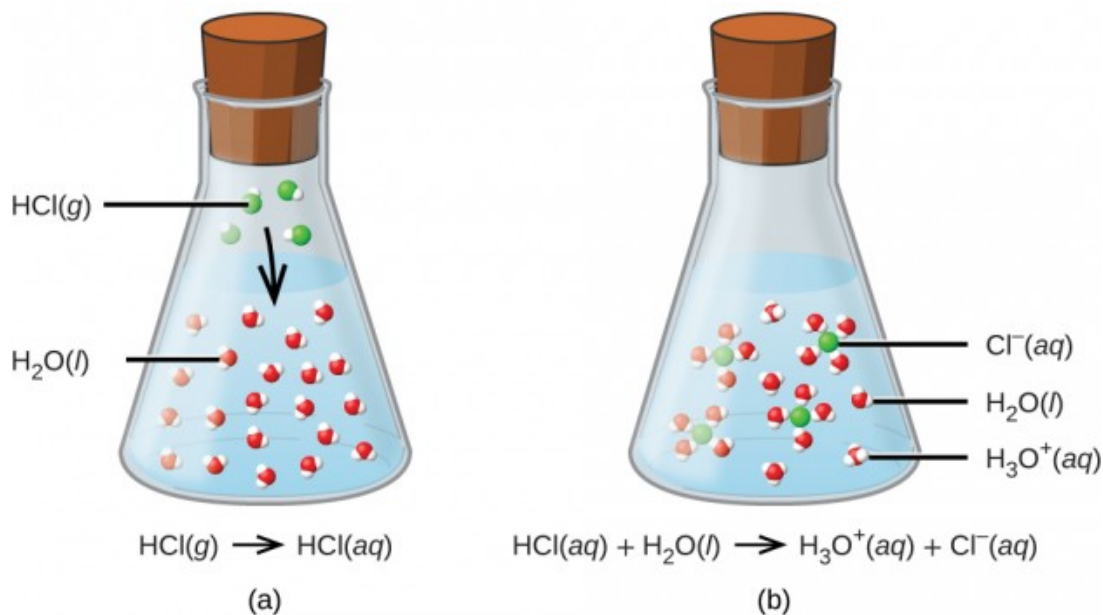


Acid Base Balance and the pH of Blood

[See online here](#)

Acid-base balance refers to the equilibrium between basic (OH⁻) and acidic (H⁺) compounds found in the blood that results in a normal pH range of 7.35-7.45. Acid-base balance is maintained by different mechanisms happening in the lungs, kidneys, and buffer systems. There is an inverse relationship between a human body's pH and the hydrogen ion concentration. Minor deviations in this balance may result in severe effects on the brain, arteries, heart, muscle, and other organs.



Review of [H⁺] and pH

$$\text{pH} = -\log_{10} [\text{H}^+]$$

Average arterial blood pH

- pH = 7.4
- [H⁺] = 0.0000004

Thus, large changes in pH, such as in the GI system, require 10 fold changes in hydrogen concentration.

- pH = 1; [H⁺] = 0.1
- pH = 8; [H⁺] = 0.00000001

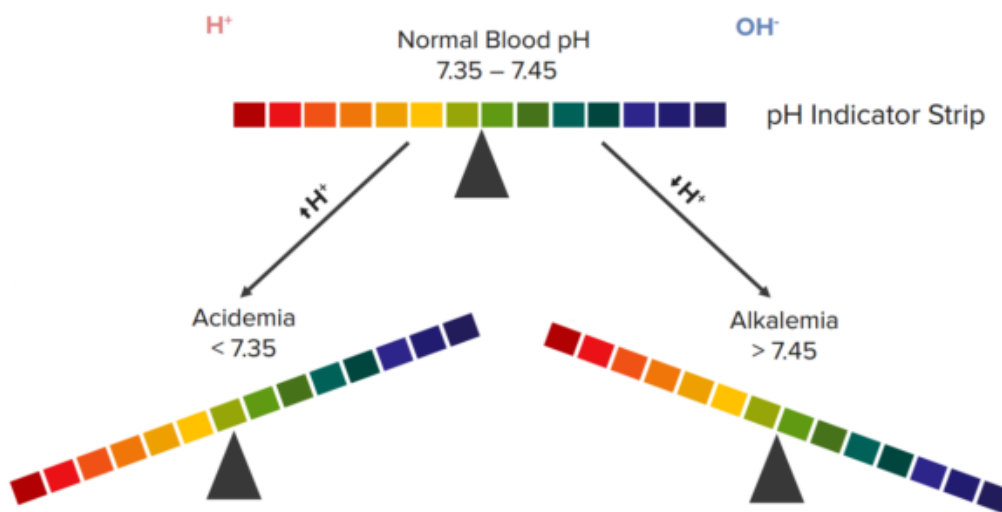


pH Indicator Strip

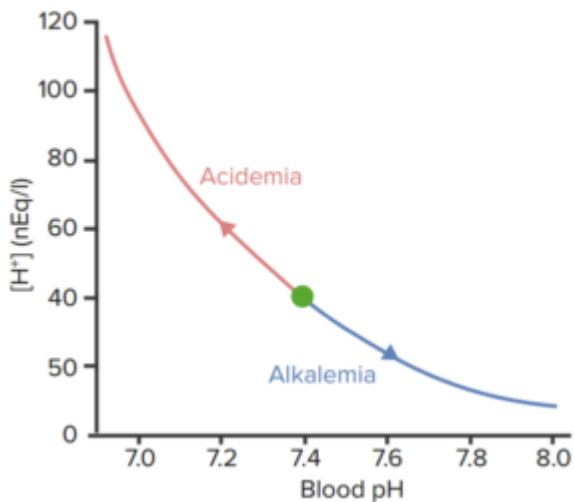
Example pH values of various fluids

Compartment	pH	
Gastric secretions (under conditions of maximal acidity)	0.7	→ H^+ - K^+ -ATPase (proton pump) in parietal cells
Lysosome	5.5	
Chromaffin granule	5.5	
Neutral H_2O at $37^\circ C$	6.81	
Cytosol of a typical cell	7.2	Range: 6.0—7.4 based in part on metabolism
Cerebrospinal fluid	7.3	
Arterial blood plasma	7.4	Range: 7.35—7.45 highly regulated
Mitochondrial inner matrix	7.5	
Secreted pancreatic fluid	8.1	→ HCO_3^- secretion ductal cells

Blood pH: Acidosis and Alkalosis



Arterial blood pH



Acids and Bases

Ionization, in chemistry and physics, is a process by which electrically neutral atoms or molecules are converted to electrically charged atoms or molecules (ions).

An acid is defined as a compound that dissociates in water and gives away its hydrogen ions. Bases are compounds that can accept hydrogen ions or gives away hydroxide ions or other negatively charged ions.

Acid solutions contain hydrogen ions. The higher the concentration of hydrogen ions, the lower is the pH. Hydrochloric acid is a strong acid and ethanoic acid is a weak acid. **Strong acids are fully ionized but weak acids are only partly ionized in solution.** Similarly, a weak base is a chemical base that does not ionize fully in an aqueous solution. A weak base may also be defined as a chemical base in which protonation (the addition of an H^+) to an atom, molecule, or ion, forming the conjugate acid) is incomplete.

Bases are proton acceptors. Accepting protons results in a relatively low pH compared to strong bases. Bases range from a pH of greater than 7 (7 is neutral, like pure water) to 14 (though some bases are greater than 14). The formula for pH is:

$$pH = -\log_{10}[H^+]$$

Since bases are proton acceptors, the base receives a hydrogen ion from water (H_2O). **The remaining H^+ concentration in the solution determines pH.** Weak bases have a higher H^+ concentration (lower pH) because they are less completely protonated than stronger bases. Therefore, more hydrogen ions remain in the solution. The pH of bases is usually calculated based on the OH^- concentration to find the pOH first. This is done because the H^+ concentration is not a part of the reaction, while the OH^- concentration is.

$$pOH = -\log_{10}[OH^-]$$

Buffers

Buffers are chemical substances that **minimize changes in pH when an acid or a base is added to a reaction by absorbing excess H^+ or OH^- ions.** In the absence of a

buffer, a minor change in H⁺ ion concentration can lead to a dramatic change in the pH. Buffers prevent large changes in pH by reacting with the newly generated H⁺ ions and neutralizing them:



The main role of buffers is to maintain a constant pH. A buffer is composed of a weak acid and its conjugate base, or a weak base and its conjugate acid. Weak acids and bases that are 50% dissociated (i.e., equally into HA and A⁻) are known to be the best buffers. The pH at which these compounds are 50% dissociated is called the pK, or ionization constant. The best buffers for the human body are those that have a pK close to 7.40; these include the physiological buffers of the human body. **If pH < pK of a buffer then HA > A⁻ and when pH > pK then A⁻ is more than HA.**

Physiologic Buffers

These **include bicarbonate and non-bicarbonate buffers** that protect the body against abnormal changes in the pH of a fluid. In these buffers, pK is near the normal blood pH. While managing patients, doctors routinely monitor the bicarbonate buffer system.

Bicarbonate buffers

In this system, bicarbonate picks up surplus H⁺ ions from the system, producing carbon dioxide (CO₂) and water.

Similarly, when H⁺ ion concentration decreases in the system, carbon dioxide combines with water to release hydrogen and bicarbonate ions. The pK of this reaction is 6.1. The Henderson-Hasselbalch equation describes the relationship among pH, pK, and the acid and conjugate base concentration. The Henderson-Hasselbalch equation for bicarbonate and carbon dioxide is as follows:

$$pH = 6.1 + \log [HCO_3^-]/[CO_2]$$

The Henderson-Hasselbalch equation contains 3 variables; if any two of these are known, the third can be calculated. CO₂ is measured clinically as mm Hg and multiplied by its solubility constant (0.03 mmol/L/mm Hg) to get the concentration.

The non-bicarbonate buffers

The non-bicarbonate buffers **include proteins and phosphates**. Protein buffers include extracellular proteins (albumin) and intracellular proteins (hemoglobin). These proteins act as a buffer in both plasma and cells. They interact exclusively with other buffer systems. The amino acid histidine can bind or release hydrogen ions. Due to this, proteins are very effective buffers. Based on the position of histidine in the protein molecule, its pK can vary. The average pK is about 6.5.

Hemoglobin and albumin both have histidine 34 and 16, respectively.

Phosphate buffers

Phosphate buffers are intracellular buffers in the plasma that are less useful than protein buffers. They are found in intracellular fluid and urine. Phosphate can bind 3 H⁺ ions. They can exist as PO₄³⁻, HPO₄²⁻, H₂PO₄¹⁻, or H₃PO₄. However, HPO₄²⁻ and H₂PO₄

1- are the most common.



As the pK of this reaction is 6.8, it is also an excellent buffer. However, it is not as good as albumin because the concentration of PO₄ in the extracellular fluid is relatively low. It is found at higher levels in the urine, where it is an important buffer.

Extracellular pH and Intracellular pH

Intracellular pH affects cell function. Any change in the intracellular pH also changes the extracellular pH in one way or another. Although intracellular pH is more important, only extracellular pH is measured clinically while managing patients. Despite this, the intracellular buffer system is more active and efficient in managing major pH changes.

Normal Acid-Base Balance

Of the three buffer systems, the bicarbonate buffer system is arguably the most important as it is the only one that is coupled to the [respiratory system](#).

Two major organs are involved in normal acid-base balance:

1. **Lungs excrete CO₂ from the system out into the environment and maintain a pCO₂ in the blood.** Central ventilation control in the CNS regulates the rate of breathing to maintain a pCO₂ between 35–45 mmHg. When the ventilation rate increases pCO₂ decreases, and when the rate of ventilation decreases pCO₂ increases.
2. **Kidneys remove endogenous acids from the body through the urine.** They maintain acid-base balance by reabsorbing bicarbonate from urine and excreting hydrogen ions into the urine.

On average 1–2 mEq/kg/24 hr of H⁺ ions are produced in the body of adults, whereas, in children, 2–3 mEq/kg/24 hr of H⁺ ions are produced. The primary sources of H⁺ ions include dietary protein metabolism, incomplete metabolism of carbohydrates and fat, and loss of bicarbonate in the stool. This shows that acid production depends on the amount of protein in the diet and the rate of catabolic activity.

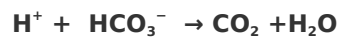
No H⁺ ions are produced upon completion of carbohydrate and fat metabolism. The end products of metabolism are water and CO₂, and CO₂ is exhaled by the lungs.

Incomplete catabolism of carbohydrates and fats produces lactic acid and keto acids, like β-hydroxybutyric acid and acetoacetic acid. Normally, this occurs in small amounts, but in various pathologic conditions like lactic acidosis and diabetic ketoacidosis, endogenous acid production is abnormally increased.

Loss of bicarbonate in the stool also contributes to the overall acid production in the body. The stomach mainly produces H⁺ ions, and the rest of the GI tract produces bicarbonate. There is an overall loss of bicarbonate from the body into the GI tract and out through the stool. **To produce bicarbonate in the GI tract, H⁺ ions are released into the bloodstream** at the rate of one H⁺ ion for each bicarbonate. This does not produce a lot of acid in the body, but it is dramatically increased in patients with watery diarrhea.

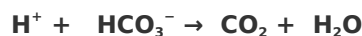
Only the lungs can regulate the CO₂ concentration, and only the kidneys can regulate the bicarbonate and H⁺ concentration.

Production of excess H⁺ ions by endogenous acid producing mechanisms in the body are neutralized by bicarbonate, which leads to a decrease in its concentration. The kidneys restore this bicarbonate deficiency through increased secretion of H⁺ ions. The lungs cannot regenerate bicarbonate, although the loss of CO₂ also lowers the H⁺ concentration:



During metabolic acidosis, an increased ventilation rate lowers the CO₂ concentration in the blood resulting in decreased H⁺ ion concentration and increased pH. This is a rapid compensation that does not last long, as eventually, the respiratory centers adapt to excess CO₂ production. When metabolic acidosis persists in the body after three days, the kidneys assume the major compensatory role.

The following reaction is occurring in the body:



Due to metabolic activity, elevated H⁺ ion concentration promotes the forward reaction increasing the CO₂ concentration and decreasing the H⁺ ion concentration. In respiratory acidosis, renal compensation by tubular reabsorption of bicarbonate and increased excretion of H⁺ restores normal pH. **Both the lungs and the kidneys can affect the H⁺ ion concentration and pH.** Only the lungs can regulate CO₂ concentration, and only the kidneys can regulate bicarbonate and H⁺ concentration.

Henderson-Hasselbalch-Examples

$$\text{pH} = 6.1 + \log \left(\frac{\text{HCO}_3^-}{(0.03 \times \text{P}_{\text{CO}_2})} \right)$$

Normal arterial blood gas	Acidic arterial blood gas	Alkalotic arterial blood gas
HCO ₃ ⁻ = 24 mM	HCO ₃ ⁻ = 26 mM	HCO ₃ ⁻ = 22 mM
PaCO ₂ = 40 mmHg	PaCO ₂ = 60 mmHg	PaCO ₂ = 20 mmHg
pH = 7.40	pH = 7.26	pH = 7.66

Renal Handling of Acids and Bases

After reclaiming filtered bicarbonate, the renal acid-base handling mechanism allows the excretion of acid formed by endogenous acid production (explained earlier). It occurs in the **collecting ducts and distal tubule**. As the hydrogen pumps in the collecting ducts cannot lower the urine pH below 4.5, urinary buffers are needed to excrete endogenous acids.

The two main urinary buffers are

1. **Phosphate buffer**
2. **Ammonia buffer**

The concentration of phosphate in the urine depends on the amount of dietary intake and the amount filtered and later reabsorbed in the proximal tubules. The serum level of phosphate is much lower than the concentration of urinary phosphate. These phosphates serve as an effective buffer through the following mechanism:



As the urine pH decreases from 7.0 to 5.0 within the collecting duct, phosphate buffers are very effective. However, the buffering capacity of this reaction is limited by its concentration. Urinary phosphate concentration cannot be modified by any mechanism.

Renal Mechanisms in Acid-Base Balance

The major mechanism by which the kidneys maintain pH is through regulation of serum bicarbonate concentration. The kidneys promote bicarbonate reabsorption and H⁺ excretion in the urine. This is a two-step process.

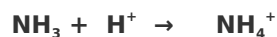
1. **Proximal tubules reabsorb bicarbonate** filtered from the blood; then
2. **Distal Tubular secretion of H⁺ ions** occurs

Excretion of H⁺ into the urine leaves behind HCO₃⁻ ions which neutralize endogenous acid production. Renal acid excretion occurs throughout the nephron directly or indirectly but mainly occurs in the distal tubules. Urinary buffers maintain the pH and allow the excretion or neutralization of endogenous acids.

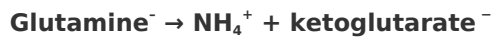
Bicarbonate reabsorption occurs in the proximal tubules.

Ammonia: NH₃ & NH₄

Ammonia production can be modified allowing for the regulation of acid excretion. The buffering capacity of ammonia is based on this reaction:



Proximal tubular cells excrete ammonia, a byproduct of the catabolism of the amino acid glutamine:



One glutamine produces two NH₄⁺ ions. Later, the metabolism of α-ketoglutarate also produces two bicarbonate ions. Ammonium ions go into the tubular lumen, and bicarbonate ions exit the proximal tubule cells via a Na⁺/HCO₃ cotransporter. **Cells in the thick ascending limb of the loop of Henle reabsorb the ammonium ions which later move into the blood neutralizing the bicarbonate ions produced earlier in the proximal tubules.** These ammonium ions are the source of H⁺ ions. Therefore, cells of the collecting ducts are an important place for the excretion of H⁺ in the form of NH₄⁺ ions.

Cells of the collecting ducts secrete H⁺ ions and regenerate bicarbonate, which moves into the bloodstream and neutralizes the endogenous acid production. Renal phosphate and ammonia buffer the H⁺ secreted. Ammonia is present at a higher concentration in the renal interstitium. Due to free permeability in the collecting ducts, ammonia diffuses into the lumen and neutralizes the H⁺ ions responsible for the low urine pH effectively buffering the pH.

Renal H⁺ ion excretion is regulated according to the body's physiological requirements. When more acid production occurs, ammonia production is also upregulated in the proximal tubules to serve as a buffer in the collecting ducts. NH₃ excretion may rise to 10-fold over the baseline values.

Extracellular pH: Regulator of Renal Acid Excretion

Extracellular pH is the most important regulator of renal acid excretion. A fall in extracellular pH due to respiratory or metabolic imbalances promotes renal acid excretion. **Through the renin-angiotensin system, aldosterone also stimulates H⁺ ion excretion in the collecting ducts with a resultant increase in serum HCO₃ concentration.**

Hypokalemia also increases acid secretion by promoting ammonia production in the proximal tubule and increasing H⁺ ion secretion in the collecting duct leading to metabolic alkalosis. Opposite effects occur in hyperkalemia leading to metabolic acidosis.

In the case of alkalosis, bicarbonate reabsorption in the proximal tubule is decreased, and bicarbonate is lost in the urine. In contrast, secretion of H⁺ ions into the lumen by the cells of the collecting duct is reduced. As an end result, bicarbonate is lost in the urine, and H⁺ ions move into the blood. Compensating for the body's alkalosis more ammonia is released.

In metabolic acidosis, the opposite phenomenon occurs where bicarbonate is reabsorbed in tubules, and H⁺ ions are secreted by the collecting ducts resulting in absorption of bicarbonates and formation of ammonia buffers.

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