Chapter 18
Approach to Metabolic Acidosis in the ICU

18.1 Introduction

Metabolic acidosis is a common acid-base disturbance in critically ill patients, characterized by a decrease in blood pH due to an accumulation of hydrogen ions (H^+) or a loss of bicarbonate (HCO_3^-). Understanding its pathophysiology, diagnosis, and management is crucial in the Intensive Care Unit (ICU) setting, as it can significantly impact cellular function and overall metabolism [1, 2] [Ref: Algorithm 18.1].

18.2 Pathophysiology

18.2.1 Acid-Base Regulation

The body's acid-base balance is tightly regulated through the interplay between hydrogen ions (H^+), bicarbonate (HCO_3^-), and carbon dioxide (CO_2), as described by the Henderson-Hasselbalch equation:

$$\mathrm{pH} = 6.1 + \log\left(\left[\mathrm{HCO_3^-}\right] / \left(0.03 \times \mathrm{PaCO_2}\right)\right)$$

This equation illustrates how pH is influenced by the ratio of bicarbonate to carbon dioxide. Metabolic acidosis occurs when there is a decrease in bicarbonate or an increase in hydrogen ions, shifting the equilibrium and lowering the pH.

S. B. Mishra et al., *Mastering ICU Care*,
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18.3 Traditional vs. Strong Ion Difference Model

18.3.1 Traditional Bicarbonate-Centered Model

This model focuses on the balance between bicarbonate and carbon dioxide in regulating pH. It emphasizes the role of the kidneys in reabsorbing bicarbonate and the lungs in excreting CO_2.

18.3.2 Strong Ion Difference (SID) Model

The SID model, proposed by Stewart, considers the role of strong ions (fully dissociated ions like Na^+, K^+, and Cl^-) in acid-base balance. According to this model, metabolic acidosis results from a decrease in SID due to an increase in strong anions (e.g., Cl^-) or a decrease in strong cations (e.g., Na^+).

Understanding both models provides a comprehensive view of acid-base regulation and aids in diagnosing complex acid-base disorders.

18.4 Compensation Mechanisms

18.4.1 Respiratory Compensation

The body responds to metabolic acidosis by increasing alveolar ventilation to reduce $PaCO_2$, a process known as respiratory compensation. This hyperventilation helps to normalize pH by shifting the equilibrium of the bicarbonate buffer system.

Winter's Formula is used to predict the expected respiratory compensation:

$$\text{Expected PaCO}_2 = \left(1.5 \times \left[\text{HCO}_3^-\right]\right) + 8 \pm 2$$

- Acute Compensation: Occurs within minutes to hours.
- Chronic Compensation: May take several days to reach maximal effect.

Clinical Application:

- Appropriate Compensation: Measured $PaCO_2$ matches the expected value from Winter's formula.
- Inadequate Compensation: Suggests concurrent respiratory acidosis.
- Excessive Compensation: Indicates a superimposed respiratory alkalosis.

18.5 Diagnostic Approach

1. **Check Compensation**

Before delving into the specifics of metabolic acidosis, it is crucial to assess whether the body is compensating for the acidosis. Compensation can be evaluated using the following formula:

$$\text{Expected PaCO2} = 1.5 \times \left[\text{HCO}_3^-\right] + 8 \pm 2$$

This equation helps determine if the respiratory system is compensating appropriately for the metabolic acidosis by reducing PaCO2 through hyperventilation.

2. **Anion Gap Calculation**

The next step is to calculate the anion gap (AG), which helps differentiate between different types of metabolic acidosis. The anion gap is calculated using the formula:

$$\text{AG} = \left[\text{Na}+\right] - \left(\left[\text{Cl}-\right] + \left[\text{HCO}_3^-\right]\right)$$

- **Normal Anion Gap Metabolic Acidosis (NAGMA):** An anion gap within the normal range suggests a non-gap metabolic acidosis.
- **High Anion Gap Metabolic Acidosis (HAGMA):** An increased anion gap indicates the presence of unmeasured anions and suggests conditions like lactic acidosis or ketoacidosis.

Corrected anion gap should be calculated in case of hypoalbuminemia using the following formula cAG = AG + 0.25 × (normalalbumin − measuredalbumin(g/L)).

3. **Normal Anion Gap Pathway**

If the anion gap is normal, further evaluation is required to pinpoint the cause of the metabolic acidosis.

18.6 Purpose of the Urinary Anion Gap (UAG)

The urinary anion gap (UAG) is used to estimate the urinary ammonium (NH4+) excretion, which is important in diagnosing the cause of metabolic acidosis, particularly in differentiating between renal and nonrenal causes of normal anion gap metabolic acidosis (NAGMA). Ammonium excretion plays a crucial role in maintaining acid-base balance by facilitating the removal of excess hydrogen ions (H+).

18.7 Calculation of Urinary Anion Gap

The UAG is calculated using the formula:

$$\mathrm{UAG} = \left(\left[\mathrm{Na}+\right]+\left[\mathrm{K}+\right]\right)-\left[\mathrm{Cl}-\right]$$

Where:

- [Na+] = Sodium concentration in urine
- [K+] = Potassium concentration in urine
- [Cl−] = Chloride concentration in urine

18.8 Interpretation of the UAG

1. **Negative UAG:**
   - A negative UAG indicates high levels of urinary ammonium excretion. This is typical in cases where the kidneys are functioning normally and can excrete excess acid effectively. Common causes include gastrointestinal bicarbonate loss (e.g., diarrhea) where the kidneys respond appropriately by increasing ammonium excretion.
2. **Positive UAG:**
   - A positive UAG suggests impaired ammonium excretion, indicating a renal cause of metabolic acidosis. This is seen in conditions like renal tubular acidosis (RTA), where the kidneys are unable to adequately excrete hydrogen ions and ammonium.

18.9 Mechanism and Clinical Relevance

Ammonium Excretion

- The kidneys help maintain acid-base balance by excreting hydrogen ions in the form of ammonium (NH4+). In states of acidosis, the kidneys increase ammonium excretion to remove excess H+ from the body.
- Ammonium is generated in the renal tubules through the metabolism of glutamine to glutamate, which produces NH4+ and bicarbonate (HCO_3^-). The bicarbonate is reabsorbed into the blood to buffer excess H+, while NH4+ is excreted in the urine.

Clinical Application

- Measuring the UAG provides an indirect estimate of urinary ammonium excretion, as direct measurement is not commonly available in routine clinical practice.

- By interpreting the UAG, clinicians can determine whether the kidneys are responding appropriately to metabolic acidosis. A negative UAG confirms that the kidneys are excreting adequate amounts of ammonium, thus pointing toward a nonrenal cause of acidosis. Conversely, a positive UAG indicates inadequate ammonium excretion, suggesting a renal cause of acidosis.

18.10 Limitations of the Urinary Anion Gap (UAG)

While the urinary anion gap (UAG) is a valuable tool for assessing ammonium excretion and differentiating causes of normal anion gap metabolic acidosis (NAGMA), there are several conditions and factors where its reliability and accuracy are compromised. Here is why the UAG might not be applicable or reliable in certain situations:

1. **Polyuria**
   - **Description:** Polyuria is the production of abnormally large volumes of dilute urine.
   - **Issue:** In polyuria, the concentrations of sodium, potassium, and chloride in urine may be significantly diluted, leading to inaccuracies in the calculation of the UAG. The diluted urine may not reflect the actual excretion rates of these electrolytes, thereby misleading the estimation of ammonium excretion.
2. **High Urine pH (>6.5)**
   - **Description:** Urine pH above 6.5 indicates a more alkaline urine.
   - **Issue:** At high urine pH levels, ammonium (NH4+) is converted to ammonia (NH3), which is a gas and can diffuse back into the bloodstream. This conversion reduces the amount of NH4+ excreted in the urine, making the UAG less reliable as it no longer accurately reflects ammonium excretion.
3. **Presence of Non-chloride Anions in Urine**
   - **Description:** Conditions where significant amounts of non-chloride anions (e.g., ketoacids, salicylates) are present in the urine.
   - **Issue:** The UAG assumes that chloride is the primary anion accompanying ammonium in the urine. When non-chloride anions are present, they can alter the balance of the equation, leading to a positive or less negative UAG that does not accurately indicate ammonium excretion. For example:
     - **Ketoacidosis:** The presence of ketoacids like beta-hydroxybutyrate can result in an inaccurate UAG.
     - **Salicylate Toxicity:** Salicylates and their metabolites can also affect the UAG calculation.

4. **Low Urinary Sodium Concentration (<20 mmol/L)**
   - **Description:** Low levels of sodium in the urine, often seen in conditions of sodium depletion or dehydration.
   - **Issue:** Adequate distal delivery of sodium to the renal tubules is necessary for proper acidification of urine and ammonium excretion. When urinary sodium levels are low, the ability to accurately use the UAG to estimate ammonium excretion is compromised.
5. **Use of Diuretics**
   - **Description:** Diuretics can alter the excretion of electrolytes in the urine.
   - **Issue:** Diuretics can increase urinary excretion of sodium and potassium, which can lead to a positive UAG even in the presence of adequate ammonium excretion. This makes the UAG unreliable for assessing renal ammonium excretion in patients on diuretics.

18.11 Urinary Osmolal Gap: Explanation and Interpretation

18.11.1 Purpose of the Urinary Osmolal Gap

The urinary osmolal gap is used to estimate the presence and concentration of unmeasured osmoles in the urine, primarily ammonium (NH4+), which is crucial in the assessment of renal function and the diagnosis of metabolic acidosis. It is particularly useful when the urinary anion gap (UAG) is unreliable, such as in conditions of polyuria, high urine pH, and the presence of non-chloride anions.

18.11.2 Calculation of the Urinary Osmolal Gap

The urinary osmolal gap (UOG) is calculated as the difference between the measured urine osmolality and the calculated urine osmolality:

$$\text{Urinary Osmolal Gap} = \text{Measured Urine Osmolality} - \text{Calculated Urine Osmolality}$$

The calculated urine osmolality is determined using the formula:

$$\text{Calculated Urine Osmolality} = 2 \times \left([\text{Na}+] + [\text{K}+] \right) + \text{Urine Urea Nitrogen} / 2.8 + \text{Urine Glucose} / 18$$

Where:

- [Na+] = Sodium concentration in urine (mmol/L)
- [K+] = Potassium concentration in urine (mmol/L)
- Urine urea nitrogen is often given in mg/dL and converted using the factor 2.8.

- Urine glucose is often given in mg/dL and converted using the factor 18.

In practice, glucose is often omitted from the calculation unless the patient is diabetic.

18.11.3 Interpretation of the Urinary Osmolal Gap

1. **Low or Normal Urinary Osmolal Gap (<10 mOsm/kg):**
   - A low or normal UOG suggests that there are few unmeasured osmoles in the urine. This can occur in cases where the kidney is effectively excreting ammonium or in conditions not associated with significant production of unmeasured osmoles.
   - It indicates that the kidney's ability to excrete ammonium is likely intact, and the metabolic acidosis is not due to a renal tubular defect.
   - **Nonrenal Causes:** Elevated UOG in metabolic acidosis typically indicates that the acidosis is due to extrarenal factors such as diarrhea, where the kidneys compensate by increasing ammonium excretion.
2. **Elevated Urinary Osmolal Gap (>10 mOsm/kg):**
   - An elevated UOG indicates the presence of significant unmeasured osmoles in the urine, most commonly ammonium (NH4+). This suggests that the kidneys are responding to metabolic acidosis by increasing ammonium excretion.
   - **Renal Causes:** In conditions like distal renal tubular acidosis (RTA), where there is impaired ammonium excretion, the UOG will be low despite metabolic acidosis.

18.11.4 Clinical Significance

- **Differentiating Causes of Metabolic Acidosis:**
  - The urinary osmolal gap helps differentiate between renal and nonrenal causes of normal anion gap metabolic acidosis. A high UOG supports a diagnosis of nonrenal causes (e.g., gastrointestinal bicarbonate loss), whereas a low UOG suggests renal causes (e.g., renal tubular acidosis).
- **Assessment of Renal Ammonium Excretion:**
  - A high UOG indicates effective renal excretion of ammonium, which is an appropriate response to metabolic acidosis. Conversely, a low UOG suggests inadequate ammonium excretion, pointing to a renal tubular defect.

3. **High Anion Gap Pathway**

If the anion gap is high, further calculations and assessments are needed.

18.12 Delta-Delta (Δ-Δ) Calculation and Interpretation

18.12.1 Purpose of Delta-Delta Calculation

The Delta-Delta (Δ-Δ) calculation is used to assess mixed acid-base disorders, specifically to identify the presence of concurrent metabolic acidosis and metabolic alkalosis or to distinguish between different types of metabolic acidosis. It compares the changes in the anion gap and bicarbonate levels to provide insight into the underlying metabolic disturbances.

18.12.2 Calculation of Delta-Delta

The Δ-Δ is calculated using the following formulas:

$$\Delta AG = \text{Measured AG} - \text{Normal AG}$$
$$\Delta HCO_3^- = \text{Normal } HCO_3^- - \text{Measured } HCO_3^-$$

The normal values commonly used are:

- Normal AG: 12 mmol/L (may vary slightly depending on the lab reference range).
- Normal HCO_3^-: 24 mmol/L.

The Δ-Δ can be interpreted as:

$$\Delta\Delta = \Delta AG - \Delta HCO_3^-$$

For lactic acidosis:

$$\Delta\Delta = \left[0.6 \times \Delta AG\right] - \Delta HCO_3^-$$

18.12.3 Interpretation of Delta-Delta

1. **Δ-Δ = −5 to + 5 mmol/L:**
   - Indicates a pure high anion gap metabolic acidosis (HAGMA) without additional metabolic disturbances.
2. **Δ-Δ > +5 mmol/L:**
   - Suggests the presence of both HAGMA and metabolic alkalosis. This means that the increase in the anion gap is greater than the decrease in bicarbonate, indicating an additional metabolic alkalosis.

3. **Δ-Δ < −5 mmol/L:**
   - Suggests the presence of HAGMA and normal anion gap metabolic acidosis (NAGMA). This means that the decrease in bicarbonate is greater than the increase in the anion gap, indicating an additional NAGMA.

18.13 Specific Formula for Lactic Acidosis

Reason for the Different Formula
- In lactic acidosis, the relationship between the increase in the anion gap and the decrease in bicarbonate is not strictly 1:1. This is because lactic acid metabolism and renal handling differ from other causes of HAGMA.
- Studies have shown that in lactic acidosis, the decrease in bicarbonate is typically 0.6 times the increase in the anion gap. This reflects the body's partial compensation for the increased $\Delta\Delta\left(\text{Lactic Acidosis}\right) = \left[0.6 \times \Delta AG\right] - \Delta\text{HCO}_3^-$.

Clinical Relevance
- This adjusted formula accounts for the partial renal and cellular buffering that occurs in lactic acidosis.
- Using the standard 1:1 Δ-Δ formula in lactic acidosis can lead to underestimating the severity of the bicarbonate decrease or missing concurrent metabolic disturbances.

18.14 Osmolar Gap: Explanation and Interpretation

18.14.1 Purpose of the Osmolar Gap

The osmolar gap is used to detect the presence of unmeasured osmoles in the blood, which can indicate the ingestion of toxic substances or other metabolic disturbances. It is particularly useful in cases of suspected poisoning or unexplained high anion gap metabolic acidosis.

18.14.2 Calculation of the Osmolar Gap

The osmolar gap is calculated as the difference between the measured serum osmolality and the calculated serum osmolality:

$$\text{Osmolar Gap} = \text{Measured Serum Osmolality} - \text{Calculated Serum Osmolality}$$

Measured Serum Osmolality
- This is determined directly using an osmometer.

Calculated Serum Osmolality

- The calculated serum osmolality is derived from the concentrations of the main solutes in the serum, typically sodium, glucose, and blood urea nitrogen (BUN).

  The formula for calculated serum osmolality is:

$$\text{Calculated Serum Osmolality} = 2 \times [\text{Na}+] + \text{Glucose} / 18 + \text{BUN} / 2.8$$

  Where:

- [Na+] = Sodium concentration in mmol/L.
- Glucose is in mg/dL (divide by 18 to convert to mmol/L).
- BUN is in mg/dL (divide by 2.8 to convert to mmol/L).

18.14.3 Interpretation of the Osmolar Gap

1. **Normal Osmolar Gap:**
   - A normal osmolar gap is typically within the range of −10 to +10 mOsm/kg.
   - This indicates that the measured and calculated serum osmolalities are in close agreement, suggesting no significant presence of unmeasured osmoles.
2. **Elevated Osmolar Gap (>10 mOsm/kg):**
   - An elevated osmolar gap indicates the presence of unmeasured osmoles in the blood.
   - Common causes include the ingestion of toxic alcohols (e.g., methanol, ethylene glycol, isopropanol, propylene glycol), which are not accounted for in the calculated osmolality formula.

18.14.4 Clinical Relevance

Toxic Alcohol Ingestion

- **Methanol and Ethylene Glycol:** Both can cause severe metabolic acidosis and elevated osmolar gap. These substances are metabolized into toxic metabolites (formic acid from methanol and glycolic/oxalic acids from ethylene glycol), leading to an increased anion gap metabolic acidosis and elevated osmolar gap.
- **Isopropanol:** Leads to elevated osmolar gap but typically does not cause metabolic acidosis because it is metabolized to acetone, which is less acidic.

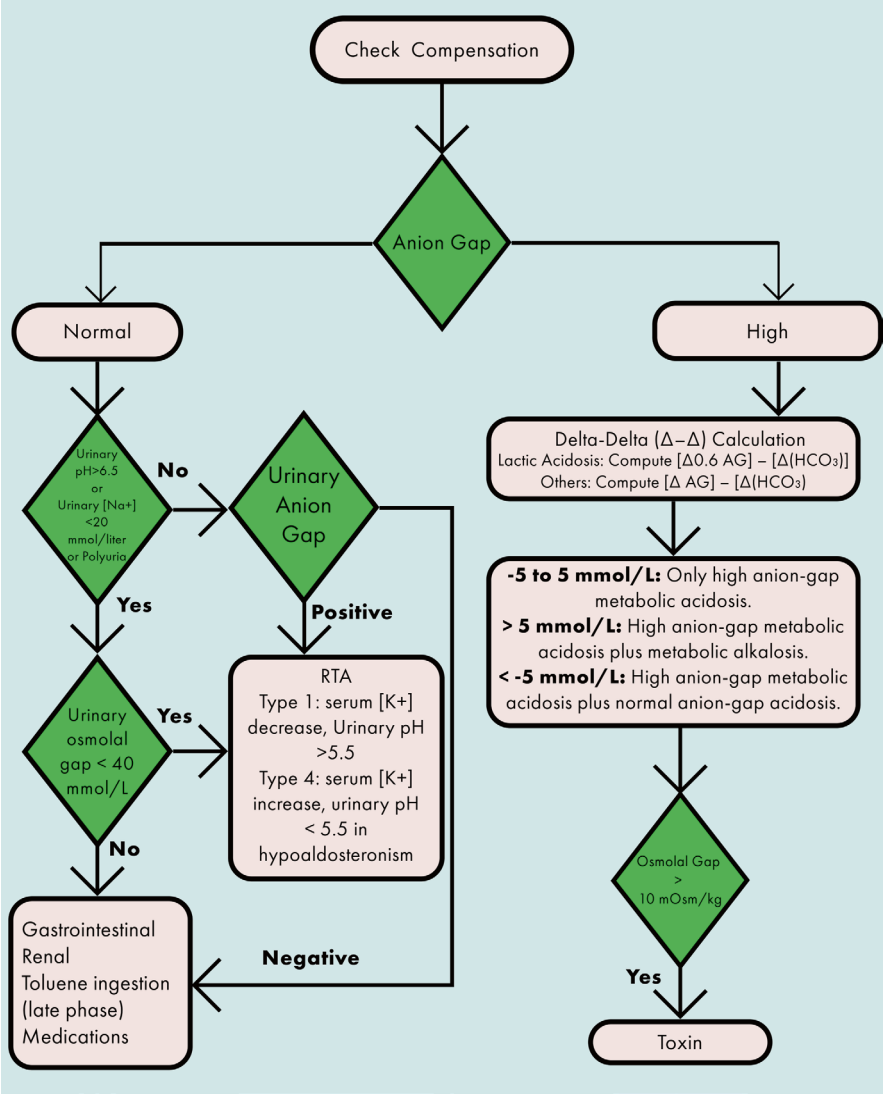
Case of Unexplained Metabolic Acidosis

- When a patient presents with high anion gap metabolic acidosis and the cause is not immediately apparent, measuring the osmolar gap can help identify the presence of unmeasured toxic substances.

18.15 Conclusion

The management of metabolic acidosis in the ICU involves a structured approach to diagnose the underlying cause. By calculating the anion gap, urinary anion gap, and delta-delta, clinicians can narrow down potential etiologies and tailor treatment accordingly. Recognizing and addressing the root cause is paramount to effective management and improving patient outcomes.

Algorithm 18.1: Approach to metabolic acidosis in the ICU



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