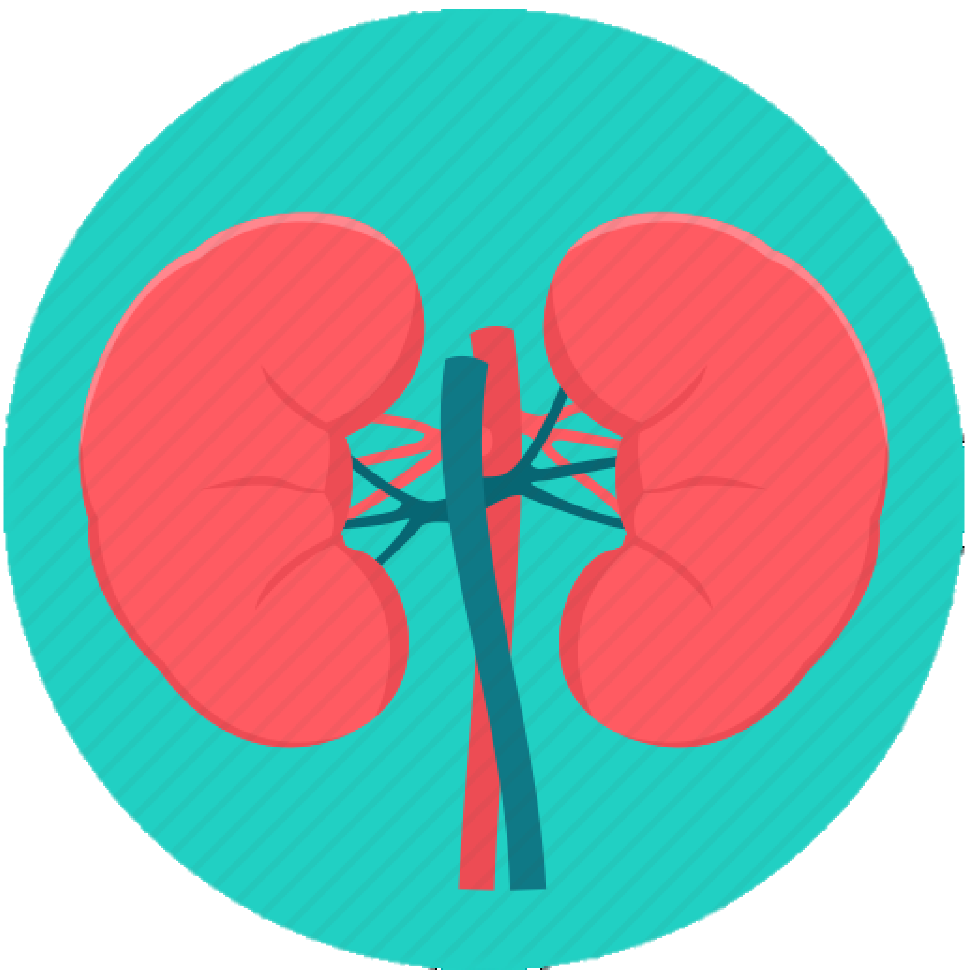
جامعة الملك سعود
King Saud University

MED438
KING SAUD UNIVERSITY

Lecture (9-11)

Acid-Base Balance



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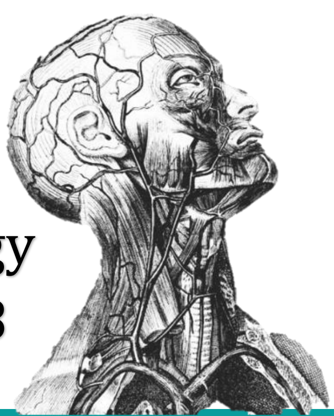


Physiology
MED438

Acids

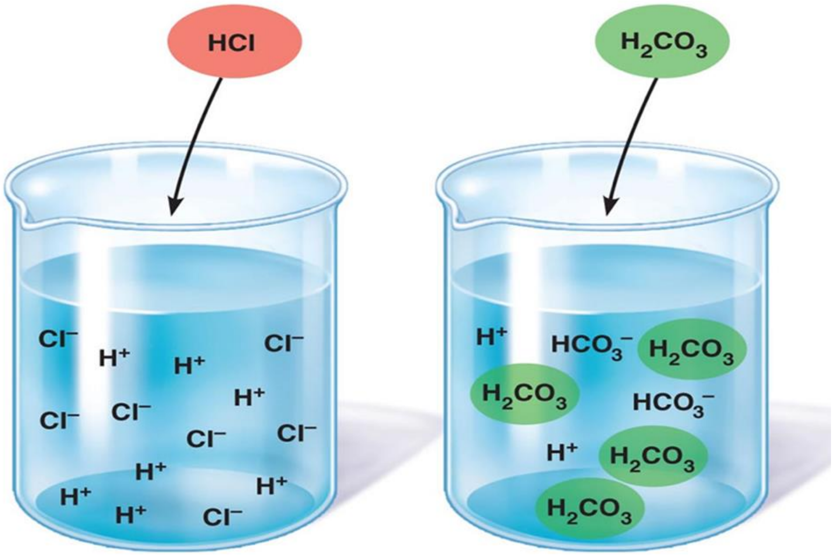
- **Acids** are molecules that **donate**, release, H^+ ions into solutions

$HCl \rightarrow H^+ + Cl^-$ in H_2O solutions

➔ Strong Acids dissociate **ALL** their H^+ when dissolved in H_2O (e.g. HCl) (hydrochloric acid)

➔ Weak acids dissociate **PARTIALLY** when dissolved in H_2O (e.g. H_2CO_3) (carbonic acid)

- Normal $[H^+]$ = **0.00004 mEq/L** (40 nEq/L) if $[Na^+]$ = 145 mEq/L
- Protons (H^+) are highly reactive chemical species that combine easily with negative charged ions and bases
- Precise H^+ control is vital because almost all enzymes are influenced by it



Bases

- **Bases** are molecules that accept H^+ ions into solutions e.g. HCO_3^- (Bicarbonate ions), $HPO4^{-2}$ (Hydrogen phosphate).

$HCO_3^- + H^+ \rightarrow H_2CO_3$ in H_2O solutions

➔ Strong bases dissociate easily in H_2O and **quickly** bind to H^+

➔ Weak bases accept H^+ more **slowly**

- Alkali is a molecule formed by one of the alkaline metals (Na, K, Li) with a highly basic ion (OH^-)

Sørensen pH Scale

- Relative to other ions H^+ levels are very low, so we express them as pH
- **pH scale** is a logarithmic function of the reciprocal of H^+ concentration

$$\mathrm{pH} = \log\frac{1}{[\mathrm{H}^+]} = -\log[\mathrm{H}^+] \qquad \mathrm{pH} = -\log[0.00000004]\,\mathrm{Eq/L} = 7.4$$

- **pH is inversely related to $[H^+]$**

➔ as $[H^+]$ increase → pH decreases → acidosis

➔ as $[H^+]$ decrease → pH increases → alkalosis

- pH levels range inside body fluids based on its function
- Normal **blood** (ECF) pH range is **7.35 - 7.45**
- Death is most likely if pH >7.8 or <6.8

	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

Dissociation Constant (K)

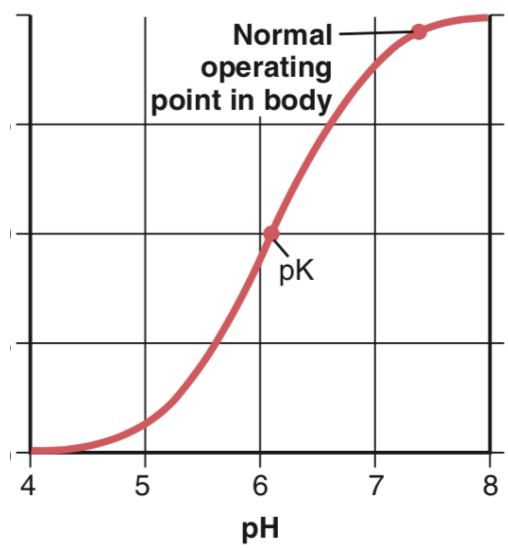
- Weak acids don't completely dissociate their H^+
- **Dissociation constant** is the extent in which acids dissociate their ions
- It can determine the **acid power**

$$AH \text{ (acid)} \leftrightarrow A^- \text{ (conjugate base)} + H^+$$

$$H_2CO_3 \text{ (carbonic acid)} \leftrightarrow HCO_3^- \text{ (bicarbonate)} + H^+$$

$$K = \frac{[H^+][A^-]}{[AH]} \qquad pK = -\log(K)$$

- **pK** is the pH point where the concentration of both the acidic and the basic components of the buffer are equal



Sources of H^+

- Generally, the body produces acids more than bases and they're of two types

1. **Volatile:** in aerobic metabolism (co_2)

$$\mathbf{CO_2} + H_2O \leftrightarrow \mathbf{H_2CO_3} \leftrightarrow H^+ + HCO_3^-$$

➔ Produces 12,500 mmol or 300 L of $\mathbf{CO_2}$/day.

➔ Mostly excreted by the lung

2. **Non-volatile:** generated by the incomplete metabolism of carbohydrates, lipids & proteins

➔ Daily acid load is 50-100 mEq/day (0.8 mEq/kg/d).

➔ E.g. phosphoric acid, lactic acid, Butyric acid, sulfuric acid)

➔ Mostly excreted by the kidneys

Henderson-Hasselbalch Equation

- Henderson-Hasselbalch equation show the relationship between pH, hydrogen ion concentration and the ratio of buffer components in a solution
- It's another way to calculate the pH using the concentrations of bicarbonate and CO_2 in blood which resembles the action of the most important buffering system in our body

$$pH = pK' + \frac{\log[HCO_3^-]}{sPCO_2} \qquad pH = 6.1 + \frac{\log(24)}{0.03 \times 40} = 7.4$$

- In a normal healthy person,

pK' =. **6.1** **s** = **0.03** at 37° C [$\mathbf{HCO_3^-}$] = **22-28** mmol/L **PCO_2** = **35-45** mmHg

If HCO_3^- is normal: ⇑ PCO_2 → acidosis ⇓ PCO_2 → alkalosis

If PCO_2 is normal: ⇑ HCO_3^-→ alkalosis ⇓ HCO_3^-→ acidosis

PH and Pco_2 = inversely proportional
PH and HCO_3^- = Directly proportional

Control of H^+

- **Why Should [H+] be Tightly Controlled?**

➔ Slight deviations in [H+] have profound effects on enzyme and protein activity and thus the body's metabolic activity in general.

➔ Changes in [H+] affects K+ levels in the body.

- **A number of processes can alter [H+] concentration in the body, such as;**

1. Metabolism of ingested food.
2. GI secretions.
3. Generation of acids & bases from metabolism of stored fat & glycogen.
4. Changes in CO2 production.

Acid-base balance is concerned with the precise regulation of free (unbound) hydrogen ion (H+) concentration in body fluids.

- **In balancing H^+ levels, three systems are involved:**

1st defense: Buffers within seconds

2nd defense: Excretion of CO_2 by lungs within minutes to hours

- Removal of volatile acids

3rd defense: excretion of H^+ by kidneys within hours to days

- Removal of fixed (non-volatile) acids
- Slowest but most powerful regulatory system

1st Defense: Buffer System

- Buffers are substances that stabilizes and limits the change of [H^+] upon addition of small amounts of acids or. bases
- They DON'T eliminate H^+ from the body. They reversibly bind to it until balance is re-established.

$$HA \leftrightarrow H^+ + A^-$$

- Reaction direction depends on the concentration
- The buffer is either a weak acid with a conjugate base or vice versa

  Weak acid: H_2CO_3 with its conjugate base $NAHCO_3^-$

  Weak base: NH_3 with its conjugate acid NH_4^+
- When we add an acid to a buffer solution the basic component will combine with the H^+ to balance its effect until it's excreted
- When we add a base to a buffer solution the acidic component will combine with the OH^- to balance its effect until it's excreted
- The buffer system exists in many forms and their work is interdependent
- **The buffer power depends on:**
  1. Relative acid:base ratio → maximum power when they're equal
  2. Absolute concentration of the buffer
  3. pK value → closer pK value to pH indicates higher effectiveness

More about H+ changes

1) Bicarbonate buffering system:

- Most important buffering system because other organs are involved in its function (main ECF buffer system)

(Carbonic anhydrase)

$$CO_2 + H_2O \underset{}{\overset{CA}{\rightleftharpoons}} \underset{\text{carbonic acid (Weak acid)}}{H_2CO_3} \rightleftharpoons H^+ + \underset{\text{bicarbonate (conjugate base)}}{HCO_3^-}$$

Acid → **H_2CO_3** will dissociate to small amounts of H^+ and HCO_3^- **(system)**

Conjugate base → **$NaHCO_3^-$** will dissociate to Na^+ and HCO_3^- **(reserve)**

- To maintain a pH of 7.4, HCO_3^-: CO2 (base: acid) ratio must be **at least 20:1**

Why is it the most important buffer system in the ECF?

- The **CO_2** component of the buffer is regulated by the **lungs**
- The **HCO_3^-** component of the buffer is regulated by the **kidneys**

2) Other buffering systems:

Buffer	Reaction	Importance	pK value
Bicarbonate	$H^+ + HCO_3^- \Leftrightarrow H_2CO_3$	In ECF	6.1
Phosphate	$H^+ + HPO_4^{2-} \Leftrightarrow H_2PO_4^-$	**In ICF**/Urine	6.8
Ammonia	$H^+ + NH_3 \Leftrightarrow NH_4^+$	In Urine	9
Amphoteric Proteins	H^+ + Prot ⇔ HProt	In **ICF**	-
Hemoglobin (due to protein's -ve charge)	H^+ + Hb ⇔ HHb	In ICF	-

- Phosphate has a closer pK to blood pH, so technically it's superior over bicarbonate in buffering power however **it's not abundant in the ECF**

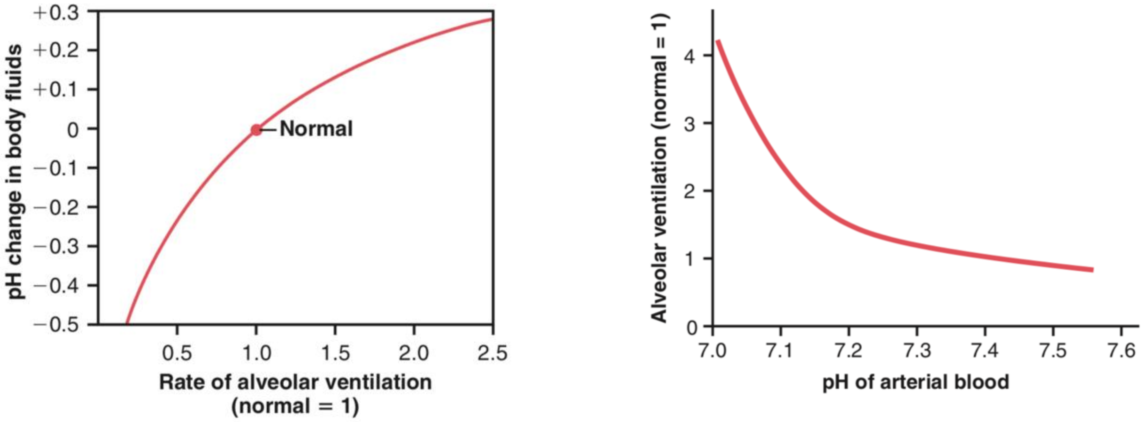
2nd Defense: Respiratory System

- Second most powerful system that works within minutes to hours
- It mainly excretes CO_2 from the body to decrease the body pH

⇓ pH → Hyperventilation → decrease CO_2 levels → ⇑ pH

⇑ pH → Hypoventilation → increase CO_2 levels → ⇓ pH

- Normally, PCO2 = 40 mmHg (35-45 mmHg)



- In figure A, as the ventilation increases the pH increases because more CO_2 is excreted
- In figure B, as the pH increases the body will hypoventilate to accumulate CO_2

3rd Defense: Renal System

- Most powerful system that works within hours to days (slowest)
- **It regulates acid base balance through:**

1) HCO_3^- reabsorption:
   - 80-90% is reabsorbed in the PCT, while 10 % is reabsorbed in the LoH
   - β-intercalated cells can secrete extra bicarbonate in the distal part
   - HCO3 reabsorption is linked to H+ secretion.
2) HCO_3^- synthesis in ammonia buffering system (explained later)
3) H^+ secretion:
   - Happens in α-intercalated cells (iCells) in the distal part of the nephron (apical membrane)
   - α-intercalated cells have H/ATPase and H/K ATPase (capable of actively secreting H^+)
   - Only a **limited** amount of free H^+ can be secreted (0.04 mmol/L)

- The lowest possible urine pH = 4.5, to excrete more H^+ we need to buffer them with other molecules in the tubular lumen

Urine Buffering Pathways

Filtered	Synthesized
Phosphate Buffer System	Ammonia Buffer System
$HPO_4^{2-} + H^+ \rightarrow H_2PO_4^-$	**$NH_3 + H^+ \rightarrow NH_4^+$**

- H^+ will combine with hydrogen phosphate to form dihydrogen phosphate which will be excreted in the urine without changing its pH
- Phosphate handling system is limited because of the **limited** amount of phosphate available in the tubular fluid (filtrated)

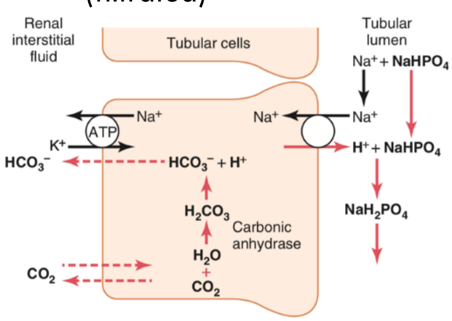
- H^+ will combine with ammonia to form ammonium **"ammoniagenesis"** which will be excreted in the urine without changing its pH, **this happens in 2 ways:**

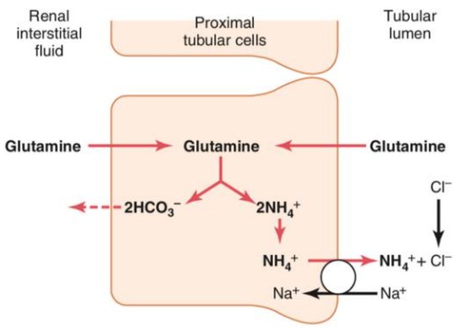
1) In PCT, Loop of Henle, and DCT

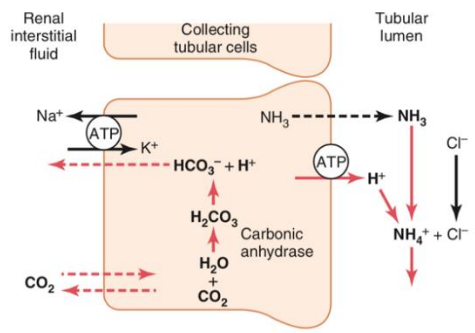
- Glutamine will synthesize 2 NH_4^+, which get secreted, and 2 HCO_3^-, which get reabsorbed, **inside the cell**

2) In CT and CD

- NH_4^+ is not permeable so NH_3 will be **secreted out** which will later combine with H^+ forming 1 NH_4^+ and 1 HCO_3^-







- Renal tubular cells can synthesize ammonium (especially PCT) which makes ammonia system more important than the phosphate system **(unlimited)**
- Ammonia system is the most important system in case of **acidosis**

Acid-Base Disorders

- Before we start let's simplify the bicarbonate reaction to:

$$CO_2 \Leftrightarrow HCO_3^- + H^+$$

- **There are 4 primary acid/base disorders:**
  1. Respiratory acidosis: ⇑ PCO_2
  2. Respiratory alkalosis: ⇓ PCO_2
  3. Metabolic acidosis: ⇓ HCO_3^-
  4. Metabolic alkalosis: ⇑ HCO_3^-

- To find out the correct primary disorder we need to analyze the following:
  - Blood gases - Plasma electrolytes - compensatory mechanisms

- Compensation is the response of the body towards a pH change through the kidneys or lungs
- For example, in respiratory acidosis there'll be an increase in PCO_2
- This will shift the equation towards the HCO_3^- side increasing it

$$\Uparrow CO_2 \Leftrightarrow \Uparrow HCO_3^- + H^+$$

- Physiologically The body normally attempts to correct the primary acid base disturbances by a **secondary** or **compensatory response** trying to restore pH towards normal.

➔ The kidneys compensate for primary respiratory disorders.

➔ The lungs compensate for primary metabolic disorders.

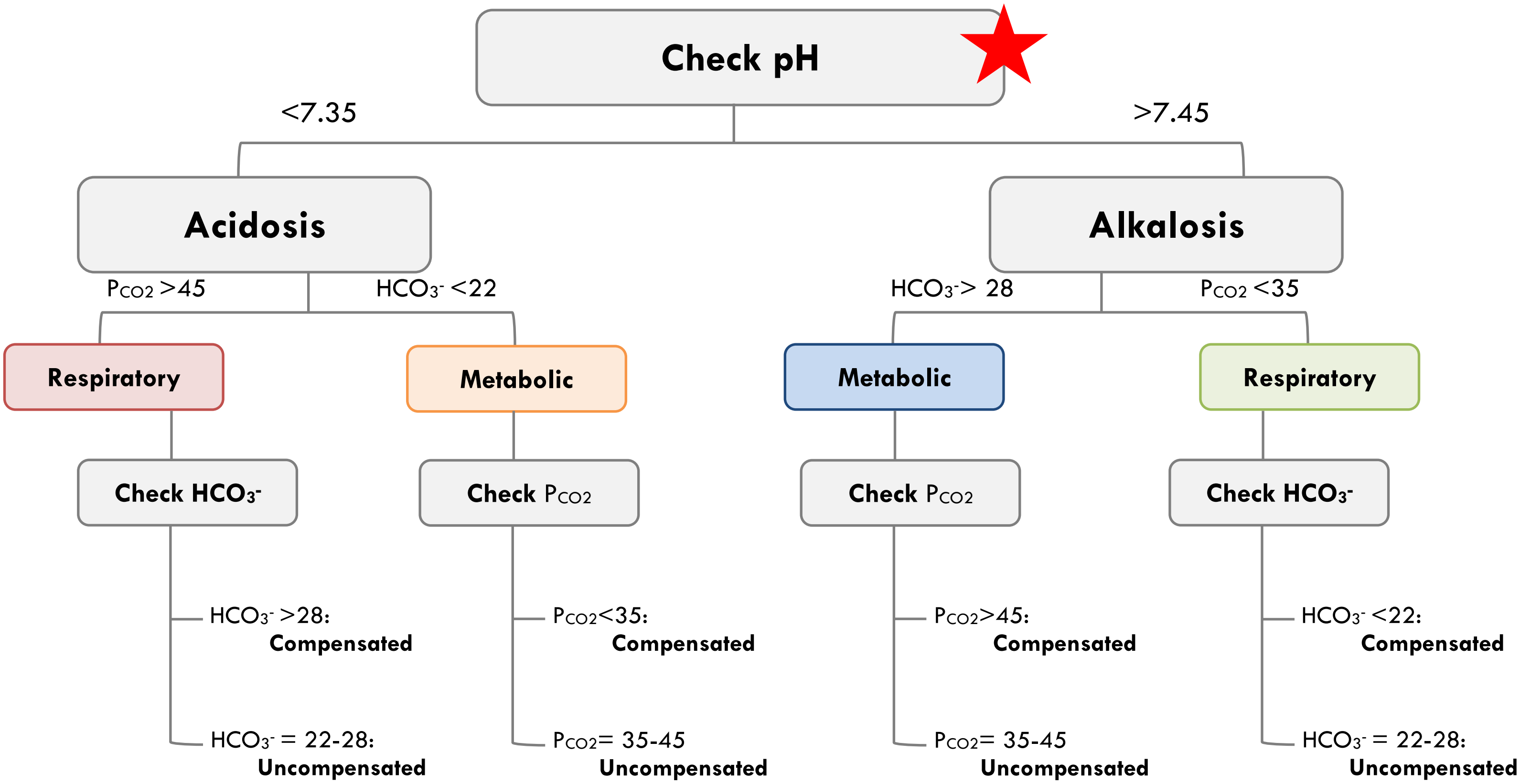
Condition		Common causes
Respiratory	Acidosis	Hypoventilation: Lung disease: COPD, pneumonia, Pulmonary edema Depression of Resp. center: (head injury, Opioids ingestion)
	Alkalosis	Hyperventilation: anxiety, pregnancy, psychoneurosis, high altitude, hypoxia, fever, initial stages of pulmonary emboli
Metabolic	Acidosis	⇑ H^+: diabetic ketoacidosis, lactic acidosis, ethylene glycol and salicylates toxicity, starvation ⇓ H^+ elimination: renal failure ⇓ HCO_3^-: diarrhea (GIT), renal tubular acidosis, CAI, Hypoaldosteronism (Kidney)
	Alkalosis	⇓ H^+: vomiting, some diuretics except CAI (K^+ wasting), Hyperaldosteronism ⇑ HCO_3^-: alkaline ingestion, antacids

My dear student, you can skip the whole lecture BUT don't't' skip this and the next page

⇑ **DON'T YOU DARE SKIP THIS** ⇑

Disorder	pH	Primary disturbance	Compensation
Respiratory acidosis	$\Downarrow$	$\Uparrow$ P_{CO_2}	$\Uparrow$ HCO_3^-
Metabolic acidosis	$\Downarrow$	$\Downarrow$ HCO_3^-	$\Downarrow$ P_{CO_2}
Metabolic alkalosis	$\Uparrow$	$\Uparrow$ HCO_3^-	$\Uparrow$ P_{CO_2}
Respiratory alkalosis	$\Uparrow$	$\Downarrow$ P_{CO_2}	$\Downarrow$ HCO_3^-

To know the exact primary disorder, we follow this flow chart



Normal values of the parameters		
pH	HCO_3^-	P_{CO_2}
7.35-7.45	22-28 mEq/L	35-45 mmHg

Mixed Acid/Base Disorders

- It's a condition were both respiratory and metabolic disorders happen at the same time, resulting in two primary disturbances
- For example: a diabetic patient who got ketoacidosis had pneumonia. His blood pH was 6.95, P_{CO2} was 80 mmHg, His $[HCO_3^-]$ was 18 mEq/L

What's the condition?

Mixed acidosis

Anion-Gap not important

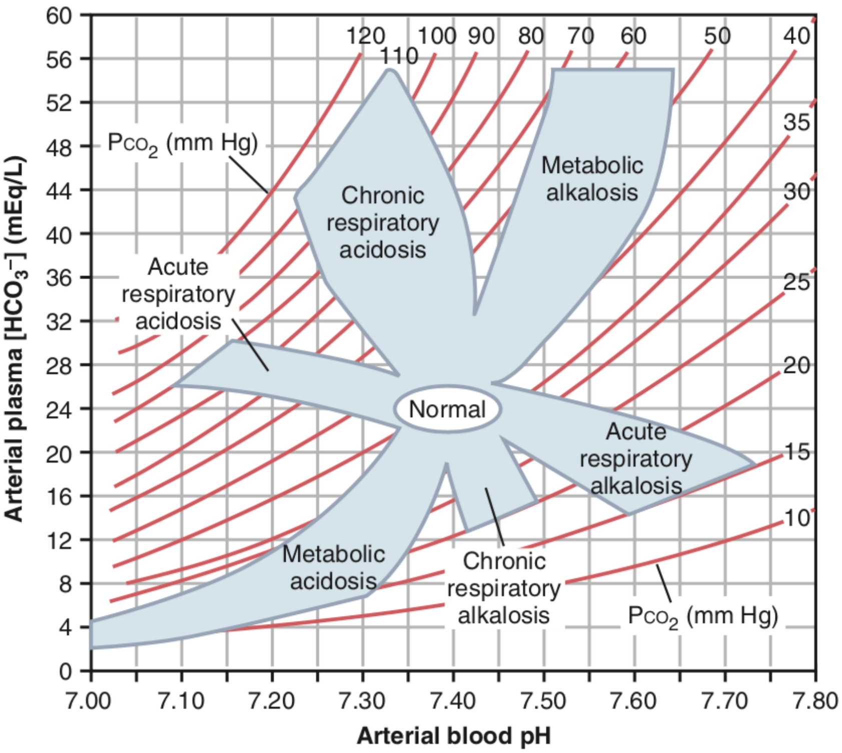
- Anion gap is the measurement of cations – anions present in the body

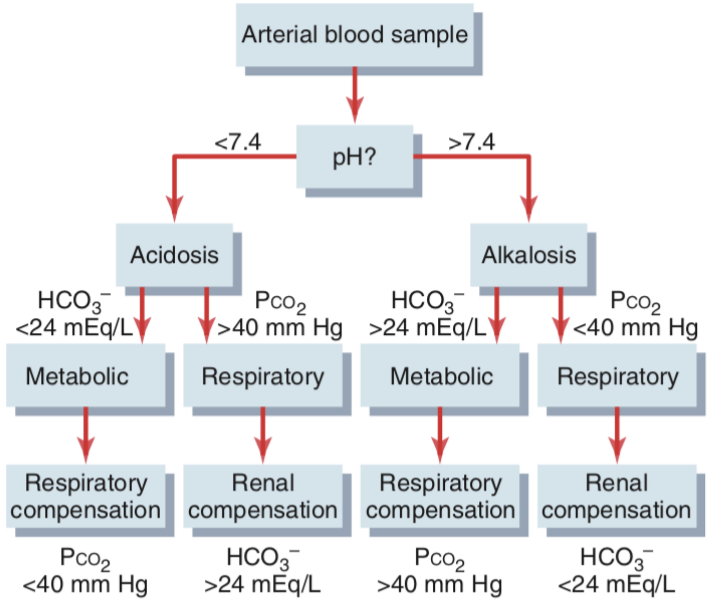
$$AG = [Na^+] – [Cl^-] – [HCO_3^-] = 12\text{-}18 \text{ mmol/L}$$

- In the body, cations must equal to anions but in clinical practice we always measure these three ions which will result in net positive result of 12-18
- Anion gap measurement will help us further classifying metabolic acidosis. Some metabolic acidosis conditions result in a high AG while others will keep the AG normal

High AG metabolic acidosis
• Diabetic acidosis • Lactic acidosis • Ethylene glycol or salicylates toxicity
Normal AG metabolic acidosis
• Diarrhea • Renal tubular acidosis

Very Important Summary





Increase H^+ Secretion and HCO_3^- Reabsorption	Decrease H^+ Secretion and HCO_3^- Reabsorption
↑ P_{CO_2}	↓ P_{CO_2}
↑ H^+, ↓ HCO_3^-	↓ H^+, ↑ HCO_3^-
↓ Extracellular fluid volume	↑ Extracellular fluid volume
↑ Angiotensin II	↓ Angiotensin II
↑ Aldosterone	↓ Aldosterone
Hypokalemia	Hyperkalemia

1-A patient known to have COPD presented with 3-day history of fever, SOB, and cough productive of yellowish sputum. His ABGs showed:
- **pH = 7.25** (low)
- **PCO2= 80 mmHg.** (High)
- **[HCO3-] = 34 mEq/L** (High)

Compensated Respiratory Acidosis

2-A 21year old man with IDDM presents to ER with mental status changes, nausea, vomiting, abdominal pain and rapid respirations. His ABGs showed:
- **pH = 7.2** (low)
- **PCO2 = 20 mmHg** (low)
- **[HCO3-] = 8 mEq/l** (low)

Compensated Metabolic Acidosis

3-A 2-year old child who is lethargic and dehydrated has a 3-day history of vomiting. His ABGs showed:
- **pH = 7.56** (High)
- **PCO2= 44 mmHg** (Normal)
- **[HCO3-] = 37 mEq/l** (High)

Uncompensated Metabolic Alkalosis

4-A 20-year old student suffered a panic attack while awaiting an exam. Her ABGs showed:
- **pH = 7.6** (High)
- **PCO2= 24 mmHg.** (Low)
- **[HCO3-] = 23 mEq/L** (Normal)

Uncompensated Respiratory Alkalosis

5-A 69-year-old patient known to have COPD presented with a 3-day history of abdominal pain and diarrhea. His ABGs showed;
- **pH = 6.96** (Low)
- **PCO2 = 55mmHg** (High)
- **[HCO3-] = 12 mmol/L C** (Low)

Mixed Disorder, (Respiratory +Metabolic) Acidosis

1- Look at the pH to determine if it is acidosis or alkalosis
2-Look at CO2 and HCO3 and see if it is consistent with the pH to determine the primary cause (e.g. acidosis indicates HIGH co2 or LOW HCO3)
3-Determine if it is compensatory or not by looking at the other one's level (e.g. if Co2 is the primary cause check to see for changes in HCO3)

E.g.
pH is 7.0
PCo2 is 58 mmHg
HCo3 is 24 mmol/L

pH indicates acidosis
PCo2 indicates resp acidosis
HCo3 indicates uncompensated resp acidosis
In case it was compensated resp acidosis, Hco3 would be elevated
If it was a mixed disorder (both metabolic and resp acidosis), Hco3 would be decreased

Quiz

1. **What is the primary way to secrete H+ in the kidneys?**

   A. NHE exchanger
   B. H ATPase
   C. H/K ATPase
   D. H/anion exchanger

2. **A patient suffering from severe diarrhea for 2 days will most likely have?**

   A. pH=7 HCO_3^-= 15 mEq/L
   B. pH=7.5 HCO_3^-= 38 mEq/L
   C. pH=7 P_{CO2}= 80 mEq/L
   D. pH=7.5 P_{CO2}= 25 mEq/L

3. **Which of the following conditions will cause low P_{CO2} alkalosis?**

   A. COPD
   B. Diabetic ketoacidosis
   C. Vomiting
   D. Pregnancy

4. **Based on the following pH=7.5, HCO_3^-= 40, P_{CO2}=55, what is the diagnosis?**

   A. Metabolic acidosis
   B. Metabolic alkalosis
   C. Respiratory acidosis
   D. Respiratory alkalosis

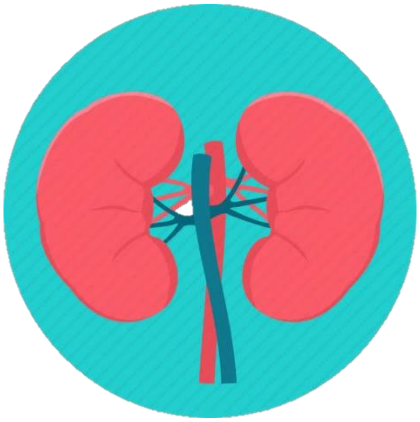
5. **A diabetic patient with COPD had the following, what is your diagnosis?**

   pH=6.9 HCO_3^-= 18 mEq/L P_{CO2}=75 mmHg

   A. Mixed alkalosis
   B. Mixed acidosis
   C. Compensatory respiratory acidosis
   D. Compensatory respiratory alkalosis

Answers: C, A, D, B, B

Thank You



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