Lecture No. 8

Role of the kidney in Acid Base Balance

Regulation of pH

The normal concentration of extracellular H^+ averages 40 nM, or 40 nEq/L. This can increase 4 times or decrease to one fourth (i.e., from 10nM to 160nM…4X4=16 times. Are you familiar with any other substance in our body, which can fluctuate 16 times without causing death?).

pH compatible with life is between 6.8 and 8.0

- **Remember**: pH = -log $[H^+]$.
- However, the lower limit of normal extracellular pH is 7.35 while the upper limit is 7.45.
- pH lower than 7.35 is referred to as acidosis while pH higher than 7.45 is referred to as alkalosis

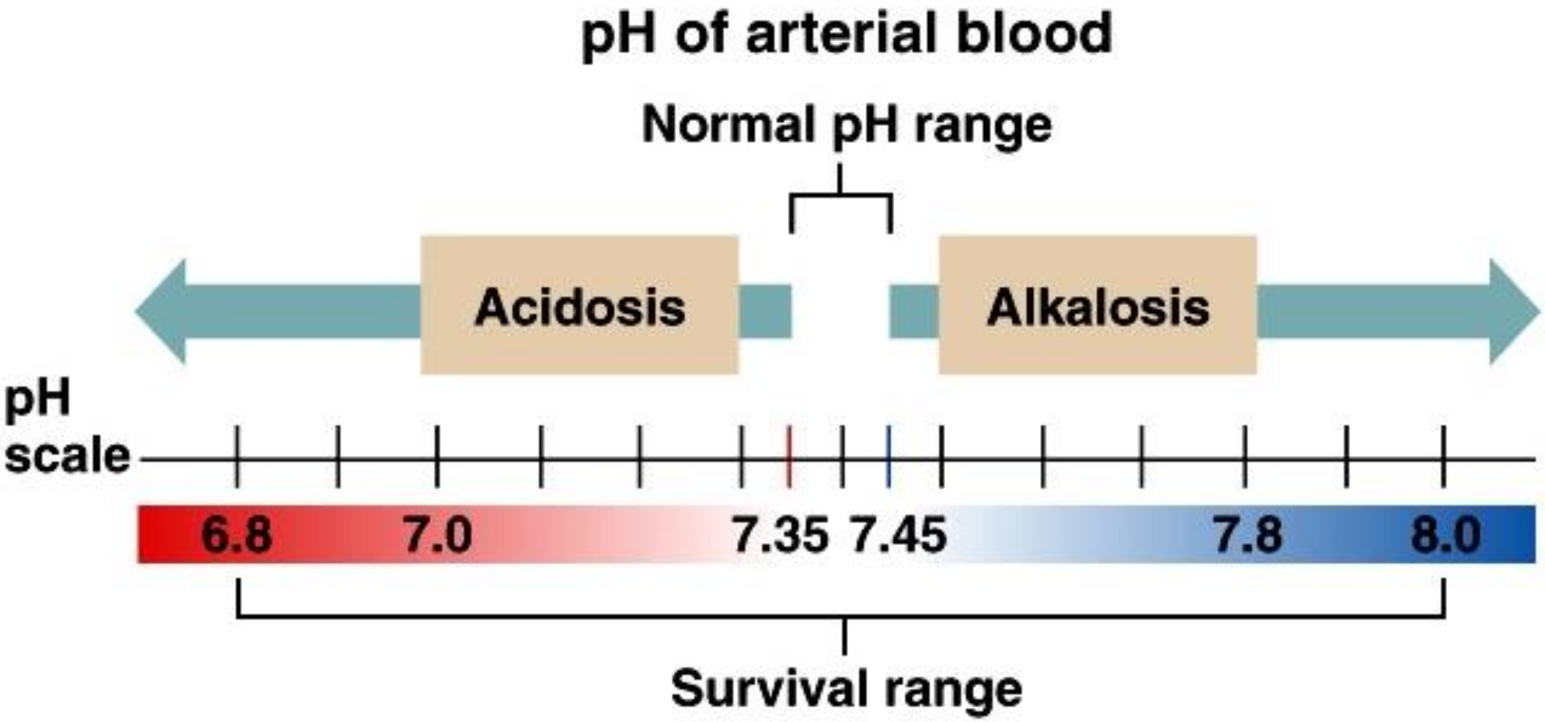
Normal Acid-Base Balance

One more time: Normal pH 7.35-7.45

- Below 7.35 acidosis   Above 7.45 alkalosis

Narrow normal range

Compatible with life 6.8 - 8.0



Normally it:

10 nanoMol ← 40 nanoMol → 160 nanoMol
Tolerated ÷4 Normal *4 tolerated
pH (8) (7.4) (6.8)

Lethal ← 6.8 ← (7.35 – 7.45) → 8 → lethal
getting acidosis Normal pH getting alkalosis

pH < 6.8 OR > 8 : Deadly

Renal Control of Acid - Base Balance

For an average 80 kg body weight male, there are 80 mEq/day of nonvolatile acids are being produced. The kidney can’t secrete 80 mM of H^+ in its free form (in the urine). We can give up 80 mM of HCO_3^- to convert H+ to CO_2. Automatically, we need to replace the lost 80 mM of HCO_3 …thanks to the kidneys. 40 mM from glutamine (NH_4^+) and 40 mM as buffers and mainly $PO_4^=$ (Titratable acids).

Kidneys must not loose HCO_3^- in the urine, a task which is more important than secreting the nonvolatile acids. 4320 mEq/day of HCO_3^- are filtered per day (this is the filtered load). Therefore 4320 mEq/day of H^+ must be secreted to reabsorb the filtered HCO_3^-. An additional of 80 mEq/day of H^+ must be secreted to rid the body from the nonvolatile acids. A total 4400 mEq/day H^+.

- The pH = -log [H^+]…p stands for “-log” or just the power of “H”
- pCa^{++}=-log [Ca^{++}] it is rarely used
- So at normal extracellular H^+ concentration (40nM/L)
- -Log 40 nM= log $4*10^{-8}$ = log 4 + log 10^{-8} = 7.4
- our arterial blood pH is equal to 7.4 (7.35-7.45)
- Venous blood and interstitial fluid pH = 7.35 due to excess CO_2
- Intracellular pH ranges from 6.0 – 7.4 (In general 7.0 is the average).
- Urine pH ranges from 4.5 – 8. usually, it is acidic (5.5)
- (Note : Hypoxia decreases intracellular pH due to acid accumulation)

- From your chemistry course:

- An acid is a proton donor, while a base is a proton acceptor.
- Strong acids or bases dissociate (ionize) completely in solution such as HCl and NaOH.
- Weak acids ionizes only partially in a solution: such as H_2CO_3.
- Weak bases also partially ionize such as $NaHCO_3^-$ or HPO_4^{-2} .

(Note : Hemoglobin and other body proteins are of the most important body bases).

Most of our body acids and bases are weak acids and weak bases

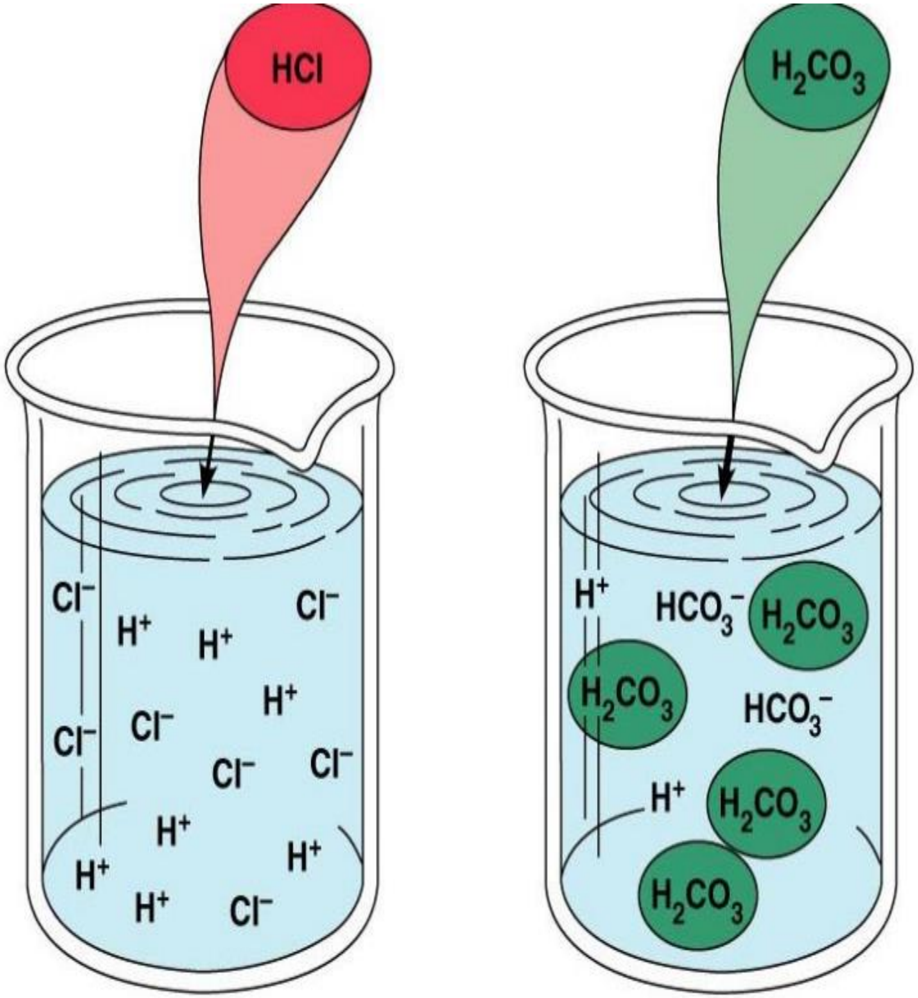
Defense against changes in hydrogen ion concentration:

Our body is at a constant threat of becoming acidic, so how does it deal with these acids (1 mMole/kg BW)?

1. First Line of defense: Chemical acid-base buffer system (Very Fast)
2. Second Line: The respiratory center (removes or retain CO_2: intermediate speed, few minutes to react and few hours to give the full response)
3. Third Line: The kidneys (the most powerful regulatory system), a slow system that takes a few hours to start working and 3-5 days to reach full response.

So, in acute acidosis, the kidney might not be able help.

Strong and weak acid



Acid-Base Balance

Small changes in pH can produce major disturbances and have dramatic effects on normal cell function

1. **Influences enzyme activity.**

   Most enzymes function only with narrow pH ranges

   Acidosis → suppression of CNS → coma → death.

   alkalosis → convulsions of the respiratory muscle → death.

2. **Affects hormones.**

3. **Affects electrolytes (Na^{+}, K^{+}, Cl^{-}, Ca^{++}).**

4. **Changes in excitability of nerve and muscle cells.**

Example: Influences on K^+ levels

- When reabsorbing Na^+ from the filtrate of the renal tubules K^+ or H^+ is secreted (exchanged).
- Normally K^+ is secreted in much greater amounts than H^+.
- If H^+ concentrations are high (acidosis) then H^+ is secreted in greater amounts.
- This leaves less K^+ than usual excreted.
- The resultant **K^+ retention** can affect cardiac function and other systems.

Acids can be volatile or Non-volatile.

Volatile Acids:

The volatile acid are in the form of H_2CO_3. Normally we exhale 300 L of CO_2/D, which corresponds to daily production of 10 M H^+ **(10 molar is 10000mM which is huge amounts), but usually it does not cause problems because it is always getting engaged in this pathway:**

$$H_2O + CO_2 \rightleftarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$$

CA: carbonic anhydrase enzyme fits here.

- * If more H+ is produced in your body: reaction shift to left CO_2 will be eliminated by the lungs.

Therefore, acidosis is corrected.

*** If H+ is less, rxn shifts to right; respiration is depressed**

More CO_2, is retained → forming H^+

Note: "CO_2 is considered as masked H^+"

Our body has tendency towards acidosis rather than towards alkalosis.

- Acids taken with foods.
- Acids produced by metabolism of lipids, carbohydrates and proteins.
- Cellular metabolism produces CO_2.

$$CO_2 + H_20 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Non-volatile acids (Fixed Acids):

-Phosphoric acid from oxidation of phosphoproteins, phospholipids, and nucleic acid.

-Sulphoric acid → oxidation of methionine and cysteine

-Others: such as lactic, pyrovic, beta-OH butyric acid, acetoacetic acids, and Krebs cycle acids.

All these acids are not in the form of CO_2 (nonvolatile)

Our body produces around 1 mmol/kg /day of these fixed acids

So, 80 mmol /day are being produced. *The body produces large amounts of acids but body fluids remain slightly alkaline.*

80 mmol/day when distributed over the 14 L of ECF; each L gets 5 mmol (correspond to pH less than 3): this is very low pH (incompatible with life)….we must get rid of these 80 mM/D

- Why not just secreting the 80 mMole of H^+ in the urine in its free form???

Bcs: Minimum pH of urine = 4.5. this correspond to less than 0.03 mM

Other option: add 80 mMole of HCO_3^- from the ECF and convert H+ to CO2, and let the lung take care of it.

$CO2+ H2O \leftrightarrow H2CO3 \leftrightarrow 80\ mM\ H^+ + 80\ mM\ HCO_3^-$

The problem has been solved, and we get rid of these acids.

The Price we pay: 80 mMole of HCO3-. By the end of the day we are deficient of 80 mM HCO3

We need a Bicarbonate Bank (continuous formation of HCO3…do we have such a bank?)

$[HCO_3^-]$ = 24 mmol /L…this is its conc.

Extracellular fluid volume is only 14 lit

How much bicarb present in 14L of ECF

24 * 14 = 336 mmol /L

→ this amount is just enough for (4-5 days)

Conclusion: Each day you need to replace the lost 80 mmol.

•So, an important function of the kidney is to make new 80 mM bicarbonate to replace the lost HCO_3^-

In AKI: Acidosis. Kidneys fail to produce new bicarbonate.

Again: Why not just excreting H^+ in the urine in its free .. ?...lets see…can we do that?

The distal part of the nephron can acidify the urine to a maximum of 4.5. This mean the H+ pump in luminal membrane can make a concentration gradient only 900 times more in the lumen than inside the cell. This correspond to luminal pH of 4.5 or [H+] of 0.03 mM. so this not going to work. To excrete this as free H^+ would require:

$$\frac{80\ \text{mmol}}{.03\text{mmol/L}} \quad > \ 2000\ \text{L of urine per day !!!}$$

:

Mechanisms of Hydrogen Ion Regulation

Regulation maintained by:

1. Body fluid chemical buffers
   - bicarbonate - ammonia
   - proteins - phosphate

2. Lungs (eliminates CO_2)

↑ $[H^+]$ ⟶ ↑ ventilation ⟶ CO_2 loss ↑

3. Kidneys

(powerful)

- eliminates non-volatile acids
- secretes H^+ - reabsorbs HCO_3^-
- generates new HCO_3^-

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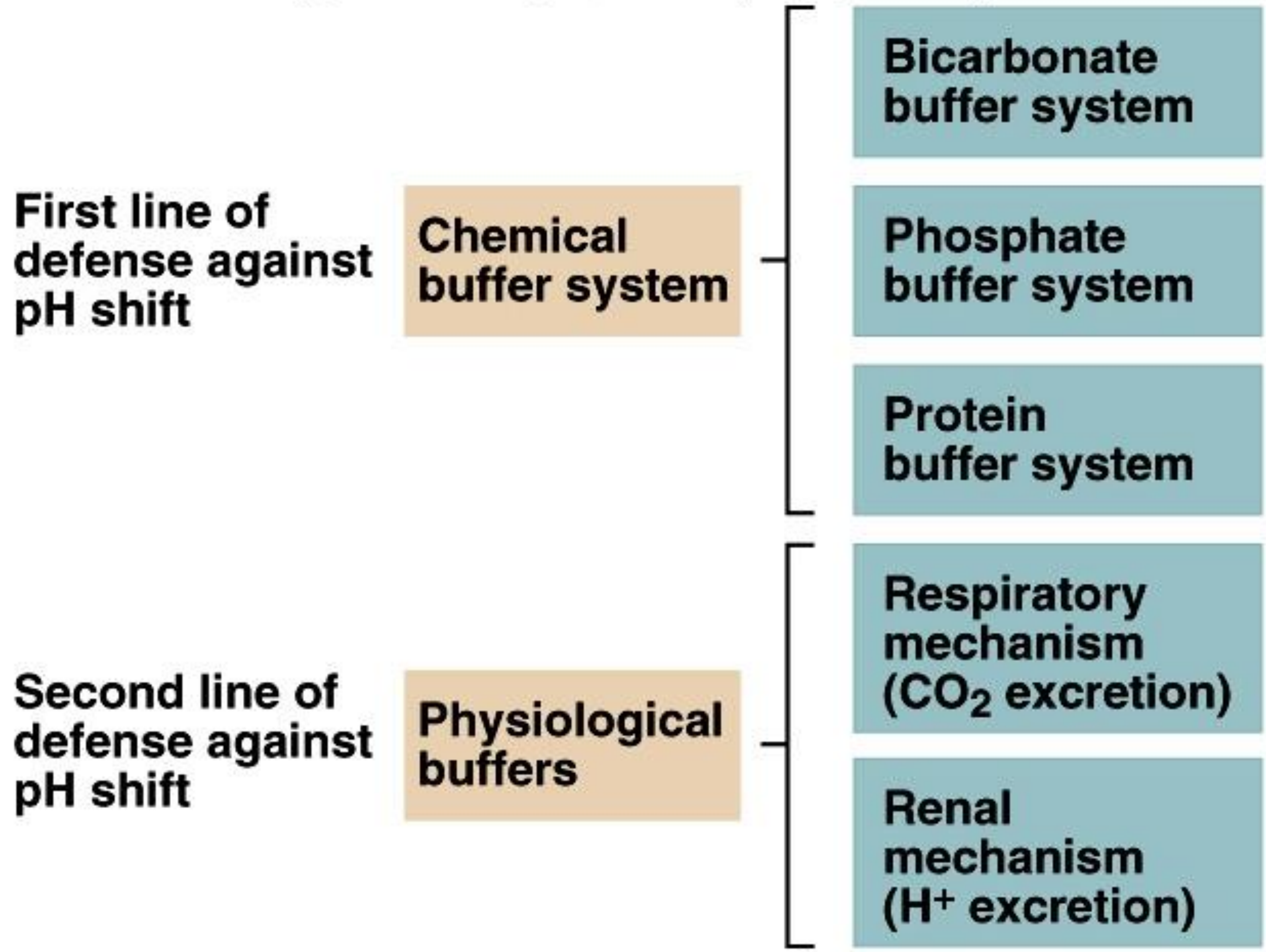


First line of defense against pH shift

Chemical buffer system

- Bicarbonate buffer system
- Phosphate buffer system
- Protein buffer system

Second line of defense against pH shift

Physiological buffers

- Respiratory mechanism (CO_2 excretion)
- Renal mechanism (H^+ excretion)

Rates of correction

- Chemical buffers function almost immediately (fraction of a second to minutes).
- Respiratory mechanisms take minutes to hours.
- Renal mechanisms may take hours to days before start working and giving full response..

The Buffer System:

Buffers React within a fraction of a second.

A buffer prevents a change in pH when H^+ is added or removed from a solution within certain limits (All chemicals can buffer up to 1000 mM H^+ before there is any significant shift in pH).

- **Buffer is a substance that releases or binds H^+ reversibly to resist marked pH changes and keep it compatible with life.** Buffers don't eliminate or add H^+ but keep it tied up until balance can be reached.

- **Principle body buffers:**

a) Bicarbonate/carbonic acid buffer system (most important system in the ECF. can be renewed**)**

b) Phosphate buffer system (HPO_4^{-2}, $H2PO_4^-$):most important intracelullar and intra-tubular

c) Proteins (important intracellular buffers, ex: Hemoglobin)

Buffer Systems in the Body

1. **Bicarbonate:** most important ECF buffer

$H_2O + CO_2 \longleftrightarrow H_2CO_3 \qquad H^+ \longleftrightarrow HCO_3^-$

2. **Phosphate:** important ICF and renal tubular buffer

$HPO_4^{--} + H^+ \longleftrightarrow H_2PO_4^-$

3. **Ammonia:** important renal tubular buffer

$NH_3 + H^+ \longleftrightarrow NH_4^+$

4. **Proteins:** important ICF and ECF buffers

$H^+ + Hb \longleftrightarrow HbH$

It is the largest buffer store in our body

Albumins and globulins, such as Hb

Bicarbonate buffer system:

Consists of a weak acid (H_2CO_3) and a bicarbonate salt, predominantly $NaHCO_3$ which ionizes completely into Na^+ and HCO_3^-

Again to the same equation:

$$CO_2 + H_2O \overset{CA}{\longleftrightarrow} H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

To calculate the pH of this buffer system, we use the ***Henderson-Hesselbalch Equation***:

$$pH = pK + \log [Salt/Acid]$$

The pK for the bicarbonate/carbonic acid is pK= 6.1

The salt is the bicarbonate ion, and the acid is CO_2

CO_2 is measured by its partial pressure (PCO_2)

To convert from mmHg to mM :multiply the mmHg by 0.03

Arterial PCO_2 = 40mm Hg correspond to 1.2 mMole (40 * 0.03)

$pH = 6.1 + \log \{HCO_3^-/[0.03 * PCO_2]\}$

Substituting the actual concentrations would give us:

$pH = 6.1 + \log [24/1.2] = 6.1 + \log 20$

$= 6.1 + 1.3$

$= 7.4$

We can calculate the pH of any buffer by using the above equation if we know the pK and the concentration of the buffer in its salt and acid forms.

Ex: pK for phosphate buffer = 6.8

$pH = 6.8 + \log [1.0\text{mmol} / 0.25]$

$= 6.8 + 0.6$

$= 7.4$

Ex: ammonia/ammonium ion system (pK = 9.2):

(Note: its not one of the buffer systems mentioned above)

$pH = 9.2 + \log [NH_3 / NH_4^+]$

the result is also 7.4

→ <u>Isohydric principle</u>:

States that all buffers in a common solution are in equilibrium with the same hydrogen ion concentration

Therefore, whenever there is a change in the ECF H^+ concentration, the balance of all other buffer systems changes at the same time.

→ Changing the balance of one buffer system changes the others because the systems actually buffer each other.

•To see how this buffer system works, if we add HCl (strong acid) to the solution, the following reaction takes place to change the strong acid (HCl) into a weak acid (H_2CO_3):

$$HCl + NaHCO_3 \longrightarrow NaCl + H_2CO_3$$

While if a strong base was added as NaOH, the buffer system changes it into a weak base ($NaHCO_3$) by the following reaction:

$$NaOH + H_2CO_3 \longrightarrow NaHCO_3 + H_2O$$

Back to Henderson-Hesselbalch Equation, to explain what exactly is “pK” (taking the bicarbonate buffer as an example): skip this slide if you wish

$$H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

K' (Dissociation constant) = $[H^+]\,[HCO_3^-] \,/\, [H_2CO_3]$
From the equation, $[H^+] = K' * ([H_2CO_3] \,/\, [HCO_3^-])$

However, the CO_2 dissolved in the blood is directly proportional to the amount of undissociated H_2CO_3
So, the equation can be rewritten as:

$$H^+ = K * (0.03 * PCO_2 \,/\, HCO_3^-)$$

Now, by taking – log of both sides, the equation will be:
$pH = pK + \log (HCO_3^- \,/\, 0.03 * Pco_2)$
log1 = zero, so when the salt form (HCO_3^-), equals the concentration of the acid form (CO_2), then the pH = pK.

- **In other words,**
  <u>pK of any buffer is the pH of a solution when the salt form is equal</u>

Bicarbonate Buffer System

$$H_2O + CO_2 \xleftrightarrow{\text{carbonic anhydrase}} H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

$$pH = pK + \log \frac{HCO_3^-}{\alpha * PCO_2}$$

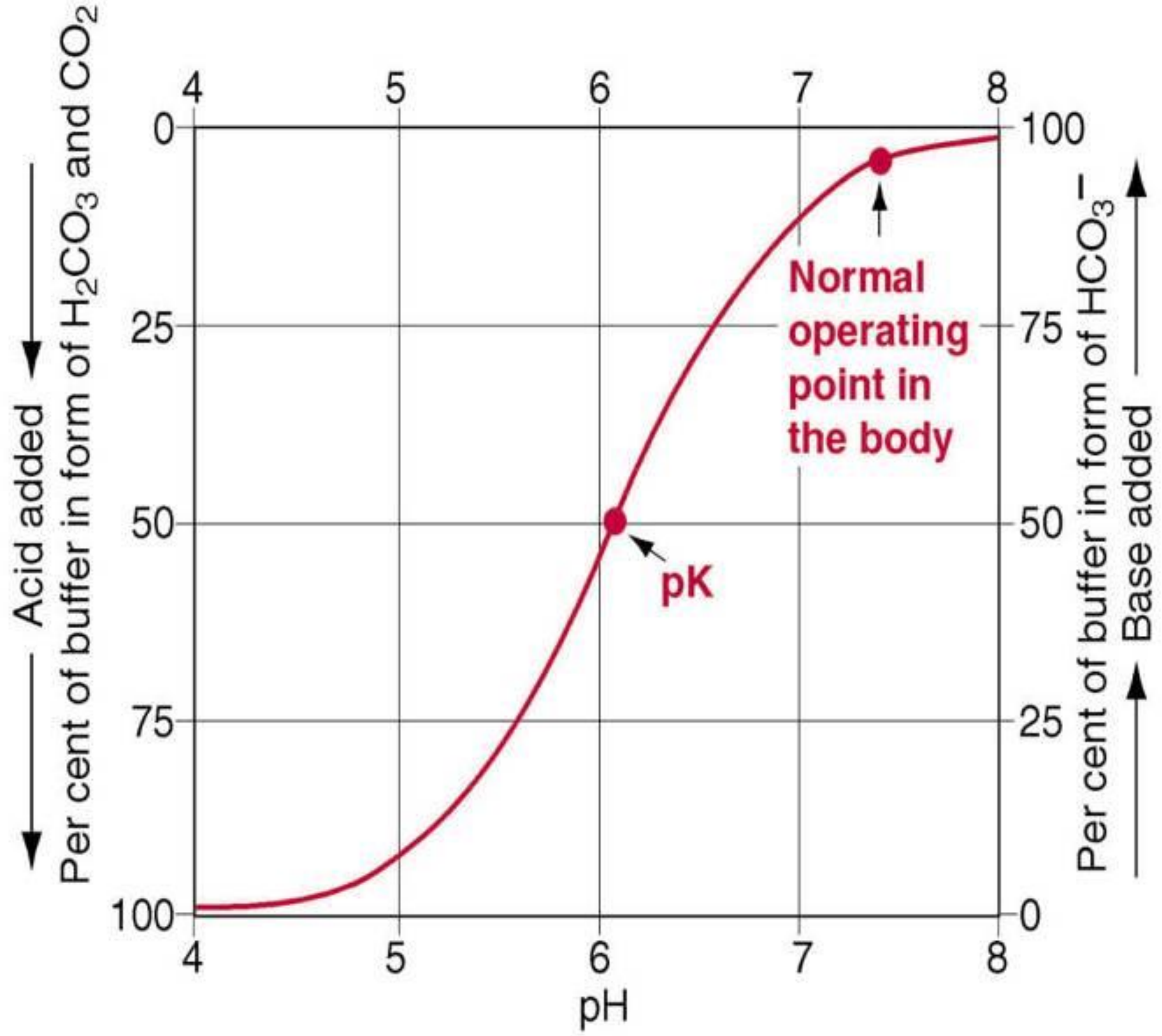
$\alpha = 0.03$

$pK = 6.1$

Effectiveness of buffer system depends on:

- concentration of reactants
- pK of system and pH of body fluids

The figure below shows the titration curve for the bicarbonate buffer system:



- when the CO_2 percentage = 50% and the HCO_3^- =50% in solution we get a pH=pK = 6.1.

- The buffer is most effective within 1.0 pH unit of the pK of the buffer (i.e the linear portion of the previous curve).

So, the bicarbonate buffer is most effective at pH range 5.1 – 7.1

- At normal body pH (7.4), the ratio of the basic form is 20 times more than the acid form.

We worry about acids in our body, and increasing H^+ will shift the curve closer to the linear portion (5.1 – 7.1), so it can work effectively.

- <u>Criteria to determine the buffering power and capacity of a system:</u>

  1. The absolute / total concentration.
  2. The relative concentration (pK of the system relative to pH of the surrounding).
  3. The renewal tendency of the buffer.
     → which is considered as the most important factor

- By applying these criteria to the bicarbonate buffer system (the most important extracellular buffer), we find that:

- It is a weak buffer in terms of pK (because plasma pH is 7.4, which is outside its most effective area) and in terms of concentration, it is an intermediate buffer having a concentration of 24mEq/L.

- The bicarbonate buffer has a good renewal capacity which makes it the most important extracellular buffer.

- Bicarbonate concentration is regulated by the kidney.
And PCO_2 is controlled by the rate of respiration.

Bicarbonate Buffer System

Is the most important buffer in extracellular fluid even though the concentration of the components are low and pK of the system is 6.1, which is not very close to normal extracellular fluid pH (7.4).

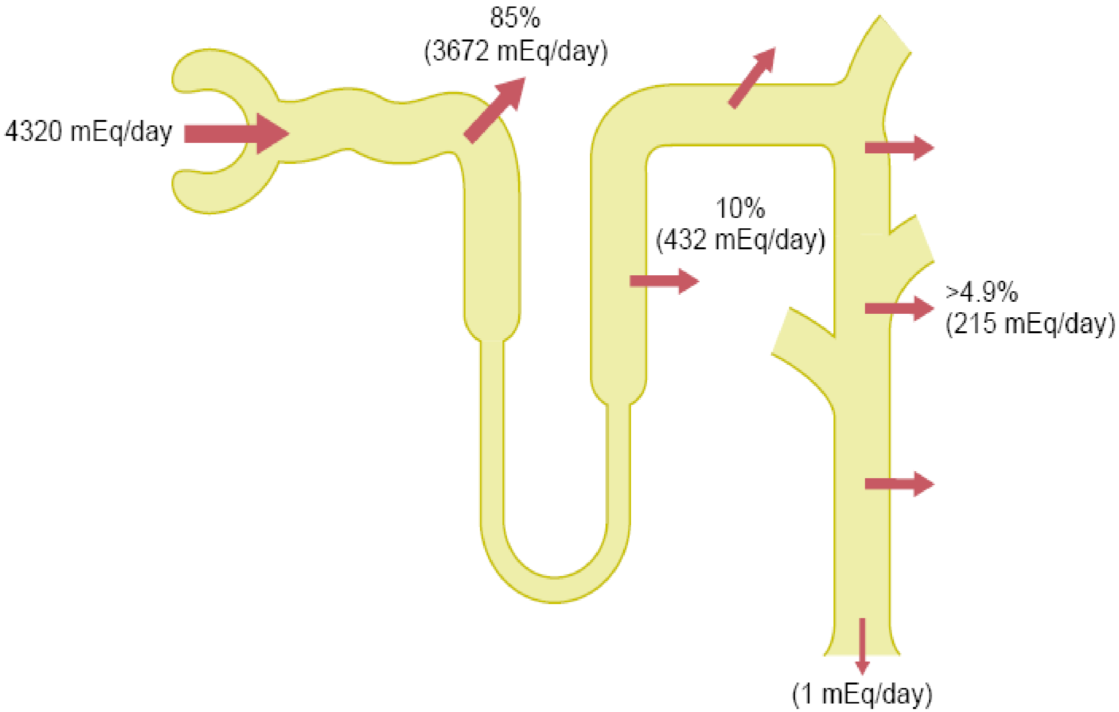
Reason: the components of the system (CO_2 and HCO_3^-) are closely regulated by the lungs and the kidneys

Renal Regulation

Bicarbonate

H^+ Secretion and HCO_3^- reabsorption occur in all tubules (mainly proximal, 85%) except the descending and ascending thin limbs of the loop of Henle.

- Kidneys filtrate 4320 mEq/day bicarbonate.
- HCO_3^- completely reabsorbed under normal conditions.
- Equal amount of H^+ is secreted.



The Phosphate buffer system…you can skip this slide too.

In our body we have 700 g of phosphorus. 85% in the bone and teeth, 15% in soft tissue, and 0.1% in ECF.

Filtered load/D= 7000 mg ≈ 200-250 mM/D

- Proximal Tubule reabsorbs 80% of the filtered phosphate.
- Distal tubule reabsorbs 10%
- The remaining 10% are execrated.
- In mM concentration: The filtered load = 1.2mM/l * 180L/D= 216 mM/D
- 90% reabsorbed , and only 10% (22 mM) excreted.
- Its concentration in ECF ≅ 1.2-1.4 mM/L (only 8% of the HCO_3 concentration).
- The free PO_4 which can be filtered is around 1.2-1.4 mmol/l (90% of the total ECF PO4). The rest is bound to protein and lipids and is not filterable (10%).
- Forms: NaH_2PO_4 (monosodium phosphate) and $Na_2HPO4=$ (disodium phosphate).
- pK = 6.8 close to 7.4. **Its salt/acid ratio ($HPO_4^=$: $H_2PO_4^=$) is only 4,** then it is not proper to
- protect the body against acids as in **HCO3-** (20 times more).
- Its level in the blood rises in ARF.
- \- Its total buffering power is less than for HCO3- in ECF.
- \- However, it is important in tubular fluid (also inside the cells) of the kidneys because:
- 1. pH of tubular fluids is closer to phosphate pK.
- 2. Their concentration ↑ because of H2O reabsorption (>99% of H_2O is reabsorbed but only 90% of phosphate. Thus, 10-times concentrated).
- The average diet contains 1000-1600 mg PO_4 per day. 90% of the ingested PO4 is excreted from the kidney under the control of PTH. Normally serum Ca^{++} X PO4 is maintained around 30-40 (mg/dl).
- Daily urine excretion of PO4 is 25 mM/D. 80% in basic form (20 mM as its salt form **HPO4=**) which means 20 mM HCO3- gain

The Phosphate Buffer System:

Note: PTH inhibits phosphate reabsorption by affecting T max.

- Its concentration in plasma is low but its pK is equal to 6.8, which is close to intracellular pH (7.0) .
- We get the phosphate mostly from food and its plasma concentration is under the control of the kidney.
- There is a Tmax for phosphate reabsorption. Phosphate is 90% reabsorbed and 10% excreted.
- Its filtration load is equal to 180L/day * (1-1.5mmol/L) = 200-250 mmol/day
- The phosphate is more concentrated intracellular and its pK is closer to intracellular pH (7.0). → phosphate is a good buffer intracellular and intratubular, but not an important extracellular buffer.

The protein Buffer System:

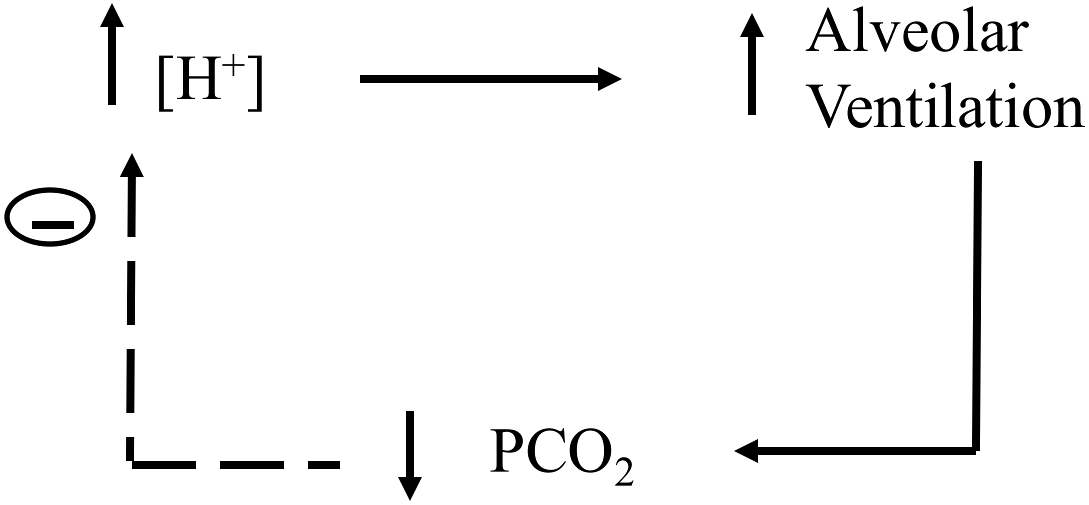
- An important intracellular buffer
- Its plasma concentration is negligible.
- Proteins have an imidazole group that binds to H^+ reversibly. The pK is around 7, (close to 7.4), so almost the same as intracellular pH.
- Intracellular proteins as hemoglobin have other functions but they work secondarily as buffers.
- Their concentrations cannot be controlled and they are not renewed.

→ the chemical buffers can buffer up to 1000 mmol of H^+.
→ 70% of the buffering is due to proteins.

Since H^+ ion can't penetrate the cell membrane easily, the proteins can't really work acutely, but in chronic conditions they help.

(The blood buffering capacity is due to: 55% HCO_3^-, 35% Hb and 5% HPO_4^-)

Respiratory Regulation of Acid-Base Balance



↑ $[H^+]$

↑ Alveolar Ventilation

↓ PCO_2

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

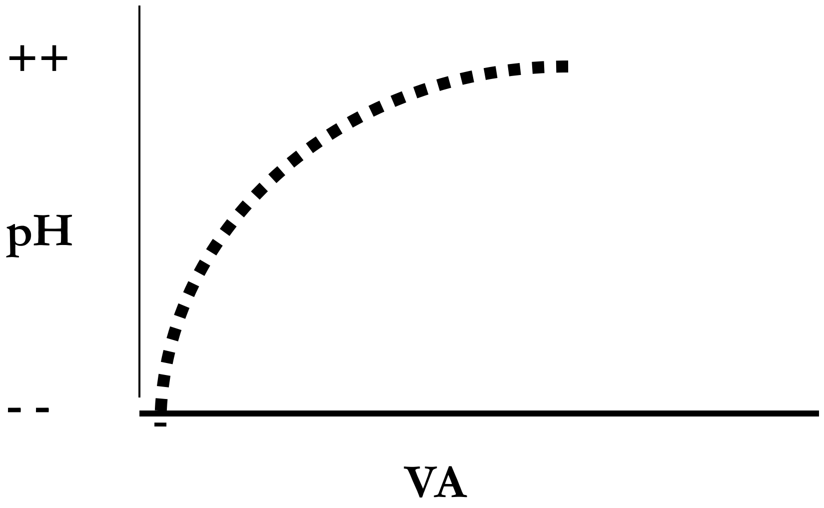
Feedback Gain = 1.0 to 3.0
(corrects 50 to 75 %)

Respiratory System:

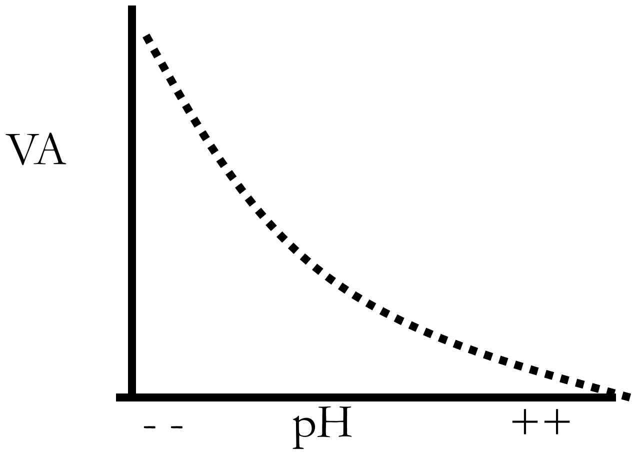
As you remember from your respiratory lectures; the effect of increasing alveolar ventilation → alkalosis by reducing P_aCO_2 as seen in the curve below.

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.

The buffering capacity of the respiratory system is 1-2 times the total buffering power of the chemicals of ECF.



This next figure shows us the effect of blood pH on alveolar ventilation:



$$pH = pK + \log\left[\frac{HCO_3-}{0.03 * PCO_2}\right]$$

Respiratory Regulation

Respiratory System controls the pH by both the rate and depth of respiration to increase or decrease the release of CO_2.

- Hyperventilation -- blow off CO_2
- Hypoventilation -- retain CO_2

Renal Regulation of Acid-Base Balance

In Summary

- Kidneys eliminate non-volatile acids (H_2SO_4, H_3PO_4) (~ 80 mmol/day)
- Filtration of HCO_3^- (~ 4320 mmol/day)
- Secretion of H^+ (~ 4400 mmol/day…this is not net secretion)
- Reabsorption of HCO_3^- (~ 4319 mmol/day)
- Production of new HCO_3^- (~ 80 mmol/day)
- Excretion of HCO_3^- (1 mmol/day)

Kidneys conserve HCO_3^- and excrete acidic or basic urine depending on body needs

Renal Regulation of Acid-Base Balance

I. Elimination of non-volatile acids (H_2SO_4, H_3PO_4)

II. Secretion of H^+

III. Reabsorption of HCO_3^-

IV. Production of new HCO_3^-

The Renal control of the Acid-Base Balance:

Reabsorption of filtered HCO_3^-

•HCO_3^- is very precious: we can't really afford losing it in urine.

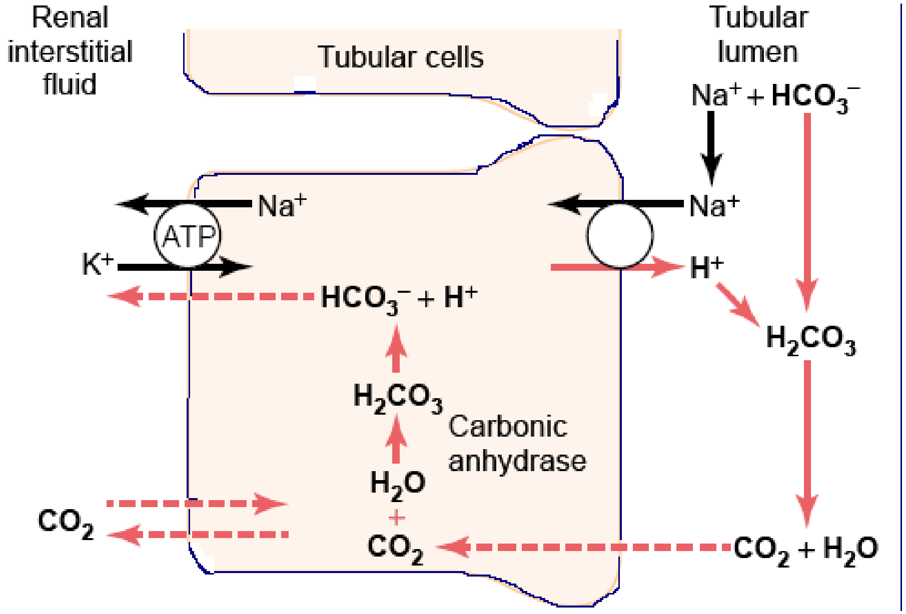
(Full reabsorption, primarily in the proximal tubules) 80-90% of the HCO_3^- reabsorption and thus H^+ secretion ocurs at proximal tubule, 10% in thick ascending, 4.9 % in collecting duct and distal tubule, and less than 0.1% is excreted.

- The filtered load of the bicarbonate is equal to
  - 180L/day * 24mEq/L = 4320 mEq/day.

- The clearance is of HCO_3^- is negative→

•Quantity aspect: The reabsorption is more important than the production since its amount (4320) is greater.

Mechanism of HCO_3^- Reabsorption and Na^+ - H^+ Exchange In Proximal Tubule and Thick Loop of Henle and Early distal Tubule



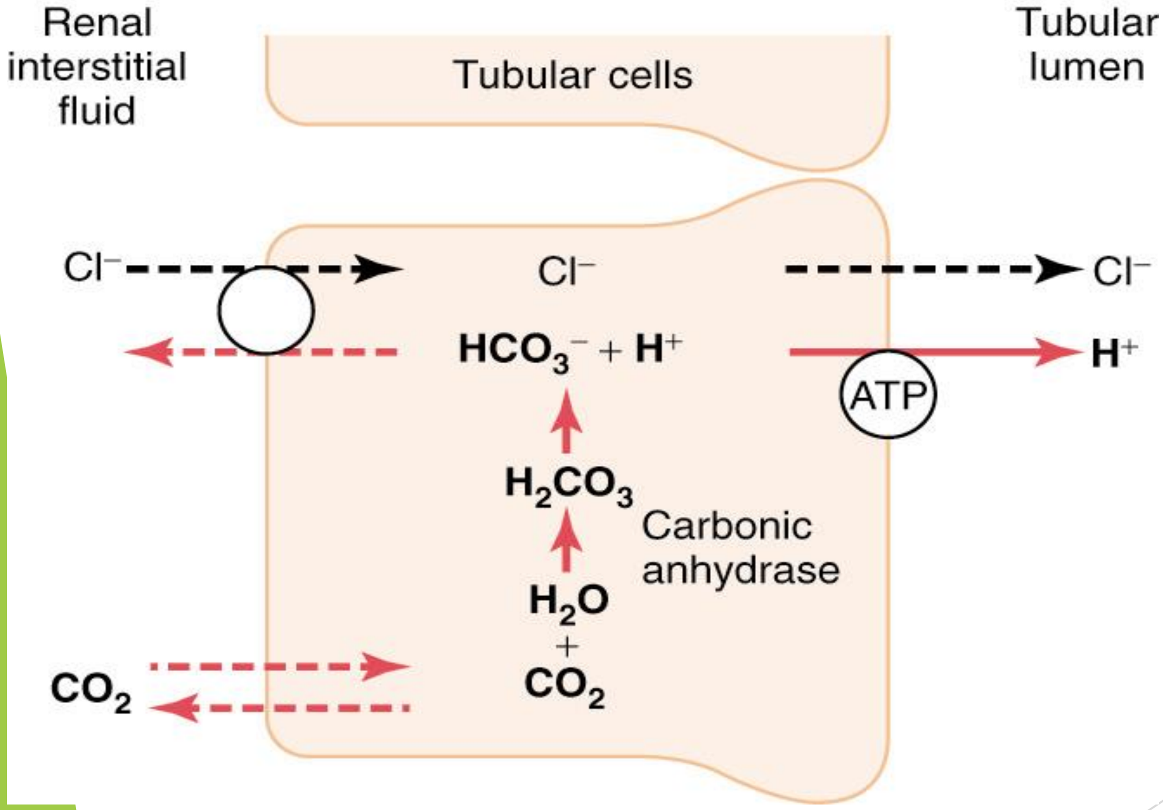
(1) Active secretion of H^+ ions into the renal tubule.

2. Tubular reabsorption of HCO3- by combination with H^+ ions to form carbonic acid, which dissociates to form carbon dioxide and water.

3) Sodium ion reabsorption in exchange for hydrogen ions secreted, by *secondary active hydrogen counter-transport.*

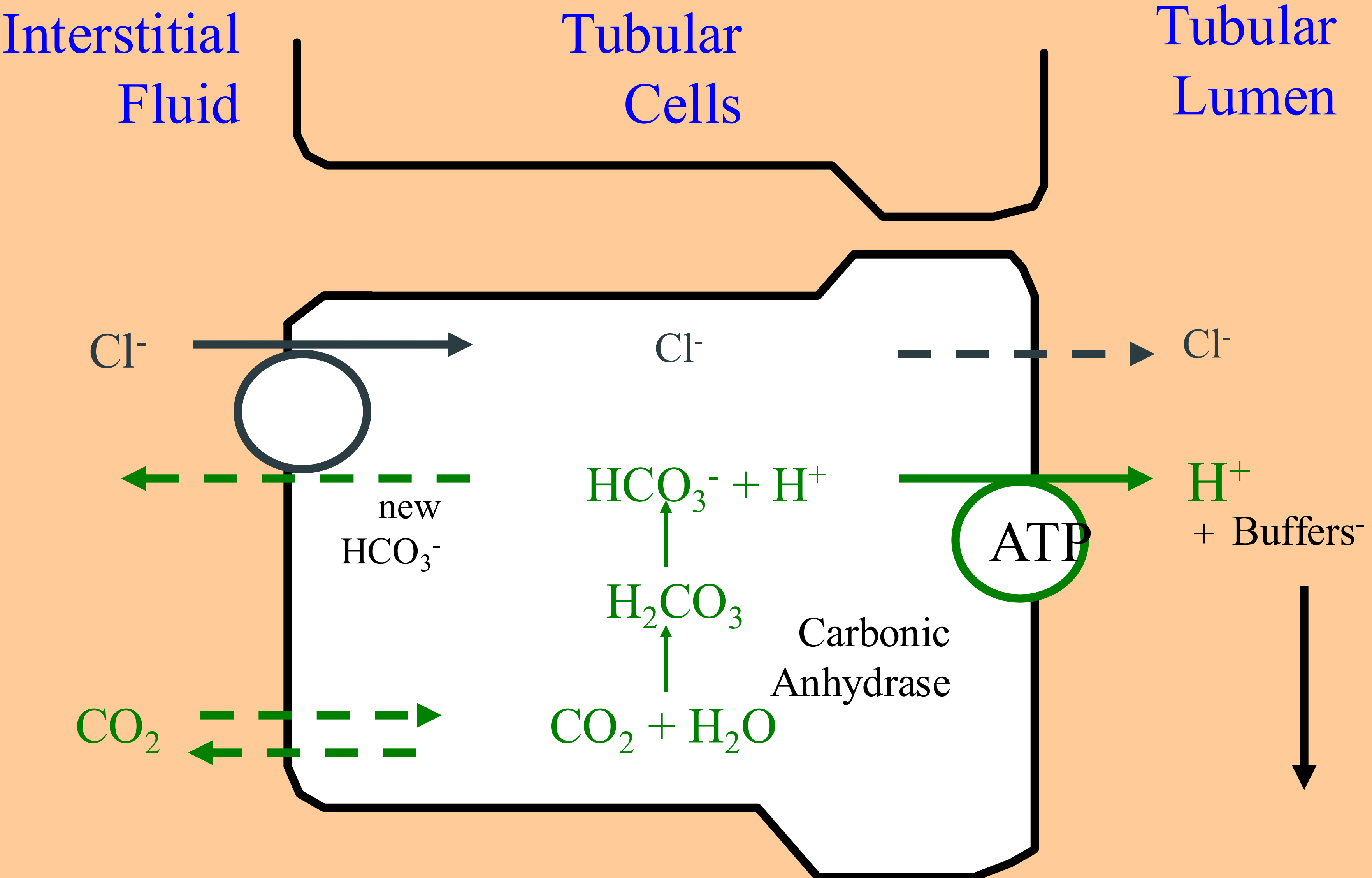
HCO_3^- Reabsorption and H^+ Secretion in Intercalated Cells of Late Distal and Collecting Tubules

H+ secreted by ***primary active transport*** in the intercalated cells of the late distal tubule and the collecting tubules via a H^+ATPase pump.

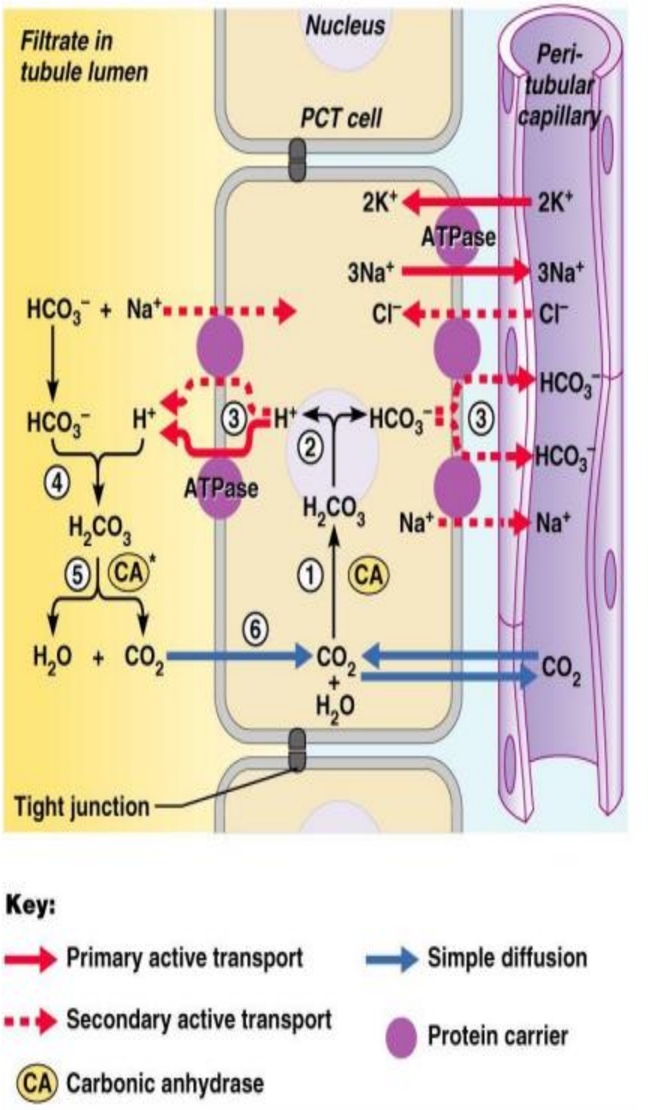


- H+ secretion represents 5% in this part of the tubule.
- H+ secretion in this part of the tubule is important in forming a maximally acidic urine.

In acidosis all HCO_3^- is titrated and excess H^+ in tubule is buffered



- Carbonic acid formed in filtrate dissociates to release carbon dioxide and water
- Carbon dioxide then diffuses into tubule cells, where it acts to trigger further hydrogen ion secretion



Bicarbonate is freely filtered.

Since it is a charged particle, it cannot cross the apical side and cannot be absorbed as it is….it must be converted to CO2.

Inside the cell, the CO_2 + H_2O unite by carbonic anhydrase to form H_2CO_3 which dissociates to form H^+ + HCO_3^-

There is a bicarbonate carrier, at the basolateral side

H^+ is actively secreted in the tubule, it binds HCO_3^- in the tubular fluid forming CO_2 which diffuses inside the cell.

Sources of Intracellular CO_2:

1. Cellular metabolism
2. Tubular fluid
3. Interstitium

- 4320 molecules of bicarbonate can be reabsorbed by only one proton (H^+), there is no net secretion of hydrogen ions so far. (H+ recycle again and again)

(bcs NET secretion of H^+ means bicarbonate gain)

\- After complete HCO_3^- reabsorption: any further H^+ secretion is net H+ secretion resulting in:

  - HCO_3^- gain
  - Shift of TF pH below 7.4

- The majority of H^+ secretion occurs in the proximal tubule by Na^+ countertransport mechanism and can cause a concentration difference across the cell membrane up to 5-6 times only: but a tremendous amount of H+ is secreted (95%)….pH of TF at this site is around 6.5 only

•Primary Active Secretion Of H+ in Intercalated Cells (brown cells) of Late Distal Tubules & Collecting Ducts

- In the collecting ducts, we have H^+ pump, and the rest of H^+ (5%) is actively secreted and it can make the concentration of H^+ 900-times more than the ultrafiltrate . This corresponds to pH =4.5 (maximum pH of the urine).

	Reabsorption of **HCO_3^-**	Gaining of **HCO_3^-**
Proximal parts	**80-85%**	**55 mM**
Distal parts	**15-20%**	**15 mM**

HCO_3^- Gain

→ After absorbing of the entire filtered bicarb, we still need additional 80mmol/day. This amount is supplied by the kidneys.

The presence of TF buffers allow us to secrete H+ and make new HCO_3^-: Main TF buffers are phosphate $HPO_4^=$ which binds H^+ to form $H_2PO_4^-$ → → →

Buffer + H^+ ↔ H-buffer.

Do we have 80 mMole of phosphate to be excreted in the urine? If yes, then we solved the problem by gaining the 80 mMole/D of HCO_3^- → → → Now, we should not worry about the 80 mMole of fixed acids anymore.

Unfortunately, we excrete only 20-30 mMole of phosphate Therefore, we still need additional 50-60 mMole of new HCO_3^- through other sources→ This source is provided by the $NH3/NH_4^+$ system.

- Most diuretics except carbonic anhydrase inhibitors induce alkalosis be washing H^+ from urine, maintaining H^+ gradient which lead to continuous secretion and removal of H^+.
- Carbonic anhydrase inhibitors: inhibit H^+ secretion and thus decrease bicarb production → → → acidosis

Ammonium production

Don't confuse ammonium NH_4^+ with ammonia NH_3 ,. ammonium is an ion; ammonia is not).

Glutamine from blood enter the proximal cells where it is converted to glutamate and then to alpha keto-glutamate which finally forms 2 NH_4^+ +$2HCO_3^-$

- Ammonia is secreted into the lumen by counter-transport mechanism in exchange with sodium in proximal tubules, thick ascending loop of Henley and distal tubules.
- In collecting tubules:

H^+ is secreted into the lumen where it combines with NH_3(ammonia) to form NH_4^+ (ammonium).

→ Collecting tubules membrane is much less permeable for ammonium than ammonia, thus NH_4^+ is trapped in the lumen , this is called → ammonia trapping.

- Ammonium production can be induced unlike phosphate buffer system which is fixed and cannot be induced.
- Whenever a hydrogen ion secreted into the tubular lumen it combines with a buffer other than bicarbonate, the net effect is the addition of new bicarbonate ion to the blood.

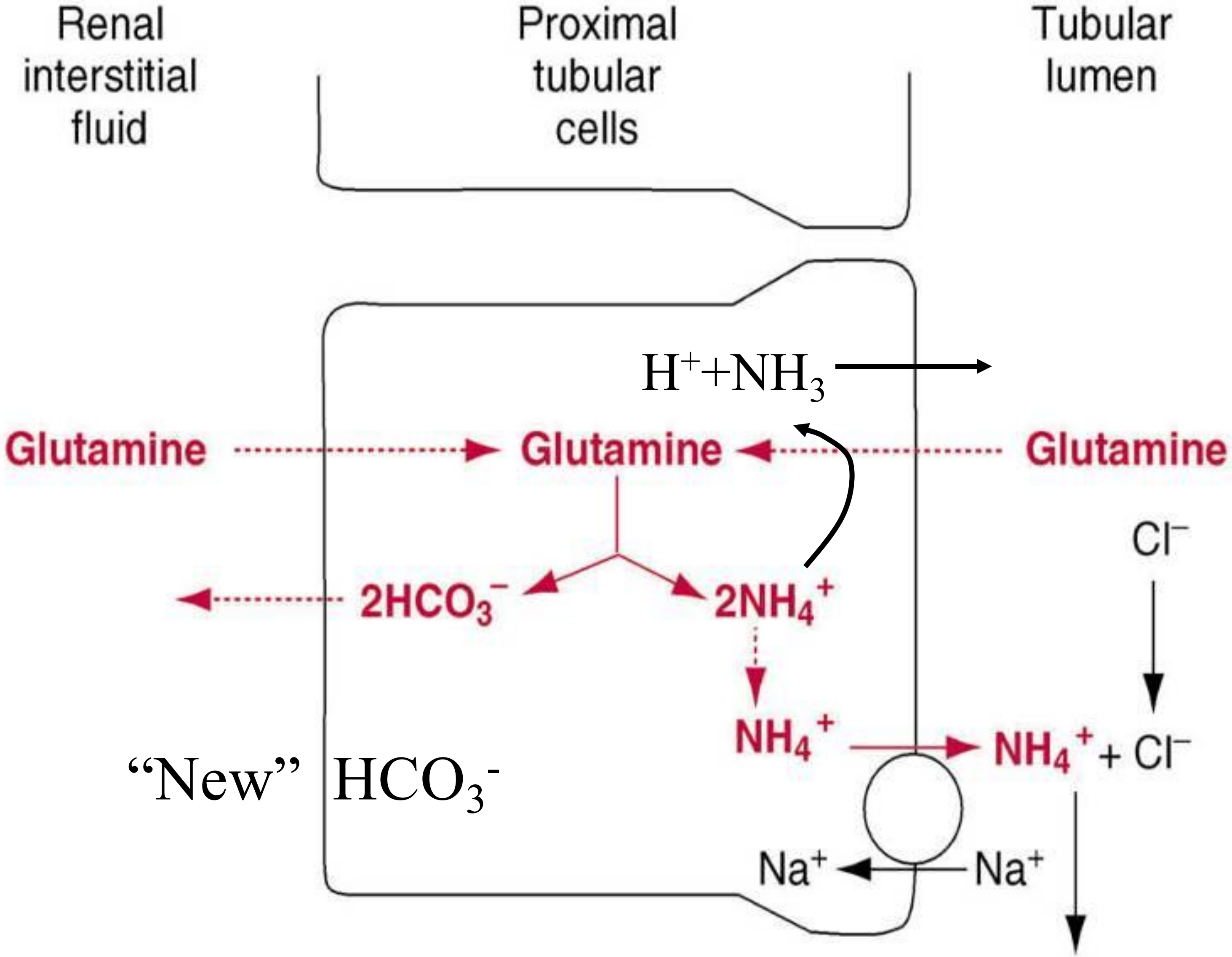
- Low blood pH induces the enzyme: glutaminase which is going to split glutamine to HCO_3^- and NH_4^+, so the urine will be full of ammonium which is secreted in the from of NH_4Cl

-"The kidney can make up to 500 mMole of NH_4^+/Day"

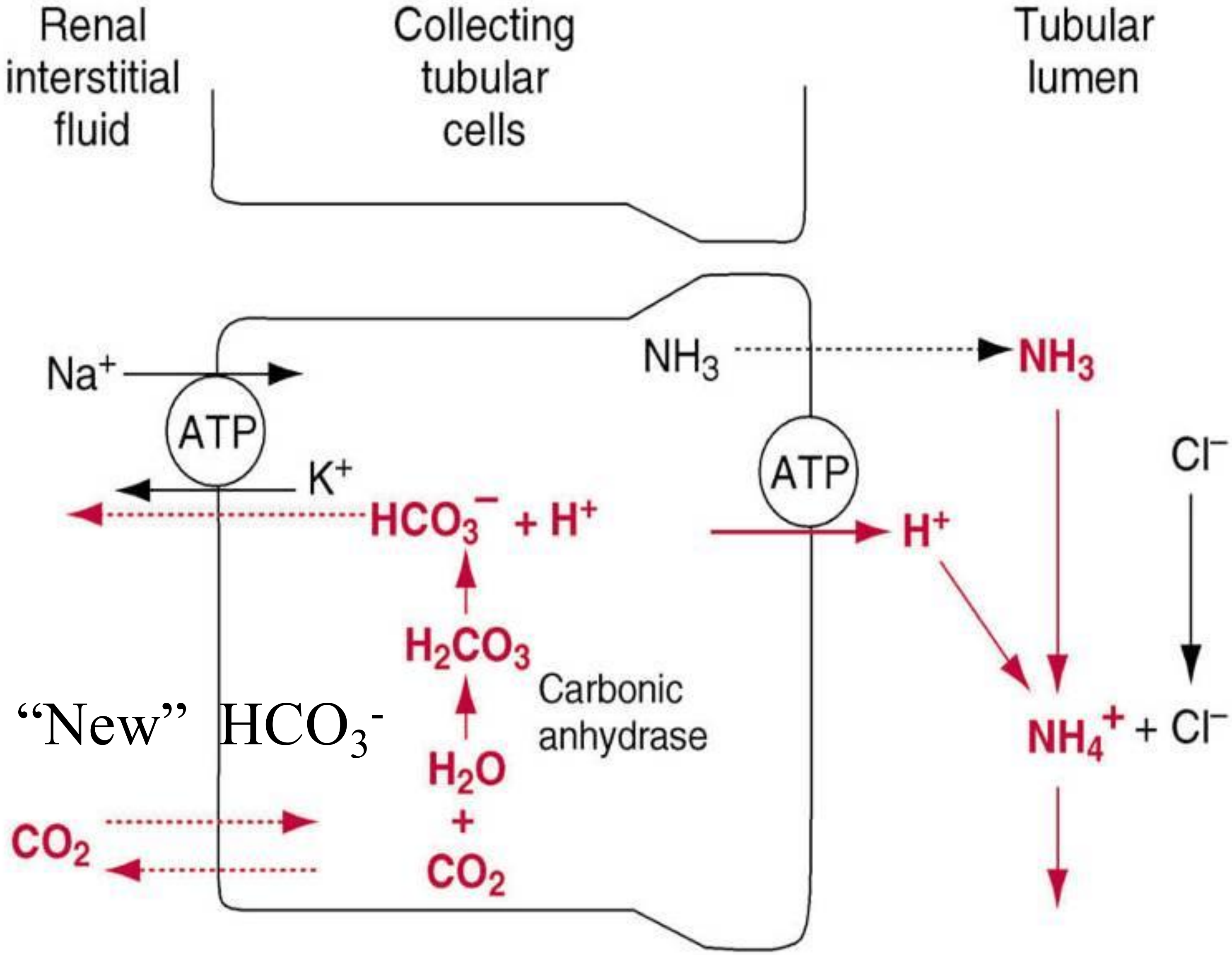
- If the kidney cannot absorb HCO_3^- or cannot secrete H+ then there is acidosis, this acidosis is called: renal tubular acidosis (several types)

- HCO_3^- added /day = NH_4Cl excretion + titratable acids - HCO_3^-

Production and secretion of NH_4^+ and HCO_3^- by proximal, thick loop of Henle, and distal tubules

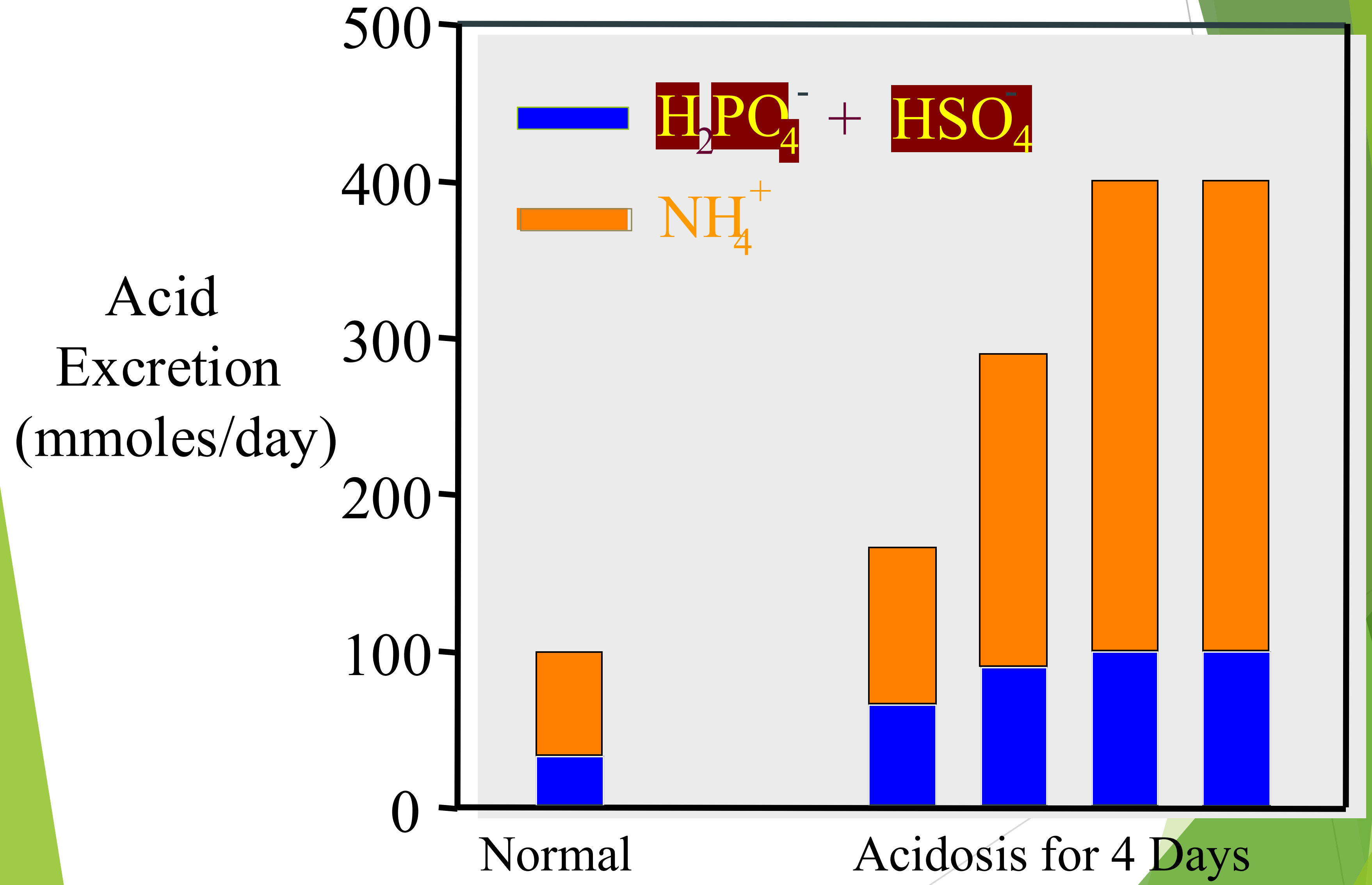


Buffering of hydrogen ion secretion by ammonia (NH_3) in the collecting tubules.



“New” HCO_3^-

Phosphate and Ammonium Buffering In Chronic Acidosis



Quantification of Normal Renal Acid-Base Regulation

Total H^+ secretion = 4400 mmol/day

= HCO_3^- reabsorption (4320 mmol/d)

+ titratable acid ($NaHPO_4^-$) (30 mmol/d)

+ NH_4^+ excretion (50 mmol/d)

Net H^+ excretion = 79 mmol/day

= titratable acid (30 mmol/d)

+ NH_4^+ excretion (50 mmol/d)

\- HCO_3^- excretion (1 mmol/d)

Acid-Base Imbalances

HCO_3^-/H^+ ratio in extracellular fluids

- Acidosis ↓ in the ratio
  - Due to a fall in HCO3 (*metabolic acidosis*) *or*
  - Due to an increase in PCO2 (*respiratory acidosis*)

- Alkalosis ↑ in the ratio
  - Due to an increase in HCO3 (*metabolic alkalosis*) *or*
  - Due to a fall in PCO2 (*respiratory alkalosis*)

Classification of Acid-Base Disorders from plasma pH, PCO_2, and HCO_3^-

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

$$pH = pK + \log \frac{HCO_3^-}{\alpha\ PCO_2}$$

Acidosis : $pH < 7.35$

- metabolic : ↓ HCO_3^-
- respiratory : ↑ PCO_2

Alkalosis : $pH > 7.45$

- metabolic : ↑ HCO_3^-
- respiratory : ↓ PCO_2

pH disturbances:

- Acidosis is more common than alkalosis.
- metabolic acidosis is more common than respiratory acidosis.

Main cause of metabolic acidosis is not diabetes mellitus because diabetes mellitus type 1 that causes ketoacidosis is not common.

→ The most common cause of M.acidosis is diarrhea.

* Diarrhea treatment: rehydration, correct electrolyte and blood pH

pH disturbance

Metabolic → it is the HCO_3^- shift

Respiratory → lit is the PCO2 shift

	pH	P_aCO_2	HCO_3^-
M. Acidosis	↓	↓	↓
M. Alkalosis	↑	↑	↑
R. Acidosis	↓	↑	↑
R. alkalosis	↑	↓	↓

To know the type of disorder:

First we see if pH is increased or decreased, second we look what causing this shift: is it the HCO_3^- (metabolic) or the CO2 (respiratory). Third and finally we look for compensation (no compensation, partial compensation or full

Classification of Acid-Base Disturbances

	Plasma			
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

Metabolic acidosis:

Metabolic Acidosis:

Non-respiratory acidosis is better term, but metabolic acidosis is most used.

1. Renal tubular acidosis

2. ↑ HCO_3^- loss: diarrhea is the most common cause of M. acidosis, another cause is deep vomiting (pancreatic juice).

3. ↑ H+ production: as in D.M, also ingestion of Aspirin or when acetoacetic acids are produced from fats.

→ Acidosis stimulate respiratory center causing hyperventilation, decreasing CO_2 as compensation.

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

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

Metabolic acidosis

- Metabolic Acidosis : ↓(HCO$_3^-$ / PCO$_2$ in plasma)
  (pH, ↓HCO$_3^-$ ↓)

  - aspirin poisoning (↑H$^+$ intake)
  - diabetes mellitus (↑H$^+$ production)
  - diarrhea (increase HCO$_3^-$ loss)
  - renal tubular acidosis (↓ H$^+$ secretion, ↓HCO$_3^-$ reabs.)
  - carbonic anhydrase inhibitors (↓ H$^+$ secretion)

- **Metabolic Alkalosis:** "not common"
- Metabolic Alkalosis : ↑ (HCO_3^- / PCO_2 in plasma)
- (↑ pH, ↑ HCO_3^-)
- 1. Diuretics with the exception of
- C.A inhibitors :↑ flow → ↑ Na^+
- reabsorption → ↑ H^+ secretion.
- 2. ↑ aldostrerone.
- 3. Vomiting of gastric content only (Pyloric stenosis)
- 4. Administration of $NaHCO_3$.

Renal Compensations for Acid-Base Disorders

- Acidosis:
  - increased H^+ secretion
  - increased HCO_3^- reabsorption
  - production of new HCO_3^-

- Alkalosis:
  - decreased H^+ secretion
  - decreased HCO_3^- reabsorption
  - loss of HCO_3^- in urine

Renal Compensation for Acidosis

Increased addition of HCO_3^- to body by kidneys
(increased H^+ loss by kidneys)

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

This can increase to as high as 500 mmol/day

Renal Compensation for Alkalosis

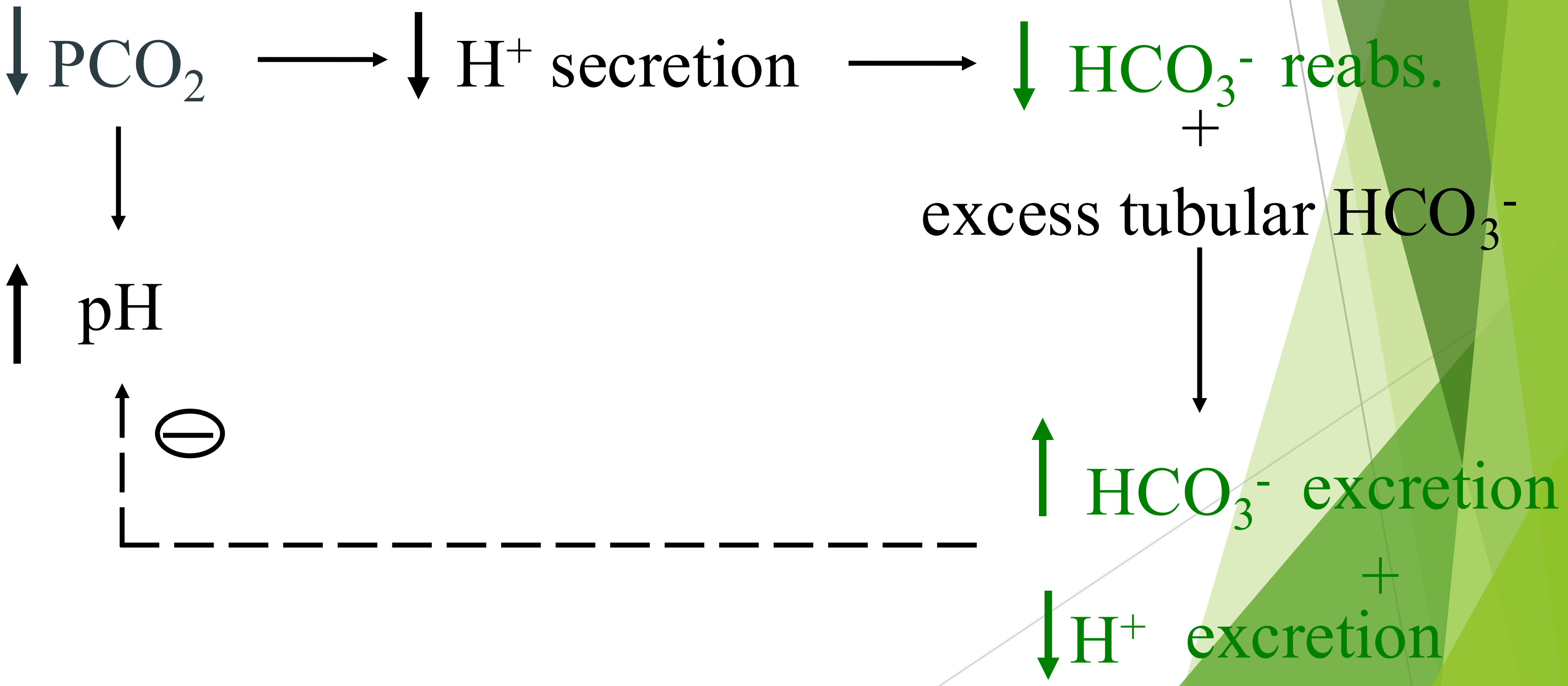
Net loss of HCO_3^- from body
(i.e. decreased H^+ loss by kidneys)

Titratable acid = 0 mmol/day (decreased)
NH_4^+ excretion = 0 mmol/day (decreased)
HCO_3^- excretion = 80 mmol/day (increased)
Total = 80 mmol/day

HCO_3^- excretion can increase markedly in alkalosis

Renal Responses to Respiratory Alkalosis

Respiratory alkalosis : ↑ pH ↓ pCO_2 ↓ HCO_3^-



↓ PCO_2 ⟶ ↓ H^+ secretion ⟶ ↓ HCO_3^- reabs.

\+

excess tubular HCO_3^-

↑ HCO_3^- excretion

\+

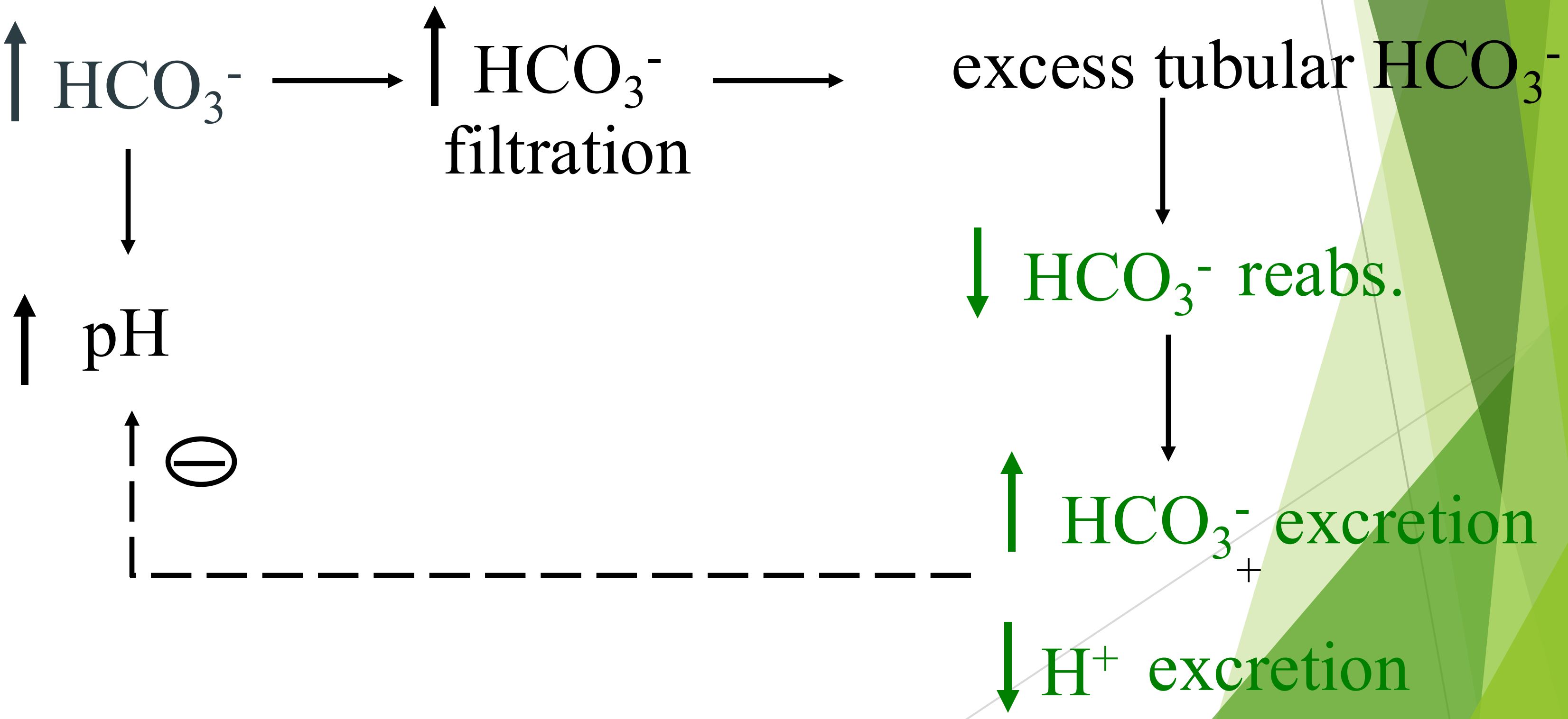
↓ H^+ excretion

↑ pH

⊖

Renal Responses to Metabolic Alkalosis

Metabolic alkalosis : ↑ pH ↑ PCO_2 ↑ HCO_3^-



↑ HCO_3^- → ↑ HCO_3^- filtration → excess tubular HCO_3^-

↓ HCO_3^- reabs.

↑ HCO_3^- excretion

+

↓ H^+ excretion

⊖

↑ pH

- Simple Versus Mixed `Acid-Base Imbalance:
- - Mixed (complex) disorder (either term can be used).
- *M. Acidosis For every ↓ 1 mEq HCO_3^- → 1.2 mm Hg PCO2 ↓ too.
- **M. Alkalosis For every 1 mEq↑ in HCO_3^- → 0.7 mmHg ↑ in PCO2
- ***R. Acidosis
- Acute: For every 10 mmHg ↑ in PCO2 → 1 mEq ↑ in HCO_3^-
- Chronic For every 10 mmHg ↑ in PCO2 →3.5 mEq↑ in HCO_3^-
- ****R. Alkalosis
- Acute For every 10 mmHg ↓ PCO2 → 2 mEq ↓ HCO_3^-
- Chronic For every 10 mmHg ↓ PCO2 → 5 mEq ↓ HCO_3^-

- * if PCO2 ↓ more than expected→ superimposed R. alkalosis too.
- * if PCO2 ↓ less than expected→ superimposed R. acidosis too.
- ** if PCO2 ↑ more than expected→ superimposed R. acidosis too.
- ** if PCO2 ↑ less than expected→ superimposed R. alkalosis too.
- *** if HCO3 ↑ more than expected→ superimposed M. alkalosis too.
- *** if HCO3 ↑ less than expected→ superimposed M. acidosis too.
- **** if HCO3 ↓ more than expected→ superimposed M. acidosis too.
- **** if HCO3 ↓ less than expected→ superimposed M. alkalosis too.
- *** In metabolic acidosis respiratory system compensate more than in metabolic alkalosis because
- acidosis induce hyperventilation while alkalosis induce hypoventilation which may be opposed by hypoxia

Question

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 ?
- What is the daily net rate of HCO_3^- addition to the
- extracellular fluids ?

Answer

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

net acid excretion = Titr. Acid + NH_4^+ excret - HCO_3^-
= (10 x 1) + (15 x 1) - (1 x 2)
= 23 mmol/day

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

Question

A plasma sample revealed the following values in a patient:

pH = 7.12

PCO_2 = 50

HCO_3^- = 18

diagnose this patient's acid-base status :

acidotic or alkalotic ?

respiratory, metabolic, or both ?

Acidotic

Both

Mixed acidosis: metabolic and respiratory acidosis

Mixed Acid-Base Disturbances

Two or more underlying causes of acid-base disorder.

pH= 7.60
PCO_2 = 30 mmHg
plasma HCO_3^- = 29 mmol/L

What is the diagnosis?

Mixed Alkalosis

- Metabolic alkalosis : increased HCO_3^-
- Respiratory alkalosis : decreased pCO_2

Question

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. **<u>metabolic acidosis with partial respiratory compensati</u>**
4. respiratory acidosis with partial renal compensation

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

Metabolic Acidosis with Respiratory Compensation

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

Anion gap = 142 - 118 - 15 = 9 (normal)

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

Indicate the Acid -Base Disorders in Each of the Following Patients

pH	HCO_3^-	PCO_2	Acid-Base Disorder ?
7.34	15	29	Metabolic acidosis
7.49	35	48	Metabolic alkalosis
7.34	31	60	Respiratory acidosis
7.62	20	20	Respiratory alkalosis
7.09	15	50	Acidosis: respiratory + metabolic

Steps to an Arterial Blood Gas Interpretation…how to diagnose?

Step One

Assess the pH to determine if the blood is within normal range, alkalotic or acidotic. If it is:

above 7.45, the blood is alkalotic.

If it is below 7.35, the blood is acidotic.

Step Two

If the blood is alkalotic or acidotic, we now need to determine if it is caused primarily by a respiratory or metabolic problem. To do this, assess the **$PaCO_2$** level. Remember that with a respiratory problem, as the pH decreases below 7.35, the PaCO2 should rise. If the pH rises above 7.45, the PaCO2 should fall. Compare the pH and the PaCO2 values. If pH and PaCO2 are

indeed moving in *opposite directions*, then the problem is primarily respiratory in nature.

Step Three

Finally, assess the HCO_3 value. Recall that with a metabolic problem, normally as the pH

increases, the HCO3 should also increase. Likewise, as the pH decreases, so should the HCO3.

Compare the two values. If they are moving *in the same direction*, then the problem is primarily metabolic in nature. The following chart summarizes the relationships between pH, PaCO2 and HCO3.

	pH	**PaCO2**	**HCO3**
Respiratory Acidosis	↓	↑	normal
Respiratory Alkalosis	↑	↓	normal
Metabolic Acidosis	↓	normal	↓
Metabolic Alkalosis	↑	normal	↑

Example

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:

PATIENT: Suha

DATE: 1/4/2026 1:43 am

pH = 7.22

$PaCO_2$ = 55

HCO_3^- = 25

Follow the steps:

1. Assess the pH. It is low (normal 7.35-7.45); therefore, we have acidosis.

2. Assess the PaCO2. It is high (normal 35-45) and in the opposite direction of the pH.

3. Assess the HCO3. It has remained within the normal range (22-26).

	pH	PCO2	HCO_3^-
Respiratory Acidosis	↓	↑	Normal

Acidosis is present (decreased pH) with the $PaCO_2$ being increased, reflecting a primary *respiratory* problem.
For this patient, we need to improve the ventilation status by providing oxygen therapy, mechanical ventilation, administering bronchodilators, etc

Example 2

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:

PATIENT: Shaher

DATE: 5/4/2026 02:30 p.m

pH = 7.50

PaCO2 = 42

HCO_3^- = 33

1. Assess the pH=7.5 It is high (normal 7.35-7.45), therefore, indicating alkalosis.
2. Assess the PaCO2.=42 It is within the normal range (normal 35-45).
3. Assess the HCO3=33. It is high (normal 22-26) and moving in the same direction as the pH.

pH	**PCO_2**	**HCO_3^-**	**Metabolic Alkalosis**
↑	normal	↑	

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.

Compensation

When a patient develops an acid-base imbalance, the body attempts to compensate. That the lungs and the kidneys are the primary buffer response systems in the body.

The body tries to overcome either a respiratory or metabolic dysfunction in an attempt to return the pH into the normal range.

A patient can be uncompensated, partially compensated, or fully compensated. When an acid-base disorder is either uncompensated or partially compensated, the pH remains outside the normal range.

In fully compensated states, the pH has returned to within the normal range,

although the other values may still be abnormal.

Be aware that neither system has the ability to overcompensate.