

HIGH-YIELD SYSTEMS

Renal

“But I know all about love already. I know precious little still about kidneys.”

—Aldous Huxley, *Antic Hay*

“This too shall pass. Just like a kidney stone.”

—Hunter Madsen

“Playing dead is difficult with a full bladder.”

—Diane Lane

Being able to understand and apply renal physiology will be critical for the exam. Important topics include electrolyte disorders, acid-base derangements, glomerular disorders (including histopathology), acute and chronic kidney disease, urine casts, diuretics, ACE inhibitors, and AT II receptor blockers. Renal anomalies associated with various congenital defects are also high-yield associations to think about when evaluating pediatric vignettes.

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▶ RENAL—EMBRYOLOGY

Kidney embryology

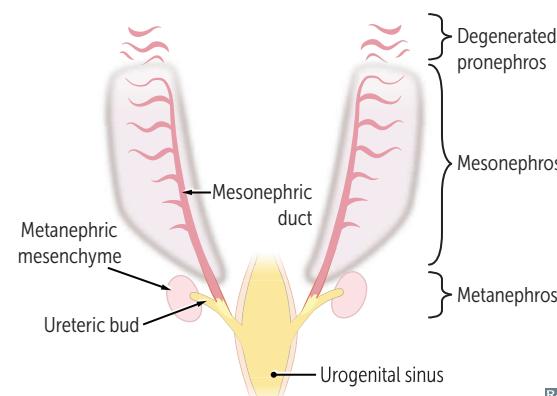
Pronephros—week 4 of development; then degenerates.

Mesonephros—week 4 of development; functions as interim kidney for 1st trimester in both sexes. Mesonephric ducts persist in the male genital system as Wolffian duct, forming ductus deferens and epididymis. Mesonephric ducts degenerate in females.

Metanephros—permanent; first appears in week 5 of development; nephrogenesis is normally completed by week 36 of gestation.

- Ureteric bud (metanephric diverticulum)—fully canalized by week 10 of development; derived from mesonephric duct to form ureters, pelvises, calyces, and collecting ducts
- Metanephric mesenchyme (ie, metanephric blastema)—ureteric bud interacts with this tissue to induce differentiation and formation of glomerulus through distal convoluted tubule (DCT)
- Aberrant interaction between these 2 tissues may result in several congenital malformations of the kidney (eg, renal agenesis, multicystic dysplastic kidney)

Ureteropelvic junction → last part of ureter to canalize; if doesn't fully canalize → congenital obstruction. Can be unilateral or bilateral. Most common pathologic cause of prenatal hydronephrosis. Detected by prenatal ultrasound.

**Potter sequence**

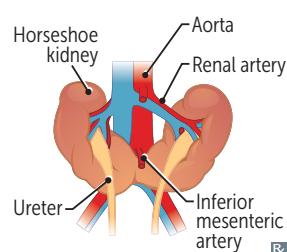
Oligohydramnios → compression of developing fetus → limb deformities (eg, club feet), facial anomalies (eg, low-set ears and retrognathia, flattened nose), compression of chest and lack of amniotic fluid aspiration into fetal lungs → pulmonary hypoplasia (cause of death).

Caused by chronic placental insufficiency or reduced fetal urine output, including ARPKD, obstructive uropathy (eg, posterior urethral valves), bilateral renal agenesis, preterm premature rupture of membranes, maternal ACE inhibitor use.

Babies who can't "Pee" in utero develop Potter sequence.

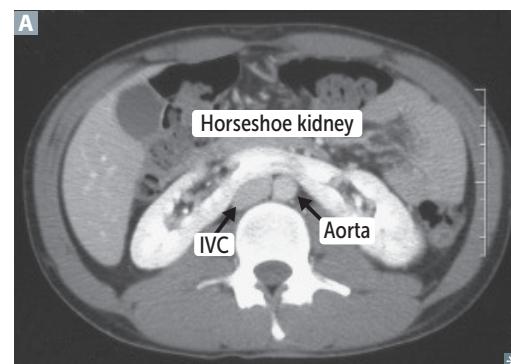
POTTER sequence associated with:

- Pulmonary hypoplasia
- Oligohydramnios (trigger)
- Twisted face
- Twisted skin
- Extremity defects
- Renal failure (in utero)

Horseshoe kidney

Inferior poles of both kidneys fuse abnormally **A**. As they ascend from pelvis during fetal development, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen. Kidneys can function normally, but associated with hydronephrosis (eg, ureteropelvic junction obstruction), renal stones, infection, ↑ risk of renal cancer.

Higher incidence in chromosomal aneuploidy (eg, Turner syndrome, trisomies 13, 18, 21).

**Congenital solitary functioning kidney**

Condition of being born with only one functioning kidney. Majority asymptomatic with compensatory hypertrophy of contralateral kidney, but anomalies in contralateral kidney are common. Often diagnosed prenatally via ultrasound bilateral agenesis or dysplasia leads to Potter sequence.

Unilateral renal agenesis

Ureteric bud fails to develop and induce differentiation of metanephric mesenchyme → complete absence of kidney and ureter.

Multicystic dysplastic kidney

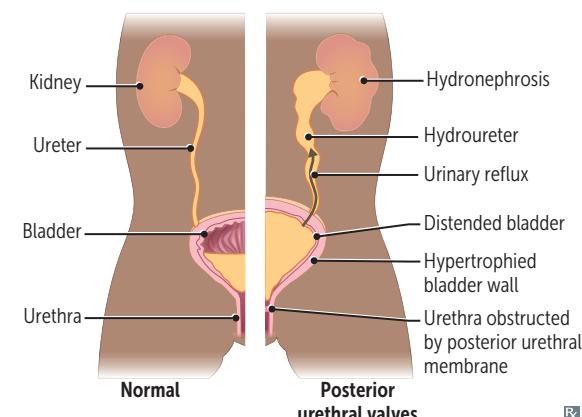
Ureteric bud develops, but fails to induce differentiation of metanephric mesenchyme → nonfunctional kidney consisting of cysts and connective tissue. Nongenetic inheritance, though tends to run in families; usually unilateral.

Duplex collecting system

Bifurcation of ureteric bud before it enters the metanephric blastema creates a Y-shaped bifid ureter. Duplex collecting system can alternatively occur through two ureteric buds reaching and interacting with metanephric blastema. Strongly associated with vesicoureteral reflux and/or ureteral obstruction, ↑ risk for UTIs. Frequently presents with hydronephrosis.

Posterior urethral valves

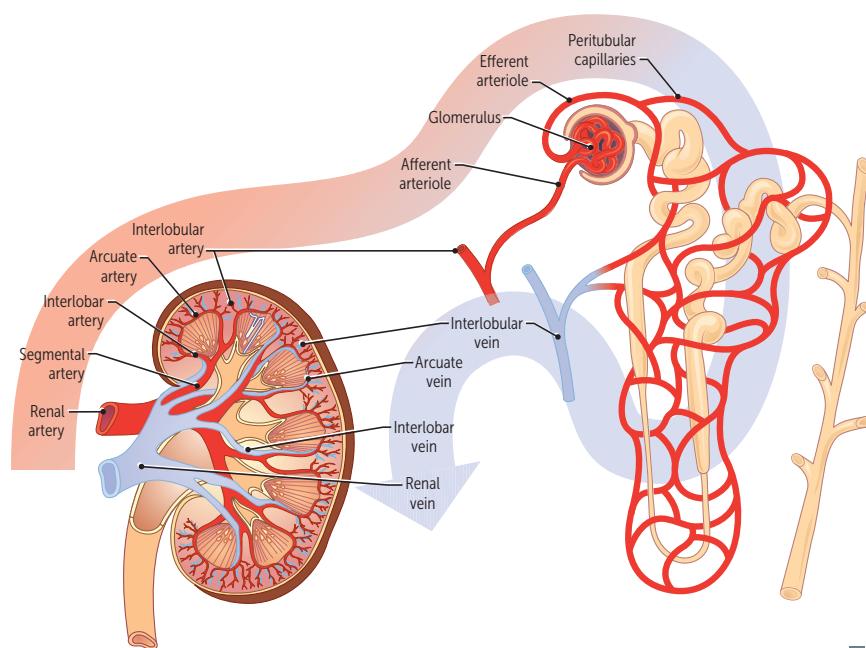
Membrane remnant in posterior (prostatic) urethra in males; its persistence can lead to urethral obstruction. Diagnosed prenatally by bilateral hydronephrosis and dilated or thick-walled bladder on ultrasound. Severe obstruction in fetus associated with oligohydramnios. Most common cause of bladder outlet obstruction in male infants.



Vesicoureteral reflux

Retrograde flow of urine from bladder toward upper urinary tract. Can be 1° due to abnormal/insufficient insertion of the ureter within the vesicular wall (ureterovesical junction [UVJ]) or 2° due to abnormally high bladder pressure resulting in retrograde flow via the UVJ. ↑ risk of recurrent UTIs.

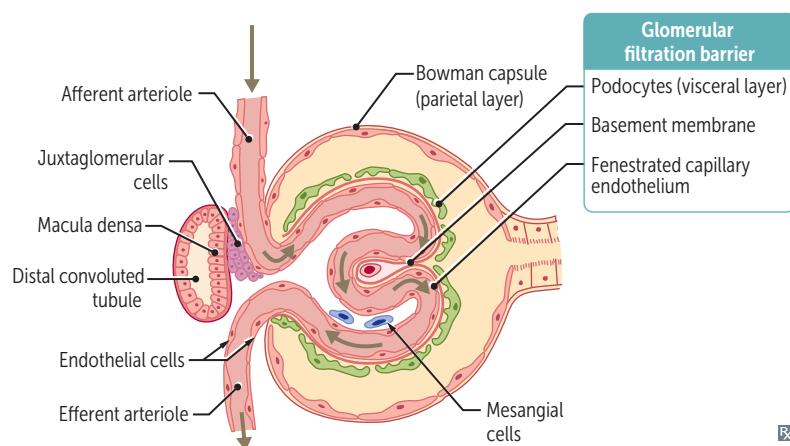
▶ RENAL—ANATOMY

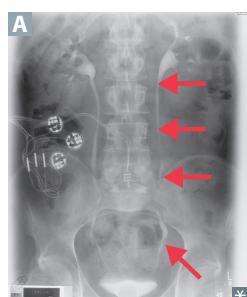
Renal blood flow

Left renal vein receives two additional veins: left suprarenal and left gonadal veins.

Renal medulla receives significantly less blood flow than the renal cortex. This makes medulla very sensitive to hypoxia and vulnerable to ischemic damage (eg, ATN).

Left kidney is most commonly taken during **Living donor transplANTation** because it has a **Longer** renal vein (**rule of Ls**).

Glomerular anatomy

Course of ureters

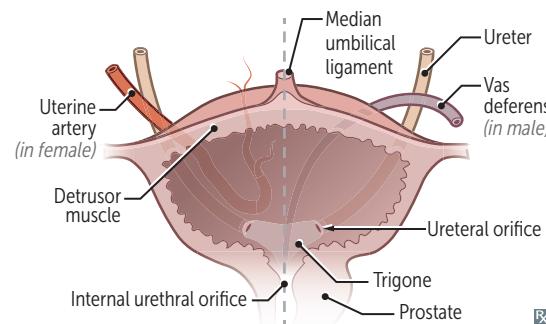
Course of ureter **A**: arises from renal pelvis, travels under gonadal arteries → over common iliac artery → under uterine artery/vas deferens (retroperitoneal).

Gynecologic procedures (eg, ligation of uterine or ovarian vessels) may damage ureter → ureteral obstruction or leak.

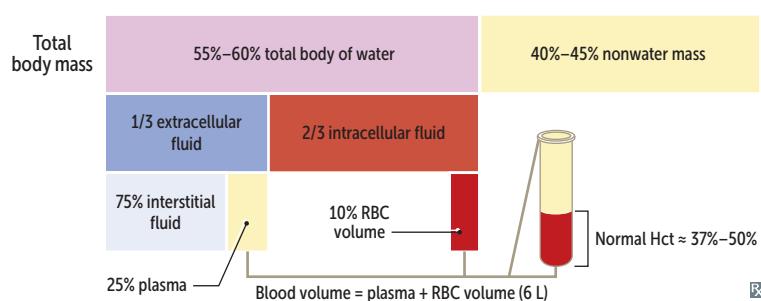
Bladder contraction compresses the intramural ureter, preventing urine reflux.

3 common points of ureteral obstruction:
ureteropelvic junction, pelvic inlet, ureterovesical junction.

Water (ureters) flows **over** the iliacs and **under** the bridge (uterine artery or vas deferens).



▶ RENAL—PHYSIOLOGY

Fluid compartments

HIKIN': HI K⁺ INtracellularly.

60–40–20 rule (% of body weight for average person):

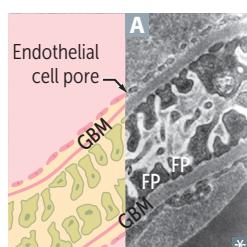
- 60% total body water
- 40% ICF, mainly composed of K⁺, Mg²⁺, organic phosphates (eg, ATP)
- 20% ECF, mainly composed of Na⁺, Cl⁻, HCO₃⁻, albumin

Plasma volume can be measured by radiolabeling albumin.

Extracellular volume can be measured by inulin or mannitol.

Serum osmolality = 275–295 mOsm/kg H₂O.

Plasma volume = TBV × (1 – Hct).

Glomerular filtration barrier

Responsible for filtration of plasma according to size and charge selectivity.

Composed of

- Fenestrated capillary endothelium
- Glomerular basement membrane (GBM) with type IV collagen chains and heparan sulfate
- Visceral epithelial layer consisting of podocyte foot processes (FPs) **A**

Charge barrier—glomerular filtration barrier contains \ominus charged glycoproteins that prevent entry of \ominus charged molecules (eg, albumin).

Size barrier—fenestrated capillary endothelium (prevents entry of > 100 nm molecules/blood cells); slit diaphragm (prevents entry of molecules > 40–50 nm).

Podocyte foot processes interpose with GBM—both charge and size barrier.

Renal clearance

$C_x = (U_x V)/P_x$ = volume of plasma from which the substance is completely cleared in the urine per unit time.

If $C_x < \text{GFR}$: net tubular reabsorption and/or not freely filtered.

If $C_x > \text{GFR}$: net tubular secretion of X.

If $C_x = \text{GFR}$: no net secretion or reabsorption.

C_x = clearance of X (mL/min).

U_x = urine concentration of X (eg, mg/mL).

P_x = plasma concentration of X (eg, mg/mL).

V = urine flow rate (mL/min).

Glomerular filtration rate

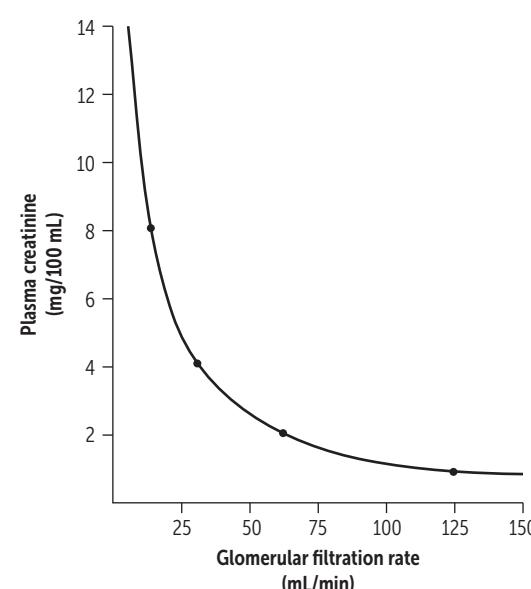
Inulin clearance can be used to calculate GFR because it is freely filtered and is neither reabsorbed nor secreted.

$$C_{\text{inulin}} = \text{GFR} = U_{\text{inulin}} \times V/P_{\text{inulin}} \\ = K_f [(P_{\text{GC}} - P_{\text{BS}}) - (\pi_{\text{GC}} - \pi_{\text{BS}})]$$

P_{GC} = glomerular capillary hydrostatic pressure; P_{BS} = Bowman space hydrostatic pressure; π_{GC} = glomerular capillary oncotic pressure; π_{BS} = Bowman space oncotic pressure; π_{BS} normally equals zero; K_f = filtration coefficient.

Normal GFR ≈ 100 mL/min.

Creatinine clearance is an approximate measure of GFR. Slightly overestimates GFR because creatinine is moderately secreted by proximal renal tubules.

**Renal blood flow autoregulation**

Autoregulatory mechanisms help maintain a constant RBF and GFR to protect the kidney from rapid fluctuations in renal perfusion pressure that could cause renal injury leading to reduced glomerular filtration. Mechanisms:

Myogenic: ↑ arterial pressure → stretch of afferent arteriole → mechanical activation of vascular smooth muscle → vasoconstriction of afferent arteriole → ↓ RBF.

Tubuloglomerular: ↑ NaCl of the filtrate sensed by macula densa cells → paracrine-driven vasoconstriction of afferent arteriole → ↓ RBF. Can also have the opposite effect on RBF if ↓ NaCl.

Effective renal plasma flow

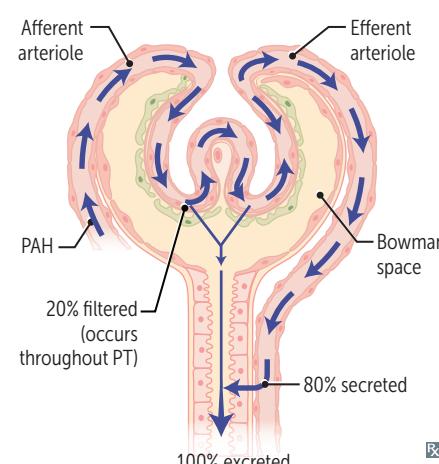
Effective renal plasma flow (eRPF) can be estimated using *para*-aminohippuric acid (PAH) clearance. Between filtration and secretion, there is nearly complete excretion of all PAH that enters the kidney.

$$eRPF = U_{\text{PAH}} \times V/P_{\text{PAH}} = C_{\text{PAH}}$$

Renal blood flow (RBF) = RPF/(1 - Hct).

Usually 20–25% of cardiac output.

eRPF underestimates true renal plasma flow (RPF) slightly.



Filtration

Filtration fraction (FF) = GFR/RPF.

Normal FF = 20%.

Filtered load (mg/min) = GFR (mL/min)
× plasma concentration (mg/mL).

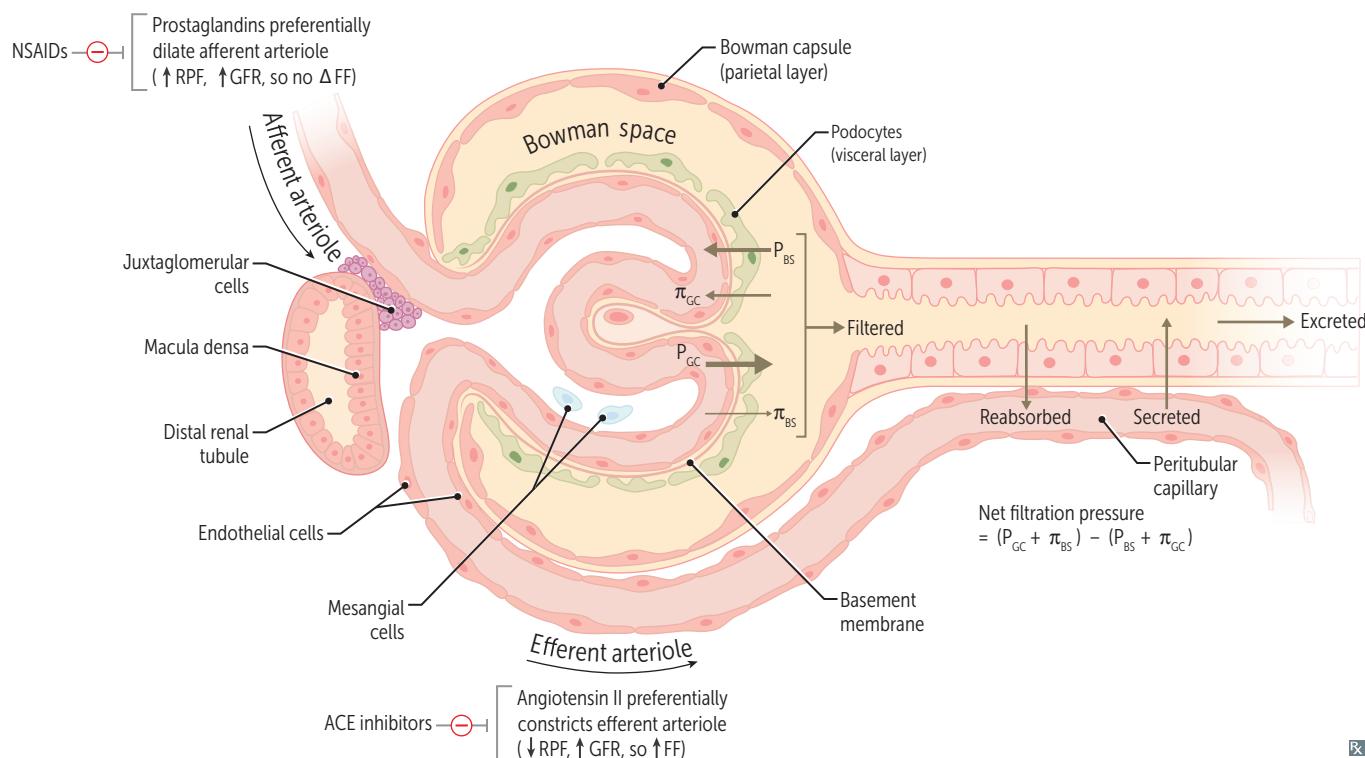
GFR can be estimated with creatinine clearance.

Prostaglandins Dilate Afferent arteriole (PDA).

Angiotensin II Constricts Efferent arteriole

(ACE).

RPF is best estimated with PAH clearance. NSAIDs and ACE inhibitors should not be given together → constriction of afferent and efferent arterioles.

**Changes in glomerular dynamics**

| | GFR | RPF | FF (GFR/RPF) |
|---------------------------------|-----|-----|--------------|
| Afferent arteriole constriction | ↓ | ↓ | — |
| Efferent arteriole constriction | ↑ | ↓ | ↑ |
| ↑ plasma protein concentration | ↓ | — | ↓ |
| ↓ plasma protein concentration | ↑ | — | ↑ |
| Constriction of ureter | ↓ | — | ↓ |
| Dehydration | ↓ | ↓↓ | ↑ |

Notably for patients undergoing nephrectomy, there is a proportionate decline in renal function (↓ nephron number)

→ ↓ remaining kidney renal function to ~50% of prenephrectomy value until long-term compensations like hypertrophy develop.

Calculation of reabsorption and secretion rate

Filtered load = $GFR \times P_x$.
 Excretion rate = $V \times U_x$.
 Reabsorption rate = filtered – excreted.
 Secretion rate = excreted – filtered.
 FENa = fractional excretion of sodium.

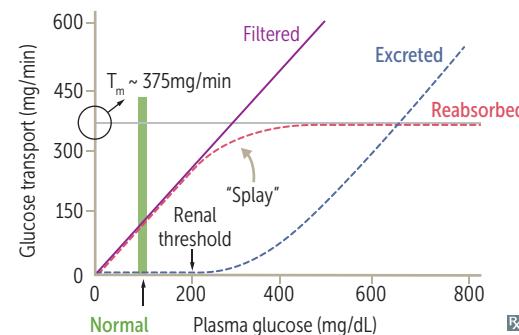
$$FENa = \frac{Na^+ \text{ excreted}}{Na^+ \text{ filtered}} = \frac{V \times U_{Na}}{GFR \times P_{Na}} = \frac{P_{Cr} \times U_{Na}}{U_{Cr} \times P_{Na}} \text{ where } GFR = \frac{U_{Cr} \times V}{P_{Cr}}$$

Glucose clearance

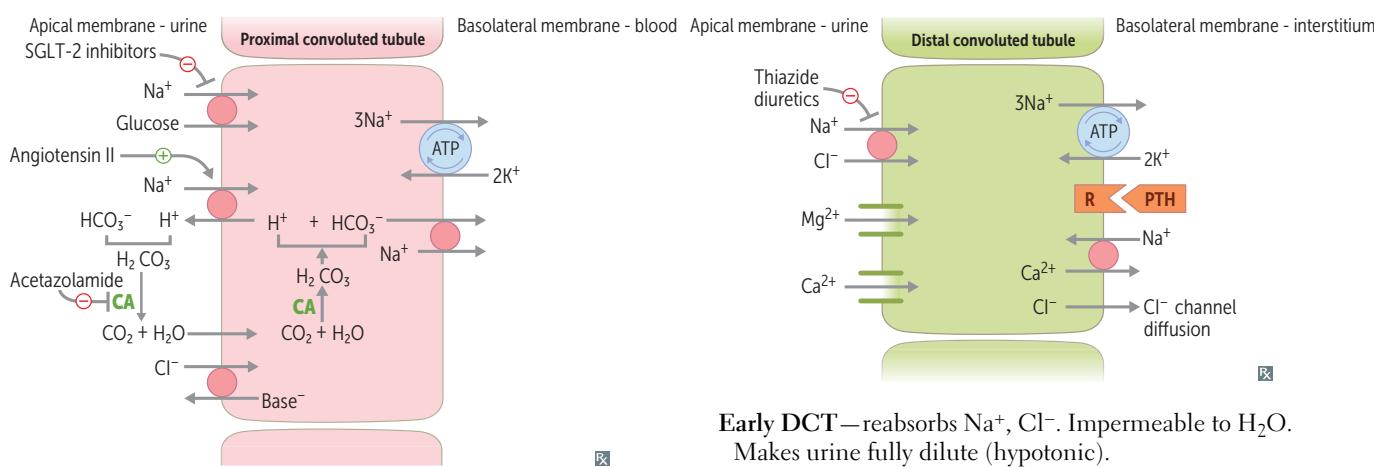
Glucose at a normal plasma level (range 60–120 mg/dL) is completely reabsorbed in proximal convoluted tubule (PCT) by Na^+ /glucose cotransport. In adults, at plasma glucose of ~ 200 mg/dL, glucosuria begins (threshold). At rate of ~ 375 mg/min, all transporters are fully saturated (T_m). Normal pregnancy is associated with ↑ GFR. With ↑ filtration of all substances, including glucose, the glucose threshold occurs at lower plasma glucose concentrations → glucosuria at normal plasma glucose levels. Sodium-glucose cotransporter 2 (SGLT2) inhibitors (eg, -floxin drugs) lead to glucosuria at plasma concentrations < 200 mg/dL.

Glucosuria is an important clinical clue to diabetes mellitus.

Splay phenomenon— T_m for glucose is reached gradually rather than sharply due to the heterogeneity of nephrons (ie, different T_m points); represented by the portion of the titration curve between threshold and T_m .



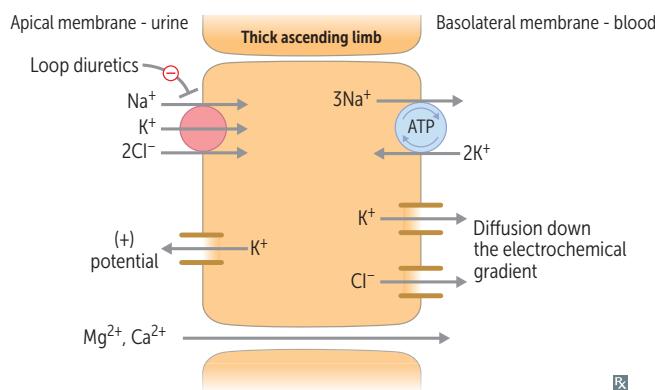
Nephron transport physiology



Early PCT—contains brush border. Reabsorbs all glucose and amino acids and most HCO₃⁻, Na⁺, Cl⁻, PO₄³⁻, K⁺, H₂O, and uric acid. Isotonic absorption. Generates and secretes NH₃, which enables the kidney to excrete (via secretion) more H⁺.

PTH— inhibits Na⁺/PO₄³⁻ cotransport → ↑ PO₄³⁻ excretion.
AT II— stimulates Na⁺/H⁺ exchange → ↑ Na⁺, H₂O, and HCO₃⁻ reabsorption (permitting contraction alkalosis). 65–80% Na⁺ and H₂O reabsorbed.

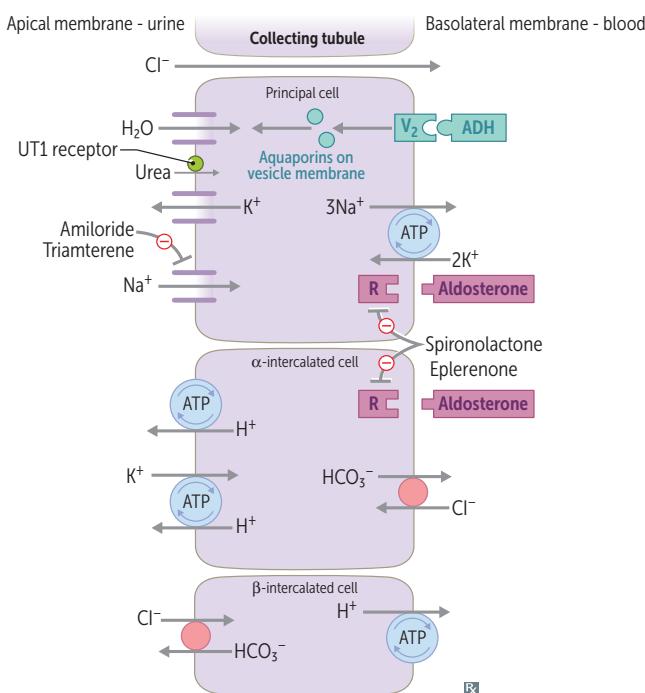
Thin descending loop of Henle—passively reabsorbs H₂O via medullary hypertonicity (impermeable to Na⁺). Concentrating segment. Makes urine hypertonic.



Thick ascending loop of Henle—reabsorbs Na⁺, K⁺, and Cl⁻. Indirectly induces paracellular reabsorption of Mg²⁺ and Ca²⁺ through + lumen potential generated by K⁺ backleak. Impermeable to H₂O. Makes urine less concentrated as it ascends. 10–20% Na⁺ reabsorbed.

Early DCT—reabsorbs Na⁺, Cl⁻. Impermeable to H₂O. Makes urine fully dilute (hypotonic).

PTH—↑ Ca²⁺/Na⁺ exchange → ↑ Ca²⁺ reabsorption.
5–10% Na⁺ reabsorbed.

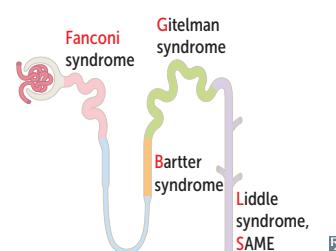


Collecting tubule—reabsorbs Na⁺ in exchange for secreting K⁺ and H⁺ (regulated by aldosterone).

Aldosterone—acts on mineralocorticoid receptor → mRNA → protein synthesis. In principal cells: ↑ apical K⁺ conductance, ↑ Na⁺/K⁺ pump, ↑ epithelial Na⁺ channel (ENaC) activity → lumen negativity → K⁺ secretion. In α-intercalated cells: lumen negativity → ↑ H⁺ ATPase activity → ↑ H⁺ secretion → ↑ HCO₃⁻/Cl⁻ exchanger activity.

ADH—acts at V₂ receptor → insertion of aquaporin H₂O channels on apical side.

3–5% Na⁺ reabsorbed. Urea reabsorption (medullary, not cortical, duct only).

Renal tubular defects Order: **Fanconi's BaGeLS**

| | DEFECTS | EFFECTS | CAUSES | NOTES |
|------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fanconi syndrome | Generalized reabsorption defect in PCT → ↑ excretion of amino acids, glucose, HCO_3^- , and PO_4^{3-} , and all substances reabsorbed by the PCT | Metabolic acidosis (proximal RTA), hypophosphatemia, hypokalemia | Hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease), ischemia, multiple myeloma, drugs (eg, ifosfamide, cisplatin, tenofovir, lead poisoning) | Growth restriction and rickets/osteopenia common due to hypophosphatemia Volume depletion also common |
| Bartter syndrome | Reabsorption defect in thick ascending loop of Henle (affects $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ cotransporter) | Metabolic alkalosis, hypochloremia, hypokalemia, hypercalciuria | Autosomal recessive | Presents similarly to chronic loop diuretic use |
| Gitelman syndrome | Reabsorption defect of NaCl in DCT | Metabolic alkalosis, hypochloremia, hypomagnesemia, hypokalemia | Autosomal recessive | Presents similarly to chronic thiazide diuretic use Less severe than Bartter syndrome |
| Liddle syndrome | Gain of function mutation → ↓ Na^+ channel degradation → ↑ Na^+ reabsorption in collecting tubules | Metabolic alkalosis, hypokalemia, hypertension, ↓ serum aldosterone | Autosomal dominant | Presents similarly to hyperaldosteronism, but aldosterone is nearly undetectable Treatment: amiloride |
| Syndrome of Apparent Mineralocorticoid Excess | Cortisol activates mineralocorticoid receptors; 11β -HSD converts cortisol to cortisone (inactive on these receptors) Hereditary 11β -HSD deficiency → ↑ cortisol → ↑ mineralocorticoid receptor activity | Metabolic alkalosis, hypokalemia, hypertension ↓ serum aldosterone level; cortisol tries to be the SAME as aldosterone | Autosomal recessive Can acquire disorder from glycyrrhetic acid (present in licorice), which blocks activity of 11β -hydroxysteroid dehydrogenase | Treatment: K^+ -sparing diuretics (↓ mineralocorticoid effects) or corticosteroids (exogenous corticosteroid ↓ endogenous cortisol production → ↓ mineralocorticoid receptor activation) |

Features of renal disorders

| CONDITION | BLOOD PRESSURE | PLASMA RENIN | ALDOSTERONE | SERUM Mg ²⁺ | URINE Ca ²⁺ |
|-----------------------------------------------------------------------|----------------|--------------|-------------|------------------------|------------------------|
| SIADH | —/↑ | —/↓ | —/↓ | — | — |
| Bartter syndrome | — | ↑ | ↑ | — | ↑ |
| Gitelman syndrome | — | ↑ | ↑ | ↓ | ↓ |
| Renin-secreting tumor | ↑ | ↑ | ↑ | — | — |
| Primary hyperaldosteronism | ↑ | ↓ | ↑ | — | — |
| Liddle syndrome, syndrome of apparent mineralocorticoid excess | ↑ | ↓ | ↓ | — | — |

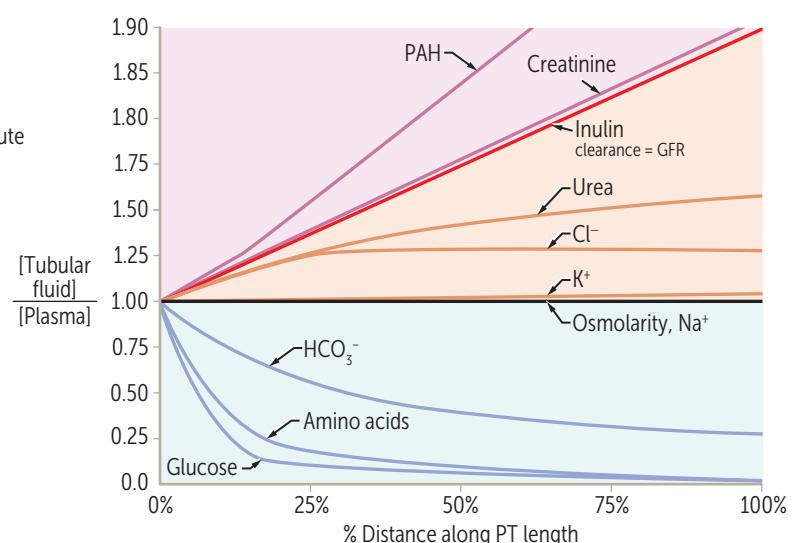
↑ ↓ = important differentiating feature.

Relative concentrations along proximal tubule

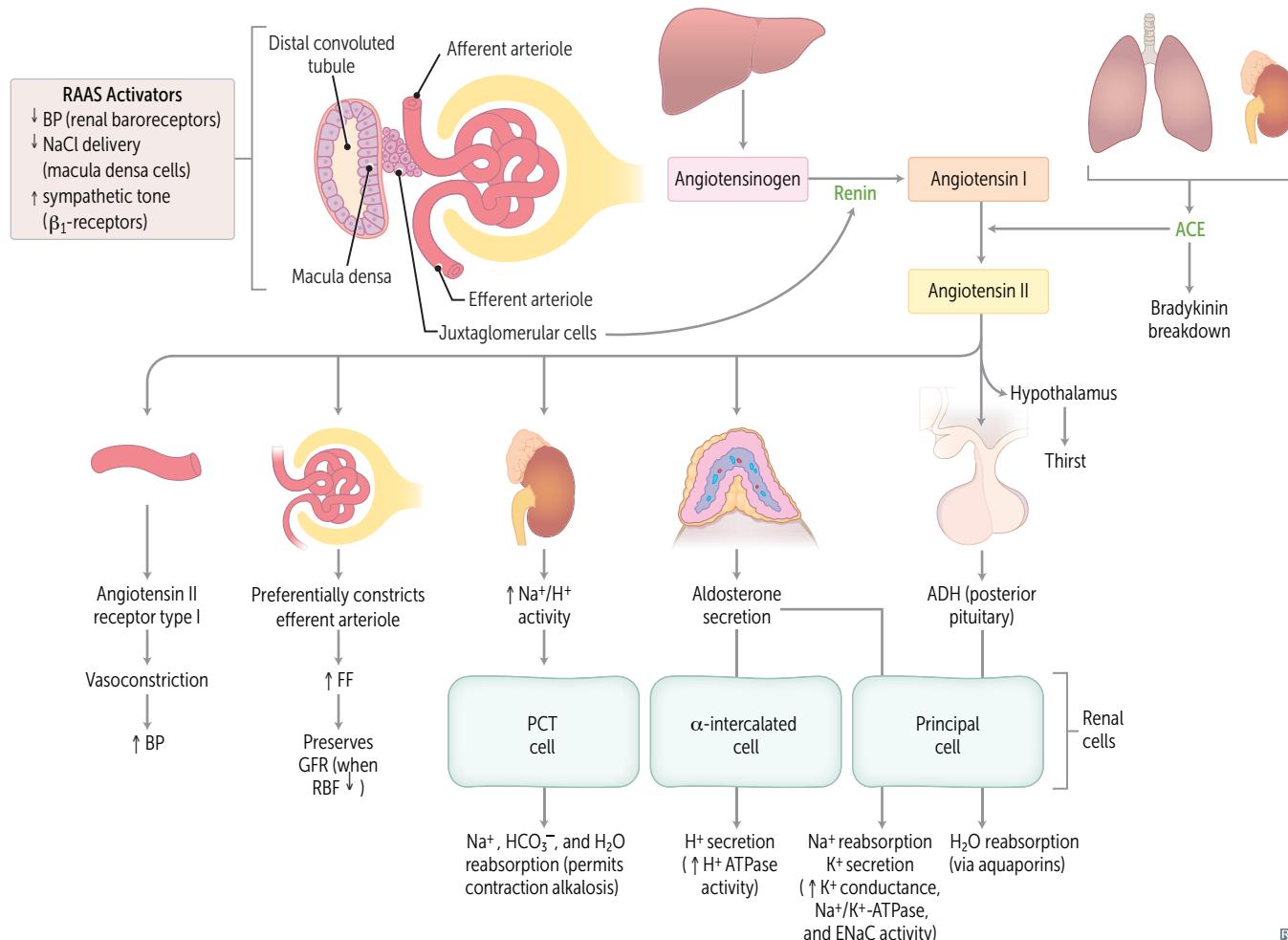
[TF/P] > 1
when solute is reabsorbed less quickly than water or when solute is secreted

[TF/P] = 1
when solute and water are reabsorbed at the same rate

[TF/P] < 1
when solute is reabsorbed more quickly than water



Tubular inulin ↑ in concentration (but not amount) along the PT as a result of water reabsorption. Cl⁻ reabsorption occurs at a slower rate than Na⁺ in early PCT and then matches the rate of Na⁺ reabsorption more distally. Thus, its relative concentration ↑ before it plateaus.

Renin-angiotensin-aldosterone system**Renin**

Secreted by JG cells in response to ↓ renal perfusion pressure (detected in afferent arteriole), ↑ renal sympathetic discharge (β_1 effect), and ↓ NaCl delivery to macula densa cells.

ACE

Catalyzes conversion of angiotensin I to angiotensin II. Located in many tissues but conversion occurs most extensively in the lung. Produced by vascular endothelial cells in the lung.

AT II

Helps maintain blood volume and blood pressure. Affects baroreceptor function; limits reflex bradycardia, which would normally accompany its pressor effects.

ANP, BNP

Released from atria (ANP) and ventricles (BNP) in response to ↑ volume; relaxes vascular smooth muscle via cGMP → ↑ GFR; ↓ renin → angiotensin-aldosterone inhibition. Dilates afferent arteriole, promotes natriuresis.

ADH (vasopressin)

Primarily regulates serum osmolality; also responds to low blood volume states. Stimulates reabsorption of water in collecting ducts. Also stimulates reabsorption of urea in medullary collecting ducts to maximize corticopapillary osmotic gradient.

Aldosterone

Primarily regulates ECF volume and Na^+ content; ↑ release in hypovolemic states. Responds to hyperkalemia by ↑ K^+ excretion.

Juxtaglomerular apparatus

Consists of mesangial cells, JG cells (modified smooth muscle of afferent arteriole), and the macula densa (NaCl sensor located at the DCT). JG cells secrete renin in response to ↓ renal blood pressure and ↑ sympathetic tone (β_1). Macula densa cells sense ↓ NaCl delivery to DCT → ↑ renin release → efferent arteriole vasoconstriction → ↑ GFR. Communication between JG cells and macula densa occurs via gap junctions.

JGA prevents short-term changes in GFR through autoregulation and maintains GFR long-term through regulation of the renin-angiotensin-aldosterone system. β -blockers ↓ BP by ↓ CO and inhibiting β_1 -receptors of the JGA → ↓ renin release.

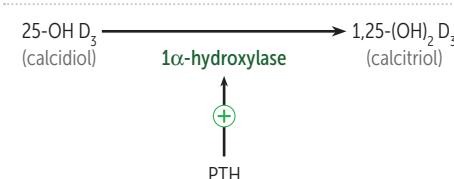
Kidney endocrine/paracrine functions**Erythropoietin**

Released by interstitial cells in peritubular capillary bed in response to hypoxia.

Stimulates RBC proliferation in bone marrow. Administered for anemia secondary to chronic kidney disease. Adverse effect: ↑ risk of HTN in some individuals.

Calciferol (vitamin D)

PCT cells convert 25-OH vitamin D₃ to 1,25-(OH)₂ vitamin D₃ (calcitriol, active form). Increases calcium absorption in small bowel.

**Prostaglandins**

Paracrine secretion vasodilates afferent arterioles to ↑ RBF.

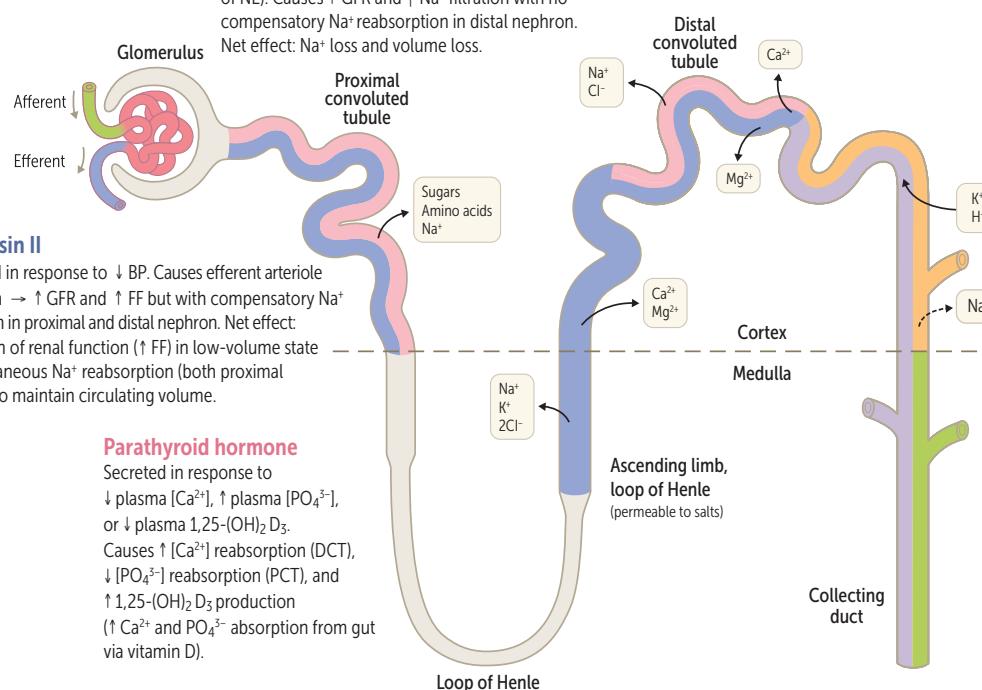
NSAIDs block renal-protective prostaglandin synthesis → constriction of afferent arteriole and ↓ GFR; this may result in acute kidney injury in low renal blood flow states.

Dopamine

Secreted by PT cells, promotes natriuresis. At low doses; dilates interlobular arteries, afferent arterioles, efferent arterioles → ↑ RBF, little or no change in GFR. At higher doses; acts as vasoconstrictor.

Hormones acting on kidney**Atrial natriuretic peptide**

Secreted in response to ↑ atrial pressure. Causes indirect afferent arteriole dilation (through inhibition of NE). Causes ↑ GFR and ↑ Na^+ filtration with no compensatory Na^+ reabsorption in distal nephron. Net effect: Na^+ loss and volume loss.

**Angiotensin II**

Synthesized in response to ↓ BP. Causes efferent arteriole constriction → ↑ GFR and ↑ FF but with compensatory Na^+ reabsorption in proximal and distal nephron. Net effect: preservation of renal function (↑ FF) in low-volume state with simultaneous Na^+ reabsorption (both proximal and distal) to maintain circulating volume.

Parathyroid hormone

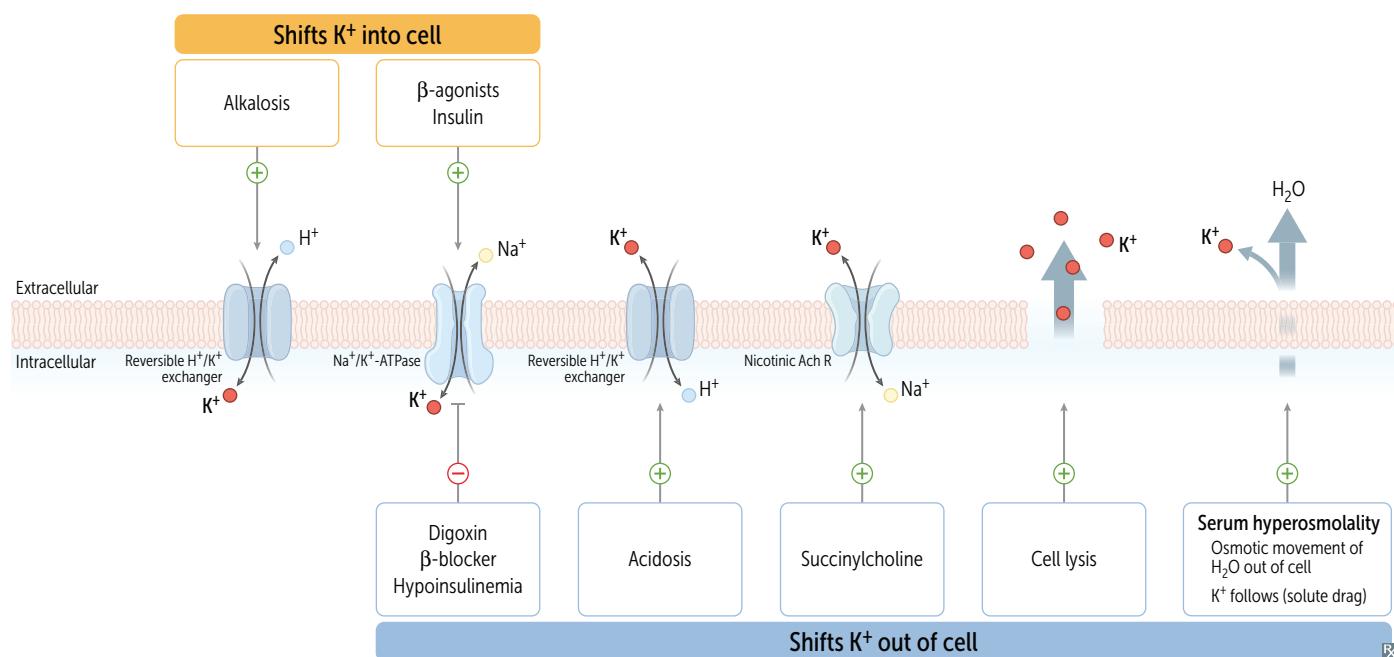
Secreted in response to ↓ plasma $[\text{Ca}^{2+}]$, ↑ plasma $[\text{PO}_4^{3-}]$, or ↓ plasma $1,25-(\text{OH})_2 \text{D}_3$. Causes ↑ $[\text{Ca}^{2+}]$ reabsorption (DCT), ↓ $[\text{PO}_4^{3-}]$ reabsorption (PCT), and ↑ $1,25-(\text{OH})_2 \text{D}_3$ production (↑ Ca^{2+} and PO_4^{3-} absorption from gut via vitamin D).

Aldosterone

Secreted in response to ↓ blood volume (via AT II) and ↑ plasma $[\text{K}^+]$; causes ↑ Na^+ reabsorption, ↑ K^+ secretion, ↑ H^+ secretion.

ADH (vasopressin)

Secreted in response to ↑ plasma osmolarity and ↓ blood volume. Binds to receptors on principal cells, causing ↑ number of aquaporins and ↑ H_2O reabsorption. ↑ reabsorption of urea in medullary collecting ducts to maximize corticopapillary osmotic gradient.

**Potassium shifts**

Electrolyte disturbances

| ELECTROLYTE | LOW SERUM CONCENTRATION | HIGH SERUM CONCENTRATION |
|------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sodium | Nausea, malaise, stupor, coma, seizures | Irritability, stupor, coma |
| Potassium | U waves and flattened T waves on ECG, arrhythmias, muscle cramps, spasm, weakness | Wide QRS and peaked T waves on ECG, arrhythmias, muscle weakness |
| Calcium | Tetany, seizures, QT prolongation, twitching (eg, Chvostek sign), spasm (eg, Trousseau sign) | Stones (renal), bones (pain), groans (abdominal pain), thrones (\uparrow urinary output frequency), psychiatric overtones (anxiety, altered mental status) |
| Magnesium | Tetany, torsades de pointes, hypokalemia, hypocalcemia (when $[Mg^{2+}] < 1.0 \text{ mEq/L}$) | \downarrow DTRs, lethargy, bradycardia, hypotension, cardiac arrest, hypocalcemia |
| Phosphate | Bone loss, osteomalacia (adults), rickets (children) | Renal stones, metastatic calcifications, hypocalcemia |

Acid-base physiology

Metabolic acid-base disorders cause HCO_3^- alterations. Respiratory acid-base disorders cause PCO_2 alterations.

| | pH | PCO_2 | $[\text{HCO}_3^-]$ | COMPENSATORY RESPONSE |
|------------------------------|--------------|----------------|--------------------|--------------------------------------------------------------|
| Metabolic acidosis | \downarrow | \downarrow | \downarrow | Hyperventilation (immediate) |
| Metabolic alkalosis | \uparrow | \uparrow | \uparrow | Hypoventilation (immediate) |
| Respiratory acidosis | \downarrow | \uparrow | \uparrow | \uparrow renal $[\text{HCO}_3^-]$ reabsorption (delayed) |
| Respiratory alkalosis | \uparrow | \downarrow | \downarrow | \downarrow renal $[\text{HCO}_3^-]$ reabsorption (delayed) |

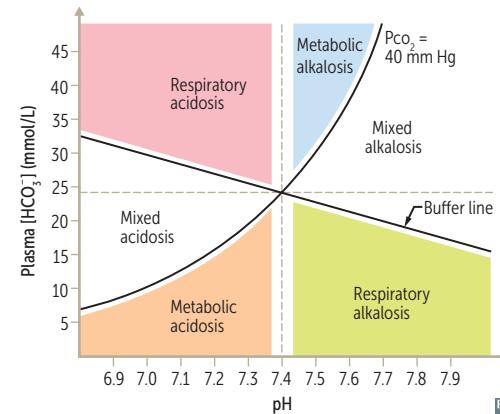
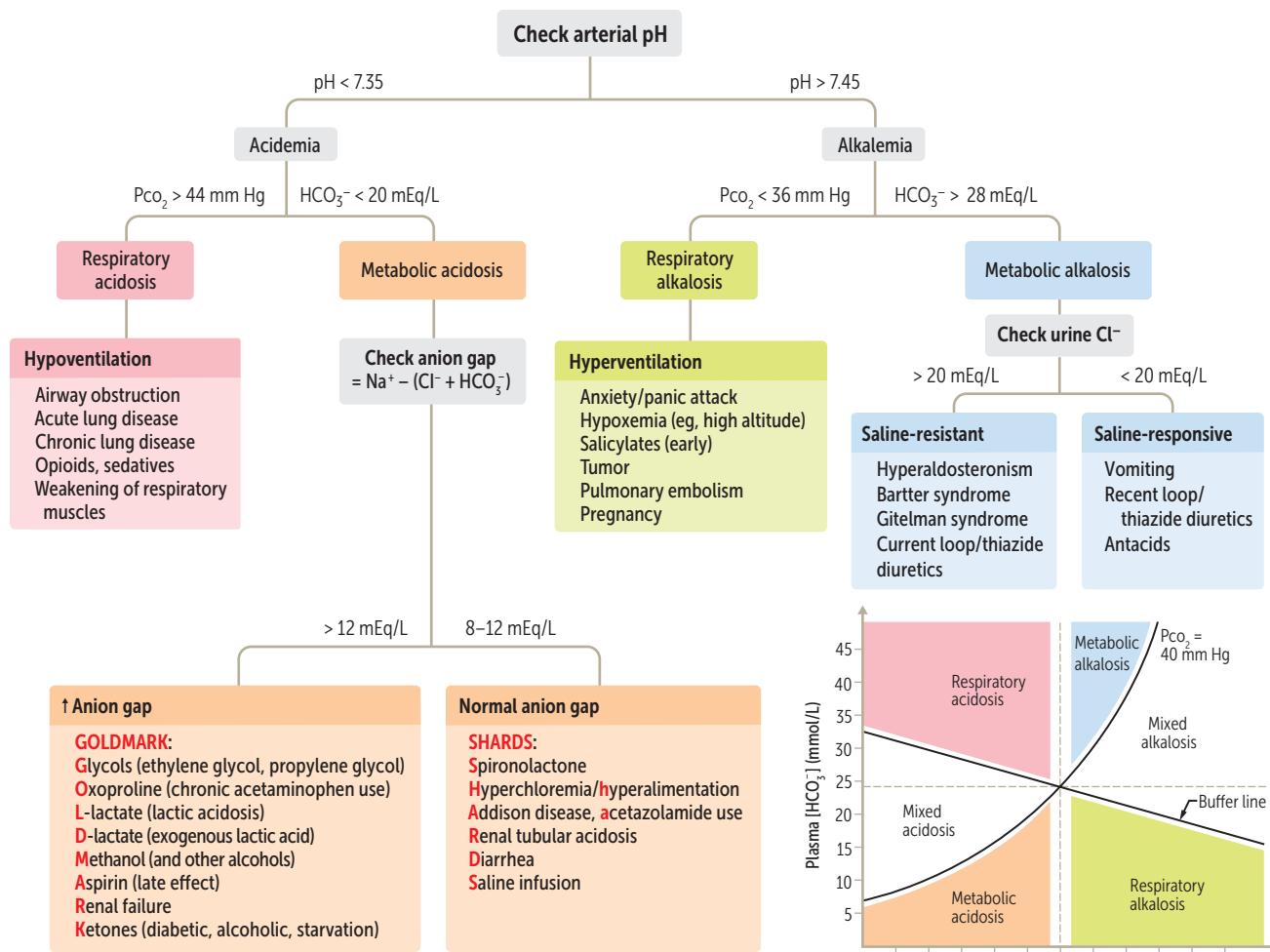
Key: \downarrow \uparrow = compensatory response.

$$\text{Henderson-Hasselbalch equation: } \text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ PCO}_2}$$

Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winters formula. If measured $\text{PCO}_2 >$ predicted $\text{PCO}_2 \rightarrow$ concomitant respiratory acidosis; if measured $\text{PCO}_2 <$ predicted $\text{PCO}_2 \rightarrow$ concomitant respiratory alkalosis:

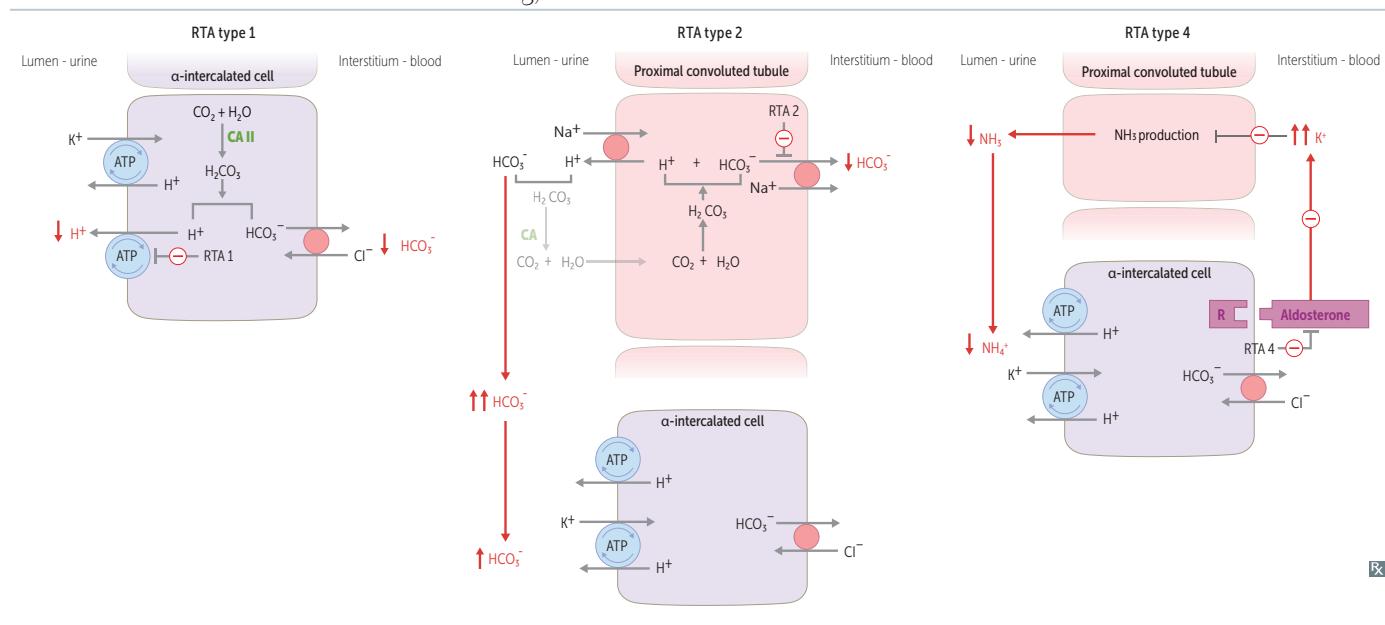
$$\text{PCO}_2 = 1.5 [\text{HCO}_3^-] + 8 \pm 2$$

Acidosis and alkalosis



Renal tubular acidosis

| | Distal renal tubular acidosis (RTA type 1) | Proximal renal tubular acidosis (RTA type 2) | Hyperkalemic tubular acidosis (RTA type 4) |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| DEFECT | Inability of α -intercalated cells to secrete $H(1)^+$ → no new HCO_3^- is generated → metabolic acidosis | Defect in PCT bi(2)carbonate (HCO_3^-) reabsorption → ↑ excretion of HCO_3^- in urine → metabolic acidosis Urine can be acidified by α -intercalated cells in collecting duct, but not enough to overcome ↑ HCO_3^- excretion | Hypoaldosteronism or aldosterone resistance; hyperkalemia → ↓ NH_3 synthesis in PCT → ↓ NH_4^+ excretion |
| URINE pH | > 5.5 | < 5.5 when plasma HCO_3^- below reduced resorption threshold > 5.5 when filtered HCO_3^- exceeds resptive threshold | Variable |
| SERUM K^+ | ↓ | ↓ | ↑ |
| CAUSES | Amphotericin B toxicity, analgesic nephropathy, congenital anomalies (obstruction) of urinary tract, autoimmune diseases (eg, SLE) | Fanconi syndrome, multiple myeloma, carbonic anhydrase inhibitors | ↓ aldosterone production (eg, diabetic hyporeninism, ACE inhibitors, ARB, NSAIDs, heparin, cyclosporine, adrenal insufficiency) or aldosterone resistance (eg, K^+ -sparing diuretics, nephropathy due to obstruction, TMP-SMX) |
| ASSOCIATIONS | ↑ risk for calcium phosphate kidney stones (due to ↑ urine pH and ↑ bone turnover related to buffering) | ↑ risk for hypophosphatemic rickets (in Fanconi syndrome) | |



▶ RENAL—PATHOLOGY

Casts in urine

Presence of casts indicates that hematuria/pyuria is of glomerular or renal tubular origin.

Bladder cancer, kidney stones → hematuria, no casts.

Acute cystitis → pyuria, no casts.

All casts contain a matrix composed primarily of Tamm-Horsfall mucoprotein (uromodulin), secreted by renal tubular cells to prevent UTIs.

RBC casts A

Glomerulonephritis, hypertensive emergency.

WBC casts

Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection.

Granular casts B

Acute tubular necrosis (ATN). Can be “muddy brown” in appearance.

Fatty casts (“oval fat bodies”)

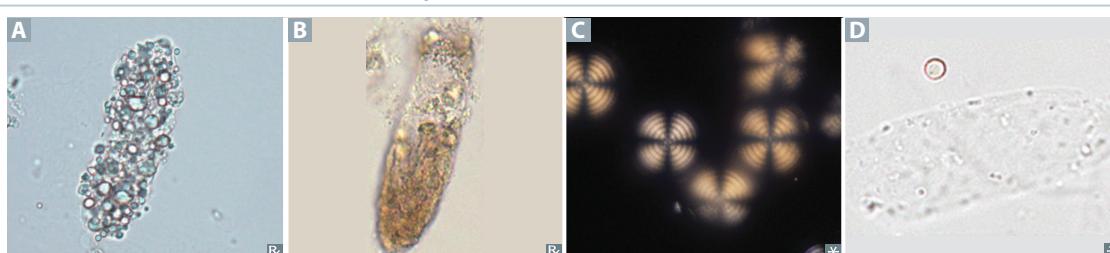
Nephrotic syndrome. Associated with “Maltese cross” sign C.

Waxy casts

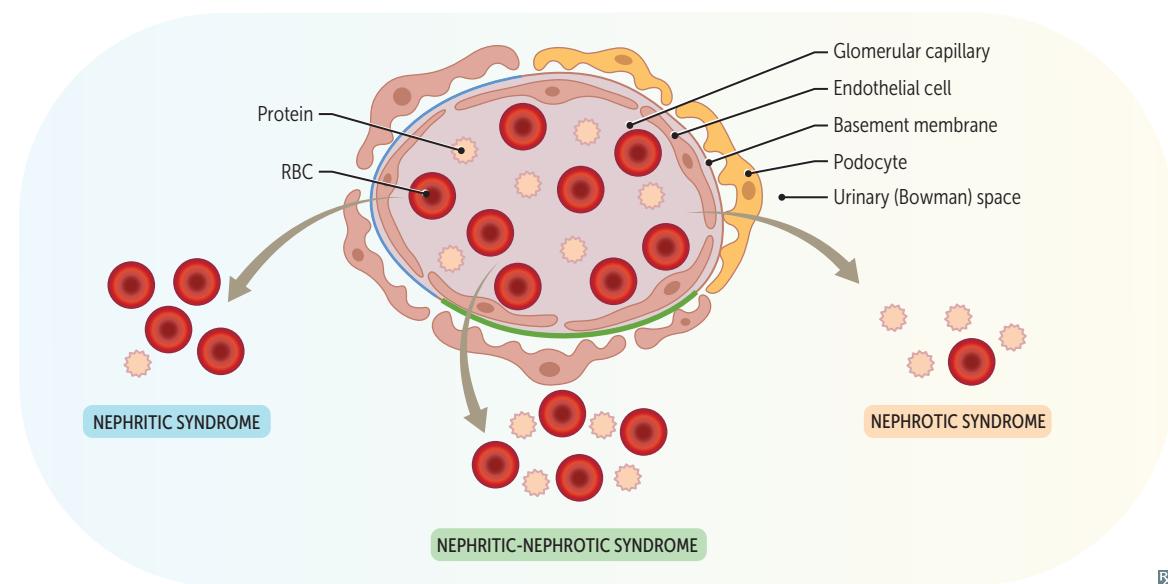
End-stage renal disease/chronic kidney disease.

Hyaline casts D

Nonspecific, can be a normal finding with dehydration, exercise, or diuretic therapy.

**Nomenclature of glomerular disorders**

| TYPE | CHARACTERISTICS | EXAMPLE |
|-------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------|
| Focal | < 50% of glomeruli are involved | Focal segmental glomerulosclerosis |
| Diffuse | > 50% of glomeruli are involved | Diffuse proliferative glomerulonephritis |
| Proliferative | Hypercellular glomeruli | Membranoproliferative glomerulonephritis |
| Membranous | Thickening of GBM | Membranous nephropathy |
| Primary glomerular disease | 1° disease of the kidney specifically impacting the glomeruli | Minimal change disease |
| Secondary glomerular disease | Systemic disease or disease of another organ system that also impacts the glomeruli | SLE, diabetic nephropathy |

Glomerular diseases

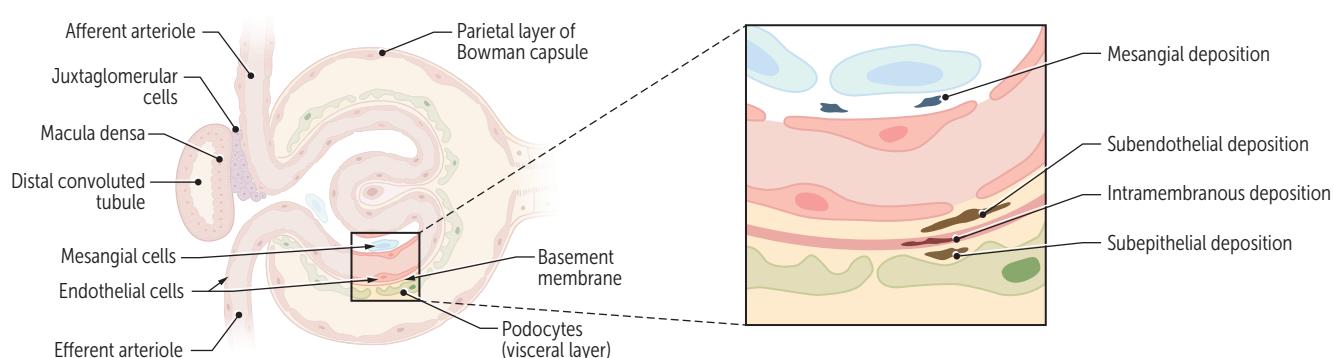
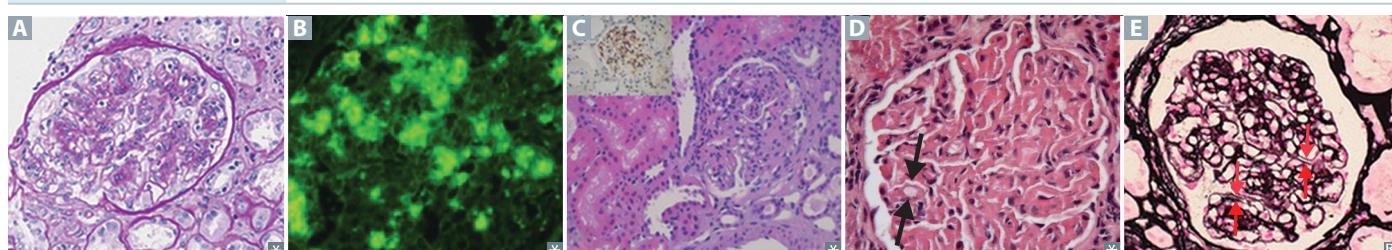
| TYPE | ETIOLOGY | CLINICAL PRESENTATION | EXAMPLES |
|-------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nephritic syndrome | Glomerular inflammation → GBM damage → loss of RBCs into urine → dysmorphic RBCs, hematuria | Hematuria, RBC casts in urine ↓ GFR → oliguria, azotemia ↑ renin release, HTN Proteinuria often in the subnephrotic range (< 3.5 g/day) but in severe cases may be in nephrotic range | <ul style="list-style-type: none"> ▪ Infection-associated glomerulonephritis ▪ Goodpasture syndrome ▪ IgA nephropathy (Berger disease) ▪ Alport syndrome ▪ Membranoproliferative glomerulonephritis |
| Nephrotic syndrome | Podocyte damage → impaired charge barrier → proteinuria | Massive proteinuria (> 3.5 g/day) with edema, hypoalbuminemia → ↑ hepatic lipogenesis → hypercholesterolemia Frothy urine with fatty casts Associated with hypercoagulable state (eg, renal vein thrombosis) due to antithrombin loss in urine and ↑ risk of infection (loss of IgGs in urine and soft tissue compromise by edema) | <p>May be 1° (eg, direct podocyte damage) or 2° (podocyte damage from systemic process):</p> <ul style="list-style-type: none"> ▪ Focal segmental glomerulosclerosis (1° or 2°) ▪ Minimal change disease (1° or 2°) ▪ Membranous nephropathy (1° or 2°) ▪ Amyloidosis (2°) ▪ Diabetic glomerulonephropathy (2°) |
| Nephritic-nephrotic syndrome | Severe GBM damage → loss of RBCs into urine + impaired charge barrier → hematuria + proteinuria | Nephrotic-range proteinuria (> 3.5 g/day) and concomitant features of nephritic syndrome | Can occur with any form of nephritic syndrome, but is most common with: <ul style="list-style-type: none"> ▪ Diffuse proliferative glomerulonephritis ▪ Membranoproliferative glomerulonephritis |

Nephritic syndrome

| | MECHANISM | LIGHT MICROSCOPY | IMMUNOFLUORESCENCE | ELECTRON MICROSCOPY |
|------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Infection-related glomerulonephritis | Type III hypersensitivity reaction with consumptive hypocomplementemia Children: seen ~2–4 weeks after group A streptococcal pharyngitis or skin infection Adults: <i>Staphylococcus</i> is additional causative agent | Enlarged and hypercellular glomeruli A | Granular (“starry sky”) appearance (“lumpy-bumpy”) B due to IgG, IgM, and C3 deposition along GBM and mesangium | Subepithelial IC humps |
| IgA nephropathy (Berger disease) | Occurs concurrently with respiratory or GI tract infections (IgA is secreted by mucosal linings) Renal pathology of IgA vasculitis | Mesangial proliferation | IgA-based IC deposits in mesangium | Mesangial IC deposition |
| Rapidly progressive (crescentic) glomerulonephritis | Poor prognosis Multiple causes: Type II HSR in Goodpasture syndrome | Crescent moon shape C ; crescents consist of fibrin and plasma proteins (eg, C3b) with glomerular parietal cells, monocytes, macrophages | Linear IF due to antibodies to GBM and alveolar basement membrane: Goodpasture syndrome—hematuria/hemoptysis Negative IF/Pauci-immune (no IgC3 deposition): granulomatosis with polyangiitis—PR3-ANCA/c-ANCA, eosinophilic granulomatosis with polyangiitis, or Microscopic polyangiitis—MPO-ANCA/p-ANCA Granular IF—PSGN or DPGN | Goodpasture syndrome: breaks in GBM, necrosis and crescent formation with no deposits Pauci-immune: usually no deposits EM features depend on underlying cause |
| Diffuse proliferative glomerulonephritis | Often due to SLE (think “wire lupus”); DPGN and MPGN often present as nephritic and nephrotic syndromes concurrently | “Wire looping” of capillaries D | Granular | Subendothelial, sometimes subepithelial or intramembranous IgG-based ICs often with C3 deposition |

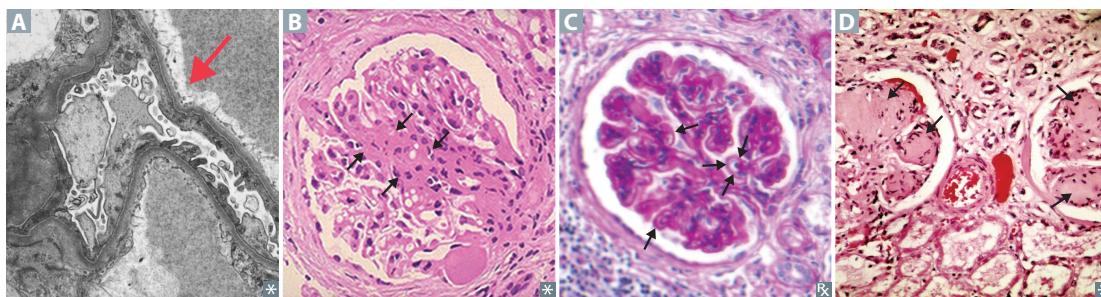
Nephritic syndrome (continued)

| | | | | |
|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Alport syndrome | Type IV collagen mutation → GBM alterations; mostly X-linked dominant. Eye problems (eg, retinopathy, anterior lenticonus), glomerulonephritis, sensorineural hearing loss (can't see, can't pee, can't hear a bee) | Irregular thinning and thickening and splitting of GBM | Initially negative; nonspecific staining (usually stays negative) | "Basket-weave" appearance due to irregular thickening and longitudinal splitting of GBM |
| Membrano-proliferative glomerulonephritis | Type I may be 2° to HBV or HCV infection; type II associated with C3 nephritic factor (IgG autoantibody that stabilizes C3 convertase → persistent complement activation → ↓ C3) | Mesangial ingrowth → GBM splitting → "tram-track" on H&E and PAS E stains | Granular | Type I—subendothelial IC deposits Type II—intramembranous deposits, also called dense deposit disease |



Nephrotic syndrome

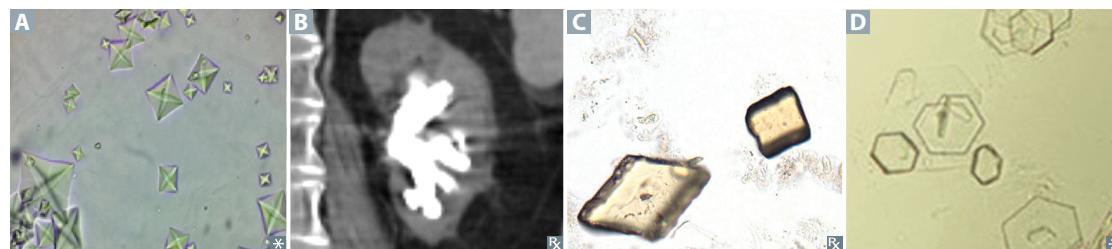
| | MECHANISM | LIGHT MICROSCOPY | IMMUNOFLUORESCENCE | ELECTRON MICROSCOPY |
|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Minimal change disease | Often 1° (idiopathic), triggered by recent infection, immunization, immune stimulus (4 I's); rarely 2° to lymphoma (eg, cytokine-mediated damage). More common in children. | Normal glomeruli (lipid may be seen in PT cells) | ⊖ | Effacement of podocyte foot processes A |
| Focal segmental glomerulosclerosis | Can be 1° (idiopathic) or 2° (eg, HIV infection, sickle cell disease, obesity, or congenital malformations); may progress to CKD. More common in Black people. | Segmental sclerosis and hyalinosis B | Often ⊖ but may be + for nonspecific focal deposits of IgM, C3, Cl | Effacement of podocyte foot processes |
| Membranous nephropathy | Also called membranous glomerulonephritis. Can be 1° (eg, antibodies to phospholipase A ₂ receptor) or 2° to drugs (eg, NSAIDs, penicillamine, gold), infections (eg, HBV, HCV, syphilis), SLE, or solid tumors. ↑ risk of thromboembolism (eg, DVT, renal vein thrombosis). | Diffuse capillary and GBM thickening C | Granular due to immune complex (IC) deposition | “Spike and dome” appearance of subepithelial deposits |
| Amyloidosis | Kidney most commonly involved organ. Associated with chronic conditions that predispose to amyloid deposition (eg, AL amyloid, AA amyloid, prolonged dialysis). | Congo red stain shows apple-green birefringence (polarized light) due to amyloid deposition in the mesangium | AL amyloidosis: may be positive for lambda and kappa light chains AA amyloidosis: positive for AA protein | Mesangial expansion by amyloid fibrils |
| Diabetic glomerulonephropathy | Most common cause of ESRD in United States. Hyperglycemia → nonenzymatic glycation of tissue proteins → mesangial expansion → GBM thickening and ↑ permeability. Hyperfiltration (glomerular HTN and ↑ GFR) → glomerular hypertrophy and glomerular scarring (glomerulosclerosis) → further progression of nephropathy. Look for albuminuria with ↑ urine albumin-to-creatinine ratio. ACE inhibitors and ARBs are renoprotective. | Mesangial expansion, GBM thickening, eosinophilic nodular glomerulonephrosclerosis (Kimmelstiel-Wilson lesions D) | Non-specific staining. Usually negative. | Prominent thickening of GBM with expanded mesangium, predominantly due to increased mesangial matrix, segmental podocyte effacement |



Kidney stones

Can lead to severe complications such as hydronephrosis, pyelonephritis, and acute kidney injury. Obstructed stone presents with unilateral flank tenderness, colicky pain radiating to groin, hematuria. Treat and prevent by encouraging fluid intake. Radiolucent stones: I can't **c** (see) **u** (you) (**c**ystine and **u**ric acid).

| CONTENT | PRECIPITATES WITH | X-RAY FINDINGS | CT FINDINGS | URINE CRYSTAL | NOTES |
|------------------------------------------------|------------------------------------|--------------------|-----------------------|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Calcium | Calcium oxalate: hypocitraturia | Radiopaque | Hyperdense | Shaped like envelope A or dumbbell | Calcium stones most common (80%); calcium oxalate more common than calcium phosphate stones. Can result from ethylene glycol (antifreeze) ingestion, vitamin C overuse, hypocitraturia (usually associated with ↓ urine pH), malabsorption (eg, Crohn disease). Treatment: thiazides, citrate, low-sodium diet. |
| | Calcium phosphate: ↑ pH | Radiopaque | Hyperdense | Wedge-shaped prism | Treatment: low-sodium diet, thiazides. |
| Ammonium magnesium phosphate (struvite) | ↑ pH | Radiopaque | Hyperdense | Coffin lid ("sarcophagus") | Account for 15% of stones. Caused by infection with urease + bugs (eg, <i>Proteus mirabilis</i> , <i>Staphylococcus saprophyticus</i> , <i>Klebsiella</i>) that hydrolyze urea to ammonia → urine alkalinization. Commonly form staghorn calculi B . Treatment: eradication of underlying infection, surgical removal of stone. |
| Uric acid | ↓ pH | Radiolucent | Visible | Rhomboid C or rosettes | About 5% of all stones. Risk factors: arid climates, acidic pH. Strong association with hyperuricemia (eg, gout). Often seen in diseases with ↑ cell turnover (eg, leukemia). Treatment: alkalinization of urine, allopurinol. |
| Cystine | ↓ pH | Faintly radiopaque | Moderately radiodense | Hexagonal D | Hereditary (autosomal recessive) condition in which Cystine-reabsorbing PCT transporter loses function, causing cystinuria. Transporter defect also results in poor reabsorption of Ornithine, Lysine, Arginine (COLA). Cystine is poorly soluble, thus stones form in urine. Usually begins in childhood. Can form staghorn calculi. Sodium cyanide nitroprusside test +. "Sixtine" stones have six sides. Treatment: low sodium diet, alkalinization of urine, chelating agents (eg, tiopronin, penicillamine) if refractory. |



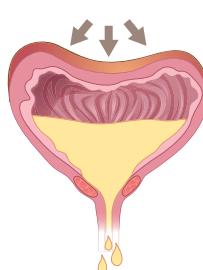
Hydronephrosis

Distention/dilation of renal pelvis and/or calyces **A**. Mostly caused by urinary tract obstruction (eg, urinary tract stones, severe BPH, congenital obstructions, locally advanced cervical cancer, injury to ureter); other causes include retroperitoneal fibrosis, vesicoureteral reflux. Dilatation occurs proximal to site of pathology. Serum creatinine becomes elevated if obstruction is bilateral or if patient has an obstructed solitary kidney. Leads to compression and possible atrophy of renal cortex and medulla.

Urinary incontinence

Mixed incontinence has features of both stress and urgency incontinence.

| Stress incontinence | Urgency incontinence | Overflow incontinence |
|---------------------|----------------------|-----------------------|
|---------------------|----------------------|-----------------------|

**MECHANISM**

Outlet incompetence (urethral hypermobility or intrinsic sphincter deficiency) → leak with ↑ intra-abdominal pressure (eg, sneezing, lifting)
⊕ bladder stress test (directly observed leakage from urethra upon coughing or Valsalva maneuver)

Detrusor overactivity → leak with urge to void immediately

Incomplete emptying (detrusor underactivity or outlet obstruction) → leak with overfilling, ↑ postvoid residual on catheterization or ultrasound

ASSOCIATIONS

Obesity, pregnancy, vaginal delivery, prostate surgery

Bladder irritation from UTI, stones, tumors, pelvic radiation

Urinary retention, polyuria (eg, diabetes), bladder outlet obstruction (eg, BPH), spinal cord injury

TREATMENT

Pelvic floor muscle strengthening (Kegel) exercises, weight loss, pessaries

Pelvic floor physical therapy, bladder training (timed voiding, distraction or relaxation techniques), antimuscarinics (eg, oxybutynin for overactive bladder), mirabegron/vibegron

Catheterization, relieve obstruction (eg, α-blockers for BPH)

Acute cystitis

Inflammation of urinary bladder. Presents as suprapubic pain, dysuria, urinary frequency, urgency.

Systemic signs (eg, high fever, chills) are usually absent.

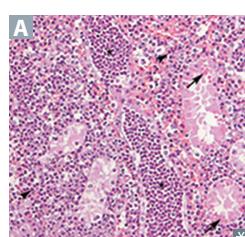
Risk factors include female sex (short urethra), sexual intercourse, indwelling catheter, diabetes mellitus, impaired bladder emptying.

Causes:

- *E coli* (most common)
- *Staphylococcus saprophyticus*—seen in sexually active young women (*E coli* is still more common in this group)
- *Klebsiella*
- *Proteus mirabilis*—urine has ammonia scent
- *Enterococcus* spp.

Labs: + leukocyte esterase. + nitrites (indicates presence of Enterobacteriaceae). Sterile pyuria (pyuria with - urine cultures) could suggest urethritis by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.

Treatment: antibiotics (eg, TMP-SMX, nitrofurantoin).

Pyelonephritis**Acute pyelonephritis**

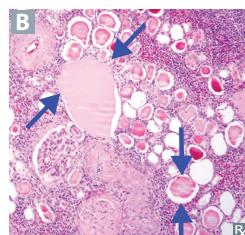
Neutrophils infiltrate renal interstitium **A**. Affects cortex with relative sparing of glomeruli/vessels. Presents with fevers, flank pain (costovertebral angle tenderness), nausea/vomiting, chills.

Causes include ascending UTI (*E coli* is most common), hematogenous spread to kidney. Presents with WBCs in urine +/- WBC casts. CT would show striated parenchymal enhancement.

Risk factors include indwelling urinary catheter, urinary tract obstruction, vesicoureteral reflux, diabetes mellitus, pregnancy (progesterone-mediated ↓ in ureter tone and compression by gravid uterus).

Complications include chronic pyelonephritis, renal papillary necrosis, perinephric abscess (with possible posterior spread to adjacent psoas muscle), urosepsis.

Treatment: antibiotics.

Chronic pyelonephritis

The result of recurrent or inadequately treated episodes of acute pyelonephritis. Typically requires predisposition to infection such as vesicoureteral reflux or chronically obstructing kidney stones. Coarse, asymmetric corticomedullary scarring, blunted calyces. Tubules can contain eosinophilic casts resembling thyroid tissue **B** (thyroidization of kidney).

Acute kidney injury

| | Prerenal azotemia | Intrinsic renal failure | Postrenal azotemia |
|-----------------------------|----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| ETIOLOGY | Hypovolemia ↓ cardiac output ↓ effective circulating volume (eg, HF, liver failure) | Tubules and interstitium: ■ Acute tubular necrosis (ischemia, nephrotoxins) ■ Acute interstitial nephritis Glomerulus: ■ Acute glomerulonephritis Vascular: ■ Vasculitis ■ Hypertensive emergency ■ TTP-HUS | Stones BPH Neoplasm Congenital anomalies |
| PATHOPHYSIOLOGY | ↓ RBF → ↓ GFR → ↑ reabsorption of $\text{Na}^+/\text{H}_2\text{O}$ and urea | In ATN, patchy necrosis → debris obstructing tubules and fluid backflow → ↓ GFR | Outflow obstruction (bilateral) |
| URINE OSMOLALITY (mOsm/kg) | >500 | <350 | Varies |
| URINE Na^+ (mEq/L) | <20 | >40 | Varies |
| FE _{Na} | <1% | >2% | Varies |
| SERUM BUN/Cr | >20 | <15 | Varies |

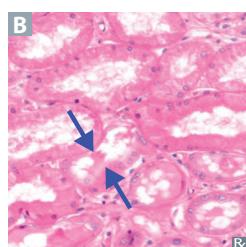
Acute interstitial nephritis

Also called tubulointerstitial nephritis. Acute interstitial renal inflammation. Pyuria (classically eosinophils) and azotemia occurring after administration of drugs that act as haptens, inducing hypersensitivity (eg, diuretics, NSAIDs, penicillin derivatives, proton pump inhibitors, rifampin, quinolones, sulfonamides). Less commonly may be 2° to other processes such as systemic infections (eg, *Mycoplasma*) or systemic inflammatory disorders (eg, Sjögren syndrome, SLE, sarcoidosis).

Associated with fever, rash, pyuria, hematuria, and costovertebral angle tenderness, but can be asymptomatic.

Remember the causes of inflammation to your **DRAINS**:

- Diuretics
- Rifampin
- Antibiotics (penicillins and cephalosporins)
- Proton pump Inhibitors
- NSAIDs
- Sulfa drugs

Acute tubular necrosis

Most common cause of intrinsic acute kidney injury in hospitalized patients. Spontaneously resolves in many cases. Can be fatal, especially during initial oliguric phase. ↑ FE_{Na}. Key finding: granular casts (often muddy brown in appearance) **A**.

3 stages:

1. Inciting event
2. Maintenance phase—oliguric; lasts 1–3 weeks; risk of hyperkalemia, metabolic acidosis, uremia
3. Recovery phase—polyuric; BUN and serum creatinine fall; risk of hypokalemia and renal wasting of other electrolytes and minerals

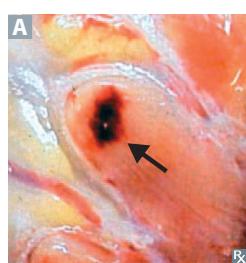
Can be caused by ischemic or nephrotoxic injury:

- Ischemic—2° to ↓ renal blood flow (eg, prerenal azotemia). Results in death of tubular cells that may slough into tubular lumen **B** (PT and thick ascending limb are highly susceptible to injury).
- Nephrotoxic—2° to injury resulting from toxic substances (eg, aminoglycosides, radiocontrast agents, lead, cisplatin, ethylene glycol, uric acid in tumor lysis syndrome), myoglobinuria (rhabdomyolysis), hemoglobinuria. PTs are particularly susceptible to injury.

Diffuse cortical necrosis

Acute generalized cortical infarction of both kidneys. Likely due to a combination of vasospasm and DIC.

Associated with obstetric catastrophes (eg, placental abruption), septic shock.

Renal papillary necrosis

Sloughing of necrotic renal papillae **A** → gross hematuria. May be triggered by recent infection or immune stimulus.

Associated with:

- Sickle cell disease or trait
- Acute pyelonephritis
- Analgesics (eg, NSAIDs)
- Diabetes mellitus

SAAD pap with **papillary necrosis**.

Consequences of renal failure

Decline in renal filtration can lead to excess retained nitrogenous waste products and electrolyte disturbances.

Consequences (**MAD HUNGER**):

- Metabolic Acidosis
- Dyslipidemia (especially ↑ triglycerides)
- High potassium
- Uremia
- Na⁺/H₂O retention (HF, pulmonary edema, hypertension)
- Growth retardation and developmental delay
- Erythropoietin deficiency (anemia)
- Renal osteodystrophy

2 forms of renal failure: acute (eg, ATN) and chronic (eg, hypertension, diabetes mellitus, congenital anomalies).

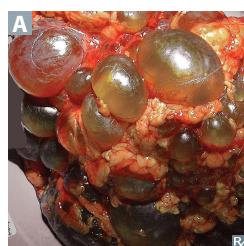
Incremental reductions in GFR define the stages of chronic kidney disease.

Normal phosphate levels are maintained during early stages of CKD due to ↑ levels of fibroblast growth factor 23 (FGF23), which promotes renal excretion of phosphate. “**FGF23 fights f(ph)osphate**.”

Uremia—syndrome resulting from high serum urea. Can present with **Pericarditis**, **Encephalopathy** (seen with asterixis), **Anorexia**, **Nausea** (pronounce “**Ure-PEAN**” [European]).

Renal osteodystrophy

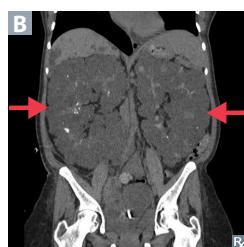
Hypocalcemia, hyperphosphatemia, and failure of vitamin D hydroxylation associated with chronic kidney disease → 2° hyperparathyroidism → 3° hyperparathyroidism (if 2° poorly managed). High serum phosphate can bind with Ca^{2+} → tissue deposits → ↓ serum Ca^{2+} .
 ↓ 1,25-(OH)₂D₃ → ↓ intestinal Ca^{2+} absorption. Causes subperiosteal thinning of bones.

Renal cyst disorders**Autosomal dominant polycystic kidney disease**

Numerous cysts in cortex and medulla **A** causing bilateral enlarged kidneys ultimately destroy kidney parenchyma. Presents with combinations of flank pain, hematuria, hypertension, urinary infection; progressive renal failure in ~ 50% of individuals.

Mutation in genes encoding polycystin protein: PKD1 (85% of cases, chromosome 16) or PKD2 (15% of cases, chromosome 4). Complications include chronic kidney disease and hypertension (caused by ↑ renin production). Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts, diverticulosis.

Treatment: If hypertension or proteinuria develops, treat with ACE inhibitors or ARBs.

Autosomal recessive polycystic kidney disease

Mutation in PKHD1 encoding fibrocystin. Cystic dilation of collecting ducts **B**. Often presents in infancy, and may be seen on prenatal ultrasound. Associated with congenital hepatic fibrosis. Significant oliguric renal failure in utero can lead to Potter sequence. Concerns beyond neonatal period include systemic hypertension, progressive renal insufficiency, and portal hypertension from congenital hepatic fibrosis.

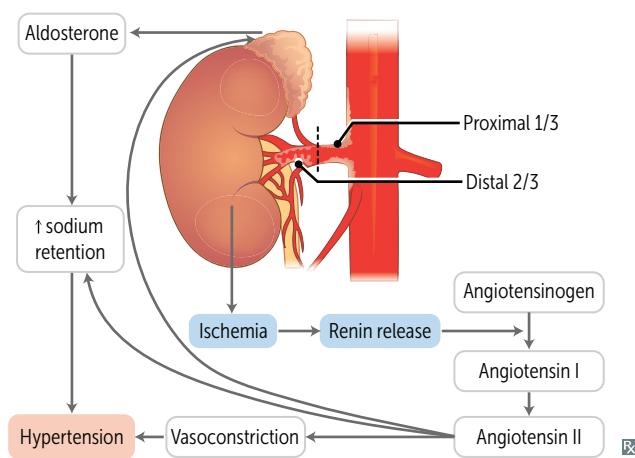
Autosomal dominant tubulointerstitial kidney disease

Also called medullary cystic kidney disease. Causes tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; smaller kidneys on ultrasound. Poor prognosis.

Simple vs complex renal cysts

Simple cysts are filled with ultrafiltrate (anechoic on ultrasound). Very common and account for majority of all renal masses. Found incidentally and typically asymptomatic.

Complex cysts, including those that are septated, enhanced, or have solid components on imaging require follow-up or removal due to possibility of renal cell carcinoma.

Renovascular disease

Unilateral or bilateral renal artery stenosis (RAS) → ↓ renal perfusion → ↑ renin → ↑ angiotensin → HTN. Most common cause of 2° HTN in adults.

Main causes of RAS:

- Atherosclerotic plaques: proximal 1/3 of renal artery, usually in older males, smokers.
- Fibromuscular dysplasia: distal 2/3 of renal artery or segmental branches, usually young or middle-aged females

For unilateral RAS, affected kidney can atrophy → asymmetric kidney size. Renal venous sampling will show ↑ renin in affected kidney, ↓ renin in unaffected kidney.

For bilateral RAS, patients can have a sudden rise in creatinine after starting an ACE inhibitor, ARB, or renin inhibitor, due to their interference on RAAS-mediated renal perfusion.

Can present with severe/refractory HTN, flash pulmonary edema, epigastric/flank bruit. Patients with RAS may also have stenosis in other large vessels.

Renal cell carcinoma

Polygonal clear cells **A** filled with accumulated lipids and carbohydrate. Often golden-yellow **B** on gross pathology, due to ↑ lipid content. Originates from PCT → invades renal vein (may develop varicocele if left sided) → IVC → hematogenous spread → metastasis to lung, bone, and liver.

Manifests with flank pain, palpable mass, hematuria (classic triad) as well as anemia, 2° polycythemia (less common), fever, weight loss.

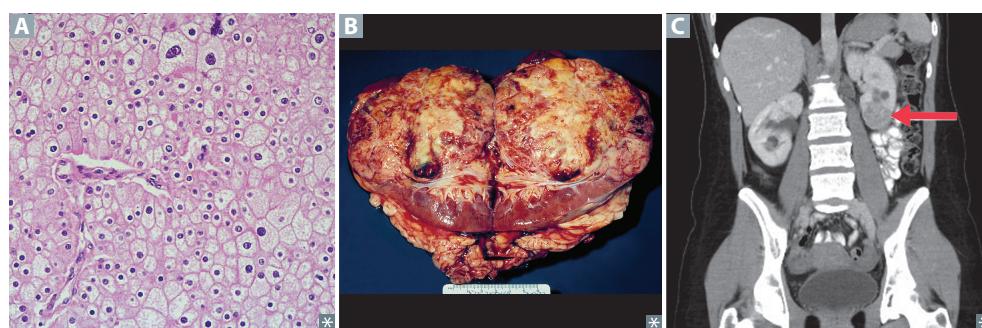
Treatment: surgery/ablation for localized disease. Immunotherapy (eg, ipilimumab) or targeted therapy for metastatic disease, rarely curative. Resistant to radiation and chemotherapy.

Most common 1° renal malignancy **C**.

Most common in males 50–70 years old, ↑ incidence with tobacco smoking and obesity. Associated with paraneoplastic syndromes, eg, PTHrP, Ectopic EPO, ACTH, Renin (“PEAR”-aneoplastic).

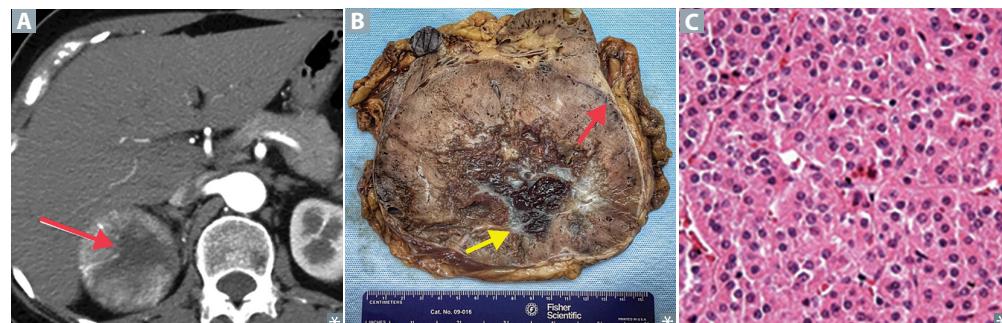
Clear cell (most common subtype) associated with gene deletion on chromosome 3 (sporadic, or inherited as von Hippel-Lindau syndrome).

RCC = 3 letters = chromosome 3 = associated with **VHL** (also 3 letters).



Renal oncocytoma

Benign epithelial cell tumor **A** arising from collecting ducts (red arrow in **B** points to well circumscribed mass; yellow arrow points to central scar). Large eosinophilic cells with abundant mitochondria without perinuclear clearing **C** (vs chromophobe renal cell carcinoma). Presents with painless hematuria, flank pain, abdominal mass. Often resected to exclude malignancy (eg, renal cell carcinoma).

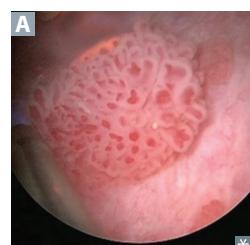
**Nephroblastoma**

Also called Wilms tumor. Most common renal malignancy of early childhood (ages 2–4). Contains embryonic glomerular structures. Most often present with large, palpable, unilateral flank mass **A** and/or hematuria and possible HTN.

Can be associated with loss-of-function mutations of tumor suppressor genes **WT1** or **WT2** on chromosome **11** (**W11ms** tumor).

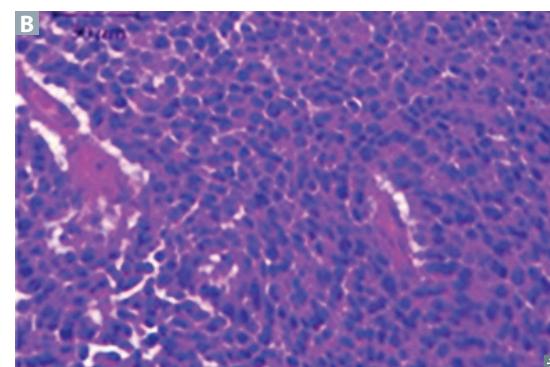
May be a part of several syndromes:

- **WAGR complex**—Wilms tumor, **A**niridia (absence of iris), **G**enitourinary malformations, **R**ange of developmental delays (**WT1** deletion)
- **Denys-Drash syndrome**—Wilms tumor, **D**iffuse mesangial sclerosis (early-onset nephrotic syndrome), **D**ysgenesis of gonads (male pseudohermaphroditism), **WT1** mutation
- **Beckwith-Wiedemann syndrome**—Wilms tumor, **i**ncrease in organ size (organomegaly), **t**ongue enlargement (macroglossia), **h**emihyperplasia (imprinting defect causing genetic overexpression, associated with **WT2** mutation), omphalocele

Urothelial carcinoma of the bladder

Also called transitional cell carcinoma. Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder) **A** **B**. Can be suggested by **P**ainless hematuria (no casts).

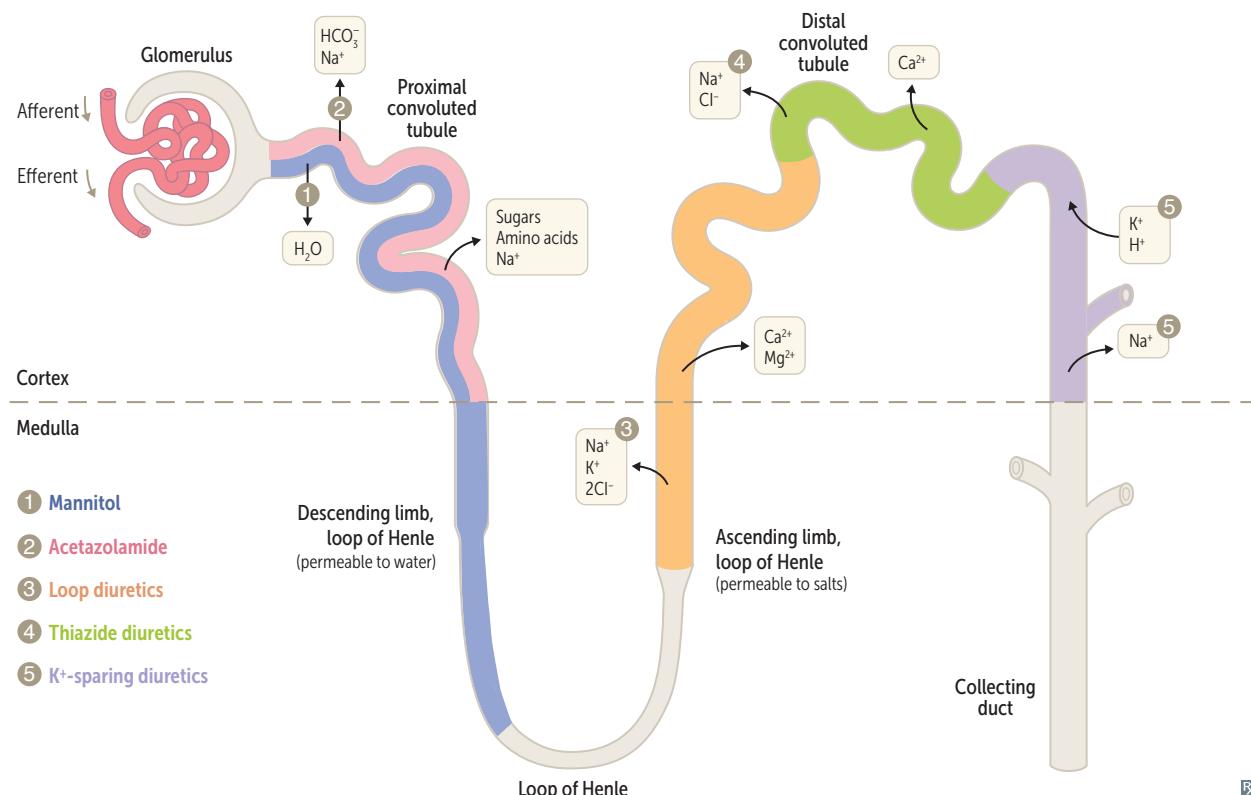
Associated with problems in your **Pee SAC**: **T**obacco **S**moking, **A**romatic amines (found in dyes), **C**yclophosphamide.

**Squamous cell carcinoma of the bladder**

Chronic irritation of urinary bladder → squamous metaplasia → dysplasia and squamous cell carcinoma.

Risk factors include **4 S's**: **S**chistosoma **h**aematobium infection (Middle East), chronic cystitis ("systitis"), **s**moking, chronic nephrolithiasis (**s**tones). Presents with painless hematuria (no casts).

▶ RENAL—PHARMACOLOGY

Diuretics: site of action**Diuretics: effects on electrolyte excretion**

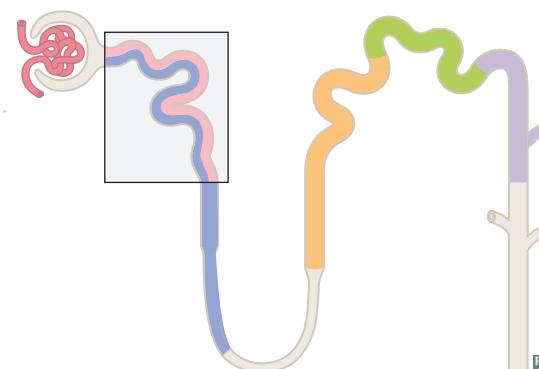
| | Na ⁺ | HCO ₃ ⁻ | K ⁺ | Cl ⁻ | Ca ²⁺ | Mg ²⁺ | H ⁺ |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------|-----------------|------------------|------------------|----------------|
| Carbonic anhydrase inhibitors | ↑ | ↑↑ | ↑↑ | —/↑ | — | — | ↓ |
| Loop diuretics | ↑↑ | ↓ | ↑↑ | ↑↑ | ↑↑ | ↑↑ | ↑ |
| Thiazide diuretics | ↑ | ↑ | ↑↑ | ↑ | ↓↓ | —/↑ | ↑ |
| K ⁺ -sparing diuretics | ↑ | — | ↓ | ↑ | ↓/— | ↓/— | ↓ |
| Blood pH | ↓ (acidemia): carbonic anhydrase inhibitors: ↓ HCO ₃ ⁻ reabsorption. K ⁺ sparing: aldosterone blockade prevents K ⁺ secretion and H ⁺ secretion. Additionally, hyperkalemia leads to K ⁺ entering all cells (via H ⁺ /K ⁺ exchanger) in exchange for H ⁺ exiting cells. ↑ (alkalemia): loop diuretics and thiazides cause alkalemia through several mechanisms: <ul style="list-style-type: none"> ▪ Volume contraction → ↑ AT II → ↑ Na⁺/H⁺ exchange in PCT → ↑ HCO₃⁻ reabsorption (“contraction alkalosis”) ▪ K⁺ loss leads to K⁺ exiting all cells (via H⁺/K⁺ exchanger) in exchange for H⁺ entering cells ▪ In low K⁺ state, H⁺ (rather than K⁺) is exchanged for Na⁺ in cortical collecting tubule → alkalosis and “paradoxical aciduria” | | | | | | |

Mannitol

| | |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| MECHANISM | Osmotic diuretic. ↑ serum osmolality → fluid shift from interstitium to intravascular space → ↑ urine flow, ↓ intracranial/intraocular pressure. |
| CLINICAL USE | Drug overdose, elevated intracranial/intraocular pressure, augmenting diuresis. |
| ADVERSE EFFECTS | Dehydration, hypo- or hypernatremia, pulmonary edema. Contraindicated in anuria, HF. |

Acetazolamide

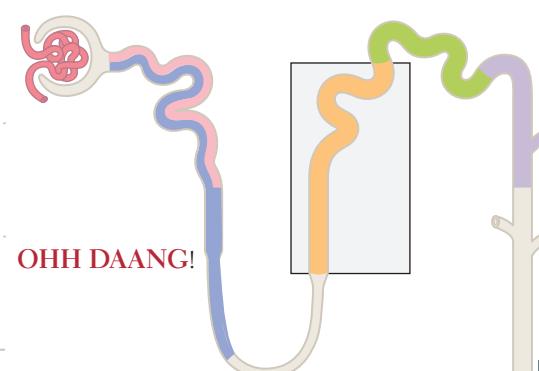
| | |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| MECHANISM | Carbonic anhydrase inhibitor. Causes self-limited NaHCO_3 diuresis and ↓ total body HCO_3^- stores. Alkalizes urine. |
| CLINICAL USE | Glaucoma, metabolic alkalosis, altitude sickness (by offsetting respiratory alkalosis), idiopathic intracranial hypertension (pseudotumor cerebri). |
| ADVERSE EFFECTS | Proximal renal tubular acidosis (type 2 RTA), paresthesias, NH_3 toxicity, sulfa allergy, hypokalemia. Promotes calcium phosphate stones (insoluble at high urine pH). |



"Acid"azolamide causes acidosis.

Loop diuretics**Furosemide, bumetanide, torsemide**

| | |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| MECHANISM | Sulfonamide loop diuretics. Inhibit cotransport system ($\text{Na}^+/\text{K}^+/2\text{Cl}^-$) of thick ascending limb of loop of Henle. Abolish hypertonicity of medulla, preventing concentration of urine. Associated with ↑ PGE (vasodilatory effect on afferent arteriole); inhibited by NSAIDs. ↑ Ca^{2+} excretion. Loops lose Ca^{2+} . |
| CLINICAL USE | Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia. |
| ADVERSE EFFECTS | Ototoxicity, Hypokalemia, Hypomagnesemia, Dehydration, Allergy (sulfa), metabolic Alkalosis, Nephritis (interstitial), Gout. |



OH DAANG!

Ethacrynic acid

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|
| MECHANISM | Nonsulfonamide inhibitor of cotransport system ($\text{Na}^+/\text{K}^+/2\text{Cl}^-$) of thick ascending limb of loop of Henle. |
| CLINICAL USE | Diuresis in patients allergic to sulfa drugs. |
| ADVERSE EFFECTS | Similar to furosemide, but more ototoxic. |

Loop earrings hurt your ears.

Thiazide diuretics

Hydrochlorothiazide, chlorthalidone, metolazone.

MECHANISM

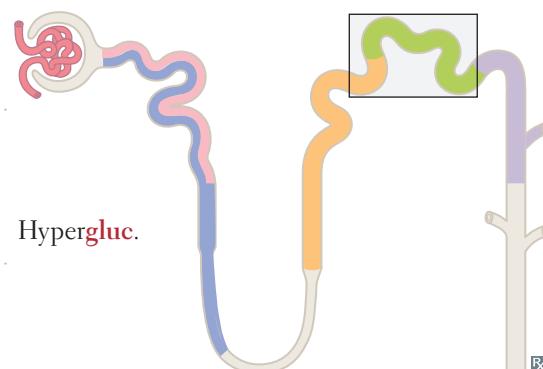
Inhibit NaCl reabsorption in early DCT
→ ↓ diluting capacity of nephron. ↓ Ca²⁺ excretion.

CLINICAL USE

Hypertension, HF, idiopathic hypercalciuria, nephrogenic diabetes insipidus, osteoporosis. Potentiates loop diuretics in refractory volume overload.

ADVERSE EFFECTS

Hypokalemic metabolic alkalosis, hyponatremia, hyperglycemia, hyperlipidemia, hyperuricemia, hypercalcemia. Sulfa allergy.

**Potassium-sparing diuretics**

Spironolactone, Eplerenone, Amiloride, Triamterene.

Keep your SEAT.

MECHANISM

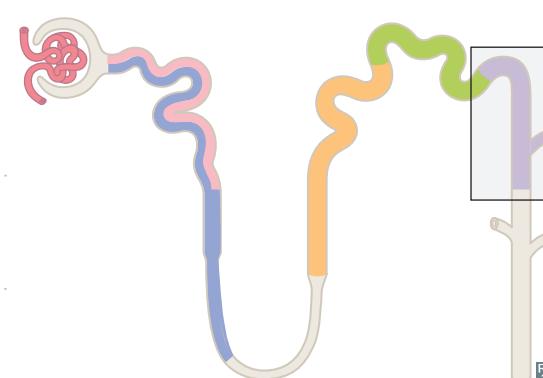
Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule. Triamterene and amiloride block Na⁺ channels at the same part of the tubule.

CLINICAL USE

Hyperaldosteronism, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride), antiandrogen (spironolactone).

ADVERSE EFFECTS

Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (eg, gynecomastia, antiandrogen effects), metabolic acidosis.



Angiotensin-converting enzyme inhibitors

| | |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| MECHANISM | Captopril, enalapril, lisinopril, ramipril. |
| CLINICAL USE | Inhibit ACE → ↓ AT II → ↓ GFR by preventing constriction of efferent arterioles. ↑ renin due to loss of negative feedback. Inhibition of ACE also prevents inactivation of bradykinin, a potent vasodilator. |
| ADVERSE EFFECTS | Hypertension, HF (↓ mortality), proteinuria, diabetic nephropathy. Prevent unfavorable heart remodeling as a result of chronic hypertension. |

| | |
|--------------|-----------------------------------------------------------------------------------------------------------|
| MECHANISM | In chronic kidney disease (eg, diabetic nephropathy), ↓ intraglomerular pressure, slowing GBM thickening. |
| CLINICAL USE | Captopril's CATCHH . |

Angiotensin II receptor blockers

| | |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| MECHANISM | Selectively block binding of angiotensin II to AT ₁ receptor. Effects similar to ACE inhibitors, but ARBs do not increase bradykinin. |
| CLINICAL USE | Hypertension, HF, proteinuria, or chronic kidney disease (eg, diabetic nephropathy) with intolerance to ACE inhibitors (eg, cough, angioedema). |
| ADVERSE EFFECTS | Hyperkalemia, ↓ GFR, hypotension; teratogen. |

Aliskiren

| | |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| MECHANISM | Direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I. Aliskiren kills renin. |
| CLINICAL USE | Hypertension. |
| ADVERSE EFFECTS | Hyperkalemia, ↓ GFR, hypotension, angioedema. Relatively contraindicated in patients already taking ACE inhibitors or ARBs and contraindicated in pregnancy. |