Back to basics: de nier

Prof. Dr. Apr. Guido R.Y. De Meyer
Fysiofarmacologie

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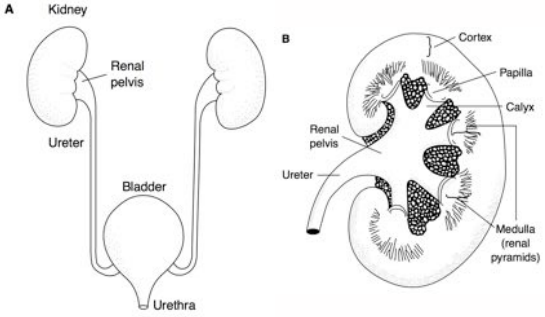
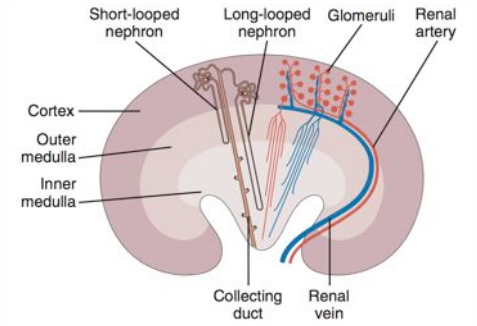
The urinary system



Vander's Renal Physiology

Coronal section through a unipapillary kidney



Comprehensive Clinical Nephrology, Fifth Edition

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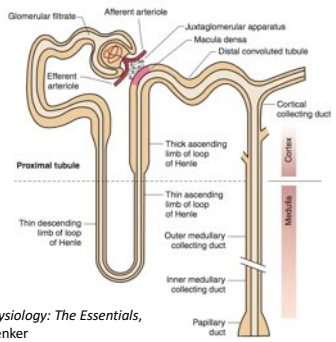
Anatomy of the nephron



Renal Pathophysiology: The Essentials, Rennke and Denker

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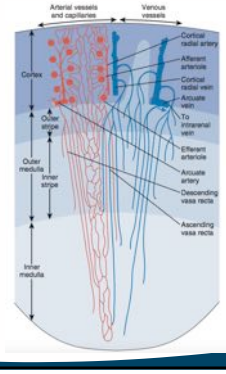
Microvasculature of the kidney



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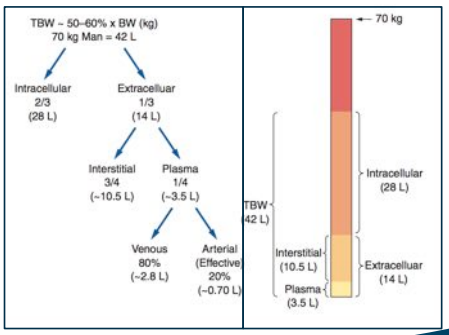
Approximate relationships of body water compartments to total body weight



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Total Body Water for 70 kg Man (60% or 42 Liters)

Electrolyte (mmol/l)	Intracellular Water (2/3 or 28 l)	Extracellular Water (1/3 or 14 l) Interstitial (3/4 or 10.5 l)	Extracellular Water (1/3 or 14 l) Blood (1/4 or 3.5 l)
Na	25	140	
K	150	4.5	
Mg	0.5	1.0	
Ca	0.01	2.4	
Cl	2	100	
HCO_3	6	25	
Phos	1.4	1.2	

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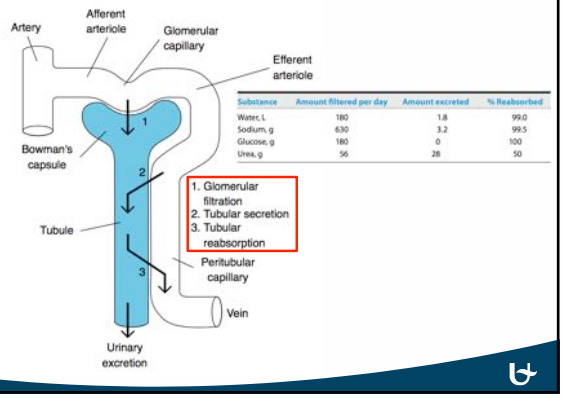
The 3 basic renal processes



Substance	Amount filtered per day	Amount excreted	% Reabsorbed
Water, L	180	1.8	99.0
Sodium, g	630	3.2	99.5
Glucose, g	180	0	100
Urea, g	56	28	50

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Reabsorption and secretion by major tubular segments

	Proximal tubule R	Proximal tubule S	Henle's loop R	Henle's loop S	Distal convoluted tubule R	Distal convoluted tubule S	Collecting-duct system R	Collecting-duct system S
Organic nutrients	X							
Urea	X		(X)				X	
Proteins, peptides	X							
Phosphate	X							
Sulfate	X							
Organic anions	X	(X can also be reabsorbed and/or secreted passively along tubule)						
Organic cations	X	(X can also be reabsorbed and/or secreted passively along tubule)						
Urate	X	X						
Sodium	X		X		X		X	
Chloride	X		X		X		X	
Water	X		X				X	
Potassium	X		X	(X)		X	X	X
Hydrogen ions		X		X		X		X
Bicarbonate	X		X		X		X	X
Ammonium		X	(X)					(X)
Calcium	X		X		X		X	

R, reabsorption; S, secretion.

Reabsorption

Secretion

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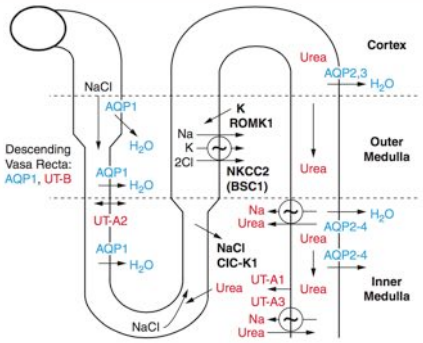
The renal concentrating mechanism



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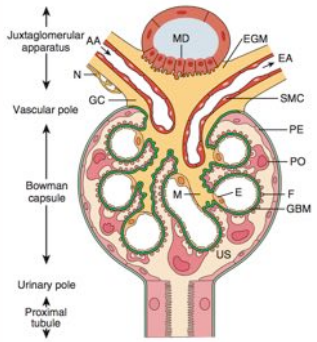
Glomerulus and juxtaglomerular apparatus



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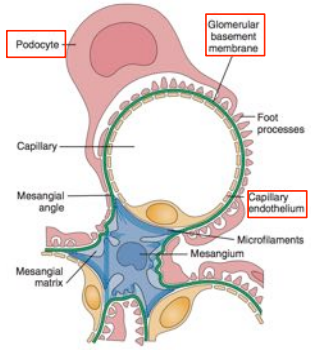
Peripheral portion of a glomerular lobule



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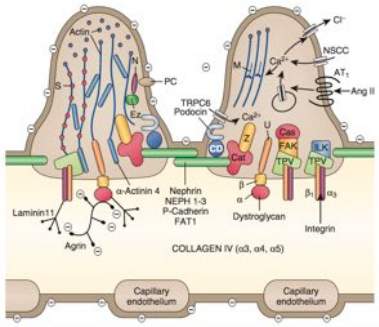
Glomerular filtration barrier



Podocyte

Glomerular Basement Membrane

Endothelium

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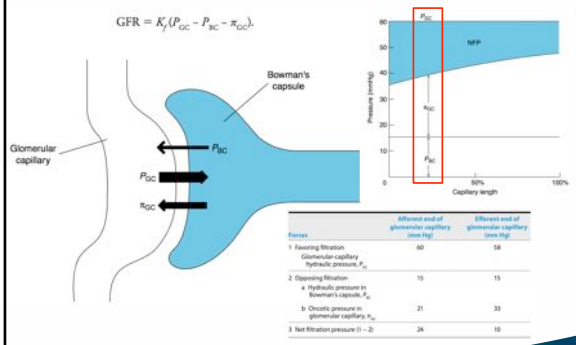
Net filtration pressure in the glomerulus



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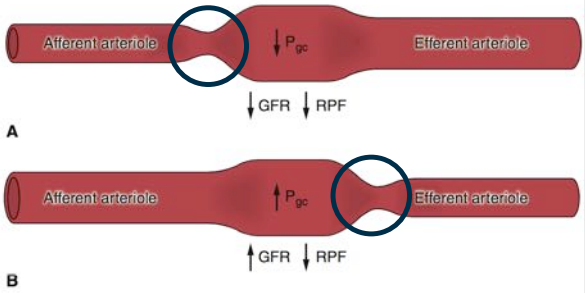
Relationship between glomerular arteriolar resistance, glomerular filtration rate (GFR), and renal plasma flow (RPF)



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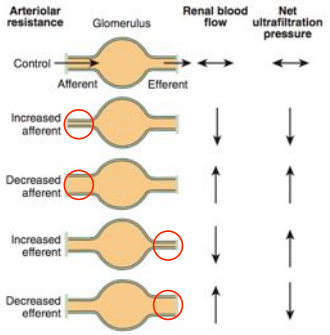
Glomerular hemodynamics



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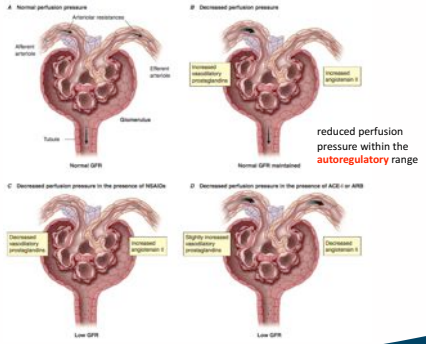
Intrarenal mechanisms for autoregulation of the GFR under decreased perfusion pressure and reduction of the GFR by drugs



reduced perfusion pressure within the autoregulatory range

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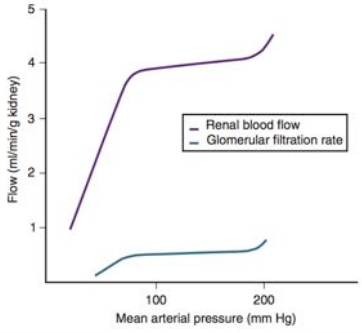
Renal autoregulation of renal blood flow and glomerular filtration rate



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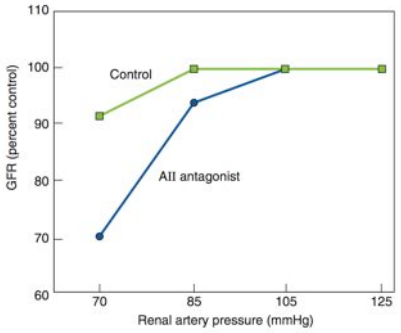
Effect of reducing renal artery pressure on glomerular filtration rate (GFR)



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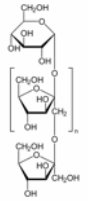
Exogenous Filtration Markers for Estimation of Glomerular Filtration Rate

Marker	Method of Administration	Comments
Inulin	Continuous IV infusion	Gold standard
Iothalamate	Bolus IV injection or subcutaneous injection	Can be administered as radioactive compound with iodine 125 (^{125}I) as the tracer or in nonradioactive form, with assay using HPLC methods. In radioactive form, potential problem of thyroid uptake of ^{125}I. Iothalamate is secreted, leading to overestimation of GFR
^{99m}Tc-DTPA	Bolus IV injection	Dissociation of ^{99m}Tc leads to plasma protein binding and underestimation of GFR
^{51}Cr-EDTA	Bolus IV injection	10% lower clearance than inulin
Iohexol	Bolus IV injection	Low incidence of adverse effects; comparable to inulin; expensive and difficult to perform assay



Tc-99m DTPA (diethylene-triamine-pentaacetate)

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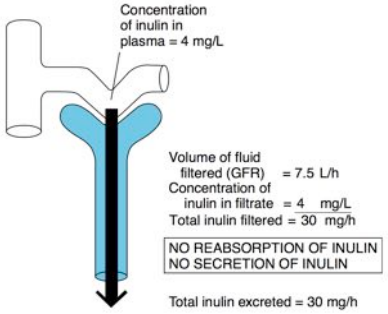
The clearance of inulin is equal to the glomerular filtration rate



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Clinical Estimation of Glomerular Filtration Rate

Inulin (or a radioisotope such as iothalamate)

1. Able to achieve a stable plasma concentration
2. Freely filtered at the glomerulus
3. Not reabsorbed, secreted, synthesized, or metabolized by the kidney

Filtered inulin = ***excreted inulin***

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Comparison of Creatinine, Urea, and Cystatin C as Filtration Markers

Variable	Creatinine	Urea	Cystatin C
Molecular Properties			
Weight (d)	113	60	13,000
Structure	Amino acid derivative	Organic molecular product of protein metabolism	Nonglycosylated basic protein
Physiologic Determinants of Serum Level			
Generation	Varies, according to muscle mass and dietary protein; lower in elderly persons, women, and whites	Varies, according to dietary protein intake and catabolism	Thought to be mostly constant by all nucleated cells; increases in hyperthyroid state and with steroid use; lower in elderly persons and women
Handling by kidney	Filtered, secreted, and excreted in urine	Filtered, reabsorbed, and excreted in urine	Filtered, reabsorbed, and catabolized
Extrarenal elimination	Yes; increases at reduced GFR	Yes; increases at reduced GFR	Preliminary evidence of increases at reduced GFR
Use in Estimating Equations for GFR			
Demographic and clinical variables as surrogates for physiologic determinants	Age, gender, and race; related to muscle mass	Not applicable	Age, gender
Accuracy	Accurate for GFR <60 ml/min/1.73 m^2	Not applicable	Unknown
Assay			
Method	Colorimetric or enzymatic	Direct measurement, enzymatic colorimetric and electrochemical	PENIA, PETIA, or ELISA
Assay precision	Very good except at low range	Precise throughout range	Precise throughout range
Clinical laboratory practice	Multiple assays; widely used nonstandard calibration	Multiple assays; enzymatic and colorimetric more common	Not on most autoanalyzers; not standardized
Standardized recommendation materials (SRMs)	SRM 967	SRM 912a	ERM-DA471/IFCC
Reference assay	IDMS	IDMS	PENIA, PETIA, or ELISA

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Normal plasma creatinine concentration (adults)

Creatinine is a breakdown product of creatine phosphate in muscle

- **0.8 to 1.3 mg/dL** in men
- **0.6 to 1.0 mg/dL** in women

  (smaller muscle mass and therefore a lower rate of creatinine production)

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RECOMMENDED EQUATIONS FOR ESTIMATION OF GLOMERULAR FILTRATION RATE (GFR) USING SERUM CREATININE CONCENTRATION (P_{Cr}), AGE, SEX, RACE, AND BODY WEIGHT

1. Equation from the Modification of Diet in Renal Disease study[a]

Estimated GFR (mL/min per 1.73 m^2) =
$$1.86 \times (P_{Cr})^{-1.154} \times (age)^{-0.203}$$
Multiply by 0.742 for women
Multiply by 1.21 for African Americans

2. Cockcroft-Gault equation

Estimated creatinine clearance (mL/min) =
$$\frac{(140 - age) \times body\ weight\ (kg)}{72 \times P_{Cr}\ (mg/dL)}$$
Multiply by 0.85 for women

[a]Equation is available in hand-held calculators and in tabular form.
Source: Adapted from AS Levey et al: Am J Kidney Dis 39: S1, 2002, with permission.
https://www.kidney.org/professionals/KDOQI/gfr_calculator

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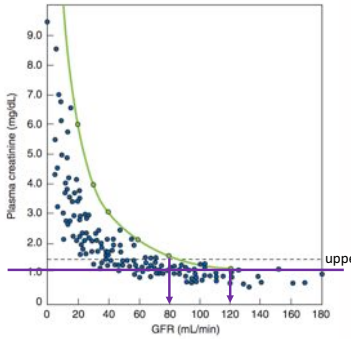
Relationship between true GFR and plasma creatinine concentration in patients with glomerular disease



1.4 mg/dL
upper limit of "normal"

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Factors Affecting Serum Creatinine Concentration

Factors	Effect on Creatinine	Mechanism/Comment
Age	Decrease	Reduced creatinine generation caused by age-related decline in muscle mass
Female gender	Decrease	Reduced creatinine generation caused by reduced muscle mass
Race		
African American	Increase	Higher creatinine generation caused by higher average muscle mass in African Americans; not known how muscle mass in other races compares with that of African Americans or Caucasians
Diet		
Vegetarian	Decrease	Decrease in creatinine generation
Ingestion of cooked meats and creatinine supplements	Increase	Transient increase in creatinine generation, although this may be blunted by transient increase in GFR
Body Habitus		
Muscular	Increase	Increased muscle generation caused by increased muscle mass and/or increased protein intake
Malnutrition, muscle wasting, amputation	Decrease	Reduced creatinine generation caused by reduced muscle mass and/or reduced protein intake
Obesity	No change	Excess mass is fat, not muscle mass, and does not contribute to increased creatinine generation.
Medications		
Trimethoprim, cimetidine, fibric acid derivatives other than gemfibrozil	Increase	Reduced tubular secretion of creatinine
Keto acids, some cephalosporins	Increase	Interference with alkaline picrate assay for creatinine

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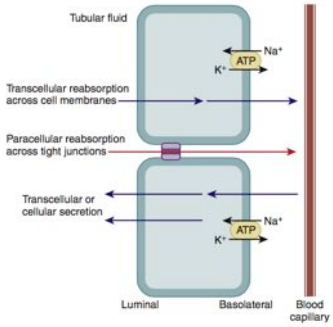
General scheme for epithelial transport



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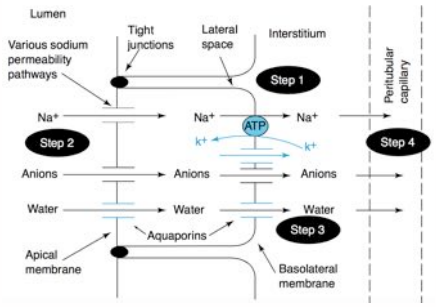
Transporting solute and water from the tubular lumen to the peritubular capillary



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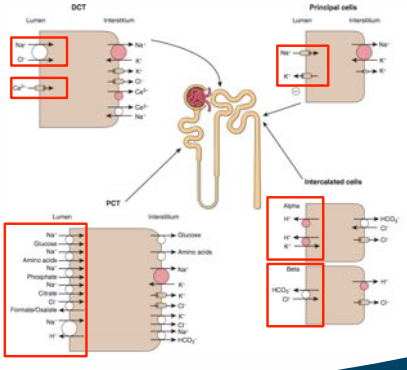
Major transport mechanisms along the nephron



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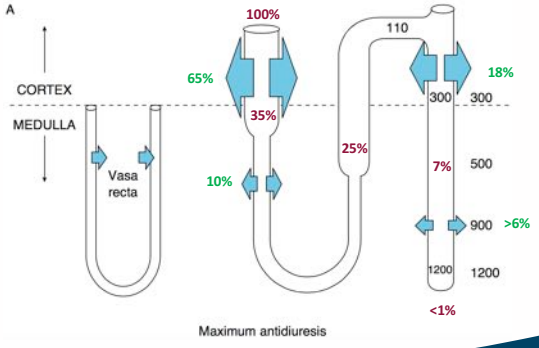
Renal water handling in maximum antidiuresis



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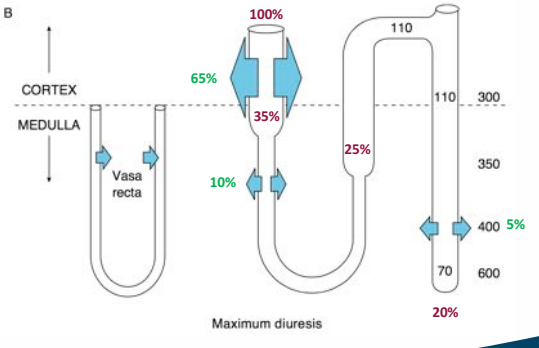
Renal water handling in maximum diuresis



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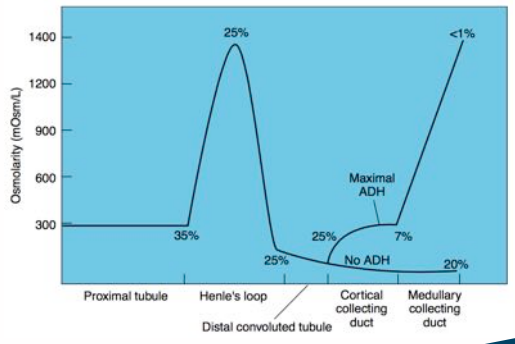
Osmolarity of the tubular fluid and the percentage of filtered water remaining at different sites along the tubule



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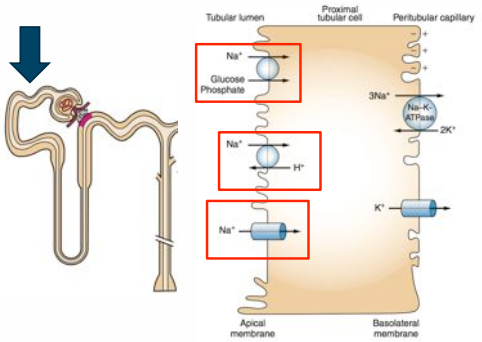
Transtubular sodium reabsorption and ion transport in the proximal tubule



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Some **organic anions** actively **secreted** by the proximal tubule

Endogenous substances	Drugs
Bile salts	Acetazolamide
Fatty acids	Chlorothiazide
Hippurates	Ethacrynate
Hydroxybenzoates	Furosemide
Oxalate	Penicillin
Prostaglandins	Probenecid
Urate	Saccharin
	Salicylates
	Sulfonamides

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Some **organic cations** actively **secreted** by the proximal tubule

Endogenous substances	Drugs
Acetylcholine	Atropine
Choline	Isoproterenol
Creatinine	Cimetidine
Dopamine	Meperidine
Epinephrine	Morphine
Guanidine	Procaine
Histamine	Quinine
Serotonin	Tetraethyl ammonium
Norepinephrine	
Thiamine	

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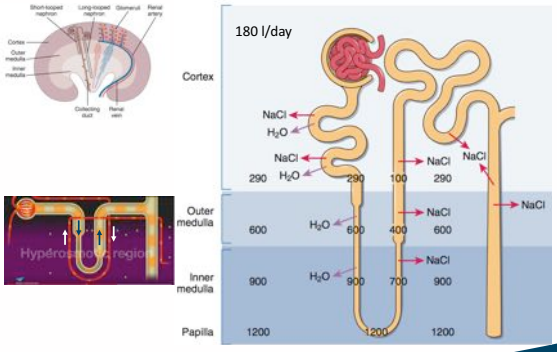
Countercurrent multiplication by loop of Henle



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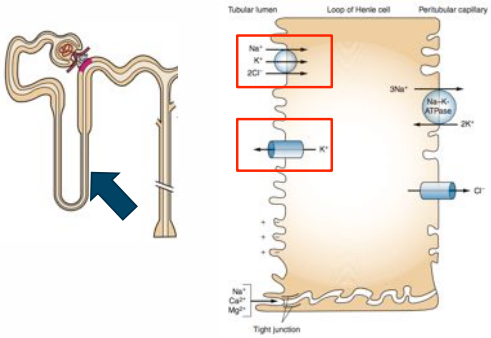
Ion transport in the thick ascending limb of the loop of Henle



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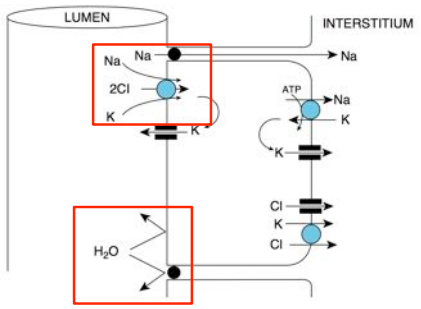
Major transport pathways for sodium and chloride in thick ascending limb cells within the loop of Henle



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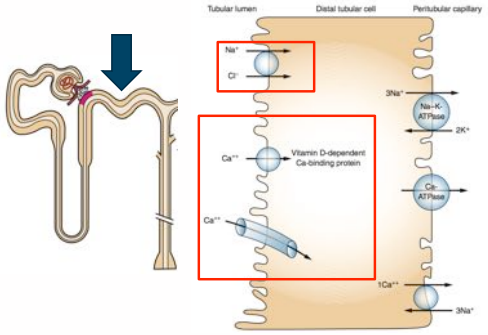
Transport mechanisms involved in sodium chloride and calcium reabsorption in the distal tubule



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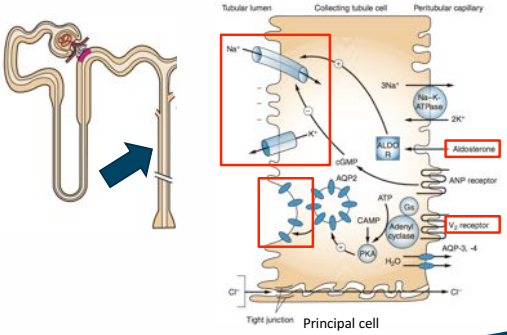
Transport pathways and hormonal factors—aldosterone, ANP, ADH—involved in sodium, potassium, and water handling in the collecting ducts



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Major Sensors and Effectors of the Osmoregulatory and Volume Regulatory Pathways

	Osmoregulation	Volume Regulation
What is sensed	Plasma osmolality	Effective tissue perfusion
Sensors	Hypothalamic osmoreceptors	Macula densa Afferent arteriole Atria Carotid sinus
Effectors	Antidiuretic hormone	Renin–angiotensin–aldosterone Atrial natriuretic peptide (ANP) ANP-related peptides Norepinephrine Antidiuretic hormone
What is affected	Urine osmolality Thirst/Water Intake	Urinary sodium Thirst

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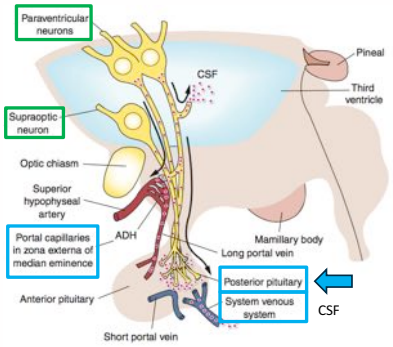
Hypothalamus and pituitary gland showing pathways for the secretion of ADH



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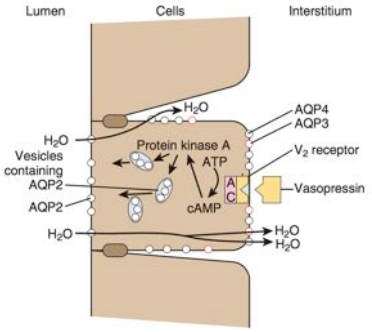
Mechanism of action of vasopressin (ADH) on the collecting duct



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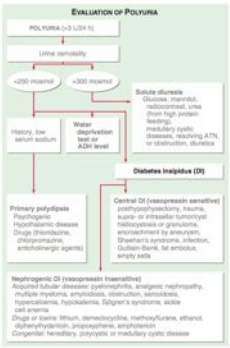
Approach to the patient with polyuria



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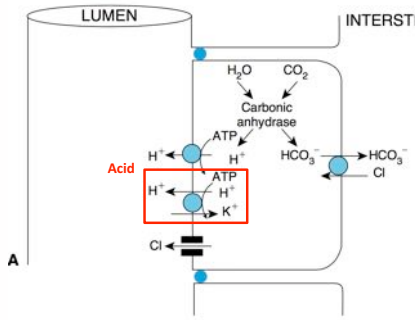
Predominant **collecting tubule** mechanisms in **Type A intercalated cells** for the secretion of hydrogen ions



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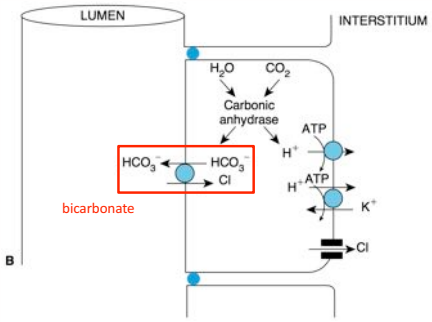
Type B intercalated cells



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What is affected	Urine osmolality Thirst/Water Intake	Urinary sodium Thirst

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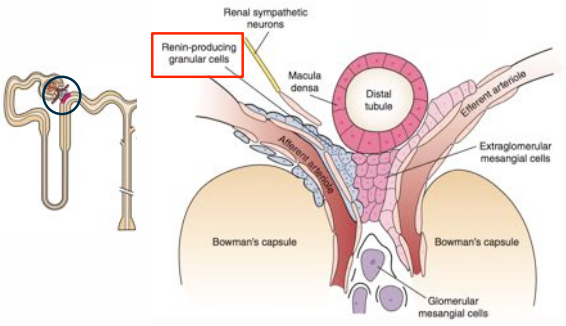
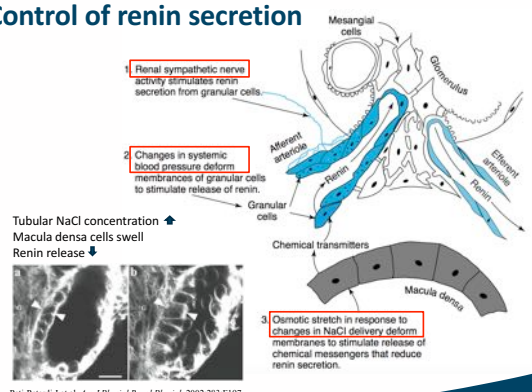
Juxtaglomerular apparatus and macula densa in tubuloglomerular feedback



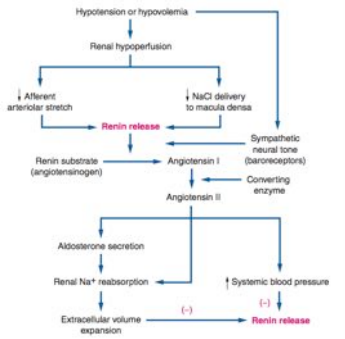
Control of renin secretion



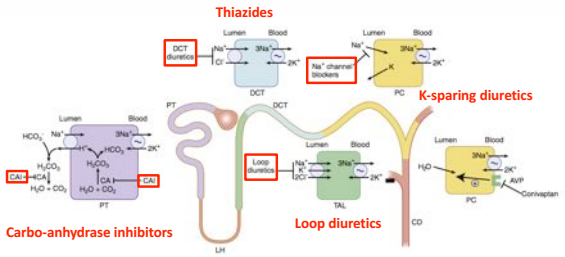
Tubular NaCl concentration ↑
Macula densa cells swell
Renin release ↓

Peti-Peterdi J et al, *Am J Physiol Renal Physiol.* 2002;283:F197

Pathway of angiotensin production



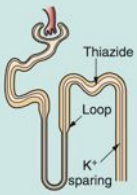
Predominant sites and mechanisms of action of clinically important diuretic drugs



Classes of diurectics

Class	Mechanism	Major site affected
Carbonic anhydrase	Inhibit secretion of hydrogen ions, which causes less reabsorption of bicarbonate and sodium	Proximal tubule
Loop diuretics	Inhibit Na, K, 2Cl cotransporter in luminal membrane	Thick ascending limb of Henle's loop
Thiazides	Inhibit Na,Cl cotransporter in luminal membrane	Distal convoluted tubule
Potassium-sparing diuretics*	Inhibit action of aldosterone	Cortical collecting duct
	Block sodium channels in Collecting-duct system luminal membrane	

Characteristics of Major Classes of Diuretics



Type	Site of Action and Transporter Inhibited	Percent Filtered Na Excreted
Loop diuretics	Thick ascending limb of loop of Henle; compete for chloride site on luminal Na^+–K^+–$2Cl^-$ cotransporter	35–40%
Thiazide-type diuretics	Distal tubule; compete for chloride site on luminal Na–Cl cotransporter	5–8%
Potassium sparing diuretics	Collecting tubules; close luminal sodium channels	2–3%

Normal contributions of tubular segments to renal **hydrogen ion** balance

Proximal tubule
- Reabsorbs most filtered bicarbonate (normally about 80%)*
- Produces and secretes ammonium

Thick ascending limb of Henle's loop
- Reabsorbs second largest fraction of filtered bicarbonate (normally about 10–15%)*

Distal convoluted tubule and collecting-duct system
- Reabsorbs virtually all remaining filtered bicarbonate as well as any secreted bicarbonate (Type A intercalated cells)*
- Produces titratable acid (Type A intercalated cells)*
- Secretes bicarbonate (Type B intercalated cells)

* Processes achieved by hydrogen ion secretion.

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Processes that acidify or alkalinize the blood

Nonrenal mechanisms of acidifying the blood
- Consumption and metabolism of protein (meat) containing acidic or sulfur-containing amino acids
- Consumption of acidic drugs
- Metabolism of substrate without complete oxidation (fat to ketones and carbohydrate to lactic acid)
- GI tract secretion of bicarbonate (puts acid in blood)

Nonrenal mechanisms of alkalinizing the blood
- Consumption and metabolism of fruit and vegetables containing basic amino acids or the salts of weak acids
- Consumption of antacids
- Infusion of lactated Ringer's solution
- GI tract secretion of acid (puts bicarbonate in the blood)

Renal mechanisms of acidifying the blood
- Allow some filtered bicarbonate to pass into the urine
- Secrete bicarbonate (Type B intercalated cells)

Renal means of alkalinizing the blood
- Secrete protons that form urine titratable acidity (Type A intercalated cells)
- Excrete NH_4^+ synthesized from glutamine

GI, gastrointestinal.

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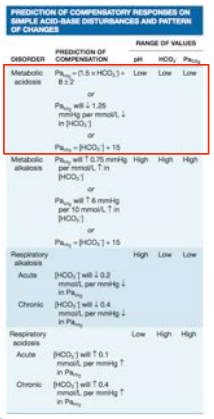
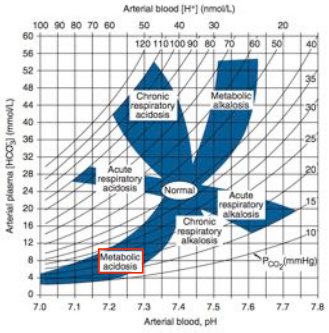

PREDICTION OF COMPENSATORY RESPONSES ON SIMPLE ACID-BASE DISTURBANCES AND PATTERN OF CHANGES

DISORDER	PREDICTION OF COMPENSATION	RANGE OF VALUES pH	HCO_3	Pa_{CO_2}
Metabolic acidosis	$Pa_{CO_2} = (1.5 \times HCO_3) + 8 \pm 2$ or Pa_{CO_2} will ↓ 1.25 mmHg per mmol/L ↓ in $[HCO_3]$ or $Pa_{CO_2} = [HCO_3] + 15$	Low	Low	Low
Metabolic alkalosis	Pa_{CO_2} will ↑ 0.75 mmHg per mmol/L ↑ in $[HCO_3]$ or Pa_{CO_2} will ↑ 6 mmHg per 10 mmol/L ↑ in $[HCO_3]$ or $Pa_{CO_2} = [HCO_3] + 15$	High	High	High
Respiratory alkalosis		High	Low	Low
Acute	$[HCO_3]$ will ↓ 0.2 mmol/L per mmHg ↓ in Pa_{CO_2}			
Chronic	$[HCO_3]$ will ↓ 0.4 mmol/L per mmHg ↓ in Pa_{CO_2}			
Respiratory acidosis		Low	High	High
Acute	$[HCO_3]$ will ↑ 0.1 mmol/L per mmHg ↑ in Pa_{CO_2}			
Chronic	$[HCO_3]$ will ↑ 0.4 mmol/L per mmHg ↑ in Pa_{CO_2}			

Acid-base nomogram



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Primary Disorder	pH	Initial Chemical Change	Compensatory Response	Expected Compensation
Metabolic acidosis	Low	↓ $[HCO_3^-]$	↓ Pco_2	$Pco_2 = (1.5 \times [HCO_3^-]) + 8 \pm 2$ $Pco_2 = [HCO_3^-] + 15$ Pco_2 = decimal digits of pH
Metabolic alkalosis*	High	↑ $[HCO_3^-]$	↑ Pco_2	Pco_2 variably increased $Pco_2 = (0.9 \times [HCO_3^-]) + 9$ $Pco_2 = (0.7 \times [HCO_3^-]) + 20$
Respiratory acidosis				
Acute	Low	↑ Pco_2	↑ $[HCO_3^-]$	$[HCO_3^-]$ increases 1 mEq/L for every 10 mm Hg increase in Pco_2
Chronic	Low	↑ Pco_2	further ↑ $[HCO_3^-]$	$[HCO_3^-]$ increases 3–4 mEq/L for every 10 mm Hg increase in Pco_2
Respiratory alkalosis				
Acute	High	↓ Pco_2	↓ $[HCO_3^-]$	$[HCO_3^-]$ decreases 2 mEq/L for every 10 mm Hg decrease in Pco_2
Chronic	High	↓ Pco_2	further ↓ $[HCO_3^-]$	$[HCO_3^-]$ decreases 5 mEq/L for every 10 mm Hg decrease in Pco_2

$[HCO_3^-]$, Serum bicarbonate concentration; Pco_2, arterial partial pressure of carbon dioxide.
*Compensation formulas for metabolic alkalosis have wide confidence limits because the Pco_2 of individuals with this disorder vary greatly at any given $[HCO_3^-]$.

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Metabolic acidosis

Results from net H^+ accumulation

Causes:
- **loss of bicarbonate through gastrointestinal or renal losses (diarrhea and proximal (type 2) RTA) that results in hyperchloremic metabolic acidosis**
- **acid generation associated with an unmeasured anion (ketoacids, lactic acids, and ingestions) that results in increased anion gap acidosis**
- **decreased renal H^+ excretion (distal (type 1) RTA and renal failure)**

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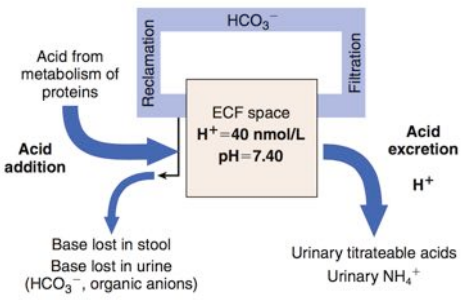
Maintenance of acid-base homeostasis



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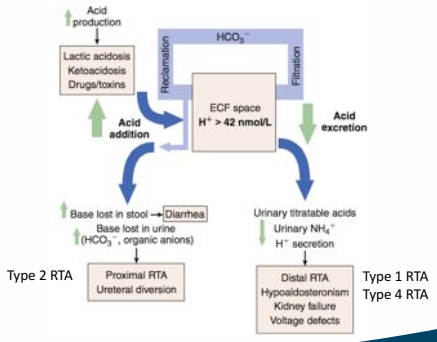
Origin of metabolic acidosis



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Major Causes of Metabolic Acidosis

Increased acid production

- A. Lactic acidosis
- B. Ketoacidosis, most often due to uncontrolled diabetes mellitus
- C. Ingestions
  1. Aspirin
  2. Ethylene glycol, a component of antifreeze and solvents
  3. Methanol (wood alcohol), a component of shellac and de-icing solutions
- C. Loss of bicarbonate
  1. Gastrointestinal—diarrhea, pancreatic, biliary or intestinal fistulas, ureterosigmoidostomy
  2. Renal—type 2 (proximal) renal tubular acidosis

Decreased acid excretion

- A. Renal failure—decreased NH_4^+ excretion
- B. Type 1 (distal) renal tubular acidosis
- C. Type 4 renal tubular acidosis (hypoaldosteronism) (discussed in Chapter 7)

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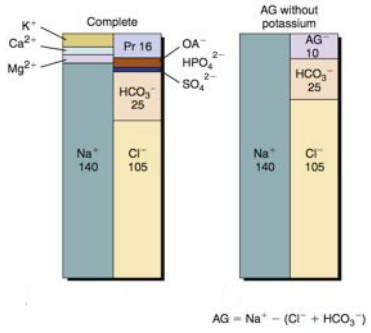
The ionic anatomy of plasma



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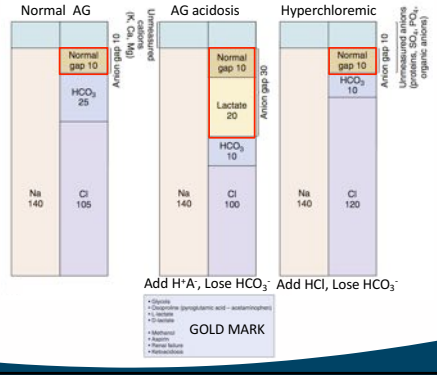
Normal anion gap (AG), AG acidosis, and hyperchloremic acidosis



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Metabolic Acidosis
Normal Anion Gap or Hyperchloremic

Normal anion gap or hyperchloremic metabolic acidosis

- A. Renal bicarbonate loss—type 2 (proximal RTA)—hereditary, drug associated (ifosfamide, tenofivir) or malignancy associated (multiple myeloma)
- B. Gastrointestinal loss of bicarbonate—diarrhea
- C. Renal dysfunction
  1. Some cases of chronic renal failure
  2. Type 1 (distal RTA) drugs, amphotericin, lithium, Sjogren syndrome, hypercalciuria
  3. Type 4 RTA (hypoaldosteronism
- D. Ingestions
  1. Ammonium chloride
  2. Toluene; hippurate
  3. Some hyperalimentation fluids

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Metabolic Acidosis
Increased Anion Gap

Increased anion gap[a]

- A. Advanced renal failure—phosphate, sulfate, urate, hippurate
- B. Lactic acidosis—lactate both L- and D-lactate
- C. Ketoacidosis—β-hydroxybutyrate
- D. Ingestions
  1. Aspirin—ketones, lactate, salicylate
  2. Ethylene and propylene glycol—glycolate, oxalate (found in anti-freeze and in solvent for some intravenous medications, respectively)
  3. Methanol—formate
  4. Paraldehyde—organic anions
  5. Pyroglytamic (5'-oxoproline) acidemia associated with acetaminophen use
- E. Massive rhabdomyolysis (severe muscle injury)

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Causes of Lactic Acidosis

Type A (Tissue Underperfusion or Hypoxia)
Cardiogenic shock
Septic shock
Hemorrhagic shock
Acute hypoxia
Carbon monoxide poisoning
Anemia

Type B (Absence of Hypotension and Hypoxia)
Hereditary enzyme deficiency (glucose 6-phosphatase)
Drugs or toxins
- Phenformin, metformin
- Cyanide
- Salicylate, ethylene glycol, methanol
- Propylene glycol[25]
- Linezolid[22]
- Propofol[24]
- Nucleoside reverse transcriptase inhibitors: stavudine, didanosine[23]
- Clenbuterol[26]
- Isoniazid

Systemic disease
- Liver failure
- Malignancy

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Renal Tubular Acidosis

	Type 1—Distal	Type 2—Proximal	Type 4—
Basic abnormality	Impaired distal acidification	Diminished proximal bicarbonate reabsorption	Aldosterone resistance or deficiency
Urine pH	>5.3	Variable; >5.3 if above reabsorption threshold	<5.3
Plasma bicarbonate	Variable; can be <10 mEq/L	Usually 14–20 mEq/L	Usually >15 mEq/L
Plasma potassium	Usually reduced or normal, but can be elevated	Normal or reduced	Elevated
Complications	Nephrocalcinosis, renal stones	Rickets or osteomalacia	None
	Decreased renal H^+ excretion	Increased H^+ production Renal bicarbonate loss	

Causes of Type 1 Renal Tubular Acidosis

Distal

Primary
Idiopathic
Familial

Secondary
Autoimmune Disorders
Hypergammaglobulinemia
Sjögren syndrome
Primary biliary cirrhosis
Systemic lupus erythematosus

Genetic Diseases
Autosomal dominant RTA: anion exchanger 1 defect
Autosomal recessive RTA: H^+-ATPase A4 subunit
Autosomal recessive with progressive nerve deafness: H^+-ATPase B1 subunit

Drugs and Toxins
Amphotericin B
Toluene

Disorders with Nephrocalcinosis
Hyperparathyroidism
Vitamin D intoxication
Idiopathic hypercalciuria

Tubulointerstitial Disease
Obstructive uropathy
Renal transplantation

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Causes of Proximal Renal Tubular Acidosis

Type 2

Isolated Defects in HCO_3 Reabsorption
- Carbonic anhydrase inhibitors
- Acetazolamide
- Topiramate
- Sulfamylon
- Carbonic anhydrase deficiency

Generalized Defects in Proximal Tubular Transport
- Cystinosis
- Wilson disease
- Lowe syndrome
- Galactosemia
- Multiple myeloma
- Light chain disease
- Amyloidosis
- Vitamin D deficiency
- Ifosfamide
- Cidofovir
- Lead
- Aminoglycosides

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Causes of Type 4 Renal Tubular Acidosis

Mineralocorticoid Deficiency
Low Renin, Low Aldosterone
Diabetes mellitus
Drugs
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Cyclosporine, tacrolimus
- β-Blockers

High Renin, Low Aldosterone
Adrenal destruction
Congenital enzyme defects
Drugs
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin II receptor blockers (ARBs)
- Heparin
- Ketoconazole

Abnormal Cortical Collecting Duct
Absent or defective mineralocorticoid receptor
Drugs
- Spironolactone, eplerenone
- Triamterene
- Amiloride
- Trimethoprim
- Pentamidine

Chronic tubulointerstitial disease

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Alkali Treatment Options

Therapy	Route	Usual Dose per Unit	Comments
Sodium bicarbonate tablet	PO	650 mg = 8 mmol	May cause gastric gas
Sodium bicarbonate	IV	50 mmol in 50 ml	Hypertonic, may cause hypernatremia
DSW with $NaHCO_3$	IV	150 mmol/l	Useful for simultaneous intravascular volume expansion and alkali administration
Sodium citrate/ citric acid (liquid)	PO	1 mmol of Na^+ and citrate per milliliter	1 mmol citrate equivalent to 1 mmol HCO_3^- Avoid concomitant aluminum-containing medications such as antacids and sucralfate.
Potassium citrate (tablet)	PO	5 and 10 mmol per tablet	Useful for simultaneous K^+ and alkali therapy
Citric acid/ potassium citrate/sodium citrate (liquid)	PO	1 mmol of Na^+ and K^+ and 2 mmol of citrate per milliliter	Avoid concomitant aluminum-containing medications.
Potassium citrate (liquid)	PO	2 mmol of K^+ and 2 mmol of citrate per milliliter	Avoid concomitant aluminum-containing medications.

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Major Causes of Metabolic Alkalosis

I. **Hydrogen loss**
   - A. **Gastrointestinal loss**
     1. Removal of gastric secretions due to vomiting or nasogastric suction
     2. Antacids in advanced renal failure
   - B. **Urinary loss**
     1. Loop or thiazide-type diuretics
     2. Primary mineralocorticoid excess (hyperaldosteronism)
     3. Posthypercapnic alkalosis
     4. Hypercalcemia and milk alkali syndrome
   - C. **Movement of H^+ into the cells**
     1. Hypokalemia

II. **Administration of bicarbonate or an organic ion that can be metabolized to bicarbonate, such as citrate in blood transfusions**

III. **Contraction alkalosis**
   - A. Loop or thiazide-type diuretics in edematous patients
   - B. Vomiting or nasogastric suction in achlorhydria
   - C. Sweat losses in cystic fibrosis

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Pathophysiologic Classification of Causes of Metabolic Alkalosis

Primary stimulation of collecting duct ion transport (Na^+ uptake, H^+ and K^+ secretion)
- Mineralocorticoid induced
- Activating genetic mutations of ENaC or its signal pathway

Secondary stimulation of collecting duct ion transport (Na^+ uptake, H^+ and K^+ secretion)
- Extrarenal Cl^- losses and secondary K^+ losses
- Renal Cl^- losses and secondary K^+ losses
  - Pharmacologic (diuretics)
  - Inactivating gene mutations of Cl^--linked Na^+ cotransporters

Alkali administration in settings in which HCO_3^- excretion is impaired (e.g., kidney failure)

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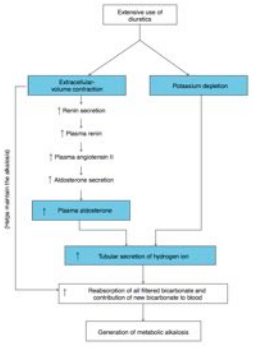
Pathway by which overuse of diuretics leads to a metabolic alkalosis



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Treatment of metabolic alkalosis

In most cases, metabolic alkalosis can be corrected by administration of :
- **NaCl**
- **KCl** (if the patient is hypokalemic)
- **HCl** (used only in patients with renal or cardiac failure)

The administration of sodium, potassium, or hydrogen must be given with chloride, the *only reabsorbable anion.*

$$HCl + NaHCO_3 \rightarrow NaCl + H_2CO_3 \rightarrow CO_2 + H_2O$$

Therapy should also be directed against the underlying disease to diminish further hydrogen loss. As an example, the administration of an **H2-blocker** to reduce the rate of gastric acid secretion may be beneficial **in a patient with continued vomiting or nasogastric suction**.

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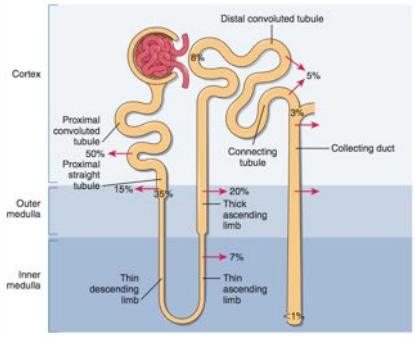
Renal sodium handling along the nephron



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Sites and Mechanisms of Renal Sodium Reabsorption

Tubule Segment	Percent Filtered Na Reabsorbed	Mechanisms of Na Entry	Regulatory Factors (Major)
Proximal tubule	50–55%	Na^+–H^+ exchange; cotransport with glucose, amino acids, phosphate, and other organic solutes	Angiotensin II; norepinephrine; glomerular filtration rate
Loop of Henle	35–40%	Na^+–K^+–$2Cl^-$ cotransport	Flow-dependent
Distal tubule	5–8%	Na^+–Cl^- cotransport	Flow-dependent
Collecting tubules	2–3%	Na^+ channels	Aldosterone; atrial natriuretic peptide

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Major Causes of Hyponatremia and Hypoosmolality

I. **Disorders in which water excretion is impaired**
- A. **Effective circulation volume depletion**
  1. Gastrointestinal losses: Vomiting, diarrhea, nasogastric tube drainage, bleeding
  2. Renal losses: Diuretics, salt-wasting kidney diseases
  3. Skin losses in which relatively dilute fluids are replaced with free water
  4. Congestive heart failure
  5. Hepatic cirrhosis
  6. Thiazide diuretics (which may act in part by inducing volume depletion)
- B. **Syndrome of inappropriate antidiuretic hormone secretion**
  1. Virtually any neuropsychiatric disorder or severe pain with or without narcotic administration
  2. Drugs: Such as the oral hypoglycemic agent chlorpropamide
  3. Ectopic production by tumors: Most often oat cell carcinoma of lung
  4. Postoperative patient, a response mediated by pain afferents
  5. Pulmonary diseases
- C. **Advanced renal failure**
- D. **Hormonal changes**
  1. Hypothyroidism
  2. Cortisol deficiency
  3. Pregnancy

II. **Primary polydipsia**

III. **Reset osmostat (see text)**

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Drugs Associated with Hyponatremia

Vasopressin Analogues	*Drugs that Potentiate Renal Action of Vasopressin*
Desmopressin (DDAVP)	Chlorpropamide
Oxytocin	Cyclophosphamide
	Nonsteroidal anti-inflammatory drugs (NSAIDs)
	Acetaminophen
Drugs that Enhance Vasopressin Release	***Drugs that Cause Hyponatremia by Unknown Mechanisms***
Chlorpropamide	*Haloperidol*
Clofibrate	Fluphenazine
Carbamazepine-oxcarbazepine	Amitriptyline
Vincristine	Thioridazine
Nicotine	Fluoxetine
Narcotics	*Methamphetamine* (MDMA, "ecstasy")
Antipsychotics/antidepressants (SSRIs)	Intravenous immune globulin (IVIG)
Ifosfamide	

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Treatment of patients with chronic "asymptomatic" hyponatremia

Treatment of Chronic Asymptomatic Hyponatremia

Treatment	Mechanism of Action	Dose	Advantages	Limitations
Fluid restriction	Decreases availability of free water	Variable	Effective and inexpensive; not complicated	Noncompliance
Pharmacologic Inhibition of Vasopressin Action				
Lithium	Inhibits kidney's response to vasopressin	900-1200 mg/day	Unrestricted water intake	Polyuria, narrow therapeutic range, neurotoxicity
Demeclocycline	Inhibits kidney's response to vasopressin	300-600 mg twice daily	Effective; unrestricted water intake	Neurotoxicity, polyuria, photosensitivity, nephrotoxicity
V_2 receptor antagonist	Antagonizes vasopressin action	—	Addresses underlying mechanisms	Limited clinical experience
Increased Solute (Salt) Intake				
With furosemide	Increases free water clearance	Titrate to optimal dose; coadminister 2-3 g NaCl	Effective	Ototoxicity, K^+ depletion
With urea	Osmotic diuresis	30-60 g/day	Effective; unrestricted water intake	Polyuria, unpalatable, gastrointestinal symptoms

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Major Causes of Hypernatremia

I. Increased water losses that are unreplaced due to impairment of thirst
- A. Insensible and sweat losses: Fever, respiratory infections
- B. Urinary losses: Central or nephrogenic diabetes insipidus, osmotic diuresis due to glucose or mannitol
- C. Gastrointestinal losses
- D. Hypothalamic lesion affecting the thirst center (very rare)

II. Administration of hypertonic sodium chloride or sodium bicarbonate

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Treatment of Central Diabetes Insipidus

Disease	Drug	Dose	Interval
Complete central diabetes insipidus	Desmopressin (DDAVP)	10-20 µg intranasally	12-24 hours
	Desmopressin (DDAVP)	0.1-0.8 mg orally	Every 12 hours
Partial central diabetes insipidus	Desmopressin (DDAVP)	10-20 µg intranasally	12-24 hours
	Aqueous vasopressin	5-10 U subcutaneously	4-6 hours
	Chlorpropamide	250-500 mg	24 hours
	Clofibrate	500 mg	6 or 8 hours
	Carbamazepine	400-600 mg	24 hours

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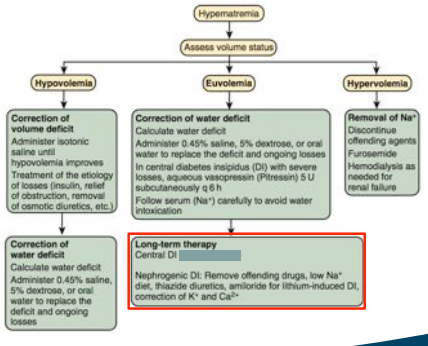
Algorithm for management of the patient with hypernatremia



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Distribution of Total Body Potassium in Organs and Body Compartments

Organ/Fluid	Total K^+ Amount	Body Compartment	K^+ Concentration
Muscle	2650 mmol	Intracellular fluid (ICF)	100-120 mmol/l
Liver	250 mmol	Extracellular fluid (ECF)	~4 mmol/l
Interstitial fluid	35 mmol		
Red blood cells	350 mmol		
Plasma	15 mmol		

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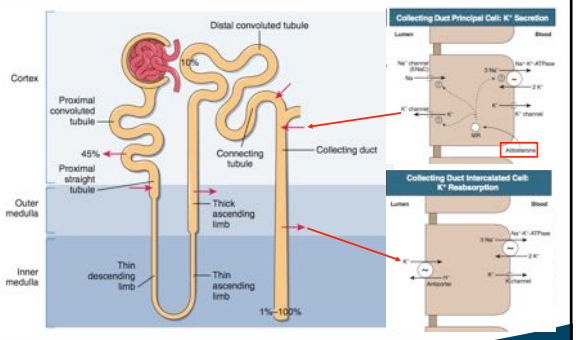
Renal potassium handling along the nephron



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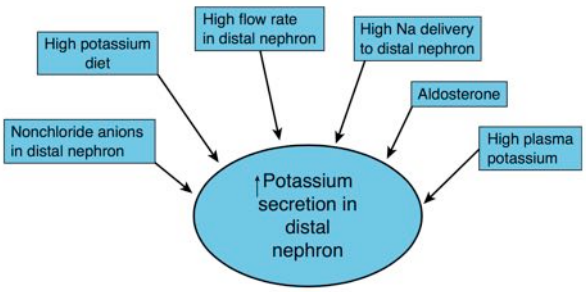
Factors that increase the secretion of K^+ by principal cells



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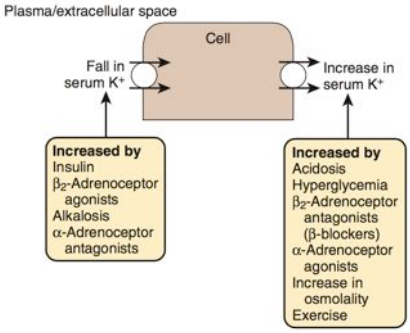
Regulation of extracellular/intracellular potassium shifts



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Major Causes of Hyperkalemia

I. Increased potassium intake—may play a contributory role but not an independent cause of hyperkalemia unless a large amount is acutely ingested or infused

II. Decreased potassium entry into cells or increased potassium release from cells
- A. Metabolic acidosis
- B. Insulin deficiency and hyperglycemia in uncontrolled diabetes mellitus
- C. β-Adrenergic blockade—may cause an enhanced rise in the plasma potassium concentration after a potassium load, but will not cause persistent hyperkalemia since the extra potassium will be excreted in the urine
- D. Increased tissue breakdown releasing potassium from cells, as with muscle breakdown (rhabdomyolysis) following trauma or a crush injury
- E. Exercise

III. Reduced potassium excretion in the urine
- A. Diminished distal delivery of sodium and water, typically associated with a significant decline in glomerular filtration rate
  1. Advanced renal failure, especially when the urine output is decreased
  2. Marked effective circulating volume depletion as in severe congestive heart failure
- B. Hypoaldosteronism
  1. Hyporeninemic hypoaldosteronism
  2. Angiotensin-converting enzyme inhibitors, which lower aldosterone release by inhibiting the formation of angiotensin II
  3. Nonsteroidal anti-inflammatory drugs, which act in part by removing the stimulatory effect of renal prostaglandins on the release of renin
  4. Potassium-sparing diuretics, which directly block sodium reabsorption and potassium secretion in the collecting tubules (see Chapter 4)
  5. Primary adrenal insufficiency

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Mechanisms for Drug-Induced Hyperkalemia

Decrease Renal Potassium Excretion

Block Sodium Channel in the Distal Nephron
Potassium-sparing diuretics: amiloride, triamterene
Antibiotics: trimethoprim, pentamidine

Block Aldosterone Production
ACE inhibitors (e.g., captopril, enalapril, lisinopril, benazepril)
Angiotensin receptor blockers
NSAIDs and COX-2 inhibitors
Heparin
Tacrolimus

Block Aldosterone Receptors
Spironolactone
Eplerenone

Block Na_2K-ATPase Activity in the Distal Nephron
Cyclosporine

Inhibit Extrarenal Potassium Disposal
Block β2-adrenergic mediated extrarenal potassium disposal; nonselective β-blockers
Block Na_2K-ATPase activity in skeletal muscles: digoxin overdose (not therapeutic doses)
Inhibit insulin release (e.g., somatostatin)

Potassium Release From Injured Cells
Drug-induced rhabdomyolysis (e.g., lovastatin, cocaine)
Drug-induced tumor lysis syndrome (chemotherapy agents in acute leukemias, high-grade lymphomas)
Depolarizing paralytic agents (e.g., succinylcholine)

Drug-Induced Acute Kidney Injury

ACE, Angiotensin converting enzyme; NSAIDs, nonsteroidal antiinflammatory drugs.

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Table 10.1 Potassium Content of Selected Foods

Food	Potassium (mg)	Potassium (mEq)
Pinto beans (1 cup)	1370	35
Raisins (1 cup)	1106	28
Honeydew (1/2 melon)	939	24
Nuts (1 cup)	688	18
Black-eyed peas (1 cup)	625	16
Collard greens (1 cup)	498	13
Banana (1 medium)	440	11
Tomato (1 medium)	366	9
Orange (1 large)	333	9
Milk (1 cup)	351	9
Potato chips (10)	226	6

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ECG Changes in Hyperkalemia

QRS Complex	Approximate Serum Potassium (mmol/l)	ECG Change
	4–5	Normal
	6–7	Peaked T waves
	7–8	Flattened P wave, prolonged PR interval, depressed ST segment, peaked T wave
	8–9	Atrial standstill, prolonged QRS duration, further peaking T waves
	>9	Sinusoid wave pattern

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Treatment of Hyperkalemia

I. Antagonism of membrane actions A. Calcium	Several minutes and then rapidly wanes
II. Increased potassium entry into cells A. Insulin and glucose B. β_2-adrenergic agonists C. Sodium bicarbonate	Each of these modalities works within 30–60 minutes, lowers the plasma potassium concentration by 0.5–1.5 mEq/L, and lasts for several hours
III. Potassium removal from the body A. Diuretics B. Cation exchange resin C. Dialysis	Diuretics take several hours but patients with advanced renal failure may show little response Exchange resins take 2–3 hours and requires repeat dosing Several hours

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Major Causes of Hypokalemia

I. Decreased dietary intake—may play a contributory role but is rarely solely responsible for hypokalemia

II. Increased entry into the cells—generally produces only a transient reduction in the plasma potassium concentration
- A. Metabolic alkalosis
- B. Increased β-adrenergic activity, as with epinephrine release during a stress response

III. Enhanced gastrointestinal losses
- A. Vomiting
- B. Diarrhea
- C. Nasogastric tube drainage

IV. Increased urinary losses—typically requires hyperaldosteronism and normal to enhanced distal flow
- A. Loop and thiazide-type diuretics
- B. Vomiting
- C. Primary mineralocorticoid excess, most often due to aldosterone-producing adrenal adenoma
- D. Secondary hyperaldosteronism due to renal artery stenosis
- E. Renal tubular acidosis

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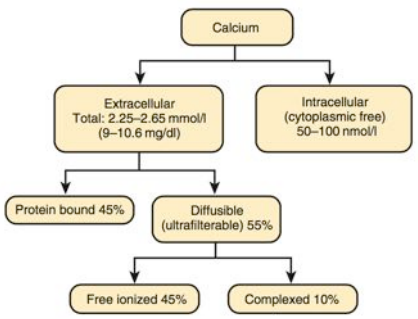
Calcium distribution in extracellular and intracellular spaces



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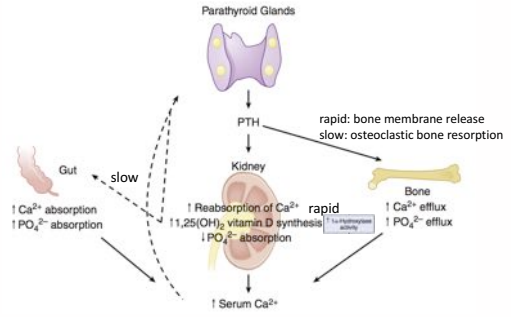
Regulation of systemic calcium homeostasis



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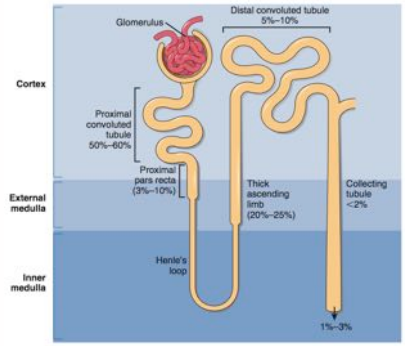
Sites of calcium reabsorption



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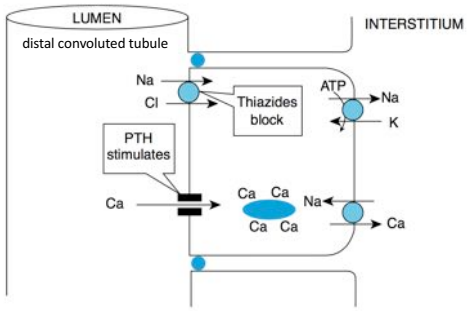
Mechanism of calcium reabsorption



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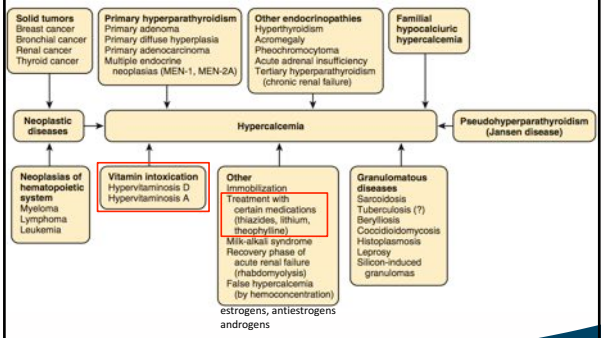
Causes of hypercalcemia



estrogens, antiestrogens
androgens

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Treatments for Hypercalcemia

Agent	Mode of Action	Dose
IV hydration with saline	Increases tubular flow and excretion of calcium	Hydration based on patient's cardiovascular status and level of kidney function; 200–500 mL/h
IV furosemide or loop diuretics	Block NKCC2 channel in loop of Henle, thus reducing positive electrochemical gradient for passive calcium reabsorption	20–40 mg intravenously after rehydration; dose may need to be adjusted based on level of kidney function
IV bisphosphonates	Inhibit osteoclastic activity	Pamidronate, 60–90 mg over 4 h Zoledronate, 4–8 mg over 15 min
Calcitonin	Inhibits bone resorption and enhances calcium excretion	4–12 IU/kg IM/SQ every 12 h
Glucocorticoids	Inhibit conversion of 25(OH)D to $1,25(OH)_2D$	Hydrocortisone, 200 mg/day IV for 3 days Prednisone, 60 mg/day PO for 10 days
Cinacalcet	Allosteric activator of CaSR, mimicking increased calcium to reduce PTH	30 mg daily to twice daily, to a maximum dose of 90 mg twice daily; give with food to reduce nausea

CaSR, Calcium-sensing receptor; *IV*, intravenous; *NKCC2*, Na^{2+}/K^+/$2Cl^-$ cotransporter; *PTH*, parathyroid hormone.

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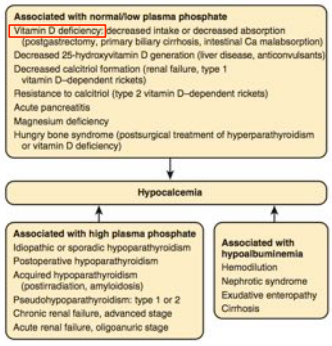
Causes of hypocalcemia



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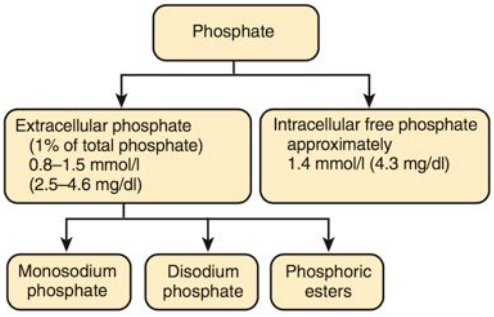
Phosphate distribution in extracellular and intracellular spaces



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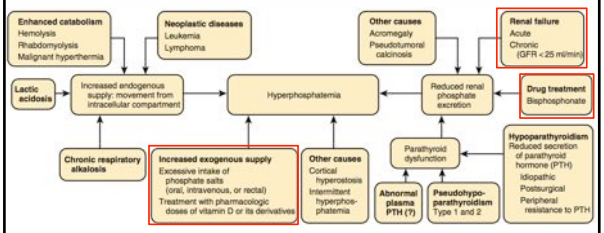
Causes of hyperphosphatemia

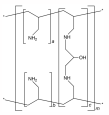


Phosphate binding drugs

→ bind phosphate in the diet to lower blood phosphate levels

Calcium acetate (Phoslo®, in Renepho®)

- a more efficient phosphate binder than calcium carbonate
- dissolves better in a non-acidic environment
- Intake: just before or with phosphate containing meals (chew)

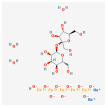


Lanthane carbonate (Fosrenol®)

Sevelamer (Renagel®, Renvela®)

- Polyallylamine that is crosslinked with epichlorohydrin
- Amine groups become partially protonated in the intestine

interact with phosphate ions through ionic and hydrogen bonding



Sucroferric-oxyhydroxide (Velphoro®)

- The carbohydrate shell stabilises the iron(III)-oxyhydroxide core

Causes of Hypophosphatemia

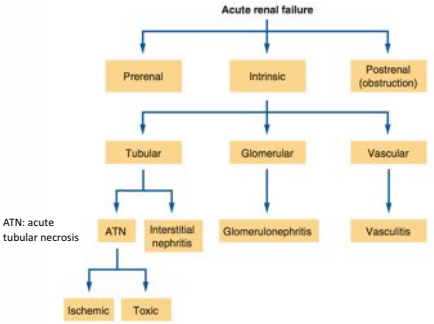
Decreased Intestinal Absorption
- Antacid abuse or excessive calcium supplement use
- Malabsorption and chronic diarrhea
- Vitamin D deficiency
- Starvation or anorexia
- Alcoholism

Increased Urinary Losses
- Primary hyperparathyroidism
- Following kidney transplantation
- Extracellular volume expansion
- Glucosuria (after treatment of DKA)
- Postobstructive or resolving ATN diuresis
- Acetazolamide
- Fanconi syndrome
- X-linked and vitamin D–dependent rickets
- Oncogenic osteomalacia

Redistribution
- Respiratory alkalosis
- Alcohol withdrawal
- Severe burns
- Postfeeding syndrome
- Leukemic blast crisis
- Treatment of hyperglycemia

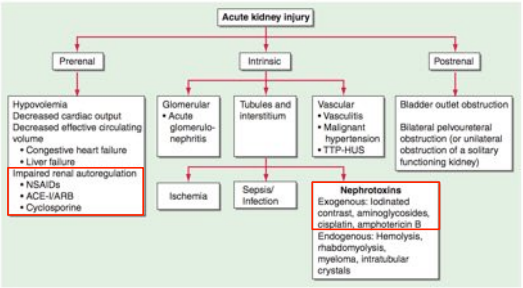
ATN, Acute tubular necrosis; *DKA*, diabetic ketoacidosis.

Main categories of acute renal failure

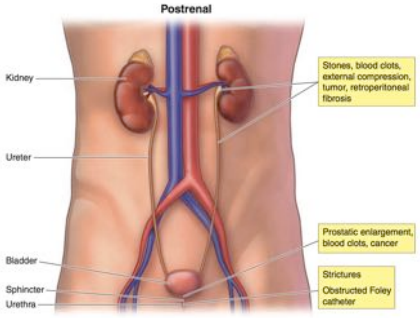


ATN: acute tubular necrosis

Classification of the major causes of acute kidney injury



Anatomic sites and causes of obstruction leading to postrenal acute kidney injury



Drug-Induced Clinical Renal Syndromes

Renal Syndrome	Causative Agents
Acute kidney injury	
Prerenal	Cyclosporine, tacrolimus, radiocontrast, AmB, ACE inhibitors, ARBs, NSAIDs, interleukin-2, exenatide
Intrarenal Vascular disease	Gemcitabine, anti-VEGF drugs, propylthiouracil, interferon
ATN	Aminoglycosides, AmB, cisplatin, tenofovir, ifosfamide, pemetrexad, polymixins, vancomycin, pentostat, zolendronate, warfarin
AIN	Penicillins, cephalosporins, sulfonamides, rifampin, NSAIDs, interferon, ciprofloxacin, others
Crystal nephropathy	Methotrexate, acyclovir, sulfonamides, indinavir, atazanavir, ciprofloxacin, sodium phosphate
Osmotic nephropathy	IVIG, HES, dextran, mannitol
Postrenal	Methysergide, drug-induced stones, alpha-agonists
Proteinuria	Gold, NSAIDs, anti-VEGF drugs, penicillamine, interferon, pamidronate
Tubulopathies	Aminoglycosides, tenofovir, cisplatin, ifosfamide, AmB, pemetrexad, cetuximab
Nephrolithiasis	Sulfadiazine, atazanavir, indinavir, topiramate, zonisamide
Chronic Kidney Disease	Li^+, analgesic abuse, cyclosporine, tacrolimus, cisplatin, nitrosourea

ACE, Angiotensin-converting enzyme; AIN, acute interstitial nephritis; AmB, amphotericin B; ARBs, angiotensin receptor blockers; ATN, acute tubular necrosis; HES, hydroxyethyl starch; IVIG, intravenous immune globulin; Li^+, lithium; NSAIDs, nonsteroidal antiinflammatory drugs; VEGF, vascular endothelial growth factor.

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NSAID Clinical Renal Syndromes

Acute kidney injury
- Prerenal azotemia
- Acute tubular necrosis

Glomerular disease
- Minimal change disease
- Membranous nephropathy

Acute interstitial nephritis

Hyperkalemia/metabolic acidosis (hyporeninemic hypoaldosteronism)

Hyponatremia

Hypertension/edema

Acute papillary necrosis

Analgesic nephropathy/chronic tubulointerstitial nephritis

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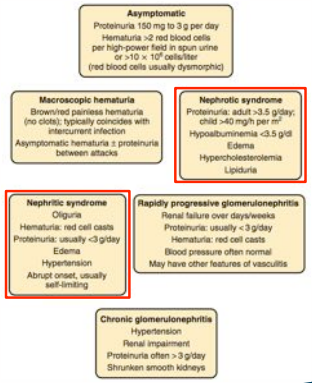
Clinical presentation of various glomerular diseases



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Differentiation Between Nephrotic Syndrome and Nephritic Syndrome

Typical Features	Nephrotic	Nephritic
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular venous pressure	Normal/low	Raised
Proteinuria	++++	++
Hematuria	May/may not occur	+++
Red blood cell casts	Absent	Present
Serum albumin	Low	Normal/slightly reduced

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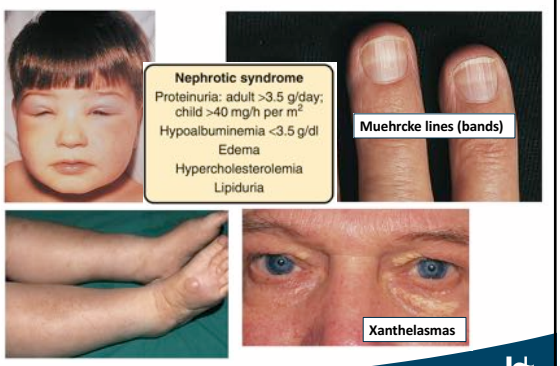
Nephrotic syndrome



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Nephrotic Syndrome

Increased glomerular permeability to macromolecules
- Heavy proteinuria (protein excretion generally above 3.5 g/day vs. a normal level of <150 mg)
- Hypoalbuminemia
- Edema

Mechanism of edema formation in this setting:
- different from that in other renal diseases
- due to hypoalbuminemia-induced underfilling of the vascular space (rather than overfilling from primary renal sodium retention)

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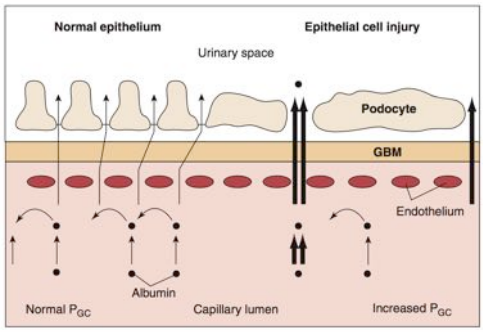
Glomerular capillary wall under normal conditions with preserved epithelium and in proteinuric states due to epithelial cell injury



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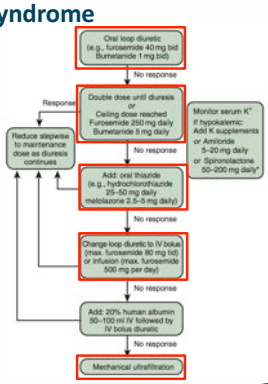
Management of edema in the patient with nephrotic syndrome



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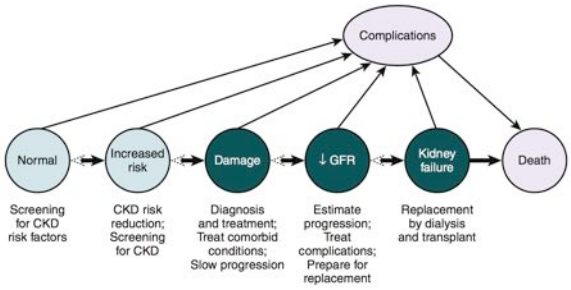
Conceptual model for chronic kidney disease



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Frequency of Primary Disease Causing End-Stage Renal Disease

Disease	Percentage (%)
Diabetes mellitus type 1	3.9
Diabetes mellitus type 2	41.0
Hypertension	27.2
Primary glomerulonephritis	8.2
Tubulointerstitial	3.6
Hereditary or cystic	3.1
Secondary glomerulonephritis or vasculitis	2.1
Neoplasm or plasma cell dyscrasias	2.1
Miscellaneous	4.6
Unknown	5.2

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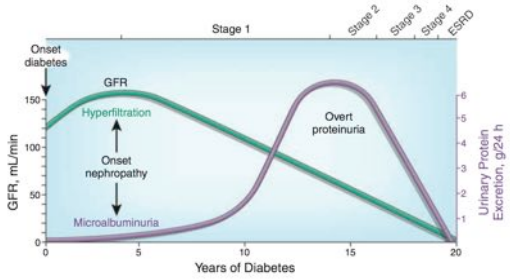
Progression of chronic renal injury



Harrison's Nephrology and acid-base disorders – Jameson and Loscalzo

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CLASSIFICATION OF CHRONIC KIDNEY DISEASE (CKD)

STAGE	GFR, mL/min PER 1.73 m²
0	>90[a]
1	≥90[b]
2	60–89
3	30–59
4	15–29
5	<15

[a]With risk factors for CKD
[b]With demonstrated kidney damage (e.g., persistent proteinuria, abnormal urine sediment, abnormal blood and urine chemistry, abnormal imaging studies).

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CAUSES OF ANEMIA IN CKD

- Relative deficiency of erythropoietin
- Diminished red blood cell survival
- Bleeding diathesis
- Iron deficiency
- Hyperparathyroidism/bone marrow fibrosis
- "Chronic inflammation"
- Folate or vitamin B_{12} deficiency
- Hemoglobinopathy
- Comorbid conditions: hypo/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs

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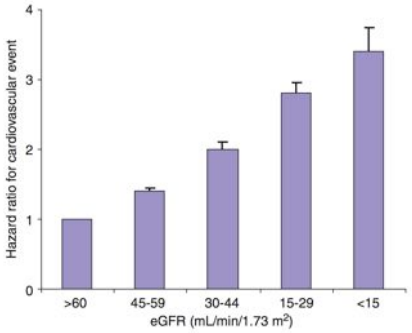
CARDIAC FUNCTION AND CARDIOVASCULAR DISEASE IN CKD

Hazard ratios for cardiovascular events according to the baseline eGFR



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Treatment for CKD is disease specific, but several generalized methods can be applied to almost all kidney diseases. The goal is slowing or reversing progression, with therapies aimed at correcting the pathophysiologic patterns. These involve blocking the renin-angiotensin-aldosterone system (RAAS) with medications, controlling blood pressure, and reducing proteinuria when present. This goal is attempted while also targeting cardiovascular risk reduction. Novel methods, which require further study, involve attacking the inflammatory and fibrotic effects of the pathophysiology.

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On-Target and Off-Target Effects of Established and Novel Drugs Used in the Management of Diabetic Nephropathy

Drug Class	On-Target Parameter	Off-Target Parameters
Antihyperglycemic Drugs		
Metformin	Glucose ↓	VCAM ↓; ICAM ↓
DPP-4 inhibitors	Glucose ↓	Blood pressure ↓; albuminuria ↓
SGLT-2 inhibitors	Glucose ↓	Blood pressure ↓; body weight ↓; uric acid ↓; albuminuria ↓
Antihypertensive Drugs		
RAAS-intervention	Blood pressure ↓	Albuminuria ↓; K^+ ↑; Hb ↓; Uric acid ↓ (losartan)
Diuretics	Blood pressure ↓	K^+ ↓; uric acid ↑
Lipid-Lowering Drugs		
Statins	LDL cholesterol ↓	C-reactive protein ↓; albuminuria ↓
Fibrates	LDL cholesterol ↓ Triglycerides ↓	Uric acid ↓; albuminuria ↓
CETP modulators	HDL cholesterol ↑	Blood pressure ↑ (mainly dalcetrapib)

CETP, Cholesterol ester transfer protein; DPP-4, dipeptidylpeptidase 4; Hb, hemoglobin; HDL, high-density lipoprotein; ICAM, intercellular cell adhesion molecule; K^+, potassium; LDL, low-density lipoprotein; SGLT-2, sodium-glucose cotransporter-2; VCAM, vascular cell adhesion molecule.

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Categories of Chronic Kidney Disease by the Level of Glomerular Filtration Rate and Corresponding Clinical Action Plan

Category	GFR Levels (mL/min/1.73 m²)	Terms	Clinical Action Plan
G1*	Greater than 90	Normal or high	Diagnose and treat the cause Treat comorbid conditions Evaluate for CKD risk factors Start measures to slow CKD progression Start measures to reduce CVD risk
G2*	60 to 89	Mildly decreased†	Estimate progression
G3a	45 to 59	Mildly to moderately decreased	Adjust medication dosages as indicated
G3b	30 to 44	Moderately to severely decreased	Evaluate and treat complications
G4	15 to 29	Severely decreased	Prepare for kidney replacement therapy (transplantation and/or dialysis) if appropriate
G5	Less than 15	Kidney failure (add D if treated by dialysis)	Start kidney replacement therapy (if uremia present)

CKD, Chronic kidney disease; CVD, cardiovascular disease; GFR, Glomerular filtration rate.
**GFR stages G1 or G2 without markers of kidney damage do not fulfil the criteria for CKD.*
†Relative to young adult level
NOTE: GFR in mL/min/1.73 m² may be converted to mL/s/1.73 m² by multiplying by 0.01667.

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Categories of Chronic Kidney Disease by the Level of Albuminuria and Corresponding Clinical Action Plan

Category	AER (mg/day)	Approximately Equivalent ACR (mg/mmol)	Approximately Equivalent ACR (mg/g)	Terms	Clinical Action Plan
A1	Less than 30	Less than 3	Less than 30	Normal to mildly increased	Diagnose and treat the cause Treat comorbid conditions Evaluate for CKD risk factors Start measures to slow CKD progression Start measures to reduce CVD risk
A2	30 to 299	3 to 30	30 to 299	Moderately increased*	Treatment with renin-angiotensin system blockers and lower blood pressure goal if hypertensive
A3	Greater than 300	≥30	Greater than 300	Severely increased	Treat nephrotic syndrome (if present)

ACR, Albumin-to-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; CVD, cardiovascular disease.
**Relative to young adult level.*

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Key recommendations

1. Over-the-counter and herbal products, as well as prescription medications, should be assessed to ensure that they are indicated.
2. The least nephrotoxic agent should be used whenever possible.
3. If a drug interaction is suspected and the clinical implication is significant, alternative medications should be used.
4. Although the MDRD eGFR equation may be used for staging CKD, the Cockcroft-Gault equation remains the standard kidney function index for drug dosage adjustment.
5. The dosage of drugs that are more than 30% renally eliminated unchanged should be verified to ensure that appropriate initial dosage adjustments are implemented.
6. Maintenance dosage regimens should be adjusted based on patient response and serum drug concentration determinations when indicated and available.

CKD, Chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *MDRD*, Modification of Diet in Renal Disease.

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