FLUID, ELECTROLYTE AND ACID BASE BALANCE

Extracellular Fluid (ECF) = interstitial fluid, plasma, lymph, CSF, synovial fluid, serous fluid, etc.

Intracellular Fluid (ICF) = cytosol

Homeostasis involves the regulation of composition and volume of both fluid divisions

Stabilizing ECF and ICF involves:
1) Fluid Balance
   Must have equal gain (food & metabolism) and loss (urine & perspiration) of water
2) Electrolyte Balance
   Electrolytes = ions from dissociated compounds that will conduct an electrical charge in solution
   Must have equal gain (absorption in GI) and loss (urine in kidney and perspiration in skin)
3) Acid-Base Balance
   The production of hydrogen ions by metabolism must be matched by loss of these H\(^+\) ions at the kidney (protons: H\(^+\)) and lungs (carbonic acid)

Fluid and Electrolyte Balance (water and ions move together)
- Average male ~ 60% H\(_2\)O (more muscle which can be ~ 75% H\(_2\)O)
- Average female ~ 50% H\(_2\)O (more adipose which is only ~ 10% H\(_2\)O)
- Most of the water in the body is found in the ICF (~ 2/3)
- The electrolytes vary depending on the fluid division:
  ECF Principal cation = Na\(^+\)
  Principal anions = Cl\(^-\), HCO\(_3^-\)
  ICF Principal cation = K\(^+\), Mg\(^{2+}\)
  Principal anions = HPO\(_4^{2-}\) and negatively charged proteins
- Although different ions dominate, both fluid divisions have the same osmotic concentrations. The ions cannot pass freely through cell membranes, but the water can by osmosis, and will move to equilibrium. Thus, solute/electrolyte concentrations of the fluid divisions will directly impact water distribution.

The Four Rules of Regulation of Fluids and Electrolytes:
1) All homeostatic mechanisms for fluid composition respond to changes in the ECF
   - Receptors monitor the composition of plasma and CSF and trigger neural and endocrine mechanisms in response to change
   - Individual cells cannot be monitored and thus ICF has no direct impact
2) No receptors directly monitor fluid or electrolyte balance
   - Only plasma volume and osmotic concentration are monitored which give an indirect measure of fluid or electrolyte levels
3) “Water follows salt”
   - Cells cannot move water by active transport
   - Water will always move by osmosis and this movement cannot be stopped
4) The body’s content of water or electrolytes rises and falls with gain and loss to and from the environment
   Too much intake = high content in the body
   Too much loss = low content in the body

Primary Regulatory Hormones:
1) Antidiuretic Hormone (ADH)
   - Osmoreceptors in the hypothalamus monitor the ECF and release ADH in response to high osmotic concentration (low water, high solute)
   - ↑ Osmotic concentration = ↑ ADH levels
   - Primary effects of ADH:
     A) stimulate water conservation at kidneys
     B) stimulate thirst center
2) Aldosterone
   - Released by the adrenal cortex to regulate Na\(^+\) absorption and K\(^+\) loss in the DCT and collecting system in the kidney
   - Retention of Na\(^+\) will result in H\(_2\)O conservation
   - Aldosterone is released in response to:
     A) high K\(^+\) or low Na\(^+\) in ECF (e.g. renal circulation)
     B) activation of the renin-angiotensin system due to a drop in BP or blood volume
     C) decline in kidney filtrate osmotic concentration at the DCT (more water less solutes)

Addison’s Disease = hypoaldosteronism: results in massive loss of NaCl and H\(_2\)O in the urine; must adjust diet to compensate.
3) Natriuretic Peptides
   - ANP (atrial) and BNP (brain) are released in response to stretching of the heart wall
   - They function to reduce thirst and block release of ADH and aldosterone resulting in diuresis (fluid loss in the kidney)

Fluid Balance:
1) Fluid movement within the ECF
   -Two important divisions of the ECF:
     1) plasma ( ~ 20%)
     2) interstitial fluid ( ~ 80%)
   -There is continuous flow between both:
     A) Hydrostatic pressure pushes water from the plasma into the interstitial fluid
     B) Colloid osmotic pressure draws water from the interstitial fluid to the plasma

Edema = abnormal amount of water leaves the plasma and accumulates in the interstitial fluid
2) Fluid exchange with the environment
   A) Water losses
      ~ 2500 mL/day in urine, feces and insensible perspiration = obligatory water loss
      - Sensible perspiration: can reach up to 4 L/hr under extreme conditions
      - Fever: for each degree rise, insensible perspiration will increase by 200 mL/day
B) Water Gains
- Must match water losses or dehydration will result
- Typical gain:
  ~1000 mL from drink
  ~1200 mL from food
  ~300 mL metabolic “waste”

(Metabolic generation of water occurs from dehydration synthesis reactions and aerobic respiration in the mitochondria: water is the waste product of these types of reactions)

- Water content is not easily measured, so ion content, particularly Na⁺, is measured and regulated instead

Hyponatremia = hypotonic hydration: condition of low Na⁺ concentration (i.e. excess water). Can be caused by:
1) Ingestion of a large volume of fresh water or injection of a hypotonic solution.
2) Inability to eliminate excess water at the kidney
3) Endocrine disorder (e.g. too much ADH)

-This results in water moving from the ECF to the ICF causing cellular damage: “water intoxication” = cerebral edema and CNS dysfunction

Hypernatremia = dehydration: condition of high Na⁺ concentration (i.e. water depletion).
-This results in decreased plasma volume and blood pressure that can lead to hypovolemic shock (inadequate circulation)

3) Fluid Shifts
-Movement of water will occur between the ECF and ICF due to changes in osmotic concentrations

-Water will always come to equilibrium:
  -If osmotic concentration of the ECF increases (becomes hypertonic) due to a loss of water but not electrolytes, water will leave the ICF
  -If osmotic concentration of ECF decreases (becomes hypotonic) due to a gain of water but not electrolytes, water will enter the ICF

-The total amount of water is greater in the ICF than ECF: this allows the ICF to act as a reserve to accommodate changes in the ECF until hormones can restore homeostasis

Electrolyte Balance:
- Electrolyte balance is important because:
  1) total electrolyte concentrations directly affect water balance
  2) concentrations of individual electrolytes can affect cell functions

-The two most important electrolytes are sodium and potassium:
  1) Sodium Balance (normal blood values: 130-145 mEq/L *)
     -Na⁺ is the dominant cation in the ECF
     -90% of the ECF osmotic concentration is due to sodium salts: NaCl and NaHCO₃
     -The total amount of Na⁺ in the ECF is due to a balance between Na⁺ uptake in the digestive system and Na⁺ excretion in urine and perspiration.
-The overall sodium concentration in body fluids rarely changes because water always moves to compensate:
  e.g. high sodium levels in the blood will cause retention of water to maintain the same Na\(^+\) concentration, but this results in a high blood volume (this is why salt is bad for hypertensive patients)
-Minor gains and losses of Na\(^+\) in the ECF are compensated by water in the ICF and later adjusted by hormonal activities:
  -ECF volume too low → renin-angiotensin system is activated to conserve water and Na\(^+\)
  -ECF volume too high → natriuretic peptides released: block ADH and aldosterone resulting in water and Na\(^+\) loss

2) Potassium Balance (normal blood values: 3.5-5.5 mEq/L)
-K\(^+\) is the dominant cation in the ICF (98% of the total body K\(^+\) is inside cells)
-The concentration of K\(^+\) in the ECF depends on absorption in the GI vs. excretion in urine
-The exchange pump at the kidney tubules secrete K\(^+\) (or H\(^+\)) in order to reabsorb Na\(^+\)
-The rate of tubular secretion of K\(^+\) in the kidney is controlled by three factors:
  1. Changes in the K\(^+\) concentration of the ECF
     \[ \uparrow \text{K}^+ \text{ in ECF} \Rightarrow \uparrow \text{K}^+ \text{ secretion} \]
  2. Changes in blood pH
     at low pH, H\(^+\) is used for Na\(^+\) reabsorption instead of K\(^+\) at the exchange pump
     \[ \downarrow \text{pH in ECF} \Rightarrow \downarrow \text{K}^+ \text{ secretion} \]
  3. Aldosterone levels
     \[ \uparrow \text{aldosterone} \Rightarrow \uparrow \text{Na}^+ \text{ reabsorption and } \uparrow \text{K}^+ \text{ secretion} \]
Hypokalemia = low K\(^+\) concentration in the ECF: will cause muscular weakness and mental confusion
It can be caused by:
  1. inadequate dietary K\(^+\) intake
  2. some diuretic drugs
  3. excessive aldosterone
  4. increased pH of ECF
Hyperkalemia = high K\(^+\) concentration in the ECF: will cause cardiac arrhythmia and flaccid paralysis
It can be caused by:
  1. renal failure
  2. diuretics that block Na\(^+\) reabsorption
  3. a decline in pH

3) Other Electrolytes
A) Calcium (normal blood values: 4.5-5.8 mEq/L or 8.5-10.5 mg/dL)
-Ca\(^{2+}\) is the most abundant mineral in the body
-99% is located in the skeleton for structure
-Ca\(^{2+}\) is important for:
  -muscular and neural cell activities
  -blood clotting
  -as a cofactor for enzymes
  -as a second messenger (intercellular signaling)
-\( \text{Ca}^{2+} \) homeostasis involves an interplay between skeletal reserves, uptake at the GI, and loss at the kidney
-Parathyroid hormone and calcitriol function to raise blood \( \text{Ca}^{2+} \) levels
-Calcitonin functions to lower blood \( \text{Ca}^{2+} \) levels

Hypercalcemia = high \( \text{Ca}^{2+} \) concentration in the ECF: can be due to hyper-parathyroidism or cancers. Can cause fatigue, confusion, cardiac arrhythmia, and calcification of organs

Hypocalcemia = low \( \text{Ca}^{2+} \) concentration in the ECF: can be due to hypo-parathyroidism, vitamin D deficiency, or renal failure. Can cause muscle spasms, convulsions, weak heartbeats, reduced clotting, and osteoporosis

B) Magnesium (normal blood values: 1.4-6 mEq/L)
- Most \( \text{Mg}^{2+} \) is located in the skeleton
- The remainder is located in the ICF
- \( \text{Mg}^{2+} \) is important as a cofactor for enzymes and as a structural component of the skeleton
- Excess magnesium can cause lethargy and coma
- Insufficient magnesium can cause convulsions

C) Phosphate (normal blood values: 1-6 mEq/L)
- Free phosphate (\( \text{HPO}_4^{2-} \)) is found in the ICF
- It is used for:
  - mineralization of bone
  - formation of high energy compounds (ATP)
  - cofactors for enzymes
  - synthesis of nucleic acids
- Phosphate tends to accompany calcium so physiological effects of excess or deficiency are related to calcium levels

D) Chloride (normal blood values: 95-105 mEq/L)
- \( \text{Cl}^- \) is the most abundant anion in the ECF
- The body has no use for it other than the fact that it travels with \( \text{Na}^+ \)
- Excess can cause metabolic acidosis
- Deficiencies can cause metabolic alkalosis

Acid Base Balance

Acid = a substance that dissociates to release \( \text{H}^+ \) ions
Base = a substance that dissociates to release \( \text{OH}^- \) ions or absorbs \( \text{H}^+ \) ions.

The pH scale is used to measure the concentration of \( \text{H}^+ \) ions in a solution (pH = “potential of Hydrogen”)
- Water is neutral: \( \text{H}^+ = \text{OH}^- \), pH 7
- An acid solution (pH 0 - 7) has more \( \text{H}^+ \) than \( \text{OH}^- \)
- A basic or alkaline solution (pH 7 - 14) has more \( \text{OH}^- \) than \( \text{H}^+ \)

Strong acids or bases dissociate completely in solution (e.g. \( \text{HCl} \rightarrow \text{H}^+ + \text{Cl}^- \))
Weak acids or bases do not completely dissociate: many molecules remain intact (e.g. \( \text{H}_2\text{CO}_3 \))
Normal pH of the ECF = 7.35 – 7.45.

Above or below this range will disrupt cell membranes and denature proteins

Acidosis = ECF pH below 7.35
Alkalosis = ECF pH above 7.45

(Acidosis is the more common problem since metabolism generates acid waste products)

1) Types of Acids
   A) Volatile Acids – can leave solution and enter the atmosphere
      e.g. \( \text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^- \)
      lungs \hspace{1cm} \text{blood}
   B) Fixed Acids – remain in solution until they are excreted
      e.g. sulfuric acid, phosphoric acid
   C) Organic Acids – the products of metabolism
      These are usually metabolized into other wastes, but they can build up under anaerobic conditions or starvation
      e.g. Lactic acid, Ketone bodies

2) Mechanisms of pH Control
   Buffers = dissolved compounds that can remove \( \text{H}^+ \) ions to stabilize pH
   Usually buffers are a weak acid and its corresponding salt

   Three major buffering systems:
   A) The Protein Buffer System
      -Proteins are used to regulate pH in the ECF and ICF (most effective in the ICF)
      -Amino acids can be used to accept or release \( \text{H}^+ \) ions:
         -At typical body pH, most carboxyl groups exist as \( \text{COO}^- \) and can accept \( \text{H}^+ \) ions if the pH begins to drop
         -Histidine and Cysteine remain as \( \text{COOH} \) at normal pH and can donate \( \text{H}^+ \) if the pH rises.
      -All proteins can provide some degree of buffering with their carboxy terminal.
      -Hemoglobin can have a great effect on blood pH

      The Hemoglobin (Hb) Buffering System
      (most effective in the ECF: blood)
      -In RBCs the enzyme carbonic anhydrase converts \( \text{CO}_2 \)
         into \( \text{H}_2\text{CO}_3 \) which then dissociates
      -The \( \text{H}^+ \) remains inside RBCs, but the \( \text{HCO}_3^- \) enters the plasma where it can absorb excess \( \text{H}^+ \)
   B) The Carbonic Acid-Bicarbonate Buffer System
      -The most important buffer for the ECF (free in plasma or aided by Hb)
      -Carbon dioxide and water form carbonic acid which dissociates into hydrogen ions and bicarbonate ions
      -The bicarbonate ions can be used to absorb excess \( \text{H}^+ \) ions in the ECF and then can be released as \( \text{CO}_2 \) and \( \text{H}_2\text{O} \) at the lungs
      -This buffering only works if:
         1. \( \text{CO}_2 \) levels are normal
         2. Respiration is functioning normally
3. Free bicarbonate ions are available
   Bicarbonate ions can be generated from \( \text{CO}_2 + \text{H}_2\text{O} \) or \( \text{NaHCO}_3 \), but to have free \( \text{HCO}_3^- \), \( \text{H}^+ \) ions must be excreted at the kidney

C) The Phosphate Buffer System
   -Phosphate is used to buffer ICF and urine
   -\( \text{H}_2\text{PO}_4^- \) or \( \text{NaPO}_4 \) can dissociate to generate \( \text{HPO}_4^{2-} \), which can absorb \( \text{H}^+ \)
   (as above, only as long as \( \text{H}^+ \) is excreted at the kidney)

3) Maintenance of Acid Base Balance
   -Buffering will only temporarily solve the \( \text{H}^+ \) problem: permanent removal as \( \text{H}_2\text{O} \) at the lungs or through secretion at the kidney is necessary to maintain pH near neutral
   -pH homeostasis:
     A) Respiratory Compensation
        -Respiration rate is altered to control pH
        \( \uparrow \text{CO}_2 = \downarrow \text{pH} \)
        \( \downarrow \text{CO}_2 = \uparrow \text{pH} \)
     B) Renal Compensation
        -The rate of \( \text{H}^+ \) and \( \text{HCO}_3^- \) secretion or reabsorption can be altered as necessary
        \( \uparrow \text{H}^+ = \downarrow \text{pH} \)
        \( \uparrow \text{HCO}_3^- = \uparrow \text{pH} \)

4) Disturbances of Acid Base Balance
   Many factors contribute:
   A) Disorders of buffers, respiratory performance or renal function
   B) Cardiovascular conditions that alter blood flow to the lungs and kidneys
   C) CNS disorders that effect cardiovascular or respiratory reflexes
Respiratory acidosis = respiratory system fails to eliminate all \( \text{CO}_2 \) generated by the peripheral tissues causing a decline in pH. Can be caused by cardiac arrest, emphysema, congestive heart failure, pneumonia, pneumothrax, etc.
Respiratory alkalosis = lungs remove too much \( \text{CO}_2 \) causing an increase in pH. Common result of hyperventilation due to anxiety or pain: this usually corrects itself
Metabolic Acidosis – 3 causes:
1. Production of fixed or organic acids
   A. Lactic acidosis – results from hypoxia and is usually linked to respiratory acidosis
   B. Ketoacidosis – results from starvation or diabetus mellitus
2. Impaired ability to excrete \( \text{H}^+ \) at kidneys, e.g. glomerulonephritis, diuretics
3. Severe bicarbonate loss, e.g. diarrhea: buffering agents from intestinal secretions are lost before they can be reabsorbed
Metabolic Alkalyosis = rare condition, caused by an increase in \( \text{HCO}_3^- \). Secretion of \( \text{HCl} \) in the stomach releases \( \text{HCO}_3^- \) in the ECF. Severe vomiting will cause continuous acid production and loss. The corresponding \( \text{HCO}_3^- \) then accumulates in the ECF. Alkalyosis can also result from chronic and excessive use of antacids.
Age Related Changes:
1) reduced water content affects solute concentrations (elderly ~ 40% H₂O)
2) reduced kidney function (loss of renal compensation)
3) loss of mineral reserves (Ca²⁺, Mg²⁺, HPO₄⁻²)
4) reduced lung function (loss of respiratory compensation)

In case you ever need to know:
*milliequivalents per liter (mEq/L) - mEq/L is a method of expressing concentration when the analytes are dissolved and disassociated in solution. mEq/L is also equal to millimoles of charge per liter (mM+/L or mM⁻/L depending on valence). To express this as mg/L, divide the molecular weight of the ion (g/mole) by the valence (charge number) and multiply by the mEq/L.

e.g. Ca²⁺
Calcium has a molecular weight of 40.08 grams/mole
Calcium has a valence of +2
The equivalent weight = (40.08 grams/mole) / (2 equivalents/mole) = 20.04 grams/Eq
(To convert to mg/mEq you simply multiply g/Eq by 1000 mg/g and divide by 1000 mEq/Eq, thus g/Eq = mg/mEq)
If the blood contains 4.5 mEq/L this is equal to 90 mg/L or 9 mg/100mL (100mL = 1dL)
(40.08 / 2) x 4.5 = 90

Optional Computer Activity: Understanding Physiology
to enhance comprehension of renal and respiratory compensation of acidosis and alkalosis:
PhysioEx Exercise 47 (On the PhysioEx CD-ROM packaged with the Marieb lab book)
pages P-116 to P-125 and P-169 (back of the book) in 8th edition
pages PEx-153 to PEx-164 (back of the book) in 9th edition