Approach to the Patient with Metabolic Acidosis or Alkalosis

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Learning Objectives:
(1) To identify determinants of renal regulation of acid-base balance
(2) To differentiate between anion gap and non-anion gap metabolic acidosis
(3) To describe the various causes of metabolic acidosis
(4) To identify determinants of generation and maintenance of metabolic alkalosis
(5) To differentiate between chloride-responsive and chloride-resistant metabolic alkalosis
(6) To describe the various causes of metabolic alkalosis
(7) To interpret arterial blood gases and serum chemistries to diagnose simple and mixed acid-base disorders

Acid-Base Homeostasis

\[ [H^+] + [HCO_3^-] \rightarrow H_2CO_3 \rightarrow H_2O + CO_2 \text{ (excreted by lungs)} \]
Henderson and Hasselbalch

$[H^+] = \frac{24 \text{ PCO}_2}{[\text{HCO}_3^-]}$ or $\text{pH} = \text{pK} + \log[\text{HCO}_3^-][\text{H}_2\text{CO}_3]$

$pH = -\log_{10}[H^+]$

<table>
<thead>
<tr>
<th>pH</th>
<th>[H+]</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1</td>
<td>80</td>
</tr>
<tr>
<td>7.2</td>
<td>61</td>
</tr>
<tr>
<td>7.3</td>
<td>51</td>
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<tr>
<td>7.4</td>
<td>40</td>
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<td>7.5</td>
<td>32</td>
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<td>7.6</td>
<td>25</td>
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<tr>
<td>7.7</td>
<td>22</td>
</tr>
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**Metabolic Acidosis**

- Metabolic acidosis is defined as a primary decrease in the bicarbonate concentration $[\text{HCO}_3^-]$ of the plasma.
- It is normally accompanied by a decrease in partial pressure of carbon dioxide (PCO$_2$)(respiratory adaptation) in order to maintain near-normal pH.
<table>
<thead>
<tr>
<th>Acid-Base Disorder</th>
<th>COMPENSATORY RESPONSES</th>
<th>Primary Abnormality</th>
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**Tubular physiology: PCT**

Bicarbonate reabsorption occurs primarily in PCT
Tubular physiology: CCT

Bicarbonate generation occurs in CCT

Renal Regulation of Acid-Base Balance

- Reabsorption of filtered bicarbonate. Most or all of bicarbonate filtered at the glomerulus is reabsorbed, primarily in the proximal tubule.
  - Failure of this reabsorption mechanism leads to proximal renal tubular acidosis (proximal RTA) (“type 2 RTA”).
- Excretion of acid. The kidney excretes acid in three fashions:
  - Free hydrogen ion (H⁺) excretion (lowers urine pH)—this is quantitatively the least important mechanism
  - Titratable acid excretion (secreted H⁺ combines with poorly reabsorbable anions such as phosphate)
  - Excretion of ammonium ion (NH₄⁺). The kidney generates ammonia (NH₃) which combines with secreted H⁺ and is excreted as ammonium ion. This is quantitatively the most important mechanism.
- Excretion of acid results in bicarbonate generation in the distal tubule.
  - Failure of H⁺ excretion and/or ammonia production/ammonium excretion result in distal renal tubular acidosis (distal RTA). Failure of H⁺ excretion results in “type 1 RTA”. Hypoaldosteronism leads to a form of distal RTA called “type 4 RTA” in which there is impaired ammonium excretion.

Electroneutrality

\[ \text{Na}^+ + UC = \text{Cl}^- + \text{HCO}_3^- + UA \]

UC = unmeasured cations
UA = unmeasured anions
Anion gap

UA - UC = AG = 10-12 meq/L

UC = unmeasured cations
UA = unmeasured anions

- Overproduction of an endogenous organic acid (H\(^+\)A\(^-\)), where A\(^-\) is the acid anion, leads to high-AG metabolic acidosis (e.g., with lactic acidosis, A\(^-\) = lactate). When lactic acid is produced, the H\(^+\) is titrated by bicarbonate, resulting in lactate accumulation:
  - H\(^+\)A\(^-\) + HCO\(_3\)\(^-\) → H\(_2\)CO\(_3\) → H\(_2\)O + CO\(_2\) + A\(^-\)
Increased Anion Gap Acidosis

- Increased organic acid production (with retention of organic anions)
  - Ketoadidosis (acetoacetate, beta-hydroxybutyrate)
  - Lactic acidosis (lactate)
  - Toxin ingestion
    - Salicylate (mostly lactate)
    - Methanol (formate)
    - Ethylene glycol (glyoxylate, oxalate)
- Failure to excrete inorganic anions
  - Renal failure (phosphate, sulfate)

Normal Anion Gap (Hyperchloremic) Acidosis

- Gastrointestinal loss of bicarbonate
  - Diarrhea
- Renal loss of bicarbonate
  - Proximal renal tubular acidosis (RTA) (Type 2)
  - Carbonic anhydrase inhibitors (prevent proximal HCO₃⁻ reabsorption)
- Failure to excrete acid
  - Distal renal tubular acidosis (RTA) (Type 1, Type 4)
  - Renal failure
- Administration of acid
  - Infusion of HCl or its congeners (ammonium chloride, TPN)
- Administration of large amounts of saline
  - Dilutional acidosis

TYPE II RTA (PROXIMAL)
TYPE I RTA (DISTAL)

Treatment of Metabolic Acidosis

- Treat underlying cause(s)
- Bicarbonate (especially with normal anion gap acidosis) – Na or K bicarbonate (or bicarbonate former) depending on etiology and electrolyte values.

Metabolic Alkalosis

- Metabolic alkalosis is defined as a primary increase in the bicarbonate concentration [HCO₃⁻] of the plasma. It is normally accompanied by an increase in partial pressure of carbon dioxide (PCO₂) (respiratory adaptation) in order to maintain near-normal pH.
Generation of Metabolic Alkalosis

- Net loss of H⁺ from ECF
- Net addition of HCO₃⁻ to ECF
- Chloride depletion, i.e., loss of fluid containing chloride in excess of bicarbonate (sometimes called “contraction alkalosis”)

Causes of H⁺ loss

- GI loss
- Renal loss
- Shift into cells

GI-loss of HCl from stomach

- HCl is normally titrated by pancreatic sodium bicarbonate
  - HCl + NaHCO₃ → NaCl + CO₂ + H₂O
  - However, if HCl is lost from the body because of vomiting or gastric drainage, there is a net gain of bicarbonate
Renal - loss of H⁺ into the urine

- Metabolic alkalosis in mineralocorticoid excess states results from
  - Excess mineralocorticoid hormone effect
  - Increased distal delivery of sodium

Tubular physiology: CCT

Aldosterone causes loss of K⁺ and H⁺ into urine

Shift into cells -- severe K⁺ deficiency

Shift of K⁺ out of cells into the extracellular fluid (ECF) in exchange for H⁺ (“loss” of H⁺ into the cells)
Causes of HCO₃⁻ gain

- Exogenous alkali administration
  - bicarbonate
  - lactate
  - citrate
  - acetate

Causes of chloride-rich fluid loss

- GI loss
- Renal loss
- Skin loss
**GI loss of chloride**

- Secretion of chloride into stool (villous adenoma)
- Failure of gut reabsorption of chloride (congenital chloridorrhea)

**Renal loss of chloride**

- Diuretics -- impaired chloride reabsorption by the kidney plus stimulation of the renin-angiotensin-aldosterone axis by volume contraction (secondary hyperaldosteronism).
- Bartter's syndrome -- genetic defect of the loop diuretic-sensitive Na-K-2Cl cotransporter in the loop of Henle ("endogenous loop diuretic").
- Gitelman's syndrome -- genetic defect of the thiazide-sensitive Na-Cl cotransporter in the distal tubule ("endogenous thiazide")

**Skin loss of chloride**

- Cystic fibrosis -- loss of chloride in excess of bicarbonate in sweat.
Maintenance of Metabolic Alkalosis

• Once metabolic alkalosis has occurred, its maintenance must indicate a failure of the kidneys to excrete the excess bicarbonate.
• This can occur either because of
  – decreased filtered load of bicarbonate (due to a decrease in GFR)
  – increased tubular bicarbonate reabsorption or decreased bicarbonate secretion.

Bicarbonate Handling by the Nephron

• Bicarbonate is filtered by the glomerulus
• Filtered load = GFR x plasma bicarbonate concentration.
• Filtered bicarbonate is then reabsorbed, primarily at proximal nephron sites.
• Bicarbonate that is consumed by endogenous acid production is generated in the distal nephron.
Maintenance of metabolic alkalosis

- ECF depletion decreases GFR and increases proximal bicarbonate reabsorption;
  - stimulates the renin angiotensin aldosterone system which increases distal H+ secretion and bicarbonate reabsorption by type A intercalated cells
- Chloride depletion (decreases distal tubular bicarbonate secretion by type B intercalated cells)
- K+ depletion (lowers intracellular pH and stimulates bicarbonate reabsorption)
- Hypercapnea (increased PCO2) (lowers intracellular pH and stimulates bicarbonate reabsorption)
Clinical Features of Metabolic Alkalosis

- History -- vomiting, gastric drainage, diuretics
- Symptoms -- often none, sometimes cramps
- Signs -- hypertension (in mineralocorticoid-excess states), hypoventilation (usually not evident on physical exam), tetany/increased deep tendon reflexes (decreased ionized calcium), cardiac arrhythmias (esp. if pH > 7.6)

Differential Diagnosis of Metabolic Alkalosis

Chloride-responsive type (urine Cl⁻ low, i.e. < 10 mmol/L):

Kidney is avidly reabsorbing chloride because of persistent volume (and chloride) depletion that developed during the generation of metabolic alkalosis.

GI - vomiting, gastric drainage, villous adenoma, chloride diarrhea
Renal - diuretics (after drug cessation)
Skin - cystic fibrosis

Chloride-resistant type (urine Cl⁻ > 20 mmol/L):

Mineralocorticoid excess states -- can be either primary (low renin) or secondary (high renin)

<table>
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<tr>
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<th>Secondary</th>
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<td>Primary hyperaldosteronism</td>
<td>Renal artery stenosis</td>
</tr>
<tr>
<td>Cushing's syndrome</td>
<td>Accelerated hypertension</td>
</tr>
<tr>
<td>Licorice ingestion</td>
<td>Renin-secreting tumor</td>
</tr>
<tr>
<td>(simulates hyperaldosteronism)</td>
<td>Estrogen therapy</td>
</tr>
<tr>
<td>Liddle syndrome</td>
<td>Bartter's syndrome</td>
</tr>
<tr>
<td>(simulates hyperaldosteronism)</td>
<td>Gitelman's syndrome</td>
</tr>
<tr>
<td>Profound potassium depletion</td>
<td>Diuretics (during drug administration)</td>
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Treatment of Metabolic Alkalosis

- Potassium administration
- Acetazolamide
- Volume repletion
- Intravenous HCl or NH₄Cl

COMPENSATORY RESPONSES

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Winter’s formula: \( \text{PCO}_2 = 1.5 \times \text{HCO}_3^- + 8 \pm 2 \)

Expected Compensation for Primary Acid-Base Disorders

<table>
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<tr>
<th>Type</th>
<th>Primary Change</th>
<th>Secondary Adaptation</th>
</tr>
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<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>decrease in HCO₃⁻ of 1 mEq/L</td>
<td>increase in PCO₂ of 1.2 mmHg*</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>increase in HCO₃⁻ of 1 mEq/L</td>
<td>increase in PCO₂ of 0.7 mmHg</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>increase in PCO₂ of 10 mmHg</td>
<td>Acute: Increase in HCO₃⁻ of 1.0 mEq/L; Chronic: Increase in HCO₃⁻ of 3.5 mEq/L</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>decrease in PCO₂ of 10 mmHg</td>
<td>Acute: Decrease in HCO₃⁻ of 2 mEq/L; Chronic: Decrease in HCO₃⁻ of 4-5 mEq/L</td>
</tr>
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Patient 1

• A 70-year-old man presents with weakness.
• Blood chemistries reveal (in mmol/L): sodium 145, potassium 3.0, chloride 120, total CO₂ 16; (in mg/dL): urea nitrogen 30, creatinine 1.2.
• Arterial blood gases (ABG) reveal: pH 7.35, PCO₂ 30 mmHg, HCO₃⁻ 16 mEq/L.

Q: What is the acid base disturbance?
A. Metabolic acidosis
B. Metabolic alkalosis
C. Mixed metabolic acidosis/metabolic alkalosis
D. No metabolic disturbance

• The ABGs show pH 7.35, PCO₂ 30 mmHg, HCO₃⁻ 16 mEq/L. Since pH is low (acidemia) there is an acidosis, and since bicarbonate is low, this is metabolic acidosis. The “delta bicarbonate” is 8, and the “delta PCO₂” should therefore be 8 x 1.2 or ~ 10, which is what is observed. Thus this is a simple metabolic acidosis.
How would you further characterize it?

A. High-anion gap acidosis  
B. Normal anion gap (hyperchloremic) acidosis

• A: The anion gap is 145 – (120 + 16) = 9. Hence, this is a non-anion gap or hyperchloremic metabolic acidosis.

What is the differential diagnosis and most likely cause?

A. Chronic kidney disease  
B. RTA (Renal Tubular Acidosis)  
C. Diarrhea (due to increased stool bicarbonate loss)  
D. Hydrochloric acid ingestion
What is the cause of the metabolic acidosis?

- The most common causes of a non-anion gap metabolic acidosis are as follows:
  - Chronic kidney disease (due to decreased urine acid excretion)
  - RTA (Renal Tubular Acidosis) (due to either decreased urine acid excretion [distal RTA] or increased urine bicarbonate excretion [proximal RTA])
  - Diarrhea (due to increased stool bicarbonate loss)

- This patient turned out to have diarrhea due to surreptitious laxative use.

Patient 2

- A 30-year-old woman presents with fatigue and weakness. She denies vomiting or diarrhea and takes no medications. Her physical examination is normal except for mild orthostatic hypotension. Blood chemistries reveal (in mmol/L): sodium 138, potassium 2.9, chloride 90, total CO₂ 40. Arterial blood gases (ABG) reveal: pH 7.50; PCO₂ 53 mmHg; HCO₃⁻ 40 mEq/L. The urine pH is 7.5. Urine chemistries reveal (in mmol/L): sodium 30, potassium 30, chloride 5.

Q: What is the acid base disorder?

A. Metabolic acidosis
B. Metabolic alkalosis
C. Mixed metabolic acidosis/metabolic alkalosis
D. No metabolic disturbance
What is the acid-base disorder?

• A: On the ABG, the pH is high, indicating alkalemia, and bicarbonate is high, indicating metabolic alkalosis. Since the delta bicarbonate is 40 - 24 = 16, the delta PCO₂ should be 0.7 x 16 = 11.2, which is close to the actual delta PCO₂ of 13. Therefore, this is a simple metabolic alkalosis.

What is the acid-base disorder?

• A: On the ABG, the pH is high, indicating alkalemia, and bicarbonate is high, indicating metabolic alkalosis. Since the delta bicarbonate is 40 - 24 = 16, the delta PCO₂ should be 0.7 x 16 = 11.2, which is close to the actual delta PCO₂ of 13. Therefore, this is a simple metabolic alkalosis.

What is the most likely diagnosis?

A. Diuretic intake
B. Bartter’s syndrome
C. Gitelman’s syndrome
D. Surreptitious vomiting
E. Hypokalemic periodic paralysis
• This patient has been vomiting. Note that urine chloride is very low (5 mEq/L), which indicates a chloride-responsive alkalosis. In vomiting, loss of HCl leads to metabolic alkalosis, which results in increased renal bicarbonate excretion (accounting for the high urine pH). Sodium and potassium are lost with bicarbonate into the urine. However chloride is retained by the kidney due to chloride depletion.

• Diuretic intake would be expected to be associated with an increase in chloride as well as sodium and potassium excretion. Bartter’s and Gitelman’s syndrome are tubular reabsorptive disorders (“endogenous diuretics”), and would also cause increased chloride as well as sodium and potassium excretion. Hypokalemic periodic paralysis is not associated with metabolic alkalosis.

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**Patient 3**

• A 60-year-old female patient presents to the emergency room (ER) with fever and confusion. She has known chronic obstructive pulmonary disease (COPD) and is on home oxygen.

• Serum chemistries reveal (in mmol/L): sodium 136; potassium 3.9; chloride 101; total CO₂ 5. ABG: pH 6.8; PCO₂ 33 mm Hg; HCO₃⁻ 5 mEq/L.

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What is the acid-base disturbance?
A. Metabolic acidosis
B. Respiratory acidosis
C. Respiratory alkalosis
D. Mixed metabolic acidosis/respiratory alkalosis
E. Mixed metabolic acidosis/respiratory acidosis
• The pH is 6.8, indicating profound acidemia, and since the HCO₃⁻ is very low, there is clearly a metabolic acidosis. The anion gap is very high (30). The delta bicarbonate is 24.5 - 19, which is equal to the delta ion gap, so this is a high anion gap metabolic acidosis.
• The PCO₂ is low, but it is not as low as it should be in the face of such profound metabolic acidosis. The delta PCO₂ should be 1.2 x delta bicarbonate, or 1.2 x 19 = 23, but hers is only 40-33 = 7. Thus she has additionally profound respiratory acidosis.

Why did the patient develop it?
• It turns out that this patient had sepsis leading to lactic acidosis. She was unable to achieve appropriate respiratory compensation due to her underlying COPD.
• Hint: Very profound acidemia should raise the possibility to a combined acidosis, i.e. both metabolic and respiratory acidosis. In addition, very profound alkalemia raises the possibility of combined alkalosis, whereas a normal pH is often seen with combined acidosis/alkalosis.

Patient 4
• A 30-year-old male patient presents to the emergency room (ER) with confusion.
• Serum chemistries reveal (in mmol/L): sodium 136; potassium 3.9; chloride 101; total CO₂ 15. ABG: pH 7.5; PCO₂ 20 mm Hg; HCO₃⁻ 15 mEq/L.
What is the acid-base disturbance?
A. Metabolic acidosis
B. Metabolic alkalosis
C. Respiratory alkalosis
D. Mixed metabolic acidosis/metabolic alkalosis
E. Mixed metabolic acidosis/respiratory alkalosis

The pH is 7.5, indicating alkalemia, and since PCO₂ is low, there is a respiratory alkalosis. For respiratory alkalosis, the compensation is as follows:
- Acute: bicarbonate decreases by 2 mEq per L for each 10 mm Hg decrease in PCO₂
- Chronic: bicarbonate decreases by 4 to 5 mEq per L for each 10 mm Hg decrease in PCO₂
Therefore, if this is chronic respiratory alkalosis, the expected bicarbonate for a delta PCO₂ of 20 would be 24 – 9 = 15, which is the observed value. Thus far, the data are consistent with a simple chronic respiratory alkalosis.

Why did the patient develop it?
- However, remember to always calculate the anion gap. The anion gap is 20, which suggests the coexistence of a high anion gap acidosis. Salicylate toxicity not only causes a high anion gap metabolic acidosis but also gives rise to acute respiratory alkalosis and is the likely culprit in this case.