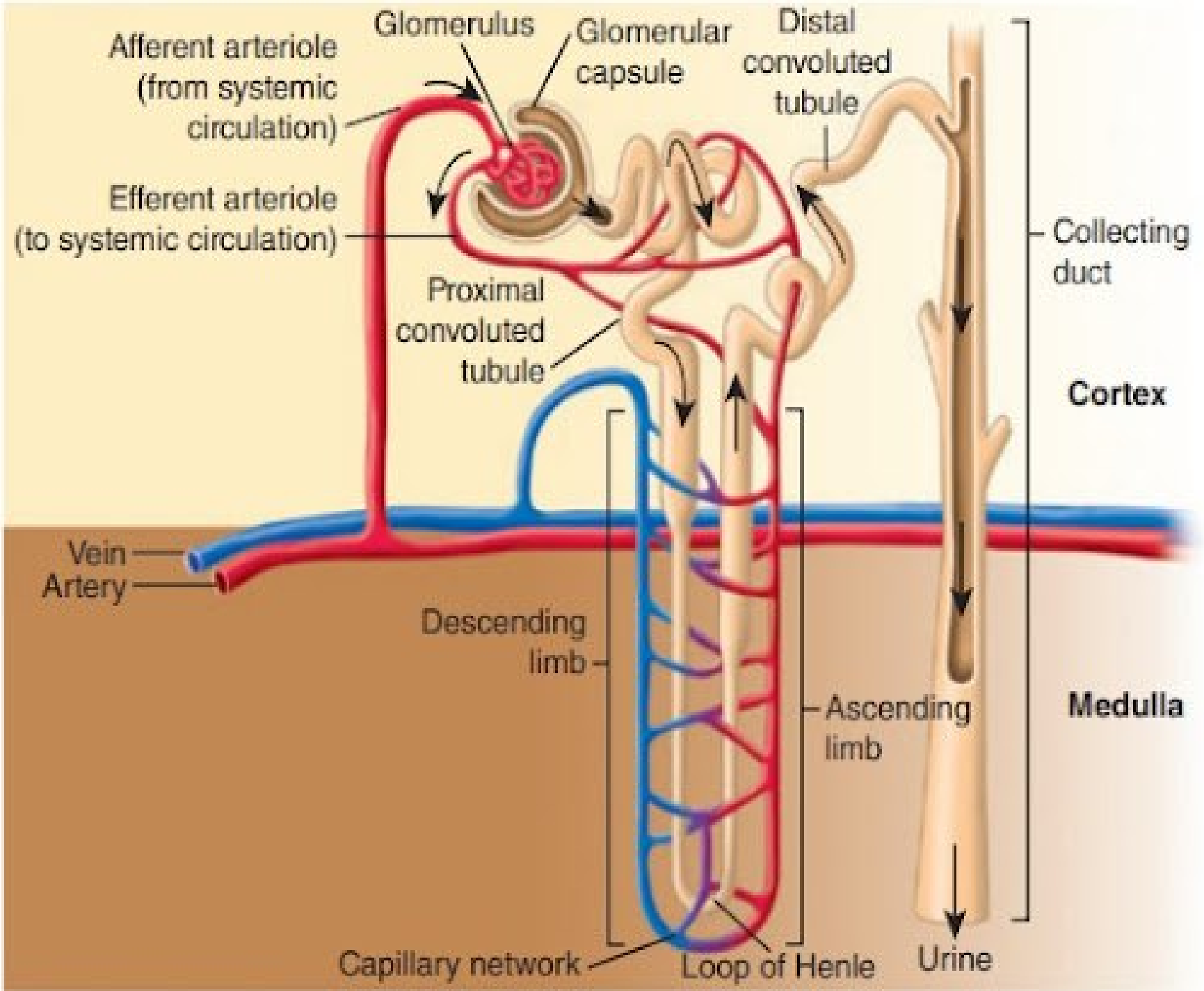
Diuretics

Dr.Samaher Jaber Younis

BCPS



RENAL ANATOMY AND PHYSIOLOGY

The basic urine-forming unit of the kidney is the nephron, which consists of a filtering apparatus, the glomerulus, connected to a long tubular portion that reabsorbs and conditions the glomerular ultrafiltrate. Each human kidney is composed of approximately one million nephrons. The nomenclature for segments of the tubular portion of the nephron has become increasingly complex as renal physiologists have subdivided the nephron into shorter and shorter named segments. These subdivisions were based initially on the axial location of the segments

THIAZIDE DIURETICS

Chlorothiazide
Hydrochlorothiazide
Chlorthalidone
Indapamide
Metolazone

LOOP DIURETICS

Ethacrynic acid
Furosemide
Bumetanide
Torsemide

POTASSIUM-SPARING DIURETICS

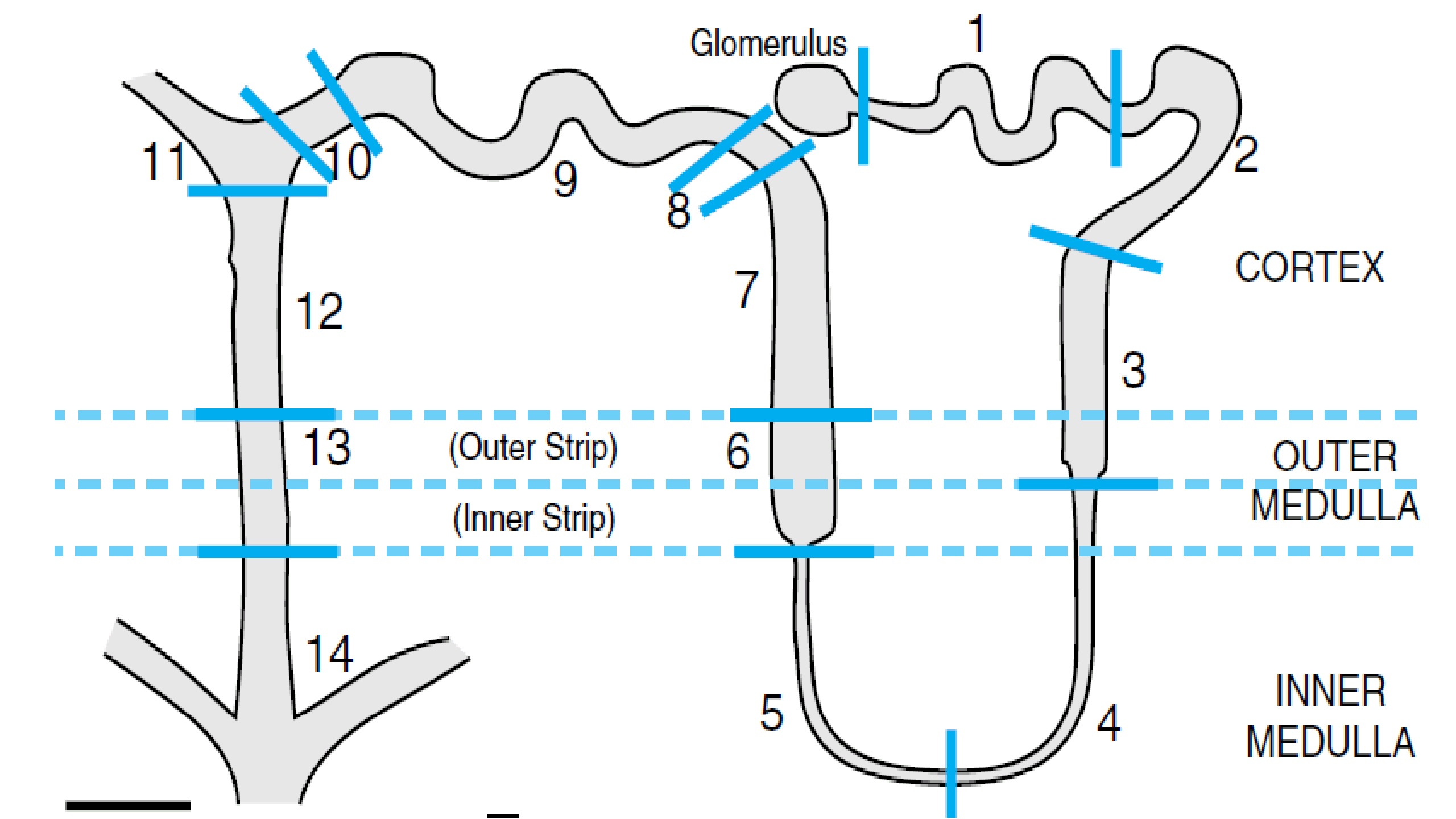
Spironolactone
Triamterene
Amiloride
Eplerenone

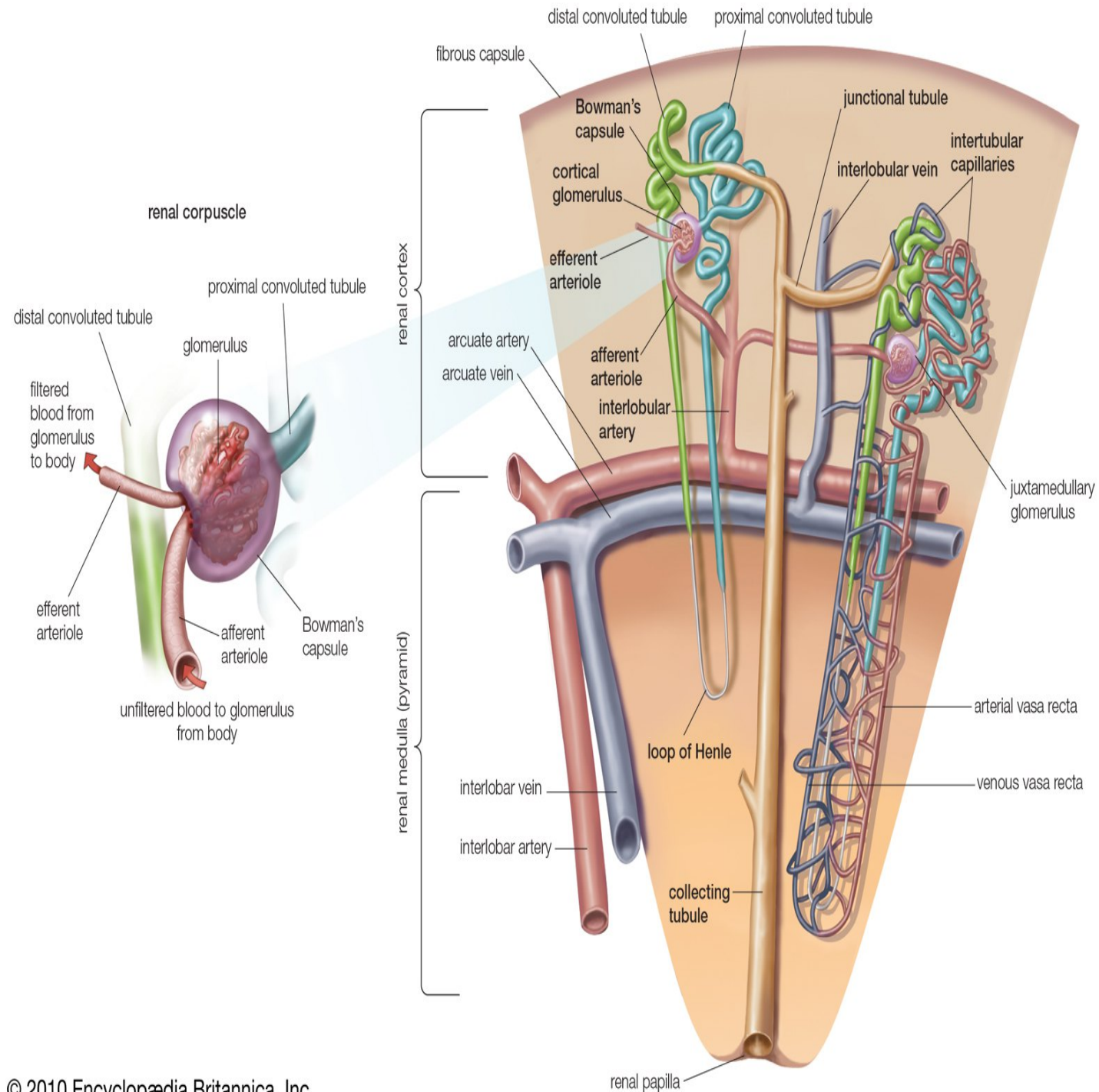
CARBONIC ANHYDRASE INHIBITORS

Acetazolamide

OSMOTIC DIURETICS

Mannitol


Glomerulus
1
2
3
4
5
6
7
8
9
10
11
12
13
14
CORTEX
OUTER MEDULLA
INNER MEDULLA
(Outer Strip)
(Inner Strip)

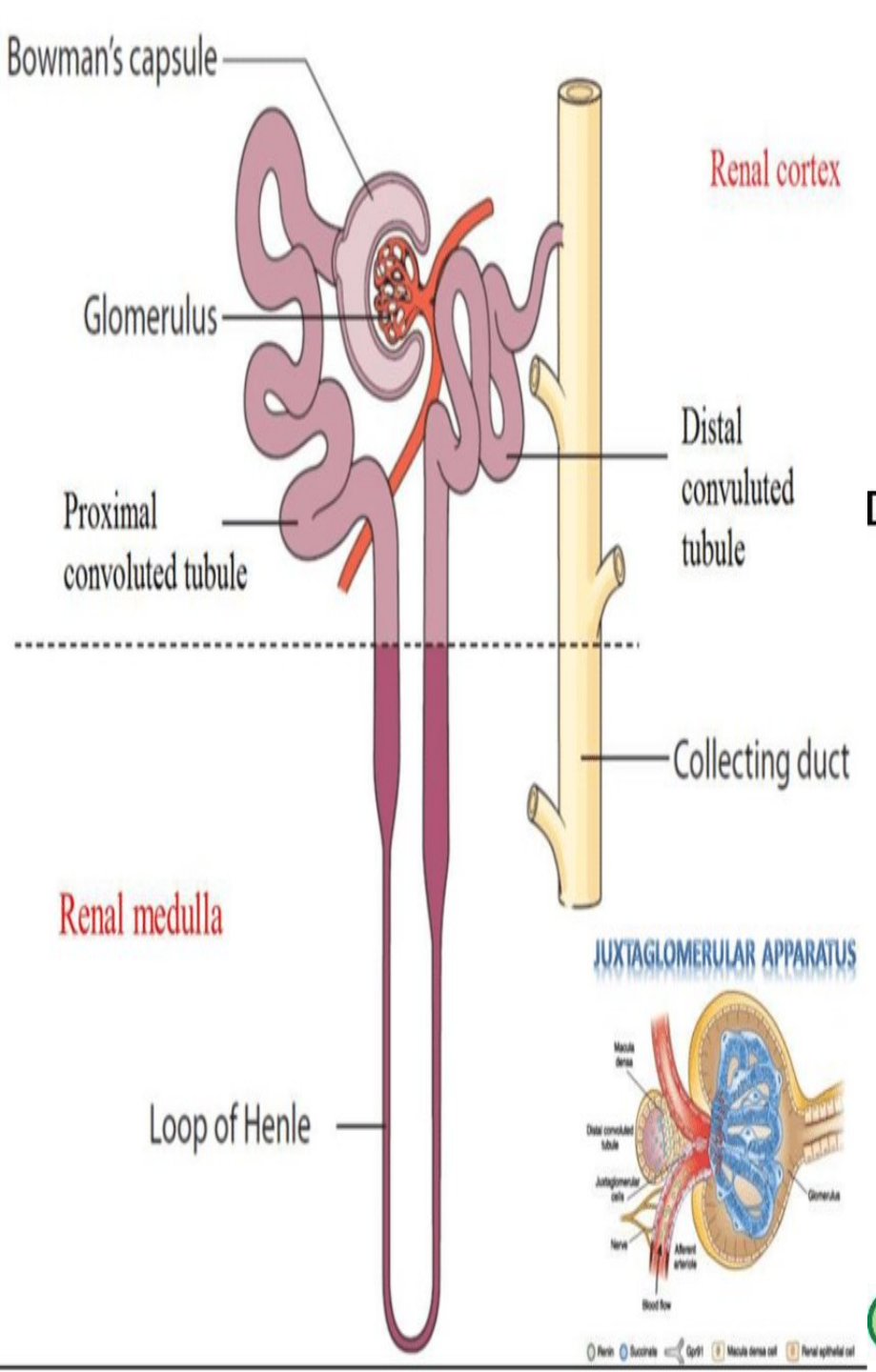


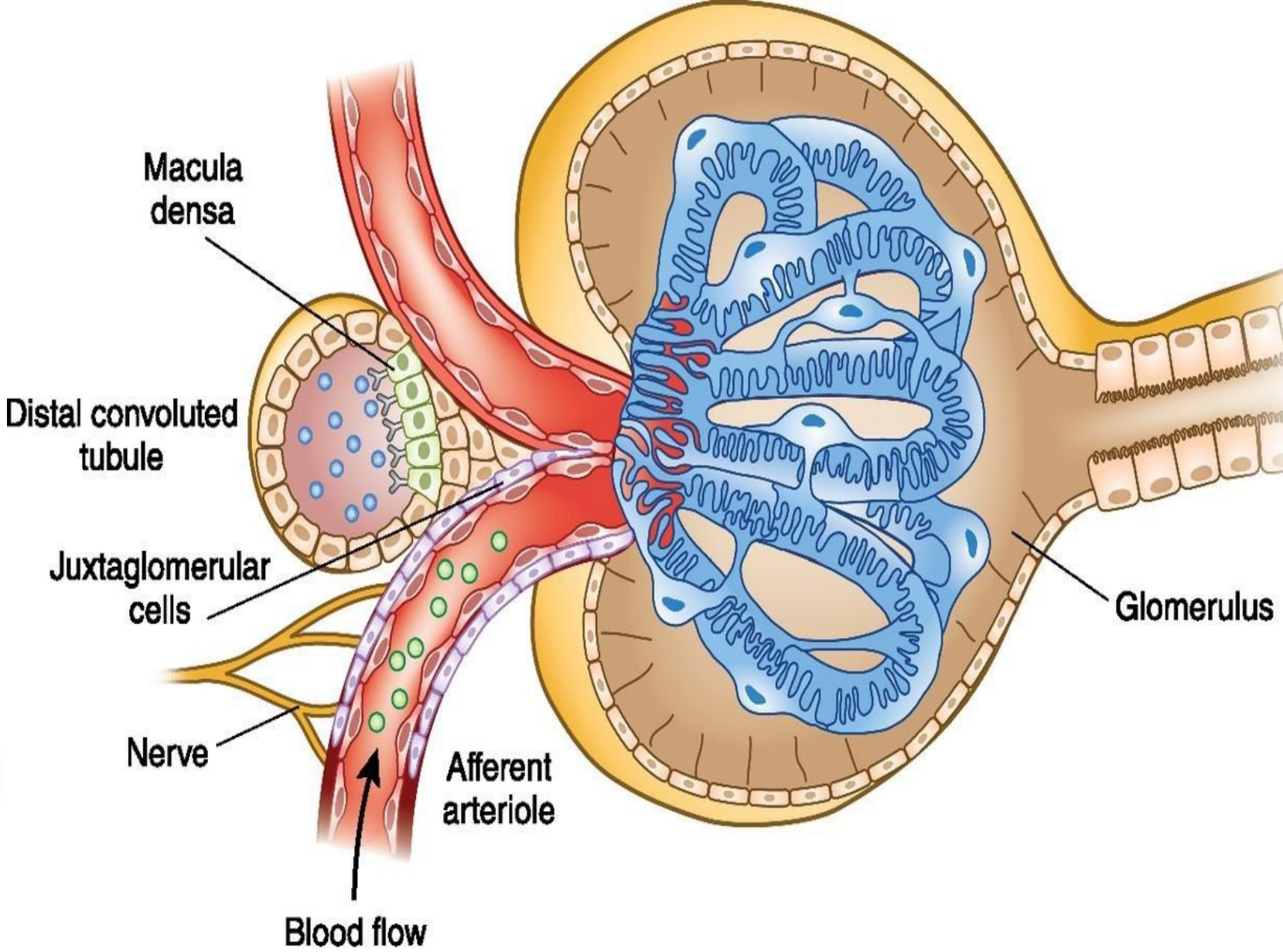
Renal Anatomy. The **main renal artery** branches near the renal hilum into **segmental arteries**, which, in turn, subdivide to form **interlobar arteries** that pierce the renal parenchyma. The interlobar arteries curve at the border of the renal medulla and cortex to form arched vessels known **as arcuate arteries**. Arcuate arteries give rise to perpendicular branches, called **interlobular arteries**, that enter the renal cortex and supply blood to **the afferent arterioles**. A single afferent arteriole penetrates the glomerulus of each nephron and branches extensively to form the **glomerular capillary nexus**. These branches coalesce to form **the efferent arteriole**. Efferent arterioles of superficial glomeruli ascend toward the kidney surface before splitting into peritubular capillaries that service the tubular elements of the renal cortex. Efferent arterioles of **juxtamedullary glomeruli** descend into the medulla and divide to form the **descending vasa recta**, which supply blood to the capillaries of the medulla. Blood returning from the medulla via the **ascending vasa recta** drains directly into the **arcuate veins**, and blood from the peritubular capillaries of the cortex enters the **interlobular veins**, which, in turn, connect with the arcuate veins. Arcuate veins drain into **interlobar veins**, which drain into **segmental veins**; blood leaves the kidney via the main renal vein.

Glomerular Filtration. In the glomerular capillaries, a portion of the plasma water is forced through a filter that has three basic components: the fenestrated capillary endothelial cells, a basement membrane lying just beneath the endothelial cells, and the filtration slit diaphragms formed by the epithelial cells that cover the basement membrane on its urinary space side. Solutes of small size flow with filtered water (solvent drag) into the urinary (Bowman's) space, whereas formed elements and macromolecules are retained by the filtration barrier. For each nephron unit, the rate of filtration [single-nephron glomerular filtration rate (SNGFR)] is a function of the hydrostatic pressure in the glomerular capillaries (PGC), the hydrostatic pressure in Bowman's space (which can be equated with pressure in the proximal tubule, PT), the mean colloid osmotic pressure in the glomerular capillaries (ΠGC), the colloid osmotic pressure in the proximal tubule (ΠT), and the ultrafiltration coefficient (Kf), according to the equation

$$\mathbf{SNGFR = Kf[(PGC - PT) - (\Pi GC - \Pi T)]}$$

If PGC – PT is defined as the transcapillary hydraulic pressure difference


Bowman's capsule
Renal cortex
Glomerulus
Distal convuluted tubule
Proximal convoluted tubule
Collecting duct
Renal medulla
Loop of Henle
JUXTAGLOMERULAR APPARATUS


Macula densa
Distal convoluted tubule
Juxtaglomerular cells
Nerve
Afferent arteriole
Blood flow
Glomerulus


Renin
Succinate
Gpr91
Macula densa cell
Renal epithelia

Overview of Nephron Function.

The kidney is designed to filter large quantities of plasma, reabsorb substances that the body must conserve, and leave behind and/or secrete substances that must be eliminated. The two kidneys in humans produce together approximately 120 ml of ultrafiltrate, yet only 1 ml/min of urine is produced. Therefore, greater than 99% of the glomerular ultrafiltrate is reabsorbed at a staggering energy cost. The kidneys consume 7% of total-body oxygen intake despite the fact that the kidneys make up only 0.5% of body weight. The proximal tubule is contiguous with Bowman's capsule and takes a tortuous path until finally forming a straight portion that dives into the renal medulla. Based on the morphology of the epithelial cells lining the tubule, the proximal tubule has been subdivided into S1, S2, and S3 segments. Normally, approximately 65% of filtered Na^+ is reabsorbed in the proximal tubule, and since this part of the tubule is highly permeable to water, reabsorption is essentially isotonic.

Between the outer and inner strips of the outer medulla, the tubule abruptly changes morphology to become the descending thin limb (DTL), which penetrates the inner medulla, makes a hairpin turn, and then forms the ascending thin limb (ATL). At the juncture between the inner and outer medulla, the tubule once again changes morphology and becomes the thick ascending limb, which is made up of three segments: a medullary portion (MTAL), a cortical portion (CTAL), and a postmacular segment. Together the proximal straight tubule, DTL, ATL, MTAL, CTAL, and postmacular segment are known as the loop of Henle. The DTL is highly permeable to water, yet its permeability to NaCl and urea is low. In contrast, the ATL is permeable to NaCl and urea but is impermeable to water. The thick ascending limb actively reabsorbs NaCl but is impermeable to water and urea. Approximately 25% of filtered Na^+ is reabsorbed in the loop of Henle, mostly in the thick ascending limb, which has a large reabsorptive capacity. The thick ascending limb passes between the afferent and efferent arterioles and makes contact with the afferent arteriole via a cluster of specialized columnar epithelial cells known as the macula densa. The

This, in turn, causes a reduction in PGC and QA and decreases SNGFR. This homeostatic mechanism, known as tubuloglomerular feedback (TGF), serves to protect the organism from salt and volume wasting. Besides mediating the TGF response, the macula densa also regulates renin release from the adjacent juxtaglomerular cells in the wall of the afferent arteriole. Approximately 0.2 mm past the macula densa, the tubule changes morphology once again to become the distal convoluted tubule (DCT). The postmacular segment of the thick ascending limb and the distal convoluted tubule often are referred to as the early distal tubule. Like the thick ascending limb, the DCT actively transports NaCl and is impermeable to water. Since these characteristics impart the ability to produce a dilute urine, the thick ascending limb and the DCT are collectively called the diluting segment of the nephron, and the tubular fluid in the DCT is hypotonic regardless of hydration status. However, unlike the thick ascending limb, the DCT does not contribute to the countercurrent-induced hypertonicity of the medullary interstitium . The collecting duct system (connecting tubule + initial collecting tubule + cortical collecting duct + outer and inner medullary collecting ducts, e.g., segments 10 to 14) is an area of fine control of ultrafiltrate composition and volume. It is here that final adjustments in electrolyte composition are made, a process modulated by the adrenal steroid aldosterone

The more distal portions of the collecting duct pass through the renal medulla, where the interstitial fluid is markedly hypertonic. In the absence of ADH, the collecting duct system is impermeable to water, and a dilute urine is excreted. In the presence of ADH, the collecting duct system is permeable to water, so water is reabsorbed. The movement of water out of the tubule is driven by the steep concentration gradient that exists between the tubular fluid and the medullary interstitium. The hypertonicity of the medullary interstitium plays a vital role in the ability of mammals and birds to concentrate urine and therefore is a key adaptation necessary for living in a terrestrial environment. This is accomplished via a combination of the unique topography of the loop of Henle and the specialized permeability features of the loop's subsegments. Although the precise mechanisms giving rise to the medullary hypertonicity have remained elusive, the "passive countercurrent multiplier hypothesis" is an intuitively attractive model that is qualitatively accurate.

General Mechanism of Renal Epithelial Transport.

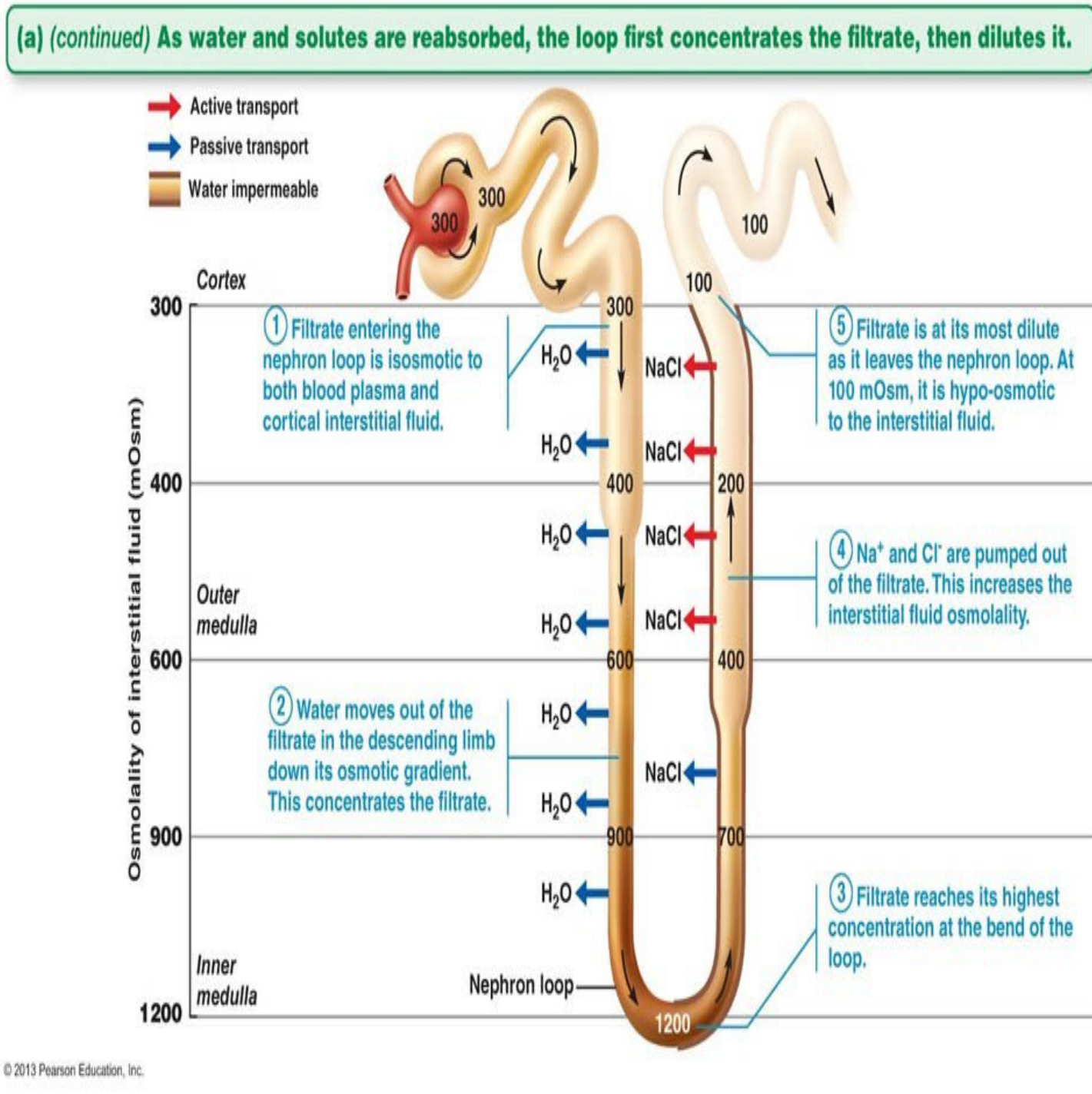
seven mechanisms by which solutes may cross renal epithelial cell membranes

1, convective flow in which dissolved solutes are "dragged" by bulk water flow; 2, simple diffusion of lipophilic solute across membrane; 3, diffusion of solute through a pore; 4, transport of solute by carrier protein down electrochemical gradient; 5, transport of solute by carrier protein against electrochemical gradient with ATP hydrolysis providing driving force; 6 and 7, cotransport and countertransport, respectively, of solutes, with one solute traveling uphill against an electrochemical gradient and the other solute traveling down an electrochemical gradient

S, symporter; A, antiporter; CH, ion channel; WP, water pore; U, uniporter; ATPase, Na_+,K_+–ATPase (sodium pump); X and Y, transported solutes; P, membrane-permeable (reabsorbable) solutes; I, membrane-impermeable (nonreabsorbable) solutes; PD, potential difference across indicated membrane or cell.

Passive countercurrent multiplier hypothesis

According to this hypothesis, the process begins with active transport in the thick ascending limb, which concentrates NaCl in the Interstitium of the outer medulla. Since this segment of the nephron is impermeable to water, active transport in the ascending limb dilutes the tubular fluid. As the dilute fluid passes into the collecting-duct system, water is extracted if, and only if, ADH is present. Since the cortical and outer medullary collecting ducts have a low permeability to urea, urea is concentrated in the tubular fluid. The inner medullary collecting duct, however, is permeable to urea, so urea diffuses into the inner medulla, where it is trapped by countercurrent exchange in the vasa recta. Since the DTL is impermeable to salt and urea, the high urea concentration in the inner medulla extracts water from the DTL and concentrates NaCl in the tubular fluid



1. Na+,K+−ATPase (sodium pump) in the basolateral membrane hydrolyzes ATP , which results in the transport of Na+ into the intercellular and interstitial spaces, the movement of K+ into the cell, and the establishment and maintenance of an electrochemical gradient for Na+ across the cell membrane directed inward. Although other ATPases exist in selected renal epithelial cells and participate in the transport of specific solutes (e.g., Ca2+−ATPase and H+−ATPase), the bulk of all transport in the kidney is due to the abundant supply of Na+,K+−ATPase in the basolateral membranes of the renal epithelial cells and the separation of Na+ and K+ across the cell membrane.

2. Na+ may diffuse across the luminal membrane via Na+ channels into the epithelial cell down the electrochemical gradient for Na+ that is established by the basolateral Na+,K+−ATPases. In addition, the free energy available in the electrochemical gradient for Na+ is tapped by integral proteins in the luminal membrane, resulting in cotransport of various solutes against their electrochemical gradients by symporters (e.g., Na+−glucose, Na+−H2PO4 −, and Na+−amino acid). This process results in movement of Na+ and cotransported solutes out of the tubular lumen into the cell. Also, antiporters (e.g., Na+−H+) move Na+ out of and some solutes into the tubular lumen.

4. The action of Na+-linked symporters in the luminal membrane causes the concentration of substrates for these symporters to rise in the epithelial cell. These electrochemical gradients then permit simple diffusion or mediated transport (e.g., symporters, antiporters, uniporters, and channels) of solutes into the intercellular and interstitial spaces.

5. Accumulation of Na+ and other solutes in the intercellular space creates a small osmotic pressure differential across the epithelial cell. In water-permeable epithelium, water moves into the intercellular spaces driven by the osmotic pressure differential. Water moves through aqueous pores in both the luminal and the basolateral cell membranes, as well as through the tight junctions (paracellular pathway). Bulk water flow carries some solutes into the intercellular space by solvent drag.

6. Movement of water into the intercellular space concentrates other solutes in the tubular fluid, resulting in an electrochemical gradient for these substances across the epithelium. Membrane-permeable solutes then move down their electrochemical gradients into the intercellular space via both the transcellular (e.g., simple diffusion, symporters, antiporters, uniporters, and channels) and paracellular pathways. Membrane-impermeable solutes remain in the tubular

7. As water and solutes accumulate in the intercellular space, the hydrostatic pressure increases, thus providing a driving force for bulk water flow. Bulk water flow carries solute (solute convection) out of the intercellular space into the interstitial space and, finally, into the peritubular capillaries. The movement of fluid into the peritubular capillaries is governed by the same Starling forces that determine transcapillary fluid movement for any capillary bed.

Mechanism of Organic Acid and Organic Base Secretion. The kidney is a major organ involved in the elimination of organic chemicals from the body. Organic molecules may enter the renal tubules by glomerular filtration of molecules not bound to plasma proteins or may be actively secreted directly into the tubules. The proximal tubule has a highly efficient transport system for organic acids and an equally efficient but separate transport system for organic bases. Both systems are powered by the sodium pump in the basolateral membrane, involve secondary and tertiary active transport, and use a facilitated-diffusion step. There are at least nine different organic acid and five different organic base transporters; the precise roles that these transporters play in organic acid and base transport remain ill defined. A family of organic anion transporters (OATs) countertransport

NORMAL REGULATION OF FLUID AND ELECTROLYTES BY THE KIDNEYS

Approximately 16% to 20% of the blood plasma entering the kidneys is filtered from the glomerular capillaries into Bowman's capsule. The filtrate, although normally free of proteins and blood cells, contains most of the low molecular weight plasma components in concentrations similar to that in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes, as well as electrolytes, such as Na^+, K^+, and Cl^-. The kidney regulates the ionic composition and volume of urine by active reabsorption or secretion of ions and/or passive reabsorption of water at five functional zones along the nephron: 1) the proximal convoluted tubule, 2) the descending loop of Henle, 3) the ascending loop of Henle, 4) the distal convoluted tubule, and 5) the collecting tubule and duct.

A. Proximal convoluted tubule

In the proximal convoluted tubule located in the cortex of the kidney, almost all the glucose, bicarbonate, amino acids , and other metabolites are reabsorbed. Approximately 65% of the filtered Na^+ (and water) is reabsorbed. Given the high water permeability, about60% of water is reabsorbed from the lumen to the blood to maintain osmolar equality. Chloride enters

Carbonic anhydrase in the luminal membrane and cytoplasm of the proximal tubular cells modulate the reabsorption of bicarbonate. The proximal tubule is the site of the organic acid and base secretory systems. The organic acid secretory system, located in the middle- third of the proximal tubule, secretes a variety of organic acids, such as uric acid, some antibiotics, and diuretics, from the bloodstream into the proximal tubular lumen. The organic acid secretory system is saturable, and diuretic drugs in the bloodstream compete for transfer with endogenous organic acids such as uric acid. A number of other interactions can also occur. For example, probenecid interferes with penicillin secretion. The organic base secretory system, located in the upper and middle segments of the proximal tubule, is responsible for the secretion of creatinine and choline.

B. Descending loop of Henle

The remaining filtrate, which is isotonic, next enters the descending limb of the loop of Henle and passes into the medulla of the kidney. The osmolarity increases along the descending portion of the loop of Henle because of the countercurrent mechanism that is responsible for water reabsorption. This results in a tubular fluid with a three-fold increase in Na^+ and Cl^- concentration. Osmotic diuretics exert part of their action in this region.

C. Ascending loop of Henle

The cells of the ascending tubular epithelium are unique in being impermeable to water. Active reabsorption of Na^+, K^+, and Cl^- is mediated by a $Na^+/K^+/2Cl^-$ cotransporter. Both Mg^{2+} and Ca^{2+} are reabsorbed via the paracellular pathway. Thus, the ascending loop dilutes the tubular fluid and raises the osmolarity of the medullary interstitium. Approximately 25% to 30% of the filtered sodium chloride is absorbed here. Because the ascending loop of Henle is a major site for salt reabsorption and no segments distally are capable of significant Na^+ and water reabsorption, drugs affecting this site, such as loop diuretics, have the greatest diuretic effect.

D. Distal convoluted tubule

The cells of the distal convoluted tubule are also impermeable to water. About 5% to 10% of the filtered sodium chloride is reabsorbed via a Na+/Cl− transporter, the target of thiazide diuretics. Calcium reabsorption, under the regulation of parathyroid hormone, is mediated by an apical channel and then transported by a Na+/Ca2+-exchanger into the interstitial fluid.

E. Collecting tubule and duct

The principal cells of the collecting tubule and duct are responsible for Na+, K+, and water transport, whereas the intercalated cells affect H+ secretion. Approximately 1% to 2% of the filtered sodium enters the principal cells through epithelial sodium channels that are inhibited by amiloride and triamterene. Once inside the cell, Na+ reabsorption relies on a Na+/K+-ATPase pump to be transported into the blood. Aldosterone receptors in the principal cells influence Na+ reabsorption and K+ secretion. Aldosterone increases the synthesis of epithelial sodium channels and of the Na+/K+−ATPase pump to increase Na+ reabsorption and K+ excretion. Antidiuretic hormone (ADH; vasopressin) binds to V2 receptors to promote the reabsorption

Diuretics 2

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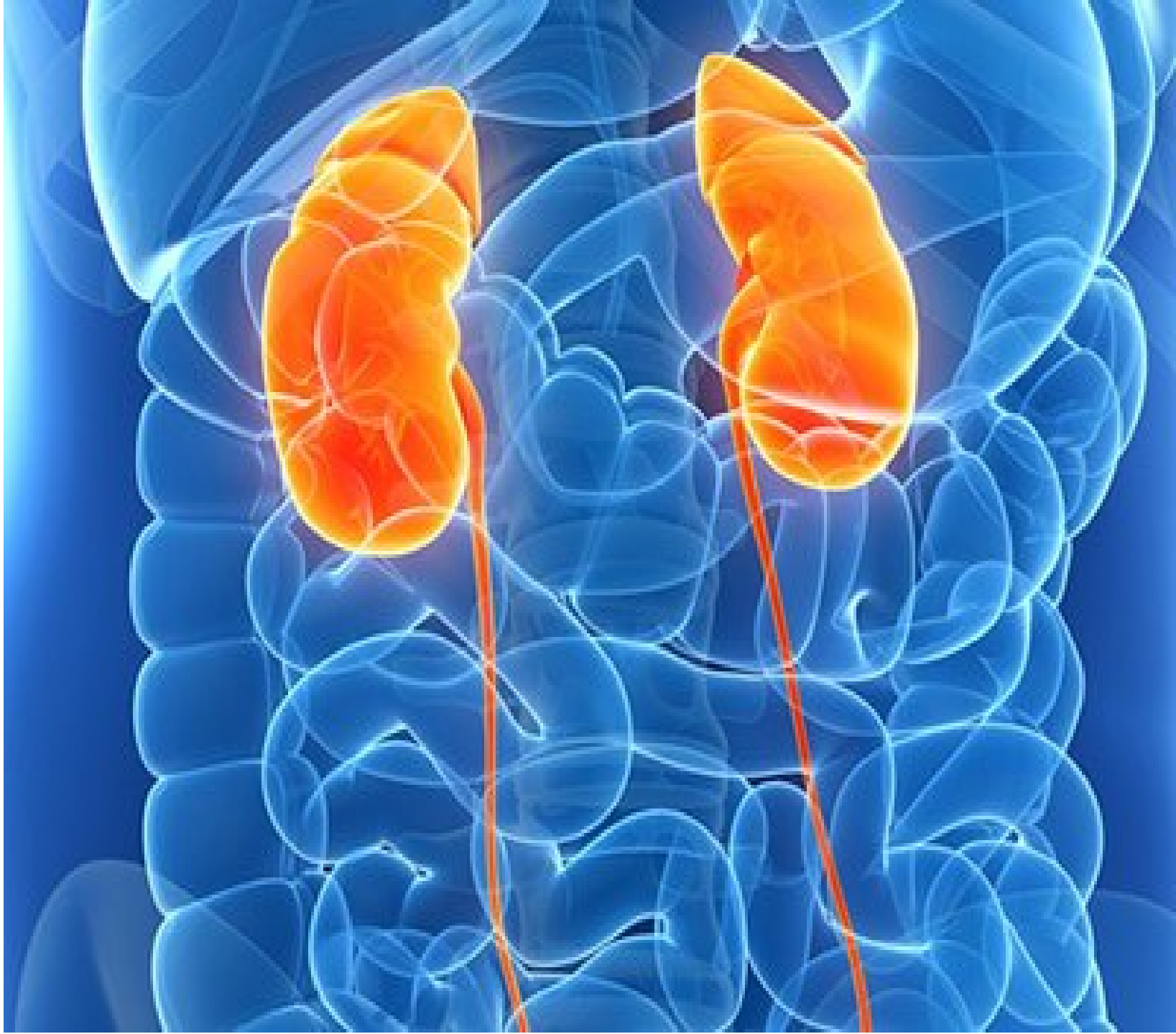


PRINCIPLES OF DIURETIC ACTION

By definition, diuretics are drugs that increase the rate of urine flow; however, clinically useful diuretics also increase the rate of excretion of Na^+ (natriuresis) and of an accompanying anion, usually Cl^-. NaCl in the body is the major determinant of extracellular fluid volume, and most clinical applications of diuretics are directed toward reducing extracellular fluid volume by decreasing total-body NaCl content. A sustained imbalance between dietary Na^+ intake and Na^+ loss is incompatible with life. A sustained positive Na^+ balance would result in volume overload with pulmonary edema, and a sustained negative Na^+ balance would result in volume depletion and cardiovascular collapse. Although continued administration of a diuretic causes a sustained net deficit in total-body Na^+, the time course of natriuresis is finite because renal compensatory mechanisms bring Na^+ excretion in line with Na^+ intake, a phenomenon known as diuretic braking. These compensatory, or braking, mechanisms include activation of the sympathetic nervous system, activation of the renin–angiotensin– aldosterone axis, decreased arterial blood pressure (which reduces pressure natriuresis), hypertrophy of renal epithelial cells, increased expression of renal epithelial transporters, and perhaps alterations in natriuretic hormones such as atrial natriuretic peptide.

INHIBITORS OF CARBONIC ANHYDRASE

Acetazolamide (DIAMOX) is the prototype of a class of agents that have limited usefulness as diuretics but have played a major role in the development of fundamental concepts of renal physiology and pharmacology.

Mechanism and Site of Action . Proximal tubular epithelial cells are richly endowed with the zinc metalloenzyme carbonic anhydrase, which is found in the luminal and basolateral membranes (type IV carbonic anhydrase, an enzyme tethered to the membrane by a glycosylphosphatidylinositol linkage), as well as in the cytoplasm (type II carbonic anhydrase). Carbonic anhydrase plays a key role in NaHCO3 reabsorption and acid secretion. In the proximal tubule, the free energy in the Na+ gradient established by the basolateral Na+ pump is used by a Na+−H+ antiporter [also referred to as a Na+−H+ exchanger (NHE)] in the luminal membrane to transport H+ into the tubular lumen in exchange for Na+. In the lumen, H+ reacts with filtered HCO3 − to form H2CO3, which decomposes rapidly to CO2 and water in the presence of carbonic anhydrase in the brush border. Normally, the reaction between CO2 and water occurs slowly, but carbonic anhydrase reversibly accelerates this reaction several thousand times. CO2 is lipophilic and rapidly diffuses across the luminal membrane into the epithelial cell, where it reacts with water to form H2CO3, a reaction catalyzed by cytoplasmic carbonic anhydrase. **(The actual reaction catalyzed by carbonic anhydrase is OH− + CO2 → HCO3 −; however, H2O → OH− + H+ and HCO3 − + H+ → H2CO3, so the net reaction is H2O + CO2 → H2CO3.**) Continued operation of the Na+−H+ antiporter maintains a low proton concentration in the cell, so H2CO3 − ionizes spontaneously to form H+ and HCO3, creating an electrochemical gradient for HCO3 − across the basolateral membrane. The electrochemical gradient for HCO3 − is used by **a Na+−HCO3 − symporter [also referred to as the Na+− HCO3 − cotransporter (NBC)]** in the basolateral membrane to transport NaHCO3 into the interstitial space. The net effect of this process is transport of NaHCO3 from the

Carbonic anhydrase inhibitors potently inhibit both the membrane-bound and cytoplasmic forms of carbonic anhydrase, resulting in nearly complete abolition of $NaHCO_3$ reabsorption in the proximal tubule. Studies with a high-molecular-weight carbonic anhydrase inhibitor that inhibits only luminal enzyme because of limited cellular permeability indicate that inhibition of both the membrane-bound and cytoplasmic pools of carbonic anhydrase contributes to the diuretic activity of carbonic anhydrase inhibitors.

Effects on Urinary Excretion. Inhibition of carbonic anhydrase is associated with a rapid rise in urinary HCO_3^- excretion to approximately 35% of filtered load. This, along with inhibition of titratable acid and NH_4^+ secretion in the collecting-duct system, results in an increase in **urinary pH to approximately 8 and development of a metabolic acidosis** . However, even with a high degree of inhibition of carbonic anhydrase, 65% of HCO_3^- is rescued from excretion by poorly understood mechanisms that may involve carbonic anhydrase-independent HCO_3^- reabsorption at downstream sites. Inhibition of the transport mechanism results in increased delivery of Na^+ and Cl^- to the loop of Henle, which has a large reabsorptive capacity and captures most of the Cl^- and a portion of the Na^+. Thus only a small increase in Cl^-excretion occurs, **HCO_3^-** being the major anion excreted along with the cations **Na^+ and K^+**. The fractional

$NaHCO_3$ reabsorption in proximal tubule and mechanism of diuretic action of carbonic anhydrase inhibitors. A, antiporter; S, symporter; CH, ion channel. (The actual reaction catalyzed by carbonic anhydrase is $OH^- + CO_2 \rightarrow HCO_3^-$; however, $H_2O \rightarrow OH^- + H^+$, and $HCO_3^- + H^+ \rightarrow H_2CO_3$, so the net reaction is $H_2O + CO_2 \rightarrow H_2CO_3$.) Numbers in parentheses indicate stoichiometry. BL and LM indicate basolateral and luminal membranes, respectively.

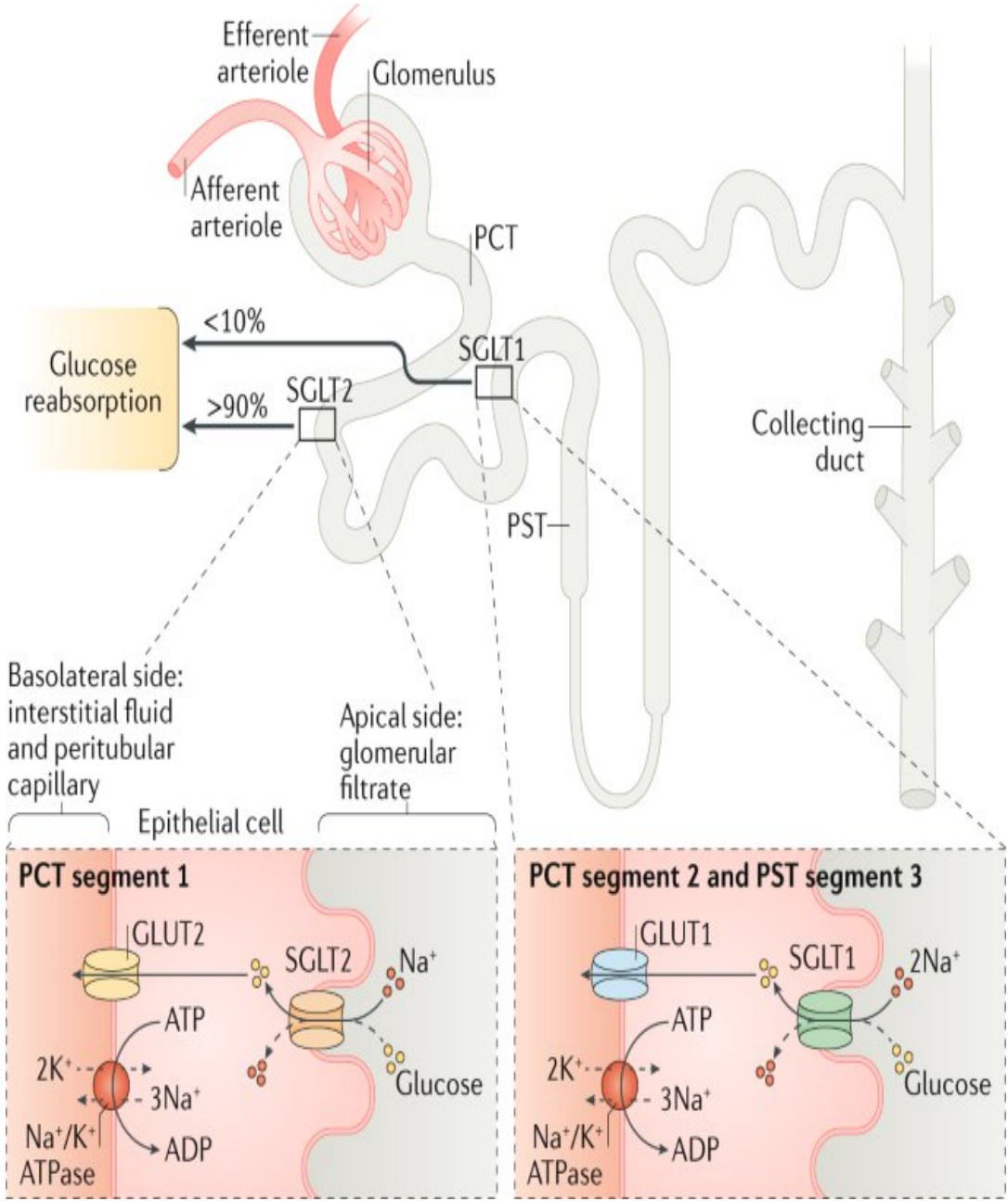
Effects on Renal Hemodynamics. By inhibiting proximal reabsorption, carbonic anhydrase inhibitors increase delivery of solutes to the macula densa. This triggers TGF, which increases afferent arteriolar resistance and reduces renal blood flow (RBF) and glomerular filtration rate (GFR).

Other Actions. Carbonic anhydrase is present in a number of extrarenal tissues, including the **eye,** gastric mucosa, pancreas, central nervous system **(CNS),** and **erythrocytes.** Carbonic anhydrase in the ciliary processes of the eye mediates the formation of large amounts of HCO_3^- in aqueous humor. Inhibition of carbonic anhydrase decreases the rate of formation of aqueous humor and consequently **reduces intraocular pressure** (IOP). Acetazolamide frequently causes paresthesias and somnolence, suggesting an action of carbonic anhydrase inhibitors in the CNS. The efficacy of acetazolamide in **epilepsy** is due in part to the production of metabolic acidosis; however, direct actions of acetazolamide in the CNS also contribute to its anticonvulsant action. Owing to interference with carbonic anhydrase activity in erythrocytes, carbonic anhydrase inhibitors increase CO_2 levels in peripheral tissues and

Toxicity, Adverse Effects, Contraindications, Drug Interactions . Serious toxic reactions to carbonic anhydrase inhibitors are infrequent; however, these drugs are sulfonamide derivatives and, like other sulfonamides, may cause **bone marrow depression**, skin toxicity, sulfonamide like renal lesions, and allergic reactions in patients hypersensitive to sulfonamides. With large doses, many patients exhibit drowsiness and paresthesias. Most adverse effects, contraindications, and drug interactions are secondary to urinary alkalinization or metabolic acidosis, including (1) diversion of ammonia of renal origin from urine into the systemic circulation, a process that may induce or worsen hepatic encephalopathy (the drugs are contraindicated in patients **with hepatic cirrhosis**); (2) **calculus** formation and ureteral colic owing to precipitation of calcium phosphate salts in an alkaline urine; (3) worsening of metabolic or respiratory acidosis (the drugs are contraindicated in patients with **hyperchloremic acidosis** or severe **chronic obstructive pulmonary** disease); and (4) reduction of the urinary excretion rate of weak organic bases.

Sodium-glucose cotransporter-2 inhibitors:

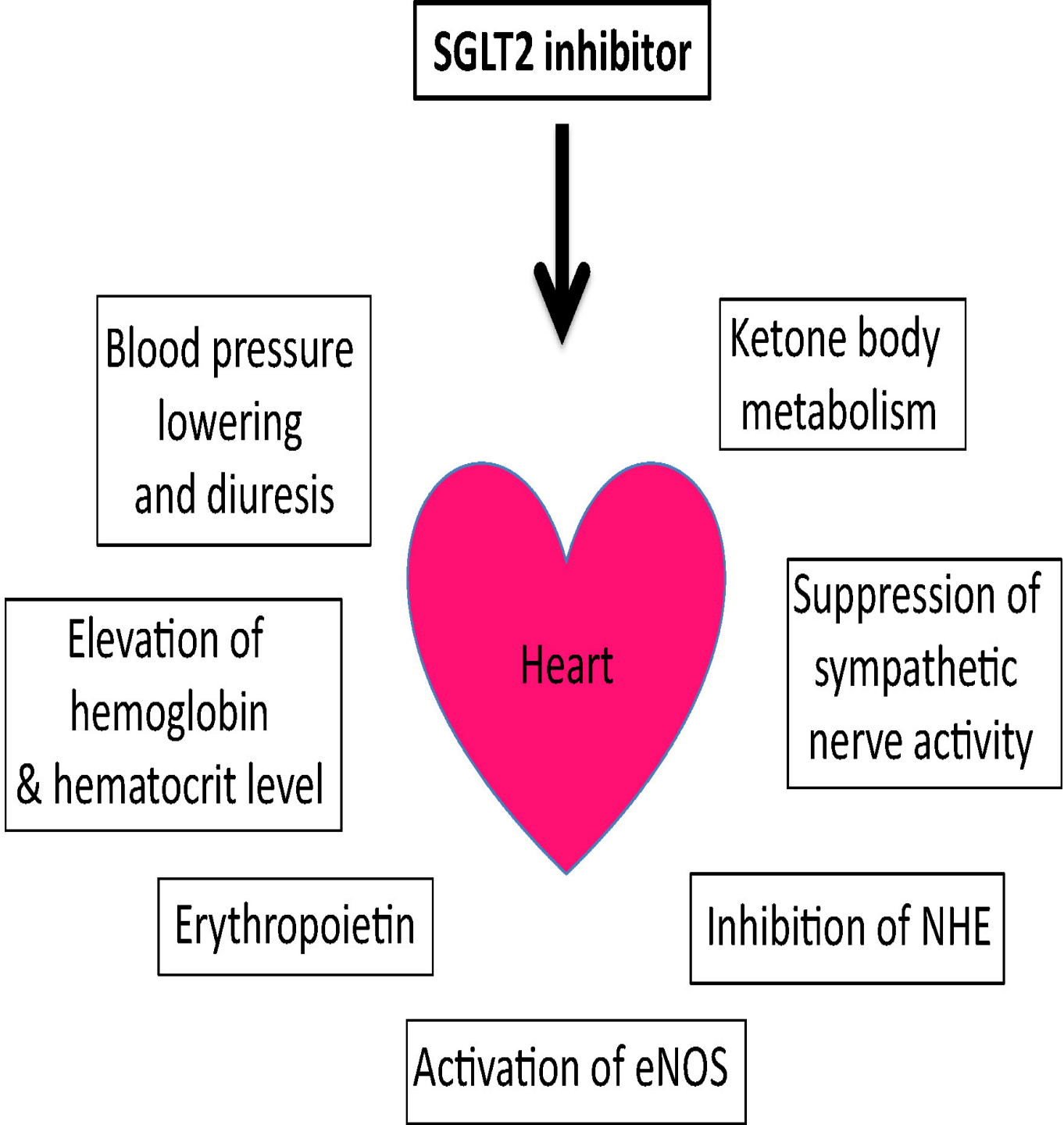
In a healthy person, the kidney filters nearly 200 g of glucose per day, almost all of which is reabsorbed. The primary transporter responsible for renal glucose reabsorption is sodium-glucose cotransporter-2 (SGLT2). Based on the impact of SGLT2 to prevent renal glucose wasting, SGLT2 inhibitors have been developed to treat diabetes and are the newest class of glucose-lowering agents approved in the United States. By inhibiting glucose reabsorption in the proximal tubule, these agents promote glycosuria, thereby reducing blood glucose concentrations and often resulting in modest weight loss. Recent work in humans and rodents has demonstrated that the clinical utility of these agents may not be limited to diabetes management: SGLT2 inhibitors have also shown therapeutic promise in improving outcomes in heart failure, atrial fibrillation, and, in preclinical studies, certain cancers. Unfortunately, these benefits are not without risk: SGLT2 inhibitors predispose to euglycemic ketoacidosis in those with type 2 diabetes and, largely for this reason, are not approved to treat type 1 diabetes. The mechanism for each of the beneficial and harmful effects of SGLT2 inhibitors—with the exception of their effect to lower plasma glucose concentrations—is an area of active investigation.

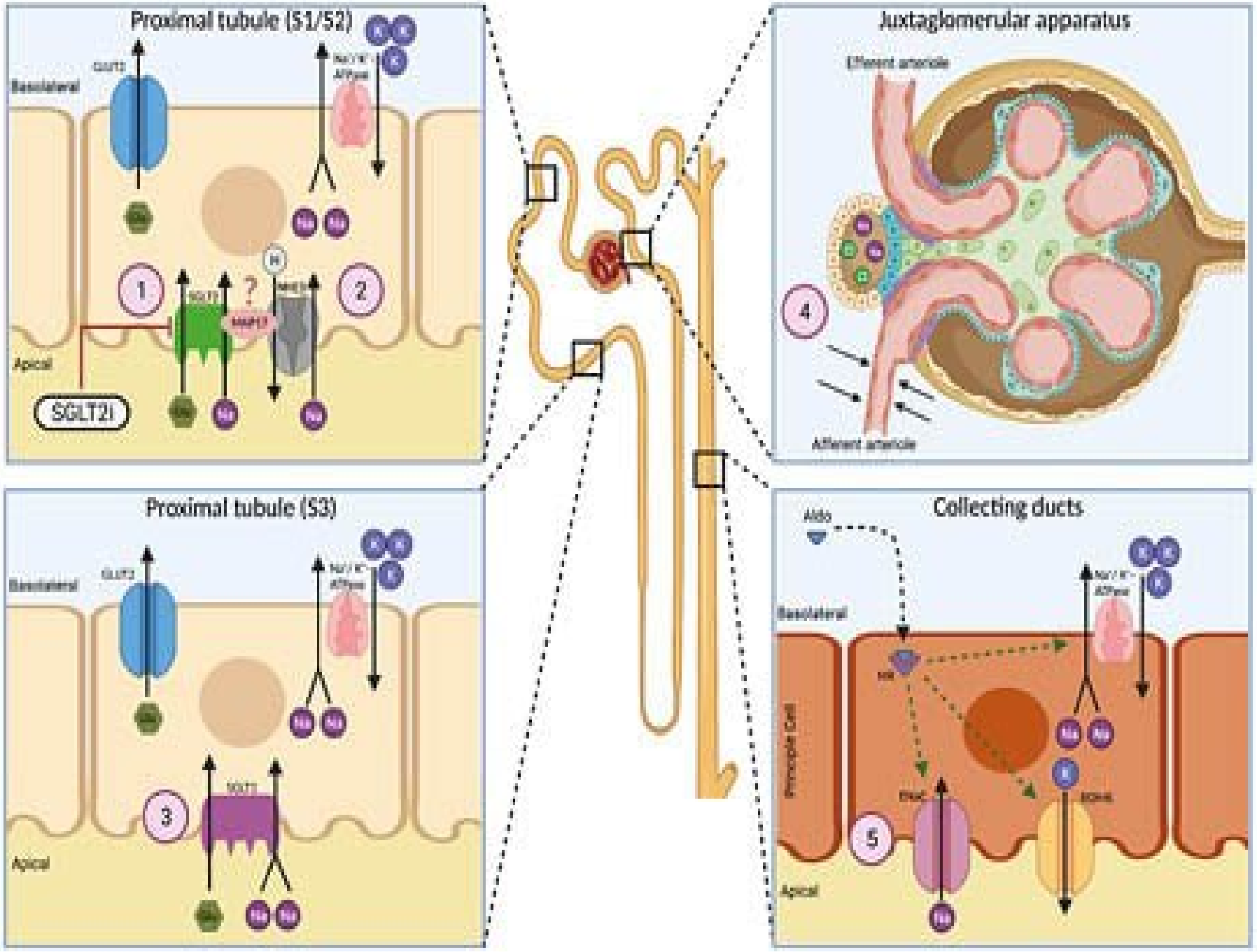


Glucose toxicity on the β-cell (i.e. damage to the insulin-producing cells in the pancreas as a consequence of chronically high circulating glucose, which often occurs concordantly with **lipotoxicity** resulting from increased circulating lipids) has been identified as a key driver of the transition from insulin resistance to diabetes. In support of this hypothesis.It was demonstrated that lowering the glucose load presented to the body, and thereby reducing systemic glucose toxicity, improved β-cell function and reversed insulin resistance.

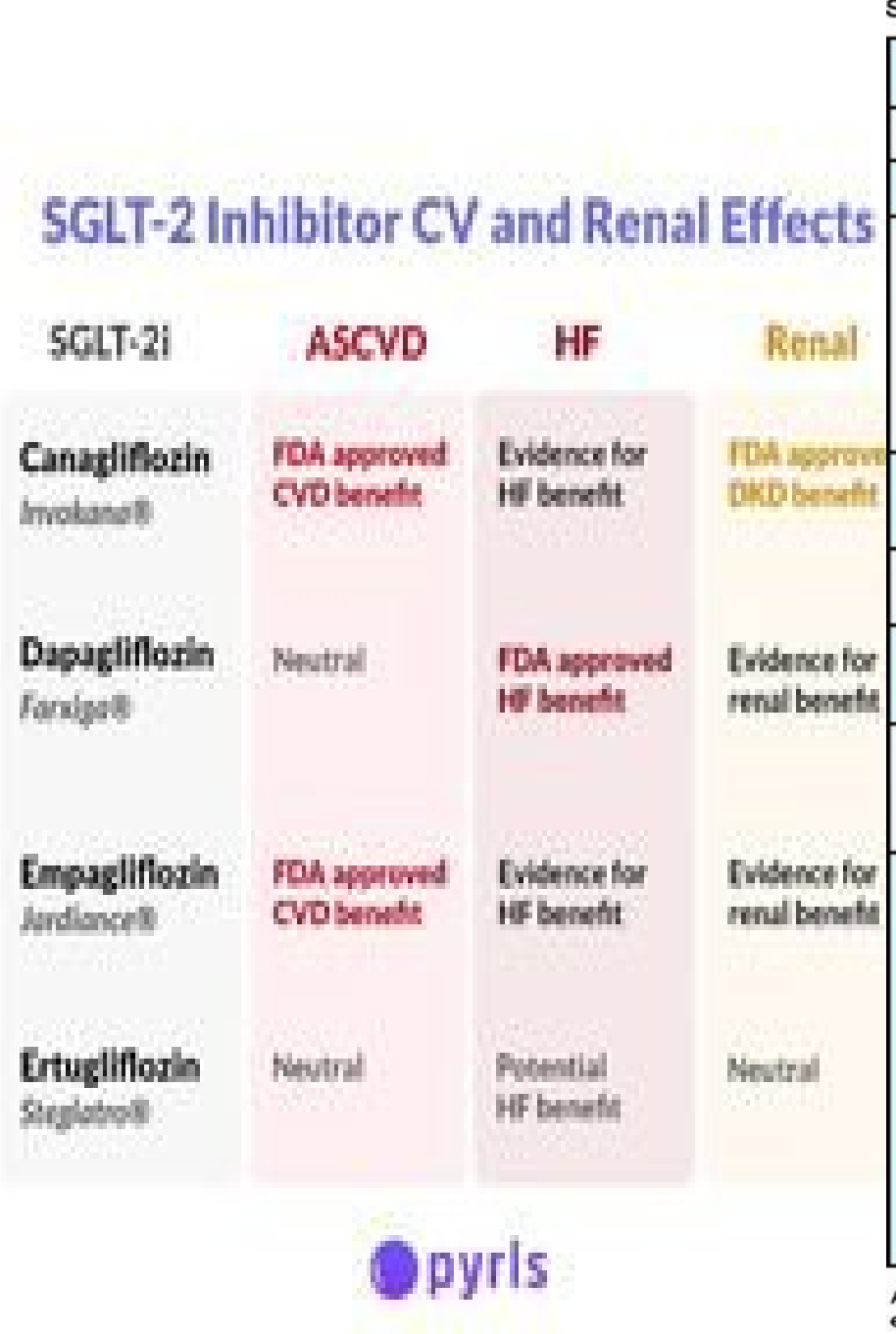
Drug	Bioavailability	$t_{½}$	Route of excretion	A1c lowering
	%	h		%
Canagliflozin	65	10–13	Urine, feces	0.8–1.0
Dapagliflozin	78	13	Urine	0.7–0.8
Empagliflozin	90	13	Urine, feces	0.6–0.8

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have now been shown to prevent cardiovascular events, especially hospitalization for heart failure, in three large randomized clinical trials: EMPA-REG OUTCOME, the CANVAS program, and the DECLARE-TIMI58 trial. It is expected, therefore, that SGLT2 inhibitors will be useful therapeutic agents for the treatment of heart failure.





1. Inhibition of SLGT2 results in the loss of glucose as well as sodium
2. Inhibition of SGLT2 results in downregulation of NHE3 through MAP17 which results in sodium loss
3. Increased glucose delivery to the S3 segment of the proximal convoluted tubule will result in increased action of SGLT1 which reabsorbs 2 sodium ions per glucose
4. Increased distal tubular sodium and chloride will cause afferent arteriolar vasoconstriction through the tubulo glomerular feedback mechanism. This decreases glomerular filtration and results in less sodium loss
5. Decreased renal purfusion will result in an increase in aldosterone due to activation of RAAS. This results in more sodium reabsorption through ENaC



Summary of kidney outcomes from completed placebo-controlled SGLT2 inhibitor outcome trials in patients with Type 2 Diabetes (4-9)

	CANVAS program (n = 10,142)	DECLARE-TIMI 58 (n = 17,160)	EMPA-REG outcome (n = 7020)	CREDENCE (n = 4401)
Intervention	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin
A1C inclusion criteria	A1C 7.0-10.5%	A1C 6.5-12.0%	A1C 7.0-10.0%	A1C 6.5-12.0%
Additional inclusion criteria	Preexisting cardiovascular disease if ≥30 years of age or >2 cardiovascular risk factors if ≥50 years of age	Preexisting cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease	Preexisting cardiovascular disease	eGFR of 30 to <90 mL/min/1.73m² UACR>300-5,000 mg/g Receiving a stable dose of an ACE inhibitor or ARB for ≥4 weeks prior to randomization
% with history of cardiovascular disease	65.6	40.6	99	50.4
Mean eGFR (mL/min/1.73m²)	76.5	85.3	74.1	56.2
UACR group (mg/g)	<30: 70% 30-300: 22% >300: 8%	<30: 69% 30-300: 24% >300: 7%	<30: 60% 30-300: 29% >300: 11%	<30: 1% 30-300: 11% >300: 88%
Primary outcome(s) (HR [95% CI])	3-point MACE 0.86 (0.75-0.97)	3-point MACE 0.93 (0.84-1.03)	3-point MACE 0.86 (0.74-0.99)	Primary composite kidney and cardiovascular outcome[a] 0.70 (0.59-0.82)
Key kidney outcomes (HR [95% CI])	Progression of albuminuria[b] 0.73 (0.67-0.79)	≥40% decrease in eGFR to <60, end-stage kidney disease, or kidney-related death 0.53 (0.43-0.66)	Doubling of serum creatinine accompanied by eGFR of ≤45, initiation of kidney replacement therapy, or kidney-related death 0.54 (0.40-0.75)	End-stage kidney disease, doubling of serum creatinine level, or renal death 0.66 (0.53-0.81)
	40% reduction in eGFR, kidney replacement therapy, or kidney-related death 0.60 (0.47-0.77)	End-stage kidney disease 0.31 (0.13-0.79)	Incident or worsening nephropathy 0.61 (0.53-0.70)	End-stage kidney disease 0.68 (0.54-0.86)
		End-stage kidney disease or kidney-related death 0.41 (0.20-0.82)	Initiation of kidney replacement therapy 0.45 (0.21-0.97)	Dialysis, kidney transplantation, or renal death 0.72 (0.54-0.97)

A1C, glycated hemoglobin; ACE, angiotensin-converting-enzyme; ARB, angiotensin-receptor blocker; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; UACR, urine albumin-to-creatinine ratio.

[a] The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73m²), a doubling of serum creatinine level, or death from renal or cardiovascular causes.

[b] On the basis of prespecified outcomes, the outcome is not viewed as statistically significant.

OSMOTIC DIURETICS

Osmotic diuretics are agents that are freely filtered at the glomerulus, undergo limited reabsorption by the renal tubule, and are relatively inert pharmacologically. Osmotic diuretics are administered in large enough doses to increase significantly the osmolality of plasma and tubular fluid.

Filtered substances that undergo little or no reabsorption result in a higher osmolarity of the tubular fluid. This prevents further water reabsorption at the descending loop of Henle and proximal convoluted tubule, resulting in osmotic diuresis with little additional Na+ excretion (aquaresis). Therefore, these agents are not useful for treating conditions in which Na+ retention occurs. They are used to maintain urine flow following acute toxic ingestion of substances capable of producing acute renal failure. Osmotic diuretics are a mainstay of treatment for patients with increased intracranial pressure. [Note: Mannitol is not absorbed when given orally and should be given intravenously.] Adverse effects include dehydration and extracellular water expansion from the osmotic effects in the systemic circulation. The expansion of extracellular water occurs because the

INHIBITORS OF NA+–K+–2CL–SYMPORT (LOOP DIURETICS, HIGH-CEILING DIURETICS)

Drugs in this group of diuretics inhibit the activity of the Na+–K+–2Cl– symporter in the thick ascending limb of the loop of Henle; hence these diuretics also are referred to as loop diuretics. Although the proximal tubule reabsorbs approximately 65% of the filtered Na+, diuretics acting only in the proximal tubule have limited efficacy because the thick ascending limb has a great reabsorptive capacity and reabsorbs most of the rejectate from the proximal tubule. Diuretics acting predominantly at sites past the thick ascending limb also have limited efficacy because only a small percentage of the filtered Na+ load reaches these more distal sites. In contrast, inhibitors of Na+–K+– 2Cl– symport in the thick ascending limb are highly efficacious, and for this reason, they sometimes are called high-ceiling diuretics. The efficacy of inhibitors of Na+– K+–2Cl– symport in the thick ascending limb of the loop of Henle is due to a combination of two factors: (1) Approximately 25% of the filtered Na+ load normally is reabsorbed by the thick ascending limb, and (2) nephron segments past

It is now well accepted that flux of Na+, K+, and Cl−from the lumen into the epithelial cells in the thick ascending limb is mediated by a Na+−K+−2Cl− symporter. This symporter captures the free energy in the Na+ electrochemical gradient established by the basolateral Na+ pump and provides for “uphill” transport of K+ and Cl− into the cell. K+ channels in the luminal membrane (called ROMK) provide a conductive pathway for the apical recycling of this cation, and basolateral Cl− channels (called CLC-Kb) provide a basolateral exit mechanism for Cl−. The luminal membranes of epithelial cells in the thick ascending limb have a large conductive pathway (channels) for K+; therefore, the apical membrane voltage is determined by the equilibrium potential for K+ (EK) and is hyperpolarized. In contrast, the basolateral membrane has a large conductive pathway (channels) for Cl−, so the basolateral membrane voltage is less negative than EK; i.e., conductance for Cl− depolarizes the basolateral membrane. Hyperpolarization of the luminal membrane and depolarization of the basolateral membrane result in a transepithelial potential difference of approximately 10 mV, with the

Inhibitors of $Na^+–K^+–2Cl^–$ symport also inhibit Ca^{2+} and Mg^{2+} reabsorption in the thick ascending limb by abolishing the transepithelial potential difference that is the dominant driving force for reabsorption of these cations.

Loop diuretics display a sigmoidal (“S”-shaped) dose-response curve with three parts: a threshold effect, a rapid increase in diuresis with small changes in drug concentration, and a ceiling effect. A dose must be selected to cross the response threshold, which is patient-specific. Reducing the effective dose with the intent of a reduction in diuresis can result in no diuresis, if the concentration of loop diuretic drops below the response threshold. Likewise, increasing the effective dose may not cause more diuresis because of the ceiling effect. Thus, after determination of an effective diuretic dose, the clinician should modify the frequency of administration to increase or decrease the daily diuresis

Effects on Urinary Excretion. Owing to blockade of the Na+–K+–2Cl– symporter, loop diuretics increase in the urinary excretion of Na+ and Cl– profoundly (i.e., up to 25% of the filtered load of Na+). Abolition of the transepithelial potential difference also results in marked increases in the excretion of Ca2+ and Mg2+. Some (e.g., furosemide) but not all (e.g., bumetanide) sulfonamide-based loop diuretics have weak carbonic anhydrase–inhibiting activity. Drugs with carbonic anhydrase–inhibiting activity increase the urinary excretion of HCO3 – and phosphate. All inhibitors of Na+–K+–2Cl– symport increase the urinary excretion of K+ and titratable acid. This effect is due in part to increased delivery of Na+ to the distal tubule. The mechanism by which increased distal delivery of Na+ enhances excretion of K+ and H ,other mechanisms contributing to enhanced K+ and H+ excretion include flow-dependent enhancement of ion secretion by the collecting duct, nonosmotic vasopressin release, and activation of the renin–angiotensin–aldosterone axis. Acutely, loop diuretics increase the excretion of uric acid, whereas chronic administration of these drugs results in reduced excretion of uric acid. The chronic effects of loop diuretics on uric acid excretion may be due to enhanced transport in the proximal tubule secondary to volume depletion, leading to increased uric acid reabsorption, or to competition between the diuretic and uric acid for the organic acid secretory mechanism in the

Effects on Renal Hemodynamics . If volume depletion is prevented by replacing fluid losses, inhibitors of Na+K+−2Cl− symport generally increase total RBF and redistribute RBF to the midcortex. However, the effects on RBF are variable. The mechanism of the increase in RBF is not known but may involve prostaglandins. Nonsteroidal antiinflammatory drugs (NSAIDs) attenuate the diuretic response to loop diuretics in part by preventing prostaglandin- mediated increases in RBF. Loop diuretics block TGF by inhibiting salt transport into the macula densa so that the macula densa no longer can detect NaCl concentrations in the tubular fluid. Therefore, unlike carbonic anhydrase inhibitors, loop diuretics do not decrease GFR by activating TGF. Loop diuretics are powerful stimulators of renin release. This effect is due to interference with NaCl transport by the macula densa and, if volume depletion occurs, to reflex activation of the sympathetic nervous system and to stimulation of the intrarenal baroreceptor mechanism. Prostaglandins, particularly prostacyclin, may play an important role in mediating the renin-release response to loop diuretics. Other Actions. Loop diuretics may cause direct vascular effects. Loop diuretics, particularly furosemide, acutely increase systemic venous capacitance and thereby decrease left ventricular filling pressure. This effect, which may be mediated by prostaglandins and requires intact kidneys, benefits patients with pulmonary edema even before diuresis

Absorption and Elimination. The oral bioavailabilities, plasma half-lives, and routes of elimination of inhibitors of Na+–K+–2Cl– symport are listed in Table. Because furosemide, bumetanide, ethacrynic acid, and torsemide are bound extensively to plasma proteins, delivery of these drugs to the tubules by filtration is limited. However, they are secreted efficiently by the organic acid transport system in the proximal tubule and thereby gain access to their binding sites on the Na+–K+–2Cl– symport in the luminal membrane of the thick ascending limb Approximately 65% of furosemide is excreted unchanged in the urine, and the remainder is conjugated to glucuronic acid in the kidney. Accordingly, in patients with renal, but not liver, disease, the elimination half-life of furosemide is prolonged. In contrast, bumetanide and torsemide have significant hepatic metabolism, so the elimination half-lives of these loop diuretics are prolonged by liver, but not renal, disease. Although the average oral availability of furosemide is approximately 60%, oral availability of furosemide varies from 10% to 100%. In contrast, oral availabilities of bumetanide and torsemide are reliably high. Heart failure patients have fewer

Toxicity, Adverse Effects, Contraindications, Drug Interactions. Adverse effects unrelated to the diuretic efficacy are rare, and most adverse effects are due to abnormalities of fluid and electrolyte balance. Overzealous use of loop diuretics can cause serious depletion of total-body Na+. This may be manifest as hyponatremia and/or extracellular fluid volume depletion associated with hypotension, reduced GFR, circulatory collapse, thromboembolic episodes, and in patients with liver disease, hepatic encephalopathy. Increased delivery of Na+ to the distal tubule, particularly when combined with activation of the renin–angiotensin system, leads to increased urinary excretion of K+ and H+, causing a hypochloremic alkalosis. If dietary K+ intake is not sufficient, hypokalemia may develop, and this may induce cardiac arrhythmias, particularly in patients taking cardiac glycosides. Increased Mg2+ and Ca2+ excretion may result in hypomagnesemia (a risk factor for cardiac arrhythmias) and hypocalcemia (rarely leading to tetany). Recent evidence suggests

increased Ca2+ excretion may have deleterious effects on bone metabolism. Loop diuretics can cause **ototoxicity that manifests as tinnitus** , hearing impairment, deafness, vertigo, and a sense of fullness in the ears. Hearing impairment and deafness are usually, but not always, reversible. Ototoxicity occurs most frequently with rapid intravenous administration and least frequently with oral administration. **Ethacrynic acid** appears to induce ototoxicity more often than do other loop diuretics and should be used only in patients who cannot tolerate the other loop diuretics. Loop diuretics also can cause **hyperuricemia** (occasionally leading to gout) and **hyperglycemia** (infrequently precipitating diabetes mellitus) and can increase plasma levels of low-density lipoprotein (**LDL)** cholesterol and **triglycerides** while decreasing plasma levels of high-density lipoprotein **(HDL**) cholesterol. Other adverse effects include skin rashes, photosensitivity, paresthesias, **bone marrow depression**, and gastrointestinal disturbances. Contraindications to the use of loop diuretics include **severe Na+ and volume depletion, hypersensitivity to sulfonamides (for sulfonamide-based loop diuretics), and anuria unresponsive to a trial dose of loop diuretic.**

Drug interactions may occur when loop diuretics are coadministered with (1) aminoglycosides (synergism of ototoxicity caused by both drugs), (2) anticoagulants (increased anticoagulant activity), (3) digitalis glycosides (increased digitalis-induced arrhythmias), (4) lithium (increased plasma levels of lithium), (5) propranolol (increased plasma levels of propranolol), (6) sulfonylureas (hyperglycemia), (7) cisplatin (increased risk of diuretic-induced ototoxicity), (8) NSAIDs (blunted diuretic response and salicylate

Thiazides

The thiazides are the most widely used diuretics because of their antihypertensive effects. However, the efficacy of thiazides for hypertension is not entirely dependent on their diuretic actions. These agents also reduce peripheral vascular resistance with long-term therapy. Despite being sulfonamide derivatives, thiazides do not generally cause **hypersensitivity reactions** in patients with allergies to sulfonamide antimicrobials such as sulfamethoxazole. All thiazides affect the **distal convoluted tubule** , and all have equal maximum diuretic effects, differing only in potency. Thiazides are sometimes called **"low ceiling diuretics,"** because increasing the dose above normal therapeutic doses does not promote further diuretic response.

Chlorothiazide was the first orally active thiazide, although **hydrochlorothiazide** and **chlorthalidone** are now used more commonly due to better bioavailability. **Hydrochlorothiazide** is more potent, so the required dose is considerably lower than that of chlorothiazide, but the efficacy is comparable to that of the parent drug. In all other aspects, hydrochlorothiazide resembles chlorothiazide. Chlorthalidone is approximately twice as potent as hydrochlorothiazide. **Chlorthalidone , indapamide, and metolazone are referred to as thiazide-like**

Medications should be avoided in sulfa allergy

Sulfa allergy is due to presence of sulfonamide group

Contraindicated

Generic name	Trade name
Sulfamethoxazole-Trimethoprim	Septrin
Sulfasalazine	Colosalazine
Glipizide	Minidiab
Glimepiride	Amaryl
Indapamide	Natrilix
Furosemide	Lasix, Lasilactone
Metolazone	Demafight, Efectinix
Torsemide	Torseretic, Examide
Acetazolamide	Cidamex
Celecoxib	Celebrex

Use with caution

Generic name	Trade name
Silver Sulfadiazine Cream	Hyalo Cream, Dermazin Cream
Mesalazine	Pentasa, Mesala
Gliclazide	Diamicron
Glibenclamide	Glucovance,
Thiazide	Exforge HCT, Erastabex plus, Co Aproval, Fortzar
Sumatriptan	Use with caution (Zolmitriptan is safe)
Tamsulosin	Tamsulin, Omnic ocas
Topiramate	Topiramax
Bosentan	Bosentadine
Sotalol	Betacor

Mechanism of action

The thiazide and thiazide-like diuretics act mainly in the distal convoluted tubule to decrease the reabsorption of Na+ by inhibition of a Na+/Cl− cotransporter. As a result, these drugs increase the concentration of Na+ and Cl− in the tubular fluid. Thiazides must be excreted into the tubular lumen at the proximal convoluted tubule to be effective. Therefore, decreasing renal function reduces the diuretic effects. The antihypertensive effects of thiazides may persist even when the glomerular filtration rate is below 30 mL/min/1.73 m2. However, hypertension at this level of renal dysfunction is often exacerbated by hypervolemia, requiring a change to loop diuretics for volume status and, therefore, blood pressure control. The efficacy of thiazides may be diminished with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, which inhibit production of renal prostaglandins, thereby reducing renal blood flow.

2. Actions

a. Increased excretion of Na+ and Cl−

Thiazide and thiazide-like diuretics cause diuresis with increased Na+ and Cl− excretion, which can result in the excretion of very hyperosmolar (concentrated) urine. This latter effect is unique, as the other diuretic classes are unlikely to

Decreased urinary calcium excretion

Thiazide and thiazide-like diuretics decrease the Ca^{2+} content of urine by promoting the reabsorption of Ca^{2+} in the distal convoluted tubule where parathyroid hormone regulates reabsorption.

Reduced peripheral vascular resistance

An initial reduction in blood pressure results from a decrease in blood volume and, therefore, a decrease in cardiac output. With continued therapy, blood volume returns to baseline. However, antihypertensive effects continue, resulting from reduced peripheral vascular resistance caused by relaxation of arteriolar smooth muscle

Therapeutic uses

Hypertension

Clinically, thiazides are a mainstay of antihypertensive treatment, because they are inexpensive, convenient to administer, and well tolerated. Blood pressure can be lowered with a daily dose of thiazide. At doses equipotent to hydrochlorothiazide, chlorthalidone is considered a preferred option by some clinicians because of its longer halflife (50 to 60 hours) and improved control of

Heart failure

Loop diuretics (not thiazides) are the diuretics of choice in reducing extracellular volume in heart failure. However, thiazide diuretics may be added in patients resistant to loop diuretics, with careful monitoring for hypokalemia. Metolazone is most frequently utilized as an addition to loop diuretics, although there is a lack of evidence that it is more effective than other thiazides for this indication when administered at equipotent doses. Historically, thiazides were prescribed to be administered 30 minutes prior to loop diuretics to allow the thiazide time to reach the site of action when combined to augment diuresis in diuretic resistance. This practice is unnecessary and not supported by current evidence.

Hypercalciuria

The thiazides can be useful in treating idiopathic hypercalciuria and calcium oxalate stones in the urinary tract, because they inhibit urinary Ca^{2+} excretion.

Diabetes insipidus

Thiazides have the unique ability to produce a hyperosmolar urine. Thiazides can be utilized as a treatment for nephrogenic diabetes insipidus. The urine volume of such individuals may drop from 11 to about 3 L/d when treated with thiazides.

Pharmacokinetics

As a class, thiazides are effective orally, with a bioavailability of 60% to 70%. Chlorothiazide has a much lower bioavailability (15% to 30%) and is the only thiazide with an intravenous dosage form. Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure and exhibit a prolonged half-life (approximately 10 to 15 hours). Indapamide differs from the class

Adverse effects

These mainly involve problems in fluid and electrolyte balance

Hypokalemia

Hypokalemia is the most frequent problem with the thiazide diuretics. Because thiazides increase Na+ in the filtrate arriving at the distal tubule, more K+ is also exchanged for Na+, resulting in a continual loss of K+ from the body with prolonged use of these drugs Thus, serum K+ should be measured periodically (more frequently at the beginning of therapy) to monitor for the development of hypokalemia. Potassium supplementation or combination with a potassium-sparing diuretic may be required. Low-sodium diets blunt the potassium depletion caused by thiazide diuretics.

Hypomagnesemia

Hyponatremia

Hyponatremia may develop due to elevation of ADH, as well as diminished diluting capacity of the kidney and increased thirst.

Hyperuricemia

Thiazides increase serum uric acid by decreasing the amount of acid excreted through competition in the organic acid secretory system. Being insoluble, uric acid deposits in the joints and may precipitate a gouty attack in predisposed individuals. Therefore, thiazides should be used with caution in patients with gout or high levels of uric acid.

Hypovolemia

This can cause orthostatic hypotension or light-headedness.

Hypercalcemia

Thiazides inhibit the secretion of Ca2+, sometimes leading to hypercalcemia (elevated levels of Ca2+ in the blood).

g. Hyperglycemia

Aldosterone antagonists: spironolactone and eplerenone

Mechanism of action

Spironolactone and eplerenone are synthetic steroids that antagonize aldosterone receptors. This prevents translocation of the receptor complex into the nucleus of the target cell, ultimately resulting in a lack of intracellular proteins that stimulate the Na+/K+-exchange sites of the collecting tubule. Thus, aldosterone antagonists prevent Na+ reabsorption and, therefore, K+ and H+ secretion. Eplerenone is more selective for aldosterone receptors and causes less endocrine effects (gynecomastia) than spironolactone, which also binds to progesterone and androgen receptors.

Actions

Spironolactone and eplerenone antagonize aldosterone receptors at renal sites, which causes diuresis, and nonrenal sites, which causes other effects. In most edematous states, blood levels of aldosterone are high, causing retention of Na+. Spironolactone antagonizes the activity of aldosterone, resulting in retention of K+ and excretion of Na+.

3. Therapeutic uses

a. Edema

Aldosterone antagonists are particularly effective diuretics when used in high doses for edema associated with secondary hyperaldosteronism, such as hepatic cirrhosis and nephrotic syndrome. pironolactone is the diuretic of choice in patients with hepatic cirrhosis with fluid in the peritoneal cavity (ascites). By contrast, in patients who have no significant circulating levels of aldosterone, there is minimal diuretic effect with use of this drug.

b. Hypokalemia

Although the aldosterone antagonists have a low efficacy in mobilizing Na+ from the body in comparison with the other diuretics, they have the useful property of causing the retention of K+. These agents are often given in conjunction with thiazide or loop diuretics to prevent K+ excretion that occurs with those diuretics.

c. Heart failure

Aldosterone antagonists are employed at lower doses to prevent myocardial remodeling mediated by aldosterone. Use of these agents has been shown to decrease mortality associated with heart failure, particularly in those with reduced ejection fraction.

d. Resistant hypertension

Pharmacokinetics

Both spironolactone and eplerenone are well absorbed after oral administration. Spironolactone is extensively metabolized and converted to several active metabolites, which contribute to the therapeutic effects. Eplerenone is metabolized by cytochrome P450 3A4.

Adverse effects

Hyperkalemia, Gynecomastia

Spironolactone, but not eplerenone, may induce gynecomastia in approximately 10% of male patients and menstrual irregularities in female patients.

Triamterene and amiloride

Triamterene and amiloride block epithelial sodium channels, resulting in a decrease in Na+/K+ exchange. Although they have a K+-sparing diuretic action similar to that of the aldosterone antagonists, their ability to block the Na+/K+-exchange site in the collecting tubule does not depend on the presence of aldosterone. Like the aldosterone antagonists, these agents are not very efficacious diuretics. Both triamterene and amiloride are commonly used in

Drugs induced Acute Kidney Injury

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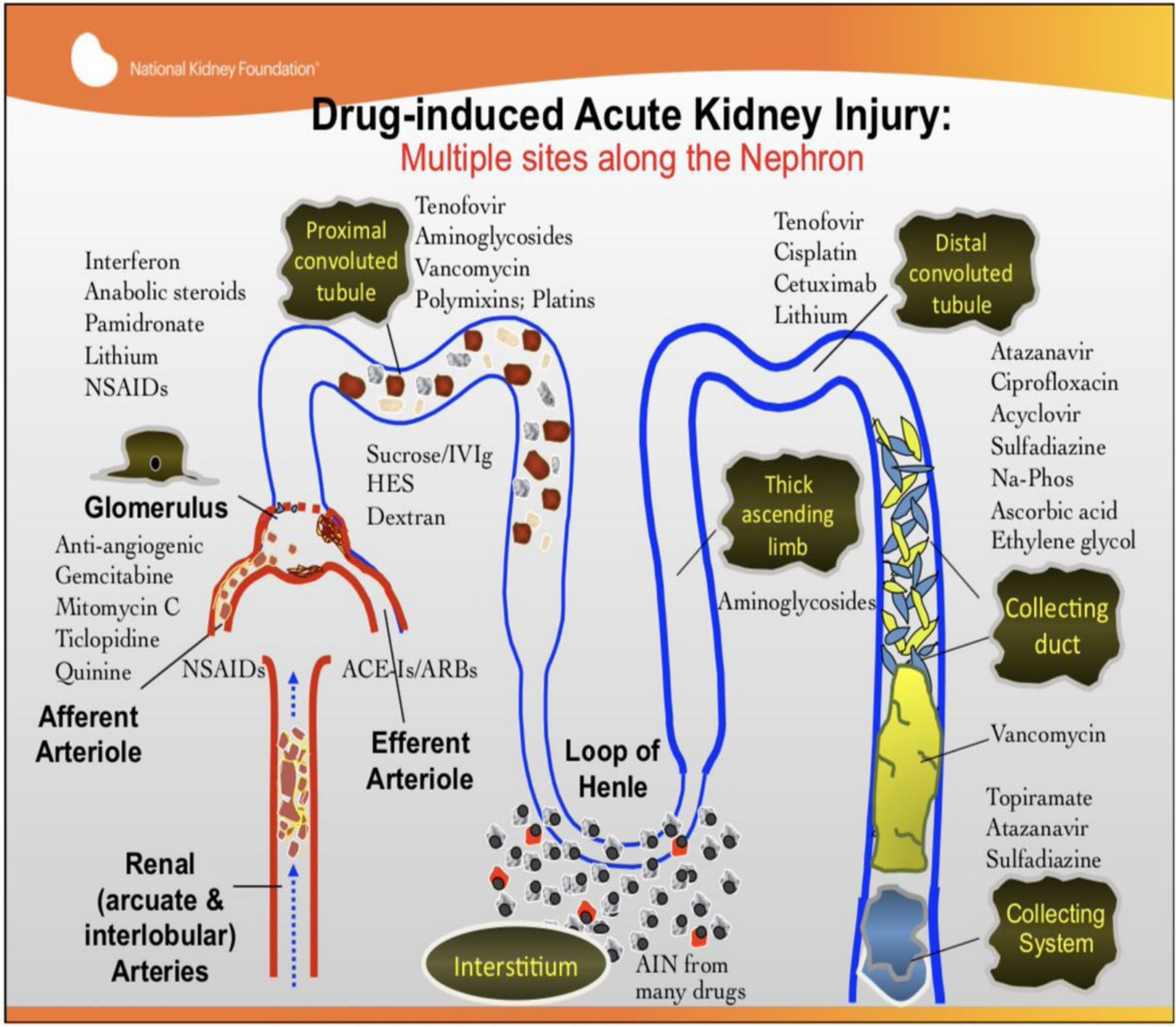

ACUTE KIDNEY INJURY OR ACUTE RENAL FAILURE

Definitions and Background

AKI is defined as an acute decrease in kidney function or GFR over hours, days, or even weeks and is associated with an accumulation of waste products and (usually) volume.

Criteria and classification of AKI

Definition of AKI according to KDIGO (not graded)

i. Increase in SCr of 0.3 mg/dL or more within 48 hours; or

ii. Increase in SCr to 1.5 times baseline or more (baseline known or presumed within prior 7 days); or

iii. Urinary volume less than 0.5 mL/kg/hour for at least 6 hours

Urinary output classification

i. Anuric: Less than 50 mL/24 hours; associated with worse outcomes

ii. Oliguric: 50–500 mL/24 hours

iii. Nonoliguric: More than 500 mL/24 hours; associated with better patient outcomes and easier to manage because of fewer problems with volume overload

Staging of AKI : Can categorize according to risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) categories or into stages 1–3 (AKIN or KDIGO) on the basis

RIFLE Classification (2004)			AKIN Criteria (2007)		KDIGO Staging (2012)		Common Criteria
	Classification	SCr or GFR Criteria	Stage	SCr	Stage	SCr	Urinary Output
R	Risk of renal dysfunction	SCr increase to 1.5 × baseline *or* GFR decrease > 25%	1	≥ 0.3-mg/dL increase *or* 1.5–1.9 × baseline	1	≥ 0.3-mg/dL increase *or* 1.5–1.9 × baseline	< 0.5 mL/kg/hr for 6–12 hr
I	Injury to kidney	SCr increase to 2 × baseline *or* GFR decrease > 50%	2	2–3 × baseline	2	2.0–2.9 × baseline	< 0.5 mL/kg/hr for ≥ 12 hr
F	Failure of kidney function	SCr increase to 3 × baseline *or* GFR decrease > 75% *or* SCr > 4 mg/dL with acute rise of > 0.5 mg/dL	3	> 3 × baseline *or* SCr ≥ 4 mg/dL with an acute increase of ≥ 0.5 mg/dL; *or* on RRT	3	≥ 3 × baseline *or* increase to ≥ 4.0 mg/dL *or* Initiation of RRT *or* in patients < 18 yr, decrease in eGFR to < 35 mL/min/1.73 m^2	< 0.3 mL/kg/hr for ≥ 24 hr *or* Anuria for ≥ 12 hr
L	Loss of kidney function	Complete loss of kidney function for > 4 wk					
E	End-stage kidney disease	Complete loss of kidney function for > 3 mo					

AKIN = Acute Kidney Injury Network; KDIGO = Kidney Disease: Improving Global Outcomes; RIFLE = risk, injury, failure, loss, end-stage (stages of AKI); RRT = renal replacement therapy

Community-acquired AKI

a. Low incidence (0.02%) in otherwise healthy patients
b. As high as 13% incidence among patients with CKD
c. Usually has a very high survival rate (70%–95%)
d. Single insult to the kidney, often drug induced
e. SCr may return to baseline but may lead to development or progression of CKD

Hospital-acquired AKI

a. Has a moderate incidence (2%–5%) and moderate survival rate (30%–50%)
b. Single or multifocal insults to the kidney
c. Can still be reversible
5. A 2015 international study of critically-ill patients found AKI in over 50% of intensive care unit patients, with mortality 4–5 times higher than in those without AKI

Stimating kidney function in AKI

a. Difficult because commonly used SCr-based equations **(Cockcroft-Gault, Modification of Diet in Renal Disease [MDRD], and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI])** are not appropriate (assume **stable SCr**)
b. Equations by **Brater and Jelliffe** are probably more accurate than the Cockcroft-Gault equation but have not been rigorously tested.
c. The **Chen formula** for kinetic eGFR provides a promising, simple method to estimate kidney function when SCr is not stable. Further study is still needed.
d. If patient is nonoliguric, can calculate **creatinine clearance (CrCl**) according to a timed urine collection and using the average of SCr samples obtained before and after the urine collection

Cockroft-Gault formula

$$\frac{(140 - \text{Age}) \times \text{IBW}}{72 \times \text{Serum creatinine}} \times \text{Multiply by } 0.85 = \text{mL/minute (In female)}$$

Ideal body weight (IBW) In female = 45.5 Kg + 2.3 Kg for each inch over 5 feet

Ideal body weight (IBW) In male = 50 Kg + 2.3 Kg for each inch over 5 feet

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Creatinine Clearance corrected

$$\frac{\text{Urine creatinine (U)} \times \text{Urine volume in mL (V)}}{\text{Serum creatinine (S)} \times \text{Collection time (minutes) T}} \times \frac{1.73}{\text{Body surface area, m2 (A)}}$$

$$\text{Corrected Creatinine Clearance} = \frac{U \times V}{S \times T} \times \frac{1.73}{A}$$

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MDRD

$$GFR = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

CKD-EPI

$$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times (1.018 \text{ if female}) \times (1.159 \text{ if African American})$$

*S_{cr} is serum creatinine in mg/dL
κ is 0.7 for females and 0.9 for males
α is -0.329 for females and -0.411 for males
min indicates the minimum of S_{cr}/κ or 1
max indicates the maximum of S_{cr}/κ or 1

Jelliffe (nonadjusted)

$$CL_{Cr} = \frac{[98 - [(0.8)(Age - 20)](0.9)}{SCr}$$

Normalized Jelliffe[11]

$$CL_{Cr} = \frac{[98 - [(0.8)(Age - 20)](0.9)\left(\frac{BSA}{1.73}\right)}{SCr}$$

Pediatric ? ?

Classifications of AKI

1. **Prerenal AKI**

a. Initially, the kidney is undamaged.

b. Characterized by hypoperfusion to the kidney

i. Systemic hypoperfusion: Hemorrhage, volume depletion, drugs, CHF

ii. Isolated kidney hypoperfusion: Renal artery stenosis, emboli

c. Physical examination: Hypotension, signs of volume depletion

d. Urinalysis will initially be **normal (no sediment) but concentrated** .

2**. Functional AKI**

a. Kidney is undamaged; often classified as prerenal azotemia

b. Caused by reduced glomerular **hydrostatic pressure** ; often without hypotension

c. In general, medication-related (cyclosporine, ACEIs and ARBs, and NSAIDs) or seen in patients with low effective blood flow (patients with CHF, patients with liver disease, and older adults) who cannot compensate for alterations in

3. **Intrinsic AKI**

a. Kidney is damaged, and damage can be linked to the structure involved: Small blood vessels, glomeruli, renal tubules, and interstitium

b. Most common cause is ATN; other causes include AIN, vasculitis, and acute glomerulonephritis.

c. History: Identifiable insult, drug use, infections

d. Physical examination: Normotensive, euvolemic, or hypervolemic depending on the cause; check

for signs of allergic reactions or embolic phenomenon

e. Urinalysis will reflect damage; urine generally is not concentrated.

4. **Postrenal AKI**

a. Kidney is initially undamaged. Bladder outlet obstruction is the most common cause of postrenal AKI. Lower urinary tract obstruction may be caused by calculi. Ureteric obstructions may be caused by clots or intraluminal obstructions. Extrarenal compression can also cause postrenal disease. Elevated intraluminal pressure upstream of the obstruction will result in damage if the obstruction is not relieved.

b. History: Trauma, benign prostatic hyperplasia, cancers

c. Physical examination: Distended bladder, enlarged prostate

d. Urinalysis may be nonspecific.

Treatment and Management of Established AKI

1. **Prerenal azotemia**: Correct primary hemodynamics.

a. **Intravenous normal saline, lactated Ringer solution** or other balanced crystalloid, if volume depleted

b. Blood pressure management, if needed

c. Blood products, if needed

d. Hold or discontinue medications that affect renal hemodynamics (i.e., ACEIs, ARBs, NSAIDs).

2**. Intrinsic**: No specific therapy universally effective

a. Eliminate the causative hemodynamic abnormality or toxin.

b. Avoid additional insults.

c. Manage **fluid and electrolytes** to prevent volume depletion or overload and electrolyte imbalances.

d. Nutrition support is important, but no specific recommendations are widely accepted.

e. Medical therapy recommendations according to the KDIGO guidelines

i. **Loop diuretics: Recommend not using to prevent AKI and suggest not using to treat AKI, except to manage hypervolemia** .

ii. Therapeutic agents (e.g., dopamine, nesiritide, fenoldopam**, mannitol**) are not indicated in AKI management and may be harmful for the patient.

ACEI = angiotensin-converting enzyme inhibitor; AIN = acute interstitial nephritis; ARB = angiotensin II receptor blocker; ATN = acute tubular necrosis; BPH = benign prostatic hypertrophy; CHF = congestive heart failure; FENa = fractional excretion of sodium; NSAID = nonsteroidal anti-inflammatory drug; RBC = red blood cell count

DRUG-INDUCED KIDNEY DAMAGE

Drugs can cause kidney damage through many mechanisms. Evaluate potential drug-induced nephropathy on the basis of the period of ingestion, patient risk factors, and the propensity of the suspected agent to cause kidney damage.

Risk factors

a. History of CKD

b. Advanced age

c. Nephrotoxic agent

d. Critical illness

e. Most implicated medications: Aminoglycosides, NSAIDs, ACEIs, intravenous contrast dye, amphotericin, piperacillin/tazobactam plus vancomycin

The kidneys are at elevated risk of toxic :

a. High exposure to toxin: Kidney receives 20%–25% cardiac output.

b. Autoregulation and specialized blood flow through glomerulus

c. High intrarenal drug metabolism

d. Tubular transport processes

e. Concentration of solutes (i.e., toxins) in tubules

f. High energy requirements of tubule epithelial cells

Indications for renal replacement therapy (RRT) in AKI

a. BUN greater than 100 mg/dL or signs of uremia (e.g., encephalopathy, pericarditis)
b. Volume overload unresponsive to diuretics
c. Life-threatening electrolyte imbalance: Hyperkalemia, hypermagnesemia
d. Refractory metabolic acidosis

Pseudo-nephrotoxicity

a. Drugs that inhibit the tubular secretion of creatinine: Trimethoprim, cimetidine
b. Drugs that increase BUN: Corticosteroids, tetracycline
c. Drugs that interfere with the creatinine assay: Cefoxitin and other cephalosporins

Acute Tubular Necrosis

Most common drug-induced kidney disease in the inpatient setting

1- Aminoglycoside nephrotoxicity

Incidence: 1.7%–58% of patients

Pathogenesis i. Caused by proximal tubular damage leading to obstruction of the lumen ii. Cationic charge of drug leads to binding to tubular epithelial cells and uptake into those cells. iii. Accumulation of phospholipids and toxicity

Presentation

i. Gradual rise in SCr concentrations and decrease in GFR after **6–10** days of therapy. Patients usually have **nonoliguric** kidney failure. Wasting of electrolytes (i.e**., hypokalemia and hypomagnesemia)** may occur.

Risk factors

i. Related to dosing: Large total cumulative dose, prolonged therapy, trough concentration exceeding 2 mg/L, recent previous aminoglycoside therapy

ii. Concurrent use of other **nephrotoxins** (cyclosporine, amphotericin B, **diuretics**, vancomycin)

iii. Preexisting kidney disease or damage, advanced age, poor nutrition, shock, gram-negative bacteremia, liver disease, hypoalbuminemia, obstructive jaundice, dehydration, and K and magnesium deficiencies

Prevention

i. Avoid use in high-risk patients.

ii. Maintain adequate hydration.

iii. Limit the total cumulative aminoglycoside dose.

iv. Avoid use of other nephrotoxins.

2-Radiographic contrast media nephrotoxicity related to intravenous contrast use

Incidence

i. Third leading cause of inpatient AKI

ii. up to 50% of patients, depending on risk

iii. Associated with a high (34%) in-hospital mortality rate

iv. Commonly used in procedures such as contrast-enhanced computed tomography (CT), cardiac catheterization, angiography, and venography

Pathogenesis

i. Renal ischemia caused by alteration in intrarenal hemodynamics

(a) **Osmotic diuresis and dehydration** . Contrast media based on osmolality:

(1) High-osmolar contrast media about **2000** mOsm/kg

(2) Low-osmolar contrast media **600–800** mOsm/kg

(3) Iso-osmolar contrast media **290** mOsm/kg

(b) Some contrast agents also cause systemic hypotension on injection and renal vasoconstriction caused by the release of **adenosine, endothelin, and other vasoconstrictors** .

ii. Direct tubular toxicity caused **by reactive oxygen species** ; directly influenced by tubular flow rates and duration of exposure of tubules

Presentation

i. Initial transient osmotic diuresis, followed by tubular proteinuria

ii. SCr rises within **24 hours and peaks 2–5 days** after the procedure.

Risk factors for toxicity

i. Preexisting kidney disease (SCr more than 1.5 mg/dL or CrCl less than 60 mL/minute/1.73 m2)

ii. Diabetes mellitus iii. Volume depletion iv. Age 75 and older v. Anemia

vi. Conditions with decreased blood flow to the kidney (e.g., CHF)

vii. Hypotension viii. Other nephrotoxins

ix. Large doses of contrast (more than 140 mL) or hyperosmolar contrast agents

Prevention

i. Volume expansion with either **intravenous isotonic saline or sodium bicarbonate** (KDIGO recommendation, grade 1A) beginning 6–12 hours before the procedure; maintain urinary output greater than 150 mL/hour. Recent data analyses from the PRESERVE trial suggest **no benefit on short-term AKI or long-term outcomes from intravenous sodium bicarbonate.**

ii. Use an alternative imaging study, if possible.

iii. Discontinue nephrotoxic agents and avoid diuretics.

iv. Use low-osmolar or iso-osmolar contrast agents in patients at risk (KDIGO recommendation,

Medications used to prevent contrast-induced nephropathy

(a) **Acetylcysteine** : Antioxidant and vasodilatory mechanism. Accumulation of **glutathione** takes time, so it may **not be as effective in emergencies**. Various dosing recommendations. Widely used. Considered safe. May use oral acetylcysteine in combination with intravenous hydration (KDIGO suggestion, grade 2D). Recent studies suggest no additional benefit over **intravenous hydration**

(b) **Ascorbic acid**: Antioxidant. One large study showed benefit when used **immediately before** . Not confirmed. Give oral ascorbic acid 3 g before procedure and 2 g twice daily for two doses after procedure. May play a role in **emergencies**

(c) **Theophylline** : Do not use (KDIGO suggestion, grade 2C).

(d) **Fenoldopam**: Do not use (KDIGO recommendation, grade 1B).

(e) **Prophylactic hemodialysis** (HD) and hemofiltration: Do not use (KDIGO suggestion,grade 2C).

Nephrogenic systemic fibrosis (a.k.a. nephrogenic fibrosing dermopathy)

i. Rare but associated with **gadolinium-based agents** used in high doses for magnetic resonance imaging/angiogram

ii. Occurs in patients with moderate CKD to end-stage renal disease (ESRD) given intravenous contrast, and systemic acidosis seems to be a risk factor

iii. Although gadolinium does not cause AKI, it is considered inappropriate for use in patients with AKI or CKD

iv. Onset **2–18 days** after exposure

v. Presents as burning; itching; swelling, hardening, or tightening of skin; skin patches; spots on eyes; joint stiffness; and muscle weakness

3**. Cisplatin and carboplatin nephrotoxicity**

Incidence: 6%–13% with appropriate dosing and administration

Pathogenesis: Complex; direct tubular toxins

Presentation

i. SCr peaks **10–12 days** after therapy begins but may continue to rise with subsequent cycles of

therapy.

ii. Renal **magnesium wasting** is common (may be severe with central nervous system symptoms) and may be accompanied by **hypokalemia and hypocalcemia** .

iii. May result in irreversible kidney damage

Risk factors for toxicity : Many courses of cisplatin, advanced patient age, dehydration, concurrent nephrotoxins, kidney irradiation, alcohol abuse

Prevention

i. Avoid concurrent use of nephrotoxins.

ii. Use smallest dose possible and decrease frequency of administration.

iii. Aggressive intravenous hydration: 1–4 L within 24 hours of high-dose cisplatin or carboplatin

4-Amphotericin B nephrotoxicity

Incidence

i. Increases as cumulative dose increases ii. Approaches 80% with cumulative doses of 4 g or more

Pathogenesis

i. Direct proximal and distal tubular toxicity ii. Arterial vasoconstriction

Presentation

i. Manifests after administration of a cumulative **dose 4 g**

ii. Loss of tubular function leads to electrolyte wasting **(especially K+, Na+, and Mg2+)** and distal tubular **acidosis.**

iii. Patients may need substantial **K+ and Mg2+ replacement**.

iv. SCr increases and GFR decreases because of a decrease in kidney blood flow from vasoconstriction caused by amphotericin.

d. Risk factors for toxicity: Existing kidney dysfunction, high average daily doses, diuretic use, volume depletion, concomitant nephrotoxins, **rapid infusion**

Prevention

i. Avoid other nephrotoxins (especially cyclosporine) and limit the total cumulative dose.

ii. Intravenous hydration with 0.9% sodium chloride at least 1 L/day before each dose

Functional (Hemodynamically Mediated) AKI

Caused by a decrease in intraglomerular pressure through the vasoconstriction of afferent arterioles or the vasodilation of efferent arterioles

1- ACEIs and ARBs

Pathogenesis

i. Vasodilation of the efferent arteriole

ii. Leads to a decrease in glomerular hydrostatic pressure and a resultant decrease in GFR

Presentation

i. Exerts a predictable dose-related reduction in GFR

ii. SCr is usually expected to rise by up to **30%.**

(a) Usually occurs within **2–5 days**

(b) Usually stabilizes in 2–3 weeks

(c) Increases greater than 30% may be

Risk factors for toxicity : Patients with bilateral (or unilateral with a solitary kidney) renal artery stenosis, decreased effective kidney blood flow (CHF, cirrhosis), preexisting kidney disease, and volume depletion

Prevention

i. Initiate therapy with low doses and gradually titrate.

ii. Change to long-acting agents once tolerance is established.

iii. Initially, monitor kidney function and SCr **concentrations daily for inpatients and weekly for outpatients.**

iv. Avoid concomitant use of diuretics, if possible, during therapy initiation.

v. Avoid concomitant use of NSAIDs

2-NSAIDs

Incidence: Estimates indicate that 500,000–2.5 million people develop NSAID-induced nephrotoxicity annually in the United States.

Pathogenesis

i. Vasodilatory prostaglandins help maintain glomerular hydrostatic pressure by afferent arteriolar dilation, especially in times of decreased kidney blood flow.

ii. NSAID administration in the setting of decreased kidney perfusion reduces this compensatory mechanism by decreasing the production of prostaglandins, resulting in afferent vasoconstriction and reduced glomerular blood flow.

Presentation

i. Can occur within days of starting therapy

ii. Patients generally have low urinary volume and Na; may also have an increase in BUN, SCr, K+, edema, and weight

Risk factors for toxicity : Preexisting kidney disease,

Prevention

i. Use therapies other than NSAIDs, when appropriate (e.g., acetaminophen for osteoarthritis).
ii. COX-2–specific inhibitors have not been shown to cause less kidney dysfunction, and they increase cardiovascular complications.

Treatment

i. If NSAID-induced AKI is suspected, discontinue drug and give supportive care.
ii. Avoid concomitant use of medications affecting the renin-angiotensin-aldosterone system.
iii. Recovery is usually rapid.

3- Cyclosporine and tacrolimus

Incidence

i. 5-year risk of developing CKD after transplantation of a nonrenal organ is 7%–21%.

ii. Occurrence of kidney failure in the transplant recipient population increases the risk of death by 4-fold.

Pathogenesis

i. **Caused by a dose-related hemodynamic mechanism; calcineurin inhibitors may also cause chronic interstitial nephritis through a separate mechanism that is not dose related**

ii. **Causes vasoconstriction of afferent** arterioles through possible increased activity of various vasoconstrictors (thromboxane A2, endothelin, sympathetic nervous system) or decreased activity of vasodilators (nitric oxide, prostacyclin)

iii. Increased vasoconstriction from angiotensin II may also contribute.

iv. Effects usually resolve with a dose reduction.

Presentation

i. Can occur within **days** of starting therapy
ii. SCr rises and eGFR decreases.
iii. Patients often have **hypertension, hyperkalemia, and hypomagnesemia**.
iv. **A biopsy** is often needed for kidney transplant recipients to distinguish drug-induced injury from acute allograft rejection.
d. Risk factors for toxicity include advanced age, high initial cyclosporine dose, kidney graft rejection, hypotension, infection, and concomitant nephrotoxins.
e. Prevention
i. Monitor serum cyclosporine and tacrolimus concentrations closely.
ii. Use lower doses in combination with other nonnephrotoxic immunosuppressants (e.g., **steroids, mycophenolate mofetil**).
iii. **Calcium channel blockers** may help antagonize the vasoconstrictor effects of cyclosporine by dilating afferent arterioles.

Tubulointerstitial Disease

Involves the renal tubules and the surrounding interstitium. Onset can be acute or chronic.

a. **Acute onset** generally involves interstitial inflammatory cell infiltrates, rapid loss of kidney function, and systemic symptoms (i.e., fever and rash).

Acute allergic interstitial nephritis
a.caused by an allergic hypersensitivity reaction that affects the interstitium of the kidney
b. Many medications and medication classes can cause this type of kidney failure, including β-lactams and NSAIDs (although the presentations are different).
i. **Penicillins**: Classic presentation of acute allergic interstitial nephritis. Signs and symptoms occur about 1–2 weeks after therapy initiation and include fever, maculopapular rash, eosinophilia, pyuria, hematuria, and proteinuria. **Eosinophiluria** may also be present.
ii**. NSAIDs**: Onset much more delayed; typically begins about 6 months into therapy. Usually occurs in older adults receiving chronic NSAID therapy. Patients do not usually have systemic symptoms.
c. Kidney biopsy may be needed to confirm the diagnosis.
d. Treatment includes discontinuing the offending agent and possibly initiating **steroid therapy**.

Chronic interstitial nephritis
a. Often progressive and irreversible
b**. Lithium**
i. Toxicity results from a duration-related decrease in response **to antidiuretic hormone** after long-term use (more than 10 years of therapy).
ii. Clinical presentation
(a) Often asymptomatic, with slow progression over years
(b) May be recognized by slow increases in blood pressure or BUN and SCr
iii. Risks include long duration of use, elevated serum concentrations, and repeated episodes of AKI from lithium toxicity.
iv. Prevention is accomplished by maintaining the lowest serum lithium concentrations possible, avoiding dehydration, and monitoring kidney function closely.
c. **Cyclosporine and tacrolimus**: Presents later in therapy (about 6–12 months) than hemodynamically

Renal tubular obstruction

a. Caused by intratubular precipitation of tissue degradation products or precipitation of drugs or

their metabolites

i. Tissue degradation products

(a) Uric acid intratubular precipitation after tumor lysis after chemotherapy

(b) **Drug-induced rhabdomyolysis** leading to intratubular precipitation of **myoglobin**

(c) Results in rapid decline in kidney function, with resultant oliguric or anuric kidney failure

ii. Drug precipitation: **Sulfonamides, methotrexate, acyclovir, ascorbic acid** ; **needlelike crystals**

observed in leukocytes found on urinalysis can prompt diagnosis

b. Prevention includes pretreatment hydration, maintenance of high urinary volume, and alkalinization of the urine.

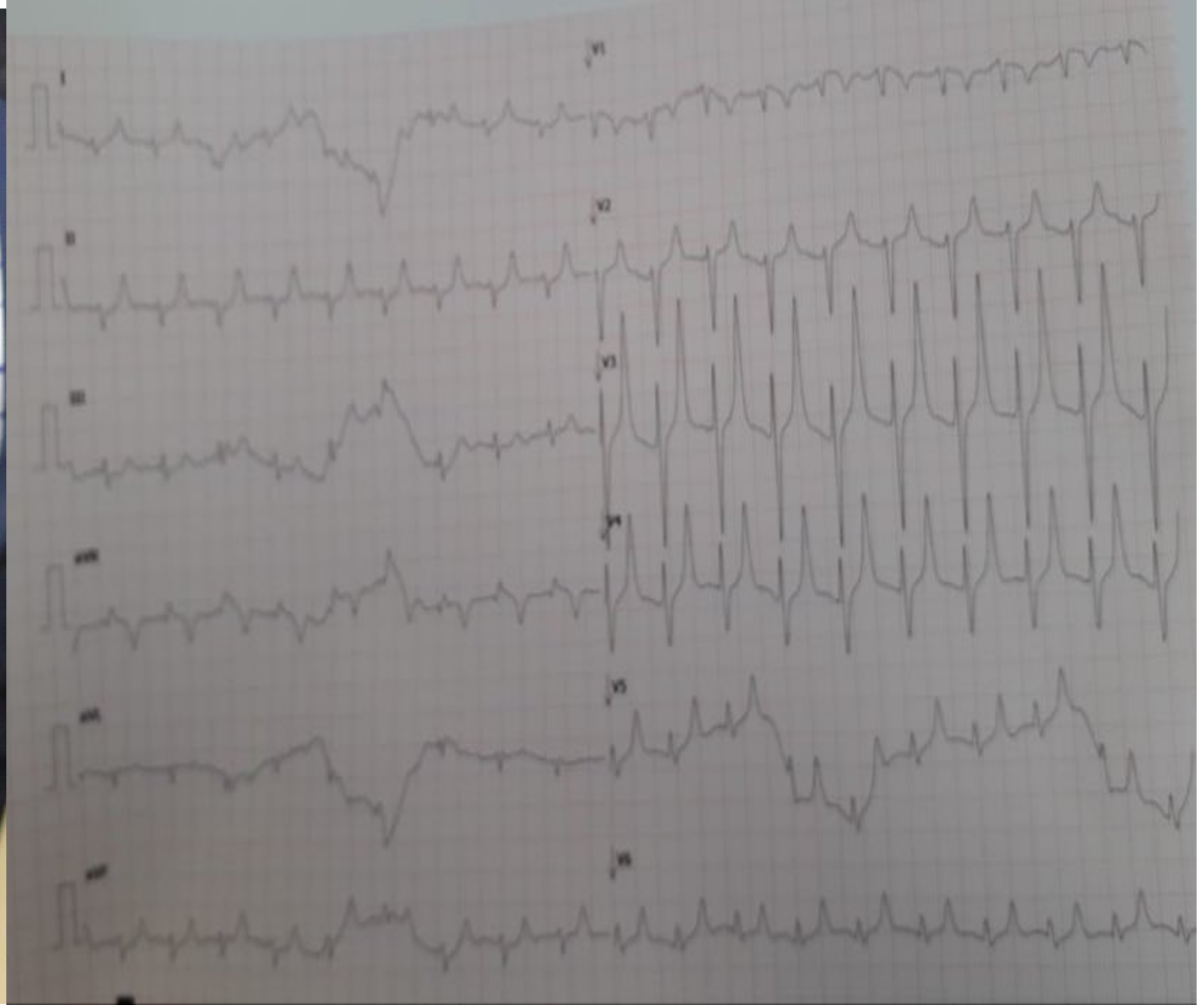
3. Extrarenal urinary tract obstruction

a. **Benign prostatic hypertrophy** can be worsened by anticholinergics.

b. Bladder outlet or ureteral obstruction from fibrosis after cyclophosphamide for hemorrhagic cystitis

4. Nephrolithiasis

a. Usually does not affect GFR, so does not have the classic signs and symptoms of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