Renal system
PHYSIOLOGY

- Very important
- Extra information

References :
- GUYTON AND HALL 12th edition
- LINDA 5th edition

* Guyton corners, anything that is colored with grey is EXTRA explanation

Basics of acid base

Objectives :

- Define: acid and base.
- Explain what is meant by strong and weak acids and bases.
- List and identify the names/formulas for the common strong acids and strong bases.
- To explain the role of Henderson-Hasselbalch equation in acid-base regulation.

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Acid – Base Balance

- **Acid – Base balance** (*as known as* **pH HOMEOSTASIS**) : one of the essential functions of the body.
- When discussing acid - base balance, we are normally concerned with regulation of **H^+ ion** balance (although HCO_3^- plays a vital role in this balance).
- **To avoid disturbances in [H^+], and to maintain its homeostasis :** the amount generated / taken in **MUST EQUAL** the amount secreted.

Why is control of [H^+] so important?

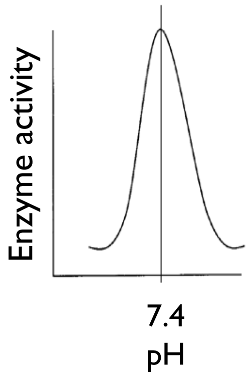
1- Highly reactive chemical species (protons). combine easily with negatively charged ions and bases

2- Most enzymes function optimally at pH ~ 7.4 (except gastric enzymes)

3- Precise [H^+] regulation is vital because activity of almost all enzyme systems / proteins (inc. ion channels) influenced by pH

(e.g. hydrogen bonding and charge on proteins altered by pH so tertiary structure and function affected.)

4- Acid-base imbalances can cause cardiac arrhythmias and abnormal neuronal excitation.



Enzymes of the body can't function properly if the H+ ions balance is disturbed

Acid – Base Balance

Definitions (Bronsted-Lowry)

- **ACIDS :** Molecules containing hydrogen atoms that can release (Donate) H^+ into solution. (e.g. HCl ⇔ $H^+ + Cl^-$).

Classified to :

Strong acids: all their H+ is dissociated completely in H_2O

weak acids: dissociate partially in H2O and are efficient at preventing pH changes

- **BASES (alkalis) :** ions or molecules that can (Accept) H^+. (e.g., $HCO_3^- + H^+ \Leftrightarrow H_2CO_3$).

Classified to :

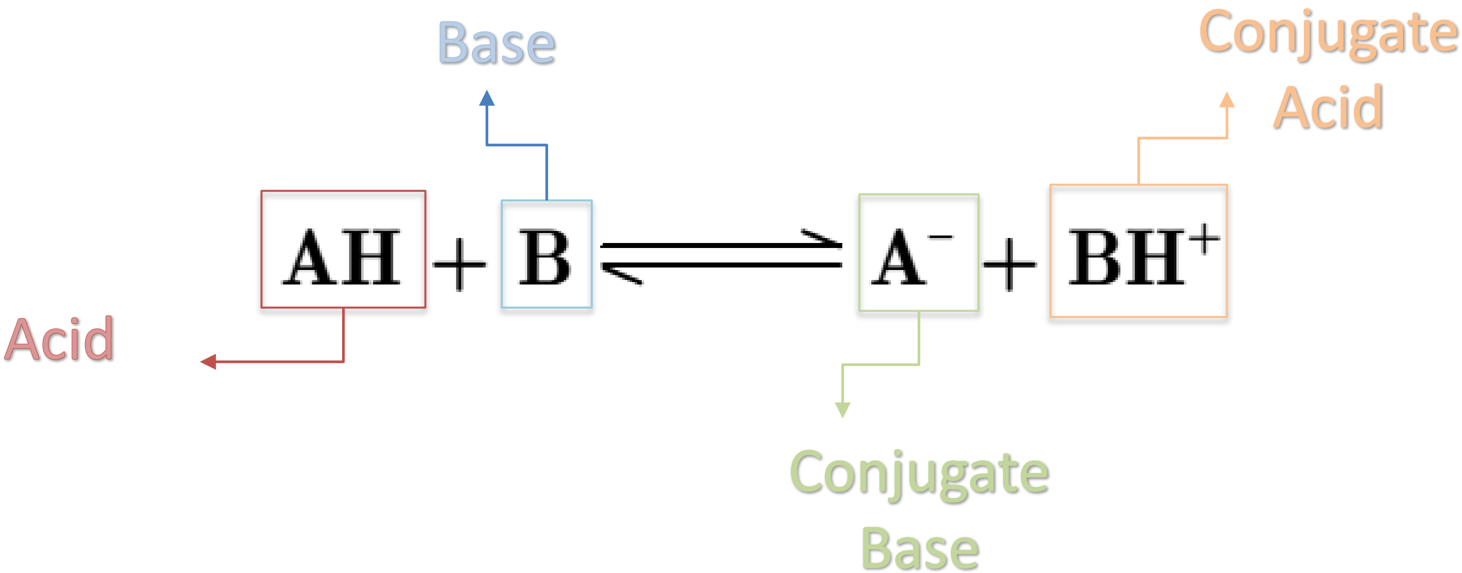
Strong bases: dissociate easily in H_2O and quickly bind H^+

weak bases: accept H^+ more slowly (e.g., HCO_3^- and NH_3)

Proteins in body function as weak bases as some constituent amino acids have net negative charge and attract H+ (e.g. HAEMOGLOBIN).

- HCO3- has negative charge → it can accept hydrogen ion to form carbonic acid.
- Proteins are negatively charged, they accept H+ ions and behave as weak bases.

- **Free hydrogen ions are extremely unstable. Therefore, for any acid and any base, the equilibrium established is:**



- Every acid has a conjugate base associated with it, and vice versa.

> - A conjugate base : is the particle that is left over after the acid loses its hydrogen ion
> - This is general equation but we can replace A with chloride or any other elements so the same equation has to be established.

Water usually is amphoteric compound depend on the added compound (acidic or basic)

When water behaves as a base, it accepts H+ and forms a hydronium ion; H_3O^+

When it behaves as an acid, it loses a proton, and forms a hydroxide ion; OH^-

The hydronium ion concentration can be found from the pH by the reverse of the mathematical operation employed to find the pH $[H_3O^+] = 10^{-pH}$

amphoteric : substances that can act as an acid or as a base.

physiology team

pH

What is pH ?

The pH of a solution is a measure of the acidity of the solution not the strength of an acid

It is defined as :

Where [H3O+] is the concentration of hydronium ions in the solution

$$pH = -\log_{10}([H_3O^+])$$

The pH of water is 7. This means that a solution of pure water has a 10^{-7} mol dm^{-3} of hydronium ions.

pH depends on two things:

The acid in the question

if we have two equally concentrated solutions of acids, the solution of a strong acid will have a lower pH than that of a weak acid, because it is more fully dissociated and therefore produces more H_3O^+ ions. HCl, for example, is completely dissociated.

The concentration of the solution

If we have two solutions of the same acid, the more concentrated solution will have more free H_3O^+ ions and therefore a lower pH.

For example, if we have 2 concentrations of the same acid (HCL) :
HCl = 5 mEq / HCl = 10 mEq
The HCl with 10 mEq will have lower pH thus it will be more acidic

Physiologically important Acids and Bases

Physiologically important acids include

- Carbonic acid (H_2CO_3)
- Phosphoric acid (H_3PO_4)
- Pyruvic acid ($C_3H_4O_3$)
- Lactic acid ($C_3H_6O_3$)

Physiologically important bases include

- Bicarbonate (HCO_3^-)
- Biphosphate (HPO_4^{-2})

These acids are dissolved in body fluids

Acid – Base Balance pH Scale (Sørensen, 1909)

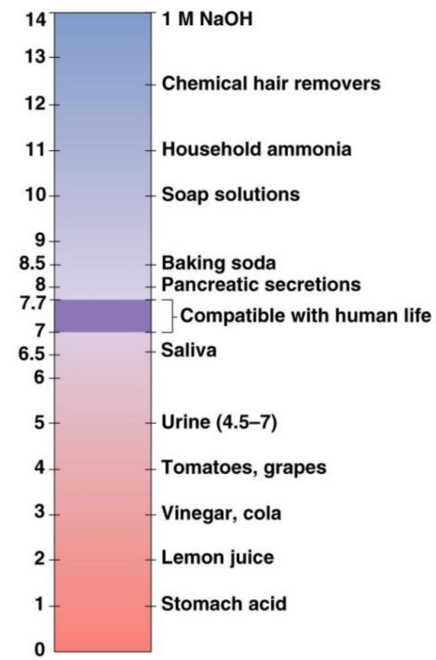
- Relative to other ions, [H+] of body fluids kept VERY LOW
  e.g., ECF [Na+] ≈ 145 mM/L
  ECF [H+] ≈ 0.00004 mM/L (40nM)
  (~ 3.5 million fold difference).

- Because $[H^+]$ so low, easier to express $[H^+]$ on a logarithmic scale ⇒ pH units.

$$pH = \log \frac{1}{[H^+]} = -\log [H^+]$$

- Normal pH = -log [0.00000004] M
  = 7.4

- Free hydrogen ions in the body are very low that's why we use Logarithm to calculate it.
- **Dr. Mona said it is very important equation**



- **Guyton corner :**

Equally important, the normal variation in H+ concentration in extracellular fluid is only about one millionth as great as the normal variation in sodium ion (Na+) concentration. Thus, the precision with which H+ is regulated emphasizes its importance to the various cell functions.

- **Linda corner:**

When using pH instead of H+ concentration, there are two points of caution. First, because of the minus sign in the logarithmic expression, a mental reversal is necessary: As H+ concentration increases, pH decreases, and conversely. Second, the relationship between H+ concentration and pH is logarithmic, not linear. Thus, equal changes in pH do not reflect equal changes in H+ concentration.

Acid – Base Balance pH Scale (Sørensen, 1909)

table 2.5 Hydrogen Ion Concentrations and pH

Grams of H^+ per Liter	pH	
0.00000000000001	14	↑
0.0000000000001	13	
0.000000000001	12	Increasingly basic
0.00000000001	11	
0.0000000001	10	
0.000000001	9	
0.00000001	8	
0.0000001	7	Neutral—neither acidic nor basic
0.000001	6	
0.00001	5	
0.0001	4	
0.001	3	
0.01	2	Increasingly acidic
0.1	1	
1.0	0	↓

Note that a change of 1 pH unit = 10x change in [H+] ($\log_{10}$ scale)

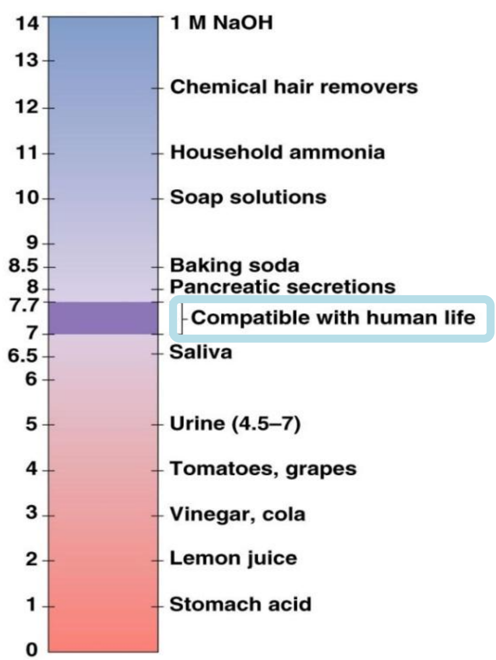
Acid – Base Balance pH Scale (Sørensen, 1909)

- **pH INVERSELY related to [H+]**

as [H+] ↑, pH ↓ – acidosis (below 7.35)
as [H+] ↓, pH ↑– alkalosis (above 7.45)

- **Normal <u>BLOOD</u> pH**

range for adults = 7.35 – 7.45
maintained by chemical buffer systems, kidneys and lungs.



pH range Compatible with human life = (6.8-7.8).
It likely cause Death: if the pH is higher or less than this range

- if the H+ is increased in the ECF → low pH → acidic
- If conc. of H+ decrease in the ECF → high pH → alkalosis
- IF THEY ASK US ABOUT BODY PH WE HAVE TO PUT RANGE (7.35-7.45) for example 7.1 is acidic / 7.8 = alkalosis
- Its lethal if the pH above 7.8 or below 6.8 it considered as emergency situation and we have to correct it .

Acid – Base Balance pH Scale (Sørensen, 1909)

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
Gastric HCl	160	0.8

Approximate pH Values of Various Body Fluids

Compartment	pH
Gastric secretions (under conditions of maximal acidity)	0.7
Lysosome	5.5
Chromaffin granule	5.5
Neutral H_2O at 37°C	6.81
Cytosol of a typical cell	7.2
Cerebrospinal fluid	7.3
Arterial blood plasma	7.4
Mitochondrial inner matrix	7.5
Secreted pancreatic fluid	8.1

There are a range of pH values within different body fluids - dependent on function.

Sources of H+

- The body generally <u>PRODUCES</u> more acids than bases.

1) **Cellular aerobic metabolism produces 15,000 mmol CO2/day**

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

(volatile acid)

Normally all volatile acid **<u>excreted by the lungs.</u>**

2) **DIET :**

incomplete metabolism of carbohydrates (lactate)، lipids (ketones) and proteins (H_2SO_4, H_3PO_4) generates fixed (non-volatile) acids ~50 -100 mEq per day.

- In order to maintain balance, acids need to be ***BUFFERED*** and/or ***EXCRETED***.

- CO2 is an important source of acidity.
- Buffered = يعدل
- Excretion by lungs → co2
- If there's no wash out of CO2 it will bind to water → High H+→ Acidosis

Extra - Sources of H+

Moles x valence = equivalents.

By definition one equivalent (or equivalent weight) of a substance is the amount of that substance which supplies or consumes one mol of reactive species. In acid-base chemistry the reactive species is the hydrogen ion (H1+) while in oxidation-reduction chemistry the reactive species is the electron. For example, in the following two reactions the equivalent weight of H2SO4 would be 49 grams or 0.5 mol in the first reaction but 98 grams or 1 mol in the second. On the other hand, sodium hydroxide has the same equivalent weight in both reactions, one mol or 40 grams.

(1) H2SO4 + 2NaOH ------> Na2SO4 + 2H2O

(2) H2SO4 + NaOH ------> NaHSO4 + H2O

In the first reaction one mol of H2SO4 supplies 2 mols of H1+ to NaOH, therefore, one-half mol of H2SO4 or 49 grams is one equivalent. The conditions are different in the second reaction because sulfuric acid only "loses" one hydrogen so the equivalent weight of sulphuric acid is one mol or 98 grams. However, sodium hydroxide behaves the same in both reactions, that is, one mol of sodium hydroxide always "consumes" one mol of H1+, so its equivalent weight remains the same at one mol or 40 grams.

Extra - Sources of H+

- **LINDA pg304 :**

***Acid Production in the Body**Arterial pH is slightly alkaline (7.4) despite the production of large amounts of acid on a daily basis. This acid production has two forms: volatile acid (carbon dioxide, CO_2) and nonvolatile, or fixed, acid. Both volatile and fixed acids are produced in large quantities and present a challenge to the normally alkaline pH.

***CO2:**

CO2, or **volatile acid**, is the end product of aerobic metabolism in the cells and is generated at a rate of 13,000 to 20,000 millimoles daily (mmol/day). CO2 itself is not an acid. However, when it reacts with water (H2O), it is converted to the weak acid carbonic acid, H2CO3: $CO2 + H20 \leftrightarrow H2CO3 \leftrightarrow H+ + HCO3$

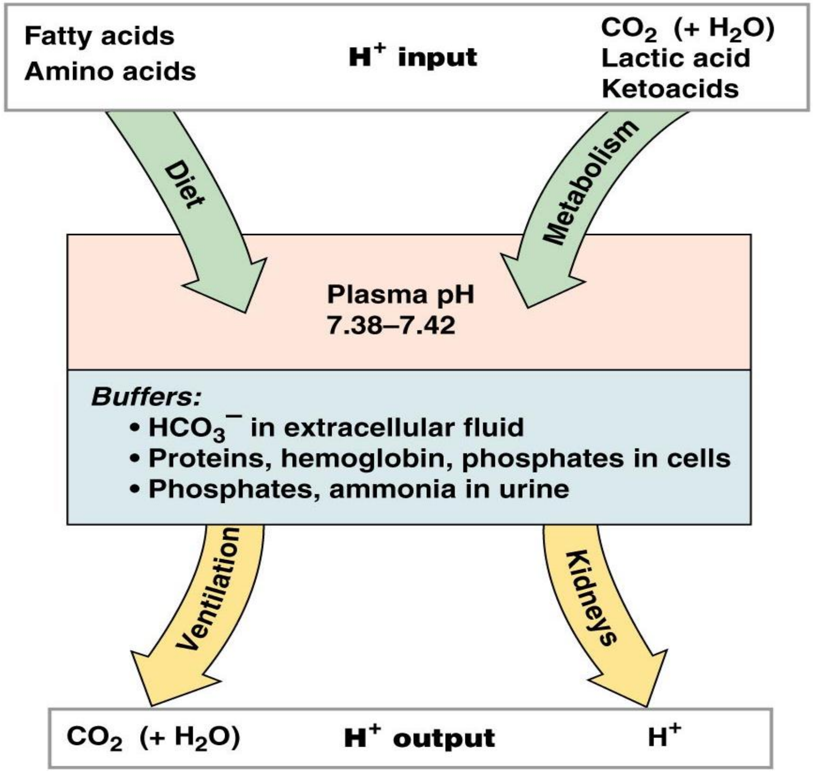
The reactions show that CO2 combines reversibly with H2O to form H2CO3, **catalyzed by the enzyme carbonic anhydrase**. H2CO3 dissociates into H+ and HCO3−, and the H+ generated by this reaction must be buffered. Recall that CO2 produced by the cells is added to venous blood, converted to H+ and HCO3− within the red blood cells, and carried to the lungs. In the lungs, the reactions occur in **reverse and CO2 is regenerated and expired. (CO2 is therefore called a volatile acid.)** Thus, buffering of the H+ that comes from CO2 is only a temporary problem

Fixed Acid

Catabolism of proteins and phospholipids results in the production of approximately 50 mmol/day of fixed acid. Proteins with the sulfur-containing amino acids (e.g., methionine, cysteine, cystine) generate **sulfuric acid** when they are metabolized, and phospholipids generate **phosphoric acid**. In contrast with CO_2, which is volatile and will be expired by the lungs, sulfuric acid and phosphoric acid are *not* volatile. Therefore, fixed acids first must be buffered in the body fluids until they can be excreted by the kidneys.

In addition to sulfuric and phosphoric acids, which are produced from *normal* catabolic processes, in certain pathophysiologic states, fixed acids can be produced in excessive quantities. These fixed acids include **β-hydroxybutyric acid** and **acetoacetic acid**, both ketoacids that are generated in untreated diabetes mellitus, and **lactic acid**, which may be generated during strenuous exercise or when the tissues are hypoxic. In addition, other fixed acids may be ingested, such as **salicylic acid** (from aspirin overdose), **formic acid** (from methanol ingestion), and **glycolic** and **oxalic acids** (from ethylene glycol ingestion). Overproduction or ingestion of fixed acids causes metabolic acidosis

Hydrogen and pH Balance in the Body



Catabolism of **SULFUR** containing amino acid AA gives H_2SO_4(sulfuric acid

Catabolism of **phospholipids/ phosphoproteins** gives H_3PO_4 (phosphoric acid)

- **LINDA pg304:** Catabolism of proteins and phospholipids results in the production of approximately 50 mmol/day of fixed acid. Proteins with the sulfur-containing amino acids (e.g., methionine, cysteine, cystine) generate **sulfuric acid** when they are metabolized , and phospholipids generate **phosphoric acid**

How is [H+] Controlled?

Three systems involved :

1) BUFFERS

- 1ST First defence
- second to second regulation of [H+]

2)Excretion of CO_2 (↓H_2CO_3) by LUNGS (removal of volatile acid)

- 2ND second defence
- regulation in minutes - to - hours

3) Excretion of H^+ (↑HCO_3^-) by KIDNEYS (fixed acids)

- 3RD third defence
- regulation over several hours to days
- *slowest, but most POWERFUL, of body's acid-base regulatory systems.*

How is [H+] Controlled?

- **GUYTON pg380:**

Defending Against Changes in H+ Concentration: Buffers, Lungs, and Kidneys

Three primary systems regulate the H+ concentration in the body fluids to prevent acidosis or alkalosis: (1) the chemical **acid-base buffer** systems of the body fluids, which immediately combine with acid or base to prevent excessive changes in H+ concentration; (2) **the respiratory center**, which regulates the removal of CO2 (and, therefore, H2CO3) from the extracellular fluid; and (3) **the kidneys**, which can excrete either acid or alkaline urine, thereby readjusting the extracellular fluid H+ concentration toward normal during acidosis or alkalosis.

*When there is a change in H+ concentration, the buffer systems of the body fluids react within seconds to minimize these changes. Buffer systems do not eliminate H+ from or add them to the body but only keep them tied up until balance can be re-established.
*The second line of defense, the respiratory system, acts within a few minutes to eliminate CO2 and, therefore, H2CO3 from the body.
*These first two lines of defense keep the H+ concentration from changing too much until the more slowly responding third line of defense, the kidneys, can eliminate the excess acid or base from the body. Although the kidneys are relatively slow to respond compared with the other defenses, over a period of hours to several days, they are by far

Henderson-hasselbalch Equation

- It's a Relative concentrations of CO_2 and HCO_3^- in plasma / ECF , determine pH.

  The relation between bicarbonate and CO2 (in other words, Kidney / Lung)

- Show the relationship between pH, hydrogen ion concentration and the ratio of buffer membrane in a solution.

$$pH = pK' + \frac{\log [HCO3^-]}{S\ (PCO_2)}$$

So:

$$pH = 6.1 + \frac{\log [HCO3^-]}{0.03 \times PCO_2}$$

$$7.4 = 6.1 + 1.3$$

PH= is the negative logarithm of H+ in mol/L.(tells us how acidic a solution is).
PK= is negative logarithm of overall dissociation constant for the reaction = 6.1 in health. (tells us how acidic or not a given hydrogen atom in a molecule is).
S= is solubility of CO2 in solution = 0.03 at 37°C. In **health**, **[HCO3-]** = 24 mmol/L & **PCO2** = 40 mm Hg

- **Linda corner:** The Henderson-Hasselbalch equation is used to calculate the pH of a buffered solution. This equation is derived from the behavior of weak acids (and bases) in solution.
- **Guyton corner :** From the Henderson-Hasselbalch equation, it is apparent that an increase in HCO_3^- concentration causes the pH to rise, shifting the acid-base balance toward alkalosis. An increase in PCO_2 causes the pH to decrease, shifting the acid-base balance toward acidosis.

PK = 6.1 / S=0.03 / HCO3- = 24 / PCO2 = 40

These numbers are very IMPORTANT!

What happen to the pH using H-H ?

Very important slide

In case if the HCO3 in Plasma remains normal

If Pco2 increased, the ratio of [HCO3]P/ 0.03 Pco2 will decrease which lead to acidosis.

If Pco2 decrease, the ratio will increase and pH will increase causing alkalosis.

In case the Pco2 remains normal

Increase bicarbonate in plasma causes an increase in the ratio which leads to alkalosis.

Decrease in bicarbonate in plasma causes a decrease in the ration which leads to acidosis.

scenario with HCO3- =35 (high)→ ratio increase→ increased pH → alkalosis (it make sense because HCO3- is base if its concentration increase which will result in alkalosis)
if the HCO3- decrease to be =19 → ratio decreased → decreased pH

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