CORE CURRICULUM IN NEPHROLOGY

Disorders of Potassium and Acid-Base Balance

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ACID-BASE DISORDERS

Physiology of Acid-Base Balance

Definitions of acid-base disorders

- Metabolic acidosis: fall in HCO^- concentration with fall in pH
- Metabolic alkalosis: rise in HCO^- concentration with rise in pH
- Respiratory acidosis: rise in CO^- concentration with fall in pH
- Respiratory alkalosis: fall in CO^- concentration with rise in pH

Compensatory response to acid-base disorders

- Metabolic acidosis: fall in pH causes increased respiration, reducing CO_2
- Metabolic alkalosis: rise in pH causes decreased respiration, increasing CO_2
- Respiratory acidosis: fall in pH causes increased renal H^+ secretion, raising HCO_3^- concentration
- Respiratory alkalosis: rise in pH causes diminished renal H^+ secretion, lowering HCO_3^- concentration
- See Table 1

Response to acid generation

Average 1 mEq/kg/d for typical Western diet.

- Blood buffering of newly formed acid by bicarbonate, creation of CO_2
- Less efficient buffering of acid by hemoglobin in red blood cells, Ca^{2+} exchange in bone
- Renal handling of acid:
  - Hydrogen excretion by proximal tubule (PT) into lumen leads to reclamation and reabsorption of HCO_3^-
  - H^+ then combines with either HPO_4^{2-} or HSo_4 ("titratable acids") or NH_3 in tubular lumen; 10 to 40 mEq of H^+ excreted each day as titratable acidity, 30 to 60 mEq/d by NH_4^+
  - Reclamation of filtered bicarbonate occurs primarily in PT
  - Under conditions of excessive acid generation (metabolic acidosis), ammoniagenesis is required to enhance acid secretion:
    - NH_4^+ produced by renal tubular cells from metabolism of amino acids (primarily glutamine)
    - NH_4^+ reabsorbed in thick ascending loop and recycled as NH_3 in renal medulla
    - NH_3 diffuses into tubular lumen, trapped as NH_4^+ by secreted H^+
    - Glutamine metabolism enhanced by hypokalemia, inhibited by hyperkalemia

Cellular mechanisms of renal adaptation

- To respiratory acidosis:
  - Increased PT cell secretion of hydrogen ion due to decreased cell pH
  - Increased PT cell secretion of H^+ via Na^+/H^+ exchanger, and increased reabsorption of HCO_3^- via $Na^+/3HCO_3^-$ cotransporter on basolateral surface
- To respiratory alkalosis:
  - Decreased PT cell activity of carbonic anhydrase
  - Decreased PT cell secretion of H^+ and decreased reabsorption of HCO_3^-

Metabolic Acidosis

Causes

- Increased acid load:
  - Lactic acidosis
  - Ketoacidosis

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Table 1. Formulae Quantifying the Degree of Compensation

Disorder	Compensation
Metabolic acidosis	CO2 decreases by 1.0-1.5 × the decrease in arterial HCO_3^-
Metabolic alkalosis	CO2 increases by 0.25-1.0 × the increase in arterial HCO_3^-
Respiratory acidosis	
Acute	HCO_3^- increases by about 1 for each 10–mm Hg increase in CO_2
Chronic	HCO_3^- increases by about 4 for each 10–mm Hg increase in CO_2
Respiratory alkalosis	
Acute	HCO_3^- decreases by about 1 for each 10–mm Hg decrease in CO_2
Chronic	HCO_3^- decreases by about 4 for each 10–mm Hg decrease in CO_2

- Ingestions:
  - Salicylates
  - Methanol
  - Ethylene glycol
  - Paraldehyde
  - Sulfur
  - Toluene
  - Ammonium chloride
  - Hyperalimentation fluids
- Extrarenal acidosis:
  - HCO_3^- losses via gastrointestinal loss:
    - Diarrhea
    - Intestinal fistula
    - Ureterosigmoidostomy
- Renal acidosis:
  - Defect in HCO_3^- reclamation:
    - Type 2 "proximal" renal tubular acidosis (RTA)
  - Defect in HCO_3^- regeneration:
    - Diminished NH_4^+ production (renal failure, hypoaldosteronism-type IV RTA)
    - Diminished H^+ secretion (type I RTA)
- Utility of plasma and urine anion gap:
  - Plasma anion gap:
    - $[Na^+] - ([Cl^-] + [HCO_3^-])$; normally 8 to 11 mEq/L (mmol/L)
    - Buffering of HA (proton-anion) by HCO_3^- in setting of increased acid load leads to increased unmeasured anions (A^-) and increased anion gap
  - Urine anion gap:
    - $([Na^+] + [K^+]) - [Cl^-]$
    - In setting of metabolic acidosis with normal plasma anion gap ("hyperchloremic metabolic acidosis"), urine anion gap is useful to distinguish between extrarenal and renal acidosis
      - Urine anion gap greater than 0 suggests failure to excrete acid load (eg, RTA)
      - Urine anion gap less than 0 suggests extrarenal bicarbonate loss (eg, diarrhea)

Renal tubular acidosis

Hyperchloremic metabolic acidosis, normal serum anion gap, urine anion gap greater than 0.

Type I RTA (defect in H^+ secretion in distal tubule).

- Physiology:
  - H^+-adenosine triphosphatase (ATPase) located in cortical collecting tubule (intercalated cells only), where H^+ secretion influenced by Na^+ reabsorption in principal cells, and in medullary collecting duct
- Pathophysiology:
  - Defect in distal H^+-ATPase pump (Sjögren syndrome), increased collecting duct membrane permeability with back-diffusion of H^+ (amphotericin B), decreased distal delivery of Na^+ with failure to exchange for H^+ and K^+ (volume depletion), or decreased cortical reabsorption of Na^+ with net increase in luminal charges and inhibition of H^+ and K^+ secretion ("hyperkalemic type I RTA," as in urinary tract obstruction or sickle cell disease)
  - Calcium and phosphate release from bone to buffer acidemia leads to propensity for nephrocalcinosis in type I RTA
- Diagnosis:
  - Urine pH >5.3
  - Plasma K^+ usually low or normal (except with voltage defect)

- Plasma HCO_3^- low (<14 mEq/L [mmol/L])
- Treatment:
  - HCO_3^- 1-2 mEq/kg/d

Type II RTA (defect in PT HCO_3^- reclamation).

- Physiology:
  - Filtered HCO_3^- reabsorbed primarily in the PT after the addition of a proton in lumen (Na^+/H^+ antiporter), forming H_2CO_3, and conversion to CO_2 and H_2O facilitated by carbonic anhydrase
  - CO_2 diffuses across apical membrane and converted to HCO_3^- again by carbonic anhydrase
  - HCO_3^- then transported to blood by $Na^+/3HCO_3^-$ cotransporter
  - Distal nephron contributes a trivial amount of HCO_3^- reabsorption via intercalated cell of collecting duct
- Pathophysiology:
  - Injury to luminal Na^+/H^+ antiporter or basolateral Na^+-K^+-ATPase pump (likely etiologies for type II RTA in multiple myeloma, Fanconi syndrome, ifosfamide therapy) or deficient/inhibited carbonic anhydrase (cystinosis, acetazolamide therapy)
  - Acidosis milder than type I RTA due to intact reabsorption of HCO_3^- in distal nephron
  - Often evidence of generalized PT dysfunction is present, with glycosuria, aminoaciduria, and phosphaturia
- Diagnosis:
  - Urine pH >5.3 if above reabsorptive threshold, <5.3 in steady state, plasma K^+ usually low, plasma HCO_3^- 14 to 20 mEq/L (mmol/L)
- Treatment:
  - HCO_3^- 10 to 15 mEq/kg/d

Type IV RTA (aldosterone deficiency or resistance).

- Physiology:
  - Aldosterone promotes distal Na^+ reabsorption, K^+ and H^+ secretion
  - Direct effects of aldosterone on Na and K channels in luminal membrane of principal cells in cortical collecting tubule, increased Na^+-K^+-ATPase pump activity in basolateral membrane, and H^+-ATPase pump activity in intercalated cells in cortical collecting duct, medullary collecting tubule cells
  - Indirect effects of aldosterone in H^+ secretion secondary to electrochemical gradient induced by Na^+ reabsorption
- Pathophysiology:
  - Decreased adrenal aldosterone production (heparin, tuberculosis, adrenal insufficiency)
  - Decreased activity of renin-angiotensin system (diabetes, renal insufficiency, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers)
  - Resistance to aldosterone (potassium-sparing diuretics, trimethoprim, pseudohypoaldosteronism)
  - Acidosis exacerbated by hyperkalemia-induced inhibition of glutaminase with diminished ammoniagenesis
- Diagnosis:
  - Urine pH <5.3, plasma K^+ high, plasma HCO_3^- 14 to 20 mEq/L (mmol/L)
- Treatment:
  - Correct hyperkalemia, HCO_3^- 1 to 2 mEq/kg/d

RTA of renal insufficiency (reduction in nephron mass).

- Physiology:
  - Under normal conditions, ammonium excretion increases in response to an acid load, as described earlier in the Physiology/Response to Acid Generation subsection; this increase can be up to 3 to 4 times normal, but is limited by glomerular filtration rate (GFR)
- Pathophysiology:
  - Fibrosis that occurs with chronic kidney disease leads to diminished functional nephron number and diminished capacity for ammoniagenesis
  - At GFR less than 40 to 50 mL/min (0.67 to 0.83 mL/s), total ammonium excretion diminishes
  - H^+ is retained but a reduction in HCO_3^- is stabilized at serum levels of 12 to 20 mEq/L by calcium buffering from bone
- Diagnosis:
  - Measurement of GFR

- Treatment:
  - $NaHCO_3$ therapy can be used to minimize bone buffering of acidemia and delay development of osteopenia, but this benefit must be weighed against risks of sodium retention
  - Indications for use of alkali include:
    - Dyspnea/inability to maintain respiratory compensation
    - Chronic kidney disease in children (at risk of growth retardation)
    - Severe acidosis with plasma HCO_3^- less than 12 mEq/L (mmol/L)

Treatment

Anion gap acidosis.

- Treat underlying disease process
- With saline hydration, NaCl + HA $\rightarrow$ kidney excretes NaA rather than NH_4^+
- Transition from "anion gap" to "nonanion gap" acidosis in the hydrated patient during treatment

Lactic acidosis and ketoacidosis.

- Treat underlying disease process
- Controversies surround use of bicarbonate-containing fluids in ketoacidosis and lactic acidosis due to potential risk of worsening intracellular acidosis and lack of clinical benefit

Ingestions.

- Competitive inhibition of alcohol dehydrogenase with ethanol or fomepizole for alcohol ingestions
- Indications for hemodialysis treatment under conditions of ethylene glycol, methanol, and salicylate ingestion

Rhabdomyolysis.

- Enhancement of myoglobin excretion with alkalinization of urine with bicarbonate-containing fluids, hemodialysis

Renal tubular acidosis.

- Identify type of RTA by urine pH, serum potassium
- Calculate bicarbonate deficits, replacement needs, and maintenance dosing of bicarbonate in cases of RTA types I, II, and IV

Metabolic Alkalosis

Causes

Two phases of metabolic alkalosis:

Generation phase.

Factors that generate a metabolic alkalosis:

- Loss of hydrogen due to gastrointestinal losses:
  - Gastric suction
  - Vomiting
  - Antacid therapy
  - Chloride-losing diarrhea
- Renal losses:
  - Diuretics
  - Mineralocorticoid excess
  - Hypercalcemia/milk-alkali syndrome
  - Low chloride intake
- H^+ shift into cells:
  - Hypokalemia
  - Refeeding
- Retention of bicarbonate:
  - Massive blood transfusions
  - $NaHCO_3$ administration
- Contraction alkalosis:
  - Diuretics
  - Sweat losses in cystic fibrosis

Maintenance phase.

Factors that permit maintenance of metabolic alkalosis:

- Decreased GFR (due to volume depletion or renal failure) or
- Increased tubular reabsorption of HCO_3^- (due to volume depletion, chloride depletion, hypokalemia, hyperaldosteronism)

Urinary chloride measurement in diagnosis of metabolic alkalosis.

- Urine $Cl^- < 10$ mEq/L (mmol/L):
  - Vomiting
  - Nasogastric suction
  - Diuretics
- Urine $Cl^- > 20$ mEq/L (mmol/L):
  - In hypertension:
    - Cushing syndrome
    - Primary hyperaldosteronism
    - Hypokalemia
    - Glucocorticoid remediable aldosteronism
    - Conditions of apparent mineralocorticoid excess
  - With normal/low blood pressure:
    - Bartter syndrome
    - Gitelman syndrome

Treatment

- Metabolic alkalosis with low urinary chloride:

- Normal saline or ½ normal saline lowers plasma HCO_3^- by reversing the stimulus to renal Na^+ retention, permitting $NaHCO_3$ excretion, and increasing distal Cl^- delivery, which promotes HCO_3^- secretion ("saline-responsive alkalosis")
- Metabolic alkalosis with high urinary chloride:
  - Treatment of underlying disorder (eg, adrenal adenoma resection) and repletion of potassium

Respiratory Acidosis

Causes

- Inhibition of respiratory drive:
  - Opiates
  - Anesthetics
  - Sedatives
  - Central sleep apnea
  - Obesity
  - Central nervous system lesions
- Disorders of respiratory muscles:
  - Muscle weakness:
    - Myasthenia gravis
    - Periodic paralysis
    - Aminoglycosides
    - Guillain-Barré syndrome
    - Spinal cord injury
    - Acute lateral sclerosis
    - Multiple sclerosis
  - Kyphoscoliosis
- Upper airway obstruction:
  - Obstructive sleep apnea
  - Laryngospasm
  - Aspiration
- Lung disease:
  - Pneumonia
  - Severe asthma
  - Pneumothorax
  - Acute respiratory distress syndrome
  - Chronic obstructive pulmonary disease
  - Interstitial lung disease

Renal adaptation

- Elevated P_{CO_2} in PT leads to decreased intracellular pH, enhances H^+ secretion in PT, leading to increased HCO_3^- generation over 5 days (3 to 5 mEq/L [mmol/L] HCO_3^- for every 10–mm Hg increase in P_{CO_2})

Treatment

- Ventilatory support
- $NaHCO_3^-$ therapy controversial in this disorder:
  - Perhaps beneficial in severely acidemic patient (eg, status asthmaticus) versus
  - Hazards of therapy in patients with reversible hypercapnea (eg, chronic obstructive pulmonary disease in which respiratory drive is depressed)

Respiratory Alkalosis

Causes

- Hypoxemia
  - Pulmonary diseases:
    - Pneumonia
    - Interstitial fibrosis
    - Emboli
    - Edema
  - Congestive heart failure
  - Anemia
- Stimulation of the medullary respiratory center:
  - Hyperventilation
  - Hepatic failure
  - Septicemia
  - Salicylate intoxication
  - Pregnancy
  - Neurologic disorders
- Mechanical ventilation

Symptoms

- Lightheadedness
- Paresthesias
- Cramps
- Carpopedal spasm

Renal adaptation

- Decreased P_{CO_2} in PT leads to increased intracellular pH, inhibits H^+ secretion in the PT, leading to decreased HCO_3^- generation over 5 days (reduces serum concentration of HCO_3^- 3 to 5 mEq/L [mmol/L] for every 10–mm Hg decrease in P_{CO_2})

Treatment

- Correction of underlying disorder
- Increasing P_{CO_2} in inspired air (breathing into paper bag) in setting of acute respiratory alkalosis

Mixed Acid-Base Disorders

Diagnosis

- Identified by inappropriate or inadequate correction using the formulae for renal and respiratory compensation described in Table 1

Common scenarios

- Mixed respiratory acidosis and metabolic alkalosis (eg, chronic obstructive pulmonary disease and diuretic therapy)
- Mixed metabolic acidosis and metabolic alkalosis (eg, ketoacidosis and vomiting)
- Mixed respiratory alkalosis and metabolic acidosis (salicylate intoxication)

Change in serum anion gap (ΔAG)

- Use of ΔAG to determine if mixed acid-base disturbance is present
- The ΔAG = measured anion gap – expected anion gap
- The ΔAG is most useful to distinguish concomitant metabolic alkalosis and anion gap metabolic acidosis
- If ΔAG + measured bicarbonate is greater than physiologic bicarbonate concentrations (eg, 21 to 27 mEq/L [mmol/L]), an underlying metabolic alkalosis is present

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DISORDERS OF POTASSIUM (K)

Physiology of K Balance

Total body K determined by internal and external K balance:

Internal balance

Factors that regulate:

- Acid-base/metabolic acidosis: differences between organic (limited K shifts) and inorganic hyperchloremic acidosis
- Insulin: K moves from extracellular to intracellular sites
- Tonicity: hyperglycemia, mannitol moves K from intracellular to extracellular sites

- B_2 adrenergic receptor: Catecholamines through B_2 adrenergic receptor move K into cells; α adrenergic receptor prevents K movement from extracellular to cellular compartments
- Clinical correlate: "stress hypokalemia"

External balance

Renal K physiology:

- K freely filtered
- Filtered K reabsorbed in proximal convoluted tubule and proximal straight tubule
- K added to distal loop of Henle (at least in deep glomeruli) so that, at tip of loop, fractional excretion of K (FE_K) 150% of filtered load
- K reabsorbed in ALH (Na, K2Cl cotransporter) so that, at beginning of distal convoluted tubule, FE_K 15% of filtered load
- K added to lumen of cortical collecting tubule so that, at end of this tubule, FE_K 100% of filtered load
- K secretion mediated by Na reabsorption through Na channel followed by Na extrusion by basolateral Na, K ATPase, resulting in increases in cell K and K extrusion into the lumen through K channels
- K secretion regulated by aldosterone secretion (regulated by angiotensin II and total body K) and action (regulated by 11 B-oH steroid dehydrogenase and mineralocorticoid receptor) as well as distal nephron Na delivery and concentration
- K reabsorbed by collecting tubule, through K/H exchange (regulated by decreases in total body K)
- Urine K is independent of GFR above 30 mL/min (0.50 mL/s)
- Increases in urinary K are due to increases in K secretion or decreases in K reabsorption

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Hypokalemia

Definition

- Serum K less than 3.5 mEq/L (mmol/L)

Causes

Normal total body K/transcellular shift.

- Alkalemia
- Insulin excess
- "Stress" (eg, asthma attack, acute coronary syndrome, drug intoxication [cocaine] or withdrawal [alcohol], B_2 adrenergic drugs)
- Hypokalemic periodic paralysis
- Thyrotoxicosis
- Refeeding syndromes
- Barium
- Cesium hypothermia

Decreased total body K.

- Decreased K intake, or
- Increased K losses:
  - Gastrointestinal
  - Renal

Spurious.

- Extreme leukocytosis

Diagnostic approach

To decreases in total body K: use of urine K concentration, 24-hour urine K, transtubular K gradient:

Low 24-hour urine K (<20 mEq [mmol]/d): extrarenal losses.

- Metabolic acidosis: gastrointestinal losses
- Normal pH: decreased intake, gastrointestinal losses
- Metabolic alkalosis: gastrointestinal losses

High 24-hour urine K (>20 mEq [mmol]/d): renal losses.

- Metabolic alkalosis:
  - Low urine chloride (<10 mEq [mmol]/d): vomiting, diuretics
  - High urine chloride (>20 mEq [mmol]/d): hypertension:

- "Normal" aldosterone: Cushing syndrome, Liddle syndrome, apparent mineralocorticoid excess syndrome
- High aldosterone: primary aldosteronism, glucocorticoid remediable aldosteronism
- Normal or low blood pressure: diuretics (during therapy), severe K depletion, Bartter syndrome, Gitelman syndrome

- Variable pH:
  - Magnesium depletion
  - Anionic drugs
- Metabolic acidosis
  - RTA types I and II

Clinical manifestations

- Cardiovascular:
  - Arrhythmias
  - Digitalis toxicity
- Neuromuscular:
  - Smooth muscle:
    - Ileus
  - Skeletal muscle:
    - Weakness
    - Paralysis
    - Rhabdomyolysis
- Endocrine:
  - Glucose intolerance
- Renal/electrolyte:
  - Vasopressin resistance
  - Increased ammonia production
  - Metabolic alkalosis
- Structural changes:
  - Renal cysts
  - Interstitial changes
  - PT dilation, vacuolization

Treatment

- Estimate of K deficit: serum K may not reflect total body K
- Reverse source of K loss
- Symptomatic: intravenous K (rate, complications)
- Asymptomatic:
  - Metabolic acidosis:
    - K plus citrate, or
    - HCO_3
  - Metabolic alkalosis:
    - K plus NaCl (chloride responsive)
    - Role of spironolactone, amiloride (chloride resistant)
  - Importance of magnesium therapy

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Hyperkalemia

Definition (mmol/L)

- Serum K $\geq$5.0 mEq/L (mmol/L)

Causes

Normal total body K: transcellular shift.

- Exercise, especially in setting of β adrenergic receptor blockade and mineral acidosis
- Hyperchloremic metabolic acidosis
- Insulin deficiency
- Hypertonicity
- α adrenergic receptor stimulation
- Tissue breakdown or ischemia, for example:
  - Rhabdomyolysis
  - Gastrointestinal
  - Brain

Increased total body K.

- Increased intake: rare as sole cause
- Decreased renal K excretion

Spurious.

- Thrombocytosis
- Leukocytosis
- Ischemic blood draw

Diagnostic approach

To increases in total body K: use of urine K concentration, 24-hour urine K, and/or transtubular K gradient (S_K/Urine K $\div$ Sosm/Uosm):

Normal to high 24-hour urinary K (>40 to 60 mEq [mmol]/d):

- Relative increase in K intake

Low 24-hour urinary K (<20 to 40 mEq [mmol]/d):

- Decrease renal K excretion:
  - GFR >20 mL/min (0.33 mL/s):

- Decreased distal nephron Na delivery
- Decreased mineralocorticoid production or action
- Decreased total body Na
- Increased total body Na:
  - heart failure
  - cirrhosis
- Decreased production:
  - Addison disease
  - Isolated hypoaldosteronism (hereditary, acquired, drugs [angiotensin-converting enzyme inhibitors, heparin, nonsteroidal anti-inflammatory drugs, COX_2 inhibitors], infection [human immunodeficiency virus], chronic kidney disease [diabetes, tubular interstitial diseases, others])
- Decreased action:
  - Hereditary (pseudohypoaldosteronism types I and II)
  - Acquired (drugs [angiotensin receptor blockers, amiloride, spironolactone, triamterene] and pseudohypoaldosteronism [hereditary, acquired: sickle cell disease, renal allograft disease, obstruction])

- GFR <20 mL/min (0.33 mL/s):
  - Endogenous or exogenous K
  - Drugs that impair K excretion

Clinical manifestations

- May be disproportionately greater than level of serum K
- Cardiovascular:
  - T-wave abnormalities
  - Lengthened segments
  - Bradyarrhythmias
- Neuromuscular:
  - Ileus
  - Paresthesias
  - Weakness
  - Paralysis
- Renal/electrolyte:
  - Decreased ammonia production
  - Metabolic acidosis

Treatment

- Who requires emergent therapy:
  - Electrocardiogram abnormalities
  - Ileus
  - Paralysis
- Emergent therapies:
  - Doses, pharmacology
  - Stabilize cell membrane: Ca
  - Shift K from extra to intracellular compartments:
    - Insulin (± glucose)
    - HCO_3
    - Albuterol (B_2 adrenergic receptor agonist)
  - Decrease total body K
    - K exchange resin (oral or rectal)
    - Hemodialysis
- Prevention of hyperkalemia:
  - Importance of diet
  - Recognition of drugs that decrease K secretion
  - Role of adequate distal Na delivery
  - K exchange resins

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