The Clinical Approach to Acid-Base Disorders:

Metabolic Acidosis and Metabolic Alkalosis

Objectives

By the end of this chapter, you should be able to:

1. Understand the clinical approach to acid-base disorders, including the basic equation, questions to ask about each disorder, the use of venous electrolytes, arterial blood gases, and the acid-base nomogram.

2. Identify metabolic acidosis, calculate the anion gap, understand the pathophysiology of the most common causes, including chronic renal failure, and use the calculation for the amount of bicarbonate to administer in acute treatment situations.

3. Identify metabolic alkalosis, separate the two basic types, understand the pathophysiology of the most common causes.

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I. Clinical Approach to Acid-Base Disorders

A. Use of the Venous Electrolytes

The venous electrolytes are probably the most commonly ordered set of laboratory tests in clinical medicine. They provide valuable inferences about the causes of almost all acid-base disorders. Normal values are shown in Table 1. These inferences may sometimes be sufficient, but can at times mislead you about the cause of a disorder.

The total venous CO2 content, since it consists mostly of bicarbonate, is generally used as a proxy for the HCO_3^- concentration in the venous blood.

\[ \text{Total Venous} = \text{dissolved CO}_2 + \text{HCO}_3^- \]

\[ \text{dissolved CO}_2 = (0.0301 \times p\text{CO}_2) = 1.2 \text{ mM/L} \]

B. Use of the Arterial Blood “gases”

The arterial pH and pCO_2 are measured using electrodes, within minutes of the time the sample is drawn, and the HCO_3^- is calculated from these two measured values. If the venous electrolytes are drawn at roughly the same time, you can then compare the calculated HCO_3^- from the arterial sample to the total CO2 content from the venous sample. They should be within 2-3 mEq/L of each other if both measurements are accurate.

Normal values for arterial pH are 7.37-7.43, and 36-44 mmHg for pCO_2. The arterial values give you a precise picture of acid-base balance when used in conjunction with the equation below and the acid-base nomogram. However, it is often necessary to use the history and venous electrolytes along with these values to clarify how the disturbance developed.

C. Use of the basic clinical equation and acid base nomogram

\[ [\text{H}^+] = \frac{24 \times p\text{CO}_2}{[\text{HCO}_3^-]} \]

Normally \[ \text{H}^+ = 40 \text{ nEq/L} \]

\[ p\text{CO}_2 = 40 \text{ mmHg} \]

\[ \text{HCO}_3^- = 24 \text{ mEq/L} \]

This equation is based on the Henderson-Hassellbach equation and converts pH to hydrogen ion concentration to simplify clinical calculations and provide a powerful conceptual framework for considering any acid-base disturbance. Approximate values for H+ concentrations at different pH values are shown in Table 2.
The pCO$_2$ varies directly with ventilation, and is the primary abnormality in the respiratory acid-base disorders.

The HCO$_3^-$ concentration is regulated by the kidney, and is the primary abnormality in the metabolic acid-base disturbances discussed below.

D. The 3 key questions to ask about any acid-base disorder are:

1. Is the disturbance an acidosis or alkalosis (obviously the arterial pH will definitively answer this question)?
2. Is the primary event a change in the pCO$_2$ (respiratory) or a change in the HCO$_3^-$ concentration (metabolic)?
3. Has the expected "compensation" for the primary event occurred?

E. What does "compensation" for acid-base disorders mean?

In response to every primary acid-base disturbance, either metabolic (HCO$_3^-$) or respiratory (pCO$_2$), there is a secondary physiologic response of the other component, which tends to limit the change in pH produced by the primary disturbance. This "corrective" response is never great enough to restore the pH to normal.

For example, if the HCO$_3^-$ concentration is reduced primarily, there will be a compensatory, physiologic, secondary decrease in the pCO$_2$ due to a compensatory increase in minute ventilation.

Each of the primary acid-base disturbances has been studied to determine what compensatory response to expect, across the range of abnormal primary values for the disturbance. Based on these studies, the acid-base nomogram (Figure 1) has been constructed. The expected change in pCO$_2$ from

![Figure 1](attachment:image.png)
respiratory compensation when the HCO$_3^-$ is decreased, for example, from 24 to 10 mEq/L is determined from the nomogram as follows:

1. Starting from a pH of 7.40 and pCO$_2$ of 40 mmHg, follow the pCO$_2$ line of 40 down to a bicarbonate of 10 mEq/L.
2. The appropriate respiratory compensation can be estimated by moving toward the right at a HCO$_3^-$ level of 10 mEq/L into the shaded area of delineating “metabolic acidosis.”

In this case the expected pCO2 with normal respiratory compensation is approximately 25 mmHg, and the final pH is about 7.22. Note that although the respiratory compensation raises the pH closer to 7.4, the pH never reaches 7.4 with compensation alone.

II. Metabolic Acidosis

A. Definition and general causes

Metabolic acidosis is defined as a disturbance in acid-base balance that is associated with a primary decrease in HCO$_3^-$ concentration. It may occur, in general, from any abnormality producing an excess of hydrogen ions (most commonly), or from a primary loss from the body of HCO$_3^-$ (less common).

B. Approach to differential diagnosis, use of the Anion Gap

The anion gap is determined using three of the venous electrolytes:

\[
\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-) \\
140 - (104 + 24) = 12 \text{ mEq/L}
\]

The normal anion gap of 12 mEq/L is shown above, indicating that there are normally about 12 mEq/L of unmeasured anions, that is, anions other than Cl$^-$ and HCO$_3^-$ that balance the positively charged Na$^+$ ions in the extracellular fluid (Figure 2). Most labs now calculate and report the anion gap along with the venous electrolytes.

In metabolic acidosis, when the HCO$_3^-$ concentration is reduced, it will be “replaced” in the ECF by either additional unmeasured anions, in which case the anion gap increases, or by chloride, a measured anion, in which case the anion gap will be unchanged. This simple distinction serves to divide the causes of metabolic acidosis into 2 types with differing etiologies: those with and without an increase in the anion gap.
C. Metabolic acidosis with an increased Anion Gap

The causes of increased anion gap metabolic acidosis are often recalled by use of a mnemonic such as MUDPIES:

- Methanol poisoning
- Uremia (advanced, SO₄, PO₄)
- Diabetic ketoacidosis-Other ketones (EtOH)
- Paraldehyde
- Ischemia-Lactate
- Ethylene glycol
- Salicylate toxicity

Diabetic ketoacidosis and lactic acidosis are characterized by endogenous overproduction of strong acids that are completely dissociated at body pH into H⁺ and its accompanying anion. The H⁺ combines with HCO₃⁻ in the ECF to reduce its concentration, while the dissociated anion of the strong acid accumulates “in place” of the HCO₃⁻ that has been consumed, thus increasing the concentration of unmeasured anions. Typical venous electrolytes (not including potassium) and arterial blood gases are illustrated in Figure 3.

Note that the HCO₃⁻ concentration is decreased (from the normal 24) by about the same amount the anion gap is increased (from the normal 12). Typically the rise in the AG is usually 1-2 times the fall in the serum bicarbonate concentration. An exact 1:1 ratio between the change in the anion gap the fall in the HCO₃⁻ is not always observed because a portion of the excess acid load is buffered by cells rather than HCO₃⁻.
In diabetic ketoacidosis (DKA), the overproduction of strong organic acids is due to the incomplete oxidation of fatty acids in the absence of insulin, leading to the production of acetoacetic acid and beta-hydroxybutyric acid. The clinical picture and renal response to this disorder are discussed in detail in the small group session.

Lactic acidosis occurs when oxygen delivery or utilization at the tissue level is impaired. Most commonly this is observed in patients with sepsis or the systemic inflammatory response syndrome, where maldistribution of blood flow and hypotension lead to impaired tissue perfusion and decreased oxygen delivery.

In the case of drugs and toxins, the ingestion of the compound leads to the overproduction of strong organic acids, as is the case with methanol alcohol or ethylene glycol (anti-freeze) ingestion, or with aspirin overdose. The latter can also produce a primary respiratory alkalosis by direct central stimulation of respiration. A representative case of acid-base values for a patient with salicylate toxicity is shown in Figure 4. In this case a mixed acid base disorder is present, since the pCO₂ value is lower than would be expected with secondary respiratory compensation alone.

D. Metabolic acidosis with a normal Anion Gap (hyperchloremic metabolic acidosis)

The major causes of hyperchloremic acidosis are diarrhea, during which HCO₃⁻ is lost in the stool, and the various forms of renal tubular acidosis, in which there is diminished H⁺ excretion in the urine, at a time when the filtration rate is normal (in contrast to chronic renal failure). The electrolyte and acid-base profile for a patient with diarrhea is illustrated in Figure 5. As the plasma HCO₃⁻ concentration falls, chloride anions are retained, and the anion gap remains normal.
The metabolic acidosis that regularly accompanies advanced chronic renal failure (CRF) is a clinical example where both an increased gap and normal gap metabolic acidosis are observed concurrently. The acidosis results mainly from a decrease in NH$_3$ production and diminished NH$_4^+$ excretion. The resulting H$^+$ retention causes the fall in plasma HCO$_3^-$ concentration and a normal anion gap metabolic acidosis. At the same time, retention of sulfates, phosphates and other organic acids results in a rise in the anion gap and an increased AG metabolic acidosis.

E. Respiratory Compensation for metabolic acidosis

The expected, physiologic, secondary response to a primary fall in the plasma HCO$_3^-$ concentration, is a compensatory reduction in the pCO$_2$. This compensatory response minimizes, but does not entirely correct the disturbance in pH produced by the fall in HCO$_3^-$. In fact, the nature and extent of this response have been well studied across the range of reduced values that may occur in metabolic acidosis. The change in pCO$_2$ is roughly similar in value to the change in HCO$_3^-$, as the HCO$_3^-$ falls. For every 1 mEq/L fall in the serum bicarbonate, the pCO$_2$ will fall approximately 1.2 mmHg. Thus, if the plasma HCO$_3^-$ concentration is reduced by 10 mEq/L from 24 to 14, the pCO$_2$ will be reduced from 40 to 28 mmHg. Using our equation the resulting H$^+$ will be:

$$\text{H}^+ = \frac{28}{14} = 48 \text{ nEq/L}$$

$$\text{pH} = -\log 4.8 \times 10^{-8} = 7.32$$

### Decreased Efficacy of Respiratory Compensation with Worsening Acidosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>HCO$_3^-$</th>
<th>pCO$_2$</th>
<th>H$^+$</th>
<th>pH</th>
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<tbody>
<tr>
<td>Normal</td>
<td>24</td>
<td>40</td>
<td>40</td>
<td>7.40</td>
</tr>
<tr>
<td>Moderately Severe</td>
<td>15</td>
<td>30</td>
<td>50</td>
<td>7.30</td>
</tr>
<tr>
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<td>5</td>
<td>20</td>
<td>100</td>
<td>7.00</td>
</tr>
</tbody>
</table>

The degree of respiratory compensation is increasingly less effective at restoring pH toward normal as the acidosis becomes more severe (Table 3).

F. Approach to treatment of metabolic acidosis

When the acidosis is severe or when the plasma HCO$_3^-$ concentration is dropping rapidly, i.v. HCO$_3^-$ is given to temporarily stabilize and/or raise the plasma pH. The amount of HCO$_3^-$ to administer to raise the plasma HCO$_3^-$ by a given amount is based on an understanding of the “space of distribution” for HCO$_3^-$. Although HCO$_3^-$ is restricted as an anion to the ECF, 50% of the buffering of administered HCO$_3^-$ results from the release of hydrogen from intracellular sites. Therefore, the space of distribution for HCO$_3^-$ is roughly 2 x ECF volume: i.e. 2 x 20% = 40% of the body weight in kgs. For a 70 Kg male this “space” would be 28 liters. In practice small increments in plasma HCO$_3^-$ are made and arterial blood gases are obtained frequently to reassess the arterial pH.

In severe metabolic acidosis, it is generally recommended to administer enough bicarbonate to raise the pH to 7.20 to 7.25. This will serve to minimize the harmful cardiovascular effects of acidosis and provide sufficient buffer to prevent catastrophic decreases in pH with small increases in acid production.
Correction of pH to levels greater than 7.25 in critically ill patients is not recommended for several reasons, including:

1. The dissociation curve for oxygen-Hgb is shifted to the left, increasing oxy-hemoglobin affinity and decreasing tissue oxygen delivery.
2. Bicarbonate administration may cause sodium and volume overload.
3. Bicarbonate administration may precipitate or worsen hypercarbia.

III. Metabolic Alkalosis

A. Definition and general causes

Metabolic alkalosis is defined as a disturbance in acid-base balance that is associated with a primary increase in HCO$_3^-$ concentration. It may occur, in general, from any abnormality producing a loss of hydrogen ions, or from a primary gain of body HCO$_3^-$. 

The 2 basic types of metabolic alkalosis are:

1. Those developing in the context of volume contraction (or “perceived” volume contraction) where the BP is normal or low, mainly due to vomiting or gastric drainage, or to the administration of certain diuretics.
2. Those developing under conditions of volume expansion and hypertension, mainly hyperaldosteronism

B. Metabolic Alkalosis associated with volume contraction

The main causes of this type of metabolic alkalosis are diuretic administration, vomiting, and nasogastric suction. Less common causes involve inherited renal tubular defects that have recently been identified through genetic analysis, at the same two sites where the loop and thiazide diuretics produce an acquired blockade of NaCl transport.

The diagnosis and treatment of the metabolic alkalosis associated with volume contraction involves understanding two components of its pathophysiology: the generation phase and the maintenance phase.

In the generation phase of metabolic alkalosis with vomiting or gastric drainage, there is a loss of Hydrogen ions from the stomach: (at a normal gastric pH of 1.0 this loss of H$^+$ would be 100mEq/L, at a pH of 2 it would be only 10 mEq/L, and at a pH of 3 it would be a mere 1 mEq/L). This leads to a dissociation of H$_2$CO$_3$ in the plasma and a transient rise in plasma HCO$_3^-$ concentration. There is then a rise in the filtered load of HCO$_3^-$ due to the increase in plasma concentration, and the excess filtered HCO$_3^-$ is initially delivered into the urine, along with Na$^+$ as well as potassium. Due to the presence of HCO$_3^-$ (which is not normally in the urine) the urine pH is above a pH of 5.5, and in this case it would be close to 7.0 (Figure 6).
The maintenance phase now ensues as volume contraction develops due to the loss of NaCl: Na\(^+\) into the urine (with the excess HCO\(_3\)-), and Cl\(^-\) with the gastric contents (accompanied by H\(^+\)). As a result, there is an increase in sodium reabsorption along the nephron, along with chloride, eliminating chloride from the urine. Early in the maintenance phase, when the urine pH is above 5.5, there is dissociation of the levels of sodium and chloride measured in the urine. That is, the urine sodium concentration remains above 15 mEq/L as it is excreted in the urine along with bicarbonate. The urine chloride level, on the other hand, is <15 mEq/L as it is avidly being reabsorbed in the nephron along with Na\(^+\) in response to the volume depletion (Figure 7).

As the degree of volume depletion worsens and the filtered load of chloride correspondingly decreases, sodium is then reabsorbed along the proximal nephron with both chloride and bicarbonate. This leads to the rise in the serum bicarbonate level and maintenance of the metabolic alkalosis. The urine pH then falls to less than 5.5 once all of the filtered bicarbonate is reabsorbed proximally. Both urine sodium and chloride levels will then be less than 15 mEq/L once the urine pH is less than 5.5, reflecting avid reabsorption of sodium, chloride and bicarbonate in the proximal nephron as a response to marked volume depletion.

Also as a consequence of the volume contraction, aldosterone secretion is stimulated, via the release of renin and formation of angiotensin. Distal sodium reabsorption is increased resulting in an increase in the secretion of both hydrogen and potassium in response to the increased electronegativity of the lumen imparted by avid sodium reabsorption.

The increased hydrogen secretion serves to combine with distally delivered HCO\(_3\)-, also contributing to elimination of HCO\(_3\)- from the urine. This now serves both to maintain the alkalosis and to restore the pH of the urine to < 5.5. The presence of an acidic urine despite systemic metabolic alkalosis is often referred to as “paradoxical aciduria,” given the continued excretion of hydrogen ions despite the presence of alkalosis (Figure 8).

The increased potassium secretion leads to increased potassium excretion and further contributes to the hypokalemia.

Even if the vomiting or gastric drainage ceases at this point, the alkalosis, hypochloremia and hypokalemia will persist as long as volume depletion persists.
The development and maintenance phases of metabolic alkalosis with diuretics vary somewhat from the above.

Sodium and chloride are lost together in the urine due to the tubular blockade in the loop of Henle or distal convoluted tubule (depending on whether a loop diuretic (furosemide) or thiazide diuretic is being used). Volume contraction develops along with some increase in potassium secretion and excretion due to the delivery of more volume to the site of potassium secretion in the cortical collecting duct.

Aldosterone is stimulated, as above, from the ensuing volume contraction, and there is an increase in hydrogen and potassium secretion. This results from increased electronegativity in the lumen as a consequence of avid sodium reabsorption at the site where aldosterone acts in the cortical collecting duct.

The increase in hydrogen secretion initially generates new HCO$_3^-$ anions into the plasma, creating the metabolic alkalosis. The additional hydrogen ions that are secreted combine with NH$_3$ to form NH$_4^+$ and are excreted with Cl$^-$, then producing a degree of hypochloremia that matches the increase in plasma HCO$_3^-$ concentration.

The increased hydrogen ions that continue to be secreted subsequently combine with the excess filtered HCO$_3^-$ that is now delivered to the distal nephron, and reabsorb it, thus sustaining the alkalosis. At this point acid excretion in the urine returns to normal.

The increased potassium ions that continue to be secreted and excreted contribute to the ongoing hypokalemia.

The pathogenesis of metabolic alkalosis in 2 congenital syndromes, Bartter’s and Gitelman’s Syndromes, largely parallels that of diuretics. In Bartter’s syndrome, there is a defect in the thick ascending limb of Henle’s loop at the Na-K-2Cl transport site. Gitelman’s Syndrome, a phenotype first described at UNC in 1966 in a family from Haw River, is a defect in the distal convoluted tubule at the NaCl transport site. These patients present with metabolic alkalosis and hypokalemia with a normal blood pressure in the absence diuretic use or the presence of vomiting.

D. Metabolic Alkalosis with volume expansion

Metabolic alkalosis associated with volume expansion and hypertension, due to primary excess secretion of aldosterone, usually secondary to adrenal hyperplasia or adenoma, is considerably less common than the volume contraction associated causes noted above. In fact, less that 1% of patients with hypertension are found to have this condition as a cause.

The pathophysiology is much the same as that reviewed above for the secondary aldosteronism that occurs as a consequence of diuretic induced volume contraction. In this case, obviously, the increased sodium reabsorption at the aldosterone site is a primary event. It results in a mild degree of volume expansion, with associated hypertension, as well as an increase in hydrogen and potassium secretion, with the development of metabolic alkalosis, hypochloremia, and hypokalemia.

E. Respiratory Compensation for metabolic alkalosis

Respiratory compensation for metabolic alkalosis consists of an increase in pCO$_2$ induced by a decrease in ventilation. The increase in pCO$_2$ as compensation for an increase in plasma HCO$_3^-$ concentration in metabolic alkalosis, is not of the same degree as the decrease in pCO$_2$ that occurs as compensation for the decrease in plasma HCO$_3^-$ concentration in metabolic acidosis. In part this is due to the fact that substantial decreases in ventilation create a risk of hypoxemia. For every 1 mEq/L rise in the serum bicarbonate, the pCO$_2$ rises 0.6-0.7 mmHg.