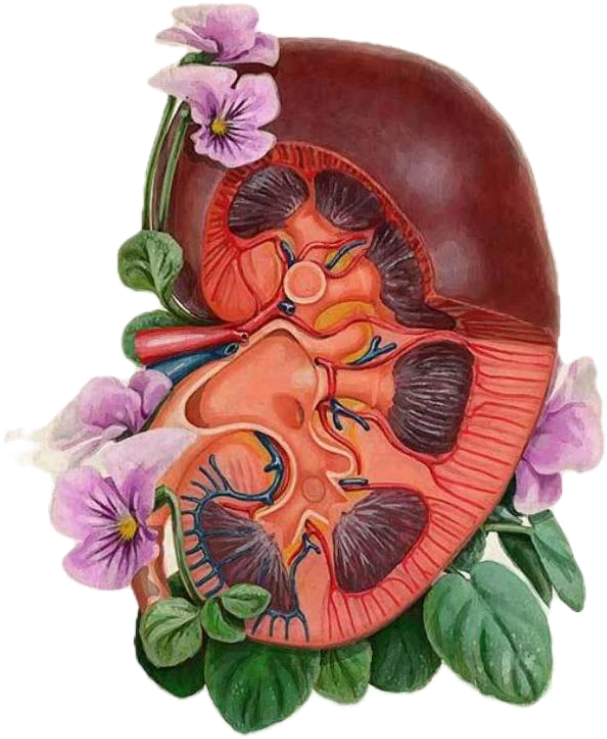
UGS Physiology Sheet (8-10)



اللهم اجعل هذا العمل خالصًا لوجهك الكريم وبارك فيه وانفع به واكتب لنا به الأجر

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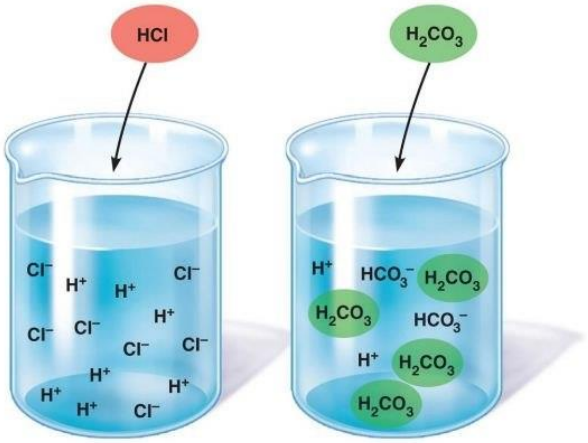
Before studying the sheet, watch the 8-10 lectures fully then move to the sheet to form a comprehensive view of the acid-base balance!

Definitions and Classification of Acids and Bases

- An acid is a substance that donates hydrogen ions (H^+) in solution, whereas a base is a substance that accepts hydrogen ions (H^+).
- Acids and bases are classified according to the extent of their dissociation in solution into strong and weak forms.
- Strong acids and bases dissociate completely in solution. Examples include hydrochloric acid (HCl) and sodium hydroxide (NaOH), which fully ionize when dissolved.
- Weak acids and bases dissociate only partially in solution. A weak acid, such as carbonic acid (H_2CO_3), releases hydrogen ions incompletely. Weak bases, such as bicarbonate (HCO_3^-) and hydrogen phosphate (HPO_4^{2-}), accept hydrogen ions only to a limited extent.
- Proteins in the body also function as bases because some amino acids carry net negative charges that readily accept hydrogen ions.
- Most acids and bases present in extracellular fluids and involved in normal acid–base regulation are weak acids and weak bases.



pH and Expression of Hydrogen Ion Concentration

Plasma hydrogen ion concentration is about **40 nmol/L ≈ 4×10^{-8} mol/L**. This is extremely low compared with most other physiological ions. For example, extracellular sodium concentration is about 140 mmol/L, meaning that sodium is roughly 3.5 million times higher in concentration than hydrogen ions.

Because of this very small value, it is impractical to use raw H^+ concentrations in physiological descriptions or calculations. Instead, hydrogen ion concentration is expressed using a logarithmic scale called pH.

pH is defined as the negative logarithm of hydrogen ion concentration: pH = **-** log $[H^+]$

The use of the negative logarithm allows small concentrations to be expressed as convenient positive numbers:

$[H^+] = 4\times10^{-8}$ mol/L → pH = **-** log $[4\times10^{-8}]$ → pH = − (log 4+ log 10^{-8}) = − (0.6−8) = 7.4

Thus, a normal plasma hydrogen ion concentration corresponds to a pH of 7.4.

Physiological Range of Hydrogen Ions

Every ion in the body is maintained within a relatively narrow physiological range. Even small deviations from these ranges can have significant functional consequences. For example, K^+ normally ranges between 3.5 and 5.5 mmol/L. A rise to about twice its normal level can be life-threatening, as it may cause severe cardiac arrhythmias.

In contrast, the hydrogen ion H^+ concentration, although its absolute concentration is extremely low, can vary over a relatively wide physiological range. The normal plasma H^+ concentration is about 40 nmol/L, but physiologically it may range between approximately 10 nmol/L (pH=8) and 160 nmol/L (pH=6.8). These represent the extreme limits of compatibility with life rather than everyday variation.

The body is generally more capable of handling increases in hydrogen ion concentration (acidosis) than decreases in hydrogen ion concentration (alkalosis). In other words, the body's defense mechanisms are better prepared to deal with acid attacks than with alkali attacks! (This is physiologically expected because our body produces acid continuously; Acids taken with foods, acids are produced by the metabolism of lipids, carbohydrates, and proteins, and cellular metabolism produces CO_2: $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$)

- Values below 10 nmol/L or above 160 nmol/L are not compatible with life.
- Normal arterial blood pH is therefore tightly regulated between 7.35 and 7.45, and deviation outside this range indicates significant acid–base disturbance (Below 7.35 is acidosis, and above 7.45 is alkalosis).

Table 31.1 pH and H^+ Concentration of Body Fluids

	H^+ Concentration (mEq/L)	pH
Extracellular Fluid		
• Arterial blood	4.0×10^{-5}	7.40
• Venous blood	4.5×10^{-5}	7.35
• Interstitial fluid	4.5×10^{-5}	7.35
Intracellular fluid	1×10^{-3} to 4×10^{-5}	6.0–7.4
Urine	3×10^{-2} to 1×10^{-5}	4.5–8.0

Acid-base balance is essential for normal cellular and systemic function, as even small changes in pH can produce major disturbances;

1. Influences enzyme activity. Most enzymes function properly at their optimal pH.
   Acidosis → suppression of CNS enzymes → coma → death.
   Alkalosis → convulsions of the respiratory muscle → death.
2. Affects hormones.
3. Affects electrolyte balance (Na^+, K^+, Cl^-, Ca^{++}).
4. Changes in excitability of nerve and muscle cells.

Types of Acids in the Body

Acids in the body are classified into volatile and non-volatile (fixed) acids.

❖ Volatile acid is mainly carbonic acid (H_2CO_3), which is in equilibrium with dissolved CO_2. It is eliminated through the lungs.
Daily metabolism produces large amounts of CO_2 (≈ 300 L/day), corresponding to about 10 moles of H^+ per day (huge amount). This does not lead to acid accumulation because CO_2 is continuously excreted. In body fluids, CO_2 combines with water to form H_2CO_3, which dissociates into H^+ and HCO_3^-.

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

If more H^+ is produced, the reaction shifts to left and CO_2 will be eliminated by the lungs. Therefore, acidosis is corrected.

If H^+ is less than normal: reaction shifts to right; respiration is depressed, and more CO_2 is retained → forming H^+. Alkalosis is corrected.

❖ Non-volatile (fixed) acids cannot be converted to CO_2 and therefore cannot be eliminated by the lungs; they require renal excretion.
They include:

- Phosphoric acid from oxidation of phosphoproteins, phospholipids, and nucleic acids.
- Sulphuric acid → oxidation of methionine and cysteine
- Others: lactic acid, pyruvic acid, beta-OH butyric acid, acetoacetic acids, and Krebs cycle acids.

The production of fixed acids is approximately 1 mmol/kg/day (≈ 80 mmol/day in an 80 kg individual).
If this amount were retained and distributed in the extracellular fluid (14 L), 80/14 = 5.5 mmol. This would raise H^+ concentration to levels corresponding to a pH < 3, which is not compatible with life!
Despite this continuous acid production, body pH remains tightly controlled!
<u>The question then is: how can the body eliminate this acid load?</u>
A first idea would be to excrete hydrogen ions directly in urine. However, this quickly proves inefficient as the minimal urine concentration of H^+ that can be achieved by the collecting ducts is only 0.03 mEq/L (minimal urine pH = **-** log (3 x 10^{-5}) = 4.5). Thus, if 80mEq of H^+ must be excreted at this concentration:
Urine volume = 80/0.03 > 2000 liters of urine must be excreted per day!!!
This is clearly impossible. Therefore, free H^+ excretion alone cannot solve the problem.

A second possibility is to buffer the 80 mmol of H^+ with bicarbonate, 80 mmol HCO_3^- in the extracellular fluid. In this case: $H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$
The CO_2 is then eliminated by the lungs, which seems efficient. However, this process consumes bicarbonate, and the total extracellular bicarbonate reserve is limited:
ECF [HCO_3^-] = 24 mEq/L. Since we have 14L as ECF volume: **14*24 = 336**. This reserve would be depleted in only a few days. After that, ECF pH would shift dramatically! (Memorize the numbers in bold)

Actually, the truth is: pH does not shift. The reason is that the kidneys not only excrete hydrogen ions but also generate new bicarbonate. In doing so, they replace the bicarbonate that is consumed in buffering, allowing continuous acid elimination without depletion of the body's buffer stores.

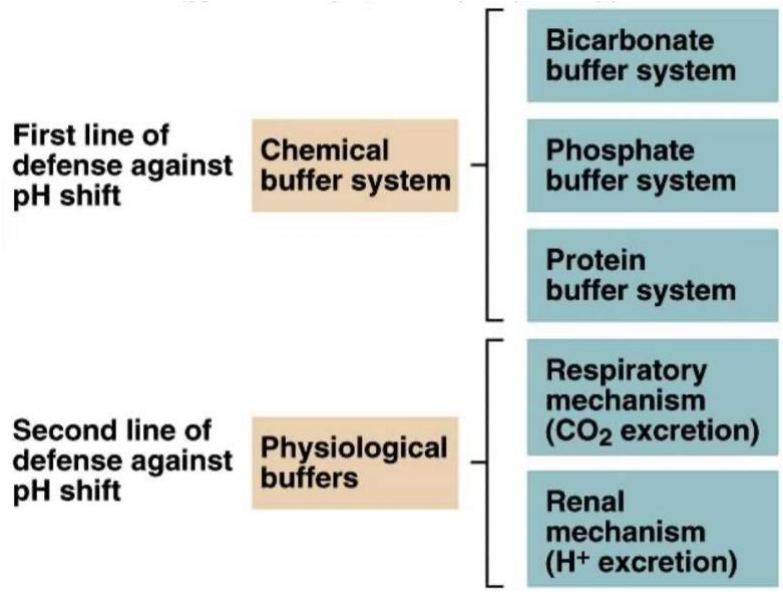
Defense against changes in hydrogen ion concentration:

1. First Line: Chemical acid-base buffer systems, which immediately combine with an acid or a base to prevent excessive changes in H+ concentration. Instantaneous (very fast)!!! E.g.:

1. Bicarbonate: most important ECF buffer $\mathbf{H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O}$
2. Phosphate: important ICF and renal tubular buffer $\mathbf{HPO_4^{-2} + H^+ \rightarrow H_2PO_4^-}$
3. Ammonia: important renal tubular buffer $\mathbf{NH_3 + H^+ \rightarrow NH_4^+}$
4. Proteins: important ICF and ECF buffers $\mathbf{H^+ + Hb \rightarrow HHb}$. Largest buffer store in the body. Albumins and globulins such as Hb.

2. Second Line: The respiratory system, which regulates the removal of CO2. Intermediate speed, few minutes to start reacting and few hours to reach its maximum response.

3. Third Line: The kidneys (the most powerful regulatory system), which eliminate non-volatile acids, secrete H^+, Reabsorb the entire filtered HCO_3^-, and generate new HCO_3^- (the bicarbonate gain). A slow system that takes a few hours to start working and 3-5 days to reach full response.



Chemical Buffer System:

- What is a buffer? A buffer is any substance that can reversibly bind or release H^+ to resist the change in pH.
- Buffers don't eliminate or add H^+ but keep it "tied up" until lungs or kidneys take action.

- General Buffering Reaction: $H^+ + A^- \rightleftharpoons HA$
- Three factors determine the strength of any buffer:

1. The pK of the buffer relative to the surrounding solution. $pH = pK_a + \log \frac{[base]}{[acid]}$

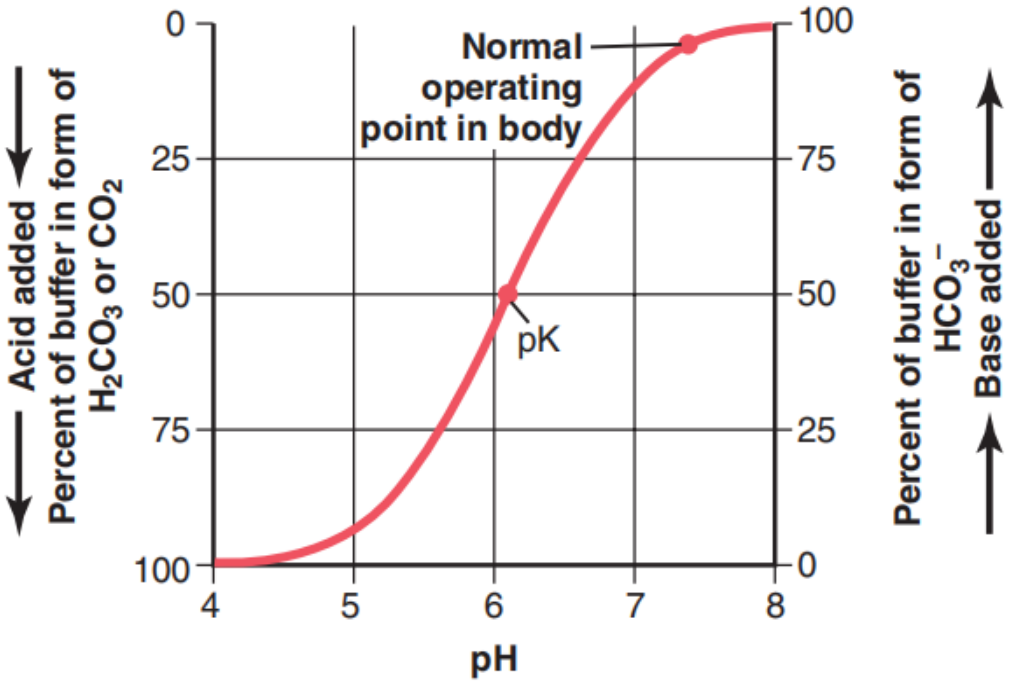
pK represents the pH at which the acid and base forms are present in equal concentrations. At this point: pH = pK because the ratio base/acid=1, and log 1 = 0. In general, a buffer is most effective when the surrounding pH is close to its pK, typically within ±1 pH unit.

2. The absolute concentration of the buffer.
This is a key determinant of the buffering capacity because when buffer concentration is low, even small additions of acids or bases produce considerable changes in pH. Said that, the higher the buffer concentration the better.

3. The buffer renewal ability (most important factor).

- These three factors can be better understood when applied to the principal buffer systems in the body: bicarbonate, phosphate, ammonia, and proteins:

❖ **Bicarbonate buffer system** (the most important extracellular buffer): It is a weak buffer in terms of pKa because plasma pH is 7.4, which is outside its most effective area pKa for bicarbonate carbonic acid system 6.1 ±1 => (5.1 to 7.1). This means that this system operates on the portion of the buffering curve where the slope is low and the buffering power is poor. Looking at this aspect only, phosphate is a much better buffer than bicarbonate; its pKa of 6.8 is closer to our ECF pH 7.4.



- Second, the concentrations of the two elements of the bicarbonate system, CO_2 and HCO_3^-, are not high (still higher than phosphate extracellularly).
- Despite these characteristics, the bicarbonate buffer system is the most powerful extracellular buffer in the body. This apparent paradox is due mainly to the fact that the two elements of the buffer system, HCO_3^- and CO_2, are regulated, respectively, by the kidneys and lungs. (Phosphate has no renewal capacity).

- **Phosphate Buffer System** $H^+ + HPO_4^{-2} \rightleftharpoons H_2PO_4^-$

  Phosphate buffer system plays a minimal role extracellularly, but a major role in renal tubular fluid and intracellular fluid where it works at its maximum buffering strength. Why?
  - Water is normally reabsorbed to a greater extent than phosphate by renal tubules, reabsorption of water = 99% while reabsorption of phosphate= 90%, this is why phosphate becomes greatly concentrated in the tubule, and the remaining tubular fluid has approximately ten times the phosphate concentration of plasma.
  - pKa of Phosphate is 6.8, phosphate buffer is effective in maintaining the intracellular pH of 7.0. In addition, the pH of the proximal tubular fluid is 6.5, which is very close to the phosphate pKa as well.
  - Note that the phosphate concentration is low in plasma and it has poor renewable ability (it depends on dietary intake rather than endogenous production).

- **Ammonia buffer system**
  - It is composed of ammonia (NH_3) and the ammonium ion (NH_4^+)
  - pKa of this system is 9.2
  - Ammonia (NH_3) doesn't actually work as an extracellular buffer why? Because its concentration is too low and its pKa is not close to pH.

  Although the pKa is not close enough to the tubular pH, it's actually even more important quantitatively than phosphate in the tubules. This will be discussed in detail later.

  Previous Question: If the Ammonia pKa is 9.2, will the plasma concentrations will be higher for ammonia or ammonium? (Hint: use the Henderson-Hasselbalch equation)

- **Proteins**

  The chemical buffers can buffer up to 1000mmol of H+, approximately 70% of the total chemical buffering of the body fluids results from the intracellular proteins. However, the slow rate at which H^+ and HCO_3^- move through the cell membranes due to their charge often delays the maximum ability of the intracellular proteins to buffer extracellular acid–base abnormalities (e.g. taking a whole pack of aspirin) for several hours. (Cannot work acutely).

In addition to the high concentration of proteins in the cells, another factor that contributes to their buffering power is the fact that the pKs of many of these protein systems are fairly close to intracellular pH (around 7.0).

In the red blood cell, hemoglobin (Hb) is an important buffer (accounts for 35% of blood's buffering capacity, (bicarbonate system contributes about 55%) :
$H^+ + Hb \rightleftharpoons HHb$

More about the Bicarbonate Buffer System:

Consists of carbonic acid H_2CO_3, and bicarbonate HCO_3^-.

H_2CO_3 is a weak acid formed by a reaction between CO_2 and H_2O catalyzed by carbonic anhydrase.

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

When a strong acid such as HCl is added, the increased H^+ released from the acid is buffered by HCO_3^- to form the very weak acid H_2CO_3. As a result, more H_2CO_3 is formed, causing increased CO_2 and H_2O production. This excess CO_2 greatly stimulates respiration, which eliminates it from the ECF.

$$\uparrow H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$$

When a strong base, such as NaOH, is added, the OH^- released from the NaOH combines with H_2CO_3 to form additional HCO_3^-. Thus, the weak base HCO_3^- replaces the strong base NaOH. As a result, the concentration of H_2CO_3 decreases (because it reacts with NaOH), causing more CO_2 to combine with H_2O to replace the H_2CO_3. This decreases CO_2 levels in the blood, which inhibits respiration and decreases the rate of CO_2 expiration. Also, the rise in blood HCO_3^- is compensated for by increased renal excretion of HCO_3^-.

$$\begin{array}{ccccc} CO_2 + H_2O & \longrightarrow & H_2CO_3 & \longrightarrow & \uparrow HCO_3^- + H_2O \\ & & + & & + \\ & & NaOH & & Na \end{array}$$

Henderson-Hasselbalch equation: $pH = pK_a + \log \frac{[base]}{[acid]}$

For the bicarbonate buffer system: $pH = 6.1 + \log \frac{HCO3-}{0.03 \times PCO2}$

Why not H_2CO_3?

The concentration of undissociated H_2CO_3 cannot be measured in solution because it rapidly dissociates into CO_2 and H_2O or into H^+ and HCO_3^-. However, the CO_2 dissolved in the blood is directly proportional to the amount of undissociated H_2CO_3.

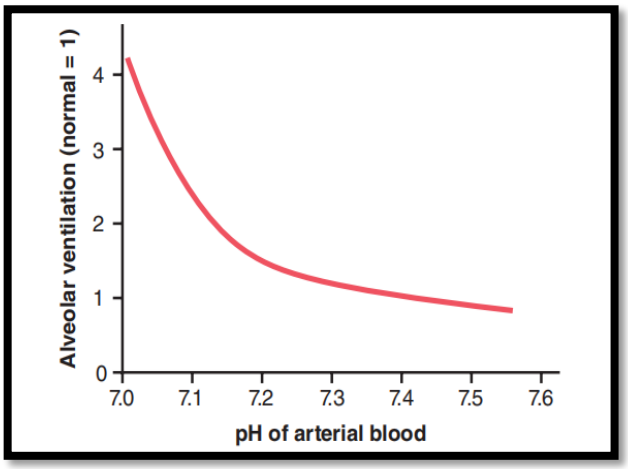
Why PCO_2?

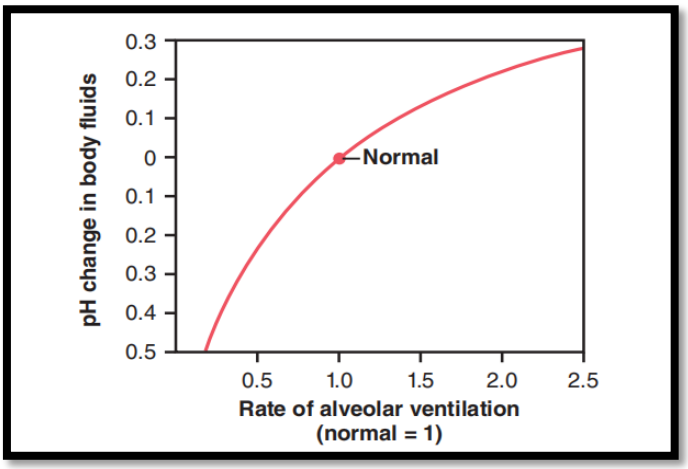
Most clinical laboratories measure the blood CO_2 tension (Pco_2) rather than the actual amount of CO_2. Fortunately, the amount of CO_2 in the blood is a linear function of Pco_2 multiplied by the solubility coefficient for CO_2; under physiological conditions, the solubility coefficient for CO_2 is 0.03 mmol/L per mm Hg at body temperature. This means that 0.03 mmol/L of CO_2 is present in the blood for each mm Hg Pco_2 measured.

The Respiratory System:

The second line of defence against acid–base disturbances is the lungs' control of extracellular fluid CO_2 concentration. An increase in ventilation removes CO_2 from extracellular fluid, thereby reducing the H^+ concentration by mass action. Conversely, decreased ventilation increases CO_2 and H^+ concentrations in the extracellular fluid.

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$





When a person develops metabolic acidosis, such as after ingestion of excess acids (e.g., aspirin), the increase in hydrogen ion concentration shifts the bicarbonate buffer reaction toward the formation of CO_2. As a result, CO_2 concentration increases. Respiratory compensation can return pH back to normal up to 50-75% normal only. The response start within 3-12 min. For full compensation, you need 6-12 hrs.

This rise in CO_2 stimulates the respiratory center, leading to hyperventilation in order to eliminate the excess CO_2.

A similar response occurs when bicarbonate concentration decreases, such as in conditions like diarrhea or deep vomiting (loss of bicarbonate rich pancreatic secretions not gastric juice), where HCO_3^- is lost. This also stimulates the respiratory center, resulting in hyperventilation to reduce CO_2 levels.

This increased ventilation (hyperventilation), enhances the exhalation of CO_2, but it doesn't add any O_2 to the blood because of the sigmoidal shape of the O_2-Hb dissociation curve. Therefore, there is no increase in O_2 to counterbalance acidosis → this hyperventilation isn't opposed by any other factor.

In contrast, when there is an increase in bicarbonate concentration, such as after ingestion of bicarbonate (e.g., for relief of gastric acidity), metabolic alkalosis develops. In this case, the respiratory response is hypoventilation, which leads to increased PCO_2 and decreased PO_2.

However, hypoventilation is limited. When PO_2 falls to about 60 mmHg or lower, the resulting hypoxia becomes a strong stimulus (peripherally in carotid bodies) for ventilation and limits the respiratory compensation for metabolic alkalosis.

Therefore, a decrease in pH (acidosis) produces a stronger respiratory response than an increase in pH (alkalosis). This is because hyperventilation is generally safe, whereas hypoventilation is restricted by the risk of hypoxemia.

- Respiratory control cannot return H+ concentration all the way back to normal when a disturbance outside the respiratory system has altered the pH. Ordinarily, the respiratory mechanism for controlling H+ concentration is approximately 50% to 75% effective, corresponding to a feedback gain of 1 to 3. Feedback gain = Correction produced by the System / Remaining Error.

Renal Regulation of Acid-Base Balance

The kidneys regulate extracellular fluid H^+ concentration through three fundamental mechanisms:

(1) Secretion of H^+.

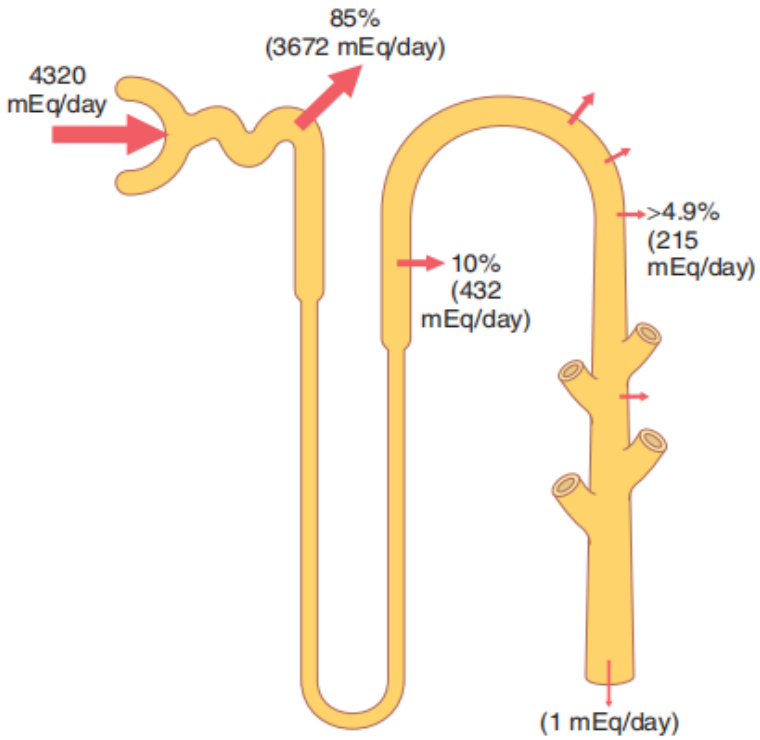
(2) Reabsorption of filtered HCO_3^-. (Most important function of the kidneys)

(3) Production of new HCO_3^-.

H^+ secretion and HCO_3^- reabsorption:

HCO3- is freely filtered to Bowman's space. The amount of HCO_3^- that enters Bowman's space (Filtered Load) = GFR x $[HCO_3^-]_{plasma}$ = 180 x 24= 4320 mmol/day.

All bicarbonate filtered must be reabsorbed. We cannot tolerate losing bicarb in the urine. You might notice that 1mEq/ day of bicarbonate is secreted daily, however, in comparison with the total 4320 mmol/day, it's negligible, hence, we say that it's fully reabsorped.



<u>H+ secretion in the proximal tubule, thick ascending loop of Henle, and the early distal tubule:</u>

→ Within the cell of the proximal tubule, CO_2 exists (either diffuses into the tubular cells or is formed by metabolism in the tubular epithelial cells).

→ When it is combined with water under the influence of the enzyme carbonic anhydrase, it forms H_2CO_3

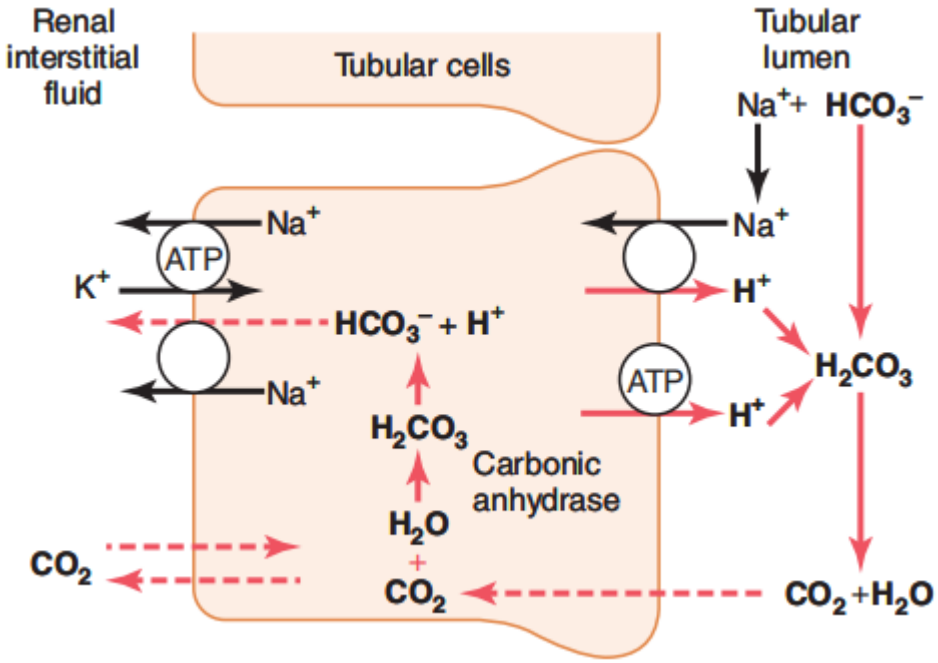
→ H_2CO_3 dissociates into H^+ and HCO_3^-. HCO_3^- is reabsorbed into the peritubular capillary through the basolateral membrane

→ H^+, on the other hand, is secreted to the lumen of the proximal tubule by Na^+/H^+ counter-transporter, which uses the energy released by transporting Na^+ downhill to secrete H^+ uphill (secondary active transport). Because this is not H^+ pump, it makes $[H^+]$ gradient only 5-6 times more in the TF. Therefore, the pH of the proximal TF drops only to 6.5.

→ H^+ joins HCO_3^- and form H_2CO_3. H_2CO_3 dissociates to water and CO_2 by the action of carbonic anhydrase on the luminal membrane.

→ CO_2 re-enters the cell to contribute to the cycle all over again.

- Note that HCO_3^- which enters the blood is not the same HCO_3^- filtered.



- For each HCO_3^- reabsorbed from the tubules, H^+ must be secreted into the tubules. However, this is not Net H^+ secretion. Because H^+ is recycled again and reabsorbed (re-enter) by the tubules in the form of CO_2.
- In other words, one proton is enough to reabsorb the entire filtered bicarb, meaning no net H^+ secretion. However, after the filtered amount of bicarb has been reabsorbed, any additional H^+ secretion is net secretion and is accompanied by bicarbonate gain.
- Drugs that inhibit carbonic anhydrase (e.g., some diuretics) decrease H^+ secretion and HCO_3^- reabsorption, thereby increasing the risk of acidosis.

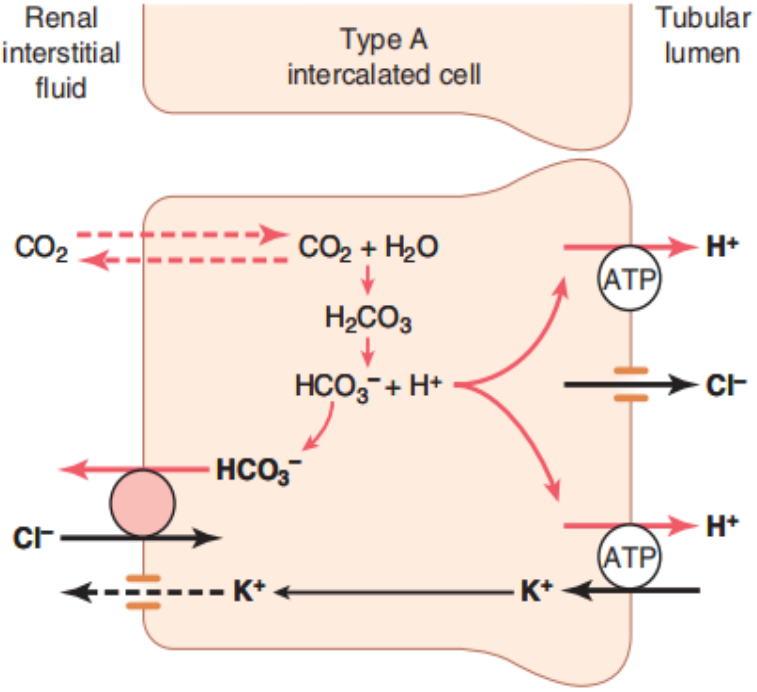
<u>H+ secretion in the late distal and collecting tubules:</u>

⇨ HCO_3^- and H^+ are formed by the same reactions.

⇨ At the luminal membrane of the Intercalated cells of these segments, H^+ is secreted by H^+ ATPase, which uses the energy released by the breakdown of an ATP molecule to transport H^+ uphill (primary active transport) 900X gradient NOT more.

⇨ Therefore, the pH of the inner medullary TF is 900 more concentrated than inside the cells. This is the maximum capacity of the pump. Hence, pH of TF (and urine) does not go below 4.5 ($-\log(10^{-7} \times 900) = 4.5$).

⇨ **Suggested questions :** If you had a question asking you about the odd choice, and a urine of a pH of 3.5 was a choice, it will be the answer, since urine pH can never go below 4.5



Reabsorption of Filtered HCO_3^-

- HCO_3^- does not permeate the luminal membrane (charged molecule).
- HCO_3^- in the tubular fluid combines with H^+ to form H_2CO_3 which dissociates into CO_2 and H_2O.
- CO_2 easily crosses the luminal membrane to enter the cell, where it recombines with H_2O to form H_2CO_3, which dissociates into HCO_3^- and H^+. (Remember: CO_2 can cross any biological membrane as if the membrane does not exist)
- HCO_3^- transport at the basolateral membrane is facilitated by Na^+/HCO_3^- cotransporter in the proximal tubule and Cl^-/HCO_3^- counter-transporter in the late distal tubule, thick ascending loop of Henle, and in the collecting tubules and ducts.

HCO_3^- and H^+ titrate each other in the tubules:

H^+ secreted into the tubules is buffered by HCO_3^-, keeping tubular pH with slight change. After reabsorption of the 4320 milliequivalents of HCO_3^-, other buffers in the tubules bind to the excess H^+, as discussed later.

So, the kidney's main function is to reabsorb every single molecule of HCO_3^- 4320 mmol/day. But is that enough???

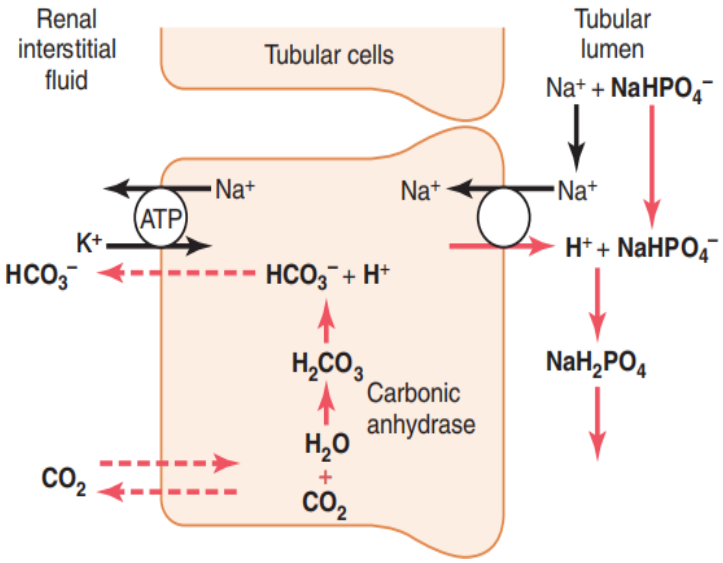
Reabsorbing 4320 mEq of HCO_3^- (the filtered load of HCO_3^-) is not enough. We still need the kidney to produce an extra 80 mM of HCO_3^- within its renal vein; unless it does that, the body can't neutralize the fixed acids represented by 80 mM of H^+.

Note: clearance of HCO_3^- is negative.

New HCO_3^- Generation:

- The moment bicarbonate is depleted within the tubular fluid, any further secretion of H^+ is a bicarbonate gain.
- Excess H^+ in the tubules, which does not react with HCO_3^-, combines with tubular buffers, of which the most important is phosphate buffer.

Phosphate Buffer:

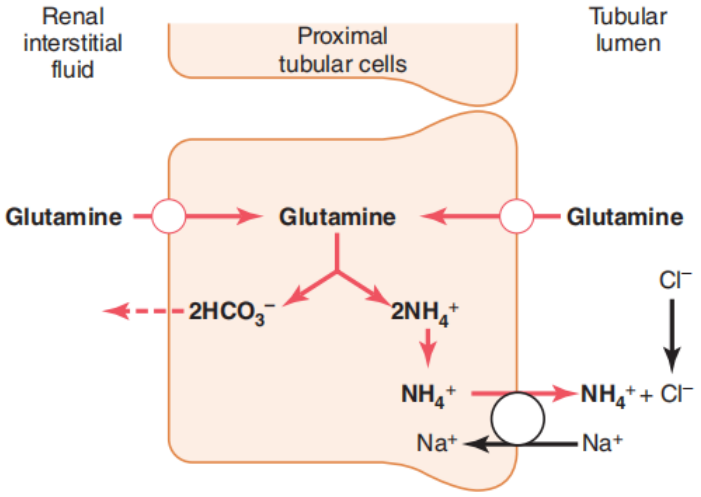


- H+ reacts with HPO_4^{2-} in the tubule to form $H_2PO_4^-$ which is excreted in the urine.
- This produces new HCO_3^- in the cell to be formed & will eventually enter the blood.
- Therefore, it is apparent that whenever H^+ in the tubular fluid combines with a buffer other than HCO_3^-, a **new** HCO_3^- is added to the blood.
- The pKa of phosphate buffer is 6.8 (close to the proximal pH=6.5. Therefore, in the tubules, the phosphate buffer system functions at its most effective range of pH.
- The filtered load of phosphate is 180 L/day x 1.5 mmol/L = 270 mmol/day.
- Phosphate is actively reabsorbed in the proximal tubule (about 85–90%) via a carrier-mediated system that has a Tmax. This process is regulated by parathyroid hormone (PTH).
- When plasma phosphate rises, the filtered load increases, and once it exceeds the Tmax, the excess phosphate is excreted. In the tubular fluid, this phosphate buffers secreted H^+ to form titratable acid.
- I can claim the kidney participate in phosphate homeostasis.
- If 90% of the filtered phosphate is reabsorbed, we are only left with 10%, which corresponds to only 27 ≈ 30 mEq/day available for buffering H^+, and only 30 mEq of bicarb gain. There must be another way to make the additional 50 mEq of bicarb.

Ammonia-ammonium Buffer system:

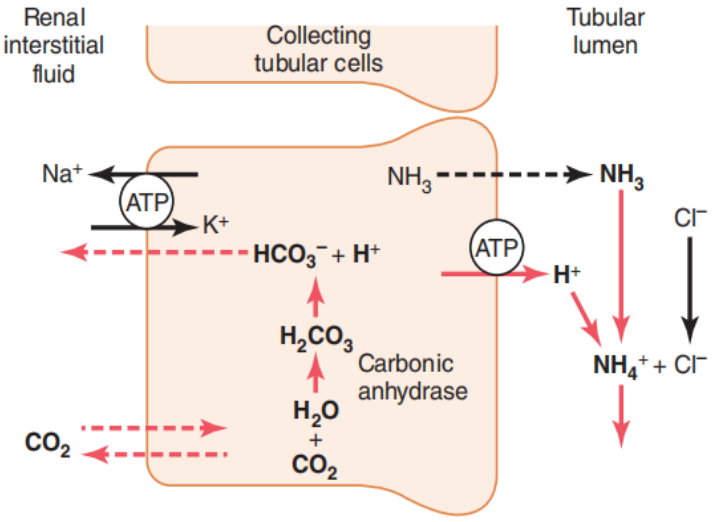
The cells of the proximal tubule benefit from the catabolism of glutamine, an amino acid, via glutaminase to yield 2 HCO_3^- and 2 NH_4^+.

The $2NH_4^+$ are secreted into the lumen by a counter-transport mechanism in exchange for Na^+, which is reabsorbed. The $2HCO_3^-$ are considered new and are transported across the basolateral membrane, along with the reabsorbed Na^+.

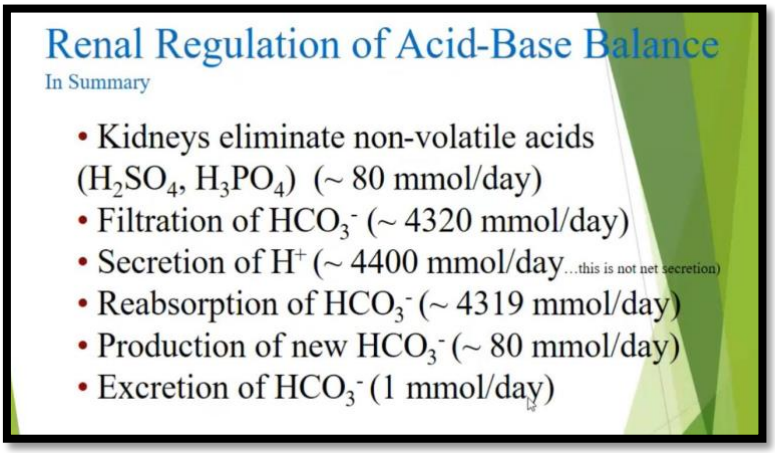


In the collecting tubules, the addition of NH_4^+ to the tubular fluids occurs through a different mechanism. Here, H^+ is secreted by the tubular membrane into the lumen, where it combines with NH_3 to form NH_4^+, which is then excreted. This is called ammonia trapping. (The collecting ducts are permeable to NH_3, which can easily diffuse into the tubular lumen. However, the luminal membrane of this part of the tubules is much less permeable to NH_4^+; therefore, once the H^+ has reacted with NH_3 to form NH_4^+, the NH_4^+ is trapped in the tubular lumen and eliminated in the urine.)

For each NH_4^+ excreted, a new HCO_3^- is generated and added to the blood.



- NH4 in urine has two sources: NH_4^+ is mainly produced through the catabolism of glutamate. However, a minor percentage of NH_4^+ is due to Ammonia that is added to the hydrogen ion in the distal part of the tubule.



Net H^+ Excretion (or Net HCO_3^- Gain):

Net HCO_3^- Gain = NH_4^+ excretion + urine titratable acids - HCO_3^- excretion

Remember that around 30mM of H^+ was buffered using HPO_4^-. However, many other buffers also played a part in this process e.g. citrate, lactate; yet it is not feasible to calculate every single buffer alone, so all of these buffers were referred to as Titratable Acids.

These acids when found in urine are tittered using NaOH, how many millimoles of NaOH added (until pH of 7.4 is achieved) indicates how many millimoles of H^+ were buffered; and thus, how many millimoles of HCO_3^- were produced.

Because pKa of the reaction, $NH_3 + H^+ = NH_4^+$, is 9.2. Thus, titration to a pH of 7.4 doesn't remove an H^+ from NH_4^+. Thus NH_4^+ excretion is calculated by multiplying the urinary flow rate by NH_4^+ urinary concentration.

Acid-Base Imbalances

Acidosis: a condition in which the blood has too much acid (or too little base), resulting in a decrease in blood pH (< 7.35)

Alkalosis: a condition in which the blood has too much base (or too little acid), resulting in an increase in blood pH (> 7.45)

HCO_3^- /H^+ ratio in extracellular fluids:

$$pH = 6.1 + \log \frac{HCO_3^-}{0.03 \times Pco_2}$$

Acidosis: ↓ in the ratio

- Due to a fall in HCO_3^- (metabolic acidosis)
- Due to an increase in PCO_2 (respiratory acidosis)

Alkalosis ↑ in the ratio

- Due to an increase in HCO_3^- (metabolic alkalosis)
- Due to a fall in PCO_2 (respiratory alkalosis)

General Notes about Acid-Base Disturbances:

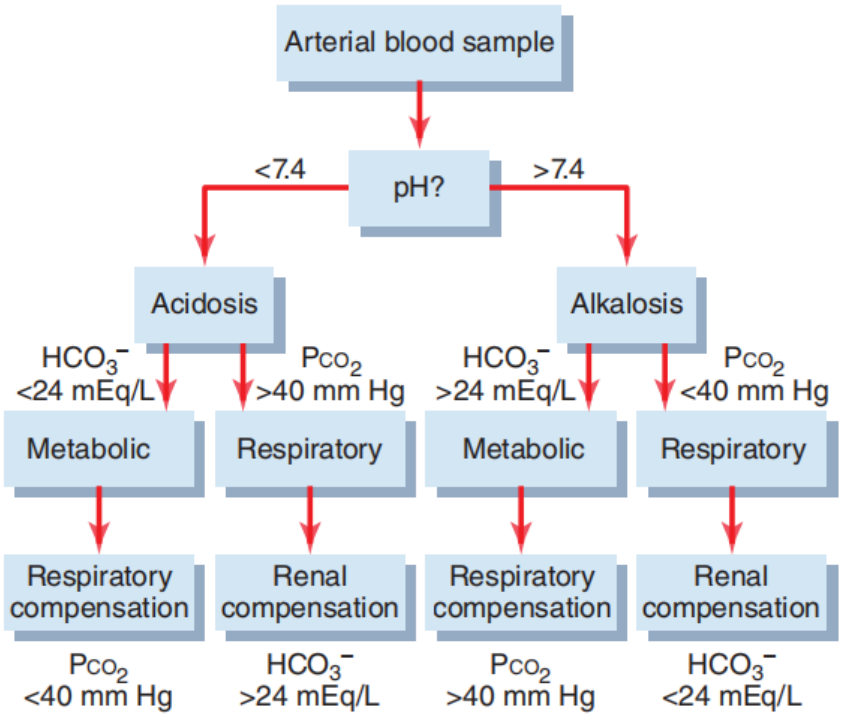
* Acidosis is more common than alkalosis.
* Metabolic acidosis is more common than respiratory acidosis.
* The most common cause of metabolic acidosis is diarrhea, not diabetes mellitus, because diabetes mellitus type 1, which causes ketoacidosis, is not common.

Disturbance:	pH:	HCO_3^-:	PCO_2:	Compensation:
metabolic acidosis	↓	↓	↓	ventilation → ↓PCO2 renal HCO_3 production
respiratory acidosis	↓	↑	↑	renal HCO_3 production
metabolic alkalosis	↑	↑	↑	ventilation renal HCO_3 excretion
respiratory alkalosis	↑	↓	↓	renal HCO_3 excretion

To know the type of disorder and as it shows in the table above, you have to do three steps:

- First: take a look at the **pH level**; increased (alkalosis) or decreased (acidosis).
- Second: search for the **cause**: is it the HCO_3^- who is causing this shift (metabolic) or the CO_2 (respiratory). Normally, HCO_3^- = 24mEq (normal range: 22 - 26mEq), PCO_2 = 40 mmHg (normal range: 35-45).

- Third: look to see if there is **compensation** from the other element. In compensation, always the two elements move in the same direction; if one increases, the other will increase to maintain a constant value of pH.



1. Metabolic acidosis:

1. Renal tubular acidosis: decreased H^+ secretion and HCO_3^- reabsorption.
2. ↑ HCO_3^- loss: diarrhea (most common cause), deep vomiting with the pancreatic secretions, which are full of bicarb. (Gastric vomiting, as in pyloric stenosis, causes metabolic alkalosis because of excessive HCl loss from the stomach).
3. ↑ H^+ production: as in D.M (DKA).
4. Ingestion of Aspirin or when acetoacetic acids are produced from fats.

In Metabolic Acidosis, respiratory center is stimulated causing hyperventilation → washing out CO_2 as a compensation.

Respiratory compensation starts to act after minutes, full effect after hours.

Acute metabolic acidosis (not for long period of time) is not accompanied with respiratory compensation.

2. Metabolic Alkalosis: Not Common.

1. Diuretics except carbonic anhydrase inhibitors:
   ↑ flow → ↑ TF flow rate → ↑ H^+ secretion→ ↑ H^+ loss in the urine → Metabolic alkalosis.
2. ↑ Aldosterone.
3. Vomiting of gastric content only (Pyloric stenosis).
4. Administration of $NaHCO_3$.

3. Respiratory Acidosis: COPD

4. Respiratory Alkalosis

Renal Compensation for Acidosis:

- Increased H^+ secretion, increased HCO_3^- reabsorption, Production of new HCO_3^-.
  - Titratable acid = 35 mmol/day (small increase)
  - NH_4^+ excretion = 165 mmol/day (increased)
  - HCO_3^- excretion = 0 mmol/day (decreased)
  - Total = 200 mmol/day

Renal Compensation for Alkalosis:

- Decreased H^+ secretion, decreased HCO_3^- reabsorption, loss of HCO_3^-.
  - Titratable acid = 0 mmol/day (decreased
  - NH_4^+ excretion = 0 mmol/day (decreased)
  - HCO_3^- excretion = 80 mmol/day (increased
  - Total = 80 mmol/day

Questions from Slides:

Q1: The following data were taken from a patient:

Urine volume = 1.0 liter/day

Urine HCO_3^- concentration = 2 mmol/liter

Urine NH_4^+ concentration = 15 mmol/liter

Urine titratable acid = 10 mmol/liter

What is the daily net acid excretion in this patient? And what is the daily net rate of HCO_3^- addition to the extracellular fluids?

Answer:

Net acid excretion = Titrated Acid + NH_4+ excretion - HCO_3^-

= (10x1) + (15x1) - (1 x 2)

= 23mmol/day

Net rate of HCO_3^- addition to body = 23 mmol /day

Q2: A plasma sample revealed the following values in a patient: pH = 7.12, PCO2 = 50, HCO_3^- = 18. Diagnose this patient's acid-base status: acidotic or alkalotic? Respiratory, metabolic, or both?

Answer: Acidotic, Both (mixed acidosis).

Mixed acid-base disturbance: two or more underlying causes of acid-base disorder.

Q3: pH= 7.6, PCO_2 = 30 mmHg, plasma HCO_3^- = 29 mmol/L. What is the diagnosis?

Answer: Mixed Alkalosis.

Q4: A patient presents in the emergency room, and the following data are obtained from the clinical labs: plasma pH = 7.15, HCO_3^- = 8 mmol/L, PCO_2= 24 mmHg. This patient is in a state of:

1. Metabolic alkalosis with partial respiratory compensation
2. Respiratory alkalosis with partial renal compensation
3. Metabolic acidosis with partial respiratory compensation
4. Respiratory acidosis with partial renal compensation

Answer: 3

Q4: Laboratory values for a patient include the following:

Arterial pH = 7.34

Plasma HCO_3^- = 15 Plasma

PCO_2 = 29 Plasma Cl^-= 118

Plasma Na^+ = 142

What type of acid-base disorder does this patient have? What is his anion gap?

Answer: Metabolic Acidosis with Respiratory Compensation

Anion gap isn't required in the exam material.

Q5: Which of the following are the most likely causes of his acid-base disorder?

a. diarrhea

b. diabetes mellitus

c. aspirin poisoning

d. primary aldosteronism

Answer: a

Q6: Indicate the acid-base disorders in each of the following patients:

	pH:	HCO_3^- :	PCO_2:	acid-base disorder:
1.	7.34	15	29	Metabolic acidosis
2.	7.49	35	48	Metabolic alkalosis
3.	7.34	31	60	Respiratory acidosis
4.	7.62	20	20	Respiratory alkalosis
5.	7.09	15	50	Acidosis (respiratory & metabolic)

Q7: Suha is a 45-year-old female admitted to the E.R with a severe asthma attack. She has been experiencing increasing shortness of breath since admission three hours ago. Her arterial blood gas result is as follows:
pH = 7.22, PCO_2 = 55, HCO_3^- = 25
Answer: respiratory acidosis without kidney compensation.
Acidosis is present (decreased pH) with the PCO_2 being increased, reflecting a primary respiratory problem. For this patient, we need to improve the ventilation status by providing oxygen therapy, mechanical ventilation, and administering bronchodilators.

Q8: Shaher is a 55-year-old male admitted to E.R with a recurring bowel obstruction. He has been experiencing intractable vomiting for the last several hours despite the use of antiemetics. Here is his arterial blood gas result:

pH = 7.50, PCO_2 = 42, HCO_3^- = 33

Answer: metabolic alkalosis.

Alkalosis is present (increased pH) with the HCO_3^- increased, reflecting a primary metabolic problem. Treatment of this patient might include the administration of I.V. fluids and measures to reduce the excess base.