

ACID BASE MAINTAINENCE

ECF - Bicarbonate, plasma proteins, phosphate

ICF - Proteins, phosphate, hemoglobin (RBCs)

MAINTENANCE OF BLOOD pH

The body has developed **three lines of defense** to regulate the body's acid-base balance and maintain the blood pH (around 7.4).

I. **BLOOD BUFFERS**

II. **RESPIRATORY MECHANISM**

III. **RENAL MECHANISM.**

BLOOD BUFFERS

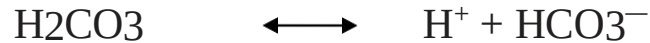
- Buffer resist in change of pH by addition of an acid or a base
- The buffer system acts as a shock absorber, it doesn't remove the H^+ ions but it temporarily reduces its concentration.
- The H^+ ion are later removed by the renal mechanisms
- The blood contains 3 buffer systems
 1. Bicarbonate buffer
 2. Phosphate buffer
 3. Protein buffer
 4. Hemoglobin

1. Bicarbonate buffer system :(Carbonic Acid–Bicarbonate)

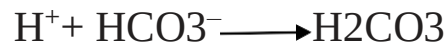
- This system is based on **bicarbonate ion which acts as a weak base** and **Carbonic acid which acts as a weak acid**.

- Sodium bicarbonate and carbonic acid (NaHCO_3 – H_2CO_3) is the most **predominant buffer** system of the **extracellular fluid**, particularly the **plasma**

- Carbonic acid dissociates into hydrogen (H^+) and bicarbonate (HCO_3^-)

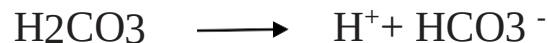


- If there is an **excess of H^+ ions** in the body, the HCO_3^- can function as a weak base and remove the excess H^+ ions as follows



- The **carbonic acid** produced can **dissociate into water and carbon dioxide**, which can be exhaled from the lungs.

- If there is an **shortage of H^+ ions** the H_2CO_3 can function of weak acid and provide H^+ ions as follows



- **At 7.4 pH of blood the ratio of bicarbonate to carbonic acid is 20:1**

- The concentration of HCO_3^- ions is known as the **alkali reserve**

- The alkali reserve is responsible for the effective buffering of the H^+ ions produced by the body

- In normal circumstances, the concentration of bicarbonate and carbonic acid concentration determines the pH of the blood.

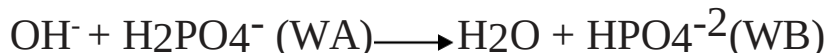
2. Phosphate buffer system:

- **Sodium dihydrogen phosphate** and **Disodium hydrogen phosphate** (NaH_2PO_4 – Na_2HPO_4) constitute the phosphate buffer system

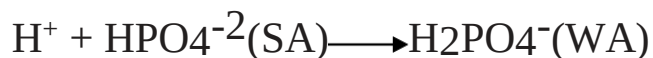
- It is **mostly an intracellular buffer** and is of less importance in plasma due to its low concentration

- The component ions of this buffer system are (H_2PO_4^-) and (HPO_4^{2-})

- The H_2PO_4^- acts as a weak acid and can buffer strong bases as follows



- The HPO_4^{2-} acts as a weak base and can buffer strong acid as follows

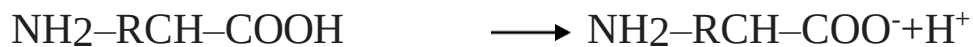


- Since the concentration of phosphate is more in the ICF the phosphate Buffer system is an important regulator of pH in the cytoplasm.

- **So, at physiological pH, the base-to-acid ratio is approximately 4:1.**

3. Protein buffer system

- It is the most **abundant buffer system in the ICF**
- The **plasma proteins and hemoglobin** together constitute the protein buffer system of the blood
- The free carboxyl group (COOH) present at one end of the protein act like an acid by releasing H⁺ ions. When pH rises it dissociates as follows



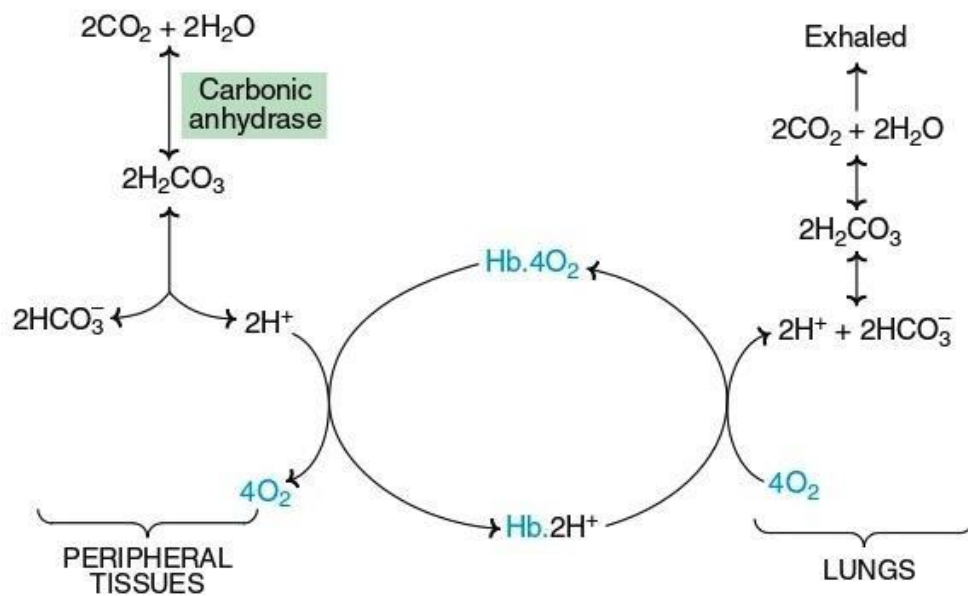
The H⁺ ions formed can react with the excess on OH⁻ to form water

- The amino group(-NH₂) present at the other end of the protein act like a base by combining with the H⁺ ions formed



2. Respiratory mechanism

- Respiratory system provides a rapid mechanism for the maintenance of acid-base balance.
- This is achieved by regulating the concentration of carbonic acid (H_2CO_3) in the blood.



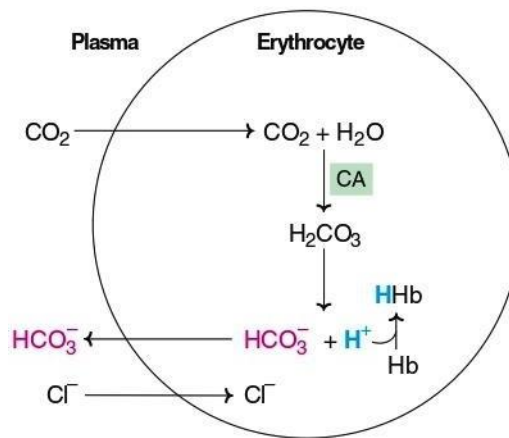
- The large volumes of CO_2 produced by the cellular metabolic activity endanger the acid-base equilibrium of the body. But in normal circumstances, all of this CO_2 is eliminated from the body in the expired air via the lungs.



- The rate of respiration (or the rate of removal of CO_2) is controlled by a respiratory centre, located in the medulla of the brain.
- This centre is highly sensitive to changes in the pH of blood. Any decrease in blood pH causes hyperventilation to blow off CO_2 , thereby reducing the H_2CO_3 concentration.
- Simultaneously, the H^+ ions are eliminated as H_2O .
- Respiratory control of blood pH is rapid but only a short term regulatory process, since hyperventilation cannot proceed for long.

Hemoglobin as a buffer: Hemoglobin of erythrocytes is also important in the respiratory regulation of pH.

- At the tissue level, hemoglobin binds to H^+ ions and helps to transport CO_2 as HCO_3^- with a minimum change in pH.
- In the lungs, as hemoglobin combines with O_2 , H^+ ions are removed which combine with HCO_3^- to form H_2CO_3 . The latter dissociates to release CO_2 to be exhaled
- **Generation of HCO_3^- by RBC:** Due to lack of aerobic metabolic pathways, **RBC** produce very little CO_2 .



- The plasma CO_2 diffuses into the RBC along the concentration gradient where it combines with water to form H_2CO_3 . This reaction is catalysed by **carbonic anhydrase** (also called carbonate dehydratase).
- In the RBC, H_2CO_3 dissociates to produce H^+ and HCO_3^- . The H^+ ions are trapped and buffered by hemoglobin. As the concentration of HCO_3^- increases in the RBC, it diffuses into plasma along with the concentration gradient, in exchange for Cl^- ions, to maintain electrical neutrality. This phenomenon, referred to as **chloride shift**, helps to generate HCO_3^- .

III. Renal mechanism

- The kidney plays a very important role in the maintenance of acid-base balance of the body.
- The **renal mechanism** tries to provide a **permanent solution to the acid- base disturbances**.
- The kidneys regulate the blood pH by **maintaining the alkali reserve, besides excreting or reabsorbing the acidic or basic substances**, as the situation demands.

Urine Ph is normally lower than blood pH:

- The pH of urine is normally acidic (~**6.0**). This clearly indicates that the kidneys have contributed to the acidification of urine, when it is formed from the blood plasma (pH 7.4).
- In other words, the H^+ ions generated in the body in the normal circumstances, are eliminated by acidified urine.
- Hence the pH of urine is normally acidic (~6.0), while that of blood is alkaline (7.4).

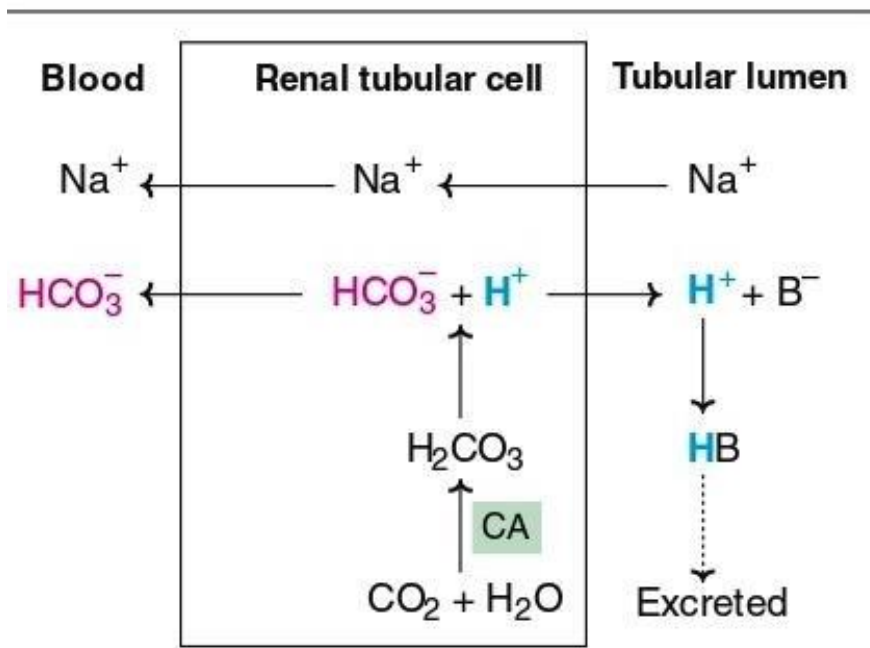
Carbonic anhydrase and renal regulation of pH:

The enzyme carbonic anhydrase is of central importance in the renal regulation of pH which occurs by the following mechanisms.

1. Excretion of H^+ ions
2. Reabsorption of bicarbonate
3. Excretion of titratable acid
4. Excretion of ammonium ions.

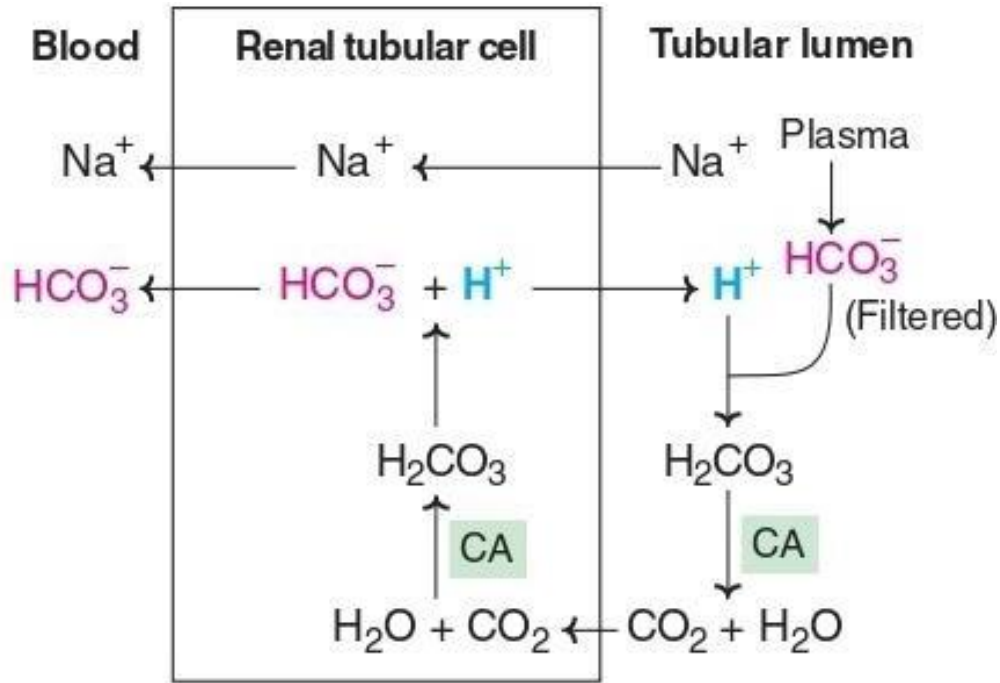
1. Excretion of H^+ ions:

- Kidney is the only route through which the H^+ can be eliminated from the body. H^+ excretion occurs in the proximal convoluted tubules (renal tubular cells) and is coupled with the regeneration of HCO_3^- .



- Carbonic anhydrase catalyses the production of carbonic acid (H_2CO_3) from CO_2 and H_2O in the renal tubular cell.
- H_2CO_3 then dissociates to H^+ and HCO_3^- . The H^+ ions are secreted into the tubular lumen in exchange for Na^+ .
- The Na^+ in association with HCO_3^- is reabsorbed into the blood. This is an effective mechanism to eliminate acids (H^+) from the body with a simultaneous generation of HCO_3^- base and is excreted in urine.

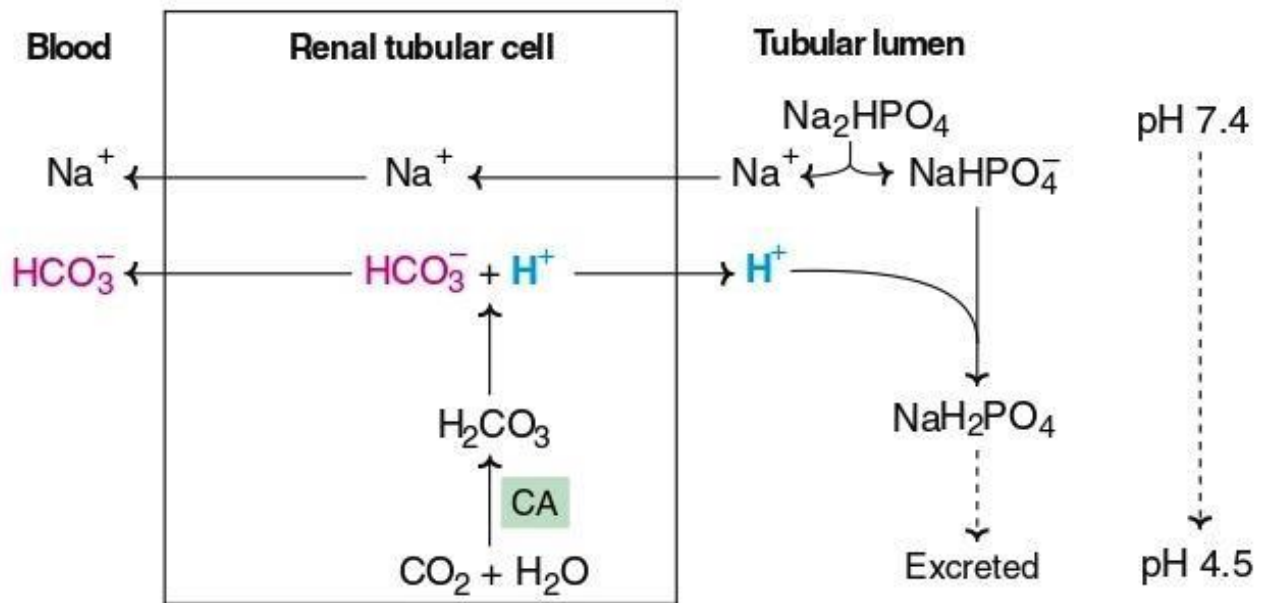
2. **Reabsorption of bicarbonate:** This mechanism mainly responsible to conserve the blood HCO_3^- , with a simultaneous excretion of H^+ ions. The normal urine is almost free from HCO_3^- .



- Bicarbonate freely diffuses from the plasma into the tubular lumen. Here HCO_3^- combines with H^+ , secreted by tubular cells, to form H_2CO_3 .
- H_2CO_3 is then cleaved by carbonic anhydrase (of tubular cell membrane) to form CO_2 and H_2O .
- As the CO_2 concentration builds up in the lumen, it diffuses in to the tubular cells along the concentration gradient.
- In the tubular cell, CO_2 again combines with H_2O to form H_2CO_3 which then dissociates into H^+ and HCO_3^- .
- The H^+ is secreted into the lumen in exchange for Na^+ . The HCO_3^- is reabsorbed into plasma in association with Na^+ .

3. Excretion of titratable acid:

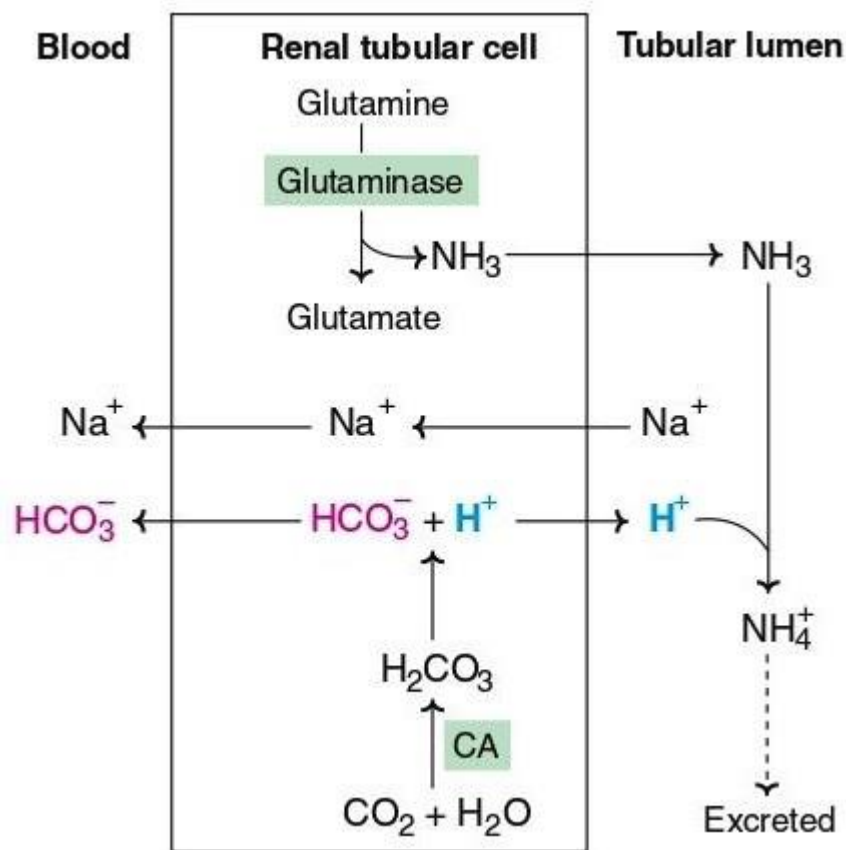
- Titratable acidity is a measure of **acid excreted into urine** by the kidney. This can be estimated by titrating urine back to the normal pH of blood.
- Titratable acidity reflects the H^+ ions excreted into urine which resulted in a fall of pH from 7.4 (that of blood).
- The excreted H^+ ions are actually buffered in the urine by phosphate buffer as depicted below.



- H^+ ion is secreted into the tubular lumen in exchange for Na^+ ion.
- This Na^+ is obtained from the base, disodium hydrogen phosphate.
- The NaH_2PO_4 in turn combines with H^+ to produce the acid, sodium dihydrogen phosphate (NaH_2PO_4).
- As the tubular fluid moves down the renal tubules, more and more H^+ ions are added, resulting in the acidification of urine. This causes a fall in the pH of urine to as low as 4.5

4. Excretion of ammonium ions:

- This is another mechanism to buffer H^+ ions secreted into the tubular fluid.
- The H^+ ion combines with NH_3 to form ammonium ion (NH_4^+).
- The renal tubular cells deaminate, glutamine to glutamate and NH_3 . This reaction is catalysed by the enzyme glutaminase.
- The NH_3 , liberated in this reaction, diffuses into the tubular lumen where it combines with H^+ to form NH_4^+



- Ammonium ions cannot diffuse back into tubular cells and, therefore, are excreted into urine. NH_4^+ is a major urine acid.

DISORDERS OF ACID-BASE BALANCE

1. Acidosis—a decline in blood pH

- (a) Metabolic acidosis—due to a decrease in bicarbonate.
- (b) Respiratory acidosis—due to an increase in carbonic acid.

2. Alkalosis—a rise in blood pH

- (a) Metabolic alkalosis—due to an increase in bicarbonate.
- (b) Respiratory alkalosis—due to a decrease in carbonic acid.

Clinical causes of acid-base disorders

<i>Metabolic acidosis</i>	<i>Respiratory acidosis</i>
Diabetes mellitus (ketoacidosis)	Severe asthma Pneumonia Cardiac arrest
Renal failure	Obstruction in airways
Lactic acidosis	Chest deformities
Severe diarrhea Renal tubular acidosis	Depression of respiratory center (by drugs e.g. opiates)
<i>Metabolic alkalosis</i>	<i>Respiratory alkalosis</i>
Severe vomiting	Hyperventilation
Hypokalemia	Anemia High altitude
Intravenous administration of bicarbonate	Salicylate poisoning

METABOLIC ACIDOSIS

- The primary defect in metabolic acidosis is a **reduction in bicarbonate concentration** which leads to a fall in blood pH.
- The bicarbonate concentration may be decreased due to
 - Utilization in buffering H^+ ions
 - Loss in urine or gastrointestinal tract
 - Failure to be regenerated.
- The most important cause of metabolic acidosis is due to an **excessive production of organic acids** which combine with HCO_3^- and **deplete the alkali reserve**.
- Metabolic acidosis is commonly seen in **severe uncontrolled diabetes mellitus** which is associated with excessive production of acetoacetic acid and β -hydroxybutyric acid (both are organic acids).

Compensation of metabolic acidosis:

- The acute metabolic acidosis is usually compensated by **hyperventilation of lungs**.
- This leads to an increased elimination of CO_2 from the body (hence H_2CO_3 decreases). but respiratory compensation is only short-lived.
- Renal compensation sets in within 3-4 days and the H^+ ions are excreted as NH_4^+ ions.

RESPIRATORY ACIDOSIS

- The primary defect in respiratory acidosis is due to retention of **CO₂** (**H₂CO₃** increases).
- There are several causes for respiratory acidosis which include depression of the respiratory centre (overdose of drugs), pulmonary disorders (bronchopneumonia) and breathing air with high content of CO₂.
- The renal mechanism comes for the rescue to compensate respiratory acidosis. More **HCO₃⁻** is generated and retained by the kidneys which add up to the alkali reserve of the body.
- The excretion of **titratable acidity** and **NH₄⁺** is **elevated in urine**.

METABOLIC ALKALOSIS

- The primary abnormality in metabolic alkalosis is an **increase in HCO₃⁻ concentration**.
- This occurs due to excessive vomiting (resulting in loss of H⁺) or an excessive intake of sodium bicarbonate for therapeutic purposes (e.g. control of gastric acidity).
- Metabolic alkalosis is commonly associated with low K⁺ concentration (hypokalemia). In severe K⁺ deficiency, H⁺ ions are retained inside the cells to replace missing K⁺ ions.
- **Compensation by hypoventilation** to retain CO₂ (hence H₂CO₃ increases). This is slowly taken over by renal mechanism which excretes more HCO₃⁻ and retains H⁺.

RESPIRATORY ALKALOSIS

- The primary abnormality in respiratory alkalosis is a **decrease in H₂CO₃ concentration**.
- This may occur due to prolonged hyperventilation resulting in increased exhalation of CO₂ by the lungs.
- Hyperventilation is observed in conditions such as hysteria, hypoxia,

BIOCHEMICAL FINDINGS

The biochemical findings of **acidosis** and **alkalosis** are understood by looking at changes in blood pH, bicarbonate (HCO_3^-), carbon dioxide (PaCO_2), and electrolyte levels. They are classified as either **metabolic** or respiratory disorders.

Parameter	Metabolic Acidosis	Metabolic Alkalosis	Respiratory Acidosis	Respiratory Alkalosis
Blood pH	↓ (<7.35)	↑ (>7.45)	↓ (<7.35)	↑ (>7.45)
HCO_3^-	↓	↑	↑ (compensation, chronic)	↓ (compensation, chronic)
PaCO_2	↓ (respiratory compensation)	↑ (respiratory compensation)	↑ (primary change)	↓ (primary change)

1. Metabolic Acidosis

Biochemical findings:

- **Blood pH:** Decreased (<7.35)
- **Serum bicarbonate (HCO_3^-):** Decreased
- **PaCO_2 :** Decreased due to compensatory hyperventilation
- **Anion gap:** Increased in conditions such as diabetic ketoacidosis, lactic acidosis, and renal failure; normal in diarrhea and renal tubular acidosis
- **Serum potassium (K^+):** Often increased (hyperkalemia)
- **Serum chloride (Cl^-):** Increased in normal anion gap acidosis

2. Metabolic Alkalosis

Biochemical findings:

- **Blood pH:** Increased (>7.45)
- **Serum bicarbonate (HCO_3^-):** Increased
- **PaCO_2 :** Increased due to compensatory hypoventilation

- **Serum potassium:** Usually decreased (hypokalemia)
- **Serum chloride:** Often decreased (hypochloremia)

3. Respiratory Acidosis

Biochemical findings:

- **Blood pH:** Decreased
- **PaCO₂:** Increased (primary abnormality)
- **HCO₃⁻:** Normal initially; increased if chronic due to renal compensation
- **Serum potassium:** May be mildly increased

4. Respiratory Alkalosis

Biochemical findings:

- **Blood pH:** Increased
- **PaCO₂:** Decreased (primary abnormality)
- **HCO₃⁻:** Normal initially; decreased with renal compensation if chronic
- **Serum potassium:** May be decreased
- **Ionized calcium:** Often decreased, which can cause paresthesias and muscle cramps