Acid-Base Balance and the Anion Gap

1. The body strives for electrical neutrality.
   
   a. Cations = Anions

   b. One of the cations is very special, H⁺, and its concentration is monitored and regulated very closely.

   c. Volatile acid (CO₂) and non-volatile acids, lactate, H₂PO₄⁻, H₂CO₃

2. Blood pH is described by the Henderson-Hasselbalch equation

   \[ pH = 6.1 + \log \frac{HCO_3^-}{PaCO_2 \times 0.0301} \]

3. Note the importance of

   a. Arterial CO₂, indicated as PaCO₂
   b. Bicarbonate, HCO₃⁻
   c. Carbonic anhydrase

4. We measure the pH of arterial blood.

   a. Arterial blood has been through the lungs and should be at optimal pH.

   b. This is not the case for venous blood.

   c. 7.35-7.45

   d. Central nervous system control of respirations and therefore PaCO₂

   e. The control of bicarbonate, HCO₃⁻, by the kidneys
      i. Retention or
      ii. Excretion
5. So how does it all work under normal circumstances to keep our pH about 7.4?

a. Normally, CO₂ production and loss are matched

b. PaCO₂ is maintained at about 40 mmHg

c. PaCO₂ is regulated by respiration rate, either slowing down or speeding up respirations, to either blow off or retain CO₂.
   a. Control comes from the CNS by regulating respiration rate.
   b. Production rate of CO₂ is not subject to regulation,

d. The kidney regulates plasma [HCO₃⁻] (by extension [H⁺] and pH) by three mechanisms
   a. Reabsorption of filtered HCO₃⁻, this is a recovery operation
   b. Formation of titratable acid, H₂PO₄⁻ distal tubule
   c. Excretion of NH₄⁺ distal tubule
Get this. The kidney glomerulus passively filters on the order of 4000 mmol of HCO₃⁻ each day. This has to be reabsorbed. To lose it would be a disaster. In order to reabsorb this filtered load of HCO₃⁻, the tubular cells must therefore secret 4000 mmol of hydrogen ions. This allows the conversion of carbonic acid to CO₂ and water, which will passively come back into the proximal tubular cell. The secretion of titratable acid by the kidney, used to actually modify the blood pH, goes on in the distal tubule.

6. Basically, the regulation of arterial pH includes
   a. Regulation of PaCO₂ by the respiratory system.
   b. Regulation of HCO₃⁻ by the kidneys
   c. Chemical buffering in the form of NH₄⁺ and H₂PO₄⁻ secretion by the distal convoluted tubule cells.

7. Simple acid/base disorders, adjustments and compensation for running a road race.
   a. Primary respiratory and/or metabolic disturbances invoke predictable compensatory changes to restore the PaCO₂ and pH to normal.

   If uncomplicated by other factors, a high PaCO₂ means a lowered pH. Respiration picks up because of the elevated PaCO₂. The increased respiration rate results in the blowing off CO₂, which pulls the pH back up into the healthy range.

   Buffering capacity comes thanks to the miracle of carbonic anhydrase.

   ![Carbonic Anhydrase](image)

   Metabolic acidosis means extra H⁺ ions are coming from a metabolic derangement, such as lactic acidosis in a diabetic, which will result in excessive respiration rate, lowering the PaCO₂, while at the same time raising the PaO₂.
Predict the degree of respiratory compensation with a metastolic acidosis.

\[ \text{PaCO}_2 = (1.5 \times [\text{HCO}_3^-]) + 8 \]

\( \text{PaCO}_2 \) decreases 12 mmol/L for each mmol/L of \( \text{HCO}_3^- \)

Thus a patient with a metabolic acidosis and 12 mmol/L of \( \text{HCO}_3^- \) would be expected to have a \( \text{PaCO}_2 \) between 24 and 28. If it’s higher or lower, there is something else going on, in other words a mixed acid/base disorder.

For simple acid/base disturbances, the diagram below can be quite helpful.
8. Mixed acid-base disorders. Here several problems of acid-base management are colliding at the same time. It’s definitely not just a matter of the body trying to compensate for one such disorder.

   a. An example would be a diabetic with ketoacidosis, who also happens to have emphysema, or develops a bad pneumonia (which is not all that unusual), and as a result develops a respiratory acidosis.

   b. You can even have a mixed condition consisting of an acidosis and alkalosis. Here the pH might even be in the reference range. How would know there is a actually a serious problem underlying things?

      i. Look at the **anion gap**.

      ii. **Bicarb gap**


   a. Get arterial blood gases and electrolytes at the same time.

   b. Compare the $\text{HCO}_3^-$ value from the blood gases and lytes to verify accuracy.

   c. Calculate the anion gap (AG)

   d. Review the four common causes of high AG acidosis

      i. ketoacidosis

      ii. lactic acidosis

      iii. renal failure

      iv. toxin

   e. Review the two major causes of hyperchloremic, or non-gap, acidosis

      i. $\text{HCO}_3^-$ loss from the GI tact

      ii. renal tubular acidosis

   f. Estimate compensatory response.

   g. Compare $\Delta \text{AG}$ and $\Delta \text{HCO}_3^-$

   h. Compare change in $[\text{Cl}^-]$ with change in $[\text{Na}^+]$

   i. **A good history and physical**

      - Renal failure, chronic vomiting, sepsis, heart failure, pneumonia, COPD, drug use, especially sedatives and loop type diuretics (thiazidess) and carbonic anhydrase inhibitors (acetazolamide)

      - Better watch serum $[\text{K}^+]$, remember shifts with high $[\text{H}^+]$. 


10. The **anion gap**, is really not a gap at all, it just represents the anions we don’t usually measure.

   a. \( \text{AG} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-) \), typically about 10 to 12 mmol

   b. The AG represents anions such as proteins, phosphates, sulfates and organic anions.

   c. **Increase in the AG**

      i. Is most often due to increased serum lactate or acetoacetate.

      ii. Rarely, an increased AG may be due to a decrease in cations such as \( \text{Ca}^{2+} \), magnesium and/or \( \text{K}^+ \)

   d. **Decrease in the AG**

      i. Increase in unmeasured cations

      ii. Addition of something new to the blood such as \( \text{Li}^+ \)

      iii. Reduction in a major plasma protein such as albumin (renal loss).

      iv. Hyperlipidemias and other less common causes.

11. **Basic rules to keep in mind for simple, one cause, problems.**

   a. Is a pH disturbance metabolic or respiratory in origin?

      - Respiratory acidosis, \( \text{PaCO}_2 \) is > 44

      - Metabolic acidosis, \( \text{HCO}_3^- \) is < 22

      - Respiratory alkalosis, \( \text{PaCO}_2 \) is < 36

      - Metabolic alkalosis, \( \text{HCO}_3^- \) is > 26

   b. If the primary change is

      - \( \text{HCO}_3^- \), then the underlying cause is most likely metabolic

      - \( \text{CO}_2 \), the underlying cause is most likely respiratory

   c. Metabolic acidosis with calculated ion gap

      - increased endogenous acid production
         - lactate
         - ketoacidosis
o accumulation of endogenous acids with renal failure
o loss of HCO₃⁻, diarrhea
o Toxic stuff like methanol and antifreeze

d. metabolic acidosis with no ion gap

o loss of HCO₃⁻, diarrhea
o renal loss of HCO₃⁻, renal tubular acidosis
o Carbonic anhydrase inhibition

e. metabolic alkalosis

- vomiting
- milk-alkali syndrome
- K⁺ wasting as with Conn’s syndrome
- Loss of H⁺
- Compensate is respiratory, retain CO₂

f. Respiratory acidosis

- CNS
- Airway obstruction
- Neuromuscular and faulty respiration
- CO₂ is high and the reason is poor ventilation
- Compensation must be to increase HCO₃⁻

g. Respiratory alkalosis

- CO₂ is low
- Pregnancy
- Sepsis
- Anxiety and physical pain leading to increased resp rate
- Salicylates
- Liver disease

12. If only life could be this simple all the time. But, a person may have more than one disease at a time that can cause an acid-base disturbance. So, how do you know?

a. With the coexistence of two metabolic acid-base disorders may be made apparent by calculating the difference between the change in the anion gap (delta AG), and the change in the serum CO₂ (delta CO₂).

b. This value goes by several names, either the delta or bicarbonate gap.
\[ \text{Delta (bicarbonate) gap} = \text{delta } AG \ - \ \text{delta } \text{HCO}_3^- \]

Where

\[ \text{Delta } AG = \text{patient’s } AG \ - \ 12 \text{ mEq/L} \]
\[ \text{Delta } \text{HCO}_3^- = 27 \text{ mEq/L} \ - \ \text{patient’s } \text{HCO}_3^- \]

If there is just one acid-base abnormality, there should be a 1:1 correlation between the rise in the anion gap and a corresponding drop in the bicarbonate.

Example: if the AG goes up by 10, then the HCO$_3^-$ should drop by 10.

\[ \text{Delta } AG \ - \ \text{delta } \text{HCO}_3^- = 10 - 10 = 0 \]

Just one acid-base problem here.

**Variation of the bicarbonate gap from zero, either + or – means there is a mixed acid-base problem. However, it certainly doesn’t tell you the type.**

13. Let’s see how this operates with two different mixed acid-base conditions.

**Case:** This 22 year-old man presents with several days of vomiting, nausea and abdominal pain. His blood pressure is low and he has tenting of the skin. His electrolytes are Na$^+$ = 144, Cl$^-$ = 95, K$^+$ = 4.2, HCO$_3^-$ = 14.

\[ \text{AG} = 35 \]
\[ \text{Delta } AG = 23 \ (35 - 12) \]
\[ \text{Delta } \text{HCO}_3^- = 13 \ (27 - 14) \]
\[ \text{Delta (HCO}_3^- \text{) gap} = +10 \]

The high HCO$_3^-$ gap indicates there are **two conditions** at work.

- **Metabolic acidosis** from dehydration and poor tissue perfusion (lactatic acid accumulation).
- **Metabolic alkalosis** from vomiting and loss of stomach acid.
14. Renal acidosis is in a league of its own.

a. The renal tubules reabsorb HCO₃⁻ and secretes acid

b. Failure of either leads to renal tubular acidosis

c. All forms of renal tubular acidosis are characterized by
   - minimally elevated to normal ion gap
   - hyperchlormia
   - net retention of HCl⁻, generally
   - Three basic patterns
     - Distal type (type 1 RTA)
     - Proximal type (type 2 RTA)
     - Type 3 RTA is absence of carbonic anhydrase.
     - Hypoaldosteronism (type 4 RTA)

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<thead>
<tr>
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<th>Type 1 RTA</th>
<th>Type 2 RTA</th>
<th>Type 4 RTA</th>
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<tbody>
<tr>
<td>Primary defect</td>
<td>Impaired distal acidification</td>
<td>Reduced proximal bicarbonate reabsorption</td>
<td>Decreased aldosterone secretion or effect</td>
</tr>
<tr>
<td>Plasma bicarbonate</td>
<td>Variable, may be below 10 meq/L</td>
<td>Usually 12 to 20 meq/L</td>
<td>Greater than 17 meq/L</td>
</tr>
<tr>
<td>Urine pH</td>
<td>Greater than 5.3</td>
<td>Variable, greater than 5.3 if above bicarbonate reabsorptive threshold</td>
<td>Usually less than 5.3</td>
</tr>
<tr>
<td>Plasma potassium</td>
<td>Usually reduced but hyperkalemic forms exist; hypokalemia largely corrects with alkali therapy</td>
<td>Reduced, made worse by bicarbonaturia induced by alkali therapy</td>
<td>Increased</td>
</tr>
</tbody>
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A case of renal related acidosis: Amy is a 24 year-old mother of one who develops acute renal failure after a perforated ulcer gave her peritonitis and shock. Her labs are Na⁺ 140 mEq/L, K⁺ 4 mEq/L, Cl⁻ 115 mEq/L, CO₂ 5 mEq/L, pH = 7.12, PaCO₂ 13 mmHg, and HCO₃⁻ 4 mEq/L.

AG = 20 = (140 – (Cl⁻ + HCO₃⁻))

\[ \text{Delta AG} = 9 = (21-12) \]

\[ \text{Delta HCO}_3^- = 23 = (27-4) \]

\[ \text{Delta (HCO}_3^- \text{ gap} = -14 = delta AG – delta HCO}_3^- \]
Her anion gap is up, but not off the chart. The bicarbonate gap is off.

So, her \( \text{Delta (HCO}_3^- \) is significantly off at -14 mEq/L; that is 14 mEq/L lower than would be expected given her excess anion gap of 9 (above normal). Were this a simple ‘one cause’ acidosis, the acid causing her drop in pH should have lowered her CO\(_2\) to only about 19 mEq/L. The fact that her CO\(_2\) is actually 5 mEq/L means there must an additional reason for her acidosis.

- In this case a hyperchloremic metabolic acidosis, which is commonly seen with renal failure. Below are her two renal related problems.
  - Uremia from kidney failure causing the elevated AG.
  - The tubular related problem of HCO\(_3^-\) recovery and acid secretion, which leads to a non-ion gap acidosis with hyperchloremia.

Summing it up

Respiratory, metabolic and mixed problems
Compensation
Anion and bicarb gap
Renal contribution to normal pH and problems of renal acidosis
Hyperchloremia