGS)
3. Membranous nephropathy
4. Diabetic Nephropathy
5. Amyloidosis
6. Membranoproliferative Glomerulonephritis

# Glomerular Filtration Barrier



# Minimal Change Disease

Effacement  
(flattening)  
Foot Processes



# Minimal Change Disease

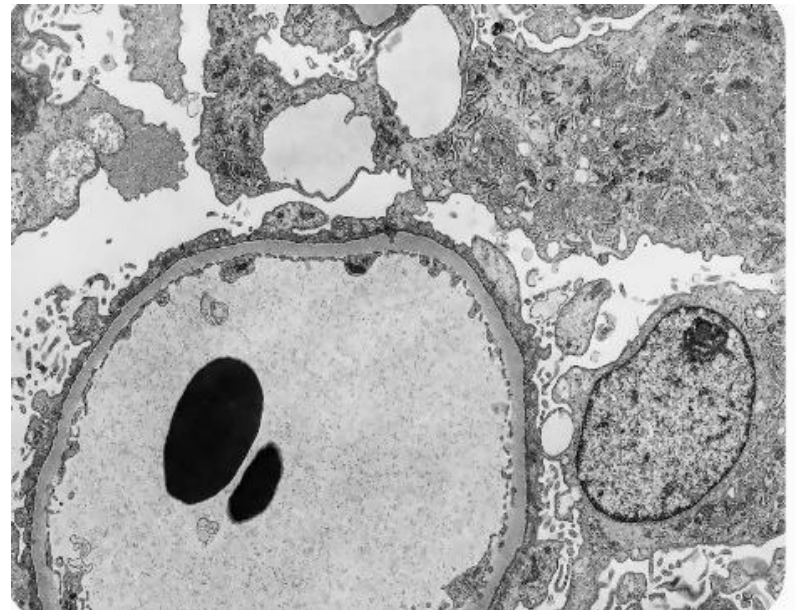
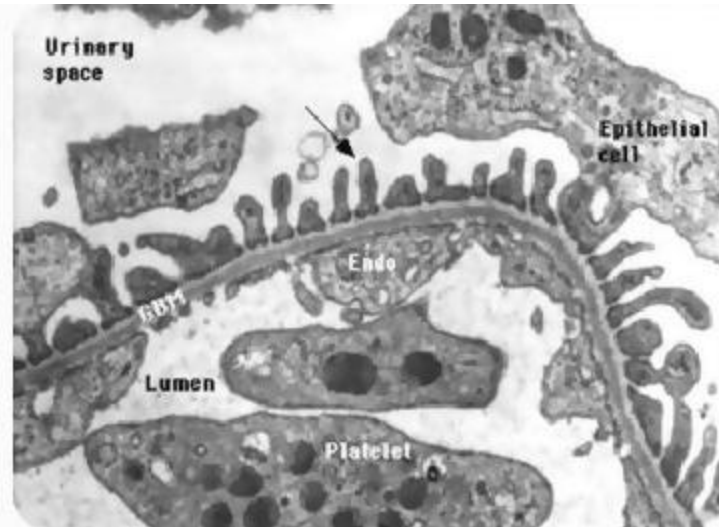
## Pathology

- Caused by **effacement of foot processes**
- Loss of anion (-) charge barrier GBM
- Triggered by **cytokines** → damage to podocytes
- Usually idiopathic
- Associated with Hodgkin Lymphoma

# Minimal Change Disease

## Renal Biopsy

- Normal light microscopy
- No important findings IF
- Only major finding is **effacement foot processes EM**



# Minimal Change Disease

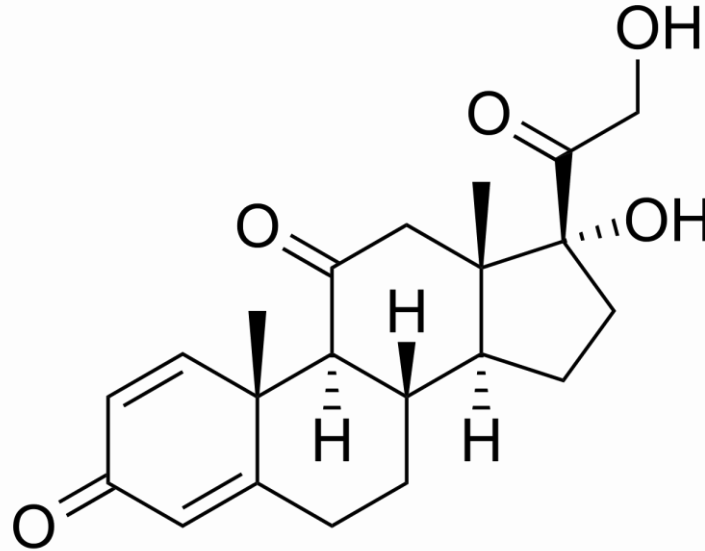
## Other Features

- Sometimes has immunological trigger (days before)
  - **Viral infection (URI)**
  - Allergic reaction (bee sting)
  - Recent immunization
- **“Selective”** proteinuria
  - Only albumin in urine (not immunoglobulin)
  - Contrast with other glomerular disease “non-selective”
- Most common cause nephrotic syndrome in children
  - Classic presentation is a child with recent URI

# Minimal Change Disease

## Prognosis and Treatment

- Favorable prognosis
- Responds very well to **steroids**
  - Unique among nephrotic syndrome causes

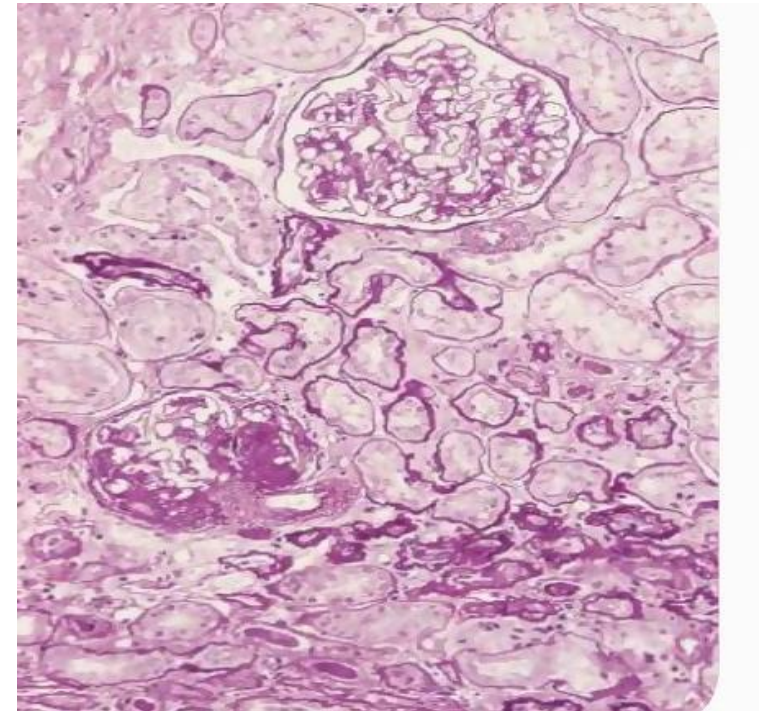


Prednisone

# FSGS

## Focal segmental glomerulosclerosis

- Focal
  - Only some glomeruli involved
- Segmental
  - Only portion of glomerulus involved
- Glomerulosclerosis
  - Pink/dense deposition of collagen in glomerulus
- Cause: podocyte damage from unknown agent
- Electron microscopy: effacement of foot processes



bilalbanday



# FSGS

## Epidemiology

- **African-Americans**
  - Most common ethnic association with nephrotic syndrome

### Nephrotic Syndrome Causes

	African-American	Caucasian
<b>FSGS</b>	<b>57%</b>	23%
Membranous	17%	36%
Minimal Change	14%	20%

# FSGS

## Focal segmental glomerulosclerosis

- Primary FSGS
- Secondary FSGS
  - HIV
  - Sickle cell anemia
  - Heroin users
  - Massive obesity
- Interferon treatment
  - Used to treat HCV and HBV
- Loss of nephrons
  - Single kidney, surgical kidney removal



Psychonaught/Wikipedia



Tibor Végh

# FSGS

## Focal segmental glomerulosclerosis

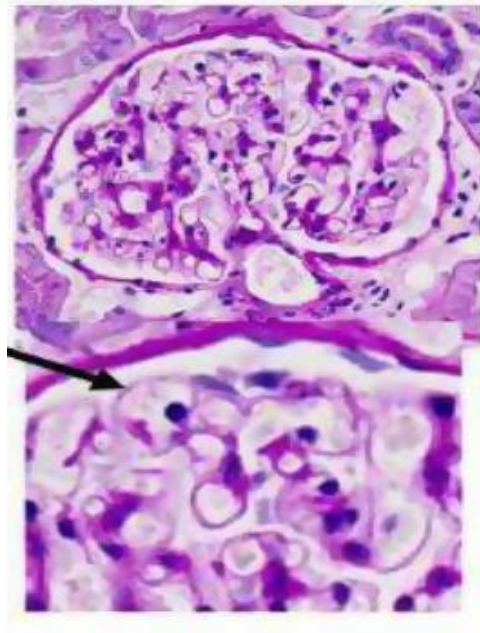
- Diagnosis: renal biopsy
  - Light microscopy: FSGS
  - Electron microscopy: Effacement of foot processes
- Treatment:
  - Treat associated causes (HIV, HepC)
  - Some evidence for immunosuppression (controversial)
- **Often progresses to chronic renal failure**
  - 40-60% within 10 to 20 years



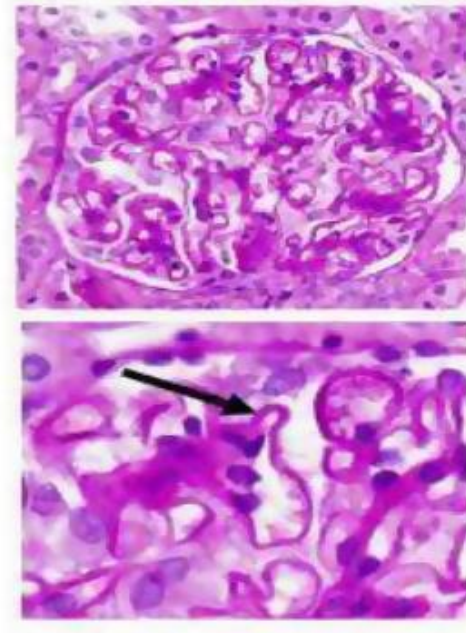
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# Membranous Nephropathy

- **Thick glomerular basement membrane**
  - “Membranous”



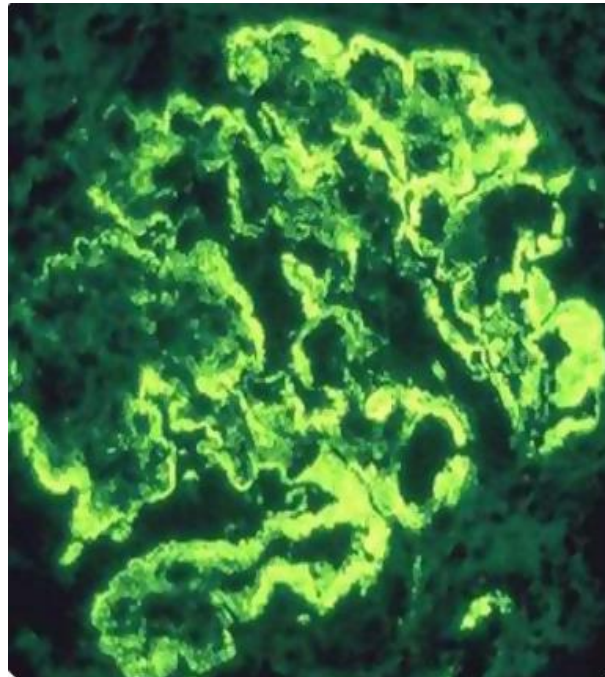
Normal



Membranous

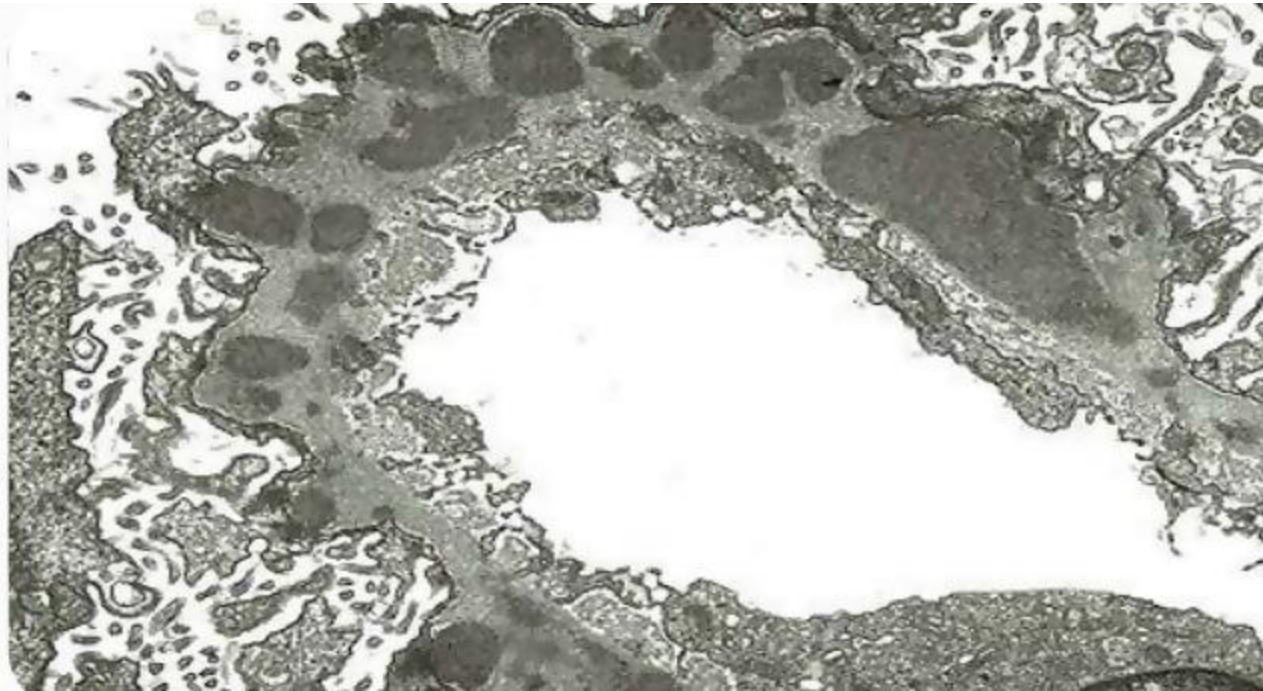
# Membranous Nephropathy

- Membrane thick from **immune complex deposition**
  - Immunofluorescence microscopy very useful
  - “Granular” deposits of IgG and C3 staining





# Subepithelial Deposits



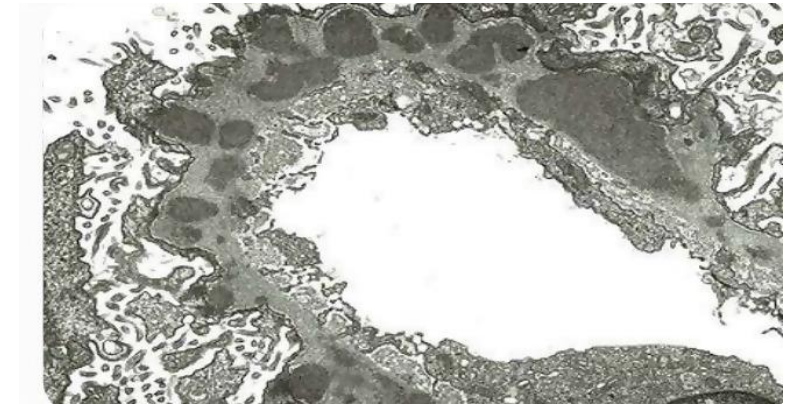
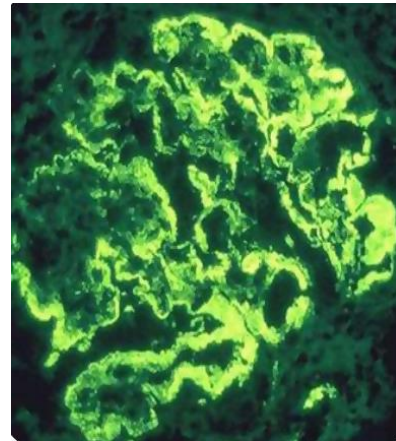
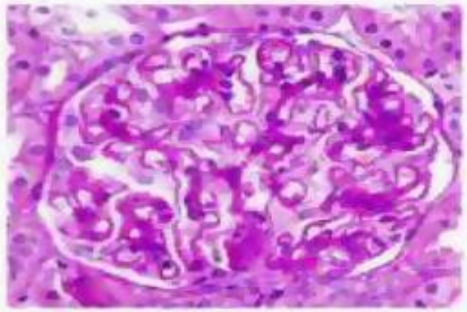
Bilalbanday/Public Domain

Spike and Dome  
Appearance

# Membranous Nephropathy

## Renal Biopsy

- Light microscopy: capillary/BM thickening
- Immunofluorescence: granular IgG/C3
- Electron microscopy: subepithelial deposits



# Membranous Nephropathy

- Most common form: idiopathic
- Associated with autoantibodies 70-80% of cases
  - Antigen: phospholipase A2 receptor (PLA2R)
  - Expressed on podocytes
- **Positive serum anti-PLA2R antibody test** suggest MN
- Antibody tests can avoid need for biopsy



# Membranous Nephropathy

## Secondary Causes

- Systemic lupus erythematosus (SLE)
- Most lupus renal disease in nephritic
- Diffuse proliferative glomerulonephritis
- If nephrotic, this is cause (10-15%)



Wikipedia/Public Domain

# Membranous Nephropathy

## Secondary Causes

- Solid tumors
  - Colon cancer, lung cancer, melanoma
- Infections
  - Hep B, Hep C
- Drugs
  - Penicillamine, gold, NSAIDs
  - All used to treat **rheumatoid arthritis**

**Tumor  
Hepatitis  
Rheumatoid Arthritis**

# Membranous Nephropathy

## Other Features

- Most common cause nephrotic syndrome in adults
- Excellent prognosis in children
- Some adults develop ESRD
- Spontaneous remission may occur
- Treatment primary MN:
  - **Rituximab, steroids and cyclophosphamide** in high risk patients

## Nephrotic Syndrome Causes

	African-American	Caucasian
FSGS	57%	23%
<b>Membranous</b>	17%	<b>36%</b>
Minimal Change	14%	20%

# Diabetic Nephropathy

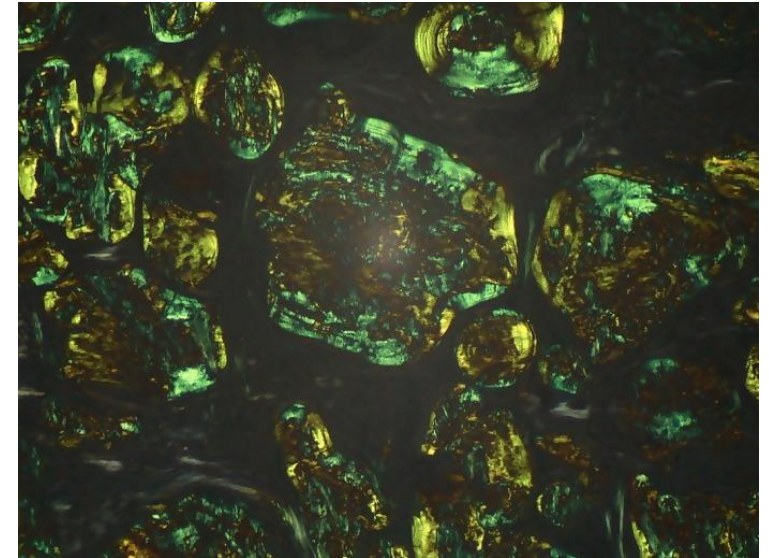
- Non-enzymatic glycosylation
- Basement membranes: leakage of protein
- Long term effect: sclerosis of glomerulus
- **Proteinuria**
- Can develop nephrotic syndrome



Wikipedia/Public Domain

# Amyloidosis

- Extracellular buildup of amyloid proteins
- Classic biopsy findings
  - Apple-green birefringence
  - Congo red stain
- Kidney is **most commonly involved organ**



Ed Uthman, MD

# MPGN

## Membranoproliferative Glomerulonephritis

- Rare glomerular disorders
- Can cause nephritic or nephrotic syndrome
- Varying degrees of renal dysfunction
- Renal failure ( $\uparrow$ BUN/Cr)
- Hematuria
- Proteinuria (+/- nephrotic range)
- Treated with steroids and immunosuppressants

# MPGN

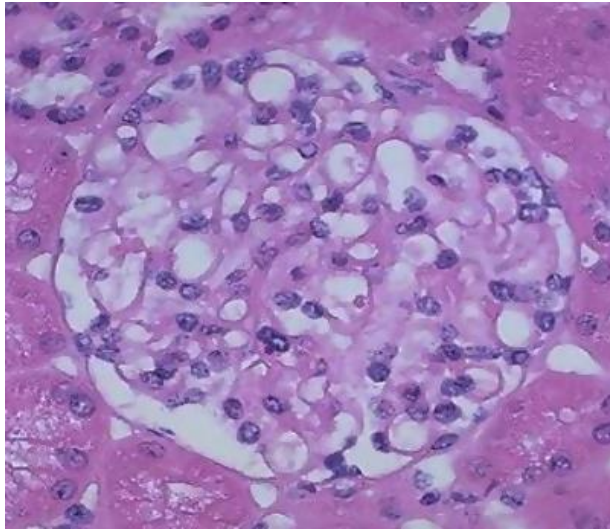
## Membranoproliferative Glomerulonephritis

- Two major types
- Type I much more common
- Type II (dense deposit disease) rare

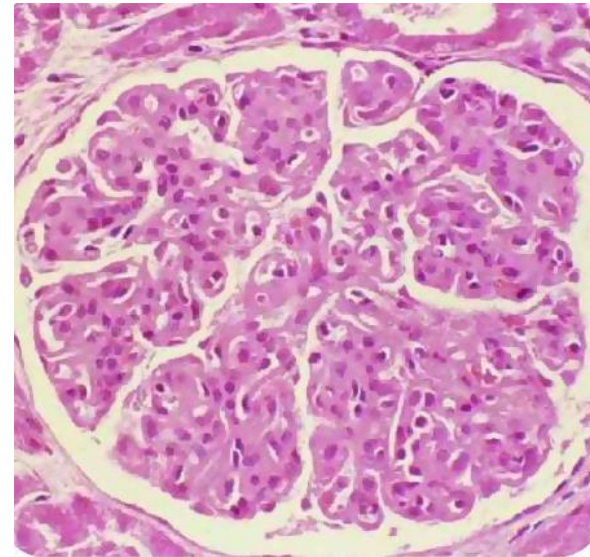
# MPGN

## Membranoproliferative Glomerulonephritis

- Membrano
  - Thick basement membrane
- Proliferative
  - Proliferation of mesangial cells, mesangial matrix



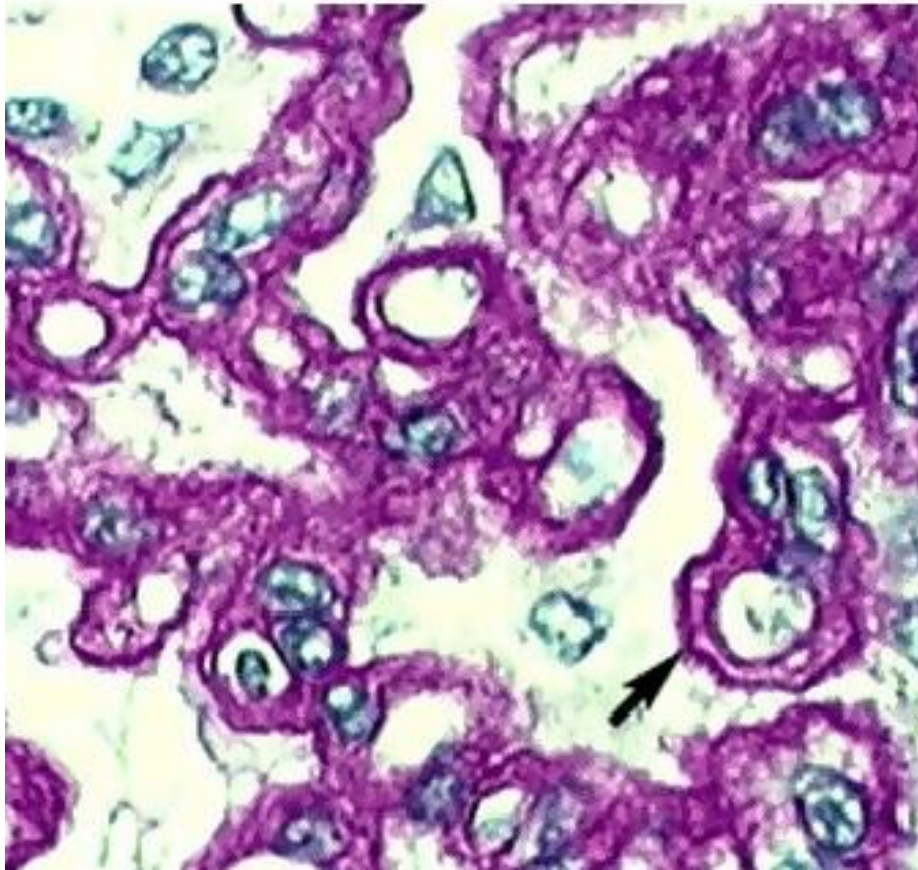
Normal



MPGN: Hypercellular, Thick walls



# MPGN Type I



Type I: Tram Tracks

**Immune complex deposition**

IgG → complement activation

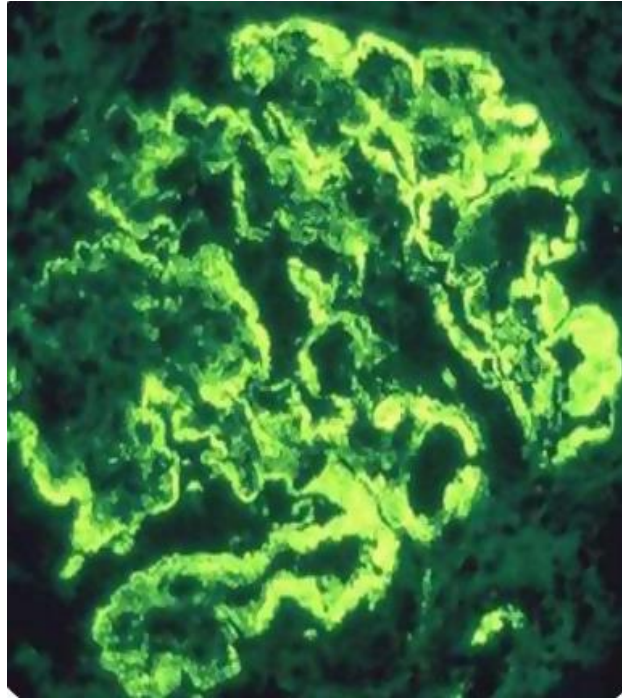
IC deposits split basement membrane

**“Tram track” appearance on light microscopy**

Common (80%) in Type I

# MPGN Type I

- Subendothelial antibodies/complexes
- Granular IF for IgG and C3



Images courtesy of bilalbanday

# MPGN Type I

- May be idiopathic/primary
- Can be secondary to **hepatitis B or C infection**

# MPGN Type II

## Dense Deposit Disease

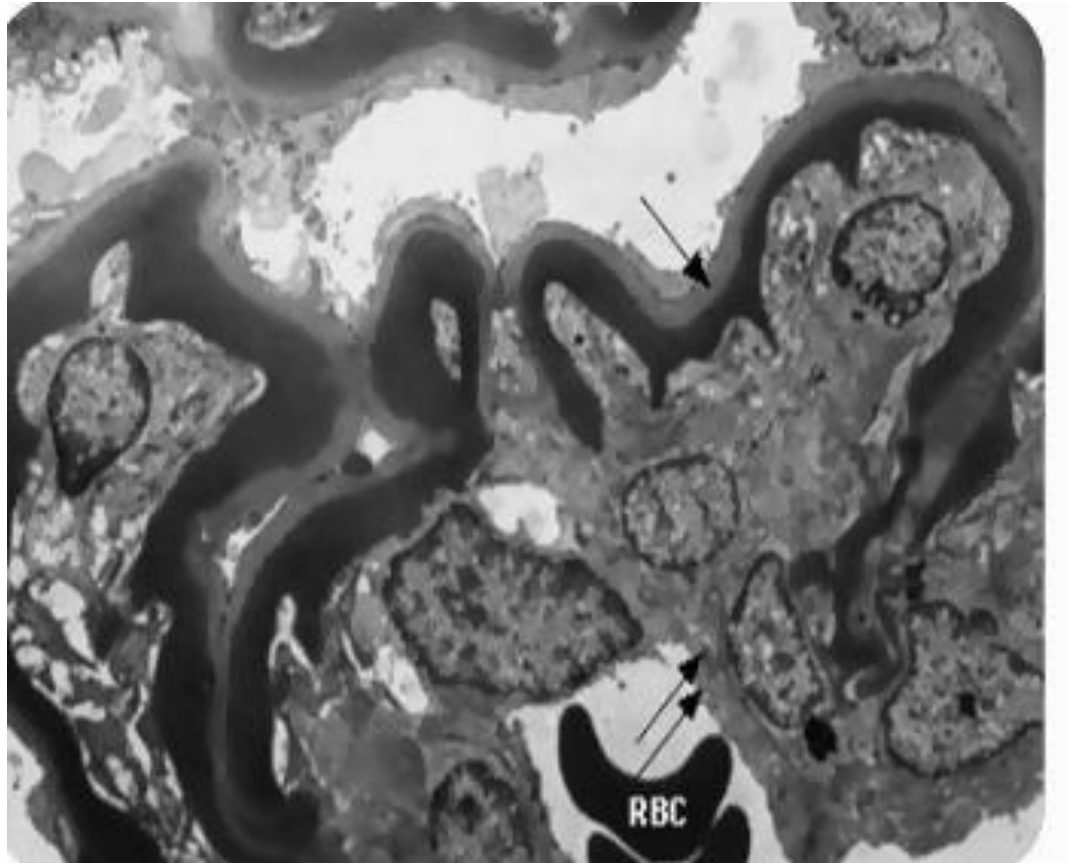


Image courtesy of bilalbanday

Type II: Dense Deposits  
IF shows C3 but not IgG

Type II  
Basement Membrane  
“**Electron dense**” deposits  
Mediated by **complement**  
IgG usually absent

# C3 Nephritic Factor

## C3 Convertase Stabilizing Antibody

- Found in > 80% patients with MPGN II
- C3 convertase activates **alternative pathway**
- Stabilized by C3 nephritic factor
- Over activation of complement system
- Hypocomplementemia ( $\downarrow$ C3)

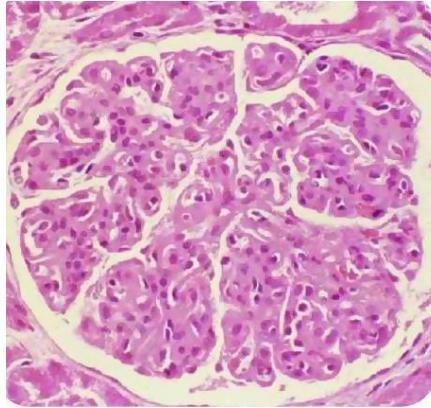
# MPGN Type II

## Dense Deposit Disease

- Mostly a disease of **children**
- Usually 5 to 15 years old
- 50% develop ESRD within ten years

# MPGN

## Membranoproliferative Glomerulonephritis



	Type I	Type II
Pathology	Immune Complex	Complement (C3)
Microscopy	LM: Tram Tracks	EM: Dense Deposits
Associations	Hepatitis	Children

# RPGN

Jason Ryan, MD, MPH

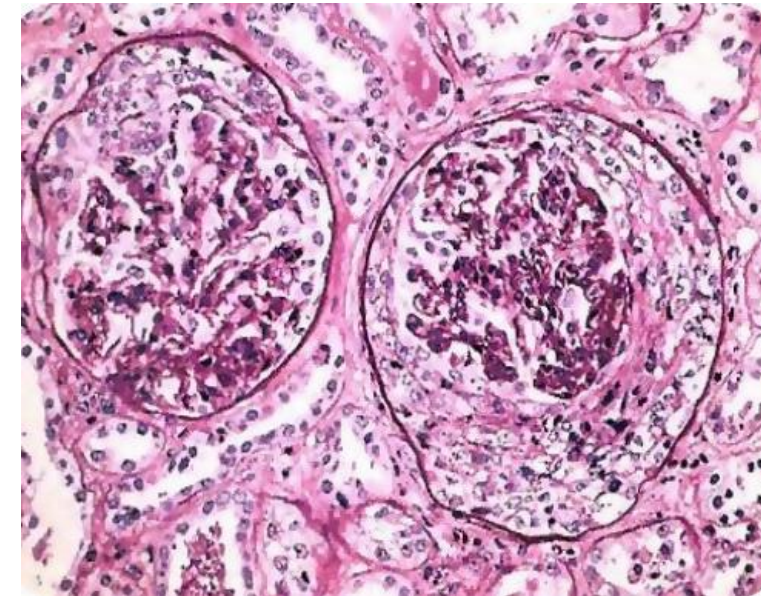




# RPGN

## Rapidly progressive glomerulonephritis

- Clinical syndrome
- Urinalysis consistent with glomerular disease
  - Proteinuria
  - RBC casts
- Rapid loss of renal function over days, weeks or months
- Often presents as **acute renal failure**
- Characterized by **crescent formation** on biopsy



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# RPGN

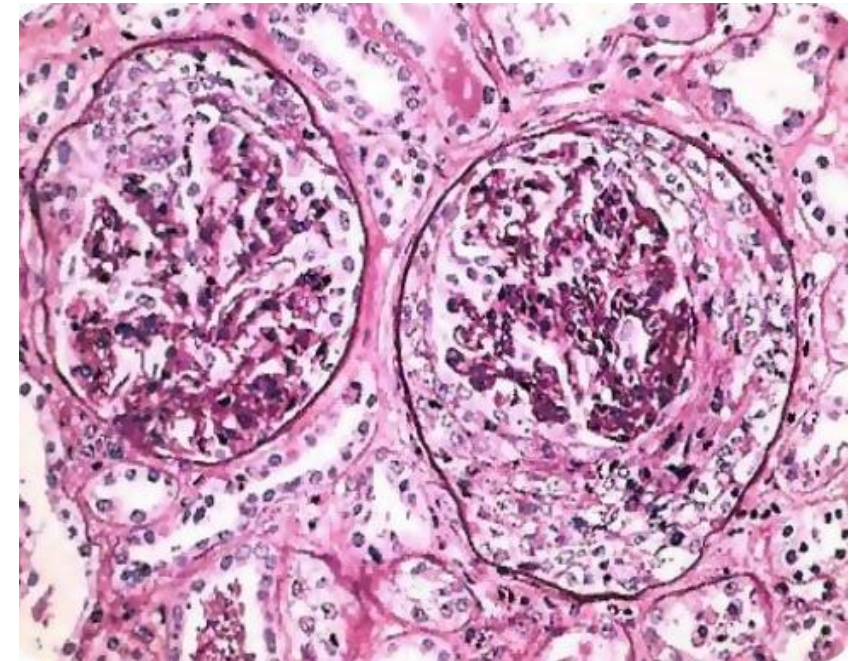
## Rapidly progressive glomerulonephritis

- Generalized symptoms: fatigue, anorexia
- Untreated leads to ESRD in weeks to months
- Treatment (all causes):
  - Intravenous steroids
  - Cyclophosphamide

# RPGN

## Rapidly progressive glomerulonephritis

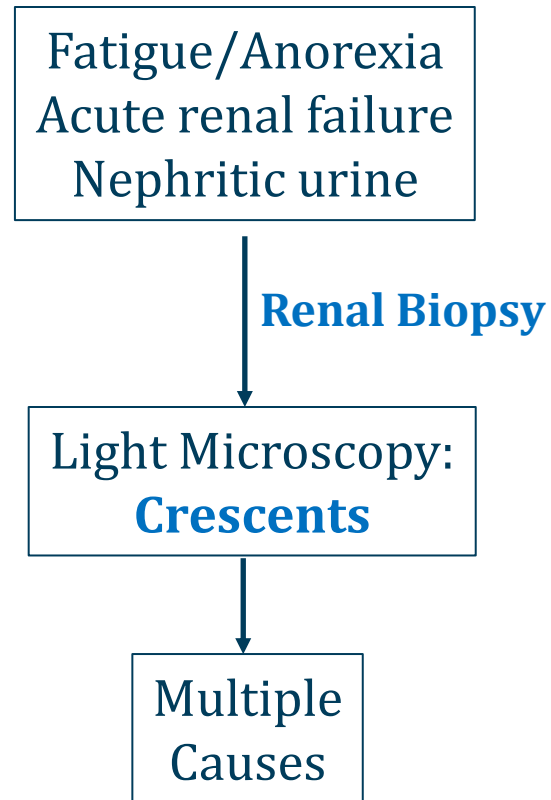
- Also called “crescentic” glomerulonephritis
- Pathologic description: many causes
  - Many diseases lead to this condition
- Crescents formed by **inflammation**
  - Monocytes/macrophages
  - Fibrin



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# RPGN

Rapidly progressive glomerulonephritis

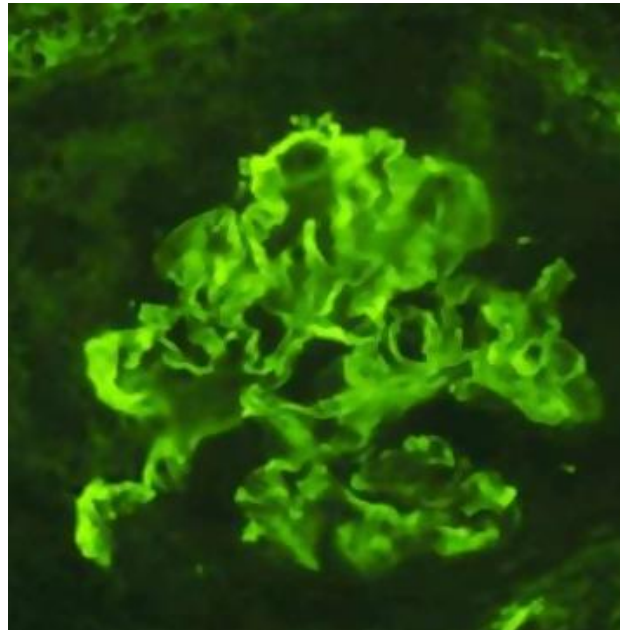


# RPGN

## Rapidly progressive glomerulonephritis

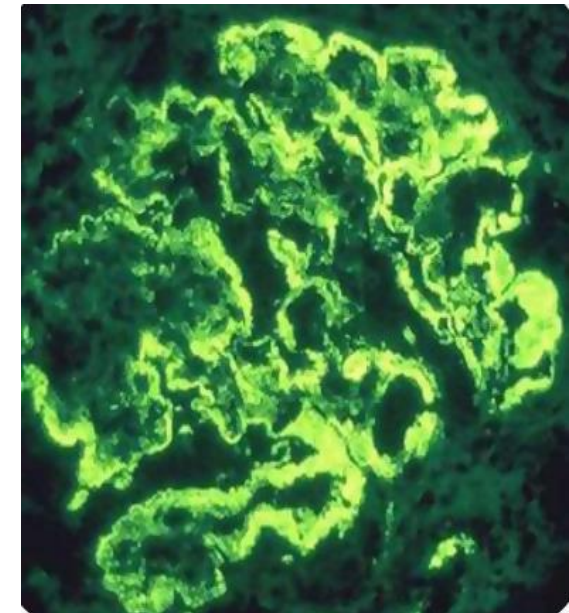
- Causes distinguished based on immunofluorescence
- Type I: Linear IF
- Type II: Granular IF
- Type III: Negative IF

Linear



Images courtesy of bilalbanday

Granular

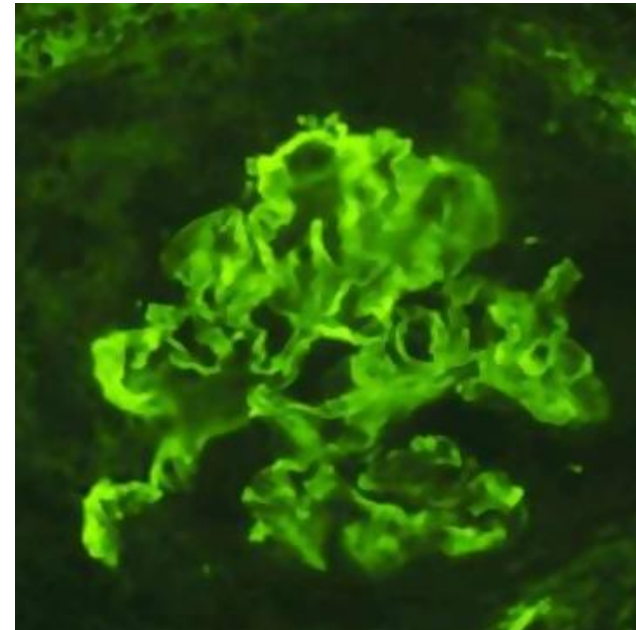


Images courtesy of bilalbanday

# RPGN Type I

- Anti-glomerular basement membrane antibodies
  - “Anti-GBM antibodies”
- Antibodies against GBM antigens
  - Unknown stimulus
  - Type II hypersensitivity
- **Linear IF**
  - IgG antibodies
  - Linear pattern

Linear



Images courtesy of bilalbanday

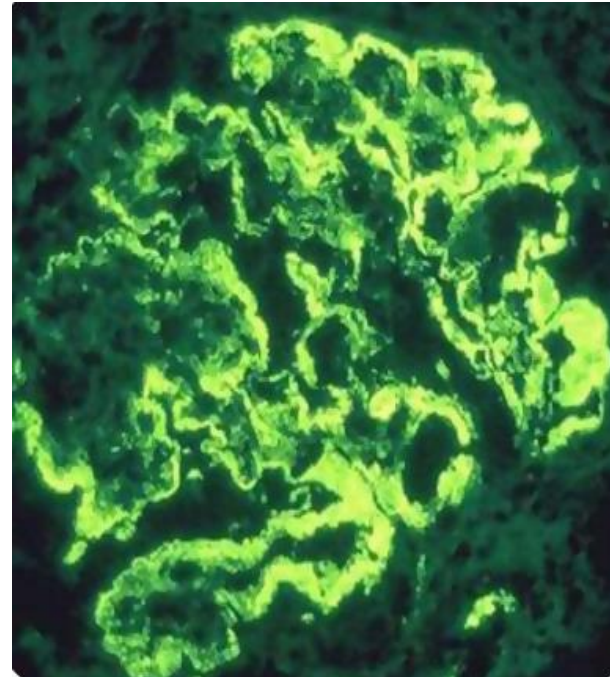


# Goodpasture's Syndrome

- Antibody to collagen
- Antibodies to **alpha-3 chain** of type IV collagen
  - Found in GBM and alveoli
- Hemoptysis and nephritic syndrome
- Classic case
  - Young adult
  - Male
  - Hemoptysis
  - Hematuria

# RPGN Type II

- Immune complex deposition
  - Type III hypersensitivity
- Granular IF



Images courtesy of bilalbanday

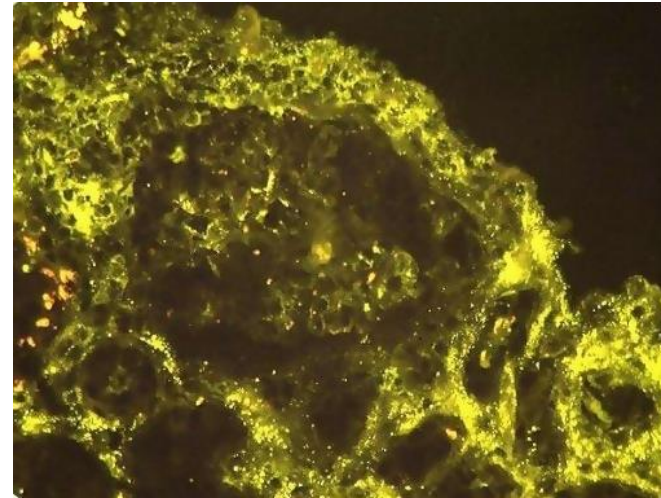


# RPGN Type II

- **Post-streptococcal glomerulonephritis**
  - Can progress to RPGN
  - Most common cause RPGN
- **Systemic lupus erythematosus (SLE)**
  - Diffuse proliferative glomerulonephritis
  - Can progress to RPGN

# RPGN Type III

- Negative IF
  - No staining for IgG, IgA, etc.
- “Pauci-immune”
- Most patients **ANCA positive**
  - c-ANCA or p-ANCA
- Most patients have a **vasculitis syndrome**



Images courtesy of bilalbanday

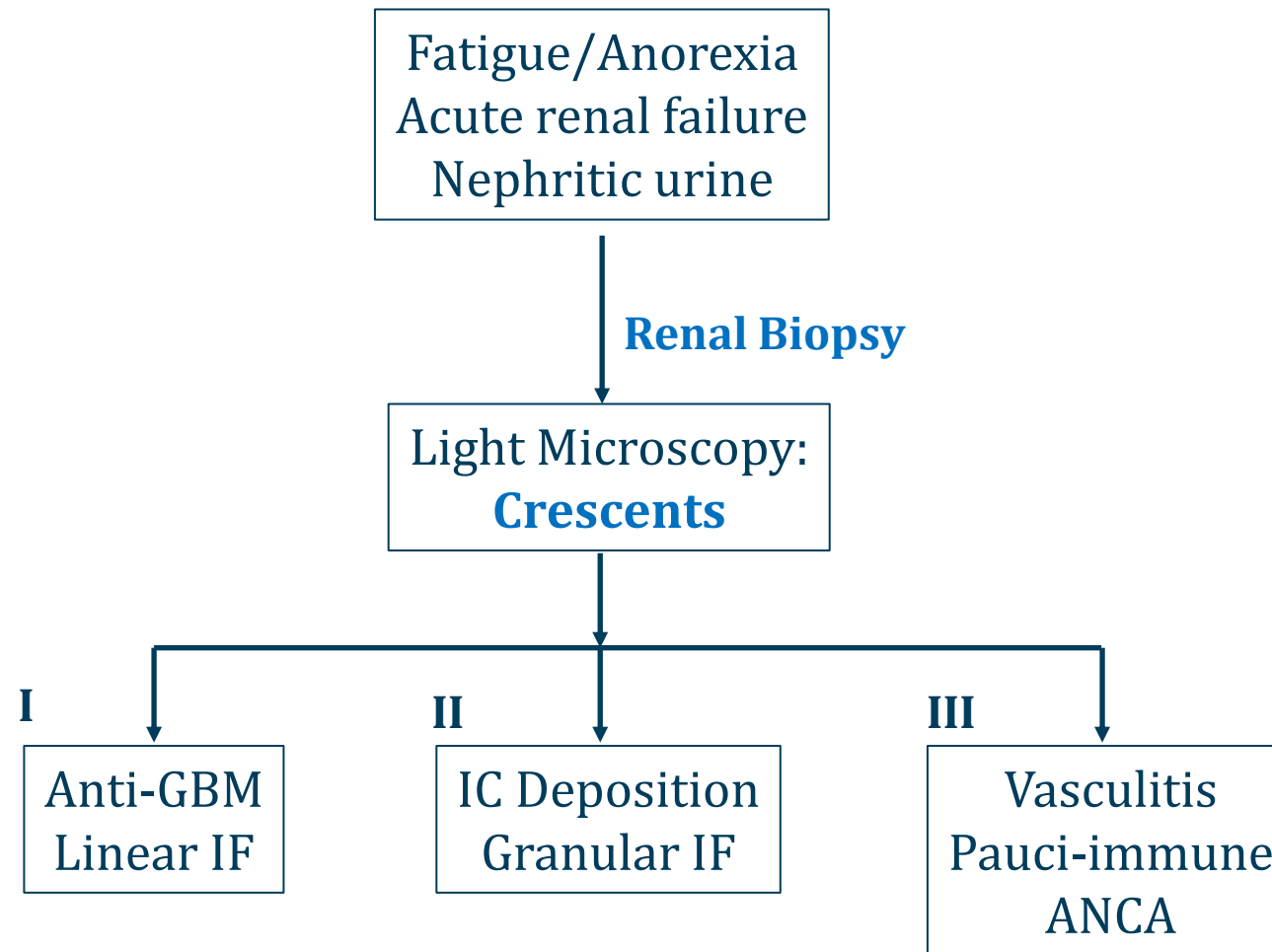
# ANCA Diseases

Anti-neutrophil cytoplasmic antibodies

- Wegener's Granulomatosis (c-ANCA)
  - Granulomatosis with polyangiitis
- Microscopic Polyangiitis (p-ANCA)
- Churg-Strauss syndrome (p-ANCA)
  - Eosinophilic granulomatosis with polyangiitis
- All can lead to pauci-immune nephritis

# RPGN

Rapidly progressive glomerulonephritis



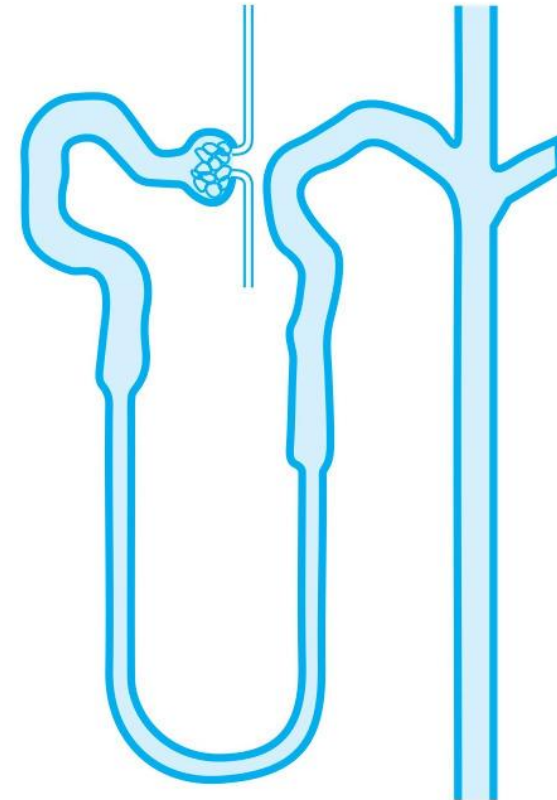
# Tubulointerstitial Disorders

Jason Ryan, MD, MPH



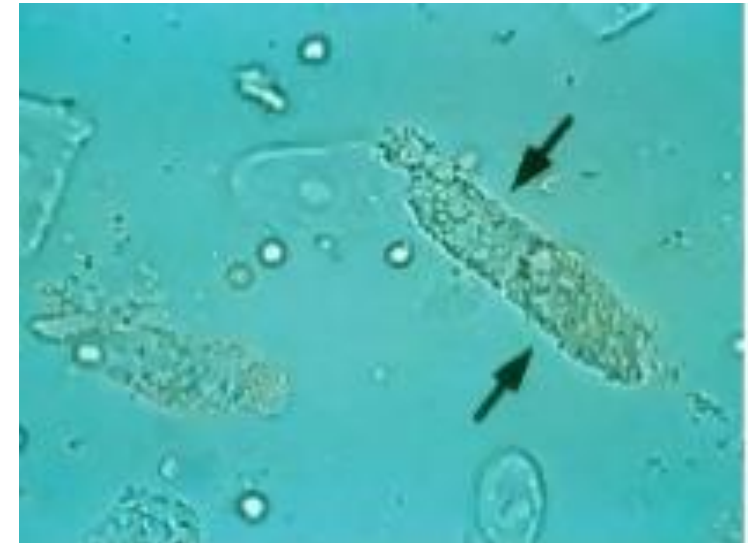
# Acute Tubular Necrosis

- Sudden damage to **tubular epithelial cells**
  - Ischemia (ANY cause severe ↓ blood flow)
  - Drugs
  - Toxins
- Cause **acute kidney injury**



# Acute Tubular Necrosis

- Tubular epithelial cells die, slough off into urine
- Obstructs urine flow → **intrinsic renal failure**
  - ↓ GFR
  - ↑ BUN and Cr
- Epithelial cells form **casts in tubules**
  - Granular casts
  - “Muddy brown”




Anwar Siddiqui

# Acute Tubular Necrosis

## Phases

- Oliguric phase
  - Oliguria
  - Rising BUN/Cr
  - **Hyperkalemia**
  - AG metabolic acidosis
  - May last weeks
- Polyuric phase
  - Polyuria
  - Recovery
  - Risk of **hypokalemia**

1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca



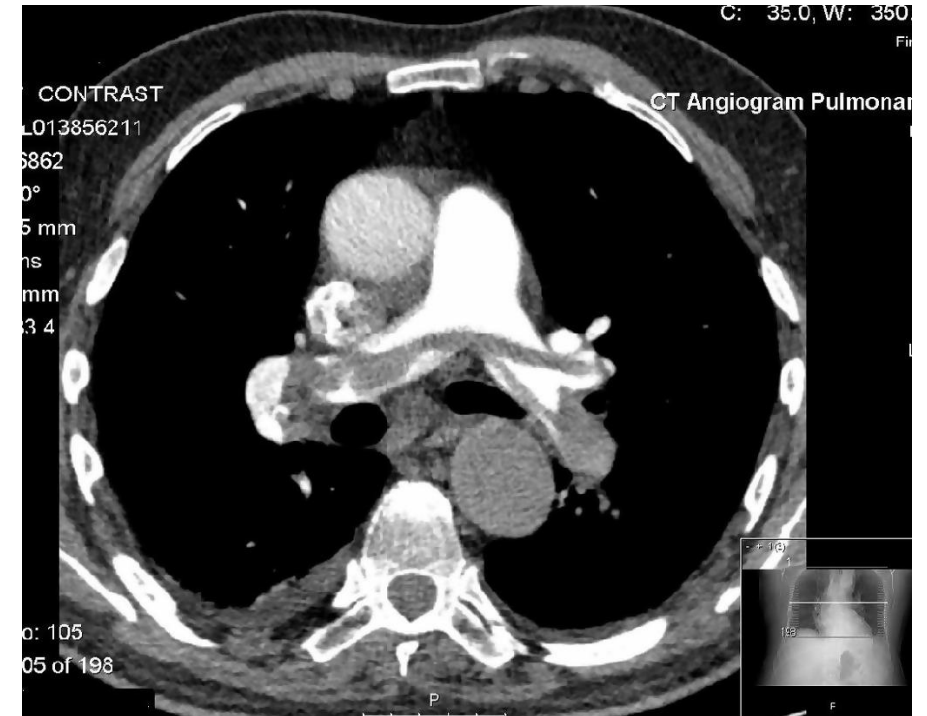




# Acute Tubular Necrosis

## Contrast-Induced ATN

- May cause ATN within 24 hours after exposure
  - Usually non-oliguric
- Risk factors: CKD and diabetes
- ATN mechanisms:
  - Direct toxicity
  - Spasm of afferent arteriole
- **Unusual urinary findings**
  - Similar to pre-renal AKI
  - $\text{FeNa} < 1\%$



Wikipedia/Public Domain

# Acute Tubular Necrosis

## Contrast-Induced ATN

- Prevention: **saline hydration before contrast**



# Acute Tubular Necrosis

## Drugs

- **Antibiotics:** vancomycin, aminoglycosides, amphotericin
- Other drugs: cisplatin, acyclovir, cyclosporine
- Slow onset ATN: **Usually 5 to 10 days**
- Dose-dependent

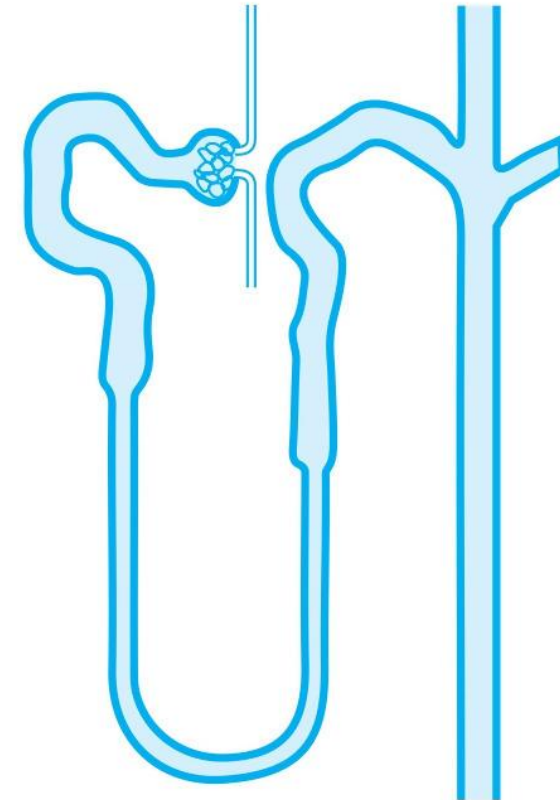


Public Domain

# Acute Tubular Necrosis

## Treatment and Prognosis


- Treatment: supportive
- Some patients require temporary dialysis
- Kidney function usually recovers
- Tubular cells capable of regeneration
  - “Tubular re-epithelialization”
- Unhelpful treatments:
  - Diuretics
  - Steroids
  - Low-dose dopamine



# Magnesium Wasting

- May occur due to ATN
- Causes hypomagnesemia
- Also causes hypokalemia
- **Potassium will not correct if Mg is low**

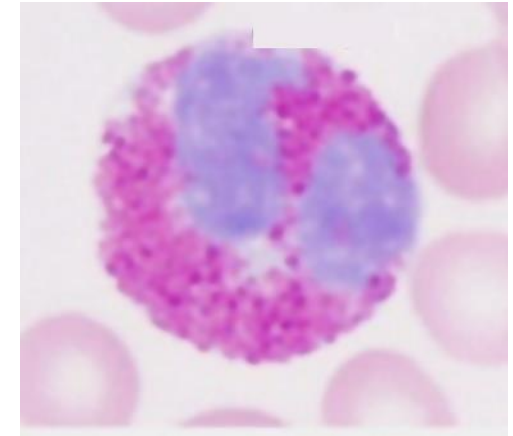
1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca



# Acute Interstitial Nephritis

## Tubulointerstitial Nephritis

- Inflammation of renal tubules and “interstitium”
  - Space between cells
- Hypersensitivity (allergic) reaction
  - Mediated by eosinophils and neutrophils
- Usually triggered by drugs
  - Less commonly infections or autoimmune disease
- Usually resolves with stopping offending agent



# Acute Interstitial Nephritis

## Tubulointerstitial Nephritis

- Main clinical feature is **acute kidney injury**
- Absence of nephritic/nephrotic syndrome
  - Considered a glomerular disease when occur together

Na+	Cl-	<b>BUN</b>	Glucose
K+	HCO <sub>3</sub>	<b>Cr</b>	



# Acute Interstitial Nephritis

## Tubulointerstitial Nephritis

- **Drugs – 75% of cases**
  - Sulfonamides (TMP-SMX)
  - Rifampin
  - Penicillin and cephalosporins
  - Diuretics (furosemide, bumetanide, thiazides)
  - NSAIDs



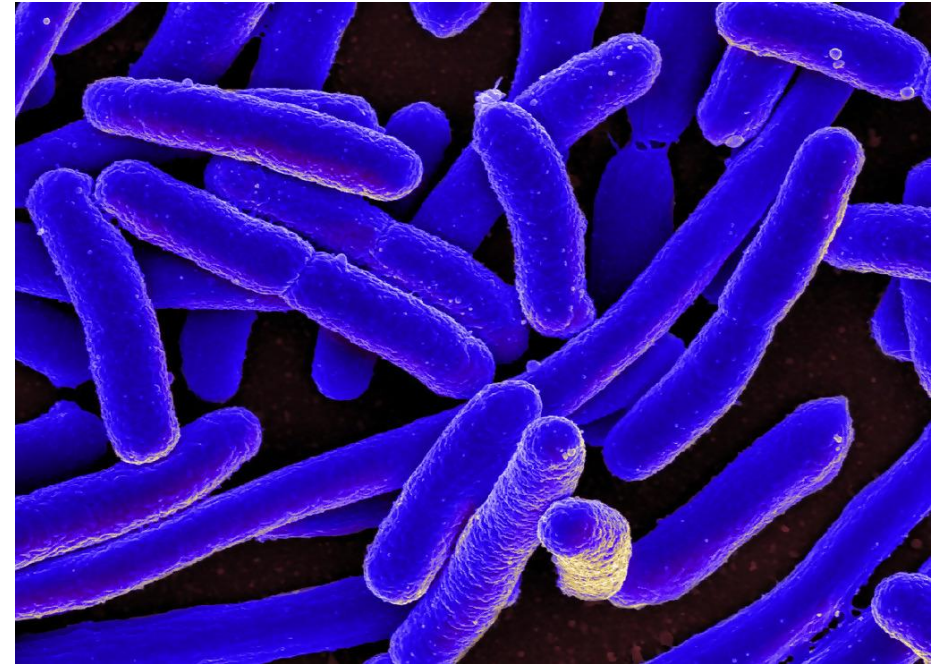
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# Acute Interstitial Nephritis

## Tubulointerstitial Nephritis

- Infection – 5-10% of cases
  - Multiple organisms reported
  - Legionella, Leptospira, CMV, TB
- Systemic diseases – 5-10% of cases
  - Sarcoidosis
  - Sjögren's syndrome
  - SLE

**Bacteria**



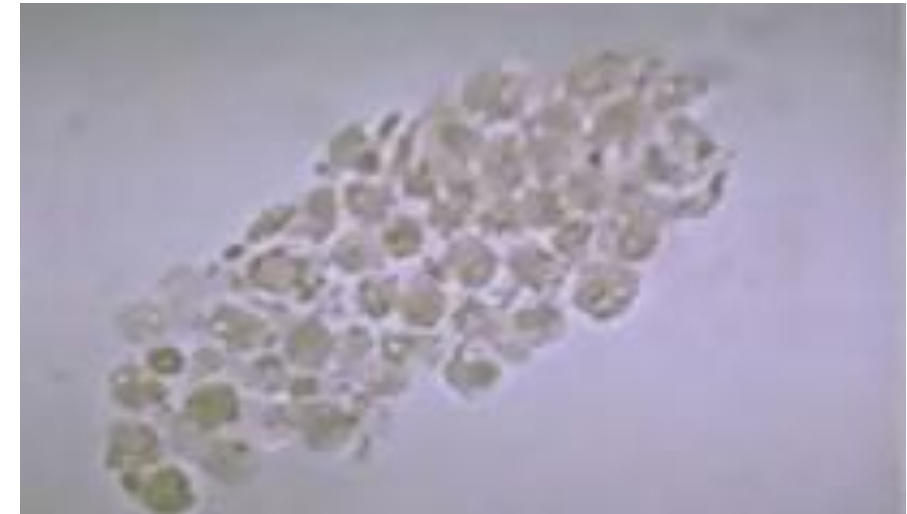
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# Acute Interstitial Nephritis

## Tubulointerstitial Nephritis

- Classic presentation:
  - Exposure to a trigger
  - Fever, rash, malaise
  - Acute kidney injury ( $\uparrow$  BUN/Cr)
  - **WBC casts** (*without* symptoms of cystitis)
  - “Sterile pyuria”
  - Peripheral eosinophilia
  - **Urine eosinophils** (rare)

**WBC Cast**



Anwar Siddiqui

# Acute Interstitial Nephritis

- Usually resolves with **stopping offending agent**
- Rarely steroids required
- Rarely progresses to papillary necrosis



# Chronic Interstitial Nephritis

- Mononuclear cell infiltration
- Fibrosis and atrophy of tubules
- Seen with longstanding use of **NSAIDs**
  - “Analgesic nephropathy”
- Mild elevation of BUN/Cr
- Resolves with stoppage of drugs
- Classic case:
  - Patient on NSAIDs for chronic pain
  - Mild, indolent increase BUN/Cr
  - Renal function improves with stoppage of drug



Wikipedia/Public Domain



# NSAIDs

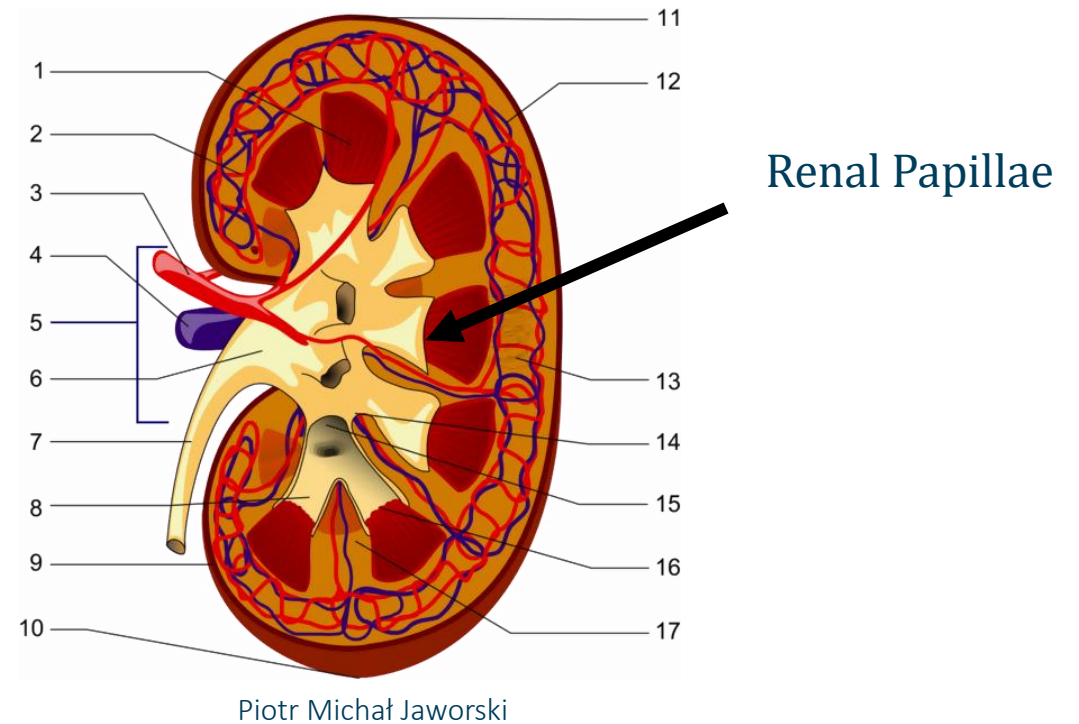
- Acute interstitial nephritis (fever, renal failure)
- Chronic interstitial nephritis (renal failure)
- Acute tubular necrosis
  - Ischemia
  - Block PG-induced vasodilation of afferent arteriole
- Membranous glomerulonephritis
  - Nephrotic syndrome
- Papillary necrosis



Wikipedia/Public Domain

# Renal Papillary Necrosis

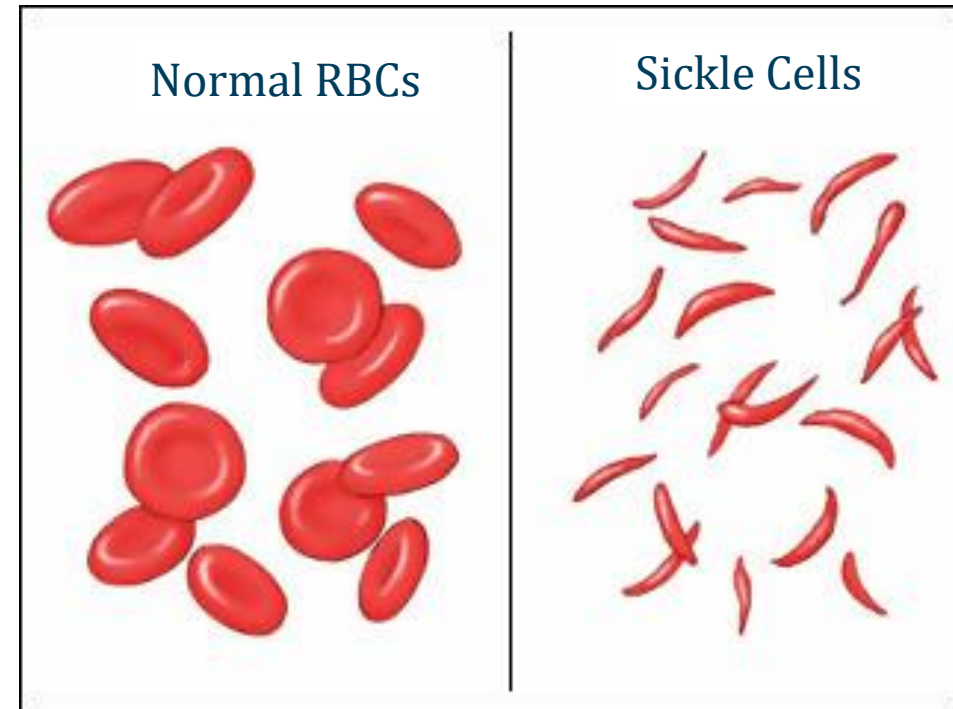
- Necrosis of renal papillae
- Sloughing of tissue
- **Causes gross hematuria**
- May obstruct urine flow → flank pain



# Papillary Necrosis

## Classic Causes

- Chronic NSAID use
- Diabetes
- Sickle cell disease including trait
- Pyelonephritis





# Papillary Necrosis

## Clinical Features

- **Hematuria** and/or **flank pain**
- Typical trigger
- Best initial test: urinalysis
  - White/red cells
  - Necrotic tissue
  - No bacteria
  - No casts
- Diagnosis: urogram or CT scan
  - Visualize necrotic areas
  - Excludes other causes of hematuria

## Hematuria



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# Papillary Necrosis

## Treatment

- Supportive care
- Treat underlying condition

# Renal Tubular Acidosis

Jason Ryan, MD, MPH

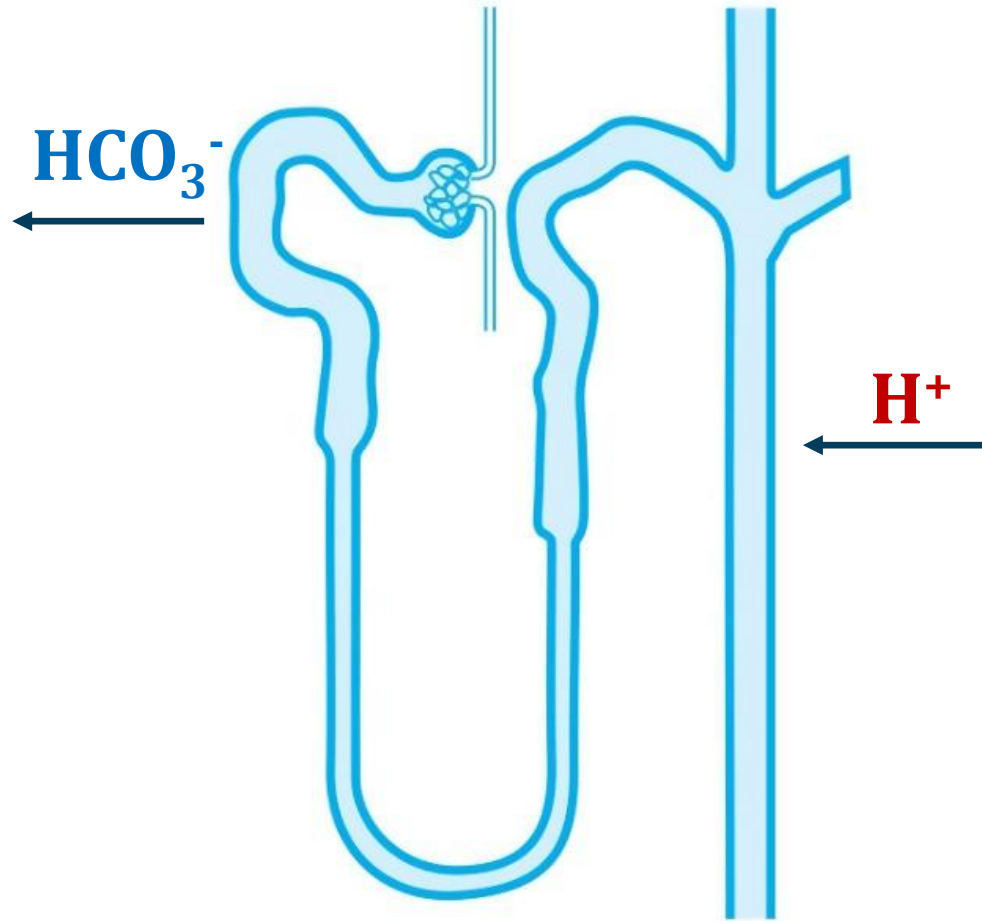


# Renal Tubular Acidosis

- Rare disorders of nephron ion channels
- All cause **non-anion-gap metabolic acidosis**
- Often present with **low  $[\text{HCO}_3^-]$**  or **abnormal  $\text{K}^+$**

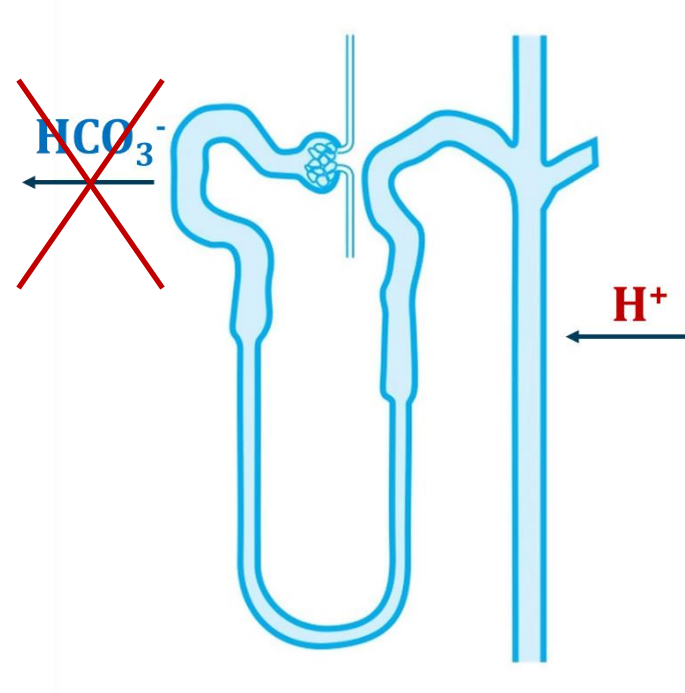
**$\text{pH} < 7.37$**   
 **$\downarrow \text{HCO}_3^-$**

# Renal Acid Handling



# Type II (proximal) RTA

- Defect in proximal tubule  $\text{HCO}_3^-$  resorption
- **Bicarbonate lost in urine**
- New steady state  $[\text{HCO}_3^-]$ 
  - Normal = 24 mEq/L
  - Type II RTA: 12 – 20 mEq/L
- Non-anion gap metabolic acidosis
- Often asymptomatic



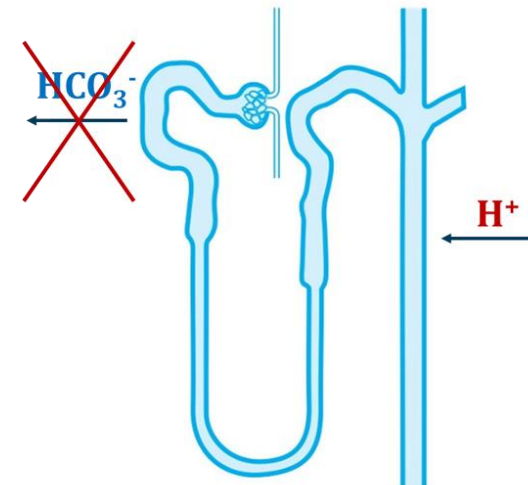
# Type II (proximal) RTA

- **Hypokalemia**

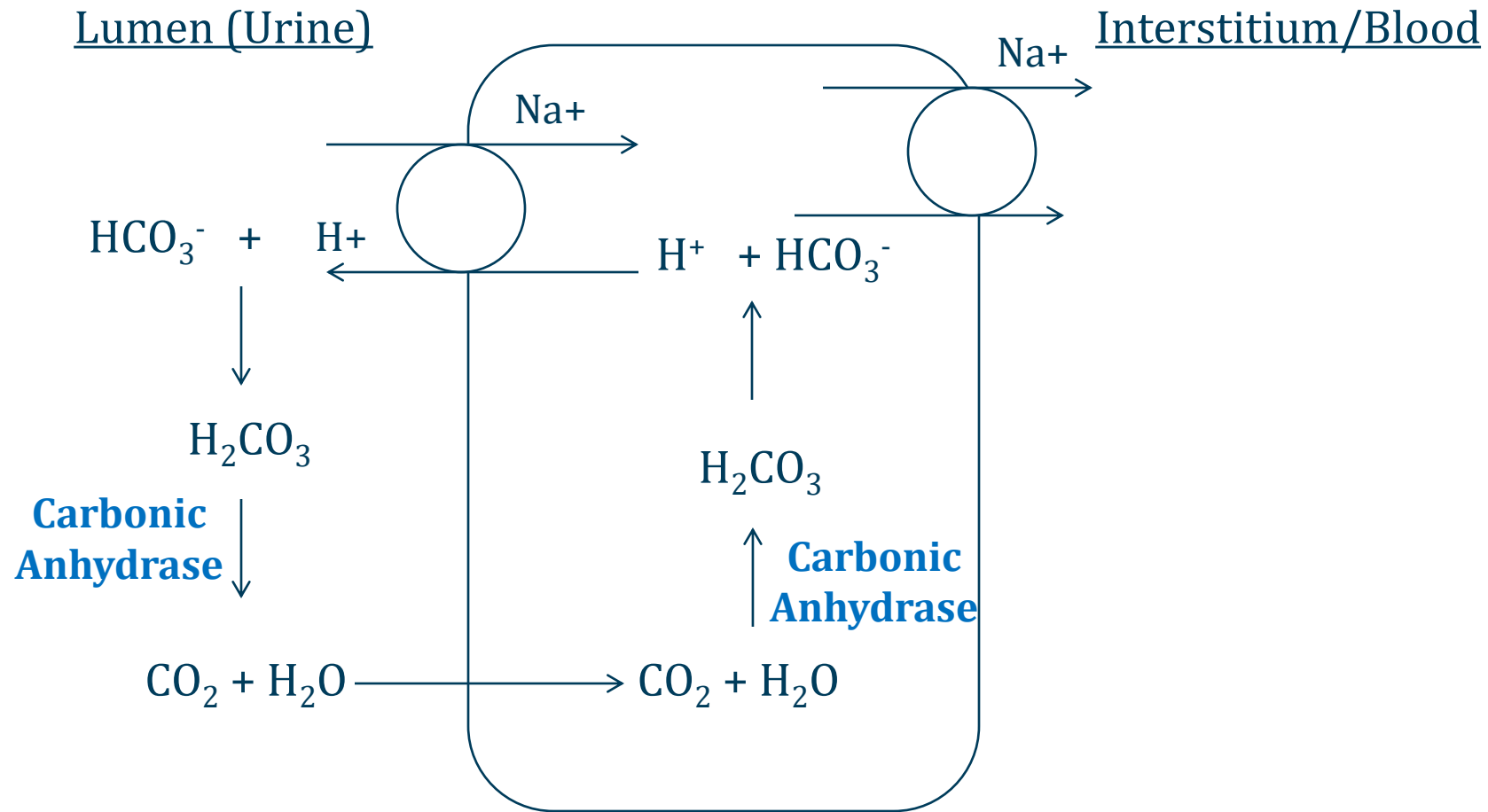
- Loss of  $\text{HCO}_3^-$  resorption  $\rightarrow$  less  $\text{Na}/\text{H}_2\text{O}$  resorption
- Volume contraction  $\rightarrow$  RAAS  $\rightarrow$   $\uparrow$  aldosterone  $\rightarrow$   $\uparrow$  K excretion  $\rightarrow$  hypokalemia

- Urine pH < 5.5 (low)

- Distal tubule excretes  $\text{H}^+$  as acidosis becomes established
- Urine becomes acidic
- Negative urine anion gap
- No kidney stones



# Bicarbonate





# Type II (proximal) RTA

- Milder than type I:  $\text{HCO}_3^-$  12-20
  - Distal intercalated cells function normally
  - Secrete acid to compensate

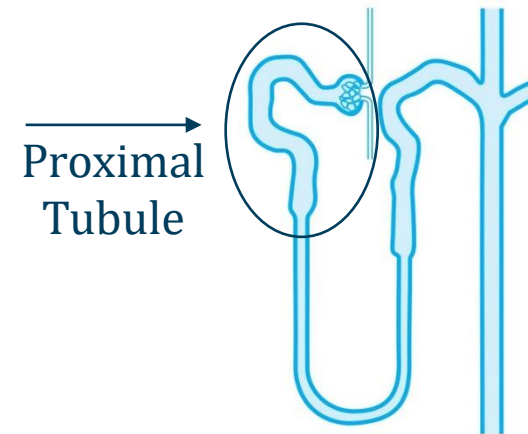
	Normal	Proximal (II)	Distal (I)	Type IV
$\text{HCO}_3^-$ mg/dL	24	12-20	< 10	> 17

# Type II (proximal) RTA

- Sample Case
  - No symptoms : routine blood work
  - Mild weakness (low K)
  - Mildly reduced  $\text{HCO}_3^-$  (12 – 20)
  - Hypokalemia
  - Urine pH is low (< 5.3)
- Treatment: Sodium bicarbonate

# Type II (proximal) RTA

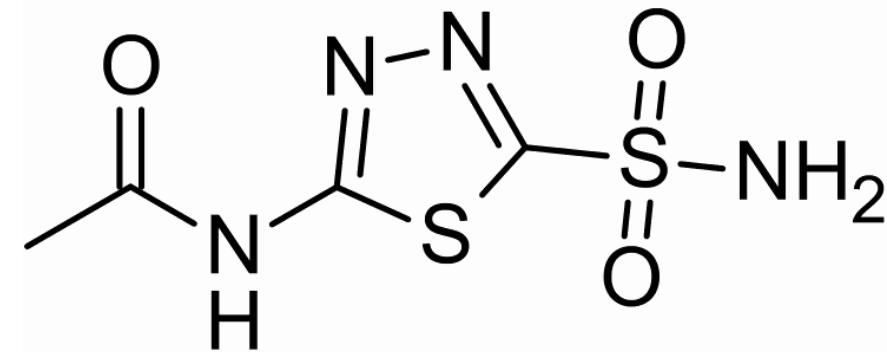
- Can be seen with **Fanconi syndrome**
  - Generalized failure of proximal tubule
  - Urine loss of phosphate, glucose, amino acids, urate, protein
  - Inherited cases in children
  - Drug causes: tenofovir (HIV) and ifosfamide (alkylating agent)
- Can be seen in **multiple myeloma**
  - Some forms of light chains toxic to proximal tubule
  - May cause Fanconi syndrome
- Heavy metal poisoning
  - Lead, cadmium and mercury



# Type II (proximal) RTA

## Drug Causes

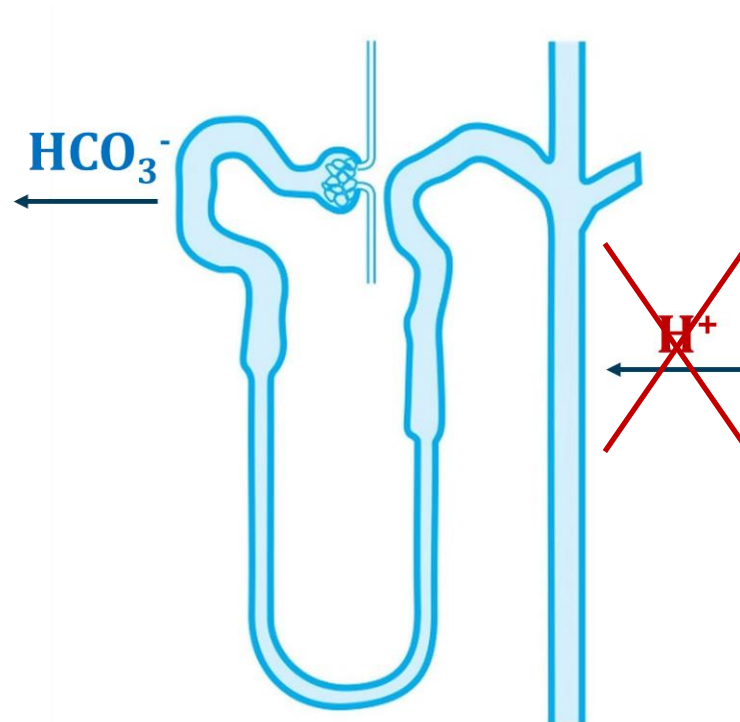
- Acetazolamide
  - Carbonic anhydrase inhibitor
  - Weak diuretic effect
  - Block some Na resorption
  - Causes increased elimination of  $\text{HCO}_3^-$
- **Topiramate (anti-seizure)**
  - Carbonic anhydrase inhibiting effects



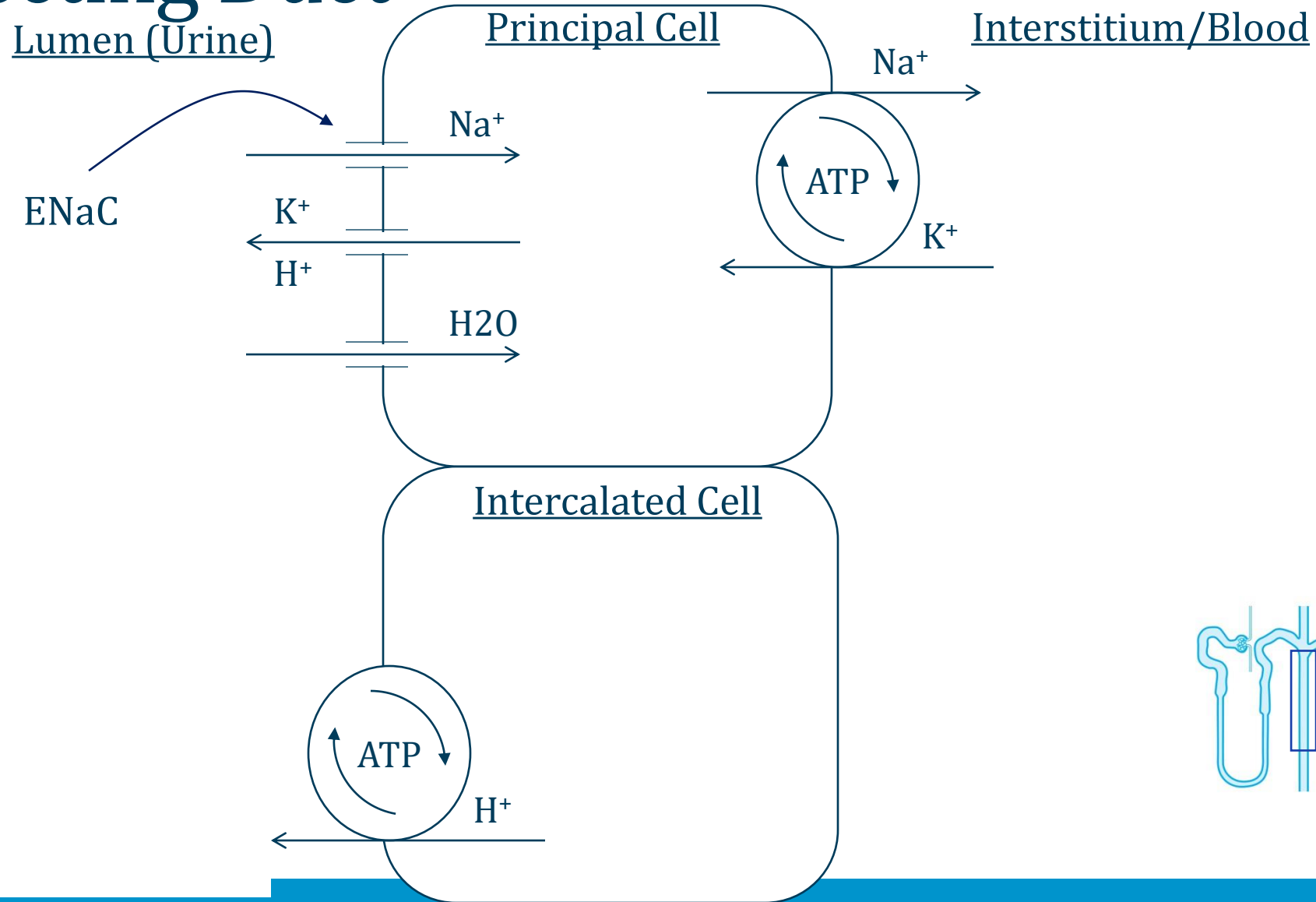
Acetazolamide

# Type I (distal) RTA

- Impaired **acidification of urine** by distal nephron
- Non-anion gap metabolic acidosis
- ↓ excretion  $\text{H}^+$  (acidemia)
- ↑ excretion  $\text{K}^+$  (hypokalemia)



# Collecting Duct

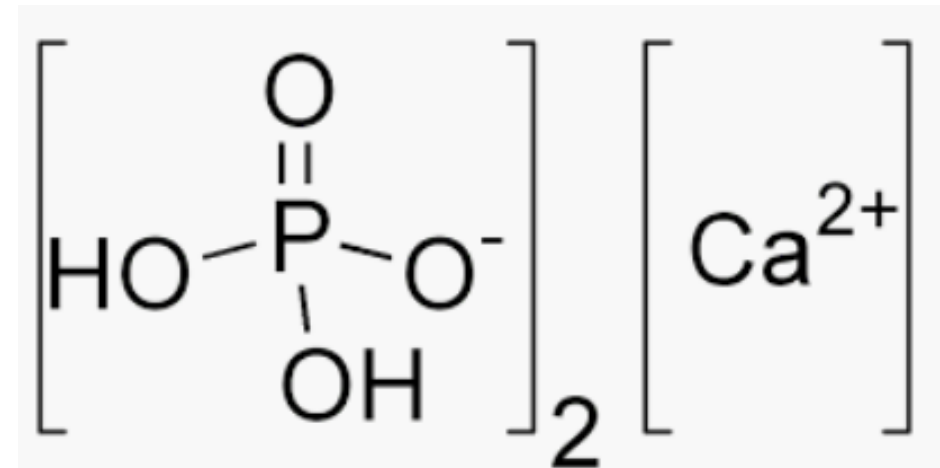


# Type I (distal) RTA

- **Very low  $\text{HCO}_3^-$  (often  $< 10 \text{ meq/L}$ )**
- Hypokalemia
- Urine pH is high
  - Distal tubule cannot “acidify” the urine
  - Urine is alkaline
- Diagnosis established if:
  - Alkaline urine ( $\text{pH} > 5.5$ )
  - Despite a metabolic acidosis (with normal kidneys)

# Type I (distal) RTA

- Key symptoms: **chronic kidney stones**
  - **Calcium phosphate** stones
  - Alkaline urine precipitates stones (sometimes bilateral)
  - Acidosis suppresses calcium resorption ( $\uparrow$ Ca in urine)
- Rickets and osteoporosis
  - Acidosis  $\rightarrow$   $\uparrow$  Ca from bones
  - Growth failure in children



**Calcium Phosphate**



# Type I (distal) RTA

- Many etiologies
- Associated with **autoimmune diseases**
  - Sjögren's syndrome
  - Rheumatoid arthritis
- Medications
  - Amphotericin B
- Rare genetic forms

# Urine Anion Gap

- Used for diagnosis of metabolic acidosis
- Evaluation of **renal acid excretion**
- In acidosis, excess  $\text{NH}_4$  excreted (removes  $\text{H}^+$ )
- $\text{NH}_4$  not measured directly
- Surrogate: **urinary anion gap**
- $\text{NH}_4$  leaves with  $\text{Cl}$
- **Negative** UAG when acid ( $\text{H}^+$ ) being excreted
- UAG should be negative in acidosis

$$\text{UAG} = \text{Na} + \text{K} - \text{Cl}$$

# Urine Anion Gap

- In GI metabolic acidosis (diarrhea):
  - UAG becomes **negative**
  - Excretion of  $\text{NH}_4$  with Cl increases
  - Urine Cl concentration goes up
- Also negative in proximal (type II) RTA
  - Intact distal  $\text{H}^+$  secretion intact

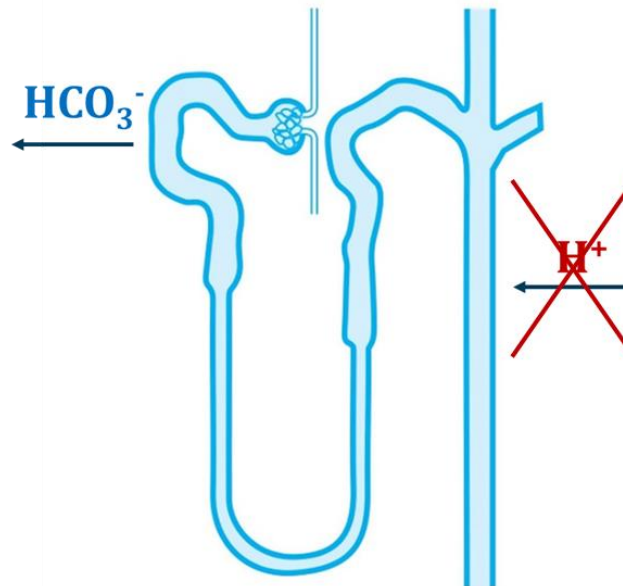
$$\text{UAG} = \text{Na} + \text{K} - \text{Cl}$$

**neGUTive in GI**

# Urine Anion Gap

$$\text{UAG} = \text{Na} + \text{K} - \text{Cl}$$

- In distal RTA and type IV RTA UAG is **positive**
  - Kidneys can't excrete  $\text{H}^+$
  - $\text{NH}_4$  and  $\text{Cl}^-$  don't increase
  - $\text{UAG} (\text{Na} + \text{K} - \text{Cl})$  does not become negative



# Ammonium Chloride Challenge

- Used for diagnosis of metabolic acidosis
- “Challenge” patient with  $\text{NH}_4\text{Cl}$
- Gives an acid load
- Should lower urine pH
- In distal RTA, **urine pH remains >5.3**

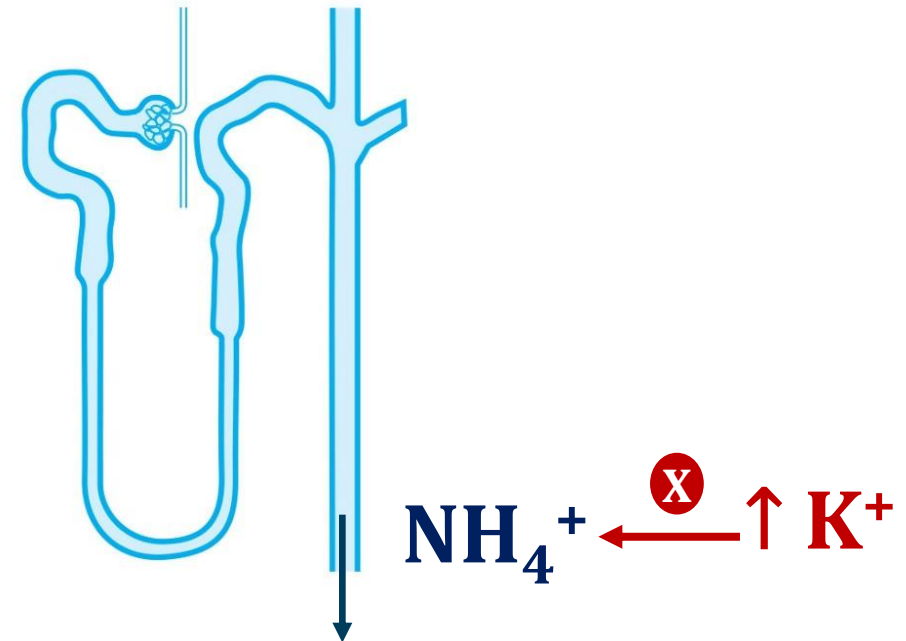


# Type I (distal) RTA

- Classic case
  - Patient with Sjogren's disease
  - Recurrent kidney stones
  - Very low bicarb on blood work ( $< 10$ )
  - Hypokalemia
  - Urine pH is high ( $> 5.5$ )
  - UAG is positive
  - If given  $\text{NH}_4\text{Cl}$  urine remains with high pH
- Treatment: Sodium bicarbonate

# Type IV RTA

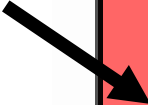
- Major feature: **hyperkalemia**
- Major pathologic defect: **decreased  $\text{NH}_4^+$  excretion**
  - Potassium suppresses proximal tubule ammonia production
  - Low urinary pH (<5.3)
- **Hyperkalemia**  $\rightarrow$   $\downarrow$  ammonium
- Mild non-anion gap metabolic acidosis
  - $\text{HCO}_3^- > 17$  (normal = 24)



# Type IV RTA

- **Hyporeninemic hypoaldosteronism**
  - Low renin activity
  - Decreased aldosterone production → hyperkalemia
  - Diabetes (associated with low renin production)
  - NSAIDs (impair renin release)
  - Other drugs

1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca

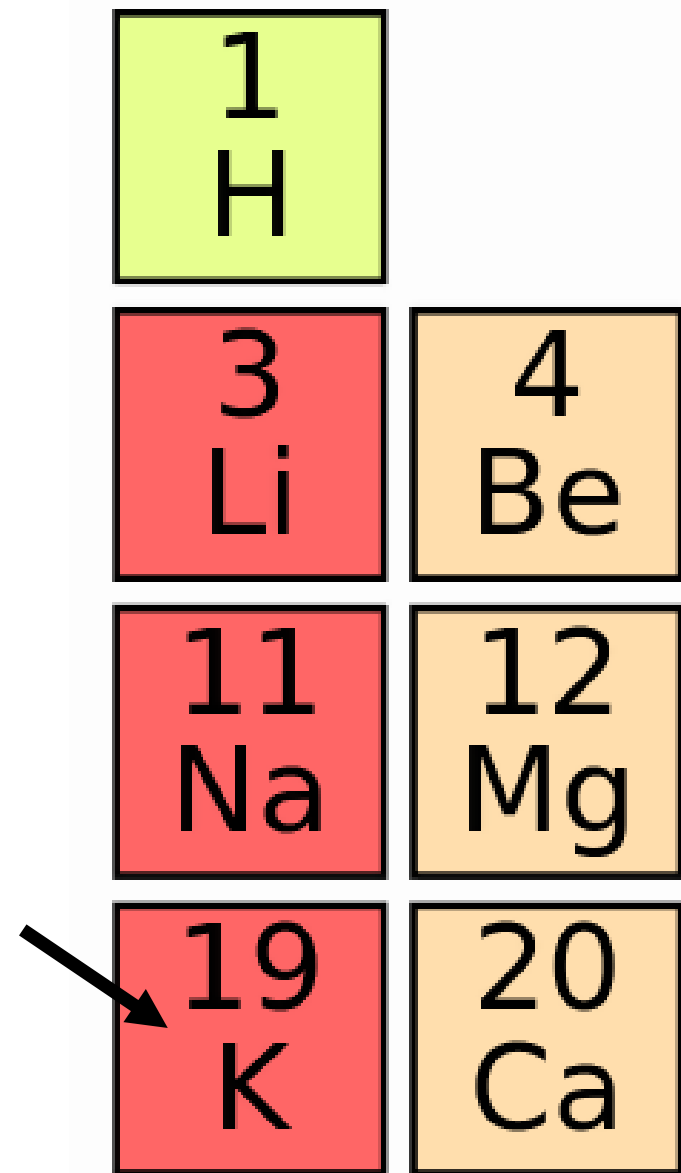




# Type IV RTA

- **RAAS drugs** (↓ aldosterone)
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Angiotensin II receptor blockers (ARBs)
  - Direct renin inhibitors (Aliskiren)
  - All cause hyperkalemia

1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca



# Type IV RTA

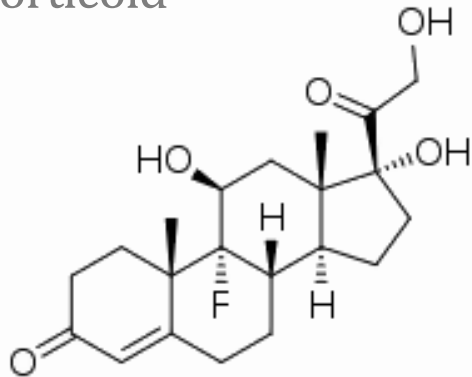
- **Aldosterone resistance**
  - Usually caused by drugs that inhibit tubular function
  - Potassium-sparing diuretics
  - TMP/SMX



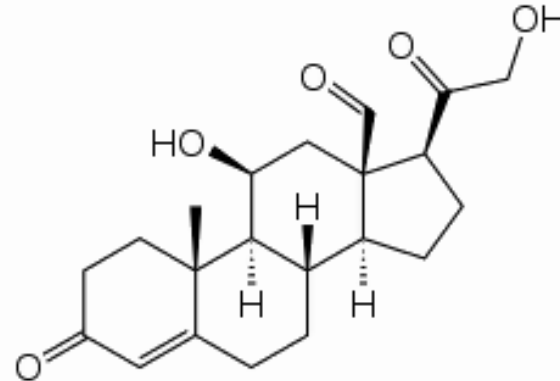
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# Type IV RTA

- Classic case:
  - Diabetic with renal insufficiency
  - Unexplained hyperkalemia
- Treatment usually aimed at potassium
- Hyporeninemic hypoaldosteronism treated with **fludrocortisone**
  - Mineralocorticoid



Fludrocortisone



Aldosterone

# Renal Tubular Acidosis

Type	Key Features
I	Distal; High urine pH; kidney stones; very low HCO <sub>3</sub> -
II	Proximal; mild acidosis; Fanconi's
IV	Aldosterone; hyperkalemia; ammonium

Type	Plasma K <sup>+</sup>	Urine pH
I	Low (< 3.5)	High (> 5.4)
II	Low (< 3.5)	Low (< 5.4)
IV	High (> 5.0)	Low (< 5.4)

# Cystic Kidney Disease

Jason Ryan, MD, MPH



# ADPKD

## Autosomal Dominant Polycystic Kidney Disease

- Microscopic cysts present at birth
  - Too small to visualize with ultrasound
  - Kidneys appear normal at birth
- Cysts develop over many years
- Presents in adulthood
- Inherited mutation of **APKD1 or APKD2 genes**

# ADPKD

## Autosomal Dominant Polycystic Kidney Disease

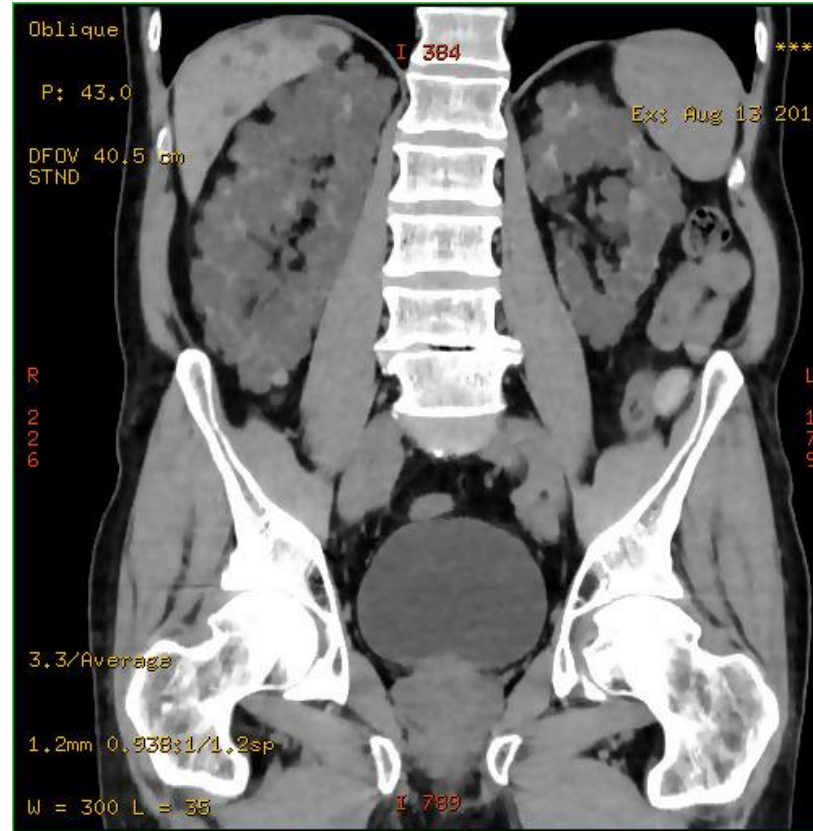
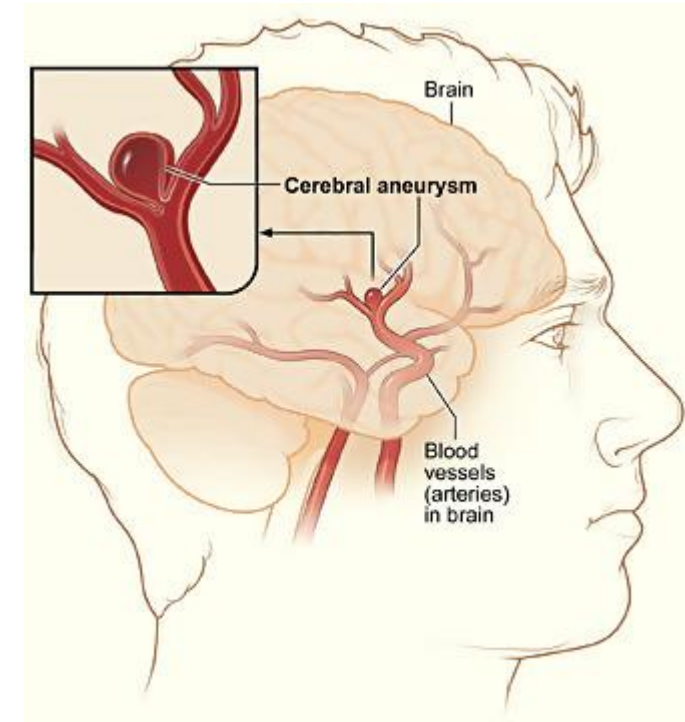


Image courtesy of Hg6996

# ADPKD

## Autosomal Dominant Polycystic Kidney Disease

- Many non-renal associated conditions
- Berry aneurysm (subarachnoid hemorrhage)
- Liver cysts
- Mitral valve prolapse



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# ADPKD

## Autosomal Dominant Polycystic Kidney Disease

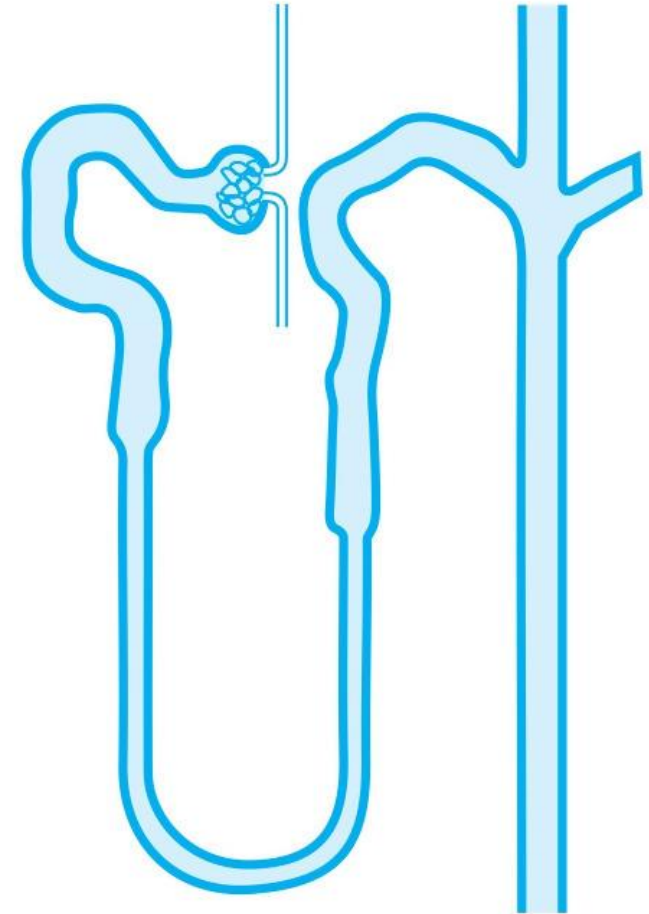
- Classic presentation
  - **Young adult**
  - **High blood pressure** (↑ RAAS system)
  - Hematuria
  - Renal failure
  - Family history of sudden death (aneurysm)
- Diagnosis: **renal ultrasound**



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# Tolvaptan

- **Vasopressin V2-receptor (V2R) antagonist**
- Blocks vasopressin action on cysts
- Slows expansion of cysts
  - Lower total kidney volume in clinical trials
- Slows decline in GFR
- Used in patients at high risk for ESRD
- Contraindicated with abnormal serum sodium



# Renal Cysts

- Often identified on imaging
- Categorized as **simple or complex**
- Simple cysts: benign
  - Commonly found in normal kidneys
  - Usually asymptomatic lesions
  - Rarely require treatment
- Complex cysts: possibly malignant
  - May require follow-up imaging, biopsy, or excision

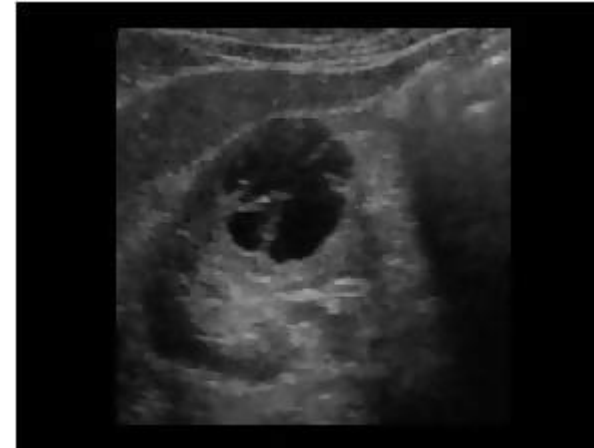


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# Renal Cysts



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Simple Cysts	Complex
Thin-walled Nonseptated Non-enhancing on CT/MRI Homogenous	Thick-walled Irregular, multilocular Enhancing on CT/MRI Heterogeneous

# Nephrolithiasis

Jason Ryan, MD, MPH



# Nephrolithiasis

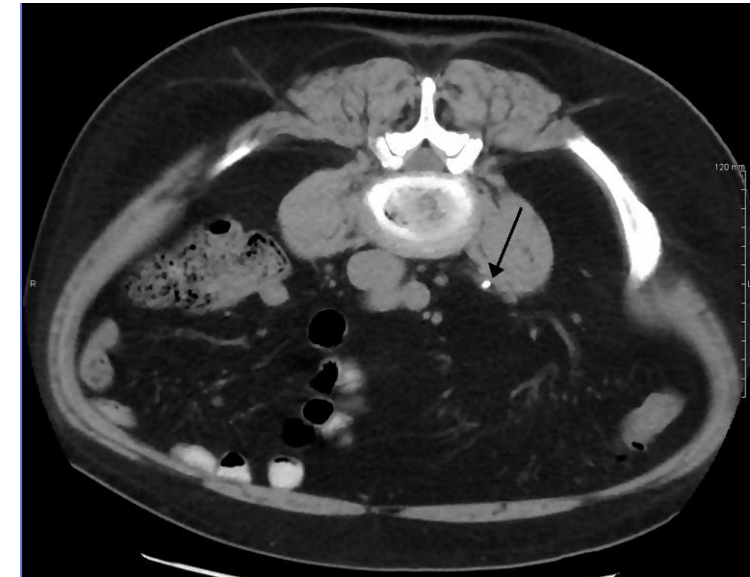
## Kidney Stones

1. Calcium
2. Struvite
3. Urate
4. Cystine

# Nephrolithiasis

## Symptoms and Diagnosis

- Flank pain (side between the ribs and the hip)
  - Stone in upper ureter or renal pelvis
- Pain radiating to groin/inner thigh/testicle
  - Stone in lower ureter or vesicoureteral junction
- Colicky (waxes and wanes in severity)
- Hematuria
- Best initial test: **noncontrast CT scan**



James Heilman, MD

# Nephrolithiasis

## Symptoms and Diagnosis

- Best initial test in pregnancy: **abdominal ultrasound**
  - Detects hydronephrosis
  - Also used when CT scan not available
- Abdominal X-ray (KUB)
  - Rarely used
  - Cannot detect hydronephrosis
  - Misses uric acid stones and small stones
- Other rarely used tests
  - IV pyelogram
  - MRI

## Hydronephrosis



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# Nephrolithiasis

## General Risk Factors

- High amount of stone substance in blood
  - Hypercalcemia
  - Hyperuricemia
- Low urine volume
  - Increases concentration of urine substances
  - Low fluid intake
  - Diuretics
- In general, hydration lowers risk of stones

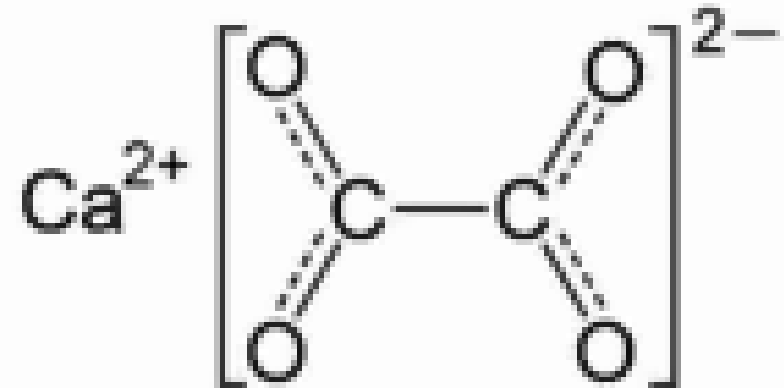


Pixabay/Public Domain

# Calcium Stones

- **Calcium oxalate** (most common)
- Calcium phosphate (~ 5%)
- Most common type of kidney stone (80%)
- Key risk factors
  - Hypercalcemia
  - High oxalate levels
- Radiopaque
  - Visible on X-ray and CT scan

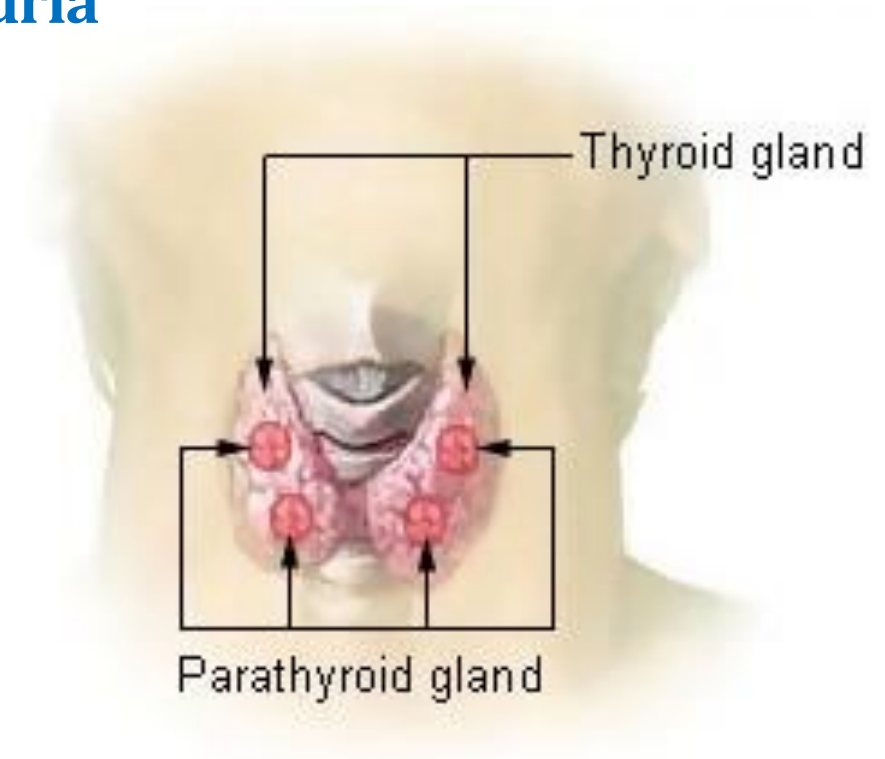
## Calcium Oxalate



# Calcium Stones

## Risk Factors

- Most common etiology: **idiopathic hypercalciuria**
  - Increased urinary calcium levels
- Hypercalcemia (hyperparathyroidism)
- Type I (distal) RTA
  - Alkaline urine
  - Calcium phosphate stones



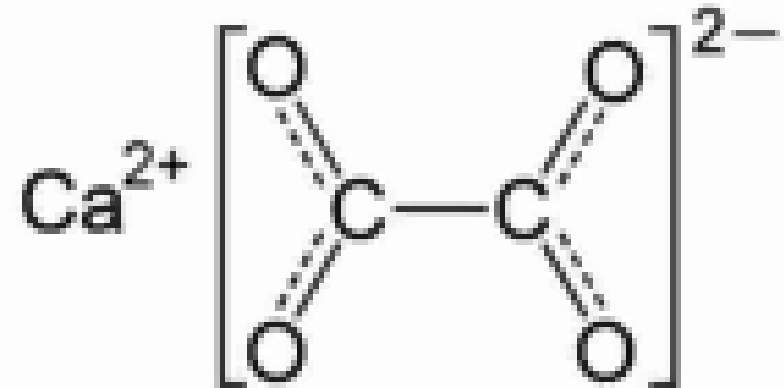
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# Calcium Stones

## Risk Factors

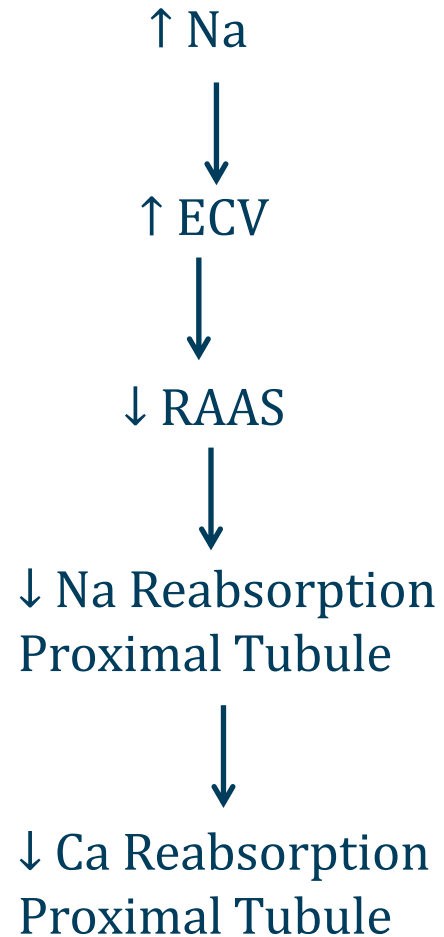
- **High oxalate levels**
  - Crohn's disease, gastric bypass patients
  - Fat malabsorption
  - Fat binds to calcium
  - Oxalate free to be absorbed
- Ethylene glycol (antifreeze)
  - Formation of oxalate
  - Increases oxalate concentration in urine
- Vitamin C abuse
  - Oxalate generated from metabolism of vitamin C

## Calcium Oxalate



# Calcium Stones

## Dietary Sodium



**More Na = More Ca Urine**  
**High Na diet = Stone formation**  
**Low Na diet = Treatment stones**

# Calcium Stones

## Classic Case

- Patient drinking less water
- Colicky flank pain, hematuria
- Calcium stone on CT scan
- Normal Ca level in plasma
- Increased calcium level in urine

# Calcium Stones

## Treatment

- **Fluids and pain control (usually NSAIDs)**
- Most stones pass on their own
- Large stones that do not pass require surgery
- Nifedipine and tamsulosin: **antispasmodics**
  - Used for larger stones
  - Cause relaxation of smooth muscle in ureters
  - Nifedipine: dihydropyridine calcium channel blocker
  - Tamsulosin: alpha-blocker



# Calcium Stones

## Treatment

- Lithotripsy: shock waves break up stones to allow passage

Stone Size	Treatment
$\leq 5$ mm	Pain control, fluids
5 – 10 mm	Fluids, pain control, antispasmodics +/- lithotripsy
$> 10$ mm	Lithotripsy

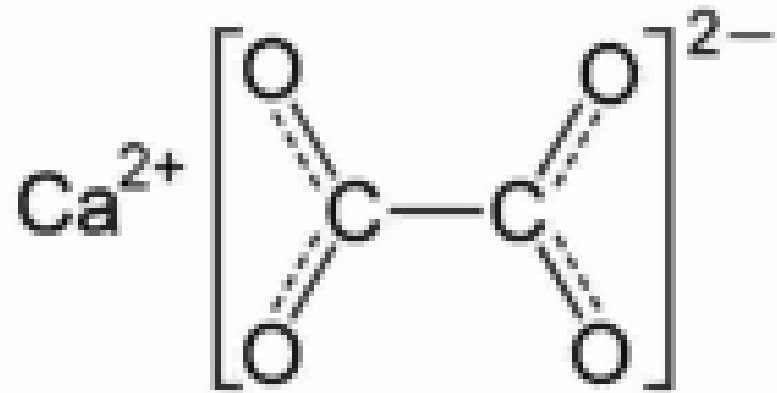


# Recurrent Calcium Stones

## Treatment

- Dietary modifications
  - Increased fluid intake
  - Limit sodium intake
  - Limit oxalate intake
  - Avoid excess vitamin C
- Calcium restriction not recommended

### Calcium Oxalate



# Recurrent Calcium Stones

## Treatment

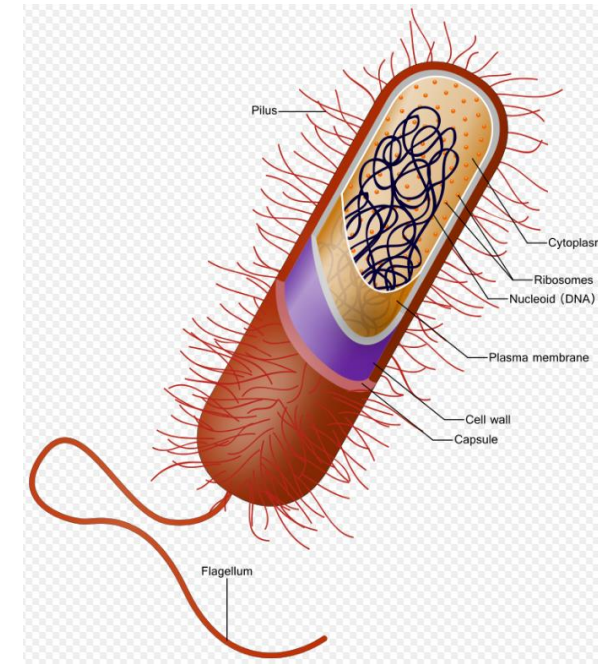
- Thiazides
  - Decrease Ca in urine
- Citrate (potassium citrate)
  - Binds with calcium but remains dissolved
  - Lowers urinary Ca available for stones
  - Inhibits of stone formation
  - Can also eat more fruits and vegetables



Public Domain

# Struvite Stones

- Ammonium-Magnesium-Phosphate stones
- 2<sup>nd</sup> most common stone type (15%)
- Consequence of **urinary tract infection**
  - Require ammonia plus high pH
- Urease-positive bacteria
  - Usually Proteus or Klebsiella
  - Hydrolyze urea to ammonia
  - Urine becomes alkaline



Wikipedia/Public Domain



# Struvite Stones

- Can form **“staghorn calculi”**
  - Stones form a cast of the renal pelvis and calices
  - Looks like horns of a stag
- Won't pass → surgery required
- Untreated → bacterial reservoir
  - Recurrent infection
- Radiopaque
  - Seen on X-ray and CT scan

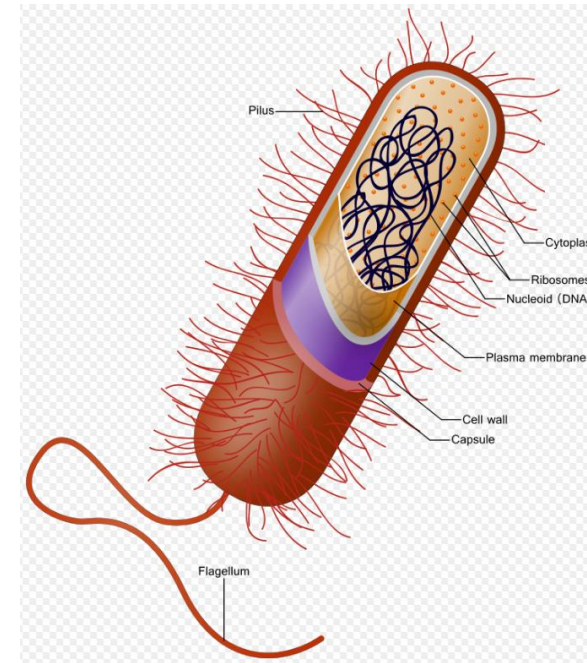


Nevit Dilmen

# Struvite Stones

- Classic presentation
  - UTI symptoms (dysuria, frequency)
  - Mild flank pain
  - Hematuria
  - Large, branching staghorn stone on imaging
- Treatment:
  - Surgery
  - Antibiotics

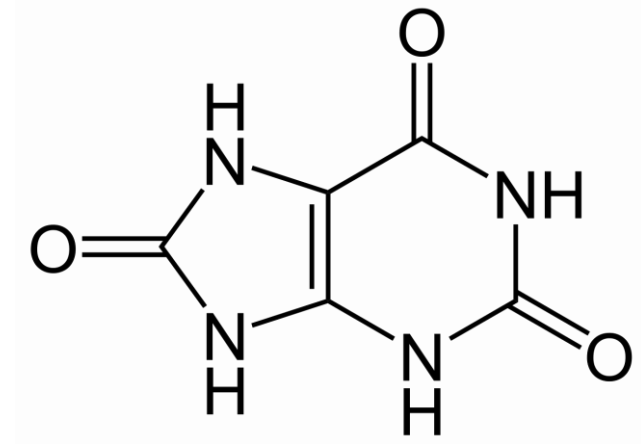
## Bacteria



Wikipedia/Public Domain

# Uric Acid Stones

- Cause by **high uric acid** in urine or **acidic urine**
- $\text{H}^+ + \text{Urate}^- \leftrightarrow \text{Uric acid}$
- Radiolucent stones
  - Not visible on X-ray
  - Can see with CT scan

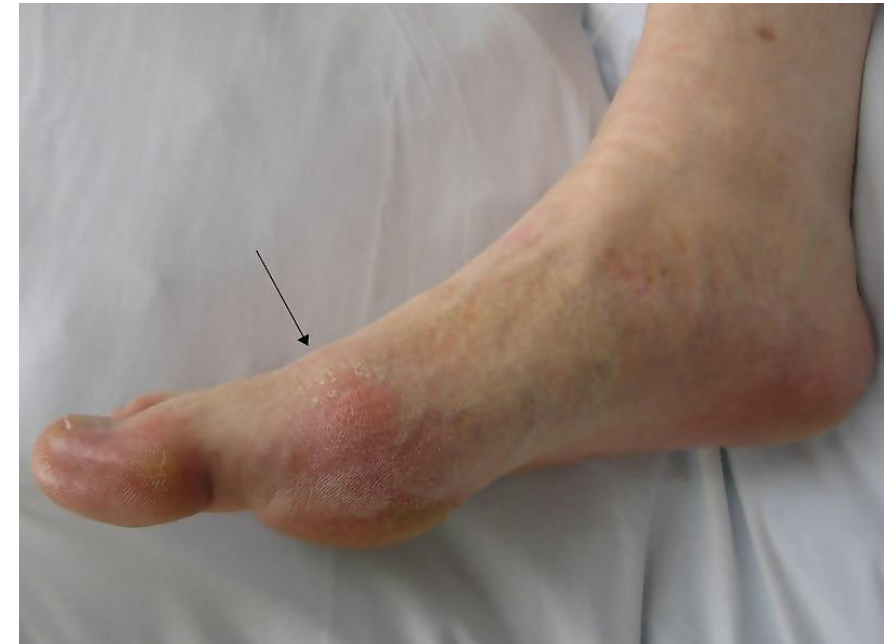


**Uric Acid**

# Uric Acid Stones

## Risk Factors

- High uric acid levels
  - Gout
  - Leukemia
  - Myeloproliferative disease
- Acidic urine (precipitates uric acid)
  - Chronic diarrhea
- More common in **hot, arid climates**
  - Low urine volume, acidic urine more common
  - 5-10% stones in US/Europe
  - 40% stones in other climates



James Heilman, MD/Wikipedia

# Uric Acid Stones

## Treatment

- Hydration
- **Alkalization of urine**
  - Potassium bicarbonate
- Rarely allopurinol
  - Xanthine oxidase inhibitor
  - Reduces uric acid production
- Medical therapy often effective
- Usually does not require surgery



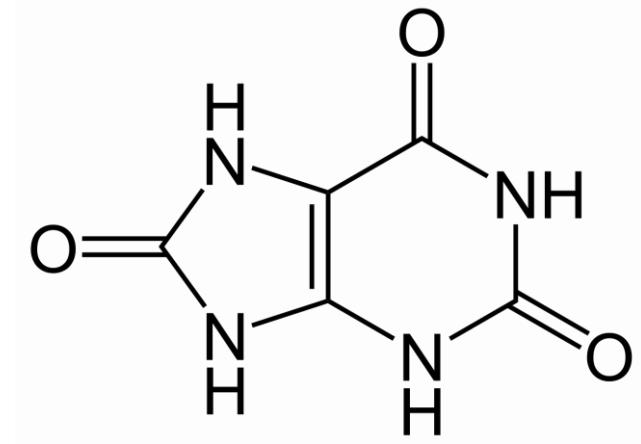
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# Uric Acid Stones

## Classic Case

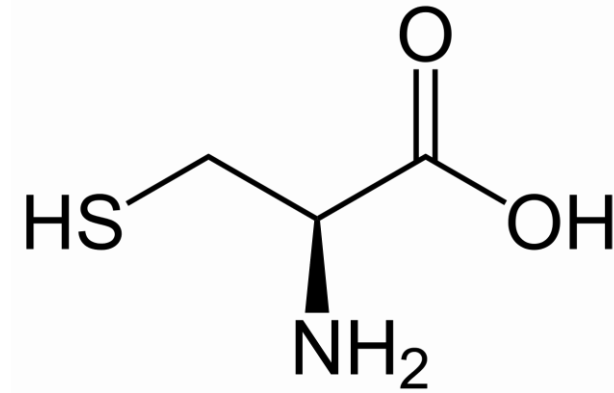
- Flank pain, hematuria
- No stone on X-ray
- Gout, leukemia, myeloproliferative disease
- **Choose medical therapy, not surgery**



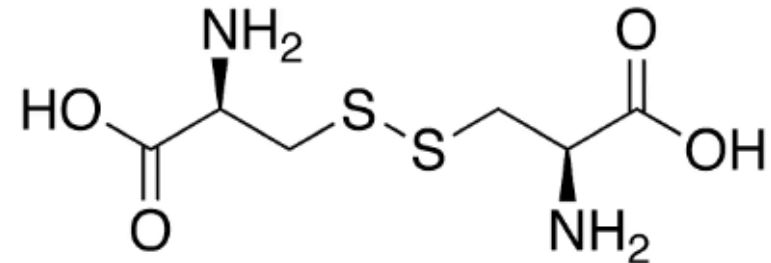
**Uric Acid**

# Cystine Stones

- Rare type of stone
- Seen in children with **cystinuria**
  - Tubular defect → cannot absorb cysteine
  - Only clinical manifestation is kidney stones
- Radiolucent (like uric acid)
  - Not visible on X-ray
  - Can see with CT scan



**Cysteine**



**Cystine**

# Cystine Stones

- Classic case
  - Child with recurrent stones
  - Family history kidney stones
  - Urine with “rotten egg” odor
  - Hexagonal cystine crystals in urine sediment
- Diagnosis: sodium cyanide-nitroprusside test
- Treatment:
  - Hydration and **alkalinization of urine (↑ solubility)**



Wikipedia/Public Domain

# Urinary Incontinence

Jason Ryan, MD, MPH



# Urinary Incontinence

- **Involuntary loss of urine**
- Common among older patients
- Three major patterns:
  - Urge incontinence
  - Stress incontinence
  - Overflow incontinence

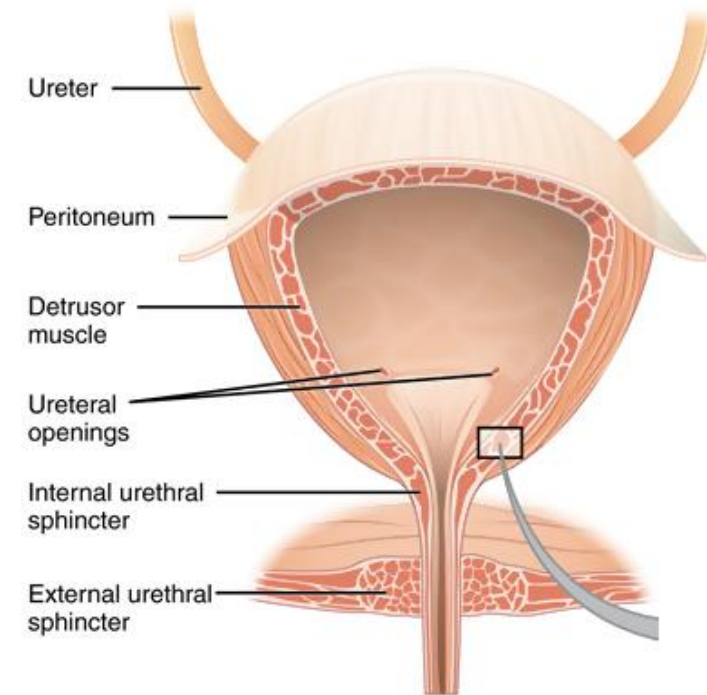


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# Urge Incontinence

## Overactive Bladder

- **Urge to void accompanied by loss of urine**
- **Detrusor muscle overactivity**
  - Involuntary contractions during bladder filling
- Diagnosis: clinical



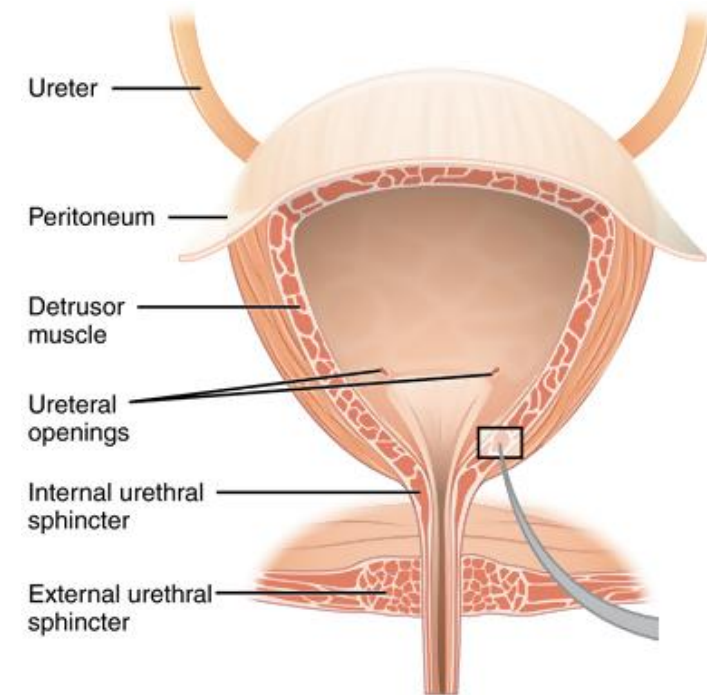
(a)

OpenStax College/Wikipedia

# Urge Incontinence

## Treatments

- **Kegel exercises**
  - Sustained pelvic floor contractions
  - Done several times per day
- Medications
  - Anticholinergics: oxybutynin
- Neurostimulators
  - Implanted devices
  - Sacral nerve



(a)

OpenStax College/Wikipedia

# Stress Incontinence

- **Loss of urine with increased abdominal pressure**
  - Cough, sneeze, heavy lifting, laughing
- Caused by **pelvic floor weakness**
  - Increased pressure → urine forced into urethra
- Associations
  - Obesity
  - Vaginal deliveries



# Stress Incontinence

## Treatment

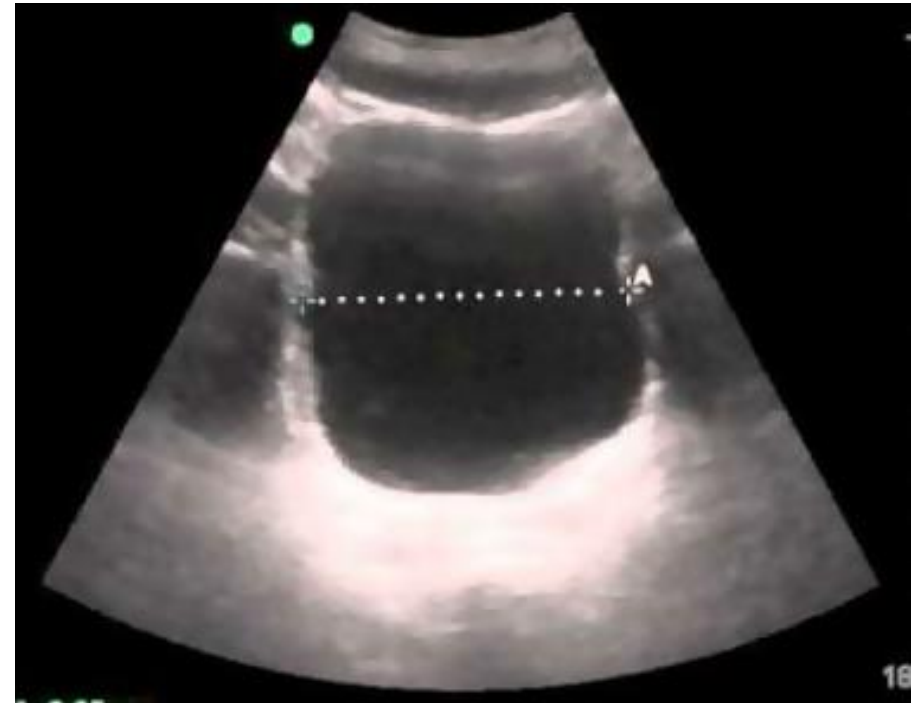
- Kegel exercises
- Topical vaginal estrogen
- Pessary
  - Vaginal support device
- Surgery



Huckfinne/Wikipedia

# Overflow Incontinence

- Associated with urinary retention
- Leakage of urine from full bladder
- Causes
  - Detrusor underactivity
  - Obstruction (men with BPH)
  - Medications (antihistamines, antimuscarinics)
  - Neuropathy (stroke, diabetes)
- Inability to void fully
- Persistent small volume urine loss
- **Elevated post-void residual**

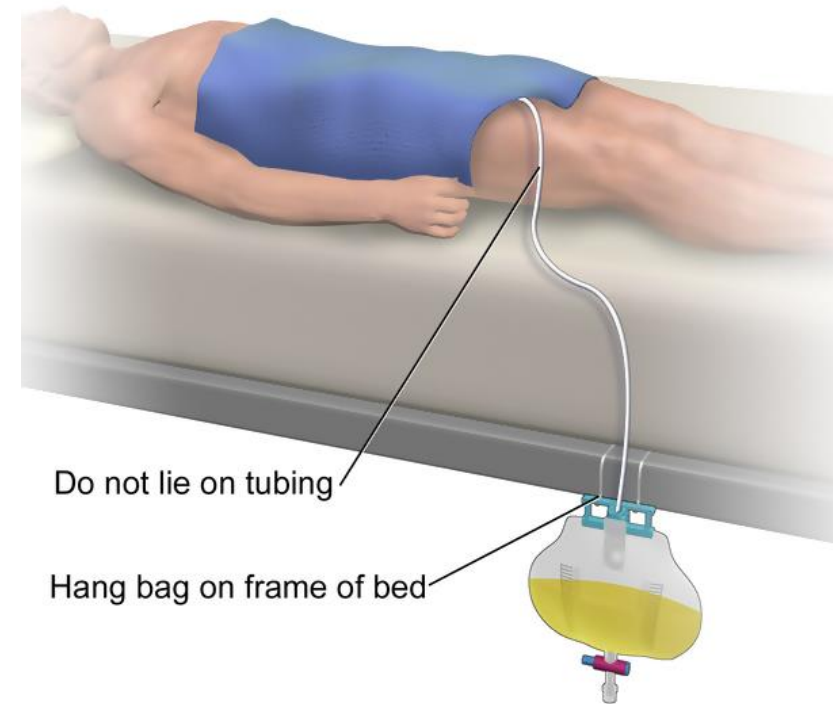


Public Domain

# Overflow Incontinence

## Treatment

- Treat underlying cause
  - Prostate surgery
  - Stop offending medications
- Urinary catheterization
- Medications
  - Cholinergic drugs: bethanechol
  - Alpha-blockers: doxazosin, terazosin
- Surgery
  - Prostate resection



BruceBlaus/Wikipedia

# Incontinence

## Gender Differences

- More common in women until age 80
  - After age 80 both genders equally affected
- Women:
  - Stress or urge incontinence (or mixed)
- Men:
  - BPH → overflow incontinence
  - Weakened pelvic floor → stress incontinence



Flickr/Public Domain

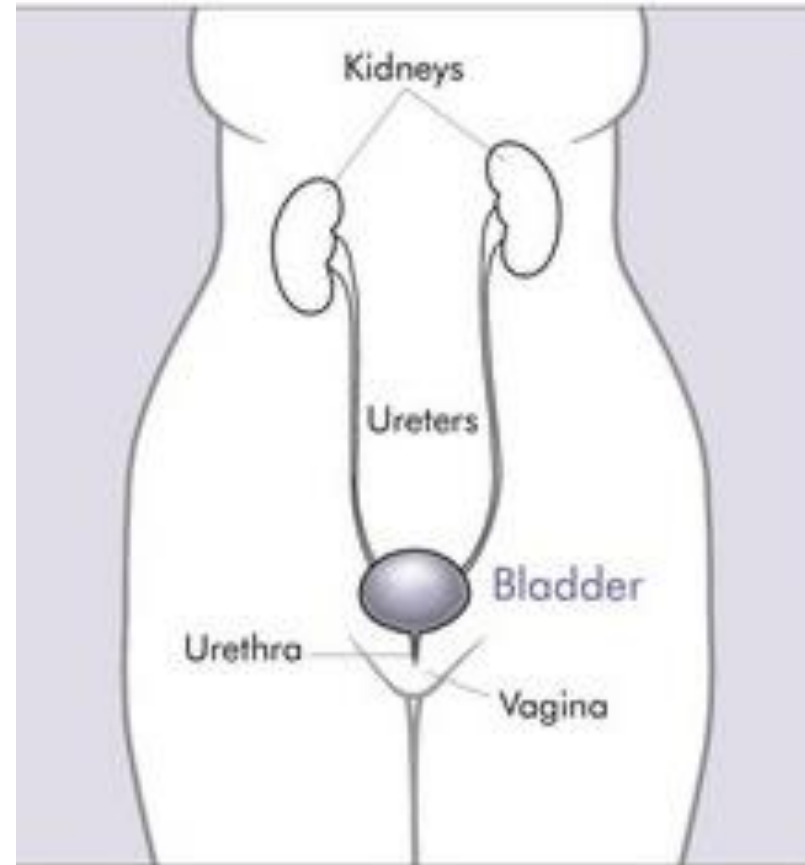
# Urinary Infections

Jason Ryan, MD, MPH



# Urinary Infections

- Cystitis
  - Infection of bladder
  - “Lower” urinary tract
- Pyelonephritis
  - Infection of kidneys
  - “Upper” urinary tract
- Most infections “ascend”
- Urethra → Cystitis → Pyelonephritis



National Cancer Institute/Public Domain

# Etiology

- **Escherichia coli (75-95%)**
- Simple cystitis
  - Proteus mirabilis
  - Klebsiella
  - Staphylococcus saprophyticus
- Complicated cystitis
  - Klebsiella
  - Staphylococcus aureus (including MRSA)
  - Enterococcus faecalis
  - Pseudomonas

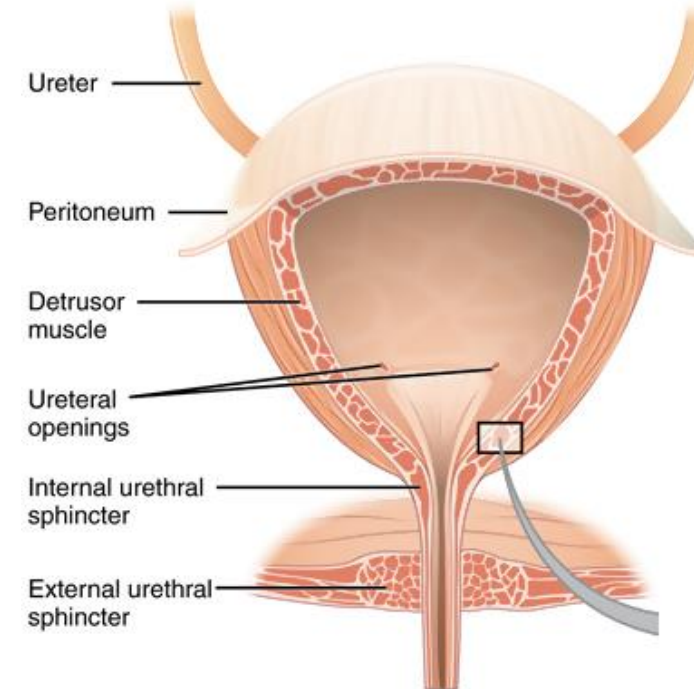


Public domain

# Clinical Features

- **Cystitis**

- Dysuria (pain with urination)
- Frequency (going a lot)
- Urgency (always feel like you have to go)
- Suprapubic pain
- No systemic symptoms
- Usually normal plasma WBC count



(a)

OpenStax College/Wikipedia

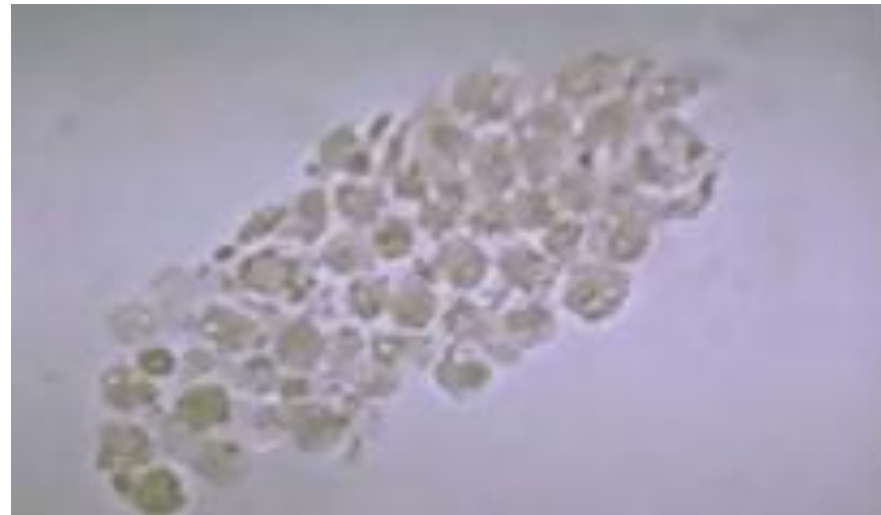


# Clinical Features

- **Pyelonephritis**

- Systemic symptoms (fever, chills)
- Flank pain
- CVA tenderness
- Hematuria
- WBC casts

**WBC Cast**



Anwar Siddiqui

# Diagnosis

- Diagnosis: **clinical plus urinalysis**
- Culture not routinely done
  - Only used in complicated cases



Wikipedia/Public Domain

# Diagnosis

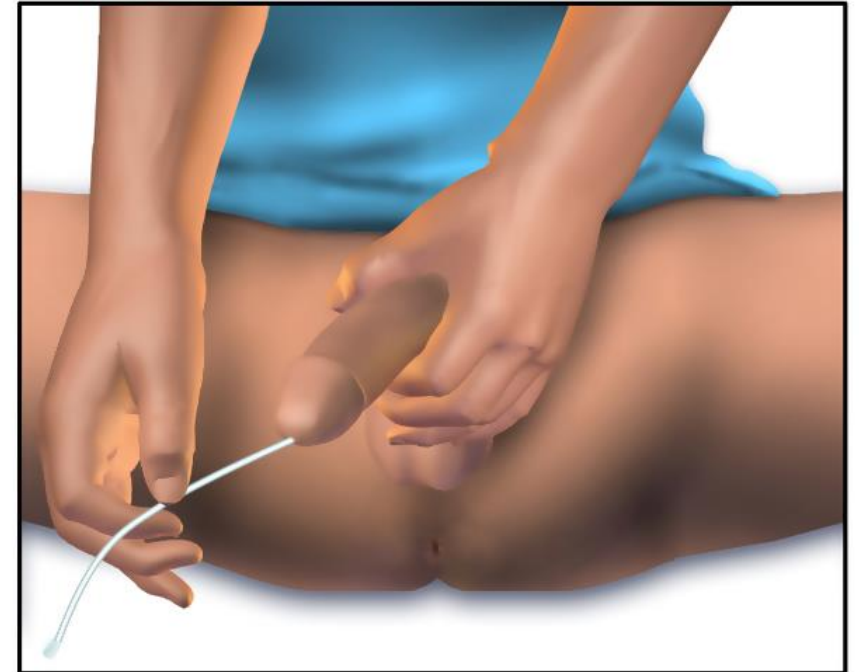
- **Urinalysis**
  - Cloudy urine
  - Leukocyte esterase (produced by WBCs in urine)
- Nitrites
  - 90% UTI bugs convert nitrates to nitrites
  - Some that don't: *enterococcus*, *staph saprophyticus*
  - Best for detecting aerobic gram-negative rods (E. Coli)



J3D3

# Risk Factors

- **Women**
  - 10x more likely than men to get UTIs
  - Shorter urethra
  - Closer to fecal flora
- Sexual activity
- Urinary catheterization
- Diabetes
- Pregnancy



Male Self-Catheterization

Wikipedia/Public Domain

# Risk Factors

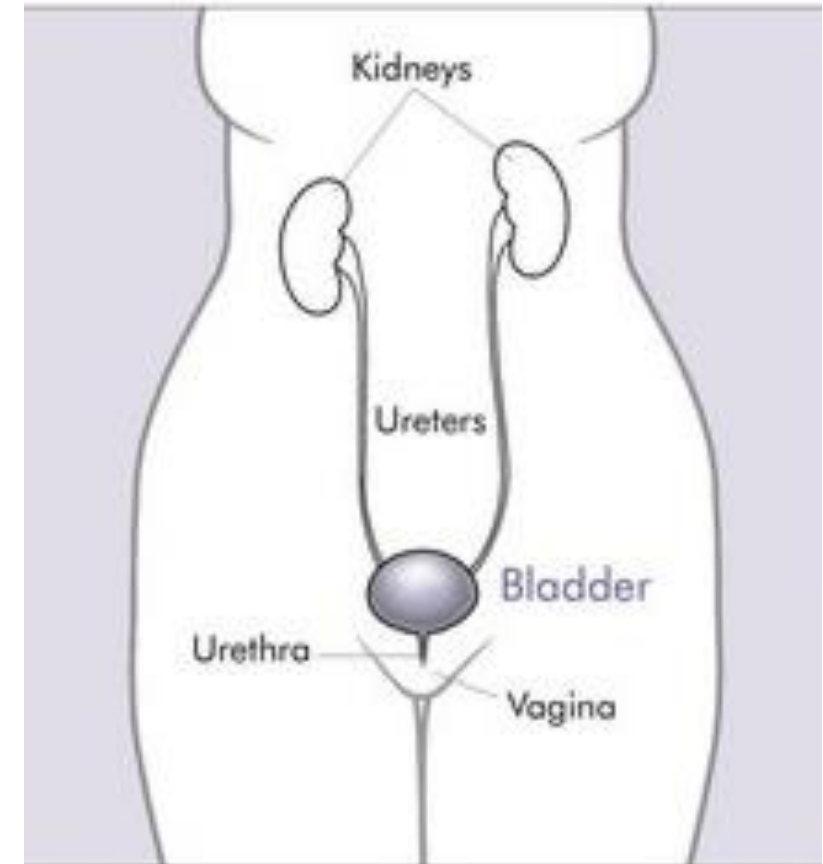
- **Infants with vesicoureteral reflux**
  - Ureters insert abnormally into bladder
  - Chronic reflux of urine back into ureters
- **Urinary obstruction**
  - Anatomic abnormalities in children
  - Bladder tumors in adults
  - Enlarged prostate in older males



Wikipedia/Public Domain

# Treatment Categories

- Uncomplicated cystitis
  - No systemic signs or symptoms (fever)
  - Presumed to be confined to bladder
- Complicated cystitis
  - Systemic signs and symptoms (fever, tachycardia)
  - Immunosuppression
  - Catheter- or procedure-related (cystoscopy)
  - Hospital acquired
  - Pregnancy, diabetes, CKD
- Pyelonephritis

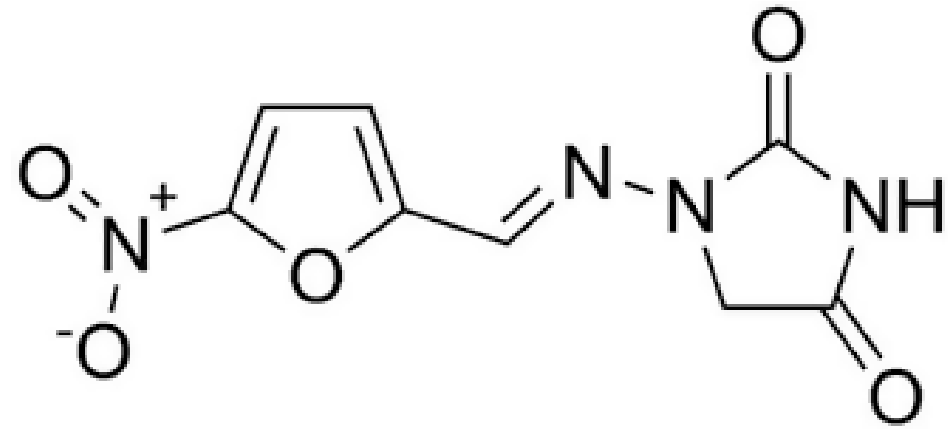


National Cancer Institute/Public Domain

# Treatment

- **Uncomplicated cystitis**

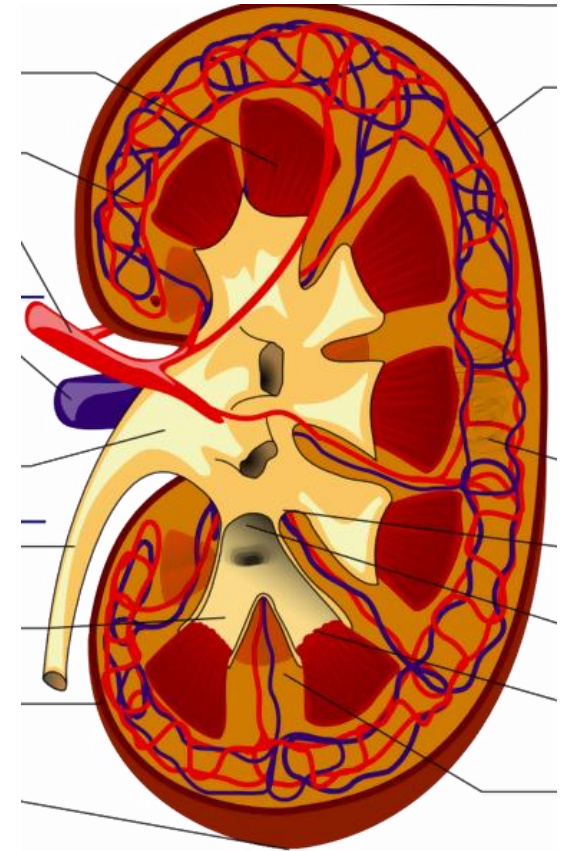
- Nitrofurantoin x 5 days
- TMP-SMX x 3 days
- Fosfomycin – single dose
- Fluoroquinolones only if above fail
- Urine culture only if treatment fails



**Nitrofurantoin**

# Treatment

- **Complicated Cystitis/Pyelonephritis**
  - IM dose Ceftriaxone plus TMP-SMX
  - Amoxicillin-clavulanic acid
  - Fluoroquinolones
- Young, otherwise healthy patients: outpatient treatment
- All others: inpatient treatment



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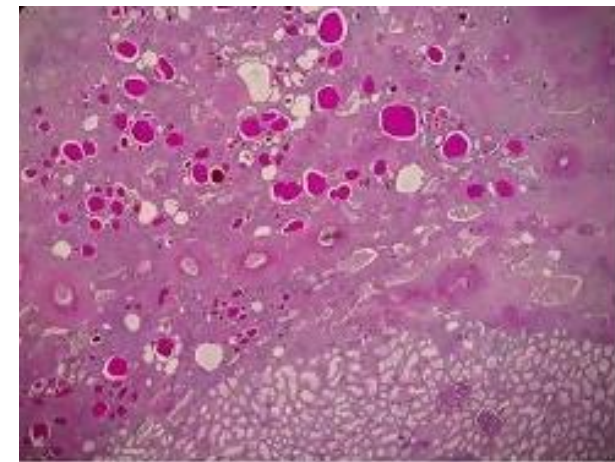


# Chronic Pyelonephritis

- Consequence of **recurrent pyelonephritis**
  - Vesicoureteral reflux in children
  - Recurrent stones in adults
- Scarring of kidneys
- Often identified on imaging
- Pathology: “thyroidization of kidney”
  - Tubules contain eosinophilic material
  - Looks like thyroid tissue on microscopy



Radiopedia.org



Public Domain

# Xanthogranulomatous Pyelonephritis

- Form of chronic pyelonephritis
- Usually caused by obstruction with infected stones
- Usually **unilateral**
- Severe kidney injury due to granulomatous inflammation
- Diagnosis: CT scan
  - Multiple, rounded dark areas
  - “Bear's paw sign”
- Usually requires nephrectomy
  - Ongoing infection, inflammation



Radiopedia.org

# Renal and Perinephric Abscess

- Usually a complication of pyelonephritis
- Renal: within kidney tissue
- Perinephric: within perirenal fat
- Clinical: **fever, abdominal pain**
- Diagnosis: CT scan or ultrasound
- Treatment: drainage plus antibiotics



Radiopedia.org

# Interstitial Cystitis

## Bladder Pain Syndrome

- Chronic bladder pain and discomfort
- Lasts > 6 weeks
- No underlying medical cause (e.g., infection)
- Associations: women, psychiatric disease
- Diagnosis of exclusion
- **First line treatment: avoid triggering foods**
- Other treatments:
  - Amitriptyline
  - Pain medication

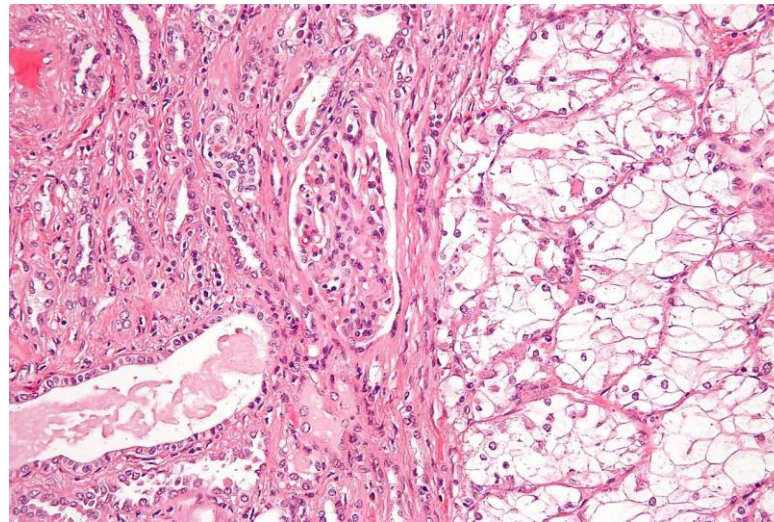
# Urinary Tract Malignancy

Jason Ryan, MD, MPH

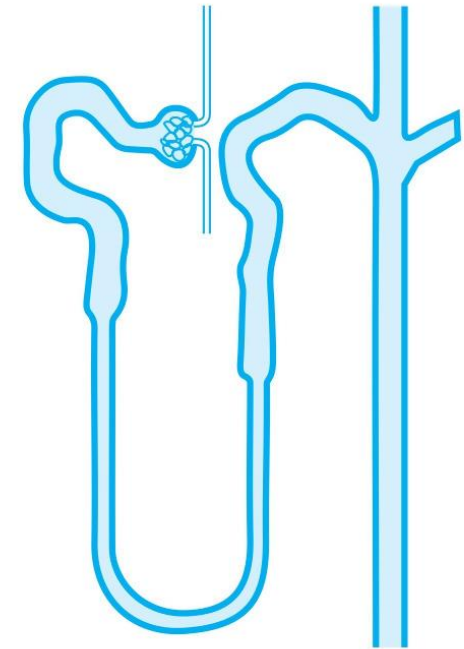


# Renal Cell Carcinoma

- **Most common kidney tumor**
- Usually derives from proximal tubular epithelial cells
- Most are composed of “clear cells”
  - “Clear cell carcinoma”



Nephron/Wikipedia





# Renal Cell Carcinoma

## Risk Factors

- Males
- Age 50-70
- Cigarette smoking
- Obesity
- Polycystic kidney disease
- Occupational exposures (asbestos)
- Von Hippel Lindau disease

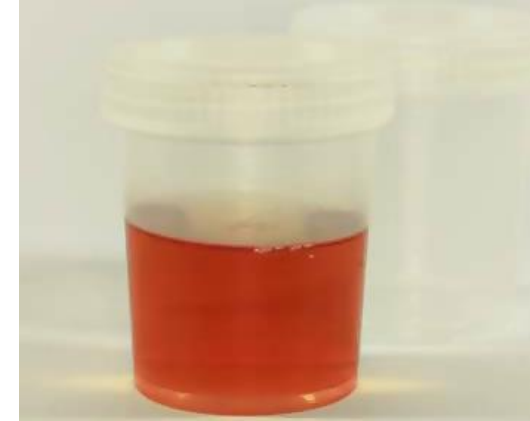


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# Renal Cell Carcinoma

## Symptoms

- **Classic triad**
  - Hematuria
  - Palpable abdominal mass
  - Flank pain
- Many patients have fever, weight loss
- Many patients asymptomatic until disease is advanced
- At presentation ~25% have metastases/advanced disease

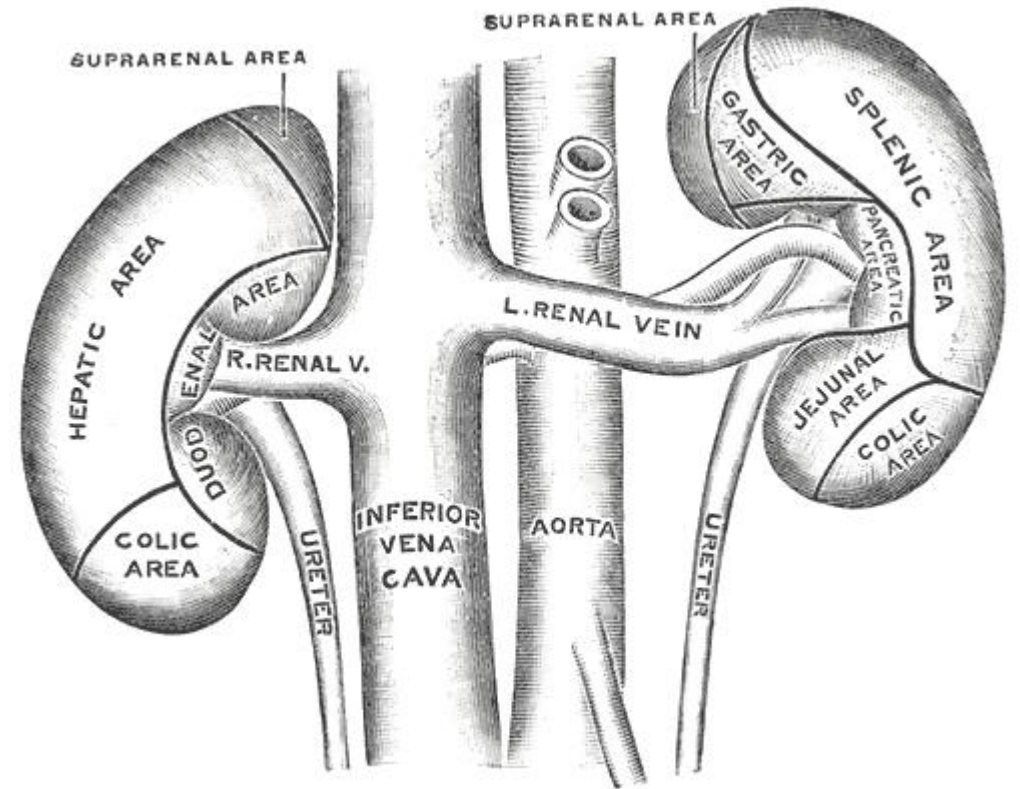




# Renal Cell Carcinoma

## Symptoms

- **Invades renal vein**
  - May cause thrombosis
  - Can block renal vein/IVC
  - Can block drainage of testicles
  - May cause a varicocele
- Spreads through venous system
- Common sites for metastasis:
  - Lung
  - Bone
- Can also spread to retroperitoneal lymph nodes



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# Renal Cell Carcinoma

## Paraneoplastic syndromes

- **Polycythemia (↑Hct)**
  - Increased EPO production by tumor
- **Hypercalcemia**
  - Tumor production of PTHrP
  - Increased Ca from bones



1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca

# Renal Cell Carcinoma

## Diagnosis

- **Abdominal CT scan**
- Biopsy



<https://radiologyassistant.nl/>

# Renal Cell Carcinoma

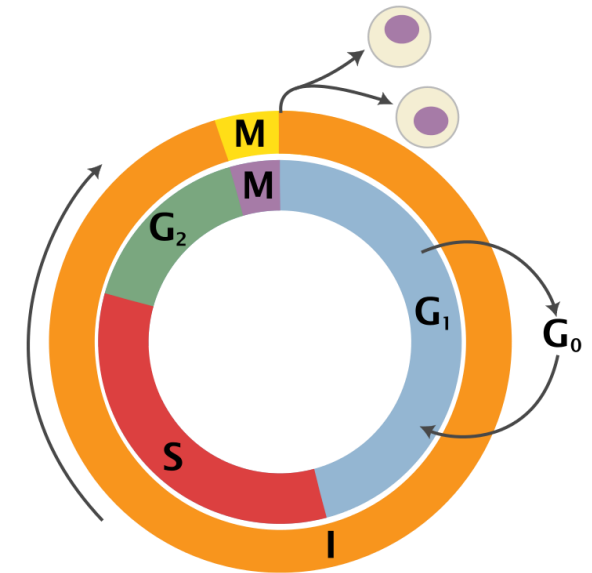
## Treatment

- **Nephrectomy**
  - Partial or radical
- Poorly responsive to chemotherapy/radiation
- **Immunotherapy**
  - Aldesleukin (interleukin-2)
  - Hypotension, fevers, chills are important side effects

# Renal Cell Carcinoma

## Treatment

- **Checkpoint inhibition**
  - Trigger T-cell growth (block checkpoint proteins)
- Nivolumab
  - PD-1 pathway (programmed cell death receptor 1)
- Ipilimumab
  - CTLA-4 pathway (cytotoxic T-lymphocyte-associated antigen 4)



Richard Wheeler (Zephyris) 2006

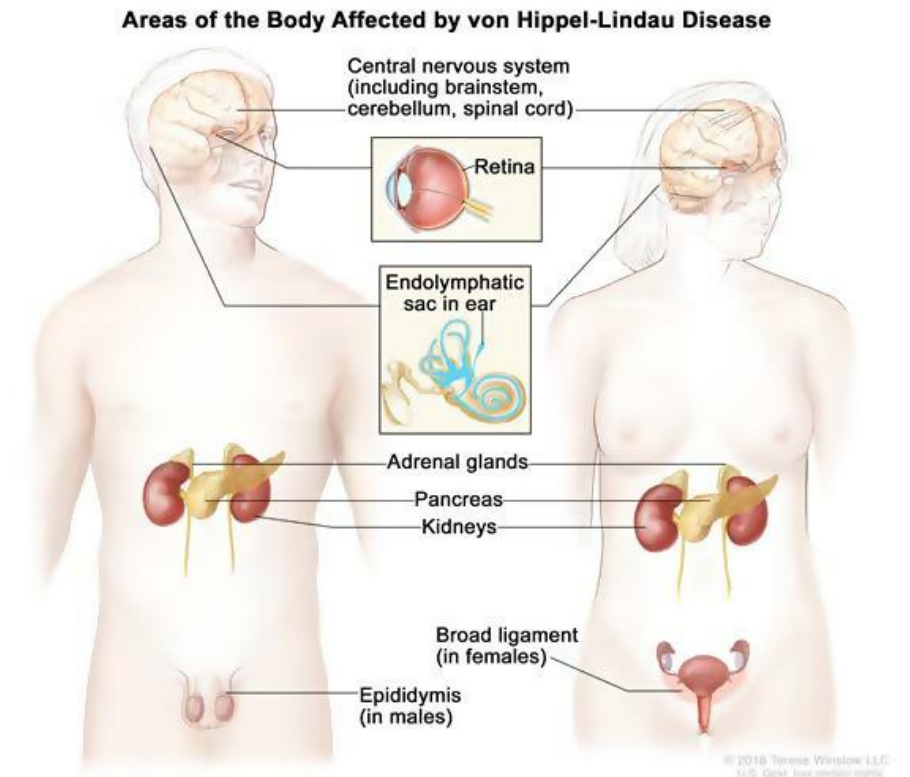
# Renal Cell Carcinoma

## Genetics

- Associated with gene deletion chromosome 3
- **Von-Hippel-Lindau (VHL) gene**
- Sporadic mutations
  - Single tumor
  - Older patient, usually smoker
- Inherited mutations
  - Younger patient
  - Multiple, bilateral tumors

# Von-Hippel-Lindau Disease

- **Autosomal dominant disorder**
  - Von-Hippel-Lindau (VHL) gene inactivation
- **Many tumors**
  - Renal cell carcinomas
  - Cerebellar hemangioblastoma
  - Retinal hemangioblastoma
- Diagnosis: genetic testing
- Annual screening:
  - Annual eye exam
  - Annual abdominal/spine/brain MRI

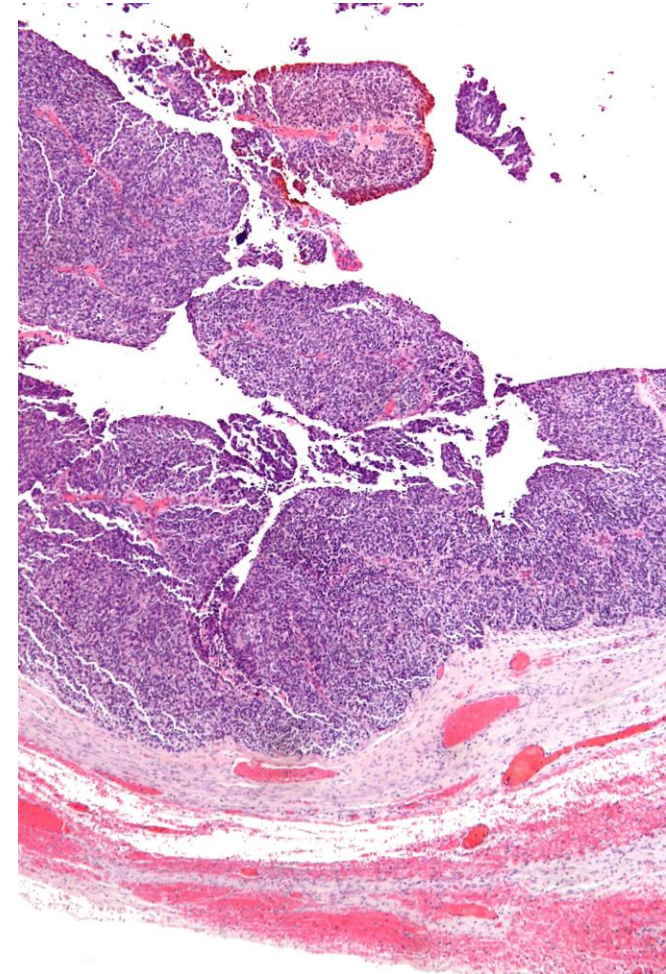




# Bladder Cancer

## Transitional Cell Carcinoma

- Most common type of **bladder cancer**
  - Also called “urothelial carcinoma”
- Most common tumor of urinary tract system
- Locations:
  - Bladder (most common)
  - Also renal calyces, renal pelvis, ureters



Wikipedia/Public Domain



# Transitional Cell Carcinoma

## Risk Factors

- **Smoking**
- Cyclophosphamide
- Phenacetin
- Aniline dyes (hair coloring)
- Workplace exposures
  - Rubber, textiles, leather
  - Naphthalene (industrial solvent)
  - Painters, machinists, printers

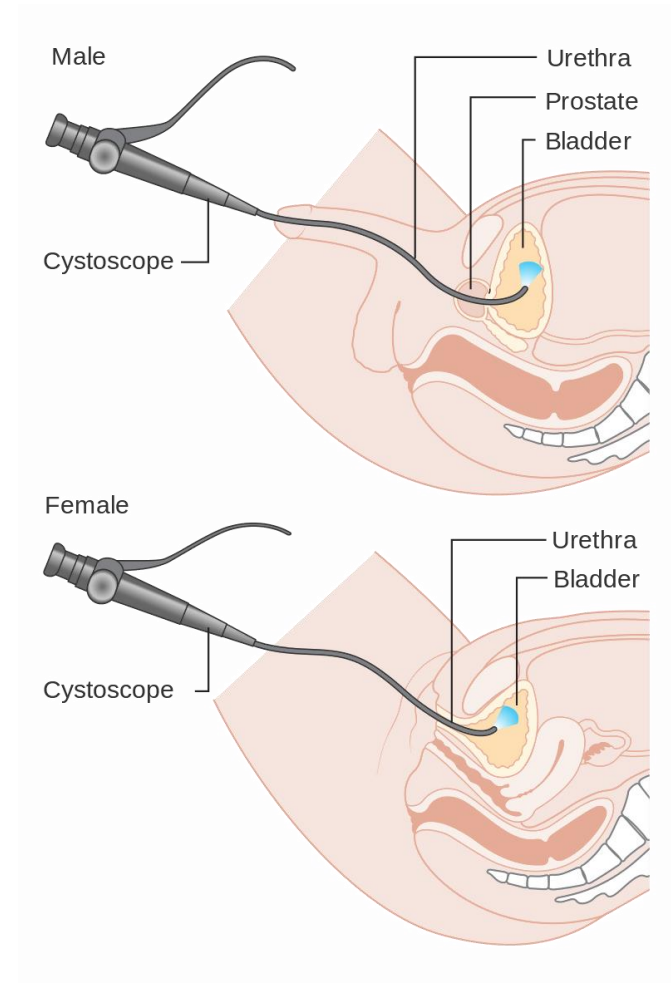
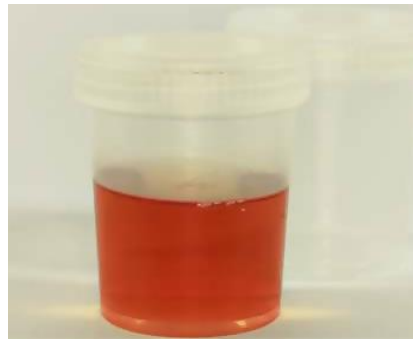


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# Transitional Cell Carcinoma

## Clinical Presentation

- Classic presentation: **painless hematuria**
- Classic case
  - Older, white male
  - Smoker
  - Painless hematuria
  - No dysmorphic red cells or casts in urine
- Test of choice: **cystoscopy and biopsy**

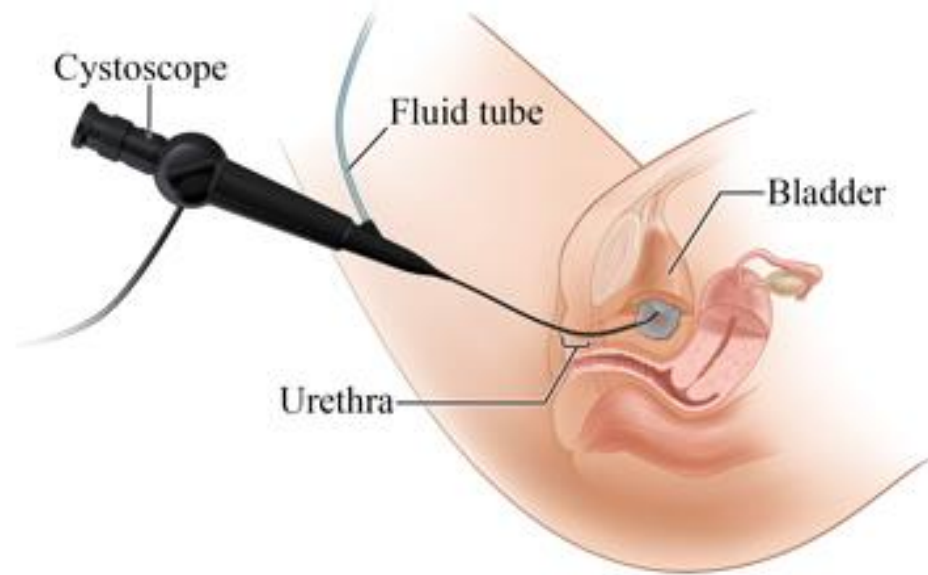


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# Bladder Cancer

## Management

- No smooth muscle invasion
  - **Transurethral resection of the bladder tumor (TURBT)**



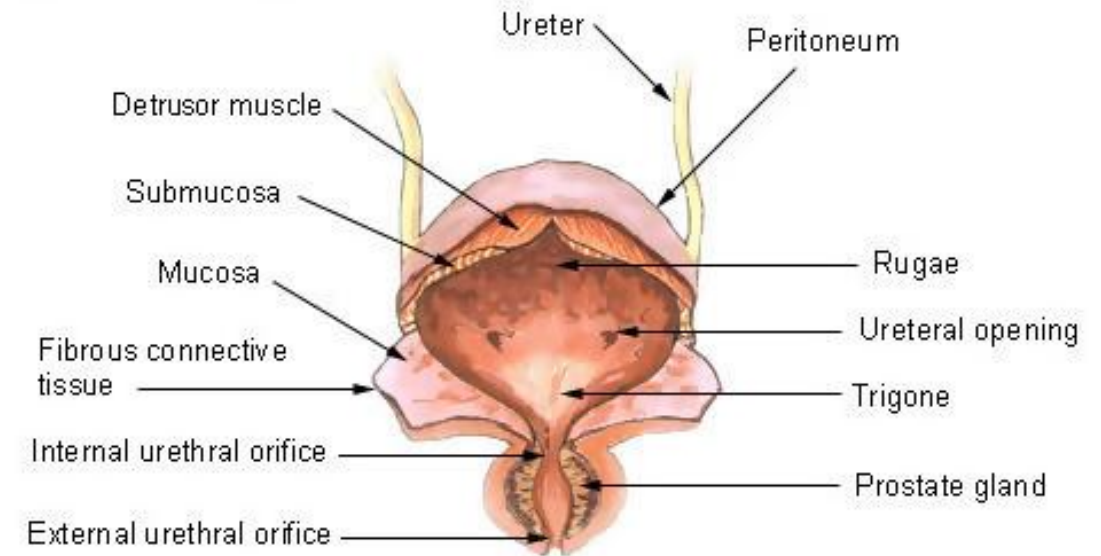
© 2016 Healthwise

# Bladder Cancer

## Management

- Smooth muscle invasion
  - Cystectomy
  - Chemotherapy
  - Intravesical BCG
- **Bacillus Calmette-Guerin**
  - Live attenuated strain of *Mycobacterium bovis*
  - Injected into bladder
  - Triggers immune response

**Urinary Bladder**

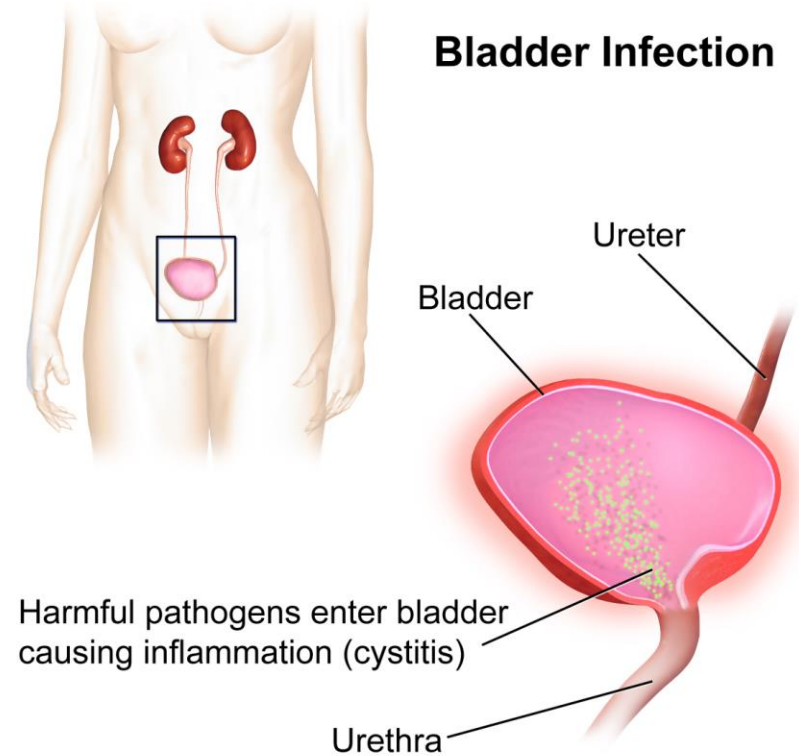


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# Bladder Cancer

## Squamous Cell Carcinoma

- Rare bladder cancer
- Caused by **chronic inflammation of bladder**
- Several key risk factors
  - Recurrent kidney stones or cystitis
  - UTI with *Schistosoma haematobium*

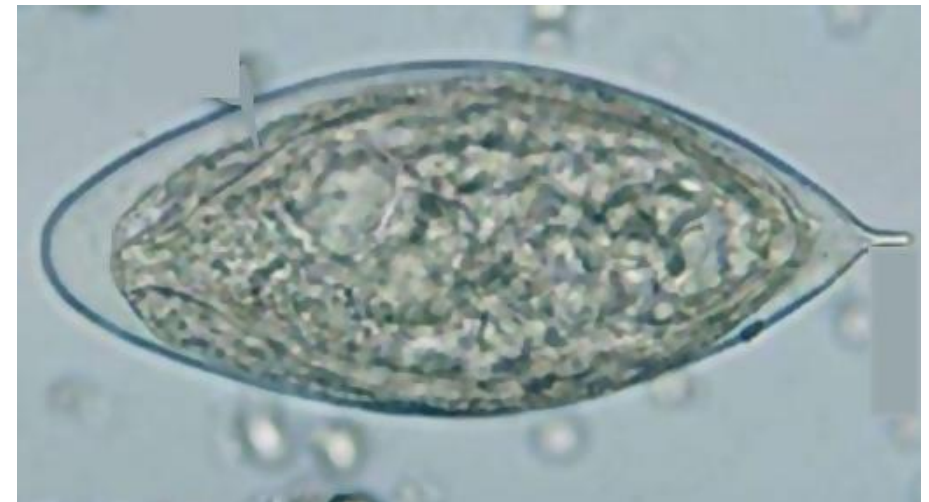


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# Schistosoma haematobium

- Trematode
- Found in **Africa and Middle East**
  - Sudan and Egypt
- Acquired from freshwater containing larvae
- Penetrate the skin
- Migrate to liver and mature to adults
- Infects bladder
- Eggs cause granulomatous inflammation
- Usually causes hematuria
- Can result in bladder cancer

**Schistosoma Egg**



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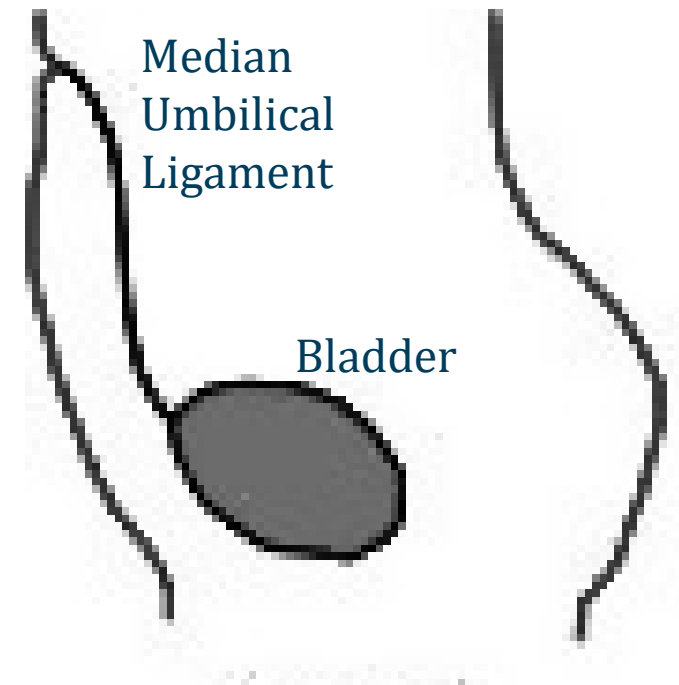
# Bladder Cancer

## Adenocarcinoma

- Very rare bladder cancer
- Glandular proliferation in bladder
- Occurs in special circumstances
  - **Urachal remnant**
  - *Schistosoma haematobium*
  - Exstrophy: bladder protrusion through abdominal wall defect

# Urachus

- Connects **dome of bladder to umbilicus**
- Obliterated at birth → median umbilical ligament
- Failed/incomplete obliteration can occur
  - Urine can leak from umbilicus
  - Also can form cyst, sinus, diverticulum
  - Can lead to infections





# Hematuria

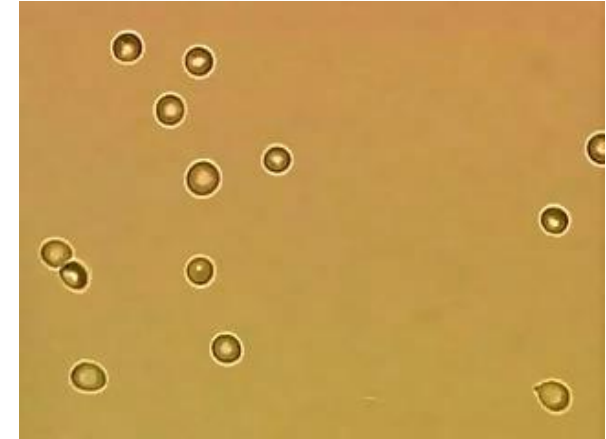
Jason Ryan, MD, MPH



# Hematuria

- **Microscopic hematuria**
  - Seen on urine microscopy
  - Often due to glomerular disease
- **Gross hematuria**
  - Grossly red urine
  - Often caused by non-glomerular disease
  - Bladder or renal cancer until proven otherwise

Microscopic Hematuria

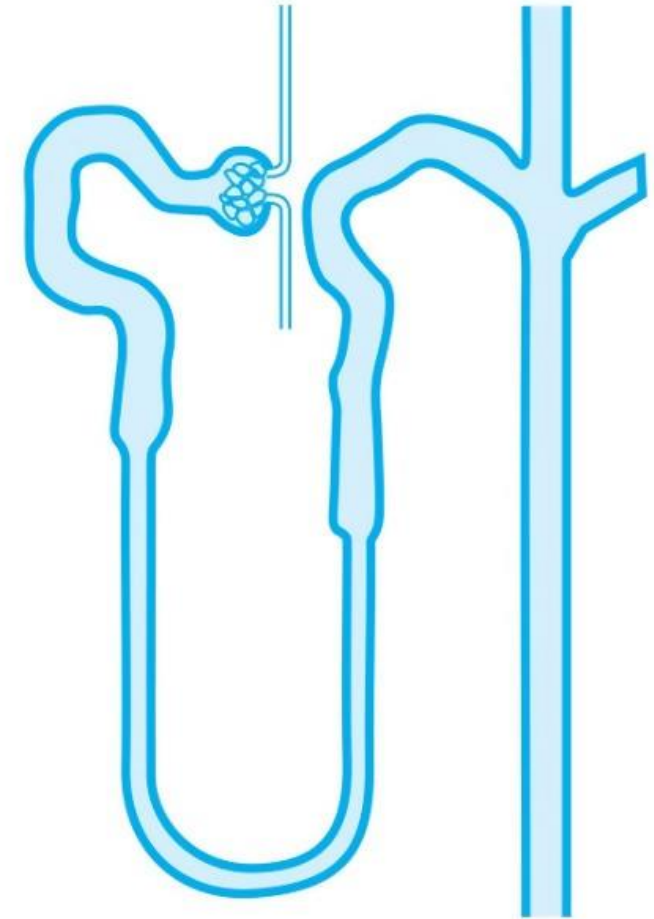


Gross Hematuria



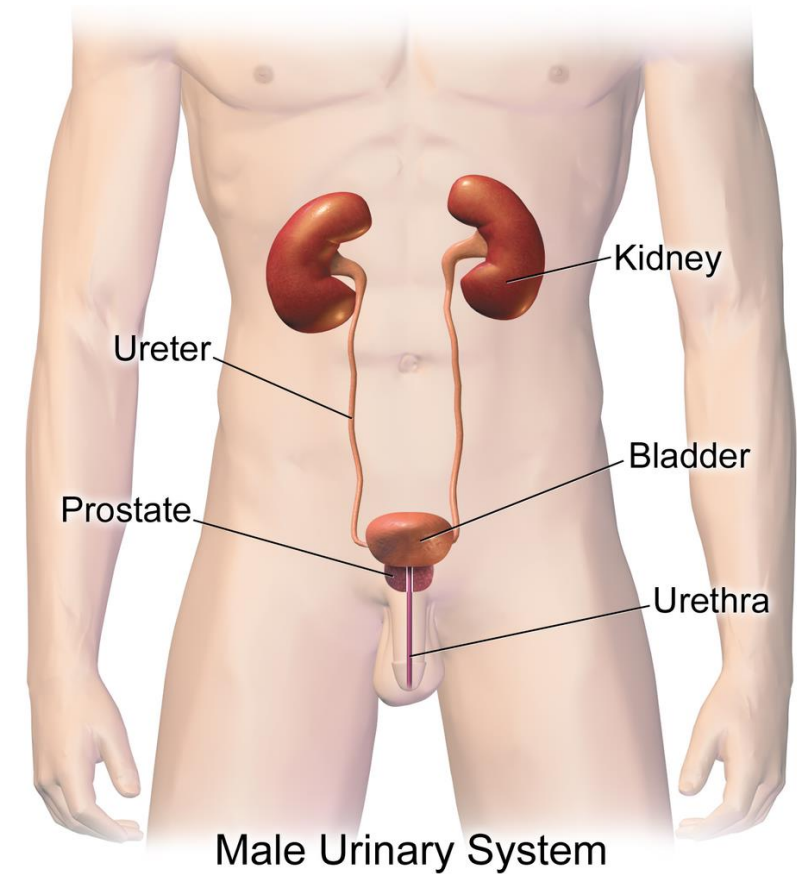
# Hematuria

- **Glomerular bleeding**
  - More likely microscopic
  - No dysuria or flank pain
  - RBC casts, dysmorphic RBCs
  - Proteinuria
  - Glomerulonephritis, etc.
- **Nonglomerular bleeding**
  - More likely gross
  - Dysuria, flank pain
  - Normal red cells
  - No protein
  - Stones, cancer, infection



# Hematuria

- **Initial**
  - Urethra injury (trauma, urethritis)
- **Terminal**
  - Bladder or prostate
  - Cystitis
  - Bladder stones or cancer
  - Prostate cancer
- **Throughout voiding**
  - Ureter or kidneys
  - Pyelonephritis
  - Nephrolithiasis
  - Upper urinary cancers



Public Domain

# Hematuria

## Selected causes

- **Stones:** kidney, ureter, bladder
- **Infection:** cystitis, pyelonephritis
- Cancer: kidney or bladder
- Glomerulonephritis
- Coagulopathy

# Hematuria

## Workup

- Urine dipstick
  - Identifies heme
- Urine microscopy
  - Identifies RBC and WBCs
  - Dysmorphic RBCs
  - Casts
- Exam: flank pain or UTI symptoms
- Other tests
  - Cystoscopy (must be done if possible bladder CA)
  - CT abdomen

### Urine test strip

Leukocytes

Nitrite

Urobilinogen

Protein

pH

Blood

Specific gravity

Ketone

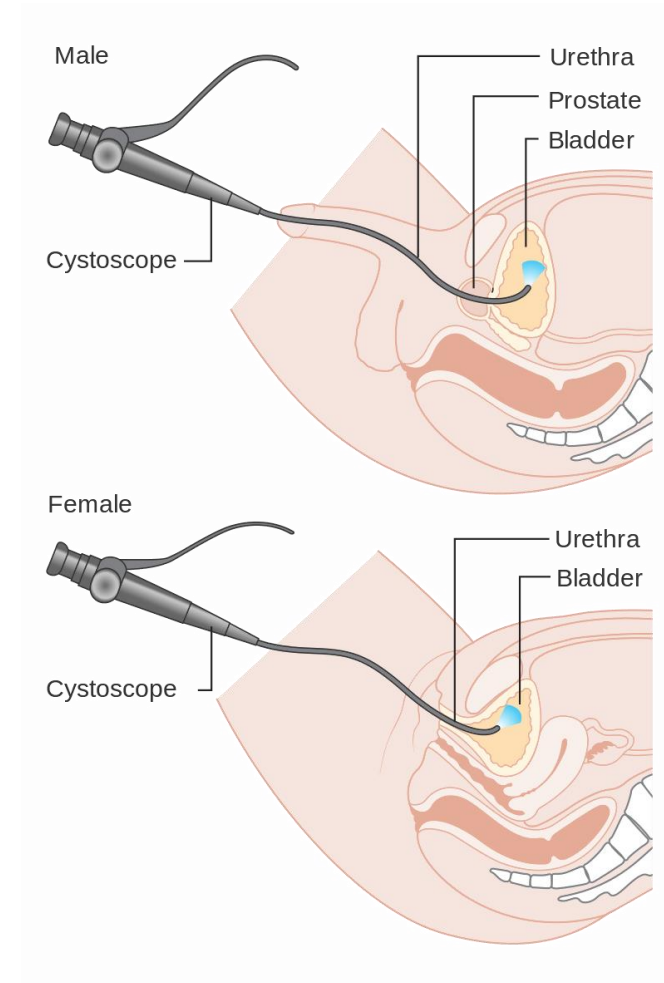
Bilirubin

Glucose



# Cystoscopy

- Camera insertion into urethra/bladder
- Used for diagnosis of bladder cancer
- **Used after renal ultrasound or CT**
  - Non-invasive tests
  - May show diagnosis (e.g., stones, renal cancer)



Wikipedia/Public Domain

# Urinary Casts

- Cylindrical structures formed in nephron tubular lumen

Type of Cast	Association
Red blood cell	Glomerulonephritis
White blood cell	Pyelonephritis, Interstitial Nephritis
Hyaline	Concentrated urine (Tamm-Horsfall mucoprotein)
Waxy, Broad	Advanced chronic kidney disease
Granular, Muddy Brown	Acute tubular necrosis (dead tubular cells)



# Other Pigments

- **Myoglobin**
  - Found in urine with rhabdomyolysis
  - Turns urine red
  - Heme positive dipstick
  - No RBCs on urinalysis
- **Bilirubin**
  - Hemolysis, biliary disease
  - Turns urine brown
  - Detected by dipstick
- Rifampin
  - TB drug
  - Turns urine orange



James Heilman, MD -



# Diuretics

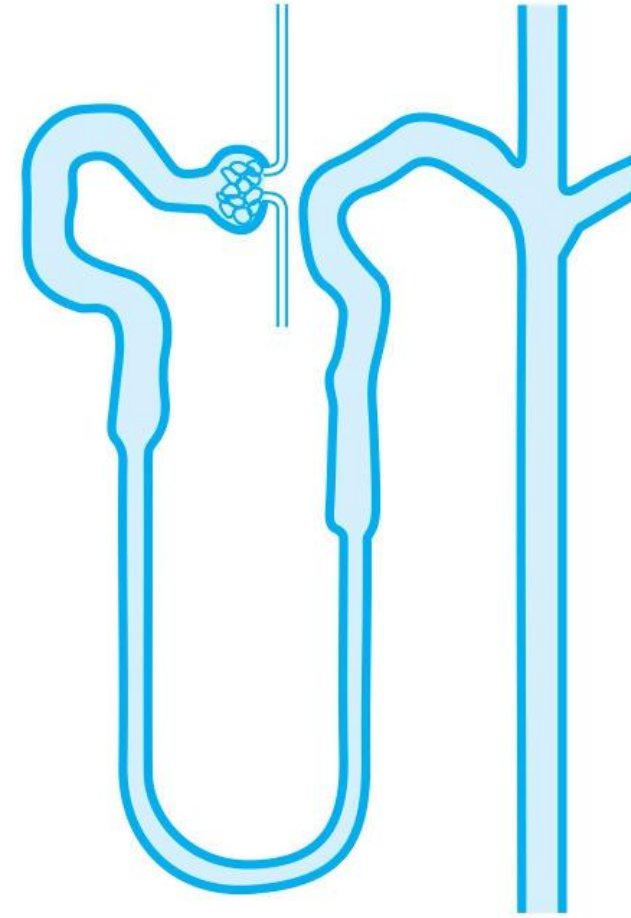
Jason Ryan, MD, MPH



# Diuretics

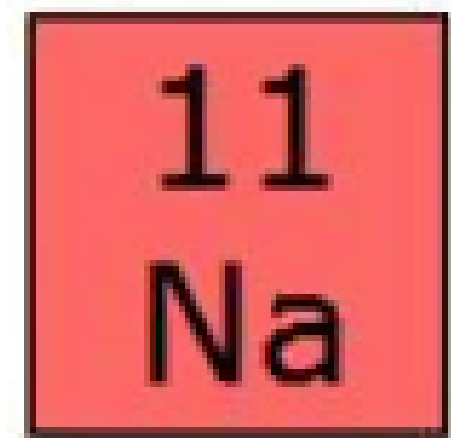
Drugs that increase urine output

1. Loop Diuretics
2. Thiazide Diuretics
3. Potassium Sparing Diuretics
4. Carbonic Anhydrase Inhibitors
5. Osmotic diuretics



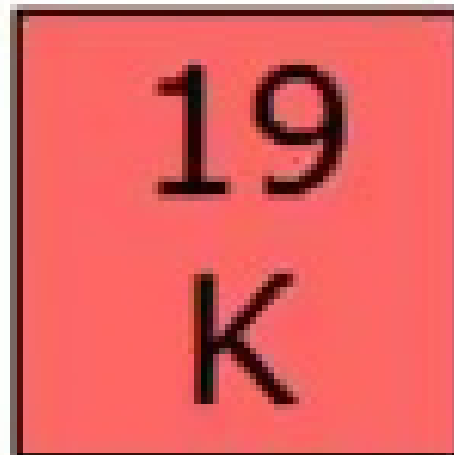
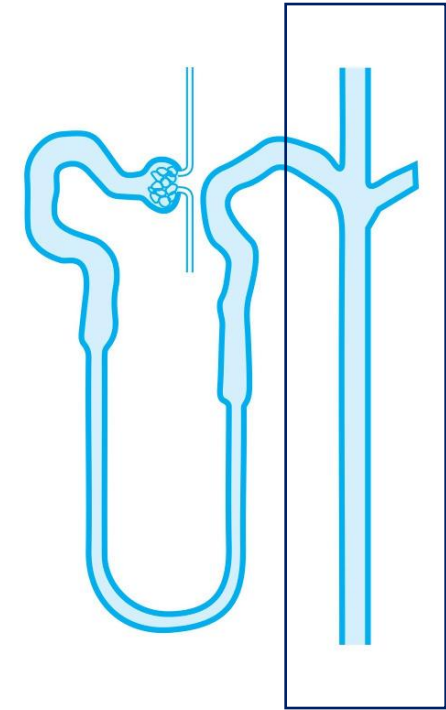
# Sodium

- Normal plasma  $[\text{Na}] = 140 \text{ meq/L}$
- $[\text{Na}]$  tightly regulated
  - Renin-angiotensin-aldosterone
  - Antidiuretic hormone (ADH)
- Sodium intake  $\rightarrow$  H<sub>2</sub>O retention  $\rightarrow [\text{Na}] = 140 \text{ meq/L}$
- **Sodium loss**  $\rightarrow$  H<sub>2</sub>O excretion  $\rightarrow [\text{Na}] = 140 \text{ meq/L}$
- Any drug that  $\uparrow$  Na excretion  $\rightarrow$  volume loss
- **Many diuretics work by  $\uparrow$  Na excretion**

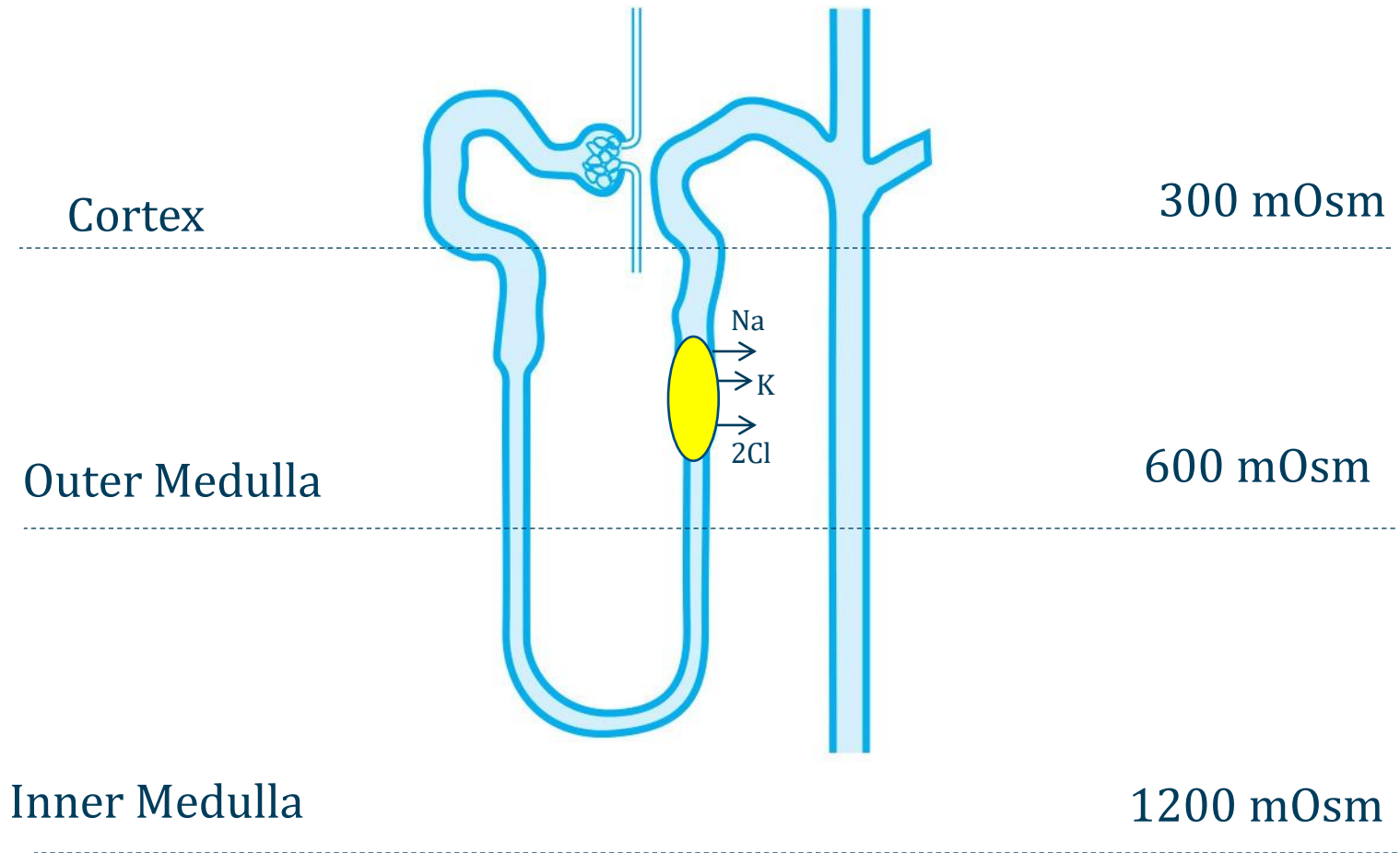


# Potassium

- Secreted by **distal tubule and collecting duct**
- Varies with Na/H<sub>2</sub>O delivery to distal nephron
- More urine flow → more secretion of potassium
- Most diuretics lead to **hypokalemia**



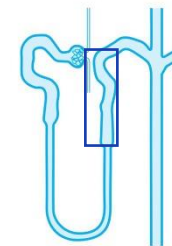
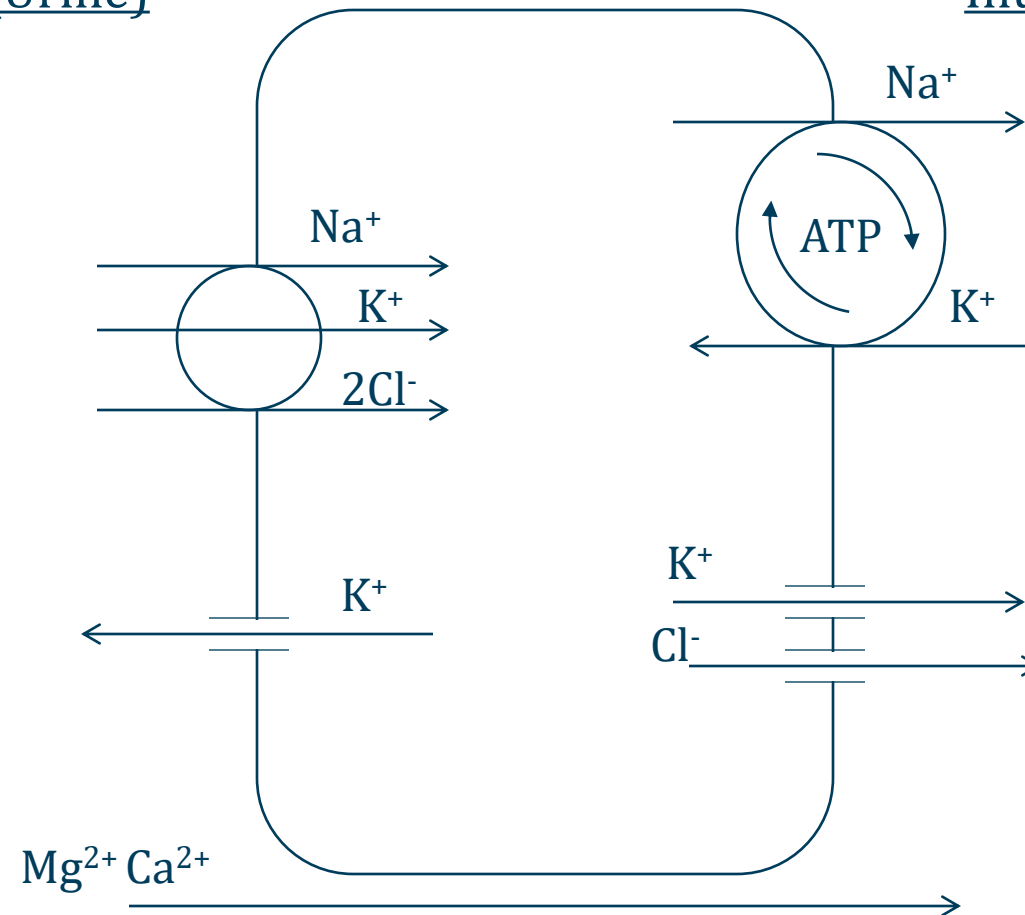
# Loop Diuretics



# Loop Diuretics

Lumen (Urine)

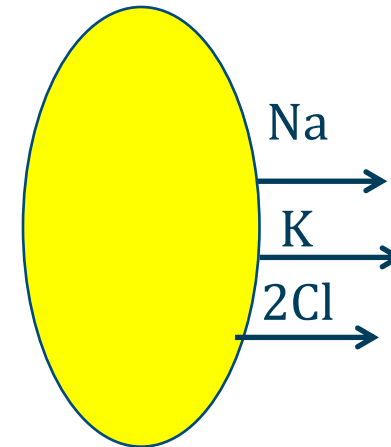
Interstitialium/Blood



# Loop Diuretics

Furosemide, bumetanide, torsemide, ethacrynic acid

- Inhibit Na-K-2Cl pump
  - Increase Na excretion
  - Increase Mg/Ca excretion
  - Increase potassium excretion
- **Strong diuretic effect**
- Used for edematous states
  - Heart failure, cirrhosis

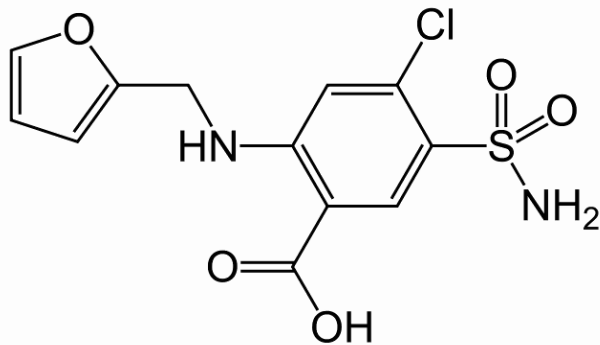




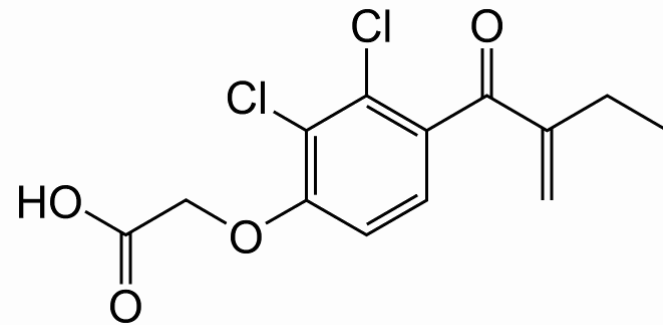
# Loop Diuretics

Furosemide, bumetanide, torsemide, ethacrynic acid

- Hypokalemia
- Hypocalcemia
- Hypomagnesemia
- Contraction alkalosis ( $\uparrow\text{HCO}_3^-$ )
- Most are sulfa drugs
- Exception: ethacrynic acid (used in allergic patients)



Furosemide

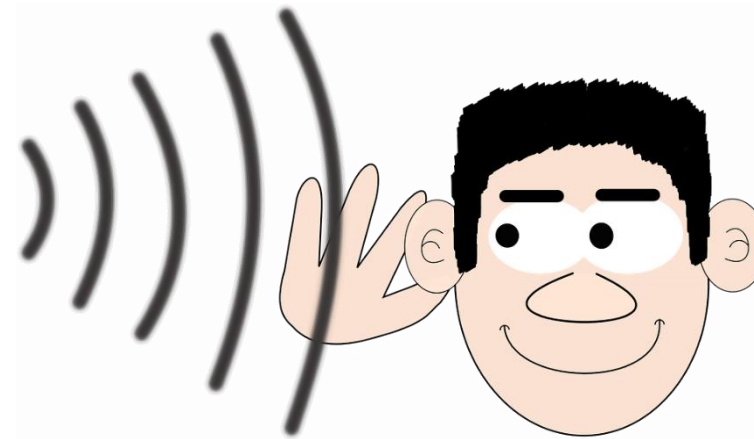


Ethacrynic Acid

# Loop Diuretics

Furosemide, bumetanide, torsemide, ethacrynic acid

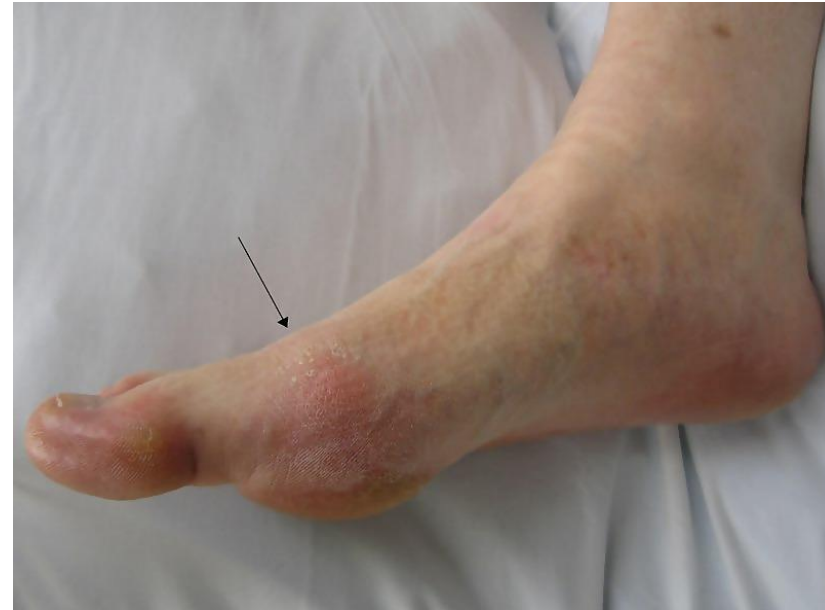
- **Ototoxicity**
  - Very high doses or given with other ototoxic agents
  - Tinnitus, loss of hearing (usually reversible)
- Acute interstitial nephritis
  - ↑BUN/Cr
  - White blood cell casts
  - Urine eosinophils
- Gout



Pixabay/Public Domain

# Uric Acid

- Complex mechanism of renal handling
- Thiazides, loop diuretics: ↑ uric acid reabsorption
- **Gout promoted by diuretics**

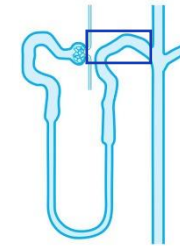
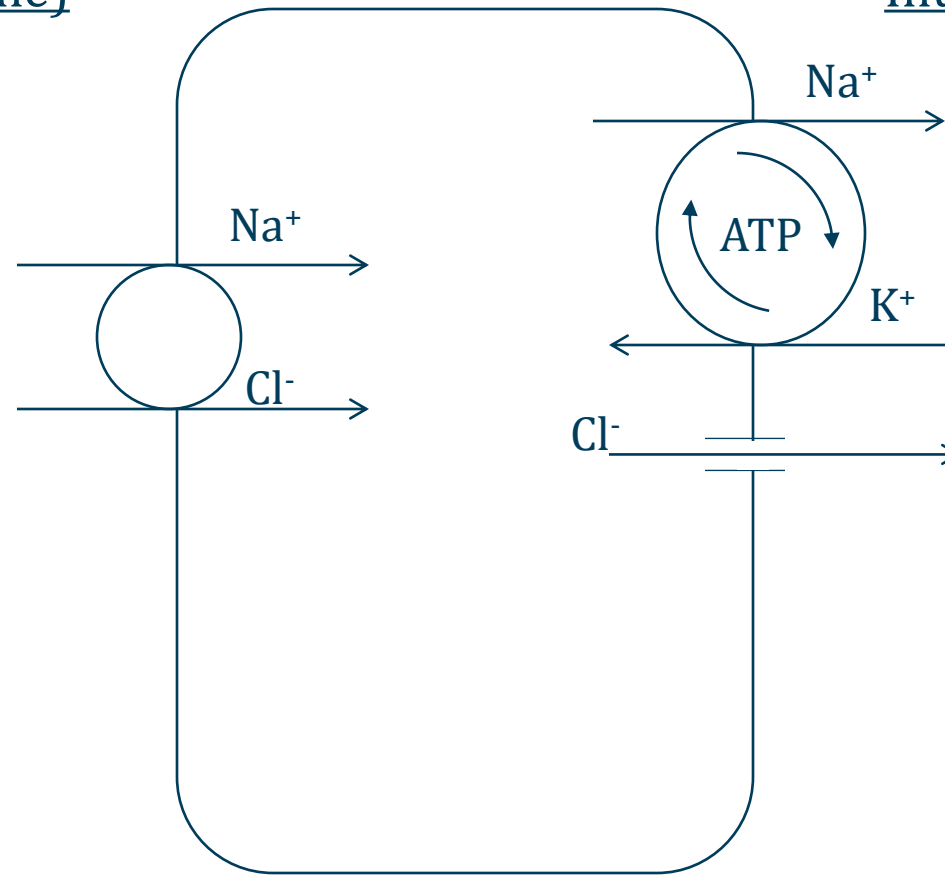


James Heilman, MD/Wikipedia

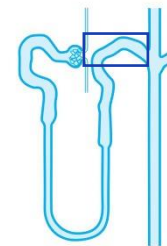
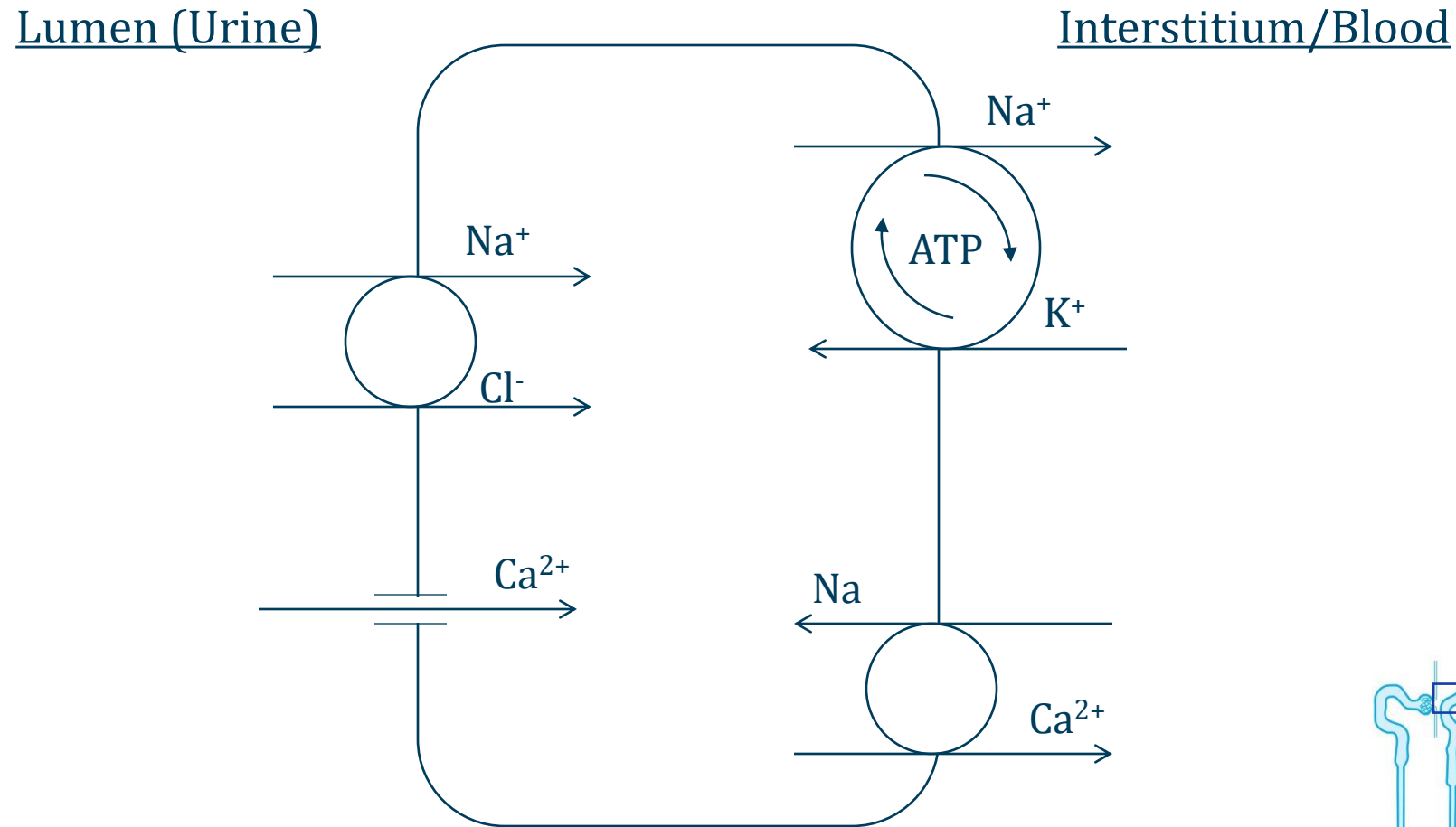
# Thiazide Diuretics

Lumen (Urine)

Interstitialium/Blood



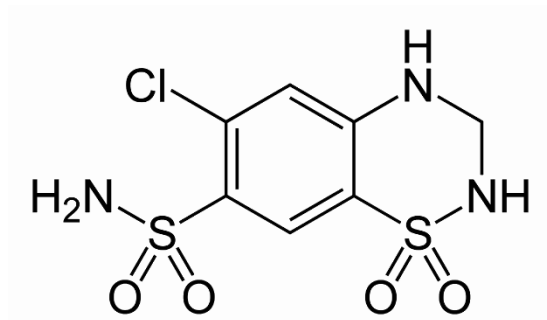
# Thiazides: Hypercalcemia



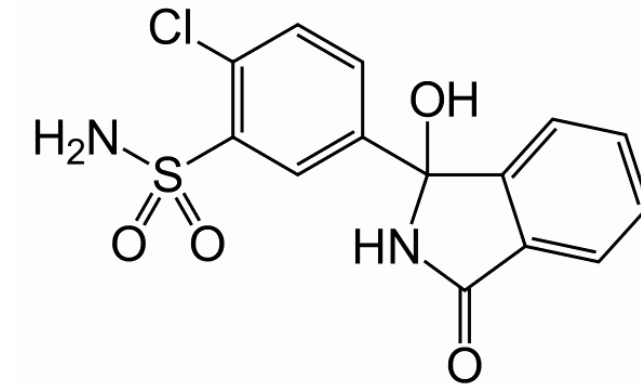
# Thiazide Diuretics

Hydrochlorothiazide, Chlorthalidone, Metolazone

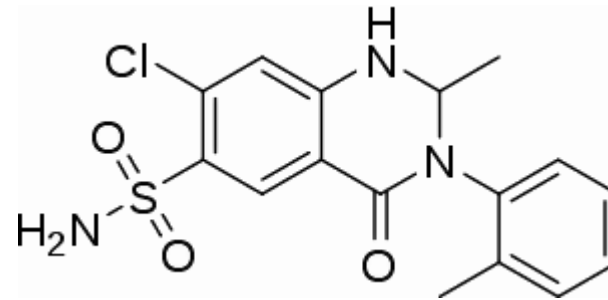
- Sulfa Drugs (allergy)



Hydrochlorothiazide



Chlorthalidone



Metolazone

# Thiazide Diuretics

Hydrochlorothiazide; chlorthalidone; metolazone

- Elevates blood levels
  - Glucose
  - Lipids
  - Uric acid
  - Calcium
- **HyperGLUC**

# Thiazide Diuretics

Hydrochlorothiazide; chlorthalidone; metolazone

- **Hyponatremia**
- Hypokalemia
- Contraction alkalosis

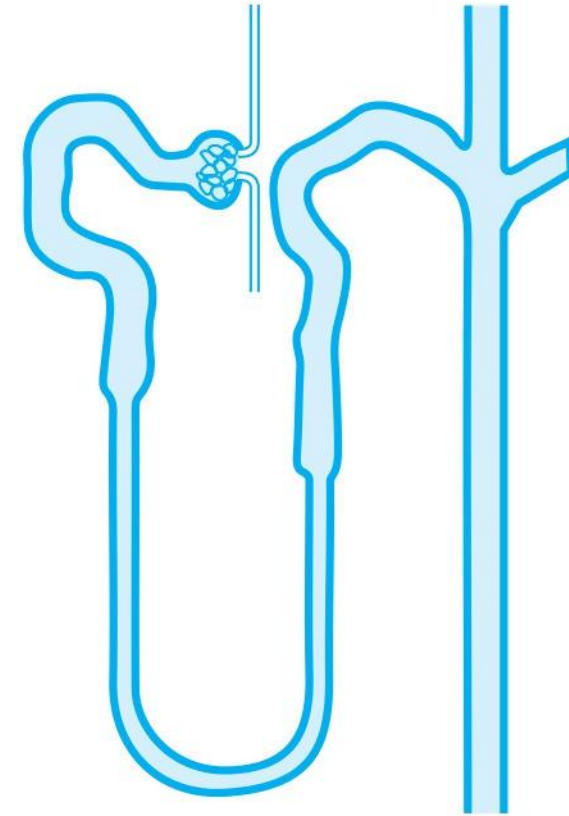
1 H			
3 Li	4 Be		
11 Na	12 Mg		
19 K	20 Ca	21 Sc	22 Ti
37 Rb	38 Sr	39 Y	40 Zr



# Thiazide Diuretics

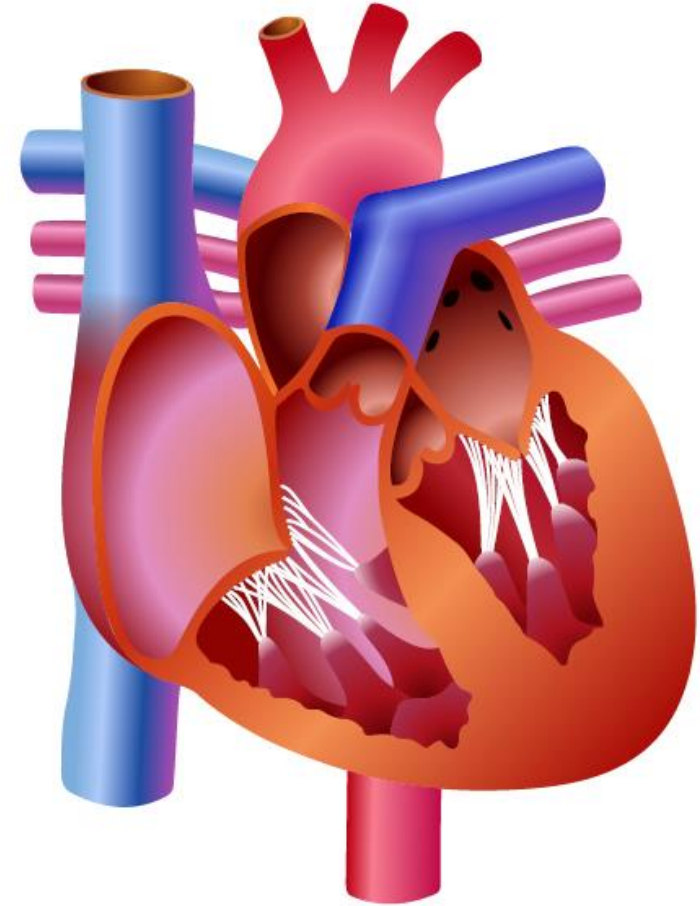
## Clinical Uses

- Hypertension
- Recurrent calcium kidney stones
  - Reduce urinary calcium
- Osteoporosis
  - Increase serum calcium
- Diabetes insipidus

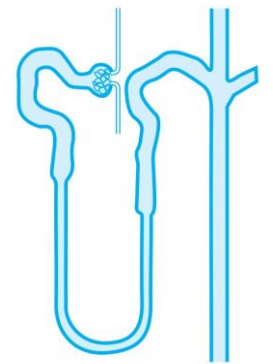
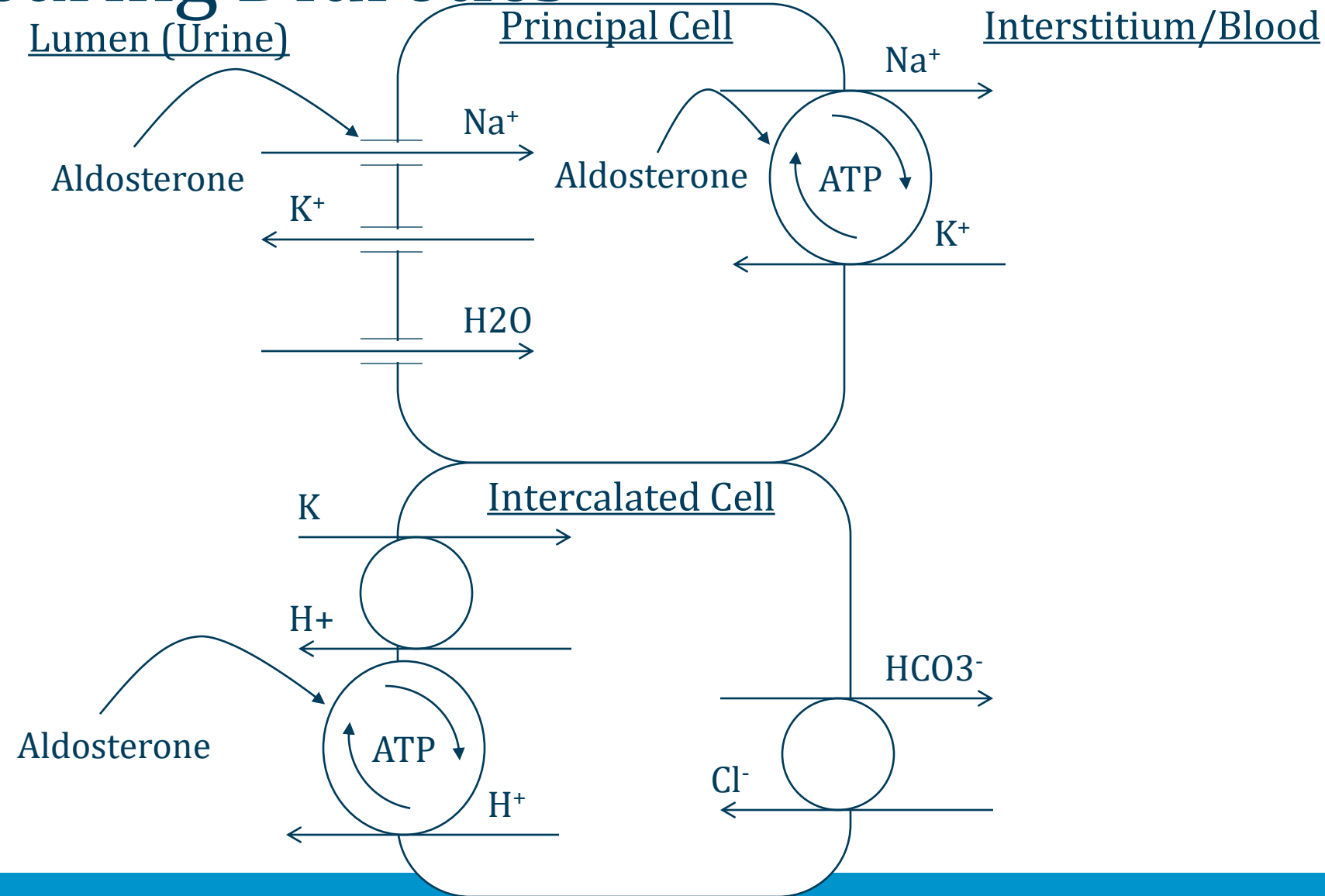


# K-Sparing Diuretics

- Spironolactone/eplerenone
  - Block aldosterone receptor site
- Triamterene/amiloride
  - Block aldosterone Na channel
- Good choice for patients with hypokalemia
  - Often from other diuretics
- Reduce mortality in systolic heart failure



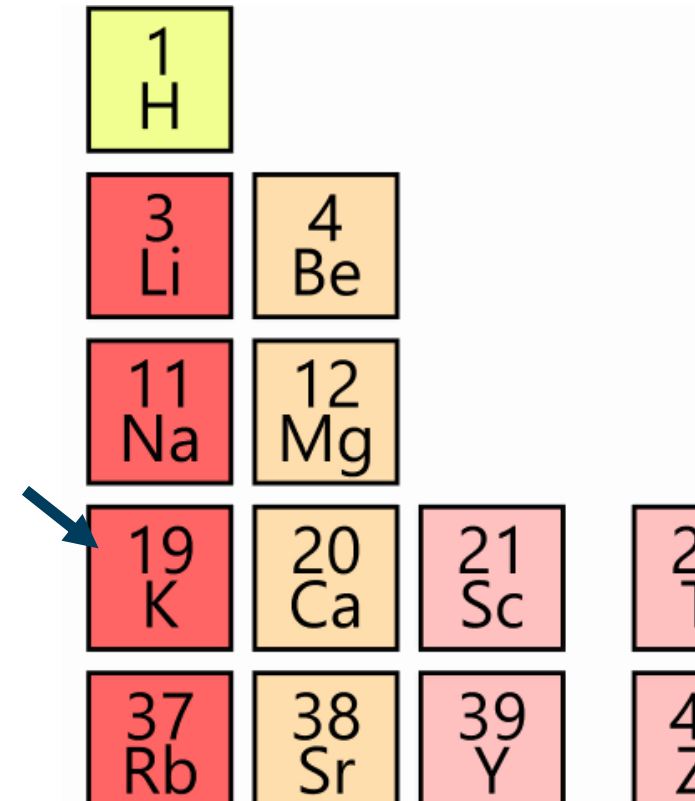
# K-Sparing Diuretics



# K-Sparing Diuretics

Spironolactone, Eplerenone, Triamterene, Amiloride

- All  $\uparrow$  Na/H<sub>2</sub>O excretion (diuretics)
- All “spare” potassium
  - Unlike other diuretics, do not increase K<sup>+</sup> excretion
- **HYPERkalemia** is side effect



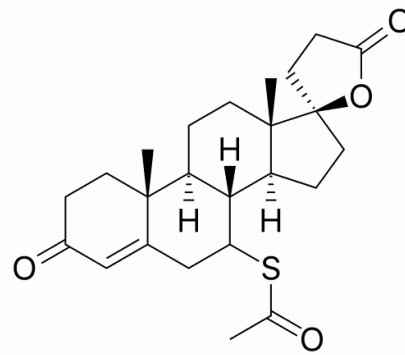
1 H			
3 Li	4 Be		
11 Na	12 Mg		
19 K	20 Ca	21 Sc	22 Ti
37 Rb	38 Sr	39 Y	40 Zr

# Spironolactone

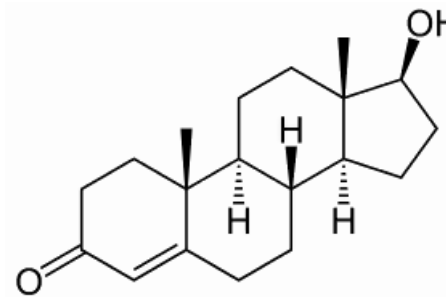
- Similar structure to testosterone
  - Blocks testosterone effects
  - **Gynecomastia** in men
  - Eplerenone: no gynecomastia
- Derivative of progesterone
  - Activates progesterone receptors
  - **Amenorrhea** in women



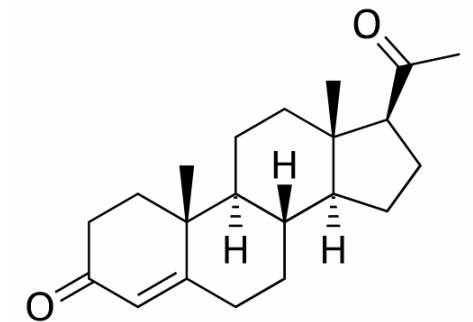
Image courtesy Dr. Mordcai Blau/Wikipedia



Spironolactone



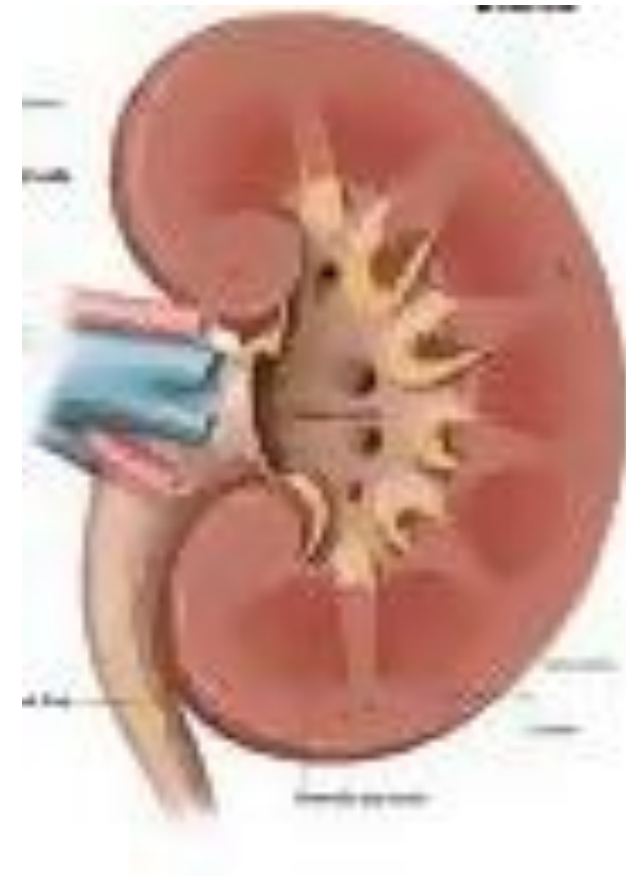
Testosterone



Progesterone

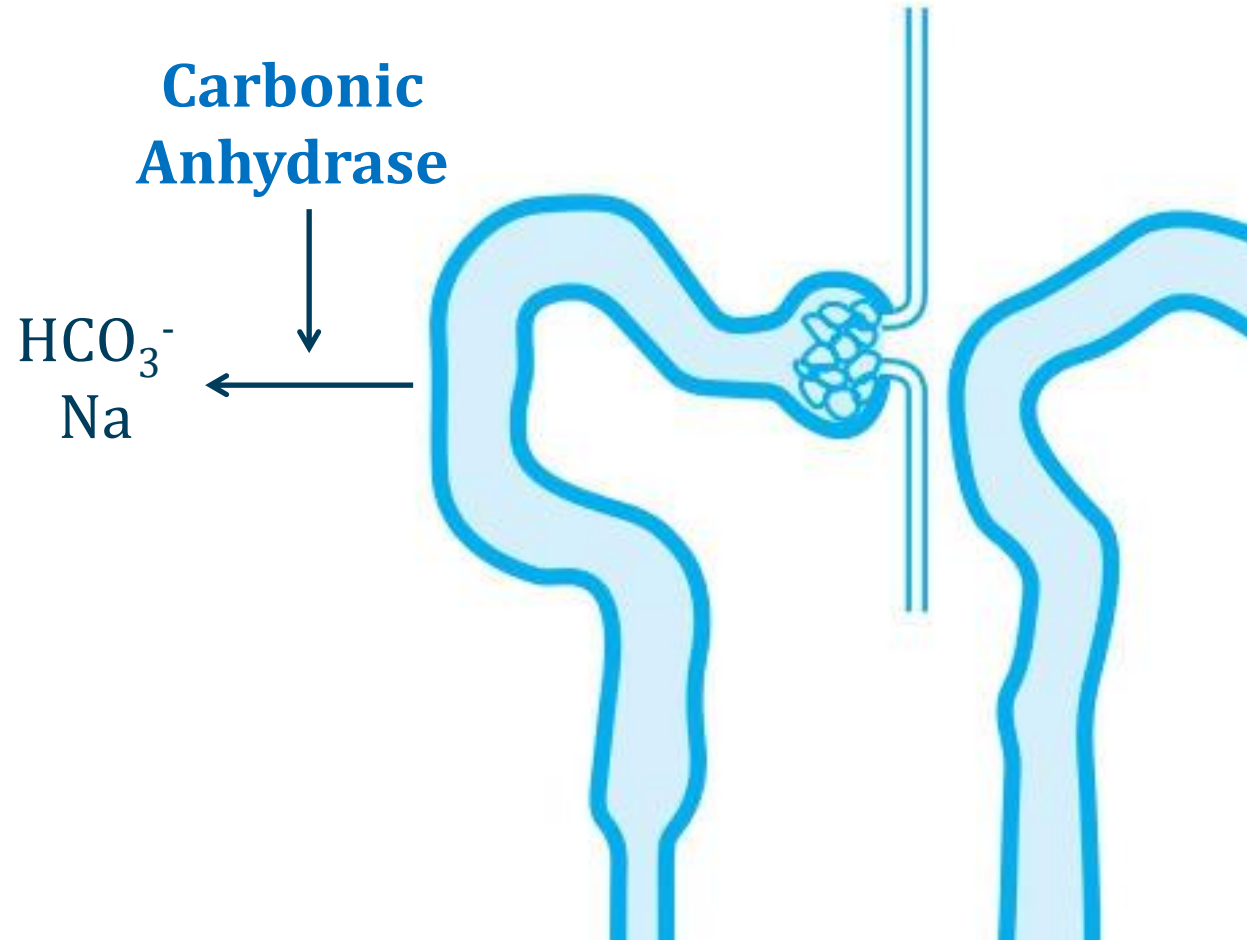
# Renal Failure

- All diuretics can cause renal failure
- $\downarrow$  ECV  $\rightarrow$   $\downarrow$  GFR
- BUN/Cr may rise in the plasma



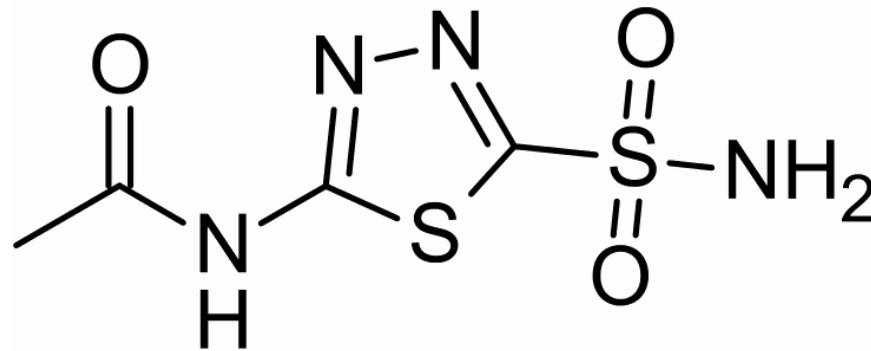
Public Domain

# Carbonic Anhydrase Inhibitors



# Carbonic Anhydrase Inhibitors

- **Acetazolamide**
- Weak diuretic effect
  - Block some Na resorption
- Causes a non-AG **metabolic acidosis**
  - Increased elimination of  $\text{HCO}_3^-$





# Carbonic Anhydrase Inhibitors

## Clinical Uses

- Severe metabolic alkalosis
- Glaucoma
  - Blocks formation of aqueous humor



Wikipedia/Public Domain

# Carbonic Anhydrase Inhibitors

## Clinical Uses

- Pseudotumor cerebri
  - Reduced rate of CSF formation
- Prevention of high-altitude sickness
  - Low  $pO_2$  at high altitude  $\rightarrow$  hyperventilation
  - Low  $CO_2 \rightarrow$  respiratory alkalosis
  - Acetazolamide  $\rightarrow$  acidosis  $\rightarrow$  reverses alkalosis

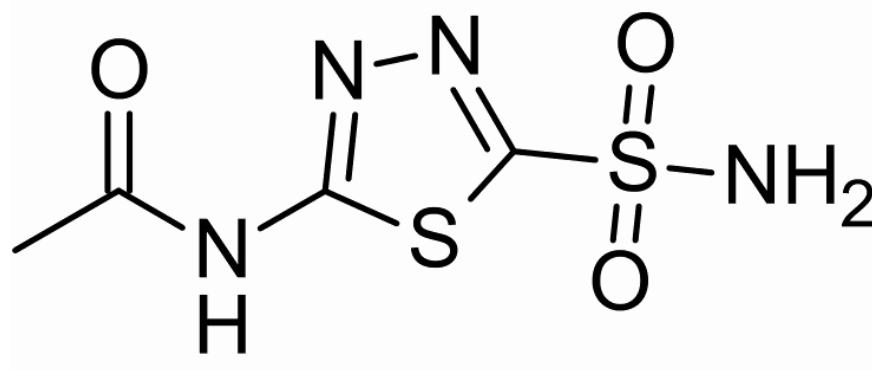


Wikipedia/Public Domain

# Carbonic Anhydrase Inhibitors

## Side Effects

- Metabolic acidosis
- Paresthesias (“tingling” in extremities)
- Sulfa allergy

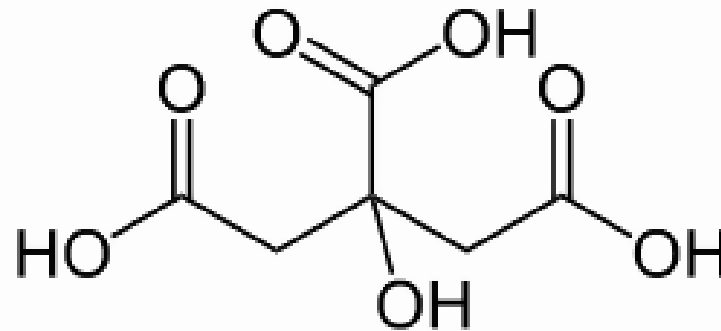


Acetazolamide

# Carbonic Anhydrase Inhibitors

## Side Effects

- Cause kidney stones
  - Reduce urinary **citrate** excretion
  - Citrate inhibits calcium stone formation

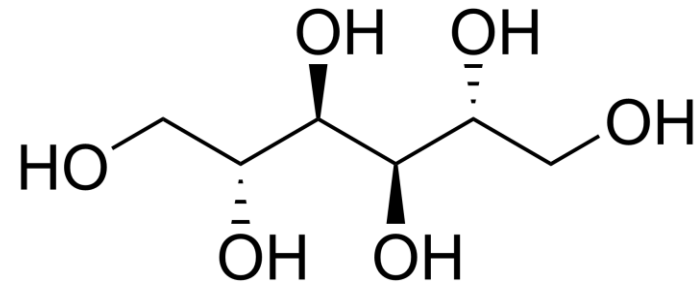
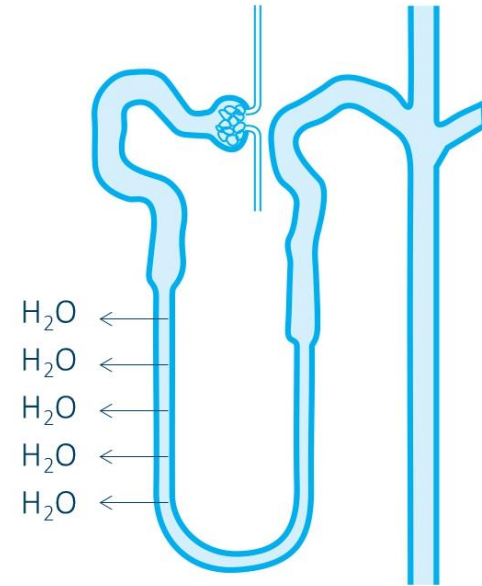


Citrate  
(Citric Acid)

# Mannitol

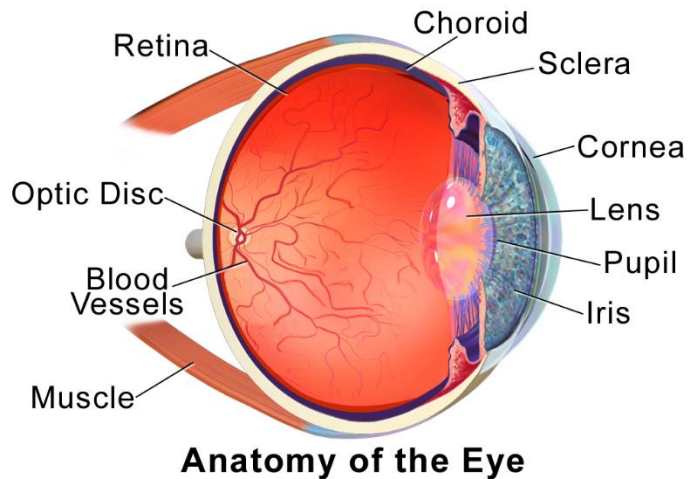
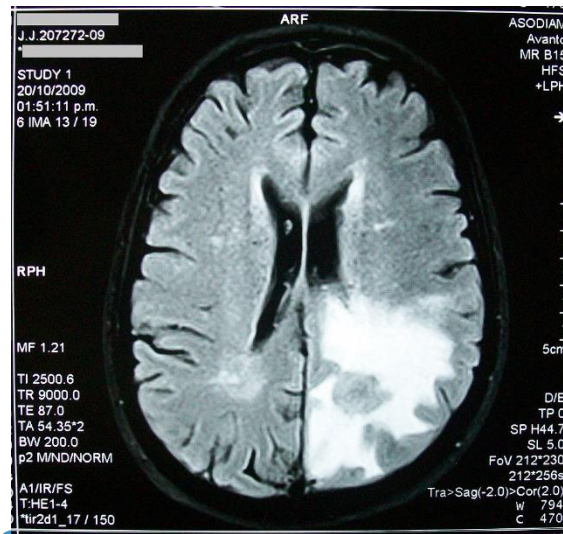
## Osmotic Diuretic

- Sugar alcohol
- Freely filtered by glomerulus
- No tubular reabsorption
- **Raises osmolality**
- Reduces water reabsorption
- Increases urine output



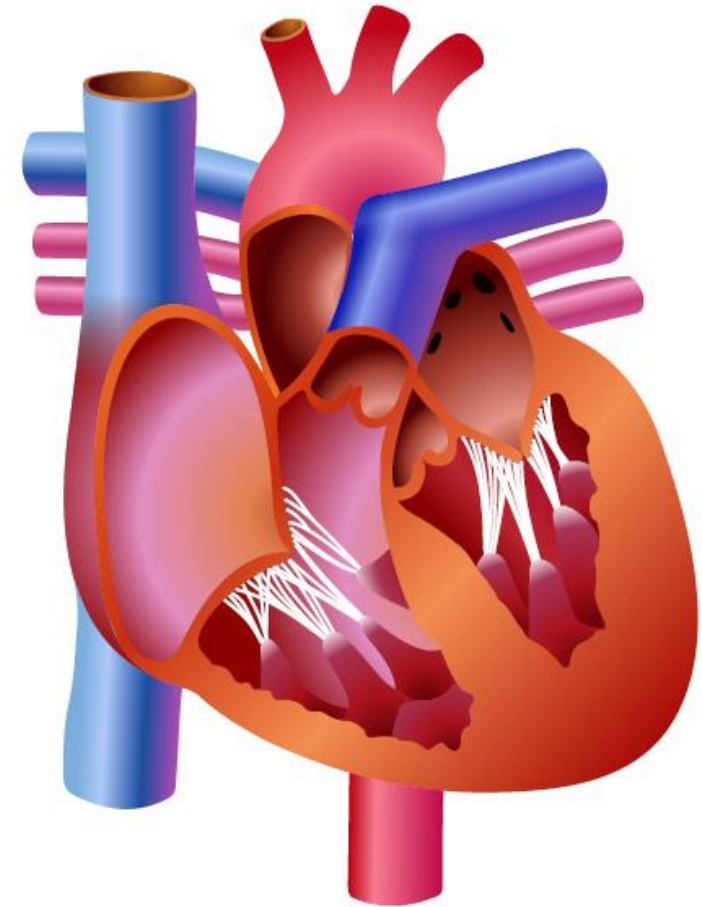
# Mannitol

- Main use is in cerebral edema, glaucoma
- Goal is to create a HYPERosmolar state
- “Osmotherapy”
- Draws fluid out (brain, eye)



# Mannitol

- Cannot use in **heart failure** patients
  - Draws fluid out of tissues
  - Expands intravascular volume
  - Can cause pulmonary edema
- Can't use with severe renal disease
  - High doses cause acute anuric renal failure
  - Mannitol can cause renal vasoconstriction → anuria



# Rhabdomyolysis

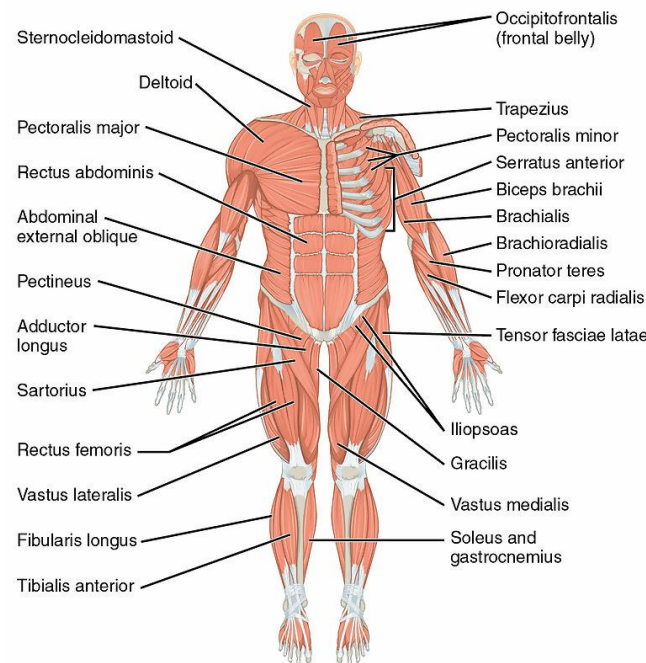
Jason Ryan, MD, MPH





# Rhabdomyolysis

- Syndrome caused by muscle necrosis
- Can lead to **renal failure** and death



# Rhabdomyolysis

## Causes of Muscle Damage

- Intense physical exercise
  - Especially if dehydrated
- **Crush injuries** (trauma)
- **Drugs**
  - Statins
  - Fibrates
  - Colchicine

# Muscle Contents

- **Creatine kinase**
  - Elevated levels are hallmark of rhabdomyolysis
- Aldolase, lactate dehydrogenase, AST/ALT

# Muscle Contents

- **Potassium** and **phosphate**
  - Hyperkalemia/hyperphosphatemia in rhabdomyolysis

19

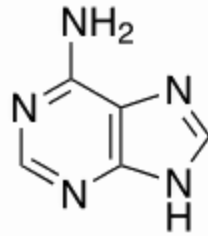
K

15

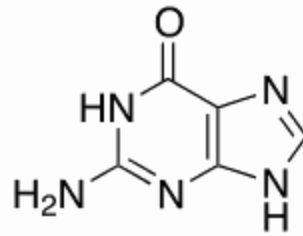
P

# Muscle Contents

- Purines
  - Metabolized to uric acid in liver
  - Can lead to **hyperuricemia**



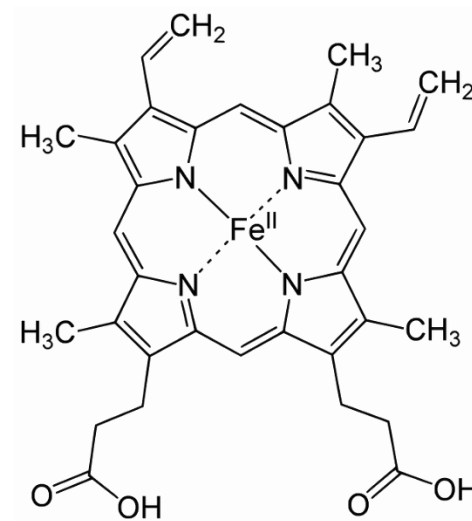
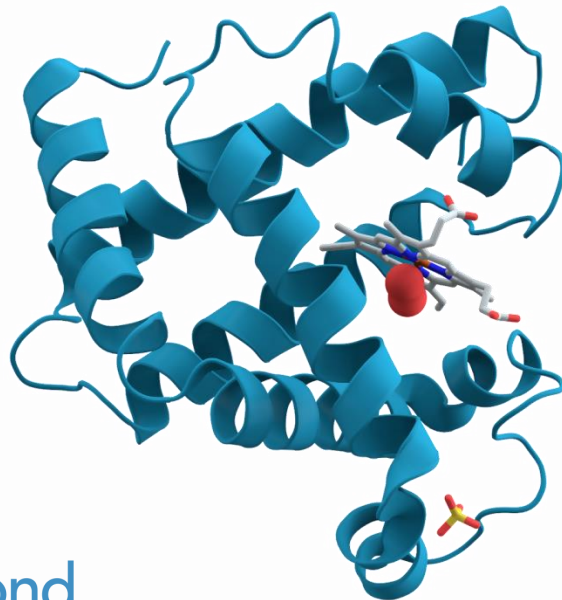
Adenine



Guanine

# Myoglobin

- Protein monomer
- Contains **heme**
- Binds oxygen for use by muscle tissue



# Myoglobin

## Renal Toxicity

- Obstructs tubules
- Toxic to proximal tubular cells
- Vasoconstriction
  - Especially in medulla
  - Leads to renal hypoxia
- Classic labs
  - Increased BUN and Cr (intrinsic renal)
  - Hyperkalemia

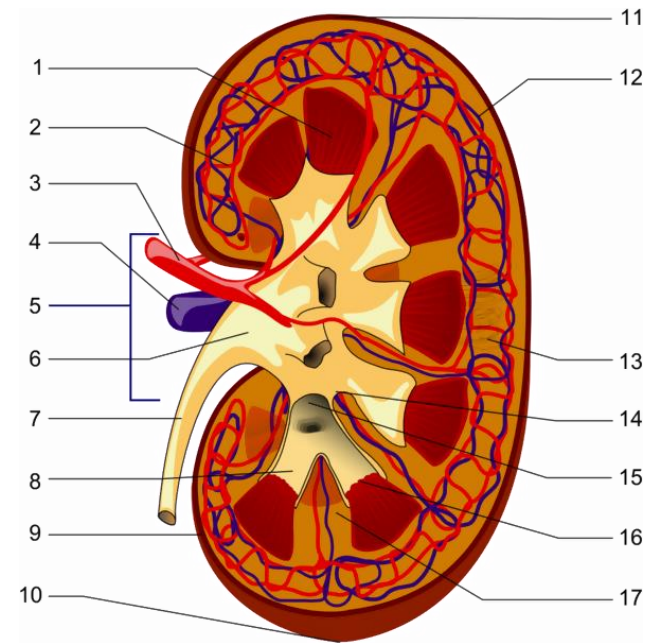


Image courtesy of Piotr Michał Jaworski

# Myoglobin

## Renal Toxicity

- Made worse by **volume depletion** in rhabdomyolysis
  - Intravascular fluid influx into muscle tissue
- Feared outcome rhabdomyolysis: **renal failure/death**





# Rhabdomyolysis

## Symptoms

- Muscle pain
- Weakness
- Dark urine (from myoglobin)



James Heilman, MD/Wikipedia

# Rhabdomyolysis

## Diagnosis

- **Creatine kinase**
  - Usually very high
  - Normal < 250 IU/L
  - Rhabdomyolysis > 1000 IU/L
  - Sometimes up to 25,000 or more IU/L

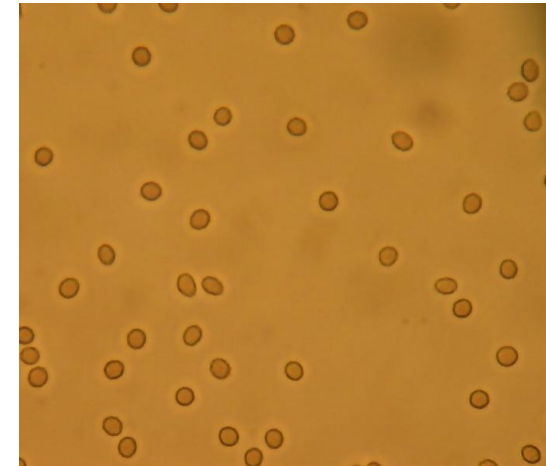
# Rhabdomyolysis

## Diagnosis

- Urinalysis for **heme**
  - Positive dipstick = hemoglobin or myoglobin
- Microscopy: no red blood cells
- Classic finding rhabdomyolysis
  - Dark urine
  - Positive dipstick for heme
  - No evidence of red blood cells



J3D3



Bobjgalindo

# Rhabdomyolysis

## Treatment

- **Volume resuscitation**
  - IV Fluids (usually isotonic saline)
  - Titrated to maintain good urine output
- Treatment of electrolyte abnormalities
- Dialysis



# Compartment Syndrome

- Increased pressure in closed anatomic space
- Can occur in severe rhabdomyolysis
- Usually after fluid resuscitation
- Worsening edema of the limb and muscle
- Pain
- Tense skin



Shutterstock

# Hypocalcemia

- Calcium deposits in damaged myocytes
- Initial phases rhabdomyolysis: **hypocalcemia**
- Recovery phase: release from myocytes
  - Levels return to normal
  - Can become elevated
- **Do not treat mild, asymptomatic hypocalcemia**

1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca

