Adapted from *High-Yield Acid-Base*, by J. Longenecker.
Henderson-Hasselbalch Equation

\[
pH = pK_a + \log \frac{[A^-]}{[HA]} \rightarrow pH = pK_a + \log \frac{[HCO_3^-]}{[H_2CO_3]} \rightarrow pH = 6.1 + \log \frac{[HCO_3^-]}{(0.03 \times pCO_2)}
\]
MASS ACTION EQUATION \[ H^+ + HCO_3^- = H_2CO_3 = CO_2 + H_2O \]

HENDERSEN-HASSELBACH EQUATION \[ pH = pK + \log \frac{HCO_3^-}{0.03pCO_2} \]

KASSIRER-BLEICH MODIFICATION \[ H^+ = 24 \frac{CO_2}{HCO_3^-} \]

<table>
<thead>
<tr>
<th>pH</th>
<th>7.0</th>
<th>7.1</th>
<th>7.2</th>
<th>7.3</th>
<th>7.4</th>
<th>7.5</th>
<th>7.6</th>
<th>7.7</th>
<th>7.8</th>
<th>7.9</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>H^+</td>
<td>100</td>
<td>80</td>
<td>64</td>
<td>51</td>
<td>40</td>
<td>32</td>
<td>26</td>
<td>20</td>
<td>16</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>ARTERIAL</td>
<td>VENOUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.40</td>
<td>&lt; 7.35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCO2</td>
<td>40</td>
<td>&gt; 40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCO3</td>
<td>24</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pO2</td>
<td>&gt; 70</td>
<td>&lt; 60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
As dictated by the Henderson-Hasselbalch equation, disturbances in either the respiratory component (pCO₂) or metabolic component (HCO₃⁻) can lead to alterations in pH.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Acidosis</td>
<td>(Too little HCO₃⁻)</td>
</tr>
<tr>
<td>Metabolic Alkalosis</td>
<td>(Too much HCO₃⁻)</td>
</tr>
<tr>
<td>Respiratory Acidosis</td>
<td>(Too much CO₂)</td>
</tr>
<tr>
<td>Respiratory Alkalosis</td>
<td>(Too little CO₂)</td>
</tr>
</tbody>
</table>

**Primary Acid-Base Disorders**
When a primary acid-base disorder exists, the body attempts to return the pH to normal via the “other half” of acid base metabolism.

Primary metabolic disorder → Respiratory compensation

Primary respiratory disorder → Metabolic compensation
## Compensation (continued)

<table>
<thead>
<tr>
<th>Primary Disorder</th>
<th>Compensatory Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>Increased ventilation</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>Decreased ventilation</td>
</tr>
</tbody>
</table>
| Respiratory acidosis              | Increased renal reabsorption of $\text{HCO}_3^-$ in the proximal tubule  
|                                   | Increased renal excretion of $\text{H}$ in the distal tubule |
| Respiratory alkalosis             | Decreased renal reabsorption of $\text{HCO}_3^-$ in the proximal tubule  
<p>|                                   | Decreased renal excretion of $\text{H}^+$ in the distal tubule |</p>
<table>
<thead>
<tr>
<th>Type of Primary Alteration</th>
<th>Secondary Response</th>
<th>Mechanism of Secondary Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic acidosis</strong></td>
<td>Decrease in plasma $[\text{HCO}_3^-]$</td>
<td>Decrease in Pa CO$_3$</td>
</tr>
<tr>
<td><strong>Metabolic alkalosis</strong></td>
<td>Increase in plasma $[\text{HCO}_3^-]$</td>
<td>Increase in PaCO$_3$</td>
</tr>
<tr>
<td><strong>Respiratory acidosis</strong></td>
<td>Increase in PaCO$_3$</td>
<td>Increase in plasma $[\text{HCO}_3^-]$</td>
</tr>
<tr>
<td><strong>Respiratory alkalosis</strong></td>
<td>Decrease in Pa CO$_3$</td>
<td>Decrease in plasma $[\text{HCO}_3^-]$</td>
</tr>
<tr>
<td>Acid-Base Disorder</td>
<td>Change in Plasma HCO₃⁻ Concentration</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>PaCO₂ should fall by 1.0 to 1.5 X the fall in plasma HCO₃⁻ concentration</td>
<td></td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>PsCO₂ should rise by 0.25 to 1.0 X the rise in plasma HCO₃⁻ concentration</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory acidosis</td>
<td>Plasma HCO₃⁻ concentration should rise by about 1 mmoles per liter for each 10 mm Hg increment in PaCO₂ (± 3 mmoles per liter).</td>
<td></td>
</tr>
<tr>
<td>Chronic respiratory acidosis</td>
<td>Plasma HCO₃⁻ concentration should rise by about 4 mmoles per liter for each 10 mm Hg increment in PaCO₂ (± 4 mmoles per liter).</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory alkalosis</td>
<td>Plasma HCO₃⁻ concentration should fall by about 1 to 3 mmoles per liter for each 10 mm Hg decrement in the PaCO₂, usually not to less than 18 mmoles per liter.</td>
<td></td>
</tr>
<tr>
<td>Chronic respiratory alkalosis</td>
<td>Plasma HCO₃⁻ concentration should fall by about 2 to 5 mmoles per liter per 10 mm Hg decrement in PaCO₂ but usually not to less than 14 mmoles per liter.</td>
<td></td>
</tr>
</tbody>
</table>
REGULATION OF $\text{CO}_2$ (Read also the separate article in the syllabus)

Plasma $\text{CO}_2$ is determined by the rate of metabolic $\text{CO}_2$ production and by alveolar ventilation:

$$p\text{CO}_2 = \frac{\text{CO}_2 \text{ production}}{\text{alveolar ventilation}} \times .84$$
• $H_2O \rightleftharpoons H^+ + OH^-$
• Only 1 in 14 million H2O molecules is ionized to H+ and OH-

• When $[H^+] = [OH^-]$ solution is neutral

$$K = [H^+][OH^-] = 1 \times 10^{-14}$$

$$K = [H^+]^2 = 1 \times 10^{-14}$$

In a neutral solution $[H^+] = 1 \times 10^{-7}$ M

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

pH of a neutral solution = $-\log(1 \times 10^{-7}) = 7$
- If pH of solution is $<7$, acidic
- If pH of solution is $>7$, basic

<table>
<thead>
<tr>
<th>solution</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1M NaOH</td>
<td>14</td>
</tr>
<tr>
<td>Human blood</td>
<td>7.4</td>
</tr>
<tr>
<td>Coffee</td>
<td>5</td>
</tr>
<tr>
<td>Coke</td>
<td>3</td>
</tr>
<tr>
<td>1M HCl</td>
<td>0</td>
</tr>
</tbody>
</table>
Acids are compounds that donate a H+ to solution

\[ \text{HCl} \rightleftharpoons \text{H}^+ + \text{Cl}^- \]

Bases are compounds that accept H+ from solution

\[ \text{H}^+ + \text{HCO}_3^- \rightleftharpoons \text{H}_2\text{CO}_3 \]
So what’s the big deal with H+?

- H+ is very reactive
- Almost all aspects of cell function can be influenced by H+
- Enzyme reactions are particularly sensitive to [H+]; there is an optimal pH above or below which the enzyme functions poorly
- Normal extracell pH=7.4
- Acidosis pH<7.4 (death <6.8)
- Alkalosis pH>7.4
The body normally produces some acids:
- Metabolism of proteins
- Lactic acid from muscle

Disturbances of Acid-Base Balance
1. **Respiratory** – changes in CO2

2. **Metabolic** – no change in CO2
Metabolic Acid-Base Disturbance

1. Metabolic Acidosis

A. Causes
   • Diarrhea (loss of HCO3-)
   • Acid ingestion (aspirin – acetylsalicylic acid)
   • Kidney failure to secrete H+

B. Effects
   • CNS depression and coma, death

2. Metabolic Alkalosis

A. Causes
   • Vomiting (loss of H+)

B. Effects
   • CNS excitability, muscle tetanus, death
1. Fluid Buffering systems
2. Kidney
3. Respiratory

Acid-Base balance
• consists of a mixture of a weak acid and its base
• **Resists changes in pH when small amounts of H\(^+\) or OH\(^-\) are added**

Major physiologically important buffer in blood plasma:

a) **Bicarbonate**

\[
CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- 
\]

**A buffering system**
General strategy

1. Balance the H+ intake and production with H+ excretion

2. Recover HCO3 to preserve buffering capability

Renal regulation of H+ and HCO3
Basic Renal HCO$_3^-$ handling
Almost all the HCO$_3^-$ in the plasma is filtered

Filtered HCO$_3^-$

HCO$_3^-$ + H$^+$

H$_2$CO$_3$

H$_2$O + CO$_2$

H$^+$

Na

K

HCO$_3^-$

CO$_2$ + H$_2$O

H$^+$

H$_2$CO$_3$

Carbonic anhydrase
1. CO2 and H2O form H2CO3, which splits into H+ and HCO3

2. HCO3 moves to the interstitial fluid and blood

3. H+ is secreted into tubule, where it reacts with filtered HCO3 to regenerate CO2 and H2O

4. For every HCO3 filtered, an HCO3 is formed within the tubular cell & transported to the interstitial fluid and blood

- “HCO3 reabsorption”

- A second important buffer in the tubular fluid is the phosphate system
- Works in the tubular fluid to buffer H+ and allows for production of new HCO3

A third important buffer in the tubular fluid is the ammonia system
- Also, works in the tubular fluid to buffer H+ and allows for production of new HCO3
Renal $\text{HPO}_4^{2-}$ handling and new $\text{HCO}_3^-$

Almost all the $\text{HPO}_4^{2-}$ in the plasma is filtered

Filtered $\text{HPO}_4^{2-}$

$\text{HPO}_4^{2-} + \text{H}^+ \rightarrow \text{H}_2\text{PO}_4^-$

$\text{H}_2\text{PO}_4^- \rightarrow \text{CO}_2 + \text{H}_2\text{O}$

$\text{Na}$

$\text{H}^+$

$\text{HCO}_3^-$

$\text{H}_2\text{CO}_3$ Carbonic anhydrase

$\text{K}$

$\text{Na}$

$\text{HCO}_3^-$

$\text{CO}_2$
Renal NH$_4^+$ handling and new HCO$_3^-$
Renal Regulation of Acid-Base

(NH₄⁺) can substitute for K⁺ on the Na/CI/K cotransporter in the loop of Henle.
Bicarbonate buffers are important in the blood and extracellular fluids

- **In the kidney:**
  - Bicarbonate allows for excretion of H+ as water and preservation of HCO3

- **Phosphate and ammonia serve as tubule** fluid specific buffers and they allow for production of ‘new’ HCO3-

**Renal Response to Acid-Base Disturbance**

1. **Metabolic Acidosis**
   - Increase HCO3 reabsorption
   - Increase H+ secretion
   - Increase new HCO3 production

2. **Metabolic Alkalosis**
   - decrease HCO3 reabsorption
   - decrease H+ secretion

**Responses to acid-base imbalance**

1. Fast - Fluid buffering systems as outlined above

2. Moderate – Respiratory chemoreceptors sensitive to CO2 and [H+] regulate breathing and CO2 levels

3. Slow (days) Renal - adjust HCO3 and H+ handling and production of new HCO3
1. Check the pH

If the pH < 7.35, acidemia (and at least 1 acidosis) is present.

If the pH > 7.45, alkalemia (and at least 1 alkalosis) is present.
2. Check the pCO$_2$

pH $< 7.35$ and pCO$_2$ $< 40$ $\rightarrow$ metabolic acidosis
pH $< 7.35$ and pCO$_2$ $> 40$ $\rightarrow$ respiratory acidosis

pH $> 7.45$ and pCO$_2$ $< 40$ $\rightarrow$ respiratory alkalosis
pH $> 7.45$ and pCO$_2$ $> 40$ $\rightarrow$ metabolic acidosis

Practical Approach
## Practical Approach

<table>
<thead>
<tr>
<th>Most prominent disorder</th>
<th>Compensation formula</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic acidosis</strong></td>
<td>$pCO_2 \approx 1.5 \ [HCO_3^-] + 8$</td>
</tr>
<tr>
<td><strong>Metabolic alkalosis</strong></td>
<td>$pCO_2 \approx 0.9 \ [HCO_3^-] + 16$</td>
</tr>
</tbody>
</table>
| **Respiratory acidosis** | For every 10 $\Delta$ in $pCO_2$, pH decreases by:  
  0.08 (in acute resp. acidoses)  
  0.03 (in chronic resp. acidoses) |
| **Respiratory alkalosis** | For every 10 $\Delta$ in $pCO_2$, pH increases by:  
  0.08 (in acute resp. alkaloses)  
  0.03 (in chronic resp. alkaloses) |
Anion "Gap"
1. An "artefact" of how we measure blood electrolytes
2. Determined by:

Normal = 10
3. If the anion gap is normal with acidosis then $\text{Cl}^-$ has increased to match $\text{HCO}_3^-$ decline
4. If the anion gap is increased some other anion is involved
Anion Gap (AG)

\[ AG = (Na^+ - (Cl^- + HCO_3^-)) \]

- Normal AG
  10-14

- AG is primarily due to albumin

- Increased AG almost always due to a rise in unmeasured anions

Anion Gap = 10

- \( Na^+ \)
- \( Cl^- \)
- \( HCO_3^- \)
- Proteins, \( SO_4^- \), organic acids

\( K^+, Mg^{++}, Ca^{++} \)
Increased anion gap metabolic acidosis

$\begin{align*}
\text{Na}^+ & : 140 \\
\text{Cl}^- & : 100 \\
\text{HCO}_3^- & : 15 \\
\text{K}^+, \text{Mg}^{++}, \text{Ca}^{++}, \text{proteins, } \text{SO}_4^{--}, \text{organic acids} & \\
\end{align*}$

Anion Gap = 25
Normal anion gap metabolic acidosis

\[ \text{Anion Gap} = 10 \]
Calculate the anion gap

Anion gap = [Na⁺] – ([Cl⁻] + [HCO₃⁻])

If the anion gap is elevated, an elevated gap metabolic acidosis is likely present.

Calculate HCO₃⁻ deficit

HCO₃⁻ deficit = (kg body weight)x (0.4) x (desired [HCO₃⁻] – measured [HCO₃⁻])

Practical Approach
The concentrations are expressed in units of milliequivalents/liter (mEq/L) or in millimoles/litre (mmol/L).

**With potassium**

It is calculated by subtracting the serum concentrations of chloride and bicarbonate (anions) from the concentrations of sodium and potassium (cations):

\[
= ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-])
\]

**Without potassium (Daily practice)**

However, the potassium is frequently ignored because potassium concentrations, being very low, usually have little effect on the calculated gap. This leaves the following equation:

\[
= [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])
\]

**Anion gap**
Anion Gap = Na - (Cl + HCO3-)
Delta Gap = Anion Gap - 12 (nl anion gap)

The delta ratio is sometimes used in the assessment of elevated anion gap metabolic acidosis to determine if a mixed acid base disorder is present.

\[
\text{Delta ratio} = \frac{\Delta \text{Anion gap}}{\Delta [\text{HCO}_3^-]} \quad \text{or} \quad \frac{\uparrow \text{anion gap}}{\downarrow [\text{HCO}_3^-]}
\]

\[
\text{Delta Delta} = \text{Measured anion gap} - \text{Normal anion gap}
\]
\[
\text{Delta del Normal} = \text{Normal [HCO}_3^-] - \text{Measured [HCO}_3^-]
\]

\[
\text{Delta Delta} = (\text{AG} - 12) \\
(24 - [\text{HCO}_3^-])
\]
<table>
<thead>
<tr>
<th>Delta ratio</th>
<th>Assessment Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.4</td>
<td>Hyperchloremic normal anion gap acidosis</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>High AG &amp; normal AG acidosis</td>
</tr>
</tbody>
</table>
| 1 to 2      | Pure Anion Gap Acidosis  
Lactic acidosis: average value 1.6  
DKA more likely to have a ratio closer to 1 due to urine ketone loss |
| > 2         | High AG acidosis and a concurrent metabolic alkalosis  
or a pre-existing compensated respiratory acidosis |
- High anion gap metabolic acidosis

- A high anion gap indicates acidosis. e.g. In uncontrolled diabetes, there is an increase in ketoacids (i.e. an increase in unmeasured anions) and a resulting increase in the anion gap. In these conditions, bicarbonate concentrations decrease, in response to the need to buffer the increased presence of acids (as a result of the underlying condition). The bicarbonate is consumed by the unmeasured anion (via its action as a buffer) resulting in a high anion gap.

- Lactic acidosis
- Ketoacidosis
- Diabetic ketoacidosis
- Alcohol abuse
- **Toxins:**
  - Ethylene glycol
  - Lactic acid
  - Uremia

  Methanol
  Propylene Glycol
  Phenformin
  Aspirin
  Cyanide, coupled with elevated venous oxygenation
  Iron
  Isoniazid

  Renal failure,
In patients with a normal anion gap the drop in HCO₃⁻ is compensated for almost completely by an increase in Cl⁻ and hence is also known as hyperchloremic acidosis.

The HCO₃⁻ lost is replaced by a chloride anion, and thus there is a normal anion gap.

Gastrointestinal loss of HCO₃⁻ (i.e., diarrhea) (note: vomiting causes hypochloraemic alkalosis)

Renal loss of HCO₃⁻ (i.e. proximal renal tubular acidosis (RTA) also known as type 2 RTA)

Renal dysfunction (i.e. distal renal tubular acidosis also known as type 1 RTA)

**Ingestions**
- Ammonium chloride and Acetazolamide, ifosfamide.
- Hyperalimentation fluids (i.e. total parenteral nutrition)

Some cases of ketoacidosis, particularly during rehydration with Na+ containing IV solutions.

Alcohol (such as ethanol) can cause a high anion gap acidosis in some patients, but a mixed picture in others due to concurrent metabolic alkalosis.

Mineralocorticoid deficiency (Addison's disease)
A low anion gap is frequently caused by hypoalbuminemia
Overview of Biochemical Homeostasis

- Produced Internally
- Consumed Internally

Outside World
- Enters via the lungs
- Enters via the GI tract
- Enters via the skin

Blood

Internal Reservoir
(Cannot be directly measured)

Outside World
- Leaves via the lungs
- Leaves via the GI tract
- Leaves via the skin
- Leaves via the urine
**Differential Diagnosis for Acid-Base Disorders**

**Produced Internally**

**Physiologic Acid Production**
- Aerobic Metabolism (carbohydrates, fats, protein → CO₂; fats, protein → non-volatile acids)

**Pathologic Acid Production**
- Anaerobic Metabolism (carbohydrates → non-volatile acids)
- Metabolism of Various Toxins (e.g. methanol, ethylene glycol)

**Consumed Internally**
- Neither H⁺ nor CO₂ is consumed internally

**Outside World**
- HCO₃⁻ and H⁺ enter via the GI tract

**Blood**
- HCO₃⁻ + H⁺ → CO₂ + H₂O

**Various Intracellular & Extracellular Buffers**

**Metabolic Acidosis**
- (Too much H⁺ / Too little HCO₃⁻)
  - Decreased intake of HCO₃⁻
  - Increased intake of H⁺
  - Increased aerobic metabolism
  - Production of pathologic acids (lactate, ketones)
  - Increased GI loss of HCO₃⁻
  - Decreased GI loss of H⁺

**Metabolic Alkalosis**
- (Too little H⁺ / Too much HCO₃⁻)
  - Decreased intake of H⁺
  - Increased intake of HCO₃⁻
  - Decreased aerobic metabolism
  - Decreased GI loss of HCO₃⁻
  - Increased GI loss of H⁺

**Respiratory Acidosis**
- (Too much CO₂)
  - Increased aerobic metabolism
  - Decreased CO₂ excretion via the lungs (aka hyperventilation)

**Respiratory Alkalosis**
- (Too little CO₂)
  - Decreased aerobic metabolism
  - Increased CO₂ excretion via the lungs (aka hyperventilation)