ABSTRACT
In order for the human body to function at its optimal level, its systems must be in balance. In the human body, cells communicate with one another through electrical charges that are made possible by minerals known as electrolytes. Electrolytes also regulate a body’s pH level, or the balance of acids and bases. When the body has either too many or too few electrolytes, the effects can be disastrous. Symptoms can range from muscle cramps to dizziness, irregular heart beat, mental confusion, and death. Fortunately, electrolyte imbalance can be easily treated in most cases. This course is designed to give clinicians a fundamental review of the organ systems, physiology, and mechanisms involved in the management of electrolyte and acid-base disorders.

ACTIVITY LENGTH
12 contact hours

LEARNING OBJECTIVES
1. Identify the forms of electrolytes and their physiological roles.
2. Differentiate between high and low concentrations of electrolytes.
3. Differentiate between strong and weak electrolytes.
4. Recognize the major human electrolytes and their normal physiological concentrations.
5. Describe the effects of electrolytes on skeletal muscle and cardiac muscle tissue.
6. Describe the effects of electrolytes on neurologic health.
7. Describe the association between electrolytes and exercise performance.
8. Define electrolyte homeostasis.
9. Explain the treatments of electrolyte disorders.
10. Explain the signs and symptoms of electrolyte disorders.
11. Identify common foods and beverages that replenish electrolytes.
12. Describe the impact that medications can have on electrolytes.
14. Recognize the impact of pH on the human body.
15. Recognize the signs and symptoms of acid base disorders.
16. Identify the physiology involved in acid-base balance and correction.
17. Explain treatments for acid-base disorders.

INTRODUCTION

History

The last century has proven to be a turning point in mankind’s understanding of acid base chemistry and its role in emergency medicine. One of the first notable scientists who contributed to this knowledge was Arrhenius, who in 1887 conducted a series of experiments that proved that dissolved salts and acids are ionized, paving the way for the scientific concept of hydrogen ions and subsequently their properties in solution. A little more than 20 years later, Henderson introduced the Henderson equation which was later used by Hasselbalch in 1916 together with Sorensen’s pH terminology to formulate the now standard Henderson-Hasselbalch equation used in calculating pH. In 1923, Bronsted and Lowry independently characterized acids and bases as “donors” and acceptors” of hydrogen ions. A year later, Van Slyke invented the Van Slyke apparatus designed to measure gas volume in the blood. In 1971, an in vivo diagram was introduced by Siggaard-Andersen and in 1974, an improved version based on the monogram of the latter using the two clinical components, metabolic acidosis and respiratory acidosis, was published by Grogono, Byles and Hawke.
Despite the advances in acid-base concepts and applications, certain controversies surround the clinical use of base excess. The so-called "great trans-Atlantic debate" that started in the 1960s found two scientists on opposing sides, with Siggaard-Andersen, the proponent in Copenhagen and Relman, the opponent, in Boston. At the start of the 1980s, a new controversy emerged; this time it was the published work of Peter Stewart that was met with scrutiny and criticism. His work proposed a radical approach to the pathophysiology of acid-base balance. Up to this day, the debate surrounding his work remains (1).

**Medical implications**

The general consensus among clinicians is that acid-base balance is important; however, they still struggle to understand its exact pathophysiologic mechanisms and clinical implications. Furthermore, conventional teaching underlines clinical data interpretation rather than pathophysiology (2). As a result, there remains doubt about the causes and treatments of acid-base imbalance. The physicochemical approach, proposed by Peter Stewart in 1981 simplified the clinical application of acid-base chemistry (3) (4) (5) (6) (7).

Acid-base balance is an integral part of fluid and electrolyte regulation. It is a result of interactions between physiological buffer systems to maintain the normal functioning of bodily processes of the renal and respiratory systems. Simply put, its homeostatic role allows normal metabolic functions to occur.

The body normally produces acid in the form of hydrogen ions as a normal part of cellular metabolism. Similarly, hydroxyl ions are also produced in concentrations that balances out the physiological effects of the hydrogen ions produced. A disruption in the acid-base balance such as in the cases of serious injuries and illnesses can result in several reversible disorders such as respiratory and metabolic alkalosis and acidosis. Knowledge of acid-base balance is critical to the practice of emergency medicine so that
appropriate assessment, monitoring, and intervention can be provided in a timely manner to optimize therapeutic outcomes and prevent health deterioration.

In this course, the discussion on acid-base disorders and fluid/electrolyte disorders are presented somewhat separately, but that doesn’t mean that both are separate and independent of each other. This was done to make the flow of information easier to handle and digest. It should be noted that electrolyte disturbances occurs frequently in conjunction with acid-base disorders. The first part of the course will focus on the discussion of electrolytes while the second part will give way to in-depth discussion on acid-base balance.

**Definition**

Electrolyte disorder – An imbalance of fluid and electrolyte (i.e. bicarbonate, calcium, chloride, magnesium, phosphate, potassium, and sodium) levels in the body.

Acid-base balance disorder - An acid base disorder is a change in the normal value of extracellular pH that may result when renal or respiratory function is abnormal or when an acid or base load overwhelms excretory capacity (8).

**Key words**

Below are some of the most commonly used terms in this course (9):

**Acidosis** - a pathological condition resulting from accumulation of acid in the blood or loss of base from the blood; arterial blood pH < 7.35

**Alkalosis** - a pathological condition resulting from accumulation of base or loss of acid from the body; arterial blood pH > 7.45

**Anion gap** - the difference between the measured cations and measured anions (Na$^+$ + K$^+$) - (Cl$^-$ + HCO$_3^-$)
**Diabetic ketoacidosis** – a life-threatening complication of uncontrolled diabetes mellitus resulting in high levels of ketones in the blood due to insulin deficiency

**Edema** - an increase in the interstitial fluid volume

**Henderson-Hasselbalch equation** - describes the relationship among pH, the pKa of a buffer system, and the ratio of the conjugate base to its corresponding weak acid

**Hypercapnia** - a condition of excess carbon dioxide in the blood

**Hypochloremic alkalosis** - a metabolic alkalosis resulting from increased blood bicarbonate secondary to loss of chloride from the body

**Hypovolemia** - an abnormally low blood volume

**Hypoxia** - a condition of low oxygen content in tissues.

**Metabolic acidosis** - primary deficit of bicarbonate; pathological accumulation of acid or loss of base from the body

**Metabolic alkalosis** - primary excess of bicarbonate; pathological accumulation of base or loss of acid in the body

**Polyuria** - excessive urine output (more than 1 to 2 L/day in the adult)

**Respiratory acidosis** - primary excess of dCO₂; pathological retention of CO₂ caused by respiratory change

**Respiratory alkalosis** - primary deficit of dCO₂; pathological decrease in CO₂ caused by respiratory change

**Syndrome of inappropriate antidiuretic hormone secretion (SIADH)** – a grouping of findings, including hypotonicity of the plasma, hyponatremia, and hypertonicity of the urine with continued sodium excretion, that is produced by excessive ADH secretion and that improves with water restriction

*Acids and Bases*
Acids are simply defined as those substances that yield hydrogen ions (H\(^+\)) or hydronium ions (H\(_3\)O\(^+\)) when dissolved in water. The latter is a combination of hydrogen ions and water molecules.

According to Bornsted-Lowry theory, an acid (HB) is a proton donor. It gives out ions (dissociates), H\(^+\) + B\(^-\) when in solution. This is best demonstrated by the following equation:

\[
HB \rightarrow H^+ + B^-
\]

Some of the most common physiological acids are shown in the table below (10).

<table>
<thead>
<tr>
<th>Name of Acid</th>
<th>Physiological importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochloric acid (HCl)</td>
<td>Stomach secretions</td>
</tr>
<tr>
<td>Carbonic acid (H(_2)CO(_3))</td>
<td>Blood buffer</td>
</tr>
<tr>
<td>Phosphoric acid (H(_3)PO(_4))</td>
<td>ATP and DNA molecules</td>
</tr>
<tr>
<td>Amino acid</td>
<td>Protein molecules</td>
</tr>
<tr>
<td>Lactic acid (HC(_3)H(_5)O(_3))</td>
<td>Muscles during exercise</td>
</tr>
</tbody>
</table>

An important fact to remember about acids is that it ionizes or dissociates in water to form an equilibrium mixture of its individual ions.

Bases are simply defined as those substances that yield hydroxide ions (OH\(^-\)) when dissolved in water. According to Bornsted-Lowry theory, a base is a proton acceptor. It combines (associates) with hydrogen ions and neutralizes the effects of the acid. This is best demonstrated by the equation below:
H^+ + B^- → HB

Some of the most common physiological acids are shown in the table below (11).

<table>
<thead>
<tr>
<th>Name of Base</th>
<th>Physiological importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium hydroxide (MgOH_2)</td>
<td>Antacid</td>
</tr>
<tr>
<td>Ammonia (NH_3)</td>
<td>Gas inhalant</td>
</tr>
<tr>
<td>Calcium hydroxide (CaOH_2)</td>
<td>Astringent</td>
</tr>
</tbody>
</table>

It is important to note that some bases do not have hydroxide ions in their chemical formula, but nevertheless react with water to form hydroxide ions. Examples include sodium carbonate and phosphate.

Acid base reactions result in the formation of salt and water. For example, when hydrochloric acid reacts with sodium hydroxide (a base), neutralization process occurs wherein the acid and base properties of each reactant (base and acid substances) are cancelled to form salt and water. The word salt is the general term for all products of acid-base reactions. The reaction is a reversible process and is indicated in the equilibria below:

\[
HB \leftrightarrow H^+ + B^-
\]

Equilibrium is a special kind of steady state in which the rate in the two-way directional (see arrow) reaction is equal. Equilibrium is reached once the rate of association is equal to the rate of dissociation. Note that the concentrations need not be equal, only the rate at which they are formed should be equal.
Look at the previous equations, the rate of association is directly proportional to the concentration of $H^+ + B^-$ and the rate of dissociation is directly proportional to the concentration of HB.

**Electrolytes**

Electrolytes are those substances that dissociate into ions in solution. When an electrolyte dissolves in solution, it forms an electrolytic solution that is capable of conducting electricity. For example, sodium chloride, a common salt, when dissolved in water forms an electrolytic solution, with the dissociated sodium (cation) and chloride (anion) ions as charge carriers. The equation is shown below:

$$NaCl + H_2O \rightarrow Na^+ + Cl^- + H_2O$$

Below is a table of other commonly found cations and anions in the body.

<table>
<thead>
<tr>
<th>Cations</th>
<th>Anions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium ($K^+$)</td>
<td>Bicarbonate ($HCO_3^-$)</td>
</tr>
<tr>
<td>Calcium ($Ca^{++}$)</td>
<td>Phosphate ($PO_4^{3-}$)</td>
</tr>
<tr>
<td>Hydrogen ($H^+$)</td>
<td></td>
</tr>
</tbody>
</table>

It is also important to remember that not all substances that dissolve in solution dissociate into ions. Examples of this include sugar and alcohol. In the body, non-electrolytes are found in the form of urea, proteins, glucose, oxygen and carbon dioxide. Bodily fluids are electrically neutral and osmotically maintained.

There are various kinds of substances that behave as electrolytes when dissolved in a solution. Each one is discussed in detail below, although not all are physiologically useful to the human body.
II. FORMS OF ELECTROLYTES

Soluble salts

As mentioned above, sodium chloride dissociates in solution to form sodium and chloride ions. The substance is a good example of a soluble salt. There are other substances that are considered soluble salts. Generally speaking, substances that forms chlorides, hydroxides, bromides, sulfates, sulfides, acetates, and carbonates form salts, some of which are soluble. To help remember them, below are some of the solubility rules, with notable exceptions (12):

1. Salts with Group I elements are very soluble. These elements are lithium, sodium, potassium, cesium, and rubidium. Another salt carrying a positive charge and very soluble in water is the ammonium salt.

2. Salts with the negatively charged ion nitrate are generally soluble.

3. Salts containing the negatively charged ions chloride, bromide, and iodide are generally soluble. Notable exceptions to this rule are halide salts of silver, lead, and mercury. Therefore, silver chloride, lead bromide, and mercuric chloride are all insoluble.

4. As mentioned in the preceding rule, silver salts are insoluble with notable exceptions such as silver nitrate and silver acetate are common soluble salts of silver.

5. Almost all sulfate salts are soluble with the exception of barium sulfate, lead sulfate, silver sulfate and strontium sulfate.

6. Most hydroxide salts are only slightly soluble with the exception of hydroxide salts formed by Group I elements which are very soluble. Hydroxide salts of Group II elements such as those formed by calcium, strontium and barium are only slightly soluble. Hydroxide salts formed by transition metals such as aluminum are insoluble. Therefore, ferric hydroxide, aluminum hydroxide, and cobalt hydroxide are insoluble.
7. Most sulfides formed by transition metals are highly insoluble. Therefore, cadmium sulfide, ferrous sulfide, zinc sulfide, and silver sulfide are all insoluble. Arsenic, antimony, bismuth, and lead sulfides are likewise insoluble.

8. Carbonates are frequently insoluble. Group II carbonates formed by the elements calcium, strontium, and barium are insoluble. Some other insoluble carbonates are ferric carbonate and lead carbonate.

9. Chromates such as lead chromate and barium chromate are frequently insoluble.

10. Phosphates such as calcium phosphate and silver phosphate are frequently insoluble.

11. Fluorides such as barium fluoride, magnesium fluoride and lead fluoride are frequently insoluble.

Acid electrolytes

Slightly soluble salts can be dissolved more easily with the aid of an acid. These salts usually have an anion that is basic i.e., they are the salts of weak acids. An example is calcium carbonate, its solubility-product equilibrium is shown below:

$$CaCO_3 \leftrightarrow Ca^{+2} + Co_3^{-2}$$

Once an acid is added to the solution above, some of the carbonate ions get protonated and become $HCO_3^-$ ions resulting in a reduced carbonate concentration. According to Le Chatelier’s principle, the system will compensate for the reduced carbonate concentration by dissolving more solid $CaCO_3$ shifting the equilibrium to the right.

Base electrolytes

Just like their acid counterparts, basic anions exhibit similar behaviors. Almost all carbonates, sulfides, hydroxides, and phosphates which are only slightly soluble in water can be dissolved with the help of an acid. Take the example of zinc sulfide whose equation is shown below.
ZnS $\leftrightarrow$ Zn$^{2+}$ + S$^{2-}$

The equilibrium of the system can be shifted to the right by reducing the concentration of the basic ions S$^{2-}$ with hydronium ions.

Sometimes, the movement in a solubility-product equilibrium caused by low pH levels may have detrimental effects. Acid rainfall is one such example. It can occur when oxides of acidic air pollutants are removed from the environment. In certain regions of the US, very low pH levels (e.g. pH 4.0) have been detected. The high acidity of these solutions dissolves marble and limestone wreaking significant property damage.

*Molten salt electrolytes*

When sodium chloride is molten, it conducts electricity as well, making it an ideal electrolyte in its molten state. Molten salts are used in electric batteries because they provide both a high energy density through appropriate pairing with reactants as well as a high power density via the high-conductivity molten salt electrolyte.

*Gas electrolytes*

Certain gases under high temperature or low pressure conditions can act as electrolytes and conduct electricity. A good example of this is hydrogen chloride.

**III. ELECTROLYTES AND THEIR PROPERTIES**

High vs. Low concentration

Electrolytes exhibit colligative properties. Since colligative properties are dependent on the concentration of particles dissolved, solutions of electrolytes are expected to show greater changes than those of non-electrolytes. Ion pairing becomes more common as the
solution concentration increases. For example, one mole of NaCl does not really produce two moles of ions since some of the Na and Cl ions reassociate temporarily, so the exact concentration of particles is still less than twice the concentration of NaCl. This demonstrates that reassociation happens at higher concentration. Therefore, the number of particles present in an electrolyte is concentration dependent.

Understanding the colligative properties of electrolytes is especially important because of its role in the physiological transport of important substances into and out of cells. Cells have semipermeable membranes which allow selective entry of substances. Generally, only smaller particles such as water molecules are allowed to pass through the membrane, blocking the entry of larger particles such as sugar. Simply put, the semipermeable membranes of cells only allow water to pass through, but not solutes. This is known as osmosis.

Osmosis is defined as the net movement of solvent from an area of higher solvent concentration (lower solute concentration) to an area of lower solvent concentration (higher solute concentration). The movement occurs in an effort by the body to establish equilibrium. In order to stop the movement, an applied pressure is needed. This pressure is called osmotic pressure ($\pi$). It prevents the inward movement of solvent through the semipermeable membrane, thus, stopping osmosis. It is calculated using the following gas equation, similar to the ideal gas law equation (13):

$$\pi V = nRT$$
$$\pi = \frac{nRT}{V}$$

where,

$V = $ volume of the solution

$n = $ number of moles of the solute

$R = $ gas constant

$T = $ temperature in Kelvin
\( \Pi = \text{osmotic pressure} \)

Osmotic pressure is an important factor in osmoregulation, a homeostatic mechanism that governs all cells. As such, it influences the tonicity of the two solutions on either side of the semipermeable membrane. Let’s take the example of blood cells.

If the osmotic pressure is equal on both sides of the membrane, the solutions on either side are considered isotonic. It causes no changes on the structural integrity of the cell. Now if one solution is of lower osmotic pressure, it is considered hypotonic with respect to the more concentrated solution. It causes a rapid influx of water into the cell, swelling it and sometimes causing it to burst (hemolysis). On the other hand, a more concentrated solution is considered hypertonic with respect to the dilute solution and causes water molecules to flow out of the cell, resulting in cellular shrinkage (crenation).

To maintain cellular structural integrity, solutions introduced into the body such as IV fluids must be isotonic with intracellular fluids of the cells.

**Strong vs. Weak Electrolytes**

Generally speaking, ionic compounds are strong electrolytes because they completely dissociate in water. On the other hand, molecular compounds do not dissociate and are non-electrolytes. The properties of electrolytes are enumerated and discussed in detail below (14):

1. Strong electrolytes conduct current very well. As the equation indicates, the arrow goes in one direction, indicating complete ionization or dissociation in the aqueous solvent.
   a. Soluble ionic compounds (salts)
b. Strong acids (HNO₃, H₂SO₄, HCl, HBr, HI, HClO₄)

\[ \text{HNO}_3 \rightarrow \text{H}^+ + \text{NO}_3^- \text{ (complete ionization)} \]

Strong acids have very low pH. They have a high degree of dissociation.

c. Strong bases (KOH and NaOH)

\[ \text{KOH} \rightarrow \text{K}^+ + \text{OH}^- \text{ (complete ionization)} \]

Strong bases have very high pH.

2. Weak electrolytes conduct only a small current. They get slightly ionized in solution.

   a. Weak acids include organic acids such as acetic acid, citric acid, butyric acid, and malic acid.

   \[ \text{HC}_2\text{H}_3\text{O}_2 \leftrightarrow \text{H}^+ + \text{C}_2\text{H}_3\text{O}_2^- \]

   b. Weak bases (e.g. ammonia)

   \[ \text{NH}_3 + \text{H}_2\text{O} \leftrightarrow \text{NH}_4^+ + \text{OH}^- \]

3. Non-electrolytes conduct no current because there are no ions present in solution.

The table below summarizes the details above.

<table>
<thead>
<tr>
<th>Strong electrolyte</th>
<th>Weak electrolyte</th>
<th>Non-electrolyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionizes completely</td>
<td>Ionizes partially</td>
<td>Does not ionize</td>
</tr>
<tr>
<td>Conducts electricity strongly</td>
<td>Conducts electricity weakly</td>
<td>Does not conduct electricity</td>
</tr>
</tbody>
</table>
So how are compounds classified based on their formula? One general method is shown below (14):

Step 1 Is it one of the seven strong acids?

Step 2 Is it of the form Metal (OH)\textsubscript{n}? Then it's a strong base.

Step 3 Is it of the form Metal (X)\textsubscript{n}? Then it's a salt.

Step 4 Does its formula start with 'H'? It's probably a weak acid.

Step 5 Does it have a nitrogen atom? It may be a weak base.

Step 6 None of those? Call it a non-electrolyte.

The steps above are not set in stone and there are exceptions to them.

III. BODY FLUID ANALYSIS, MEMBRANES AND CELLULAR TRANSPORT

Body Fluid Analysis and Compartments

Water is the major constituent of the human body. It makes up for 60\% and 50\% of the body weight in young males and females, respectively. The older a person gets, the lesser the water content is in the body; it decreases by 10\% and 6\% in males and females, respectively, by the time they reach 70 years old (15). Body fluid contains electrolytes, water and other substances such as glucose.

The body is made up of fluid compartments separated by different types of membranes. The water in the body is distributed into the four different compartments (15):

- Intracellular fluid (ICF) compartment
- Interstitial fluid (ISF) or extracellular fluid (ECF) compartment
- Plasma compartment
- Transcellular water (TCW) compartment

Plasma volume makes up for 4% of the total body weight of an adult. It can be said that it is the interstitial fluid surrounding the blood, though it has a much higher protein concentration than the latter. Plasma is needed in the assessment of the electrolyte and acid-base status of patients since ISF, ICF and TCW measurements are inappropriate for this purpose. It is virtually impossible to obtain pure samples of ISF and ICF to test fluid status. Moreover, their concentrations are not uniform throughout all the tissues, making it impossible to obtain a standard sample for measurement (15).

Plasma distributes throughout all body tissues; its gases and electrolytes equilibrate with the ISF found in all tissues. After distribution and equilibration, it enters the right ventricle of the heart wherein it obtains a composition similar to that of the extracellular fluid in the body. When a plasma sample is obtained from a peripheral vein, its composition matches the blood-gas and electrolyte composition of mixed venous blood from the right ventricle. These characteristics allow the plasma to represent the entire body’s fluid and blood gas composition as a whole (15).

The acid-base status of patients is made using a plasma sample that is obtained from a vein or artery, and then exposed to $O_2$, $CO_2$ and pH electrodes. The pH reading is then obtained, with the readings for $P_{CO2}$ and $P_{O2}$ being the same since they equilibrate to the same partial pressure in plasma and red blood cell fluids. The $HCO_3^-$ is calculated using the $P_{CO2}$ and pH values obtained (15).

The electrolyte assessment of patients is made by first obtaining a plasma sample from a vein or artery that is allowed to clot in a tube. Once the clot retracts, the serum is separated from the entire clot and analyzed for electrolyte composition. Sometimes, the plasma part is used for electrolyte analysis rather than the serum such as when there are
accuracy concerns over the potassium concentration measured in the serum. In cases like these, the plasma sample in the tube is added with an anticoagulant (15).

Membranes

Membranes provide protection to cells by separating body compartments from one another. However, they do not completely isolate one compartment from another as they do allow select molecules to go through. Cellular transport processes occur between membranes to meet the nutritional and physiological needs of cells in order for them to function properly. Water molecules mostly pass through membranes freely, allowing them to easily equilibrate between compartments (16).

Cellular membranes (semipermeable membranes) have already been briefly discussed above. They primarily serve two functions (15) (16):

- Provide attachment surfaces for ligands
- Provide a protective barrier between the intracellular and the extracellular environment

Cellular membranes are made up of a phospholipid bilayer and proteins. The phospholipid bilayer is structurally similar to triglycerides, although the former is more polar, owing to the phosphate and choline molecules. The bilayer allows cellular entry and exit of both polar and nonpolar molecules. The other part of the cellular membrane, proteins, is distributed throughout the lipid layers. Some of the proteins form aqueous pores through which water-soluble solutes enter and exit the cell. Other proteins act as carriers of large molecules to help them get carried across the cellular membrane easily. The other proteins act as receptors to ligands such as drugs and enzymes (16).

Another type of biological membrane in the body is the capillary membrane. Capillary membranes are made up of the endothelium that serves to separate the blood and the
interstitial fluid (ISF). They are porous in nature, allowing water and solutes to pass through. They restrict the movement of proteins such as albumin and RBCs into the plasma compartment. These membranes play an integral role in maintaining fluid homeostasis between the ISF and the plasma (16).

Yet another type of physiological membrane is the absorptive epithelial membrane that forms a barrier between the TCW and ISF and plasma. The membranes form the mucosal layers of the intestines, stomach, gall bladder and kidney tubules. Their specialized function is absorption rather than protection and intracellular regulation (16).

Transport mechanisms

Transport of molecules from the extracellular fluid and into the intracellular fluid is an essential part of homeostasis (17).

Transport across membranes occurs in two ways (15) (17):

- Solute transport mechanisms (e.g. diffusion, carrier mediated transport)
- Bulk flow transport mechanisms (e.g. osmosis and filtration)

Diffusion is the simplest means of cellular transport. It occurs as a random and continuous movement of molecules. It is influenced by several factors, namely (15) (17);

- Energy: The greater the energy available, the faster the rate of diffusion of molecules.
- Molecular size: Bigger molecules diffuse slower than their smaller counterparts
- Distance: The greater the distance, the slower is the rate of diffusion of molecules.

For example, the distance between alveolar space and plasma is very short, allowing the easy transport of oxygen molecules from the lungs and into the blood.
Concentration of the substance: The greater the concentration of solute, the faster is its rate of diffusion.

Surface area: The greater the surface area, the faster is the rate of diffusion of molecules. For example, the lungs have a large surface area for easy oxygen transport across the alveolar membranes and into the blood. In patients who are diagnosed with emphysema (e.g. smokers), the alveoli are compromised and their surface area substantially reduced, thereby, reducing the capacity of the lungs to oxygenate the blood.

Another form of solute transport mechanism is the carrier-mediated transport. As mentioned previously, large non-polar molecules are carried across the membrane with the aid of protein molecules. These molecules are especially important in absorptive epithelial membranes. Examples of carrier-mediated transport are facilitated diffusion and active transport. The latter requires energy. Both are equally important in fluid regulation and maintaining the acid-base balance of the body (15) (17).

Carrier-mediated transport mechanisms are generally governed by three factors (15) (17):

- Saturation: The rate of carrier-mediated transport increases as the concentration of solute increases. However, once all carriers available for transport have been used up, they are said to be saturated and there will no longer be a corresponding increase in the rate of transport. This usually occurs at higher than normal solute concentrations.

- Specificity: Carrier molecules are specific in what they carry. Carriers that carry glucose do not carry amino acids and the vice versa is also true. Sometimes, the specificity extends to the isomer of a compound. For example, glucose has many isomers and certain carriers will only carry D-glucose and not L-glucose and vice versa.

- Competition: Even with the specificity of carriers for certain molecules, there is still room for competition. This is because certain molecules are structurally
similar and can combine with the binding site of carriers that are not intended for them. As a result, the introduction of a competing molecule will substantially reduce the rate of transport.

Bulk-flow transport mechanisms occur as mass movements of either fluid or gas when pressure gradient is present. The pressure gradient may stem from hydrostatic influence such as those that result from cardiac contraction or from the unequal concentration of solutes between the extracellular and intracellular compartments. Hydrostatic pressure differences between compartments forces fluid and gas molecules to filter through pores and enter the membrane.

Bulk-flow refers to the rate at which a volume of gas or fluid moves across a membrane per unit time. There are three factors that influence this, namely (15) (17):

- Difference in pressure: The greater the pressure differences between the one compartment and the other, the greater the bulk flow of gas and fluid molecules.
- Friction: Energy is lost when the molecules come in contact with the walls of the compartment (e.g. walls of blood vessels)
- Viscosity: Energy is also lost when the molecules collide as they move across membranes.

A good example of bulk-flow transport mechanism is osmosis. It was discussed briefly in the preceding pages and will be discussed some more below (15) (17).

Osmosis is the diffusion of molecules across a semipermeable membrane against a solute concentration difference. The solutes that exhibit osmotic movement are generally small. This type of transport is influenced by a few factors, namely (18):

- Solute concentration: The greater the concentration of the solute, the faster is the rate of osmosis.
- **Temperature**: Since osmosis is a special type of diffusion, it is also influenced by temperature. The higher the temperature, the faster is the rate of osmotic flow across the semipermeable membrane.

- **Distance**: The greater the distance between the solute and the membrane, the slower is the rate of osmosis.

Osmolality is a function of particle (ions and molecules) concentration in every liter of water. It should be remembered that the osmolality of a solution does not depend on the size, molecular weight and electrical charge of its molecules (19). Osmolality is used interchangeably with tonicity. It refers to the osmolar concentration of a solution (osmoles) in every kilogram of water. Osmolarity, on the other hand, is typically expressed as milliosmoles/liter (mOsm/L) of solution (19).

### IV. FLUID VOLUME REGULATION

The relationship between the extracellular and intracellular fluid compartments in homeostasis is a crucial one as it governs the exchange of fluids and electrolytes. As discussed previously, each compartment is kept separate but not isolated by cell membranes. Both bulk-flow and solute transport mechanisms regulate the movement of water and solutes across the cell membrane. Altered levels in the fluid compartments and disruption of these transport mechanisms can result in fatal systemic response.

**Water regulation**

Homeostasis ensures constant total body weight. Its purpose is to ensure that water intake is equal to its output plus insensible water loss.

In order to stay healthy and properly hydrated, the body’s water output must equal its input. Water input mainly occurs through food and fluid ingestion; however, some of it is a product of cellular metabolism (300 mL/24 hours). Water intake is governed by the
thirst mechanism. Thirst mechanism is stimulated by the hypothalamus when plasma osmolarity decreases, resulting in symptoms such as dry mouth. Stimulation ceases once the oral mucosa is moistened and the stomach and intestines distend due to recent water intake. It should be noted that the thirst mechanism should not be relied upon for adequate water intake in critically ill children, especially infants since they may not be able to demonstrate it nor respond to it. Water output occurs through evaporation from the body’s large surface areas (e.g. lungs and skin), defecation and most importantly, urination. Urine output is governed by many factors such as hormonal, adrenal and salinity factors.

Regulation of fluid volume in the body is primarily influenced by renally-mediated factors such as water and salt input and output. As mentioned in the previous paragraph, the kidneys and certain hormones are the primary role players in this function (20).

Nephrons

Normally, ninety-nine percent of sodium intake is filtered at the glomerular capillaries and reabsorbed by the Bowman’s capsule. The volume of fluid containing sodium and other substances that is filtered per unit time is called the glomerular filtration rate (GFR). Alterations in the glomerular filtration rate adversely impact sodium reabsorption and excretion.

The glomerular filtration rate steadily increase during the first two years of life, hovering and maintaining at 30 to 50 percent of adult levels by the end of the first year and reaching adult levels by two years old (21).

When overhydration or water intoxication happens, the glomerular filtration rate and sodium and water excretion increases in response to cope with the volume expansion and return intravascular volume to the normal range. On the other hand, when dehydration
occurs, the glomerular filtration rate and sodium and water excretion decreases in order to restore intravascular volume (22).

Aldosterone

The adrenal cortex secretes aldosterone, a steroid hormone that also influences fluid homeostasis. There are several factors that stimulate its secretion and release, namely (23):

- Sodium depletion
- Elevated potassium concentration
- Angiotensin II
- Adrenocorticotropic hormone (ACTH)

Its main receptors are found in the distal tubules and collecting ducts of the nephrons. Other receptors are the sweat glands, salivary glands, and intestines (23).

The main actions of aldosterone are sodium and water retention, potassium and hydrogen secretion and excretion, and blood pressure elevation. When the sodium serum level decreases, aldosterone is secreted which results in sodium and water retention in the renal tubules. Potassium is excreted in favor of sodium. In a similar vein, when aldosterone secretion is inhibited, potassium is retained, and sodium and water are excreted. Aldosterone helps regulate blood volume by regulating sodium and potassium retention (23).

Renin-angiotensin-aldosterone axis

Renin is an enzyme that is synthesized, stored, and released by the juxtaglomerular cells of the kidneys in response to three stimuli (24):

- Decreased sodium concentration
- Decreased renal perfusion
- Decreased arterial blood pressure

It is part of the renin-angiotensin-aldosterone axis that regulates extracellular fluid volume and vasoconstriction. Renin hydrolyzes angiotensinogen to produce the biologically inactive peptide, angiotensin I. The angiotensin-converting enzyme (ACE) converts angiotensin I to the biologically active peptide, angiotensin II. Angiotensin II acts on the adrenal glands and stimulates the release of aldosterone. Aldosterone, in turn, acts on the distal tubule and collecting ducts to increase sodium and water retention, resulting in increased blood volume and pressure (24).

Moreover, the renin-angiotensin-aldosterone system also stimulates thirst and consequently, water intake, by acting on the central nervous system. It also plays a role in conserving blood volume by decreasing urinary loss through the release of vasopressin from the pituitary gland (24).

Antidiuretic hormone (ADH) or vasopressin

Vasopressin is synthesized in the hypothalamus and stored and released by the posterior pituitary gland. The primary role of vasopressin is to regulate the body’s water retention. It increases the water permeability of the distal tubule and renal collecting ducts, resulting in increased water reabsorption and excretion of concentrated urine (25).

The release of vasopressin from its pituitary storage is stimulated by three factors (25):

1. Plasma osmolality
2. Alterations in the extracellular fluid compartment volume
3. Alterations in arterial blood pressure
When there is insufficient fluid or excess water loss in the body, there is a corresponding elevation of serum osmolality. Even minute increments of 1-2 percent in serum osmolality are enough to stimulate vasopressin secretion, which in turn acts on the nephrons to encourage water conservation and reabsorption, and production of concentrated urine (25).

Vasopressin is secreted when the osmotic pressure of the extracellular fluid compartment is greater than that of the cells such as during hyperglycemic and hypernatremic conditions. When osmotic pressure of the extracellular fluid compartment is less than that of the cells, vasopressin is inhibited, resulting in renal excretion of water (25).

Various disorders can result from fluid imbalance, namely:

- Dehydration leading to hypovolemic shock and mental confusion
- Hypotonic hydration leading to cellular crenation
- Edema

During critical conditions such as hypotensive and hypovolemic states, vasopressin is also secreted. Vasopressin is a potent vasoconstrictor and stimulates peripheral vascular resistance, resulting in elevation of arterial blood pressure. This is an important coping mechanism for restoring normal blood pressure levels in individuals who are experiencing massive blood loss and hypovolemic shock (25).

Other factors may also stimulate the release of vasopressin from its storage vesicles, namely (25):

- Angiotensin II
- Medications such as opiates, nicotine, barbiturates,
- Alcohol
• Stress
• Severe pain

The release of angiotensin II, stress reaction, and severe pain leads to vasopressin secretion and result in elevated blood pressure levels. Opiates, barbiturates, and alcohol decrease vasopressin secretion and result in reduced blood pressure levels.

One of the most common causes of diabetes insipidus is vasopressin deficiency. The disease is characterized by symptoms of severe thirst and excessive excretion of diluted urine. A reduction in fluid intake does not alleviate the symptoms (25).

Natriuretic factors

Natriuretic peptides are the opposite of aldosterone and vasopressin. These are salt-losing hormones that reduce blood pressure and blood volume through inhibition of vasopressin, renin and aldosterone. They also directly cause vasodilation. They are synthesized by the hypothalamus and the left and right atrial walls of the heart. The natriuretic hormone produced by the heart is called the atrial natriuretic peptide (ANP). ANP is secreted when the atrial walls are stretched due to volume overload. Once released, ANP acts on the kidneys, where sodium reabsorption is inhibited, and salt excretion ensues (25).

Other Hormones

Estrogens share structural similarities with aldosterone, and augment salt reabsorption by the renal tubules. Another female hormone, progesterone, promotes sodium and water excretion by antagonizing the effects of aldosterone.
Gluocorticoids enhance tubular reabsorption of sodium, but also stimulate the glomerular filtration rate. Elevated concentrations promote reabsorption, which may very well result in edema (25).

Another homeostatic mechanism of the body involved in fluid balance is the baroreceptor reflex. Baroreceptors are found in the aortic arch and carotid sinuses. Their primary function is to regulate blood pressure. Elevated blood volume and pressure result in the sympathetic stimulation of the kidneys to decline and the afferent arterioles to widen. Consequently, the glomerular filtration rate and sodium and water output increase, resulting in the normalization/decrease of the blood volume and blood pressure. Low blood pressure causes reflex constriction of systemic arterioles (including afferent arterioles), reducing filtrate formation and urinary output and leading to an increase in systemic blood pressure (26).

V. ELECTROLYTES IN THE BODY

As mentioned in the previous section, body fluids such as water are distributed throughout the body compartments. Body fluids contain dissolved substances called electrolytes. Those substances that produce a positive electrical charge are called cations. Biological cations include potassium (K\(^+\)), sodium (Na\(^+\)), calcium (Ca\(^{++}\)), and magnesium (Mg\(^{++}\)). Those electrolytes that yield a negative charge are called anions which include chloride (Cl\(^-\)) and bicarbonate (HC0\(_3\)-) (27). The content and distribution of these anions in the various compartments will be discussed in the next section.

Electrolyte levels are regulated by intake, output, acid-base balance, hormonal influence, and cellular integrity. Non-electrolytes include most organic molecules such as glucose. Electrolytes have greater osmotic power because of their dissociation in water (27).

VI. MAJOR HUMAN ELECTROLYTES
The major electrolytes in the body are sodium, potassium, phosphate, chloride, calcium, magnesium and bicarbonate. Sodium chloride is primarily found in the extracellular fluid, while potassium and phosphate are the main ions in the intracellular fluid. Sodium, potassium and chloride are the three electrolytes that are commonly monitored in clinical practice. Magnesium, calcium and phosphate are likewise monitored depending on the patient’s disease or clinical indication. Calcium and phosphate are almost always discussed in conjunction with the endocrine system because of the involvement of vitamin D (calcitriol) and parathyroid hormone (PTH) in their regulation.

The table below summarizes the distribution of these major electrolytes in the various fluid compartments of the body (28).

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Extracellular volume (meq/liter)</th>
<th>Intracellular volume (meq/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>142</td>
<td>10</td>
</tr>
<tr>
<td>Potassium</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Calcium</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Magnesium</td>
<td>2</td>
<td>123</td>
</tr>
<tr>
<td>Chloride</td>
<td>105</td>
<td>2</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2</td>
<td>149</td>
</tr>
<tr>
<td>Sulfate</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>
Each of the major electrolytes is discussed in detail in the succeeding pages. Some of these electrolytes are major components of the body’s natural buffer system. However, their role as buffers is discussed in the section “buffer systems”, and not in this section.

Sodium (Na\(^+\))

Sodium is the major cation in the extracellular fluid (ECF) compartment, accounting for 90-95\% of all solutes. The normal concentration of sodium in the ECF compartment is between 135 to 145 mEq/L, while its intracellular concentration is between 3 to 5 mEq/L (29).

Sodium plays several roles in the maintenance of ECF volume and fluid distribution, namely (29);

- By exerting significant osmotic pressure (osmolality)
- By intracellular entry and moving against electrochemical gradient

Generally speaking, sodium ions go where water goes. As a result, water and sodium imbalance disorders occur simultaneously. Sodium is actively transported and absorbed by the intestines and renally and cutaneously excreted. As mentioned previously, the kidneys regulate water (and sodium) excretion through the renin-angiotensin-aldosterone axis. Renin is renally secreted during alterations in sodium concentration in the renal tubules (29).

There are two major factors to sodium excretion, namely (29):

- Glomerular filtration rate
- Aldosterone
Alterations in the sodium levels in the body are often the result of clinical conditions involving fluid volume excess or deficit. Also, alterations in the plasma sodium concentrations affect the plasma, intracellular fluid and interstitial fluid volumes and blood pressure (29).

Additionally, sodium regulates the action potentials in skeletal muscles, neurons, and cardiac muscles. The diffusion potential of cell membranes occurs due to alterations in the sodium and potassium concentrations in the extracellular and intracellular fluid compartments, respectively (29).

Potassium (K⁺)

Potassium is the primary intracellular cation. Normally, serum potassium level is between 3.5 to 5.5 mEq/L, and its intracellular concentration is 160 mEq/L. Potassium ion concentrations in the extracellular fluid are low (30).

Like sodium, it also plays a role in fluid balance. Specifically, it has four major roles in the body (29):

- It regulates the action potentials in the various systems of the body (e.g. nervous, integumentary and cardiac conduction).
- It enhances acid-base balance by maintaining the electroneutrality of body fluids.
- It is released during cellular catabolism. Additionally, carbohydrate metabolism and protein synthesis also require potassium.
- It maintains intracellular osmolarity via the sodium-potassium ion pump.
Elevated potassium levels stimulate the secretion of aldosterone through the renin-angiotensin-aldosterone axis or through the direct release of aldosterone from the adrenal cortex. Once released, aldosterone stimulates potassium ion excretion in the kidneys (29).

Moreover, the regulation of sodium and potassium in the interstitial and intracellular fluid compartments are achieved through the sodium-potassium pump. A good example of how the sodium-potassium pump works is exhibited by severely burned pediatric patients. The injury results in the movement of sodium into the interstitial spaces in place of water. The movement decreases the efficiency of the sodium pump, allowing entry of more water and sodium into the intracellular space. The resulting elevated osmotic pressure gradient propels the movement of potassium ions into the extracellular fluid compartment. Compensatory mechanisms are activated when this happens, prompting the release of aldosterone and antidiuretic hormone (ADH) to stimulate sodium and water retention (29).

Chloride (Cl\(^-\))

Chloride is the major anion found in the extracellular fluid compartment. Its primary function is to act as a buffer in the maintenance of acid-base balance. Like sodium, chloride, also plays a role in the maintenance of serum osmolality (31).

Chloride competes with bicarbonate for the cations in the extracellular fluid compartment to create electroneutrality. Chloride ions are attracted to positively charged cations (e.g. Na\(^+\), H\(^+\), K\(^+\) and Ca\(^{+2}\)), creating a balance of the positively charged electrolytes in the extracellular fluid compartment. Because of their attraction and consequent combination with major cations in the body, alterations in serum chloride levels also generally indicate alterations in other electrolytes and disruption of the acid-base balance (31).
A high concentration of chloride ions is found in gastric secretions and sweat. Under normal pH conditions, almost all (ninety nine percent) chloride ions are reabsorbed. There are two major factors that govern the excretion of chloride ions, namely (31):

- Acidosis
- Alkalosis

In acidosis, fewer chloride ions are reabsorbed in the kidneys.

Calcium (Ca\(^{2+}\))

Calcium is another cation that is found primarily in the extracellular fluid compartment. Together with phosphate and magnesium, it is crucial in nerve conduction, bone composition, and enzymatic reactions. Electrolyte balance of these three ions is achieved through intestinal absorption and renal excretion. Additionally, calcium also plays a role in blood clotting, serum complement activation, hormonal production, and cell membrane permeability (31).

About ninety to ninety nine percent of the calcium in the body is stored in the bones and teeth, with the meager remainder found in the soft tissue and serum. Only half of the serum calcium is ionized; the rest is bound to protein or combined with anions. Calcium ions play a major role in (31):

- Cardiac function
- Muscular contraction
- Nerve impulse conduction
- Blood coagulation

It is therefore important to remember that the measurement of total calcium level is insignificant in the assessment of acid-base imbalance. It is the total serum calcium that is
important and its direct measurement is critical in suspected disorders involving this ion. Ionized calcium levels are in the range of 1.14 to 1.29 Mmol/L (31).

Calcium is present in the pores of all cells. It dictates membrane permeability and action potential by controlling the ability of sodium to enter during depolarization. Hypocalcemia causes increased muscle excitability and tetany, while hypercalcemia causes cardiac arrhythmias (31).

There are two hormones that principally regulate calcium levels (31):

- Parathyroid hormone (PTH)
- Calcitriol (a hormonally active form of vitamin D)

Calcitriol controls the intestinal absorption of calcium while the parathyroid hormone regulates renal excretion of calcium. The latter is secreted when ionized calcium levels are low and is inhibited in conditions such as hypomagnesemia. Calcitriol, PTH and serum phosphate levels regulate bone deposition and resorption of calcium.

Serum calcium levels are normally stable due to the constant bone resorption and deposition. However, when this balance is upset, the rate and degree of these bone activities increases and decreases accordingly. For example, when serum calcium levels fall below the normal range, PTH is secreted, stimulating the osteoclastic release of calcium from the bones. Additionally, the PTH secretion also stimulates calcium reabsorption in the kidneys (32).

It should be noted that calcium reabsorption and phosphate excretion go together, just like sodium reabsorption occurs together with chloride excretion.
Magnesium (Mg$^{2+}$)

Magnesium is an intracellular cation that regulates muscle contractions and intracellular activity. Its distribution in the body is similar to that of potassium. It makes up roughly about sixty percent of the mineral component of bones, forty percent of the body cells, and less than 1 percent of the extracellular fluid compartment. The four primary functions of magnesium are stated below (25) (31):

- Enzyme activation
- Protein and nucleic acid synthesis
- Mediation of skeletal muscle tension
- Inhibition of electrical activity at the neuromuscular junction

The magnesium ion functions as a cofactor in many enzyme reactions involving phosphate group transfers, namely (25):

- Glucose metabolism
- Pyruvic acid
- Adenosine triphosphate (ATP)

Magnesium is needed by the ATP-synthesizing protein in the mitochondria. It is worth noting that ATP primarily exists as a complex molecule with magnesium, in the form of MgATP. MgATP is required for cell-signalling, most notably in the formation of cyclic adenosine monophosphate (cAMP) (25).

Like calcium, magnesium inhibits electrical activity in the neuromuscular junction. It does this by acting directly on the myoneural junction, thereby producing neuromuscular irritability and contraction of the cardiac and skeletal smooth muscles (31).
Regulation of serum magnesium concentration is achieved primarily by the kidneys. The gastrointestinal tract and bones also play some role. When the magnesium concentration in the glomerular filtrate goes over the normal limit, a large amount of magnesium ions are excreted in the urine. Magnesium reabsorption takes place in the ascending loop of Henle and regulated by the concentration of magnesium ions in the serum. Like calcium, the majority of magnesium is not found in the serum; therefore, measurement of its total serum concentration does not reflect the total body stores. Magnesium levels are stable and in correlation with serum calcium levels. Its concentration is inversely proportional to phosphorus.

Magnesium is absorbed primarily in the small intestine, via passive diffusion through bulk flow of water. The amount of magnesium absorbed is dependent on the amount ingested. In a usual American diet, 30-40% of magnesium is absorbed. During magnesium deficiency (i.e., 1 mmol/d), approximately 80% is absorbed, while only 25% is absorbed when the intake is normal or high (25 mmol/d). The precise mechanism by which these variations in fractional magnesium absorption happen remains obscured and ill-understood. One assumption is that only ionized magnesium is absorbed. High luminal phosphate or fat content may precipitate magnesium and reduce absorption.

In the gastrointestinal tract, calcium and magnesium have an inverse relationship on each other's absorption; a high calcium intake may reduce magnesium absorption, and a low magnesium intake may stimulate calcium absorption. The parathyroid hormone is also known to stimulate magnesium absorption. Endogenous and exogenous cortisone decreases the absorption of calcium, and appears to stimulate the transport of magnesium.

There are several factors that influence the renal processing of magnesium, namely (99):

- Increased fluid volume in the extracellular compartment stimulates sodium, magnesium and calcium elimination. As a result, reabsorption of magnesium in the loop of Henle is decreased which may be attributed to increased movement of
water and sodium to the thick ascending limb and reduction in the potential difference.

- Alterations in the glomerular filtration rate impact magnesium reabsorption in the renal tubules. In the event that the GFR and the corresponding filtered load of magnesium in chronic renal failure are reduced, partial reabsorption is likewise reduced, explaining the fact that plasma magnesium value remains normal until patients reach end-stage renal disease.

- Phosphate depletion is also known to stimulate urinary magnesium excretion, through a mechanism that is not clear.

Elevated serum calcium and magnesium prevent magnesium reabsorption through activation of the calcium-sensing receptor (CaSR). The CaSR is expressed in the basolateral membrane of the thick ascending limb of the loop of Henle. When either calcium or magnesium stimulates the receptor, the production of arachidonic acid derived 20-hydroxyeicosatetraenoic acid (20-HETE) is augmented, which in turn, temporarily causes the shutdown of the apical potassium channels (ROMK2 channels) (100). The release of potassium into the lumen affects magnesium absorption in two ways;

- It offers potassium in exchange for sodium chloride reabsorption by the Na-K-2Cl cotransporter (NKCC2)

- It renders the lumen electropositive which allows passive calcium and magnesium reabsorption (101). Thus, inhibition of ROMK2 channels in the thick ascending limb of Henle’s loop decreases active sodium transport and passive calcium and magnesium reabsorption.

Mutations in the calcium-sensing receptor results in autosomal-dominant hypocalcemia with hypercalciuria (ADHH) which is characterized by hypocalcemia, hypercalciuria, and hypomagnesemia and by low, but detectable, levels of parathyroid hormones (102) (103).
Generally, long-standing metabolic acidosis leads to urinary magnesium excretion greater than 1 mmol/day in the presence of hypomagnesemia, whereas chronic metabolic alkalosis leads to the reverse. Long-standing metabolic acidosis reduces renal TRPM6 expression in the distal convoluted tubule, promotes magnesium excretion, and reduces serum magnesium levels, whereas long-standing metabolic alkalosis results in the exact reverse effects (104).

Unlike sodium reabsorption, there’s no one single hormone responsible for the regulation of magnesium reabsorption in the kidneys. Experimental studies have shown the following hormones to play a role by coupling with adenylate cyclase in the thick ascending limb of Henle’s loop (276):

- Parathyroid hormone
- Calcitonin
- Glucagon
- Vasopressin (anti-diuretic hormone)
- Beta-adrenergic agonists

Other hypothesis include the following mechanisms (276):

- Increase in luminal positive voltage (via activation of basolateral membrane chloride conductance and NKCC2)
- Increase in paracellular permeability (possibly by the phosphorylation of paracellular pathway proteins).

Bicarbonate (HCO$_3^-$)
Bicarbonate plays an important role in the body’s natural buffer system. The bicarbonate ion is the primary physiological buffer of the extracellular fluid. Its role is maintaining the normal pH of the blood and other fluids in the body (276).

Measurements of bicarbonate levels help monitor the pH of the blood and body fluids. There are several factors that alter the normal values of these measurements, including (25):

- Foods
- Medications
- Renal function
- Pulmonary function
- Diseases

Bicarbonate level may increase or decrease in response to diseases that interfere with respiratory and kidney functions, metabolic conditions, or other causes (25).

The chemical formula for the bicarbonate ion is $\text{HCO}_3^-$. Sometimes, it is represented as the concentration of carbon dioxide ($\text{CO}_2$).

Phosphate ($\text{PO}_4^{2-}$)

Like calcium, phosphate is largely found in the bones. Approximately eighty-five percent of phosphorus is held in the bones and ten percent in the extracellular fluid compartment. The remaining amounts are distributed in the soft tissues and in the intracellular fluid compartment. Phosphate, the main intracellular anion, also exists as elemental phosphorus in the body. It should be noted that serum phosphorus levels are higher in the pediatric population at 6 mg/dl in infants and children because of the rapid skeletal growth. The normal serum phosphate levels in adults range between 2.5 to 4.5 mg/dl (25).
Other forms of phosphates such as phosphoproteins and phospholipids have a variety of physiological roles, namely (25):

- Energy production
- Tissue oxygenation
- CNS function
- Carbohydrate metabolism
- Leukocyte function

The kidney plays a crucial part in phosphorus homeostasis. More than ninety percent of plasma phosphate is filtered in the kidneys; with its reabsorption occurring mostly in the proximal tubule (25).

Additionally, like the carbonate anion, phosphate also plays an important role in the body’s natural buffer system. Unlike the carbonate anion, it acts as a buffer in the intracellular fluid. The phosphate buffer system is made up of two components, namely (25):

- Sodium salts of dihydrogen phosphate ($\text{NaH}_2\text{PO}_4^{-}$), a weak acid
- Monohydrogen phosphate ($\text{Na}_2\text{HPO}_4^{2-}$), a weak base

VI. ELECTROLYTE DISORDERS AND THEIR EFFECTS ON SPECIFIC BODY SYSTEMS

Electrolytes like sodium, potassium and magnesium have pronounced effects on muscle and nerve tissues. Most of the clinical manifestations of electrolyte imbalance are predominantly neurologic and mimic the severity of nerve damage. Furthermore, these imbalances, though reversible, may appear with seizures, or with rapidly progressive
neurologic symptoms and signs (e.g. encephalopathy and CNS neuronal depression), and thus need emergency treatment (33) (34). Seizures are common in patients with low levels of sodium, magnesium and calcium. Furthermore, potassium and magnesium depletion can lead to reversible but life-threatening arrhythmias.

The specific effects of these electrolyte imbalances on specific body systems, particularly the cardiovascular, neurologic and skeletal, are discussed in detail in the succeeding pages.

*Cardiovascular effects*

The normal basal heart rate for adults ranges from approximately 60-100 beats per minute (bpm). There is scientific evidence pointing to basal heart rate above 80 bpm to be caused by a possible underlying heart disease. A study published in *The Journal of Epidemiology & Community Health* in 2010 measured the heart beats of 50,000 healthy men and women above 20 years old and found that for every 10 bpm increment, there is a corresponding 18 percent and 10 percent increased risk of dying of a heart attack in women and men, respectively (35).

Arrhythmias adversely affect cardiac efficiency, increasing the risk of cardiac arrest, stroke or embolism (36) (37).

The normal functioning of the heart’s electrical conduction system largely depends on the levels of various electrolytes in the body. The formation of electrical impulses occurs when electrolytes such as sodium, potassium, calcium, and magnesium pass through the ion-gated channels of the cardiac cells. Electrolyte imbalance prevents the proper generation of impulses, and/or their normal conduction, resulting in arrhythmias. Many of the anti-arrhythmic medications exert their therapeutic effects by modulating the opening and closing of these ion channels (38).
Hypercalcemia

Hypercalcemia affects the conducting system of the heart and potentiates cardiac arrhythmias. Calcium has a positive inotropic effect. Hypercalcemia also causes hypertension that may be triggered by renal dysfunction and direct vasoconstriction.

Hypokalemia

Among all the electrolytes in the body, potassium and sodium play the most critical roles in maintaining normal cardiovascular health. In this section, the discussion is solely focused on the role of potassium on cardiovascular health.

The normal extracellular potassium concentration is in the range of 4.0 to 4.5 mEq/L. It is maintained by a complex interaction involving potassium excretion and consumption. Maintaining normal potassium levels is an essential preventive measure against potentially serious sequelae, particularly in patients with high risks for cardiovascular disease and complications. In such patients, several factors come into play and should be considered, namely:

- Endogenous and exogenous catecholamine activity,
- Renin-angiotensin-aldosterone system activation
- Use of potassium depleting diuretics and other medications

The role of potassium-depleting diuretics will be discussed in detail in the section, Causes and Risk Factors.

Because potassium ions mediate cardiac repolarization, potassium depletion is very arrhythmogenic, particularly when the patient is on comcomitant digoxin or antiarrhythmic therapy. Hypokalemia adversely affects myocardial refractory periods and
induce arrhythmias. On the other hand, hyperkalemia produces slow electrical conduction and conduction block which, when left untreated, can progress to asystole. Hyperkalemia can compensate for the side effects of antiarrhythmic agents and repolarizing potassium currents (69).

On an electrocardiograph, hypokalemia produces a flattening or inversion of the T wave accompanied by a prominent U wave and prolonged QT interval. These patterns are not specific to hypokalemic patients; in fact, similar findings are seen in patients on antiarrhythmic agents, or phenothiazine, or diagnosed with ventricular hypertrophy or marked bradycardia (70) (71).

In the clinical setting, hypokalemia-induced arrhythmias are usually atrial fibrillation and multifocal atrial tachycardias, with the most fatal being ventricular tachyarrhythmias. The latter can range from an increase in the frequency of premature ventricular contractions that linearly correspond to the decrease in serum potassium levels, to non-sustained ventricular tachycardias and development of monomorphic and polymorphic ventricular tachycardias such as Torsade de pointes and ventricular fibrillation. Low potassium levels can also significantly alter the effects of antiarrhythmic drugs.

Various studies completed in the last 30 years show a link between serum potassium levels and the development of ventricular arrhythmias in patients admitted with acute myocardial infarction (72) (73) (74) (75) (76). The sudden overwhelming catecholamine release that occurs during acute myocardial infarction causes a rapid, but short-lived transcellular movement of potassium ions, leading to a transient but large decrease of serum potassium concentration to about 0.5-0.6 mmol/L. These mechanisms are apparent in the autopsies of patients who died of cardiac arrest wherein their myocardial potassium content was significantly lower (about 0.063 mmol/g wet weight) when compared to those who died from trauma (0.074 mmol/g wet weight). Accordingly, myocardial
magnesium contents were also significantly lower (77). The role of magnesium in cardiovascular pathologies will be discussed later in this section.

Clinician must remember that the increased risk of primary ventricular fibrillation brought on by low potassium levels in patients with acute myocardial infarction is also somewhat relative to the size of the infarct. Larger infarctions usually result in greater surge of plasma catecholamines and consequently, also greater intracellular fluctuation of potassium ion concentration. Therefore, lower potassium values may not directly correlate with arrhythmia risk but rather infer a larger infarct size with its accompanying risk.

It is important for clinicians to see transcellular potassium movements in patients with acute myocardial infarction in the context of the underlying potassium balance or existing serum potassium levels. Therefore, a patient who had normal or high-normal serum potassium levels before the onset of acute myocardial infarction is likely to exhibit dramatically low levels that moderately increase their risk for ventricular arrhythmias. On the other hand, a hypertensive patient on potassium-depleting antihypertensive medication (e.g. furosemide) may be subjected to greater arrhythmogenic risk because of the transcellular potassium movements in the setting of total body potassium deficit.

There is no doubt that hypokalemia is an important contributing factor in cardiac deaths caused by various arrhythmias, but it should be remembered that there are other factors that come into play as well, including diuretic therapy. The use of diuretics, especially in large doses, has also been associated with lower cardiovascular deaths owing to their mechanism of action that result in lower blood volume. Moreover, the dose-dependent diuretic-induced hypokalemia does not always put patients at greater risk of arrhythmias, even in those with diagnosed left ventricular hypertrophy. A study done on patients with and without left ventricular hypertrophy followed their 4 week progress while on 100 mg of hydrochlorothiazide. As expected, hypokalemia set in, but interestingly enough, there
was no rise in ventricular premature contractions, couplets, or ventricular tachycardia noted in the patients with left ventricular hypertrophy before and after exercise (78) (79) (80).

Potassium supplementation from exogenous sources decreases blood pressure levels in hypertensive individuals (81) (82). In a meta-analysis of 33 randomized, controlled trials in more than 2600 normotensive and hypertensive adults, the effects of supplemental oral dietary potassium (median dose of 75 mmol/day) on blood pressure levels were evaluated (83). The results showed small net changes to the overall systolic and diastolic levels. In a clinical setting, clinicians may deem these changes to be insignificant; however, they may do well to remember that from a public health perspective, these results are still important. Studies on hypertensive patients who are not under antihypertensive medications also showed significant blood pressure reduction after oral potassium supplementation. Hypertensive patients experienced larger reduction of blood pressure levels compared to normotensive individuals. Additionally, studies such as the Dietary Approaches to Stop Hypertension (DASH) trial showed significant blood pressure reductions in individuals who followed diets rich high in potassium, with intakes of 37-71 mmol/day (84).

The epidemiologic and clinical trial data supporting the positive effects of potassium in hypertensive patients is now beginning to be recognized as an important aspect of electrolyte balance in this special group of patients. A reduction in sodium intake is not the only recognized beneficial move; increasing dietary potassium intake too is a positive step. This can be done through the gradual and prolonged efforts to avoid dietary factors with high salt content and substitution with fruits and vegetables. Additionally, the form of potassium supplement given does not affect the blood pressure lowering effects of the ion itself; potassium chloride, potassium phosphate, potassium citrate, and potassium acetate all appear to exhibit similar degree of antihypertensive effects.
Hypertension is an important risk factor in the development of stroke. The beneficial effects of dietary potassium intake (increase of 10 mmol/day) on stroke risk were initially brought to light by a study done by Khaw and Barrett-Conner in 1987 (85). In the recent years, other studies have also found the importance of dietary potassium in cardiovascular health, namely, the Health Professionals Study (86), the National Health and Nutrition Examination Survey I (NHANES-I) (87), and the Nurses' Health Study (87). Findings from all three studies showed that increased dietary potassium intake is inversely and dose-proportionally related to stroke risk. In the NHANES-I follow-up study (87), a dietary intake of ≤34.6 mmol of potassium over 24 hours showed significant increased risk of stroke, with a 1.28 hazard ratio.

The stroke-protective effects of increased dietary potassium intake may be due to its potency; a small increase in intake that results in a small but significant degree of blood pressure reduction. Another possible mechanism may be due to its direct endothelial effect, wherein it prevents the adherence of macrophages to the vascular walls, an important factor in stroke (88). Additionally, some studies have shown that increased potassium intake in the diet in the form of fruits and vegetables have resulted in risk reduction of ischemic stroke in men and women, independent of blood pressure, suggesting the presence of another cardioprotective mechanism (89) (90). Fruits and vegetables, though high in potassium, are also rich in other nutrients such as calcium, fiber, and antioxidants. In 2002, the Food and Drug Administration (FDA) approved a health claim that "diets containing foods that are good sources of potassium and low in sodium may reduce the risk of hypertension and stroke." Only foods that contain at least 350 mg potassium, <140 mg sodium, <3 g total fat, ≤1 g saturated fat, and ≤15% of energy from saturated fatty acids are qualified to make this claim. Examples include low-fat dairy products such as low-fat and non-fat milk, and low-fat yogurt (91).

Increased dietary potassium intake and/or potassium supplementation affords a substantial cardio- and vascular protection. Studies done on animals showed that potassium inhibits the production of free hydroxy radicals, proliferation of vascular
smooth muscle cells, platelet aggregation, and arterial thrombosis. Additionally, it reduces cholesterol aggregation on the vascular walls (92) (93) (94) (95).

As clinical understanding of potassium benefits grows, there is a corresponding prejudice against low potassium levels and greater acceptance of high to high-normal levels. Serum potassium reflects the true levels in chronic dietary intake and should be monitored in all patients who are newly diagnosed with hypertension, heart failure, or any other illness requiring therapy with a diuretic or agent that inhibits the renin-angiotensin-aldosterone system.

Hyperkalemia does not usually occur in patients with normal renal status, because potassium overload are managed efficiently and excreted rapidly (96) (97) (98). In the Studies of Left Ventricular Dysfunction (SOLVD) database, severe hyperkalemia due to enalapril therapy does not typically occur; only 6.4 percent of the 1285 patients acquired potassium levels >5.5 mmol/L (98).

In patients with congestive heart failure, cardiac arrhythmias, or hypertension, the National Council on Potassium in Clinical Practice recommends clinicians to maintain serum potassium levels at ≥4.0 mmol/L. However, to circumvent the onset of possible hypokalemia, perhaps an optimal serum potassium level in patients with these existing conditions but without comorbid renal dysfunction should be slightly higher, in the normal to high-normal range of 4.5-5.0 mmol/L.

For hypokalemic patients with coexisting cardiac conditions, the therapeutic goal should be to maintain serum potassium levels in the normal range. Clinicians need to be aware of the dose-dependent hypokalemic effects of many classes of diuretics including the thiazides, loop diuretics and carbonic anhydrase inhibitors. In cases like these, the clinician should encourage the patient to decrease sodium intake and increase potassium intake in the diet. Another measure to take may be to put the patient on oral potassium
supplementation or consider the addition of potassium-sparing diuretics to the therapy (e.g. angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or aldosterone-receptor antagonist). Finally, serum potassium levels should be regularly monitored by the clinician.

Dietary intake of foods rich in potassium should be encouraged when serum potassium levels are between 3.5 and 4 mmol/L, if for no other reason than to reduce blood pressure, which may occur at the onset of high potassium intake. If potassium levels fall below 3.5 mmol/L, which typically occurs because of exogenous potassium deficit, oral supplementation with a potassium salt such as potassium chloride may be initiated at a starting dose of 20-60 mmol/day. The use of the bicarbonate salt may be more helpful in cases of potassium depletion and coexisting metabolic acidosis. If increasing dietary potassium intake or oral supplementation does not restore potassium levels to normal or is not acceptable to the patient, the addition of potassium-sparing diuretics may be used.

Potassium homeostasis, like other electrolytes, undergoes alterations. Clinically, they are encountered often in hospitalized patients. These abnormalities, hypokalemia and hyperkalemia, are associated with specific symptom complex. Studies in the recent years have pointed out that even in the presence of normal serum potassium levels, pathophysiologic consequences of reduced dietary potassium intake are important to recognize and treat. Based on existing literature, it appears that a serum potassium value stabilized at the range of 4.0-5.0 mmol/L is both safe and likely to provide sufficient cardioprotection. However, it is not certain whether there is an increased risk that accompanies potassium values in the 3.5-3.9 mmol/L range in diuretic-treated patients. Finally, increased potassium intake should be encouraged in most patients with current clinical trial evidence supporting a daily intake of potassium ≥60 mmol/day.

Hypomagnesemia
Magnesium imbalances such as hypomagnesemia can result in abnormalities in nearly every organ system and lead to potentially fatal complications. Low magnesium levels can cause cardiovascular disturbances in the form of ventricular arrhythmia, coronary artery vasospasm, sudden death. Despite the documented significance of magnesium, abnormal levels are still a common occurrence among patients. Because of this, it has been sometimes referred to the "forgotten cation" (99).

The average American diet provides about 15 mmol of magnesium. The recommended daily intake for healthy individuals is 0.15-0.2 mmol/kg/day. Magnesium is abundant in nature; green vegetables, cereal, grain, nuts, legumes, and chocolate are all rich in magnesium. However, despite its abundance in the diet, cooking and food processing have reduced the daily intake to less than the required daily allowance (276).

As mentioned previously, magnesium is the second most common intracellular cation. It plays a fundamental role in many cellular functions including energy transfer, storage, and use; protein, carbohydrate, and fat metabolism; stabilization of cell membrane integrity and function; and the regulation of parathyroid hormone (PTH) secretion. In the cardiovascular system, magnesium lowers blood pressure and changes peripheral vascular resistance (276).

The plasma magnesium concentration is stabilized with a narrow range. Magnesium concentration in the extracellular fluid compartment is in equilibrium with those stored in the bones and soft tissues. Unlike other ions such as calcium, magnesium excess and deficiencies are approached differently because of two unique factors (276):

- Magnesium stores in the bone and is not readily mobilized to respond to low serum concentrations in the extracellular fluid space
- Limited hormonal modulation of urinary magnesium excretion occurs
As mentioned previously, hypokalemia is a common event in patients with hypomagnesemia, occurring in 40-60 percent of cases (105).

Arrhythmia

Hypomagnesemia has several cardiovascular effects including:

- Electrical activity
- Myocardial contractility
- Potentiation of digitalis effects
- Vascular tone

As such, low serum magnesium levels are linked to arrhythmias and hypertension. Additionally, epidemiologic data has found a link between magnesium deficiency and coronary artery disease (CAD).

Hypomagnesemia is now a well-known cause of cardiac arrhythmias (106) (107). Electrocardiographic changes include the following nonspecific findings:

- Prolongation of conduction
- Slight ST depression

Patients with hypomagnesemia are especially susceptible to digoxin-induced arrhythmia. The combined effects of intracellular magnesium deficiency and digoxin overload undermine the function of the Na\(^+\)/K\(^+\) ATPase pump. The resulting intracellular potassium reduction impairs the resting membrane potential and repolarization phase of the myocardial cells, augmenting the inhibitory effect of digoxin. For this reason, clinicians sometimes add intravenous magnesium supplementation as an adjunct to atrial fibrillation therapy with digoxin (108).
There’s a multitude of non-digitalis-associated arrhythmias. The clinical disturbance of greatest importance is the association of mild hypomagnesemia with ventricular arrhythmia in patients with cardiovascular disease. Patients who are most at risk are those with acute myocardial ischemia (AMI), congestive heart failure (CHF), or recent cardiopulmonary bypass, as well as acutely ill patients in the intensive care unit (106).

The effects of magnesium ion deficit on cardiac arrhythmia may be linked with a dysfunctional membrane sodium-potassium Na+/K+ pump and the increased extracellular potassium transport through the potassium channels in cardiac cells, resulting in a shortened action potential and greater risk of cardiac arrhythmia (109). Torsade de pointes, a repetitive, polymorphous ventricular tachycardia with prolongation of the QT interval has also been associated with low serum magnesium levels. The American Heart Association (AHA) recommends magnesium sulfate as an adjunct to therapy used to treat torsade de pointes.

Hypertension

Magnesium also influences blood pressure control. Specifically, a reduction in intracellular free magnesium can result in greater vascular tone and sensitivity, which in turn increases total peripheral resistance, and thus, elevated blood pressure. Another theory that has been put forward suggests the opposite; intracellular accumulation results in the activation of actin-myosin contractile proteins, which increase vascular tone and total peripheral resistance. On the other hand, epidemiologic data have failed to find a solid association between the two, with results from clinical trials examining the hypotensive effects of magnesium supplementation found to be conflicting. This is backed by the DASH study (Dietary Approaches to Stop Hypertension) wherein a diet rich in fruits and vegetables (rich in potassium and magnesium) resulted in blood pressure reduction (110). However, these findings need to be substantiated by larger, carefully performed, randomized clinical trials.
Atherosclerosis

Epidemiological data have shown that patients with existing atherosclerosis have a higher incidence of magnesium deficiency than control subjects (111)(112). Growing evidence points to magnesium deficiency as a player in the pathogenesis, initiation, morbidity, and mortality associated with myocardial infarction (276).

The serum magnesium level is inversely linked with serum cholesterol levels. Thus, a low magnesium level is closely linked with hypertension and hypercholesterolemia, all of which are established risk factors for the development of atherosclerosis. Additionally, hypomagnesemia often coexist with thrombotic tendencies, increased platelet aggregation, and increased vascular reactivity to contractile stimuli. These are significant mechanisms in the development of acute myocardial infarction. However, research evidence is also insufficient to support the clinical administration of intravenous magnesium in the setting of acute myocardial infarction with only 16% reduction in all, causing mortality being reported in a study of 2316 patients (113).

Additionally, there have been reports of increased incidence of cardiac arrhythmia in patients with hypomagnesemia in the setting of coronary artery disease. Specifically, collected study data point out that magnesium supplementation may decrease the occurrence of potentially life-threatening ventricular arrhythmia.

Patients subjected to cardiopulmonary bypass during surgery have also been reported to have developed hypomagnesemia, increasing their risk of arrhythmia (114). This complication can be circumvented with the administration of intravenous magnesium post-cardiopulmonary bypass, with study data favoring this decision and showing significant decrease in incidences of supraventricular and ventricular arrhythmia in relatively small trials of adult (115) (116) and pediatric patients (117). In line with this, clinicians need to carefully evaluate magnesium status in patients with coronary artery disease and administer magnesium supplements in patients with magnesium deficiency. It
should be noted that routine use of magnesium supplements as an adjunct in myocardial infarction remains debatable because of other available and clinically proven interventions such as the use of thrombolytics and coronary angioplasty.

**Central nervous system effects**

Just like the heart, the maintenance of electrolyte balance is essential for normal brain function. The regulation of ionic balance in the CNS involves the interplay between the following intricate mechanisms:

- Movement of molecules into and out of the brain
- Blood–brain barrier function
- Neuronal and glial membranes

Ion gradient changes across cellular membranes are known to both directly or indirectly affect the discharge of electrical impulses, leading to epileptiform dysfunctions (39).

Electrolyte imbalance in the CNS can present with a variety of neurologic symptoms. Generally, these symptoms are caused by the functional changes taking place in the brain, rather than structural changes. This means that with the appropriate and timely treatment, they are reversible (40) (41). However, clinicians will do well to remember that functional alterations such as seizures can also lead to irreversible morphologic alterations to brain tissues and therefore, require treatment of the underlying electrolyte imbalance as soon as possible.

As mentioned in the beginning of this section, sodium and fluid imbalance leads to CNS neuronal depression, characterized by encephalopathy. Additionally, these electrolyte imbalances can also provoke CNS neuronal irritability. In a similar vein, elevated calcium and magnesium serum levels produce CNS neuronal depression with encephalopathy while low levels of calcium and magnesium primarily leads to CNS
neuronal irritability with seizures. On the other hand, potassium excess or deficit rarely produce neurological symptoms, rather they are mainly associated with muscle weakness (42) (41).

CNS neuronal depression and encephalopathy are mainly characterized by the following symptoms (in the absence of focal cerebral disease and cranial nerve involvement) (40) (41):

- Confusion and other mild cognitive disturbances
- Headache
- Lethargy
- Weakness
- Tremor

The prevalence of electrolyte disorder and seizures in clinical practice is outlined in the table below.

<table>
<thead>
<tr>
<th>Electrolyte disorder</th>
<th>Frequency in clinical practice</th>
<th>Frequency of seizure in both acute and severe imbalance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Hypocalcemia</td>
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<tr>
<td>Hypercalcemia</td>
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<tr>
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<tr>
<td>Hyperkalemia</td>
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</tbody>
</table>

+++: Frequent; ++: Occasional; +: Rare; -: Absent

As seen in the table above, seizures occur frequently in hyper- and hyponatremia, hypocalcemia, and hypomagnesemia (42) (41). The type of seizure mostly seen in cases like these is the generalized tonic–clonic, although partial seizures or other seizure types can also occur. One common factor among these seizure disorders is the fact that they typically occur in rapidly developing electrolyte abnormalities rather than those progressing slowly. Because of this, it is impossible to allocate absolute electrolyte measurements above or below which trigger convulsions (42).

Hyponatremia

As mentioned earlier, low serum sodium levels or hyponatremia is a frequent cause of seizures. This is especially true in newborns younger than 6 months who do not show other apparent causes. These patients are especially vulnerable to acute cerebral edema and herniation. The principal neurologic symptoms may become apparent when hyponatremia approaches 120 mM (41).

The brain has its own adaptive mechanisms to cope with electrolyte imbalance. When serum sodium level falls, the resulting brain swelling is dealt with by two coping mechanisms. The first mechanism responds by displacing water from the interstitial space and into the cerebrospinal fluid and finally to the systemic circulation. The movement is propelled by the increase in hydrostatic pressure. The fluid volume in the brain is rapidly but only partially restored within 3 hours of the initial expulsion of the extra fluid and electrolytes from the brain cells. The second adaptive mechanism that comes into play during hyponatremia is the exit of organic osmotically active agents such as amino acids from the brain tissues. This mechanism is slow compared to the first one, able to restore normal fluid volume in the brain only after 48 hours from the start of edema (43) (44).
These organic osmotically active agents are especially important in the cellular adaptation to chronic alterations to osmolality. In cases where hyponatremia develops slowly i.e. over a period of more than 48 hours, cerebral swelling and neurologic symptoms are kept at bay by these two adaptive mechanisms, even if there is a large serum sodium excess in the tissues. On the other hand, a rapid development of hyponatremia i.e. acute cases can overwhelm these coping mechanisms, resulting in persistent cerebral edema and associated neurologic symptoms (45) (44).

The severity of brain damage from hyponatremia is a result of several factors, namely:

- Rapidity of plasma sodium decline
- Severity of hyponatremia
- Age
- Gender

It wasn’t until much recently that studies have emerged to demonstrate the influence of age and gender on the outcome of brain damage due to hyponatremia. These studies have singled out children and menstruating women to be those who are most at risk (46) (44). Another study has reinforced this finding, with results that show women to have a 25-fold increased risk compared with men of death or permanent neurologic damage as a result of the hyponatremia (47). Hypoxia and ischemia disrupt the brain’s two adaptive mechanisms to hyponatremia and further aggravate cerebral edema. This point is especially important to remember in patients with seizure disorders and why clinicians need to act quickly to circumvent these complications and undermine the body’s natural coping mechanisms. Another potential risk is osmotic demyelination. Once the adaptive mechanisms of the body begin, a “de-adaptation” process also starts. The latter is characterized by the rapid reaccumulation of electrolytes and slow reentry of organic osmotically active agents in the brain cells. Thus, in patients with chronic hyponatremia, clinicians theorize that the rapid improvement of serum sodium—before the improvement in intracellular concentration of osmotically active agents happen—leads to water deficit
in the neuronal and glial cells. Consequently, the process predisposes the patients to the risk of osmotic demyelination syndrome (ODS), which is associated with pontine and extrapontine demyelination (47) (45) (41). However, other clinicians have pointed out that ODS is not solely dependent on the rate of hyponatremia correction but also on comorbidities such as chronic alcoholism, anoxic brain injury, and severe liver dysfunction (48) (44).

The CNS signs and symptoms of hypotonic hyponatremia become more evident with the rapid and large decrease in serum sodium concentration (47) (45). Generally, the symptoms of hyponatremia correspond to the severity of cerebral edema. Chronic hypernatremia is primarily asymptomatic, with about less than half of patients showing no neurologic manifestations even with serum sodium concentrations <125 mEq/L (47). This is because the neurologic deficits do not typically appear until the serum sodium level is ≤110 mEq/L. Pediatric patients are specifically at higher risk of developing symptomatic hyponatremia because of their larger brain-to-skull size ratio.

Seizures generally occur if the plasma sodium concentration quickly deteriorates to <115 mEq/L. At this concentration, the onset of seizure is associated with high mortality rates and should therefore be considered as a life-threatening medical emergency (41). Even small increments (e.g. 5%) in the serum sodium concentration can significantly improve cerebral edema; cessation of seizures can be achieved by rapid increments of about 3 to 7 mEq/L (45). However, it may be days before symptomatic improvements become evident, especially in geriatric patients (49).

Hypernatremia

Hypernatremia occurs when the serum sodium concentration in plasma is >145 mEq/L. Unlike hyponatremia that causes seizures, hypernatremia is more likely to be a result of epileptiform activities such as generalized tonic–clonic seizures. Hypernatremia occurs when lactate, the metabolic product of intracellular glycogen in muscle tissues during
seizures, builds up and drives the intracellular movement of water and sodium into the cells.

The two adaptive mechanisms that come into play during hypoosmotic alterations also act in hypernatremia. The cellular shrinkage and increased brain cell osmolality that occur immediately after the onset of hypernatremia occurs is counteracted by the intracellular movement of electrolytes across the cell membranes, resulting in the partial restoration of brain volume within a few hours. However, complete restoration of normal brain volume does not occur until after several days as a result of the intracellular accumulation of the organic osmotically active agents (47) (50).

The brain osmolality alterations in chronic hyponatremia can be attributed to alterations in organic osmolytes. However, the same cannot be said for hypernatremia because little accumulation of these osmolytes occurs. Thus, the severity of neurologic deficits in hypernatremia is only related to the rate of elevation of serum sodium concentration. In acute hypernatremic conditions, the water loss and the resulting acute shrinkage in brain volume, particularly in pediatric patients, gives way to hypernatremic encephalopathy. On the other hand, in chronic hypernatremic conditions, CNS cells collect organic osmolytes, minimizing brain shrinkage and associated CNS symptoms.

Theoretically, the quick correction of hyponatremia can lead to brain swelling, since cerebral water uptake surpasses the removal of accumulated electrolytes and organic osmolytes. Therefore, very aggressive therapy can very well result in serious neurologic deficits due to cerebral edema (47) (50) (41). It should be noted that hypernatremic encephalopathy and death have been reported even in patients without CNS deficits (other than brain shrinkage and hyperosmolality). Some scientists explain this occurrence by attributing the changes to the morphology and physiology of brain cells to combined effects of hyperosmolality and cellular shrinkage to that ultimately lead to encephalopathy (47) (42).
The neurologic manifestations of hypernatremia are also primarily due to the rate serum sodium elevation (47) (50). Chronic hypernatremia (>170 mEq/L serum concentration) is well tolerated, as opposed to acute hypernatremia. In the case of the latter, the onset of severe symptoms occurs within hours of increased plasma sodium concentration to >158–160 mEq/L. Measurements >180 mEq/L are linked with a high mortality rate, especially in adults (50). Brain shrinkage caused by elevated serum sodium levels can lead to vascular rupture of cerebral vessels, leading to focal intracerebral and subarachnoid hemorrhages, which in turn can precipitate epileptiform activities. Infants with hypernatremia are less likely to develop seizures except in rare cases of accidental sodium overloading or aggressive rehydration (50). As mentioned previously, rapid sodium intake can cause seizures, though this is only typically true during rapid electrolyte restoration. In chronic hypernatremia, cerebral edema may become evident only when the osmolality is suddenly restored to normal levels; this corrective measure can very well lead to seizures, coma, and even death. Less than half of patients being treated for hypernatremia develop seizures by quick correction through infusion of hypotonic fluids (47).

Hypocalcemia

Hypocalcemia occurs when the plasma calcium level becomes <8.5 mg/dl or the ionized calcium concentration goes <4.0 mg/dl.

The neurological manifestations of hypocalcemia depend on the severity and the rate of falling serum ionized calcium level (51). Acute hypocalcemia mainly induces neuromuscular excitability and tetany. In the CNS, acute hypocalcemia typically manifests as convulsions and altered mental status (42) (41). Generalized tonic–clonic, focal motor, and rarely, atypical absence or akinetic seizures are known to develop. Moreover, clinicians need to remember that any one of these seizure activities may be the only apparent symptom (41) (52). Additionally, non-convulsive status epilepticus
secondary to hypocalcemia may also occur (53). Seizures can also develop in the absence of muscular tetany in patients with low serum calcium levels. Moreover, convulsions as a medical emergency can also occur in one-fourth of patients with acute hypocalcemia (54) (55).

Hypercalcemia

Hypercalcemia is relatively more common than hypocalcemia. However, it is not a common cause of seizures. Hypercalcemia occurs when serum calcium level goes ≥10.5 mg/dl.

Hypercalcemia primarily manifests in the nervous and gastrointestinal systems (51)(41). The presentation of symptoms of hypercalcemia depends on several factors, namely;

- the underlying cause of the condition
- the rate of its onset and development
- overall physical health of the patient

Rapid to moderate increments of serum calcium levels (12–13.9 mg/dl) lead to striking neurologic dysfunction, whereas longstanding and severe hypercalcemia (≥14 mg/dl) may only cause minimal and obscure neurologic symptoms (56).

The primary neurologic manifestations of hypercalcemia are:

- Lethargy
- Confusion
- Coma (rare)
Hypercalcemia does not stimulate neuronal membrane excitability, and thus, is not associated with seizures. However, hypercalcemia-induced hypertensive encephalopathy and vasoconstriction have been reported by some clinicians to cause convulsions (57) (58). The temporary vasoconstriction of the cerebral vessels in a patient with hypercalcemia-induced seizures has been reportedly seen by cerebral angiography (57).

Hypomagnesemia

Hypomagnesemia occurs when magnesium plasma concentration is <1.9 mg/dl. Magnesium is usually given as part of anticonvulsant therapy in women with preeclampsia and eclampsia (59). It has been hypothesized that its inhibition of N-methyl-D-aspartate (NMDA) glutamate receptors and the greater cerebral production of vasodilator prostaglandins are its mechanisms of action in seizures (59). Furthermore, magnesium also plays a role in neuronal membrane stability.

Symptoms of magnesium deficit generally do not appear until magnesium concentration falls to <1.2 mg/dl. Additionally, these measurements may not always correlate well with ionized magnesium levels in the serum. The major clinical manifestations of hypomagnesemia are:

- Neuromuscular irritability
- CNS overreactivity
- Cardiac arrhythmias

Very low levels of serum magnesium (<1 mEq/L) is usually associated with generalized tonic–clonic seizures in neonates and adults (41).

*Skeletal smooth muscles effects*
The electrolytes with the most profound effects on the skeletal smooth muscles are potassium and magnesium.

Rhabdomyolysis

Electrolyte imbalance disorders such as hypokalemia, hypocalcemia, hypophosphatemia, hyponatremia, and, particularly, hypernatremia and hyperosmotic conditions are linked to the development of rhabdomyolysis.

Additionally, the toxic effects of alcohol on the skeletal smooth muscles are partly due to electrolyte abnormalities, i.e., hypophosphatemia or hypokalemia (63), but malnutrition and severe illness are also contributing factors known to induce rhabdomyolysis. Hypokalemia and hypophosphatemia disappear after overt myonecrosis and renal failure have developed.

Rhabdomyolysis is the disintegration of skeletal muscles. The syndrome is the result of injury to skeletal muscle wherein potentially toxic intracellular contents are released into the circulation, and the extracellular fluid and plasma compartments (60). The ultimate common pathway of rhabdomyolysis is the perturbation in myocyte calcium homeostasis (61).

Rhabdomyolysis can be caused by various factors, namely;

- Infection
- Inherited disorders

The three classic symptoms of rhabdomyolysis are:

- Myalgias
- Generalized weakness
- Darkened urine

Because the above triad of symptoms is sometimes accompanied by nonspecific symptoms such as nausea, fever and vomiting, the physician must be observant and watchful for the subtle and sometimes confusing presentation to circumvent acute renal failure. The severity of rhabdomyolysis can range from subclinical elevation of creatinine kinase to a life-threatening medical emergency characterized by interstitial and muscle cell edema, contraction of intravascular volume, and pigment-induced acute renal failure (ARF).

The means by which rhabdomyolysis cause cellular destruction are listed below:

- Cellular membrane injury
- Muscle cell hypoxia
- Adenosine triphosphate (ATP) depletion
- Electrolyte disturbances leading to disturbance of the sodium-potassium pumps, and production of oxidative free radicals (62).

The cell membrane of skeletal smooth and cardiac muscles called sarcolemma contains several pumps (e.g. sodium-potassium pump, calcium protein-carrier pump) that modulate cellular electrochemical gradients. The normal intercellular sodium concentration, 10 mEq/L, is maintained by an ATP-driven sodium-potassium pump in the sarcolemma (64). The Na/K-ATPase pump induces the extracellular movement of sodium through active transport. As a result, the intracellular environment is more negatively charged than its extracellular counterpart because positive charges i.e. sodium ions are transported across the membrane. The concentration gradient pulls sodium back to the interior of the cell in exchange for calcium via the calcium protein-carrier pump. Additionally, an active calcium exchanger propels the entry of calcium into the sarcoplasmic reticulum and mitochondria. These processes are driven by energy in the
form of adenosine triphosphate (ATP). Exhaustion of ATP is likely the ultimate cause of rhabdomyolysis because the lack of energy interferes with cellular transport mechanisms and changes electrolyte concentrations (65).

Elevated intracellular calcium levels induce overactivity of proteases and vasoactive molecules and production of free oxygen radicals which are responsible for the degradation of myofilaments and phospholipid membrane injury that result in the release of intracellular contents into plasma. These contents are potassium, phosphate, CK, urate, and myoglobin.

Edema may lead to the accumulation of fluid within affected muscle tissues. Additionally, muscle damage is aggravated by immune responses of activated neutrophils. Inflammatory mechanism and reperfusion injury worsens and sustains muscle damage and degeneration (66) (64).

Myoglobin induces acute renal failure through the following mechanisms (67):

- Renal vasoconstriction
- Intraluminal cast formation
- Direct heme-protein-induced cytotoxicity

Myoglobin is normally filtered through the glomerular basement membrane and its concentration increases in response to continuous water reabsorption. The concentration elevation steadily progresses until myoglobin forms precipitates, leading to the renal tubular obstruction. Dehydration and renal vasoconstriction are two conditions that support the process (67). Patients with hyperuricemia and gouty arthritis are at higher risk of developing tubular obstruction. Another contributing factor to the formation of myoglobin and uric acid precipitates is tubular urine that is acidic (≤5.6 pH); this is a common finding because of the underlying acidosis. The destruction of intratubular
myoglobin leads to the release of free iron which in turn, ferrihemate, helps in the formation of free hydroxyl radicals that aggravates ischemic damage (67). However, the release of free iron is not always necessary to cause tissue injury since the heme center of myoglobin triggers lipid peroxidation and renal injury (68). On the other hand, higher pH levels prevent the occurrence of this damage by forming a stable reactive ferryl myoglobin complex.

Myoglobin precipitates in renal tubules also cause the formation of obstructive casts. Acute renal injury rarely occurs in patients with long-standing myopathies unless it is triggered by a secondary factor. The risk of renal injury is relatively low when the first CK level measurements are <15,000-20,000 U/L. CK level measurement lower than this causes renal injury in patients with sepsis, dehydration, or acidosis (61).

Gastrointestinal ischemia is quite common in patients with fluid and electrolyte disorders which results in endotoxin absorption, cytokine release and activation, and stimulation of the cascade inflammatory response.

Additionally, magnesium deficiency is associated with symptomatic aggravation of asthma because it increases smooth muscle contractility. The value of magnesium supplementation in asthma is not well defined (119), although some studies have shown its role in the reduction of bronchial hyperreactivity to methacholine and other allergy factors (120).

Effects on other tissues

Magnesium ions in the extracellular fluid compartment block neurosynaptic transmission by modulating the release of acetylcholine, as well as catecholamines from the adrenal medulla. Some studies have theorized that magnesium is an endogenous endocrine modulator of the catecholamine component of the physiologic stress response. In another note, hypomagnesemia has also been implicated in the development of migraine
headaches. However, the exact role of exogenous magnesium sources for migraine prophylaxis is not currently well understood (118).

Magnesium deficiency has also been associated with chronic fatigue syndrome, sudden death in athletes, impaired athletic performance, and sudden infant death syndrome.

Hypomagnesemia is also associated with nephrolithiasis, together with hypercalciuria characterized by distal renal tubular acidosis, alkaline urinary pH, and hypocitraturia all of which may stimulate the formation of renal stones. Nephrogenic diabetes insipidus is due to medullary calcium deposition and inhibition of aquaporin-2, the arginine-vasopressin–regulated water channel. A decrease in renal function may ensue due to hypercalcemia-induced renal vasoconstriction or chronic hypercalcemia stemming from calcium deposition (nephrocalcinosis) and interstitial renal disease.

*Syndrome of Inappropriate Anti-diuretic Hormone Secretion*

The syndrome of inappropriate anti-diuretic hormone (ADH) secretion (SIADH) characterized by hyponatremia and hypo-osmolality. It accounts for one third of all hyponatremia cases. The impaired water excretion is a result of inappropriate and sustained secretion of the anti-diuretic hormone (vasopressin) despite normal or increased plasma volume. The pathophysiologic mechanism is associated with excess water excretion rather than sodium deficit.

Clinicians should keep in mind the following points:

- Generally speaking, a slow progression of hyponatremia is linked with fewer symptoms compared to acute hyponatremia
- The clinical manifestations do not always correlate with the severity or the acuity of the drop in serum sodium level
- Some of the symptoms are suggestive of elevated ADH activity such as chronic pain, CNS symptoms or pulmonary tumors or head injury, or drug use
• The source of disproportionate fluid intake
• The history and onset of the condition must be assessed

Etiology

SIADH is triggered by the oversecretion of vasopressin by the hypothalamus in the brain or by ectopic production. Generally, the causes of SIADH may be classified into four groups:

- Nervous system disorders
- Neoplasia
- Pulmonary disorders
- Drug induced

The specific disorders or offending agents of each cause are summarized in the tables below.

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Neoplastic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute psychosis</td>
<td>Lung carcinoma</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>Mesothelioma</td>
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<tr>
<td>Brain abscess</td>
<td>Carcinomas of the duodenum</td>
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<tr>
<td>Cavernous sinus thrombosis</td>
<td>Carcinomas of the ileum</td>
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<td>Cerebellar and cerebral atrophy</td>
<td>Carcinomas of the colon</td>
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<td>Cerebrovascular accident</td>
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<td>Condition</td>
<td>Diagnosis</td>
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<td>Delirium tremens</td>
<td>Carcinomas of the bladder</td>
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<tr>
<td>Encephalitis (viral or bacterial)</td>
<td>Carcinomas of the ureter</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Carcinomas of the prostate</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>Ovarian carcinoma</td>
</tr>
<tr>
<td>Head trauma</td>
<td>Brain tumors</td>
</tr>
<tr>
<td>Herpes zoster (chest wall)</td>
<td>Carcinoid tumors</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Ewing sarcoma</td>
</tr>
<tr>
<td>Hypoxic ischemic encephalopathy</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Meningitis (viral, bacterial, tuberculous, and fungal)</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Midfacial hypoplasia</td>
<td>Nasopharyngeal carcinoma</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Neuroblastoma</td>
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<tr>
<td>Perinatal hypoxia</td>
<td>Thymoma</td>
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<tr>
<td>Rocky Mountain spotted fever</td>
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<tr>
<td>Schizophrenia</td>
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<tr>
<td>Shy-Drager syndrome</td>
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<tr>
<td>Subarachnoid hemorrhage</td>
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<tr>
<td>Subdural hematoma</td>
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<tr>
<td>Ventriculoatrial shunt obstruction</td>
<td></td>
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<tr>
<td><strong>Pulmonary disorders</strong></td>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>Acute bronchitis/bronchiolitis</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>Adenine arabinoside</td>
</tr>
<tr>
<td>Asthma</td>
<td>Anti-cancer agents</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>Opiates</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>Nicotine</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Anti-depressants (e.g. MAOIs, TCAs)</td>
</tr>
<tr>
<td>Emphysema</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td>Empyema</td>
<td>Carbachol</td>
</tr>
<tr>
<td>Pneumonia (viral, bacterial [mycoplasmal], fungal)</td>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Clofibrate</td>
</tr>
<tr>
<td>Positive pressure ventilation</td>
<td>Cyclopropane</td>
</tr>
<tr>
<td>Pulmonary abscess</td>
<td>Dibenazepines</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>Halothane</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>General anesthetics (nitrous oxide,</td>
</tr>
</tbody>
</table>
Listed below are drugs that specifically potentiate the effects of vasopressin.

<table>
<thead>
<tr>
<th>Drugs</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Clofibrate</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Triiodothyroinine (T3)</td>
</tr>
<tr>
<td>Metformin</td>
<td>Vasopressin analogs</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Phenformin</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Tolbutamide</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
</tr>
</tbody>
</table>

Listed below are drugs that affect vasopressin secretion with unsure mechanisms.

<table>
<thead>
<tr>
<th>Drugs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Phenoxybenzamine</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>Na⁺ valproate</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Thiothixene</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
</tr>
</tbody>
</table>

Additionally, psychotropic drugs are also known to cause SIADH (233). Several chemotherapeutic agents which cause nausea as an adverse effect are also implicated in the etiology of SIADH since it can stimulate vasopressin secretion. Pediatric patients who underwent chemotherapy or stem cell transplant are especially vulnerable to this adverse effect.

Listed are miscellaneous causes of SIADH

- Exercise-induced hyponatremia
- Giant cell arteritis
- HIV infection – As many as 40 percent of adult HIV positive and AIDS patients have had electrolyte imbalance disorder, particularly, hyponatremia. This may be attributed to the resulting increased stimulation of vasopressin secretion from volume depletion and pulmonary and CNS infections (234).
- Idiopathic

SIADH is diagnosed by the Bartter-Schwartz criteria, which is summarized below (235):

- Hyponatremia accompanied by hypo-osmolality
- Sustained sodium excretion by the kidneys
- Urine less than maximally dilute
- Absence of clinical evidence of volume depletion
- Absence of other causes of hyponatremia
- Correction of hyponatremia by fluid restriction
The laboratory tests used in the diagnosis of SIADH include:

- Serum sodium, potassium, chloride, and bicarbonate
- Plasma osmolality
- Serum creatinine
- Blood urea nitrogen
- Blood glucose
- Urine osmolality
- Serum uric acid
- Serum cortisol
- Thyroid-stimulating hormone

Additionally, the patient’s volume status should be evaluated to exclude the possible presence of hypovolemia.

Aside from laboratory work up, imaging studies may also be employed in the diagnosis of SIADH and may include:

- Chest radiography (possible pulmonary cause of SIADH)
- CT or MRI of the head to detect possible causes (CNS disorder) and complications (cerebral swelling) of SIADH.

Physical exam

Physical examination of the patient can reveal clues to the severity of an acute hyponatremia. The diagnostic findings may include the following:

- Confusion, disorientation, delirium
• Generalized muscle weakness, myoclonus, tremor, asterixis, hyporeflexia, ataxia, dysarthria, Cheyne-Stokes respiration, pathologic reflexes
• Generalized seizures, coma

Complications
When left untreated, SIADH is associated with the following complications:
• Cerebral edema can happen if plasma osmolality decreases at a rapid rate or more than 10 mOsm/kg/h which can result in cerebral herniation.
• Noncardiogenic pulmonary edema may be observed particularly in marathon runners (236).
• CPM is the result of an overly aggressive correction of hyponatremia. It is characterized by disorders of upper motor neurons, including spastic quadripareisis and pseudobulbar palsy, as well as mental disorders ranging from confusion to coma (237). Patients with serum Na of less than 105, hepatic failure, potassium depletion, large burns, malnutrition, and who are premenopausal and undergoing surgical procedures, are especially susceptible (238). CPM has no known proven treatment.

VIII. TREATMENT OF ELECTROLYTE DISORDERS
Electrolyte disorders need prompt medical attention to prevent deterioration and serious damage to the body systems, especially, the neurologic and cardiovascular systems.

Successful treatment of convulsions starts with the establishment of an accurate diagnosis of the underlying electrolyte disturbances. To accomplish this, the patient needs to undergo the following:

▪ Careful history
▪ Physical examination and assessment of total body water and its distribution
- Serum electrolyte concentrations
- Urine electrolyte concentrations
- Serum osmolality

Furthermore, the early detection and correction of these abnormalities are vital to controlling seizures and preventing irreversible brain damage, since the administration of antiepileptic drugs alone are generally insufficient. Clinicians should be aware of these clinical conditions and have an understanding of the underlying medical disorders, for this may provide the means of controlling the disease and initiating a rapid and appropriate therapy.

Hyponatremia

The onset of acute symptomatic hyponatremia requires prompt treatment because of the risk of irreversible damage to the brain, even when clinical symptoms are mild (45). Hypertonic saline solution is usually administered intravenously for acute symptomatic hyponatremia, causing a rapid reduction in brain volume, thus, lowering intracranial pressure. The aim of the treatment is to restore serum sodium to a range between 120 to 125 mEq/L. Clinicians should also keep in mind that overly aggressive normalization of hyponatremia with hypertonic saline solution also has its own perils, because this intervention can lead to shrinkage of the brain that triggers osmotic demyelination syndrome and cause neurologic impairment such as quadriplegia, pseudobulbar palsy, seizures, coma, and even death (47) (45) (41).

Based on clinical data, the ideal correction rate of sodium concentration is 0.5 mEq/L/hour. However, there are a few exceptions; for instance, young women with higher risk for respiratory arrest, severe neurologic sequelae, and death, the correction rate is slightly higher at 1 to 2 mEq/L/hour (121) (45). Another exception are pediatric patients who appear to tolerate higher correction rates as well (122). Additionally, there is mounting evidence pointing to the incidence of brain demyelinating lesions despite
careful correction and monitoring of hyponatremia (48) (123) (44). Therefore, it is imperative for the clinician to identify additional risk factors for brain demyelination, such as hypokalemia, hypophosphatemia, seizure-induced hypoxemia, and malnutrition with vitamin B deficiency, and initiate treatment accordingly.

**Hypernatremia**

The treatment goal in hypernatremia is to replace the water lost and consequently restore osmotic homeostasis and cell volume at a rate that provides the most therapeutic benefits devoid of complications. The rapidity of correction depends on the speed of development of hypernatremia and presenting manifestations (50) (124). It should be noted that the correction rate for chronic hypernatremia should not exceed 0.5–0.7 mEq/L/hour as the range is sufficient to circumvent cerebral edema and seizures. The ideal rate of reduction in the serum sodium concentration in patients with hypernatremia, except in those in acute cases is 10 mEq/L/day. Acute hypernatremia may be treated more aggressively, with a correction rate of 1 mEq/L/hour (47).

Patients with hypernatremia may be treated with hypotonic saline or dextrose fluids, preferably via oral route or if not possible, intravenous means. Because the risk of cerebral edema increases with the volume of the parenteral fluid, the volume should be carefully adjusted and monitored to provide only the amount required to correct hypertonicity (50). Normal saline (0.9% sodium chloride) is appropriate only in case of blunt circulatory compromise, since it is effective in producing a means of volume expansion.

**Hypocalcemia**

Treatment urgency of hypocalcemia requires two factors to take into consideration, namely;

- Severity of symptoms
Degree of hypocalcemia

Like other acute electrolyte disorders, acute hypocalcemia is considered a medical emergency that needs immediate treatment, especially those with overt symptoms because of the associated high risk of morbidity and mortality. The intravenous administration of calcium is the most appropriate therapy, at doses of 100-300 mg infused over a period of 10-20 minutes. The initial infusion rate should be 0.5 mg/kg/h and continued for several hours, with frequent assessment of calcium levels (51). Seizures induced by hypocalcemic states are best treated with calcium replacement; antiepileptic drugs are usually not required. Antiepileptic drugs may eliminate the symptoms - both overt and latent tetany - but the hypocalcemic-induced seizures may remain refractory (54) (125) (126). Like many medical conditions, treatment should be focused on the underlying cause, and not just the presenting symptoms. Oral calcium supplementation is commonly prescribed for outpatient therapy.

Hypercalcemia

The urgency of treatment for hypercalcemia is dependent on the presenting symptoms and the etiology, instead of the serum calcium concentration. Severe hypercalcemia needs aggressive treatment which includes hydration and administration of IV bisphosphonate (e.g., pamidronate or zoledronate) or calcitonin (51) (127). Patients with acute hypercalcemia usually require quick but carefully regulated correction. Initially, a vigorous rehydration with normal saline should be started at a rate of 200 to 500 ml/hour accompanied by careful monitoring of fluid overload. The next step after rehydration may be to administer intravenously 20–40 mg furosemide. Subsequently, the clinician may want to consider intravenous bisphosphonates: pamidronate (60–90 mg i.v. over a 2 hour period), and orzoledronate (4 mg i.v. over a 15 minute period). The second line agents that may be used are glucocorticoids, calcitonin, mithramycin, and gallium nitrate.

Hypomagnesemia
Mild hypomagnesemia without overt symptoms may be treated with oral magnesium (e.g., magnesium gluconate), usually administered in divided doses to achieve a total of 500 mg/day. In symptomatic or severe hypomagnesemia with convulsions (<1.2 mg/dl), it is prudent to initially administer intravenously a bolus dose of 1 to 2 g of magnesium sulfate over a 5 minute period, followed by its infusion of the same dose per hour for the next few hours. In case convulsions persist, the initial bolus may be repeated (41) (128). Potassium and magnesium concentrations need to be carefully assessed during the entire duration of therapy. It should be noted that patients with renal insufficiency may need their doses to be adjusted according to their renal function.

Hypokalemia

Hypokalemia is usually first encountered in the emergency department.

Patients with severe hypokalemia are usually subjected to the following interventions;

- Close cardiac monitoring
- Intravenous access
- Respiratory status evaluation
- Potassium replacement therapy

If the potassium level falls below 2.5 mEq/L, intravenous potassium over a period of few hours should be given.

Patients with 2.5-3.5 mEq/L serum potassium levels or mild to moderate hypokalemia generally do not experience clinical symptoms. Mild symptoms, should they exist, are usually treated with oral potassium replacement therapy. Patients with mild hypokalemia with an identified underlying cause may only need to have it treated. For example, hypokalemic patients with vomiting may not need potassium supplementation at all but
preferably treated with anti-emetics. In the setting of cardiac symptoms such as arrhythmias or other significant symptoms, a more aggressive approach to therapy such as that used in severe hypokalemia may be called for.

It should be remembered that restoration of serum potassium level to normal levels is difficult in the setting of low serum magnesium level. Therapy should aim to replenish both electrolytes.

Hyperkalemia

The aggressiveness of hyperkalemia treatment is dependent on the following factors:

- Its speed of development
- The absolute level of serum potassium
- The evidence of toxicity

The more rapid is the elevation of potassium level, the higher it has reached; the greater the evidence of cardiotoxicity, therefore, the more aggressive is the required therapy.

If the patient’s lab results points to a moderate rise in potassium level with no electrocardiographic abnormalities, potassium excretion can be enhanced using diuretics to restore normal levels (129).

The primary objective in the treatment of severe hyperkalemia is the rapid restoration of a stable myocardial cell membrane, movement of potassium to the intracellular compartment, and total body excretion of excess potassium. Additionally, immediate withdrawal from all exogenous sources of potassium should be started including intravenous and oral supplementation, total parenteral nutrition, any blood product transfusion, and drugs known to induce hyperkalemia (130).
Patients with renal failure or unresponsive to pharmacotherapy require hemodialysis. In fact, patients with significantly high serum potassium levels need dialysis since pharmacotherapy solely is insufficient to achieve adequate decrease of potassium levels in a timely manner.

After stabilizing the hypokalemic patient in the emergency department, immediate transfer to the admission unit is required. This is because continued and close scrutiny of potassium level and cardiac monitoring are still necessary.

Moreover, once a patient is stable, further workup should be started to identify the etiology of the electrolyte imbalance and thus, help prevent future episodes. The etiologic factors that need to be considered in the workup are as follows but not limited to:

- Evaluation of sources of potassium intake
- Underlying pathology in decreased renal excretion
- Causes for reduced cell uptake of potassium

Generally, all three factors contribute to the development of hyperkalemia. It is imperative that complete reevaluation is done on the use of potassium supplements in patients with renal insufficiency or in those who are given medications that interfere with potassium excretion in the kidneys.

Prior to arrival at the emergency department, patients with established hyperkalemia or renal failure with suspected hyperkalemia should have immediate IV access and placed on a cardiac monitor (131). In patients with low blood pressure or well-defined QRS widening, IV bicarbonate, calcium, and insulin given together with 50% dextrose may be considered. In patients with present history of digoxin use, magnesium sulfate at a dose
of 2 g infused over 5 minutes should be given in lieu of calcium to address the cardiac arrhythmias induced by digitalis toxicity.

In the emergency department (ED), the clinician may carry out uninterrupted ECG monitoring with regular checks on the vital signs when hyperkalemia is suspected or when laboratory values confirm hyperkalemia as the diagnosis. Intake of all potassium-sparing drugs or dietary potassium must be suspended. In patients with CHF and under digoxin therapy, digitalis toxicity should be strongly suspected and investigated. As mentioned above, in case of severe hyperkalemia (potassium >7.0 mEq/L), immediate emergency treatment should be initiated even before diagnostic investigation of the underlying cause. The primary objective in this case is patient stabilization. Treatment approach should be individualized, to reflect the patient’s presentation, potassium level, and ECG findings. The administration of calcium, insulin, glucose, and sodium bicarbonate is a temporary intervention. The only way to ensure significant elimination of potassium excess is through the use of cation exchange resins, dialysis, or increasing renal excretion. Cation exchange resin should soon follow the administration of other electrolytes and fluids.

Clinicians need to be vigilant about overdoing reduction or overprescribing potassium supplements. For instance, patients with diabetic ketoacidosis (DKA) may exhibit a high extracellular potassium level, despite a total body deficit of potassium. In this case, the clinicians need only to treat the diabetic ketoacidosis in order to achieve a normal extracellular potassium level.

Medical treatment of hyperkalemia sometimes follows a chronological approach, although the interventions may be given simultaneously. Listed below are the steps involved:

Step 1: Administration of IV calcium to treat cardiac toxicity, if present.
Step 2: Identification and removal of sources of potassium intake which involves the discontinuation of oral and parenteral potassium supplements, and dietary staples.

Step 3: Enhancement of potassium uptake by cells to reduce the serum concentration. Glucose and insulin infusions are useful in augmenting potassium uptake. Continuous infusions of insulin and glucose-containing IV fluids can be used for long term effects. It is important to note that IV insulin can cause hypoglycemia. Patients with acute or chronic renal disease are particularly vulnerable to this side effect. Glucose and potassium monitoring should be done every 2 hours. Additionally, metabolic acidosis should be treated with sodium bicarbonate. Metabolic acidosis when accompanied by chronic renal disease affects hyperkalemia in a variety of ways, making the tracking of treatment progression with sodium bicarbonate unpredictable and sometimes, less effective. Nevertheless, parenteral sodium bicarbonate is needed, especially in the onset of severe hyperkalemia.

Additionally, beta-adrenergic agonists have also found some use in hyperkalemia, although its use in this setting remains controversial and associated with frequent side effects. In the US, the most common preparation used for this purpose is nebulized albuterol at 10 mg; the dose is significantly higher than the usual dose indicated for asthma. Its administration is usually done in the presence of a respiratory therapist. Hypokalemic effects are usually seen a little more than an hour after initial administration. This type of intervention is effective and preferred to alkalinizing agents in patients with compromised renal function. Other beta-adrenergic agonist preparations used are parenteral isoproterenol and albuterol, although the former is not commonly used, and the latter is not available in the US. Notable side effects reported with the use of beta adrenergic agonists are tachycardia and chest discomfort.

Step 4: Enhancement of potassium excretion from the body. In patients with normal renal function, potassium excretion via the kidneys is easily augmented with the administration
of IV saline together with a loop diuretic (e.g., furosemide, bumetanide). Additionally, drugs known to cause hyperkalemia as side effects should be discontinued. Examples include potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-receptor blockers (ARBs). Volume status needs to be monitored closely. Additionally, renal excretion can be augmented with the use of an aldosterone analogue (e.g. 9-alpha fluorohydrocortisone acetate). Fluorohydrocortisone is particularly effective in patients with hyporeninemia or hypoaldosteronism. The drug is also commonly used in chronic hyperkalemia caused by calcineurin in patients who underwent solid-organ transplantation. Generally, serum potassium level normalizes after 2 days (132).

Gastrointestinal elimination can be augmented with the administration of cation exchange resins such as sodium polystyrene sulfonate (SPS). SPS is available in both oral and rectal preparation. The latter preparation is preferred in emergency situations because the drug’s primary site of action is the colon. Moreover, its maximum effectiveness occurs when retained for 1 hour. It should be noted that SPS is not useful in acute hyperkalemia due to its delayed onset of effects, occurring only at least two hours and peaking at four to six hours after administration. The estimated reduction caused by SPS is believed to be 2 mEq/L. The oral administration of SPS is particularly effective in patients with advanced kidney failure that are not on dialysis or underwent organ transplantation. 15 g once or twice a day is sufficient to treat mild to moderate hyperkalemia effectively. It should be noted that the FDA has recommended against the use of SPS in patients with compromised bowel movement, such as those who recently underwent surgery or those who have a history of constipation (133). Moreover, the FDA has warned against the concomitant use of SPS and sorbitol, an osmotic laxative, used to stimulate peristalsis and enhance rapid movement of the resin to the colon. Its use in this case has been associated with intestinal necrosis, some of which have been fatal (133). According to a systematic review by Harel et al., published in the American Journal of Medicine in 2013, this serious side effect can be attributed to SPS independently, even in the absence of sorbitol in the formulation (134).
Step 5: Undergoing hemodialysis is considered as a final option in life-threatening cases of hyperkalemia which are unresponsive to the interventions mentioned above, or for patients with very advanced or complete kidney failure. Starting patients on dialysis can be time consuming, sometimes lasting several hours; therefore, even if dialysis is contemplated, the other therapeutic interventions mentioned previously should be started while preparations for dialysis are underway.

Step 6: Initiate further work up in order to pinpoint the underlying pathology of hyperkalemia and help prevent future episodes. This should include examination of the following:

- Sources of potassium intake
- Causes of decreased renal excretion
- Causes for impaired cellular uptake

*Rhabdomyolysis*

The treatment of rhabdomyolysis can be tackled using several approaches.

Generally, immediate patient stabilization is the primary objective. In an emergency setting, patient’s airway, breathing and circulation (ABCs) need to be assessed and supportive care provided whenever required. Sufficient hydration and urine output monitoring should be put in place. Whenever possible, the underlying causes (e.g. trauma, infection, toxins) need to addressed and treated accordingly (135).

Other treatment objectives include fluid resuscitation, correction of electrolyte abnormalities and prevention of end-organ complications such as acute renal failure (136) 137).
Additionally, the patient’s cardiac and electrolyte status need to be monitored closely. Sequential physical exams and laboratory tests are needed to monitor for the possible onset of compartment syndrome, hyperkalemia, acute oliguric or nonoliguric kidney failure, and disseminated intravascular coagulation (DIC). Compartment syndrome requires prompt orthopedic consultation for fasciotomy. Disseminated intravascular coagulation should be treated using fresh frozen plasma, cryoprecipitate, and platelet transfusions. Additionally, cardiac monitoring is vital as well as measurements of creatine kinase (CK) levels in order to track the progress of the treatment.

Once patient stabilization has been achieved and life-threatening or otherwise serious complications have been treated, the patient may be transferred to an inpatient facility. Clinician may follow the guidelines set forth by the Consolidated Omnibus Budget Reconciliation Act (COBRA) and the Emergency Medical Treatment and Labor Act (EMTALA) (136). Additionally, after normal renal function has been restored and normal electrolyte levels and alkaline urine have been achieved, the patient may be discharged and monitored regularly as outpatients. Additional work up measures such as genetic tests during confinement should be communicated to the primary care or outpatient specialty physicians.

Fluid resuscitation

The primary objective of stabilizing the patient in the treatment of rhabdomyolysis is to promote immediate extracellular volume expansion. Currently, no randomized trials of fluid replacement regimens in any age group have been done (138). However, retrospective studies of patients with severe compression injuries that resulted in rhabdomyolysis suggest that initiation of fluid resuscitation prior to arrival at the emergency department is associated with improved prognosis (139). Sustaining intravascular volume expansion speeds up glomerular filtration rate (GFR) and oxygenation and dilutes myoglobin and other kidney tubular toxins.
Patients with elevated creatine kinase of more than twice or thrice the reference range, accompanied by positive history, and risk factors, should be strongly suspected with rhabdomyolysis. In these cases, intravenous access with a large-bore catheter is appropriate. Adults need to be administered with isotonic fluids at a rate of about 400 mL/h, which may be increased to 1000 mL/h based on the type of condition and severity, and then titrated down to sustain a minimum urine output of 200 mL/h (138).

Since myocytes with injury can isolate an excessively high volume of extracellular fluid, crystalloid requirements may likewise be great. In patients with creatine kinase measurement ≥15,000 IU/L, a larger amount of fluid, at least 6 L, are required (140). Creatine kinase measurements should be repeated every 6-12 hours to monitor the peak creatine kinase level.

Lastly, aggressive and prompt hydration with isotonic sodium chloride solution is imperative for the prevention of pigment-associated kidney failure. The composition of the replacement fluid is under debate and may also include sodium bicarbonate. The recommended initial fluid dose in young children and adolescents are 20 mL/kg; and 1-2 L/h, respectively. There are very limited studies on the use of fluid repletion in the pediatric population. Follow up hydration is also essential (141) (142).

Aside from fluid abnormalities, rhabdomyolysis also causes acid-base and metabolic abnormalities. As such, frequent monitoring of serum electrolyte levels, urine pH levels, and acid-base status is deemed necessary (136) (139). Metabolic abnormalities also need to be corrected.

Hyperkalemia may be treated with IV sodium bicarbonate, glucose, and insulin; oral or rectal sodium polystyrene sulfonate; and hemodialysis. These interventions are discussed thoroughly in the previous pages. Additionally, patients who are not stable
hemodynamically or hyperkalemic may benefit from the administration of IV calcium chloride.

Hypocalcemia usually sets in early in the development of rhabdomyolysis and generally does not pose a significant clinical danger. As such, hypocalcemia should only be corrected in patients with cardiac arrhythmias and seizures. Calcium may sequester phosphate ions, to form an intramuscular metastatic calcification. Therefore, calcium supplementation is generally not recommended, since hypercalcemia may occur late in the recovery phase.

Hyperuricemia and hyperphosphatemia rarely occurs and are not clinically significant and generally do not require treatment. Hyperphosphatemia, if needed, may be treated with alkaline diuresis. Hypercalcemia is known to develop in the recovery phase particularly in patients with acute renal injury.

*Symptoms of inappropriate anti-diuretic hormone (SIADH)*

The approach to managing SIADH depends on several factors, namely (278):

- Severity of hyponatremia
- Presence or absence of symptoms
- Duration of hyponatremia
- Urine osmolality and creatinine clearance

In cases where the onset and period of hyponatremia are unknown, and the patient has no presenting symptoms, it is rational to deduce chronic SIADH.

During emergency cases of hyponatremia, an aggressive treatment may be warranted. Specific examples are listed below:
• Presence of severe symptoms such as seizures, stupor, coma, and respiratory arrest, regardless of the degree of hyponatremia
• Early onset of moderate-to-severe hyponatremia lasting less than 48 hours

In such clinical scenarios, clinicians need to carefully weigh its benefits versus the risk of inducing central pontine myelinolysis (CMP).

The objective of the treatment is to normalize serum sodium level at a rate that does not cause neurologic complications. This may be achieved by:

• Raising serum sodium level by 0.5-1 mEq/hr, and not more than 10-12 mEq in the first 24 hours
• Targeting for a maximum serum sodium level of 125-130 mEq/L

During acute cases where patients exhibit moderate symptoms, the clinician may use the following treatment strategies:

• Administer 3% hypertonic saline (513 mEq/L)
• Add loop diuretics (e.g. furosemide) with the saline solution
• Administer vasopressin-2 receptor antagonists (aquaretics, such as conivaptan)
• Restrict water intake

During cases of chronic and asymptomatic hyponatremia, the clinician may proceed with the following approach:

• Restrict fluid intake
• Administer vasopressin-2 receptor antagonists
• In times where vasopressin-2 receptor antagonists are unavailable, the clinician may consider using loop diuretics such as furosemide, accompanied by excess sodium intake, urea, mannitol, and demeclocycline.

IX. ELECTROLYTE CONSUMPTION

The body’s sources of electrolytes are normally obtained from the diet.

*Adequate intake and dietary sources*

Below is a table listing the dietary adequate intakes (AIs), (not recommended dietary allowances) for all age groups, dietary sources and special considerations of sodium, chloride, water and sulfate. A Tolerable Upper Intake Level (UL) was set for sodium but for none of the other nutrients. This background information is provided to help highlight major knowledge gaps (143).

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Life stage group</th>
<th>AI g/day</th>
<th>UL g/day</th>
<th>Selected food sources</th>
<th>Special considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>Infants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-6 months</td>
<td>0.12</td>
<td>ND</td>
<td>Processed foods to which sodium chloride (salt) / benzoate/ phosphate have been added; salted meats, nuts, cold cuts; margarine; butter; salt added to foods during cooking or at the table. Salt is</td>
<td>The AI is set based on being able to obtain a nutritionally adequate diet for other nutrients and to meet the needs for sweat losses for individuals engaged in recommended levels of physical activity. Individuals engaged in activities at higher levels or in humid climates resulting in excessive sweat may need more than the AI. The</td>
</tr>
<tr>
<td></td>
<td>7-12 months</td>
<td>0.37</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children:</td>
<td>1-3 years</td>
<td>1</td>
<td>1.5</td>
<td></td>
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<tr>
<td></td>
<td>4-8 years</td>
<td>1.2</td>
<td>1.9</td>
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</tr>
<tr>
<td>Adults</td>
<td>9-13 years</td>
<td>1.5</td>
<td>2.2</td>
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<tr>
<td></td>
<td>14-18 years</td>
<td>1.5</td>
<td>2.3</td>
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<td></td>
<td>19-30 years</td>
<td>1.5</td>
<td>2.3</td>
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<tr>
<td></td>
<td>31-50 years</td>
<td>51-70 years</td>
<td>&gt;70 years</td>
<td>Pregnant</td>
<td>14-18 years</td>
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<tr>
<td>UI</td>
<td>1.5</td>
<td>1.3</td>
<td>1.2</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Chloride

- **Infants**
  - 0-6 months: 0.18 ND
  - 7-12 months: 0.57 ND
- **Children:**
  - 1-3 years: 1.5 2.3
  - 4-8 years: 1.9 2.9
- **Adults**
  - 9-13 years: 2.3 3.4
  - 14-18 years: 2.3 3.6
  - 19-30 years: 2.3 3.6
  - 31-50 years: 2.3 3.6
  - 51-70 years: 2 3.6
  - >70 years: 1.8 3.6
<table>
<thead>
<tr>
<th>Potassium</th>
<th>Infants</th>
<th>Adults</th>
<th>Pregnant</th>
<th>Lactating</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td><strong>Potassium</strong></td>
<td><strong>Infants</strong></td>
<td><strong>Adults</strong></td>
<td><strong>Pregnant</strong></td>
<td><strong>Lactating</strong></td>
</tr>
<tr>
<td>0-6 months</td>
<td>0.4</td>
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<tr>
<td>7-12 months</td>
<td>0.7</td>
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<td>Children:</td>
<td></td>
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<td>1-3 years</td>
<td>3</td>
<td>4.5</td>
<td>4.7</td>
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<td>4-8 years</td>
<td>3.8</td>
<td>4.7</td>
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<tr>
<td><strong>Adults</strong></td>
<td>**</td>
<td>**</td>
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<td>9-13 years</td>
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<td>14-18 years</td>
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<td>31-50 years</td>
<td>4.7</td>
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<tr>
<td>51-70 years</td>
<td>4.7</td>
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<td>4.7</td>
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<tr>
<td>&gt;70 years</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>Pregnant</strong></td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
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<tr>
<td>14-18 years</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
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<tr>
<td>19-50 years</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>Lactating</strong></td>
<td>**</td>
<td>**</td>
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<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| Fruits and vegetables; dried peas; dairy products; meats, and nuts. | | | | Individuals taking drugs for cardiovascular diseases such as ACE inhibitors, ARBs, or potassium-sparing diuretics should be careful not to consume supplements containing potassium and may need to consume less than the AI for potassium.
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Water Intake (AIs)</th>
<th>Source of Intake</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td></td>
<td>All beverages, including moisture in foods (high moisture foods include watermelon, meats, soups, etc.)</td>
<td>Recommended intakes for water are based on median intakes of generally healthy individuals who are adequately hydrated; individuals can be adequately hydrated at levels below as well as above AIs. The AIs provided are for total water in temperate climates. All sources can contribute to total water needs: beverages (including tea, coffee, juices, sodas, and drinking water) and moisture found in foods. Moisture in foods accounts for about 20% of total water intake. Thirst and consumption of beverages at meals are adequate to maintain hydration. Also, no ULs because normally functioning kidneys can handle &gt;24 oz of fluid per hour; symptoms of water intoxication</td>
</tr>
<tr>
<td>0-6 months</td>
<td>0.7</td>
<td>No UL</td>
<td></td>
</tr>
<tr>
<td>7-12 months</td>
<td>0.8</td>
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</tr>
<tr>
<td>1-3 years</td>
<td>1.3</td>
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<tr>
<td>4-8 years</td>
<td>1.7</td>
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<td></td>
</tr>
<tr>
<td>Adult males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-13 years</td>
<td>2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-18 years</td>
<td>3.3</td>
<td></td>
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<td>19-30 years</td>
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<tr>
<td>31-50 years</td>
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<tr>
<td>51-70 years</td>
<td>3.7</td>
<td></td>
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</tr>
<tr>
<td>&gt;70 years</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-13 years</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-18 years</td>
<td>2.3</td>
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<tr>
<td>19-30 years</td>
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<td>31-50 years</td>
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<tr>
<td>51-70 years</td>
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<td></td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-18 years</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-50 years</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**No UL** indicates that there is no established upper limit (UL) for this nutrient within this age group.
<table>
<thead>
<tr>
<th></th>
<th>14-18 years</th>
<th>19-50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-18 years</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>19-50 years</td>
<td>3.8</td>
<td>3.8</td>
</tr>
</tbody>
</table>

|                          | Infants     | No AI       | No UL |
|--------------------------|-------------|-------------|
| 0-6 months               |             |             |
| 7-12 months              |             |             |
| Children:                |             |             |
| 1-3 years                |             |             |
| 4-8 years                |             |             |
| Adults                   |             |             |
| 9-13 years               |             |             |
| 14-18 years              |             |             |
| 19-30 years              |             |             |
| 31-50 years              |             |             |
| 51-70 years              |             |             |
| >70 years                |             |             |
| Pregnant                 |             |             |
| 14-18 years              |             |             |
| 19-50 years              |             |             |
| Lactating                |             |             |
| 14-18 years              |             |             |

Dried fruit (dates, raisins, dried apples), soy flour, fruit juices, coconut milk, red and white wine, bread as well as meats that are high in sulfur amino acids.

No recommended AI are set because adequate sulfate is available from dietary inorganic sulfate from foods and water, and sources of organic sulfate include glutathione and the sulfur amino acids methionine and cysteine. Metabolic breakdown of recommended intake for protein and sulfur amino acids should provide adequate inorganic sulfate for the synthesis of required sulfur-containing compounds. Osmotic diarrhea was observed in areas where water supply had high sulfur levels; odor and off taste usually limit intake. Thus, no UL was set.
The table is adapted from the DRI reports. Adequate Intakes may be used as a goal for individual intake. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percent age of individuals covered by this intake; therefore, no recommended dietary allowance (RDA) was set (143).

UL= The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for potassium, water, and inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes (143).

ND= Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts (143).

Because the report was released in 2004, one cannot expect a large amount of progress in filling research gaps. For the nutrients covered in the DRI Electrolytes and Water Report, data were lacking that would be useful in setting EARs or AIs for infants, children, pregnant women, and the elderly—as was the case for most other nutrients (143).

**Fluids and electrolytes as part of parenteral nutrition (PN)**

The calculation of parenteral fluid intake requires a dynamic collaboration between all medical personnel involved in the general care of the patient. This is especially important to practice in medical teams that are otherwise usually mutually exclusive.
Fluid intake in parenteral nutrition

The fluid gains and losses such as those from parenteral, oral and enteral nutrition, other infusates, and diarrhea, respectively, must be put into consideration. Listed below are fluid intake considerations to be kept in mind in patients being parenterally fed (219).

- Patients with documented impaired water and electrolyte balance need their volume status to be closely monitored. For example, feverish patients may require more than the normal fluid requirement of approximately 30–40 ml/kg body weight/day.

- Serum electrolyte levels must be assessed before starting parenteral nutrition, and patients with normal fluid and electrolyte levels should be given the recommended dietary intake for parenteral nutrition.

- If patients require additional parenteral nutrients, a separate infusion pump should be used.

- Concentrated potassium (1 mval/ml) or 20% NaCl solutions should be infused using a central venous catheter.

- Adjustments should be made in response to the closely monitored electrolyte levels.

- When patients are hospitalized with an already altered electrolyte level status such as in the case of chronic diarrhea, vomiting and renal insufficiency, individual determination of electrolyte intake is needed.

- Generally, vitamins and trace elements must be substituted in parenteral nutrition, unless contraindicated.

- Vitamin and trace elements supplements are needed after more than a week on parenteral nutrition. The dosage given should reflect the standard recommendations, unless clinical indications dictate otherwise.
Parenteral therapy is one of the most time-proven medical practices around. The rationale behind it, specifically the substitution of vitamins and trace elements are clinically established, and not based on randomized studies.

The evaluation of a patient’s hydration status is required in the calculation of parenteral fluid requirements, particularly when there is a high index of suspicion of fluid imbalance. It is not unusual for patients like these to transition frequently between hypovolemic, euvolemic and hypervolemic states. The present fluid volume status may be assessed by the changing manifestations such as (219):

- Body weight
- Skin turgor
- Central venous pressure
- Sonographic evidence of vena cava filling
- Laboratory values (hematocrit, serum sodium, serum and urine osmolarity)

Hypovolemia is characterized by the following features (219):

- Weight loss
- Reduced skin turgor
- Dry mucous membranes
- Decreased arterial and central venous pressure
- Tachycardia
- Elevated serum sodium, serum osmolarity and, urine osmolarity (>450 mosmol/kg)

Signs of hypervolemia include the following (219):
- Development of peripheral edema in the legs or on the coccyx in bedridden patients
- Development of pulmonary edema
- Ascites
- Increased filling pressure in the large veins

Laboratory findings may show decreased plasma osmolarity and hematocrit levels. These are used as criteria to provide an estimate measure of the current fluid volume status, both at the start of and during parenteral nutrition.

Effective treatment of fluid imbalance involves treating the underlying root cause instead of just its symptoms. The causes and treatment options of fluid imbalance are discussed in the previous section. On the other hand, symptomatic treatment of fluid imbalance usually involves the administration of individually tailored parenteral nutrition. Additionally, critically ill patients and those with renal insufficiency should be strictly monitored for changes in fluid and electrolyte levels (219).

Electrolyte intake in parenteral nutrition

- Patients with normal fluid and electrolyte levels should generally be given the recommended dietary intake. Serum electrolyte levels of sodium, potassium, calcium, magnesium and phosphate should be determined before initiating parenteral nutrition.
- Electrolyte requirements are normally administered with a glucose-amino acid solution. Additional requirements are usually administered via separate infusion pumps to prevent pharmaceutical incompatibility issues. Isolated potassium (1 mval/ml) or 20% sodium chloride should be infused via a central venous catheter.
Electrolyte intake adjustments should be made to correspond with the current results of frequent laboratory tests on electrolyte levels during parenteral nutrition.

The supply of electrolytes in a parenteral solution is related to fluid intake. Below is a table of the values for standard daily electrolyte intake derived from the guidelines of the American Gastroenterological Association (AGA) (217).

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Standard daily doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>60-150 mmol</td>
</tr>
<tr>
<td>Potassium</td>
<td>40-100 mmol</td>
</tr>
<tr>
<td>Magnesium</td>
<td>4-12 mmol</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.5-7.5 mmol</td>
</tr>
<tr>
<td>Phosphate</td>
<td>10-30 mmol</td>
</tr>
</tbody>
</table>

These values serve as general guidelines in patients with normal renal and liver functions and normal serum electrolyte levels. They may be adjusted more or less to reflect the disease status of a patient. For example, patients with hypertension and cardiac insufficiency may benefit more with lower sodium intake. On the other hand, higher doses are warranted in patients with large fluid losses such as those who are vomiting and have diarrhea, large wounds, high-output fistulae, and renal dysfunction. Additionally, many of the multi-chamber bags and amino acid solutions available in the market contain electrolytes in different doses, which may not always meet the individual needs of patients.
Currently, there is lack of scientific data that assess the adequate frequency of laboratory testing of serum electrolytes during parenteral nutrition. A daily monitoring (every 24 hours) has been found to be beneficial in ICU patients at the start of parenteral nutrition (week 1–2). On the other hand, a bi-weekly monitoring for inpatients (ward) was sufficient in the absence of special risk factors (218). The gap in the time between tests may be long in patients on long term parenteral nutrition, given that the electrolyte values were constant. Electrolyte level testing every 1–2 weeks during the initial three months, followed by monthly tests in the subsequent three months is generally adequate in stable patients on at-home parenteral nutrition.

X. EXERCISE AND ELECTROLYTE REPLACEMENT

Physical activities such as sports stimulate fluid losses through sweat. Several factors influence this mechanism, namely;

- Duration of exercise
- Intensity of exercise
- Environmental conditions
- Type of clothing/equipment worn

Some of these factors are predictable due to standard temperature, clothing worn, and running speed. Nonetheless, not all sports activities have predictable and uniform sweat rates since there are also the individual factors to consider. These individual factors include (144) (145):

- Body weight
- Genetic predisposition
- Heat acclimatization state
- Metabolic efficiency
All of the above factors are influential in determining the sweat rates for a given activity. These factors along with non-individual factors result in a wide variability of sweat rates and total sweat losses among athletes between and within activities. For example, football athletes exhibit different sweat rates depending on their position and playing style as well as the total time spent on the field (146). The table below is a summary of a few competitive sports (147) (148) (149) (150) (151) (152) (153) (154).

<table>
<thead>
<tr>
<th>Sport</th>
<th>Condition</th>
<th>Mean average sweat rate (L/h⁻¹)</th>
<th>Mean average fluid intake (L/h⁻¹)</th>
<th>Mean dehydration (change in body mass)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tennis</td>
<td>Summer competition (males)</td>
<td>1.6</td>
<td>0.14</td>
<td>0.26</td>
</tr>
<tr>
<td>Squash</td>
<td>Competition (males)</td>
<td>2.37</td>
<td>0.98</td>
<td>1.28 kg</td>
</tr>
<tr>
<td>Swimming</td>
<td>Training (males and females)</td>
<td>0.37</td>
<td>0.38</td>
<td>0</td>
</tr>
<tr>
<td>Rowing</td>
<td>Summer training (males)</td>
<td>1.98</td>
<td>0.96</td>
<td>1.7</td>
</tr>
</tbody>
</table>

The above information shows that the various athletes attained variable sweating rates ranging between 0.5 to 2.0 L·h⁻¹. Additionally, the wide variability in sweating rates between individuals for a particular sport and environment can be narrowed when body size is factored in.

Climate and temperature

When muscles contract during physical activities, metabolic heat is produced and transferred to the blood and finally, to the body core. As a result, body core temperature
rises and stimulates a physiologic mechanism that aids the movement of heat from the core to skin. Heat exchange between the skin and the air depends on a host of environmental factors such as temperature, humidity and air motion, sky and ground radiation, and clothing (155). In cooler environments and during colder seasons, the capacity for dry heat loss decreases cooling requirements for evaporation, thereby minimizing sweat losses. Inversely, in times of greater environmental heat stress, the capacity for dry heat loss is reduced, therefore, sweating increases in order to stimulate cooling through evaporation. Heavy or impervious garments such as a football uniform elevate heat stress and increase evaporative cooling requirements when used in temperate to hot settings (156). The exact opposite happens when the same garments are used in cold weather, eliciting faster sweating rates (157). In cooler settings, the required sweating rates would be lower due to more dry heat loss. If secreted sweat remains on the surface of the body instead of evaporating directly, there will be more sweating required to attain the evaporative cooling requirements. On the other hand, greater air movements (wind velocity) aid evaporation and minimize dripping sweat (158) (145).

The other factor is heat acclimatization. It helps the body attain greater and prolonged sweating rates, whenever required. Likewise, aerobic exercise training produces little stimulation on sweating rate responses. Additionally, wet skin and dehydration can also inhibit the sweating rate response (145) (159).

Electrolyte losses due to sweating largely depend on the total sweat deficit and sweat electrolyte levels. The average electrolyte concentrations are enumerated in the table below (160):

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Average concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>35 mEq·L(^{-1})</td>
</tr>
<tr>
<td>Potassium</td>
<td>5 mEq·L(^{-1})</td>
</tr>
</tbody>
</table>
Calcium | 1 mEq·L$^{-1}$
---|---
Magnesium | 0.8 mEq·L$^{-1}$
Chloride | 30 mEq·L$^{-1}$

It is important to note that sex and age do not have significant effects on electrolyte concentrations (161) (162). Dehydration can produce greater concentrations of sodium and chloride in the sweat (163). These electrolytes are reabsorbed by the sweat glands, but their reabsorption rates do not increase as the sweating rate increases. Therefore, the sweat sodium and chloride concentration increases as a function of sweating rate. Heat acclimatization enhances sodium and chloride reabsorption, therefore affording heat acclimatized persons reduced sweat sodium concentrations for any given sweating rate (164).

Evaluation of hydration measures

The body’s water balance is dependent on the net difference between water input and water output (165). Water input is primarily from food and fluid consumption and from metabolism, while water loss usually occurs in the respiratory, gastrointestinal and renal systems, and sweat. The volume of water (about 0.13 g·kcal$^{-1}$) produced as a metabolic product is about the same as that lost in respiration (166) (167). The result is a zero net change in total body water volume. Water loss from the GIT is small, about 100–200 mL·d$^{-1}$, except in cases of diarrhea. Sweating is the major route of water loss during exercise-heat stress. Renal regulation of water balance is via adjustment of urine output, with minimum and maximum urine outputs of approximately 20 and 1000 mL·h$^{-1}$, respectively (165). During physical activity and heat stress, both glomerular filtration and renal blood flow are significantly decreased, reducing urine output (168).
Prolonged periods (e.g., 8–24 h) of adequate fluid and electrolytes intake are usually sufficient to fully replenish water loss and normalize total body water (165). Total body water is maintained at ± 0.2 to 0.5% of daily body mass (169). Total body water averages about 60% of body mass (165). The variability is attributed to body composition; fat-free mass is approximately 70 to 80% water, while adipose tissue is about 10% water (165). For example, an average 70 kg individual has an estimated 42 L of total body water, with a range of 31–51 L (165). Professional athletes have a higher total body weight value because of greater muscle mass and lower body fat, coupled with aerobic training effect.

When evaluating the body’s hydration status, there is no specific range of total body weight that represents “standard normal values”, and evaluation of body water fluctuations beyond a range that have functional consequences is required (165). Preferably, the hydration biological indicator must possess both sensitivity and accuracy in the detection of body water fluctuations of about 3% of total body weight. Moreover, the biological indicator needs to be practical in terms of cost, time and technical application.

Simple and practical useful indicators of hydration status are urine and body weight measurements, although these also have limitations. Nevertheless, these biomarkers can be valid and precise when employed together properly (165). For example, the first morning body weight measurement (post urinating), and the urine concentration measurement offers sufficient sensitivity in detecting differences in fluid balance. The preferable urine bio-indicators of hydration status are the quantifiable tests of urine specific gravity (USG) and osmolality. Urine color and volume are subjective measures that allow a wide room for interpretation errors. A USG value of ≤1.020 indicates euhydration status. UOsmol values can vary widely, but values ≤700 mOsmol·kg⁻¹ indicate euhydration status (170) (171) (172).
It should be noted that these urine samples should only be obtained from either in the first morning voiding or several hours after consumption of corrective hypotonic fluids because urine values obtained at any other time can provide erroneous insight into the hydration status. For instance, when dehydrated individuals ingest hypotonic fluids, they will produce large amounts of urine prior to restoration of euhydration status (173).

The other practical yet effective tool in the assessment of hydration status is body weight measurements (169) (174). For well-hydrated persons, the first morning (post voiding) nude body weight measurements are stable and may show very minimal variations (< 1%) (169) (175) (176). In order to obtain precise values, a minimum of three consecutive morning nude body weight measurements are required to establish a baseline value, which reflects the estimated euhydration value, in active men who freely consume food and fluid without restrictions (169). Conversely, women may require more body weight measurements to establish a baseline value, because of menstrual cycle that dictates body fluid levels. For example, during the luteal phase, the body will have more body water, affecting the body weight by as much 2 kg (177).

Small changes in body weight during exercise are important in the calculation of sweating rates and fluctuations in hydration status occurring in a variety of environments (174). This approach is based on assumption that 1 mL of sweat loss is equal to a 1 g loss in body weight (i.e., specific gravity of sweat is 1.0 g·mL⁻¹). The body weight measurements prior to exercise are used with the post exercise body weight measurements corrected for urine losses and drink volume. When possible, nude weights should be used to prevent corrections for sweat that dripped onto the clothes (174). There are other non-sweat dynamics that influence body weight loss during exercise including respiratory water and carbon exchange (178). When these two factors are failed to be taken into account, there may be a moderate but negligible over-estimation of sweat rate (~5–15%) during exercise.
Hydration effects on body and activity performance

Individuals are more prone to dehydration when doing physical activities, and while it is common to rehydrate during exercise, greater fluid losses may be more common than first thought (179) (180). At the start of a physical activity, the body has normal total body water with dehydration occurring over a protracted period; however, in certain sports wherein the individual started the activity already dehydrated such as when the gap between rounds is insufficient for complete rehydration or when initial body weight is a qualifying factor. For example, in boxing and mixed martial arts, individuals sometimes deliberately dehydrate to qualify and compete in lower weight divisions (181). Additionally, some individuals who train more than once or engage in extended physical activity in hot conditions may also be prone to dehydration from their prior workout into the next (182). Water deficit in the absence of sodium chloride deficit is the most common type of dehydration encountered during exercise in hot conditions.

Dehydration causes an altered physiology measured by core temperature, heart rate and perceived exertion responses during exercise-heat stress (183). The more body water is lost, the more physiologic strain produced for a given exercise task (184) (185). Dehydration that is more than 2% of body weight degrades aerobic activity and cognitive/mental performance in temperate-warm-hot settings (186) (187) (165). The more dehydrated the individual, the greater is the degradation of aerobic activity performance. The critical water shortage and degree of performance decrement are likely related to the following factors:

- Environmental temperature
- Exercise task
- Unique biological characteristics (dehydration tolerance)

The above factors explain why certain individuals are more prone or intolerant to dehydration. Minimal dehydration (3% of body weight) does not influence the degradation of aerobic exercise performance in the presence of cold stress (188).
Moreover, greater dehydration (3–5% body weight) does not adversely affect either muscular strength or anaerobic performance (189) (190) (165) (191).

The physiologic factors governing the reduction of dehydration-mediated aerobic exercise performance are (192) (193) (159):

- Increased body core temperature
- Increased cardiovascular strain
- Increased glycogen utilization
- Alterations in metabolic function
- Alterations in CNS function

Study data points to the dynamic interactions between these factors to degrade aerobic exercise performance (159). The magnitude contribution of each factor varies depending on the type of activity, environmental conditions, heat acclimatization status and athletic skills, but elevated hyperthermia may stimulate reduction in physical performance. Additionally, mental performance is also substantially degraded by dehydration and hyperthermia. Its conservation is especially important in activities that require concentration and tactical thinking (194) (195). Lastly, scientific data suggests that the negative effects exerted by hyperthermia have more deleterious influence than that of mild dehydration on degrading mental performance (196). The two are closely related during physical activities in warm-hot environments.

Overhydration or water intoxication can occur with drinking excess fluids together with binding agents (197) (198). These binding agents, as their name suggests, bind water within the cells. Examples include glycerol and other hypertonic drinks. Water intoxication does not occur by just drinking excess water. In this case, there will only be a corresponding increase in urine production (165) with the hydration status still intact. But this is not the case during periods of vigorous physical activities where there is a risk of
dilutional hyponatremia (168). Overhydration does not improve overall performance; however, it prevents dehydration (199), which can contribute to a minimal performance advantage (200).

Heat-related illnesses and electrolyte and fluid imbalances

Dehydration puts individuals at a greater risk for heat exhaustion (201) (202). It is also a risk factor for heat stroke (203) (204) (205) (206). Heat stroke is linked to other dehydration factors such as:

- Lack of heat acclimatization
- Medications
- Genetic predisposition
- Illness

Dehydration was present in approximately 17 percent of all heat stroke admissions in the U.S. Army over a 22-yr period (203). Out of 82 cases of heat stroke in Israeli soldiers, dehydration was present in approximately 16 percent of them (204). In another report, sports team doctors for American football players during summer practice reported a link between dehydration, vomiting and heat stroke (207) (208). Additionally, dehydration has also been linked with decreased autonomic cardiac stability (209), impaired intracranial volume stasis (210) and cerebral blood flow velocity responses to orthostatic challenge (211).

Skeletal muscle cramps are linked with dehydration, electrolyte losses and muscle fatigue, all of which are common occurrences in non-heat-acclimatized American football players. The most vulnerable individuals are those who incur copious sodium deficits through sweat (212) (213).
Exercise-associated hyponatremia

The symptoms of hyponatremia begin to appear when plasma sodium quickly falls to approximately 130 mmol·L$^{-1}$ and below. The risk for dilutional encephalopathy and pulmonary edema is greatest when plasma sodium levels:

- Are very low
- Descend rapidly
- Remain low for very long

Survival and deaths have been reported with plasma sodium concentrations as low as 109 mmol·L$^{-1}$ and above 120 mmol·L$^{-1}$, respectively. When there is a continued fall of an already very low plasma sodium (less than 125 mmol·L$^{-1}$), patients will experience worsening headache, vomiting, swollen hands and feet, restlessness, undue fatigue, confusion and disorientation (due to progressive encephalopathy), and wheezy breathing (due to pulmonary edema). When left untreated and plasma sodium declines to less than 120 mmol·L$^{-1}$, the prognosis becomes worst and patients will exhibit cerebral edema with seizure, coma, brainstem herniation, respiratory arrest, and ultimately, death (214).

The following are factors that influence the development of exercise-associated hyponatremia (215):

- Overdrinking of hypotonic fluids
- Excessive loss of total body sodium

Athletes with genetic predisposition for cystic fibrosis are more susceptible to salt depletion and exercise-associated hyponatremia (216).

XI. ACID-BASE HOMEOSTASIS
Another essential component of the body fluid’s homeostatic mechanism is its acid-base balance. In the beginning of this course, the topic of acid and bases was discussed. In the following pages, greater detail is given to the role of acid-base balance in the body and the disorders associated with the loss of this balance.

A major feature of blood is its degree of acidity or basicity (alkalinity). Acidity and basicity are measured using the pH scale, which ranges from 0 (very acidic) to 14 (very basic). A pH of 7.0, in the middle of this scale, is neutral.

The normal pH of the blood leans slightly toward the basic side, at a range of 7.35 to 7.45. Normally, the body keeps the blood pH near 7.40. This value goes down or becomes acidic when the concentration of acidic compounds in the body increases or when the concentration of basic compounds in the body drops. The exact opposite occurs when blood alkalinity goes up. Keeping these concentrations within the normal range of acidity and alkalinity is referred to as acid-base balance. Acidosis and alkalosis are manifestations of an acid-base imbalance. Depending on their primary underlying cause, they are either metabolic or respiratory in nature. Metabolic acidosis and metabolic alkalosis results from an imbalance in the formation of acids or bases and their elimination by the kidneys. On the other hand, respiratory acidosis and respiratory alkalosis are usually the result of changes in carbon dioxide exhalation due to respiratory diseases (240).

The blood's acid-base balance is under the tight control of the body’s main excretory organs because minor deviations from the normal range can pose serious risks. The role of each component is discussed in detail below.

*Lungs*

Carbon dioxide is a mildly acidic arterial blood gas that is a metabolic waste product of cellular metabolism. Therefore, carbon dioxide accumulation results in an increase in the
acidity of blood. When the body becomes more acidic than normal, it releases carbon dioxide from the lungs. The brain controls the amount of carbon dioxide that is exhaled by regulating the speed and depth of breathing. The amount of carbon dioxide exhaled, and consequently the pH of the blood, increases as an individual breathes faster and deeper. Adjustments in the speed and depth of breathing allow the brain and lungs to control the blood pH minute by minute. In short, its compensatory components are (241):

- Hyperventilation (to decrease pCO₂)
- Hypoventilation (to increase pCO₂)

**Kidneys**

The kidneys also play a role in the regulation of blood pH. The kidneys regulate the amount of acid and bases being excreted slowly, usually over a period of several days. Its compensatory components are (242):

- Sodium-hydrogen ion exchange (renal tubules)
- Hydrogen phosphate formation
- Bicarbonate reclamation (formation)
- Ammonia production

**Buffer systems and compensatory mechanisms**

The body has its own buffer system, and its most important component is the blood. The pH buffer systems are comprised of the body's own endogenous weak acids and weak bases which exist in pairs under normal pH levels. A good example of this is carbonic acid (a weak acid formed from the carbon dioxide dissolved in blood) and bicarbonate ion (its weak base pair). The ratio of bicarbonate to carbonic acid is the pH of the blood. The carbonic acid-bicarbonate buffer system is the most important buffer system in plasma for the maintenance of physiological pH. It is represented by the equation below (242).
\[ \text{H}_2\text{O} + \text{CO}_2 \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+ \]

Carbonic acid (\(\text{H}_2\text{CO}_3\)) is the tie that binds both the respiratory and metabolic systems together. Both systems are independent of each other, each one able to compensate in case the other system falters (220). The onset of either acidosis or alkalosis is an important clue as to the severity of a disease and the urgency required of its treatment.

The Henderson-Hasselbalch (H-H) equation may also be employed to represent the concepts of respiratory and metabolic acidosis and alkalosis. It also represents the ratio of bicarbonate to carbonic acid which is 20:1. The general equation is shown below (243).

\[
\text{pH} = \text{pKa} + \log \left( \frac{\text{base}}{\text{acid}} \right) = \text{pka} + \log \left( \frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3} \right)
\]

where:
- \(\text{pKa}_{\text{H}_2\text{CO}_3}\) is the dissociation constant of carbonic acid. It is equal to 6.1.
- \([\text{HCO}_3^-]\) is the concentration of bicarbonate in the blood
- \([\text{H}_2\text{CO}_3]\) is the concentration of carbonic acid in the blood

If enough acid or base is added to change the pH, two things will occur:
- Elevation of bicarbonate ion concentration
- Respiratory compensation

For example, respiratory compensation occurs when blood pH increases to 7.5. This change can be quantified using the above equation. If cells produce excess acid (\(\text{H}^+\)), the \(\text{H}^+\) combines with and lowers the bicarbonate (\(\text{HCO}_3^-\)) levels. Now if the cells produce excess base, carbonic acid dissociates into protons to neutralize the base. The result is an increase in bicarbonate concentration. Faster and deeper breaths facilitate the removal of carbonic acid via carbonic anhydrase into carbon dioxide (respiratory alkalosis) while shallow breaths increase the concentration of carbonic acid (respiratory acidosis). The
occurrence of both results in the change of pH to its normal value (pH 7.4). It should be kept in mind that these mechanisms do not require large or dramatic changes in bicarbonate or pH before the body initiates them. Respiratory compensation starts as soon as the pH level shifts, so that by the time a patient arrives in the hospital, bicarbonate and carbonic acid changes have already occurred. On the other side of the equation, excess acid or excess alkali can be excreted renally. The normal ratio is about 20:1 bicarbonate to carbonic acid (244). As carbon dioxide is directly proportional to the carbonic acid (H$_2$CO$_3$), and can be directly measured, it will be substituted into the H-H equation.

\[
\text{PaCO}_2 = 33 \times \text{H}_2\text{CO}_3 \quad \text{or} \quad \text{H}_2\text{CO}_3 = 0.03\times\text{PaCO}_2
\]

By substituting the correct values, the equation below is derived:

\[
\text{pH} = \text{pK} + \log \left( \frac{\text{HCO}_3^-}{\text{PaCO}_2 \times 0.03} \right)
\]

Thus, by measuring serum pH and PaCO2, the serum bicarbonate can be calculated as:

\[
\log (\text{HCO}_3^-) = \text{pH} + \log (\text{PaCO}_2) - 7.604
\]

When calculating the compensatory mechanisms at play, keep the following notes in mind:

- PaCO$_2$ is the partial pressure of CO$_2$ in arterial blood. Its measurement is usually taken as mmHg which can be converted to mM by multiplying by 0.03.
- H$_2$CO$_3$ is regulated by the brain and lungs.
- Normal value for the bicarbonate buffer system in a normal person is measured in pKa of 6.1.
- Normal pH value is 7.4
Arterial blood gas measurement

Arterial blood gas measurements are usually taken in patients who (221):

- Are in respiratory failure
- Are critically ill
- Deteriorate unexpectedly such as those with sepsis or multi-organ failure
- Have uncontrolled diabetes mellitus
- Are suspected of drug or toxin overdose

Steps in the interpretation

There are several steps involved in the interpretation of arterial blood gas measurements. Look at the table and then follow the step by step process outlined below (245).

<table>
<thead>
<tr>
<th>Blood gas components</th>
<th>Normal readings</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>PaCO₂ (partial pressure of carbon dioxide)</td>
<td>4.7-6.0 kPa (35 mm Hg-45 mm Hg)</td>
</tr>
<tr>
<td>PaO₂ (partial pressure of oxygen)</td>
<td>11-13.5 kPa (83 mm Hg-102 mm Hg)</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>22-28 mmol/L</td>
</tr>
<tr>
<td>Anion gap</td>
<td>10-16 mmol/L</td>
</tr>
</tbody>
</table>

Step 1: Determine the presence of an acid-base abnormality. Check the pH level if it is outside the normal range.
Step 2: Determine the primary cause of disturbance. Check if the respiratory (PaCO₂) or the metabolic (HCO₃⁻) component is abnormal and if it is the primary cause of the acid-base abnormality. For example, consider a patient with alkalemia (pH 7.5) with PaCO₂ and HCO₃⁻ readings of 4 kPa (30 mm Hg) and 24 mmol/L, respectively. In this case, the respiratory component is the cause. The PaCO₂ is lower than the normal value indicating loss of the acidic carbon dioxide and accounting for the alkaline pH of the blood.

Now if there is metabolic acidosis—that is, low pH and low HCO₃⁻ the clinician may consider taking the extra step to calculate the anion gap. The formula to determine the anion gap is found below.

\[ \text{Anion gap} = (\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-) = 10-16 \text{mmol/L} \]

Ideally, the total number of anions and cations should match, however, a standard blood test does not include all of them, creating a difference of about 10-16 mmol/L. Certain pathologic conditions that cause metabolic acidosis result in an increased anion gap and others result in a normal anion gap.

Step 3: Evaluate the compensation. Identify the compensatory mechanisms at work. For example, if the cause is a respiratory disorder, then the metabolic compensatory components should be at work. It should be noted that no overcompensation occurs (220). These compensatory components usually improve the blood pH, though it never completely restores it, which is why the terms partial and full compensation are misleading (222).

Step 4: Assess the results of PaO₂. A patient may have respiratory failure if the PaO₂ is less than 8 kPa (61 mm Hg) (223). There are two types of respiratory failure, Type I and Type II. The former occurs when the patient has hypoxemia in the absence of hypercapnia while the latter occurs when the patient has both hypoxemia and hypercapnia, signifying hypoventilation (245).
When assessing the patient’s PaO\textsubscript{2}, the clinician should take into account the inspired oxygen. Ideally, the difference between the partial pressure of inspired oxygen and PaO\textsubscript{2} should be approximately below 10 kPa because of the alveolar-arterial (A-a) gradient. If the difference is more, the likelihood of reduced oxygen transfer efficiency from alveoli to blood—for example, a ventilation/perfusion (or VQ) mismatch is present. The fraction of oxygen in room air is 21 kPa and the corresponding PaO\textsubscript{2} in the blood is at least 11 kPa. If a patient has a PaO\textsubscript{2} of 11 kPa when breathing 35 percent oxygen, then the patient most likely has a disorder affecting oxygen transfer. The association between PaO\textsubscript{2} and oxygen saturation is the sigmoid oxyhemoglobin dissociation curve (245).

From the Henderson-Hasselbalch (H-H) equation, the blood pH can be calculated from the buffering constituents using the equation below.

- \( \text{pH} = 6.1 + \log [\text{HCO}_3^-] 
\)
- \( (0.03 \times \text{PaCO}_2) \)

Where,

pH is the acidity in the blood

\([\text{HCO}_3^-]\) is the concentration of serum bicarbonate in mmol/L and,

\(\text{PaCO}_2\) is the partial pressure of carbon dioxide in mm Hg

The relationship between pH, CO\textsubscript{2} and HCO\textsubscript{3}\textsuperscript{−} can be summarized below:

<table>
<thead>
<tr>
<th>Primary condition</th>
<th>pH</th>
<th>PaCO\textsubscript{2}</th>
<th>Bicarbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory acidosis</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
XII. ACID-BASE DISORDERS

Acid base disorders are classified into four groups:

- Metabolic acidosis
- Metabolic alkalosis
- Respiratory acidosis
- Respiratory alkalosis

Metabolic acidosis

Metabolic acidosis is a major fall in serum HCO₃⁻ level and manifests as acidemia. As discussed previously, its onset is marked by the activation of the pulmonary compensatory mechanism, hyperventilation. The normal range with which PaCO₂ drops is between 1-1.3 mm Hg for every 1-mEq/L fall in serum HCO₃⁻ concentration. However, if PaCO₂ level is outside this range, then a mixed acid-base disturbance is likely present. One sure method of diagnosing metabolic acidosis is by simultaneously measuring serum electrolyte concentrations and arterial blood gases (ABGs) (247).

A normal serum HCO₃⁻ concentration does not necessarily mean the absence of metabolic acidosis, because HCO₃⁻ can fall from a high baseline in patients with preexisting metabolic alkalosis to a serum HCO₃⁻ level within the normal range. Generally, patients with renal failure and chronic uremic acidosis have serum HCO₃⁻ concentration >12 mEq/L. Further deterioration of these conditions is stopped by the buffering actions of bones which can very well lead to calcium loss and subsequently, osteopenia and osteomalacia (247).
Anion gap

As mentioned previously, the total number of cations should be equal to the number of anions in the plasma. The cations and the anions being referred to are sodium and, chloride and bicarbonate, respectively. Now the anion gap (AG) refers to the difference between the sodium, and chloride and bicarbonate concentrations. An increase in the anion gap can result in the following electrolyte imbalance (247):

- Hypokalemia
- Hypocalcemia
- Hypomagnesemia
- Hyperphosphatemia

The identification of an increased anion gap enables the clinician to formulate a differential diagnosis for the underlying cause of the acidosis.

\[ HA + NaHCO_3 \leftrightarrow NaA + H_2 CO_3 \leftrightarrow CO_2 + H_2 O \]

The equation above shows that the addition of an acid (HA) leads to the utilization of \( HCO_3^- \) with the addition of anions that is the cause of anion gap increase. Metabolic acidosis is classified on the basis of anion gap into normal- and high-anion gap metabolic acidosis (247).

Urinary anion gap is useful in the assessment of certain cases of non-anion gap metabolic acidosis. However, patients with ketonuria may not benefit from this test due to the negatively charged ketones being unmeasured resulting in a positive or zero anion gap despite the ongoing renal acidification and increasing ammonium concentration (247).

The role of potassium ions and renal acid secretion
Serum potassium levels affect renal acid secretion. Renal acid secretion happens when there is movement of potassium between compartments. Patients with hypokalemia can develop intracellular acidosis, while those with hyperkalemia are at risk of intracellular alkalosis (247).

Ammonia secretion in the kidneys is stimulated during hypokalemic states, leading to increased renal acid excretion. Elevated ammonia levels may lead to hepatic encephalopathy in patients who have advanced liver dysfunction. This is a reversible process that can be easily addressed by treating the hypokalemia. The most common etiologies for hypokalemia and metabolic acidosis are diarrhea and laxative use. The uncommon causes for hypokalemia are renal loss of potassium secondary to renal tubular acidosis (247).

Hyperkalemia affects the acid-base regulation completely in the opposite way. Patients with hyperkalemia will experience reduced ammonia production and reabsorption in the kidneys, resulting in lowered ammonia concentration and consequently, net renal acid secretion. These mechanisms are primarily seen in patients with primary or secondary hypoaldosteronism. Like hypokalemia, these metabolic acidosis effects are easily countered with the treatment of hyperkalemia (247).

Causes and diagnostic considerations

Metabolic acidosis can be classified into two groups (248):

- Normal anion gap (non-anion gap)
- High anion gap

Some of the mechanisms that lead to non-anion gap metabolic acidosis are (248):

- Addition of hydrochloric acid to body fluids
• Renal or GIT HCO$_3^-$ loss
• Fast volume expansion with normal saline

The specific etiologies of non-anion gap metabolic acidosis are (248):

- Acid load
- Chronic renal failure
- Carbonic anhydrase inhibitors
- Renal tubular acidosis (RTA)
- Ureteroenterostomy
- Volume expansion

The specific etiologies of anion gap metabolic acidosis are discussed further in the succeeding pages.

Specific causes of non-anion gap metabolic acidosis

1. Loss of HCO$_3^-$ via the GI tract
Gastrointestinal secretions are primarily basic in nature, except those from the stomach which is hydrochloric acid. Copious losses of lower gastrointestinal secretions lead to metabolic acidosis, particularly when renal function is not able to cope, thereby increasing net renal acid excretion. These losses occur in patients with diarrhea, fistula with drainage from the pancreas, and vomiting induced by intestinal obstruction. Additionally, chronic laxative users are also more prone to non-AG metabolic acidosis (248).

2. Distal renal tubular acidosis (type 1 RTA)
There is a decrease in net H⁺ produced by the A-type intercalated cells of the collecting duct which leads to the reduction in its urinary concentration and total H⁺ buffered by urinary phosphate. This cause of metabolic acidosis should be strongly suspected in any patient having non-anion gap metabolic acidosis and urine pH <5.0 (248).

Usually, the serum potassium concentration is decreased in patients with distal RTA due to the defects in H⁺ production or back-diffusion of H⁺ which stimulates urinary potassium wasting. Listed below are factors that contribute to potassium wasting (248):

- Reduced net H⁺ secretion leads to increased Na⁺ reabsorption in exchange for K⁺ secretion.
- Decreased serum HCO₃⁻ decreases the amount of Na⁺ reabsorbed by the Na⁺/H⁺ exchanger in the proximal tubule, resulting in volume reduction.
- Defect in K⁺/H⁺–ATPase leads to reduced H⁺ release and reduced K⁺ reabsorption.

Aside from hypokalemia, patients with type 1 renal tubular acidosis are susceptible to nephrocalcinosis and nephrolithiasis.

3. Proximal renal tubular acidosis (type 2 RTA)

Type 2 renal tubular acidosis is characterized by a defective proximal tubular HCO₃⁻ reabsorption mechanism. HCO₃⁻ excretion normally takes place only when serum HCO₃⁻ exceeds 24-28 mEq/L. However, patients with type 2 renal tubular acidosis have a lower threshold for excretion of HCO₃⁻, resulting in a deficit of filtered HCO₃⁻ until the serum HCO₃⁻ level arrive at the lower threshold. When this happens, anion excretion stops and the urine achieves complete acidification (248).

4. Type 4 renal tubular acidosis (type 4 RTA)
Type 4 renal tubular acidosis is the most frequently seen type of renal tubular acidosis in adults. It is a result of hypoaldosteronism. Aldosterone deficiency is linked with decreased collecting duct Na\(^+\) reabsorption, hyperkalemia, and metabolic acidosis. Elevated serum potassium level decreases proximal tubular NH\(_4\)\(^+\) production and absorption at the thick ascending limb, resulting in lower medullary interstitial ammonia level. This mechanism compromises the renal capacity to excrete acid and aggravates the acidosis (248).

Patients with type 4 renal tubular acidosis will most likely have an elevated serum potassium level, although not all of them exhibit symptoms. The cause of hyperkalemia is multifactorial and associated with aldosterone deficiency and some form of renal insufficiency. The acidosis and hyperkalemia, however, are not in proportion to the severity of renal failure (248).

The following are the etiologies of type 4 RTA:

- **Hypoaldosteronism (low renin)** - Hyporeninemic hypoaldosteronism (diabetes mellitus/mild renal impairment, chronic interstitial nephritis, nonsteroidal anti-inflammatory drugs, beta-blockers)
- **Hypoaldosteronism (high renin)** - Primary adrenal defect (isolated: congenital hypoaldosteronism; generalized: Addison disease, adrenalectomy, AIDS), inhibition of aldosterone secretion (heparin, ACE inhibitors, AT1 receptor blockers)
- **Aldosterone resistance (drugs)** - Diuretics (amiloride, triamterene, spironolactone), calcineurin inhibitors (cyclosporine, tacrolimus), antibiotics (trimethoprim, pentamidine)
- **Aldosterone resistance (genetic)** - Pseudohypoaldosteronism (PHA) types I and II

5. Early renal failure
Metabolic acidosis occurs with renal failure. During the early to moderate stages of chronic renal disease, metabolic acidosis is associated with a normal anion gap. During advanced stages of kidney failure, the acidosis is associated with a high anion gap (248).

It is important to keep in mind that patients with hypobicarbonatemia from kidney failure do not have the compensatory ability to handle the extra \( \text{HCO}_3^- \) deficit from other sources of losses (e.g. diarrhea), allowing the rapid development of severe metabolic acidosis (248).

6. Urinary diversion
Patients who underwent a urinary diversion procedure such as a sigmoid bladder or an ileal conduit are susceptible to the development of hyperchloremic metabolic acidosis (248).

7. Infusion of acids
The addition of an acid that contains \( \text{Cl}^- \) as an ion (e.g., \( \text{NH}_4 \text{Cl} \)) can result in a normal-anion gap acidosis because the drop in \( \text{HCO}_3^- \) is accompanied by an increase in \( \text{Cl}^- \).

The use of arginine or lysine hydrochloride as amino acids during hyperalimentation can have the same result (248).

Specific causes of high-anion gap metabolic acidosis
1. Lactic acidosis
L-lactate is an intermediate product of metabolism. Normally, a healthy person produces about 20 mEq/kg/day of lactate which is metabolized in the various organs. The build up of lactic acid in the blood occurs when production is increased or its metabolism is
decreased. Usually, an upward deviation of approximately 4-5 mEq/L from the reference range is considered diagnostic of lactic acidosis (248).

Lactic acid occurs in two forms (248):

- Type A lactic acidosis which occurs in hypoxic states
- Type B which occurs in the absence of hypoxia

2. Ketoacidosis

Ketoacidosis is the result of increased delivery of free fatty acids to the liver or conversion of fatty acids to ketoacids. This is most commonly seen in diabetic patients (diabetic ketoacidosis or DKA) during periods of uncontrolled blood sugar levels. The metabolic acidosis associated with it is usually a high-anion gap acidosis secondary to the presence of ketones in the blood (248).

Another form of ketoacidosis is called alcoholic ketoacidosis which is a result of excessive alcohol intake in malnourished individuals. This particular diagnosis should be strongly suspected in alcoholic patients who have an unexplained anion gap acidosis, accompanied by the presence of beta-hydroxybutyric acid in the serum without hyperglycemia. Starvation ketoacidosis is known to happen after extended periods of fasting (248).

3) Advanced renal failure

Patients with a glomerular filtration rate <20 mL/min usually have a high-anion gap acidosis. The high-anion gap leads to sulfate, urate and phosphate build up because of the diminished renal function (248).

4) Salicylate overdose
Salicylate toxicity can lead to a high-anion gap acidosis. There are three factors that contribute to its development, namely (248):

- Unmeasured salicylate anion
- Increased ketoacid levels
- Lactic acid levels

The metabolic acidosis allows the passage of salicylate into the CNS, resulting in respiratory alkalosis and CNS toxicity.

5) Methanol poisoning

Methanol toxicity is linked with high-anion gap metabolic acidosis. Formaldehyde is the primary cause of methanol toxicity, resulting in optic nerve injury and CNS toxic manifestations. On the other hand, the build up of its metabolic product, formic acid, in association with increased lactic acid and ketoacid accumulation accounts for the high anion gap (248).

6) Ethylene glycol toxicity

The high anion gap metabolic acidosis is a result of the accumulation of its acidic products. The presence of oxalate crystals and elevated osmolar gap in the urine offer a highly suggestive diagnosis of its toxicity (248).

**Metabolic alkalosis**

Metabolic alkalosis refers to the elevation of serum bicarbonate level. It happens as a result of hydrogen ion loss from the body or a gain in bicarbonate ions. A reading of pH >7.40 is its diagnostic finding. When metabolic alkalosis occurs, the body responds by stimulating alveolar hypoventilation in an effort to increase arterial carbon dioxide tension (249).
The primary organs involved in the pathophysiology of metabolic alkalosis are the kidneys and gastrointestinal tract. The disease process of metabolic alkalosis involves two mechanisms that often intertwine (249).

Generation of metabolic alkalosis

Metabolic alkalosis may be generated by one of the following mechanisms (249):

1. Loss of hydrogen ions via the kidneys and GI tract

Vomiting and nasogastric aspiration causes loss of GIT secretions, especially hydrochloric acid, leading to metabolic alkalosis. This is because for every hydrogen ion that is eliminated, a bicarbonate ion is released into the extracellular space. Hydrogen ions can also be lost via the kidneys. This happens when the distal delivery of sodium increases due to the stimulation of surplus aldosterone. The result is stimulation of the electrogenic epithelial sodium channel (ENaC) in the collecting duct which is the site of sodium reabsorption. When this happens, the tubular lumen becomes more electronegative, resulting in the release of hydrogen ions and potassium ions into the lumen.

2. Shift of hydrogen ions into the intracellular space

The hypokalemia that often accompanies metabolic alkalosis promotes the movement of hydrogen ions into the intracellular space. When potassium level in the extracellular space falls, potassium ions move out of the cells in response. This movement in turn stimulates the movement of hydrogen ions into the intracellular space in an effort to maintain neutrality.

3. Alkali administration

When excess sodium bicarbonate is administered beyond the capacity of its renal excretion, the alkali overload may cause metabolic alkalosis. The renal capacity for
bicarbonate excretion is decreased when less bicarbonate is filtered (e.g. renal failure), or when there is an increase in reabsorption of bicarbonate (e.g. volume depletion).

4. Contraction alkalosis

Contraction alkalosis happens when there is a disproportionate loss of fluid without a corresponding loss in bicarbonate concentration. As a result, the extracellular volume contracts around the available bicarbonate causing its level to rise and correspondingly, the blood pH. This is most commonly seen in patients who are on diuretics.

Maintenance of metabolic alkalosis

Metabolic alkalosis may be maintained by one of the following mechanisms (249):

1. Reduced renal perfusion

Reduced renal perfusion occurs in states of volume depletion or edema (e.g. congestive heart failure, cirrhosis) stimulates the renin-angiotensin-aldosterone system (RAAS). The result is the promotion of sodium ion reabsorption in all cells of the kidneys, including the principal cells of the collecting duct, enhancing hydrogen ion secretion via the apical proton pump H^+ adenosine triphosphatase (ATPase) in the adjacent A-type intercalated cells.

2. Aldosterone release

Aldosterone can act on the apical proton pump in the collecting duct and stimulate its hydrogen secretory function. The increased hydrogen ion secretion into the tubular lumen results in a corresponding gain of bicarbonate ion into the systemic circulation via the basolateral Cl^-/HCO_3^- exchanger.

3. Chloride depletion

Chloride depletion is caused by a number of factors, namely:
- Gastrointestinal loss of gastric secretions (rich in chloride)
- Loop or thiazide diuretics therapy

Chloride depletion can independently promote bicarbonate reabsorption, regardless of volume status. The mechanisms behind this are explained thoroughly below.

The Na\(^+\)/K\(^+\)/2Cl\(^-\) co-transporter in the apical membrane of the macula densa present in the late thick ascending limb (TAL) and early distal tubule specialized cells are primarily controlled by chloride ion concentration. In the setting of chloride depletion, less chloride ions are present in the transporter. The chloride deficit stimulates the macula densa to signal the juxtaglomerular apparatus to secrete renin, which in turn stimulates aldosterone secretion via angiotensin II (249).

When there is excess alkali in the blood, renal compensatory mechanisms stimulate the secretion of excess bicarbonate via the apical chloride/bicarbonate exchanger, pendrin, in the B-type intercalated cells of the collecting duct. The result is increased proton levels in the systemic circulation via the basolateral H\(^+\) ATPase. In the setting of chloride depletion, there are less chloride ions available for exchange with bicarbonate ions, reducing the renal capacity for excess bicarbonate excretion (249).

The etiologies of metabolic alkalosis are often linked with hypokalemia. Hypokalemia sustains metabolic alkalosis via five different mechanisms, namely (249):

- Intracellular shift of hydrogen which augments bicarbonate reabsorption in the collecting duct.
- Stimulation of the apical H\(^+\)/K\(^+\) ATPase in the collecting duct results in teleologically appropriate potassium ion reabsorption with a corresponding hydrogen ion secretion which in turn increases bicarbonate gain, maintaining alkalosis.
- Stimulation of renal ammonia genesis, reabsorption, and secretion.
- Impairment of chloride ion reabsorption in the distal nephron which leads to luminal electronegativity, and resulting augmentation of hydrogen ion secretion.
- Decreased glomerular filtration rate slows down renal excretion of excess bicarbonate.

The two usual causes of metabolic alkalosis are (249):
- Diuretics
- External loss of gastric secretions

These two causes and others are classified into three distinct groups (249):
- Chloride-responsive alkalosis
- Chloride-resistant alkalosis
- Other causes

Chloride-responsive alkalosis
Causes of chloride-responsive alkalosis (urine chloride < 20 mEq/L) are (250):
1. Loss of gastric secretions
When hydrochloric acid is expelled via vomiting or nasogastric aspiration, a corresponding net gain of bicarbonate in the blood occurs, generating a metabolic alkalosis. The loss of fluids maintains alkalosis. The simultaneous administration of copious amounts of nonabsorbable antacids such as magnesium hydroxide with a cation-exchange resin can generate metabolic alkalosis. The resin binds with the cation, freeing the bicarbonate.

2. Loss of colonic secretions
Rare causes of metabolic alkalosis are villous adenomas. It causes diarrhea and typically result in metabolic acidosis due to a deficit in colonic secretions, although they sometimes cause metabolic alkalosis. Its pathologic role in metabolic alkalosis is not well understood, though some scientists suggest that the hypokalemia induced by these tumors may be responsible. Congenital chloridorrhea is another rare cause of metabolic alkalosis which also induces diarrhea. Genetic mutations cause chloride/bicarbonate exchange dysfunction in the intestines, resulting in the stimulation of chloride secretion and bicarbonate reabsorption.

3. Thiazides and loop diuretics (after discontinuation)

Potassium-depleting diuretics such as hydrochlorothiazide and furosemide augment sodium chloride excretion in the distal convoluted tubule and the thick ascending loop, respectively. They cause metabolic alkalosis by facilitating chloride deficit and delivery of sodium ions into the collecting duct, increasing the secretion of potassium and hydrogen ions.

4. Posthypercapnia

After hypercapnia, urinary chloride level is elevated, resulting in rapid chloride elimination. After correction of respiratory acidosis, excess bicarbonate ions are not readily excreted due to a minimal level of luminal chloride.

5. Cystic fibrosis

Pediatric patients with cystic fibrosis are susceptible to metabolic alkalosis and volume depletion.

Chloride-resistant alkalosis

The etiologies of chloride-resistant alkalosis are further classified into two groups, namely:
- With accompanying elevated blood pressure
- With accompanying low or normal blood pressure

Causes of chloride-resistant alkalosis (urine chloride >20 mEq/L) accompanied by elevated blood pressure are (250):

1. Primary hyperaldosteronism

Primary hyperaldosteronism can be caused by underlying benign and metastatic etiologies, namely:

- Adrenal adenoma
- Bilateral adrenal hyperplasia
- Adrenal carcinoma

Primary hyperaldosteronism can also be caused by glucocorticoid-responsive aldosteronism, a familial disorder, wherein there is ectopic production of aldosterone in the zona fasciculata of the adrenal cortex. Its production is regulated by the adrenocorticotropic hormone (ACTH) instead of the angiotensin II and potassium, the primary controllers. As its name suggests, it is responsive to glucocorticoid therapy, which inhibits aldosterone secretion by suppressing ACTH. The mineralocorticoid receptor in the collecting duct usually responds to aldosterone and cortisol. Although cortisol has a higher affinity for the receptor, it may be inhibited by 11-beta-hydroxysteroid dehydrogenase type 2 (11B-HSD2), making the way for aldosterone to access its receptor.

2. 11B-HSD2 deficiency

Low concentration of the 11B-HSD2 enzyme can result in the cortisol activation of the mineralocorticoid receptor which in turn activates the ENaC. In this setting, the actions of cortisol mimic that of a mineralocorticoid. It causes blood pressure levels to rise
accompanied by decreased renin and aldosterone secretions, hypokalemia, and metabolic alkalosis. Lab tests will reveal serum cortisol to be within the reference range because the negative feedback of cortisol on adrenocorticotropic hormone (ACTH) is fully functional.

3. CAH

Congenital adrenal hyperplasia (CAH) may be caused by low levels of either 11-beta-hydroxylase or 17-alpha-hydroxylase, which play a role in the synthesis of adrenal steroids. 11-beta-hydroxylase or 17-alpha-hydroxylase deficiency increases the concentrations of 11-deoxycortisol and impede the synthesis of cortisol and aldosterone.

4. Current use of diuretics in hypertension

The most frequent cause of metabolic alkalosis in patients on antihypertensives are the use of either thiazides or loop diuretics.

5. Cushing syndrome

Patients with Cushing syndrome experience superior mineralocorticoid effect due to the occupation of the mineralocorticoid receptor by the elevated plasma cortisol level. Hypokalemia and metabolic alkalosis in patients with Cushing syndrome is largely attributed to the ectopic ACTH production (about ninety percent) than in any other causes. This is due to the higher level of plasma cortisol and the increased defective 11B-HSD activity that ensues in ectopic ACTH production.

6. Exogenous mineralocorticoids or glucocorticoids

External sources of mineralocorticoids can cause metabolic alkalosis.

7. Liddle syndrome
Liddle syndrome is an uncommon familial disease caused by an extra-functional mutation in the beta \((SCNN1B)\) or gamma subunit \((SCNN1G)\) of the ENaC in the collecting duct. The mutation causes the channel to open indefinitely resulting in unregulated reabsorption of sodium ions and ultimately, volume expansion and hypertension. The uncontrolled sodium reabsorption causes secondary renal hydrogen ion and potassium ion losses which do not respond to aldosterone inhibition.

8. Renovascular hypertension

The narrowing of the renal arteries either unilaterally or bilaterally stimulates the renin-angiotensin-aldosterone system, resulting in elevated blood pressure and hypokalemic metabolic alkalosis (250).

Renin- or deoxycorticosterone-secreting tumors are uncommon but are also known to trigger renovascular hypertension. These tumors secrete excess renin or deoxycorticosterone in the juxtaglomerular apparatus, promoting the secretion of aldosterone (250).

Causes of chloride-resistant alkalosis (urine chloride >20 mEq/L) without elevated blood pressure are (250):

1. Bartter syndrome

Chloride-resistant alkalosis may be a symptom of Bartter syndrome, a familial disorder. Patients with Bartter syndrome have dysfunctional sodium and chloride reabsorption mechanisms in the thick ascending loop of Henle, resulting in the ionic movement towards the distal nephron. The ineffective reabsorption of sodium and chloride in the loop of Henle is attributed to mutational dysfunction of one of several transporters in the nephron, namely the:

- Furosemide-sensitive \(\text{Na}^+/\text{K}^+/2\text{Cl}^-\) cotransporter \((NKCC2)\)
- Basolateral chloride ion channel \((CLCNKB)\)
• Inwardly rectifying apical potassium ion channel (*ROMK1*)
• Varttin (BSND), the beta-subunit of the chloride channels, CLC-Ka and CLC-Kb
• Calcium sensing receptor (CaSR)

*CLCNKB* mutations are the most common cause of Bartter syndrome, while mutations of the other 2 transporters appear with the antenatal form of Bartter syndrome. It is often accompanied by hypercalciuria because the damaged reabsorption mechanism of sodium chloride prevents paracellular reabsorption of calcium. Like loop diuretics, it inhibits the Na^+/-K^+/2Cl^- transporter causing electrolyte imbalance similar to those caused by loop diuretics. Edema and hypertension are notably absent.

2. **Gitelman syndrome**

Gitelman syndrome is a familial disease characterized by a dysfunctional thiazide-sensitive sodium/chloride transporter (*NCCT*) in the distal convoluted tubule. The dysfunctional transporter leads to increased movement of solute to the distal convoluted tubule and inappropriate renal sodium excretion. As a compensatory response, the renin-angiotensin-aldosterone system is stimulated leading to hypokalemic metabolic alkalosis. Other notable electrolyte disorders of the syndrome are hypocalciuria and hypomagnesemia.

3. **Severe potassium depletion**

Severe potassium ion depletion is the etiology behind mild metabolic alkalosis. However, when accompanied by hyperaldosteronism, the alkalosis is worst. There are several mechanisms attributed to this type of alkalosis, namely:

• Enhanced proximal bicarbonate reabsorption
• Stimulated renal ammonia genesis
• Dysfunctional renal chloride reabsorption
• Intracellular acidosis in the distal nephron with resulting increase in hydrogen secretion

4. Current use of thiazides and loop diuretics

5. Hypomagnesemia

Magnesium ion deficit can also result in metabolic alkalosis. The mechanism behind this etiology is not entirely understood but it may involve hypokalemia, which is usually caused by or associated with magnesium loss.

Other causes of metabolic alkalosis are:
1. Exogenous alkali administration

The administration of bicarbonate to correct a metabolic acidosis may lead to ion overload after the patient recovers. Patients who are volume depleted or with renal failure are most susceptible to this type of metabolic alkalosis (250).

2. Milk-alkali syndrome

Milk-alkali syndrome is characterized by hypercalcemia, renal insufficiency, and metabolic alkalosis. This was mostly seen in patients with increased intake of antacids. However, this is largely a thing of the past now since H2 blockers became the drugs of choice for the management of peptic ulcers. Now, milk alkali syndrome is mostly seen in geriatric patients on chronic calcium carbonate supplementation to prevent osteoporosis (239).

3. Hypercalcemia
The volume depletion and improved bicarbonate reabsorption that occurs in patients with hypercalcemia can lead to metabolic alkalosis. One exception to this is the hypercalcemia secondary to primary hyperparathyroidism which is typically linked to the development of metabolic acidosis (250).

4. Dialysis

Patients with end-stage renal disease are dialyzed with high carbonate dialysate to treat the accompanying metabolic acidosis. However, the amount of bicarbonate administered is sometimes more than the required to buffer the acidosis resulting in a short-lived alkalosis. The severity of alkalosis may be exacerbated by the presence of vomiting (250).

Metabolic alkalosis has also been observed in patients who underwent regional citrate anticoagulation in hemodialysis or continuous renal replacement therapies. Citrate prevents coagulation in the blood inflow line by binding with calcium. The dialyzer does not fully remove the citrate, resulting in the increased risk of it reaching the general circulation. Once in the blood, it is metabolized to bicarbonate which may lead to its accumulation and subsequently, metabolic alkalosis (250).

Patients with autoimmune diseases often undergo plasmapheresis. One of the complications of this procedure is metabolic alkalosis, particularly in patients with compromised renal function (e.g. renal failure). Citrate is also used to prevent blood coagulation in the extracorporeal circuit and in the stored blood from which the fresh frozen plasma is prepared (250).

5. Intravenous penicillin

Patients administered with intravenous penicillin, carbenicillin, or other semisynthetic penicillins are at risk of hypokalemic metabolic alkalosis. The alkalosis is the result of
distal delivery of nonreabsorbable anions with an absorbable cation such as sodium (250).

6. Refeeding alkalosis

Patients who are re-fed with a carbohydrate-rich diet after chronic fasting are susceptible to mild metabolic alkalosis because of improved metabolism of ketoacids to bicarbonate (250).

7. Massive blood transfusion

Citrate infusion is also used as an anticoagulant in massive blood transfusion. The transfused blood is metabolized to bicarbonate by the liver. Patients with compromised renal function are more likely to develop metabolic alkalosis because of the greater risk of bicarbonate accumulation in the blood (250).

8. Hypoproteinemia

Metabolic alkalosis is also associated with hypoproteinemia. The mechanism behind this etiology is unclear but may be attributed to loss of negative charges of albumin. A reduction in plasma albumin of 1 g/dL is linked with an increase in plasma bicarbonate of 3.4 mEq/L (250).

Complications

The complications associated with metabolic alkalosis are:

- Tetany
- Seizures
- Impaired mental status
- Reduced coronary blood flow increasing the risk of refractory arrhythmias
- Hypoxemia particularly in patients with poor respiratory reserve
- Difficult weaning from mechanical ventilation
- May trigger hepatic encephalopathy in susceptible individuals

Respiratory acidosis

Respiratory acidosis occurs as a result of alveolar hypoventilation. Carbon dioxide is produced more rapidly than it is being eliminated, leading to ventilation dysfunction that immediately increases the partial pressure of arterial carbon dioxide (PaCO₂) (224). This mechanism reduces the bicarbonate (HCO₃⁻)/PaCO₂ ratio, resulting in the lowering of blood pH.

Respiratory acidosis exists in two forms (251):

- Acute respiratory acidosis
- Chronic respiratory acidosis

The main difference between the two lies in the change in pH levels. In acute respiratory acidosis, there is a dramatic rise in PaCO₂ level above the normal limit, which is more than 45 mm Hg. It is most often accompanied by acidemia. On the other hand, in chronic respiratory acidosis, there is a rise in PaCO₂ but with normal or near-normal pH and increased serum bicarbonate level (251).

Acute respiratory acidosis occurs when there is a sudden disruption to ventilation which may result from dysfunction of the central respiratory center by any of the following causes (251):

- CNS depression
- Neuromuscular disorders such as myasthenia gravis, amyotrophic lateral sclerosis, Guillain-Barré syndrome, muscular dystrophy.
Airway Obstruction (e.g. asthma)

Chronic respiratory acidosis occurs with preexisting hypoventilating conditions such as (251):

- COPD
- Obesity hypoventilation syndrome (OHS)
- Neuromuscular disorders
- Severe restrictive ventilatory defects (e.g. interstitial fibrosis and thoracic skeletal deformities)

Physiologic compensation

The body compensates in periods of acute respiratory acidosis in two steps, namely (251):

- Initial cellular buffering increases plasma bicarbonate values
- Renal elimination and reabsorption of carbonic acid and bicarbonate increase, respectively

The estimated change in serum bicarbonate level during respiratory acidosis can be calculated by (251):

- Acute respiratory acidosis – Bicarbonate rises by 1 mEq/L for each 10-mm Hg elevation of PaCO₂. The acute change in bicarbonate level is minimal and produced by the blood, extracellular fluid, and cellular buffering system.
- Chronic respiratory acidosis – Bicarbonate rises by 3.5 mEq/L for each 10-mm Hg elevation of PaCO₂. The dramatic change in bicarbonate level is generated by the kidneys.
The pH change associated with respiratory acidosis may be calculated by the equations (251):

- Acute respiratory acidosis – Change in pH = 0.008 × (40 – PaCO$_2$)
- Chronic respiratory acidosis – Change in pH = 0.003 × (40 – PaCO$_2$

Electrolyte levels largely remain unchanged in respiratory acidosis. There may be minor effects on calcium and potassium levels. It may decrease the binding of calcium to protein, thereby, increasing serum ionized calcium concentrations. Additionally, low pH level leads to the extracellular movement of potassium (225). It should be noted that respiratory acidosis hardly ever causes hyperkalemia that is clinically important.

Complications

Because respiratory acidosis causes an increase in partial arterial pressure of carbon dioxide (PaCO$_2$) and bicarbonate levels, a corresponding obligatory reduction in partial pressure of arterial oxygen (PaO$_2$) also takes place. This is why the complications of respiratory acidosis are usually associated which chronic hypoxemia, which may lead to stimulation of erythropoiesis, resulting in secondary polycythemia. Chronic hypoxia causes constriction of the pulmonary blood vessels, which when left untreated for a long time, may result in pulmonary hypertension, right ventricular failure, and cor pulmonale.

Other complications of respiratory acidosis are hypopneas and apneas which affect the quality of sleep and cerebral vasodilation causing morning headaches, daytime fatigue, and somnolence. Additionally, increased concentration of CO$_2$ may result in confusion. A late complication of cerebral vasodilation is papilledema (229).

Respiratory alkalosis

Respiratory alkalosis is also caused by alveolar ventilation dysfunction, specifically hyperventilation. It results in a decreased partial pressure of arterial carbon dioxide
(PaCO₂) which in turn results in the elevation of bicarbonate concentration to PaCO₂ ratio. The increase raises the pH level. Hypocapnia sets in when there is a rapid and increased removal of carbon dioxide by the respiratory system than being produced by the cellular metabolism (252).

Respiratory alkalosis can also be acute or chronic. The main difference between the two lies in the pH change. In acute respiratory alkalosis, the PaCO₂ level is less than the reference range accompanied by a basic pH. In chronic respiratory alkalosis, the PaCO₂ level is still below the reference range but the pH level remains normal or near normal (252).

Respiratory alkalosis commonly occurs in patients who are critically ill, especially those in mechanical ventilation. Several cardiac and pulmonary diseases have respiratory alkalosis as one of its symptoms. When clinically present, both minor and fatal diseases should be considered in the differential diagnosis (252).

Alveolar ventilation is a physiological process that ensures the body’s oxygen requirements are met and removal of carbon dioxide occurs normally. The respiratory system regulates this process by sensing the change in pressure gradients. The PaCO₂ level needs to be stable to make sure that hydrogen ion concentrations are kept within the normal reference range needed for optimum protein and enzyme function. On the other hand, PaO₂ level do not require close monitoring because sufficient hemoglobin saturation can be easily attained and is not specific to a narrow range of PaO₂ levels (252).

Cellular metabolism of carbohydrates produces and increases carbon dioxide (226). Carbon dioxide then binds with water molecules to form carbonic acid. The lungs eliminate the volatile acid via ventilation which prevents the build up of acid. Impaired ventilation can disrupt this mechanism and result in respiratory acid-base imbalance.
PaCO₂ is normally maintained in the range of 35-45 mm Hg. Central and peripheral chemoreceptors detect hydrogen levels and regulate ventilation to compensate for alterations in PCO₂ and pH. Several disease mechanisms may stimulate ventilation followed by hyperventilation, which when left untreated, results in hypocapnia (252).

Acute hypocapnia causes hypokalemia and hypophosphatemia secondary to increased intracellular movement of potassium and phosphate ions. Additionally, hypocalcemia also occurs which is secondary to increased binding of calcium to serum proteins due to the pH alterations. Therefore, several manifestations of respiratory alkalosis are associated with hypocalcemia (227).

Acute hyperventilation with hypocapnia results in minimal and early reduction of serum bicarbonate concentrations. Plasma pH and bicarbonate level fluctuate proportionately with the PaCO₂ between 15-40 mm Hg. The relationship of PaCO₂ to arterial hydrogen and bicarbonate is 0.7 mmol/L per mm Hg and 0.2 mmol/L per mm Hg, respectively (228). Renal compensation starts several hours after the onset of respiratory alkalosis which mainly involves the reduction of bicarbonate reabsorption. A patient with normal kidney function and stable intravascular status may benefit from the renal compensation after several days. The alteration in serum bicarbonate level may be calculated by (252):

- **Acute - Bicarbonate (HCO₃⁻) falls 2 mEq/L for each decrease of 10 mm Hg in the PCO₂**; that is, ΔHCO₃⁻ = 0.2(ΔPCO₂); maximum compensation: HCO₃⁻ = 12-20 mEq/L
- **Chronic - Bicarbonate (HCO₃⁻) falls 5 mEq/L for each decrease of 10 mm Hg in the PCO₂**; that is, ΔHCO₃⁻ = 0.5(ΔPCO₂); maximum compensation: HCO₃⁻ = 12-20 mEq/L
Clinicians should keep in mind that a plasma bicarbonate concentration of <12 mmol/L is uncommon in pure respiratory alkalosis and be alert to the possibility of metabolic acidosis (227).

The pH alterations in respiratory alkalosis may be calculated using the following equations:

- Acute respiratory alkalosis: Change in pH = 0.008 X (40 – PCO₂)
- Chronic respiratory alkalosis: Change in pH = 0.017 X (40 – PCO₂)

**XIII. HISTORY AND PRESENTATION**

*Metabolic acidosis*

**Symptoms**

Metabolic acidosis usually presents with general symptoms. The compensatory hyperventilation that occurs following stimulation of the respiratory center in metabolic acidosis results in dyspnea. Other symptoms include (253):

- Chest pain
- Palpitations
- Headache
- Confusion
- Generalized weakness
- Bone pain
- Nausea
- Vomiting
- Decreased appetite
Because the symptoms are non-specific, clinicians need to look at the patient’s clinical history, age of onset, and family history to establish the underlying cause. The age of onset and family history can provide clues as to whether the acidosis is caused by a familial disorder. Listed below are significant clues to consider when looking at a patient’s history (253):

- Diarrhea
- History of diabetes mellitus, alcoholism, chronic starvation
- Polyuria, increased thirst, epigastric pain, vomiting, diabetic ketoacidosis
- Nocturia, polyuria, pruritus, and anorexia
- Overdose on drugs such as salicylates, acetazolamide, cyclosporine
- Ingestion of toxic substances such as ethylene glycol, methanol
- Renal stones

Physical exam

The characteristic physical sign observed in patients with severe metabolic acidosis is the Kussmaul respirations. It’s characterized by labored breathing, compensatory respiratory efforts to cause a rise in minute ventilatory volume. In pediatric patients, chronic metabolic acidosis is linked with retarded growth and rickets (254).

Patients with severe metabolic acidosis may become hypotensive and sink into a coma. Other physical signs of metabolic acidosis are nonspecific, and depend on the etiology involved. They may include but are not limited to (254):

- Xerosis
- Scratch marks on the skin
- Pallor
- Drowsiness
- Fetor
- Asterixis
- Pericardial rub for renal failure
- Reduced skin turgor
- Dry mucous membranes
- Fruity breath for patients with diabetic ketoacidosis

**Metabolic alkalosis**

Symptoms of metabolic alkalosis are not specific. Since it is almost always accompanied by hypokalemia, the following symptoms may be reported (255):

- Muscle weakness
- Myalgia
- Polyuria
- Cardiac arrhythmias

Clinicians need to look into the patient’s clinical history when trying to pinpoint the underlying cause of metabolic alkalosis. Listed below are significant clues (255):

- Loss of hydrochloric acid through vomiting or diarrhea
- Familial disorders such as Bartter syndrome
- Renal failure
- History of use of potassium-wasting diuretic such as loop and thiazide diuretics
- Chronic use of licorice
- Tobacco chewing
- History of use of carbenoxolone
- History of steroid use such as fludrocortisones and glucocorticoids
• History of antacid use such as magnesium hydroxide and calcium carbonate
• History of GI surgery such as ileostomy

Physical exam

The physical signs are also non-specific and vary according to the severity of alkalosis. Hypoventilation is caused by the inhibition of the central respiratory center and reduces ionized calcium level. Therefore, patients with metabolic alkalosis present with symptoms of hypocalcemia which include (256):

- Nervousness
- Perioral tingling
- Muscle spasms
- Tetany
- Chvostek sign
- Trousseau sign
- Impaired mental status
- Convulsions

Physical examination, especially the evaluation of volume status and hypertension, are important aspects in the differential diagnosis of metabolic alkalosis. Hypertension is associated with several causes of metabolic alkalosis. The evaluation of volume status may involve the assessment of the following (256):

- Orthostatic changes in blood pressure and heart rate
- Mucous membranes
- Presence or absence of edema
- Skin turgor
- Weight change
• Urine output

Volume depletion is associated with chloride-responsive alkalosis, while volume expansion is linked with chloride-resistant alkalosis.

Bulimia

Patients who frequently self-induce vomiting typically present with teeth abnormalities and dental caries because of repeated exposure to gastric acid secretions (256).

Cushing syndrome

Physical signs of Cushing syndrome are rather obvious and include the following (256):

• Obesity
• Moon face
• Buffalo hump
• Hirsutism
• Violaceous skin striae
• Acne

Congenital adrenal hyperplasia (CAH)

Pediatric patients with CAH secondary to 11-hydroxylase deficiency usually present with hypertension and growth retardation. Male infants experience premature sexual development, while female infants develop male characteristics. In 17-hydroxylase deficiency, males develop sexual ambiguity, while females have sexual infantilism (256).

*Respiratory acidosis*
The symptoms of respiratory acidosis vary widely, depending on the underlying etiology, its severity and the development of hypercapnia. These may include (257):

- Anxiety that may progress to delirium
- Dyspnea
- Impaired quality of sleep
- Daytime hypersomnolence
- Confusion

Physical exam

The results of physical exam in patients with respiratory acidosis are usually general and associated with the underlying etiology. The findings may include the following (258):

- COPD: diffuse wheezing, barrel chest, decreased breath sounds, hyperresonance on percussion, and prolonged expiration
- Hypoxemia: cyanosis
- COPD: digital clubbing
- Impaired mental status
- Asterixis
- Myoclonus
- Seizures
- Papilledema
- Dilated conjunctival and superficial facial blood vessels

Respiratory alkalosis

Generally, the signs and symptoms of respiratory alkalosis also depend on its duration, severity, and etiology. Patients may present with the following:
• Hyperventilation syndrome: paresthesias, circumoral numbness, chest pain or tightness, dyspnea, and tetany (230)
• Acute onset of hypocapnia: dizziness, mental confusion, syncope, and seizures. Hypoxemia is not necessary to experience these symptoms (228).
• Spontaneous hyperventilation: dizziness and tingling resulting in tetany
• Voluntary hyperventilation: Paresthesias, numbness and sweating of the hands, and cerebral symptoms following voluntary hyperventilation (231).

Physical exam
The results of physical examination in patients with respiratory alkalosis are nonspecific. The following may be noted, according to the underlying etiology:
• Hyperventilation syndrome: anxiety, tachycardia, tachypnea
• Acute hyperventilation: increased chest wall movement and breathing rate
• Positive Chvostek and Trousseau signs (227)
• Pulmonary disease: crackles, wheezes, or rhonchi and cyanosis (hypoxic patient)
• Neurologic disease: depression of consciousness (232)
• Cardiovascular disease: Reduced cardiac output and systemic blood pressure, sedation and positive-pressure ventilation on venous return, systemic vascular resistance, and heart rate. Cardiac rhythm disturbances is seen in patients with increased tissue hypoxia (228)

XIV. TREATMENTS

Metabolic acidosis
The primary staple in the treatment of metabolic acidosis is alkali therapy to elevate and stabilize the plasma pH level ≥7.20. This is particularly significant in two clinical scenarios (259):
• A continued drop of serum bicarbonate concentration will aggravate an already low serum pH <7.20.

• Bicarbonate therapy in well-compensated metabolic acidosis with impending respiratory failure.

The alkali agent most often used in the treatment of metabolic acidosis is sodium bicarbonate (NaHCO₃). The HCO₃⁻ deficit can be calculated by using the following equation (259):

$$\text{HCO}_3^- \text{deficit} = \text{deficit/L (desired serum HCO}_3^- - \text{measured HCO}_3^-) \times 0.5 \times \text{body weight (volume of distribution for HCO}_3^-)$$

The equation above can give an approximation of the amount of HCO₃⁻ required to treat the metabolic acidosis. Both the serum bicarbonate level and pH should be monitored and evaluated frequently (259).

One of the adverse effects of alkali treatment is volume overload which may be treated using loop diuretics. Another adverse effect is an elevated PaCO₂ which is most often seen in patients with decreased ventilatory reserve (259).

Potassium citrate may be indicated when acidosis coexists with hypokalemia. This salt should be used judiciously in patients with compromised renal function and contraindicated in patients with hyperkalemia (259).

1) Type 1 renal tubular acidosis

Patients are usually given 1-3 mEq/kg/day of potassium citrate or other alkali salts to buffer the daily acid load from dietary sources. When acidosis is treated, hypokalemia
consequently resolves, although potassium supplements are sometimes required to achieve this (260).

2) Type 2 renal tubular acidosis

This form of renal tubular acidosis is significantly more difficult to treat because of the copious excretion of bicarbonate ions into the urine, therefore; its dose requirements are also significantly higher 10-30 mEq/kg/day. Additionally, potassium supplements are also needed during the administration of bicarbonate particularly in patients with coexisting hypokalemia (261).

3) Type 4 renal tubular acidosis

Hyperkalemia is a given comorbid condition in patients with type 4 renal tubular acidosis. Therefore, the main objective of the treatment is to reduce serum potassium level which is achieved by the following measures (262):

- Placing the patient on a low potassium diet
- Withdrawal of potassium-sparing drugs such as ACE inhibitors.

In non-hypovolemic patients, loop diuretics may be indicated to decrease serum potassium levels.

4) Early renal failure

The main objective of the treatment of metabolic acidosis in patients with early kidney failure is to prevent the progression of bone loss to osteopenia or osteoporosis. Additionally, children are especially prone to growth retardation (263).

Sodium bicarbonate is the preferred agent. Ideally, it is administered in a dosage sufficient to elevate serum bicarbonate concentration to >20 mEq/L (263).
5) Starvation, alcohol acidosis and diabetic ketoacidosis (DKA)

Intravenous glucose is usually given in patients with metabolic acidosis that resulted from starvation and alcohol use to stimulate insulin secretion and prevent lipolysis and ketosis (264).

Patients with diabetic ketoacidosis are given IV insulin to stimulate glucose uptake, decrease gluconeogenesis, and prevent lipolysis and the production of ketone bodies. Additionally, normal saline may be given to replace the extracellular volume loss (264).

6) Lactic acidosis

Because lactic acidosis is a symptom rather than a disorder itself, the main objective in the treatment of lactic acidosis is to address its underlying etiology. The restitution of tissue perfusion is significant in patients with hypoxia (265).

It should be remembered that studies examining the benefits of alkali therapy in the treatment of lactic acidosis is conflicted. This is why hemodialysis or continuous venovenous hemofiltration is preferred over it. Additionally, once lactic acid level has been restored to normal, the liver uses it to produce $\text{HCO}_3^-$ on an equimolar basis. The significance of this mechanism lies in the fact that rebound alkalosis may develop if the patient has received an excessive amount of alkali during therapy.

7) Salicylate poisoning

Salicylate toxicity is best treated with alkali therapy because of its two primary benefits, including (266):

- Correction of acidemia reduces the amount of salicylate passing into the blood-brain barrier.
• Elevation of urinary pH facilitates salicylate excretion. This may be done with the administration of intravenous NaHCO₃ or carbonic acid anhydrase therapy (e.g. acetazolamide).

8) Methanol and ethylene glycol poisoning

The standard treatment involves the administration of a loading dose of 4-methylpyrazole (fomepizole). An alternative is the use of oral ethanol to inhibit the metabolism of methanol or ethylene glycol to its toxic metabolites.

Bicarbonate therapy, given in large doses, is also administered to address the acidosis. Additionally, patients with severe metabolic acidosis may be put on hemodialysis to effectively clear the methanol and ethylene glycol and their toxic metabolites from the circulation.

Metabolic alkalosis

Since metabolic alkalosis is a prevailing symptom, rather than the disease itself, its treatment depends on the resolution of its underlying causes as well as the patient’s volume status. The management of each etiology associated with metabolic alkalosis is discussed in detail in the following pages.

Chloride-responsive alkalosis

IV infusion of sodium chloride is usually administered when volume depletion occurs. Since chloride-responsive alkalosis also causes hypokalemia, potassium chloride may also be administered to correct it. Potassium chloride is also preferred over sodium chloride in patients with congestive heart failure to prevent volume overload. Additionally, the ensuing edema may be corrected with the use of amiloride (268).
Chloride-resistant alkalosis

The primary objective of the management of chloride resistant alkalosis is to target each specific etiology (269).

Primary hyperaldosteronism

The primary agents used in this form of metabolic alkalosis are the potassium-sparing diuretics such as (269):

- Amiloride
- Spirinolactone
- Triamterene

If the underlying etiology is an adrenal adenoma or carcinoma, surgical removal of the tumor will also treat the metabolic alkalosis. If the cause is glucocorticoids, both the hypertension and metabolic alkalosis may be treated with the administration of dexamethasone (269).

Cushing syndrome

Potassium sparing diuretics are also used temporarily in Cushing Syndrome until surgery is done to permanently correct it (269).

Syndrome of apparent mineralocorticoid excess (AME)

Potassium sparing diuretics are also useful in the management of metabolic alkalosis in patients with syndrome AME. Dexamethasone may also be used to inhibit cortisol production (269).

Licorice ingestion
Immediate withdrawal of licorice will treat the alkalosis. Since the period of recovery is long after chronic licorice use, potassium-sparing diuretics is useful during this time (269).

Bartter syndrome and Gitelman syndrome

Metabolic alkalosis may be initially treated with potassium supplements, spirinolactone, NSAIDs, or ACE inhibitors (269).

Liddle syndrome

The preferred treatment of metabolic alkalosis associated with Liddle Syndrome is either amiloride or triamterene. These two drugs inhibit the apical sodium ion channel in the collecting duct correcting both the alkalosis and the hypertension (269).

Other therapies used in all types of alkalosis

Hydrochloric acid

Hydrochloric acid administered intravenously is warranted in severe metabolic alkalosis. It is also used as an alternative to sodium or potassium chloride when patients have volume overload, advanced kidney failure. It is also useful in severe cases such as cardiac arrhythmias, hepatic encephalopathy, and digoxin cardiotoxicity (270).

Dialysis

Dialysis is indicated in patients with coexisting advanced kidney failure, volume overload and unresponsive to acetazolamide (270).

Respiratory acidosis

Because respiratory acidosis is a symptom more than a disease, its management is mainly to treat the underlying etiology or pathophysiologic process. There are no specific drugs
to treat respiratory acidosis. Pharmacotherapy is generally used to treat the cause of hyperventilation and, therefore, respiratory acidosis. Clinicians must take care not to rush the correction of chronic hypercapnia since it can very well lead to metabolic alkalemia. Additionally, alkalinization of the cerebrospinal fluid may trigger convulsions (271).

The factors that determine the severity of respiratory acidosis and subsequent need for admission into the intensive care unit (ICU) varies individually but generally include (271):

- Patient confusion
- Lethargy
- Respiratory muscle fatigue
- Low pH
- Requiring tracheal intubation
- Requiring mechanical ventilation

Additionally, since multiple organs are involved, clinicians may need to seek the expert opinion of pulmonologists and neurologists in the assessment and treatment of respiratory acidosis.

Listed below are classes of drugs frequently used in the treatment of the underlying etiology.

**Bronchodilators**

Bronchodilators are helpful in treating patients with obstructive airway disorders and severe bronchospasm. They may be grouped into three classes, namely (272);

- Beta agonists (e.g. albuterol and salmeterol),
- Anticholinergic agents (e.g. ipratropium bromide and tiotropium)
- Methylxanthines (e.g. theophylline)

Respiratory stimulants

Respiratory stimulants are useful but have limited efficacy in respiratory acidosis.

Medroxyprogesterone stimulates central respiratory drive which may be helpful in obesity-hypoventilation syndrome (OHS), COPD and alveolar hypoventilation. However, this drug may increase the risk of thromboembolism which makes it unpopular in stimulating alveolar ventilation (272).

Acetazolamide is a carbonic anhydrase inhibitor that promotes bicarbonate excretion and the development of metabolic acidosis, which in turn stimulates ventilation. This treatment approach should be done carefully and judiciously since inducing metabolic acidosis in a patient with preexisting respiratory acidosis may lead to very low pH level. Failure to compensate for the induced metabolic acidosis may lead to hyperkalemia and even fatal arrhythmias (272).

Theophylline is a bronchodilator that strengthens the diaphragm muscle and promotes the central ventilation drive, all of which are useful in the management of respiratory acidosis (272).

Drug antagonists

Drug antagonists are useful in the reversal of toxic effects of offending drugs in the case of overdose. One example is naloxone which reverses the respiratory depression brought about by narcotic overdose. Flumazenil is another example of a drug antagonist which is used to reverse the effects of benzodiazepines (272).
Bicarbonate

Intravenous sodium bicarbonate has no clinical role in the management of respiratory acidosis. If indicated, it is usually in patients who underwent cardiopulmonary arrest and have an extremely low pH (< 7.0-7.1) (272).

Oxygen

Hypercapnic patients are often hypoxemic and require oxygenation. Oxygen therapy prevents the consequences of chronic hypoxemia. The benefits of oxygen therapy include (273):

- In COPD: decreased mortality
- In pulmonary hypertension: reduced symptoms

Oxygen therapy should be used judiciously since it can aggravate hypercapnia in certain cases. One example is patients with COPD who may exhibit exacerbation of hypercapnia during oxygen therapy. This process is not completely understood, however, some authors attribute it to the mismatch of ventilation-perfusion mechanism (273).

Hypercapnia can be prevented by the titration of oxygen delivery to stabilize oxygen saturation in the low 90% range and partial arterial pressure of oxygen (PaO$_2$) in the range of 60-65 mm Hg (273).

Patients with severe hypercapnia and respiratory acidosis may need nonpharmacotherapy measures, which may include (274):

- Endotracheal intubation with mechanical ventilation
- Noninvasive positive pressure ventilation (NIPPV) (e.g. nasal continuous positive-pressure ventilation (NCPAP) and nasal bilevel ventilation). The latter
technique is the preferred intervention in OHS and neuromuscular disorders, because it helps improve PaO₂ and reduce the partial pressure of arterial carbon dioxide (PaCO₂).

- Noninvasive external negative-pressure ventilation devices are useful in certain patients with chronic respiratory failure.

These techniques require caution and a slower rate of administration when correcting hypercapnia since a rapid correction may lead to alkalemia (274).

**Respiratory alkalosis**

Respiratory alkalosis is a symptom, rather than the disease itself, and its management is mainly aimed at correcting the underlying etiology. It is not fatal and its emergent treatment is usually not warranted unless the pH level climbs to >7.5. Additionally, the correction of PaCO₂ level should be done slowly in patients with chronic respiratory alkalosis to prevent the onset of metabolic acidosis due to the compensatory drop in serum bicarbonate concentration by the kidneys (275).

Patients who are on mechanical ventilation may require their respiratory rate to be reduced. Insufficient sedative and pain control may aggravate the respiratory alkalosis in patients breathing more than the set ventilator rate.

Patients with hyperventilation syndrome may manage their acute episodes by re-breathing into a paper bag and being treated for the stress that triggers it. Anxiolytics and antidepressants may be used but is generally reserved for patients who are non-responsive to conservative treatment. Beta blockers are effective in controlling the adrenergic symptoms that may result in hyperventilation syndrome in certain patients (227).
In the differential diagnoses, clinicians should always use a step by step approach in managing patients with hyperventilation in order to carefully screen fatal and organic etiologies from those less serious causes.

**XV. CONCLUSION**

Electrolyte and acid base disorders impair the body’s normal and optimal physiological integrity. Pure electrolyte and acid-base disorders are, for the most part, reversible and with the advent of today’s modern emergency medicine, fatalities are low. However, when combined with other life-threatening disorders such as renal failure and cardiac disorders, the combined physiological strain on the body’s organs may lead to fatal consequences. Electrolyte and acid-base disorders are caused by a variety of factors, including existing disease states, dehydration, water intoxication, vomiting, autosomal diseases and other etiologies.

The electrolyte imbalances that disrupt the normal workings of the various organ systems involve the following extracellular and intracellular ions; sodium, potassium, magnesium, calcium, phosphate, bicarbonate and chloride. These ions play significant roles in the neurological and cardiovascular physiology of the body. Serious consequences of electrolyte imbalances include seizures, neurological deficits, hypertension and arrhythmias. Electrolyte deficiencies are usually corrected with oral and parenteral fluids.

The acid-base disorders occur due to the deviation of blood pH from its normal range. Serious consequences can result from untreated acid-base disorders, such as hypoxemia and cardiovascular complications. Compensatory responses are mainly elicited by the kidneys and lungs. However, sometimes, these mechanisms are inadequate or ill-equipped (e.g. renal failure) to handle the physiological burdens imposed by the acid-base imbalance and pharmacotherapy, and other interventions may be required. The appropriate rate of electrolyte correction is essential to the treatment approach of acid-base disorders, to avoid treatment complications.
REFERENCES


25) Roberts, K. Fluid and Electrolyte Regulation. University of Pennsylvania. Retrieved from [http://repository.upenn.edu/cgi/viewcontent.cgi?filename=10&article=1003&context=miscellaneous_papers&type=additional](http://repository.upenn.edu/cgi/viewcontent.cgi?filename=10&article=1003&context=miscellaneous_papers&type=additional).


ELECTROLYTES AND ACID-BASE DISORDERS

Self Evaluation Exercises

Select the best answer for each question and check your answers at the bottom of the page.

You do not need to submit this self-evaluation exercise with your participant sheet.

1. Acids are substances that yield hydrogen ions (H\(^+\)) or hydronium ions (H\(_3\)O\(^+\)) when dissolved in water.
   True           False

2. All substances that dissolve in solution dissociate into ions.
   True           False

3. If the osmotic pressure is equal on both sides of the membrane, the solutions on either side are considered hypotonic.
   True           False

4. Plasma volume makes up for 4\% of the total body weight of an adult.
   True           False

5. In the movement of substances between compartments, when the concentration of solute is high, its diffusion rate is also high.
   True           False

6. The normal extracellular potassium concentration is in the range 4.0 to 4.5 mEq/L.
   True           False
7. Hyperkalemia does not usually occur in patients with normal renal status, because potassium overload are managed efficiently and excreted rapidly.
   True          False

8. High serum magnesium levels are linked to arrhythmias and hypertension.
   True          False

9. Patients with hypermagnesemia are especially susceptible to digoxin-induced arrhythmia.
   True          False

10. Hypernatremia occurs when the serum sodium concentration in plasma is >145 mEq/L.
    True          False

11. Pediatric patients who underwent chemotherapy or stem cell transplant are especially vulnerable to SIADH.
    True          False

12. The onset of acute symptomatic hyponatremia requires prompt treatment because of the risk of irreversible damage posed to the brain, even when clinical symptoms are mild.
    True          False
13. Hypotonic saline solution is usually administered intravenously for acute symptomatic hyponatremia, causing a rapid reduction in brain volume, thus, lowering intracranial pressure.

True   False

14. The evaluation of a patient’s hydration status is required in the calculation of parenteral fluid requirements, particularly when there is a high index of suspicion of fluid imbalance.

True   False

15. Electrolyte losses due to sweating largely depend on the total sweat deficit and sweat electrolyte levels.

True   False

16. In hotter environments and during warmer seasons, the capacity for dry heat loss decreases cooling requirements for evaporation, thereby minimizing sweat losses.

True   False

17. Athletes with genetic predisposition for cystic fibrosis are more susceptible to salt depletion and exercise-associated hyponatremia.

True   False

18. The normal pH of the blood leans slightly toward the acidic side, at a range of 6.35 to 6.45.

True   False
19. PaCO₂ is normally maintained in the range of 35-45 mm Hg.
   True          False

20. Ammonia secretion in the kidneys is stimulated during hyperkalemic states, leading to increased renal acid excretion.
   True          False

21. Chloride depletion can independently promote bicarbonate reabsorption, regardless of volume status.
   True          False

22. Potassium-wasting diuretics such as carbonic anhydrase inhibitors cause metabolic alkalosis by facilitating chloride deficit and delivery of sodium ions into the collecting duct, increasing the secretion of potassium and hydrogen ions.
   True          False

23. Milk-alkali syndrome is characterized by hypercalcemia, renal insufficiency, and metabolic alkalosis.
   True          False

24. A late complication of cerebral vasodilation is papilledema.
   True          False
25. Intravenous sodium bicarbonate plays an important clinical role in the management of respiratory acidosis.

True False