Workshop on Electrolyte and Acid-Base Disturbances

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Workshop on Electrolyte and Acid-Base Disturbances

Date: January 30, 2009

Time: 2.00 pm – 6.00 pm

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Praveen Aggarwal, All India Institute of Medical Sciences
New Delhi

Faculty
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- Chhavi Sawhney, New Delhi
- Sanjeev Bhoi, New Delhi
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1. Fluid and Electrolyte Disturbances

Sanjeev Bhoi, Chhavi Sawhney

The Body Water

About a billion years ago, life began-in the sea. The sea possessed unique properties for the maintenance of life. For example, the water of the sea is a solvent for the electrolytes and the oxygen that are necessary for life. The sea is also a solvent for the carbon dioxide that accumulates during life’s processes. Since the carbon dioxide is volatile, it can be easily dissipated from the surface of the sea. In addition, the volume of the sea is so great that it can absorb large amounts of heat, or lose large amounts of heat, with only relatively small changes in temperature. The volume of the sea is also so great that significant changes in its composition occur only over a period of hundreds of thousands of years. Finally, its dielectric constant, its surface tension, and other physical properties are all important in maintaining and protecting life.

As a result, the water that surrounds the cells of vertebrates and of humans, namely, the extracellular water, still has an electrolyte composition similar to what the sea had in pre-recorded times, in spite of all the countless changes in evolution that have occurred. Over the years, the rivers of the world have eroded land and washed elements into the sea. This has caused the electrolytes of the sea to become more concentrated. In spite of this, there is still a remarkable similarity between the proportional composition of electrolytes in seawater and in extracellular water.

The total amount of water in the body can be determined by introducing into the body a known quantity of a substance that diffuses evenly throughout the extracellular water and the cells, and then determining its concentration. Antipyrine, urea, thiourea, and more recently “heavy water” (deuterium oxide or tritium oxide) have been used for this purpose.

The Extracellular Water

The body water is usually divided into two main compartments: the extracellular water (extracellular fluid) and the intracellular water (intracellular fluid). The extracellular water includes the plasma water and the interstitial water (the fluid in the tissue spaces, lying between the cells). Gastrointestinal secretions, urine, sweat, exudates, and transudates can also be considered as specialized portions of the extracellular water, because when these are lost a severe loss of extracellular water occurs.

The relation of the body water to the body weight are as follows:

<table>
<thead>
<tr>
<th>Water Compartment</th>
<th>Percentage of Body Weight</th>
<th>Volume in Liters (man, 70 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma water (plus)</td>
<td>4</td>
<td>2.8</td>
</tr>
<tr>
<td>Interstitial water</td>
<td>16</td>
<td>11.2</td>
</tr>
<tr>
<td>Total extracellular water (plus)</td>
<td>= 20</td>
<td>= 14</td>
</tr>
<tr>
<td>Intracellular water</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>Total average body water in a man</td>
<td>= 60</td>
<td>= 42</td>
</tr>
<tr>
<td>Total average body water in a 70 kg woman</td>
<td>50</td>
<td>35</td>
</tr>
</tbody>
</table>

These figures represent average values that we shall use in calculating water and electrolyte requirements in this book.

The total body water varies. It is related principally to the fat content of the body, and to sex. Fat has relatively less water associated with it; therefore a fat person will have relatively less water than a thin person. In addition, a woman has a lower content of body water than a man. The water content of the body also decreases with age.

The average water content of a man is approximately 60%. The average water content of a woman is approximately 50%.

Body water is also composed of inaccessible bone water and transcellular fluids.

Transcellular fluids include the fluid of organs such as the kidneys, liver, pancreas, skin and the mucous membranes of the gastrointestinal and respiratory tracts; and so on. It is difficult to measure the volume of the fluid in these compartments.

Body water, including percentage of fat and of lean body tissue, can now be measured using a bioelectrical
impedance analyzer.

The Electrolytes in the Extracellular Water

Chemists are able to determine the nature and the concentration of the electrolytes in both the extracellular water and the cells. However, the determination of electrolyte concentration in the cells requires special research techniques. Therefore, physicians must rely on the changes in electrolyte concentration in the extracellular water, particularly in the plasma or serum, in treating patients.

The relative concentration of electrolytes in the extracellular water and in the cells is shown in Table 1. Notice that sodium (Na) and chloride (Cl) are the principal electrolytes in the extracellular water. However, potassium (K) and phosphates (PO₄) are the principal electrolytes in the cells.

Table 1: The Electrolyte concentration of body fluids (mEq/L)*

<table>
<thead>
<tr>
<th>Solution</th>
<th>Extracellular Fluid</th>
<th>Intracellular Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>142</td>
<td>10</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.5</td>
<td>150</td>
</tr>
<tr>
<td>Magnesium</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Calcium</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>153</td>
<td>200</td>
</tr>
<tr>
<td><strong>Anions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>Phosphates</td>
<td>2</td>
<td>120</td>
</tr>
<tr>
<td>Sulphates</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>Protein</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>Organic acids</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>153</td>
<td>200</td>
</tr>
</tbody>
</table>


It should be noted that the electrolyte concentration of the plasma (or serum) is slightly different from the electrolyte concentration in the interstitial portion of the extracellular water. The major difference is that the protein concentration of the plasma is greater than that of the interstitial portion of the extracellular water. This is due to the fact that the capillary walls prevent the outward movement of most of the protein from the plasma. As a result, the sodium concentration in plasma is slightly greater than the sodium concentration in the interstitial water. Conversely, the chloride concentration in the plasma is slightly less than the chloride concentration in the interstitial water.

The electrolyte concentrations are given in terms of milliequivalents per liter of serum or plasma (mEq/L).

Milliequivalents

The electrolytes of the body are in solution, mostly in the form of ions. Their concentration can be described in terms of weight, such as milligrams (mg) per deciliter (dL) of blood (mg/dL: a deciliter, or one tenth of a liter, is the same as 100 mL). Since the concentrations of the various electrolytes are small, they are expressed as milliequivalents per liter, mEq/L.

These values are shown in Table 1. Notice that the concentration of the cations is the same as the concentration of the anions in blood, serum or plasma when expressed in terms of milliequivalents. In other words, each liter of blood has 153 mEq of cations (Na, K, Ca, Mg) and 153 mEq of anions (bicarbonate, chloride, sulphate, phosphate, organic acids and protein anions).

The relationship between milliequivalents and milligrams

The relationship between milliequivalents and milligrams can be expressed as follows: The weight of a salt in milligrams can be converted into milliequivalents by dividing its weight in milligrams by its molecular weight, and multiplying by the valence.

Example:

\[
1 \text{ g of NaCl} = \frac{1000}{58.5} \text{ mEq of NaCl} = 17.1 \text{ mEq}
\]

Na (at. wt. 23; valence 1)  Cl (at. wt. 35.5; valence 1)

Na + Cl = 58.5

Since the electrolyte concentration in blood and serum are usually expressed in mEq/L, the following formulas can be used to convert mg/dL into mEq/L, or vice versa:

\[
\text{mEq/L} = \frac{\text{mg/dL} \times 10 \times \text{valence}}{\text{Atomic weight}}
\]

\[
\text{mg/dL} = \frac{\text{mEq/L} \times 10 \times \text{atomic weight}}{10 \times \text{valence}}
\]
**The activity constant of ions**

Measurement of the concentration of an ion or electrolyte in the blood does not necessarily indicate the quantity is completely available for chemical reactions, because a portion may be bound to proteins, water, or other ions. A familiar example is the serum calcium concentration, which is partly bound to serum albumin, and is partly ionized. A similar situation exists with other ions, as Dahms and others have shown. The ionized and non-ionized percentages of these ions in the blood can both be measured. However, the clinical importance of this information is still not known for most ions.

**Cation-anion balance**

Table 1 shows that the sum of the cations in serum or plasma equals 153 mEq/L and the sum of the anions also equals 153 mEq/L.

This electrical equivalence of cations and anions in serum or plasma is maintained regardless of whether the sum of the cations (and anions) is greater or less than 153 mEq/L. It may be greater, for example, when water loss occurs. It is often less that 153 mEq/L when electrolytes are lost from the body, as in vomiting or diarrhea.

All the cations can be determined clinically, although it is usual to determine only sodium, potassium, and calcium routinely. Chloride is the only anion that is routinely determined in studying electrolyte disturbances. The bicarbonate concentration can be calculated from the CO₂ content. Under ordinary conditions, it is usually between 0.6 and 1.8 mEq/L less than the CO₂ content. However, for purpose of simplicity one can calculate HCO₃ concentration by subtracting 1 mEq/L from the CO₂ content.

The sum of phosphates, sulphates, organic acid anions, and proteins is described by the symbol R.

**The significance of anions labeled R**

The term R (residual ions) was used to describe unmeasured ions, such as plasma proteins and inorganic and organic acid anions in the plasma, which may be present normally or may accumulate in some patients with metabolic acidosis.

R is calculated as follow:

\[ R = Na + K + 6.5 \text{ (the sum of Ca and Mg)} - (HCO_3 + Cl) \]

Normally, the value of R is 22 mEq/L or less.

However, measurement of the anion gap (see below) is a simpler way of describing an accumulation of abnormal anions.

**The anion gap**

The anion gap (or delta) also describes the residual or unmeasured anions.

Since the concentration of anions such as phosphates, sulphates, and organic acid and protein anions is not ordinarily measured, the sum of the measured cations (Na, K, Ca) will be greater than the sum of the measured anions (HCO₃ and Cl). This difference is known as the anion gap (or delta).

The following simple formula can be used to determine if an abnormal gap is present:

\[ \text{Anion gap} = (Na + K) - (HCO_3 + Cl) \]

Normally, the anion gap is 16 mEq/L or less. (An anion gap of less than 9 mEq/L is extremely unlikely, and is probably the result of a laboratory error).

An alternate formula for measuring the anion gap is:

\[ \text{Anion gap} = Na - (HCO_3 + Cl) \]

When this formula is used, the average, normal value for the anion gap is 12 mEq/L, with a range of 8 to 16 mEq/L.

**Example:**

<table>
<thead>
<tr>
<th>Na</th>
<th>142</th>
<th>K</th>
<th>4</th>
<th>HCO₃</th>
<th>27</th>
<th>Cl</th>
<th>103 mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anion Gap = (Na + K) – (HCO₃ + Cl).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(142 + 4) – (27 + 103)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>146 – 130 = 16 mEq/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This is normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Increased anion gap**

1. Increased unmeasured anions, such as the accumulation of lactic acid in lactic acidosis; aceto-acetic acid in diabetic ketoacidosis; organic or keto acids caused by the ingestion of salicylates, paraldehyde, and ethylene glycol; organic acids in hyperosmolar hyperglycaemic non-ketoacidotic diabetic coma; phosphoric, sulphuric, and organic acids in azotaemia; formic acid in methanol (methyl alcohol) poisoning; ketogutaric acid in hepatic failure; other anions, including high doses of (sodium) penicillin, and (sodium) carbenicillin.
2. Decreased unmeasured cations, for example, potassium, in hypokalaemia (if the alternate formula above is used); calcium in hypocalcaemia; magnesium in hypomagnesaemia.

3. Metabolic alkalosis. The plasma proteins give up H ions and increase their net negative charge. As a result, the measured anion concentration of the plasma is apparently low. In addition, alkalosis is usually associated with a decreased extracellular.

(The total anion value must equal the total cation value of the plasma. When alkalosis develops, the anion value of the proteins increases. However, the anion value of the proteins is not measured Therefore, there is a spurious decrease of the measured anions, and an apparent increase in the anion gap).

4. Increased unmeasured anions, such as increased phosphate, or sulphate ions, or due to treatment with intravenous solutions containing lactate, citrate or acetate ions.

5. Laboratory errors, with falsely high serum Na or falsely low serum Cl or HCO₃ values.

The relation of serum sodium, bicarbonate and chloride concentrations

There is another relation between the cations and anions that can be used, namely, the relation between serum sodium concentration and the sum of the serum bicarbonate and chloride ions. In Table 1, it will be noted that the most important cation is sodium, and that the most important anions are bicarbonate and chloride. In most cases, the following relations between these three ions exist:

\[ \text{Na} = \text{HCO}_3^- + \text{Cl} + 12 \text{ mEq/L} \]

Example:

\[
\begin{align*}
\text{Na} & = 142 \\
\text{HCO}_3^- & = 27 \\
\text{Cl} & = 103 \\
142 & = 27 + 103 + 12
\end{align*}
\]

In other words, if the bicarbonate and chloride ion concentration in serum or plasma are known, the concentration of sodium can be determined from these values, using the above rule.

The major exception to this rule occurs in patients with a metabolic acidosis who show an abnormal anion gap, because the abnormal anions are not ordinarily measured (see above). This increased anion concentration in the plasma causes the bicarbonate concentration to be reduced without necessarily affecting the sodium or chloride concentration.

Osmotic Pressure

A solute is a substance, such as sodium chloride, potassium phosphate, glucose, or protein, which can dissolve in a solvent, such as water, to make a solution. The measure of the osmotic pressure of the salt solution is dependent upon the number of particles or ions of the salt in a given volume of solution. In other words, a more concentrated salt solution would have a greater osmotic pressure, and a less concentrated salt solution would have a lesser osmotic pressure.

Osmotic pressure is measured in terms of osmoles (Osm) or millimoles (mOsm). An osmole (or a millimole) of a substance such as glucose, which does not dissociate into ions, is the same as a mole (or a millimole). However, a mole of a salt such as sodium chloride, which dissociates almost completely into sodium and chloride ions, equals 2 moles.

A mole of a salt such as sodium bicarbonate, which dissociates into sodium (Na) and bicarbonate (HCO₃⁻) ions, also equals 2 moles. A mole of a more complex salt such as Na₂HPO₄, which dissociates into two Na and one HPO₄⁻ ions, equals 3 moles. The total osmotic pressure of a solution therefore is calculated from the sum of all the ions in solution.

In the human, the osmotic pressure of the extracellular water and of the cells are the same. Water will flow from a region of low to a region of higher osmotic pressure.

In the human, the osmotic pressure of the extracellular water and of the cells is 310 mOsm/L. The significance of this is the following: In the extracellular fluid, sodium concentration is 142 mEq/L and the total cation concentration is 155 mEq/L. Practically all the osmotic pressure of the extracellular water is a result of monovalent salts, which ionize into two ions each. Therefore, the osmotic pressure of the extracellular water is twice the cation (or anion) concentration, or 2 x 155 = 310 mOsm/L. We can make the following assumption: Sodium is the chief cation of the extracellular water; therefore osmotic pressure should vary proportionately with the sodium concentration of the serum or plasma. In other words, we should be able to use the serum sodium concentration as measure of the osmotic pressure of the extracellular water. Unfortunately, this relationship is valid only in normal subjects.
The difference between osmotic pressure and oncotic pressure

The term “osmotic pressure” should be differentiated from the term “oncotic pressure,” or “colloid osmotic pressure.” The osmotic pressure of a solution varies with the number of molecules in a solution, as was pointed out above. When the molecular weight of a substance is low, there will be more molecules of the substance per unit weight, and the osmotic pressure will be greater. For example, a substance such as mannitol, which has a low molecular weight, will increase the osmotic pressure when given intravenously. However, a substance such as human albumin, or dextran, which has high molecular weight around 80,000, will not increase the osmotic pressure greatly. However, such a substance exerts an oncotic pressure (colloid osmotic pressure) because it is confined by a membrane (the vascular system) to which it is relatively impermeable. Therefore, an infusion of albumin or dextran will greatly increase the oncotic pressure of the blood and will prevent the loss of excessive fluid from the capillaries. However, it will have an almost negligible effect on the osmotic pressure of the blood. Oncotic pressure is measured in terms of pressure units (mm Hg).

Factors regulating the osmotic pressure and the volume of the extracellular water

We have just pointed out that a primary change of osmotic pressure, either in the extracellular water or in the cells, is associated with a shift of water into or out of the extracellular water, and consequently is associated with a change in the volume of the extracellular water.

In the maintenance of life, the body has homeostatic or regulatory mechanisms that help to maintain the osmotic pressure and the volume of the extracellular water within physiological limits. The osmotic pressure of the extracellular water is controlled by the posterior pituitary antidiuretic hormone and volume of extracellular fluid partly by the adrenal cortical hormone, aldosterone.

Hypovolaemia

Manifestations

Symptoms are usually non-specific and secondary to electrolyte imbalances and tissue hypoperfusion. These include, thirst, fatigue, weakness, muscle cramps, and postural dizziness. More severe degrees of volume contraction can lead to syncope and coma. Diminished skin turgor and dry mucous membranes are poor markers of decreased interstitial fluid. Signs of intravascular volume contraction include decreased jugular venous pressure, postural hypotension, and postural tachycardia. Mild degrees of volume depletion are often not clinically detectable. Weight loss can help estimate the magnitude of the volume deficit. Larger fluid losses often present as hypovolaemic shock, heralded by hypotension, tachycardia, peripheral vasoconstriction, and hypoperfusion-cyanosis, cold and clammy extremities, oliguria, and altered mental status. A thorough history and physical examination are generally sufficient to determine the presence and cause of ECF volume contraction. Laboratory data confirm and support the clinical diagnosis. Measurement of the fractional excretion of Na\(^+\) and BUN-creatinine ratio may provide additional diagnostic information. There may be a relative elevation in haematocrit (haemoconcentration) and plasma albumin concentration.

Aetiology

Extracellular fluid (ECF) volume depletion reflects a deficit in total body Na\(^+\) content as a result of renal or extrarenal losses that exceed Na\(^+\) intake. Renal losses may be secondary to diuretics (pharmacological or osmotic), interstitial renal disease (Na\(^+\) wasting), or...
mineralocorticoid deficiency. Excessive renal losses of Na\(^+\) and water may also occur during the diuretic phase of ATN and after the relief of bilateral urinary tract obstruction. Non-renal causes of hypovolaemia include fluid loss from the GI tract (vomiting, nasogastric suction, fistula drainage, diarrhoea), skin and respiratory losses, third-space accumulations (burns, pancreatitis, peritonitis), and haemorrhage.

**Treatment**

The therapeutic goal is to restore normovolaemia with fluid similar in composition to that which was lost, as well as to replace ongoing losses. Mild volume contraction can usually be corrected via the oral route. More severe cases of hypovolaemia require IV therapy. Patients with significant haemorrhage, anaemia, or third-spacing may require blood transfusion or colloid-containing solutions (albumin, dextran). Isotonic or normal saline (0.9% NaCl or 154 mEq/L Na\(^+\)) is the solution of choice in normonatraemic and mildly hyponatraemic individuals and should also be used initially in patients with hypotension or shock. Severe hyponatraemia may require hypertonic saline (3.0% NaCl or 513 mEq/L Na\(^+\)). Hypokalaemia may be present initially or may ensue as a result of increased urinary K\(^+\) excretion and should be corrected by adding appropriate amounts of KCl to replacement solutions. Finally, the appropriate management of hypovolaemia must include correction of the underlying cause.

**Hypernatraemia**

Hypernatraemia is defined as a plasma [Na\(^+\)] of greater than 145 mEq/L and presents a state of hyperosmolality. Maintenance of osmotic equilibrium in hypernatraemia results in ICF volume contraction and cerebral cell shrinkage. Hypernatraemia may be caused by a primary Na\(^+\) gain or water deficit. The two components of an appropriate response to hypernatraemia are increased water intake stimulated by thirst and the excretion of the minimum volume of maximally concentrated urine, reflecting vasopressin secretion in response to an osmotic stimulus.

**Aetiology**

A. **Impaired thirst**: The degree of hyperosmolality is typically mild unless the thirst mechanism is abnormal or access to water is limited. The latter occurs in infants, the physically handicapped, patients with impaired mental status, individuals in the post-operative state, and intubated patients in the ICU. Rarely, impaired thirst may be caused by primary hypodipsia, as a result of damage to the hypothalamic osmoreceptors that control thirst. Primary hypodipsia may be caused by a variety of pathologic changes, including granulomatous disease, vascular occlusion, and tumours.

B. **Hypernatraemia due to water loss** accounts for the majority of cases of hypernatraemia. Because water is distributed between the ICF and the ECF in a 2:1 ratio, a given amount of solute-free water loss results in the same percentage change but, quantitatively, a twofold greater absolute reduction in the ICF compartment than the ECF compartment.

1. **Non-renal water loss** may be due to evaporation from the skin and respiratory tract (insensible losses) or loss from the GI tract. Insensible losses are increased with fever, exercise, heat exposure, severe burns, and in mechanically ventilated patients. Diarrhoea is the most common GI cause of hypernatraemia. Specifically, osmotic diarrhoeas (induced by lactulose, sorbitol, or malabsorption of carbohydrate) and viral gastroenteritis result in water loss exceeding that of Na\(^+\) and K\(^+\).

2. **Renal water loss** is the most common cause of hypernatraemia and results from either osmotic diuresis or diabetes insipidus. The most frequent cause of an osmotic diuresis is hyperglycaemia and glycosuria in poorly controlled diabetes mellitus. IV administration of mannitol and increased production of urea (high-protein diet) can also result in an osmotic diuresis. Hypernatraemia secondary to non-osmotic urinary water loss is usually caused by (1) central diabetes insipidus (CDI) characterized by impaired vasopressin secretion or (2) nephrogenic diabetes insipidus (NDI) that results from resistance to the actions of vasopressin. The most common cause of CDI is destruction of the neurohypophysis as a result of trauma, neurosurgery, granulomatous disease, neoplasms, vascular accidents, or infection. In many cases, CDI is idiopathic and may occasionally be hereditary. NDI may either be inherited or acquired. The latter can be further subdivided into disorders associated with renal medullary disease or with impaired vasopressin action. The causes of sporadic NDI are numerous and include drugs (especially lithium),...
hypercalcaemia, hypokalaemia, and conditions that impair medullary hypertonicity (e.g., papillary necrosis or osmotic diuresis).

C. Hypernatraemia due to Na\(^+\) gain occurs infrequently. This is most commonly seen in patients with diabetic ketoacidosis (DKA) and an osmotic diuresis (urine Na\(^+\) < 50 mEq/L) treated with isotonic saline. Inadvertent administration of hypertonic NaCl or NaHCO\(_3\) or replacing sugar with salt in infant formula can also lead to hypernatraemia.

D. Transcellular water shift from ECF to ICF occurs in rare circumstances (e.g., secondary to seizures or rhabdomyolysis). Hypernatraemia is accompanied by ECF volume contraction with no change in body weight.

Manifestations
The major symptoms of hypernatraemia are neurologic and include altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, and occasionally coma or seizures. Patients may also complain of polyuria or thirst. For unknown reasons, patients with polydipsia from CDI tend to prefer ice-cold water. The signs and symptoms of volume depletion are often present in patients with a history of excessive sweating, diarrhoea, or osmotic diuresis. As with hyponatraemia, the severity of the clinical manifestations is related to the acuity and magnitude of the rise in plasma [Na\(^+\)]. Chronic hypernatraemia is generally less symptomatic as a result of adaptive mechanisms designed to defend cell volume.

Diagnosis
A complete history and physical examination often provide clues as to the underlying cause of hypernatraemia. The history should include a list of current and recent medications, and the physical examination is incomplete without a thorough mental status and neurologic assessment.

1. Assessment of urine volume and osmolality is essential in the evaluation of hyperosmolality. The appropriate renal response to hypernatraemia is excretion of the minimum volume (500 mL/day) of maximally concentrated urine (urine osmolality > 800 mOsm/kg). These findings suggest extrarenal or remote renal water loss or administration of hypertonic Na\(^+\) salt solutions. A primary Na\(^+\) excess can be confirmed by the presence of ECF volume expansion and natriuresis (urine [Na\(^+\)] usually > 100 mEq/L). Many causes of hypernatraemia are associated with polyuria and a submaximal urine osmolality. Calculation of the total daily solute excretion (24-hr urine volume x urine osmolality) is helpful in determining the basis of polyuria. To maintain a steady state, total solute excretion must equal solute production. As mentioned previously, a daily solute excretion in excess of 900 mOsm defines an osmotic diuresis. This can be confirmed by measuring urine glucose and urea.

2. CDI and NDI generally present with polyuria and hypotonic urine (urine osmolality < 250 mOsm/kg). The degree of hypernatraemia is usually mild unless the patient has an associated thirst abnormality. The clinical history, physical examination, and pertinent laboratory data can often rule out causes of acquired NDI. CDI and NDI can be distinguished by administering the vasopressin analog DDAVP (10 microgram intranasally) after careful water restriction. The urine osmolality should increase by at least 50% in CDI and does not change in NDI. The diagnosis is sometimes difficult due to partial defects in vasopressin secretion and action.

Treatment
The therapeutic goals are (1) to stop ongoing water loss and (2) to correct the water deficit. The ECF volume should be restored in hypovolaemic patients. The quantity of water required to correct the deficit can be calculated from the following equation:

\[
\text{Water deficit} = \frac{(\text{plasma } [\text{Na}^+] - 140)}{140} \times \text{total body water (in liters)}
\]

1. The rate of correction: Rapid correction of hypernatraemia is potentially dangerous due to a rapid shift of water into brain cells, increasing the risk of seizures or permanent neurologic damage. Therefore, the water deficit should be corrected slowly over at least 48-72 hours. When calculating the rate of water replacement, ongoing losses should be taken into account, and the plasma sodium should be lowered by 0.5 mEq/L/hour and by no more than 12 mEq/L over the first 24 hours. The safest route of administration of water is by mouth or via a nasogastric tube. Alternatively, half-isotonic saline can be given IV.

2. CDI: The appropriate treatment of CDI consists of administering DDAVP intranasally.

3. NDI: The concentrating defect in NDI may be
reversible by treating the underlying disorder or eliminating the offending drug. Symptomatic polyuria caused by NDI can be treated with a low Na\(^+\) diet and thiazide diuretics. This results in mild volume depletion, enhanced proximal reabsorption of salt and water, and decreased delivery to the site of action of vasopressin, the collecting duct. NSAIDs potentiate vasopressin action and thereby increase urine osmolality and decrease urine volume.

### Hyponatraemia

This is a condition in which the sodium concentration in the plasma is low (hypo means below in Greek; in this case, below 135 mmol/L).

#### Aetiology

**A. Hyponatraemia with a low plasma osmolality**

Most causes of hyponatraemia are associated with a low plasma osmolality (high ICF volume). In general, hypotonic hyponatraemia is caused either by a primary water gain or Na\(^+\) loss. The ECF volume, reflecting total body Na\(^+\) content, may be decreased, normal, or increased in hyponatraemia.

1. **Hyponatraemia associated with ECF volume depletion** may result from renal or non-renal causes of net Na\(^+\) loss. A decreased effective arterial volume stimulates thirst. It also stimulates vasopressin release from the posterior pituitary gland, which impairs the capacity to excrete a dilute urine. Hyponatraemia develops as a consequence of electrolyte-free water retention. Furthermore, certain causes of hypovolaemic hyponatraemia (e.g., diuretics or vomiting) may be associated with a large K\(^+\) deficit, resulting in transcellular ion exchange (K\(^+\) exits and Na\(^+\) enters cells), which contributes to hyponatraemia.

2. **Hyponatraemia associated with ECF volume excess** is usually a consequence of oedematous states, such as CHF, hepatic cirrhosis, and nephrotic syndrome. These disorders all have in common a decreased effective circulating volume, leading to increased thirst and vasopressin levels. The increase in total body Na\(^+\) is exceeded by the rise in total body water. The degree of hyponatraemia often correlates with the severity of the underlying condition and is therefore an important prognostic factor.

**Oliguric acute and chronic renal failure may be associated with hyponatraemia if water intake exceeds the kidney's limited ability to excrete equivalent volumes.**

3. **Hyponatraemia associated with a normal ECF volume**

- **The syndrome of inappropriate antidiuretic hormone secretion (SIADH)** is the most common cause of normovolaemic hyponatraemia. This disorder is caused by the non-physiologic release of vasopressin from the posterior pituitary or an ectopic source, resulting in impaired renal free water excretion. Common causes of SIADH include neuropsychiatric disorders, pulmonary diseases, and malignant tumours. SIADH is characterized by (1) hypotonic hyponatraemia, (2) an inappropriately concentrated urine (urine osmolality >100 mOsm/kg), (3) euvolemma, and (4) normal renal, adrenal, and thyroid function.

- **Glucocorticoid deficiency and hypothyroidism** may present with hyponatraemia and should not be confused with SIADH. Although decreased mineralocorticoids may contribute to the hyponatraemia seen in Addison's disease, it is the cortisol deficiency that leads to hypersecretion of vasopressin directly (co-secreted with corticotropin-releasing factor) and indirectly (secondary to volume depletion). The mechanisms by which hypothyroidism leads to hyponatraemia include decreased cardiac output and glomerular filtration rate (GFR) and increased vasopressin secretion in response to haemodynamic stimuli.

- **Pharmacologic agents** may cause hyponatraemia by one of at least three mechanisms: (1) stimulation of vasopressin release (e.g., nicotine, carbamazepine, tricyclic antidepressants, antipsychotic agents, antineoplastic drugs, narcotics), (2) potentiation of antidiuretic action of vasopressin [e.g., chlorpropamide, methylxanthines, non-steroidal anti-inflammatory drugs (NSAIDs)], or (3) vasopressin analogs [e.g., oxytocin, desmopressin acetate (DDAVP)].

- **Physical and emotional stress** are often
associated with vasopressin release, possibly secondary to nausea and/or hypotension associated with stress-induced vasovagal reactions.

e. **Acute hypoxia or hypercapnia** also stimulates vasopressin secretion.

f. **Psychogenic polydipsia** refers to a condition of compulsive water consumption that may overwhelm the normally large renal excretory capacity of 12 L/day. These patients often have psychiatric illnesses and may be taking medications, such as phenothiazines, that enhance the sensation of thirst by causing a dry mouth.

g. **Beer potomania** is similar to psychogenic polydipsia but with an associated lower renal excretory capacity of water. Urine can be maximally diluted to 50 mOsm/L. The low-solute and low-protein diet seen with excessive beer intake may only result in the generation of 200-250 mOsm/day (600-900 mOsm/day is normal). Thus, only 4-5 L/day of urine can be generated. Beer drunk in excess of this capacity results in hyponatraemia. A similar state, often referred to as the tea-and-toast diet, has been observed in malnourished elderly patients who maintain fluid intake without an adequate diet.

h. **Cerebral salt wasting** is a controversial and poorly understood syndrome that has been associated with neurosurgery and CNS trauma. It is purportedly distinguished from SIADH by a negative sodium balance and intravascular volume depletion after a CNS injury. The controversy centers on the tenet that the underlying hyponatraemia is best treated with hydration and saline, and not with fluid restriction.

B. **Hyponatraemia with a normal or high plasma osmolality**

1. **Pseudohyponatraemia** is hyponatraemia associated with a normal plasma osmolality. It occurs as a result of a decrease in the aqueous phase of plasma. Plasma is 93% water, with the remaining 7% consisting of plasma proteins and lipids. Because Na\(^+\) ions are dissolved in plasma water, increasing the non-aqueous phase artificially lowers the Na\(^+\) measured per liter of plasma (except when Na\(^+\) sensitive glass electrodes are used). The plasma osmolality and the Na\(^+\) measured per liter of plasma water remain normal.

2. Hyponatraemia associated with a **hyperosmolar state** is usually caused by an increase in the concentration of a solute that is largely restricted to the ECF compartment. The resulting osmotic gradient leads to water shift from the ICF to the ECF, and hyponatraemia ensues. Hypertonic hyponatraemia is usually caused by hyperglycaemia or occasionally IV administration of mannitol. Quantitatively, the plasma [Na\(^+\)] falls by 1.4 mEq/L for every 100 mg/dl rise in the plasma glucose concentration.

**Manifestations**

The clinical features of acute hyponatraemia are related to osmotic water shift leading to increased ICF volume, specifically cerebral oedema. Therefore, the symptoms are primarily neurologic, and their severity is dependent on the rapidity of onset and absolute decrease in plasma [Na\(^+\)]. Patients may be asymptomatic or may complain of nausea and malaise. As, the plasma [Na\(^+\)] falls, the symptoms progress to include headache, lethargy, confusion, and obtundation. Stupor, seizures, and coma do not usually occur unless the plasma [Na\(^+\)] falls acutely below 120 mEq/L. In chronic hyponatremia, adaptive mechanisms designed to defend cell volume occur and tend to minimize the increase in ICF volume and its symptoms.

**Diagnosis**

The underlying cause of hyponatraemia can often be ascertained from an accurate history and physical examination, including an assessment of ECF volume status and effective circulating arterial volume. Three laboratory findings often provide useful information and can narrow the differential diagnosis of hyponatraemia: (1) the plasma osmolality, (2) the urine osmolality, and (3) the urine [Na\(^+\)] + [Cl\(^-\)].

1. **Plasma osmolality**: Because ECF tonicity is determined primarily by the [Na\(^+\)], most patients with hyponatraemia have a decreased plasma osmolality. If the plasma osmolality is not low, pseudohyponatraemia and hypertonic hyponatraemia must be ruled out.

2. **Urine osmolality and volume**: The appropriate renal
**2. Oedematous states:**

1. **ECF volume contraction:** Clinical significance and requires no treatment. Mild asymptomatic hyponatraemia is generally of little importance.

The goals of therapy are threefold: (1) raise the plasma 

**Na**⁺ concentration, (2) replace the **Na**⁺ and **K**⁺ deficit(s), and (3) correct the underlying disorder. Mild asymptomatic hyponatraemia is generally of little clinical significance and requires no treatment.

1. **ECF volume contraction:** Management of asymptomatic hyponatraemia should include **Na**⁺ repletion, generally in the form of saline that is isotonic to the patient, to avoid rapid changes in ICF volume.

2. **Oedematous states:** Hyponatraemia in CHF and cirrhosis tends to reflect the severity of the underlying disease and is usually asymptomatic. Treatment should include restriction of **Na**⁺ and water intake, correction of hypokalaemia, and promotion of water loss in excess of **Na**⁺. The latter may require the use of loop diuretics with replacement of a proportion of the urinary **Na**⁺ loss to ensure net free water excretion. Dietary water restriction should be less than the urine output. Correction of **K**⁺ deficit may raise the plasma [**Na**⁺].

3. **The rate of correction of hyponatraemia** depends on the absence or presence of neurologic dysfunction. This, in turn, is related to the rapidity of onset and magnitude of the fall in plasma **Na**⁺. The risks of correcting hyponatraemia too rapidly are ECF volume excess and the development of osmotic demyelination or central pontine myelinolysis. This disorder, in its most overt form is characterized by flaccid paralysis, dysarthria, and dysphagia. The diagnosis is occasionally suspected clinically and can be confirmed by appropriate neuroimaging studies (CT scan or MRI). In addition to rapid or over-correction of hyponatraemia, risk factors for osmotic demyelination include hypokalaemia and malnutrition, especially secondary to alcoholism.

4. **Acute hyponatraemia** tends to present with altered mental status or seizures, or both, and requires more rapid correction. Severe symptomatic hyponatraemia should be treated with hypertonic saline, and the plasma **Na**⁺ should be raised only by 1-2 mEq/L/hour and by no more than 8 mEq/L during the first 24 hours. The quantity of **Na**⁺ that is required to increase the plasma **Na**⁺ concentration by a given amount can be estimated by multiplying the desired change in plasma **Na**⁺ by the total body water (e.g., 5 mEq/L x 30 L = 150 mEq = 300 ml 3% NaCl). In asymptomatic patients, the plasma **Na**⁺ should be raised by no more than 0.3 mEq/L/hour and equal to or less than 8 mEq/L over the first 24 hours.

5. **Water restriction in primary polydipsia and IV saline therapy** in ECF volume-contracted patients may also lead to overly rapid correction of hyponatraemia as a result of vasopressin suppression and a brisk water diuresis. This can be prevented by administration of water or use of a vasopressin analog to slow down the rate of free water excretion.

6. **The hyponatraemia of SIADH** can be treated by limiting the intake of water or promoting its reabsorption and a urine [**Na**⁺] of less than 20 mEq/L. The finding of a urine [**Na**⁺] of greater than 20 mEq/L in hypovolaemic hyponatraemia implies diuretic therapy, hypoaldosteronism, or occasionally, vomiting.

**Treatment**

The goals of therapy are threefold: (1) raise the plasma [**Na**⁺] (lowering the ICF volume) by restricting water intake and promoting water loss, (2) replace the **Na**⁺ and **K**⁺ deficit(s), and (3) correct the underlying disorder.

- **ECF volume contraction:**
  - Management of asymptomatic hyponatraemia should include **Na**⁺ repletion, generally in the form of saline that is isotonic to the patient, to avoid rapid changes in ICF volume.

- **Oedematous states:** Hyponatraemia in CHF and cirrhosis tends to reflect the severity of the underlying disease and is usually asymptomatic. Treatment should include restriction of **Na**⁺ and water intake, correction of hypokalaemia, and promotion of water loss in excess of **Na**⁺. The latter may require the use of loop diuretics with replacement of a proportion of the urinary **Na**⁺ loss to ensure net free water excretion. Dietary water restriction should be less than the urine output. Correction of **K**⁺ deficit may raise the plasma [**Na**⁺].

3. **Urine **Na**⁺ concentration:** Because **Na**⁺ is the major ECF cation and is largely restricted to this compartment, ECF volume contraction represents a deficit in total body **Na**⁺ content. Therefore, volume depletion in patients with normal underlying renal function results in enhanced tubule **Na**⁺ reabsorption and a urine [**Na**⁺] of less than 20 mEq/L. The finding of a urine [**Na**⁺] of greater than 20 mEq/L in hypovolaemic hyponatraemia implies diuretic therapy, hypoaldosteronism, or occasionally, vomiting.

6. **The hyponatraemia of SIADH** can be treated by limiting the intake of water or promoting its reabsorption and a urine [**Na**⁺] of less than 20 mEq/L. The finding of a urine [**Na**⁺] of greater than 20 mEq/L in hypovolaemic hyponatraemia implies diuretic therapy, hypoaldosteronism, or occasionally, vomiting.
Fig. 2: Differential diagnosis of hyponatraemia.
Excretion, or both. The standard first-line therapy is water restriction. If this fails or if the patient is symptomatic, agents that enhance water excretion can be tried. Loop diuretics impair the ability to excrete concentrated urine and, when combined with Na\(^+\) replacement in the form of salt tablets, can enhance free water excretion. In SIADH, the urine osmolality is relatively fixed. Therefore, the maximum urine output is a direct function of the solute excretion rate, which can be increased by dietary modification (high salt, high protein) or by administering urea, leading to increased urine output and water excretion. Drugs that interfere with the collecting tubules ability to respond to vasopressin include lithium and demeclocycline. These agents are rarely used and should only be considered in severe hyponatraemia that is unresponsive to more conservative measures.

**Hypokalaemia**

Hypokalaemia refers to the condition in which the concentration of potassium in the blood is low. The prefix hypo- means low (contrast with hyper-, meaning high). Kal refers to kalium, the Neo-Latin for potassium, and -emia means “in the blood”.

Normal serum potassium level is between 3.5 to 5.0 mEq/L. At least 95% of the body’s potassium is found inside cells, with the remainder in the blood. This concentration gradient is maintained principally by the Na\(^+/K^+\)-ATPase pump.

**Pathophysiology**

- Potassium is essential for many body functions, including muscle and nerve activity
- Decreased potassium levels in the extracellular space will cause hyperpolarization of the resting membrane potential
- In certain conditions, this will make cells less excitable. However, in the heart, it causes myocytes to become hyperexcitable.
- This delayed repolarization may promote reentrant arrhythmias

**Aetiologies**

- Renal losses
  - Renal tubular acidosis
  - Hyperaldosteronism
  - Magnesium depletion
- GI losses
  - Vomiting or nasogastric suctioning
  - Diarrhoea
  - Enemas or laxative use
  - Ileal loop
- Medication effects
  - Diuretics (most common cause)
  - Beta-adrenergic agonists
  - Steroids
  - Theophylline
  - Aminoglycosides
- Transcellular shift
  - Insulin
  - Alkalosis
- Malnutrition or decreased dietary intake, parenteral nutrition

**Manifestations**

**History**

The history may be vague
Common symptoms include the following:
- Palpitations
- Skeletal muscle weakness or cramping
- Paralysis, paraesthesias
- Constipation
- Nausea or vomiting
- Abdominal cramping
- Polyuria, nocturia, or polydipsia
- Psychosis, delirium, or hallucinations
- Depression

**Physical examination**

- Signs of ileus
- Hypotension
- Ventricular arrhythmias
- Cardiac arrest
- Bradycardia or tachycardia
- Premature atrial or ventricular beats
- Hypoventilation, respiratory distress
- Respiratory failure
- Lethargy or other mental status changes
- Decreased muscle strength, fasciculations, or tetany
- Decreased tendon reflexes
- Cushingoid appearance (e.g., oedema)
**Lab studies**
- Serum potassium level <3.5 mEq/L (3.5 mmol/L)
- BUN and creatinine level
- Glucose, magnesium, calcium, and/or phosphorus level if co-existent electrolyte disturbances are suspected.
- Consider digoxin level if the patient is on a digitalis preparation; hypokalaemia can potentiate digitalis-induced arrhythmias
- Consider arterial blood gas (ABG). Alkalosis can cause potassium to shift from extracellular to intracellular space

**Imaging studies**
- CT scan of the adrenal glands is indicated if mineralocorticoid excess is evident (rarely needed emergently)

**Electrocardiography** (Figure 3)
- T-wave flattening or inverted T waves
- Prominent U wave that appears as QT prolongation
- ST-segment depression
- Ventricular arrhythmias (e.g., premature ventricular contractions [PVCs], torsade de pointes, ventricular fibrillation)
- Atrial arrhythmias (e.g., premature atrial contractions [PACs], atrial fibrillation)

**Treatment**

**Pre-hospital care**
- Be attentive to the ABCs.
- If the patient is severely bradycardic or manifesting cardiac arrhythmias, appropriate pharmacologic therapy or cardiac pacing should be considered.

**Emergency department care**
- Patients in whom severe hypokalaemia is suspected should be placed on a cardiac monitor; establish intravenous access and assess respiratory status.
- Direct potassium replacement therapy by the symptomatology and the potassium level. Begin therapy after laboratory confirmation of the diagnosis.
- Usually, patients who have mild to moderate hypokalaemia (potassium of 2.5-3.5 mEq/L), are asymptomatic, or have only minor symptoms and need only oral potassium replacement therapy. If cardiac arrhythmias or significant symptoms are present, then more aggressive therapy is warranted. This treatment is similar to the treatment of severe hypokalaemia.
- If the potassium level is less than 2.5 mEq/L, intravenous potassium should be given. Admission or observation in emergency department is indicated; replacement therapy takes more than a few hours.
- Serum potassium level is difficult to replenish if serum magnesium level is also low. Look to replace both.

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![Fig. 3: ECG showing prominent U waves after T waves and a premature ventricular ectopic (interposed between two QRS complexes).](image-url)
Medication

**Potassium chloride**

Potassium depletion sufficient to cause 1 mEq/L drop in serum potassium indicates loss of about 100-200 mEq of potassium from total body store. In the symptomatic patient with severe hypokalaemia, administer up to 40 mEq/h of this IV preparation; maintain close follow-up; provide continuous ECG monitoring, and check serial potassium levels. Higher dosages may increase risk of cardiac complications.

**Adult dose** 10-20 mEq/h IV via peripheral or central line

**Pediatric dose** 0.5-1 mEq/kg/dose over 1 h; not to exceed adult maximum dose

**Contraindications**

Hyperkalaemia; renal failure; conditions in which potassium is retained; oliguria or azotaemia; crush syndrome; severe haemolytic reactions; anuria; adrenocortical insufficiency

**Precautions**

Do not infuse rapidly; high plasma concentrations of potassium may cause death due to cardiac depression, arrhythmias, or arrest; plasma levels do not necessarily reflect tissue levels; monitor potassium replacement therapy whenever possible by continuous or serial ECGs; when concentration >40 mEq/L infused, local pain and phlebitis may occur.

Follow-up

**Further inpatient care**

- Continue intravenous replacement of potassium as needed.
- Continue cardiac monitoring in severe hypokalaemia.
- Repeat potassium level measurement every 1-3 hours.
- Identify the aetiology of the hypokalaemia.

**Further outpatient care**

- Repeat potassium level in 2-3 days.

**Inpatient or outpatient medication**

- Consider switching to potassium-sparing diuretic if diuretic therapy is needed.
- Take 40 mEq KCl daily for 2-3 days and repeat the potassium level.

Complications

- Replacing potassium too quickly can cause a rapid rise in the blood potassium level, leading to a relative hyperkalaemia with subsequent cardiac complications.
- If hypokalaemia is not corrected easily with replacement therapy, search for other co-existent metabolic abnormalities (e.g., hypomagnesaemia). Hypokalaemia may be refractory to treatment until hypomagnesaemia is corrected.
- Hypokalaemia can potentiate digitalis toxicity in patients who are taking digoxin.

Patient education

- Diet modification is recommended for those patients who are predisposed to hypokalaemia. Increase intake of bananas, tomatoes, oranges, and peaches because they are high in potassium.

Special concerns

- Do not overcorrect potassium in patients with periodic hypokalaemic paralysis. This condition is a transcellular maldistribution, not a true deficit.
- Diuretic therapy, diarrhoea, and chronic laxative abuse are the most common causes of hypokalaemia in elderly patients.
- In patients with hypokalaemia and diabetic ketoacidosis, part of the serum potassium should be administered as potassium phosphate.

Hyperkalaemia

**Hyperkalaemia** is defined as potassium level greater than 5.5mEq/L. Based on serum potassium concentration, hyperkalaemia can be divided into mild, moderate or severe.

- **Mild** : 5.5 - 6.0 mEq/L
- **Moderate** : 6.1 - 7.0 mEq/L
- **Severe** : > 7 mEq/L

**Etiologies of hyperkalaemia**

1. Intercompartmental shift:
   - Acidosis
   - Hypertonicity
   - Rhabdomyolysis
   - Succinylcholine
   - Digoxin intoxication

Electrolyte and Acid-Base Disturbances  •  APICON 2009  •  Jan. 29 - Feb. 1, 2009 17
Hyperkalaemic familial periodic paralysis
2. Decreased renal potassium excretion
   - Renal failure
   - Decreased mineralocorticoid activity
   - Defective tubular secretion (renal tubular acidosis 2 & 4)
   - Drugs (Spironolactone, ACE inhibitors, cyclosporine, NSAIDs)
3. Increased potassium intake
   - Salt substitute
4. Pseudohyperkalaemia
   - Haemolysis
   - Thrombocytosis
   - Leucocytosis
   - Improper venepuncture technique (ischaemic blood drawn due to prolonged tourniquet application)

Clinical manifestations

**Skeletal and cardiac muscle**

Skeletal muscle weakness is seen when potassium level is greater than 8 mEq/L. It occurs due to spontaneous sustained depolarization and inactivation of sodium channels on muscle membrane resulting in ascending paralysis. Cardiac manifestations occur when potassium level is above 7 mEq/L. This results in delayed depolarization of cardiac muscles.

Various signs and symptoms of hyperkalaemia include the following:

- Generalised fatigue
- Weakness
- Paraesthesias
- Paralysis (Decreased motor power, diminished deep tendon reflexes)
- Palpitations, extrasystoles
- Bradycardia, junctional rhythm, heart blocks
- Hypoventilation (rare)
- Signs of trauma (leading to hyperkalaemia)
- Signs of renal failure (oedema, skin changes)
- Death occurs from cardiac arrest

ECG features

1. Peaking of T waves and shortened QT interval
2. Potassium > 6 mEq/L produces wide QRS (Bundle branch block)
3. Potassium > 7 mEq/L produces wide p wave, delayed AV conduction, prolonged PR interval
4. Potassium >7.5 mEq/L leads to cessation of atrial contraction and QRS widens resembling a sine wave. Death occurs due to ventricular fibrillation or cardiac arrest.

**Management of hyperkalaemia**

Diagnosis depends upon lab. studies, clinical features and ECG changes.

1. Calcium gluconate
   - Intravenous 10 ml calcium gluconate 10% over 2-5 minutes.
   - Onset of action – 5 minutes
   - Duration of action – 30-60 minutes
   - Repeat dose in 3-5 minutes
   - Mechanism of action – Potassium antagonism and membrane stabilization

2. Insulin-dextrose infusion
   - Mechanism of action – Intracellular shift of potassium
   - Onset of action – 20-30 minutes
   - Dose – 10 to 20 units regular insulin and 25-50 g glucose

3. Intravenous infusion of sodium bicarbonate
   - Mechanism of action – Intracellular shift of potassium
   - Dose – 8.4% solution in children and adults and 4.2% in infants. Give 1 mEq/Kg slow intravenously as infusion.
   - Precaution – Bicarbonate can bind with calcium; therefore, administer bicarbonate 30-60 minutes after calcium gluconate.

4. Beta 2 agonist (salbutamol)
   - Promotes cellular uptake of potassium via cyclic GMP receptor cascade.
   - Dose – 5-20 mg mixed with 5 mL of saline via a high flow nebulizer over 20 minutes.

5. Diuretics
   - Furosemide 20-40 mg intravenously
   - Onset of action – 60 minutes

6. Sodium polystyrene sulfonate (Kayexalate)
   - Dose – 10-15 g mixed with 100 mL of 20% sorbitol orally or per rectally

7. Dialysis is the most effective method when other methods fail.
2. Acid-Base Disturbances

Praveen Aggarwal

Disturbances in acid-base balance are commonly encountered in the intensive care units and emergency departments. These disorders may be life-threatening in themselves without regard to the underlying conditions causing them. Appropriate diagnosis and management of these disorders in an acutely ill patient require accurate and timely interpretation of specific data. Physicians must be able to interpret the “numbers” rapidly and accurately. In the present topic, a brief of physiological mechanisms by which acid-base balance is maintained in the body will be discussed. This will be followed by various definitions used in acid-base disorders, and detailed description of acid-base disorders and their treatments. Finally, step-by-step approach to analyze acid-base disturbance will be discussed which will be followed by a case to illustrate various principles of acid-base interpretation.

Normal Physiology of Acid-Base Balance

Acids are produced continuously during normal metabolism of body. About 20,000 mmol of carbonic acid and 80 mEq of non-volatile acids are produced daily. Despite this, the pH of extracellular fluid is maintained between 7.36-7.44. The defense against fluctuations in pH is provided by three physiological buffer systems, respiratory mechanics and renal mechanics.

A. Physiological buffers

The body buffers which are primarily weak acids, are able to take up or release H⁺ so that changes in the free H⁺ concentration are minimized. In the body, three type of physiological buffers exist. These are as follows:

1. The major physiological buffer is the bicarbonate-carbonic acid system. Bicarbonate is converted into water and carbon dioxide whenever H⁺ ions are added. Carbon dioxide thus liberated is excreted by the lungs. As the total buffering capacity of this system is about 15 mEq/L, at normal rate of production of non-volatile acids, the buffers will be depleted within a period of 15-20 days. However, kidneys have the ability to regenerate bicarbonate and therefore help in maintaining the buffering capacity of the extracellular fluid (ECF). Other minor buffers in ECF include phosphates and proteins.

2. The second physiological buffers are the intracellular proteins, of which, haemoglobin is most important. It can buffer large amounts of H⁺ ions without disturbing the pH. In the red cells, carbon dioxide combines with water to form carbonic acid which dissociates to produce H⁺ ions that are buffered by haemoglobin. Other buffers are intracellular proteins and phosphates.

3. Bone contains large amount of bicarbonate and can buffer parts of acute acid load. An acid load is associated with uptake of some of the excess H⁺ ions by bone. This can occur in exchange for surface Na⁺ and K⁺, and by dissolution of bone mineral, resulting in the release of buffer compounds such as NaHCO₃ and KHCO₃, initially and then CaCO₃ and CaHPO₄ into extracellular fluid. The role of bone buffers may be even greater in the presence of a chronic acid retention, such as seen in patients with chronic renal failure.

B. Pulmonary mechanisms

The principal volatile acid of metabolism is carbon dioxide which is equivalent to potential carbonic acid. The normal concentration of carbon dioxide in the body is maintained around 1.2 mmol/L by the lungs. At this concentration, the pulmonary excretion equals the metabolic production of carbon dioxide.

C. Renal mechanisms

Kidneys reabsorb the filtered bicarbonate and also regenerate fresh bicarbonate. Bicarbonate is reabsorbed both in the proximal (75%) and distal segments (25%) by secretion of protons into the tubular fluid. For each molecule of bicarbonate filtered, one molecule is added to the blood by this mechanism (Figure 1).

New bicarbonate is regenerated by secretion of
protons onto urinary buffers. About one-third is titrated to phosphate while the remaining is secreted as ammonium. (Figure 2 and Figure 3).

The net acid excretion by kidneys = urinary NH₄⁺ plus urinary “titrable acid” (H₂PO₄⁻) minus urinary HCO₃⁻. Urinary bicarbonate is almost nil.

The rate of proton secretion by the kidneys is influenced by a number of factors:

1. **Carbon dioxide tension**: Bicarbonate reabsorption is directly related to the ECF carbon dioxide tension. Hypercaponea stimulates and hypocaponea inhibits renal bicarbonate reabsorption.

2. **Extracellular fluid volume**: Contraction of extracellular volume enhances renal bicarbonate reabsorption.

3. **Aldosterone levels**: Hyperaldosteronism stimulates bicarbonate reabsorption by the kidneys and can lead to alkalosis.

4. **Body potassium stores**: Severe potassium depletion produces increased hydrogen ion secretion and therefore produces alkalosis due to increased bicarbonate reabsorption.

**Evaluation of Acid-Base Status**

Evaluation of acid-base status of a patient is dependent upon changes in the major buffer i.e., the bicarbonate-carbonic acid system. The relationship between bicarbonate and carbonic acid is described by the Henderson-Hasselbach equation:

\[
\text{pH} = \text{pK}_a \times \log \frac{\text{Bicarbonate}}{\text{Carbonic acid}}
\]

\( \text{pK}_a \) is known as the dissociation constant and for carbonic acid-bicarbonate system, it is 6.1. Carbonic acid can be expressed as dissolved carbon dioxide and equals \( \alpha \times \text{pCO}_2 \) where \( \alpha \) represents solubility coefficient and equals 0.031 mmol/L/mmHg of CO₂. At a \( \text{pCO}_2 \) of 40 mmHg, carbonic acid will be 1.2 mmol/L. The arterial blood gas analyzers measure the pH and \( \text{pCO}_2 \) and bicarbonate concentration is calculated using the above-mentioned formula. By modifying the equation stated above, a more practical equation can be derived:

\[
\text{H}^+ \text{ in nmol/L} = 24 \times \frac{\text{pCO}_2}{\text{HCO}_3^-}
\]

At a pH of 7.4, the \( \text{H}^+ \) concentration is 40 nmol/L.

It is also important to check the validity of results
obtained by the blood gas analyzer. For this above-
mentioned equation is used to calculate the hydrogen
ion concentration and the same is also derived from pH
(Table 1). If there is discrepancy between the two results,
the blood should be analyzed again.

Table 1: Relation between pH and Hydrogen ion
concentration

<table>
<thead>
<tr>
<th>pH</th>
<th>7.7</th>
<th>7.6</th>
<th>7.5</th>
<th>7.4</th>
<th>7.3</th>
<th>7.2</th>
<th>7.1</th>
<th>7.0</th>
<th>6.9</th>
<th>6.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>H+</td>
<td>20</td>
<td>25</td>
<td>32</td>
<td>40</td>
<td>50</td>
<td>64</td>
<td>80</td>
<td>101</td>
<td>128</td>
<td>160</td>
</tr>
<tr>
<td>(nmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example:
pH = 7.2, pCO₂ = 30, HCO₃ = 22
64 = 24 x 30/22
64 ≠ 32 (LAB ERROR)

Common Terms used in Evaluation of Acid-
Base Status

Several terms are used in the evaluation of acid-base
disorder.

Acidaemia: A state when blood pH is below 7.36
Alkalaemia: A state when blood pH is above 7.44
Acidosis: Any disorder which adds acid or removes base
from the body
Alkalosis: Any disorder which adds alkali or removes
acid from the body.

(Note: In general, acidosis induces acidaemia and alkalosis
induces alkalaemia. However, the difference between these
phenomenon becomes important in those patients who have
mixed acid-base disturbances in which both acidic and
alkalotic processes may coexist. In this setting, the net pH
may be acadaemic, even though a disorder which induces
an alkalosis is also present).

Respiratory disorders: Disorders where there is
alteration in carbon dioxide concentration initially.

Metabolic disorders: Disorders which affect the
bicarbonate concentration initially.

Besides these basic terms, a standard blood gas machine
measures certain parameters which may be required in
some patients. These are discussed below.

1. Buffer base and standard bicarbonate: To recognize
and quantify metabolic disorders, changes in plasma
bicarbonate are usually evaluated. However, since
plasma bicarbonate concentration is also affected
by changes in pCO₂, i.e., the respiratory disturbances,
buffer base and standard bicarbonate have been used
to indicate purely metabolic changes. Standard
bicarbonate is the bicarbonate concentration in
plasma in a completely oxygenated blood sample
equilibrated with a pCO₂ of 40 mmHg at 37°C. A
standard bicarbonate value below 24 mmol/L
indicates metabolic acidosis and above 24 mmol/L
metabolic alkalosis. This conclusion is based on the
assumption that titration of whole-blood with CO₂
produces the same bicarbonate variations in-vitro
and in-vivo. Unfortunately, this is not always the
case. Buffer base represents the total equivalent
concentration of all anionic (basic) buffer
components of the blood, namely hemoglobin,
bicarbonate, plasma proteins and phosphates. It is
normally 48 mmol/L.

2. Base excess or base deficit: Base excess indicates
the deviation of base buffer from its normal value.
It can also be defined as the number of mmol of
strong acid that is needed to adjust the pH to 7.4
when blood is equilibrated at a pCO₂ of 40 mmHg.
It is calculated from pH, paCO₂ and haemoglobin.
An increase in the amount of buffer base is termed
as base excess while a decrease may be referred to
as a base deficit or negative base excess. The BE of
oxygenated blood with an Hb of 15 g/dl at a pH of
7.4 and pCO₂ of 40mmHg is zero. The BE is strongly
influenced by the Hb concentration, which is the
main buffer in blood.

3. Standard base excess: It was noted that changes in
pCO₂ on HCO₃ in vivo differed from that observed
in-vitro and that the discrepancy could be reduced
by using a Hb value of 5 g/dL. This empiric value
was presumed to reflect the average concentration
of Hb of the fluid space through which bicarbonate
distributes (between Hb of 15 g/dl in blood to Hb
of 0 g/dl in extracellular fluid). This was called the
standard base excess (SBE). As the SBE was
independent of pCO₂, it was used to define the
metabolic component of an acid-base disturbance.
However, this has not been found useful in many
cases and its use is infrequent in analysis of acid-
base disorders.

4. Calculated oxygen saturation (%sO₂c): It is
calculated assuming that the oxyhaemoglobin
dissociation curve is not shifted. It will be affected
if carboxyhaemoglobin is also present in the sample.

Anion Gap
An important tool employed in evaluating metabolic
acidosis is anion gap. It is calculated as: (Na\(^+\)) - (HCO\(_3\) + Cl\(^-\)) and is equal to 8-12 mmol/L. This is because of presence of unmeasured anions. Table 2 lists commonly present anions and cations which are not measured routinely. Since major anion is albumin, AG must always be corrected if patient has significant hypoalbuminaemia. For every 1 g/dL albumin below 4 g/dL, add 2.5 to the calculated serum AG.

Table 2: Unmeasured anions and cations

<table>
<thead>
<tr>
<th>Unmeasured Cations</th>
<th>Unmeasured Anions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 11 mEq/L</td>
<td>Total 23 mEq/L</td>
</tr>
<tr>
<td>Potassium 4</td>
<td>Sulphates 1</td>
</tr>
<tr>
<td>Calcium 5</td>
<td>Phosphates 2</td>
</tr>
<tr>
<td>Magnesium 2</td>
<td>Albumin 16</td>
</tr>
<tr>
<td></td>
<td>Lactic acid 1</td>
</tr>
<tr>
<td></td>
<td>Org. acids 3</td>
</tr>
</tbody>
</table>

Example:

A patient has following ABG values: pH 7.20; pCO\(_2\) 26; HCO\(_3\) 10; Na\(^+\) 139; Cl\(^-\) 110. His albumin is 2 g/dL.

The anion gap = 139 – (110 + 10) = 19 mmol/L

Albumin correction: 2.5 x 2 = 5 mmol/L

Corrected Anion Gap: 19 + 5 = 24 mmol/L

Alterations in the concentration of unmeasured ions can lead to misestimation of the baseline AG. As an example, both hypoalbuminaemia (reduced unmeasured anions) and hyperkalaemia (increased unmeasured cations) can lower the AG. Thus a patient with one or both of these disorders may have a baseline AG of 2 rather than 8 meq/L. In this setting, an AG of 14 meq/L, which is only mildly above the normal limit, represents a true elevation in the AG of as much as 12 meq/L.

**Metabolic Acidosis**

Metabolic acidosis is initiated by a reduction in plasma bicarbonate concentration. A pH < 7.2 may be life threatening because (i) the enzyme systems become unreliable, (ii) electrolyte concentration is altered, (iii) electrophysiological functions of the body become unreliable and this includes impaired cardiac contractility and reduced threshold for ventricular fibrillation, and (iv) the autonomic responses to drugs are altered.

**Compensation in metabolic acidosis**

Because of increased H\(^+\) ion concentration in ECF, there is a shift of H\(^+\) from the ECF to intracellular fluid while potassium comes out from the cells into ECF resulting in hyperkalaemia. The reduced pH stimulates the central respiratory centre leading to hyperventilation and reduction in carbon dioxide. This in turn reduces the changes in pH produced by the initial pathology. For each 1 mEq/L decrease in bicarbonate, CO\(_2\) reduces by 1.2 mmHg. Winter’s formula for determining compensation in metabolic acidosis is:

\[ pCO_2 = 1.5 [HCO_3^-] + 8 \pm 2 \]

However, full compensation of pH does not occur and in acute metabolic acidosis, the minimum CO\(_2\) which can be achieved is 10 mmHg while in chronic acidosis, it is 15 mmHg.

**Pathophysiology**

Metabolic acidosis can be caused by three mechanisms:

1. Increased production of acids.
2. Decreased excretion of acids by the kidneys
3. Loss of alkali from the body

**Anion gap**

An important tool employed in evaluating metabolic acidosis is anion gap. It is calculated as: (Na\(^+\)) - (HCO\(_3\) + Cl\(^-\)) and is equal to 8-12 mmol/L. This is because of presence of unmeasured anions. Increased accumulation of these unmeasured anions leads to acidosis with raised anion gap. In some patients of acidosis, there is exchange of bicarbonate with chloride leading to loss of bicarbonate and hyperchlorinaemia. This leads to a normal anion gap with acidosis.

It is important to calculate AG in all patients when acid-base interpretation is being done. An AG > 12 mmol/L can indicate metabolic acidosis while an AG > 20 mmol/L always indicates metabolic acidosis.

Diabetic ketoacidosis is typically associated with an elevated AG. If renal function and volume status is well maintained, however, some or many of the excess ketone anions may be excreted in the urine as the sodium and potassium salts. The net effect is that the rise in the AG may be much less than expected from the severity of metabolic acidosis. Furthermore, the loss of these organic anions is equivalent to the loss of bicarbonate, since metabolism of ketoacid anions results in regeneration of bicarbonate. Thus a normal AG acidosis is typically seen during the treatment phase of DKA due to the urinary loss of these bicarbonate precursors.
**Aetiology**

Important causes of metabolic acidosis are listed in Table 3.

**Table 3: Causes of metabolic acidosis**

*Increased Anion Gap*
1. Severe renal failure
2. Increased production of organic acids
   a. Diabetic ketoacidosis
   b. Alcoholic ketosis
   c. Starvation ketosis
   d. Poisonings: Methanol, salicylates, ethylene glycol, carbon monoxide, cyanide
   e. Increased lactic acid production:
      - Cardiorespiratory arrest
      - Convulsions
      - Shock
      - Septicaemia
      - Liver failure

*Normal anion gap (Hyperchlorinaemia)*
1. Diarrhea (Loss of alkali)
2. Potassium sparing diuretics (renal tubular dysfunction)

Another way to remember various causes is given below (Table 4)

**Table 4. Causes of Metabolic Acidosis**

<table>
<thead>
<tr>
<th>High Anion Metabolic Acidosis (MUDPILES-R)</th>
<th>Non-anion Gap Metabolic Acidosis (HARDUPS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>Hyperalimentation</td>
</tr>
<tr>
<td>Uraemia</td>
<td>Acetazolamide, amphotericin</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>Paraldehyde</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Iron, INH</td>
<td>Ureteral diversions</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>Pancreatic fistula</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Saline resuscitation</td>
</tr>
<tr>
<td>Salicylates</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical features**

Features of metabolic acidosis are non-specific. The patients usually hyperventilate due to stimulation of respiratory centre. This is called Kussmaul’s breathing that is characterised by increased rate as well as tidal volume of breath. This can produce respiratory fatigue in seriously ill patients. Other non-specific features include fatigue, confusion, coma, and cardiovascular features due to vasodilatation and reduced cardiac contractility which may lead to shock and cardiac failure. Presence of hyperkalaemia (due to shift of intracellular potassium) may mask significant loss of potassium from body stores. Presence of hypokalaemia in metabolic acidosis indicates severe potassium loss from the body.

**Diagnosis**

The first step is to calculate whether the patient has adequate respiratory compensation or whether he has associated other acid-base disorders. The next step is to calculate anion gap, delta-delta ratio and osmolar gap. Urinary anion gap (UAG) may be of some use in differential diagnosis.

**Delta-Delta ratio or delta ratio**

\[
\text{Delta ratio} = \frac{\text{Increase in Anion Gap}}{\text{Decrease in bicarbonate}}
\]

The normal value is between 1 and 1.6. A low delta gap suggests the presence of a concomitant non-gap acidosis, whereas a delta gap greater than 1.6 suggests the presence of a concomitant metabolic alkalosis.

It might be assumed that there is a 1:1 relationship between the increase in AG (\( \Delta AG \)) and the decrease in plasma bicarbonate (\( \Delta HCO_3^- \)). However, the \( \Delta / \Delta \) ratio is typically greater than 1 in lactic acidosis, since the space of distribution of the hydrogen ion and the lactate anion are different. Most of the lactate anions remain in the extracellular fluid, thereby raising the AG. In comparison, more than 50 per cent of the excess hydrogen ions is buffered in the cells and in bone in mild metabolic acidosis, a process that does not lower the plasma bicarbonate concentration. Thus, the rise in anion gap tends to exceed the reduction in the plasma bicarbonate concentration in lactic acidosis.

In ketoacidosis, the \( \Delta / \Delta \) ratio averages about 1:1. In this disorder, the loss of ketoacid anions in the urine lowers the AG without affecting the plasma bicarbonate concentration, therefore tending to balance the effect of intracellular buffering of hydrogen. The amount of ketoacid anions excreted in ketoacidosis depends on the degree to which glomerular filtration is maintained. Patients with impaired renal function (due to underlying diabetic nephropathy or volume depletion) will retain the ketoacid anions and have a relatively high anion gap in relation to the fall in the plasma bicarbonate concentration.
concentration, similar to that in lactic acidosis.

**Delta gap**

Another term used in the analysis of acid-base disorder is the delta gap. In pure high anion gap metabolic acidosis, for every 1 mEq/L rise in anion gap, there should be a concomitant fall of 1 meq/l in bicarbonate. Any significant deviation from this relationship suggests presence of a mixed acid-base disorder. This can be expressed as the delta gap. It equals deviation in anion gap from normal minus deviation in bicarbonate from normal. The usual range of delta gap is -6 to +6 and in case of a pure high anion gap metabolic acidosis, it should be zero. If the calculated delta gap is > 6, this suggests that the bicarbonate has not dropped to the expected extent and thus there is concomitant metabolic alkalosis or rarely respiratory acidosis. A delta gap of lesser than – 6 implies a greater loss of bicarbonate than can be accounted for by the metabolic acidosis and suggests a concurrent normal anion gap metabolic acidosis or rarely respiratory alkalosis. However, the information gained from delta gap is same as that gained from delta-delta ratio.

**Osmolar gap**

Osmolality of a solution is the number of osmoles of solute per kilogram of solvent. Osmolarity of a solution is the number of osmoles of solute per litre of solution. The osmolar gap is the difference between the measured osmolality and the calculated osmolarity.

Calculated osmolarity: 2 (Na\(^+\)) + glucose/18 + BUN/2.8

Normal osmolar gap is < 10 mOsm/L. It is elevated in several conditions including poisoning with ethanol, methanol, and ethylene glycol.

**Urinary anion gap**

In normal circumstances, urine is free of HCO\(_3\). Spot urine electrolytes are measured to calculate UAG. NH\(_4\) is the predominant unmeasured cation in urine. It is accompanied by Cl\(^-\).

\[
\text{UAG} = \text{Na}^+ + \text{K}^+ - \text{Cl}^- \\
\text{Normal UAG} = -20 \text{ to positive}
\]

If non-renal source of non-anion gap metabolic acidosis is present (e.g., diarrhea), there is dramatic increase in NH\(_4\) excretion in urine and therefore UAG becomes more negative ( < -20 and may even become -50). If patient has renal tubular acidosis (RTA), UAG is positive (exception is type 2 RTA). UAG is not useful in oliguria and hypovolaemia.

**Urine pH**

In non-anion metabolic acidosis, urine pH may be useful if the source of loss of fluids is not from intestines. If urine pH > 5.5, type 1 renal tubular acidosis is likely. If urine pH < 5.5, check serum potassium. If serum potassium is low, RTA type 2 is likely; if serum potassium is high, type 4 RTA is likely.

**Treatment**

Whenever possible, efforts should be directed at identifying and treating the underlying process which gave rise to metabolic acidosis. When metabolic acidosis results from inorganic acids (i.e., hyperchloremic or normal anion gap acidosis), HCO\(_3\) is required to treat the acid-base disturbance. However, when acidosis results from organic acid accumulation (ie, increased anion gap acidosis), as in lactic acidosis, ketoacidosis, or the intoxication syndromes, the role of NaHCO\(_3\) is controversial. Use of intravenous sodium bicarbonate should be restricted to patients with severe acidosis i.e., bicarbonate < 6 mEq/L.

In normal individuals, approximately equal amounts of H\(^+\) are buffered by ECF bicarbonate and ICF buffers. Therefore, half of the administered bicarbonate will accept H\(^+\) from ICF and will be destroyed. Hence, the dose of bicarbonate required = Desired increase in plasma bicarbonate x 40% of body weight (40% is double the ECF volume). This volume of 40% of body weight is called bicarbonate space. In severe acidosis, bicarbonate space may be large due to intracellular shift of H\(^+\) and buffering of H\(^+\) by bone and cellular buffers. Therefore, frequent determinations of acid-base status are required. Half of the calculated bicarbonate should be administered first and acid-base estimation is repeated after that before further bicarbonate is administered.

**Example:**

A patient weighing 70 kg has following blood gas values:

\[\text{pH} = 7.1; \text{pCO}_2 = 20 \text{ mmHg; HCO}_3 = 6 \text{ meq/L}\]

The pH should be raised to 7.2. At the pH of 7.2, the H\(^+\) concentration will be 65 nmol/L. Therefore, using the modified Henderson-Hasselbach formula,

\[65 = 24 \times 20/\text{HCO}_3 \text{ or HCO}_3 = 8 \text{ meq/L}\]

Presuming bicarbonate space of 70%, the amount of bicarbonate required to increase pH to 7.2 will be:
Desired increase in bicarbonate x bicarbonate space x weight
= 2 x 70/100 x 70 = 98 mEq

Initially, half of this i.e., 50 mEq should be administered intravenously. If situation is not very urgent, it may be administered over a period of 15 minutes.

Dangers of bicarbonate: There are some dangers of bicarbonate therapy, particularly when administered in excess, and due to these limitations, bicarbonate therapy is at present not recommended in the initial phase of resuscitating patients with cardiorespiratory arrest. Various dangers of bicarbonate therapy are:

1. Hypokalaemia (due to shift of potassium intracellularly)
2. Tetany (due to alkalosis)
3. Congestive heart failure due to sodium overload
4. Respiratory alkalosis: Due to reaction of administered bicarbonate with H+ ions, carbon dioxide is liberated which diffuses into the brain and produces acidosis of cerebrospinal fluid. This stimulates the respiratory centre leading to respiratory alkalosis.
5. Metabolic alkalosis can occur due to excessive administration of bicarbonate. Another cause of metabolic alkalosis is that with the successful treatment of primary disorder, there is rapid conversion of lactate and ketones into bicarbonate which may lead to alkalosis.
6. Intracellular acidosis may occur because of intracellular diffusion of liberated carbon dioxide. Intracellular acidosis may hamper the functions of metabolic enzymes.

Other options
Carbicarb: It consists of equimolar concentrations of sodium bicarbonate and sodium carbonate. Because carbonate is a stronger base, it is used in preference to bicarbonate for buffering hydrogen ions, generating bicarbonate rather than carbon dioxide in the process (CO\(_3\)\(^-\) + H\(^+\) = HCO\(_3\)\(^-\)). In addition, the carbonate ion can react with carbonic acid, thereby consuming carbon dioxide (CO\(_3\)\(^-\) + H\(_2\)CO\(_3\) = 2HCO\(_3\)\(^-\)). Thus, Carbicarb limits but does not eliminate the generation of carbon dioxide. However, the risks of hypervolemia and hypertonicity are similar to bicarbonate, and neither agent prevents progressive reduction in myocardial-cell pH in animals with ventricular fibrillation.

THAM: Another carbon dioxide-consuming alkalinizing agent is THAM, a commercially available solution of 0.3 N-tromethamine. This sodium-free solution buffers both metabolic acids (THAM + H\(^+\) = THAM\(^+\)) and respiratory acids (THAM + H\(_2\)CO\(_3\) = THAM\(^+\) + HCO\(_3\)\(^-\)). Like Carbicarb, THAM limits carbon dioxide generation and increases both extracellular and intracellular pH. Nevertheless, THAM has not been documented to be clinically more efficacious than bicarbonate. In fact, serious side effects, including hyperkalemia, hypoglycemia, ventilatory depression, local injury in cases of extravasation, and hepatic necrosis in neonates, markedly limit its usefulness.

Metabolic Alkalosis
Metabolic alkalosis is usually initiated by an increased loss of acid from stomach or kidneys. Hypokalaemia occurs because of shift of potassium into intracellular area.

Compensation
Alkalosis gives rise to hypoventilation and hence retention of CO\(_2\) which attenuates the increase in systemic pH. The compensatory response is that for each 1 mEq/L increase in bicarbonate, CO\(_2\) increases by about 0.6 mmHg. Even in the absence of underlying lung disease, secondary hypoventilation is accompanied by some degree of hypoxia.

Pathophysiology
Under normal conditions, kidneys excrete excessive bicarbonate rapidly so that alkalosis will not be sustained unless bicarbonate reabsorption in the kidneys is enhanced or alkali is generated at a great rate. The maintenance of alkalosis is due to three factors:

1. Stimulation of bicarbonate reabsorption due to volume depletion when renal conservation of sodium takes precedence over correction of alkalosis. Since a large fraction of plasma sodium is bound with bicarbonate, complete absorption of filtered sodium requires reabsorption of bicarbonate as well. Alkalosis is sustained till volume depletion exists. On administering sodium chloride, tubular avidity for sodium decreases. Also, chloride is available as an alternative to bicarbonate.

2. Another mechanism which can maintain alkalosis is hypermineralocorticoidism which stimulates increased renal H\(^+\) secretion as ammonium and titrable acidity. The patients are not volume-depleted
or chloride-dependent and therefore, do not respond
to saline infusion.

3. The third mechanism of sustaining alkalosis is severe
potassium depletion as renal conservation of
potassium takes precedence over H⁺ resulting in loss
of H⁺ in the urine and hence acidic urine in presence
of alkalosis.

Based on above, various causes of metabolic alkalosis
are listed in Table 5.

### Table 5: Causes of metabolic alkalosis

**Saline Responsive (Urinary Na⁺ and Cl⁻ < 10 meq/L)**

1. Loss of chloride-rich, bicarbonate-poor sweat (cystic
fibrosis)
2. Diuretics (volume contraction)
3. Use of poorly reabsorbable anions like carbenicillin
(loss of H⁺).
4. Post-hypercapneic alkalosis
5. Gastric alkalosis

**Saline Un-responsive (Urinary Na⁺ and Cl⁻ > 15-20
meq/L)**

1. Severe potassium depletion due to any cause
2. Primary aldosteronism and Cushing’s syndrome

In patients with chronic hypercapnoea due to respiratory
insufficiency, the plasma bicarbonate is high due to renal
compensation. If the primary condition improves (as
with ventilatory support), pCO₂ falls promptly. However,
urinary excretion of excessive bicarbonate takes a
number of days. In patients who are on low salt diet or
on diuretic and are therefore volume depleted, post-
hypercapneic alkalosis will persist as kidneys will not
be able to excrete bicarbonate from the body.

Patients who are having repeated vomiting or are on
continuous gastric aspiration, there is loss of acid leading
to initiation of alkalosis. However, volume and
potassium depletion both tend to maintain alkalosis.

### Clinical features

There are no specific manifestations of metabolic
alkalosis. Arteriolar constriction can produce reduced
cerebral and coronary blood flow. Severe alkalosis may
cause apathy, confusion or stupor. The patients may have
increased neuromuscular irritability due to increased
binding of calcium to proteins whereby reducing ionized
calcium and also because of increased acetylcholine
release at the neuromuscular junctions. This may
produce tetany and seizures. The cardiac manifestations
are increased QT interval and prominence of U waves
on ECG, and increased susceptibility to dysrrhythmias.
These are either due to hypokalaemia or alkalosis per
se. Hypoventilation due to compensation may be
significant in patients with compromised respiration.

### Treatment

Mild-to-moderate alkalosis rarely requires any specific
treatment. In presence of severe, saline-responsive
alkalosis, infusion of saline and potassium is sufficient
to enhance renal excretion of bicarbonate. The ensuing
increase in NaHCO₃ excretion is due primarily to two
events occurring in the collecting tubules – decreased
reabsorption and increased secretion of bicarbonate.
Repletion of the extracellular volume removes the
stimulus to sodium retention, thereby allowing less
bicarbonate to be reabsorbed. The increase in distal
chloride delivery will raise the chloride concentration
in the tubular lumen. This will create a more favorable
gradient for chloride entry into the cells, thereby
allowing increased bicarbonate secretion in the cortical
collecting tubule.

In saline-resistant cases, specific treatment of primary
disorder is required. Hypokalaemia should be corrected.
Spironolactone inhibits secretion of H⁺ and hence may
correct alkalosis. In patients not responding to these
therapeutic measures, acetazolamide may be used.

In severe cases, intravenous acidifying agents (dilute
solutions of arginine hydrochloride, lysine
hydrochloride, and hydrogen chloride) may be required.
Hydrochloric acid administered intravenously as a 0.1
to 0.2 N solution (that is, one containing 100 to 200
mmol of hydrogen per liter) is safe and effective for the
management of severe metabolic alkalosis. The acid can
be infused as such or can be added to amino acid and
dextrose solutions containing electrolytes and vitamins
without causing adverse chemical reactions. Because of
its sclerosing properties, hydrochloric acid must be
administered through a central venous line at an infusion
rate of no more than 0.2 mmol per kilogram of body
weight per hour. However, it can also be administered
through a peripheral vein if it is added to an amino acid
solution and mixed with a fat emulsion. Calculation of
the amount of hydrochloric acid solution to be infused
is based on a bicarbonate space of 50 percent of body
weight. Thus, to reduce plasma bicarbonate from 50 to
40 mmol per liter in a 70-kg patient, the estimated
amount of hydrochloric acid required is 10 x 70 x 0.5,
or 350 mmol. Precursors of hydrochloric acid, such as
ammonium chloride (20 g per liter, with 374 mmol of
hydrogen per liter) and arginine monohydrochloride
Electrolyte and Acid-Base Disturbances

(100 g per liter, with 475 mmol of hydrogen per liter), can substitute for hydrochloric acid, but they entail substantial risks and are used less commonly. Both of these preparations are hyperosmotic solutions; to avoid local tissue injury, they must be infused through a central catheter. In addition, ammonium chloride can raise serum ammonia concentrations in patients with liver failure, and arginine monohydrochloride can induce serious hyperkalemia in patients with renal failure, especially when there is coexisting liver disease.

**Respiratory Acidosis**

Hypoventilation due to any cause leads to prompt increase in pCO$_2$, leading to respiratory acidosis. Because lungs are so efficient at expiring CO$_2$, any abnormal increase in carbon dioxide can directly be attributed to an abnormality affecting this organ system.

**Compensation**

In the ECF, there is no buffer to bind CO$_2$ as bicarbonate cannot bind it. In acute respiratory acidosis, the only buffers available are intracellular proteins and bicarbonate formed as a result of intracellular buffering diffuses out of cells into ECF increasing its bicarbonate levels and reducing change in pH. In chronic acidosis, renal acid secretion is enhanced and bicarbonate is reabsorbed. The response occurs because increased arterial pCO$_2$ increases intracellular pCO$_2$ in proximal tubular cells and this causes increased H$^+$ secretion from the tubular cells into the tubular lumen. Chloride is secreted in place of bicarbonate leading to hypochlorinemic acidosis. Due to these changes, in acute and chronic respiratory acidosis, the bicarbonate increases by 1 mEq/L and 3.5 mEq/L respectively.

**Pathophysiology**

Any process which decreases ventilation leads to respiratory acidosis. Important causes of respiratory acidosis are listed in Table 6.

**Table 6: Causes of respiratory acidosis**

<table>
<thead>
<tr>
<th>Disorders of Gas Exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute</td>
</tr>
<tr>
<td>a. Severe asthma</td>
</tr>
<tr>
<td>b. Acute exacerbation of obstructive lung disease</td>
</tr>
<tr>
<td>c. Late stages of pulmonary edema</td>
</tr>
<tr>
<td>d. Laryngospasm</td>
</tr>
<tr>
<td>e. Foreign body inhalation</td>
</tr>
<tr>
<td>f. Malfunctioning ventilators</td>
</tr>
</tbody>
</table>

2. Chronic
   a. Chronic obstructive lung disease

**Disorders of Musculo-skeletal System**

1. Acute
   a. Flail chest
   b. Tension pneumothorax
   c. Use of aminoglycosides

2. Chronic
   a. Myasthenia gravis
   b. Poliomyelitis

**Respiratory Centre Abnormalities**

1. Acute
   a. Overdose with opiates and sedatives
   b. Use of general anesthetic agents
   c. Cardiac arrest

2. Chronic
   a. Central nervous system lesions

**Clinical features**

It is often difficult to separate manifestations of respiratory acidosis from those of associated hypoxia and hypercapnia. Because of hypercapnia, patients may have asterixis and they may be obtunded or confused. They have increased sweating. Fundus examination may show papilledema.

**Treatment**

The only treatment for severe respiratory acidosis is correction of underlying disorder and use of assisted ventilation. Rapid infusion of alkali in the early phase of cardiac arrest is not recommended due to various complications of bicarbonate therapy.

**Respiratory Alkalosis**

Respiratory alkalosis is due to hyperventilation leading to decrease in carbon dioxide. Because carbon dioxide is excreted by the lungs, the only cause of respiratory alkalosis is hyperventilation.

**Compensation**

In acute respiratory alkalosis, reduction of CO$_2$ leads to release of H$^+$ from intracellular buffers which decrease plasma bicarbonate levels and hence reduce pH changes. In chronic hypocapnia, plasma bicarbonate is further reduced as decreased CO$_2$ inhibits renal reabsorption of bicarbonate. In acute and chronic respiratory alkalosis, the bicarbonate decreases by 2 mEq/L and 5 mEq/L for...
every 10 mmHg decrease in CO₂.

**Pathophysiology**

Hyperventilation can be due to systemic disorders or primary lung disorders (Table 7).

**Table 7: Causes of respiratory alkalosis**

<table>
<thead>
<tr>
<th>Central Mechanisms</th>
<th>Pulmonary Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anxiety</td>
<td>1. Interstitial lung disease</td>
</tr>
<tr>
<td>2. Fever</td>
<td>2. Asthma</td>
</tr>
<tr>
<td>3. CNS infections</td>
<td>3. Pneumonia</td>
</tr>
<tr>
<td>5. Metabolic encephalopathy</td>
<td>5. Pulmonary embolism</td>
</tr>
<tr>
<td>6. Septicemia</td>
<td></td>
</tr>
<tr>
<td>7. Salicylate poisoning</td>
<td></td>
</tr>
<tr>
<td>8. Cirrhosis of liver</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical features**

The clinical manifestations of respiratory alkalosis depend on the severity and acuteness of alkalosis. In acute cases, hyperventilation is evident and the patient complains of paresthesias, numbness, tingling and in some cases, tetany. In severe cases, confusion and coma can occur due to cerebral vasospasm produced by hypocapnea.

**Treatment**

The mainstay of treatment is control of underlying disease. In acute hyperventilation syndrome due to anxiety, with syncope and tetany, sedation and rebreathing are required.

**Primary and Compensatory Changes in Acid-Base Disorders**

Table 8 and 9 summarize the primary and compensatory changes in various disorders of acid-base imbalance.

### Table 8: Primary and compensatory responses in various acid-base disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>pH</th>
<th>Primary response</th>
<th>Compensatory response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>Decreased</td>
<td>Decreased HCO₃</td>
<td>Decreased pCO₂</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>Increased</td>
<td>Increased HCO₃</td>
<td>Increased pCO₂</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>Decreased</td>
<td>Increased CO₂</td>
<td>Increased HCO₃</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>Increased</td>
<td>Decreased CO₂</td>
<td>Decreased HCO₃</td>
</tr>
</tbody>
</table>

### Table 9: Compensatory responses in acid-base disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Compensation</th>
<th>Limit of compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>For every 1 mEq/L fall in HCO₃, pCO₂ falls by 1.2 mmHg</td>
<td>pCO₂ does not fall below 10 mmHg</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>For every 1 mEq/L rise in HCO₃, pCO₂ rises by 0.6 mmHg</td>
<td>pCO₂ does not rise above 55 mmHg</td>
</tr>
<tr>
<td>Acute respiratory acidosis</td>
<td>For every 10 mmHg rise in pCO₂, HCO₃ rises by 1 mEq/L</td>
<td>HCO₃ does not rise above 30 mEq/L</td>
</tr>
<tr>
<td>Chronic respiratory acidosis</td>
<td>For every 10 mmHg rise in pCO₂, HCO₃ rises by 3.5 mEq/L</td>
<td>HCO₃ does not rise above 45 meq/L</td>
</tr>
<tr>
<td>Acute respiratory alkalosis</td>
<td>For every 10 mmHg fall in pCO₂, HCO₃ falls by 2 mEq/L</td>
<td>HCO₃ does not fall below 18 mEq/L</td>
</tr>
<tr>
<td>Chronic respiratory alkalosis</td>
<td>For every 10 mmHg fall in pCO₂, HCO₃ falls by 5 mEq/L</td>
<td>HCO₃ does not fall below 12 mEq/L</td>
</tr>
</tbody>
</table>
Mixed Acid-Base Disorders

Disorders of mixed acid-base imbalance are quite common in sick patients as these patients may be on multiple drugs and ventilatory support. Important causes of mixed acid-base disturbances are shown in Table 10.

Table 10: Causes of mixed acid-base disorders

<table>
<thead>
<tr>
<th>Respiratory Acidosis with Metabolic Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cardiac arrest</td>
</tr>
<tr>
<td>2. Severe pulmonary edema</td>
</tr>
<tr>
<td>3. Drug poisoning with severe respiratory depression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory Alkalosis with Metabolic Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hepatic failure with diuretic use</td>
</tr>
<tr>
<td>2. Patients on ventilator and nasogastric suction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mixed Acute and Chronic Respiratory Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chronic obstructive airway disease with superimposed infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory Alkalosis with Metabolic Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Septic shock</td>
</tr>
<tr>
<td>2. Salicylate overdose</td>
</tr>
<tr>
<td>3. Renal failure with sepsis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory Acidosis with Metabolic Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. COAD with diuretic use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic Acidosis with Metabolic Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diarrhea and vomiting</td>
</tr>
<tr>
<td>2. Metabolic acidosis with excessive bicarbonate therapy</td>
</tr>
</tbody>
</table>

Summary

Fig. 4 Shows approach to interpretation of acid-base disorders.

Step-by-Step Approach to Interpret

**Step 1:** Comprehensive history and examination. Comprehensive history taking and physical examination can often give clues as to the underlying acid-base disorder. For example, patients with hypotension, severe diarrhea or renal failure are likely to have metabolic acidosis. Patients with recurrent vomiting, nasogastric aspiration or on diuretics may have metabolic alkalosis. Similarly, patients with chronic obstructive lung disease and flail chest are likely to have respiratory acidosis while those with pulmonary embolism may have respiratory alkalosis. Presence of sepsis may point towards mixed metabolic acidosis and respiratory alkalosis. Further, acid-base abnormalities should be suspected in patients who are critically ill, are experiencing extreme dyspnoea, or have abnormal mental status.

**Step 2:** Acidemia or alkalemia. Whether values suggest academia (pH < 7.38) or alkalemia (pH > 7.42).

**Step 3:** Identify primary disorder. Look at pH, pCO₂ and HCO₃⁻. If the pH is below 7.38, and both pCO₂ and bicarbonate are low, metabolic acidosis is present. If pH is below 7.38 and both pCO₂ and bicarbonate are high, it indicates presence of respiratory acidosis. If the pH is higher than 7.42, alkalosis is present. Again measure pCO₂ and bicarbonate. If both carbon dioxide and bicarbonate are high, metabolic alkalosis is present. If both carbon dioxide and bicarbonate are low, respiratory alkalosis is present.

**Step 4:** Calculate compensatory response. The formulas are listed in table 9. In acute metabolic acidosis for example, Winter’s Formula can be used to calculate whether the respiratory compensation is appropriate. In metabolic acidosis, pCO₂ should be equal to 1.5 times bicarbonate levels plus 8 ± 2. If the patient’s pCO₂ is higher, the patient has a superimposed respiratory acidosis. If the pCO₂ is below this range, the patient has a superimposed respiratory alkalosis.

**Step 5:** Calculate anion gap. Presence of high anion gap indicates high anion-gap metabolic acidosis.

**Step 6:** Calculate delta-delta ratio.

\[
\text{Delta-Delta} = \frac{\text{Measured AG} - \text{Normal AG}}{\text{Normal } [\text{HCO}_3^-] - \text{Measured } [\text{HCO}_3^-]}
\]

Delta-delta ratio < 1 indicates associated non-anion gap metabolic acidosis. A delta-delta ration > 1.6 indicates associated metabolic alkalosis.

**Step 7:** Calculate osmolar gap. (if metabolic acidosis is detected). A high osmolar gap indicates presence of one of the alcohols.

**Step 8:** Formulate differential diagnosis. What is the cause of acid-base disorder?
Lastly, one case scenario will be discussed to give step-by-step approach to acid-base interpretation.

**Practice Case**
- 60 year male presents to the ED with rapid breathing and less responsive than usual. No other history is available.

<table>
<thead>
<tr>
<th>ABG: pH</th>
<th>Chem: Na⁺</th>
<th>K⁺</th>
<th>Cl⁻</th>
<th>HCO₃⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.31</td>
<td>123</td>
<td>5.0</td>
<td>99</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABG: pH</th>
<th>Chem: K⁺</th>
<th>Cl⁻</th>
<th>HCO₃⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>5</td>
<td>99</td>
<td>5</td>
</tr>
</tbody>
</table>

**Step 1: Is there an acidemia or alkalemia?**

- **Acidemia**
  - ABG: pH 7.31
  - Chem: Na⁺ 123
  - PCO₂ 10
  - HCO₃ 5

- **Alkalemia**
  - ABG: pH 7.44
  - Chem: Na⁺ 123
  - PCO₂ 40
  - HCO₃ 5

---

Fig. 4: Interpretation of Arterial Blood Gas Report.
Step 2. Is the primary process metabolic or respiratory?

PCO₂ = 10 should drive pH ↑
HCO₃⁻ = 5 should drive pH ↓

ABG: pH 7.31 Chem: Na⁺ 123
PCO₂ 10 K⁺ 5.0
HCO₃⁻ 5 Cl 99
HCO₃⁻ 5

Step 3: Choose appropriate compensation formula:

In Metabolic acidosis, pCO₂ = 1.5 [HCO₃⁻] + 8 ± 2

ABG: pH 7.31 Chem: Na⁺ 123
PCO₂ 10 K⁺ 5.0
HCO₃⁻ 5 Cl 99
HCO₃⁻ 5

Step 4: Is the respiratory compensation adequate?

Metabolic acidosis pCO₂ = 1.5 [HCO₃⁻] + 8 ± 2

Expected pCO₂ = 1.5 (5) + 8 ± 2 = [13.5 – 17.5]

PCO₂ = 10, additional respiratory alkalosis

ABG: pH 7.31 Chem: Na⁺ 123
PCO₂ 10 K⁺ 5.0
HCO₃⁻ 5 Cl 99
HCO₃⁻ 5

Step 5: Calculate the anion gap:

Anion gap = [Na⁺] – [(Cl⁻) + (HCO₃⁻)]

Anion gap = 123 – (99 + 5) = 19

Step 6: If high anion gap acidosis, calculate delta-delta ratio

Delta-Delta = Measured AG – Normal AG
Normal [HCO₃⁻] – Measured [HCO₃⁻]

Delta-Delta = (19 – 10)/(24 – 5) = 0.47

Step 7: If high anion gap acidosis, calculate Osmolar gap

Osmolar gap = Measured Osmolality – Calculated Osmolarity

Calculated Osmolarity = 2 (Na) + (Glucose/18) + (BUN/2.8)
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